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3-(2-oxo-2-Phenylethylidene)-1-((1-phenyl-*1H*-1,2,3-triazol-4-yl) methyl)indolin-2-ones: Synthesis, characterization and antibacterial activity

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ABSTRACT

*The novel 3-(2-oxo-2-phenylethylidene)-1-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)indolin-2-one derivatives were synthesized from Cu-catalyzed [3+2] cyclo addition reaction of alkyne with various aryl azides. The synthesized 1,2,3-triazoles were characterized by IR, ^{1}HNMR and Mass spectral techniques and evaluated for their anti-bacterial activity. Compounds **3a**, **3d**, **3f**, **3h** and **3i** showed significant antibacterial activity when compared to standard drug Streptomycin.*

Keywords: Indoline-2,3-dione; 1,2,3-triazoles; Cu(I)-catalyst; Antibacterial activity.

INTRODUCTION

The synthesis of N-Heterocyclic compounds has always drawn the attention of chemists over the years mostly their significant biological properties. The 1,2,3-triazole skeleton is one of the most attractive structure works with a broad range of biological and pharmacological activities. Many researchers have described synthesis of 1,2,3-triazoles and its derivatives along with its applications in literature. A large number of heterocyclic compounds containing the 1,2,3-triazole ring are associated with diverse pharmacological properties such as antibacterial [1,2], antifungal [3], Anticancer [4], Antidiabetic [5], Anti-inflammatory [6], Anti-HIV [7]. Antimicrobial [8].

Led by these considerations, it appeared of interest to synthesize novel 1,4-disubstituted 1,2,3-triazole derivatives and to investigate for their antibacterial activities.

MATERIALS AND METHODS

All chemicals were purchased from Sigma Aldrich Chemicals / S.D. Fine Chemicals Limited and were used without further purification. The reactions were monitored by thin layer chromatography on silica gel G plates (Merck silica-60 F258).Visualization of the developed chromatogram was performed by UV light (254 nm). Melting points were determined using a Cintex apparatus and were uncorrected. Elemental analysis was measured by means of Perkin

Elmer 2400 CHN elemental analyzer. 1H NMR was obtained on Bruker DRX-500 Avance spectrometer operating at 400MHz. Samples were prepared in CDCl3 solvent with TMS as an internal reference. Coupling constant (J) values are presented in Hertz (Hz) and spin multiples are given as s (singlet), d (doublet), t (triplet), and m (multiplet). Fourier-transform infrared (FT-IR) spectra were obtained as KBr discs on Shimadzu spectrometer. Mass spectra were recorded by using ESI–MS. The synthetic route for 1,2,3-triazole derivatives is depicted in **Scheme 1**.

Synthesis of 1-(prop-2-ynyl)indoline-2,3-dione(1):
A mixture of indoline-2,3-dione (0.034 mol) and propargyl bromide (0.04 mol) in acetone was mixed in a round bottom flask, Cs_2CO_3 (0.068 mol) was added. Resulting mixture was stirred at room temperature for 30 min. After poured into crushed ice the precipitate obtained was filtered and washed twice with cold water. The resulting solid was allowed to air dry and recrystallized from ethanol. Yield (5.5g, 88%); IR spectra showing an absorption bands at 1750, 1700, ^{1}H NMR(400 MHz, $CDCl_3$):7.53–7.87 (4H, m, Ar-H), 4.25(1H, s, N-C*H*$_2$), 2.18(1H,s,C*H*); EI-MS m/z (M+H) -186; Anal. Calcd for $C_{11}H_7NO_2$: C, 71.35; H, 3.81; N, 7.56; found: C, 71.29; H, 3.88; N, 7.51.

Synthesis of 3-(2-oxo-2-phenylethylidene)-1-(prop-2-ynyl)indolin-2-one(2):
To a mixture of 1-(prop-2-ynyl) indoline-2,3-dione (0.027 mol) and Acetophenone (0.027 mol) in ethanol at 0 ^{o}C. 10 % aqueous sodium hydroxide solution added drop wise. Resulting mixture was stirred for 1h at room temperature, poured into crushed ice and acidified with dilute HCl. The precipitate obtained was filtered and washed twice with cold water. The resulting solid was allowed to air dry and re-crystallized from ethanol. Yield (6.2g, 80%); 1720,1665,1600; ^{1}H NMR (400 MHz, $CDCl_3$): 7.89 (2H, m, Ar-H),7.80 (3H, m, Ar-H), 7.71(2H, m, Ar-H),7.20(2H, d, *J*= 7.2 Hz, Ar-H), 6.97 (1H, s, C=C*H*), 4.27(1H, s, N-C*H*$_2$), 2.22(1H,s,C*H*); EI-MS m/z (M+H) -288; Anal. Calcd for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.88; found: C, 79.39; H, 4.63; N, 4.51.

