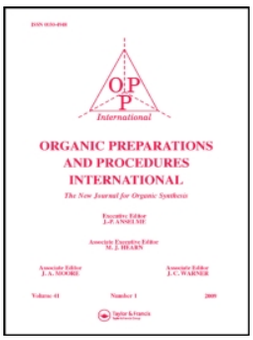

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Organic Preparations and Procedures International

The New Journal for Organic Synthesis

ISSN: 0030-4948 (Print) 1945-5453 (Online) Journal homepage: http://www.tandfonline.com/loi/uopp20

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**To cite this article:** Mohamed R. Aouad (2017) Click Synthesis and Antimicrobial Screening of Novel Isatin-1,2,3-Triazoles with Piperidine, Morpholine, or Piperazine Moieties, Organic Preparations and Procedures International, 49:3, 216-227, DOI: 10.1080/00304948.2017.1320515

**To link to this article:** http://dx.doi.org/10.1080/00304948.2017.1320515

Published online: 01 Jun 2017.

*Organic Preparations and Procedures International*, 49:216–227, 2017

ISSN: 0030-4948 print / 1945-5453 online
DOI: 10.1080/00304948.2017.1320515

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# Click Synthesis and Antimicrobial Screening of Novel Isatin-1,2,3-Triazoles with Piperidine, Morpholine, or Piperazine Moieties

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Indoles are one of the most prevalent classes of pharmacologically active azoles and have found applications as antibacterial, antifungal, anti-mycobacterial, antiviral, anti-HIV, antitumor and anticonvulsant agents.[1–6] Among these, some 1*H*-indole-2,3-dione (isatin) compounds incorporating a 1,2,3-triazole scaffold were recently found to exhibit significant antimalarial and anticancer activities.[7–10] The 1,2,3-triazole ring system is a common structural motif for a number of chemotherapeutic agents that have exhibited remarkable biological potential in areas that include antitubercular, anti-inflammatory, antifungal, antibacterial, and anticancer activities.[11–16] Recent advances in modern heterocyclic chemistry have introduced the 1,2,3-triazole moiety as a connecting spacer to link two pharmacophore sites together and generate original bifunctional drugs.[17,18] Conversely, the piperidine, morpholine and piperazine moieties are key structural units in drug design due to their insertion into several drug molecules, including thioridazine, linezolid, levofloxacin, trifluoroperazine, gatifloxacin, itraconazole, posaconazole and eperezolid.[19–22] In view of the fact that the presence of two pharmacophoric sites in one molecule could generate relevant compounds with increased medicinal potentialities,[23–25] the present study reports the click synthesis and antimicrobial screening of novel isatin-1,2,3-triazoles appended with piperidine, morpholine or piperazine moieties connected *via* a methylene and/or an acetyl linkage.

Two classes of isatin-1,2,3-triazole hybrids were synthesized by the Cu(I)-mediated click chemistry approach *via* regioselective addition of the N-propargylated isatin **1** with different cyclic secondary amine azides **2a-h** (*Scheme 1*) or by the addition of azidoacetyl isatin **5** with various propargylated cyclic secondary amines **6a-h** (*Scheme 2*). For that purpose, isatin was used as a starting material, which, when treated with propargyl bromide in the presence of NaH and DMF, yielded the precursor N-propargylated isatin.[8]

Received January 1, 2017; in final form January 26, 2017.
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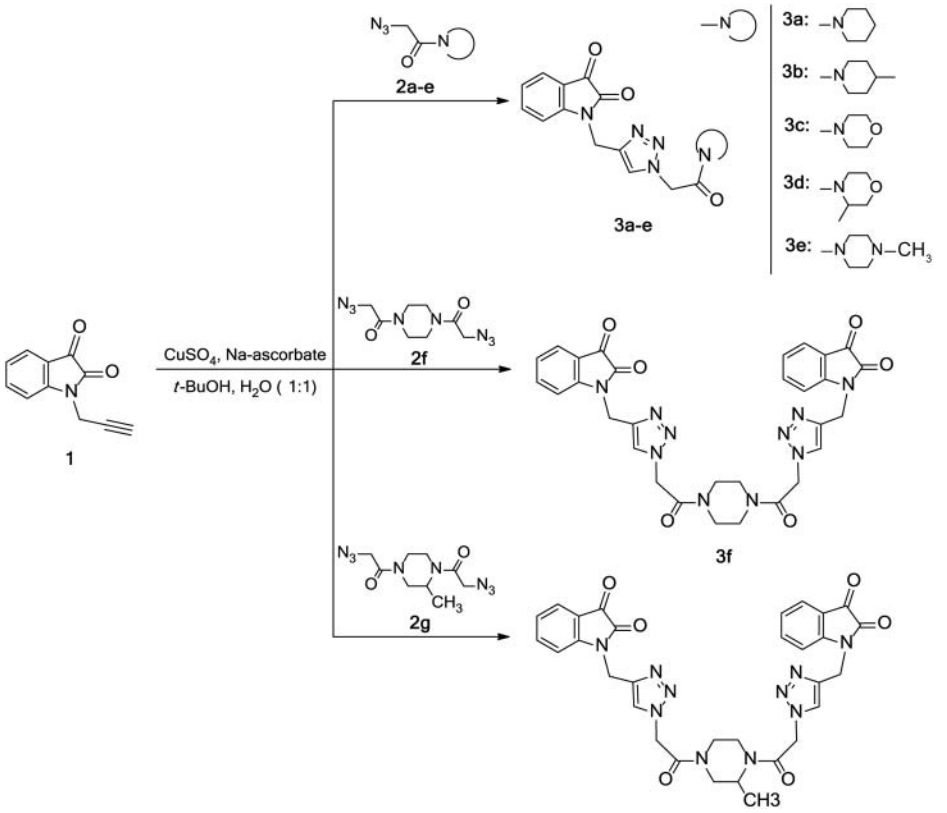
The second precursors, namely, N-azidoacetyl-tethered piperidine, morpholine or piperazine derivatives **2a-g**, were synthesized by an initial base-catalyzed acylation of the corresponding cyclic secondary amines with bromoacetyl bromide based on previously reported methods.[26, 27] The obtained $\alpha$-bromoacetamides were treated with sodium azide to yield the azidoacetamide derivatives **2a-g**. These derivatives, when treated with propargylated isatin **1**, ligated the terminal C≡C bond of **1** to the azide building blocks of the heterocyclic units using Huisgeńs copper(I)-catalyzed 1,3-dipolar cycloaddition to yield targeted hybrids **3a-g** with an acetyl linkage between the isatin and the 1,2,3-triazole. The reaction was conducted in *t*-BuOH/$H_2O$ (1:1) in the presence of sodium ascorbate and copper sulfate at room temperature for 5–8 h to afford the target compounds with yields of 82–89% (*Scheme 1*).

