Universität Rostock

Traditio et Innovatio

Synthesis of Functionalized Isatins, Benzoxazoles, Isoflavones, Coumarins, by Site-Selective Suzuki-Miyaura Cross-Coupling Reactions

Dissertation

zur

Erlangung des akademischen Grades

doctor rerum naturalium (Dr. rer. nat.)

der Mathematisch-Naturwissenschaftlichen Fakultät

der Universität Rostock

vorgelegt von

M.Sc. **Aws Mardan Hamdy Al-Abo** geb. am 09. Sep. 1975 in Mosul, Iraq

Rostock, 2015.

urn:nbn:de:gbv:28-diss2015-0197-1

1. Dekan: **Prof. Dr. Klaus Neymeyr**, Mathematisch-Naturwissenschaftliche Fakultät, Universtät Rostock.

2. Gutachter: **Prof. Dr. Dieter E. Kaufmann**, Institute für Organische Chemie, Technische Universtät Clausthal.

3. Gutachter: **Prof. Dr. Peter Langer**, Institute für Organische Chemie, Universtät Rostock.

Tag der Promotion: 27.10.2015

DEDICATION

I feel a great pleasure to dedicate all of this work to…….

The spirit of my father……..

…….Never forget him.

ACKNOWLEDGMENTS

In the name of ALLAH, the Most Gracious, the Ever Merciful, he is the Omniscient, worthy of all praise, and without his blessings this work would never have been accomplished.

I would like to express my sincere appreciation to Prof. Dr. Dr. h.c. mult. Peter Langer, S.QA., my academic supervisor for his encouragement and guidance that helped me to work independently with patience and insistence.

Overall it has been a privilege to work under his kind supervision.

The other members of my thesis committee deserve my gratitude for their support and general comments over the last few years. I would like especially to thank Dr. Dirk Michalik deeply for doing 2D NMR and also to clarify certain matters relating to elucidate the compounds, I will always be grateful to him. In addition, I am indebted to Dr. Alexander Villinger for spending a long time to prepare the X-ray crystallography measurements and all members of technical sections (NMR, IR and Mass spectrometry) at the Department of Chemistry and LIKAT (Leibniz-Institut für Katalyse). Many thanks to Prof. Dr. Najim Al-Masoudi for biological activity tests.

I would like to thank my research colleagues who have been instrumental in assorted ways of help.

I would definitely make use of this opportunity to thank the DAAD and Iraqi Ministry of Higher Education for granting me a scholarship over three and a half years, deep gratitude for the contact person of Iraqi section Mrs Denise Walter for her kind help.

My dear family deserves a sincere appreciation for all what they have done for me; they have provided me with endless support over the last years as a student. I am truly nothing without them. I have to thank the most important person in my life, my mother. You have

always been an inspiration to me, so thank you for always being there for me emotionally. I appreciate your support during all the past years.

I owe sincere and heartiest gratitude to my wife who tolerated my busy hours with my surprising behavior working hardly to finish my PhD, and for her being never-doubting in my ability to reach the goal.

It is also worth mentioning brothers and sisters for their efforts to provide me the most suitable environment for my studies throughout.

And finally, I want to thank all of my friends, for their selfless sacrifices, and for supporting me in every way possible.

Aws

Abbreviations

EtOAc	Ethylacetate
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
NEt_3	Triethylamine
Tf_2O	Trifluoromethanesulfonic Anhydride
THF	Tetrahydrofurane
DIPEA	Ethyldiisopropylamine
NMR	Nuclear Magnetic Resonance
HMQC	Heteronuclear Multiple Quantum Coherence
HMBC	Heteronuclear Multiple Bond Correlation
COSY	Correlated Spectroscopy
NOESY	Nuclear Overhauser and Exchange Spectroscopy
DEPT	Distortionless Enhancement by Polarisation Transfer
MS	Mass Spectrometry
EI	Electronic Impact
ESI	Electrospray Ionization
HRMS	High Resolution Mass Spectroscopy
IR	Infrared Spectroscopy
UV	Ultraviolet Spectroscopy
Ar	Aromatic
Ph	Phenyl
TLC	Thin Layer Chromatography
Sphos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
Xphos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
Hz	Hertz
DME	Dimethylether
$Pd_2(dbo)_3$	Tris(dibenzylideneacetone)dipalladium(0)
NNRTI	Non-nucleoside reverse transcriptase inhibitors

Abstract

This PhD thesis includes regioselective palladium(0)-catalyzed Suzuki-Miyaura cross-coupling reactions of isatins, benzoxazols, isoflavones, and coumarins. These classes of compounds are of pharmacological relevance. Suzuki-Miyaura cross-coupling reactions of 4,7-dichloro-1-methylindoline-2,3-dione afforded arylated isatins. The reactions proceeded with very good site-selectivity. The Suzuki-Miyaura reaction of 2,6-dichlorobenzoxazol, of the bis(triflate) of 4',7-dihydroxyisoflavone, and of the bis(triflate) of 4-methyl-6,7-dihydroxycoumarin, with different boronic acids, gave the corresponding site-selective mono-arylated, homo bis-arylated and mixed bis-arylated derivatives, most of them with very good site-selectivity. The reaction of the bis(triflates) of 3-bromo-4-methyl-6,7-dihydroxycoumarin with arylboronic acids gave triarylcoumarins in very good yields. The anti-*HIV* properties of various arylisatins and arylcoumarins were studied.

Diese Dissertation umfasst Palladium(0)-katalysierte Suzuki-Kreuzkupplungsreaktionen von Isatinen, Benzoxazolen Isoflavonen, und Cumarinen. Auf Grund der pharmakologischen Bedeutung dieser Substanzklassen wurden unter Anwendung der genannten Methodik neue Derivate synthetisiert. Suzuki-Kreuzkupplungsreaktionen von 4,7-Dichlor-1-methylindolin-2,3-dion ergaben arylierte Isatinderivate. Die Reaktionen wiesen eine gute Regioselektivität auf. Die Suzuki-Miyaura-Reaktionen mit dem bis(Triflat) des Dichlorbenzoxazols, den Bis(triflaten) des 4',7-Dihydroxyisoflavons und des 4-Methyl-6,7-dihydroxycoumarins mit unterschiedlichen Boronsäuren ergaben die entsprechenden mono-arylierten, homo bis-arylierten und gemischt bis-arylierten Derivate. Der Großteil der Reaktionen verlief dabei mit sehr guter Regioselektivität. Die Reaktion des Bis(triflates) des 3-Brom-4-methyl-6,7-dihydroxycumarins mit Boronsäuren führte in sehr guten Ausbeuten zu Triarylcoumarinen. Die Anti-*HIV* Eigenschaften verschiedener Arylisatine und Aryl-Cumarine wurden untersucht.

TABLE OF CONTENTS

1 Back ground and introduction

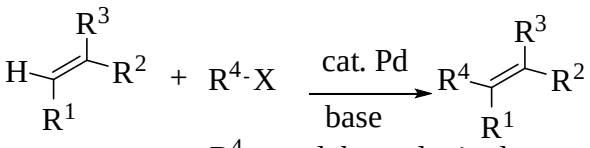
1.1 General introduction

Carbon-carbon bond-formation reactions have played a significant role in the development of organic chemistry. The importance of the synthesis of carbon-carbon bonds is reflected by the fact that Nobel Prizes in Chemistry have been previously given in this area: The Grignard reaction (1912), the Diels-Alder reaction (1950), the Wittig reaction (1979), and olefin metathesis developed by Y. Chauvin, R. H. Grubbs, and R. R. Schrock (2005). Palladium-catalysed cross-coupling reactions (defined as transition-metal catalysed substitution of an organic halide or related electrophile by a nucleophile)[1] have been proved to be especially important as carbon-carbon bond formation reactions, due to many benefits of these reactions, such as high productivity, atom economy, potential recycling of the catalyst and mild reaction conditions. They have been increasingly valuable, for example, in the pharmaceutical and fine chemical industries and natural product synthesis.[2-5] One event that stimulated research in palladium catalysis in organic chemistry was the discovery that ethylene is oxidized to acetaldehyde by air in a palladium-catalyzed reaction which became the industrially important Wacker process.[6] In 2010, the Nobel Prize in chemistry was awarded jointly to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for the development of methods for palladium-catalyzed cross-couplings syntheses.

1.2 Palladium(0) catalysis

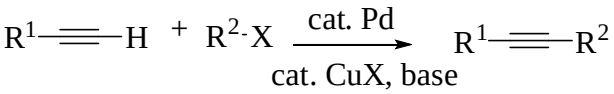
During recent decades an abundance of palladium(0) catalysed coupling reactions has been developed. These coupling reactions have found widespread use in large areas of chemistry,[7] for example in medicinal and pharmacological chemistry,[8] total synthesis, nanotechnology, and synthesis of advanced materials. Various types of palladium-catalyzed cross-coupling reactions are known in organic synthesis, such as the Heck, Stille, Suzuki, Sonogashira, Tsuji-Trost and Negishi reactions[9,10] (Scheme 1).

Heck Reaction



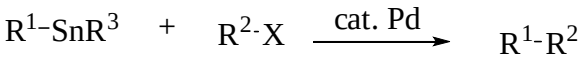
R^4 = aryl, benzyl, vinyl
X = Cl, Br, I, OTf

Sonogashira Reaction



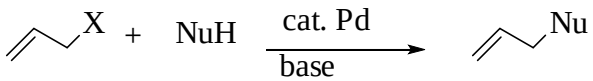
R^1 =alkyl, aryl, vinyl
R^2 = aryl, benzyl, vinyl
X = Br, Cl, I, OTf

Stile Reaction



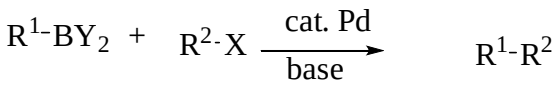
R^1 = alkyl, alkynyl, aryl, vinyl
R^2 = acyl, alkynyl, allyl, benzyl
X = Br, Cl, I, OTf, OAc

Tsuji-Trost Reaction



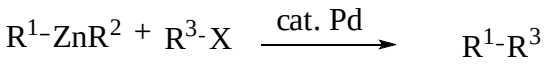
X = Br, Cl,OCOR,
NuH = enamines, enolates

Suzuki Reaction



R^1 = alkyl, aryl, vinyl
R^2 = alkyl, alkynyl, vinyl, benzyl
X = Br, Cl, I, OTf, OTs

Negishi Reaction

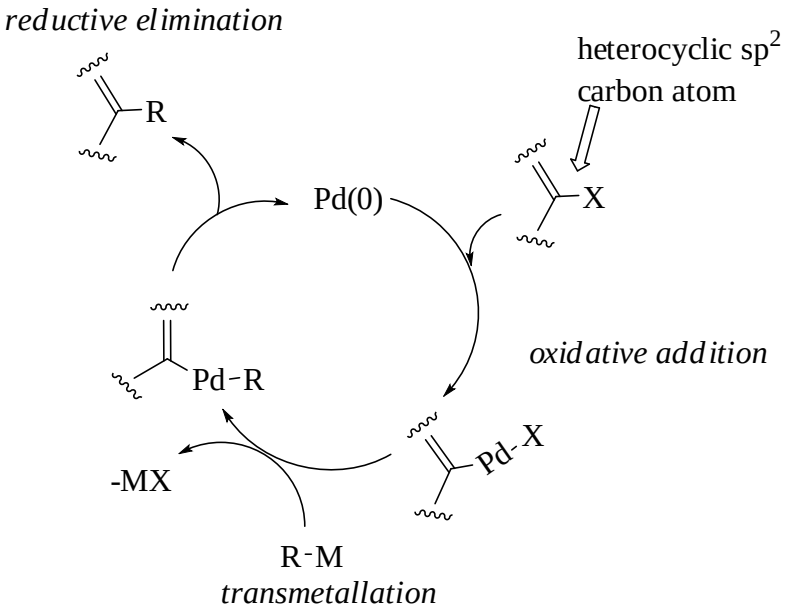


R^1 = alkyl, akynyl, aryl, vinyl
R^3 = acyl, aryl, benzyl, vinyl
X = Br, I, OTf, OTs

Heck: R1,

Scheme 1. Palladium(0)-catalyzed cross-coupling reactions. (The picture was taken from *Angew. Chem. Ind. Ed.* **2005**, *44*, 4442).

Most of the coupling reactions presented above proceed in three steps (Scheme 2). Each cycle starts by oxidative addition of an organohalide (I, Br, Cl) to a palladium(0) species a triflate or diazonium salt to generate an organo-palladium(II) species.[11,12] The second step of the reaction is the transmetallation process. In this process an organic moiety is transferred from a main group metal, *e.g.* Mg, Cu, Zn, Sn, B or Si, to a metal that is more electronegative, such as palladium, to give a diorganopalladium complex. In the last step of the reaction, this complex undergoes a reductive elimination to create a carbon-carbon bond and the palladium catalyst is regenerated.[13, 14]



Scheme 2. General mechanism for palladium(0)-catalyzed cross-coupling reactions. M = BY_2 (Suzuki), SnR_3, (Stille), ZnX (Negishi), MgX (Kumada) or SiR_3 (Hiyama) (picture was taken from *Tetrahedron*, **2005**, *61*, 2245).

1.3 Palladium catalyzed Suzuki Miyaura reaction

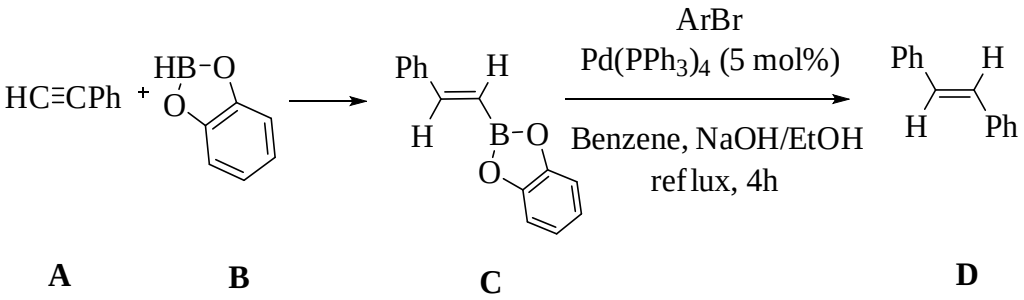
The Suzuki-Miyaura cross-coupling reaction is an extremely versatile methodology for the generation of carbon carbon $C(sp^2)$-$C(sp^2)$ bonds,[15] but more recently it was extended to accommodate carbon atoms in other hybridization states, such as sp^3.[16] Suzuki reactions are defined as Pd catalyzed cross-coupling reactions between organic electrophiles, such as aryl-, vinyl- or alkyl-halides or triflate, with organoboron compounds in the presence of a stoichiometric amount of base (Scheme 3).[17,18]

$$R\text{-}X \quad + \quad R^1\text{-}BY^2 \xrightarrow[\text{base}]{\text{Pd(0)}} R\text{-}R^1$$

R= alkyl, alkenyl, aryl, benzyl, vinyl
R^1= alkyl, alkynyl, aryl, vinyl
X= I, Br, Cl, OTf

Scheme 3. Palladium catalysed Suzuki coupling.

The Suzuki-Miyaura reaction is widely used to synthesize poly-olefins, styrenes and substituted biphenyls. The first example of this reaction was reported in 1979 by Akira Suzuki and co-workers, The reaction of alkyne **A** with borate **B** in benzene using 5 mol-% of tetrakis(triphenylphosphine)palladium $Pd(PPh_3)_4$ gave (*E*)-1,2-diphenylethene **D** in decent yields (Scheme 4). This reaction was done in presence of base, such as sodium ethoxide in ethanol or sodium hydroxide in ethanol.[19, 20]

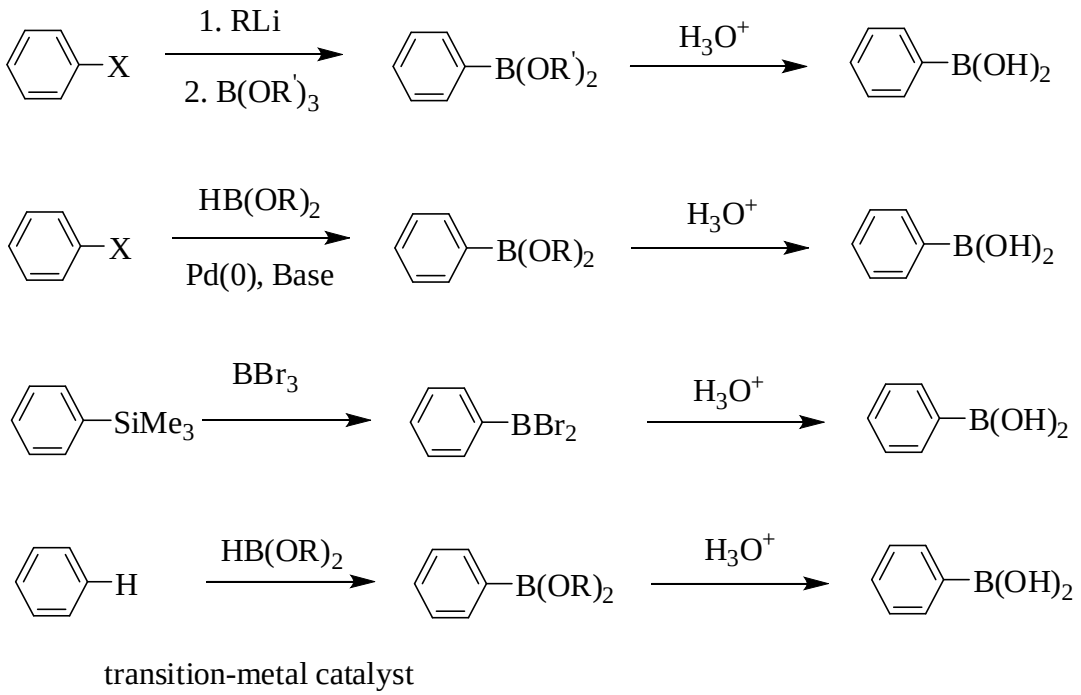


Scheme 4. An example of a Suzuki coupling reaction.

Organoboranes and boronic acids are attractive coupling partners, as they are widely commercially available. Moreover, they are generally relatively tolerant to air and moisture, tolerate a wide variety of functional groups, and are easy to handle. The by-products formed in coupling reactions of organoboranes are usually non-toxic and water soluble. All these fearures make organoboranes an attractive class of synthetic intermediate from an environmental point of view.[15] These interesting advantages make the Suzuki-Miyaura cross-coupling reaction an important tool in medicinal chemistry and also in the preparation of fine chemicals as well as in large scale pharmaceutical industry.[21]

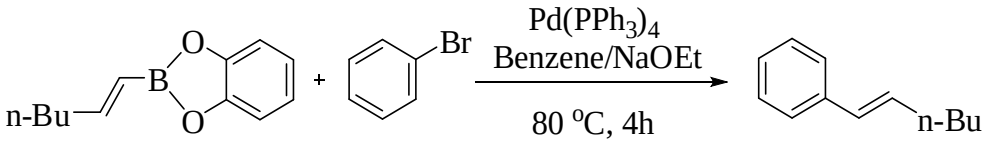
Several different organoboranes are used in transition-metal-catalyzed coupling reactions, for example, organoboronic acid, organoboronic esters and organotrifluoroborate salts which have gained popularity during the past few years, due to their low sensitivity to oxidation and nucleophilic substitutions. The trifluoroborate salts are easily prepared from their corresponding boronic acids or esters by treatment with an excess of

KHF_2.[22,23,24] The most frequently employed reagents are organoboronic acids. Organoboranes can be synthesized from different substrates, some examples are shown below (Scheme 5).



Scheme 5. Methods for the synthesis of boronic acids.

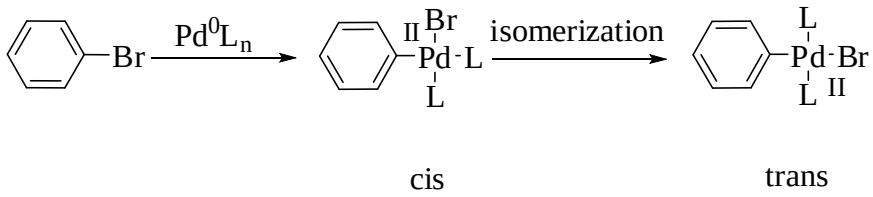
A Suzuki-Miyaura cross-coupling reaction of organic aryl, vinyl halides and triflates with organoboronic esters can be exemplified by the reaction shown in Scheme 6.[19]



Scheme 6. Suzuki coupling reaction of a boronic ester and bromobenzene.

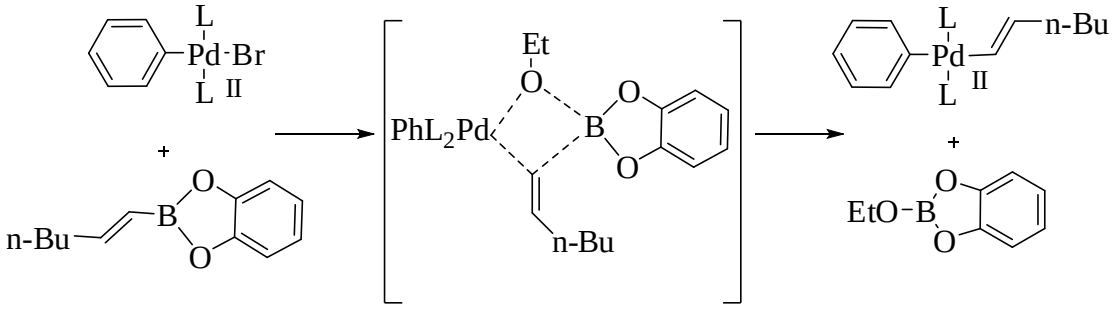
In the first step of the reaction, the oxidative addition of organic halides or triflates to the Pd(0) complex gives a stable *trans*- б-palladium(II) complex (Scheme 7).[25] The reaction proceeds with complete retention of the stereochemistry for alkenyl halides and with

inversion for allylic and benzylic halides. In the oxidative addition step of the Suzuki reaction, the reactivity of the reacting substrates has a vital role to play. Generally, the reactivity of various substrates is observed in the following order, Ar-I > Ar-OTf >Ar-Br > Ar-Cl and follows the bond strength of the C-X bond to be broken.[26,27,28] However, the reaction rate can also be influenced by electron-rich spectator ligands, which increase the nucleophilicity of the palladium center, or by introduction of electron-poor substituents to the aryl substrate.[29, 30]



Scheme 7. Oxidative addition.

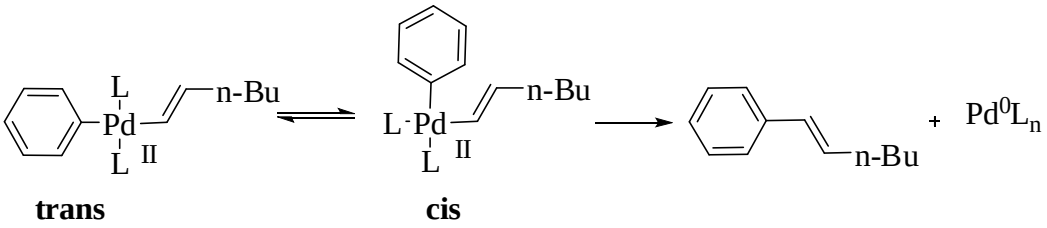
The next step is the transmetallation (Scheme 8) which is defined as a ligand exchange process between two metals, Pd(II) and M. The base supports the transmetallation step of the Suzuki reaction.[31] The presence of a base usually enhances the nucleophilicity of the organoborane compound by formation of an organoborate containing a tetravalent boron atom. Different types of bases are used in this reaction, e.g. potassium carbonate, potassium phosphate , cesium carbonate and sodium ethoxide.



Scheme 8. Transmetallation processes.

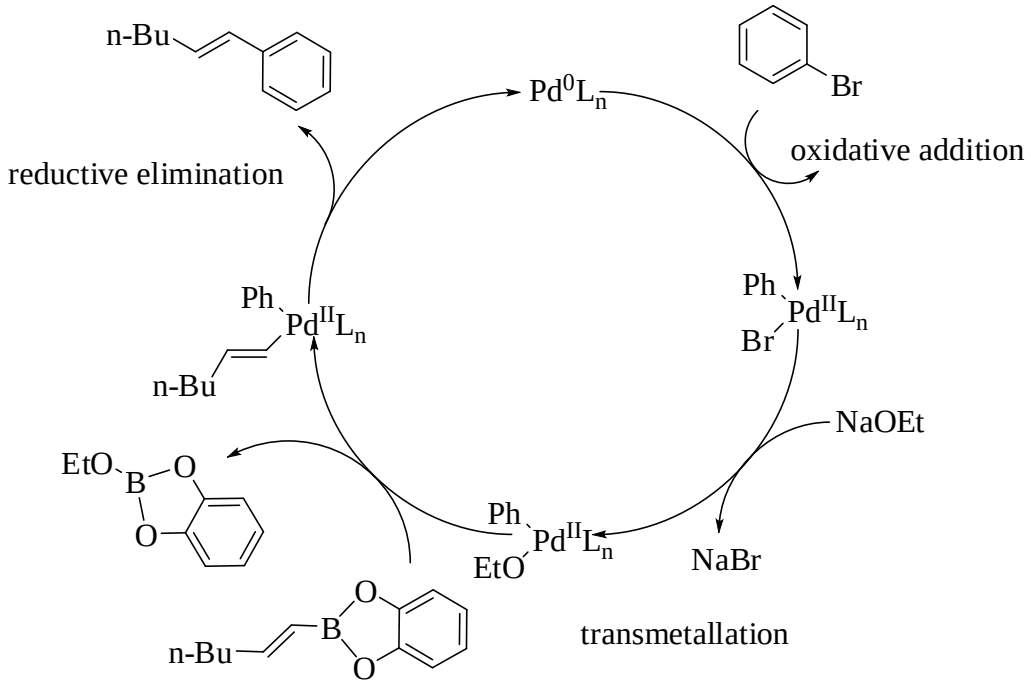
The last step is the reductive elimination (Scheme 9) which can be considered to be the reverse process to the oxidative addition.[31] This step completes the catalytic cycle and

releases Pd (0). Isomerization to the *cis* complex is required before the reductive elimination can occur.



Scheme 9. Reductive elimination.

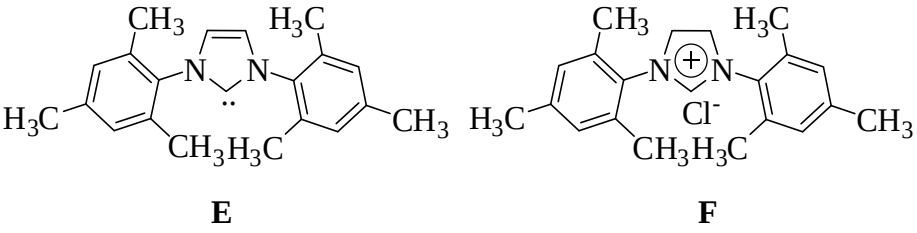
The complete catalytic cycle of Suzuki coupling reactions is shown below (Scheme 10)



Scheme 10. Catalytic cycle of Suzuki coupling reaction.

Several catalysts are used for this reaction, e.g. $Pd(PPh_3)_4$ and $Pd_2(dba)_3$, $Pd(PPh_3)_2Cl_2$ or $Pd(OAc)_2$ together with phosphine ligands (such as PPh_3, PCy_3, SPhos and XPhos).[32] *N*-heterocyclic carbenes[33] (Figure 1) are also used as an alternative to phosphine ligands.

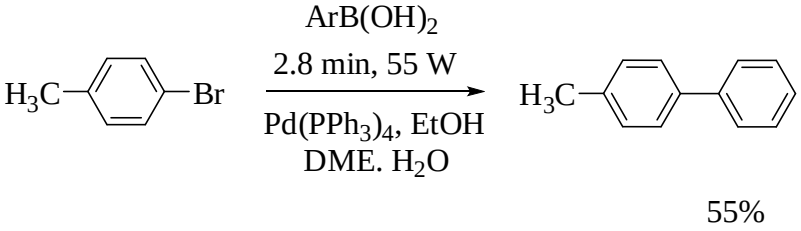
The nucleophilic *N*-heterocyclic carbene **E** is the active ligand which is formed in situ from **F**.



E **F**

Figure 1. *N*-hetrocyclic carbene ligands.

Other factors, that also affect the rate of the reaction, are the variation of the solvent of the reaction[34] and the application of microwave. The use of microwave was reported for the first time by Hallberg an co-workers[35] in 1996 to enhance the rate of the carbon-carbon formation (Scheme 11). They confirmed that many metal-catalyzed reactions are completed within a few minutes. The reactions were carried out in water, ethylene glycol, or DMF, due to the ability of polar solvents to efficiently absorb microwave irradiation.



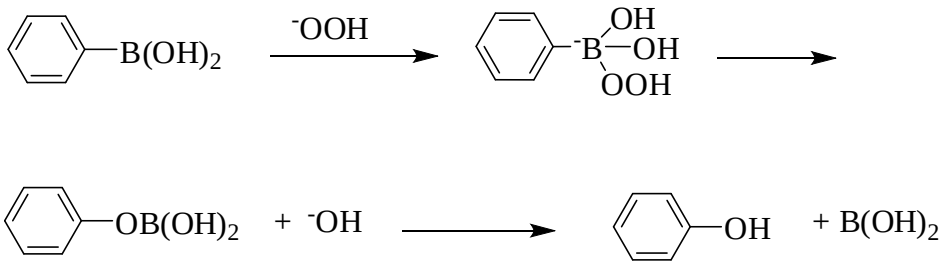
Scheme 11. Microwave-assisted Suzuki coupling reaction.

1.4 Side reactions

Organoboronic acids are relatively stable, due to the low polarity of the boron-carbon bond (electronegativity of boron 2.0 and carbon 2.5, according to the Pauling scale). Orrganoboronic acids are relatively unwilling to undergo transmetalation with palladium (electonegativity of 2.2). In order for arylboronic acids to become sufficiently reactive for efficient transmetallation with palladium, they require coordination of a base or Lewis base to form a tetracoordinated boronate anion which is more susceptible to transmetallation than the free boronic acid.[23]

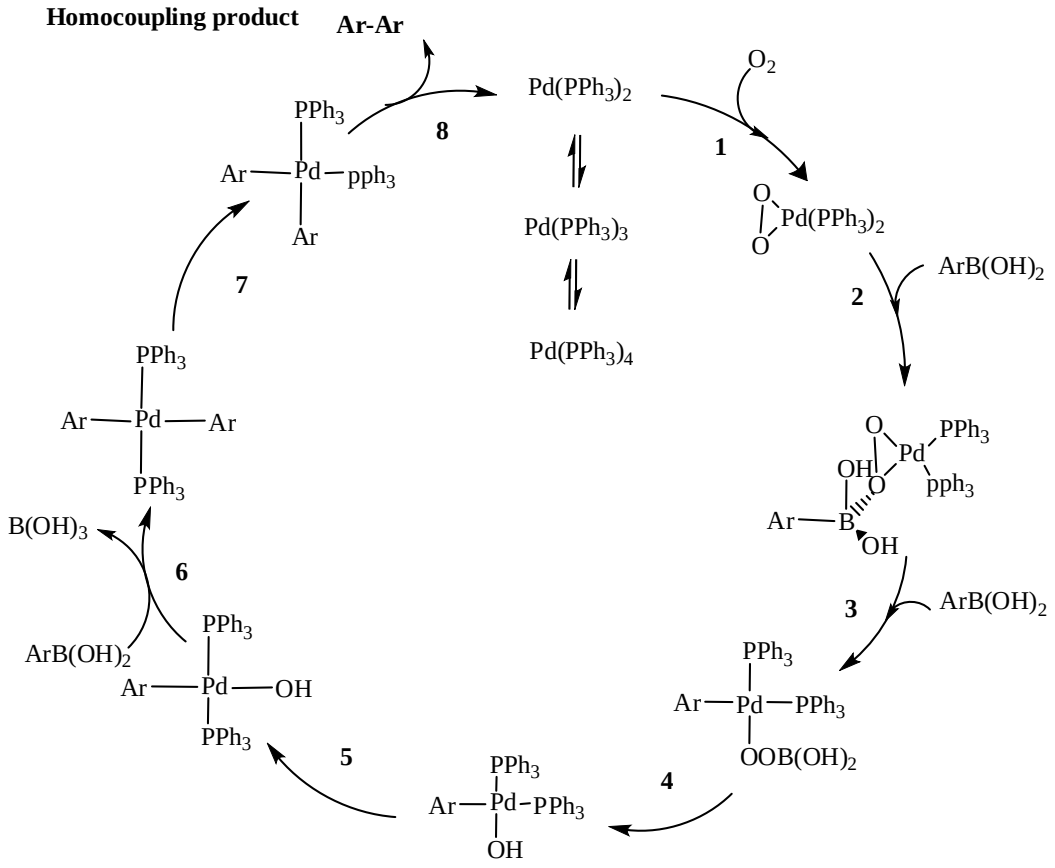
Although organoboronic acids are apparently stable, they often undergo side reactions during transition-metal-catalyzed coupling reactions. A public side reaction is the protodeboronation. Protodeboronation seldom occurs in the absence of transition metals under neutral conditions, even at high temperature.[36] In highly acidic or basic aqueous solutions, on the other hand, protodeboronation may be a fairly fast process.[37] Several metal ions, Pd(II), Ni(II), Zn(II), Ag(I), Cu(II), can induce protodeboronation in water by the formation of an aryl-metal intermediate.[38]

Other kinds of side reactions are the oxidation of the arylboronic acid to the corresponding alcohol. Challenger reported the formation of phenol by treating arylboronic acids with hydrogen peroxide in 1930,[39] and other oxidants, such as oxone[40] and sodium perborate.[41] Scheme 12 explains the mechanism for the oxidation of boronic acid in aqueous solution.[42]



Scheme 12. Oxidation of boronic acids**.**

In 1996 and 2005 Moreno-Manas et al. have been reported in their pioneering work on palladium-catalyzed biaryl formation by homocoupling of arylboronic acids as a side reaction under palladium oxidative conditions.[43]Amatore and Jutad[44] published a thorough mechanistic investigation. Their investigation demonstrated that the reaction was catalyzed by palladium(II) and required dioxygen to form the active peroxo-palladium complex, $(\eta^2\text{-}O_2)PdL_2$, generated by reaction of dioxygen and palladium(0) (Scheme 13).



Scheme 13. Palladium-catalyzed homocoupling of arylboronic acids (*pictures were taken from refs.44*).

1.5 Site selective and chemo selectivity Suzuki Miyaura cross-coupling reactions

Recently, site-selective Suzuki coupling reactions became important. Complex compounds can be prepared by successive coupling reactions of substrates containing two or more possible reactive sites. The first attack usually occurs at the more electron deficient and less sterically hindered postion.[45,46] In a couple of years, Prof. Peter Langer's research group studied site-selective Suzuki-Miyaura reactions of polyhalogenated heteroaromatic and aromatic compounds or their triflates. The site-selective Suzuki coupling reaction of indole **G** was found to be in favour of the 2-position (Figure 2). This is due to the fact that the electronic character of C-2 and C-3 appears to be sufficiently different and so site-selective transformations are observed.[47] 2,3-Dibromoindenone **H** gives a very good site-selectivity. The first attack occurred at position 3.[48]

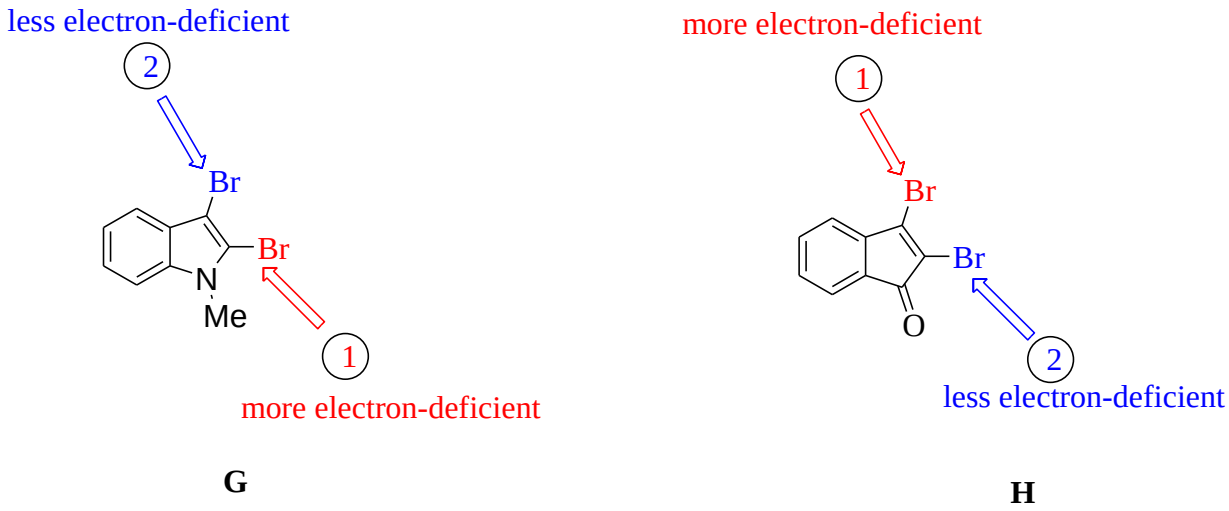


Figure 2. Possible explanation for the site-selectivity of **G** and **H.**

The substrates 2,3,4-tribromothiophene (**I**) and 2,3,5-tribromothiophene (**J**) showed a very good site selectivity. For compound **I**, the first coupling occurred at carbon atom C-2, the second coupling took place at carbon atom C-4. In case of **J**, the first coupling is preferred at carbon atom C-5 and the second one at carbon atom C-2. The selectivity can be explained based on the different electronic and steric properties of the three different C–Br bonds of **I** and **J** (Figure 3).[49]

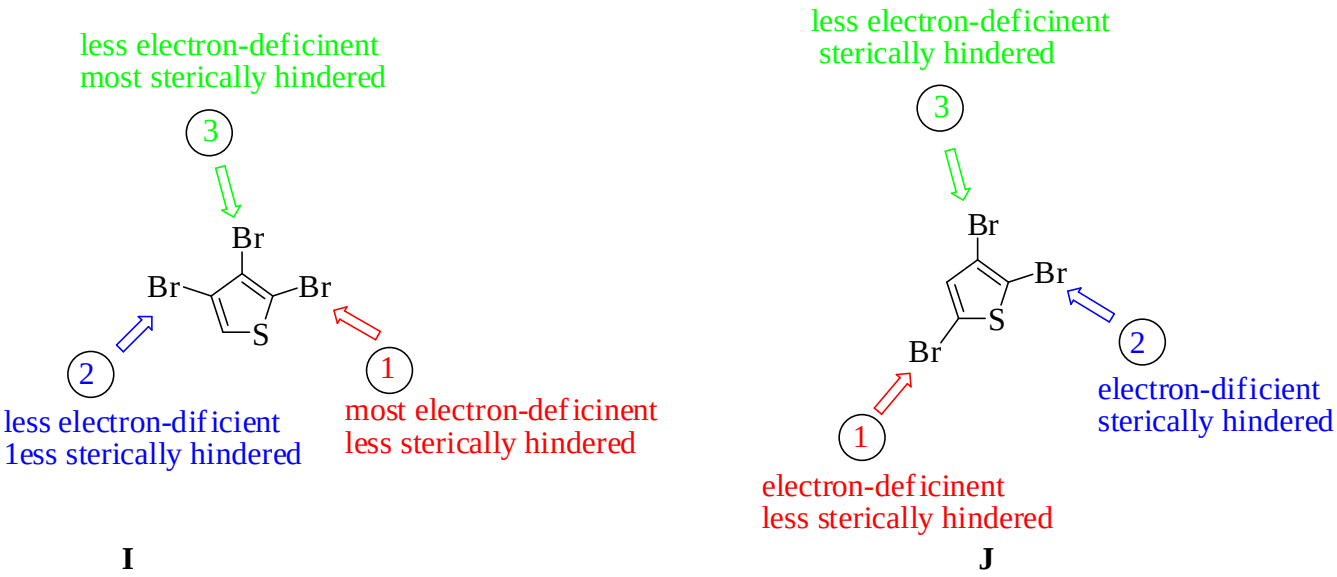


Figure 3. Possible explanation for the site-selectivity of **I** and **J.**

The Suzuki-Miyaura reaction also provided excellent results for triflates. Phenolic OH groups my be converted into OTf groups by using triflic anhydride, After wards the site-selectivity of Suzuki reactions were studied. The Langer group reported regioselective Suzuki-Miyaura cross-coupling reactions of the bis(trifluoromethylsulfonyloxy) of many substrates. For example, for the bis(trifluoromethylsulfonyloxy) of 1,2-dihydroxyanthraquinone **K** and 1,3-dihydroxyanthraquinone **L**,[50] the first attack occurs at position 1 which is more sterically hindered, but also more electron deficient. In case of phenyl 1,4-bis(trifluoromethylsulfonyloxy)naphthoate **M**, the first attack occurs at the more sterically hinderd and more electron deficient position 1.[51] In case of the 7,8-bis(trifluoromethylsulfonyloxy)flavone **N**, the first palladium(0) catalyzed cross-coupling reactions generally occurs at the more electron deficient and sterically less hindered position.[4,15] Position 7 of compound **N** is sterically less hindered than position 8. In addition, position 7 is considerably more electron-deficient than position 8 (located *ortho* to the ether oxygen atom and *meta* to the carbonyl group).[52] The reactions of all mentioned substrates proceeded with excellent site selectivities (Figure 4).

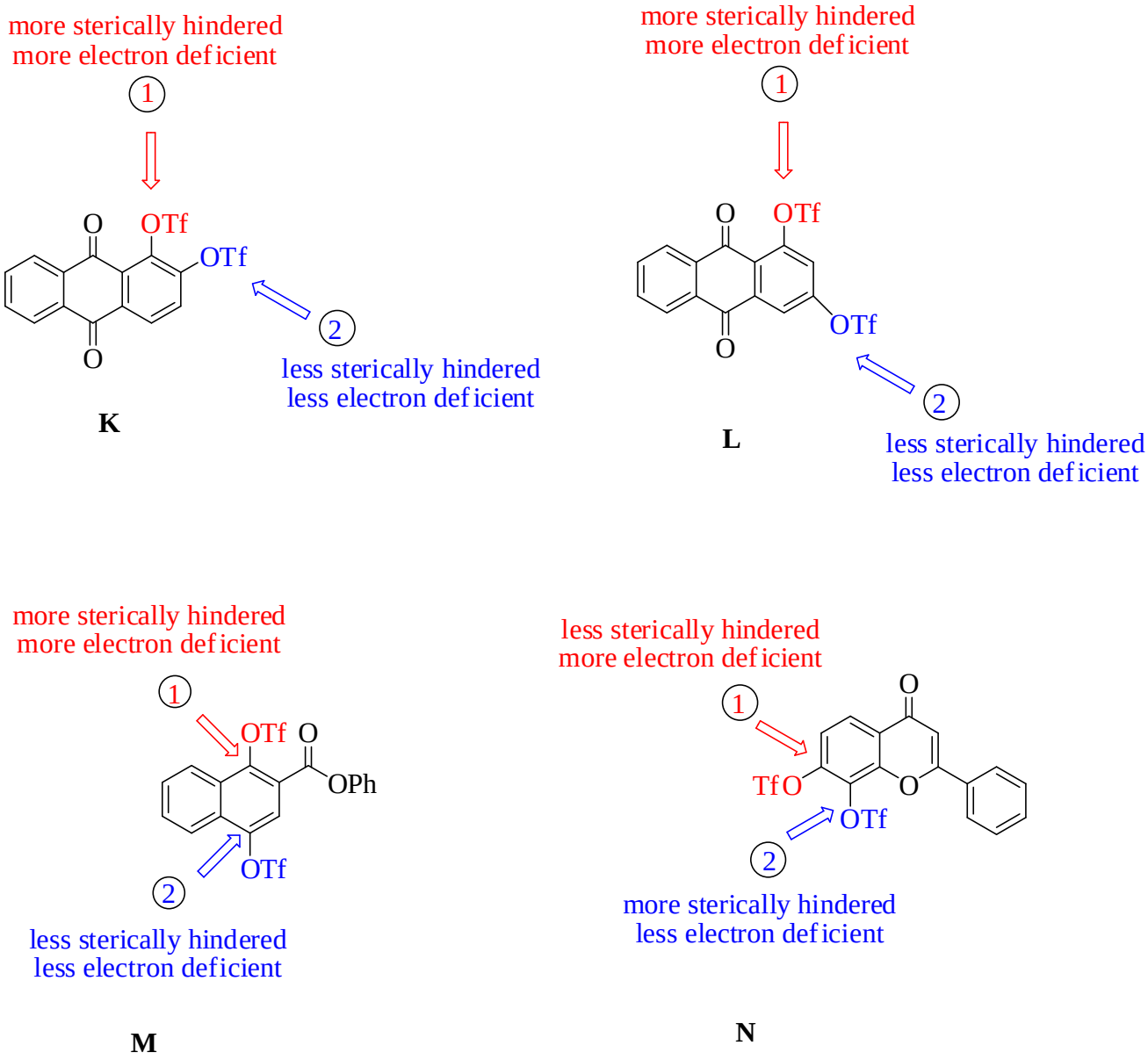
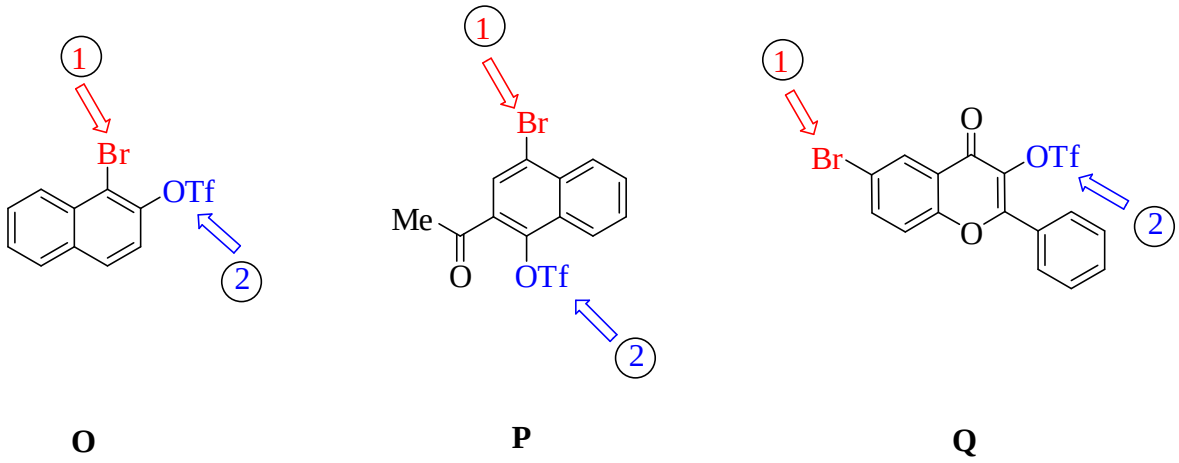


Figure 4. Possible explanation for the site-selectivity observed for **K, L, M,** and **N** .

Interesting results have been obtained investigating the chemoselectivity between the bromide and triflate position. It is found that the reactions proceed with very good chemo-selectivity in favor of the bromide position[53,54] (Figure 5).



O **P** **Q**

Figure 5. Possible explanation for the chemo selectivity observed for **O, P** and **Q**.

Aryl bromides generally undergo Suzuki-Miyaura reactions faster than aryl triflates.This reactivity order is different for other palladium catalyzed cross-coupling reactions. One of the justifications for that is based on the high borane-halide affinity. Nevertheless, other parameters control the selectivity as well.[54]

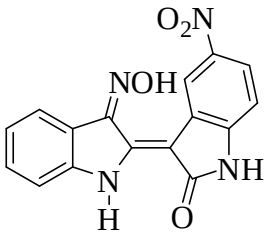
2. Efficient synthesis of arylated methylisatin by site-selective Suzuki-Miyaura cross-coupling reactions of the 4,7-dichloro-1-methylisatin , anti *HIV* activity and modeling study

2.1 Introduction

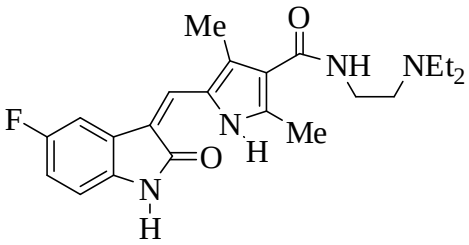
Isatin molecule (1*H*-indole-2,3-dione) is a versatile moiety that displays diverse biological activities[55] such as antibacterial,[56] antifugal,[57] antiinflammatory[58] and anticonvulsant agents.[59] The synthetic flexibility of isatin has led to the synthesis of a varierty of substituted derivatives, however, the susceptibility of isatin to attack by nucleophiles at C-3 has resulted in the generation of a large number of 3-substituted isatin in particular. This is reflected by numerous biologically active 3-substituted indolin-2-ones that are reported in the literature.[60-62] Most recently, Grewal[63] have extensively screened the synthesis and various biological activities of isatin derivatives. Further, isatin derivatives have received considerable attention due to their potent anticancer activities,[64-66] meanwhile Liu and colleagues[67] identified a class of isatin *O*-acyl oximes that selectivity inhibited neuronal ubiquitin *C*-terminal hydrolase (UCH-L1) in a H1299 lung cancer cell line, which is proposed to be linked to tumor progression upon upregulation. Lee *et al*.[68] have reported a novel indirubin analog, indirubin-5-nitro-3′-monoxime, inhibited cell proliferation against various human cancer cells, meanwhile sunitinib maleate (Sutent®) had been approved by FDA for the treatment of advanced renal carcinoma,[69] and gastrointestinal stromal tumors.[70] Vine *et al.*[71] have reported that the introduction of electron withdrawing groups to the benzene ring of isatin are generally found to induce cancer cell death *via* apoptosis.

Owing to the broad spectrum chemotherapeutic properties of isatin derivatives, several researchers[72-78] found that such derivatives were ideal drugs for AIDS treatment which suppresses *HIV* replication. Examples of such analogues were 4-[(1,2-dihydro-2-oxo-3*H*-indol-3-ylidene)amino]-*N*-(4,6-dimethyl-2-pyrimidinyl)-benzene sulphonamide and its *N*-acetyl derivative.[79] Furthermore, several isatin derivatives showed remarkable anti-*HIV* activity like sulfonamide-benzene derivatives and Schiff and Mannich bases of isatin.[80-82]

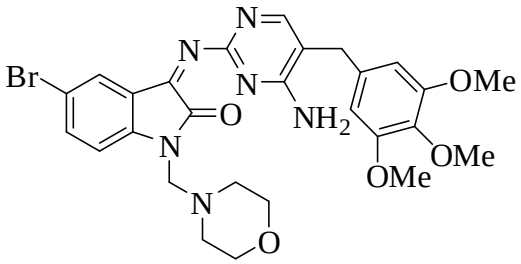
I report here a convenient approach to arylated isatins by what are, to the best of our knowledge, the first Suzuki-Miyaura cross-coupling reactions of 4,7-dichloro-1-methylindoline-2,3-dione. Surprisingly, the reactions proceed with very good regioselectivity in favor of position 4. Besides, the new arylated isatin derivatives were evaluated for their anti-*HIV* activity in addition to study of the molecular modeling structure.



Indirubin-5-nitro-3'monoxime



Sunitinib maleate(Sutent®)

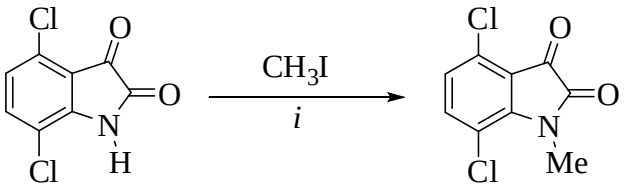


4-[(1,2-dihydro-2-oxo-3*H*-indol-3-ylidene)amino]-*N*-(4,6-dimethyl-2-pyrimidinyl)-benzene sulphonamide

Figure 6. Some potentially active isatin derivatives.

