Click Chemistry Approach to Isoindole-1,3-dione Tethered 1,2,3-Triazole Derivatives

Rajneesh Kaur⁴
Raman Singh⁵
Antresh Kumar⁶
Kuldeep Singh⁴,⁷

⁴ Department of Chemistry, MMMEC, Maharishi Markandeshwar (Deemed to be University), Mullana, Haryana, 133207, India
singh@orgsyn.in
⁵ Department of Biotechnology, Central University of South Bihar, Panchanpur, Gaya-824236, India

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Abstract A convenient and efficient approach for the synthesis of novel 1,2,3-triazole tethered isoindol-1,3-dione conjugates by a nucleophilic substitution reaction of phthalic anhydride with 1,2,3-triazole containing carbohydrazide is described. The latter were prepared by using click chemistry.

Key words amidazition, hydrazinolysis, carbohydrazide, carboxamide, click chemistry

Functionalized isoindole-1,3-dione derivatives exhibit a vast range of biological activities such as antibacterial, teratogenic, anticancer (multiple myeloma), PPAR-γ agonist, and anti-inflammatory activities. Bioactive molecules containing an isoindol-1-3-dione moiety include Thalidomide 1, Pomalidomide 2, and Apremilast 3 (Figure 1).

Compounds containing the 1,2,3-triazole moiety also show antitubercular activity and phthalic anhydride derivatives also showed antitubercular activity. Based on these findings, new molecules were designed, and the synthesis of 1,2,3-triazole moieties connected to isoindole-1,3-dione derivatives via a hydrazide linkage is reported herein. PASS Online predicts these compounds may be antimycobacterial or antineoplastic agents. Thus, the synthesis of 1,2,3-triazole-isoindole-1,3-dione derivatives has been explored.

The desire to construct biologically relevant molecules starting from simple molecules leads to a constant demand for new synthetic methodologies. A simple and straightforward strategy to access the desired isoindole-1,3-dione-tethered 1,2,3-triazole derivatives would involve click chemistry (Scheme 1), with the fragments being connected by following either path A or Path B. In the present work, we followed Path A as it helps to generate and introduce diversity in the final product. Diversity in the final products can be introduced at three points by varying the azide, alkyne, and the phthalic anhydride, thus permitting access to multifunctional, highly substituted derivatives.
To start with, aromatic amines 9 were converted into the corresponding azides 6 via reaction of their respective diazonium salt with sodium azide by following reported procedures (Scheme 2).\(^{13,14}\) The azides were used without further purification and were subjected to 1,3-dipolar cycloaddition\(^{15}\) with an ethyl propynoate in H\(_2\)O/t-BuOH (1:1) to yield the corresponding cycloaddition products 5 in good to excellent yields (Scheme 2).\(^{16}\) These compounds were fully characterized by \(^1\)H and \(^13\)C NMR spectroscopy. For instance, compound 5a showed eleven resonances in its \(^13\)C NMR spectrum and, in its \(^1\)H NMR spectrum, a resonance at \(\delta = 9.91\) ppm could be assigned to the C-5 proton of the triazole.

![Scheme 2 Preparation of triazole ester 5a–d. Reagents and conditions: (a) HCl/H\(_2\)O (1:1), sodium azide, sodium acetate, sodium nitrite, 0–5\(^\circ\)C (b) t-BuOH/H\(_2\)O (1:1), ethyl propynoate, copper acetate, sodium ascorbate.](image)

Next, hydrazides 11 were prepared by reacting carboxylate derivatives 5 with hydrazine hydrate in ethanol at reflux (Scheme 3).\(^{17}\) The absence of resonances at \(\delta = 61.6\) and 14.3 ppm in the \(^13\)C NMR spectra of hydrazides 11 supported their formation. The \(^1\)H NMR spectra of hydrazides 11a–d still exhibited the characteristic resonance due to the C-5 proton of the triazole moiety, but the ethyl ester resonances had been replaced by NH and NH\(_2\) resonances at \(\delta = 9.91\) (bs, 1H) and 4.53 ppm (bs, 2H).

![Scheme 3 Preparation of hydrazide 11a–d](image)

After synthesizing 1,2,3-triazole carbohydrazides 11, preparation of isoindole-1,3-dione derivatives 4 was performed (Scheme 4). 1,2,3-Triazole carbohydrazides 11 were treated with the phthalic anhydride 8 under a range of reaction conditions; the results are summarized in Table 1. These studies revealed that a catalytic amount of glacial acetic acid is required for complete amidation. Reactions without glacial acetic acid were slower and lower yielding. This sluggishness is presumably due to the lower nucleophilicity of the NH\(_2\) group attached to a 1,2,3-triazole compared with aliphatic and aromatic amines.

![Scheme 4 Preparation of triazole carboxamide 4a–d. Reagents and conditions: (a) ethanol, reflux (b) Glacial acetic acid, toluene.](image)

Thus, the reaction of compounds 11 with phthalic anhydride in toluene using a catalytic amount of glacial acetic acid at 110 \(^\circ\)C to afford isoindole-1,3-dione derivatives 4 was found to be optimal (Scheme 4).\(^{18}\) All compounds were fully characterized spectroscopically.