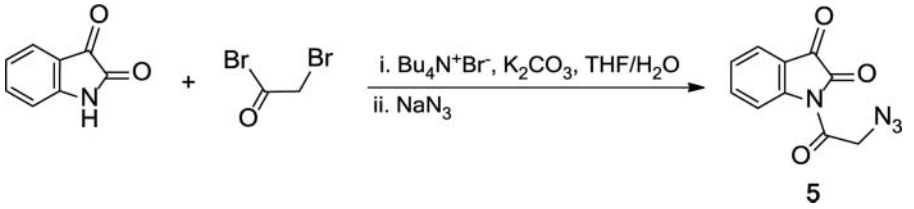



**Scheme 1** Click synthesis of isatin-1,2,3-triazole hybrids **3a-g**.

Spectroscopic characterization (IR, NMR, MS and EA) of these compounds confirmed the success of the click reaction. The disappearance of the azido and alkyne absorbance bands in the IR (2100–2200 $cm^{-1}$) for compounds **3a-g** confirmed their involvement in the dipolar cycloaddition reaction. All compounds contained common features in their $^1$H NMR and $^{13}$C NMR spectra. Their $^1$H NMR spectra displayed a characteristic singlet at $\delta_H$ 8.08–8.25 ppm corresponding to the aromatic proton of C-5 on the triazole ring, while the N-$CH_2$ protons appeared at $\delta_H$ 4.83–4.99 ppm as a singlet.

The resonances of the methylene protons of the acetyl group were observed as two distinct singlets at $\delta_H$ 5.41–5.67 ppm. In addition, the proton NMR spectrum of **3c** revealed the appearance of a triplet at $\delta_H$ 2.50 ppm and a multiplet at $\delta_H$ 3.45–3.57 ppm that were attributed to the morpholine $NCH_2$ and $OCH_2$ protons, respectively. Conversely, the eight piperazine protons in **3f** appeared as two triplets at $\delta_H$ 2.75 and 2.84 ppm. In the $^{13}C$ NMR spectrum of compound **3c**, the methylene carbons of the morpholine ring were observed at $\delta_c$ 35.0 and 50.6 ppm, while the methylene carbon flanked between the isatin and 1,2,3-triazole moieties appeared at $\delta_c$ 40.4 ppm, and the acetyl methylene carbon was observed at $\delta_H$ 64.3 ppm.

The azidoacetyl isatin **5** required for the preparation of the second class of 1,2,3-triazole hybrids **7a-g** was prepared initially by phase transfer catalysis acylation ($Bu_4N^+Br^-$, $K_2CO_3$, THF/$H_2O$) with bromoacetyl bromide at 0°C for 2 h, followed by azidolysis with sodium azide at room temperature for 12 h (*Scheme 2*).

