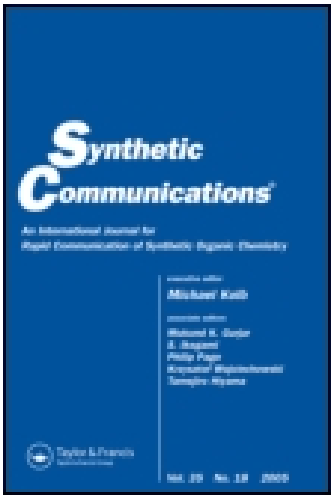

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David Ellis [a]
[a] Discovery Chemistry , Pfizer Global Research and Development , Kent , United Kingdom
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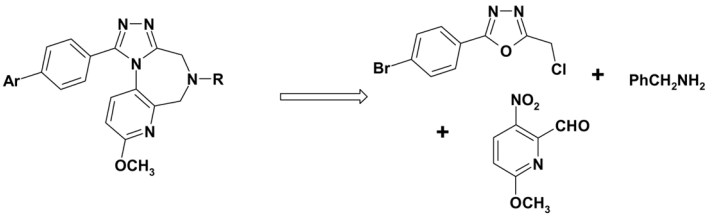
VERSATILE SYNTHESIS OF FUSED TRICYCLIC 1,2,4-TRIAZOLE DERIVATIVES

David Ellis
Discovery Chemistry, Pfizer Global Research and Development, Kent, United Kingdom

GRAPHICAL ABSTRACT



Ar = 2-Methylphenyl and 2-Methoxyphenyl

R = Methyl, acetyl, methanesulfonyl and methylcarbamoyl

Abstract *The synthesis of a small series of fused tricyclic 1,2,4-triazoles is described. The key reaction is an intramolecular two-stage, one-pot reduction/cyclization sequence of a nitropyridine/oxadiazole substrate to give the key tricyclic triazole. Further standard transformations convert this template into a series of final target compounds.*

Keywords Fused tricyclic ring system; intramolecular reduction cyclization; Suzuki reaction; 1,2,4-triazole; vicarious nucleophilic substitution

INTRODUCTION

We required tricyclic 1,2,4-triazole derivatives **1** (Fig. 1) as part of an oxytocin (OT) antagonist program. These were designed as conformationally restricted analogs of the previously disclosed triazoles **2**.[1]

Retrosynthetic Analysis

The synthetic route adopted for previous triazoles utilized the well-precedented conversion of 1,3,4-oxadiazoles to 1,2,4-triazoles with amines under thermal, acid-catalyzed conditions[2] (Scheme 1).

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Address correspondence to David Ellis, Discovery Chemistry, Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK. E-mail: david.ellis@pfizer.com

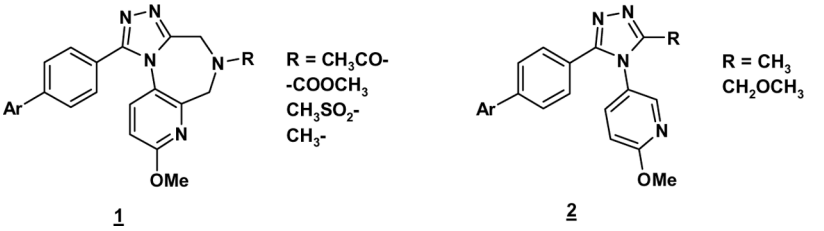
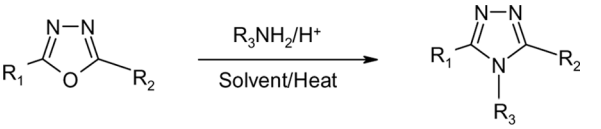


Figure 1. Required triazole targets and earlier analogs.

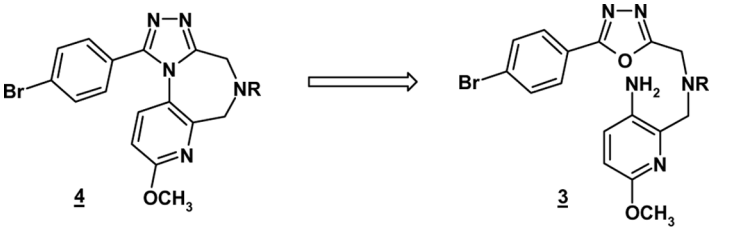


Scheme 1. Precedented oxadiazole to triazole conversion.

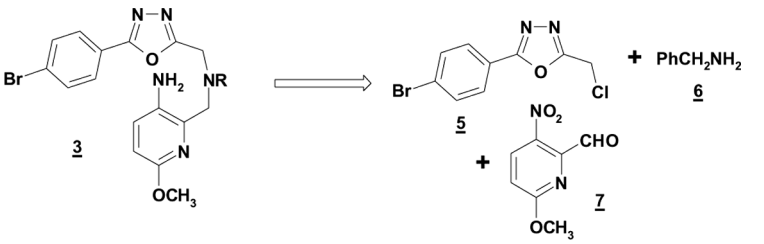
This strategy influenced the retrosynthetic analysis of the tricyclic analogs where an oxadiazole precursor **3** could be cyclized to the required template **4** and the distal aryl ring attached via a standard Suzuki reaction (Scheme 2).