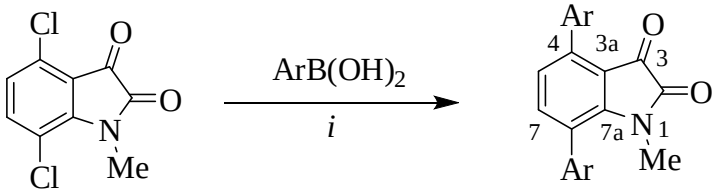
2.2 Results and discussion

The commercially available 4,7-dichloroisatin **(1)** was converted into *N*-methyl-4,7-dichloroisatin (**2)** in 90 % yield by using DMF as a solvent, MeI and K_2CO_3 as a base at rt.[83] (Scheme 14). Treatment of **2** with arylboronic acids **3a-f** (2.0 equiv.) by applying Suzuki-Miyaura reaction afforded the *N*-methyl-4,7-diarylisatins **4a-f** in 52-82 % yield (Scheme 15). Both electron-poor and electron-rich arylboronic acids could be successfully employed. The best yields were obtained by using $Pd(PPh_3)_4$ (6 mol-%) as a catalyst and K_3PO_4 (3.0 equiv) as a base in 1,4-dioxane at 120°C for 8 h.



1 **2**

Scheme 14. Synthesis of **2**. *Reagents and conditions*: *i*, K_2CO_3 (1.2 equiv.), DMF (1 ml per 0.1 mmol of isatin) 1 hr, 4°C, 20°C. CH_3I (1.1 equiv.), KI (cat., 0.2 equiv.), 80°C, 5 h.



2 **4a-f**

Scheme 15. Synthesis of **4a-f**. *Reagents and conditions*: *i*, **2** (1.0 equiv), **3** (2.0 equiv.), K_3PO_4 (3.0 equiv.), $Pd(PPh_3)_4$ (6 mol-%), 1,4-dioxane 120°C, 8 h.

Table 1. Synthesis of **4a-f.**

3,4	Ar	4 (%) [a]
a	3,5-$(Me)C_6H_3$	61
b	4-$(MeO)C_6H_4$	82
c	4-ClC_6H_4	52
d	4-MeC_6H_4	58
e	4-EtC_6H_4	65
f	4-FC_6H_4	72

[a] Yields of isolated products

Optimization of the synthesis of **4a** was carried out by using various reaction conditions such as K_2CO_3, KF, K_3PO_4 and NEt_3 as bases, in different solvents like toluene, DMF, Dioxane and THF, $Pb(OAc)_2$ and $Pd(PPh_3)_2Cl_2$ as catalysts at 65-130°C. Table 2 summarize these conditions and showing the yield percentages of **4a** (25-83 %).

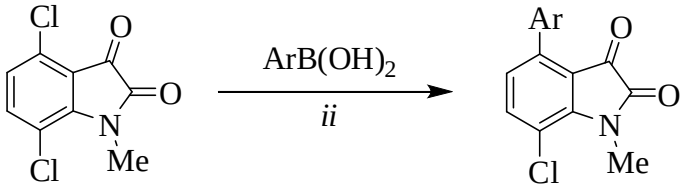
Table 2. Optimization of the synthesis of **4a.**

Entry	Base[a]	Solvent[b]	T (°C)[c]	Catalyts[d]	T (h)[e]	Yield (%)[f]
1	K_3PO_4	Toluene	100	$Pd(OAc)_2$	8	25
2	K_2CO_3	DMF	130	$Pd(PPh_3)_4$	9	38
3	KF	Dioxane	80	$Pd(OAc)_2$	10	47
4	NEt_3	THF	65	$Pd(PPh_3)_2Cl_2$	7	34
5	K_3PO_4	Dioxane	120	$Pd(PPh_3)_4$	8	83
6	K_2CO_3	Toluene	90	$Pd(OAc)_2$	10	25

[a] K_3PO_4 (3.0 equiv.); [b] Dioxane (3 ml); [c] 120°C; [d] $Pd(PPh_3)_4$ (6 mol-%); [e] 8 h

[f] Yield of isolated products

Best results were obtained by using K_3PO_4 as a base, 1,4-dioxane as solvent, $Pd(PPh_3)_4$ as a catalyst. Suzuki-Miyaura reaction of **(2)** with arylboronic acids (**3)** (1.0 equiv.) afforded the 7-chloro-4-aryl-1-methylindoline-2,3-dione **5a-d,f-m** in 49-87 % yield with very good site-selectivity (Scheme 16). During the optimization, it proved to be important to use (1.2 equiv) of the arylboronic acid carry out the reaction at 70 instead of 120°C and to use 1,4-dioxane as a solvent (reaction time 6 h). Both electron-poor and electron-rich arylboronic acids were successfully used.



2 **5a-d,f-m**

Scheme 16. Synthesis of **5a-d,f-m**. *Reagent and conditions*: *ii*, **2** (1.0 equiv), **3** (1.2 equiv.), K_3PO_4 (1.5 equiv.), $Pd(PPh_3)_4$ (3 mol-%), 1,4-dioxane, 70°C, 6 h.

Table 3. Synthesis of **5a-d,f-m.**

3,5	Ar	5 (%) [a]
a	3,5-$(Me)_2C_6H_3$	63
b	4-$(MeO)C_6H_4$	83
c	4-ClC_6H_4	52
d	4-MeC_6H_4	79
f	4-FC_6H_4	87
g	4-$(EtO)C_6H_4$	85
h	4-*i*ProC_6H_4	73
i	4-*t*BuC_6H_4	78
j	3-MeC_6H_4	51
k	3,5-$(MeO)_2C_6H_3$	87
l	4-$(Acetyl)C_6H_4$	53
m	4-$(Vinyl)C_6H_4$	49

[a] Yields of isolated products

The structures of the newly prepared compounds were confirmed by their IR, ^{1}H, ^{13}C NMR and by mass spectra, where **4a-f**, **5a-m,** exhibited additional signals for the protons of the newly introduced aromatic rings. The aromatic protons have been assigned. In the ^{13}C NMR spectra of these analogues, carbonyl carbon atoms at C-2 of the isatin ring resonated at δ 158.4-168.3 ppm, while the lower field resonances at δ 178.2-181.9 ppm were assigned for the carbonyl carbon atoms at C-3 of isatin moiety. The signal of C-5 of isatin ring were observed at δ 124.1-127.4 ppm, while the resonances at δ 144.4-148.3 ppm were assigned to C-7a of the fused rings. In addition, the *N*-Me group of isatins appeared at δ 28.6-33.7 ppm. The aromatic carbon atoms and the substituents were fully analysed. Compound **5b** was selected for further study *via* their HMBC[84] and NOESY[85] NMR spectroscopic measurements. The gradient-selected HMBC spectrum of **5b** showed a $^3J_{C,H}$ heteronuclear correlation of C-4 of isatin ring (δ_C 133.9 ppm) to the H-2'/H-6' proton (δ_H 7.32 ppm) of the aromatic moiety at C-4 of isatin. The ^{1}H, ^{1}H NOESY spectrum was characterized by two correlations: one indicated by correlation of protons

of methoxy group at δ_H 3.72 ppm with H-3'/H-5' of the same aromatic ring at δ_H 6.87 ppm, while the other one was observed between the H-1'/H-6' of the aromatic ring at δ_H 7.32 ppm with H-5 of the isatin ring at δ_H 6.87 ppm (Figure. 7).

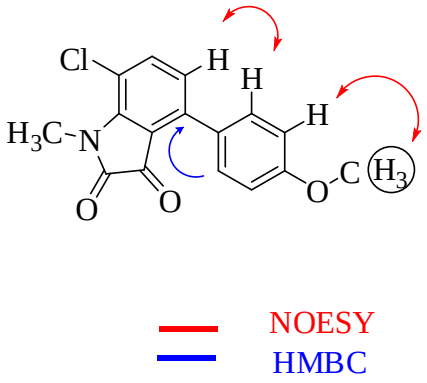


Figure 7. $J_{C,H}$ correlations in the HMBC (single head arrow), and NOESY (double head arrow) correlations of **5b.**

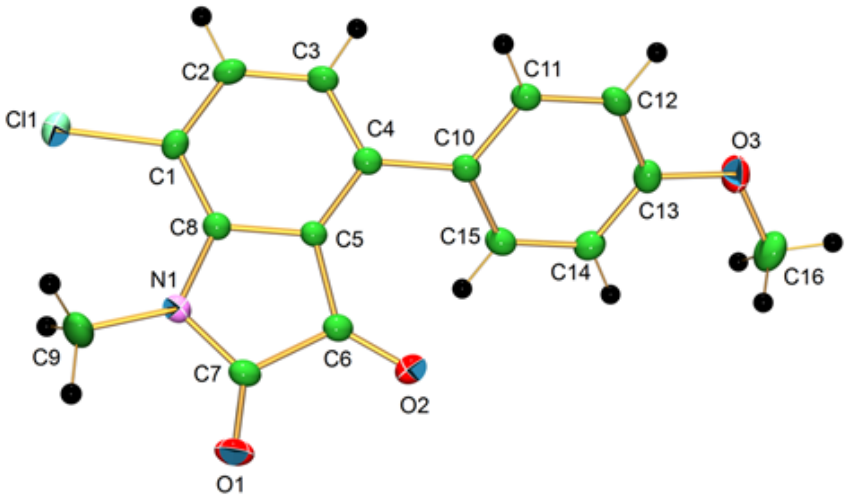


Figure 8. Molecular structure of 7-chloro-4-(4-methoxyphenyl)-1-methylindoline-2,3-dione **(5b)** in the crystal. Displacement ellipsoids are drawn at 50 % probability level.

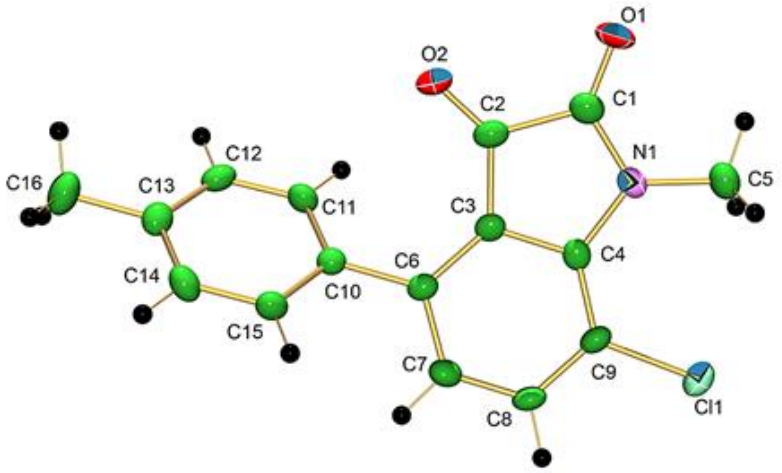
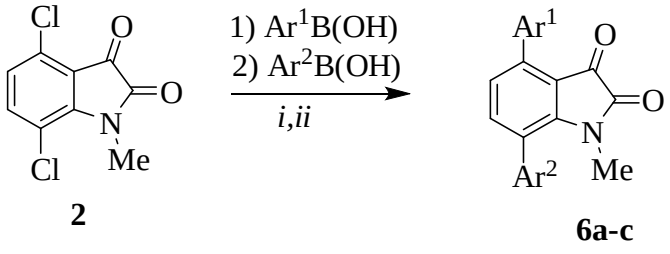


Figure 9. Molecular structure of **7**-chloro-1-methyl-4-(*p*-tolyl)indoline-2,3-dione **(5d)** in the crystal. Displacement ellipsoids are drawn at 50 % probability level.

Is is interesting to study the regioselectivity of Suzuki-Miayura reaction of dichloroisatin **2** having two different electron deficient centers (C-4 and C-7). Thus, one-pot Suzuki-Miayura reaction of **2** with two different arylboronic acids **3** (sequential addition of 1.2 equiv. of each boronic acid) afforded the *N*-methyl-4,7-diarylisatins **6a-c** in 57-70 % yields . The reactions were carried out at 70°C for the first step (to avoid double coupling) and at 120°C for second step (Scheme 17).



2 **6a-c**

Scheme 17. Synthesis of **6a-c**. *Reagents and conditions*: *i*, **2** (1.0 equiv), $Ar^1B(OH)_2$ (1.2 equiv.), K_3PO_4 (1.5 equiv.), $Pd(PPh_3)_4$ (3 mol-%), 1,4-dioxane, 70°C 6 h. *ii*, $Ar^2B(OH)_2$ (1.2 equiv.), K_3PO_4 (1.5 equiv.), $Pd(PPh_3)_4$ (3 mol-%), 1,4-dioxane, 120°C 6 h.

Table 4. Synthesis of **6a-c**.

3	6	Ar^1	Ar^2	6 (%)[a]
i,d	**a**	4-*t*BuC_6H_4	4-MeC_6H_4	57
k,b	**b**	3,5-$(MeO)_2C_6H_3$	4-(MeO)C_6H_4	70
d,b	**c**	4-MeC_6H_4	4-(MeO)C_6H_4	68

[a] Yields of isolated products

The above results (Scheme17) revealed that the chlorine residue at C-4 of the isatin ring has been initially replaced by an aryl group due to the highler electron deficiency at this position compared with position 7. The second replacement occured in the second step indicating the lower electron deficiency at C-7 (Figure. 10).

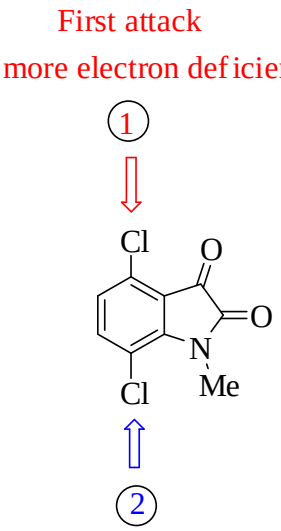


Figure 10. Stepwise Suzuki-Miayura coupling reaction starting form compound **2**.

2.3 In vitro anti *HIV* assay

Compounds **2**, **4a-f**, **5a-d**,**f-m** and **6a-c**, were tested for their in vitro anti-*HIV*-1 (strain III_B) and *HIV*-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells, using MTT method.[86] This work was carried out by our collaboration partners (group of Prof. Dr. Najim Al-Masoudi). The results are summarized in Table 1, in which the data for azidothymidine (DDN/AZT)[87] and lamuvidine (3TC)[88] were included for comparison purposes. Compound **5l** was found to be the only compound from the series inhibiting *HIV*-2 replication in cell culture. Compound **5l** showed an EC_{50} value of > 3.47 μM and a CC_{50} value of 13.43 μM, resulting in a selectivity index (SI) of 4 and maximum protection of 66 %, meanwhile exhibited no selectivity (SI < 1) against *HIV*-1 (EC_{50} = 13.43 μM). Derivatives **2**, **5c**, **5g** and **5m** demonstrated low CC_{50} values of > 2.21 μM, > 2.24 μM, 3.11 μM and 2.24 μM, respectively, at concentration of 100 μM, in comparison to the other analogues.

Based on the chemical structure of compound **5l**, this molecule can be proposed to act as NNRTI. However, the activity spectrum that is limited to *HIV*-2 is completely in contrast with what was observed with NNRTIs. However, the above data suggested that the halo group binding the benzene ring of isatin backbone (*e.g.*: **5**) considerably increased the anti-*HIV* activity, meanwhile substitution the benzene ring of isatin by an arylketo group like **5l** would enhanced such inhibition for *HIV* in comparison to the effectiveness of other functional groups.

In conclusion, the identification of **5l** as a NNRTI of *HIV*-2 may be an important lead for the development of a more potent and selective molecule which could be used in combination with other drugs to treat individuals infected with *HIV*.

Table 5. *In-vitro* anti-*HIV*-1[a] and *HIV*-2[b] of new *N*-methylisatin derivatives

Entry	*HIV* (III_B) IC_{50} (μM)[c]	*HIV* (ROD) IC_{50} (μM)[c]	CC_{50} (μM)[d]	Max. Prot.[e] (%)	Max. Prot.[f] (%)	SI[g]
2	> 2.21	> 2.21	2.21	2	6	< 1
4a	> 61.75	> 61.75	61.75	5	5	< 1
4b	> 35.28	> 35.28	35.28	3	2	< 1
4c	> 10.92	> 10.92	10.92	3	4	< 1
4d	> 12.30	> 12.30	12.30	4	2	< 1
4e	> 4.88	> 4.88	4.88	8	7	< 1
4f	> 12.75	> 12.75	12.75	3	3	< 1
5a	> 30.35	> 30.35	30.35	3	5	< 1
5b	> 125.0	> 125.0	125.0	11	14	< 1
5c	> 2.24	> 2.24	2.24	6	3	< 1
5d	> 15.12	> 15.12	2.24	3	3	< 1
5f	> 10.85	> 10.85	10.85	10	7	< 1
5g	> 3.11	> 3.11	3.11	8	14	< 1
5h	> 4.39	> 4.39	4.39	8	5	< 1
5i	> 9.96	> 9.96	9.96	6	6	< 1
5j	> 12.93	> 12.93	12.93	3	7	< 1
5k	> 68.33	> 68.33	68.33	12	40	< 1
5l	> 13.43	> 3.47	13.43	6	66	< 1 (**4**)
5m	> 2.24	> 2.24	2.24	1	6	< 1
6a	> 33.16	> 33.16	33.16	7	7	< 1
6b	> 42.13	> 42.13	42.13	4	8	< 1
6c	> 12.28	> 12.28	12.28	3	6	< 1
AZT	0.0019	0.0018	> 25	66	71	> 13144 (> 14245)
3TC	0.51	2.02	> 20	90	79	> 39 (> 10)

[a] Anti-*HIV*-1 activity measured with strain III_B; [b] anti-*HIV*-2 activity measured with strain ROD; [c] compound concentration required to achieve 50 % protection of MT-4 cells from the *HIV*-1 and *HIV*-2 induced cytopathogenic effect; [d] compound concentration that reduces the viability of mock-infected MT-4 cells by 50 %; [e] (III_B); [f] (ROD); [g] SI: selectivity index (CC_{50}/EC_{50})

2.4 Molecular modeling analysis

Our molecular docking analysis of the new analogs is based on the modeling studies which were performed to understand the binding mode of these analogs with the *HIV*-RT binding pocket (NIBP) (PDB code: 1MU2[89]). The molecular docking was performed using SYBYL-X 1.1, and the results were visualized with PYMOL.[90]

HIV-2 reverse transcriptase (RT) demonstrates an intrinsic resistance to non-nucleoside RT inhibitors (NNRTIs), one of two classes of anti-AIDS drugs that target the viral RT, however, *HIV*-2 RT has a similar overall fold to *HIV*-1 RT but has structural differences within the "NNRTI pocket" at both conserved and nonconserved residues.[91] Compound **5l** has been selected for the docking modeling study, since showed a good binding energy score (-9.2) (Figure. 11). As shown in Figure 6, the isatin backbone is located in the middle of the binding pocket, anchoring the two carbonyl groups at C-2 and C-3 in a favorable position for hydrogen bonding with the Lys102 and Thr107 of the reverse transcriptase (RT) enzyme, respectively. Further, the amino acids in the binding pocket of RT enzyme are mainly lipophilic with aromatic residues.[92] Therefore, not only hydrogen bonding but hydrophobic interactions also play vital role in deciding anti-*HIV* activity.[93] The aromatic ring (PhCOMe) of **5l** fitted into an aromatic rich subpocket surrounded by the aromatic side chain of Tyr188. Detailed analysis of the binding mode showed that the aromatic ring of PhCOMe group pointed toward the aromatic ring of Tyr188 residue apparently developing π-π stacking interactions, where the electrostatic interaction is stabilized by these stacking type interactions. Overall, the combination of hydrophobic interaction and hydrogen bondings appears to govern the binding of **5l** with *HIV*-2 RT.

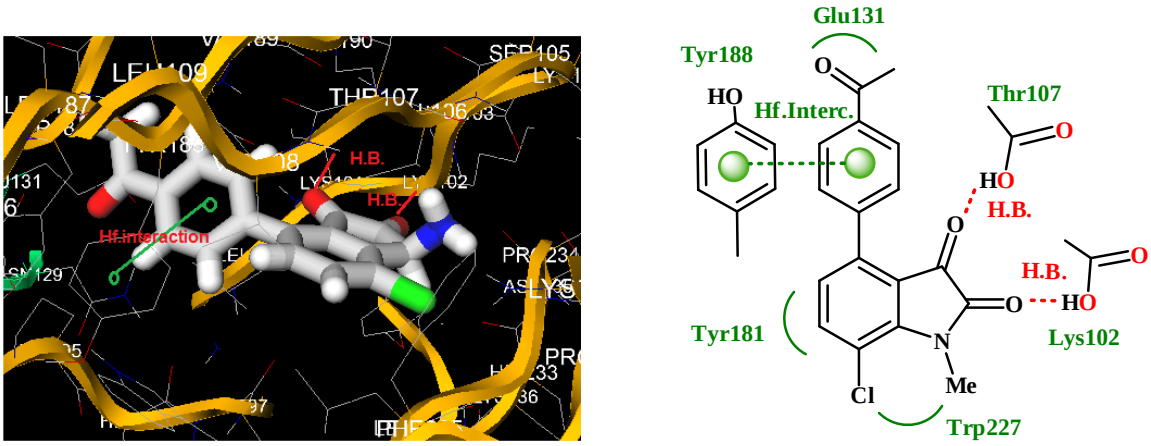


Figure 11. Docked conformation of **5l** showing two hydrogen bonds: Thr107 with oxygen atom at C-3 of isatin ring and Lys102 with oxygen atom at C-2 of the same ring. In addition, a hydrophobic interaction was observed between the phenyl group of acetophenone moiety at C-4 of isatin backbone and Tyr188 of reverse transcriptase (RT) enzyme residues.

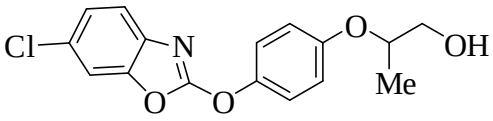
2.5 Conclusion

I have synthesized arylated methylisatins by Suzuki-Miyaura reactions of 4,7-dichloro-1-methylisatin **(2)**. The reactions proceed with excellent site-selectivity in favour of position 4, due to electronic reasons. All the new analogues were evaluated by our collaboration partners *in vitro* for their antiviral activity against the replication of *HIV*-1 and *HIV*-2 in MT4 cells using MTT assay. Compound **5l**, with an 4-acetylgroup at C(4) of the isatin backbone, showed an EC_{50} value of >3.47 μM against *HIV*-2 with a therapeutic index (SI) of 4. This means that **5l** was cytotoxic to MT-4 cells at a CC_{50} value of 13.43 μM; also compounds **2**, **5c**, **5g** and **5m** were cytotoxic to MT-4 cells within > 2.21-3.11 μM concentration range. In a docking study, **5l** interacted with several amino acids in the reverse transcriptase (RT) binding site of *HIV*.

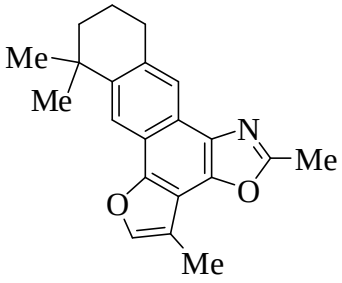
3. Efficient synthesis of arylated benzoxazoles by site-selective Suzuki-Miyaura cross coupling reactions of the 2,6-dichlorobenzoxazole

3.1 Introduction

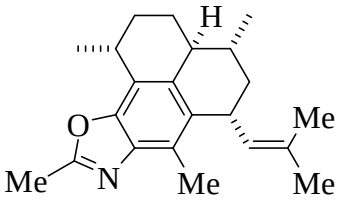
The benzoxazole unit is an important heterocyclic core structure which occurs in several natural products. Examples include pseudopteroxazole and salvianen (Figure 12).[94,95] Benzoxazoles also represent important molecules in medicinal chemistry.[96] Previous reports revealed that substituted benzoxazoles, such as the drug fenoxaprop, possess diverse chemotherapeutic activities, including antibiotic,[97] antimicrobial,[98-102] antivirial[103], and antitumor activities.[104]



Fenoxaprop



Salvianen



Pseudopteroxazole

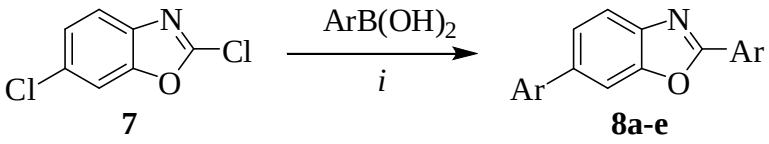
Figure 12. Benzoxazoles in natural products and drugs.

Traditional methods for the synthesis of substituted benzoxazoles include the condensation of ortho-aminophenols with aldehydes.[105] Recently, general methods for the copper-catalyzed intramolecular C-O coupling reaction of 2-haloanilides were reported.[106] Nagasawa *et al.* reported that 2-arylbenzoxazoles can be prepared by copper-catalyzed intramolecular oxidative C-O coupling of benzanilides.[107] Palladium catalyzed multi-component reactions of aryl halides, isocyanides, and aminoalcohols have also been used for the synthesis of benzoxazoles.[108] In recent years, site-selective Pd catalyzed

cross-coupling reactions have attracted considerable attention.[109,110] Herein, I report a new approach to arylated benzoxazoles by site-selective Suzuki-Miyaura cross-coupling reactions of commercially available 2,6-dichlorobenzoxazole **(7**) with arylboronic acids.

3.2 Results and discussion

The Suzuki-Miayura reaction of commercially available 2,6-dichlorobenzoxazole **7** with 2.2 equiv. of various arylboronic acids **3a-c,e,n** afforded the 2,6-diarylbenzoxazoles **8a-e** in 75-89 % yields (Scheme 18, Table 6). The reactions had to be carried out at a higher temperature (120°C) as compared to the synthesis of mono arylated products **9**. Very good yields were obtained for products derived from both electron rich and poor arylboronic acids.



7 **8a-e**

Scheme 18. Synthesis of **8a-e**. *Reagents and conditions: i,* **7** (1.0 equiv.), **3a-c,e,n** (2.2 equiv.), $Pd(PPh_3)_4$ (26 mg, 6 mol-%), K_2CO_3 (aq. solution, 2 M), 1,4-dioxane, 120°C, 8 h.

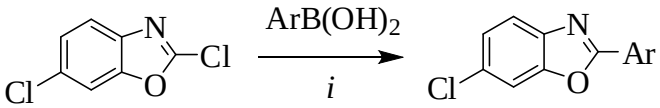
Table 6. Synthesis of **8a-e.**

3	**8**	**Ar**	**8 (%)** [a]
a	**a**	3,5-$(Me)_2C_6H_3$	89
b	**b**	4-$(MeO)C_6H_4$	88
c	**c**	4-ClC_6H_4	75
e	**d**	4-EtC_6H_4	88
n	**e**	3-FC_6H_4	75

[a] Yields of isolated products

The Suzuki-Miayura reaction of 2,6-dichlorobenzoxazole **7** with 1.2 equiv. of arylboronic acids **3a-c,e,g-j,m-r** afforded the 2-aryl-6-chlorobenzoxazoles **9a-n** in 75-89 % yields with very good site-selectivity (Scheme 19, Table 7).

The reactions were carried out under standard conditions for Suzuki-Miyaura reactions $Pd(PPh_3)_4$ (3.0 mol-%) was employed as the catalyst and an aqueous solution of K_2CO_3 was used as the base (dioxane, 80°C, 6 h). Very good yields were obtained for both electron rich and poor arylboronic acids. During the optimization, it proved to be important to carry out the reactions at 80°C. A higher temperature resulted in the formation of significant amounts of diarylated products.



7 **9a-n**

Scheme 19. Synthesis of **9a-n**. *Reagents and conditions: i*, **7** (1.0 equiv), **3a-c,e,g-j,m-r** (1.2 equiv.), $Pd(PPh_3)_4$ (3 mol-%), K_2CO_3 (aq. solution, 2 M), 1,4-dioxane, 80°C, 6 h.

Table 7. Synthesis of **9a-n.**

3	9	Ar	9 (%) [a]
a	**a**	3,5-$(Me)_2C_6H_3$	90
b	**b**	4-$(MeO)C_6H_4$	90
c	**c**	4-ClC_6H_4	88
e	**d**	4-EtC_6H_4	81
g	**e**	4-$EtOC_6H_4$	80
h	**f**	4-*i*ProC_6H_4	75
i	**g**	4-*t*BuC_6H_4	72
j	**h**	3-MeC_6H_4	87
m	**i**	4-(Vinyl)C_6H_4	65
n	**j**	3-FC_6H_4	83
o	**k**	2,3,4-$(MeO)_3C_6H_2$	80
p	**l**	C_6H_5	90
q	**m**	4-$(F_3C)C_6H_4$	83
r	**n**	3-$(MeO)C_6H_4$	75

[a] Yields of isolated products

The structure of product **9b** was elucidated by 2D NMR spectroscopy (NOESY, COSY, HMBC, HSQC). A clear and important HMBC correlation between the *ortho* protons of the 4-methoxyphenyl group and carbon C-2 of oxazol ring was visible, which confirmed that the aryl moiety is attached at carbon C-2.

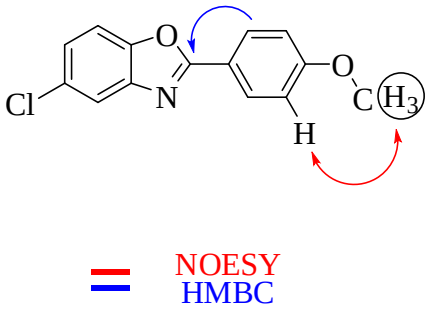
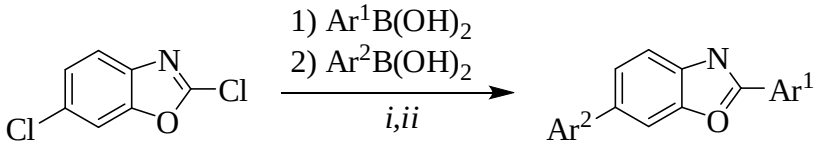


Figure 13. Important HMBC (single head arrows), NOESY (double head arrows) correlations of **9b.**

The one-pot reaction of **7** with two different arylboronic acids was next studied. The reaction of **7** with 1.2 equiv. of an arylboronic acid and subsequent addition of a second arylboronic acid (1.2 equiv.) afforded the 2,6-diarylbenzoxazoles **10a,b** containing two different aryl groups in good yields (Scheme 20, Table 8). During the optimization, it proved to be important to carry out the first step at 80°C and the second step at 120 °C. It was also proved to be important to add a fresh portion of catalyst together with the second aryl boronic acid. The structure of **10b** was independently confirmed by X-ray crystal structure analysis (Figure 14).



7 **10a,b**

Scheme 20. Synthesis of **10a-b**. *Reagents and conditions: i,* **7** (1.0 equiv), $Ar^1B(OH)_2$ (1.2 equiv.), $Pd(PPh_3)_4$ (3 mol-%), K_2CO_3 (aq. solution, 2 M), 1,4-dioxane, 80°C, 6 h; *ii*, $Ar^2B(OH)_2$ (1.2 equiv.), $Pd(PPh_3)_4$ (3 mol-%), K_2CO_3 (aq. solution, 2 M), 120°C, 8 h.

Table 8. Synthesis of **10a-b.**

3	**10**	**Ar[1]**	**Ar[2]**	**10 (%)[a]**
c,a	**a**	4-ClC_6H_4	3,5-$(Me)_2C_6H_3$	84
i,b	**b**	4-*t*BuC_6H_4	4-$(MeO)C_6H_4$	72

[a] Yields of isolated produc

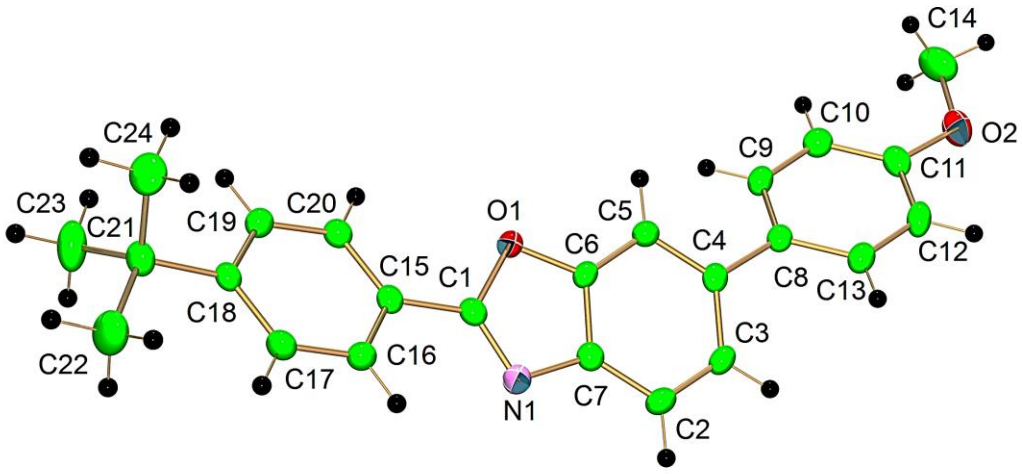


Figure 14. Molecular structure of 2-(4-tert-butylphenyl)-6-(4-methoxyphenyl)-benzoxazole **10b** in the crystal. Displacement ellipsoids are drawn at 50 % probability level**.**

The structures of the newly prepared compounds were confirmed by their IR, ^{1}H, ^{13}C NMR and by mass spectra, where **8a-e, 9a-n, 10a-b** exhibited additional signals for the protons of the newly introduced aromatic ring.

The site-selectivity in favour of position 2 can be explained by the fact that carbon C-2 is more electron deficient than carbon C-6. Palladium catalyzed cross-coupling reactions usually occur at the electronically more deficient position. [109,110]

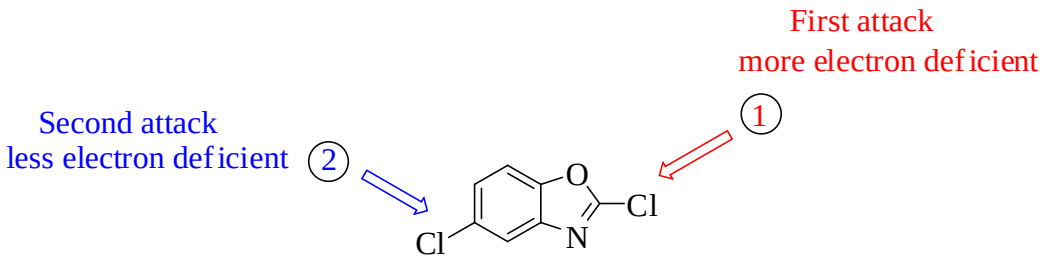


Figure 15. possible explanation for the reaction.

3.3 Conclusion

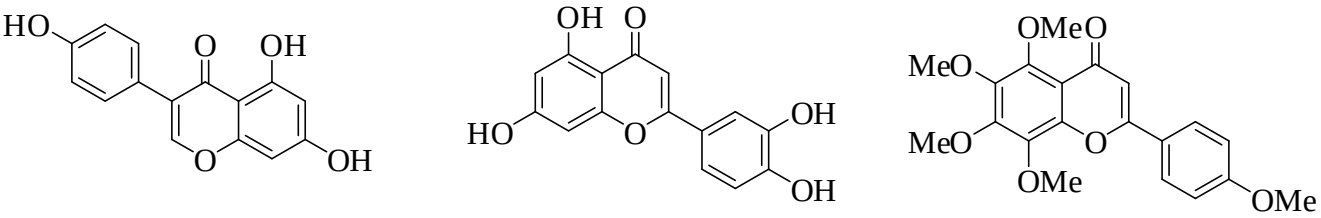
I have successfully synthesized homo 2,6-diarylbenzoxazole derivatives of the 2,6-dichlorobenzoxazole by Suzuki-Miyaura reactions. Starting with the same benzoxazole 2-monoaryl and mixed 2,6-diaryl derivatives could be prepared in a highly site-selective way. The monoarylated products were isolated with good site-selectivity, employing electron-rich and electron-poor arylboronic acids. In conclusion, a general Pd(0)-catalyzed arylation of 2,6-dichlorobenzoxazole with a number of arylboronic acids was achieved by Suzuki-Miyaura reactions. The first attack proceeded with very good site-selectivity at position C-2 which is more electron deficient.

4. Efficient synthesis of arylated isoflavones by site-selective Suzuki-Miyaura cross coupling reactions of the bis(triflates) of 4´,7-dihydroxyisoflavone

4.1 Introduction

Flavones and Isoflavones (3-arylchromones) are very important oxygenated heterocyclic compounds, which belong to the flavonoid group that occur naturally as secondary metabolites in fruits, vegetables, seeds and flowers. They play important roles in plant development, reproduction and defence and possess a wide range of biological and pharmaceutical activities. This includes antiviral, anti-inflammatory, hepatoprotective, antioxidant, antithrombotic, vasodilating and anticarcenogenic activity combining high efficiency and low toxicity.[111-114] Many studies have shown that e.g. Chrysin has anti-inflammatory, anti-cancer and anti-oxidative, and *anti-HIV* effects.[115] The natural occurring anti-oxidant tangeretin (Fig. 16) shows significant protective effects against Parkinson's disease.[116] The main synthetic methods of flavones include the Kostanecki reaction, Allan and Robinson synthesis, the Baker-Venkataraman rearrangement and several more methods.[117-120] several applications of palladium catalyzed cross-coupling reactions to flavone-derived halides or triflates have been reported to date[121]. Flavones and Isoflavones are avaliable by transition-metal-catalyzed cross-coupling reactions, such as the cyclization of 2-halophenols with terminal acetylenes and carbon monoxide[122] or by Suzuki-Miyaura cross-coupling reactions of halogenated chromones.[123] Flavones have been prepared by oxidative addtion of arylboronic acid to chromones[124] Prof. Langer's group recently reported the synthesis of arylated flavones by regioselective Suzuki-Miyaura reactions of the bis(triflates) of 5,7- and 7,8-dihydroxyflavones.[125-126]

Herein, I report a convenient approach to arylated isoflavones by what are, to the best of my knowledge, the first Suzuki-Miyaura cross-coupling reactions of the bis(triflates) of 4´,7-dihydroxyisoflavone.

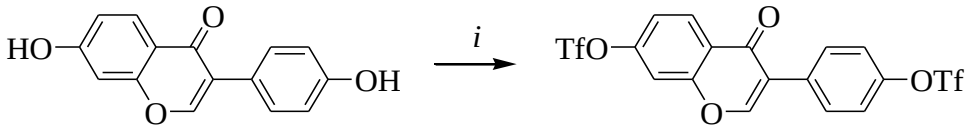


Chrysin Luteolin Tangeretin

Figure 16. Some examples of flavones natural product.

4.2 Results and discussion

Commercially available 4´,7-Dihydroxyisoflavone **(11)** was converted to 4-oxo-3-[4-(trifluoromethylsulfonyloxy)phenyl]-4*H*-chromen-7-yl trifluoromethanesulfonate **12** in high yield (Scheme 21).



11 **12**

Scheme 21. Synthesis of **12**. *Reagents and conditions*: *i*, **11** (1.0 equiv.), pyridine (1.2 equiv.), CH_2Cl_2 (20 ml.), Tf_2O (1.2 equiv.), 50°C, 4 h.

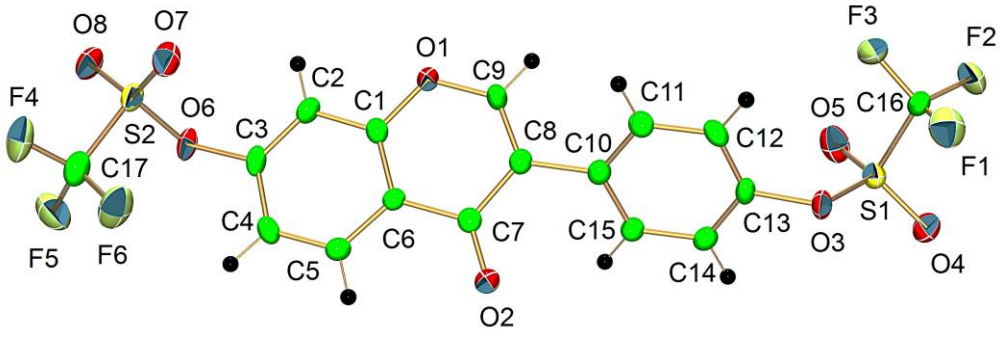
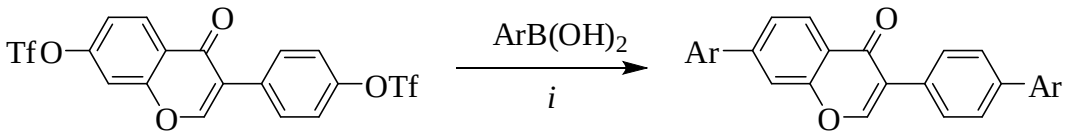


Figure 17. Molecular structure of 4-oxo-3-[4-(trifluoromethylsulfonyloxy)phenyl]-4*H*-chromen-7-yl trifluoro-methanesulfonate **12** in the crystal. Displacement ellipsoids are drawn at 50 % probability level.

The Suzuki-Miyaura reaction of 1**2** with arylboronic acids **3b,e,g,h** (2.2 equiv.), in the presence of (2.2 equiv, 6 mol-%), $Pd(PPh_3)_4$, K_2CO_3 (2 M, 2 ml), DMF (4 ml), gave the 4´,7- Bis(aryl)isoflavones **13a-d** in 71-82 % yields (Scheme 22, Table 9). During the optimization, it proved to be important to carry out the reactions at 130°C. A higher temperature resulted in the formation of significant amounts of diarylated products **13**.



12 **13a-d**

Scheme 22. Synthesis of **13a-d**. *Reagents and conditions*: *i*, **12** (1.0 equiv.), **3b,e,g,h** (2.2 equiv.), $Pd(PPh_3)_4$ (2.2 equiv, 6 mol-%), K_2CO_3 (2 M, 2 ml), DMF (4 ml), 130°C, 10 h.

Table 9. Synthesis of **13a-d.**

3	**13**	**Ar**	**13 (%)** [a]
b	**a**	4-(MeO)C_6H_4	82
e	**b**	4-EtC_6H_4	71
g	**c**	4-(OEt)C_6H_4	77
h	**d**	4-*i*ProC_6H_4	80

[a] Yields of isolated products

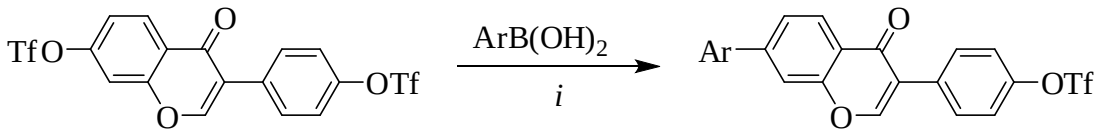
Optimization of the synthesis of **13a** was carried out by using various condition reactions, such as K_2CO_3, KF and NEt_3 as bases, in different solvents like toluene, dioxane, DMF and THF, besides $Pb(OAc)_2$ and $Pd(PPh_3)_2Cl_2$ as catalysts at 80-130°C. In Table 10 are summarized these conditions showing the yield percentages of **13a** (25-85 %).

Table 10. Optimization of the synthesis of **13a.**

Entry	Base[a]	Solvent[b]	T(0C)[c]	Catalyts[d]	T(h)[e]	Yield(%)[f]
1	K_3PO_4	Toluene	100	$Pd(OAC)_2$	8	25
2	KF	DMF	110	$Pd(PPh_3)_4$	9	38
3	KF	Dioxane	80	$Pd(OAC)_2$	10	47
4	NEt_3	THF	120	$Pd(PPh_3)_2Cl_2$	7	34
5	K_3PO_4	Dioxane	120	$Pd(PPh_3)_4$	8	45
6	K_2CO_3	Toluene	90	$Pd(OAC)_2$	10	25
7	K_2CO_3	DMF	130	$Pd(PPh_3)_4$	10	85

[a] K_2CO_3 (2 M, 2 ml); [b] DMF (4 ml); [c] 130°C; [d] $Pd(PPh_3)_4$(6 mol-%); [e] 10 h; [f] Yield of isolated products

Best results were obtained by using K_2CO_3 as a base, DMF as solvent, $Pd(PPh_3)_4$ as a catalyst. Suzuki-Miyaura reaction of **12** with only (1.0 equiv.) of **3a-c,e-i,l,q-t** in the presence of $Pd(PPh_3)_4$ (3 mol-%), K_2CO_3 (2 M, 1 ml), DMF (4 ml), 85°C, 6 h, afforded the 4-(4-oxo-7-aryl-4*H*-chromen-3yl)phenyl trifluoromethanesulfonates **14a-l** in 52-88 % yields (Scheme 23, Table11). The reactions proceeded with very good rigio-selectivity in favour of position 7. Very good yields were obtained for products derived from both electron poor and rich arylboronic acids. The structure of **14a** was confirmed by X-ray structure (Figure 19).



12 **14a-l**

Scheme 23. Synthesis of **14a-l**. *Reagents and conditions*: *i*, **12** (1.0 equiv.), **3a-c,e-i,l,q,s,t** (1.0 equiv.), $Pd(PPh_3)_4$ (3 mol-%), K_2CO_3 (2 M, 1 ml), DMF (4 ml), 85°C, 6 h.

Table 11. Synthesis of **14a-l.**

3	14	Ar	14 (%) [a]
a	**a**	3,5-$(Me)_2C_6H_3$	76
b	**b**	4-$(MeO)C_6H_4$	80
c	**c**	4-ClC_6H_4	58
e	**d**	4-EtC_6H_4	70
f	**e**	4-FC_6H_4	62
g	**f**	4-$(EtO)C_6H_4$	88
h	**g**	4-*i*ProC_6H_4	78
i	**h**	4-*t*BuC_6H_4	65
l	**i**	4-$(Acetyl)C_6H_4$	52
q	**j**	4-$(F_3C)C_6H_4$	66
s	**k**	3-ClC_6H_4	58
t	**l**	3,4-$(Me)_2C_6H_3$	70

[a] Yields of isolated products

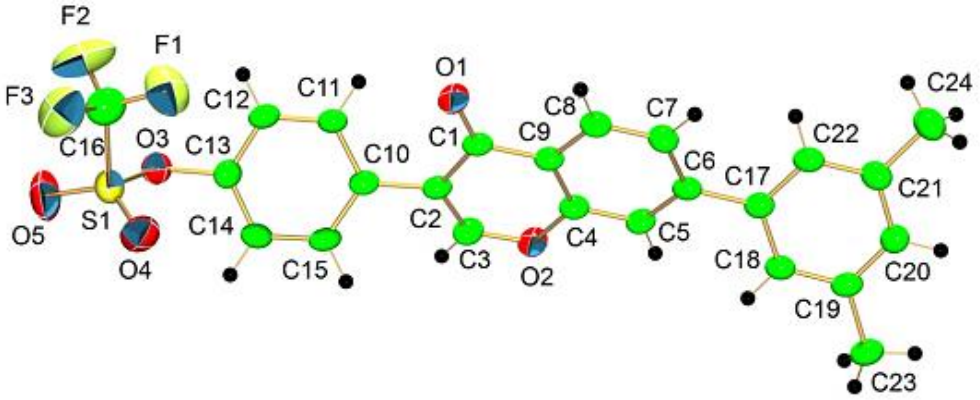
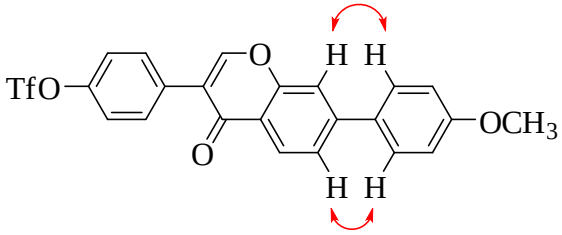


Figure 18. Molecular structure of 4-[7-(3,5-dimethylphenyl]-4-oxo-4*H*-chromen-3-yl)phenyl trifluoromethanesulfonate **(14a)** in the crystal. Displacement ellipsoids are drawn at 50 % probability level**.**

The structure of product **14b** was elucidated by 2D NMR spectroscopy (NOESY, COSY, HMBC, HSQC). A clear and important NOESY correlation between hydrogen atoms H-6 and H-8 with the *ortho* protons of the 4-methoxyphenyl group was found.



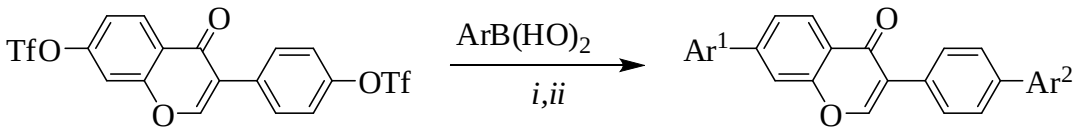
14b

NOESY

Figure 19. Important NOESY correlations of **14b.**

The one-pot reaction of **12** with two different arylboronic acids (sequential addition of the arylboronic acids) afforded 4´,7- bis(aryl)isoflavones **15a-c** in 57-68 % yield (Scheme 24). The reaction was carried out at 85 °C for the first step (to avoid double coupling) and at 130°C in the second step. An additional amount of catalyst and base had to be added

together with the second arylboronic acid, also DMF (4 ml) has to be added to complete the reaction.



12 **15a-c**

Scheme 24. Synthesis of 15a-c. *Reagents and conditions*: *i*, $Ar^1B(OH)$ (1.0 equiv.), $Pd(PPh_3)_4$ (3 mol-%), K_2CO_3 (2 M, 1 ml), DMF (4 ml), 85°C, 6 h.; *ii*, $Ar^2B(OH)$ (2.0 equiv.), $Pd(PPh_3)_4$ (6 mol-%), K_2CO_3 (2 M, 2 ml), DMF (4 ml), 130°C, 10 h.

Table 12. Synthesis of **15a-c.**

3	**15**	**Ar^1**	**Ar^2**	**15 (%)[a]**
e,b	**a**	4-EtC_6H_4	4-$(MeO)C_6H_4$	70
a,b	**b**	3,5-$(Me)_2C_6H_3$	4-$(MeO)C_6H_4$	81
t,b	**c**	3,4-$(Me)_2C_6H_3$	4-$(MeO)C_6H_4$	60

[a] Yields of isolated products

The structures of the newly prepared compounds were confirmed by their IR, ^1H, ^{13}C NMR and by mass spectra, where **13a-d, 14a-l, 15a-c** exhibited additional signals for the protons of the newly introduced aromatic ring.

Positions 4' and 7 of bis(triflates) **12** are sterically similar. However, the regioselectivity of Suzuki-reactions of bis(triflates) **12** in favor of position seven can be explained by electronic reasons. Position seven is located *para* to the electron-withdrawing vinylogous ester group.

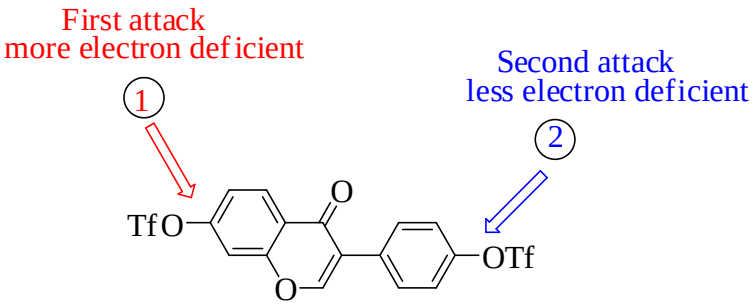


Figure 20. Possible explanation for the reaction of bis(triflates) **12**.

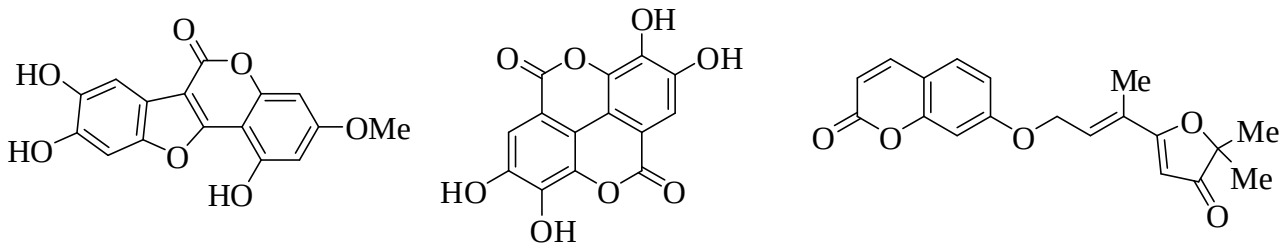
4.3 Conclusion

I have successfully synthesized homo 4´,7-diaryl derivatives of the 4´,7-bis(trifluoromethylsulfonyloxy)isoflavone by Suzuki-Miyaura reactions. Starting with the same isoflavone 7-monoaryl and mixed 4´,7-diaryl derivatives could be prepared in a highly site-selective way. In an equimolar reaction the first attack proceeded with very good regio-selectivity at position C-7 which is more electron deficient. This method provides a conveniet access to aryl-substituted isoflavones which are not readily available by other methoed.

