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RESEARCH ARTICLE

Synthesis, Characterization and Antimicrobial Activities of Newer 3,4,5-Trisubstituted [1,2,4]-Triazoles Derivatives

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ABSTRACT

In the present work, a series of 2-{[4-Phenyl-5-(4-isobutylphenyl)ethyl-4*H*-[1,2,4]-triazol-3-yl]sulfanyl}-arylethanones were synthesized in good yield by the *S*-alkylation of 4-phenyl-5-substituted-2,4-dihydro-3*H*-[1,2,4]-triazole-3-thione with various substituted phenacyl bromides. The structures of newly synthesized compounds were characterized by the spectral studies and evaluated for their anti-microbial activity. Among the synthesized compounds, **7b** showed comparable activity as that of standard drug against all the fungal strains and **7a**, **7e**, **7j** and **7k** exhibited moderate antifungal activity. The compounds **7b**, **7c**, **7i**, **7j** and **7k** showed moderate activity against all the bacterial strains.

KEYWORDS

[1,2,4]-triazole, Thiosemicarbazide, *S*-alkylation, Antimicrobial, Antibacterial, Antifungal

INTRODUCTION

The 1,2,4-triazoles are an important class of heterocycles that are found in a variety of pharmaceutically active molecules and possess high degree of antimicrobial activities. During the last two decades the substituted-1,2,4-triazoles have received most attention as potential antimicrobial agents[1-2]. There are a number of drugs such as tricyclazole and Itraconazole (antifungal agents), Maraviroc (antiviral agent), Rizatriptan (antimigraine agent), Alprazolam (anxiolytic agent) are the therapeutically interesting molecules possessing triazole nucleus.

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The biological and commercial significance of the 1,2,4-triazoles, have prompted us to the synthesis of [1,2,4]-triazole derivatives possessing comprehensive bioactivities such as antibacterial[3], antifungal[4], anti-inflammatory[5], analgesic[6], anticonvulsant[7], anticancer[8,9], antituberculosis[10], antidepressant activities[11]. Various 1,2,4-triazole derivatives have also been reported to possess pesticidal[12], herbicidal[13,14], antichagasic[15] and hypoglycemic activities[16].

MATERIALS AND METHODS

All the melting points were determined by an open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. The 1H NMR and 13C NMR spectra were recorded (CDCl3/DMSO-d6 mixture) on a BRUKER AVANCE II-400 (400 MHz) spectrometer using

TMS as an internal standard. Mass spectra were recorded in Agilent Technology LC-mass spectrometer. Elemental analyses (CHNS) were performed on the CHNS Elementar Vario EL III and results are summarized in Table 1. The progress of the reactions was monitored by thin layer chromatography (TLC) on silica gel plates.

Table 1: Characterization data of the compounds, 7a-l

Comp	R	Molecular Formula (M W)	M.P. (°C)	Yield (%)	% Analysis of C, H, N Found (calculated)		
					C	H	N
28a	H	$C_{28}H_{29}N_3OS$ (455.20)	140-141	80	73.80 (73.81)	6.40 (6.42)	9.24 (9.22)
28b	4-F	$C_{28}H_{28}FN_3OS$ (473.19)	118-120	82	71.00 (71.01)	5.98 (5.96)	8.89 (8.87)
28c	2-Cl	$C_{28}H_{28}ClN_3OS$ (489.16)	177-179	83	68.61 (68.62)	5.72 (5.76)	8.59 (8.57)
28d	4-Cl	$C_{28}H_{28}ClN_3OS$ (489.16)	167-169	80	68.63 (68.62)	5.74 (5.76)	8.58 (8.57)
28e	4-Br	$C_{28}H_{28}BrN_3OS$ (533.11)	175-177	85	62.95 (62.92)	5.30 (5.28)	7.89 (7.86)
28f	2-NO_2	$C_{28}H_{28}N_4O_3S$ (500.18)	152-154	88	67.19 (67.18)	5.66 (5.64)	11.14 (11.19)
28g	4-NO_2	$C_{28}H_{28}N_4O_3S$ (500.18)	169-171	82	67.16 (67.18)	5.67 (5.64)	11.18 (11.19)
28h	4-CH_3	$C_{29}H_{31}N_3OS$ (469.21)	144-146	75	74.19 (74.17)	6.67 (6.65)	8.93 (8.95)
28i	4-OCH_3	$C_{29}H_{31}N_3O_2S$ (485.21)	153-154	67	71.69 (71.72)	6.40 (6.43)	8.62 (8.65)
28j	2,4-Cl_2	$C_{28}H_{27}Cl_2N_3OS$ (523.12)	170-172	69	64.15 (64.12)	5.20 (5.19)	8.04 (8.01)
28k	3-Cl-4-F	$C_{28}H_{27}ClFN_3OS$ (507.15)	174-176	65	66.17 (66.19)	5.39 (5.36)	8.30 (8.27)
28l	2,4,5-Cl_3	$C_{28}H_{26}Cl_3N_3OS$ (557.08)	180-182	70	60.19 (60.17)	4.71 (4.69)	7.55 (7.52)

