Universität Rostock

Traditio et Innovatio

Design and Synthesis of Pyrimidine *C*-Nucleosides, 5-Polyfluoroalkyl-5-deazaalloxazines and Spiro[pyrimido[4,5-*b*]quinoline-3',5-indoline-2'-one]-3,10-dihydro-2,4-diones

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Declaration

Hereby I declare that this thesis has been written without any assistance from third parties. Furthermore, I confirm that no sources have been used in the preparation of this thesis other than those indicated in the thesis itself.

Erklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig angefertigt und ohne fremde Hilfe verfasst habe, keine außer den von mir angegebenen Hilfsmitteln und Quellen dazu verwendet habe und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen als solche kenntlich gemacht habe.

Sergii Dudkin

Rostock, January 2013

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Abstract

The present thesis is mainly dedicated to heterocyclic and organofluorine compounds as well as *C*-nucleosides. Within the study new synthetic approaches to above-mentioned substances have been developed. In addition, the reactivity of newly synthesized products was investigated. A wide range of novel 2-(*β*-D-ribofuranosyl)pyrimidines including perfluoroalkyl-containing derivatives was synthesized by 3+3 cyclocondensation between 1-(*β*-D-ribofuranosyl)formamidine and various dielectrophiles, such as 3-(di)alkoxy- and 3-chloro-1-(polyfluoroalkyl)propen-1-ones, 3-nitro- and 3-(phenylethynyl)chromones and (het)aryl acetylenic ketones. Reaction of 6-arylamino-1,3-dialkyluracils with perfluorinated carboxylic acid anhydrides or chloroanhydrides in the presence of pyridine and subsequent cyclization in concentrated sulphuric acid gave the corresponding 1,3-dialkyl-5-(polyfluoroalkyl)-5-deazaalloxazines. The reactivity of these compounds towards nucleophilic and reducing reagents, such as acetophenone, nitromethane, potassium cyanide, indole, *p*-thiocresol, sodium cyanoborohydride and Hantzsch dihydropyridine, was studied. The nucleophilic addition, which takes place at position 5 of the 5-deazaalloxazine system, is in most cases irreversible and leads to 5,10-dihydro derivatives in good to excellent yields. An unexpected recyclization in the series of spiro[indole-3,5'-pyrimido[4,5-b]quinoline]-2,2',4'-trione derivatives, carried out via a three-component reaction of (thio)barbituric acids, isatins and electron-rich aromatic amines, was observed.

Kurzzusammenfassung

Die vorliegende Arbeit ist vor allem den heterocyclischen und fluororganischen Verbindungen sowie *C*-Nukleosiden gewidmet. Im Rahmen der Studie wurden neue synthetische Zugänge zu oben erwähnten Substanzen entwickelt. Zusätzlich wurde die Reaktivität der neu synthetisierten Produkte untersucht. Eine breite Palette von neuen 2-(*β*-D-ribofuranosyl)pyrimidinen einschließlich perfluoralkylhaltigen Derivaten wurde durch [3+3]-Cyclokondensation zwischen 1-(*β*-D-Ribofuranosyl)formamidin und verschiedenen Dielektrophilen, wie 3-(Di)alkoxy- und 3-Chlor-1-(polyfluoralkyl)propen-1-onen, 3-Nitro- und 3-(Phenylethinyl)chromonen und acetylenischen (Het)arylketonen, synthetisiert. Die Reaktion von 6-Arylamino-1,3-dialkyluracilen mit perfluorierten Carbonsäureanhydriden oder chlorhaltigen Anhydriden in Gegenwart von Pyridin und nachfolgende Cyclisierung in konzentrierter Schwefelsäure ergibt die entsprechenden 1,3-Dialkyl-5-polyfluoralkyl-5-deazaalloxazine. Die Reaktivität dieser Verbindungen gegen nucleophile und reduzierende Reagenzien, wie Acetophenon, Nitromethan, Kaliumcyanid, Indol, *p*-Thiokresol, Natriumcyanoborhydrid und das

Hantzsche Dihydropyridin, wurde untersucht. Die nukleophile Addition, die an der 5-Position des 5-Deazaalloxazinsystems stattfindet und in den meisten Fällen irreversibel ist, führt zu 5,10-Dihydro-Derivaten in guten bis sehr guten Ausbeuten. Eine unerwartete Recyclisierung konnte bei der Dreikomponentenreaktion zwischen (Thio)barbitursäuren, Isatinen und elektronenreichen aromatischen Aminen beobachtet werden, durch die die Reihe der Spiro[indol-3,5'-pyrimido[4,5-b]chinolin]-2,2',4'-trion-Derivate gebildet wurde.

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General Introduction

Nowadays organic chemistry is probably one of the most rapidly developing fields of natural science. Advances in supramolecular chemistry, stereoselective organocatalysis, oxidative coupling and C-H activation, decarboxylative coupling, as well as achievements in artificial photosynthesis and water photolysis together with other fascinating discoveries become hot research topics over the last few decades.

Science exerts influence on life, and life in turn has an impact on science. For instance, organic chemistry is closely related with biology; understanding of intracellular processes enables, on the on hand, a treatment of various diseases, and on the other hand, serves as a source of inspiration for new synthetic methods.

Since in 1964 George H. Heilmeier achieved the switching of colors by electric-field-induced realignment of dichroic dyes, organic liquid crystals have been successfully used in LCD (Liquid Crystals Displays). The last ones tend to be replaced by monitors based on OLED (Organic Light-Emitting Diode) technology. Synthetic chemistry relationship to other branches of industry and science can be continued.

A great number of organic compounds being of importance to mankind belong to the heterocyclic class, which forms by far the largest division of classical organic chemistry. Approximately 20 million chemical compounds had been identified by the end of the second millennium; about one half of them contain heterocyclic systems. Heterocycles occur in many natural products, such as alkaloids, vitamins, hormones, antibiotics, as well as pharmaceuticals, herbicides, dyes, and other products of technical importance (advanced materials, corrosion inhibitors, sensitizers, stabilizing agents, etc.).[1] The majority of pharmaceutical products that mimic biologically active natural products are heterocycles as well. More than 90% of new drugs contain a heterocyclic moiety, and the interface between chemistry and biology is crossed by heterocyclic compounds.[2]

Other important aspect of our research work is organofluorine chemistry. Thus, more than two thirds of newly synthesized compounds described within the present thesis contain fluorine. The last one is the most electronegative element with very tight bound valence electrons, which in turn results in low atomic polarizability and small size (van der Waals radius = 1.47 Å). The C-F binding energy ranges as high as 130 kcal/mol.[3]

Fluorine can be highly favourable in pharmaceutical and agrochemical compounds. One or just a few atoms in an organic molecule can dramatically change its chemical and biological nature, including its stability, lipophilicity, and bioactivity.

Manfred Schlosser, professor of chemistry at the Swiss Federal Institute of Technology, Lausanne, says: "Smuggling fluorine into a lead structure enhances the probability of landing a hit

almost 10-fold". Fluorinated drugs have made up approximately 5-15% of the total number of launched drugs worldwide over the past 50 years with a noticeable increase in the past decade.[4] The trifluoroethylamine moiety, $CF_3CH(R)NHR'$, is known to be an amide isostere, while substituent fluorine itself is an analog of hydrogen. On the other hand, according to Grimm's Hydride Displacement Law, fluorine can be considered as a bioisostere of OH, NH_2 and CH_3-group.[5] Despite organofluorine compounds are rare in nature, fluorinase enzymes have been discovered in living organisms.[6]

1 Design and Synthesis of Novel Pyrimidine *C*-Nucleosides from 1-(*β*-D-Ribofuranosyl)formamidine

1.1 Introduction

1.1.1 Natural and synthetic *C*-nucleosides. Biological role

C-Nucleosides are generally considered as compounds containing a heterocyclic aglycone and a carbohydrate moiety linked together by a carbon-carbon bond. However, *C*-nucleosides considerably differ from the most common nucleosides, in which sugar and heterocyclic aglycone are connected by a C–N bond. First of all, the C–C bond is responsible for the resistance of *C*-nucleosides to hydrolytic and enzymatic cleavage.

C-Nucleosides are suitable candidates for extension of the genetic alphabet, and consequently, for usage as building blocks of DNA. In contrast to naturally occurring nucleosides, they are able to form artificial base-pairs based not only on hydrogen bonding, but also on hydrophobic interactions and metal bridges.[7]

Natural *C*-nucleosides, having C1 of their sugar moieties linked to nitrogen-containing heterocycles through a carbon-carbon bond, have been known since 1957, when pseudouridine **1** (Figure 1), the first member of this class of compounds, was isolated from yeast RNA. The elucidation of its structure was accomplished two years later. Since then other members of this important class of natural compounds have been isolated.[8]

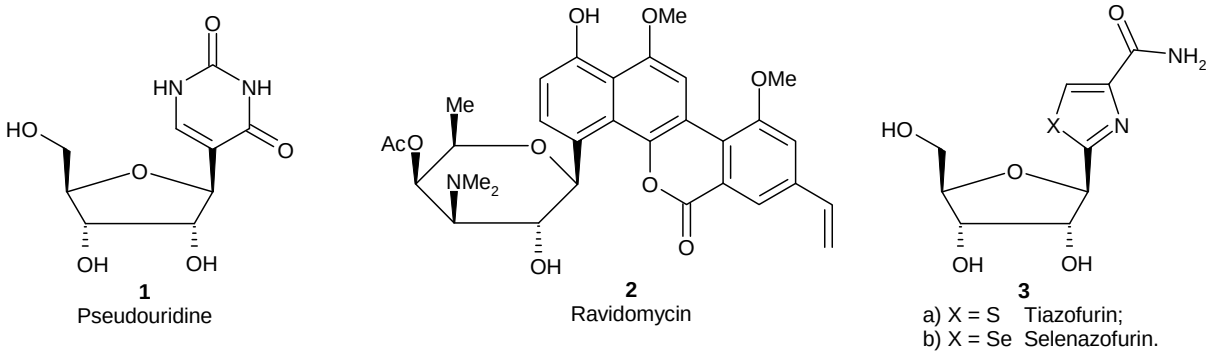


Figure 1. Natural (**1**, **2**) and synthetic (**3a,b**) C-nucleosides.

C-Nucleosides (as well as standard N-nucleosides) can in principle target various enzymes involved in nucleic acid metabolism. The major advantage of *C*-nucleosides is the stability toward hydrolytic and enzymatic cleavage of the nucleosidic bond, due to the replacement of the nucleosidic C-N bond by the nonhydrolyzable C-C bond.[7]

Aryl *C*-glycoside antibiotics constitute an emerging class of biologically active natural products. Ravidomycin, the congener of the gilvocarcin-class antitumor antibiotics possessing an amino sugar, shows an enhanced antitumor activity.[9]

Tiazofurin **3a** and selenazofurin **3b** are two widely studied synthetic *C*-nucleosides. The

biological effects of these nucleosides appear to be due to inhibition of inosine monophosphate dehydrogenase (IMPDH), which induces the shutdown of guanine nucleotide synthesis. IMP dehydrogenase is associated with cell proliferation and is a possible target for cancer chemotherapy.[10] Selenazofurin **3b** the selenium analog of **3a**, shows effective antitumor and antiviral activity, as well as efficacy as a maturation-inducing agent.[11]

However, pyrimidine *C*-nucleosides bearing a carbohydrate moiety at the C-2 atom have not received much attention despite the fact that some of them are useful in treating a wide variety of diseases including infections, infestations, neoplasms, and autoimmune diseases.[12]

1.1.2 Fluorinated pyrimidine nucleosides

Some special position among all classes of pharmacologically active nucleosides has been occupied by fluoro-containing congeners with fluorine functionality at the heterocyclic part (Figure 2). Fluorinated nucleosides and their analogues represent the class of organofluorine compounds, which in the last three decades have found an extensive application in biological chemistry, life-science and medicine branches.[13, 14]

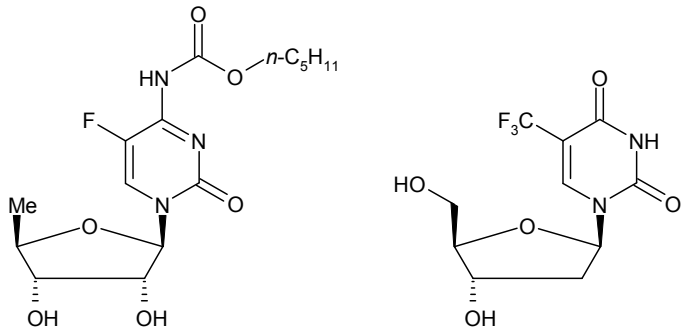


Figure 2. Fluorinated pyrimidine nucleosides clinically used as antimetabolites.

1.1.3 Cytidine deaminase as a potential biological target

We consider desired *C*-nucleosides first of all as potential cytidine deaminase inhibitors.

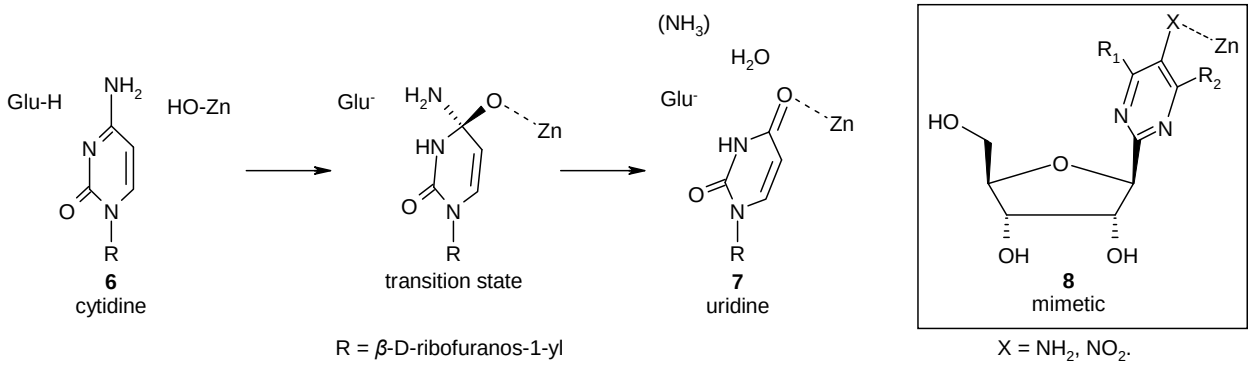
Cytidine deaminase (CDA, EC 3.5.4.5) is a homotetrameric zinc-protein belonging to the pyrimidine salvage pathway, which catalyzes the deamination of cytidine and deoxycytidine. Furthermore, CDA deaminates also several cytosine nucleoside based drugs used as antineoplastic and antiviral agents causing the loss of their therapeutic efficiency.[15]

Deamination by an apolipoprotein B mRNA editing enzyme (APOBEC) called activation-induced cytidine deaminase (AID) is critical for generating high-affinity antibodies, and

deamination by APOBEC-3 proteins can inhibit retrotransposons and the replication of retroviruses such as human immunodeficiency virus and hepatitis B virus.[16] The absolute dependence of antibodies somatic hypermutation on cytidine residues was also established.[17] Hence 2-(*β*-D-ribofuranosyl)pyrimidines may be potential immunosuppressive agents, which are very useful for transplantology and therapy of autoimmune diseases.

Despite of the structural differences between the amino acid sequences (e.g. between the *E. coli* and human CDA there is only about 30% of identity), catalytic mechanism of all above mentioned cytidine deaminases must be similar. It is proved by numerous chemical,[18, 19] structural[15, 16] and computational[20, 21] studies.

In recent years cytidine deaminases attract more and more attention of scientists. Articles devoted to CDA have been published in high-impact journals such as *Nature*[16] and *Science*[17].



Scheme 1. Catalytic pathway for the conversion of cytidine by CDA.[18, 19] Only the minima are displayed. Compare with desired mimetics **8**!

1.1.4 Task setting and motivation

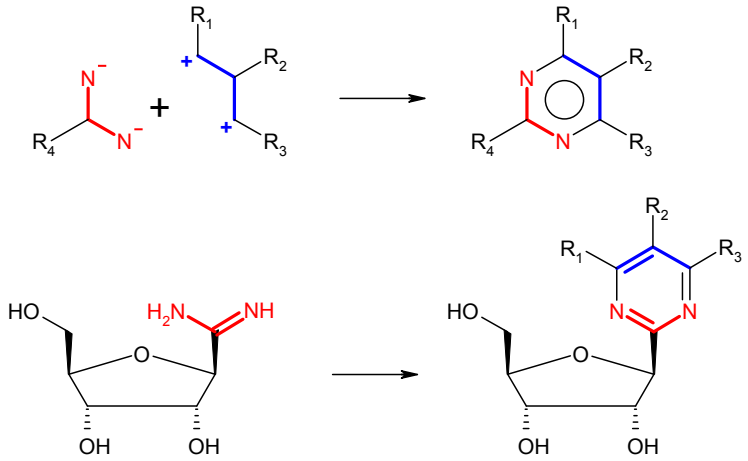
Inspired by the relevance of *C*-nucleosides as well as fluorinated pyrimidine nucleosides, we have undertaken the current study to develop a new type of pyrimidine *C*-ribosides furnished with polyfluoralkyl-substituents at position 4 or 6. At the same time, taking into account our interest in CDA inhibition, design and synthesis of various non-fluorinated *C*-nucleosides was the second important task within the present work.

1.2 Synthetical approach: 1,3-binucleophile + 1,3-bielectrophile

There are different applicable approaches to the synthesis of a variety of C-nucleosides. They can be classified into four categories based on the strategies they use:[7]

1) Construction of an aglycone unit upon a carbohydrate moiety;
2) Construction of a carbohydrate moiety upon an aglycone unit;

3) Direct coupling of a carbohydrate moiety with a preformed aglycone unit;
4) Modification of the existing *C*-nucleosides.



Scheme 2. The key stage of the synthesis of pyrimidine *C*-nucleosides according to the chosen strategy.

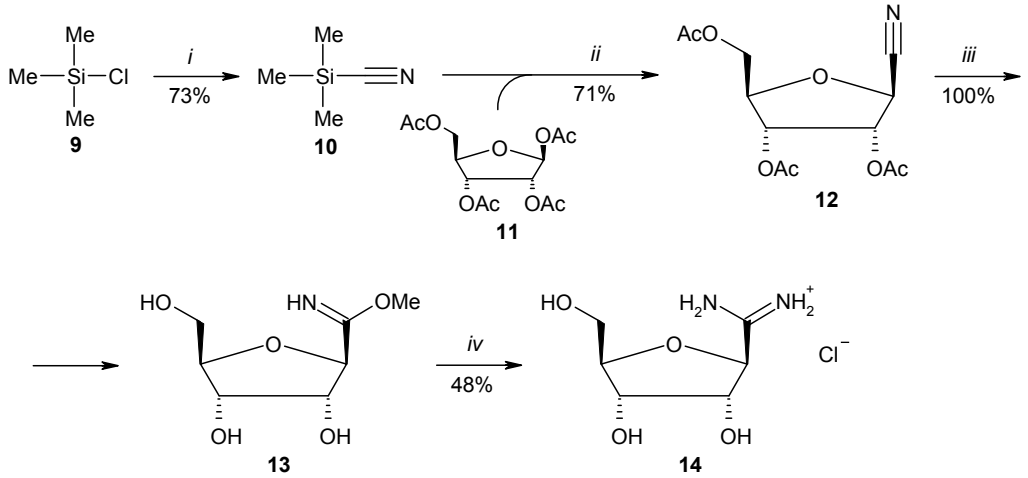
Our synthetic approach is based on the initial functionalization of *β*-D-ribofuranose, followed by formation of the aglycone via 3+3 cyclocondensation: the 1,3-binucleophile, namely 1-(*β*-D-ribofuranosyl)formamidine, reacts with different 1,3-bielectrophiles to form the desired pyrimidine ring (Scheme 2). Afterwards, some of the obtained *C*-nucleosides were further modified. Thus, the first and fourth strategies were applied during this study.

Taking into account that we have to deal with unprotected sugars, the synthetic manipulations should be conducted preferably in mild reaction conditions; otherwise the carbohydrate moiety can be damaged.

1.3 Synthesis of 1-(*β*-D-ribofuranosyl)formamidine hydrochloride, the starting material

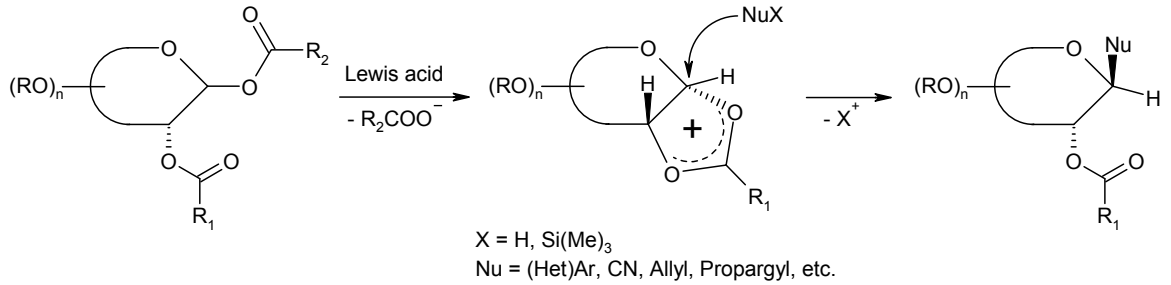
The key synthetic building block **14** was synthesized in three steps from 1,2,3,5-tetra-*O*-acetyl-*β*-D-ribofuranose **11** using known procedures (Scheme 3).

The synthesis of 2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl cyanide **12**,[23] the key step in the 1-(β-D-ribofuranosyl)formamidine preparation, is referred to the Lewis acid-mediated electrophilic substitution. The first Lewis acid-catalyzed glycosylation for the synthesis of aryl C-glycosides was reported in 1945.[28] The same principle can be applied for another type of *C*-nucleosides. Usually the reaction occurs with high *α*/*β*-selectivity. The general principle of glycosylation with Lewis acids is shown in Scheme 4. The selectivity of this reaction with different sugars, substrates and catalysts has been studied.[29, 30] The best result in our hands showed the method using tin tetrachloride as a Lewis acid, developed by M. T. Reetz and coworkers, which hereby showed an extremely high stereospecificity (no *α*-anomer has been detected).



Scheme 3. Synthesis of 1-(*β*-D-ribofuranosyl)formamidine hydrochloride.

Reagents and conditions: *i*: KCN, KI, NMP, r.t., 48 h;[22] *ii*: $SnCl_4$, DCM, 24 h at r.t., then 6 h reflux;[23, 24] *iii*: MeOH, NaOMe, 72 h;[25, 26] *iv*: NH_3 in MeOH, NH_4Cl, 72 h.[27]



Scheme 4. General mechanism of glycosylation under Lewis acid catalysis, which explains the high stereoselectivity of the reaction.

Next, the obtained nitrile **12** was treated with a catalytic amount of sodium methoxide in methanol to give the deprotected *β*-D-ribofuranosyl-1-carboximidic acid methyl ester, which afforded 1-(*β*-D-ribofuranosyl)formamidine hydrochloride after treatment with a methanolic solution of ammonia and ammonium chloride.

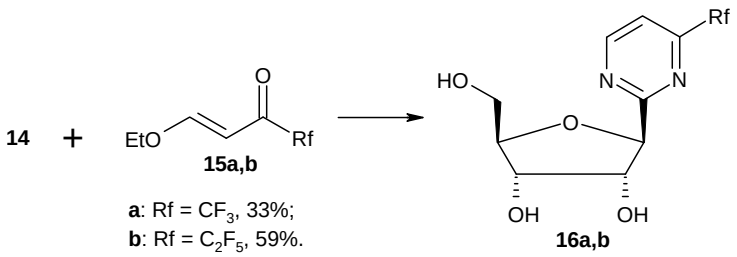
1.4 Syntheses of various 2-(*β*-D-ribofuranosyl)pyrimidines

1.4.1 Syntheses of 2-(*β*-D-ribofuranosyl)-4-(perfluoroalkyl)pyrimidines

Condensation with *β*-ethoxy-*α*,*β*-unsaturated perfluoroalkyl ketones affords corresponding 4-(perfluoroalkyl)pyrimidine *C*-nucleosides. In fact, ethoxymethylene group constitutes a hidden aldehyde function.

Previously reported condensation of 4-ethoxy-1,1,1-trifluorobut-3-en-2-one with amidines gave a mixture of the corresponding tetrahydropyrimidines and pyrimidines.[31] After some optimization we found that treatment of amidine **14** with 4-ethoxy-1,1,1-trifluorobut-3-en-2-one **15a** in DMF at 80 °C in the presence of MeONa and DBU resulted in the formation of 2-(*β*-D-ribofuranosyl)-4-(trifluoromethyl)pyrimidine **16a**. Using potassium carbonate with molecular sieves

4Å at 60 °C, perfluoroethylated analogue **16b** was prepared in even better yield. The current method constitutes a convenient approach to 5,6-unsubstituted pyrimidines.



Scheme 5. Syntheses of 2-(*β*-D-ribofuranosyl)-4-(perfluoroalkyl)pyrimidines.

Reagents and conditions: **a**: NaOMe, DBU, DMF, 80 °C, 3 h; **b**: K_2CO_3, molecular sieves 4Å, DMF, 60 °C, 5 h, under argon.[31, 32]

The steric configuration of the anomeric center is confirmed by X-ray analysis of the nucleoside **16a**, which crystallizes from EtOAc/$CHCl_3$ solution in monoclinic system (space group $P2_1$) with one equivalent of chloroform. Thus, we can conclude the same configuration for the whole *C*-nucleoside range synthesized from 1-(*β*-D-ribofuranosyl)formamidine **14**.

4-Ethoxy-1,1,1-trifluoro-3-buten-2-one and 1-ethoxy-4,4,5,5,5-pentafluoro-1-penten-3-one were synthesized by the known method[33] from ethyl vinyl ether and corresponding trifluoroacetic or pentafluoropropionic acid anhydride respectively in the presence of 4-*N*,*N*-dimethylaminopyridine as a catalyst.

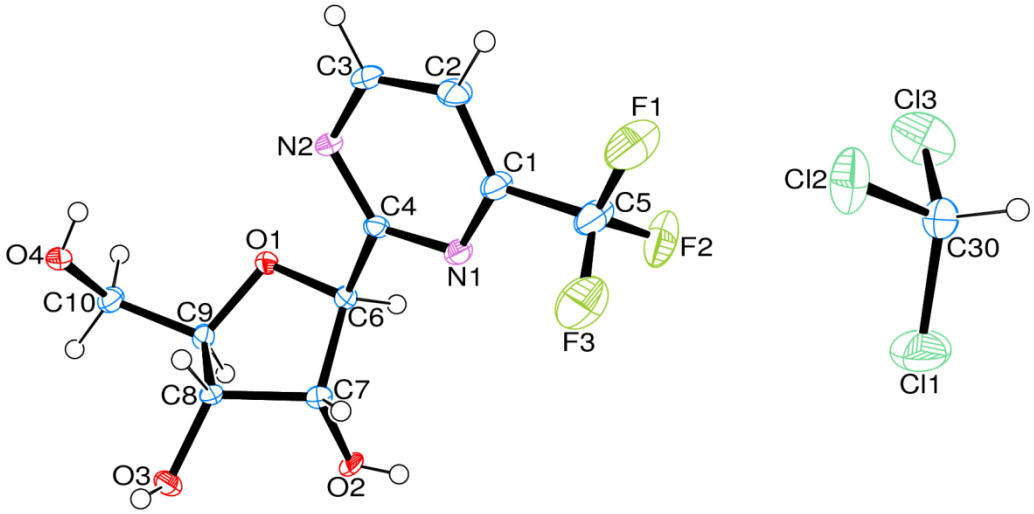
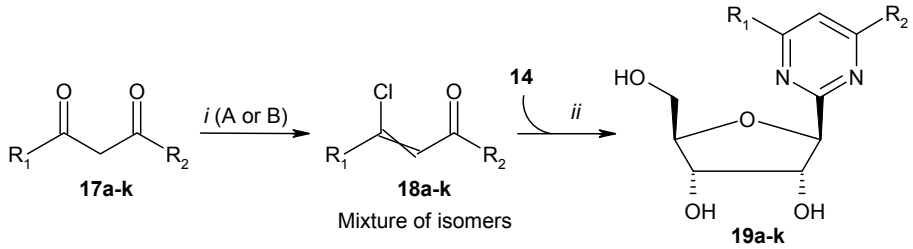


Figure 3. Ortep plot of 2-(*β*-D-ribofuranosyl)-4-(trifluoromethyl)pyrimidine **16a** (40% probability level). Crystal solvate with 1 eq of chloroform.

1.4.2 Synthesis of *C*-nucleosides from 1,3-diketones

Next, we decided to involve 1,3-diketones in this study to obtain the corresponding 4,6-substituted 2-(*β*-D-ribofuranosyl)pyrimidines, and to our great disappointment, we were confronted

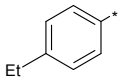
with significant difficulties. As opposed to benzamidine, used in the trial experiments, ribosylamidine **14** turned out to be insufficiently reactive under the same conditions and seems to decompose before the reaction starts (see Chapter 1.4). So after several unsuccessful attempts we decided to substitute the enolic OH-group for a more easily replaceable chlorine atom, which is a weaker π-electron-donating group, and therefore, less deactivates the conjugated double bond (Michael acceptor) towards nucleophiles in the initial addition reaction, which is the rate-limiting stage of the current cyclocondensation.[34] Moreover, *β*-chloro-*α*,*β*-unsaturated ketones proved to be so reactive that the reaction with 2-(*β*-D-ribofuranosyl)formamidine shows a marked exothermic effect and should be conducted under cooling to suppress undesirable side processes (Scheme 6). Finally, in order to establish the generality of this cyclization, a variety of nucleosides **19** was successfully obtained (Table 1). These results clearly show that despite some limitations (see Chapter 1.4, Table 2, product **19m**) the present reaction can be applicable to different *β*-chloro-*α*,*β*-unsaturated ketones **18**, providing a reliable route to the synthesis of a wide range of the 4,6-disubstituted pyrimidine *C*-nucleosides **19**.

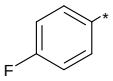


Scheme 6. Synthesis of *C*-nucleosides from 1,3-diketones.

Reagents and conditions: *i*(A): $SOCl_2$, $CHCl_3$, boiling under reflux, 3 h;[35] *i*(B): oxalyl chloride, DMF, DCM, –78 to r.t.;[36] *ii*: K_2CO_3, molecular sieves 4Å, DMF, 0 °C, 2 h.[37]

Table 1. Synthesis of *C*-nucleosides **19** from activated 1,3-diketones.

Entry	R_1	R_2	Yield, %[c]	
			18	**19**
a	Ph	CF_3	92[a]	71
b		CF_3	81[a]	73
c	Ph	*n*-C_3F_7	93[a]	55
d		CF_3	99[a]	42
e	Me	CF_3	52[b]	57
f	Ph	COOMe	97[b]	33
g		CF_3	88[b]	67
h	*i*-Pr	CF_3	63[b]	55

Entry	R_1	R_2	Yield, %[c]	
			18	**19**
i	2-Naphthyl	CF_3	57[a]	38
j		COOMe	86[b]	42
k		*n*-C_3F_7	74[a]	49

[a] – *α*,*β*-unsaturated *β*-chloroketone was prepared according to the method A (with $SOCl_2$);

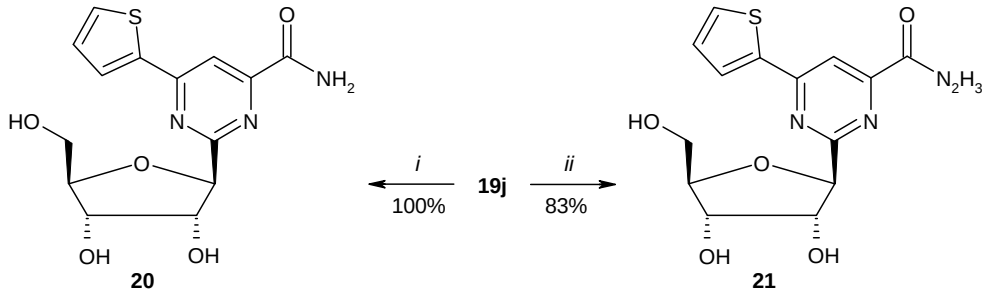
[b] – *α*,*β*-unsaturated *β*-chloroketone was prepared according to the method B (with $(COCl)_2$);

[c] – yields refer to pure isolated products.

At the 1,3-diketone activation stage an application of thionyl chloride in boiled chloroform is possible only in case of perfluorosubstituted diketones and if they are not sensitive to acids (e.g. diketones containing furan ring cannot be used). In other cases, either no reaction or decomposition was observed. Next, the products were distilled in a high vacuum to afford a yellow or green liquid consisting of a mixture of structural and *cis*/*trans* isomers **18**, which were not separated and used without additional purification. The synthesis of *β*-ethoxy-*α*,*β*-unsaturated ketones from the corresponding 1,3-diketones was particularly studied and considered by K. I. Pashkevich[35] (method with thionyl chloride) and R. E. Mewshaw[36] (method with oxalyl chloride).

Diketones **17d**, **f**, **h** and **k** were synthesized via classical Claisen condensation in the presence of sodium methylate, while others were purchased from chemical supply companies.

1.4.3 Aminolysis and hydrazinolysis of methyl 2-(*β*-D-ribofuranosyl)-6-(2-thienyl)pyrimidine-4-carboxylate



Scheme 7. Aminolysis and hydrazinolysis of methyl 2-(*β*-D-ribofuranosyl)-6-(2-thienyl)pyrimidine-4-carboxylate. *Reagents and conditions*: *i*: 7N ammonia in MeOH, r.t., overnight; *ii*: N_2H_4, MeOH, r.t., overnight.

One congener (**19j**), obtained from *α*,*β*-unsaturated *β*-chloroketone and bearing an ester group, was employed for the synthesis of other non-fluorinated nucleoside derivatives. When this compound was dissolved in methanolic ammonia and allowed to stir at room temperature overnight,

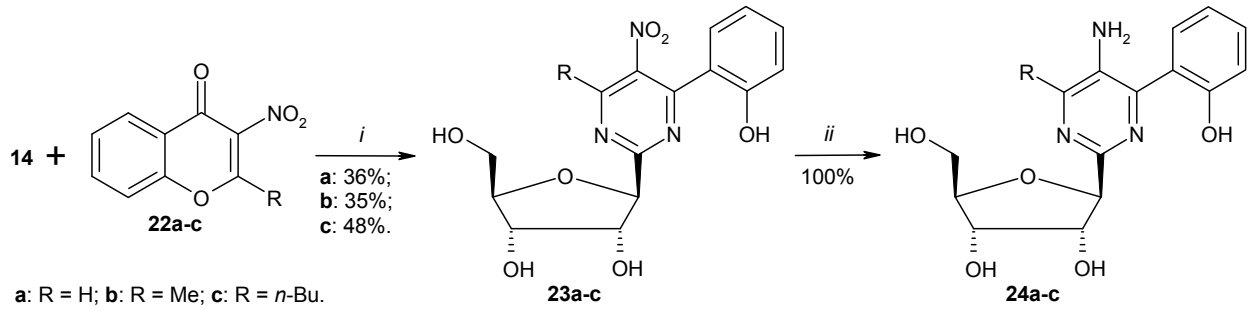
nucleoside **20** possessing a carboxamide function at the 2-position was obtained in quantitative yield. Treatment of **19j** with hydrazine hydrate in methanol at room temperature afforded the corresponding hydrazide **21** in 83% yield (Scheme 7).

As we see, these simple reactions proceed under mild conditions and in high yields. In addition, no labour-intensive work up of the reaction mixture is required.

1.4.4 Synthesis of 2-(*β*-D-ribofuranosyl)-4-(2-hydroxyphenyl)-5-nitropyrimidines and catalytic reduction of nitro group

We continued to search for applicable 1,3-dinucleophiles. It is known that 3-nitrochromone **22a** reacts with amidines to give the corresponding 5-nitropyrimidines.[38] Thus, we decided to test the reaction on our 2-(*β*-D-ribofuranosyl)formamidine **14**. As a result, 5-nitropyrimidine *C*-nucleosides were successfully synthesized from the corresponding 3-nitrochromones (Scheme 8). The 2-position of the chromone is activated by the nitro group, and hence easily participates in the Michael addition, followed by a chromone ring-opening reaction and subsequent cyclocondensation to give the 5-nitropyrimidine.

The cyclization took place in the presence of sodium methoxide, acetic acid and triethylamine in methanol yielding 5-nitropyrimidine **23a** in 36% yield. A buffer solution is required to provide the optimal pH. On the one hand, the initial amidine **14** is inactive in its protonated form. On the other hand, basic media can destroy the product (especially at the air; an easily oxidized phenolate anion forms) as well as the 3-nitrochromone. So the optimal pH level was found to be neutral. A similar result was obtained with 2-methyl- and 2-butyl-3-nitrochromones in DMF instead of methanol, which gave compounds **23b** and **c** in 35% and 48% yields, respectively.



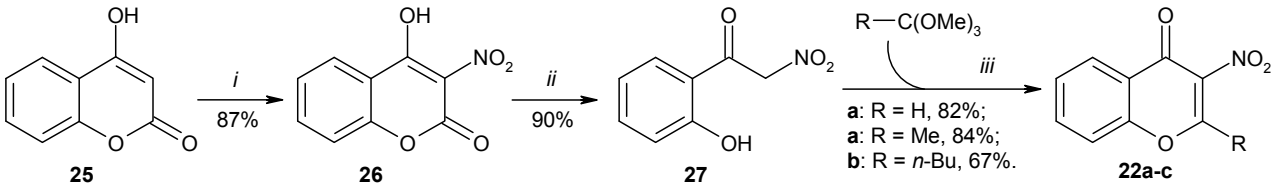
Scheme 8. Synthesis of 2-(*β*-D-ribofuranosyl)-4-(2-hydroxyphenyl)-5-nitropyrimidines and catalytic reduction of nitro group.

Reagents and conditions: *i*(**a**): NaOMe, AcOH, NEt_3, MeOH, 80 °C, 1,5 h; *i*(**b,c**): NaOMe, AcOH, NEt_3, DMF, 50 °C, 5 h, under argon;[38] *ii*: H_2, Pd (10 % on charcoal), MeOH, r.t., 2 days.

The obtained 5-nitropyrimidine *C*-nucleosides **23a-c** were catalytically reduced using 10 wt. % Pd/C as the catalyst under a hydrogen pressure of 1 atm to give the corresponding 5-amino

compounds **24a-c**. The latter are especially interesting for us because of their ability to mimic the substrate or its transition state (see Introduction, Scheme 1). 5-Amino-substituted 2-(*β*-D-ribofuranosyl)pyrimidines are remarkably similar to cytidine and are expected to be able to form stable chelate complexes with a zinc cation and hereby to inhibit cytidine deaminase (compare with **6**).

It is worth to say a few words about the 3-nitrocromone synthesis, which has been significantly improved (Scheme 9). The nitration of 4-hydroxycoumarin **25** was carried out under mild conditions in the presence of a catalytic amount of sodium nitrite. In this case the reaction runs smoothly and without spontaneous overheating. The reaction conditions of the hydrolysis of 4-hydroxy-3-nitrocoumarin **26** and of the subsequent neutralization were also optimized and led to increasing of the yield up to 90%. The reaction was carried out at 55 °C for 90 min. Then the reaction mixture was neutralised in an ice bath with 1.3 eq of acetic acid (calculated on taken alkali) and then carefully acidified with 0.5 eq of hydrochloric acid. Also a novel approach is to apply orthoesters in the presence of sulphuric acid (instead of previously used carboxylic acid anhydrides)[39] in order to obtain 3-nitrocromones from 2-nitro-2'-hydroxyacetophenone **27**. This advantage is especially essential in case of 2-unsubstituted product because the preparation and use of unstable acetic formic anhydride can be avoided.[40]

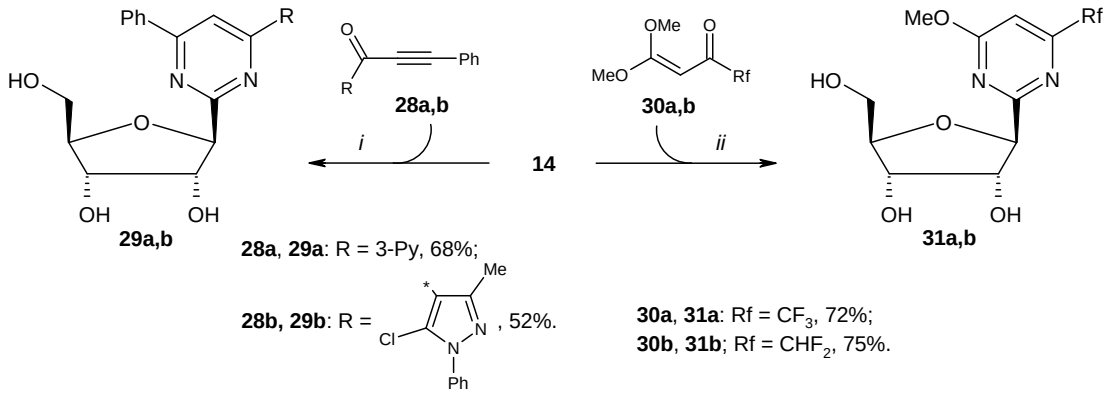


Scheme 9. Synthesis of 3-nitrocromone.

Reagents and conditions: *i*: HNO_3, AcOH (glacial), $NaNO_2$ (cat.) 40 °C, 2 h; *ii*: KOH in H_2O, 55 °C, 1,5 h;[41] *iii*: H_2SO_4(cat.), boiling 8 h.[39]

1.4.5 Synthesis of *C*-nucleosides from conjugated ketoalkynes and *β*,*β*-dimethoxy-*α*,*β*-unsaturated ketones

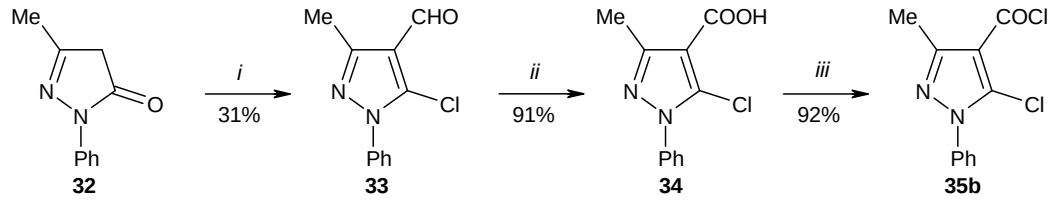
In order to increase the variety of *C*-nucleosides, we tested different binucleophiles such as conjugated ketoalkynes and *β*,*β*–dimethoxyketoalkenes, which, as it has turned out, show a good reactivity towards ribosylamidine **14** (Scheme 10). In fact, *β*,*β*–dimethoxyketoalkenes have been relatively poorly investigated so far as convenient precursors of pyrimidines with alkoxy group at position 4 or 6 (depending on the opposite substituent). The application of *α*,*β*-ynones is essential for pyridyl-substituted pyrimidines because they cannot be obtained neither from 1,3-diketones nor *β*-ethoxy-*α*,*β*-unsaturated ketones (see Chapter 1.2.2 and 1.4).



Scheme 10. Synthesis of *C*-nucleosides from various precursors.

Reagents and conditions: *i*: K_2CO_3, molecular sieves 4Å, DMF, 70 °C, 4 h, under argon;[42] *ii*: K_2CO_3, molecular sieves 4Å, DMF, 60 °C, 5½ h, under argon.[43]

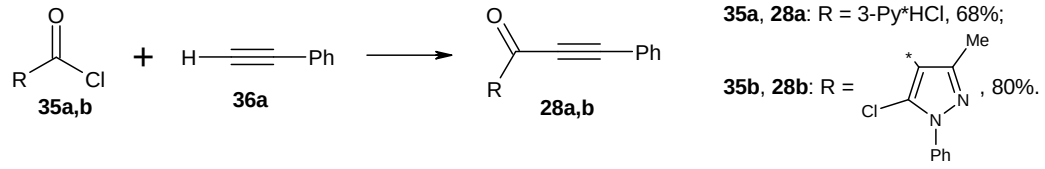
4,4-Dimethoxy-1,1,1-trifluoro-3-buten-2-one **30a** and 4,4-dimethoxy-1,1-difluoro-3-buten-2-one **30b** were prepared by a reported procedure from 1,1-dimethoxyethylene and the corresponding anhydride in the presence of pyridine as a base.[44]



Scheme 11. Synthesis of 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid chloroanhydride **35b**.

Reagents and conditions: *i*: DMF, $POCl_3$, 70 °C, 2 h; *ii*: $KMnO_4$, acetone, r.t., 12 h; *iii*: $SOCl_2$, reflux, 3 h.[45, 46]

Next, the acyl chlorides were coupled with phenylacetylene **36a** by standard methods to give the desired *α,β* unsaturated ynones (Scheme 12).



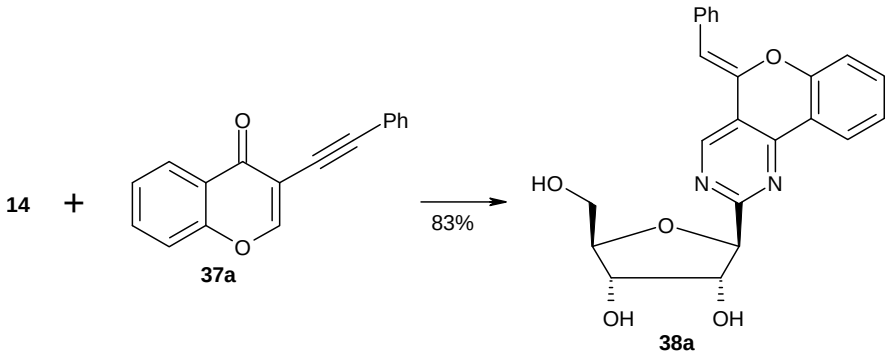
Scheme 12. Sonogashira coupling with acyl chlorides.

Reagents and conditions: $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, dioxane, r.t. (**a**) or 70 °C (**b**), 2 h, under argon.[46, 47]

1.4.6 Synthesis of *C*-nucleosides from 3-(phenylethynyl)-4*H*-chromen-4-one

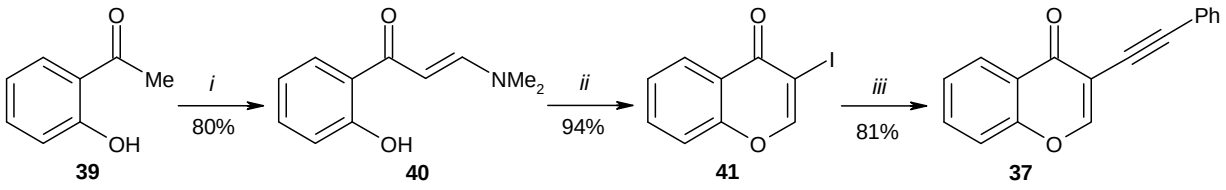
Finally, 3-phenylacetylenylcromone appears to react with ribofuranosyl formamidine in the presence of K_2CO_3 and molecular sieves in DMF giving the desired product **38a** in a high yield (Scheme 13). This unusual type of reaction was first described by Dewen Li, Shudong Duan and Youhong Hu as a convenient tool for combinatorial chemistry. The authors unambiguously

confirmed the *Z*-configuration of the obtained products by 1D-NOE difference experiments and X-ray crystal structure analyses as well.[48] The reaction runs smoothly. The product **38a** does not need a complicated purification and can be isolated in pure state by simple recrystallization from methanol.



Scheme 13. Synthesis of *C*-nucleoside from 3-(phenylethynyl)-4*H*-chromen-4-one.
Reagents and conditions: K_2CO_3, molecular sieves 4Å, DMF, 60 °C, 6 h, under argon.[48]

The initial 3-phenylacetylenylcromone was synthesized in three steps from 2'-hydroxyacetophenone **39** using known procedures (Scheme 14). The condensation product with DMFDMA[49] **40** was treated with the iodine-pyridine complex in chloroform giving 3-iodochromone **41**.[50-52] The latter underwent the Sonogashira coupling with phenylacetylene to afford the desired 3-(phenylethynyl)chromone **37a**.[53, 54]



Scheme 14. Synthesis of 3-(phenylethynyl)-4*H*-chromen-4-one.
Reagents and conditions: *i*: DMFDMA, 90 °C, reflux, 2 h;[49] *ii*: I_2, pyridine, $CHCl_3$, 0 °C, 1 h;[50-52] *iii*: phenylacetylene, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, DMF, r.t., 2 days, under argon.[53, 54]

1.5 Spectral considerations

The structures of all *C*-nucleosides were characterized by IR, ^1H, ^{13}C NMR spectral data as well as MS and HRMS analysis.

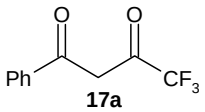
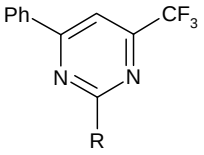
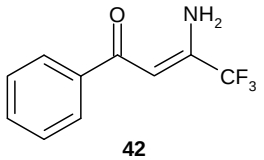
All NMR signals of the *β*-D-ribofuranosyl moiety were easily assigned since they have been already described in the literature.[55] In addition, HSQC correlation spectrum of compound **19k** was measured and vicinity of corresponding C and H atoms was additionally confirmed. The coupling between neighbouring OH and CH protons is clearly observed in the spectra acquired in DMSO-d_6, unlike chloroform-*d*. In case when R_F = C_2F_5 or *n*-C_3F_7, the polyfluoroalkyl groups appear as

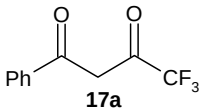
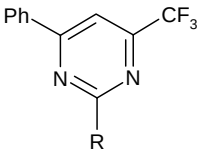
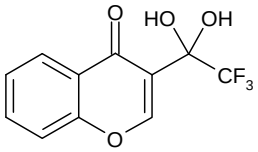
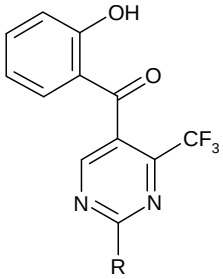
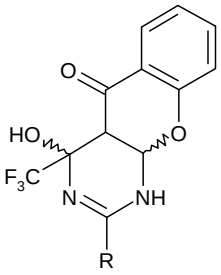
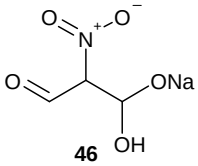
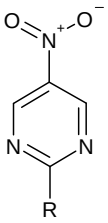
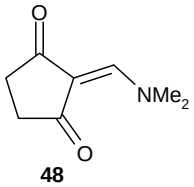
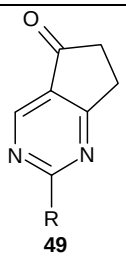
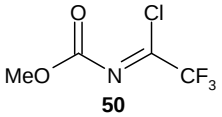
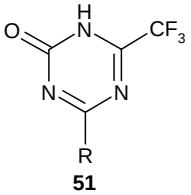
undecipherable multiplets. In addition, the presence of fluorinated alkyl groups was confirmed by ^{19}F NMR.

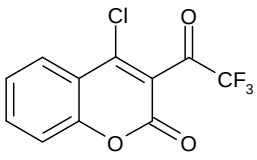
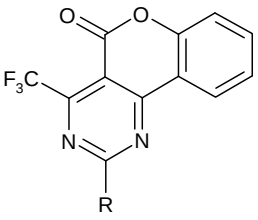
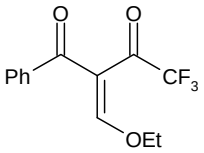
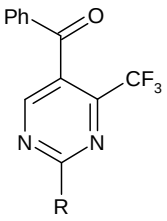
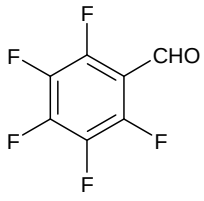
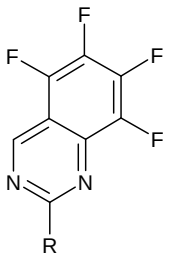
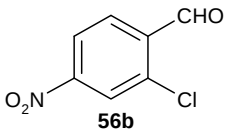
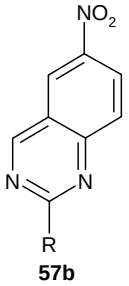
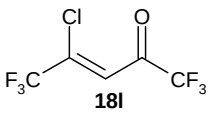
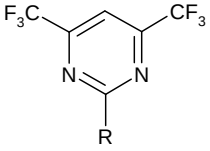
1.6 Negative results

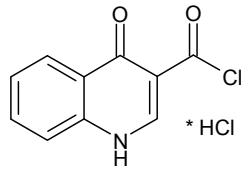
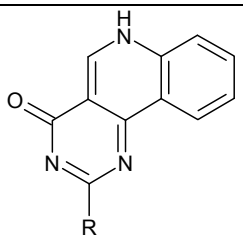
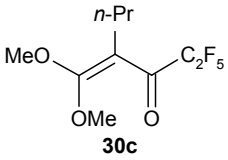
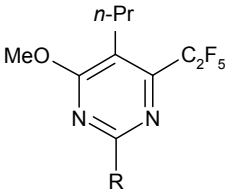
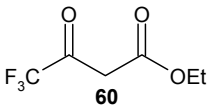
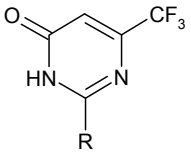
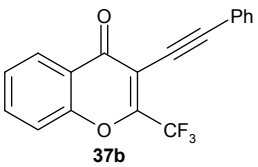
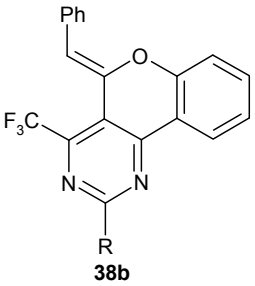
To our great disappointment, we have not succeeded in synthesizing the majority of predesigned *C*-nucleosides. Many of them are unstable against nucleophiles because of the high number of electron withdrawing groups present in the pyrimidine ring (**19l**, **53** and **55**) and have not been isolated in pure state, or the 1-(*β*-D-ribofuranosyl)formamidine decomposes during the reaction (**48**, **56a** and **b**). The negative results and the corresponding reaction conditions with comments are briefly summarized in Table 2.

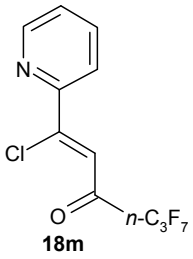
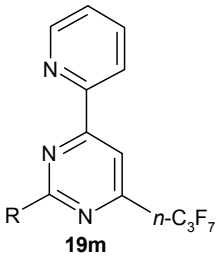
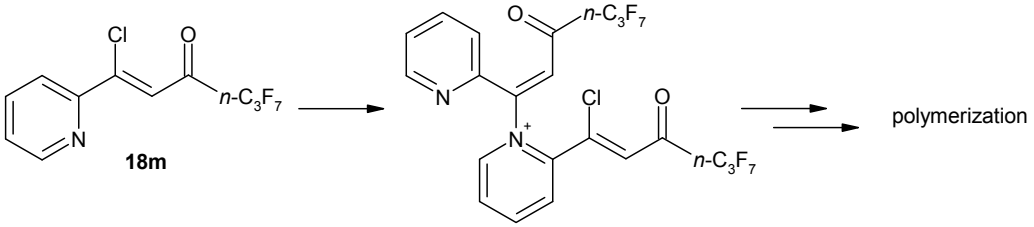
Table 2. Negative results.

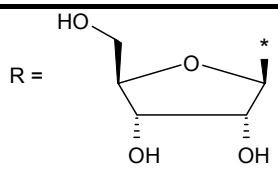
Starting material	Product	Reaction condition	Comments
 **17a**	 **19a**	NaOAc, AcOH (cat.), dioxane, 115 °C, 12 h.	Despite, for example, benzamidine ready react with 4,4,4-trifluoro-1-phenylbutane-1,3-dione in dioxane at 115 °C in the presence of a catalytic amount of acetic acid, 1-(*β*-D-ribofuranosyl)form-amidinedoes notenterintothisreaction. Only the following product was isolated:  **42** The problem is based on the solubility of starting material.
		NaOAc, AcOH (cat.), methanol, 80 °C, 3 h.	No reaction was observed.

Starting material	Product	Reaction condition	Comments
 **17a**	 **19a**	NaOAc, AcOH (cat.), methanol, 110 °C, 20 h.	Only the initial diketone and some products of decompositions were detected by TLC.
		DBU, DMF, heating.	Desired product was not observed.
		$TMSCl$, NEt_3, DBU, heating.	–″–
 **43**	 **44**	NaOAc, DMF, heating 110 °C, 9 h.	Products are difficult to separate. The main supposed by-product is shown below:  **45** [31]
		DBU, DMF, heating.	
 **46**	 **47**	MeOH, 60 °C, 1 h.	No desired product was isolated. Product decomposes on TLC. Only a mixture of by-products was isolated.
		MeOH, r.t., 3 h.	No reaction was observed.
 **48**	 **49**	MeONa, DBU, DMF, heating under argon.	No reaction was observed.
 **50**	 **51**	DMF, NEt_3, heating.	Unclear TLC. High polarity of the expected product and consequently high binding affinity to silica gel.

Starting material	Product	Reaction condition	Comments
 **52**	 **53**	K_2CO_3, DMF. TMSCl, NEt_3, DMF. TMSCl, NEt_3, DMF, pressure tube, 120 °C	4-Chloro-3-(trifluoro-acetyl)coumarin is unstable in basic media. The product also seems to be unstable because of electron withdrawing groups in the pyrimidine ring.
 **54**	 **55**	NaOMe, DBU, DMF, r.t., 1 d. DBU, DMF, r.t., 1 d. K_2CO_3, DMF, 80 °C, 4 h.	The reaction was observed on TLC but the product decomposes on silica gel. Purification is impossible.[56]
 **56a**	 **57a**	K_2CO_3, molecular sieves 4Å, DMF, 110 °C, 6 h.	The aldehyde probably reacts, but cyclization does not occur at this temperature. Low reactivity of *o*-fluorine and decomposition of the sugar moiety at high temperature.
 **56b**	 **57b**	K_2CO_3, KF, molecular sieves 4Å, DMF, 90 °C, 3 h.	_″_
 **18l**	 **19l**	NaOAc, molecular sieves 4Å, DMF, 0 °C, 2 h.	*α,β*-Unsaturated *β*-chloro-ketone decomposes before the reaction started.
		K_2CO_3, molecular sieves 4Å, DMF, 0 °C, 2 h.	The product decomposes on silica gel because of electron withdrawing groups in the pyrimidine ring.

Starting material	Product	Reaction condition	Comments
 **58**	 **59**	K_2CO_3, molecular sieves 4Å, DMF, 60 °C, 2 h.	Unclear TLC. High polarity of the expected product and consequently high binding affinity to silica gel.
 **30c**	 **31c**	K_2CO_3, molecular sieves 4Å, DMF, 60 °C, 5 h, under argon.	The problem lies in the starting material. Despite the ^{1}H NMR spectrum seems to correspond to the desired *α*,*β*-unsaturated *β*,*β*-dimethoxyketone, the substance has an extremely low boiling point and cannot be the right product.
 **60**	 **61**	K_2CO_3, molecular sieves 4Å, DMF, 60 °C, 4 h, under argon.	The *β*-ketoester decomposes in basic media. 1-(*β*-D-Ribofuranosyl)formamidine trifluoroacetate was isolated.
 **37b**	 **38b**	—	The problem lies in the starting material. Reaction of 3-bromo-2-trifluoromethyl-chromen-4-one with phenylacetylene is not clean. A lot of side products are formed.

Starting material	Product	Reaction condition	Comments
 **18m**	 **19m**	—	The problem lies in the starting material. It cannot be synthesized at r.t. because it reacts with itself. See reaction below:
 **18m**			



As we have already mentioned in the report, cyclization of amidine **1** with 3-(2,2,2-trifluoro-1,1-dihydroxy-ethyl)chromen-4-one failed. We suppose that four side-products (it follows from ^{19}F NMR spectrum) are a mixture of tricyclic stereoisomers **45** (Table 2).[31]

1.7 Conclusions

A wide range of pyrimidine *C*-nucleosides have been synthesized starting from 1,2,3,5-tetra-*O*-acetyl-*β*-D-ribofuranose. Among them are many fluoro-containing compounds. We developed useful methods for 3+3 cyclocondensations between 1-(*β*-D-ribofuranosyl)formamidine and a variety of 1,3-bielectrophiles as well as for further transformations, such as reduction of the nitro group, aminolysis and hydrazinolysis of the ester group. However, since the last stages involve unprotected carbohydrate derivatives, harsh reaction conditions should be avoided. Thus, 1,3-diketones were replaced by more reactive *β*,*β*-dimetoxy-*α*,*β*-unsaturated ketones. While potassium carbonate was found to be an appropriate base (except reaction with 3-nitrochromones), DMF is the most suitable solvent for the 3+3 cyclocondensation. The applicable reaction temperature lies in the range 0 to 70 °C depending on the 1,3-bielectrophile.

Examples **16a**, **19a**,**b**, **23a** and **24a** have been sent to be tested. The pharmacological evaluation is performed by Dr. M. Lalk (University of Greifswald).

2 Synthesis and Reactivity of Polyfluoroalkyl-5-deazaalloxazines

2.1 Introduction

2.1.1 Flavin, alloxazine and their derivatives. Structure of heterocyclic cores and definitions

Flavin **62a** (or benzo[*g*]pteridine-2,4(3*H*,10*H*)-dione) and alloxazine **62b** (or benzo[*g*]pteridine-2,4(1*H*,3*H*)-dione) are closely related structures and constitute two different tautomers with the same skeleton (Figure 4). The 5,10-dihydro derivative **63** can be considered both as reduced form of **62a** and **62b**. The same is also valid for the corresponding 5-deaza compounds **64a**, **b** and **65**. Substituents at position 1 and 10 are decisive to assign the compounds to flavins or alloxazines.

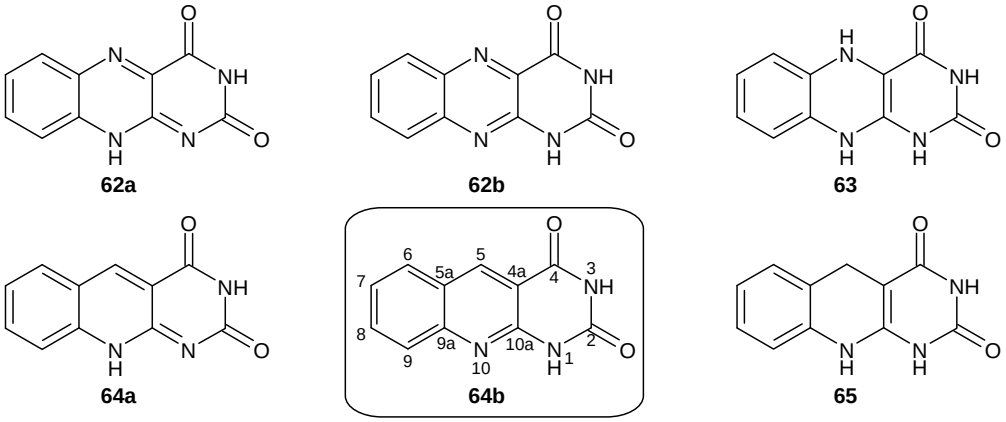


Figure 4. Flavin **62a**, alloxazine **62b** and dihydro form **63**. Below are shown their 5-deaza derivatives **64a**, **b** and **65**.

According to IUPAC nomenclature, the parent 5-deazaalloxazin structure **64b** is referred to as pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione.

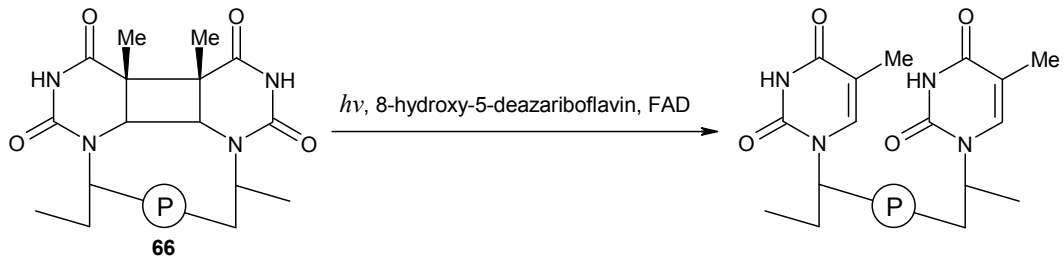
2.1.2 Natural flavins and 5-deazaflavins: biological role and pharmacological relevance

Flavins are versatile and, in many aspects, essential redox-active natural compounds, which play important roles as enzyme cofactors in numerous biochemical processes.[57] Thus, riboflavin **67**, also known as vitamin B_2, plays a key role in energy metabolism (Figure 5). Reduced flavin mononucleotide is a source of 5,6-dimethylbenzimidazole, the lower ligand of vitamin B12.[58]

8-Hydroxy-5-deazariboflavin plays an impotent role in the repair of cyclobutane DNA lesions **66** caused by 200-400 nm light irradiation (Scheme 15).[59] These intrastrand *cis*,*syn*-thymidine dimmers, the predominant UV-induced DNA damage, are cancerogenic, mutagenic and lethal for cells in a variety of organisms.[60] 8-Hydroxy-5-deazariboflavin takes part in the absorption of light, which is one of the critical steps in the light-driven repair reaction.[59] Afterwards, energy is transferred from the excited molecule to flavin adenine dinucleotide ($FADH^-$). The following

cyclobutane DNA lesion cleavage is based on the radical mechanism promoted by electron transfer from excited $FADH^-$. Unstable Pyr<>$Pyr^{\bullet-}$ species undergo spontaneous splitting followed by a back electron transfer to the $FADH^{\bullet}$.[60] Moreover, as was shown by experiments *in vitro*, photoexcited 8-hydroxy-5-deazariboflavin is able to repair the cyclobutane lesions directly.[61, 62]

As we see, stability of flavin/5-deazariboflavin radicals is of crucial importance to the photosensitized cleavage of thymine dimer. In this context, it should be noted that perfluoroalkyl groups cannot be classified as radical stabilizing or destabilizing in an absolute sense. Instead, R_F groups enhance the radical stabilizing ability of electron donor groups conjugated with a radical center (so called captodative effect), and decreases the radical stabilizing ability of electron withdrawing groups.[63]

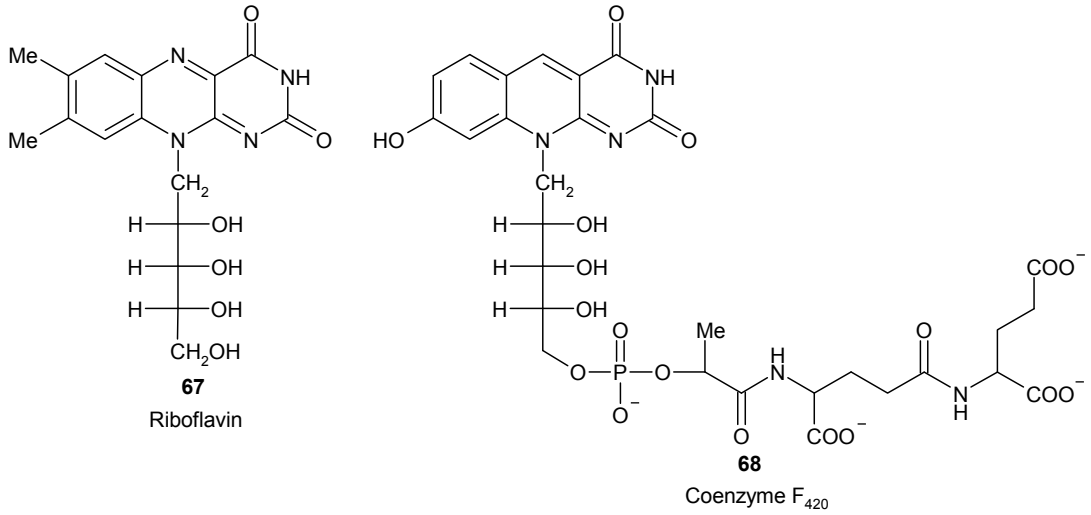


66

Scheme 15. Splitting cyclobutane DNA lesion with the participation of flavin adenine dinucleotide and light-harvesting 8-hydroxy-5-deazariboflavin.

The 5-deazaflavin moiety is a part of a unique coenzyme known as Factor 420 (F420) **68** from anaerobic thermophilic methanogenic bacteria (Figure 5), Methanobacterium (strain M.o.H.).[64]

Later deazaflavins were also found in streptomycetes[65] and in halobacteria.[66, 67]



67
Riboflavin

68
Coenzyme F_{420}

Figure 5. Natural compounds containing flavin (**67**) and deazaflavin moiety (**68**).

$$CO_2 + 4H_2 \rightarrow CH_4 + 2H_2O$$

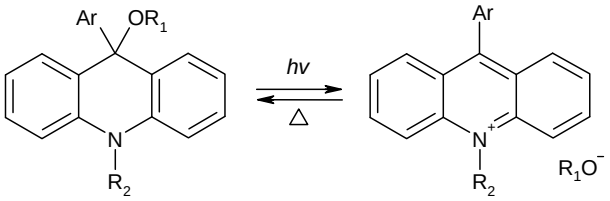
Scheme 16. Bacterial methanogenesis.

2.1.3 Pharmacological relevance and other applications

5-Deazaflavins are of considerable pharmacological relevance and attract significant attention of scientists. Thus, the synthesis of cytochrome P450 3A4 inhibitor containing 5-deazaflavin residue as well as the synthesis and photophysical properties of a deazaflavin-bridged porphyrinatoiron(III), which mimics the interaction of the above mentioned deazaflavin inhibitor with the Heme-Thiolate Cofactor of Cytochrome P450 3A4, has been reported.[68] RNA molecules that specifically bind riboflavin have been isolated.[69] In addition, 5-deazaflavins attract attention as perspective antitumor agents.[70, 71] Thus, one can expect some interesting biological activities in the range of desired bioisosteric compounds within the current project.

To our surprise, 5-deazaalloxazines have not received much attention despite the close similarity to above discussed 5-deazaflavins. Of particular interest is the development of fluorescent nucleosides based on 5-deazaalloxazine that maintain the hydrogen-bonding properties of natural nucleoside bases.[72]

As mentioned in chapters 2.3 and 2.7, we dealt with 5-disubstituted 5,10-dihydro-5-deazaalloxazines, which can be considered as a product of addition of a nucleophile to position 5 of the corresponding 5-deazaalloxazine or 10-substituted 5-deazaalloxazin-10-ium cation. In this sense these compounds are very similar to 9-alkoxyacridanes **69**. The last ones have been depicted by W. Abraham and coworkers as the main part of photoswitchable rotaxanes and calixarene-based photoswitchable ionophores.[73-77] The effect is based on reversible photo-driven dissociation of the 9-methoxy group (Scheme 17).



69a **69b**

Scheme 17. Photoheterolysis of 9-alkoxyacridane and the corresponding thermal back reaction.[73-77]

2.1.4 Task setting and motivation

Our interest to 5-polyfluoroalkyl-5-deazaalloxazines can be summed up in the following bullet points:

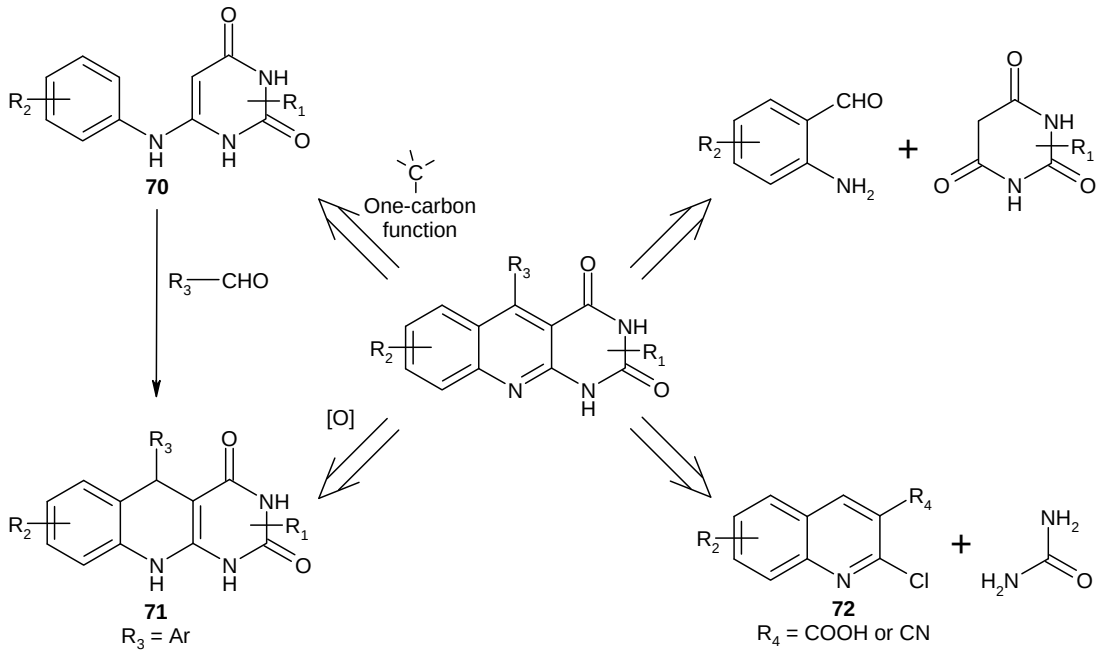
- Close similarity to biologically relevant natural compounds;
- Target structures contain fluorine with all the resulting consequences;
- Redox properties;

- Fluorescent properties.

The combination of these attributes presents intriguing possibilities for biological and pharmacological properties. Moreover, during the current study there were found other remarkable properties of 5-deazaalloxazines, such as distorted structures, due to intramolecular interaction, molecular shape and tendency to add various nucleophiles to position 5. At the same time, fluoro-containing 5-deazaalloxazines have not received much attention despite their potential interest as highly reactive substrates in organic synthesis and biologically active compounds with useful physicochemical applications. Therefore, we have undertaken the current study in order to develop a convenient synthetic approach to 5-polyfluoroalkyl-5-deazaalloxazines and at least partially investigate their striking chemical properties.

2.2 Syntheses of 5-polyfluoroalkyl-5-deazaalloxazines

2.2.1 Existing methods



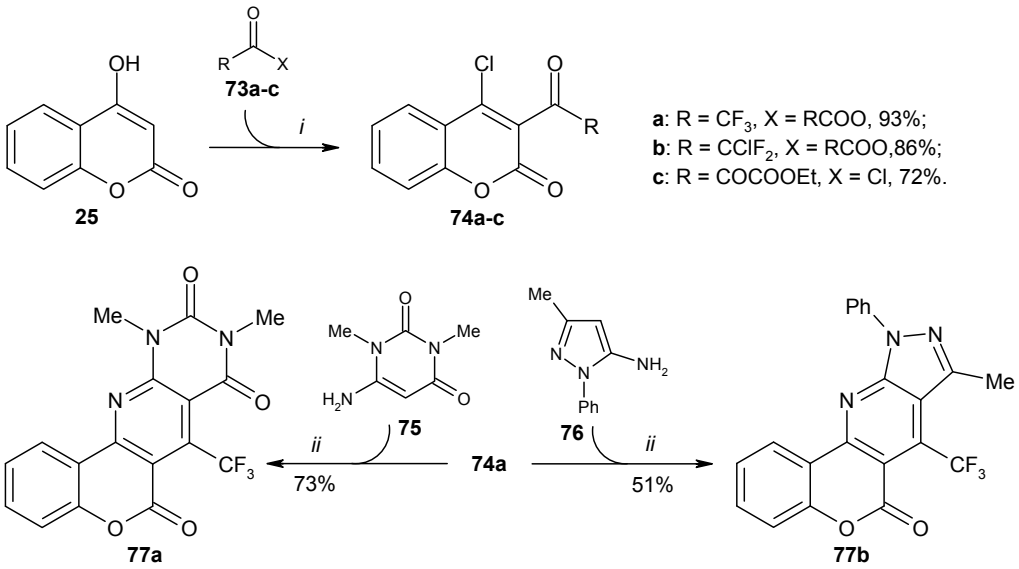
Scheme 18. Existing synthetic approaches to 5-deazaalloxazines overview.[78-84]

5-Deazaalloxazines have previously been synthesized by cyclization of 6-(arylamino)uracils with one-carbon reagents (triethyl orthoformate, dimethylformamide dimethylacetal,[78] carbon disulfide,[79] *N*,*N*-dimethyldichloromethyleniminium chloride[80] and the Vilsmeier reagent[81]). Similarly, treatment of 6-arylamino-1,3-dimethyluracils **70** with aromatic aldehydes provided 5-aryl-1,3-imethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-diones **71**, followed by dehydrogenation with thionyl chloride to give 5-aryl-1,3-dimethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones.[78] 5-Deazaalloxazines can be obtained via cyclocondensation of urea with 2-chloroquinoline-3-carboxamide[82] or 2-chloroquinoline-3-carbonitrile **72**.[83] Friedländer reaction

between *o*-aminobenzaldehydes and barbituric acid has been successfully applied as well[84] (Scheme 18).

2.2.2 Prehistory and first trials

Before the work on 5-polyfluoroalkyl-5-deazaalloxazines was started, we had synthesized structurally similar compounds **77a** and **b** (Scheme 19). Thus, each of them constitutes a doubly annelated pyridine bearing a trifluoromethyl group at the 4-position.



Scheme 19. One-pot synthesis of 3-acyl-4-chlorocoumarines **74a-c** and subsequent cyclocondensation with aminoheterocycles.

Reagents and conditions: *i*: 1) TMSCl, pyridine, dioxane, r.t., 1 h;[85] 2) corresponding anhydride or chloroanhydride was added, 90 °C, 2 h (**a**, **b**) or ½ h (**c**); 3) $POCl_3$, 60 °C, 2 h; *ii*: DMF, TMSCl, 80 °C, 4 h.

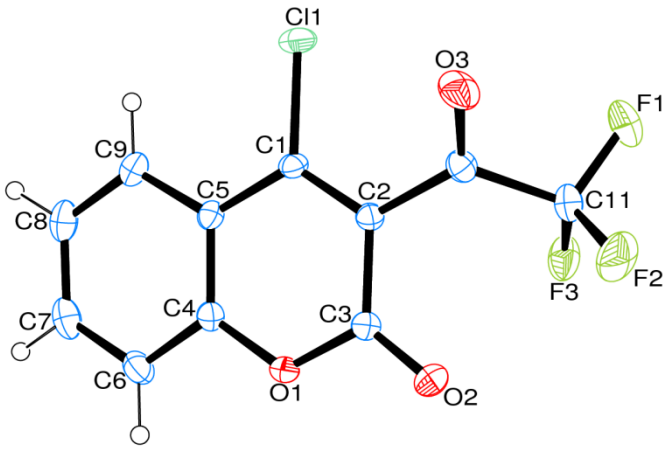
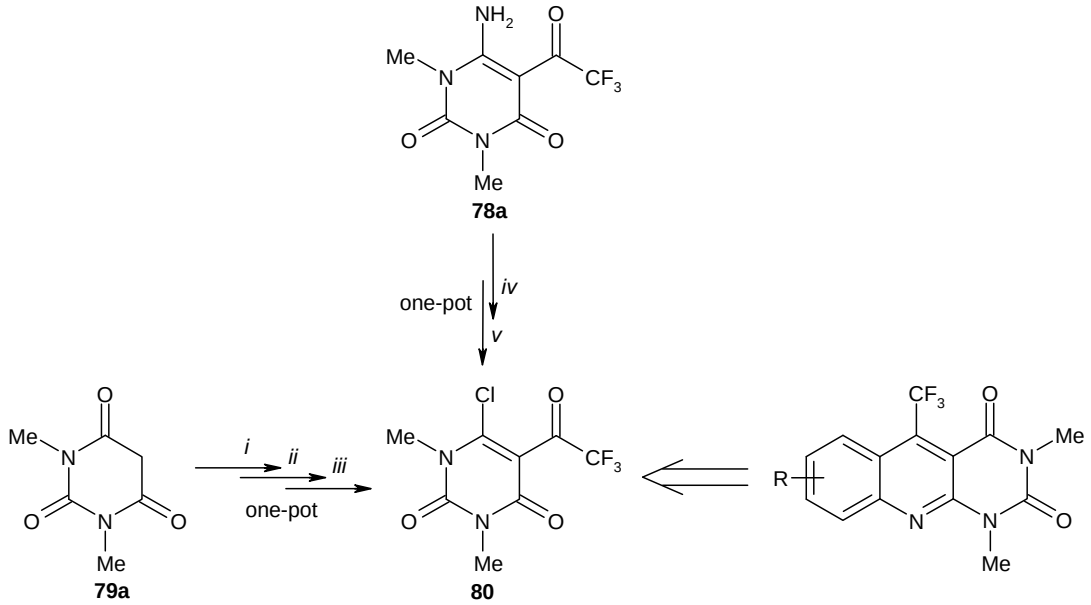


Figure 6. Ortep plot of 3-trifluoroacetyl-4-chlorocoumarine **74a** (35% probability level).