Oxadiazole **3** then could be further broken down into simpler fragments (Scheme 3).

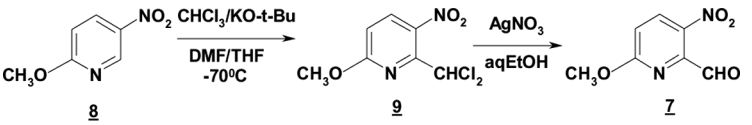
Previous in-house work had already shown that chloromethyloxadiazoles such as **5** could be easily synthesized, which supported this approach. Benzylamine **6** was



Scheme 2. Proposed intramolecular cyclization.



Scheme 3. Key fragments in the retrosynthesis.



Scheme 4. Initial vicarious nucleophilic substitution.

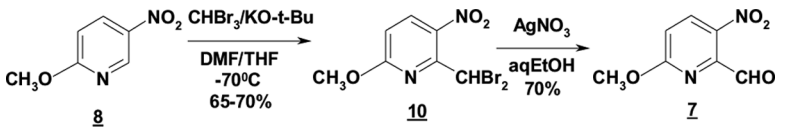
chosen as the protected amine fragment, and the pyridine derivative chosen was 6-methoxy-3-nitropyridine-2-carboxaldehyde **7**, which was to be accessed from the known 2-dichloromethyl-6-methoxy-3-nitropyridine[3] **9**. Masking the 3-aminopyridine as a nitro group would remove potential protecting group conflicts between the two amines later on. The aldehyde would also be more stable than the corresponding halomethylpyridine derivative. Therefore, the synthesis relied initially on obtaining 6-methoxy-3-nitropyridine-2-carboxaldehyde **7**. The aldehyde is now commercially available from Anichem.

Synthesis of 6-Methoxy-3-nitropyridine-2-carboxaldehyde 7

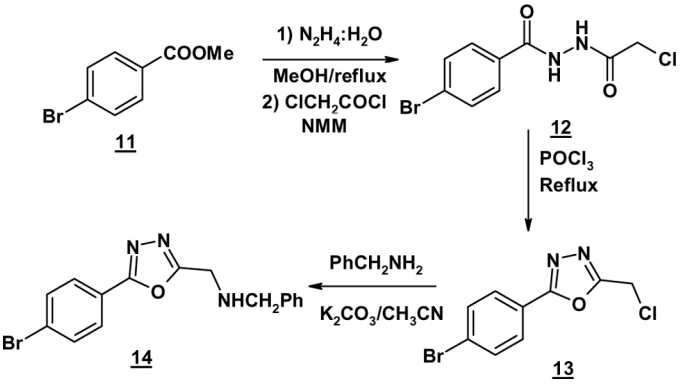
This compound is prepared by the vicarious nucleophilic substitution (VNS)[3,4] reaction of chloroform onto commercial 2-methoxy-5-nitropyridine **8**, followed by hydrolysis of the dichloride to the aldehyde (Scheme 4).

Initial reaction to the dichloro compound **9**, though successful, gave poor yields (45%). The low temperature required to avoid problems resulting from dichlorocarbene formation also caused solubility problems with the base and starting nitropyridine. Magnetic stirring of the reaction was awkward, and the addition time of the reactants was also lengthy because of the exothermic nature of the reaction. Hydrolysis of the dichloride was also slow and incomplete under the conditions shown. This was thought to be due to the difficulty of hydrolysis of the strong C-Cl bond, a factor that has been noted in the synthesis of other triazole analogs from their trichloromethyl derivatives.[5]

Substitution of bromoform for chloroform showed problems in the VNS reaction similar to that seen with chloroform, with addition times of ~2 h for a 10-g reaction. However, the yield was much improved, and over two consecutive experiments 65–70% yields of the dibromide **10** were obtained (Scheme 5). These yielded sufficient material to continue, and the conditions of the VNS reaction were not investigated further. Scope clearly exists for potential optimization of this step. For reactions above the 10-g scale, mechanical stirring would be obligatory. During the second experiment, the temperature was allowed to reach $-50\,^{\circ}C$ at times, and the yield of this reaction was not greatly different than the yield obtained in the first reaction,



Scheme 5. Improved vicarious nucleophilic substitution.



Scheme 6. Key oxadiazole synthesis.

which was maintained at −70 °C. Therefore, it may be possible to raise the temperature of the reaction somewhat with benefits for solubility and addition times.

