Preparation of Acidic 5-Hydroxy-1,2,3-triazoles via the Cycloaddition of Aryl Azides with β-Ketoesters

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ABSTRACT: Herein, a high-yielding cycloaddition reaction of β-ketoesters and azides to provide 1,2,3-triazoles is described. The reactions employing 2-unsubstituted β-ketoesters were found to provide 5-methyl-1,2,3-triazoles, whereas 2-alkyl-substituted β-ketoesters provided 5-hydroxy-1,2,3-triazoles (shown to be relatively acidic) in high yields and as single regioisomers. Several novel compounds were reported and characterized including long-chain 5-hydroxy-1,2,3-triazoles potentially bioisosteric to hydroxamic acids.

INTRODUCTION

1,2,3-Triazoles are important scaffolds employed in medicinal chemistry,1 catalysis,2 materials science,3 and biology.4 The electronic and physicochemical properties of triazoles bear a close similarity to those of the amide functionality and therefore can be classiﬁed as amide bioisosteres.5,6 Copper-catalyzed alkyne−azide cycloaddition is the most accredited method to synthesize substituted 1,2,3-triazoles,7−11 while the less well-known reactions of malonates or β-ketoesters with aromatic azides have become attractive alternatives as they do not require metal catalysts to proceed (Figure 1).12

β-Ketoesters react quickly with mild bases, providing highly reactive enolates that have a myriad of reported applications in organic chemistry.13,14 Dimroth reported a cycloaddition of β-ketoesters and azides in 190215 where ethyl acetoacetate reacted with azidobenzene in the presence of sodium ethoxide to provide 5-hydroxytriazoles in poor yields. This material was properly identiﬁed; however, it was not characterized beyond the physical constants and, notably, their remarkable acidity was overlooked. More recently, Wang and co-workers reported the cycloaddition of β-ketoesters and azides, via organocatalysis, to yield 1,4-disubstituted 1,2,3-triazoles.16 Intrigued by these reports15,16 where the same reagents gave rise to different products under similar basic conditions, and in a continuation of our studies on the reactivity of azides and enolates (Figure 1),17 we decided to re-examine the cycloaddition of simple ketoesters and aromatic azides in the presence of organic bases.

RESULTS AND DISCUSSION

This work involved reacting a selection of pyridyl- or aryl-azides and β-ketoesters and showed that distinct triazole products could be obtained in high yields via a divergent reaction pathway that led to either disubstituted 1,2,3-triazoles or 5-hydroxy-1,2,3-triazoles depending upon the nature of the β-ketoester. These ﬁndings were subsequently exploited to prepare a family of 5-hydroxytriazoles, whose acidity has been shown to be even stronger (pK_a = 4.20 for 5a) than those for

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Table 1. Cycloaddition of β-Ketoester 1a with Aryl Azides 2•

| entry | keto ester | aryl azide | Py | product | catalyst | solvent | yield (%) |
|-------|------------|------------|----|---------|----------|---------|-----------|
| 1     | 1a         | 2a         | 4py | 3a      | MeCN     | 80      |
| 2     | 1a         | 2b         | 3py | 3b      | MeCN     | 72      |
| 3     | 1a         | 2c         | 2py | 3c      | MeCN     | 0       |
| 4     | 1a         | 2c         | 2py | 3c      | Cu(O Tf)₂C₅H₃ | 50      |

*Reaction conditions are as follows: 1a (1.2 equiv), 2a–c (1 equiv), DBU (1.2 equiv), and solvent (0.2 M). *Isolated yield.