### Table 1 Reaction Conditions for Amidation Reaction

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Additive</th>
<th>Conditions</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF</td>
<td>–</td>
<td>reflux</td>
<td>24</td>
<td>no reaction</td>
</tr>
<tr>
<td>DMSO</td>
<td>–</td>
<td>reflux</td>
<td>24</td>
<td>no reaction</td>
</tr>
<tr>
<td>THF</td>
<td>–</td>
<td>reflux</td>
<td>24</td>
<td>no reaction</td>
</tr>
<tr>
<td>toluene</td>
<td>–</td>
<td>reflux</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>DMF</td>
<td>glacial AcOH (0.004 mmol)</td>
<td>reflux</td>
<td>24</td>
<td>no reaction</td>
</tr>
<tr>
<td>DMSO</td>
<td>glacial AcOH (0.004 mmol)</td>
<td>reflux</td>
<td>24</td>
<td>no reaction</td>
</tr>
<tr>
<td>THF</td>
<td>glacial AcOH (0.004 mmol)</td>
<td>reflux</td>
<td>24</td>
<td>no reaction</td>
</tr>
<tr>
<td>toluene</td>
<td>glacial AcOH (0.004 mmol)</td>
<td>reflux</td>
<td>2</td>
<td>63–79</td>
</tr>
</tbody>
</table>

Table 2 summarizes the yields of the various compounds synthesized. The infrared spectra of carboxylates 5 exhibited a characteristic peak for an ester carbonyl group; whereas there was a sharp decrease in the IR frequency for the carbohydrazide carbonyl group in 11 due to the amide linkage.

### Table 2 Melting Points of Compounds 5, 11, and 4

<table>
<thead>
<tr>
<th>Substituent R</th>
<th>Melting point (°C)</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-Me</td>
<td>oil 80–82</td>
<td>256–258 (decomp.)</td>
</tr>
<tr>
<td>O-NO(_2)</td>
<td>78–80 136–138</td>
<td>276–275 (decomp.)</td>
</tr>
<tr>
<td>p-NO(_2)</td>
<td>166–168 260–262 (decomp.)</td>
<td>296–298 (decomp.)</td>
</tr>
<tr>
<td>m-NO(_2)</td>
<td>110–112 182–184</td>
<td>258–260 (decomp.)</td>
</tr>
</tbody>
</table>
These molecules were subjected to in vitro antibacterial activity against *Mycobacterium smegmatis* and were found to be inactive.19

In conclusion, a methodology to prepare triazole-isoindole-1,3-dione derivatives is described. The methodology tolerates various functional groups and provides a way to introduce three points of diversity into the core skeleton. The molecules were designed to be active against tuberculosis; however, the experimental results did not show the predicted activity.

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References

16. General procedure for the synthesis of carboxylates 5a–d: To an equimolar solution of azide 6 and alkyne 10 in t-BuOH and water (1:1); sodium ascorbate (20 mmol%) and Cu(OAc)₂ (10 mmol%) were added. The reaction was stirred at room temperature until completion of reaction (TLC monitoring). The reaction mixture was filtered, extracted with ethyl acetate, dried over sodium sulfate, filtered, concentrated, and, with the exception of 5a, purified by recrystallization.

Ethyl 1-(methylphenyl)-1H-1,2,3-triazole-4-carboxylate (5b) (ref. 27): Yield: 7%; yellow amorphous solid; mp 78–80 °C. 1H NMR (400 MHz, CDCl₃): δ = 2.20 (s, 3 H), 3.82 (s, 3 H). 13C NMR (100 MHz, CDCl₃): δ = 158.7, 143.9, 142.3, 134.2, 131.2, 128.9, 127.6, 127.3, 125.4. FTIR (thin film): 3378, 3301, 1697, 1516, 1337, 1251 cm⁻¹.

Ethyl 1-(nitrrophenyl)-1H-1,2,3-triazole-4-carboxylate (5c) (ref. 28): Yield: 71%; yellow amorphous solid; mp 110–112 °C. 1H NMR (400 MHz, CDCl₃): δ = 6.92 (s, 1 H), 8.10 (t, J = 2 Hz, 1 H), 8.48–8.46 (m, 1 H), 8.35–8.33 (m, 1 H), 7.87 (t, J = 8.2 Hz, 1 H), 4.42 (q, J = 7.12 Hz, 2 H), 1.42 (t, J = 7.12 Hz, 3 H). 13C NMR (100 MHz, CDCl₃): δ = 159.8, 148.4, 140.1, 136.7, 131.3, 127.5, 126.2, 123.4, 115.1, 60.7, 14.1. FTIR (thin film): 3378, 3101, 1697, 1516, 1337, 1251 cm⁻¹.


(18) General procedure for the synthesis of carbamoylazides 11a–d: Ester 5 (1.84 mmol) was transferred into a 50 mL flask, and ethanol (10 mL) added. A solution of hydrazine hydrate 12 (80% w/v, 37 mmol) was then added and the mixture was heated to reflux for 30 min at 80 °C. After the completion of the reaction, the solid products were isolated by filtration.