The hydrolysis of the dibromide **10** was much more rapid than that of the dichloro analog as expected and was complete in 1–2 h at reflux. The yields were consistent at ~70%, and thus large quantities of this useful trifunctionalized pyridine were available for the next stages of the synthesis.

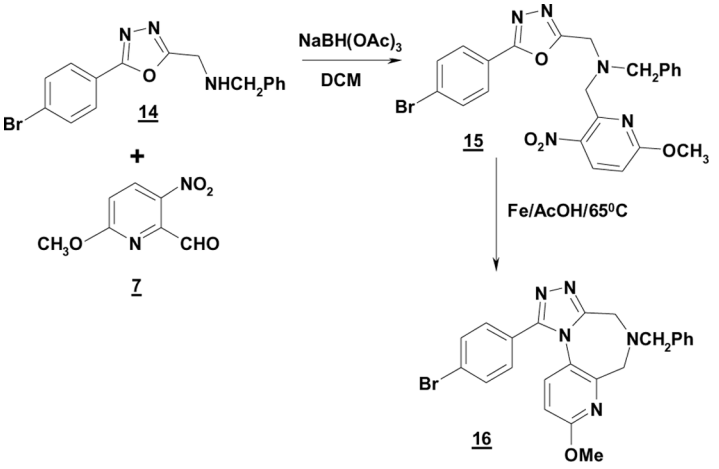
Synthesis of 2-Chloromethyl-5-(4-bromophenyl)-1,3,4-oxadiazole 14

Once again, previous project methodology was used to assemble this key fragment as shown in Scheme 6.

The commercial ester **11** was readily converted to the hydrazide by heating with hydrazine hydrate in methanol. Acylation with chloroacetyl chloride was straightforward and rapid, though the insolubility of the product **12** caused minor issues during the workup. It was easier to evaporate the solvent and treat the residue with hot water. Filtration followed by further washes with water successfully removed the HCl salt of the N-methylmorpholine (NMM) and all other by-products, furnishing the required hydrazide **12** in good yield. Dehydrative cyclization of the di-acylhydrazide to the oxadiazole **13** in refluxing $POCl_3$ was also rapid and clean, giving a good yield of the oxadiazole after a simple aqueous/organic workup.[6] Displacement of the chloride with benzylamine proceeded cleanly at rt, though heating to 50 °C significantly shortened the reaction time to a few hours. A simple workup then furnished the desired amino-oxadiazole **14** in 52% yield. No chromatography was required throughout this sequence.

Assembly of the Tricyclic Template

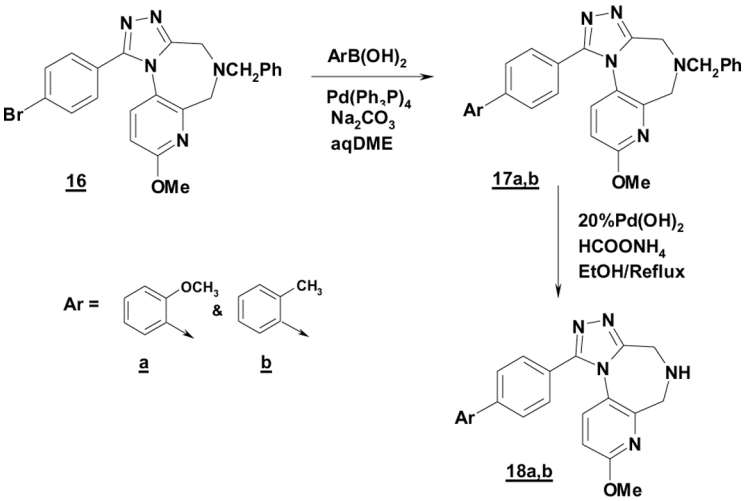
With large amounts of the key amino-oxadiazole **14** to hand, the crucial joining of this fragment and the pyridine aldehyde could be attempted by reductive amination. The use of secondary benzylamine **14** has two benefits in such an approach. It reduces the tendency for overreaction with the aldehyde to give tertiary amine



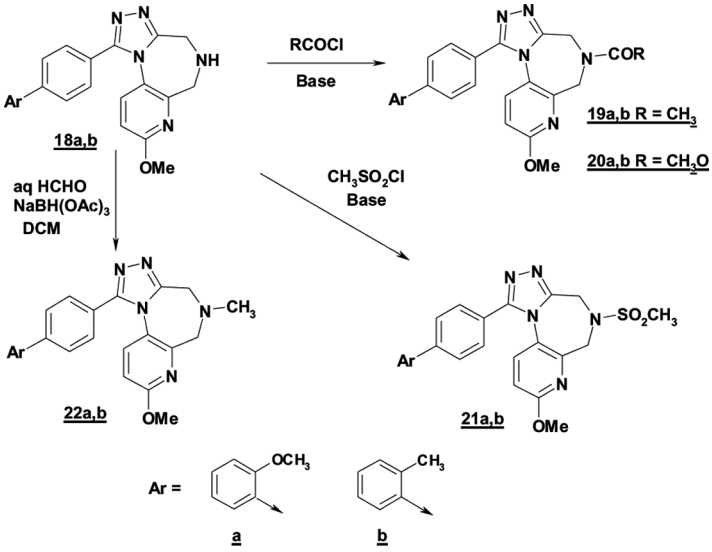
Scheme 7. Assembly of tricyclic template.

by-products (earlier attempts with the aldehyde and an aminomethyloxadiazole were not encouraging) and also provides a suitable protecting group to facilitate late-stage modification of the template.