Table 2. Cycloaddition of β-Ketoesters and Aryl Azides to Give 5-Hydroxytriazoles

| entry | ketoester | Arroy | product | time (h) | yield (%) |
|-------|-----------|-------|---------|----------|-----------|
| 1     | 1a        | 4a    | 5a      | 18       | 87        |
| 2     | 1b        | 4a    | 5a      | 6        | 80        |
| 3     | 1b        | 4a    | 5b      | 18       | 87        |
| 4     | 1b        | 4b    | 5c      | 6        | 82        |
| 5     | 1b        | 4c    | 5d      | 6        | 74        |
| 6     | 1b        | 4c    | 5e      | 6        | 86        |
| 7     | 1b        | 4d    | 5f      | 6        | 82        |
| 8     | 1b        | 4f    | 5g      | 6        | 83        |
| 9     | 1b        | 4g    | 5h      | 6        | 86        |
| 10    | 1b        | 4h    | 5i      | 6        | 86        |
| 11    | 1b        | nBu   | 5j      | 6        | 85        |
| 12    | 1b        | 4j    | 5k      | 6        | 87        |
| 13    | 1c        | 4a    | 5l      | 6        | 87        |

*Reaction conditions are as follows: 1b or 1c (1.2 equiv), 4a–j (1 equiv), and DBU (1.2 equiv) in MeCN (0.2 M) at 50 °C. *Isolated yield.

The high yield obtained when reacting 1b with 4a in the presence of solid KOH (potassium hydroxide) as a base and TBAB (tetrabutylammonium bromide) as a PTC (phase-transfer catalyst) encouraged us to study the scope of this transformation (Table 3). Phase-transfer conditions were found to be particularly effective with electron-poor and electron-neutral azides, such as 4a, 4g, and 4h, with yields up to 95%. However, when bulky azide substrates were present, such as 4e, only the hydrolyzed product 6 was favored over cyclization (Table 3). Since compound 5a
Cu²⁺ salts to provide blue-violet and red-colored solutions, accompanied by both organic and inorganic bases, thus justifying their attractiveness as candidates for drug discovery. We further expanded the scope of the cyclization reaction to hydroxytriazoles to be highly soluble in water when bound metals. Compounds bioisosterism, which makes them excellent ligands for enzyme-inhibitor. To exemplify the potential of the 5-hydroxytriazoles and hydroxamic acids. Hydroxamic acids behaved as a relatively strong Brønsted acid, we decided to carry out a titration experiment to better characterize its properties. The pKₐ of 5a was found to be 4.2, which is comparable to that of a carboxylic acid (see the Supporting Information). This result was very unexpected compared to the pKₐ values of the related 4-hydroxy-1,2,3-triazoles, which were found to be significantly less acidic than those reported by Pippione and co-workers. Moreover, we found 5-hydroxytriazoles to be highly soluble in water when accompanied by both organic and inorganic bases, thus justifying their attractiveness as candidates for drug discovery. We further expanded the scope of the cyclization reaction to include cyclic β-ketoesters 7a–c to provide novel long-chain 5-hydroxytriazoles 8. Interestingly, poor conversion was observed when the reaction was performed in solvent, while we saw a notable improvement when the cyclization was performed solvent-free with yields up to 79% (Table 4).

Table 3. Synthesis of 5-Hydroxytriazoles: PTC-Mediated Cycloaddition of β-Ketoester 1b and Aryl Azides 4a

| entry | aryl azide | Ar | product | time (h) | yield (%) |
|-------|------------|----|---------|---------|----------|
| 1     | 4a         | Ph | 5a      | 4       | 95       |
| 2     | 4e         | 1-naphthyl | 5e  | 18      | n.r.*   |
| 3     | 4g         | 4-NO₂C₆H₄ | 5f  | 4       | 76       |
| 4     | 4h         | 2-NO₂-4-MeC₆H₅ | 5g  | 4       | 83       |

“Reaction conditions are as follows: 1b (1.2 equiv), 4 (1.2 equiv), TBAB (0.1 equiv), and KOH (2.2 equiv) in Et₂O (0.2 M) at 20 °C.”