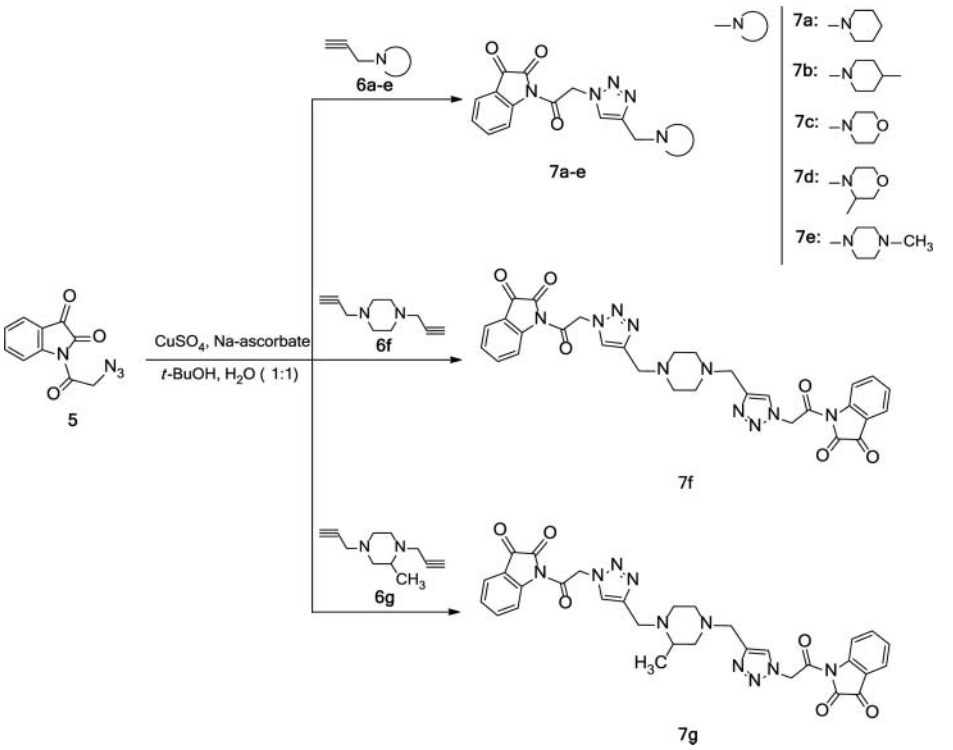



**Scheme 2** Synthesis of 1-(2-azidoacetyl)indoline-2,3-dione (**5**).

For compound **5**, the presence of the azido group was inferred by the presence of a characteristic absorption band at 2110 $cm^{-1}$ in its IR spectrum. In the $^1H$ NMR spectrum, the azidomethylene protons resonated as one singlet at $\delta_H$ 4.02 ppm. The aromatic isatin protons appeared at their usual chemical shifts ($\delta_H$ 7.28–7.78 ppm). The $^{13}C$ NMR spectrum showed one signal in the aliphatic region at $\delta_C$ 50.8 ppm, which was attributed to the azidomethyl carbon.

The synthesis of the propargylated piperidine, morpholine and piperazine derivatives **6a-g** was carried out using previously published protocols involving base-assisted alkylation of the appropriate cyclic secondary amines with propargyl bromide,[28–30] resulting in the isolation of precursors **6a-g**. To build the targeted isatin-1,2,3-triazole hybrids **7a-g** attached to the un/substituted piperidine, morpholine or piperazine rings *via* an acetyl spacer, the propargylated building blocks **6a-g** were treated with **5** (*Scheme 3*). For example, the coupling of **5** with the propargylated piperidine **6a** in a 1:1 *t*-BuOH/$H_2O$ mixture and a catalytic amount of $Na_2SO_4$ and $CuSO_4$ for 6 h afforded the novel isatin-1,2,3-triazole hybrid 1-(2-(4-(piperidin-1-ylmethyl)-1*H*-1,2,3-triazol-1-yl)acetyl)indoline-2,3-dione (**7a**) in 86% yield (*Scheme 3*). The synthesis has also been adopted for the other six analogues of **6a** to afford the respective isatin-based cyclic secondary amines carrying a 1,2,3-triazole ring **7b-g** in 80–87% yields.

The structures of the 1,2,3-triazole hybrids **7a-g** have been established by IR, $^1H$ NMR, $^{13}C$ NMR and MS. In their IR spectra, the lack of absorption bands in the 2100–2200 $cm^{-1}$ region characteristic of the azido and the C≡C groups confirmed the formation of the 1,2,3-triazole ring. All the synthesized click products **7a-g** showed one distinct singlet in the aromatic region around $\delta_H$ 7.95–8.12 ppm that was attributable to the triazolyl C5-H proton. The singlets at $\delta_H$ 3.73–4.02 ppm and $\delta_H$ 4.78–5.24 ppm were assigned to the methylene protons of the triazole –$CH_2R$ and the acetyl connecting units, respectively. In addition, all




**Scheme 3** Click synthesis of isatin-1,2,3-triazole hybrids **7a-g**.

the aliphatic protons of the cyclic secondary amine residues resonated in the upfield region (see experimental details). The success of the cycloaddition reaction was further supported by $^{13}$C NMR, as the peaks due to the alkyne carbons were replaced with new resonances due to the carbons of the triazole ring; these new resonances appeared in the region characteristic of $sp^2$ carbons ($\delta_c$ 117.4–120.8 ppm).

The preliminary antimicrobial activity results are expressed as the minimum inhibition concentration (MIC) using the broth dilution method and are summarized in *Table 1*.[31, 32] It is obvious from the screening results that the antimicrobial activity of the designed click products appeared to be governed by the nature of the cyclic secondary amine (piperidine, morpholine or piperazine) as well as the position of the acetyl linkage in the skeleton moieties. The majority of the tested compounds displayed promising inhibition activity with MIC values of 4–16 $\mu$g/ml. Based on the antimicrobial bioassay results, compounds **3a-d** were found to be more potent towards bacterial strains compared to the fungal strains. In general, the highest antibacterial inhibitions, with an MIC range of 8–16 $\mu$g/ml, were displayed by compounds containing a piperazine moiety **(3e-g)**. The antifungal screening data of compounds **3a-d** showed weak antifungal inhibition with an MIC range of 62.5–125 $\mu$g/ml against all of the tested fungal strains. The incorporation of a piperazine moiety was found to confer higher antifungal activity with an MIC of 16 $\mu$g/ml, as exhibited by compounds **3e-g**. Another interesting observation is based on the position of the acetyl linkage with regards to the 1,2,3-triazole scaffold. The presence of the acetyl group between the indole and the 1,2,3-triazole moieties plays a significant role in enhancing antibacterial and antifungal activities. This conclusion is supported by the promising antimicrobial inhibition displayed by the seven compounds **7a-g** towards