The reductive amination shown in Scheme 7 was straightforward, and after a simple workup, the crude product **15** was triturated with ether and filtered to yield analytically pure material. This nitropyridine substrate was then stirred in acetic acid at 65 °C in the presence of 5 equivalents of iron powder to effect reduction of the nitro group to the amine, which cyclized intramolecularly to the desired tricyclic triazole template **16**. Once again, after a simple workup, the material was isolated and analytically pure without the need for chromatography.



Scheme 8. Initial modifications to tricyclic template.



Scheme 9. Final variation of tricyclic template.

Modification of the Tricyclic Template

With a robust route to multigram quantities of the tricyclic triazole template **16**, attention now turned to the late-stage modification to yield final target compounds.

Previous SAR had indicated just two key variants of the distal aromatic ring would allow an assessment of the activity of these templates. These were o-methylphenyl and o-methoxyphenyl. These were installed via a standard Suzuki coupling reaction.[7] The couplings were straightforward and gave good yields of the biphenyl products **17a,** and **b** (Scheme 8).

The N-benzyl group was removed via catalytic transfer hydrogenation[8] using 20% $Pd(OH)_2/C$ and ammonium formate in ethanol at reflux to yield key amines **18a** and **b**. Alternative hydrogenation conditions as well as the use of 1-chloroethyl-chloroformate (ACE-Cl)[9] had either failed or given a less clean reaction profile. The necessity of using hydrogenation to remove the benzyl group confirmed the decision to react the bromine prior to deprotection as the correct course. It was also gratifying that the hydrogenation had cleaved only the desired N-benzyl group in preference to the other two ''pseudo-benzylic'' bonds.

The final modifications of the tricyclic template were carried out by standard acylation and alkylation reactions to give a small series of eight analogs for testing (Scheme 9).

CONCLUSION

A straightforward and versatile synthesis of an interesting tricyclic 1,2,4-triazole template has been described. The key features of the method include modification of a VNS reaction using $CHBr_3$ instead of $CHCl_3$ to access a useful

trifunctional nitropyridine aldehyde. Furthermore, once this aldehyde is attached to an amino-oxadiazole via reductive amination, a sequential reduction/cyclization sequence furnishes the required tricyclic template with two points of diversity. The reactions used are all straightforward and simple to carry out, and the use of chromatography throughout the sequence is minimal.

EXPERIMENTAL

All ^{1}H NMR spectra were obtained on a 400-MHz Varian Mercury spectrometer using either $CDCl_3$ or dimethylsulfoxide (DMSO-d_6) as solvents. The chemical shifts are reported in parts per million (ppm) relative to the deuterated solvent. Mass spectra were recorded on an Agilent 1100 series liquid chromatography/mass spectrometry (LC/MS) instrument in the electrospray and atmospheric pressure (ES/AP) ionization modes. All chromatography was performed using Merck silica using a gradient elution profile unless otherwise stated. Thin-layer chromatography (TLC) was performed using Merck TLC plates. Solvent systems used are given with the TLC/Rf data.

Synthesis of 2-Dibromomethyl-6-methoxy-3-nitropyridine 10

Preparation. A solution of bromoform (18.86 g, 74.6 mmol) and 6-methoxy-3-nitropyridine (10 g, 64.9 mmol) in a mixture of THF (30 mL) and DMF (15 mL) was added dropwise to a cold (−70 °C) solution of potassium t-butoxide (29.0 g, 260 mmol) in THF (100 mL) and DMF (30 mL) under nitrogen while maintaining the internal temperature between −60 °C and −70 °C. The addition takes approximately 2 h. The resulting dark red mixture was left at −60 °C for 20 min before quenching the reaction with acetic acid (30 mL) and allowing it to warm to ambient temperature. The mixture was poured with stirring onto a mixture of crushed ice and EtOAc (200 mL). When the ice had melted, the organic layer was separated, and the aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with 2 M HCl (4 × 50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), and brine (50 mL), dried over $MgSO_4$, filtered, and evaporated. The residue was dissolved in MeOH (50 mL) and treated with charcoal at reflux for 5 min. The mixture was filtered, the filtrate was evaporated, and the resulting solid was triturated with pentane and filtered to yield the title compound **10** as a fawn solid, which was pure enough to use directly in the next stage. Yield: 15 g, 70%; amorphous fawn solid.

