Int J Pharm Bio Sci 2012 Oct; 3(4): (P) 183 - 192

Research Article **Medicinal Chemistry**

International Journal of Pharma and Bio Sciences

ISSN 0975-6299

ONE POT SYNTHESIS OF 3-(SUBSTITUTED PHENOXYMETHYL)-6-PHENYL/SUBSTITUTED PHENOXYMETHYL-1,2,4-TRIAZOLO[3,4-B][1,3,4] THIADIAZOLE DERIVATIVES AS ANTIMICROBIAL AGENTS

RAJESH D. HUNASHAL[1]* AND D. SATYANARAYANA[2]

[1]Department of Pharmacology, Karnataka Institute of Medical Sciences, Vidhyanagar, Hubli-580 021, Karnataka, India
[2] Department of Pharmaceutical Chemistry, NGSM Institute of Pharmaceutical Sciences, Paneer, Deralakatte, Mangalore-574 160, Karnataka. India

ABSTRACT

The reaction of thiocarbohydrazide with substituted phenoxy acetic acid to obtained 3-substituted-4-amino-5-mercapto-1,2,4-triazoles (1) by condensing compound 1 with aromatic carboxylic acid and substituted phenoxy acetic acids resulted the title compound triazolothiadiazoles 2a-j. The purity of the newly synthesized compounds was confirmed by TLC. Structures of all the newly synthesized compounds were confirmed by spectral data. All the newly synthesized compounds were screened for their *in-vitro* antimicrobial activity. Among the series the compounds 2e, 2f and 2b, 2c, 2f, 2d, 2i were exhibited equipotent antibacterial and antifungal activity at MIC of 1 µg/mL when compared with standard drugs respectively. From the results the compounds 2c, 2f, 2j were showed comparable antitubercular activity against *M. tuberculosis* $H_{37}R_v$ at MIC of 0.50 µg/mL, when compared with standard drug Rifampin and INH which showed MIC of 0.25 µg/mL.

KEYWORDS: 1,2,4-triazoles, triazolothiadiazoles, antimicrobial activity, antibacterial activity, antifungal activity, antitubercular activity

RAJESH D. HUNASHAL
Department of Pharmacology, Karnataka Institute of Medical Sciences, Vidhyanagar, Hubli-580 021, Karnataka, India

**Corresponding author*

INTRODUCTION

Microbial infections are the major threat in the world; these infections are treated with different antimicrobial agents. Resistance to antimicrobial agents by microorganism was recognized from the beginning[1]. The spread of this phenomenon is abetted by short generation time and genetic versatility of microorganisms, as well as by poor antibiotics prescribing and utilization practices. The antibiotics prescribed have the different adverse effects, such as; sulphonamides, fluroquinolones and β–lactam antibiotics are allergic to some individuals, cephalosporin and polyene antibiotics share common nephrotoxicity[2], aminoglycoside antibiotics exert ototoxic, antitubercular drugs cause progressive liver damage and antiviral drugs causes hematologic toxicity particularly in human immunodeficiency viruses (HIV) infection produced[3]. The azole antifungal agents in clinical use contain either two or three nitrogens in the azole ring and are thereby classified as imidazoles (e.g., ketoconazole, miconazole, clotrimazole) or triazoles (e.g., voriconazole, genaconazole**,** terconazole, itraconazole, fluconazole)respectively. With the exception of ketoconazole, use of the imidazoles is limited to the treatment of superficial mycoses, whereas the triazoles have a broad range of applications in the treatment of both superficial and systemic fungal infections. Diseases which very recently seemed on their way of extinction, such as fungal and tuberculosis are once again becoming serious public health problems because of societal changes and resistance emergence by pathogens[4]. These developments and the associated increase in microbial infections intensified the search for new, safer and more efficacious agents to combat serious microbial infections. Therefore there is a need to develop novel molecules as antimicrobial, antitubercular and antifungal agents.

