Synthesis and Characterization of Benzo-[1,8]-naphthyridine-4(1*H*)-ones, Benzo[*b*]pyrazolo-[5,1-*f*][1,6]-naphthyridines, Benzo-[4',5']-imidazo-[1',2':1,2]-pyrido-[4,3-*b*]indoles and Fluorinated Arenes.

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Affectionately

Dedicated to

My Dearest Parents.

Declaration / Erklärung

Here by I declare that this work has so for neither been submitted to the Faculty of Mathematics and Natural Science of the University of Rostock nor to any other scientific institute for the purpose of doctorate. Furthermore, I declare that I have written this thesis myself and I havn't used any other sources, other than mentioned earlier in this work.

Hier erkläre ich, dass diese Arbeit zuvor weder an der Fakultät für Mathematik und Naturwissenschaften der Universität Rostock noch an einem anderen wissenschaftlichen Institut zum Zweck der Promotion vorgelegt wurde. Desweiteren erkläre ich, dass ich diese Arbeit selbst geschrieben und keine Quellen verwendet habe, die nicht in diesem Werk erwähnt wurden.

Zahid, Muhammad

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Zahid, Muhammad

Abstract

Domino amination/conjugate addition reactions have been used to synthesize a new class of 4-quinolones. An efficient route for the synthesis of benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines via silver triflate-catalyzed one-pot tandem reactions has also been developed which proceeds with good functional group tolerance under mild conditions with high efficiency and excellent selectivity. A high yielding route for the synthesis of fluorinated arenes, which are difficult to obtain, has been developed by direct acyl-alkylation of benzyne.

Domino Aminierungs / Michael-Typ Reaktionen wurden verwendet, um eine neue Klasse von 4-Chinolonen zu synthetisieren. Weiterhin wurde ein effizienter Weg zur Synthese von Benzo[*b*]pyrazolo[5,1-*f*][1,6]Naphthyridine über Silbertriflat-katalysierte Eintopf-Tandem-Reaktionen entwickelt, die mit guter Toleranz gegenüber funktionellen Gruppen, unter milden Bedingungen, mit hoher Effizienz und ausgezeichneter Selektivität verlaufen. Fluorierte Aromaten, die anderweitig schwer zu erhalten sind, wurden erstmals durch direkte Acyl-Alkylierung von Benz-in hergestellt.

1. An efficient [5+1] strategy for the synthesis of benzo-[1,8]-naphthyridine-4(1*H*)-ones by domino amination / conjugate addition reaction of 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-ones with amines.

1.1 General Introduction to Quinolones

Over the years nitrogen-containing heterocycles have been gaining much importance in medicinal, photochemical and synthetic chemistry.[1] Among these, naphthyridinone and quinolones are bioactive members of nitrogen-containing heterocycles.

Synthetic quinolone antibiotics were discovered by George Lesher and coworkers as a byproduct of chloroquine manufacture in the 1960s.[2] Nalidixic acid is the first of the synthetic quinolone antibiotics found to be effective against both gram-positive and gram-negative bacteria. Particularly interesting from a biological point of view are 3-carboxyquinolin-4-ones and 3-carboxy-1,8-naphthyridin-4-ones which are well known antibacterial agents.[3] F. J. Dutko and coworker studied, that quinolin-4-ones, substituted at position 3 by electron-withdrawing functionalities, such as amide or sulfinyl groups, also possess strong antiviral activity.[4] K. Robinson explored flosequinan as a drug for the treatment of congestive heart failure.[5] Although compounds with antibacterial activities have been known as natural products for centuries, synthetic antibiotics evolved starting from the pioneering discoveries of penicillin by Fleming in 1928 and sulphonamides in 1935.[6] The original potent quinolone was 1,8-naphthyridine-nalidixic acid and the synthetic 4-quinolones, which were later prepared by J. T. Smith, are analogues of the original molecule.[7] Nalidixic acid possesses limited in-vitro activity against Gram-negative bacteria and its use was restricted to oral treatment of patients with urinary tract infections. Modifications to this drug in the 1970s gave rise to similar compounds (oxolinic acid, rosoxacin, cinoxacin and flumequine) which were also available only for use in patients with urinary tract infections. A piperazine substitution at position 7 of the naphthyridine core and fluorination at position 6 resulted in improved activities against Gram-negative and Gram-positive pathogens, respectively. These are nowadays the so-called fluoroquinolone antibiotics. In 1980, H. Koga and coworkers reported norfloxacin as the first of the fluoroquinolones to possess an increased activity against Gram-negative bacteria; including *Pseudomonas aeruginosa*.[8] Its use was restricted to the treatment of patients with urinary tract infections. Quinolones proved to be a unique class of molecules which act against bacteria by inhibiting DNA gyrase. This is an enzyme which is necessary for the replication of nucleic acid. These agents were first described by Lescher *et al*.[9] Since then, more than 10,000 quinolone

derivatives have been synthesized world-wide. Very few have entered into clinical development and less than ten have been approved for clinical use.[10] Some important 1,8-naphthyridinones are shown in Figure 1.

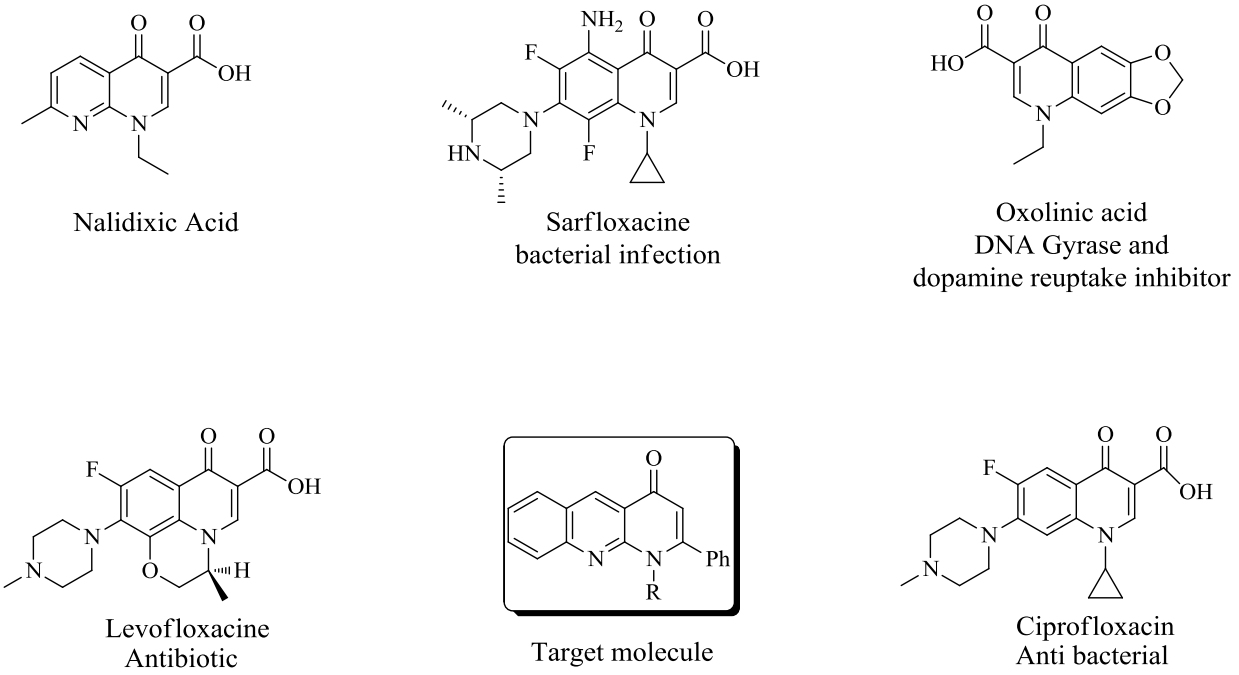


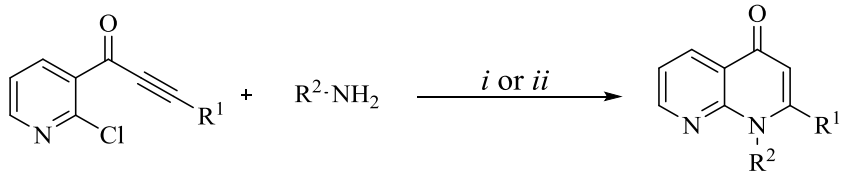
Figure 1. Important 1,8-naphthyridinones**.**

Numerous synthetic routes to 1,8-naphthyridones have been reported. Stephen L. Buchwald reported an approach to 2-aryl-4-quinolones by copper-catalyzed amidation of o-halophenones followed by a base-promoted Camps cyclization of the resulting N-(2-ketoaryl)amides.[11] G. M. Coppola developed a 4-quinolone synthetic route, by the reaction of isatoic anhydrides with enolates of ketones.[12-15] K. Lemr and coworkers established a novel strategy via cyclization of N-substituted phenacyl or acetonyl anthranilates in polyphophoric acid.[16] G. I. Georg reported a quinolone synthesis via cyclization of substituted anthranilic acid derived ynone intermediates under mild conditions.[17] F. W. Heinemann and coworkers estsblished an interesting transformation of electron-deficient alkynes to quinolones, thiochromones and pyrazoles via activated Michael systems.[18] Djakovitch and co-workers explored a one-pot two-step multi-catalyzed synthesis of 4-quinolone.[19] Several interesting methodologies were also found, including cycloaddition of aniline derivatives,[20] palladium-catalyzed carbonylative Sonogashira coupling of 2-iodoaniline with arylacetylene,[21] and metal free intramolecular amination.[22] Although these methods are effective and give relatively high

yields,[23,24] most of them give 1-unsubstituted and 2-substituted 4-quinolones, or 1,3-disubstituted 4-quinolones. Only a few examples were reported in the literature for 1,2-disubstituted 4-quinolone syntheses.

1.2 1,8-Naphthyridin-4-ones

In my thesis, I have studied, together with my colleague Dr. Ingo Knepper (dissertation, University of Rostock, 2011), the synthesis of 1,8-naphthyridines based on formal [5 + 1]-cyclizations of 1-(2-chloropyridin-3-yl)prop-2-yn-1-ones with a set of aromatic and aliphatic amines (Scheme 1).[25]



Scheme 1. Conditions for the synthesis of 1,8-naphthyridin-4(1*H*)-ones.**:** (*i*) $Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (2 equiv.), DMF 150 °C, under dry Ar, 16 hr. (*ii*) Catalyst free, K_2CO_3 (2 equiv.), DMF 150 °C, under dry Ar, 16 hr.

1.3 Synthetic scope of Benzo[*b*][1,8]naphthyridin-4(1*H*)-ones

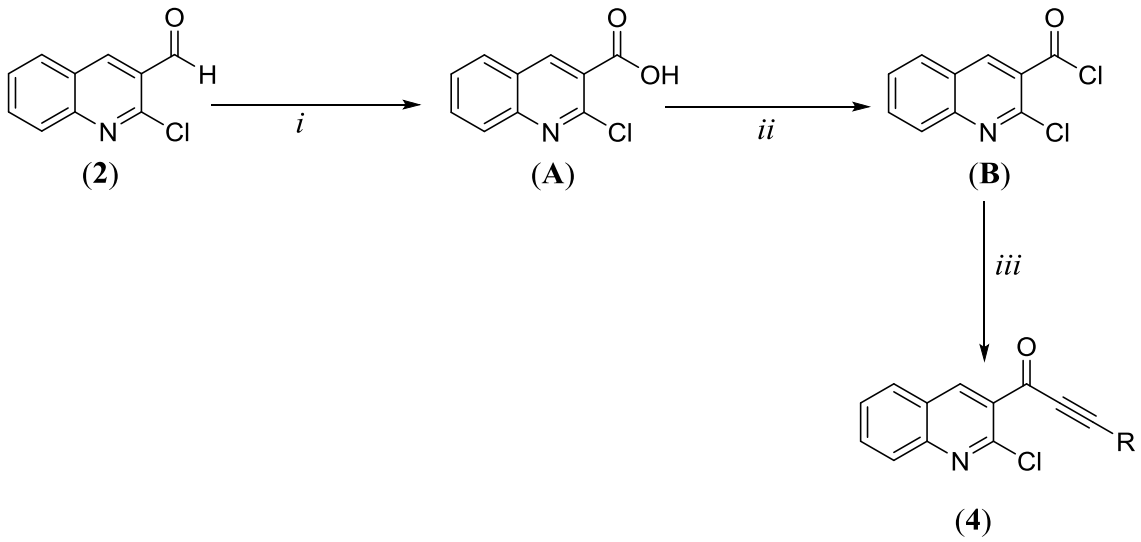
To the best of my knowledge, 1,2-disubstituted benzo[*b*][1,8]naphthyridin-4(1*H*)-ones have not been reported so far. In view of the prime biological reputation among the family of 1,8-naphthyridin-4(1*H*)-ones, I was encouraged to extend my synthetic work to the synthesis of novel benzo[*b*][1,8]-naphthyridin-4-ones based on [5 + 1]-cyclization of 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-ones using different aromatic and aliphatic amines in good to excellent yields (Scheme 3 & 4, below).

1.3.1 Results and Discussion

My focus was to synthesize novel 1,2-disubstituted naphthyridinones starting from cheap starting materials. In this effort, I started from acetanilide (**1**, 400 mg scale), after formylation with $POCl_3$ in DMF and got 2-chloroquinoline-3-carbaldehyde (**2**) in higher yield (93%) than reported in literature (80%).[26] During the synthesis of compound **2**, I faced as a main problem the neutralization of $POCl_3$ in the reaction mixture. As reported in the literature,

we have to neutralize the reaction mixture after refluxing the reaction mixture for 10 hr. However, the litereature procedure proved to be less effective regarding the yield and the possibility to have an effective separation of the compound from the aqueous mixture. I was able to solve the problem by a change of the procedure. After reflux for 10 h at 80 °C, the reaction mixture was carefully added to crushed ice with constant stirring. In this process, compound **2** was separated by precipitation, filtered and washed with water to remove the excess of $POCl_3$. While adding the reaction mixture to ice, it is important to make sure that the temperature should not increase. This was achieved by adding small amounts of the reaction mixture and batch-wise recovery of the product. When the temperature increased, then the separation of the desired compound was very difficult. This method proved to be extremely suitable for the synthesis of pure compound **2** in higher yield as reported in the literature. The next step was to convert compound **2** to compound **4**; for that I considered two pathways.

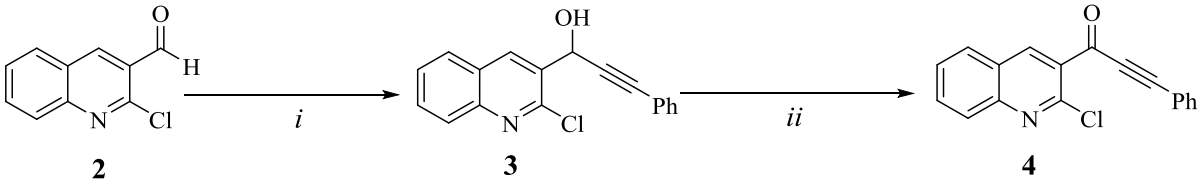
Path A.



Scheme 2. Possible conditions for the synthesis of **4**: (*i*) Oxidation. (*ii*) $SOCl_2$, Reflux. (*iii*) 1-Alkyne, $PdCl_2(PPh_3)_2$ (2 mol%), CuI (4 mol%), THF, dry Ar.

A familiar and straightforward route was path A. Compound **2** can easily be converted to compound **A** by using a variety of oxidants. Compound **B** can be achieved by treating acid **A** with $SOCl_2$ under anhydrous conditions and finally compound **4** can be synthesized using well-established conditions[25] from compound **3**. This route was already studied by me together with Dr. Ingo Knepper for a different substrate. Although path A might be feasible, my interest remained on a new synthetic path, i.e. path B.

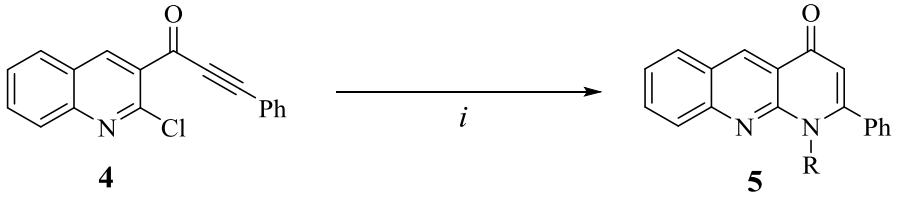
Path B.



Scheme 3, Conditions for the synthesis of **4**: (*i*) *n*-BuLi, PhCCH, THF, -78C. (*ii*) MnO_2, CH_2Cl_2, reflux (30 min).

Path B proved to be efficient for the generation of substrate **4**.[27] In the first step, compound **2** was introduced to a Schlenk flask fitted with argon supply, anhydrous THF was used to dissolve compound **2**, followed by addition of the alkyne and of *n*-BuLi at -78°C. The most important point in this step was to control the temperature during the addition of *n*-BuLi, otherwise the yield dropped. After addition of *n*-BuLi, the temperature was increased to room temperature. The reaction mixture was allowed to stir for 3 hr and subsequently quenched with a saturated NH_4Cl solution in H_2O, followed by extraction with ethyl acetate. Purification of compound **3** was very challenging as some unreacted starting material was still found along with product **3**, even with extended reaction times. Initially, I purified compound **3** by using a capillary column, but this could not be helpful to synthesize the compound in higher amount. Therefore, it was really important for me to find a solution of this problem. Fortunately, when I was evaporating the ethyl acetate extract, addition of DCM resulted in precipitation of a white solid. This, on analysis, was found to be analytically pure compound **3**. The final established procedure was very simple and high yielding. I washed the dried ethyl acetate extract with DCM to get the pure compound **3**. Confirmation of this transformation was done by using ^{1}H-NMR, GC-MS, CHN-analysis. In the ^{1}H-NMR, the aldehyde proton (δ, 10.78) of compound **2** was diagnostic as it is not observed in compound **3**. For the preparation of compound **4**, I used the mild oxidizing reagent MnO_2. Optimized reaction conditions were found after a series of experiments. It was important to apply the following conditions: 2 equivalents of MnO_2 or pyridiniumchlorochromate (PCC) in DCM were refluxed for 30 min. Extended reflux time resulted in decomposition of compound **4** to give compound **2**. Analytical techniques were used for the confirmation of this transformation. In the ESI-TOF/MS analysis for compound **3** a quasi molecular ion peak was found at 294.0677 $[M+H]^+$ and for compound **4** a peak at 292.0524 $[M+H]^+$ was found. ^{1}H-NMR was also helpful for comparison of these two compounds. The propargylic alcohol proton signal (δ, 6.72) of compound **3** was not observed in compound **4**. In

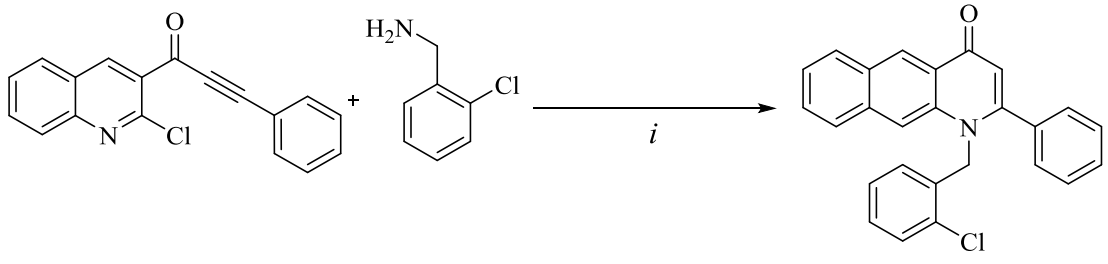
the ^{13}C-NMR spectrum, appearance of a signal at *δ,* 174.6 was observed for compound **4** confirmed the oxidation of alcoholic carbon of compound **3** to carbonyl carbon. The application of this method, to the best of my knowledge has not been reported for this substrate so far. It is noteworthy that both compounds **3** and **4** were synthesized by me in higher yields than previously reported. Finally, compound **4** was transformed to **5**. It required a lot of optimizations to establish conditions which gave high yields and a facile conversion. Several reaction conditions were applied and various conditions were used (catalyst, base, solvent and temperature). I started without catalyst in DMF, use of an inorganic base K_2CO_3. The reaction took 9 hr at 120 °C for completion and only gave 23% isolated product **5**. It was observed that the use of organic bases, like DIPA, did not improve the course of the reaction significantly. Therefore, my focus remained with inorganic bases. Among various parameters, I found K_2CO_3 as best base, DMF as best solvent, $Pd(PPh_3)_4$ as most suitable catalyst, 120 °C best temperature and 3 hr as best reaction time.



4 **5**

Scheme 4. Conditions for synthesis derivatives of 2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-ones: (*i*) RNH_2, $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (2 equiv.), DMF, 120 °C, under dry Ar, 3hr.

During the optimization of the reaction conditions, I have found that the use of $Pd(PPh_3)_4$ (10 mol%) as a catalyst, 2.0 equiv. of K_2CO_3, and DMF as a solvent (120 °C) was essential to get good yields of **5a-l**. These conditions were optimized for aliphatic and benzylic amines (Table 1, Scheme 5).



4 **5k**

Scheme 5. Reaction condition optimization for **5k**: (*i*) $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (2 equiv.), DMF, 120 °C, under dry Ar, 3hr.

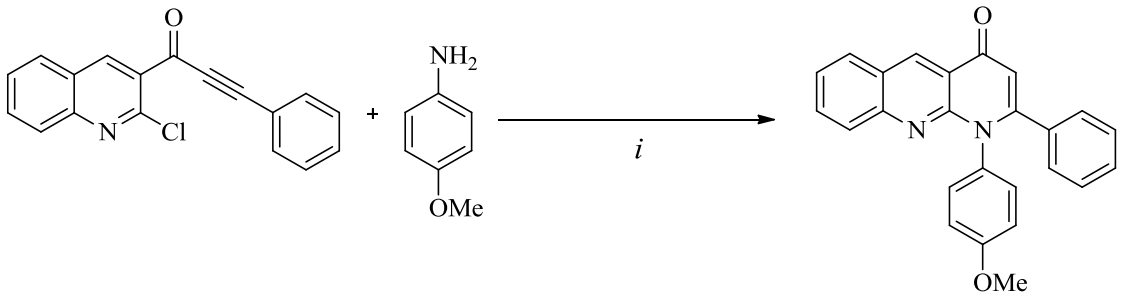
I have investigated product **5k** by using all analytical techniques, NMR, CHN-analysis, X-ray and HRMS (ESI-TOF), in order to confirm structure **5k**.

Table 1. Reaction condition optimizations for **5k**

Entry	Catalyst	Solvent	Base	T (°C)	Time(hr)	**5k**(%)[a]
1	$Pd(PPh_3)_4$	Toluene	K_2CO_3	90	6	67
2	$Pd(PPh_3)_4$	DMF	K_2CO_3	120	3	86
3	$Pd(PPh_3)_4$	Toluene	Cs_2CO_3	90	6	77
4	$Pd(PPh_3)_4$	DMF	K_3PO_4	120	7	73
5	$PdCl_2/PPh_3$	DMF	K_2CO_3	120	6	69
6	$Pd(OAc)_2$	DMF	K_2CO_3	120	6	58
7	$Pd(dba)_2/PPh_3$	Toluene	K_2CO_3	90	7	54
8	$Pd(PPh_3)_4$	CH_3CN	K_2CO_3	90	7	53
9	$Pd(PPh_3)_4$ /BINAP	DMF	K_2CO_3	90	3	96
10	$Pd(PPh_3)_4$	Toluene	DIPA	90	9	17
11	Catalyst Free	DMF	K_2CO_3	120	9	23

[a] yields of isolated products.

Aliphatic and benzylic amines are considerably more nucleophilic than anilines and their reactions proceeded smoothly, while anilines required improved reaction conditions (Table 2).



4 **5m**

Scheme 6. Reaction condition optimization for **5m**: (*i*) $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (2 equiv.), Toluene, 90 °C, under dry Ar, 6 hr.

For more comprehensive understanding about the scope of cyclization, I have further extended my studies using a variety of anilines. However, the yields of expected products were very low under the established reaction conditions. It was noted that a higher amount of catalyst did not improve the yield. The whole procedure was revised under different reaction conditions. Best reaction conditions were observed when I used $Pd(PPh_3)_4$ (0.05 mmol), aniline (0.7 mmol), Cs_2CO_3 (1.2 mmol), **4** (0.6 mmol), and toluene as a solvent for 5-6 hr at 90 °C (Table 3). The solvent always played a crucial role during the optimization (table 2).

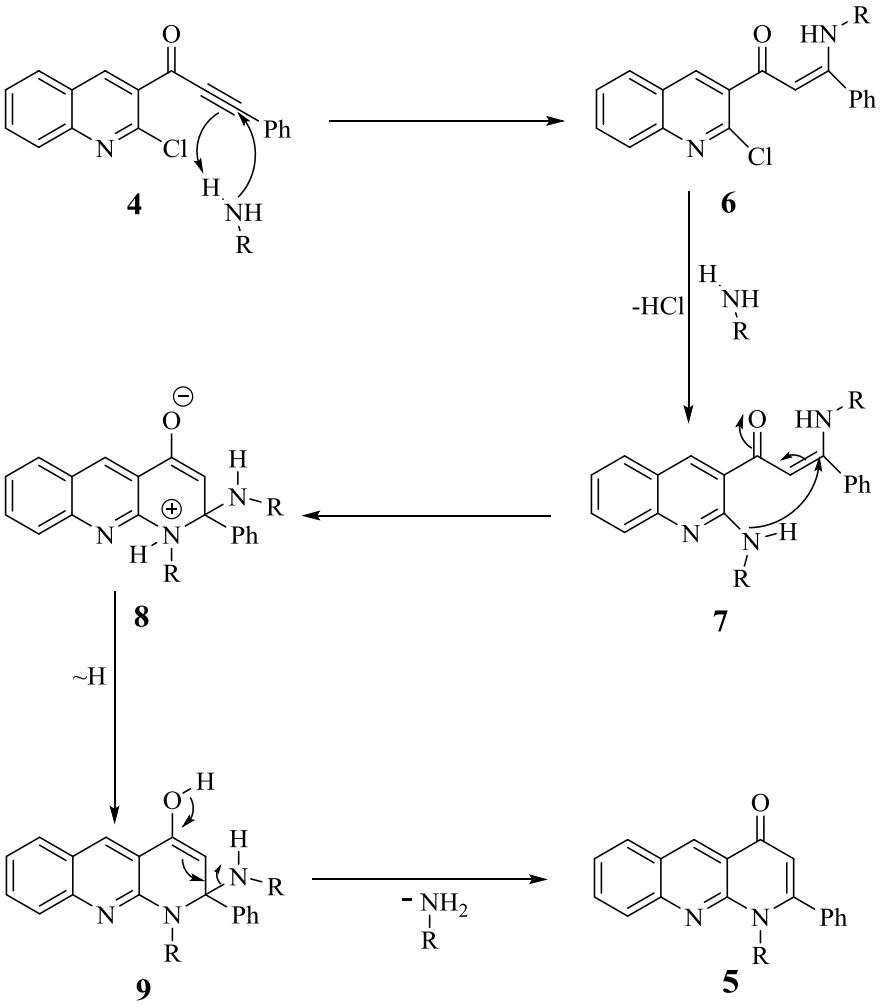
Table 2. Optimization of the reaction conditions (**5m**)

Entry	Catalyst	Solvent	Base	T(°C)	Time(hr)	**5m**(%)[a]
1	$Pd(PPh_3)_4$	Toluene	Cs_2CO_3	90	6	73
2	$Pd(PPh_3)_4$	DMF	Cs_2CO_3	120	6	63
3	$Pd(PPh_3)_4$	Toluene	K_2CO_3	90	6	57
4	$Pd(PPh_3)_4$	Toluene	K_3PO_4	100	7	67
5	$PdCl_2/PPh_3$	Toluene	Cs_2CO_3	90	6	68
6	$Pd(OAc)_2$	Toluene	Cs_2CO_3	90	6	57
7	$Pd(dba)_2/PPh_3$	Toluene	Cs_2CO_3	90	7	45
8	$Pd(PPh_3)_4$	CH_3CN	Cs_2CO_3	90	7	55
9	$Pd(PPh_3)_4$, BINAP	Toluene	Cs_2CO_3	90	3	87
10	$Pd(PPh_3)_4$	Toluene	DIPA	90	9	17
11	Catalyst Free	Toluene	Cs_2CO_3	90	9	23

[a] yields of isolated products.

1.3.2 Proposed Mechanism

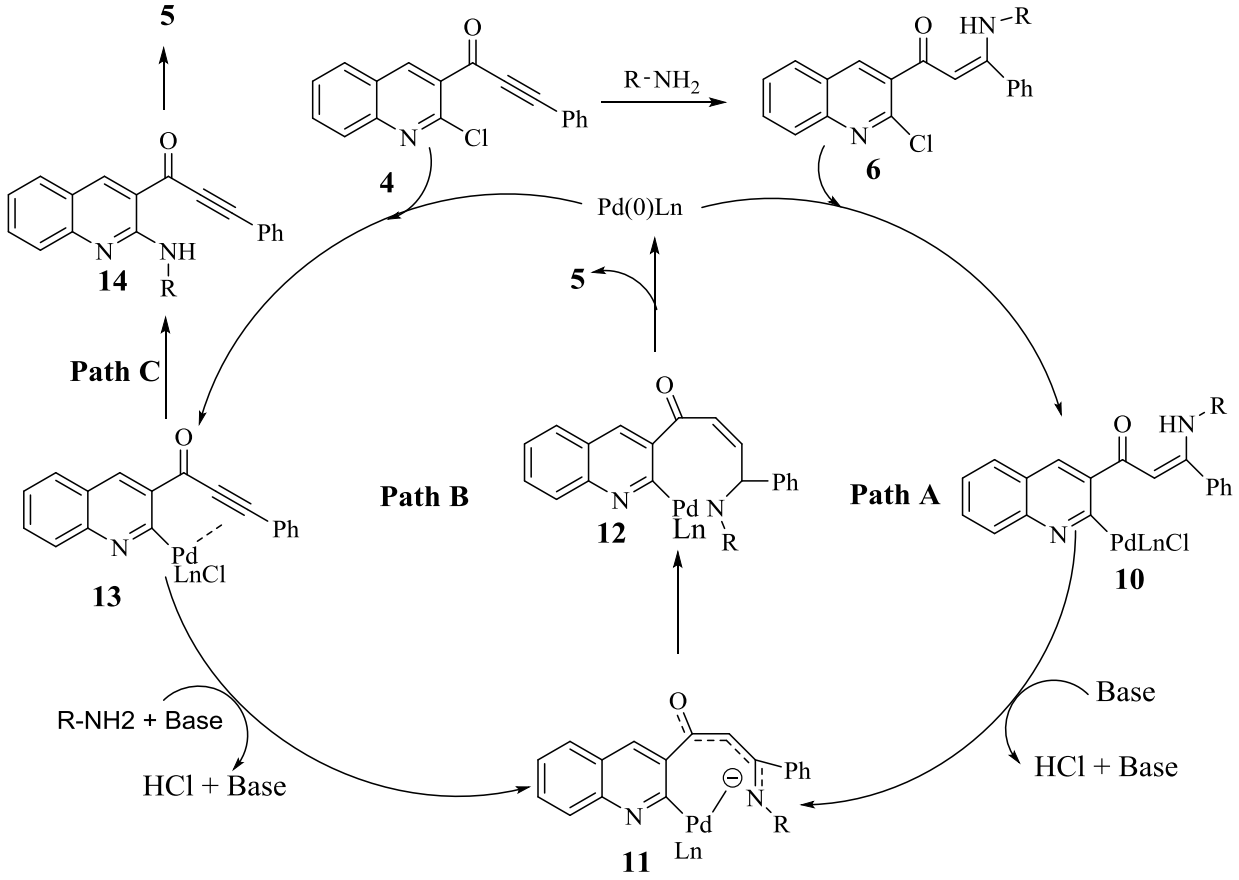
Mechanistic studies, for the cyclization either with or without catalyst, were taken into account.[25] The proposed catalyst-free mechanism is given in Scheme 7.



Scheme 7. Proposed catalyst free reaction mechanism and cyclization pattern.

In the presence of a catalyst several mechanistic paths are possible (Scheme 8). The reaction might proceed by formation of intermediate **6** by conjugate addition of the amine to the ynone moiety. Oxidative addition of Pd(0) to **6** resulted in the formation of organopalladium species **10** (path A). The reaction with base gave intermediate **11**. Intramolecular Buchwald–Hartwig reaction via organopalladium species **12** and reductive elimination of Pd (0) gave product **5**. On the other hand, intermediate **11** can be alternatively formed by a slightly different path. Initial oxidative addition of Pd to halide **4** may result in the formation of intermediate **13**. The addition of the amine might deliver intermediate **11** (path B). Intermediate **13** can also be

directly attacked by the amine (Buchwald–Hartwig reaction) to deliver intermediate **14**. The latter can undergo a cyclization by intramolecular Michael addition giving rise to products **5** (path C). Isolation of intermediates **6** in a related reaction suggests that the reaction preceded via path A. Analysing the literature, I have found some controversial arguments[27] for some of the paths of the mechanism presented in this thesis.



Scheme 8. Proposed Pd (0) catalyzed mechanism of cyclization.[25,27]

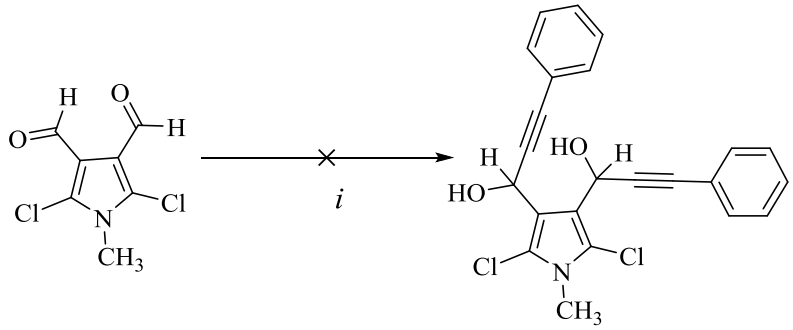
Using the optimized conditions in hand, I have synthesized a variety of 1,2-disubstituted benzonaphthyridones using commercially available aliphatic and benzylic amines (products **5a-l**) and various anilines (products **5m-u**) (Table 3). Different anilines with strong electron donating groups and with electron withdrawing groups were tried. It was noted that electron donating groups improved the reaction and resulted in high yields, whereas anilines with strong electron withdrawing groups were found to be less reactive. Anilines with electron-withdrawing groups took longer reaction times and proceed in very low yields.