5.1 Efficient synthesis of arylated coumarins by site-selective Suzuki-Miyaura cross-coupling reactions of the 6,7-bis(trifluoromethanesulphonyloxy)-4-methyl-2*H*-chromen-2-one and *in vitro* anti *HIV* activity

5.1.1 Introduction

Coumarin and its derivatives are an important classes of heterocyclic compounds which occur in many natural products with pharmacological activities.[127-132] For example, wedelolactone , its isolated from *Eclipta elba*, and ellagic acid showed highly potential biological activity,[133-136] while other coumestans were isolated from the roots of *Hedysarum multijugum*,[137] and exhibited anti-*HIV* activity.[138] Coumarin compounds are known to possess a wide range of biological activities such as antibacterial,[139] anticancer,[140,141] and anticoagulants effects.[142] Furthermore they may act as anti-*HIV* protease inhibitors,[143] anti-*HIV* integrases,[144-145] serine protease inhibitors,[146] inhibitors of steroid 5α-reductase,[147] and NO synthase inhibitors.[148] Geiparvarin , a naturally occurring product bearing the coumarin residue, has been shown to possess a significant inhibitory activity against a variety of cell lines including sarcoma 180, Lewis lung carcinoma, P-388 lymphocytic leukaemia, and Walker 256 carcinosarcoma.[149] New furanocoumar in ethers of falcarindol, named japonagelol, have been prepared as novel antiproliferative agents.[150] In addition, coumarins are widely used as additives in food, perfumes, agrochemicals, cosmetics, and dispersed fluorescent and laser dyes.[127,151-153] Coumarins can be synthesized by various methods, such as Pechmann,[154] Perkin,[155] Knoevenagel,[156] and Wittig,[157-159] reactions. Palladium-catalyzed site-selective cross-coupling reactions of 3-bromo-4-trifluormethylsulfonyloxycoumarin or 3-bromo-4-tosyloxycoumarin provide an efficient and facile route for the synthesis of 3,4-disubstituted coumarins.[160] Herein, I report a new and convenient synthesis of arylated coumarins by site-selective Suzuki-Miyaura cross-coupling reactions of the bis(triflates) of 4-methyl-6,7-dihydroxycoumarin aiming at an evaluation of their anti-*HIV* activity. The products reported herein are not readily available by other methods.



Wedelolactone Ellagic acid Geiparvarine

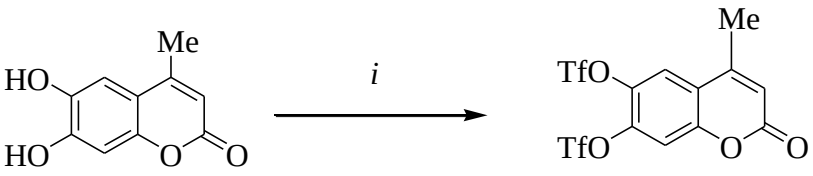
Figure 21. Natural occurring coumarin derivatives.

5.1.2 Results and discussion

4-Methyl-6,7-dihydroxycoumarin **(16)** has been selected as a key intermediate for the synthesis of new coumarin analogues. Thus, treatment of **16** with triflic anhydride (2.4 equiv.) in the presence of Et_3N (4.0 equiv) at -78°C afforded the bis(triflates) analogue **17** in 75 % yield. Reaction of **17** with arylboronic acids **3** (2.0 equiv.) *via* Suzuki-Miyaura reaction gave 4-methyl-6,7-diarylcoumarines **18a-e** in 70-88 % yield (Scheme 26). Both electron-poor and electron-rich arylboronic acids could be successfully employed. The best yields were obtained by using $Pd(PPh_3)_4$ (6 mol-%) as a catalyst and K_3PO_4 (3.0 equiv) as a base in dioxane at 120°C for 6 h.

The structures of **17** and **18a-e** were assigned on the basis of their ^1H and ^{13}C NMR, and mass spectra. In The ^1H NMR spectra H-3 of the coumarin ring appeared in the region δ 6.22-6.37 ppm as a doublet ($J_{CH3,H3}$ ~ 1.2 Hz), while methyl groups at C-4 were resonated in the region δ 2.38-2.41 ppm as a doublet as well. H-5 and H-8 protons appeared as broad singlets in the regions δ 7.41-7.53 and δ 7.27-7.59 ppm, respectively. The other aromatic protons and those of the methoxy and other methyl groups were fully analyzed. The ^{13}C NMR spectra of **17** and **18a-e** contained similar resonance signals of the coumarin carbons ring C-2 - C-8a. The higher-field signals between δ_C 158.2 and 160.9 ppm were assigned to the carbonyl group of the benzopyran ring (C-2), while the resonances in the regions of δ_C 112.4-115.1 ppm were assigned to C-3. The chemical shifts in the regions δ_C 151.4-154.4 and 150.5-152.5 ppm were attributed to C-4 and C-8a, respectively. The resonances at δ_C 137.1-141.1 and δ_C 110.9-118.5 ppm were

assigned to the coumarin carbons C-7, and C-8, respectively. C-4a carbon atom appeared between δ_C 117.6 and 120.1 ppm, except for **17**, which resonated at δ_C 112.7 ppm. The resonances at the regions δ_C 125.1-126.4 ppm were attributed to C-5, C-6 and carbons of aromatic ring, whereas the methyl groups at C-4 appeared in the range δ_C 17.6-20.3 ppm. The carbon atom of CF_3 group of **17** appeared as a doublet at δ_C 117.9 ppm ($J_{C,F}$ = 317.0 Hz).



16 **17 (75 %)**

Scheme 25. Synthesis of **17**, *Reagent and conditions*: *i* Et_3N, CH_2Cl_2, 20°C, then Tf_2O, -87°C to 20°C, 6 h.

The structure of **17** was independently confirmed by X-ray crystal structure analysis (Figure 22).

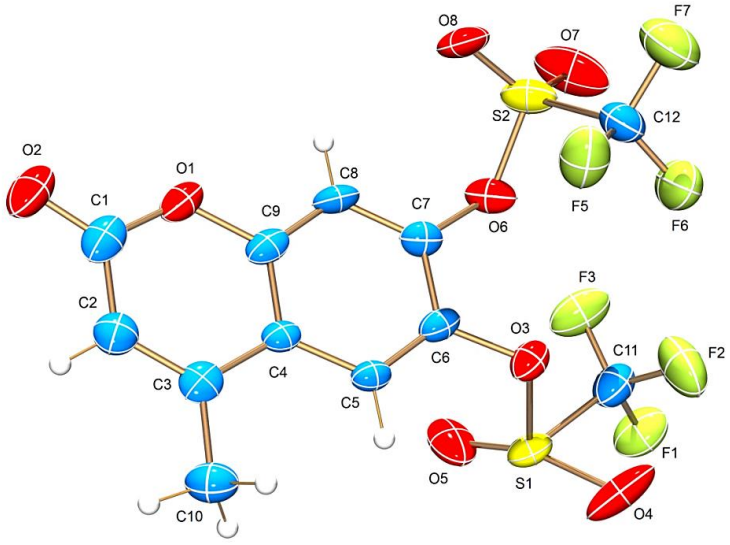
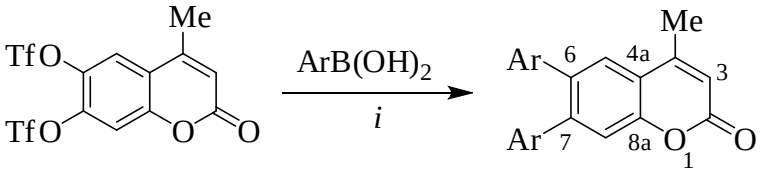


Figure 22. Molecular structure of 6,7-bis(trifluoromethanesulphonyloxy)-4-methyl-2*H*-chromen-2-one **17** in the crystal. Displacement ellipsoids are drawn at the 50 % probability level**.**



17 **18a-e**

Scheme 26. Synthesis of **18a-e**. *Reagent and conditions*: *i*, **17** (1.0 equiv), **3 a-c,g,p** (2.0 equiv.), K_3PO_4 (3.0 equiv.), $Pd(PPh_3)_4$ (6 mol-%), 1,4-dioxane 120°C, 6 h.

Table 13. Synthesis of **18a-e.**

3	18	Ar	18 (%) [a]
a	**a**	3,5-$(Me)_2C_6H_3$	75
b	**b**	4-$(MeO)C_6H_4$	83
c	**c**	4-ClC_6H_4	83
g	**d**	4-$(EtO)C_6H_4$	88
p	**e**	C_6H_4	70

[a] Yields of isolated products

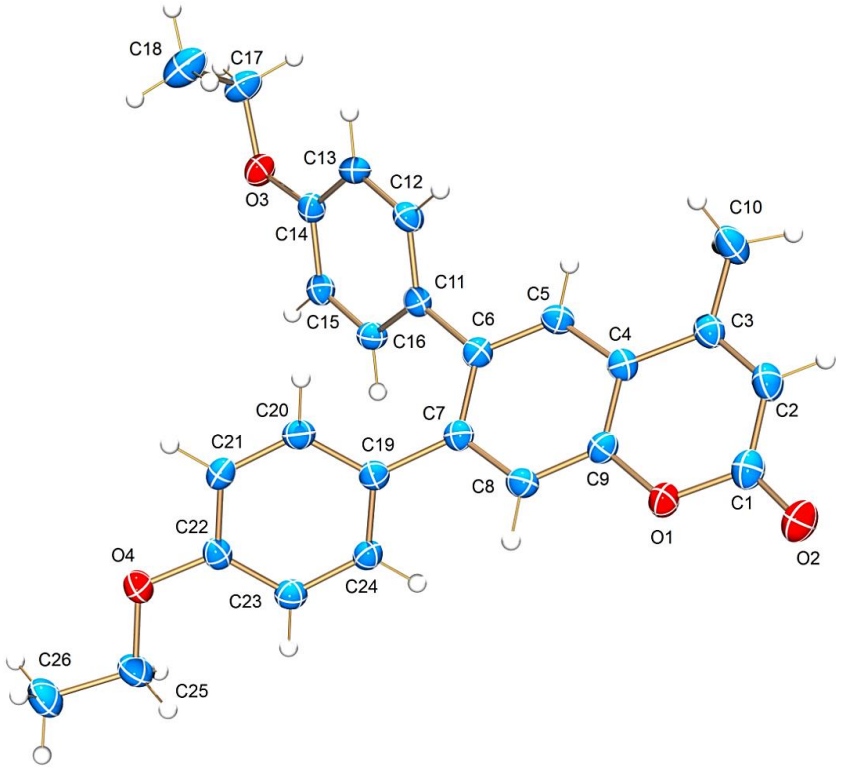
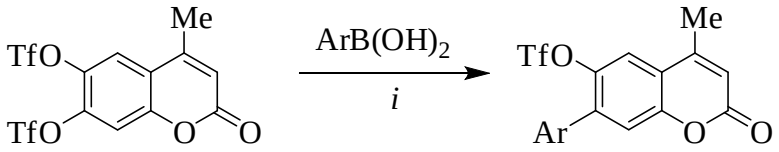


Figure 23. Molecular structure of 6,7-bis(4-ethoxyphenyl)-4-methyl-2*H*-chromen-2-one **18d** in the crystal. Displacement ellipsoids are drawn at the 50 % probability level**.**

Next, treatment of **17** with arylboronic acids **3** (1.2 equiv.) *via* Suzuki-Miyaura reaction furnished 7-aryl-4-methyl-6-trifluorosulfonyloxy-coumarins **19a-m** in 70-90 % yield with highly site-selectivity (Scheme 27). During the optimization, it proved to be important to use (1.2 equiv.) of the arylboronic acid and to carry out the reaction at 70 ^{o}C instead of 120 °C by using dioxane as a solvent for 6 h. Both electron-poor and electron-rich arylboronic acids were successfully used.

The one-pot Suzuki-Miayura reaction of bis-triflates **17** with two different arylboronic acids **3** (sequential addition of 1.2 equiv. of each boronic acid), first with 4-methoxphenylboronic acid **(3b)** (1.2 equiv.) gave the unseparated **19b**, which on further treatment with arylboronic acids **3a,c,f,j** (1.2 equiv.) afforded the 6,7-diaryl-4-methylcoumarin **20a-d** 73-81% yields. The reactions were carried out at 70°C for the first step (to avoid double coupling) and at 120°C for the second step.



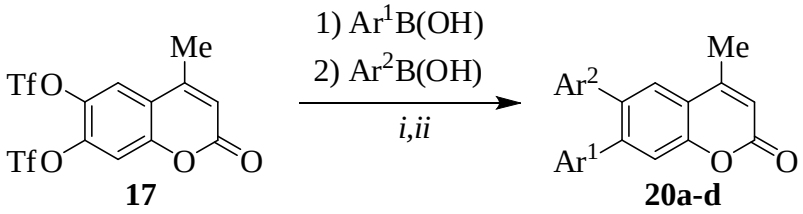
17 **19a-m**

Scheme 27. Synthesis of **19a-m**. *Reagent and conditions*: *i*, **17** (1.0 equiv), **3a-f,g,i-j,o-r** (1.2 equiv.), K_3PO_4 (1.5 equiv.), $Pd(PPh_3)_4$ (3 mol-%), 1,4-dioxane, 70°C, 6 h.

Table 14. Synthesis of **19a-m.**

3	19	Ar	19 (%) [a]
a	**a**	3,5-$(Me)_2C_6H_3$	75
b	**b**	4-$(MeO)C_6H_4$	80
c	**c**	4-ClC_6H_4	85
d	**d**	4-MeC_6H_4	75
e	**e**	4-EtC_6H_4	84
f	**f**	4-FC_6H_4	78
g	**g**	4-$(EtO)C_6H_4$	90
i	**h**	4-*t*BuC_6H_4	77
j	**i**	3-MeC_6H_4	80
o	**j**	2,3,4$(MeO)_3C_6H_2$	90
p	**k**	C_6H_5	72
q	**l**	4-$(F_4C)C_6H_4$	83
r	**m**	3-$(MeO)C_6H_4$	70

[a] Yields of isolated products



Scheme 28. Synthesis of **20a-d**. *Reagent and conditions*: *i*, **2** (1.0 equiv), $Ar^1B(OH)_2$ (1.2 equiv.), K_3PO_4 (1.5 equiv.), $Pd(PPh_3)_4$ (3 mol-%), 1,4-dioxane, 70°C 6 h. *ii*, $Ar^2B(OH)_2$ (1.2 equiv.), K_3PO_4 (1.5 equiv.), $Pd(PPh_3)_4$ (3 mol-%), 1,4-dioxane, 120°C 6 h.

Table 15. Synthesis of **20a-d**.

3	**20**	**Ar^1**	**Ar^2**	**20 (%)[a]**
b,c	**a**	4-(MeO)C_6H_4	4-ClC_6H_4	73
b,f	**b**	4-(MeO)C_6H_4	4-FC_6H_4	78
b,j	**c**	4-(MeO)C_6H_4	3-MeC_6H_4	75
b,a	**d**	4-(MeO)C_6H_4	3,5$(Me)_2C_6H_3$	81

[a] Yields of isolated products

Compounds **19a-m** were identified from the ^{1}H NMR and ^{13}C NMR spectra, which showed almost similar resonances of benzopyran ring atoms as those of **18a-e**. H-3, and methyl group at C-4 appeared as two doublets with long range couplings in the regions δ_H 2.31-2.42 and 6.24-6.33 ppm, respectively ($J_{CH3,H3}$ ~ 1.3 Hz). H-5 and H-8 protons appeared as broad singlets in the regions δ_H 7.52-7.36 and 7.45-7.52 ppm, respectively. The aromatic protons resonated as multiplets or doublets between δ_H 6.80 and 7.47 ppm, while the other alkyl protons were fully analyzed.

In the ^{13}C-NMR spectra of **19a-m**, the resonances at δ_c = 158.4-163.9 ppm were attributed to the carbonyl group (C-2). The carbon atoms C-3 and C-4 of the benzopyran ring resonated in the regions δ_c = 113.8-115.6 and 158.6-150.9 ppm, respectively, while C-4a and C-5 appeared in the regions δ_c = 115.5-119.5 and 115.1-117.5 ppm, respectively. Aromatic C-6 - C-8a, atoms and carbons atoms of the substituents were

fully assigned. Compound **19b** was selected for further NMR studies. In the gradient-selected HMBC spectrum[161] of **19b**, the olefinic proton (H-3) at δ_H = 6.50 ppm showed two $^2J_{C,H}$ couplings: one to the carbonyl carbon atom of the the coumarin ring (C-2) at δ_C 160.9 ppm and the other coupling was with C-4 at δ_C 151.3 ppm. A $^3J_{C,H}$ between coupling between H-8 of coumarin ring at δ_H 6.60 ppm and aromatic carbon atom (C-1') at δ_C 136.8 ppm was assigned. Furthermore, in the NOESY spectrum,[162] a correlation between the protons of methyl group at C-4 and H-3 as well as between H-8 of coumarin ring and the aromatic protons H-2' and H-6' (Figure 24) was detected.

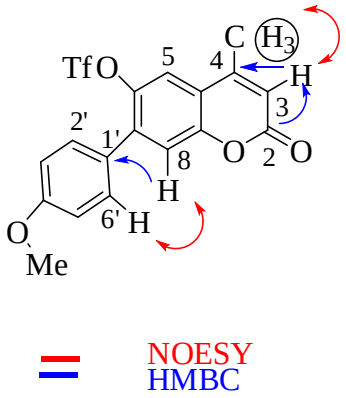


Figure 24. $J_{C,H}$ correlations in the HMBC (single head arrows), and NOESY (double head arrows) correlations of **19b.**

The ^{1}H NMR and ^{13}C NMR spectra of **20a-d** were in agreement with the suggested structures. The resonances of H-5 and H-8 prortons oriented in the regions at δ_H 7.46-7.48 and 7.26-7.28 ppm, respectively, which differ from those of the analogues **19a-m** due to the substitution of the triflates group at C-6 by the aryl moieties. In the ^{13}C NMR spectra, C-5 and C-6 carbon atoms appeared in the regions δ_C 129.7-130.5 and 131.0-135.4 ppm, respectively, whereas C-8 carbon atoms were resonated in the region δ_C 117.1-117.8 ppm. Additional support of the proposed structures comes from mass spectral data.Mass spectra of the prepared compounds **19** and **20** showed the correct molecular ions, (M+·), as suggested by their molecular formulas.

The structure of **19b** was independently confirmed by X-ray crystal structure analysis (Figure. 25).

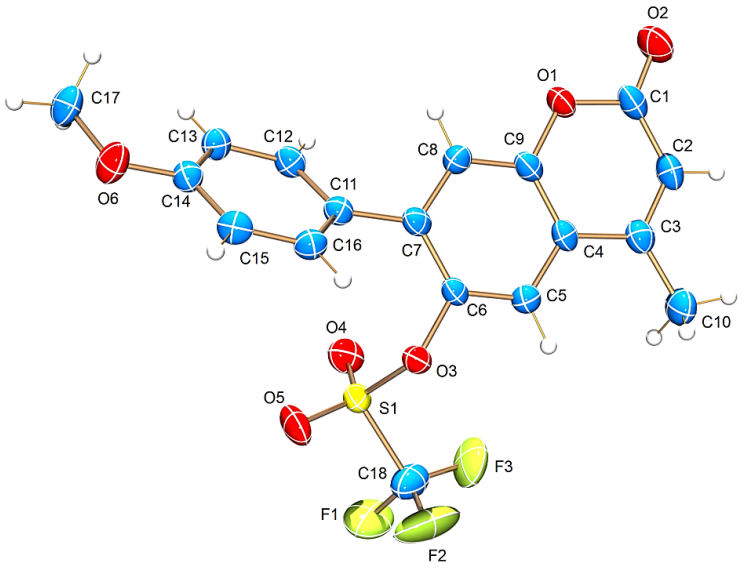


Figure 25. Molecular structure of 7-(4-methoxyphenyl)-4-methyl-6-*O*-trifluoromethanesulphonyloxy-2*H*-chromen-2-one **(19b)** in the crystal. Displacement ellipsoids are drawn at the 50 % probability level.

Positions six and seven of bis (triflates) **17** are sterically similar. However, the regioselectivity of Suzuki reactions of bis (triflates) **17** in favor of position seven can be explained by electronic reasons. Position seven is located *para* to the electron-withdrawing vinylogous ester group, while position six is located *para* to the electron-donating oxygen atom.

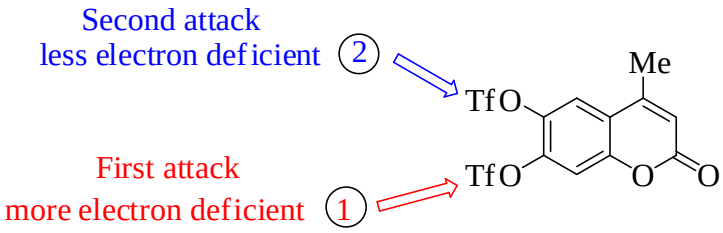


Figure 26. possible explanation for the reaction .

The reactions proceed with excellent regioselectivity in faver of the electronically more deficient position.

5.1.3 *In vitro* anti *HIV* activity

Compounds **18a-e**, **19a-m** and **20a-d** were tested by our collaboration partners (group of Prof. Dr. Najim Al-Masoudi) for their *in vitro* anti-HIV-1 (strain III_B) and HIV-2 (strain ROD) activity in human (MT-4) cells based on an MTT assay.[163] The results are summarized in Table 16, in which the data for nevirapine (BOE/BIRG587)[164] and azidothymidine (DDN/AZT)[165] are included for comparison purposes. Compound-induced cytotoxicity was also measured in MT-4 cells parallel with the antiviral activity.

Compounds **18a** and **19j** were found to be the only compounds from the series inhibiting HIV-1 replication in a cell culture, which showed an IC_{50} of 4.57 μg mL^{-1} and 13.20 μg mL^{-1} with CC_{50} of 14.40 μg mL^{-1} and 61.34 μg mL^{-1}, respectively, resulting in a selectivity index of 3 and 5. On the other hand, **19k**, **20a**, and **20d** showed some activity against HIV-1 (III_B strain) with $IC_{50} > 2.13$, > 2.06 and > 2.08 μg mL^{-1}, respectively, but no selectivity was witnessed ($SI < 1$).

However, implantation of methyl groups in 3 and 5 positions of both phenyl groups at C-6 and C-7 of the coumarin ring (compound **18a**) or methyl group in 3 position of phenyl residue at C-7 together with the triflates at C-6 of the coumarin ring (compound **19j**) considerably increased the anti-*HIV*-1, anti-*HIV*-1 activity, in comparison to the effectiveness of other functional groups.

Table 16. *In vitro* anti-*HIV*-1[a] and *HIV*-2[b] activity and cytotoxicity of some new coumarins.

Entry	*HIV*-1 (III_B) IC_{50} (μg mL^{-1})[c]	*HIV*-2 (ROD) IC_{50} (μg mL^{-1})[c]	CC_{50} (μg mL^{-1})[d]	SI[e] (III_B)	SI[e] (ROD)
17	>43.50	>43.50	43.50	<1	<1
18a	4.57	>14.40	14.40	3	<1
18b	>11.00	>11.00	11.00	<1	<1
18c	>15.98	>15.98	15.98	<1	<1
18p	>13.78	>13.78	13.78	<1	<1
18g	>37.31	>37.31	37.31	<1	<1
19a	>33.10	>33.10	33.10	<1	<1
19b	>10.60	>10.60	≥10.60	<orX1	<orX1
19c	>30.65	>35.65	35.65	<1	<1
19d	>12.55	>12.55	12.55	<1	<1
19e	>27.20	>27.20	≥27.20	<orX11	<orX1
19f	>10.63	>10.63	10.63	<1	<1
19g	>80.33	>80.33	80.33	<1	<1
19h	>11.00	>11.00	11.00	<1	<1
19i	13.20	>61.34	61.34	5	<1
19j	>18.86	>18.86	18.86	<1	<1
19k	>2.13	>2.13	2.13	<1	<1
19l	>10.28	>10.28	10.28	<1	<1
20a	>2.06	>2.06	2.06	<1	<1
20b	>10.92	>10.92	10.92	<1	<1
20c	>7.40	>7.40	7.40	<1	<1
20d	>2.08	>2.08	2.08	<1	<1
Nevirapine	0.050	>4.00	>4.00	>80	<1
AZT	0.0022	0.00094	>25	>11363	>26596

[a] Anti-*HIV*-1 activity measured with strain III_B; [b] anti-*HIV*-2 activity measured with Strain ROD; [c] compound concentration required to achieve 50% protection of MT-4 cells from the *HIV*-1 and *HIV*-2-induced cytopathic effect;[d] compound concentration that reduces the viability of mock-infected MT-4 cells by 50 %; [e] SI: selectivity index (CC_{50}/IC_{50})

5.1.4 Conclusion

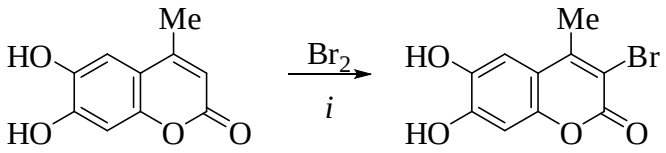
I have successfully synthesized homo 6,7-diaryl derivatives of the 4-methyl-6,7-(trifluoromethylsulfonyloxy)coumarin by Suzuki-Miyaura reactions. Starting with the same coumarin 7-monoaryl and mixed 6,7-diaryl derivatives could be prepared in a highly site-selective way.The first attack proceeded with very good regio-selectivity at position C-7 which is more electron deficient.

The anti-*HIV* activity and the selectivity of these compounds are too limited to perform extensive mode-of-action studies, and **18a** and **19j** might be considered as a new lead in the development of antiviral agents as non-nucleoside reverse transcriptase inhibitors.

5.2 Arylation of 3-bromo-4-methyl-6,7-triflate coumarin by Suzuki-Miyaura cross-coupling reactions

5.2.1 Results and discussion

At first I would like to present a simple bromination method to prepare 3-bromo-6,7-dihydroxy-4-methyl-2*H*-chromen-2-one **(21)** in one step, and high yield by using bromine. The bromodihydroxycoumarin was prepared by reaction of commercially available 4-methyl-6,7-dihdroxycoumarin **(16)** with bromine in glacial acitic acid within 2 h (Scheme 29) .



16 **21**

Scheme 29. Synthesis of **21** *Reagent and conditions*: *i* **16** (1.0 equiv), Br_2 (2.0 equiv), CH_3CO_2H (20 ml), 30°C, 2 h.

The structure of **21** was independently confirmed by ^{1}H NMR ,^{13}C, mass spectroscopy and 2D NMR (Figure 27).

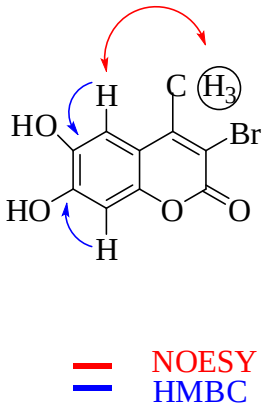
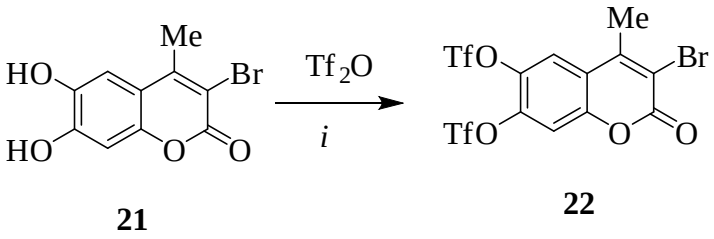


Figure 27. $J_{C,H}$ correlations in the HMBC (single head arrow), and NOESY (double head arrow) correlations of **21.**

In the next step synthesis of 3-bromo-4-methyl-2-oxo-2*H*-chromene-6,7-diylbis(trifluoromethanesulfonate) **(22)** by the treatment of compound **(21)** with Tf_2O at -78°C. The mixture was allowed to warm to 20°C and stirred for 6 h.



21 **22**

Scheme 30. Synthesis of **22.** *Reagent and conditions*: *i* **21** (1.0 equiv), Et_3N (4.0 equiv), CH_2Cl_2, 20°C; Tf_2O (2.4 equiv), -78°C to 20°C, 6 h.

The structure of **22** was independently confirmed by X-ray ceystal structure analysis (Figure 28).

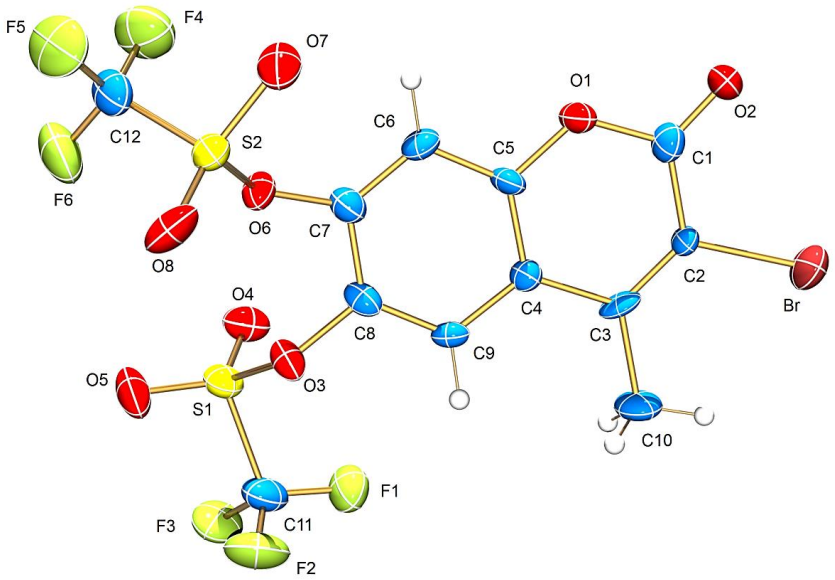
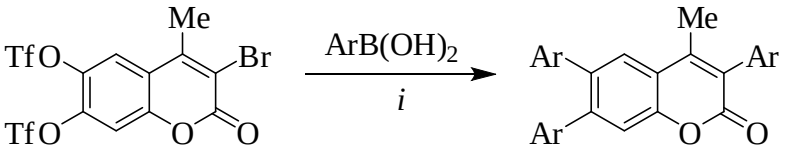


Figure 28. Molecular structure of 3-bromo-4-methyl-2-oxo-2H-chromene-6,7-diylbis(trifluoromethanesulfonate) **(22)** in the crystal. Displacement ellipsoids are drawn at the 50 % probability level.

The Suzuki-Miyaura reaction of **22** with arylboronic acids **3a-j,o,q,r,u** (3.1 equiv.) afforded 4-methyl-3,6,7-tris(aryl)coumarines **23a-o** 60- 84 % yields (Scheme 31, Table 17). The best yields were obtained when the reactions were carried out using $Pd(pph_3)_4$ as the catalyst and K_2CO_3 as the base (dioxane, 120°C, 10 h). Both electron-rich and electron-poor arylboronic acid were successfully employed. The yield of the products derived from arylboronic acids containing electron-withdrawing substituents, which are less nucleophilic, were lower than the yield of products derived from arylboronic acid containing electron-donating substituents. Unfortunately, all attempts to develop regioselective Suzuki-Miyaura reactions failed.



22 **23a-o**

Scheme 31. Synthesis of **23a-o**. *Reagents and conditions: i*, **22** (1.0 equiv.), **3a-j,o,q,r-u** (3.1 equiv.), $Pd(PPh_3)_4$ (14 mg, 9 mol-%), K_2CO_3 (aq. solution, 2 M), 1,4-dioxane, 120°C, 10 h.

Table 17. Synthesis of **23a-o.**

3	23	Ar	23 (%) [a]
a	**a**	3,5-$(Me)_2C_6H_3$	70
b	**b**	4-$(MeO)C_6H_4$	80
c	**c**	4-ClC_6H_4	60
d	**d**	4-MeC_6H_4	75
e	**e**	4-EtC_6H_4	75
f	**f**	4-FC_6H_4	70
g	**g**	4-$(EtO)C_6H_4$	84
h	**h**	4-*i*ProC_6H_4	77
i	**i**	4-*t*BuC_6H_4	62
j	**j**	3-MeC_6H_4	70
o	**k**	2,3,4-$(MeO)_3C_6H_2$	80
q	**l**	4-$(F_3C)C_6H_4$	63
r	**m**	3-$(MeO)C_6H_4$	80
t	**n**	3,4-$(Me)_2C_6H_4$	60
u	**o**	4-*i*PrC_6H_4	70

[a] Yields of isolated products

The structure of **23f** was independently confirmed by 2D NMR (Figure 29).

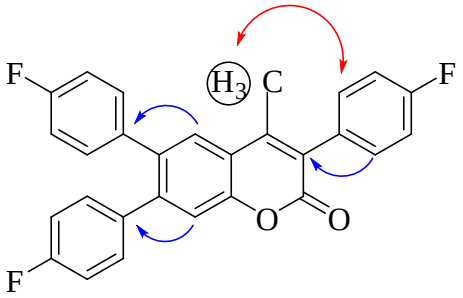


Figure 29. $J_{C,H}$ correlations in the HMBC (single head arrow), and NOESY (double head arrow) correlations of **23f.**

The structure of **23i** was independently confirmed by X-ray crystal structure analysis (Figure 30).

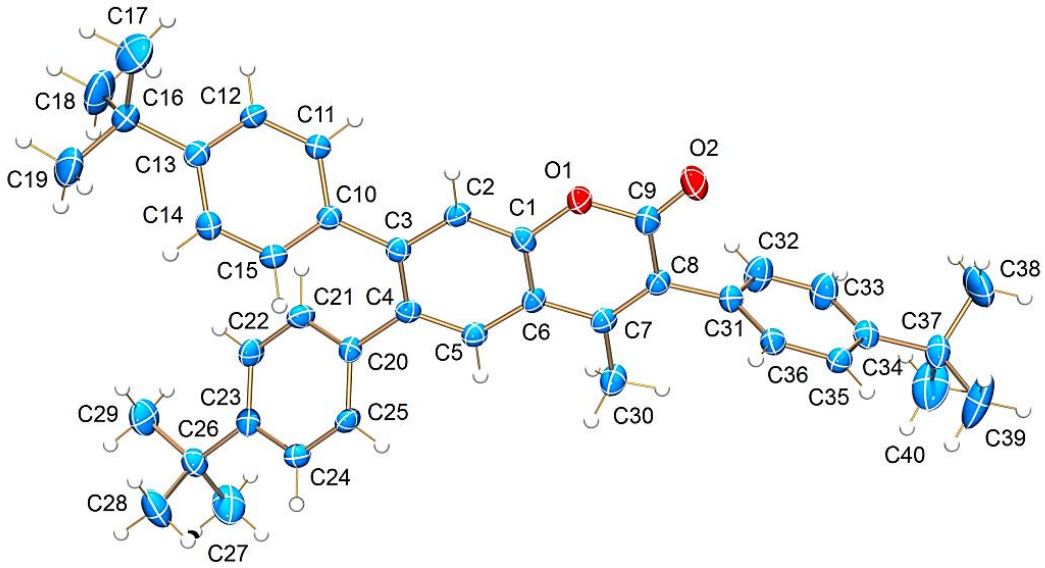


Figure 30. Ortep plot of **23i.**

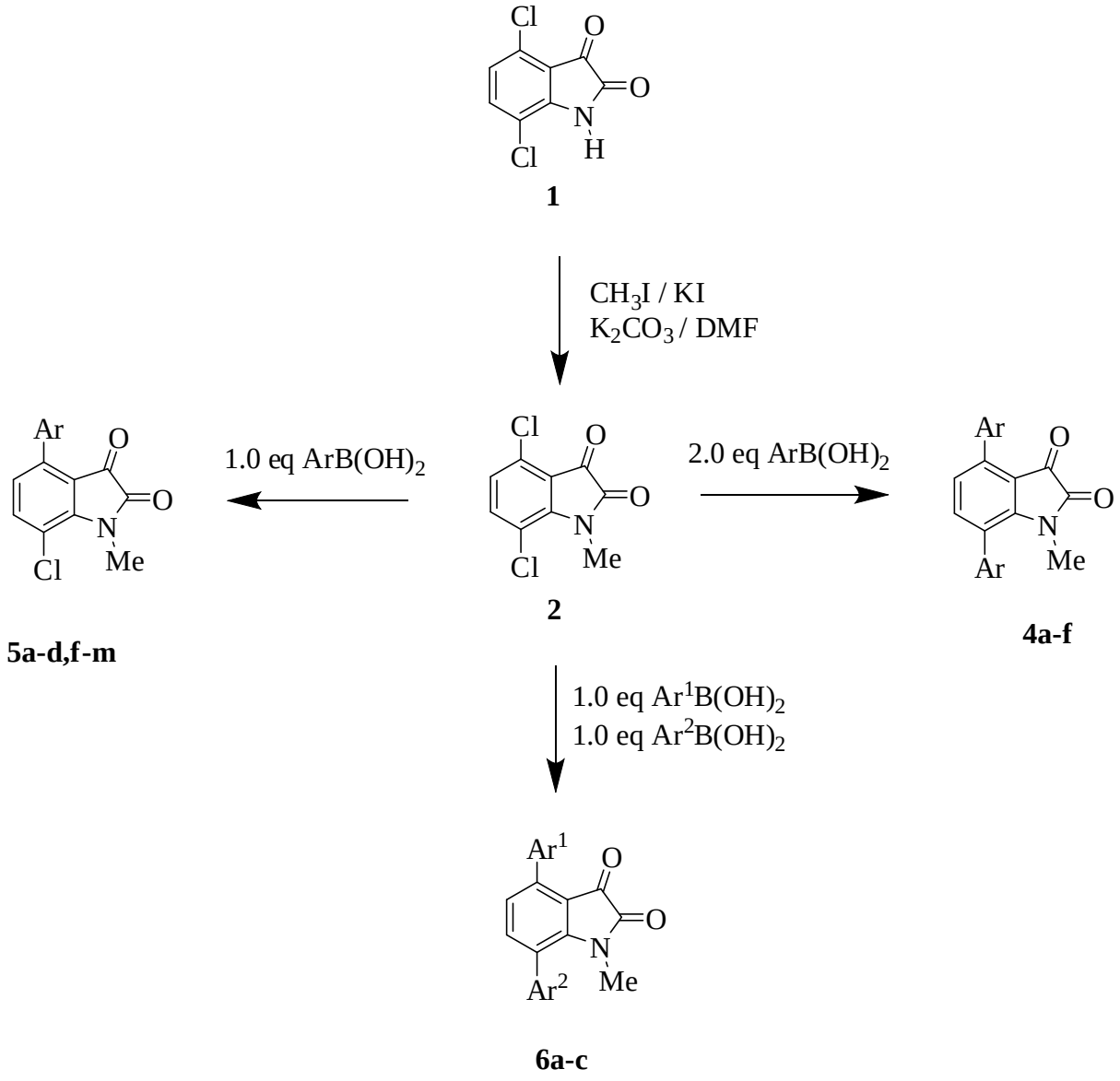
5.2.2 Conclusion

I have synthesized 4-methyl-3,6,7-tris(aryl)coumarines **(23)** from 3-bromo-4-methyl-2-oxo-2*H*-chromene-6,7-diyl bis(trifluoromethanesulfonate) by Suzuki-Miyaura reactions. Both electron-poor and rich-arylboronic acids were successfully employed, This method provides a conveniet access to triarylsubstituted coumarines which are not readily available by other methods. Unfortunately, all attempts to develop regioselective Suzuki-Miyaura reactions failed.

SUMMARY

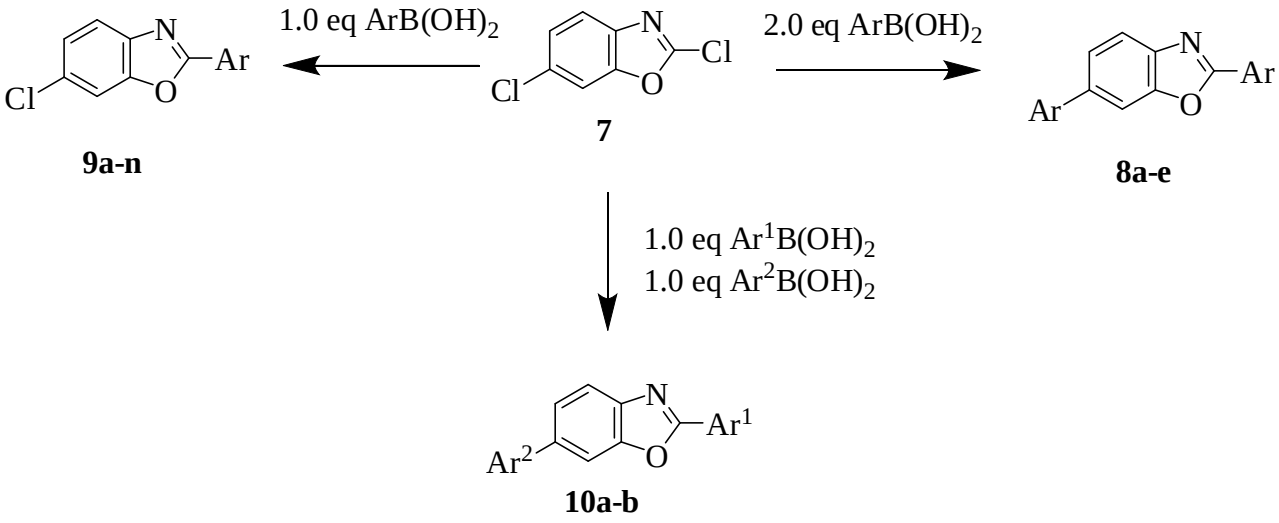
A significant part of this dissertation has been published (see list of publications). The task of my thesis was to study palladium(0) catalyzed Suzuki cross-coupling reactions of various types of triflates or bromine compounds of different molecules (isatins, banzoxazols, isoflavones, coumarines). The triflates are readily available from the corresponding hydroxy compounds. The issue of site-selectivity plays an important role in my thesis. In this context, steric and electronic parameters have been investigated.

I was studying palladium(0) catalyzed Suzuki cross-coupling reactions of 4,7-dichloromethylisatin. The reactions proceed with excellent site-selectivity. The first attack occurs at position C-4 which is more electron deficient than position C-7 (Scheme I). Palladium catalyzed cross-coupling reactions usually occur at the electronically more deficient position.



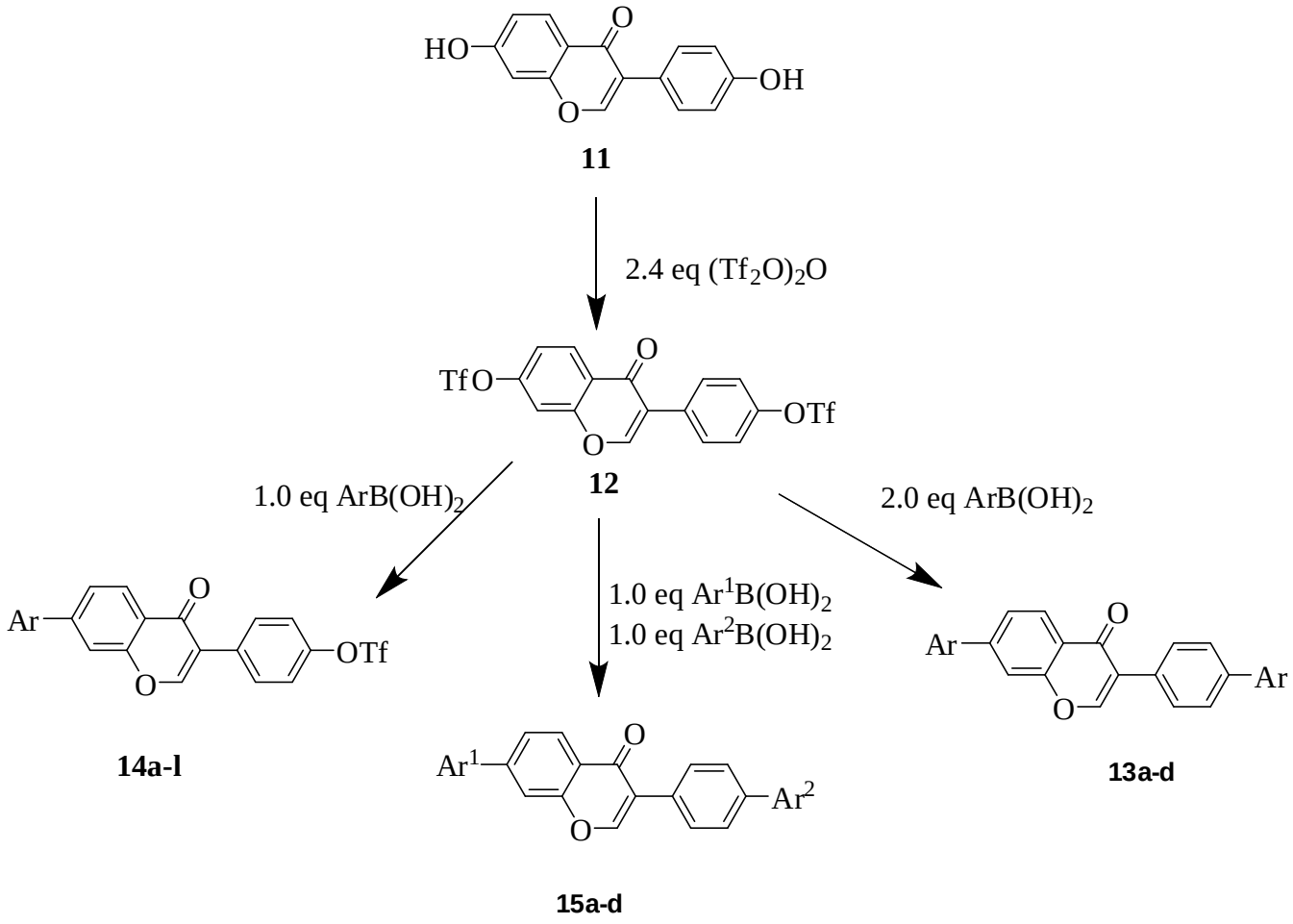
Scheme I

Suzuki-Miyaura reactions of the 2,6-dichlorobenzoxazole proceed with very good site-selectivity in favour of position C-2 which is more electron deficient than position C-6 (Scheme II). Palladium catalyzed cross-coupling reactions usually occur at the electronically more deficient position.



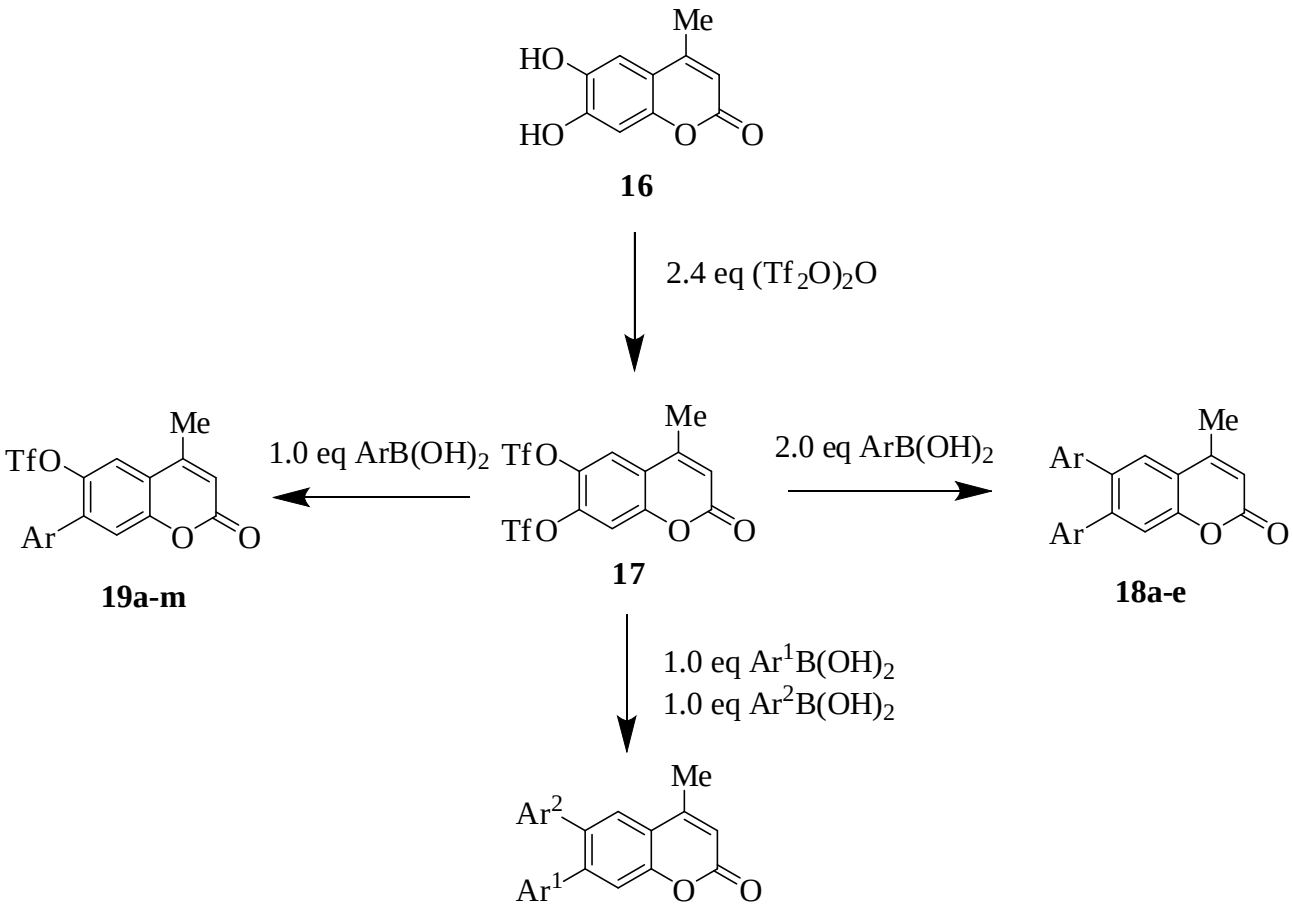
Scheme II

The reaction of 4´,7-dihydroxyisoflavone with two equivalent of triflic anhydride leads to preparations of 4´,7-bis(trifluoromethylsulfonyloxy)isoflavone.The subsequent Suzuki-Miyaura reaction of the product allows the synthesis of 7-monoaryl, homo 4´,7-diaryl and imixed 4´,7-diaryl derivatives. The reactions proceed with very good site-selectivity in favour of position C-7 which is more electron deficient than position C-4´ (Scheme III).



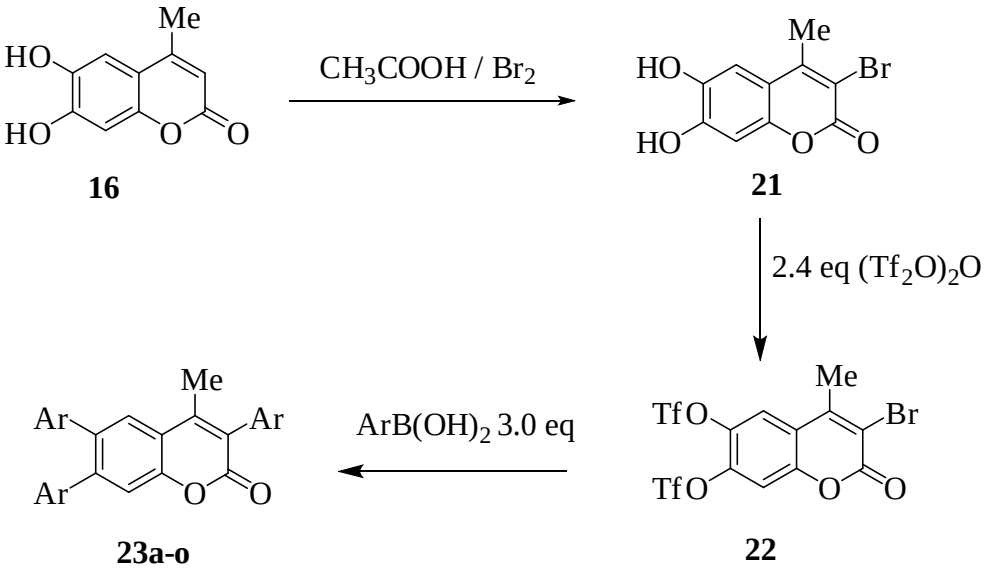
Scheme III

The treatment of 4-methyl-6,7-dihydroxycoumarin with two equivalent of triflic anhydride leads to preparations of 4-methyl-6,7-bis(trifluoromethylsulfonyloxy)coumarin.The subsequent palladium(0) catalyzed reaction of the product afforded various 4-methyl-6,7-di(aryl)coumarins.The reactions proceed with very good site-selectivity in favour of position C-7 which is more electron deficient than position C-6 (Scheme IV).