The efficiency of triazole derivatives as chemotherapeutic agent is well established and their chemistry has been comprehensively studied. Literature survey revealed that various compounds of 1,2,4-triazoles bearing aryl groups or heterocyclic residues[5] and condensed heterocyclic derivatives of 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole rings which possess excellent biological activities, viz. Antibacterial[6,7] antifungal[8], antitubercular[9,10], cytotoxic[11], anticancer[12,13], anti-inflammatory[14-16], analgesic[17], anticonvulsant[18] and anthelmintic[19] activities. In view of these facts and in continuation of our research program on synthesis and biological importance of various heterocyclic compounds[20-23], now we are reporting the synthesis and antimicrobial activity of 3,6-disubstituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives as shown in scheme 1.

Experimental section

All research chemicals were purchased from Acros organics, Sigma-Aldrich, Lancaster Co. and used as such for the reactions. Reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel plates from E. Merck and Co. Melting points of synthesized compounds were determined in Thermonik melting point apparatus and uncorrected and IR spectra were recorded on Thermo Nicolet IR200 FT-IR spectrometer. The ^{1}H NMR and ^{13}C NMR were recorded on Bruker AVANCE II 400. Chemical shifts are reported in δ ppm units with respect to TMS. The mass spectra were recorded using GCMS-QP 2010. A novel series of substituted triazolothiadiazoles 2a-j were synthesized as shown in scheme 1 by the reaction between thiocarbohydrazide and substituted phenoxy acetic acid, which on fusion to form 3-(substituted phenoxymethyl)-4-amino-5-mercapto-1,2,4-triazole (1). General method for synthesis of 3-(substituted phenoxymethyl)-6-phenyl/substituted phenoxy methyl-1,2,4-triazolo[3,4-b][1,3,4] thiadiazole (2a-j) Equimolar proportions of N′-4-amino-5-(substituted phenoxymethyl)-2*H*-1,2,4-triazole-3(4*H*)-thione (1) and aromatic carboxylic acid or substituted phenoxy acetic acid was

added to 10 ml of dry phosphorous oxy chloride and the solution was refluxed on water bath for 6 hr. Excess of phosphorous oxychloride was removed under vacuum. The thick mass obtained was treated with water and left overnight. Solid thus obtained was filtered washed with 2% sodium carbonate solution, then with cold water, dried and recrystallized from ethanol.