**Table 1**
Antimicrobial Screening Results of Compounds **3a-g** and **7a-g** Expressed as MIC ($\mu$g/mL)

| | Gram-Positive Organisms | | | Gram-Negative Organisms | | | Fungi | |
|---|---|---|---|---|---|---|---|---|
| Compounds | *Sp* | *Bs* | *Sa* | *Pa* | *Ec* | *Kp* | *Af* | *Ca* |
| **3a** | 16 | 31.25 | 31.25 | 16 | 16 | 31.25 | 62.5 | 62.5 |
| **3b** | 16 | 31.25 | 31.25 | 31.25 | 16 | 31.25 | 125 | 62.5 |
| **3c** | 16 | 16 | 31.25 | 16 | 16 | 31.25 | 62.5 | 62.5 |
| **3d** | 16 | 16 | 31.25 | 31.25 | 16 | 16 | 125 | 62.5 |
| **3e** | 16 | 8 | 8 | 16 | 16 | 16 | 16 | 16 |
| **3f** | 8 | 16 | 8 | 16 | 16 | 8 | 16 | 16 |
| **3g** | 8 | 8 | 16 | 16 | 8 | 8 | 16 | 16 |
| **7a** | 8 | 8 | 16 | 16 | 16 | 8 | 31.25 | 16 |
| **7b** | 16 | 8 | 16 | 16 | 8 | 16 | 31.25 | 16 |
| **7c** | 8 | 8 | 16 | 8 | 8 | 16 | 16 | 16 |
| **7d** | 8 | 16 | 16 | 16 | 8 | 16 | 16 | 16 |
| **7e** | 8 | 8 | 4 | 8 | 4 | 8 | 16 | 16 |
| **7f** | 8 | 4 | 4 | 8 | 4 | 8 | 16 | 8 |
| **7g** | 4 | 4 | 4 | 8 | 4 | 4 | 16 | 16 |
| Ciprofloxacin | ≤5 | ≤1 | ≤5 | ≤5 | ≤1 | ≤1 | — | — |
| Fluconazole | — | — | — | — | — | — | ≤1 | ≤1 |

all bacterial and fungal strains with MIC values of 4–8 $\mu$g/ml and 16–31.25 $\mu$g/ml, respectively. Among them, those with a piperazine moiety, **7e-g**, showed the greatest antibacterial (MIC 4–8 $\mu$g/ml) and antifungal (MIC 8–16 $\mu$g/ml) inhibition activity.

In conclusion, novel isatin-1,2,3-triazoles appended with piperidines, morpholines or piperazines connected *via* an acetyl or methylene linkage were synthesized and screened for their antibacterial and antifungal activities against a panel of pathogenic bacterial and fungal strains. Antimicrobial activity profiles confirmed the dependence of the activity on the nature of the cyclic secondary amine appended to the 1,2,3-triazole ring. Interestingly, the isatin-1,2,3-triazole hybrids containing a piperazine unit appeared to be the most active among the tested compounds with an MIC of 4–8 $\mu$g/ml.

## Experimental Section

All melting points were recorded on a Mel-temp apparatus (SMP10) and are uncorrected. The IR spectra were measured in a KBr matrix using a SHIMADZU FTIR-8400S spectrometer. NMR spectra were measured with an Advance Bruker NMR spectrometer operating at 400 MHz (for $^{1}$H) and 100 MHz (for $^{13}$C). Tetramethylsilane (TMS) was used as the internal standard. The EI mass spectra were measured by a Finnigan MAT 95XL spectrometer. Elemental analyses were measured using a GmbH-Vario EL III Element Analyzer.

### *Typical Procedure for the Synthesis of Isatin-1,2,3-Triazole Hybrids 3a-g*

To a stirred solution of equimolar amounts of the propargylated isatin **1** and the appropriate azidoacetamide cyclic secondary amine **2a-g** dissolved in a 1:1 mixture of *t*-BuOH

and water was added $CuSO_4$ (0.3 eq) and Na-ascorbate (0.6 eq) at ambient temperature. The reaction was stirred for an additional 5–8 h at ambient temperature until the consumption of the starting material was confirmed by TLC. The reaction mixture was quenched with water and the crude product was extracted with ethyl acetate (3 × 50 mL). The organic phase was dried over anhydrous sodium sulfate, the excess solvent was reduced under vacuum to yield the targeted 1,2,3-triazoles **3a-g**, and the crude products were crystallized from ethanol.

### 1-((1-(2-Oxo-2-(Piperidin-1-yl)Ethyl)-1*H*-1,2,3-Triazol-5-yl)Methyl)Indoline-2,3-Dione (3a)

Yield 88%, mp 180–181°C; IR: 3048 (Ar-H), 2837–2979 (CH str.), 1725 (C=O), 1615 $cm^{-1}$ (C=O). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 1.29–1.33 (2H, m, $CH_2CH_2CH_2$), 1.69–1.80 (4H, m, 2 x $NCH_2CH_2$), 2.35 (2H, t, $J$ = 4.0 Hz, $NCH_2$), 2.65 (2H, t, $J$ = 4.0 Hz, $NCH_2$), 4.90 (2H, s, $NCH_2$-C=C), 5.41 (1H, s, NCHCO), 5.44 (1H, s, NCHCO), 7.18–7.25 (2H, m, ArH), 7.62–7.69 (2H, m, ArH), 8.21 (1H, s, CH-1,2,3-triazole); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ 22.2 ($CH_2CH_2CH_2$), 24.8 ($NCH_2CH_2$), 37.9 ($NCH_2$), 42.0 ($NCH_2$-C=C), 64.8 ($NCH_2CO$), 112.4, 118.6, 123.9, 125.5, 126.8, 137.9, 151.5, 157.8, 165.0, 184.1 (Ar-C, C=O). EI MS (m/z): 353.23 (M+).

*Anal.* Calcd. For $C_{18}H_{19}N_5O_3$: C, 61.18; H, 5.42; N, 19.82. Found: C, 61.29; H, 5.55; N, 19.69.

### 1-((1-(2-(4-Methylpiperidin-1-yl)-2-Oxoethyl)-1*H*-1,2,3-Triazol-5-yl)Methyl)-Indoline-2,3-di-one (3b)

Yield 86%, mp 198–199°C; IR: 3064 (Ar-H), 2848–2937 (CH str.), 1717 (C=O), 1604 $cm^{-1}$ (C=O). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 1.06 (3H, d, $J$ = 4.0 Hz, $CH_3$), 1.25–1.30 (1H, m, $CH_2CHCH_2$), 1.52–1.74 (4H, m, 2 x $NCH_2CH_2$), 2.22–2.28 (2H, m, $NCH_2$), 2.41–2.47 (2H, m, $NCH_2$), 4.83 (2H, s, $NCH_2$-C=C), 5.48 (1H, s, NCHCO), 5.55 (1H, s, NCHCO), 7.10–7.17 (2H, m, ArH), 7.58–7.66 (2H, m, ArH), 8.17 (1H, s, CH-1,2,3-triazole); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ 14.9 ($CH_3$), 21.8 ($CH_2CHCH_2$), 24.1 ($NCH_2CH_2$), 38.4 ($NCH_2$), 42.2 ($NCH_2$-C=C), 65.7 ($NCH_2CO$), 112.1, 117.4, 123.5, 125.6, 126.9, 137.4, 151.1, 157.4, 164.5, 184.7 (Ar-C, C=O). EI MS (m/z): 367.22 (M+).