Scheme IV

Development simple bromination method to prepare 3-bromo-6,7-dihydroxy-4-methyl-2*H*-chromen-2-one in one step.The treatment of the bromocoumarin with two equivalent of triflic anhydride leads to preparations of 3-bromo-6,7-bis(trifluoromethylsulfonyloxy)-coumarin.The palladium(0) catalyzed Suzuki cross-coupling reaction of the product afforded various 3,6,7-triarylcoumarins in very good yields (Scheme V).



Scheme V

7. Experimental Section

7.1 General: 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, HMBC) were applied as well. All NMR spectra presented in this work were collected in $CDCl_3$ solution. All chemical shifts are 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 Structures

Bruker X8Apex diffractometer with CCD camera (Mo K_α radiation and graphite monochromator, $\lambda = 0.71073$ Å). The space group is determined by the XPREP program and the structures were solved via the SHELX-97 program package. Refinements were carried out according to the minimum square error method.

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

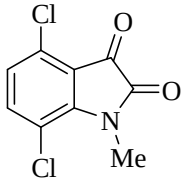
Column chromatography was performed with Merck Silica Gel 60 or Macherey-Nagel Silica Gel 60 (0.063-0.200 mm, 70-230 mesh). The finer Merck Silica Gel 60 (0.040-0.063 mm, 230-400 mesh) was chosen when appropriate.

Chemicals and work technique

All solvents for using were distilled by standard methods. All reactions were carried out under an inert atmosphere, oxygen and humidity exclusion. All of the chemicals are standard, commercially available from Merck®, Aldrich®, Arcos® and others.

7.2 Procedures and spectroscopic data

Synthesis of 4,7-dichloro-1-methylindoline-2,3-dione (2):

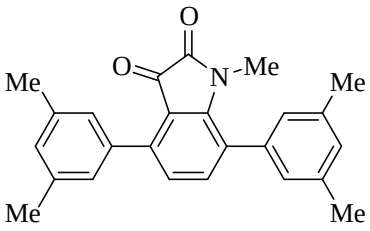


Isatin (1 equiv.) was taken up in anhydrous DMF (1 ml per 0.1 mmol isatin) and cooled on ice with stirring. Solid K_2CO_3 (1.2 equv.) was added in one portion, and the dark colored suspension was brought to room temperature and stirred for afurther 1 h.The appropriate CH_3I (1.1 equiv.) and KI (0.2 equiv.) were added, and the reaction material had been consumed (TLC). The reaction mixture was poured into HCl (0.5 M, 50 ml) and extracted with ethyl acetate (1 x 50 ml).The ethyl acetate layer was washed with brine and dried over Mg_2SO_4. The solvent was removed, and the curde product was purified via flash column chromatography using CH_2Cl_2, **2** was isolated as orange solid (69 mg, 90 %); mp 173-175°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.57 (s, 3H, CH_3), 6.95 (d, J = 8.78 Hz, 1H, ArH), 7.37 (d, J = 8.78 Hz, 1H, ArH).^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 29.8 (NCH_3), 115.7, 116.6 (C), 126.6 (CH), 132.8 (C), 140.3 (CH), 147.7 (C), 157.7, 179.3 (CO). IR (KBr, cm^{-1}): v = 3450, 3075, 3063, 2952, 2921, 2851, 1788 (w), 1728, 1584 (s), 1584, 1494 (w). GC-MS (EI, 70 eV): *m/z* (%) = 228 ([M]$^+$, 2x[^{35}Cl] ,100), 203 (21), 201 (21), 200 (10), 174 (78), 160 (12), 158 (16), 151 (12), 111 (17). HRMS (EI, 70 eV): calcd for $C_9H_5{}^{35}Cl_2NO_2$ [M]$^+$: 228.96973; found: 228.96932.

General procedure for synthesis (4a-f)

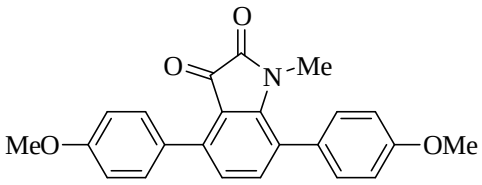
The reactions were carried out in a pressure tube.To a dioxane suspension (3 ml) of **2** (70 mg, 0.3043 mmol), $Pd(PPh_3)_4$ (21 mg, 6 mol-%, 0.01818 mmol), arylboronic acid **3** (0.669 mmol) K_3PO_4 (202 mg, 0.91302 mmol) was added.The mixture was heated at 120^{o}C under Argon atmosphere for 8 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 x 25 ml). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, EtOAc / heptane = 8:2).

4,7-Bis(3,5-dimethylphenyl)-1-methylindoline-2,3-dione (4a):



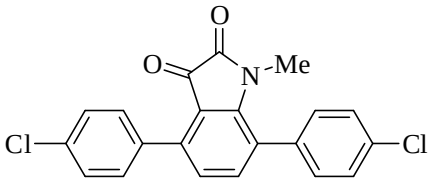
Starting with **2** (70 mg, 0.3043 mmol) , **3a** (100 mg, 0.6695 mmol), $Pd(PPh_3)_4$ (21 mg, 6 mol-%, 0.01818 mmol), K_3PO_4 (202 mg, 0.9130 mmol), and 1,4-dioxane (3 ml), **4a** was isolated as a red solid (69 mg, 61 %); mp164 -166°C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 12H, 4xCH_3), 3.20 (s, 3H, CH_3), 6.70 (d, *J* = 8.6 Hz, 2H, ArH), 6.97 (d, *J* = 8.3 Hz, 2H, ArH), 7.16 - 7.19 (m, 2H, ArH), 7.57 (t, *J* = 8.3 Hz, 2H, ArH).^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 21.3 (4xCH_3), 33.7 (NCH_3), 126.7, 130.8, 137.5 (CH), 125.7, 129.7 (C), 131.8, 137.5, 139.2 (CH), 143.3, 145.0, 147.6, 147.8, 152.2, 157.3, 157.5, 158.2 (C), 166.4, 180.9 (CO). IR (KBr, cm^{-1}): *ν* = 3075, 2953, 2919, 2852 (w), 1742, 1723 (s), 1605, 1585, 1564, 1499 (m). GC-MS (EI, 70 eV): *m/z* (%) = 369 ($[M]^+$,100), 344 (23), 332 (11), 220 (16), 163 (10), 120 (10) . HRMS (EI, 70 eV) calcd for $C_{25}H_{23}NO_2$ ($[M]^+$): 369.17233 found: 369.17211.

4,7-Bis(4-methoxyphenyl)-1-methylindoline-2,3-dione (4b):



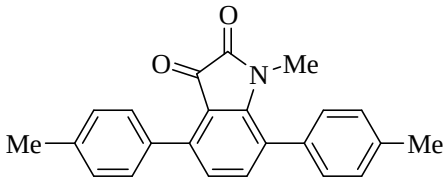
Starting with **2** (70 mg, 0.3043 mmol) , **3b** (102 mg, 0.6695 mmol), $Pd(PPh_3)_4$ (21 mg, 6 mol-%, 0.01818 mmol), K_3PO_4 (202 mg, 0.91302 mmol), and 1,4-dioxane (3 ml), **4b** was isolated as a red solid (93 mg, 82 %); mp 220-222°C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.20 (s, 6H, 2xOCH_3), 3.79 (s, 3H, CH_3), 6.73 (dd, *J* = 8.3, 2.4 Hz, 2H, ArH), 6.97 (d, *J* = 8.0 Hz, 2H, ArH), 7.16 - 7.19 (m, 4H, ArH), 7.55 (d, *J* = 8.0 Hz, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 20.8 (NCH_3), 33.7 (2xOCH_3), 38.1 (C), 119.3, 124.7, 125.1, 128.6, 128.9, 129.6 (CH), 130.6, 130.8, 132.4, 132.4, 134.9, 144.3, 146.5 (C), 160.6, 181.2 (CO). IR (KBr, cm^{-1}): *ν* = 3074, 2952, 2918, 2851 (w), 1743, 1724 (m), 1605, 1586, 1564, 1497, 1488 (s). GC-MS (EI, 70 eV): *m/z* (%) = 373 ($[M]^+$,100), 364 (23), 365 (11), 310 (16), 311 (32), 210 (34), 174 (10), 134 (23) . HRMS (EI, 70 eV) calcd for $C_{23}H_{19}NO_4$ ($[M]^+$): 373.13141; found: 373.13100.

4,7-Bis(4-chlorophenyl)-1-methylindoline-2,3-dione (4c):



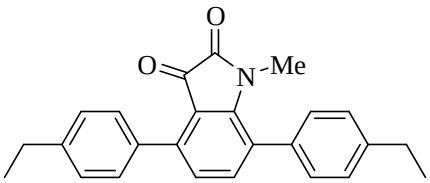
Starting with **2** (70 mg, 0.3043 mmol) , **3c** (104 mg, 0.6695 mmol), $Pd(PPh_3)_4$ (21 mg, 6 mol-%, 0.01818 mmol), K_3PO_4 (202 mg, 0.91302 mmol), and 1,4-dioxane (3 ml), **4c** was isolated as a red solid (60 mg, 52 %); mp 231-232°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.20 (s, 3H, CH_3), 6.81 (d, J = 8.2 Hz, 2H, ArH), 7.10 (d, J = 8.1 Hz, 2H, ArH), 7.22 - 7.26 (m, 4H, ArH), 7.10 (t, J = 7.8 Hz, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 33.0 (NCH_3), 107.8, 112.6, 119.2, 124.5, 127.2, 128.4 (C), 129.2, 130.9 (CH), 132.5, 134.9 (C), 140.7, 144.1, 146.6, 151.3 (CH), 156.4, 180.9 (CO). IR (KBr, cm^{-1}): ν = 3074, 2952, 2919, 2851 (w), 1743, 1724 (s), 1605, 1586, 1565, 1499 (m). GC-MS (EI, 70 eV): *m/z* (%) = 381 ([M]$^+$, 2x [^{35}Cl],100), 352 (23), 252 (11), 250 (16) . HRMS (EI, 70 eV) calcd for $C_{21}H_{13}{}^{35}Cl_2NO_2$ ([M]$^+$, 2x [^{35}Cl]): 381.03233; found: 381.03211.

1-Methyl-4,7-di*p*-tolylindoline-2,3-dione (4d):



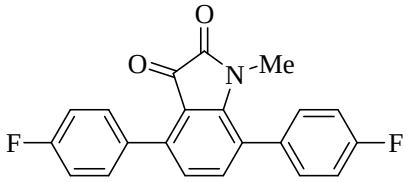
Starting with **2** (70 mg, 0.3043 mmol) , **3d** (90 mg, 0.6695 mmol), $Pd(PPh_3)_4$ (21 mg, 6 mol-%, 0.01818 mmol), K_3PO_4 (202 mg, 0.91302 mmol), and 1,4-dioxane (3 ml), **4d** was isolated as a red solid (60 mg, 58 %); mp154-155°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 6H, 2xCH_3), 3.19 (s, 3H, CH_3), 6.73 (d, J = 8.3 Hz, 2H, ArH), 6.99 (d, J = 8.0 Hz, 2H, ArH), 7.16 (t, J = 7.8 Hz, 4H, ArH), 7.57 (t, J = 8.3 Hz, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 26.8 (2xCH_3), 33.7 (NCH_3), 108.1, 113.7, 120 (CH), 125.7, 129.7 (C), 131.8, 137.5, 139.2 (CH), 143.3, 145.0, 147.6, 147.6, 152.2, 157.9 (C), 165.4, 181.9 (CO). IR (KBr, cm^{-1}): ν = 3074, 2952, 2918, 2851 (w), 1743, 1724 (s), 1605, 1586, 1564, 1497 (m). GC-MS (EI, 70 eV): *m/z* (%) = 341 ([M]$^+$,100), 244 (23), 232 (11), 210 (16), 164 (10) . HRMS (EI, 70 eV) calcd for $C_{23}H_{19}NO_2$ ([M]$^+$): 341.14158, found: 341.14124.

4,7-Bis(4-ethylphenyl)-1-methylindoline-2,3-dione (4e):



Starting with **2** (70 mg, 0.3043 mmol) , **3e** (100 mg, 0.6695 mmol), $Pd(PPh_3)_4$ (21 mg, 6 mol-%, 0.01818 mmol), K_3PO_4 (202 mg, 0.91302 mmol), and 1,4-dioxane (3 ml), **4e** was isolated as a red solid (73 mg, 65 %); mp 123-125°C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (m, 6H, 2xCH_3), 2.22 (m, 4H, 2xCH_2), 3.19 (s, 3H, CH_3), 6.73 (dd, *J* = 8.3, 2.4 Hz, 2H, ArH), 6.99 (d, *J* = 8.0 Hz, 2H, ArH), 7.16 (d, *J* = 7.8 Hz, 4H, ArH), 7.57 (t, *J* = 8.3 Hz, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 20.8 (2xCH_3), 24.6 (2xCH_2), 33.7 (NCH_3), 37.1 (C), 119.1, 124.8, 125.0, 128.7, 128.8, 129.6 (CH), 130.7, 130.9, 132.4, 132.5, 134.9, 144.1, 146.6 (C), 160.4, 180.2 (CO). IR (KBr, cm^{-1}): *v* = 3074, 2952, 2918, 2851 (w), 1743, 1724 (s), 1605, 1586, 1564, 1497 (m). GC-MS (EI, 70 eV): *m/z* (%) = 369 ($[M]^+$,100), 344 (23), 332 (11), 210 (16), 164 (10), 154 (23) . HRMS (EI, 70 eV) calcd for $C_{25}H_{23}NO_2$ ($[M]^+$): 369.17288, found: 369.17255.

4,7-Bis(4-fluorophenyl)-1-methylindoline-2,3-dione (4f):

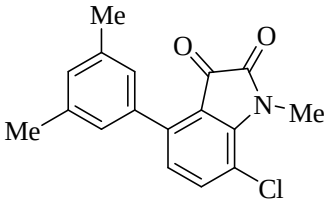


Starting with **2** (70 mg, 0.3043 mmol) , **3f** (92 mg, 0.6695 mmol), $Pd(PPh_3)_4$ (21 mg, 6 mol-%, 0.01818 mmol), K_3PO_4 (202 mg, 0.91302 mmol), and 1,4-dioxane (3 ml), **4f** was isolated as a red solid (76 mg, 72 %); mp 190-192°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.10 (s, 3H, CH_3), 6.75 - 6.79 (m, 2H, ArH), 6.94 - 7.05 (m, 4H, ArH), 7.31 (t, *J* = 8.2 Hz, 2H, ArH), 7.46 - 7.50 (m, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 19.6 (NCH_3), 69.2, 77.2, 100.6 (d, J = 26.4 Hz), 100.7 (d, J = 22.6 Hz), 100.8 (d, J = 20.6 Hz), 110.9 (d, J = 30.6 Hz)(CH), 115.2 (q, $J_{F,C}$ = 322.1 Hz), 115.5 (q, $J_{F,C}$ = 280.1 Hz)(CF), 124.4, 125.7, 128.9 (C), 130.2 (q, $J_{F,C}$ = 280.1 Hz)(CF), 130.9 (q, $J_{F,C}$ = 280.1 Hz)(CF), 146.2 (C), 160.3, 180.1 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -114.4, -112.0 (ArF). IR (KBr, cm^{-1}): *v* = 3273, 3065, 2957, 2922, 2851 (w), 1782 (s), 1727, 1716, 1687, 1603, 1580 (w). GC-MS (EI, 70 eV): m/z (%) = 394 ($[M]^+$, 100), 370 (17), 369 (30), 265 (10), 255 (23), 188 (34), 165 (12). HRMS (EI, 70 eV) calcd for $C_{21}H_{13}F_2NO_2$ $[M]^+$: 349.09144 ; found: 349.09100.

General procedure for synthesis (5a-d,f-m)

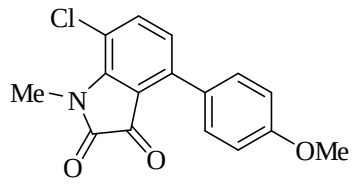
The reactions were carried out in a pressure tube.To a 1,4-dioxane suspension (3 ml) of **2** (70 mg, 0.3043 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), and arylboronic acid (0.365 mmol) was added K_3PO_4 (96 mg, 0.4565 mmol), The mixture was heated at 70°C under Argon atmosphere for 6 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 x 25 ml). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, EtOAc / heptane = 8:2).

7-Chloro-4-(3,5-dimethylphenyl)-1-methylindoline-2,3-dione (5a):



Starting with **2** (70 mg, 0.3043 mmol), **3a** (65 mg, 0.365 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), and 1,4-dioxane (3 ml), **5a** was isolated as a red solid (57 mg, 63 %); mp 124-125°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 6H, 2xCH_3), 3.59 (s, 3H, CH_3), 6.87 (d, *J* = 8.4 Hz, 1H, ArH), 7.11-7.16 (m, 3H, ArH), 7.41 (d, *J* = 8.3 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.2 (2xCH_3), 28.9 (NCH_3), 114.9 (C), 125.5, 125.9, 130.0 (CH), 134.0, 136.8 (C), 138.5 (CH), 141.5, 142.3, 145.6, 146.1 (C), 157.2, 180.0 (CO). IR (KBr, cm^{-1}): *v* = 3446, 3073, 3047, 3032, 2950, 2922, 2853 (w), 1727 (s), 1637 (w), 1585, 1581, 1557 (w). GC-MS (EI, 70 eV): *m/z* (%) = 299 ($[M]^+$, [^{35}Cl],100), 272 (12), 255 (23), 250 (30), 246 (11), 244 (16), 228 (15), 222 (18), 221 (25), 199 (17). HRMS (EI, 70 eV) calcd for $C_{17}H_{14}{}^{35}ClNO_2$ ($[M]^+$): 299,07076 ; found: 299.07033.

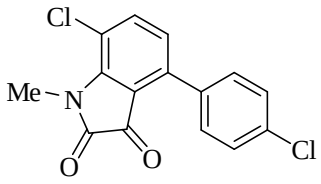
7-Chloro-4-(4-methoxyphenyl)-1-methylindoline-2,3-dione (5b):



Starting with **2** (70 mg, 0.3043 mmol), **3b** (54 mg, 0.356 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), and 1,4-dioxane (3 ml), **5b** was isolated as a red solid (76 mg, 83 %); mp 114-115°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.47 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 6.87 (dd, *J* = 4.3, 8.7 Hz, 3H, ArH), 7.32 (d, *J* = 8.6 Hz, 2H, ArH), 7.40 (d, *J* = 8.2 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.9 (NCH_3), 54.5 (OCH_3), 112.7 (CH), 115.3 (C), 126.3

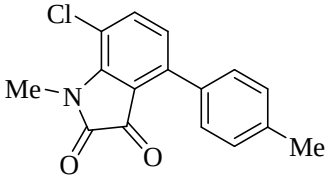
(CH), 127.0, 129.4 (C), 128.6 (CH), 133.9 (C), 138.5 (CH), 141.0, 146.2, 157.4 (C), 159.5, 180.5 (CO). IR (KBr, cm^{-1}): ν = 3068, 3044, 3019, 2999, 2956, 2845 (w), 1741, 1728, 1605, 1591, 1561 (m). GC-MS (EI, 70 eV): *m/z* (%) = 303 ($[M]^+$, [^{37}Cl], 34), 301 ($[M]^+$, [^{35}Cl], 100), 275 (12), 273 (33), 272 (15), 245 (13), 244 (17), 242 (37), 238 (11), 230 (21), 210 (46), 173 (12), 167 (16). HRMS (EI, 70 eV), calcd for $C_{16}H_{12}{}^{37}ClNO_3$ ($[M]^+$): 303.04783 ; found: 303.04707 ; calcd for $C_{16}H_{12}{}^{35}ClNO_3$ ($[M]^+$): 301.04983 ; found: 301.05002.

7-Chloro-4-(4-chlorophenyl)-1-methylindoline-2,3-dione (5c):



Starting with **2** (70 mg, 0.3043 mmol), **3c** (57 mg, 0.365 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), and 1,4-dioxane (3 ml), **5c** was isolated as a red solid (48 mg, 52 %); mp 183-184°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.14 (s, 3H, CH_3), 6.87 (d, *J* = 8.4 Hz, 1H, ArH), 7.28 - 7.34 (m, 4H, ArH), 7.47 (d, *J* = 8.7 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 30.0 (NCH_3), 114.7, 116.1 (C), 125.2, 127.7, 128.9 (CH), 132.2 (C), 138.3 (CH), 138.2, 141.5, 146.2 (C), 160.5, 179.0 (CO). IR (KBr, cm^{-1}): ν = 3077, 2952, 2921, 2852 (w), 1730, 1580, 1558 (s), 1610 (w). GC-MS (EI, 70 eV): *m/z* (%) = 305 ($[M]^+$, 2x[^{35}Cl], 97), 279 (13), 259 (16), 277 (25), 250 (10), 249 (12), 248 (14), 242 (38), 216 (14), 164 (32). HRMS (EI, 70 eV) : calcd for $C_{15}H_9{}^{35}Cl_2NO_2$ ($[M]^+$): 305.00049 ; found: 305.00044.

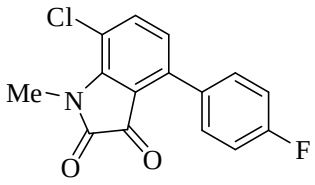
7-Chloro-1-methyl-4-*p*-tolylindoline-2,3-dione (5d):



Starting with **2** (70 mg, 0.3034 mmol), **3d** (49 mg, 0.365 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), and 1,4-dioxane (3 ml), **5d** was isolated as a red solid (69 mg, 79 %); mp 141-142°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 6.82 (d, *J* = 8.4 Hz, 1H, ArH), 7.09 (d, *J* = 8.2 Hz, 2H, ArH), 7.18 (d, *J* = 8.0 Hz, 2H, ArH), 7.38 (d, *J* = 8.0 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.3 (CH_3), 28.8 (NCH_3), 114.7, 115.1 (C), 125.2, 127.7, 127.9 (CH), 131.2 (C), 138.4 (CH), 138.6, 141.1, 146.1, 146.8 (C), 157.5, 180.0 (CO). IR (KBr, cm^{-1}): ν = 3469, 3451, 3089, 3068, 3043, 3026, 3003, 2952,

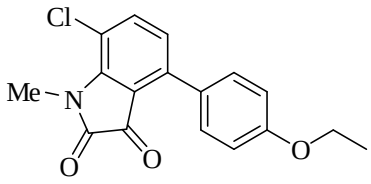
2919, 2854 (w), 1731 (s), 1610 (w), 1589, 1580, 1559 (w). GC-MS (EI, 70 eV): *m/z* (%) = 287 ($[M]^+$, [^{37}Cl], 35), 285 ($[M]^+$, [^{35}Cl], 97), 270 (13), 259 (10), 257 (33), 256 (23), 244 (16), 229 (15), 228 (18), 227 (14), 195 (16). HRMS (EI, 70 eV) calcd for $C_{16}H_{12}{}^{37}ClNO_2$ ($[M]^+$): 287.05271 ; found: 287.05245 ; calcd for $C_{16}H_{12}{}^{35}ClNO_2$ ($[M]^+$): 285.05566 ; found: 285.05522.

7-Chloro-4-(4-fluorophenyl)-1-methylindoline-2,3-dione (5f):



Starting with **2** (70 mg, 0.3043 mmol), **3f** (50 mg, 0.365 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), and 1,4-dioxane (3 ml), **5f** was isolated as a red solid (77 mg, 87 %); mp 202-203°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.59 (s, 3H, CH_3), 6.90 (d, J = 8.9 Hz, 1H, ArH), 7.05 (t, J = 8.3 Hz, 2H, ArH), 7.33 - 7.35 (m, 2H, ArH), 7.45 (d, J = 8.5 Hz, 1H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 28.9 (NCH_3), 114.2 (d, J = 21.6 Hz), 115.3 (d, J = 8.2 Hz) (CH), 125.2, 125.6 (CH), 129.8 (q, $J_{F,C}$ = 245.1 Hz, CF), 138.7, 139.9 (d, J = 3.3 Hz), 146.3, 147.1, 157.1 (C), 164.0, 180.1 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.5 (ArF). IR (KBr, cm^{-1}): ν = 3458, 3081, 2956, 2916, 2849 (w), 1736, 1727 (s), 1637 (w), 1596, 1569 (M). GC-MS (EI, 70 eV): *m/z* (%) = 291 ($[M]^+$, [^{37}Cl], 22), 289 ($[M]^+$, [^{35}Cl], 62), 261 (23), 260 (10), 233 (13), 232 (20), 199 (15), 182 (13). HRMS (EI, 70 eV) : calcd for $C_{15}H_9{}^{37}ClFNO_2$ ($[M]^+$): 289.03004 ; found: 289.03004 ; calcd for $C_{15}H_9{}^{35}ClFNO_2$ ($[M]^+$): 291.02709; found: 291.02803.

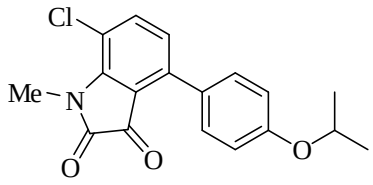
7-Chloro-4-(4-ethoxyphenyl)-1-methylindoline-2,3-dione (5g):



Starting with **2** (70 mg, 0.3043 mmol), **3g** (61 mg, 0.365 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), and 1,4-dioxane (3 ml), **5g** was isolated as a red solid (82 mg, 85 %); mp 154-15°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 (t, J = 8.0 Hz 3H, CH_3), 3.18 (s, 3H, CH_3), 3.32 (q, J = 6.5, 2.8 Hz 2H, CH_2), 7.28 (t, J = 8.0 Hz, 3H, ArH), 7.36 - 7.38 (m, 3H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.9 (CH_3), 28.8 (NCH_3), 58.8 (OCH_2), 113.1 (CH) 126.5, 127.0, 127.4, 127.5 (C), 131.9, 132.2, 134.4 (CH), 131.2, 146.8 (C), 157.5,

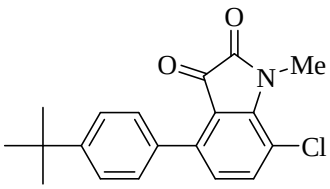
180.0 (CO). IR (KBr, cm^{-1}): ν = 3056, 3021, 2972, 2962, 2923, 2898, 2852 (w), 1726 (s), 1608, 1581, 1559,1514, 1501 (w). GC-MS (EI, 70 eV): *m/z* (%) =317 ($[M]^+$, $[^{37}Cl]$, 34), 315 ($[M]^+$, $[^{35}Cl]$, 100), 287 (21), 259 (27), 258 (21), 242 (23), 230 (20), 224 (20), 196 (67). HRMS (EI, 70 eV) calcd for $C_{17}H_{14}{}^{37}ClNO_3$ ($[M]^+$): 317.06327; found: 317.06310; calcd for $C_{17}H_{14}{}^{35}ClNO_3$ ($[M]^+$): 315.06567; found: 315.06544.

7-Chloro-4-(4-isopropoxyphenyl)-1-methylindoline-2,3-dione (5h):



Starting with **2** (70 mg, 0.3043 mmol), **3h** (64 mg, 0.365 mmol), $Pd(PPh_3)$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), and 1,4-dioxane (3 ml), **5h** was isolated as a red solid (73 mg, 73 %); mp 178-180 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 6.4 Hz, 6H, 2xCH_3), 3.32 (s, 3H, CH_3), 3.61 - 3.65 (m, 1H, CH), 6.80 (d, *J* = 8.2 Hz, 1H, ArH), 6.91 (d, *J* = 8.5 Hz, 2H, ArH), 7.29 - 7.35 (m, 3H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.0 (2xCH_3), 28.9 (NCH_3), 68.9 (OCH), 114.3, 125.9, 139.5, 141.0 (CH), 115.3 (C), 126.3 (CH), 146.6, 138.5, 139.4, 146.1, 146.6, 156.5 (C), 159.5, 178.2 (CO). IR (KBr, cm^{-1}): ν = 3444, 3062, 3022, 2978, 2951, 2945 (w), 1728, 1579 (s), 1563, 1514, 1479 (m). GC-MS (EI, 70 eV): *m/z* (%) = 331 ($[M]^+$, $[^{37}Cl]$, 24), 329 ($[M]^+$, $[^{35}Cl]$, 100), 289 (23), 288 (14), 287 (77), 245 (13), 261 (23), 260 (18), 259 (74), 258 (22), 242 (24), 197 (14). HRMS (EI, 70 eV), calcd for $C_{18}H_{16}{}^{37}ClNO_3$ ($[M]^+$): 331.07895 ; found: 331.07837 ; calcd for $C_{18}H_{16}{}^{35}ClNO_3$ ($[M]^+$): 329.08116 ; found: 329.08132.

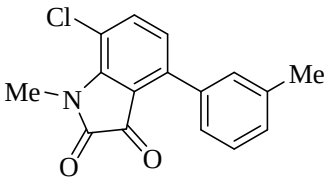
4-(4-Tert-butylphenyl)-7-chloro-1-methylindoline-2,3-dione (5i):



Starting with **2** (70 mg, 0.3043 mmol), **3i** (65 mg, 0.365 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), and 1,4-dioxane (3 ml), **5i** was isolated as a red solid (78 mg, 78 %); mp 104-105°C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.53 (s, 9H, 3xCH_3), 2.34 (s, 3H, CH_3), 6.81 (d, *J* = 8.6 Hz, 2H, ArH), 7.02 (d, *J* = 8.0 Hz, 2H, ArH), 7.18 (d, *J* = 8.0 Hz, 2H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 19.3 (3xCH_3), 35.8 (NCH_3), 114.7, 115.1 (C), 125.2, 127.7, 127.9 (CH), 131.2 (C), 138.4 (CH), 138.6, 141.1, 146.1, 146.8 (C), 157.5, 180.0 (CO). IR

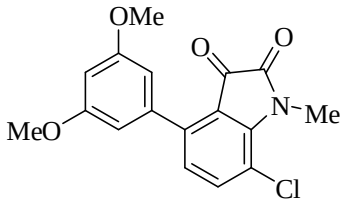
(KBr, cm^{-1}): ν = 3469, 3451, 3089, 3068, 3043, 3026, 3003, 2952, 2919, 2854 (w), 1731 (s), 1610 (w), 1589, 1580, 1559 (w). GC-MS (EI, 70 eV): *m/z* (%) = 327 ([M]$^+$, [^{35}Cl], 97), 270 (13), 259 (10), 257 (33), 256 (23), 244 (16), 229 (15), 228 (18), 227 (14), 195 (16). HRMS (EI, 70 eV) calcd for $C_{19}H_{18}{}^{35}ClNO_2$ ([M]$^+$): 327.10261 ; found: 327.10245.

4-7-Chloro-1-methyl-4-*m*-tolylindoline-2,3-dione (5j):



Starting with **2** (70 mg, 0.3043 mmol), **3j** (49 mg, 0.365 mmol), $Pd(PPh_3)_4$(11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), and 1,4-dioxane (3 ml), **5j** was isolated as a red solid (44 mg, 51 %); mp 211-212°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 6.87 (d, *J* = 8.4 Hz, 1H, ArH), 7.12 - 7.23 (m, 4H, ArH), 7.41 (d, *J* = 8.3 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.3 (CH_3), 28.9 (NCH_3), 115.0, 115.2 (C), 124.8, 125.2, 125.9, 127.1, 128.4, 129.0 (CH), 134.0, 136.9, 140.1, 141.2, 146.1, (C), 157.2, 180.0 (CO). IR (KBr, cm^{-1}): ν = 3447, 3074, 3048, 3033, 2952, 2921, 2854 (w), 1728 (s), 1637 (w), 1588, 1581, 1558 (w). GC-MS (EI, 70 eV): *m/z* (%) = 287 ([M]$^+$, [^{37}Cl], 35), 285 ([M]$^+$, [^{35}Cl], 97), 270 (13), 259 (10), 257 (33), 256 (23), 244 (16), 229 (15), 228 (18), 227 (14), 195 (16). HRMS (EI, 70 eV) calcd for $C_{16}H_{12}{}^{37}ClNO_2$ ([M]$^+$): 287.05271 ; found: 287.05245 ; calcd for $C_{16}H_{12}{}^{35}ClNO_2$ ([M]$^+$): 285.05566 ; found: 285.05522.

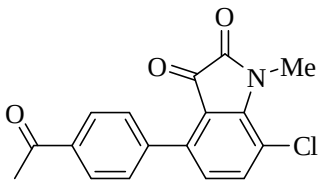
7-Chloro-4-(3,5-dimethoxyphenyl)-1-methylindoline-2,3-dione (5k):



Starting with **2** (70 mg, 0.3043 mmol), **3k** (67 mg, 0.365 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), and 1,4-dioxane (3 ml), **5k** was isolated as a red solid (88 mg, 87 %); mp 121-122°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.58 (3H, CH_3), 3.72 (6H, 2xOCH_3), 6.43 - 6.49 (m, 3H, ArH), 6.92 (d, *J* = 8.7 Hz, 1H, ArH), 7.42 (d, *J* = 8.4 Hz, 1H, ArH).^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 30.0 (NCH_3), 55.5 (2xOCH_3), 101.6, 106.9 (CH), 116.3 (C), 126.8, 128.0, 129.5 (CH), 134.4, 134.6, 135.0, 137.0, 141.3, 147.3, (C), 158.5, 160.5 (CO). IR (KBr, cm^{-1}): ν = 3455, 3094, 3077, 3053, 3011, 2947, 2841 (w), 1731 (s), 1695, 1684,

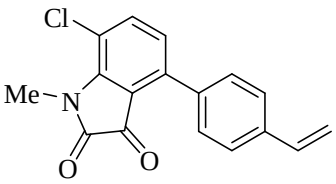
1652, 1646, 1635, 1601(w). GC-MS (EI, 70 eV): *m/z* (%) = 331 ([M]$^+$, [^{35}Cl], 100), 316 (13), 303 (11), 302 (21), 288 (11), 252 (16), 245 (10). HRMS (EI, 70 eV) calcd for $C_{17}H_{14}{}^{35}ClNO_4$ ([M]$^+$): 331.06114 ; found: 331.06122.

4-(4-Acetylphenyl)-7-chloro-1-methylindoline-2,3-dione (5l):



Starting with **2** (70 mg, 0.3043 mmol), **3l** (61 mg, 0.365 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), and 1,4-dioxane (3 ml), **5l** was isolated as a red solid (51 mg, 53 %); mp 74-75°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.52 (s, 3H, $COCH_3$), 3.56 (s, 3H, CH_3), 6.95 (d, *J* = 8.4 Hz, 1H, ArH), 7.49 (t, *J* = 8.7 Hz, 3H, ArH), 7.93 (d, *J* = 8.8 Hz, 2H, ArH).^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 26.7 ($COCH_3$), 30.7 (NCH_3), 116.2, 117.1 (C), 127.4, 128.1 (CH), 128.3 (C), 129.1 (CH), 130.8, 133.2, 137.4 (C), 139.9 (CH), 158.5 (C), 181.1, 197.5 (CO). IR (KBr, cm^{-1}): *v* = 3072, 3058, 3006, 2958, 2921, 2850 (w), 1731, 1681, 1583, 1556 (s). GC-MS (EI, 70 eV): *m/z* (%) = 315 ([M]$^+$, [^{37}Cl], 30), 313 ([M]$^+$, [^{35}Cl], 88), 298 (28), 285 (11), 272 (33), 271 (16), 244 (14), 242 (40), 214 (13), 207 (11), 180 (36), 164 (22), 150 (25). HRMS (EI, 70 eV), calcd for $C_{17}H_{12}{}^{37}ClNO_3$ ([M]$^+$): 315.04707 ; found: 315.04762 ; calcd for $C_{17}H_{12}{}^{35}ClNO_3$ ([M]$^+$): 313.05002 ; found: 313.04983.

7-Chloro-1-methyl-4-(4-vinylphenyl)indoline-2,3-dione (5m):



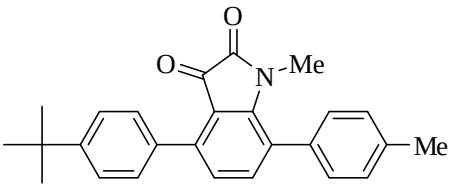
Starting with **2** (70 mg, 0.3043 mmol), **3m** (53 mg, 0.365 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), and 1,4-dioxane (3 ml), **5m** was isolated as a red solid (44 mg, 49 %); mp 188-189°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.56 (3H, CH_3), 5.09 (d, *J* = 1.8 Hz, 1H, CH), 5.76 (d, *J* = 1.9 Hz, 1H, CH), 6.67 (q, *J* = 7.06, 2.16 Hz, 1H, CH), 6.91 (d, *J* = 8.9 Hz, 2H, ArH), 7.33 - 7.42 (m, 4H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 29.9 (NCH_3), 115.12 (CH_2), 116.59 (C), 126.12, 126.31, 126.86, 129.18 (CH), 13451, 136.23, 138.61 (C), 139.75 (CH), 140.43, 141.73 (C), 158.30, 180.11 (CO). IR (KBr, cm^{-1}): *v* = 3449, 3067, 2944, 2922, 2851 (w), 1734 (s), 1627 (w), 1581 (s), 1554, 1478, 1458, 1438 (w). GC-MS (EI, 70 eV): *m/z* (%) = 299 ([M]$^+$, [^{37}Cl], 34), 297 ([M]$^+$, [^{35}Cl], 100), 271 (14), 270 (17), 269

(42), 268 (30), 252 (16), 242 (21), 240 (40), 239 (11), 234 (18). HRMS (EI, 70 eV), calcd for $C_{17}H_{12}{}^{37}ClNO_2$ ($[M]^+$): 299.05216; found: 299.05303; calcd for $C_{17}H_{12}{}^{35}ClNO_2$ ($[M]^+$): 297.05511 ; found: 297.05455.

General procedure for synthesis (6a-c)

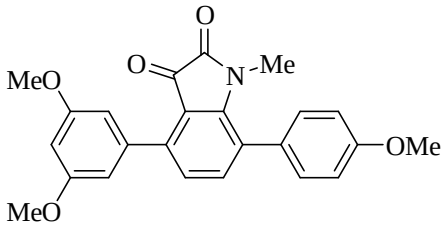
The reactions were carried out in a pressure tube.To a 1,4-dioxane suspension (3 ml) of **2** (70 mg, 0.304 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), and arylboronic acid $Ar^1B(OH)$ (0.365 mmol) was added K_3PO_4 (96 mg, 0.4565 mmol), The mixture was heated at 70 °C under Argon atmosphere for 6 h. The mixture was cooled to 20°C. arylboronic acid $Ar^2B(OH)$ (0.365 mmol) was added $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), The mixture was heated at 120 °C under Argon atmosphere for 6 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 x 25 ml). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, EtOAc / heptane = 8:2).

4-(4-Tert-butylphenyl)-1-methyl-7-*p*-tolylindoline-2,3-dione (6a):



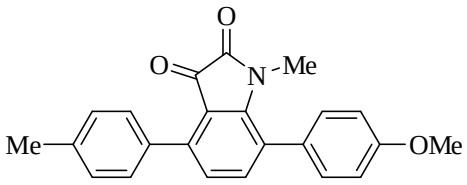
Starting with **2** (70 mg, 0.3043 mmol) , **3i** (65 mg, 0.365 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), **3d** (49 mg, 0.365 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), and 1,4-dioxane (3 ml), **6a** was isolated as a red solid (66 mg, 57 %); mp 172-174°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 9H, 3xCH_3), 2.31 (s, 3H, CH_3), 3.19 (s, 3H, CH_3), 6.71 (d, *J* = 8.4 Hz, 2H, ArH), 6.66 (d, *J* = 8.1 Hz, 2H, ArH), 7.11 (t, *J* = 7.3 Hz, 4H, ArH), 7.57 (d, *J* = 8.3 Hz, 2H, ArH).^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 19.1 (3xCH_3), 20.2 (NCH_3), 33.7 (CH_3), 124.1, 124.5 (C), 124.7, 127.7, 127.9, 128.5 (CH), 132.0, 133.4 (C), 137.2, 139.6 (CH), 141.2, 147.8, 148.3, 151.1 (C), 158.3, 181.9 (CO). IR (KBr, cm^{-1}): *v* = 3074, 2952, 2918, 2851 (w), 1743, 1724 (s), 1605, 1586, 1564, 1497 (m). GC-MS (EI, 70 eV): *m/z* (%) = 383 ($[M]^+$,100), 369 (27), 368 (94), 340 (18), 327 (22), 326 (30), 313 (12), 312 (43), 310 (10), 299 (10), 296 (11), 284 (10), 283 (12), 282(10), 141 (22). HRMS (EI, 70 eV) calcd for $C_{26}H_{25}NO_2$ ($[M]^+$): 383.18853, found: 383.18788.

4-(3,5-Dimethoxyphenyl)-7-(4-methoxyphenyl)-1-methylindoline-2,3-dione (6b):



Starting with **2** (70 mg, 0.3043 mmol) , **3k** (67 mg, 0.365 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), **3b** (54 mg, 0.365 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), and 1,4-dioxane (3 ml), **6b** was isolated as a red solid (86 mg, 70 %); mp 172-174°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3H, CH_3), 3.59 (s, 9H, 3xOCH_3), 6.70 (d, J = 8.4 Hz, 2H, ArH), 7.12 (t, J = 7.3 Hz, 5H, ArH), 7.55 (d, J = 8.3 Hz, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 20.2 (NCH_3), 33.7 (3xOCH_3), 124.1, 124.5 (C), 124.7, 127.7, 127.9, 128.5 (CH), 132.0, 133.4 (C), 137.2, 139.6, 140.1 (CH), 141.2, 147.8, 148.3, 151.1, 152.3 (C), 168.3, 180.9 (CO). IR (KBr, cm^{-1}): ν = 3070, 2951, 2917, 2851 (w), 1747, 1723 (s), 1604, 1585, 1564, 1497 (m). GC-MS (EI, 70 eV): *m/z* (%) = 403 ($[M]^+$,100), 379 (27), 378 (94), 350 (18), 337 (22), 323 (12), 322 (43), 320 (10), 289 (10), 286 (11), 284 (13), 283 (12), 282(10), 141 (22). HRMS (EI, 70 eV) calcd for $C_{24}H_{21}NO_5$ ($[M]^+$): 403.14197, found: 403.14145.

7-(4-Methoxyphenyl)-1-methyl-4-*p*-tolylindoline-2,3-dione (6c):



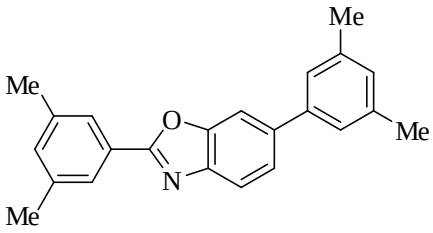
Starting with **2** (70 mg, 0.3043 mmol) , **3d** (49 mg, 0.365 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), **3b** (55 mg, 0.365 mmol), $Pd(PPh_3)_4$ (11 mg, 3 mol-%, 0.00952 mmol), K_3PO_4 (96 mg, 0.4565 mmol), and 1,4-dioxane (3 ml), (**6c**) was isolated as a red solid (74 mg, 68 %); mp 172-174°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3H, CH_3), 3.54 (s, 3H, OCH_3), 6.71 (d, J = 8.1 Hz, 2H, ArH), 6.64 (d, J = 8.6 Hz, 2H, ArH), 7.11- 7.15 (m,4H, ArH), 7.50 (d, J = 8.0 Hz, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 20.2 (NCH_3), 33.7 (OCH_3), 124.1, 124.5 (C), 124.7, 127.7, 127.9, 128.5 (CH), 132.0, 133.4 (C), 137.2, 139.6 (CH), 141.2, 147.8, 148.3, 151.1 (C), 158.3, 181.9 (CO). IR (KBr, cm^{-1}): ν = 3174, 2952, 2818, 2751 (w), 1843, 1824 (s), 1705, 1686, 1564, 1497 (m). GC-MS (EI, 70 eV): *m/z* (%) = 357 ($[M]^+$,100), 349 (27), 348

(94), 340 (18), 326 (30), 310 (17), 283 (13), 280 (10), 145 (22). HRMS (EI, 70 eV) calcd for $C_{23}H_{19}NO_3$ ($[M]^+$): 357.13649; found: 357.13623.

General procedure for synthesis (8a-e)

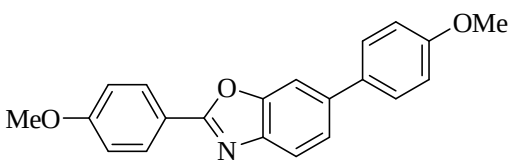
The reactions were carried out in a pressure tube. To a 1,4-dioxane suspension (3 ml) of **7** arylboronic acid (2.2 equiv.), aqueous K_2CO_3 and $Pd(PPh_3)_4$ (6 mol-%) was heated at 120 °C for 8 h under argon atmosphere. After cooling to 20°C, H_2O was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 25 ml). The organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silicagel, heptane/EtAOc = 8:2).

2,6-Bis(3,5-dimethylphenyl)benzoxazole (**8a**)**:**



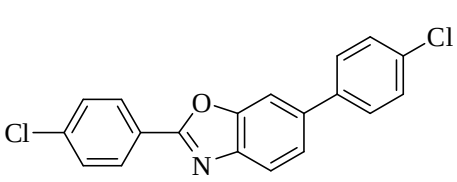
Starting with **7** (70 mg, 0.372 nmol), **3a** (122 mg, 0.8184 mmol) and $Pd(pph_3)_4$ (26 mg, 6mol-%, 0.0225 mmol) , K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **8a** was isolated as a white solid (109 mg, 89 %), mp 169-170°C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 6H, 2xCH_3), 2.34 (s, 6H, 2xCH_3), 6.94 (br. s, 1H, ArH), 7.09 (br. s, 1H, ArH), 7.17 (br. s, 2H, ArH), 7.48 (dd, *J* = 1.8, 8.0 Hz, 1H, ArH) 7.67 - 7.70 (m, 2H, ArH), 7.82 (br. s, 2H, ArH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.25 (2xCH_3), 22.70 (2xCH_3), 109.0, 119.6, 124.1, 125.3, 125.41 (CH), 126.9 (C), 129.0, 133.3 (CH), 133.3, 138.4, 138.6, 139.1, 140.9, 141.3, 151.3, 125.3, 129.0 (C). IR (KBr, cm^{-1}): ν = 3008, 2951, 2916, 2855, 2732, 1888, 1760, 1737, 1619 (w),1592, 1551, 1459, 1410 (m). GC-MS (EI, 70 eV): *m/z* (%) = 328 ($[M+H]^+$, 23), 327 ($[M]^+$, 100), 311 (10). HRMS (EI, 70 eV) calcd for $C_{23}H_{21}NO$ $[M]^+$: 327.16177 ; found: 327.16159 .

2,6-Bis(4-methoxyphenyl)benzoxazole (8b):



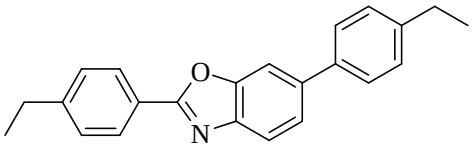
Starting with **7** (70 mg, 0.372 mmol), **3b** (124 mg, 0.8184 mmol) and $Pd(pph_3)_4$ (26 mg, 6mol-%, 0.0225 mmol) , K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **8b** was isolated as a white solid (108 mg, 88 %), mp 180-182ºC.^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (d, J = 8.0 Hz, 6H, 2xOCH_3), 6.93 (t, J = 7.4 Hz, 4H, ArH), 7.42-7.45 (m, 3H, ArH), 7.61-7.67 (m, 2H, ArH), 8.12 (d, J = 8.5 Hz, 2H, ArH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 55.3, 55.4 (OCH_3), 107.3, 113.3, 113.4, 118.4 (CH), 118.7 (C), 122.6, 127.3, 128.3 (CH),132.4, 137.1, 140.1, 150.3, 158.2, 161.2, 162.3 (C). IR (KBr, cm^{-1}): ν = 3071, 3038, 3012, 2955 (w), 2920, 2851 (s), 2548, 2478, 2418, 2402, 1892, 1730 (w), 1614, 1603, 1580, 1556, 1520 (m). GC-MS (EI, 70 eV): *m/z* (%) = 332 ($[M+H]^+$, 23), 331 ($[M]^+$, 100), 317 (10), 316 (46), 288 (10), 165 (14). HRMS (EI, 70 eV) calcd for $C_{21}H_{17}NO_3$ $[M]^+$: 331.12029 ; found: 331.120195.

2,6-Bis(4-chlorophenyl)benzoxazole (**8c**):



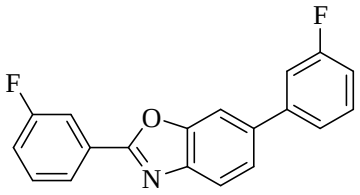
Starting with **7** (70 mg, 0.372 mmol), **3c** (122 mg, 0.8184 mmol) and $Pd(pph_3)_4$ (26 mg, 6 mol-%, 0.0225 mmol), K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **8a** was isolated as a white solid (95 mg,75 %), mp 370-372ºC .^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (dd, J = 2.2, 8.2 Hz, 1H, ArH), 7.41 (d, J =8.6 Hz, 2H, ArH), 7.54 - 7.58 (m, 3H, ArH), 7.59 - 7.65 (m, 3H, ArH), 8.22 (d, J = 8.7 Hz, 2H, ArH).^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 110.2, 119.4, 124.3 (CH), 124.7 (C), 126.4, 127.1, 127.3, 128.1 (CH), 129.7, 133.3, 137.2, 139.9, 142.1, 149.9, 162.3 (C). IR (KBr, cm^{-1}): ν = 3092, 3066, 3044, 3028, 2923, 2852, 1927, 1910, 1878, 1616, 1602, 1580, 1564, 1551, 1513 (w) . GC-MS (EI, 70 eV): *m/z* (%) = 340 ($[M]^+$,2x[^{35}Cl], 100), 305 (15), 98 (17) . HRMS (EI, 70 eV) calcd for $C_{19}H_{11}{}^{35}Cl_2NO$ ($[M]^+$, 2x[^{35}Cl]): 340.2013 found 340.0301.

2,6-Bis(4-ethylphenyl)benzoxazole (**8d**):



Starting with **7** (70 mg, 0.372 nmol), **3e** (97 mg, 0.8184 mmol) and $Pd(pph_3)_4$ (26 mg, 6 mol-%, 0.0225 mmol) , K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **8d** was isolated as a white solid (108 mg, 88 %), mp 74-77°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.5 Hz, 6H, 2xCH_3), 2.68 (q, J = 7.5 Hz, 4H, 2xCH_2), 7.21 (d, J = 8.0 Hz, 2H, ArH), 7.26 (d, J = 8.0 Hz, 2H, ArH), 7.46-7.50 (m, 3H, ArH), 7.66 - 7.70 (m, 2H, ArH), 8.10 (d, J = 8.0 Hz, 2H, ArH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.2, 15.5 (CH_3), 28.5, 28.9 (CH_2), 108.8, 119.7, 123.9 (CH), 124.6 (C), 127.3, 127.7, 128.4, 128.5 (CH), 138.3, 138.7, 141.3, 143.6, 148.2, 151.3, 163.6 (C). IR (KBr, cm^{-1}): ν = 3023 (w), 2959, 2926, 2868, 1617 (m), 1603, 1577, 1567, 1551, 1520 (w). GC-MS (EI, 70 eV): *m/z* (%) = 328 ($[M+H]^+$, 25), 327 ($[M]^+$, 100), 312 (60), 297 (19), 152 (10), 148 (17). HRMS (EI, 70 eV) calcd for $C_{23}H_{21}NO$ $[M]^+$: 327.16177; found: 327.161480 .