3-phenoxymethyl-6-phenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (2a)
IR (KBr, cm^{-1}): 3048.1 (Ar C-H), 2914.2 (OCH_2), 2747.1 (CH_2), 1587.8 (C=N).
^1H NMR (400 MHz, DMSO-d_6, δ ppm): 7.4-6.7 (m, 10H, Ar-H), 5.1 (s, 2H, OCH_2).
^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 175.0 (thiadiazole-C_2), 162.8 (triazole-C_3), 147.9 (triazolothiadiazole-C_5), Ar C [160.2 (C_1), 129.3 (C_3 and C_5), 115.1 (C_2), 114.0 (C_4 and C_6)], Ar C (thiadiazole) [134.6 (C_1), 129.3 (C_3 and C_5), 128.2 (C_4), 127.6 (C_2 and C_6)], 65.8 (OCH_2).
MS (ESI) (M+1) : m/z 309.2; calcd.308.3.
3,6-bis(phenoxymethyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (2b)
IR (KBr, cm^{-1}): 3050.1 (Ar C-H), 2910.3 (OCH_2), 2745.5 (CH_2), 1587.8 (C=N).
^1H NMR (400 MHz, DMSO-d_6, δ ppm): 7.4-6.7 (m, 10H, Ar-H), 5.2 (s, 4H, $(OCH_2)_2$).
^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 172.4 (thiadiazole-C_2), 161.9 (triazole-C_3), 147.2 (triazolothiadiazole-C_5), Ar C [153.2 (C_1), 129.9 (C_3 and C_4), 125.2 (C_5), 117.0 (C_2 and C_6)], Ar C (thiadiazole) [158.6 (C_1), 129.3 (C_3 and C_5), 122.1 (C_4), 112.2 (C_2 and C_6)], 65.5 $(OCH_2)_2$.
MS (ESI) : m/z 338.2; calcd.338.2.
6-[(2,4-dichlorophenoxy)methyl]-3-phenoxymethyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (2c)
IR (KBr, cm^{-1}): 3056.2 (Ar C-H), 2911.6 (OCH_2), 2744.3 (CH_2), 1617.5 (C=N).
^1H NMR (400 MHz, DMSO-d_6, δ ppm): 7.1-6.6 (m, 8H, Ar-H), 5.1 (s, 4H, $(OCH_2)_2$).
^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.2 (thiadiazole-C_2), 162.2 (triazole-C_3), 147.3 (triazolothiadiazole-C_5), Ar C [152.4 (C_1), 130.7 (C_3), 129.3 (C_2 and C_4), 128.3 (C_5), 116.8 (C_6)], Ar C (thiadiazole) [156.5 (C_1), 130.4 (C_3 and C_5), 122.6 (C_4), 113.8 (C_2 and C_6)], 66.2 $(OCH_2)_2$.
MS (ESI) (M+1) : m/z 408.3; calcd.407.2.
3-[(4-chlorophenoxy)methyl]-6-phenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (2d)
IR (KBr, cm^{-1}): 3050.2 (Ar C-H), 2915.6 (OCH_2), 2745.6 (CH_2), 1650.2 (C=N), 765.2 (C-Cl).
^1H NMR (DMSO-d_6, δppm): 7.4-6.7 (m, 9H, Ar-H), 5.2 (s, 2H, OCH_2).
MS (ESI) (M+1): m/z 342.7; calcd: 343.8.
3-[(4-chlorophenoxy)methyl]-6-phenoxymethyl-1,2,4-triazolo [3,4-b][1,3,4]thiadiazole (2e)
IR (KBr, cm^{-1}): 3045.1 (Ar C-H), 2912.6 (OCH_2), 2747.5 (CH_2), 1665.8 (C=N), 766.7 (C-Cl).
^1H NMR (400 MHz, DMSO-d_6, δ ppm): 7.4-6.7(m, 9H, Ar-H), 5.2 (s, 4H, $(OCH_2)_2$).
MS (ESI) (M+1) : m/z 373.2; calcd.372.2.
6-[(2,4-dichlorophenoxy)methyl]-3-[(4-chlorophenoxy)methyl]-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (2f)
IR (KBr, cm^{-1}): 3050.5 (Ar C-H), 2918.8 (OCH_2), 2740.2 (CH_2), 1660.7 (C=N), 775.2 (C-Cl).
^1H NMR (400 MHz, DMSO-d_6, δ ppm): 7.1-6.6 (m, 7H, Ar-H), 5.1 (s, 4H, $(OCH_2)_2$).
^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.2 (thiadiazole-C_2), 162.7 (triazole-C_3), 148.0 (triazolothiadiazole-C_5), Ar C [152.7 (C_1), 131.1 (C_3), 130.3 (C_2 and C_4), 128.1 (C_5), 116.4 (C_6)], Ar C (thiadiazole) [153.7 (C_1), 130.4 (C_3), 123.7 (C_4), 127.9 (C_2), 127.7 (C_5), 116.8 (C_6)], 66.7 $(OCH_2)_2$.
MS (ESI) (M+2) : m/z 443.7; calcd.441.7.
3-[(4-nitrophenoxy)methyl]-6-phenyl-1,2,4-triazolo[3,4-b] [1,3,4] thiadiazole (2g)
IR (KBr, cm^{-1}): 3068.8 (Ar C-H), 2922.1 (OCH_2), 2746.3 (CH_2), 1617.5 (C=N).
^1H NMR (400 MHz, DMSO-d_6, δ ppm): 8.1-7.1 (m, 9H, Ar-H), 5.2 (s, 2H, OCH_2).
MS (ESI) : m/z 453.3; calcd.453.3.

