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Skeletal Diverse Synthesis of N-Fused Polycyclic Heterocycles via the Sequence of Ugi-Type MCR and CuI-Catalyzed Coupling/Tandem Pictet–Spengler Reaction

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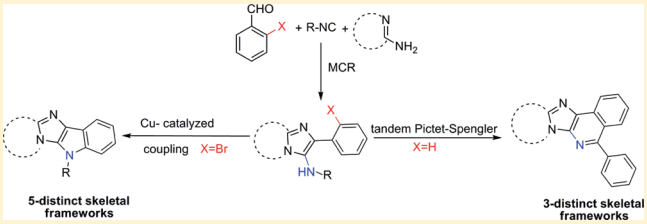
Supporting Information

ABSTRACT: Several diversity-oriented syntheses of N-fused polycyclic heterocycles have been demonstrated but most of them are based on point diversity within the same library and usually involve time-consuming sequential multistep syntheses, which also suffer from low yields and/or poor precursor scopes. We have developed a new strategy for the syntheses of skeletal diverse N-fused polycyclic compounds via an Ugi-type MCR followed by a CuI-catalyzed coupling reaction or tandem Pictet–Spengler reaction. This two-step sequence provides eight distinct skeleton of fused {6–5–5–6}, {5–5–5–6}, {6–5–6–6}, and {5–5–6–6} ring systems that have applications in medicinal chemistry and chemical genetics too.



INTRODUCTION

Diversity-oriented synthesis (DOS) with an emphasis on skeletal diversity has been developed for rapid access to natural product and druglike small molecules with complex and diverse molecular structures.[1] Pioneering work in skeletal DOS has been done by Schreiber and co-workers to establish a diverse collection of nitrogen-containing small molecules with application in drug discovery and chemical genetics.[2] Nitrogen-containing polycyclic molecules and analogues have attracted much attention due to their presence in biologically active natural products and pharmaceuticals. These *N*-fused polycycles displayed a wide range of biological activities (antifungal/antibacterial, antineoplastic, anticancer, antiplasmodial, DNA intercalators).[3] For example, columbamine **1**, an isoquinoline alkaloid, showed antiplasmodial, antiamoebic, and cytotoxic activities; cryptolepine **2** and quindoline **3** are potent antiplasmodial indole alkaloids (Figure 1).[4] On the other hand, the

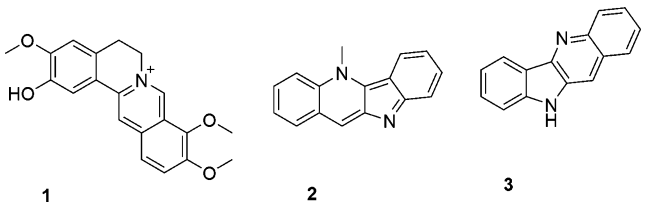


Figure 1. Some biologically active N-fused polycyclic heterocycles.

N-fused aromatic polycyclic systems having the ability to increase the DNA intercalation properties[5] and contain an untoward number of aromatic rings in the context of their ability to provide a quality medicinal chemistry leads.

Several natural products inspired diversity-oriented synthesis of N-fused polycyclic heterocycles have been demonstrated, but most of them are based on point diversity within the same library[6] and usually involve a time-consuming sequential multistep synthesis and also suffer from low yields and/or poor precursor scopes.[7]

Recently, isocyanide-based multicomponent reactions (IMCR) followed by other synthetic transformations emerged as a powerful tool for creating fused multicyclic skeletons.[8] As a part of our program to discover novel heterocycles as anti-infective agents[9] and encouraged by the skeletal diversity of N-rich polycyclic compounds, we report our efforts toward the synthesis of skeletal diverse N-fused polycyclic heterocycles through an Ugi-type MCR (Groebke–Blackburn–Bienayme reaction)[10] (Figure 2) coupled with Cu-catalyzed intramolecular

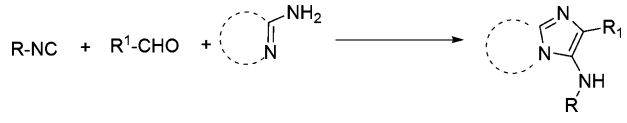


Figure 2. Groebke–Blackburn–Bienayme MCR.

C–N bond formation or in situ cyclization through the Pictet–Spengler reaction.

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We envisaged that substrates containing halogen functionalities such as product **5** can undergo CuI-catalyzed intramolecular cyclization for the synthesis of **4**, whereas polycyclic heterocycle **9** can be obtained by the tandem Pictet-Spengler reaction of **10** and aldehydes. IMCR products **5** and **10** can be obtained by the reaction of aldehyde, isocyanide and aromatic heterocyclic 2-aminoazines (Figure 3).

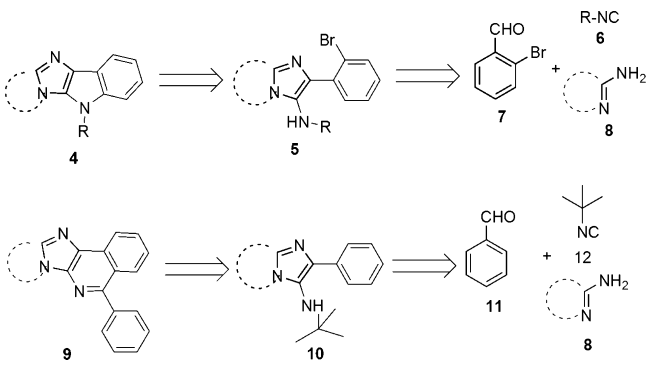


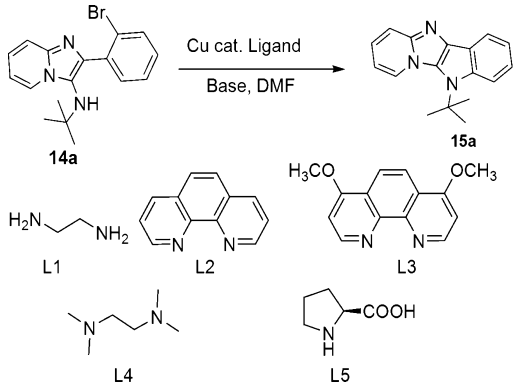
Figure 3. Retrosynthetic analysis.

