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Iodine Mediated Oxidative Cross-Coupling of Unprotected Anilines and Heteroarylation of Benzothiazoles with 2-Methylquinoline

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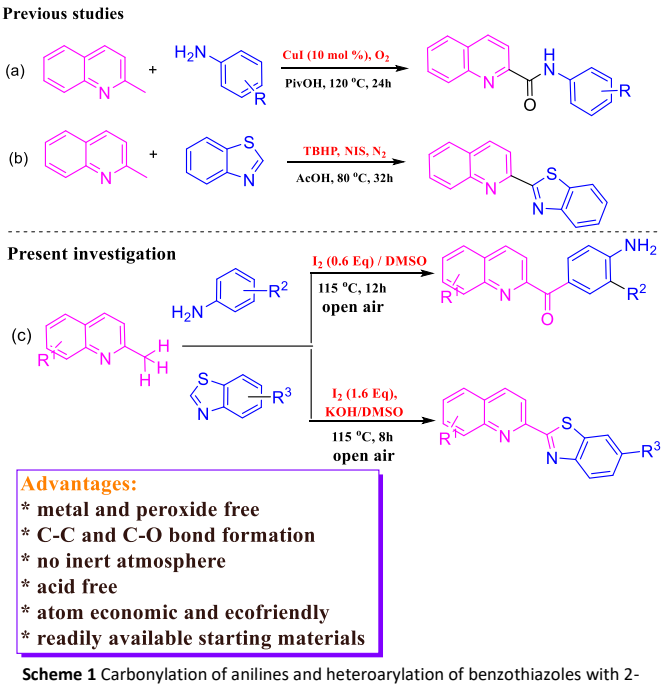
Abdul Rahim,[a,b] Siddiq Pasha Shaik,[a,b] Mirza Feroz Baig,[a,b] Abdullah Alarifi,[c] and Ahmed Kamal*[a,b,c,d]

Iodine-promoted oxidative C-H/C-H cross-coupling of unprotected anilines and 2-methyl quinoline to furnish the C4-carbonylated aniline (4-aminophenyl)(quinoline-2-yl) methanone in moderate to good yields has been demonstrated. This work provides first site-selective approach for the synthesis of free amino group containing methanone including unprecedented C-H functionalization rather than N-H functionalization of unprotected anilines via Kornblum oxidation of 2-methyl quinoline. Further, we noticed that incorporation of KOH under the standard conditions provides 2-heteroarylbenzothiazoles from benzothiazoles and 2-methyl quinoline in good to excellent yields. These transformations do not require any transition metal and peroxide and tolerate various functional groups such as methoxy, hydroxy, bromo, chloro and nitro groups. Moreover, plausible mechanistic pathway is proposed.

Introduction

Pre-functionalization of substrates can be avoided by direct oxidative coupling and it represents ideal chemical synthesis.[1,2] Recent advances have been focused on the oxidative coupling of Csp^3-H of aryls and hetero-aryls with N-H in anilines to allow *N*-dicarbonylation of anilines to prepare α-ketoamides.[3] 2-Methyl azaarenes have been used by Deng and co-workers in the presence of oxygen atmosphere under catalytic CuI to provide *N*-heteroarylamide (Scheme1a).[4] It is evident that carbon is a weaker nucleophile than nitrogen, especially the free N–H of anilines, therefore direct oxidative Csp^3–H/Csp^2–H cross-coupling of unprotected anilines to construct C–C rather than C–N bonds will be a greater challenge. In this view, the direct oxidative Csp^3-H/Csp^2-H of unprotected anilines and cross-coupling to C4-dicarbonylation of anilines has been recently reported.[5]

In the present work, the direct oxidative carbonylation of anilines with 2-methyl quinoline via sp^2C-H and sp^3C-H double activation was achieved under the transition metal-free reaction conditions. This transformation proceeds regioselectively in the facile I_2/DMSO system to produce the valuable (4-aminophenyl)(quinoline-2-yl) methanones from the easily available starting materials in moderate to good yields (Scheme1c). Quinoline derivatives endowed with various activities, such as anti-tuberculosis, antimalarial, anti-inflammatory, anticancer, antibiotic, and anti-hypertensive.[6] Chloroquine, primaquine, mefloquine and quinine are the examples of the drugs that contains a quinoline scaffold.



Scheme 1 Carbonylation of anilines and heteroarylation of benzothiazoles with 2-methyl quinoline

[a] Medicinal Chemistry and Biotechnology Division, CSIR-Indian Institute of Chemical Technology (IICT), Hyderabad-500007, India
[b] Academy of Scientific and Innovative Research, New Delhi, 110 025, India
[c] Catalytic Chemistry Research Chair, Chemistry Department, College of Science, King Saud University, Riyadh 11451, Saudi Arabia
[d] School of Pharmaceutical Education and Research, Jamia Hamdard University, New Delhi, 110062, India

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Similarly, amino-containing compounds are ubiquitous among biologically active molecules, natural products and material sciences, and they can act as potentially valuable synthetic intermediates in organic synthesis.[7] Moreover, diarylmethanones are a class of important units that occur in variety of natural products and synthetic drugs.[8] They are also useful as significant synthetic intermediates and building blocks in inorganic synthesis and material sciences.[9]

Thus, continuous efforts have been devoted in developing more efficient methods for their preparation.[10,11] However, current strategies inevitably required longer reaction time, use of transition metals, peroxides and special directing groups, leading to the potential issues of low synthetic efficiency and metal contamination in the products.[11] The development of a complementary metal and peroxide-free method to achieve the direct oxidative carbonylation of sp^2C-H bonds with 2-methyl azaarenes is of great challenge and appreciation.