2,6-Bis(3-fluorophenyl)benzoxazol (8e):



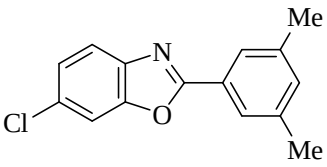
Starting with **7** (70 mg, 0.372 mmol), **3n** (112 mg, 0.8184 mmol), $Pd(PPh_3)_4$ (26 mg, 6 mol-%, 0.0225 mmol), K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **8e** was isolated as a white solid (86 mg , 75 %), mp 100°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14-7.18 (m, 2H, ArH), 7.21 - 7.25 (m, 1H, ArH), 7.30 -7.33 (m, 1H, ArH), 7.35 (d, J = 8.15 Hz, 1H, ArH), 7.38 - 7.40 (m, 1H, ArH), 7.48 (dd, J = 2.71 , 8.15 Hz, 1H, ArH), 7.67 (d, J = 2.10 Hz, 1H, ArH), 7.72 (d, J = 8.06 Hz, 1H, ArH), 7.84 - 7.88 (m, 1H, ArH), 7.95 - 7.98 (m, 1H, ArH) .^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 108.1 (CH), 114.1 (d, $J_{C,F}$ = 21.0 Hz,CH), 114.2 (d, $J_{C,F}$ = 21.0 Hz,CH), 114.4 (d, $J_{C,F}$ = 21.8 Hz,CH), 117.5 (d, $J_{C,F}$ = 21.1 Hz,CH), 119.2 (CH), 121.9 (d, $J_{C,F}$ = 2.7 Hz,CH), 122.3 (d, $J_{C,F}$ = 2.7 Hz,CH), 123.2 (CH), 130.4 (d, $J_{C,F}$ = 8.4 Hz,CH), 130.6 (d, $J_{C,F}$ = 8.0 Hz,CH), 136.9 (d, $J_{C,F}$ = 2.3 Hz,C), 140.7, 141.8, 141.9 (C), 161.4 (d, $J_{C,F}$ = 3.5 Hz,C), 163.5 (d, $J_{C,F}$ = 247.5 Hz,CF), 163.8 (d, $J_{C,F}$ = 245.5 Hz,CF), 150.3 (C). ^{19}F NMR (282.40 MHz , $CDCl_3$): δ = -111.6, -112.6 (ArF) . IR (KBr, cm^{-1}): ν = 3088.9, 3069.3, 2954.1, 2922.3, 2852.5, 1946.2, 1873.5, 1789.0, 1731.0, 1608.6 (w), 1577.2, 1556.6 (m).

GC-MS (EI, 70 eV): *m/z* (%) = 308 ($[M+H]^+$, 20), 307 ($[M]^+$, 100), 157 (33). HRMS (EI,70eV) calcdfor $C_{19}H_{11}F_2NO[M]^+$: 307.08032; found: 307.080780.

General procedure for synthesis (9a-n)

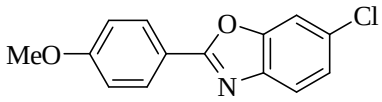
The reactions were carried out in a pressure tube. To a 1,4-dioxane suspension (3 ml) of **7** arylboronic acid (1.2 equiv.), aqueous K_2CO_3 and $Pd(PPh_3)_4$ (3 mol-%) was heated at 80 °C for 6 h under argon atmosphere. After cooling to 20°C, H_2O was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 25 ml). The organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silicagel, heptane/EtOAc = 9:1).

6-Chloro-2-(3,5-dimethyl)benzoxazole(9a):



Starting with **7** (70 mg, 0.372 nmol), **3a** (66 mg, 0.446 mmol) and $Pd(pph_3)_4$ (13 mg, 3 mol-%, 0.01125 mmol), K_2CO_3 (2M, 1.0 ml), and 1,4-dioxane (3 ml), **9a** was isolated as a white solid (86 mg, 90 %), mp 98-100°C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 6H, 2xCH_3), 7.09 (dr, s, 1H, ArH), 7.24 (dd, *J* = 1.9, 8.4 Hz, 1H, ArH), 7.48 (d, *J* = 2.0 Hz, 1H, ArH), 7.56 (d, *J* = 8.4 Hz, 1H, ArH), 8.07 (br, s, 2H, ArH).^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.1 (2xCH_3), 110.1, 116.6, 119.2 (C), 123.3, 124.1, 124.3 (CH), 125.3 (C), 127.3 (CH), 129.4 (C), 132.5 (CH), 139.8, 149.8 (C). IR (KBr, cm^{-1}): *v* = 1865, 17321, 1616, 1600 (w), 1556, 1451, 1425 (m). GC-MS (EI, 70 eV): *m/z* (%) = GC-MS (EI, 70 eV): *m/z* (%) = 259 ($[M]^+$, [^{37}Cl], 33), 258 ($[M+H]^+$, [^{35}Cl], 22), 257 ($[M]^+$, [^{35}Cl], 100), 256 (20), HRMS (ESI-TOF/MS): calcd for $C_{15}H_{12}{}^{37}ClNO_2$ ($[M+H]^+$, [^{37}Cl]): 259.05724, found 259.057595, calcd for $C_{15}H_{12}{}^{35}ClNO_2$ ($[M+H]^+$, [^{35}Cl]): 257.06019; found: 257.060137.

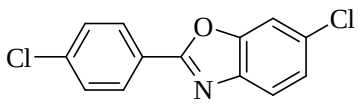
6-Chloro-2-(4-methoxyphenyl)benzoxazole (9b):



Starting with **7** (70 mg, 0.372 nmol), **3b** (67 mg, 0.446 mmol) and $Pd(pph_3)_4$ (13 mg, 3 mol-%, 0.01125 mmol), K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **9b** was isolated as a white solid (87 mg, 90 %), mp140-142°C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H, OCH_3), 6.94 (d, *J* = 9.1

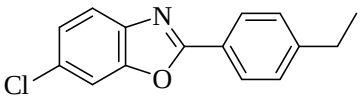
Hz, 2H, ArH), 7.22 (dd, *J* = 1.9, 8.4 Hz, 1H, ArH), 7.46 (d, *J* = 2.0 Hz, 1H, ArH), 7.54 (d, *J* = 8.4 Hz, 1H, ArH), 8.07 (d, *J* = 9.0 Hz, 2H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 111.0, 114.4 (CH), 119.1 (C), 120.0, 125.0, 129.4 (CH), 130.0, 141.0, 150.8, 162.5, 163.8 (C). IR (KBr, cm): *v* = 3073, 3042, 3004, 2978, 2946, 2902, 2840, 2038, 1917, 1866 (w), 1616, 1601 (m), 1580 (w), 1502 (m), 1467 (w). GC-MS (EI, 70 eV): *m/z* (%) = 261 ($[M]^+$, $[^{37}Cl]$, 30), 260 ($[M+H]^+$, $[^{35}Cl]$, 15), 259 ($[M]^+$, $[^{35}Cl]$, 100), 244 (32), 216 (27) . HRMS (ESI-TOF/MS) calcd for $C_{14}H_{10}{}^{35}Cl\ NO_2$ ($[M+H]^+$, $[^{35}Cl]$): 260.478 :found 260.046 .

6-Chloro-2-(4-chlorophenyl)benzoxazole (**9c**)**:**



Starting with **7** (70 mg, 0.372 mmol), **3c** (66 mg, 0.446 mmol) and $Pd(pph_3)_4$ (13 mg, 3 mol-%, 0.01125 mmol), K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **9c** was isolated as a white solid (86 mg, 88 %), mp 197-200ºC .^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (dd, *J* = 1.9, 8.5 Hz, 1H, ArH), 7.35 - 7.39 (m, 1H, ArH), 7.49 - 7.53 (m, 2H, ArH), 7.63 (d, *J* = 8.5 Hz, 2H, ArH), 8.22 (d, *J* = 8.36 Hz, 1H, ArH).^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 111.2, 120.4, 125.3, 125.7, 129.1 (CH), 130.7, 134.3, 138.2, 140.9, 143.1, 150.9 (C). IR (KBr, cm^{-1}): *v* = 3091, 3065, 3043, 3027, 2922, 2851, 1926, 1909, 1879, 1615, 1601, 1579, 1563, 1550, 1512 (w) . GC-MS (EI, 70 eV): *m/z* (%) = 266 ($[M]^+$,$[^{37}Cl]$, 34), 265 ($[M+H]^+$, $[^{35}Cl]$, 21), 264 ($[M]^+$,$[^{35}Cl]$, 100), 242 (19), 63 (13) . HRMS (EI, 70 eV) calcd for $C_{13}H_7{}^{37}Cl_2\ NO$ ($[M]^+$, $[^{37}Cl]$): 266.04159 found 266.04216. calcd for $C_{13}H_7{}^{35}Cl_2\ NO$ ($[M]^+$, $[^{35}Cl]$): 264.04454; found : 264.04216.

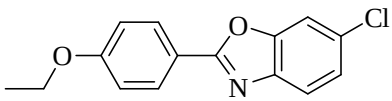
6-Chloro-2-(4-ethylphenyl)benzoxazole (**9d**)**:**



Starting with **7** (70 mg, 0.372 mmol), **3e** (53 mg, 0.446 mmol) and $Pd(pph_3)_4$ (13 mg, 3 mol-%, 0.01125 mmol), K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **9d** was isolated as a white solid (78 mg, 81 %), mp 90-92ºC.^{1}H NMR (300 MHz, $CDCl_3$): δ =1.21 (t, *J* = 7.3 Hz 3H, CH_3), 2.65 (q, *J* = 7.5 Hz 2H, CH_2), 7.25 (m, 3H, ArH), 7.49 (d, J = 1.8 Hz, 1H, ArH), 7.57 (d, J =8.4 Hz, 1H, ArH), 8.05 (d, J = 8.2 Hz, 2H, ArH).^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.2 (CH_3), 29.7 (CH_2), 111.1 , 120.2 (CH), 124.1 (C),125.1, 127.7, 128.5 (CH), 130.4, 141.0,

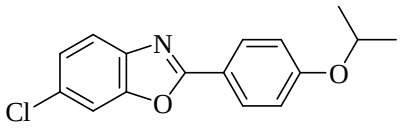
148.6, 150.8, 163.9 (C). IR (KBr, cm^{-1}): ν = 3028, 2961, 2927, 2869, 2852, 1939, 1864, 1741, 1682 (w), 1615 (s), 1602, 1575, 1555, 1496, 1487 (w). GC-MS (EI, 70 eV): *m/z* (%) = 259 ([M]$^+$, [^{37}Cl], 33), 258 ([M+H]$^+$, [^{35}Cl], 21), 257, ([M]$^+$, [^{35}Cl], 100), 256 (15), 244 (33) 243 (18). . HRMS (EI, 70 eV) calcd for $C_{15}H_{12}{}^{37}ClNO$ ([M]$^+$,[^{37}Cl]): 259.05724 found 259.057607. calcd for $C_{15}H_{12}{}^{35}ClNO$ ([M]$^+$, [^{35}Cl]): 259.05724; found : 259.057607.

6-Chloro-2-(4-ethoxyphenyl)benzoxazole (**9e**)**:**



Starting with **7** (70 mg, 0.372 nmol), **3g** (74 mg, 0.446 mmol) and $Pd(pph_3)_4$ (13 mg, 3 mol-%, 0.01125 mmol), K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **9e** was isolated as a white solid (91 mg, 89 %), mp145-147^{o}C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (t, *J* = 2.0 Hz, 3H, CH_3), 3.94 (q, *J* = 1.2, 8.1 Hz, 2H, OCH_2), 6.87 (d, *J* = 8.2 Hz, 2H, ArH), 7.13 (dd, *J* = 1.5, 8.4 Hz, 1H, ArH), 7.54 (d, *J* = 8.2 Hz, 2H, ArH), 8.23 (d, *J* = 8.1 Hz, 2H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 1.34 (CH_3), 58.8 (OCH_2), 111.1, 114.3 (CH), 119.2 (C), 125.4, 129.3, 129.4 (CH), 133.2, 142.2, 153.8, 161.4, 163.5 (C). IR (KBr, cm^{-1}): ν = 3073, 3042, 3004, 2978, 2946, 2902, 2840, 2038, 1917, 1866 (w), 1616, 1601 (m), 1580 (w), 1502 (m).GC-MS (EI, 70 eV): *m/z* (%) = 275 ([M]$^+$, [^{37}Cl], 20), 273 ([M]$^+$, [^{35}Cl], 100), 247 (33), 246 (15), 245 (80), 216 (11) . HRMS (ESI-TOF/MS) calcd for $C_{15}H_{12}{}^{37}Cl\ NO_2$ ([M]$^+$, [^{37}Cl]): 275.05216; found: 275.05252, calcd for $C_{15}H_{12}{}^{35}Cl\ NO_2$ ([M]$^+$, [^{35}Cl]): 273.05511; found: 273.05477.

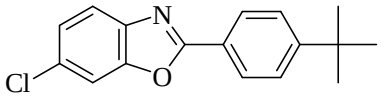
6-Chloro-2-(4-isopropoxyphenyl)benzoxazole (**9f**)**:**



Starting with **7** (70 mg, 0.372 nmol), **3h** (80 mg, 0.446 mmol) and $Pd(pph_3)_4$ (13 mg, 3 mol-%, 0.01125 mmol), K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **9f** was isolated as a white solid (80 mg, 75 %), mp145-147^{o}C .^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 3.5 Hz, 6H, 2xCH_3), 4.49 (q, *J* = 1.3, 8.2 Hz, 1H, OCH), 6.94 (d, *J* = 8.0 Hz, 2H, ArH), 7.59 (dd, *J* = 1.5, 8.4 Hz, 1H, ArH), 7.50 (d, *J* = 8.2 Hz, 2H, ArH), 8.11 (d, *J* = 8.1 Hz, 2H, ArH).^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.97 (2xCH_3), 70.17 (OCH), 121.1, 116.3 (CH), 119.3 (C), 123.2, 125.6, 128.3 (CH), 137.2, 143.2, 154.8, 162.4, 163.3 (C). IR (KBr, cm^{-1}): ν = 3073, 3042, 3004, 2840, 2038, 1917, 1866

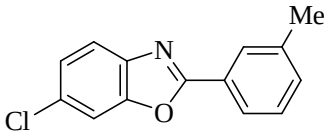
(w), 1616, 1601 (m), 1580 (w), 1502 (m). GC-MS (EI, 70 eV): *m/z* (%) = 287 ($[M]^+$, [^{35}Cl], 100), 247 (33), 246 (16), 245 (90). HRMS (ESI-TOF/MS) calcd for $C_{16}H_{14}{}^{35}Cl\ NO_2$ ($[M]^+$, [^{35}Cl]): 287.07131, found 287.07122.

2-(4-Tert-butylphenyl)-6-chlorobenzoxazole(9g):



Starting with **7** (70 mg, 0.372 mmol), **3i** (79 mg, 0.446 mmol) and $Pd(pph_3)_4$ (13 mg, 3 mol-%, 0.01125 mmol) , K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **9g** was isolated as a white solid (77 mg, 72 %), mp 98^{o}C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.5 (s, 9H, 3xCH_3), 6.47 (dd, J = 1.9, 8.4 Hz, 1H, ArH), 6.71 (m, 3H, ArH), 6.81 (d, J = 8.4 Hz 1H, ArH), 7.29 (d, J = 8.5 Hz 2H, ArH).^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 31.1 (3xCH_3), 35.1 (C), 111.1, 120.3 (CH), 123.8 (C), 125.1, 125.9, 126.2 (CH), 130.4, 141.0, 150.8, 155.4, 163.9 (C) . IR (KBr, cm^{-1}): ν = 3093, 3062, 3041, 2956, 2924, 2902, 2860, 1916, 1692, 1673 (w), 1617 (m), 1601, 1573, 1553 (w), 1495, 1459 (m). GC-MS (EI, 70 eV): *m/z* (%) = 287 ($[M]^+$, [^{37}Cl], 13), 286 ($[M+H]^+$, [^{35}Cl], 10), 285, ($[M]^+$, [^{35}Cl], 100), 272 (34), 271 (19), 242 (17). HRMS (EI, 70 eV) calcd for $C_{17}H_{16}{}^{37}Cl\ NO$ ($[M]^+$, [^{37}Cl]): 287.08854; found: 287.08896, calcd for $C_{17}H_{16}{}^{35}Cl\ NO$ ($[M]^+$, [^{35}Cl]): 285.09149; found: 285.98189 .

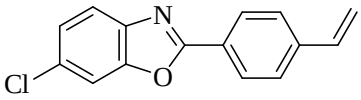
6-Chloro-2-*m*-tolylbenzoxazole (9h):



Starting with **7** (70 mg, 0.372 mmol), **3j** (60 mg, 0.446 mmol) and $Pd(pph_3)_4$ (13 mg, 3 mol-%, 0.01125 mmol), K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **9h** was isolated as a white solid (79 mg, 87 %), mp 99-101^{o}C .^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3H, CH_3), 7.23 (dd, *J* = 2.0, 8.7 Hz, 1H, ArH), 7.27 (d, *J* = 6.3 Hz, 1H, ArH), 7.32 (d, *J* = 8.0 Hz, 1H, ArH), 7.47 (d, *J* =2.1 Hz, 1H, ArH), 7.56 (d, *J* = 8.62 Hz, 1H, ArH), 7.91 (t, *J* = 7.3 Hz, 2H, ArH).^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.3 (CH_3), 111.1, 120.3, 124.7, 125.2 (CH), 126.5 (C), 128.1, 128.8, 130.5 (CH), 132.6, 138.8, 140.8, 150.8, 163.8 (C). IR (KBr, cm^{-1}): ν = 3085, 3063, 3040, 3023, 2953, 2922, 2855, 1955, 1865, 1828, 1789, 1731, 1619, 1602 (w), 1552 (m), 1504 (w), 1485 (m), 1470 (w), 1452, 1427 (m). GC-MS (EI, 70 eV): *m/z* (%) = 245 ($[M]^+$,[^{37}Cl], 34), 244 ($[M+H]^+$, [^{35}Cl], 21), 243, ($[M]^+$, [^{35}Cl], 100), 242 (19), 63 (13) . HRMS (EI, 70 eV) calcd for $C_{14}H_{10}{}^{37}Cl\ NO$ ($[M]^+$,[^{37}Cl]):

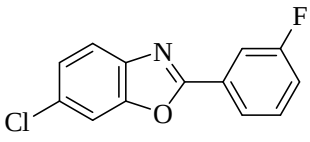
245.04159; found: 245.04216. calcd for $C_{14}H_{10}{}^{35}Cl$ NO ([M]$^+$, [^{35}Cl]): 243.04454; found: 245.04216.

6-Chloro-2-(4-vinylphenyl)benzoxazole (9i):



Starting with **7** (70 mg, 0.372 nmol), **3m** (66 mg, 0.446 mmol) and $Pd(pph_3)_4$ (13 mg, 3 mol-%, 0.01125 mmol), K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **9i** was isolated as a white solid (62 mg, 65 %), mp130-132ºC.^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.33 (d, *J* = 8.0 Hz, 1H, CH), 5.93 (d, *J* = 8.1 Hz, 1H, CH), 6.79 (q, *J* = 1.2, 8.1 Hz, 1H, CH), 6.33 (d, *J* = 8.2 Hz, 2H, ArH), 7.10 (dd, *J* = 1.6, 8.2 Hz, 1H, ArH), 7.30 (d, *J* = 8.5 Hz, 2H, ArH), 8.33 (d, *J* = 8.1 Hz, 2H, ArH).^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 111.2 (CH_2), 136.2 , 117.1, 117.3 (CH), 119.3 (C), 120.1, 125.3, 129.4 (CH), 133.0, 143.1, 152.8, 162.4, 163.2 (C). IR (KBr, cm^{-1}): *v* = 3042, 3004, 2902, 2840, 2038, 1917, 1866 (w), 1616, 1601 (m), 1580 (w), 1502 (m), 1467 (w). GC-MS (EI, 70 eV): *m/z* (%) = 255 ([M]$^+$, [^{35}Cl], 100), 242 (33), 241 (15), 235 (80), 211 (11) . HRMS (ESI-TOF/MS) calcd for $C_{15}H_{10}{}^{35}Cl$ NO ([M]$^+$, [^{35}Cl]): 255.04509; found: 255.04533.

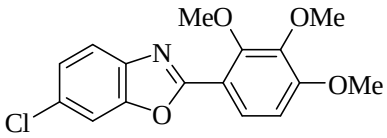
6-Chloro-2-(3-fluorophenyl)benzoxazole(9j):



Starting with **7** (70 mg, 0.372 mmol), **3n** (61 mg, 0.446 mmol), $Pd(PPh_3)_4$ (13 mg, 3 mol-%, 0.01125 mmol), K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **9j** was isolated as a white solid (77 mg , 83 %), mp 122-124°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14 - 7.21 (m, 1H, ArH), 7.28 (dd, *J* = 2.11, 8.23 Hz, 1H, ArH), 7.39 - 7.47 (m, 1H, ArH), 7.53 (d, *J* = 2.11 Hz, 1H, ArH), 7.60 (d, *J* = 8.45 Hz, 1H, ArH), 7.82 - 7.86 (m, 1H, ArH), 7.93-7.96 (m, 1H, ArH).^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 111.3 (CH), 114.55 (d, $J_{C,F}$ = 2.0 Hz, CH), 118.70 (d, $J_{C,F}$ = 21.8 Hz, CH), 120.7 (CH), 123.3 (d, $J_{C,F}$ = 3 Hz, CH), 125.5 (CH), 128.6 (C), 130.7 (d, $J_{C,F}$ =8.0 Hz, CH), 131.1, 140.7, 150.9, 161.2 (C), 163.0 (d, $J_{C,F}$ = 245 Hz, CF) .^{19}F NMR (282.40 MHz , $CDCl_3$): δ = -111.52 (ArF). IR (KBr, cm^{-1}): *v* = 3078, 3065, 3041, 2953, 2921, 2851, 1953, 1937, 1872, 1607.7, 1589 (w), 1555 (m),1519, 1504 (w). GC-MS (EI, 70 eV): *m/z* (%) = 249 ([M]$^+$, [^{37}Cl], 30), 248 ([M+H]$^+$, [^{35}Cl], 12), 247 ([M]$^+$, [^{35}Cl], 100), 219 (10), 184 (10), 63 (10), HRMS (ESI-TOF/MS):

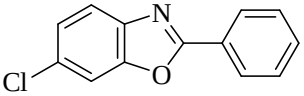
calcd for $C_{13}H_7{}^{37}ClFNO$ ($[M+H]^+$, $[^{37}Cl]$): 250.02467 , found 250.02516. calcd for $C_{14}H_7{}^{35}ClFNO$ ($[M+H]^+$, $[^{35}Cl]$): 248.0273, found 248.02771.

6-Chloro-2-(2,3,4-trimethoxyphenyl)benzoxazole (9k):



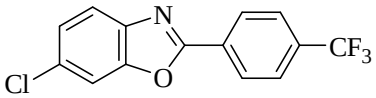
Starting with **7** (70 mg, 0.372 mmol), **3o** (80 mg, 0.446 mmol) and $Pd(pph_3)_4$ (13 mg, 3 mol-%, 0.01125 mmol) , K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **9k** was isolated as a white solid (95 mg, 80 %), mp 76-78°C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.86 (s, 6H, 2xOCH_3), 3.94 (s, 3H, OCH_3), 6.73 (d, J = 8.8 Hz, 1H, ArH), 7.22 (dd, J = 1.6, 8.0 Hz, 1H, ArH), 7.49 (d, J = 1.8 Hz, 1H, ArH), 7.59 (d, J = 8.8 1H, ArH), 7.77 (d, J = 8.8 Hz, 1H, ArH).^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 56.1, 61.1, 61.7 (OCH_3), 107.7, 111.0, (CH), 114.0 (C), 120.4, 124.9, 125.8 (CH), 130.2, 140,9, 143.2, 150.5, 153.6, 156.7, 161.9 (C). IR (KBr, cm^{-1}): ν = 3091, 3068, 2994, 2962, 2935, 2874, 2849, 2838, 1862, 1609 (w), 1592 (m), 1573, 1555 (w), 1487, 1454, 1441, 1428, 1408 (s). GC-MS (EI, 70 eV): *m/z* (%) = 321 ($[M]^+$, $[^{37}Cl]$, 32), 220 ($[M+H]^+$, $[^{35}Cl]$, 19), 319, ($[M]^+$, $[^{35}Cl]$, 100), 304 (19), 290 (26) 230 (25). HRMS (EI, 70 eV) calcd for $C_{16}H_{14}{}^{35}Cl\ NO_4$ ($[M]^+$, $[^{35}Cl]$): 319.06059; found: 319.06103 .

6-Chloro-2-phenylbenzoxazole(9l):



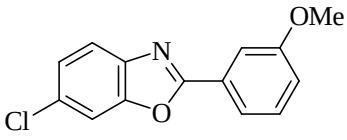
Starting with **7** (70 mg, 0.372 mmol), **3p** (60 mg, 0.446 mmol) and $Pd(pph_3)_4$ (13 mg, 3 mol-%, 0.01125 mmol) , K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **9l** was isolated as a white solid (77 mg, 90 %), mp 92-94 °C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (dd, J = 1.1, 8.1 Hz, 1H, ArH), 7.44 -7.47 (m, 3H, ArH), 7.52 (d, J = 1.0 Hz, 1H, ArH), 7.59 (d, J = 8.1 Hz 1H, ArH), 8.14 (dd, J = 2.0, 8.6 Hz, 2H, ArH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 110.6 (C), 111.2 (CH), 120.0 (C), 120.4, 125.0 (CH), 126.6 (C), 127.6, 128.9 (CH), 130.0, 130.6 (C), 131.8 (CH). IR (KBr, cm^{-1}): ν = 3090, 3059, 3040, 2953, 2921, 2851, 1958, 1893, 1865, 1747, 1615, 1600, 1573, 1567 (w), 1551 (m),1538, 1531, 1519, 1504, 1488 (w). GC-MS (EI, 70 eV): *m/z* (%) = 231 ($[M]^+$, $[^{37}Cl]$, 44), 230 ($[M+H]^+$, $[^{35}Cl]$, 20), 229, ($[M]^+$, $[^{35}Cl]$, 100), 201 (13), 166 (26) . HRMS (EI, 70 eV) calcd for $C_{13}H_8{}^{37}Cl\ NO$ ($[M]^+$, $[^{37}Cl]$): 231.02594; found: 231.02641. calcd for $C_{13}H_8{}^{35}Cl\ NO$ ($[M]^+$, $[^{35}Cl]$): 229.02889; found: 229.02889.

6-Chloro-2-[4-(trifluoromethyl)phenyl]benzoxazol(9m):



Starting with **7** (70 mg, 0.372 mmol), **3q** (84 mg, 0.446 mmol), $Pd(PPh_3)_4$ (13 mg, 3 mol-%, 0.01125 mmol), K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **9m** was isolated as a white solid (92 mg , 83 %), mp 112-115°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (dd, J = 1.72, 8.50 Hz, 1H, ArH), 7.54 (d, J = 2.37 Hz, 1H, ArH), 7.61 (d, J = 8.70 Hz, 1H, ArH), 7.72 (d, J = 8.30 Hz, 2H, ArH), 8.26 (d, J = 8.64 Hz, 2H, ArH).^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 111.4 , 120.9 (CH), 123.4 (q, $J_{C,F}$ = 271 Hz,CF), 125.7, 126.0 (q, $J_{C,F}$ = 3.8 Hz, CH) , 127.9 (CH), 130.0, 131.5 (C), 133.2 (d, $J_{C,F}$ = 32.0 Hz,C), 140.6, 151.0, 162.1 (C). ^{19}F NMR (282.40 MHz , $CDCl_3$): δ = -63.04 ($ArCF_3$), . IR (KBr, cm^{-1}): ν = 3100, 3080, 2954, 2922, 2852, 2638, 1931, 1889, 1804, 1683 (w), 1614, 1605 (m), 1569 (w), 1557 (m), 1512, 1500 (w), 1461 (s), 1426, 1409 (m). GC-MS (EI, 70 eV): *m/z* (%) = 299 ($[M]^+$, [^{37}Cl], 32), 298 ($[M+H]^+$, [^{35}Cl], 16), 297 ($[M]^+$, [^{35}Cl], 100), 269 (10), 63 (17) HRMS (ESI-TOF/MS): calcd for $C_{14}H_7{}^{37}ClF_3NO$ ($[M+H]^+$, [^{37}Cl]): 299.01333 ; found: 299.01347. calcd for $C_{14}H_7{}^{35}ClF_3NO$ ($[M+H]^+$, [^{35}Cl]): 297.01628 ; found: 297.01630.

6-Chloro-2-(3-methoxyphenyl)benzoxazol (**9n**)**:**

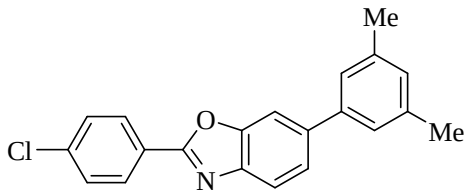


Starting with **7** (70 mg, 0.372 nmol), **3r** (68 mg, 0.446 mmol) and $Pd(pph_3)_4$ (13 mg, 3 mol-%, 0.01125 mmol), K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **9n** was isolated as a white solid (72 mg, 75 %), mp145-147ºC.^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OCH_3), 6.74 (d, J = 8.1 Hz, 2H, ArH), 7.21 (dd, J = 1.7, 8.3 Hz, 1H, ArH), 7.44 (d, J = 2.0 Hz, 1H, ArH), 7.53 (d, J = 8.0 Hz, 1H, ArH), 8.03 (d, J = 8.0 Hz, 2H, ArH).^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 55.3 (OCH_3), 111.1, 114.3 (CH), 119.2 (C), 120.2, 125.4, 129.3 (CH), 133.0, 141.2, 152.8, 162.4, 163.7 (C). IR (KBr, cm^{-1}): ν = 3073, 3042, 3004, 2978, 2946, 2902, 2840, 2038, 1917, 1866 (w), 1616, 1601 (m), 1580 (w), 1502 (m), 1467 (w). GC-MS (EI, 70 eV): *m/z* (%) = 259 ($[M]^+$, [^{35}Cl], 100), 244 (32), 216 (27), 211 (10), 195 (23), 122(15) . HRMS (ESI-TOF/MS) calcd for $C_{14}H_{10}{}^{35}ClNO_2$ ($[M+H]^+$, [^{35}Cl]): 259.03946; found: 259.03923.

General procedure for synthesis (10a-b)

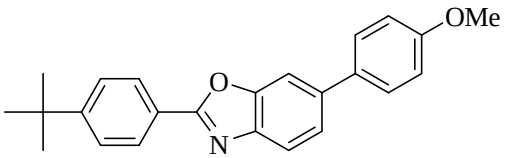
The reactions were carried out in a pressure tube. To a 1,4-dioxane suspension (3 ml) of **7** arylboronic acid $Ar^1B(OH)_2$ (1.2 equiv.) and $Pd(PPh_3)_4$ (3 mol-%) was added an aqueous solution of K_2CO_3 and the resulting solution was degassed by bubbling argon through the solution for 10 min. The mixture was heated at 80°C under an argon atmosphere for 6 h. The mixture was cooled to 20°C. Arylboronic acid $Ar^2B(OH)_2$ (1.2 equiv.) and $Pd(PPh_3)_4$ (3 mol-%), K_2CO_3 (2 M, 0.1 ml) and 1,4-dioxane (2 ml) were added. The reaction mixture was heated under an argon atmosphere for 8 h at 120°C. Then it was diluted with H_2O and extracted with CH_2Cl_2 (3 × 25 ml). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, heptane/EtAOc = 8:2).

2-(4-Chlorophenyl)-6-(3,5-dimethylphenyl)benzoxazole (**10a**)**:**



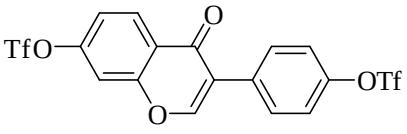
Starting with **7** (70 mg, 0.372 nmol), **3c** (66 mg, 0.446 mmol) and $Pd(pph_3)_4$ (13 mg, 3 mol-%, 0.01125 mmol), K_2CO_3 (2 M, 1.0 ml). **3a** (66 mg, 0.446 mmol) and $Pd(pph_3)_4$ (13 mg, 3 mol-%, 0.01125 mmol) , K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane (3 ml), **10a** was isolated as a white solid (104 mg, 84 %), mp 57-59°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 6H, 2xCH_3), 6.94 (d, *J* = 5.2 Hz, 1H, ArH), 7.15-7.19 (m, 3H, ArH), 7.49 (dd, *J* = 1.9, 8.6 Hz, 1H, ArH), 7.63-7.71 (m, 3H, ArH), 8.21 (d, *J* = 8.4 Hz, 2H, ArH).^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.3 (2xCH_3), 107.9, 118.6, 121.2 (CH), 123.2, 124.0, 124.3 (C), 124.7, 126.5, 126.9, 128.0 (CH), 128.6, 137.3, 137.4, 139.8, 140.4, 143.4 (C). IR (KBr, cm^{-1}): *v* = 3015, 2961, 2913, 2853, 2730, 1614, 1598, 1573, 1556, 1552, 1538, 1531, 1497, 1487, 1462 (w). GC-MS (EI, 70 eV): *m/z* (%) = 335 ($[M]^+$, [^{37}Cl], 34), 334 ($[M+H]^+$, [^{35}Cl], 21), 333 ($[M]^+$, [^{35}Cl], 100), 331 (17), 167 (12) . HRMS (EI, 70 eV) calcd for $C_{21}H_{16}{}^{37}Cl$ NO ($[M]^+$, [^{37}Cl]): 335.08854; found: 335.08862.calcd for $C_{21}H_{16}{}^{35}Cl$ NO ($[M]^+$, [^{35}Cl]): 333.09149; found: 333.09147.

2-(4-Tert-butylphenyl)-6-(4-methoxyphenyl)benzoxazole (**10b**)**:**



Starting with **7** (70 mg, 0.372 nmol), **3i** (79 mg, 0.446 mmol) and $Pd(pph_3)_4$ (13mg, 3mol-%, 0.01125 mmol), K_2CO_3 (2 M, 1.0 ml), **3b** (67 mg, 0.446 mmol) and $Pd(pph_3)_4$ (13mg, 3mol-%, 0.01125 mmol) , K_2CO_3 (2 M, 1.0 ml), and 1,4-dioxane(3 ml), **10b** was isolated as awhite solid (96 mg, 72%), mp 100°C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 9H, 3xCH_3), 3.74 (s, 3H, OCH_3), 6.90 (d, J = 8.0 Hz, 2H, ArH), 7.42 - 7.48 (m, 5H, ArH), 7.62 (d, J = 1.3 Hz, 1H, ArH), 7.67 (d, J = 8.4 Hz, 1H, ArH), 8.08 (d, J = 8.4 Hz, 2H, ArH).^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 30.1 (3xCH_3), 54.2 (OCH_3), 107.4, 113.3, 118.6, 122.6 (CH), 123.3 (C), 124.8, 126.3, 127.3 (CH), 132.3, 137.3, 140.0, 150.3, 154.0, 157.6, 158.2, 162.3 (C). IR (KBr, cm^{-1}): ν = 3064, 3032, 3002, 2961, 2953, 2927, 2900, 2865, 2832, 1617 (w), 1605 (m), 1573, 1552 (w), 1517, 1495, 1471, 1434 (m) . GC-MS (EI, 70 eV): *m/z* (%) = 358 ($[M+H]^+$, 25), 357 ($[M]^+$, 100), 342 (66), 157 (11). HRMS (EI, 70 eV) calcd for $C_{24}H_{23}NO_2$ $[M]^+$: 357.17233; found: 357.17182.

4-Oxo-3-[4-(trifluoromethylsulfonyloxy)phenyl]-4*H*-chromen-7-yl trifluoro-methanesulfonate (12):



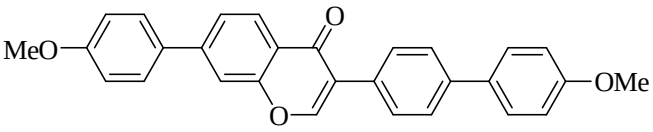
A solution of **11** (0.5 g, 1.96 mmol) in CH_2Cl_2 (20 ml) was added pyridine (0.6 ml, 7.86 mmol) and the solution was stirred at room temperature. To the solution was added Tf_2O (0.8 ml, 4.72 mmol) and the solution was stirred at room temperature for 10 min. Subsequently, the solution was stirred at 40°C for 30 min. After cooling, the reaction mixture was concentrated in vacuo. Product was isolated by rapid column chromatography (flash silica gel, heptane-EtOAc = 8:2) as a white solid (0.90 g, 90 %); mp 182-184 °C. ^{1} H NMR (300 MHz, $CDCl_3$): δ 7.61 - 7.70 (m, 3H, ArH), 7.80 (d, J = 2.3 Hz, 1H, ArH), 7.90 (d, J = 2.2 Hz, 1H, ArH), 7.92 - 8.00 (m, 2H, ArH), 8.75 (s, 1H, CH=).^{13}C- NMR (75.4 MHz, $CDCl_3$): δ = 112.5 (CH), 116.0 (q, J_{CF} = 320 Hz, CF_3),119.20 (CH), 120.0 (q, J_{CF} = 320 Hz, CF_3), 121.3 (CH), 122, 123.8 (C), 128.5, 131.2 (CH), 132.1, 148.8, 151.8, 155.9 (C), 156.0 (CH),174.0 (CO). ^{19}F NMR (282.4 MHz. $CDCl_3$): = -72.53 (3F, CF_3), -72.74 (3F, CF_3). IR (KBr, cm^{-1}): ν = 3093, 2918,

2849 (w), 1648 (s), 1614 (m), 1578, 1551, 1536, 1530 (w). GC-MS (EI, 70 eV): *m/z* (%) = 519 ($[M+H]^+$, 23), 518 ($[M]^+$, 100), 454 (12). HRMS (EI, 70 eV): calcd for $C_{17}H_8F_6O_8S_2$ $[M]^+$: 517.95593; found: 517.95651.

General procedure for synthesis (13a-d)

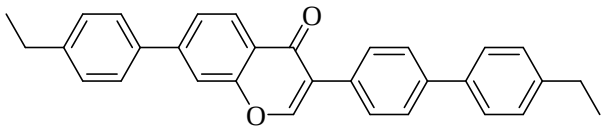
The reactions were carried out in a pressure tube. A solution of **12** (70 mg, 0.135 mmol), K_2CO_3 (2 M, 2 ml), $Pd(PPh_3)_4$ (6 mol-%) and arylboronic acid (2.2 equiv.) in DMF (4 ml) was stirred at 130°C for 10 h. under argon atmosphere. To the reaction mixture H_2O (20 ml) and CH_2Cl_2 (25 mL) were added. The organic and the aqueous layers were separated and the latter was extracted with CH_2Cl_2 (2 x 20 ml). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuum* .The residue was purified by column chromatography (silica gel, heptane/EtOAc = 9:1).

3-(4'-Methoxybiphenyl-4-yl)-7-(4-methoxyphenyl)-4*H*-chromen-4-one (13a):



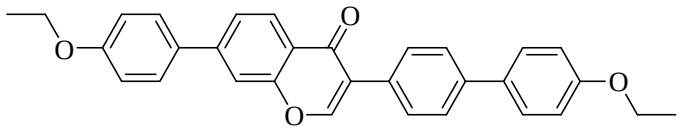
Starting with **12** (70 mg, 0.135 mmol) , **3b** (45 mg, 0.297 mmol), $Pd(PPh_3)_4$ (10 mg, 6 mol-%, 0.008658 mmol), K_2CO_3 (2 M, 2 ml), and DMF (4 ml), **13a** was isolated as a white solid (48 mg, 82 %); mp 188-190°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 6H, 2xOCH_3), 6.97 (d, *J* = 8.5 Hz, 4H, ArH), 7.18 (s, Hz, 2H, ArH), 7.54 -7.56 (m, 7H, ArH), 7.97 (s, 2H, ArH), 8.25 (d, *J* = 8.7, 1H, CH=).^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 29.7, 54.4 (2xOCH_3), 114.5, 115.1, 122.8, 122.9 (CH), 123.2, 125.5 (C), 126.8, 128.1, 128.4, 128.5 (CH), 128.6, 128.7, 128.8. 129.1, 135.2, 135.8, 136.6, 153.0 (C), 156.6 (CH), 160.5 (CO). IR (KBr, cm^{-1}): *v* = 3073, 3053, 3013, 2959, 2918, 2849 (w), 1901, 1732 (w), 1641, 1620, 1606, 1578, 1555, 1518 (m). GC-MS (EI, 70 eV): *m/z* (%) = 434 ($[M]^+$, 100), 344 (24), 343 (35), 315 (13). HRMS (EI, 70 eV): calcd for $C_{29}H_{22}O_4$ $[M]^+$: 434.15181; found: 434.15156.

3-(4'-Ethylbiphenyl-4-yl)-7-(4-ethylphenyl)-4*H*-chromen-4-one (13b):



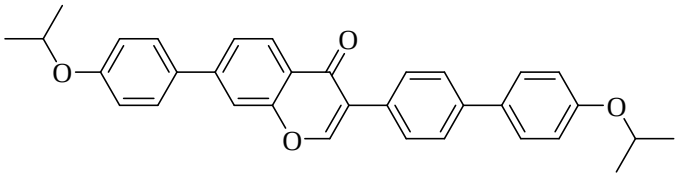
Starting with **12** (70 mg, 0.135 mmol), **3e** (45 mg, 0.297 mmol), $Pd(PPh_3)_4$ (10 mg, 6 mol- %, 0.008658 mmol), K_2CO_3 (2 M, 2 ml), and DMF (4 ml), **13b** was isolated as a white solid (45 mg, 71 %); mp 182 - 184°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, J = 6.89 Hz, 6H, 2xCH_3), 2.80 (q, J = 6.97, 2.33 Hz, 4H, 2xCH_2), 6.22 (d, J = 8.5 Hz, 4H, ArH), 7.11 (s, Hz, 2H, ArH), 7.52 - 7.54 (m, 7H, ArH), 7.88 (s, 2H, ArH), 8.22 (d, J = 8.5, 1H, CH=).^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 14.44 (2xCH_3), 44.5 (2xCH_2), 114.2, 115.1, 122.6, 122.8,122.9 (CH), 123.2, 124.5 (C), 125.9, 128.2, 128.3, 128.4 (CH), 128.5, 128.6, 128.8. 129.1, 135.2, 135.6, 136.6, 153.2 (C), 156.6 (CH), 160.8 (CO). IR (KBr, cm^{-1}): v = 3062, 3041, 3023, 2946, 2927, 2839 (w), 1911, 1723 (w), 1632, 1610, 1605, 1568, 1544, 1528 (m). GC-MS (EI, 70 eV): *m/z* (%) = 430 ([M]$^+$, 100), 333 (22), 243 (33), 215 (13), 112 (10). HRMS (EI, 70 eV): calcd for $C_{31}H_{26}O_2$ [M]$^+$: 430.19273; found: 430. 19253.

3-(4'-Ethoxybiphenyl-4-yl)-7-(4-ethoxyphenyl)-4*H*-chromen-4-one (13c):



Starting with **12** (70 mg, 0.135 mmol) , **3g** (49 mg, 0.297 mmol), $Pd(PPh_3)_4$ (10 mg, 6 mol- %, 0.008658 mmol), K_2CO_3 (2 M, 2 ml), and DMF (4 ml), **13c** was isolated as a white solid (48 mg, 77 %); mp 108-110°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, J = 6.89 Hz, 6H, 2xCH_3), 3.90 (q, J = 6.97, 2.33 Hz, 4H, 2xOCH_2), 6.97 (d, J = 8.5 Hz, 4H, ArH), 7.18 (s, Hz, 2H, ArH), 7.54 -7.56 (m, 7H, ArH), 7.97 (s, 2H, ArH), 8.25 (d, J = 8.7, 1H, CH=). ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 14.72 (2xCH_3), 63.5 (2xOCH_2), 114.3, 115.1, 122.7, 122.9, 123.1 (CH), 123.3, 125.5 (C), 126.9, 128.1, 128.3, 128.5, (CH), 128.6, 128.7, 128.9. 129.2, 135.2, 135.7, 136.6, 153.1 (C), 156.7 (CH), 160.4 (CO). IR (KBr, cm^{-1}): v = 3072, 3051, 3013, 2956, 2917, 2849 (w), 1901, 1733 (w), 1642, 1620, 1605, 1578, 1554, 1518 (m). GC-MS (EI, 70 eV): *m/z* (%) = 462 ([M]$^+$, 100), 444 (24), 443 (35), 315 (13), 122 (10). HRMS (EI, 70 eV): calcd for $C_{31}H_{26}O_4$ [M]$^+$: 462.18311; found: 462.18322.

3-(4'-Isopropoxybiphenyl-4-yl)-7-(4-isopropoxyphenyl)-4*H*-chromen-4-one (13d):

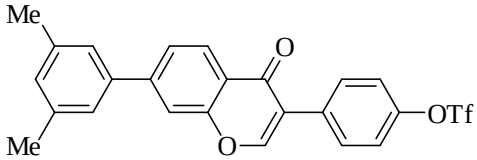


Starting with **12** (70 mg, 0.135 mmol) , **3h** (54 mg, 0.297 mmol), $Pd(PPh_3)_4$ (10 mg, 6 mol-%, 0.008658 mmol), K_2CO_3 (2 M, 2 ml), and DMF (4 ml), **13d** was isolated as a white solid (53 mg, 80 %); mp 190-192 °C.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (d, J = 6.05 Hz, 12H, 4xCH_3), 4.47 - 4.59 (m, 2H, 2xOCH), 6.97 (d, J = 8.5 Hz, 4H, ArH), 7.18 (s, Hz, 2H, ArH), 7.54 -7.56 (m, 7H, ArH), 7.97 (s, 2H, ArH), 8.25 (d, J = 8.7, 1H, CH=).^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 12.72 (4xCH_3), 53.5 (2xOCH_2), 114.3, 115.1, 122.7, 122.9 (CH), 123.3, 125.5 (C), 126.9, 128.1, 128.2, 128.3, 128.5 (CH), 128.6, 128.7, 128.9. 129.2, 135.2, 135.7, 136.6, 153.1 (C), 156.7 (CH), 160.4 (CO). IR (KBr, cm^{-1}): ν = 3072, 3051, 3013, 2956, 2917, 2849 (w), 1901, 1733 (w), 1642, 1620, 1605, 1578, 1554, 1518 (m). GC-MS (EI, 70 eV): *m/z* (%) = 490 ($[M]^+$, 100), 465 (20), 440 (35), 211 (13). HRMS (EI, 70 eV): calcd for $C_{33}H_{30}O_4$ $[M]^+$: 490.21441, found 490. 21455.

General procedure for synthesis (14a-k)

The reactions were carried out in a pressure tube. A solution of **12** (70 mg, 0.135 mmol), K_2CO_3 (2 M, 2 ml), $Pd(PPh_3)_4$ (3 mole-%) and arylboronic acid (1.2 equiv.) in DMF (4 ml) was stirred at 85°C for 6 h under argon atmosphere. To the reaction mixture H_2O (20 ml) and CH_2Cl_2 (25 ml) were added. The organic and the aqueous layers were separated and the latter was extracted with CH_2Cl_2 (2 x 20 ml). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, heptane/EtOAc = 9:1).

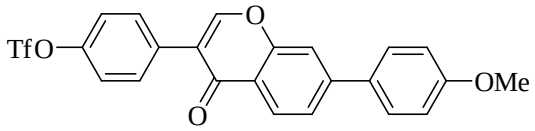
4-[7-(3,5-Dimethylphenyl)-4-oxo-4*H*-chromen-3-yl]phenyl trifluoromethanesulfonate (14a):



Starting with **12** (70 mg, 0.135 mmol), **3a** (25 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml), and DMF (4 ml), **14a** was isolated as a white solid (49 mg, 76 %); mp 173-175°C. ^{1}H NMR (300

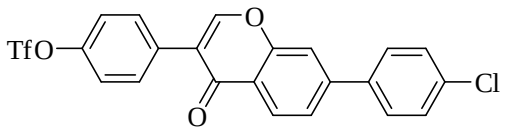
MHz, $CDCl_3$): δ = 2.23 (s, 6H, 2xCH_3), 7.23 (s, 2H, ArH), 7.34 (d, J = 8.41 Hz, 2H, ArH).7.50 - 7.53 (m, 5H, ArH), 7.71 (s, 1H, ArH), 7.97 (d, J = 8.5 Hz, 1H, CH=).^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 21.3 (2xCH_3), 114.9 (CH), 115.9, 117.5 (C), 120.4 (CH), 122.6 (q, J_{CF} = 318 Hz, CF_3),122.9, 123.8 (C), 124.7, 125.2, 126.6, 129.1, 130.7 (CH), 132.4, 138.7, 138.8, 147.5, 149.3, 153.4 (C), 156.5 (CH), 175.6 (CO).^{19}F NMR (282.4 MHz $CDCl_3$): = -72.75 (3F, CF_3), IR (KBr, cm^{-1}): ν = 3088, 3040, 2921, 2850 (w), 1636, 1621, 1603 (m), 1555, 1499 (w). GC-MS (EI, 70 eV): *m/z* (%) = 474 ($[M]^+$, 100), 342 (24), 341 (32), 313 (13). HRMS (EI, 70 eV): calcd for $C_{24}H_{17}O_5F_3S$ $[M]^+$: 474.07433, found 476.07403.

4-[7-(4-Methoxyphenyl)-4-oxo-4*H*-chromen-3-yl]phenyl trifluoro-methanesulfonate (14b):



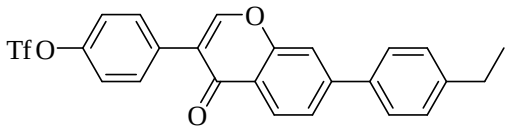
Starting with **12** (70 mg, 0.135 mmol), **3b** (25 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml),and DMF (4 ml), **14b** was isolated as a white solid (51 mg, 80 %); mp 173-175°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H, OCH_3), 6.94 (d, J = 1.5 Hz, 2H, ArH), 7.26 (d, J = 1.5 Hz, 2H, ArH), 7.53-7.63 (m, 5H, ArH), 7.97 (s, 1H, ArH), 8.25 (d, J = 6.7, 1H, CH=).^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 54.4 (OCH_3), 113.2, 114.1 (CH), 115.2 (q, J_{CF} = 320 Hz, CF_3),, 120.3 (C), 121.5 (CH), 122.8 (C), 123.2, 125.7, 127.5 (CH), 129.7 (C), 130.1(CH), 131.4, 145.7, 148.3, 152.3, 155.6 (C), 159.3 (CH), 174.5 (CO).^{19}F NMR (282.4 MHz $CDCl_3$): = -72.75 (3F, CF_3), IR (KBr, cm^{-1}): ν = 3085, 3036, 2955, 2916, 2848, 2670, 2559 (w), 1633, 1621, 1604 (m), 1585, 1552, 1518 (w). GC-MS (EI, 70 eV): *m/z* (%) = 476 ($[M]^+$, 100), 344 (24), 343 (35), 315 (13). HRMS (EI, 70 eV): calcd for $C_{23}H_{15}O_6F_3S$ $[M]^+$: 476.05359; found: 476.05270.

4-[7-(4-Chlorophenyl)-4-oxo-4*H*-chromen-3-yl]phenyl trifluoromethanesulfonate (14c):



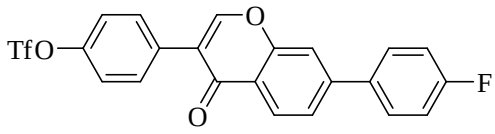
Starting with **12** (70 mg, 0.135 mmol), **3c** (25 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml), and DMF (4 ml), **14c** was isolated as a white solid (37 mg, 58 %); mp 173-175°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 (d, J = 8.77 Hz, 2H, ArH), 7.40 (d, J = 8.79 Hz, 2H, ArH), 7.49 -7.63 (m, 7H, ArH), 8.25 (d, J = 8.85 Hz, 1H, CH=).^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 115.9 (CH), 120.9 (C), 121.4 (CH), 123.3 (q, J_{CF} = 320 Hz, CF_3), 123.3 (C), 123.4, 123.9, 127.1 (CH), 128.3 (C), 128.6 (CH), 129.0 (C), 129.3, 130.7 (CH), 132.2, 135.0, 135.1, 137.3, 145.5, 149.4 (C), 156.5 (CH), 175.9 (CO).^{19}F NMR (282.4 MHz $CDCl_3$): = -72.74 (3F, CF_3), IR (KBr, cm^{-1}): ν = 3084, 3067, 3048, 2958, 2918, 2849 (w), 1635, 1621 (s), 1589, 1570, 1552, 1521, 1501, 1476 (w). GC-MS (EI, 70 eV): *m/z* (%) = 480 ([M]$^+$,[^{35}Cl], 100), 350 (10), 349 (36), 348 (23) 347 (80), 319 (17). HRMS (EI, 70 eV): calcd for $C_{22}H_{12}O_5{}^{35}Cl_1F_3S$ [M]$^+$: 480.00406; found: 480.00333.