Data. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.20$ (s, 3H), 6.85 (d, $J = 7.14$ Hz, 1H), 7.63 (s, 1H), 8.25 (d, $J = 7.14$ Hz, 1H). TLC Rf 0.4 (EtOAc/pentane 1:9), Rf 0.79 (DCM/MeOH 98:2).

Synthesis of 6-Methoxy-3-nitropyridine-2-carboxaldehyde 7

Preparation. A solution of $AgNO_3$ (2.34 g, 13.80 mmol) in water (5 mL) was added to a solution of 2-dibromomethyl-6-methoxy-3-nitropyridine (1.5 g, 4.60 mmol) in EtOH (15 mL). The resulting mixture was heated to reflux under nitrogen for 2 h. The EtOH was then evaporated, and the aqueous residue was diluted

with EtOAc (30 mL). The precipitate of AgBr was filtered, and the organic layer then separated, washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography eluting with EtOAc/pentane (5:95–1:3 in 5% stages of EtOAc) to yield the title compound **7**, which was pure enough to use directly in the next stage. Yield: 1.0 g; 71% amorphous pale yellow solid.

Data. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.15$ (s, 3H), 7.02 (d, $J = 8.6$ Hz, 1H), 8.30 (d, $J = 8.6$ Hz, 1H), 10.35 (s, 1H). MS APCI: m/z 183 $[M + H^+]$. Anal. calcd. for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 45.56; H, 3.30; N, 15.14.

Synthesis of 2-Benzylaminomethyl-5-(4-bromophenyl)-1,3,4-oxadiazole 14

Preparation. Potassium carbonate (5.04 g, 36.55 mmol) was added in one portion to a solution of 2-chloromethyl-5-(4-bromophenyl)-1,3,4-oxadiazole **13** (5 g, 18.28 mmol) prepared as shown in Scheme 6 by the late Olga Wallace and benzylamine (2.25 g, 21.02 mmol) in CH_3CN (50 mL) at room temperature. The resulting mixture was heated to 50 °C for 6 h. The CH_3CN was evaporated, and the residue was partitioned between EtOAc (100 mL) and water (50 mL). The EtOAc was separated, washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and evaporated. The white residue was triturated with ether and filtered to furnish the title compound **14**. Yield: 3.3 g, 52%; amorphous white solid.

Data. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.00$ (s, 1H), 3.90 (s, 2H), 4.10 (s, 2H), 7.20–7.40 (m, 5H), 7.68 (d, 2H), 7.80 (d, 2H). MS APCI: m/z 344/346 $[M + H^+]$, 1 bromine pattern. Anal. calcd. for $C_{16}H_{14}BrN_3O$: C, 55.83; H, 4.10; N, 12.21. Found: C, 55.67; H, 4.04; N, 12.10.

Representative Reductive Amination Procedure

Preparation. $NaBH(OAc)_3$ (2.64 g, 12.46 mmol) was added portionwise to a stirred ice-cold solution of 6-methoxy-3-nitropyridine-2-carboxaldehyde **7** (2.10 g, 11.50 mmol) and 2-benzylaminomethyl-5-(4-bromophenyl)-1,3,4-oxadiazole **14** (3.30 g, 9.59 mmol) in DCM (30 mL) over 5 min. The solution was allowed to warm to rt. After 18 h, the reaction mixture was washed with $NaHCO_3$ solution (2×10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and evaporated. The residue was triturated with a mixture of MeOH and ether (1:9) to give a solid, which was filtered and washed with fresh ether to give **15**. Yield: 4.40 g, 90%; amorphous white solid.

Data. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.85$–4.00 (br s, 2H), 4.05 (s, 3H), 4.10 (s, 2H), 4.40 (s, 2H), 6.75 (d, $J = 10.75$ Hz, 1H), 7.18–7.35 (m, 5H), 7.67 (d, 6.90 Hz, 2H), 7.92 (d, $J = 8.60$ Hz, 2H), 8.12 (d, $J = 10.75$ Hz, 1H). MS (APCI+ve): m/z (%) = 510/512 (100%) $[M + H^+]$, 1 bromine pattern. MS (APCI-ve): m/z (%) = 509/511 (100%) $[M - H^+]$, 1 bromine pattern. Anal. calcd. for $C_{23}H_{20}BrN_5O_4$: C, 54.12; H, 3.95; N, 13.72. Found: C, 53.97; H, 4.00; N, 13.60. TLC Rf 0.69 (EtOAc/pentane 1:1), Rf 0.76 (DCM/MeOH 95:5).