*Anal.* Calcd. For $C_{19}H_{21}N_5O_3$: C, 62.11; H, 5.76; N, 19.06. Found: C, 61.95; H, 5.59; N, 19.20.

### 1-((1-(2-Morpholino-2-Oxoethyl)-1*H*-1,2,3-Triazol-5-yl)Methyl)Indoline-2,3-Dione (3c)

Yield 89%, mp 211–212°C; IR: 3078 (Ar-H), 2855–2960 (CH str.), 1722 (C=O), 1610 $cm^{-1}$ (C=O). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 2.50 (4H, t, $J$ = 4.0 Hz, 2 x $NCH_2$), 3.45–3.57 (4H, m, 2 x $OCH_2$), 4.99 (2H, s, $NCH_2$-C=C), 5.46 (1H, s, NCHCO), 5.49 (1H, s, NCHCO), 7.12–7.20 (2H, m, ArH), 7.56–7.66 (2H, m, ArH), 8.15 (1H, s, CH-1,2,3-triazole); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ 35.0 ($NCH_2$), 40.4 ($NCH_2$-C=C), 50.6 ($OCH_2$), 64.3 ($NCH_2CO$), 111.2, 117.5, 123.6, 124.4, 125.2, 138.0, 150.1, 157.7, 164.3, 183.0 (Ar-C, C=O). EI MS (m/z): 355.04 (M+).

*Anal.* Calcd. (%) for $C_{17}H_{17}N_5O_4$: C, 57.46; H, 4.82; N, 19.71. Found: C, 57.60; H, 4.76; N, 19.59.

**1-((1-(2-(3-Methylmorpholino)-2-Oxoethyl)-1*H*-1,2,3-Triazol-5-yl)Methyl)-Indoline-2,3-Dione (3d)**

Yield 87%, mp 234–235°C; IR: 3078 (Ar-H), 2828–2948 (CH str.), 1725 (C=O), 1620 $cm^{-1}$ (C=O). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 1.31 (3H, d, $J$ = 4.0 Hz, $CH_3$), 2.56–2.72 (m, 3H, C*H*$CH_3$, $NCH_2$), 3.52–3.59 (4H, m, 2 x $OCH_2$), 4.95 (2H, s, $NCH_2$-C=C), 5.42 (1H, s, NCHCO), 5.45 (1H, s, NCHCO), 7.16–7.21 (2H, m, ArH), 7.51–7.60 (2H, m, ArH), 8.14 (1H, s, CH-1,2,3-triazole); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ 18.5 ($CH_3$), 32.6, 36.2 ($NCH_2$), 41.1 (N*C*$H_2$-C=C), 50.4, 51.1 ($OCH_2$), 66.1 (N*C*$H_2$CO), 111.7, 116.9, 123.8, 125.0, 125.8, 139.2, 151.2, 157.8, 166.7, 184.5 (Ar-C, C=O). EI MS (m/z): 369.21 (M+).

*Anal.* Calcd. (%) for $C_{18}H_{19}N_5O_4$: C, 58.53; H, 5.18; N, 18.96. Found: C, 58.67; H, 5.11; N, 19.13.

**1-((1-(2-(4-Methylpiperazin-1-yl)-2-Oxoethyl)-1*H*-1,2,3-Triazol-5-yl)Methyl) Indoline-2,3-Dione (3e)**

Yield 88%, mp 248–249°C; IR: 3047 (Ar-H), 2844–2982 (CH str.), 1726 (C=O), 1624 $cm^{-1}$ (C=O). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 2.23 (3H, s, $NCH_3$), 2.66 (4H, t, $J$ = 4.0 Hz, 2 x $NCH_2$), 2.74 (4H, t, $J$ = 4.0 Hz, 2 x $NCH_2$), 4.87 (2H, s, $NCH_2$-C=C), 5.48 (1H, s, NCHCO), 5.53 (1H, s, NCHCO), 7.11–7.17 (2H, m, ArH), 7.50–7.58 (2H, m, ArH), 8.08 (1H, s, CH-1,2,3-triazole); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ 32.3 ($NCH_3$), 36.2 ($NCH_2$), 41.6 (N*C*$H_2$-C=C), 44.5 ($NCH_2$), 60.8 (N*C*$H_2$CO), 111.8, 118.0, 124.1, 124.9, 125.7, 139.4, 151.4, 156.9, 165.2, 184.3 (Ar-C, C=O). EI MS (m/z): 368.04 (M+).

*Anal.* Calcd. (%) for $C_{18}H_{20}N_6O_3$: C, 58.69; H, 5.47; N, 22.81. Found: C, 58.77; H, 5.56; N, 22.74.