Table 3. Synthesis of 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one **5**

5	R	**5**(%)[a]
a	Cy	72
b	$C_6H_5CH_2$	85
c	4-(MeO)C_6H_4	64
d	PhC_2H_4	46
e	*n*-C_7H_{16}	65
f	*c*Pr	57
g	H	96
h	3-morpholinopropyl	86
i	2-(OH)C_2H_4	72
j	3-(MeO)C_6H_4	52
k	2-ClC_6H_4	86
l	3-(1*H*-imidazol-1-yl)propyl	70
m	4-(MeO)C_6H_4	73
n	3,4-$(MeO)_2C_6H_3$	76
o	3,5-$(MeO)_2C_6H_3$	64
p	3,4,5-$(MeO)_3C_6H_2$	77
q	3,5-$(Me)_2C_6H_3$	58
r	2,4-$(MeO)_2C_6H_3$	58
s	4-$(Et_2N)C_6H_4$	77
t	4-EtC_6H_4	50
u	2-FC_6H_4	30

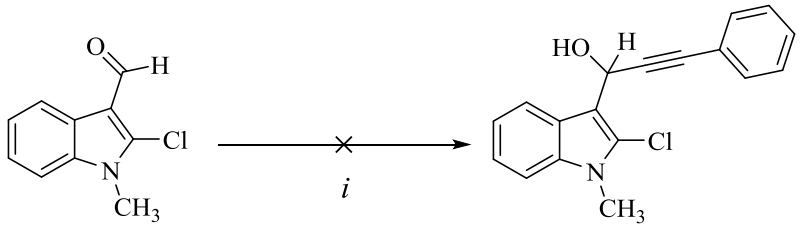
[a] yields of isolated products.

The established methodology was tested on several molecules. I got very interesting transformations with 2-chloroquinoline-3-carbaldehyde (**2**). I have tried this methodology on some other molecules, like 2,5-dichloro-1-methyl-1*H*-pyrrole-3,4-dicarbaldehyde (**15**) and 2-chloro-1-methyl-1*H*-indole-3-carbaldehyde (**17**).



15 **16**

Scheme 9. Conditions used for the synthesis of compound **16**: (*i*) *n*-BuLi, PhCCH, THF, -78C.



17 **18**

Scheme 10. Conditions used for the synthesis of compound **18**: (*i*) *n*-BuLi, PhCCH, THF, -78C.

In these transformations, which were unsuccessful, the most crucial step was the nucleophillic addition of phenylacetylene to the aldehyde group in the presence of *n*-BuLi. I have tried different reaction conditions in term of bases, like *n*-BuLi, NaH, Cs_2CO_3 and different inert solvents, like toluene, THF and acetonitrile. To my surprise, neither 2,5-dichloro-1-methyl-1*H*-pyrrole-3,4-dicarbaldehyde (**15)** nor 2-chloro-1-methyl-1*H*-indole-3-carbaldehyde (**17**) gave desired results. Investigations are in progress in the Langer group to find, based on my initial studies, suitable reaction conditions for this transformation.

1.4 Structural description

1.4.1 Structure description for compound 5e

The structure of **5e** was independently confirmed by X-ray crystal structure analysis (Figure 2). The colourless crystals showed a triclinic crystal lattice with $C_{25}H_{26}N_2O$ as the empirical formula. The heterocyclic system was in plane and the phenyl group was twisted out

of plane. Two bulky groups present at adjacent positions caused repulsion, so torsion was observed. For example, the torsion angle between C4-C5-C13-C18 was 96.38, and the torsion angle between C4-C5-C13-C14 was found to be –79.53. This difference in torsion angles contributed to the different repulsion caused by the acyclic side chain. As far as bond lengths were concerned, C-N bond lengths were found to be 1.377 ppm, which is specific for aromatic nitrogen containing heterocycles. All other bond lengths and dihedral angles were found to be more or less according to reported values.

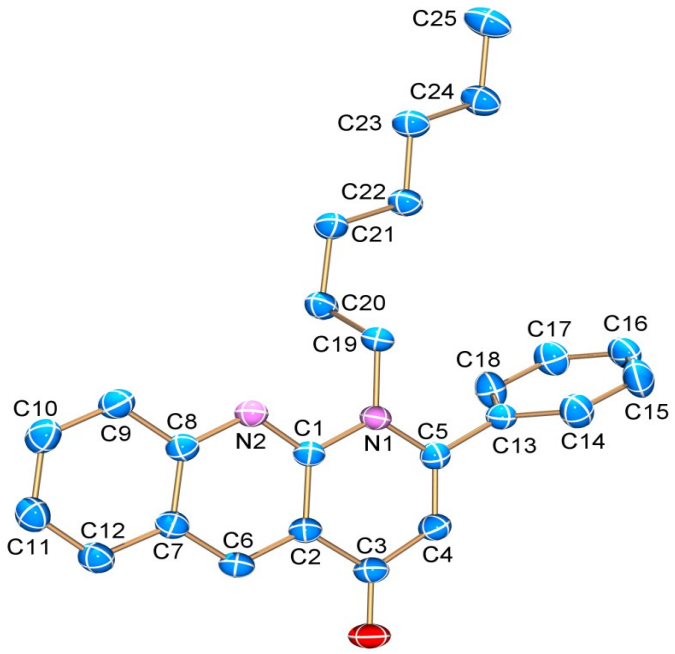


Figure 2. ORTEP illustration of compound **5e**.

1.4.2 Structure description for compound 5f

The structure of compound **5f** was also confirmed by X-ray crystal structure analysis (Figure 3). The colourless crystal showed a monoclinic crystal system with $C_{21}H_{16}N_2O$ (empirical formula). The fused hetrocyclic rings showed ring strain in which N1 and O1 were twisted out of plane by 2° and 7.08°, respectively, which was attributed to stonger repulsion between phenyl and cyclopropyl rings at adjacent positions. At position C5, phenyl showed torsion angles of 47.06° (C4-C5-C16-C17) and 49.65° (N2-C5-C16-C21). The cyclopropyl group showed a 13.42° twist out of the main system. Torsion angles for the cyclopropyl rings were found to be -55.99° (C1-N2-C6-C7) and 50.16° (C5-N2-C6-C8). The bond length for C6-N2 was found to be 1.452 ppm which is 0.017 ppm shorter than the normal C-N bond length (1.469), attributed to sp^2 hybridized N. Extended torsional strain and angle strain resulted in slight abnormality of bond lengths in the entire system.

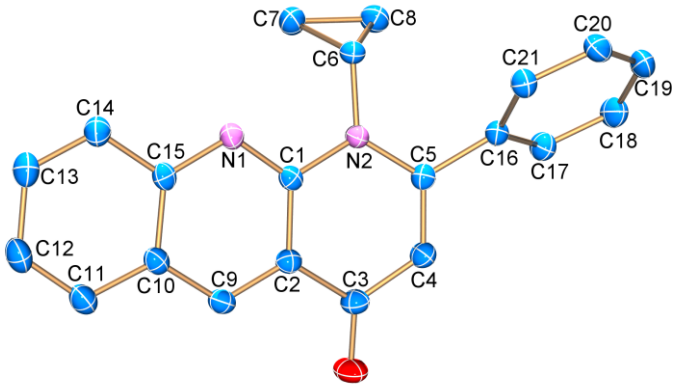


Figure 3. ORTEP illustration of compound **5f.**

1.4.3 Structure description for compound 5k

Similarly the compound **5k** was also subjected to X-ray crystal structure analysis (Figure 4) to verify its structure. The colourless crystal showed a monoclinic crystal system with $C_{25}H_{17}N_2OCl$ as the empirical formula.

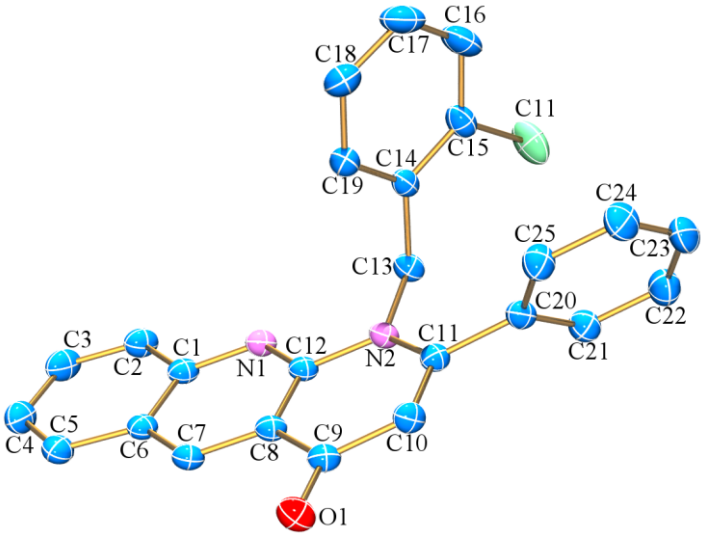


Figure 4. ORTEP illustration of compound **5k.**

1.4.4 Structure description for compound 5t

The structure of compound **5t** was confirmed by X-ray crystal structure analysis as well (Figure 5). The colourless crystal showed a monoclinic crystal system with $C_{21}H_{16}N_2O$ (empirical formula). Both aryl substituents were twisted out of plane of the main heterocyclic skeleton. The heterocyclic system was by 2.57° (N1-N2-C9) twisted out of plane. The torsion angle between both aryl groups was found to be -9.95° (C19-N1-C5-C13). Torsion angles -

88.20° (C1-N1- C19-C24) and -75.99° (C5-N1-C19-C20) were observed. The bond length for carbonyl group 1.243 (O1-C3) showed no significant deviation with respect to literature values.

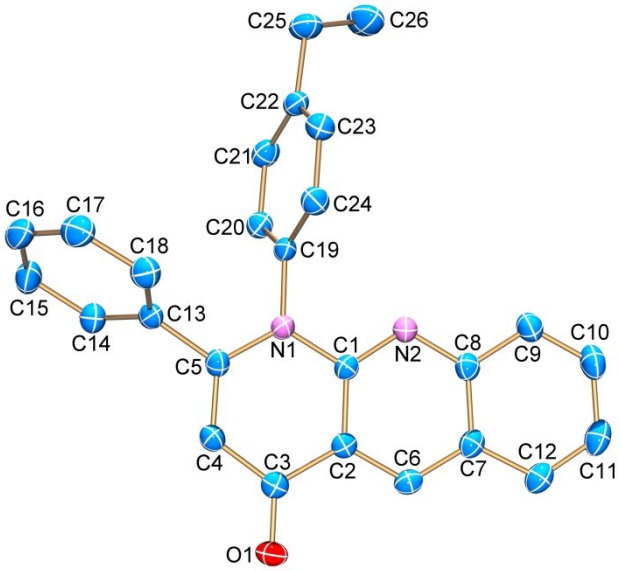


Figure 5. ORTEP illustration of compound **5t.**

The heterocyclic system experienced very little torsional strain, 2.78° (C5-C7-C9) and 3.1° (C2-N1-N2) out of plane. The phenyl and 2-chlorobenzyl groups were found twisted out of plane. The 2-chlorobenzyl was twisted by 7.5° out of plane. Torsional angles for 2-chlorobenzyl was -32.89° (N2-C13-C14-C19) and 146.95° (N2-C13-C14-C15) on either sides of plane, reflected the effect of chloro in benzyl group. Bond lengths for C=O 1.236 (C9-O1) and for C-Cl 1.736 (C15-Cl1) were in accordance to literature values.

1.5 Conclusion

I have developed an efficient approach for the synthesis of novel benzo-1,8-naphthyridin-4(1*H*)-ones from commercially available starting materials based on a domino amination/conjugate addition protocol. Scope and limitations of the reaction have been studied. Further studies related to the application of the methodology to the synthesis of other nitrogen-based heterocycles are currently under way by other students in our group. The molecules prepared can be excellent candidates for testing as antibiotics and enzyme inhibition.

2. Facile Assembly of benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines via silver triflate-catalyzed one-pot reaction of 2-alkynylquinoline-3-carbaldehyde, tosylhydrazine and carbonyl compounds.

2.1 Introduction

The 1,6-naphthyridine nucleus is one of the most abundant structural motifs found in natural products and biologically active molecules,[28] as recognized by K. W. Bentley. The versatile skeleton attracts attention for applications in pharmaceutical science, display devices and synthetic chemistry.

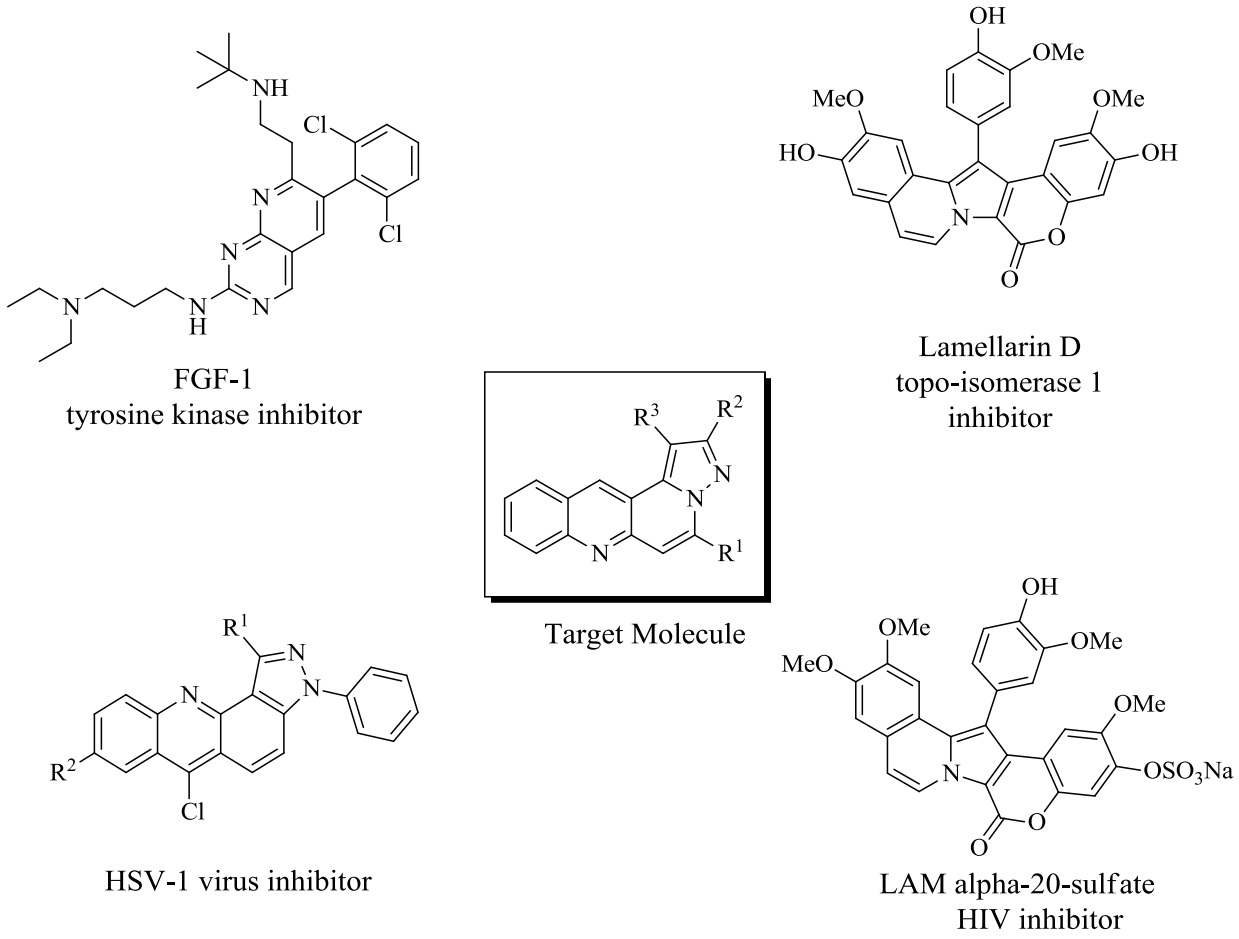


Figure 6. Some important naphthyridines.

1,6-Naphthryridines exhibit a broad range of pharmacological activity, including antifungal, antimalarial, antihypertensive, antitumor, and antihistaminic activity.[29-32] Georg Merck discovered the alkaloid papaverine, used as a vasodilator.[33] S. Hong and coworkers, discovered that decumbenine B is efficient for inhibition of spontaneous contraction of the

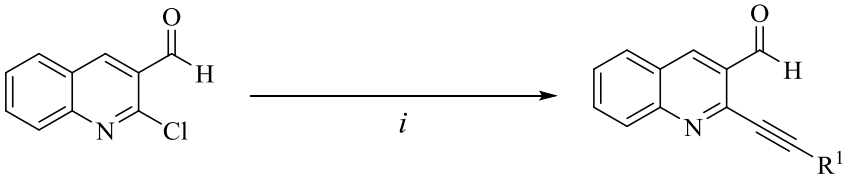
intestine.[29] Fused isoquinolines have attracted much attention. The lamellarin alkaloids, which constitute a family of novel marine natural products, contain a highly substituted fused 1,2-dihydroisoquinoline core.[32] Lamellarin D has been discovered as a potent inhibitor of human topoisomerase-1[32] and lamellarin α-20-sulfate displays selective inhibition against HIV-1 integrase in vitro.[34] J. Wu and coworkers found that pyrazolo[5,1-*a*]isoquinolines are effective for inhibition of PTP1B (protein tyrosine phosphatase 1 B, IC_{50} 1.75 μg/mL).[35] Herpes simplex virus type-1 (HSV-1) is the primary cause of facial lesions (mouth, lips, and eyes) in humans. The widespread use of acyclovir and nucleoside analogues has led to emergence of HSV strains that are resistant to these drugs. Recently, Z. Chen discovered non-nucleoside anti-HSV compounds[34] which have received considerable attention. 1,6-Naphthyridines are a class of heterocyclic compounds that exhibit a broad spectrum of biological activities,[35] such as inhibitor of HIV-1 integrase, HCMV, FGF receptor-1 tyrosine kinase, and the enzyme acetylcholinesterase (Figure 6, above).

It was confirmed that 1,6-naphthyridines constitute a versatile class of display devices. J. Dresner used 1,6-naphthyridines for the fabrication of practical electroluminescent (EL) devices.[36] Initially K. H. Drexhage explored that 1,6-naphthyridines exhibit extremely high fluorescence quantum efficiencies in the visible spectrum[37,38] including the blue region, some approaching 100%. In this regard, these are ideally suited for multicolor display applications. For full color applications, red, green, and blue (RGB) emissions are required. An efficient blue emission is of particular interest because other colors can be converted from the blue emission. There are a number of efficient blue dyes developed in the past several years.[39-45] Some of them possess reasonable or high glass transition temperature, T_g. This property has been suggested to be desirable for morphological stability reasons.[46-48] There is increasing interest in the development of efficient fluorescent materials, particularly those emitting in the blue spectral region. These materials are potential candidates for use in opto- or optoelectronic devices, such as tuneable lasers and amplifers, optical fibres, switches or modulators. They have a variety of applications in optical communications, photonics, medicine, optical spectroscopy and information displays, for example, organic electroluminescent devices.[49-53] From these, it was observed that the photophysical properties of pyrazolonaphthyridines were little explored. Thus, suitable blue emitters with high brightness along with good thermostability still remain to be developed. Thus, the development of new syntheses for a rapid approach to functionalized isoquinolines under mild conditions is very important.

Only few attempts have been made in recent years to develop simple synthetic routes, for this promising family of compounds. A.M. Kolodziejczyk used multicomponent reactions for the synthesis of such structures.[54] These reactions are important for construction of natural product-like compounds. In 2007, K. Orito reported studies toward the design and synthesis of pyrazolonaphthyridines.[32] Jie Wu and coworkers reported a multi-component reaction for the construction of pyrazolo[5,1-*a*]isoquinolines via silver triflate-catalyzed one-pot tandem reaction of 2-alkynylbenzaldehyde, tosylhydrazine, and ketone or aldehyde under mild conditions in good yields.[55] W. A. Denny prepared 3-aryl-7-halo-1,6-naphthyridin-2-amines and 3-aryl-7-halo-1,6-naphthyridin-2(1*H*)-ones by diazotization of 3-aryl-1,6-naphthyridine-2,7-diamines.[56] These reactions were ideally suited for the construction of natural product-like libraries.[57] Herein, I reported, for the first time, an efficient one-pot strategy for the synthesis of novel benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine **17** via a AgOTf catalyzed multicomponent approach (Scheme 12). The reaction proceeded smoothly with high yields under established reaction conditions.

2.2 Results and discussion

Starting from already synthesized 2-chloroquinoline-3-carbaldehyde[26] (**2**), I got 2-(phenylethynyl)quinoline-3-carbaldehyde[58] (**19a**) after Sonogashira coupling. In Sonoghashira coupling main problem was dimmer formation, I solved this issue by maintaining inert atmosphere throughout reaction and use of least amount of solvent. These two preventions gave me two benefits; firstly argon bubbling in reaction mixture avoid moisture and atmospheric gases to come in contact, secondly amount of solvent was kept low in reaction mixture which also avoid moisture. In addition to phenylacetylene, I have used 1-heptyne, cyclopropylacetylene and trimethylsilylacetylene. By this I was able to minimize dimer formation to a great extent.



2 **19**

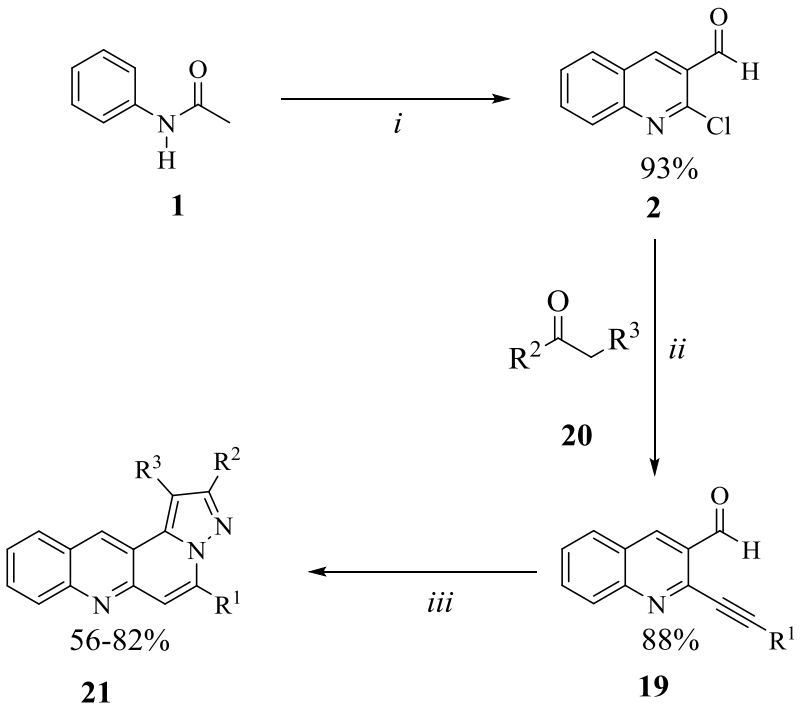
Scheme 11. Conditions for Sonogashira coupling **19**: $PdCl_2(PPh_3)_2$ (4 mol%), $HCCR^1$, CH_3CN, 80 °C, dry Ar, 3 hr.

Table 5. Synthesis of 2-(alkylethynyl)quinoline-3-carbaldehyde

19	R^1	**19** (%)[a]
a	Ph	88
b	*n*-C_5H_{11}	84
c	cPr	74
d	$(CH_3)_3Si$	71

[a] yields of isolated products.

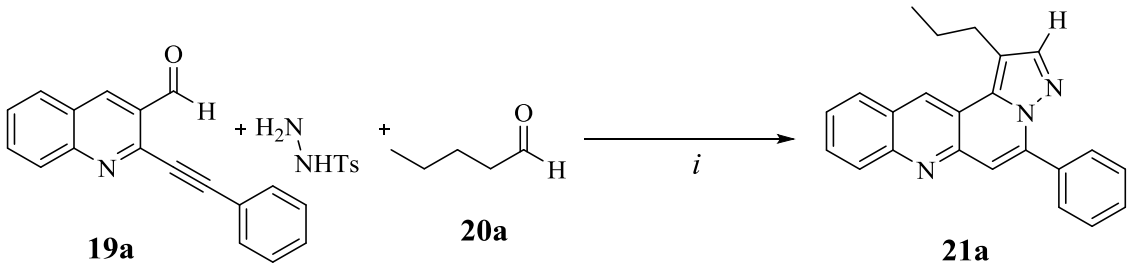
2.2.1 Synthetic scope for benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines 21



Scheme 12. Synthesis of derivatives of benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines **21**. Conditions**:** (*i*) $POCl_3$, DMF, 10 hr, 80 °C (*ii*) $PdCl_2(PPh_3)_2$ (4 mol%), $HCCR^1$, CH_3CN, 80 °C, dry Ar, 3hr. (*iii*) NH_2NHOTs, ETOH, AgOTf, K_3PO_4, Reflux, 3 hr.

Initially, a set of experiments were carried out using 2-(phenylethynyl)quinoline-3-carbaldehyde (**19a**), tosylhydrazine, and pentanal (**20a**) as model substrates (Scheme 13) The

condensation worked efficiently in EtOH for the reaction of 2-(phenylethynyl)quinoline-3-carbaldehyde (**19a**) with tosylhydrazine, and AgOTf was demonstrated as the most effective catalyst for the subsequent 6-endocyclization.[55] Therefore, at the outset the reactions were catalyzed by AgOTf (10 mol%) in EtOH in the presence of different bases.



Scheme 13. Optimization studies for **21a.** Conditions: (*i*) ETOH, AgOTf, K_3PO_4, Reflux, 3 hr.

Table 6. Optimization of the reaction condition for **21a**

ntry	Catalyst	Solvent	Base	T(°C)	Time(hr)	**21a**(%)[a]
1	AgOTf	EtOH	K_3PO_4	70	6	82
2	AgOTf	EtOH	K_2CO_3	70	6	73
3	AgOTf	EtOH	DIPA	70	6	27
4	AgOTf	EtOH	proline	70	7	36
5	AgOTf	EtOH	piperidine	70	6	28
6	AgOTf	EtOH	TEA	70	6	37
7	Catalyst Free	EtOH	K_3PO_4	70	7	15
8	AgOTf	MeCN	K_3PO_4	90	7	55
9	$Pd(PPh_3)_2Cl_2$	Toluene	K_3PO_4	90	3	67
10	$Pd(PPh_3)_4$	Toluene	K_3PO_4	90	9	47
11	AgOTf	Toluene	K_3PO_4	90	9	34

[a] yields of isolated products.

To my delight, small amounts of product (**21a**) was formed when diisopropylamine (DIPA), proline, or piperidine were utilized in the reaction. However, the large major product isolated was the isoquinolium-2-yl amide.

Table 7. Synthesis of benzo[*b*]pyrazolo [5, 1-*f*][1,6]naphthyridines **21**

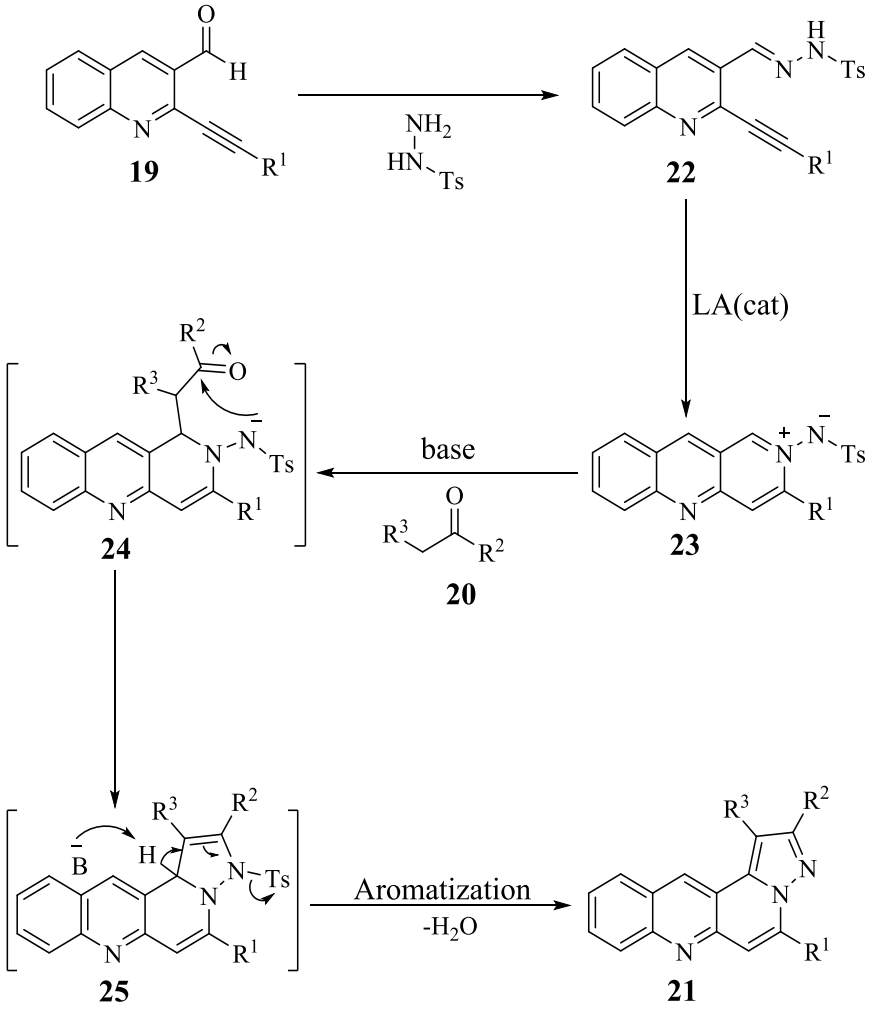
R^1	R^2	R^3	**21**	**21** (%)[a]
C_6H_5	H	*n*-C_3H_7	**a**	82
C_6H_5	H	*n*-C_6H_{13}	**b**	75
C_6H_5	H	*n*-C_8H_{17}	**c**	68
C_6H_5	H	*n*-$C_{10}H_{21}$	**d**	70
C_6H_5	H	1-C_9H_{17}	**e**	60
C_6H_5	CH_3	H	**f**	91
C_6H_5	C_2H_5	C_2H_5	**g**	84
C_6H_5		-$(CH_2)_3$-	**h**	64
C_6H_5		-$(CH_2)_4$-	**i**	87
C_6H_5		-$CH(CH_3)$-CH_2-$(CH_2)_2$-	**j**	75
C_6H_5		-$(CH_2)_5$-	**k**	63
C_6H_5		-$(CH_2)_6$-	**l**	60
C_6H_5	CO_2CH_3	CH_3	**m**	84
C_6H_5	CH_3	C_6H_5	**n**	64
C_6H_5	H	*p*-$(CH_3O)C_6H_4$	**o**	62
n- C_5H_{11}	CH_3	H	**p**	72
n- C_5H_{11}	H	*n*-C_3H_7	**q**	72
n- C_5H_{11}		-$(CH_2)_4$-	**r**	66
n- C_5H_{11}		-CH_2-$CH(CH_3)$-$(CH_2)_2$-	**s**	75
n- C_5H_{11}		-$(CH_2)_3$-	**t**	76
n- C_5H_{11}	C_2H_5	CH_3	**u**	89
cPr		-CH_2-$CH(CH_3)$-$(CH_2)_2$-	**v**	75
cPr	H	*n*-C_3H_7	**w**	74
cPr		-$(CH_2)_4$-	**x**	76
H	H	*n*-C_3H_7	**y**	72

[a] yields of isolated products.

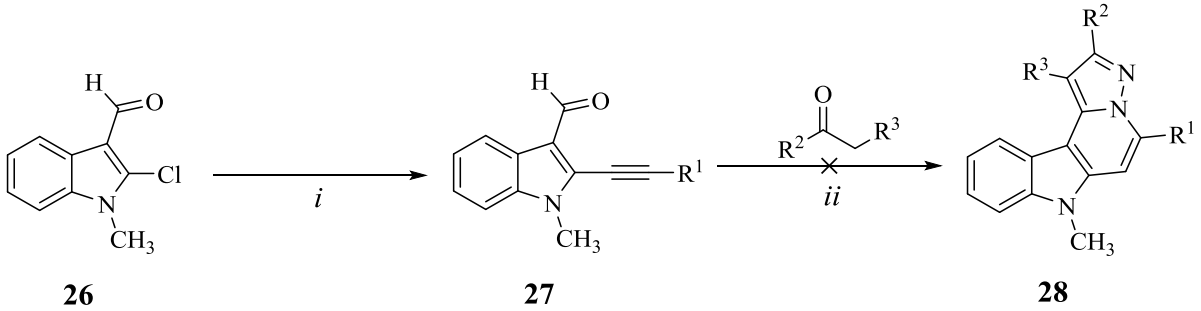
Elevating the reaction temperature or increasing the amount of pentanal could not improve the result. I then shifted my focus on inorganic bases. Gratifyingly, the reaction

proceeded smoothly in the presence of K_2CO_3 at 70 °C, which gave rise to the desired product (**21a**) in 73% isolated yield. Further investigation revealed that K_3PO_4 was the best choice with an 82% isolated yield (Table 6, above). This silver-catalyzed formation of benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines **21** was found to be workable for esters, acetophenones, cyclic and acyclic ketones, and aldehydes. In addition to phenyl groups attached to the triple bond, 2-alkynylquinoline-3-carbaldehydes **19** with cyclopropyl, *n*-pentyl and TMS groups were found to be suitable as well to generate the desired products in good yields (Scheme 12, Table 7). For example, a high yield (87%) of compound **21i** was obtained.

Using the mild conditions [AgOTf (10 mol %), K_3PO_4 (3.0 equiv.), EtOH, 70 °C], the mechanism was studied in view of other cascade reactions[59] using 2-alkynylbenzaldehydes as versatile building blocks for the construction of heterocycles.[57] Based on these results, I have developed an efficient route for the construction of nitrogen containing heterocycles starting from 2-(phenylethynyl)quinoline-3-carbaldehyde (**19**). Prompted by the advancement of multi-component reactions, I conceived that benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines **21** might be easily accessible via a one-pot tandem reaction of 2-(alkynyl)quinoline-3-carbaldehydes **19**, tosylhydrazine, and carbonyl compounds (Scheme 12). 2-(Alkynyl) quinoline-3-carbaldehyde (**19**) could be easily obtained via a Sonogashira reaction of 2-chloroquinoline-3-carbaldehyde with alkynes.[58] After condensation with tosylhydrazine, 2-chloroquinoline-3-carbaldehyde (**2**), N'-(2-alkynylquinolinidene) tosylhydrazine (**22**), would be afforded. Subsequently, the 6-*endo*-cyclization would occur to generate the (benzo[*b*][1,6]naphthyridin-2-ium-2-yl)(tosyl)amide (**23**) in the presence of a suitable Lewis acid. In this step, the formation of a π-complex via coordination of the alkynyl moiety of **19** to the Lewis acid would be involved, thus activating the triple bond for further cyclization. Meanwhile, the *in situ* formed enolate (derived from ketone or aldehyde in the presence of base) would attack the (benzo[*b*][1,6]naphthyridin-2-ium-2-yl)(tosyl)amide (**23**) to produce intermediate **24**. Subsequent intra-molecular condensation and aromatization would give rise to the desired benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine (**21**). However, there are several questions associated with the proposed synthetic route, such as selectivity, compatibility, and relative rates. Thus to verify the practicability of the proposed route as shown in Scheme 14, I have initiated the search for suitable conditions for this transformation. This synthetic methodology worked efficiently with quinoline moiety, but purification required attention. I did purification by flash column chromatography, with the use of diethylamine for basifying silica. It was recommended that solvent saturated with little diethylamine facilitated smooth and high yield separation of product.



