



**ULTRASOUND MEDIATED SYNTHESIS, CHARACTERISATION OF 3-(4,5-DIPHENYL-1-(( SUBSTITUTED 1-PHENYL-1H-1,2,3-TRIAZOL-4-YL)METHYL)-1H-IMIDAZOL-2-YL)-1-((SUBSTITUTED 1-PHENYL-1H-1,2,3-TRIAZOL-4-YL)METHYL)-1H-INDOLE AND EVALUATION OF THEIR ANTI MICROBIAL ACTIVITIES**

**K.Bhaskar<sup>a</sup>, Srinivas Gali<sup>a</sup>, K. Anjaneyulu<sup>a</sup>, GugulothRavi<sup>c</sup> & G.V.R. Sai Madhukar<sup>b\*</sup>**

<sup>a</sup>=Department of Chemistry, Government Degree College (Autonomous) Siddipet, Osmania University, Hyderabad, 502103, Telangana, India.

<sup>b</sup>= Department of Chemistry, S.K.N.R Government Arts & Science College, Jagtial, Satavahana University, Karimnagar, 505327, Telangana, India.

<sup>c</sup>= SRP(Synthetic Research Pharma) Laboratories Pvt.Ltd. Road No-18, IDA Nacharam, Hyderabad-500073, Telangana, India.

Corresponding Author email: [gsmadhukar@gmail.com](mailto:gsmadhukar@gmail.com)

**Abstract:**

In an attempt to find potential anti-cancer agents, a series of novel 3-(4,5-diphenyl-1-((substituted 1-phenyl-1H-1,2,3-triazol-4-yl)methyl)-1H-imidazol-2-yl)-1-((substituted 1-phenyl-1H-1,2,3-triazol-4-yl)methyl)-1H-indole (**3a-1**) were synthesized in good yields from 3-(4,5-Diphenyl-1-prop-2-ynyl-1H-imidazol-2-yl)-1-prop-2-ynyl-1H-indole with suitable different substituted aromatic azides by click reaction in ultrasound irradiation method and target molecules were characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR and mass spectral analysis. These compounds were further evaluated for their antimicrobial activity.

**Key words:** Ultrasound irradiation, 3-(4,5-diphenyl-1-((substituted 1-phenyl-1H-1,2,3-triazol-4-yl)methyl)-1H-imidazol-2-yl)-1-((substituted 1-phenyl-1H-1,2,3-triazol-4-yl)methyl)-1H-indole, anti-microbial activity.

**Introduction**

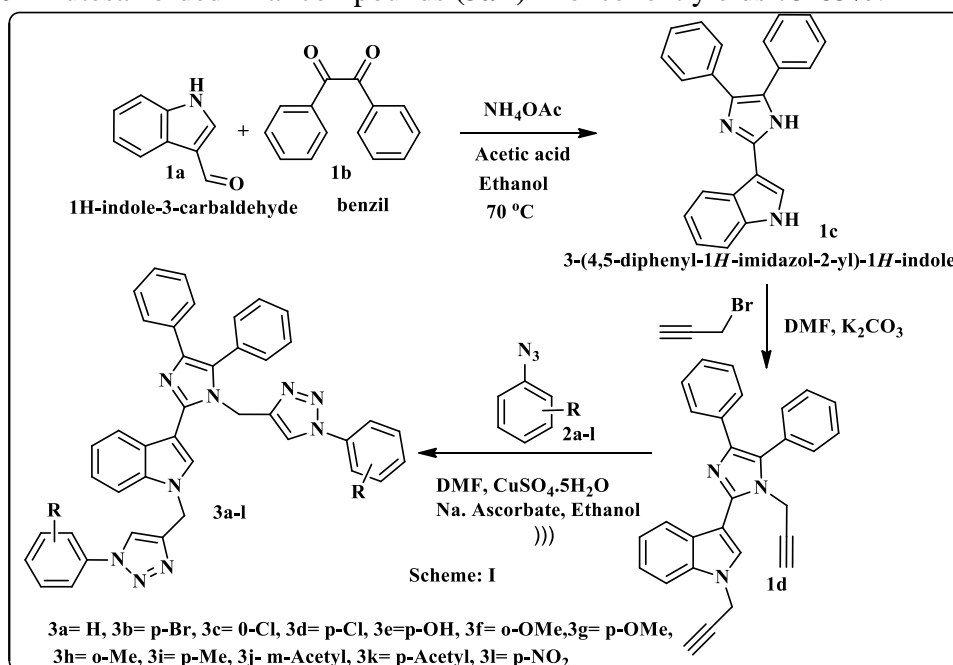
Indole or 1H-benzo[b]pyrrole is a bicyclic heterocycle with fused benzene and pyrrolo ring. Indole is considered as a biologically privileged scaffold, widely distributed in natural products such as alkaloids, plant, animal and microbial hormones [i-vi].d. It shows broad spectrum of biological activities such as antibacterial, antiviral [vii], antifungal [viii-xii], antioxidant [xiii-xvi], anti-inflammatory [xvii-xxii], anticholinesterase [xxiii, xxiv], antihistamine [xxv], anti-diabetic [xxvi], and anticancer [xxvii-xxxii].

