

## Design and Synthesis of Chromenone-Benzimidazole/Bezoazole-1,2,3-triazole Hybrids and their Antimicrobial Activity

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Received: 11 March 2022;

Accepted: 21 April 2022;

Published online: 15 June 2022;

AJC-20861

A novel series of chromenone-benzimidazole/bezoazole-1,2,3-triazole hybrids have been designed and synthesized using 4-hydroxy-chromenone. The 4-hydroxychromenone was used to produce terminal alkynated chromenone, which in turn reacted with different benzimidazole and benzoazole aryl azides using Click reaction condition to afford respective title compounds in good yields. All the synthesized 1,2,3-triazole derivatives were screened for their *in vitro* antimicrobial activity against four bacterial and two fungal strains, among them compounds **3a**, **3f** and **3j** were showed potent antimicrobial activity.

**Keywords:** Chromenone, 1,2,3-Triazole, Benzimidazole, Benzoazole, Click reaction, Antimicrobial activity.

### INTRODUCTION

Due to its biological properties, coumarin occupies irreplaceable position in the synthetic organic chemistry and natural products. Coumarin is abundant in nature and shows important pharmacological activities, such as antifungal [1], antibacterial [2], antitumor [3], anti-inflammatory [4], antiviral [5], antioxidant [6], anti-thrombotic [7] and anti-allergic [8] properties. It is also employed as an additive in cosmetics, food and optical brightening agents [9]. The derivatives of coumarin serve as tannin frameworks, which are receiving importance due to the health-promoting effects of tannins available in vegetables, red wine, teas, and fruits [10]. Additionally, in past few decades, 1,2,3-triazole and its derivatives have gained substantial attention because of their chemotherapeutical and other properties, including anti-inflammatory, antimicrobial, anticonvulsant, anti-HIV, anticancer and anti-tubercular activities [11].

Moreover, numerous synthetic and natural bioactive substances comprising benzimidazole/benzoazole scaffolds exhibit various biological properties, such as antileishmanial, antimalarial, antimicrobial, antiviral, anti-inflammatory and anticancer activities [12]. In the absence of a structural target receptor, pharmacophore selection is a crucial process involved

in drug design. Thus, several novel molecules comprising multifunctional pharmacophores in one single-target molecule is developed and designed. The biological properties of 1,2,3-triazole, chromenone and benzoazole/benzimidazole derivatives encouraged us to synthesize chromenone-benzimidazole/bezoazole-1,2,3-triazole hybrids.

### EXPERIMENTAL

The melting points were estimated in open capillary tubes and are not corrected. Compound purity was determined through TLC by using the precoated silica gel plates 60<sub>254</sub> (Merck). On a Shimadzu FT-IR-8400s spectrophotometer, the IR (KBr) spectra were recorded. On a Bruker Avance II 400 MHz spectrometer, <sup>1</sup>H & <sup>13</sup>C NMR spectra were measured by using DMSO-*d*<sub>6</sub> and TMS as the solvent and internal standard, respectively. On a GCMS-QP 1000 EX mass spectrometer, the mass spectra were recorded.

**Synthesis chromenone-benzimidazole/bezoazole-1,2,3-triazole hybrids (3a-1):** A mixture of aryl azide (**2a-d**) (1.2 mmol), 4-(prop-2-yn-1-yloxy)-2H-chromen-2-ones (**1a-c**) (1 mmol), sodium ascorbate (3 mol%), and copper sulphate (2 mol %) was stirred in 5 mL of *tert.*-butanol:water (2:1) at room temperature for 3-4 h. The reaction progress was moni-

tored using TLC. After the completion of reaction, the reaction solution was poured in ice-cold water. A solid precipitate slowly formed. The precipitate was filtered, washed with water, dried, and purified through column chromatography by using an eluent of chloroform:methanol (8:2) to obtain pure chromanone-1,2,3-triazole derivatives (**3a-l**) (Scheme-I).

