

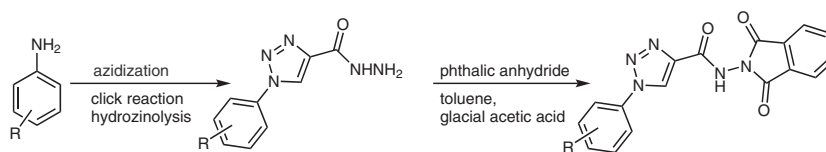


Click Chemistry Approach to Isoindole-1,3-dione Tethered 1,2,3-Triazole Derivatives

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Abstract A convenient and efficient approach for the synthesis of novel 1,2,3-triazole tethered isoindole-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 amidiazation, hydrazinolysis, carbohydrazide, carboxamide, click chemistry

Functionalized isoindole-1,3-dione derivatives exhibit a vast range of biological activities¹ such as antibacterial,² teratogenic,³ anticancer (multiple myeloma),⁴ PPAR- γ agonist,⁵ and anti-inflammatory activities.⁶ Bioactive molecules containing an isoindole-1,3-dione moiety include Thalidomide **1**, Pomalidomide **2**, and Apremilast **3** (Figure 1).

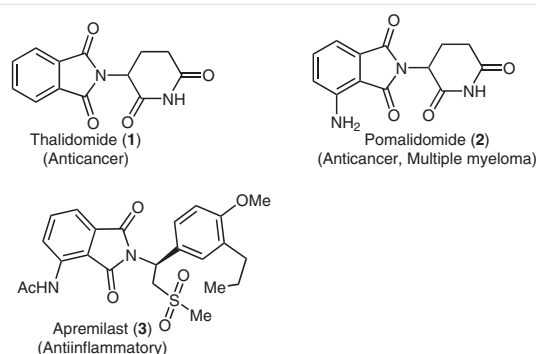
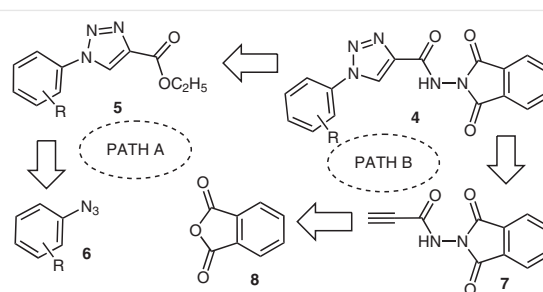


Figure 1 Representative examples of isoindole-1,3-dione containing bioactive molecules

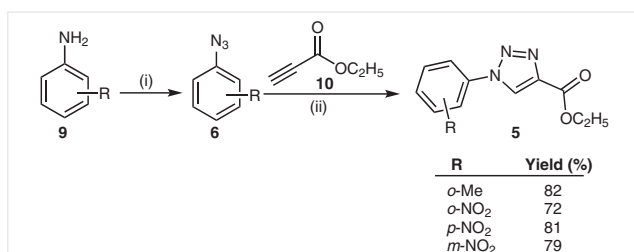
Compounds containing the 1,2,3-triazole moiety also show antitubercular activity⁷ and, phthalic anhydride derivatives also showed antitubercular activity.⁸ Based on these findings, new molecules were designed, and the synthesis of 1,2,3-triazole moieties connected to isoindole-1,3-dione derivatives via a hydrazide linkage is reported herein. *PASS Online* predicts these compounds may be antimycobacterial or antineoplastic agents.⁹ 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.^{10–12} 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.



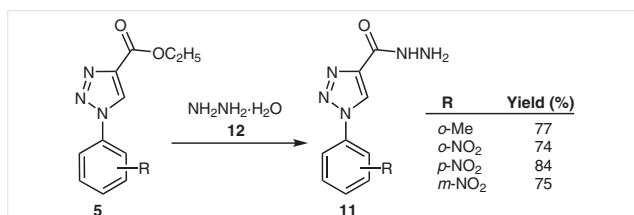
Scheme 1 Strategy to generate derivatives **4** containing 1,2,3-triazole units connected to isoindole-1,3-dione

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 cycloaddition¹⁵ with ethyl propynoate **10** using Cu(OAc)₂/sodium ascorbate (10 mol% and 20 mol%, respectively) in H₂O/*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 ¹H and ¹³C NMR spectroscopy. For instance, compound **5a** showed eleven resonances in its ¹³C NMR spectrum and, in its ¹H NMR spectrum, a resonance at δ = 9.62 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/H₂O (1:1), sodium azide, sodium acetate, sodium nitrite, 0–5 °C; (b) *t*-BuOH/H₂O (1:1), ethyl propynoate, copper acetate, sodium ascorbate.

