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Copper-catalyzed oxidative cyclization of 2-amino-azaarenes with lignin models: synthesis of 3-phenoxy imidazo heterocycles

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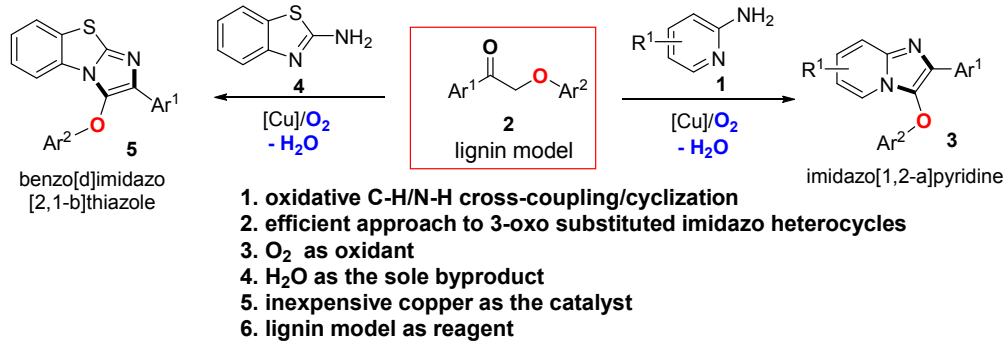


Abstract: A catalytic oxidative cyclization of 2-aminopyridines or 2-aminobenzothiazole with 2-phenoxyacetophenones (a kind of lignin platform compounds) was developed, efficiently providing valuable 3-phenoxy imidazo[1,2-a]pyridines or 3-phenoxy benzo[d]imidazo[2,1-b]thiazoles. The reaction was realized under oxygen by simply using inexpensive CuI as the catalyst.

Introduction

Lignin, a wide occurring aromatic biopolymer responsible for the strength and shape of plants, constitutes 30% of non-fossil organic carbon.[1] The primary structure of lignin is

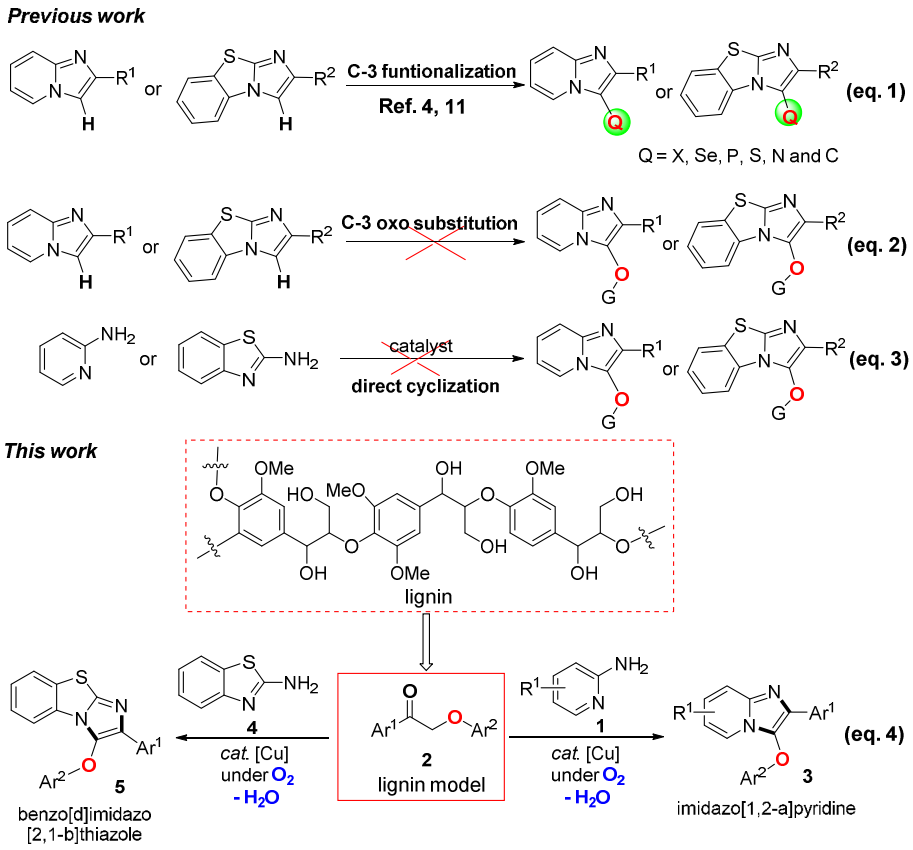
composed of a diversely linked network of electron-rich phenylpropanols. Due to world's depleting petroleum reserves and lignin's abundance in nature, intense efforts have been made to controlled conversion of lignin into well-defined aromatic chemicals.[2,3] 2-Phenoxyaceto-phenones is a kind of lignin platform molecules, which have been widely used as model compounds to produce various aromatics.[3] However, transformation of lignin into valuable nitrogen-containing chemicals is still very limited owing to the lack of efficient conversion methods for lignin-derived chemicals.

Imidazo[1,2-a]pyridines have drawn the attention of chemists in recent years due to their immense applications in different fields.[4] In particular, imidazo[1,2-a]pyridines scaffold is one of the most privileged nitrogen containing heterocycles in drug design, widely used at the core of many pharmaceutical drugs.[5a-f] As a consequence, a large number of synthetic methodologies have been developed, and there are mainly two routes to construct imidazo[1,2-a]pyridines. One is cyclization by oxidative amination or cascade reactions.[6] The other approach is transition-metal-catalyzed functionalization of imidazo[1,2-a]pyridines *via* direct cross-coupling reactions, such as alkenylation, ethoxycarbonyl difluoromethylation, trifluoro-methylation, thiocyanation, sulfenylation, nitrosylation and selenylation (Scheme 1, eq. 1).[7] For instance, Cao's group developed a copper-catalyzed selective cross-coupling for the synthesis of *C*-3 carbonyl imidazo[1,2-a]pyridine derivatives.[7g] These methodologies afforded the *C*-3 position functionalized imidazopyridines due to its nucleophilicity. The pharmacological activities of these heterocycles are dependent on the nature of the substituent on the imidazo ring.[6,7] Among them, structures related to imidazo[1,2-a]pyridin-3-ol with 2-aryl substituents are biologically active with both antifungal and anthelmintic activity.[8,9] Unfortunately, very limited procedures have been developed to make such compounds with special properties.[9] Actually, there is still no

catalytic, efficient and green method for synthesis of *C*-3 oxo substituted imidazo[1,2-a]pyridines (Scheme 1, eq. 2 and eq. 3).