**4-((1-(3-(1*H*-Benzo[d]imidazol-2-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2*H*-chromen-2-one (3a):** Off-white colour solid; yield: 82%; m.p.: 135-137 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 9.31 (s, 1H), 8.74 (s, 1H), 8.34-8.32 (d, *J* = 8.0 Hz, 1H), 8.25-8.23 (d, *J* = 8.0 Hz, 1H), 7.90-7.84 (m, 4H), 7.69-7.65 (m, 1H), 7.51-7.35 (m, 4H), 6.23 (s, 1H), 5.57 (s, 2H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 164.3, 161.5, 161.1, 152.7, 150.3, 142.5, 141.3, 137.1, 132.7, 131.7, 130.6, 126.0, 124.1, 123.4, 122.9, 122.4, 120.0, 118.4, 116.3, 115.0, 111.1, 91.4, 62.7. MS (ESI): *m/z* 436 [M+H]<sup>+</sup>.

**4-((1-(3-(Benzo[d]oxazol-2-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2*H*-chromen-2-one (3b):** Off-white colour solid; Yield: 86%; m.p.: 141-143 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 9.31 (s, 1H), 8.74 (s, 1H), 8.32-8.34 (d, 1H), 8.22-8.25 (d, 1H), 7.84-7.90 (m, 4H), 7.65-7.69 (dd, 1H), 7.35-7.51 (m, 4H), 6.23 (s, 1H), 5.57 (s, 2H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 164.6, 161.4, 161.1, 152.7, 150.3, 142.4, 141.3, 137.1, 132.8, 131.1, 128.0, 127.3, 126.4, 125.6, 123.6, 123.2, 123.0, 122.0, 121.2, 118.4, 116.4, 115.2, 111.1, 91.3, 62.6. MS (ESI): *m/z* 437 [M+H]<sup>+</sup>.

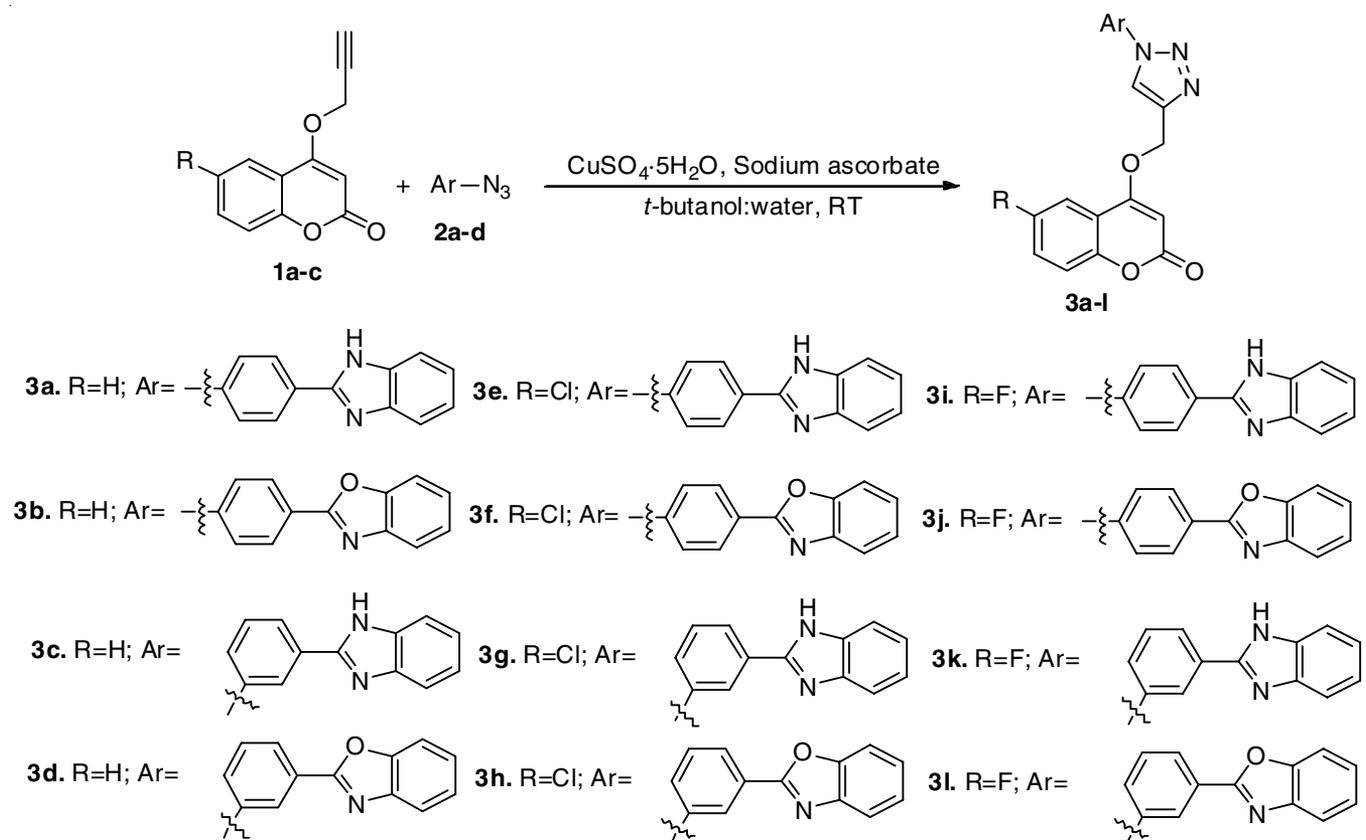
**4-((1-(4-(1*H*-Benzo[d]imidazol-2-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2*H*-chromen-2-one (3c):** Off-white colour solid; Yield: 84%; m.p.: 126-128 °C. <sup>1</sup>H NMR (400 MHz,