General Procedure for the Preparation of Phenacyl bromides (2)

To a cold solution of substituted acetophenone (**1**) (0.01 mol) in acetic acid (30 mL), bromine (0.61 mL, 0.012 mol) in acetic acid (8 mL) was gradually added for about 30 min. with continuous stirring and maintaining the temperature of the reaction mixture at 15°C. After the complete addition, the reaction mixture was slowly brought to the room temperature and stirring was continued for another 4-6 h. The solvent was removed under reduced pressure and the residue obtained was poured into ice water, filtered, washed with water and dried. The crude product was recrystallized from ethanol to afford the pure phenacyl bromide.

General Procedure for the Preparation of Aroylhydrazides (4)

The ethyl ester was prepared by refluxing ibuprofen (**3**) in excess absolute ethanol in the presence of few drops of conc. sulfuric acid as per the general method employed for the esterification. The resulting ester had been judged to be pure by TLC. The mixture of ethyl ester of ibuprofen (0.1 mol) and hydrazine hydrate (0.2 mol) was refluxed in absolute alcohol (50 mL) for 8 h. The excess solvent was then distilled off under reduced pressure and the concentrated solution was quenched in to ice cold water. The solid separated was filtered, washed and dried. The crude product was purified by recrystallization from ethanol.

General Procedure for the Preparation of 2-{2-[4-isobutylphenyl]- propanoyl}-*N*-phenylhydrazinecarbothioamide (5)

A mixture of 4-isobutylphenylethylhydrazide (**4**) (0.10 mol), phenyl isothiocyanate (13.5 g, 0.10 mol) and ethanol (50 mL) was refluxed on steam bath for 8 h. The solid thus separated out was filtered, washed with ethanol, dried and recrystallized from ethanol.

General Procedure for the Preparation of 5-{1-[4-isobutylphenyl]ethyl}-4-phenyl-4*H*-[1,2,4]-triazole-3-thione (6)

A mixture of 2-substituted-*N*-phenyl hydrazine-carbothioamide **(5)** (0.1 mol) and 5 % sodium hydroxide (100 mL) was refluxed for 3 h. The reaction mixture was then poured into ice cold water and acidified with dilute hydrochloric acid. The precipitate thus obtained was filtered, dried and recrystallized from ethanol.

General Procedure for the Preparation 2-{[4-Phenyl-5-(4-isobutylphenyl)ethyl-4*H*-[1,2,4]-triazol-3-yl]sulfanyl}-arylethanone (7)

A equimolar mixture of 5-{1-[4-isobutylphenyl]ethyl}-4-phenyl-4*H*-[1,2,4]-triazole-3-thione (**6**) (0.01 mol), various substituted phenacyl bromides (**2**) (0.01 mol) and dry potassium carbonate (0.01 mol) were refluxed for 6 hours in 20 mL of absolute alcohol and excess of solvent was removed by distillation under reduced pressure. After cooling to the room temperature, reaction mixture was poured into 50 mL of water. The product precipitated was filtered off, washed with methanol and dried. The crude product was recrystallized from ethanol.

