Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2012, 4(4):1667-1673
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis, antimicrobial activities and structure activity relationship of some dithiocarbazinate, 1,2,4-triazoles and 1,2,4-triazolo[3,4b][1,3,4]thiadiazoles

Surendra N Pandeya[1], AmitChattree[2] and Iffat Fatima[2]

[1]*Department of Pharmacy, Saroj Institute of Technology and Management, 12th Km. Stone, Lucknow-Sultanpur Road, Lucknow, Uttar Pradesh, India.*
[2]*Department of Chemistry, Sam Higginbottom Institute of Agriculture, Technology and Science, Naini, Allahabad- 211007, Uttar Pradesh, India*

ABSTRACT

The reaction of substituted benzoic acid hydrazide with carbondisulfide and potassium hydroxide followed by treatment with hydrazinehydrate afforded 4-amino-5-aryl-4H-1, 2, 4-triazole-3-thiol ***(4)****. Condensation of* ***(4)*** *with various aromatic carboxylic acids in the presence of phosphorus oxy chloridegives 3,6disubstituted-[1,2,4]triazolo[3,4b][1,3,4]thiadiazoles****(5)*** *and with various aroylthiocyanate in the presence of ethanol gives N,3 disubstituted-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-amine* ***(6)****. The structure of these newly synthesized compounds was characterized by elementalanalysis, IR, ^{1}H NMR studies. All the synthesized compoundswere screened for their antibacterial activity against H.pylori, P.aeroginosa, E.coli, S.aureus and Methcyclin resistant strain(MRSA) and antifungal activity against A.niger, A.foeniculum and P.chrysogenum. Some of compounds exhibited promising antibacterial and antfungal activities.Most active antifungalcompound was****4a*** *(4-amino-5-phenyl-4H-1, 2, 4-triazole-3-thiol) with MIC (Minimum Inhibitory Concentration) 57.14 µg/ml and Zone of inhibition 14 mmagainst A.foeniculum. Most potent antibacterial compound was****5b*** *(3-(4-nitrophenyl)-6-phenyl-[1, 2, 4]-triazolo [3, 4-b] [1, 3, 4] thiadiazole) with MIC 10 µg/ml, Zone of inhibition 8mmagainst H.pylori.*

Keywords: Triazoles, Triazolothiadiazoles, Antibacterial Activity, Antifungal Activity.

INTRODUCTION

In the last few decades, the chemistry 0f 1, 2, 4-triazoles andtheir fused heterocyclic derivatives such as 1, 3, 4-thiadiazoleshas received considerable attention because of their syntheticand effective biological importance [1-4]. In addition to N-bridged heterocyclic derived from triazoles have wide application in medicine [5-7]. 1,2,4-triazole moieties havebeen incorporated into wide variety of therapeutically interesting drug candidates including antibacterial, antidepressants, antiviral, antitumor, anti-inflammatory agents,antimicrobials, CNS stimulants, sedatives, antianxietycompounds, pesticides, herbicides, lubricating and analyticalagents [8-11] and antimycotics ones such as fluconazole,itraconazole.There aredrugs like Alprazolam [12, 13],Triazolam [14]**(Figure 1)** that are in the market.

Among these heterocycles, the mercapto and thione substituted1, 2, 4-triazole ring systems **(Figure 2)** have been well studiedand so far a variety of biological activities have been reportedfor a large number of their derivatives such as antibacterial[15-20]antifungal [21,22], antitibercular [23],antimycobacterial [24], anticancer [25,26], diuretic [27,28], and antihypoglycemic [29] properties.In addition to theseimportant biological applications, mercapto 1, 2, 4-triazoles are also of great utility in preparative organic chemistry, for example, im the presence of various reagents undergo different types of reactions to yield other heterocyclic compounds, example- thiazolotriazoles,

triazolothiazepines and triazolothiadiazenes. Recently it was reported that the 1, 2, 4-triazolo [3, 4-b] [1, 3, 4] thiadiazoles possess cytotoxic activity [30].Moreover, the triazolothiadiazoles substituted in the 3 & 6 positions by aryl, alkyl or heterocyclic moiety possess pharmacological activities such as antibacterial [31], anti-inflammatory [32], and herbicidal [33] and anti HIV-1 effects [34].

