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EFFICIENT SYNTHESIS OF 2-FUNCTIONALIZED BENZOXAZOLES CATALYZED BY COPPER IODIDE

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Abstract – We reported an efficient synthesis of 2-functionalized benzoxazoles in mild condition and excellent yields. The synthetic process includes two steps. The step one contains a reaction of pendent halide formamidine derivatives and 2-aryloxyacetyl chloride generating highly selective (*Z*)-*N*-(2-halophenyl)-3-(dimethylamino)-2-aryloxyacrylamides, and the step two undergoes copper iodide catalyzed intramolecular C-O bond formation to yield title compounds. This strategy is not only providing newly discovered key intermediates **6a-l** which contain multiple functional groups on 2-position (as building blocks), but also expanded the scope of methodologies for making diverse benzoxazoles with multiple functional groups.

INTRODUCTION

2-Substituted benzoxazole is one of the most important motifs, which exhibit wide spectrum of pharmacological properties such as anticancer activities,[1-5] anti-inflammatory,[6-10] and anticonvulsant.[11-16] Such benzoxazole compounds also show excellent activities against Gram-positive bacteria and Gram-negative bacteria.[17-22] By looking at several marketed drugs (Figure 1), they all have benzoxazole as core active moiety like, Calcimycin, Caboxamycin - antibiotics against Gram positive bacteria and fungi; Tafamidis is used to delay impairment of peripheral nerve function in adults with familial amyloid polyneuropathy; Benoxaprofen and Flunoxaprofen are nonsteroidal anti-inflammatory drugs (NSAID); Suvorexant is a medication for the treatment of insomnia. Most interestingly, a slight modification at the C-2 position results in distinguishable different biological activities.

For this reason, development of many methods which resulted in the formation of 2-functionalized benzoxazole and their derivatives has been demonstrated by many research groups.[23-26] Such development and preparation have attracted much attention to drug discovery companies and institutes. In most cases, formation of benzoxazole ring is via the condensation reaction of 2-aminophenols with carboxylic acids catalyzed by strong acids or aldehydes / alcohols under oxidative cyclization conditions.

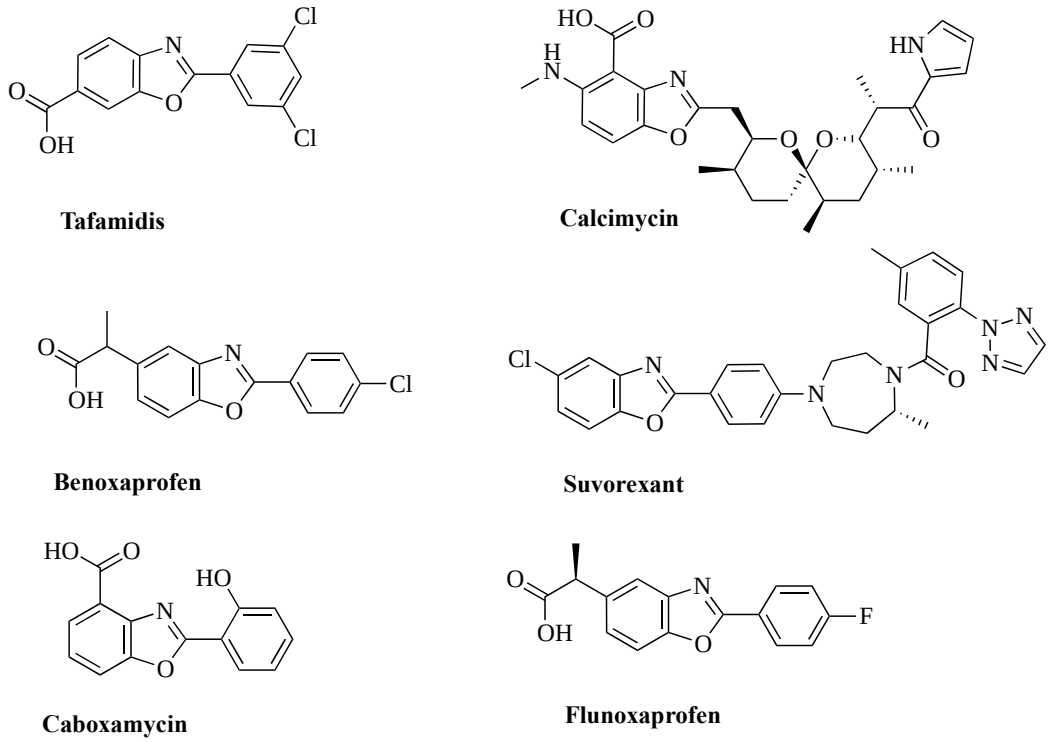


Figure 1. Marketed drugs containing 2-substituted benzoxazole

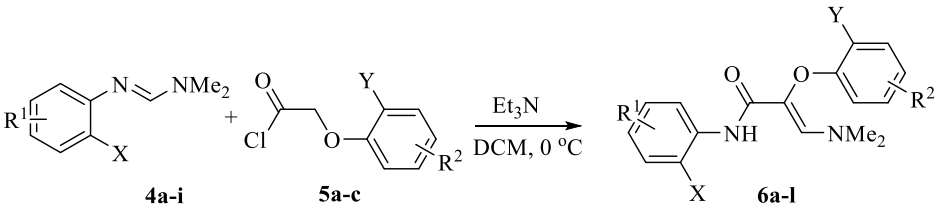
RESULTS AND DISCUSSION

As part of our ongoing project towards the further applications of pendent halide formamidine for synthesis of heterocyclic compounds and drug discovery programs, we carried out the reaction of compounds **4e** and **5a** in the presence of triethylamine in DCM at 0 ^{o}C. The compound **6e**, (*Z*)-*N*-(2-bromophenyl)-3-(dimethylamino)-2-phenoxyacrylamide was highly selectively synthesized and isolated in 93% yield.

Immediately, it drew our attention to explore the synthesis of 2-functionalized benzoxazole derivatives. In order to expand the scope of such chemistry, enaminoamides **6a-l** were prepared by reacting formamidines **4a-i** with corresponding aryloxyacetyl chloride **5a-c** in the presence of triethylamine at 0 ^{o}C (summarized in Table 1). The *Z*-isomer of enaminoamide was only product further confirmed by single crystal X-ray analysis of compound **6g** (Supporting Information). All those reactions were obtained in excellent yields and are tolerant with functional groups such as -F, -Cl, -Br, -I, -OMe. In the course of

studies on the chemistry of pendent halide formamidine derivatives, *(E)*-*N*, *N*-dimethyl-*N'*-(2-halophenyl)formamidines **4** and **6a-l** are novel building blocks with structural feature of highly polarized push-pull interaction C=N double bond, and halogen atoms, *N*, *N*-dimethyl group and -OAr could be as leaving groups in the chemical transformation for further development.