Spectral data of 1-(4-fluorophenyl)-2-(5-(1-(4-isobutylphenyl)ethyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio)ethanone (7b)

IR (KBr, γmax, cm^{-1}): 3065 (ArC-H), 2924(C-H), 1686 (C=O), 1564 (C=N), 960 (C-F). **1H NMR (400 MHz, DMSO, δ ppm):** 0.80 (d, 6H, CH_3, *J* = 8 Hz), 1.54 (d, 3H, CH_3, *J* = 7.2 Hz), 1.71-1.74 (m, l H, CH), 2.32 (d, 2H, CH_2, *J* = 6.8 Hz), 3.96 (q, 1H, CH, *J* = 7.2 Hz), 4.99 (s, 2H, S-CH_2), 6.71 (d, 2H, ibuprofen, *J* = 8 Hz), 6.9 (d, 2H, ibuprofen, *J* = 8 Hz), 7.14 (t, 2H, 4-fluorophenyl, *J* = 20 Hz), 7.37-7.46 (m, 5H, phenyl), 7.53-7.57 (dd, 2H, 4-fluorophenyl, *J* = 16Hz). **LC MS:** *m/z* (%) = 473(M+, 54 %).

Spectral data of 1-(2-chlorophenyl)-2-(5-(1-(4-isobutylphenyl)ethyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio)ethanone (7c)

IR (KBr, γmax, cm^{-1}): 3072 (ArC-H), 2962 (C-H), 1688 (C=O), 1580 (C=N), 735 (C-Cl). **1H NMR (400 MHz, DMSO, δ ppm):** 0.80 (d, 6H, CH_3, *J* = 8 Hz), 1.52 (d, 3H, CH_3, *J* = 8 Hz), 1.72-1.78 (m, l H, CH), 2.42 (d, 2H, CH_2, *J* = 8 Hz), 4.13 (q, 1H, CH, *J* = 4 Hz), 4.98 (s, 2H, S-CH_2), 6.92 (d, 2H, ibuprofen, *J* = 8 Hz), 7.04 (d, 2H, ibuprofen, *J* = 8 Hz), 7.18-7.36 (m, 5H,

phenyl), 7.42-7.52 (m, 4H, 2-chlorophenyl). **LC MS:** *m/z* (%) = 489 (M+, 54 %), 491 (M+2, 18 %).

Spectral data of 1-(2,4-dichlorophenyl)-2-(5-(1-(4-isobutylphenyl)ethyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio)ethanone(7j) IR (KBr, γmax, cm-1): 3088 (ArC-H), 2984 (C-H), 1681 (C=O), 1580 (C=N), 765 (C-Cl). **1H NMR (400 MHz, DMSO, δ ppm):** 0.81 (d, 6H, CH3, *J* = 8 Hz), 1.54 (d, 3H, CH_3, *J* = 8 Hz), 1.71-1.76 (m, l H, CH), 2.39 (d, 2H, CH_2, *J* = 8 Hz), 4.09 (q, 1H, CH, *J* = 4 Hz), 4.99 (s, 2H, S-CH_2), 6.88 (d, 2H, ibuprofen, *J* = 8 Hz), 7.02 (d, 2H, ibuprofen, *J* = 8 Hz), 7.10-7.34 (m, 5H, phenyl), 7.48-7.59 (m, 3H, 2,4-dichlorophenyl). **LC MS:** *m/z* (%) = 523 (M+, 45 %), 525 (M+2, 15 %).

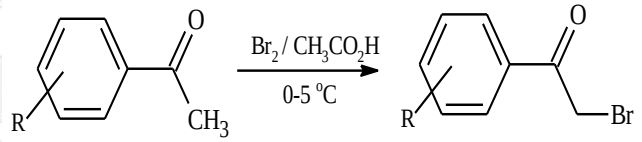
Spectral data of 1-(2,4,5-trichlorophenyl)-2-(5-(1-(4-isobutylphenyl)ethyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio)ethanone(7l) IR (KBr, γmax, cm^{-1}): 3078 (ArC-H), 2970 (C-H), 1691 (C=O), 1591 (C=N), 758 (C-Cl), 743 (C-Cl). **1H NMR (400 MHz, DMSO, δ ppm):** 0.82 (d, 6H, CH_3, *J* = 8 Hz), 1.53 (d, 3H, CH_3, *J* = 8 Hz), 1.76-1.82 (m, l H, CH), 2.43 (d, 2H, CH_2, *J* = 8 Hz), 4.10 (q, 1H, CH, *J* = 4 Hz), 5.01 (s, 2H, S-CH_2), 7.01 (d, 2H, ibuprofen, *J* = 8 Hz), 7.05 (d, 2H, ibuprofen, *J* = 8 Hz), 7.37-7.48 (m, 5H, phenyl), 7.90 (s, 1H, 2,4,5-trichlorophenyl), 8.12 (s, 1H, 2,4,5-trichlorophenyl), 10.12 (s, 1H, NH). **LC MS:** *m/z* (%) = 557 (M++1, 90 %), 559 (M++3, 85 %), 561 (M++5, 32 %).

