Research Article

Flow and Microwave Induced Pellizzari Reactions: Synthesis of Heterocyclic Analogues of the Benzoxazepine Antipsychotic Agents Loxapine and JL-13

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An expeditious route to fused triazolo-pyrido benzoxazepines has been developed using flow and microwave-mediated cyclization chemistry. A range of substituted aryl hydrazides are coupled with a core chloroimine in good to excellent yield via a Pellizzari type process, producing 1,2,4-triazolo-pyrido [2,3-*b*] [1,5] benzoxazepines with structural similarity to known antipsychotic agents. Modifications allow for strategically functionalized derivatives, and installation of a fluoro group for use in PET imaging is also demonstrated. Given the affinity of the tricyclic core for 5-HT and dopamine receptors, the derivatives are expected to find utility in CNS research.

1. Introduction

Heterocyclic derivatives of the benzodiazepine and benzoxazepine class are of considerable interest in medicinal chemistry due to their pharmacologic and metabolic profiles [1, 2]. Prominent examples include the anxiolytic Alprazolam (Xanax®), Loxapine, and the atypical antipsychotic JL13, which has been investigated as a next-generation clozapine analogue [3–5]. One of the pharmacologic targets of the agents is the 5-HT_{2a} receptor, and a number of heterocyclic analogues demonstrate high affinity including Asenapine which despite its altered geometry compares favorably to traditional agents Loxapine and Clozapine [6] (see Scheme 1). Given promising preclinical data reported for JL13 [7–9], we elected to study the potential of additional heterocyclic variants which might be readily accessible using efficient coupling strategies and which also highlights the benefits of green chemistry approaches [10, 11]. Given the functional flexibility of the triazole group and its presence in a number of

pharmacologically active molecules [12], we sought to investigate use of the Pellizzari method [13], which relies on one pot coupling, and closure of imino chlorides with substituted hydrazides.

2. Results and Discussion

For initial studies we designed a series of hybrid triazole-benzoxazepine mimics of Loxapine and JL13, investigating the benefit of microwave and flow-mediated Pellizzari reactions as green approaches to these classes. A chloropyridyl amide substrate **1** was firstly prepared by condensation of 2-chloro nicotinoyl chloride with 2-amino phenol (DIPEA, 94%). This was subjected to microwave accelerated base-mediated intramolecular closure to form **2** (Scheme 2) with KOtBu (90%) preferable to both NaOH (72%) and NaH (59%) with a 5 min irradiation. The cyclic amide was converted to the corresponding chloroimine, allowing us to probe the key

SCHEME 1

TABLE 1: Intramolecular cyclization to form triazolo benzoxepines **3** (% isolated yield).

Entry	3	Ar	Thermal ^a	MW ^b	Flow ^c
1	3a	Ph	38	54	57
2	3b	2-Cl-C ₆ H ₄	48	86	78
3	3c	4-Cl-C ₆ H ₄	66	96	84
4	3d	2-OH-C ₆ H ₄	29	89	>99
5	3e	4-OH-C ₆ H ₄	41	67	72
6	3f	3-OMe-C ₆ H ₄	28	92	82
7	3g	3-pyridyl	57	84	98
8	3h	2-F-C ₆ H ₄	25	88	>99
9	3i	3-F-C ₆ H ₄	32	83	85
10	3j	4-Me-C ₆ H ₄	39	98	88
11	3k	3-NO ₂ -C ₆ H ₄	17	81	85
12	3l	3-Cl-C ₆ H ₄	44	80	—

^a*n*-BuOH, Δ, 118°C, 6 h; ^b300 W, 200°C, *n*-BuOH 15 min. ^cBoth pumps of the reactor were set to flow at equal rates (2 μl/min) at 190°C with a solution of 5-chlorobenzo[b]pyrido[3,2-*f*][1,4]oxazepine (0.04 M) and hydrazide (0.04 M) in *n*-BuOH with residence time of 2.5 min. Experiments represent *n* > 3.

triazole forming reaction to produce **3** (All new compounds were fully characterized by appropriate spectroscopic and analytical techniques.). A range of aryl hydrazide substrates were probed under thermal, microwave, and flow conditions at 100 mg scale and the results are summarized in Table 1.