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 δ = 61.6 and 14.3 ppm in the ¹³C NMR spectra of hydrazides **11** supported their formation. The ¹H 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 NH₂ resonances at δ = 9.91 (bs, 1H) and 4.53 ppm (bs, 2H).



Scheme 3 Preparation of hydrazide **11a–d**

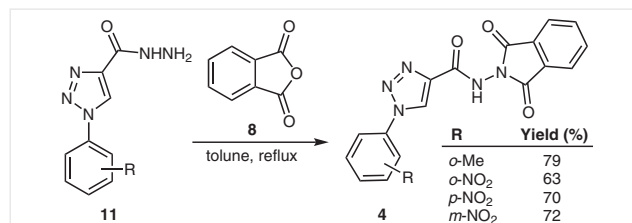
After synthesizing 1,2,3-triazole carbohydrazides **11**, preparation of isoindole-1,3-dione derivatives **4** was performed (Scheme 4). 1,2,3-Triazole carbohydrazides **11** were treated with phthalic anhydride **8** under a range of reaction conditions; the results are summarized in Table 1. These 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 NH₂ group attached to a 1,2,3-triazole compared with aliphatic and aromatic amines.

Table 1 Reaction Conditions for Amidation Reaction

Solvent	Additive	Conditions	Time (h)	Yield (%)
DMF	–	reflux	24	no reaction
DMSO	–	reflux	24	no reaction
THF	–	reflux	24	no reaction
toluene	–	reflux	24	20
DMF	glacial AcOH (0.004 mmol)	reflux	24	no reaction
DMSO	glacial AcOH (0.004 mmol)	reflux	24	no reaction
THF	glacial AcOH (0.004 mmol)	reflux	24	no reaction
toluene	glacial AcOH (0.004 mmol)	reflux	2	63–79

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



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

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**

Substituent R	Melting point (°C)		
	5	11	4
<i>O</i> -Me	oil	80–82	256–258 (decomp.)
<i>O</i> -NO ₂	78–80	136–138	276–275 (decomp.)
<i>p</i> -NO ₂	166–168	260–262 (decomp.)	296–298 (decomp.)
<i>m</i> -NO ₂	110–112	182–184	258–260 (decomp.)

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-isoin-dole-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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- 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-(o-methylphenyl)-1H-1,2,3-triazole-4-carboxylate (5a) (ref. 20): Yield: 82%; orange oil. ¹H NMR (400 MHz, CDCl₃): δ = 8.28 (s, 1 H), 7.47–7.44 (m, 1 H), 7.40–7.38 (m, 1 H), 7.36–7.33 (m, 2 H), 4.47 (q, *J* = 7.12 Hz, 2 H), 2.22 (s, 3 H), 1.44 (t, *J* = 7.16 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 160.8, 140.1, 135.7, 133.7, 131.6, 130.4, 128.9, 127.0, 125.9, 61.5, 17.8, 14.3. FTIR (thin film): 3361, 3311, 1725, 1019 cm^{−1}.
Ethyl 1-(o-nitrophenyl)-1H-1,2,3-triazole-4-carboxylate (5b) (ref. 21): Yield: 72%; orange amorphous solid; mp 78–80 °C. ¹H NMR (400 MHz, CDCl₃): δ = 8.43 (s, 1 H), 8.16 (dd, *J* = 8.08, 1.48 Hz, 1 H), 7.88–7.83 (m, 1 H), 7.80–7.76 (m, 1 H), 7.65 (dd, *J* = 1.44, 7.8 Hz, 1 H), 4.46 (q, *J* = 7.12 Hz, 2 H), 1.44 (t, *J* = 7.12 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 160.2, 144.2, 140.7, 134.2, 131.6, 129.6, 129.3, 128.3, 125.9, 61.7, 14.3. FTIR (thin film): 3125, 1690, 1510, 1342, 1250 cm^{−1}.
Ethyl 1-(p-nitrophenyl)-1H-1,2,3-triazole-4-carboxylate (5c) (ref. 22): Yield: 81%; yellow amorphous solid; mp 166–168 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.61 (s, 1 H), 8.46–8.42 (m, 2 H), 8.35–8.31 (m, 2 H), 4.42 (q, *J* = 7.08 Hz, 2 H), 1.41 (t, *J* = 7.12 Hz, 3 H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 159.7, 146.9, 140.4, 140.3, 127.1, 125.1, 120.8, 60.8, 14.0. FTIR (thin film): 3123, 1695, 1505, 1338, 1257 cm^{−1}.
Ethyl 1-(m-nitrophenyl)-1H-1,2,3-triazole-4-carboxylate (5d) (ref. 23): Yield: 79%; yellow amorphous solid; mp 110–112 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.62 (s, 1 H), 8.90 (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, DMSO-*d*₆): 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}.
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1-(o-Methylphenyl)-1H-1,2,3-triazole-4-carbohydrazide (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): 3326, 3139, 1649, 1260 cm^{−1}.
1-(o-Nitrophenyl)-1H-1,2,3-triazole-4-carbohydrazide (11b): Yield: 74%; white amorphous solid; mp 136–138 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.87 (bs, 1 H), 9.02 (s, 1 H), 8.21–8.19 (m, 1 H), 7.96–7.92 (m, 1 H), 7.87–7.82 (m, 2 H), 4.47 (bs, 2 H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 158.7, 143.9, 142.3, 134.2, 131.2, 128.9, 127.6, 127.3, 125.4. FTIR (thin film): 3303, 3100, 1666, 1519, 1344 cm^{−1}.
1-(p-Nitrophenyl)-1H-1,2,3-triazole-4-carbohydrazide (11c): Yield: 84%; white amorphous solid; mp 260–262 °C (decomp.). ¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.90 (bs, 1 H), 9.47 (s, 1 H), 8.46–8.42 (m, 2 H), 8.33–8.28 (m, 2 H), 4.50 (bs, 2 H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 159.1, 146.9, 143.1, 140.5, 125.3, 124.6, 120.7. FTIR (thin film): 3339, 3103, 1663, 1502, 1346 cm^{−1}.