**1,1′-((1,1′-(Piperazine-1,4-Diyl)bis(2-Oxoethane-2,1-Diyl))bis(1*H*-1,2,3-Triazole-5, 1-Diyl))bis-(Methylene))bis(Indoline-2,3-Dione) (3f)**

Yield 84%, mp 265–266°C; IR: 3082 (Ar-H), 2827–2951 (CH str.), 1722 (C=O), 1618 $cm^{-1}$ (C=O). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 2.75 (4H, t, $J$ = 4.0 Hz, 2 x $NCH_2$), 2.84 (4H, t, $J$ = 4.0 Hz, 2 x $NCH_2$), 4.83 (2H, s, $NCH_2$-C=C), 4.90 (2H, s, $NCH_2$-C=C), 5.36 (2H, s, 2 x NCHCO), 5.45 (2H, s, 2 x NCHCO), 7.16–7.23 (4H, m, ArH), 7.46–7.52 (4H, m, ArH), 8.16 (2H, s, 2 x CH-1,2,3-triazole); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ 38.7 ($NCH_2$), 40.8 ($NCH_2$), 42.9 (N*C*$H_2$-C=C), 60.1 (N*C*$H_2$CO), 111.3, 118.7, 124.0, 125.1, 125.8, 139.7, 152.8, 156.3, 165.7, 185.8 (Ar-C, C=O). EI MS (m/z): 622.29 (M+).

*Anal.* Calcd. (%) for $C_{30}H_{26}N_{10}O_6$: C, 57.87; H, 4.21; N, 22.50. Found: C, 57.69; H, 4.13; N, 22.66.

**1,1′-((1,1′-((2-Methylpiperazine-1,4-Diyl)bis(2-Oxoethane-2,1-Diyl))bis(1*H*-1,2, 3-Triazole-5,1-Diyl))bis(Methylene))bis(Indoline-2,3-Dione) (3g)**

Yield 82%, mp 288–289°C; IR: 3064 (Ar-H), 2842–2964 (CH str.), 1718 (C=O), 1628 $cm^{-1}$ (C=O). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 1.34 (3H, d, $J$ = 4.0 Hz, $CH_3$), 2.51–2.60 (2H, m, C*H*$CH_3$, $NCH_2$), 2.70–2.76 (1H, m, $NCH_2$), 2.82 (2H, t, $J$ = 4.0 Hz, $NCH_2$), 2.92–2.99 (2H, m, $NCH_2$), 4.91 (2H, s, $NCH_2$-C=C), 5.06 (2H, s, $NCH_2$-C=C),

5.37 (1H, s, NCHCO), 5.44 (2H, s, $NCH_2CO$), 5.67 (1H, s, NCHCO), 7.12–7.27 (4H, m, ArH), 7.46–7.63 (4H, m, ArH), 8.19 (1H, s, CH-1,2,3-triazole), 8.25 (1H, s, CH-1,2,3-triazole); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ 17.9 ($CH_3$), 31.4, 37.8, 39.0, 41.6 ($NCH_2$), 42.7, 44.2 ($NCH_2$-C=C), 65.3, 67.9 ($NCH_2CO$), 111.5, 112.4, 115.7, 123.4, 124.0, 125.2, 125.7, 138.4, 139.7, 150.1, 151.9, 157.2, 158.8, 165.4, 166.0, 183.1, 184.7 (Ar-C, C=O). EI MS (m/z): 636.30 (M+).

*Anal.* Calcd. (%) for $C_{31}H_{28}N_{10}O_6$: C, 58.49; H, 4.43; N, 22.00. Found: C, 58.58; H, 4.52; N, 21.88.

### *Synthesis and Characterization of 1-(2-Azidoacetyl)Indoline-2,3-Dione (5)*

To a stirred solution of isatin (1 eq), $K_2CO_3$ (1.2 eq), $Bu_4N^+Br^-$ (0.4 eq) in a mixture of THF:water (5:1) (10 mL), was added bromoacetyl bromide (1.2 eq) at 0°C. The reaction continued for 2 h at 0°C and was monitored by TLC. Upon completion, the reaction mixture was treated with sodium azide (2.0 equiv.) at room temperature for 12 h. The crude product was extracted with ethyl acetate (3 × 20 mL), and the organic extracts were washed with brine solution and finally water. The excess solvent was removed under reduced pressure to afford compound **5**. Yield 92%, mp 164–165°C; IR: 3020 (Ar-H), 2848–2936 (CH str.), 1715 (C=O), 1580 $cm^{-1}$ (C=C). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 4.02 (2H, s, $CH_2$), 7.28–7.37 (2H, m, ArH), 7.68–7.78 (2H, m, ArH); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ 53.4 ($CH_2$), 111.9, 122.0, 123.9, 129.8, 136.1, 151.8, 165.8, 170.2, 184.3 (Ar-C, C=O). EI MS (m/z): 230.13 (M+).

*Anal.* Calcd. (%) for $C_{10}H_6N_4O_3$: C, 52.18; H, 2.63; N, 24.34. Found: C, 52.32; H, 2.50; N, 24.48.

### *Typical Procedure for the Synthesis of Isatin-1,2,3-Triazole Hybrids 7a-g*

To a stirred solution of equimolar amounts of **5** and the appropriate propargylated cyclic secondary amine **6a-g** dissolved in a 1:1 mixture of *t*-BuOH and water was added $CuSO_4$ (0.3 eq) and Na-ascorbate (0.6 eq) at ambient temperature. The reaction was stirred for an additional 6–10 h at ambient temperature until TLC confirmed the complete reaction of the starting material. The reaction mixture was quenched with water and the crude product was extracted with ethyl acetate (3 × 50 mL). The organic phase was dried over anhydrous sodium sulfate, the excess solvent was reduced under vacuum to yield the targeted 1,2,3-triazoles **7a-g,** and the crude products were crystallized from ethanol.