Though moderate conversion was observed within 6 h of conventional thermolysis, the MW methods allowed very high yields of product within 15 mins with *n*-butanol being the most effective solvent. Essentially comparable, flow-mediated reactions (conducted using a Chemtrix Labtrix S1 system equipped with T-mixer) in some cases produced even higher yields, a presumed consequence of improved mixing interactions [14].

Given literature reports citing the importance of both basic amino functionality and a hydrophobic substituent (e.g., chloroaryl group) for optimal receptor binding [15, 16], a more elaborate substrate **5** was also prepared from hydrazide **4** (readily available from *m*-chloro-*o*-toluic acid), leading to the target compound in 87% yield (see Scheme 3). Given

the impressive results with the MW Pellizzari reaction, a second family of analogues were prepared which contain the chloroaryl functionality on the parent tricyclic ring system. Amide **6** (prepared from 2-chloro nicotinoyl chloride and 2-amino-4-chloro phenol) was subjected to base induced oxepane formation and subsequent chlorination to give **7** in good yield (Scheme 4). Microwave induced Pellizzari reactions were conducted with various hydrazides to give substituted analogues **8**.

A range of decorated analogues **9–16** were produced in good to excellent yield (see Scheme 6), which, coupled with those depicted in Table 1, will allow insightful structure-activity studies to be performed with binding assays against key receptors (5-HT_{2a}, 5-HT_{2c}, D₁, D₂, and D_{4.2} being of importance, with the 5-HT_{2a}/D₂ ratio especially significant) [17]. In a preliminary assay, compound **5** showed a *K_i* of 16 μM against 5-HT_{2a}, which bodes well for in depth assays [18]. Finally, and with a potential view to studying biodistribution of these ligands via *in vivo* imaging methods, proof

SCHEME 2: MW and flow based synthesis of triazolo-pyrido-benzoxazepines.

SCHEME 3

SCHEME 4: Modification of core for MW Pellizzari route to chlorinated series.

SCHEME 5: MW induced fluorodenitration.

of principal was demonstrated for installation of a fluoro group via nucleophilic displacement. Following extensive optimization of parameters (temp, time, and stoichiometry), nitroarene **17** was subjected to MW induced fluorodenitration to give **18** in good yield within 15 mins at 140°C using 2 equivalents of TBAF in DMSO (Scheme 5) [19]. Given the half-life of its γ emitting sister ^{18}F isotope (~ 120 mins) this rapid transformation is compatible with late stage labeling for PET imaging.

3. Conclusions

Both MW and flow based Pellizzari reactions were effective and efficient for the production of new classes of substituted triazolo-pyrido fused benzoxazepines. The route provides access to compounds which may be useful probes of the 5-HT and dopamine receptors, based on similarity to known antipsychotic agents. A specimen compound shows measurable affinity for one of the receptor subtypes and

derivatization of the core via nucleophilic fluorination provides a means to utilize the class in PET imaging studies. A comprehensive screening of these agents will be reported in due course.

Appendix

A. General Experimental Procedures

All solvents were of reagent or anhydrous grade quality and purchased from Sigma-Aldrich, Alfa Aesar, or Fisher Scientific. All reagents were purchased from Sigma-Aldrich, Alfa Aesar, Fisher Scientific, or Oakwood Chemical, unless otherwise stated. All deuterated solvents were purchased from Cambridge isotopes. Analytical thin-layer chromatography (TLC) was performed on precoated glass-backed plates (EMD TLC Silica gel 60 F_{254}) and visualized using a UV lamp (254 nm) and potassium permanganate stain. Silica gel for manual flash chromatography was high purity grade

SCHEME 6

40–63 μm pore size and purchased from Sigma-Aldrich. Yields refer to purified and spectroscopically pure compounds. Unless otherwise noted, compounds were recrystallized from toluene-hexanes. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) and ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) spectra were obtained with a Varian instrument.