Benzo[d]imidazo[2,1-b]thiazole represents another important fused bicyclic sulfur and nitrogen-containing heterocycles, which have been reported to be associated with promising biological activities such as antitumor agents, antimicrobial agents and kinase inhibitors.[5g-k] However, only a few methods have been developed for the synthesis of these fused heterocycles.[10] In particular, no efficient method has been developed for the synthesis of *C*-3 oxo substituted benzo[d]imidazo[2,1-b]thiazole derivatives (Scheme 1, eq. 2 and eq. 3).[11]

Scheme 1. Synthesis of C-3 functionalized imidazo heterocycles.

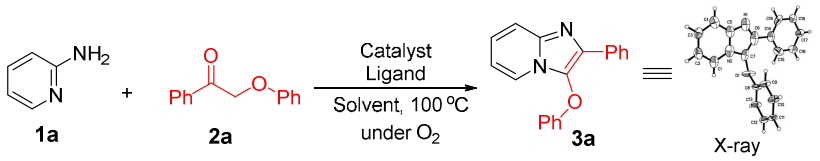


The main goal of our research is the design and synthesis of valuable chemicals from easily available starting materials.[12] Thus, the immense applications of imidazo[1,2-a]pyridines and benzo[d]imidazo[2,1-b]thiazoles together with the widely occurring lignin-derived compounds, such as 2-phenoxy acetophenone derivatives, prompted us to explore novel and green methodologies for the synthesis of special and valuable 3-*O* substituted imidazo heterocycles. Molecular oxygen is considered as an ideal oxidant in view of green and sustainable chemistry due to its abundant, natural and environmental friendly properties.[13] Herein, we disclosed an efficient aerobic oxidative annulation between 2-amino-azaarenes and lignin models, delivering valuable 3-*O* imidazo[1,2-a]pyridine and benzo[d]imidazo [2,1-b]thiazole derivatives (Scheme 1, eq. 4).

Results and Discussion

Our tactics for oxidative conversion of the lignin models would commence with imine formation from ketone and amine by water elimination, and the enamine formed from imine might undergo following intramolecular cyclization by C-N bond formation,[6,14] providing the *C*-3 *O*-substituted imidazo heterocycles. 2-Phenoxyaceto-phenone (**2a**) as a lignin model substrate was examined to react with 2-aminopyridine (**1a**) under copper-catalyzed conditions. To our delight, the reaction provided desired imidazo[1,2-a]pyridine product **3a** in 59% using toluene as the solvent (Table 1, entry 1).[15] Next, a series of representative solvents were examined (Table 1, entries 2-5). High polar aprotic solvents such as DMF led to only 25% yield (Table 1, entry 2). Meanwhile, the reaction proceeded much better in 1,4-dioxane, with 71% yield obtained (Table 1, entry 3). Interestingly, protic solvent such as ethanol also led to moderate yield (Table 1, entry 4). It is worthy to note that the desired imidazo[1,2-a]pyridine (**3a**) was obtained in 77% yield using DCE as the solvent, and no amide was detected (Table 1, entry 5).[6,14-15] The structure of a newly

Table 1. Optimization of reaction conditions[a]



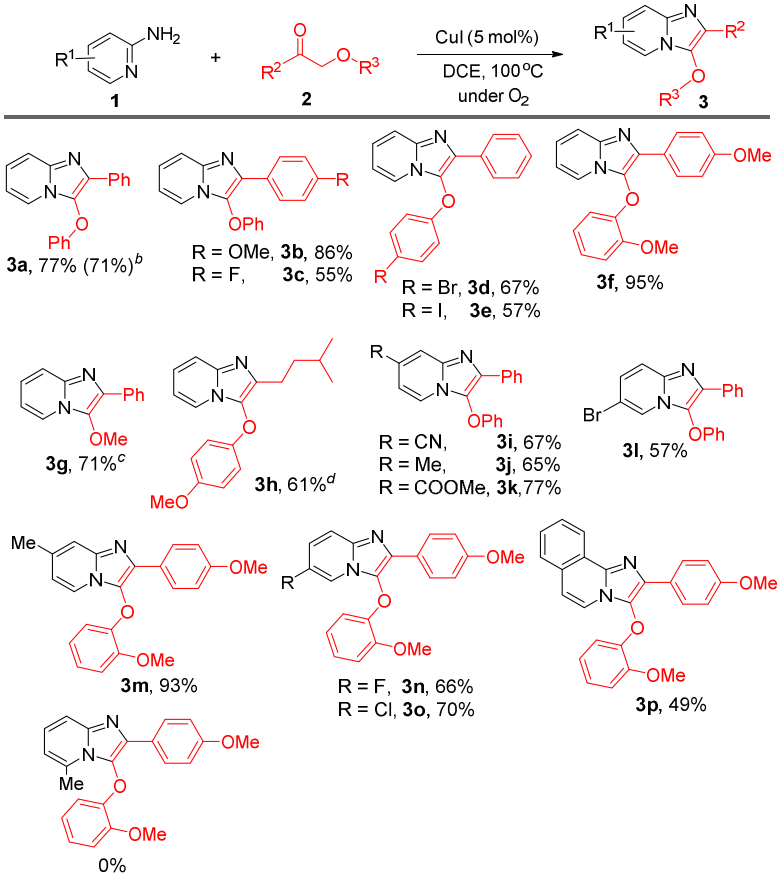
entry	catalyst	ligand	solvent	yield (%)
1	CuI	-	toluene	59
2	CuI	-	DMF	25
3	CuI	-	dioxane	71
4	CuI	-	EtOH	42
5	**CuI**	-	**DCE**	**77**
6	CuI	-	H_2O	45
7[b]	CuI	-	-	53
8	CuI	1,10-Phen	DCE	42
9	CuI	pyridine	DCE	21
10	$CuBr_2$	-	DCE	70
11[c]	$CuBr_2$	-	DCE	81
12[d]	CuI	-	DCE	65
13[e]	CuI	-	DCE	60
14[f]	-	-	DCE	< 5
15	$FeCl_3$	-	DCE	11
16	$RuCl_3$	-	DCE	24