Scheme 14. Possible route for one-pot tandem reaction of 2-(alkynyl)quinoline-3-carbaldehyde (**19**), tosylhydrazine, and carbonyl compounds.



Scheme 15. Failed trial for compound **28.** Reaction conditions: (*i*) $PdCl_2(PPh_3)_2$ (4 mol%), $HCCR^1$, CH_3CN, 80 °C, dry Ar, 3hr. (*ii*) NH_2NHOTs, ETOH, AgOTf, K_3PO_4, Reflux, 3 hr.

Encouraged by findings I got for synthesis of compounds **21a-y**, I have utilized 2-chloro-1-methyl-1*H*-indole-3-carbaldehyde (**26**) as a starting material for the synthesis of compound **28**. It was noted that established transformation which worked really well for quinoline moiety **19,** did not work with indole moiety **26**. It was observed that 2-chloro-1-methyl-1*H*-indole-3-carbaldehyde (**26**) underwent a Sonogashira coupling under established conditions. To my surprise, 1-methyl-2-(phenylethynyl)-1*H*-indole-3-carbaldehyde (**27**) could not be transformed to the final product.

Table 8. Optimization of the reaction condition for compound **28**

Entry	Catalyst	Solvent	Base	T(°C)	Time(hr)	**17a**(%)[a]
1	AgOTf	EtOH	K_3PO_4	70	6-10	-----
2	AgOTf	EtOH	K_2CO_3	70	6-10	-----
3	AgOTf	EtOH	DIPA	70	6	-----
4	AgOTf	EtOH	proline	70	7	-----
5	AgOTf	EtOH	piperidine	70	6	-----
6	AgOTf	EtOH	TEA	70	6	-----
7	Catalyst Free	EtOH	K_3PO_4	70	7	-----
8	AgOTf	MeCN	K_3PO_4	90	7	-----
9	$Pd(PPh_3)_2Cl_2$	Toluene	K_3PO_4	90	8	trace
10	$Pd(PPh_3)_4$	Toluene	K_3PO_4	90	9	-----
11	AgOTf	Toluene	K_3PO_4	90	9	-----

[a] yields of isolated products.

During this investigation, the first step was to treat compound (**27**) with tosylhydrazide in a variety of solvents at room temperature; no significant transformation was observed. Finally, at 70 °C a partial transformation to the Schiff base was observed. After separation of this intermediate, I treated it further with AgOTf to induce a cyclization, but this was not observed even at extended reaction time and high temperatures. Herein, I summarized reaction conditions utilized for this domino transformation (Table 8). Only trace amount of product was observed by GC-MS when $Pd(PPh_3)_2Cl_2$ (catalyst), K_3PO_4 (base), toluene (solvent) were used (8 hr at 90 °C). Further investigations are in progress to find out suitable conditions for this conversion.

2.3 Structural description

2.3.1 Structure description for compound 21i

The structure of compound **21i** was confirmed by X-ray crystal structure analysis as well (Figure 7). The colourless crystal showed a triclinic crystal system with $C_{24}H_{19}N_3$ (empirical formula). The heterocyclic system was in plane and the phenyl group is twisted out of plane. The fused cyclohexyl ring was found to be by 18.17° twisted out of plane. One bond fused with the pyrazol ring caused torsional strain, by -49.02° (C1-C2-C3-C4), by 63.11° (C2-C3-C4-C5), by -40.63° (C3-C4-C5-C6), and by 0.11° (C4-C5-C6-C1). For the phenyl ring, which was by 7.71° twisted out of plane, torsional angles were -45.02° (N1-C18-C19-C20) and -41.96° (C17-C18-C19-C24). A difference in C-C bond lengths was observed, i.e. fused aromatic C8-C16 bond length of 1.435 pm and isolated aromatic C8-C9 bond length of 1.378 pm. This C-C bond length abnormality attributed to torsional strain imparted by substituents and by the presence of nitrogen in the ring (electronic situation of the pyridine moiety).

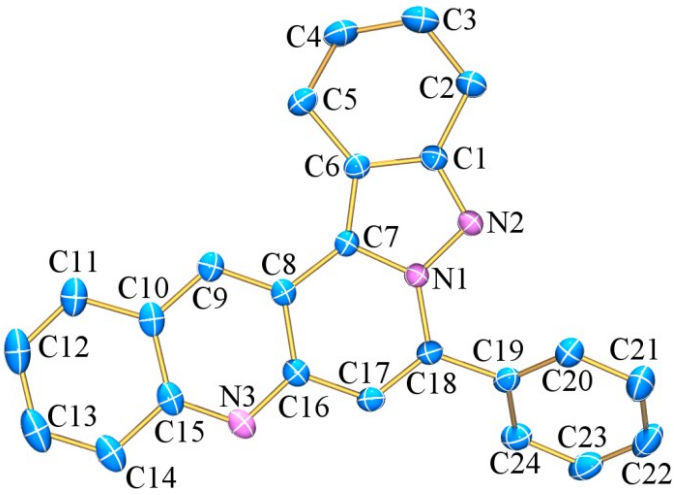


Figure 7. ORTEP illustration of compound **21i** (50% probability ellipsoids)

2.3.2 Structure description for the compound 21q

The structure of compound **21q** was confirmed by X-ray crystal structure analysis as well (Figure 8). The colourless crystal showed a triclinic crystal system with $C_{22}H_{25}N_3$

(empirical formula). The heterocyclic system was partially twisted with by 3.33°(C11-C13-C1) and by 2.16° (C8-N3-C5) out of plane. The pyrazol ring was out of plane by 5.37°. The pyrazol ring torsional strain was not significant as acyclic substituent offered least steric effect. Here also bond abnormality was observed, i.e. 1.38 pm (C13-C14) and 1.419 pm (C12-C7). This bond abnormality reflected the unequal electronic distribution over all centers which in turn were because of heteroatoms and ring strain imposed by substituents.

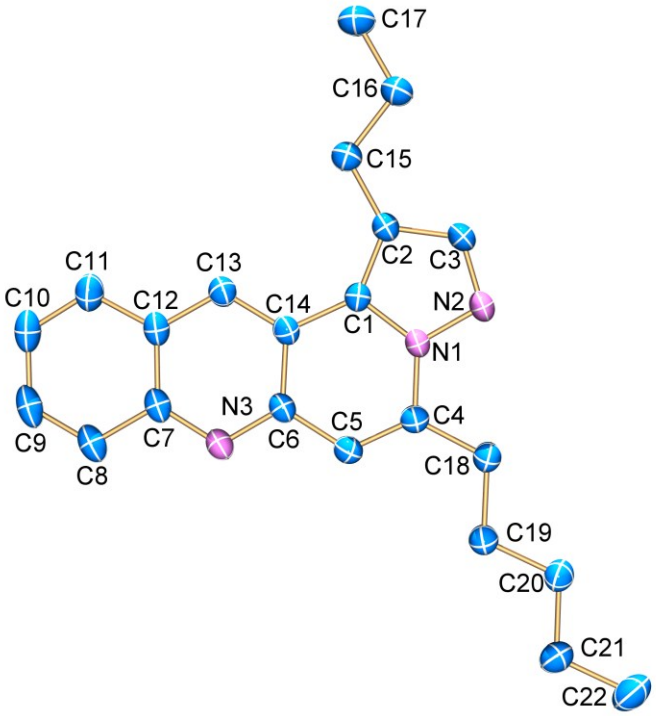


Figure 8. ORTEP illustration of compound **21q** (50% probability ellipsoids)

2.3.3 Structure description for the compound 21w

The structure of compound **21w** was confirmed by X-ray crystal structure analysis as well (Figure 9). The yellow crystal showed a monoclinic crystal system with $C_{20}H_{19}N_3$ (empirical formula). Hexagonal fused aromatic rings were lying in a plane, but pyrazol experienced a slight distortion by 4.61°. It was observed that both substituents, cyclopropyl at N1 and *n*-propyl at C2, were oriented in opposite directions. The cyclopropyl ring was twisted by 7.08° above the plane of the main skeleton. A torsion angle for the cyclopropyl ring was found to be -15.51° (C9-C10-C11-C12), and 85.84° (C9-C10-C11-C13). The cyclopropyl ring

with bond angles 60.51°, 59.95°, and 59.53° confirmed a high degree of torsional strain and angle strain associated with it.

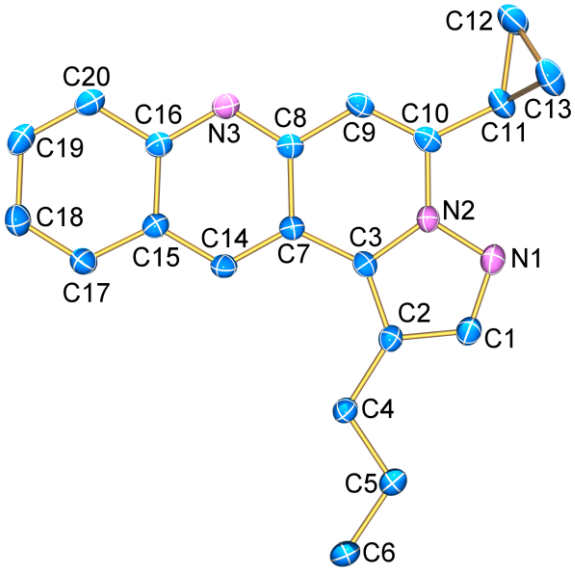


Figure 9. ORTEP illustration of compound **21w** (50% probability ellipsoids)

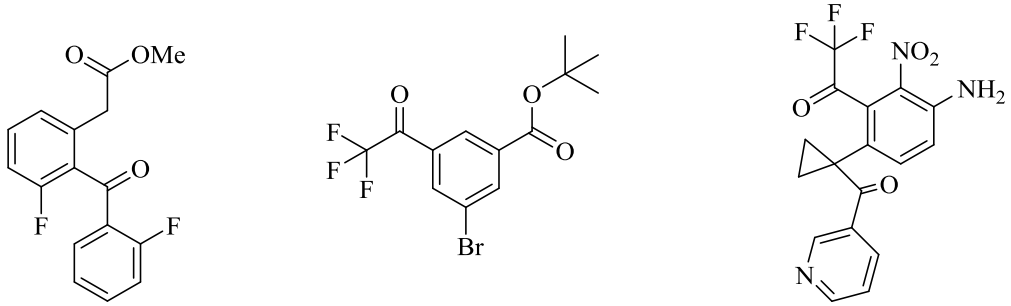
2.4 Conclusion

In conclusion, I have described a novel and efficient route for the generation of benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines **21** via AgOTf-catalyzed one-pot tandem reaction of 2-(alkanylethynyl)quinoline-3-carbaldehyde (**19**), tosylhydrazine, and carbonyl compounds. This reaction proceeded with good functional group tolerance under mild conditions with high efficiency and excellent selectivity.

3. An efficient approach for the synthesis of fluorinated arenes via direct acyl-alkylation of benzyne.

3.1 Introduction

Organofluorine molecules play an important role as synthetic drugs.[60] 5-Fluorouracil was the first fluorinated drug which was developed as an anti-tumor agent in 1957.[61] The importance of fluorine containing compounds is based on their metabolic stability and lipophilicity and, thus, high bioavailability. The incorporation of fluoroalkyl groups and particularly the trifluoromethyl (CF_3) group in pharmaceutically and agrochemically relevant molecules have a significant impact on their physical and biological properties.[62] Fluorinated aceto- and benzophenones, containing a 1,5-dicarbonyl unit connected by a benzene moiety, are of considerable relevance as synthetic intermediates in medicinal chemistry. For example, benzophenone **A**, prepared by a multistep synthetic synthesis starting from 3-(4-fluorophenyl)propanoic acid, was used as a key intermediate during the synthesis of fluorinated pteridines which were reported to act as anti-viral drugs for the treatment of liver diseases (HCV).[63] Trifluoroacetophenone **B**, available by a multistep synthesis starting with 3-bromo-5-iodobenzoic acid, was reported to show considerable activity against pain.[64] Trifluoroacetophenone C, which was also prepared in many steps, was reported to exhibit a pronounced antithrombotic activity (figure 10).[65]

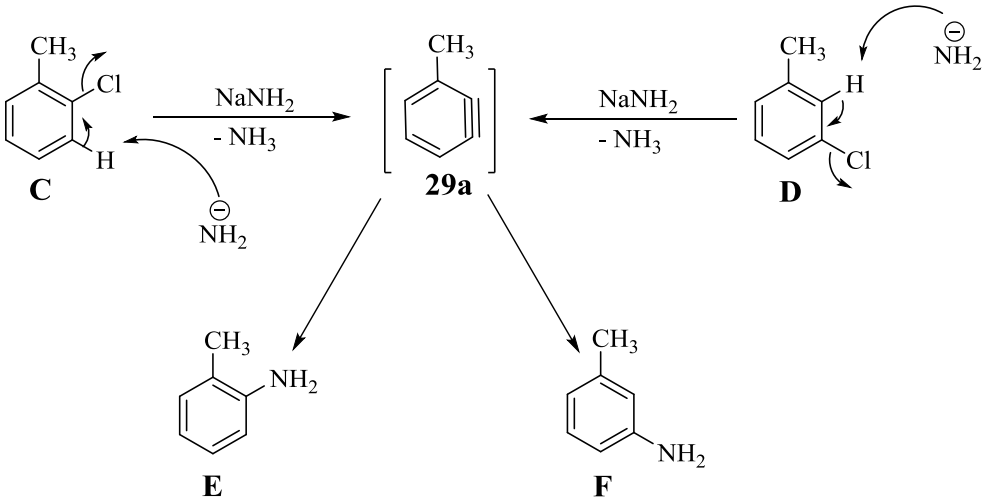


A **B** **C**

Figure 10. Some important fluorinated 1,5-dicarbonyl compounds

Herein, I report a new and convenient synthesis of fluorinated aceto- and benzophenones based on the reaction of benzyne with fluorinated 1,3-dicarbonyl compounds. First evidence for the existence of an aryne was reported in 1902 at the University of Rostock: Stoermer and

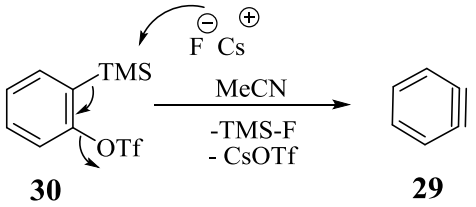
Kahlert observed the formation of 2-ethoxybenzofuran on treatment of 3-bromobenzofuran with bases in ethanol and postulated the formation of *ortho*-didehydrobenzofuran.[66] In 1927, W. E. Bachmann and H. T. Clarke suspected benzyne as a reactive intermediate of the Wurtz-Fittig synthesis.[67] Wittig, in 1942, suggested the existence of benzyne.[68] During the last 50 years, the discovery of benzyne had a strong impact in the field of organic chemistry.[69] Despite of the indirect evidence for the existence of benzyne, a direct proof was not reported before 2001.[70] It was Professor John D. Roberts, who in 1953 published a communication on the existence of benzyne; an electronically neutral and unstable benzene ring with a triple bond which bears diradical character. This structural explaination of benzyne was made in context of Professor Robert's work to elucidate the mechanism for forming anilines from substituted chloroarenes and metal amides. Before 1953, many chemists believed that metal amides attacked the aromatic ring in S_nAr fashion, but this mechanism could not account for all the experimental data on the amination of unsymmetrical haloarenes. Professor Robert suggested the transient existence of benzyne during the amination of halobenzenes (**Scheme 16**).[71]



Scheme 16. Mechanistic evidance for benzyne generation

Benzyne as a reagent in synthetic organic chemistry suffered from several drawbacks, such as its high reactivity and the harsh basic conditions required for its generation by the classic protocol.[69] In 1983, Kobayashi described a mild method for the generation of benzyne at moderate temperature which relies on a fluoride-induced 1,2-elimination reaction of *ortho*-(trimethylsilyl)aryltriflates.[72] Because of their extreme reactivity, arynes must be generated in situ in the presence of reaction partners. This has limited their use in the development of

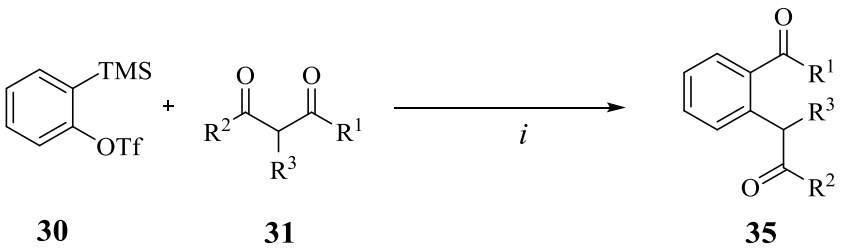
selective organic reactions because the harsh conditions that are used to generate arynes may have an adverse effect on other reactants. In 1983 Kobayashi described a mild method for the in situ preparation of benzyne at moderate temperatures that exploits the fluoride-induced elimination of *ortho*-silyl aryltriflates (Scheme 17).[72] Recently, this method has been used to develop mild reactions involving aryne intermediates.



Scheme 17. Generation of benzyne.

Although Stoermer and Kahlert discovered benzyne 100 years ago, only recently have organic chemists realized the potential for this reactive intermediate to insert directly into σ-bonds. Recently, Stoltz and coworkers reported the insertion of benzyne into б-bonds of 1,3-dicarbonyl compounds to give (2-acylphenyl)acetates and related products.[73] It was presumed that the reaction proceeds by formal [2+2] cycloaddition and subsequent fragmentation. While benzyne insertions into metal-metal, heteroatom-metal, heteroatom-heteroatom, carbon-metal, and carbon-heteroatom б-bonds had been reported before, the work of Stoltz represented the first mild and direct insertion of benzyne into a carbon-carbon б-bond. Herein, we report what is, to the best of our knowledge, the first application of this method to fluorinated 1,3-dicarbonyl compounds (Scheme 18). The transformations reported herein provide an efficient access to fluorinated aceto- and benzophenones which contain a 1,5-dicarbonyl unit connected by a benzene moiety. The products are not readily available by other methods.

3.2 Synthetic scope



Scheme 18. Synthesis of **35a-j.** Condition*s:* (*i*) CsF, MeCN, 80 °C, 40-60 min.

During my thesis, I had the task to apply the methodology of Stoltz to fluorinated *β*-ketoesters and 1,3,5-tricarbonyl compounds.

3.3 Results and Discussion

The CsF mediated reaction of fluorinated *β*-ketoesters **31a-d** with *ortho*-silylaryltriflate **30**, following conditions reported by Brian M. Stoltz, afforded the desired acyl-alkylation products **35a-j** in good yields (Table 9). Additionally, the substitution pattern of fluorine on *β*-ketoesters was varied (**31a-d**), and the efficiency of the reaction was thus studied. For example, fluorinated, trifluoromethyl- and perfluoroalkyl-substituted ketoesters and diketones gave the desired acyl-alkylation products in good yields. I further examined the coupling of aryne precursor **30** with fluorinated *β*-diketones **31f-j**. To my delight these *β*-diketones reacted with **30** to produce side-chain fluorinated *ortho*-disubstituted arenes **35f-j** in good yields.

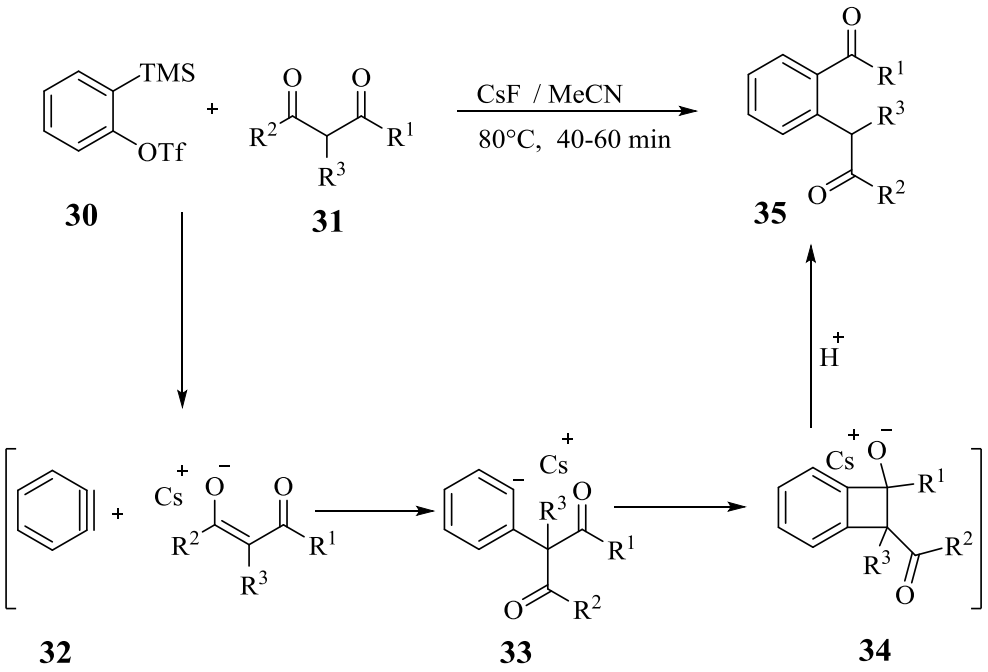
Table 9. Acyl-alkylation of benzyne

31	R^1	R^2	R^3	**35**	**35**(%)[a]
a	Me	EtO	F	**a**	71
b	CF_3	EtO	H	**b**	71
c	4-FC_6H_4	MeO	H	**c**	87
d	4-FC_6H_4	EtO	H	**d**	79
e	4-$(NO_2)C_6H_4$	EtO	H	**e**	85
f	$CF_2CF_2CF_3$	*t*-Bu	H	**f**	50
g	CF_3	Ph	H	**g**	73
h	CF_3	2-Naphthyl	H	**h**	57
i	CF_3	Me	H	**i**	67
j	CF_3	2-Furyl	H	**j**	70

[a] yields of isolated products.

In this reaction two carbon-carbon bonds are formed in a single step, often with exquisite regiocontrol. The acyl-alkylation reaction is the net result of benzyne insertion into the *α,β* (C-C) single bond of the *β*-ketoesters and *β*-diketones, presumably by a formal [2+2] cycloaddition/fragmentation cascade.[73] The insertion of benzyne into the *α,β* (C-C) single bond of the *β*-ketoesters and *β*-diketones presumably proceeds by a domino [2+2]

cycloaddition/fragmentation reaction via intermediates **32**, **33**, and **34** (Scheme 19). Related domino reactions were reported by other authors.[74,75]



Scheme 19. Proposed mechanism of benzyne insertion to 1,3-dicarbonylcompounds.[71]

3.4 Structural description for compounds 35a-j

3.4.1 Structural description for compound 35b

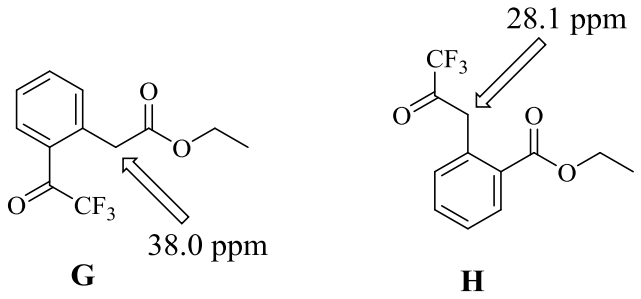
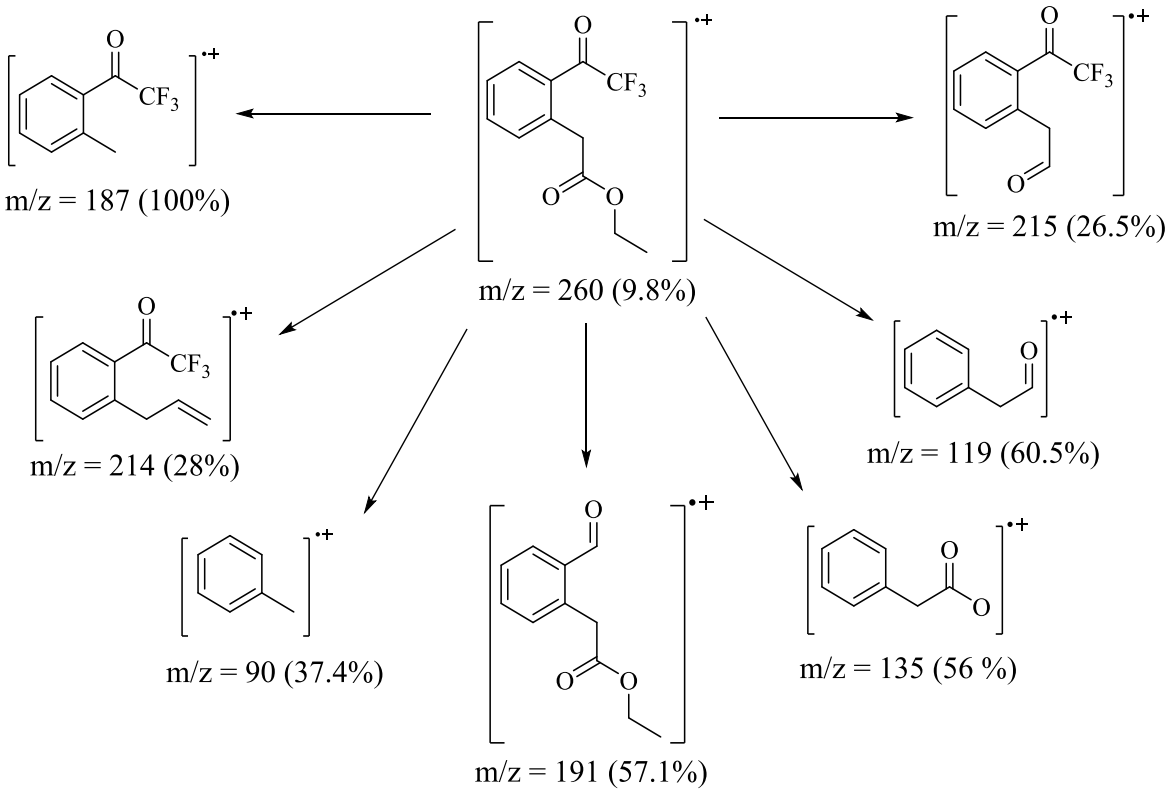


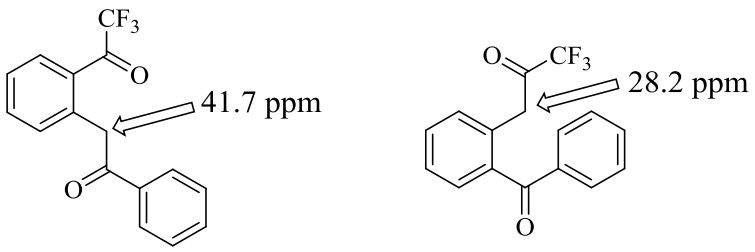
Figure 11 Possible regiomers of **35b** (with calculated shift values).

Structure and regioselectivity was investigated by NMR and MS spectroscopy. I took into account two molecules **35b** with *β*-ketoester and **35g** with *β*-diketone moiety, respectively (Figure 11above). First of all, I took into accout the position of the CH_2 group, either connected to $COCF_3$ or to CO_2Et. By NMR, it was suggested that the CH_2 group was not attached to the $COCF_3$ group, as no splitting was observed in ^{13}C NMR which should be present in case of possibility **H**. The comparisons between calculated and observed δ values were in favour of regiomer **G,** where δ for CH_2 was observed to be 41.1. Mass fragmentation pattern was extremely helpful for confirmation of regioselectivity. It was cleared from GC-MS that the $[M^+]$ peak appeared at m/z, 260 (9.8%). The base peak was of great importance, with m/z, 187 which gave evidence for the directly bonded trifluoroacetyl group to benzene. This base peak could be obtained by sequential loss of ethyl and CO_2. In case of possibility **H**, there should be two fragments, i.e one with m/z, 111 and second ethyl benzoate with m/z, 150. Both of these fragments were found to be absent, which clearly favour possibility **G** as the only regeoisomer. Possibility **G** showed the expected fragments shown in scheme (20).



Scheme 20. Mass fragmentation pattern of **35b**.

3.4.2 Structural description for compound 35g



I **J**

Figure 12. Possible regiomers of **35g** (with calculated shift values)

In the ^{13}C-NMR spectra, I took the CH_2 group in account to locate its attachment either to the trifluoroacetyl or benzoyl group. I got a first clue that CH_2 appeared at δ, 37.1 which was quite different from the theoretical calculated value (δ, 28.2) and disfavoured isomer **J,** but favoured isomer isomer **I**. Secondly, if there was any possibility for the existence of isomer **J** then there should be splitting of the CH_2 carbon signals, because of the CF_3. Furthermore, no long-rang splitting of the CH_2 signal was observed indicating that CH_2 was not bonded to the trifluoroacetyl group, supporting the absence of isomer **J** and existence of isomer **I**. Thus, on the basis of ^{13}C-NMR spectroscopy, the formation of isomer **I** is strongly favoured.

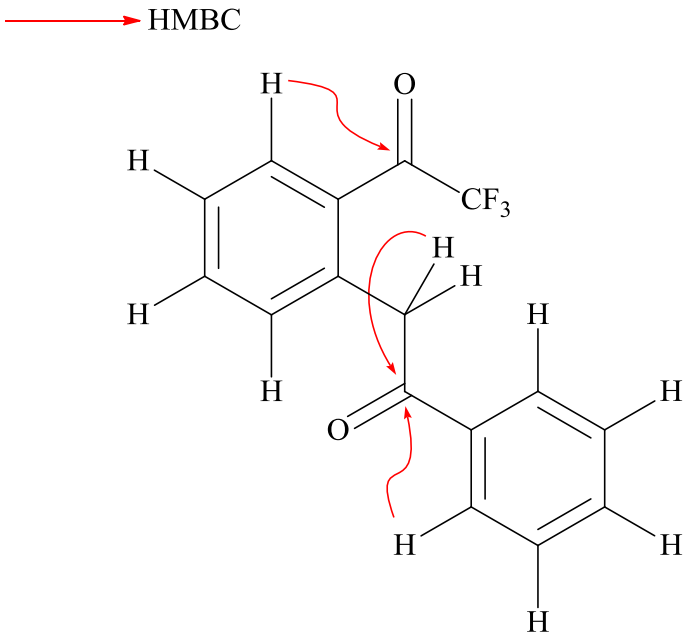


Figure 13. HMBC interpretation of **35g**

Finally structure **I** was independently confirmed by 2D-NMR. Also I took both carbonyl groups into account. It was found that carbonyl group with δ, 198.3 showed a clear HMBC interaction with the protons of CH_2 (δ, 37.1), also one HMBC interaction between a proton at δ, 7.72 and carbon of $COCF_3$ group confirmed direct bonding of the $COCF_3$ group with the aromatic system. Further position of each proton and carbon was located by NOESY, COSY, ^{13}C-NMR and ^{1}H-NMR.

3.4.3 Structural description for compound 35e

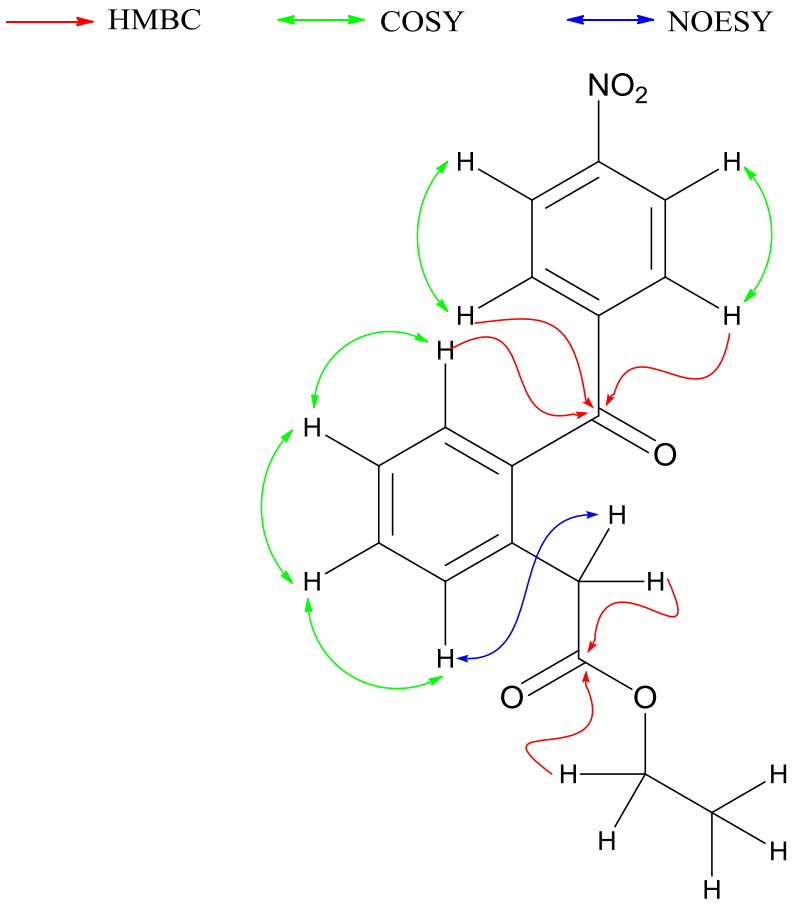


Figure 14. HMBC, NOESY and COSY interpretation of **35e.**

The structure of **35e** was verified by 2D NMR experiments (COSY, HMBC, NOESY). Here two carbonyl groups were taken into account. A clear HMBC correlation of the carbonyl carbon (δ ,196.2) with two protons (δ, 7.89) of the first benzene ring (having a nitro group) and another HMBC correlation with a proton (δ, 7.46) of the second benzene ring. The ester

carbonyl carbon showed a clear correlation with the proton of both CH_2 groups (δ, 3.88 and 3.95) on its either sides. I further studied COSY interactions to locate the exact position of correlating protons. NOESY correlations were also useful to confirm the structure as shown in figure 14 (above).

3.5 Conclusion

I have developed a mild, direct, and efficient approch for the acyl-alkylation of arynes to produce interesting *ortho*-disubstituted arenes via an unusual reaction cascade. Overall, the transformation results in the formation of two new C−C bonds by the net insertion of an arene unit into the α,β-single bond of fluorinated β-ketoester or β-diketones. This facile methodology provides a convergent, single-step, high-yielding access to a variety of side chain fluorinated, *ortho*-disubstituted arenes structures that would otherwise be difficult to be obtained.

4. $AgNO_3$-catalyzed domino intramolecular cyclization: a facile and efficient approach to the synthesis of benzimidazole based polycyclic indole derivatives.

4.1 General Introduction.

All heterocyclic compounds have a great interest in pharmaceutical chemistry. Out of these heterocyclic compounds the benzfuzed heterocyclic i.e Benzimidazole and Indole derivatives have wide variety of biological activities. Indole-based fused heterocycles belong to the most widely distributed naturally occurring compounds, isolated from plants, fungi and marine organisms.[76] The range of applications for these therapeutically relevant compounds include protein kinase C inhibitors, 5-HT agonists, melatonin agonists and glucocorticoid receptor modulators, displaying cytotoxic, antiviral, antimicrobial, antiparasitic, anti-inflammatory, antiserotonin, Ca2þ, calmodulinantagonistic and antitopoisomerase-I activities[77] These polyheterocycles frequently feature structurally diverse novel frameworks and remain a source of new natural product-inspired[78] chemical entities for chemical biology research.