A.1. Synthesis of 5-Chlorobenzo[b]pyrido[3,2-*f*][1,4]oxazepine.

A mixture of amide, benzo[b]pyrido[3,2-*f*][1,4]oxazepine-5(6H)-one (**2**, 1.08 g, 5.08 mmol), phosphorous oxychloride (1.42 mL, 15.26 mmol), and *N,N*-dimethylaniline (2.57 mL, 20.32 mmol) in dry toluene (10 mL) was heated at reflux for 2 h. The reaction mixture was cooled to ambient temperature and excess solvents were evaporated under reduced pressure. The resulting residue was dissolved in THF (20 mL) and Na_2CO_3 (30 mL of 2 M solution) and heated at 80°C for 1 h. The reaction mixture was cooled to ambient temperature and THF was removed under reduced pressure. The resulting aqueous layer was extracted with EtOAc (3 $\times$ 120 mL). The combined organic layers were washed with brine (1 $\times$ 100 mL) and dried over MgSO_4 and solvents were evaporated. The resulting residue was purified by column chromatography using 5% MeOH in dichloromethane to afford the title compound (1.09 g, 93%) as a light green solid m.p. 141.9–142.7°C; ^1H NMR: δ 8.49 (dd, J = 5.2, 8 Hz, 1H), 8.26 (dd, J = 2, 7.2 Hz, 1H), 7.45 (dd, J = 5.2, 8 Hz, 1H), 7.33 (d, 8 Hz, 1H), 7.24–7.14 (m, 3H) ppm; ^{13}C NMR: δ 164.4, 162.3, 152.4, 148.1, 142.4, 130.5, 126.3, 125.3, 122.5, 121.8, 121.7, 120.0 ppm. HRMS calc. for $\text{C}_{12}\text{H}_7\text{ClN}_2\text{O}$: 230.0246 obs: 230.0244.

A.1.1. General Procedure for Synthesis of **3 in MW.** 5-Chlorobenzo[b]pyrido[3,2-*f*][1,4]oxazepine (0.14 g, 0.61 mmol, 1 eq) and hydrazide (0.61 mmol, 1 eq) were dissolved in 1-butanol

(3 mL) in a 10 mL glass microwave tube. The vial was capped with a CEM corp. PL cap (SP1318A) and stirred in the cavity of a CEM Discover® Lab Mate reactor set at 200°C for 15 min (300 W, 250 psi). The contents of the tube were poured onto crushed ice/cold water (30 mL) and extracted with EtOAc (3 $\times$ 25 mL). The combined organic layers were washed with brine (1 $\times$ 25 mL) and dried over MgSO_4 . Removal of solvents under reduced pressure followed by silica gel chromatography (CH_2Cl_2 , with 1–10% MeOH gradient) afforded the corresponding adduct **3**.

A.1.2. General Procedure for Synthesis of **3 in Flow [20, 21].** Synthesis was performed using a ChemTrix Labtrix S1 flow chemistry reactor containing a T-mixer [14]. Syringe **A** was loaded with a 0.04 M solution of 5-chlorobenzo[b]pyrido[3,2-*f*][1,4]oxazepine in *t*-butanol and syringe **B** was loaded with a 0.04 M solution of corresponding hydrazide in *t*-butanol. Syringes **A** and **B** were pumped through a 10 μL glass microreactor heated to 190°C with a combined flow rate of 4 $\mu\text{L}/\text{min}$. The output collected was poured over crushed ice/cold water (20 mL) and extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were washed with brine (1 $\times$ 20 mL) and dried over MgSO_4 . The solvents were removed under reduced pressure and the crude product was purified by silica gel chromatography (CH_2Cl_2 , with 1–10% MeOH gradient).