[a]Unless otherwise described, the reaction conditions were as follows: 2-amino pyridine (**1a**, 0.6 mmol), 2-phenoxyacetophenone (**2a**, 0.2 mmol), catalyst (5 mol%), ligand (10 mol%), solvent (0.8 mL), 100 °C, 16 h, under oxygen (1 atm). The isolated yield was obtained by silica gel column chromatography. [b]Without solvent [c]2.2 equiv. $CuBr_2$ was used under N_2. [d]20 mol% CuI was used. [e]Microwave irradiation. [f]Without copper salt.

synthesized compound **3a** was unambiguously confirmed by single crystal X-ray diffraction studies (see the ESI for details). Notably, the reaction can be performed in water or even without any solvent, producing the desired heterocycles in 45% and 53% yields respectively (entries 6 and 7). Addition of *N*-containing ligands was not effective, even leading to lower yields (Table 1, entries 8 and 9). Employment of other copper salt such as $CuBr_2$ could not further improve the yield (Table 1, entry 10). Interestingly, if 2.2 equivalent amount of $CuBr_2$ was used, the reaction also provided **3a** in 81% yield under inert atmosphere, indicating that re-oxidation of the reduced copper by molecular oxygen completes the catalytic cycle (Table 1, entry 11).[6,14] The reaction

can not been further improved by using 20 mol% CuI (Table 1, entry 12). Also, microwave irradiation failed to promote the reaction more efficiently (Table 1, entry 13). Moreover, the reaction remained sluggish in the absence of copper salt (Table 1, entry 14). Other transition-metal salts, such as $FeCl_3$ and $RuCl_3$, only showed very limited catalytic activity (Table 1, entries 15 and 16).

Table 2. Synthesis of imidazo[1,2-a]pyridines[a]

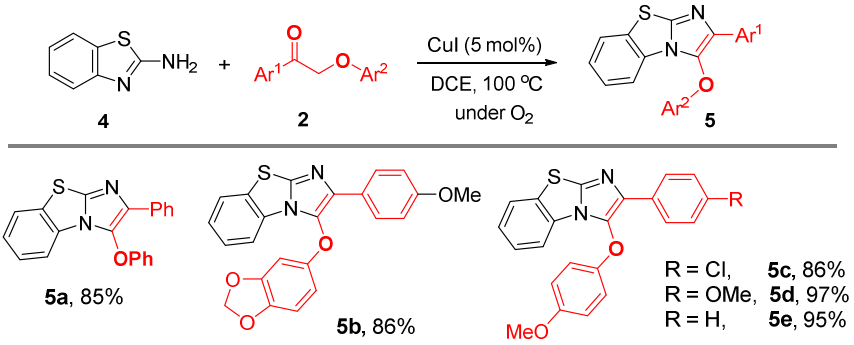


[a]Unless otherwise described, the reaction conditions were as follows: 2-amino pyridine (**1**, 0.6 mmol), 2-phenoxyacetophenone (**2**, 0.2 mmol), CuI (5 mol%), DCE (0.8 mL), 100 °C, 14-16 h, under oxygen (1 atm). The yields indicated are isolated yields were obtained by silica gel column chromatography. [b]Gram scale (**2a**, 1.02 g, 4.8 mmol, 1.0 equiv.). [c]2-Methoxy-acetophenone was used. [d]1-(4-Methoxyphen- oxy)-5-methyl-hexan-2-one was used.

With this optimized catalytic conditions in hand, we turned to examine the scope of the differently substituted ketones (Table 2). It was observed that installing electron-donating

functional group such as methoxyl group to *C*-terminus phenyl ring resulted in corresponding product in higher yield, while installing electron-deficient functional group gave opposite result (Table 2, **3b** and **3c**). Electron effects on *O*-terminus phenyl ring gave the same results (Table 2, **3d-3f**). Ketones **2** with alkyl groups were also examined. To our delight, both of 2-methoxyacetophenone and 1-(4-methoxyphenoxy)-5-methyl-hexan-2-one reacted smoothly and provided corresponding heterocyclic products in good yields (Table 2, **3g** and **3h**). Differently functionalized 2-aminopyridines were also tested to react with ketones **2**. A series of functional groups R^1 on pyridyl ring of **1**, such as CN, COOMe, Br, F and Cl, could be well tolerated in the catalytic conditions, regardless of electron-donating or electron-withdrawing properties (Table 2, **3i-3o**). Furthermore, 2-aminoisoquinoline also reacted well, affording fused imidazo isoquinoline **3p** in 49% yield. However, 2-amino-6-methylpyridine was totally inactive due to its steric hinderance even at elevated temperatures. This oxidative cyclization also proceeded well on gram scale, and the product **3a** was obtained in 71% yield, showing the robustness of this method.

Table 3. Synthesis of fused benzoimidazothiazole derivatives from 2-aminobenzothiazole[a]

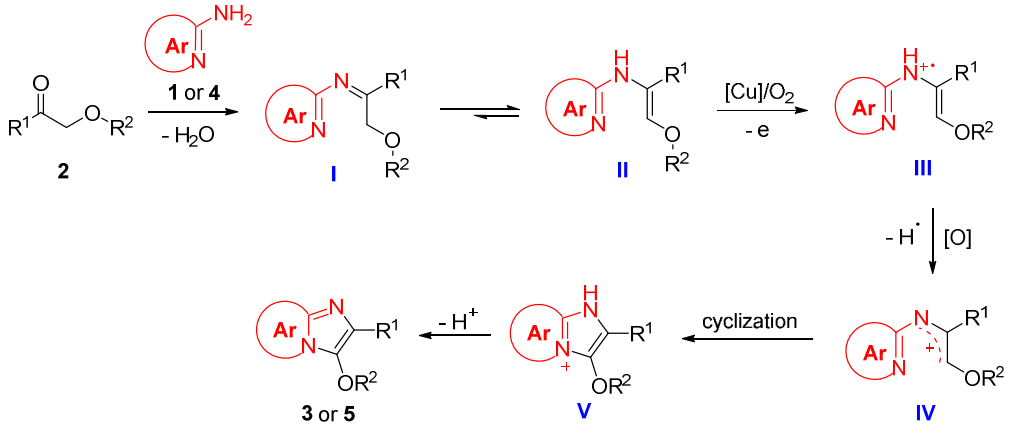


[a]Unless otherwise described, the reaction conditions were as follows: 2-aminobenzothiazole (**4**, 0.6 mmol), 2-phenoxyacetophenone (**2**, 0.2 mmol), CuI (5 mol%), DCE (0.8 mL), 100 °C, 16 h, under oxygen (1 atm). The isolated yields were obtained by silica gel column chromatography.