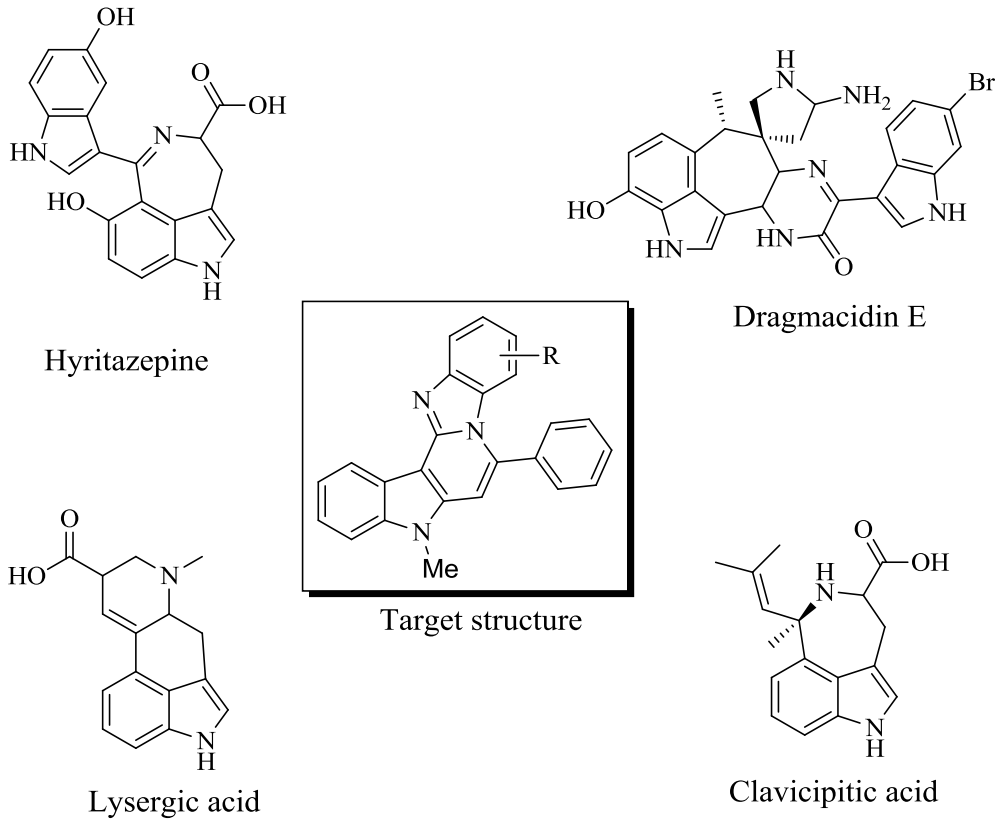


Figure 15. Important indole derivatives

In addition to that, benzimidazoles have played a very important role in the development of theory in heterocylic chemistry and also extensively in organic synthesis.[79] Extensive

biochemical and pharmacological studies have confirmed that derivatives are effective against various strains of microorganisms. One reason for a special interest of researchers toward benzimidazole derivatives has been 5,6-dimethylbenzimidazole which is a constituent of naturally occurring vitamin B12. Although vitamin B12 is capable of inducing the growth of bacteria, the benzimidazole component and some of its derivatives repress the bacterial growth. Due to the structural similarity to purine, antibacterial ability of benzimidazoles is explained by their competition with purines resulting in inhibition of the synthesis of bacterial nucleic acids and proteins.[80] Benzimidazole drugs are widely used for prevention and treatment of parasitic infections.

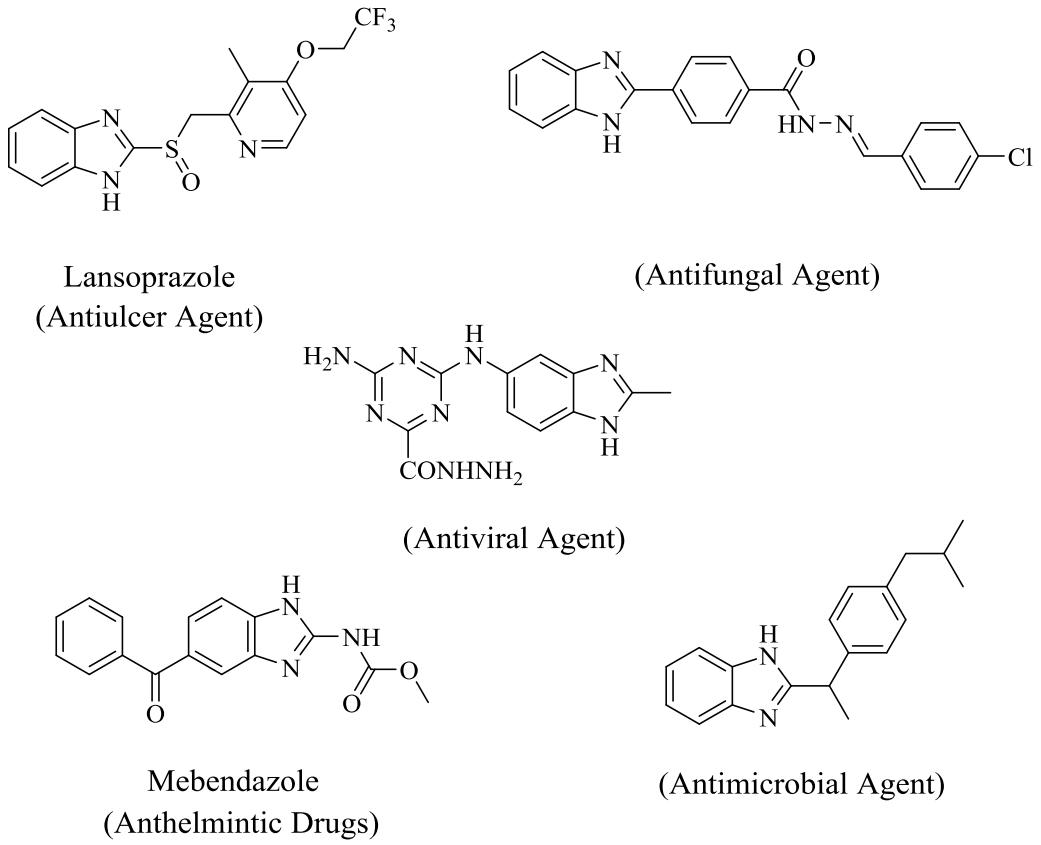


Figure 16. Important benzopyrazol derivatives.

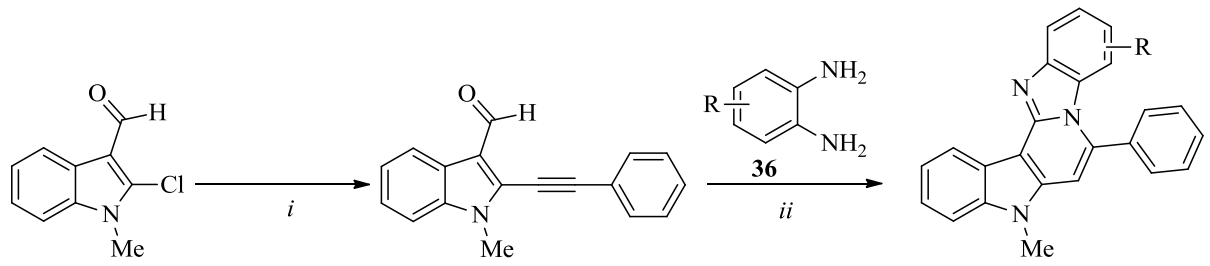
Thiabendazole (TBZ) was the first benzimidazole to be marketed over 40 years ago. It has been widely used for the treatment of gastrointestinal nemtodes, lungworms and as a fungicidal agent. Incouraged by this discovery, a number of alternative benzimidazoles offering similar activity came to the market, such as parbendazole (PAR), cambendazole (CAM), mebendazole (MBZ) and oxibendazole (OXI). Benzimidazoles possessing sulphide and sulpoxide functional groups are offering a wide spectrum of activity and efficiacy. Albendazole

(ABZ), fenbendazole FBZ) and oxfendazole (OFZ) were the first such imidazoles to be successfully used in the treatment of all growth stages of gastrointestinal nematodes. Triclabendazole (TCB) was introduced as an antihelmenthic agent for treatment of all growth stages of liver fluke, but it is ineffective against nematodes. Luxabendazole (LUX) is another benzimidazole-sulphide used in the food producing animals, but is not lisenced in the Europe.[81]

Several synthetic routes were reported: Huang-Che Ouyang[82] and coworkers reported an efficient tandem route to the synthesis of iodoisoquinoline-fused benzimidazole derivatives via tandem iodocyclization reaction with benzenediamines and 2-ethynylbenzaldehydes in DMSO. Noriko Okamoto and co-workers[83] introduced direct efficient syntheses of the benzimidazo[2,1-*a*]isoquinoline ring system from 2-bromoarylaldehydes, terminal alkynes, and 1,2-phenylenediamines by a microwave-accelerated tandem process in which a Sonogashira coupling, 5-endo cyclization, oxidative aromatization, and 6-endo cyclization can be performed in a single synthetic operation. In addition, isoquinoline-fused benzimidazoles have attracted considerable interest, due to their outstanding biological activities, such as anti-HIV-1, anticancer, antimicrobial and antifungal properties.[84] Thus, the development of novel and important compounds, like indole-fused benzimidazoles, will be an interesting addition to existing biologically active compounds. In this regard, some progress has been accomplished *via* tandem nucleophilic addition and electrophilic cyclization using *o*-alkylbenzaldehyde and phenylenediamine in the presence of various alkynophilic Lewis acid catalysts.[85] Vineeta Rustagi,[86] and coworkers introduced a straightforward methodology for the synthesis of isoquinolino[2,1-*a*]pyrrolo/indolo[2,1-*c*]quinoxalines and benzimidazo[2,1-*a*]isoquinolines *via* a $AgNO_3$-catalyzed one-pot tandem sequence in water using *o*-alkynylaldehydes andiamines with tethered nucleophiles.

4.2 Synthetic scope

Herein, I am going to report a facile synthesis of benzo-[4',5']-imidazo-[1',2':1,2]-pyrido-[4,3-*b*]indole **37**, which combine benzimidazol and indole moieties. This heterocyclic core structure has, to the best of my knowledge, not been previously reported (scheme 21).



26 **27** **37**

Scheme 21. Synthesis of benzo[4',5']imidazo[1',2':1,2]pyrido[4,3-*b*]indoles **37**. Conditions: (*i*) $PdCl_2(PPh_3)_2$ (4 mol%), HCCPh, DMF, 20 °C, Et_3N, under dry Ar, 3hr. (*ii*) $AgNO_3$, H_3O.

4.3 Results and discussion

Starting from compound **26,** compound **27** was prepared according to literature reported procedure [87]. In water, 1-methyl-2-(phenylethynyl)-1*H*-indole-3-carbaldehyde (**27**) was heated with benzene-1,2-diamine at various time and temperature. It was observed that reaction proceeded in good yield and afforded product **37** in good yield, when water was the solvent. I have used different Lewis acids and solvents to check the course of reaction. The most important results were obtained with water and $AgNO_3$ as a catalyst. Here, lower temperature and long reaction time favour the yield of reaction, whereas high temperature did not give high yields of product. It was noted that the reaction proceeded in comparative yield, when DMF was used as solvent at 120°C for 3 hr (Table 10).

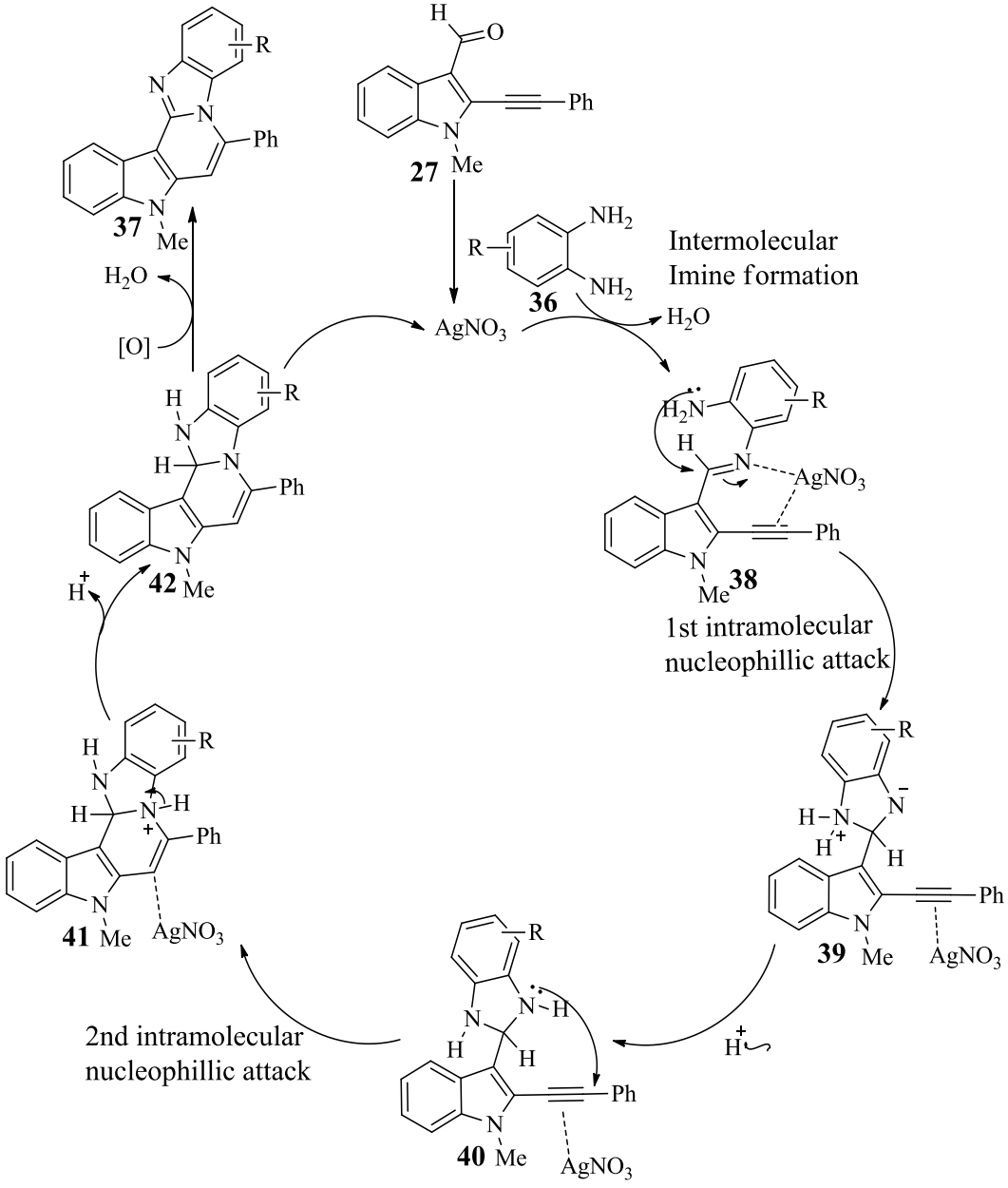
Table 10. Optimized reaction conditions for compound **37a.**

Entry	Catalyst	Solvent	T °C	Time(hr)	Yield (%)[a]
1	AgOTf	Toluene	90	8	23
2	$PdCl_2$	Toluene	90	8	----
3	$Pd(OAc)_2$	Toluene	90	8	----
4	AgI	Toluene	90	8	----
5	$AgNO_3$	Toluene	90	8	48
6	$AgNO_3$	DMF	120	3-9	62
7	$AgNO_3$	THF	80	8	37
8	$AgNO_3$	H_2O	80	8	83
9	$AgNO_3$	H_2O	85	3	32
10	$AgNO_3$	H_2O	85	4	43
11	$AgNO_3$	H_2O	85	6	61
12	$AgNO_3$	H_2O	85	8	73
13	$AgNO_3$	EtOH	80	8	41

[a] yields of isolated products.

I have employed various benzene-1,2-diamines to check the scope of this reaction. To my delight, my methodology worked in good to very good yields. Further studies in order to study regioselectivity for various phenylene diamines are in the prosses of investigation.

Mechanistic studies were carried out by Vineeta Rustagi, [86] where **27** and **36** underwent condensation to generate specie **38** which was activated by $AgNO_3$, resulted in the nucleophillic attack from the free NH_2 group to generate dihydroimidazole ring **39**.



Scheme 22. Proposed mechanism for **37**

In the next step, a proton shift produced intermediate **40.** π-Complexation between the alkyne and Ag(1) rendered a regioselective 2nd intramolecular attack of the nucleophilic NH onto the alkyne to form intermediate **41**, which on subsequent deprotonation led to the formation of cyclized product **42**. Finally, aromatization via oxidation resulted in final product **37.**

It was observed that different benzene-1,2-diamines followed well this transformation with different isolated yields. Although still different variations in term of substitution pattern will be studied, I got several examples with different benzene-1,2-diamines (Table 11). Structures were verified by using IR, NMR and mass spectroscopic methods.

Table 11. Synthesis of benzo[4',5']imidazo[1',2':1,2]pyrido[4,3-*b*]indole (37).

37	**36**	**37**(%)[a]
a	1,2-$(NH_2)_2C_6H_4$	81
b	4,5-$(Cl)_2$-1,2-$(NH_2)_2C_6H_2$	66

[a] yields of isolated products.

4.4 Conclusion

I have developed a novel combination of two versatile moieties, the indole and benzimidazole, in a single heterocyclic system in very good yields. This new class can be extremely useful in medicinal and display devices. Owing to the great diversity of the substitution pattern, this developed chemistry can be used for the generation of libraries of various heterocyclic systems. Further investigations in this area are currently under way and will be reported in due course.

5 Experimental Section

General Remarks: Reactions were carried out under inert atmosphere (Argon 4.6) in order to simultaneously exclude oxygen and water when appropriate. Pressure tubes were used to avoid condenser. Solvents for reactions were dried and distilled by standard methods or purchased from Merck®, Aldrich®, Acros Organics®, and others whenever exclusion of water was desired. Solvents for liquid chromatography and extraction were always distilled prior to use and partly reused after fractional distillation (*n*-heptane, ethyl acetate).

5.1 Equipment, Chemicals and Work Technique

NMR Spectroscopy: Bruker AC 250, Bruker ARX 300, Bruker ARX 500. For NMR characterization the one-dimensional ^{1}H NMR, proton-decoupled ^{13}C NMR, and DEPT 135 spectra were collected. If necessary other techniques (NOESY, COSY, HMQC, and HMBC) were applied as well. All NMR spectra presented in this work, were collected in DMSO-d_6 and $CDCl_3$ solution. All chemical shifts were given in ppm. References (^{1}H NMR): TMS (δ, 0.00) or residual $CHCl_3$ (δ, 7.26) were taken as internal standard. References (^{13}C NMR): TMS (δ, 0.0) or residual $CHCl_3$ (δ, 77.0) were taken as internal standard. 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).

Infrared Spectroscopy (IR): Nicolet 205 FT-IR, Nicolet Protége 460 FT-IR Peaks are given the following assignments: w = weak, m = medium, s = strong, br = broad.

Mass Spektrometry (MS): AMD MS40, Varian MAT CH 7, MAT 731 (EI, 70 eV), Intecta AMD 402 (EI, 70 eV and CI), Finnigan MAT 95 (CI, 200 eV).

High Resolution Mass Spectrometry (HRMS): Varian MAT 311, Intecta AMD 402.

Elemental Analysis: LECO CHNS-932 Thermoquest Flash EA 1112.

Melting Points: Micro heating table HMK 67/1825 Kuestner (Büchi Apparatus). Leitz Labolux 12 Pol with heating table Mettler FP 90. Melting points are uncorrected.

X-ray crystal structure analysis: Bruker X8Apex Diffractometer with CCD-Kamera (Mo-K_a und Graphit Monochromator, λ = 0.71073 Å) or Bruker Apex Kappa-II CCD diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073).

Thin Layer Chromatography (TLC): Merck Kieselgel 60 F254 on aluminium foil from Macherey-Nagel. Detection was carried out under UV light at 254 nm and 365 nm. As colourizing reagent the following mixtures were used: 1-2/100 p-Anisaldehyde or vanillin, 10/100 glacial acetic acid, 5/100 sulphuric acid, 83-84/100 methanol.

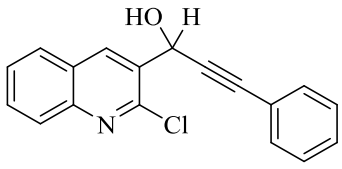
Column Chromatography: Column chromatography was performed with Merck Silica Gel 60 or Macherey-Nagel Silica Gel 60 (0.063-0.200 mm, 70-230 mesh). The finer Merck Silica Gel 60 (0.040-0.063 mm, 230-400 mesh) was chosen when appropriate.

5.2 Procedures and Spectroscopic Data

Synthesis of benzo[1,8]-naphthyridine-4(1*H*)-ones

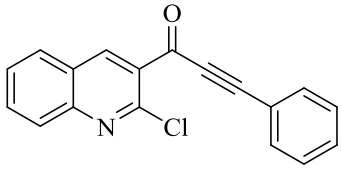
Compounds **2, 3** and **4** were prepared according to a method reported in literature.[26, 27]

1-(2-Chloroquinolin-3-yl)-3-phenylprop-2-yn-1-ol (3):[26,27] The reaction was carried out following the reported procedure starting with 2-chloroquinoline-3-carbaldehyde (**2**) (400 mg, 2.1 mmol), phenylacetylene (257 mg, 2.5 mmol) and *n*-BuLi (1.0 ml, 2.5 mmol). After stirring for 1 hr at -78 °C, the solution was allowed to warm to 25 °C. HCl (10%, 25 ml) was added, and the organic layers were extracted with ethylacetate (3 × 50 ml). The combined organic layers were dried, filtered and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, *n*-heptane/EtOAc = 9:1) to give **3** a white solid (600 mg, 98%), m.p. = 194-196 °C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 5.95 (d, J = 5.2 Hz, 1H, CH), 6.72 (d, J = 5.6 Hz, 1H, OH), 7.40-7.45 (m, 5H, Ar), 7.65-7.68 (m, 1H, Ar), 7.89-7.92 (m, 1H, Ar), 8.11 (d, J = 7.4 Hz, 1H, Ar), 8.21 (d, J = 6.9 Hz, 1H, Ar), 8.75 (s, 1H, Ar);



^{13}C-NMR (75 MHz, DMSO-d_6): δ = 60.3 (CHOH), 84.6, 89.2 (C≡C), 121.8, 127.0 (C), 127.5, 127.9, 128.3, 128.7, 128.8, 130.1, 130.9, 131.4, (CH), 133.5 (C), 135.9, 136.5 (CH), 146.4, 148.3 (C); IR (ATR): $\tilde{\nu}$ = 3233, 3065, 2228, 1591 (w), 1489, 1329 (m), 1165 (w), 1068, 929 (m), 857 (w), 779 (m), 747 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 295 [M^+,^{37}Cl], 293 [M^+,^{35}Cl], 258 (100), 241 (9), 228 (24), 101 (10.61), 75 (9.58). Anal.calcd. (%) for $C_{18}H_{11}OClN$ (293.747): C = 73.60, H = 4.12, N = 4.77; Found: C = 73.63, H = 4.15, N = 4.77. HRMS (ESI-TOF): calcd. For $C_{18}H_{12}NClO$ [$(M+H)^+$,^{35}Cl]: 294.0680. Found: 294.0680.

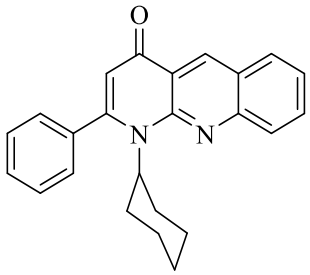
1-(2-Chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**):[26,27] The reaction was carried out following the reported procedure starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-ol (**3**) (400 mg, 1.4 mmol) and activated MnO_2 (299 mg, 3.5 mmol), **4** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellow solid (362 mg, 91 %), m.p. = 101-103 ^{o}C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 7.57-7.61 (m, 3H, Ar), 7.80-7.82 (m, 3H, Ar), 8.01-8.06 (m, 2H, Ar), 8.36 (d, *J* = 8.1 Hz, 1H, Ar), 9.31 (s, 1H, Ar). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 87.5, 94.2 (C≡C), 118.7, 125.8 (C), 127.7, 128.3 (CH), 129.0 (C), 129.1, 129.2, 129.8, 131.8, 133.2, 133.3, 133.8, 144.1 (CH), 145.6, 147.7 (C), 174.6 (C=O). IR (ATR): $\tilde{\nu}$ = 3062 (w), 2194 (m), 1630 (s), 1557, 1485 (m), 1392 (w), 1319 (m), 1212 (w), 1096 (s), 1000 (w), 978 (m), 805 (w), 775 (m), 749 (s), 597 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 294 (4. ^{37}Cl, $[M + H]^+$), 293 (23, ^{37}Cl), 292 (14, ^{35}Cl, $[M + H]^+$), 291 (M^+, 64), 263 (96), 228 (32), 129 (100), 101 (22), 75 (27). Anal. calcd. (%) for $C_{18}H_{10}OClN$ (291.747): C = 74.11, H = 3.46, N = 4.8. Found: C = 73.98, H = 3.56, N = 4.77. HRMS (ESI-TOF): calcd. For $C_{18}H_{11}NClO$ [$(M+H)^+$, ^{35}Cl] : 292.0524. Found: 292.0524. $C_{18}H_{11}NClO$ [$(M+H)^+$, ^{37}Cl] : 294.0500. Found: 294.0500.



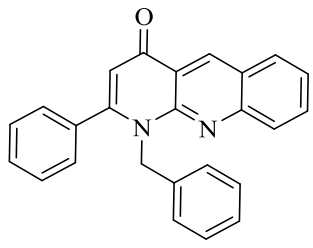
General procedure for 5a-l: A mixture of **4** (0.6 mmol), amine (0.7 mmol), K_3CO_3 (1.2 mmol), and $Pd(PPh_3)_4$ (0.05 mmol) was refluxed in 10 ml of DMF for 3 hr at 120 ^{o}C. The reaction mixture was quenched with a saturated aq. solution of NH_4Cl, followed by extraction with ethyl acetate (3 × 15 ml). The residue then was obtained after removing solvent under reduced pressure and was purified by column chromatography on silica gel to afford the pure product.

General procedure for compounds 5m-u: A mixture of **4** (0.6 mmol), amine (0.7 mmol), Cs_2CO_3 (1.2 mmol), $Pd(PPh_3)_4$ (0.05 mmol) was refluxed in 10 ml of toluene for 6 hr at 90 ^oC. The reaction mixture was quenched with saturated NH_4Cl, followed by extraction with ethyl acetate (3 × 15 ml). The residue then obtained, after removing the solvent under reduced pressure and was purified by column chromatography on silica gel to afford the pure product.

1-Cyclohexyl-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5a**): Starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), cyclohexylamine (70 mg, 0.7 mmol), K_2CO_3 (162 mg, 1.2 mmol), $Pd(PPh_3)_4$ (5 mol%) and DMF (10 ml), reflux at 120 ^oC for 3 hr, **5a** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 2:1) as a yellow solid (150 mg, 73%), m.p. = 280–282 ^oC. ^1H-NMR (300 MHz,$CDCl_3$): δ = 0.90-0.93 (m, 2H, CH_2), 1.19-1.22 (m, 1H, CH_2), 1.52 (d, J = 6.8 Hz, 1H, CH_2), 1.87-1.91 (m, 4H, CH_2), 3.12-3.15 (m, 2H, CH_2), 4.01-4.04 (m, 1H, CH), 6.08 (s, 1H, Ar), 7.36-7.41 (m, 6H, Ar), 7.70-7.74 (m, 1H, Ar), 7.94 (dd, J = 8.5, 9.3 Hz, 2H, Ar), 9.19 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 25.3, 26.5, 26.6, 30.5, 30.5 (CH_2), 63.8, 111.4 (CH), 121.5, 125.1 (C), 125.6, 127.4, 127.5, 128.1, 128.8, 128.8, 129.2, 129.4, 131.9, 137.1 (CH), 137.2, 148.3, 150.1, 158.3, 178.6 (C=O). IR (ATR): $\tilde{\nu}$ = 3046 (w), 2940, 1616 (m), 1578 (s), 1420 (m), 1164 (w), 1116, 1041 (m), 893 (w), 976, 844 (s), 796 (m), 758 (s), 617, 537 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 354 ($[M]^+$, 6), 273 (23.16), 272 (100), 244 (31.79), 140 (6.82). Anal.calcd. (%) for $C_{24}H_{22}N_2O$ (354.1732: C = 81.33, H = 6.26, N = 7.90. Found: C = 80.98, H = 6.46, N = 7.75. HRMS (ESI-TOF): calcd. For $C_{24}H_{23}N_2O$ $[M+H]^+$: 355.1805. Found: 355.1805.

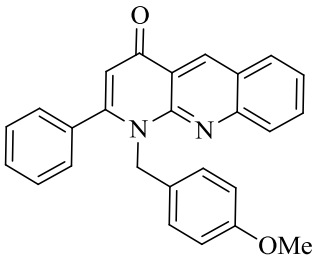


1-Benyl-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5b**): Starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one **(4),** (170 mg, 0.6 mmol), benzylamine (75 mg, 0.7 mmol), K_2CO_3 (162 mg, 1.17 mmole), $Pd(PPh_3)_4$ (5 mol%) and DMF (10 ml), reflux at 120 ^oC for 3 hr, **5b** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 2:1) as a yellow solid (180 mg, 84.91 %), m.p. = 238-239 ^oC. ^1H-NMR (300 MHz, $CDCl_3$): δ = 5.71 (s, 2H, CH_2), 6.21 (s, 1H, CH), 6.78-6.81 (m, 2H, Ar), 7.06-7.08 (m, 3H, Ar), 7.18-7.22 (m, 2H, Ar), 7.28-7.49 (m, 4H, Ar), 7.69-7.74 (m, 1H, Ar), 7.91 (d, J = 8.1 Hz, 1H, Ar), 7.98 (d, 1H, J = 8.1 Hz, Ar), 9.26 (s, 1H, Ar). ^{13}C-NMR



(75 MHz, $CDCl_3$): δ = 49.4 (CH_2), 111.6 (CH), 120.6, 125.5 (C), 125.7, 126.7, 126.7, 127.1, 128.2, 128.3, 128.3, 128.3, 128.3, 128.4, 128.5, 129.3, 129.6, 132.2 (CH), 135.6 (C), 137.7 (CH), 137.9, 149.1, 149.6, 157.4 (C), 178.8 (CO). IR (ATR): $\tilde{\nu}$ = 3048 (w), 1616 (s), 1552 (m), 1494 (w), 1328 (m), 1184 (w), 1145 (m), 1072 (w), 1023 (m), 928 (w), 831 (s), 790 (m), 755 (s), 609 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 363 ($[M+H]^+$, 11), 362 ($[M]^+$, 50), 361 (100), 91 (22). Anal.calcd. (%) for $C_{25}H_{18}N_2O$ (362.1419): C = 82.85, H = 5.01, N = 7.73; Found: C = 82.84, H = 5.06, N = 7.71. HRMS (ESI-TOF): calcd. For $C_{25}H_{19}N_2O$ $[M+H]^+$: 363.1492. Found: 363.1495.

1-(4-Methoxybenyl)-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5c**): Starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), *p*-methoxybenzylamine (96 mg, 0.7 mmol), K_2CO_3 (162 mg, 1.17 mmole), $Pd(PPh_3)_4$ (5 mol%) and DMF (10 ml), reflux at 120 °C for 3 hr, **5c** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 3:1) as a yellow solid (146 mg, 64 %), m.p. = 174-176 °C. ^{1}H-NMR (300 MHz,$CDCl_3$): δ = 3.64 (s, 3H, CH_3), 5.65 (s, 2H, CH_2), 6.59 (d, *J* = 8.1 Hz, 2H, Ar), 6.74 (d, *J* = 8.2 Hz, 2H, Ar), 7.21-7.49 (m, 7H, Ar), 7.70-7.73 (m, 1H, Ar), 7.96 (dd, *J* = 7.5,7.7 Hz, 2H, Ar), 9.25 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 48.8 (CH_2), 55.2 (CH_3), 111.7, 113.6, 113.6 (CH), 120.7, 125.5 (C), 125.7, 128.2, 128.3, 128.3, 128.4, 128.4, 128.5, 128.5, 129.3, 129.5 (CH), 129.9 (C), 132.2 (CH), 135.7 (C), 137.5, 137.6 (CH), 149.6, 157.4, 158.7 (C), 178.8 (CO). IR (ATR): $\tilde{\nu}$ = 2958 (w), 1580 (s), 1511 (m), 1478 (s), 1282 (m), 1245 (s), 1145 (m), 845 (m), 828 (s), 787 (m), 568 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 393($[M+H]^+$, 18), 392 ($[M]^+$, 59), 391 (27), 121 (100); Anal. calcd. (%) for $C_{26}H_{20}N_2O_2$ (392.1525): C = 79.57, H = 5.14, N = 7.14. Found: C = 79.56, H = 5.15, N = 7.14. HRMS (ESI-TOF): calcd. For $C_{26}H_{21}N_2O_2$ $[M+H]^+$: 393.1598. Found: 393.1605.



1-Phenethyl-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5d**): Starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.586 mmol), 2-phenylethanamine (85 mg, 0.7 mmol), K_2CO_3 (162 mg, 1.2 mmol), $Pd(PPh_3)_4$ (5 mol%) and DMF (10 ml), reflux at 120 ^oC for 3 hr, **5d** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 3:1) as a yellow solid (99 mg, 46 %), m.p. = 232-233 ^oC. ^1H-NMR (300 MHz,$CDCl_3$): δ = 2.81 (t, J = 8.1 Hz, 2H, CH_2), 4.42 (t, J = 8.1 Hz, 2H, CH_2), 6.01 (s, 1H, CH), 6.71 (d, J = 6.7 Hz, 2H, Ar), 6.98-7.04 (m, 3H, Ar), 7.09-7.12 (m, 2H, Ar), 7.28-7.39 (m, 4H, Ar), 7.63-7.68 (m, 1H, Ar), 7.90 (dd, J = 9.3, 8.1 Hz, 2H, Ar), 9.13 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 35.4, 48.4 (CH_2), 110.9 (CH), 125.5 (C), 125.8, 126.6, 128.1, 128.1, 128.3, 128.3, 128.6, 128.6, 128.7, 128.7, 128.8, 129.4, 129.6, 132.4 (CH), 135.6 (C), 137.7 (CH), 138.2, 148.2, 148.5, 149.1, 149.3 (C), 157.4 (CO). IR (ATR): $\tilde{\nu}$ = 3044 (w), 1582 (s), 1552 (m), 1514 (w), 1477 (s), 1445, 1329, 1146, 976 (m), 829 (s), 573 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 376 ($[M]^+$, 4), 285 (46), 284 (13), 273 (18), 272 (100). Anal.calcd. (%) for $C_{26}H_{20}N_2O$ (376.1576): C = 82.62, H = 5.27, N = 7.71. Found: C = 82.63, H = 5.26, N = 7.72. HRMS (ESI-TOF): calcd. For $C_{26}H_{21}N_2O$ $[M+H]^+$: 377.1648. Found: 377.1654.