### 1-(2-(4-(Piperidin-1-yl)Methyl-1*H*-1,2,3-Triazol-1-yl)Acetyl)Indoline-2,3-Dione (7a)

Yield 86%, mp 193–194°C; IR: 3031 (Ar-H), 2868–2940 (CH str.), 1708 (C=O), 1611 $cm^{-1}$ (C=O). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 1.49–1.60 (6H, m, $CH_2CH_2CH_2$, 2 x $NCH_2CH_2$), 2.42 (2*H*, dd, $J$ = 4.0 Hz, 12.0 Hz, $NCH_2$), 2.63 (2*H*, dd, $J$ = 4.0 Hz, 12.0 Hz, $NCH_2$), 3.84 (2H, s, $NCH_2$-C=C), 4.95 (1H, s, NCHCO), 5.16 (1H, s, NCHCO), 7.23–7.32 (2H, m, ArH), 7.68–7.77 (2H, m, ArH), 7.96 (1H, s, CH-1,2,3-triazole); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ 23.6 ($CH_2CH_2CH_2$), 25.3 ($NCH_2CH_2$), 38.6 ($NCH_2$), 46.4 ($NCH_2$-C=C), 65.0 ($NCH_2CO$), 112.8, 117.4, 123.2, 126.7, 128.1, 138.8, 154.7, 162.4, 172.7, 185.6 (Ar-C, C=O). EI MS (m/z): 353.04 (M+).

*Anal.* Calcd. (%) for $C_{18}H_{19}N_5O_3$: C, 61.18; H, 5.42; N, 19.82. Found: C, 61.05; H, 5.54; N, 19.66.

**1-(2-(4-((4-Methylpiperidin-1-yl)Methyl)-1*H*-1,2,3-Triazol-1-yl)Acetyl)Indoline-2, 3-Dione (7b)**

Yield 84%, mp 215–216°C; IR: 3084 (Ar-H), 2826–2950 (CH str.), 1720 (C=O), 1616 $cm^{-1}$ (C=O). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 1.11 (3H, d, $J = 4.0$ Hz, $CH_3$), 1.33–1.36 (1H, m, $CH_2CHCH_2$), 1.48–1.52 (2H, m, $NCH_2CH_2$), 1.68–1.73 (2H, m, $NCH_2CH_2$), 2.32–2.38 (2H, m, $NCH_2$), 2.56–2.61 (2H, m, $NCH_2$), 3.73 (2H, s, $NCH_2$-C=C), 4.86 (1H, s, NCHCO), 5.04 (1H, s, NCHCO), 7.26–7.33 (2H, m, ArH), 7.65–7.73 (2H, m, ArH), 7.95 (1H, s, CH-1,2,3-triazole); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ 15.6 ($CH_3$), 22.5 ($CH_2CHCH_2$), 24.9 ($NCH_2CH_2$), 37.9 ($NCH_2$), 47.1 ($NCH_2$-C=C), 66.5 ($NCH_2CO$), 112.4, 118.3, 123.1, 125.9, 127.8, 137.2, 155.3, 161.2, 171.9, 184.9 (Ar-C, C=O). EI MS (m/z): 367.11 (M+).

*Anal.* Calcd. (%) for $C_{19}H_{21}N_5O_3$: C, 62.11; H, 5.76; N, 19.06. Found: C, 62.22; H, 5.59; N, 19.16.

**1-(2-(4-(Morpholinomethyl)-1*H*-1,2,3-Triazol-1-yl)Acetyl)Indoline-2,3-Dione (7c)**

Yield 87%, mp 228–229°C; IR: 3043 (Ar-H), 2838–2976 (CH str.), 1726 (C=O), 1614 $cm^{-1}$ (C=O). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 2.58 (4H, dd, $J = 4.0$ Hz, 12 Hz, 2 x $NCH_2$), 3.73 (4H, dd, $J = 4.0$ Hz, 12 Hz, 2 x $OCH_2$), 3.92 (2H, s, $NCH_2$-C=C), 4.99 (1H, s, NCHCO), 5.18 (1H, s, NCHCO), 7.21–7.28 (2H, m, ArH), 7.59–7.68 (2H, m, ArH), 8.01 (1H, s, CH-1,2,3-triazole); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ 38.4 ($NCH_2$), 46.6 ($NCH_2$-C=C), 52.8 ($OCH_2$), 66.8 ($NCH_2CO$), 111.7, 118.1, 123.9, 125.8, 126.8, 138.7, 151.4, 162.0, 172.1, 185.3 (Ar-C, C=O). EI MS (m/z): 355.06 (M+).

*Anal.* Calcd. (%) for $C_{17}H_{17}N_5O_4$: C, 57.46; H, 4.82; N, 19.71. Found: C, 57.33; H, 4.94; N, 19.67.

**1-(2-(4-((3-Methylmorpholino)Methyl)-1*H*-1,2,3-Triazol-1-yl)Acetyl)Indoline-2, 3-Dione (7d)**

Yield 85%, mp 247–248°C; IR: 3029 (Ar-H), 2844–2980 (CH str.), 1728 (C=O), 1603 $cm^{-1}$ (C=O). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 1.18 (3H, d, $J = 4.0$ Hz, $CH_3$), 2.49–2.60 (3H, m, $CHCH_3$, $NCH_2$), 3.50 (1H, dd, $J = 4.0$ Hz, 12 Hz, OCH), 3.68–3.77 (3H, m, 2 x $OCH_2$), 3.96 (2H, s, $NCH_2$-C=C), 5.03 (1H, s, NCHCO), 5.20 (1H, s, NCHCO), 7.18–7.24 (2H, m, ArH), 7.56–7.64 (2H, m, ArH), 7.99 (1H, s, CH-1,2,3-triazole); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$C 19.3 ($CH_3$), 39.2, 43.4 ($NCH_2$), 48.9 ($NCH_2$-C=C), 53.2, 55.0 ($OCH_2$), 67.9 ($NCH_2CO$), 112.2, 117.8, 123.5, 125.6, 126.2, 139.0, 151.9, 162.5, 172.4, 185.3 (Ar-C, C=O). EI MS (m/z): 369.20 (M+).

*Anal.* Calcd. (%) for $C_{18}H_{19}N_5O_4$: C, 58.53; H, 5.18; N, 18.96. Found: C, 58.62; H, 5.30; N, 19.09.