DMSO-*d*<sub>6</sub>) δ ppm: 13.1 (s, 1H), 9.19 (s, 1H), 8.77 (s, 1H), 8.41-8.39 (d, 1H), 8.18-8.16 (d, 2H), 8.00-7.85 (m, 2H), 7.70-7.59 (m, 3H), 7.44-7.24 (m, 4H), 6.22 (s, 1H), 5.56 (s, 2H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 164.2, 161.4, 152.7, 137.1, 132.7, 127.7, 124.1, 123.2, 122.9, 122.5, 120.4, 116.3, 114.9, 91.3, 62.7. MS (ESI): *m/z* 436 [M+H]<sup>+</sup>.

**4-((1-(3-(Benzo[d]oxazol-2-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2*H*-chromen-2-one (3d):** Off-white colour solid; Yield: 85%; m.p.: 136-138 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 9.24 (s, 1H), 8.44-8.42 (d, 2H), 8.25-8.22 (d, 2H), 7.87-7.85 (m, 3H), 7.69-7.66 (t, 1H), 7.50-7.34 (m, 4H), 6.22 (s, 1H), 5.56 (s, 2H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 164.2, 161.3, 138.6, 132.9, 129.0, 125.9, 125.1, 124.3, 123.4, 123.1, 120.8, 120.0, 116.5, 111.1, 91.5, 62.7. MS (ESI): *m/z* 436 [M+H]<sup>+</sup>.

**4-((1-(3-(1*H*-benzo[d]imidazol-2-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-6-chloro-2*H*-chromen-2-one (3e):** Off-white colour solid; Yield: 81%; m.p.: 132-134 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 13.08 (s, 1H), 9.33 (s, 1H), 8.76 (s, 1H), 8.33-8.31 (d, 1H), 8.07-8.05 (d, 1H), 7.95-7.92 (m, 1H), 7.83-7.80 (m, 1H), 7.72-7.53 (m, 4H), 7.49-7.47 (d, 1H), 7.25-7.19 (m, 2H), 6.30 (s, 1H), 5.58 (s, 2H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 163.2, 161.1, 151.4, 142.2, 137.1, 132.5, 131.8, 130.7, 128.3, 126.5, 123.7, 122.4, 122.1, 121.3, 118.6, 118.1, 116.5, 92.3, 63.0, 34.2. MS (ESI): *m/z* 470 [M+H]<sup>+</sup>.