3-[(4-nitrophenoxy)methyl]-6-phenoxymethyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (2h)
IR (KBr, cm^{-1}): 3052.1 (Ar C-H), 2915.3 (OCH_2), 1583.3 (C=N).
^1H NMR (400 MHz, DMSO-d_6, δ ppm): 7.4-6.7 (m, 8H, Ar-H), 5.2 (s, 4H, $(OCH_2)_2$).
MS (ESI): m/z 482.9; calcd.483.2.
3-[(2,4-dichlorophenoxy)methyl]-6-phenyl-1,2,4-triazolo[3,4-b] [1,3,4]thiadiazole (2i)
IR (KBr, cm^{-1}): 3070.2 (Ar C-H), 2917.3 (OCH_2), 2747.1 (CH_2), 1617.2(C=N).
^1H NMR (400 MHz, DMSO-d_6, δ ppm): 7.4-6.6 (m, 10H, Ar-H), 5.2 (s, 2H, OCH_2).
^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 173.5 (thiadiazole-C_2), 161.2 (triazole-C_3), 147.3 (triazolothiadiazole-C_5), Ar C [153.6 (C_1), 131.1 (C_3), 129.3 (C_2 and C_4), 129.1 (C_5), 116.7 (C_2)], Ar C (thiadiazole) [133.2 (C_1), 130.1 (C_3 and C_5), 128.6 (C_4), 127.2 (C_2 and C_6)], 66.2 (OCH_2).
MS (ESI) (M+2) : m/z 379.2; calcd.377.2.
3-[(2,4-dichlorophenoxy)methyl]-6-phenoxymethyl-1,2,4-triazolo [3,4-b][1,3,4] thiadiazole (2j)
IR (KBr, cm^{-1}): 3050.1 (Ar C-H), 2910.3 (OCH_2), 1587.8 (C=N).
^1H NMR (400 MHz, DMSO-d_6, δ ppm): 7.4-6.7 (m, 8H, Ar-H), 5.2 (s, 4H, $(OCH_2)_2$).
^{13}C-NMR (400 MHz, DMSO-d_6, δ ppm): 163.2 (thiadiazole-C_2), 162.2 (triazole-C_3), 147.3 (triazolothiadiazole-C_5), Ar C [152.4 (C_1), 130.7 (C_3), 129.3 (C_2 and C_4), 128.3 (C_5), 116.8 (C_6)], Ar C (thiadiazole) [156.5 (C_1), 130.4 (C_3 and C_5), 122.6 (C_4), 113.8 (C_2 and C_6)], 66.2 $(OCH_2)_2$.
In-vitro antimicrobial activity
Antibacterial and antifungal activity of the synthesized compounds were performed by agar dilution method[24] using standard bacterial and fungal strains, such as; *Streptococcus aureus* (ATCC 9144), *Bacillus subtilis* (ATCC 6633), *Psedomonas aeruginosa* (ATCC 25668), *Escherichia coli* (ATCC 25922), *Candida albicans* (ATCC 2091), *Aspergillus niger* (ATCC 6275) and *Aspergillus fumigatus* (ATCC 13073) respectively. Antitubercular activities of the synthesized compounds were performed by broth dilution assay[25] by incubated the test compounds at 37°C for 21 days using middle brook 7H9 broth media against *M. tuberculosis* $H_{37}R_v$ strain.