In addition to this, 2-substitued benzothiazoles have been reported to present promising activities, such as anticancer, antitumor, hydrolyse inhibitors, protease inhibitors, fluorescent dyes and material sciences.[12,13] Several methods have been reported for the formation of 2-substitued benzothiazoles including condensation of amino thiophenol with benzaldehydes, nitriles, carboxylic acids and acyl chlorides.[14-17] They have also been prepared by cross coupling reactions of benzothiazoles with arylsilanes, aryl halides, aryl boronic acids, aryl triflates and sodium sulfinates.[18-23]

However, these methods have some limitations like high temperatures, strong acidic conditions, longer reaction time and use of transition metal catalyst. To overcome these problems, development of a transition metal-free, direct, and efficient method from cost-effective starting materials needs to be explored. In this regards, Gao and co-workers developed a KI-catalysed condensation of aryl aldehydes with benzothiazole to obtain 2-aryl benzothiazoles.[24] Most recently, Chen Ma and co-workers reported the synthesis of 2-heteroaryl benzothiazoles by the oxidative condensation of 2-methylquinoline derivatives with benzothiazoles in the presence of acid and peroxides (Scheme1b).[25] Inspired by these reports, we envisioned a I_2/DMSO promoted synthesis of 2-heteroaryl benzothiazoles by the oxidative condensation of 2-methylquinolines with benzothiazoles under acid and peroxide-free conditions (Scheme1c).

Results and discussion

In continuation of our previous work on oxidative amination of 2-methylquinoline with *o*-phenylenediamine to build 2-heteroaryl benzimidazole,[26] we came across the formation of a new C–C bond via oxidative cross-coupling with 2-methylquinoline (**1a**) and aniline (**2a**) in the presence of molecular iodine at 100 °C in DMSO (Table 1, entry 1). Having obtained an initial and promising result, we next focused on the optimization of the reaction conditions. We first examined the effect of different equivalents of **2a** and found that lowering and increasing the amount of **2a** resulted in lower yields (Table 1, entries 2-6), with the best result obtained with 1.0 equivalent of **2a** (Table 1, entry 1).

Further, temperature was examined between 60 and 130 °C and was found to play an important influence on the reaction yield (Table1, entries 7–11). Decreasing or increasing the I_2 dosage from 0.6 equivalents greatly decreased the yield (Table1, entries 13–16). However, the reaction did not occur in the absence of I_2 or with other iodine sources (Table 1, entries 17 and 18), indicating that molecular iodine was essential for the reaction (Table 1, entry 12). A series of Brønsted and Lewis

Table 1 Optimization of the reaction conditions[a]

1a 2a 3aa

entry	2a (equiv)	iodine (equiv)	temp(°C)	acid	yield (%)[b]
1	1.0	0.6	100		64
2	0.5	0.6	100		42
3	0.8	0.6	100		55
4	1.2	0.6	100		50
5	1.5	0.6	100		39
6	2.0	0.6	100		trace
7	1.0	0.6	60		trace
8	1.0	0.6	80		35
9	1.0	0.6	90		46
10	**1.0**	**0.6**	**115**		**78**
11	1.0	0.6	130		52
12	1.0	0	115		0
13	1.0	0.1	115		38
14	1.0	0.3	115		50
15	1.0	2.0	115		47
16	1.0	2.5	115		45
17	1.0	0.6 (NIS)	115		0
18	1.0	0.6 (TBAI)	115		0
19	1.0	0.6	110	$TsOH·H_2O$	73
20	1.0	0.6	110	CF_3SO_3H	78
21	1.0	0.6	110	HCl	72
22	1.0	0.6	110	$FeCl_3$	70
23	1.0	0.6	110	$AlCl_3$	60
24	1.0	0.6	110	$Zn(OTf)_2$	57
25[c]	1.0	0.6	115		70
26[d]	1.0	0.6	115		76

[a]Reaction conditions: **1a** (1.0 mmol), **2a**, I_2, heated in 4 mL of DMSO within 12 h. [b]Products were obtained in isolated yields based on quinoline. [c]N_2 atmosphere. [d]O_2 atmosphere.

Acids ($TsOH·H_2O$, CF_3SO_3H, HCl, $FeCl_3$, $AlCl_3$, and $Zn(OTf)_2$) were screened as additives for the reaction, but no benefit was found in promoting the reaction (Table1, entries 19-24). Notably, no remarkable increase to the isolated yield was obtained in presence of N_2 or O_2 (Table1, entries 25-26). The optimal conditions determined were **1a** (1.0 mmol) with **2a**

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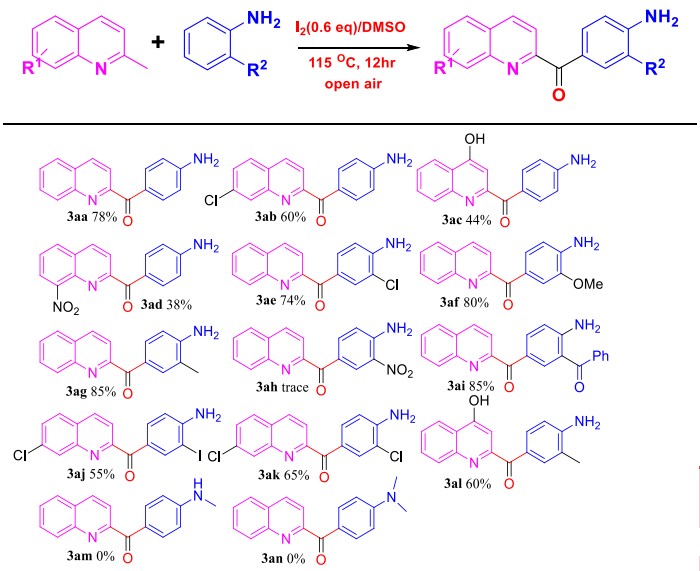
(1.0 mmol) in the presence of I_2 (0.6 mmol) in DMSO at 115 °C to afford the desired product in 78% yield (Table 1, entry 10).

With the optimized reaction conditions in hand, we investigated the substrate generality of this I_2-promoted oxidative coupling reaction with 2-methylquinoline substrates. A series of substituted 2-methylquinolines were found to undergo the desired transformation to give the corresponding products in moderate to good yield (38–85%, Scheme 2).

Scheme 2 Scope of anilines and 2-methylquinolines



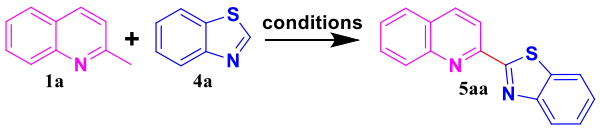
[a]Reaction conditions: **1a** (1.0 mmol), **2a**(1.0 mmol), heated in 4 mL of DMSO within 12 h.