Synthesis of 1,4-disubstituted 1,2,3-triazoles (3a-3j):
To a solution of alkyne (2) (0.5g, 1.7 mmol) and aryl azide (1.8 mmol) in THF, Cu (I) (10 mol%) was added. Resulting mixture was stirred at room temperature for 6-8 h. Check TLC the reaction was stopped by addition of H_2O and the product was extracted with ethyl acetate. Then the crude product was further purified by column chromatography.

1-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-(2-oxo-2-phenylethylidene)indolin-2-one (3a): White solid; m.p. 127–129 ^{o}C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ in ppm: 7.82 (m, 2H); 7.80 (s, triazole-H, 1H); 7.72 (d, *J*= 8.0 Hz, Ar, 2H); 7.65(m, 3H), 7.31 (d, *J=8.0 Hz*, Ar, 2H); 7.24 (m, Ar, 4H); 6.97 (s, 1H); 5.58 (s, N-CH_2, 2H); 3.83 (s, O-CH_3, 3H); IR(KBr,cm^{-1}) 3144, 1720,1665,1600, 1594, 1514, 1400; EI-MS m/z (M+H)- 437; Anal. Calcd for $C_{26}H_{20}N_4O_3$: C, 71.55; H, 4.62; N, 12.84; found : C, 71.61; H, 4.58; N, 12.92

1-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-(2-oxo-2-phenylethylidene)indolin-2-one (3b): Pale yellow solid; m.p. 148–150 ^{o}C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ in ppm: 7.87 (m, 2H); 7.81 (s, triazole-H, 1H); 7.77 (m, Ar, 3H); 7.62 (m, Ar, 2H); 7.48 (m, Ar, 3H); 7.34(m, 2H); 6.82 (s, 1H); 5.59 (s, N-CH_2, 2H); IR(KBr,cm^{-1}) 3131, 1728,1675,1618, 1597, 1515, 1397; EI-MS m/z (M+H) - 452; Anal. Calcd for $C_{25}H_{17}N_5O_4$: C, 66.51; H, 3.80; N, 15.51; found : C, 66.49; H, 3.76; N, 15.57.

1-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-(2-oxo-2-phenylethylidene)indolin-2-one (3c): Yellow solid; m.p. 142–144 ^{o}C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ in ppm: 7.89 (m, 2H); 7.82 (s, triazole-H, 1H); 7.73 (m, Ar, 3H); 7.66 (d, *J*= 8.0 Hz, Ar, 2H); 7.58 (m, Ar, 3H); 7.42(d, *J*= 8.0 Hz, Ar, 2H); 6.80 (s, 1H); 5.52 (s, N-CH_2, 2H); IR(KBr,cm^{-1}) 3133,1728, 1666, 1600, 1594, 1498, 1400; EI-MS m/z (M+H)-486; Anal. Calcd for $C_{25}H_{17}BrN_4O_2$: C, 61.87; H, 3.53; N, 11.54; found : C, 61.92; H, 3.57; N, 11.49.

1-((1-(2,3-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-(2-oxo-2-phenylethylidene)indolin-2-one (3d): White solid; m.p. 131–133 ^{o}C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ in ppm: 7.88 (m, 2H); 7.80 (s, triazole-H, 1H); 7.76 (m, Ar, 2H); 7.62 (d, *J*=8.0 Hz, Ar, 2H); 7.54 (m, Ar, 3H); 7.42(m, 3H); 6.81 (s, 1H); 5.55(s, N-CH_2, 2H); 2.28 (s, Ar-CH_3, 3H); 2.19 (s, Ar-CH_3, 3H); IR(KBr,cm^{-1}) 3141, 1727,1665,1604, 1593, 1511, 1400; EI-MS m/z (M+H)-435; Anal. Calcd for $C_{27}H_{22}N_4O_2$: C, 74.64; H, 5.10; N, 12.89; found : C, 74.59; H, 5.14; N, 12.92

1-((1-(3-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-(2-oxo-2-phenylethylidene)indolin-2-one (3e): White solid; m.p. 144–146 ^{o}C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ in ppm: 7.90 (m, 2H); 7.84 (s, triazole-H, 1H); 7.77 (m, Ar, 3H); 7.60 (d, *J*= 7.2 Hz, Ar, 2H); 7.51 (m, Ar, 3H); 7.40(d, *J*= 7.2 Hz, Ar, 2H); 6.82(s, 1H); 5.52 (s, N-CH_2, 2H); IR(KBr,cm^{-1}) 3131, 1720,1685,1608, 1593, 1511, 1399; EI-MS m/z (M+H) - 441; Anal. Calcd for $C_{25}H_{17}ClN_4O_2$: C, 68.11; H, 3.89; N, 12.71; found : C, 68.17; H, 3.93; N, 12.85

