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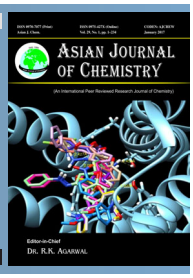

Design and New Synthetic Approach of Indole Based 1,2,3-Triazoles: A Potent Antimicrobial Agents

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A series of novel 5-methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid phenylamides **(6a-f)** have been synthesized in good to excellent yields by treating 5-methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carbonyl chloride **(5)** with different aromatic amines. To get the target compounds, the initial intermediate, 1-methyl-1*H*-indol-3-yl-methyldiazonium chloride **(2)** was achieved from the raw material, 1-methyl-1*H*-indol-3-yl-methylamine **(1)** through diazotization. Further compound, 1-methyl-1*H*-indol-3-yl-methylazide **(3)** was prepared from the reaction between compound **2** and sodium azide. Additionally, intermediate **3** is turned into 5-methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid **(4)** with ethyl acetoacetate. Finally, the last intermediate, 5-methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carbonyl chloride **(5)** was obtained from the reaction between compound **4** and thionyl chloride. The chemical structures of the all newly synthesized compounds were elucidated by their IR, ^{1}H and ^{13}C NMR, mass spectral data and elemental analysis. The target compounds were used to find their antimicrobial activity against various microorganisms. According to the screening results, compounds **6a, 6c, 6d** and **6f** and showed significant antibacterial activity and compounds **6d** and **6e** performed remarkable antifungal activity.

Keywords: Indole, 1,2,3-Triazole, Antimicrobial activity.

INTRODUCTION

1,2,3-Triazoles have been the subject of considerable research, mainly due to their usefulness in synthetic organic chemistry and also due to their variety of interesting biological activities such as antibacterial and antituberculosis [1], anti-cancer [2], antifungal [3], antimalarial [4], antileishmanial [5], cytostatic [6], antitubercular [7], antiviral [8], anti-HSV-1 [9], cytotoxic [10], anti HIV-1 [11], anti-inflammatory activity [12]. Indole derivatives constitute an important class of therapeutic agents in medicinal chemistry including anti-inflammatory [13], antimicrobial [14] as well as cytotoxic [15] activities.

EXPERIMENTAL

Synthesis of 1-methyl-1*H*-indol-3-yl-methylazide (3): 1-Methyl-1*H*-indol-3-yl-methylamine **(1)** (0.01 mol) was dissolved in dilute HCl (1:1) (20 mL) and the reaction mixture was cooled to 0-5 °C. Sodium nitrite (0.01 mol) was added in five portions to the reaction mixture by maintaining the temperature between 0-5 °C and uniformly stirred the reaction mixture for 3 h. Then the solution of sodium azide (0.01 mol in 12 mL of H_2O) was added drop-wise to the reaction mixture at 0-5 °C. After completion of the addition, the reaction mixture was constantly stirred at 0-5 °C for 2 h. Sodium acetate solution (0.01 mol in 10 mL H_2O) was added slowly to the reaction mixture and steadily stirred for another 1 h at 0-5 °C. After completion of the reaction (monitored by the TLC), the product was extracted by using ethyl acetate and washed with water. Organic layer was dried with anhydrous calcium chloride and concentrated by distillation at room temperature to give pure 1-methyl-1*H*-indol-3-yl-methylazide **(3)**.

Synthesis of 5-methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid (4): To the solution of sodium ethoxide (0.01 mol) and ethyl acetoacetate (0.01 mol) (0.01 mol) was added 1-methyl-1*H*-indol-3-yl-methylazide **(3)** (0.01 mol). The mixture was refluxed for 4 h with constant stirring. After accomplishment of the reaction (checked by the TLC), the mixture was poured into ice-cold water and the pH of the mixture is neutralized by adding 10 N HCl to form crude product. It is collected by filtration, washed with cold water, dried and recrystallized from ethyl acetate to achieve 5-methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid **(4)** in pure form.

Synthesis of 5-methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carbonyl chloride (5): To a suspension of 5-methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]-triazole-4-carboxylic acid **(4)** (0.01 mol) in $CHCl_3$ (10 mL) was added thionyl chloride at room temperature. Then the

reaction mixture was heated at reflux temperature on uniform stirring for 5 h. After achievement of the reaction (scanned by the TLC), the excess thionyl chloride is distilled off and resulted mixture is precipitated after poured in ice-cold water. The crude product was filtered off and washed with hexane, dried and recrystallized with ethyl acetate to get pure 5-methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carbonyl chloride **(5)**.