This approach seemed to be most convenient for the synthesis of 5-deazaalloxazines.

Initially we tried to synthesize 6-chloro-1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione **80** from 1,3-dimethylbarbituric acid **79a** in the same manner as 4-chloro-3-

(trifluoroacetyl)-2*H*-chromen-2-one from 4-hydroxycoumarin.[86] After these attempts have been failed, we tried to convert an amino group of 6-amino-1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione **78** into chlorine through diazotation (Scheme 20).

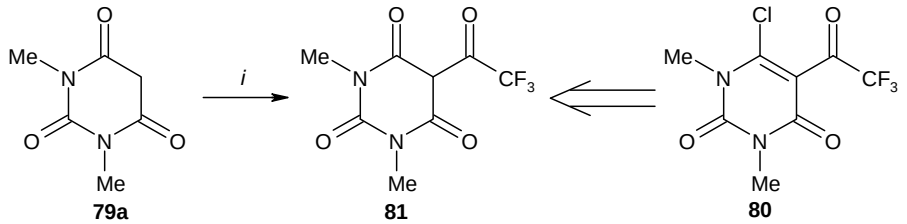


Scheme 20. Unsuccessful attempts to synthesize 6-chloro-1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione, which was expected to be a convenient precursor of 5-trifluoromethyl-5-deazaalloxazines.

Reagents and conditions: *i*: pyridine, dioxane, TMSCl, r.t., 2 h; *ii*: TFAA, 90 °C; *iii*: $POCl_3$, 60 °C; *iv*: HCl, $NaNO_2$, water, 0 °C; *v*: CuCl, $CuCl_2$, 60 °C.

In both cases only the starting materials were isolated after the reactions; no diazotation was observed under employed reaction conditions.

Even attempts to synthesize 1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **81** experienced failure, despite the simple acetic anhydride reacted with 1,3-dimethylbarbituric acid smoothly and in 95% yield (Scheme 21).



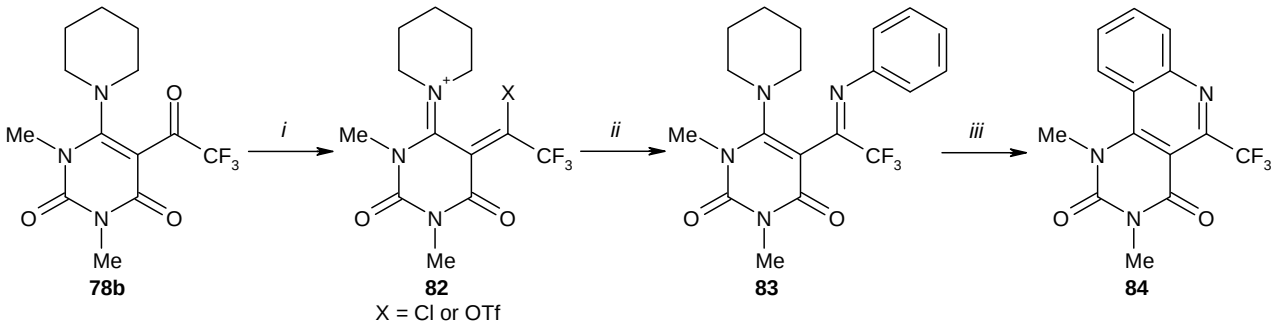
Scheme 21. Unsuccessful attempts to synthesize 1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione which represents the possible precursor to 6-chloro-1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione.

Reagents and conditions: *i*: DMAP, dioxane, TFAA, reflux, 2 h.

In this case also only the starting material was isolated.

2.2.3 Attempts to synthesize pyrimido[5,4-*c*]quinoline-2,4(1*H*,3*H*)-diones, the structural isomers of 5-deazaalloxaziness. Negative results.

The pyrimido[5,4-*c*]quinoline-2,4(1*H*,3*H*)-dione core (**84**) is structurally isomeric to the 5-deazaalloxazine core. It can be easily constructed from 4-aminoquinoline-3-carboxylic acid amide or ester.[87] Nevertheless, convenient synthetic methods for 5-polyfluorsubstituted derivatives have not been developed so far. Taking on this task, we attached special importance to the combinatorial aspect. According to our plan, 1,3-dimethyl-6-piperidin-1-yl-5-(trifluoroacetyl)uracil **78b** is activated by phosphorus pentachloride or triflic anhydride, followed by cyclocondensation with aniline (Scheme 22). In fact, we considered compound **82** as a building block similar to **80**, but with inversed order of reacting centers.



Scheme 22. Unsuccessful attempts to synthesize 1,3-dimethyl-5-(trifluoromethyl)pyrimido[5,4-*c*]quinoline-2,4(1*H*,3*H*)-dione.

Reagents and conditions: *i*: PCl_5 in $CHCl_3$ or Tf_2O in DCM, r.t., 1 d; *ii*: aniline, r.t., 1 d; *iii*: H_2SO_4, r.t., 1 d.

To our great disappointment, this chosen strategy has not been successful in our hands. All the stages were carried out in one-pot protocols and always resulted to unidentifiable mixture.

2.2.4 Three-step synthesis of 5-polyfluoroalkyl-5-deazaalloxazines from 6-chlorouracils, anilines and polyfluoroacyl chlorides/anhydrides

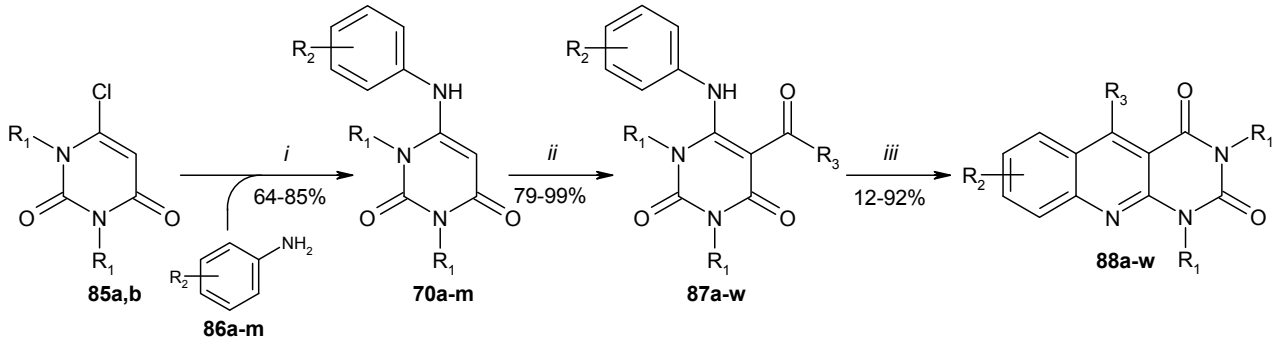
5-Polyfluoroalkyl-5-deazaalloxazines were synthesized from 6-chloro-1,3-dialkylyluracils in three steps using a 2+3+1 strategy (Scheme 23).

6-Chloro-1,3-dipropyluracil, the starting material for 1,3-dipropyl-5-deazaalloxazines, was prepared from *N*,*N*'-dipropyl urea and malonic acid in 2 steps and 54% overall yield.[88, 89] *N*,*N*'-Dimetyl- and *N*,*N*'-dipropylbarbituric acids were converted into **85a** and **85b**, respectively, using the method with water and phosphorus oxychloride developed by W. Pfleiderer and K.-H. Schündehütte.[89]

On the first stage, the chlorine atom is substituted by the aniline. Three different procedures have been used depending on the initial amine reactivity. Coupling of 6-chloro-1,3-dialkylyluracils

with anilines was carried out mostly at 180 °C under argon,[78] where the excess of anilines plays a role as a base. When dibasic anilines were used, contrariwise, a 20% excess of **85a** was employed in combination with 1 equivalent of quinoline (calculated on chlorouracil **85a)**. Only in case of inactive anilines, such as 5-amino-3-methyl-1-phenylpyrazole or α-naphthylamine, application of *n*-butyllithium as a base was necessary.

Then the 5-position of obtained 6-aminouracil is acylated by perfluorinated carboxylic acid anhydride or chloroanhydride, and afterwards 5-deazaalloxazines **88** form by cyclization under acidic conditions.



Scheme 23. Syntheses of 5-polyfluoroalkyl-pyrimido[4,5-b]quinoline-2,4-diones.

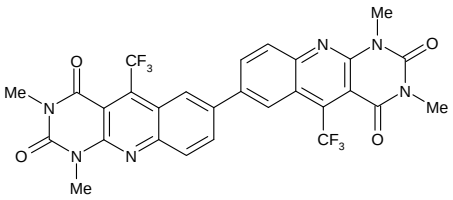
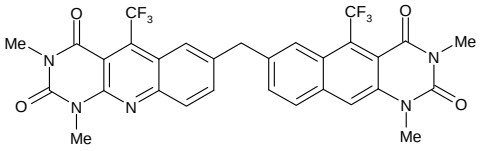
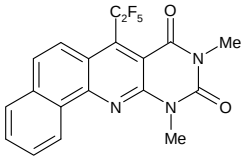
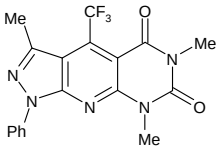
Reagents and conditions: *i*: aniline (2.2 eq), 180 °C, 3 h, under argon (Method A),[78] or aniline (0.8 eq), quinoline, 180 °C, 3 h, under argon (Method B), or aniline (2.2 eq), *n*-BuLi, THF, –78 to °C, under argon (Method C);[90] *ii*: anhydride of polyfluorinated carbonic acid (or cloroanhydride), pyridine, dioxane, r.t., overnight;[91] *iii*: H_2SO_4, (conc.), r.t., 3 h.

Taking into account that compounds are slowly hydrolyzed, their contact with water during the isolation should be minimized and carried out at ~0 °C, but firstly the solvent should be evaporated and the residue needs to be dried in high vacuum on a boiling water bath.

5-Polyfluoroalkyl-5-deazaalloxazines **88** are yellow colored compounds mostly good soluble in chloroform and less soluble in DMSO and methanol. They are also soluble in sulphuric and trifluoroacetic acid. Addition of TFA increases their solubility in chloroform.

Table 3. Two-step synthesis of 1,3-dimethyl-5-poly-fluoroalkyl-pyrimido[4,5-b]quinoline-2,4-diones **88**.

Entry	R_1	R_2	R_3	Yield, %[a]	
				87	**88**
a	CH_3	H	CF_3	93	89
b	CH_3	H	*n*-C_3F_7	96	73
c	CH_3	7,9-diMe	CF_3	90	84
d	CH_3	7,9-diMe	C_2F_5	88	84
e	CH_3	7,9-diMe	*n*-C_3F_7	87	92
f	CH_3	7-Et	CF_3	88	50

Entry	R_1	R_2	R_3	Yield, %[a]	
				87	**88**
g	CH_3	7-Et	$CClF_2$	97	57
h	CH_3	7-Et	C_2F_5	94	81
i	CH_3	9-MeO	CF_3	90	49
j	CH_3	9-MeO	$CClF_2$	92	67
k	CH_3	8-MeO	CF_3		12[b]
l	CH_3	8-MeO	$CClF_2$		40[b]
m	CH_3	8-MeO	*n*-C_3F_7	94	32
n	CH_3	8-CF_3	CF_3	99	51
o	CH_3	7-NO_2	CF_3	79	82
p	CH_3	7-Br	CF_3	94	84
q	CH_3	7-EtO	CF_3	82	73
r	CH_3	7-EtO	CHF_2	99	80
s	*n*-Pr	7-MeO	CHF_2		86[b]
t	*n*-Pr	7-MeO	C_2F_5	86	81
u				93	46
v				98	51
w				86	54
x					75[c]

[a] – yields refer to pure isolated products; [b] – yield after 2 stages (the product of acylation was introduced into the reaction without purification); [c] – after acylation the already cyclized product was isolated.

As the target molecules bear a polyfluoroalkyl group at position 5, the C-F coupling of C-5, C-6 and the polyfluoroalkyl residue itself was observed by ^{13}C NMR spectra. In case when R_F = C_2F_5 or *n*-C_3F_7, the polyfluoroalkyl group appears as undecipherable multiplets merging with noise. In addition, the presence of fluorinated alkyl groups was confirmed by ^{19}F NMR. Example **88f** was

additionally measured by 2D COSY, HSQC and HMBC. These data were used to assign H and C signals of **88f** as well as other examples by similarity of their chemical shift.

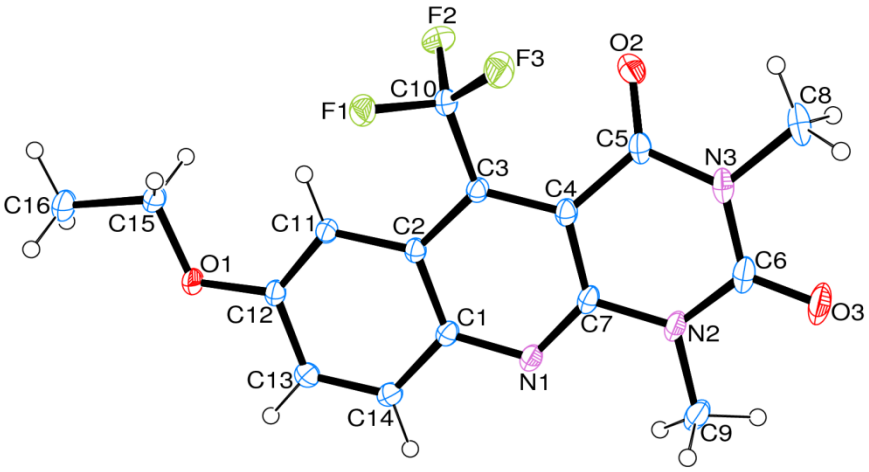


Figure 7. Ortep plot of 7-ethoxy-1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione **88n** (35% probability level).

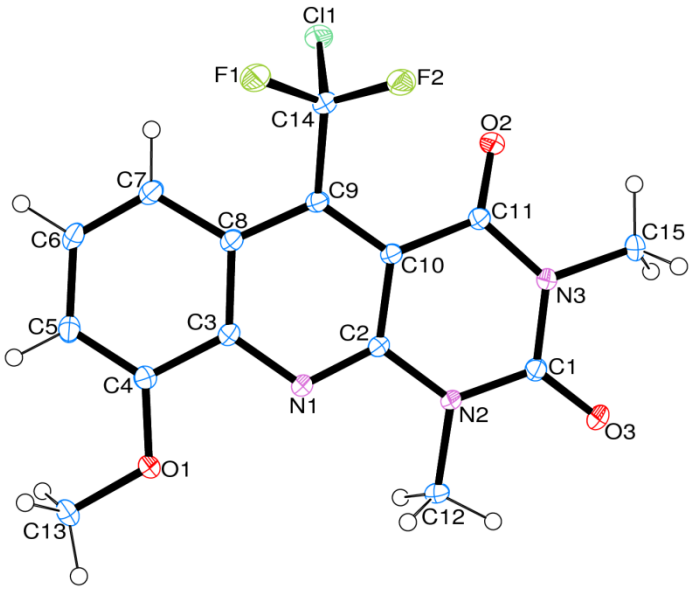


Figure 8. Ortep plot of 5-[chloro(difluoro)methyl]-9-methoxy-1,3-dimethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione **88j** (35% probability level).

As seen from Figures 7, 8, 9 and 12, the pyrido-pyrimidine part of the molecules is slightly twisted (Table 4, entry 2 and 3). Despite the aromaticity, they are not planar due to repulsion between the polyfluoroalkyl group and the neighboring oxygen (Entry 1). The distance between the oxygen and the nearest fluorine atom lies in the range between 2.50 and 2.48 Å (Entry 5), which is significantly less than the sum of van der Waals radii according to Bondi (the expected value should be 2.99 Å).[92] Moreover, short intramolecular contacts were observed between the nearest F and H atoms (Entry 9). Thus, the rotation angle of the polyfluoroalkyl group (Entry 4) is dictated mainly by Van der Waals repulsion from the neighboring H and O atoms.

We also believe that the reason for the repulsion is not only due to close intramolecular

contacts, but also due to a strong electrostatic dipole-dipole interaction between CO and C-CF_3. Thus, the longest O···F distance (Entry 5) is observed in case of the less bulky (as compared with *n*-C_3F_7 and $CClF_2$), but more electronegative CF_3-group in examples **88n** and **92a**.

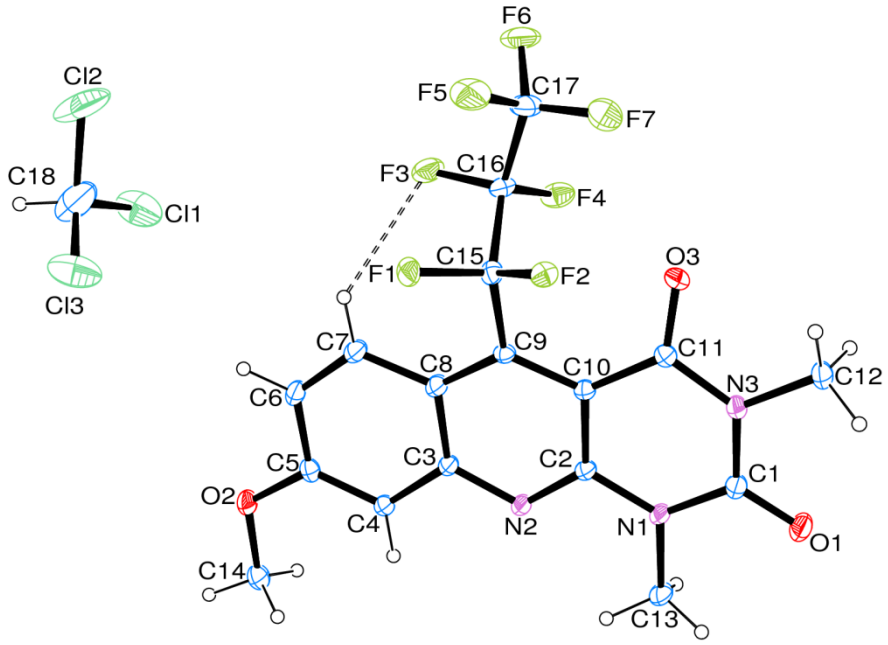


Figure 9. Ortep plot of 5-(heptafluoropropyl)-8-methoxy-1,3-dimethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione **88m** (25% probability level). Crystal solvate with 1 eq of chloroform.

As we see in Figure 9, a short intramolecular F3···H7 contact of 2.434 Å is also observed in structure **88m**, which is a little bit beyond the normal van der Waals contact distance (~2.65 Å[92]).

Table 4. Torsion angles φ and interatomic distances r (atom numeration according to Ortep plot).

	Entry	**88n**	**88j**	**88m**	**92a**
φ_{ABCD}, °	1	C10C3C5O2, −32.18	C14C9C11O2, −27.28	C15C9C11O3, −25.97	C12C3C1O1, 35.47
	2	C3N1N2C5, −6.99	C9N1N2C11, −5.94	C9N2N1C11, −4.57	C3N1N2C1, 11.62
	3	C10N1N2O2, −15.40	C14N1N2O2, −13.24	C15N2N1O3, −11.71	C12N1N2O1, 19.76
	4	C2C3C10F2, −89.07	C8C9C14Cl1, −87.89	C8C9C15C16, −85.22	C4C3C12F3, 84.10
r_{AB}, Å	5	F3O2, 2.548	F2O2, 2.510	F2O3, 2.500	F1O1, 2.548
	6	F2O2, 2.974	Cl1O2, 3.148	O3F4, 2.706	F3O1, 3.109
	7	C10O2, 2.902	C14O2, 2.878	C15O3, 2.887	C12O1, 2.965
	8	C3C5, 2.531	C9C11, 2.531	C9C11, 2.542	C3C1, 2.541
	9	F1H11, 2.204	F1H7, 2.246	F1H7, 2.253	F2H5, 2.208

In cases of meta-substituted anilines, the formation of two regioisomers is possible. Isolation of the pure isomer required thorough recrystallization; therefore, yields are lower than for other anilines (Table 2).

Table 5. The selectivity of the cyclization in the case of *meta*-substituted anilines.

	8/6-Substituted isomers ratio[a]			
R_1	MeO	MeO	MeO	CF_3
R_2	CF_3	*n*-C_3F_7	$CClF_2$	CF_3
	87 / 13	50 / 50	92 / 8	86 / 14

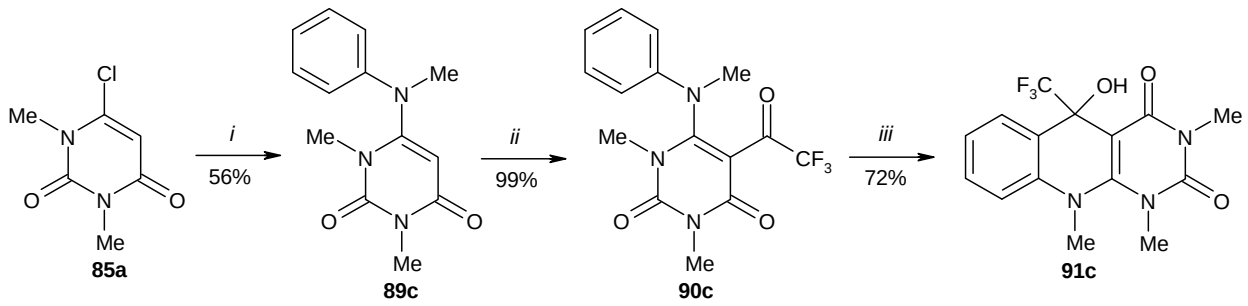
[a] – determined by ^{1}H NMR.

Electrophilic attack of the less sterically hindered position leads to predomination of the 8-substituted isomer. On the other hand, hydrophobic interaction can take place between the substituent attached to the aniline ring and the polyfluoroalkyl group. This balance between attraction and repulsion is supposed to be decisive for the observed regioisomeric ratio.

Isomers were assigned using ^{1}H NMR data. Thus, the spectra of 8-substituted isomers contain a doublet with coupling constant ^4J = 2.65-2.83 Hz or narrow multiple in case of **88o** (due to through space interaction between H-6 and CF_3 groups).

2.3 Syntheses of 5-hydroxy-5,10-dihydro-5-deazaalloxazines and their conversion into 5-deazaalloxazines

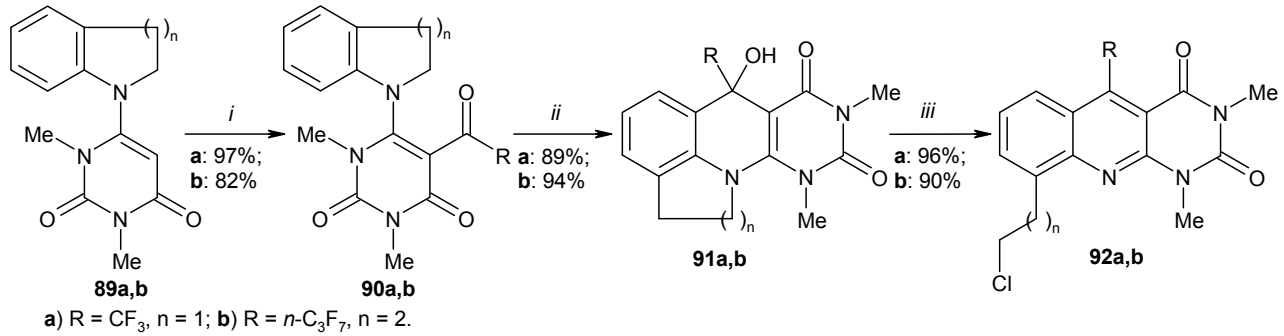
Next, we were interested, what the product will be in case of *N*,*N*-disubstituted 6-aminouracil. After acylation and cyclization in sulfuric acid, compounds **90**, which contain a tertiary amino group, give the corresponding 5-hydroxy-5,10-dihydro-5-deazaalloxazines **91** (Scheme 24, 25). As we estimated, under strong acidic conditions the compounds **90a-c** form 5-deazaalloxazine-10-ium cation **95**. The latter undergoes reaction with an hydroxyl anion immediately after dilution with water.



Scheme 24. Syntheses of 5-hydroxy-1,3,10-trimethyl-5-trifluoromethyl-5,10-dihydro-5-deazaalloxazine.

Reagents and conditions: *i*: *N*-methylaniline, 180 °C, 3 h;[78] *ii*: trifluoroacetic anhydride, pyridine, dioxane, r.t., overnight;[91] *ii*: H_2SO_4, (conc.), r.t..

Treatment of 5-hydroxy-5,10-dihydro-5-deazaalloxazines **91** with thionyl chloride resulted in cleavage of the C-N bond. In this way we obtained 5-deazaalloxazines **92** bearing a ω-chloroalkyl group at position 9. This result can be explained by the higher chloride anion nucleophilicity in contrast to hydrogensulfate. Other expected but not obtained products are represented in Figure 10.



Scheme 25. Syntheses of 5-hydroxy-5,10-dihydro-5-deazaalloxazines and their conversion into5-deazaalloxazines. *Reagents and conditions*: *i*: anhydride of polyfluorinated carbonic acid (or cloroanhydride), pyridine, r.t., overnight;[91] *ii*: H_2SO_4, (conc.), r.t., 3 h; *iii*: $SOCl_2$, $CHCl_3$, boiling under reflux, 3 h.

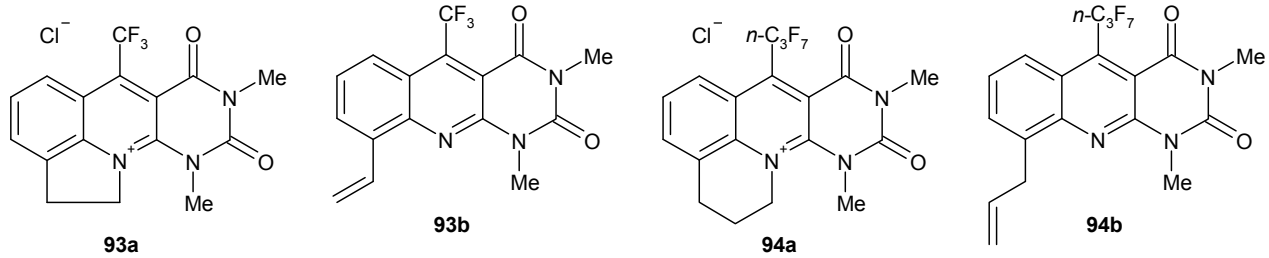


Figure 10. Alternative products (not obtained).

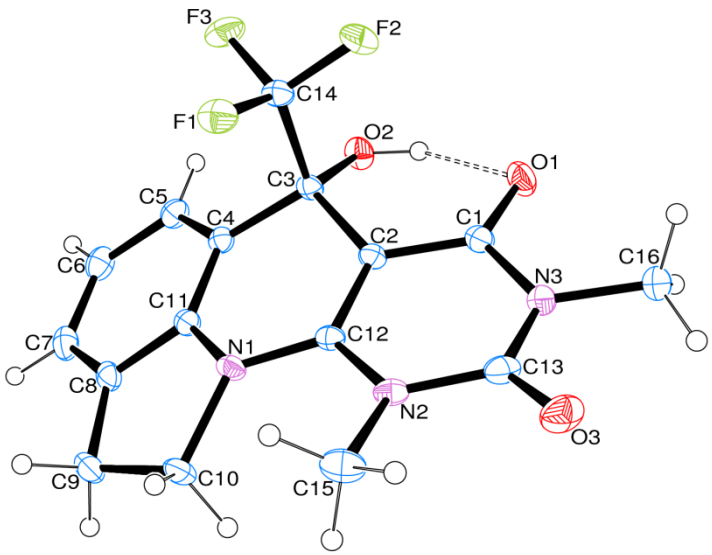


Figure 11. Ortep plot of 6-hydroxy-8,10-dimethyl-6-(trifluoromethyl)-1,2-dihydro-6*H*-pyrimido[4,5-*b*]pyrrolo[3,2,1-*ij*]quinoline-7,9(8*H*,10*H*)-dione **91a** (35% probability level).

Besides other methods, the structure of **91a** was confirmed by X-ray crystallographic

analysis. As we see in Figure 11, a strong intramolecular hydrogen bond of 1.765 Å length is present there.

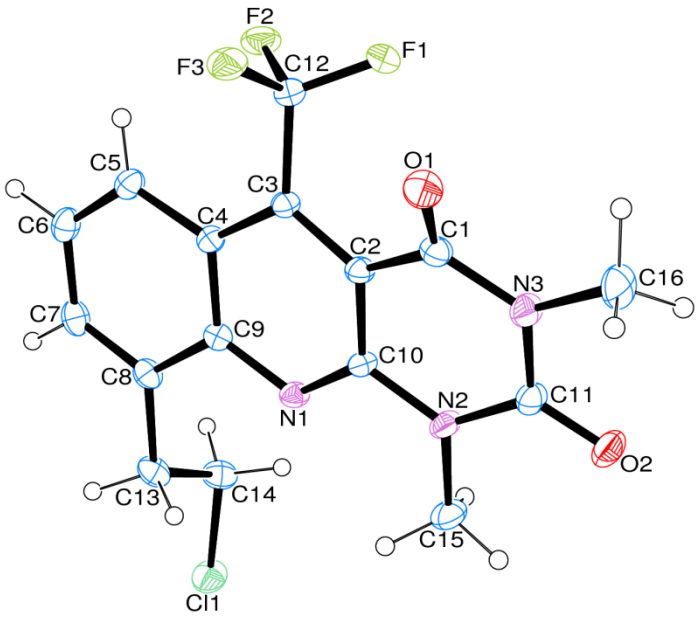
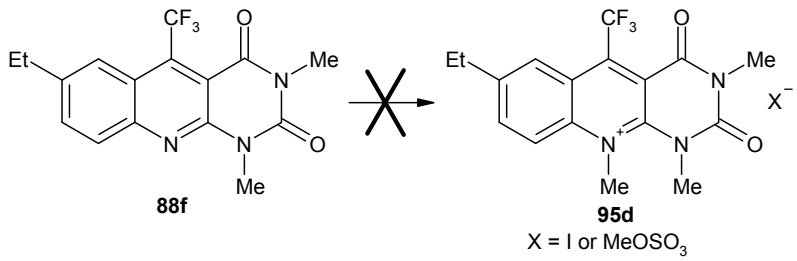


Figure 12. Ortep plot of 9-(2-Chloroethyl)-1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione **92a** (35% probability level).

The structure of **92a** was confirmed by X-ray analysis as well (see discussion in Chapter 2.2.4)

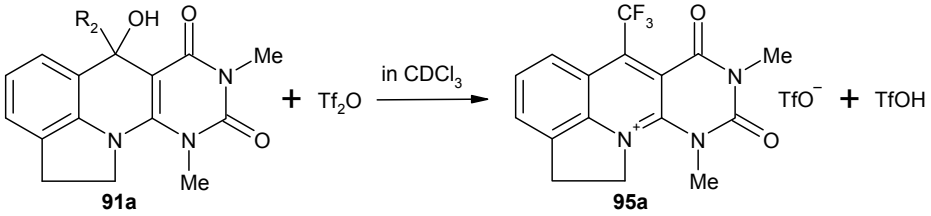
2.3.1 Mechanistic pathway consideration



Scheme 26. 7-Ethyl-1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione doesn't undergo alkylation.

Reagents and conditions: xylene, methyl iodide or dimethyl sulphate, heating up to 150 °C.

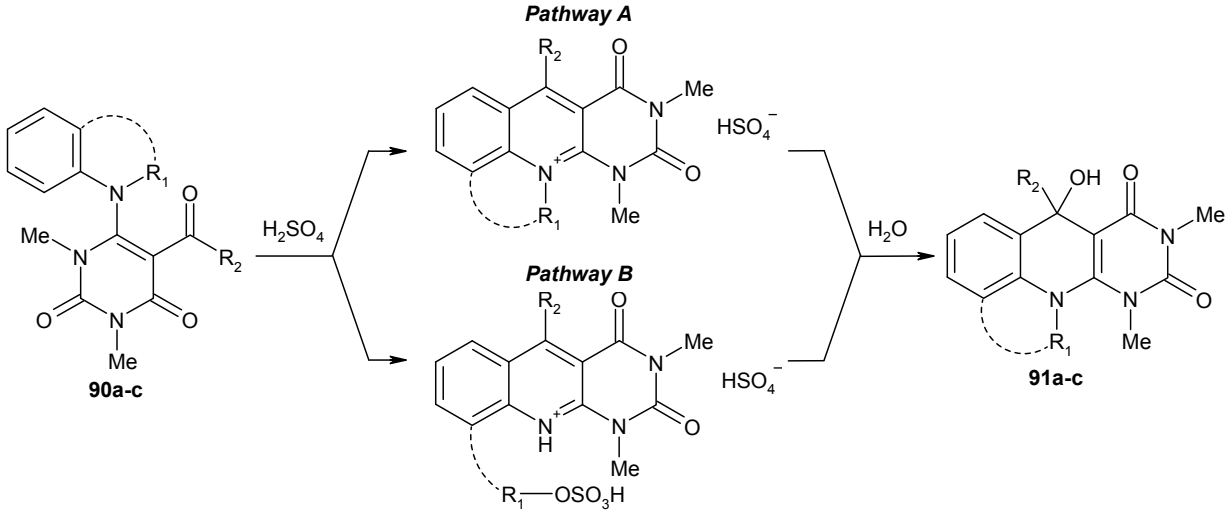
5-Deazaalloxazines do not undergo alkylation, but existence of 5-deazaalloxazines containing a quaternized nitrogen **95** was proved by ^{1}H and ^{13}C NMR. For this purpose, 6-hydroxy-8,10-dimethyl-6-(trifluoromethyl)-1,2-dihydro-6*H*-pyrimido[4,5-*b*]pyrrolo[3,2,1-*ij*]quinoline-7,9(8*H*,10*H*)-dione **91a** was dissolved in deuterochloroform, followed by addition of triflic anhydride (Scheme 27).



Scheme 27. Formation of 5-deazaalloxazine-10-ium cation **95a**.

The CH_2-protons appears as two triplets. It indicates equivalence of protons within each methylene group and consequently the molecular symmetry (the methylene groups lie in the mirror plane). In the opposite case, the pattern of the signals would be more complicated, namely four doublets of doublets of doublets. In addition, the MS(GC) and HRMS spectra of **92a** contain strong peaks corresponding to the above mentioned cation **95a**, namely $[M\text{-}Cl]^+$. The same is valid for 9-(3-chloropropyl)-5-(heptafluoropropyl)-1,3-dimethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione **92b**.

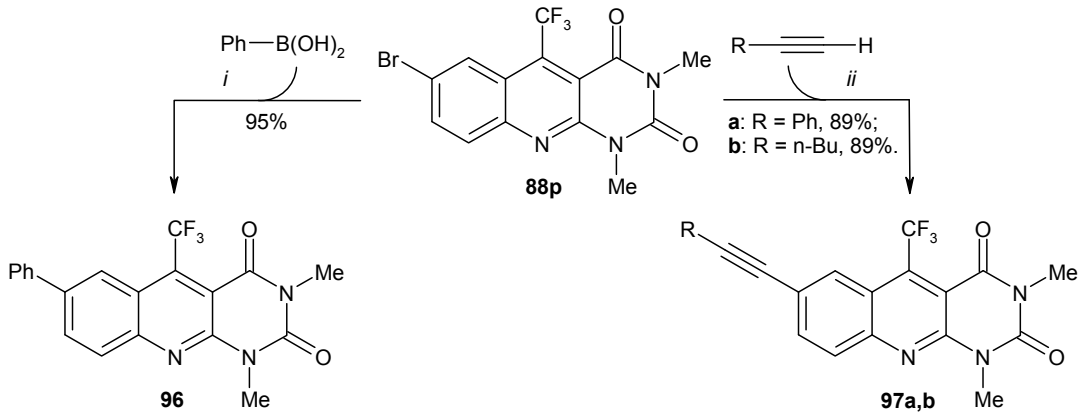
All this facts together with the successful synthesis of 5-hydroxy-1,3,10-trimethyl-5-(trifluoromethyl)-5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione **91c** suggest ***Pathway A*** to be right; no C-N bond cleavage takes place (Scheme 28).



Scheme 28. Mechanistic pathways.

2.4 Suzuki and Sonogashira coupling with 7-bromo-5-trifluoromethyl-5-deazaalloxazine

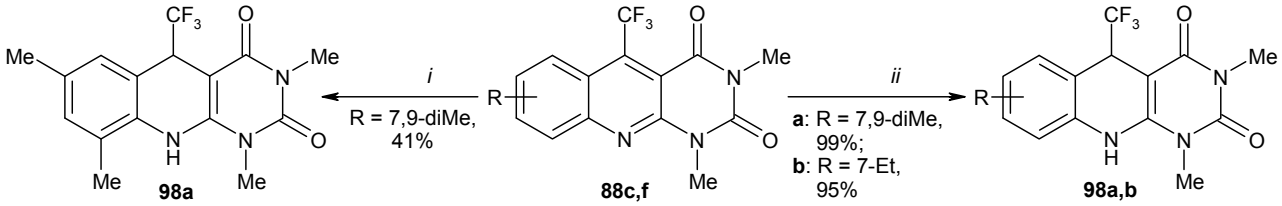
The 8-bromo derivative **88p** undergoes Suzuki and Sonogashira reaction in high yields. Thereby, the conjugated π-electron system is extended that exerts a significant influence on the photophysical properties.



Scheme 29. Suzuki and Sonogashira coupling with 7-bromo-5-trifluoromethyl-pyrimido[4,5-b]quinoline-2,4-dione.

Reagents and conditions: *i*: $Pd(PPh_3)_4$, K_2CO_3, dioxane, H_2O, 100 °C, ½ h, under argon;[93] *ii*: $Pd(PPh_3)_2Cl_2$, CuI, DIPA, THF, r.t., 48 h, under argon.[94]

2.5 Reduction of 5-deazaalloxazines



Scheme 30. Reduction of 5-deazaalloxazines.

Reagents and conditions: *i*: diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (6 eq), xylene, TsOH, 155 °C, 5 h, under argon; *ii*: $NaBH_3CN$, THF, AcOH, 4 days.[95]

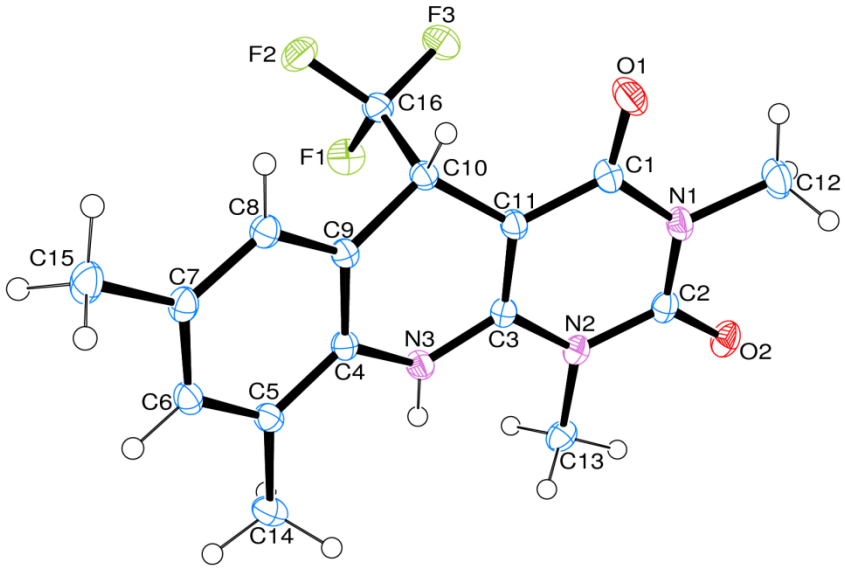


Figure 13. Ortep plot of 1,3,7,9-Tetramethyl-5-(trifluoromethyl)-5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione **98a** (40% probability level).

5-Deazaalloxazines are reduced by Hantzsch dihydropyridine or sodium cyanoborohydride

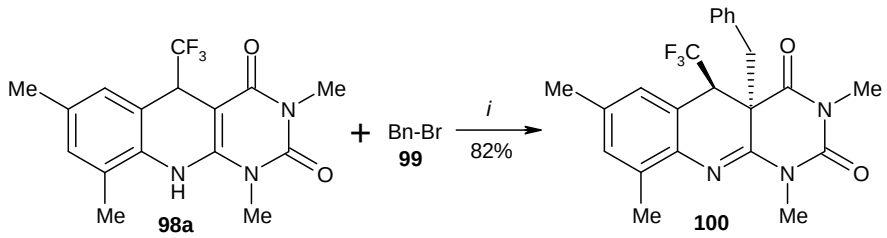
to the corresponding 5,10-dihydro-5-deazaalloxazines **98a** and **b**. The reduction of compounds **88c** and **f** with sodium cyanoborohydride[95] was carried out in excellent yield and under milder conditions as compared to the primarily used 1,4-dihydropyridinedicarboxylate.

Sodium cyanoborohydride is known as a selective and stable reducing agent which is used in slightly acidic media. Moreover, it is cheaper than diethyl 1,4-dihydropyridinedicarboxylate and easy to handle.

The structure of product **98a** was unambiguously confirmed by X-ray analysis.

2.6 Alkylation of 1,3,7,9-tetramethyl-5-(trifluoromethyl)-5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione

Theoretically two main positions for alkylation were expected: N-10 and C-4a. As we estimated, alkylation took place at the carbon atom. From the 2D NOESY spectrum of **100** it is clearly seen that benzylic methylene group is located in the neighbourhood of H-5 (corresponding cross-peak at 3.12 and 4.00 ppm). In fact, this is in agreement with a result obtained by H. Fenner and W. Bauch. The authors reported about alkylation at position 4a of 1,3-dimethyl-5,10-dihydro-5-deazaalloxazine, carried out with methyl iodide.[96]



Scheme 31. Benzylation of 5,10-dihydro-5-deazaalloxazine **98a**.

Reagents and conditions: *i*: K_2CO_3, DMF, r.t., overnight, under argon.

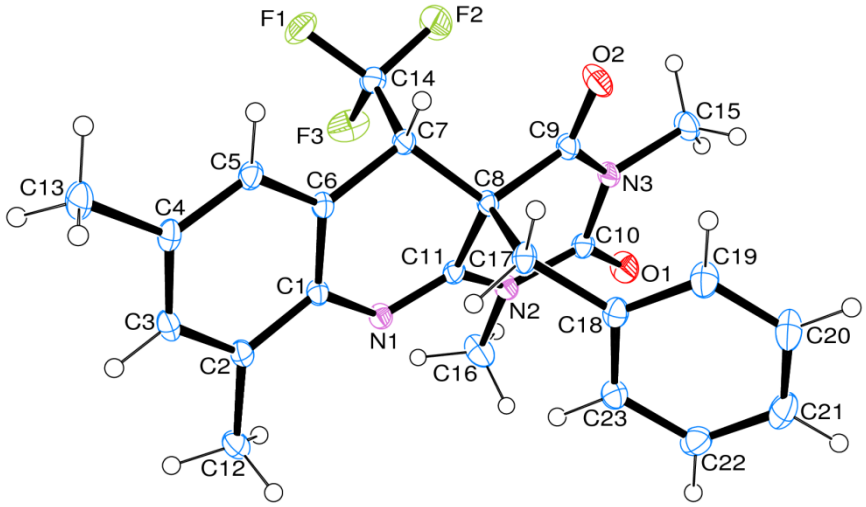
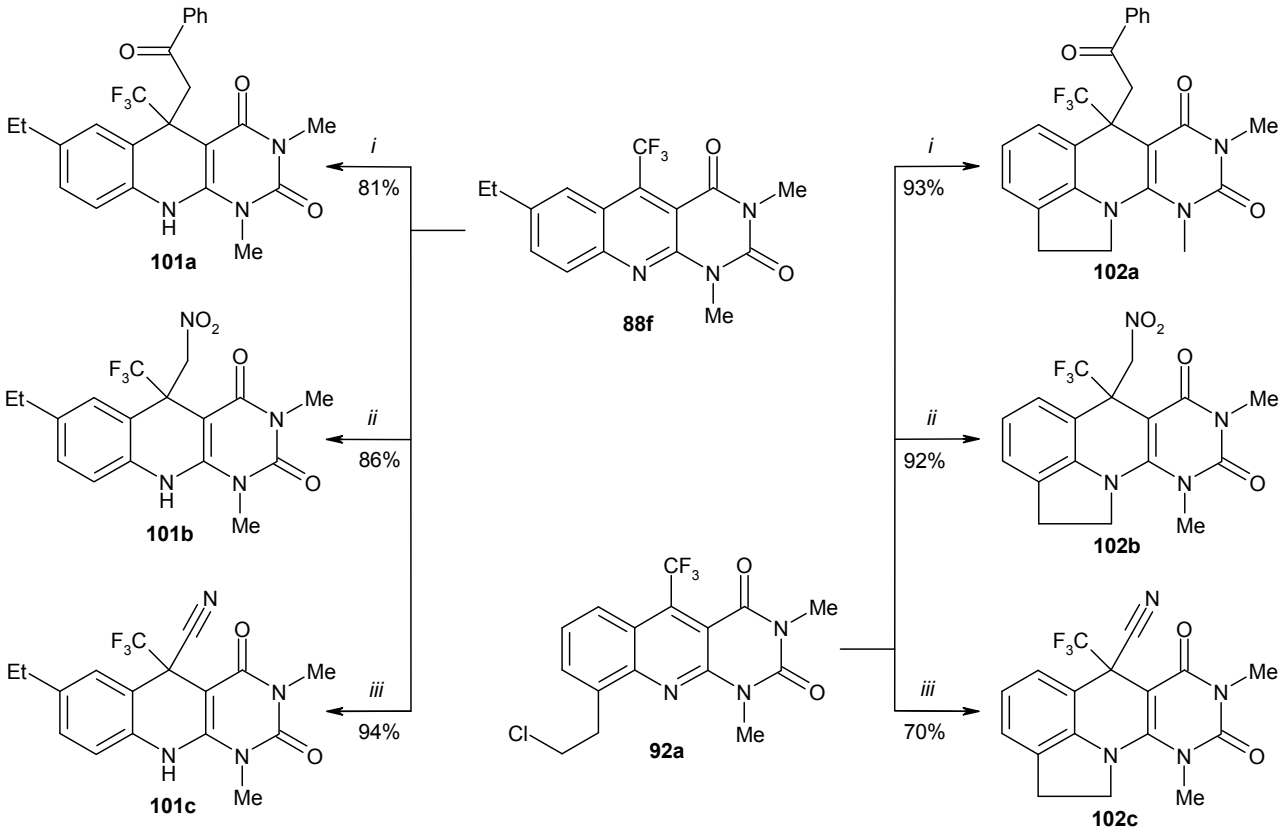


Figure 14. Ortep plot of 1,3,7,9-tetramethyl-5-(trifluoromethyl)-5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione **100** (35% probability level).

In our case, the reaction proceeded with high diastereoselectivity. Therefore, it raises the question concerning the relative configuration at C-4 and C-5. In order to accomplish the structure elucidation, a single crystal was grown. Thus, according to X-ray data (Figure 14), the obtained substance constitutes a diastereomeric mixture of 4a*R*,5*R*- and 4a*S*,5*S*-enantiomers. As expected, benzyl bromide attacks the substrate from the less sterically hindered side.

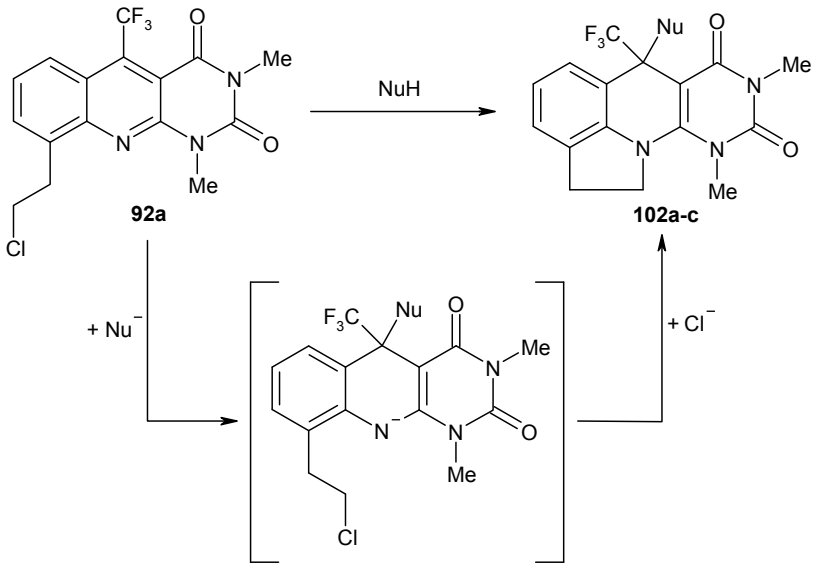
2.7 Reaction of 5-deazaalloxazines with C- and N-nucleophiles

Another remarkable feature of 5-polyfluoroalkyl-5-deazaalloxazines has been found during the study, namely the ability to react with some nucleophiles, such as acetophenone, nitromethane and hydrogen cyanide, under basic conditions in excellent yields (Scheme 32). A similar reaction has been previously reported for 10-substituted 5-deasaflavines, since H.-J. Duchstein, H. Fenner and W. Bauch published their results in the year 1989,[97, 98] but not for 5-deazaalloxazines.



Scheme 32. Interaction of 5-trifluoromethyl-5-deazaalloxazines with C-nucleophiles.
Reagents and conditions: *i*: acetophenone, NaH (60% in mineral oil), THF, r.t., overnight; *ii*: $MeNO_2$, NaOMe, THF, MeOH, r.t., overnight; *iii*: KCN, DMSO, r.t., overnight.

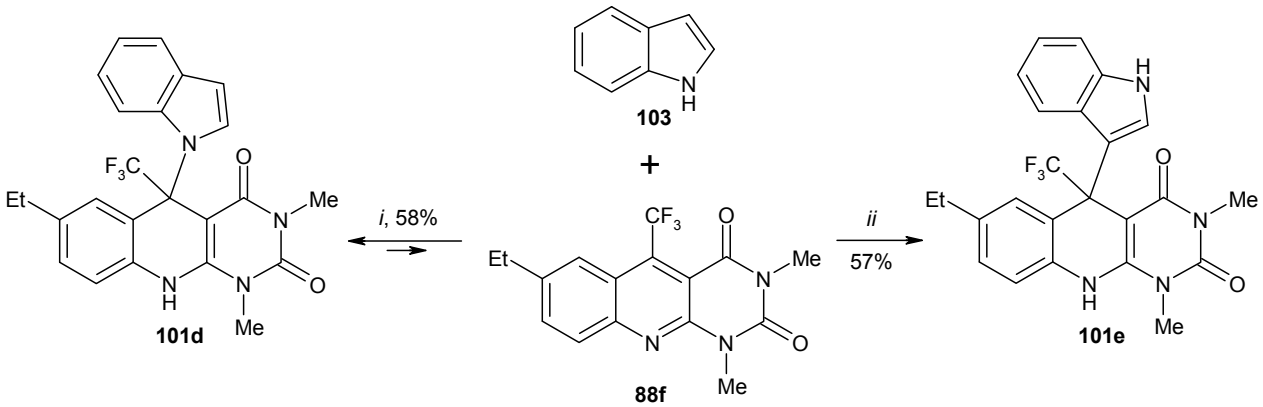
In case of 9-(2-chloroethyl)-5-deazaalloxazine **92a**, a further cyclization takes place. Taking into account that 5-deazaalloxazines do not undergo alkylation, this reaction can be rationalized by a cascade mechanism (Scheme 33).



Scheme 33. Proposed mechanism.

Especially interesting in this context is a reaction with indole, which rapidly couples 5-deazaalloxazine **88f** in the presence of a strong base (Scheme 34). The resulting σ-complex undergoes rearrangement at 80 °C in 5 hours to form a thermodynamically more stable *C*-isomer. *N*-Adduct **101d** can be decomposed by heating and to form hereby the initial materials **88f** and **103**, especially in the presence of traces of bases. Addition of a small amount of acetic acid stabilizes the product. Both isomers were isolated.

The direction of the nucleophilic addition was confirmed by ^{13}C NMR spectroscopy. The quaternary carbon atom C-5 of **101a-e** and **102a-c** appears as a quadruplet ($^{2}J_{(C\text{-}F)}$ = 25.7-33.0 Hz) in the aliphatic region at 46.2-50.2 and 65.3 ppm (the outstanding value refers to the 5-(indol-1-yl) derivative **101d**).

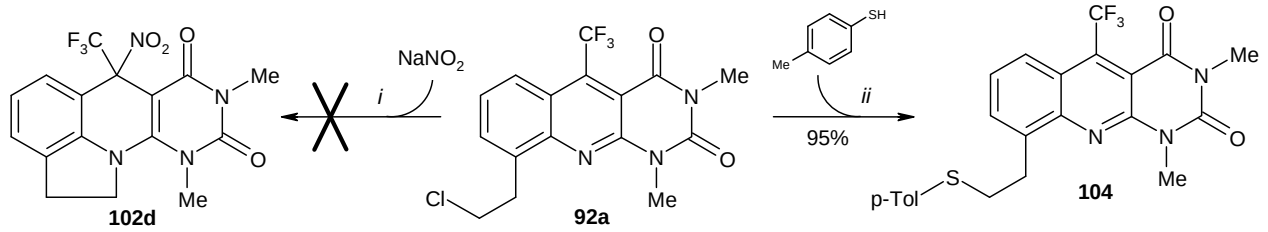


Scheme 34. Indole as N- and C-nucleophile. Reaction with 5-deazaalloxazines.

Reagents and conditions: *i*: NaH (60% in mineral oil), THF, r.t., 3 min; *ii*: NaH (60% in mineral oil), DMF, 80 °C, 5 h, under argon.

In some cases, a simple substitution of chlorine for the nucleophile was observed instead of addition to the 5-position. In other cases, 5-deazaalloxazine **92a** does not enter into the reaction at

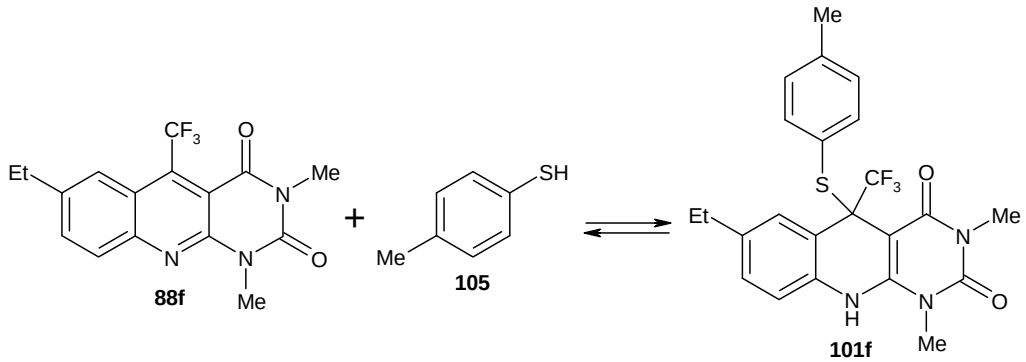
all (Scheme 35).



Scheme 35. Reaction of 9-(2-cloroethyl)-1,3-dimethyl-5-trifluoromethyl-pyrimido[4,5-b]quinoline-2,4-dione **24a** with N- and S-nucleophiles.

Reagents and conditions: *i*: DMSO, r.t., overnight; *ii*: DMSO, NaOMe, r.t., overnight.

5-Deazaalloxazine **88f** reacts reversibly with *p*-thiocresol **105** to form **101f** (Scheme 36). The reaction requires base catalysis. In this case, the equilibrium is shifted almost completely toward the product. While the starting materials disappeared, the product was observed on TLC, but, unfortunately, has never been isolated in a pure state, because most of it decomposes during the isolation. The additional evidence of the chemical transformation is bleaching of the mixture during the reaction. 5,10-Dihydro-5-deazaalloxazines, in contrast to yellow 5-deazaalloxazines, are colourless.



Scheme 36. Reversible reaction of 5-deazaalloxazine **88f** with *p*-thiocresol **105**.

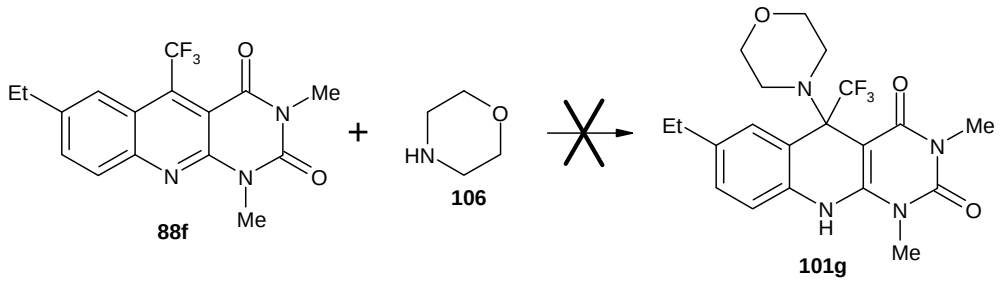
Reagents and conditions: NaOMe, DMF, r.t., overnight.

A product of the reaction of **88f** with morpholine **106** was not observed, even when sodium hydride was used as a base (Scheme 37). In contrast to the previous case with *p*-thiocresol, even bleaching of the mixture was not noticed. According to the poor literature data, addition of amines to fused pyridines may take place, but the equilibrium is strongly shifted towards the starting material.[99, 100]

It should be mentioned here that nucleophilic addition is more characteristic for pyridinium salts (this reaction is closely associated with the name of Fritz Kröhnke[101]) rather than non-quaternized pyridines.[102]

The easiness with which 5-polyfluoroalkyl-5-deazaalloxazines react with nucleophiles requires some consideration. First of all, the pyridine core is fused with two other aromatic rings;

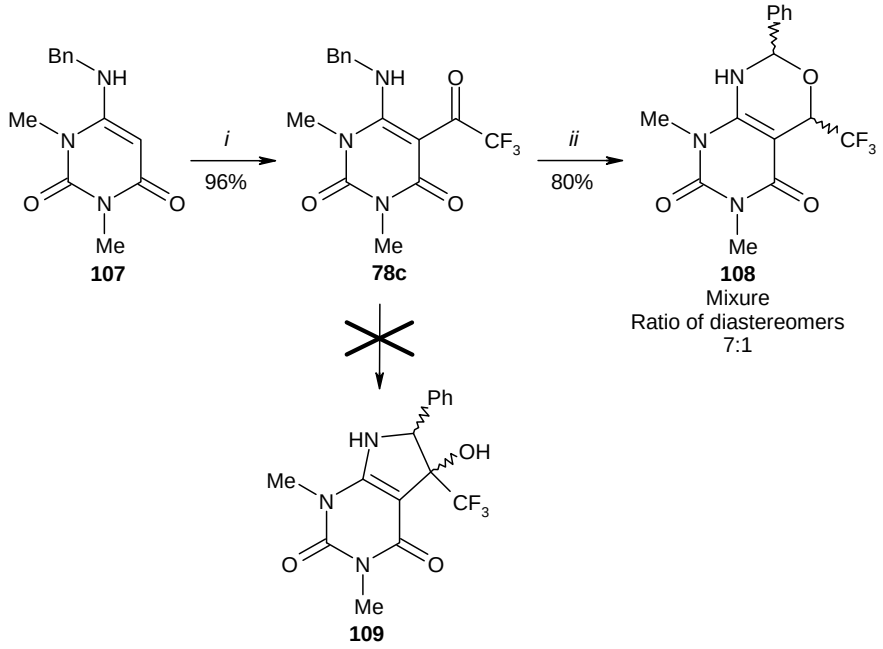
this circumstance substantially reduces aromaticity of the central cycles. Secondly, we should take into account the influence of substituents, especially at the reacting center. Thus, the perfluoroalkyl group causes a strong negative inductive effect. Moreover, according to the charge-alternation rules, the mesomeric effect distributed from pyrimidin-2,4-dione ring appears to be electron-withdrawing at the 5-position. Thirdly, the 5-polyfluoroalkyl-5-deazaalloxazine ring system is slightly twisted (see X-ray structures **88n**, **88j**, **88m** and **92a**) and consequently has decreased aromaticity compared to its planar state.



Scheme 37. No reaction between 5-deazaalloxazine **88f** and morpholine **106**.

Reagents and conditions: NaH (60% in mineral oil), THF, r.t., overnight.

2.8 Cyclization of 6-(Benzylamino)-1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione under basic conditions



Scheme 38. Cyclization of 6-(Benzylamino)-1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione under basic conditions.

Reagents and conditions: *i*: TFAA, pyridine, dioxane, r.t., overnight;[91] *ii*: NEt_3, DMF, 125 °C, 10 h, under argon.

Next, we tried to do the cyclization in case of N-benzyl-6-aminouracil where the methylene

group between the nitrogen atom and the phenyl group should prevent aromatization of the new ring. Unfortunately, it was not possible to isolate any clear product when sulfuric acid was applied. But another interesting reaction took place when the reaction was catalyzed by triethylamine. Thereby, a six-member ring is formed (Scheme 38).

The obtained product **108**, contrary to the expected structure **109**, shows a quadruplet in the ^{13}C DEPT spectrum with a significant coupling constant $^{2}J_{(C\text{-}F)}$ = 31.9 Hz, which was surprising. Therefore, the product was confirmed by X-ray analysis (Figure 15).

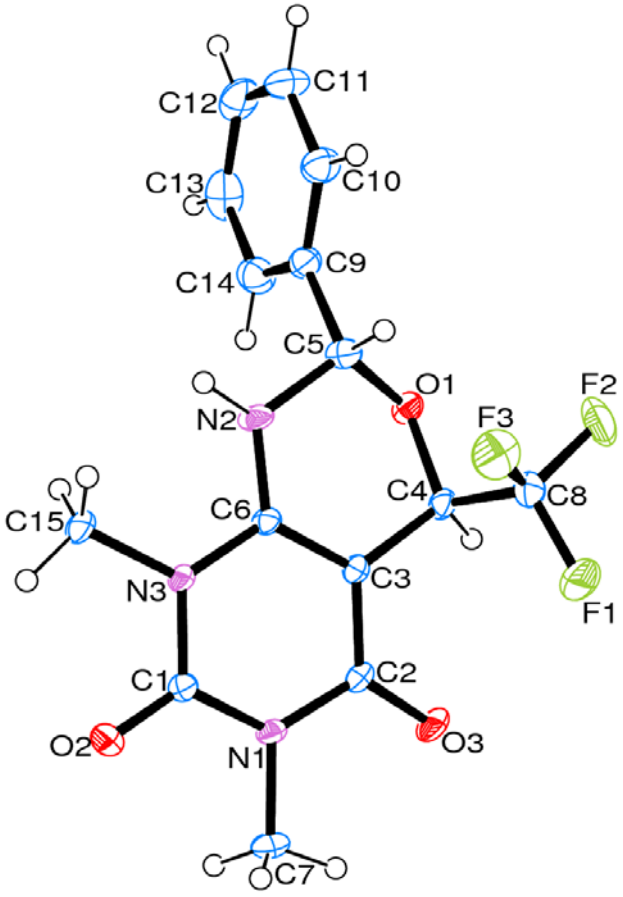


Figure 15. 6,8-Dimethyl-2-phenyl-4-(trifluoromethyl)-4,8-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazine-5,7(1*H*,6*H*)-dione **108** (40% probability level).

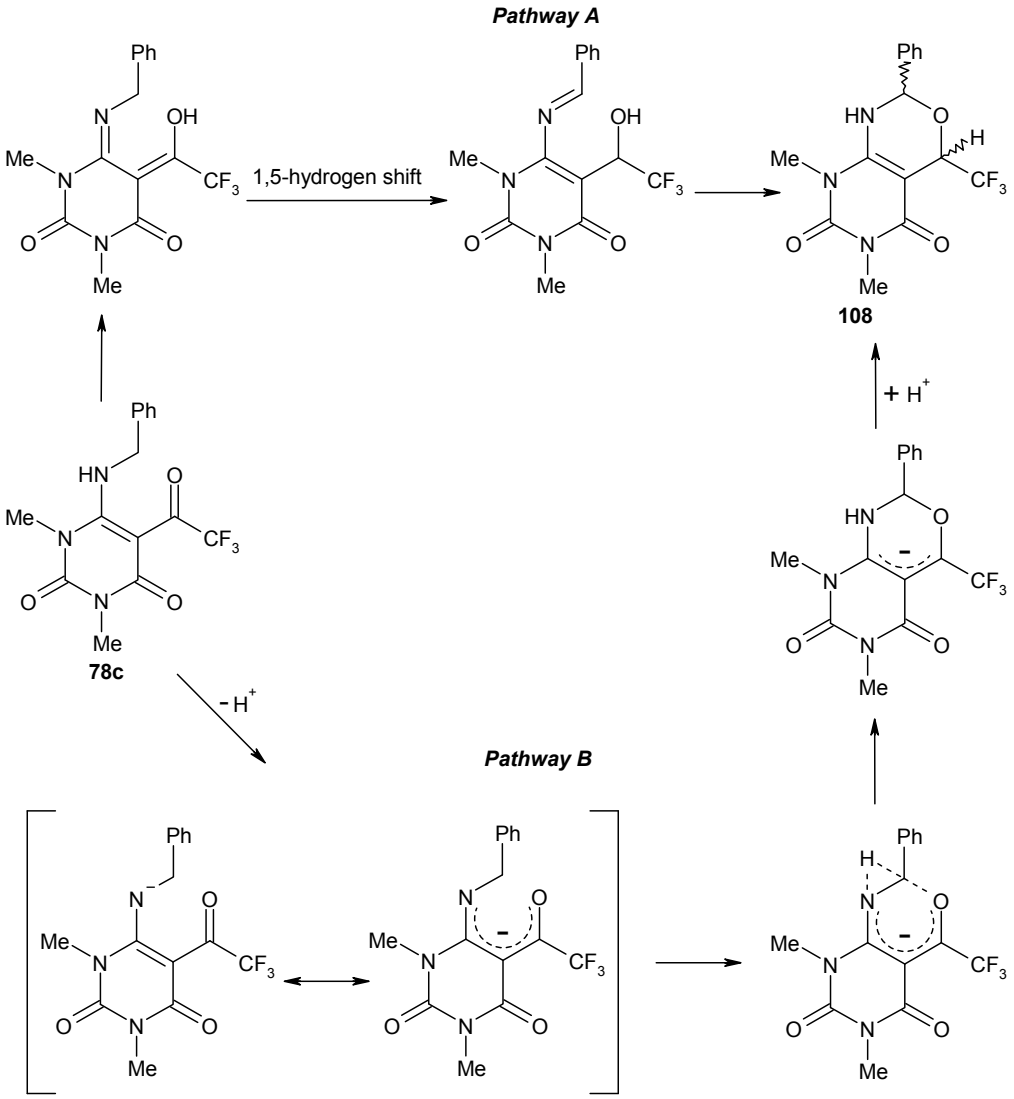
2.8.1 Discussion of the mechanistic pathway

According to literature data, this type of cyclization is rationalized by a 1,5-hydrogen shift, followed by an usual nucleophilic addition of the hydroxyl group to the imine (Scheme 39, ***Pathway A***).[103-106] The [1,5]-H migration was confirmed by an experiment with deuterotrifluoroacetic acid as a reaction medium; no deuterium was found in the product.[107]

But our example somewhat differs from the already described reactions in the literature. To the best of our knowledge, no similar reactions with secondary amines have been reported hitherto.

Only reactions involving tertiary amines were reported. This phenomenon is strongly associated with the so-called *tert*-amino effect. Secondly, these reactions proceed mostly either under acidic catalysis (TFA,[103, 107] silica gel,[106] $Sc(OTf)_3$[105]) or at high temperature,[104] and never in basic media. Taking into account the NH-acidic properties of **78c**, other possible pathways have to be considered, too.

We propose the following alternative mechanism of this reaction (Scheme 39, ***Pathway B***):



Scheme 39. Proposed mechanisms.

As the reaction runs in the presence of triethylamine, deprotonation is supposed to be the first step. The negative charge is delocalized over several atoms, particularly over the deprotonated nitrogen and oxygen of the trifluoroacetyl group. Then two synchronous transformations take place: a 1,2-hydrogen shift and a bond formation between carbon and oxygen atoms. Now the negative charge is delocalized over C-6 and the carbon atom adjacent to the CF_3 group. Finally, protonation leads to the obtained product **108**.

2.9 Photophysical properties of 5-polyfluoroalkyl-5-deazaalloxazines

Molar absorption coefficients, absorption maxima, fluorescence band maxima and Stokes shifts for 6 compounds were determined within the study (Figure 16, 17; Table 6). As expected, the synthesized 5-deazaalloxazines have pronounced fluorescence properties.

Table 6. Photophysical properties of 5-deazaalloxazines in chloroform: molar absorption coefficients ε at absorption maxima λ_a, fluorescence band maxima λ_f, and Stokes shift $\Delta\nu_{St}$.

Compd	λ_a, nm	ε, $M^{-1}\cdot cm^{-1}$	λ_f, nm	$\Delta\nu_{St}$, cm^{-1}
88w	405	9500	460	2950
88x	353	12400	516	8950
88f	397	5200	468	3820
88u	410	17500	480	3560
97a	417	9800	494	3740
92b	395	5400	466	3860

As seen from Table 6, compound **97a** exhibits the most pronounced bathochromic shift among all other examples. The absorption coefficient values lie within 5200-17500 $M^{-1}\cdot cm^{-1}$, which is too high to be explained by a n – π* electronic transition. Hereby one can assume that this maxima correspond to π – π* transition. The structure of **88x** has an outstanding value of Stokes shift that can be rationalized by vibrational energy relaxation. The highest absorption coefficient is observed for **88u**, the structure having the longest conjugated π-electron system.

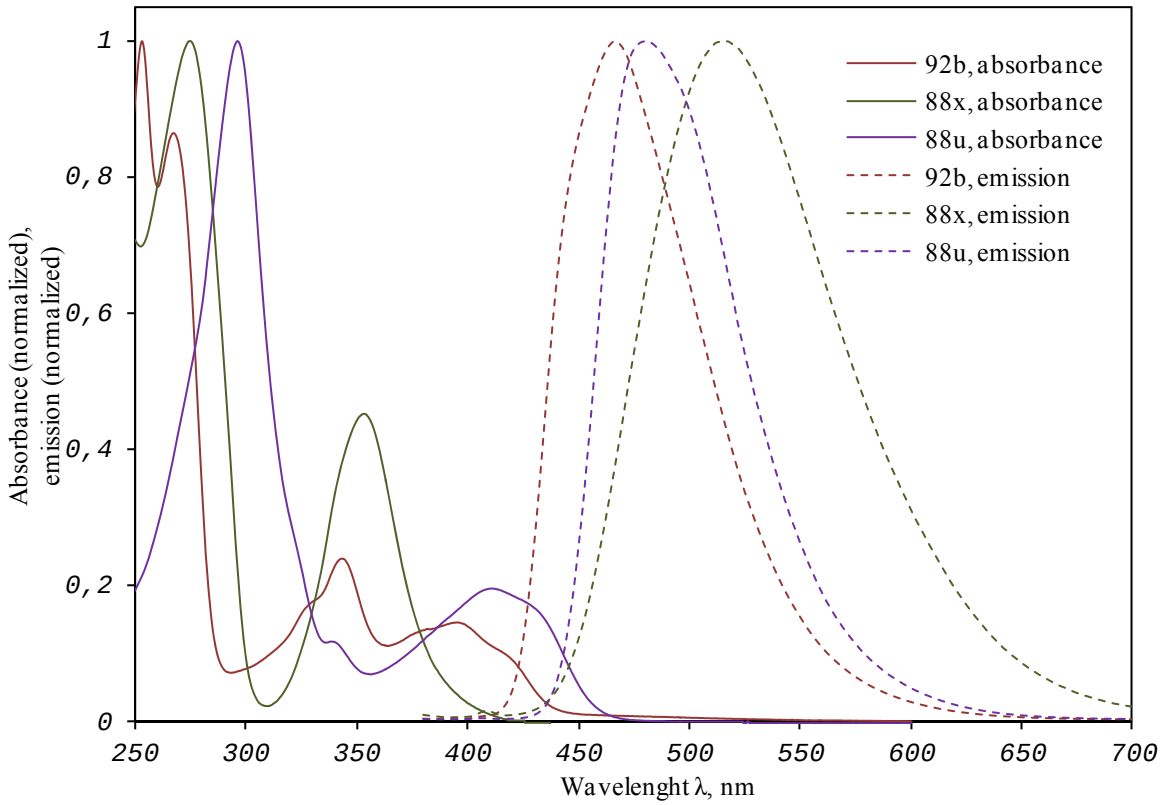


Figure 16. Normalized absorption and uncorrected emission spectra of compounds **92b**, **88x** and **88u** in chloroform.

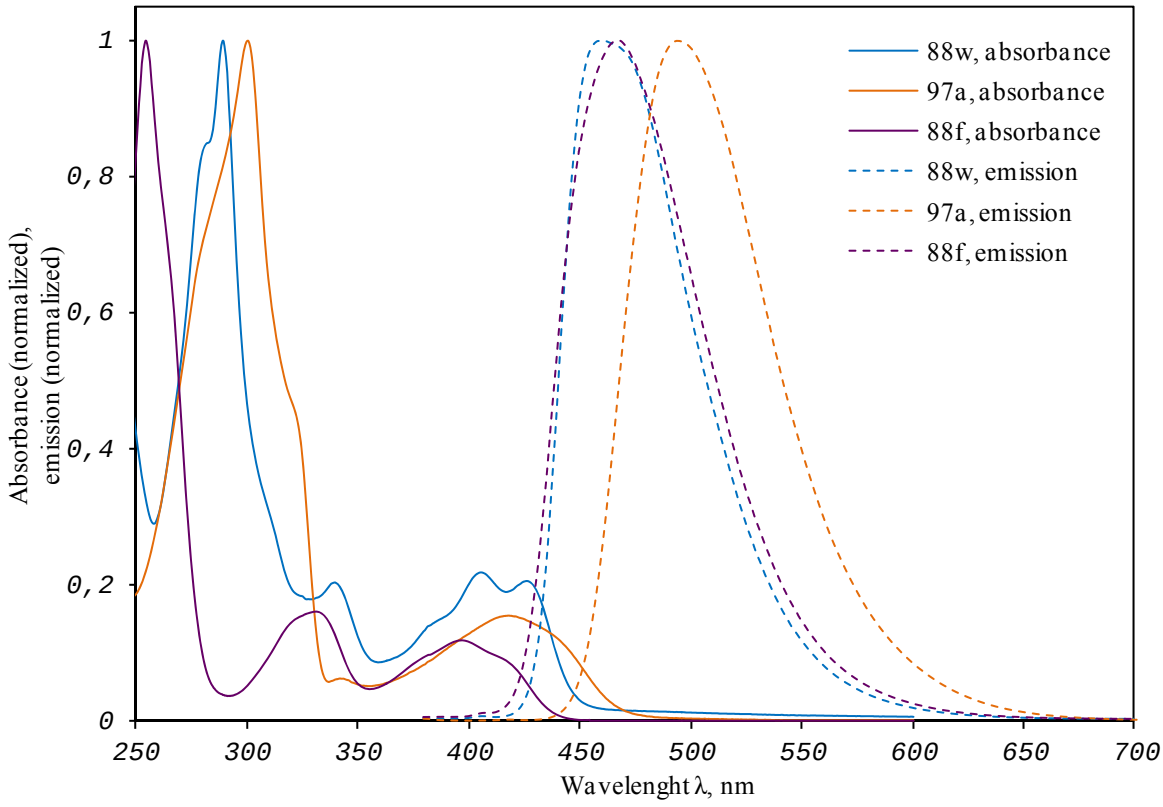


Figure 17. Normalized absorption and uncorrected emission spectra of compounds **88w**, **97a** and **88f** in chloroform.

2.10 Conclusions

In conclusion, we have developed a convenient and inexpensive approach for the synthesis of 5-polyfluoroalkyl-5-deazaalloxazines. These compounds are not readily available by other methods.

5-Acyl-6-aminouracils containing a tertiary amino group cyclize in sulfuric acid to the corresponding 5-hydroxy-5,10-dihydro-5-deazaalloxazines. The latter can be converted into 5-deazaalloxazines via C-N bond cleavage promoted by thionyl chloride.

In case of 5-acyl-*N*-benzyl-6-aminouracil an unusual cyclization leading to a six-membered ring was observed.

Unlike Hantzsch dihydropyridine, sodium cyanoborohydride was found to be an excellent reductant for 5-polyfluoroalkyl-5-deazaalloxazines to convert them into the corresponding 5,10-dihidro derivatives. The obtained product undergoes highly regio- and diastereoselective alkylation with benzyl bromide. The possibility to reduce the pyridine fragment of 5-polyfluoroalkyl-5-deazaalloxazines is a crucial feature important for development of artificial FAD/$FADH_2$ system analogues with tunable redox potential.

Suzuki and Sonogashira couplings with 8-bromo-5-deazaalloxazine derivative were carried out successfully and in high yields.

Another remarkable feature of 5-deazaalloxazines has been found during the study, namely the ability to react with a variety of nucleophiles at position 5. In case of 9-(2-chloroethyl)-5-deazaalloxazines, a further cyclization leads to 7,9-dioxo-1,2,7,8,9,10-hexahydro-6*H*-pyrimido[4,5-*b*]pyrrolo[3,2,1-*ij*]quinolines.

As expected, the synthesized 5-deazaalloxazines have pronounced fluorescence properties.

Examples **77a**, **77b**, **88b**, **88h**, **88j**, **88n** and **88q** have been sent to be tested. The pharmacological evaluation is performed by Dr. M. Lalk (University of Greifswald).

3 Synthesis of Spiro[pyrimido[4,5-*b*]quinoline-3',5-indoline-2'-one]-3,10-dihydro-2,4-diones via Three-Component Reaction and Unexpected Recyclization

3.1 Introduction

3.1.1 Biological relevance of similar structures

This chapter is devoted to spiro[pyrimido[4,5-*b*]quinoline-3',5-indoline-2'-one]-3,10-dihydro-2,4-diones. The target scaffold can be mentally divided into several biologically relevant moieties. First of all, it is the heterocyclic oxindole system containing one carbon atom common to two rings. Presence of the chiral spiro carbon leads to the sterically constrained spiro structure and is one of the important factors of the biological activities. Spirooxindole and spiroindoline ring systems are widely distributed among natural alkaloids, including anesthetics (horsfiline **112**),[108] mammalian cell cycle inhibitors, antibiotics, antitumor agents (spirotryprostatin B),[109] and in synthetic drugs (for instance, ibutamoren **111**, the orally active growth hormone secretagogue).[110]

On the other hand, the target scaffold includes so important motifs, such as 6-aminouracil and 1,4-dihydropyridine. The last moiety occurs in a large number of pharmaceutical products known as L-type calcium channel blockers (almodipine **114**)[111] and calcium agonists (CGP-28392).[112] AEAC, which refers to 6-aminouracils, is a thymidine phosphorylase inhibitor and exhibits antitumor activity.[113] Thus, the combination of these moieties presents intriguing possibilities for pharmacological studies and drug design (Figure 18).

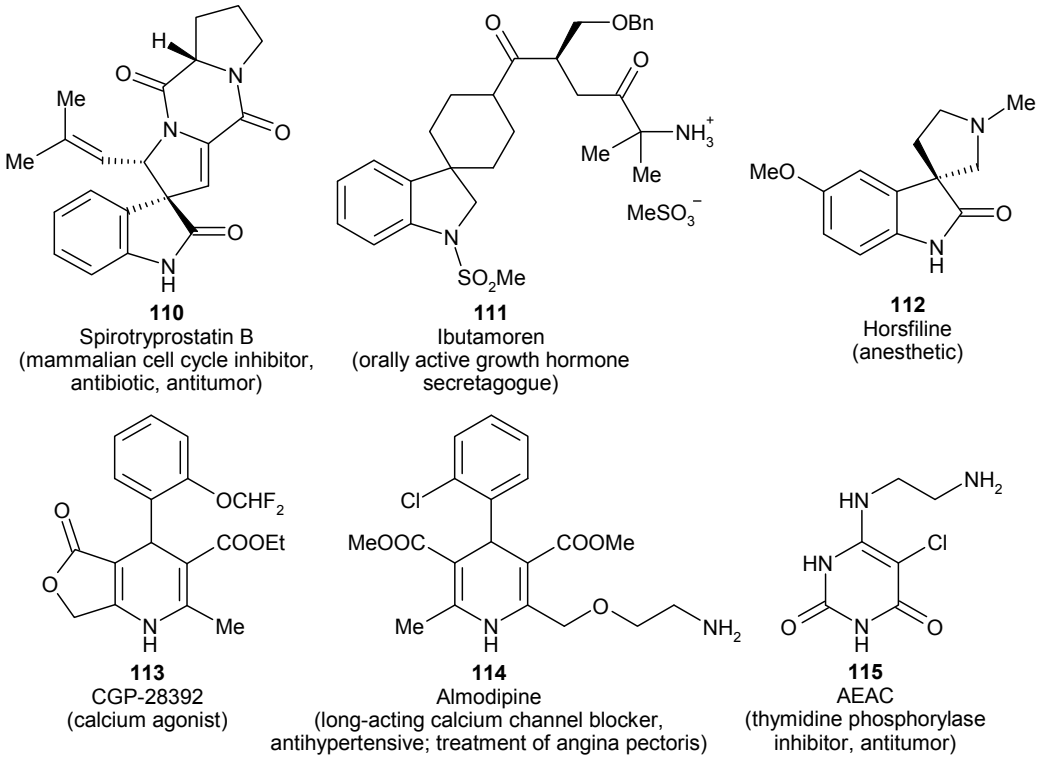


Figure 18. Representatives of closely related heterocycles and their biological activities.[108-113]

3.1.2 Multicomponent reactions as a powerful synthetic method

Multicomponent reactions (MCRs) are very advantageous in many aspects. For instance, such reactions that provide maximum diversity are especially desirable in combinatorial chemistry and perfectly amenable to automation.[114] On the other hand, MCRs usually lead to minimization of energy consumption and waste production due to their atom economy and facile execution.