Representative Two-Stage, One-Pot Reduction/Cyclization Procedure

Preparation. Iron powder (1.43 g, 25.57 mmol) was added to a suspension of **15** (4.35 g, 8.52 mmol) in AcOH (45 mL) in one portion. The resulting mixture was heated to 65 °C under nitrogen for 3 h. The remaining iron powder was filtered and washed well with fresh AcOH. The filtrate was then evaporated to dryness. The residue was azeotroped with toluene (2 × 10 mL) and then partitioned between EtOAc (60 mL) and saturated $NaHCO_3$ solution (30 mL). This mixture was filtered through a pad of celite to remove residual iron powder. The organic phase was then separated; washed with 10% aqueous citric acid solution, water (10 mL), and brine (10 mL), dried over $MgSO_4$, filtered, and evaporated to give **16**. Yield: 2.40 g, 61%; amorphous fawn solid.

Data. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.60$–4.10 (br m, 6H), 4.05 (s, 3H), 6.70 (d, $J = 7.15$ Hz, 1H), 7.10 (d, $J = 7.15$ Hz, 1H), 7.30–7.60 (m, 9H). MS (APCI+ve): m/z (%) = 462/464 (100%) [$M + H^+$], 1 bromine pattern. Anal. calcd. for $C_{23}H_{20}BrN_5O$: C, 59.74; H, 4.36; N, 15.15. Found: C, 59.52; H, 4.37; N, 14.80. TLC Rf 0.60 (EtOAc), Rf 0.42 (DCM/MeOH 95:5).

Representative Suzuki Coupling Reaction

Preparation. A solution of Na_2CO_3 (445 mg, 4.20 mmol) in water (3 mL) and tetrakistriphenylphosphine (100 mg) was added to a stirred and degassed solution of **16** (971 mg, 2.10 mmol) and 2-methoxyphenylboronic acid (478 mg, 3.15 mmol) in 1,2-dimethoxyethane (10 mL). The reaction flask was then immersed in an oil bath preheated to 120 °C. After 5 h, the reaction was evaporated to low volume and diluted with EtOAc (20 mL) and water (10 mL). The organic phase was separated, washed with saturated $NaHCO_3$ solution (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and evaporated. The oily residue crystallized readily and was triturated with ether and filtered to yield the biphenyl product **17a**. Yield: 950 mg, 92%; amorphous white solid.

Data. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.70$–4.10 [m, 10H inc 3.80 (s, 3H) and 4.05 (s, 3H)], 6.65–6.80 (m, 1H), 6.95–7.10 (m, 2H), 7.20–7.65 (m, 12H). MS (APCI+ve): m/z (%) = 490 (100%) [$M + H^+$]. Anal. calcd. for $C_{30}H_{27}N_5O_2 \cdot 0.4H_2O$: O: C, 72.53; H, 5.64; N, 14.10. Found: C, 72.87; H, 5.57; N, 13.73. TLC Rf 0.44 (EtOAc), Rf 0.22 (DCM/MeOH 95:5).

Data for Compound 17b (Ar = 2-Methylphenyl). Yield: 1 g, 98%; amorphous white solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.30$ (s, 3H), 3.75–4.05 (m, 6H), 4.05 (s, 3H), 6.70–6.78 (d, $J = 8.60$ Hz, 1H), 7.20–7.60 (m, 14H). MS (APCI+ve): m/z (%) = 474 (100%) [$M + H^+$]. Anal. calcd. for $C_{30}H_{27}N_5O \cdot 0.5H_2O$: C, 74.67; H, 5.85; N, 14.51. Found: C, 74.44; H, 5.77; N, 13.58. TLC Rf 0.45 (EtOAc), Rf 0.34 (DCM/MeOH 95:5).

Representative Debenzylation of Biphenyl Products

Preparation. The N-benzyl derivative **17a** (Ar = 2-methoxyphenyl) (869 mg, 1.77 mmol) was added to a suspension of 20% $Pd(OH)_2$ / C (50 mg) in EtOH

(20 mL) under nitrogen. Ammonium formate (1.12 g, 17.75 mmol) was then added, and then mixture was heated to reflux. After 8 h, the catalyst was filtered, and the filtrate evaporated. The residue was partitioned between EtOAc (20 mL) and water (10 mL). The organic phase was separated, washed with $NaHCO_3$ solution (10 mL) and brine, dried over $MgSO_4$, filtered, and evaporated. The resulting solid was triturated with ether and filtered to yield the product **18a**, which was pure enough to use in subsequent reactions. Yield: 410 mg, 58%; amorphous white solid.

Data. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.20$–2.60 (br s, 1H), 3.75 (s, 3H), 3.95 (s, 3H), 3.90–4.10 (br m, 4H), 6.62 (d, $J = 8.50$ Hz, 1H), 6.90–7.00 (m, 2H), 7.17 (d, $J = 8.50$ Hz, 1H), 7.22–7.30 (m, 2H), 7.45–7.55 (m, 4H). MS (APCI+ve): m/z (%) = 400 (100%) [$M + H^+$]. TLC Rf 0.41 (DCM/MeOH/aqueous NH_4OH 90:10:1).