RESULTS AND DISCUSSION

Initially, the syntheses of Ugi type products **14a−m** and **17a−g** (Tables 3 and 5) were achieved by the condensation of aromatic heterocyclic 2-aminoazines, aldehydes, and isocyanides in methanol catalyzed by PTSA (Scheme 1).[11]

Once these IMCR products were synthesized, a set of experiments were carried out using **14a** as the model substrate to optimize reaction conditions for the metal-catalyzed intramolecular cyclization reaction, including catalysts, bases, and solvents. CuI was the best catalyst among all the three copper catalysts tested as shown in Table 1. Subsequently, the effect of ligands was further investigated; 1,10-phenanthroline was found as the most efficient ligand to push the reaction forward. Cs_2CO_3 emerged as base of choice for the coupling reaction among the several bases used (Table 1). When loading of catalyst was decreased from 10 to 5 mol %, lowering of the yield from 72% to 50% (Table 1, entry 11) was observed. The effect of solvent was also investigated, and DMF was found to be the best solvent at 120 °C (Table 2). Further, the optimized conditions equally applied for the synthesis of a wide variety of N-fused polycyclic heterocycles **15a−m** starting from IMCRs **14a−m** (Table 3).Very good yields were observed for the

Table 1. Survey of the Reaction Condition for Cu-Catalyzed Coupling Reaction[a]



entry	catalyst	ligand	base	yield[b] (%)
1			Cs_2CO_3	0[c]
2	CuTC	L2	Cs_2CO_3	16
3	CuI	L1	Cs_2CO_3	45
4	CuBr	L2	Cs_2CO_3	22
5	CuI	L2	K_3PO_4	34
6	**CuI**	**L2**	**Cs_2CO_3**	**72**
7	CuI	L3	Cs_2CO_3	60
8	CuI	L4	Cs_2CO_3	32
9	CuI	L5	Cs_2CO_3	16
10	CuI	L2	K_2CO_3	51
11	CuI	L2	Cs_2CO_3	50[d]

[a]Reaction conditions: substrate **14a** (1 mmol), catalyst (10 mol %), ligand (10 mol %), base (2 mmol), solvent (2 mL) under nitrogen atmosphere, reaction temperature (120 °C), reaction time (2 h), [b]Isolated yield. [c]No addition of catalyst. [d]Loading of catalyst (5 mol %).

2-aminopyridine- and 2-aminopiperazine-based IMCRs **14a−f**, whereas moderate yield of product was obtained in the case of 2-aminopyrimidine- and 2-aminotrizole-based IMCRs **14g** and **14h** (Table 3).

In recent years, Domling et al. reported an Ugi reaction (IMCR) followed by a Pictet−Spengler reaction as a powerful tool for the synthesis of N-fused polycyclic heteocycles.[12] Therefore, our aim was shifted toward diversity generation by the use of Pictet−Spengler reaction. Removal of the *tert*-butyl group in IMCR by TFA[13] inspired us to use TFA for the efficient transformation through Pictet−Spengler reaction. In the first instance, substrate **17a** was subjected to 4-methoxybenzaldehyde using several acidic protocols (Table 4).

Scheme 1. Two Step Synthesis of *N*-Fused Polycyclic Heterocycles

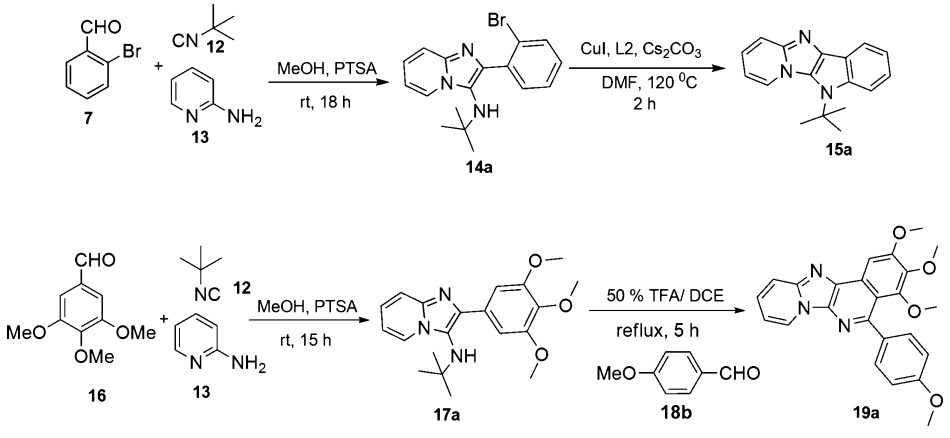


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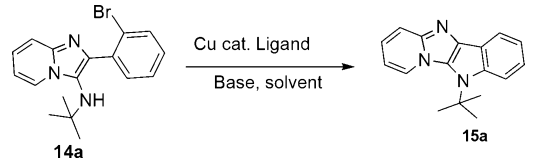
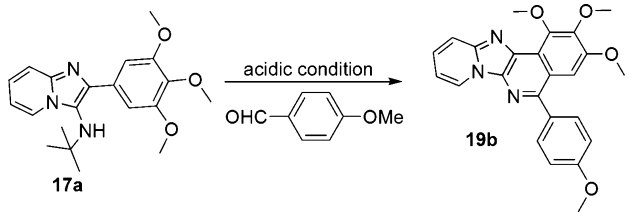
Table 2. Screening of Solvent for Coupling Reaction



entry	solvent	conversion (%)
1	DMSO	56
2	dioxane	63
3	DMF	72
4	NMP	52
5	toluene	38

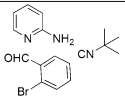
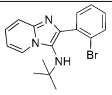
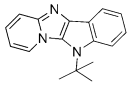
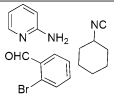
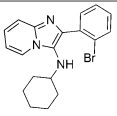
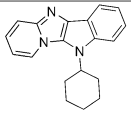
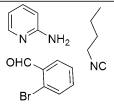
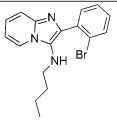
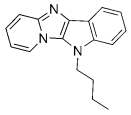
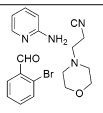
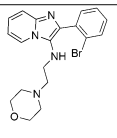
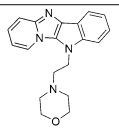
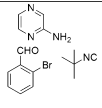
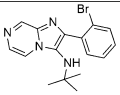
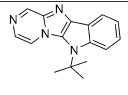
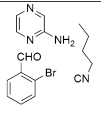
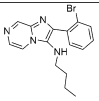
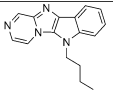
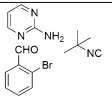
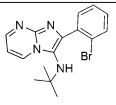
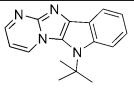
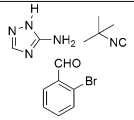
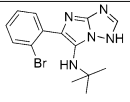
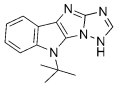
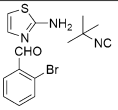
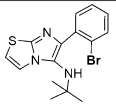
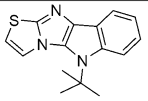
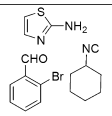
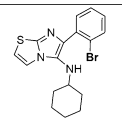
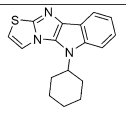
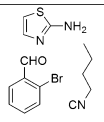
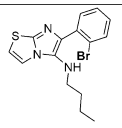
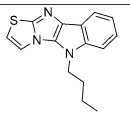
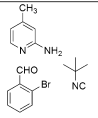
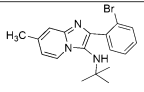
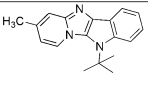
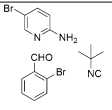
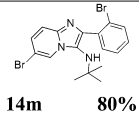
It has been found that 50% TFA in DCE at reflux was the optimal condition for the tandem Pictet–Spengler reaction. We next explored the efficacy of IMCRs **17a–g** (Table 5) to undergo π-cyclizations with a variety of aldehydes. The electron-rich trimethoxybenzaldehyde-derived products **17a–e** were found to be reactive in the subsequent Pictet–Spengler ring closure, and both the 4-chlorobenzaldehyde- and *p*-anisaldehyde-derived products **17f** and **17g** were observed not to afford the desired Pictet–Spengler products and instead led only to the loss of the *tert*-butyl group to afford **20a** and **20b**. An interesting feature of this unique tandem reaction involves de-*tert*-butylation, π-cyclization, and aromatization. To the best of our knowledge, there is no report available on this type of tandem Pictet–Spengler sequence.