**4-((1-(3-(Benzo[d]oxazol-2-yl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-6-chloro-2*H*-chromen-2-one (3f):** Off-white colour solid; Yield: 84%; m.p.: 140-142 °C. <sup>1</sup>H NMR (400



Scheme-I: Synthesis of chromenone-benzimidazole/bezoxazole-1,2,3-triazole hybrids (**3a-l**)

MHz, DMSO- $d_6$ )  $\delta$  ppm: 9.32 (s, 1H), 8.73 (s, 1H), 8.34-8.32 (d, 1H), 8.24-8.22 (d, 1H), 7.90-7.70 (m, 3H), 7.65-7.61 (m, 2H), 7.51-7.44 (m, 4H), 6.30 (s, 1H), 5.57 (s, 2H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  ppm: 163.3, 161.3, 151.5, 150.4, 141.4, 137.2, 132.7, 131.3, 128.5, 128.1, 127.5, 126.2, 125.3, 123.9, 123.4, 122.2, 120.2, 118.7, 118.6, 116.6, 111.2, 92.4, 63.1. MS (ESI):  $m/z$  471 [M+H] $^+$ .

**4-((1-(4-(1H-Benzo[d]imidazol-2-yl)phenyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-chloro-2H-chromen-2-one (3g):** White colour solid; Yield: 82%; m.p.: 129-131 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 13.06 (s, 1H), 9.30 (s, 1H), 8.76 (s, 1H), 8.42-8.41 (d, 2H), 8.18-8.16 (d, 2H), 7.95 (m, 1H), 7.80-7.60 (m, 2H), 7.49-7.47 (d, 1H), 7.24-7.20 (m, 3H), 6.29 (s, 1H), 5.57 (s, 2H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  ppm: 163.2, 162.4, 161.1, 151.4, 142.3, 137.2, 132.6, 128.4, 127.8, 123.5, 122.5, 121.1, 120.3, 118.6, 116.5, 92.3, 63.0. MS (ESI):  $m/z$  470 [M+H] $^+$ .

**4-((1-(4-(Benzo[d]oxazol-2-yl)phenyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-chloro-2H-chromen-2-one (3h):** Off-white colour solid; Yield: 84%; m.p.: 133-135 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 9.25 (s, 1H), 8.76 (s, 1H), 8.44-8.42 (d, 2H), 8.24-8.22 (d, 2H), 7.86-7.79 (m, 3H), 7.72-7.70 (m, 1H), 7.49-7.43 (m, 3H), 6.29 (s, 1H), 5.57 (s, 2H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  ppm: 163.1, 161.1, 161.0, 151.3, 150.2, 141.3, 138.5, 132.5, 128.8, 128.2, 126.4, 125.8, 125.0, 122.0, 120.7, 119.9, 118.5, 116.4, 110.9, 92.3, 63.2. MS (ESI):  $m/z$  471 [M+H] $^+$ .

**4-((1-(3-(1H-Benzo[d]imidazol-2-yl)phenyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-fluoro-2H-chromen-2-one (3i):** Off-white colour solid; Yield: 81%; m.p.: 132-134 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 13.06 (s, 1H), 9.32 (s, 1H), 8.74 (s, 1H), 8.34-8.32 (d, 2H), 8.22-8.20 (d, 2H), 7.98-7.70 (m, 2H), 7.65-7.55 (m, 3H), 7.36-7.22 (m, 2H), 6.25 (s, 1H), 5.56 (s, 2H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  ppm: 163.4, 161.5, 155.3, 151.5, 150.5, 141.4, 137.2, 132.7, 131.2, 128.6, 128.2, 127.3, 126.2, 125.3, 123.8, 123.6, 122.4, 120.2, 119.7, 119.5, 114.9, 110.9, 92.2, 62.8. MS (ESI):  $m/z$  454 [M+H] $^+$ .