Spectral data of 1-(3-chloro-4-fluorophenyl)-2-(5-(1-(4-isobutylphenyl)ethyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio)ethanone(7j) IR (KBr, γmax, cm^{-1}): 3076 (ArC-H), 2955 (C-H), 1689 (C=O), 1563 (C=N), 698 (C-Cl), 877 (C-F). **1H NMR (400 MHz, DMSO, δ ppm):** 0.80 (d, 6H, CH_3, *J* = 6.4 Hz), 1.54 (d, 3H, CH_3, *J* = 6.8 Hz), 1.71-1.74 (m, l H, CH), 2.32 (d, 2H, CH_2, *J* = 7.2 Hz), 3.96 (q, 1H, CH, *J* = 7.2 Hz), 4.98 (s, 2H, S-CH_2), 6.71 (d, 2H, ibuprofen, *J* = 8 Hz), 6.9 (d, 2H, ibuprofen, *J* = 8 Hz), 7.11(d, 2H, *J*=8Hz), 7.31-7.46 (m, 5H, phenyl), 7.75(t, 1H, 2-chloro-4-fluorophenyl). **LC MS:** *m/z* (%) = 507(M+, 45 %), 509 (M+2, 15 %).

Similarly, other compounds **7a-l** were prepared. Their characterization data are recorded in Table 1.

RESULTS AND DISCUSSION

The phenacyl bromides **2** were prepared from the corresponding substituted acetophenones by bromination using bromine in acetic acid **Scheme 1**. The 4-isobutylphenylethylhydrazide **4** was prepared by esterification of 4-2-(4-isobutylphenyl)propionic acid **3** with absolute ethanol in the presence of catalytic amount of conc, sulfuric acid followed by the treatment with hydrazine hydrate in absolute ethanol. This hydrazide was then treated with phenylisothiocyanate in the presence of ethanol to afford the corresponding thiosemicarbazide **5**. The compound 5 was then subjected to cyclization with 5% aqueous NaOH solution to yield 4-phenyl-5-substituted-2,4-dihydro-3H-[1,2,4]-triazole-3-thione **6**. This triazole-thione was then subjected to S-alkylation with various phenacyl bromides **2** in absolute alcohol in the presence of anhydrous potassium carbonate to yield target compounds **7a-l Scheme 2**.