Synthesis of 5-methyl-1-(1-methyl-1*H*-indol-3-yl-methyl)-1*H*-[1,2,3]triazole-4-carboxylic acid phenylamides (6a-f): To a solution of aniline (0.01 mol) in dichloromethane (10 mL) was added a solution of 5-methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carbonyl chloride **(5)** in dichloromethane (10 mL) at room temperature. The reaction mixture is stirred uniformly for 4 h at room temperature. After fulfillment of the reaction (checked by the TLC), the mixture was poured in ice-cold water and the organic layer is collected and washed with 2 N NaOH solution followed by water. Then the organic layer was dried with anhydrous sodium sulfate and recrystallized from ethyl acetate to obtain 5-methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid phenylamide **(6a)**. Similar procedure is followed to prepare compounds **6b-f**.

Physical and spectral data

1-Methyl-1*H*-indol-3-yl-methylazide (3): Yield: 74 %, m.p.: 141-143 °C; IR (KBr, ν_{max}, cm^{-1}): 3025 (C-H, Ar), 2971 (C-H, CH_3), 2162 (N=N), 1568 (C=C, Ar). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.65-7.28 (m, 4H, Ar-H), 7.60 (s, 1H, CH), 3.18 (s, 2H, CH_2), 2.52 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 132.8, 126.5, 122.3, 121.5, 119.6, 116.5, 111.0, 52.3, 41.4; MS: *m/z* 186 (M^+); Elemental analysis: Calculated for $C_{10}H_{10}N_4$: C-64.50, H-5.41, N-30.09. Found: C-62.69, H-5.02, N-29.14.

5-Methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid (4): Yield: 76 %, m.p.: 121-123 °C; IR (KBr, ν_{max}, cm^{-1}): 3155 (O-H), 3020 (C-H, Ar), 2966 (C-H, CH_3), 2155 (N=N), 1720 (C=O), 1572 (C=C, Ar). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.21 (s, 1H, COOH), 7.58-7.32 (m, 4H, Ar-H), 7.55 (s, 1H, CH), 3.23 (s, 2H, CH_2), 3.15 (s, 3H, CH_3), 2.62 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 153.2, 142.3, 138.4, 133.6, 124.1, 122.38, 121.8, 120.3, 114.7, 109.7, 47.5, 42.6, 22.3; MS: *m/z* 270 (M^+); Elemental analysis: Calculated for $C_{14}H_{14}N_4O_2$: C-62.21, H-5.22, N-20.73, O-11.84. Found: C-60.69, H-5.12, N-19.87, O-11.15.

5-Methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carbonyl chloride (5): Yield: 72 %, m.p.: 155-157 °C; IR (KBr, ν_{max}, cm^{-1}): 3032 (C-H, Ar), 2958 (C-H, CH_3), 2166 (N=N), 1785 (C=O), 1562 (C=C, Ar). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.55-7.25 (m, 4H, Ar-H), 7.52 (s, 1H, CH), 3.25 (s, 2H, CH_2), 3.18 (s, 3H, CH_3), 2.58 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 158.6, 145.8, 139.7, 133.6, 125.8, 121.7, 119.8, 117.4, 113.5, 111.5, 47.6, 43.2, 22.7; MS: *m/z* 288 (M^+); Elemental analysis: Calculated for $C_{14}H_{13}N_4OCl$: C-58.24, H-5.45, Cl-12.28, N-19.40, O-5.54. Found: C-57.36, H-5.25, Cl-11.84, N-18.89, O-5.28.

5-Methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid phenylamide (6a): Yield: 70 %, m.p.: 130-132 °C; IR (KBr, ν_{max}, cm^{-1}): 3255 (N-H), 3018 (C-H, Ar), 2981 (C-H, CH_3), 2168 (N=N), 1660 (C=O), 1559 (C=C, Ar). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.72-7.36 (m, 9H, Ar-H), 7.55 (s, 1H, CH), 7.49 (s, 1H, CONH), 3.36 (s, 2H, CH_2), 3.21 (s, 2H, CH_2), 2.48 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 158.2, 143.2, 139.6, 133.6, 132.5, 131.2, 130.5, 127.6, 125.3, 120.3, 118.5, 117.4, 113.2, 110.2, 47.8, 40.3, 25.6; MS: *m/z* 330 (M^+); Elemental analysis: Calculated for $C_{20}H_{18}N_4O$: C-72.71, H-5.49, N-16.96, O-4.84. Found: C-70.12, H-5.21, N-15.98, O-4.56.