**4-((1-(3-(Benzo[d]oxazol-2-yl)phenyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-fluoro-2H-chromen-2-one (3j):** Off-white colour solid; Yield: 80%; m.p.: 134-137 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 9.33 (s, 1H), 8.76 (s, 1H), 8.33-8.31 (d, 2H), 8.07-8.05 (d, 1H), 7.95-7.92 (m, 1H), 7.83-7.80 (m, 2H), 7.72-7.47 (m, 3H), 7.25-7.21 (m, 2H), 6.27 (s, 1H), 5.56 (s, 2H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  ppm: 163.2, 161.1, 151.4, 142.2, 137.1, 132.5, 131.8, 130.7, 128.3, 126.5, 123.7, 122.4, 122.1, 121.3, 118.6, 118.1, 116.5, 92.3, 63.0, 34.2. MS (ESI):  $m/z$  455 [M+H] $^+$ .

**4-((1-(3-(1H-Benzo[d]imidazol-2-yl)phenyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-fluoro-2H-chromen-2-one (3k):** White colour solid; Yield: 83%; m.p.: 128-130 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 13.06 (s, 1H), 9.32 (s, 1H), 8.34 (s, 1H), 8.24-8.17 (m, 3H), 7.95-7.86 (m, 2H), 7.64-7.60 (m, 3H), 7.43-7.20 (m, 3H), 6.21 (s, 1H), 5.56 (s, 2H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  ppm: 163.2, 161.6, 161.2, 155.5, 151.3, 150.2, 141.4, 138.5, 132.4, 128.8, 128.3, 126.4, 125.5, 125.1, 124.5, 122.0, 120.3, 119.7, 118.4, 116.0, 110.9, 91.2, 63.2. MS (ESI):  $m/z$  454 [M+H] $^+$ .

**4-((1-(4-(Benzo[d]oxazol-2-yl)phenyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-fluoro-2H-chromen-2-one (3l):** White colour solid; Yield: 80%; m.p.: 137-139 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 9.24 (s, 1H), 8.76 (s, 1H), 8.44-8.42 (d, 2H), 8.24-8.11 (m, 2H), 7.95-7.82 (m, 2H), 7.69-7.33 (m, 3H), 7.26-7.22 (m, 2H), 6.20 (s, 1H), 5.56 (s, 2H).  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  ppm: 163.9, 161.3, 161.1, 153.9, 150.2, 142.5, 141.3, 138.4, 132.2, 128.8, 127.1, 126.4, 125.8, 125.3, 125.0, 124.6, 123.3, 120.6, 111.9, 110.9, 103.8, 90.5, 62.8. MS (ESI):  $m/z$  455 [M+H] $^+$ .

## RESULTS AND DISCUSSION

The title 1,2,3-triazoles derivatives were obtained by the cyclization of 4-(prop-2-yn-1-yloxy)-2H-chromen-2-ones [13] (**1a-c**) with benzimidazole/benzoxazolephenylazides (**2a-d**) under Click reaction condition in the presence of copper sulphate as catalyst using sodium ascorbate in *t*-butanol:water medium at room temperature to give corresponding 1,2,3-triazoles derivatives (**3a-l**) in good yield. The key intermediates of the three 4-(prop-2-yn-1-yloxy)-2H-chromen-2-ones (**1a-c**) were prepared from three different 4-hydroxycoumaraine such as 4-hydroxycoumaraine, 6-chloro-4-hydroxycoumaraine and 6-fluoro-4-hydroxycoumaraine as per previous reported synthetic procedure. On the other hand, two benzimidazolephenylazides and two benzoxazolephenylazides were prepared in two synthetic step as per previous literature, in the first step corresponding aminobenzoic acids reacted with 2-aminophenol and *o*-phenylenediamine to produce benzimidazolephenylamine and two benzoxazolephenylamine, which were further converted amine to azide to afford desired azide derivatives (**2a-d**).