Considering the anti-antimicrobial activity exhibited by both indole derivatives and 1,2,3-Triazole derivatives from literature search, it was hypothesized that fusion of indole and 1,2,3 triazoles could result in molecules having greater anti-microbial activity due to synergistic effect of both indole and 1,2,3 triazoles scaffolds. Hence, a series of novel hybrid derivatives have been synthesized and evaluated for their anti-microbial activity using different Gram +ve, Gram -Ve and different fungi's.

## 2. Results and discussion:

### Chemistry

In **Scheme-I**, the synthesis of 3-(4,5-diphenyl-1-((substituted-phenyl-1H-1,2,3-triazol-4-yl)methyl)-1H-imidazol-2-yl)-1-((substituted-phenyl-1H-1,2,3-triazol-4-yl)methyl)-1H-indole **3a-l** was outlined. **Step: 1**, 3-(4,5-diphenyl-1H-imidazol-2-yl)-1H-indole (**1c**) was prepared by condensing 1H-indole-3-carbaldehyde (**1a**), benzil (**1b**) and ammonium acetate in presence of ethanol and acetic acid under reflux condition for 6 h, in good yield. **Step: 2**, Compound (**1c**) was propargylated with 3-bromoprop-1-yne using  $K_2CO_3$  in DMF solvent at  $30^\circ C$  for 15-17 hours, afforded bis-propargylated compound (**1d**). **Final step**, Synthesis of 3-(4,5-diphenyl-1-((substituted-phenyl-1H-1,2,3-triazol-4-yl)methyl)-1H-imidazol-2-yl)-1-((substituted-phenyl-1H-1,2,3-triazol-4-yl)methyl)-1H-indole (**3a-l**) were carried out by ultra sound assisted click reaction, in which bis-propargylated compound (**1d**) (0.1 mmol) was reacted with different aryl azides (**2a-l**) (0.2 mmol) in presence of  $CuSO_4 \cdot 5H_2O$ -sodium ascorbate catalytic system in DMF solvent under ultra sound irradiation for 15-20 minutes afforded final compounds (**3a-l**) in excellent yields 75-85%.



**Scheme 1:** The

synthetic route 3-(4,5-diphenyl-1-((substituted 1-phenyl-1H-1,2,3-triazol-4-yl)methyl)-1H-imidazol-2-yl)-1-((substituted 1-phenyl-1H-1,2,3-triazol-4-yl)methyl)-1H-indole

### 2.1. Antibacterial Activity

All the synthesized compounds **3a-l** were assayed for their antibacterial activity in opposition to Gram-positive bacteria viz. *Bacillus subtilis* (MTCC 441), *Bacillus sphaericus* (MTCC 11), *Staphylococcus aureus* (MTCC 96), and Gram-negative bacteria viz. *Pseudomonas aeruginosa* (MTCC 741), *Klebsiella aerogenes* (MTCC 39), *Chromobacterium violaceum* (MTCC 2656) by disc diffusion method [10], and the data of mean inhibition zone reported in **Table-1**. All assays incorporate the solvent and reference controls. Standard drug used as streptomycin.

The exploration of screening data antibacterial activity discloses that almost all synthesized compounds **3a-l** are potent and exhibit tolerable to marvelous antibacterial activity. Among them compounds containing **3b** [1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl], **3d** [(1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)], **3j** [(1-(3-acetylphenyl)-1,2,3-triazol-4-yl)], **3k** [(1-(4-acetylphenyl)-1H-1,2,3-triazol-4-yl)] and **3l** [(1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)]

moiety exhibit noteworthy antibacterial activity, almost equal/greater than the activity compare to standard drug streptomycin.

## 2.2. Antifungal Activity

All the synthesized compounds **3a-l** were assayed for their antifungal activity in opposition to Gram-positive bacteria *viz* *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185), and *Trichophyton mentagrophytes* (IFO 40996) in dimethyl sulfoxide (DMSO) by disc diffusion method. Amphotericin B was used as a standard drug and the data of mean inhibition zone (MZI) reported in **Table-2**. MZI data measured and compared with controls, the MZI values of the compounds screened.

The exploration of screening data antifungal activity discloses that almost all synthesized compounds **3a-l** are potent and exhibit tolerable to marvelous antifungal activity. Among them, compounds containing **3b** [1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl], **3d** [(1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)], **3j** [(1-(3-acetylphenyl)-1,2,3-triazol-4-yl)], **3k** [(1-(4-acetylphenyl)-1H-1,2,3-triazol-4-yl)] and **3l** [(1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)] moiety exhibit noteworthy antifungal activity, almost equal/greater than the activity compare to standard drug streptomycin.