1-((1-(3,5-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-(2-oxo-2-phenylethylidene)indolin-2-one (3f): Yellow solid; m.p. 139–141 ^{o}C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ in ppm: 7.87(m, 2H); 7.82 (s, triazole-H, 1H); 7.79 (s, Ar, 1H);7.69(s, Ar, 2H); 7.60 (m, Ar, 2H); 7.42(m, 2H); 6.88 (s, 1H); 5.57 (s, N-CH_2, 2H); IR(KBr,cm^{-1}) 3137,

1728,1669,1618, 1590, 1511, 1396; EI-MS m/z (M+H)-476; Anal. Calcd for $C_{25}H_{16}Cl_2N_4O_2$: C, 63.17; H, 3.39; N, 11.79; found : C, 63.21; H, 3.43; N, 11.82

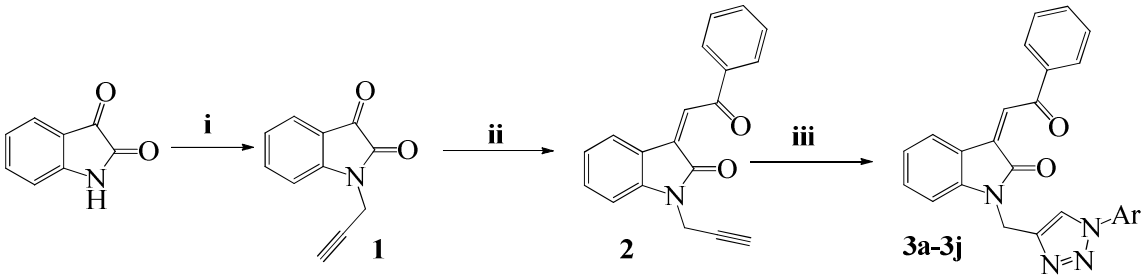
1-((1-(4-butylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-(2-oxo-2-phenylethylidene)indolin-2-one (3g): White solid; m.p. 118–120 ^oC; ^1H-NMR (400 MHz, $CDCl_3$) δ in ppm: 7.87 (m, 2H); 7.82 (s, triazole-H, 1H); 7.72 (m, Ar, 3H); 7.67 (d, *J*= 8.0 Hz, Ar, 2H); 7.60 (m, Ar, 3H); 7.57(d, *J*= 8.0 Hz, Ar, 2H); 6.84(s, 1H); 5.54 (s, N-CH_2, 2H); 2.70(t, *J*= 7.2 Hz , 2H), 1.32-1.65 (m, 4H), 0.96 (t, *J*=8 Hz, 3H); IR(KBr,cm^{-1}) 3131, 1719, 1672, 1635, 1592, 1511, 1399; EI-MS m/z (M+H)-463; Anal. Calcd for $C_{29}H_{26}N_4O_2$: C, 75.30; H, 5.67; N, 12.11; found : C, 75.27; H, 5.72; N, 12.17

3-(2-oxo-2-phenylethylidene)-1-((1-m-tolyl-1H-1,2,3-triazol-4-yl)methyl)indolin-2-one (3h):
Pale red solid ; m.p. 147–149 ^oC; ^1H-NMR (400 MHz, $CDCl_3$) δ in ppm: 7.88 (m, 2H); 7.79 (s, triazole-H, 1H); 7.70 (m, Ar, 3H); 7.65 (m, Ar, 2H); 7.66 (m, Ar, 3H); 7.54 (d, Ar, 2H); 6.82(s, 1H); 5.54 (s, N-CH_2, 2H); 2.27(s, Ar-CH_3, 3H); IR(KBr,cm^{-1}) 3147, 1715,1675,1608, 1589, 1521, 1408; EI-MS m/z (M+H)-421; Anal. Calcd for $C_{26}H_{20}N_4O_2$: C, 74.27; H, 4.79; N, 13.33; found : C, 74.32; H, 4.76; N, 13.30.

1-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-(2-oxo-2-phenylethylidene)indolin-2-one (3i)*:* White solid; m.p. 162–164 ^oC; ^1H-NMR (400 MHz, $CDCl_3$) δ in ppm: 7.91 (m, 2H); 7.86 (s, triazole-H, 1H); 7.79 (m, Ar, 3H); 7.70 (m, Ar, 2H); 7.66 (m, Ar, 3H); 7.52(m, Ar, 2H); 6.87(s, 1H); 5.58 (s, N-CH_2, 2H); IR(KBr,cm^{-1}) 3140, 1722,1663,1611, 1594, 1518, 1399; EI-MS m/z (M+H) - 452; Anal. Calcd for $C_{25}H_{17}N_5O_4$: C, 66.51; H, 3.80; N, 15.51; found : C, 66.56; H, 3.87; N, 15.55.