Table 1. Preparation of enaminoamides **6a–l** from compounds **4a–i**

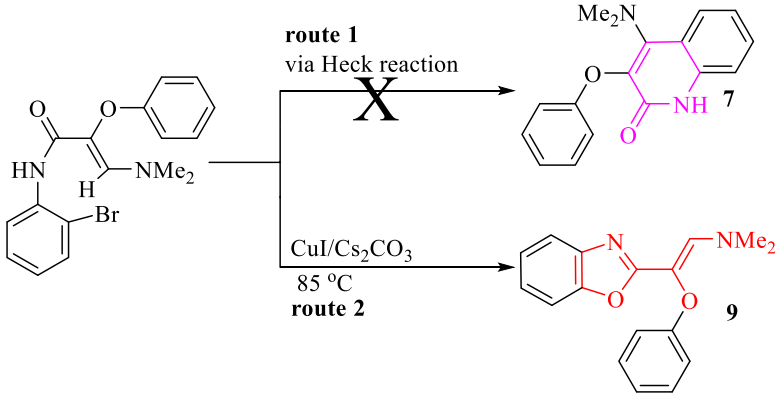


4a-i **5a-c** **6a-l**

Entry	**4,** -X, -R^1	**5,** -Y, -R^2	**6**	Yield (%) [a]
1	**4a**, Br, 4-Me	**5a,** H, H	**6a**	89
2	**4b**, Br, 3-Me	**5a,** H, H	**6b**	93
3	**4c**, Br, 4-Br	**5a,** H, H	**6c**	92
4	**4d**, Br, 5-Br	**5a,** H, H	**6d**	90
5	**4e**, Br, H	**5a,** H, H	**6e**	93
6	**4f**, Br,5-OMe	**5a,** H, H	**6f**	95
7	**4g**, Br, 5-F	**5a,** H, H	**6g**	90
8	**4h**, Br, 5-Cl	**5a,** H, H	**6h**	91
9	**4i**, I, H	**5a,** H, H	**6i**	89
10	**4e**, Br, H	**5b,** H, 4-Cl	**6j**	91
11	**4i**, I, H	**5c,** Br, H	**6k**	91
12	**4c**, Br, 4-Br	**5b,** H, 4-Cl	**6l**	92

[a]Reagents and conditions: formamidines **4a-i** (3 mmol), triethylamine (12 mmol), DCM (6 mL), **5a-c** (4.5 mmol), 0 °C overnight. [b]Purified by chromatograph or crystallization from MeOH.

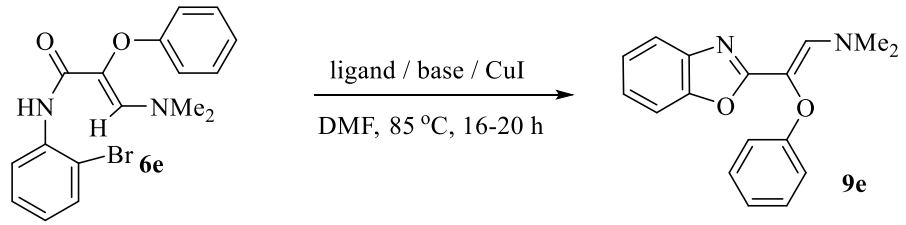
By looking at the compound **6**, we designed the following routes to prepare compound **7** containing quinolin-2(1*H*)-one ring with multiple functional groups on, and compound **9** having 2-functionalized benzoxazoles with functional groups on as well for our ongoing programs. We have successfully obtained compound **9**, and failed to yield **7** (Scheme 1).



Scheme 1. Proposals for synthesis of heterocyclic compounds

To find the optimal reaction condition, the substrate (*Z*)-*N*-(2-bromophenyl)-3-(dimethylamino)-2-phenoxyacrylamide **6e** was selected for the model reaction. Fifteen reactions were run under different conditions, and the corresponding results were summarized in Table 2. The use of catalytic CuI proved superior to CuOAc, CuCl and CuBr (entries 1, 5-7). Three ligands have been examined, 1,10-phenanthroline showed best results (up to 86% yield, entry 13), L-proline gave reasonable yields (entries 8-10) and 1,2-diaminocyclohexane yielded trace desired product by LCMS analysis. It also indicated that increasing the amount of ligand (entries 8-13) afforded higher yields of compound **9e**. While 1,10-phenanthroline (40% mol) was applied to the reaction, it did not increase the reaction yield (entry 15) as expected. The multiple bases were screened without ligand and found that Cs_2CO_3 was the best one out them (entries 1-4) catalyzed by CuI at 85 ^oC in DMF.