In the view of the facts mentioned above, we have synthesized some dithiocarbazinates, 4-amino-5-arylsubstituted-4H-[1,2,4]triazole-3-thiols and 3,6-(arylsubstituted) -1,2,4-triazolo [3,4-b] [1,3,4]thiadiazoles and screened their antibacterial and antifungal activitiesand then their SAR was determined. The intermediate dithiocarbazinate were also screened to see the effect of cyclization of dithiocarbazinate.

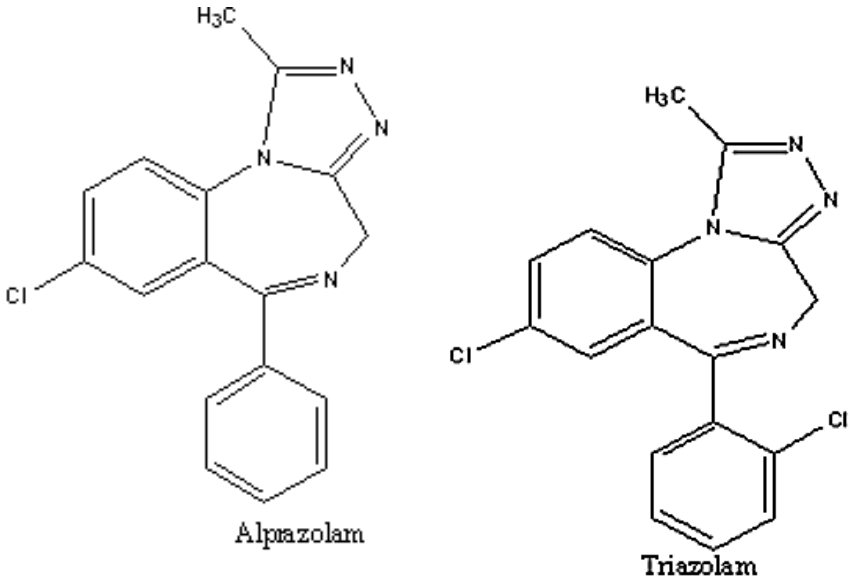


Figure 1

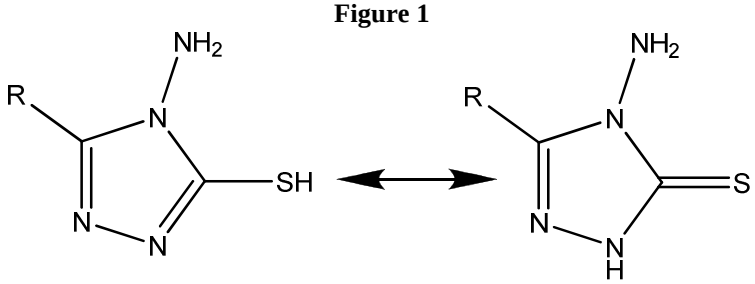


Figure 2

MATERIALS AND METHODS

Experimental

Melting points were measured in open capillaries on Jindal melting point apparatus and were uncorrected. The completion of reaction and the purity of the products were monitored by thin layer chromatography (TLC). Silica gel 60 was used for TLC.TheIR spectra were recorded using potassium bromide on Jasco FT-IR 6100 spectrophotometer.^{1}HNMR spectra were recorded on Bruker 300 MHz Spectrophotometer in $CDCl_3$ using TMS (TetramethylSilane) as an internal standard. Elemental analysis was performed on a CHN-O-rapid elemental analyzer for C, H, N and the results are within ± 0.4% of the theoretical values.

General method of synthesis of aryl benzoates (1a-1b)

To a solution of benzoic acid/ substituted benzoic acid and methanol (equimolar solution), conc. H_2SO_4 was added and refluxed for 2 h. The product obtained was filtered and washed with water and dried and recrstallized from ethanol.

General method of synthesis of arylcarbohydrazide (2a-2b)

Mixture of aryl benzoates **(1)** and hydrazine hydrate (equimolar solution) in 10 ml of methanol was heated under reflux for 2-3 h. and after cooling solid obtained was collected by filteration. It was washed with methanol, dried and recrystallized from methanol.