Table 4. Optimization of Acidic Protocols for Pictet–Spengler Reaction



entry	solvent	TFA (%)	yields (%)
1	DCM	20	NR
2	DCM	50	30
3	DCE	20	26
4	DCE	50	71
5	THF	50	59

Table 3. Two-Step Synthesis of IMCR-Coupling Product[a]

Entry	Starting material	IMCR product (14), Yield% [b]	Coupling product (15), Yield% [b]
1		 **14a 93%**	 **15a 72%**
2		 **14b 89%**	 **15b 67%**
3		 **14c 91%**	 **15c 71%**
4		 **14d 65%**	 **15d 52%**
5		 **14e 87%**	 **15e 61%**
6		 **14f 82%**	 **15f 63%**
7		 **14g 75%**	 **15g 56%**
8		 **14h 62%**	 **15h 49%**
9		 **14i 85%**	 **15i 68%**
10		 **14j 79%**	 **15j 64%**
11		 **14k 87%**	 **15k 62%**
12		 **14l 86%**	 **15l 63%**
13		 **14m 80%**	**15m 59%**

[a]Reaction conditions: under nitrogen atmosphere, substrate **14** (1 mmol), CuI (10 mol %), L2 (10 mol %), Cs_2CO_3 (2 mmol), DMF (2 mL), 120 °C, 2–4 h. [b]Isolated yield.

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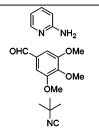
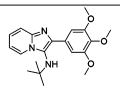
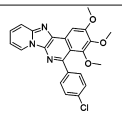
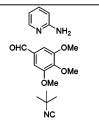
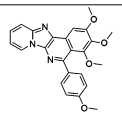
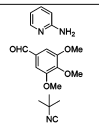
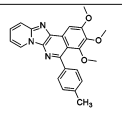
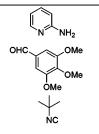
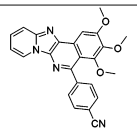
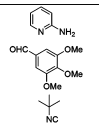
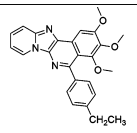
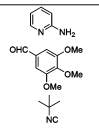
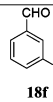
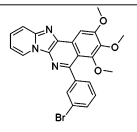
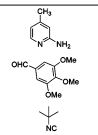
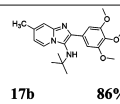
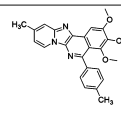
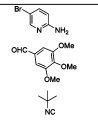
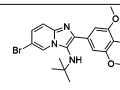
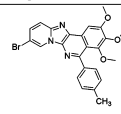
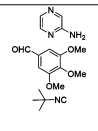
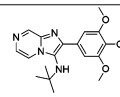
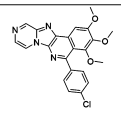
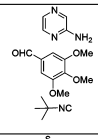
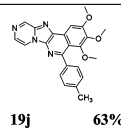
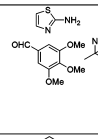
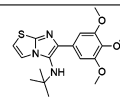
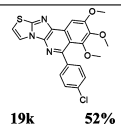
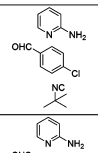
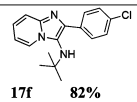
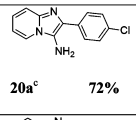
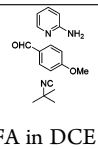
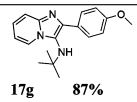
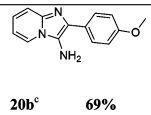
Table 5. Two-Step Synthesis of IMCR–PS Product[a]

Entry	Starting material	IMCR product (17), Yield%[b]	Aldehydes (18)	P-S product (19), Yield%[b]
1		 **17a** 91%	 **18a**	 **19a** 56%
2		**17a**	 **18b**	 **19b** 68%
3		**17a**	 **18c**	 **19c** 62%
4		**17a**	 **18d**	 **19d** 51%
5		**17a**	 **18e**	 **19e** 62%
6		**17a**	 **18f**	 **19f** 59%
7		 **17b** 86%	**18c**	 **19g** 56%
8		 **17c** 79%	**18c**	 **19h** 62%
9		 **17d** 86%	**18a**	 **19i** 60%
10		**17d**	**18c**	 **19j** 63%
11		 **17e** 79%	**18a**	 **19k** 52%
12		 **17f** 82%	**18b**	 **20a**[c] 72%
13		 **17g** 87%	**18b**	 **20b**[c] 69%

[a]Reaction conditions: substrate **1** (1 mmol), aromatic aldehyde (1.2 mmol), 50% TFA in DCE (5 mL), reflux, 5–6 h. [b]Isolated yield. [c]Only de-*tert*-butylated products **20a** and **20b** were observed; PS = Pictet–Spengler reaction.

CONCLUSION

In summary, we have developed a highly efficient approach for the synthesis of eight distinct skeletal frameworks of fused {6–5–5–6}, {5–5–5–6}, {6–5–6–6}, and {5–5–6–6} ring systems of N-rich polycyclic heterocycles via the IMCR-CuI catalyzed/tandem Pictet–Spengler reaction sequence. This synthetic approach has various prominent features such as less reaction steps, good yields and operational simplicity, ultimately leading to a diverse array of medicinally relevant N-fused heterocycles. Biological screening of synthesized compounds are currently under progress in our lab and will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures. All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with a 200, 300, and 400 MHz spectrometers for ^{1}H NMR and 50 and 75 MHz for ^{13}C NMR in deuterated solvents with TMS as internal reference (chemical shifts δ in ppm, coupling constant J in Hz). Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad singlet (br, s). Melting points were determined in open capillary tubes on an electrically heated block and are uncorrected. Mass spectra and HRMS were taken in the ESI positive-ion mode. The reaction progress was routinely monitored by thin-layer chromatography (TLC) on precoated silica gel plates. Column chromatography was performed over silica gel (230–400 flash). All compounds were characterized by TLC, ^{1}H NMR and ^{13}C NMR, MS, and HRMS.