4-[7-(4-Ethylphenyl)-4-oxo-4*H*-chromen-3-yl]phenyltrifluoro methanesulfonate (14d):



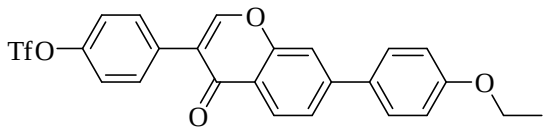
Starting with **12** (70 mg, 0.135 mmol), **3e** (24 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml),and DMF (4 ml), **14d** was isolated as a white solid (45 mg, 70 %), mp 173-175°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.59 Hz, 3H, CH_3), 2.68 (q, J = 7.50 Hz, 2H, CH_2), 7.53 - 7.63 (m, 4H, ArH), 7.53 - 7.63 (m, 5H, ArH), 6.94 (d, J = 8.5 Hz, 1H, ArH), 8.23 (d, J = 8.5 Hz, 1H, CH=).^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 15.5 (CH_3), 29.3 (CH_2), 115.6 (CH), 121.4 (q, J_{CF} = 318 Hz, CF_3), 124.3 (CH), 126.8, 127.1, 128.3, 128.6, 128.7, 129.2 (CH), 130.5, 130.8, 136.2, 138.1, 141.0, 143.6, 147.2 (C), 153.4 (CH), 156.6 (CO).^{19}F NMR (282.4 MHz $CDCl_3$): = -72.74 (3F, CF_3), IR (KBr, cm^{-1}): ν = 3083, 3025, 2964, 2918, 2873, 2849 (w), 1635, 1620 (m), 1571, 1548, 1536, 1530 (w). GC-MS (EI, 70 eV): *m/z* (%) = 474 ([M]$^+$, 100), 342 (24), 341 (32). HRMS (EI, 70 eV): calcd for $C_{24}H_{17}O_5F_3S$ [M]$^+$: 474.07433, found 474.07410.

4-[7-(4-Fluorophenyl)-4-oxo-4*H*-chromen-3-yl]phenyltrifluoromethanesulfona (14e):



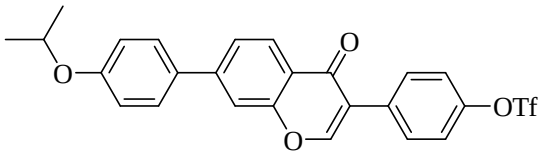
Starting with **12** (70 mg, 0.135 mmol), **3f** (22 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml),and DMF (4 ml), **14e** was isolated as a white solid (38 mg, 62 %); mp 214-216°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09 -7.13 (m, 4H, ArH), 7.27 (d, J = 8.85 Hz, 2H, ArH), 7.54 - 7.57 (m, 3H, ArH), 7.16 (d, J = 8.17 Hz, 2H, ArH), 8.24 (d, J = 8.17 Hz, 1H, CH=).^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 105.4, 106.2 (CH), 109.6 (C), 110.0, 116.0 (d, J = 21.6 Hz, (CH)), 126.4, 129.0 (d, J = 8.2 Hz, (CH)), 129.1 (CH), 131.1 (C), 132.0 (CH), 135.4 (d, J = 3.2 Hz), 147.4, 156.6, 160.8 (C), 163.2 (d, J_{CF} = 248.9 Hz, CF_3), 164.6 (CH), 183.1 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): = -112.90 (ArF), , -72.72 (3F,CF_3) . IR (KBr, cm^{-1}): v = 3083, 3047, 2952, 2920, 2850 (w), 1633, 1621 (m), 1605, 1555 (w), 1514, 1502, 1482 (w). GC-MS (EI, 70 eV): *m/z* (%) = 464 ($[M]^+$, 100), 332 (23), 331 (88), 303 (18), 157 (10). HRMS (EI, 70 eV): calcd for $C_{22}H_{12}O_5F_4S$ $[M]^+$: 464.03361; found: 464.03350.

4-[7-(4-Ethoxyphenyl)-4-oxo-4*H*-chromen-3-yl]phenyltrifluoromethanesulfonate (14f):



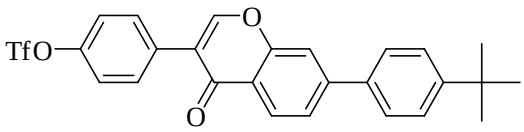
Starting with **12** (70 mg, 0.135 mmol), **3g** (27 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml), and DMF (4 ml), **14f** was isolated as a white solid (58 mg, 88 %), mp 173-175°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, J = 6.89 Hz, 3H, CH_3), 3.90 (q, J = 6.97, 2.33 Hz, 2H, OCH_2), 6.91 (d, J = 8.85 Hz, 2H, ArH), 7.25 (d, J = 8.70 Hz, 2H, ArH), 7.46 - 7.60 (m, 7H, ArH), 8.22 (d, J = 8.70 Hz, 1H, CH=).^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 14.76 (CH_3), 63.6 (OCH_2), 115.1, 121.4, (CH), 122.5 (C), 123.7 (q, J_{CF} = 319 Hz, CF_3), 124.2, 126.7, 128.5, 130.7 (CH), 130.9, 132.4, 146.8, 149.3, 153.3, 156.6, 156.7 (C), 159.7 (CH), 175.5 (CO). ^{19}F NMR (282.4 MHz $CDCl_3$): = -72.76 (3F, CF_3), IR (KBr, cm^{-1}): v = 3090, 3037, 2918, 2849 (w), 1657 (m), 1637, 1623, 1604 (s),1574, 1552, 1536, 1518, 1501 (w). GC-MS (EI, 70 eV): *m/z* (%) =490 ($[M]^+$, 100), 358 (24), 357 (90), 330 (10), 329 (45), 301 (13), 300 (10). HRMS (EI, 70 eV): calcd for $C_{24}H_{17}O_6F_3S$ $[M]^+$: 490.06925; found: 490.06905.

4-[7-(4-Isopropoxyphenyl)-4-oxo-4*H*-chromen-3-yl]phenyltrifluoromethanesulfonate (14g):



Starting with **12** (70 mg, 0.135 mmol), **3h** (29 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml), and DMF (4 ml), **14g** was isolated as a white solid (53 mg, 78 %); mp 173-175°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (d, J = 6.05 Hz, 6H, 2xCH_3), 4.49 - 4.55 (m, 1H,OCH), 6.88 (d, J = 8.16 Hz, 2H, ArH), 7.26 (d, J = 8.96 Hz, 2H, ArH), 7.48 - 7.60 (m, 6H, ArH), 7.91 (s, 1H, ArH), 8.98 (d, J = 8.96 Hz, 1H, CH=).^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 22.0 (2xCH_3), 69.9 (OCH), 115.9, 116.3, 121.4 (CH), 122.5 (q, J_{CF} = 320 Hz, CF_3), 123.8 (C), 124.2, 126.7, 128.5 (CH), 129.2 (C), 130.8 (CH), 132.4, 146.8, 149.3, 153.4, 156.6 (C), 158.8 (CH), 175.6 (CO).^{19}F NMR (282.4 MHz $CDCl_3$): = -72.75 (3F, CF_3), IR (KBr, cm^{-1}): ν = 3388, 3086, 3041, 2981, 2918, 2849 (w), 1639, 1624 (m), 1602, 1553, 1524 (w), 1502 (m). GC-MS (EI, 70 eV): *m/z* (%) =504 ([M]$^+$, 100), 426 (24), 330 (23), 329 (80), 301 (13). HRMS (EI, 70 eV): calcd for $C_{25}H_{19}O_6F_3S$ [M]$^+$: 504.08490; found: 504.08522.

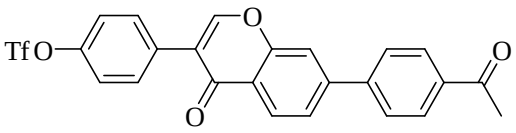
4-[7-(4-Tert-butylphenyl)-4-oxo-4*H*-chromen-3-yl]phenyl trifluoromethanesulfonate (14h):



Starting with **12** (70 mg, 0.135 mmol), **3i** (29 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml), and DMF (4 ml), **14h** was isolated as a white solid (44 mg, 65 %); mp 173-175°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 9H, 3xCH_3), 7.27 (d, J = 8.67 Hz, 2H, ArH), 7.45 (d, J = 8.60 Hz, 2H, ArH), 7.54 -7.63 (m, 7H, ArH), 8.28 (d, J = 8.57 Hz, 1H, CH=).^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 31.2 (3xCH_3), 115.7, 121.4 (CH), 122.9 (C), 123.8 (q, J_{CF} = 316 Hz, CF_3), 124.5, 126.1 (CH), 126.8 (C), 127.0, 127.4 (CH), 129.1 (C), 130.8 (CH), 132.4, 127.0, 127.4, 130.8, 149.3, 153.4 (C), 156.6 (CH), 175.6 (CO).^{19}F NMR (282.4 MHz $CDCl_3$): = -72.75 (3F, CF_3), IR (KBr, cm^{-1}): ν = 3091, 3037, 2989, 2920, 2850 (w), 1636, 1623, 1604 (m), 1575, 1552, 1519, 1500, 1475 (w). GC-MS (EI, 70 eV): *m/z* (%) =

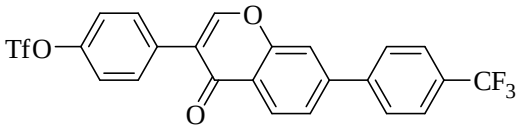
502 ([M]$^+$, 100), 489 (10), 488 (28), 487 (80), 370 (14), 369 (54), 354 (29) 326 (11), 325 (12). HRMS (EI, 70 eV): calcd for $C_{26}H_{21}O_5F_3S$ [M]$^+$: 502.10563; found: 502.10544.

4-[7-(4-Acetylphenyl)-4-oxo-4*H*-chromen-3-yl]phenyltrifluoromethanesulfonate (14i):



Starting with **12** (70 mg, 0.135 mmol), **3l** (27 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml),and DMF (4 ml), **14i** was isolated as a white solid (34 mg, 52 %); mp 173-175°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.50 (s, 3H, $COCH_3$), 7.27 - 7.30 (m, 4H, ArH), 7.37 - 7.46 (m, 4H, ArH), 7.60 (d, J = 8.62 Hz, 2H, ArH), 8.26 (d, J = 8.40 Hz, 1H, CH=).^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 2.28 ($COCH_3$), 115.5, 121.3 (CH), 122.9 (C), 123.7 (q, J_{CF} = 319 Hz, CF_3), 124.4, 126.3 (CH), 126.9 (C), 127.2, 127.5 (CH), 129.2 (C), 130.9 (CH), 127.0, 127.4, 130.8, 149.3, 153.5 (CH), 156.6 (CO), 175.6 (CO).^{19}F NMR (282.4 MHz $CDCl_3$): = -73.50 (3F, CF_3), IR (KBr, cm^{-1}): ν = 3078, 2959, 2918, 2849, 1732, 1684 (w), 1636 (s), 1616, 1572, 1539, 1502 (w). GC-MS (EI, 70 eV): *m/z* (%) = 488 ([M]$^+$, 100), 372 (14), 362 (54), 351 (29) 322 (11), 311 (10). HRMS (EI, 70 eV): calcd for $C_{24}H_{15}O_6F_3S$ [M]$^+$: 488.05414; found: 488.05409.

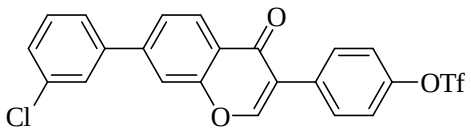
4-[4-Oxo-7-(4-(trifluoromethyl)phenyl)-4*H*-chromen-3-yl]phenyl trifluoromethane-sulfonate (14j):



Starting with **12** (70 mg, 0.135 mmol), **3q** (31 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml), and DMF (4 ml), **14j** was isolated as a white solid (46 mg, 66 %); mp 214-216°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (d, J = 8.16 Hz, 4H, ArH), 7.55 - 7.62 (m, 7H, ArH), 8.29 (d, J = 8.64 Hz, 1H, CH=).^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 116 (CH), 116.6, 118.7 (C), 120.9 (d, J_{CF} = 248.9 Hz, CF_3), 121.5 (d, J = 21.6 Hz, CH), 122.1, 123.3 (C), 124.0, 124.4 (d, J = 8.2 Hz, CH), 127.1, 127.2, 128.4 (CH), 132.2 (C), 133.0 (CH), 134.4 (d, J = 3.2 Hz), 146.4, 153.6, 160.5 (C), 163.2 (d, J_{CF} = 248.9 Hz, CF_3), 183.1 (CO).^{19}F NMR (282 MHz, $CDCl_3$): = -67.31, -56.31 (3F,CF_3) . IR (KBr, cm^{-1}): ν = 3058, 2955, 2918,

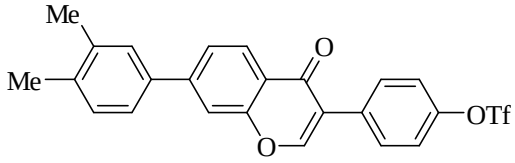
2849 (w), 1633, 1622, 1607 (m), 1556, 1522, 1485, 1441 (w). GC-MS (EI, 70 eV): *m/z* (%) = 514 ([M]$^+$, 100), 382 (24), 381 (90), 353 (19). HRMS (EI, 70 eV): calcd for $C_{23}H_{12}O_5F_4S$ [M]$^+$: 514.03041; found: 514.0300.

4-[7-(3-Chlorophenyl)-4-oxo-4*H*-chromen-3-yl]phenyl trifluoromethanesulfonate (14k):



Starting with **12** (70 mg, 0.135 mmol), **3s** (25 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml),and DMF (4 ml), **14k** was isolated as a white solid (37 mg, 58 %); mp 173-175°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ =7.27 -7.31 (m, 7H, ArH), 7.40 (d, *J* = 8.20 Hz, 2H, ArH), 7.57 (d, *J* = 8.16 Hz, 2H, ArH), 8.25 (d, *J* = 8.85 Hz, 1H, CH=).^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 111.6, 113.6, 114.5 (CH), 116.5 (C), 119.0 (CH), 120.8 (q, J_{CF} = 315 Hz, CF_3), 121.6 (CH), 122.2, 124.1, 124.5 (C), 129.2, 130.7 (CH), 131.4 (C), 134.7, 135.8 (CH), 149.6, 152.3, 153.7 (C), 156.3 (CH), 174.5 (CO).^{19}F NMR (282.4 MHz $CDCl_3$): = -72.54 (3F, CF_3). IR (KBr, cm^{-1}): ν = 3094, 2919, 2850 (w), 1648, 1615 (s), 1578, 1552, 1536 (w), 1503 (m), 1482, 1468 (m). GC-MS (EI, 70 eV): *m/z* (%) = 480 ([M]$^+$,[^{35}Cl] 100), 334 (10), 333 (36), 321 (23) , 319 (17). HRMS (EI, 70 eV): calcd for $C_{22}H_{12}O_5{}^{35}ClF_3S$ [M]$^+$: 480.00416; found: 480.00413.

4-[7-(3,4-Dimethylphenyl)-4-oxo-4*H*-chromen-3-yl]phenyl trifluoromethane-sulfonate (14l):



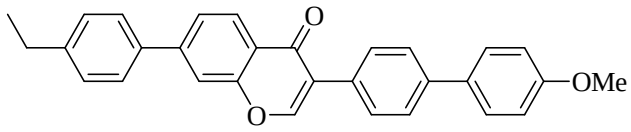
Starting with **12** (70 mg, 0.135 mmol), **3t** (24 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml),and DMF (4 ml), **14l** was isolated as a white solid (44 mg, 70 %); mp 173-175°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25 (d, *J* = 6.30 Hz, 6H, 2xCH_3), 7.17 (d, *J* = 8.15 Hz, 1H, ArH), 7.25 - 7.36 (m, 5H, ArH), 7.58 - 7.62 (m, 4H, ArH), 7.22 (d, *J* = 8.58 Hz, 1H, CH=).^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 19.5, 19.95 (2xCH_3), 115.6, 121.4 (CH), 122.8 (q, J_{CF} = 319 Hz, CF_3),122.9, 123.8 (C), 124.5, 124.7, 126.7, 128.5, 130.4, 130.8 (CH), 132.4, 136.4, 137.4, 137.7, 147.3, 149.3, 153.4 (C), 156.6 (CH), 175.6 (CO).^{19}F NMR (282.4

MHz $CDCl_3$): = -72.72 (3F, CF_3), IR (KBr, cm^{-1}): ν = 3070, 3048, 3013, 2974, 2948, 2922, 2856 (w), 1640, 1622 (m), 1570, 1553, 1499 (w). GC-MS (EI, 70 eV): *m/z* (%) = 474 ($[M]^+$, 100), 342 (25), 341 (88), 313 (14). HRMS (EI, 70 eV): calcd for $C_{24}H_{17}O_5F_3S$ $[M]^+$: 474.07433; found: 474.07428.

General procedure for synthesis (15a-c)

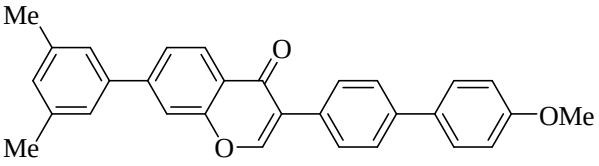
The reactions were carried out in a pressure tube. A DMF solution of **12** (70 mg, 0.135 mmol), $Ar^1B(OH)_2$ (1.2 equiv.), K_2CO_3 2 M (2 ml) and $Pd(PPh_3)_4$ (3 mol-%) was heated at 60 °C for 6h under argon atmosphere. After cooling to 20°C, $Ar^2B(OH)_2$ (1.2 equiv.), $Pd(PPh_3)_4$ (3 mol-%) were added and the reaction mixture was heated at 130°C for further 10 h. The reaction mixture was cooled again to 20°C, H_2O was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 25 ml).The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (heptane / EtOAc = 9:1).

7-(4-Ethylphenyl)-3-(4'-methoxybiphenyl-4-yl)-4*H*-chromen-4-one (15a):



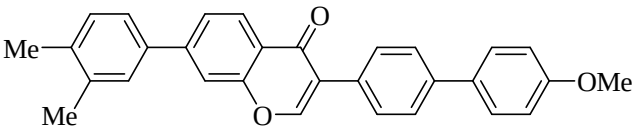
Starting with **12** (70 mg, 0.135 mmol) , **3e** (24 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml), **3b** (25 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml), and DMF (4 ml), **15a** was isolated as a white solid (41 mg, 70 %); mp 203-204°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.55 Hz, 3H, CH_3), 2.68 (q, *J* = 7.51 Hz, 2H, CH_2), 3.82 (s, 3H, OCH_3), 6.97 (d, *J* = 8.3 Hz, 5H, ArH), 7.11 (s, Hz, 2H, ArH), 7.52 -7.54 (m, 6H, ArH), 7.93 (s, 2H, ArH), 8.22 (d, *J* = 8.1, 1H, CH=).^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 1.6 (CH_3), 2.2 (CH), 55.5 (OCH_3), 113.4, 114.1, 121.5, 122.4 (CH), 123.2, 124.4 (C), 125.8, 128.1, 128.5, 128.6 (CH), 128.7, 128.8, 128.9. 129.1, 135.3, 135.9, 136.6, 153.2 (C), 156.3 (CH), 160.5 (CO). IR (KBr, cm^{-1}): ν = 3059, 3053, 3012, 2958, 2916, 2849 (w), 1902, 1730 (w), 1641, 1620, 1606, 1578, 1554, 1518 (m). GC-MS (EI, 70 eV): *m/z* (%) = 432 ($[M]^+$, 100), 411 (20), 222 (33), 100 (23). HRMS (EI, 70 eV): calcd for $C_{30}H_{24}O_3$ $[M]^+$: 432.17254; found: 432.17223.

7-(3,5-dimethylphenyl)-3-(4'-methoxybiphenyl-4-yl)-4*H*-chromen-4-one (15b):



Starting with **12** (70 mg, 0.135 mmol), **3a** (25 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml), **3b** (25 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml), and DMF (4 ml), **15b** was isolated as a white solid (47 mg, 81 %); mp 152-154°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.53 (s, 6H, 2xCH_3), 3.82 (s, 3H, OCH_3), 6.97 (d, J = 8.5 Hz, 4H, ArH), 7.11 (s, Hz, 2H, ArH), 7.50 -7.52 (m, 6H, ArH), 7.93 (s, 2H, ArH), 8.20 (d, J = 8.3, 1H, CH=).^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 22.4 (2xCH_3), 50.8 (OCH_3), 113.5, 114.1, 121.7, 122.6 (CH), 123.4, 124.4 (C), 125.8, 126.1, 126.5, 126.6, 127.2, 127.8 (CH), 128.5, 128.6, 128.8, 129.2, 135.3, 135.7, 136.6, 152.1 (C), 155.8 (CH), 163.8 (CO). IR (KBr, cm^{-1}): ν = 3059, 3053, 3012, 2958, 2916, 2849 (w), 1902, 1730 (w), 1641, 1620, 1606, 1578, 1554, 1518 (m). GC-MS (EI, 70 eV): *m/z* (%) = 432 ([M]$^+$, 100), 341 (22), 323 (30), 315 (23), 133 (10). HRMS (EI, 70 eV): calcd for $C_{30}H_{24}O_3$ [M]$^+$: 432.17200 ;found: 432.17244.

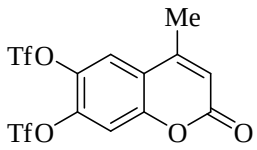
7-(3,4-Dimethylphenyl)-3-(4'-methoxybiphenyl-4-yl)-4*H*-chromen-4-one (15c):



Starting with **12** (70 mg, 0.135 mmol) , **3t** (25 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml), **3b** (25 mg, 0.162 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.004327 mmol), K_2CO_3 (2 M, 2 ml), and DMF (4 ml), **15c** was isolated as a white solid (35 mg, 60 %); mp102-105°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.50 (s, 6H, 2xCH_3), 3.80 (s, 3H, OCH_3), 6.97 (d, J = 8.5 Hz, 5H, ArH), 7.11 (s, Hz, 2H, ArH), 7.53 -7.56 (m, 6H, ArH), 7.93 (s, 2H, ArH), 8.11 (d, J = 8.1, 1H, CH=).^{13}C-NMR (75.4 MHz, $CDCl_3$): δ = 25.6 (2xCH_3), 52.8 (OCH_3), 112.5, 113.1, 120.8, 121.8 (CH), 123.2, 124.4 (C), 125.7, 128.2, 128.4, 128.5 (CH), 128.6, 128.7, 128.8, 129.2, 134.3, 135.8, 136.4, 153.2 (C), 156.7 (CH), 161.8 (CO). IR (KBr, cm^{-1}): ν = 3059, 3053, 3012, 2958, 2916, 2849 (w), 1902, 1730 (w), 1641, 1620, 1606, 1578, 1554, 1518 (m). GC-MS (EI, 70 eV): *m/z* (%) =

432 ([M]$^+$, 100), 340 (20), 333 (30), 310 (23), 123 (22). HRMS (EI, 70 eV): calcd for $C_{30}H_{24}O_3$ [M]$^+$: 432.17254; found: 432.17244.

4-Methyl-2-oxo-2*H*-chromene-6,7-diyl bis(trifluoromethanesulfonate) (17):

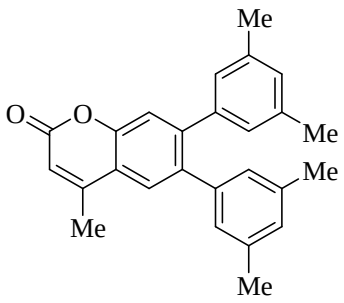


To a solution of 4-methyl-6,7-dihydroxycoumarine **16** (0.5 g, 2.60 mmol) in CH_2Cl_2 (30 ml) was added triethylamine (0.36 ml, 10.4 mmol) at room temperature under an argon atmosphere. After 10 min, Tf_2O (1.0 ml , 6.2 mmol) was added at -78°C. The mixture was allowed to warm to 20°C and stirred for 6 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography (flash silica gel, heptane / EtOAc = 8 : 2) without aqueous work up to give **17** as a white solid (0.9 g, 75 %); mp 125-127°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41 (d, J = 1.5 Hz, CH_3), 6.37 (d, J = 1.2 Hz, 1H, CH=), 7.41 (br. s , 1H, ArH), 7.59 (br. s, 1H, ArH).^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 18.64 (CH_3), 110.9, 112.7, 113.1 (CH), 116.0 (q, $J_{F,C}$ = 317.0 Hz, CF_3), 117.3 (q, $J_{F,C}$ = 317.0 Hz, CF_3), 118.1, 136.4, 141.7, 150.5, 152.6 (C), 158.2 (CO). ^{19}F NMR (282.4, MHz): δ = -72.8, -72.7 (3F, CF_3). IR (KBr, cm^{-1}): ν = 3124, 3053, 2964, 2926 (w), 1740 (s), 1673, 1625, 1613, 1570 (w), 1498 (m). GC-MS (EI, 70 eV): *m/z* (%) = 455 ([M]$^+$, 100), 324 (10), 323 (84), 232 (10), 203 (33), 162 (13), 134 (26), 69 (55). HRMS (EI, 70 eV) calcd for $C_{12}H_6F_6O_8S_2$ ([M]$^+$): 455.94028; found: 455.94130.

General procedure for synthesis (18a-e)

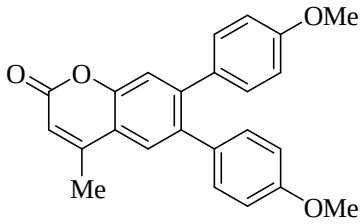
The reactions were carried out in a pressure tube. To a 1,4-dioxane suspension (3 ml) of bis(triflates) analogue **17** (70 mg, 0.1534 mmol), $Pd(PPh_3)_4$ (11 mg, 6 mol -%, 0.0092 mmol), and arylboronic acid (2.2 equiv.), was added K_3PO_4 (98 mg, 0.4602 mmol). The mixture was heated at 120°C under Argon atmosphere for 6 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 x 25 ml). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, heptane/EtOAc = 9:1).

6,7-Bis(3,5-dimethlyphenyl)-4-methyl-2*H*-chromen-2-one (18a):



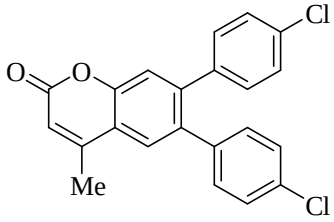
Starting with **17** (70 mg, 0.1534 mmol) , **3a** (51 mg, 0.3374 mmol), $Pd(PPh_3)_4$ (11 mg, 6 mol -%, 0.0092 mmol), K_3PO_4 (98 mg, 0.4602 mmol), and 1,4-dioxane (3 ml), **18a** was isolated as a white solid (42 mg, 75 %); mp 121-122°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.13 (s, 6H, 2xCH_3), 2.14 (s, 6H, 2xCH_3), 2.39 (d, J = 1.3 Hz, 3H, CH_3), 6.24 (d, J = 1.2 Hz, 1H, CH=), 6.67 - 6.80 (m, 6H, ArH), 7.30 (br. s, 1H, ArH) , 7.49 (br. s, 1H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 17.6 (2xCH_3) , 20.1 (2xCH_3), 26.1 (CH_3), 113.9, 117.2 (CH), 117.7, 120.1 (C), 125.1, 126.4, 126.6, 127.4, 127.9 (CH), 136.3, 136.3, 138.5, 139.1, 143.7, 151.2, 151.5, 154.4, 156.1 (C), 160.9 (CO). IR (KBr, cm^{-1}): ν = 3015, 3082, 3066, 2868, 2732, 2645 (w), 1722 (s), 1618, 1607 (m), 1573, 1537, 1516, 1485 (w). GC-MS (EI, 70 eV): *m/z* (%) = 368 ([M]$^+$,100), 353 (12), 338 (10) . HRMS (EI, 70 eV) calcd for $C_{26}H_{24}O_2$ [M]$^+$: 368.17708; found: 368.17685.

6,7-Bis(4-methoxyphenyl)-4-methyl-2*H*-chromen-2-one (18b):



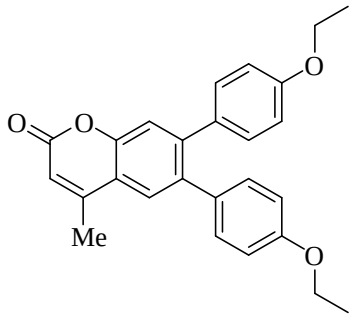
Starting with **17** (70 mg, 0.1534 mmol) , **3b** (51 mg, 0.3374 mmol), $Pd(PPh_3)_4$ (11 mg, 6 mol-%, 0.0092 mmol), K_3PO_4 (98 mg, 0.4602 mmol), and 1,4-dioxane (3 ml), **18b** was isolated as a white solid (47 mg, 83 %); mp 103-105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (d, J = 1.2 Hz, 3H, CH_3), 3.72 (s, 6H, 2OCH_3), 6.23 (d, J = 1.2 Hz, 1H, CH=), 6.69 - 6.74 (m, 4H, ArH), 6.97 - 7.01 (m, 4H, ArH), 7.27 (br. s, 1H, ArH) , 7.47 (br. s, 1H, ArH).^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 18.6 (CH_3), 22.6, 29.3 (OCH_3), 55.2, 113.6, 114.8, 118.2 (CH), 118.6 (C), 126.3, 130.7, 130.8 (CH), 132.1, 132.7, 136.6, 144.1, 152.1, 152.5, 158.6, 158.8 (C), 160.9 (CO). IR (KBr, cm^{-1}): ν = 3115, 3092, 3076, 2968, 2932, 2845 (w), 1732 (s), 1628, 1607 (m), 1583, 1547, 1526, 1495 (w). GC-MS (EI, 70 eV): *m/z* (%) = 372 ([M]$^+$,100), 357 (12), 341 (11), 229 (10). HRMS (EI, 70 eV) calcd for $C_{24}H_{20}O_4$ [M]$^+$: 372.13561; found: 372.13535.

7-Bis(4-chlorophenyl)-4-methyl-2*H*-chromen-2-one (18c):



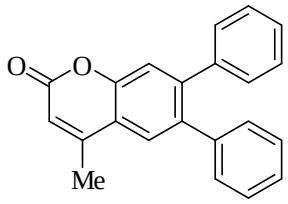
Starting with **17** (70 mg, 0.1534 mmol) , **3c** (51 mg, 0.3374 mmol), $Pd(PPh_3)_4$ (11 mg, 6 mol- %, 0.0092 mmol), K_3PO_4 (98 mg, 0.4602 mmol), and 1,4-dioxane (3 ml), **18c** was isolated as a white solid (49 mg, 83 %); mp 221-222°C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (d, J = 1.3 Hz, 3H, CH_3), 6.27 (d, J = 1.2 Hz, 1H, CH=), 6.97 - 6.99 (m, 4H, ArH), 7.15 - 7.19 (m, 4H, ArH), 7.28 (br. s, 1H, ArH) , 7.48 (br. s, 1H, ArH).^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 17.6 (CH_3), 114.5, 117.5 (CH), 118.3 (C), 125.4, 127.4, 127.5, 129.8, 130.0 (CH), 132.4, 132.9, 134.7, 136.7, 137.2, 142.0, 150.8, 151.8 (C), 159.4 (CO). IR (KBr, cm^{-1}): ν = 3065, 2959, 2922, 2852 (w), 1727, 1715 (s), 1621, 1614 (m), 1594, 1573, 1568, 1543, 1510, 1505, 1479 (w). GC-MS (EI, 70 eV): *m/z* (%) = 380 ($[M]^+$, 2x[^{35}Cl], 100), 352 (11), 252 (18), 253 (13) . HRMS (EI, 70 eV) calcd for $C_{22}H_{14}{}^{35}Cl_2O_2$ ($[M]^+$, 2x[^{35}Cl]): 380.03654, found: 380.03632.

6,7-Bis(4-ethoxyphenyl)-4-methyl-2*H*-chromen-2-one (18d):



Starting with **17** (70 mg, 0.1534 mmol) , **3g** (56 mg, 0.3374 mmol), $Pd(PPh_3)_4$ (11 mg, 6 mol- %, 0.0092 mmol), K_3PO_4 (98 mg, 0.4602 mmol), and 1,4-dioxane (3 ml), **18d** was isolated as a white solid (54 mg, 88 %); mp 188-190 °C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, J = 6.5 Hz, 6H, 2xCH_3), 2.38 (d, J = 1.2 Hz, 3H, CH_3), 3.94 (q, J = 6.9 Hz, 4H, 2xOCH_2), 6.22 (d, J = 1.2 Hz, 1H, CH=), 6.68 - 6.72 (m, 4H, ArH), 6.95 - 6.9 (m, 4H, ArH), 7.27 (br. s, 1H, ArH) , 7.46 (br. s, 1H, ArH).^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 13.8, 17.6, 20.3 (CH_3), 28.6, 62.3 (OCH_2), 113.2, 113.8, 114.4, 117.2 (CH), 117.6 (C), 125.2, 129.7, 129.8 (CH), 130.9, 131.6, 135.7, 143.1, 151.2, 151.5, 157.0, 157.3 (C), 160.9 (CO). IR (KBr, cm^{-1}): ν = 3118, 3093, 3079, 2971, 2935, 2848 (w), 1735 (s), 1631, 1609 (m), 1585, 1549, 1528, 1497 (w). GC-MS (EI, 70 eV): *m/z* (%) = 400 ($[M]^+$,100), 344 (15) . HRMS (EI, 70 eV) calcd for $C_{26}H_{24}O_4$ $[M]^+$: 400.16691; found: 400.16654.

4-Methyl-6,7-diphnyl-2*H*-chromen-2-one (18e):

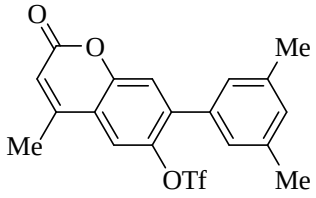


Starting with **17** (70 mg, 0.1534 mmol), **3p** (46 mg, 0.3374 mmol), $Pd(PPh_3)_4$ (11 mg, 6 mol-%, 0.0092 mmol), K_3PO_4 (98 mg, 0.4602 mmol), and 1,4-dioxane (3 ml), **18e** was isolated as a white solid (34 mg, 70 %); mp 163-165°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (d, J = 1.1 Hz, 3H, CH_3), 6.25 (d, J = 1.2 Hz, 1H, CH=), 7.04 - 7.07 (m, 4H, ArH), 7.16 -7.18 (m, 6H, ArH), 7.33 (br. s, 1H, ArH) , 7.53 (br. s, 1H, ArH).^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 18.6 (CH_3), 30.8, 115.1, 118.5, 126.4, 126.9, 127.4, 128.1, 129.6, 129.8 (CH), 137.1, 139.6, 140.1, 144.4, 152.1, 152.6, 153.6 (C), 160.8 (CO). IR (KBr, cm^{-1}): ν = 3110, 3087, 3071, 2963, 2927, 2840 (w),1727 (s), 1623, 1602 (m), 1578, 1542, 1521, 1490 (w). GC-MS (EI, 70 eV): *m/z* (%) = 312 ($[M]^+$,100), 311 (12), 284 (11), 283 (15), 252 (10), 239 (17). HRMS (EI, 70 eV) calcd for $C_{22}H_{16}O_2$ $[M]^+$: 312.11448; found: 312.11468.

General procedure for synthesis (19a-m)

The reactions were carried out in a pressure tube.To a 1,4-dioxane suspension (3 ml) of **17** (70 mg, 0.1534 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol -%, 0.00432 mmol), and arylboronic acid (1.2 equiv.), was added K_3PO_4 (49 mg, 0.230 mmol). The mixture was heated at 70 ^{o}C under Argon atmosphere for 6 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 x 25 ml). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, heptane/EtOAc = 9:1).

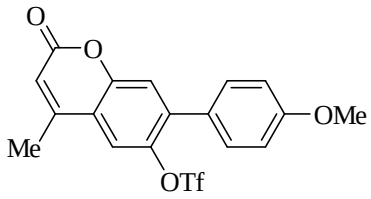
7-(3,5-Dimethylphenyl)-4-methyl-2-oxo-2*H*-chromen-6-yl trifluoromethane-sulfonate (19a):



Starting with **17** (70 mg, 0.1534 mmol), **3a** (28 mg, 0.184 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.00432 mmol), K_3PO_4 (49 mg, 0.230 mmol), and 1,4-dioxane (3 ml), **19a** was isolated as a white solid (47 mg, 75 %); mp 165-167°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 6H, 2xCH_3), 2.31 (d, J = 1.4 Hz, 3H, CH_3), 6.31 (d, J = 1.4 Hz, 1H, CH=), 6.67 (br. s, 1H, ArH), 7.17 (d, J = 8.8 Hz, 3H, ArH), 7.33 (d, J = 8.4 Hz,

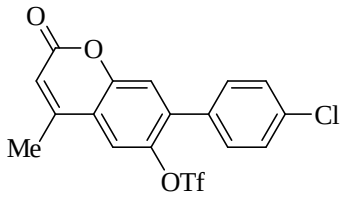
1H, ArH), 7.48 (br. s, 1H, ArH).^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 17.6 (2xCH_3), 20.1 (CH_3), 113.9, 115.2, 118.7 (CH), 125.4 (q, $J_{F,C}$ = 320.4 Hz, CF_3), 126.4, 127.9 (CH), 129.8, 132.8, 136.3, 137.3, 138.4, 141.5, 149.8, 151.3 (C), 160.1 (CO). ^{19}F NMR (282.4, MHz): δ = -73.8 (3F, CF_3). IR (KBr, cm^{-1}): ν = 3057, 2950, 2910, 2838 (w), 1721 (s), 1611, 1606 (m), 1538 (w), 1509, 1491 (m). GC-MS (EI, 70 eV): *m/z* (%) = 412 ($[M]^+$, 100), 280 (20), 279 (30), 264 (12), 235 (11). HRMS (EI, 70 eV) calcd for $C_{19}H_{15}F_3O_5S$ $[M]^+$: 412.05868; found: 412.05840.

7-(4-Methoxyphenyl)-4-methyl-2-oxo-2*H*-chromen-6-yltrifluoro-methanesulfonate (19b):



Starting with **17** (70 mg, 0.1534 mmol), **3b** (28 mg, 0.184 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.00432 mmol), K_3PO_4 (49 mg, 0.230 mmol), and 1,4-dioxane (3 ml), **19b** was isolated as a white solid (51 mg, 80 %); mp 134-136°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (d, *J* = 1.2 Hz, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.30 (d, *J* = 1.3 Hz, 1H, CH=), 6.93 (d, *J* = 8.9 Hz, 2H, ArH), 7.33 - 7.37 (m, 3H, ArH), 7.48 (br. s, 1H, ArH).^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 18.5 (CH_3), 55.3 (OCH_3), 114.3, 116.1, 118.4, (CH), 119.1 (q, $J_{F,C}$ = 320.1 Hz, CF_3), 119.5 (CH), 120.4, 126.3 (C), 130.6 (CH), 138.8, 142.6, 150.9, 152.4, 159.7 (C), 160.9 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -73.6 (3F, CF_3). IR (KBr, cm^{-1}): ν = 3112, 3089, 3074, 2965, 2929, 2841 (w), 1729 (s), 1621, 1605 (m), 1576, 1543, 1520, 1491 (w). GC-MS (EI, 70 eV): *m/z* (%) = 414 ($[M]^+$,100), 282 (20), 281 (30). HRMS (EI, 70 eV) calcd for $C_{18}H_{13}F_3O_6S$ $[M]^+$: 414.03794; found: 414.03813.

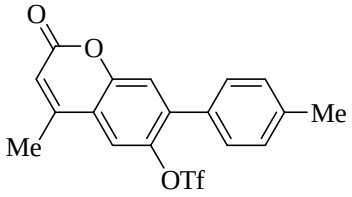
7(4-Chlorophenyl)-4-methyl-2-oxo-2*H*-chromen-6-yltrifluoro-methanesulfonate (19c):



Starting with **17** (70 mg, 0.1534 mmol), **3c** (28 mg, 0.1840 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.00432 mmol), K_3PO_4 (49 mg, 0.230 mmol), and 1,4-dioxane (3 ml), **19c** was isolated as a white solid (55 mg, 85 %); mp 124-125°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (d, *J* = 1.1 Hz, 3H, CH_3), 6.33 (d, *J* = 1.0 Hz, 1H,

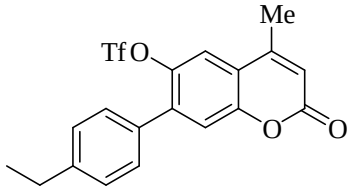
CH=), 6.96 -7.42 (m, 6H, ArH).^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.6 (CH_3), 115.6, 117.5, 119.3,128.1 (CH), 129.4 (q, $J_{F,C}$ = 320.3 Hz, CF_3), 129.6 (CH), 131.4, 134.6, 136.7, 141.3, 149.7, 150.0, 151.3 (C), 158.4 (CO). ^{19}F NMR (282.4, MHz): δ = -73.5 (3F, CF_3). IR (KBr, cm^{-1}): ν = 3080, 3065, 2921, 2850 (w), 1738, 1732, 1615 (s), 1592, 1574, 1538 (w), 1505 (m), 1477 (m). GC-MS (EI, 70 eV): *m/z* (%) = 418 ($[M]^+$, [^{35}Cl], 100), 287 (34), 285 (20), 251 (10), 222 (41), 165 (25). HRMS (EI, 70 eV) calcd for $C_{17}H_{10}O_5{}^{35}ClF_3S$ ($[M]^+$): 417.98841; found: 417.98743.

4-Methyl-2-oxo-7-(*p*-tolyl)-2*H*-chromen-6-yl trifluoromethanesulfonate (19d):



Starting with **17** (70 mg, 0.1534 mmol), **3d** (25 mg, 0.184 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol -%, 0.00432 mmol), K_3PO_4 (49 mg, 0.230 mmol), and 1,4-dioxane (3 ml), **19d** was isolated as a white solid (46 mg, 75 %); mp 135-136°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25 (s, 3H, CH_3), 2.40 (d, *J* = 1.3 Hz, 3H, CH_3), 6.32 (d, *J* = 1.4 Hz, 1H, CH=), 7.11 (d, *J* = 8.2 Hz, 1H, ArH), 7.417 (d, *J* = 8.3 Hz, 1H, ArH),7.32 - 7.42 (m, 3H, ArH), 7.50 (br. s, 1H, ArH).^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 17.51, 17.62 (CH_3), 114.8, 115.1, 115.5, 117.2 (CH), 118.5 (q, $J_{F,C}$ = 319.4 Hz, CF_3), 118.7 (CH),130.3, 136.9, 141.4, 149.7, 151.3, 159.5, 160.6 (C), 163.9 (CO). ^{19}F NMR (282.4, MHz): δ = -73.8 (3F, CF_3). IR (KBr, cm^{-1}): ν = 3067, 2960, 2920, 2848 (w), 1731 (s), 1621, 1606 (m),1548 (w), 1519, 1491 (m). GC-MS (EI, 70 eV): *m/z* (%) = 398 ($[M]^+$, 100), 265 (16), 238 (17), 237 (85), 209 (34), 165 (32). HRMS (EI, 70 eV) calcd for $C_{18}H_{13}F_3O_5S$ $[M]^+$: 398.04303; found: 398.04309.

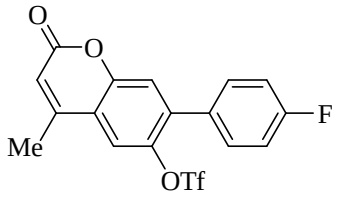
7-(4-Ethylphenyl)-4-methyl-2-oxo-2*H*-chromen-6-yltrifluoromethanesulfonate (19e):



Starting with **17** (70 mg, 0.1534 mmol), **3e** (22 mg, 0.1840 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.00432 mmol), K_3PO_4 (49 mg, 0.230 mmol), and 1,4-dioxane (3 ml), **19e** was isolated as a white solid (53 mg, 84 %); mp 92-94°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 6.3 Hz, 3H, CH_3), 2.38 (d, *J* = 1.3 Hz, 3H, CH_3), 2.61 (q, *J* = 6.2 Hz, 2H, CH_2), 6.23 (d, *J* = 1.4 Hz, 1H, CH=), 6.96 -7.02 (m, 5H, ArH), 7.50 (br. s, 1H, ArH).^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 14.38, 17.62 (CH_3), 28.6

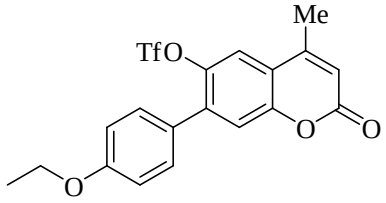
(CH_2), 113.9, 117.4 (CH), 117.7 (C),125.4, 126.5, 128.5 (CH), 128.6 (C), 136.0 (q, $J_{F,C}$ = 320.6 Hz, CF_3), 141.9, 142.4, 143.4, 151.2, 151.5 (C), 159.9 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -73.7 (3F, CF_3). IR (KBr, cm^{-1}): ν = 3458, 3074, 3040 (w), 2962, 2920, 2847 (m), 2351, 1805 (w), 1736, 1612 (s), 1574, 1529, 1495 (w). GC-MS (EI, 70 eV): *m/z* (%) = 412 ([M]$^+$, 100), 280 (19), 279 (84), 222 (25), 221 (15), 165 (15). HRMS (EI, 70 eV) calcd for $C_{19}H_{15}O_5F_3S$ [M]$^+$: 412.0568; found: 412.05853.

7(4-Fluorophenyl)4-methyl-2-oxo-2*H*-chromen-6-yltrifluoromethanesulfonate (19f):



Starting with **17** (70 mg, 0.1534 mmol), **3f** (25 mg, 0.1840 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.00432 mmol), K_3PO_4 (49 mg, 0.230 mmol), and 1,4-dioxane (3 ml), **19f** was isolated as a white solid (48 mg, 78 %); mp 111-112°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (d, J = 1.3 Hz, 3H, CH_3), 6.23 (d, J = 1.2 Hz, 1H, CH=), 6.94 - 6.98 (m, 4H, ArH), 7.29 (br. s, 1H, ArH), 7.49 (br. s, 1H, ArH).^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 17.6 (CH_3), 20.1, 117.4, 117.8 (CH), 118.8 (q, $J_{F,C}$ = 320.1 Hz, CF_3), 127.8 (d, J = 21.6 Hz), 128.6 (d, J = 8.2 Hz) (CH), 135.6, 135.8 (d, J = 3.3 Hz), 136.1, 136.4, 143.4, 146.8 (d, $J_{F,C}$ = 248.9 Hz) (CF), 151.7 (C), 159.9 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -112.4 (ArF), -73.8 (3F, CF_3). IR (KBr, cm^{-1}): ν = 3022, 2961, 2918, 2851 (w), 1731, 1715 (s), 1651 (w), 1621, 1610 (m), 1573, 1568, 1543, 1519, 1514, 1485 (w). GC-MS (EI, 70 eV): *m/z* (%) = 402 ([M]$^+$, 100), 270 (17), 269 (30), 165 (12). HRMS (EI, 70 eV) calcd for $C_{17}H_{10}F_4O_5S$ [M]$^+$: 402.01796; found: 402.01766.

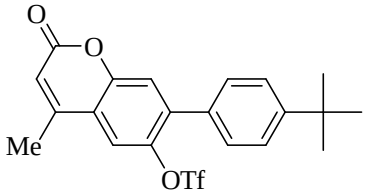
7-(4-Ethoxyphenyl)-4-methyl-2-oxo-2*H*-chromen-6-yltrifluoromethanesulfonate (19g):



Starting with **17** (70 mg, 0.1534 mmol), **3g** (31 mg, 0.1840 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.00432 mmol), K_3PO_4 (49 mg, 0.230 mmol), and 1,4-dioxane (3 ml), **19g** was isolated as a white solid (59 mg, 90 %); mp 122 -124°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (t, J = 6.9 Hz, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.03 (q, J = 9.0 Hz, CH_2), 6.29 (d, J = 1.6 Hz, 1H, CH=), 6.92 (d, J = 8.8 Hz, 2H,

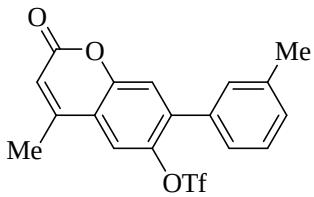
ArH), 7.29 - 7.39 (m, 3H, ArH), 7.48 (br. s, 1H, ArH).^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 18.4, 18.6 (CH_3), 63.5 (OCH_2), 114.7, 116.0, 117.3 (CH), 118.2 (q, $J_{F,C}$ = 320.2 Hz, CF_3), 119.5 (CH), 127.3 (C), 130.5 (CH), 138.8, 142.6, 150.0, 150.8, 152.5, 158.2 (C), 159.8 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -73.7 (3F, CF_3). IR (KBr, cm^{-1}): *v* = 3119, 3081, 2988, 2923, 2852 (w), 1728 (s), 1660 (w), 1607 (m), 1576, 1542, 1522, 1496 (w). GC-MS (EI, 70 eV): *m/z* (%) = 428 ($[M]^+$,100), 296 (19), 295 (30), 267 (69). HRMS (EI, 70 eV) calcd for $C_{19}H_{15}F_3O_6S$ $[M]^+$: 428.05359; found: 428.05397.

7-(4-Tert-butylphenyl)-4-methyl-2-oxo--2*H*-chromen-6-yltrifluoromethanesulfonate (19h):



Starting with **17** (70 mg, 0.1534 mmol), **3i** (33 mg, 0.1840 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.00432 mmol), K_3PO_4 (49 mg, 0.230 mmol), and 1,4-dioxane (3 ml), **19h** was isolated as a white solid (52 mg,77 %); mp 131-133°C. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 1.23 (s, 9H, $3CH_3$), 2.40 (d, *J* = 1.2 Hz, 3H, CH_3), 6.31 (d, *J* = 1.4 Hz, 1H, CH=), 7.34 (d, *J* = 8.8 Hz, 3H, ArH), 7.44 (d, *J* = 8.3 Hz, 2H, ArH),7.50 (br. s, 1H, ArH).^{13}C NMR (75.47 MHz, $CDCl_3$): *δ* = 17.5 (CH3), 30.20 ($3CH_3$), 33.7 (C), 115.2, 117.1, 118.7, 124.7 (CH), 125.1 (q, $J_{F,C}$ = 320.4 Hz, CF_3), 127.9 (CH), 138.0, 141.7, 138.0, 141.7, 149.9, 151.3, 151.6 (C), 158.7 (CO). ^{19}F NMR (282.4, MHz): *δ* = -73.7 (3F, CF_3). IR (KBr, cm^{-1}): *v* = 3070, 2963, 2923, 2851 (w), 1734 (s), 1624, 1609 (m), 1551 (w), 1521, 1494 (m). (w). GC-MS (EI, 70 eV): *m/z* (%) = 440 ($[M]^+$, 100), 265 (16), 238 (17), 237 (85), 209 (34), 165 (32). HRMS (EI, 70 eV) calcd for $C_{21}H_{19}F_3O_5S$ $[M]^+$: 440.08998; found: 440.04309.