A.2. 5-Chlorobenzo[b]pyrido[3,2-*f*][1,4]oxazepine. To a cooled solution of **2** (1.08 g, 5.08 mmol) in dry toluene (10 mL) POCl_3 was added (1.42 mL, 15.26 mmol) in a 50 mL round bottom flask under an atmosphere of argon followed by *N,N*-dimethylaniline (2.57 mL, 20.32 mmol). After refluxing for 2 h the mixture was concentrated under reduced pressure to

remove excess POCl_3 and *N,N*-dimethylaniline. The resulting mixture was dissolved in THF (20 mL) and Na_2CO_3 (30 mL of a 2 M solution) and heated at 80°C . After 1 h the mixture was cooled to room temperature and THF was removed under reduced pressure. The resulting aqueous layer was extracted to EtOAc (3×120 mL) and the combined organic layers were washed with brine (1×100 mL), dried over MgSO_4 , and concentrated in vacuo. The residue was purified using silica gel chromatography (5% MeOH in CH_2Cl_2) to afford 5-chlorobenzo[*b*]pyrido[3,2-*f*][1,4]oxazepine as a light green solid (1.09 g, 93%). mp: $141.9\text{--}142.7^\circ\text{C}$; ^1H NMR: ppm 8.49 (dd, $J = 8, 5.2$ Hz, 1H), 8.26 (d, $J = 7.2$ Hz, 1H), 7.45 (dd, $J = 7.8, 4.8$ Hz, 1H), 7.33 (d, $J = 7.2$ Hz, 1H), 7.24–7.14 (m, 3H) ^{13}C NMR: ppm 164.4, 162.2, 152.3, 148.0, 142.3, 130.5, 130.3, 126.3, 125.5, 122.4, 121.8, 119.9 MS (ESI+), m/z $\text{C}_{12}\text{H}_8\text{ClN}_2\text{O}$ ($\text{M} + \text{H}$) $^+$ calcd: 231.03 obsd: 232.0.

A.2.1. Synthesis of 5 from Hydrazide 4. Compound 4 (0.615 mmol, 0.14 g) and 5-chlorobenzo[*b*]pyrido[3,2-*f*][1,4]oxazepine (0.615 mmol, 0.14 g) were dissolved in 3 mL of *n*-BuOH in a 10 mL glass microwave vial and subjected to MW irradiation at 200°C for 15 min. The resulting mixture was concentrated in vacuo and purified by silica gel chromatography (1% MeOH in CH_2Cl_2) to afford 5 as a pale yellow solid (0.21 g, 87%). mp: $140\text{--}143^\circ\text{C}$ ^1H NMR: ppm 8.58 (dd, $J = 7.7, 1.8$ Hz, 1H), 8.48 (dd, $J = 4.8, 1.8$ Hz, 1H), 7.61 (d, $J = 8$ Hz, 1H), 7.45–7.39 (m, 4H), 7.33–7.31 (m, 1H), 7.01 (t, $J = 7.7$ Hz, 1H), 6.82 (d, $J = 8$ Hz, 1H), 3.89 (s, 2H), 2.25 (s, 6H); ^{13}C NMR: ppm 158.9, 158.3, 151.0, 133.6, 133.5, 132.0, 131.9, 131.6, 131.5, 131.2, 130.8, 130.3, 130.2, 130.1, 126.5, 124.6, 124.0, 122.9, 60.7, 45.4; HRMS (ESI+), m/z $\text{C}_{22}\text{H}_{19}\text{ClN}_5\text{O}$ ($\text{M} + \text{H}$) $^+$ calc: 404.1278 obs: 404.1282.

A.3. Spectroscopic Data [See Supplemental Information for ^{13}C Assignments]. See Supplemental Information for ^{13}C assignments in Supplementary Material available online at <https://doi.org/10.1155/2017/8147421>.