Considering the wide utilizations of benzo[d]imidazo [2,1-b]thiazoles, we turned to examine the reaction of 2-amino-benzothiazole (**4**) with ketones **2**, employing the same oxidative catalytic conditions (Table 3). Satisfactorily, ketones (**2**) bearing electron-donating as well as electron-

withdrawing substituents reacted well and afforded the corresponding benzo[d]-imidazo[2,1-b]thiazoles with excellent yields (Table 3, **5a-5e**).

On the basis of the results obtained above and previous reports,[6,14-15] a plausible mechanism is illustrated in Scheme 2. The first step involves a coupling of the substrates **1** or **4** and **2** to produce imine **I** with the elimination of water. The imine **I** is then equilibrates to enamine **II**. A one-electron oxidation of intermediate **II** by copper catalyst leads to nitrenium ion **IV** by hydride abstraction. Finally, intermediate **IV** undergoes intra-molecular nucleophilic cyclization to give intermediate **V**, and the subsequent proton elimination occurs to afford product **3** or **5**.



Scheme 2. Proposed mechanism

In conclusion, we have developed a simple and efficient catalytic oxidative annulation method for the cyclization of lignin model 2-phenoxyacetophenones with 2-aminopyridines or 2-aminobenzothiazole. With the assistance of catalytic amount of copper salt, this aerobic protocol provides an efficient, greener and straightforward methodology for the preparation of biologically valuable imidazo[1,2-a]pyridines and benzo[d]imidazo[2,1-b]thiaz-oles, producing water as the sole by-product. These novel and special *C*-3 oxo-substituted imidazo heterocycles could have important impact on drug discovery.

■Experimental Section

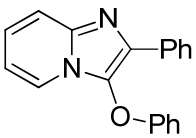
General considerations

All commercially available reagents for the catalytic reactions were used as received: AR grade 1, 2-dichloroethane, 2-amino pyridines and CuI were obtained from TCI. The starting materials of lignin model were prepared according to the reported method.[3] ^{1}H NMR spectra were performed on a Bruker 500 MHz spectrometer and are reported in ppm downfield from $SiMe_4$ (δ = 0.0) and relative to the signal of chloroform-*d* (δ = 7.27 ppm, singlet). Proton-decoupled ^{13}CNMR spectra were recorded on a 500 (125 MHz) or ECA-400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.23 ppm). IR spectra were recorded as thin films on KBr plates on a Bio-Rad FTS 165 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectral analysis (HRMS) was performed on Waters Q-Tof Permies Mass Spectrometer. Note: the obtained imidazo[1,2-a]pyridines and benzo[d]imidazo[2,1-b]thiazoles are generally instable, suffering from slow and gradual degradation under air, and they should been kept under an inert atmosphere.

General Procedure for the Synthesis of imidazo[1,2-a]pyridines and benzo[d]imidazo[2,1-b]thiazoles

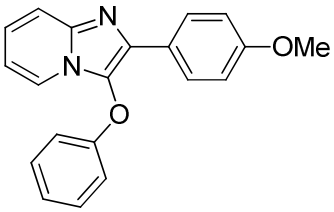
An oven dried vial was charged with CuI (1.9 mg, 0.010 mmol, 5 mol%), 2-aminopyridine **1** (0.6 mmol) or 2-aminobenzothiazole **4** (0.6 mmol), ketone **2** (0.2 mmol) and dry 1,2-dichloroethane (0.8 mL). The vial was then sealed under an oxygen atmosphere, and the reaction was heated to 100 °C with stirring for 14-16 h. After cooling down, the mixture was diluted with ethyl acetate, filtered and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product, which was purified through a flash column chromatography (ethyl acetate in hexane solution) to afford **3** or **5** as product.

Characterization data for the imidazo[1,2-a]pyridines and benzo[d]imidazo[2,1-b]thiazoles



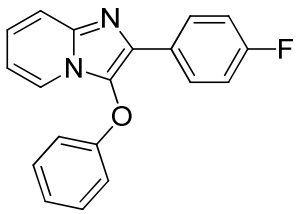
3-Phenoxy-2-phenyl imidazo[1,2-a]pyridine (**3a**)**:**

This compound was prepared by the General Procedure described above and was obtained as a white solid (44 mg, yield = 77%), m.p.: 145-146 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 7.6 Hz, 2H), 7.73 (d, *J* = 6.8 Hz, 1H), 7.63 (d, *J* = 9.2 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.25-7.31 (m, 3H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.74 (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.1, 139.9, 132.5, 131.1, 130.2, 128.7, 127.8, 126.5, 124.4, 123.7, 121.6, 117.9, 115.0, 112.3. FTIR (NaCl, cm^{-1}): 3053.3, 2985.8, 1647.2, 1495.6, 1421.5, 1390.1, 1362.2, 1265.3, 1201.7, 895.0, 738.7, 706.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{19}H_{14}N_2O$ 287.1184; Found 287.1184.



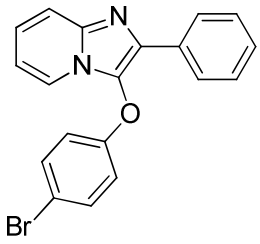
3-Phenoxy-2-(4-methoxyphenyl) imidazo[1,2-a]pyridine (**3b**)

This compound was prepared by the General Procedure described above and was obtained as a white solid (54 mg, yield = 86%), m.p.: 145-147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99-8.01 (m, 2H), 7.71-7.74 (dt, *J* = 1.2 Hz, *J* = 6.8 Hz, 1H), 7.61-7.64 (dt, *J* = 1.2 Hz, *J* = 9.2 Hz, 1H), 7.28-7.33 (m, 2H), 7.09-7.19 (m, 2H), 6.93-6.97 (m, 4H), 6.72-6.75 (td, *J* = 6.8 Hz, *J* = 0.8 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 156.2, 139.8, 131.2, 130.2, 129.3, 127.8, 125.2, 124.1, 123.6, 121.5, 117.6, 115.0, 114.1, 112.1, 55.2. FTIR (NaCl, cm^{-1}): 3053.3, 2985.8, 1707.0, 1568.1, 1506.4, 1421.5, 1359.8, 1265.3, 1201.7, 1032.0, 895.0, 837.1, 738.7, 706.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{20}H_{16}N_2O_2$ 317.1285; Found 317.1282.