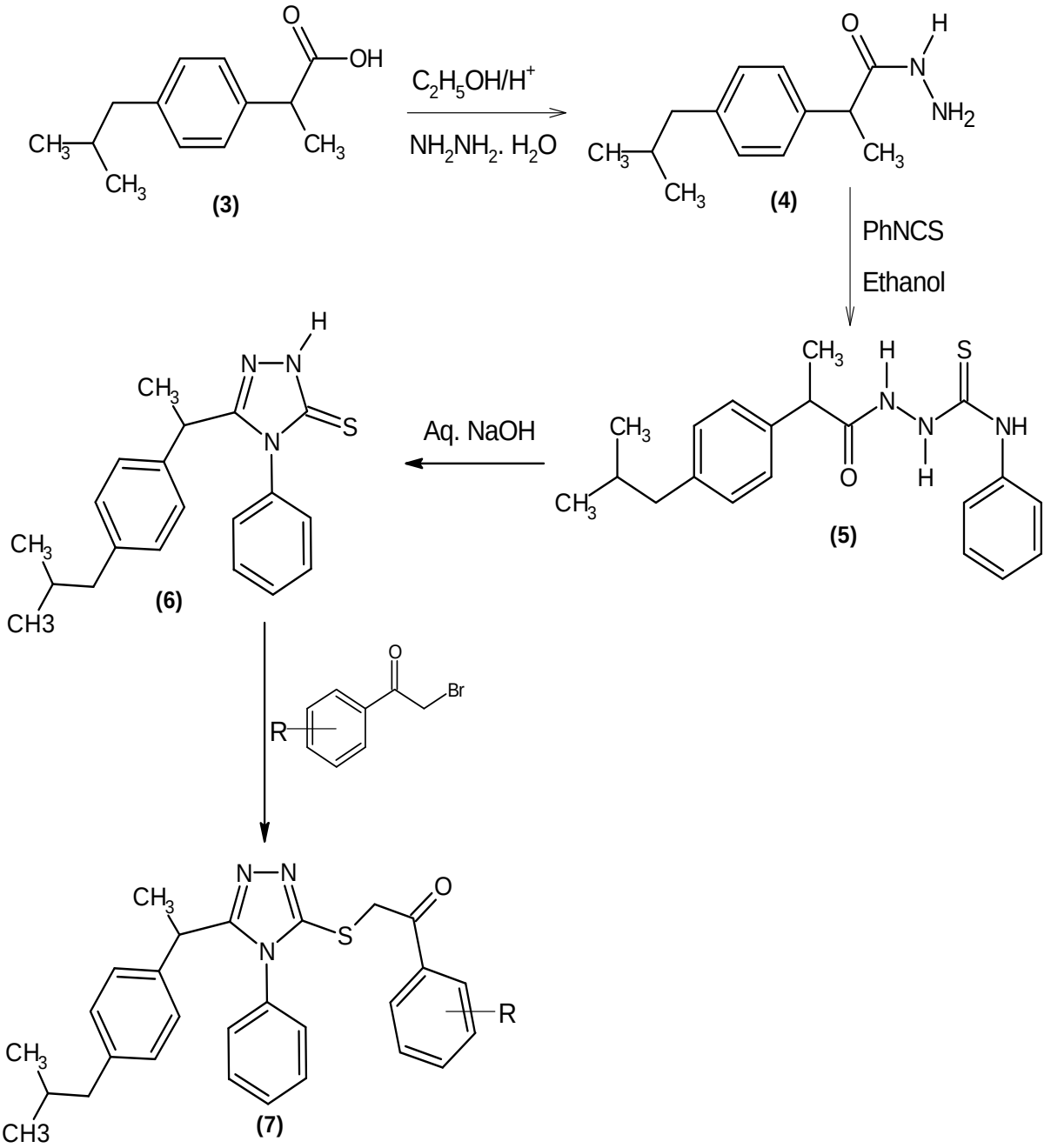


(1) (2)

Scheme 1: Preparation of phenacyl bromides

The general IR spectral characters of compounds **7b** showed absorption bands at 3055 cm-1 for ArC-H, 1686 cm-1 for C=O, 1628 cm-1 for C=N and 929 cm-1 for C-F groups. In the 400 MHz 1H NMR spectrum of this compound, The spectrum showed two distinct doublets at δ 0.80 ppm with *J* = 8.0 Hz and δ 1.53 ppm with *J* = 7.2 Hz for its methyl protons. Isopropyl methyne proton was observed as a multiplet in the region δ 1.71-1.74 ppm and the other methyne proton was observed as a quartet at δ 3.96 ppm. Methylene protons were resonated as a doublet at δ 2.33 with *J* = 6.8 Hz. The two protons of SCH_2 group appeared as singlet at δ 4.98. The aromatic protons of ibuprofen appeared as two doublets at δ 6.71 and δ 6.90 ppm with *J* = 7.6 Hz. The remaining aromatic protons were appeared as three multiplets in the region δ 7.11-7.16 (2H), δ 7.44-7.46 (2H), δ 7.53-7.56 (2H) and a broad

peak at δ 7.37 (3H). The 400 MHz 13C NMR spectrum of **7b** showed signals at δ 20.75, 22.00, 22.08, 29.64, 30.84, 35.80, 36.01, 39.94 44.16 115.20, 115.51, 120.94, 121.02, 126.71, 127.40, 128.96, 129.53, 129.87, 132.73, 135.20, 135.23, 139.39, 139.44, 150.17, 157.00, 158.18, 159.39, 162.44 and 166.66 for its carbon atoms. The LC MS spectrum of **7b** showed the molecular ion peak at *m/z* 474, in confirmity with its molecular formula, $C_{28}H_{28}N_3OSF$.