Because of their high productivity, the multicomponent reactions have attracted considerable attention as a source of a colossal number of substances to bioscreening and medicinal chemistry research, and are particularly useful for the preparation of spiroheterocyclic systems.

3.2 Results and discussion

3.2.1 Synthetic strategy based on Hantzsch- and Biginelli-type reactions

The 3+2+1 strategy, where 1,3-binucleophiles, such as -*CCN*-, -*CCO*- and -*NCN*-, 1-*C*-nucleophile-2-*C*-electrophile and 1,1-*C*-bielectrophile form a heterocyclic ring by one-pot cyclocondensation, is one of the most important approaches toward the synthesis of 1,4-dihydropyridines (DHPs),[115, 126] 4*H*-pyranes[114, 127] and Biginelli compounds.[128] The following starting materials have been successfully used in the synthesis of DHP:

- 1,3-*CCN*-Binucleophiles

5-Aminopyrazoles,[115, 117, 119, 122, 123] 6-aminouracils,[124] *β*-naphthylamine,[116, 118, 121] 5-amino-isooxazoles[120] and 6-amino-2-(methylthio)pyrimidin-4(1*H*)-one.[126]

- 1-*C*-Nucleophile-2-*C*-electrophiles

Barbituric[115, 117-121, 123, 125] and thiobarbituric[120] acids, simple ketones,[126] 1,3-diketones,[116, 119, 124, 126] cyanomethyl ketones,[122] etc.[119]

- 1,1-*C*-Bielectrophiles

Isatin,[115-117, 119, 120, 122] aromatic aldehydes.[118, 121, 123-126]

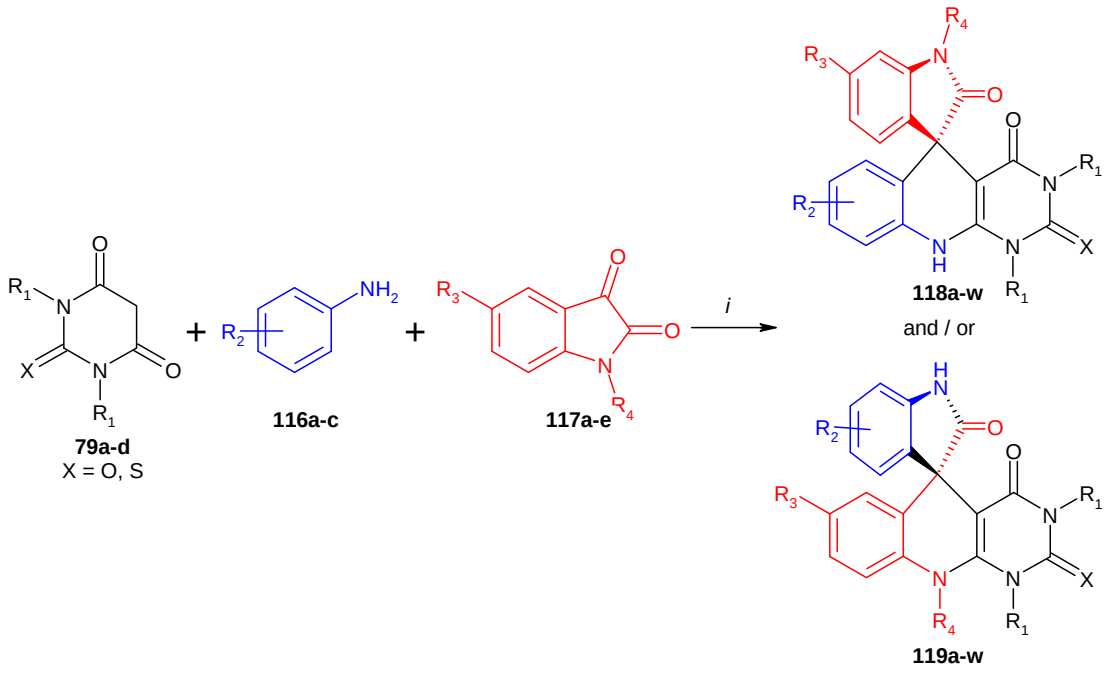
The first component (1,3-binucleophile) can be generated in situ, for example, from a ketone that contains an active methylene group in *α*-position and from an amine[125] or ammonia itself as in the classical Hantzsch dihydropyridine synthesis. Another variation is the two-component condensation, where one of them plays a double role: namely as 1,3-binucleophile and 1-nucleophile-2-electrophile (Scheme 40).[129, 130]

3.2.2 Synthesis of spiro[pyrimido[4,5-*b*]quinoline-3',5-indoline-2'-one]-3,10-dihydro-2,4-diones and unexpected recyclization

In recent year (2012) a significant attention has been paid to multicomponent DHPs synthesis involving isatin as a carbonyl component and 1,1-*C*-bielectrophile.[115, 117, 120] But in the light of our study, the possibility of the formation of the opposite isomer in such reactions with the similar spectral and analytical data has not received adequate attention.

We developed an efficient one-pot three-component synthesis of compounds **118/119 a-w** (Scheme 40). As the first component, derivatives of barbituric or thiobarbituric acid **79** were used. The second component is an electron-rich aniline, and the third one is isatin.

This reaction occurs in normal atmosphere and usually gives moderate to high yields mostly depending on the initial aniline. Initially we tested briefly various solvents and catalysts and found conditions proposed by X.-S. Wang and coworkers (EtOH, I_2, r.t.) to be the best. It is worth to mention here that the reaction runs successfully at r.t. even without iodine, but, however, in little bit lower yields. The progress of the reaction was monitored by TLC, and in most cases the synthesis was complete after 24 h. The results are summarized in Table 7. A completely unexpected result was observed, namely that the expected structure of some products proved to be wrong. As shown in Scheme 40, two products are possible: the normal one **118** and isomeric one **119**.



Scheme 40. Synthesis of spiro[pyrimido[4,5-*b*]quinoline-3',5-indoline-2'-one]-3,10-dihydro-2,4-diones.
Reagents and conditions: *i*: EtOH, I_2 (cat.), r.t., 24 h.[118]

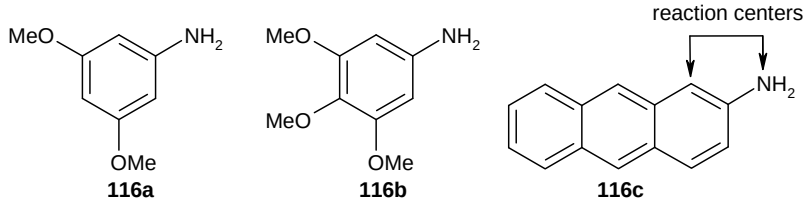


Figure 19. Variety of anilines

Table 7. Syntheses of spiro[pyrimido[4,5-*b*]quinoline-3',5-indoline-2'-one]-3,10-dihydro-2,4-diones **118** and **119** via three-component condensation.

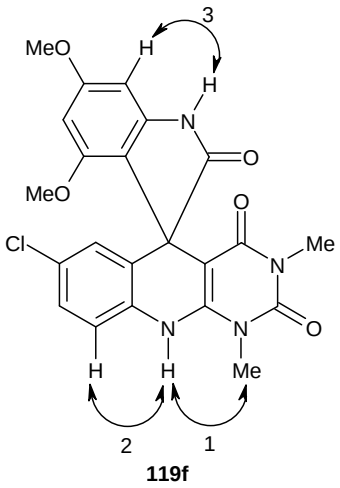
Entry	Barbituric acid		Aniline **116**		Isatin		Product	
	R_1	X	№	R_2	R_3	R_4	Isomer[c]	Yield, %[a]
a	Pr	O	**a**	3,5-diMeO-	H	H	**119**	79
b	Pr	O	**b**	3,4,5-triMeO-	H	H	**119**	26
c	Pr	O	**c**	2-anthracenamine	H	H	**119**	91
d	H	O	**a**	3,5-diMeO-	H	H	**119**	51
e	Me	O	**a**	3,5-diMeO-	H	H	**119**	57
f	Me	O	**a**	3,5-diMeO-	Cl	H	**119**	72
g	Me	O	**a**	3,5-diMeO-	H	Et	**118**	82
h	Me	O	**b**	3,4,5-triMeO-	H	Et	**118**	55
i	Me	O	**a**	3,5-diMeO-	F	H	**119**	75
j	Me	O	**a**	3,5-diMeO-	H	Me	**118**	86
k	Me	O	**b**	3,4,5-triMeO-	H	Me	**118**	52
l	Me	O	**b**	3,4,5-triMeO-	NO_2	H	**118**(85), **119**(15)	67 / 23[b]
m	Et	S	**a**	3,5-diMeO-	H	H	**119**	81
n	Et	S	**b**	3,4,5-triMeO-	H	H	**119**	53
o	Et	S	**a**	3,5-diMeO-	H	Et	**118**	72
p	Et	S	**a**	3,5-diMeO-	Cl	H	**119**	68
q	Et	S	**b**	3,4,5-triMeO-	H	Et	**118**	47
r	Et	S	**a**	3,5-diMeO-	F	H	**119**	59
s	Et	S	**b**	3,4,5-triMeO-	F	H	**119**	36
t	Et	S	**a**	3,5-diMeO-	H	Me	**118**	56
u	Et	S	**a**	3,4,5-triMeO-	H	Me	**118**	47
v	Et	S	**a**	3,5-diMeO-	NO_2	H	**118**(25), **119**(75)	63 / 19[b]
w	Et	S	**c**	2-anthracenamine	H	Et	**118**	73[b]

[a] – yields refer to pure isolated products; [b] – yield of isolated mixture / yield of the major isomer isolated in a pure state; [c] – in brackets are given isomers ratio.

After first trials, four commercially available barbituric acid derivatives **79a-d**, three aromatic amines **116**, and six isatins **117** were chosen for the library extension and validation of the

observed results. Let us consider what the product distribution depends on. In case of *N*-substituted isatins exclusively the normal product **118** was isolated. For R_4 = H only the opposite isomer **119** forms. And only in case of 5-nitroisatin both isomers were detected. As we see, the product depends entirely on the type of isatin.

The isomers were identified by X-ray analysis or NOESY. The decisive correlations are shown in Figure 20. The peak of the amine proton can be assigned by the first correlation. Another NH-signal belongs to the amide. The second and third cross-peaks indicate the position of each aromatic ring being in neighborhood to the corresponding acidic protons. In case of *N*-alkyl structures, the algorithm of explanation is the same except that the 1-ethyl or methyl protons are taken into consideration instead of the NH.



119f

Figure 20. Determination of regioisomer by NOESY. Arrows show the decisive correlations.

The structures of products **118** and **119** were characterized by IR, ^{1}H, ^{13}C NMR spectral data as well as MS and HRMS analysis. For examples **119f**, **118g**, **119c** and **118u** were measured COSY and HSQC correlations. In addition, HMBC spectra of **118g** and **118u** were obtained. The regiochemistry of **119b** and **119e** is confirmed by X-ray analysis. Isomeric structures of **119c**, **119f**, **118g**, **118l**, **118u**, **119v** were determined using 2D NOESY-methods. In those cases, when *N*-alkylisatins were employed in the reaction, isomers can be easily assigned by the signal of the NH-proton, which are in the range of 9.14 (**118g**) to 9.40 ppm (**118w**) in DMSO. The dihydropyridine NH proton appears at 9.14 to 9.98 ppm, whereas the NH of the indolin-2-one fragment comes out at 10.32 to 11.05 ppm. Therefore, we draw the conclusion that *N*-alkylisatins give the expected isomer. The isomeric structure of other substances was determined by comparing the most decisive carbon and proton chemical shifts related to the di- and trimethoxyaniline moieties with the examples confirmed for sure by X-ray or NOESY. The NMR data are summarized in Tables 8-11.

Table **8**. The ^{1}H and ^{13}C NMR data for isomers **119** from 3,5-dimethoxyaniline.

	^{1}H NMR				^{13}C NMR			
Compd	MeO-4	MeO-6	H-5	H-7	MeO-4	MeO-6	CH-5	CH-7
4e	3.50	3.76	6.04	6.12	—	—	—	—
4a	3.49	3.75	6.03	6.11	56.4	56.1	92.9	90.1
4f	3.53	3.77	6.07	6.14	56.5	56.2	93.1	90.2
4i	3.52	3.77	6.07	6.13	56.5	56.2	93.1	90.2
4m	3.51	3.76	6.05	6.13	56.5	56.2	93.1	90.2
4p	3.54	3.77	6.09	6.15	56.6	56.2	93.2	90.3
4r	3.53	3.77	6.08	6.15	56.5	56.2	93.2	90.3
4v	3.54	3.78	6.10	6.20	56.6	56.2	93.3	90.4

Table **9**. The ^{1}H and ^{13}C NMR data for isomers **118** from 3,5-dimethoxyaniline.

	^{1}H NMR				^{13}C NMR			
Compd	MeO-6'	MeO-8'	H-7'	H-9'	MeO-6'	MeO-8'	CH-7'	CH-9'
4g	3.32	3.77	6.13	6.67	56.2	56.1	95.5	95.0
4j	3.36	3.77	6.12	6.67	56.8	56.1	95.5	95.0
4o	3.34	3.79	6.16	6.80	—	—	—	—
4t	3.38	3.78	6.15	6.79	56.9	56.2	96.0	95.2

Table **10**. The ^{1}H and ^{13}C NMR data for isomers **119** from 3,5-3,4,5-trimethoxyaniline.

	^{1}H NMR				^{13}C NMR			
Compd	MeO	MeO	MeO	H-7	MeO	MeO	MeO	CH-7
4b	3.29	3.59	3.83	6.36	56.8	60.8	61.3	92.0
4n	3.28	3.59	3.83	6.38	56.9	60.8	61.4	92.1
4s	3.33	3.61	3.84	6.40	56.9	60.9	61.4	92.2

Table **11**. The ^{1}H and ^{13}C NMR data for isomers **118** from 3,5-3,4,5-trimethoxyaniline.

	^{1}H NMR				^{13}C NMR			
Compd	MeO-6'	MeO-7'	MeO-8'	H-9'	MeO-6'	MeO-7'	MeO-8'	CH-9'
4h	3.03	3.60	3.83	6.92	60.1	61.1	56.6	97.2
4k	3.12	3.60	3.83	6.93	60.4	61.2	56.6	97.2
4l	3.27	3.62	3.85	6.96	60.4	61.2	56.7	97.3
4q	3.04	3.61	3.80	7.05	60.2	61.1	56.7	97.5

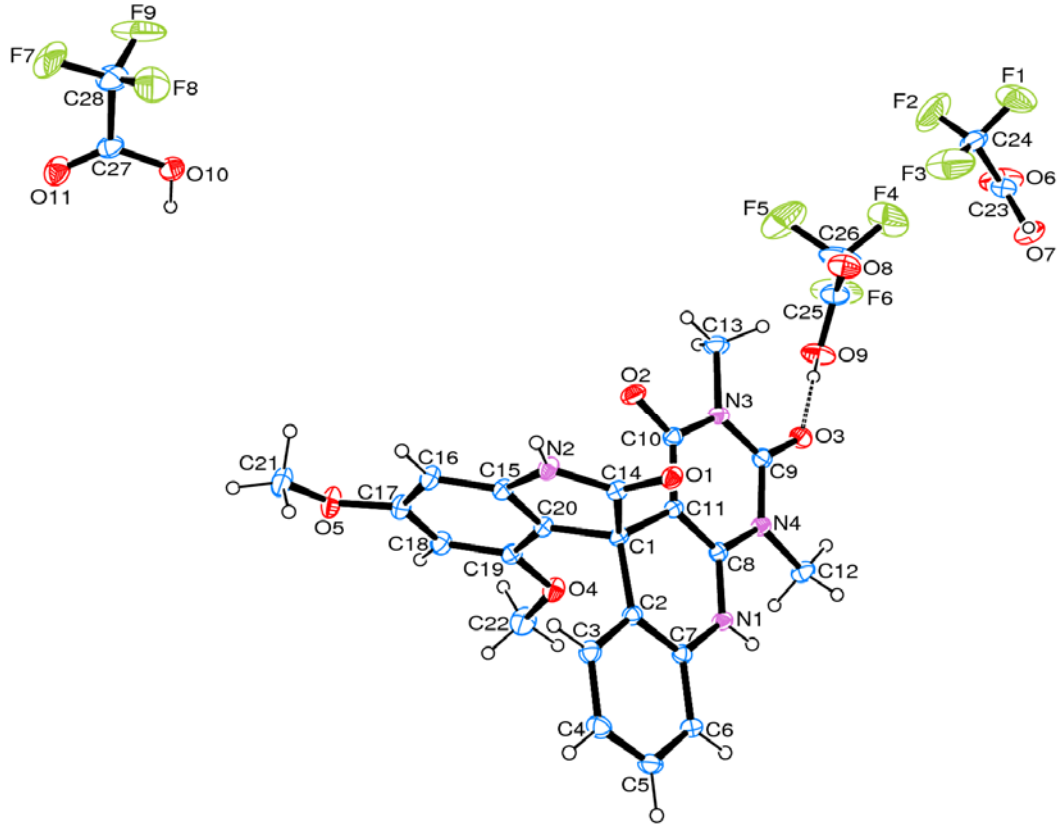


Figure 21. Ortep plot of 5,7-dimethoxy-1',3'-dimethyl-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,2',4'(1*H*,3'*H*,10'*H*)-trione **119e** (30% probability level). Crystal solvate with 3 eq of trifluoroacetic acid.

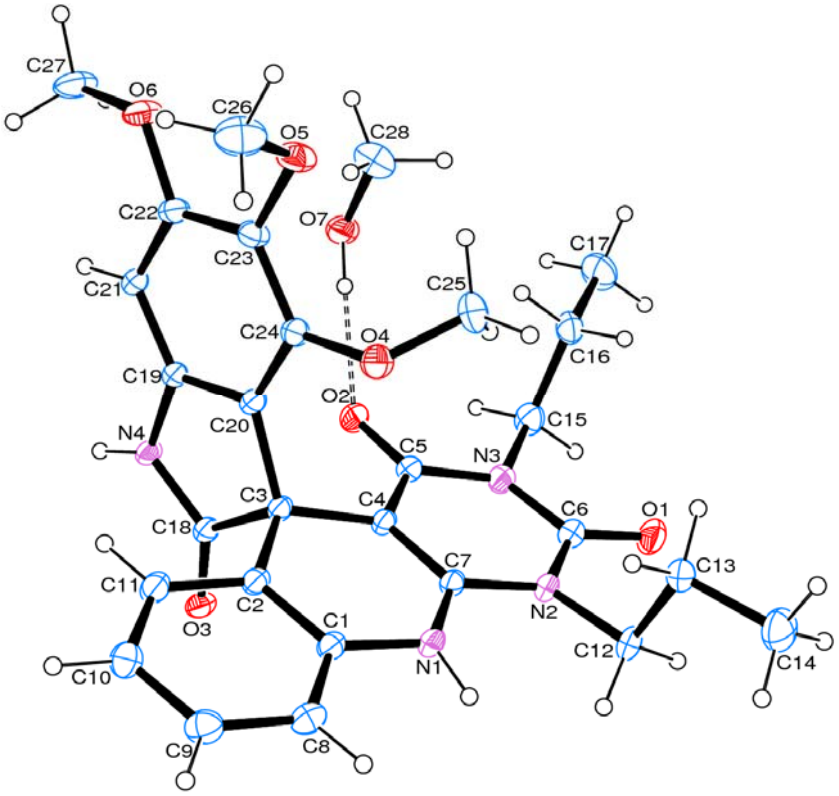
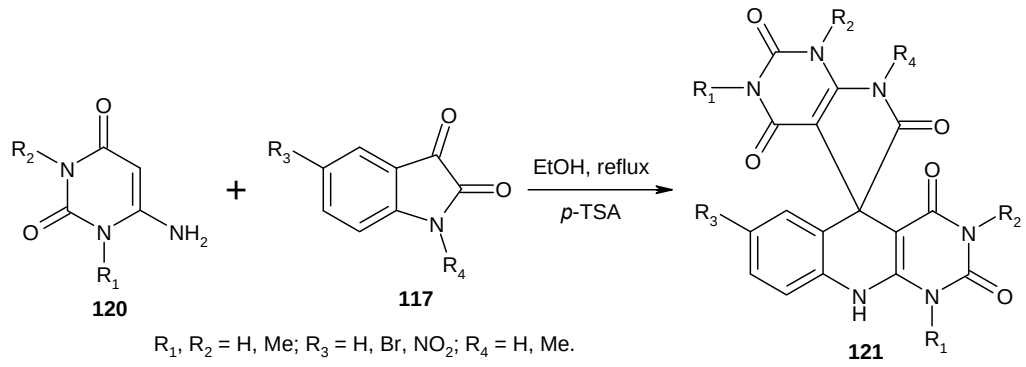


Figure 22. Ortep plot of 4,5,6-trimethoxy-1',3'-dipropyl-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,2',4'(1*H*,3'*H*,10'*H*)-trione **119b** (25% probability level). Crystal solvate with 1 eq of methanol.

As seen from crystallographic data, configuration of the spiro carbon atom is near to

tetrahedral: The angle values appear within the range of 100° to 115° (in tetrahedron ~109.47°). Indolin-2-one and 5,10-dihydropyrimido[4,5-*b*]quinoline-2,4-dione moieties lie in orthogonal planes. Torsion angles C19C1N1C6 (**119e**) and C24C3N1C8 (**119b**) make up −90.00° and 94.05° respectively.

All synthesized spiro compounds are novel, but nevertheless, similar to previously described derivatives. Remarkably, despite a substantial number of publications dedicated to three-component spiroindolinone synthesis via Hantzsch-like reaction,[115-117, 119, 120, 122] the possible recyclization has not been considered yet. The isomers have similar analytical data and, therefore, without additional X-ray crystallographic investigation or NOESY experiment could be wrongly assigned. The only similar transformation was described by A. Bazgir and coworkers for a two-component reaction, where 6-aminouracil **120** plays double role (Scheme 41).[129, 130] The authors concluded the structure of one congener ($R_1 = R_2 = R_3 = CH_3$, $R_4 = H$) using X-ray analysis, but the regiochemistry of the other products **121**, particularly the one obtained from N-methylisatin, was not confirmed.

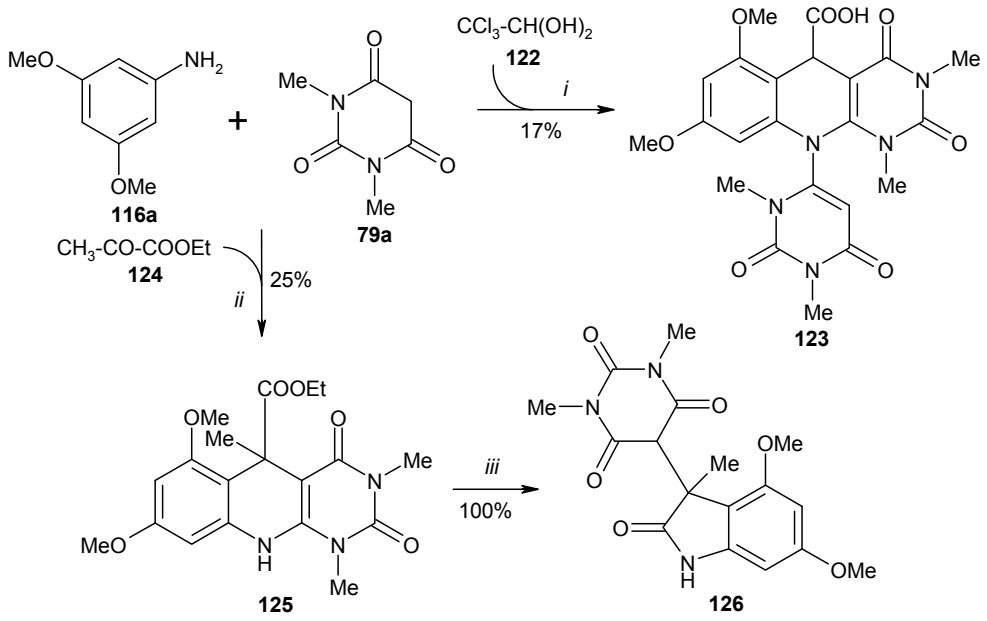


Scheme 41. Two-component condensation accomplished by reamidation reported by A. Bazgir and coworkers.[129, 130]

3.2.3 Reactions of other carbonyl compounds instead of isatins

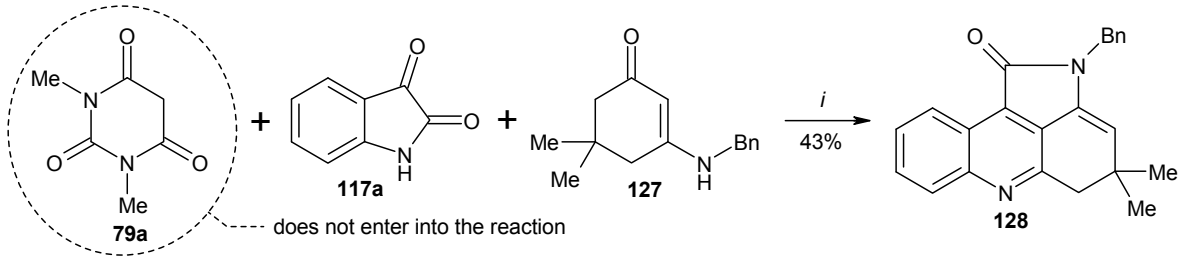
The study of the three-component condensation between barbituric acids, anilines and carbonyl compounds was continued (Scheme 42). The reaction was carried out successfully only with electron-rich anilines and relatively active carbonyl compounds.

Next, we tried to replace isatins by other active carbonyl compounds, such as chloral hydrate and ethyl pyruvate. When chloral hydrate was introduced into analogous reaction, unexpected product **123** with hydrolyzed trichloromethyl group was obtained under the same conditions in 17% yield. Fused 1,4-dihydropyridine **125**, prepared from ethyl pyruvate in 25% yield, is unstable and rearranges slowly at room temperature under the action of atmospheric moisture affording quantitatively indolinone **126** (Scheme 42). The structures of compounds **123** and **125** were characterized by IR, ^{1}H, ^{13}C NMR spectral data as well as MS, HRMS and elemental analysis. The structure of **126** was additionally confirmed by X-ray diffraction analysis (Figure 23).



Scheme 42. Three-component condensation leading to 5,10-dihydro-5-deazaalloxazines and its following rearrangement.

Reagents and conditions: *i*: I_2, EtOH, r.t., 5 days; *ii*: I_2, EtOH, r.t., overnight; *iii*: slowly conversion during storage at r.t.



Scheme 43. Using of 3-benzylamino-5,5-dimethyl-cyclohex-2-enone leads to formation of quinoline derivative.

Reagents and conditions: *i*: I_2, EtOH, r.t., overnight.

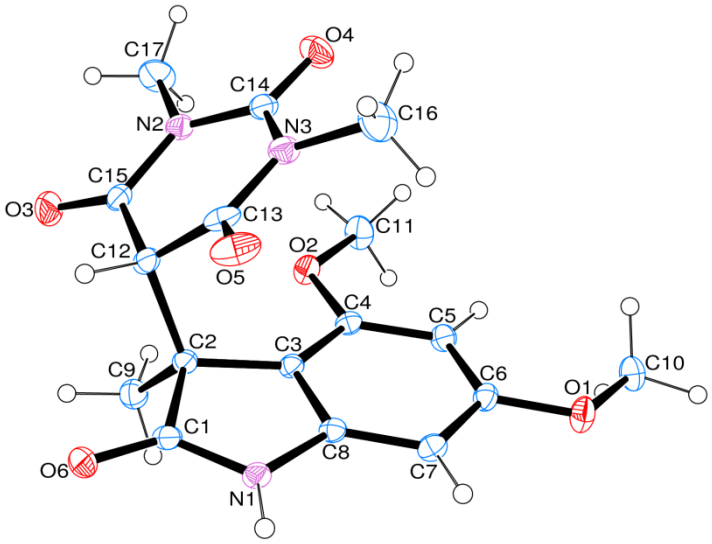


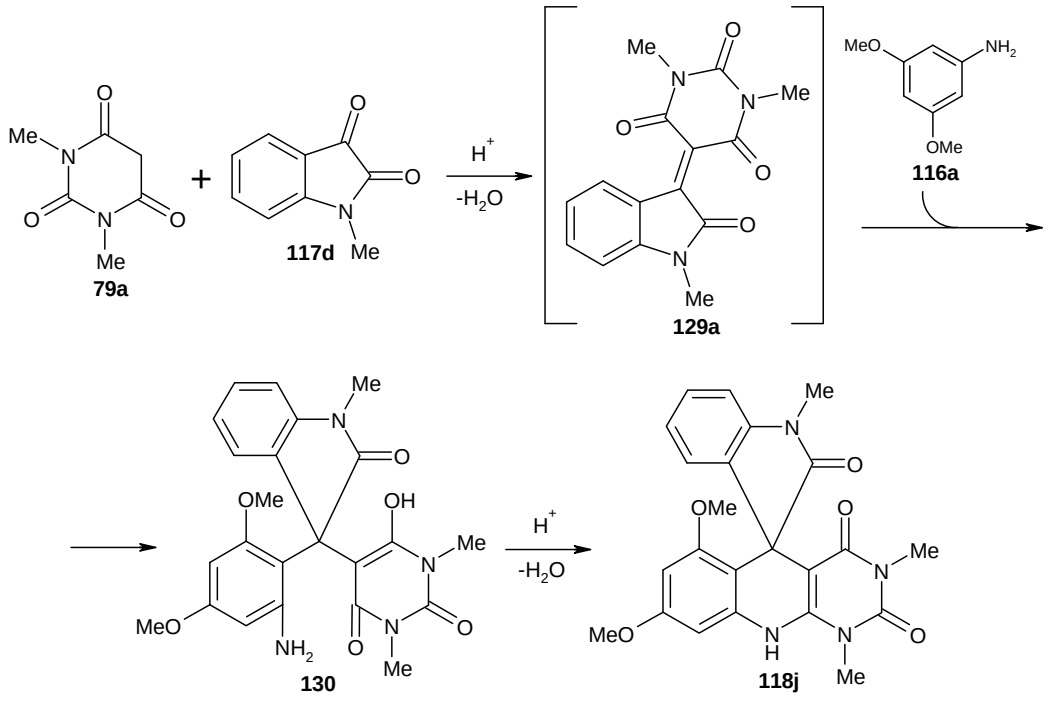
Figure 23. Ortep plot of 5-(4,6-Dimethoxy-3-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1,3-dimethyl-pyrimidine-2,4,6-trione **126** (35% probability level).

If 3-benzylamino-5,5-dimethyl-cyclohex-2-enone **127** is used instead of polymethoxy-

anilines **116a-c**, 1,3-dimethylbarbituric acid **79a** does not enter into the reaction (Scheme 43). As a result, the quinoline derivative **128** was obtained in 43% yield. Very recently, this reaction has been described by H. Kefayati and coworkers for the three-component condensation of isatin, dimedone and various amines.[131]

3.2.4 Interpretation of the results

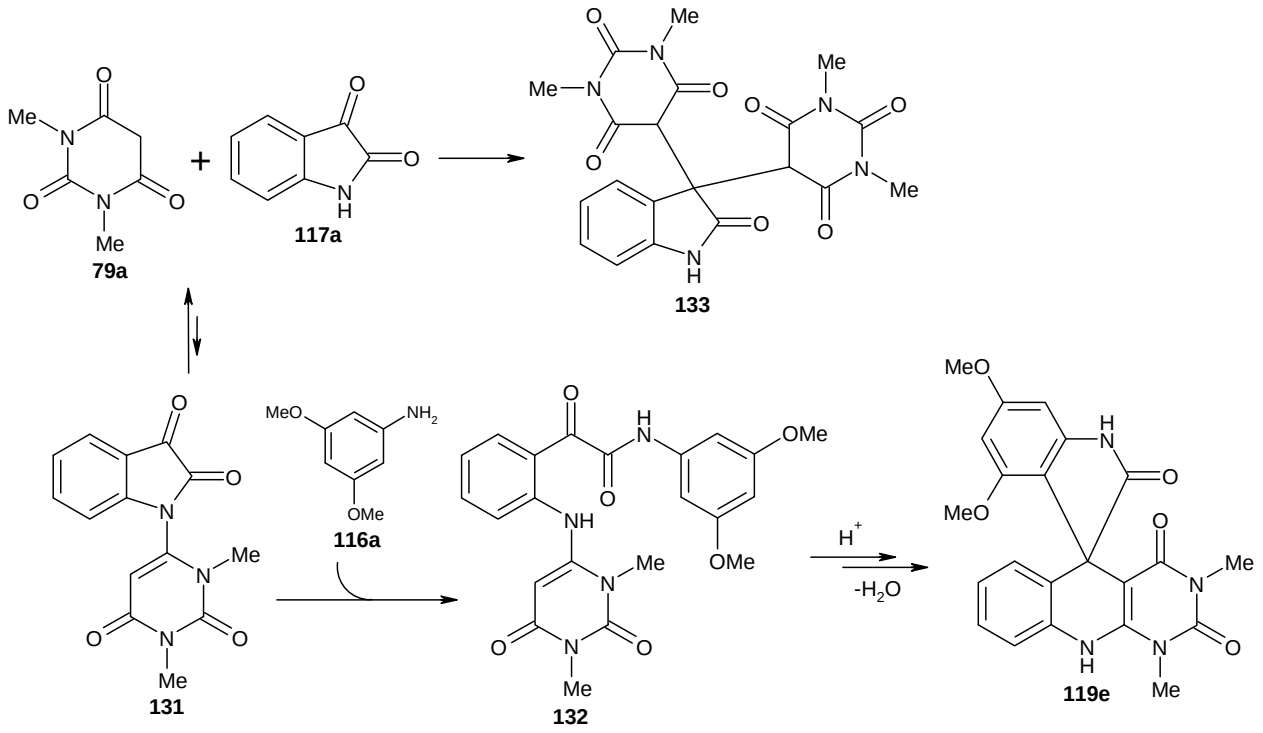
The formation of the normal isomer can be rationalized by the mechanism analogous to the one proposed for the case of aromatic aldehydes instead of isatins (Scheme 44).[121] We believe that intermediate **129a** is unstable because no convincing examples of the synthesis and unambiguous characterization of Knoevenagel products synthesized from barbituric acids and isatins have been published so far.[132]



Scheme 44. Proposed reaction mechanism of formation of **118**.

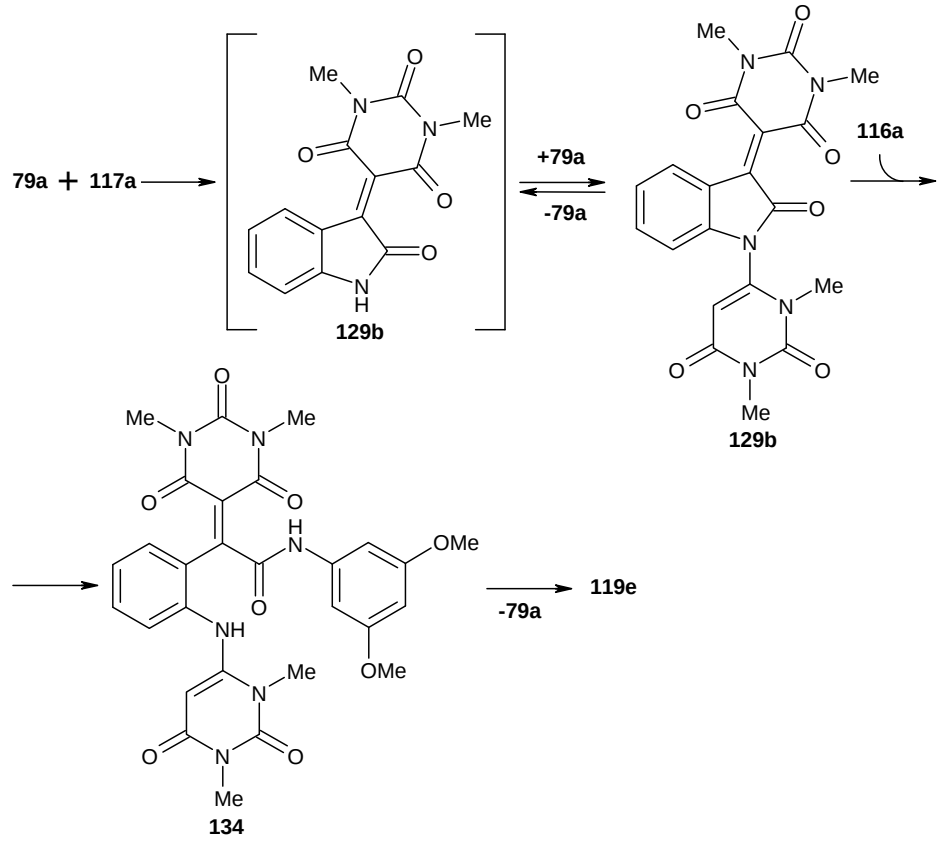
The formation of isomeric products **119** needs individual consideration. We have not established the exact mechanism, however, a reasonable suggestion is offered in Scheme 45. In fact, the alkyl group on the nitrogen protects isatin from the ring opening reaction. This in turn suggests that the amide carbonyl of isatin is activated during the reaction by attachment of an electron withdrawing group to the nitrogen atom. Then reamidation takes place and subsequent cyclocondensation leads to the final product **119e**. Normally, isatin and barbituric acid form the corresponding dibarbiturates **133**,[132] but we suppose the existence of an equilibrium between starting materials and intermediate **131**. The latter, being activated by a conjugated CO group, reacts rapidly with aniline. Normally, the isatin ring opens not easily, but *N*-acylderivatives[133-139] as

well as *N*-carbamides[140] (activated by isocyanates) and *N*-substituted isatins,[141] conjugated with a CO group via a double bond, react readily with amines and other nucleophiles with ring opening. It is interesting that the reamidation takes place also in the presence of other 1,3-dicarbonyl compounds[131] and substances similar to barbituric acid (Scheme 41 and 43).[129, 130] The first step definitely is deprotonation of the initial isatin. It is obvious that 5-nitroisatin forms an anion more easily than other isatins used in the current study. But on the other hand, delocalization of negative charge on the NO_2 group leads to significantly decreased nucleophilicity of the anion. Thus, it partially prevents formation of isomeric product **119l** or **v**.



Scheme 45. Proposed reaction mechanism of formation of **119** and possible intermediate **133**.

We also found that product **119e** can be obtained from dibarbiturate **133** under the same conditions. But the question still remains, whether compound **133** loses one or two molecules of barbituric acid **79a**, before deprotonation and subsequent alkylation of the amide nitrogen takes place. Of course, we cannot exclude the possibility that an adduct of one molecule of barbituric acid to isatin (Scheme 46) is the key intermediate.



Scheme 46. Product of Knoevenagel condensation between isatin and *N*,*N*-dimethylbarbituric acid (considered to be unstable[132]) as intermediate.

In any case, the exact mechanism of this transformation is still open to question.

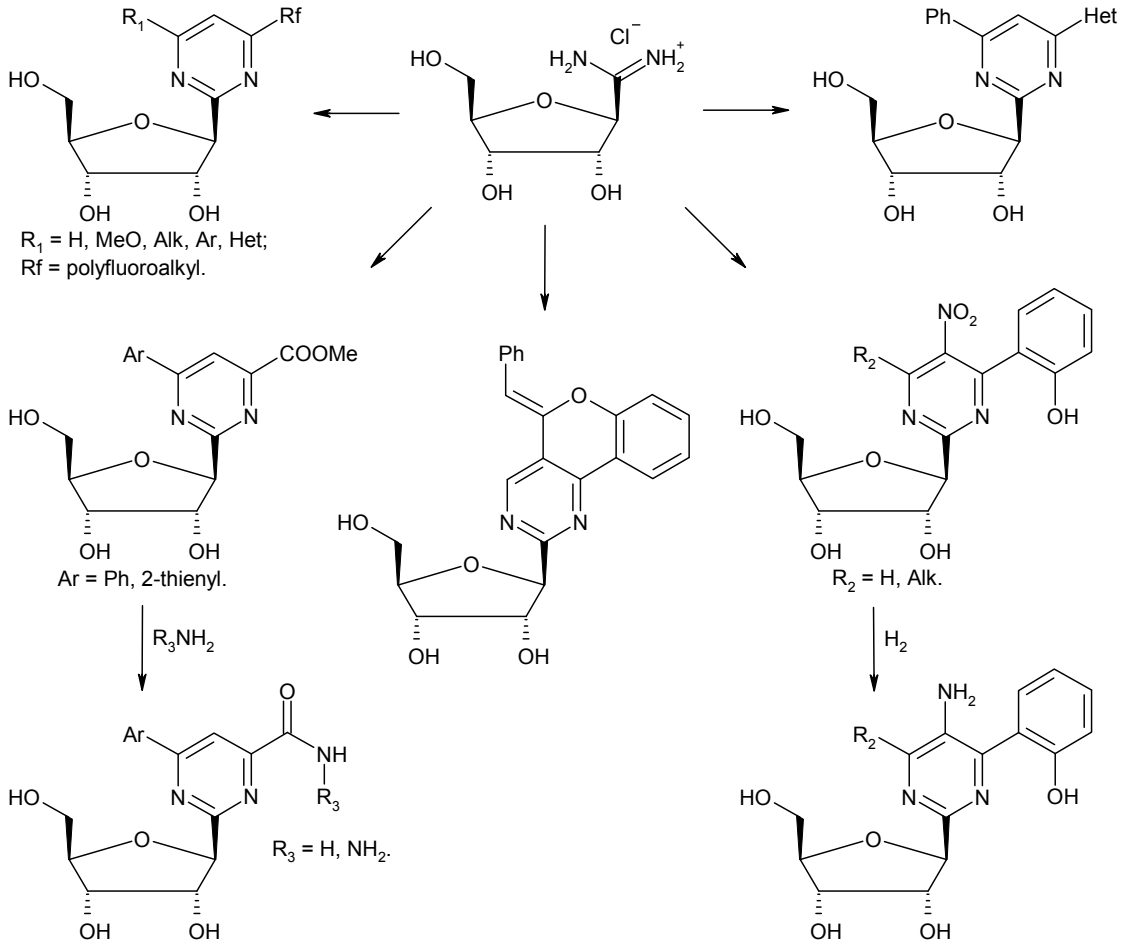
3.3 Conclusions

A novel and efficient synthesis of spiroindolinones via three-component reaction between (thio)barbituric acids, electron-rich anilines and isatins has been developed. The described reactions proceed in ethanolic media in the presence of iodine and constitute a simple, practical, and environmentally friendly method for obtaining heterocyclic compounds containing a spiroindole-3,5'-pyrimido[4,5-*b*]quinoline system. During the study, an unexpected recyclization related to the isatin ring opening was observed. A possible mechanistic pathway has been proposed.

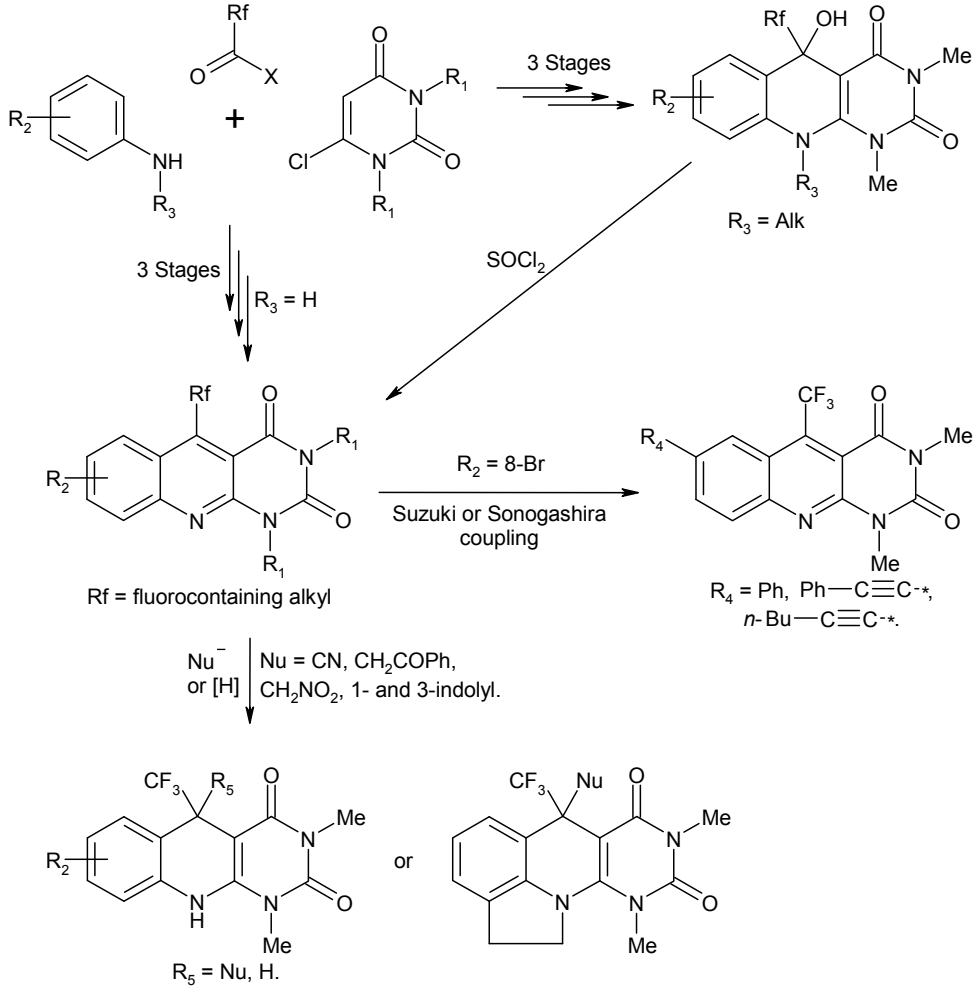
In addition, the combinatorial aspect of the developed synthetical approach can be useful in biologically-orientated syntheses and drug-discovery.

Examples **119a**, **119b**, **119c** and **119e** have been sent to be tested. The pharmacological evaluation is performed by Dr. M. Lalk (University of Greifswald).

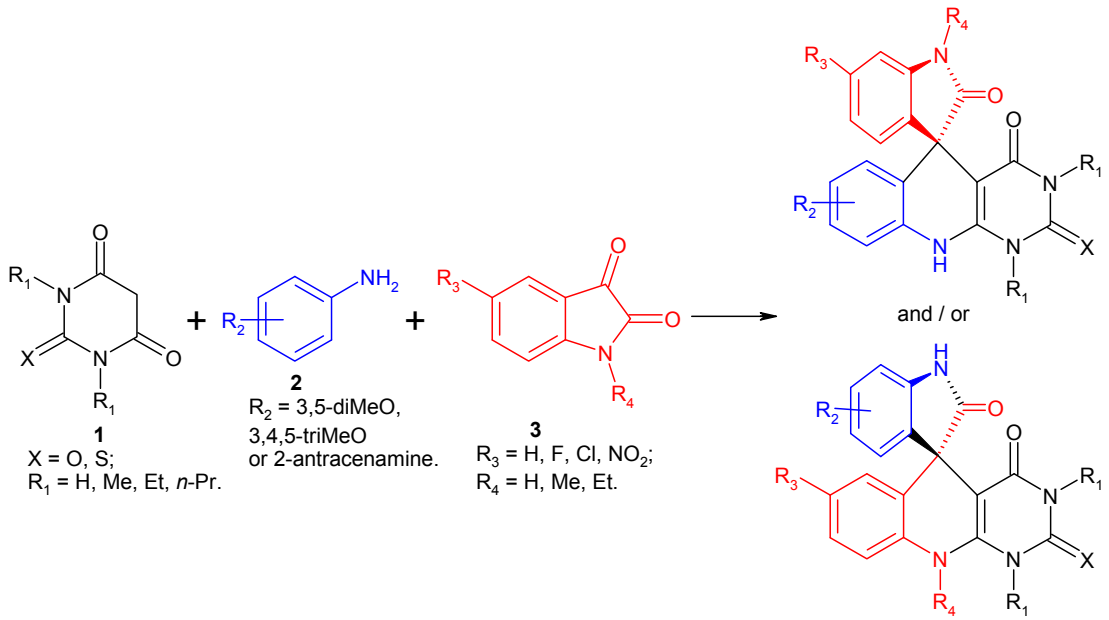
Graphical Overview



Scheme 47. To Chapter 1. Pyrimidine *C*-nucleosides.



Scheme 48. To Chapter 2. 5-Polyfluoroalkyl-5-deazaalloxazines.



Scheme 49. To Chapter 3. Spiro[pyrimido[4,5-*b*]quinoline-3',5-indoline-2'-one]-3,10-dihydro-2,4-diones.

4 Experimental Part

4.1 General: analytical equipment, chemicals and work technique

NMR Spectroscopy: ^{1}H NMR spectra (250.13, 300.13 and 500.13 MHz) and ^{13}C NMR spectra (62.90, 75.47 and 125.77 MHz) were recorded on Bruker instruments AVANCE 250, ARX 300, and AVANCE 500 respectively using CDCl3, DMSO-d_6 and CF_3COOD as solvents. The spectra were calibrated according to the solvent signals ($CDCl_3$: ^{1}H = 7.26, ^{13}C = 77.36; DMSO-d_6: ^{1}H = 2.54, ^{13}C = 40.45; CF_3COOD: ^{1}H = 11.50, ^{13}C = 116.60 (q, $^{1}J_{(C-F)}$ = 283.19 Hz) and 164.20 (q, $^{2}J_{(C-F)}$ = 43.99 Hz)). ^{19}F-NMR spectra were recorded at 235.33 or 282.38 MHz on AVANCE 250 and ARX 300 respectively considering $CFCl_3$-signal as a zero point of the scale. All chemical shifts are given in ppm. All coupling constants *J* are indicated in Hz.

Multiplicities are given as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal. More complex coupling patterns are represented by combinations of the respective symbols. For example, td indicates a triplet of doublets with the larger coupling constant associated with the first symbol (here: triplet).

The ^{1}H and ^{13}C NMR signals were assigned by DEPT and two-dimensional ^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY and ^{1}H-^{13}C correlation spectra (HMBC and HSQC).

Mass spectrometry (MS):

a) Finnigan MAT 95 XP (Thermo Electron Corporation), EI, 70 eV;

b) GC 6890/ MS D 5973 (Agilent Technologies), MS(GC), 70 eV.

High resolution MS (HRMS):

a) Finnigan MAT 95 XP (Thermo Electron Corporation), EI, 70 eV;

b) 6210 Time-of-Flight LC/MS (Agilent Technologies), ESI.

Only the measurements with an average deviation from the theoretical mass of ± 2 µDa were accounted as correct.

Infrared spectroscopy (IR): Nicolet 380 FT-IR spectrometer with ATR sampling technique for solids as well as liquids. Signal characterization: (w) = weak, (m) = medium, (s) = strong.

Elemental analysis (EA): Flash EA 1112 (Thermoquest).

X-ray crystallography: Bruker Apex Kappa-II diffraktometer with CCD camera (Mo-K_α radiation and graphite monochromator, λ = 0.71073 Å). The space group is determined by the

XPREP program and the structures were solved via the SHELX-97 program package. Refinements were carried out according to the minimum square error method.

UV/Vis spectroscopy: Lambda 2 (Perkin Elmer). Cuvette length l = 1 cm.

Fluorescence spectroscopy: HITACHI F-4010. Cuvette length l = 1 cm, cuvette width w = = 1 cm.

Thin layer chromatography (TLC): Merck HPTLC silica gel 60 F_{254} (aluminium sheets 20x20 cm). Detection with UV light at 254 and 366 nm; afterwards development with vanillin-sulfuric acid solution (1 g of vanillin, 14 mL of acetic acid and 1 mL of conc. sulfuric acid in 85 mL of methanol).

Melting Points: All the measurements were carried out on the FP900 Thermosystem (Mettler) using a polarized light microscope Laborlux 12 POL S (Leitz). The melting points are uncorrected.

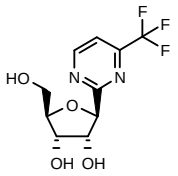
Column chromatography: Separation on Acros or Merck silica gel 60 Å (0.060-0.200 mm, 70-230 mesh). Eluents were distilled before use.

All chemicals were purchased from the standard chemical suppliers, such as Sigma-Aldrich®, Arcos®, Merck® and others.

4.2 General procedures and product characterisations

4.2.1 Synthesis of pyrimidine *C*-nucleosides

2-(*β*-D-Ribofuranosyl)-4-(trifluoromethyl)pyrimidine (16a)



Into a 25-mL flask were placed 0.3 g of 1-(*β*-D-ribofuranosyl)formamidine (1.41 mmol, 1 eq), 0.069 g of MeONa (1.27 mmol, 0.9 eq), 0.043 g of 1,8-diazabicyclo[5.4.0]undec-7-ene (0.282 mmol, 0.2 eq) and DMF (3 mL). Then 0.474 g of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one (2.82 mmol, 2 eq) was added and the reaction mixture was stirred at 80 °C for 3 hours under argon. After cooling to room temperature the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography: silica gel (120 g) / EtOAc (R_f = 0.08–0.14).

Yield 0.130 g (33%), white solid, mp 93-95 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.50-3.60 (m, 1H, H-5a'), 3.61-3.71 (m, 1H, H-5b'), 3.93-4.01 (m, 1H, H-4'), 4.02-4.11 (m, 1H, H-3'), 4.22-4.30 (m, 1H, H-2'), 4.70 (dd, 1H, $^3J_1$ = 6.61 Hz, $^3J_2$ = 4.72 Hz, OH-5'), 4.92 (d, 1H, ^3J = 4.72 Hz, H-1'), 5.04 (d, 1H, ^3J = 5.85 Hz, OH-3'), 5.28 (d, 1H, ^3J = 5.67 Hz, OH-2'), 8.02 (d, 1H, ^3J = 5.10 Hz, H-5), 9.25 (d, 1H, ^3J = 5.10 Hz, H-6).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 63.0 (CH_2OH), 72.3 (CH-3'), 76.8 (CH-2'), 86.1 (CH-4'), 86.5 (CH-1'), 117.3 (CH-5), 121.5 (q, $^1J_{(C\text{-}F)}$ = 275.2 Hz, CF_3), 154.9 (q, $^2J_{(C\text{-}F)}$ = 35.6 Hz, C-4), 162.1 (CH-6), 170.3 (C-2).

^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –68.6 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 280 ($[M]^+$, 0.36), 203 ($[M–CF_3]^+$, 11), 191 (100), 189 (18), 178 (17), 177 (33).

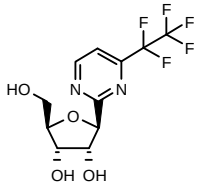
HRMS (ESI): Calcd. for $C_{10}H_{12}F_3N_2O_4$ $[M+H]^+$: 281.07437, found: 281.07441.

Anal. Calcd for $C_{10}H_{11}F_3N_2O_4$: C, 42.86; H, 3.96; N, 10.00. Found: C, 41.00; H, 3.68; N, 8.41.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3390 (m), 3153 (m), 2979 (w), 2929 (w), 2817 (w), 1588 (w), 1576 (m), 1462 (w), 1449 (w), 1418 (m), 1337 (s), 1320 (w), 1307 (m), 1295 (w), 1250 (w), 1225 (w), 1202 (m), 1171 (s), 1150 (s), 1119 (s), 1100 (m), 1079 (s), 1042 (m), 1002 (w), 975 (w), 909 (m), 887 (m), 851 (m), 800 (w), 761 (m), 719 (m), 703 (m), 677 (s), 649 (s), 586 (w), 542 (m), 528 (m).

2-(*β*-D-Ribofuranosyl)-4-(pentafluoroethyl)pyrimidine (16b)

Into a 25-mL flask were placed 0.2 g of 1-(*β*-D-ribofuranosyl)formamidine (0.94 mmol, 1 eq), 0.26 g of K_2CO_3 (1.88 mmol, 2 eq), molecular sieves 4Å (0.3 g) and DMF (4 mL). Then



0.205 g of 1-etoxy-4,4,5,5,5-pentafluoro-1-penten-3-one (0.94 mmol, 1 eq) was added at 0 °C and the reaction mixture was stirred at 60 °C for 4 hours under argon. After cooling to room temperature the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography: silica gel (75 g) / EtOAc (R_f = 0.09–0.21).

Yield 0.185 g (59%), white solid, mp 72 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.48-3.59 (m, 1H, H-5a'), 3.60-3.69 (m, 1H, H-5b'), 3.93-4.01 (m, 1H, H-4'), 4.03-4.10 (m, 1H, H-3'), 4.22-4.29 (m, 1H, H-2'), 4.67 (dd, 1H, $^3J_1$ = 6.42 Hz, $^3J_2$ = 4.91 Hz, OH-5'), 4.91 (d, 1H, ^3J = 4.53 Hz, H-1'), 5.04 (d, 1H, ^3J = 5.86 Hz, OH-3'), 5.28 (d, 1H, ^3J = 5.66 Hz, OH-2'), 8.07 (d, 1H, ^3J = 5.10 Hz, H-5), 9.26 (d, 1H, ^3J = 5.10 Hz, H-6).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 63.1 (CH_2OH), 72.5 (CH-3'), 76.8 (CH-2'), 86.1 (CH-4'), 86.5 (CH-1'), 118.8 (CH-5), 154.9 (t, $^2J_{(C-F)}$ = 26.4 Hz), 161.9 (CH-6), 170.2 (C-2).

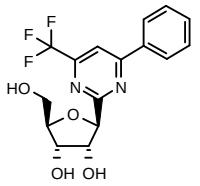
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –118.0 (q, J = 2.1 Hz, CF_2), –82.2 (t, J = 2.1 Hz, CF_3).

MS (GC, 70 eV): *m/z* (%) = 330 ([M]$^+$, 0.73), 253 (12), 241 (100), 239 (17), 228 (15), 227 (33).

HRMS (EI): Calcd. for $C_{11}H_{11}F_5N_2O_4$ [M]$^+$: 330.06335, found: 330.06274.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3419 (w), 3263 (m), 2945 (w), 2883 (w), 1574 (s), 1456 (m), 1435 (w), 1429 (w), 1423 (w), 1404 (m), 1385 (w), 1362 (w), 1335 (m), 1302 (m), 1277 (w), 1205 (s), 1159 (s), 1130 (s), 1107 (s), 1093 (s), 1051 (s), 1030 (s), 1014 (s), 999 (s), 984 (m), 947 (m), 933 (m), 895 (m), 874 (m), 847 (m), 833 (m), 797 (m), 770 (m), 735 (s), 690 (m), 681 (m), 667 (s), 635 (m), 615 (s), 534 (s).

2-(*β*-D-Ribofuranosyl)-4-phenyl-6-(trifluoromethyl)pyrimidine (19a)



Initial diketone was previously activated via conversion into corresponding *α,β*-unsaturated *β*-chloroketone:

To a solution of 4,4,4-trifluoro-1-phenylbutane-1,3-dione (2 g, 9.25 mmol, 1 eq) in chloroform (6 mL) was added 2.258 g of $SOCl_2$ (27.8 mmol, 3 eq), followed by the addition of DMF (0.034 g, 0.46 mmol, 0.05 eq). The mixture was refluxed for 3 hours. After that the solvent with an excess of $SOCl_2$ was evaporated, and the residue was distilled in a high vacuum to afford a green liquid consisting of mixture of isomers (1.994 g, 92%).

Into a 25-mL flask were placed 0.15 g of 1-(*β*-D-ribofuranosyl)formamidine (0.71 mmol, 1 eq), 0.39 g of K_2CO_3 (2.82 mmol, 4 eq) and DMF (3 mL). Then 0.182 g of the previously prepared *α,β*-unsaturated *β*-chloroketone (0.78 mmol, 1.1 eq) was added at 0 °C and the reaction was stirred at this temperature for the next 1½ hours. After that the mixture was allowed to stand at r.t.

overnight. The next day the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography: silica gel (40 g) / EtOAc (R_f = 0.30–0.39).

Yield 0.178 g (71%), light green solid, mp 77-78 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 4.73 (dd, 1H, ^2J = 12.28 Hz, ^3J = 1.32 Hz, H-5a'), 3.93 (br s, 3H, OH), 4.04 (dd, 1H, ^2J = 12.28 Hz, ^3J = 2.46 Hz, H-5b'), 4.28 (s 1H, H-4'), 4.41-4.50 (m, 2H, H-2', H-3'), 5.27 (d, 1H, ^3J = 2.65 Hz, H-1'), 7.45-7.60 (m, 3H, CH_{Ph}), 7.84 (s 1H, H-5), 7.99-8.08 (m 2H, CH_{Ph}).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 62.2 (CH_2OH), 71.6 (CH-3'), 78.0 (CH-2'), 85.2 (CH-4'), 85.9 (CH-1'), 111.9 (CH-5), 120.7 (q, $^1J_{(C-F)}$ = 275.6 Hz, CF_3), 127.9 (CH_{Ar}), 129.6 (CH_{Ar}), 132.7 (CH_{Ar}), 135.2, 156.5 (q, $^2J_{(C-F)}$ = 36.0 Hz, C-6), 167.8, 170.6.

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –69.8 (s, CF_3).

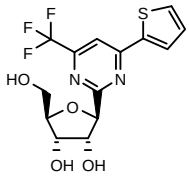
MS (GC, 70 eV): *m/z* (%) = 356 ($[M]^+$, 1.8), 268 (15), 267 (100), 253 (32).

HRMS (ESI): Calcd. for $C_{16}H_{16}F_3N_2O_4$ $[M+H]^+$: 357.10567, found: 357.10634.

Anal. Calcd for $C_{16}H_{15}F_3N_2O_4$: C, 53.94; H, 4.24; N, 7.86. Found: C, 54.70; H, 4.30; N, 7.10.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3354 (s), 3078 (w), 2925 (m), 2854 (w), 1595 (s), 1548 (s), 1501 (w), 1479 (w), 1454 (w), 1427 (w), 1388 (s), 1333 (w), 1282 (w), 1261 (s), 1207 (m), 1179 (s), 1136 (s), 1100 (s), 1078 (s), 1051 (s), 1025 (s), 1001 (m), 990 (m), 943 (m), 929 (m), 880 (m), 833 (m), 802 (w), 770 (s), 750 (m), 711 (m), 687 (s), 666 (m), 633 (s), 596 (m), 573 (m), 548 (s).

2-(*β*-D-Ribofuranosyl)-4-(2-thienyl)-6-(trifluoromethyl)pyrimidine (19b)



Initial diketone was previously activated via conversion into corresponding *α*,*β*-unsaturated *β*-chloroketone:

To a solution of 4,4,4-trifluoro-1-(2-thienyl)butane-1,3-dione (2 g, 9.00 mmol, 1 eq) in chloroform (6 mL) was added 3.213 g of $SOCl_2$ (27.0 mmol, 3 eq), followed by the addition of DMF (0.033 g, 0.4 mmol, 0.05 eq). The mixture was refluxed for 3 hours. After that the solvent with an excess of $SOCl_2$ was evaporated, and the residue was distilled in a high vacuum to afford a yellow-green liquid consisting of mixture of isomers (1.772 g, 81%). The product partially crystallized at r.t..

Into a 25-mL flask were placed 0.15 g of 1-(*β*-D-ribofuranosyl)formamidine (0.71 mmol, 1 eq), 0.39 g of K_2CO_3 (2.82 mmol, 4 eq) and DMF (3 mL). Then 0.187 g of the previously prepared *α*,*β*-unsaturated *β*-chloroketone (0.78 mmol, 1.1 eq) was added at 0 °C and the reaction was stirred at this temperature for the next 2 hours. After that the mixture was allowed to stand at r.t. overnight. The next day the inorganic precipitate was filtered off and the filtrate was evaporated under reduced

pressure. The crude product was purified by column chromatography: silica gel (65 g) / EtOAc (R_f = 0.31–0.36).

Yield 0.187 g (73%), white solid, mp 165-167 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.57-3.67 (m, 1H, H-5a'), 3.67-3.77 (m, 1H, H-5b'), 3.95-4.04 (m, 1H, H-4'), 4.09-4.18 (m, 1H, H-3'), 4.24-4.32 (m, 1H, H-2'), 4.66 (dd, 1H, $^3J_1$ = 6.52 Hz, $^3J_2$ = 5.01 Hz, OH-5'), 4.89 (d, 1H, ^3J = 3.96 Hz, H-1'), 5.03 (d, 1H, ^3J = 6.04 Hz, OH-3'), 5.32 (d, 1H, ^3J = 5.47 Hz, OH-2'), 7.36 (dd, 1H, $^3J_1$ = 4.91 Hz, $^3J_2$ = 3.78 Hz, H-4''), 8.02 (dd, 1H, ^3J = 4.91 Hz, ^4J = 1.13 Hz, H-3''), 8.41 (dd, 1H, ^3J = 3.78 Hz, ^4J = 1.13 Hz, H-5''), 8.47 (s, 1H, H-5).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 63.4 (CH_2OH), 72.6 (CH-3'), 76.7 (CH-2'), 85.9 (CH-4'), 86.7 (CH-1'), 111.2 (CH-5), 121.7 (q, $^1J_{(C-F)}$ = 275.4 Hz, CF_3), 130.3 (CH_{Ar}), 132.4 (CH_{Ar}), 134.4 (CH_{Ar}), 141.5, 155.6 (q, $^2J_{(C-F)}$ = 35.2 Hz, C-6), 162.6, 170.6.

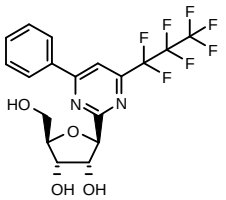
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –68.5 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 362 ([M]$^+$, 0.51), 274 (15), 273 (100), 271 (12), 259 (29).

HRMS (ESI): Calcd. for $C_{14}H_{14}F_3N_2O_4S$ [M+H]$^+$: 363.06209, found: 363.06229.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3511 (w), 3251 (s), 3114 (w), 2930 (w), 2878 (w), 1603 (s), 1575 (w), 1547 (m), 1529 (m), 1504 (w), 1494 (w), 1463 (w), 1455 (w), 1418 (s), 1396 (m), 1382 (m), 1347 (w), 1316 (w), 1290 (m), 1270 (s), 1229 (m), 1210 (m), 1168 (s), 1149 (s), 1137 (s), 1103 (s), 1092 (s), 1074 (s), 1067 (s), 1049 (s), 1038 (s), 1020 (s), 994 (m), 984 (m), 941 (m), 930 (m), 879 (m), 864 (m), 855 (m), 802 (m), 793 (m), 767 (m), 752 (s), 743 (m), 731 (s), 701 (s), 684 (s), 667 (m), 631 (s), 592 (m), 568 (m), 544 (m).

2-(*β*-D-Ribofuranosyl)-4-(heptafluoropropyl)-6-phenylpyrimidine (19c)



Initial diketone was previously activated via conversion into corresponding *α,β*-unsaturated *β*-chloroketone:

To a solution of 4,4,5,5,6,6,6-heptafluoro-1-phenylhexane-1,3-dione (2 g, 6.33 mmol, 1 eq) in chloroform (6 mL) was added 2.258 g of $SOCl_2$ (19.0 mmol, 3 eq), followed by the addition of DMF (0.023 g, 0.32 mmol, 0.05 eq). The mixture was refluxed for 3 hours. After that the solvent with an excess of $SOCl_2$ was evaporated, and the residue was distilled in a high vacuum to afford a green liquid consisting of single isomer (1.973 g, 93%).

Into a 25-mL flask were placed 0.15 g of 1-(*β*-D-ribofuranosyl)formamidine (0.71 mmol, 1 eq), 0.39 g of K_2CO_3 (2.82 mmol, 4 eq) and DMF (3 mL). Then 0.260 g of the previously prepared *α,β*-unsaturated *β*-chloroketone (0.78 mmol, 1.1 eq) was added at 0 °C and the reaction was stirred at this temperature for the next 2 hours. After that the mixture was allowed to stand at r.t. overnight. The next day the inorganic precipitate was filtered off and the filtrate was evaporated under reduced

pressure. The crude product was purified by column chromatography: silica gel (50 g) / EtOAc : $CHCl_3$ = 1:2, then pure EtOAc (R_f = 0.38–0.48).

Yield 0.176 g (55%), white solid, mp 124 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.39 (br s, 3H, OH), 3.74 (d, 1H, ^2J = 12.27 Hz, H-5a'), 4.04 (d, 1H, ^2J = 12.27 Hz, H-5b'), 4.30 (s, 1H, H-4'), 4.42-4.52 (m, 2H, H-2', H-3'), 5.29 (d 1H, ^3J = 2.83 Hz, H-1'), 7.48-7.62 (m, 3H, CH_{Ph}), 7.89 (s, 1H, H-5), 8.03-8.12 (m, 2H, CH_{Ph}).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 62.4 (CH_2OH), 72.0 (CH-3'), 78.3 (CH-2'), 85.6 (CH-4'), 85.9 (CH-1'), 113.9 (CH-5), 128.0 (CH_{Ar}), 129.7 (CH_{Ar}), 132.8 (CH_{Ar}), 135.3, 156.8 (t, $^2J_{(C-F)}$ = 26.4 Hz, C-4), 167.6, 170.6.

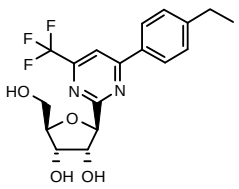
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –126.1 (m, CF_2), –116.9 (m, CF_2), –80.0 (t, J = 9.20 Hz, CF_3).

MS (EI, 70 eV): *m/z* (%) = 456 ($[M]^+$, 14), 425 (16), 407 (14), 383 (10), 379 (27), 368 (69), 367 (100), 366 (16), 365 (46), 355 (11), 354 (45), 353 (79), 351 (16), 339 (14), 338 (31), 325 (15), 206 (16), 128 (18), 103 (29).

HRMS (ESI): Calcd. for $C_{18}H_{16}F_7N_2O_4$ $[M+H]^+$: 457.09928, found: 457.09909.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3457 (s), 3409 (m), 3099 (w), 2942 (w), 1587 (s), 1542 (m), 1498 (w), 1452 (w), 1411 (w), 1392 (w), 1376 (m), 1349 (m), 1338 (m), 1302 (w), 1278 (m), 1233 (s), 1204 (s), 1181 (s), 1160 (m), 1127 (m), 1108 (s), 1084 (s), 1074 (s), 1055 (m), 1040 (m), 1027 (m), 1001 (m), 983 (w), 974 (w), 961 (m), 929 (w), 917 (s), 890 (m), 874 (s), 797 (m), 776 (m), 767 (m), 744 (s), 734 (s), 692 (s), 665 (m), 637 (s), 613 (m), 601 (m), 580 (m), 557 (m), 543 (s).

2-(*β*-D-Ribofuranosyl)-4-(4-ethylphenyl)-6-(trifluoromethyl)pyrimidine (19d)



Initial diketone was previously activated via conversion into corresponding *α,β*-unsaturated *β*-chloroketone:

To a solution of 1-(4-ethylphenyl)-4,4,4-trifluorobutane-1,3-dione (2 g, 8.19 mmol, 1 eq) in chloroform (6 mL) was added 2.923 g of $SOCl_2$ (24.6 mmol, 3 eq), followed by the addition of DMF (0.03 g, 0.4 mmol, 0.05 eq). The mixture was refluxed for 3 hours. After that the solvent with an excess of $SOCl_2$ was evaporated, and the residue was distilled in a high vacuum to afford a green liquid consisting of mixture of isomers (2.120 g, 99%).

Into a 25-mL flask were placed 0.2 g of 1-(*β*-D-ribofuranosyl)formamidine (0.94 mmol, 1 eq), 0.26 g of K_2CO_3 (3.76 mmol, 4 eq), molecular sieves 4Å (0.3 g) and DMF (4 mL). Then 0.272 g of the previously prepared *α,β*-unsaturated *β*-chloroketone (1.03 mmol, 1.1 eq) was added at 0 °C and the reaction was stirred at this temperature for the next 2 hours. After that the mixture was allowed to stand at r.t. overnight. The next day the inorganic precipitate was filtered off and the

filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography: silica gel (50 g) / EtOAc : $CHCl_3$ = 1:1 (R_f = 0.09–0.14).

Yield 0.152 g (42%), white solid, mp 89 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.27 (t, 3H, ^3J = 7.56 Hz, Et), 2.75 (q, 2H, ^3J = 7.56 Hz, Et), 3.61 (dd, 1H, ^2J = 11.52 Hz, ^3J = 4.53 Hz, H-5a'), 3.72 (dd, 1H, ^2J = 11.52 Hz, ^3J = 4.06 Hz, H-5b'), 3.97-4.05 (m, 1H, H-4'), 4.12-4.21 (m, 1H, H-3'), 4.31-4.38 (m, 1H, H-2'), 4.71 (s, 1H, OH-5'), 4.97 (d, 1H, ^3J = 4.34 Hz, H-1'), 5.04 (s, 1H, OH-3'), 5.31 (s, 1H, OH-2'), 7.48 (d, 2H, ^3J = 8.40 Hz, H-3'', H-5''), 8.32 (d, 2H, ^3J = 8.40 Hz, H-2'', H-6''), 8.48 (s, 1H, H-5).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 16.2 (CH_3), 29.0 (CH_2), 63.1 (CH_2OH), 72.5 (CH-3'), 76.7 (CH-2'), 85.9 (CH-4'), 86.8 (CH-1'), 112.5 (CH-5), 121.7 (q, $^1J_{(C-F)}$ = 275.7 Hz, CF_3), 128.8 (CH_{Ar}), 129.6 (CH_{Ar}), 133.4, 149.7, 155.9 (q, $^2J_{(C-F)}$ = 35.1 Hz, C-6), 167.4, 170.5.

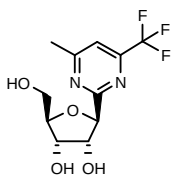
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –68.3 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 349 (15), 348 (89), 347 (14), 332 (22), 331 (32), 329 (11), 320 (21), 319 (100), 291 (32), 252 (27).

HRMS (ESI): Calcd. for $C_{18}H_{20}F_3N_2O_4$ $[M+H]^+$: 385.1370, found: 385.1374.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3313 (m), 2964 (w), 2931 (w), 2874 (w), 1595 (s), 1543 (m), 1514 (w), 1495 (w), 1460 (w), 1435 (m), 1390 (s), 1286 (m), 1263 (s), 1209 (m), 1178 (s), 1147 (s), 1099 (s), 1078 (s), 1049 (s), 1026 (s), 991 (s), 943 (m), 930 (m), 881 (m), 874 (m), 862 (m), 839 (s), 800 (m), 777 (m), 762 (m), 741 (m), 706 (s), 683 (s), 658 (m), 636 (s), 581 (s), 550 (s).

2-(*β*-D-Ribofuranosyl)-4-methyl-6-(trifluoromethyl)pyrimidine (19e)



Initial diketone was previously activated via conversion into corresponding *α*,*β*-unsaturated *β*-chloroketone:

In 15 mL of DCM were dissolved 2 g of 1,1,1-trifluoropentane-2,4-dione (13.0 mmol, 1 eq) and 1.233 g of DMF (16.9 mmol, 1.3 eq). Then the solution was cooled to –78 °C and oxalyl chloride (1.977 g, 15.6 mmol, 1.2 eq) was added. After that the mixture was carefully heated to r.t. (gas evaluation!) and allowed to stand at this temperature for 2 hours. Afterwards the reaction mixture was diluted with ice water. The organic layer was separated and water phase was extracted twice with DCM. Combined organic layers were dried over sodium sulfate and evaporated. The residue was distilled in vacuum to afford a colorless liquid consisting of mixture of isomers (1.155 g, 52%).

Into a 25-mL flask were placed 0.2 g of 1-(*β*-D-ribofuranosyl)formamidine (0.94 mmol, 1 eq), 0.26 g of K_2CO_3 (3.76 mmol, 4 eq), molecular sieves 4Å (0.3 g) and DMF (4 mL). Then 0.179 g of the previously prepared *α*,*β*-unsaturated *β*-chloroketone (1.03 mmol, 1.1 eq) was added at 0 °C and the reaction was stirred at this temperature for the next 2 hours. After that the mixture was

allowed to stand at r.t. overnight. The next day the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography: silica gel (50 g) / EtOAc (R_f = 0.16–0.22).

Yield 0.158 g (57%), white solid, mp 138-139 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.66 (s, 3H, CH_3), 3.51-3.62 (m, 1H, H-5a'), 3.65-3.74 (m, 1H, H-5b'), 3.94-4.02 (m, 1H, H-4'), 4.04-4.12 (m, 1H, H-3'), 4.19-4.26 (m, 1H, H-2'), 4.77 (dd, 1H, $^3J_1$ = 7.18 Hz, $^3J_2$ = 4.16 Hz, OH-5'), 4.88 (d, 1H, ^3J = 4.15 Hz, H-1'), 5.02 (d, 1H, ^3J = 5.85 Hz, OH-3'), 5.29 (d, 1H, ^3J = 5.66 Hz, OH-2'), 7.94 (s, 1H, H-5).

^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 25.0 (CH_3), 62.8 (CH_2OH), 72.0 (CH-3'), 76.7 (CH-2'), 85.8 (CH-4'), 86.5 (CH-1'), 116.8 (CH-5), 121.6 (q, $^1J_{(C\text{-}F)}$ = 275.1 Hz, CF_3), 154.5 (q, $^2J_{(C\text{-}F)}$ = 35.1 Hz, C-6), 170.0, 172.3.

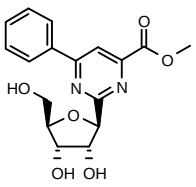
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –68.6 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 294 ([M]$^+$, 0.46), 206 (11), 205 (100), 203 (17), 192 (11), 191 (37).

HRMS (ESI): Calcd. for $C_{11}H_{13}F_3N_2NaO_4$ [M+Na]$^+$: 317.07196, found: 317.07175.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3321 (m), 3207 (m), 2912 (w), 1601 (m), 1564 (m), 1433 (m), 1398 (s), 1377 (m), 1321 (m), 1308 (m), 1284 (m), 1242 (s), 1203 (m), 1171 (s), 1149 (s), 1130 (s), 1119 (s), 1097 (s), 1084 (s), 1049 (s), 1028 (s), 1001 (m), 982 (m), 962 (m), 933 (m), 885 (s), 876 (s), 866 (s), 804 (m), 777 (m), 750 (m), 717 (m), 696 (m), 683 (m), 644 (m), 554 (s).

Methyl 2-(*β*-D-ribofuranosyl)-6-phenylpyrimidine-4-carboxylate (19f)



Initial diketone was previously activated via conversion into corresponding *α,β*-unsaturated *β*-chloroketone:

In 15 mL of DCM were dissolved 1 g of methyl 2,4-dioxo-4-phenylbutanoate (4.84 mmol, 1 eq) and 0.745 g of DMF (10.2 mmol, 2.1 eq). Then the solution was cooled to –78 °C and oxalyl chloride (0.739 g, 5.82 mmol, 1.2 eq) was added. After that the mixture was carefully heated to r.t. (gas evaluation!) and allowed to stand at this temperature for 2 hours. Afterwards the reaction mixture was diluted with ice water. The organic layer was separated and water phase was extracted twice with DCM. Combined organic layers were dried over sodium sulfate and evaporated. The residue was distilled in high vacuum to afford a yellow liquid consisting of mixture of isomers (1.056 g, 97%).

Into a 25-mL flask were placed 0.2 g of 1-(*β*-D-ribofuranosyl)formamidine (0.94 mmol, 1 eq), 0.520 g of K_2CO_3 (3.76 mmol, 4 eq), molecular sieves 4Å (0.3 g) and DMF (4 mL). Then 0.232 g of the previously prepared *α,β*-unsaturated *β*-chloroketone (1.03 mmol, 1.1 eq) was added at 0 °C and the reaction was stirred at this temperature for the next 2 hours. After that the mixture was

allowed to stand at r.t. overnight. The next day the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography: silica gel (30 g) / EtOAc (R_f = 0.06–0.13).