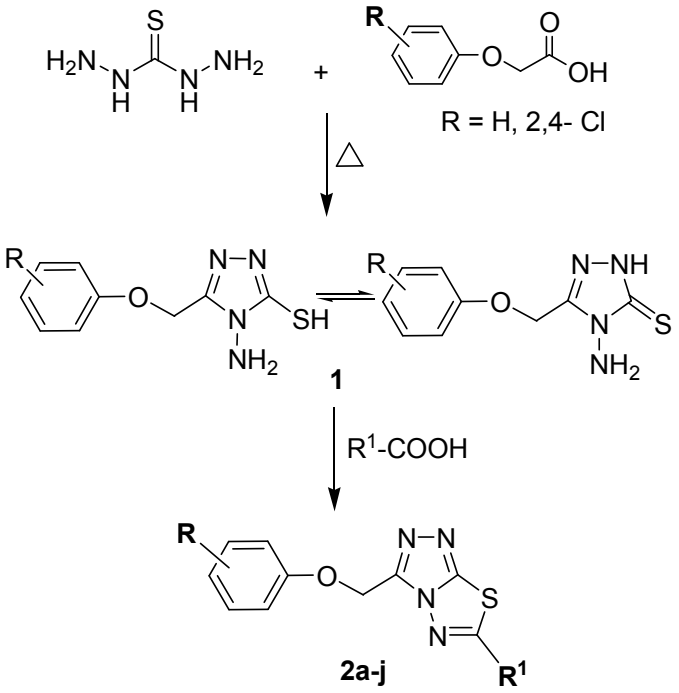
RESULTS AND DISCUSSION

The IR spectrum of compound **1** showed characteristic absorption bands at 3457.4 cm^{-1} was assigned to NH_2 and the other at 1282.1/2580 cm^{-1} was attributed to C=S/SH. These were disappeared by the formation of triazolothiadiazoles 2a-j. Similarly the ^1H NMR characteristic signal singlet showed at δ 13.2/7.8 due to SH/NH proton derived from tautomeric equilibrium of compound 1 and δ 2.1 due to NH_2 protons. Which were absent in the ^1H NMR spectra of triazolothiadiazoles. It suggest that Cyclocondensation of the SH and NH_2 functions of **1** with aromatic carboxylic acid and substituted phenoxy acetic acids resulted triazolothiadiazoles ring. The structure of compounds was further conformed by evidence for the formation of triazolothiadiazoles ring which was obtained by recording mass spectral data. The characterization data of all compounds is tabulated in Table 1.

In-vitro antimicrobial activity

Antibacterial and antifungal screening data revealed that all the compounds showed moderate to good antibacterial and antifungal activity respectively. Antibacterial and antifungal results are given in Table 2. Compounds showed antibacterial and antifungal activity at MIC values of 1-64 µg/mL respectively. Compounds 2e (R=4-Cl, R^1=$C_6H_5OCH_2$), 2f (R=4-Cl, R^1=2,4-$ClC_6H_3OCH_2$) inductively electron withdrawing substituents on phenoxy methyl rings were exhibited equipotent

antibacterial activity against *S. aureus, B. substilis* at MIC of 1 µg/mL whereas these compounds showed comparable activity against gram negative bacteria *P. aeruginosa, E.coli* at MIC of 2 µg/mL. Compounds 2c (R=H, R^1=2,4-$ClC_6H_3OCH_2$), 2d (R=4-Cl, R^1=C_6H_5) showed comparable antibacterial activity against gram positive bacteria *S. aureus, B. substilis* at MIC of 2 µg/mL. Compounds 2j (R=4-Cl, R^1= $C_6H_5OCH_2$), 2d (R=4-Cl, R^1=C_6H_5) showed comparable antibacterial activity against *E.coli* at MIC of 2 µg/mL. Rest of the compounds showed weak activity against both gram positive (*S. aureus, B. substilis)* and gram negative (*P. aeruginosa, E. coli)* bacteria, when compared with standard drug Ceftriaxone which showed MIC of 1µg/mL. The compound 2f (R=4-Cl, R^1=2,4-$ClC_6H_3OCH_2$) having electron withdrawing moiety on phenoxy methyl rings were found to be equipotent antifungal activity against *A. niger* and *A. fumigatus* at MIC of 1 µg/mL. Compounds 2d (R=4-Cl, R^1=C_6H_5), 2i (R=2,4-Cl, R^1=C_6H_5) showed equipotent antifungal activity against *A. niger* at MIC of 1 µg/mL. Whereas compounds 2b (R=H, R^1=$C_6H_5OCH_2$), 2c (R=H, R^1=2,4-$ClC_6H_3OCH_2$), 2f (R=4-Cl, R^1=2,4-$ClC_6H_3OCH_2$) were exhibited equipotent antifungal activity against *A. fumigatus* and compounds 2b (R=H, R^1=$C_6H_5OCH_2$), 2c (R=H, R^1=2,4-$ClC_6H_3OCH_2$), 2f (R=4-Cl, R^1=2,4-$ClC_6H_3OCH_2$) were showed equipotent antifungal activity against *A. fumigatus* at MIC of 1 µg/mL respectively. The compounds 2e (R=4-Cl, R^1=$C_6H_5OCH_2$), 2j (R=4-Cl, R^1= $C_6H_5OCH_2$) showed equipotent antifungal activity against *A. niger* and *A. fumigatus* at MIC of 2 µg/mL. Out of ten synthesized compounds, compound 2f (R=4-Cl, R^1=2,4-$ClC_6H_3OCH_2$) showed comparable antifungal activity against *C. albican.* In contrary, all compounds have shown less antifungal activity against *C. Albicans* when compared with standard drug Fluconazole which showed at MIC of 1 µg/mL. In general these compounds are found to possess more antifungal activity than antibacterial activity. Hence, it reveals that the compounds having electron withdrawing substituents on phenoxy methyl rings were found to be more active. The compounds showed antitubercular activity at MIC values of 0.25-2 µg/mL. From the results the compounds 2c (R=H, R^1=2,4-$ClC_6H_3OCH_2$), 2f (R=4-Cl, R^1=2,4-$ClC_6H_3OCH_2$), 2j (R=4-Cl, R^1= $C_6H_5OCH_2$) having chloro groups on phenoxymethyl rings were showed comparable antitubercular activity against *M. tuberculosis* $H_{37}R_v$ at MIC of 0.50 µg/mL, when compared with standard drug Rifampin and INH which showed MIC of 0.25 µg/mL. Rest of the compounds in the series showed moderate antitubercular activity. The results are shown in Table 2.