1-Heptyl-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5e**): Starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), *n*-heptylamine (81 mg, 0.7 mmol), K_2CO_3 (162 mg, 1.17 mmol), $Pd(PPh_3)_4$ (5 mol%) and DMF (10 ml), reflux at 120 ^oC for 3 hr, **5e** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 2:1) as a yellow solid (140 mg, 64.8 %), m.p. = 315-316 ^oC. ^1H-NMR (250 MHz, $CDCl_3$): δ = 0.76 (t, J = 6.8 Hz, 3H, CH_3), 1.09-1.18 (m, 8H, CH_2), 1.62 (t, J = 6.9 Hz, 2H, CH_2), 4.34 (t, J = 8.0 Hz, 2H, CH_2), 6.14 (s, 1H, Ar), 7.37-7.50 (m, 6H, Ar), 7.71-7.78 (m, 1H, Ar), 7.98 (d, J = 8.1 Hz, 2H, Ar), 9.24 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.1(CH_3), 22.5, 26.5, 28.5, 28.9, 31.3, 46.7 (CH_2), 111.04 (CH), 120.7, 125.3 (C), 125.5 (CH), 127.8 (C), 128.1, 128.1, 128.5, 128.6, 129.2, 129.4, 132.0 (CH), 135.9 (C), 137.3 (CH), 148.9, 149.1, 157.1 (C), 178.5 (CO). IR (ATR): $\tilde{\nu}$ = 3048 (w), 2918 (m), 1632 (s), 1411, 1332 (m), 1126, 1074 (w), 976, 774 (m), 753 (s), 719, 611 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 370 ($[M]^+$, 28), 313 (13), 285 (41), 272 (100), 244 (26), 128 (11), 77 (2). Anal.calcd. (%) for $C_{25}H_{26}ON_2$ (370.2045): C =

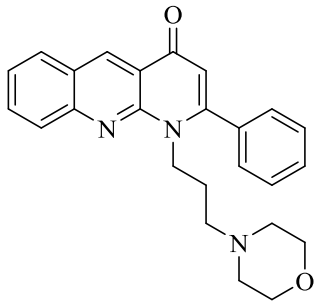
81.05, H = 7.07, N = 7.56. Found: C = 80.98, H = 7.078, N = 7.49. HRMS (ESI-TOF): calcd. For $C_{25}H_{27}O\,N_2$ $[M+H]^+$: 371.2118; Found: 371.2118.

1-Cyclopropyl-2-phenylbenzo[*b*][1,8]naphthyridin-4-(1*H*)-one (**5f**)**:** Starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), cyclopropylamine (40 mg, 0.7 mmol), K_2CO_3 (162 mg, 1.2 mmole), $Pd(PPh_3)_4$ (5 mol%) and DMF (10 ml), reflux at 120 ^oC for 3 hr, **5f** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 4:1) as a yellow solid (61 mg, 57 %), m.p. = 193-194 ^oC. ^1H-NMR (250 MHz, $CDCl_3$): δ = 0.46 (q, J = 8.8 Hz, 2H, CH_2), 0.89-0.97 (m, 2H, CH_2), 3.40-3.49 (m, 1H, CH), 6.24 (s, 1H, Ar), 7.43-7.56 (m, 6H, Ar), 7.75-7.81 (m, 1H, Ar), 7.99 (d, J = 8.1 Hz, 1H, Ar), 8.10 (d, J = 8.1 Hz, 1H, Ar), 9.21 (s, 1H, Ar), ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 12.7, 12.7 (CH_2), 32.2 (CH), 111.6 (CH), 120.8, 125.4 (C), 125.6, 128.2, 128.4, 128.4, 128.5, 128.5, 129.3, 129.4, 132.1 (CH), 136.8 (C), 137.1 (CH), 148.9, 151.7, 158.2 (C), 179.3 (CO). IR (ATR): $\tilde{\nu}$ = 3060 (w), 1633 (s), 1616 (m), 1350 (w), 1263 (m), 1143 (w), 1031 (m), 931, 885 (w), 791 (m), 773, 744 (s), 605 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 312 ($[M]^+$, 26), 311 (100), 283 (22), 181 (4), 140(6). Anal.calcd. (%) for $C_{21}H_{16}O\,N_2$ (312.1263): C = 80.75, H = 5.16, N = 8.97. Found: C = 79.98, H = 5.06, N = 8.97. HRMS (ESI-TOF): calcd. For $C_{21}H_{17}O\,N_2$ $[M+H]^+$: 313.1335. Found: 313.1335.

2-Phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5g**): Starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), allylamine (40 mg, 0.7 mmol), K_2CO3 (162 mg, 1.17 mmol), $Pd(PPh_3)_4$ (5 mol%) and DMF (10 ml), reflux at 120 ^oC for 3 hr, **5g** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 2:1) as a yellow solid (61 mg, 96 %), m.p. = 286-288 ^oC. ^1H-NMR (250 MHz, DMSO-d_6): δ = 6.37 (s, 1H, CH), 7.51-7.58 (m, 5H, Ar), 7.84-7.91 (m, 3H, Ar), 7.99 (d, J = 8.0 Hz, 1H, Ar), 8.23 (d, J = 8.1 Hz, 1H, Ar), 9.2 (s, 1H, Ar), 12.33 (s, 1H, NH), ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 106.2 (CH), 119.3 (C), 125.2, 126.7, 127.7, 127.7, 128.8, 128.8, 129.8, 130.8, 132.5, 133.6 (CH), 136.6, 148.7, 149.0, 150.2, 153.1 (C), 178.2 (CO). IR (ATR): $\tilde{\nu}$ = 1650 (w), 1540 (m), 1454 (m), 1227 (w), 1266 (m), 1154 (w), 958 (w), 855 (m), 791 (m), 740 (s), 690 (s), 613 (m), 547 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 273 (19), 272 ($[M]^+$, 100), 27 (14), 245 (19), 244 (78), 243 (15), 242 (12), 122 (11). Anal.calcd. (%) for $C_{18}H_{12}ON_2$

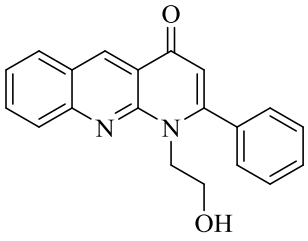
(272.0949): C = 79.39, H = 4.44, N = 10.29. Found: C = 79.19, H = 4.46, N = 10.26. HRMS (ESI-TOF): calcd. For $C_{18}H_{13}O\,N_2$ $[M+H]^+$: 273.1022. Found: 273.1022.

1-(3-Morpholinopropyl)-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (5h): Starting with



1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), 3-(4-morpholinyl)propylamine (101 mg, 0.7 mmol), K_2CO_3 (162 mg, 1.17 mmole), $Pd(PPh_3)_4$ (5 mol%) and DMF (10 ml), reflux at 120 ^oC for 3 hr, **5h** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 3:1) as a solid (200 mg, 86.6 %), m.p. = 188-189 ^oC. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.71-1.82 (m, 2H, CH_2), 2.13-2.21 (m, 6H, CH_2), 3.49 (t, J = 5.2 Hz, 4H, CH_2), 4.43 (dd, J = 8.1, 8.1 Hz, 2H, CH_2), 6.11 (s, 1H, CH), 7.37-7.49 (m, 6H, Ar), 7.71-7.76 (m, 1H, Ar), 7.94 (dd, J = 12.5, 12.5 Hz, 2H, Ar), 9.22 (s, 1H, Ar), ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 25.8, 45.1, 53.4, 53.4, 55.9, 66.8, 66.9 (CH_2), 111.2 (CH), 120.9, 125.4 (C), 125.6, 128.1, 128.2, 128.2, 128.7, 128.7, 129.4, 129.5, 132.2 (CH), 135.8 (C), 137.6 (CH), 149.1, 149.3, 157.0 (C), 178.6 (CO). IR (ATR): $\tilde{\nu}$ = 2914 (w), 2814 (w), 1633 (s), 1551 (m), 1474 (5), 1353 (w), 1264 (m), 1114 (s), 1036 (m), 995 (w), 937 (m), 835 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 399 ($[M]^+$, 73), 313 (21), 299 (24), 286 (25), 285 (100), 273 (66), 244 (14), 128 (18), 100 (26). Anal.calcd. (%) for $C_{25}H_{25}O_2N_3$ (399.1950): C = 75.16, H = 6.31, N = 10.52. Found: C = 74.98, H = 6.36, N = 10.54. HRMS (ESI-TOF): calcd. For $C_{25}H_{26}O_2N_3$ $[M+H]^+$: 400.2021. Found: 400.2029.

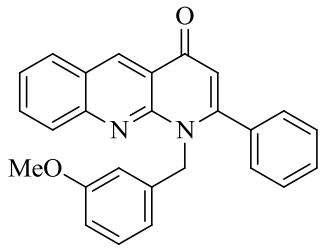
1-(2-Hydroxyethyl)-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (5i): Starting with 1-(2-



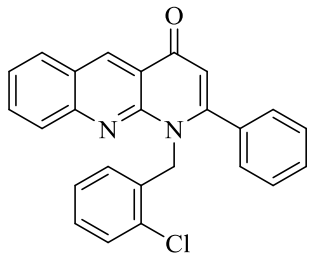
chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), ethanolamine (32 mg, 0.7 mmol), K_2CO_3 (162 mg, 1.2 mmol), $Pd(PPh_3)_4$ (5 mol%) and DMF (10 ml), reflux at 120 ^oC for 3 hr, **5i** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 2:1) as a yellow solid (150 mg, 73 %), m.p. = 204-205^oC. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.01 (dd, J = 9.3, 9.2 Hz, 2H, CH_2), 4.51 (dd, J = 8.4,8.3 Hz, 2H, CH_2), 4.86 (t, J = 7.6 Hz, 1H, OH), 6.18 (s, 1H, CH), 7.45-7.55 (m, 6H, Ar), 7.79-7.84 (m, 1H, Ar), 7.92 (d, J = 7.8 Hz, 1H, Ar), 8.01 (d, J = 7.9 Hz, 1H, Ar), 9.11 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 50.5, 62.5 (CH_2), 111.6 (CH), 120.7, 125.4 (C), 125.9, 127.5, 128.5, 128.5, 128.8, 128.8, 129.3, 129.7, 132.7 (CH), 135.8 (C), 138.1, 148.5, 150.2, 157.8 (C), 178.4 (CO). IR (ATR): $\tilde{\nu}$ = 3206 (w), 1614, 1480 (s), 1338, 1293 (m), 1176 (w),

1156, 1066 (m), 959 (w), 825 (s), 612, 559 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 316 ($[M]^+$, 11), 297 (18), 285 (67), 284 (16), 273 (20), 272 (100), 255 (11), 128 (22). Anal.calcd. (%) for $C_{20}H_{16}N_2O_2$ (316.1212): C = 75.93, H = 5.10, N = 8.86. Found: C = 75.90, H = 5.08, N = 8.86. HRMS (ESI-TOF): calcd. For $C_{20}H_{17}N_2O_2$ $[M+H]^+$: 317.1285. Found: 317.1285.

1-(3-Methoxybenzyl)-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5j**): Starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), 3-methoxybenzylamine (96 mg, 0.7 mmol), K_2CO_3 (162 mg, 1.17 mmole), $Pd(PPh_3)_4$ (5 mol%) and DMF (10 ml), reflux at 120 °C for 3 hr, **5j** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 2:1) as a solid (120 mg, 52%), m.p. = 114-116 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.67 (s, 3H, OCH_3), 6.29 (s, 1H, CH), 6.48-6.51 (m, 2H, Ar), 6.72 (dd, *J* = 5.3, 5.3 Hz, 1H, Ar), 7.07 (t, *J* = 8.1 Hz, 1H, Ar), 7.28-7.59 (m, 7H, Ar), 7.79-7.85 (m, 1H, Ar), 8.02 (d, *J* = 8.1 Hz, 1H, Ar), 8.09 (d, *J* = 8.1 Hz, 1H, Ar), 9.36 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 49.3 (CH_2), 55.1 (CH_3), 111.7, 112.3, 112.7, 119.1(CH), 120.6, 125.5 (C), 125.7, 128.2, 128.2, 128.3, 128.3, 128.5, 129.3, 129.3, 129.6, 132.3 (CH), 135.7 (C), 137.7 (CH), 139.6, 149.2, 149.6, 157.5, 159.6 (C), 178.87 (CO). IR (ATR): $\tilde{\nu}$ = 2921 (w), 1660, 1631 (m), 1582 (s), 1486 (w), 1349, 1274, 1158, 1092, 976, 847 (m), 698 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 393 (11), 392($[M]^+$, 54), 391 (100), 283 (10), 121 (17), 91 (8). Anal.calcd. (%) for $C_{26}H_{19}N_2O_2$ (391.1441): C = 74.11, H = 3.46, N = 4.8. Found: C = 73.98, H = 3.56, N = 4.77. HRMS (EI): calcd. For $C_{26}H_{19}N_2O_2$ $[M]^+$ 391.1441. Found: 391.1444.

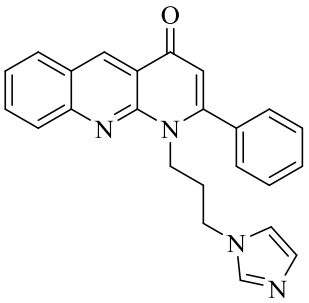


1-(2-Chlorobenzyl)-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5k**): Starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), 2-chlorobelnzyamine (99 mg, 0.7 mmol), K_2CO3 (162 mg, 1.2 mmol), $Pd(PPh_3)_4$ (5 mol%) and DMF (10 ml), reflux at 120 °C for 3 hr, **5k** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 2:1) as a yellow solid (200 mg, 86%). m.p. = 238-239 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.81 (s, 2H, CH_2), 6.33 (s, 1H, CH), 6.76 (d, *J* = 8.2 Hz, 1H, Ar), 7.03-7.06 (m, 1H, Ar), 7.12-7.17 (m, 1H, Ar), 7.26-7.31 (m, 3H, Ar), 7.36-7.58 (m, 4H, Ar), 7.77-7.82 (m, 1H, Ar), 7.95 (d, *J* = 8.7 Hz, 1H, Ar), 8.07 (d, *J* = 8.7 Hz, 1H, Ar), 9.38 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 47.6 (CH_2), 111.7 (CH), 120.5, 125.6 (C), 125.8,



126.8, 127.2, 127.8, 127.9, 128.1, 128.4, 128.5, 128.6, 129.2, 129.3, 129.7 (CH), 132.1 (C), 132.3 (CH), 135.2, 135.6 (C), 137.6 (CH), 149.1, 149.5, 157.4 (C), 178.7 (CO). IR (ATR): $\tilde{\nu}$ = 2964 (w), 1616 (s), 1552 (m), 1499 (w), 1410, 1328 (m), 1200 (w), 1147 (m), 1088, 850 (w), 832 (s), 611 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 397 (43), 396 ($[M]^+$, 51), 395 (100), 361 (19), 283 (15), 125 (18), 89 (7). Anal.calcd. (%) for $C_{25}H_{17}OClN_2$ (396.1029): C = 75.66, H = 4.32, N = 7.06. Found: C = 75.98, H = 4.46, N = 7.06. HRMS (ESI-TOF): calcd. For $C_{25}H_{18}OClN_2$ $[(M+H)^+,^{35}Cl]$: 397.1102. Found: 397.1104. $C_{25}H_{18}OClN_2$ $[(M+H)^+,^{37}Cl]$: 399.1083. Found: 397.1088

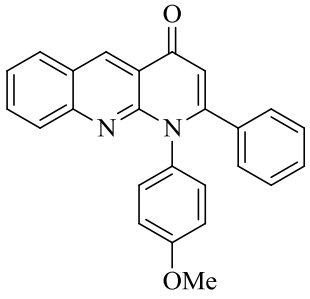
1-(3-(1H-Imidazol-1-yl)propyl)-2-phenylbenzo[*b*][1,8]naphthyridin-4-(1*H*)-one (**5l**) :



Starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), N-(3-aminopropyl)imidazole (88 mg, 0.7 mmol), K_2CO3 (162 mg, 1.2 mmol), $Pd(PPh_3)_4$ (5 mol%) and DMF (10 ml), reflux at 120 ^oC for 3 hr, **5l** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 5:1) as a yellow solid (135 mg, 70%), m.p. = 229-230 ^oC. ^1H-NMR (250 MHz, $CDCl_3$): δ = 2.16-2.19 (m, 2H, CH_2), 3.91 (t, *J* = 6.3 Hz, 2H, CH_2), 4.41 (t, *J* = 7.8 Hz, 2H, CH_2), 6.18 (s, 1H, CH), 6.76 (s, 1H, Ar), 7.02 (s, 1H, Ar), 7.38-7.43 (m, 3H, Ar), 7.49-7.54 (m, 4H, Ar), 7.81-7.83 (m, 1H, Ar), 8.01 (dd, *J* =7.3,7.3 Hz, 2H, Ar), 9.28 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 30.2, 43.8, 44.5 (CH_2), 111.4 (CH), 120.6 (C), 125.4, 125.8, 127.9, 127.9, 128.0, 129.0, 129.1, 129.3, 129.9, 132.5 (CH), 135.4 (C), 137.7, 137.8, 137.9 (CH), 149.0, 149.1, 156.5, 156.5 (C), 178.5 (CO). IR (KBr): $\tilde{\nu}$ = 2921 (w), 1660, 1631 (m), 1582 (s), 1486 (w), 1349, 1274, 1158, 1092, 976, 847 (m), 698 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 381 (10), 380 ($[M]^+$, 28), 299 (13), 285 (100), 273 (18), 272 (17), 207 (25). Anal.calcd. (%) for $C_{24}H_{20}ON_4$ (380.4421): C = 75.77, H = 5.30, N = 14.73. Found: C = 75.98, H = 5.46, N = 14.66. HRMS (ESI-TOF): calcd. For $C_{24}H_{21}ON_4$ $[M+H]^+$: 381.1719. Found: 381.1718.

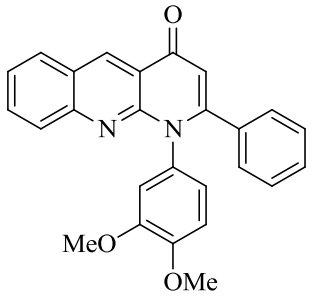
1-(4-Methoxyphenyl)-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5m**): Starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), *p*-methoxyanniline (76 mg, 0.62 mmol), Cs_2CO_3 (235 mg, 0.72 mmol), $Pd(PPh_3)_4$ (5 mol%) and toluene (10 ml), reflux at 90 ^oC for 6 hr, **5m** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 1:1) as a yellow solid (142 mg, 73 %), m.p. = 290-291 ^oC. ^1H-NMR (300

MHz, $CDCl_3$): δ = 3.81 (s, 3H, OCH3), 6.43 (s, 1H, CH), 6.84 (d, J = 8.9 Hz, 2H, Ar), 7.12 (d, J = 8.9 Hz, 2H, Ar), 7.24-7.36 (m, 5H, Ar), 7.49-7.54 (m, 1H, Ar), 7.69-7.75 (m, 1H, Ar), 7.82 (d, J = 6.2 Hz, 1H, Ar), 8.04 (d, J = 8.9 Hz, 1H, Ar), 9.38 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 111.3, 113.7, 113.7 (CH), 120.2, 125.7 (C), 125.7, 128.0, 128.0, 128.6, 128.7, 129.0, 129.0, 129.1, 131.3, 131.3, 131.9 (CH), 131.9, 136.1 (C), 137.3, 149.1, 150.9, 157.1, 158.8 (C), 179.2 (CO).



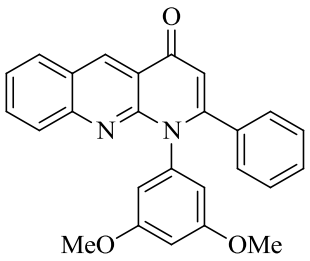
IR (ATR): $\tilde{\nu}$ = 2921 (w), 1660, 1631 (m), 1582 (s), 1486 (w), 1349, 1274, 1158, 1092, 976, 847 (m), 698 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 379 (14), 378 ($[M]^+$, 65), 377 (100). Anal.calcd. (%) for $C_{25}H_{18}N_2O_2$ (378.1368): C = 79.35, H = 4.79, N = 7.40. Found: C = 78.98, H = 4.69, N = 7.40. HRMS (ESI-TOF): calcd. For $C_{25}H_{19}N_2O_2$ $[M+H]^+$: 379.1441. Found: 379.1440.

1-(3,4-Dimethoxyphenyl)-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5n**): Starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), 3,4-dimethoxyanniline (95 mg, 0.62 mmol), Cs_2CO_3 (235 mg, 0.72 mmol), $Pd(PPh_3)_4$ (5 mol%) and toluene (10 ml), reflux at 90 ^oC for 6 hr, **5n** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 2:1) as a yellow solid (150 mg, 76 %), m.p. = 234-235 ^oC. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.66 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 6.35 (s, 1H, C=C), 6.66 (s, 1H Ar), 6.71 (s, 2H, Ar), 7.15-7.21 (m, 5H, Ar), 7.43 (t, J = 7.5 Hz, 1H, Ar), 7.65 (t, J = 7.5 Hz, 1H, Ar), 7.75 (d, J = 9.2 Hz, 1H, Ar), 7.95 (d, J = 8.7 Hz, 1H, Ar), 9.25 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 55.9, 56.1 (OCH_3), 110.3, 111.4, 114.0 (CH), 120.2 (C), 122.9 (CH), 125.6 (C), 125.7, 128.0 (CH), 128.2, 128.2 (C), 128.6, 128.8, 128.8, 128.8, 129.1, 129.1, 131.9 (CH), 136.2 (C), 137.3 (CH), 148.4, 148.4, 148.7, 149.1, 150.8, 157.1 (C), 179.1 (CO). IR (ATR): $\tilde{\nu}$ = 2833 (w), 1633, 1509, 1471 (m), 1398, 1255 (s), 1208, 1132 (m), 1026 (s), 841 (m), 759, 705 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 409 (18), 408 ($[M]^+$, 78), 407 (100), 391 (12), 321 (14). Anal.calcd. (%) for $C_{26}H_{20}N_2O_3$ (408.1474): C = 76.45, H = 4.94, N = 6.86. Found: C = 75.97, H = 4.91, N = 6.84. HRMS (ESI-TOF): calcd. For $C_{26}H_{21}N_2O_3$ $[M+H]^+$: 409.1550. Found: 409.1550.

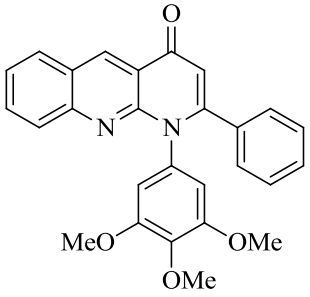


1-(3,5-Dimethoxyphenyl)-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-on (**5o**): Starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), 3,5-

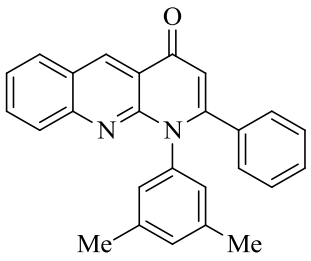
dimethoxyanniline (95 mg, 0.62 mmol), Cs_2CO_3 (235 mg, 0.72 mmol), $Pd(PPh_3)_4$ (5 mol%) and toluene (10 ml), reflux at 90 °C for 6 hr, **5o** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 5:1) as a yellow solid (135 mg, 64%), m.p. = 239-240 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.58 (s, 6H, OCH3), 6.28-6.32 (m, 4H, Ar), 7.15-7.22 (m, 5H, Ar), 7.41 (t, J = 8.7 Hz, 1H, Ar), 7.63 (t, J = 8.7 Hz, 1H, Ar), 7.76 (d, J = 7.3 Hz, 1H, Ar), 7.93 (d, J = 7.3 Hz, 1H, Ar), 9.22 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 55.5, 55.6 (OCH_3), 100.4, 109.3, 109.4, 111.4 (CH), 120.0, 120.2, 125.6 (C), 125.7, 127.9, 128.0, 128.7, 128.9, 128.9, 129.1, 131.9 (CH), 136.1 (C), 137.3 (CH), 140.5, 149.1, 149.1, 150.4, 156.6, 160.4 (C), 179.1 (CO). IR (ATR): $\tilde{\nu}$ = 3053 (w), 1637 (m), 1582 (s), 1403, 1316 (m), 1150 (s), 1060 (m), 950 (w), 826, 773, 705 (m), 613 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 409 (15), 408 ($[M]^+$, 66), 407 (100), 391 (3), 321 (4), 153(10). Anal.calcd. (%) for $C_{26}H_{20}N_2O_3$ (408.1474): C = 76.45, H = 4.94, N = 6.86. Found: C = 76.37, H = 4.89, N = 6.85. HRMS (ESI-TOF): calcd. For $C_{26}H_{21}N_2O_3$ $[M+H]^+$: 409.1557. Found: 409.1558.



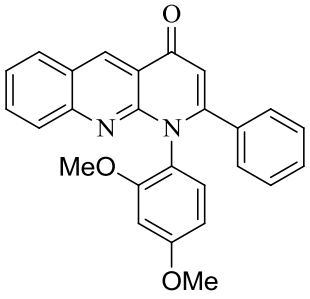
2-Phenyl-1-(3,4,5-trimethoxyphenyl)benzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5p**): Starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), 3,4,5-trimethoxyanniline (113.13 mg, 0.62 mmol), Cs_2CO_3 (235 mg,0.72 mmol), $Pd(PPh_3)_4$ (5 mol%) and toluene (10 ml), reflux at 90 °C for 6 hr, **5p** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 6:1) as a yellow solid (173 mg, 76.9%), m.p. = 253-254 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.62 (s, 6H, OCH_3), 3.78 (s, 3H, OCH_3), 6.35 (s, 1H, CH), 6.39 (s, 2H, Ar), 7.15-7.22 (m, 5H, Ar), 7.44 (t, J = 7.6 Hz, 1H, Ar), 7.67 (t, J = 7.6 Hz, 1H, Ar), 7.8 (d, J = 9.1 Hz, 1H, Ar), 7.96 (d, 1H, J = 9.2 Hz, 1H, Ar), 9.26 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 56.3, 56.3, 61.1 (OCH_3), 108.6, 108.6, 111.4 (CH), 120.1, 125.6, 125.7 (C), 125.8, 128.3, 128.6, 128.6, 128.9, 129.0, 129.2, 129.4, 132.1 (CH), 134.4, 136.2 (C), 137.4 (CH),137.7, 149.1, 150.5, 152.9, 156.8 (C), 179.11 (CO). IR (ATR): $\tilde{\nu}$ = 2964 (w), 1637 (m), 1556 (w), 1495, 1404 (m), 1227 (s), 949, 854 (w), 825, 712, 643 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 439 (28.08), 438 ($[M]^+$, 100), 437 (62.67), 423 (21.23), 392 (12.47), 391(19.48). Anal.calcd. (%) For $C_{27}H_{22}N_2O_4$ (438.1580): C = 73.96, H = 5.06, N = 6.39. Found: C = 73.37, H = 4.99, N = 6.35. HRMS (ESI-TOF): calcd. For $C_{27}H_{23}N_2O_4$ $[M+H]^+$: 439.1652. Found: 439.1650.



2-Phenyl-1-(3,5-dimethylphenyl)benzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5q**): Starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), 3,5-dimethylanniline (75 mg, 0.62 mmol), Cs_2CO_3 (235 mg, 0.72 mmol), $Pd(PPh_3)_4$ (5 mol%) and toluene (10 ml), reflux at 90 °C for 6 hr, **5q** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 3:1) as a yellow solid (112 mg, 58%), m.p. = 255-256 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 6H, CH3), 6.45 (s, 1H, CH), 6.85 (s, 2H, Ar), 6.91 (s, 1H, Ar), 7.27 (s, 5H, Ar), 7.53 (t, *J* = 6.9 Hz, 1H, Ar), 7.74 (t, *J* = 6.9 Hz, 1H, Ar), 7.85 (d, *J* = 9.3 Hz, 1H, Ar), 8.10 (d, *J* = 9.3 Hz, 1H, Ar), 9.37 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.1, 21.1 (CH_3), 111.2 (CH), 120.1, 125.5 (C), 125.6, 127.8, 128.1, 128.1, 128.6, 128.7, 128.7, 128.8, 128.9, 129.1, 129.5, 131.9 (CH), 136.1 (C), 137.3 (CH), 138.0, 138.0, 138.8, 149.1, 150.7, 157.0 (C), 179.9 (CO). IR (ATR): $\tilde{\nu}$ = 3057 (w), 1628, 1550 (m), 1403 (s), 1335 (m), 138 (s), 1438, 1148, 971, 840 (m), 756 (s), 588 (m) cm^{-1}. GCMS (EI, 70 eV): m/z (%) = 377 (17), 376 ([M]$^+$, 72), 375 (100), 347 (10). Anal.calcd. (%) for $C_{26}H_{20}N_2O$ (376.1576): C = 82.95, H = 5.35, N = 7.44. Found: C = 82.87, H = 5.29, N = 7.44. HRMS (ESI-TOF): calcd. For $C_{26}H_{21}N_2O$ [M+H]$^+$: 377.1648. Found: 377.1642.

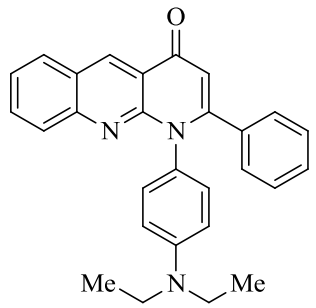


2-Phenyl-1-(2,4-dimethoxyphenyl)benzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5r**): Starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), 3,5-dimethoxyanniline (126 mg, 0.62 mmol), Cs_2CO_3 (235 mg, 0.72 mmol), $Pd(PPh_3)_4$ (5 mol%) and toluene (10 ml), reflux at 90 °C for 6 hr, **5r** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 6:1) as a yellow solid (112 mg, 58%), m.p. = 274-275 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.52 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 6.33-6.37 (m, 3H, Ar), 7.03 (d, *J* = 7.3 Hz, 1H, Ar), 7.18-7.21 (m, 5H, Ar), 7.43 (t, *J* = 10.3 Hz, 1H, Ar), 7.64 (t, *J* = 10.3 Hz, 1H, Ar), 7.74 (d, *J* = 8.3 Hz, 1H, Ar), 7.97 (d, *J* = 8.3 Hz, 1H, Ar), 9.27 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 55.4, 55.48 (OCH_3), 99.0, 104.1, 110.8 (CH), 120.3, 121.6 (C), 125.4 (CH), 125.6 (C), 127.6, 127.6, 128.4, 128.4, 128.6, 128.8, 129.1, 131.7, 131.8 (CH), 136.1 (C), 137.1(CH), 149.3, 150.6, 156.2, 157.8, 160.7 (C), 179.5 (CO). IR (ATR): $\tilde{\nu}$ = 2921 (w), 1660, 1631 (m), 1582 (s), 1486 (w), 1349, 1274, 1158, 1092, 976, 847 (m), 698 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 408 (M$^+$, 3), 379 (4), 378 (28), 377 (100). Anal.calcd. (%) for $C_{26}H_{20}N_2O_3$ (408.1474): C = 82.95, H = 5.35, N = 7.44. Found:



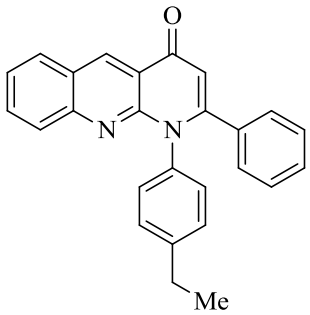
C = 82.87, H = 5.29, N = 7.44. HRMS (ESI-TOF): calcd. For $C_{26}H_{21}N_2O_3$ $[M+H]^+$: 409.1547. Found: 409.1549.

1-(4-(Diethylamino)phenyl)-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5s**)**:** Starting



with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg,0.6 mmol), N,N-diethylbenzene-1,4-diamine (112 mg, 0.62 mmol), Cs_2CO_3 (235 mg, 0.72 mmol), $Pd(PPh_3)_4$ (5 mol%) and toluene (10 ml), reflux at 90 ^oC for 6 hr, **5s** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 3:1) as a yellow solid (167 mg, 77 %), m.p. = 319-320 ^oC. ^1H-NMR (300 MHz, $CDCl_3$): δ = 0.31 (t, J = 6.9 Hz, 6H, CH_3), 2.49 (q, J = 10.8 Hz, 4H, CH_2), 5.59 (s, 1H, CH), 5.71 (d, J = 8.0 Hz, 2H, Ar), 6.14 (d, J = 8.0 Hz, 2H, Ar), 6.42 (s, 5H, Ar), 6.66 (t, J = 7.6 Hz, 1H, Ar), 6.87 (t, J = 7.6 Hz, 1H, Ar), 7.04 (d, J = 8.0 Hz, 1H, Ar), 7.19 (d, J = 8.0 Hz, 1H, Ar), 8.51(s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 12.4, 12.4 (CH_3), 44.4, 44.4 (CH_2), 111.1, 111.2, 111.2 (CH), 120.3 (C), 125.5 (CH), 127.1 (C), 127.8, 127.8, 128.5, 128.7, 129.0, 129.1, 129.1, 130.8, 130.8, 131.7 (CH), 136.6, 136.5 (C), 137.2 (CH), 147.1, 149.2, 151.2, 157.7 (C), 179.2 (CO). IR (ATR): $\tilde{\nu}$ = 2968 (w), 1634 (m), 1515 (s), 1473, 1262, 1195 (m), 1009 (w), 827 (m), 741 (s), 701, 605 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 420 (22), 419 ($[M]^+$, 72), 418 (18), 405 (30), 404 (100), 374 (24), 159 (10). Anal.calcd. (%) for $C_{28}H_{25}N_3O$ (419.1998): C = 80.16, H = 6.01, N = 10.02. Found: C = 80.21, H = 6.06, N = 10.02. HRMS (ESI-TOF): calcd. For $C_{28}H_{26}N_3O$ $[M+H]^+$: 420.2070. Found: 420.2070.

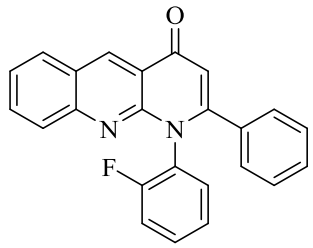
1-(4-Ethylphenyl)-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5t**): Starting with 1-(2-



chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), *p*-ethylanniline (75 mg, 0.62 mmol), Cs_2CO_3 (235 mg, 0.72 mmol), $Pd(PPh_3)_4$ (5 mol%) and toluene (10 ml), reflux at 90 ^oC for 6 hr, **5t** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 5:1) as a yellow solid (96 mg, 50%), m.p. = 228-229 ^oC. ^1H-NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, J = 7.8 Hz, 3H, CH_3), 2.55 (q, J = 10.4 Hz, 2H, CH_2), 6.34 (s, 1H, CH), 6.99-7.06 (m, 4H, Ar), 7.14 (s, 5H, Ar), 7.41 (t, J = 7.8 Hz, 1H, Ar), 7.61 (t, J = 7.8 Hz, 1H, Ar), 7.72 (d, J = 8.2 Hz, 1H, Ar), 7.94 (d, J = 8.2 Hz, 1H, Ar), 9.24 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 15.2 (CH_3), 28.4 (CH_2), 111.3 (CH), 120.1, 125.6 (C), 125.7, 127.8, 127.8, 128.6, 128.7, 128.7, 129.0, 129.1,

129.1, 130.2, 130.2, 131.9, 131.9 (CH), 136.1, 136.7 (C), 137.3 (CH), 143.9, 149.1, 150.8, 157.0 (C), 179.3 (CO). IR (ATR): $\tilde{\nu}$ = 3029, 3004 (w), 1637, 1473 (m), 1184, 1062 (w), 828 (s), 778, 739, 560 (m), 545 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 377 (12), 376 ($[M]^+$, 55), 375 (100), 345 (6), 217 (6). Anal.calcd. (%) for $C_{26}H_{20}N_2O$ (376.1576): C = 82.95, H = 5.35, N = 7.44. Found: C = 82.92, H = 5.26, N = 7.43. HRMS (ESI-TOF): calcd. For $C_{26}H_{21}N_2O$ $[M+H]^+$: 377.1655. Found: 377.1656.