3-Phenoxy-2-(4-fluorophenyl) imidazo[1,2-a]pyridine (**3c**)

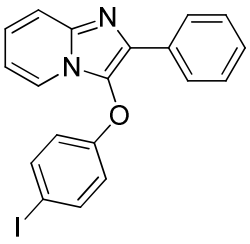
This compound was prepared by the General Procedure described above and was obtained as a white solid (33 mg, yield = 55%), m.p.: 114-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02-8.05 (m, 2H), 7.74-7.76 (dt, *J* = 6.8 Hz, *J* = 1.2 Hz, 1H), 7.62-7.64 (dt, *J* = 9.2 Hz, *J* = 1.2 Hz, 1H), 7.28-7.35 (m, 2H), 7.18-7.22 (qd, *J* = 6.8 Hz, *J* = 1.2 Hz, 1H), 7.07-7.15 (m, 3H), 6.95-6.97 (m, 2H), 6.75-6.79 (td, *J* = 6.8 Hz, *J* = 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4 (*J* = 246 Hz), 156.0, 139.9, 130.3 (*J* = 16 Hz), 128.8, 128.7, 128.2 (*J* = 8 Hz), 124.4, 123.8, 121.6, 117.8, 115.6 (*J* = 21 Hz), 115.0, 112.4. FTIR (NaCl, cm^{-1}): 3053.3, 2985.8, 1574.2, 1504.5, 1489.1, 1421.5, 1392.6, 1359.8, 1265.3, 1201.7, 1159.2, 895.0, 842.5, 738.7, 704.5. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{19}H_{13}FN_2O$ 305.1090; Found 305.1088.



3-(4-bromophenoxy)-2-phenyl imidazo[1,2-a]pyridine (**3d**)

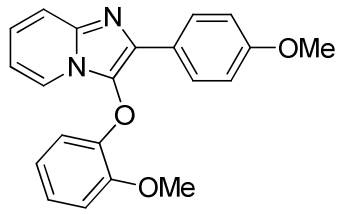
This compound was prepared by the General Procedure described above and was obtained as a pink oil (49 mg, yield = 67%). ^{1}H NMR (500 MHz, CDCl3): δ = 7.92-7.94 (m, 2H), 7.64 (d, *J* = 7.0 Hz, 1H), 7.56 (d, *J* = 9.5 Hz, 1H), 7.29-7.34 (m, 4H), 7.18-7.22 (m, 1H), 7.09-7.13 (m, 1H), 6.75-6.78 (m, 2H), 6.67-6.70 (td, *J* = 1.0 Hz, *J* = 7.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.3, 140.0, 133.1, 132.3, 131.3, 129.7, 128.7，127.9, 126.5, 124.5, 121.4, 118.0, 116.8, 116.2, 112.5. FTIR (NaCl, cm^{-1}): 3053.3, 2985.8, 1481.3, 1421.5, 1362.6, 1265.3, 1201.7, 1159.2, 895.0,

738.7, 706.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{19}H_{13}BrN_2O$ 365.0290, 367.0271; Found 365.0288, 368.0302.



3-(4-Iodophenoxy)-2-phenyl imidazo[1,2-a]pyridine (**3e**)

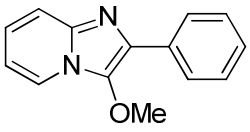
This compound was prepared by the General Procedure described above and was obtained as a white solid (47 mg, yield = 57%), m.p.: 138-140 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.91-7.93 (m, 2H), 7.62 (d, *J* = 7.0 Hz, 1H), 7.55 (d, *J* = 9.5 Hz, 1H), 7.51(d, *J* = 9.0 Hz, , 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.18-7.22 (m, 1H), 7.09-7.12 (m, 1H), 6.63-6.69 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.1,140.0,139.1,132.3,131.3,129.5,127.2, 126.5, 124.5, 121.4, 118.0, 117.3, 112.5, 86.5. FTIR (NaCl, cm^{-1}): 3942.5, 3689.8, 3053.3, 2985.8, 2684.9, 1684.2, 1645.2, 1577.8, 1562.3, 1506.4, 1479.4, 1433.1, 1421.5, 1390.7, 1363.7, 1265.3, 1203.6, 1161.2, 1149.6, 1004.9, 895.0, 823.6, 752.2, 727.2, 706.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{19}H_{13}IN_2O$ 413.0151; Found 413.0153.



3-(2-Methoxyphenoxy)-2-(4-methoxyphenyl)-imidazo[1,2-a]pyridine (**3f**)

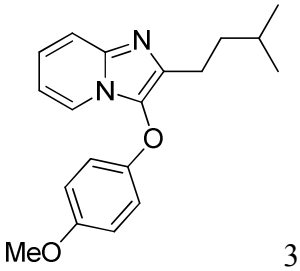
This compound was prepared by the General Procedure described above and was obtained as a white solid (66 mg, yield = 95%), m.p.: 121-122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02-8.04 (dd, *J* = 2.0 Hz, *J* = 6.8 Hz, 2H), 7.79 (d, *J* = 6.8 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.14-7.18 (m, 1H), 7.05-7.07 (m, 2H), 6.93-6.95 (dd, *J* = 2.0 Hz, *J* = 6.8 Hz, 2H), 6.70-6.76 (m, 2H), 6.55 (d, *J*

= 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 149.0, 145.1, 139.7, 131.3, 129.7, 127.8, 125.3, 124.2, 124.1, 121.5, 121.1, 117.5, 114.7, 114.1, 112.8, 112.1, 56.2, 55.2. FTIR (NaCl, cm^{-1}): 3053.3, 2986.8, 1701.2, 1614.4, 1568.1, 1498.7, 1456.3, 1421.5, 1394.5, 1361.7, 1265.3, 1251.8, 1199.7, 1174.7, 1114.9, 1030.0, 895.0, 837.2, 738.7, 704.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{21}H_{18}N_2O_3$ 347.1396; Found 347.1393.



3-Methoxy-2-phenyl imidazo[1,2-a]pyridine (**3g**)

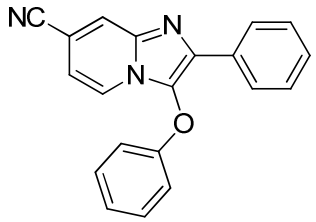
This compound was prepared by the General Procedure described above and was obtained as a colorless oil (32 mg, yield = 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 6.8 Hz, 1H), 7.56 (d, *J* = 9.2 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.12-7.16 (m, 1H), 6.83 (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.0, 133.4, 113.5, 128.7, 127.4, 126.4, 123.7, 121.3, 117.9, 113.2, 112.0, 61.1. FTIR (NaCl, cm^{-1}): 2985.8, 1707.0, 1587.4, 1568.1, 1501.2, 1421.6, 1386.8, 1359.8, 1265.3, 1207.8, 968.3, 896.0, 748.4, 706.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{14}H_{12}N_2O$ 225.1028; Found 225.1029.