Scheme 2: Preparation of target compounds 7(a-l)

R = H, 4-F, 2-Cl, 4-Cl, 4-Br, 2-NO_2, 4-NO_2, 4-CH_3, 4-OCH_3, 2,4-Cl_2, 3-Cl-4-F, 2,4,5-Cl_3

Biological Screening

Antimicrobial Activity

The newly synthesized compounds were screened for their *in-vitro* antibacterial activity against three Gram negative bacterial strains such as *Escherichia coli (ATTC-25922)*, *Pseudomonas aeruginosa* (*ATTC-27853)*, *Klebsiella pneumonia* (*recultured*) and one Gram positive bacterial strain, *Staphylococcus aureus* (*ATTC-25923*), by employing serial plate dilution method[17-18]. Antifungal activity against *Aspergillus flavus (NCIM No. 524), Aspergillus fumigatus (NCIM No. 902), Penicillium marneffei (recultured)* and *Candida albicans (recultured)* in DMSO by serial plate dilution method[19-20]. The MIC values were evaluated at concentration range, 1.56-25 μg/mL. The figures in the table show the MIC values in μg/mL and the corresponding zone of inhibition in mm in the parentheses.

The investigation of antibacterial and antifungal screening data Table 2 and Table 3 revealed that all the tested compounds **7a-l** exhibited moderate activity. Among the tested compounds against antibacterial activity, compounds **7b**, **7c**, **7i**, **7j** and **7k** showed moderate activity against all the bacterial strains. The observed activity for these compounds can be attributed to the presence of 4-fluoro, 2-chloro, 4-methoxy, 2,4-dichloro and 3-chloro-4-fluoro attached to triazole ring system. However, the antibacterial activities of remaining compounds **7a**, **7d**, **7g, 7h** and **7l** were very marginal.

Table 2: Antibacterial activity of the compounds, 7a-l

Compound	**MIC in μg/mL and zone of inhibition (mm) in parantheses**			
	S. aureus	***E. coli***	***P. aeruginosa***	***K. pneumonia***
28a	25(<10)	25(<10)	25(<10)	25(<10)
28b	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
28c	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
28d	25(<10)	25(<10)	25(<10)	25(<10)
28e	25(<10)	25(<10)	25(<10)	25(<10)
28f	25(<10)	25(<10)	25(<10)	25(<10)
28g	25(<10)	25(<10)	25(<10)	25(<10)
28h	25(<10)	25(<10)	25(<10)	25(<10)
28i	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
28j	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
28k	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
28l	25(<10)	25(<10)	25(<10)	25(<10)
Standard (Ciprofloxacin)	1.56(22-30)	6.25(30-40)	6.25(25-33)	6.25(23-27)

Table 3: Antifungal activity of the compounds, 7a-l

Compound	MIC in μg/mL and zone of inhibition (mm) in parantheses			
	P. marneffei	*C. albicans*	*A. flavus*	*A. fumigates*
28a	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
28b	6.25(18-21)	6.25(18-21)	6.25(18-21)	6.25(18-21)
28c	25(<10)	25(<10)	25(<10)	25(<10)
28d	25(<10)	25(<10)	25(<10)	25(<10)
28e	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
28f	25(<10)	25(<10)	25(<10)	25(<10)
28g	25(<10)	25(<10)	25(<10)	25(<10)
28h	25(<10)	25(<10)	25(<10)	25(<10)
28i	25(<10)	25(<10)	25(<10)	25(<10)
28j	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
28k	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
28l	25(<10)	25(<10)	25(<10)	25(<10)
Standard (Ciclopiroxolamine)	1.56(22-30)	6.25(30-40)	6.25(25-33)	6.25(23-27)

Compounds **7b** showed comparable activity against all the fungal strains. The good activity can be attributed to the presence of 4-fluoro moiety attached to triazole ring system. The compounds **7a**, **7j** and **7k** exhibited moderate antifungal activity and the remaining compounds were less active.

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