Table 2. Optimization of reaction conditions

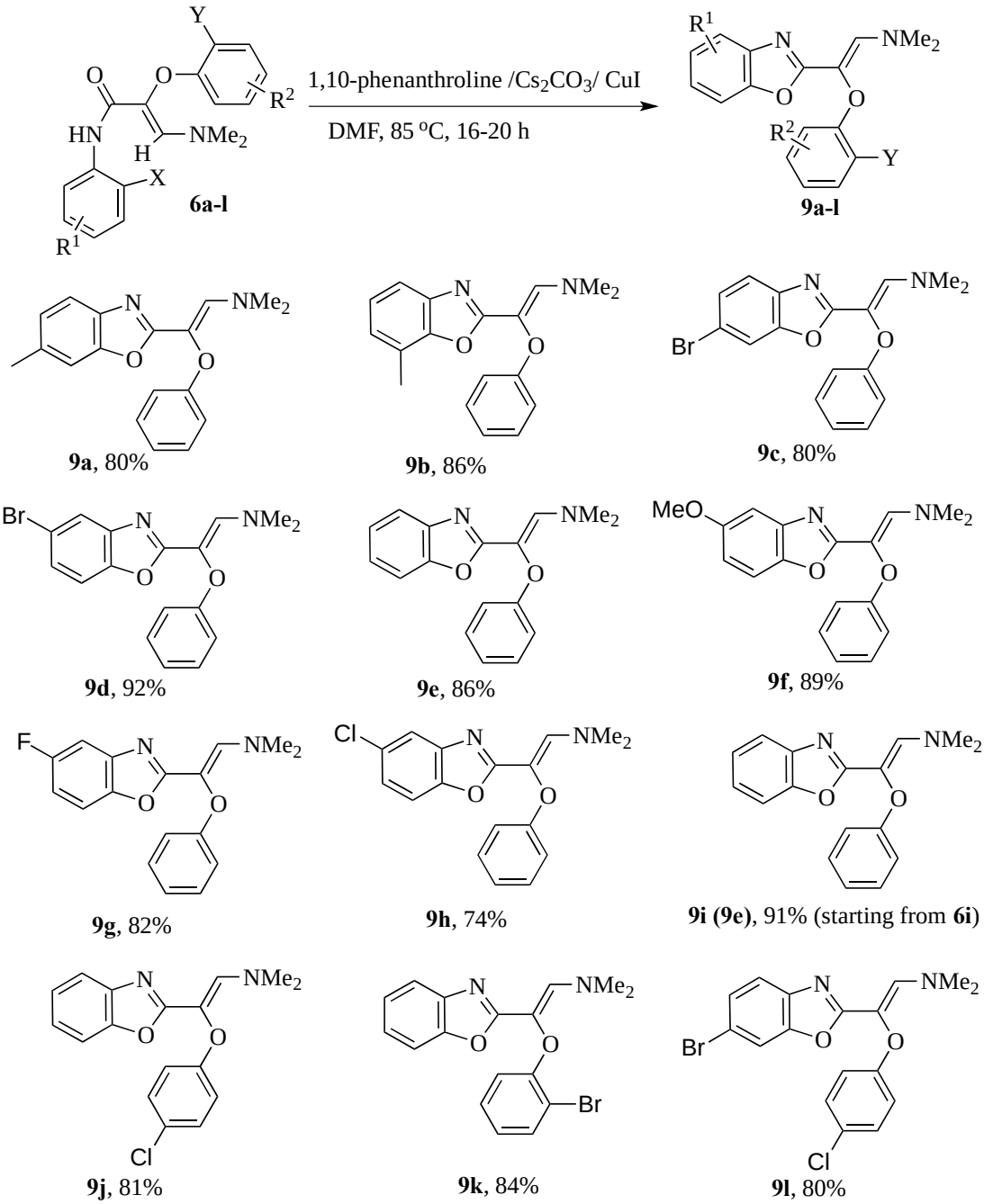


Entry	Catalyst (mol%)	Ligand (mol%)	Base (equivalent)	Yield (%)[a]
1	CuI (10%)	0	Cs_2CO_3 (2.0)	31
2	CuI (10%)	0	KOH (2.0)	22
3	CuI (10%)	0	K_3PO_4 (2.0)	13
4	CuI (10%)	0	K_2CO_3 (2.0)	19
5	CuOAc (10%)	0	Cs_2CO_3 (2.0)	0
6	CuCl (10%)	0	Cs_2CO_3 (2.0)	0
7	CuBr (10%)	0	Cs_2CO_3 (2.0)	0
8	CuI (10%)	L-proline (5%)	Cs_2CO_3 (2.0)	45
9	CuI (10%)	L-proline (10%)	Cs_2CO_3 (2.0)	52
10	CuI (10%)	L-proline (20%)	Cs_2CO_3 (2.0)	69
11	CuI (10%)	1,10-phenanthroline (5%)	Cs_2CO_3 (2.0)	53
12	CuI (10%)	1,10-phenanthroline (10%)	Cs_2CO_3 (2.0)	68
13	CuI (10%)	1,10-phenanthroline (20%)	Cs_2CO_3 (2.0)	86
14	CuI (10%)	1,2-diaminocyclohexane (20%)	Cs_2CO_3 (2.0)	<5[b]
15	CuI (20%)	1,10-phenanthroline (40%)	Cs_2CO_3 (2.0)	86

[a]Isolated yield. [b]Based on LC-MS analysis.

Having established the optimal reaction condition, we explored the scope of the catalyzed reactions of enaminoamides **6a-l** for preparation of 2-functionalized benzoxazoles. The results were summarized in Table 3. Overall, all reactions gave excellent yields and other halides tolerated to catalytical system. The stereochemistry selectivity was remained as confirmed by single crystal X-ray analysis of **9e** (Figure 2).

Table 3. Synthesis of 2-functionalized benzoxazoles **9a–l** [a,b]



[a]Reagents and condition: CuI (0.019 g, 0.1 mmol), 1,10-phenanthroline (0.036 g, 0.2 mmol), enaminoamide **6** (1.0 mmol) and Cs_2CO_3 (0.652 g, 2.0 mmol) in anhydrous DMF (2 mL). [b]Isolated yields.

To understand the reaction pathway, a plausible reaction mechanism was proposed and depicted in Scheme 2. The intermediate **A** (salt) was formed from the reaction of compounds **4** and **5** and followed by deprotonation (in blue) on alpha carbon generating **B**. It undergoes intramolecular cyclization to form beta-lactam **C**. The electron pair on the nitrogen in -NMe_2 in **C** helps rapid ring opening via N-C bond cleavage as shown to give enamino amide **6e** through **D**. The ligand is tethered with copper iodide and

forms complex **E**. Copper inserted into C-Br bond (oxidative addition) to generate complex **F** and then the desired product was obtained via reductive elimination of **F**.