General method of synthesis of dithiocarbazinates (3a-3b)
Aryl carbohydrazide**(2)**was treated with a solution of KOH dissolved in 25 ml of methanol at 0-5°C under stirring. Then carbon disulfide was added slowly (in equimolar quantity) and the reaction mixture was stirred for 2-3 h. The solid product of potassium dithiocarbazinate was filtered, washed with methanol and dried.

General method of synthesis of 4-amino-5-(substituted phenyl)-4H-[1, 2, 4] triazole-3-thiol (4a-4b)
Potassisumdithiocarbazinate**(3)** in 10 ml water and hydrazine hydrate (equimolar solution) was refluxed for 2-3 h. During progress of reaction, the reaction mixture was turned to green with evolution of H_2S and finally it becomes homogeneous. It was then diluted with little cold water and acidified with conc. HCl. The precipitate was filtered, washed with cold water and recrystallized from methanol.

General method of synthesis of 3, 6-(substituted phenyl)-[1, 2, 4] triazolo[3, 4-b][1, 3, 4]thiadiazole (5a-5b)
A mixture of **(4)** and substituted benzoic acid (equimolar solution) in $POCl_3$(5 ml) was refluxed for 2-3 h. The reaction mixture was slowly poured into crushed ice with stirring and neutralized with solid sodium bicarbonate. Solid material was filtered, washed with cold water, dried and recrystallized from chloroform.

General method of synthesis of N,3(substituted phenyl)-N-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole-6-amine (6a-6b)
A mixture of **4** and aroylthiocyanate (equimolar solution) in 10 ml of ethanol was refluxed for 5-6 h. The product obtained was filtered, washed with water and dried. The crude product was recrystallized with methanol.

Physical properties and Spectral data of target compounds:
Methyl Benzoate **(1a):** Yield: 90%; M.P.: -12.5°C; FTIR (cm^{-1}): 3030 (aromatic C-H), 1610 (aromatic C=C), 1735 (-$COOCH_3$). Anal.Calcd. for $C_8H_8O_2$ (136.15): C, 70.51; H, 5.87. Found: C, 70.11; H, 5.47.

4-nitro methyl benzoate **(1b)**: Yield: 85%; M.P.: 94-98°C; FTIR (cm-1) 3040 (aromatic C-H), 1615 (aromatic C=C), 1736 (-$COOCH_3$), 1560, 1375 (NO_2). Anal.Calcd. for $C_8H_7NO_2$ (181.15): C, 52.89; H, 3.85; N, 7.71. Found: C, 52.49; H, 3.45; N, 7.31.

Benzohydrazide**(2a)**: Yield: 80%; M.P.: 112-114°C; FTIR (cm^{-1}) 3300. 3235 (-NH_2), 3038 (aromatic C-H), 1675 (C=O), 1540 (C=C). Anal.Calcd. for $C_7H_8N_2O$ (136.12): C, 61.71; H, 5.87; N, 20.57. Found: C, 61.31; H, 5.47; N, 20.17.

4-nitrobenzhydrazide **(2b)**: Yield: 82%; M.P.: 210-214°C; FTIR (cm^{-1}) 3300. 3235 (-NH_2), 3038 (aromatic C-H), 1675 (C=O), 1540 (C=C), 1560, 1375 (NO_2). Anal.Calcd. for $C_7H_7N_3O_3$ (181.15): C, 46.28; H, 3.85; N, 23.14. Found: C, 45.88; H, 3.45; N, 22.74.

Potassium 2-benzoyl-N-mercapto hydrazine carbothioamide or Potassium dithiocarbazinate of benzohydrazide**(3a)**: Yield: 75%; M.P.: 108-112°C; FTIR (cm^{-1}) ^{1}H NMR (ppm) δ 8.0 (s, 1H NH sec. amide), δ 2.0 (s.1H, NH amine), δ7.70-8.03 (m, 5H, phenyl). Anal.Calcd. for $C_8H_8N_3OS_2K^+$ (226): C, 42.47; H, 3.53; N, 18.58. Found: C, 42.07; H, 3.13; N, 18.18.

Potassium N-mercapto- 2- (4-nitro benzoyl) hydrazine carbothioamide or Potassium dithicarbazinate of 4-nitrobenzhydrazide**(3b)**: Yield: 80%; M.P.: 208-212°C; FTIR (cm^{-1}) ^{1}H NMR (ppm) δ 8.0 (s, 1H NH sec. amide), δ 2.0 (s.1H, NH amine), δ 8.11-8.44 (m, 4H, phenyl). Anal.Calcd. for $C_8H_7N_3O_3S_2K^+$ (271): C, 35.42; H, 2.58; N, 15.49. Found: C, 35.02; H, 2.18; N, 15.09.