Table 4. Synthesis of Long-Chain 5-Hydroxytriazoles

| entry | ketoester | R | n | solvent | product | yield (%) |
|-------|-----------|---|---|---------|---------|----------|
| 1     | 7a        | Et | 1 | MeCN    | 8a      | 29       |
| 2     | 7a        | Et | 1 | none    | 8a      | 44       |
| 3     | 7b        | Me | 2 | none    | 8b      | 79       |
| 4     | 7c        | Et | 3 | none    | 8c      | 38       |

“Reaction conditions are as follows: 7 (1.2 equiv), 4a (1 equiv), and DBU (1.2 equiv) at 50 °C for 18 h.”

A literature search highlighted the structural similarity of 5-hydroxytriazoles and hydroxamic acids. Hydroxamic acids and 5-hydroxytriazoles share similar pKₐ values and amide-like bioisosterism, which makes them excellent ligands for enzyme-bound metals. Compounds 5a–g and 8 reacted with Fe²⁺ and Cu²⁺ salts to provide blue-violet and red-colored solutions, indicating a ligand-like behavior similar to that of hydroxamic acids. Suberanilohydroxamic acid 9 (SAHA) is a hydroxamic acid that is active as a histone deacetylase (HDAC) inhibitor. To exemplify the potential of the 5-hydroxytriazole nucleus in medicinal chemistry, we set out to convert long-chain 5-hydroxytriazoles 8a–c into terminal N-phenylamide-substituted triazoles 10a–c, which bear a close structural relationship to hydroxamic acid 9 (Figure 3).

The preparation of 10a–c (n = 1–3, respectively) is reported in the Experimental section. The structural and functional similarities between hydroxamic acid 9 and 5-hydroxytriazoles 10 are highlighted in Figure 3 and include the following: (i) nominally similar scaffolds and chemical functionalities; (ii) analogous lone pairs (circled in red) of the carbonyl oxygen of the hydroxamic acid and the pyridyl-like N of the triazole system; (iii) hydrophobic backbones (circled in green), which are essential for interaction with active sites of HDAC isoforms, e.g., zinc-binding groups; and (iv) aromatic rings (in pink), which are essential for the correct positioning in the enzyme active site via π−π stacking.

Based on the reactivity observed, two reaction mechanisms have been proposed (Scheme 1), which lead to distinct products via analogous intermediates 12a and 12b. Intermediates 12a and 12b arise from reaction of enolate 11 with aryl azides (pathway a or pathway b), respectively. In pathway a, species 12a is formed and will evolve toward cyclic amide 13a, which contains no enolizable proton, and the concomitant elimination of ethoxide. A subsequent attack of ethoxide to the acetoxyl group in 13a will lead to the elimination of ethyl acetate and the formation of 5. Conversely, in the presence of an enolizable proton such as in 12b (pathway b), the following cyclization to 13b and its subsequent protonation will generate 14b, which will provide compounds 3 after dehydration. A rationale similar to ours used to explain the mechanism in Scheme 1 has been reported by Pedersen and Begtrup for the reaction between phenyl azides and amides of malonic acids.
In conclusion, we have demonstrated that aryl azides undergo two distinct cycloaddition reactions with enolizable β-ketoesters depending on the substitution pattern on the β-ketoester, leading to different products. The cycloaddition of 2-alkyl-substituted β-ketoester with pyridyl azides and phenyl azide was found to lead to 5-methyl-triazoles, whereas the cycloaddition of 2-alkyl-substituted β-ketoesters with phenyl azide and substituted aryl azides was found to lead to 5-hydroxy-triazoles, where the structure of one of the products has been confirmed via X-ray diffraction (see Figure 2 and the Supporting Information). The reaction of phenyl azide and substituted aryl azides with 2-alkyl-substituted β-ketoesters has been shown to be a fast, mild, and high-yielding method for the synthesis of 5-hydroxy-1,2,3-triazoles. The relatively acidic nature we observed for the 5-hydroxy-triazoles has led us to propose the study of 5-hydroxy-triazole analogues as a new class of bioisosteres of hydroxamic acids. Future work will involve an investigation of this novel class of compounds as potential biological targets and their potential as a bioisosteric relative of biologically active hydroxamic acids.