5-Methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid (3-nitrophenyl)amide (6b): Yield: 68 %, m.p.: 169-171 °C; IR (KBr, ν_{max}, cm^{-1}): 3262 (N-H), 3028 (C-H, Ar), 2975 (C-H, CH_3), 2174 (N=N), 1666 (C=O), 1548 (C=C, Ar) 1535 (N-O). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.79-7.29 (m, 7H, Ar-H), 7.54 (s, 1H, CH), 7.46 (s, 1H, CONH), 7.42 (s, 1H, Ar-H), 3.29 (s, 2H, CH_2), 3.22 (s, 2H, CH_2), 2.57 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 148.5, 143.6, 139.7, 133.6, 133.2, 132.0, 128.7, 126.4, 124.8, 123.5, 121.4, 119.7, 118.4, 117.4, 114.7, 112.3, 47.8, 43.6, 22.3; MS: *m/z* 375 (M^+); Elemental analysis: Calculated for $C_{20}H_{17}N_5O_3$: C-63.99, H-4.56, N-18.66, O-12.79. Found: C-62.36, H-4.36, N-17.89, O-12.12.

5-Methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid (4-nitrophenyl)amide (6c): Yield: 75 %, m.p.: 120-122 °C; IR (KBr, ν_{max}, cm^{-1}): 3274 (N-H), 3034 (C-H, Ar), 2968 (C-H, CH_3), 2155 (N=N), 1662 (C=O), 1555 (C=C, Ar), 1544 (N-O). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.58-7.21 (m, 4H, Ar-H), 7.52 (s, 1H, CH), 7.49 (d, 2H, *J* = 7.0 Hz, Ar-H), 7.39 (d, 2H, *J* = 7.0 Hz, Ar-H), 7.34 (s, 1H, CONH), 3.20 (s, 2H, CH_2), 3.16 (s, 2H, CH_2), 2.50 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 154.8, 153.3, 143.2, 141.0, 138.4, 131.5, 130.8, 127.4, 123.5, 122.4, 121.0, 119.8, 114.5, 112.6, 47.6, 43.2, 25.7; MS: *m/z* 375 (M^+); Elemental analysis: Calculated for $C_{20}H_{17}N_5O_3$: C-63.99, H-4.56, N-18.66, O-12.79. Found: C-62.36, H-4.36, N-17.89, O-12.12.

5-Methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid (4-chlorophenyl)amide (6d): Yield: 71 %, m.p.: 117-119 °C; IR (KBr, ν_{max}, cm^{-1}): 3284 (N-H), 3040 (C-H, Ar), 2977 (C-H, CH_3), 2166 (N=N), 1658 (C=O), 1560 (C=C, Ar). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.68-7.29 (m, 4H, Ar-H), 7.62 (s, 1H, CH), 7.60 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.52 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.50 (s, 1H, CONH), 3.30 (s, 2H, CH_2), 3.22 (s, 2H, CH_2), 2.58 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 155.8, 152.1, 144.8, 143.2, 139.7, 133.2, 131.7, 125.8, 122.5, 121.0, 120.7, 118.7, 116.3, 113.2, 48.6, 45.7, 27.6; MS: *m/z* 364 (M^+); Elemental analysis: Calculated for $C_{20}H_{17}N_4OCl$: C-65.84, H-4.70, Cl-9.72, N-15.65, O-4.39. Found: C-63.69, H-4.56, Cl-9.48, N-14.98, O-4.21.

5-Methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid (4-bromophenyl)amide (6e): Yield: 76 %, m.p.: 155-157 °C; IR (KBr, ν_{max}, cm^{-1}): 3278 (N-H), 3044 (C-H, Ar), 2984 (C-H, CH_3), 2174 (N=N), 1662 (C=O), 1574 (C=C, Ar). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.72-7.36 (m, 4H, Ar-H), 7.58 (s, 1H, CH), 7.55 (d, 2H, *J* = 7.4 Hz, Ar-H), 7.48 (d, 2H, *J* = 7.4 Hz, Ar-H), 7.43 (s, 1H,