4- amino-5-phenyl-4H-1, 2, 4-triazole-3-thiol **(4a)**Yield: 60%; M.P.: 193-197: FTIR (cm^{-1}) 3300 (NH_2), 2665 (SH), 1617 (C=N), 964 (N-C=S). ^{1}H NMR (ppm) δ 5.77 (s, 2H, NH amine), δ 13.79 (s, 1H aromatic C-SH), δ 7.41-8.28 (m, 5H phenyl).Anal.Calcd. for $C_8H_8N_4S$ (192): C, 50; H, 4.16; N, 29.16. Found: C, 49.6; H, 3.78; N, 28.76.

4-amino-5-(4-nitro phenyl)-4H-1, 2, 4-triazole-3-thiol **(4b)** Yield: 75%; M.P.: 78-82°C; FTIR (cm^{-1}) 3300 (NH_2), 2665 (SH), 1615 (C=N), 965 (N-C=S), 1562, 1370 (NO_2). ^{1}H NMR (ppm) δ 5.77 (s, 2H, NH amine), δ 13.79 (s, 1H aromatic C-SH), δ 8.05-8.32 (m, 4H phenyl).Anal.Calcd. for $C_8H_7N_4O_2S$ (223): C, 43.04; H, 3.13; N, 25.11. Found: C, 42.64; H, 2.73; N, 24.71.

3,6-diphenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole**(5a)** Yield: 70%; M.P.: 262-265°C; FTIR (cm^{-1}) 3065 (aromatic C-H), 1640 (C=N). ^{1}H NMR (ppm) δ 7.41-8.28 (m, 5H phenyl attached to triazole nucleus), δ 7.41-8.03 (m, 5H phenyl attached to thiadiazole nucleus).Anal.Calcd. for $C_{15}H_{10}N_4S$ (278): C, 64.74; H, 3.59; N, 20.14. Found: C, 64.34; H, 3.19; N, 19.74.

3-(4-nitrophenyl)-6-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole **(5b)** Yield: 55%; M.P.: 238-242°C; FTIR (cm^{-1}) 3060 (aromatic C-H), 1645 (C=N), 1560, 1375 (NO_2). ^{1}H NMR (ppm) δ 8.05-8.32 (m, 4H phenyl attached to triazole nucleus), δ 7.41-8.03 (m, 5H phenyl attached to thiadiazole nucleus).Anal.Calcd. for $C_{15}H_8N_4O_2S$ (308): C, 58.44; H, 2.59; N, 18.18. Found: C, 58.04; H, 2.19; N, 17.78.
N,3-diphenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-amine**(6a)** Yield: 80%; M.P.: 192-206°C; FTIR (cm^{-1}) 3065 (aromatic C-H), 1640 (C=N), 3300 (NH). ^{1}H NMR (ppm) δ 4.0 (s, 1H aromatic C-NH), δ 7.41-8.28 (m, 5H phenyl attached to thiadiazole nucleus).Anal.Calcd. for$C_{15}H_{11}N_5S$ (293): C, 61.43; H, 3.75; N, 23.89. Found: C, 61.03; H, 3.35; N, 23.49.

3-(4-nitrophenyl)-N-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-amine **(6b)** Yield: 65%; M.P.: 50-54º(d);FTIR (cm^{-1}) 3060 (aromatic C-H), 1645 (C=N), 3300 (NH) 1560, 1375 (NO_2). ^{1}H NMR (ppm) δ 4.0 (s, 1H aromatic C-NH), δ 8.05-8.32 (m, 4H phenyl attached to triazole nucleus), δ 6.81-7.63 (m, 5H phenyl attached to thiadiazole nucleus).Anal.Calcd. for $C_{15}H_9N_6O_2S$ (337): C, 53.41; H, 2.67; N, 24.92. Found: C, 53.01; H, 2.27; N, 24.42.