**EXPERIMENTAL SECTION**

1H and 13C{1H} NMR spectra were recorded on a Bruker 400 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent signals (1H NMR, 7.26 ppm for CDCl3, 2.50 ppm for DMSO-d6, and 3.31 ppm for CD3OD). 13C{1H} NMR spectra were acquired with the 1H broad band decoupled mode. Coupling constants (J, Hz) are in hertz (Hz). Melting points were measured using a Stuart scientific melting point apparatus and were uncorrected. Infrared spectra (IR) were recorded with KBrs discs using a Bruker Tensor27 FT-IR instrument. High-resolution mass spectra were obtained on a Waters Micromass GCT PremierMS spectrometer or on a Bruker microTOF-Q III LC-MS spectrometer (APCI method). Optical rotations were measured on a PerkinElmer 343 polarimeter. HPLC chromatograms were recorded on a YMC-Triart Phenyl 150 × 4.6 mm column using a 5 μL injection volume (60-40 MeCN/H2O) at two different wavelengths of 190 and 254 nm, respectively. The purity of the final products was verified by HPLC analysis and 1H and 13C{1H} NMR spectroscopy. Analytical-grade solvents and commercially available reagents were used as received. Dry DCM was purchased from Sigma-Aldrich. Reactions were monitored by TLC (Merck, silica gel 60 F254). Flash column chromatography was performed using silica gel 60 (0.040–0.063 mm, 230–400 mesh). Substituted arylazides 4a–f and pyridyl azides 2a–c were prepared according to reported procedures.5,10 β-Ketoesters 1a–c and modified ketoesters 7a–c were purchased from Sigma-Aldrich and used without further purification. 5-Hydroxy-1,2,3-triazoles 5a, 5e, 5f, and 5g were synthesized via phase-transfer catalysis according to GP3 and via DBU-promoted synthesis according to GP2, while 5-hydroxy-1,2,3-triazoles 5b, 5c, 5d, and 5k were synthesized according to GP2 via a DBU-promoted synthesis. 5-Methyl-1,2,3-triazole 3a–b were synthesized according to the GP1 procedure. 5-Methyl-1,2,3-triazole 3c was synthesized according to a modified version of GP1. Long-chained 5-hydroxy-1,2,3-triazole-based SAHA analogs 10b–c were synthesized according to GP6 via long-chained 5-hydroxy-1,2,3-triazole precursors 8a–c, which were synthesized according to GP4. The long-chained 5-hydroxy-1,2,3-triazole-based SAHA analog 10a was synthesized according to a modified version of GP4.

**General Procedure for the DBU-Promoted Synthesis of 5-Methyl-1,2,3-triazoles 3a and 3b (GP1).** To a solution of pyridyl azides 2a or 2b (0.5 mmol, 1 equiv) and β-ketoester 1a (0.6 mmol, 1.2 equiv) in MeCN (2.5 mL, 0.2M) was added DBU (0.6 mmol, 1.2 equiv), and the reaction mixture was stirred at 50 °C in an oil bath overnight. The crude mixture was evaporated under vacuum and purified by flash column chromatography (MeOH/DCM/AcOH 90:10:0.1) to afford title compounds 3a and 3b as solids.

*Ethyl 5-Methyl-1-(pyridin-4-yl)-1H-1,2,3-triazole-4-carboxylate 3a.* Yellow solid (93 mg, 80% yield). 1H NMR (400 MHz, CDCl3): δ 8.88 (d, J = 6.1 Hz, 2H), 7.51 (d, J = 6.1 Hz, 2H), 4.48 (q, J = 6.1 Hz, 2H), 2.72 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H). 13C{1H} NMR (101 MHz, CDCl3): δ 161.4, 151.7, 142.5, 138.7, 61.4, 14.4, 14.3, 10.3. IR (KBr, cm−1): 3278, 3132, 3100, 1748, 1560, 1480. mp 76.8, 61.3, 14.4, 9.9. All analytical data are consistent with those reported in the literature.