The electronic nature of the 2-methylquinolines was shown to have little influence on the reaction efficiency. The presence of electron-donating (4-OH), and electron-deficient (8-NO_2) groups had more effect on reactivity, and the corresponding (4-aminophenyl)(quinoline-2-yl) methanone were obtained in low yields (44% and 38% for **3ac** and **3ad**) compared to the electron-neutral group containing compound **3aa** with 78 % yield. The optimized conditions were also compatible with 2-methylquinolines bearing halogen substituents (7-Cl), with the corresponding products **3ab** obtained in 60% yields. We next investigated using substituted anilines as substrates to further expand the scope of this coupling reaction and the results are displayed in Scheme 2.

2-methoxyaniline and o-Toluidine performed well, giving the desired products **3af**–**3ag** in 80–85% yield. Notably, halogen-substituted anilines (2-Cl) afforded the oxidative coupling products in good yield (74%, **3ae**). A benzoyl groups (2-PhCO), as an electron-withdrawing group attached to the phenyl ring, exhibited excellent reactivity (85%) to give products **3ai**. In case of strong electron-withdrawing group (2-NO_2) product obtained was in trace amount (**3ah**). These results indicate that the electron density of the phenyl ring of anilines has a substantial effect on the reaction.

To extend the scope, we also made miscellaneous products (**3aj-3al**) with good yield (55-65%). To further test, if this transformation could occur at the ortho position to the amino group in aniline, 4-methylaniline was used under the same reaction conditions, but no corresponding o-acylated product was formed, indicating that this transformation does not occur at the ortho position of the aniline. Moreover, the reaction of N-substituted aryl amines like N-methylaniline and N,N-dimethylaniline was also investigated, where number of products were formed and isolated but unfortunately none of them could be characterized as the desired products. Probably the reason for the formation of multiple products could be due to the presence of more electron-donating groups like N-Me and N,N-dimethyl with less nucleophilic nature (due to steric hindrance), thus indicating that unprotected aniline is a prerequisite for this transformation. Similarly, other electron rich arenes like 4-methoxy benzene was also investigated which failed to give the desired product.

Table 2 Optimization of the reaction conditions[a]



entry	I_2 (equiv)	Additives	solvent	temp (°C)	yield[b](%)
1	1.6	$K_2S_2O_8$	DMSO	115	8
2	1.6	$K_2S_2O_8$	DMSO/H_2O(1:1)	115	47
3	1.6	$K_2S_2O_8$	DMSO/H_2O(2:1)	115	69
4	1.6	$K_2S_2O_8$	DMSO/H_2O(3:1)	115	83
5	1.6	$K_2S_2O_8$	H_2O	115	0
6	1.6	$K_3PO_4{\cdot}3H_2O$	DMSO/H_2O(3:1)	115	52
7	1.6	K_2CO_3	DMSO/H_2O(3:1)	115	28
8	1.6	t-BuOK	DMSO/H_2O(3:1)	115	85
9	**1.6**	**KOH**	**DMSO/H_2O(3:1)**	**115**	**88**
10	1.6	Cs_2CO_3	DMSO/H_2O(3:1)	115	12
11	1.6	NaOH	DMSO/H_2O(3:1)	115	50
12	1.6	$LiOH{\cdot}H_2O$	DMSO/H_2O(3:1)	115	48
13	1.6	$NaHCO_3$	DMSO/H_2O(3:1)	115	0
14	1.6		DMSO/H_2O(3:1)	115	0
15	1.2	KOH	DMSO/H_2O(3:1)	115	81
16	1.0	KOH	DMSO/H_2O(3:1)	115	48
17		KOH	DMSO/H_2O(3:1)	115	0
18[c]	1.6	KOH	DMSO/H_2O(3:1)	115	75
19[d]	1.6	KOH	DMSO/H_2O(3:1)	115	72
20	1.6	KOH	DMSO/H_2O(3:1)	60	15
21	1.6	KOH	DMSO/H_2O(3:1)	90	77
22	1.6	KOH	DMSO/H_2O(3:1)	130	85

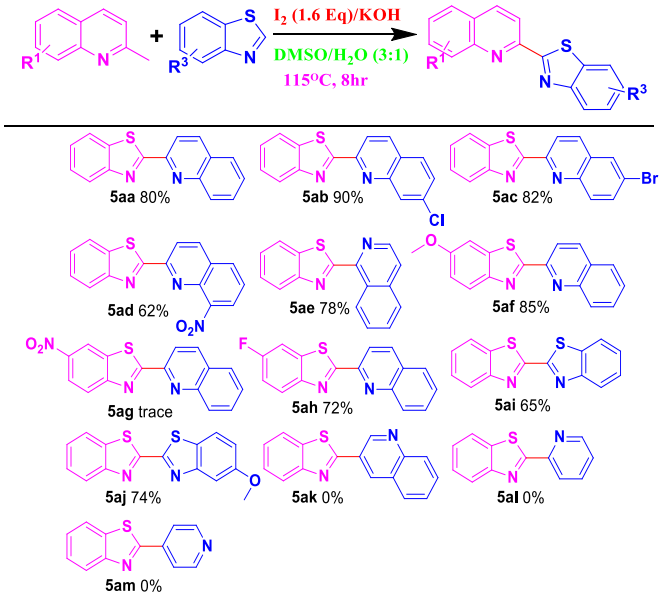
[a]Reaction conditions: **1a** (1.0 mmol), **4a** (1.2 mmol), base (1.2 mmol), solvent (4 mL). [b]Isolated yields. [c]**4a**(1.5 mmol).[d]**4a**(1.0 mmol)

It is worth mentioning that structures of the products were established as para-carbonylated anilines on the basis of their ^1H NMR spectra (based on splitting pattern). In another scheme, an I_2/KOH synergistically promoted heteroarylation of benzothiazoles with 2-methylquinoline is described. We initiated the study with 2-methylquinoline (**1a**) and benzothiazole (**4a**) as model substrates. It was found that the

reaction led to the desired product 2-heteroarylbenzothiazole (**5aa**) in a very low yield of 8% (Table 2, entry 1). To our surprise, the reaction could perform in moderate yield in the presence of H_2O (Table 2, entry 2). When the ratio of DMSO to H_2O was changed from 1:1 to 3:1, the yield increased to 83% (Table 2, entry 3 and 4). When H_2O taken as solvent reaction did not occur and starting material were recovered (Table 2, entry 5).Other bases were also tested, which demonstrated that KOH was the best choice (Table 2, entries 6–13). However, heterorylation of benzothiazole was not observed in the absence of either base or iodine, indicating that an I_2/KOH combination is crucial for the reaction (Table 2, entries 14 and 17).