Yield 0.108 g (33%), white solid, mp 132-134 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.57-3.68 (m, 1H, H-5a'), 3.71-3.80 (m, 1H, H-5b'), 4.00 (s, 3H, MeO), 4.00-4.06 (m, 1H, H-4'), 4.14-4.22 (m, 1H, H-3'), 4.30-4.37 (m, 1H, H-2'), 4.80 (dd, 1H, $^3J_1$ = 7.37 Hz, $^3J_2$ = 4.35 Hz, OH-5'), 5.00 (d, 1H, ^3J = 4.16 Hz, H-1'), 5.02 (d, 1H, ^3J = 6.04 Hz, OH-3'), 5.31 (d, 1H, ^3J = 5.67 Hz, OH-2'), 7.59-7.70 (m, 3H, H_{Ph}), 8.28-8.35 (m, 2H, H_{Ph}), 8.45 (s, 1H, H-5).

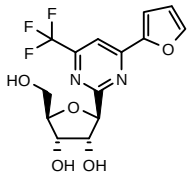
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 54.0 (OMe), 63.0 (CH_2OH), 72.2 (CH-3'), 76.9 (CH-2'), 85.8 (CH-4'), 87.0 (CH-1'), 115.9 (CH-5), 128.4 (CH_{Ph}), 130.1 (CH_{Ph}), 132.8 (CH_{Ph}), 136.3, 156.6, 165.2, 166.6, 170.3.

MS (EI, 70 eV): *m/z* (%) = 245 (11), 234 (21), 233 (89), 231 (25), 220 (17), 219 (100), 217 (14).

HRMS (ESI): Calcd. for $C_{17}H_{19}N_2O_6$ $[M+H]^+$: 347.12376, found: 347.12335.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3257 (m), 2937 (w), 1732 (s), 1589 (s), 1539 (s), 1504 (w), 1497 (w), 1452 (m), 1441 (m), 1416 (m), 1373 (s), 1336 (m), 1281 (m), 1255 (s), 1198 (s), 1149 (m), 1105 (s), 1086 (s), 1074 (s), 1049 (s), 1028 (s), 1003 (s), 991 (m), 980 (m), 947 (s), 935 (m), 914 (m), 903 (m), 895 (m), 868 (m), 849 (m), 802 (m), 777 (m), 768 (m), 754 (s), 721 (s), 687 (s), 633 (s), 548 (s).

2-(*β*-D-Ribofuranosyl)-4-(2-furyl)-6-(trifluoromethyl)pyrimidine (19g)



Initial diketone was previously activated via conversion into corresponding *α*,*β*-unsaturated *β*-chloroketone:

In 15 mL of DCM were dissolved 1 g of 4,4,4-trifluoro-1-(2-furyl)butane-1,3-dione (4.85 mmol, 1 eq) and 0.745 g of DMF (10.2 mmol, 2.1 eq). Then the solution was cooled to –78 °C and oxalyl chloride (0.739 g, 5.82 mmol, 1.2 eq) was added. After that the mixture was carefully heated to r.t. (gas evaluation!) and allowed to stand at this temperature for 2 hours. Afterwards the reaction mixture was diluted with ice water. The organic layer was separated and water phase was extracted twice with DCM. Combined organic layers were dried over sodium sulfate and evaporated. The residue was distilled in vacuum to afford a brownish liquid consisting of mixture of isomers (0.962 g, 88%). The product partially crystallized at r.t..

Into a 25-mL flask were placed 0.2 g of 1-(*β*-D-ribofuranosyl)formamidine (0.94 mmol, 1 eq), 0.26 g of K_2CO_3 (3.76 mmol, 4 eq), molecular sieves 4Å (0.3 g) and DMF (4 mL). Then 0.232

g of the previously prepared *α*,*β*-unsaturated *β*-chloroketone (1.03 mmol, 1.1 eq) was added at 0 °C and the reaction was stirred at this temperature for the next 2 hours. After that the mixture was allowed to stand at r.t. overnight. The next day the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography: silica gel (50 g) / EtOAc (R_f = 0.26–0.34).

Yield 0.220 g (67%), white solid, mp 102-103 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.56-3.67 (m, 1H, H-5a'), 3.69-3.79 (m, 1H, H-5b'), 3.98-4.06 (m, 1H, H-4'), 4.09-4.18 (m, 1H, H-3'), 4.24-4.32 (m, 1H, H-2'), 4.75 (dd, 1H, $^3J_1$ = 7.18 Hz, $^3J_2$ = 4.35 Hz, OH-5'), 4.94 (d, 1H, ^3J = 3.97 Hz, H-1'), 5.03 (d, 1H, ^3J = 6.04 Hz, OH-3'), 5.36 (d, 1H, ^3J = 5.47 Hz, OH-2'), 6.87 (dd, 1H, $^3J_1$ = 3.59 Hz, $^3J_2$ = 1.70 Hz, H-4''), 7.72 (dd, 1H, ^3J = 3.50 Hz, ^4J = 0.67 Hz, H-3''), 8.12-8.16 (m, 2H, H-5, H-5'').

^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 62.9 (CH_2OH), 72.1 (CH-3'), 76.8 (CH-2'), 85.8 (CH-4'), 86.7 (CH-1'), 110.6 (CH_{Ar}), 114.4 (CH-5), 116.9 (CH_{Ar}), 121.5 (q, $^1J_{(C\text{-}F)}$ = 275.3 Hz, CF_3), 148.8 (CH_{Ar}), 150.8, 155.7 (q, $^2J_{(C\text{-}F)}$ = 35.3 Hz, C-6), 158.2, 170.9.

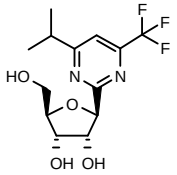
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –68.7 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 346 ($[M]^+$, 1.14), 258 (18), 257 (100), 255 (16), 243 (50).

HRMS (ESI): Calcd. for $C_{14}H_{14}F_3N_2O_5$ $[M+H]^+$: 347.08493, found: 347.08476.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3356 (m), 3103 (w), 1606 (s), 1599 (s), 1543 (m), 1479 (s), 1435 (m), 1423 (w), 1396 (m), 1371 (s), 1335 (w), 1317 (m), 1298 (m), 1267 (s), 1228 (m), 1215 (m), 1190 (m), 1178 (s), 1153 (s), 1138 (s), 1107 (s), 1076 (s), 1057 (s), 1026 (s), 991 (s), 932 (m), 918 (w), 891 (s), 885 (s), 874 (m), 851 (m), 808 (s), 795 (m), 768 (s), 760 (s), 743 (s), 704 (s), 687 (s), 648 (s), 608 (s), 592 (s), 548 (s).

2-(*β*-D-Ribofuranosyl)-4-isopropyl-6-(trifluoromethyl)pyrimidine (19h)



Initial diketone was previously activated via conversion into corresponding *α*,*β*-unsaturated *β*-chloroketone:

In 15 mL of DCM were dissolved 2 g of 1,1,1-trifluoro-5-methylhexane-2,4-dione (10.9 mmol, 1 eq) and 1.043 g of DMF (14.3 mmol, 1.3 eq). Then the solution was cooled to –78 °C and oxalyl chloride (1.673 g, 13.2 mmol, 1.2 eq) was added. After that the mixture was carefully heated to r.t. (gas evaluation!) and allowed to stand at this temperature for 2 hours. Afterwards the reaction mixture was diluted with ice water. The organic layer was separated and water phase was extracted twice with DCM. Combined organic layers were dried over sodium sulfate and evaporated. The residue was distilled in vacuum to afford a colorless liquid consisting of mixture of isomers (1.396 g, 63%).

Into a 25-mL flask were placed 0.2 g of 1-(*β*-D-ribofuranosyl)formamidine (0.94 mmol, 1

eq), 0.26 g of K_2CO_3 (3.76 mmol, 4 eq), molecular sieves 4Å (0.3 g) and DMF (4 mL). Then 0.218 g of the previously prepared *α,β*-unsaturated *β*-chloroketone (1.03 mmol, 1.1 eq) was added at 0 °C and the reaction was stirred at this temperature for the next 2 hours. After that the mixture was allowed to stand at r.t. overnight. The next day the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography: silica gel (50 g) / EtOAc (R_f = 0.31–0.39).

Yield 0.167 g (55%), white solid, mp 65-67 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.30 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 3.21 (sept, 1H, i-Pr), 3.51-3.62 (m, 1H, H-5a'), 3.65-3.74 (m, 1H, H-5b'), 3.95-4.02 (m, 1H, H-4'), 4.07-4.15 (m, 1H, H-3'), 4.21-4.28 (m, 1H, H-2'), 4.72 (dd, 1H, $^3J_1$ = 7.09 Hz, $^3J_2$ = 4.44 Hz, OH-5'), 4.90 (d, 1H, ^3J = 3.97 Hz, H-1'), 5.02 (d, 1H, ^3J = 6.04 Hz, OH-3'), 5.29 (d, 1H, ^3J = 5.67 Hz, OH-2'), 7.93 (s, 1H, H-5).

^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –68.4 (s, CF_3).

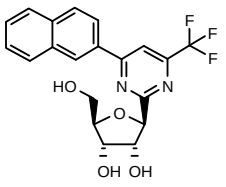
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 22.2 (CH_3), 22.2 (CH_3), 36.5 (CH_{Pr}), 63.0 (CH_2OH), 72.3 (CH-3'), 76.9 (CH-2'), 85.8 (CH-4'), 86.8 (CH-1'), 114.8 (CH-5), 121.7 (q, $^1J_{(C-F)}$ = 275.3 Hz, CF_3), 155.0 (q, $^2J_{(C-F)}$ = 35.1 Hz, C-6), 170.2, 180.3.

MS (EI, 70 eV): *m/z* (%) = 322 ([M]$^+$, 2.47), 245 (11), 234 (21), 233 (89), 231 (25), 220 (18), 219 (100), 217 (14).

HRMS (ESI): Calcd. for $C_{13}H_{18}F_3N_2O_4$ $[M+H]^+$: 323.12132, found: 323.12123.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3317 (m), 2962 (w), 2918 (m), 2881 (w), 1601 (m), 1585 (m), 1558 (s), 1470 (w), 1456 (w), 1431 (m), 1398 (m), 1379 (m), 1333 (s), 1302 (m), 1242 (s), 1223 (m), 1194 (m), 1176 (s), 1138 (s), 1119 (s), 1097 (s), 1049 (s), 1028 (s), 987 (m), 953 (m), 935 (m), 903 (m), 887 (s), 874 (s), 843 (m), 831 (m), 808 (m), 771 (s), 748 (m), 716 (s), 687 (s), 667 (s), 642 (s), 550 (m).

2-(*β*-D-Ribofuranosyl)-4-(2-naphthyl)-6-(trifluoromethyl)pyrimidine (19i)



Initial diketone was previously activated via conversion into corresponding *α,β*-unsaturated *β*-chloroketone:

To a solution of 4,4,4-trifluoro-1-(2-naphthyl)butane-1,3-dione (1 g, 3.76 mmol, 1 eq) in chloroform (3 mL) was added 1.341 g of $SOCl_2$ (11.3 mmol, 3 eq), followed by the addition of DMF (0.014 g, 0.18 mmol, 0.05 eq). The mixture was refluxed for 3 hours. After that the solvent with an excess of $SOCl_2$ was evaporated, and the residue was distilled in a high vacuum to afford a yellow liquid consisting of mixture of isomers (0.611 g, 57%).

Into a 25-mL flask were placed 0.2 g of 1-(*β*-D-ribofuranosyl)formamidine (0.94 mmol, 1

eq), 0.52 g of K_2CO_3 (3.76 mmol, 4 eq), molecular sieves 4Å (0.3 g) and DMF (4 mL). Then 0.295 g of the previously prepared *α,β*-unsaturated *β*-chloroketone (1.03 mmol, 1.1 eq) was added at 0 °C and the reaction was stirred at this temperature for the next 2 hours. After that the mixture was allowed to stand at r.t. overnight. The next day the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography: silica gel (50 g) / $CHCl_3$, mixture EtOAc : $CHCl_3$ = 1:1. R_f = 0.28–0.35 (in EtOAc).

Yield 0.144 g (38%), white solid, mp 192-193 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.61-3.72 (m, 1H, H-5a'), 3.72-3.82 (m, 1H, H-5b'), 4.02-4.09 (m, 1H, H-4'), 4.18-4.25 (m, 1H, H-3'), 4.37-4.45 (m, 1H, H-2'), 4.76 (dd, 1H, $^3J_1$ = 6.52 Hz, $^3J_2$ = 4.52 Hz, OH-5'), 5.04 (d, 1H, ^3J = 4.34 Hz, H-1'), 5.08 (d, 1H, ^3J = 6.04 Hz, OH-3'), 5.36 (d, 1H, ^3J = 5.67 Hz, OH-2'), 7.63-7.74 (m, 2H, H_{Naph}), 8.03-8.09 (s, 1H, H_{Naph}), 8.12-8.19 (m, 2H, H_{Naph}), 8.47 (dd, 2H, ^3J = 8.78 Hz, ^4J = 1.79 Hz, H_{Naph}), 8.69 (s, 1H, H-5), 9.06 (d, 1H, ^4J = 1.51 Hz, H_{Naph}).

^{13}C NMR (125.77 MHz, DMSO-d_6): δ = 63.1 (CH_2OH), 72.5 (CH-3'), 76.7 (CH-2'), 86.0 (CH-4'), 86.8 (CH-1'), 113.1 (CH-5), 121.8 (q, $^1J_{(C-F)}$ = 275.6 Hz, CF_3), 124.8 (CH_{Ar}), 128.0 (CH_{Ar}), 128.6 (CH_{Ar}), 129.2 (CH_{Ar}), 129.7 (CH_{Ar}), 129.7 (CH_{Ar}), 130.1 (CH_{Ar}), 133.2, 133.6, 135.6, 156.0 (q, $^2J_{(C-F)}$ = 35.2 Hz, C-6), 167.3, 170.6.

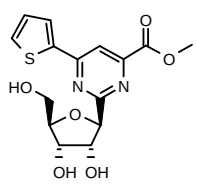
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –68.26 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 406 ($[M]^+$, 1.71), 371 (10), 370 (44), 341 (41), 340 (17), 318 (17), 317 (100), 313 (11), 303 (25), 274 (14), 153 (13), 152 (13).

HRMS (ESI): Calcd. for $C_{20}H_{18}F_3N_2O_4$ $[M+H]^+$: 407.12132, found: 407.12157.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3479 (w), 3207 (w), 2920 (w), 1595 (m), 1585 (m), 1552 (s), 1471 (w), 1444 (w), 1429 (m), 1390 (s), 1346 (m), 1306 (m), 1279 (m), 1265 (s), 1234 (m), 1200 (m), 1174 (s), 1153 (s), 1138 (s), 1124 (s), 1099 (s), 1051 (s), 1034 (s), 984 (m), 962 (m), 945 (m), 930 (m), 885 (m), 870 (s), 827 (m), 804 (m), 791 (m), 760 (s), 752 (s), 723 (m), 710 (s), 683 (s), 621 (m), 602 (m), 569 (m), 559 (m).

Methyl 2-(*β*-D-ribofuranosyl)-6-(2-thienyl)pyrimidine-4-carboxylate (19j)



Initial diketone was previously activated via conversion into corresponding *α,β*-unsaturated *β*-chloroketone:

In 15 mL of DCM were dissolved 2 g of methyl 2,4-dioxo-4-(2-thienyl)butanoate (9.42 mmol, 1 eq) and 1.447 g of DMF (19.8 mmol, 2.1 eq). Then the solution was cooled to –78 °C and oxalyl chloride (1.435 g, 11.3 mmol, 1.2 eq) was added. After that the mixture was carefully heated to r.t. (gas evaluation!) and allowed to stand at

this temperature for 2 hours. Afterwards the reaction mixture was diluted with ice water. The organic layer was separated and water phase was extracted twice with DCM. Combined organic layers were dried over sodium sulfate and evaporated. The crude residue was purified via short-path column chromatography: silica gel (14 g) / DCM (140 mL) to give a greyish-green solid consisting of mixture of isomers (1.876 g, 86%).

Into a 50-mL flask were placed 0.7 g of 1-(*β*-D-ribofuranosyl)formamidine (3.29 mmol, 1 eq), 0.835 g of K_2CO_3 (13.2 mmol, 4 eq), molecular sieves 4Å (1.05 g) and DMF (14 mL). Then 0.835 g of the previously prepared *α,β*-unsaturated *β*-chloroketone (3.62 mmol, 1.1 eq) was added at 0 °C and the reaction was stirred at this temperature for the next 2 hours. After that the mixture was allowed to stand at r.t. overnight. The next day the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography: silica gel (100 g) / EtOAc (R_f = 0.05–0.09).

Yield 0.483 g (42%), white solid, mp 136-138 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.59-3.70 (m, 1H, H-5a'), 3.71-3.80 (m, 1H, H-5b'), 3.97-4.05 (m, 1H, H-4'), 3.98 (s, 3H, MeO), 4.11-4.19 (m, 1H, H-3'), 4.23-4.31 (m, 1H, H-2'), 4.75 (dd, 1H, $^3J_1$ = 7.18 Hz, $^3J_2$ = 4.54 Hz, OH-5'), 4.91 (d, 1H, ^3J = 3.78 Hz, H-1'), 5.01 (d, 1H, ^3J = 6.04 Hz, OH-3'), 5.32 (d, 1H, ^3J = 5.29 Hz, OH-2'), 7.32 (dd, 1H, $^3J_1$ = 4.91 Hz, $^3J_2$ = 3.78 Hz, H-4''), 7.97 (dd, 1H, ^3J = 4.91 Hz, ^4J = 1.13 Hz, H-3''), 8.32 (dd, 1H, ^3J = 3.78 Hz, ^4J = 1.13 Hz, H-5''), 8.38 (s, 1H, H-5).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 54.0 (MeO), 63.2 (CH_2OH), 72.3 (CH-3'), 76.9 (CH-2'), 85.8 (CH-4'), 86.9 (CH-1'), 114.3 (CH-5), 130.2 (CH_{Ar}), 131.5 (CH_{Ar}), 133.6 (CH_{Ar}), 141.8, 156.2, 161.8, 165.2, 170.4.

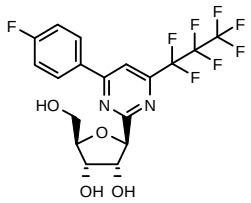
MS (EI, 70 eV): *m/z* (%) = 352 ($[M]^+$, 0.29), 264 (11), 263 (100), 249 (19), 134 (36).

HRMS (ESI): Calcd. for $C_{15}H_{17}N_2O_6S$ $[M+H]^+$: 353.08018, found: 353.08025.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3225 (m), 3105 (m), 2941 (w), 1745 (w), 1716 (s), 1587 (s), 1537 (s), 1444 (s), 1435 (s), 1410 (m), 1377 (s), 1344 (m), 1325 (m), 1300 (m), 1269 (s), 1236 (s), 1200 (s), 1142 (m), 1101 (s), 1086 (s), 1051 (s), 1039 (s), 1022 (s), 997 (s), 989 (s), 978 (m), 932 (s), 903 (m), 883 (m), 856 (s), 831 (m), 798 (w), 779 (m), 762 (s), 746 (s), 729 (s), 716 (s), 671 (m), 631 (s), 611 (s), 544 (s).

2-(*β*-D-Ribofuranosyl)-4-(4-fluorophenyl)-6-(heptafluoropropyl)pyrimidine (19k)

Initial diketone was previously activated via conversion into corresponding *α,β*-unsaturated *β*-chloroketone:



To a solution of 4,4,5,5,6,6,6-heptafluoro-1-(4-fluorophenyl)hexane-1,3-dione (1.17 g, 3.50 mmol, 1 eq) in chloroform (3.5 mL) was added 1.25 g of $SOCl_2$ (10.5 mmol, 3 eq), followed by the addition of DMF (0.013 g, 0.18 mmol, 0.05 eq). The mixture was refluxed for 3 hours. After that the solvent with an excess of $SOCl_2$ was evaporated, and the residue was distilled in a high vacuum to afford a yellow liquid consisting of mixture of isomers (0.911 g, 74%).

Into a 25-mL flask were placed 0.2 g of 1-(*β*-D-ribofuranosyl)formamidine (0.94 mmol, 1 eq), 0.52 g of K_2CO_3 (3.76 mmol, 4 eq) , molecular sieves 4Å (0.3 g) and DMF (4 mL). Then 0.365 g of the previously prepared *α*,*β*-unsaturated *β*-chloroketone (1.22 mmol, 1.1 eq) was added at 0 °C and the reaction was stirred at this temperature for the next 2 hours. After that the mixture was allowed to stand at r.t. overnight. The next day the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography: silica gel (50 g) / EtOAc : $CHCl_3$ = 1:2, then pure EtOAc (R_f = 0.44–0.51).

Yield 0.219 g (49%), white solid, mp 117-118 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.54-3.64 (m, 1H, H-5a'), 3.65-3.74 (m, 1H, H-5b'), 3.97-4.05 (m, 1H, H-4'), 4.11-4.19 (m, 1H, H-3'), 4.29-4.37 (m, 1H, H-2'), 4.68 (dd, 1H, $^3J_1$ = 6.42 Hz, $^3J_2$ = 5.10 Hz, OH-5'), 4.98 (d, 1H, ^3J = 4,34 Hz, H-1'), 5.06 (d, 1H, ^3J = 6.04 Hz, OH-3'), 5.32 (d, 1H, ^3J = 5.48 Hz, OH-2'), 7.43-7.53 (m, 2H, H-3'', H-5''), 8.46-8.54 (m, 2H, H-2'', H-6''), 8.57 (s, 1H, H-5).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 63.2 (CH_2OH), 72.7 (CH-3'), 76.7 (CH-2'), 86.0 (CH-4'), 86.8 (CH-1'), 114.3 (CH-5), 117.2 (d, $^2J_{(C-F)}$ = 21.9 Hz, CH-3''), 131.5 (d, $^3J_{(C-F)}$ = 9.2 Hz, CH-2''), 132.3 (d, $^4J_{(C-F)}$ = 2.9 Hz, C-1''), 156.2 (t, $^2J_{(C-F)}$ = 26.5 Hz, C-6), 165.7 (d, $^1J_{(C-F)}$ = 251.0 Hz, CH-4''), 166.2, 170.4.

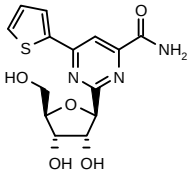
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –125.7 (s, CF_2), –115.4 (m, CF_2), –107.7 (s, CF_{Ar}) – 79.7 (t, J = 9.20 Hz, CF_3).

MS (EI, 70 eV): *m/z* (%) = 474 ([M]$^+$, 2.1), 386 (13), 385 (100), 371 (34), 78 (31), 63 (36).

HRMS (ESI): Calcd. for $C_{18}H_{15}F_8N_2O_4$ [M+H]$^+$: 475.08986, found: 475.08976.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3491 (m), 3460 (m), 3406 (m), 2947 (w), 2904 (w), 1605 (m), 1587 (s), 1545 (m), 1512 (m), 1417 (m), 1389 (m), 1377 (m), 1348 (m), 1336 (m), 1300 (m), 1279 (m), 1230 (s), 1203 (s), 1182 (s), 1161 (s), 1126 (s), 1109 (s), 1095 (s), 1086 (s), 1072 (s), 1053 (s), 1038 (s), 1009 (m), 997 (m), 962 (m), 918 (s), 891 (s), 878 (m), 868 (m), 849 (s), 825 (s), 806 (m), 779 (m), 743 (s), 725 (m), 694 (m), 662 (m), 625 (m), 611 (m), 573 (s), 559 (s), 544 (m).

2-(*β*-D-Ribofuranosyl)-6-(2-thienyl)pyrimidine-4-carboxamide (20)



Methyl 2-(*β*-D-ribofuranosyl)-6-(2-thienyl)pyrimidine-4-carboxylate (0.1 g, 0.28 mmol, 1 eq) was dissolved in 0.81 mL of 7M ammonia solution in methanol (5.7 mmol, 20 eq) and stirred at room temperature overnight. The next day the solvent was evaporated under reduced pressure and the residue was properly dried in high vacuum to give a pure product.

Yield 0.096 g (100%), white amorphous solid foam.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.57-3.67 (m, 1H, H-5a'), 3.67-3.77 (m, 1H, H-5b'), 3.94-4.01 (m, 1H, H-4'), 4.15-4.23 (m, 1H, H-3'), 4.32-4.39 (m, 1H, H-2'), 4.74 (dd, 1H, $^{3}J_1$ = 6.23 Hz, $^{3}J_2$ = 5.29 Hz, OH-5'), 4.90 (d, 1H, ^{3}J = 4,54 Hz, H-1'), 4.98 (d, 1H, ^{3}J = 5.86 Hz, OH-3'), 5.24 (d, 1H, ^{3}J = 5.48 Hz, OH-2'), 7.31 (dd, 1H, $^{3}J_1$ = 4.91 Hz, $^{3}J_2$ = 3.78 Hz, H-4''), 7.94 (dd, 1H, ^{3}J = 4.91 Hz, ^{4}J = 1.13 Hz, H-3''), 8.06 (br s, 1H, NH-a), 8.26 (br s, 1H, NH-b), 8.28 (dd, 1H, ^{3}J = 3.78 Hz, ^{4}J = 1.13 Hz, H-5''), 8.33 (s, 1H, H-5).

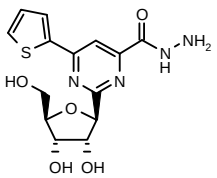
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 63.3 (CH_2OH), 72.7 (CH-3'), 76.4 (CH-2'), 85.9 (CH-4'), 86.7 (CH-1'), 111.7 (CH-5), 130.2 (CH_{Ar}), 131.0 (CH_{Ar}), 133.1 (CH_{Ar}), 142.2, 159.1, 161.6, 165.7, 169.2.

MS (EI, 70 eV): *m/z* (%) = 337 ([M]$^+$, 078), 301 (16), 292 (10), 249 (12), 248 (100), 234 (27), 161 (11), 134 (52), 108 (11).

HRMS (ESI): Calcd. for $C_{14}H_{16}N_3O_5S$ [M+H]$^+$: 338.08052, found: 338.08071.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3306 (s), 3093 (m), 2928 (m), 2874 (m), 1682 (s), 1574 (s), 1525 (s), 1429 (s), 1394 (s), 1344 (s), 1317 (s), 1228 (m), 1200 (m), 1095 (s), 1078 (s), 1034 (s), 991 (s), 947 (m), 889 (s), 858 (s), 812 (m), 779 (m), 714 (s), 665 (s), 617 (s), 534 (s).

2-(*β*-D-Ribofuranosyl)-6-(2-thienyl)pyrimidine-4-carbohydrazide (21)



Methyl 2-(*β*-D-ribofuranosyl)-6-(2-thienyl)pyrimidine-4-carboxylate (0.1 g, 0.28 mmol, 1 eq) was dissolved in 2 mL of methanol. Then hydrazine hydrate (0.178 g, 2.84 mmol, 10 eq) was added. After few minutes a white precipitate begins to appear. The next day it was filtered off, washed with methanol and dried in high vacuum to give a pure product.

Yield 0.083 g (83%), white solid, mp 226-228 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.56-3.66 (m, 1H, H-5a'), 3.67-3.76 (m, 1H, H-5b'), 3.93-4.00 (m, 1H, H-4'), 4.14-4.22 (m, 1H, H-3'), 4.34-4.42 (m, 1H, H-2'), 4.74 (dd, 1H, $^{3}J_1$ = 6.24 Hz, $^{3}J_2$ = 5.28 Hz, OH-5'), 4.79 (br s, 2H, NH_2), 4.88 (d, 1H, ^{3}J = 4,72 Hz, H-1'), 4.97 (d, 1H, ^{3}J = 5.66 Hz, OH-3'), 5.23 (d, 1H, ^{3}J = 5.67 Hz, OH-2'), 7.31 (dd, 1H, $^{3}J_1$ = 4.91 Hz, $^{3}J_2$ = 3.77 Hz, H-

4"), 7.94 (dd, 1H, ^{3}J = 4.91 Hz, ^{4}J = 1.13 Hz, H-3"), 8.28 (dd, 1H, ^{3}J = 3.77 Hz, ^{4}J = 1.13 Hz, H-5"), 8.28 (s, 1H, H-5), 10.14 (br s, 1H, NH).

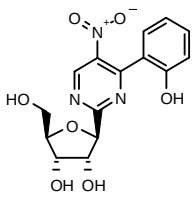
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 63.2 (CH_2OH), 72.7 (CH-3'), 76.2 (CH-2'), 86.0 (CH-4'), 86.6 (CH-1'), 111.5 (CH-5), 130.2 (CH_{Ar}), 131.0 (CH_{Ar}), 133.2 (CH_{Ar}), 142.2, 158.6, 161.5, 161.9, 169.0.

MS (EI, 70 eV): *m/z* (%) = 452 ($[M]^+$, 1.81), 129 (34), 115 (15), 101 (15), 98 (18), 97 (14), 87 (23), 85 (20), 84 (19), 83 (23), 81 (11), 74 (13), 73 (87), 71 (34), 70 (15), 69 (32), 67 (13), 61 (15), 60 (100), 59 (10), 57 (46), 56 (20), 55 (53), 45 (53), 44 (38), 43 (92), 42 (19), 41 (56), 39 (17).

HRMS (ESI): Calcd. for $C_{14}H_{17}N_4O_5S$ $[M+H]^+$: 353.09142, found: 353.09165.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3340 (m), 3269 (m), 3103 (m), 2922 (m), 1713 (s), 1587 (s), 1525 (s), 1516 (s), 1464 (m), 1435 (s), 1377 (s), 1346 (m), 1302 (m), 1267 (m), 1246 (w), 1213 (m), 1194 (m), 1178 (m), 1126 (s), 1113 (s), 1099 (m), 1088 (s), 1051 (s), 1028 (s), 987 (s), 939 (s), 920 (m), 899 (m), 870 (m), 851 (m), 802 (w), 779 (w), 764 (s), 750 (s), 723 (s), 640 (s), 619 (s), 582 (s), 532 (s).

2-(*β*-D-Ribofuranosyl)-4-(2-hydroxyphenyl)-5-nitropyrimidine (23a)



A sealed ACE pressure tube was charged with 0.3 g of 1-(*β*-D-ribofuranosyl)formamidine (1.41 mmol, 1 eq), 0.080 g of NaOMe (1.48 mmol, 1.05 eq), 0.008 g of AcOH (0.14 mmol, 0.1 eq), 0.143 g of NEt_3 (1.41 mmol, 1 eq) and MeOH (4.5 mL). After 3-nitro-4*H*-chromen-4-one (0.493 g, 1.41 mmol, 1 eq) was added, the reaction mixture was stirred at 80 °C for 1½ hours under argon. After cooling to room temperature the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography: silica gel (110 g) / EtOAc (R_f = 0.11–0.19).

Yield 0.176 g (36%), yellow amorphous solid foam.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.52-3.62 (m, 1H, H-5a'), 3.62-3.72 (m, 1H, H-5b'), 3.95-4.04 (m, 1H, H-4'), 4.07-4.16 (m, 1H, H-3'), 4.28-4.37 (m, 1H, H-2'), 4.71 (dd, 1H, $^{3}J_1$ = 6.42 Hz, $^{3}J_2$ = 4.91 Hz, OH-5'), 4.97 (d, 1H, ^{3}J = 4.72 Hz, H-1'), 5.05 (d, 1H, ^{3}J = 5.86 Hz, OH-3'), 5.34 (d, 1H, ^{3}J = 5.67 Hz, OH-2'), 6.94 (dd, 1H, $^{3}J_1$ = 8.12 Hz, ^{4}J = 0.95 Hz, H-3"), 7.07 (ddd, 1H, $^{3}J_1$ = 7.65 Hz, $^{3}J_2$ = 7.37 Hz, ^{4}J = 0.95 Hz, H-5"), 7.45 (ddd, 1H, $^{3}J_1$ = 8.12 Hz, $^{3}J_2$ = 7.37 Hz, ^{4}J = 1.7 Hz, H-4"), 7.71 (dd, 1H, $^{3}J_1$ = 7.65 Hz, ^{4}J = 1.7 Hz, H-6"), 9.37 (s, 1H, H-6), 10.52 (s, 1H, OH-2").

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 63.0 (CH_2OH), 72.5 (CH-3'), 76.9 (CH-2'), 86.1 (CH-4'), 86.5 (CH-1'), 116.4 (CH_{Ar}), 120.7 (CH_{Ar}), 122.7, 131.5 (CH_{Ar}), 133.8 (CH_{Ar}), 144.4, 154.2 (CH_{Ar}), 156.4, 158.2, 171.7.

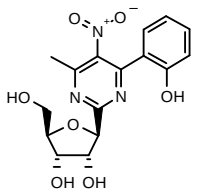
MS (EI, 70 eV): *m/z* (%) = 349 ($[M]^+$, 59), 313 (16), 303 (39), 267 (10), 260 (100), 258 (12),

249 (14), 246 (66), 230 (13), 217 (11), 216 (10), 214 (17), 213 (46), 201 (13), 200 (30), 199 (25), 197 (13), 186 (26), 185 (14), 173 (12), 172 (19), 171 (42), 170 (31), 169 (20), 144 (13), 116 (11), 115 (13), 102 (11), 91 (12), 89 (24), 63 (11), 43 (15).

HRMS (EI): Calcd. for $C_{15}H_{15}N_3O_7$ $[M]^+$: 349.09045, found: 349,09066.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3242 (s), 2932 (w), 2879 (w), 1606 (w), 1581 (s), 1545 (s), 1524 (m), 1504 (w), 1453 (m), 1427 (m), 1355 (s), 1303 (m), 1265 (m), 1210 (w), 1159 (w), 1070 (s), 1080 (s), 1047 (s), 984 (w), 943 (w), 910 (w), 888 (w), 850 (s), 807 (w), 756 (s), 706 (m), 687 (m), 665 (m), 624 (s), 579 (m), 542 (s).

2-(*β*-D-Ribofuranosyl)-4-(2-hydroxyphenyl)-6-methyl-5-nitropyrimidine (23b)



Into a 50-mL flask were placed 0.7 g of 1-(*β*-D-ribofuranosyl)formamidine (3.29 mmol, 1 eq), 0.187 g of NaOMe (3.46 mmol, 1.05 eq), 0.018 g of AcOH (0.33 mmol, 0.1 eq), 0.333 g of NEt_3 (3.29 mmol, 1 eq), molecular sieves 4Å (1.05 g) and DMF (10.5 mL). After 2-methyl-3-nitro-4*H*-chromen-4-one (0.675 g, 3.29 mmol, 1 eq) was added, the reaction mixture was stirred at 70 °C for 2 hours under argon. After cooling to room temperature the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography: silica gel (100 g) / EtOAc (R_f = 0.16–0.25).

Yield 0.416 g (35%), yellow amorphous solid foam.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.68 (s, 3H, Me-6), 3.51-3.63 (m, 1H, H-5a'), 3.63-3.74 (m, 1H, H-5b'), 3.96-4.04 (m, 1H, H-4'), 4.08-4.17 (m, 1H, H-3'), 4.26-4.34 (m, 1H, H-2'), 4.75 (dd 1H, $^3J_1$ = 4.34 Hz, $^3J_2$ = 6.99 Hz, OH-5'), 4.92 (d 1H, ^3J = 4.15 Hz, H-1'), 5.02 (d 1H, ^3J = 5.86 Hz, OH-3'), 5.34 (d 1H, ^3J = 5.48 Hz, OH-2'), 6.89-6.96 (m, 1H, H-3''), 6.98-7.07 (m, 1H, H-5''), 7.36-7.45 (m, 1H, H-4''), 7.51-7.58 (m, 1H, H-6''), 10.40 (s, 1H, OH-2'').

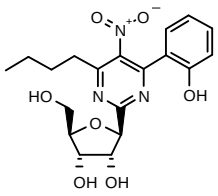
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 22.7 (CH_3), 62.9 (CH_2OH), 72.2 (CH-3'), 76.9 (CH-2'), 85.9 (CH-4'), 86.5 (CH-1'), 116.4 (CH_{Ar}), 120.5 (CH_{Ar}), 122.7, 131.6 (CH_{Ar}), 133.3 (CH_{Ar}), 144.8, 156.3, 158.8, 161.4, 169.7.

MS (EI, 70 eV): *m/z* (%) = 364 ($[M+H]^+$, 14), 363 ($[M]^+$, 78), 318 (15), 317 (83), 274 (100), 272 (12), 260 (50), 244 (10), 228 (19), 227 (75), 215 (12), 214 (27), 213 (24), 211 (12), 200 (36), 199 (18), 198 (11), 185 (14), 57 (10), 44 (16), 43 (11).

HRMS (EI): Calcd. for $C_{16}H_{17}N_3O_7$ $[M]^+$: 363.10610, found: 363.10664.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3252 (s), 2930 (m), 1699 (w), 1606 (w), 1573 (s), 15 27 (s), 1455 (m), 1435 (m), 1386 (w), 1354 (s), 1294 (m), 1265 (w), 1227 (w), 1153 (w), 1094 (s), 1046 (m), 972 (w), 941 (w), 884 (m), 847 (s), 828 (w), 807 (w), 756 (s), 675 (m), 667 (m), 641 (m), 610 (m), 575 (m), 576 (m).

2-(*β*-D-Ribofuranosyl)-4-(2-hydroxyphenyl)-6-butyl-5-nitropyrimidine (23c)



Into a 50-mL flask were placed 0.65 g of 1-(*β*-D-ribofuranosyl)formamidine (3.06 mmol, 1 eq), 0.173 g of NaOMe (3.21 mmol, 1.05 eq), 0.018 g of AcOH (0.31 mmol, 0.1 eq), 0.309 g of NEt_3 (3.06 mmol, 1 eq), molecular sieves 4Å (0.975 g) and DMF (10 mL). After 2-butyl-3-nitro-4*H*-chromen-4-one (0.756 g, 3.06 mmol, 1 eq) was added, the reaction mixture was stirred at 50 °C for 5 hours under argon. After cooling to room temperature the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography: silica gel (100 g) / EtOAc (R_f = 0.21–0.35).

Yield 0.600 g (48%), light beige solid, mp 167-169 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 0.95 (t, 3H, ^3J = 7.37 Hz, Me), 1.34-1.48 (m, 2H, CH_2-c), 1.70-1.83 (m, 2H, CH_2-b), 2.90 (t, 2H, ^3J = 7.55 Hz, CH_2-a), 3.51-3.62 (m, 1H, H-5a'), 3.63-3.73 (m, 1H, H-5b'), 3.96-4.03 (m, 1H, H-4'), 4.09-4.16 (m, 1H, H-3'), 4.27-4.34 (m, 1H, H-2'), 4.71 (dd 1H, $^3J_1$ = 6.99 Hz, $^3J_2$ = 4.54 Hz, OH-5'), 4.93 (d 1H, ^3J = 4.16 Hz, H-1'), 5.02 (d 1H, ^3J = 6.05 Hz, OH-3'), 5.33 (d 1H, ^3J = 5.47 Hz, OH-2'), 6.90-6.95 (m, 1H, H-3''), 6.98-7.05 (m, 1H, H-5''), 7.36-7.44 (m, 1H, H-4''), 7.49-7.54 (m, 1H, H-6''), 10.36 (s, 1H, OH-2'').

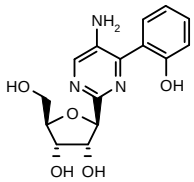
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 14.6 (CH_3), 22.8 (CH_2-c), 30.7 (CH_2-b), 34.1 (CH_2-a), 63.0 (CH_2OH), 72.4 (CH-3'), 76.9 (CH-2'), 85.8 (CH-4'), 86.7 (CH-1'), 116.4 (CH_{Ar}), 120.5 (CH_{Ar}), 122.6, 131.7 (CH_{Ar}), 133.2 (CH_{Ar}), 144.8, 156.2, 159.0, 164.1, 169.8.

MS (EI, 70 eV): *m/z* (%) = 406 ($[M+H]^+$, 11), 405 ($[M]^+$, 51), 360 (15), 359 (79), 317 (16), 316 (100), 302 (19), 269 (37), 228 (14), 214 (14).

HRMS (EI): Calcd. for $C_{19}H_{23}N_3O_7$ $[M]^+$: 405.15305, found: 405.15371.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3512 (w), 3331 (m), 2956 (w), 2929 (w), 2874 (w), 2860 (w), 1614 (m), 1595 (m), 1576 (s), 1525 (s), 1452 (s), 1417 (m), 1381 (m), 1360 (s), 1321 (m), 1294 (m), 1269 (m), 1232 (m), 1211 (m), 1180 (w), 1155 (w), 1105 (s), 1095 (s), 1074 (s), 1047 (s), 1028 (m), 1012 (m), 980 (m), 939 (m), 905 (w), 887 (m), 876 (m), 858 (m), 845 (s), 824 (m), 814 (m), 797 (w), 754 (s), 737 (m), 704 (m), 692 (m), 636 (s), 602 (s), 586 (m), 555 (s), 544 (s).

2-(*β*-D-Ribofuranosyl)-5-amino-4-(2-hydroxyphenyl)-pyrimidine (24a)



Into a 25-mL flask were placed 0.118 g of 2-(*β*-D-ribofuranosyl)-4-(2-hydroxyphenyl)-5-nitropyrimidine (0.34 mmol), 0.012 g of Pd/C (10 wt. %) and MeOH (3.5 mL). The system was washed three times with argon and afterwards three times with hydrogen. The reaction mixture was stirred for 2 days at r.t. and under atmospheric pressure. As the reduction was complete (monitoring by TLC),

the mixture was filtered through a Celite pad (2-3 cm). The Celite was washed three times with MeOH. The filtrate was evaporated under reduced pressure and the residue was properly dried in high vacuum to give a pure product.

Yield 0.108 g (100%), pale yellow amorphous solid foam.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.50 (dd, 1H, ^{2}J = 11.71 Hz, ^{3}J = 3.77 Hz, H-5a'), 3.65 (dd, 1H, ^{2}J = 11.71 Hz, ^{3}J = 3.69 Hz, H-5b'), 3.88-3.97 (m, 1H, 4H'), 4.05-4.13 (m, 1H, H-3'), 4.18-4.27 (m, 1H, H-2'), 4.76 (d, 1H, ^{3}J = 4.54 Hz, H-1'), 4.78-5.86 (br m, 5H, OH, NH_2), 6.94-7.06 (m, 2H, CH_{Ar}), 7.31-7.79 (m, 1H, CH_{Ar}), 7.45 (dd, 1H, ^{3}J = 7.74 Hz, ^{4}J = 1.51 Hz, CH_{Ar}), 8.29 (s, 1H, H-6), 10.44 (br s, 1H, OH-2'').

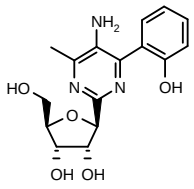
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 62.9 (CH_2OH), 72.2 (CH-3'), 76.6 (CH-2'), 85.4 (CH-4'), 86.4 (CH-1'), 117.3 (CH_{Ar}), 120.3 (CH_{Ar}), 124.3, 131.4 (CH_{Ar}), 131.6 (CH_{Ar}), 140.1, 144.7 (CH_{Ar}), 149.2, 156.0, 157.2.

MS (EI, 70 eV): *m/z* (%) = 319 ([M]$^+$, 54), 230 (100), 217 (12), 216 (83), 214 (14), 201 (10).

HRMS (EI): Calcd. for $C_{15}H_{17}N_3O_5$ [M]$^+$: 319.11627, found: 319.11684.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3324 (s), 3207 (s), 2928 (m), 2873 (m), 1633 (w), 1608 (w), 1568 (m), 1558 (m), 1549 (w), 1504 (w), 1495 (w), 1488 (w), 1447 (s), 1418 (m), 1398 (m), 1327 (m), 1295 (m), 1249 (m), 1206 (m), 1158 (w), 1097 (s), 1082 (s), 1047 (s), 985 (m), 911 (m), 889 (m), 857 (m), 831 (m), 799 (m), 756 (s), 700 (s), 667 (s), 633 (s), 596 (s), 534 (s).

2-(*β*-D-Ribofuranosyl)-5-amino-6-methyl-4-(2-hydroxyphenyl)-pyrimidine (24b)



Into a 50-mL flask were placed 0.25 g of 2-(*β*-D-ribofuranosyl)-4-(2-hydroxyphenyl)-6-methyl-5-nitropyrimidine (0.69 mmol), 0.025 g of Pd/C (10 wt. %) and MeOH (7.5 mL). The system was washed three times with argon and afterwards three times with hydrogen. The reaction mixture was stirred for 2 days at r.t. and under atmospheric pressure. As the reduction was complete (monitoring by TLC), the mixture was filtered through a Celite pad (2-3 cm). The Celite was washed three times with MeOH. The filtrate was evaporated under reduced pressure and the residue was properly dried in high vacuum to give a pure product.

Yield 0.229 g (100%), yellow amorphous solid foam.

^{1}H NMR (250.13 MHz, DMSO-d_6): δ = 2.42 (s, 3H, CH_3), 3.51 (dd, 1H, ^{2}J = 11.62 Hz, ^{3}J = 3.08 Hz, H-5a'), 3.69 (dd, 1H, ^{2}J = 11.62 Hz, ^{3}J = 3.31 Hz, H-5b'), 3.89-3.98 (m, 1H, 4H'), 4.09-4.16 (m, 1H, H-3'), 4.16-4.22 (m, 1H, H-2'), 4.74 (d, 1H, ^{3}J = 3.62 Hz, H-1'), 4.40-5.80 (br m, 5H, OH, NH_2), 6.92-7.00 (m, 1H, CH_{Ar}), 7.02 (d, 1H, ^{3}J = 8.04 Hz, CH_{Ar}), 7.29-7.39 (m, 2H, CH_{Ar}), 10.28 (br s, 1H, OH-2'').

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 21.4 (CH_3), 62.7 (CH_2OH), 71.7 (CH-3'), 76.9 (CH-

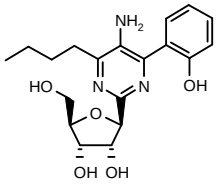
2'), 85.1 (CH-4'), 86.5 (CH-1'), 117.2 (CH_{Ar}), 120.2 (CH_{Ar}), 124.6, 131.2 (CH_{Ar}), 131.8 (CH_{Ar}), 137.8, 148.3, 152.0, 155.8, 156.6.

MS (EI, 70 eV): *m/z* (%) = 334 ($[M+H]^+$, 10), 333 ($[M]^+$, 52), 332 (17), 305 (14), 289 (21), 265 (15), 245 (14), 244 (100), 243 (12), 242 (25), 231 (13), 230 (84), 228 (23), 225 (25), 215 (11), 177 (11), 164 (15), 57 (57), 41 (16).

HRMS (ESI): Calcd. for $C_{16}H_{20}N_3O_5$ $[M+H]^+$: 334.13975, found: 334.13978.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3334 (m), 3232 (m), 2962 (m), 2918 (m), 2872 (m), 1633 (m), 1622 (m), 1608 (m), 1591 (m), 1564 (s), 1558 (s), 1539 (m), 1504 (m), 1495 (m), 1487 (m), 1470 (m), 1446 (s), 1435 (s), 1429 (s), 1392 (s), 1385 (s), 1362 (s), 1344 (m), 1338 (m), 1294 (s), 1250 (m), 1223 (s), 1194 (m), 1157 (m), 1097 (s), 1080 (s), 1047 (s), 1038 (s), 989 (m), 972 (s), 939 (s), 870 (s), 841 (s), 816 (m), 800 (m), 756 (s), 716 (s), 673 (s), 665 (s), 621 (s), 598 (s), 540 (s).

2-(*β*-D-Ribofuranosyl)-5-amino-6-butyl-4-(2-hydroxyphenyl)-pyrimidine (24c)



Into a 50-mL flask were placed 0.2 g of 2-(*β*-D-ribofuranosyl)-4-(2-hydroxyphenyl)-6-butyl-5-nitropyrimidine (0.49 mmol), 0.02 g of Pd/C (10 wt. %) and MeOH (6 mL). The system was washed three times with argon and afterwards three times with hydrogen. The reaction mixture was stirred for 2 days at r.t. and under atmospheric pressure. As the reduction was complete (monitoring by TLC), the mixture was filtered through a Celite pad (2-3 cm). The Celite was washed three times with MeOH. The filtrate was evaporated under reduced pressure and the residue was properly dried in high vacuum to give a pure product.

Yield 0.185 g (100%), pale green amorphous solid foam.

^{1}H NMR (250.13 MHz, DMSO-d_6): δ = 0.97 (t, 3H, ^3J = 7.37 Hz, Me), 1.37-1.51 (m, 2H, CH_2-c), 1.64-1.77 (m, 2H, CH_2-b), 2.75 (t, 2H, ^3J = 7.46 Hz, CH_2-a), 3.51 (dd, 1H, ^2J = 11.43 Hz, ^3J = 4.67 Hz, H-5a'), 3.68 (dd, 1H, ^2J = 11.43 Hz, ^3J = 2.93 Hz, H-5b'), 3.89-3.98 (m, 1H, 4H'), 4.09-4.17 (m, 1H, H-3'), 4.17-4.25 (m, 1H, H-2'), 4.75 (d, 1H, ^3J = 3.78 Hz, H-1'), 4.77-4.95 (br m, 3H, OH, NH_2), 5.04-5.19 (br m, 2H, OH), 6.93-7.01 (m, 1H, CH_{Ar}), 7.03 (d, 1H, ^3J = 7.55 Hz, CH_{Ar}), 7.29-7.39 (m, 2H, CH_{Ar}), 10.27 (br s, 1H, OH-2'').

^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 14.8 (CH_3), 23.0 (CH_2-c), 29.3 (CH_2-b), 33.0 (CH_2-a), 62.8 (CH_2OH), 72.0 (CH-3'), 76.9 (CH-2'), 85.1 (CH-4'), 86.7 (CH-1'), 117.1 (CH_{Ar}), 120.3 (CH_{Ar}), 124.7, 131.1 (CH_{Ar}), 131.8 (CH_{Ar}), 137.2, 148.7, 155.2, 155.5, 156.7.

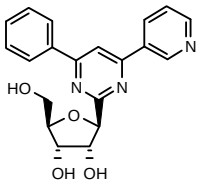
MS (EI, 70 eV): *m/z* (%) = 376 ($[M+H]^+$, 11), 375 ($[M]^+$, 50), 374 (13), 346 (20), 333 (100), 287 (12), 286 (73), 284 (14), 273 (11), 272 (63), 256 (16), 243 (12), 242 (14).

HRMS (EI): Calcd. for $C_{19}H_{25}N_3O_5$ $[M]^+$: 375.17887, found: 375.17847.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3342 (m), 3226 (m), 2953 (m), 2928 (m), 2866 (m), 1622 (m), 1608

(m), 1593 (w), 1558 (s), 1539 (m), 1504 (w), 1495 (w), 1487 (w), 1450 (s), 1429 (s), 1392 (m), 1377 (m), 1344 (m), 1338 (m), 1294 (m), 1223 (m), 1155 (m), 1097 (s), 1080 (s), 1047 (s), 976 (m), 937 (m), 866 (m), 845 (m), 820 (m), 806 (m), 797 (m), 756 (s), 696 (s), 673 (s), 665 (s), 621 (s), 584 (s), 571 (s), 542 (s).

2-(*β*-D-Ribofuranosyl)-4-phenyl-6-pyridin-3-ylpyrimidine (29a)



Into a 25-mL flask were placed 0.2 g of 1-(*β*-D-ribofuranosyl)formamidine (0.94 mmol, 1 eq), 0.195 g of 1-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-3-phenylprop-2-yn-1-one (0.94 mmol, 1 eq), 0.26 g of K_2CO_3 (1.88 mmol, 2 eq), molecular sieves 4Å (0.3 g) and DMF (4 mL). Then the reaction mixture was stirred at 70 °C for 4 hours under argon. After cooling to room temperature the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude residue was purified via short-path column chromatography: silica gel (12 g) / $CHCl_3$ (1 L), than 1.5 L of EtOAc (R_f = 0.03–0.09). The fraction of EtOAc was evaporated to give the desired product.

Yield 0.156 g (68%), yellow amorphous solid foam.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.60-3.71 (m, 1H, H-5a'), 3.72-3.81 (m, 1H, H-5b'), 4.01-4.08 (m, 1H, H-4'), 4.21-4.29 (m, 1H, H-3'), 4.39-4.47 (m, 1H, H-2'), 4.86 (dd, 1H, $^3J_1$ = 6.23 Hz, $^3J_2$ = 4.91 Hz, OH-5'), 5.02 (d, 1H, ^3J = 4.15 Hz, H-1'), 5.03 (d, 1H, ^3J = 5.85 Hz, OH-3'), 5.28 (d, 1H, ^3J = 5.47 Hz, OH-2'), 7.60-7.71 (m, 4H, CH_{Ph}), 8.37-8.45 (m, 2H, CH_{Ar}), 8.65 (s, 1H, H-5), 8.69-8.75 (m, 1H, CH_{Ar}), 8.78-8.85 (m, 1H, CH_{Ar}), 9.55 (s, 1H, CH_{Ar}).

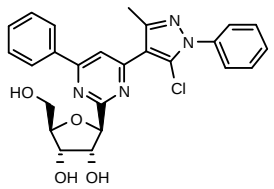
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 63.2 (CH_2OH), 72.7 (CH-3'), 76.8 (CH-2'), 85.7 (CH-4'), 87.4 (CH-1'), 112.8 (CH-5), 124.9 (CH_{Ar}), 128.4 (CH_{Ar}), 129.9 (CH_{Ar}), 132.3 (CH_{Ar}), 132.9, 135.8 (CH_{Ar}), 137.1, 149.6 (CH_{Ar}), 152.7 (CH_{Ar}), 163.3, 165.4, 169.9.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3271 (m), 3063 (m), 2918 (m), 2872 (m), 1585 (s), 1574 (s), 1556 (m), 1531 (s), 1504 (m), 1485 (m), 1471 (m), 1452 (m), 1427 (m), 1417 (m), 1410 (m), 1365 (s), 1331 (m), 1294 (m), 1244 (m), 1192 (m), 1101 (s), 1078 (s), 1043 (s), 1026 (s), 1001 (s), 991 (s), 941 (m), 876 (m), 827 (m), 818 (m), 768 (s), 743 (s), 690 (s), 665 (s), 633 (s), 540 (s).

MS (EI, 70 eV): *m/z* (%) = 365 ([M]$^+$, 9.1), 277 (29), 276 (100), 274 (14), 263 (20), 262 (75), 248 (10), 247 (16), 234 (14), 233 (13), 105 (12), 104 (12).

HRMS (ESI): Calcd. for $C_{20}H_{20}N_3O_4$ [M+H]$^+$: 366.14483, found: 366.14506.

2-(*β*-D-Ribofuranosyl)-4-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-6-phenylpyrimidine (29b)



Into a 25-mL flask were placed 0.15 g of 1-(*β*-D-ribofuranosyl)-formamidine (0.71 mmol, 1 eq), 0.226 g of 1-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-3-phenylprop-2-yn-1-one (0.71 mmol, 1 eq), 0.215 g of K_2CO_3 (1.55 mmol, 2.2 eq), molecular sieves 4Å (0.225 g) and DMF (3 mL). Then the reaction mixture was stirred at 70 °C for 4 hours under argon. After cooling to room temperature the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography: silica gel (50 g) / EtOAc (R_f = 0.20–0.31).

Yield 0.175 g (52%), beige amorphous solid foam.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.59 (s, 3H, CH_3), 3.55-3.66 (m, 1H, H-5a'), 3.67-3.77 (m, 1H, H-5b'), 3.99-4.06 (m, 1H, H-4'), 4.16-4.24 (m, 1H, H-3'), 4.41-4.48 (m, 1H, H-2'), 4.83 (dd, 1H, $^3J_1$ = 6.71 Hz, $^3J_2$ = 4.82 Hz, OH-5'), 4.98 (d, 1H, ^3J = 4.72 Hz, H-1'), 5.02 (d, 1H, ^3J = 5.67 Hz, OH-3'), 5.24 (d, 1H, ^3J = 5.66 Hz, OH-2'), 7.54-7.72 (m, 8H, CH_{Ph}), 8.20 (s, 1H, H-5), 8.22-8.30 (m, 2H, $CH_{p\text{-}Ph}$).

^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 15.1 (CH_3), 63.3 (CH_2OH), 72.8 (CH-3'), 76.7 (CH-2'), 85.9 (CH-4'), 87.3 (CH-1'), 114.6 (CH-5), 116.8, 126.4 (CH_{Ar}), 127.9, 128.1 (CH_{Ar}), 129.9 (CH_{Ar}), 130.1 (CH_{Ar}), 130.3 (CH_{Ar}), 132.2 (CH_{Ar}), 137.2, 138.3, 150.2, 160.0, 164.6, 169.6.

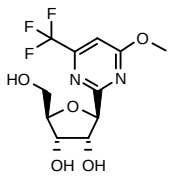
MS (EI, 70 eV): *m/z* (%) = 478 ([M, ^{35}Cl]$^+$, 16), 442 (20), 413 (10), 391 (33), 390 (26), 389 (100), 387 (16), 377 (24), 376 (24), 375 (63), 373 (17), 361 (10), 360 (15), 129 (14), 104 (10), 97 (12), 85 (13), 84 (13), 83 (16), 77 (21), 73 (39), 71 (14), 70 (11), 69 (34), 67 (10), 60 (50), 57 (25), 56 (14), 55 (31), 46 (12), 45 (23), 44 (72), 43 (56), 41 (29).

HRMS (ESI): Calcd. for $C_{25}H_{24}ClN_4O_4$ [M+H, ^{35}Cl]$^+$: 479.1481, found: 479.1485; calcd. for $C_{15}H_{12}ClF_2N_3O_3$ [M+H, ^{37}Cl]$^+$: 481.1463, found: 481.1469.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3317 (m), 3130 (w), 3064 (w), 2924 (m), 1574 (s), 1547 (m), 1525 (s), 1498 (s), 1479 (m), 1471 (m), 1462 (m), 1454 (m), 1404 (s), 1379 (m), 1346 (s), 1317 (m), 1292 (m), 1248 (m), 1223 (m), 1190 (m), 1159 (w), 1097 (s), 1074 (s), 1047 (s), 1030 (s), 993 (m), 941 (m), 922 (m), 876 (m), 837 (m), 822 (m), 804 (w), 762 (s), 717 (m), 690 (s), 673 (s), 654 (s), 635 (s), 608 (m), 596 (m), 544 (m), 528 (m).

2-(*β*-D-Ribofuranosyl)-4-methoxy-6-(trifluoromethyl)pyrimidine (31a)

Into a 25-mL flask were placed 0.2 g of 1-(*β*-D-ribofuranosyl)formamidine (0.94 mmol, 1 eq), 0.190 g of 4,4-dimethoxy-1,1,1-trifluoro-3-buten-2-one (1.03 mmol, 1.1 eq), 0.26 g of K_2CO_3



(1.88 mmol, 2 eq), molecular sieves 4Å (0.3 g) and DMF (4 mL). Then the reaction mixture was stirred at 60 °C for 5½ hours under argon. After cooling to room temperature the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude residue was purified via short-path column chromatography: silica gel (10 g) / $CHCl_3$ (400 mL), than EtOAc (R_f = 0.19–0.29). The fraction of EtOAc was evaporated to give the desired product.

Yield 0.209 g (72%), white solid, mp 129 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.52-3.63 (m, 1H, H-5a'), 3.63-3.72 (m, 1H, H-5b'), 3.92-4.00 (m, 1H, H-4'), 4.06 (s, 3H, MeO), 4.06-4.14 (m, 1H, H-3'), 4.20-4.27 (m, 1H, H-2'), 4.65 (dd, 1H, $^3J_1$ = 6.80 Hz, $^3J_2$ = 4.72 Hz, OH-5'), 4.80 (d, 1H, ^3J = 3.96 Hz, H-1'), 5.00 (d, 1H, ^3J = 6.04 Hz, OH-3'), 5.28 (d, 1H, ^3J = 5.66 Hz, OH-2'), 7.45 (s, 1H, H-5).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 55.7 (MeO), 63.0 (CH_2OH), 72.4 (CH-3'), 76.6 (CH-2'), 85.7 (CH-4'), 86.6 (CH-1'), 105.3 (CH-5), 121.5 (q, $^1J_{(C-F)}$ = 274.6 Hz, CF_3), 155.3 (q, $^2J_{(C-F)}$ = 35.0 Hz), 171.0, 171.7.

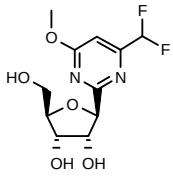
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –68.7 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 311 ($[M+H]^+$, 1.74), 310 ($[M]^+$, 1.25), 233 (12), 222 (16), 221 (100), 219 (27), 208 (16), 207 (90), 205 (19), 68 (11).

HRMS (ESI): Calcd. for $C_{11}H_{14}F_3N_2O_5$ $[M+H]^+$: 311.08493, found: 311.08440.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3346 (m), 3159 (m), 3118 (w), 2966 (w), 2937 (w), 2908 (w), 2889 (w), 1606 (m), 1585 (w), 1558 (m), 1504 (w), 1479 (s), 1456 (w), 1435 (m), 1383 (s), 1348 (m), 1331 (m), 1304 (m), 1267 (m), 1225 (m), 1201 (s), 1186 (m), 1176 (m), 1151 (s), 1140 (s), 1099 (s), 1057 (s), 1034 (s), 1026 (s), 986 (s), 957 (s), 899 (m), 879 (s), 870 (s), 839 (m), 800 (m), 768 (s), 756 (s), 723 (m), 687 (s), 631 (s), 586 (m), 561 (m).

2-(*β*-D-Ribofuranosyl)-4-(difluoromethyl)-6-methoxypyrimidine (31b)



Into a 25-mL flask were placed 0.2 g of 1-(*β*-D-ribofuranosyl)formamidine (0.94 mmol, 1 eq), 0.188 g of 4,4-dimethoxy-1,1-difluoro-3-buten-2-one (1.13 mmol, 1.2 eq), 0.26 g of K_2CO_3 (1.88 mmol, 2 eq), molecular sieves 4Å (0.3 g) and DMF (4 mL). Then the reaction mixture was stirred at 60 °C for 5½ hours under argon. After cooling to room temperature the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude residue was purified via short-path column chromatography: silica gel (30 g) / $CHCl_3$ (1.2 L), than EtOAc (R_f = 0.14–0.17). The fraction of EtOAc was evaporated to give the desired product.

Yield 0.205 g (75%), white solid, mp 114-115 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.52-3.63 (m, 1H, H-5a'), 3.64-3.73 (m, 1H, H-5b'),

3.92-3.99 (m, 1H, H-4'), 4.02 (s, 3H, MeO), 4.07-4.14 (m, 1H, H-3'), 4.20-4.27 (m, 1H, H-2'), 4.71 (dd, 1H, $^{3}J_{1}$ = 6.90 Hz, $^{3}J_{2}$ = 4.63 Hz, OH-5'), 4.78 (d, 1H, ^{3}J = 3.96 Hz, H-1'), 4.99 (d, 1H, ^{3}J = 6.04 Hz, OH-3'), 5.25 (d, 1H, ^{3}J = 5.67 Hz, OH-2'), 6.95 (t, 1H, $^{2}J_{(H-F)}$ = 54.11 Hz, CHF_2), 7.15 (s, 1H, H-5).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 55.3 (MeO), 63.0 (CH_2OH), 72.4 (CH-3'), 76.6 (CH-2'), 85.7 (CH-4'), 86.7 (CH-1'), 104.6 (t, $^{3}J_{(C-F)}$ = 4.6 Hz, CH-5), 113.0 (t, $^{1}J_{(C-F)}$ = 239.7 Hz, CHF_2), 161.1 (t, $^{2}J_{(C-F)}$ = 24.7 Hz, C-4), 170.4, 171.4.

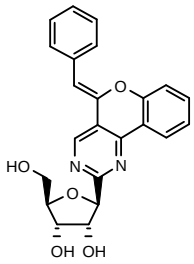
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –120.2 (s, CHF_2).

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3340 (m), 3271 (m), 2953 (w), 2910 (m), 1606 (s), 1564 (s), 1485 (m), 1471 (s), 1435 (m), 1381 (s), 1360 (m), 1338 (m), 1321 (m), 1296 (m), 1282 (m), 1228 (w), 1200 (m), 1184 (m), 1171 (m), 1122 (s), 1099 (s), 1088 (s), 1076 (s), 1045 (s), 1026 (s), 991 (s), 982 (s), 964 (s), 943 (m), 933 (s), 903 (m), 879 (m), 864 (s), 824 (m), 808 (m), 791 (m), 768 (m), 752 (m), 727 (m), 700 (s), 675 (m), 627 (m), 598 (m), 577 (s), 559 (s).

MS (GC, 70 eV): *m/z* (%) = 203 (100), 201 (15), 189 (51), 187 (12), 31 (13).

HRMS (EI): Calcd. for $C_{11}H_{14}N_2O_5F_2$ $[M]^+$: 292.08653, found: 292.08698.

2-(*β*-D-Ribofuranosyl)-(5*Z*)-5-benzylidene-5*H*-chromeno[4,3-*d*]pyrimidine (38a)



Into a 25-mL flask were placed 0.15 g of 1-(*β*-D-ribofuranosyl)formamidine (0.71 mmol, 1 eq), 0.174 g of 3-(phenylethynyl)-4H-chromen-4-one (0.71 mmol, 1 eq), 0.293 g of K_2CO_3 (2.1 mmol, 3 eq), molecular sieves 4Å (0.225 g) and DMF (3 mL). Then the reaction mixture was stirred at 60 °C for 6 hours under argon. After cooling to room temperature the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was recrystallized from MeOH to afford a pure substance.

Yield 0.237 g (83%), yellow solid, mp 204-206 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.56-3.69 (m, 1H, H-5a'), 3.70-3.81 (m, 1H, H-5b'), 3.97-4.06 (m, 1H, H-4'), 4.12-4.22 (m, 1H, H-3'), 4.28-4.37 (m, 1H, H-2'), 4.84-4.95 (m, 2H, H-1', OH-5'), 5.03 (d, 1H, ^{3}J = 6.05 Hz, OH-3'), 5.29 (d, 1H, ^{3}J = 5.67 Hz, OH-2'), 6.77 (s, 1H, =CH–Ph), 7.23-7.38 (m, 3H, CH_{Ar}), 7.41-7.51 (m, 2H, CH_{Ar}), 7.56-7.65 (m, 1H, CH_{Ar}), 7.89 (d 1H, ^{3}J = 7.55 Hz, CH_{Ar}), 8.20-8.27 (m, 1H, CH_{Ar}), 9.34 (s, 1H, H-6).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 63.1 (CH_2OH), 72.4 (CH-3'), 76.8 (CH-2'), 85.7 (CH-4'), 86.9 (CH-1'), 106.5 (CH), 117.5 (CH), 118.9, 120.3, 124.6 (CH_{Ar}), 125.2 (CH_{Ar}), 127.9 (CH_{Ar}), 129.5 (CH_{Ar}), 129.8 (CH_{Ar}), 135.1 (CH_{Ar}), 135.4, 144.2, 152.4, 154.3 (CH_{Ar}), 155.5, 169.2.

MS (EI, 70 eV): *m/z* (%) = 405 ($[M+H]^+$, 64), 404 ($[M]^+$, 100), 368 (20), 316 (56), 315 (99), 314 (51), 313 (30), 302 (50), 301 (88), 300 (15), 299 (12), 286 (23), 285 (32), 273 (13), 272 (11),

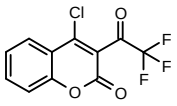
271 (32), 256 (11), 247 (16)m 246 (78), 206 (15), 189 (12), 128 (12), 73 (11), 44 (16), 43 (14).

HRMS (ESI): Calcd. for $C_{23}H_{21}N_2O_5$ $[M+H]^+$: 405.14450, found: 405.14481.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3273 (s), 3064 (m), 2916 (m), 2871 (w), 1658 (w), 1644 (w), 1607 (m), 1595 (m), 1573 (m), 1543 (m), 1494 (w), 1461 (m), 1447 (m), 1424 (m), 1415 (m), 1392 (w), 1331 (m), 1316 (m), 1281 (m), 1242 (m), 1210 (w), 1189 (w), 1161 (w), 1098 (s), 1052 (s), 1043 (s), 1019 (m), 985 (m), 942 (w), 908 (m), 865 (m), 837 (w), 825 (w), 813 (w), 792 (w), 759 (s), 746 (s), 731 (m), 716 (m), 687 (s), 675 (m), 665 (m), 639 (s), 627 (s), 606 (m), 551 (m).

4.2.2 Synthesis of 3-acyl-4-chlorocoumarines

4-Chloro-3-(trifluoroacetyl)coumarin (74a)



Procedure for the synthesis of compound 4a. Synthesis was conducted in a pressure tube. To the suspension of 4-hydroxycoumarin (2.5 g, 15.4 mmol) in dry dioxane (20 mL) was added 2.56 g (32.4 mmol) of dry pyridine. After a brief stirring, when the mixture became completely homogeneous, were added 2.01 g (18.5 mmol) of trimethylsilyl chloride. The reaction mixture was stirred for 1 h at room temperature. Then was added 4.21 g (20.0 mmol) of trifluoroacetic anhydride and the mixture was stirred for another 2 h at 80-90 °C. To the cooled reaction mass was added 2.36 g (15.4 mmol) of phosphorus oxychloride and the mixture was stirred for 2 h at 60 °C. Then the reaction mass was diluted with ice water and extracted with chloroform (50 ml), the chloroform layer was separated, and the water phase was extracted two times with chloroform (50 ml). The combined extract was dried under sodium sulphate, chloroform was removed and the residue was dried in a high vacuum on a boiling water bath. Yield 3.94 g (93%). To obtain product of extra high purity sublimation in vacuum was used. In this case, the yield is 3.29 g (77%).

White solid, mp 115-117 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.43 (d, 1H, ^3J = 8.31 Hz, H-8), 7.44-7.52 (m, 1H, H-6), 7.72-7.80 (m, 1H, H-7), 7.98 (d, 1H, ^3J = 8.12 Hz, H-5).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 115.2 (q, $^1J_{(C-F)}$ = 290.7, CF_3), 117.2, 117.7 (CH-8), 121.1, 126.1 (CH-6), 127.0 (CH-5), 135.9 (CH-7), 150.6, 153.2, 156.2, 181.2 (q, $^2J_{(C-F)}$ = 40.8, CO).

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –75.8 (s, CF_3).

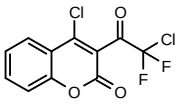
MS (GC, 70 eV): *m/z* (%) = 276 ($[M]^+$, ^{35}Cl, 11), 209 (34), 208 (11), 207 (100), 135 (20), 123 (16), 69 (15), 62 (11).

HRMS (EI): Calcd. for $C_{11}H_4{}^{35}ClF_3O_{23}$ $[M]^+$: 275.97956, found: 275.97919.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3086 (w), 3051 (w), 1728 (s), 1605 (s), 1593 (m), 1566 (m), 1549 (s), 1539 (s), 1479 (m), 1452 (s), 1333 (m), 1315 (s), 1275 (m), 1236 (m), 1196 (s), 1169 (s), 1155 (s),

1134 (s), 1072 (s), 1034 (m), 974 (s), 959 (s), 851 (s), 820 (s), 781 (m), 768 (s), 743 (s), 723 (s), 658 (s), 625 (m), 606 (m), 600 (m), 582 (s), 573 (s).

4-Chloro-3-[chloro(difluoro)acetyl]coumarin (74b)



The title substance was prepared starting from 0.5 g of 4-hydroxycoumarin, 0.512 g of pyridine, 0.402 g of TMSCl, 0.974 g of chlorodifluoroacetic anhydride, 0.473 g of $POCl_3$ and 4 mL of dioxane, using the same procedure as in case of **74a**. Yield of crude product and purified by sublimation is 0.781 g (86%) and 0.631 g (70%) respectively. White solid, mp 82-84 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.44 (d, 1H, ^3J = 8.31 Hz, H-8), 7.44-7.51 (m, 1H, H-6), 7.72-7.79 (m, 1H, H-7), 7.98 (d, 1H, ^3J = 8.12 Hz, H-5).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 117.3, 117.7 (CH-8), 119.6 (t, $^1J_{(C-F)}$ = 305.2, $CClF_2$), 121.5, 126.1 (CH-6), 126.9 (CH-5), 135.7 (CH-7), 150.2, 153.1, 156.2, 181.7 (t, $^2J_{(C-F)}$ = 34.9, CO).

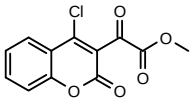
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –64.3 (s, CF_2Cl).

MS (GC, 70 eV): *m/z* (%) = 292 ($[M]^+$, $^{35}Cl_2$, 2.1), 209 (33), 308 (11), 207 (100), 135 (19), 123 (19), 99 (10), 87 (10), 85 (11), 62 (11).

HRMS (EI): Calcd. for $C_{11}H_4{}^{35}Cl_2F_2O_{23}$ $[M]^+$: 291.95001, found: 291.94975.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3080 (w), 1747 (s), 1714 (s), 1682 (m), 1599 (s), 1566 (s), 1556 (m), 1539 (m), 1504 (m), 1481 (m), 1452 (s), 1317 (s), 1294 (m), 1246 (w), 1230 (w), 1198 (s), 1165 (s), 1132 (s), 1084 (m), 1034 (m), 976 (s), 962 (s), 922 (s), 901 (s), 870 (m), 851 (s), 810 (m), 785 (s), 771 (s), 758 (s), 714 (s), 648 (s), 633 (s), 611 (m), 581 (s), 571 (s), 544 (m).

4-Chloro-3-(methoxalyl)coumarin (74c)



To a suspension of 4-hydroxycoumarin (15 g, 93 mmol, 1 eq) in 120 mL of dry dioxane was added dry pyridine (15.366 g, 194 mol, 2.1 eq). After a brief stirring, when the solution became completely homogeneous, trimethylsilyl chloride (12.06 g, 111 mmol, 1.2 eq) was added. The reaction mixture was stirred for 1 h at room temperature, followed by addition of methyl oxalyl chloride (14.733 g, 120 mmol, 1.3 eq). After stirring for ½ h at 80-90 °C the mixture was cooled to r.t. and 14.184 g of phosphorus oxychloride (93 mmol, 1 eq) was added. Then the mixture was stirred for 2 h at 60 °C. Afterwards the reaction mass was diluted with ice water and the product was extracted with chloroform. The combined extract was dried under sodium sulphate, chloroform was evaaporated and the residue was recrystallized from benzene to give 17.76 g of the pure product.

Yield 17.76 g (72%), beige solid, mp 110-112 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.96 (s, 3H, MeO), 7.42 (d, 1H, ^{3}J = 8.31 Hz, H-8), 7.43-7.50 (m, 1H, H-6), 7.70-7.78 (m, 1H, H-7), 8.04 (d, 1H, ^{3}J = 8.12 Hz, H-5).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 53.8 (MeO), 117.6 (CH-8), 118.1, 121.8, 126.0 (CH-6), 127.4 (CH-5), 135.6 (CH-7), 151.7, 153.1, 157.9, 161.5, 181.9 (CO).

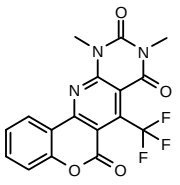
MS (GC, 70 eV): *m/z* (%) = 266 ([M]$^{+}$, ^{35}Cl, 2.4), 209 (34), 208 (11), 207 (100), 135 (16), 123 (19).

HRMS (ESI): Calcd. for $C_{12}H_8{}^{35}ClO_5$ [M+H]$^{+}$: 267.00548, found: 267.00565.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3091 (w), 1761 (s), 1713 (s), 1699 (s), 1668 (s), 1651 (m), 1633 (m), 1603 (s), 1587 (s), 1549 (s), 1539 (s), 1520 (s), 1504 (s), 1481 (m), 1450 (s), 1435 (s), 1365 (m), 1335 (m), 1313 (s), 1294 (s), 1259 (s), 1238 (s), 1205 (s), 1159 (m), 1136 (m), 1105 (m), 1088 (s), 1036 (s), 1003 (s), 960 (s), 881 (m), 856 (s), 835 (m), 814 (m), 793 (m), 779 (s), 762 (s), 741 (s), 733 (s), 683 (m), 662 (s), 650 (m), 611 (s), 604 (m), 584 (s), 557 (m).

4.2.3 Synthesis of fused pyridines from 4-chloro-3-(trifluoroacetyl)coumarin

9,11-Dimethyl-7-(trifluoromethyl)-6*H*-chromeno[3',4':5,6]pyrido[2,3-*d*]pyrimidine-6,8,10(9*H*,11*H*)-trione (77a)



A sealed ACE pressure tube was charged with 0.3 g of 4-chloro-3-(trifluoroacetyl)coumarin **74a** (1.09 mmol, 1 eq), 0.169 g of 6-amino-1,3-dimethyluracil, 5 mL of dry DMF and 1 mL of trimethylsilyl chloride. The reaction mixture was stirred at 80 °C for 4 h, cooled to r.t. and diluted with methanol. The precipitate was filtered off, washed twice with methanol and dried in a high vacuum.

Yield 0.3 g (73%), white solid, mp 267-269 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.41 (s, 3H, CH_3-9), 3.70 (s, 3H, CH_3-11), 7.30-7.38 (m, 1H, H-2), 7.47 (d, 1H, ^{3}J = 8.31 Hz, H-4), 7.70-7.78 (m, 1H, H-3), 8.32 (d, 1H, ^{3}J = 8.12 Hz, H-1).

^{13}C NMR (75.47 MHz, 12% TFA-*d* in $CDCl_3$): δ = 30.3 (CH_3), 31.6 (CH_3), 105.8, 112.4, 114.9, 117.8 (CH_{Ar}), 120.3 (q, $^{1}J_{(C-F)}$ = 276.8, CF_3), 124.7 (CH_{Ar}), 131.3 (CH_{Ar}), 136.0 (CH_{Ar}), 151.3, 152.0, 152.5, 153.5, 153.6 (q, $^{2}J_{(C-F)}$ = 37.9), 157.7, 160.8.

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –64.3 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 377 ([M]$^{+}$, 49), 376 (100).

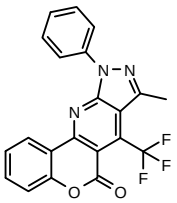
HRMS (ESI): Calcd. for $C_{17}H_{11}F_3N_3O_4$ [M+H]$^{+}$: 378.06962, found: 378.06916.

Anal. Calcd for $C_{17}H_{10}F_3N_3O_4$: C, 54.12; H, 2.67; N, 11.14. Found: C, 54.07; H, 2.59; N, 10.89.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2960 (w), 1757 (m), 1714 (s), 1660 (s), 1606 (m), 1589 (s), 1564 (s),

1552 (s), 1462 (s), 1412 (m), 1396 (m), 1365 (m), 1323 (w), 1308 (m), 1288 (m), 1244 (s), 1230 (s), 1215 (s), 1194 (s), 1173 (s), 1155 (s), 1134 (s), 1082 (m), 1059 (m), 1047 (m), 1011 (s), 970 (m), 935 (m), 891 (m), 872 (w), 833 (w), 824 (m), 775 (s), 760 (m), 748 (m), 733 (s), 692 (m), 685 (m), 660 (m), 642 (m), 623 (m), 609 (w), 569 (w), 542 (w).

8-methyl-10-phenyl-7-(trifluoromethyl)chromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(10*H*)-one (77b)



This product was prepared following the same procedure used for **74a**, starting from 0.3 g of 4-chloro-3-(trifluoroacetyl)coumarin (1.09 mmol, 1 eq), 0.188 g of 5-amino-3-methyl-1-phenyl-1*H*-pyrazol (1.09 mmol, 1 eq) and 1 mL of TMSCl in 5 mL of DMF.

Yield 0.219 g (51%), yellow solid, mp 219 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.76 (s, 3H, $^{6}J_{(H\text{-}F)}$ = 3.72 Hz, CH_3-8), 7.33 (d, 1H, ^{3}J = 8.31 Hz, H-4), 7.35-7.43 (m, 2H, H-2, $CH_{p\text{-}Ph}$), 7.54-7.63 (m, 3H, H-3, CH_{Ph}), 8.22-8.29 (m, 2H, CH_{Ph}), 8.52 (d, 1H, ^{3}J = 8.03 Hz, H-1).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 17.2 (q, $^{6}J_{(C\text{-}F)}$ = 6.89, CH_3), 109.9, 115.2, 117.2 (CH_{Ar}), 118.8, 121.8 (CH_{Ar}), 122.3 (q, $^{1}J_{(C\text{-}F)}$ = 275.8, CF_3), 125.1 (CH_{Ar}), 126.0 (CH_{Ar}), 127.2 (CH_{Ar}), 129.5 (CH_{Ar}), 133.6 (CH_{Ar}), 137.0 (q, $^{2}J_{(C\text{-}F)}$ = 36.8), 138.5, 144.3, 152.2, 152.4, 152.9, 157.8.