*Synthesis of Ethyl 5-Methyl-1-(pyridin-2-yl)-1H-1,2,3-triazole-4-carboxylate 3b.* To a solution of 2c (100 mg, 0.83 mmol, 1 equiv) in DMSO (1.4 mL, 0.6M) were added 1a (141 ul, 1 mmol, 1.2 equiv), DBU (150 ul, 1 mmol, 1.2 equiv), and Cu(OtBu)2. CD3OD (43 mg, 0.083 mmol, 0.1 equiv). The reaction mixture turned from light brown to black upon the addition of the catalyst and was stirred for 48 h. TLC showed the complete consumption of 2c, and the mix was cooled to room temperature and extracted with DCM/H2O three times. The collected organic phases were filtered through a Celite pad and concentrated in vacuo. The crude product was purified by flash column chromatography (DCM/AcOEt 90:10) to afford the product 3c in a modest yield (58 mg, 50% yield) as a yellow oil. TLC showed the product to be visible as a brilliant purple spot under an UV lamp at a short wavelength. All analytical data are consistent with those reported in the literature.

**General Procedure for the DBU-Promoted Synthesis of 5-Hydroxy-1,2,3-triazoles 5a–k (GP2).** To a solution of aryl azides 4 (0.5 mmol, 1 equiv) and β-ketoester 1 (0.6 mmol, 1.2 equiv) in MeCN (0.2M) was added DBU (0.6 mmol, 1.2 equiv), and the reaction mixture was stirred at 50 °C in an oil bath overnight. The crude mixture was evaporated under vacuum and purified via flash column chromatography (MeOH/DCM/AcOH 90:10:0.1) to afford title compounds 5a–k as solids. In some cases where the chromatography, products 5a–k still contained traces of the DBU salt, which were easily removed by the trituration of the solid with a minimum quantity of water.

**General Procedure for the Synthesis of 5-Hydroxy-1,2,3-triazoles 5a and 5e–g via Phase-Transfer Catalysis (GP3).** To a solution of aryl azides 4a, 4e–g (1.2 mmol, 1 equiv), and β-ketoester 1 (1.2 mmol, 1 equiv) in diethyl ether (0.2M) were added tetrabutylammonium bromide (0.11 mmol, 10 mol %) and finely ground KOH (2.4 mmol, 2 equiv) at room temperature. After 4 h of vigorous stirring, the white precipitate was collected by vacuum filtration. The solid, a potassium salt of 5, was dispersed in 1 mL of MeCN, and acetic acid was added until dissolution. The mixture was evaporated and purified via flash column chromatography (MeOH/DCM 1:9) to afford the products 5a and 5e–g.

*5-Hydroxy-1,2,3-triazole 5a.* Prepared according both GP2 and GP3 to provide 5a as a white solid (70 mg, 80% yield and 201 mg, 95% yield, respectively). 1H NMR (400 MHz, CDCl3): δ 8.28 (bs, 1H), 7.80 (d, J = 7.7 Hz, 2H), 7.44 (t, J = 7.7 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 2.25 (s, 3H). 13C{1H} NMR (101 MHz, CDCl3): δ 152.2, 151.8, 129.1, 128.4, 123.4, 119.6, 13.8, 13.7. HRMS (ESI) m/z: [M + H]+ calc'd for C11H12N4O2 190.0826, found 190.0831.