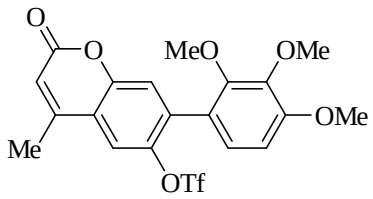
4-Methyl-2-oxo-7-(*m*-tolyl)-2*H*-chromen-6-yl trifluoromethanesulfonate (19i):



Starting with **17** (70 mg, 0.1534 mmol), **3j** (25 mg, 0.1840 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.00432 mmol), K_3PO_4 (49 mg, 0.230 mmol), and 1,4-dioxane (3 ml), **19i** was isolated as a white solid (48 mg, 80 %); mp 85-86°C. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 2.20 (s, 3H, CH_3), 2.39 (d, *J* = 1.2 Hz, 3H, CH_3), 6.24 (d, *J* = 1.3 Hz, 1H, CH=), 6.8 (d, *J* = 8.3 Hz, 2H, ArH), 7.01 - 7.03 (m, 2H, ArH), 7.31 (br. s, 1H, ArH) ,

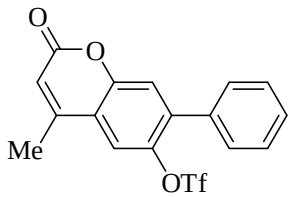
7.50 (br. s, 1H, ArH).^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 17.51, 17.62 (CH_3), 114.8, 115.1, 115.5, 117.2 (CH), 118.5 (q, $J_{F,C}$ = 319.4 Hz, CF_3), 118.7 (CH), , 130.3, 136.9, 141.4, 149.7, 151.3, 159.5, 160.6 (C), 163.9 (CO). ^{19}F NMR (282.4, MHz): δ = -73.7 (3F, CF_3). IR (KBr, cm^{-1}): ν = 3070, 2961, 2921, 2849 (w), 2961 (s), 2905, 2855 (m), 1548 (w), 1519, 1491 (m). GC-MS (EI, 70 eV): *m/z* (%) = 398 ([M]$^+$, 100), 266 (18), 265 (30), 209 (11). HRMS (EI, 70 eV) calcd for $C_{18}H_{13}F_3O_5S$ [M]$^+$: 398.04303; found: 398.04297.

4-Methyl-2-oxo-7-(2,3,4-trimethoxyphenyl)- 2*H*-chromen-6-yl trifluoromethane-sulfonate (19j):



Starting with **17** (70 mg, 0.1534 mmol), **3o** (33 mg, 0.184 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.00432 mmol), K_3PO_4 (49 mg, 0.230 mmol), and 1,4-dioxane (3 ml), **19j** was isolated as a white solid (65 mg, 90 %); mp 155-157°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (d, *J* = 1.2 Hz, 3H, CH_3), 3.78 (s, 3H, OCH_3), 3.84 (d, *J* = 6.9 Hz, 6H, 2xOCH_3), 6.31 (d, *J* = 1.3 Hz, 1H, CH=), 6.68 (d, *J* = 8.4 Hz, 1H, ArH), 6.89 (d, *J* = 8.3 Hz, 1H, ArH), 7.31 (br. s, 1H, ArH), 7.45 (br. s, 1H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 17.4 (CH_3), 55.0, 59.8, 59.9 (OCH_3), 106.1, 115.1, 116.1 (CH), 118.8 (C), 119.1 (q, $J_{F,C}$ = 319.1 Hz, CF_3), 119.5 (CH), 119.6 (C), 124.4 (CH), 135.2, 141.1, 142.5, 149.9, 150.3, 151.0, 154.0, (C), 158.8 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -73.9 (3F, CF_3). IR (KBr, cm^{-1}): ν = 3110, 3087, 3072, 2963, 2927, 2839 (w), 1727 (s), 1619, 1603 (m), 1574, 1541, 1520, 1492 (w). GC-MS (EI, 70 eV): *m/z* (%) = 474 ([M]$^+$,100), 341 (22), 310 (30), 295 (12). HRMS (EI, 70 eV) calcd for $C_{20}H_{17}F_3O_8S$ [M]$^+$: 474.05907; found: 474.05931.

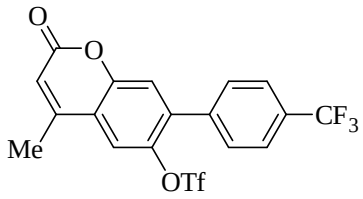
4-Methyl-2-oxo-7-phenyl-2*H*-chromen-6-yl trifluoromethanesulfonate (19k):



Starting with **17** (70 mg, 0.1534 mmol), **3p** (22 mg, 0.1840 mmol), $Pd(PPh_3)_4$ (5 mg, 3mol-%, 0.00432 mmol), K_3PO_4 (49 mg, 0.230 mmol), and 1,4-dioxane (3 ml), **19k** was isolated as a white solid (42 mg, 72 %); mp 95-96°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3H, CH_3), 6.26 (s, 1H, CH=), 7.07 - 7.18 (m, 5H, ArH), 7.36 (d, *J* = 8.3 Hz, 1H, ArH), 7.53 (br. s, 1H, ArH) .^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 17.64

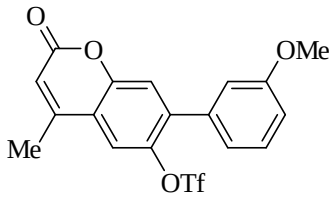
(CH_3), 114.2, 117.5, 125.4, 126.4 (CH), 127.7 (q, $J_{F,C}$ = 320.2 Hz, CF_3), 128.2, 128.8 (CH), 136.1, 138.6, 139.2, 143.4, 151.1, 151.7 (C), 159.8 (CO). ^{19}F NMR (282.4, MHz): δ = -73.7 (3F, CF_3). IR (KBr, cm^{-1}): ν = 3090, 2981, 2941, 2869 (w), 2981 (s), 2925, 2875 (m), 1568 (w), 1529, 1496 (m). GC-MS (EI, 70 eV): *m/z* (%) = 384 ($[M]^+$, 100), 252 (18), 251 (30), 195 (19), 152 (13). HRMS (EI, 70 eV) calcd for $C_{17}H_{11}F_3O_5S$ $[M]^+$: 384.02738; found: 384.02760.

4-Methyl-2-oxo-7-[4-(trifluoromethan)phenyl]-2*H*-chromen-6-yl trifluorometha-nesulfonate (19l):



Starting with **17** (70 mg, 0.1534 mmol), **3g** (35 mg, 0.184 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol -%, 0.00432 mmol), K_3PO_4 (49 mg, 0.230 mmol), and 1,4-dioxane (3 mL), **19l** was isolated as a white solid (58 mg, 83 %); mp 101-102°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42 (d, *J* = 1.3 Hz, 3H, CH_3), 6.30 (d, *J* = 1.2 Hz, 1H, CH=), 7.17 (d, *J* = 8.07 Hz, 2H, ArH), 7.33 (br. s, 1H, ArH), 7.46 (d, *J* = 8.24 Hz, 2H, ArH), 7.54 (br. s, 1H, ArH) .^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 17.6 (CH_3), 114.9, 117.8, 118.8 (CH), 122.2 (q, $J_{F,C}$ = 320.4 Hz, CF_3), 124.3 (d, *J* = 21.6 Hz), 125.7 (d, *J* = 8.2 Hz) (CH), 135.6 (d, *J* = 32.6 Hz), 135.8, 136.1(d, *J* = 1.1 Hz),, 136.4, 143.4, 146.8 (d, $J_{F,C}$ = 248.9 Hz, CF_3) , 151.7, 152.1 (C), 159.9 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -112.4, - 62.6 (3F, CF_3) . IR (KBr, cm^{-1}): ν = 3053, 2961, 2905, 2854 (w), 1723, 1614 (s), 1574, 1547, 1488 (w). GC-MS (EI, 70 eV): *m/z* (%) = 452 ($[M]^+$, 100), 270 (17), 269 (30), 165 (12). HRMS (EI, 70 eV) calcd for $C_{18}H_{10}F_6O_5S$ $[M]^+$: 452.01476 ; found: 452.12567.

7-(3-Methoxyphenyl)-4-methyl-2-oxo-2*H*-chromen-6-yltrifluoromethanesulfonate (19m):



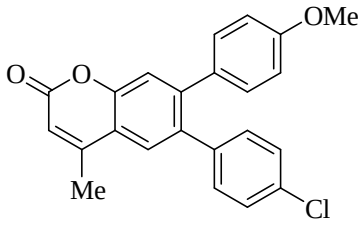
Starting with **17** (70 mg, 0.1534 mmol), **3r** (28 mg, 0.184 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol- %, 0.00432 mmol), K_3PO_4 (49 mg, 0.230 mmol), and 1,4-dioxane (3 ml), **19m** was isolated as a white solid (44 mg,70 %); mp 112-114°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (d, *J* = 1.3 Hz, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.32 (d, *J* = 1.3 Hz, 1H, CH=), 6.91 - 6.93 (m, 2H, ArH), 6.95 (d, *J* = 8.8 Hz, 1H, ArH), 7.30

(d, J = 8.8 Hz 1H, ArH), 7.36 (br. s, 1H, ArH), 7.49 (br. s, 1H, ArH).^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 17.5 (CH_3), 54.3 (OCH_3), 113.8, 113.9, 115.1, 115.4, 118.8 (CH), 119.1 (q, $J_{F,C}$ = 320.1 Hz, CF_3), 120.6, 128.8 (CH), 134.2, 137.9, 141.5, 149.7, 151.3, 158.6, 159.1 (C), 160.9 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -73.7 (3F, CF_3). IR (KBr, cm^{-1}): ν = 3112, 3089, 3074, 2965, 2929, 2841 (w), 1731 (s), 1621, 1600, 1582 (m), 1547, 1506, 1482, 1468 (w). GC-MS (EI, 70 eV): *m/z* (%) = 414 ($[M]^+$,100), 282 (18), 281 (40), 67 (18). HRMS (EI, 70 eV) calcd for $C_{18}H_{13}F_3O_6S$ $[M]^+$: 414.03794; found: 414.03799.

General procedure for synthesis (20a-d)

The reactions were carried out in a pressure tube. A 1,4-dioxane suspension (3 ml) of bis(triflates) analogue **17** (70 mg, 0.1534 mmol), $Pd(PPh_3)$ (5 mg, 3 mol -%, 0.00432 mmol), and $Ar^1B(OH)_2$ (1.2 equiv.), K_3PO_4 (49 mg, 0.2301 mmol) was added. The mixture was heated at 70°C under Argon atmosphere. After 6 h, a dioxan (3 ml) suspension of $Ar^2B(OH)_2$ (1.2 equiv.), $Pd(PPh_3)_4$ (5 mg, 3mol-%, 0.00432 mmol), K_3PO_4 (49 mg, 0.2301 mmol) was added. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 x 25 ml). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, heptane/EtOAc = 8:2).

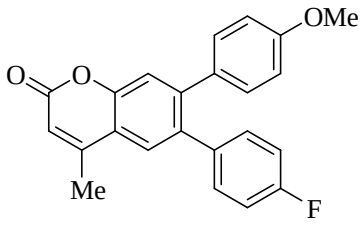
6-(4-Chlorophenyl)-7-(4-methoxyphenyl)-4-methyl-2*H*-chromen-2-one (20a):



Starting with **17** (70 mg, 0.1534 mmol) , **3b** (28 mg, 0.1840 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol -%, 0.00432 mmol), K_3PO_4 (49 mg, 0.2301 mmol), **3c** (28 mg, 0.1840 mmol), $Pd(PPh_3)_4$ (5 mg, 3mol-%, 0.00432 mmol), K_3PO_4 (49 mg, 0.2301 mmol), and 1,4-dioxane (3 ml), **20a** was isolated as a white solid (42 mg, 73 %); mp 172-174°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (d, J = 1.1 Hz, 3H, CH_3), 3.73 (s, 3H, OCH_3), 6.24 (d, J = 1.3 Hz, 1H, CH=), 6.72 (d, J = 8.1 Hz, 2H, ArH), 6.95 - 6.99 (m, 5H, ArH), 7.16 (d, J = 8.1 Hz, 2H, ArH), 7.46 (br. s, 1H, ArH) .^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 17.6 (CH_3), 54.2 (OCH_3), 112.7, 114.1, 117.4 (CH), 117.8 (C), 125.3, 127.4, 129.8, 130.0 (CH), 130.5, 132.0,

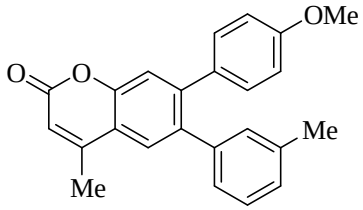
134.7, 137.8, 143.1, 151.0, 151.9, 158.1 (C), 159.7 (CO). IR (KBr, cm^{-1}): ν = 3115, 3092, 3076, 2966, 2932, 2845 (w), 1731 (s), 1620, 1600 (m), 1580, 1540, 1522, 1493 (w). GC-MS (EI, 70 eV): *m/z* (%) = 376 ($[M]^+$,[^{35}Cl], 100), 348 (13) . HRMS (EI, 70 eV) calcd for $C_{23}H_{17}{}^{35}ClO_3$ ($[M]^+$): 376.08607; found 376.08589.

6-(4-Florophenyl)-7-(4-methoxyphenyl)-4-methyl-2*H*-chromen-2-one (20b):



Starting with **17** (70 mg, 0.1534 mmol) , **3b** (28 mg, 0.1840 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol -%, 0.00432 mmol), K_3PO_4 (49 mg, 0.2301 mmol), **3f** (25 mg, 0.1840 mmol), $Pd(PPh_3)_4$ (5 mg, 3mol-%, 0.00432 mmol), K_3PO_4 (49 mg, 0.2301 mmol), and 1,4-dioxane (3 ml), **20b** was isolated as a white solid (43 mg, 78 %); mp 192-194°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (d, *J* = 1.3 Hz, 3H, CH_3), 3.72 (s, 3H, OCH_3), 6.24 (d, *J* = 1.2 Hz, 1H, CH=), 6.70 (d, *J* = 8.4 Hz, 2H, ArH), 6.88 - 7.03 (m, 6H, ArH), 7.28 (br. s, 1H, ArH), 7.46 (br. s, 1H, ArH) .^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 17.6 (CH_3), 54.2 (OCH_3), 112.7, 114.2 (d, *J* = 8.2 Hz), 117.3 (CH), 117.7 (C) ,125.3, 129.8, 130.3 (d, *J* = 21.6 Hz), 130.7 (CH), 134.9 (q, $J_{F,C}$ = 273.1 Hz)(CF), 135.4 143.1, 151.0, 151.8, 158.1, 159.3, 159.8 (C), 162.5 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = - 115.3 (ArF) . IR (KBr, cm^{-1}): ν = 3115, 3092, 3076, 2966, 2932, 2845 (w), 1731 (s), 1620, 1600 (m), 1580, 1540, 1522, 1493 (w). GC-MS (EI, 70 eV): *m/z* (%) = 360 ($[M]^+$, 100), 348 (13) . HRMS (EI, 70 eV) calcd for $C_{23}H_{17}FO_3$ ($[M]^+$): 360.11562; found: 360.11580.

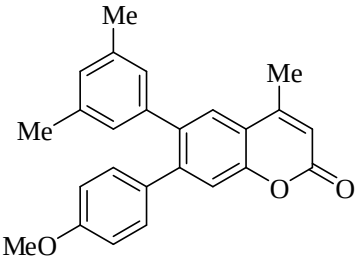
7-(4-Methoxyphenyl)-4-methyl-6-(*m*-tolyl)-2*H*-chromen-2-one (20c):



Starting with **17** (70 mg, 0.1534 mmol) , **3b** (28 mg, 0.1840 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.00432 mmol), K_3PO_4 (49 mg, 0.2301 mmol as solid?), **3j** (25 mg, 0.1840 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.00432 mmol), K_3PO_4 (49 mg, 0.2301 mmol), and 1,4-dioxane (3 ml), **20c** was isolated as a white solid (41 mg, 75 %); mp 209-211°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.21 (s, 3H, CH_3), 2.37 (d, *J* = 1.2 Hz, 3H, CH_3), 3.69 (s, 3H, OCH_3), 6.21 (d, *J* = 1.3 Hz, 1H, CH=), 6.70 (d, *J* = 8.4 Hz, 2H, ArH), 6.81 (d, *J* = 8.9 Hz, 2H, ArH), 6.93 - 7.06 (m, 4H, ArH), 7.27

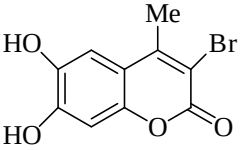
(br. s, 1H, ArH) , 7.48 (br. s, 1H, ArH).^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 17.6, 20.3 (CH_3), 54.1 (OCH_3), 112.5, 113.8, 117.1 (CH), 117.6 (C), 152.4, 125.9, 126.6, 126.9, 129.3, 129.7 (CH), 131.0, 136.1, 136.8, 139.3, 143.1, 151.2, 151.6, 158.0 (C), 159.9 (CO). IR (KBr, cm^{-1}): *ν* = 3111, 3094, 3077, 2967, 2931, 2846 (w), 1732 (s), 1624, 1606 (m), 1583, 1547, 1526, 1495 (w). GC-MS (EI, 70 eV): *m/z* (%) = 356 ($[M]^+$,100), 341(10) . HRMS (EI, 70 eV) calcd for $C_{24}H_{20}O_3$ ($[M]^+$) : 356.14070; found: 356.14106.;

6-(3,5-Dimethlyphenyl)-7-(4-methoxyphenyl)-4-methyl-2*H*-chromen-2-one (20d):



Starting with **17** (70 mg, 0.1534 mmol) , **3b** (28 mg, 0.1840 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.00432 mmol), K_3PO_4 (49 mg, 0.2301 mmol), **3a** (27 mg, 0.1840 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol-%, 0.00432 mmol), K_3PO_4 (49 mg, 0.2301 mmol), and 1,4-dioxane (3 ml), **20d** was isolated as a white solid (46 mg, 81 %); mp 203-205°C. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 2.15 (6H, 2xCH_3), 2.38 (d, *J* = 1.4 Hz, 3H, CH_3), 3.71 (s, 3H, OCH_3), 6.22 (d, *J* = 1.3 Hz, 1H, CH=), 6.67 - 6.79 (m, 5H, ArH), 6.99 (d, *J* = 8.4 Hz, 2H, ArH), 7.28 (br. s, 1H, ArH) , 7.47 (br. s, 1H, ArH).^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 17.6 (2xCH_3), 21.6 (CH_3), 54.2 (OCH_3), 113.8, 114.1 (CH), 117.1 (C), 117.5 (CH), 125.3 (C), 126.4, 126.6, 127.5, 129.7, 131.0 (CH), 136.2, 136.5, 136.6, 139.2, 143.1, 151.2, 151.6, 157.9 (C), 159.9 (CO). IR (KBr, cm^{-1}): *ν* = 3117, 3094, 3078, 2969, 2934, 2847 (w), 1734 (s), 1627, 1609 (m), 1585, 1549, 1528, 1497 (w). GC-MS (EI, 70 eV): *m/z* (%) = 370 ($[M]^+$,100), 355 (12), 300 (11). HRMS (EI, 70 eV) calcd for $C_{25}H_{22}O_3$ ($[M]^+$) : 370.15635; found: 370.15622.

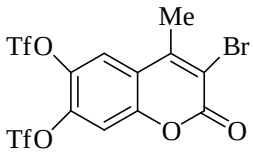
3-Bromo-6,7-dihydroxy-4-methyl-2*H*-chromen-2-one (21):



To asolution of 4-Methyl-6,7-dihydroxycoumarin **16** (1.0 equive, 0.0026 mol, 0.5 gm) in glacial acetic acid (20 ml) bromine (2.0 equive, 0.0052 mol, 0.8 gm) were added dropwise under argon atmosphere, the reaction mixture was stirred at 30°C for 2 hr, the reaction monitored by TLC (heptane / EtOAc = 9.5 : 0.5). the reaction mixture mpoured in ice-cold water (250

ml), stirred with a solution of sodium hydrogen sulphite till the yellow color disappears, filtered and the residue was purified by column chromatography (silica gel, heptane / EtOAc = 10 : 1).to give **21** as a yellow solid (0.52 g, 75 %), mp 181-183°C. NMR (300 MHz, $CDCl_3$): δ = 2.50 (s, 3H, CH_3), 6.77 (s, 1H, ArH), 7.09 (s, 1H, ArH), 9.80 (s, 1H, OH), 10.30 (s, 1H, OH).^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 19.4 (CH_3), 102.4 (CH), 107.6 (C) , 109.9 (CH), 111.2, 143.3, 146.1, 150.5 (C), 161.3 (CO). IR (KBr, cm^{-1}): ν = 3057, 2995, 2950, 2930, 2831 (w), 1599 (s), 1574, 1551 (w). GC-MS (EI, 70 eV): *m/z* (%) = 272 ($[M+H]^+$, [^{81}Br], 100), 271 ($[M]^+$, [^{81}Br], 26), 270 ($[M+H]^+$, [^{79}Br], 99), 269 ($[M]^+$, [^{79}Br], 10), 244 (20), 242 (22), 192 (12), 191 (17),164 (58), 89 (16). HRMS (EI, 70 eV) calcd for $C_{10}H_8{}^{81}BrO_4$ $[M+H]^+$: 272.9581, found: 272.9574, $C_{10}H_8{}^{79}BrO_4$ $[M+H]^+$: 270.96005, found: 270.95949

3-Bromo-4-methyl-2-oxo-2*H*-chromene-6,7-diylbis-(trifluoromethanesulfonate) (22):

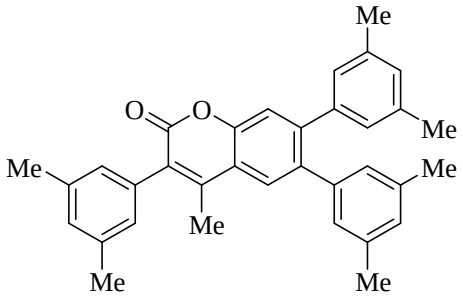


To a solution of 3-bromo-4-methyl-6,7-dihydroxycoumarine **21** (0.5 g, 2.60 mmol) in CH_2Cl_2 (30 ml) was added triethylamine (0.36 ml, 10.4 mmol) at room temperature under an argon atmosphere. After 10 min, Tf_2O (1.0 ml, 6.2 mmol) was added at -78°C. The mixture was allowed to warm to 20°C and stirred for 6 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography (flash silica gel, heptane / EtOAc = 8 : 2) without aqueous work up to give **22** as a white solid (0.9 g, 75 %); mp 125-27°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.58 (CH_3), 7.45 (s , 1H, ArH), 7.79 (s, 1H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 18.80 (CH_3), 111.6 (CH), 115.2 (C), 115.5 (q, $J_{F,C}$ = 316.0 Hz, CF_3), 118.9 (C), 119.2 (CH), 120.3 (q, $J_{F,C}$ = 316.0 Hz, CF_3), 135.9, 140.6, 147.6, 149.7 (C), 153.9 (CO). ^{19}F NMR (282.4, MHz): δ = -72.7, -72.9 (3F, CF_3). IR (KBr, cm^{-1}): ν = 3123, 3051, 2962, 2925 (w), 1742 (s), 1670, 1621, 1612, 1571 (w), 1492 (m). GC-MS (EI, 70 eV): *m/z* (%) = 535 ($[M]^+$,[^{81}Br], 19), 533 ($[M]^+$,[^{79}Br], 17), 403 (27), 401 (24), 311 (28), 281 (11), 309 (29), 202 (13), 77 (25). HRMS (EI, 70 eV) calcd for $C_{12}H_5O_8{}^{81}BrF_6S_2$ $[M]^+$: 535.84875, found: 535.84860, $C_{12}H_5O_8{}^{79}BrF_6S_2$ $[M]^+$: 533.85079, found: 533.85079.

General procedure for synthesis (23a-o)

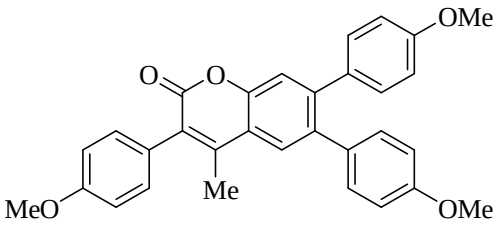
The reactions were carried out in a pressure tube. A 1,4-dioxane solution (3 ml) of **22,** arylboronic acid (3.1equiv.), aqueous K_2CO_3 (2 M, 2 ml) and $Pd(PPh_3)_4$ (14 mg, 9 mol-%, 0.01212 mmol) was heated at 120°C for 10 h under argon atmosphere. After cooling to 20°C, H_2O was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 25 ml). The organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, heptane/EtOAc = 9:1).

3,6,7-Tris(3,5-dimethylphenyl)-4-methyl-2*H*-chromen-2-one (23a):



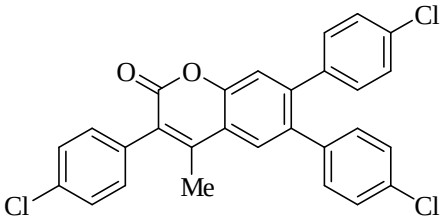
Starting with **22** (70 mg, 0.1308 mmol), **3a** (61 mg, 0.406 mmol) and $Pd(pph_3)_4$ (14 mg, 9 mol-%, 0.01212 mmol) , K_2CO_3 (2 M, 2 ml), and 1,4-dioxane (3 ml), **23a** was isolated as a white solid (43 mg, 70 %), mp 190-192°C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.13 (s, 6H, 2xCH_3), 2.14 (s, 6H, 2xCH_3), 2.24 (s, 3H, CH_3), 2.28 (s, 6H, 2xCH_3), 6.68 - 6.69 (m, 5H, ArH), 6.79 - 6.84 (m, 5H, ArH), 6.94 (d, *J* = 8.6, Hz, 1H, ArH), 7.32 (s, 1H, ArH). 7.55 (br. s, 2H, ArH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.5 (2xCH_3), 20.2 (2xCH_3), 20.3 (2xCH_3), 28.6 (CH_3), 116.9 (CH), 118.3 (C), 125.6, 126.4, 126.5, 126.6, 127.3, 127.8, 127.9 (CH), 133.4, 136.3, 136.3, 136.8, 138.6, 139.3, 143.1, 143.1, 143.2, 146.3, 147.4, 150.6, 154.2 (C),161.2 (CO). IR (KBr, cm^{-1}): *v* = 3012, 2955 (w), 2919 (m), 2853 (w), 1707 (s), 1610, 1597 (m), 1552, 1495 (w). GC - MS (EI, 70 eV): *m/z* (%) = 472 ([M]$^+$, 100), 444 (15), 429 (12), 214 (14), 179 (10). HRMS (EI, 70 eV) calcdfor $C_{34}H_{32}O_2$ [M]$^+$: 472.240 ; found: 472.24014.

3,6,7-Tris(4-methoxyphenyl)-4-methyl-2*H*-chromen-2-one (23b):



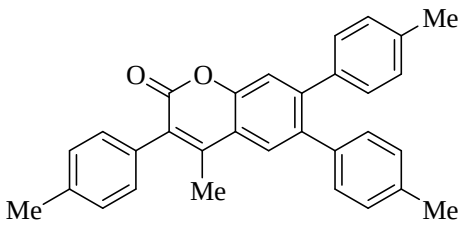
Starting with **22** (70 mg, 0.1308 mmol), **3b** (62 mg, 0.406 mmol), $Pd(PPh_3)_4$ (14 mg, 9 mol-%, 0.01212 mmol), K_2CO_3 (2 M, 2 ml), and 1,4-dioxane (3 ml), **23b** was isolated as a white solid (50 mg, 80 %), mp 169-170°C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3H, CH_3), 3.72 (s, 6H, 2xOMe), 3.78 (s, 3H, OMe), 6.73 (dd, *J* = 1.7, 8.3 Hz, 4H, ArH), 6.93 (d, *J* = 8.6, Hz, 2H, ArH), 6.99 (dd, *J* = 1.6, 8.6 Hz, 4H, ArH), 7.23 (d, *J* = 8.6, Hz, 2H, ArH), 7.30 (s, 1H, ArH), 7.53 (s, 1H, ArH).^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 16.6 (CH_3), 55.2, 55.3, 55.5 (OMe), 113.6, 113.8, 117.9, 119.4, 126.6 (CH), 126.7, 126.9 (C), 130.8, 130.9, 131.3, 131.6 (CH),132.2, 132.9, 136.6, 143.4, 147.1, 151.6, 158.6, 158.9, 159.4 (C), 161.3 (CO). IR (KBr, cm^{-1}): ν = 3059, 2993, 2952, 2931, 2834 (w), 1715, 1599 (s), 1574, 1551 (w). GC-MS (EI, 70 eV): *m/z* (%) = 478 ($[M]^+$, 100), 450 (14), 207 (13). HRMS (EI, 70 eV) calcd for $C_{31}H_{26}O_5$ $[M]^+$: 478.53514; found: 478.53412.

3,6,7-Tris(4-chlorophenyl)-4-methyl-2*H*-chromen-2-one (23c):



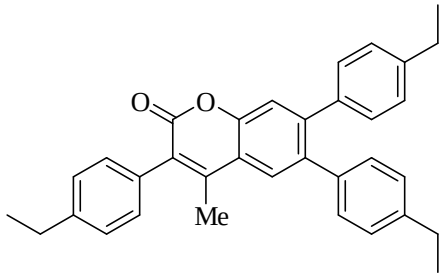
Starting with **22** (70 mg, 0.1308 mmol), **3c** (61 mg, 0.406 mmol) and $Pd(pph_3)_4$ (14 mg, 9 mol-%, 0.01212 mmol) , K_2CO_3 (2 M, 2 ml), and 1,4-dioxane (3 ml), **23c** was isolated as a white solid (39 mg, 60 %), mp 200-201°C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3H, CH_3), 6.97 - 7.02 (m, 3H, ArH), 7.14 - 7.21 (m, 5H, ArH), 7.27 - 7.40 (m, 6H, ArH) .^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 16.6 (CH_3), 114.1, 114.2, 114.3, 115.2, 117.8, 119.3 (CH), 124.4 (C), 124.7, 124.8 (CH), 128.7, 128.8, 130.3, 132.0, 132.8, 134.6, 143.4, 145.2, 150.5, 151.5, 156.9 (C), 160.4 (CO). IR (KBr, cm^{-1}): ν = 3067, 3032, 2979, 2927, 2918, 2888, 2839 (w), 1715, 1599 (s), 1572, 1548, 1519 (w), 1512 (m). GC-MS (EI, 70 eV): *m/z* (%) = GC - MS (EI, 70 eV): *m/z* (%) = 490 ($[M]^+$, 3×[^{35}Cl], 99), 345 (45), 270 (15). HRMS (EI, 70 eV) calcd for $C_{28}H_{17}{}^{35}Cl_3O_2$ $[M]^+$: 490.02886, found 490.02834.

4-Methyl-3,6,7-trip-tolyl-2*H*-chromen-2-one (23d):



Starting with **22** (70 mg, 0.1308 mmol), **3d** (55 mg, 0.406 mmol) and $Pd(pph_3)_4$ (14 mg, 9 mol-%, 0.01212 mmol) , K_2CO_3 (2 M, 2 ml), and 1,4-dioxane (3 ml), **23d** was isolated as a white solid (42 mg, 75 %), mp 163-165^oC.^1H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 6.99 (br. s, 1H, ArH) 7.12 (d, *J* = 8.3, Hz, 2H, ArH), 7.18 - 7.23 (m, 5H, ArH), 7.28 - 7.34 (m, 2H, ArH), 7.55 (s, 2H, ArH), 7.64 (br. s, 2H, ArH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.2, 16.3, 20.1, 20.3 (CH_3), 28.5 (C), 117.2, 118.1, 118.2 (CH), 118.5 (C), 125.6, 125.9, 126.1, 126.4, 126.3 (CH), 129.4, 133.2, 136.1, 136.3, 137.0, 138.5, 139.4, 143.2, 146.2, 150.6 (C), 160.3 (CO). IR (KBr, cm^{-1}): *v* = 2962, 2923, 2854 (w), 1715 (s), 1608 (m), 1586, 1551, 1479 (w). GC-MS (EI, 70 eV): *m/z* (%) = 430 ($[M]^+$, 100), 420 (22), 413 (13), 186 (18). HRMS (EI, 70 eV) calcd for $C_{31}H_{26}O_2$ $[M]^+$: 430.19328 ; found: 430.19355.

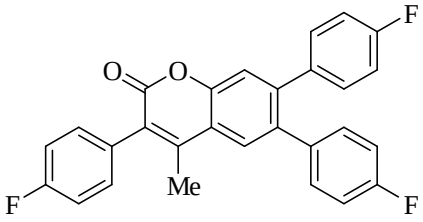
3,6,7-Tris(4-ethylphenyl)-4-methyl-2*H*-chromen-2-one (23e):



Starting with **22** (70 mg, 0.1308 mmol), **3e** (61 mg, 0.406 mmol) and $Pd(pph_3)_4$ (14 mg, 9 mol-%, 0.01212 mmol) , K_2CO_3 (2 M, 2 ml), and 1,4-dioxane (3 ml), **23e** was isolated as a white solid (46 mg, 75 %), mp 134-135^oC.^1H NMR (300 MHz, $CDCl_3$): δ = 1.11 - 1.23 (m, 9H, 3xCH_3), 2.26 (s, 3H, CH_3), 2.50 - 2.61 (m, 6H, 3xCH_2), 6.68 - 6.71 (m, 4H, ArH), 6.77 (d, *J* = 8.6, Hz, 2H, ArH), 6.87 (dd, *J* = 1.6, 8.6 Hz, 4H, ArH), 7.13 (d, *J* = 8.6, Hz, 3H, ArH), 7.51 (s, 1H, ArH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.3, 15.4, 15.5, 16.6 (CH_3), 28.4, 28.6, 28.7 (CH_2), 118.1, 119.5, 127.1 (CH), 127.2, 127.6 (C), 127.9, 129.6, 129.7, 130.1, 131.7 (CH), 137.0, 137.1, 137.8, 142.9, 143.4, 143.9, 144.2, 147.3, 151.7, 152.8, (C), 161.2 (CO). IR (KBr, cm^{-1}): *v* = 3407, 3071, 3024, 2962, 2927, 2871, 2854 (w), 1722 (s), 1613, 1604 (m), 1573, 1568, 1556, 1552 (w). GC-MS (EI, 70 eV): *m/z* (%) = 472 ($[M]^+$,

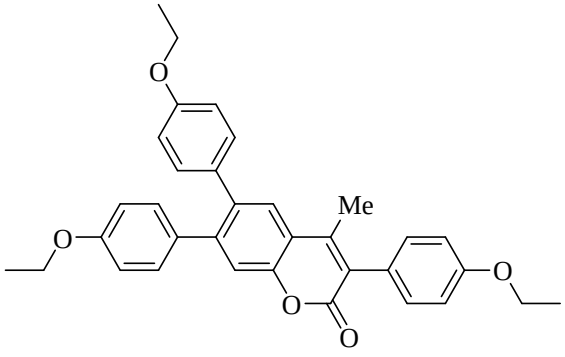
100), 444 (13), 443 (12). HRMS (EI, 70 eV) calcd for $C_{34}H_{32}O_2$ $[M]^+$: 472.23968; found: 472.23912.

3,6,7-Tris(4-fluorophenyl)-4-methyl-2*H*-chromen-2-one (23f):



Starting with **22** (70 mg, 0.1308 mmol), **3f** (59 mg, 0.406 mmol), $Pd(PPh_3)_4$ (14 mg, 9 mol-%, 0.01212 mmol), K_2CO_3 (2 M, 2 ml), and 1,4-dioxane (3 ml), **23f** was isolated as a white solid (40 mg, 70 %), mp. 222- 224°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3H, CH_3) , 6.86 - 6.92 (m, 4H, ArH), 7.00 - 7.04 (m, 4H, ArH), 7.12 (d, J = 8.52 Hz, 2H, ArH), 7.21 - 7.26 (m, 2H, ArH), 7.32 (s, 1H, ArH), 7.56 (s, 1H, ArH).^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.6 (CH_3), 114.1 (d, $J_{F,C}$ = 21.4 Hz), 114.4 (d, $J_{F,C}$ = 21.4 Hz), 115.6 (d, $J_{F,C}$ = 21.4 Hz), 117.2 (CH), 118.6, 125.6 (C), 126.0 (CH), 129.1 (d, $J_{F,C}$ = 3.5 Hz) (C), 130.2, 130.3 (CH), 130.4 (C), 130.8 (d, $J_{F,C}$ = 1.7 Hz) (CH), 142.0, 146.5, 150,9, 159.3, 159.6, 159.7 (C), 159.9 (d, $J_{F,C}$ = 246.9 Hz)(CF), 162.6 (d, $J_{F,C}$ = 246.0 Hz) (CF), 162.9 (d, $J_{F,C}$ = 247.4 Hz)(CF), 163.2 (CO). ^{19}F NMR (282.4, MHz): δ = -113.1, -144.8, -114.9 (ArF). IR (KBr, cm^{-1}): ν = 3038, 2929, 2859, 1892 (w), 1604 (m), 1558 (w), 1507 (s), 1490 (m). GC-MS (EI, 70 eV): *m/z* (%) = 442 ($[M]^+$, 100), 441 (21), 415 (10), 414 (38), 413 (20). HRMS (EST-TOF/MS): calcd for. $C_{28}H_{17}O_2F_3$ $[M]^+$: 442.11752 ; found: 442.11697.

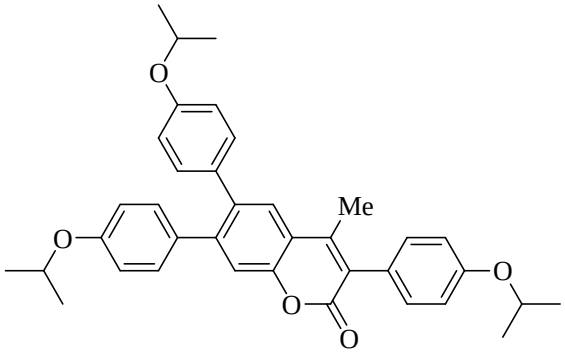
3,6,7-Tris(4-ethoxyphenyl)-4-methyl-2*H*-chromen-2-one (23g):



Starting with **22** (70 mg, 0.1308 mmol), **3g** (67 mg, 0.406 mmol) and $Pd(pph_3)_4$ (14 mg, 9 mol-%, 0.01212 mmol) , K_2CO_3 (2 M, 2 ml), and 1,4-dioxane (3 ml), **23g** was isolated as a white solid (57 mg, 84 %), mp 179-180°C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 - 1.35 (m, 9H, 3xCH_3), 2.26 (s, 3H, CH_3), 3.91 - 3.98 (m, 6H, 3xOCH_2), 6.67 - 6.72 (m, 4H, ArH), 6.88 (d, J = 8.6, Hz, 2H, ArH), 6.97 (dd, J = 1.9, 8.6 Hz, 4H, ArH), 7.15 (d, J = 8.6, Hz, 3H, ArH), 7.53 (s, 1H,

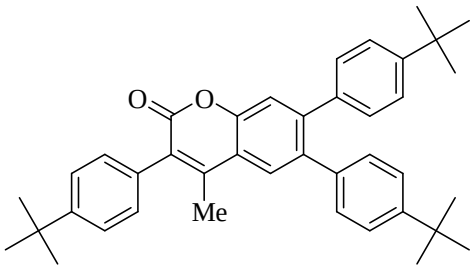
ArH).^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.7, 14.8, 14.9, 16.6 (CH_3), 63.4, 63.5, 63.6 (OCH_2), 113.1, 113.2, 113.3, 114.2, 116.8, 118.3 (CH), 125.4 (C), 125.7, 125.8 (CH), 129.7, 129.8, 130.3, 131.0, 131.8, 135.6, 142.4, 146.2, 150.5, 150.5, 156.9 (C), 160.4 (CO). IR (KBr, cm^{-1}): ν = 3066, 3031, 2978, 2928, 2919, 2887, 2849 (w), 1716, 1599 (s), 1573, 1548, 1519 (w), 1510 (m). GC-MS (EI, 70 eV): *m/z* (%) = 520 ($[M]^+$, 100), 492 (14), 209 (13). HRMS (EI, 70 eV) calcd for $C_{34}H_{32}O_5$ $[M]^+$: 520.22497 ; found: 520.22478.

3,6,7-Tris(4-isopropoxyphenyl)-4-methyl-2*H*-chromen-2-one (23h):



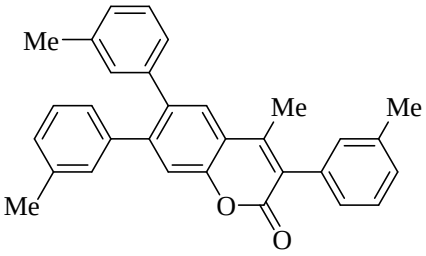
Starting with **22** (70 mg, 0.1308 mmol), **3h** (73 mg, 0.406 mmol) and $Pd(pph_3)_4$ (14 mg, 9 mol-%, 0.01212 mmol) , K_2CO_3 (2 M, 2 ml), and 1,4-dioxane (3 ml), **23h** was isolated as a white solid (57 mg, 77 %), mp 210-211°C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (q, *J* = 7.4 Hz, 18H, 6xCH_3), 2.28 (s, 3H, CH_3), 4.38 - 4.59 (m, 3H, 3xOCH), 6.64 - 6.72 (m, 4H, ArH), 6.97 (d, *J* = 8.4 Hz, 3H, ArH), 6.99 (dd, *J* = 1.7, 8.2 Hz, 4H, ArH), 7.18 (d, *J* = 8.3 Hz, 2H, ArH), 7.30 (s, 1H, ArH).^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.6 (2xCH_3), 21.0 (2xCH_3), 21.1 (2xCH_3), 23.7 (CH_3), 67.2, 68.8, 68.8 (OCH), 114.4, 114.5, 114.6, 116.8, 118.3 (CH), 125.3, 125.7 (C), 129.8, 129.9, 130.4 (CH), 130.9, 131.7, 135.6, 142.4, 146.1, 150.5, 150.6, 155.8, 156.2, 156.7 (C), 160.4 (CO). IR (KBr, cm^{-1}) : ν = 3062, 3030, 2970, 2920, 2851 (w), 1721 (s), 1650, 1644, 1633 (w), 1599 (m), 1573 (w), 1518, 1506, 1484, 1463, 1455 (w). GC-MS (EI, 70 eV): *m/z* (%) = 562 ($[M]^+$, 100), 520 (10), 478 (10), 473 (27), 436 (93), 435 (19), 408 (24), 407 (14). HRMS (EI, 70 eV) calcd for $C_{37}H_{38}O_2$ $[M]^+$: 562.27138 ; found : 562.27101.

3,6,7-Tris(4-tert-butylphenyl)-4-methyl-2*H*-chromen-2-one (23i):



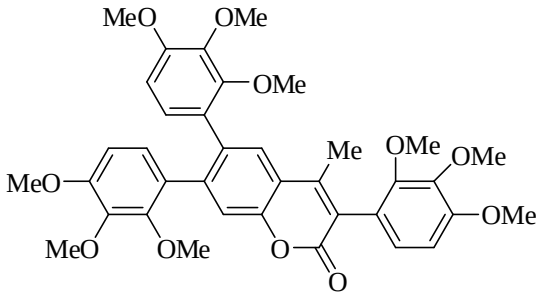
Starting with **22** (70 mg, 0.1308 mmol), **3i** (72 mg, 0.406 mmol) and $Pd(pph_3)_4$ (14 mg, 9 mol-%, 0.01212 mmol) , K_2CO_3 (2 M, 2 ml), and 1,4-dioxane (3 ml), **23i** was isolated as a white solid (45 mg, 62 %), mp 150-152°C.^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (s, 9H, 3xCH_3), 1.23 (s, 9H, 3xCH_3), 1.28 (s, 9H, 3xCH_3), 2.27 (s, 3H, CH_3), 7.01 (d, *J* = 8.3, Hz , 4H, ArH), 7.16 - 7.20 (m, 7H, ArH), 7.38 (t, *J* = 7.2, Hz, 3H, ArH).^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.7 (CH_3), 30.2 (3xCH_3), 30.3 (3xCH_3), 30.4 (3xCH_3), 33.4, 33.5, 33.6, 117.0 (C), 118.4, 123.8, 123.8, 124.2 (CH), 125.9, 126.1 (C), 128.3, 128.4, 128.7 130.4 (CH),135.7, 136.0, 136.5, 142.9, 146.3, 148.8, 149.3, 149.9, 150.6 (C), 160.2 (CO). IR (KBr, cm^{-1}): *v* = 3030 (w), 2959 (s), 2903, 2865 (w), 1719 (s), 1609, 1604, 1564, 1557, 1547, 1505 (w). GC-MS (EI, 70 eV): *m/z* (%) = 556 ($[M]^+$, 100), 542 (18), 541 (49), 385 (11), 251 (18), 149 (18), 71 (10). HRMS (EI, 70 eV) calcd for $C_{40}H_{44}O_2$ $[M]^+$: 556.33358 ; found : 556.33339.

4-Methyl-3,6,7-trim-tolyl-2*H*-chromen-2-one (23j):



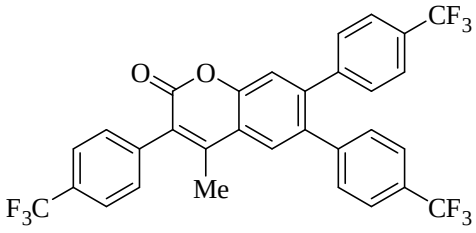
Starting with **22** (70 mg, 0.1308 mmol), **3j** (55 mg, 0.406 mmol) and $Pd(pph_3)_4$ (14 mg, 9 mol-%, 0.01212 mmol) , K_2CO_3 (2 M, 2 ml), and 1,4-dioxane (3 ml), **23j** was isolated as a white solid (39 mg, 70 %), mp 143- 145°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.20 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 6.83 (br. s, 2H, ArH) 6.94 - 7.06 (m, 6H, ArH), 7.15 (t, *J* = 7.3, Hz, 2H, ArH), 7.25 (t, *J* = 7.2, Hz, 2H, ArH), 7.35 (s, 1H, ArH), 7.58 (br. s, 1H, ArH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.6, 16.6, 20.4, 20.5 (CH_3), 28.6 (C), 117.1, 118.2, 118.3 (CH), 118.4 (C), 125.8, 125.9, 126.0, 126.5, 126.6, 126,8, 127.0, 127.3, 127.9, 129.3, 129.4 (CH),129.5, 133.4, 136.2, 136.6, 137.0, 138.6, 139.3, 143.1, 146.3, 150.7 (C), 160.2 (CO). IR (KBr, cm^{-1}): *v* = 2961, 2920, 2853 (w), 1711 (s), 1607 (m), 1585, 1552, 1478 (w). GC-MS (EI, 70 eV): *m/z* (%) = 430 ($[M]^+$, 100), 429 (21), 415 (10), 402 (18), 186 (10). HRMS (EI, 70 eV) calcd for $C_{31}H_{26}O_2$ $[M]^+$: 430.19328 ; found: 430.19373**.**

4-Methyl-3,6,7-tris(2,3,4-trimethoxyphenyl)-2*H*-chromen-2-one (23k):



Starting with **22** (70 mg, 0.1308 mmol), **3k** (86 mg, 0.406 mmol) and $Pd(pph_3)_4$ (14 mg, 9 mol-%, 0.01212 mmol) , K_2CO_3 (2 M, 2 ml), and 1,4-dioxane (3 ml), **23k** was isolated as a white solid (69 mg, 80 %), mp 110-112 ^oC.^1H NMR (300 MHz, $CDCl_3$): δ = 2.20 (s, 3H, CH_3), 3.63 (s, 9H, 3xOCH_3), 3.66 (s, 9H, 3xOCH_3), 3.85 (s, 9H, 3xOCH_3), 6.99 (dd, J = 1.9, 8.4 Hz, 2H, ArH), 6.62 - 6.70 (m, 3H, ArH), 6.18 (d, J = 8.3 Hz, 1H, ArH), 7.34 (s, 1H, ArH), 7.59 (s, 1H, ArH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.5 (CH_3), 28.6 (3xOCH_3), 54.9 (3xOCH_3), 55.0 (3xOCH_3), 105.3, 105.4, 106.3, 108.3, 108.4, 112.2, 112.4, 117.2 (CH), 120.3, 122.7, 124.2, 124.3, 124.7, 125.7, 126.0, 133.3, 140.5, 140.8, 140.9, 141.3, 147.8, 150.1, 150.3, 150.9, 152.0, 152.2, 153.0 (C), 160.2 (CO). IR (KBr, cm^{-1}) : v = 3065, 3034 (w), 2971 (m), 2931, 2920, 2881, 1887 (w), 1721, 1600 (s), 1573, 1557, 1552, 1518, 1506, 1485 (w). GC-MS (EI, 70 eV): *m/z* (%) = 658 ($[M]^+$, 100), 620 (10), 577 (20), 438 (17), 411 (25), 207 (14). HRMS (EI, 70 eV) calcd for $C_{37}H_{38}O_{11}$ $[M]^+$: 658.24141 ; found : 658.24135.

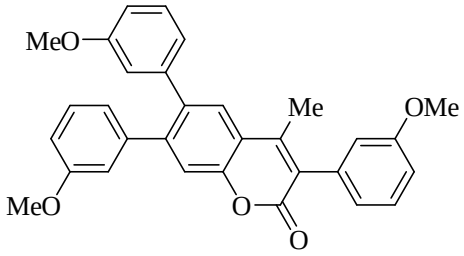
4-Methyl-3,6,7-tris[4-(trifluoromethyl)phenyl]-2*H*-chromen-2-one(23l):



Starting with **22** (70 mg, 0.1308 mmol), **3q** (77 mg, 0.406 mmol), $Pd(PPh_3)_4$ (14 mg, 9 mol-%, 0.01212 mmol), K_2CO_3 (2 M, 2 ml), and 1,4-dioxane (3 ml), **23l** was isolated as a white solid (49 mg, 63 %), m.p 188-189°C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3H, CH_3) , 6.52 - 6.59 (m, 5H, ArH), 7.00 - 7.06 (m, 3H, ArH), 7.14 (d, J = 8.52 Hz, 2H, ArH), 7.23 - 7.27 (m, 2H, ArH), 7.30 (s, 1H, ArH), 7.53 (s, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.6 (CH_3), 115.1 (d, $J_{F,C}$ = 21.4 Hz), 115.4 (d, $J_{F,C}$ = 21.4 Hz), 115.6 (d, $J_{F,C}$ = 21.4 Hz), 117.3 (CH), 118.7, 125.8 (C), 126.2 (CH), 129.4 (d, $J_{F,C}$ = 3.5 Hz) (C), 130.1, 130.3 (CH), 130.4 (C), 130.9 (d, $J_{F,C}$ = 1.7 Hz) (CH), 133.2 (d, $J_{F,C}$ = 3.6 Hz), 142.1, 146.6 (d, $J_{F,C}$ = 3.3 Hz), 150. 9, 159.2, 159.5, 159.6, 159.8 (C), 159.9 (d, $J_{F,C}$ = 246.9 Hz) (CF_3), 162.7 (d, $J_{F,C}$ = 246.0 Hz) (CF_3),

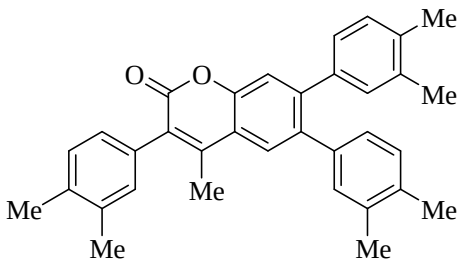
162.9 (d, $J_{F,C}$ = 247.4 Hz) (CF_3), 163.3 (CO). ^{19}F NMR (282.4, MHz): δ = - 62.5, - 62.6, - 62.7(3F,CF_3). IR (KBr, cm^{-1}): ν = 3069, 2959, 2921, 2850 (w), 1721 (s), 1650, 1645, 1615, 1575, 1556, 1486, 1463, 1455 (w) . GC-MS (EI, 70 eV): *m/z* (%) = 592 ($[M]^+$, 100), 591 (45), 573 (13), 565 (11), 564 (37), 563 (18), 419 (15). HRMS (EST-TOF/MS): calcd for. $C_{31}H_{17}O_2F_9$ $[M]^+$: 592.10794 ; found: 592.10714.