**Table.1: Antibacterial Activity of Compounds 5a-l**

Compound	Mean zone inhibition (MZI) <sup>a</sup> in 100 µg/mL					
	<i>B. subtilis</i>	<i>B. sphaericus</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>K. aerogenes</i>	<i>C. violaceum</i>
3a	19	16	17	20	25	23
<b>3b</b>	<b>29</b>	<b>26</b>	<b>25</b>	<b>21</b>	<b>25</b>	<b>23</b>
3c	12	14	13	16	17	16
<b>3d</b>	<b>32</b>	<b>29</b>	<b>32</b>	<b>23</b>	<b>29</b>	<b>26</b>
3e	21	22	20	18	13	14
3f	20	10	11	14	16	17
3g	18	20	16	16	20	21
3 h	16	22	21	20	23	18
3i	19	20	23	20	26	23
<b>3j</b>	<b>32</b>	<b>26</b>	<b>27</b>	<b>20</b>	<b>28</b>	<b>23</b>
<b>3k</b>	<b>33</b>	<b>26</b>	<b>28</b>	<b>22</b>	<b>26</b>	<b>22</b>
<b>3l</b>	<b>30</b>	<b>26</b>	<b>28</b>	<b>20</b>	<b>26</b>	<b>23</b>
<b>Streptomycin</b>	<b>31</b>	<b>27</b>	<b>26</b>	<b>19</b>	<b>27</b>	<b>24</b>

<sup>a</sup>Values are mean (n = 3).

**Table 2. Antifungal Activity of Compounds 6.3a-l**

Compound	Mean zone inhibition (MZI) <sup>a</sup> in 100 µg/mL			
	<i>C. albicans</i>	<i>A. fumigatus</i>	<i>T. rubrum</i>	<i>T. mentagrophytes</i>
3a	16	15	14	18
<b>3b</b>	<b>28</b>	<b>24</b>	<b>15</b>	<b>28</b>
3c	21	18	20	18
<b>3d</b>	<b>28</b>	<b>26</b>	<b>26</b>	<b>26</b>
3e	21	22	22	24
3f	16	15	16	12
3g	18	18	18	20

3h	21	20	22	23
3i	20	19	10	25
3j	<b>28</b>	<b>24</b>	<b>23</b>	<b>25</b>
3k	<b>28</b>	<b>24</b>	<b>23</b>	<b>26</b>
3l	<b>30</b>	<b>26</b>	<b>25</b>	<b>26</b>
<b>Amphotericin B</b>	29	25	24	27

<sup>a</sup>Values are mean (n = 3).

### 3. Conclusions

A new sequence of 3-(4,5-diphenyl-1-((substituted 1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazol-2-yl)-1-((substituted 1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indole (**3a-l**) has been synthesized and appraise for their antimicrobial activity against Gram-Positive, Gram-negative bacteria and fungi. Most of the compounds exhibit a average degree of antimicrobial activity. Among them, compounds consists **3b** [(1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)], **3d** [(1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)], **3j** [(1-(3-acetylphenyl)-1,2,3-triazol-4-yl)], **3k** [(1-(4-acetylphenyl)-1*H*-1,2,3-triazol-4-yl)] and **3l** [(1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)] moiety showed average or more activity against standard drug streptomycin, Amphotericin respectively and emerged as potential molecules for further evaluation.

### 4. Experimental:

#### 4.1. Synthesis of 3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole (1c)

This process involved condensing of 1*H*-indole-3-carbaldehyde (1a), benzil (1b), and ammonium acetate in presence of ethanol and acetic acid at 70°C. The reaction proceeded for 6h, leading to the formation of the desired 3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole (1c). Yield: 71%

#### 4.2. Synthesis of 3-(4,5-diphenyl-1-(prop-2-ynyl)-1*H*-imidazol-2-yl)-1-(prop-2-ynyl)-1*H*-indole (1d)

To the stirred solution of 3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole (1c) (10 mmol) in DMF was added 3-bromoprop-1-yne (12 mmol), K<sub>2</sub>CO<sub>3</sub> (25 mmol) at 30°C for 15-17 hours. After confirming completion by TLC, the reaction was quenched with water, extracted with ethyl acetate, dried, and concentrated. The product 1d was purified via column chromatography (25% ethyl acetate in hexane), yielding 68%.

#### 4.3. General procedure for the preparation of 3-(4,5-diphenyl-1-((substituted 1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazol-2-yl)-1-((substituted 1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indole (3a-l)

bis-propargylated compound (**1d**) (0.1 mmol) was reacted with different aryl azides (**2a-l**) (0.2mmol) using Click chemistry in CuSO<sub>4</sub>.5H<sub>2</sub>O with sodium ascorbate and DMF under ultrasound irradiation for 15-20 minutes. The progress of the reaction was monitored by TLC. Upon completion the contents of the flask poured into a 100 ml beaker containing crushed ice. Solids at the bottom were filtered through a Buchner funnel and dried in vacuum at reduced pressure to yield crude compounds which were purified by column chromatography using hexane/ ethyl acetate (1:3 v/v) to afford 3-(4,5-diphenyl-1-(( substituted 1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazol-2-yl)-1-((substituted 1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indole (**3a-l**) gave excellent yields 75-85%.

### Acknowledgements:

The authors are thankful to the SRP (Synthetic Research Pharma) Laboratories Pvt.Ltd, Hyderabad for providing laboratory facilities. Authors also thank full to Principal, SRR Govt. Degree College (A), Karimnagar and Principal, Government Degree College (A), Siddipet. We thank CFRD analytical team for providing spectral analytical facilities.