General Procedure for the Synthesis of IMCR Products 14a–m and 17a–g. To the solution of the aromatic heteroarylamine (1 mmol) and aromatic benzaldehyde (1.2 mmol) in methanol (3 mL) was added isocyanide (1 mmol) through a microsyringe at room temperature, and then *p*-toluenesulfonic acid (20 mol %) was added. After stirring at room temperature for 15–18 h, the solvent was removed to obtain crude products on which purification by flash column chromatography on silica gel (eluent: hexane/EtOAc) afforded Ugi type product **14a–m** and **17a–g** in 62–93% yields.

General Procedure for the Synthesis of Coupling Products 15a–m. CuI (10 mol %), 1,10-phenanthroline (10 mol %), Ugi-type product (**14a–m**) (1 mmol), and DMF (2 mL) as a solvent were added to a dry Schlenk tube under nitrogen. The reaction mixture was stirred and heated at 120 °C for 2–4 h. After completion of the reaction as indicated by TLC, the resulting mixture was cooled to room temperature and filtered through a pad of Celite, and the Celite was rinsed with EtOAc. The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc) to afford the corresponding polycyclic products **15a–m** in 49–72% yields.

General Procedure for the Synthesis of Pictet–Spengler Products 19a–k. IMCR adduct (**17a–g**) (1 mmol) was dissolved in 50% TFA in DCE (5 mL), the corresponding aromatic aldehyde (1.2 mmol) was added, and the reaction mixture was stirred and refluxed for 5–6 h. The completion of tandem Pictet–Spengler cyclization was monitored by TLC. After completion, the reaction mixture was evaporated, and the residue so obtained was neutralized with saturated $NaHCO_3$. It was then extracted with EtOAc (20 mL),

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and the combined organic layer was washed with water (10 mL) and dried over sodium sulfate. EtOAC was evaporated to dryness under reduced pressure, and the crude obtained was purified by column chromatography (eluent: $CHCl_3$/MeOH) to afford cyclized products **19a–k** in 51–68% yield.

Characterization of Compounds. *Compound **14a**:* solid; yield 93%; mp = 127–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 6.9 Hz, 1H), 7.68–7.63 (m, 2H), 7.57 (d, J = 9.0 Hz, 1H), 7.43 (t, J = 6.9 Hz, 1H), 7.26–7.14 (m, 2H), 6.82 (t, J = 6.3 Hz, 1H), 3.22 (br s, 1H), 0.93(s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 139.0, 136.7, 133.0, 132.6, 129.4, 127.4, 124.6, 124.3, 123.6, 122.6, 117.3, 111.4, 55.7, 29.9 ppm; HRMS (ESI) calcd for $C_{17}H_{19}BrN_3$ $[M + H]^+$ 344.0762, found 344.0731.

*Compound **14b**:* semisolid; yield 89% ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 6.0 Hz, 1H), 7.67–7.55 (m, 3H), 7.43 (t, J = 6.9 Hz, 1H), 7.28–7.14 (m, 2H), 6.84 (t, J = 6.0 Hz, 1H), 2.68 (s, 1H), 1.68–1.47 (m, 5H), 1.06 (s, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 131.7, 131.5, 128.2, 126.3, 126.2, 124.8, 122.6, 122.5, 121.9, 121.8, 116.4, 110.4, 55.3, 32.7, 24.6, 23.4 ppm; HRMS (ESI) calcd for $C_{19}H_{21}BrN_3$ $[M + H]^+$ 370.0918, found 370.0906.

*Compound **14c**:* oil; yield 91%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.58–7.49 (m, 3H), 7.34–7.28 (m, 1H), 7.19–7.06 (m, 2H), 6.73 (s, 1H), 3.34 (br s, 1H), 2.76 (s, 2H), 1.39–1.16 (m, 4H), 0.71 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 136.0, 135.6, 132.6, 132.5, 129.3, 127.1, 123.4, 123.3, 122.5, 117.5, 111.5, 47.8, 32.4, 19.8, 13.6 ppm; HRMS (ESI) calcd for $C_{17}H_{19}BrN_3$ $[M + H]^+$ 344.0762, found 344.0790.

*Compound **14d**:* semisolid; yield 65%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 6.6 Hz, 1H), 7.68–7.56 (m, 3H), 7.42 (t, J = 7.2 Hz, 1H), 7.24–7.14 (m, 2H), 6.87 (t, J = 6.3 Hz, 1H), 3.57 (s, 4H), 2.91 (s, 2H), 2.38 (t, J = 5.4 Hz, 2H), 2.19 (s, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.3, 135.9, 135.1, 132.8,132.7, 129.5, 127.4, 123.8, 123.5, 122.7, 117.7, 111.9, 66.9, 57.5, 53.2, 44.3 ppm; HRMS (ESI) calcd for $C_{19}H_{22}BrN_4O$ $[M + H]^+$ 401.0977, found 401.0970.

*Compound **14e**:* semisolid; yield 87%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.86–8.83 (m, 1H), 8.53–8.51 (m, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.64 (d, J = 6.0 Hz, 1H), 7.49 (t, J = 6.6 Hz, 1H), 7.37–7.32 (m, 1H), 7.09–7.06 (m, 1H), 4.09 (br s, 1H), 0.87 (s, 9H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.6, 144.2, 140.1, 135.9, 133.2, 133.1, 132.7, 130.5, 127.9, 123.8, 123.2, 109.0, 55.5, 29.9 ppm; HRMS (ESI) calcd for $C_{16}H_{18}BrN_4$ $[M + H]^+$ 345.0715, found 345.0723.

*Compound **14f**:* semisolid; yield 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07–7.84 (m, 2H), 7.69–7.55 (m, 3H), 7.42–7.29 (m, 2H), 4.54 (br s, 1H), 2.88 (s, 2H), 1.33–1.19 (m, 4H), 0.76 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 137.7, 134.7, 134.1, 132.8, 132.6, 130.2, 127.5, 123.3, 47.3, 32.4, 19.8, 13.6 ppm; HRMS (ESI) calcd for $C_{16}H_{18}BrN_4$ $[M + H]^+$ 345.0714, found 345.0729.

*Compound **14g**:* solid; yield 75%; mp = 119–122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, J = 6.6 Hz, 1H), 8.62–8.54 (m, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.29–7.24 (m, 1H), 6.92–6.88 (m, 1H), 0.92 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 144.9, 140.4, 135.9, 133.3, 132.6, 131.3, 129.8, 127.6, 123.1, 122.4, 108.2,55.9, 29.9 ppm; HRMS (ESI) calcd for $C_{16}H_{18}BrN_4$ $[M + H]^+$ 345.0715, found 345.0718.

*Compound **14h**:* solid; yield 62%; mp = 170–173 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.82 (s, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 3.95 (br s, 1H), 0.96 (s, 9H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.3, 148.2, 133.9, 133.2, 131.6, 131.1, 128.0, 124.5, 123.0, 121.7, 54.4, 30.2 ppm; HRMS (ESI) calcd for $C_{14}H_{17}BrN_5$ $[M + H]^+$ 334.0667, found 334.0674.