Decreasing the I_2 dosage from 1.6 equivalents greatly decreased the yield (Table 2, entries 15–16). As the reactions were performed in open air and some of the *in situ* generated HI is probably escaping, thus we have used stoichiometric amount of iodine. We also examined the effect of different equivalents of **4a** and found that lowering or increasing the amount of **4a** resulted in lower yields (Table 2, entries 18-19), with the best result obtained with 1.2 equivalent of **4a** (Table **2**, entry 9). Further, temperature was examined between 60 and 130 °C and was found to play an important influence on the reaction yield (Table 2, entries 20–22).

Scheme 3 Scope of benzothiazoles and 2-methylquinolines



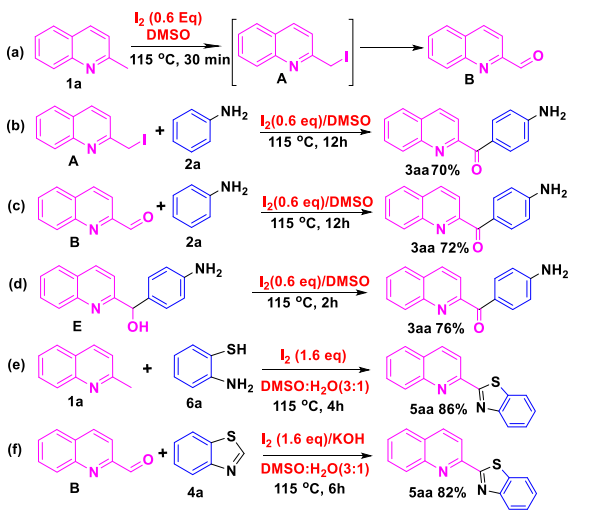
[a]Reaction conditions: **1a** (1.0 mmol), **4a** (1.2 mmol), base (1.2 mmol), solvent (4 mL).

After achieving the optimized reaction conditions (Table 2, entry 9), the scope of 2-methylquinoline (**1a**) and benzothiazole (**4a**) were explored (Scheme 3). 2-Methylquinoline bearing electron-neutral (4-H) and electron-deficient (8-NO_2) groups participated well in this reaction to afford the desired 2-heteroaryl benzothiazoles in moderate to excellent yields (90% and 62% for **5aa** and **5ad**).

Much to our satisfaction, the conditions were mild enough to be compatible with halogenated (7-Cl, 6-Br) substrates (82–90%; **5ab**–**5ac**). When 1-methylisoquinoline was used as the starting material, the corresponding product was also obtained in good yield (78%, **5ae**). However, under the optimized conditions, 2-methylpyridine, 4-methylpyridine and 3-methylquinoline could not convert to the corresponding products (**5ak**-**5am**). This could be due to the isomerization of 2-methylquinoline into an enamine intermediate **1a`** under the usual reaction conditions as shown in Scheme **5a.** Therefore, in case of 2-methylpyridine and 3-methylquinoline it may be difficult to perform the de-aromatization process as such the desired product was not obtained.

Next, various benzothiazoles were coupled with 2-methylquinoline to provide the corresponding products. Substrates with an electron-donating substituent (**5af**, 85%) afforded higher yield than that with an electron-withdrawing substituent (Scheme 3, **5ah**, 72%). In case of strong electron-withdrawing substituent (6–NO_2) could give corresponding product but with trace amount (Scheme 3, **5ag**). Furthermore, the reaction of 2-methyl benzothiazole and 6-methoxy-2-methyl benzothiazole with simple benzothiazole under standard conditions furnished the corresponding products in good yields (65% and 74% for **5ai** and **5aj**).

Scheme 4 Control experiments

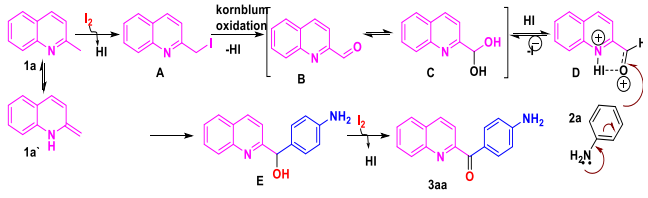


To gain some insights into the mechanism of the reaction, a series of control experiments were performed (Scheme 4). According to previously reported results,[27,28] we easily converted 2-methylquinoline **1a** into **A** and **B** products with higher yields (85%) in the presence of I_2/DMSO system (Scheme 4, a). When compound **A** and **B** were reacted with aniline 2a, under standard conditions, **3aa** was obtained in 70% and 72% yields, respectively (Scheme 4, b and c). These results clearly confirmed that **A** and **B** were the key intermediates for this transformation. Furthermore, when intermediate **E** was taken as starting material we got the product **3aa** in 76 % yield (Scheme 4, d). In case of another

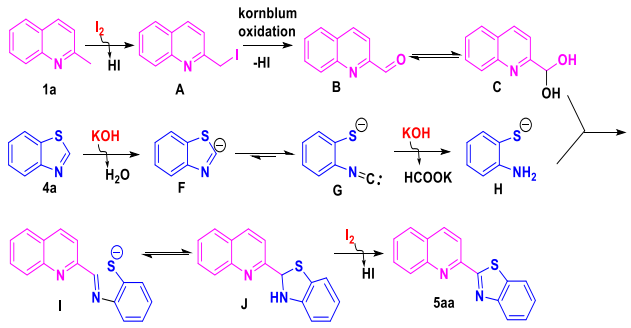
Scheme, benzothiazole (**4a**) can be converted to 2-aminobenzenethiol in 82% yield under I_2/KOH/DMSO reaction conditions. The treatment of 2-aminobenzenethiol with 2-methylquinoline gave **5aa** in 86% yield (Scheme 4, e). Similarly, quinoline-2-carbaldehyde was obtained upon reaction of 2-methylquinoline with benzothiazole (**4a**) affords **5aa** in 82% yield under the standard conditions (Scheme 4, f).