3a ($\text{R}=\text{Ph}$): mp. $246\text{--}247^\circ\text{C}$; ^1H NMR: ppm 8.59 (d, $J = 7.2$ Hz, 1H), 8.48–8.47 (m, 1H), 7.96–7.95 (m, 1H), 7.64 (d, $J = 7.6$ Hz, 2H), 7.53–7.45 (m, 3H), 7.40–7.38 (m, 2H), 7.05 (t, $J = 7.7$ Hz, 1H), 6.87 (d, $J = 8$ Hz, 1H); ^{13}C NMR: ppm 161.6, 153.9, 151.0, 133.0, 131.0, 130.8, 130.3, 129.3, 129.2, 126.8, 126.4, 125.9, 124.4, 124.2, 122.9, 122.0, 118.6, 115.2, 114.9; HRMS (ESI+), m/z $\text{C}_{19}\text{H}_{13}\text{N}_4\text{O}$ ($\text{M} + \text{H}$) $^+$ calc: 313.1089 obs: 313.1092.

3b ($\text{R}=\text{o-ClC}_6\text{H}_5$): mp. $241\text{--}244^\circ\text{C}$; ^1H NMR: ppm 8.57 (d, $J = 7.2$ Hz, 1H), 8.48 (d, $J = 4.4$ Hz, 1H), 7.77 (d, $J = 4.4$ Hz, 1H), 7.62 (d, $J = 8.1$ Hz, 1H), 7.52–7.34 (m, 5H), 7.00 (t, $J = 8$ Hz, 1H), 6.74 (d, $J = 8$ Hz, 1H); ^{13}C NMR: ppm 162.0, 161.8, 151.1, 150.5, 150.3, 139.6, 134.2, 132.7, 132.3, 130.6, 130.3, 127.8, 127.6, 126.8, 126.5, 124.2, 123.5, 122.8, 115.3; HRMS (ESI+), m/z $\text{C}_{19}\text{H}_{12}\text{ClN}_4\text{O}$ ($\text{M} + \text{H}$) $^+$ calc: 347.0700 obs: 347.0694.

3c ($\text{R}=\text{p-ClC}_6\text{H}_5$): mp. $236\text{--}238^\circ\text{C}$; ^1H NMR: ppm 8.60 (d, $J = 7.2$ Hz, 1H), 8.50 (d, $J = 4.4$ Hz, 1H), 7.67 (d, $J = 8.1$ Hz, 1H), 7.60 (d, $J = 8.8$ Hz, 2H), 7.46–7.40 (m, 4H), 7.10 (t, $J = 7.7$ Hz, 1H), 6.88 (d, $J = 8$ Hz, 1H); ^{13}C NMR: ppm 152.7, 151.1, 147.5, 146.2, 141.4, 139.8, 137.1, 136.4, 132.8, 130.5, 129.6, 126.5, 125.3, 124.3, 123.1, 116.3, 115.1; HRMS (ESI+), m/z $\text{C}_{19}\text{H}_{12}\text{N}_4\text{ClO}$ ($\text{M} + \text{H}$) $^+$ calc: 347.0700 obs: 347.0706.

3e ($\text{R}=\text{pOHC}_6\text{H}_5$): mp. $264\text{--}265^\circ\text{C}$; ^1H NMR: ppm 8.61 (d, $J = 7.3$ Hz, 1H), 8.50 (d, $J = 4.4$ Hz, 1H), 8.10 (d, $J = 8$ Hz, 1H), 7.51 (d, $J = 8$ Hz, 2H), 7.42 (d, $J = 8.1$ Hz, 2H), 7.10 (t, $J = 7.2$ Hz, 1H), 6.95–6.93 (m, 3H), 6.69 (bs, 1H); ^{13}C NMR: ppm 202.6, 161.7, 161.3, 152.0, 151.6, 150.1, 141.0, 131.3, 131.2, 131.1, 130.85, 128.5, 126.5, 124.0, 123.9, 121.4, 116.5; HRMS (ESI+), m/z $\text{C}_{19}\text{H}_{13}\text{N}_4\text{O}_2$ ($\text{M} + \text{H}$) $^+$ calc: 329.1039 obs: 329.1038.