**Conflict of interest:**

Authors declare no conflict of interest

**Spectral data:**

**3-(4,5-diphenyl-1-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazol-2-yl)-1-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indole(3a)**

Yield 85%, mp: 187-189°C; Rf = 0.40 (EtOAc:n-Hexane 2:3); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.49 (s, 2H), 7.78 (d, J = 7.57 Hz, 2H), 7.76 (d, J = 7.57 Hz, 2H), 7.72 (d, J = 7.90 Hz, 1H), 7.64 (d, J = 7.85 Hz, 2H), 7.58 (s, 1H), 7.50 (dd, J = 7.90, 6.99 Hz, 1H), 7.44 (d, J = 7.85 Hz, 1H), 7.43 (dd, J = 7.85, 7.45 Hz, 2H), 7.41 (dd, J = 7.57, 7.20 Hz, 2H), 7.41 (dd, J = 7.85, 7.45 Hz, 2H), 7.41 (t, J = 7.45 Hz, 2H), 7.37 (t, J = 7.20 Hz, 2H), 7.36 (d, J = 7.85 Hz, 2H), 7.35 (dd, J = 7.57, 7.20 Hz, 2H), 7.33 (t, J = 7.45 Hz, 1H), 7.20 (dd, J = 7.85, 6.99 Hz, 1H), 5.38 (s, 2H), 5.33 (s, 2H). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 150.1, 144.2, 143.9, 143.3, 139.6, 137.4, 135.7, 133.2, 130.1, 129.8, 129.4, 128.6, 128.5, 128.0, 127.9, 127.8, 127.6, 125.0, 124.8, 124.4, 124.3, 123.0, 122.7, 120.7, 112.8, 110.1, 50.1, 50.0.

**1-((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-(1-((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole(3b)**

Yield 80%, mp: 191-193°C; Rf = 0.40 (EtOAc:n-Hexane 2:3); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.49 (s, 1H), 8.48 (s, 1H), 7.96 (d, J = 8.30, 9.30 Hz, 2H), 7.81 (d, J = 8.30, 9.30 Hz, 2H), 7.72 (d, J = 7.90 Hz, 1H), 7.64 (d, J = 7.85 Hz, 2H), 7.58 (s, 1H), 7.56 (d, J = 8.30, 9.30 Hz, 2H), 7.53 (d, J = 8.30, 9.30 Hz, 2H), 7.45 (dd, J = 7.85, 7.45 Hz, 2H), 7.44 (t, J = 7.45 Hz, 1H), 7.42 (dd, J = 7.90, 6.99 Hz, 1H), 7.40 (d, J = 7.85 Hz, 1H), 7.39 (t, J = 7.85 Hz, 2H), 7.36 (d, J = 7.85 Hz, 2H), 7.33 (t, J = 7.45 Hz, 1H), 7.16 (dd, J = 7.85, 6.99 Hz, 1H), 5.32 (s, 2H), 5.30 (s, 2H). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 145.21, 12.13, 140.14, 139.72, 135.77, 133.68, 132.14, 130.27, 128.73, 128.37, 127.83, 127.67, 127.30, 127.04, 125.07, 124.33, 124.06, 122.03, 121.02, 120.12, 119.54, 118.95, 118.82, 110.41, 109.41, 40.13, 38.12.

**1-((1-(2-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-(1-((1-(2-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole(3c)**

Yield 78%, mp: 195-197°C; Rf = 0.38 (EtOAc:n-Hexane 2:3); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.47 (s, 1H), 8.45 (s, 1H), 8.21 (s, 1H), 7.96 (dd, J = 7.51, 2.03 Hz, 1H), 7.47-7.36 (m, J = 7.80, 7.49, 2.02 Hz, 14H), 7.30 (m, 7.50, 2.0 Hz, 2H), 7.21 (t, J = 7.85, 6.99 Hz, 1H), 5.23 (s, 2H), 4.97 (s, 2H). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 145.43, 141.87, 140.26, 139.94, 125.84, 133.96, 133.84, 132.02, 131.96, 130.27, 128.76, 128.52, 128.30, 127.98, 127.83, 127.60, 127.51, 127.49, 127.03, 125.09, 124.38, 124.17, 122.05, 121.37, 120.50, 119.38, 118.94, 110.42, 109.36, 40.36, 38.52.

**1-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-3-(1-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole(3d)**

Yield 80%, mp: 193-195°C; Rf = 0.38 (EtOAc:n-Hexane 2:3); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.49 (s, 1H), 8.48 (s, 1H), 7.92 (d, J = 8.43 Hz, 2H), 7.82 (d, J = 8.43 Hz, 2H), 7.72 (d, J = 7.90 Hz, 1H), 7.64 (d, J = 7.85 Hz, 2H), 7.58 (s, 1H), 7.44 (t, J = 7.45 Hz, 1H), 7.42 (dd, J = 7.90, 6.99 Hz, 1H), 7.41 (dd, J = 7.85, 7.45 Hz, 2H), 7.40 (d, J = 7.85 Hz, 1H), 7.39 (dd, J = 7.85, 7.45 Hz, 2H), 7.36 (d, J = 7.85 Hz, 2H), 7.33 (t, J = 7.45 Hz, 1H), 7.23 (d, J = 8.43 Hz, 2H), 7.22 (d, J = 8.43 Hz, 2H), 7.16 (dd, J = 7.85, 6.99 Hz, 1H), 5.32 (s, 2H), 5.30 (s, 2H). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 145.48, 142.13, 140.26, 139.75, 135.82, 133.82, 132.97, 132.53, 132.08, 130.34, 130.26, 128.74, 158.35, 127.86, 127.64, 127.06, 125.07, 124.39, 124.18, 122.07, 121.47, 119.56, 118.94, 110.42, 109.32, 40.12, 38.17.