Based on the above results and previous reports, we proposed a plausible mechanistic pathway for C4-carbonylation of aniline (Scheme 5, a) and heteroarylation of benzothiazole (Scheme 5, b). Initially, 2-methylquinoline **1a** with molecular iodine results in the formation of the α-iodoquinoline **A**, which is converted to quinoline-2-carbaldehyde **B** (which is in equilibrium with **C**) and releases HI by a subsequent Kornblum oxidation.[29] The aldehyde group of **B** is activated by coproduct HI to give positively charged **D**, which is trapped in situ by aniline **2a** via a Friedel–Crafts-type reaction to give intermediate **E**.

Scheme 5 Plausible mechanisms



(a)Mechanism for the synthesis of carbonylated aniline



(b) Mechanism for the heteroarylation of benzothiazole

Intermediate **E** is rapidly oxidized by I_2 to afford the desired product **3aa**.[30] As reported by Yin et al, DMSO can convert in situ generated HI into iodine and thus, apprehend a catalytic cycle for the regeneration of iodine.[31] In the same manner, in case of another Scheme, **1a** was converted to α-iodoquinoline (**A**) in the presence of I_2. Subsequently, further oxidation of **A** by DMSO took place to **B** and **C**. At the same time, the ring-opened intermediate **G** was generated by deprotonation of **4a** under the assistance of KOH. This intermediate G through hydroxylation give rise to intermediate H,[32] which in turn reacts with in situ trapped **B** to give **I**. Finally, this intermediate **I** via Michael addition and oxidative dehydrogenation sequences, furnished the desired product **5aa** by using iodine.

Conclusions

In summary, a highly site-selective I_2-promoted oxidative cross-coupling of 2-methyl quinoline and anilines for the preparation of (4-aminophenyl)(quinoline-2-yl) methanones under mild conditions has been established. This work provides the first approach for the synthesis of free amino group containing methanone scaffold by the dual C-H activation of Csp^3–H of 2-methylquinoline and Csp^2–H of anilines for the construction of C–C and C-O bonds. Further, we have developed one-pot, metal and peroxide free, simple strategy for the synthesis of 2-heteroarylbenzothiazoles by the oxidative condensation of 2-methylquinoline derivatives with benzothiazoles using KOH/I_2/DMSO system. Moreover, studies to elucidate a detailed mechanism and to identify the synthetic applications for these protocols are currently underway in our laboratory.

Experimental Section

General

All reagents, starting materials, and solvents were purchased from Aldrich (Sigma-Aldrich, St. Louis, MO, USA) or Alfa Aesar (Johnson Matthey Company, Ward Hill, MA, USA) and used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254, and visualization on TLC was achieved by UV light or using an iodine indicator. Column chromatography was performed with Merck 60–120 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded with 75, 100, 300, 400, and 500 MHz spectrometer in $CDCl_3$ and DMSO-d_6 solutions. Chemical shifts (δ) are expressed in ppm relative to the internal standard TMS and multiplicities of NMR signals are represented as singlet (s), broad singlet (bs), doublet (d), triplet (t), double doublet (dd), triplet of doublet (td) and multiplets (m). High-resolution mass spectra (ESI-HRMS) were obtained by using ESI-QTOF mass spectrometer. Melting points were determined on an electrothermal melting point apparatus and are uncorrected.

Procedure for the synthesis of 2-(iodomethyl)quinoline (A)

In a 25mL round bottom flask equipped with a magnetic stir bar, the 2-methylquinoline (100 mg, 0.69mmol) was dissolved in DMSO (4 mL) and molecular iodine (60 mol%)) was added and heated at 115°C for 1 hr. After this time, the reaction mixture was cooled to room temperature, quenched with saturated solution of $Na_2S_2O_3$ (40 mL) and 2-(iodomethyl) quinoline was extracted with ethyl acetate (3x 40 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate (EA): petroleum ether (PE) (4:100) as eluent to provide compound **A**. white solid; **M.P.**: 58-64 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.5 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 8.7 Hz, 2H),

4.68 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.41, 147.54, 137.29, 130.01, 129.05, 127.55, 127.10, 126.90, 121.12, 6.83; 68 mg, 36%; R_f = 0.30 (10% EA:PE).; **ESI-Mass** $[M+1]^+$ 269.

Procedure for the synthesis of quinoline-2-carbaldehyde (B)

In a 25mL round bottom flask equipped with a magnetic stir bar, the 2-methylquinoline (100 mg, 0.69mmol) was dissolved in DMSO (4 mL) and molecular iodine (60 mol%)) was added and heated at 115°C for 30 min. After this time, the reaction mixture was cooled to room temperature, quenched with saturated solution of $Na_2S_2O_3$ (40 mL) and quinoline-2-carbaldehyde was extracted with ethyl acetate (3x 40 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate (EA): petroleum ether (PE) (2:100) as eluent to provide compound **B**. white solid, **M.P**.: 72-73 °C;**^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.83 (t, *J* = 7.2 Hz, 1H), 7.69 (t, *J* = 7.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.77, 152.62, 147.96, 137.43, 130.52, 130.45, 129.23, 127.89, 117.38; 71 mg, 64%; R_f = 0.36 (10% EA:PE).; **ESI-Mass** $[M+1]^+$ 158.

General procedure for (4-aminophenyl) (quinolin-2-yl) methanones (3aa-3al)

In a 25mL round bottom flask equipped with a magnetic stir bar, the mixture of 2-methylquinoline (100 mg, 0.69 mmol), 2-substituted anilines (0.69 mmol) and molecular iodine (60 mol%) were taken in DMSO (4 mL) and heated at 115°C for 12 h. After completion of reaction, the reaction mixture was cooled to room temperature, quenched with saturated solution of $Na_2S_2O_3$ (40 mL) and the reaction was extracted with ethyl acetate (3x 40 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate: petroleum ether (5-20 % EA:PE) Petroleum ether as eluent to provide compounds **3aa-3al**.