3f ($\text{R}=\text{mOCH}_3\text{C}_6\text{H}_5$): mp. $255\text{--}256^\circ\text{C}$; ^1H NMR: ppm 8.54 (d, $J = 8$ Hz, 1H), 8.43 (d, $J = 7.2$ Hz, 1H), 7.61–7.59 (m, 1H), 7.37–7.32 (m, 3H), 7.19 (s, 1H), 7.10–7.08 (m, 1H), 7.05–6.98 (m, 2H), 6.92 (d, $J = 8$ Hz, 1H), 3.75 (s, 3H); ^{13}C NMR: ppm 161.6, 160.0, 154.3, 150.8, 150.4, 130.3, 130.2, 126.3, 125.9, 127.8, 127.5, 126.3, 125.9, 124.0, 122.9, 121.6, 117.0, 115.1, 114.2, 55.6; HRMS (ESI+), m/z $\text{C}_{20}\text{H}_{15}\text{N}_4\text{O}_2$ ($\text{M} + \text{H}$) $^+$ calc: 343.1195 obs: 343.1191.

3g ($\text{R}=\text{mpyridyl}$): mp. $226\text{--}227^\circ\text{C}$; ^1H NMR: ppm 8.92 (s, 1H), 8.76 (d, $J = 3.2$ Hz, 1H), 8.61 (dd, $J = 8, 2.4$ Hz, 1H), 8.50 (dd, $J = 4.8, 1.8$ Hz, 1H), 8.38 (dd, $J = 7.7, 1.8$ Hz, 1H), 8.30–8.29 (m, 1H), 7.46–7.44 (m, 1H), 7.31 (dd, $J = 7.7, 4.8$ Hz, 1H), 7.21–7.19 (m, 2H), 7.08–7.06 (m, 1H). ^{13}C NMR: ppm 172.6, 167.2, 161.5, 161.1, 157.3, 150.4, 146.9, 146.4, 141.5, 128.5, 126.7, 125.3, 125.2, 123.9, 123.0, 122.3, 121.2, 119.8; HRMS (ESI+), m/z $\text{C}_{18}\text{H}_{12}\text{N}_5\text{O}$ ($\text{M} + \text{H}$) $^+$ calc: 314.1042 obs: 314.1042.

3h ($\text{R}=\text{oFC}_6\text{H}_5$): mp. $247\text{--}249^\circ\text{C}$; ^1H NMR: ppm 8.59 (d, $J = 7.2$ Hz, 1H), 8.49–8.48 (m, 1H), 7.86 (t, $J = 7.2$ Hz, 1H), 7.64–7.65 (m, 1H), 7.55 (d, $J = 5.1$ Hz, 1H), 7.41–7.35 (m, 3H), 7.13–7.03 (m, 2H), 6.86 (d, $J = 8$ Hz, 1H); ^{13}C NMR: ppm 167.7, 156.7, 150.0, 143.7, 139.5, 137.6, 132.9, 131.8, 130.1, 126.4, 126.0, 125.1, 123.9, 123.4, 122.8, 116.6, 116.3, 115.7, 115.1; HRMS (ESI+), m/z $\text{C}_{19}\text{H}_{12}\text{FN}_4\text{O}$ ($\text{M} + \text{H}$) $^+$ calc: 331.0995 obs: 331.0992.

3i ($\text{R}=\text{m-ClC}_6\text{H}_5$): mp. $236\text{--}237^\circ\text{C}$ ^1H NMR: ppm 8.59 (dd, $J = 7.7, 1.8$ Hz, 1H), 8.49–8.48 (m, 1H), 7.73–7.75 (m, 1H), 7.68–7.66 (m, 1H), 7.49–7.46 (m, 3H), 7.37–7.36 (m, 2H), 7.13–7.09 (m, 1H), 6.89 (dd, $J = 7.8, 1.5$ Hz, 1H); ^{13}C NMR: ppm 151.2, 148.5, 142.7, 142.2, 132.9, 131.9, 130.9, 130.6, 130.4, 130.3, 129.3, 128.5, 127.3, 126.5, 125.7, 124.9, 124.3, 122.9, 118.9; HRMS (ESI+), m/z $\text{C}_{19}\text{H}_{12}\text{ClN}_4\text{O}$ ($\text{M} + \text{H}$) $^+$ calc: 347.0700 obs: 347.0700.