*5-Hydroxy-1,2,3-triazole 5b.* Prepared according to GP2. Off-white solid (110 mg, 87% yield). 1H NMR (400 MHz, DMSO-d6): δ 8.18 (bs, 1H), 7.70–7.74 (m, 4H),
Hydroxy-1,2,3-triazolecarboxylic acids 11a

Ethyl 7-(5-Hydroxy-1-phenyl-1,2,3-triazol-4-yl)heptanoic ester 8b. Off-white solid (275 mg, 79% yield in solvent-free conditions). 1H NMR (400 MHz, DMSO-d6): δ 1.20 (t, J = 7.3 Hz, 2H), 7.44–7.46 (m, 2H), 7.50 (m, 2H), 7.48–7.50 (m, 2H), 7.46–7.48 (m, 2H), 7.25–7.27 (m, 2H), 1.70–1.72 (m, 2H), 1.59–1.61 (m, 2H), 1.56–1.58 (m, 2H), 1.49–1.51 (m, 2H), 1.38–1.40 (m, 2H). 13C{1H} NMR (101 MHz, DMSO-d6): δ 135.8, 129.2, 128.0, 124.2, 122.2, 63.5, 28.8, 28.7, 24.8, 24.3, 22.6. IR (KBr, cm⁻¹): 2921, 1714, 1606. mp 110–112°C. HRMS (ESI) m/z: [M + H]⁺ calcld for C12H11N3O2 218.0951, found 218.0954.

General Procedure for the Synthesis of Long-Chain 5-Hydroxy-1,2,3-triazolylcarboxylic acids 11a-c (GPS). To a dispersion of 1,2,3-triazole esters 8a-c (0.5 mmol, 1 equiv) in water (0.1 M) at 0 °C was added KOH pellets (5.0 mmol, 10 equiv). Upon the complete dissolution of KOH and the ester, the ice bath was removed, and the reaction mixture was vigorously stirred for 2 h at room temperature. The reaction mixture was again cooled to 0 °C, and HCl (37%aq.) was added dropwise to reach pH1 and precipitate out the free form of the desired compound. The latter was collected by vacuum filtration and dried under vacuum to afford 5-hydroxy-1,2,3-triazolylcarboxylic acids 11a-c in their pure form.

Ethyl 5-(5-Hydroxy-1-phenyl-1,2,3-triazol-4-yl)pentanoic acid 11a. White solid (79 mg, 60% yield). 1H NMR (400 MHz, DMSO-d6): δ 1.19 (s, 3H), 1.20 (t, J = 7.6 Hz, 2H), 7.45–7.50 (m, 2H), 7.48–7.50 (m, 2H), 1.61–1.62 (m, 2H), 1.38–1.40 (m, 2H). 13C{1H} NMR (101 MHz, DMSO-d6): δ 174.5, 135.8, 129.4, 128.0, 122.2, 33.5, 28.4, 24.2, 24.3. IR (KBr, cm⁻¹): 3340, 2350, 1700, 1601, 1562. mp 122–122.8°C. HRMS (ESI) m/z: [M + H]⁺ calcld for C14H17N3O2 276.1348, found 276.1343.

Synthesis of N-Phenyl-5-(5-hydroxy-1,2,3-triazol-4-yl)pyridanamide 10a. Carboxylic acid 11a (0.49 mmol, 1 equiv) was dissolved in triethylchloride (0.49 M). The reaction mixture was refluxed at 60 °C for 2 h in an oil bath. The reaction mixture was evaporated under vacuum to remove the excess triethylchloride. The crude acyl chloride was dissolved in dry DCM (1 mL), and to the solution were added aniline (0.54 mmol, 1 equiv) and triethylamine (0.54 mmol, 1 equiv). The reaction mixture was stirred at room
temperature under nitrogen overnight. The crude was diluted in AcOEt (20 mL) and washed with saturated sodium bicarbonate (5 mL) and HCl (5 mL of 1 M aq.). The organic phase was dried over sodium sulfate and evaporated under vacuum. The crude amide was purified by flash column chromatography (AcOEt/petroleum ether 1:1 to 1:0) to yield the target compound 10b in 61% yield (101 mg) as a white solid. 3H NMR (400 MHz, DMSO-d$_6$): δ 8.90 (s, 1H), 7.72 (d, J = 7.8 Hz, 2H), 7.64−7.51 (m, 4H), 7.48−7.39 (m, 1H), 7.32−7.23 (m, 2H), 7.06−6.97 (m, 1H), 2.67−2.58 (m, 2H), 2.42−2.31 (m, 2H), 1.75−1.60 (m, 4H). 13C{1H} NMR (101 MHz, DMSO-d$_6$): δ 171.3, 139.4, 135.8, 129.3, 128.7, 128.0, 123.0, 122.2, 119.1, 36.4, 28.6, 24.9, 23.2. IR (KBr, cm$^{-1}$): 2372, 1649, 1590. mp 152−153 °C. HRMS (ESI) m/z: [M + H]$^+$ calc'd for C$_{21}$H$_{23}$N$_4$O$_2$ 337.1676, found 337.1676.