1-(2-Fluorophenyl)-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5u**): Starting with 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**4**), (170 mg, 0.6 mmol), *o*-fluoroanniline (76 mg, 0.62 mmol), Cs_2CO_3 (235 mg, 0.72 mmol), $Pd(PPh_3)_4$ (5 mol%) and toluene (10 ml), reflux at 90 °C for 6 hr, **5u** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 3:1) as a yellow solid (62 mg, 29%), m.p. = 242-243 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.36 (s, 1H, CH), 7.01-7.05 (m, 3H, Ar), 7.13-7.18 (m, 6H, Ar), 7.43-7.48 (m, 1H, Ar), 7.62-7.68 (m, 2H, Ar), 7.97 (d, *J* = 8.4 Hz, 1H, Ar), 9.26 (s, 1H, Ar). ^{19}F-NMR δ = - 118.4 (s, 1F, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 111.3 (CH), 115.7 (C), 116.1 (CH), 120.0 (C), 124.1, 124.2, 126.1 (d, *J* = 16 Hz, CF-CH), 126.3 (d, *J* = 15 Hz, CF-CH), 128.1, 128.4, 128.5, 129.2, 129.2 (CH), 129.3, 129.4 (C), 130.2, 131.7 (CH), 131.8 (C), 133.5 (d, *J* = 10 Hz, CF-CH), 135.1 (d, *J* = 5Hz, CF-CH), 136.3 (d, *J* = 15Hz, CF-C), 137.4, 137.5, 149.2 (C), 179.4 (CO). IR (ATR): $\tilde{\nu}$ = 2919 (w), 1581 (s), 1554, 1209 (m), 1156 (w), 1031, 950 (m), 851 (w), 774 (s), 562 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 367 (13), 366 ($[M]^+$, 52), 365 (16), 348 (26), 347 (100), 346 (7). Anal.calcd. (%) for $C_{24}H_{15}FN_2O$ (366.1168): C = 78.68, H = 4.13, N = 7.65. Found: C = 78.38, H = 4.10, N = 7.62. HRMS (ESI-TOF): calcd. For $C_{24}H_{16}FN_2O$ $[M+H]^+$: 367.1241. Found: 367.1241.

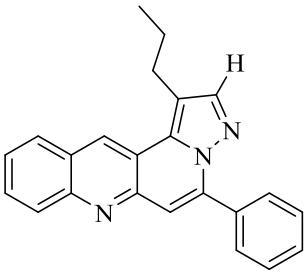


Synthesis of Benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines (**21**)

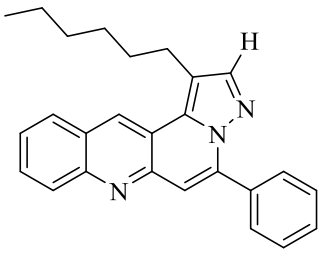
General procedure for synthesis of 2-alkynylquinoline-3-carbaldehydes 19a-d: The known products **19a-d** were prepared by the following reported procedure:[58] The reaction of **2** (0.25 mmol) with alkynes (0.26 mmol) were carried out in the presence of $Pd(PPh_3)_2Cl_2$ (4 mol %), triphenylphosphine (8 mol %) and triethylamine (2 equiv) in CH_3CN as a solvent at 80 °C under an inert atmosphere for 3-6 hr (tlc control). The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel using EtOAc/hexane as eluent.

General procedure for synthesis of Benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines 21a-y: 2-Alkynylquinoline-3-carbaldehyde **19** was added to a solution of tosylhydrazine in EtOH. The mixture was stirred at room temperature for 10 min. Then AgOTf was added and the reaction mixture was heated to 70 °C. Subsequently, **20** and K_3PO_4 were added to the mixture. After completion of reaction as indicated by TLC, the mixture was diluted with ethyl acetate and quenched with H_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue obtained was purified by flash chromatography column on silica gel to provide the desired product **21**.

5-Phenyl-1-propylbenzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine (**21a**): Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde **19a** (150 mg, 0.583 mmol), tosylhydrazine (186 mg, 1.0 mmol), pentanal **20a** (83 mg, 0.96 mmol), AgOTf (10.8 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21a** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (162 mg, 82 %), m.p. = 150-152 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.09 (t, J = 7.3 Hz, 3H, CH_3), 1.80-1.92 (m, 2H, CH_2), 3.04 (t, J = 7.8 Hz, 2H, CH_2), 7.25 (s, 1H, Ar), 7.44-7.55 (m, 4H, Ar), 7.67-7.74 (m, 1H, Ar), 7.82-7.87 (m, 3H, Ar), 7.93 (d, J = 8.6 Hz, 1H, Ar), 8.10 (d, J = 8.6 Hz, 1H, Ar), 8.81 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_3), 22.2, 28.2 (CH_2), 113.2 (CH), 119.0, 119.74 (C), 126.4 (CH), 126.5, 127.8 (C), 128.2 (CH), 128.4 (2×CH), 128.8 (CH), 129.5 (2×CH), 129.8, 130.2, 130.4 (CH), 133.3, 133.4 (C), 141.7 (CH), 143.6, 147.7 (C). IR (ATR): $\tilde{\nu}$ = 1614, 1492 (w), 1460, 1334 (m), 1049 (w), 912 (m), 744 (s), 617 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 337 (39, $[M]^+$), 309 (24), 308 (100), 154 (16). HRMS (EI): calcd. For $C_{23}H_{19}N_3$ $[M]^+$: 337.15735. Found: 337.15732.

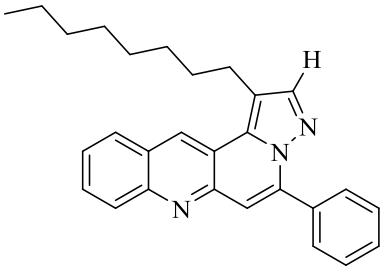


1-Hexyl-5-phenylbenzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine (**21b**): Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde **19a** (150 mg, 0.583 mmol), tosylhydrazine (186 mg, 1.0 mmol), octanal **20b** (123 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21b** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (166 mg, 75 %), m.p. = 103-105 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.8 Hz, 3H, CH_3), 1.34-

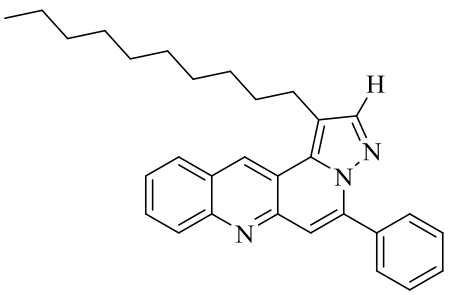


1.36 (m, 4H, CH_2), 1.51 (p, J = 7.0 Hz, 2H, CH_2), 1.82 (p, J = 7.0 Hz, 2H, CH_2), 3.04 (t, J = 7.3 Hz, 2H, CH_2), 7.24 (s, 1H, Ar), 7.49-7.51 (m, 4H, Ar), 7.70-7.73 (m, 1H, Ar), 7.83-7.86 (m, 3H, Ar), 7.92 (d, J = 8.1 Hz, 1H, Ar), 8.10 (d, J = 8.2 Hz, 1H, Ar), 8.79 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.1, 28.89, 29.4, 31.8 (CH_2), 113.3 (CH), 119.3, 119.7 (C), 126.4 (CH), 126.5 (C), 128.1 (CH), 128.4 (2xCH), 128.9, 129.5 (CH), 129.8 (2xCH), 130.1, 130.3 (CH), 133.3, 133.4 (C), 141.6 (CH), 143.6, 147.7, 147.8 (C). IR (ATR): $\tilde{\nu}$ = 1613, 1492 (w), 1456 (m), 1170, 1073 (w), 910 (m), 740, 694 (s), 618 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 379 (33, $[M]^+$), 309 (24), 308 (100), 154 (6). HRMS (EI): calcd. For $C_{26}H_{25}N_3$ $[M]^+$: 379.20430. Found: 379.20415.

1-Octyl-5-phenylbenzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine (**21c**): Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**19a**) (150 mg, 0.583 mmol), tosylhydrazine (186 mg, 1 mmol), decanal (**20c**) (150 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21c** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (161 mg, 68 %), m.p. = 70-72 ^{o}C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.78-0.81 (m, 3H, CH_3), 1.17-1.19 (m, 10H, CH_2), 1.78 (p, J = 8.3 Hz, 2H, CH_2), 3.01 (t, J = 7.7 Hz, 2H, CH_2), 7.21 (s, 1H, Ar), 7.43-7.45 (m, 4H, Ar), 7.65-7.67 (m, 1H, Ar), 7.81-7.83 (m, 4H, Ar), 8.03 (d, J = 8.3 Hz, 1H, Ar), 8.73 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.1(CH_3), 22.7, 26.1, 28.9, 29.4, 29.5, 29.7, 31.9 (CH_2), 118.3 (CH), 119.2, 119.7 (C), 126.3, 126.5, 128.1 (CH), 128.4 (2×CH), 128.9 (CH), 129.5 (2×CH), 129.7, 130.0, 130.3, 133.3 (CH), 133.4 (C), 141.6 (CH), 143.5, 147.7, 147.9 (C). IR (ATR): $\tilde{\nu}$ = 1614, 1493 (w), 1459, 1338 (s), 1226, 989 (w), 911, 857, 694 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 407 (37, $[M]^+$), 309 (27), 308 (100), 154 (6). HRMS (EI): calcd. For $C_{28}H_{29}N_3$ $[M]^+$: 407.23560. Found: 407.23578.

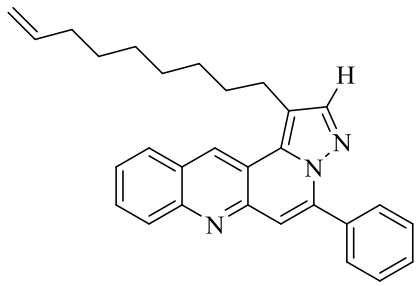


1-Decyl-5-phenylbenzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine (**21d**): Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**19a**) (150 mg, 0.583 mmol), tosylhydrazine (186 mg, 1 mmol), dodecanal (**20d**) (177 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21d** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (177 mg, 70 %),



m.p. = 56-58 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, J = 6.6 Hz, 3H, CH_3), 1.20-1.21 (m, 12H, CH_2), 1.47-1.49 (m, 2H, CH_2), 1.80 (p, J = 8.1 Hz, 2H, CH_2), 3.03 (t, J = 7.6 Hz, 2H, CH_2), 7.23 (s, 1H, Ar), 7.46-7.47 (m, 4H, Ar), 7.68-7.69 (m, 1H, Ar), 7.82-7.83 (m, 3H, Ar), 7.91 (d, J = 8.1 Hz, 1H, Ar), 8.11 (d, J = 8.5 Hz, 1H, Ar), 8.79 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.1, 28.9, 29.4, 29.5, 29.6, 29.7, 29.8, 31.9 (CH_2), 113.4 (CH), 119.3, 119.7 (C), 126.4, 126.5, 128.2 (CH), 128.4 (2×CH), 128.9 (CH), 129.6 (2×CH), 129.8, 130.1, 130.3 (CH), 133.3, 133.4 (C), 141.7 (CH), 143.5, 147.8, 147.9 (C). IR (ATR): $\tilde{\nu}$ = 2915 (s), 1614, 1492 (w), 1456 (s), 1340 (m), 1072 (w), 912, 852 (m), 743, 687 (s), 619 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 379 (33, $[M]^+$), 309 (24), 308 (100), 154 (6). HRMS (EI): calcd. For $C_{30}H_{33}N_3$ $[M]^+$: 435.26690. Found: 435.26663.

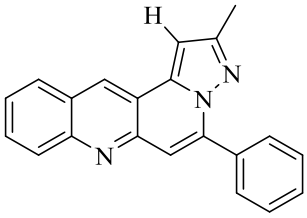
1-(Non-8-en-1-yl)-5-phenylbenzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine (**21e**): Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**19a**) (150 mg, 0.583 mmol), tosylhydrazine (186 mg, 1 mmol), undecylenicaldehyde (**20e**) (162 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21e** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (146 mg, 60 %),



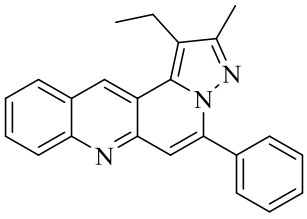
m.p. = 77-79 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.33-1.35 (m, 8H, CH_2), 1.80-1.81 (m, 2H, CH_2), 1.96-1.98 (m, 2H, CH_2), 3.02 (t, J = 7.7 Hz, 2H, CH_2), 4.86-4.88 (m, 2H, C=C), 5.71-5.73 (m, 1H, C=C), 7.22 (s, 1H, Ar), 7.47-7.49 (m, 4H, Ar), 7.67-7.68 (m, 1H, Ar), 7.81 (s, 1H, Ar), 7.83-7.85 (m, 2H, Ar), 7.90 (d, J =8.5 Hz, 1H, Ar), 8.07 (d, J = 8.5 Hz, 1H, Ar), 8.77 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 26.1 (CH_2), 28.9 (2×CH_2), 29.1, 29.4, 29.6, 33.8 (CH_2), 113.4 (CH), 114.3 (CH_2), 119.2, 119.7 (C), 126.4 (CH), 126.5 (C), 128.1, 128.4 (2×CH), 128.9, 129.5 (CH), 129.8 (2×CH), 130.0, 130.3 (CH), 133.3, 133.4 (C), 139.1, 141.1 (CH), 143.49, 147.8, 147.9 (C). IR (ATR): $\tilde{\nu}$ = 2920 (m), 1613, 1492 (w), 1457 (m), 1358 (w), 1336 (m), 1138, 988 (w), 896, 745, 692 (s), 618 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 420 (11, $[M+1]^+$), 419 (34, $[M]^+$), 309 (27), 308 (100). HRMS (EI): calcd. For $C_{29}H_{29}N_3$ $[M]^+$: 419.23560. Found: 419.23542.

2-Methyl-5-phenylbenzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine (**21f**): Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**19a**) (150 mg, 0.583 mmol), tosylhydrazine (186 mg, 1 mmol), acetone (**20f**) (56 mg, 0.96 mmol), AgOTf (15 mg,10 mol%), K_3PO_4 (382 mg, 1.8

mmol) in EtOH (3 ml), **21f** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (162 mg, 91%), m.p. = 150-152 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 6.88 (s, 1H, Ar), 7.16 (s, 1H, Ar), 7.43-7.45 (m, 4H, Ar), 7.63-7.66 (m, 1H, Ar), 7.81 (d, J = 8.1 Hz, 1H, Ar), 7.84-7.87 (m, 2H, Ar), 8.03 (d, J = 8.2 Hz, 1H, Ar), 8.59 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.3 (CH_3), 100.7 (CH), 122.9 (C), 125.4 (CH), 125.5 (C), 126.3 (CH), 127.1 (C), 127.9 (CH), 128.4 (2×CH), 128.6, 129.5, 129.8 (CH), 130.2 (2×CH), 133.3 (CH), 139.2, 147.3, 148.7, 148.9, 151.1 (C). IR (ATR): $\tilde{\nu}$ = 1613, 1555, 1494 (w), 1428, 1328 (m), 1180, 858 (w), 793 (m), 747, 693 (s), 622 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 310 (18, $[M+1]^+$), 309 (89, $[M]^+$), 308 (100), HRMS (EI): calcd. for $C_{21}H_{15}N_3$ $[M]^+$: 309.12506. Found: 309.12509.

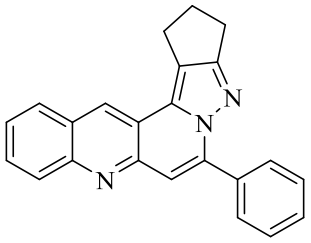


1-Ethyl-2-methyl-5-phenylbenzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine (**21g**): Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**19a**) (150 mg, 0.583 mmol), tosylhydrazine (186 mg, 1 mmol), 2-pentanone (**20g**) (83 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21g** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (165 mg, 84 %), m.p. = 189-191 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.1 Hz, 3H, CH_3), 2.54 (s, 3H, CH_3), 2.76 (q, J = 6.3 Hz, 2H, CH_2), 7.13 (s, 1H, Ar), 7.42-7.44 (m, 4H, Ar), 7.64 (t, J = 7.1 Hz, 1H, Ar), 7.84 (d, J = 8.7 Hz, 1H, Ar), 7.90-7.92 (m, 2H, Ar), 8.03 (d, J = 8.5 Hz, 1H, Ar), 8.74 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 10.7, 13.9 (CH_3), 20.0 (CH_2), 111.1 (C), 112.2 (CH), 119.8 (C), 126.1 (CH), 126.4 (C), 128.1, 128.2 (CH), 128.6 (2×CH), 128.8 (CH), 129.6 (2×CH), 129.7, 130.1 (CH), 133.5, 134.5, 143.3, 147.8, 148.1, 155.5 (C). IR (ATR): $\tilde{\nu}$ = 1613, 1555, 1494 (w), 1428, 1328(m), 1180, 858 (w), 793 (m), 747, 693 (s), 622 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 338 (24, $[M+1]^+$), 337 (100, $[M]^+$), 336 (54), 281 (22). HRMS (EI): calcd. For $C_{23}H_{19}N_3$ $[M]^+$: 337.15735. Found: 337.15705.

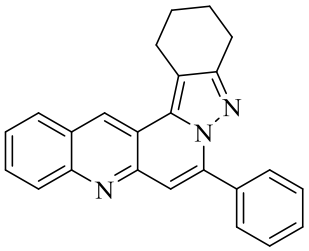


6-Phenyl-2,3-dihydro-1*H*-benzo[*b*]cyclopenta[3,4]pyrazolo[5,1-*f*][1,6]naphthyridine (**21h**): Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**19a**) (150 mg, 0.583 mmol), tosylhydrazine (186 mg, 1 mmol), cyclopentanone (**20h**) (81 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21h** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (125 mg, 64 %), m.p. =

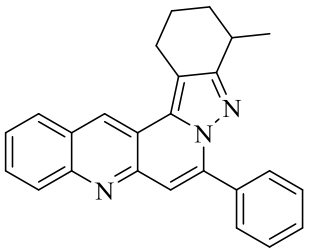
223-225 °C. ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.56 (q, J = 7.6 Hz, 2H, CH_2), 2.87 (t, J = 6.7 Hz, 2H, CH_2), 3.01 (t, J = 6.7 Hz, 2H, CH_2), 7.09 (s, 1H, Ar), 7.40-7.42 (m, 4H, Ar), 7.60-7.62 (m, 1H, Ar), 7.76 (d, J = 6.9 Hz, 1H, Ar), 7.80-7.82 (m, 2H, Ar), 8.01 (d, J = 6.9 Hz, 1H, Ar), 8.53 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 24.3, 25.1, 30.2 (CH_2), 111.6 (CH), 118.8, 121.7 (C), 126.1 (CH), 126.5 (C), 127.7 (2×CH), 128.4, 128.9 (CH), 129.4 (2×CH), 129.7, 130.1, 130.4 (CH), 132.1, 133.6, 144.3, 147.6, 148.3, 164.1 (C). IR (ATR): $\tilde{\nu}$ = 2917, 1633, 1595, 1494 (w), 1438(m), 1288, 1126 (w), 894, 771 (m), 747, 697 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 336 (24, $[M+1]^+$), 335 (100, $[M]^+$), 334 (74), 167 (15). HRMS (EI): calcd. For $C_{23}H_{17}N_3$ $[M]^+$: 335.14170; Found: 335.14115.



7-Phenyl-1,2,3,4-tetrahydrobenzo[*b*]indazolo[3,2-*f*][1,6]naphthyridine (**21i**): Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**19a**) (150 mg, 0.583 mmol), tosylhydrazine (186 mg, 1 mmol), cyclohexanone (**20i**) (94 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21i** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 12:1) as a yellowish solid (177 mg, 87 %), m.p. = 235-237 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.84-1.86 (m, 4H, CH_2), 2.81 (t, J = 6.9 Hz, 2H, CH_2), 3.01 (t, J = 5.9 Hz, 2H, CH_2), 7.11 (s, 1H, Ar), 7.42-7.44 (m, 4H, Ar), 7.60-7.63 (m, 1H, Ar), 7.76 (d, J = 8.3 Hz, 1H, Ar), 7.80-7.83 (m, 2H, Ar), 8.01 (d, J = 8.1 Hz, 1H, Ar), 8.52 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 22.9, 22.9, 23.3, 24.2 (CH_2), 112.2 (CH), 118.2, 118.6, 119.6 (C), 126.1 (CH), 126.4 (C), 127.9, 128.4 (2×CH), 128.6 (C), 128.8 (CH), 129.6 (2×CH), 129.7, 129.8, 130.0 (CH), 133.5, 143.4, 147.8, 151.8 (C). IR (ATR): $\tilde{\nu}$ = 2936, 1614, 1571 (w), 1449, 1351 (m), 1197 (w), 895, 766 (m), 742 (s), 611 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 350 (25, $[M+1]^+$), 349 (100, M^+), 348(47), 321 (30). HRMS (EI): calcd. For $C_{24}H_{19}N_3$ $[M]^+$: 349.15735. Found: 349.15695.

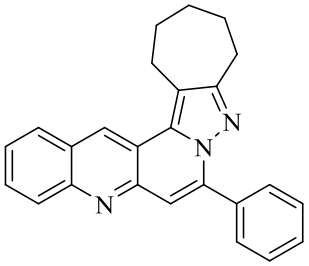


4-Methyl-7-phenyl-1,2,3,4-tetrahydrobenzo[*b*]indazolo[3,2-*f*][1,6]naphthyridine (**21j**): Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**19a**) (150 mg, 0.583 mmol), tosylhydrazine (186 mg, 1 mmol), 2-methylcyclohexanone (**20j**) (108 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21j** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a

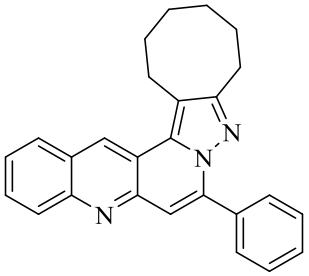


yellowish solid (159 mg, 75 %), m.p. = 157-159 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.35 (d, J = 5.9 Hz, 3H, CH_3), 1.49-152 (m, 1H, CH), 1.80-1.81 (m, 1H, CH_2), 2.05-2.07 (m, 2H, CH_2), 3.03-3.05 (m, 3H, CH_2), 7.18 (s, 1H, Ar), 7.44-7.46 (m, 4H, Ar), 7.66-7.68 (m, 1H, Ar), 7.86 (d, J = 9.5 Hz, 1H, Ar), 7.94-7.96 (m, 2H, Ar), 8.07 (d, J = 8.34 Hz, 1H, Ar), 8.67 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 20.4 (CH_3), 22.1, 23.3 (CH_2), 29.8 (CH), 31.9 (CH_2), 112.1 (CH), 118.2, 118.6, 119.6 (C), 126.1 (CH), 126.4 (C), 127.9 (CH), 128.4 (2×CH), 128.6 (CH), 128.8 (2×CH), 129.5 (CH), 129.6 (C), 129.7, 130.0 (CH), 133.4, 143.4, 147.9,151.8 (C). IR (ATR) $\tilde{\nu}$ = 2846, 1613, 1567 (w), 1486, 1349 (m), 1138, 895, 856, 765 (m), 742, 694 (s), 611 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 364 (28, $[M+1]^+$), 363 (100, $[M]^+$), 362 (28), 334 (25). HRMS (EI): calcd. For $C_{25}H_{21}N_3$ $[M]^+$: 363.17300. Found: 363.17269.

7-Phenyl-11,12,13,14-tetrahydro-10*H*-benzo[*b*]cyclopenta[3,4]pyrazolo[5,1-*f*][1,6]-naphthyridine (**21k**): Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**19a**) (150 mg, 0.583 mmol), tosylhydrazine (186 mg, 1 mmol), cycloheptanone (**20k**) (108 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21k** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (133 mg, 63 %), m.p. = 205-207 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.70-1.72 (m, 2H, CH_2), 1.85-1.87 (m, 4H, CH_2), 2.89-2.92 (m, 2H, CH_2), 3.22-3.24 (m, 2H, CH_2), 7.11 (s, 1H, Ar), 7.42-7.44 (m, 4H, Ar), 7.67-7.69 (m, 1H, Ar), 7.86-7.88 (m, 3H, Ar), 8.06 (d, J = 8.1 Hz, 1H, Ar), 8.96 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 26.2, 27.1, 28.4, 29.3, 31.5 (CH_2), 112.2 (CH), 118.9, 119.9 (C), 126.2 (CH), 126.3 (C), 128.1(CH), 128.3 (2×CH), 128.7, 129.6 (CH), 129.7 (2×CH), 129.8, 130.2 (CH), 133.5, 133.6, 143.4, 147.8, 148.2, 156.8 (C). IR (ATR): $\tilde{\nu}$ = 2922 (m), 1632, 1614 (w), 1477, 1320 (m), 1125 (w), 849, 769 (m), 744, 692 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 364 (26, $[M+1]^+$), 363 (100, $[M]^+$), 362 (46), 334 (23). HRMS (EI): calcd. For $C_{25}H_{21}N_3$ $[M]^+$: 363.17300. Found: 363.17242.

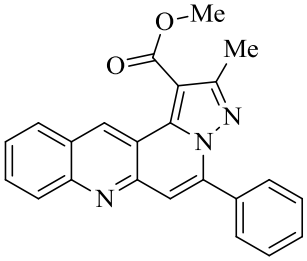


7-Phenyl-10,11,12,13,14,15-hexahydrobenzo[*b*]cyclopenta[3,4]pyrazolo[5,1-*f*][1,6]naph-thyridine (**21l**): Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**19a**) (150 mg, 0.583 mmol), tosylhydrazine (186 mg, 1 mmol), cycloctanone (**20l**) (121 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21l** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a



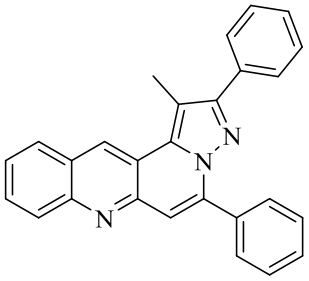
yellowish solid (132 mg, 60 %), m.p. = 165-167 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.37-1.39 (m, 2H, CH_2), 1.52 (p, J = 6.8 Hz, 2H, CH_2), 1.69 (p, J = 6.1 Hz, 2H, CH_2), 1.89 (p, J = 6.1 Hz, 2H, CH_2), 2.88 (t, J = 6.1 Hz, 2H, CH_2), 3.15 (t, J = 6.1 Hz, 2H, CH_2), 7.11-7.14 (m, 1H, Ar), 7.43-7.45 (m, 4H, Ar), 7.65-7.68 (m, 1H, Ar), 7.88-7.90 (m, 3H, Ar), 8.04 (d, J = 8.1 Hz, 1H, Ar), 8.79 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.7, 24.6, 25.1, 25.8, 26.7, 30.0 (CH_2), 111.1 (CH), 115.0, 118.6 (C), 125.1 (CH), 125.4 (C), 127.0 (CH), 127.3 (2×CH), 127.8, 128.4, 128.6 (CH), 128.7 (2×CH), 129.1 (CH), 132.5, 132.6, 142.4, 146.8, 146.9, 154.4 (C). IR (ATR): $\tilde{\nu}$ = 3054, 2845, 1633, 1568 (w), 1483, 1438, 1353(m), 1255, 899 (w), 840 (m), 748, 693 (s), 610 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 378 (29, $[M+1]^+$), 377 (100, $[M]^+$), 376(21), 349 (33), 334(38). HRMS (EI): calcd. For $C_{26}H_{23}N_3$ $[M]^+$: 377.18865. Found: 377.18819.

Methyl-2-methyl-5-phenylbenzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine-1-carboxylate (**21m**):



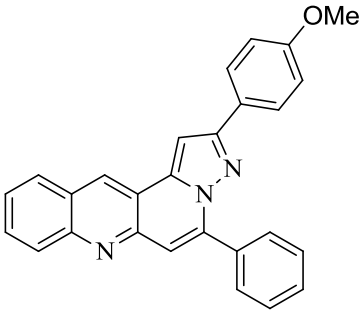
Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**19a**) (150 mg, 0.583 mmol), tosylhydrazine (186 mg, 1.0 mmol), methylacetoacete (**20m**) (111 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21m** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (180 mg, 84 %), m.p. = 87-89 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.58 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), 7.50-753 (m, 5H, Ar), 7.76-7.78 (m, 1H, Ar), 7.84-7.87 (m, 2H, Ar), 8.10 (q, J = 7.7 Hz, 2H, Ar), 10.59 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.9, 50.7 (CH_3), 107.9 (C), 114.4 (CH), 116.8, 125.4 (C), 125.5, 127.3 (2×CH), 128.4, 128.5, 128.9, 129.1, 130.5 (CH), 131.9 (C), 135.4 (CH), 139.2, 141.6, 146.3, 147.8, 152.8 (C), 164.4 (CO). IR (ATR): $\tilde{\nu}$ = 2924 (w), 1704 (m), 1616 (w), 1533 (m), 1493 (w), 1448, 1257, 1190 (m), 1081 (s), 855 (m), 744, 688 (s), 628 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 368 (24, $[M+1]^+$), 367 (100, $[M]^+$), 366 (62), 336 (33): HRMS (EI): calcd. for $C_{23}H_{17}N_3O_2$ $[M]^+$: 367.13153. Found: 367.13064.

1-Methyl-2,5-diphenylbenzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine (**21n**): Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**19a**) (150 mg, 0.583 mmol), tosylhydrazine (186 mg, 1.0 mmol), propiophenone (**20n**) (129 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21n** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (144 mg, 64 %), m.p. = 208-210 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.69 (s, 3H, CH_3), 7.21 (s, 1H, Ar), 7.36-7.38 (m, 7H, Ar), 7.62-7.66 (m, 3H,



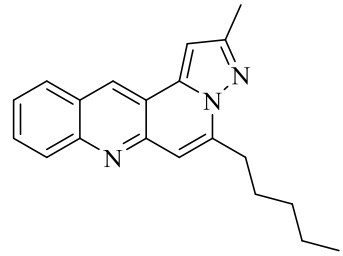
Ar), 7.85 (d, J = 8.1 Hz, 1H, Ar), 7.96-7.99 (m, 2H, Ar), 8.04 (d, J = 8.7 Hz, 1H, Ar), 8.81(s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 11.9 (CH_3), 111.3 (CH), 118.3, 119.8, 126.3 (C), 126.3, 128.1 (CH), 128.3, 128.5 (2×CH), 128.9, 129.0 (CH), 129.2 (2×CH), 129.6, 129.7 (CH), 129.8 (2×CH), 130.3 (CH), 133.2, 135.2, 143.2, 147.8, 147.9, 152.9, 171.2 (C). IR (ATR): $\tilde{\nu}$ = 3053, 1613, 1555, 1493 (w), 1467, 1327 (m), 1173 (w), 1020, 913, 783 (m), 744, 696 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 386 (26, $[M+1]^+$), 385 (100, $[M]^+$), 384 (76), 281 (21). HRMS (EI): calcd. For $C_{27}H_{19}N_3$ $[M]^+$: 385.15735. Found: 385.15666.

2-(4-Methoxyphenyl)-5-phenylbenzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine (**21o**): Starting with 2-(phenylethynyl)quinoline-3-carbaldehyde (**19a**) (150 mg, 0.583 mmol), tosylhydrazine (186 mg, 1 mmol), *p*-methoxyacetophenone (**20o**) (144 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21o** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (145 mg, 62 %), m.p. = 195-197 ^{o}C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.91 (s, 3H, OCH_3), 7.01 (d, J = 8.2 Hz, 2H, Ar), 7.21 (s, 1H, Ar), 7.41 (s, 1H, Ar), 7.52 (s, 1H, Ar), 7.59-7.61 (m, 4H, Ar), 7.81-7.82 (m, 1H, Ar), 7.98-8.01 (m, 2H, Ar), 8.04 (d, J = 8.1 Hz, 1H, Ar), 8.10-8.13 (m, 2H, Ar), 8.23 (d, J = 8.1 Hz, 1H, Ar), 8.92 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 55.3 (OCH_3), 97.3, 113.1 (CH), 114.1 (2×CH), 118.1, 125.6 (C), 126.4 (CH), 126.6 (C), 127.6 (2×CH), 127.9 (CH), 128.2 (2×CH), 129.1, 129.8 (CH), 129.8 (2×CH), 130.4, 130.5 (CH), 133.1, 139.7, 143.2, 147.3, 148.8, 152.7, 159.9 (C). IR (ATR): $\tilde{\nu}$ = 2924 (w), 1704 (m), 1616 (w), 1533 (m), 1493 (w), 1448, 1257, 1190 (m), 1081 (s), 855 (m), 744, 688 (s), 628 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 402 (29, $[M+1]^+$), 401 (100, $[M]^+$), 400 (39). HRMS (EI): calcd. For $C_{27}H_{19}N_3O$ $[M]^+$: 401.15226. Found: 401.15168.

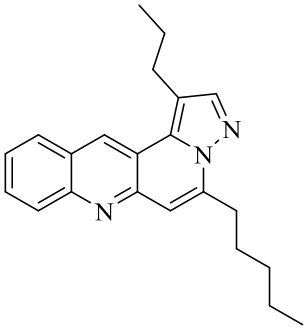


2-Methyl-5-pentylbenzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine (**21p**): Starting with 2-(hept-1-yn-1-yl)quinoline-3-carbaldehyde, (**19b**) (146 mg, 0.583 mmol), tosylhydrazine (186 mg, 1.0 mmol), acetone (**20f**) (56 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21p** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (127 mg, 72 %), m.p. = 95-97 ^{o}C. ^{1}H-NMR (300

MHz, $CDCl_3$): δ = 0.89 (t, J = 7.1 Hz, 3H, CH_3), 1.39-142 (m, 4H, CH_2), 1.88 (dd, J = 8.1, 7.1 Hz, 2H, CH_2), 2.49 (s, 3H, CH_3), 3.12 (t, J = 8.1 Hz, 2H, CH_2), 6.89 (s, 1H, Ar), 6.99 (s, 1H, Ar), 7.47 (t, J = 7.1 Hz, 1H, Ar), 7.71 (t, J = 7.1 Hz, 1H, Ar), 7.86 (d, J = 8.1 Hz, 1H, Ar), 8.11 (d, J = 8.1 Hz, 1H, Ar), 8.65 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.0, 14.2 (CH_3), 22.6, 26.3, 30.8, 31.5 (CH_2), 100.4, 109.3 (CH), 125.4 (C), 126.0 (CH), 126.2 (C), 127.9, 128.9, 130.3, 130.5 (CH), 138.5, 144.9, 147.3, 148.5, 150.8 (C). IR (ATR) $\tilde{\nu}$ = 3051, 1808 (w), 1639 (s), 1615, 1497 (m), 1326 (s), 1180, 1077 (w), 973, 903 (m), 754, 732 (s), 587 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 304 (10, $[M+1]^+$), 303 (45, $[M]^+$), 302 (17), 248 (22), 247 (100). HRMS (EI): calcd. For $C_{20}H_{21}N_3$ [M]+: 303.17300. Found: 303.17270.