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –55.0 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 396 ($[M+H]^+$, 23), 395 ($[M]^+$, 100), 394 (12).

HRMS (ESI): Calcd. for $C_{21}H_{13}F_3N_3O_2$ $[M+H]^+$: 396.09544, found: 396.09499.

Anal. Calcd for $C_{21}H_{12}F_3N_3O_2$: C, 63.80; H, 3.06; N, 10.63. Found: C, 63.44; H, 2.98; N, 10.42.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3072 (w), 1738 (s), 1614 (w), 1593 (m), 1568 (s), 1516 (w), 1498 (s), 1466 (m), 1443 (m), 1419 (s), 1390 (m), 1365 (m), 1340 (m), 1323 (w), 1275 (m), 1261 (w), 1242 (s), 1213 (s), 1174 (s), 1136 (s), 1117 (s), 1097 (m), 1074 (s), 1036 (m), 1020 (m), 1003 (w), 991 (m), 955 (w), 906 (w), 887 (m), 858 (w), 835 (w), 814 (w), 797 (m), 768 (s), 752 (s), 731 (s), 714 (m), 687 (s), 677 (m), 656 (s), 648 (m), 631 (m), 598 (w), 584 (m), 546 (w), 536 (m), 528 (w).

4.2.4 Synthesis of 6-amino-1,3-dialkylpyrimidine-2,4(1*H*,3*H*)-diones

General procedure for the synthesis of 6-amino-1,3-dialkylpyrimidine-2,4(1*H*,3*H*)-diones 70.

Method A (for simple anilines):

In a Schlenk tube were placed 1 eq of 6-chloro-1,3-dialkyluracil and 2,2 eq of amine. Then

the reaction mass was heated under argon at 180 °C for 3 hours. After cooling to 100 °C the mixture was treated by hot water, cooled to r.t. and triturated with diethyl ether. The formed solid was filtered off by suction, washed twice with water and diethyl ether and dried in a high vacuum.

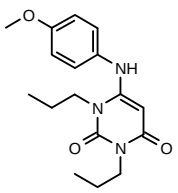
Method B (for anilines with two amino groups):

In a Schlenk tube were placed 1 eq of amine and 1.2 eq of 6-chloro-1,3-dimethyluracil (molar ratio = 1 : 2.4). Then 1 eq of quinoline was added and the reaction mass was heated under argon at 180 °C for 3 hours. After cooling to 70 °C the mixture was treated by hot ethanol and boiled few minutes under reflux. The precipitate was filtered off by suction, washed twice with ethanol and dried in a high vacuum.

Method C (for inactive amines):

In a Schlenk flask was prepared solution of amine (2.2 eq) in dry THF. Then 2.2 eq of *n*-butyl lithium (2.5 M solution in hexane) was added at –78 °C under argon. To obtained lithium salt previously prepared solution of 6-chloro-1,3-dialkyluracil (1 eq) in THF was added dropwise and afterwards the reaction mixture was allowed to warm to r.t.. The next day the solution was acidified with acetic acid and the solvent was evaporated. The solid rest was triturated with water and diethyl ether, filtered off by suction, washed twice and dried in a high vacuum.

6-[(4-Methoxyphenyl)amino]-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione (70a)



The product was prepared according to the **Method A**, starting from 1.2 g of 6-chloro-1,3-dipropyluracil and 1.409 g of *p*-anisidine.

Yield 1.133 g (69%), pinkish solid, mp 109-111 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.86 (t, 3H, ^{3}J = 6.99 Hz), 0.95 (t, 3H, ^{3}J = 7.09 Hz), 1.46-1.82 (m, 4H, CH_2), 3.68-3.88 (m, 5H, CH_2, MeO), 3.96 (t, 1H, ^{3}J = 6.99 Hz), 4.66 (s, 1H, H-5), 6.78 (br s, 1H, NH), 6.84 (d, 2H, ^{3}J = 6.84 Hz, CH_{Ph}), 7.01 (d, 2H, ^{3}J = 6.84 Hz, CH_{Ph}).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 11.4 (CH_3), 11.6 (CH_3), 21.4 (CH_2), 21.9 (CH_2), 42.9 (CH_2), 44.2 (CH_2), 55.8 (MeO), 78.1 (CH-5), 115.1 (CH_{Ar}), 128.0 (CH_{Ar}), 129.8, 151.9, 153.8, 158.7, 163.3.

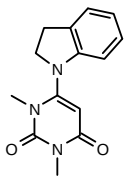
MS (GC, 70 eV): *m/z* (%) = 318 ($[M+H]^+$, 19), 317 ($[M]^+$, 99), 275 (46), 274 (49), 260 (12), 233 (20), 190 (31), 189 (20), 175 (17), 174 (20), 162 (22), 153 (10), 149 (18), 148 (25), 147 (27), 146 (15), 134 (13), 133 (18), 132 (18), 123 (100), 121 (13), 108 (16), 77 (11), 68 (15), 43 (15), 41 (19).

HRMS (ESI): Calcd. for $C_{17}H_{24}N_3O_3$ $[M+H]^+$: 318.18122, found: 318.18072.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3273 (w), 2958 (m), 2875 (w), 2837 (w), 1687 (s), 1606 (s), 1587 (s), 1531 (s), 1506 (s), 1479 (s), 1456 (s), 1437 (s), 1412 (s), 1392 (s), 1379 (s), 1360 (s), 1335 (m),

1319 (m), 1286 (s), 1267 (m), 1242 (s), 1205 (m), 1178 (s), 1165 (s), 1105 (m), 1049 (m), 1032 (s), 1011 (m), 937 (m), 895 (m), 878 (m), 831 (m), 777 (s), 764 (s), 750 (s), 737 (s), 712 (m), 673 (m), 644 (m), 629 (s), 552 (s).

6-(2,3-Dihydro-1*H*-indol-1-yl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (70b)



The product was prepared according to the **Method A**, starting from 0.7 g of 6-chloro-1,3-dimethyluracil and 1.051 g of indoline.

Yield 0.714 g (69%), white solid, mp 148-149 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.15 (t, 2H, ^3J = 7.93 Hz, CH_2-3'), 3.36 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 3.77 (t, 2H, ^3J = 7.93 Hz, CH_2-2'), 5.56 (s, 1H, H-5), 6.67 (d, 1H, ^3J = 7.93 Hz, H-7'), 6.89-6.98 (m, 1H, H-5'), 7.09-7.18 (m, 1H, H-6'), 7.23 (d, 1H, ^3J = 7.37 Hz, H-4').

^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 28.2 (CH_3), 29.1 (CH_2-3'), 33.6 (CH_3), 54.3 (CH_2-2'), 89.7 (CH-5), 112.8 (CH_{Ar}), 122.6 (CH_{Ar}), 125.7 (CH_{Ar}), 127.8 (CH_{Ar}), 131.9, 145.6, 153.2, 154.5, 163.6.

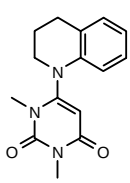
MS (GC, 70 eV): *m/z* (%) = 258 ($[M+H]^+$, 15), 257 ($[M]^+$, 100), 256 (19), 119 (50), 118 (31), 117 (10), 82 (47).

HRMS (EI): Calcd. for $C_{14}H_{15}N_3O_2$ $[M]^+$: 257.11588, found: 257.11583.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3049 (w), 2949 (w), 2860 (w), 1695 (s), 1651 (s), 1635 (s), 1614 (s), 1605 (s), 1591 (s), 1504 (w), 1485 (s), 1435 (s), 1381 (m), 1362 (m), 1354 (m), 1336 (m), 1302 (m), 1292 (m), 1265 (s), 1230 (m), 1217 (m), 1169 (m), 1159 (w), 1149 (w), 1093 (w), 1065 (w), 1047 (w), 1024 (w), 989 (m), 937 (w), 924 (w), 879 (w), 868 (w), 827 (w), 806 (w), 797 (s), 756 (s), 748 (s), 725 (m), 716 (m), 694 (m), 683 (m), 671 (m), 604 (w), 554 (m), 538 (m).

6-(3,4-Dihydroquinolin-1(2*H*)-yl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (70c)

The product was prepared according to the **Method C**, using a solution of 1,2,3,4-tetrahydroquinoline (1.846 g) in dry THF (22 mL), 5.5 mL of *n*-butyl lithium (2.5 M solution in hexane) and a solution of 6-chloro-1,3-dimethyluracil (1.1 g) in dry THF (22 mL).



Yield 1.494 g (87%), brownish oil.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.00-2.13 (m, 2H, CH_2-3'), 2.86 (t, 2H, ^3J = 6.71 Hz, CH_2-4'), 3.25 (s, 3H, CH_3), 3.37 (s, 3H, CH_3), 3.46 (t, 2H, ^3J = 5.86 Hz, CH_2-2'), 5.51 (s, 1H, H-5), 6.55 (d, 1H, ^3J = 8.12 Hz, H-8'), 6.86-6.96 (m, 1H, H-6'), 7.01-7.09 (m, 1H, H-7'), 7.11 (d, 1H, ^3J = 7.74 Hz, H-5').

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 22.5 (CH_2), 26.8 (CH_2), 28.3 (CH_3), 32.5 (CH_3), 49.8 (CH_2-2'), 95.3 (CH-5), 117.7 (CH_{Ar}), 122.3 (CH_{Ar}), 126.5, 127.3 (CH_{Ar}), 130.0 (CH_{Ar}), 141.3,

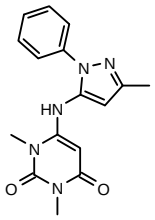
153.1, 156.3, 163.6.

MS (GC, 70 eV): *m/z* (%) = 272 ([M+H]$^+$, 16), 271 ([M]$^+$, 100), 270 (69), 254 (34), 186 (12), 185 (55), 133 (19), 132 (35), 130 (21), 117 (27), 82 (58), 77 (11).

HRMS (ESI): Calcd. for $C_{15}H_{18}N_3O_2$ [M+H]$^+$: 272.13935, found: 272.13934.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2932 (m), 2859 (w), 1697 (m), 1644 (s), 1615 (s), 1598 (s), 1587 (s), 1491 (s), 1425 (s), 1389 (m), 1368 (m), 1296 (m), 1253 (m), 1229 (m), 1192 (m), 1171 (m), 1114 (w), 1072 (w), 1020 (w), 996 (m), 941 (w), 910 (w), 888 (w), 875 (w), 850 (w), 806 (m), 749 (s), 716 (m), 700 (m), 690 (m), 654 (w), 645 (w), 596 (w), 547 (m).

1,3-Dimethyl-6-[(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)amino]pyrimidine-2,4(1*H*,3*H*)-dione (70d)



The product was prepared according to the **Method C**, using a solution of 5-amino-3-methyl-1-phenylpyrazole (0.764 g) in dry THF (7 mL), 1.76 mL of *n*-butyl lithium (2.5 M solution in hexane) and a solution of 6-chloro-1,3-dimethyluracil (0.35 g) in dry THF (7 mL).

Yield 0.51 g (82%), white solid, mp 125-126 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.32 (s, 3H, CH_3-3'), 3.10 (s, 3H, CH_3), 3.39 (s, 3H, CH_3), 4.38 (s, 1H, H-5), 6.36 (s, 1H, H-4'), 7.34-7.42 (m, 1H, $CH_{p\text{-Ph}}$), 7.46-7.60 (m, 4H, CH_{Ph}), 8.83 (br s, 1H, NH).

^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 14.8 (CH_3-3'), 28.2 (CH_3), 30.9 (CH_3), 78.0 (CH-5), 105.9, 123.6 (CH_{Ph}), 128.1 (CH_{Ph}), 130.1 (CH_{Ph}), 136.5, 139.2, 149.4, 152.1, 153.8, 162.3.

MS (GC, 70 eV): *m/z* (%) = 312 ([M+H]$^+$, 19), 311 ([M]$^+$, 100), 184 (18), 82 (13), 77 (23), 55 (19).

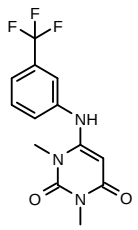
HRMS (ESI): Calcd. for $C_{16}H_{18}N_5O_2$ [M+H]$^+$: 312.14550, found: 312.14612.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3452 (w), 3331 (w), 3138 (w), 3030 (w), 2902 (w), 1701 (s), 1651 (s), 1633 (s), 1605 (s), 1593 (s), 1549 (s), 1497 (s), 1471 (s), 1435 (s), 1417 (s), 1381 (s), 1362 (m), 1313 (m), 1286 (m), 1230 (m), 1198 (m), 1173 (m), 1144 (m), 1076 (m), 1049 (w), 1022 (m), 1014 (m), 995 (m), 908 (w), 854 (w), 837 (w), 798 (w), 783 (s), 752 (s), 743 (s), 712 (m), 692 (s), 667 (m), 650 (m), 619 (s), 602 (s), 575 (s).

1,3-Dimethyl-6-{[3-(trifluoromethyl)phenyl]amino}pyrimidine-2,4(1*H*,3*H*)-dione (70e)

The product was prepared according to the **Method A**, starting from 1.1 g of 6-chloro-1,3-dimethyluracil and 2.233 g of 3-(trifluoromethyl)aniline.

Yield 1.587 g (84%), white solid, mp 198-200 °C.



^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.25 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 4.91 (s, 1H, H-5), 7.25 (br s, 1H, NH), 7.28-7.35 (m, 1H, CH_{Ar}), 7.36 (s, 1H, CH_{Ar}), 7.39-7.47 (m, 2H, CH_{Ar}).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 28.3 (CH_3), 30.1 (CH_3), 79.7 (CH-5), 121.6 (q, $^{3}J_{(C-F)}$ = 3.8 Hz, CH), 123.1 (q, $^{3}J_{(C-F)}$ = 3.8 Hz, CH), 123.8 (q, $^{1}J_{(C-F)}$ = 272.7 Hz, CF_3), 128.0 (CH), 130.5 (CH), 132.5 (q, $^{2}J_{(C-F)}$ = 32.9 Hz), 138.5, 152.2, 153.1, 163.6.

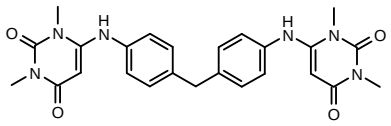
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –62.9 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 300 ($[M+H]^+$, 15), 299 ($[M]^+$, 100), 280 (16), 241 (15), 214 (18), 213 (67), 212 (11), 200 (33), 199 (33), 186 (20), 185 (35), 172 (20), 145 (69), 127 (46), 126 (12), 95 (10), 82 (35), 55 (21), 54 (10), 42 (13).

HRMS (ESI): Calcd. for $C_{13}H_{13}F_3N_3O_2$ $[M+H]^+$: 300.09544, found: 300.09553.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3307 (w), 3066 (w), 1699 (m), 1633 (s), 1605 (s), 1591 (m), 1537 (s), 1493 (s), 1471 (m), 1443 (m), 1421 (m), 1383 (m), 1362 (m), 1331 (s), 1315 (s), 1281 (m), 1265 (m), 1213 (w), 1171 (s), 1124 (s), 1093 (s), 1066 (s), 1003 (m), 933 (m), 920 (m), 891 (m), 816 (m), 777 (s), 750 (s), 743 (s), 702 (s), 673 (w), 662 (s), 648 (m), 638 (m), 582 (m).

6,6'-[Methylenebis(4,1-phenyleneimino)]bis(1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione) (70f)



The product was prepared according to the **Method B**, starting from 0.442 g of 6-chloro-1,3-dimethyluracil, 0.209 g of 4,4'-diaminodiphenylmethane and 0.392 g of quinoline.

Yield 0.387 g (77%), brownish solid, mp 308-310 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.14 (s, 6H, CH_3), 3.46 (s, 6H, CH_3), 4.02 (s, 2H, CH_2), 4.63 (s, 2H, H5, H5'), 7.22 (d, 4H, ^{3}J = 8.50 Hz, CH_{Ar}), 7.33 (d, 4H, ^{3}J = 8.50 Hz, CH_{Ar}), 8.50 (s, 2H, NH).

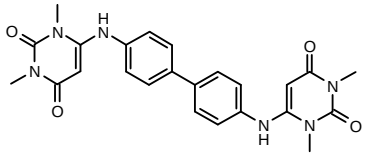
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.1 (CH_3), 30.9 (CH_3), 40.8 (CH_2), 77.8 (CH-5, CH-5'), 126.2 (CH), 130.6 (CH), 137.2, 139.7, 152.5, 154.3, 162.5.

MS (GC, 70 eV): *m/z* (%) = 475 ($[M+H]^+$, 20), 474 ($[M]^+$, 72), 473 (100), 334 (13), 229 (10), 145 (12), 104 (16), 82 (12), 40 (11).

HRMS (ESI): Calcd. for $C_{25}H_{27}N_6O_4$ $[M+H]^+$: 475.20883, found: 475.20938.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3209 (w), 2953 (w), 1695 (s), 1622 (s), 1589 (s), 1525 (s), 1510 (s), 1462 (s), 1441 (s), 1431 (s), 1414 (s), 1381 (s), 1360 (s), 1282 (s), 1257 (s), 1192 (m), 1178 (m), 1107 (m), 1020 (m), 999 (m), 912 (m), 860 (m), 812 (m), 777 (s), 752 (s), 723 (m), 667 (m), 648 (s), 635 (s), 577 (m), 542 (s).

6,6'-[Biphenyl-4,4'-diyldi(imino)]bis(1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione) (70g)



The product was prepared according to the **Method B**, starting from 0.455 g of 6-chloro-1,3-dimethyluracil, 0.2 g of benzidine and 0.404 g of quinoline.

Yield 0.452 g (91%), grey solid, mp >375 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.17 (s, 6H, CH_3), 3.50 (s, 6H, CH_3), 4.82 (s, 2H, H5, H5'), 7.38 (d, 4H, ^3J = 8.59 Hz, CH_{Ar}), 7.80 (d, 4H, ^3J = 8.59 Hz, CH_{Ar}), 8.63 (s, 2H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.2 (CH_3), 31.1 (CH_3), 78.6 (CH-5, CH-5'), 125.8 (CH), 128.3 (CH), 137.2, 138.8, 152.5, 154.0, 162.5.

MS (EI, 70 eV): *m/z* (%) = 461 ($[M+H]^+$, 23), 460 ($[M]^+$, 100), 374 (11).

HRMS (EI): Calcd. for $C_{24}H_{24}O_4N_6$ $[M]^+$: 460.18535, found: 460.185839.

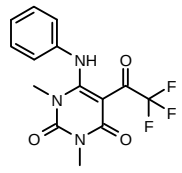
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3219 (m), 3109 (w), 3043 (w), 2958 (w), 2895 (w), 1701 (s), 1624 (s), 1597 (s), 1581 (s), 1525 (s), 1497 (s), 1466 (s), 1429 (s), 1383 (s), 1363 (s), 1321 (m), 1288 (s), 1275 (s), 1254 (s), 1192 (m), 1051 (m), 1009 (m), 997 (m), 912 (m), 818 (s), 775 (s), 754 (s), 729 (m), 698 (m), 669 (m), 654 (m), 642 (m), 602 (s), 538 (m).

4.2.5 Synthesis of 5-(polyfluoroacyl)-6-amino-1,3-dialkyl-pyrimidine-2,4(1*H*,3*H*)-diones

General procedure for the synthesis of 5-(polyfluoroacyl)-6-amino-1,3-dialkyl-pyrimidine-2,4(1*H*,3*H*)-diones 87a-w and 90a-c.

To a solution of 6-amino-1,3-dialkyl-pyrimidine-2,4(1*H*,3*H*)-dione **70** (0.4 g) in 4 mL of dry dioxane was added dry pyridine (1.2 eq) and corresponding anhydride (or chloroanhydride, if R_F = *n*-C_3F_7) of polyfluorocarboxylic acid (2 eq). Then the solution was allowed to stand at r.t. overnight. The next day the solvent was evaporated and the residue was dried in high vacuum at 100 °C. Then the crude product was triturated with water, filtered off by suction and dried in a high vacuum.

6-Anilino-1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione (87a)



The product was prepared according to the general procedure from 0.4 g of 6-anilino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, 0.164 g of pyridine and 0.727 g of trifluoroacetic anhydride in 4 mL of dry dioxane.

Yield 0.524 g (93%), white solid, mp 143-145 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.09 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 7.22-7.40 (m, 3H, CH_{Ph}), 7.40-7.51 (m, 2H, ^3J = 7.27 Hz, $CH_{m\text{-}Ph}$), 11.10 (br s, 1H, NH).

^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –71.4 (s, CF_3).

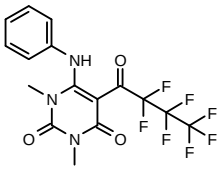
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 28.6 (CH_3), 36.1 (CH_3), 93.3, 117.7 (q, $^{1}J_{(C-F)}$ = 288.6 Hz, CF_3), 124.2 (CH), 127.1 (CH), 130.5 (CH), 139.4, 151.6, 159.0, 160.7, 179.0 (q, $^{2}J_{(C-F)}$ = 35.8 Hz, CO).

MS (EI, 70 eV): *m/z* (%) = 328 ($[M+H]^+$, 10), 327 ($[M]^+$, 69), 309 (40), 259 (27), 258 (100), 230 (11), 201 (64), 197 (53), 133 (11), 92 (12), 77 (20), 69 (11).

HRMS (ESI): Calcd. for $C_{14}H_{13}F_3N_3O_3$ $[M+H]^+$: 328.09035, found: 328.09031.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3057 (w), 2955 (w), 1726 (m), 1668 (s), 1651 (s), 1614 (s), 1585 (s), 1514 (s), 1495 (s), 1446 (s), 1416 (m), 1387 (m), 1325 (m), 1308 (s), 1284 (m), 1240 (m), 1203 (s), 1173 (s), 1155 (s), 1084 (s), 1053 (m), 1028 (m), 1014 (m), 995 (s), 926 (m), 872 (w), 860 (w), 845 (w), 824 (m), 795 (s), 760 (s), 748 (s), 719 (m), 696 (s), 687 (s), 662 (s), 615 (m), 594 (m), 567 (m), 530 (s).

6-Anilino-5-(2,2,3,3,4,4,4-heptafluorobutanoyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (87b)



The product was prepared according to the general procedure from 0.4 g of 6-anilino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, 0.164 g of pyridine and 0.804 g of heptafluorobutyryl chloride in 4 mL of dry dioxane.

Yield 0.712 g (96%), white solid, mp 127-128 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.08 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 7.27 (t, 1H, ^{3}J = 7.27 Hz, $CH_{p\text{-Ph}}$), 7.19 (d, 2H, ^{3}J = 7.55 Hz, $CH_{o\text{-Ph}}$), 7.40-7.49 (m, 2H, $CH_{m\text{-Ph}}$), 10.84 (br s, 1H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.7 (CH_3), 36.2 (CH_3), 94.7 (C-5), 124.1 (CH), 127.0 (CH), 130.5 (CH), 139.3, 151.7, 158.5, 160.7, 181.9 (t, $^{2}J_{(C-F)}$ = 26.6 Hz, CO).

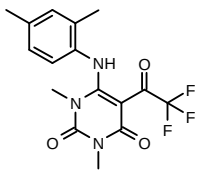
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –121.2 (s, CF_2), –111.0 (q, J = 10.22 Hz, CF_2), –79.9 (t, J = 9.70 Hz, CF_3).

MS (GC, 70 eV): *m/z* (%) = 427 ($[M]^+$, 7.8), 259 (16), 258 (100), 201 (30), 92 (11), 77 (12).

HRMS (EI): Calcd. for $C_{16}H_{12}O_3N_3F_7$ $[M]^+$: 427.07614, found: 427.076505.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3014 (w), 2956 (w), 1720 (m), 1666 (s), 1624 (s), 1576 (s), 1495 (s), 1444 (s), 1408 (m), 1379 (m), 1336 (s), 1311 (m), 1282 (s), 1213 (s), 1176 (s), 1147 (s), 1122 (s), 1088 (m), 1078 (m), 1065 (m), 1028 (m), 1005 (m), 951 (m), 932 (m), 914 (m), 893 (s), 860 (m), 808 (m), 789 (s), 777 (s), 754 (s), 721 (s), 694 (s), 685 (s), 654 (s), 615 (m), 594 (s), 567 (m), 528 (s).

6-[(2,4-Dimethylphenyl)amino]-1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione (87c)



The product was prepared according to the general procedure from 0.39 g of 6-[(2,4-dimethylphenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, 0.143 g of pyridine and 0.632 g of trifluoroacetic anhydride in 3.9 mL of dry dioxane.

Yield 0.481 g (90%), white solid, mp 136-138 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.31 (s, 3H, Ar-CH_3), 2.32 (s, 3H, Ar-CH_3), 2.96 (s, 3H, N-CH_3), 3.22 (s, 3H, N-CH_3), 7.10 (d, 1H, ^{3}J = 8.12 Hz, CH_{Ar}), 7.17-7.23 (m, 2H, CH_{Ar}), 11.43 (br s, 1H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 17.5 (Ar-CH_3), 20.4 (Ar-CH_3), 27.7 (N-CH_3), 35.2 (N-CH_3), 91.7 (C-5), 117.0 (q, $^{1}J_{(C-F)}$ = 287.8 Hz, CF_3), 124.9 (CH), 127.4 (CH), 131.7 (CH), 132.0, 134.0, 136.8, 150.5, 159.1, 159.4, 177.6 (q, $^{2}J_{(C-F)}$ = 35.8 Hz, CO).

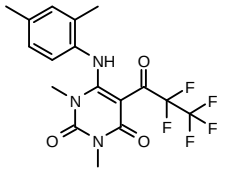
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –71.1 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 355 ([M]$^+$, 31), 287 (13), 286 (100), 229 (12), 128 (14), 120 (11), 69 (13).

HRMS (EI): Calcd. for C16H16O3N3F3 [M]$^+$: 355.11383, found: 355.11345.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 2359 (w), 1726 (m), 1668 (s), 1645 (m), 1614 (s), 1583 (s), 1514 (s), 1504 (s), 1454 (s), 1441 (s), 1387 (m), 1379 (m), 1317 (s), 1281 (m), 1246 (m), 1228 (m), 1213 (s), 1196 (s), 1173 (s), 1155 (s), 1080 (s), 1057 (m), 1036 (m), 995 (s), 947 (m), 893 (m), 883 (w), 852 (m), 824 (m), 795 (s), 773 (m), 758 (s), 733 (s), 706 (m), 685 (m), 650 (m), 581 (m), 569 (m), 557 (m), 532 (m).

6-[(2,4-Dimethylphenyl)amino]-1,3-dimethyl-5-(2,2,3,3,3-pentafluoropropanoyl)pyrimidine-2,4(1*H*,3*H*)-dione (87d)



The product was prepared according to the general procedure from 0.35 g of 6-[(2,4-dimethylphenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, 0.128 g of pyridine and 0.837 g of pentafluoropropionic anhydride in 3.5 mL of dry dioxane.

Yield 0.481 g (88%), yellowish solid, mp 193-195 °C.

^{1}H NMR (250.13 MHz, DMSO-d_6): δ = 2.30 (s, 3H, Ar-CH_3), 2.32 (s, 3H, Ar-CH_3), 2.91 (s, 3H, N-CH_3), 3.23 (s, 3H, N-CH_3), 7.10 (d, 1H, ^{3}J = 8.04 Hz, CH_{Ar}), 7.18-7.25 (m, 2H, CH_{Ar}), 11.42 (br s, 1H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 18.5 (CH_3), 21.4 (CH_3), 28.8 (CH_3), 36.4 (CH_3),

94.1 (C-5), 126.0 (CH), 128.4 (CH), 132.6 (CH), 133.0, 134.8, 137.8, 151.5, 160.2, 160.3, 181.0 (t, $^{2}J_{(C\text{-}F)}$ = 27.1 Hz, CO).

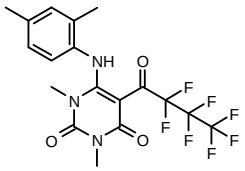
^{19}F NMR (235.33 MHz, DMSO-d_6): δ = –115.2 (s, CF_2), –78.5 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 405 ([M]$^+$, 65), 387 (18), 287 (27), 286 (100), 275 (14), 258 (17), 229 (24), 120 (11).

HRMS (ESI): Calcd. for $C_{17}H_{17}F_5N_3O_3$ [M+H]$^+$: 406.11846, found: 406.11903.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 2929 (w), 2351 (w), 1724 (s), 1668 (s), 1614 (s), 1583 (s), 1516 (s), 1504 (s), 1454 (s), 1444 (s), 1385 (m), 1363 (s), 1315 (s), 1279 (m), 1225 (s), 1173 (s), 1140 (s), 1111 (s), 1061 (m), 1030 (m), 960 (s), 939 (s), 889 (m), 852 (m), 816 (s), 804 (m), 787 (s), 760 (s), 739 (s), 729 (s), 704 (m), 687 (s), 656 (m), 642 (s), 586 (m), 569 (m), 561 (m), 536 (m).

6-[(2,4-Dimethylphenyl)amino]-5-(2,2,3,3,4,4,4-heptafluorobutanoyl)-1,3-dimethyl-pyrimidine-2,4(1*H*,3*H*)-dione (87e)



The product was prepared according to the general procedure from 0.35 g of 6-[(2,4-dimethylphenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, 0.128 g of pyridine and 0.627 g of heptafluorobutyryl chloride in 3.5 mL of dry dioxane.

Yield 0.535 g (87%), white solid, mp 130 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.31 (s, 3H, Ar-CH_3), 2.32 (s, 3H, Ar-CH_3), 2.95 (s, 3H, N-CH_3), 3.22 (s, 3H, N-CH_3), 7.10 (d, 1H, ^{3}J = 8.12 Hz, CH_{Ar}), 7.18-7.23 (m, 2H, CH_{Ar}), 11.14 (br s, 1H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 18.5 (CH_3), 21.4 (CH_3), 28.7 (CH_3), 36.2 (CH_3), 94.0 (C-5), 125.9 (CH), 128.4 (CH), 132.6 (CH), 133.0, 134.9, 137.7, 151.6, 159.7, 160.5, 181.6 (t, $^{2}J_{(C\text{-}F)}$ = 26.3 Hz, CO).

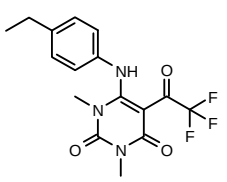
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –120.8 (s, CF_2), –110.3 (q, J = 169.62 Hz, CF_2), –79.8 (t, J = 9.70 Hz, CF_3).

MS (GC, 70 eV): *m/z* (%) = 455 ([M]$^+$, 22), 287 (18), 286 (100), 258 (11), 229 (13).

HRMS (EI): Calcd. for $C_{18}H_{16}O_3N_3F_7$ [M]$^+$: 455.10744, found: 455.107556.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956 (w), 2928 (w), 2145 (w), 1724 (m), 1672 (s), 1606 (s), 1574 (s), 1502 (s), 1443 (s), 1406 (m), 1387 (m), 1333 (m), 1315 (s), 1282 (m), 1267 (m), 1254 (m), 1221 (s), 1207 (s), 1198 (s), 1165 (s), 1140 (s), 1120 (s), 1086 (m), 1066 (s), 1055 (s), 1039 (m), 1007 (m), 959 (m), 951 (m), 933 (s), 924 (s), 893 (m), 856 (m), 816 (s), 802 (m), 787 (s), 758 (s), 743 (s), 725 (s), 706 (m), 685 (s), 675 (s), 640 (s), 596 (m), 561 (m), 546 (m).

6-[(4-Ethylphenyl)amino]-1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione (87f)



The product was prepared according to the general procedure from 0.3 g of 6-[(4-ethylphenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, 0.11 g of pyridine and 0.486 g of trifluoroacetic anhydride in 3 mL of dry dioxane.

Yield 0.362 g (88%), grey solid, mp 141-143 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.21 (t, 3H, ^{3}J = 7.55 Hz, Et), 2.64 (q, 2H, ^{3}J = 7.55 Hz, Et), 3.06 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 7.26 (d, 2H, ^{3}J = 8.78 Hz, CH_{Ar}), 7.29 (d, 2H, ^{3}J = 8.78 Hz, CH_{Ar}), 11.22 (br s, 1H, NH).

^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –71.3 (s, CF_3).

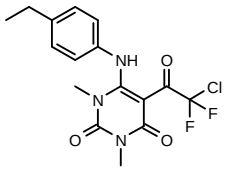
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 16.4 ($CH_{3(Et)}$), 28.5 (CH_2), 28.6 (CH_3), 36.3 (CH_3), 93.1, 117.8 (q, $^{1}J_{(C-F)}$ = 288.5 Hz, CF_3), 124.4 (CH), 129.8 (CH), 136.8, 143.0, 151.6, 159.2, 160.6, 178.7 (q, $^{2}J_{(C-F)}$ = 35.8 Hz, CO).

MS (EI, 70 eV): *m/z* (%) = 355 ([M]$^+$, 41), 337 (52), 327 (22), 322 (12), 309 (16), 287 (13), 286 (100), 272 (13), 259 (15), 258 (90), 229 (13), 225 (36), 201 (23), 197 (17), 128 (15), 91 (11), 82 (19), 77 (12), 66 (27), 65 (15), 39 (15).

HRMS (ESI): Calcd. for $C_{16}H_{17}F_3N_3O_3$ [M+H]$^+$: 356.12165, found: 356.12154.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3045 (w), 2972 (w), 2879 (w), 1722 (s), 1666 (s), 1622 (s), 1589 (s), 1558 (m), 1539 (m), 1514 (s), 1506 (s), 1456 (s), 1446 (s), 1435 (s), 1414 (m), 1389 (m), 1373 (m), 1311 (s), 1282 (m), 1244 (m), 1236 (m), 1211 (s), 1182 (s), 1174 (s), 1155 (s), 1119 (m), 1086 (s), 1061 (m), 1020 (m), 995 (s), 957 (m), 874 (m), 837 (m), 791 (s), 760 (s), 733 (s), 721 (m), 687 (s), 654 (m), 633 (m), 584 (m), 554 (m), 542 (m), 532 (m).

5-[Chloro(difluoro)acetyl]-6-[(4-ethylphenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (87g)



The product was prepared according to the general procedure from 0.3 g of 6-[(4-ethylphenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, 0.11 g of pyridine and 0.562 g of chlorodifluoroacetic anhydride in 3 mL of dry dioxane.

Yield 0.417 g (97%), grey solid, mp 133-135 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.20 (t, 3H, ^{3}J = 7.55 Hz, Et), 2.63 (q, 2H, ^{3}J = 7.55 Hz, Et), 3.10 (s, 3H, CH_3), 3.22 (s, 3H, CH_3), 7.22 (d, 2H, ^{3}J = 8.50 Hz, CH_{Ar}), 7.28 (d, 2H, ^{3}J = 8.50 Hz, CH_{Ar}), 10.90 (br s, 1H, NH).

^{13}C NMR (125.77 MHz, DMSO-d_6): δ = 16.4 (CH_3), 28.5 (CH_2), 28.7 (CH_3), 35.9 (CH_3),

92.3 (C-5), 121.3 (t, $^{1}J_{(C-F)}$ = 302.0 Hz, $CClF_2$), 124.2 (CH), 129.8 (CH), 137.0, 142.8, 151.6, 158.9, 160.3, 180.8 (t, $^{2}J_{(C-F)}$ = 29.9 Hz, CO).

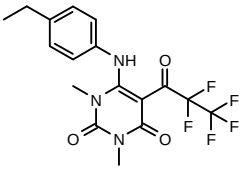
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –59.9 (s, $CClF_2$).

MS (GC, 70 eV): *m/z* (%) = 371 ($[M]^+$, ^{35}Cl, 5.2), 320 (19), 319 (100), 305 (16), 304 (77), 247 (10), 207 (38), 192 (10), 82 (13).

HRMS (ESI): Calcd. for $C_{16}H_{17}ClF_2N_3O_3$ $[M+H, {}^{35}Cl]^+$: 372.09210, found: 372.09257.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 2931 (w), 2874 (w), 1720 (m), 1660 (s), 1622 (s), 1574 (s), 1504 (s), 1452 (s), 1441 (s), 1404 (s), 1367 (s), 1311 (m), 1279 (s), 1254 (m), 1174 (s), 1134 (s), 1095 (m), 1070 (s), 1059 (m), 1005 (s), 953 (m), 930 (s), 914 (s), 870 (s), 841 (m), 825 (s), 804 (s), 793 (s), 773 (s), 756 (s), 743 (s), 716 (m), 669 (s), 646 (s), 625 (s), 567 (m), 534 (s).

6-[(4-Ethylphenyl)amino]-1,3-dimethyl-5-(2,2,3,3,3-pentafluoropropanoyl)pyrimidine-2,4(1*H*,3*H*)-dione (87h)



The product was prepared according to the general procedure from 0.35 g of 6-[(4-ethylphenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, 0.128 g of pyridine and 0.837 g of pentafluoropropionic anhydride in 3.5 mL of dry dioxane.

Yield 0.516 g (94%), greyish solid, mp 161-163 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.21 (t, 3H, ^{3}J = 7.59 Hz, Et), 2.64 (q, 2H, ^{3}J = 7.59 Hz, Et), 3.02 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 7.29 (s, 4H, CH_{Ar}), 11.23 (br s, 1H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 16.4 (CH_3), 28.5 (CH_2), 28.7 (CH_3), 36.7 (CH_3), 94.6 (C-5), 124.5 (CH), 129.7 (CH), 136.6, 143.1, 151.7, 159.2, 160.4, 181.1 (t, $^{2}J_{(C-F)}$ = 27.0 Hz, CO).

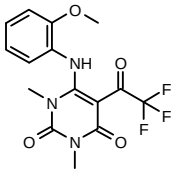
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –115.6 (s, CF_2), –78.7 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 405 ($[M]^+$, 41), 387 (16), 287 (30), 286 (100), 275 (13), 229 (25).

HRMS (EI): Calcd. for $C_{17}H_{16}O_3N_3F_5$ $[M]^+$: 405.11063, found: 405.11084.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2966 (w), 2935 (w), 2874 (w), 1728 (m), 1670 (s), 1591 (s), 1576 (s), 1504 (s), 1454 (s), 1441 (s), 1408 (m), 1375 (s), 1315 (s), 1281 (s), 1254 (m), 1215 (s), 1176 (s), 1147 (s), 1117 (s), 1065 (m), 1030 (m), 1020 (m), 959 (s), 933 (s), 874 (m), 839 (m), 820 (m), 810 (s), 795 (s), 760 (s), 735 (s), 714 (m), 685 (s), 656 (m), 646 (s), 629 (s), 567 (m), 538 (m).

6-[(2-Methoxyphenyl)amino]-1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione (87i)



The product was prepared according to the general procedure from 0.3 g of 6-[(2-methoxyphenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, 0.109 g of pyridine and 0.482 g of trifluoroacetic anhydride in 3 mL of dry dioxane.

Yield 0.369 g (90%), greyish solid, mp 174-176 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.97 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 3.90 (s, 3H, OMe), 7.00-7.10 (m, 1H, CH_{Ar}), 7.21 (d, 1H, ^{3}J = 8.69 Hz, CH_{Ar}), 7.29-7.38 (m, 2H, CH_{Ar}), 11.51 (br s, 1H, NH).

^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –71.0 (s, CF_3).

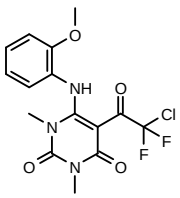
^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 28.7 (CH_3), 36.5 (CH_3), 56.9 (OMe), 93.2, 113.2 (CH), 118.0 (q, $^{1}J_{(C-F)}$ = 287.6 Hz, CF_3), 121.7 (CH), 126.0 (CH), 126.8, 129.2 (CH), 151.5, 152.8, 159.8, 160.3, 178.3 (q, $^{2}J_{(C-F)}$ = 35.9 Hz, CO).

MS (EI, 70 eV): *m/z* (%) = 358 ($[M+H]^+$, 13), 357 ($[M]^+$, 100), 339 (21), 338 (11), 326 (15), 289 (13), 288 (96), 274 (11), 273 (86), 128 (12).

HRMS (ESI): Calcd. for $C_{15}H_{15}F_3N_3O_4$ $[M+H]^+$: 358.10092, found: 358.10099.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2976 (w), 2841 (w), 1734 (m), 1714 (m), 1660 (s), 1622 (s), 1585 (s), 1520 (s), 1498 (s), 1464 (s), 1441 (s), 1417 (m), 1385 (m), 1327 (m), 1296 (s), 1269 (m), 1242 (m), 1232 (m), 1217 (s), 1207 (s), 1188 (s), 1174 (s), 1144 (s), 1115 (s), 1082 (s), 1049 (m), 1020 (s), 995 (s), 949 (m), 872 (w), 858 (w), 824 (m), 793 (s), 756 (s), 733 (s), 712 (m), 692 (m), 675 (m), 660 (s), 598 (m), 577 (m), 550 (m), 527 (s).

5-[Chloro(difluoro)acetyl]-6-[(2-methoxyphenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (87j)



The product was prepared according to the general procedure from 0.3 g of 6-[(2-methoxyphenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, 0.109 g of pyridine and 0.558 g of chlorodifluoroacetic anhydride in 3 mL of dry dioxane.

Yield 0.395 g (92%), greyish solid, mp 163-165 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.00 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 3.89 (s, 3H, OMe), 7.04 (dd, 1H, $^{3}J_1$ = 7.57 Hz, $^{3}J_2$ = 7.55 Hz, CH_{Ar}), 7.19 (d, 1H, ^{3}J = 8.67 Hz, CH_{Ar}), 7.29-7.38 (m, 2H, CH_{Ar}), 11.26 (br s, 1H, NH).

^{13}C NMR (125.77 MHz, DMSO-d_6): δ = 28.7 (CH_3), 36.4 (CH_3), 56.9 (CH_3), 92.4 (C-5),

113.2 (CH), 121.4 (t, $^{1}J_{(C-F)}$ = 301.3 Hz, $CClF_2$), 121.7 (CH), 125.9 (CH), 126.9, 129.0 (CH), 151.5, 152.8, 159.6, 160.1, 180.5 (t, $^{2}J_{(C-F)}$ = 29.8 Hz, CO).

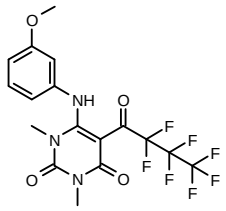
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –59.7 (s, $CClF_2$).

MS (GC, 70 eV): *m/z* (%) = 375 ($[M]^+$, ^{37}Cl, 5.5), 373 ($[M]^+$, ^{35}Cl, 18), 338 (10), 289 (16), 288 (100), 274 (11), 273 (79), 244 (10), 81 (17).

HRMS (EI): Calcd. for $C_{15}H_{14}O_4N_3ClF_2$ [M, ^{37}Cl]$^+$: 373.06354, found: 373.063406.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3005 (w), 2953 (w), 2845 (w), 1724 (s), 1660 (s), 1628 (s), 1599 (s), 1576 (s), 1520 (s), 1497 (s), 1454 (s), 1443 (s), 1392 (s), 1362 (s), 1325 (m), 1290 (s), 1267 (s), 1232 (s), 1194 (m), 1171 (s), 1136 (s), 1115 (s), 1072 (s), 1045 (s), 1030 (s), 1005 (s), 978 (m), 935 (m), 920 (s), 866 (m), 851 (m), 800 (s), 775 (s), 748 (s), 717 (s), 685 (m), 665 (s), 656 (s), 619 (s), 590 (m), 571 (m), 552 (m).

5-(2,2,3,3,4,4,4-Heptafluorobutanoyl)-6-[(3-methoxyphenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (87m)



The product was prepared according to the general procedure from 0.4 g of 6-[(3-methoxyphenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, 0.145 g of pyridine and 0.712 g of heptafluorobutyryl chloride in 4 mL of dry dioxane.

Yield 0.658 g (94%), grey solid, mp 136-138 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.11 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 3.78 (s, 3H, OMe), 6.84 (d, 1H, ^{3}J = 8.31 Hz, CH_{Ar}), 6.89 (d, 1H, ^{3}J = 7.93 Hz, CH_{Ar}), 6.98 (s, 1H, H-2'), 7.33 (dd, 1H, $^{3}J_1$ = 8.31 Hz, $^{3}J_2$ = 7.93 Hz, H-5'), 10.78 (br s, 1H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.7 (CH_3), 36.0 (CH_3), 56.2 (CH_3), 94.8 (C-5), 109.5 (CH), 112.9 (CH), 116.1 (CH), 131.2 (CH), 140.5, 151.7, 158.3, 160.7, 161.1, 182.0 (t, $^{2}J_{(C-F)}$ = 26.4 Hz, CO).

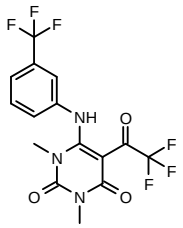
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –121.1 (s, CF_2), –110.8 (q, J = 10.22 Hz, CF_2), –80.0 (t, J = 9.70 Hz, CF_3).

MS (GC, 70 eV): *m/z* (%) = 440 (11), 439 (55), 411 (11), 328 (15), 327 (100), 270 (14).

HRMS (ESI): Calcd. for C17H15F7N3O4 $[M+H]^+$: 458.0945, found: 458.0943.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2949 (w), 2847 (w), 2046 (w), 1795 (w), 1716 (m), 1662 (s), 1628 (s), 1605 (m), 1587 (s), 1564 (s), 1495 (s), 1441 (s), 1408 (m), 1377 (m), 1335 (s), 1317 (m), 1294 (s), 1259 (m), 1211 (s), 1182 (s), 1144 (s), 1122 (s), 1088 (s), 1051 (s), 1012 (m), 960 (m), 920 (w), 897 (m), 876 (s), 820 (m), 797 (m), 781 (s), 756 (s), 729 (s), 689 (s), 671 (s), 650 (s), 594 (s), 575 (m), 548 (m).

1,3-Dimethyl-5-(trifluoroacetyl)-6-{[3-(trifluoromethyl)phenyl]amino}pyrimidine-2,4(1*H*,3*H*)-dione (87n)



The product was prepared according to the general procedure from 0.4 g of **70e**, 0.127 g of pyridine and 0.561 g of trifluoroacetic anhydride in 4 mL of dry dioxane.

Yield 0.523 g (99%), pinkish amorphous solid.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.24 (s, 3H, CH_3), 3.27 (s, 3H, CH_3), 7.50-7.58 (m, 2H, CH_{Ar}), 7.61-7.71 (m, 2H, CH_{Ar}), 10.40 (br s, 1H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.6 (CH_3), 34.7 (CH_3), 93.3 (C-5), 117.0 (q, $^{1}J_{(C-F)}$ = 289.4 Hz, CF_3), 119.7 (CH), 122.7 (CH), 124.7 (q, $^{1}J_{(C-F)}$ = 272.5 Hz, CF_3), 127.5 (CH), 131.2 (q, $^{2}J_{(C-F)}$ = 32.1 Hz), 131.7 (CH), 141.2, 151.6, 158.3, 161.0, 179.9 (q, $^{2}J_{(C-F)}$ = 36.1 Hz, CO).

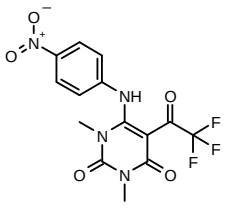
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –72.4 (s, CF_3), –61.4 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 395 ([M]$^+$, 27), 377 (26), 327 (27), 326 (100), 269 (39), 265 (57), 201 (32), 145 (15), 128 (12), 82 (12), 69 (11).

HRMS (EI): Calcd. for $C_{15}H_{11}O_3N_3F_6$ [M]$^+$: 395.06991, found: 395.07016.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3078 (w), 2964 (w), 1790 (w), 1722 (m), 1668 (s), 1585 (s), 1514 (m), 1504 (s), 1495 (s), 1441 (s), 1402 (m), 1371 (m), 1327 (s), 1240 (m), 1159 (s), 1124 (s), 1068 (s), 995 (s), 976 (s), 924 (m), 906 (m), 887 (m), 858 (w), 822 (m), 795 (s), 756 (s), 733 (m), 725 (s), 698 (s), 658 (s), 635 (m), 594 (m), 565 (m), 532 (m).

1,3-Dimethyl-6-[(4-nitrophenyl)amino]-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione (87o)



The product was prepared according to the general procedure from 0.336 g of 1,3-dimethyl-6-[(4-nitrophenyl)amino]pyrimidine-2,4(1*H*,3*H*)-dione, 0.115 g of pyridine and 0.511 g of trifluoroacetic anhydride in 3.4 mL of dry dioxane.

Yield 0.359 g (79%), brownish solid, mp 256-258 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.25 (s, 3H, CH_3), 3.27 (s, 3H, CH_3), 7.39 (d, 2H, ^{3}J = 9.26 Hz, CH-2', CH-6'), 8.25 (d, 2H, ^{3}J = 9.26 Hz, CH-3', CH-5'), 10.40 (br s, 1H, NH).

^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 28.7 (CH_3), 34.6 (CH_3), 96.5 (C-5), 116.9 (q, $^{1}J_{(C-F)}$ = 290.1 Hz, CF_3), 121.4 (CH_{Ar}), 126.3 (CH_{Ar}), 143.8, 147.4, 151.6, 157.1, 160.9, 180.3 (q, $^{2}J_{(C-F)}$ = 36.3 Hz, CO).

^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –72.3 (s, CF_3).

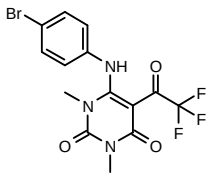
MS (GC, 70 eV): *m/z* (%) = 277 (14), 276 (100), 275 (45), 218 (17), 191 (10), 190 (42), 174

(30), 163 (16), 162 (23), 149 (12), 147 (26), 145 (11), 144 (18), 131 (12), 127 (62), 116 (10), 90 (41), 89 (16), 82 (49), 76 (20), 75 (12), 63 (21), 55 (38), 56 (16), 50 (14), 42 (15).

HRMS (ESI): Calcd. for $C_{14}H_{10}F_3N_4O_5$ $[M+H]^+$: 371.06123, found: 371.06123.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3247 (m), 3078 (w), 2913 (w), 1711 (w), 1691 (w), 1660 (w), 1640 (w), 1633 (m), 1616 (m), 1602 (m), 1578 (m), 1539 (s), 1528 (s), 1520 (s), 1479 (m), 1471 (s), 1434 (m), 1383 (w), 1371 (w), 1341 (s), 1292 (s), 1265 (m), 1194 (s), 1176 (m), 1143 (m), 1107 (m), 1183 (w), 1064 (w), 1008 (w), 992 (w), 916 (w), 883 (w), 859 (m), 838 (m), 821 (m), 791 (s), 759 (s), 736 (s), 716 (s), 645 (s), 667 (m), 632 (s), 578 (m), 537 (s).

6-[(4-Bromophenyl)amino]-1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione (87p)



The product was prepared according to the general procedure from 1.2 g of 6-[(4-bromophenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, 0.367 g of pyridine and 1.625 g of trifluoroacetic anhydride in 12 mL of dry dioxane.

Yield 94%, violet solid, mp 186 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.15 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 7.27 (d, 2H, ^3J = 8.88 Hz, CH-2', CH-6'), 7.62 (d, 2H, ^3J = 8.88 Hz, CH-3', CH-5'), 10.75 (br s, 1H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.6 (CH_3), 35.7 (CH_3), 93.5 (C-5), 117.4 (q, $^1J_{(C-F)}$ = 289.0 Hz, CF_3), 119.1, 125.9 (CH_{Ar}), 133.3 (CH_{Ar}), 139.1, 151.6, 158.6, 160.7, 179.2 (q, $^2J_{(C-F)}$ = 35.9 Hz, CO).

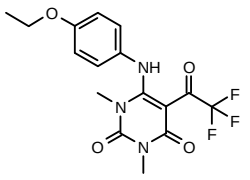
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –71.7 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 407 ($[M]^+$, ^{81}Br, 40), 405 ($[M]^+$, ^{79}Br, 40), 389 (33), 387 (40), 339 (15), 338 (97), 337 (16), 336 (100), 321 (18), 319 (20), 291 (12), 281 (34), 279 (27), 277 (43), 275 (42), 257 (19), 229 (16), 224 (11), 223 (10), 211 (10), 209 (21), 208 (15), 207 (43), 178 (15), 172 (23), 171 (13), 170 (16), 157 (12), 155 (13), 145 (15), 128 (32), 127 (13), 91 (12), 82 (25), 81 (15), 80 (11), 76 (14), 75 (15), 69 (23), 63 (13), 60 (12), 44 (13), 32 (35).

HRMS (ESI): Calcd. for $C_{14}H_{12}BrF_3N_3O_3$ [M+H, ^{79}Br]$^+$: 406.00087, found: 406.00136.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3293 (w), 3191 (w), 3099 (w), 2962 (w), 1766 (w), 1722 (m), 1672 (s), 1639 (s), 1568 (s), 1503 (s), 1490 (s), 1454 (s), 1443 (s), 1384 (m), 1319 (m), 1301 (m), 1278 (m), 1244 (m), 1217 (s), 1193 (s), 1176 (s), 1151 (s), 1088 (m), 1071 (s), 1054 (m), 1015 (m), 998 (s), 960 (m), 941 (m), 871 (m), 825 (s), 814 (s), 796 (s), 783 (s), 755 (s), 733 (s), 718 (s), 681 (s), 671 (s), 628 (m), 608 (m), 575 (s), 529 (m).

6-[(4-Ethoxyphenyl)amino]-1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione (87q)



The product was prepared according to the general procedure from 0.37 g of 6-[(4-ethoxyphenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, 0.127 g of pyridine and 0.565 g of trifluoroacetic anhydride in 3.7 mL of dry dioxane.

Yield 0.416 g (82%), brownish solid, mp 119-121 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.36 (t, 3H, ^{3}J = 6.99 Hz, EtO), 3.03 (s, 3H, CH_3), 3.22 (s, 3H, CH_3), 4.07 (q, 2H, ^{3}J = 6.99 Hz, EtO), 7.00 (d, 2H, ^{3}J = 8.88 Hz, CH_{Ar}), 7.29 (d, 2H, ^{3}J = 8.88 Hz, CH_{Ar}), 11.34 (br s, 1H, NH).

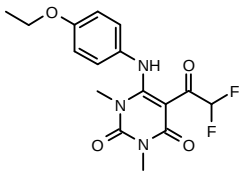
^{13}C NMR (125.77 MHz, DMSO-d_6): δ = 15.4 ($CH_{3(EtO)}$), 28.6 (CH_3), 36.3 (CH_3), 64.3 ($CH_{2(EtO)}$), 92.7 (C-5), 116.1 (CH), 117.9 (q, $^{1}J_{(C-F)}$ = 287.9 Hz, CF_3), 126.3 (CH), 131.5, 151.7, 157.9, 159.4, 160.6, 178.4 (q, $^{2}J_{(C-F)}$ = 35.7 Hz, CO).

MS (GC, 70 eV): *m/z* (%) = 371 ([M]$^{+}$, 11), 353 (10), 276 (21), 275 (100), 274 (19), 247 (10), 246 (73), 189 (16), 162 (10), 161 (14), 148 (20), 147 (22), 134 (15), 133 (15), 132 (17), 82 (24).

HRMS (EI): Calcd. for C16H16O4N3F3 [M]$^{+}$: 371.10874, found: 371.10840.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2982 (w), 1722 (m), 1668 (s), 1614 (s), 1576 (s), 1504 (s), 1485 (s), 1454 (s), 1441 (s), 1408 (m), 1389 (m), 1315 (s), 1304 (m), 1281 (m), 1257 (s), 1242 (s), 1211 (s), 1188 (s), 1169 (s), 1151 (s), 1113 (s), 1080 (s), 1045 (s), 995 (s), 957 (m), 932 (m), 922 (m), 874 (m), 833 (s), 824 (m), 795 (s), 758 (s), 737 (s), 721 (m), 689 (s), 656 (s), 633 (m), 586 (m), 567 (s), 534 (m).

5-(Difluoroacetyl)-6-[(4-ethoxyphenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (87r)



The product was prepared according to the general procedure from 0.04 g of 6-[(4-ethoxyphenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, 0.14 g of pyridine and 0.506 g of difluoroacetic anhydride in 4 mL of dry dioxane.

Yield 0.508 g (99%), brownish solid, mp 144-146 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.37 (t, 3H, ^{3}J = 6.90 Hz, EtO), 2.91 (s, 3H, CH_3), 3.24 (s, 3H, CH_3), 4.08 (q, 2H, ^{3}J = 6.90 Hz, EtO), 7.03 (d, 2H, ^{3}J = 8.88 Hz, CH_{Ar}), 7.17 (t, 1H, $^{2}J_{(H-F)}$ = 54.01 Hz, CHF_2), 7.35 (d, 2H, ^{3}J = 8.88 Hz, CH_{Ar}), 12.54 (br s, 1H, NH).

^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 15.5 ($CH_{3(EtO)}$), 28.7 (CH_3), 37.1 (CH_3), 64.3

($CH_{2(EtO)}$), 94.0 (C-5), 109.2 (t, $^{1}J_{(C-F)}$ = 242.3 Hz, CHF_2), 116.1 (CH_{Ar}), 126.6 (CH_{Ar}), 131.0, 151.6, 158.1, 159.8, 162.0, 185.5 (t, $^{2}J_{(C-F)}$ = 23.8 Hz, CO).

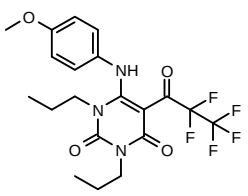
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –125.7 (s, CHF_2).

MS (EI, 70 eV): *m/z* (%) = 354 ($[M+H]^+$, 21), 353 ($[M]^+$, 92), 333 (21), 304 (56), 303 (23), 302 (100), 275 (21), 274 (86), 245 (20), 217 (19), 182 (29), 160 (15), 108 (12), 82 (19), 81 (10).

HRMS (EI): Calcd. for $C_{16}H_{17}F_2N_3O_4$ $[M]^+$: 353.11816, found: 353.11822.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3334 (w), 3080 (w), 2977 (w), 1724 (w), 1651 (m), 1592 (s), 1582 (s), 1549 (w), 1510 (s), 1445 (s), 1396 (w), 1319 (w), 1319 (w), 1305 (m), 1291 (w), 1240 (s), 1189 (w), 1176 (w), 1142 (m), 1116 (m), 1080 (m), 1043 (s), 1004 (s), 943 (w), 918 (w), 899 (m), 867 (m), 844 (m), 818 (m), 807 (s), 777 (s), 769 (s), 760 (s), 751 (s), 712 (w), 694 (m), 666 (m), 628 (w), 579 (m), 556 (m), 534 (m).

6-[(4-Methoxyphenyl)amino]-5-(2,2,3,3,3-pentafluoropropanoyl)-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione (87t)



The product was prepared according to the general procedure from 0.35 g of **70a**, 0.105 g of pyridine and 0.684 g of pentafluoropropionic anhydride in 3.5 mL of dry dioxane.

Yield 0.439 g (86%), pinkish solid, mp 85-87 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 0.72 (t, 3H, ^{3}J = 7.37 Hz, CH_3), 0.91 (t, 3H, ^{3}J = 7.46 Hz, CH_3), 1.42-1.72 (m, 4H, CH_2), 3.70-3.89 (m, 7H, CH_2, MeO), 7.00 (d, 2H, ^{3}J = 8.87 Hz, CH_{Ar}), 7.29 (d, 2H, ^{3}J = 8.87 Hz, CH_{Ar}), 10.61 (br s, 1H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 11.5 (CH_3), 12.0 (CH_3), 21.3 (CH_2), 21.4 (CH_2), 43.3 (CH_2), 47.2 (CH_2), 56.3 (MeO), 93.3 (C-5), 115.7 (CH_{Ar}), 126.4 (CH_{Ar}), 131.8, 151.2, 158.0, 158.8, 160.2, 181.6 (t, $^{2}J_{(C-F)}$ = 26.8 Hz, CO).

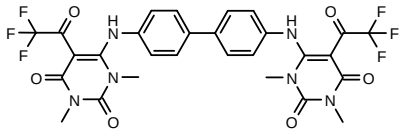
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –116.0 (s, CF_2), –78.7 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 464 ($[M+H]^+$, 15), 463 ($[M]^+$, 85), 445 (15), 403 (18), 345 (20), 344 (100), 302 (24), 260 (56), 243 (14), 214 (12), 123 (18), 43 (16), 41 (11).

HRMS (ESI): Calcd. for $C_{20}H_{23}F_5N_3O_4$ $[M+H]^+$: 464.16032, found: 464.16109.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2964 (w), 2877 (w), 1716 (m), 1670 (s), 1593 (s), 1504 (s), 1443 (s), 1416 (s), 1385 (s), 1360 (m), 1329 (m), 1300 (s), 1279 (s), 1246 (s), 1213 (s), 1184 (s), 1171 (s), 1144 (s), 1109 (s), 1086 (m), 1061 (m), 1032 (s), 962 (s), 953 (s), 932 (s), 910 (m), 870 (m), 845 (m), 831 (s), 808 (m), 797 (s), 775 (s), 750 (s), 729 (s), 687 (s), 654 (m), 638 (s), 629 (s), 548 (m).

6,6'-[Biphenyl-4,4'-diyldi(imino)]bis[1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione] (87u)



The product was prepared from 0.25 g of **70g**, 0.103 g of pyridine and 0.456 g of trifluoroacetic anhydride in 5 mL of dry dioxane according to the general procedure, except that the synthesis was carried out in a pressure tube at 80 °C for 3 h.

Yield 0.329 g (93%), beige solid, mp 246 °C (dec.).

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.15 (s, 6H, CH_3), 3.24 (s, 6H, CH_3), 7.42 (d, 4H, ^{3}J = 8.60 Hz, CH_{Ar}), 7.79 (d, 4H, ^{3}J = 8.60 Hz, CH_{Ar}), 11.07 (br s, 2H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.7 (CH_3), 36.2 (CH_3), 93.6 (C-5, C-5'), 117.6 (q, $^{1}J_{(C\text{-}F)}$ = 286.2 Hz, CF_3), 124.4 (CH), 128.5 (CH), 137.4, 138.9, 151.7, 158.8, 160.7, 179.0 (q, $^{2}J_{(C\text{-}F)}$ = 35.8 Hz, CO).

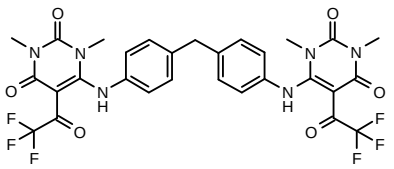
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –71.4 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 652 ([M]$^{+}$, 3.6), 634 (15), 617 (31), 616 (100), 565 (15), 504 (26), 496 (12).

HRMS (EI): Calcd. for $C_{28}H_{22}O_6N_6F_6$ [M]$^{+}$: 652.14995, found: 652.14898.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958 (w), 2359 (w), 1730 (m), 1674 (s), 1605 (s), 1587 (s), 1514 (s), 1498 (s), 1441 (s), 1404 (m), 1387 (m), 1335 (m), 1298 (m), 1286 (m), 1267 (m), 1238 (m), 1209 (s), 1194 (s), 1163 (s), 1082 (s), 995 (s), 872 (m), 825 (s), 797 (s), 756 (s), 727 (m), 708 (m), 694 (m), 667 (m), 640 (m), 594 (m), 571 (m), 534 (m).

6,6'-[Methylenebis(4,1-phenyleneimino)]bis[1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione] (87v)



The product was prepared according to the general procedure from 0.333 g of **70f**, 0.133 g of pyridine and 0.59 g of trifluoroacetic anhydride in 6.6 mL of dry dioxane.

Yield 0.458 g (98%), beige solid, mp 129-131 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.07 (s, 6H, CH_3), 3.22 (s, 6H, CH_3), 3.98 (s, 2H, CH_2), 7.26 (d, 4H, ^{3}J = 8.69 Hz, CH_{Ar}), 7.29 (d, 4H, ^{3}J = 8.69 Hz, CH_{Ar}), 11.05 (br s, 2H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.6 (CH_3), 36.0 (CH_3), 40.7 (CH_2), 93.0 (C-5, C-5'), 120.3 (q, $^{1}J_{(C\text{-}F)}$ = 288.5 Hz, CF_3), 124.4 (CH), 130.8 (CH), 137.4, 140.1, 151.6, 159.0, 160.7, 178.9 (q, $^{2}J_{(C\text{-}F)}$ = 35.5 Hz, CO).

^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –71.4 (s, CF_3).

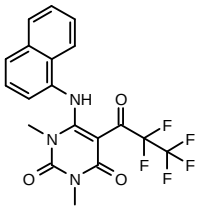
MS (EI, 70 eV): *m/z* (%) = 631 (38), 630 (100), 553 (11), 552 (35), 518 (13), 498 (18), 203

(12).

HRMS (ESI): Calcd. for $C_{29}H_{25}F_6N_6O_6$ $[M+H]^+$: 667.17343, found: 667.17425.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 1724 (m), 1668 (s), 1593 (s), 1512 (s), 1506 (s), 1454 (s), 1443 (s), 1435 (s), 1387 (m), 1309 (m), 1284 (s), 1242 (m), 1209 (s), 1186 (s), 1149 (s), 1082 (s), 1020 (m), 995 (s), 926 (m), 879 (m), 824 (m), 816 (m), 795 (s), 756 (s), 725 (m), 710 (m), 694 (m), 662 (m), 631 (m), 579 (m), 561 (m), 534 (m).

1,3-Dimethyl-6-(1-naphthylamino)-5-(2,2,3,3,3-pentafluoropropanoyl)pyrimidine-2,4(1*H*,3*H*)-dione (87w)



The product was prepared according to the general procedure from 0.341 g of 1,3-dimethyl-6-(1-naphthylamino)pyrimidine-2,4(1*H*,3*H*)-dione, 0.105 g of pyridine and 0.413 g of pentafluoropropionic anhydride in 3.4 mL of dry dioxane.

Yield 0.443 g (86%), yellowish solid, mp 156 °C (dec.).

^{1}H NMR (250.13 MHz, DMSO-d_6): δ = 2.90 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 7.53-7.63 (m, 2H, CH_{Ar}), 7.64-7.78 (m, 2H, CH_{Ar}), 7.93-8.03 (m, 1H, CH_{Ar}), 8.08 (d, 1H, ^3J = 6.94 Hz, CH_{Ar}), 8.15 (d, 1H, ^3J = 8.19 Hz, CH_{Ar}), 11.80 (br s, 1H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.8 (CH_3), 36.2 (CH_3), 94.8 (C-5), 123.0 (CH), 123.4 (CH), 126.6 (CH), 128.0 (CH), 128.4 (CH), 128.5 (CH), 128.5, 129.4 (CH), 134.5, 134.8, 151.5, 160.3, 160.7, 181.5 (t, $^2J_{(C\text{-}F)}$ = 27.1 Hz, CO).

^{19}F NMR (235.33 MHz, DMSO-d_6): δ = –115.2 (s, CF_2), –78.5 (s, CF_3).

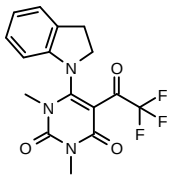
MS (EI, 70 eV): *m/z* (%) = 428 ($[M+H]^+$, 13), 427 ($[M]^+$, 77), 409 (49), 309 (18), 308 (100), 297 (25), 280 (40), 251 (18), 195 (15), 127 (11), 115 (13).

HRMS (ESI): Calcd. for $C_{19}H_{15}F_5N_3O_3$ $[M+H]^+$: 428.10281, found: 428.10233.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3018 (w), 2962 (w), 1728 (m), 1674 (s), 1588 (s), 1574 (s), 1558 (m), 1538 (m), 1515 (s), 1506 (s), 1455 (s), 1435 (s), 1399 (m), 1385 (m), 1368 (m), 1331 (m), 1305 (m), 1283 (m), 1232 (s), 1174 (s), 1139 (s), 1112 (s), 1063 (m), 1032 (m), 1013 (w), 984 (w), 959 (s), 938 (m), 907 (w), 883 (w), 861 (w), 824 (w), 804 (m), 783 (s), 770 (s), 758 (s), 740 (m), 731 (s), 712 (s), 685 (m), 647 (s), 593 (m), 559 (m), 531 (m).

6-(2,3-Dihydro-1*H*-indol-1-yl)-1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione (90a)

The product was prepared according to the general procedure from 4.085 g of **89a**, 1.507 g of pyridine and 6.669 g of trifluoroacetic anhydride in 41 mL of dry dioxane.



Yield 5.428 g (97%), yellow solid, mp 199 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.07-3.33 (m, 2H, CH_2-3'), 3.26 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 3.72-3.84 (m, 1H, CH_2-2'a), 3.91-4.04 (m, 1H, CH_2-2'b), 6.80 (d, 1H, ^3J = 7.75 Hz, H-7'), 6.88-6.97 (m, 1H, CH_{Ar}), 7.05-7.15 (m, 1H, CH_{Ar}), 7.30 (d, 1H, ^3J = 6.99 Hz, H-4').

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.6 (CH_3), 29.9 (CH_2-3'), 35.0 (CH_3), 54.8 (CH_2-2'), 99.3 (C-5), 112.6 (CH_{Ar}), 116.2 (q, $^1J_{(C-F)}$ = 290.8 Hz, CF_3), 123.4 (CH_{Ar}), 126.4 (CH_{Ar}), 128.4 (CH_{Ar}), 133.6, 146.0, 152.2, 159.1, 161.6, 181.9 (q, $^2J_{(C-F)}$ = 36.7 Hz, CO).

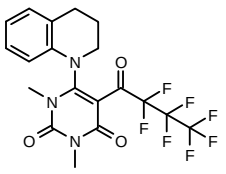
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –73.3 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 353 ([M]$^+$, 24), 285 (18), 284 (100), 178 (18), 167 (14), 128 (31), 118 (31), 110 (11).

HRMS (ESI): Calcd. for $C_{16}H_{15}F_3N_3O_3$ [M+H]$^+$: 354.10600, found: 354.10633.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3057 (w), 2963 (w), 1722 (w), 1696 (m), 1645 (s), 1549 (m), 1483 (s), 1434 (s), 1401 (s), 1363 (m), 1331 (w), 1303 (w), 1265 (w), 1236 (w), 1229 (w), 1191 (s), 1156 (m), 1141 (s), 1096 (w), 1082 (w), 1045 (w), 1033 (w), 1017 (w), 986 (m), 968 (s), 940 (w), 873 (w), 861 (w), 833 (w), 819 (w), 797 (w), 785 (w), 753 (s), 713 (m), 704 (m), 686 (m), 608 (w), 581 (w), 561 (m), 549 (w), 534 (w).

6-(3,4-Dihydroquinolin-1(2*H*)-yl)-5-(2,2,3,3,4,4,4-heptafluorobutanoyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (90b)



The product was prepared according to the general procedure from 1.444 g of **89b**, 0.505 g of pyridine and 1.485 g of heptafluorobutyryl chloride in 14 mL of dry dioxane.

Yield 82%, yellow solid, mp 131-133 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.90-2.19 (m, 2H, CH_2-3'), 2.84 (t, 2H, ^3J = 6.42 Hz, CH_2-4'), 3.21 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 3.36-3.54 (m, 2H, CH_2-2'), 6.83 (d, 1H, ^3J = 8.12 Hz, H-8'), 6.84-6.92 (m, 1H, CH_{Ar}), 6.99-7.08 (m, 1H, CH_{Ar}), 7.30 (d, 1H, ^3J = 7.36 Hz, H-5').

^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 21.8 (CH_2), 26.8 (CH_2), 28.6 (CH_3), 34.1 (CH_3), 50.7 (CH_2-2'), 104.2 (C-5), 117.1 (CH_{Ar}), 122.3 (CH_{Ar}), 125.5, 127.8 (CH_{Ar}), 130.7 (CH_{Ar}), 140.8, 152.3, 159.3, 161.6, 185.3 (t, $^2J_{(C-F)}$ = 28.5 Hz, CO).

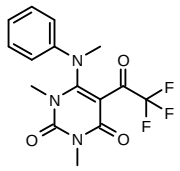
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –122.2 (s, CF_2), –112.5 (m, CF_2), –80.4 (t, J = 9.20 Hz, CF_3).

MS (GC, 70 eV): *m/z* (%) = 467 ([M]$^+$, 38), 299 (18), 298 (99), 278 (13), 271 (17), 270 (100), 185 (40), 169 (11), 132 (22), 130 (18), 128 (11), 117 (12), 86 (14), 82 (11), 81 (15), 69 (14).

HRMS (ESI): Calcd. for $C_{16}H_{15}F_3N_3O_3$ [M+H]$^+$: 468.11527, found: 468.11572.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2953 (w), 2867 (w), 1738 (w), 1705 (m), 1657 (s), 1651 (s), 1602 (w), 1591 (w), 1574 (m), 1557 (w), 1538 (w), 1494 (m), 1472 (m), 1428 (s), 1396 (m), 1370 (w), 1344 (m), 1320 (w), 1295 (w), 1275 (w), 1217 (s), 1195 (s), 1179 (s), 1150 (s), 1116 (s), 1079 (m), 1026 (w), 994 (m), 966 (w), 920 (w), 881 (m), 871 (w), 817 (w), 804 (m), 773 (m), 758 (s), 749 (m), 721 (m), 687 (m), 652 (m), 624 (w), 596 (w), 555 (m), 540 (w).

1,3-Dimethyl-6-[methyl(phenyl)amino]-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione (90c)



The product was prepared according to the general procedure from 0.35 g of ,3-dimethyl-6-[methyl(phenyl)amino]pyrimidine-2,4(1*H*,3*H*)-dione, 0.135 g of pyridine and 0.599 g of trifluoroacetic anhydride in 3.5 mL of dry dioxane.

Yield 0.484 g (99%), yellow solid, mp 137-139 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.16 (s, 3H, CH_3), 3.26 (s, 6H, CH_3), 6.95-7.08 (m, 3H, CH_{Ph}), 7.26-7.34 (m, 2H, CH_{Ph}).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.6 (CH_3), 33.6 (CH_3), 39.5 (CH_3), 103.9 (C-5), 115.9 (q, $^{1}J_{(C-F)}$ = 290.9 Hz, CF_3), 117.5 (CH), 122.8 (CH), 130.2 (CH), 145.6, 152.3, 161.4, 161.7, 182.2 (q, $^{2}J_{(C-F)}$ = 37.2 Hz, CO).

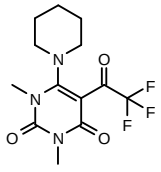
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –73.9 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 341 ($[M]^+$, 35), 273 (16), 272 (100), 257 (11), 244 (49), 178 (12), 159 (53), 132 (13), 128 (27), 106 (20), 77 (28), 69 (15), 60 (10).

HRMS (ESI): Calcd. for $C_{15}H_{15}F_3N_3O_3$ $[M+H]^+$: 342.10600, found: 342.10622.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3051 (w), 3022 (w), 1703 (s), 1651 (s), 1645 (s), 1603 (m), 1587 (m), 1566 (s), 1487 (s), 1441 (s), 1417 (s), 1394 (s), 1331 (m), 1300 (m), 1240 (m), 1230 (m), 1221 (m), 1188 (s), 1159 (s), 1142 (s), 1117 (s), 1105 (s), 1080 (s), 1049 (m), 1026 (m), 974 (s), 932 (m), 903 (m), 825 (s), 812 (m), 787 (m), 754 (s), 710 (s), 698 (s), 650 (s), 617 (m), 582 (m), 548 (s).

1,3-Dimethyl-6-piperidin-1-yl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione (78b)



To a solution of 1,3-dimethyl-6-piperidin-1-ylpyrimidine-2,4(1*H*,3*H*)-dione (2.39 g, 10.7 mmol, 1 eq) in 7.2 mL of dry dioxane was added trifluoroacetic anhydride (4.497 g, 21.4 mmol, 2 eq). Next day the starting material was still observed on TLC. The solvent was evaporated and the residue was dried in a high vacuum at 100 °C. Then a new portion of dry dioxane (3.6 mL) and trifluoroacetic anhydride (2.248 g, 10.7 mmol, 1 eq) was added and the mixture was allowed to stay at r.t. for 3 days. After evaporation and proper drying at 100 °C in a high vacuum the pure title

product was obtained.

Yield 3.401 g (100%), beige solid, mp 253-255 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.60-1.75 (m, 6H, CH_2-3', CH_2-4', CH_2-5'), 2.83-2.92 (m, 4H, CH_2-2', CH_2-6'), 3.19 (s, 3H, CH_3), 3.40 (s, 3H, CH_3).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 24.2 (CH_2), 25.7 (CH_2), 28.3 (CH_3), 35.8 (CH_3), 53.1 (CH_2-2', CH_2-6'), 97.3 (C-5), 116.6 (q, $^{1}J_{(C\text{-}F)}$ = 290.4 Hz, CF_3), 152.4, 161.7, 163.3, 182.5 (q, $^{2}J_{(C\text{-}F)}$ = 36.4 Hz, CO).

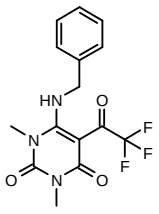
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –73.1 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 319 ([M]$^+$, 0.31), 251 (14), 250 ([M–CF_3]$^+$, 100), 222 (20), 128 (12), 110 (15), 84 (26), 82 (22), 69 (16).

HRMS (EI): Calcd. for $C_{13}H_{16}F_3N_3O_3$ [M]$^+$: 353.11383, found: 319.11437.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3006 (w), 2947 (m), 2856 (w), 1780 (w), 1716 (w), 1684 (m), 1650 (s), 1552 (m), 1487 (s), 1436 (s), 1401 (m), 1371 (s), 1336 (w), 1300 (w), 1284 (w), 1259 (w), 1245 (w), 1235 (w), 1217 (m), 1193 (s), 1158 (m), 1139 (s), 1114 (m), 1079 (m), 1067 (w), 1050 (w), 1020 (m), 980 (s), 956 (m), 912 (w), 858 (m), 826 (m), 811 (w), 793 (s), 758 (s), 715 (m), 706 (m), 698 (m), 643 (m), 585 (w), 565 (m).

6-(Benzylamino)-1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione (78c)



To a solution of 6-(benzylamino)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (1.825 g, 7.44 mmol, 1 eq) in 9.1 mL of dry dioxane was added trifluoroacetic anhydride (3.125 g, 14.9 mmol, 2 eq). Next day the starting material was still observed on TLC. The solvent was evaporated and the residue was dried in a high vacuum at 100 °C. Then a new portion of dry dioxane (4.5 mL) and trifluoroacetic anhydride (3.125 g, 14.9 mmol, 2 eq) was added and the mixture was allowed to stay at r.t. for one day. After that the formed precipitate was filtered off, washed with diethyl ether and dried in a high vacuum.

Yield 2.441 (96%), white solid, mp 177 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.19 (s, 3H, CH_3), 3.53 (s, 3H, CH_3), 4.68 (d, 2H, *J* = 5.10 Hz, CH_2), 7.34-7.48 (m, 5H, CH_{Ph}), 10.30 (br s, 1H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.6 (CH_3), 36.2 (CH_3), 51.3 (CH_2), 91.6 (C-5), 118.1 (q, $^{1}J_{(C\text{-}F)}$ = 288.0 Hz, CF_3), 128.7 (CH_{Ph}), 129.0 (CH_{Ph}), 129.7 (CH_{Ph}), 137.4, 151.6, 160.4, 161.5, 177.4 (q, $^{2}J_{(C\text{-}F)}$ = 35.4 Hz, CO).

^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –70.8 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 341 ([M]$^+$, 6.0), 273 (16), 272 ([M–CF_3]$^+$, 100), 243 (16), 242 (49), 226 (25), 157 (13), 122 (31), 105 (11), 91 (73), 82 (27).

HRMS (ESI): Calcd. for $C_{15}H_{15}F_3N_3O_3$ $[M+H]^+$: 342.10600, found: 342.10562.

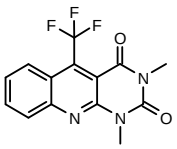
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3036 (w), 2142 (w), 2012 (w), 1965 (w), 1720 (w), 1668 (m), 1597 (s), 1582 (s), 1525 (m), 1496 (w), 1485 (w), 1461 (m), 1447 (m), 1439 (m), 1413 (w), 1383 (w), 1357 (m), 1328 (w), 1304 (m), 1268 (w), 1239 (w), 1222 (w), 1208 (s), 1164 (s), 1150 (s), 1099 (m), 1082 (m), 1061 (w), 1033 (w), 1025 (w), 995 (s), 972 (w), 963 (m), 930 (w), 907 (w), 853 (w), 829 (m), 820 (s), 787 (w), 775 (w), 758 (m), 742 (s), 731 (m), 713 (m), 695 (s), 657 (s), 620 (w), 596 (w), 584 (m), 538 (w).