1-(*m*-Nitrophenyl)-1*H*-1,2,3-triazole-4-carbohydrazide

(11d): Yield: 75%; white amorphous solid; mp 182–184 °C. ¹H NMR (400 MHz, DMSO-*d*₆): 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-*d*₆): 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-Dioxoisindolin-2-yl)-1-(*o*-methylphenyl)-1*H*-1,2,3-triazole-4-carboxamide (4a):** Yield: 79%; white amorphous solid; 256–258 °C (decomp.). ¹H NMR (400 MHz, DMSO-*d*₆): 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-*d*₆): δ = 164.9, 164.5, 158.6, 140.1, 135.6, 134.9, 133.12, 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-Dioxoisindolin-2-yl)-1-(*o*-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxamide (4b):** Yield: 63%; white amorphous solid; mp 276–275 °C (decomp.). ¹H NMR (400 MHz, DMSO-*d*₆): δ = 10.59 (s, 1 H), 9.16 (s, 1 H), 8.23 (dd, *J* = 1.2, 8 Hz, 1 H), 7.96–7.95 (m, 1 H), 7.90–7.88 (m, 1 H), 7.87–7.83 (m, 2 H), 7.68–7.66 (m, 1 H), 7.63–7.59 (m, 1 H), 7.58–7.54 (m, 1 H). ¹³C NMR (100 MHz,

DMSO-*d*₆): δ = 167.6, 167.4, 158.0, 146.9, 142.4, 140.5, 135.8, 134.8, 131.1, 130.8, 129.5, 128.2, 125.3, 125.2, 123.4, 120.9, 120.7. FTIR (thin film): 3117, 1646, 1534, 1344, 1481, 1268 cm⁻¹.

***N*-(1,3-Dioxoisindolin-2-yl)-1-(*p*-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxamide (4c):** Yield: 70%; white amorphous solid; mp 296–298 °C (decomp.). ¹H NMR (400 MHz, DMSO-*d*₆): δ = 11.52 (s, 1 H), 9.74 (s, 1 H), 8.92 (t, *J* = 2.04 Hz, 1 H), 8.52–8.49 (m, 1 H), 8.38–8.35 (m, 1 H), 7.98–7.89 (m, 5 H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 164.7, 158.2, 148.4, 141.2, 136.8, 134.8, 131.2, 129.5, 126.5, 126.2, 123.5, 123.4, 115.2. FTIR (thin film): 3268, 3146, 1701, 1579, 1344, 1517, 1262 cm⁻¹.

***N*-(1,3-Dioxoisindolin-2-yl)-1-(*m*-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxamide (4d):** Yield: 72%; white amorphous solid; mp 258–260 °C (decomp.). ¹H NMR (400 MHz, DMSO-*d*₆): 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-*d*₆): 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.

- (19) These molecules were tested for activity against *Mycobacterium smegmatis* using a spot assay method.
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