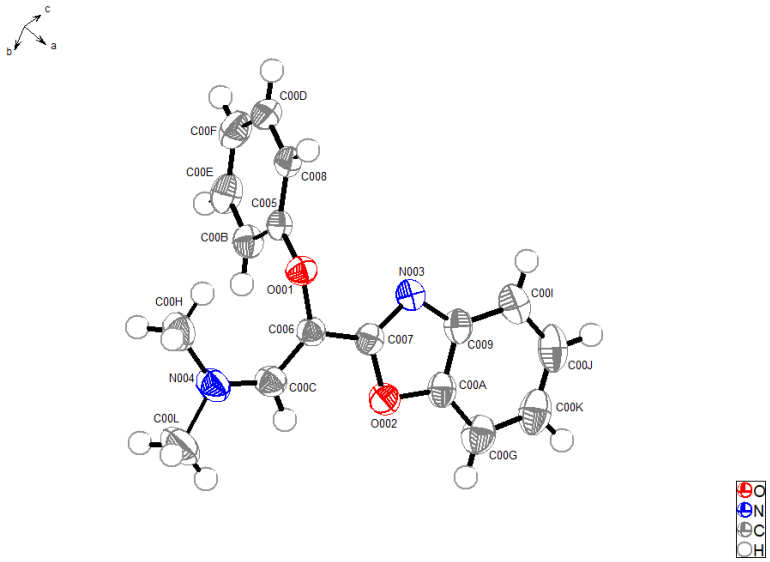
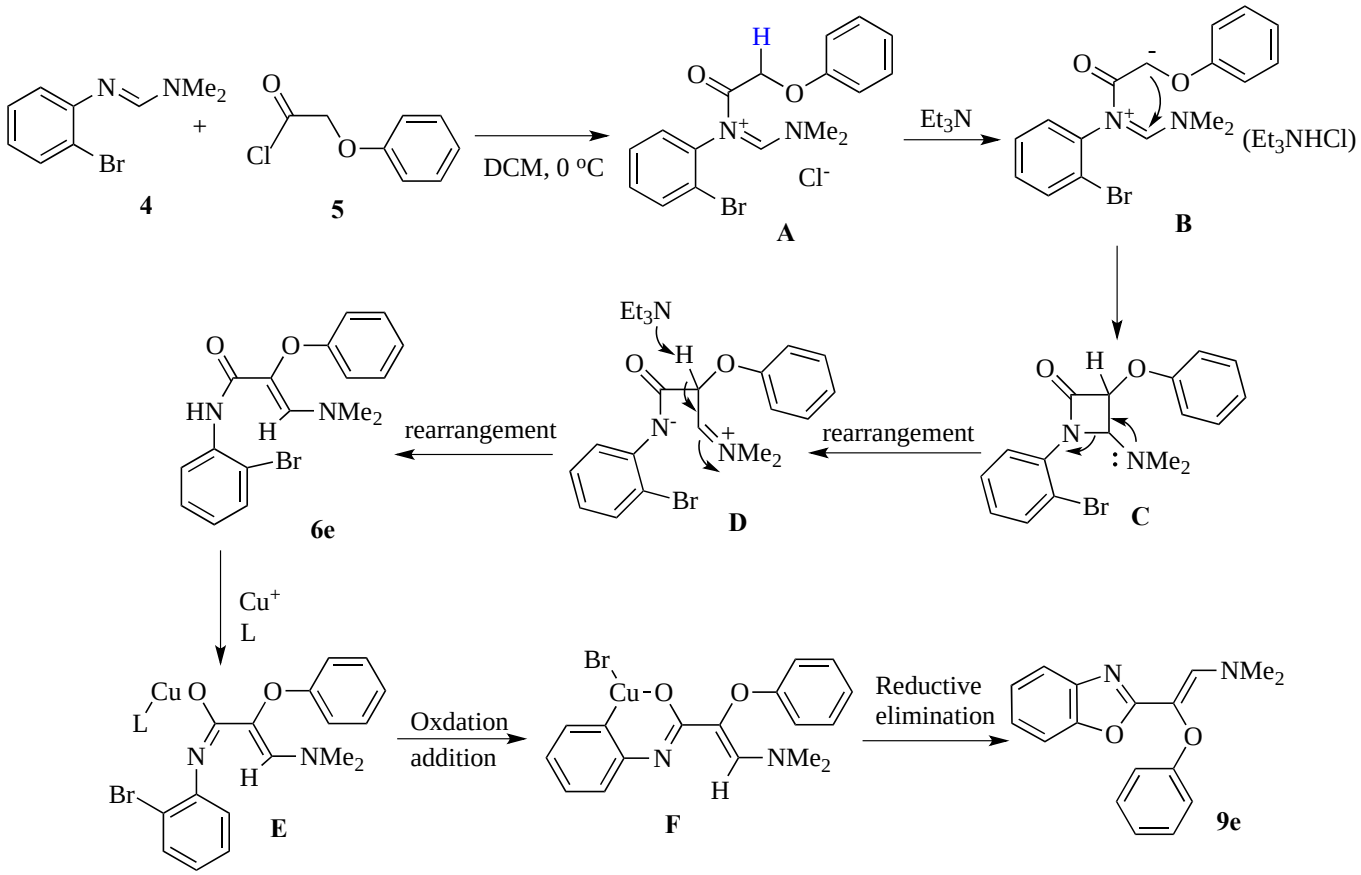


Figure 2. X-Ray structure of **9e**



Scheme 2. A plausible mechanism for the formation of compounds **6e** and **9e**

In summary, we have developed a new method for the synthesis of 2-functionized benzoxazoles in mild condition and excellent yields. The synthetic process includes two steps. The step one contains a reaction of a pendent halide formamidine derivatives and 2-phenoxyacetyl chloride generating highly selective (*Z*)-*N*-(2-halophenyl)-3-(dimethylamino)-2-phenoxyacrylamides and the step two undergoes copper iodide catalyzed intramolecular C-O bond formation to yield 2-functionized benzoxazoles. This strategy is not only providing alternative method for the preparation of 2-functionized benzoxazoles, but also discovered key intermediates **6a-l** which contain multiple functional groups - good building blocks for organic synthesis. Further application of such intermediates will be reported in near future.

EXPERIMENTAL

All reagents including starting compounds **5a-c** and solvents were obtained from commercial suppliers and used without further purification. All reagents were weighed and handled in air at room temperature. Melting points were recorded on a RY-1 microscopic melting apparatus and uncorrected. ^{1}H NMR spectra were recorded on 400 MHz and ^{13}C NMR spectra were recorded on 101 MHz by using a Bruker Avance 400 spectrometer. Chemical shifts were reported in parts per million (δ) relative to tetramethylsilane (TMS). HRMS data were recorded on Agilent 6530 Accurate-Mass Q-TOF LCMS spectrometer by ESI in positive mode. The X-ray single-crystal diffraction was performed on an Agilent Supernova CCD diffractometer instrument.

General procedure for synthesis of formamidines 4a-i

A typical procedure is as follows: After 1.5 eq of 2-pyridinesulfonyl chloride was dissolved in DMF for 5 min, an amine (1.0 eq) was added at room temperature. The reactions were checked by TLC on silica gel plates using a mixture of petroleum and EtOAc as eluent. Then the solvent was removed, K_2CO_3 solution (4M) was added. The mixture was then extracted with Et_2O. The Et_2O solution was dried over Na_2SO_4 and the solvent was removed to generate the pure product.[27]

N'-(2-Bromo-4-methylphenyl)-*N*, *N*-dimethylformimidamide (4a)

Yellow oil; yield: 94.8%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 (s, 1H), 7.35 (dd, *J* = 2.0, 0.8 Hz, 1H), 6.97 (ddd, *J* = 8.0, 2.0, 0.8 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 3.02 (s, 6H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.42, 147.66, 133.17, 128.81, 120.61, 118.37, 40.20, 34.49, 20.40. HRMS (ESI-TOF) *m/z* calcd for $C_{10}H_{14}BrN_2$ [$(M + H)^+$] 241.0335, found 241.0342.