4.2.6 Synthesis of 5-polyfluoroalkyl-5-deazaalloxazines

General procedure for the synthesis of 5-polyfluoroalkyl-pyrimido[4,5-b]quinoline-2,4-diones 88a-x.

Initial 5-(polyfluoroacyl)-6-amino-1,3-dialkylpyrimidine-2,4(1H,3H)-dione **87** (0.3 g) was dissolved in concentrated H_2SO_4 (1.5 mL) and allowed to stand at r.t. for 3 hours. Then the solution was poured into ice water and formed precipitate was filtered off by suction and recrystallized from methanol giving the pure product.

1,3-Dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88a)



The product was prepared according to the general procedure, starting from 0.474 g of **87a** and 2.4 mL of H_2SO_4.

Yield 0.269 g (89%), yellow solid, mp 195 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.52 (s, 3H, CH_3-3), 3.83 (s, 3H, CH_3-1), 7.55-7.62 (m, 1H, H-7), 7.81-7.89 (m, 1H, H-8), 8.01-8.06 (m, 1H, H-9), 8.30-8.36 (m, 1H, H-6).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 29.4 (CH_3-3), 30.6 (CH_3-1), 110.4 (C-4a), 121.7, 123.3 (q, $^1J_{(C-F)}$ = 278.7 Hz, CF_3), 126.1 (q, $^4J_{(C-F)}$ = 6.1 Hz, CH-6), 127.2, 129.1 (CH_{Ar}), 133.4 (CH_{Ar}), 138.7 (q, $^2J_{(C-F)}$ = 33.4 Hz, C-5), 148.2, 150.2, 151.1 (CO-2), 159.3 (CO-4).

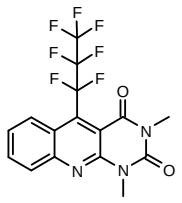
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –52.5 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 310 ($[M+H]^+$, 13), 309 ($[M]^+$, 77), 197 (100).

HRMS (ESI): Calcd. for $C_{14}H_{11}F_3N_3O_2$ $[M+H]^+$: 310.07979, found: 310.07967.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956 (w), 1713 (s), 1669 (s), 1614 (w), 1583 (s), 1565 (m), 1494 (m), 1464 (s), 1419 (m), 1378 (s), 1332 (m), 1286 (m), 1216 (m), 1194 (m), 1156 (s), 1142 (s), 1124 (s), 1100 (s), 1069 (m), 1030 (m), 989 (s), 929 (w), 877 (w), 856 (w), 812 (m), 775 (s), 756 (s), 745 (s), 712 (w), 624 (s), 592 (m), 550 (m), 532 (w).

5-(Heptafluoropropyl)-1,3-dimethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88b)



The product was prepared according to the general procedure, starting from 0.662 g of **87b** and 3.3 mL of H_2SO_4.

Yield 0.461 g (73%), yellow solid, mp 183 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.51 (s, 3H, CH_3-3), 3.84 (s, 3H, CH_3-1), 7.54-7.64 (m, 1H, H-7), 7.81-7.90 (m, 1H, H-8), 8.06 (d, 1H, ^3J = 8.50 Hz, H-9), 8.32 (m, 1H, ^3J = 8.88 Hz, H-6).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 29.7 (CH_3-3), 30.8 (CH_3-1), 111.7 (C-4a), 122.7, 127.0 (CH-6), 127.4 (CH_{Ar}), 129.4 (CH_{Ar}), 133.3 (CH_{Ar}), 140.0 (t, $^2J_{(C\text{-}F)}$ = 24.3 Hz, C-5), 148.4, 150.3, 151.1 (CO-2), 159.1 (CO-4).

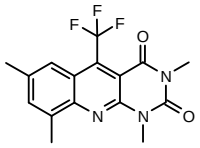
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –116.6 (s, CF_2), –92.0 (br s, CF_2), –80.0 (t, J = 9.20 Hz, CF_3).

MS (GC, 70 eV): *m/z* (%) = 410 ($[M+H]^+$, 11), 409 ($[M]^+$, 60), 298 (13), 297 (100).

HRMS (ESI): Calcd. for $C_{16}H_{11}F_7N_3O_2$ $[M+H]^+$: 410.07340, found: 410.07322.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3154 (w), 1720 (m), 1615 (s), 1614 (w), 1502 (w), 1463 (m), 1424 (m), 1392 (m), 1376 (m), 1347 (w), 1329 (m), 1293 (w), 1271 (w), 1251 (w), 1225 (s), 1202 (s), 1190 (s), 1146 (m), 1128 (m), 1111 (s), 1029 (w), 978 (w), 969 (w), 941 (s), 899 (s), 899 (s), 877 (w), 825 (m), 769 (s), 748 (s), 726 (s), 691 (m), 621 (m), 599 (w), 539 (m).

1,3,7,9-Tetramethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88c)



The product was prepared according to the general procedure, starting from 0.429 g of **87c** and 2.1 mL of H_2SO_4.

Yield 0.343 g (84%), yellow solid, mp 192 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.52 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 3.51 (s, 3H, CH_3-3), 3.82 (s, 3H, CH_3-1), 7.56s1H (s, 1H, H-8), 7.91s1H (s, 1H, H-8).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 18.5 (CH_3), 22.4 (CH_3), 29.3 (CH_3-3), 30.4 (CH_3-1), 109.6 (C-4a), 121.9, 122.4 (q, $^4J_{(C\text{-}F)}$ = 5.8 Hz, CH-6), 123.4 (q, $^1J_{(C\text{-}F)}$ = 278.2 Hz, CF_3), 135.8 (CH-8), 136.4, 137.2 (q, $^2J_{(C\text{-}F)}$ = 33.1 Hz, C-5), 138.4, 146.6, 148.0, 151.2 (CO-2), 159.5 (CO-4).

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –52.4 (s, CF_3).

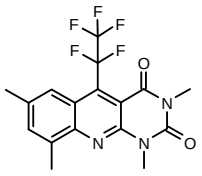
MS (GC, 70 eV): *m/z* (%) = 338 ($[M+H]^+$, 19), 337 ($[M]^+$, 100), 309 (10), 268 (14), 226 (10), 225 (83).

HRMS (EI): Calcd. for $C_{16}H_{14}F_3N_3O_2$ $[M]^+$: 337.10326, found: 337.10302.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 1713 (m), 1669 (s), 1625 (w), 1570 (s), 1500 (w), 1468 (s),

1435 (m), 1408 (m), 1374 (s), 1348 (m), 1317 (m), 1282 (s), 1239 (s), 1198 (m), 1176 (m), 1150 (s), 1136 (s), 1112 (m), 1101 (s), 1057 (w), 1041 (m), 996 (m), 974 (m), 962 (m), 921 (w), 860 (m), 847 (w), 827 (w), 811 (s), 776 (w), 764 (w), 750 (s), 729 (w), 705 (m), 690 (m), 674 (w), 660 (m), 585 (m), 567 (w), 543 (w).

1,3,7,9-Tetramethyl-5-(pentafluoroethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88d)



The product was prepared according to the general procedure, starting from 0.431 g of **87d** and 2.2 mL of H_2SO_4.

Yield 0.345 g (84%), yellow solid, mp 225 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.52 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 3.51 (s, 3H, CH_3-3), 3.82 (s, 3H, CH_3-1), 7.56 (s, 1H, H-8), 7.84 (s, 1H, H-8).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 18.7 (CH_3), 22.6 (CH_3), 29.5 (CH_3-3), 30.6 (CH_3-1), 110.6 (C-4a), 122.81 (CH-6), 122.85, 135.8 (CH-8), 136.7, 137.0, 139.4 (t, $^2J_{(C\text{-}F)}$ = 24.1 Hz, C-5), 146.8, 148.0, 151.2 (CO-2), 159.7 (CO-4).

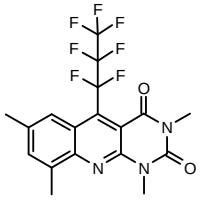
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –91.0 (s, CF_2), –74.8 (t, *J* = 2.0 Hz, CF_3).

MS (GC, 70 eV): *m/z* (%) = 388 ($[M+H]^+$, 18), 387 ($[M]^+$, 92), 359 (11), 330 (11), 276 (15), 275 (100), 268 (12).

HRMS (EI): Calcd. for $C_{17}H_{14}F_5N_3O_2$ $[M]^+$: 387.10007, found: 387.09992.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3369 (w), 2919 (w), 1713 (m), 1668 (s), 1625 (w), 1566 (s), 1504 (w), 1470 (m), 1444 (m), 1435 (m), 1378 (m), 1348 (w), 1292 (m), 1232 (w), 1209 (s), 1192 (s), 1182 (m), 1162 (s), 1133 (s), 1107 (s), 1062 (s), 1037 (m), 1020 (s), 985 (s), 958 (m), 906 (w), 859 (m), 816 (m), 763 (w), 737 (w), 762 (w), 742 (s), 727 (s), 691 (m), 658 (m), 599 (w), 586 (m), 567 (m), 552 (w), 531 (m).

5-(Heptafluoropropyl)-1,3,7,9-tetramethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88e)



The product was prepared according to the general procedure, starting from 0.485 g of **87e** and 2.4 mL of H_2SO_4.

Yield 0.429 g (92%), yellow solid, mp 198-200 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.53 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 3.51 (s, 3H, CH_3-3), 3.84 (s, 3H, CH_3-1), 7.58 (s, 1H, H-8), 7.93 (s, 1H, H-8).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 18.7 (CH_3), 22.6 (CH_3), 29.6 (CH_3-3), 30.7 (CH_3-1),

111.0 (C-4a), 123.0, 123.3 (CH-6), 135.8 (CH-8), 136.7, 137.0, 139.0 (t, $^{2}J_{(C-F)}$ = 23.8 Hz, C-5), 146.9, 148.1, 151.3 (CO-2), 159.4 (CO-4).

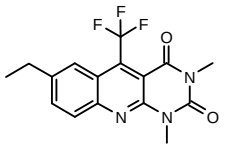
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –116.5 (s, CF_2), –90.2 (br s, CF_2), –80.0 (t, *J* = 8.7 Hz, CF_3).

MS (GC, 70 eV): *m/z* (%) = 438 ($[M+H]^+$, 20), 437 ($[M]^+$, 100), 409 (10), 380 (11), 326 (16), 325 (100), 268 (10), 220 (14), 206 (12).

HRMS (EI): Calcd. for $C_{18}H_{14}F_3N_3O_2$ $[M]^+$: 437.09688, found: 437.09679.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2929 (w), 1722 (m), 1678 (s), 1626 (w), 1568 (s), 1494 (w), 1469 (m), 1444 (m), 1376 (s), 1346 (m), 1313 (w), 1289 (w), 1266 (w), 1255 (w), 1228 (s), 1219 (s), 1198 (s), 1176 (s), 1130 (m), 1114 (s), 1055 (w), 1035 (w), 1001 (w), 977 (w), 913 (s), 861 (w), 815 (m), 785 (w), 758 (w), 746 (m), 732 (s), 693 (w), 658 (w), 623 (m), 599 (w), 584 (w), 564 (w), 535 (m).

7-Ethyl-1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88f)



The product was prepared according to the general procedure, starting from 0.363 g of **87f** and 1.8 mL of H_2SO_4.

Yield 0.173 g (50%), yellow solid, mp 164 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.30 (t, 3H, ^{3}J = 7.55 Hz, Et), 2.79 (q, 2H, ^{3}J = 7.55 Hz, Et), 3.41 (s, 3H, CH_3-3), 3.69 (s, 3H, CH_3-1), 7.61 (dd, 1H, ^{3}J = 8.69 Hz, ^{4}J = 1,80 Hz, H-8), 7.80 (d, 1H, ^{3}J = 8.69 Hz, H-9), 7.96 (s, 1H, H-6).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 15.4 ($CH_{3(Et)}$), 29.4 (CH_3-3), 29.6 ($CH_{2(Et)}$), 30.5 (CH_3-1), 110.2 (C-4a), 121.9 (C-5a), 123.4 (q, $^{1}J_{(C-F)}$ = 278.7 Hz, CF_3), 123.5 (q, $^{4}J_{(C-F)}$ = 5.9 Hz, CH-6), 128.9 (CH, C-9), 134.8 (CH, C-8), 137.8 (q, $^{2}J_{(C-F)}$ = 33.3 Hz, C-5), 143.5 (C-9a), 147.7 (C-10a), 149.2 (C-7), 151.2 (CO-2), 159.5 (CO-4).

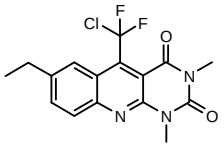
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –52.5 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 338 ($[M+H]^+$, 19), 337 ($[M]^+$, 100), 322 (27), 309 (10), 268 (16), 265 (16), 226 (11), 225 (77), 224 (11), 210 (12).

HRMS (ESI): Calcd. for $C_{16}H_{15}F_3N_3O_2$ $[M+H]^+$: 338.11109, found: 338.11193.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3380 (w), 2970 (w), 1716 (m), 1674 (s), 1620 (w), 1576 (s), 1498 (w), 1457 (s), 1413 (m), 1376 (s), 1356 (m), 1352 (m), 1286 (m), 1251 (w), 1221 (m), 1196 (m), 1147 (s), 1130 (s), 1109 (s), 1071 (m), 1056 (m), 989 (m), 944 (w), 883 (w), 860 (w), 843 (s), 823 (w), 809 (m), 776 (w), 748 (s), 700 (m), 674 (m), 636 (m), 602 (w), 568 (m), 535 (w).

5-[Chloro(difluoro)methyl]-7-ethyl-1,3-dimethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88g)



The product was prepared according to the general procedure, starting from 0.369 g of **87g** and 1.8 mL of H_2SO_4.

Yield 0.199 g (57%), yellow solid, mp 188 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.36 (t, 3H, ^3J = 7.56 Hz, Et), 2.87 (q, 2H, ^3J = 7.56 Hz, Et), 3.51 (s, 3H, CH_3-3), 3.81 (s, 3H, CH_3-1), 7.71 (d, 1H, ^3J = 8.68 Hz, H-8), 7.94 (d, 1H, ^3J = 8.68 Hz, H-9), 8.08 (s, 1H, H-6).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 15.4 ($CH_{3(Et)}$), 29.4 (CH_3-3), 29.6 ($CH_{2(Et)}$), 30.6 (CH_3-1), 108.3 (C-4a), 120.7 (C-5a), 123.7 (t, $^4J_{(C\text{-}F)}$ = 7.8 Hz, CH-6), 123.9 (t, $^1J_{(C\text{-}F)}$ = 290.6 Hz, $CClF_2$), 128.8 (CH, C-9), 134.6 (CH, C-8), 143.1 (C-9a), 143.3 (t, $^2J_{(C\text{-}F)}$ = 27.4 Hz, C-5), 147.6 (C-10a), 149.1 (C-7), 151.2 (CO-2), 159.6 (CO-4).

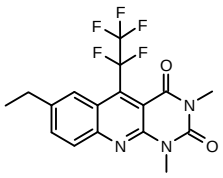
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –40.7 (br s, $CClF_2$).

MS (GC, 70 eV): *m/z* (%) = 355 ($[M+H]^+$, ^{37}Cl, 35), 354 ($[M+H]^+$, ^{35}Cl, 20), 353 ($[M]^+$, ^{35}Cl, 100), 338 (22), 319 (17), 318 (83), 303 (13), 268 (18), 243 (20), 241 (59).

HRMS (ESI): Calcd. for $C_{16}H_{15}ClF_2N_3O_2$ [M+H, ^{35}Cl]$^+$: 354.08154, found: 354.08121.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3370 (w), 2966 (w), 1715 (m), 1667 (s), 1622 (w), 1573 (s), 1503 (w), 1470 (m), 1454 (s), 1414 (m), 1378 (s), 1358 (m), 1322 (m), 1291 (m), 1274 (m), 1253 (w), 1204 (w), 1192m 1152 (m), 1140 (m), 1115 (s), 1095 (m), 1069 (m), 1005 (s), 994 (m), 552 (s), 927 (s), 881 (w), 845 (s), 832 (w), 817 (m), 796 (s), 770 (w), 793 (s), 689 (w), 675 (w), 661 (m), 632 (w), 621 (w), 580 (w), 560 (m).

7-Ethyl-1,3-dimethyl-5-(pentafluoroethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88h)



The product was prepared according to the general procedure, starting from 0.466 g of **87h** and 2.3 mL of H_2SO_4.

Yield 0.359 g (81%), yellow solid, mp 235 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.35 (t, 3H, ^3J = 7.55 Hz, Et), 2.86 (q, 2H, ^3J = 7.55 Hz, Et), 3.51 (s, 3H, CH_3-3), 3.82 (s, 3H, CH_3-1), 7.72 (d, 1H, ^3J = 8.88 Hz, H-8), 7.97 (d, 1H, ^3J = 8.88 Hz, H-9), 8.01 (s, 1H, H-6).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 15.3 ($CH_{3(Et)}$), 29.6 (CH_3-3), 29.6 ($CH_{2(Et)}$), 30.7 (CH_3-1), 111.1 (C-4a), 122.7 (C-5a), 123.9 (CH-6), 129.1 (CH, C-9), 134.9 (CH, C-8), 139.4 (t, $^2J_{(C\text{-}F)}$ = 24.0 Hz, C-5), 143.4 (C-9a), 147.9 (C-10a), 149.1 (C-7), 151.2 (CO-2), 159.5 (CO-4).

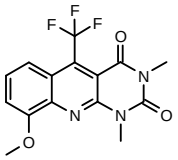
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –91.4 (s, CF_2), –75.0 (t, J = 2.0 Hz, CF_3).

MS (GC, 70 eV): *m/z* (%) = 388 ([M+H]$^+$, 18), 387 ([M]$^+$, 91), 372 (24), 359 (11), 315 (19), 276 (14), 275 (100), 268 (12), 260 (12).

HRMS (EI): Calcd. for $C_{17}H_{14}F_5N_3O_2$ [M]$^+$: 387.10007, found: 387.09992.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3381 (w), 2973 (w), 1719 (m), 1675 (s), 1621 (w), 1568 (s), 1504 (w), 1494 (w), 1454 (s), 1410 (m), 1376 (m), 1339 (w), 1313 (w), 1294 (s), 1229 (m), 1176 (s), 1146 (s), 1128 (s), 1107 (s), 1069 (m), 1036 (s), 1006 (w), 969 (s), 939 (m), 895 (w), 846 (s), 822 (w), 805 (m), 758 (w), 746 (s), 736 (m), 725 (s), 683 (m), 672 (m), 635 (w), 598 (w), 578 (w), 557 (m).

9-Methoxy-1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88i)



The product was prepared according to the general procedure, starting from 0.319 g of **87i** and 1.6 mL of H_2SO_4.

Yield 0.147 g (49%), yellow solid, mp 220 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.52 (s, 3H, CH_3-3), 3.87 (s, 3H, CH_3-1), 4.08 (s, 3H, MeO), 7.19 (d, 1H, ^3J = 7.74 Hz, H-8), 7.49 (dd, 1H, $^3J_1$ = 9.06 Hz, $^3J_2$ = 7.74 Hz, H-7), 7.84-7.92 (m, 1H, H-6).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 29.4 (CH_3-3), 30.7 (CH_3-1), 56.7 (MeO), 110.6 (C-4a), 111.3 (CH_{Ar}), 117.6 (q, $^4J_{(C-F)}$ = 6.1 Hz, CH-6), 122.9, 123.2 (q, $^1J_{(C-F)}$ = 278.7 Hz, CF_3), 127.3 (CH_{Ar}), 138.5 (q, $^2J_{(C-F)}$ = 33.5 Hz, C-5), 142.5, 147.4, 151.2 (CO-2), 154.8 (C-9), 159.4 (CO-4).

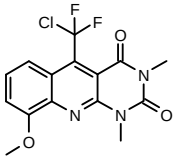
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –52.6 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 340 ([M+H]$^+$, 17), 339 ([M]$^+$, 100), 310 (37), 309 (12), 281 (20), 267 (13), 253 (26), 252 (12), 227 (24).

HRMS (EI): Calcd. for $C_{15}H_{12}F_3N_3O_3$ [M+H]$^+$: 339.08253, found: 339.08253.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2953 (w), 2848 (w), 1714 (m), 1667 (s), 1611 (w), 1566 (m), 1504 (w), 1485 (m), 1465 (m), 1444 (w), 1421 (m), 1393 (w), 1376 (m), 1353 (w), 1318 (w), 1287 (s), 1256 (w), 1233 (s), 1207 (m), 1197 (m), 1161 (s), 1147 (s), 1122 (s), 1099 (m), 1059 (m), 1004 (s), 976 (m), 877 (w), 862 (w), 838 (w), 822 (w), 788 (s), 778 (m), 757 (m), 747 (s), 714 (m), 700 (s), 688 (m), 674 (w), 615 (m), 595 (w), 586 (w), 538 (w).

5-[Chloro(difluoro)methyl]-9-methoxy-1,3-dimethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88j)



The product was prepared according to the general procedure, starting from 0.344 g of **87j** and 1.7 mL of H_2SO_4.

Yield 0.218 g (67%), yellow solid, mp 210 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.52 (s, 3H, CH_3-3), 3.87 (s, 3H, CH_3-1), 4.08 (s, 3H, MeO), 7.18 (d, 1H, ^{3}J = 7.74 Hz, H-8), 7.50 (dd, 1H, $^{3}J_1$ = 9.07 Hz, $^{3}J_2$ = 7.74 Hz, H-7), 7.86-7.93 (m, 1H, H-6).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 29.5 (CH_3-3), 30.7 (CH_3-1), 56.7 (MeO), 108.7 (C-4a), 111.2 (CH_{Ar}), 117.9 (t, $^{4}J_{(C-F)}$ = 7.9 Hz, CH-6), 121.8, 123.9 (t, $^{1}J_{(C-F)}$ = 291.2 Hz, CF_3), 127.0 (CH_{Ar}), 142.4, 144.0 (t, $^{2}J_{(C-F)}$ = 27.5 Hz, C-5), 147.3, 151.2 (CO-2), 154.8 (C-9), 159.5 (CO-4).

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –40.1 (br s, $CClF_2$).

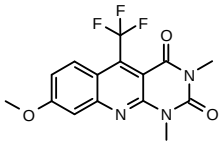
MS (GC, 70 eV): *m/z* (%) = 357 ($[M]^+$, ^{37}Cl, 34), 356 ($[M+H]^+$, ^{35}Cl, 28), 355 ($[M]^+$, ^{35}Cl, 100), 354 (37), 328 (12), 327 (10), 326 (33), 325 (11), 320 (33), 297 (12), 269 (15), 263 (15), 243 (21).

HRMS (EI): Calcd. for $C_{15}H_{12}ClF_2N_3O_3$ [M, ^{35}Cl]$^+$: 355.05298, found: 355.05262; calcd. for $C_{15}H_{12}ClF_2N_3O_3$ [M, ^{37}Cl]$^+$: 357.05003, found: 357.05014.

Anal. Calcd for $C_{15}H_{12}ClF_2N_3O_3$: C, 50.65; H, 3.40; N, 11.81. Found: C, 50.87; H, 3.30; N, 11.96.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3377 (w), 2963 (w), 1717 (s), 1667 (s), 1611 (w), 1578 (s), 1564 (s), 1504 (m), 1485 (m), 1463 (m), 1454 (m), 1421 (s), 1392 (m), 1371 (m), 1350 (m), 1317 (w), 1277 (s), 1249 (m), 1214 (s), 1186 (m), 1126 (s), 1101 (m), 1092 (s), 1059 (m), 1013 (s), 980 (m), 952 (s), 926 (s), 880 (m), 862 (w), 825 (w), 782 (s), 773 (s), 756 (m), 746 (s), 706 (w), 680 (m), 662 (m), 629 (w), 610 (m), 587 (w), 563 (w), 534 (w).

8-Methoxy-1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88k)



The product was prepared according to the general procedures for the synthesis of **87** and **88**, starting from 0.4 g of 6-[(3-methoxyphenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **70f**, 0.145 g of pyridine and 0.643 g of trifluoroacetic anhydride in 4 mL of dioxane; than to isolated crude product were added 2.5 mL of H_2SO_4.

Yield 0.062 g (12% after two steps; calculated on **70f**), yellow solid, mp 232-235 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.49 (s, 3H, CH_3-3), 3.80 (s, 3H, CH_3-1), 4.01 (s, 3H, MeO), 7.20 (dd, 1H, ^{3}J = 9.63 Hz, ^{4}J = 2.65 Hz, H-7), 7.28 (d, 1H, ^{4}J = 2.65 Hz, H-9), 8.20 (dq, 1H, ^{3}J = 9.63 Hz, $^{5}J_{(H-F)}$ = 2.08 Hz, H-6).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 29.4 (CH_3-3), 30.6 (CH_3-1), 56.2 (MeO), 106.7 (CH_{Ar}), 107.6 (C-4a), 117.3, 121.3 (CH_{Ar}), 123.4 (q, $^{1}J_{(C-F)}$ = 278.5 Hz, CF_3), 127.5 (q, $^{4}J_{(C-F)}$ = 6.3 Hz, CH-6), 138.3 (q, $^{2}J_{(C-F)}$ = 33.8 Hz, C-5), 149.0, 151.3 (CO-2), 153.0, 159.5 (CO-4), 163.8 (CH-8).

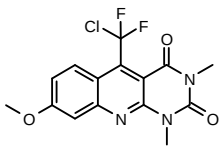
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –52.4 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 340 ([M+H]$^+$, 11), 339 ([M]$^+$, 66), 311 (12), 270 (21), 228 (13), 227 (100).

HRMS (EI): Calcd. for $C_{15}H_{12}F_3N_3O_3$ [M+H]$^+$: 339.08253, found: 339.08256.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3373 (w), 2953 (w), 1716 (m), 1669 (s), 1620 (m), 1569 (m), 1504 (w), 1480 (m), 1471 (m), 1451 (m), 1412 (m), 1381 (m), 1352 (m), 1329 (w), 1289 (m), 1273 (w), 1233 (s), 1215 (s), 1157 (s), 1132 (s), 1019 (m), 992 (m), 976 (m), 959 (w), 895 (w), 853 (s), 832 (m), 803 (s), 749 (s), 733 (w), 698 (m), 673 (w), 639 (s), 571 (w), 544 (w).

5-[Chloro(difluoro)methyl]-8-methoxy-1,3-dimethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88l)



The product was prepared according to the general procedures for the synthesis of **87** and **88**, starting from 0.4 g of 6-[(3-methoxyphenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **70f**, 0.145 g of pyridine and 0.744 g of chlorodifluoroacetic anhydride in 4 mL of dioxane; than to isolated crude product were added 2.7 mL of H_2SO_4.

Yield 0.218 g (40% after two steps; calculated on **70f**), yellow solid, mp 272-274 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.51 (s, 3H, CH_3-3), 3.81 (s, 3H, CH_3-1), 4.01 (s, 3H, MeO), 7.22 (dd, 1H, ^3J = 9.63 Hz, ^4J = 2.83 Hz, H-7), 7.29 (d, 1H, ^4J = 2.83 Hz, H-9), 8.22 (dt, 1H, ^3J = 9.63 Hz, $^5J_{(H-F)}$ = 2.90 Hz, H-6).

^{13}C NMR (75.47 MHz, 12% TFA-*d* in $CDCl_3$): δ = 30.2 (CH_3), 31.7 (CH_3), 56.9 (OMe), 103.3 (CH), 105.8 (C-4a), 116.3, 122.6 (CH), 123.0 (t, $^1J_{(C-F)}$ = 292.1 Hz, $CClF_2$), 129.0 (t, $^4J_{(C-F)}$ = 8.2 Hz, CH-6), 147.9, 148.1, 148.2 (t, $^2J_{(C-F)}$ = 28.6 Hz), 150.7 (CO-2), 158.7 (CO-4), 166.7.

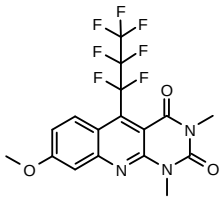
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –40.4 (br s, $CClF_2$).

MS (GC, 70 eV): *m/z* (%) = 357 ([M]$^+$, ^{37}Cl, 29), 356 ([M+H]$^+$, ^{35}Cl, 14), 355 ([M]$^+$, ^{35}Cl, 83), 327 (11), 321 (16), 320 (41), 270 (36), 245 (33), 244 (14), 243 (100), 209 (10).

HRMS (EI): Calcd. for $C_{15}H_{12}ClF_2N_3O_3$ [M, ^{35}Cl]$^+$: 355.05298, found: 355.05401.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3366 (w), 2952 (w), 1713 (s), 1668 (s), 1619 (m), 1566 (s), 1503 (m), 1482 (s), 1470 (m), 1449 (s), 1411 (m), 1380 (s), 1348 (m), 1326 (w), 1288 (m), 1269 (w), 1232 (s), 1190 (m), 1136 (s), 1114 (s), 1020 (m), 1003 (s), 975 (w), 959 (m), 946 (s), 851 (s), 826 (m), 804 (m), 791 (s), 767 (m), 749 (s), 742 (m), 729 (w), 702 (w), 679 (w), 664 (m), 634 (s), 606 (w), 557 (m), 528 (m).

5-(Heptafluoropropyl)-8-methoxy-1,3-dimethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88m)



The product was prepared according to the general procedure, starting from 0.658 g of **87m** and 3.3 mL of H_2SO_4.

Yield 0.204 g (32%), yellow solid, mp 214-216 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.50 (s, 3H, CH_3-3), 3.82 (s, 3H, CH_3-1), 4.02 (s, 3H, MeO), 7.21 (dd, 1H, ^3J = 9.82 Hz, ^4J = 2.79 Hz), H-7, 7.31 (d, 1H, ^4J = 2.79 Hz, H-9), 8.20 (d, 1H, ^3J = 9.82 Hz, H-6).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 29.6 (CH_3-3), 30.7 (CH_3-1), 56.2 (MeO), 106.8 (CH_{Ar}), 108.9 (C-4a), 118.3, 121.3 (CH_{Ar}), 128.4 (CH-6), 139.4 (t, $^2J_{(C-F)}$ = 23.5 Hz, C-5), 149.2, 151.3 (CO-2), 153.0, 159.2 (CO-4), 163.7 (CH-8).

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –116.8 (s, CF_2), –90.4 (br s, CF_2), –80.0 (t, J = 8.7 Hz, CF_3).

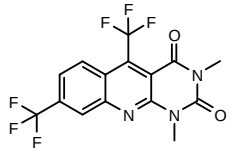
MS (GC, 70 eV): *m/z* (%) = 440 ($[M+H]^+$, 12), 439 ($[M]^+$, 64), 411 (12), 328 (14), 327 (100), 270 (11).

HRMS (ESI): Calcd. for $C_{17}H_{13}F_7N_3O_3$ $[M+H]^+$: 440.08397, found: 440.08478.

Anal. Calcd for $C_{17}H_{12}F_7N_3O_3$: C, 46.48; H, 2.75; N, 9.57. Found: C, 46.65; H, 2.55; N, 10.06.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3151 (w), 2953 (w), 2848 (w), 1715 (m), 1682 (s), 1620 (m), 1565 (s), 1504 (m), 1485 (s), 1446 (m), 1410 (m), 1380 (s), 1348 (m), 1288 (m), 1271 (w), 1233 (s), 1200 (s), 1185 (s), 1172 (s), 1141 (s), 1132 (s), 1112 (s), 1069 (w), 1041 (w), 1017 (m), 1002 (m), 975 (w), 961 (w), 931 (s), 854 (s), 824 (m), 804 (m), 790 (m), 770 (w), 752 (s), 734 (m), 723 (m), 703 (w), 692 (w), 654 (w), 641 (m), 620 (m), 597 (w), 558 (m), 537 (w).

1,3-Dimethyl-5,8-bis(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88n)



The product was prepared according to the general procedure, starting from 0.475 g of **87n** and 2.4 mL of H_2SO_4.

Yield 0.233 g (51%), yellow solid, mp 199-201 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.53 (s, 3H, CH_3-3), 3.84 (s, 3H, CH_3-1), 7.75 (dd, 1H, ^3J = 9.16 Hz, ^4J = 1.98 Hz, H-7), 8.33-8.36 (m, 1H, H-9), 8.42-8.50 (dm, 1H, ^3J = 9.16 Hz, H-6).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 29.6 (CH_3-3), 30.9 (CH_3-1), 112.2 (C-4a), 122.7 (CH_{Ar}), 122.9 (q, $^1J_{(C-F)}$ = 278.4 Hz, CF_3), 123.0, 123.5 (q, $^1J_{(C-F)}$ = 273.0 Hz, CF_3), 126.8 (q, $^4J_{(C-F)}$ = 4.4 Hz, CH_{Ar}), 127.8 (q, $^4J_{(C-F)}$ = 6.2 Hz, CH_{Ar}), 134.7 (q, $^2J_{(C-F)}$ = 33.4 Hz), 139.1 (q, $^2J_{(C-F)}$ = 33.9 Hz),

149.3, 149.4, 150.9 (CO-2), 158.9 (CO-4).

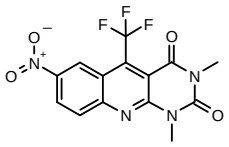
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –63.7 (s, CF_3-8), –52.7 (s, CF_3-5).

MS (GC, 70 eV): *m/z* (%) = 377 ($[M]^+$, 52), 265 (100).

HRMS (EI): Calcd. for $C_{15}H_9F_6N_3O_2$ $[M]^+$: 377.05935, found: 377.05920.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3388 (w), 3107 (w), 2966 (w), 1722 (m), 1668 (s), 1585 (m), 1565 (m), 1511 (w), 1464 (m), 1422 (m), 1393 (w), 1378 (m), 1361 (m), 1336 (m), 1300 (m), 1272 (m), 1222 (w), 1172 (s), 1122 (s), 1104 (s), 1072 (s), 966 (m), 945 (m), 910 (s), 885 (m), 831 (m), 804 (s), 780 (w), 760 (w), 745 (s), 710 (m), 700 (s), 679 (m), 673 (m), 657 (w), 630 (m), 581 (w), 553 (w).

1,3-Dimethyl-7-nitro-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88o)



The product was prepared according to the general procedure, starting from 0.309 g of **87o** and 1.5 mL of H_2SO_4.

Yield 0.242 g (82%), yellow solid, mp 232-234 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.53 (s, 3H, CH_3-3), 3.85 (s, 3H, CH_3-1), 8.17 (d, 1H, ^3J = 9.54 Hz, H-9), 8.61 (d, 1H, ^3J = 9.54 Hz, H-8), 9.32 (s, 1H, H-6).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 29.8 (CH_3-3), 31.1 (CH_3-1), 112.5 (C-4a), 120.2, 122.7 (q, $^1J_{(C\text{-}F)}$ = 278.6 Hz, CF_3), 123.6 (q, $^4J_{(C\text{-}F)}$ = 6.7 Hz, CH-6), 126.7 (CH_{Ar}), 130.8 (CH_{Ar}), 141.0 (q, $^2J_{(C\text{-}F)}$ = 34.1 Hz, C-5), 145.8, 150.7, 150.8, 152.0 (CO-2), 158.5 (CO-4).

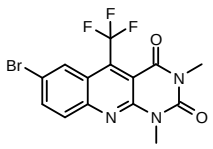
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –52.6 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 354 ($[M]^+$, 49), 243 (12), 242 (100), 196 (13).

HRMS (EI): Calcd. for $C_{14}H_9F_3N_4O_4$ $[M]^+$: 354.05704, found: 354.05725.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3392 (w), 3133 (w), 2965 (w), 1725 (m), 1680 (s), 1623 (w), 1586 (m), 1574 (s), 1532 (m), 1496 (m), 1471 (s), 1417 (w), 1373 (m), 1363 (w), 1340 (w), 1294 (m), 1280 (s), 1230 (w), 1203 (m), 1180 (m), 1155 (s), 1136 (s), 1110 (s), 1070 (w), 993 (m), 986 (m), 972 (w), 948 (w), 907 (m), 868 (m), 844 (s), 810 (w), 793 (w), 723 (w), 760 (w), 748 (s), 740 (s), 713 (w), 703 (m), 675 (w), 647 (m), 633 (m), 565 (m), 539 (w), 527 (w).

7-Bromo-1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88p)



The product was prepared according to the general procedure, starting from 1.401 g of **87p** and 7 mL of H_2SO_4.

Yield 1.121 g (84%), yellow solid, mp 200 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.49 (s, 3H, CH_3-3), 3.78 (s, 3H,

CH_3-1), 7.86 (s, 2H, H-8, H-9), 8.41 (s, 1H, H-6).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 29.5 (CH_3-3), 30.7 (CH_3-1), 111.1 (C-4a), 121.5, 122.5, 123.0 (q, $^{1}J_{(C-F)}$ = 278.3 Hz, CF_3), 128.2 (q, $^{4}J_{(C-F)}$ = 6.6 Hz, CH-6), 130.6 (CH_{Ar}), 136.8 (CH_{Ar}), 137.8 (q, $^{2}J_{(C-F)}$ = 33.8 Hz, C-5), 148.5, 148.8, 151.0 (CO-2), 159.0 (CO-4).

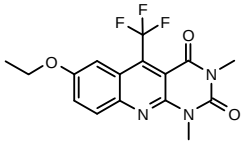
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –52.7 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 390 ($[M+H]^+$, ^{81}Br, 13), 389 ($[M]^+$, ^{81}Br, 81), 388 ($[M+H]^+$, ^{79}Br, 15), 387 ($[M]^+$, ^{79}Br, 84), 291 (15), 289 (16), 278 (11), 277 (97), 276 (15), 275 (100), 263 (11), 261 (11), 182 (11), 176 (11).

HRMS (EI): Calcd. for $C_{14}H_9BrF_3N_3O_2$ [M, ^{79}Br]$^+$: 386.98248, found: 386.9826; calcd. for $C_{14}H_{11}F_3N_3O_2$ [M, ^{81}Br]$^+$: 388.98043, found: 388.98055.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3380 (w), 3116 (w), 2962 (w), 2849 (w), 1719 (m), 1668 (s), 1581 (s), 1564 (s), 1556 (m), 1463 (s), 1447 (s), 1410 (m), 1384 (m), 1372 (s), 1358 (m), 1320 (m), 1295 (m), 1281 (s), 1228 (w), 1205 (m), 1162 (s), 1129 (s), 1103 (s), 1075 (s), 986 (s), 969 (m), 936 (m), 875 (w), 858 (w), 831 (s), 808 (m), 797 (w), 772 (w), 757 (w), 748 (s), 713 (w), 702 (s), 672 (m), 639 (s), 630 (m), 559 (m), 552 (m), 532 (m).

7-Ethoxy-1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88q)



The product was prepared according to the general procedure, starting from 0.397 g of **87q** and 2 mL of H_2SO_4.

Yield 0.276 g (73%), yellow solid, mp 210-212 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.44 (t, 3H, ^{3}J = 7.55 Hz, EtO), 3.44 (s, 3H, CH_3-3), 3.74 (s, 3H, CH_3-1), 4.11 (q, 2H, ^{3}J = 7.55 Hz, EtO), 7.41-7.48 (m, 2H, H-6, H-8), 7.85 (d, 1H, ^{3}J = 10,01 Hz, H-9).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.9 ($CH_{3(EtO)}$), 29.5 (CH_3-3), 30.6 (CH_3-1), 64.4 ($CH_{2(EtO)}$), 103.9 (q, $^{4}J_{(C-F)}$ = 6.3 Hz, CH-6), 110.3 (C-4a), 123.1, 123.6 (q, $^{1}J_{(C-F)}$ = 277.29 Hz, CF_3), 127.5 (CH_{Ar}), 130.5 (CH_{Ar}), 136.2 (q, $^{2}J_{(C-F)}$ = 33.1 Hz, C-5), 146.8, 146.9, 151.2 (CO-2), 157.6 (C-7), 159.6 (CO-4).

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –53.1 (s, CF_3).

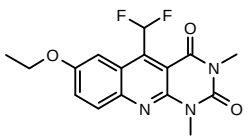
MS (GC, 70 eV): *m/z* (%) = 354 ($[M+H]^+$, 17), 353 ($[M]^+$, 100), 325 (20), 268 (14), 267 (15), 241 (11), 213 (41).

HRMS (EI): Calcd. for $C_{16}H_{14}F_3N_3O_3$ $[M]^+$: 353.09818, found: 353.09811.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2991 (w), 1742 (s), 1675 (s), 1623 (m), 1583 (s), 1504 (w), 1471 (m), 1455 (m), 1425 (m), 1414 (s), 1386 (s), 1372 (s), 1324 (w), 1288 (s), 1232 (s), 1209 (s), 1171 (s), 1159 (s), 1123 (s), 1066 (w), 1040 (s), 988 (m), 953 (w), 916 (w), 861 (w), 845 (s), 830 (m), 806

(m), 773 (w), 764 (w), 748 (s), 709 (w), 698 (s), 679 (m), 667 (w), 653 (w), 578 (s), 559 (w), 537 (w).

5-(Difluoromethyl)-7-ethoxy-1,3-dimethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88r)



The product was prepared according to the general procedure, starting from 0.469 g of **87r** and 2.3 mL of H_2SO_4.

Yield 0.354 g (80%), yellow solid, mp 238 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.50 (t, 3H, ^3J = 6.99 Hz, EtO), 3.51 (s, 3H, CH_3-3), 3.81 (s, 3H, CH_3-1), 4.19 (q, 2H, ^3J = 6.99 Hz, EtO), 7.50 (dd, 1H, ^3J = 9.26 Hz, ^4J = 2.64 Hz, H-8), 7.76 (d, 1H, ^4J = 2.64 Hz, H-6), 7.89 (d, 1H, ^3J = 9.26 Hz, H-9), 8.86 (t, 1H, $^2J_{(H-F)}$ = 53.92 Hz, CH_2F).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.9 ($CH_{3(EtO)}$), 29.3 (CH_3-3), 30.6 (CH_3-1), 64.3 ($CH_{2(EtO)}$), 105.2 (t, $^4J_{(C-F)}$ = 6.0 Hz, CH-6), 108.6 (C-4a), 112.1 (t, $^1J_{(C-F)}$ = 239.6 Hz, CHF_2), 123.0, 127.6 (CH_{Ar}), 130.3 (CH_{Ar}), 141.9 (t, $^2J_{(C-F)}$ = 23.7 Hz, C-5), 146.5, 146.5, 151.0 (CO-2), 157.2, 161.9.

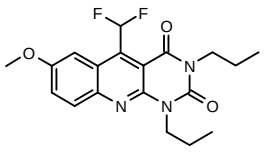
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –112.5 (s, CHF_2).

MS (GC, 70 eV): *m/z* (%) = 336 ($[M+H]^+$, 18), 335 ($[M]^+$, 100), 307 (46), 306 (13), 279 (14), 256 (13), 195 (43).

HRMS (EI): Calcd. for $C_{16}H_{15}F_2N_3O_3$ $[M]^+$: 335.10760, found: 335.10773.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3353 (w), 3139 (w), 3078 (w), 2989 (w), 2942 (w), 2918 (w), 2849 (w), 1705 (s), 1659 (s), 1621 (m), 1583 (m), 1538 (w), 1499 (w), 1477 (m), 1462 (m), 1450 (m), 1422 (m), 1412 (m), 1384 (m), 1321 (w), 1290 (m), 1271 (w), 1251 (w), 1223 (m), 1185 (m), 1148 (m), 1116 (m), 1095 (m), 1029 (s), 992 (m), 978 (m), 955 (w), 936 (m), 900 (w), 843 (s), 827 (m), 806 (s), 767 (w), 759 (w), 747 (s), 719 (m), 682 (m), 581 (s), 555 (m).

5-(Difluoromethyl)-7-methoxy-1,3-dipropylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88s)



The product was prepared according to the general procedures for the synthesis of **87** and **88**, starting from 0.3 g of 6-[(4-methoxyphenyl)amino]-1,3-dipropylpyrimidine-2,4(1*H*,3*H*)-dione **70a**, 0.09 g of pyridine and 0.329 g of difluoroacetic anhydride in 3 mL of dioxane; than to isolated crude product were added 2 mL of H_2SO_4.

Yield 0.307 g (86% after two steps; calculated on **70a**), yellow solid, mp 167-168 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.94-1.11 (m, 6H, $CH_{3(Pr-1)}$, $CH_{3(Pr-3)}$), 1.66-1.89 (m, 4H, $CH_{2(Pr-1)}$, $CH_{2(Pr-3)}$), 3.95 (s, 3H, MeO), 4.06 (t, 2H, ^{3}J = 7.55 Hz, NCH_2-3), 4.41 (t, 2H, ^{3}J = 7.46 Hz, NCH_2-1), 7.48 (d, 1H, H-8), 7.77 (s, 1H, H-6), 7.88 (d, 1H, ^{3}J = 9.15 Hz, H-9), 8.86 (t, 1H, $^{2}J_{(H-F)}$ = 54.01 Hz, CH_2F).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 11.6 ($CH_{3(Pr)}$), 11.7 ($CH_{3(Pr)}$), 21.3 ($CH_{2(Pr)}$), 21.4 ($CH_{2(Pr)}$), 44.3 ($CH_{2(Pr)}$), 45.0 ($CH_{2(Pr)}$), 55.9 (MeO), 104.5 (t, $^{4}J_{(C-F)}$ = 6.0 Hz, CH-6), 108.8 (C-4a), 112.2 (t, $^{1}J_{(C-F)}$ = 239.11 Hz, CHF_2), 122.9, 127.2 (CH_{Ar}), 130.4 (CH_{Ar}), 142.0 (t, $^{2}J_{(C-F)}$ = 23.7 Hz, C-5), 146.3, 146.7, 150.5 (CO-2), 157.7, 161.6.

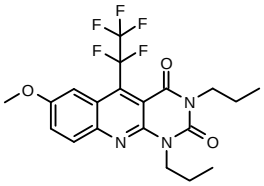
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –112.4 (s, CHF_2).

MS (GC, 70 eV): *m/z* (%) = 378 ($[M+H]^+$, 17), 377 ($[M]^+$, 76), 336 (18), 335 (100), 307 (17), 294 (21), 293 (100), 277 (26), 265 (15), 263 (23), 250 (14), 249 (18), 236 (12), 208 (14), 188 (16).

HRMS (EI): Calcd. for $C_{19}H_{21}F_3N_3O_3$ $[M]^+$: 377.15455, found: 377.15478.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3356 (w), 3093 (w), 3004 (w), 2963 (w), 2936 (w), 2876 (w), 2834 (w), 1703 (m), 1655 (s), 1622 (m), 1589 (s), 1572 (s), 1505 (w), 1457 (m), 1442 (s), 1423 (w), 1411 (s), 1396 (s), 1370 (m), 1348 (w), 1322 (m), 1302 (w), 1282 (w), 1271 (m), 1253 (w), 1226 (s), 1187 (w), 1175 (w), 1142 (m), 1112 (m), 1049 (m), 1031 (w), 1015 (s), 966 (w), 920 (w), 903 (w), 872 (w), 837 (s), 807 (m), 772 (w), 759 (w), 749 (m), 729 (w), 707 (m), 696 (w), 674 (m), 622 (w), 570 (m), 560 (m), 530 (m).

7-Methoxy-5-(pentafluoroethyl)-1,3-dipropylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (88t)



The product was prepared according to the general procedure, starting from 0.342 g of **87t** and 1.7 mL of H_2SO_4.

Yield 0.265 (81%), yellow solid, mp 115 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.98 (t, 3H, ^{3}J = 7.55 Hz, $CH_{3(Pr)}$), 1.03 (t, 3H, ^{3}J = 7.36 Hz, $CH_{3(Pr)}$), 1.66-1.89 (m, 4H, $CH_{2(Pr-1)}$, $CH_{2(Pr-3)}$), 3.93 (s, 3H, MeO), 4.05 (t, 2H, ^{3}J = 7.55 Hz, NCH_2-3), 4.40 (t, 2H, ^{3}J = 7.55 Hz, NCH_2-1), 7.44-7.53 (m, 2H, H-6, H-8), 7.91 (d, 1H, ^{3}J = 9.07 Hz, H-9).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 11.58 ($CH_{3(Pr)}$), 11.64 ($CH_{3(Pr)}$), 21.37 ($CH_{2(Pr)}$), 21.43 ($CH_{2(Pr)}$), 44.4 ($CH_{2(Pr)}$), 45.0 ($CH_{2(Pr)}$), 55.8 (MeO), 103.6 (CH-6), 111.5 (C-4a), 123.7, 127.0 (CH_{Ar}), 130.7 (CH_{Ar}), 137.7 (t, $^{2}J_{(C-F)}$ = 23.8 Hz, C-5), 146.7, 146.9, 150.7 (CO-2), 158.0 (C-7), 159.4 (CO-4).

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –92.6 (s, CF_2), –74.9 (s, CF_3).

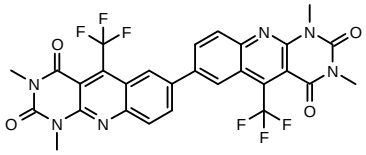
MS (GC, 70 eV): *m/z* (%) = 446 ($[M–F]^+$, 18), 445 (80), 404 (20), 403 (100), 375 (12), 361

(18), 346 (11), 345 (28), 334 (38), 333 (26), 331 (38), 319 (18), 318 (64), 317 (33), 304 (16), 277 (12), 274 (10), 206 (10), 41 (14).

HRMS (EI): Calcd. for $C_{20}H_{20}F_5N_3O_3$ $[M]^+$: 455.14193, found: 455.14179.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3371 (w), 2969 (w), 2940 (w), 2882 (w), 2833 (w), 1712 (m), 1668 (s), 1622 (m), 1565 (m), 1504 (m), 1449 (s), 1442 (s), 1407 (m), 1390 (s), 1368 (m), 1325 (m), 1301 (m), 1272 (w), 1255 (w), 1226 (s), 1181 (s), 1157 (s), 1140 (s), 1120 (s), 1047 (s), 1030 (m), 1011 (s), 975 (m), 959 (m), 902 (w), 895 (w), 872 (w), 845 (s), 828 (m), 802 (m), 755 (m), 742 (m), 724 (s), 691 (m), 685 (m), 676 (m), 642 (w), 635 (w), 600 (m), 564 (s), 529 (m).

1,1',3,3'-Tetramethyl-5,5'-bis(trifluoromethyl)-7,7'-bipyrimido[4,5-*b*]quinoline-2,2',4,4'(1*H*,1'*H*,3*H*,3'*H*)-tetrone (88u)



The product was prepared according to the general procedure, starting from 0.329 g of **87u** and 1.6 mL of H_2SO_4.

Yield 0.143 (46%), yellow solid, mp > 375 °C.

^{1}H NMR (300.13 MHz, 12% TFA-*d* in $CDCl_3$): δ = 3.60 (s, 6H, CH_3-3, CH_3-3'), 3.96 (s, 6H, CH_3-1, CH_3-1'), 8,30 (s, 4H, H-8, H-9, H-8', H-9'), 8.66 (s, 2H, H-6, H-6').

^{13}C NMR (75.47 MHz, TFA-*d*): δ = 31.5 (CH_3), 33.0 (CH_3), 114.3 (C-4a, C-4a'), 124.0, 124.1 (q, $^1J_{(C-F)}$ = 278.9 Hz, CF_3), 127.1 (CH), 127.8 (q, $^4J_{(C-F)}$ = 5.7 Hz, CH-6, CH-6'), 138.1 (CH), 142.0, 145.5, 147.1 (q, $^2J_{(C-F)}$ = 35.4 Hz), 150.0, 152.6 (CO-2, CO-2'), 160.9 (CO-4, CO-4').

^{19}F NMR (282.38 MHz, 12% TFA-*d* in $CDCl_3$): δ = –52.7 (s, CF_3).

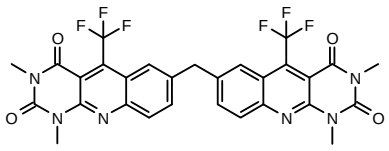
MS (EI, 70 eV): *m/z* (%) = 617 ($[M+H]^+$, 26), 616 ($[M]^+$, 100), 504 (39), 406 (10), 196 (22), 69 (11).

HRMS (EI): Calcd. for $C_{28}H_{18}F_6N_6O_4$ $[M]^+$: 616.12882, found: 616.12925.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3070 (w), 2960 (w), 1716 (s), 1680 (s), 1619 (w), 1567 (s), 1499 (w), 1468 (m), 1434 (s), 1399 (m), 1384 (m), 1370 (m), 1357 (m), 1331 (s), 1288 (m), 1271 (m), 1205 (m), 1168 (s), 1145 (s), 1106 (s), 1062 (m), 1044 (w), 986 (m), 926 (w), 868 (w), 835 (s), 808 (m), 788 (w), 771 (w), 760 (w), 747 (s), 727 (w), 712 (w), 699 (m), 677 (w), 643 (m), 602 (m), 555 (m), 535 (w).

7,7'-Methylenebis[1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione] (88v)

The product was prepared according to the general procedure, starting from 0.46 g of **87v** and 2.3 mL of H_2SO_4.



Yield 0.224 (51%), yellow solid, mp 368-370 °C.

^{1}H NMR (300.13 MHz, 12% TFA-*d* in $CDCl_3$): δ = 3.60 (s, 6H, CH_3-3, CH_3-3'), 3.96 (s, 6H, CH_3-1, CH_3-1'), 4.46 (s, 2H, CH_2), 7.80 (d, 2H, ^{3}J = 8.87 Hz, H-8, H-8'), 8.14 (d, 2H, ^{3}J = 8.87 Hz, H-9, H-9'), 8.24 (s, 2H, H-6, H-6').

^{13}C NMR (62.90 MHz, 12% TFA-*d* in $CDCl_3$): δ = 30.1 (CH_3), 31.3 (CH_3), 42.8 (CH_2), 110.2, 122.4, 123.0 (q, $^{1}J_{(C\text{-}F)}$ = 278.4 Hz, CF_3), 125.6 (q, $^{4}J_{(C\text{-}F)}$ = 5.9 Hz, CH-6, CH-6'), 129.4 (CH), 136.0 (CH), 139.5 (q, $^{2}J_{(C\text{-}F)}$ = 35.7 Hz), 139.8, 147.7, 149.2, 152.2 (CO-2, CO-2'), 160.2 (CO-4, CO-4').

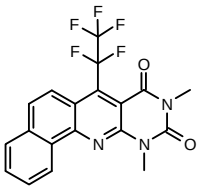
^{19}F NMR (282.38 MHz, 12% TFA-*d* in $CDCl_3$): δ = –52.8 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 631 ($[M+H]^+$, 30), 630 ($[M]^+$, 100), 561 (13), 518 (19), 498 (32), 429 (16), 203 (30), 69 (29), 44 (16), 40 (21).

HRMS (EI): Calcd. for $C_{29}H_{20}F_6N_6O_4$ $[M]^+$: 630.14447, found: 630.14403.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3372 (w), 3078 (w), 2952 (w), 1719 (m), 1667 (s), 1621 (w), 1580 (s), 1564 (m), 1495 (w), 1470 (s), 1462 (s), 1456 (s), 1414 (m), 1292 (m), 1272 (m), 1215 (m), 1192 (m), 1163 (s), 1127 (s), 1108 (s), 1064 (m), 987 (m), 920 (w), 897 (w), 860 (w), 847 (w), 837 (m), 820 (w), 811 (m), 770 (w), 747 (s), 721 (w), 708 (m), 696 (m), 677 (w), 667 (w), 638 (m), 574 (m), 564 (w), 542 (w).

9,11-Dimethyl-7-(pentafluoroethyl)benzo[*h*]pyrimido[4,5-*b*]quinoline-8,10(9*H*,11*H*)-dione (88w)



The product was prepared according to the general procedure, starting from 0.393 g of **87w** and 2 mL of H_2SO_4.

Yield 0.307 (54%), yellow solid, mp 313-315 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.55 (s, 3H, CH_3-9), 3.98 (s, 3H, CH_3-11), 7.73-7.86 (m, 3H, CH_{Ar}), 7.91 (d, 1H, ^{3}J = 7.55 Hz, CH_{Ar}), 8.02-8.11 (m, 1H, CH_{Ar}), 9.20 (d, 1H, ^{3}J = 7.74 Hz, CH_{Ar}).

^{13}C NMR (62.90 MHz, 12% TFA-*d* in $CDCl_3$): δ = 30.1 (CH_3), 31.2 (CH_3), 109.4 (C-7a), 122.0 (CH-6), 122.2, 126.5 (CH), 128.2 (CH), 128.5 (CH), 129.7 (CH), 130.1, 131.7 (CH), 134.7, 139.4 (t, $^{2}J_{(C\text{-}F)}$ = 24.2 Hz), 147.6, 150.6, 152.5, 160.3 (CO-4).

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –90.9 (s, CF_2), –74.9 (s, CF_3).

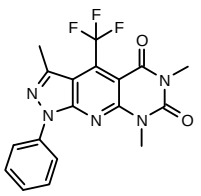
MS (GC, 70 eV): *m/z* (%) = 410 ($[M+H]^+$, 23), 409 ($[M]^+$, 100), 352 (11), 311 (12), 298 (12), 297 (72).

HRMS (EI): Calcd. for $C_{19}H_{12}F_5N_3O_2$ $[M]^+$: 409.08442, found: 409.08417.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3377 (w), 3056 (w), 2959 (w), 1719 (m), 1673 (s), 1620 (w), 1573 (m),

1562 (s), 1513 (w), 1503 (m), 1470 (m), 1450 (m), 1435 (w), 1422 (m), 1387 (w), 1367 (s), 1336 (m), 1295 (m), 1239 (w), 1226 (m), 1189 (s), 1159 (m), 1138 (s), 1113 (m), 1101 (m), 1074 (w), 1047 (m), 1028 (m), 997 (m), 969 (s), 934 (w), 885 (w), 878 (w), 834 (w), 810 (m), 796 (w), 787 (m), 761 (m), 747 (m), 735 (s), 726 (m), 708 (m), 682 (m), 663 (w), 628 (w), 594 (w), 566 (w), 558 (w), 543 (w).

3,6,8-Trimethyl-1-phenyl-4-(trifluoromethyl)-1*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (88x)



The product was prepared according to the general procedure for the synthesis of compounds **87** (!) from 0.477 g of **70d**, 0.136 g of pyridine and 0.603 g of trifluoroacetic anhydride in 4.5 mL of dry dioxane.

Yield 0.42 g (75%, calculated on 1,3-dimethyl-6-[(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)amino]pyrimidine-2,4(1*H*,3*H*)-dione **70d**, which cyclizes immediately while acylated by TFAA; non-cyclized intermediate product hasn't been obtained), yellow solid, mp 254 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.73 (q, 3H, $^{6}J_{(H-F)}$ = 3.07 Hz, CH_3-3) 3.51 (s, 3H, CH_3-6), 3.78 (s, 3H, CH_3-8), 7.36 (t, 1H, ^{3}J = 7.46 Hz, CH_{Ph}), 7.50-7.59 (m, 2H, CH_{Ph}), 8.12-8.20 (m, 2H, CH_{Ph}).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 17.5 (q, $^{5}J_{(C-F)}$ = 7.4 Hz, CH_3-3), 29.3 (CH_3-6), 31.1 (CH_3-8), 104.5, 111.8, 121.3 (CH_{Ph}), 122.3 (q, $^{1}J_{(C-F)}$ = 278.8 Hz, CF_3), 127.0 (CH_{Ph}), 129.4 (CH_{Ph}), 136.7 (q, $^{2}J_{(C-F)}$ = 37.3 Hz, C-4), 138.4, 144.5, 151.00, 151.04, 151.06, 159.1 (CO-5).

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –54.6 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 390 ($[M+H]^+$, 20), 389 ($[M]^+$, 100), 277 (33), 276 (17), 77 (21).

HRMS (EI): Calcd. for $C_{18}H_{14}F_3N_5O_2$ $[M]^+$: 389.10941, found: 389.10929.

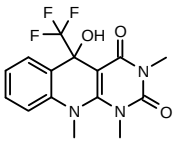
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3114 (w), 2996 (w), 2956 (w), 1715 (s), 1669 (s), 1593 (m), 1575 (s), 1532 (m), 1504 (m), 1489 (s), 1470 (m), 1462 (m), 1456 (m), 1421 (s), 1411 (s), 1385 (m), 1367 (s), 1336 (s), 1272 (m), 1227 (s), 1210 (m), 1179 (m), 1152 (s), 1135 (s), 1117 (s), 1062 (m), 1043 (m), 1025 (m), 1000 (w), 987 (m), 970 (w), 911 (w), 864 (m), 845 (w), 805 (m), 774 (w), 763 (s), 754 (m), 746 (s), 700 (m), 691 (s), 661 (m), 645 (w), 632 (w), 601 (m), 539 (w).

4.2.7 Synthesis of 5-hydroxy-1,3-dimethyl-5-perfluoroalkyl-5,10-dihydro-5-deazaalloxazines

General procedure for the synthesis of 5-hydroxy-1,3-dimethyl-5-perfluoroalkyl-5,10-dihydro-1*H*-pyrimido[4,5-*b*]quinoline-2,4-diones 91a-c.

Initial 5-(perfluoroacyl)-6-amino-1,3-dimethylrimidine-2,4(1*H*,3*H*)-dione **90** (1 g) was dissolved in concentrated H_2SO_4 (5 mL) and allowed to stand at r.t. for 2 hours. Then the solution was poured into ice water and extracted with chloroform, extracts were died over Na_2SO_4 and evaporated by rotovap. The crude product was purified via short-part column chromatography (silica gel / $CHCl_3$), followed by recrystallization from methanol to give pure product.

5-Hydroxy-1,3,10-trimethyl-5-(trifluoromethyl)-5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (91c)



The product was prepared following the general procedure, starting from 0.25 g of **90c** and 1.3 mL of H_2SO_4.

Yield 0.18 g (72%), white solid, mp 216-218 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.26 (s, 3H, CH_3), 3.48 (s, 3H, CH_3), 3.51 (s, 3H, CH_3), 7.32 (dd, 1H, $^3J_1$ = 7.74 Hz, $^3J_2$ = 7.17 Hz, H-7), 7.46 (d, 1H, ^3J = 8.31 Hz, H-9), 7.55 (dd, 1H, $^3J_1$ = 8.31 Hz, $^3J_2$ = 7.17 Hz, H-8), 7.67 (d, 1H, ^3J = 7.74 Hz, H-6), 8.45 (br s, 1H, OH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.5 (CH_3), 37.3 (CH_3), 41.8 (CH_3), 71.8 (q, $^2J_{(C\text{-}F)}$ = 30.5 Hz), 88.1 (C-4a), 119.3 (CH), 125.2 (CH), 126.2 (q, $^1J_{(C\text{-}F)}$ = 290.5 Hz, CF_3), 126.7 (CH), 130.8 (CH), 141.7, 152.4, 153.3, 165.0.

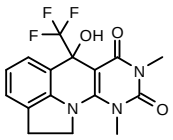
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –83.1 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 273 (41), 272 (100), 257 (10).

HRMS (ESI): Calcd. for $C_{15}H_{15}F_3N_3O_3$ $[M+H]^+$: 342.10600, found: 342.10635.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3271 (w), 3190 (w), 2980 (w), 1703 (s), 1687 (m), 1622 (s), 1608 (s), 1574 (m), 1504 (s), 1487 (s), 1470 (s), 1464 (s), 1456 (s), 1423 (s), 1396 (m), 1381 (m), 1323 (m), 1254 (s), 1207 (m), 1161 (s), 1119 (s), 1090 (m), 1070 (s), 1049 (s), 972 (m), 955 (w), 937 (m), 922 (s), 866 (w), 833 (m), 779 (s), 768 (s), 760 (s), 746 (s), 710 (s), 662 (s), 642 (s), 602 (m), 565 (m), 550 (m), 538 (m).

6-Hydroxy-8,10-dimethyl-6-(trifluoromethyl)-1,2-dihydro-6*H*-pyrimido[4,5-*b*]pyrrolo[3,2,1-*ij*]quinoline-7,9(8*H*,10*H*)-dione (91a)



The product was prepared following the general procedure, starting from 0.336 g of **90a** and 1.7 mL of H_2SO_4.

Yield 0.299 g (89%), white solid, mp 253-255 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.25 (s, 3H, CH_3), 3.26-3.49 (m, 2H, CH_2-2), 3.67 (s, 3H, CH_3), 4.22-4.35 (m, 1H, CH_2-1a), 4.80-4.92 (m, 1H, CH_2-1b), 7.25 (dd, 1H, $^3J_1$ = 7.74 Hz, $^3J_2$ = 7.36 Hz, H-4), 7.39 (d, 1H, ^3J = 7.36 Hz, CH_{Ar}), 7.45 (d, 1H, ^3J = 7.74 Hz, CH_{Ar}), 8.69 (s, 1H, OH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.5 (CH_3), 29.1 (CH_2), 37.7 (CH_3), 54.1 (CH_2), 72.7 (q, $^2J_{(C-F)}$ = 30.7 Hz, C-6), 80.6 (C-6a), 116.7 125.0 (CH_{Ar}), 125.9 (CH_{Ar}), 126.3 (CH_{Ar}), 126.7 (q, $^1J_{(C-F)}$ = 291.2 Hz, CF_3), 130.3, 140.8, 152.0, 152.7, 164.7.

^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –82.5 (s, CF_3).

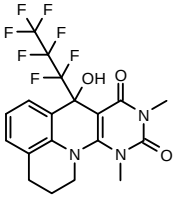
MS (GC, 70 eV): *m/z* (%) = 285 ($[M+H–CF_3]^+$, 17), 284 ($[M–CF_3]^+$, 100), .

HRMS (ESI): Calcd. for $C_{16}H_{14}F_3N_3NaO_3$ $[M+Na]^+$: 376.08795, found: 376.08866.

Anal. Calcd for $C_{16}H_{14}F_3N_3O_3$: C, 54.39; H, 3.99; N, 11.89. Found: C, 54.30; H, 4.05; N, 11.52.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3029 (m), 2967 (m), 1695 (s), 1639 (w), 1606 (m), 1544 (m), 1494 (s), 1462 (s), 1455 (s), 1443 (s), 1430 (s), 1401 (m), 1379 (m), 1360 (m), 1344 (m), 1301 (w), 1259 (m), 1242 (s), 1233 (s), 1220 (m), 1184 (w), 1156 (s), 1129 (s), 1157 (s), 1035 (m), 1005 (w), 991 (m), 964 (s), 936 (m), 866 (m), 832 (w), 783 (s), 773 (m), 764 (m), 753 (s), 745 (m), 716 (m), 704 (s), 679 (m), 616 (w), 574 (w), 534 (w).

7-(Heptafluoropropyl)-7-hydroxy-9,11-dimethyl-2,3-dihydro-1*H*,7*H*-pyrido[3,2,1-*ij*]pyrimido[4,5-*b*]quinoline-8,10(9*H*,11*H*)-dione (91b)



The product was prepared following the general procedure, starting from 0.2 g of **90b** and 1 mL of H_2SO_4.

Yield 0.188 g (94%), white solid, mp 177 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.09-2.23 (m, 1H, CH_2-2a), 2.24-2.43 (m, 1H, CH_2-2b), 2.94-3.05 (m, 2H, CH_2-3), 3.25-3.35 (m, 1H, CH_2-1a), 3.35 (s, 3H, CH_3), 3.50 (s, 3H, CH_3),3.92-4.02 (m, 1H, CH_2-1b), 7.12-7.21 (m, 2H, CH_{Ar}), 7.60-7.67 (m, 1H, CH_{Ar}), 8.41 (s, 1H, OH).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 22.8 (CH_2), 25.4 (CH_2), 28.3 (CH_3), 37.5 (CH_3), 47.3 (CH_2-1), 74.4 (t, $^2J_{(C-F)}$ = 25.2 Hz, C-7), 88.9 (C-7a), 123.1, 124.6 (CH_{Ar}), 125.3 (CH_{Ar}), 126.7,

129.7, 136.5 (CH_{Ar}), 150.5, 152.8, 165.1.

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –125.3 (dd, ^2J = 289.17 Hz, ^3J = 9.19 Hz, CF_2-1a), –123.6 (dd, ^2J = 289.17 Hz, ^3J = 7,16 Hz, CF_2-1b), 121.6 (m, CF_2-2), –80.8 (t, J = 12.27 Hz, CF_3).

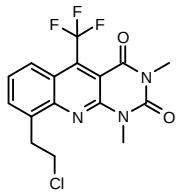
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3216 (m), 2956 (w), 2849 (w), 1693 (m), 1622 (m), 1601 (m), 1575 (m), 1504 (m), 1462 (s), 1455 (s), 1428 (s), 1407 (m), 1389 (w), 1371 (m), 1345 (m), 1286 (w), 1250 (w), 1206 (s), 1184 (s), 1116 (s), 1091 (m), 1061 (m), 1045 (m), 1032 (m), 1003 (w), 984 (w), 942 (w), 907 (w), 878 (w), 856 (m), 827 (w), 807 (w), 782 (m), 769 (m), 746 (s), 733 (w), 701 (m), 676 (w), 667 (m), 646 (s), 589 (w), 575 (w), 568 (w), 550 (w), 530 (w).

4.2.8 Synthesis of 9-(ω-chloroalkyl)-1,3-dimethyl-5-trifluoromethyl-5-deazaalloxazines

Synthesis of 9-(2-Chloroethyl)-1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione 92a and 9-(3-Chloropropyl)-5-(heptafluoropropyl)-1,3-dimethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione 92b. General procedure.

A starting material (6-hydroxy-8,10-dimethyl-6-(trifluoromethyl)-1,2-dihydro-6*H*-pyrimido-[4,5-*b*]pyrrolo[3,2,1-*ij*]quinoline-7,9(8*H*,10*H*)-dione **91a** or 7-(heptafluoropropyl)-7-hydroxy-9,11-dimethyl-2,3-dihydro-1*H*,7*H*-pyrido[3,2,1-*ij*]pyrimido[4,5-*b*]quinoline-8,10(9*H*,11*H*)-dione **91b**) was dissolved in chloroform and then refluxed with thionyl chloride (2 eq) for 3 hours till the solid phase disappeared. Afterwards the solvent was evaporated and the crude product was purified via short-part column chromatography (silica gel / $CHCl_3$), followed by recrystallization from methanol.

9-(2-Chloroethyl)-1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (92a)



The product was prepared following the general procedure, starting from 0.4 g of **91a**, 0.269 g of thionyl chloride and 8 mL of chloroform.

Yield 100%, yellow solid, mp 151-153 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.52 (s, 3H, CH_3-3), 3.67 (t, 2H, ^3J = 7.55 Hz, Ar-CH_2-), 3.83 (s, 3H, CH_3-1), 3.94 (t, 2H, ^3J = 7.55 Hz, CH_2Cl), 7.55 (dd, 1H, $^3J_1$ = 8.97 Hz, $^3J_2$ = 6.99 Hz, H-7), 7.78 (d, 1H, ^3J = 6.99 Hz, H-8), 8.23-8.30 (dm, 1H, ^3J = 8.97 Hz, H-6).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 29.5 (CH_3-3), 30.7 (CH_3-1), 36.1 (Ar-CH_2-), 44.2 (CH_2Cl), 110.4 (C-4a), 122.1, 123.2 (q, $^1J_{(C-F)}$ = 278.3 Hz, CF_3), 125.4 (q, $^4J_{(C-F)}$ = 6.0 Hz, CH-6), 126.9 (CH_{Ar}), 134.4 (CH_{Ar}), 136.1, 139.3 (q, $^2J_{(C-F)}$ = 33.5 Hz, C-5), 147.6, 148.6, 151.2 (CO-2), 159.3 (CO-4).

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –52.4 (s, CF_3).

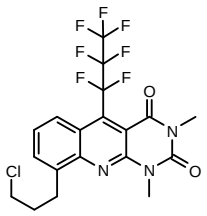
MS (GC, 70 eV): *m/z* (%) = 371 ($[M]^+$, ^{35}Cl, 7.9), 337 ($[M+H–Cl]^+$, 20), 336 ($[M–Cl]^+$, 100), 279 (29).

HRMS (ESI): Calcd. for $C_{16}H_{13}F_3N_3O_2$ $[M-Cl]^+$: 336.09544, found: 336.09572.

Anal. Calcd for $C_{16}H_{13}ClF_3N_3O_2$: C, 51.69; H, 3.52; N, 11.30. Found: C, 47.85; H, 3.52; N, 10.05.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2953 (w), 1718 (m), 1669 (s), 1607 (w), 1574 (s), 1494 (w), 1479 (m), 1464 (m), 1467 (m), 1445 (m), 1421 (m), 1391 (m), 1375 (m), 1352 (m), 1327 (m), 1290 (m), 1277 (m), 1224 (s), 1195 (m), 1158 (s), 1134 (s), 1116 (s), 1079 (m), 1032 (m), 977 (m), 928 (w), 875 (m), 845 (w), 828 (w), 794 (m), 780 (m), 770 (s), 746 (s), 723 (m), 711 (m), 700 (s), 682 (m), 605 (w), 579 (m), 564 (m), 551 (m), 541 (m).

9-(3-Chloropropyl)-5-(heptafluoropropyl)-1,3-dimethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (92b)



The product was prepared following the general procedure, starting from 1.2 g of **91a**, 0.611 g of thionyl chloride and 24 mL of chloroform.

Yield 1.121 g (90%), yellow solid, mp 113-114 °C.

^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 2.19-2.34 (m, 2H, CH_2), 3.40 (t, 2H, ^3J = 7.41 Hz, Ar-CH_2-), 3.51 (s, 3H, CH_3-3), 3.60 (t, 2H, ^3J = 6.31 Hz, CH_2Cl), 3.85 (s, 3H, CH_3-1), 7.52 (dd, 1H, $^3J_1$ = 8.99 Hz, $^3J_2$ = 6.94 Hz, H-7), 7.76 (d, 1H, ^3J = 6.94 Hz, H-8), 8.22 (d, 1H, ^3J = 8.99 Hz, H-5).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 29.7 (CH_3-3), 30.0 (CH_2), 30.9 (CH_3-1), 33.1 (CH_2), 45.0 (CH_2), 111.5 (C-4a), 123.1 (C-5a), 125.5 (m, CH-6), 127.1 (CH), 133.4 (CH), 139.4, 140.4 (t, $^2J_{(C-F)}$ = 24.0 Hz, C-5), 147.7, 148.7, 151.1 (CO-2), 159.1 (CO-4).

^{19}F NMR (235.33 MHz, $CDCl_3$): δ = –116.5 (s, CF_2), –90.4 (br s, CF_2), –80.0 (t, *J* = 9.54 Hz, CF_3).

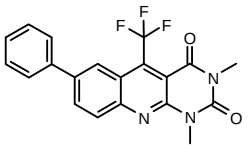
MS (GC, 70 eV): *m/z* (%) = 485 ($[M]^+$, ^{35}Cl, 15), 451 (21), 450 (100), 436 (36), 423 (28), 393 (16), 311 (10).

HRMS (ESI): Calcd. for $C_{19}H_{16}ClF_7N_3O_2$ $[M+H, ^{35}Cl]^+$: 486.08138, found: 486.08130.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958 (w), 2929 (w), 1722 (s), 1678 (s), 1612 (w), 1568 (s), 1504 (m), 1479 (m), 1462 (m), 1423 (s), 1392 (m), 1371 (m), 1344 (m), 1319 (m), 1311 (m), 1288 (m), 1269 (m), 1255 (m), 1227 (s), 1211 (s), 1188 (s), 1171 (s), 1132 (s), 1113 (s), 1078 (s), 1047 (m), 1020 (m), 980 (m), 949 (m), 910 (s), 878 (m), 825 (m), 798 (m), 785 (s), 777 (s), 760 (s), 743 (s), 731 (s), 721 (s), 700 (s), 692 (s), 623 (s), 617 (s), 590 (m), 565 (m), 550 (s), 536 (m).

4.2.9 Suzuki–Miyaura cross-coupling with 7-bromo-1,3-dimethyl-5-(trifluoromethyl)-5-deazaalloxazine

1,3-Dimethyl-7-phenyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (96)



A sealed ACE pressure tube was charged with 0.05 g of 7-bromo-1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione **88p** (0.13 mmol, 1 eq), 0.019 g of phenylboronic acid (0.15 mmol, 1.2 eq), 0.053 g of K_2CO_3 (0.039 mmol, 3 eq), 0.003 g of $Pd(PPh_3)_4$ (0.0026 mmol, 0.02 eq), 2.5 mL of dioxane and 0.5 mL of water. The reaction mixture was stirred under argon at 100 °C for half an hour. After cooling to r.t. formed precipitate was filtered off by suction, washed twice with methanol and dried in high vacuum to give the pure product.

Yield 0.047 g (95%), green solid, mp 230 °C.

^{1}H NMR (300.13 MHz, 12% TFA-*d* in $CDCl_3$): δ = 3.58 (s, 3H, CH_3-3), 3.94 (s, 3H, CH_3-1), 7.44-7.59 (m, 3H, CH_{Ph}), 7.68-7.74 (m, 2H, CH_{Ph}), 8.23 (s, 2H, H-8, H-9), 8.53 (s, 1H, H-6).

^{13}C NMR (62.90 MHz, 12% TFA-*d* in $CDCl_3$): δ = 30.1 (CH_3-3), 31.3 (CH_3-1), 110.3 (C-4a), 122.6, 122.7 (q, $^1J_{(C\text{-}F)}$ = 278.4 Hz, CF_3), 123.8 (q, $^4J_{(C\text{-}F)}$ = 6.0 Hz, CH-6), 128.1 (CH_{Ar}), 129.0 (CH_{Ar}), 129.1 (CH_{Ar}), 129.7 (CH_{Ar}), 134.9 (CH_{Ar}), 139.5, 140.1 (q, $^2J_{(C\text{-}F)}$ = 33.8 Hz, C-5), 141.4, 147.4, 149.2, 152.2 (CO-2), 160.3 (CO-4).

^{19}F NMR (282.38 MHz, 12% TFA-*d* in $CDCl_3$): δ = –52.8 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 386 ($[M+H]^+$, 23), 385 ($[M]^+$, 100), 316 (10), 287 (16), 274 (14), 273 (78), 259 (13).

HRMS (EI): Calcd. for $C_{20}H_{14}F_3N_3O_2$ $[M]^+$: 385.10326, found: 385.10314.

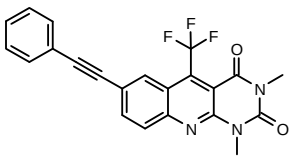
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3379 (w), 3054 (w), 2958 (w), 1720 (m), 1668 (s), 1651 (m), 1621 (w), 1574 (s), 1516 (w), 1469 (s), 1433 (s), 1328 (m), 1293 (m), 1281 (m), 1212 (m), 1165 (s), 1152 (s), 1131 (s), 1074 (m), 1027 (w), 994 (m), 942 (w), 918 (w), 894 (w), 883 (w), 860 (w), 843 (m), 807 (m), 765 (m), 756 (s), 744 (s), 706 (m), 694 (s), 674 (m), 639 (m), 617 (w), 607 (w), 594 (w), 557 (m), 540 (w).

4.2.10 Sonogashira cross-coupling with 7-bromo-1,3-dimethyl-5-(trifluoromethyl)-5-deazaalloxazine

Sonogashira coupling with 7-bromo-1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione 88p. General procedure.

Into a flask were placed 7-bromo-1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione **88p** (1 eq), terminal acetylene (1.2 eq), $Pd(PPh_3)_2Cl_2$ (0.02 eq), CuI (0.01 eq), diisopropylamine (10 eq) and THF (1 mL per 0.05 g of starting aryl bromide). The mixture was stirred for 3 hours and then allowed to stay at r.t. for two days. After that the reaction mixture was diluted with water, the formed precipitate was filtered off by suction, washed with methanol and heptane and dried in high vacuum.

1,3-Dimethyl-7-(phenylethynyl)-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (97a)



The product was prepared following the general procedure, starting from 0.05 g of 8-bromo derivative **88p**, 0.016 g of phenylacetylene, 0.9 mg of $Pd(PPh_3)_2Cl_2$, 0.12 mg of CuI, 0.13 g of diisopropylamine and 1 mL of THF.

Yield 0.047 g (89%), yellow solid, mp 269 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.51 (s, 3H, CH_3-3), 3.82 (s, 3H, CH_3-1), 7.35-7.44 (m, 3H, CH_{Ph}), 7.55-7.62 (m, 2H, CH_{Ph}), 7.90 (d, 1H, ^3J = 8.88 Hz, H-8), 7.99 (d, 1H, ^3J = 8.88 Hz, H-9), 8.46 (s, 1H, H-6).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 29.6 (CH_3-3), 30.8 (CH_3-1), 88.8 (C-sp), 92.4 (C-sp), 111.0 (C-4a), 121.6, 122.7, 122.8, 123.2 (q, $^1J_{(C-F)}$ = 278.4 Hz, CF_3), 128.8 (CH_{Ar}), 129.19 (q, $^4J_{(C-F)}$ = 6.1 Hz, CH-6), 129.26 (CH_{Ph}), 129.29 (CH_{Ph}), 132.1 (CH_{Ph}), 136.0 (CH_{Ar}), 138.2 (q, $^2J_{(C-F)}$ = 33.6 Hz, C-5), 148.7, 149.7, 151.1 (CO-2), 159.2 (CO-4).