**4-(4-((2-(1-((1-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indol-3-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)phenol(3e)**

Yield 75%, mp: 189-191°C; Rf = 0.30 (EtOAc:n-Hexane 2:3); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 9.41 (s, 1H), 8.60 (s, 1H), 8.49 (s, 1H), 7.72 (d, J = 7.90 Hz, 1H), 7.64 (d, J = 7.85 Hz,

2H), 7.58 (s, 1H), 7.57 (d, J = 8.43 Hz, 4H), 7.47 (dd, J = 7.90, 6.99 Hz, 1H), 7.44 (d, J = 7.85 Hz, 1H), 7.41 (dd, J = 7.85, 7.45 Hz, 2H), 7.41 (t, J = 7.45 Hz, 1H), 7.39 (dd, J = 7.85, 7.45 Hz, 2H), 7.36 (d, J = 7.85 Hz, 2H), 7.33 (t, J = 7.45 Hz, 1H), 7.20 (dd, J = 7.85, 6.99 Hz, 1H), 6.84 (d, J = 8.43 Hz, 2H), 6.83 (d, J = 8.43 Hz, 2H), 5.33 (s, 2H), 5.32 (s, 2H). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 157.6, 150.1, 144.2, 143.9, 139.7, 139.6, 137.4, 136.0, 134.1, 130.9, 129.8, 128.6, 128.3, 128.1, 128.0, 127.8, 126.1, 125.0, 124.1, 123.2, 122.9, 120.7, 115.3, 112.8, 110.1, 50.3, 50.1.

**1-((1-(2-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-(1-((1-(2-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1H-imidazol-2-yl)-1H-indole(3f)**

Yield 77%, mp: 187-189°C; Rf = 0.36 (EtOAc:n-Hexane 2:3); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.44 (s, 1H), 8.41 (s, 1H), 8.19 (s, 1H), 7.86 (d, J = 7.90 Hz, 1H), 7.37 - 7.35 (m, 4H), 7.21 - 7.19 (m, 5H), 7.01 (m, 2H), 5.18 (s, 2H), 5.03 (s, 2H), 3.82 (s, 6H). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 154.6, 145.42, 141.53, 140.39, 139.68, 125.82, 133.85, 132.06, 130.27, 128.74, 128.46, 128.37, 127.85, 127.02, 125.06, 124.37, 124.23, 123.09, 122.04, 120.84, 118.95, 118.32, 114.72, 110.48, 109.36, 55.67, 40.32, 38.52.

**1-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-(1-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1H-imidazol-2-yl)-1H-indole(3g)**

Yield 79%, mp: 184-186°C; Rf = 0.36 (EtOAc:n-Hexane 2:3); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.52 (s, 1H), 8.49 (s, 1H), 8.21 (s, 1H), 7.86 (d, J = 7.90 Hz, 1H), 7.65 (m, 2H), 7.55 - 7.54 (m, 4H), 7.48 - 7.42 (m, 6H), 7.37 - 7.35 (m, 4H), 7.19 (dd, J = 7.85, 6.98 Hz, 1H), 7.08 - 7.07 (m, 4H), 5.23 (s, 2H), 5.23 (s, 2H), 3.80 (s, 2H). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 158.82, 145.42, 142.13, 140.36, 139.72, 135.34, 133.87, 132.06, 130.28, 128.75, 128.36, 128.29, 127.84, 127.53, 127.03, 125.03, 124.35, 124.29, 122.07, 120.98, 119.53, 118.97, 118.72, 116.23, 110.42, 109.38, 55.87, 40.17, 38.12.

**3-(4,5-diphenyl-1-((1-(*o*-tolyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-imidazol-2-yl)-1-((1-(*o*-tolyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-indole(3h)**

Yield 76%, mp: 183-185°C; Rf = 0.42 (EtOAc:n-Hexane 2:3); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.43 (s, 1H), 8.42 (s, 1H), 8.21 (s, 1H), 7.86 (d, J = 7.91 Hz, 1H), 7.65 (m, J = 7.49, 2.01 Hz, 2H), 7.53 - 7.21 (m, 19H), 5.24 (s, 2H), 5.10 (s, 2H), 2.28 (s, 3H), 2.26 (s, 3H). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 145.47, 141.56, 140.13, 139.05, 135.82, 135.34, 133.85, 132.06, 130.95, 130.24, 129.26, 128.74, 128.36, 127.98, 127.63, 127.54, 127.25, 127.09, 125.08, 124.35, 124.26, 122.05, 120.37, 119.63, 118.95, 118.54, 110.47, 109.38, 40.32, 38.53, 17.39.