N'-(2-Bromo-3-methylphenyl)-*N*, *N*-dimethylformimidamide (4b)

Yellow oil; yield: 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 (s, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 6.70 (dd, *J* = 7.9, 1.6 Hz, 1H), 3.06 (d, *J* = 10.4 Hz, 6H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.31, 150.31, 138.98, 127.27, 124.74, 121.49, 118.39, 40.34, 34.70, 23.99. HRMS (ESI-TOF) *m/z* calcd for $C_{10}H_{14}BrN_2$ [$(M + H)^+$] 241.0335, found 241.0348.

***N*'-(2,4-Dibromophenyl)-*N*, *N*-dimethylformimidamide (4c)**

Pink solid; mp 37-39 °C; yield: 93.2%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 2.3 Hz, 1H), 7.35 (s, 1H), 7.23 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 2.99 (d, *J* = 13.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.30, 149.35, 134.74, 130.95, 121.66, 119.44, 114.53, 40.24, 34.51. HRMS (ESI-TOF) *m/z* calcd for $C_9H_{11}Br_2N_2$ [$(M + H)^+$] 304.9283, found 304.9287.

***N*'-(2,5-Dibromophenyl)-*N*, *N*-dimethylformimidamide (4d)**

Yellow oil; yield: 92.3%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 6.99 (t, *J* = 1.7 Hz, 1H), 6.97-6.93 (m, 1H), 3.05 (d, *J* = 8.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.57, 151.47, 133.84, 126.22, 123.56, 121.37, 117.78, 40.42, 34.71. HRMS (ESI-TOF) *m/z* calcd for $C_9H_{11}Br_2N_2$ [$(M + H)^+$] 304.9283, found 304.9289.

***N*'-(2-Bromophenyl)-*N*, *N*-dimethylformimidamide (4e)**

Yellow oil; yield: 95.5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.42 (s, 1H), 7.17 (td, *J* = 7.6, 1.5 Hz, 1H), 6.88-6.81 (m, 2H), 3.04 (d, *J* = 16.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.46, 150.08, 132.82, 128.17, 123.57, 121.06, 118.78, 40.29, 34.60. HRMS (ESI-TOF) *m/z* calcd for $C_9H_{12}BrN_2$ [$(M + H)^+$] 227.0184, found 227.0183.

***N*'-(2-Bromo-5-methoxyphenyl)-*N*, *N*-dimethylformimidamide (4f)**

Yellow oil; yield: 94.4%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 (d, *J* = 2.2 Hz, 1H), 7.37 (dd, *J* = 9.4, 2.2 Hz, 1H), 6.44-6.39 (m, 2H), 3.79-3.67 (m, 3H), 3.01 (d, *J* = 13.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.66, 153.50, 150.91, 132.81, 109.48, 109.18, 106.84, 55.41, 40.20, 34.48. HRMS (ESI-TOF) *m/z* calcd for $C_{10}H_{14}BrN_2O$ [$(M + H)^+$] 257.0284, found 257.0293.

***N*'-(2-Bromo-5-fluorophenyl)-*N*, *N*-dimethylformimidamide (4g)**

Colorless oil; yield: 93.9%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46-7.43 (m, 1H), 7.42 (s, 1H), 6.62-6.53 (m, 2H), 3.04 (d, *J* = 14.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.85, 161.40, 153.69, 151.39 (d, *J* = 8.7 Hz), 133.30 (d, *J* = 9.4 Hz), 113.21 (d, *J* = 3.1 Hz), 110.28 (d, *J* = 22.8 Hz), 107.77 (d, *J* = 22.7 Hz), 40.39, 34.69. HRMS (ESI-TOF) *m/z* calcd for $C_9H_{11}BrFN_2$ [$(M + H)^+$] 245.0084, found 245.0098.

***N*'-(2-Bromo-5-chlorophenyl)-*N*, *N*-dimethylformimidamide (4h)**

Yellow oil; yield: 94.1%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45-7.42 (m, 2H), 6.84-6.80 (m, 2H), 3.05 (d, *J* = 9.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.57, 151.37, 133.50, 123.24, 120.61, 117.01, 40.38, 34.65. HRMS (ESI-TOF) *m/z* calcd for $C_9H_{11}BrClN_2$ [$(M + H)^+$] 260.9789, found 260.9794.

***N*'-(2-Iodophenyl)-*N*, *N*-dimethylformimidamide (4i)**

Brown oil; yield: 91.7%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.40 (s, 1H), 7.22 (td, *J* = 7.6, 1.5 Hz, 1H), 6.82 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.70 (td, *J* = 7.5, 1.5 Hz, 1H), 3.06 (d, *J* = 18.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.06, 152.67, 138.86, 129.15, 123.86, 118.95, 96.64, 40.18, 34.62. HRMS (ESI-TOF) *m/z* calcd for $C_9H_{12}IN_2$ [$(M + H)^+$] 275.0045, found 275.0042.

General procedure for the preparation of enaminoamides 6a-l

To a mixture of formamidine **4a** (0.723 g, 3 mmol), triethylamine (1.214 g, 12 mmol), and CH_2Cl_2 (3 mL), a solution of phenoxyacetyl chloride **5a** (0.768 g, 4.5 mmol) in CH_2Cl_2 (3 mL) was added over a period of 30 min at 0 ºC with stirring. The reaction mixture was allowed to warm-up to room temperature and stirred further overnight. The reaction mixture was washed with water (5 mL x 3) and dried over Na_2SO_4. The solution was passed through short column or by crystallization from MeOH to give pure enamino-amide **6a**.

(*Z*)-*N*-(2-Bromo-4-methylphenyl)-3-(dimethylamino)-2-phenoxyacrylamide (6a)

Gray solid; mp 142-144 ºC; yield: 89.3%; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.21 (s, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.42-7.30 (m, 3H), 7.25 (s, 1H), 7.10 (ddd, *J* = 6.6, 3.5, 1.3 Hz, 3H), 7.05 (dd, *J* = 11.4, 4.1 Hz, 1H), 2.93 (s, 6H), 2.21 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 163.04, 158.92, 137.78, 134.37, 132.69, 130.47, 129.23, 122.81, 121.73, 117.07, 115.42, 113.67, 42.05, 20.35. HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{20}BrN_2O_2$ [(M + H)$^+$] 375.0708, found 375.0683.