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –52.6 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 410 ($[M+H]^+$, 25), 409 ($[M]^+$, 100), 311 (15), 298 (11), 297 (54), 283 (16).

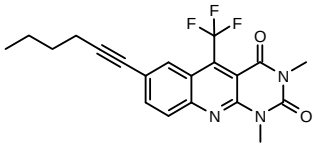
HRMS (ESI): Calcd. for $C_{22}H_{15}F_3N_3O_2$ $[M+H]^+$: 410.11109, found: 410.11143.

Anal. Calcd for $C_{22}H_{14}F_3N_3O_2$: C, 50.22; H, 3.58; N, 11.71. Found: C, 49.43; H, 3.21; N, 10.13.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3375 (w), 3061 (w), 2952 (w), 2213 (w), 1714 (s), 1674 (s), 1652 (m), 1616 (w), 1574 (s), 1558 (m), 1512 (w), 1505 (w), 1490 (w), 1470 (m), 1440 (s), 1418 (m), 1405

(m), 1386 (m), 1373 (s), 1324 (m), 1303 (m), 1290 (m), 1275 (m), 1207 (m), 1162 (s), 1143 (s), 1128 (s), 1070 (m), 1027 (w), 996 (m), 985 (m), 919 (w), 884 (w), 864 (w), 835 (s), 807 (w), 783 (w), 755 (m), 744 (s), 704 (m), 689 (s), 674 (w), 662 (m), 641 (w), 578 (m), 538 (w), 529 (m).

7-Hex-1-yn-1-yl-1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (97b)



The product was prepared following the general procedure, starting from 0.25 g of 8-bromo derivative **88p**, 0.063 g of phenylacetylene, 4.52 mg of $Pd(PPh_3)_2Cl_2$, 0.61 mg of CuI, 0.652 g of diisopropylamine and 5 mL of THF.

Yield 0.234 (89%), yellow solid, mp 180 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.97 (t, 3H, ^3J = 7.27 Hz, Bu), 1.43-1.70 (m, 4H, Bu), 2.47 (t, 2H, Bu, ^3J = 7.08 Hz), 3.49 (s, 3H, CH_3-3), 3.78 (s, 3H, CH_3-1), 7.74 (d, 1H, ^3J = 8.87 Hz, H-8), 7.87 (d, 1H, ^3J = 8.87 Hz, H-9), 8.28 (s, 1H, H-6).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 13.9 ($CH_{3(Bu)}$), 19.5 ($CH_{2(Bu)}$), 22.4 ($CH_{2(Bu)}$), 29.5 (CH_3-3), 30.7 (CH_3-1), 30.9 ($CH_{2(Bu)}$), 80.1 (C-sp), 94.0 (C-sp), 110.8 (C-4a), 121.5, 123.1 (q, $^1J_{(C-F)}$ = 278.5 Hz, CF_3), 123.4, 128.7 (q, $^4J_{(C-F)}$ = 6.1 Hz, CH-6), 128.9 (CH_{Ar}), 136.3 (CH_{Ar}), 137.8 (q, $^2J_{(C-F)}$ = 33.5 Hz, C-5), 148.3, 149.2, 151.0 (CO-2), 159.2 (CO-4).

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –52.7 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 390 ($[M+H]^+$, 21), 389 ($[M]^+$, 100), 388 (12), 360 (23), 346 (30), 317 (14), 289 (21), 277 (27), 261 (10), 234 (23), 220 (15).

HRMS (ESI): Calcd. for $C_{20}H_{19}F_3N_3O_2$ $[M+H]^+$: 390.14239, found: 390.14253.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3379 (w), 3089 (w), 2960 (w), 2934 (w), 2862 (w), 2228 (w), 1726 (m), 1671 (s), 1614 (w), 1581 (s), 1468 (s), 1451 (s), 1411 (m), 1386 (m), 1370 (s), 1322 (w), 1287 (m), 1240 (w), 1205 (m), 1173 (s), 1159 (s), 1145 (s), 1132 (s), 1108 (s), 1071 (m), 1019 (w), 989 (m), 956 (w), 933 (w), 887 (m), 858 (w), 854 (s), 807 (m), 775 (w), 761 (w), 748 (s), 728 (w), 704 (s), 689 (w), 672 (m), 659 (w), 641 (m), 589 (w), 575 (m), 538 (w).

4.2.11 Reduction of 5-(trifluoromethyl)-5-deazaalloxazines

Reduction of 5-polyfluoroalkyl-pyrimido[4,5-b]quinoline-2,4-diones 88. General procedure.

Method A

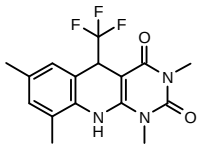
Into a 50-mL flask were placed 5-polyfluoroalkyl-pyrimido[4,5-b]quinoline-2,4-dione **88** (1.48 mmol, 1 eq), sodium cyanoborohydride (5.93 mmol, 4 eq) and THF (10 mL). Then the

mixture was cooled to 0 °C and acetic acid (11.9 mmol, 8 eq) was added. Afterwards the reaction mixture was allowed to warm to r.t.. Three days later the reaction was monitored by TLC and stirred 8 hours at 45 °C, if the starting material still was detected. After that mixture was diluted with water. Precipitate was filtered off to give a pure product.

Method B

A sealed ACE pressure tube was charged with 0.1 g of 1,3,7,9-tetramethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione **88c** (0.30 mmol, 1 eq), 0.451 g of diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (1.78 mmol, 6 eq), 0.0056 g of TsOH (0.03 mmol, 0.1 eq) and 3 mL of xylene. The reaction mixture was stirred under argon at 155 °C for 5 hours. Then the solution was cooled to r.t. and formed precipitate was filtered off, washed twice with xylene and dried in high vacuum to give the desired product.

1,3,7,9-Tetramethyl-5-(trifluoromethyl)-5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (98a)



Yield 99% (**Method A**; starting from 0.5 g of **88c**, 0.373 g of sodium cyanoborohydride, 0.712 g of acetic acid and 10 mL of THF) and 41% (**Method B**), white solid, mp 263-265 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.32 (s, 6H, CH_3-7, CH_3-9), 3.40 (s, 3H, CH_3), 3.60 (s, 3H, CH_3), 4.88 (q, 1H, $^{3}J_{(H-F)}$ = 8.22 Hz, CH-5), 6.40 (br s, 1H, NH), 7.01 (s, 1H, CH_{Ar}), 7.04 (s, 1H, CH_{Ar}).

^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 17.9 (Ar-CH_3), 21.1 (Ar-CH_3), 28.7 (N-CH_3), 30.4 (N-CH_3), 40.2 (q, $^{2}J_{(C-F)}$ = 29.2 Hz, CH-5), 79.6, 117.5, 126.4, 129.0 (CH), 127.4 (q, $^{1}J_{(C-F)}$ = 284.3 Hz, CF_3), 132.3 (CH), 133.6, 134.1, 148.7, 151.8, 161.7.

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –73.7 (s, CF_3).

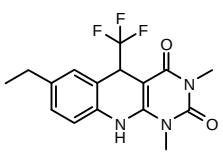
MS (GC, 70 eV): *m/z* (%) = 339 ($[M]^+$, 5.0), 271 (17), 270 ($[M–CF_3]^+$, 100), 213 (11).

HRMS (ESI): Calcd. for $C_{16}H_{17}F_3N_3O_2$ $[M+H]^+$: 340.12674, found: 340.12665.

Anal. Calcd for $C_{16}H_{16}F_3N_3O_2$: C, 56.64; H, 4.75; N, 12.38. Found: C, 56.72; H, 4.73; N, 12.10.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3457 (m), 3322 (w), 2914 (w), 1693 (m), 1633 (s), 1611 (m), 1520 (s), 1489 (m), 1475 (s), 1445 (m), 1418 (w), 1382 (w), 1354 (w), 1336 (m), 1326 (m), 1275 (w), 1240 (s), 1218 (m), 1180 (w), 1146 (s), 1107 (s), 1057 (w), 1042 (w), 991 (w), 968 (w), 951 (w), 936 (w), 900 (w), 870 (w), 844 (m), 820 (w), 777 (w), 768 (m), 751 (s), 710 (w), 696 (w), 681 (w), 667 (m), 580 (w), 568 (w).

7-Ethyl-1,3-dimethyl-5-(trifluoromethyl)-5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (98b)



The product was prepared according to the **Method A**, starting from 0.15 g of **88f**, 0.112 g of sodium cyanoborohydride, 0.214 g of acetic acid and 3 mL of THF.

Yield 0.144 g (95%), white solid, mp 241 °C.

^{1}H NMR (250.13 MHz, DMSO-d_6): δ = 1.20 (t, 3H, ^{3}J = 7.57 Hz, Et), 2.61 (q, 2H, ^{3}J = 7.57 Hz, Et), 3.24 (s, 3H, CH_3), 3.51 (s, 3H, CH_3), 4.91 (q, 1H, $^{3}J_{(H-F)}$ = 8.51 Hz, CH-5), 7.23 (dd, 1H, ^{3}J = 8.20 Hz, ^{4}J = 1.82 Hz, H-8), 7.28 (s, 1H, H-6), 7.35 (d, 1H, ^{3}J = 8.20 Hz, H-9), 9.57 (br s, 1H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 16.5 (CH_3), 28.4 (CH_2), 28.7 (CH_3), 30.9 (CH_3), 40.0 (q, $^{2}J_{(C-F)}$ = 28.9 Hz, CH-5), 77.3 (C-4a), 115.6, 117.6 (CH_{Ar}), 127.4 (q, $^{1}J_{(C-F)}$ = 284.3 Hz, CF_3), 129.3 (CH_{Ar}), 130.0 (CH_{Ar}), 136.4, 140.0, 148.5, 151.6, 161.6.

^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –72.7 (s, CF_3).

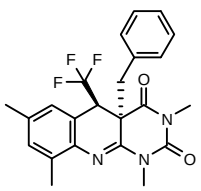
MS (GC, 70 eV): *m/z* (%) = 339 ($[M]^+$, 3.7), 271 (18), 270 ($[M–CF_3]^+$, 100), 213 (13).

HRMS (EI): Calcd. for $C_{16}H_{16}F_3N_3O_2$ $[M]^+$: 339.11891, found: 339.11894.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3275 (m), 3206 (w), 3139 (w), 2973 (w), 2893 (w), 1701 (s), 1633 (m), 1607 (s), 1557 (s), 1497 (s), 1476 (s), 1460 (m), 1429 (m), 1394 (w), 1368 (w), 1328 (m), 1312 (m), 1292 (w), 1282 (w), 1258 (m), 1237 (s), 1217 (m), 1189 (m), 1157 (s), 1148 (m), 1141 (m), 1121 (m), 1113 (s), 1049 (w), 981 (m), 952 (w), 929 (w), 895 (w), 846 (m), 833 (m), 813 (w), 803n (w), 773 (m), 750 (m), 727 (w), 713 (m), 676 (m), 667 (m), 642 (m), 577 (w), 555 (w), 545 (w).

4.2.12 Alkylation of 1,3,7,9-tetramethyl-5-(trifluoromethyl)-5,10-dihydro-5-deazaalloxazine

(4a*R*,5*R*)- and (4a*S*,5*S*)-4a-Benzyl-1,3,7,9-tetramethyl-5-(trifluoromethyl)-4a,5-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (100), racemic mixture of enantiomers.



A mixture of 1,3,7,9-tetramethyl-5-(trifluoromethyl)-5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione **98a** (0.1 g, 0.29 mmol, 1 eq), benzyl bromide (0.055 g, 0.32 mmol, 1.1 eq), K_2CO_3 (0.081 g, 0.59 mmol, 2 eq) and DMF (2 mL) was stirred overnight under argon. The next day the reaction mixture was diluted with water and heptane. The formed precipitate was filtered off by suction, washed twice with water and heptanes and dried in high vacuum to give the pure product.

Yield 104 g (82%), white solid, mp 159-161 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.39 (s, 3H, Ar-CH_3), 2.51 (s, 3H, Ar-CH_3), 3.00 (d, 1H, ^2J = 12.56 Hz, CH_2-a), 3.09 (d, 1H, ^2J = 12.56 Hz, CH_2-b), 3.15 (s, 3H, N-CH_3), 3.28 (s, 3H, N-CH_3), 4.00 (q, 1H, $^3J_{(H-F)}$ = 8.25 Hz, H-5), 6.82-6.91 (m, 2H, $CH_{o\text{-Ph}}$), 6.99 (s, 1H, H-6), 7.17 (s, 1H, H-8), 7.20-7.32 (m, 3H, CH_{Ph}).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 17.9 (CH_3), 21.4 (CH_3), 28.4 (CH_3), 29.8 (CH_3), 42.9 (CH_2), 47.8 (C-4a), 48.8 (q, $^2J_{(C-F)}$ = 26.8 Hz, CH), 118.7, 125.4 (q, $^1J_{(C-F)}$ = 283.4 Hz, CF_3), 128.7 (CH), 128.7 (CH), 128.7 (CH), 129.4 (CH), 133.0 (CH), 133.5, 134.4, 136.0, 139.2, 150.2, 151.6, 168.8.

^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –65.5 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 430 ($[M+H]^+$, 14), 429 ($[M]^+$, 51), 91 (100).

HRMS (EI): Calcd. for $C_{23}H_{22}O_2N_3F_3$ $[M]^+$: 429.16586, found: 429.16570.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2933 (w), 2920 (w), 1726 (m), 1682 (s), 1622 (s), 1597 (s), 1471 (m), 1443 (s), 1427 (s), 1381 (s), 1344 (m), 1325 (s), 1315 (s), 1294 (s), 1273 (s), 1255 (s), 1238 (s), 1215 (m), 1196 (m), 1151 (s), 1119 (s), 1068 (m), 1051 (m), 1032 (m), 995 (m), 982 (m), 959 (m), 939 (m), 916 (m), 893 (m), 870 (w), 858 (m), 851 (m), 831 (m), 804 (m), 791 (m), 770 (m), 764 (m), 743 (s), 702 (s), 671 (m), 648 (m), 582 (m), 571 (m), 548 (m).

4.2.13 Nucleophilic additions to position 5 of 5-polyfluoroalkyl-5-deazaalloxazines

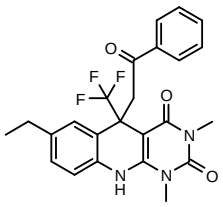
4.2.13.1 Addition of acetophenone

Addition of acetophenone to 1,3-dialkyl-5-polyfluoroalkyl-pyrimido[4,5-b]quinoline-2,4-diones. General procedure.

Into a flask were placed 1,3-dialkyl-5-polyfluoroalkyl-pyrimido[4,5-b]quinoline-2,4-dione (1 eq), acetophenone (1.5 eq), dry THF (20 mL per 1 g of starting material) and sodium hydride (60% in mineral oil, 2 eq). The reaction mixture was stirred for half an hour at r.t. and then allowed to stay overnight. Afterwards 2.5 eq of acetic acid was added and the mixture was diluted with water. The formed precipitate was filtered off by suction, washed with heptane and recrystallized from methanol/water giving the pure product.

7-Ethyl-1,3-dimethyl-5-(2-oxo-2-phenylethyl)-5-(trifluoromethyl)-5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (101a)

The product was prepared according to the general method, starting from 0.2 g of **88f**, 0.107 g of acetophenone, 0.047 g of sodium hydride (60% in mineral oil) and 4 mL of THF.



Yield 0.219 g (81%), white solid, mp 233 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.09 (t, 3H, ^{3}J = 7.55 Hz, Et), 2.53 (q, 2H, ^{3}J = 7.55 Hz, Et), 3.09 (s, 3H, CH_3), 3.59 (s, 3H, CH_3), 4.33 (d, 1H, ^{2}J = 18.70 Hz, CH_2CO-a), 5.50 (d, 1H, ^{2}J = 18.70 Hz, CH_2CO-b), 7.18 (d, 1H, ^{3}J = 8.12 Hz, H-8), 7.36 (d, 1H, ^{3}J = 8.12 Hz, H-9), 7.41 (s, 1H, H-6), 7.50-7.60 (m, 2H, $CH_{m\text{-Ph}}$), 7.62-7.70 (m, 1H, $CH_{p\text{-Ph}}$), 7.95-8.04 (m, 2H, $CH_{o\text{-Ph}}$) 9.38 (br s, 1H, NH).

^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 16.6 (CH_3), 28.5 (CH_2), 28.6 (CH_3), 31.2 (CH_3), 38.5 (CH_2CO), 47.5 (q, $^{2}J_{(C\text{-}F)}$ = 25.7 Hz, C-5), 79.9 (C-4a), 117.6 (CH_{Ar}), 119.9, 127.0 (CH_{Ar}), 128.6 (q, $^{1}J_{(C\text{-}F)}$ = 287.3 Hz, CF_3), 128.7 (CH_{Ar}), 128.9 (CH_{Ar}), 129.5 (CH_{Ar}), 133.9 (CH_{Ar}), 135.0, 137.6, 139.6, 148.1, 151.1, 161.6, 195.8.

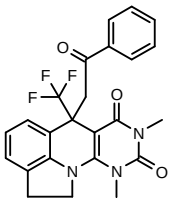
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –75.8 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 457 ($[M]^+$, 1.7), 338 ($[M–CF_3]^+$, 42), 337 (28), 225 (35), 105 (100), 77 (33).

HRMS (ESI): Calcd. for $C_{24}H_{23}F_3N_3O_3$ $[M+H]^+$: 458.16860, found: 458.16921.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3375 (w), 3340 (m), 2959 (w), 2873 (w), 1707 (w), 1694 (m), 1681 (s), 1634 (s), 1615 (m), 1598 (s), 1531 (s), 1504 (s), 1477 (m), 1447 (m), 1404 (m), 1387 (m), 1367 (m), 1319 (w), 1261 (m), 1234 (s), 1218 (s), 1184 (m), 1157 (s), 1144 (s), 1094 (w), 1056 (w), 1043 (w), 1030 (w), 1003 (m), 963 (w), 948 (w), 928 (w), 896 (w), 879 (w), 828 (m), 795 (w), 772 (m), 752 (s), 730 (w), 706 (w), 687 (m), 675 (m), 643 (w), 628 (w), 599 (w), 576 (m), 551 (m), 534 (m).

8,10-Dimethyl-6-(2-oxo-2-phenylethyl)-6-(trifluoromethyl)-1,2-dihydro-6*H*-pyrimido[4,5-*b*]pyrrolo[3,2,1-*ij*]quinoline-7,9(8*H*,10*H*)-dione (102a)



The product was prepared according to the general method, starting from 0.15 g of **92b**, 0.073 g of acetophenone, 0.032 g of sodium hydride (60% in mineral oil) and 3 mL of THF.

Yield 0.171 g (93%), white solid, mp 304-305 °C.

^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 3.18 (s, 3H, CH_3), 3.20-3.44 (m, 2H, CH_2-2), 3.64 (s, 3H, CH_3), 3.85 (d, 1H, ^{2}J = 18.36 Hz, CH_2CO-a), 4.00-4.14 (m, 1H, CH_2-1a), 4.54-4.65 (m, 1H, CH_2-1b), 5.63 (d, 1H, ^{2}J = 18.36 Hz, CH_2CO-b), 7.00 (dd, 1H, $^{3}J_1$ = 7.18 Hz, $^{3}J_2$ = 8.12 Hz, H-4), 7.11-7.19 (m, 2H, CH_{Ar}), 7.39-7.49 (m, 2H, CH_{Ar}), 7.54 (t, 1H, ^{3}J = 7.25 Hz, $CH_{p\text{-Ph}}$), 7.91-7.98 (m, 2H, CH_{Ar}).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 28.5 (CH_3), 28.9 (CH_2), 38.4 (CH_2), 38.6 (CH_3), 47.8 (q, $^{2}J_{(C\text{-}F)}$ = 26.7 Hz), 53.4 (CH_2), 84.7 (C-6a), 117.6, 124.4 (CH), 124.8 (CH), 125.0 (CH), 127.5 (q, $^{1}J_{(C\text{-}F)}$ = 286.6 Hz, CF_3), 128.2 (CH), 128.8, 128.9 (CH), 133.3, 137.2, 141.8, 152.9, 152.9,

162.0, 195.7.

^{19}F NMR (235.33 MHz, $CDCl_3$): δ = –76.8 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 455 ([M]$^+$, 5.8), 387 (26), 386 (100), 336 (15), 105 (38), 77 (14).

HRMS (ESI): Calcd. for $C_{24}H_{21}F_3N_3O_3$ [M+H]$^+$: 456.15295, found: 456.15399.

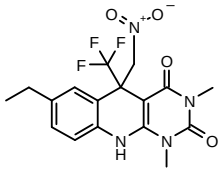
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3043 (w), 3016 (w), 2929 (w), 1691 (s), 1633 (s), 1626 (s), 1539 (s), 1498 (s), 1464 (s), 1446 (s), 1435 (s), 1408 (s), 1375 (s), 1360 (s), 1342 (m), 1302 (m), 1242 (s), 1227 (s), 1201 (m), 1186 (m), 1176 (m), 1155 (s), 1120 (s), 1078 (m), 1057 (m), 1041 (m), 1028 (m), 1001 (m), 976 (m), 964 (m), 939 (m), 912 (m), 897 (w), 860 (w), 847 (w), 779 (s), 770 (m), 756 (s), 748 (s), 737 (s), 714 (m), 694 (s), 658 (m), 617 (s), 581 (m), 569 (m), 528 (m).

4.2.13.2 Addition of nitromethane

Addition of nitromethane to 1,3-dialkyl-5-polyfluoroalkyl-pyrimido[4,5-*b*]quinoline-2,4-diones. General procedure.

Into a flask were placed 1,3-dialkyl-5-polyfluoroalkyl-pyrimido[4,5-b]quinoline-2,4-dione (1 eq), nitromethane (10 eq), dry THF (20 mL per 1 g of starting material), dry methanol (20 mL per 1 g of starting material) and sodium methylate (2 eq). The reaction mixture was allowed to stay at r.t. overnight. Afterwards 2.5 eq of acetic acid was added and the mixture was diluted with water. The formed precipitate was filtered off by suction and recrystallized from methanol/water giving the pure product.

7-Ethyl-1,3-dimethyl-5-(nitromethyl)-5-(trifluoromethyl)-5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (101b)



The product was prepared according to the general method, starting from 0.45 g of **88f**, 0.814 g of nitromethane, 0.144 g of sodium methylate, 9 mL of methanol and 9 mL of THF.

Yield 0.457 g (86%), white solid, mp 351-353 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.19 (t, 3H, ^3J = 7.55 Hz, Et), 2.62 (q, 2H, ^3J = 7.55 Hz, Et), 3.22 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 5.93 (d, 1H, ^2J = 14.78 Hz, CH_2NO_2-a), 6.90 (d, 1H, ^2J = 14.78 Hz, CH_2NO_2-b), 7.27 (d, 1H, ^3J = 8.31 Hz, H-8), 7.41 (d, 1H, ^3J = 8.31 Hz, H-9), 7.62 (s, 1H, H-6), 9.54 (br s, 1H, NH).

^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 16.5 (CH_3), 28.6 (CH_2), 28.7 (CH_3), 31.4 (CH_3), 49.8 (q, $^2J_{(C\text{-}F)}$ = 26.6 Hz, C-5), 72.8 (CH_2NO_2), 77.4 (C-4a), 116.3, 118.2 (CH_{Ar}), 127.0 (q, $^1J_{(C\text{-}F)}$ = 288.9 Hz, CF_3), 127.3 (CH_{Ar}), 130.1 (CH_{Ar}), 134.9, 140.1, 148.6, 151.0, 162.0.

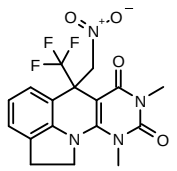
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –73.8 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 398 ($[M]^+$, 8.6), 338 (22), 337 ($[M–CH_3NO_2]^+$, 77), 329 (60), 322 (18), 284 (30), 283 (100), 282 (37), 268 (15), 265 (12), 225 (77), 224 (11), 210 (11).

HRMS (ESI): Calcd. for $C_{17}H_{18}F_3N_4O_4$ $[M+H]^+$: 399.12747, found: 399.12780.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3362 (m), 3034 (w), 2967 (w), 2879 (w), 1688 (m), 1614 (s), 1552 (s), 1530 (s), 1511 (s), 1479 (s), 1435 (s), 1438 (m), 1392 (m), 1375 (s), 1338 (w), 1318 (m), 1302 (w), 1289 (w), 1264 (m), 1229 (s), 1208 (m), 1183 (s), 1170 (s), 1163 (s), 1147 (s), 1103 (m), 1062 (w), 1017 (m), 986 (w), 969 (m), 949 (w), 900 (w), 831 (s), 787 (w), 773 (m), 752 (m), 738 (w), 692 (w), 668 (s), 592 (m), 568 (m), 538 (w).

8,10-Dimethyl-6-(nitromethyl)-6-(trifluoromethyl)-1,2-dihydro-6*H*-pyrimido[4,5-*b*]pyrrolo[3,2,1-*ij*]quinoline-7,9(8*H*,10*H*)-dione (102b)



The product was prepared according to the general method, starting from 0.05 g of **92a**, 0.082 g of nitromethane, 0.015 g of sodium methylate, 1 mL of methanol and 1 mL of THF.

Yield 0.049 g (92%), white solid, mp 285-286 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.19-3.45 (m, 2H, CH_2-2), 3.32 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 3.95-4.70 (m, 1H, CH_2-1a), 4.55-4.65 (m, 1H, CH_2-1b), 5.22 (d, 1H, ^2J = 14.17 Hz, CH_2NO_2-a), 7.11 (dd, 1H, $^3J_1$ = 7.36 Hz, $^3J_2$ = 8.12 Hz, H-4), 7.16 (d, 1H, ^2J = 14.17 Hz, CH_2NO_2-b), 7.22 (d, 1H, ^3J = 7.36 Hz, H-3), 7.29 (d, 1H, ^3J = 8.12 Hz, H-5).

^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 28.7 (CH_3), 28.8 (CH_2), 38.6 (CH_3), 50.2 (q, $^2J_{(C\text{-}F)}$ = 27.8 Hz), 53.6 (CH_2), 72.1 (CH_2), 82.5 (C-6a), 113.6, 124.8 (CH), 125.5 (CH), 125.9 (q, $^1J_{(C\text{-}F)}$ = 288.0 Hz, CF_3), 126.0 (CH), 129.5, 141.7, 152.6, 153.0, 162.3.

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –74.4 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 396 ($[M]^+$, 8.2), 327 (33), 282 (18), 281 (100),

HRMS (ESI): Calcd. for $C_{17}H_{16}F_3N_4O_4$ $[M+H]^+$: 397.11182, found: 397.11096.

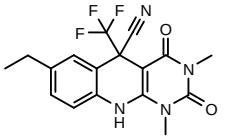
IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3034 (w), 2974 (w), 1697 (s), 1626 (s), 1545 (s), 1497 (s), 1471 (s), 1446 (s), 1417 (s), 1404 (s), 1381 (s), 1371 (s), 1304 (m), 1267 (m), 1255 (s), 1227 (s), 1184 (s), 1159 (s), 1134 (s), 1124 (s), 1078 (m), 1065 (m), 1047 (m), 1030 (m), 1011 (s), 968 (s), 943 (m), 933 (m), 864 (m), 849 (m), 779 (s), 768 (s), 748 (s), 731 (s), 714 (m), 677 (s), 654 (m), 606 (m), 581 (m), 571 (m), 546 (m), 532 (m).

4.2.13.3 Addition of hydrogen cyanide

Addition of hydrogen cyanide to 1,3-dialkyl-5-polyfluoroalkyl-pyrimido[4,5-b]quinoline-2,4-diones. General procedure.

Initial 1,3-dialkyl-5-polyfluoroalkyl-pyrimido[4,5-b]quinoline-2,4-dione (1 eq) was suspended in DMSO. Then KCN (2 eq) was added. Reaction mixture was stirred overnight and afterwards acetic acid (2 eq) was carefully added under fume hood. Then mixture was diluted with water. The formed precipitate was filtered off by suction and recrystallized from methanol/water giving the pure product.

7-Ethyl-1,3-dimethyl-2,4-dioxo-5-(trifluoromethyl)-1,2,3,4,5,10-hexahydropyrimido[4,5-*b*]quinoline-5-carbonitrile (101c)



The product was prepared according to the general method, starting from 0.2 g of **88f**, 0.077 g of KCN and 4 mL of DMSO.

Yield 0.203 g (94%), white solid, mp 179 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.22 (t, 3H, ^{3}J = 7.56 Hz, Et), 2.70 (q, 2H, ^{3}J = 7.56 Hz, Et), 3.26 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 7.43 (dd, 1H, ^{3}J = 8.39 Hz, ^{4}J = 1.79 Hz, H-8), 7.51 (d, 1H, ^{3}J = 8.39 Hz, H-9), 7.53 (s, 1H, H-6), 9.96 (br s, 1H, NH).

^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 16.4 (CH_3), 28.3 (CH_2), 28.8 (CH_3), 31.4 (CH_3), 46.3 (q, $^{2}J_{(C\text{-}F)}$ = 31.9 Hz, C-5), 74.5 (C-4a), 112.6, 115.9, 118.7 (CH_{Ar}), 124.8 (q, $^{1}J_{(C\text{-}F)}$ = 289.3 Hz, CF_3), 128.4 (CH_{Ar}), 131.7 (CH_{Ar}), 134.6, 141.0, 148.3, 151.0, 160.4.

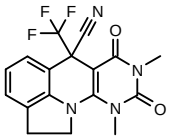
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –75.1 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 364 ($[M]^+$, 1.03), 338 (17), 337 ($[M–HCN]^+$, 97), 322 (27), 309 (11), 296 (10), 295 (53), 280 (11), 268 (19), 265 (23), 239 (10), 238 (16), 237 (11), 226 (12), 225 (100), 224 (13), 210 (17), 196 (11).

HRMS (ESI): Calcd. for $C_{17}H_{16}F_3N_4O_2$ $[M+H]^+$: 365.12199, found: 365.12186.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3526 (w), 3326 (m), 2977 (w), 1688 (m), 1633 (m), 1613 (s), 1601 (m), 1531 (s), 1502 (s), 1472 (s), 1435 (s), 1414 (m), 1392 (w), 1368 (w), 1338 (w), 1300 (w), 1260 (w), 1232 (w), 1218 (m), 1180 (s), 1159 (m), 1145 (m), 1101 (w), 1068 (w), 1035 (m), 1002 (w), 965 (m), 940 (w), 894 (w), 866 (w), 835 (s), 771 (m), 759 (m), 733 (w), 706 (w), 692 (w), 661 (w), 577 (m), 565 (m), 545 (m), 531 (w).

8,10-Dimethyl-7,9-dioxo-6-(trifluoromethyl)-1,2,7,8,9,10-hexahydro-6*H*-pyrimido[4,5-*b*]pyrrolo[3,2,1-*ij*]quinoline-6-carbonitrile (102c)



The product was prepared according to the general method, starting from 0.2 g of **92a**, 0.105 g of KCN and 4 mL of DMSO.

Yield 0.136 g (70%), white solid, mp 242 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.26-3.54 (m, 2H, CH_2-2), 3.34 (s, 1H, CH_3), 3.68 (s, 1H, CH_3), 4.03-4.16 (m, 1H, CH_2-1a), 4.65-4.77 (m, 1H, (m, 1H, CH_2-1b), 7.23 (dd, 1H, $^{3}J_1$ = 7.74 Hz, $^{3}J_2$ = 7.37 Hz, CH-4), 7.32 (d, 1H, ^{3}J = 7.37 Hz, CH_{Ar}), 7.62 (d, 1H, ^{3}J = 7.74 Hz, CH_{Ar}).

^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 28.7 (CH_3), 29.0 (CH_2), 38.0 (CH_3), 46.2 (q, $^{2}J_{(C-F)}$ = 33.0 Hz, C-6), 53.8 (CH_2), 79.5 (C-6a), 110.8, 115.0, 124.0 (q, $^{1}J_{(C-F)}$ = 288.7 Hz, CF_3), 126.3 (CH_{Ar}), 126.8 (CH_{Ar}), 127.3 (CH_{Ar}), 129.5, 140.9, 152.2, 152.2, 160.3.

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –75.8 (s, CF_3).

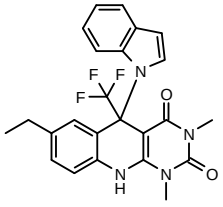
MS (GC, 70 eV): *m/z* (%) = 362 ($[M]^+$, 2.0), 294 (18), 293 ($[M–CF_3]^+$, 100), 236 (23).

HRMS (EI): Calcd. for $C_{17}H_{13}F_3N_4O_2$ $[M]^+$: 362.09851, found: 362,09826.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3071 (w), 2951 (w), 2858 (w), 1716 (m), 1640 (m), 1633 (m), 1545 (m), 1498 (m), 1449 (s), 1435 (s), 1403 (m), 1363 (m), 1342 (w), 1300 (w), 1285 (w), 1266 (w), 1224 (w), 1208 (m), 1185 (s), 1174 (s), 1161 (s), 1107 (m), 1054 (w), 1025 (w), 1001 (w), 987 (m), 964 (m), 939 (m), 867 (w), 826 (w), 796 (s), 768 (s), 746 (s), 712 (m), 679 (w), 666 (w), 611 (w), 571 (w), 539 (w).

4.2.13.4 Addition of indole

7-Ethyl-5-(1*H*-indol-1-yl)-1,3-dimethyl-5-(trifluoromethyl)-5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (101d)



Initial 7-ethyl-1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione **88f** (0.25 g, 0.74 mmol, 1 eq) was added to a mixture of indole (0.13 g, 1.11 mmol, 1,5 eq) and sodium hydride (60% in mineral oil, 0.044g, 1.11 mmol, 1.5 eq) in dry THF (2.5 mL). The reaction mixture was stirred for 5 min at r.t., followed by addition of acetic acid (0.1 g, 1.67 mmol, 2.25 eq) and dilution with water. The formed precipitate was filtered off by suction, washed with water, recrystallized from DMSO containing one drop of acetic acid (just to stabilize the product) and dried in high vacuum at 60 °C (avoid overheating!).

Yield 0.194 g (58%), white solid, mp 212 °C (dec.).

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 0.89 (t, 3H, ^{3}J = 7.56 Hz, Et), 2.33 (q, 2H, ^{3}J = 7.56 Hz, Et), 2.97 (s, 3H, CH_3), 3.65 (s, 3H, CH_3), 6.42 (s, 1H, CH_{Ar}), 6.61 (d, 1H, ^{3}J = 3.21 Hz, CH_{Ar}), 6.69 (d, 1H, ^{3}J = 8.31 Hz, CH_{Ar}), 6.74-6.82 (m, 1H, CH_{Ar}), 6.89-6.98 (m, 1H, CH_{Ar}), 7.28 (d, 1H, ^{3}J = 7.93 Hz, H-8), 7.55 (m, 2H, CH_{Ar}), 7.71 (s, 1H, H-5), 9.92 (br s, 1H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 16.2 (CH_3), 28.2 (CH_2), 28.3 (CH_3), 31.5 (CH_3), 65.3 (q, $^{2}J_{(C-F)}$ = 29.7 Hz), 78.7 (C-4a), 101.9 (CH), 112.9 (CH), 117.7, 117.8 (CH), 120.1 (CH), 121.4 (CH), 121.7 (CH), 126.4 (q, $^{1}J_{(C-F)}$ = 290.5 Hz, CF_3), 127.2 (CH), 129.6, 130.2 (CH), 130.7 (CH), 134.1, 135.7, 139.8, 147.9, 151.2, 159.4.

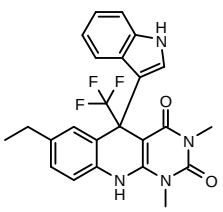
^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –72.2 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 338 (25), 337 (100), 322 (40), 309 (11), 280 (11), 268 (17), 265 (23), 239 (10), 226 (14), 225 (95), 224 (13), 210 (15), 117 (92), 90 (30), 89 (18).

HRMS (ESI): Calcd. for $C_{24}H_{22}F_3N_4O_2$ $[M+H]^+$: 455.16894, found: 455.16903.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3273 (w), 3207 (w), 1713 (s), 1626 (s), 1614 (s), 1599 (m), 1527 (s), 1504 (s), 1479 (s), 1456 (s), 1444 (m), 1390 (m), 1369 (w), 1315 (w), 1298 (m), 1259 (m), 1238 (s), 1211 (m), 1203 (m), 1173 (s), 1161 (s), 1153 (s), 1140 (m), 1126 (w), 1059 (m), 1016 (w), 984 (m), 939 (w), 916 (w), 891 (s), 879 (w), 847 (w), 827 (m), 770 (m), 739 (s), 708 (s), 692 (m), 679 (m), 658 (m), 625 (w), 596 (w), 582 (m), 563 (m), 542 (w).

7-Ethyl-5-(1*H*-indol-3-yl)-1,3-dimethyl-5-(trifluoromethyl)-5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (101e)



Initial 7-ethyl-1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione **88f** (0.15 g, 0.44 mmol, 1 eq) was added to a mixture of indole (0.078 g, 0.67 mmol, 1,5 eq) and sodium hydride (60% in mineral oil, 0.036 g, 0.89 mmol, 2 eq) in dry DMF (3 mL). The reaction mixture was stirred for 5 hours at 60 °C under argon. After cooling to r.t. 0.134 g of acetic acid (2.22 mmol, 3.75 eq) and water were added. The formed precipitate was filtered off by suction and recrystallized from methanol giving the pure product.

Yield 0.115 g (57%), pinkish solid, mp 295-297 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 0.92 (t, 3H, ^{3}J = 7.55 Hz, Et), 2.31 (q, 2H, ^{3}J = 7.55 Hz, Et), 2.96 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 6.64-6.72 (m, 2H, CH_{Ar}, NH-1'), 6.91-7.01 (m, 2H, CH_{Ar}), 7.13 (dd, 1H, ^{3}J = 8.22 Hz, ^{4}J = 2.00 Hz, CH_{Ar}), 7.33-7.42 (m, 3H, CH_{Ar}), 9.47 (s, 1H, H-2'), 11.00 (s, 1H, NH-10).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 16.4 (CH_3), 28.3 (CH_2), 28.3 (CH_3), 31.2 (CH_3), 49.1 (q, $^{2}J_{(C-F)}$ = 27.0 Hz), 81.1 (C-4a), 112.3 (CH), 114.4, 117.2 (CH), 118.9 (CH), 120.1 (CH), 120.4, 121.4 (CH), 121.7 (q, $^{1}J_{(C-F)}$ = 288.4 Hz, CF_3), 123.9 (CH), 126.8, 129.1 (CH), 130.1 (CH),

134.7, 137.0, 138.7, 148.0, 151.4, 159.7.

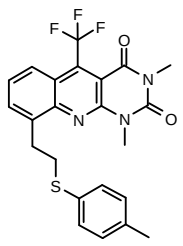
MS (EI, 70 eV): *m/z* (%) = 454 ([M]$^+$, 3.0), 385 (16), 338 (28), 337 (100), 322 (42.92), 309 (12), 280 (13), 268 (20), 265 (26), 239 (11), 237 (10), 226 (16), 225 (96), 224 (14), 210 (15), 196 (10), 117 (34), 90 (11), 60 (10).

HRMS (EI): Calcd. for $C_{24}H_{21}F_3N_4O_2$ [M]$^+$: 454.16111, found: 454.16137.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3271 (w), 3207 (w), 2914 (w), 1713 (s), 1626 (s), 1614 (s), 1599 (s), 1525 (s), 1504 (s), 1479 (s), 1454 (s), 1444 (s), 1390 (m), 1369 (m), 1315 (m), 1298 (m), 1288 (m), 1259 (m), 1238 (s), 1211 (m), 1173 (s), 1153 (s), 1126 (m), 1099 (m), 1057 (s), 1016 (m), 982 (m), 941 (w), 916 (w), 891 (s), 879 (m), 847 (m), 827 (m), 770 (s), 739 (s), 708 (s), 692 (m), 679 (m), 658 (m), 625 (m), 596 (m), 582 (m), 563 (m), 542 (m).

4.2.14 Synthesis of 1,3-dimethyl-9-{2-[(4-methylphenyl)thio]ethyl}-5-(trifluoromethyl)-5-deazaalloxazine

1,3-Dimethyl-9-{2-[(4-methylphenyl)thio]ethyl}-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (104)



Into a 10-mL flask were placed 0.5 g of 9-(2-chloroethyl)-1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione **92a** (0.13 mmol, 1 eq), 0.33 g of 4-methylthiophenol (0.27 mmol, 2 eq), 0.013 g of sodium methylate (0.24 mmol, 1.8 eq) and 1 mL of DMF. The reaction mixture was stirred for 4 hours and then diluted with water. The formed precipitate was filtered off by suction, washed with water and recrystallized from methanol giving the pure product.

Yield 0.059 g (95%), yellow solid, mp 142-143 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.31 (s, 3H, CH_3), 3.28 (t, 2H, CH_2-Ar), 3.45-3.55 (m, 5H, CH_3, CH_2-S), 3.66 (s, 1H, CH_3), 7.06 (d, 2H, ^3J = 7.93 Hz, H-2', H-6'), 7.25 (d, 2H, ^3J = 7.93 Hz, H-3', H-5'), 7.50 (dd, 1H, $^3J_1$ = 7.11 Hz, $^3J_2$ = 8.62 Hz, H-7), 7.70 (d, 1H, ^3J = 7.11 Hz, H-8), 8.19 (d, 1H, ^3J = 8.62 Hz, H-6).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 21.3 (Ar-CH_3), 29.5 (CH_3-3), 30.5 (CH_3-1), 33.1 (CH_2), 35.4 (CH_2), 110.1 (C-4a), 122.0, 123.6 (q, $^1J_{(C-F)}$ = 278.3 Hz, CF_3), 124.9 (q, $^4J_{(C-F)}$ = 5.9 Hz, CH-6), 127.0 (CH), 129.9 (CH), 131.3 (CH), 132.5, 133.8 (CH), 137.0, 138.4, 139.1 (q, $^2J_{(C-F)}$ = 33.2 Hz, C-5), 147.4, 148.6, 151.2 (CO-2), 159.3 (CO-4).

^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –52.4 (s, CF_3).

MS (GC, 70 eV): *m/z* (%) = 459 ([M]$^+$, 35), 337 (19), 336 (100), 279 (29), 137 (68).

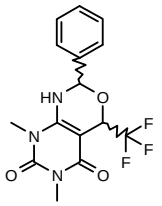
HRMS (EI): Calcd. for $C_{23}H_{20}O_2N_3F_3S$ [M+H]$^+$: 459.12228, found: 459.122964.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2955 (w), 2929 (w), 1728 (s), 1666 (s), 1608 (w), 1585 (s), 1574 (s),

1485 (s), 1470 (s), 1421 (s), 1394 (m), 1379 (s), 1356 (s), 1333 (m), 1286 (s), 1261 (m), 1227 (s), 1198 (m), 1169 (s), 1134 (s), 1115 (s), 1082 (m), 1039 (m), 1014 (m), 982 (m), 930 (m), 883 (w), 856 (w), 820 (m), 804 (s), 789 (s), 779 (s), 762 (s), 748 (s), 739 (m), 702 (s), 685 (m), 675 (m), 667 (m), 590 (w), 555 (m), 542 (w).

4.2.15 Cyclisation of 6-(benzylamino)-1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione

6,8-Dimethyl-2-phenyl-4-(trifluoromethyl)-4,8-dihydro-2*H*-pyrimido[4,5-*d*][1,3]oxazine-5,7(1*H*,6*H*)-dione (108)



Mixure
Ratio of diastereomers
7:1

Major isomers: 2R,4S and 2S4R;
minor isomers: 2R,4R and 2S4S.

A sealed ACE pressure tube was charged with 1 g of 6-(benzylamino)-1,3-dimethyl-5-(trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione **78c** (2.93 mmol, 1 eq), 1.186 g of dry triethylamine (11.7 mmol, 4 eq) and 10 mL of dry DMF. The reaction mixture was stirred for 10 hours at 125 °C under argon. Then the solvent was evaporated and the crude product was purified via short-part column chromatography (silica gel / EtOAc), following by washing with ether.

Yield 0.798 g (80%), white solid, mp 220-222 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.31 (s, 3H, CH_3-6-a), 3.32 (s, 0.15H, CH_3-6-b), 3.32 (s, 0.15H, CH_3-8-b), 3.36 (s, 3H, CH_3-8-a), 5.27 (q, 1H, $^{4}J_{(H-F)}$ = 7.18 Hz, H-4-a), 5.49.(q, 0.15H, $^{4}J_{(H-F)}$ = 5.29 Hz, H-4-b), 5.55 (d, 0.15H, *J* = 3.11 Hz, H-2-b), 5.91 (br s, 1H, H-2-a), 7.48-7.64 (m, 5.75H, CH_{Ph}-a, CH_{Ph}-b), 8.11 (d, 0.15H, *J* = 3.11 Hz, NH-b), 8.15 (br s, 1H, NH-a).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 28.2 (CH_3-6-a,b), 30.1 (CH_3-8-b), 30.4 (CH_3-8-a), 69.6 (q, $^{2}J_{(C-F)}$ = 31.6 Hz, CH-4-a), 70.5 (q, $^{2}J_{(C-F)}$ = 31.9 Hz, CH-4-b), 77.2 (4a-a), 81.9 (CH-2-a), 82.2 (4a-b), 83.0 (CH-2-b), 125.7 (q, $^{1}J_{(C-F)}$ = 287.6 Hz, CF_3-a), 128.5 ($CH_{o\text{-}Ph}$-b), 128.6 ($CH_{o\text{-}Ph}$-a), 129.3 ($CH_{m\text{-}Ph}$-b), 129.4 ($CH_{m\text{-}Ph}$-a), 130.4 ($CH_{p\text{-}Ph}$-b), 130.8 ($CH_{p\text{-}Ph}$-a), 137.0 (C_{Ph}-b), 137.6 (C_{Ph}-a), 150.5 (C-8-a), 151.5 (CO-7-b), 151.6 (CO-7-a), 154.0 (C-8-b), 160.2 (CO-5-a), 160.4 (CO-5-b).

^{19}F NMR (282.38 MHz, DMSO-d_6): δ = –75.5 (s, CF_3-b), –71.3 (s, CF_3-a).

MS (EI, 70 eV): *m/z* (%) = 341 ($[M]^+$, 16), 273 (32), 272 (100), 258 (17), 110 (11), 105 (15), 82 (12), 77 (12).

HRMS (ESI): Calcd. for $C_{15}H_{15}F_3N_3O_3$ $[M+H]^+$: 342.10600, found: 340.10654.

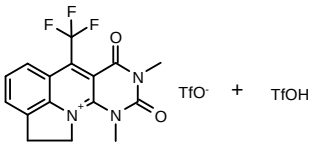
Anal. Calcd for $C_{15}H_{14}F_3N_3O_3$: C, 52.79; H, 4.13; N, 12.31. Found: C, 52.95; H, 3.87; N, 11.79.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3243 (s), 3097 (w), 3040 (w), 2952 (w), 1707 (s), 1616 (s), 1556 (s),

1482 (s), 1459 (m), 1439 (m), 1395 (w), 1383 (m), 1360 (m), 1335 (w), 1321 (m), 1307 (w), 1290 (w), 1258 (s), 1248 (s), 1234 (m), 1167 (s), 1123 (s), 1076 (m), 1053 (m), 1028 (w), 1005 (m), 998 (m), 982 (w), 967 (m), 670 (s), 650 (w), 634 (s), 617 (w), 582 (m), 531 (m).

4.2.16 Detection of 5-deazaalloxazine-10-ium cation

8,10-Dimethyl-7,9-dioxo-6-(trifluoromethyl)-1,2,7,8,9,10-hexahydropyrimido[4,5-*b*]pyrrolo[3,2,1-*ij*]quinolin-11-ium trifluoromethanesulfonate (95a)



The solution of title salt was prepared inside a NMR tube by addition of triflic anhydride to 6-hydroxy-8,10-dimethyl-6-(trifluoromethyl)-1,2-dihydro-6*H*-pyrimido[4,5-*b*]pyrrolo[3,2,1-*ij*]quinoline-7,9(8*H*,10*H*)-dione **91a** dissolved in pure $CDCl_3$ or $CDCl_3/CD_2Cl_2$ mixture.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.42 (s, 3H, CH_3-3), 3.80 (t, 2H, ^3J = 7.27 Hz, Ar-CH_2-), 3.96 (s, 3H, CH_3-1), 5.48 (t, 2H, ^3J = 7.27 Hz, -CH_2-N_{Ar}^+), 7.89 (dd, 1H, $^3J_1$ = 8.59 Hz, $^3J_2$ = 7,27 Hz, H-4), 8.03 (d, 1H, ^3J = 7.27 Hz, H-3), 8.24-8.32 (dm, 1H, ^3J = 8.59 Hz, H-5), 13.99 (s, 1.67H, TfOH).

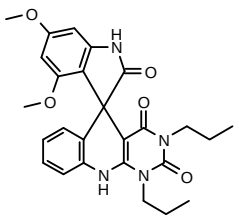
^{13}C NMR (75.47 MHz, $CD_2Cl_2/CDCl_3$): δ = 27.8 (CH_2-2), 30.0 (CH_3-8), 36.6 (CH_3-10), 60.0 (CH_2-1), 115.6 (C-6a), 118.8 (q, $^1J_{(C\text{-}F)}$ = 317.6 Hz, TfOH/TfO^-), 120.5, 121.6 (q, $^1J_{(C\text{-}F)}$ = 279.6 Hz, CF_3), 124.6 (q, $^4J_{(C\text{-}F)}$ = 5.9 Hz, CH-5), 131.9 (CH_{Ar}), 133.1 (CH_{Ar}), 134.5, 143.3, 145.2 (q, $^2J_{(C\text{-}F)}$ = 35.9 Hz, C-6), 149.2, 149.3, 155.9.

4.2.17 Synthesis of spiro[pyrimido[4,5-*b*]quinoline-3',5-indoline-2'-one]-3,10-dihydro-2,4-diones

General procedure for the synthesis of spiro[pyrimido[4,5-*b*]quinoline-3',5-indoline-2'-one]-3,10-dihydro-2,4-diones 118/119 a-w.

Into a 25-mL flask were placed barbituric acid (1.92 mmol, 1 eq), isatin (1.92 mmol, 1 eq), aromatic amine (1.92 mmol, 1 eq) and 6 ml of ethanol. After that 0.096 mmol (0.05 eq) of iodine was added and the mixture was stirred at r.t. overnight. The next day formed precipitate was filtered off, washed with ethanol and recrystallized from appropriate solvent (DMF or TFA/EtOH), if necessary.

4,6-Dimethoxy-1',3'-dipropyl-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,2',4'(1*H*,3'*H*,10'*H*)-trione (119a)



The product was prepared according to the general procedure, starting from 0.245 g of 1,3-dipropylbarbituric acid, 0.177 g of 3,5-dimethoxyaniline, 0.170 g of isatin, 0.015 g of iodine and 4.9 mL of ethanol.

Yield 0.436 (79%), white solid, mp 303-305 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 0.78 (t, 3H, ^3J = 7.46 Hz, $NCH_2CH_2\underline{CH_3}$-3'), 0.97 (t, 3H, ^3J = 7.37 Hz, $NCH_2CH_2\underline{CH_3}$-1'), 1.36-1.52 (m, 2H, $NCH_2\underline{CH_2}CH_3$-3'), 1.64-1.78 (m, 2H, $NCH_2\underline{CH_2}CH_3$-1'), 3.49 (s, 3H, MeO-4), 3.66 (t, 2H, ^3J = 7.37 Hz, $N\underline{CH_2}CH_2CH_3$-3'), 3.75 (s, 3H, MeO-6), 4.06-4.30 (m, 2H, $N\underline{CH_2}CH_2CH_3$-1'), 6.03 (d, 1H, ^4J = 2.08 Hz, H-5), 6.11 (d, 1H, ^4J = 2.08 Hz, H-7), 6.71 (d, 1H, ^3J = 7.94 Hz, H-9'), 6.85-6.93 (m, 1H, H-7'), 7.13-7.21 (m, 1H, H-8'), 7.31 (d, 1H, ^3J = 8.12 Hz, H-6'), 9,14 (br s, 1H, NH-10'), 10.32 (br s, 1H, NH-1).

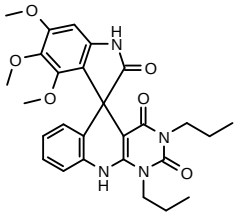
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 11.5 (CH_3), 11.9 (CH_3), 21.6 (CH_2), 22.0 (CH_2), 42.6 (N-CH_2), 43.8 (N-CH_2), 51.0 (C-5',3), 56.1 (MeO-6), 56.4 (MeO-4), 85.1 (C-4a'), 90.1 (CH-7), 92.9 (CH-5), 117.2 (CH_{Ar}), 118.0, 122.9, 124.2 (CH_{Ar}), 126.7 (CH_{Ar}), 128.5 (CH_{Ar}), 136.7, 143.8, 146.2, 151.2, 156.7, 160.2, 161.5, 181.9 (CO-2).

MS (EI, 70 eV): *m/z* (%) = 477 ([M+H]$^+$, 10), 476 ([M]$^+$, 27), 448 (34), 325 (20), 324 (100), 282 (33), 240 (42), 217 (18), 169 (13), 43 (17), 41 (13).

HRMS (ESI): Calcd. for $C_{26}H_{29}N_4O_5$ [M]$^+$: 477.21325, found: 477.21398.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3182 (m), 2955 (m), 2833 (w), 1707 (s), 1691 (s), 1626 (s), 1606 (s), 1593 (s), 1531 (s), 1489 (s), 1460 (s), 1443 (s), 1394 (m), 1338 (m), 1325 (s), 1306 (m), 1277 (m), 1254 (s), 1238 (m), 1215 (s), 1194 (s), 1144 (s), 1124 (s), 1113 (s), 1092 (s), 1041 (m), 1016 (m), 991 (m), 947 (m), 935 (m), 914 (w), 887 (w), 862 (m), 816 (m), 789 (m), 775 (s), 744 (s), 725 (m), 710 (s), 673 (s), 631 (m), 617 (s), 604 (m), 561 (m), 548 (m), 530 (m).

4,5,6-Trimethoxy-1',3'-dipropyl-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,2',4'(1*H*,3'*H*,10'*H*)-trione (119b)



The product was prepared according to the general procedure, starting from 0.245 g of 1,3-dipropylbarbituric acid, 0.211 g of 3,4,5-trimethoxyaniline, 0.170 g of isatin, 0.015 g of iodine and 4.9 mL of ethanol.

Yield 0.153 g (26%), white solid, mp 300 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 0.78 (t, 3H, ^3J = 7.46 Hz, $NCH_2CH_2\underline{CH_3}$-3'), 0.99 (t,

3H, ^{3}J = 7.37 Hz, $NCH_2CH_2\underline{CH_3}$-1'), 1.33-1.54 (m, 2H, $NCH_2\underline{CH_2}CH_3$-3'), 1.63-1.78 (m, 2H, $NCH_2\underline{CH_2}CH_3$-1'), 3.29 (s, 1H, MeO), 3.59 (s, 1H, MeO), 3.61-3.73 (m, 2H, $N\underline{CH_2}CH_2CH_3$-3'), 3.83 (s, 1H, MeO), 4.10-4.23 (m, 2H, $N\underline{CH_2}CH_2CH_3$-1'), 6.36 (s, 1H, H-7), 6.71 (d, 1H, ^{3}J = 7.93 Hz, H-9'), 6.88-6.96 (m, 1H, H-7'), 7.16-7.24 (m, 1H, H-8'), 7.36 (d, 1H, ^{3}J = 8.12 Hz, H-6'), 9,19 (br s, 1H, NH-10'), 10.31 (br s, 1H, NH-1).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 11.6 (CH_3), 11.9 (CH_3), 21.6 (CH_2), 22.2 (CH_2), 42.6 (N-CH_2), 44.0 (N-CH_2), 51.7 (C-5',3), 56.8 (MeO), 60.8 (MeO), 61.3 (MeO), 85.5 (C-4a'), 92.0 (CH-7), 117.5 (CH_{Ar}), 123.0, 123.5, 124.4 (CH_{Ar}), 126.8 (CH_{Ar}), 128.7 (CH_{Ar}), 136.4, 137.2, 138.2, 146.1, 150.2, 151.1, 154.4, 160.3, 181.7 (CO-2).

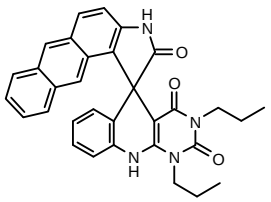
MS (EI, 70 eV): *m/z* (%) = 507 ($[M+H]^+$, 11), 506 ($[M]^+$, 55), 463 (10), 325 (22), 324 (100), 282 (21), 240 (33), 169 (10), 43 (13).

HRMS (EI): Calcd. for $C_{27}H_{30}N_4O_6$ $[M]^+$: 506.21599, found: 506.216186.

Anal. Calcd for $C_{27}H_{30}N_4O_6$: C, 64.02; H, 5.97; N, 11.06. Found: C, 62.77; H, 5.98; N, 10.77.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3271 (w), 2962 (m), 2933 (m), 2874 (w), 1689 (s), 1610 (s), 1591 (s), 1533 (s), 1487 (s), 1471 (s), 1435 (s), 1421 (s), 1392 (s), 1325 (s), 1286 (m), 1254 (s), 1232 (s), 1194 (m), 1138 (s), 1117 (s), 1095 (s), 1049 (s), 1011 (m), 995 (m), 974 (m), 943 (m), 922 (m), 895 (m), 860 (m), 814 (m), 798 (m), 775 (m), 760 (s), 744 (s), 700 (s), 690 (s), 608 (s), 561 (s).

1',3'-Dipropyl-1'*H*-spiro[naphtho[2,3-*e*]indole-1,5'-pyrimido[4,5-*b*]quinoline]-2,2',4'(3*H*,3'*H*,10'*H*)-trione (119c)



The product was prepared according to the general procedure, starting from 0.23 g of 1,3-dipropylbarbituric acid, 0.209 g of 2-anthracenamine, 0.159 g of isatin, 0.014 g of iodine and 4.6 mL of ethanol.

Yield 0.512 g (91%), dark goldish solid, mp 300-302 °C.

^{1}H NMR (500.13 MHz, DMSO-d_6): δ = 0.66 (t, 3H, ^{3}J = 7.46 Hz, $NCH_2CH_2\underline{CH_3}$-3'), 1.07 (t, 3H, ^{3}J = 7.56 Hz, $NCH_2CH_2\underline{CH_3}$-1'), 1.26-1.40 (m, 2H, $NCH_2\underline{CH_2}CH_3$-3'), 1.85-1.97 (m, 2H, $NCH_2\underline{CH_2}CH_3$-1'), 3.56 (t, 2H, ^{3}J = 7.37 Hz, $N\underline{CH_2}CH_2CH_3$-3'), 4.25-4.43 (m, 2H, $N\underline{CH_2}CH_2CH_3$-1'), 6.73 (d, 1H, ^{3}J = 7.84 Hz, H-6'), 6.82 (m, 1H, H-7'), 7.18 (m, 1H, H-8'), 7.35-7.40 (m, 1H, H-8), 7.41 (d, 1H, H-4), 7.41-7.45 (m, 1H, H-9), 7.50 (d, 1H, ^{3}J = 8.03 Hz, H-9'), 7.66 (d, 1H, ^{3}J = 8.31 Hz, H-10), 7.90 (s, 1H, H-11), 7.98 (d, 1H, ^{3}J = 8.31 Hz, H-7), 8.09 (d, 1H, ^{3}J = 8.69 Hz, H-5), 8.57 (s, 1H, H-6), 9.59 (br s, 1H, NH-10'), 10.68 (br s, 1H, NH-3).

^{13}C NMR (125.77 MHz, DMSO-d_6): δ = 11.7 ($NCH_2CH_2\underline{CH_3}$-1'), 11.8 ($NCH_2CH_2\underline{CH_3}$-3'), 21.5 ($NCH_2\underline{CH_2}CH_3$-3'), 22.2 ($NCH_2\underline{CH_2}CH_3$-1'), 42.7 ($N\underline{CH_2}CH_2CH_3$-3'), 44.1 ($N\underline{CH_2}CH_2CH_3$-1'),

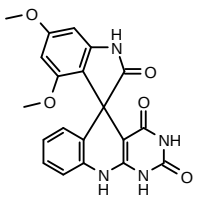
53.2 (C-5',1), 86.2 (C-4a'), 114.3 (CH-4), 117.9 (CH-9'), 118.5 (CH-11), 122.4, 124.8 (CH-7'), 125.3 (CH-8), 127.0 (CH-6'), 127.0 (CH-9), 127.6, 128.1 (CH-10), 128.4, 129.1 (CH-8'), 129.2 (CH-7), 129.3 (CH-6), 130.0, 130.0, 130.6 (CH-5), 132.4, 136.4, 139.6, 146.4, 151.2, 160.3, 182.9 (CO-2), 19.5 and 57.0 – traces of EtOH.

MS (EI, 70 eV): *m/z* (%) = 517 ($[M+H]^+$, 36). 516 ($[M]^+$, 100), 515 (10), 514 (16), 489 (14), 488 (48), 487 (80), 474 (14), 388 (14), 360 (13), 346 (14), 324 (41), 318 (30), 316 (13).

HRMS (ESI): Calcd. for $C_{32}H_{29}N_4O_3$ $[M+H]^+$: 517.22342, found: 517.22319.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3167 (m), 2960 (m), 2872 (m), 1689 (s), 1606 (s), 1583 (s), 1566 (s), 1525 (s), 1504 (s), 1485 (s), 1429 (s), 1406 (s), 1369 (s), 1336 (s), 1319 (s), 1234 (s), 1205 (m), 1182 (m), 1157 (m), 1130 (m), 1097 (m), 1065 (m), 1001 (m), 957 (m), 943 (m), 935 (m), 895 (m), 879 (m), 864 (s), 827 (m), 802 (m), 775 (s), 744 (s), 716 (s), 689 (s), 673 (s), 644 (s), 617 (s), 600 (s), 573 (s), 554 (s).

4,6-Dimethoxy-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,2',4'(1*H*,3'*H*,10'*H*)-trione (119d)



The product was prepared according to the general procedure, starting from 0.3 g of barbituric acid, 0.359 g of 3,5-dimethoxyaniline, 0.345 g of isatin, 0.03 g of iodine and 6 mL of ethanol.

Yield 0.469 g (51%), white solid, mp 357-359 °C.

^{1}H NMR (300.13 MHz, TFA-*d*): δ = 3.56 (s, 1H, MeO), 3.92 (s, 1H, MeO), 6.83 (d, 1H, ^3J = 2.08 Hz, H-9'), 6.95-7.03 (m, 1H, H-7'), 7.02 (d, 1H, ^3J = 2.08 Hz, H-6'), 7.20-7.29 (m, 1H, H-8').

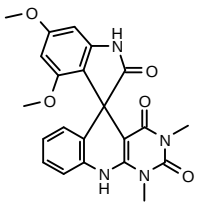
MS (EI, 70 eV): *m/z* (%) = 393 ($[M+H]^+$, 13), 392 ($[M]^+$, 52), 390 (16), 365 (13), 364 (60), 363 (58), 348 (11), 347 (10), 333 (14), 240 (21), 169 (10), 153 (21), 78 (32), 45 (11), 44 (100), 43 (19).

HRMS (ESI): Calcd. for $C_{20}H_{17}N_4O_5$ $[M+H]^+$: 393.11935, found: 393.11992.

Anal. Calcd for $C_{20}H_{16}N_4O_5$: C, 61.22; H, 4.11; N, 14.28. Found: C, 62.03; H, 3.99; N, 14.25.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3267 (w), 3072 (w), 1722 (s), 1699 (s), 1626 (s), 1608 (s), 1549 (s), 1504 (s), 1493 (s), 1475 (s), 1462 (s), 1446 (s), 1385 (s), 1342 (s), 1319 (s), 1261 (m), 1219 (s), 1201 (m), 1167 (m), 1149 (s), 1109 (s), 1049 (m), 1036 (m), 993 (m), 959 (m), 951 (m), 933 (m), 916 (m), 862 (m), 827 (s), 793 (s), 777 (s), 744 (s), 727 (s), 714 (m), 673 (s), 638 (s), 625 (s), 604 (s), 588 (s), 555 (s), 532 (s).

4,6-Dimethoxy-1',3'-dimethyl-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,2',4'(1*H*,3'*H*,10'*H*)-trione (119e)



The product was prepared according to the general procedure, starting from 0.3 g of 1,3-dimethylbarbituric acid, 0.294 g of 3,5-dimethoxyaniline, 0.283 g of isatin, 0.024 g of iodine and 6 mL of ethanol.

Recrystallized from DMF. Yield 0.457 g (57%), white solid, mp 335 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.08 (s, 3H, NCH_3-3'), 3.50 (s, 3H, MeO-4), 3.57 (s, 3H, NCH_3-1'), 3.76 (s, 3H, MeO-6), 6.04 (d, 1H, ^4J = 2.08 Hz, H-5), 6.12 (d, 1H, ^4J = 2.08 Hz, H-7), 6.69 (d, 1H, ^3J = 7.93 Hz, H-9'), 6.85-6.93 (m, 1H, H-7'), 7.13-7.21 (m, 1H, H-8'), 7.29 (d, 1H, ^3J = 8.22 Hz, H-6'), 9,27 (br s, 1H, NH-10'), 10.34 (br s, 1H, NH-1).

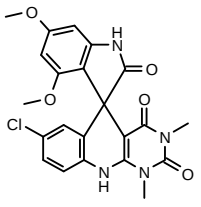
MS (GC, 70 eV): *m/z* (%) = 420 ($[M]^+$, 3.6), 419 ($[M–H]^+$, 22), 418 (85), 387 (33), 377 (10), 376 (43), 281 (12), 254 (42), 209 (16), 208 (17), 207 (100), 191 (14).

HRMS (ESI): Calcd. for $C_{22}H_{21}N_4O_5$ $[M+H]^+$: 421.15065, found: 421.15040.

Anal. Calcd for $C_{22}H_{20}N_4O_5$: C, 62.85; H, 4.79; N, 13.33. Found: C, 62.25; H, 4.86; N, 13.30.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3450 (w), 3184 (m), 2839 (w), 1707 (m), 1693 (s), 1674 (s), 1643 (s), 1606 (s), 1593 (s), 1533 (s), 1512 (s), 1489 (s), 1464 (s), 1450 (s), 1425 (s), 1394 (m), 1373 (m), 1342 (m), 1317 (s), 1257 (s), 1219 (s), 1201 (s), 1149 (s), 1126 (s), 1117 (s), 1086 (m), 1065 (m), 1047 (m), 1001 (m), 989 (m), 939 (m), 932 (m), 916 (m), 868 (m), 818 (m), 797 (m), 777 (s), 750 (s), 739 (s), 702 (s), 671 (s), 638 (s), 623 (s), 582 (s), 528 (s).

7'-Chloro-4,6-dimethoxy-1',3'-dimethyl-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,2',4'(1*H*,3'*H*,10'*H*)-trione (119f)



The product was prepared according to the general procedure, starting from 0.3 g of 1,3-dimethylbarbituric acid, 0.294 g of 3,5-dimethoxyaniline, 0.349 g of 5-chloroisatin, 0.024 g of iodine and 6 mL of ethanol.

Yield 0.63 (72%), white solid, mp >320 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.08 (s, 3H, NCH_3-3'), 3.53 (s, 3H, MeO-4), 3.56 (s, 3H, NCH_3-1'), 3.77 (s, 3H, MeO-6), 6.07 (d, 1H, ^4J = 2.08 Hz, H-5), 6.14 (d, 1H, ^4J = 2.08 Hz, H-7), 6.59 (d, 1H, ^4J = 2.45 Hz, H-6'), 7.26 (dd, 1H, ^3J = 8.69 Hz, ^4J = 2.45 Hz, H-8'), 7.34 (d, 1H, ^3J = 8.69 Hz, H-9'), 9,45 (br s, 1H, NH-10'), 10.45 (br s, 1H, NH-1).

^{13}C NMR (75.48 MHz, DMSO-d_6): δ = 28.3 (NCH_3-3'), 31.0 (NCH_3-1'), 51.0 (C-5',3), 56.2 (MeO-6), 56.5 (MeO-4), 84.6 (C-4a'), 90.2 (CH-7), 93.1 (CH-5), 117.3, 119.4 (CH-9'), 125.0 (C-

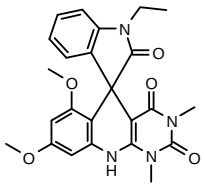
5a'), 125.9 (C H-6'), 127.5, 128.7 (C H-8'), 135.9 (C-9a'), 143.7, 146.7, 151.3, 156.8, 160.3, 161.8, 181.3 (CO-2).

MS (GC, 70 eV): *m/z* (%) = 454 ([M]$^+$, ^{35}Cl, 35), 453 (27), 452 (100), 423 (14), 421 (39), 412 (21), 411 (15), 410 (57), 290 (19), 289 (10), 288 (51).

HRMS (ESI): Calcd. for $C_{22}H_{20}{}^{35}ClN_4O_5$ [M+H]$^+$: 455.11167, found: 455.11218.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3232 (m), 3001 (w), 1709 (s), 1687 (s), 1633 (s), 1622 (s), 1606 (s), 1589 (s), 1525 (s), 1506 (s), 1479 (s), 1464 (s), 1456 (s), 1435 (s), 1402 (m), 1371 (m), 1333 (m), 1321 (m), 1306 (m), 1292 (m), 1277 (m), 1254 (s), 1215 (s), 1196 (s), 1144 (s), 1128 (m), 1113 (s), 1084 (s), 1066 (m), 1039 (m), 997 (m), 989 (m), 945 (m), 866 (m), 827 (s), 818 (s), 806 (m), 785 (w), 771 (s), 754 (s), 698 (m), 675 (s), 665 (s), 625 (s), 588 (m), 557 (s), 552 (s), 542 (s).

1-Ethyl-6',8'-dimethoxy-1',3'-dimethyl-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,2',4'(1*H*,3'*H*,10'*H*)-trione (118g)



The product was prepared according to the general procedure, starting from 0.3 g of 1,3-dimethylbarbituric acid, 0.294 g of 3,5-dimethoxyaniline, 0.337 g of 1-ethylisatin, 0.024 g of iodine and 6 mL of ethanol.

Yield 0.704 g (82%), white solid, mp >320 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.29 (t, 3H, ^3J = 7.18 Hz, Et), 3.00 (s, 3H, NCH$_3$-3'), 3.32 (s, 3H, MeO-6'), 3.55 (s, 3H, NCH$_3$-1'), 3.66-3.75 (m, 1H, CH$_2$-a), 3.75-3.84 (m, 1H, CH$_2$-b), 3.77 (s, 3H, MeO-8'), 6.13 (d, 1H, ^4J = 2.55 Hz, H-7'), 6.67 (d, 1H, ^4J = 2.55 Hz, H-9'), 6.77-6.84 (m, 1H, H-5), 6.85 (d, 1H, ^3J = 7.27 Hz, H-4), 6.90 (d, 1H, ^3J = 7.55 Hz, H-7), 7.11-7.19 (m, 1H, H-6), 9,16 (br s, 1H, NH).

^{13}C NMR (125.77 MHz, TFA-*d*): δ = 13.1 (CH$_{3(Et)}$), 30.5 (NCH$_3$-3'), 31.8 (NCH$_3$-1'), 38.8 (CH$_{2(Et)}$), 53.4 (C-5',3), 56.9 (MeO-6'), 57.4 (MeO-8'), 89.4 (C-4a'), 97.4 (CH-9'), 97.8 (CH-7'), 104.5 (C-9a'), 111.4 (CH-7), 125.7 (CH-4), 127.2 (CH-5), 130.9, 137.9 (CH-6), 138.1, 143.9, 149.8, 154.0, 161.1, 162.7, 165.0, 185.0 (CO-2).

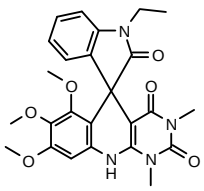
MS (EI, 70 eV): *m/z* (%) = 449 ([M+H]$^+$, 28), 448 ([M]$^+$, 100), 421 (13), 420 (48), 419 (29), 405 (35), 390 (24), 389 (46), 362 (15), 328 (16), 327 (24), 312 (15), 310 (11), 303 (12), 302 (45), 73 (11), 69 (11), 60 (16), 44 (28), 43 (14).

HRMS (ESI): Calcd. for $C_{24}H_{25}N_4O_5$ [M+H]$^+$: 449.18195, found: 449.18176.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2972 (w), 1703 (s), 1682 (s), 1645 (s), 1601 (s), 1537 (s), 1487 (s), 1462 (s), 1454 (s), 1441 (s), 1412 (m), 1392 (m), 1371 (s), 1352 (m), 1296 (m), 1279 (m), 1232 (s), 1219 (s), 1174 (m), 1153 (s), 1132 (s), 1092 (m), 1078 (m), 1059 (m), 1045 (m), 1020 (m), 1007 (m), 984 (m), 957 (m), 945 (m), 933 (m), 912 (m), 856 (w), 841 (w), 822 (s), 806 (s), 795 (m), 771 (s), 752 (s), 725 (m), 712 (m), 694 (m), 683 (m), 669 (m), 654 (s), 621 (m), 602 (m), 582 (m), 563

(m), 534 (m).

1-Ethyl-6',7',8'-trimethoxy-1',3'-dimethyl-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,2',4'(1*H*,3'*H*,10'*H*)-trione (118h)



The product was prepared according to the general procedure, starting from 0.3 g of 1,3-dimethylbarbituric acid, 0.352 g of 3,4,5-trimethoxyaniline, 0.337 g of 1-ethylisatin, 0.024 g of iodine and 6 mL of ethanol.

Yield 0.503 g (55%), white solid, mp >320 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.30 (t, 3H, ^3J = 7.18 Hz, Et), 3.01 (s, 3H, NCH_3-3'), 3.03 (s, 1H, MeO-6'), 3.55 (s, 3H, NCH_3-1'), 3.60 (s, 3H, MeO-7'), 3.78 (q, 2H, ^3J = 7.18 Hz, Et), 3.83 (s, 3H, MeO-8'), 6.82-6.89 (m, 1H, H-5), 6.92 (d, 1H, ^3J = 6.80 Hz, CH_{Ar}), 6.92 (s, 1H, H-9'), 6.97 (d, 1H, ^3J = 7.74 Hz, CH_{Ar}), 7.15-7.22 (m, 1H, H-6), 9,17 (br s, 1H, NH).

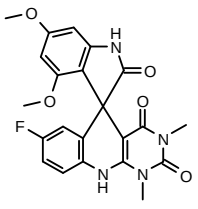
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 13.0 ($CH_{3(Et)}$), 28.3 (NCH_3-3'), 31.1 (NCH_3-1'), 35.3 ($CH_{2(Et)}$), 50.1 (C-5',3), 56.6 (MeO-8'), 60.1 (MeO-6'), 61.1 (MeO-7'), 86.6 (C-4a'), 97.2 (CH-9'), 107.9 (CH_{Ar}), 109.7, 122.1 (CH_{Ar}), 124.2 (CH_{Ar}), 128.4 (CH_{Ar}), 132.8, 137.5, 138.3, 144.7, 146.1, 151.2, 152.0, 153.8, 160.1, 179.0 (CO-2).

MS (EI, 70 eV): *m/z* (%) = 479 ($[M+H]^+$, 26), 478 ($[M]^+$, 100), 463 (11), 450 (16), 449 (16), 435 (17), 420 (16), 419 (40), 358 (22), 332 (17), 147 (34), 82 (11), 79 (14), 78 (88), 77 (15), 75 (70), 73 (32), 71 (11), 69 (26), 66 (60), 65 (31), 63 (98), 62 (13), 61 (21), 60 (40), 57 (18), 55 (19), 48 (10), 47 (26), 46 (15), 45 (34), 44 (81), 43 (39), 41(20), 40 (29), 39 (25), 36 (11).

HRMS (ESI): Calcd. for $C_{25}H_{27}N_4O_6$ $[M+H]^+$: 479.19251, found: 479.19276.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2972 (m), 2947 (w), 1703 (s), 1678 (s), 1639 (s), 1606 (s), 1539 (s), 1489 (s), 1468 (s), 1450 (s), 1435 (s), 1383 (s), 1371 (s), 1354 (m), 1284 (m), 1271 (m), 1234 (s), 1213 (m), 1180 (m), 1161 (m), 1136 (s), 1115 (m), 1092 (s), 1059 (s), 1026 (m), 1001 (m), 980 (m), 959 (m), 941 (m), 920 (m), 874 (m), 852 (w), 827 (s), 793 (m), 777 (m), 752 (s), 741 (s), 714 (m), 702 (m), 681 (s), 656 (m), 642 (m), 594 (m), 557 (m), 540 (m), 528 (m).

7'-Fluoro-4,6-dimethoxy-1',3'-dimethyl-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,2',4'(1*H*,3'*H*,10'*H*)-trione (119i)



The product was prepared according to the general procedure, starting from 0.3 g of 1,3-dimethylbarbituric acid, 0.294 g of 3,5-dimethoxyaniline, 0.317 g of 5-fluoroisatin, 0.024 g of iodine and 6 mL of ethanol.

Yield 0.628 (75%), white solid, mp >320 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.08 (s, 3H, NCH_3-3'), 3.52 (s,

3H, MeO-4), 3.56 (s, 3H, NCH_3-1'), 3.77 (s, 3H, MeO-6), 6.07 (d, 1H, ^4J = 2.08 Hz, H-5), 6.13 (d, 1H, ^4J = 2.08 Hz, H-7), 6.37 (dd, 1H, $^3J_{(H-F)}$ = 9.45 Hz, ^4J = 2.83 Hz, H-6'), 7.03-7.12 (m, 1H, H-8'), 7.35 (dd, 1H, ^3J = 9.06 Hz, $^4J_{(H-F)}$ = 5.29 Hz, H-9'), 9,36 (br s, 1H, NH-10'), 10.42 (br s, 1H, NH-1).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.3 (NCH_3-3'), 31.0 (NCH_3-1'), 51.3 (C-5',3), 56.2 (MeO-6), 56.5 (MeO-4), 84.0 (C-4a'), 90.2 (CH-7), 93.1 (CH-5), 112.5 (d, $^2J_{(C-F)}$ = 23.3 Hz, CH_{Ar}), 115.9 (d, $^2J_{(C-F)}$ = 22.7 Hz, CH_{Ar}), 117.2, 119.2 (d, $^3J_{(C-F)}$ = 8.1 Hz, CH-9'), 124.7 (d, $^3J_{(C-F)}$ = 6.9 Hz, C-5a'), 133.4 (d, $^4J_{(C-F)}$ = 2.0 Hz, C-9a'), 143.8, 146.9, 151.4, 156.8, 159.0 (d, $^1J_{(C-F)}$ = 239.0 Hz, C-7'), 160.4, 161.8, 181.3 (CO-2).

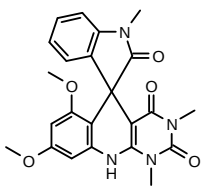
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –120.2 (s, F-7').

MS (EI, 70 eV): *m/z* (%) = 439 ($[M+H]^+$, 6.4), 438 ($[M]^+$, 27), 437 (25), 436 (100), 410 (30), 409 (20), 405 (29), 395 (15), 394 (67), 286 (48), 272 (58), 201 (15).

HRMS (ESI): Calcd. for $C_{22}H_{20}FN_4O_5$ $[M+H]^+$: 439.14122, found: 439.14209.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3207 (m), 2841 (w), 1709 (s), 1687 (s), 1643 (s), 1622 (s), 1606 (s), 1539 (s), 1495 (s), 1464 (s), 1441 (s), 1410 (s), 1392 (m), 1373 (m), 1335 (m), 1323 (m), 1296 (m), 1277 (m), 1255 (s), 1217 (s), 1200 (s), 1146 (s), 1117 (s), 1090 (m), 1065 (m), 1041 (m), 999 (m), 987 (m), 945 (m), 922 (w), 878 (m), 860 (s), 822 (s), 804 (m), 771 (s), 752 (s), 700 (m), 681 (s), 627 (s), 592 (m), 557 (s).

6',8'-Dimethoxy-1,1',3'-trimethyl-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,2',4'(1*H*,3'*H*,10'*H*)-trione (118j)



The product was prepared according to the general procedure, starting from 0.18 g of 1,3-dimethylbarbituric acid, 0.177 g of 3,5-dimethoxyaniline, 0.186 g of 1-methylisatin, 0.015 g of iodine and 3.6 mL of ethanol.