3-(4-Methoxyphenoxy)-2-isopentyl imidazo[1,2-a]pyridine (**3h**)

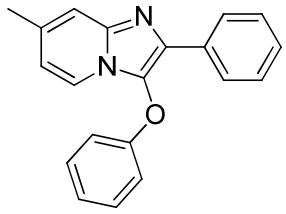
This compound was prepared by the General Procedure described above and was obtained as a colourless oil (38 mg, yield = 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 6.8 Hz, 1H), 7.50 (d, *J* = 9.2 Hz, 1H), 7.06-7.10 (m, 1H), 6.80 (s, 4H), 6.67-6.71 (m, 1H), 3.75 (s, 3H), 2.66 (t, *J* = 8.0 Hz, 2H), 1.53-1.63 (m, 3H), 0.86 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =155.6, 151.1, 139.4, 133.6, 131.7, 123.2, 121.3, 117.4, 115.7, 114.9, 111.7, 55.7, 37.9, 27.9,

24.6, 22.4. FTIR (NaCl, cm^{-1}): 3053.3, 2985.8, 1562.2, 1502.6, 1421.5, 1265.3, 1198.05, 1031.9, 895.0, 831.2, 738.7, 706.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{19}H_{22}N_2O_2$ 311.1760; Found 311.1756.



3-Phenoxy-2-phenyl-7-cyano imidazo[1,2-a]pyridine (**3i**)

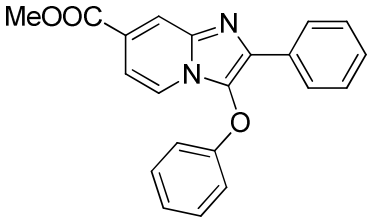
This compound was prepared by the General Procedure described above and was obtained as a white solid (42 mg, yield = 67%), m.p.: 204-206 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98-8.03 (m, 3H), 7.78-7.80 (dd, *J* = 1.2 Hz, *J* = 7.2 Hz, 1H), 7.29-7.41 (m, 5H), 7.12 (t, *J* = 7.2 Hz, 1H), 6.90-6.92 (m, 2H), 6.86-6.88 (dd, *J* = 1.6 Hz, *J* = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 137.4, 135.0, 131.7, 131.4, 130.4, 128.9, 128.7, 126.8, 124.3, 124.0, 122.2, 117.7, 115.0, 112.6, 106.7. FTIR (NaCl, cm^{-1}): 3053.3, 3009.1, 2304.9, 2227.8, 1556.6, 1485.2, 1421.5, 1361.7, 1265.3, 1203.6, 1159.2, 895.0, 746.5, 704.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{20}H_{13}N_3O$ 312.1137; Found 312.1138.



3-Phenoxy-2-phenyl-7-methyl imidazo[1,2-a]pyridine (**3j**)

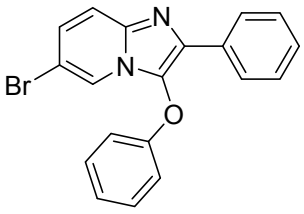
This compound was prepared by the General Procedure described above and was obtained as a white solid (39 mg, yield = 65%), m.p.: 158-160 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.93-7.95(m, 2H), 7.53 (d, *J* = 5.0 Hz, 1H), 7.16-7.30 (m, 6H), 7.02 (t, *J* = 5.5 Hz, 1H), 6.86-6. 87 (m, 2H), 6.48-6.49 (dd, *J* = 1.5 Hz, *J* =7.0 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.3, 140.4, 135.3, 132.7, 130.7, 130.6,130.2, 129.7, 128.6, 127.5, 126.4, 123.6, 120.9, 116.2,

115.0, 114.9, 21.4. FTIR (NaCl, cm^{-1}): 3053.3, 2985.8, 2924.1, 1643.4, 1583.6, 1568.1, 1489.1, 1446.6, 1421.5, 1394.5, 1363.7, 1265.3, 1201.7, 1159.2, 1072.4, 1026.1, 895.0, 731.0, 704.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{20}H_{16}N_2O$ 301.1341; Found 301.1345.



3-Phenoxy-2-phenyl imidazo[1,2-a]pyridine-7-carboxylic acid methyl ester (**3k**)

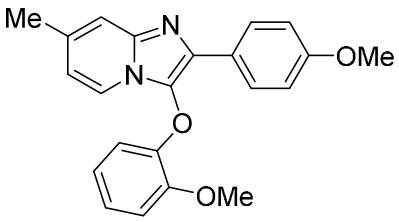
This compound was prepared by the General Procedure described above and was obtained as a white solid (53 mg, yield = 77%), m.p.: 132-134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35-8.36 (dd, *J* = 0.8 Hz, *J* = 1.6 Hz, 1H), 8.03-8.05 (m, 2H), 7.73-7.75 (dd, *J* = 0.8 Hz, J = 7.2 Hz, 1H), 7.25-7.40 (m, 6H), 7.08-7.12 (td, *J* = 8.0 Hz, *J* = 0.8 Hz, 1H), 6.90-6.93 (m, 2H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 155.8, 138.6, 134.2, 132.0, 131.3, 130.3, 128.7, 128.3, 126.7, 125.6, 124.0, 121.1, 120.7, 115.0, 111.7, 52.6. FTIR (NaCl, cm^{-1}): 3053.3, 3004.5, 2304.9, 1718.6, 1556.6, 1487.1, 1404.2, 1367.5, 1334.7, 1265.3, 1232.5, 1203.6, 1159.2, 1091.7, 895.0, 738.7, 704.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{21}H_{16}N_2O_3$ 345.1239; Found 345.1238.