Data for compound 18b (Ar = 2-methylphenyl). Yield: 371 mg, 92%; white foam. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.00$–2.60 (br s, 1H), 2.25 (s, 3H), 4.05 (s, 3H), 4.10–4.25 (m, 4H), 6.70 (d, $J = 7.86$ Hz, 1H), 7.15–7.30 (m, 5H), 7.37 (d, $J = 8.60$ Hz, 2H), 7.57 (d, $J = 8.60$ Hz, 2H). MS (APCI+ve): m/z (%) = 384 (100%) [$M + H^+$]. TLC Rf 0.22 (DCM/MeOH/aqueous NH_4OH 90:10:1).

Representative Methylation Procedure

Preparation. To a stirred solution of **18a** (Ar = 2-methoxyphenyl) (100 mg, 0.25 mmol) in DCM (3 mL) was added a 37% aqueous solution of formaldehyde (81 µl, 1 mmol). The resulting mixture was stirred at rt for 30 mins. Sodium triacetoxyborohydride 964 mg, 0.30 mmol) was then added. After 1 hr $NaHCO_3$ solution (3 mL) was added and the stirring continued for 20 mins. The organic layer was then separated and washed with brine (3 mL), dried over $MgSO_4$ filtered and evaporated to give the product **22a**. Yield: 80 mg, 77%; white foam.

Data. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.60$ (s, 3H), 3.70 (s, 3H), 3.75–3.95 (m, 4H), 4.05 (s, 3H), 6.70 (d, $J = 7.20$ Hz, 1H), 6.95–7.10 (m, 2H), 7.20–7.40 (m, 3H), 7.50–7.65 (m, 4H). MS (APCI+ve): m/z (%) = 414 (100%) [$M + H^+$]. Anal. calcd. for $C_{24}H_{23}N_5O_2$:0.5H_2O: C, 68.23; H, 5.73; N, 16.58. Found: C, 68.20; H, 5.64; N, 16.28. TLC Rf 0.15 (DCM:MeOH 95:5).

Data for compound 22b (Ar = 2-methylphenyl). Yield: 83 mg, 89%; white foam. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.25$ (s, 3H), 2.65–2.75 (br s, 3H), 3.70–4.20 (m, 4H), 4.05 (s, 3H), 6.75 (d, $J = 7.15$ Hz, 1H), 7.20–7.35 (m, 5H), 7.38 (d, $J = 7.15$ Hz, 2H), 7.60 (d, $J = 7.15$ Hz, 2H). MS (APCI+ve): m/z (%) = 398 (100%) [$M + H^+$]. Anal. calcd. for $C_{24}H_{23}N_5O \cdot 0.5H_2O$: C, 70.92; H, 5.95; N, 17.23. Found: C, 70.64; H, 5.87; N, 16.95. TLC Rf 0.14 (DCM/MeOH 95:5).

Representative Acylation Procedures

Preparation. Acetyl chloride (21 µl, 23 mg, 0.29 mmol) was added to a stirred ice-cold solution of **18a** (Ar = 2-methoxyphenyl) (90 mg, 0.22 mmol) and di-isopropylethylamine (41 mg, 0.31 mmol). The resulting solution was allowed to warm to rt. After 1 h, the solution was diluted with DCM (5 mL); washed with water

(3 mL), $NaHCO_3$ solution (3 mL), and brine (3 mL); dried over $MgSO_4$; filtered; and evaporated to give the product **19a** (R = CH_3). Yield: 74 mg, 75%; white foam.

Data. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 and 2.40 (2 × s, 3H, rotamers), 3.80 (s, 3H), 4.00 (s, 3H), 4.60–5.00 (m, 4H), 6.70–6.80 (m, 1H), 6.98–7.10 (m, 2H), 7.25–7.40 (m, 3H), 7.50–7.70 (m, 4H). MS (APCI+ve): m/z (%) = 442 (100%) [M + H$^+$]. Anal. calcd. for $C_{25}H_{23}N_5O_3 \cdot 0.4H_2O$: C, 66.92; H, 5.35; N, 15.61. Found: C, 67.31; H, 5.31; N, 15.45. TLC Rf 0.16 (DCM/MeOH 95:5), Rf 0.27 (DCM/MeOH/aqueous NH_4OH 90:10:1).

Data for compound 19b (Ar = 2-methylphenyl). Yield: 60 mg, 68%; white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3H), 2.38 and 2.40 (2 × s, 3H, rotamers), 4.00 (s, 3H), 4.65–5.00 (m, 4H), 6.70–6.80 (m, 1H), 7.20–7.65 (m, 9H). MS (APCI+ve): m/z (%) = 426 (100%) [M + H$^+$]. Anal. calcd. for $C_{25}H_{23}N_5O_2 \cdot 0.5H_2O$: O: C, 69.11; H, 5.57; N, 16.12. Found: C, 69.14; H, 5.50; N, 15.95. TLC Rf 0.13 (DCM/MeOH 95:5), Rf 0.61 (DCM/MeOH/aqueous NH_4OH 90:10:1).