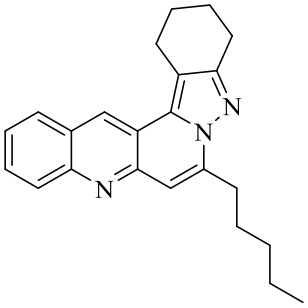


5-Pentyl-1-propylbenzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine (**21q**): Starting with 2-(hept-1-yn-1-yl)quinoline-3-carbaldehyde (**19b**) (146 mg, 0.583 mmol), tosylhydrazine (186 mg, 1.0 mmol), pentanal **(20a**) (83 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21q** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (138 mg, 72 %), m.p. = 88-90 ^{o}C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, J = 7.1 Hz, 3H, CH_3), 1.11 (t, J = 7.1 Hz, 3H, CH_3), 1.38-1.40 (m, 4H, CH_2), 1.78-1.81 (m, 4H, CH_2), 2.89 (t, J = 7.1 Hz, 2H, CH_2), 3.08 (t, J = 7.1 Hz, 2H, CH_2), 7.01 (s, 1H, Ar), 7.43-7.46 (m, 1H, Ar), 7.64-7.67 (m, 1H, Ar), 7.78 (s, 1H, Ar), 7.81 (d, J = 8.1 Hz, 1H, Ar), 8.01 (d, J = 8.1 Hz, 1H, Ar), 8.72 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.0, 14.2 (CH_3), 22.2, 22.5, 26.5, 28.1, 30.9, 31.5 (CH_2), 110.3 (CH), 118.8, 119.3 (C), 126.0 (CH), 126.2 (C), 128.1, 128.7, 130.1, 130.2 (CH), 132.8 (C), 141.1 (CH), 145.1, 147.6, 147.7 (C). IR (ATR): $\tilde{\nu}$ = 3099 (w), 2927 (m), 1614, 1494 (w), 1462, 1333 (m), 1192, 986 (w), 899, 853, 752, 647 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 332 (20, $[M+1]^+$), 331 (86, $[M]^+$), 330(48), 303 (24), 302 (100), 288 (17). HRMS (EI): calcd. For $C_{22}H_{25}N_3$ $[M]^+$: 331.20430. Found: 331.20399.



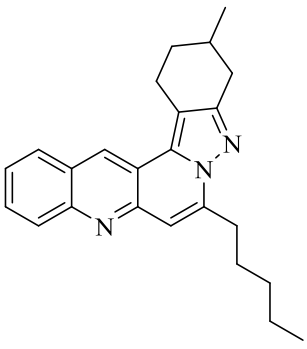
7-Pentyl-1,2,3,4-tetrahydrobenzo[*b*]indazolo[3,2-*f*][1,6]naphthyridine (**21r**): Starting with 2-(hept-1-yn-1-yl)quinoline-3-carbaldehyde (**19b**) (146 mg, 0.583 mmol), tosylhydrazine (186 mg, 1.0 mmol), cyclohexanone (**20i**) (94 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4

(382 mg, 1.8 mmol) EtOH (3 ml), **21r** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (131 mg, 66 %), m.p. = 194-196 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, J = 7.1 Hz, 3H, CH_3), 1.39-1.42 (m, 4H, CH_2), 1.88-1.90 (m, 6H, CH_2), 2.89 (t, J = 5.1 Hz, 2H, CH_2), 3.01-3.06 (m, 4H, CH_2), 6.97-7.01 (m, 1H, Ar), 7.35-7.43 (m, 1H, Ar), 7.67-7.71 (m, 1H, Ar), 7.81 (d, J = 8.1 Hz, 1H, Ar), 8.1 (d, J = 8.1 Hz, 1H, Ar), 8.6 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.6, 22.9, 23.0, 23.3, 24.0, 26.4, 30.8, 31.5 (CH_2), 77.4, 108.9 (CH), 113.4, 119.2 (C), 125.8 (CH), 126.2 (C), 127.9, 128.7, 130.0 (CH), 132.8, 145.2, 147.5, 147.7, 151.4 (C). IR (ATR): $\tilde{\nu}$ = 3054 (w), 2921, 1635, 1573 (m), 1538 (w), 1485 (s), 1391 (w), 1348 (s), 1129 (m), 977 (w), 855 (s), 787 (m), 759, 696 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 344 (14, $[M+1]^+$), 343 (56, $[M]^+$), 342 (39), 288 (24), 287 (100), 259 (30). HRMS (EI): calcd. For $C_{23}H_{25}N_3$ $[M]^+$: 343.20430. Found: 343.20376.

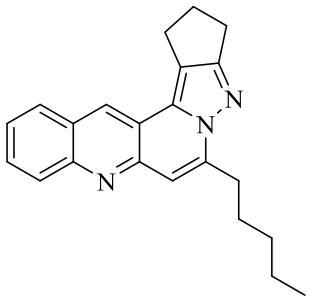


3-Methyl-7-pentyl-1,2,3,4-tetrahydrobenzo[*b*]indazolo[3,2-*f*][1,6]naphthyridine (**21s**):

Starting with 2-(hept-1-yn-1-yl))quinolone-3-carbaldehyde (**19b**) (146 mg, 0.583 mmol), tosylhydrazine (186 mg, 1.0 mmol), 3-methylcyclohexanone (**20p**) (108 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21s** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (156 mg, 75 %), m.p. = 162-164 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.03 (t, J = 6.8 Hz, 3H, CH_3), 1.21 (d, J = 6.8 Hz, 3H, CH_3), 1.48-1.51 (m, 5H, CH_2), 1.97-2.01 (m, 4H, CH_2), 2.53 (q, J = 9.7 Hz, CH), 2.96-3.24 (m, 5H, CH_2), 7.01 (s, 1H, Ar), 7.48-7.53 (m, 1H, Ar), 7.71-7.75 (m, 1H, Ar), 7.88 (d, J = 7.8 Hz, 1H, Ar), 8.11 (d, J = 8.1 Hz, 1H, Ar), 8.6 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.0, 21.6 (CH_3), 22.2, 22.6, 26.3 (CH_2), 29.3 (CH), 30.8, 31.4, 31.5, 32.2 (CH_2), 108.9 (CH), 112.9, 119.0 (C), 125.7, 127.8, 128.6, 129.9, 130.1 (CH), 132.6, 145.1, 147.6, 147.7, 151.5 (C). IR (ATR): $\tilde{\nu}$ = 3051 (w), 2922, 2851 (m), 1574 (w), 1486 (s), 1369 (m), 1319 (s), 1129 (m), 977 (w), 900 (m), 826 (w), 757 (s), 653 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 358 (13, $[M+1]^+$), 357 (57, $[M]^+$), 356 (39), 302 (25), 301 (100), 259 (25). HRMS (EI): calcd. For $C_{24}H_{27}N_3$ $[M]^+$: 357.21995. Found: 357.21921.

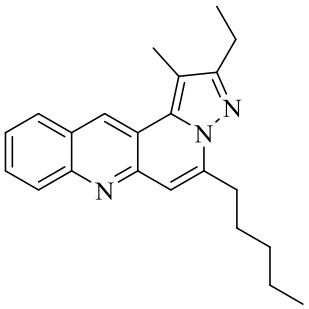


6-Pentyl-2,3-dihydro-1*H*-benzo[*b*]cyclopenta[3,4]pyrazolo[5,1-*f*][1,6]naphthyridine (**21t**):



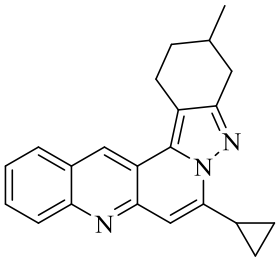
Starting with 2-(hept-1-yn-1-yl)quinolone-3-carbaldehyde (**19b**) (146 mg, 0.583 mmol), tosylhydrazine (186 mg, 1.0 mmol), cyclopentanone (**20h**) (81 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21t** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (145 mg, 76 %), m.p. = 152-154 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, J = 7.1 Hz, 3H, CH_3), 1.42 (t, J = 7.1 Hz, 6H, CH_2), 1.78-1.82 (m, 2H, CH_2), 2.58-2.62 (m, 2H, CH_2), 2.89-2.93 (m, 2H, CH_2), 2.97-3.03 (m, 2H, CH_2), 6.93 (s, 1H, Ar), 7.38-7.42 (m, 1H, Ar), 7.70-7.73 (m, 1H, Ar), 7.92 (d, J = 8.1 Hz, 1H, Ar), 8.11 (d, J = 8.1 Hz, 1H, Ar), 8.53 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 11.2 (CH_3), 22.5, 24.2, 24.9, 26.5, 30.2, 30.3, 31.5 (CH_2), 77.4, 108.9 (CH), 113.4, 119.2 (C), 125.8 (CH), 126.2 (C), 127.9 (CH), 128.7 (CH), 130.0 (CH), 132.8, 145.2, 147.5, 147.7, 151.4(C). IR (ATR): $\tilde{\nu}$ = 3050 (w), 2924, 1481 (m), 1349 (s), 1127, 971 (w), 902, 757 (s), 603 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 330 (11, $[M+1]^+$), 329 (55, $[M]^+$), 328 (83), 273 (100), 272 (40). HRMS (EI): calcd. For $C_{22}H_{23}N_3$ $[M]^+$: 329.18920. Found: 329.18951.

2-Ethyl-1-methyl-5-pentylbenzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine (**21u**): Starting with 2-



(hept-1-yn-1-yl)quinolone-3-carbaldehyde (**19b**) (146 mg, 0.583 mmol), tosylhydrazine (186 mg, 1.0 mmol), 3-pentanone (**20g**) (83 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21u** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (171 mg, 89 %), m.p. = 137-139 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.1 Hz, 3H, CH_3), 1.31 (t, J = 7.1 Hz, 3H, CH_3), 1.42 (t, J = 7.1 Hz, 8H, CH_2), 1.89-1.93 (m, 2H, CH_2), 2.62 (s, 3H, CH_3), 7.01 (s, 1H, Ar), 7.53 (t, J = 8.1 Hz, 1H, Ar), 7.71 (t, J = 8.1 Hz, 1H, Ar), 7.92 (d, J = 8.1 Hz, 1H, Ar), 8.21 (d, J = 8.1 Hz, 1H, Ar), 8.82 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 10.6, 11.2, 13.9 (CH_3), 20.0, 22.5, 26.4, 30.8, 31.5 (CH_2), 77.4, 109.9 (CH), 116.4, 120.2 (C), 125.3 (CH), 126.7 (C), 127.5, 128.3, 131.2 (CH), 133.8, 146.2, 147.1, 147.9, 152.1 (C). IR (ATR): $\tilde{\nu}$ = 3053, 1613, 1555, 1493 (w), 1467, 1327 (m), 1173 (w), 1020, 913, 783 (m), 744, 696 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 332 (12, $[M+1]^+$), 331 (50, $[M]^+$), 330 (18), 276 (22), 274 (100). HRMS (EI): calcd. For $C_{22}H_{25}N_3$ $[M]^+$) : 331.20430. Found: 331.20405.

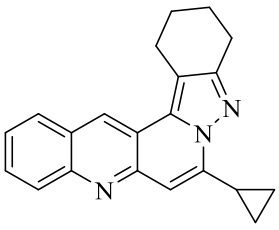
7-Cyclopropyl-4-methyl-1,2,3,4-tetrahydrobenzo[*b*]indazolo[3,2-*f*][1,6]naphthyridine



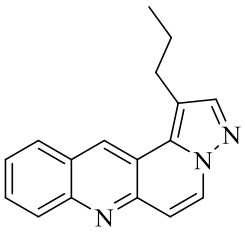
(**21v**): Starting with 2-(cyclopropylethynyl)quinoline-3-carbaldehyde (**19c**) (129 mg, 0.583 mmol), tosylhydrazine (186 mg, 1.0 mmol), 3-methylcyclohexanone (**20j**) (108 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21v** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (143 mg, 75 %), m.p. = 92-94 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 7.1 Hz, 3H, CH_3), 1.18-1.23 (m, 2H, CH_2), 1.37-1.42 (m, 6H), 1.85-1.94 (m, 2H, CH_2), 3.17 (t, J = 7.6 Hz, 2H, CH_2), 7.11 (s, 1H, Ar), 7.47-7.53 (m, 1H, Ar), 7.67-7.72 (m, 1H, Ar), 7.91 (d, J = 8.1 Hz, 1H, Ar), 8.11 (d, J = 8.1 Hz, 1H, Ar), 8.81 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.3 (CH_3), 22.8, 26.5, 30.0, 31.5, 31.8 (CH_2), 77.2, 100.6, 110.6 (CH), 117.5, 118.2, 126.3 (C), 126.7 (CH), 128.2, 128.3 (C), 129.2 (CH), 129.3 (C), 130.5, 130.8 (CH), 131.1, 138.1 (C), 141.4 (CH). IR (ATR): $\tilde{\nu}$ = 3050 (w), 2951 (m), 2926 (s), 1639, 1443 (m), 1332 (s), 1247 (w), 921, 740, 614, 528 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 327 (4, $[M]^+$), 312 (24), 299 (42), 286 (100). HRMS (EI): calcd. For $C_{26}H_{17}N_3$ $[M]^+$: 327.17325. Found: 327.17307.

5-Cyclopropyl-1-propylbenzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine (**21w**): Starting with 2-(cyclopropylethynyl)quinoline-3-carbaldehyde (**19c**) (129 mg, 0.583 mmol), tosylhydrazine (186 mg, 1.0 mmol), pentanal (**20a**) (83 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21w** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (129 mg, 74 %), m.p. = 227-229 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.94-0.98 (m, 2H, CH_2), 1.11 (t, J = 6.7 Hz, 3H, CH_3), 1.15-1.18 (m, 2H, CH_2), 1.78-1.83 (m, 2H, CH_2), 2.67-2.72 (m, 1H, CH), 3.01 (t, J = 7.6 Hz, 2H, CH_2), 6.72 (s, 1H, Ar), 7.43 (t, J = 7.6 Hz, 1H, Ar), 7.71 (t, J = 8.1 Hz, 1H, Ar), 7.78-7.81 (m, 2H, Ar), 8.21 (d, J = 7.9 Hz, 1H, Ar), 8.62 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 8.1, 8.2 (CH_2), 11.3 (CH), 14.2 (CH_3), 22.2, 28.1 (CH_2), 106.8 (CH), 118.9, 119.0 (C), 126.0 (CH), 126.1 (C), 128.1, 128.6, 130.1, 130.2 (CH), 132.8 (C), 141.3 (CH), 146.8, 147.6, 147.8 (C). IR (ATR): $\tilde{\nu}$ = 2865 (m), 2819 (s), 2479 (m), 2387 (w), 1390 (s), 1158, 805 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 302 (16, $[M+1]^+$), 301 (74, $[M]^+$), 300 (25), 286 (32), 273 (22), 272 (100). HRMS (EI): calcd. For $C_{20}H_{19}N_3$ $[M]^+$: 301.15735. Found: 301.15695.

7-Cyclopropyl-1,2,3,4-tetrahydrobenzo[*b*]indazolo[3,2-*f*][1,6]naphthyridine (**21x**): Starting with 2-(cyclopropylethynyl)quinolone-3-carbaldehyde (**19c**) (129 mg, 0.583 mmol), tosylhydrazine (186 mg, 1.0 mmol), cyclohexanone (**20i**) (94 mg, 0.96 mmol), AgOTf (15 mg,10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21x** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (138 mg, 76 %), m.p. = 183-185 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.93-0.97 (m, 2H, CH_2), 1.12-1.17 (m, 2H, CH_2), 1.87-1.93 (m, 4H, CH_2), 2.67-2.71 (m, 1H, CH), 2.89-2.92 (m, 2H, CH_2), 2.67-2.71 (m, 2H, CH_2), 6.59-6.62 (s, 1H, Ar), 7.41 (t, J = 7.3 Hz, 1H, Ar), 7.62 (t, J = 7.3 Hz, 1H, Ar), 7.72 (d, J = 8.1 Hz, 1H, Ar), 7.91 (d, J = 8.1 Hz, 1H, Ar), 8.53 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 8.5, 8.6 (CH_2), 11.2 (CH), 22.8, 22.9, 23.2, 24.1 (CH_2), 104.9 (CH), 113.5, 118.8, 125.7 (C), 125.9, 127.9 (CH), 128.4 (C), 129.9, 130.0 (CH), 132.7, 147.0, 147.4, 147.7 (C), 151.5 (CH). IR (ATR): $\tilde{\nu}$ = 2930, 1614, 1557 (w), 1486 (m), 1200, 1048 (w), 970, 894 (m), 740 (s), 657, 624 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 314 (22, $[M+1]^+$), 313 (100, $[M]^+$), 312 (84), 298 (82). HRMS (EI): calcd. For $C_{21}H_{19}N_3$ $[M]^+$: 313.15735. Found: 313.15659.



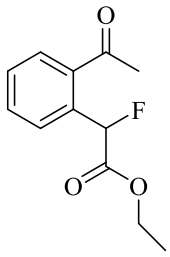
1-Propylbenzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine (**21y**): Starting with 2-((trimethylsilyl)ethynyl)quinoline-3-carbaldehyde (**19d**) (147 mg, 0.583 mmol), tosylhydrazine (186 mg, 1.0 mmol), pentanal (**20a**) (83 mg, 0.96 mmol), AgOTf (15 mg, 10 mol%), K_3PO_4 (382 mg, 1.8 mmol) in EtOH (3 ml), **21y** was isolated after column chromatography (silica gel, *n*-heptane/EtOAc = 9:1) as a yellowish solid (122 mg, 81 %), m.p. = 127-128 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.11 (t, J = 7.1 Hz, 3H, CH_3), 1.81 (dt, J = 8.1, 7.1 Hz, 2H, CH_2), 3.02 (t, J = 7.1 Hz, 2H, CH_2), 7.13 (d, J = 8.1 Hz, 1H, Ar), 7.48-7.53 (m, 1H, Ar), 7.67-7.72 (m, 1H, Ar), 7.77 (s, 1H, Ar), 7.91 (d, J = 8.1 Hz, 1H, Ar), 8.13 (d, J = 7.4 Hz, 1H, Ar), 8.22 (d, J = 6.9 Hz, 1H, Ar), 8.71 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_3), 22.2, 28.0 (CH_2), 112.9 (CH), 118.8, 120.1, 126.5 (C), 126.6 (CH) 128.1 (CH), 129.0, 130.3, 130.5, 131.5 (CH), 132.5 (C), 142.0 (CH), 147.5, 147.6 (C). IR (ATR): $\tilde{\nu}$ = 3053, 1613, 1555, 1493 (w), 1467, 1327 (m), 1173 (w), 1020, 913, 783 (m), 744, 696 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 262 (6, $[M+1]^+$), 261 (100, $[M]^+$), 233 (19), 232 (50), 205 (11). HRMS (EI): calcd. For $C_{26}H_{17}N_3$ $[M]^+$: 261.12636. Found: 261.12626.



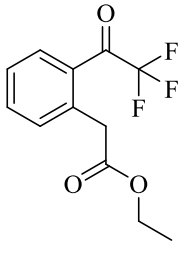
Synthesis of compound (35)

General procedure for compounds 35a-j: A flame dried 100 ml round bottom flask equipped with magnetic stir bar was charged with acetonitrile (3 ml). β-Ketoester / β-diketone **31** (0.4 mmol, 1.0 equiv), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**30**) (0.5 mmol, 1.25 equiv), and cesium fluoride (1.0 mmol, 2.5 equiv) were sequentially added to the flask. A septum was placed on the reaction vessel, and the mixture was then heated at 80 °C for 45-60 minutes. When benzyne precursor was consumed (TLC analysis), the mixture was extracted with brine (4 ml). The aqueous layer was extracted with DCM (3× 4 ml). The organic layers were combined and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure and purified by flash chromatography.

Ethyl 2-(2-acetylphenyl)-2-fluoroacetate (**35a**): Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**30**) (186 mg, 0.63 mmol), ethyl 2-fluoro-3-oxobutanoate (**31a**) (74 mg, 0.5 mmol), CsF (190 mg, 1.25 mmol) in MeCN (3 ml), **35a** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colourless oil (80 mg, 71 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.4 Hz, 3H, CH_3), 2.54 (s, 3H, CH_3), 4.15 (q, J = 7.7 Hz, 2H, Ar), 6.51 (d, J = 45 Hz, 1H, CH-F), 7.42 (t, J = 7.4 Hz, 1H, Ar), 7.53 (t, J = 7.4 Hz, 1H, Ar), 7.73 (d, J = 8.2 Hz, 1H, Ar), 7.77 (d, J = 8.2 Hz, 1H, Ar). ^{19}F-NMR (63MHz, $CDCl_3$): δ = -185.6 (s, 1F, CH-F). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.0, 28.5 (CH_3), 61.8 (CH_2), 87.9 (d, J = 177 Hz, F-CH), 126.9 (d, J = 14.3 Hz, CH, Ar), 128.8 (d, J = 1.7 Hz, CH, Ar), 129.8 (CH), 132.6 (d, J = 1.4 Hz, CH, Ar), 135.1 (d, J = 18.7 Hz, C, Ar), 136.6 (d, J = 2.8 Hz, C, Ar), 168.1 (d, J = 25 Hz, CO), 200.7 (CO). IR (ATR): $\tilde{\nu}$ = 2979 (w), 1731(S), 1599, 1368 (w), 1212, 1023 (s), 888 (m), 759, 695 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 224 ([M]$^+$, 5), 195 (11), 177 (29), 149 (100), 105(13), 77 (10). HRMS (EI): calcd. For $C_{12}H_{13}O_3F$ [M]$^+$: 224.0849. Found: 224.0850.

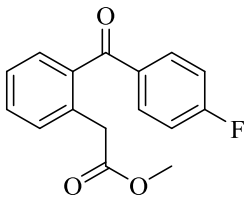


Ethyl 2-(2-(2,2,2-trifluoroacetyl)phenyl)acetate (**35b**): Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**30**) (186 mg, 0.63 mmol), ethyl 4,4,4-trifluoro-3-oxobutanoate (**31b**) (92 mg, 0.5 mmol), CsF (190 mg, 1.25 mmol) in MeCN (3 ml), **35b** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colourless oil (92 mg, 71 %). ^{1}H- NMR (300 MHz,

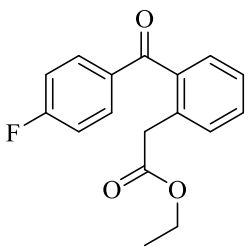


$CDCl_3$): δ = 1.18 (t, J = 7.2 Hz, 3H, CH_3), 3.90 (s, 2H, CH_2), 4.08 (q, J = 7.2 Hz, 2H, Ar), 7.28 (dd, J = 7.6, 0.8 Hz, 1H, Ar), 7.38 (dt, J = 7.7, 1.2 Hz, 1H, Ar), 7.53 (dt, J = 7.6, 1.3 Hz, 1H, Ar), 7.88 (dd, J = 7.8, 1.6 Hz, 1H, Ar). ^{19}F-NMR (63MHz, $CDCl_3$): δ = -71.3 (s, 3F, CF_3).^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 40.1, 61.1 (CH_2), 116.3 (q, J = 292 Hz, CF_3), 127.6 (CH), 129.9 (C), 130.4 (q, J = 3.8 Hz, CH, Ar), 133.1 (CH), 134.2 (CH), 137.2 (C), 170.6 (CO), 182.5 (q, J = 34.7 Hz, CO). IR (ATR): $\tilde{\nu}$ = 3218 (w), 1740 (m), 1465, 1405, 1268 (w), 1170 (s), 1097, 1030, 895 (m), 870, 846 (w), 773, 736, 712 (s), 612, 544 (m) cm^{-1}. GC-MS (EI, 70 eV): m/z (%) = 260 ($[M]^+$, 10), 215 (26), 214 (28), 191 (57), 187 (100), 137 (47), 135 (56), 119 (60), 90 (37), 89 (40). HRMS (EI): calcd. For $C_{18}H_{11}O_3F_3$ $[M]^+$: 260.0659. Found: 260.0655.

Methyl 2-(2-(4-fluorobenzoyl)phenyl)acetate (**35c**): Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**30**) (186 mg, 0.63 mmol), methyl 3-(4-fluorophenyl)-3-oxopropanoate (**31c**) (98 mg, 0.5 mmol), CsF (190 mg, 1.25 mmol) in MeCN (3 ml), **35c** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colourless oil (118 mg, 87 %). ^{1}H- NMR (300 MHz, $CDCl_3$): δ = 3.45 (s, 3H, CH_3), 3.7 (s, 2H, CH_2), 7.02 (t, J = 9.2 Hz, 2H, Ar), 7.23-7.26 (m, 3H, Ar), 7.34-7.39 (m, 1H, Ar), 7.73 (dd, J = 5.4, 5.2 Hz, 2H, Ar). ^{19}F-NMR (63MHz, $CDCl_3$): δ = -105.3(s, F).^{13}C-NMR (75 MHz, $CDCl_3$): δ = 37.5 (CH_2), 51.3(CH_3), 114.4 (d, J = 22.1 Hz, CH, Ar), 125.4 (C), 125.6(CH), 127.6 (C), 128.7, 129.9, 130.8 (CH), 132.1 (d, J = 9.4 Hz, CH, Ar), 132.8(C), 133.1 (d, J = 2.9 Hz, CH, Ar), 137.1, 164.6 (d, J = 250 Hz, C, Ar), 170.7, 190.5 (CO). IR (ATR): $\tilde{\nu}$ = 2997 (w), 1732, 1656, 1595 (s), 1503, 1434, 1408 (w), 1267, 1223, 1147 (s), 1095, 1010, 941 (w), 918, 851 (m), 808, 783 (w), 741 (s), 632 (w), 600 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 272 ($[M]^+$, 6), 213 (36), 212 (100), 183 (28), 123 (12), 95 (13). HRMS (EI): calcd. For $C_{16}H_{13}FO_3$ $[M]^+$: 272.0843. Found: 272.0839.



Ethyl 2-(2-(4-fluorobenzoyl)phenyl)acetate (**35d**): Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**30**) (186 mg, 0.63 mmol), ethyl 3-(4-fluorophenyl)-3-oxopropanoate (**31d**) (105 mg, 0.5 mmol), CsF (190 mg, 1.25 mmol) in MeCN (3 ml), **35d** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colourless oil (113 mg, 79 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.03 (t, J = 7.8 Hz, 3H, CH_3), 4.79 (s, 2H, CH_2), 4.94 (q, J = 7.1 Hz, 2H, CH_2), 8.04 (t, J = 10.1 Hz, 2H, CH, Ar),



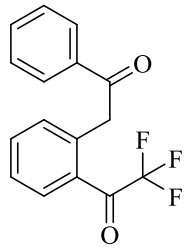
8.24-8.29 (m, 3H, Ar), 8.36-8.42 (m, 1H, Ar), 8.76 (dd, J = 6.3, 3.9 Hz, 2CH, Ar).^{19}F-NMR (63MHz, $CDCl_3$): δ = -105.3 (s, F). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 38.7, 60.8 (CH_2), 115.4 (d, J = 21.5 Hz, CH, Ar), 126.5, 129.7, 130.9, 131.8 (CH), 133.0 (d, J = 8.6 Hz, CH, Ar), 134.0 (C), 134.1 (d, J = 4.5 Hz, C, Ar), 138.5 (C), 165.7 (d, J = 248.6 Hz, C, Ar), 171.3, 198.5 (CO). IR (ATR): $\tilde{\nu}$ = 2980 (w), 1730, 1656, 1595 (s), 1503 (m), 1446, 1408, 1368, 1333 (w), 1267, 1147 (s), 1094, 1026, 918, 850 (m), 783 (w), 741 (w), 688 (m), 601 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 286 ([M]$^+$, 3), 257 (19), 241 (15), 213 (47), 212 (100), 183 (30), 165 (12). HRMS (EI): calcd. For $C_{17}H_{15}FO_3$ [M]$^+$: 286.0999 ; Found: 286.0992.

Ethyl 2-(2-(4-nitrobenzoyl)phenyl)acetate (**35e**): Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**30**) (186 mg, 0.63 mmol), ethyl 3-(4-nitrophenyl)-3-oxopropanoate (**31e**) (119 mg, 0.5 mmol), CsF (190 mg, 1.25 mmol) in MeCN (3 ml), **35e** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colourless oil (133 mg, 85 %). ^{1}H- NMR (300 MHz, $CDCl_3$): δ = 1.07 (t, J = 6.9 Hz, 3H, CH_3), 3.88 (s, 2H, CH_2), 3.95 (q, J = 5.9 Hz, 2H, CH_2), 7.26-7.38 (m, 3H, Ar), 7.41-7.46 (m , 1H, Ar), 7.89 (d, J = 8.8 Hz, 2H, Ar), 8.22 (d, J = 9.8 Hz, 2H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 38.7, 60.9 (CH_2), 123.4, 126.7 (CH), 129.1, 129.5 (C), 130.1, 131.1, 131.7, 132.1, 134.5, 137.1 (CH), 142.8, 150.0 (C), 171.2, 196.2 (CO). IR (ATR): $\tilde{\nu}$ = 2980 (w), 1727, 1667 (s), 1601 (w), 1521 (s), 1445, 1406 (w), 1343, 1263, 1213, 1153 (s), 1025, 920, 866 (m), 850 (s), 821, 789 (w), 759 (m), 710 (s), 652 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 313 ([M]$^+$, 7), 296 (36), 268 (21), 267(16), 240 (33), 239 (100), 194 (41), 165 (64). HRMS (EI): calcd. For $C_{17}H_{15}NO_5$ [M]$^+$: 313.0945; Found: 313.0941.

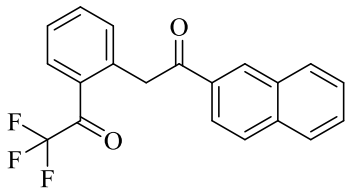
3,3,4,4,5,5,5-Heptafluoro-1-(2-pivaloylphenyl)pentan-2-one (**35f**): Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**30**) (186 mg, 0.63 mmol), 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dione (**31f**) (74 mg, 0.5 mmol), CsF (148 mg, 1.25 mmol) in MeCN (3 ml), **35f** was isolated after column chromatography (silica gel, 1% EtOAc in *n*-heptane) as a colourless oil (93 mg, 50 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.25 (s, 9H, 3CH_3), 3.42 (s, 2H, CH_2), 7.30 (d, J = 7.6 Hz, 1H, Ar), 7.36 (t, J = 8.6 Hz, 1H, Ar), 7.59 (t, J = 7.6 Hz, 1H, Ar), 8.17 (d, J = 8.6 Hz, 1H, Ar). ^{19}F-NMR (63MHz, $CDCl_3$): δ = -124.9 (m, CF_2), -80.5 (m, CF_2), -71.4 (CF_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 27.9 (3CH_3), 35.6

(CH_2), 66.1 (C), 99.7- 101.2 (m, CF_2), 105.8-106.2 (m, CF_2), 119.1-120.3 (m, CF_3), 125.5, 127.6, 129.3, 134.6 (CH), 136.8, 137.7(C), 162.9, 196.3 (CO). IR (ATR): $\tilde{\nu}$ = 3233, 3065, 2228, 1591 (w), 1489, 1329 (m), 1165 (w), 1068, 929 (m), 857 (w), 779 (m), 747 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%) = 372 ($[M]^+$, 6), 202 (64), 188 (12), 187 (100), 169 (13), 160 (47), 145 (32), 131 (18), 89 (43). HRMS (EI): calcd. For $C_{16}H_{15}F_7O_2$ $[M]^+$: 372.0960; Found: 372.0968.

3-(2-Benzoylphenyl)-1,1,1-trifluoropropan-2-one (**35g**): Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**30**) (186 mg, 0.63 mmol), 4,4,4-trifluoro-1-phenylbutane-1,3-dione (**31g**) (108 mg, 0.5 mmol), CsF (148 mg, 1.25 mmol) in MeCN (3 ml), **35g** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colourless oil (107 mg, 73%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.34 (s, 2H, CH_2), 7.21-7.34 (m, 2H, Ar), 7.36-7.49 (m, 2H, Ar), 7.59 (d, *J* = 7.6 Hz, 1H, Ar), 7.72 (t, *J* = 7.6 Hz, 2H, Ar), 7.89 (d, *J* = 7.6 Hz, 2H, Ar). ^{19}F-NMR (63MHz, $CDCl_3$): δ = -71.4 (s, 3F, CF_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 37.1 (CH_2), 112.4 (C), 116.3 (q, *J* = 292 Hz, CF_3), 126.4, 128.3, 129.1 (CH), 129.7 (C), 130.2, 130.3, 130.5, 132.9, 133.1, 133.9(CH), 136.7, 138.4(C),182.5 (q, *J* = 34.5 Hz, $COCF_3$), 198.3 (CO). IR (ATR): $\tilde{\nu}$ = 3062 (w), 1715 (m), 1659 (s), 1596 (m), 1571, 1485 (w), 1447, 1269 (m), 1180, 1138 (s), 1000 (w), 935, 733, 698, 664, 639 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 292 ($[M]^+$,48), 195 (21), 187 (100), 165 (32), 105 (51), 77 (43). HRMS (EI): calcd. For $C_{16}H_{11}F_3O_2$ $[M]^+$: 292.0711. Found: 292.0708.