*Compound **14i**:* solid; yield 85%; mp = 129–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (t, J = 8.1 Hz, 2H), 7.42–7.34 (m, 2H), 7.21 (d, J = 6.6 Hz, 1H), 6.75 (s, 1H), 0.92 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 139.4, 136.6, 132.9, 132.6, 129.1, 127.4, 126.8, 122.5, 117.9, 111.6, 55.3, 29.9 ppm; HRMS (ESI) calcd for $C_{15}H_{17}BrN_3S$ $[M + H]^+$ 350.0326, found 350.0342.

*Compound **14j**:* semisolid; yield 79%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 7.2 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.40 (t, J = 6.3 Hz, 2H), 7.25–7.20 (m, 1H), 6.80 (d, J = 4.5 Hz, 1H), 2.70 (s, 1H), 1.68–1.51 (m, 5H), 1.12–0.99 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 139.5, 136.5, 132.9, 132.7, 132.6, 129.2, 127.3, 121.7, 117.1, 111.9, 57.1, 33.7, 25.4, 24.5 ppm; HRMS (ESI) calcd for $C_{17}H_{19}BrN_3S$ $[M + H]^+$ 376.0483, found 376.0530.

*Compound **14k**:* oil; yield 87% ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 7.8 Hz, 1H), 7.42–7.28 (m, 4H), 6.79 (d, J = 4.2 Hz, 1H), 2.88 (t, J = 6.6 Hz, 2H), 1.51–1.41(m, 2H), 1.25–1.17 (m, 2H), 0.80 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 141.3, 139.5, 132.8, 132.7, 132.6, 129.2, 127.3, 123.1, 116.8, 112.1, 48.6, 32.2, 19.8, 13.7 ppm; HRMS (ESI) calcd for $C_{15}H_{17}BrN_3S$ $[M + H]^+$ 350.0327, found 350.0339.

*Compound **14l**:* solid; yield 86%; mp = 120–125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 6.9 Hz, 1H), 7.67 (t, J = 7.8 Hz, 2H), 7.42 (t, J = 7.2 Hz, 1H), 7.25–7.19 (m, 2H), 6.65 (d, J = 6.3 Hz, 1H), 3.18 (br, s, 1H), 2.39 (s, 3H), 0.93 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 137.0, 134.9, 133.0, 132.5, 129.2, 127.4, 124.1, 122.8, 122.7, 115.7, 114.0, 55.6, 29.9, 21.2 ppm; HRMS (ESI) calcd for $C_{18}H_{21}BrN_3$ $[M + H]^+$ 358.0918, found 358.0964.

*Compound **14m**:* solid; yield 80%; mp = 130–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.66 (d, J = 8.1 Hz, 2H), 7.55–7.39 (m, 2H), 7.33–7.23 (m, 2H), 0.95 (s, 9H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.6, 140.1, 136.4, 133.2, 133.0, 130.0, 128.1, 127.9, 125.2, 124.1, 122.9, 118.4, 107.0, 56.2, 30.3 ppm; HRMS (ESI) calcd for $C_{17}H_{18}Br_2N_3$ $[M + H]^+$ 421.9867, found 421.9904.

*Compound **15a**:* solid; yield 72%; mp = 125–128 °C; FT-IR (KBr) ν (cm^{-1}) 3409, 2932, 1632, 1220, 771; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J = 7.2 Hz, 1H), 8.15 (d, J = 6.9 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.33–7.26 (m, 2H), 0.7.18–7.12 (m, 1H), 6.87–6.83 (m, 1H), 1.97 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 142.4, 131.3, 123.8, 123.4, 121.6, 119.8, 119.4, 119.3, 118.7, 114.8, 111.0, 58.6, 32.5 ppm; HRMS (ESI) calcd for $C_{17}H_{18}N_3$ $[M + H]^+$ 264.1500, found 264.1490.

*Compound **15b**:* semisolid; yield 67% FT-IR (neat) ν (cm^{-1}) 3462, 3419, 2360, 2360, 1638, 1220, 771; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 6.90 Hz, 1H), 8.15 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 9.3 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.40 (t, J = 7.2 Hz, 1H),7.30–7.25 (m,1H), 7.15–7.10 (m,1H), 6.89 (t, J = 6.3 Hz, 1H), 4.67–4.56 (m, 1H), 2.16–2.07 (m, 6H), 1.95–1.90 (m, 1H) 1.63–1.38 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 140.8, 131.9, 130.0, 123.2, 122.6, 121.4, 119.7, 119.6, 118.7, 117.9, 111.2, 111.0, 55.9, 33.5, 26.2, 25.4 ppm; HRMS (ESI) calcd for $C_{19}H_{20}N_3$ $[M + H]^+$ 290.1657, found 290.1654.

*Compound **15c**:* semisolid; yield 71%; FT-IR (neat) ν (cm^{-1}) 3418, 2929, 1634, 1220, 771; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 6.6 Hz, 1H), 8.10 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 9.3 Hz, 1H), 7.40–7.32 (m, 2H), 7.25 (d, J = 6.6 Hz, 1H), 7.13 (m, 1H), 6.86 (t, J = 6.6 Hz, 1H), 4.44 (t, J = 6.9 Hz, 2H), 1.87–1.78 (m, 2H), 1.42–1.30 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 128.6, 127.9, 122.6, 121.7, 120.7, 119.0, 118.8, 116.8, 116.1, 111.0, 108.9, 43.4, 32.1, 19.2, 12.8 ppm; HRMS (ESI) calcd for $C_{17}H_{18}N_3$ $[M + H]^+$ 264.1500, found 264.1501.

*Compound **15d**:* semisolid; yield 52%; FT-IR (neat) ν (cm^{-1}) 3426, 2366, 1638, 1220,772; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41–8.32 (m, 1H), 8.03 (d, J = 7.2 Hz, 2H), 7.75 (d, J = 9.0 Hz, 1H), 7.49–7.41 (m, 2H), 7.34–7.32 (m, 1H), 6.97–6.93 (m, 1H), 3.83–3.80 (m, 4H), 3.19 (s, 2H), 2.75–2.72 (m, 2H), 2.69–2.62 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 141.0, 135.9, 134.3, 133.8, 128.6, 127.4, 127.1, 126.4, 124.3, 122.5, 117.1, 111.9, 66.7, 58.2, 53.6, 43.9 ppm; HRMS (ESI) calcd for $C_{19}H_{21}N_4O_1$ $[M + H]^+$ 321.1715, found 321.1730.

*Compound **15e**:* semisolid; yield 61%; FT-IR (KBr) ν (cm^{-1}) 3419, 2364, 1634, 770; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.43 (d, J = 4.8 Hz, 1H), 8.20 (d, J = 7.2 Hz, 1H), 7.95–7.87 (m, 2H), 7.40–7.28 (m, 2H), 1.99 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 143.5, 141.2, 136.0, 131.1, 128.0, 125.1, 120.4, 120.3, 118.6, 116.2, 114.8, 58.8, 32.4; HRMS (ESI) calcd for $C_{16}H_{17}N_4$ $[M + H]^+$ 265.1453, found 265.1452.