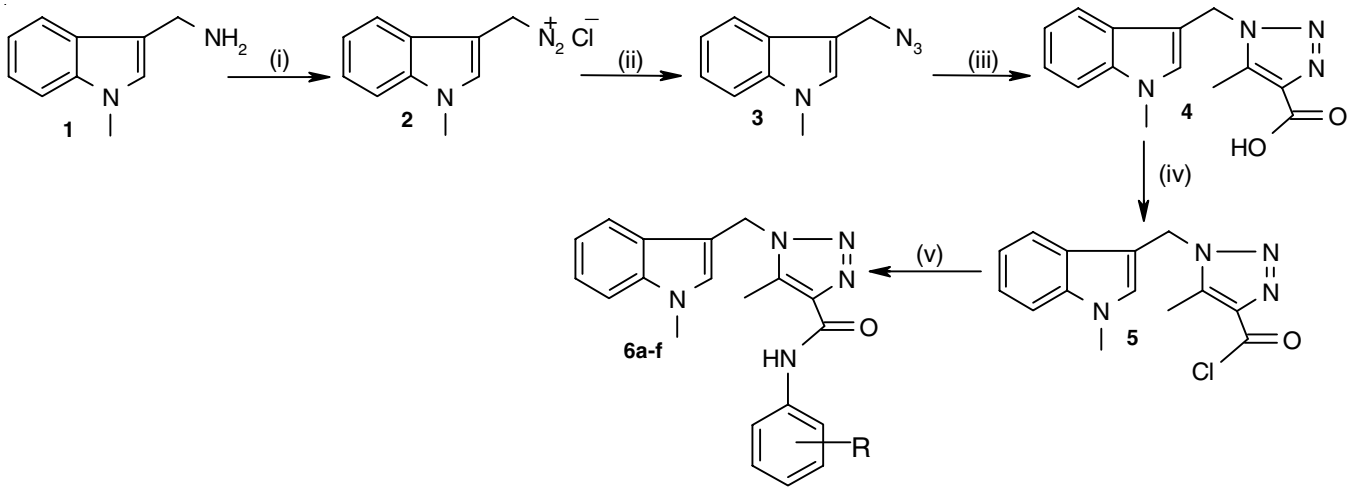
CONH), 3.36 (s, 2H, CH_2), 3.28 (s, 2H, CH_2), 2.62 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 152.8, 150.7, 145.4, 144.7, 139.7, 133.2, 131.7, 125.7, 124.7, 123.2, 120.2, 117.8, 116.3, 114.2, 48.7, 44.3, 26.7; MS: *m/z* 409 (M^+); Elemental analysis: Calculated for $C_{20}H_{17}N_4OBr$: C-58.69, H-4.19, Br-19.52, N-13.69, O-3.91. Found: C-57.58, H-4.12, Br-18.87, N-12.98, O-3.58.

5-Methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid (4-methyl-phenyl)amide (6f): Yield: 70 %, m.p.: 125-127 °C; IR (KBr, ν_{max}, cm^{-1}): 3270 (N-H), 3030 (C-H, Ar), 2966 (C-H, CH_3), 2180 (N=N), 1672 (C=O), 1577 (C=C, Ar). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.77-7.36 (m, 4H, Ar-H), 7.62 (s, 1H, CH), 7.55 (d, 2H, *J* = 7.0 Hz, Ar-H), 7.52 (d, 2H, *J* = 7.0 Hz, Ar-H), 7.48 (s, 1H, CONH), 3.27 (s, 2H, CH_2), 3.25 (s, 2H, CH_2), 2.86 (s, 3H, CH_3), 2.50 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 155.2, 154.7, 144.1, 140.2, 136.4, 133.2, 132.0, 125.6, 124.1, 123.2, 120.2, 117.4, 115.6, 113.4, 48.4, 42.3, 33.6, 26.4; MS: *m/z* 344 (M^+); Elemental analysis: Calculated for $C_{21}H_{20}N_4O$: C-73.23, H-5.85, N-16.27, O-4.65. Found: C-71.23, H-5.54, N-15.84, O-4.32.