Scheme 1

Table 1
Characterization data of 2a-j

Compound	R	R^1	Yield (%)	Melting point* (^{0}C)	R_f Value#	Mol. formula
2a	H	C_6H_6	60.0	153-154	0.54	$C_{16}H_{12}N_4OS$
2b	H	$C_6H_5OCH_2$	62.5	212-214	0.33	$C_{17}H_{14}N_4O_2S$
2c	H	2,4-$ClC_6H_5OCH_2$	54.0	235-237	0.40	$C_{17}H_{12}Cl_2N_4O_2S$
2d	4-Cl	C_6H_6	60.0	198-200	0.52	$C_{16}H_{11}ClN_4OS$
2e	4-Cl	$C_6H_5OCH_2$	59.0	188-190	0.53	$C_{17}H_{11}ClN_4O_2S$
2f	4-Cl	2,4-$ClC_6H_5OCH_2$	58.0	203-206	0.49	$C_{17}H_{11}ClN_4O_2S$
2g	4-NO_2	C_6H_6	63.2	186-188	0.39	$C_{16}H_{11}N_5O_3S$
2h	4-NO_2	$C_6H_5OCH_2$	60.2	190-192	0.42	$C_{17}H_{13}N_5O_4S$
2i	2,4-Cl	C_6H_6	62.3	189-191	0.35	$C_{16}H_{10}Cl_2N_4OS$
2j	2,4-Cl	$C_6H_5OCH_2$	63.8	218-220	0.47	$C_{17}H_{12}Cl_2N_4O_2S$

The C, H, N analysis was found to be ± 0.4 %.
**** Recrystallization solvent ethanol.***
#Stationary Phase: Silica gel G, Mobile phase: Chloroform: Benzene (1:1), Iodine vapors as visualizing agent.

Table 2
***In-vitro* antimicrobial activity of 2a-j**

Compound	R	R^1	MIC values (µg/mL)							
			Sa[a]	Bs[a]	Pa[b]	Ec[b]	Ca[c]	An[c]	Af[c]	Mt[d]
2a	H	C_6H_5	16	8	8	32	32	64	16	1
2b	H	$C_6H_5OCH_2$	16	16	64	64	32	64	1	1
2c	H	$2,4\text{-}ClC_6H_3OCH_2$	2	2	8	8	64	64	1	0.50
2d	4-Cl	C_6H_5	2	2	8	16	64	1	16	1
2e	4-Cl	$C_6H_5OCH_2$	1	1	2	4	32	2	2	2
2f	4-Cl	$2,4\text{-}ClC_6H_3OCH_2$	1	1	2	2	2	1	1	0.50
2g	$4\text{-}NO_2$	C_6H_5	16	16	8	8	32	32	64	2
2h	$4\text{-}NO_2$	$C_6H_5OCH_2$	8	16	8	16	64	16	32	2
2i	2,4-Cl	C_6H_5	4	4	8	16	64	1	64	1
2j	2,4-Cl	$C_6H_5OCH_2$	4	8	4	2	32	2	2	0.50
Ceftriaxone			1	1	1	1	ND	ND	ND	ND
Fluconazole			ND	ND	ND	ND	1	1	1	ND
Rifampin			ND	ND	ND	ND	ND	ND	ND	0.25
INH			ND	ND	ND	ND	ND	ND	ND	0.25

[a] The screening organism. Gram-positive bacteria: Streptococcus aureus (ATCC 9144, Sa), Bacillus subtilis (ATCC 6633, Bs).
[b] The screening organisms. Gram-nagative bacteria: Psedomonas aeruginosa (ATCC 25668, Pa), Escherichia coli (ATCC 2091, Ec).
[c] The screening fungal organisms: Candida albicans (ATCC 2091,Ca), Aspergillus niger (ATCC 6275, An), Aspergillus fumigatus (ATCC 13073, Af).
[d] The screening organisms: Mycobacterium tuberculosis $H_{37}R_v$ (Mt); ND: Not determined.