3-(2-Methoxyphenoxy)-2-(4-methoxyphenyl)-6-bromo imidazo[1,2-a]pyridine (**3l**)

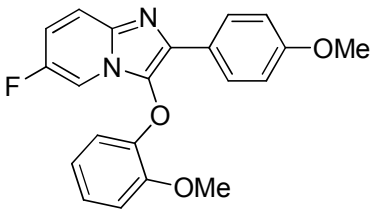
This compound was prepared by the General Procedure described above and was obtained as a white solid (41 mg, yield = 57%), m.p.: 159-161°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99-8.01 (m, 2H), 7.86-7.87 (dd, *J* = 0.8 Hz, *J* = 1.6 Hz, 1H), 7.49-7.51 (dd, *J* = 0.8 Hz, *J* = 9.6 Hz, 1H),

7.20-7.38 (m, 6H), 7.09-7.13 (m, 1H), 6.92-6.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 138.2, 132.2, 132.0, 130.3, 130.1, 128.7, 128.1, 127.9, 126.5, 124.0, 121.6, 118.6, 115.0, 107.3. FTIR (NaCl, cm^{-1}): 3053.3, 3012.2, 1596.3, 1526.3, 1489.1, 1421.5, 1401.3, 1325.1, 1265.3, 1199.7, 1159.2, 895.0, 798.5, 738.7, 704.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{19}H_{13}BrN_2O$ 365.0284; Found 365.0277.



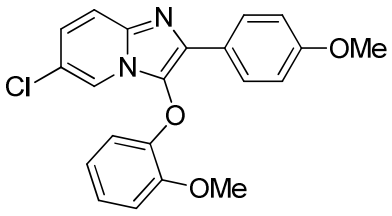
3-(2-Methoxyphenoxy)-2-(4-methoxyphenyl)-7-methyl imidazo[1,2-a]pyridine (**3m**)

This compound was prepared by the General Procedure described above and was obtained as a white solid (67 mg, yield = 93%), m.p.: 154-156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95-7.98 (dd, *J* = 2.0 Hz, *J* = 6.8 Hz, 2H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 1.2 Hz, 1H), 7.01-7.05 (m, 2H), 6.87-6.90 (m, 2H), 6.66-6.70 (m, 1H), 6.50-6.54 (m, 2H), 4.03 (s, 3H), 3.78 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 149.0, 145.3, 140.2, 135.0, 130.7, 129.3, 127.7, 125.5, 124.1, 121.1, 120.8, 115.9, 114.7, 114.6, 114.0, 112.7, 56.2, 55.2, 21.4. FTIR (NaCl, cm^{-1}): 3053.3, 2983.9, 2839.2, 1695.4, 1643.4, 1614.4, 1570.1, 1498.7, 1456.3, 1440.8, 1421.5, 1392.6, 1361.7, 1296.2, 1265.3, 1249.9, 1199.7, 1170.8, 1114.9, 1030.0, 895.0, 837.1, 738.7, 704.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{22}H_{20}N_2O_3$ 361.1552; Found 361.1553.



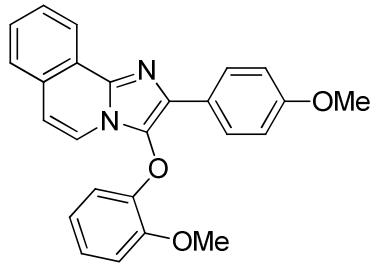
3-(2-Methoxyphenoxy)-2-(4-methoxyphenyl)-6-fluoro imidazo[1,2-a]pyridine (**3n**)

This compound was prepared by the General Procedure described above and was obtained as a white solid (48 mg, yield = 66%), m.p.: 134-136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96-7.99 (m, 2H), 7.70-7.72 (m, 1H), 7.51-7.55 (m, 1H), 7.01-7.06 (m, 3H), 6.89-6.93 (m, 2H), 6.69-6.73 (m, 1H), 6.53 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 155.3 (*J* = 236 Hz), 149.1, 144.8, 137.2, 133.0, 131.1, 127.8, 125.0, 124.5, 121.1, 118.1 (*J* = 9 Hz), 116.0 (*J* = 26 Hz), 114.9, 114.1, 112.9, 108.2 (*J* = 41 Hz), 56.2, 55.2. FTIR (NaCl, cm^{-1}): 3053.3, 2839.2, 2304.9, 1651.1, 1564.3, 1535.3, 1500.6, 1421.5, 1421.5, 1369.5, 1328.9, 1298.1, 1265.3, 1251.8, 1209.4, 1180.4, 1116.8, 1208.1, 839.0, 810.1, 746.5, 704.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{21}H_{17}FN_2O_3$ 365.1301; Found 365.1302.



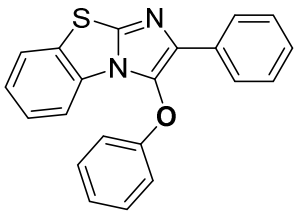
3-(2-Methoxyphenoxy)-2-(4-methoxyphenyl)-6-chloro imidazo[1,2-a]pyridine (**3o**)

This compound was prepared by the General Procedure described above and was obtained as a white solid (53 mg, yield = 70%), m.p.: 130-132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96-7.98 (dd, *J* = 2.0 Hz, *J* = 6.8 Hz, 2H), 7.82-7.83 (dd, *J* = 0.8 Hz, *J* = 2.0 Hz, 1H), 7.49-7.52 (dd, *J* = 0.8 Hz, *J* = 9.6 Hz, 1H), 7.05-7.10 (m, 3H), 6.90-6.92 (dd, *J* = 2.0 Hz, *J* = 6.8 Hz, 2H), 6.69-6.74 (m, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 4.04 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 149.1, 144.9, 138.0, 132.5, 130.1, 127.9, 125.5, 124.8, 124.5, 121.2, 120.5, 119.4, 117.9, 114.8, 114.2, 112.9, 56.2, 55.3. FTIR (NaCl, cm^{-1}): 3015.6, 2839.2, 1498.7, 1419.6, 1392.6, 1325.1, 1298.1, 1265.3, 1251.8, 1199.7, 1174.7, 1116.7, 1028.1, 895.0, 837.1, 798.5, 738.7, 704.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{21}H_{17}ClN_2O_3$ 381.1006; Found 381.1003.



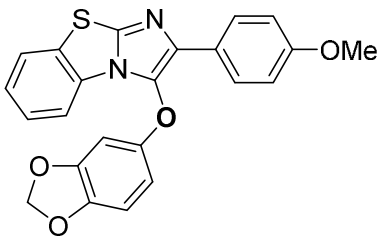
3-(2-Methoxyphenoxy)-2-(4-methoxyphenyl) imidazo[2,1-a]isoquinoline (**3p**)

This compound was prepared by the General Procedure described above and was obtained as a white solid (39 mg, yield = 49%), m.p.: 108-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72 (d, *J* = 8.0 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.61-7.67 (m, 3H), 7.54 (t, *J* = 7.2 Hz, 1H), 6.92-7.07 (m, 5H), 6.68-6.72 (m, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 4.05 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 149.0, 145.7, 129.3, 128.2, 128.1, 127.6, 127.1, 124.1, 122.9, 121.2, 119.1, 114.8, 114.1, 112.8, 112.7, 56.3, 55.2. FTIR (NaCl, cm^{-1}): 3005.6, 2839.2, 1583.6, 1578.6, 1498.7, 1454.3, 1419.6, 1377.2, 1265.3, 1251.8, 1199.7, 1174.7, 1026.1, 895.0, 792.7, 738.7, 704.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{25}H_{20}N_2O_3$ 397.1552; Found 397.1549.