The products were characterized by IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR and ESI-MS data. In IR spectrum of the compound **3a** showed the oxime C=N stretching band at 1600  $\text{cm}^{-1}$ , C-O absorption band at 1251  $\text{cm}^{-1}$  and O-C=O band was located at 1575  $\text{cm}^{-1}$ . In  $^1\text{H}$  NMR spectrum of **3a** showed a singlet at  $\delta$  5.57 ppm integrated for two protons were corresponding to methylene group, a another appeared at  $\delta$  6.23 ppm integrated for one proton was assigned to chromene ring and another characteristic triazole ring proton observed at  $\delta$  8.74 ppm as a singlet. In the  $^{13}\text{C}$  NMR spectrum of **3a**, showed a carbon at  $\delta$  62.7 ppm was assigned to methylene carbon and carbon at  $\delta$  164.3 ppm was corresponds to carbonyl carbon of the chromone ring. The mass spectrum of compound **3a** displayed the molecular ion peak at  $m/z$  436 [M+H] $^+$ .

**Antibacterial activity:** The synthesized compounds (**3a-l**) were evaluated for *in vitro* antibacterial activity against four bacterial strains Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) by paper disc method and norfloxacin used as the standard drug by measuring the zone of inhibition in mm. The synthesized compounds were screened at the concentrations of 100  $\mu\text{g}/\text{mL}$  in DMSO. Compounds **3a**, **3f**, **3j** and **3l** were showed good antibacterial activity against all the bacterial stains and reaming compounds showed the moderate to low activity (Table-1).

TABLE-1  
ANTIMICROBIAL ACTIVITY OF CHROMENONE-BENZIMIDAZOLE/BEZOAZOLE-1,2,3-TRIAZOLE HYBRIDS (3a-l)

Compd.	Bacteria				Fungi	
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>A. niger</i>	<i>Sclerotiumrol fsii</i>
<b>3a</b>	18.6	15.2	16.0	19.9	9.8	11.5
<b>3b</b>	20.9	13.0	13.5	11.2	11.0	9.9
<b>3c</b>	9.6	8.0	13.0	20.5	10.2	11.4
<b>3d</b>	16.1	20.0	11.8	13.2	9.5	10.2
<b>3e</b>	8.5	13.7	10.2	18.7	8.0	10.0
<b>3f</b>	22.3	19.5	17.6	22.2	7.9	9.2
<b>3g</b>	25.0	13.0	11.6	13.6	10.8	12.0
<b>3h</b>	12.2	11.5	9.6	9.8	11.0	11.8
<b>3i</b>	16.0	18.2	11.8	12.0	10.9	9.2
<b>3j</b>	10.0	20.2	22.3	25.0	12.9	10.8
<b>3k</b>	11.9	10.8	9.6	14.0	15.1	13.3
<b>3l</b>	23.3	18.9	15.2	16.5	13.0	14.0
Norfloxacin	25.6	19.2	24.2	24.0	–	–
Ketoconazole	–	–	–	–	18.3	22.1

**Antifungal activity:** The synthesized compounds (**3a-l**) were evaluated for *in vitro* antifungal activity against two fungal strains (*Sclerotium rolfsii* and *Aspergillus niger*) at a concentration of 500 mg/mL by disc diffusion method, zone of inhibition measured in mm and ketoconazole used as the standard. A careful observation results indicated that compounds **3a**, **3f** and **3j** showed better antifungal activity, whereas the remaining compounds showed the moderate activity against both organisms (Table-1).

#### ACKNOWLEDGEMENTS

One of the authors, Kutumbarao Mattela thanks Department of Chemistry and Central Facilities for Research & Development (CFRD), Osmania University, Hyderabad, India for the providing research facilities.

#### CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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