**3-(4,5-diphenyl-1-((1-(*p*-tolyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-imidazol-2-yl)-1-((1-(*p*-tolyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-indole(3i)**

Yield 77%, mp: 181-183°C; Rf = 0.42 (EtOAc:n-Hexane 2:3); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.53 (s, 1H), 8.50 (s, 1H), 8.21 (s, 1H), 7.86 (d, J = 7.92 Hz, 1H), 7.65 (m, 2H), 7.49 - 7.33 (m, 18H), 7.21 (t, J = 7.85, 6.97 Hz, 1H), 5.25 (s, 2H), 5.10 (s, 2H), 2.36 (s, 6H). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 145.47, 142.13, 140.18, 139.67, 137.85, 135.89, 133.84, 132.09, 131.95, 130.82, 145.25, 128.74, 128.39, 127.76, 127.63, 127.59, 127.28, 125.06, 124.36, 124.28, 122.04, 119.68, 119.35, 119.08, 118.94, 110.47, 109.38, 40.18, 38.17, 21.14.

**1-(3-(4-((2-(1-((1-(3-acetylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-indol-3-yl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)phenyl)ethan-1-one(3j)**

Yield 78%, mp: 189-191°C; Rf = 0.38 (EtOAc:n-Hexane 2:3); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.55 (s, 1H), 8.54 (s, 1H), 8.25 (d, J = 2.01 Hz, 1H), 8.23 (d, J = 2.02 Hz, 1H), 8.21 (d, J = 2.00 Hz, 1H), 7.86 (m, 3H), 7.76 - 7.73 (m, 2H), 7.65 - 7.62 (m, 4H), 7.48 - 7.35 (m, 10H), 7.19 (dd, J = 7.85, 6.97 Hz, 1H), 5.23 (s, 2H), 4.92 (s, 2H), 2.55 (s, 6H). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 197.26, 145.42, 142.23, 139.96, 139.74, 136.85, 136.32, 135.84, 133.86, 131.96, 130.17, 129.34, 128.74, 128.36, 127.85, 127.65, 127.35, 127.14, 124.02, 124.37, 123.98, 122.05, 121.45, 120.49, 119.63, 118.94, 118.02, 110.42, 109.63, 43.41, 39.38, 26.75.

**1-(4-(4-((2-(1-((1-(4-acetylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-1H-indol-3-yl)-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)phenyl)ethan-1-one(3k)**

Yield 82%, mp: 192-194°C; Rf = 0.38 (EtOAc:n-Hexane 2:3); <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.49 (s, 1H), 8.48 (s, 1H), 7.76 (d, J = 8.43 Hz, 4H), 7.74 (d, J = 8.43 Hz, 2H), 7.72 (d, J = 7.90 Hz, 1H), 7.71 (d, J = 8.43 Hz, 2H), 7.64 (d, J = 7.85 Hz, 2H), 7.58 (s, 1H), 7.42 (t, J = 7.45 Hz, 1H), 7.41 (dd, J = 7.90, 6.99 Hz, 1H), 7.40 (d, J = 7.85 Hz, 1H), 7.39 (dd, J = 7.85, 7.45 Hz, 2H), 7.38 (dd, J = 7.85, 7.45 Hz, 2H), 7.36 (d, J = 7.85 Hz, 2H), 7.32 (t, J = 7.45 Hz, 1H), 7.12 (dd, J = 7.85, 6.99 Hz, 1H), 5.31 (s, 2H), 5.30 (s, 2H), 2.56 (s, 6H). <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>) δ 196.84, 145.47, 142.16, 139.98, 139.74, 137.85, 136.22, 135.84, 133.84, 131.96, 130.32, 130.17, 128.74, 128.36, 127.85, 127.63, 127.12, 127.03, 125.02, 124.39, 123.95, 122.07, 119.53, 118.97, 118.85, 110.47, 109.47, 43.42, 39.3, 26.4.

**1-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-3-(1-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-4,5-diphenyl-1H-imidazol-2-yl)-1H-indole(3l)**

Yield 80%, mp: 193-195°C; Rf = 0.36 (EtOAc:n-Hexane 2:3); <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.49 (s, 1H), 8.41 (s, 1H), 8.36 (d, J = 9.20 Hz, 2H), 8.29 (d, J = 9.20, 10.00 Hz, 2H), 7.79 (d, J = 9.20, 10.00 Hz, 2H), 7.73 (d, J = 9.20, 10.00 Hz, 2H), 7.72 (d, J = 7.90 Hz, 1H), 7.64 (d, J = 7.85 Hz, 2H), 7.58 (s, 1H), 7.42 (t, J = 7.45 Hz, 1H), 7.41 (dd, J = 7.90, 6.99 Hz, 1H), 7.40 (d, J = 7.85 Hz, 1H), 7.39 (dd, J = 7.85, 7.45 Hz, 2H), 7.38 (dd, J = 7.85, 7.45 Hz, 2H), 7.36 (d, J = 7.85 Hz, 2H), 7.32 (t, J = 7.45 Hz, 1H), 7.12 (dd, J = 7.85, 6.99 Hz, 1H), 5.31 (s, 2H), 5.24 (s, 2H). <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>) δ 146.05, 145.47, 142.17, 139.98, 139.75, 135.82, 131.97, 130.17, 128.76, 128.36, 127.84, 127.66, 127.13, 127.04, 126.17, 125.03, 124.38, 123.98, 121.95, 120.14, 119.53, 118.92, 118.87, 110.42, 109.63, 43.48, 39.31.

