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

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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-HT2a 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
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Scheme 1

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

| Entry | 3   | Ar      | Thermal<sup>a</sup> | MW<sup>b</sup> | Flow<sup>c</sup> |
|-------|-----|---------|---------------------|---------------|-----------------|
| 1     | 3a  | Ph      | 38                  | 54            | 57              |
| 2     | 3b  | 2-Cl-C₆H₄ | 48                  | 86            | 78              |
| 3     | 3c  | 4-Cl-C₆H₄ | 66                  | 96            | 84              |
| 4     | 3d  | 2-OH-C₆H₄ | 29                  | 89            | >99             |
| 5     | 3e  | 4-OH-C₆H₄ | 41                  | 67            | 72              |
| 6     | 3f  | 3-OMe-C₆H₄ | 28                  | 92            | 82              |
| 7     | 3g  | 3-pyridyl | 57                  | 84            | 98              |
| 8     | 3h  | 2-F-C₆H₄  | 25                  | 88            | >99             |
| 9     | 3i  | 3-F-C₆H₄  | 32                  | 83            | 85              |
| 10    | 3j  | 4-Me-C₆H₄ | 39                  | 98            | 88              |
| 11    | 3k  | 3-NO₂-C₆H₄ | 17                  | 81            | 85              |
| 12    | 3l  | 3-Cl-C₆H₄ | 44                  | 80            | —               |

<sup>a</sup>n-BuOH, Δ, 118°C, 6 h; <sup>b</sup>300 W, 200°C, n-BuOH 15 min. <sup>c</sup>Both 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.

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<sub>2a</sub>, 5-HT<sub>2c</sub>, D<sub>1</sub>, D<sub>2</sub>, and D<sub>4</sub> being of importance, with the 5-HT<sub>2a</sub>/D<sub>2</sub> ratio especially significant) [17]. In a preliminary assay, compound 5 showed a K<sub>i</sub> of 16 µM against 5-HT<sub>2a</sub>, 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
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.
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. \(^{1}\)H NMR (400 MHz, DMSO-\(d_6\)) and \(^{13}\)C NMR (100 MHz, 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 \(\text{Na}_2\text{CO}_3\) (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 × 25 mL). The combined organic layers were washed with brine (1 × 25 mL) and dried over MgSO\(_4\). Removal of solvents under reduced pressure followed by silica gel chromatography (CH\(_2\)Cl\(_2\), with 1–10% MeOH gradient) afforded the corresponding adduct 3.

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 (SPI318A) 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 × 25 mL). The combined organic layers were washed with brine (1 × 25 mL) and dried over MgSO\(_4\). Removal of solvents under reduced pressure followed by silica gel chromatography (CH\(_2\)Cl\(_2\), with 1–10% MeOH gradient) afforded the corresponding adduct 3.

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 POCl₃ and N,N-dimethylaniline. The resulting mixture was dissolved in THF (20 mL) and Na₂CO₃ (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 MgSO₄, and concentrated in vacuo. The residue was purified using silica gel chromatography (% MeOH in CH₂Cl₂) to afford 5-chlorobenz[b]pyrido[3,2,1-f][1,4]oxazepine (0.615 mmol, 0.14 g) and 5-chlorobenz[b]pyrido[3,2,1-f][1,4]oxazepine as a light green solid (1.09 g, 93%). mp: 141.9–142.7°C. ¹H NMR: ppm 8.49 (dd, J = 8, 5.2 Hz, 1H), 8.26 (dd, J = 7.2 Hz, 1H), 7.75 (dd, J = 7.8, 4.8 Hz, 1H), 7.33 (d, J = 7.2 Hz, 1H), 7.24–7.14 (m, 3H). ¹³C 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, 121.3, 116.3, 115.1; HRMS (ESI+), m/z [C₁₉H₁₂N₄ClO] (M + H)⁺ calcd: 329.1039 obsd: 329.1038.

3f (R=5-methylpyridyl): m.p. 255–256°C. ¹H NMR: ppm 8.54 (d, J = 8 Hz, 1H), 8.43 (d, J = 7.2 Hz, 1H), 7.61–7.59 (m, 9H), 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). ¹³C 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 [C₂₀H₁₈N₄O₂ (M + H)⁺ calcd: 343.195 obsd: 343.191.

A.2.1. Synthesis of 5 from Hydrazide 4. Compound 4 (0.615 mmol, 0.14 g) was dissolved in a 10 mL microwavable 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 (% MeOH in CH₂Cl₂) to afford 5 as a pale yellow solid (0.21 g, 87%). mp: 150–154°C. ¹H NMR: ppm 8.59 (d, J = 7.2 Hz, 1H), 8.49 (d, J = 8.1 Hz, 1H), 8.26 (dd, J = 7.2 Hz, 1H), 7.75–7.39 (m, 4H), 7.33–7.31 (m, 1H), 7.01 (t, J = 7.7 Hz, 1H), 6.82 (d, J = 8 Hz, 3H) 1H), 3.89 (s, 2H), 2.25 (s, 6H). ¹³C 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, 126.5, 124.6, 124.0, 122.9, 60.7, 45.4; HRMS (ESI+), m/z [C₂₂H₂₂ClN₅O (M + H)⁺ calcd: 404.1278 obsd: 404.1282.

A.3. Spectroscopic Data [See Supplemental Information for ¹³C Assignments]. See Supplemental Information for ¹³C assignments in Supplemental Material available online at https://doi.org/10.1155/2017/8174742.

3a (R=Ph): m.p. 246–247°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), 7.23–7.35 (m, 4H), 7.11–7.04 (m, 2H). 7.00 (t, J = 7.7 Hz, 1H). ¹³C NMR: ppm 151.0, 150.3, 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 [C₁₉H₁₄N₄O] (M + H)⁺ calcd: 313.1089 obsd: 313.109.

3b (R=o-C₆H₄Cl₂): m.p. 241–244°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 Hz, 1H), 7.52–7.54 (m, 5H), 7.00 (t, J = 8 Hz, 1H), 6.74 (d, J = 8 Hz, 1H). ¹³C NMR: ppm 163.8, 155.8, 155.0, 151.5, 139.4, 138.5, 132.7, 132.3, 130.6, 130.3, 127.8, 126.9, 126.5, 124.2, 123.5, 122.8, 115.3; HRMS (ESI+), m/z [C₁₉H₁₄Cl₃N₂O] (M + H)⁺ calcd: 347.0700 obsd: 347.0694.

3c (R=p-C₆H₄Cl₂): m.p. 236–238°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). ¹³C 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, 121.3, 116.3, 115.1; HRMS (ESI+), m/z [C₁₉H₁₂N₄ClO] (M + H)⁺ calcd: 347.0700 obsd: 347.0706.
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