CONCLUSION

In conclusion the synthesized title compounds resulted in good yields. The SAR study of the title compounds reveals better activity. Indicating the triazolothiadiazole ring scaffold influences the pharmacological activity. From the activity data, the compounds having electron withdrawing group such as halogens are found to be more activity as compared to others. It is observed that the chloro at *ortho* and *para* position on phenoxymethyl rings increases the activity. However, the difference in activity profile with structural modifications provides further scope to explore these compounds for better bioactivity. Thus substituted triazolothiadiazole moieties appear to be another interesting source of antifungal and anti-tubercular agents. Further studies are required to

know the mechanism of action of these compounds.The authors have declared no conflict of interest.

ACKNOWLEDGEMENT

The authors are thankful to Dr. Vasantha Kamath, Director, and Dr. U. S. Hangaraga, Principal, Karnataka Institute of Medical Sciences, Hubli, India for providing necessary facilities to carry out this research work. We are grateful to director, SAIF, Punjab University, Chandigarh, India for providing the spectral data.

REFERENCES

1. M. Rama Prabha1 and K. Vasantha. Phytochemical and antibacterial activity of *alotropis procera* (ait.) R. Br. Flowers. Int J Pharma Bio Sci,1:P-1-6, (2012)
2. J. G. Hardman and L. E. Limbird. Goodman and Gilman's The Pharmacological basis of therapeutics, 10th Edn, McGraw-Hill publisher: 1143-1165, (2001)
3. K. D. Thripathi. Essesntials of Medical Pharmacology, 4th Edn, Japyee Brothers Medical Publishers (P) Ltd.: 627-698, (2003)
4. L. A. Mitscher. Foye's Principles of medicinal Chemistry, 5th eds, Lippincott Williams and Wilkins, A Wolters Kluwer Company: 819-820, (2002)
5. Olcay B., Bahittin K., Murat K. Synthesis and anticancer evaluation of some new unsymmetrical 3,5-diaryl-4H-1,2,4-triazole derivatives. Turk J Chem, 30: 29- 40, (2006)
6. Francis G., Cedric L., Fabrice P., Damien C., Patrice L., Marc Le, B. Design, synthesis, and evaluation of 1-(N-benzylamino)-2-phenyl-3-(1H-1,2,4-triazol-1-yl)propan-2-ols as antifungal agents. Bioorg Med Chem Lett, 18:1820-1824, (2008)
7. Ilango K., Valentina P. Synthesis and biological activities of novel 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazoles. Der Pharma Chemica, 2(2): 16-22, (2010)
8. Desai N. C., Shukla H. K., Thaker K. A. Synthesis of some new 5-[2-{(1,2,3-benzotriazol)-1-yl-methyl}-1'-(4'-substituted aryl-3'-chloro-2'-oxoazetidine)]-amino-1,3,4-thiadiazoles: Antifungal and antibacterial agents. J Indian Chem Soc, 61:239-241(1984).
9. Iraj C., Charalabou Z., Panagiotis G., Athina S., Jasmina G. Sulfonamide-1,2,4-triazole derivatives as antifungal and antibacterial agents: Synthesis, biological evaluation, lipophilicity and conformational studies**.** Bioorg Med Chem, 16:1150-1161, (2008)
10. Kucukguzel I., Esra T., Guniz Kucukguzel S., Rollas S., De Clercq E. Synthesis of some novel thiourea derivatives obtained from 5-[(4-aminophenoxy)methyl]-4-alkyl/aryl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones and evaluation as antiviral/anti-HIV and anti-tuberculosis agents. Eur J Med Chem, 43:381-392, (2008).
11. Ilango K., Valentina P. Facile synthesis and cytotoxic activity of 3,6-disubstituted 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazoles. Eur J Med Chem, 1 (1): 50-53, (2010)
12. Mahendra R. S., Kiran K. M., Hanimi R. G., Tatikonda S., Chakravarthy A. K., Dolly P. Synthesis of new S-derivatives of clubbed triazolyl thiazole as anti-mycobacterium tuberculosis agents. Bioorg Med Chem, 15: 3997- 4008, (2007)
13. Upadhayaya R. S., Sinha N., Jain S., Kishore N., Chandra R., Arora S. Optically active antifungal azoles: synthesis and antifungal activity of (2*R*, 3*S*)-2-(2,4-difluorophenyl)-3-(5-{2-