General procedure for 2-(quinolin-2-yl)-benzo[*d*]thiazoles(5aa-5aj)

In a 25mL round bottom flask equipped with a magnetic stir bar, the 2-methylquinoline (100 mg, 0.69mmol) and 6-subtituted benzothiazoles (0.69 mmol) were dissolved in DMSO (4 mL). To this solution, aqueous KOH (0.83 mmol) and molecular iodine (1.6 Eq) were added and heated at 115°C for 8 h. After completion of reaction, the reaction mixture was cooled to room temperature, quenched with saturated solution of $Na_2S_2O_3$ (40 mL) and the reaction was extracted with ethyl acetate (3x 40 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate: petroleum ether (5-10 % EA:PE) as eluent to provide compounds **5aa-5aj**.

(4-aminophenyl) (quinolin-2-yl) methanone (3aa)

Yellow solid (75 %), **M.P**.: 158-159 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 8.2 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 8.8 Hz, 2H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.78 (t, *J* = 8.4 Hz, 1H), 7.67 – 7.61 (m, 1H), 6.70 (d, *J* = 8.8 Hz, 2H), 4.20 (s, 2NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 191.95, 156.15, 151.64, 146.66, 136.97, 134.17, 130.33, 129.98, 128.66, 127.97, 127.67, 126.13, 121.00, 113.65; **HRMS**(ESI)calculated for $C_{16}H_{13}ON_2$ $(M+H)^+$ 249.10224; found: 249.106236.

(4-aminophenyl) (7-chloroquinolin-2-yl) methanone (3ab)

Yellow solid (60 %), **M.P**.: 204-206 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.5 Hz, 1H), 8.21 (d, *J* = 1.8 Hz, 1H), 8.12 (d, *J* = 8.7 Hz, 2H), 8.00 (t, *J* = 8.9 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.58 (dt, *J* = 10.1, 5.1 Hz, 1H), 6.69 (d, *J* = 8.7 Hz, 2H), 4.24 (s, 2NH);**^{13}CNMR** (100 MHz, $CDCl_3$): δ 191.41, 157.01, 151.65, 146.99, 136.81, 135.86, 134.16, 129.25, 128.98, 128.84, 126.98, 125.96, 121.25, 113.66; **HRMS**(ESI)calculated for $C_{16}H_{12}ON_2Cl$ $(M+H)^+$ 283.06327; found: 283.06352.

(4-aminophenyl) (4-hydroxyquinolin-2-yl) methanone (3ac)

Green solid (44 %), **M.P**.: 246-248 °C; **^{1}HNMR** (400 MHz, DMSO-d_6): δ 12.05 (s, 1H), 8.11 (d, *J* = 7.9 Hz, 1H), 7.80–7.63 (m, 4H), 7.37 (t, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 8.7 Hz, 2H), 6.50 (s, 2NH), 6.17 (s, 1H);**^{13}CNMR** (75 MHz, DMSO-d_6): δ 187.33, 176.98, 155.25, 146.13, 140.02, 133.02, 132.32, 125.56, 124.79, 123.61, 121.48, 119.02, 112.81, 109.73; **HRMS**(ESI)calculated for $C_{16}H_{13}O_2N_2$ $(M+H)^+$ 265.09715; found: 265.09715.

(4-aminophenyl) (8-nitroquinolin-2-yl) methanone (3ad)

Red solid (38 %), **M.P**.: 196-198 °C; **^{1}HNMR** (300 MHz, DMSO-d_6): δ 8.76 (d, *J* = 8.6 Hz, 1H), 8.38 (t, *J* = 7.1 Hz, 1H), 8.30 (s, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 7.90 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 8.8 Hz, 2H), 6.37 (s, 2NH); **^{13}CNMR** (125 MHz, DMSO-d_6): δ 189.49, 158.36, 155.05, 148.50, 138.50, 137.32, 134.27, 132.59, 129.12, 127.67, 124.68, 124.48, 122.84, 122.66, 112.99; **HRMS**(ESI)calculated for $C_{16}H_{12}O_3N_3$ $(M+H)^+$ 294.08732; found: 294.08721.

(4-amino-3-chlorophenyl) (quinolin-2-yl) methanone (3ae)

Yellow solid (74 %), **M.P**.: 170-172 °C; **^{1}HNMR** (500 MHz, $CDCl_3$): δ 8.33 (dd, *J* = 5.1, 3.2 Hz, 2H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.09 (dd, *J* = 8.5, 1.9 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.79 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.69–7.62 (m, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 4.62 (s, 2NH);**^{13}CNMR** (100 MHz, $CDCl_3$): δ 190.73, 155.40, 147.56, 146.64, 137.11, 133.71, 132.12, 130.46, 130.08, 128.80, 128.22, 127.67, 126.91, 120.94, 118.22, 114.25; **HRMS**(ESI)calculated for $C_{16}H_{12}ON_2Cl$ $(M+H)^+$ 283.06327; found: 283.06280.

(4-amino-3-methoxyphenyl) (quinolin-2-yl) methanone (3af)

Brown solid (80 %), **M.P**.: 137-139 °C; **^{1}HNMR** (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 8.5 Hz, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 1.7 Hz, 1H), 7.80–7.75 (m, 2H), 7.67–7.60 (m, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 4.41 (s, 2NH), 3.93 (s, 3H); **^{13}CNMR** (100 MHz, $CDCl_3$): δ 191.92, 156.34, 146.68, 146.52, 146.32, 142.30, 136.90, 130.34, 129.97, 128.63, 128.30, 127.91, 127.66, 126.01, 121.09, 112.55, 112.14, 55.68; **HRMS**(ESI)calculated for $C_{17}H_{14}O_2N_2Na$ $(M+Na)^+$ 301.09475; found: 301.09465.

(4-amino-3-methylphenyl) (quinolin-2-yl) methanone (3ag)

Yellow solid (85 %), **M.P**.: 144-146 °C; **^{1}HNMR** (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.4 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 8.04 – 7.94 (m, 3H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.77 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.63 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.68 (d, *J* = 8.2 Hz,

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1H), 4.17 (s, 2NH), 2.20 (s, 3H); **^{13}CNMR** (100 MHz, $CDCl_3$): δ 192.31, 156.34, 150.03, 146.70, 136.88, 134.38, 132.21, 130.39, 129.92, 128.64, 127.89, 127.65, 126.21, 121.01, 120.93, 113.46, 17.27; **HRMS**(ESI)calculated for $C_{17}H_{15}ON_2$ $(M+H)^+$ 263.11789; found: 263.11776.