General Procedure for the Synthesis of Long-Chain N-Phenyl-5-hydroxy-1,2,3-triazoleamides 10b and 10c (GP6). To a solution of carboxylic acid 11b or 11c (0.40 mmol, 1 equiv) in dry DCM (0.2M) in a round-bottom flask was added triethylamine (0.48 mmol, 1.2 equiv) and aniline (0.48 mmol, 1.2 equiv). The solution was added with carbonyldiimidazole (CDI) (0.48 mmol, 1.2 equiv) and stirred overnight at room temperature. The crude mixture was diluted with AcOEt (20 mL), washed with HCl (5 mL of 0.5 M aq.), dried over sodium sulfate, and evaporated under vacuum. The crude amide was purified by flash column chromatography (AcOEt/petroleum ether 1:1 to 1:0) to yield the title compounds 10b and 10c as white solids.

1H NMR (49 mg, 35% yield). 3H NMR (400 MHz, DMSO-d$_6$): δ 11.36 (bs, 1H), 9.86 (s, 1H), 7.71 (d, J = 6.7 Hz, 2H), 7.62−7.50 (m, 4H), 7.48−7.40 (m, 1H), 7.32−7.22 (m, 2H), 7.05−6.96 (m, 1H), 2.58 (t, J = 7.5 Hz, 2H), 2.31 (t, J = 7.4 Hz, 2H), 1.72−1.55 (m, 4H), 1.45−1.33 (m, 2H). 13C{1H} NMR (101 MHz, DMSO-d$_6$): δ 171.3, 139.4, 135.8, 129.3, 128.7, 127.9, 122.9, 122.2, 119.0, 36.4, 28.7, 28.4, 25.0, 23.2. IR (KBr, cm$^{-1}$): 2378, 1654, 1559. mp 148−149.3 °C. HRMS (ESI) m/z: [M + H]$^+$ calc'd for C$_{13}$H$_{14}$NO$_2$ 231.1821, found 231.1815.

11b: 3H NMR (40 mg, 35% yield). 3H NMR (400 MHz, DMSO-d$_6$): δ 9.87 (s, 1H), 7.71 (d, J = 7.8 Hz, 2H), 7.62−7.49 (m, 4H), 7.48−7.40 (m, 1H), 7.31−7.21 (m, 2H), 7.05−6.96 (m, 1H), 2.57 (t, J = 7.5 Hz, 2H), 2.30 (t, J = 7.4 Hz, 2H), 1.66−1.55 (m, 4H), 1.41−1.29 (m, 4H). 13C{1H} NMR (101 MHz, DMSO-d$_6$): δ 171.3, 139.4, 135.8, 129.3, 128.7, 127.9, 122.9, 122.2, 119.0, 36.4. IR (KBr, cm$^{-1}$): 2367, 1658, 1535. mp 142−146 °C. HRMS (ESI) m/z: [M + H]$^+$ calc'd for C$_{21}$H$_{23}$N$_4$O$_2$ 351.1821, found 351.1815.

Accession Codes
CCDC 2051417 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes
The authors declare no competing financial interest.

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