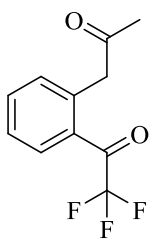


2,2,2-Trifluoro-1-(2-(2-(naphthalen-2-yl)-2-oxoethyl)phenyl)ethanone (**35h**): Starting with 2-(trimethylsilyl)phenyltrifluoromethanesulfonate (**30**) (186 mg, 0.63 mmol), 4,4,4-trifluoro-1-(naphthalen-2-yl)butane-1,3-dione (**31h**) (133 mg, 0.5 mmol), CsF (148 mg, 1.25 mmol) in MeCN (3 ml), **35h** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colourless oil (97 mg, 57 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.14 (s, 2H, CH_2), 7.37 (dd, *J* = 7.6, 7.2 Hz, 1H, Ar), 7.49-7.52 (m, 2H,Ar), 7.70-7.88 (m, 4H, Ar), 8.04 (d, *J* = 7.6 Hz, 1H, Ar), 8.08 (d, *J* = 7.6 Hz, 1H, Ar), 8.16 (d, *J* = 8.6 Hz, 1H, Ar), 8.42 (s, 1H, Ar). ^{19}F-NMR (63MHz, $CDCl_3$): δ = -71.3 (s, 3F, CF_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 37.2 (CH_2), 117.3 (q, *J* = 280 Hz, CF_3), 120.9(C), 124.4, 126.7, 126.9, 127.9, 128.3, 128.6, 128.9, 129.1, 129.4, 129.9, (CH), 132.5, 132.7, 134.6 (C), 135.9 (CH), 138.5 (C), 180.6 (q, *J* = 33.5 Hz, CO), 198.2 (CO). IR (ATR): $\tilde{\nu}$ = 3058 (w), 1714

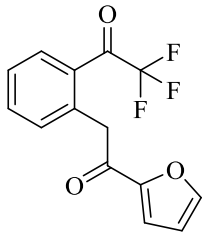


(m), 1654 (s), 1625, 1596 (m), 1571 1486, 1464, 1446, 1352 (w), 1291, 1275 (m), 1181, 1138 (s), 982 (w), 937 (s), 865, 825 (w), 784 (m), 750, 732, 663 (s), 602 (m), 574 (w) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 342 ($[M]^+$, 7), 258 (100), 245 (34), 228 (24), 155 (45), 127 (100), 114 (34), 105 (37), 75 (9). HRMS (EI): calcd. For $C_{20}H_{13}F_3O_2$ $[M]^+$: 342.0868; Found: 342.0869.

1-(2-(2,2,2-trifluoroacetyl)phenyl)propan-2-one (**35i**): Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**30**) (186 mg, 0.63 mmol), 1,1,1-trifluoropentane-2,4-dione (**31i**) (77 mg, 0.5 mmol), CsF (103 mg, 1.25 mmol) in MeCN (3 ml), **35i** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colourless oil (77 mg, 67%). ^{1}H- NMR (300 MHz, $CDCl_3$): δ = 3.09 (s, 3H, CH_3), 4.19 (s, 2H, CH_2), 6.26 (d, *J* = 7.5Hz, 1H, Ar), 6.37 (t, *J* = 6.4 Hz,1H, Ar), 6.59 (t, *J* = 6.4 Hz,1H, Ar), 7.17 (d, *J* = 7.4 Hz,1H, Ar). ^{19}F-NMR (63MHz, $CDCl_3$): δ = -70.8 (s, 3F, CF_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 19.7 (CH_3), 103.5 (CH), 116.6 (q, *J* = 274.7 Hz, CF_3), 123.6 (C), 124.8, 127.5, 129.5, 129.9, 134.7 (CH), 136.5 (C), 163.6 (q, *J* = 34.5 Hz, CO), 173.1 (CO). IR (ATR): $\tilde{\nu}$ = 2953 (w), 1585, 1402 (m), 1278, 1069 (s), 973 (m), 900, 796, 735, 694, 672 (s), 639, 555 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 230 ($[M]^+$, 10), 179 (32), 185 (14), 173 (41), 151 (100), 152 (10), 77 (51), 75 (14). HRMS (EI): calcd. For $C_{11}H_9F_3O_2$ $[M]^+$: 230.0555 ; Found: 230.0557.



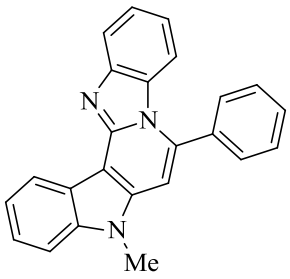
2,2,2-Trifluoro-1-(2-(2-(furan-2-yl)-2-oxoethyl)phenyl)ethanone (**35j**): Starting with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**30**) (186 mg, 0.63 mmol), 4,4,4-trifluoro-1-(furan-2-yl)butane-1,3-dione (**31j**) (119 mg, 0.5 mmol), CsF (103 mg, 1.25 mmol) in MeCN (3ml), **35j** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a colourless oil (99 mg, 70%). ^{1}H- NMR (300 MHz, $CDCl_3$): δ = 5.42 (s, 2H, CH_2), 6.71 (d, *J* = 5.9 Hz, 2H, Ar), 6.85 (t, *J* = 6.8 Hz, 1H, Ar), 7.42-7.46 (m, 2H, Ar), 7.81 (d, *J* = 8.8 Hz, 1H, Ar), 8.22 (d, *J* = 8.8 Hz, 1H, Ar). ^{19}F-NMR (63MHz, $CDCl_3$): δ = -69.8 (s, 3F, CF_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 43.7 (CH_2), 112.6 (CH), 114.6 (q, *J* = 274.7 Hz, CF_3), 118.4, 127.1, 127.5, 127.9, 128.5, 128.9 (CH), 129.8 (C), 147.5 (CH), 151.4 (C), 184.2 (q, *J* = 34.5 Hz,CO), 207.6 (CO). IR (ATR): $\tilde{\nu}$ = 3150 (w), 1731 (s), 1642 (m), 1478 (s), 1549 (m), 1445 (m), 1228 (m), 1162 (m), 1003 (m), 815 (m), 746 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 282 ($[M]^+$, 2), 213 (14), 212 (100), 184 (79), 128 (73), 89 (17). HRMS (EI): calcd. For $C_{14}H_9F_3O_3$ $[M]^+$: 282.0504. Found: 282.0506.



Synthesis of benzo[4',5']imidazo[1',2':1,2]pyrido[4,3-*b*]indole (37).

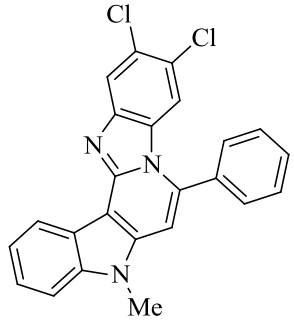
General procedure for compounds 37 a-e: The reactions were performed following the procedure given for the synthesis of products **21** using *o*-alkynylaldehyde **27** (0.50 mmol), amine **36** (0.50 mmol), 10 mol% of $AgNO_3$ in 2.0 mL of H_2O at 85 °C for 7-10 hrs (TLC control). The reaction mixture was quenched with saturated NH_4Cl, followed by extraction with ethyl acetate (3 × 15 ml). The residue then obtained, after removing the solvent under reduced pressure and was purified by column chromatography on silica gel to afford the pure product **37**.

5-methyl-7-phenyl-5*H*-benzo[4',5']imidazo[1',2':1,2]pyrido[4,3-*b*]indole (**37a**): Starting with



1-methyl-2-(phenylethynyl)-1*H*-indole-3-carbaldehyde (**27**) (129.5 mg, 0.50 mmol), benzene-1,2-diamine (**36a**), (54 mg, 0.50 mmol), AgNO3 (10 mol%), **37a** was isolated after column chromatography (silica gel, 2% EtOAc in *n*-heptane) as a white solid (140 mg, 81 %), m.p. = 137-138 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.91 (s, 3H, CH_3), 6.47 (d, J = 8.3 Hz, 1H, CH), 6.88 (s, 1H, CH, Ar), 6.93 (ddd, J = 8.5, 7.1, 1.1 Hz, 1H, Ar), 7.40 (ddd, J = 8.5, 7.1, 1.1 Hz, 1H, Ar), 7.42-7.50 (m, 3H, Ar), 7.61-7.71 (m, 5H, Ar), 8.01 (d, J = 8.2 Hz, 1H, Ar), 8.77 – 8.80 (m, 1H, Ar). ^{13}C-NMR (62 MHz, $CDCl_3$): δ = 29.7 (CH_3), 99.7 (CH), 104.7 (C), 109.1, 114.1, 118.9, 119.5, 121.2, (CH), 122.5 (C) 122.6, 124.3, 124.6, 129.1, 129.1, 129.3, 129.3 (CH), 129.6 (C), 129.9 (CH), 135.2, 138.9, 139.2, 139.4, 145.6, 147.1 (C). IR (ATR): $\tilde{\nu}$ = 3053, 1613, 1555, 1493 (w), 1467, 1327 (m), 1173 (w), 1020, 913, 783 (m), 744, 696 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 348 (26.4, $[M+1]^+$), 347 (100, $[M]^+$), 346 (14.7), 331 (17.6), 173 (15.8), 166 (7.8). ESI-TOF/MS : calcd. For $C_{26}H_{17}N_3$ $[M+H]^+$: 348.1500. Found: 348.1502.

10,11-dichloro-5-methyl-7-phenyl-5H-benzo[4',5']imidazo[1',2':1,2]pyrido[4,3-b]indole



(**37b**): Starting with 1-methyl-2-(phenylethynyl)-1*H*-indole-3-carbaldehyde (**27**) (129.5 mg, 0.50 mmol), 4,5-dichlorobenzene-1,2-diamine (**36b**), (87.5 mg, 0.50 mmol), $AgNO_3$ (10 mol%), in 2 ml H_2O, **37b** was isolated after column chromatography (silica gel, 3% EtOAc in *n*-heptane) as a yellowish solid (137 mg, 66 %), m.p. =

114-115 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.14 (s, 3H, CH_3), 5.61 (s,1H, Ar), 6.22 (s, 1H, Ar), 6.65-7.01 (m, 8H, Ar), 7.22 (s, 1H, Ar), 8.06 (s, 1H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 29.9 (CH_3), 102.2 (C), 109.6, 114.3, 118.7, 120.4, 120.7, 121.2, 121.8 (CH), 124.7 (C),124.9, 126.4, 126.8, 126.8 (CH), 127.8, 127.9 (C), 128.6, 128.6 (CH) 137.8, 138.7, 141.8, 143.9, 148.4, 155.7 (C). IR (ATR): $\tilde{\nu}$ = 3053, 1613, 1555, 1493 (w), 1467, 1327 (m), 1173 (w), 1020, 913, 783 (m), 744, 696 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 420 (2.2), 419 (12.5), 418 (23.4), 417 (62.3), 416 (23.7), 415 (100, $[M]^+$), 208 (26.5), 189 (69.9), 182 (21.7), 172 (12.5), 159 (10.8), 158 (12.5). ESI-TOF/MS (EI): calcd. For $C_{24}H_{15}Cl_2N_3$ ($[M+H]^+$, ^{35}Cl): 416.0716. Found: 416.0721. $C_{24}H_{15}Cl_2N_3$ ($[M+H]^+$, ^{37}Cl): 418.0691. Found: 416.0694.

Appendix

A1 Crystallographic details

Crstallographic data for 5e.

Table 12 Crstallographic details for **5e**

Identification code	IS_MZ10
Empirical formula	$C_{25}H_{26}N_2O$
Formula weight	370.48
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group (H.-M.)	P -1
Space group (Hall)	-P 1
Unit cell dimensions	a = 9.4099 (2) Å α = 82.8690°
	b = 9.5876 (2) Å β = 89.3550°
	c = 11.7606 (3) Å γ = 74.3840°
Volume (Z)	1013.68 (4) $Å^3$
Density (calculated)	1.214 Mg/m^3
Absorption coefficient	0.074 mm^{-1}
F(000)	396
Crystal size	0.34 x 0.31 x 0.23 mm^3
Θrange for data collection	7.891 to 59.925°
Reflections collected	5869
Independent reflections	2986 [R(int) = 0.032]
Absorption correction	multi-scan
Max. and min. transmission	0.9753 and 0.9832
Refinement method	Full-matrix
Goodness-of-fit on F^2	1.064
Final R indices [I>2σ(I)]	R_1 = 0.0470, wR_2 = 0.1376
R indices (all data)	R_1 = 0.0616, wR_2 = 0.1276

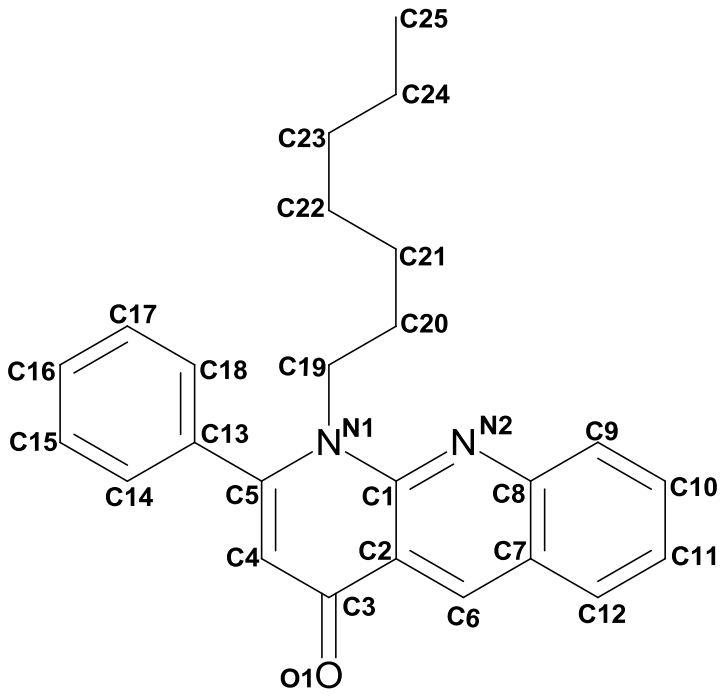


Figure 17. Numbering scheme for 1-Heptyl-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5e**)

Crstallographic data for 5f

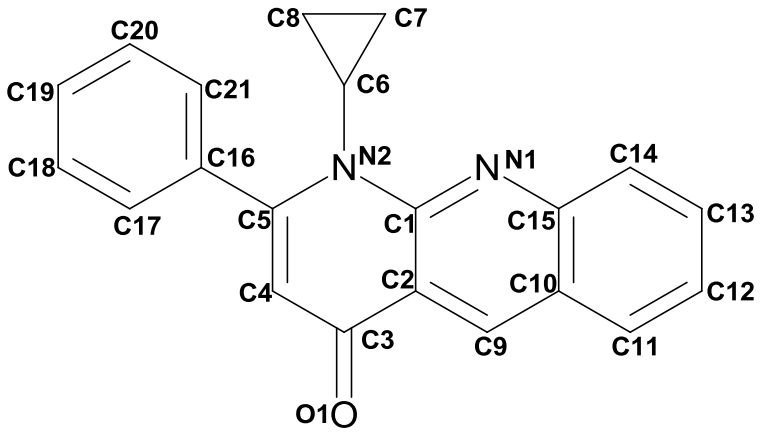


Figure 18. Numbering scheme for 1-Cyclopropyl-2-phenylbenzo[*b*][1,8]naphthyridin-4-(1*H*)-one (**5f**)

Table 13. Crystal data and structural refinement for **5f**

Identification code	IS_MZ11
Empirical formula	$C_{21}H_{16}N_2O$
Formula weight	312.36
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group (H.-M.)	P 21/C
Space group (Hall)	-P 2ybc
Unit cell dimensions	a = 11.0964 (4) Å α = 90.000°
	b = 15.9489 (5) Å β = 90.73°
	c = 8.8191 (7) Å γ = 90.00°
Volume (Z)	1560.64 (10) $Å^3$
Density (calculated)	1.329 Mg/m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	656
Crystal size	0.54 x 0.32 x 0.23 mm^3
Θrange for data collection	7.891 to 59.925°
Reflections collected	4557
Independent reflections	2986 [R(int) = 0.032]
Absorption correction	multi-scan
Max. and min. transmission	0.9506 and 0.9812
Refinement method	Full-matrix
Goodness-of-fit on F^2	1.055
Final R indices [I>2σ(I)]	R_1 = 0.0443, wR_2 = 0.1170
R indices (all data)	R_1 = 0.0594, wR_2 = 0.1258

Crstallographic data for 5k

Table 14. Crystal data and structural refinement for **5k**

Identification code	IS_MZ23
Empirical formula	$C_{25}H_{17}N_2OCl$
Formula weight	396.86
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group (H.-M.)	P 1 21/C 1
Space group (Hall)	-P 2ybc
Unit cell dimensions	a = 11.2627 (4) Å α = 90.000°
	b = 6.9156 (3) Å β = 94.914°
	c = 24.5274 (9) Å γ = 90.00°
Volume (Z)	1903.38 (13) $Å^3$
Density (calculated)	1.385 Mg/m^3
Absorption coefficient	0.220 mm^{-1}
F(000)	824
Crystal size	0.56 x 0.49 x 0.43 mm^3
Θrange for data collection	7.891 to 59.925°
Reflections collected	4557
Independent reflections	[R(int) = 0.032]
Absorption correction	multi-scan
Max. and min. transmission	0.8866 and 0.9113
Refinement method	Full-matrix
Goodness-of-fit on F^2	1.069
Final R indices [I>2σ(I)]	R_1 = 0.0433, wR_2 = 0.1191
R indices (all data)	R_1 = 0.0557, wR_2 = 0.1257

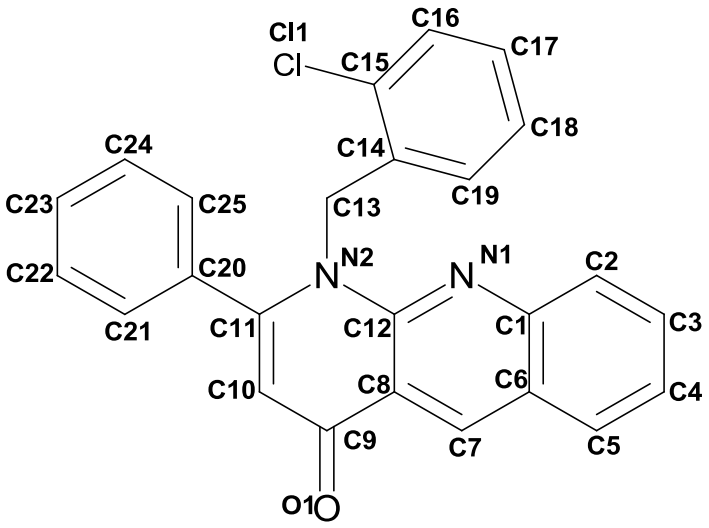


Figure 19. Numbering scheme for 1-(2-Chlorobenzyl)-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5k**)

Crstallographic data for 5t

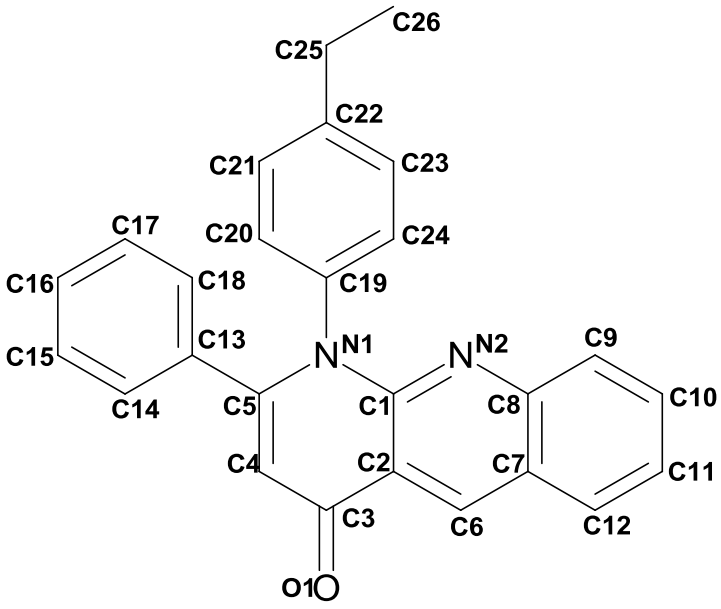


Figure 20. Numbering scheme for 1-(4-Ethylphenyl)-2-phenylbenzo[*b*][1,8]naphthyridin-4(1*H*)-one (**5t**)

Table 15. Crystal data and structural refinement for **5t**

Identification code	av_MZ42b
Empirical formula	$C_{26}H_{20}N_2O$
Formula weight	376.44
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group (H.-M.)	C c
Space group (Hall)	C - 2yc
Unit cell dimensions	a = 16.0307 (4) Å α = 90.000°
	b = 17.5259 (5) Å β = 95.2370°
	c = 6.9720 (2) Å γ = 90.00°
Volume (Z)	1950.62 (9) $Å^3$
Density (calculated)	1.282 Mg/m^3
Absorption coefficient	0.079 mm^{-1}
F(000)	792
Crystal size	0.61 x 0.13 x 0.09 mm^3
Θrange for data collection	7.891 to 59.925°
Reflections collected	11877
Independent reflections	[R(int) = 0.032]
Absorption correction	multi-scan
Max. and min. transmission	0.9536 and 0.9930
Refinement method	Full-matrix
Goodness-of-fit on F^2	1.018
Final R indices [I>2σ(I)]	R_1 = 0.0391, wR_2 = 0.0914
R indices (all data)	R_1 = 0.0455, wR_2 = 0.0958

Crstallographic data for 21i

Table 16. Crystal data and structural refinement for **21i**

Identification code	IS_MZ94
Empirical formula	$C_{24}H_{19}N_3$
Formula weight	349.157
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group (H.-M.)	-P1
Space group (Hall)	P-1
Unit cell dimensions	a = 11.9967 (4) Å α = 70.8560°
	b = 13.6656 (5) Å β = 83.1840°
	c = 16.3845 (7) Å γ = 73.5200°
Volume (Z)	2432.37 (10) $Å^3$
Density (calculated)	1.443 Mg/m^3
Absorption coefficient	0.562 mm^{-1}
F(000)	1084
Crystal size	0.64 x 0.29 x 0.12 mm^3
Θrange for data collection	7.891 to 59.925°
Reflections collected	4557
Independent reflections	14091 [R(int) = 0.032]
Absorption correction	multi-scan
Max. and min. transmission	0.7151 and 0.9357
Refinement method	Full-matrix
Goodness-of-fit on F^2	1.062
Final R indices [I>2σ(I)]	R_1 = 0.0410, wR_2 = 0.1012
R indices (all data)	R_1 = 0.0639, wR_2 = 0.1104

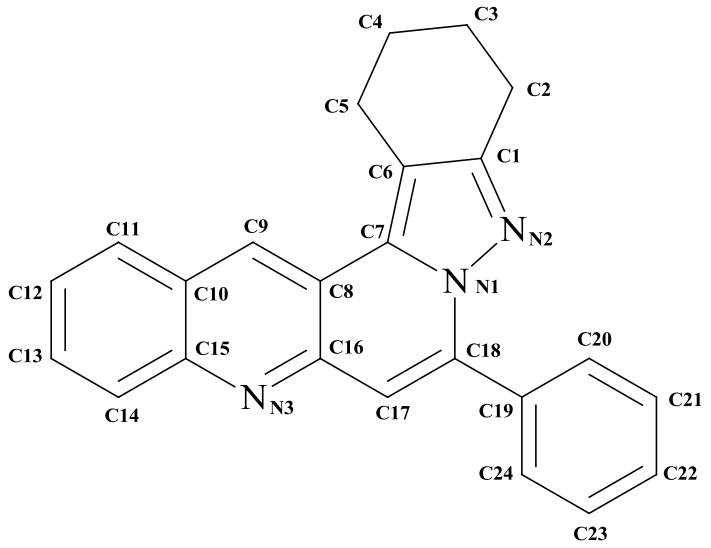


Figure 21. Numbering scheme for 7-Phenyl-1,2,3,4-tetrahydrobenzo[*b*]indazolo[3,2-*f*][1,6]naphthyridin (**21i**)

Crstallographic data for 21q

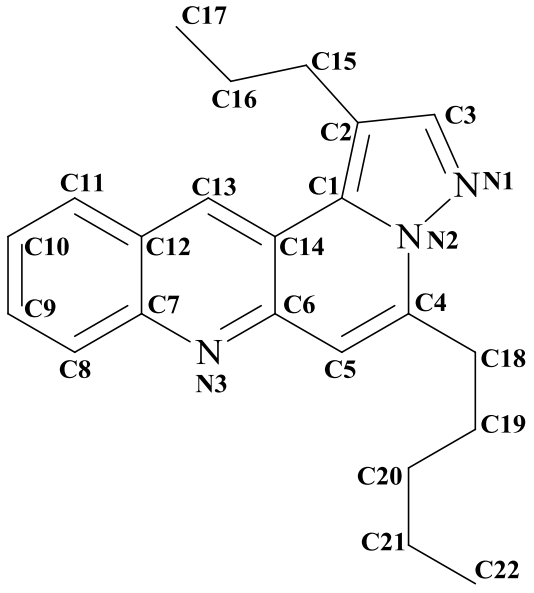


Figure 22. Numbering scheme for 7-Phenyl-1,2,3,4-tetrahydrobenzo[*b*]indazolo[3,2-*f*][1,6]naphthyridin (**21q**)

Table 17. Crystal data and structural refinement for **21q**

Identification code	CH_MZ149
Empirical formula	$C_{22}H_{25}N_3$
Formula weight	331.45
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group (H.-M.)	-P 1
Space group (Hall)	P 2yn
Unit cell dimensions	a = 7.7666 (2) Å α = 90.000°
	b = 22.2827 (6) Å β = 97.734°
	c = 17.8505 (5) Å γ = 90.000°
Volume (Z)	3061.12 (14) $Å^3$
Density (calculated)	1.308 Mg/m^3
Absorption coefficient	0.079 mm^{-1}
F(000)	1280
Crystal size	0.48 x 0.10 x 0.05 mm^3
Θrange for data collection	7.891 to 59.925°
Reflections collected	4557
Independent reflections	14091 [R(int) = 0.032]
Absorption correction	multi-scan
Max. and min. transmission	0.7151 and 0.9357
Refinement method	Full-matrix
Goodness-of-fit on F^2	1.022
Final R indices [I>2σ(I)]	R_1 = 0.1348, wR_2 = 0.1358
R indices (all data)	R_1 = 0.0602, wR_2 = 0.1053

Crstallographic data for 21w

Table 18. Crystal data and structural refinement for **21w**

Identification code	CH_MZ141
Empirical formula	$C_{20}H_{19}N_3$
Formula weight	301.38
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group (H.-M.)	-P 1 21/n 1
Space group (Hall)	P 2yn
Unit cell dimensions	a = 7.7666 (2) Å α = 90.000°
	b = 22.2827 (6) Å β = 97.734°
	c = 17.8505 (5) Å γ = 90.000°
Volume (Z)	3061.12 (14) $Å^3$
Density (calculated)	1.308 Mg/m^3
Absorption coefficient	0.079 mm^{-1}
F(000)	1280
Crystal size	0.48 x 0.10 x 0.05 mm^3
Θrange for data collection	7.891 to 59.925°
Reflections collected	4557
Independent reflections	14091 [R(int) = 0.032]
Absorption correction	multi-scan
Max. and min. transmission	0.7151 and 0.9357
Refinement method	Full-matrix
Goodness-of-fit on F^2	1.022
Final R indices [I>2σ(I)]	R_1 = 0.1348, wR_2 = 0.1358
R indices (all data)	R_1 = 0.0602, wR_2 = 0.1053

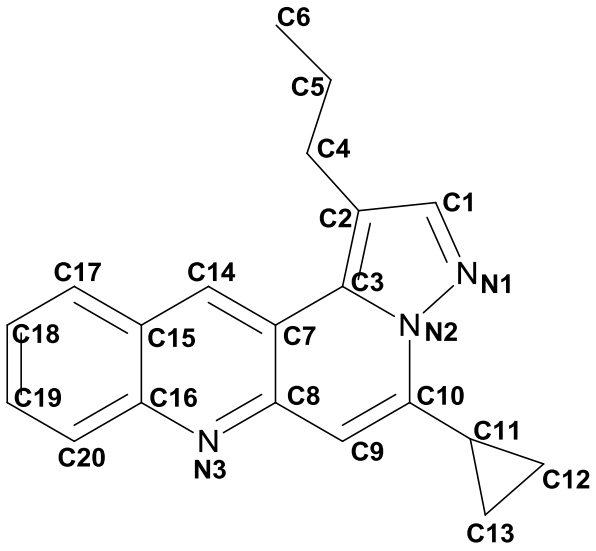


Figure 23. Numbering scheme for 5-Cyclopropyl-1-propylbenzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridine (**21w**)

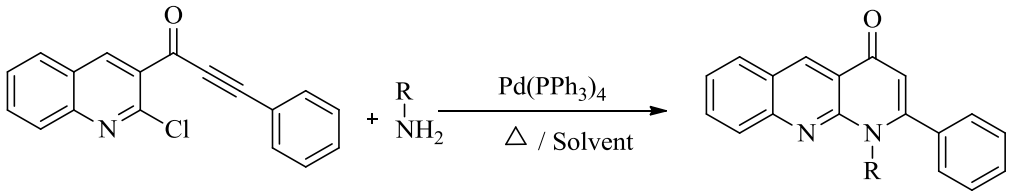
Abbreviations

Ac	Acetyl
Anal.	Elemental Analysis
bp.	Boiling point
calcd	Calculated
CI	Chemical Ionization
COSY	Correlated Spectroscopy
DEPT	Distortionless Enhancement by Polarization Transfer
dr	Diastereomeric ratio
ee	Enantiomeric excess
Et_2O	Diethyl ether
EtOH	Ethanol
GC	Gas Chromatography
GP	General Procedure
EI	Electron Impact
HMBC	Heteronuclear Multiple Bond Correlation
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
IR	Infrared Spectroscopy
MS	Mass Spectrometry
mp	Melting point
NaOEt	Sodium ethanolate
*n*BuLi	*n*-Butyllithium
NEt_3	Triethylamine
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser and Exchange Spectroscopy
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OTf	Triflate
Ph	Phenyl
ppm	Parts per million
Rf	Retention factor
Tf_2O	Trifluoromethanesulfonic anhydride (triflic anhydride)
TFA	Trifluoroacetic acid

THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
Tol Tolyl	(*p*-MeC_6H_4)
Bn	Benzyl
Cy	Cyclohexyl
Tos Tosyl	(*p*-$MeC_6H_4SO_2$)
CPr	Cyclopropyl
DIPA	Disopropylamine
m/z	Mass to charge ratio

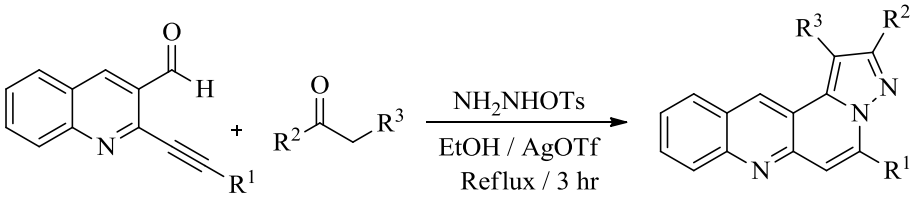
Summary

In chapter one, I have developed a new class of 4-quinolones named as benzo-[1,8]-naphthyridine-4(1*H*)-ones, by domino amination/conjugate addition reactions of 1-(2-chloroquinolin-3-yl)-3-phenylprop-2-yn-1-ones with amines. The purpose of this work is to (later) study the pharmacological properties of the benzo[1,8]-naphthyridine-4(1*H*)-ones.



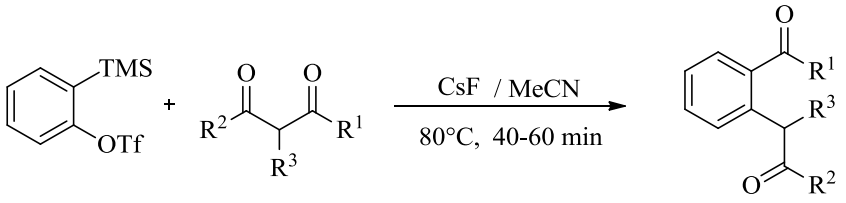
4 **5**

The second chapter contains an efficient route for the synthesis of benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines via silver triflate-catalyzed one-pot tandem reactions. This reaction proceeds with good functional group tolerance under mild conditions with high efficiency and excellent selectivity.



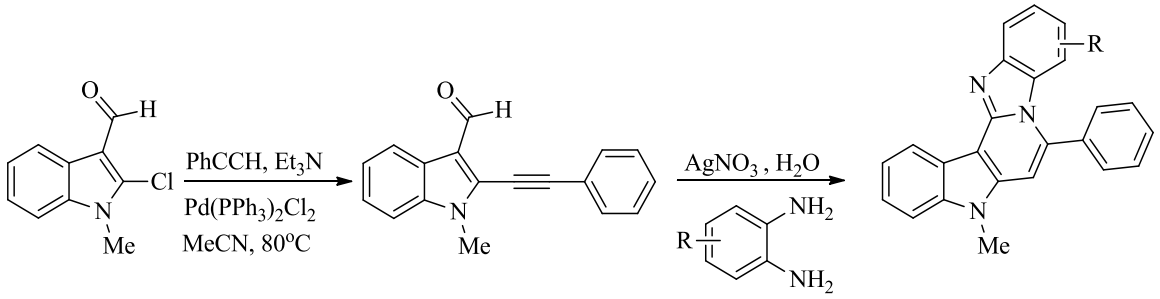
19 **20** **21**

The third chapter includes a high yield route for the synthesis of fluorinated arenes by direct acyl-alkylation of benzyne. This facile methodology provides a single step, high yielding access to a variety of fluoro-substituted arenes, which are otherwise difficult to obtain.



30 **31** **35**

The fourth chapter covers a simple strategy for the generation of noval benzo[4',5']imidazo[1',2':1,2]pyrido[4,3-*b*]indole, having indole and benzimidazole as a single entity. This reaction proceeds in aqeous medium with high yild and regioselectivity. This noval combination could be a potential contributor for biochemical and pharmacological investigation.



26 **27** **36** **37**

Publications :

1. Efficient [5+1]-Strategy for the Assembly of 1,8-Naphthyridines by Domino Amination/Conjugate Addition Reactions of 1-(2-Chloropyridin-3-yl)prop-2-yn-1-ones with Amines**.**V. O. Iaroshenko, I. Knepper, **M. Zahid**, R. Kuzora, S. Dudkin, A. Villinger and P. Langer, *Org. Biomol.Chem.*, **2012**, *10*, 2955-2959.

2. 3-Acylindoles as versatile Starting Materials for Pyridine Ring Annulation: Synthesis of 1-Desazapurine Isosteres, I. Knepper, V. O. Iaroshenko, M. V. Herrera, L. Domke, S. Mkrtchyan, **M. Zahid**, A. Tolmachev, A. Villinger and P. Langer, *Tetrahedron,* **2011**, *67*, 5293-5303.

3. Reaction of benzyne with fluorinated 1,3-dicarbonyl compounds, **Muhammad Zahid**, Muhammad Farooq Ibad, Zharylkasyn A. Abilov, Peter Langer, *Journal of Fluorine, Chemistry,* **2013 ,** *146*, 80-85.

4. Convenient Synthesis of Benzo[*b*]pyrazolo-[5,1-*f*][1,6]-naphthyridines by Silver Triflate Catalyzed Three-Component Reaction of 2-Alkynyl-3-formylquinolines, Tosylhydrazine and Carbonyl Compounds, **Muhammad Zahid**, Viktor Iaroshenko, Peter Langer, *Tetrahedron,* **2013**, (in press)

5. Efficient synthesis of novel benzo[b][1,8]-naphthyridin-4(1H)-ones and pyrido[2,3-b]quinoxalin-4(1H)-ones from ynones and primary amines, **Viktor O. Iaroshenko, Muhammad Zahid**, Satenik Mkrtchyan, Ashot Gevorgyan, Kai Altenburger, Ingo Knepper, Alexander Villinger, Vyacheslav Ya. Sosnovskikh, Peter Langer. *Tetrahedron***. 2013,** *69*, 2309-2318.

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