**References:**

- i Hanahan D.; Weinberg R.A.; The hallmarks of cancer, Cell; 2000, **100**, 57-70.
- ii <https://www.who.int/cancer/en/> - accessed on 30<sup>th</sup> February, (2021).
- iii Jayashree B.; Nigam S.; Pai A.; Patel H.K.; Reddy N.; Kumar N.; Rao C.; Targets in anticancer research—A review; 2015
- iv Ali R.; Mirza Z.; Ashraf G.M.; Kamal M.A.; Ansari S.A.; Damanhour G.A.; Abuzenadah A.M.; Chaudhary A.G.; Sheikh I.A.; New anticancer agents: recent developments in tumor therapy; *Anticancer Res.*; 2012, **32**(7), 2999-3005. PMID: 22753764.
- v Lakhdar S.; Westermaier M.; Terrier F.; Goumont R.; Boubaker T.; Ofial A.R.; Mayr H.; Nucleophilic reactivities of indoles; The Journal of organic chemistry; 2006, **71**, 9088-9095.
- vi Diss L.B.; Robinson S.D.; Wu Y.; Fidalgo S.; Yeoman M.S.; Patel B.A.; Age related changes in melatonin release in the murine distal colon; ACS chemical neuroscience; 2013, **4**, 879- 887.
- vii Sivaprasad G.; Perumal P.T.; Prabavathy V.R.; Mathivanan N.; Synthesis and anti-microbial activity of pyrazolylbisindoles—promising anti-fungal compounds; Bioorganic & medicinal chemistry letters; 2006, **16**, 6302-6305.
- viii Donawade D.S.; Raghunath A.; Gadaginamath G.S.; Synthesis and antimicrobial activity of some new 1-substituted-3-pyrrolyl amino carbonyl/oxadiazolyl/triazolyl/5-methoxy-2-methylindoles and benz [g] indoles; Indian Journal of Chemistry; 2006, **45B**, 689-696.
- ix Samosorn S.; Bremner J.B.; Ball A.; Lewis K.; Synthesis of functionalised 2-aryl-5-nitro-1H-indoles and their activity as bacterial NorA efflux pump

- inhibitors; *Bioorganic & medicinal chemistry*; 2006, **14**, 857-865.
- x Al-Hiari Y.M.; Qaisi A.M.; El-Abadelah M.M.; Voelter W.; Synthesis and antibacterial activity of some substituted 3-(aryl)-and 3-(heteroaryl) indoles; *Monatshefte für Chemie/Chemical Monthly*; 2006, **137**, 243-248.
- xi Leboho T.C.; Michael J.P.; van Otterlo W.A.; van Vuuren S.F.; de Koning C.B.; The synthesis of 2-and 3-aryl indoles and 1, 3, 4, 5-tetrahydropyrano [4, 3-b] indoles and their antibacterial and antifungal activity; *Bioorganic & medicinal chemistry letters*; 2009, **19**, 4948-4951.
- xii Hu W.; Guo Z.; Yi X.; Guo C.; Chu F.; Cheng G.; Discovery of 2-phenyl-3-sulfonylphenyl-indole derivatives as a new class of selective COX-2 inhibitors; *Bioorganic & medicinal chemistry*; 2003, **11**, 5539-5544.
- xiii Narayana B.; Ashalatha B.; Raj K.V.; Fernandes J.; Sarojini B.; Synthesis of some new biologically active 1, 3, 4-oxadiazolyl nitroindoles and a modified Fischer indole synthesis of ethyl nitro indole- 2-carboxylates; *Bioorganic & medicinal chemistry*; 2005, **13**, 4638-4644.
- xiv Radwan M.A.; Ragab E.A.; Sabry N.M.; El-Shenawy S.M.; Synthesis and biological evaluation of new 3-substituted indole derivatives as potential anti-inflammatory and analgesic agents; *Bioorganic & medicinal chemistry*; 2007, **15**, 3832-3841.
- xv Kuduk S.D.; Chang R.K.; Wai J.M.-C.; Di Marco C.N.; Cofre V.; DiPardo R.M.; Cook S.P.; Cato M.J.; Jovanovska A.; Urban M.O.; Amidine derived inhibitors of acid-sensing ion channel-3(ASIC3); *Bioorganic & medicinal chemistry letters*; 2009, **19**, 4059-4063.
- xvi Kumar D.; Kumar N.; Kumar S.; Singh T.; Singh C.; Synthesis of pharmacologically active 2-phenylsulpha/substituted Indoles; *Int. J. Eng. Sci. and Tech*; 2010, **2**, 2553-2557.
- xvii Rahaman S.; Prasad Y.R.; Bhuvaneshwari K.; Kumar P.; Synthesis and antihistaminic activity of novel pyrazoline derivatives; *Int. J. Chem. Tech. Res*; 2010, **1**, 16-20.
- xviii Battaglia S.; Boldrini E.; Da Settimo F.; Dondio G.; La Motta C.; Marini A.M.; Primofiore G.; Indole amide derivatives: synthesis, structure–activity relationships and molecular modelling studies of a new series of histamine H<sub>1</sub>-receptor antagonists; *European journal of medicinal chemistry*; 1999, **34**, 93-105.
- xix Sharma V.; Kumar P.; Pathak D.; Biological importance of the indole nucleus in recent years: a comprehensive review; *Journal of Heterocyclic Chemistry*; 2010, **47**, 491-502.
- xx Estevão M.S.; Carvalho L.C.; Ribeiro D.; Couto D.; Freitas M.; Gomes A.; Ferreira L.; Fernandes E.; Marques M.M.B.; Antioxidant activity of unexplored indole derivatives: Synthesis and screening; *European journal of medicinal chemistry*; 2010, **45**, 4869-4878.
- xxi Mohamed M.S.; Youns M.M.; Ahmed N.M.; Novel indolyl-pyrimidine derivatives: synthesis, antimicrobial, and antioxidant evaluations; *Medicinal Chemistry Research*; 2014, **23**, 3374-3388.
- xxii Karaaslan C.; Kadri H.; Coban T.; Suzen S.; Westwell A.D.; Synthesis and antioxidant properties of substituted 2-phenyl-1H-indoles; *Bioorganic & medicinal chemistry letters*; 2013, **23**, 2671-2674.
- xxiii Li Y.-Y.; Wu H.-S.; Tang L.; Feng C.-R.; Yu J.-H.; Li Y.; Yang Y.-S.; Yang B.; He Q.-J.; The potential insulin sensitizing and glucose lowering