3-(2-oxo-2-phenylethylidene)-1-((1-o-tolyl-1H-1,2,3-triazol-4-yl)methyl)indolin-2-one (3j):
Pale red solid; m.p. 162–164 ^oC; ^1H-NMR (400 MHz, $CDCl_3$) δ in ppm: 7.86 (m, 2H); 7.80 (s, triazole-H, 1H); 7.72 (m, Ar, 3H); 7.68 (m, Ar, 2H); 7.59 (m, Ar, 3H); 7.50 (d, Ar, 2H); 6.87(s, 1H); 5.55(s, N-CH_2, 2H); 2.32(s, Ar-CH_3, 3H); IR(KBr,cm^{-1}) 3131, 1726,1658,1610, 1594, 1510, 1407; EI-MS m/z (M+H)-421; Anal. Calcd for $C_{26}H_{20}N_4O_2$: C, 74.27; H, 4.79; N, 13.33; found : C, 74.31; H, 4.85; N, 13.30.

Antibacterial activity:
All the synthesized compounds(3a-3j) were screened for their antibacterial activity by using agar diffusion method [9] against *B. subtilis* (MTCC 441) and *S.aureus* (MTCC 96) Gram positive bacteria and *S. paratyphi-B* (MTCC 733), *E-coli* (MTCC 443), Gram negative bacteria in nutrient agar medium. Streptomycin was used as standard drug for the comparison of antibacterial activity. Serial dilutions of the test compounds as well as standards were performed at concentrations ranging from 150 to 0.97 mg mL^{-1} in a 200 mL culture medium final volume; afterwards each well was seeded with a 50 µL microbial suspension of 0.5 MacFarland density. In each test a microbial culture control and a sterility control (negative) were performed. The plates were incubated for 24 h at 37 ^oC.



Ar: **a**- 4-methoxyphenyl; **b**-4-nitrophenyl; **c**-4-bromophenyl; **d**-2,3-dimethylphenyl
e-3-chlorophenyl; **f**-3,5-dichlorophenyl; **g**-4-butylphenyl; **h**-3-methyl phenyl
i- 3-nitrophenyl; **j**- 2-methylphenyl

Scheme 1: **i)** Propargyl bromide/ Cs_2CO_3, Acetone, rt, 30 min; **ii)** $PhCOCH_3$ / 10% NaOH, EtOH,rt
iii) Arylazide/ Cu(I), THF, rt, 6-8h.

RESULTS AND DISCUSSION

Chemistry

In this paper, the synthesis and characterization of some novel 1,4-disubstituted 1,2,3-triazoles have been presented. These 1,2,3-triazoles were prepared from terminal alkyne with aryl azides by using Copper catalyzed[3+2] cyclo addition reaction[10]. The intermediate alkyne was prepared by using indoline-2,3-dione and propargyl bromide and acetophenone. Initially the indoline-2,3-dione was reacted with propargyl bromide at room temperature using Cs_2CO_3 as base to afford 1-(prop-2-ynyl) indoline-2,3-dione(2) [11]. These alkyne further condensation with acetophenone using 10% NaOH solution in ethanol to form 3-(2-oxo-2-phenylethylidene)-1-(prop-2-ynyl)indolin-2-one in good yield.

Biology

The screening results indicate that the compound **3a** was found to be active against *S. aureus* (MTCC-96). The compound **3d** and **3f** were found to be active against *B. subtilis* (MTCC-441). Compound **3h** was found to be active against *E. coli* (MTCC-443) and **3i** was found to be active against *S.paratyphi-B* (MTCC-733). Whereas the remaining compounds were found to be moderate to good activity against all tested bacterias.

Table 1: antibacterial activity of new 1,2,3-triazole derivatives (3a-3j)

ZOI(mm)					
S. No	**Analog**	***S.aureus MTCC-96***	***B.subtilis MTCC-441***	***E.coli MTCC-443***	***S.paratyphi-B MTCC-733***
1	3a	20	12	16	08
2	3b	14	08	14	08
3	3c	10	08	08	12
4	3d	08	22	08	10
5	3e	08	17	14	08
6	3f	18	23	10	17
7	3g	08	12	08	15
8	3h	10	16	20	14
9	3i	12	08	08	19
10	3j	14	08	08	12
11	**S**	**22**	**26**	**22**	**20**

CONCLUSION

In conclusion, the present work a convenient method for the synthesis of biologically active novel 1, 2, 3-triazole derivatives. All the compounds were screened for antimicrobial activity. Among all the synthesized compounds, **3a**, **3d**, **3f** , **3h** and **3i** showed significant antibacterial activity against both gram positive and negative bacterial strains.

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