Yield 0.501 g (86%), white solid, mp >320 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.01 (s, 3H, NCH_3-3'), 3.20 (s, 3H, NCH_3-1), 3.36 (s, 3H, MeO-6'), 3.55 (s, 3H, NCH_3-1'), 3.77 (s, 3H, MeO-8'), 6.12 (d, 1H, ^4J = 2.55 Hz, H-7'), 6.67 (d, 1H, ^4J = 2.55 Hz, H-9'), 6.77-6.85 (m, 1H, H-5), 6.85 (d, 1H, ^3J = 7.18 Hz, H-4), 6.88 (d, 1H, ^3J = 7.74 Hz, H-7), 7.13-7.20 (m, 1H, H-6), 9,17 (br s, 1H, NH).

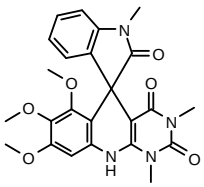
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 27.1 (NCH_3-1), 28.3 (NCH_3-3'), 31.1 (NCH_3-1'), 49.6 (C-5',3), 56.1 (MeO-8'), 56.8 (MeO-6'), 87.2 (C-4a'), 95.0 (CH-9'), 95.5 (CH-7'), 105.2, 107.4 (CH_{Ar}), 122.2 (CH_{Ar}), 123.7 (CH_{Ar}), 128.2 (CH_{Ar}), 136.8, 138.1, 145.6, 146.2, 151.2, 159.1, 160.1, 160.6, 179.8 (CO-2).

MS (EI, 70 eV): *m/z* (%) = 435 ($[M+H]^+$, 14), 434 ($[M]^+$, 59), 406 (18), 376 (34), 375 (100), 318 (11), 44 (16).

HRMS (EI): Calcd. for $C_{23}H_{22}N_4O_5$ $[M]^+$: 434.15847, found: 434.15903.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2964 (w), 1695 (s), 1682 (s), 1633 (s), 1608 (s), 1537 (s), 1489 (s), 1471 (s), 1441 (s), 1410 (s), 1379 (s), 1362 (s), 1298 (m), 1259 (m), 1238 (s), 1219 (s), 1201 (m), 1192 (m), 1178 (m), 1153 (s), 1130 (s), 1092 (s), 1053 (s), 1041 (s), 1022 (m), 1005 (s), 980 (m), 962 (m), 949 (m), 933 (m), 924 (m), 912 (m), 854 (m), 841 (m), 820 (s), 797 (m), 771 (s), 750 (s), 741 (s), 727 (s), 696 (s), 687 (s), 656 (s), 640 (s), 602 (m), 582 (m), 569 (s), 544 (s), 536 (s).

6',7',8'-Trimethoxy-1,1',3'-trimethyl-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,2',4'(1*H*,3'*H*,10'*H*)-trione (118k)



The product was prepared according to the general procedure, starting from 0.18 g of 1,3-dimethylbarbituric acid, 0.211 g of 3,4,5-trimethoxyaniline, 0.186 g of 1-methylisatin, 0.015 g of iodine and 3.6 mL of ethanol.

Yield 0.275 g (52%), white solid, mp >320 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 3.01 (s, 3H, NCH_3-3'), 3.12 (s, 3H, MeO-6'), 3.22 (s, 3H, NCH_3-1), 3.55 (s, 3H, NCH_3-1'), 3.60 (s, 3H, MeO-7'), 3.83 (s, 3H, MeO-8'), 6.82-6.89 (m, 1H, H-5), 6.90 (d, 1H, ^3J = 7.37 Hz, H-4), 6.93 (s, 1H, H-9'), 6.94 (d, 1H, ^3J = 7.75 Hz, H-7), 7.16-7.23 (m, 1H, H-6), 9,19 (br s, 1H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 27.2 (NCH_3-1), 28.3 (NCH_3-3'), 31.1 (NCH_3-1'), 50.0 (C-5',3), 56.6 (MeO-8'), 60.4 (MeO-6'), 61.2 (MeO-7'), 86.6 (C-4a'), 97.2 (CH-9'), 107.9 (CH-7), 109.7, 122.3 (CH-5), 124.0 (CH-4), 128.4 (CH-6), 132.8, 137.3, 138.3, 145.4, 146.1, 151.2, 151.9, 153.8, 160.1, 179.7 (CO-2).

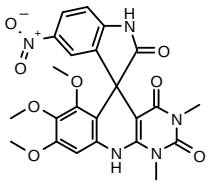
MS (GC, 70 eV): *m/z* (%) = 465 ($[M+H]^+$, 32), 464 ($[M]^+$, 100), 449 (17), 433 (12), 406 (31), 405 (89), 390 (18), 376 (12), 375 (30), 358 (25), 204 (16).

HRMS (EI): Calcd. for $C_{24}H_{24}N_4O_6$ $[M]^+$: 464.16904, found: 464.16820.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2945 (m), 1703 (s), 1678 (s), 1645 (s), 1633 (s), 1606 (s), 1537 (s), 1487 (s), 1470 (s), 1450 (s), 1435 (s), 1402 (s), 1379 (s), 1358 (s), 1304 (m), 1284 (m), 1269 (s), 1230 (s), 1200 (m), 1153 (m), 1126 (s), 1090 (s), 1061 (s), 1032 (m), 1020 (m), 997 (s), 976 (s), 933 (m), 920 (m), 872 (m), 851 (m), 827 (s), 791 (m), 777 (m), 764 (m), 750 (s), 704 (s), 681 (s), 662 (s), 638 (m), 592 (m), 563 (m), 542 (s), 528 (s).

6',7',8'-Trimethoxy-1',3'-dimethyl-5-nitro-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,2',4'(1*H*,3'*H*,10'*H*)-trione (118l)

The product was prepared according to the general procedure, starting from 0.3 g of 1,3-dimethylbarbituric acid, 0.352 g of 3,4,5-dimethoxyaniline, 0.369 g of 5-nitroisatin, 0.024 g of



iodine and 6 mL of ethanol.

Yield of the mixture of the both isomers: 0.636 g (67%). Yield of the pure major isomer obtained after recrystallization from TFA: 0.215 g (23%), yellowish solid, mp >320 °C.

^{1}H NMR (500.13 MHz, DMSO-d_6): δ = 3.03 (s, 3H, NCH_3-3'), 3.27 (s, 3H, MeO-6'), 3.56 (s, 3H, NCH_3-1'), 3.62 (s, 3H, MeO-7'), 3.85 (s, 3H, MeO-8'), 6.96 (s, 1H, H-9'), 6.99 (d, 1H, ^3J = 8.72 Hz, H-7), 7.73 (d, 1H, ^4J = 2.42 Hz, H-4), 8.12 (dd, 1H, ^3J = 8.72 Hz, ^4J = 2.42 Hz, H-6), 9.29 (br s, 1H, NH),), 11.05 (br s, 1H, NH-1).

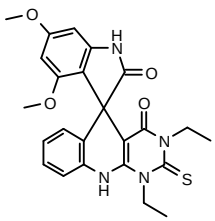
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 28.4 (NCH_3-3'), 31.2 (NCH_3-1'), 50.6 (C-5',3), 56.7 (MeO-8'), 60.4 (MeO-6'), 61.2 (MeO-7'), 85.7 (C-4a'), 97.3 (CH-9'), 108.5, 109.0 (CH_{Ar}), 119.6 (CH_{Ar}), 126.1 (CH_{Ar}), 133.0, 138.2, 139.1, 142.5, 146.6, 151.1, 151.2, 151.9, 154.3, 160.5, 182.0 (CO-2).

MS (EI, 70 eV): *m/z* (%) = 495 ([M]$^+$, 4.9), 494 (22), 493 (100), 467 (39), 450 (10), 434 (17), 421 (24), 420 (28), 406 (21), 360 (13), 44 (12).

HRMS (ESI): Calcd. for $C_{23}H_{22}N_5O_8$ $[M+H]^+$: 496.14629, found: 496.14622.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3294 (w), 2945 (w), 1786 (m), 1705 (m), 1693 (s), 1622 (s), 1591 (s), 1539 (s), 1516 (s), 1481 (s), 1454 (s), 1435 (s), 1406 (s), 1392 (s), 1367 (m), 1335 (s), 1296 (m), 1275 (m), 1228 (s), 1207 (s), 1157 (s), 1119 (s), 1092 (s), 1068 (s), 1034 (m), 997 (s), 982 (s), 939 (m), 918 (m), 839 (s), 818 (s), 791 (m), 775 (m), 766 (s), 756 (s), 739 (m), 687 (s), 656 (m), 625 (s), 555 (s), 530 (s).

1',3'-Diethyl-4,6-dimethoxy-2'-thioxo-2',3'-dihydro-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,4'(1*H*,10'*H*)-dione (119m)



The product was prepared according to the general procedure, starting from 0.2 g of 1,3-diethylthiobarbituric acid, 0.153 g of 3,5-dimethoxyaniline, 0.147 g of isatin, 0.016 g of iodine and 4 mL of ethanol.

Yield 0.376 g (81%), beige solid, mp >320 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.10 (t, 3H, ^3J = 6.80 Hz, $CH_{3(Et)}$), 1.36 (t, 3H, ^3J = 6.90 Hz, $CH_{3(Et)}$), 3.51 (s, 3H, MeO-4), 3.76 (s, 3H, MeO-6), 4.25-4.43 (m, 2H, NCH_2-3'), 4.50-5.40 (br m, 2H, NCH_2-1'), 6.05 (d, 1H, ^4J = 1.89 Hz, H-5), 6.13 (d, 1H, ^4J = 1.89 Hz, H-7), 6.72 (d, 1H, ^3J = 7.85 Hz, H-9'), 6.89-6.97 (m, 1H, H-7'), 7.16-7.24 (m, 1H, H-8'), 7.40 (d, 1H, ^3J = 8.22 Hz, H-6'), 9,38 (br s, 1H, NH-10'), 10.44 (br s, 1H, NH-1).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 12.5 ($CH_{3(Et)}$-3'), 13.3 ($CH_{3(Et)}$-1'), 43.6 (NCH_2-3'), 45.0 (NCH_2-1'), 51.0 (C-5',3), 56.2 (MeO-6), 56.5 (MeO-4), 89.8 (C-4a'), 90.2 (CH-7), 93.1 (CH-5), 117.5, 117.7 (CH_{Ar}), 122.7, 124.7 (CH_{Ar}), 126.6 (CH_{Ar}), 128.7 (CH_{Ar}), 136.4, 143.8, 146.3, 156.7,

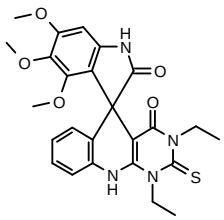
157.6, 161.7, 175.7 (CS), 181.3 (CO-2).

MS (GC, 70 eV): *m/z* (%) = 464 ([M]$^+$, 7.6), 463 (22), 462 (81), 461 (27), 435 (10), 434 (32), 433 (100), 429 (21), 403 (29), 402 (13), 401 (13), 375 (12), 374 (10), 364 (15), 346 (10), 343 (15), 333 (11), 332 (38), 60 (15), 46 (14).

HRMS (ESI): Calcd. for $C_{24}H_{25}N_4O_4S$ [M+H]$^+$: 465.15910, found: 465.15934.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3296 (m), 2970 (w), 2929 (w), 1699 (s), 1614 (s), 1589 (s), 1531 (s), 1504 (s), 1487 (s), 1456 (s), 1416 (s), 1394 (s), 1377 (s), 1360 (s), 1336 (s), 1308 (m), 1265 (s), 1254 (s), 1228 (s), 1209 (s), 1198 (s), 1144 (s), 1126 (s), 1111 (s), 1039 (s), 1009 (m), 993 (m), 949 (m), 935 (m), 914 (m), 864 (m), 816 (s), 795 (m), 773 (s), 743 (s), 712 (s), 694 (m), 683 (m), 667 (s), 642 (s), 621 (s), 536 (s).

1',3'-Diethyl-4,5,6-trimethoxy-2'-thioxo-2',3'-dihydro-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,4'(1*H*,10'*H*)-dione (119n)



The product was prepared according to the general procedure, starting from 0.2 g of 1,3-diethylthiobarbituric acid, 0.183 g of 3,4,5-dimethoxyaniline, 0.147 g of isatin, 0.016 g of iodine and 4 mL of ethanol.

Yield 0.262 g (53%) , white solid, mp 318-319 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.10 (t, 3H, ^3J = 6.80 Hz, $CH_{3(Et)}$), 1.38 (t, 3H, ^3J = 6.89 Hz, $CH_{3(Et)}$), 3.28 (s, 3H, MeO), 3.59 (s, 3H, MeO), 3.83 (s, 3H, MeO), 4.27-4.44 (m, 2H, NCH_2-3'), 4.50-5.50 (br m, 2H, NCH_2-1'), 6.38 (s, 1H, H-7), 6.74 (d, 1H, ^3J = 7.84 Hz, H-9'), 6.92-6.99 (m, 1H, H-7'), 7.19-7.27 (m, 1H, H-8'), 7.45 (d, 1H, ^3J = 8.22 Hz, H-6'), 9,42 (br s, 1H, NH-10'), 10.43 (br s, 1H, NH-1).

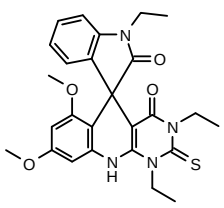
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 12.5 ($CH_{3(Et)}$-3'), 13.3 ($CH_{3(Et)}$-1'), 43.6 (NCH_2-3'), 45.2 (NCH_2-1'), 51.6 (C-5',3), 56.9 (MeO), 60.8 (MeO), 61.4 (MeO), 90.2 (C-4a'), 92.1 (CH-7), 118.0 (CH_{Ar}), 122.7, 123.0, 124.9 (CH_{Ar}), 126.7 (CH_{Ar}), 129.0 (CH_{Ar}), 136.1, 137.3, 138.2, 146.2, 150.2, 154.6, 157.7, 175.7 (CS), 181.1 (CO-2).

MS (GC, 70 eV): *m/z* (%) = 494 ([M]$^+$, 10), 493 (29), 492 (100), 491 (24), 464 (29), 463 (92), 459 (21), 450 (13), 433 (29), 432 (12), 373 (17), 362 (31), 60 (14), 29 (17).

HRMS (ESI): Calcd. for $C_{25}H_{27}N_4O_5S$ [M+H]$^+$: 495.16967, found: 495.16962.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3311 (m), 2931 (m), 1699 (s), 1622 (s), 1589 (s), 1533 (s), 1495 (s), 1479 (s), 1462 (s), 1416 (s), 1392 (s), 1360 (m), 1350 (s), 1325 (s), 1306 (m), 1288 (m), 1261 (s), 1255 (s), 1236 (s), 1194 (s), 1176 (m), 1138 (s), 1105 (s), 1068 (s), 1047 (s), 1039 (s), 995 (s), 972 (s), 957 (m), 924 (m), 856 (m), 810 (m), 793 (m), 781 (m), 766 (s), 744 (s), 710 (s), 694 (s), 671 (s), 644 (s), 611 (s), 534 (m).

1,1',3'-Triethyl-6',8'-dimethoxy-2'-thioxo-2',3'-dihydro-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,4'(1*H*,10'*H*)-dione (118o)



The product was prepared according to the general procedure, starting from 0.2 g of 1,3-diethylthiobarbituric acid, 0.153 g of 3,5-dimethoxyaniline, 0.175 g of 1-ethylisatin, 0.016 g of iodine and 4 mL of ethanol.

Yield 0.354 (72%), white solid, mp >320 °C.

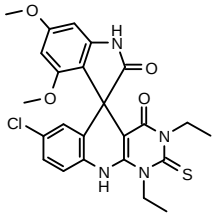
^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.03 (t, 3H, ^3J = 6.89 Hz, $CH_{3(Et)}$), 1.30 (t, 3H, ^3J = 7.18 Hz, $CH_{3(Et)}$-1), 1.38 (t, 3H, ^3J = 6.99 Hz, $CH_{3(Et)}$), 3.34 (s, 3H, MeO-6'), 3.64-3.88 (m, 2H, NCH_2-1), 3.79 (s, 3H, MeO-8'), 4.17-4.34 (m, 2H, NCH_2-3'), 4.40-5.40 (br m, 2H, NCH_2-1'), 6.16 (d, 1H, ^4J = 2.46 Hz, H-7'), 6.80 (d, 1H, ^4J = 2.46 Hz, H-9'), 6.83 (d, 1H, ^3J = 7.37 Hz, H-4), 6.89-6.95 (m, 1H, H-5, H-7), 7.14-7.21 (m, 1H, H-6), 9,20 (br s, 1H, NH).

MS (EI, 70 eV): *m/z* (%) = 493 ($[M+H]^+$, 17), 492 ($[M]^+$, 65), 464 (17), 459 (13), 433 (16), 362 (11), 346 (11), 129 (19), 101 (13), 87 (13), 85 (13), 84 (12), 78 (13), 73 (77), 71 (15), 69 (21), 63 (15), 61 (12), 60 (100), 57 (21), 55 (28), 45 (14), 44 (35), 43 (32), 41 (33).

HRMS (ESI): Calcd. for $C_{26}H_{29}N_4O_4S$ $[M+H]^+$: 493.19040, found: 493.19056.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2980 (m), 1784 (m), 1684 (s), 1639 (m), 1614 (s), 1603 (s), 1585 (s), 1539 (s), 1487 (s), 1464 (s), 1452 (s), 1431 (s), 1406 (s), 1373 (s), 1360 (s), 1319 (m), 1298 (m), 1282 (m), 1267 (s), 1254 (s), 1232 (s), 1200 (s), 1176 (m), 1157 (s), 1130 (s), 1109 (s), 1097 (s), 1057 (s), 1003 (m), 922 (m), 910 (m), 822 (s), 795 (m), 773 (s), 750 (s), 723 (m), 690 (s), 677 (s), 669 (m), 656 (m), 646 (m), 636 (m), 581 (m), 559 (m), 538 (s).

7'-Chloro-1',3'-diethyl-4,6-dimethoxy-2'-thioxo-2',3'-dihydro-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,4'(1*H*,10'*H*)-dione (119p)



The product was prepared according to the general procedure, starting from 0.2 g of 1,3-diethylthiobarbituric acid, 0.153 g of 3,5-dimethoxyaniline, 0.181 g of 5-chloroisatin, 0.016 g of iodine and 4 mL of ethanol.

Yield 0.337 (68%), white solid, mp >320 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.10 (t, 3H, ^3J = 6.89 Hz, $CH_{3(Et)}$), 1.36 (t, 3H, ^3J = 6.89 Hz, $CH_{3(Et)}$), 3.54 (s, 3H, MeO-4), 3.77 (s, 3H, MeO-6), 4.24-4.43 (m, 2H, NCH_2-3'), 4.50-5.50 (br m, 2H, NCH_2-1'), 6.09 (d, 1H, ^4J = 1.89 Hz, H-5), 6.15 (d, 1H, ^4J = 1.89 Hz, H-7), 6.63 (d, 1H, ^4J = 2.39 Hz, H-6'), 7.26 (dd, 1H, ^3J = 8.82 Hz, ^4J = 2.39 Hz, H-8'), 7.34 (d, 1H, ^3J = 8.82 Hz, H-9'), 9,53 (br s, 1H, NH-10'), 10.52 (br s, 1H, NH-1).

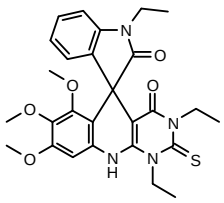
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 12.5 ($CH_{3(Et)}$-3'), 13.2 ($CH_{3(Et)}$-1'), 43.7 (NCH_2-3'), 45.1 (NCH_2-1'), 50.9 (C-5',3), 56.2 (MeO-6), 56.6 (MeO-4), 89.5 (C-4a'), 90.3 (CH-7), 93.2 (CH-5), 116.9, 119.7 (CH_{Ar}), 124.6, 125.7 (CH_{Ar}), 128.0, 128.9 (CH_{Ar}), 135.6, 143.6, 146.2, 156.8, 157.6, 162.0, 175.7 (CS), 180.9 (CO-2).

MS (GC, 70 eV): *m/z* (%) = 501 ($[M+H]^+$, ^{37}Cl, 7.8), 500 ($[M]^+$, ^{37}Cl, 36), 499 ($[M+H]^+$, ^{35}Cl, 24), 498 ($[M]^+$, ^{35}Cl, 95), 472 (20), 471 (29), 480 (49), 469 (47), 443 (16), 442 (13), 441 (32), 439 (13), 437 (14), 426 (11), 411 (18), 382 (13), 349 (10), 348 (41), 347 (19), 346 (100), 320 (24), 319 (15), 318 (66), 292 (11), 290 (34), 274 (11), 219 (19), 204 (11), 203 (11), 175 (11), 162 (12), 140 (10), 125 (18), 122 (11), 86 (20), 69 (14), 60 (14), 29 (22).

HRMS (ESI): Calcd. for $C_{24}H_{24}{}^{35}ClN_4O_4S$ $[M+H]^+$: 499.12013, found: 499.12035.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3190 (w), 2966 (w), 1705 (s), 1645 (m), 1622 (s), 1587 (s), 1527 (s), 1506 (s), 1481 (s), 1456 (s), 1444 (s), 1427 (s), 1387 (s), 1360 (m), 1338 (m), 1317 (m), 1290 (m), 1259 (s), 1252 (s), 1217 (s), 1198 (s), 1178 (m), 1147 (s), 1109 (s), 1066 (m), 1041 (m), 1009 (m), 991 (m), 964 (m), 945 (m), 872 (m), 827 (m), 812 (s), 771 (m), 744 (m), 690 (m), 669 (m), 638 (m), 625 (m), 552 (m).

1,1',3'-Triethyl-6',7',8'-trimethoxy-2'-thioxo-2',3'-dihydro-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,4'(1*H*,10'*H*)-dione (118q)



The product was prepared according to the general procedure, starting from 0.2 g of 1,3-diethylthiobarbituric acid, 0.183 g of 3,4,5-dimethoxyaniline, 0.175 g of 1-ethylisatin, 0.016 g of iodine and 4 mL of ethanol.

Yield 0.245 g (47%), white solid, mp >320 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.04 (t, 3H, ^3J = 6.89 Hz, $CH_{3(Et)}$), 1.30 (t, 3H, ^3J = 7.18 Hz, $CH_{3(Et)}$-1), 1.38 (t, 3H, ^3J = 6.90 Hz, $CH_{3(Et)}$), 3.04 (s, 3H, MeO-6'), 3.61 (s, 3H, MeO-7'), 3.80 (q, 2H, ^3J = 7.18 Hz, NCH_2-1), 3.85 (s, 3H, MeO-8'), 4.17-4.35 (m, 2H, NCH_2-3'), 4.40-5.40 (br m, 2H, NCH_2-1'), 6.83-6.91 (m, 1H, H-5), 6.96-7.02 (m, 2H, H-4, H-7), 7.05 (s, 1H, H-9'), 7.17-7.25 (m, 1H, H-6), 9,19 (br s, 1H, NH).

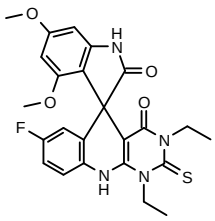
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 12.5 ($CH_{3(Et)}$-3'), 13.0 ($CH_{3(Et)}$-1), 13.3 ($CH_{3(Et)}$-1'), 35.3 (NCH_2-1), 43.6 (NCH_2-3'), 45.4 (NCH_2-1'), 50.2 (C-5',3), 56.7 (MeO-8'), 60.2 (MeO-6'), 61.1 (MeO-7'), 91.3 (C-4a'), 97.5 (CH-9'), 108.0 (CH-7), 109.4, 122.2 (CH-5), 124.3 (CH-4), 128.6 (CH-6), 132.5, 136.9, 138.6, 144.7, 145.5, 151.9, 153.9, 157.3 (CO-4'), 175.6 (CS), 178.5 (CO-2).

MS (EI, 70 eV): *m/z* (%) = 523 ($[M+H]^+$, 31), 522 ($[M]^+$, 100), 494 (21), 493 (17), 489 (26), 479 (14), 465 (11), 464 (12), 463 (35), 450 (11), 402 (12), 392 (17), 391 (11), 376 (14), 364 (15).

HRMS (ESI): Calcd. for $C_{27}H_{31}N_4O_5S$ $[M+H]^+$: 523.20097, found: 523.20090.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2972 (m), 2933 (m), 1678 (s), 1660 (s), 1622 (s), 1614 (s), 1593 (s), 1537 (s), 1489 (s), 1464 (s), 1423 (s), 1387 (s), 1371 (s), 1358 (s), 1317 (m), 1269 (s), 1244 (s), 1200 (s), 1176 (m), 1136 (s), 1109 (s), 1097 (s), 1065 (s), 1030 (m), 1001 (s), 964 (m), 928 (s), 874 (w), 827 (s), 795 (m), 775 (m), 754 (s), 744 (s), 702 (m), 689 (m), 679 (m), 662 (m), 648 (m), 621 (m), 598 (m), 559 (m), 536 (m).

1',3'-Diethyl-7'-fluoro-4,6-dimethoxy-2'-thioxo-2',3'-dihydro-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,4'(1*H*,10'*H*)-dione (119r)



The product was prepared according to the general procedure, starting from 0.2 g of 1,3-diethylthiobarbituric acid, 0.153 g of 3,5-dimethoxyaniline, 0.165 g of 5-fluoroisatin, 0.016 g of iodine and 4 mL of ethanol.

Yield 0.286 g (59%), white solid, mp >320 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.10 (t, 3H, ^{3}J = 6.90 Hz, $CH_{3(Et)}$), 1.36 (t, 3H, ^{3}J = 6.89 Hz, $CH_{3(Et)}$), 3.53 (s, 3H, MeO-4), 3.77 (s, 3H, MeO-6), 4.24-4.43 (m, 2H, NCH_2-3'), 4.50-5.50 (br m, 2H, NCH_2-1'), 6.08 (d, 1H, ^{4}J = 1.99 Hz, H-5), 6.15 (d, 1H, ^{4}J = 1.99 Hz, H-7), 6.42 (dd, 1H, $^{3}J_{(H-F)}$ = 9.35 Hz, ^{4}J = 2.93 Hz, H-6'), 7.06-7.15 (m, 1H, H-8'), 7.46 (dd, 1H, ^{3}J = 9.07 Hz, $^{4}J_{(H-F)}$ = 5.10 Hz, H-9'), 9,45 (br s, 1H, NH-10'), 10.49 (br s, 1H, NH-1).

^{13}C NMR (125.77 MHz, DMSO-d_6): δ = 12.5 ($CH_{3(Et)}$-3'), 13.2 ($CH_{3(Et)}$-1'), 43.6 (NCH_2-3'), 45.0 (NCH_2-1'), 51.2 (C-5',3), 56.2 (MeO-6), 56.5 (MeO-4), 88.9 (C-4a'), 90.3 (CH-7), 93.2 (CH-5), 112.3 (d, $^{2}J_{(C-F)}$ = 23.2 Hz, CH_{Ar}), 116.1 (d, $^{2}J_{(C-F)}$ = 22.8 Hz, CH_{Ar}), 116.8, 119.5 (d, $^{3}J_{(C-F)}$ = 7.9 Hz, CH-9'), 124.4 (d, $^{3}J_{(C-F)}$ = 7.1 Hz, C-5a'), 133.1 (d, $^{4}J_{(C-F)}$ = 1.6 Hz, C-9a'), 143.6, 146.3, 156.8, 157.6, 159.3 (d, $^{1}J_{(C-F)}$ = 239.5 Hz, CH-7'), 161.9 (CS), 175.7 (CS), 180.8 (CO-2).

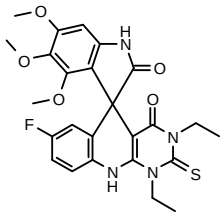
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –119.6 (s, F-7').

MS (GC, 70 eV): *m/z* (%) = 483 ($[M+H]^+$, 19), 482 ($[M]^+$, 76), 454 (38), 453 (24), 426 (12), 425 (26), 421 (11), 366 (10), 331 (18), 330 (100), 303 (12), 302 (65), 274 (34), 203 (18), 187 (14), 86 (11), 29 (19).

HRMS (ESI): Calcd. for $C_{24}H_{24}FN_4O_4S$ $[M+H]^+$: 483.14968, found: 483.14980.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3294 (m), 2972 (w), 2929 (w), 2839 (w), 1703 (s), 1622 (s), 1597 (s), 1537 (s), 1497 (s), 1487 (s), 1464 (s), 1441 (s), 1425 (s), 1408 (m), 1392 (s), 1379 (s), 1362 (s), 1336 (m), 1323 (s), 1288 (m), 1265 (s), 1254 (s), 1238 (s), 1209 (s), 1196 (s), 1180 (m), 1144 (s), 1111 (s), 1041 (m), 1012 (m), 984 (m), 945 (s), 918 (m), 862 (s), 833 (m), 814 (s), 797 (m), 787 (m), 771 (s), 743 (s), 716 (m), 698 (m), 683 (m), 667 (s), 644 (s), 627 (s), 586 (m), 569 (m), 555 (m).

1',3'-Diethyl-7'-fluoro-4,5,6-trimethoxy-2'-thioxo-2',3'-dihydro-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,4'(1*H*,10'*H*)-dione (119s)



The product was prepared according to the general procedure, starting from 0.2 g of 1,3-diethylthiobarbituric acid, 0.183 g of 3,5-trimethoxyaniline, 0.165 g of 5-fluoroisatin, 0.016 g of iodine and 4 mL of ethanol.

Yield 0.182 g (36%), white solid, mp 310-312 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.09 (t, 3H, ^{3}J = 6.99 Hz, $CH_{3(Et)}$), 1.38 (t, 3H, ^{3}J = 6.90 Hz, $CH_{3(Et)}$), 3.33 (s, 3H, MeO), 3.61 (s, 3H, MeO), 3.84 (s, 3H, MeO), 4.26-4.43 (m, 2H, NCH_2-3'), 4.50-5.50 (br m, 2H, NCH_2-1'), 6.40 (s, 1H, H-7), 6.44 (dd, 1H, $^{3}J_{(H-F)}$ = 9.45 Hz, ^{4}J = 2.84 Hz, H-6'), 7.10-7.18 (m, 1H, H-8'), 7.46 (dd, 1H, ^{3}J = 8.98 Hz, $^{4}J_{(H-F)}$ = 5.20 Hz, H-9'), 9,49 (br s, 1H, NH-10'), 10.48 (br s, 1H, NH-1).

^{13}C NMR (125.77 MHz, DMSO-d_6): δ = 12.5 ($CH_{3(Et)}$-3'), 13.3 ($CH_{3(Et)}$-1'), 43.6 (NCH_2-3'), 45.2 (NCH_2-1'), 51.9 (C-5',3), 56.9 (MeO), 60.9 (MeO), 61.4 (MeO), 89.2 (C-4a'), 92.2 (CH-7), 112.4 (d, $^{2}J_{(C-F)}$ = 23.42 Hz, CH_{Ar}), 116.3 (d, $^{2}J_{(C-F)}$ = 22.7 Hz, CH_{Ar}), 119.9 (d, $^{3}J_{(C-F)}$ = 8.0 Hz, CH-9'), 122.2, 124.4 (d, $^{3}J_{(C-F)}$ = 7.1 Hz, C-5a'), 132.8 (d, $^{4}J_{(C-F)}$ = 1.5 Hz, C-9a'), 137.3, 138.0, 146.2, 150.2, 154.9, 157.7, 159.3 (d, $^{1}J_{(C-F)}$ = 240.1 Hz, C-7'), 175.8 (CS), 180.6 (CO-2).

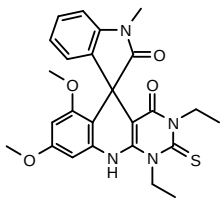
^{19}F NMR (282.38 MHz, $CDCl_3$): δ = –119.2 (s, F-7').

MS (GC, 70 eV): *m/z* (%) = 513 ($[M+H]^+$, 17), 512 ($[M]^+$, 71), 331 (21), 330 (100), 303 (12), 302 (43), 301 (13), 274 (25), 273 (10), 203 (14), 182 (23), 168 (11), 29 (13).

HRMS (ESI): Calcd. for $C_{25}H_{26}FN_4O_5S$ $[M+H]^+$: 513.16025, found: 513.16026.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3313 (m), 2978 (m), 2933 (m), 1699 (s), 1643 (s), 1622 (s), 1597 (s), 1539 (s), 1497 (s), 1475 (s), 1444 (s), 1435 (s), 1394 (s), 1362 (s), 1327 (s), 1288 (s), 1267 (s), 1254 (s), 1232 (s), 1211 (s), 1196 (s), 1178 (s), 1165 (s), 1130 (s), 1109 (s), 1095 (s), 1066 (s), 1041 (s), 1012 (m), 993 (s), 974 (s), 920 (s), 885 (m), 868 (s), 824 (s), 814 (s), 791 (s), 773 (m), 754 (m), 735 (m), 712 (s), 694 (s), 671 (s), 656 (s), 638 (s), 588 (s), 569 (s).

1',3'-Diethyl-6',8'-dimethoxy-1-methyl-2'-thioxo-2',3'-dihydro-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,4'(1*H*,10'*H*)-dione (118t)



The product was prepared according to the general procedure, starting from 0.2 g of 1,3-diethylthiobarbituric acid, 0.153 g of 3,5-dimethoxyaniline, 0.161 g of 1-methylisatin, 0.016 g of iodine and 4 mL of ethanol.

Yield 0.269 g (56%), white solid, mp >320 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.04 (t, 3H, ^{3}J = 6.89 Hz, $CH_{3(Et)}$), 1.38 (t, 3H, ^{3}J = 6.90 Hz, $CH_{3(Et)}$), 3.22 (s, 3H, NCH_3-1), 3.38 (s, 3H, MeO-6'), 3.78 (s, 3H, MeO-8'), 4.18-4.34 (m, 2H, NCH_2-3'), 4.50-5.40 (br m, 2H, NCH_2-1'), 6.15 (d, 1H, ^{4}J = 2.46 Hz, H-7'), 6.79 (d, 1H, ^{4}J = 2.46 Hz, H-9'), 6.80-6.88 (m, 1H, H-5), 6.88-6.94 (m, 2H, H-4, H-7), 7.15-7.22 (m, 1H, H-6), 9,22 (br s, 1H, NH).

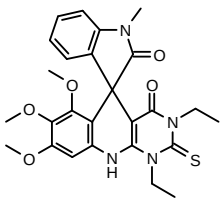
^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 12.5 ($CH_{3(Et)}$-3'), 13.4 ($CH_{3(Et)}$-1'), 27.2 (NCH_3-1), 43.7 (NCH_2-3'), 45.4 (NCH_2-1'), 49.6 (C-5',3), 56.2 (MeO-8'), 56.9 (MeO-6'), 92.0 (C-4a'), 95.2 (CH-9'), 96.0 (CH-7'), 105.0, 107.5 (CH-7), 122.3 (CH-5), 123.9 (CH-4), 128.5 (CH-6), 136.1, 137.8, 145.5, 145.8, 157.4, 159.0, 160.7, 175.6 (CS), 179.3 (CO-2).

MS (EI, 70 eV): *m/z* (%) = 479 ($[M+H]^+$, 26), 478 ($[M]^+$, 97), 450 (11), 445 (21), 420 (22), 419 (75), 391 (15), 378 (16), 348 (21), 332 (115), 320 (18), 292 (24), 291 (15), 78 (20), 73 (14), 69 (16), 63 (22), 60 (18), 45 (17), 44 (100), 43 (19), 42 (10).

HRMS (ESI): Calcd. for $C_{27}H_{31}N_4O_5S$ $[M+H]^+$: 479.17475, found: 479.17422.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3267 (w), 2983 (w), 2679 (w), 1782 (m), 1687 (s), 1641 (m), 1614 (s), 1605 (s), 1585 (s), 1537 (s), 1489 (s), 1454 (s), 1433 (s), 1408 (s), 1390 (s), 1373 (s), 1358 (s), 1321 (m), 1300 (m), 1267 (m), 1252 (s), 1236 (m), 1201 (s), 1153 (s), 1132 (s), 1109 (s), 1084 (s), 1057 (s), 1005 (s), 922 (s), 910 (m), 822 (s), 812 (s), 793 (m), 773 (s), 756 (s), 725 (m), 690 (s), 681 (s), 667 (s), 656 (s), 646 (s), 636 (s), 579 (s), 538 (s).

1',3'-Diethyl-6',7',8'-trimethoxy-1-methyl-2'-thioxo-2',3'-dihydro-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,4'(1*H*,10'*H*)-dione (118u)



The product was prepared according to the general procedure, starting from 0.2 g of 1,3-diethylthiobarbituric acid, 0.183 g of 3,4,5-trimethoxyaniline, 0.161 g of 1-methylisatin, 0.016 g of iodine and 4 mL of ethanol.

Yield 0.232 g (47%), white solid, mp >320 °C.

^{1}H NMR (500.13 MHz, DMSO-d_6): δ = 1.04 (t, 3H, ^{3}J = 6.94 Hz, $CH_{3(Et)}$-3'), 1.38 (t, 3H, ^{3}J = 6.94 Hz, $CH_{3(Et)}$-1'), 3.14 (s, 3H, MeO-6'), 3.24 (s, 3H, NCH_3-1), 3.61 (s, 3H, MeO-7'), 3.85 (s, 3H, MeO-8'), 4.19-4.33 (m, 2H, NCH_2-3'), 4.50-5.40 (br m, 2H, NCH_2-1'), 6.85-6.90 (m, 1H, H-5), 6.95 (d, 1H, H-4), 6.97 (d, 1H, H-7), 7.05 (s, 1H, H-9'), 7.19-7.24 (m, 1H, H-6), 9,22 (br s, 1H, NH).

^{13}C NMR (125.77 MHz, DMSO-d_6): δ = 12.4 ($CH_{3(Et)}$-3'), 13.3 ($CH_{3(Et)}$-1'), 27.3 (NCH_3-1), 43.6 (NCH_2-3'), 45.4 (NCH_2-1'), 50.0 (C-5',3), 56.7 (MeO-8'), 60.4 (MeO-6'), 61.2 (MeO-7'), 91.3 (C-4a'), 97.5 (CH-9'), 108.0 (CH-7), 109.4 (C-5a'), 122.4 (CH-5), 124.1 (CH-4), 128.7 (CH-6), 132.4 (C-9a'), 136.6 (C-3a), 138.6 (C-7'), 145.4, 145.6, 151.7 (C-6'), 153.9 (C-8'), 157.3 (CO-4'),

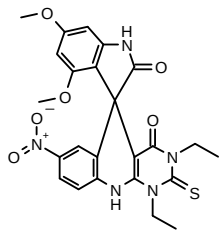
175.6 (CS), 179.2 (CO-2).

MS (EI, 70 eV): *m/z* (%) = 509 ([M+H]$^+$, 25), 508 ([M]$^+$, 100), 480 (11), 475 (22), 450 (13), 449 (43), 378 (15), 350 (15), 322 (15).

HRMS (ESI): Calcd. for $C_{26}H_{29}N_4O_5S$ [M+H]$^+$: 509.18532, found: 509.18526.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3248 (w), 3196 (w), 2933 (w), 1680 (s), 1651 (s), 1626 (s), 1606 (s), 1593 (s), 1537 (s), 1493 (s), 1471 (s), 1456 (s), 1423 (s), 1387 (s), 1358 (s), 1338 (s), 1315 (m), 1269 (s), 1240 (s), 1203 (s), 1186 (m), 1174 (m), 1132 (s), 1105 (s), 1088 (s), 1066 (s), 1028 (s), 997 (s), 957 (m), 926 (s), 912 (m), 878 (m), 852 (m), 825 (s), 791 (m), 777 (m), 768 (m), 756 (s), 744 (s), 702 (m), 679 (s), 665 (m), 640 (s), 621 (m), 596 (m), 575 (m), 557 (m), 534 (m).

1',3'-Diethyl-4,6-dimethoxy-7'-nitro-2'-thioxo-2',3'-dihydro-1'*H*-spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,4'(1*H*,10'*H*)-dione (119v)



The product was prepared according to the general procedure, starting from 0.2 g of 1,3-diethylthiobarbituric acid, 0.153 g of 3,5-dimethoxyaniline, 0.192 g of 5-nitroisatin, 0.016 g of iodine and 4 mL of ethanol.

Yield of the mixture of the both isomers: 0.32 g (63%). Yield of the pure major isomer obtained after recrystallization from TFA/EtOH: 0.098 g (19%), yellow solid, mp >320 °C.

^{1}H NMR (500.13 MHz, DMSO-d_6): δ = 1.12 (t, 3H, ^3J = 6.94 Hz, $CH_{3(Et)}$), 1.38 (t, 3H, ^3J = 7.09 Hz, $CH_{3(Et)}$), 3.54 (s, 3H, MeO-4), 3.78 (s, 3H, MeO-6), 4.27-4.43 (m, 2H, NCH_2-3'), 4.50-5.50 (br m, 2H, NCH_2-1'), 6.10 (d, 1H, ^4J = 1.89 Hz, H-5), 6.20 (d, 1H, ^4J = 1.89 Hz, H-7), 7.53 (d, 1H, ^4J = 2.63 Hz, H-6'), 7.67 (d, 1H, ^3J = 8.93 Hz, H-9'), 8.14 (dd, 1H, ^3J = 8.93 Hz, ^4J = 2.63 Hz, H-8'), 9,98 (br s, 1H, NH-10'), 10.67 (br s, 1H, NH-1).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 12.4 ($CH_{3(Et)}$-3'), 13.4 ($CH_{3(Et)}$-1'), 43.8 (NCH_2-3'), 45.4 (NCH_2-1'), 50.7 (C-5',3), 56.2 (MeO-6), 56.6 (MeO-4), 90.4 (CH-7), 90.5 (C-4a'), 93.3 (CH-5), 117.2, 118.6 (CH_{Ar}), 122.2 (CH_{Ar}), 123.5, 124.9 (CH_{Ar}), 142.4, 143.4, 143.7, 145.9, 156.9, 157.6, 162.2, 175.8 (CS), 180.6 (CO-2).

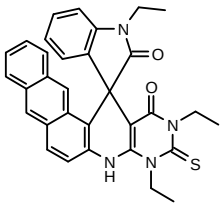
MS (EI, 70 eV): *m/z* (%) = 509 ([M]$^+$, 18), 508 (30), 507 (100), 506 (31), 491 (11), 481 (11), 480 (16), 479 (28), 478 (73), 474 (23), 449 (12), 448 (33), 447 (19), 409 (13), 377 (21).

HRMS (ESI): Calcd. for $C_{24}H_{24}N_5O_6S$ [M+H]$^+$: 510.14418, found: 510.14363.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3400 (w), 3203 (w), 2972 (w), 2935 (w), 1716 (m), 1703 (m), 1651 (s), 1633 (s), 1622 (s), 1591 (m), 1547 (s), 1506 (s), 1485 (s), 1446 (s), 1429 (s), 1392 (s), 1363 (m), 1329 (s), 1257 (s), 1217 (s), 1198 (s), 1171 (m), 1151 (s), 1107 (s), 1066 (m), 1041 (m), 1012 (m), 974 (m), 941 (m), 922 (m), 897 (m), 879 (m), 839 (m), 831 (m), 814 (s), 800 (m), 771 (m), 743 (s),

687 (m), 669 (s), 638 (s), 623 (m), 606 (m), 563 (m), 538 (s).

1,2',4'-Triethyl-3'-thioxo-3',4'-dihydro-2'*H*-spiro[indole-3,14'-naphtho[2,3-*f*]pyrimido[4,5-*b*]quinoline]-1',2(1*H*,5'*H*)-dione (118w)



The product was prepared according to the general procedure, starting from 0.2 g of 1,3-diethylthiobarbituric acid, 0.193 g of 2-anthracenamine, 0.175 g of 1-ethylisatin, 0.016 g of iodine and 4 mL of ethanol.

Recrystallized from TFA. Yield 0.388 g (73%), yellow solid, mp >320 °C.

^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.93 (t, 3H, ^{3}J = 6.89 Hz, $CH_{3(Et)}$), 1.33 (t, 3H, ^{3}J = 6.90 Hz, $CH_{3(Et)}$), 1.63 (t, 3H, ^{3}J = 7.27 Hz, $CH_{3(Et)}$), 2.55-3.00 (br m, 1H, NCH_2-4'a), 3.10-3.5 (br m, 1H, NCH_2-4'b), 3.99-4.14 (m, 1H, NCH_2), 4.25-4.60 (m, 3H, NCH_2), 6.90-6.97 (m, 1H, CH_{Ar}), 7.06 (d, 1H, ^{3}J = 7.46 Hz, CH_{Ar}), 7.21 (d, 1H, ^{3}J = 7.74 Hz, CH_{Ar}), 7.25-7.50 (m, 5H, CH_{Ar}), 7.01 (s, 1H, CH_{Ar}), 7.92 (d, 1H, ^{3}J = 7.27 Hz, CH_{Ar}), 8.23 (s, 1H, CH_{Ar}), 9.17 (NH-5').

^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 11.8 (CH_3), 12.3 (CH_3), 13.0 (CH_3), 36.3 (NCH_2-1), 43.5 (NCH_2-4'), 44.2 (NCH_2-2'), 54.0 (C-14',3), 92.3 (C-14a'), 108.4 (CH-7), 109.2, 118.2 (CH_{Ar}), 121.4 (CH_{Ar}), 124.3 (CH_{Ar}), 125.0 (CH_{Ar}), 125.8 (CH_{Ar}), 126.5 (CH_{Ar}), 128.1 (CH_{Ar}), 128.4 (CH_{Ar}), 129.2 (CH_{Ar}), 129.2 (CH_{Ar}), 129.2, 129.6, 130.3, 130.9 (CH_{Ar}), 132.7, 134.6, 135.9, 144.0, 144.3, 158.3, 174.9 (CS), 180.4 (CO-2).

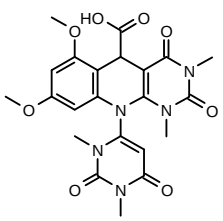
MS (EI, 70 eV): *m/z* (%) = 533 ($[M+H]^+$, 33), 532 ($[M]^+$, 100), 530 (22), 516 (10), 504 (21), 503 (13), 499 (15), 489 (26), 475 (10), 473 (12), 472 (13), 461 (11), 402 (17), 386 (19), 374 (20), 346 (10), 345 (12), 344 (12), 326 (10), 318 (16), 316 (11), 315 (10).

HRMS (ESI): Calcd. for $C_{32}H_{27}N_4O_2S$ $[M-H]^-$: 531.18602, found: 531.18696.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3252 (w), 2968 (m), 1790 (m), 1682 (s), 1659 (s), 1651 (s), 1608 (s), 1593 (s), 1574 (s), 1552 (m), 1520 (s), 1479 (s), 1464 (s), 1431 (s), 1417 (s), 1396 (s), 1371 (s), 1362 (s), 1350 (s), 1306 (m), 1269 (s), 1250 (s), 1232 (s), 1207 (s), 1169 (s), 1155 (s), 1132 (s), 1111 (s), 1092 (s), 1053 (m), 1007 (m), 959 (m), 941 (m), 924 (m), 883 (s), 858 (s), 797 (m), 777 (m), 754 (s), 737 (s), 692 (s), 681 (s), 667 (m), 652 (m), 633 (m), 621 (m), 592 (s), 538 (m).

4.2.18 Synthesis of 5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones via Hantzsch-like reaction

10-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-6,8-dimethoxy-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,10-hexahydropyrimido[4,5-*b*]quinoline-5-carboxylic acid (123)



Into a 25-mL flask were placed 1,3-dimethylbarbituric acid (0.6 g, 3.84 mmol, 2 eq), chloral hydrate (0.35 g, 2.11 mmol, 1.1 eq), 3,5-dimethylaniline (0.353 g, 2.31 mmol, 1.2 eq) and 6 ml of ethanol. After that 0.024 g of iodine (0.096 mmol, 0.05 eq) was added and the mixture was stirred at r.t. overnight. After 5 days the formed precipitate was filtered off, washed with ethanol and dried in a high vacuum to give 0.155 g of pinkish solid.

Yield 17%, white solid, mp 302-304 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.88 (s, 3H, NCH_3), 3.22 (s, 3H, N-CH_3), 3.29 (s, 3H, N-CH_3), 3.31 (s, 3H, N-CH_3), 3.66 (s, 3H, MeO), 3.79 (s, 3H, MeO), 4.99 (s, 1H, H-5'), 5.60 (s, 1H, H-5), 6.34 (d, 1H, ^4J = 1.89 Hz, H-7), 6.94 (d, 1H, ^4J = 1.89 Hz, H-9), 13.00 (br s, 1H, COOH).

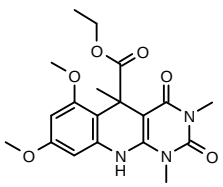
MS (EI, 70 eV): *m/z* (%) = 486 ($[M+H]^+$, 11), 485 ($[M]^+$, 47), 397 (24), 331 (39), 330 (100), 156 (10), 78 (11), 63 (12), 42 (10).

HRMS (ESI): Calcd. for $C_{22}H_{24}N_5O_8$ $[M+H]^+$: 486.16194, found: 486.16123.

Anal. Calcd for $C_{22}H_{23}N_5O_8$: C, 54.43; H, 4.78; N, 14.43. Found: C, 52.76; H, 4.88; N, 13.68.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3186 (w), 2962 (w), 2843 (w), 1699 (s), 1672 (s), 1622 (s), 1614 (s), 1545 (s), 1504 (s), 1444 (s), 1417 (s), 1379 (s), 1363 (s), 1336 (s), 1286 (s), 1267 (s), 1230 (m), 1207 (s), 1169 (m), 1140 (s), 1122 (s), 1095 (s), 1047 (s), 1024 (s), 964 (m), 943 (m), 852 (m), 839 (m), 812 (s), 795 (s), 783 (s), 756 (s), 727 (s), 704 (m), 694 (m), 671 (m), 662 (s), 644 (m), 600 (m), 552 (m).

Ethyl 6,8-dimethoxy-1,3,5-trimethyl-2,4-dioxo-1,2,3,4,5,10-hexahydropyrimido[4,5-*b*]quinoline-5-carboxylate (125)



Into a 25-mL flask were placed barbituric acid (0.3 g, 1.92 mmol, 1 eq), ethyl pyruvate (0.669 g, 5.76 mmol, 3 eq), aromatic amine (0.294 g, 1.92 mmol, 1 eq) and 6 ml of ethanol. After that 0.024 g of iodine (0.096 mmol, 0.05 eq) was added and the mixture was stirred at r.t. overnight. The next day formed precipitate was filtered off, washed with ethanol and dried in a high vacuum. The product should be stored in hermetic package at low temperature preferably in presence of drying

agent ($CaCl_2$, etc.).

Yield 0.187 g (25%), white solid, mp 248-249 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.18 (t, 3H, ^3J = 7.18 Hz, Et), 1.47 (s, 3H, CH_3-5), 3.15 (s, 3H, NCH_3-3), 3.50 (s, 3H, NCH_3-1), 3.70 (s, 3H, MeO), 3.78 (s, 3H, MeO), 4.05 (q, 2H, ^3J = 7.18 Hz, Et), 6.25 (d, 1H, ^4J = 2.37 Hz, H-7), 6.55 (d, 1H, ^4J = 2.37 Hz, H-9), 8.99 (br s, 1H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 15.0 ($CH_{3(Et)}$), 25.8 (CH_3-5), 28.4 (N-CH_3), 30.9 (N-CH_3), 44.4, 56.1 (MeO), 56.3 (MeO), 60.5 ($CH_{2(Et)}$), 90.1 (C-4a), 94.7 (CH_{Ar}), 95.1 (CH_{Ar}), 108.2, 137.2, 145.3, 151.3, 158.8, 160.2, 160.9, 175.1.

MS (EI, 70 eV): *m/z* (%) = 389 ([M]$^+$, 23), 374 (13), 328 (20), 318 (60), 317 (100), 316 (80), 315 (72), 302 (15), 301 (56), 300 (67), 287 (23), 286 (26), 260 (21), 259 (89), 258 (12), 216 (11), 215 (14), 206 (61), 205 (13), 203 (40), 202 (50), 201 (25), 189 (29), 188 (10), 187 (25), 186 (15), 174 (12), 173 (20), 172 (17), 171 (11), 158 (35), 156 (10), 146 (15), 130 (10), 122 (15), 42 (15).

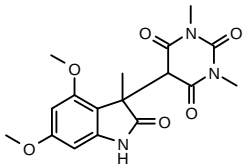
HRMS (ESI): Calcd. for $C_{19}H_{24}N_3O_6$ [M+H]$^+$: 390.16596, found: 390.16679.

Anal. Calcd for $C_{19}H_{23}N_3O_6$: C, 58.60; H, 5.95; N, 10.79. Found: C, 56.37; H, 5.58; N, 11.15.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3190 (w), 2945 (w), 1745 (w), 1699 (s), 1660 (s), 1633 (s), 1539 (s), 1495 (s), 1470 (s), 1441 (s), 1423 (s), 1373 (s), 1342 (s), 1304 (m), 1290 (s), 1271 (s), 1257 (s), 1234 (m), 1221 (s), 1196 (m), 1186 (m), 1176 (m), 1146 (s), 1122 (s), 1099 (s), 1022 (m), 986 (s), 947 (m), 912 (m), 870 (m), 814 (s), 787 (m), 771 (s), 760 (s), 750 (s), 727 (m), 694 (m), 646 (m), 635 (m), 571 (m), 554 (m), 538 (m).

4.2.19 Formation of 5-(4,6-dimethoxy-3-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione

5-(4,6-Dimethoxy-3-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (126)



This substance was formed from compound **125**, during the storage at r.t. in untight package for 6 month.

Yield 100%, white solid, mp 243-244 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.33 (s, 3H, CH_3), 2.76 (s, 3H, N-CH_3), 3.22 (s, 3H, N-CH_3), 3.66 (s, 3H, MeO), 3.76 (s, 3H, MeO), 3.80 (s, 1H, H-5), 6.05 (d, 1H, ^4J = 2.08 Hz, H-5'), 6.14 (d, 1H, ^4J = 2.08 Hz, H-7'), 10.53 (br s, 1H, NH).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 21.1 (CH_3), 28.5 (N-CH_3), 29.0 (N-CH_3), 51.5, 54.4 (CH-5), 56.3 (MeO), 56.7 (MeO), 90.3 (CH_{Ar}), 92.3 (CH_{Ar}), 108.9, 144.6, 152.6, 157.3, 162.4,

167.2, 167.7, 180.3.

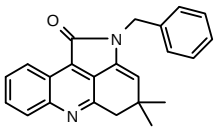
MS (EI, 70 eV): *m/z* (%) = 361 ([M]$^+$, 15), 316 (13), 207 (36), 206 (100), 205 (38), 176 (17), 156 (21), 42 (14).

HRMS (EI): Calcd. for $C_{17}H_{18}N_3O_6$ [M−H]$^-$: 360.11956, found: 360.12922.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3192 (w), 2943 (w), 1745 (w), 1699 (s), 1682 (s), 1660 (s), 1633 (s), 1608 (s), 1539 (m), 1510 (s), 1495 (m), 1470 (s), 1454 (s), 1435 (s), 1423 (s), 1373 (s), 1342 (s), 1325 (m), 1304 (m), 1290 (s), 1269 (s), 1221 (s), 1196 (m), 1186 (s), 1176 (m), 1146 (s), 1120 (s), 1097 (s), 1028 (s), 986 (s), 947 (m), 912 (m), 870 (m), 816 (s), 787 (m), 771 (m), 760 (s), 750 (s), 727 (s), 692 (s), 671 (m), 646 (s), 635 (s), 615 (m), 600 (m), 571 (m).

4.2.20 Synthesis of 2-benzyl-4,4-dimethyl-4,5-dihydropyrrolo[2,3,4-*kl*]acridin-1(2*H*)-one

2-Benzyl-4,4-dimethyl-4,5-dihydropyrrolo[2,3,4-*kl*]acridin-1(2*H*)-one (128)



Into a 25-mL flask were placed 0.188 g of isatin (0.128 mmol, 1 eq), 0.293 g of 3-(benzylamino)-5,5-dimethylcyclohex-2-en-1-one and 6 ml of ethanol. After that 0.016 g of iodine (0.064 mmol, 0.05 eq) was added and the mixture was stirred at r.t. overnight. The next day the solvent was evaporated and the residue purified with short path column chromatography using chloroform as eluent.

Yield 0.187 g (43%), brownish solid, mp 136-138 °C.

^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 1.26 (s, 3H, CH_3), 3.13 (s, 2H, H-5), 5.01 (s, 2H, $CH_{2(Bn)}$), 5.43 (s, 1H, H-3), 7.23-7.36 (m, 5H, Ph), 7.60-7.67 (m, 1H, CH_{Ar}), 7.69-7.76 (m, 1H, CH_{Ar}), 8.14 (d, 1H, ^3J = 8.41 Hz, CH_{Ar}), 7.80 (d, 1H, ^3J = 8.12 Hz, CH_{Ar}).

^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 31.2 (CH_3), 37.4, 44.1 (CH_2), 44.5 (CH_2), 118.0 (CH-3), 122.9, 124.5 (CH_{Ar}), 125.8, 126.9, 127.7 (CH_{Ar}), 127.9 (CH_{Ar}), 127.9 (CH_{Ar}), 129.0 (CH_{Ar}), 129.7 (CH_{Ar}), 129.7 (CH_{Ar}), 133.2, 137.1, 150.0, 154.7, 167.9.

MS (EI, 70 eV): *m/z* (%) = 340 ([M]$^+$, 17), 326 (26), 325 (100), 247 (14), 91 (65).

HRMS (EI): Calcd. for $C_{23}H_{20}N_2O$ [M]$^+$: 340.15701, found: 340.15714.

IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2953 (m), 2924 (w), 2862 (w), 1697 (s), 1660 (s), 1585 (w), 1524 (m), 1495 (m), 1464 (m), 1456 (m), 1441 (m), 1417 (m), 1406 (m), 1379 (m), 1358 (m), 1338 (s), 1296 (m), 1261 (m), 1252 (m), 1221 (w), 1205 (m), 1192 (m), 1144 (m), 1124 (m), 1101 (m), 1076 (m), 1049 (w), 1030 (m), 1016 (m), 968 (m), 959 (m), 949 (m), 914 (m), 899 (m), 885 (w), 876 (w), 827 (s), 820 (m), 798 (m), 770 (s), 746 (s), 729 (m), 696 (s), 631 (s), 586 (m), 575 (s), 550 (m).

4.3 Crystal data and structure refinement

Crystal data and structure refinement for **16a**

Identification code	sd217	
Empirical formula	$C_{10}H_{11}F_3N_2O_4 \cdot CHCl_3$	
Formula weight	399.58	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1$	
Space group (Hall)	P 2yb	
Unit cell dimensions	a = 10.5112(5) Å	α = 90°
	b = 6.1932(3) Å	β = 101.793(2)°
	c = 12.5665(6) Å	γ = 90°
Volume	800.79(7) $Å^3$	
Z	2	
Calculated density	1.657 Mg/m^3	
Absorption coefficient	0.622 mm^{-1}	
F(000)	404	
Crystal size	0.33 × 0.07 × 0.05 mm	
Θ range for data collection	2.83 to 30.00°	
Index ranges	$-14 \le h \le 11$, $-8 \le k \le 8$, $-16 \le l \le 17$	
Reflections collected	9501	
Independent reflections	4419 [R(int) = 0.0327]	
Completeness to Θ = 30.00°	99.8 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9696 and 0.8210	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3051 / 1 / 220	
Goodness-of-fit on F2	1.018	
Final R indices [I>2sigma(I)]	R1 = 0.0494, wR2 = 0.0821	
R indices (all data)	R1 = 0.0883, wR2 = 0.0914	
Largest diff. peak and hole	0.314 and −0.357 e.$Å^{-3}$	

Crystal data and structure refinement for **74a**

Identification code	sd084	
Empirical formula	$C_{11}H_4ClF_3O_3$	
Formula weight	276.59	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/c$	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 11.1587(6) Å	α = 90°
	b = 5.2079(2) Å	β = 102.836(2)°
	c = 18.8468(9) Å	γ = 90°
Volume	1067.88(9) $Å^3$	
Z	4	
Calculated density	1.720 Mg/m^3	
Absorption coefficient	0.397mm^{-1}	
F(000)	522	
Crystal size	0.54 × 0.15 × 0.07 mm	
Θ range for data collection	2.56 to 32.50°	
Index ranges	$-16 \le h \le 16, -7 \le k \le 7, -27 \le l \le 28$	
Reflections collected	14509	
Independent reflections	3774 [R(int) = 0.0239]	
Completeness to Θ = 32.50°	97.8 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9728 and 0.8143	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2930 / 0 / 163	
Goodness-of-fit on F2	1.073	
Final R indices [I>2sigma(I)]	R1 = 0.0365, wR2 = 0.0943	
R indices (all data)	R1 = 0.0514, wR2 = 0.1013	
Largest diff. peak and hole	0.389 and −0.310 e.$Å^{-3}$	

Crystal data and structure refinement for **88n**

Identification code	sd184	
Empirical formula	$C_{16}H_{14}F_3N_3O_3$	
Formula weight	353.30	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	$P\bar{1}$	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 7.6951(3) Å	α = 65.724(2)°
	b = 10.1134(5) Å	β = 82.426(2)°
	c = 10.1134(5) Å	γ = 71.772(2)°
Volume	734.82(6) $Å^3$	
Z	2	
Calculated density	1.597 Mg/m^3	
Absorption coefficient	0.137 mm^{-1}	
F(000)	364	
Crystal size	0.48 × 0.35 × 0.10 mm	
Θ range for data collection	2.31 to 29.99°	
Index ranges	$-10 \le h \le 10, -13 \le k \le 13, -14 \le l \le 14$	
Reflections collected	15164	
Independent reflections	3881 [R(int) = 0.0317]	
Completeness to Θ = 29.99°	99.2 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9864 and 0.9371	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3116 / 0 / 229	
Goodness-of-fit on F2	1.041	
Final R indices [I>2sigma(I)]	R1 = 0.0380, wR2 = 0.1056	
R indices (all data)	R1 = 0.0503, wR2 = 0.1129	
Largest diff. peak and hole	0.363 and −0.265 $e.Å^{-3}$	

Crystal data and structure refinement for **88j**

Identification code	sd194	
Empirical formula	$C_{15}H_{12}ClF_2N_3O_3$	
Formula weight	355.73	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	$P\bar{1}$	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 8.6849(7) Å	α = 115.546(2)°
	b = 9.3993(4) Å	β = 101.079(2)°
	c = 10.0441(4) Å	γ = 98.711(3)°
Volume	700.09(7) $Å^3$	
Z	2	
Calculated density	1.687 Mg/m^3	
Absorption coefficient	0.319 mm^{-1}	
F(000)	364	
Crystal size	0.41 × 0.22 × 0.21 mm	
Θ range for data collection	2.35 to 30.99°	
Index ranges	$-12 \le h \le 12, -13 \le k \le 13, -14 \le l \le 14$	
Reflections collected	15923	
Independent reflections	4451 [R(int) = 0.0355]	
Completeness to Θ = 30.99°	99.8 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9360 and 0.8803	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3595 / 0 / 220	
Goodness-of-fit on F2	1.052	
Final R indices [I>2sigma(I)]	R1 = 0.0363, wR2 = 0.0995	
R indices (all data)	R1 = 0.0487, wR2 = 0.1062	
Largest diff. peak and hole	0.397 and −0.325 $e.Å^{-3}$	

Crystal data and structure refinement for **88m**

Identification code	sd206	
Empirical formula	$C_{17}H_{12}F_7N_3O_3 \cdot CHCl_3$	
Formula weight	558.66	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/m$	
Space group (Hall)	-P 2yb	
Unit cell dimensions	a = 12.2256(8) Å	α = 90°
	b = 6.8967(4) Å	β = 95.776(3)°
	c = 12.7724(8) Å	γ = 90°
Volume	1071.45(12) $Å^3$	
Z	2	
Calculated density	1.732 Mg/m^3	
Absorption coefficient	0.516 mm^{-1}	
F(000)	560	
Crystal size	0.85 × 0.33 × 0.08 mm	
Θ range for data collection	3.21 to 28.00°	
Index ranges	$-16 \le h \le 16, -9 \le k \le 9, -16 \le l \le 16$	
Reflections collected	10034	
Independent reflections	2781 [R(int) = 0.0223]	
Completeness to Θ = 28.00°	99.7 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9599 and 0.6680	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2118 / 0 / 260	
Goodness-of-fit on F2	1.060	
Final R indices [I>2sigma(I)]	R1 = 0.0478, wR2 = 0.1365	
R indices (all data)	R1 = 0.0658, wR2 = 0.1491	
Largest diff. peak and hole	0.532 and −0.311 $e.Å^{-3}$	

Crystal data and structure refinement for **91a**

Identification code	sd283	
Empirical formula	$C_{16}H_{14}F_3N_3O_3$	
Formula weight	353.30	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	$P\bar{1}$	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 7.4835(3) Å	α = 92.445(2)°
	b = 8.5920(3) Å	β = 104.160(2)°
	c = 11.4002(4) Å	γ = 93.761(2)°
Volume	707.90(5) $Å^3$	
Z	2	
Calculated density	1.657 Mg/m^3	
Absorption coefficient	0.142 mm^{-1}	
F(000)	364	
Crystal size	0.48 × 0.17 × 0.10 mm	
Θ range for data collection	2.92 to 30.00°	
Index ranges	$-10 \le h \le 10, -12 \le k \le 12, -16 \le l \le 15$	
Reflections collected	15295	
Independent reflections	4101 [R(int) = 0.0186]	
Completeness to Θ = 30.00°	99.5 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9859 and 0.9349	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3515 / 0 / 232	
Goodness-of-fit on F2	1.026	
Final R indices [I>2sigma(I)]	R1 = 0.0390, wR2 = 0.1002	
R indices (all data)	R1 = 0.0472, wR2 = 0.1053	
Largest diff. peak and hole	0.419 and −0.278 $e.Å^{-3}$	

Crystal data and structure refinement for **92a**

Identification code	sd284	
Empirical formula	$C_{16}H_{13}ClF_3N_3O_2$	
Formula weight	371.74	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/c$	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 19.9679(8) Å	α = 90°
	b = 20.1167(8) Å	β = 111.103(2)°
	c = 16.4722(7) Å	γ = 90°
Volume	6172.9(4) $Å^3$	
Z	16	
Calculated density	1.600 Mg/m^3	
Absorption coefficient	0.298 mm^{-1}	
F(000)	3040	
Crystal size	0.72 × 0.31 × 0.09 mm	
Θ range for data collection	1.49 to 26.99°	
Index ranges	$-19 \le h \le 25, -25 \le k \le 25, -20 \le l \le 16$	
Reflections collected	55556	
Independent reflections	13379 [R(int) = 0.0341]	
Completeness to Θ = 26.99°	99.5 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9737 and 0.8142	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10025 / 0 / 909	
Goodness-of-fit on F2	1.035	
Final R indices [I>2sigma(I)]	R1 = 0.0418, wR2 = 0.1005	
R indices (all data)	R1 = 0.0643, wR2 = 0.1095	
Largest diff. peak and hole	0.346 and −0.396 e.$Å^{-3}$	

Crystal data and structure refinement for **98a**

Identification code	sd228	
Empirical formula	$C_{16}H_{16}F_3N_3O_2$	
Formula weight	339.32	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/c$	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 8.5186(3) Å	α = 90°
	b = 9.1302(3) Å	β = 96.8670(10)°
	c = 19.1613(6) Å	γ = 90°
Volume	1479.61(9) $Å^3$	
Z	4	
Calculated density	1.523 Mg/m^3	
Absorption coefficient	0.128 mm^{-1}	
F(000)	704	
Crystal size	0.50 × 0.39 × 0.30 mm	
Θ range for data collection	2.47 to 31.03°	
Index ranges	$-6 \le h \le 12$, $-12 \le k \le 13$, $-27 \le l \le 27$	
Reflections collected	16967	
Independent reflections	4698 [R(int) = 0.0164]	
Completeness to Θ = 30.50°	99.2 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9627 and 0.9389	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4099 / 0 / 225	
Goodness-of-fit on F2	1.064	
Final R indices [I>2sigma(I)]	R1 = 0.0368, wR2 = 0.1077	
R indices (all data)	R1 = 0.0428, wR2 = 0.1119	
Largest diff. peak and hole	0.461 and −0.256 e.$Å^{-3}$	

Crystal data and structure refinement for **100**

Identification code	sd402	
Empirical formula	$C_{23}H_{22}F_3N_3O_2$	
Formula weight	429.44	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	$P\bar{1}$	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 8.6107(7) Å	α = 102.613(5)°
	b = 11.0873(10) Å	β = 91.556(6)°
	c = 11.3982(10) Å	γ = 106.607(5)°
Volume	1012.95(15) $Å^3$	
Z	2	
Calculated density	1.408 Mg/m^3	
Absorption coefficient	0.110 mm^{-1}	
F(000)	448	
Crystal size	0.33 × 0.13 × 0.10 mm	
Θ range for data collection	2.94 to 32.50°	
Index ranges	$-13 \le h \le 13, -16 \le k \le 16, -17 \le l \le 16$	
Reflections collected	28093	
Independent reflections	7309 [R(int) = 0.0327]	
Completeness to Θ = 32.50°	99.9 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9891 and 0.9646	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4879 / 0 / 284	
Goodness-of-fit on F2	1.012	
Final R indices [I>2sigma(I)]	R1 = 0.0495, wR2 = 0.1179	
R indices (all data)	R1 = 0.0856, wR2 = 0.1380	
Largest diff. peak and hole	0.377 and −0.258 $e.Å^{-3}$	

Crystal data and structure refinement for **108**

Identification code	sd341	
Empirical formula	$C_{15}H_{14}F_3N_3O_3$	
Formula weight	341.29	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/c$	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 17.9524(3) (6) Å	α = 90°
	b = 6.20460(10) Å	β = 109.1480(10)°
	c = 14.3442(2) Å	γ = 90°
Volume	1509.37(4) $Å^3$	
Z	4	
Calculated density	1.502 Mg/m^3	
Absorption coefficient	0.130 mm^{-1}	
F(000)	704	
Crystal size	0.30 × 0.17 × 0.16 mm	
Θ range for data collection	2.85 to 29.99°	
Index ranges	$-25 \le h \le 25, -7 \le k \le 8, -20 \le l \le 19$	
Reflections collected	17011	
Independent reflections	4381 [R(int) = 0.0229]	
Completeness to Θ = 29.99°	99.7 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9794 and 0.9619	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3462 / 0 / 223	
Goodness-of-fit on F2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0510, wR2 = 0.1278	
R indices (all data)	R1 = 0.0663, wR2 = 0.1387	
Largest diff. peak and hole	0.890 and –0.364 $e.Å^{-3}$	

Crystal data and structure refinement for **119e**

Identification code	sd209	
Empirical formula	$C_{22}H_{20}N_4O_5 \cdot 3C_2HF_3O_2$	
Formula weight	762.50	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	$P\bar{1}$	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 9.6401(6) Å	α = 78.929(3)°
	b = 12.6637(8) Å	β = 71.301(3)°
	c = 14.1111(9) Å	γ = 83.218(3)°
Volume	1598.41(17) $Å^3$	
Z	2	
Calculated density	1.584 Mg/m^3	
Absorption coefficient	0.155 mm^{-1}	
F(000)	776	
Crystal size	0.63 × 0.48 × 0.35 mm	
Θ range for data collection	2.23 to 28.00°	
Index ranges	$-12 \le h \le 12, -16 \le k \le 16, -18 \le l \le 18$	
Reflections collected	30889	
Independent reflections	7716 [R(int) = 0.0283]	
Completeness to Θ = 28.00°	99.9 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9479 and 0.9089	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6188 / 19 / 577	
Goodness-of-fit on F2	1.085	
Final R indices [I>2sigma(I)]	R1 = 0.0493, wR2 = 0.1368	
R indices (all data)	R1 = 0.0623, wR2 = 0.1448	
Largest diff. peak and hole	0.609 and −0.397 $e.Å^{-3}$	

Crystal data and structure refinement for **119b**

Identification code	sd222	
Empirical formula	$C_{27}H_{30}N_4O_6 \cdot CH_4O$	
Formula weight	538.59	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/n$	
Space group (Hall)	-P 2yn	
Unit cell dimensions	a = 13.2916(3) Å	α = 90°
	b = 13.4393(3) Å	β = 109.5340(10)°
	c = 16.4546(4) Å	γ = 90°
Volume	2770.11(11) $Å^3$	
Z	4	
Calculated density	1.291 Mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	1144	
Crystal size	0.36 × 0.33 × 0.30 mm	
Θ range for data collection	1.71 to 30.50°	
Index ranges	$-18 \leq h \leq 17, -18 \leq k \leq 19, -21 \leq l \leq 23$	
Reflections collected	33513	
Independent reflections	8447 [R(int) = 0.0386]	
Completeness to Θ = 30.50°	100.0 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9724 and 0.9670	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5909 / 2 / 423	
Goodness-of-fit on F2	1.091	
Final R indices [I>2sigma(I)]	R1 = 0.0465, wR2 = 0.1274	
R indices (all data)	R1 = 0.0723, wR2 = 0.1391	
Largest diff. peak and hole	0.289 and −0.258 $e.Å^{-3}$	

Crystal data and structure refinement for **126**

Identification code	sd303	
Empirical formula	$C_{17}H_{19}N_3O_6$	
Formula weight	361.35	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/c$	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 8.4358(8) Å	α = 90°
	b = 8.6118(9) Å	β = 97.003(3)°
	c = 23.023(2) Å	γ = 90°
Volume	1660.1(3) $Å^3$	
Z	4	
Calculated density	1.446 Mg/m^3	
Absorption coefficient	0.111 mm^{-1}	
F(000)	760	
Crystal size	0.89 × 0.39 × 0.03 mm	
Θ range for data collection	1.78 to 29.99°	
Index ranges	$-11 \le h \le 11, -12 \le k \le 11, -32 \le l \le 32$	
Reflections collected	17062	
Independent reflections	4819 [R(int) = 0.0381]	
Completeness to Θ = 29.99°	99.8 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9967 and 0.9076	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2996 / 0 / 244	
Goodness-of-fit on F2	1.021	
Final R indices [I>2sigma(I)]	R1 = 0.0469, wR2 = 0.1020	
R indices (all data)	R1 = 0.0963, wR2 = 0.1145	
Largest diff. peak and hole	0.271 and −0.277 $e.Å^{-3}$	

List of Symbols and Abbreviations

–″–	symbol indicating the repetition
(m)	medium
(s)	strong
(w)	weak
Ac	Acetyl group
AID	Activation-induced cytidine deaminase
APOBEC	Apolipoprotein B mRNA editing enzyme
Ar	Aryl group
ART	Attenuated total reflection
br	broad signal
cat.	catalyst
CDA	Cytidine deaminase
Compd	Compound
conc.	concentrated
COSY	Correlation spectroscopy
d	doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEPT	Distortionless enhancement by polarization transfer
DHP	1,4-Dihydropyridine
dioxane	1,4-dioxane
DIPA	Diisopropylamine
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMFDMA	*N*,*N*-Dimethylformamide dimethyl acetal
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EA	Elemental analysis
EI	Electron ionization
eq	chemical equivalent
ESI	Electrospray ionization
Et	Ethyl group
EWG	Electron-withdrawing group
FAD	Flavin adenine dinucleotide

GC	Gas chromatography
h	hour
Het	Hetaryl group
HMBC	Heteronuclear multiple-bond correlation
HMQC	Heteronuclear multiple-quantum correlation
HPTLC	High-performance TLC
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
IMP	Inosine-5'-monophosphate
IMPDH	IMP dehydrogenase
IR	Infrared (spectroscopy)
IUPAC	International Union of Pure and Applied Chemistry
J	Coupling constant, Hz
l	cuvette length
LC	Liquid chromatography
LCD	Liquid crystals displays
m	multiplet
Me	Methyl group
Me	Methyl group
MRC	Multicomponent reaction
mRNA	Messenger RNA
MS	Mass spectrometry
N	Normality (concentration)
n-BuLi	*n*-Butyllithium
NMP	N-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	NOE spectroscopy
Nu	Nucleophile
OLED	Organic light-emitting diode
Ph	Phenyl group
Py	Pyridil group
q	quartet
R_f	Chromatographic retention factor
Rf or R_F	Polyfluoroalkyl group
RNA	Ribonucleic acid

s	singlet
t	triplet
Tf	Triflic group
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl group
TsOH	*p*-Toluenesulfonic acid
UV	Ultraviolet
$\tilde{\nu}$	wavenumber, cm^{-1}
Vis	Visible
w	cuvette width
wt. %	weight percent
Z	number of formula units in unit cell
δ	chemical shift, ppm
$\Delta\nu St$	Stokes shift, cm-1
ε	molar absorption coefficient, $M^{-1}\cdot cm^{-1}$
λ	wavelength, Å
λ_a	absorption maximum, nm
λ_f	fluorescence band maxima, nm

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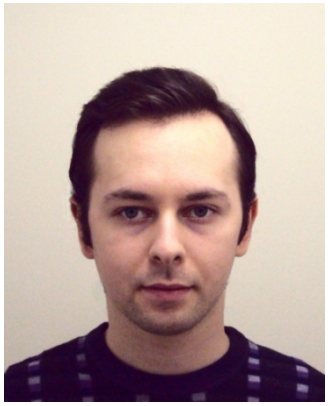
Curriculum Vitae

Personal Information



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2009	**M.Sc.**: First Class in Chemistry, V.N. Karazin Kharkiv National University, diploma with merit; average mark is 5.00 (according to the 5-point grade system)
2008	**B.Sc.**:V.N. Karazin Kharkiv National University diploma with merit; average mark is 4.91 (according to the 5-point grade system)
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Scholarships and Awards

10.2010 – 03.2013 DAAD Scholarship holder

List of Publications

Articles in journals

1. **"Synthesis of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones by cyclocondensation of 1,3-bis(trimethylsilyloxy)buta-1,3-dienes with 4-chloro-3-nitrocoumarin"**

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2. **"Synthesis of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones by cyclocondensation of 1,3-dicarbonyl compounds with 4-chloro-3-nitrocoumarin"**

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3. **"Regioselective synthesis of benzo[*c*]chromen-6-ones by one-pot cyclocondensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde"**

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4. **"An efficient synthesis of 6-nitro- and 6-amino-3*H*-imidazo[4,5-*b*]pyridines by cyclocondensation of 1-substituted-1*H*-imidazol-5-amines with 3-nitro-4*H*-chromen-4-one"**

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5. **"3-Formylchromones, acylpyruvates, and chalcone as valuable substrates for the syntheses of fused pyridines"**

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6. **"3-Methoxalylchromone—a novel versatile reagent for the regioselective purine isostere synthesis"**

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7. **"4-Chloro-3-(trifluoroacetyl)coumarin as a novel building block for the synthesis of 7-(trifluoromethyl)-6*H*-chromeno[4,3-*b*]quinolin-6-ones"**

   Viktor O. Iaroshenko, Sajid Ali, Tariq Mahmood Babar, Sergii Dudkin, Satenik Mkrtchyan, Nasim H. Rama, Alexander Villinger, Peter Langer, *Tetrahedron Lett.* **2011**, *52*, 373–376.

8. **"4-Chloro-3-(trifluoroacetyl)- and 4-chloro-3-(methoxalyl)coumarins as novel and efficient building blocks for the regioselective synthesis of 3,4-fused coumarins"**

   Viktor O. Iaroshenko, Friedrich Erben, Satenik Mkrtchyan, Ani Hakobyan, Marcelo Vilches-Herrera, Sergii Dudkin, Alina Bunescu, Alexander Villinger, Vyacheslav Ya. Sosnovskikh, Peter Langer, *Tetrahedron* **2011**, *67*, 7946–7955.

9. **"Efficient [5 + 1]-strategy for the assembly of 1,8-naphthyridin-4(1*H*)-ones by domino amination/conjugate addition reactions of 1-(2-chloropyridin-3-yl)prop-2-yn-1-ones with amines"**

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10. **"Recyclization in the series of spiro[indole-3,5'-pyrimido[4,5-*b*]quinoline]-2,2',4'-triones prepared by a three-component reaction of isatins with (thio)barbituric acids and electron-rich anilines"**

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Conferences attended

1. **"Synthesis of 4-alkoxy-6-aminoquinolines"**

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2. **"3-(1,2,4-oxadiazol-5-il)-quinoline-4(1*H*)-ones – bioisosteric analogues of antibacterial drugs of quinonone series"**

   Sergii V. Dudkin, Oleksandr S. Detistov, // *NINTH UKRAINIAN CONFERENCE of STUDENTS and POST-GRADUATE STUDENTS*. Kiev, 14-16th May, **2008**, p. 64.