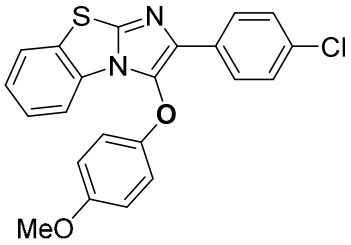
3-phenoxy-2-phenylbenzo[d] imidazo[2,1-b]thiazole (**5a**)

This compound was prepared by the General Procedure described above and was obtained as a brown solid (58 mg, yield = 85%), m.p.: 173-174 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.0 Hz, 2H), 7.51-7.56 (m, 1H), 7.35-7.37 (m, 1H), 7.24-7.27 (m, 4H), 7.12-7.16 (m, 3H), 6.99-7.02 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.5, 141.2, 132.6, 131.4, 131.1, 130.6, 129.3, 128.9, 127.6, 126.1, 125.2, 124.5, 123.8, 122.9, 122.8, 114.0, 112.4. FTIR (KCl, cm^{-1}): 2359.2，1488.0，1372.1，1210.7，1161.3，1022.6，743.6，667.9，499.8. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{21}H_{15}N_2OS$ 343.0900; Found 343.0900.



3-(1,3-benzodioxol-5-oyl)-2-(4-methoxyphenyl) benzo[d] imidazo[2,1-b]thiazole (**5b**)

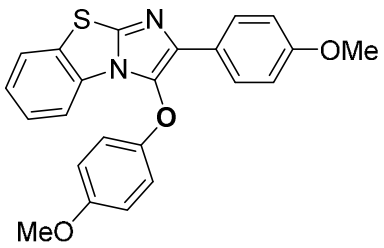
This compound was prepared by the General Procedure described above and was obtained as a dark red oil (72 mg, yield = 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.23-7.28 (m, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.64-6.68 (m, 2H), 6.48 (dd, *J* = 2.0 Hz, *J* = 8.0 Hz, 1H), 5.92 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.8, 151.9, 148.9, 143.8, 142.0, 131.7, 130.5, 129.9, 126.8, 126.3, 125.3, 124.7, 124.0, 114.1, 114.0, 113.3, 108.5, 106.6, 101.8, 97.8, 55.3. FTIR (KCl, cm^{-1}):3774.3，3033.3，3896.9，2390.9，2348.9，1658.9，1563.3，1529.9，1402.13，832.2，745.3. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calculated for $C_{23}H_{16}N_2O_4SNa$ 439.0723; Found 439.0718.



3-(4-methoxyphenoxy)-2-(4-chlorophenyl)benzo[d] imidazo[2,1-b]thiazole (**5c**)

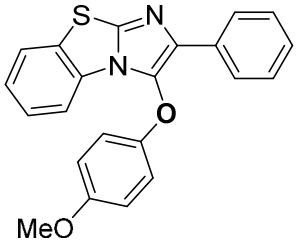
This compound was prepared by the General Procedure described above and was obtained as a yellow solid (70 mg, yield = 86%), m.p.: 183-184 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75 (brs, 2H), 7.52-7.54 (m, 1H), 7.36-7.37 (m, 1H), 7.16-7.21 (m, 4H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.74 (d, *J* = 9.0 Hz, 2H), 3.64 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.9, 150.3, 132.9, 132.7, 131.6, 131.2, 129.9, 129.3, 129.2, 128.8, 126.7, 126.3, 124.9, 124.0, 115.7, 115.3, 113.5,

55.7. FTIR (KCl, cm^{-1}): 3564.3, 3472.4, 3354.9, 2351.5, 1494.4, 1455.0, 1417.0, 1393.0, 1359.68, 1181.1, 828.8. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{22}H_{16}ClN_2O_2S$ 407.0616; Found 407.0619.



3-(4-methoxyphenoxy)-2-(4-methoxyphenyl) benzo[d] imidazo[2,1-b]thiazole (**5d**)

This compound was prepared by the General Procedure described above and was obtained as a dark red oil (78 mg, yield = 97%). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.5 Hz, 2H), 7.53 (t, *J* = 4.0 Hz, 1H), 7.37 (t, *J* = 4.5 Hz, 1H), 7.14-7.17 (m, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.80 (d, *J* = 8.0 Hz, 2H), 6.74 (d, *J* = 9.0 Hz, 2H), 3.70 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.7, 154.7, 149.5, 130.7, 129.5, 128.8, 125.8, 125.2, 124.3, 123.6, 122.9, 114.9, 114.7, 114.2, 113.6, 113.0, 112.3, 54.5, 54.2. FTIR (KCl, cm^{-1}): 3564.2, 3444.6, 2969.4, 2350.1, 1704.2, 1682.3, 1567.7, 1245.8, 1173.3, 830.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{23}H_{18}N_2O_3S$ 403.1111; Found 403.1109.



3-(4-methoxyphenoxy)-2-phenyl benzo[d] imidazo[2,1-b]thiazole (**5e**)

This compound was prepared by the General Procedure described above and was obtained as a yellow oil (71 mg, yield = 95%). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.5 Hz, 2H), 7.51-7.53 (m, 1H), 7.36-7.38 (m, 1H), 7.25 (t, *J* = 8.0 Hz. 2H), 7.11-7.16 (m, 3H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.73 (d, *J* = 9.0 Hz, 2H), 3.63 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.7,

149.4, 141.0, 133.1, 131.6, 131.0, 130.6, 128.9, 127.6, 126.0, 125.2, 124.5, 123.7, 122.9, 114.7, 114.2, 112.4, 54.6. FTIR (KCl, cm^{-1}): 3417.9, 3355.2, 2341.0, 1887.5, 1714.9, 1574.2, 1372.2, 1208.2, 1022.9, 744.8. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calculated for $C_{22}H_{17}N_2O_2S$ 373.1005; Found 373.1009.

■ASSOCIATED CONTENT

Supporting Information

^1H, ^{13}C NMR spectra

■AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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