[4-aryl-piperazin-1-yl]-ethyl}-tetrazol-2-yl/1-yl)-1-[1,2,4]-triazol-1-yl-butan-2-ol. Bioorg Med Chem, 12: 2225-2228, (2004)

14. Navidpour L., Shafaroodi H., Abdi K., Amini M., Ghahremani M. H., A. Dehpour R., Shafiee A. Design, synthesis, and biological evaluation of substituted 3-alkylthio-4,5-diaryl-4*H*-1,2,4-triazoles as selective COX-2 inhibitors. Bioorg Med Chem, 14:2507-2517, (2006)
15. El Shehry M.F., Abu-Hashem A.A., El-Telbani E.M. Synthesis of 3-[(2,4-dichlorophenoxy)methyl]-1,2,4-triazolo(thiadiazoles and thiadiazines) as anti-inflammatory and molluscicidal agents. Eur J Med Chem**,** 45:1906–1911, (2010)
16. Metwally K. A., Yaseen S. H., Lashine E. M., El-Fayomi H. M., El-sadek M. E. Non-carboxylic analogues of arylpropionic acids: Synthesis, anti-inflammatory activity and ulcerogenic potential. Eur J Med Chem, 42: 152-160, (2007)
17. Srivastava V., Sen S., Shekar R. New Bridgehead nitrogen heterocycles of furan as potent antimicrobial agents. Indian J Chem, 33: 344, (1994)
18. Almarirad A., Mehrdad T., Kebriaeezadeh A., Mehrabi N., Dalvandia A., Shafieea, A. Synthesis and anticonvulsant activity of new 2-substituted-5-[2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazoles and 1,2,4-triazoles. Bioorg Med Chem Lett, 14: 6057-6059, (2004)
19. Imitiaz Hussain M., Kumar V. Synthesis of 3- [2-benzotiazolyl methyl-1,2,4 triazolo [3,4b] [1,3,4] thiadiazole-6-yl-subsituted as possible anthelmintics. Indian J Chem, 31B: 673-676, (1992)
20. Ronad P. M., Satyanarayana D., Hunashal R. D., Maddi V. S. Synthesis of novel Substituted 7-(benzylidenamino)-4-methyl-2*H*-chromen-2-one derivatives as anti-inflammatory and analgesic agents. Arch Pharm Chem Life Sci, 341: 696-700 (2008)
21. Hunashal R. D., Satyanarayana D., Maddi V. S. Synthesis and Antimicrobial activity of 2-[4-(substituted benzylidenamino)-5-(substituted phenoxymethyl)-4*H*-1,2,4-triazol-3-yl thio] acetic acid derivatives. E J Chem, 9: 1206-1212, (2012)
22. Ronad P. M., Hunashal R. D., Satyanarayana D., Maddi V. S. Synthesis and evaluation of antiinflammatory and analgesic activities of a novel series of substituted N-(4-methyl-2oxo-2H-chromen-7-yl) benzamides. Arzneim Forsch, 58: 641-646, (2008)
23. Hunashal R. D., Ronad P. M., Satyanarayana D., Maddi V. S., Kamadod M. A., Synthesis and biological activities of N'-[4-(substituted benzylidenamino)-3-(2′,4′-dichlorophenoxymethyl)-1,2,4-triazol-5yl)] isonicotinyl hydrazides. Int J Drug Design Drug Disc, 1:107-114, (2010)
24. Murry P.R., Baron E.J., Pfaller M.A., Tenover F.C., Yolken R.H. Comparison of disc diffusion and E test methods with agar dilution for antimicrobial susceptibility testing. Am Soc Microbiol 20: 556-563, (1995)
25. Richard S., Lynn S. M., Avery C. G. Antimicrobial Susceptibility Testing Protocols, CRC Press, Taylor and Francis Group publisher: 58-64, (2007)