1-1-(Methylphenyl)-1H-1,2,3-triazole-4-carboxyhydrazide (11a): Yield: 77%; white amorphous solid; mp 80–82 °C. 1H NMR (400 MHz, CDCl₃): δ = 8.44 (bs, 1 H), 8.28 (s, 1 H), 7.48–7.44 (m, 1 H), 7.41–7.32 (m, 3 H), 4.13 (bs, 2 H), 2.22 (s, 3 H). 13C NMR (100 MHz, CDCl₃): δ = 160.8, 141.7, 135.8, 133.6, 131.7, 130.4, 127.1, 126.9, 125.9, 17.8. FTIR (thin film): 3362, 3139, 1697, 1516, 1337, 1251 cm⁻¹.
1-(m-Nitrophenyl)-1H-1,2,3-triazole-4-carbohydrazide (11d): Yield: 75%; white amorphous solid; mp 182–184 °C. 1H NMR (400 MHz, DMSO-d6): δ = 9.91 (bs, 1 H), 9.50 (s, 1 H), 8.81 (s, 1 H), 8.46–8.44 (m, 1 H), 8.35–8.33 (m, 1 H), 7.90 (t, J = 8.2 Hz, 1 H), 4.53 (bs, 2 H). 13C NMR (100 MHz, DMSO-d6): δ = 158.5, 148.3, 142.9, 136.8, 131.2, 125.9, 124.6, 123.1, 114.9. FTIR (thin film): 3412, 3337, 1661, 1520, 1351 cm\(^{-1}\).

General procedure for the synthesis of carboxamides 4a–d: To a 25-mL round-bottom flask fitted with a magnetic stir bar and reflux condenser, were added carbohydrazide 11 (5 mmol), phthalic anhydride 8 (5 mmol), toluene (2 mL) and a catalytic amount of glacial acetic acid. The mixture was heated to reflux for 2 hours with stirring. Following cooling to room temperature, the resulting solid was filtered off and the crude product was purified by recrystallization using various hexane/ethyl acetate mixtures to afford the purified product.

N-(1,3-Dioxoisoindolin-2-yl)-1-(o-methylphenyl)-1H-1,2,3-triazole-4-carboxamide (4a): Yield: 79%; white amorphous solid; 256–258 °C (decomp.). 1H NMR (400 MHz, DMSO-d6): δ = 11.45 (s, 1 H), 9.07 (s, 1 H), 7.99–7.97 (m, 2 H), 7.96–7.92 (m, 1 H), 7.53–7.49 (m, 2 H), 7.47–7.40 (m, 1 H), 7.24–7.20 (m, 1 H), 7.15–7.12 (m, 1 H), 2.24 (s, 3 H). 13C NMR (100 MHz, DMSO-d6): δ = 164.9, 164.5, 158.6, 140.1, 135.6, 134.9, 133.1, 131.2, 130.1, 129.5, 129.1, 128.7, 127.9, 126.8, 125.9, 125.1, 123.6, 17.4. FTIR (thin film): 3215, 1720, 1417, 1225 cm\(^{-1}\).

N-(1,3-Dioxoisoindolin-2-yl)-1-(o-nitrophenyl)-1H-1,2,3-triazole-4-carboxamide (4b): Yield: 63%; white amorphous solid; mp 258–260 °C (decomp.). 1H NMR (400 MHz, DMSO-d6): δ = 11.51 (s, 1 H), 9.77 (s, 1 H), 8.89 (t, J = 1.88 Hz, 1 H), 8.51 (d, J = 1.32 Hz, 1 H), 8.38 (d, J = 1.72 Hz, 1 H), 8.01–7.91 (m, 5 H). 13C NMR (100 MHz, DMSO-d6): δ = 167.6, 167.5, 158.2, 143.8, 141.5, 135.8, 134.2, 131.3, 131.2, 130.8, 130.3, 129.2, 128.9, 128.2, 128.1, 127.7, 125.4. FTIR (thin film): 3265, 3150, 1698, 1560, 1330, 1510, 1250 cm\(^{-1}\).

N-(1,3-Dioxoisoindolin-2-yl)-1-(m-nitrophenyl)-1H-1,2,3-triazole-4-carboxamide (4d): Yield: 72%; white amorphous solid; mp 258–260 °C (decomp.). 1H NMR (400 MHz, DMSO-d6): δ = 11.51 (s, 1 H), 9.77 (s, 1 H), 8.89 (t, J = 1.88 Hz, 1 H), 8.51 (d, J = 1.32 Hz, 1 H), 8.38 (d, J = 1.72 Hz, 1 H), 8.01–7.91 (m, 5 H). 13C NMR (100 MHz, DMSO-d6): δ = 167.6, 167.5, 158.2, 143.8, 141.5, 135.8, 134.2, 131.3, 131.2, 130.8, 130.3, 129.2, 128.9, 128.2, 128.1, 127.7, 125.4. FTIR (thin film): 3265, 3150, 1698, 1560, 1330, 1510, 1250 cm\(^{-1}\).

These molecules were tested for activity against Mycobacterium smegmatis using a spot assay method.

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