*Compound **15f**:* solid; yield 63%; mp = 120–123 °C; FT-IR (KBr) ν (cm^{-1}) 3418, 1634, 1220, 771; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.15 (d, J = 7.5 Hz, 1H), 8.06 (d, J = 3.6 Hz, 1H), 7.86

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(d, J = 3.9 Hz, 1H), 7.46−7.39 (m, 2H), 7.33−7.28 (m, 1H), 4.43 (t, J = 6.9 Hz, 2H), 1.90−1.81 (m, 2H), 1.41−1.32 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 142.3, 139.6, 133.3, 129.8, 127.6, 124.8, 120.2, 120.0, 117.1, 114.0, 109.8, 44.1, 32.7, 20.0, 13.6 ppm; HRMS (ESI) calcd for $C_{16}H_{17}N_4$ $[M + H]^+$ 265.1453, found 265.1447.

Compound ***15g:*** semisolid; yield 56%; FT-IR (neat) ν (cm^{-1}) 3470, 2364, 1631, 1219, 771; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55−8.48 (m, 2H), 7.99 (d, J = 7.2, 2H), 7.46−7.28 (m, 3H), 1.04 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 148.4, 134.9, 133.6, 130.2, 127.5, 127.4, 127.3, 126.9, 124.6, 106.9, 55.7, 29.4 ppm; HRMS (ESI) calcd for $C_{16}H_{17}N_4$ $[M + H]^+$ 265.1453, found 265.1456.

Compound ***15h:*** solid; yield 49% mp =152−155 °Cy FT-IR (KBr) ν (cm^{-1}) 3415, 2364, 1632, 1218, 771; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.3 (br, s, 1H), 7.94 (s, 1H), 7.89 (d, J = 7.5 Hz, 1H), 7.65−7.62 (m, 1H), 7.23−7.14 (m, 2H), 1.92 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 157.5, 140.7, 129.0, 126.6, 124.7, 122.2, 120.8, 120.7, 119.9, 63.2, 35.7 ppm; HRMS (ESI) calcd for $C_{14}H_{16}N_5$ $[M + H]^+$ 254.1405, found 254.1412.

Compound ***15i:*** semisolid; yield 68%; FT-IR (neat) ν (cm^{-1}) 3421, 2338, 1629, 1219, 772; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99−7.96 (m, 1H), 7.80−7.77 (m, 2H), 7.25−7.20 (m, 2H), 6.80 (d, J = 4.8 Hz, 1H), 1.92 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 137.8, 133.4, 129.7, 120.9, 118.8, 118.5, 117.5, 113.5, 108.3, 56.9, 30.5 ppm; HRMS (ESI) calcd for $C_{15}H_{16}N_3S_1$ $[M + H]^+$ 270.1064, found 270.1073.

Compound ***15j:*** semisolid; yield 64%; FT-IR (neat) ν (cm^{-1}) 3416, 2367, 1637, 1220, 771; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (dd, J = 23.7, 7.5 Hz, 1H), 7.76 (d, J = 4.8 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.32−7.21 (m, 2H), 6.84 (d, J = 4.8 Hz, 1H), 4.51−4.43 (m, 1H), 2.31−1.80 (m, 7H), 1.64−1.35 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 137.0, 132.0, 128.6, 120.7, 118.7, 117.3, 117.3, 116.2, 109.4, 109.1, 53.9, 32.7, 25.0, 24.6 ppm; HRMS (ESI) calcd for $C_{17}H_{18}N_3S_1$ $[M + H]^+$ 296.1221, found 296.1203.

Compound ***15k:*** semisolid; yield 62%; FT-IR (Neat) ν (cm^{-1}) 3442, 2359, 1612, 1119, 773; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95−7.92 (m, 1H), 7.42 (d, J = 4.5 Hz, 1H), 7.30−7.18 (m, 3H), 6.71 (d, J = 4.5 Hz,1H), 4.17 (t, J = 6.9 Hz, 2H), 1.79−1.69 (m, 2H), 1.33−1.21 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 138.2, 131.5, 130.3, 121.5, 119.6, 118.4, 118.2, 115.3, 110.7, 109.7, 44.3, 32.4, 20.2, 13.7 ppm; HRMS (ESI) calcd for $C_{15}H_{16}N_3S_1$ $[M + H]^+$ 270.1064, found 270.1071.

Compound ***15l:*** solid; yield 63%; mp =150−152 °C; FT-IR (KBr) ν (cm^{-1}) 3404, 3221, 1641, 1217, 768; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 6.9 Hz, 1H), 7.92 (d, J = 6.9 Hz, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.34 (d, J = 9.0 Hz, 1H), 6.63 (d, J = 6.9 Hz, 1H), 2.40 (s, 3H), 1.04 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 138.8, 135.2, 135.1, 132.7, 128.2, 128.1, 127.2, 122.7, 115.6, 114.0, 56.3, 30.3, 21.2 ppm; HRMS (ESI). for $C_{18}H_{20}N_3$ $[M + H]^+$ 278.1657, found 278.1664.

Compound ***15m:*** solid; yield 59%; mp = 170−173 °C; FT-IR (KBr) ν (cm^{-1}): 2871, 1217, 760; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.89 (d, J = 7.2 Hz, 2H), 7.46−7.42 (m, 2H), 7.36−7.31 (m, 1H), 7.21−7.17 (m, 1H), 1.05 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 134.8, 128.3, 128.1, 127.6, 127.3, 123.8, 123.7, 106.2, 118.0, 56.5, 30.3 ppm; HRMS (ESI) calcd for $C_{17}H_{17}BrN_3$ $[M + H]^+$ 342.0606, found 342.0615.

Compound ***17a:*** semisolid; yield 91%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 6.3 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.25 (s, 2H), 7.12 (t, J = 6.9 Hz, 1H), 6.76 (t, J = 6.6 Hz, 1H), 3.90 (s, 6H), 3.85 (s, 3H), 1.05 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 141.4, 138.5, 137.4, 130.2, 124.4, 123.3, 123.2, 116.7, 111.5, 105.3, 60.8, 56.2, 56.1, 30.4 ppm; HRMS (ESI) calcd for $C_{20}H_{26}N_3O_3$ $[M + H]^+$ 356.1974, found 356.1992.

Compound ***17b:*** semisolid; yield 86% ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 6.9 Hz, 1H), 7.26 (d, J = 4.5 Hz, 2H), 6.64−6.60 (m, 2H), 3.94 (s, 6H), 3.89 (s, 3H), 2.39 (s, 3H), 1.09 (s, 9H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 153.0, 141.8, 137.7, 135.9, 122.7, 122.6, 115.1, 114.5, 105.5, 103.9, 60.9, 56.3, 56.2, 30.5, 21.2 ppm; HRMS (ESI) calcd for $C_{21}H_{28}N_3O_3$ $[M + H]^+$ 370.2130, found 370.2136.