10: yellow oil. ^1H NMR: ppm 8.57 (dd, $J = 7.7, 1.8$ Hz, 1H), 8.48 (dd, $J = 4.8, 1.8$ Hz, 1H), 7.79–7.77 (m, 1H), 7.63 (d, $J = 8$ Hz, 1H), 7.04–7.02 (m, 1H), 6.87–6.85 (m, 1H), 3.87 (s, 2H), 2.25 (s, 6H); ^{13}C NMR: ppm 159.9, 150.9, 149.2, 146.1, 135.6, 132.1, 131.9, 131.6, 126.6, 124.6, 123.9, 123.7, 115.3, 62.1, 46.4 HRMS (ESI+), m/z $\text{C}_{16}\text{H}_{15}\text{ClN}_5\text{O}$ ($\text{M} + \text{H}$) $^+$ calc: 328.0965 obs: 328.0958.

12: mp. $217\text{--}219^\circ\text{C}$; ^1H NMR: ppm 8.77–8.75 (m, 1H), 8.48–8.43 (m, 2H), 7.54 (d, $J = 8$ Hz, 1H), 7.42–7.38 (m, 2H), 3.72 (s, 2H), 2.83–2.80 (m, 4H), 2.57–2.55 (m, 4H), 2.34 (s, 3H) ^{13}C NMR: ppm 161.6, 151.6, 151.1, 150.1, 149.0, 139.9, 131.9, 129.9, 128.3, 126.1, 124.9, 123.0, 115.3, 55.1, 52.5, 51.7, 46.1; HRMS (ESI+), m/z $\text{C}_{19}\text{H}_{20}\text{ClN}_6\text{O}$ ($\text{M} + \text{H}$) $^+$ calc: 383.1387 obs: 383.1391.

13: mp $191\text{--}193^\circ\text{C}$; ^1H -NMR: δ 8.57–8.54 (m, 2H), 7.92 (dd, $J = 5.0, 0.8$ Hz, 1H), 7.69 (d, $J = 8.8$ Hz, 1H), 7.63–7.58 (m, 2H), 7.37 (dd, $J = 3.5, 0.7$ Hz, 1H), 7.29 (d, $J = 2.4$ Hz, 1H), 7.24 (dd, $J = 4.9, 3.8$ Hz, 1H); ^{13}C -NMR: δ 160.3, 151.3, 149.4, 148.7, 139.5, 130.4, 130.4, 130.0, 129.9, 128.2, 127.7, 126.4, 125.6, 124.8, 123.6, 123.6, 114.0. HRMS (ESI+), m/z $\text{C}_{17}\text{H}_9\text{ClN}_4\text{OS}$ ($\text{M} + \text{H}$) $^+$ calc: 353.0263 obs: 353.0257.

14: m.p. 201–203°C; $^1\text{H-NMR}$: δ 8.58–8.55 (m, 2H), 7.98 (d, $J = 1.1$ Hz, 1H), 7.67 (d, $J = 8.8$ Hz, 1H), 7.64–7.59 (m, 2H), 7.19 (dd, $J = 3.3, 0.5$ Hz, 1H), 7.17 (d, $J = 2.5$ Hz, 1H), 6.81 (dd, $J = 3.5, 1.8$ Hz, 1H). $^{13}\text{C-NMR}$: δ 160.3, 151.3, 149.4, 148.3, 145.8, 140.0, 139.6, 130.3, 130.1, 127.7, 125.1, 124.6, 123.6, 119.8, 114.2, 113.9, 112.3. HRMS (ESI+), m/z $\text{C}_{17}\text{H}_9\text{ClN}_4\text{O}_2$; (M + H) $^+$ calc: 337.0492 obs: 337.0486.