**1-(2-(4-((4-Methylpiperazin-1-yl)Methyl)-1*H*-1,2,3-Triazol-1-yl)Acetyl)Indoline-2, 3-Dione (7e)**

Yield 87%, mp 263–264°C; IR: 3019 (Ar-H), 2865–2923 (CH str.), 1718 (C=O), 1600 $cm^{-1}$ (C=O). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 2.31 (3H, s, $NCH_3$), 2.47–2.53 (4H, m, 2 x $NCH_2$), 2.67 (2H, t, $J = 4.0$ Hz, $NCH_2$), 2.74 (2H, t, $J = 4.0$ Hz, $NCH_2$), 3.94 (2H, s, $NCH_2$-C=C), 4.96 (1H, s, NCHCO), 5.13 (1H, s, NCHCO), 7.15–7.22 (2H, m, ArH), 7.52–7.59 (2H, m, ArH), 8.05 (1H, s, CH-1,2,3-triazole); $^{13}$C NMR (100 MHz,

DMSO-$d_6$) $\delta_C$ 34.6 ($NCH_3$), 39.0, 46.1 ($NCH_2$), 52.4 (N*C*$H_2$-C=C), 68.3 (N*C*$H_2$CO), 112.0, 118.4, 124.5, 125.2, 126.2, 139.8, 151.1, 162.4, 173.9, 185.0 (Ar-C, C=O). EI MS (m/z): 368.04 (M+).

*Anal.* Calcd. (%) for $C_{18}H_{20}N_6O_3$: C, 58.69; H, 5.47; N, 22.81. Found: C, 58.54; H, 5.38; N, 22.95.

**1,1′-(2,2′-(4,4′-(Piperazine-1,4-Diyl)bis(Methylene))bis(1*H*-1,2,3-Triazole-4,1-Diyl)) bis(Acetyl))bis-(Indoline-2,3-Dione) (7f)**

Yield 81%, mp 278–279°C; IR: 3062 (Ar-H), 2856–2970 (CH str.), 1714 (C=O), 1613 $cm^{-1}$ (C=O). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 2.60–2.64 (4H, m, 2 x $NCH_2$), 2.72–2.75 (4H, m, 2 x $NCH_2$), 4.02 (4H, s, 2 x $NCH_2$-C=C), 4.98 (2H, s, 2 x NCHCO), 5.22 (2H, s, 2 x NCHCO), 7.12–7.21 (4H, m, ArH), 7.48–7.61 (4H, m, ArH), 8.00 (2H, s, 2 x CH-1,2,3-triazole); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ 43.6 ($NCH_2$), 44.2 ($NCH_2$), 52.9 (N*C*$H_2$-C=C), 65.4 (N*C*$H_2$CO), 111.6, 118.0, 124.4, 125.9, 126.4, 139.2, 152.5, 162.7, 172.1, 185.0 (Ar-C, C=O). EI MS (m/z): 622.29 (M+).

*Anal.* Calcd. (%) for $C_{30}H_{26}N_{10}O_6$: C, 57.87; H, 4.21; N, 22.50. Found: C, 57.80; H, 4.35; N, 22.38.

**1,1′-(2,2′-(4,4′-((2-Methylpiperazine-1,4-Diyl)bis(Methylene))bis(1*H*-1,2,3-Triazole-4,1-Diyl))bis(Acetyl))bis(Indoline-2,3-Dione) (7g)**

Yield 80%, mp 296–297°C; IR: 3087 (Ar-H), 2871–2935 (CH str.), 1729 (C=O), 1602 $cm^{-1}$ (C=O). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta_H$ 1.21 (3H, d, $J$ = 4.0 Hz, $CH_3$), 2.46–2.52 (1H, m, C*H*$CH_3$), 2.65–2.71 (2H, m, $NCH_2$), 2.75–2.81 (1H, m, NCH), 2.84–2.90 (2H, m, $NCH_2$), 3.05–3.09 (1H, m, NCH), 3.79 (2H, s, $NCH_2$-C=C), 3.95 (2H, s, $NCH_2$-C=C), 4.78 (1H, s, NCHCO), 4.90 (1H, s, NCHCO), 5.13 (1H, s, NCHCO), 5.24 (1H, s, NCHCO), 7.18–7.26 (4H, m, ArH), 7.43–7.69 (4H, m, ArH), 8.08 (1H, s, CH-1,2,3-triazole), 8.12 (1H, s, CH-1,2,3-triazole); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta_C$ 18.4 ($CH_3$), 42.6, 47.8, 49.9 ($NCH_2$), 54.4, 56.8 (N*C*$H_2$-C=C), 61.7, 65.2 (N*C*$H_2$CO), 111.9, 112.1, 118.8, 120.8, 124.5, 126.7, 127.2, 138.7, 139.8, 151.3, 152.6, 162.1, 163.0, 172.6, 172.9, 185.7, 186.1 (Ar-C, C=O). EI MS (m/z): 636.14 (M+).

*Anal.* Calcd. (%) for $C_{31}H_{28}N_{10}O_6$: C, 58.49; H, 4.43; N, 22.00. Found: C, 58.34; H, 4.48; N, 21.82.

### *Antibacterial and Antifungal Screening*

The designed click products **3a-g** and **7a-g** were assessed for their antibacterial and antifungal inhibition potency using the broth dilution method[31, 32] towards six pathogenic bacterial strains (gram-positive: *Bacillus subtilis, Streptococcus pneumonia* and *Staphylococcus aureus*; gram-negative: *Escherichia coli, Pseudomonas aeruginosa* and *Klebsiella pneumonia*) and two fungal strains (*Aspergillus fumigatus* and *Candida albicans*).

## Acknowledgment

The author is very grateful to Dr. Linda Aouad, Faculty of Medicine, University of Djilali Liabes, Sidi Bel Abbes, Algeria, for her valuable assistance in the biological screening.

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