Compound ***17c:*** solid; yield 79%; mp = 215−218 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.25 (s, 2H), 7.19−7.12 (m, 2H), 3.89 (s, 3H), 3.79 (s, 6H), 1.06 (s, 9H) ppm; ^{13}C NMR (75 MHz, CDCl3) δ 153.2, 142.2, 140.2, 139.3, 135.3, 134.0, 128.8, 125.7, 105.2, 60.8, 56.3, 56.1, 30.6 ppm; HRMS (ESI) calcd for $C_{20}H_{25}BrN_3O_3$ $[M + H]^+$ 434.1079, found 434.1099.

Compound ***17d:*** solid; yield 86%; mp = 140−143 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (s,1H), 8.14 (d, J = 3.3 Hz, 1H), 7.90 (d, J = 4.5 Hz, 1H), 7.29 (s, 2H), 3.97 (s, 6H), 3.92 (s, 3H), 1.12 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2,143.1, 141.9, 138.2, 137.0, 129.5, 129.0, 124.6, 116.1, 105.5, 61.0, 56.9, 56.3, 30.5 ppm; HRMS (ESI) calcd for $C_{19}H_{25}N_4O_3$ $[M + H]^+$ 357.1926, found 357.1976.

Compound ***17e:*** semisolid; yield 79% ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 4.5 Hz, 1H), 7.29 (s, 2H), 6.75 (d, J = 4.5 Hz, 1H), 3.92 (s, 6H), 3.88 (s, 3H),1.13 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 145.4, 139.6, 137.0, 130.5, 125.0, 117.8, 111.7, 104.4, 60.9, 56.1, 55.7, 30.4 ppm; HRMS (ESI) calcd for $C_{18}H_{24}N_3O_3S$ $[M + H]^+$ 362.1538, found 362.1599.

Compound ***17f:*** solid; yield 82%; mp = 142−145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 6.9 Hz, 1H), 7.91 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 9 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.15−7.09 (m, 1H), 6.77−6.72 (m, 1H), 1.02 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 141.4, 138.5, 137.6, 133.7, 131.6, 130.2, 124.4, 123.3, 116.7, 111.5, 106.6, 105.4, 52.8, 30.4 ppm; HRMS (ESI) calcd for $C_{17}H_{19}ClN_3$ $[M + H]^+$ 300.1268, found 300.1284.

Compound ***17g:*** solid; yield 87%; mp = 130−133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 6.9 Hz, 1H), 7.86 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 9.0 Hz, 1H), 7.11−7.06 (m, 1H), 6.96 (d, J = 8.7 Hz, 2H), 6.72 (t, J = 6.6 Hz, 1H), 3.82 (s, 3H), 1.02 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 141.6, 138.9, 129.3, 127.3, 124.1, 123.4, 122.9, 116.8, 113.6, 111.3, 56.3, 55.2, 30.3 ppm; HRMS (ESI) calcd for $C_{18}H_{22}N_3O$ $[M + H]^+$ 296.1763, found 296.1774.

Compound ***19a:*** solid; yield 56% mp = 170−173 °C; FT-IR (KBr) ν (cm^{-1}): 3423, 2364, 1635, 1219, 839, 771; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (d, J = 5.7 Hz, 1H), 8.69 (s, 1H), 8.34 (br s, 1H), 8.02 (br s, 1H), 7.49 (s, 5H), 4.28 (s, 3H), 3.98 (s, 3H), 3.42 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 154.5, 150.5, 143.3, 140.0, 138.3, 134.4, 133.2, 131.5, 129.1, 126.6, 124.2, 123.4, 121.1, 117.1, 115.3, 113.2, 113.1, 100.1, 60.4, 60.3, 56.8 ppm; HRMS (ESI) calcd for $C_{23}H_{19}Cl_1N_3O_3$ $[M + H]^+$ 420.1114, found 420.1103.

Compound ***19b:*** solid; yield 68%; mp = 167−170 °C; FT-IR (KBr) ν (cm^{-1}) 3487, 2361, 1631, 771; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.02 (s,1H), 7.84 (br s, 1H), 7.54 (s, 3H), 7.02 (s, 3H), 4.18 (s, 3H), 3.98 (s, 3H), 3.93 (s, 3H), 3.39 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 157.0, 152.4, 151.6, 146.0, 142.5, 140.8, 139.2, 136.2, 130.2, 129.6, 128.3, 124.4, 117.4, 117.2, 117.1, 114.0, 112.6, 111.7, 98.4, 61.2, 61.0, 56.5, 55.3 ppm; HRMS (ESI) calcd for $C_{24}H_{22}N_3O_4$ $[M + H]^+$ 416.1610, found 416.1619.

Compound ***19c:*** semisolid; yield 62% FT-IR (neat) ν (cm^{-1}) 3438, 1635, 1472 751; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (d, J = 6.8 Hz, 1H), 7.91 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 7.6 Hz, 2H), 7.14 (t, J = 6.8 Hz, 2H), 4.10 (s, 3H), 3.83 (s, 3H), 3.27 (s, 3H), 2.42 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 152.4, 151.6, 146.4, 142.3, 140.9, 136.8, 134.7, 130.9, 130.7, 129.1,128.7, 128.5, 127.8, 124.4, 117.3, 117.0, 111.3, 98.1, 61.1, 61.0, 56.4, 21.3 ppm; HRMS (ESI) calcd for $C_{24}H_{22}N_3O_3$ $[M + H]^+$ 400.1661, found 400.1660.

Compound ***19d:*** semisolid; yield 51%; FT-IR (neat) ν (cm^{-1}) 3480, 2935, 2340, 1216, 762 ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 6.6 Hz, 1H), 7.96 (d, J = 7.8 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 9.0 Hz, 1H), 7.36 (d, J = 6.9 Hz, 1H), 7.04−6.96 (m, 2H), 3.94 (s, 3H), 3.85 (s, 6H) ppm, ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 152.9, 140.7, 132.9, 128.5, 126.5, 123.7, 119.6, 118.8, 117.9, 114.2, 113.4, 105.9, 61.3, 56.5 ppm; HRMS (ESI) calcd for $C_{24}H_{19}N_4O_3$ $[M + H]^+$ 411.1457, found 411.1465.

Compound ***19e:*** solid; yield 62%; mp = 150−158 °C; FT-IR (KBr) ν (cm^{-1}) 3442, 2904, 1214, 762 ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (d, J = 6.9 Hz, 1H), 8.02 (s, 1H), 7.85 (d, J = 9.3 Hz, 1H), 7.52

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(d, J = 8.1 Hz, 3H), 7.32 (d, J = 7.8 Hz, 2H), 6.99 (t, J = 6.9 Hz, 1H), 4.17 (s, 3H), 3.96 (s, 3H), 3.37 (s, 3H), 2.81 (q, J = 7.5 Hz, 2H), 1.36 (t, J = 3.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 152.6, 151.7, 146.4, 143.2, 142.4, 141.2, 134.8, 130.8, 128.8, 128.5, 126.6, 124.4, 117.4, 117.1, 111.3, 106.3, 98.1, 61.1, 61.0, 56.4, 28.8, 15.7 ppm; HRMS (ESI) calcd for $C_{25}H_{24}N_3O_3$ $[M + H]^+$ 414.1817, found 414.1849.