(4-amino-3-benzoylphenyl) (quinolin-2-yl) methanone (3ai)

Yellow solid (85 %), **M.P**.: 114-116 °C; **^{1}HNMR** (500 MHz, $CDCl_3$): δ 8.81 (d, *J* = 2.0 Hz, 1H), 8.29 (dd, *J* = 12.5, 5.6 Hz, 2H), 8.03 (dd, *J* = 8.4, 3.5 Hz, 2H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.79 – 7.71 (m, 3H), 7.67–7.61 (m, 1H), 7.43 (dd, *J* = 5.0, 3.7 Hz, 1H), 7.41–7.37 (m, 2H), 6.81 (d, *J* =8.8 Hz, 1H), 6.78 (bs, 2-NH);**^{13}CNMR** (100 MHz, $CDCl_3$): δ 198.86, 190.60, 155.40, 154.85, 146.44, 141.00, 139.49, 137.08, 136.83, 131.31, 130.36, 129.86, 129.20, 128.75, 128.25, 128.18, 127.64, 123.98, 120.94, 116.72, 116.53; **HRMS**(ESI)calculated for $C_{23}H_{17}O_2N_2$ $(M+H)^+$ 353.12845; found: 353.12863.

(4-amino-3-iodophenyl) (7-chloroquinolin-2-yl) methanone (3aj)

Yellow solid (55 %), **M.P**.: 190-192 °C; **^{1}HNMR** (400 MHz, $CDCl_3$): δ 8.67 (d, *J* = 1.9 Hz, 1H), 8.30 (d, *J* = 8.5 Hz, 1H), 8.21 (d, *J* = 1.8 Hz, 1H), 8.16–8.11 (m, 1H), 8.02 (dd, *J* = 8.6, 3.8 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.60 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 4.69 (bs, 2NH); **^{13}CNMR** (75 MHz, $CDCl_3$+DMSO-d_6): δ 194.42, 161.27, 157.42, 151.55, 147.96, 141.92, 140.51, 138.21, 133.98, 133.77, 133.61, 131.78, 130.90, 125.82, 123.78, 117.63, 86.75; **HRMS**(ESI)calculated for $C_{16}H_{11}ON_2ClI$ $(M+H)^+$ 408.95991; found: 408.96025.

(4-amino-3-chlorophenyl) (7-chloroquinolin-2-yl) methanone (3ak)

Yellow solid (65 %), **M.P**.: 182-184 °C; **^{1}HNMR** (500 MHz, $CDCl_3$): δ 8.30 (dd, *J* = 4.8, 3.2 Hz, 2H), 8.22 (s, 1H), 8.07 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.60 (dd, *J* = 8.7, 1.8 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 4.64 (s, 2NH); **^{13}CNMR** (100 MHz, $CDCl_3$): δ 190.26, 156.27, 147.69, 146.95, 136.98, 136.02, 133.64, 132.11, 129.30, 129.24, 128.85, 127.11, 126.63, 121.18, 118.24, 114.22; **HRMS**(ESI)calculated for $C_{16}H_{11}ON_2Cl_2$ $(M+H)^+$ 317.02429; found: 317.02447.

(4-amino-3-methylphenyl) (4-hydroxyquinolin-2-yl) methanone (3al)

Yellow solid (60 %), **M.P**.: 253-254 °C; **^{1}HNMR** (400 MHz, DMSO-d_6): δ 12.03 (s, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.86–7.66 (m, 3H), 7.60 (d, *J* = 10.4 Hz, 2H), 7.38 (t, *J* = 7.1 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 6.28 (s, 2NH), 6.18 (s, 1H), 2.12 (s, 3H); **^{13}CNMR** (100 MHz, DMSO-d_6): δ 188.07, 177.43, 154.08, 146.69, 140.55, 133.38, 132.82, 131.51, 126.03, 125.28, 124.15, 122.26, 120.82, 119.56, 113.14, 110.33, 17.82; **HRMS**(ESI)calculated for $C_{17}H_{15}O_2N_2$ $(M+H)^+$ 279.11280; found: 279.11265.

2-(quinolin-2-yl)-benzo[*d*]thiazole (5aa)

White solid (80 %), **M.P**.: 178-180 °C; **^{1}HNMR** (300 MHz, $CDCl_3$): δ 8.43 (d, *J* = 8.6 Hz, 1H), 8.24 (d, *J* = 8.6 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 7.96–7.89 (m, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.71 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.57–7.50 (m, 1H), 7.50–7.42 (m, 1H), 7.42–7.34 (m, 1H); **^{13}CNMR** (100 MHz, $CDCl_3$): δ 169.90, 154.40, 151.35, 147.96, 137.04, 136.52, 130.14, 129.78, 129.03, 127.77, 127.61, 126.31, 125.90, 123.81, 122.06, 118.38; **HRMS**(ESI)calculated for $C_{16}H_{10}N_2S$ $(M+H)^+$ 263.06375; found: 263.06338.

2-(7-chloroquinolin-2-yl)-benzo[*d*]thiazole (5ab)

White solid (90 %), **M.P**.: 214-216 °C; **^{1}HNMR** (400 MHz, $CDCl_3$): δ 8.49 (d, *J* = 8.5 Hz, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.22 (d, *J* = 1.8 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 7.7 Hz, 1H), 7.81 (d, *J* = 8.7 Hz, 1H), 7.57–7.50 (m, 2H), 7.49–7.42 (m, 1H); **^{13}CNMR** (100 MHz, $CDCl_3$): δ 154.35, 148.27, 136.88, 136.09, 128.93, 128.68, 128.59, 127.33, 126.41, 126.10, 123.91, 122.11, 118.58; **HRMS** (ESI) calculated for $C_{16}H_9N_2SCl$ $(M+H)^+$ 297.02477; found: 297.02452.