(*Z*)-*N*-(2-Bromo-3-methylphenyl)-3-(dimethylamino)-2-phenoxyacrylamide (6b)

Yellow solid; mp 171-173 ºC; yield: 93.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.38 (s, 1H), 8.13 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.37 (dd, *J* = 8.7, 7.4 Hz, 2H), 7.27 (s, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 7.11 (dd, *J* = 8.7, 0.9 Hz, 2H), 7.05 (t, *J* = 7.3 Hz, 1H), 7.01-6.94 (m, 1H), 2.94 (s, 6H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 163.07, 138.39, 137.97, 130.50, 127.95, 125.45, 122.86, 118.79, 117.03, 115.43, 42.04, 23.85. HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{19}BrN_2O_2Na$ [(M + Na)$^+$] 397.0528, found 397.0504.

(*Z*)-*N*-(2,4-Dibromophenyl)-3-(dimethylamino)-2-phenoxyacrylamide (6c)

Orange solid; mp 183-185 ºC; yield: 91.7%; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.30 (s, 1H), 8.21 (d, *J* = 8.9 Hz, 1H), 7.78 (d, *J* = 2.3 Hz, 1H), 7.52 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.37 (dd, *J* = 8.7, 7.4 Hz, 2H), 7.29 (s, 1H), 7.10 (dd, *J* = 8.7, 0.9 Hz, 2H), 7.05 (t, *J* = 7.3 Hz, 1H), 2.94 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 163.13, 158.84, 138.36, 136.43, 134.40, 131.62, 130.52, 122.92, 116.74, 115.43, 115.18, 114.49, 42.13. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{16}Br_2N_2O_2Na$ [(M+Na)$^+$] 460.9476, found 460.9455.

(*Z*)-*N*-(2,5-Dibromophenyl)-3-(dimethylamino)-2-phenoxyacrylamide (6d)

Pale yellow solid; mp 172-175 ºC; yield: 90.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.52 (d, *J* = 2.4 Hz, 1H), 8.29 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.38 (dd, *J* = 8.7, 7.3 Hz, 2H), 7.30 (s, 1H), 7.12 (ddd, *J* = 8.6, 5.2, 1.7 Hz, 3H), 7.06 (t, *J* = 7.3 Hz, 1H), 2.95 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ = 163.21, 158.78, 138.64, 138.20, 134.21, 130.55, 127.14, 123.38, 122.98, 121.34, 116.53, 115.40, 112.24, 42.25. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{17}Br_2N_2O_2$ [(M+H)$^+$] 438.9657, found 438.9631.

(*Z*)-*N*-(2-Bromophenyl)-3-(dimethylamino)-2-phenoxyacrylamide (6e)

Yellow solid; mp 136-138 ºC; yield: 92.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.32-8.23 (m, 2H), 7.53 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.38 (dd, *J* = 8.8, 7.3 Hz, 2H), 7.34-7.28 (m, 1H), 7.28 (s, 1H), 7.15-7.08 (m,

2H), 7.08-7.01 (m, 1H), 6.94 (ddd, *J* = 8.0, 7.4, 1.6 Hz, 1H), 2.94 (s, 6H); ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ = 163.12, 158.89, 138.06, 136.84, 132.67, 130.50, 128.76, 124.80, 122.87, 121.64, 116.93, 115.42, 113.57, 42.08. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{18}BrN_2O_2$ [(M+H)$^+$] 361.0552, found 361.0530.

(*Z*)-*N*-(2-Bromo-5-methoxyphenyl)-3-(dimethylamino)-2-phenoxyacrylamide (6f)

Black solid; mp 157-159 ºC, yield: 95.3%; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ = 8.22 (s, 1H), 8.04 (d, *J* = 3.0 Hz, 1H), 7.47-7.34 (m, 3H), 7.30 (s, 1H), 7.11 (dd, *J* = 8.7, 0.9 Hz, 2H), 7.05 (t, *J* = 7.3 Hz, 1H), 6.56 (dd, *J* = 8.9, 3.1 Hz, 1H), 3.72 (s, 3H), 2.94 (s, 6H); ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ = 163.13, 159.46, 158.81, 138.26, 137.44, 132.80, 130.54, 122.94, 116.80, 115.38, 110.24, 106.91, 103.46, 55.77, 42.01. HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{20}BrN_2O_3$ [(M+H)$^+$] 391.0657, found 391.0633.

(*Z*)-*N*-(2-Bromo-5-fluorophenyl)-3-(dimethylamino)-2-phenoxyacrylamide (6g)

Orange solid; mp 162-165 ºC; yield: 90.2%; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ = 8.31 (s, 1H), 8.22 (dd, *J* = 11.7, 3.1 Hz, 1H), 7.58 (dd, *J* = 8.9, 6.0 Hz, 1H), 7.38 (dd, *J* = 8.7, 7.4 Hz, 2H), 7.32 (s, 1H), 7.12 (dd, *J* = 8.7, 0.9 Hz, 2H), 7.06 (t, *J* = 7.3 Hz, 1H), 6.83 (ddd, *J* = 8.8, 8.1, 3.1 Hz, 1H), 2.96 (s, 6H); ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ = 163.24, 162.97, 160.56, 158.75, 138.72, 138.08 (d, $^3J_{C\text{-}F}$ = 12.4 Hz), 133.73 (d, $^4J_{C\text{-}F}$ = 9.5 Hz), 130.58, 123.03, 116.47, 115.38, 111.29 (d, $^2J_{C\text{-}F}$ = 23.1 Hz), 107.75 (d, $^1J_{C\text{-}F}$ = 29.3 Hz), 107.40 (d, $^5J_{C\text{-}F}$ = 3.0 Hz). HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{16}BrFN_2O_2Na$ [(M+Na)$^+$] 401.0277, found 401.0253.

(*Z*)-*N*-(2-Bromo-5-chlorophenyl)-3-(dimethylamino)-2-phenoxyacrylamide (6h)

Pale yellow solid; mp 167-169 ºC; yield: 91.3%; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ = 8.39 (d, *J* = 2.6 Hz, 1H), 8.31 (s, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.42-7.34 (m, 2H), 7.31 (s, 1H), 7.11 (dd, *J* = 8.7, 0.9 Hz, 2H), 7.06 (t, *J* = 7.3 Hz, 1H), 7.02 (dd, *J* = 8.6, 2.6 Hz, 1H), 2.95 (s, 6H); ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ = 163.25, 158.77, 138.68, 137.98, 133.92, 133.08, 130.57, 124.25, 123.0, 120.46, 116.48, 115.39, 111.51, 42.07. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{16}BrClN_2O_2Na$ [(M+Na)$^+$] 416.9981, found 416.9958.