15: m.p. 221–223°C; $^1\text{H-NMR}$: δ 8.58 (dd, $J = 7.6, 1.9$ Hz, 1H), 8.46 (dd, $J = 4.8, 1.9$ Hz, 1H), 7.57 (d, $J = 8.8$ Hz, 1H), 7.43–7.38 (m, 3H), 7.33 (dd, $J = 8.7, 2.4$ Hz, 1H), 6.98 (d, $J = 2.4$ Hz, 1H), 6.73 (d, $J = 8.5$ Hz, 2H), 4.07 (s, 2H). $^{13}\text{C-NMR}$: δ 161.0, 154.6, 150.7, 149.9, 149.0, 148.7, 139.6, 131.5, 130.4, 129.8, 128.8, 125.6, 125.0, 123.0, 115.2, 115.1, 115.0. HRMS (ESI+), m/z $\text{C}_{19}\text{H}_{12}\text{ClN}_5\text{O}$ (M + H) $^+$ calc: 362.0809 obs: 362.0804.

16: m.p. 177–179°C; $^1\text{H NMR}$: ppm 8.59 (dd, $J = 7.3, 1.5$ Hz, 1H), 8.49 (dd, $J = 4.81, 1.8$ Hz, 1H), 7.60–7.56 (m, 3H), 7.45 (d, $J = 8$ Hz, 2H), 7.43–7.40 (m, 1H), 7.34 (dd, $J = 8.8, 2.9$ Hz, 1H), 6.78 (d, $J = 2.2$ Hz, 1H), 3.60 (s, 2H), 2.74–2.50 (m, 8H), 2.46 (s, 3H); $^{13}\text{C NMR}$: ppm 163.6, 153.5, 153.2, 145.2, 138.8, 136.3, 133.5, 133.2, 131.4, 131.1, 129.6, 128.9, 125.8, 125.3, 123.4, 122.9, 118.9, 62.3, 59.8, 54.7, 46.8; HRMS (ESI+), m/z $\text{C}_{25}\text{H}_{24}\text{ClN}_6\text{O}$ (M + H) $^+$ calc: 459.1700 obs: 459.1701.

17: m.p. 241–243°C; $^1\text{H NMR}$: ppm 8.57–8.62 (m, 1H), 8.45 (d, $J = 1.5$ Hz, 1H), 8.38–8.37 (m, 1H), 7.97 (d, $J = 8.1$ Hz, 1H), 7.73–7.72 (m, 1H), 7.65–7.64 (m, 1H), 7.59–7.58 (m, 1H), 7.49–7.48 (m, 1H), 7.17–7.16 (m, 1H), 7.01 (dd, $J = 8, 1.5$ Hz, 1H), 6.86 (t, $J = 7.2$ Hz, 1H); $^{13}\text{C NMR}$: ppm 157.9, 153.4, 152.6, 151.0, 150.6, 148.2, 140.3, 135.8, 133.4, 133.2, 132.4, 132.0, 131.4, 128.7, 127.3, 126.7, 125.7, 124.5, 114.8; HRMS (ESI+), m/z $\text{C}_{19}\text{H}_{12}\text{N}_5\text{O}_3$ (M + H) $^+$ calc: 358.0940 obs: 358.0949.

18: m.p. 251–252°C; $^1\text{H NMR}$: ppm 8.57 (dd, $J = 7.2, 1.8$ Hz, 1H), 8.37 (dd, $J = 8.2, 2$ Hz, 1H), 7.87–7.86 (m, 1H), 7.66–7.63 (m, 1H), 7.52–7.49 (m, 1H), 7.46–7.44 (m, 2H), 7.32–7.29 (m, 1H), 7.21–7.18 (m, 2H), 6.90–6.88 (m, 1H); $^{13}\text{C NMR}$: ppm 167.2, 165.2, 163.3, 160.9, 153.0, 148.6, 143.1, 138.0, 131.5, 131.0, 129.6, 127.2, 127.1, 126.3, 125.4, 124.3, 122.5, 121.0, 120.8; HRMS (ESI+), m/z $\text{C}_{19}\text{H}_{12}\text{FN}_4\text{O}$ (M + H) $^+$ calc: 331.0995 obs: 331.0992.

Conflicts of Interest

The authors report no conflicts of interest.

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