- effects of a novel indole derivative in vitro and invivo; Pharmacological research; 2007, **56**, 335-343.
- xxiv Anjaneyulu B.; Rao GD.; Bajaj T.; Click chemistry: In vitro evaluation of glycosyl hybrid phosphorylated/thiophosphorylated 1, 2, 3-triazole derivatives as irreversible acetyl cholinesterase (AChE) inhibitors; Results in Chemistry; 2021, **3**, 100093.
- xxv Abdel-Gawad H.; Mohamed H.A.; Dawood K.M.; Badria F.A.-R.; Synthesis and antiviral activity of new indole-based heterocycles; Chemical and Pharmaceutical Bulletin; 2010, **58**, 1529-1531.
- xxvi Ghanei-Nasab S.; Khoobi M.; Hadizadeh F.; Marjani A.; Moradi A.; Nadri H.; Emami S.; Foroumadi A.; Shafiee A.; Synthesis and anticholinesterase activity of coumarin-3- 1carboxamidesbearing tryptamine moiety; European journal of medicinal chemistry; 2016, **121**, 40-46.
- xxvii Akrami H.; Mirjalili B.F.; Khoobi M.; Nadri H.; Moradi A.; Sakhteman A.; Emami S.; Foroumadi A.; Shafiee A.; Indolinone-based acetylcholinesterase inhibitors: synthesis, biological activity and molecular modeling; European journal of medicinal chemistry; 2014, **84**, 375-381.
- xxviii MacDonough M.T.; Strecker T.E.; Hamel E.; Hall J.J.; Chaplin D.J.; Trawick M.L.; Pinney K.G.; Synthesis and biological evaluation of indole-based, anti-cancer agents inspired by the vascular disrupting agent 2-(3'-hydroxy-4'-methoxyphenyl)-3-(3'',4'',5''-trimethoxybenzoyl)-6-methoxyindole (OXi8006); Bioorganic & medicinal chemistry; 2013, **21**, 6831-6843.
- xxix Akkoc M.K.; Yuksel M.Y.; Durmaz Đ.; Atalay R.Ç.; Design, synthesis, and Biological evaluation of indole-based 1, 4-disubstituted piperazines as cytotoxic agents; Turkish Journal of Chemistry; 2012, **36**, 515-525.
- xxx Kumar D.; Kumar N.M.; Noel B.; Shah K.; A series of 2-arylamino-5-(indolyl)-1, 3, 4- thiadiazoles as potent cytotoxic agents; European journal of medicinal chemistry; 2012, **55**, 432-438.
- xxxi Queiroz M.-J.R.; Abreu A.S.; Carvalho M.S.D.; Ferreira P.M.; Nazareth N.; Nascimento M.S.-J.; Synthesis of new heteroaryl and heteroannulatedindoles from dehydrophenylalanines: Antitumor evaluation; Bioorganic & medicinal chemistry; 2008, **16**, 5584-5589.
- xxxii Zhang F.; Zhao Y.; Sun L.; Ding L.; Gu Y.; Gong P.; Synthesis and anti-tumor activity of 2-amino-3-cyano-6-(1H-indol-3-yl)-4-phenylpyridine derivatives in vitro; European journal of medicinal chemistry; 2011, **46**, 3149-3157.

Received on September 27, 2024.