(*Z*)-3-(Dimethylamino)-*N*-(2-iodophenyl)-2-phenoxyacrylamide (6i)

Pale solid; mp 132-135 ºC; yield: 88.6%; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ = 8.23 (s, 1H), 8.16 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.74 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.42-7.34 (m, 2H), 7.34-7.28 (m, 1H), 7.27 (s, 1H), 7.12 (dd, *J* = 8.7, 1.0 Hz, 2H), 7.08-7.02 (m, 1H), 6.78 (m, 1H), 2.93 (s, 6H); ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ = 163.19, 158.92, 139.57, 139.16, 137.88, 130.45, 129.32, 125.43, 122.79, 121.43, 116.93, 115.55, 91.21, 42.09. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{18}IN_2O_2$ [(M+H)$^+$] 409.0413, found 409.0395.

(*Z*)-*N*-(2-Bromophenyl)-2-(4-chlorophenoxy)-3-(dimethylamino)acrylamide (6j)

Yellow solid; mp 121-123 ºC; yield: 90.9%; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ = 8.29 (s, 1H), 8.19 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.55 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.46-7.38 (m, 2H), 7.36-7.29 (m, 1H), 7.27 (s, 1H), 7.19-7.09 (m, 2H), 7.01-6.92 (m, 1H), 2.94 (s, 6H); ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ = 162.88, 157.86,

138.09, 136.82, 132.69, 130.28, 128.74, 126.54, 125.08, 122.21, 117.31, 116.99, 114.21, 42.03. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{17}BrClN_2O_2$ [$(M+H)^+$] 395.0162, found 395.0139.

(*Z*)-2-(2-Bromophenoxy)-3-(dimethylamino)-*N*-(2-iodophenyl)acrylamide (6k)

Brown solid; mp 152-154 ºC; yield: 91.3%; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.12 (dd, *J* = 8.2, 1.5 Hz, 1H), 8.00 (s, 1H), 7.75 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.68 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.44-7.27 (m, 3H), 7.07 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.00 (td, *J* = 7.7, 1.4 Hz, 1H), 6.86-6.76 (m, 1H), 2.92 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 162.66, 155.16, 139.38, 139.22, 137.92, 134.06, 129.82, 129.33, 125.72, 124.25, 122.01, 116.36, 114.93, 110.81, 91.12, 42.01. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{16}BrIN_2O_2Na$ [$(M+Na)^+$] 508.9338, found 508.9312.

(*Z*)-2-(4-Chlorophenoxy)-*N*-(2,4-dibromophenyl)-3-(dimethylamino)acrylamide (6l)

Pale yellow solid; mp 160-162 ºC; yield: 91.7%; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.31 (s, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 2.2 Hz, 1H), 7.52 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.47-7.37 (m, 2H), 7.28 (s, 1H), 7.19-7.08 (m, 2H), 2.94 (s, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ = 162.89, 157.82, 138.37, 136.43, 134.43, 131.59, 130.29, 126.57, 123.51, 117.32, 116.83, 115.51, 115.16, 42.17. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{15}Br_2ClN_2O_2Na$ [$(M+Na)^+$] 494.9087, found 494.9065.

General procedure for the preparation of benzo[*d*]oxazole derivatives 9a-l

A suspension of CuI (0.019 g, 0.1 mmol), 1,10-phenanthroline (0.036 g, 0.2 mmol), enaminoamide **6a** (0.375 g, 1.0 mmol) and $CsCO_3$ (0.652 g, 2.0 mmol) in anhydrous DMF (2 mL) was stirred under inert atmosphere (nitrogen) at 85 ºC. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated at reduced pressure. The residue was dissolved in EtOAc (30 mL), washed with water and brine solution (10 mL x 3), dried over anhydrous Na_2SO_4 and organic layer was concentrated in vacuo below 50 ºC. The crude product was purified by column chromatography over silica gel (PE / EtOAc, 10:1) to give **9a**.

(*Z*)-*N, N*-Dimethyl-2-(6-methylbenzo[*d*]oxazol-2-yl)-2-phenoxyethenamine (9a)

Yellow solid; mp 121-122 ºC; yield: 80.1%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (d, *J* = 8.0 Hz, 1H), 7.23-7.17 (m, 2H), 7.10 (s, 1H), 7.07-7.04 (m, 1H), 7.01-6.97 (m, 2H), 6.94-6.88 (m, 2H), 2.94 (d, *J* = 2.2 Hz, 6H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.77, 158.09, 149.33, 134.70, 131.92, 128.59, 123.84, 120.72, 116.50, 113.99, 108.91, 41.33, 20.55. HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{19}N_2O_2$ [$(M+H)^+$] 295.1447, found 295.1448.

(*Z*)-*N, N*-Dimethyl-2-(7-methylbenzo[*d*]oxazol-2-yl)-2-phenoxyethenamine (9b)

Pale yellow solid; mp 141-143 ºC; yield: 86.2%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 (d, *J* = 7.9 Hz, 1H), 7.27 (m, 3H), 7.07 (dd, *J* = 14.2, 7.7 Hz, 3H), 6.98 (t, *J* = 7.3 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 3.05 (s, 6H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.88, 158.07, 147.95, 128.58, 123.06, 122.88,

120.79, 119.02, 114.07, 41.42, 14.00. HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{19}N_2O_2$ [$(M+H)^+$] 295.1447, found 295.1434.

(*Z*)-2-(6-Bromobenzo[*d*]oxazol-2-yl)-*N, N*-dimethyl-2-phenoxyethenamine (9c)

Pale solid; mp 127-129 ºC; yield: 79.9%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44 (d, *J* = 1.5 Hz, 1H), 7.33-7.25 (m, 4H), 7.18 (s, 1H), 7.06-7.01 (m, 2H), 7.00-6.95 (m, 1H), 3.02 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.88, 158.99, 150.67, 142.12, 136.61, 129.71, 127.10, 121.93, 118.99, 114.95, 112.99, 42.44. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{16}BrN_2O_2$ [$(M+H)^+$] 359.0395, found 359.0381.

(Z)-2-(5-Bromobenzo[*d*]oxazol-2-yl)-*N, N*-dimethyl-2-phenoxyethenamine (9d)

Yellow solid; mp 135-137 ºC; yield: 92.4%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 (d, *J* = 1.4 Hz, 1H), 7.36 (s, 1H), 7.32-7.27 (m, 2H), 7.21 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.08-7.03 (m, 2H), 7.00 (t, *J* = 7.3 Hz, 1H), 3.05 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.55, 157.93, 148.15, 143.41, 135.84, 128.67, 124.30, 120.90, 119.92, 115.55, 113.89, 111.91, 109.56, 41.39. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{16}BrN_2O_2$ [$(M+H)^+$] 359.0395, found 359.0381.