Methylchloroformate (23 µl, 28 mg, 0.29 mmol) was added. to a stirred ice-cold solution of **18a** (Ar = 2-methoxyphenyl) (90 mg, 0.22 mmol) in DCM (3 mL) and di-isopropylethylamine (41 mg, 0.31 mmol). The resulting solution was allowed to warm to rt. After 1 h, the solution was diluted with DCM (5 mL), washed with water (3 mL), $NaHCO_3$ solution (3 mL), and brine (3 mL); dried over $MgSO_4$; filtered; and evaporated. The residue was triturated with ether and filtered to give the product **20a** (R = OCH_3). Yield: 74 mg, 72%; amorphous white solid.

Data. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 6H), 4.02 (s, 3H), 4.60–4.90 (m, 4H), 6.74 (d, J = 7.15 Hz, 1H), 6.95–7.08 (m, 2H), 7.20–7.40 (m, 3H), 7.50–7.63 (m, 4H). MS (APCI+ve): m/z (%) = 458 (100%) [M + H$^+$]. Anal. calcd. for $C_{25}H_{23}N_5O_4$: C, 65.63; H, 5.06; N, 15.31. Found: C, 65.35; H, 5.08; N, 15.10. TLC Rf 0.24 (DCM/MeOH 95:5), Rf 0.33 (DCM/MeOH/aqueous NH_4OH 90:10:1).

Data for compound 20b (Ar = 2-methylphenyl). Yield: 54 mg, 58%; amorphous white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.26 (s, 3H), 3.80 (s, 3H), 4.02 (s, 3H), 4.60–4.85 (m, 4H), 6.75 (d, J = 7.15 Hz, 1H), 7.20–7.34 (m, 5H), 7.39 (d, J = 7.15 Hz, 2H), 7.58 (d, J = 7.15 Hz, 2H). MS (APCI+ve): m/z (%) = 442 (100%) [M + H$^+$]. Anal. calcd. for $C_{25}H_{23}N_5O_3 \cdot 0.4H_2O$: C, 66.92; H, 5.35; N, 15.61. Found: C, 67.04; H, 5.26; N, 15.52. TLC Rf 0.17 (DCM/MeOH 95:5), Rf 0.77 (DCM/MeOH/aqueous NH_4OH 90:10:1).

Representative Sulfonamide Formation

Preparation. Methanesulfonyl chloride (22 µl, 23 mg, 0.29 mmol) was added to a stirred ice-cold solution of **18a** (Ar = 2-methoxyphenyl) (90 mg, 0.22 mmol) and di-isopropylethylamine (41 mg, 0.31 mmol) in DCM (3 mL). The resulting solution was allowed to warm to rt. After 1 h, the solution was diluted with DCM (5 mL); washed with water (3 mL), $NaHCO_3$ solution (3 mL), and brine (3 mL); dried over $MgSO_4$; filtered; and evaporated. The residue was triturated in ether and filtered to give the product **21a** (R = CH_3SO_{2-}). Yield: 76 mg, 70%; amorphous white solid.

Data. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.96$ (s, 3H), 3.80 (s, 3H), 4.02 (s, 3H), 4.40–4.80 (m, 4H), 6.75 (d, $J = 7.15$ Hz, 1H), 6.97–7.10 (m, 2H), 7.25–7.40 (m, 3H), 7.55–7.65 (m, 4H). MS (APCI+ve): m/z (%) = 478 (100%) [$M + H^+$]. Anal. calcd. for $C_{24}H_{23}N_5O_4S$: C, 60.36; H, 4.85; N, 14.66. Found: C, 59.99; H, 4.98; N, 14.35. TLC Rf 0.24 (DCM/MeOH 95:5), Rf 0.31 (DCM/MeOH/aqueous NH_4OH 90:10:1).

Data for compound 21b (Ar = 2-methylphenyl). Yield: 57 mg, 59%; white foam. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.25$ (s, 3H), 2.98 (s, 3H), 4.02 (s, 3H), 4.40–4.80 (m, 4H), 6.82 (d, 1H), 7.20–7.35 (m, 5H), 7.41 (d, 2H), 7.58 (d, 2H). MS (APCI+ve): m/z (%) = 462 (100%) [$M + H^+$]. Anal. calcd. for $C_{24}H_{23}N_5O_3S \cdot H_2O$: C, 60.11; H, 5.25; N, 14.60. Found: C, 60.13; H, 5.04; N, 14.13. TLC Rf 0.17 (DCM/MeOH 95:5), Rf 0.75 (DCM/MeOH/aqueous NH_4OH 90:10:1).

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