Compound ***19f:*** semisolid; yield 59% FT-IR (neat) ν (cm^{-1}) 3415, 2943, 2314, 1607, 1126, 769,^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (d, J = 6.9 Hz, 1H), 8.0 (s, 1H), 7.86 (d, J = 9.0 Hz, 1H), 7.75 (s, 1H), 7.60−7.49 (m, 4H), 7.08−6.99 (m, 1H), 4.18 (s, 3H), 3.97 (s, 3H), 3.46 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 151.6, 146.6, 146.0, 142.8, 132.0, 130.5, 130.3, 129.0, 127.9, 124.8, 121.5, 117.6, 112.3, 98.6, 61.5, 61.2, 56.9 ppm; HRMS (ESI) calcd for $C_{23}H_{19}BrN_3O_3$ $[M + H]^+$ 464.0610, found 464.0622.

Compound ***19g:*** solid; yield 56%; mp = 140−144 °C; FT-IR (KBr) ν (cm^{-1}) 3480, 2960, 2343, 1607, 1120, 760,^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (d, J = 6.9 Hz, 1H), 8.25 (s, 2H), 7.46 (d, J = 7.8 Hz, 2H), 7.32−7.19 (m, 3H), 4.21 (s, 3H), 3.97 (s, 3H), 3.40 (s, 3H), 2.68(s, 3H), 2.49 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 156.2, 151.7, 148.0, 143.9, 141.8, 139.8,137.7, 132.6, 128.5, 127.9, 124.4, 123.9, 121.8, 118.4, 118.1, 113.0, 99.5, 61.2, 56.8, 22.3, 21.3 ppm; HRMS (ESI) calcd for $C_{25}H_{24}N_3O_3$ $[M + H]^+$ 414.1817, found 414.1797.

Compound ***19h:*** solid; yield 62%; mp = 125−128 °C; FT-IR (KBr) ν (cm^{-1}) 3480, 2935, 1216, 928, 762, 670; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.97 (s, 1H), 7.71−7.67 (m, 1H), 7.53−7.46 (m, 3H), 7.29 (s, 2H), 4.18 (s, 3H), 3.96 (s, 3H), 3.40 (s, 3H), 2.49 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 153.7, 152.1, 145.0, 142.8, 141.2, 137.3, 134.8, 132.4, 131.6, 128.9, 128.2, 124.9, 118.5, 117.5, 106.0, 98.3, 61.5, 61.4, 56.8, 21.7 ppm; HRMS (ESI) calcd for $C_{24}H_{21}BrN_3O_3$ $[M + H]^+$ 478.0766, found 478.0800.

Compound ***19i:*** solid; yield 60%; mp = 210−213 °C; FT-IR (KBr) ν (cm^{-1}) 3415, 2933, 2360, 1607, 1126, 769; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1H), 8.97−8.96 (m, 1H), 8.12 (d, J = 4 Hz, 1H), 7.99 (s, 1H), 7.54 (s, 4H), 4.13 (s, 3H), 3.85 (s, 3H), 3.33 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 154.0, 151.7, 144.7, 143.0, 141.8, 140.5, 133.9, 133.6, 132.0, 130.0, 129.0, 128.5, 127.4, 117.2, 116.7, 98.4, 61.2, 61.0, 56.5 ppm; HRMS (ESI) calcd for $C_{22}H_{18}Cl_1N_4O_3$ $[M + H]^+$ 421.1067, found 421.1044.

Compound ***19j:*** semisolid; yield 63%; FT-IR (neat) ν (cm^{-1}) 3439, 2923, 2363, 1636, 771; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 (s, 1H), 8.94 (d, J = 4.4 Hz, 1H), 8.10 (d, J = 4.4 Hz, 1H), 7.97 (s, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 4.13 (s, 3H), 3.83 (s, 3H), 3.29 (s, 3H), 2.43 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 155.7, 152.1, 144.6, 143.0, 140.6, 140.3, 139.2, 137.3, 134.0, 131.8, 129.1, 128.4, 128.3, 127.9, 117.5, 116.8, 114.0, 98.4, 61.2, 61.1, 56.5, 21.3 ppm; HRMS (ESI) calcd for $C_{23}H_{21}N_4O_3$ $[M + H]^+$ 401.1613, found 401.1595.

Compound ***19k:*** solid; yield 52%; mp = 160−163 °C; FT-IR (KBr) ν (cm^{-1}) 2362, 1262, 1098,1028, 805; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (d, J = 4.4 Hz, 1H), 7.73 (s, 1H), 7.48 (s, 4H), 7.45 (d, J = 4.4 Hz, 1H), 4.07 (s, 3H), 3.80 (s, 3H), 3.29 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 153.1, 152.2, 151.0, 142.6, 141.4, 134.9, 133.6, 130.0, 127.4, 126.8, 117.9, 116.5, 114.4, 97.6, 61.2, 60.9, 56.5 ppm; HRMS (ESI) calcd for $C_{21}H_{17}ClN_3O_3S_1$ $[M + H]^+$ 426.0679, found 426.066.

Compound ***20a:*** solid; yield 72%; mp = 110−113 °C; FT-IR (KBr) ν (cm^{-1}) 3466, 2363, 1635, 1220, 771; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.29 (d, J = 6.9 Hz, 1H), 7.96 (d, J = 8.7 Hz, 2H), 7.72 (d, J = 9.0 Hz, 1H), 7.61 (d, J = 8.7 Hz, 2H), 7.47−7.42 (m, 1H), 7.11 (t, J = 6.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.5, 157.1, 142.9, 133.3, 132.0, 129.3, 128.7, 126.7, 124.4, 117.5, 113.5 ppm; HRMS (ESI) calcd for $C_{13}H_{11}Cl_1N_3$ $[M + H]^+$ 244.0641, found 244.0640.

Compound ***20b:*** solid; yield 69%; mp = 122−125 °C; FT-IR (KBr) ν (cm^{-1}) 3449, 1634, 1219, 771; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (d, J = 6.6 Hz, 1H), 7.90 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 9.0 Hz, 1H), 7.39 (t, J = 6.9 Hz, 1H), 7.09−6.99 (m, 3H), 3.82 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.8, 142.7, 128.4, 126.1, 125.7, 124.1, 117.8, 117.2, 114.9, 114.6, 113.0, 55.6 ppm; HRMS (ESI) calcd for $C_{14}H_{14}N_3O$ $[M + H]^+$ 240.1137, found 240.1142.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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