(*Z*)-2-(Benzo[*d*]oxazol-2-yl)-*N, N*-dimethyl-2-phenoxyethenamine (9e) (9i)

Yellow solid; mp 139-140 ºC; yield: 86.1%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.32-7.24 (m, 3H), 7.20 (s, 1H), 7.16 (td, *J* = 7.6, 1.2 Hz, 1H), 7.10 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 2H), 7.00-6.94 (m, 1H), 3.00 (d, *J* = 1.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.25, 158.05, 149.06, 135.08, 128.59, 122.81, 121.60, 120.74, 117.09, 113.95, 112.41, 108.47, 41.31. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{17}N_2O_2$ [$(M+H)^+$] 281.1290, found 281.1289.

(*Z*)-2-(5-Methoxybenzo[*d*]oxazol-2-yl)-*N, N*-dimethyl-2-phenoxyethenamine (9f)

Orange solid; mp 109-112 ºC; yield: 89.2%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37-7.26 (m, 3H), 7.19 (d, *J* = 8.8 Hz, 1H), 7.09-7.05 (m, 2H), 7.04 (d, *J* = 2.5 Hz, 1H), 7.02-6.96 (m, 1H), 6.70 (dd, *J* = 8.8, 2.6 Hz, 1H), 3.79 (s, 3H), 3.03 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.19, 159.10, 156.99, 144.72, 143.43, 136.08, 129.66, 121.81, 115.00, 113.50, 110.38, 109.50, 102.02, 55.91, 42.39. HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{19}N_2O_3$ [$(M+H)^+$] 311.1396, found 311.1397.

(*Z*)-2-(5-Fluorobenzo[*d*]oxazol-2-yl)-*N, N*-dimethyl-2-phenoxyethenamine (9g)

Light green solid; mp 131-133 ºC; yield: 81.9%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (dd, *J* = 20.9, 12.8 Hz, 3H), 7.17 (ddd, *J* = 11.1, 8.8, 3.3 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 7.01-6.95 (m, 1H), 6.83 – 6.76 (m, 1H), 3.04-3.00 (m, 6H); ^{13}C NMR (101 MHz, DMSO) δ = 160.40, 156.40, 154.16 (d, *J* = 25.5 Hz), 141.69, 131.91, 124.96, 117.17, 110.20, 108.41, 104.70 (d, *J* = 8.1 Hz), 99.99 (d, *J* = 26.0 Hz), 37.68. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{16}FN_2O_2$ [$(M+H)^+$] 299.1196, found 299.1194.

(*Z*)-2-(5-Chlorobenzo[*d*]oxazol-2-yl)-*N, N*-dimethyl-2-phenoxyethenamine (9h)

White solid; mp 125-127 ºC; yield: 74.0%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (d, *J* = 1.8 Hz, 1H), 7.37 (s, 1H), 7.29 (dd, *J* = 8.5, 7.5 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 1H), 7.06 (ddd, *J* = 8.7, 3.9, 1.5 Hz, 3H), 7.03

-6.97 (m, 1H), 3.05 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.72, 157.92, 147.69, 142.92, 135.83, 128.66, 128.18, 121.52, 120.89, 116.92, 113.88, 111.89, 108.99, 41.38. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{16}ClN_2O_2$ [$(M+H)^+$] 315.0900, found 315.0897.

(*Z*)-2-(Benzo[*d*]oxazol-2-yl)-*N, N*-dimethyl-2-phenoxyethenamine (9i) (9e)

Yellow solid; mp 138-140 ºC; yield: 91.1%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 (dd, *J* = 7.8, 0.5 Hz, 1H), 7.35-7.24 (m, 3H), 7.18 (s, 1H), 7.13 (ddd, *J* = 20.5, 7.7, 1.2 Hz, 2H), 7.06 (d, *J* = 8.7 Hz, 2H), 7.00 -6.94 (m, 1H), 3.00 (d, *J* = 0.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.26, 158.07, 149.10, 141.72, 134.99, 128.61, 122.80, 121.60, 120.74, 117.16, 113.97, 112.44, 108.48, 41.34. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{17}N_2O_2$ [$(M+H)^+$] 281.1290, found 281.1298.

(*Z*)-2-(Benzo[*d*]oxazol-2-yl)-2-(4-chlorophenoxy)-*N, N*-dimethylethenamine (9j)

Yellow solid; mp 127-129 ºC; yield: 80.9%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 = (dd, *J* = 7.8, 0.7 Hz, 1H), 7.31 (dd, *J* = 7.9, 0.6 Hz, 1H), 7.24-7.19 (m, 2H), 7.19-7.07 (m, 3H), 7.01-6.96 (m, 2H), 3.00 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.85, 157.76, 150.08, 142.66, 136.06, 129.59, 126.70, 123.95, 122.84, 118.30, 116.38, 113.47, 109.51, 42.42. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{16}ClN_2O_2$ [$(M+H)^+$] 315.0900, found 315.0891.

(*Z*)-2-(Benzo[*d*]oxazol-2-yl)-2-(2-bromophenoxy)-*N, N*-dimethylethenamine (9k)

Yellow solid; mp 142-144 ºC; yield: 84.3%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.24 (s, 1H), 7.16 (dqd, *J* = 19.9, 7.6, 1.1 Hz, 3H), 6.95 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.87 (td, *J* = 7.7, 1.4 Hz, 1H), 3.03 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.75, 154.52, 149.11, 141.67, 134.90, 132.56, 127.50, 122.87, 121.87, 121.66, 117.14, 113.46, 112.08, 109.80, 108.61, 41.37. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{16}BrN_2O_2$ [$(M+H)^+$] 359.0395, found 359.0386.

(*Z*)-2-(6-Bromobenzo[*d*]oxazol-2-yl)-2-(4-chlorophenoxy)-*N,N*-dimethylethenamine (9l)

Pale yellow solid; mp 162-165 ºC; yield: 80.3%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (d, *J* = 1.5 Hz, 1H), 7.31 (q, *J* = 8.5 Hz, 2H), 7.24-7.20 (m, 2H), 7.01-6.92 (m, 2H), 3.04 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.43, 157.61, 150.58, 141.92, 136.69, 129.65, 127.22, 126.87, 119.04, 116.30, 115.24, 112.99, 42.47. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{15}BrClN_2O_2$ [$(M+H)^+$] 393.0005, found 393.0004.

Characterization data of all target compounds, copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds. This material can be found via the "Supplementary".

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