3,6,7-Tris(3-methoxyphenyl)-4-methyl-2*H*-chromen-2-one (23m):



Starting with **22** (70 mg, 0.1308 mmol), **3k** (62 mg, 0.406 mmol) and $Pd(pph_3)_4$ (14 mg, 9 mol-%, 0.01212 mmol) , K_2CO_3 (2 M, 2 ml), and 1,4-dioxane (3 ml), **23m** was isolated as a white solid (50 mg, 80 %), mp 101-103ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 3H, CH_3), 3.57 (s, 6H, 2x OCH_3), 3.76 (s, 3H, OCH_3), 6.60 - 6.62 (m, 3H, ArH), 6.68 - 6.74 (m, 3H, ArH), 6.78 - 6.81(m, 3H, ArH), 7.10 (d, *J* = 8.6, Hz, 1H, ArH), 7.17 (d, *J* = 8.4, Hz, 1H, ArH), 7.28 - 7.37 (m, 2H, ArH), 7.61 (s, 1H, ArH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 16.6 (CH_3), 55.1, 55.2, 55.3 (OCH_3), 112.7, 113.5, 113.7, 115.0, 115.4, 115.7, 118.1 (CH), 119.6 (C), 122.0, 122.2, 122.3, 126.9 (CH), 127.7 (C), 129.2, 129.3, 129.5 (CH), 136.4, 136.9, 141.4, 141.7, 143.8, 147.5, 151.9, 159.2, 159.3, 159.5 (C), 160.8 (CO). IR (KBr, cm^{-1}): ν = 3054, 2998, 2952, 2934, 2823 (w), 1712, 1598, 1575, (s), 1556 (m),1477 (w). GC - MS (EI, 70 eV): *m/z* (%) = 478 ($[M]^+$, 100), 477 (22), 207 (13). HRMS (EI, 70 eV) calcd for $C_{31}H_{26}O_5$ $[M]^+$: 478.17748 ; found : 478.17709.

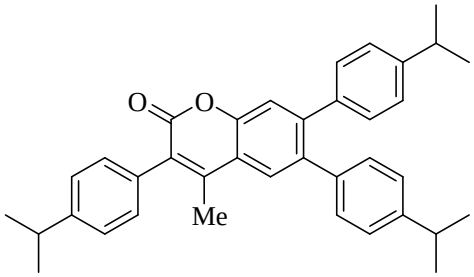
3,6,7-Tris(3,4-dimethylphenyl)-4-methyl-2*H*-chromen-2-one (23n):



Starting with **22** (70 mg, 0.1308 mmol), **3t** (61 mg, 0.406 mmol) and $Pd(pph_3)_4$ (14 mg, 9 mol-%, 0.01212 mmol) , K_2CO_3 (2 M, 2 ml), and 1,4-dioxane (3 ml), **23n** was isolated as a white solid (37 mg, 60 %), mp 171-172ºC.^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.11 (s, 3H, CH_3), 2.13 (s, 6H, 2xCH_3), 2.16 (s, 6H, 2xCH_3), 2.23 (s, 6H, 2xCH_3), 6.75 (br. s, 2H, ArH) 6.87 - 7.01 (m, 5H, ArH), 7.16 (t, *J* = 7.4, Hz, 2H, ArH),

7.31 (s, 1H, ArH), 7.53 (s, 1H, ArH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.5 (2xCH_3), 18.3 (2xCH_3), 18.6 (2xCH_3), 18.7 (CH_3), 28.6 (C), 117.1 (CH), 118.3 (C), 125.9, 126.1, 126.2, 126.3, 126.4, 128.2, 128.6, 129.7, 129.8, 1390.0 (CH), 131.2, 134.1, 134.6, 135.2, 135.3, 135.5, 135.6, 136.0, 126.3, 137.1, 142.9, 146.2, 149.5 (C), 160.3 (CO). IR (KBr, cm^{-1}): ν = 2961, 2919, 2854 (w), 1713 (s), 1609 (m), 1573, 1568, 1549, 1503, 1484 (w). GC-MS (EI, 70 eV): *m/z* (%) = 472 ([M]$^+$, 100), 471 (26), 457 (10), 445 (17), 443 (11), 429 (13), 414 (11), 207 (16). HRMS (EI, 70 eV) calcd for $C_{34}H_{32}O_2$ [M]$^+$: 472.23968 ; found: 472.23921.

3,6,7-Tris(4-isopropylphenyl)-4-methyl-2*H*-chromen-2-one (23o):



Starting with **22** (70 mg, 0.1308 mmol), **3u** (66 mg, 0.406 mmol) and $Pd(pph_3)_4$ (14 mg, 9 mol-%, 0.01212 mmol) , K_2CO_3 (2 M, 2 ml), and 1,4-dioxane (3 ml), **23o** was isolated as a white solid (47 mg, 70 %), mp 120-122ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 (s, 6H, 2xCH_3), 1.16 (s, 6H, 2xCH_3), 1.22 (s, 6H, 2xCH_3), 2.25 (s, H, CH_3), 2.27 - 2.91 (m, 3H, 3xCH), 6.96 - 7.01 (m, 8H, ArH), 7.15 (d, *J* = 8.4, Hz, 2H, ArH), 7.24 (d, *J* = 8.2, Hz, 2H, ArH), 7.33 (s, 1H, ArH), 7.56 (s, 1H, ArH).^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.6 (2xCH_3), 22.8 (2xCH_3), 22.9 (2xCH_3), 24.7 (CH_3), 32.6, 32.7, 32,9 (CH), 117.0 (C), 118.4, 124.7 (CH), 125.0, 125.4 (C), 126.0, 126.1, 128.3, 128.5, 128.9, 130.7 (CH) 136.1, 136.2, 136.9, 142.9, 146.3, 146.5, 147.1, 147.6, 150.6 (C), 160.3 (CO). IR (KBr, cm^{-1}) : ν = 3064, 3041, 3024 (w), 2957 (s), 2924, 2865 (w), 1724 (s), 1613, 1604 (m), 1568, 1551, 1510, 1506, 1484 (w). GC-MS (EI, 70 eV): *m/z* (%) = 514 ([M]$^+$, 100), 500 (10), 499 (17),

X-Ray Crystals Data

Crystal data and structure refinement for 7-Chloro-4-(4-methoxyphenyl)-1-methylindoline-2,3-dione (5b):

Identification code	**is_ac13**	
Empirical formula	**$C_{16}H_{12}ClNO_3$**	
Formula weight	301.72	
Temperature	173 (2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group (H.-M.)	*C c*	
Space group (Hall)	C -2yc	
Unit cell dimensions	a = 16.9602 (3) Å	α= 90.00 (0)°
	b = 25.6488 (5) Å	β= 105.2530 (3)°
	c = 12.4814 (4) Å	γ = 90.00 (0)°
Volume	5381.42 (17) $Å^3$	
Z	12	
Density (calculated)	1.386 Mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	2328	
Crystal size	0.30 x 0.19 x 0.17 mm	
Θ range for data collection	2.75° to 27.62°.	
Reflections collected	57186	
Independent reflections	15084	
Completeness to Θ = 32.50°	99.2 %	
Absorption correction	multi-scan	
Max. and min. transmission	0.9165 and 0.9514	
Refinement method	Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	1.024	
Final R indices [$F^2>2\sigma(F^2)$]	R1 = 0.0472, wR = 0.0885	
R indices (all data)	R1 = 0.0750, $wR(F^2)$ = 0.0966	
Largest diff. peak and hole	0.326 and -0.227 e.$Å^{-3}$	

Crystal data and structure refinement for 7-Chloro-1-methyl-4-*p*-tolylindoline-2,3-dione (5d):

Identification code	**is_ac 7**	
Empirical formula	**$C_{16}H_{12}ClNO_2$**	
Formula weight	285.72	
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 = 16.9602 (3) Å	α= 90.00 (0)°
	b = 25.6488 (5) Å	β= 105.2530 (3)°
	c = 12.4814 (4) Å	γ = 90.00 (0)°
Volume	5381.42 (17) $Å^3$	
Z	12	
Density (calculated)	1.386 Mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	2328	
Crystal size	0.99 x 0.03 x 0.03 mm	
Θ range for data collection	2.75° to 27.62°.	
Reflections collected	57186	
Independent reflections	15084	
Completeness to Θ = 27.50°	99.1 %	
Absorption correction	multi-scan	
Max. and min. transmission	0.7563 and 0.9911	
Refinement method	Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	1.024	
Final R indices [$F^2>2\sigma(F^2)$]	R1 = 0.0472, wR = 0.0885	
R indices (all data)	R1 = 0.0750, $wR(F^2)$ = 0.0966	
Largest diff. peak and hole	0.363 and -0.387 $e.Å^{-3}$	

Crystal data and structure refinement for 2-(4-Tert-butylphenyl)-6-(4-methoxyphenyl)benzoxazole (10b):

Identification code	**is_ax0199**	
Empirical formula	**$C_{24}H_{23}NO_2$**	
Formula weight	357.43	
Temperature	173 (2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group (H.-M.)	*C c*	
Space group (Hall)	C -2yc	
Unit cell dimensions	a = 16.9602 (3) Å	α= 90.00 (0)°
	b = 25.6488 (5) Å	β= 105.2530 (3)°
	c = 12.4814 (4) Å	γ = 90.00 (0)°
Volume	5381.42 (17) $Å^3$	
Z	12	
Density (calculated)	1.386 Mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	2328	
Crystal size	0.39 x 0.24 x 0.14 mm	
Θ range for data collection	1.16° to 27.99°.	
Reflections collected	57186	
Independent reflections	15084	
Completeness to Θ = 27.99°	100 %	
Absorption correction	multi-scan	
Max. and min. transmission	0.9166 and 0.9923	
Refinement method	Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	1.024	
Final R indices [$F^2>2\sigma(F^2)$]	R1 = 0.0472, wR = 0.0885	
R indices (all data)	R1 = 0.0750, $wR(F^2)$ = 0.0966	
Largest diff. peak and hole	0.197 and -0.162 $e.Å^{-3}$	

Crystal data and structure refinement for 4-Oxo-3-(4-(trifluoromethylsulfonyloxy)phenyl)-4*H*-chromen-7-yl trifluoromethanesulfonate (12):

Identification code	**is_fi**	
Empirical formula	**$C_{17}H_8F_6O_8S_2$**	
Formula weight	518.35	
Temperature	173 (2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	*C c*	
Space group (Hall)	C -2yc	
Unit cell dimensions	a = 16.9602 (3) Å	α= 90.00 (0)°
	b = 25.6488 (5) Å	β= 105.2530 (3)°
	c = 12.4814 (4) Å	γ = 90.00 (0)°
Volume	5381.42 (17) $Å^3$	
Z	12	
Density (calculated)	1.386 Mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	2328	
Crystal size	0.23 x 0.12 x 0.02 mm	
Θ range for data collection	2.73° to 28.00°.	
Reflections collected	57186	
Independent reflections	15084	
Completeness to Θ = 28.00°	99.9 %	
Absorption correction	multi-scan	
Max. and min. transmission	0.9166 and 0.9923	
Refinement method	Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	1.024	
Final R indices [$F^2>2\sigma(F^2)$]	R1 = 0.0472, wR = 0.0885	
R indices (all data)	R1 = 0.0750, $wR(F^2)$ = 0.0966	
Largest diff. peak and hole	0.506 and -0.403 $e.Å^{-3}$	

Crystal data and structure refinement for 4-[7-(3,5-Dimethylphenyl)-4-oxo-4*H*-chromen-3-yl]phenyl trifluoromethanesulfonate (14a):

Identification code	**is_fi5**	
Empirical formula	**$C_{24}H_{17}F_3O_5S$**	
Formula weight	456.29	
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 = 16.9602 (3) Å	α= 90.00 (0)°
	b = 25.6488 (5) Å	β= 105.2530 (3)°
	c = 12.4814 (4) Å	γ = 90.00 (0)°
Volume	5381.42 (17) $Å^3$	
Z	12	
Density (calculated)	1.386 Mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	2328	
Crystal size	0.39 x 0.12 x 0.11 mm	
Θ range for data collection	2.34° to 35.50°.	
Reflections collected	57186	
Independent reflections	15084	
Completeness to Θ = 28.00°	99.9 %	
Absorption correction	multi-scan	
Max. and min. transmission	0.9223 and 0.9772	
Refinement method	Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	1.024	
Final R indices [$F^2>2\sigma(F^2)$]	R1 = 0.0472, wR = 0.0885	
R indices (all data)	R1 = 0.0750, $wR(F^2)$ = 0.0966	
Largest diff. peak and hole	0.331 and -0.425 $e.Å^{-3}$	

Crystal data and structure refinement for 4-Methyl-2-oxo-2*H*-chromene-6,7-diyl bis(trifluoromethanesulfonate) (17):

Identification code	**is_aq1**	
Empirical formula	**$C_{12}H_6F_6O_8S_2$**	
Formula weight	456.29	
Temperature	173 (2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	*C c*	
Space group (Hall)	C -2yc	
Unit cell dimensions	a = 16.9602 (3) Å	α= 90.00 (0)°
	b = 25.6488 (5) Å	β= 105.2530 (3)°
	c = 12.4814 (4) Å	γ = 90.00 (0)°
Volume	5381.42 (17) $Å^3$	
Z	12	
Density (calculated)	1.386 Mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	2328	
Crystal size	0.30 x 0.19 x 0.17 mm	
Θ range for data collection	2.77° to 25.00°.	
Reflections collected	57186	
Independent reflections	15084	
Completeness to Θ = 25.00°	98.2 %	
Absorption correction	multi-scan	
Max. and min. transmission	0.9174 and 0.9850	
Refinement method	Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	1.024	
Final R indices [$F^2>2\sigma(F^2)$]	R1 = 0.0472, wR = 0.0885	
R indices (all data)	R1 = 0.0750, $wR(F^2)$ = 0.0966	
Largest diff. peak and hole	0.518 and -0.339 $e.Å^{-3}$	

Crystal data and structure refinement for 6,7-Bis(4-ethoxyphenyl)-4-methyl-2*H*-chromen-2-one (18g):

Identification code	**is_aq6**	
Empirical formula	**$C_{26}H_{24}O_4$**	
Formula weight	456.29	
Temperature	173 (2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group (H.-M.)	*C c*	
Space group (Hall)	C -2yc	
Unit cell dimensions	a = 16.9602 (3) Å	α= 90.00 (0)°
	b = 25.6488 (5) Å	β= 105.2530 (3)°
	c = 12.4814 (4) Å	γ = 90.00 (0)°
Volume	5381.42 (17) $Å^3$	
Z	12	
Density (calculated)	1.386 Mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	2328	
Crystal size	0.24 x 0.16 x 0.15 mm	
Θ range for data collection	1.91° to 29.73°.	
Reflections collected	57186	
Independent reflections	15084	
Completeness to Θ = 29.73°	99.3 %	
Absorption correction	multi-scan	
Max. and min. transmission	0.9795 and 0.9871	
Refinement method	Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	1.024	
Final R indices [$F^2>2\sigma(F^2)$]	R1 = 0.0472, wR = 0.0885	
R indices (all data)	R1 = 0.0750, $wR(F^2)$ = 0.0966	
Largest diff. peak and hole	0.184 and -0.218 $e.Å^{-3}$	

Crystal data and structure refinement for 7-(4-Methoxyphenyl)-4-methyl-2-oxo-2*H*-chromen-6-yl trifluoromethanesulfonate (19b):

Identification code	**is_aq3**	
Empirical formula	**$C_{18}H_{13}F_3O_3S$**	
Formula weight	414.34	
Temperature	173 (2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group (H.-M.)	*C c*	
Space group (Hall)	C -2yc	
Unit cell dimensions	a = 16.9602 (3) Å	α= 90.00 (0)°
	b = 25.6488 (5) Å	β= 105.2530 (3)°
	c = 12.4814 (4) Å	γ = 90.00 (0)°
Volume	5381.42 (17) $Å^3$	
Z	12	
Density (calculated)	1.386 Mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	2328	
Crystal size	0.60 x 0.13 x 0.08 mm	
Θ range for data collection	2.24° to 30.50°.	
Reflections collected	57186	
Independent reflections	15084	
Completeness to Θ = 30.50°	98.6 %	
Absorption correction	multi-scan	
Max. and min. transmission	0.7563 and 0.9911	
Refinement method	Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	1.024	
Final R indices [$F^2>2\sigma(F^2)$]	R1 = 0.0472, wR = 0.0885	
R indices (all data)	R1 = 0.0750, $wR(F^2)$ = 0.0966	
Largest diff. peak and hole	0.349 and -0.296 $e.Å^{-3}$	

Crystal data and structure refinement for 3-Bromo-4-methyl-2-oxo-2*H*-chromene-6,7-diyl bis(trifluoromethanesulfonate) (22):

Identification code	**is_qb1**	
Empirical formula	**$C_{12}H_5BrF_6O_3S_2$**	
Formula weight	535.19	
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 = 16.9602 (3) Å	α= 90.00 (0)°
	b = 25.6488 (5) Å	β= 105.2530 (3)°
	c = 12.4814 (4) Å	γ = 90.00 (0)°
Volume	5381.42 (17) $Å^3$	
Z	12	
Density (calculated)	1.386 Mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	2328	
Crystal size	0.29 x 0.05 x 0.02 mm	
Θ range for data collection	2.55° to 27.50°.	
Reflections collected	57186	
Independent reflections	15084	
Completeness to Θ = 29.00°	94.3 %	
Absorption correction	multi-scan	
Max. and min. transmission	0.5096 and 0.9482	
Refinement method	Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	1.024	
Final R indices [$F^2>2\sigma(F^2)$]	R1 = 0.0472, wR = 0.0885	
R indices (all data)	R1 = 0.0750, $wR(F^2)$ = 0.0966	
Largest diff. peak and hole	0.504 and -0.681 $e.Å^{-3}$	

Crystal data and structure refinement for 3,6,7-Tris(4-tert-butylphenyl)-4-methyl-2*H*-chromen-2-one (23i):

Identification code	**is_ qb 16**	
Empirical formula	**$C_{40}H_{44}O_2$**	
Formula weight	556.75	
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 = 16.9602 (3) Å	α= 90.00 (0)°
	b = 25.6488 (5) Å	β= 105.2530 (3)°
	c = 12.4814 (4) Å	γ = 90.00 (0)°
Volume	5381.42 (17) $Å^3$	
Z	12	
Density (calculated)	1.386 Mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	2328	
Crystal size	0.25 x 0.14x 0.09 mm	
Θ range for data collection	2.75° to 27.62°.	
Reflections collected	57186	
Independent reflections	15084	
Completeness to Θ = 27.62°	99.1 %	
Absorption correction	multi-scan	
Max. and min. transmission	0.9833 and 0.9939	
Refinement method	Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	1.024	
Final R indices [$F^2>2\sigma(F^2)$]	R1 = 0.0472, wR = 0.0885	
R indices (all data)	R1 = 0.0750, $wR(F^2)$ = 0.0966	
Largest diff. peak and hole	0.198 and -0.209 $e.Å^{-3}$	

References:

[1] Buchwald, S. L. *Acc. Chem. Res*. **2008**, *41*, 1439-1442.

[2] Blass, H-U.; Indoless, A.; Naud, F.; Nettekoven, U. Schnyderm, A. *Adv. Synth. Catal*. **2004**, *346*, 1583-1589.

[3] Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahydron* **2008**, *64*, 3047-3054.

[4] Corbet, J.-P.; Mignam, G. *Chem. Rev*. ***2006***, *106*, 2651-2658.

[5] Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 4442-4449.

[6] Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Ruttinger, R.; and Kojer, H. *Angew. Chem*. **1959**, *71*, 176-183.

[7] Tusji, J. *Palladium Reagents and Catalysts-new Perpectives for the 21 st century*, 2 ed.; John Wiley& Sons Ltd: Chichester, **2004**; Vol. *1*, P165.

[8] Garrett, C. E.; Prasad, K. *Adv. Syth. Catal.* **2004**, *346*, 889-895.

[9] Ishiyanam, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett*. **1992**, 691-698.

[10] Nicolauo, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4451.

[11] Goossen, L. J.; Koley, D.; Hermann, Thiel, W. *Chem. Commun*. **2004**, 2141-2150.

[12] Belestskaya, I.P.; Cheprakov, A. V. Chem. Rev. **2000**, *100*, 3009-3018.

[13] Casado, A. L.; Espinte, P. J. *Am. Chem. Soc*. **1998**, 120, 8978-8982.

[14] Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed*. **2004**, *43*, 4704-4714.

[15] Miyaura, N.; Yanagi, T.; Sukzuki, A. *Syth. Commum*. **1981**, *11*, 513-520.

[16] See, for instance: (a) Miyaura, N.; Suginome, H.; Suzuki, A. *Tetrahedron Lett.* **1984**, *25*, 761. (b) Ishiyama, T.; Abe, S.; Miyaura, N.; Sukzuki, A. *Chem. Lett.* **1992**, 691. (c) Oh-e, T.; Miyaura, N.; Sukzui, A. *J. Org. Chem.* **1993**, *58*, 2201. (d) Moriya, T.; Furuuch, T.; Miyaura, N.; Sukzuki, A. *Tetrahedron* **1994**, *50*, 7961-7972.

[17] Geissler, H. *In Tranasition Metals for Organic Synthesis*; Beller, M. Bolm, C., Eds.; Wiley-VCH: Weinheim, **1998**; Vol. *1*, P158.

[18] Suzuki, A. *In Metal-catalyzed Cross-coupling Reactions*; 1 ed. Diederich, Stang, P. J., Eds.l; Wiley-VCH: Weinheim, **1998**; Vol. *1*, P 49.

[19] Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, *19*, 866-876.

[20] Miyaura, N.; Yamada, k.; Sukzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437-3449.

[21] Liptot, M. F.; Mauragis, M. A.; Maloney, M. T. *Org Process Dev*, **2003**, *7*, 385-397.

[22] Hall, D. G. F.; *Boronic acid: Preparation and Applications in Organic Synthesis and Medicine;* WILY-VCH Verlag& CO. KGaA: Weinheim, **2005**; Vol. *1*, P179.

[23] Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lolyd-Jones, G. C.; Murray, P. M. *Angew. Chem. Int. Ed*. **2010**, *49*, 5156-5167.

[24] Molander, G. A.; Biolatto, B. *J.Org. Chem.* **2003**, *68*, 4302-4312.

[25] Jira, R. *Angew. Chem., Int. Ed*. **2009**, *48*, 9034-9042.

[26] Tsuji, J. *Palladium Reagent and Catalysts. Innovations in Organic Sythesis*; Wily: Chichester, **1995**; Vol. *1*, P186.

[27] Still, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434-443.

[28] Meijere, A.; Diederich, F. *Metal-Catayzad Cross-Coupling Reactions*. 2nd Ed., Willy-VCH, **2004**; Vol. *1*, P 203

[29] Larhed, M.; Hallberg, A. *In Handbook of Organoplladium Chemistry For Organic Synthesis*, Negishi, E., Ed.; Wiley-Interscience: New Yory, **2002**; Vol. *1*, P 1133.

[30] Whitcombe, N. j.; Hii, K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449-7456.

[31] For a review on Suyuki-Miyaura cross-coupling reactions see: Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457-2465.

[32] (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem.Soc.* **2005**, *127*, 4685; (b) Baxter, J.; Steinhuebel, D.; Palucki, M.; Davies, I. W. *Org. Lett*. **2005**, 7, 215; (c) Kingston, J. V.; Verkade, *J. Org. Chem*. **2007**, *72*, 2816-2826.

[33] Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem*. **1999**. *64*, 3804-3815.

[34] Casalnuovo, A. L.; Calabrese, J.C. *J. Am. Chem. Soc*. **1999**, *112*, 4324-4335.

[35] (a) Larhed, M.; Lindeberg, G.; Hallberg, A. Tetrahedron Lett. 1996, 37, 8219; (b) Larhed, M.; hallberg, A. *J. Org. Chem*. **1996**, *61*, 9582-9593.

[36] Challenger, F.; Riuchards, O. V. *J. Chem. Soc*. **1934**, 405-413.

[37] Syyder, H, R. Wyman, F. W. *J. Chem. Soc.* **1948**, *70*, 234-241.

[38] Kuivial, H. G.; Mangravi. J; Reuwer, J. F. *J. Chem. Soc.* **1964,** *86*, 2666-2675.

[39] Ainley, A. D.; Challenger, F. *J. Chem. Soc.* **1930**, 2171-2185.

[40] Webb, K. S.; Levy, D. *Tetrahydron lett.* **1995**, *36*, 5117-5127.

[41] Fontani, P.; Carboni, B.; Vauitier, M.; Mass, G. *Sythesis* **1991**, 605-614.

[42] Kuivila, H. G.; Armour, A. G. *J. Am. Chem. Soc.* **1957**, *79*, 5659-5668.

[43] Moreno-Manas, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346-2356.

[44] Adamo, C.; Amatore, C.; Ciofini, I.; Jutand, A.; Lakmini, H. *J. Am. Chem. Soc.* **2006**, *128*, 6829-6838.

[45] Tikad, A.; Routier, S.; Akssia, M.; Leger, J.-M.; Jarry, C.; Guillaumet, G. *Org. Lett.* **2007**, *9*, 4673-4685.

[46] Wellmar, U.; Homfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1995**, *32*, 1159-1168.

[47] Ibad, M. F.; Hussain, M.; Abid, O.-U.-Rahman.; Ali.; Ullah, I.; Zinad, D. S.; Langer, P. *Synlett* **2010**, 411-423.

[48] Hussian, M.; Nguyen, T. H.; Khera, R. A.; Villinger, A.; Langer, P. *Tetrahedron Lett*. **2011**, *52*, 184-197.

[49] (a) Toguem. S.-M, T.; Villinger, A.; Langer, P.; Synlett 2010, 909. (b) Toguem. S.-M, T.; Villinger, A.; Langer, P.; *Synlett* **2009**, *2009*, 3311-3322.

[50] (a) Mahal, A.; Villinger, A.; Langer, P.; *Synlett* **2010**, 7, 1085. (b) Omer A. Akrawi.; Munawar, H.; Langer, P.; *Tetrahedron Lett.* **2011**, 52, 1093.

[51] Abid, O.R.; Ibad, M. F.; Nawaz, M.; Ali, A.; Sher, M.; Rama, N. H.; villinger, A.; Langer, P.; *Tetrahedron Lett*. **2010**, *51*, 1541-1552.

[52] Malik, I.; Hussain, M.; Hung, N. T.; Villinger, A.; Langer, P. *Synlett* **2010**, 2244-2253.

[53] Akrawi, O. A.; Potany, T.; Konya, K.; Langer, P. *Synlett* **2013**, *24*, 860-864.

[54] Hassan, Z.; Hussain M.; Villinger, A.; Langer, P. *Tetrahedron* **2012**, 68, 6305-6313.

[55] Pandeya, S. N.; Smitha, S.; Jyoti, M.; Sridhar, S. K. *Acta Pharm.* **2005**, *55*, 27-46.

[56] Wang, Y.; Chan, F-Y.; Sun, N.; Lui, H.-K.; So, P.-K.; Yan, S.-C.; Chan, K.-F.; Chiou, J.; Chen, S.; Adagyan, R.; Leung, Y.-C.; Wong, Y-.C.; wong, K.-Y. *Chem. Biol. Drug Des*. **2014**, *84*, 685-696.

[57] Breinholt, J.; Demuth, H.; Hiede, M.; Jensen, G. W.; Moller, I, L.; Nielesen, R. I.; Olsen, C. E.; Rosendahl, C. N. *Acta Chem Scand*. **1996**, *50*, 443-445.

[58] Abele, E.; Abele, R.; Dzenistis, O.; Lukevics, E. *Chem. Heterocyc. Comp*. **2003**, *39*, 33-35.

[59] Sridhar, S. K.; Pandeya, S. N.; Stables, J. P.; Ramesh, A. *Eur. J. Pharm. Sci*. **2002**, *16*, 129-132.

[60] Bramson, H. N.; Corona, J.; Davis, S. T.; Dickerson, S. H.; Edelstein, M. *J. Med. Chem.* **2001**, *44*, 4339-4358.

[61] Andreeani, A.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Garaliene, V.; Welsh, W.; Arora, S.; Farruggia, G.; Masotti, L. *J. Med. Chem.* **2005**, *48*, 5604-5607.

[62] Chem, Z.; Merta, P. J.; Lin, N. H.; Tahir, S. K.; Kovar, P.; Sham, H. L.; Zhang, H. *Mol. Cancer Ther*. **2005**, *4*, 562-568.

[63] Grewal, A. S. *Interm. J. Pharm. Res*. **2014**, *6*, 1-7.

[64] Cane, A.; Tournaire, M. C.; Barritault, D.; Crumeyrolle-Arias, M. *Biophys. Res. Commun*. **2000**, *276*, 379-384.

[65] Vine, K. L.; Loke, J. M.; Ranson, M.; Benkendoff, K.; Pyne, S. G.; Bremmer, J. B. *Bioorg. Med. Chem* **2007**, *15*, 931-938.

[66] Vine, K. L.; Matesic, L.; Locke, J. M.; Ranson, M.; Skropeta, D. Anti-Cancer Agents Med Chem. 2009, 9, 397-414(review).

[67] Liu, Y.; Lashuel, H. A.; Chio, S.; Xing, X.; Case, A.; Ni, J.; Yeh, L. A.; Cuny, G. D.; Stein, R, L.; Lansbury, P. T. *Chem. Biol*. **2003**, *10*, 837-846.

[68] Lee, J. W.; Moon, M. J.; Min, H. Y.; Chung, H. J.; Park, H. J.; Hong, J. Y.; Kim, Y. C.; Lees, S. K. *Bioog. Chem. Lett.* **2005**, *15*, 3948-3952.

[69] Motzer, R. J.; Michaelson, M. D.; Redman, B. G.; Hudes, G. R.; Wilding, G.; Figlin, R. A.; Ginsbery, M. S.; Kim, S. T.; Baum, C. M.; Deprimo, S. E.; Deprino, S. E.; Li, J. Z.; Bello, C. L.; Theuer, C. P.; George, D. J.; Rini, B. I. J. *Clin. Oncol*. **2006**, *24*, 16-24.

[70] Prenen. H.; Cools, J.; Mentens, N.; Folens, C.; Sciot, R.; Schoffski, P.; Van Oosterom, A.; Marynen, P.; Debiec-Rychter, M. *Clin. Cancer. Res.* **2006**, *12*, 2622-2627.

[71] Vine, K. L.; Matesic, L.; Locke, J. M.; Skropeta, D. Recent highlidhts in the development of isatin-based anticanceragents. In M. prudhomme (Eds), Advances in Anticancer Agents in Medicinal Chemistry (PP. 254-312). Sharjah, UAE: Bentham Science Publiushers.

[72] Selvam, P.; Murugesh, N.; Chandramohan, M.; Keith, K. A.; kern, E. R. *Antivir. Chem. Chemother*. **2006**, *17*, 107-110.

[73] Teitz, Y.; Ronen, D.; Vansover, A.; Stematsky. T.; Rigg, J. L. *Antiviral Res*. **1994**, *24*, 304-314.

[74] Pandeya, S. N.; Sriram, D.; Clereq, Pannecouque, C.; Witvrouw, M. *Indian J. Pharm. Sci.* **1998**, *60*, 207-212.

[75] Pandeya, S. N.; Sriram, D.; Nath, G.; De Clercq, E. *Eur. J. Phaem. Sci.* **1999**, *9*, 25-31.

[76] Pandeya, SN, Sriram, D, Nath, G, De Clercq, E. *Pharm. Acta. Helv.* **1999**, *74*, 11-17 .

[77] Pandeya, SN, Sriram, D, Nath, G, De Clercq E. *Eur. J. Med. Chem*. **2000**, *35*, 249-255.

[78] Siram, D.; Bal, T. R.; Yogeeswari, p. *Med. Chem*. **2005**, *1*, 277-285.

[79] Selvam, P.; Chandramohan, M.; De Clereq, E.; Pannecouque, C.; Witrouw, M. *Eur. J. Pharm. Sci*. **2001**, *14*, 313-316.

[80] Selvam, P.; Murugesh, Chandramohan, M.; Debyser, Z.; Witvorow, M. *Indian J. Pharm. Sci*. **2008**, *70*, 779-782.

[81] Pandeya, S. N.; Sriram, D.; Nath, G.; De Clerceq, E. *Arzneimittelfors*ch. *Drug Res*. **2000**, *50*, 55-59.

[82] Pandeya, S. N.; Yogeeswari, P.; Sriram, D.; De Clercq, E.; pannecouque, C.; Witvrouw. M. *Chemother*. **1999**, *45*, 192-196.

[83] Vine, K. L.; Locke, J. M.; Ronson, Pyne, S. G.; Bremner, J. B. *J. Med. Chem.* **2007**, *50*, 5109-5117.

[84] Willker, W.; Leibfritz, D.; Kerssebaum, R.; Bermel, W. Magn. *Reson. Chem.* **1993**, *31*, 287-292.

[85] Anderson, W, A.; Freeman, R. *J. Chem. Phys*. **1962**, *37*, 411-415.

[86] Pannecouque. C.; Daelmans, D.; De Clercq E. *Nat. Protoc*. **2008**, *3*, 427-434.

[87] Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; Clair, M. H. St.; Lehrmann, S. N.; Gallo, R. proc. *Natl. Acad. Sci. USA.* **1985**, *82*, 7096-7100.

[88] Coates, J. A.; Cammack, N.; Jenkinson, H. J.; Jowett, A. J.; Pearson, B. A.; Penn, C. R.; Rouse, P. L.; Viner, K. C.; Cameron, *J. M. Antimicrob. Agents Chemother.* **1992**, *36*, 733-739.

[89] P. Zhan, X. Liu, Z. Li, Z. Fang, C. pannecouque, E. De Clercq, *Chem Biodiversity*.. **2010**, *7*, 1717-1727.

[90] Seeliger, S.; De Groot, B. L. *J. Comput.-Aided Mol. Des*. **2010**, *24*, 417-422.

[91] Ren, J.; Bird, e.; Chamberlain, P. P.; Stwart-Joness, G. B.; Stuart, D. I.; Stammers, D. K. Proc. *Natl. Acad. Sci. USA.* **2002**, *99*, 14410-14415.

[92] Hemmateeneijad, B.; Tabaei, S. M. H.; Namvaran, F. *J. Iran. Chem. Soc.* **2007**, *4*, 481-489.

[93] Cremer, N. S.; temiz, N. A.; Bahar, I. *Curr. HIV Res.* **2004**, *2*, 323-332.

[94] (a) Rodriguez, A.; Ramirez, C.; Rodriguez, I.; Gonzalez, E. Org. Lett. 1999, 1, 527. (b) Davidson, J.; Corey, E. *J. Am. Chem. Soc.* **2003**, *125*, 13486.

[95] Don, M.; Shen, C.; Lin, Y.; Syu, W.; Ding, Y.; Sun, C. *J. Nat. Prod.* **2005**, *68*, 1066-1075.

[96] Evindar, G.; Batey, R. *J. Org Chem.* **2006**, *71*, 1802-1813.

[97] Prudhomme, M.; guyot, J.; Jeminet, G. *J. Antibiotics*. **1986**, *39*, 934-945.

[98] Rodriguez, A.; Ramirez, C.; Rodriguez, I.; Gonzalez, E. *Org. Lett*. **1999**, *1*, 527-538.

[99] Oren, I.; Ozlem. T.; Ismail, y.; Esin, A.; Altanlar, N. *J. Eur. Pharm. Sci.* **1998**, *7*, 153-167.

[100] Ozlem. T.; Esin, A. I.; Ismail, y.; Altanlar, N. Arch. Pharm. 2002, 6, 283-292.

[101] Ozlem. T.; Ozdemir, A.; Ismail, Y.; Esin, A.; Altanlar, N. *Arch. Pharm*. **2005**, *105*, 338-347.

[102] Vinsova, J.; Horak, V.; Buchta, V.; Kaustova, *J. Molecules*. **2005**, *10*, 783-792.

[103] Huang S.; Hsei, I.; Chen, C. *Bioorg. Med. Chem.* **2006**, *14*, 6106-6118.

[104] Pinar, A.; Yurdakul, P.; Yildiz, I.; Ozlem, T.; Acan, N.; Esin, A.; Ismail, Y.; *Biochem. Biophys. Res. Commun.* **2004**, 317, 670-683.

[105] For aldehydes, see: (a) Kawashita, Y.; Nakamichi, N.; Kawabata, H.; and Hayashi, M. *Org. Lett.* **2003**, *5*, 3713. (b) Chang, J.; Zhao K.; Pan, S. *Tetrahedron Lett***. 2002**, *43*, 951. (c) Varma, R.; Kumar, D. J.; *Heterocycl. Chem.* **1998**, *35*, 1539. For carboxylic acid derivatives, see: (d) Pottorf, R.; Chadha, N.; Katkevics, M.; Ozola,

V.; Suna, E.; Ghane, H.; Regberg, T.; Player, M. *Tetrahedron Lett*. **2003**, *44*, 175. (e) Bougrin, K.; Loupy, A.; Fiaoui, M.; *Tetrahedron* **1998**, *54*, 8055. (f) Terashima, M.; Ishii, M.; and Kanaoka, Y. *Synthesis* **1982**, 484-496.

106 (a) Viirre, R.; Evindar, G.; Batey, R. *J. Org. Chem*. **2008**, *73*, 3452. (b) Evindar, G.; Batey, R. *J. Org. Chem*. **2006**, *71*, 1802. (c) Barbero, N.; Carril, M.; San Martin, R.; Dominguez, E. *Tetrahedron* **2007**, *63*, 10425-10437.

107 Ueda, S.; Nagasawa, H. *Angew. Chem*. **2008**, *47*, 6411-6422.

108 Patrick, J.; Hamilton, Z.; Lang, S.; Murphy, A.; Suckling, *J. Org. Lett*. **2011**, *13*, 23-35.

109 For reviews of cross-coupling reactions of polyhalogenated heterocycles, see: (a) Schroter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245. (b) Schnurch, M.; Flasik, R.; Khan, A. F.; Spina, M. Mihovilovic, M. D.; Stanetty, P. Eur. *J. Org. Chem*. **2006**, 3283. (c) Rossi, R.; Bellina, F.; Lessi, M. *Adv. Synth. Catal.* **2012**, *354*, 1181-1198.

110 Handy, S. T.; Zhang, Y. *Chem. Commun.* **2006**, 299-314.

111 Nagao, T.; Abe, F.; Kinjo, J.; Okabe, H. *Biol. Pharm. Bull*. **2002**, *7*, 875.

112 (a) Daskiewies, J.; Depeint, F.; Viornery, L.; Bayet, C.; Geraldine, C.; Comte, G.; Gee, J.; Johnson, I.; Ndjoko, K.; Hostettmann, K.; Barron, D. *J. Med. Chem*. **2005**, *48*, 2790. (b) Rao, Y. K.; Fang, S. H.; Tzeng, Y. M. *Bioorg, Med. Chem*. **2005**, *13*, 6850. (c) Wang, S. F.; Jiang, Q.; Ye, Y. H.; Li, Y.; Tan, R. X. *Bioorg. Med. Chem.* **2005**, *13*, 4880. (d) Gao, H.; Kawabata, J. *Bioorg. Med. Chem*. **2005**, *13*, 1661. (e) Gao, G. Y.; Li, D. J.; Keung, W. M. *J. Med. Chem*. **2001**, *44*, 3320.

113 (a) Su, b.; Hackett, J. c.; Diaz-Cruz, E. S.; Kim, Y. W.; Brueggemeier, R. W. *Bioor. Med. Chem*. **2005**, *13*, 6571. (b) Kim, Y. W.; Hackett, J. C.; Brueggemeier, R. W. *J. Med. Chem.* **2004**, *47*, 4032. (c) Traxler, P.; Green, J.; Mett, H.; Sequin, U.; Furet, P. *J. Med. Chem.* **1999**, *42*, 1018. (d) Cushman, M.; Zhu, H.; Geahlen, R. L.; Kraker, A. J. *J. Med. Chem*. **1994**, *37*, 3353-3368. Havsteen, B. *Biochem, Pharmac.* **1983**, *321*, 141-153.

114 (a) Harborne, T. B. the Flavonoids: Advances in Research since: chapman and Hall London, 1986; (b) Middleton, E. J.; Kandaswami, C.; Theoharides, T. C. *Pharmacol.*

Rev. **2000**, *52*, 673-751; (c) Yang, C. S.; Prabhu, S.; Landau, *J. Drug Metab. Rev*. **2001**, *33*, 237-253; (d) Haghiac, M.; Walle, T. *Nutr. Cancer*. **2005**, *33*, 220-231.

115 (a) Habtemariam, S. *J. Nat. Prod.* **1997**, *60*, 775; (b) Koganov, m. M.; Dueva, O. V. and Tsorin, B. L. *J. Nat. Prod*. **1999**, *62*, 481; (c) Lapidot, T.; Walker, M. D. andKanner, J. *J. Agric. Food Chem*. **2002**, *50*, 7220; (d) Cho, H.; Yun, C. W.; Park, W. K.; Kong, J. Y.; Lee, s. and Kim, B. *Pharmacol. Res.* **2004**, *49*, 37; (e) Critchfield, J. W.; Butera, S. T. and Folks, T. M. *AIDS. Res. Hum. Retroviruses.* **1996**, *12*, 39-48.

116 Datla, K. P.; Christidou, M.; Widmer, W. W.; Rooprai, H. K.; Dexter, D. T. *Neuroreport*. **2001**, *12*, 3871-3882.

117 Banerij, A.; Goomer, N. *Synthesis* **1980**, 874-884.

118 Allan, J.; Robinson, R. *J. Chem. Soc.* **1924**, *20*, 2192-2201.

119 Khanna, M. S.; Singh, O. V.; Garg, C. P.; Kapoor, R. P. *J. Chem. Soc*., Perkin Trans. **1992**, 2565-2574.

120 LooKer, J. H.; Hanneman, W. W. *J. Org. Chem.* **1962**, *27*, 381-392.

121 (a) Zembower, D.; Zhang, H. *J. Org. Chem*. **1998**, *63*, 9300. (b) Zheng, X.; Meng, W.; Qing, F. *Tetrahedron Lett*. **2004**, *45*, 8083. (c) Huang, X.; Tang, E.; Xu, W. M.; Cao, J. *J. Comb. Chem.* **2005**, *7*, 802. (d) Peng, W-.J.; Han, X-. W.; B. *Chinese J. Chem*. **2006**, *24*, 1154-1164.

122 Yang, Q.; Alper, H. *J. Org. Biomol. Chem.* **2012**. *75*, 948-957.

123 Rao, M. L, N.; Venkatesh, V.; Jadhav, D. N. *Synlett* **2009**, 2597.

124 Kim, D.; ham, K.; Homg, S. *Org. Biomol. Chem*. **2012**, *10*, 7305-7316.

125 Akrawi, A.; Patonay, T.; Konya, K.; Langer, P. *Synlett* **2013**, *24*, 860-864.

126 Eleya, N.; Malik, I.; Reimann, S.; Wittler, K.; Hein, M.; Patonay, T.; Villinger, A.; Ludwig, R.; Langer, P. *Eur. J. Org. Chem.* **2012**, *14*, 1639-1652.

127 Ito, C.; Chiliro, M.; Katsuno, S.; Omura, M.; Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. prod*. **2000**, *63*, 1218-1226.

128 (a) Adyshev, A. Z.; D Yachuk, G. I.; Semenov, E. V.; Pukhov, M. P. *Pharm. Chem. J.* **1993**, *27*, 66-74.

129 Kontogiorgis, C. A.; Hadjipavlou, D. *J. Bioorg. Med. Chem. Lett*. **2004**, *14*, 611-621.

[130] Abyshev, A. Z.; Alekseev, A. T.; Platonov, V. G.; Byrkin, I. A. *Pharm. Chem. J.* **1996**, *30*, 441-450.

[131] Teran, C.; Santana, L.; Uriarte, E.; Fall, Y.; Lena, L.; Tolf, B.-R. *Bioogr. Med. Chem. Lett.* **1998**, *8*, 3570-3581.

[132] Wang, T.-C.; Chen, Y.-L.; Cherng, C.-C.; Liou, S.-S.; Cheng, C.-M. *Helv. Chim. Acta.* 1**996**, *79*, 1620-1631.

[133] Saxena, A. K. Singh, B.; Anand, K. K. *J. Ethnopharmacology.* **1993**, *40*, 155-165.

[134] Simonsen, H. T.; Nordskjoid, J. B.; Smitt, U. W.; Nyman, U.; Palpu, P.; Joshi, P.; Varughese, G. *J. Ethnopharmacology*. **2001**, *74*, 195-107.

[135] Thakur, V. D.; Mengi, S. A. *J. Ethnopharmacology.* **2005**, **102**, 23-32.

[136] Narayanan, B. A.; Geoffroy, Willingham, M. C.; Re, G.; Nixon, D. W. *Cancer Lett*. **1999**, *136*, 215-224.

[137] Wang, W.; Zhao, Y. Y.; Liang, H.; Jia, Q.; Chen, H. B. *J. Nat. Prod*. **2006**, *69*, 876-886.

[138] Kaushik-Basu, N.; Bopda-Waffo, A.; Talele, T. T.; Basu, A.; Costa, P. R.; da Silva, A. J. M.; Sarafianos, S. G.; Noel, N. *Nucleic Acid Res*. **2008**, *36*, 1482-1493.

[139] Kayser, O.; Kolodziej, H. *Planta Med*. **1997**, *36*, 508-516.

[140] Wang, C. J.; Hsieh, Y. J.; Chu, c. Y.; Lin, Y. L.; Tseng, T. H. Cancer Lett. **2002**, *183*, 163-172.

[141] Itoigawa, M.; Ito, C.; Tan, H. T.-W.; Kuchide, M.; Tokudo, H.; Nishino, H.; Furukawa, H. *Cancer Lett*. **2000**, *169*, 15-26.

[142] Cravotto, G.; Nano, G. M.; Palmisano, G.; Tagliapietra, S. *Tetrahedron: Asym.* **2001**, *12*, 707-715.

[143] Al-Soud, Y. A.; Al-Masoudi, I. A.; Saeed, B.; Beifub, U.; Al-Masoudi, N. A. *Chem. Heterocyc. Comp*. **2006**, *42*, 583-593.

[144] Kirkiacharian, S.; thuy, d. T.; Sicsci, S.; Bakhchinian, R.; Kurkjian, R.; Tonnaire, R. *IL Farmaco.* **2002**, *57*, 703-713.

[145] Yamaguchi, T.; Fukuda, T.; Ishibashi, f.; Iwao, M. *Tetrahedron Lett*. **2006**, *47*, 3755-3765.

[146] Pochet, l.; Frederic, R.; Masereel, B. *Curr. Pharm. Design*. **2004**, *10*, 3781-3789.

[147] Fan, G. j.; Mar, W.; Park, M. K.; Choi, E. w.; Kim, K.; Kim, S. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 2361-2373.

[148] Murakami, A.; Gao, G.; Omura, M.; Yano, M.; Ito, C.; Furukawa, H.; Takahashi, D.; Koshimizu, K.; Ohigashli, H. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 5-17.

[149] Jerris, j. P.; Smith, A. B. *J. Org. Chem*. **1988**, *46*, 577-589.

[150] Furumi, K.; Fujioka, T.; Fujii, h.; Okab, H.; Nakano, Y.; Matsunaga, H.; Katano, M. Mori, Mihashi, K. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 93-109.

[151] Takadate, A.; Tahara, T.; Fujino, H.; Goya, S. *Chem. Pharm. Bull.* **1982**, *30*, 4120-4131.

[152] Jimenez, M.; Mateo, J. J.; Mateo, R. *J. Chromatogr*. *A.* **2000**, *870*, 473-483.

[153] Subhas, b. O.; Rudradas, A. P.; Babu, M. H. *Tetrahedron Lett*. **2002**, 43, 9195-9199.

[154] Sethna, S. M.; Phadke, R. *Org. React*. **1953**, *7*, 1-9.

[155] Donnelly, b. J.; Donnelly, D. X.; Sullivan, A. M. O. *Tetrahedron* **1968**, *24*, 2617-2621.

[156] (a) Jones, G. Org. React. 1967, 15, 204; (b) Bigi, F.; Chesini, L.; Maggi, R.; Sartori, G. *J. Org. Chem*. **1999**, *64*, 1033-1036.

[157] Yavari, I.; Hekmat-Shoar, R.; Zonuzi, A.; *Tetrahedron Lett*. **1998**, *39*, 2391-2395.

[158] Nadkarni, A. J.; Kudav, N. A. *Ind, J. Chem.* **1981**, *20B*, 719-725.

[159] Bose, D. S.; Rudradas, A. P.; Badu, M. H. *Tetrahedron Lett.* **2002**, *43*, 9195-9198.

[160] Wang, L.; Xia, J.; Tian, H.; Qian, C.; ma, Y. *Indian J. Chem. Sect. B: org. Inc. Med. Chem*. **2003**, *42*, 2097-2081.

[161] Willker, W.; Leibfritz, D.; Kerssebaum, R.; Bermel, W. *Mag. Reson. Chem.* **1993**, *31*, 287-298.

[162] Aue, W. P.; Bartholdi, E.; Ernst, R. R. *J. Chem. Physics*, **1976**, *64*, 2229-2234.

[163] Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; De Clercq, E. *J. Virol. Methods.* **1988**, *20*, 309-315.

[164] Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; Clair, M. H. St.; Lehrmann, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. USA.* **1985**, *82*, 7096-7098.

[165] Hargrave, K. D.; Proudfoot, J. R.; Grozinger, K. G.; Cullen, E.; Kapadia, s. R.; Patel, U. R.; Fuchs, V. U.; Mauldin, S. C.; Vitous, J.; behnke, M. L.; Klunder, J. M.; Pal,

K.; Skiles, J. W.; McNeil, D. W.; Rose, J. M.; Chow, G. C.; skoog, M. T.; Wu, J. C.; Schmidt, G.; Engel, W. W.; Eberlein, W. G,; Saboe, T. D.; Campbell, T. D.; Rosenthal, a. S.; Adam, J. *J. med. Chem.* **1991**, *34*, 2231-2235.

LIST OF PUBLICATIONS

1. Zien Khaddour, Omer A. Akrawi, **Aws M. Hamdy**, Ali Suleiman, Kinan Jamous, Alexander Villinger, Peter Langer, *Tetrahedron Lett.* **2015**, *56*, 554-557.

2. **Aws M. Hamdy**, Nadi Eleya, Hamid H. Mohammed, Tamas Potonay, Alexander Villinger, Peter Langer, *Tetrahedron* **2013**, *69*, 2081-2086.

3. **Aws M. Hamdy**, Nadi Eleya, Hamid Mohammed, Zine Khaddour, Tamas Patonay, Alexander Villinger, Peter Langer, *Tetrahedron Lett.* **2013**, *54*, 3568-3571.

4. Najim A. Al-Masoudi, Hamid H. Mohammed, **Aws M. Hamdy**, Omer A. Akraw, Christophe Pannecouque, Peter Langer, *Z. Naturforsch. B* **2013**. *68b*, 229-238.

5. Zin Khaddour, Nadi Eleya, Omer A. Akrawi, **Aws M. Hamdy**, Tamas Patonay, Alexander Villinger, Peter Langer, *Synlett* **2013**, *24*, 2114-2118.

6. Zin Khaddour, Nadi Eleya, Omer A. Akrawi, **Aws M. Hamdy**, Tamas Patonay, Alexander Villinger, Peter Langer, *Tetrahedron Lett*. **2013**, *54*, 5201-5203.

ABOUT THE AUTHOR

Name: Aws Mardan Hamdy AL-Abo

Date of Birth: 08.09.1975

Nationality: Iraqi

Gender: Male

Marital status: Marreid

Languages: Arabic (mother language), English (second language)

E-mail: awsmardan@yahoo.com

Professional Qualifications

2000 MSc. Chemistry University of Mosul

1998 BSc. Chemistry University of Mosul

1994 The Baccalaureate Al-Mostaqbal

Employment Details

2001 - Now Lecturer, University of Mosul, Iraq.

Teaching Duties

- Practical organic Chemistry (*Synthesis of organic Compounds, including techniques and characterization).* Chemistry Laboratories 3rd grade, Depart. of Chemistry - College of Science.

- Practical organic Chemistry (*Identification of organic compounds)* Laboratories 4th grade, Depart. of Chemistry - College of Science.

- Practical organic Chemistry 2nd grade. Depart. of Chemistry - College of Science.

Scholarship

2011-2015 German Academic Exchange Service (DAAD) Fellowship, University of Rostock, Germany.

Membership in Societies

Membership in Iraqi Chemists Union, Iraq, 1998.

Declaration / Erklärung

Here by I declare that this work has so far neither submitted to the Faculty of Mathematics and Natural Sciences at the University of Rostock nor to any other scientific Institution for the purpose of doctorate. Further more, I declare that I have written this work by myself and that I have not used any other sources, other than mentioned earlier in this work.

Hiermit erkläre ich, daß diese Arbeit bisher von mir weder an der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock noch einer anderen wissenschaftlichen Einrichtung zum Zwecke der Promotion eingereicht wurde.

Ferner erkläre ich, dass ich diese Arbeit selbständig verfasst und keine anderen als die darin angegebenen Hilfsmittel benutzt habe.

I hereby apply irrevocably to take oral examination in the form of a private viva voce and a public presentation.

_____

Aws Al-Abo