2-(6-bromoquinolin-2-yl)-benzo[*d*]thiazole (5ac)

White solid (82 %), **M.P**.: 240-242 °C; **^{1}HNMR** (500 MHz, $CDCl_3$): δ 8.51 (d, *J* = 8.6 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 8.03 (d, *J* = 2.1 Hz, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.83 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.53 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.48–7.43 (m, 1H); **^{13}CNMR** (100 MHz, $CDCl_3$): δ 169.28, 154.35, 151.72, 146.49, 136.51, 135.98, 133.65, 131.38, 129.98, 129.84, 126.41, 126.07, 123.90, 122.08, 121.65, 119.28; **HRMS** (ESI) calculated for $C_{16}H_9BrN_2S$ $(M+H)^+$ 340.97426; found: 340.97419.

2-(8-nitroquinolin-2-yl)-benzo[*d*]thiazole (5ad)

Yellow solid (62 %), **M.P**.: 206-207 °C;**^{1}HNMR** (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 8.6 Hz, 1H), 8.39 (d, *J* = 8.6 Hz, 1H), 8.15–8.09 (m, 2H), 8.07 (dd, *J* = 8.3, 1.2 Hz, 1H), 8.00–7.94 (m, 1H), 7.68–7.61 (m, 1H), 7.56–7.50 (m, 1H), 7.46 (td, *J* = 7.7, 1.2 Hz, 1H); **^{13}CNMR** (100 MHz, $CDCl_3$): δ 168.63, 154.32, 153.34, 147.92, 139.16, 137.19, 137.00, 131.96, 129.54, 126.48, 126.38, 126.11, 124.66, 124.05, 122.22, 119.96; **HRMS** (ESI) calculated for $C_{16}H_{10}O_2N_3S$ $(M+H)^+$ 308.04882; found: 308.04856.

2-(isoquinolin-2-yl)-benzo[*d*]thiazole (5ae)

White solid (78%), **M.P**.: 180-182 °C; **^{1}HNMR** (400 MHz, $CDCl_3$): δ 10.00 (d, *J* = 8.2 Hz, 1H), 8.64 (d, *J* = 5.5 Hz, 1H), 8.21 (d, *J* = 8.1 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.94–7.86 (m, 1H), 7.84–7.73 (m, 3H), 7.59–7.49 (m, 1H), 7.49–7.41 (m, 1H); **^{13}CNMR** (100 MHz, $CDCl_3$): δ 170.82, 154.83, 149.39, 141.81, 137.31, 136.07, 130.53, 129.06, 127.85, 127.00, 126.10, 125.93, 124.13, 123.05, 121.67; **HRMS** (ESI) calculated for $C_{16}H_{10}N_2S$ $(M+H)^+$ 263.0637; found: 263.0633.

6-methoxy-2-(quinolin-2-yl)-benzo[*d*]thiazole (5af)

White solid (85%), **M.P**.: 178-180 °C; **^{1}HNMR** (400 MHz, $CDCl_3$): δ 8.44 (d, *J* = 8.6 Hz, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 9.0 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.75 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.57 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.42 (d, *J* = 2.5 Hz, 1H), 7.12 (dd, *J* = 9.0, 2.6 Hz, 1H), 3.92 (s, 3H); **^{13}CNMR** (100 MHz, $CDCl_3$): δ 167.32, 158.41, 151.51, 148.98, 147.94, 138.07, 136.92, 130.06, 129.65, 128.84, 127.75, 127.39, 124.38, 118.20, 116.07, 104.16, 77.37, 77.05, 76.73, 55.85; **HRMS** (ESI) calculated for $C_{17}H_{12}N_2OS$ $(M+H)^+$293.07431; found: 293.07336.

6-fluoro-2-(quinolin-2-yl)-benzo[*d*]thiazole (5ah)

Yellow solid (72%), **M.P**.: 207-209 °C; **^{1}HNMR** (400 MHz, $CDCl_3$): δ 8.49 (d, *J* = 8.4 Hz, 1H), 8.33 (d, *J*= 8.7 Hz, 1H), 8.24 (d, *J* = 8.4Hz, 1H), 8.11-8.06 (m, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.81-7.76 (m, 1H), 7.68-7.59 (m, 2H), 7.30-7.23 (m,1H); **^{13}CNMR** (100 MHz, CDCl3): δ 162.69 (d, *J* = 245.3 Hz); 150.94, 147.79,

137.76 (d, *J* = 11.3 Hz), 137.17, 130.23, 129.63, 128.99, 127.73, 127.70, 124.86 (d, *J* = 9.0 Hz), 118.21, 115.25 (d, *J* = 24.8 Hz), 108.30 (d, *J* = 26.3 Hz); **HRMS** (ESI) calculated for $C_{16}H_9FN_2S$ $(M+H)^+$ 281.0543; found: 281.0563.

2, 2`-dibenzo[*d*]thiazole (5ai)

White solid (65 %), **M.P**.: 239-240 °C;**^{1}HNMR** (500 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J*= 7.8 Hz, 1H), 7.86 (s, 4H), 7.56 (td, *J* = 8.1, 1.1 Hz, 1H), 7.49 (td, *J* = 8.0, 1.1 Hz, 1H); **^{1}H ^{13}CNMR** (125 MHz, $CDCl_3$): δ 161.56, 153.65, 135.90, 126.80, 126.59, 124.12, 122.00; **HRMS** (ESI) calculated for $C_{14}H_9N_2S_2$ $(M+H)^+$ 269.02017; found: 269.01997.

6-methoxy-2, 2`-dibenzo[*d*]thiazole (5aj)

White solid (74 %), **M.P**.: 278-280 °C;**^{1}HNMR** (300 MHz, $CDCl_3$): δ 8.44 (d, *J* = 8.6 Hz, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 8.01 (d, *J* = 9.0 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.81–7.70 (m, 1H), 7.63–7.53 (m, 1H), 7.42 (d, *J* = 2.5 Hz, 1H), 7.12 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.92 (s, 3H); **^{13}CNMR** (100 MHz, $CDCl_3$): δ 162.49, 161.60, 159.49, 154.88, 153.59, 135.77, 127.84, 126.83, 126.56, 124.04, 122.24, 122.02, 117.48, 105.71, 77.37, 77.05, 76.73, 55.69; **HRMS** (ESI) calculated for $C_{15}H_{11}N_2S_2$ $(M+H)^+$ 299.03073; found: 299.03042.

Conflicts of interest

There are no conflicts to declare.

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