RESULTS AND DISCUSSION

Due to the biological profile of different 1,2,3-triazoles, a convenient route for the synthesis of indole associated 1,2,3-triazoles **(6a-f)** is achieved. The target compounds with two active pharmacophores in a single molecular frame work have been performed with escalated biological activities. Thus we have designed and synthesized various novel 5-methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid phenylamides **(6a-f)**. The target compounds were synthesized by using commercially available 1-methyl-1*H*-indol-3-yl-methylamine **(1)** as starting material. Thus the initial intermediate, 1-methyl-1*H*-indol-3-yl-methyldiazonium chloride **(2)** has been prepared from compound **1** on diazotization with sodium nitrite and HCl at cold condition (0-5 °C) on uniform stirring for 3 h. The next intermediate, 1-methyl-1*H*-indol-3-yl-methylazide **(3)** was afforded from the reaction between compound **2** and sodium azide in presence of sodium acetate at 0 °C on constant stirring for 2 h. Then compound **3** is turned into the next intermediate, 5-methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid **(4)** on cyclization with ethyl acetoacetate in presence of sodium ethoxide under reflux for 5 h with steady stirring. Further, the final intermediate, 5-methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carbonyl chloride **(5)** was afforded on substitution reaction between compound **4** and thionyl chloride in chloroform on stable stirring at reflux temperature for 5 h. Finally the title compounds, 5-methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid phenylamides **(6a-f)** were synthesized from the substitution reaction of compound **5** with different aromatic amines in dichloromethane on uniform stirring at room temperature for 4-5 h. The chemical structures of the newly prepared compounds were confirmed by their IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analysis. All the title compounds were screened for their ability towards antimicrobial activity.

Antimicrobial activity: The antibacterial activity of the newly synthesized compounds, 5-methyl-1-(1-methyl-1*H*-indol-3-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid phenylamides **(6a-f)** is carried out by cup-plate method [16] against two representative Gram-positive bacteria namely *Staphylococcus aureus* and *Bacillus subtilis* and towards two Gram-negative bacteria such as *Klebsiella pneumonia* and *Escherichia coli* by using ciprofloxacin as standard. The antifungal activity of the title compounds **6a-f** is also examined against one fungal organism like *Aspergillus niger* by applying ketoconazole as reference. The stock solutions of the target compounds were developed in dimethyl sulfoxide at two different concentrations 100 and 200 µg/mL. Nutrient agar was employed as culture media for this study. The sterilization of the nutrient broth, culture tubes, pipette and other glassware was done by autoclaving. The incubation was carried out at 37 °C for 24 h and 25 ± 2 °C for 72 h for antibacterial and



(i) $NaNO_2$, HCl, 0-5 °C, 3 h; (ii) NaN_3, CH_3COONa, 0 °C, 2 h; (iii) EAA, EtONa, reflux, 4 h, (iv) $SOCl_2$, $CHCl_3$, reflux, 5 h; (v) Aryl amine, CH_2Cl_2, RT, 4-5 h

6 (a) R= H; (b) R= 3-NO_2; (c) R= 4-NO_2; (d) R= 4-Cl; (e) R= 4-Br; (f) R= 4-CH_3

Scheme-I

TABLE-1
ANTIMICROBIAL ACTIVITY OF COMPOUNDS **6a-f** (DIAMETER OF ZONES OF INHIBITION, mm)[a,b]

Compound	Antibacterial activity				Antifungal activity
	S. aureus	*B. subtilis*	*K. pneumonia*	*E. coli*	*A. niger*
6a	13/18	15/18	14/17	15/17	14/17
6b	14/16	12/15	15/18	16/19	13/16
6c	10/14	08/13	09/13	09/14	17/19
6d	08/12	07/10	08/12	07/13	14/16
6e	13/15	13/17	13/16	15/17	10/15
6f	12/14	12/15	15/17	14/16	11/14
Standard	20/20	21/21	22/22	23/23	24/24

[a]Activity at 100 µg/mL; [b]Activity at 200 µg/mL.

antifungal studies respectively. Diameters of zone of inhibition were measured for the plates in which the zones of inhibition in mm for each organism. The results of zone of inhibition of target compounds are outlined in Table-1. As per the consequences of the activity study, the compounds **6a, 6c, 6d** and **6f** and showed significant antibacterial activity and compounds **6d** and **6e** performed remarkable antifungal activity. The remaining all compounds displayed moderate to good antimicrobial activity. It is interesting to note that, none of the compound is inactive towards any microorganism and this outstanding property may be obtained to the target compound by integrating 1,2,3-triazole moiety into indole ring.

Conclusion

The outstanding properties of this new class of antibacterial and antifungal substances deserve further investigation in order to clarify the mode of action at molecular level, responsible for the activity observed. More extensive study is also warranted to determine additional physicochemical and biological parameters to have a deeper insight into structure activity relationship and to optimize the effectiveness of this series of molecules.

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