Antifungal and Antibacterial Activities
Bacterial and fungal growth inhibition was performed by serial dilution method in nutrient agar (for bacteria) and Sabouraud Dextrose Agar (for fungi) medium. Levofloxacin and Ketoconazole were used as reference standards for bacteria and fungi respectively. Test compounds and standards were dissolved in DMSO (Dimethyl Sulfoxide). The activity was checked at two concentrations, 100 µg/ml and 10 µg/ml. Solution was applied by micropipette on the filter paper disks, placed on the agar plate. The surfaceof the plate was inoculated with bacteria and fungi. Following incubation for 24 h at 37^{0}C, the inhibition zone around each disk, if any was recorded and the MIC (Minimum inhibitory concentration) was calculated.

RESULTS AND DISCUSSION

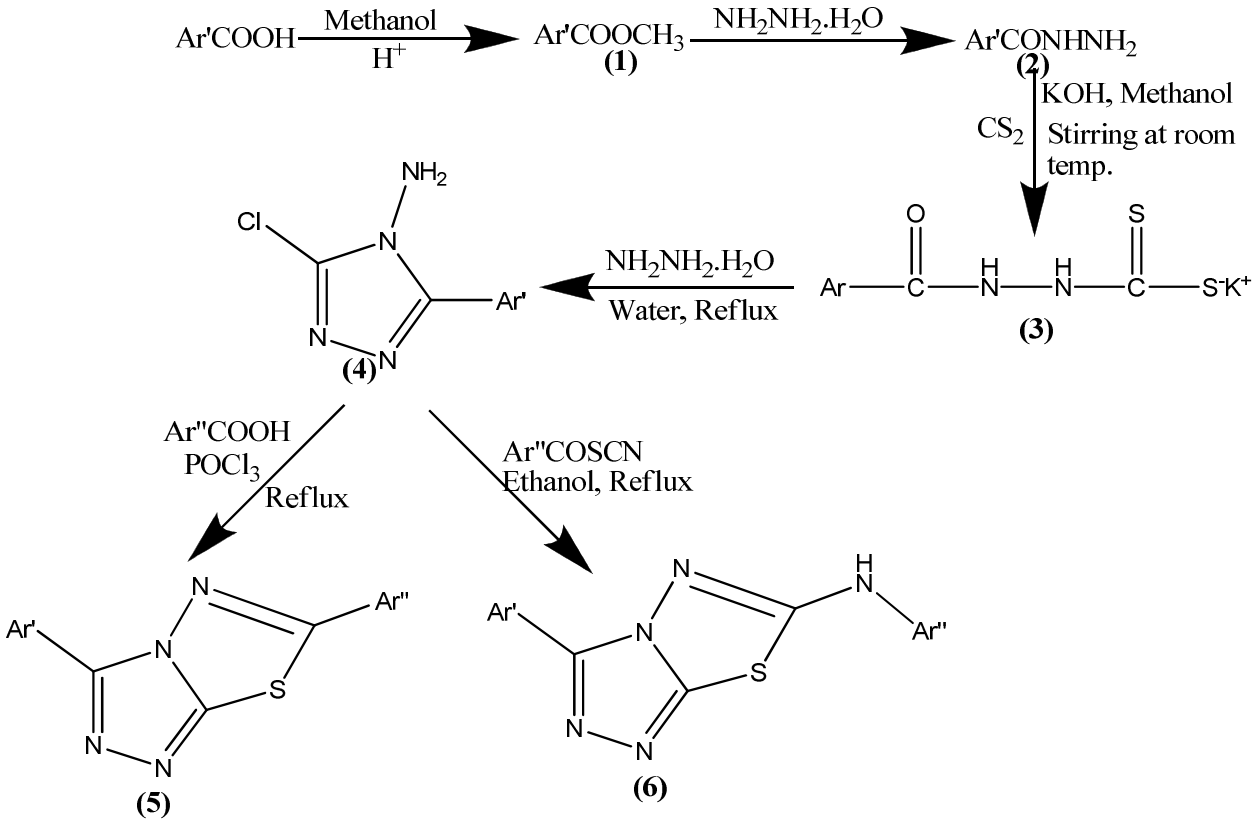
The reaction sequence employed for the synthesis of title compounds are depicted in **Scheme-1**. Esterification of substituted aromatic acids with methanol followed by hydrazinolysis with hydrazine hydrate resulted in compound **2**. The acid hydrazide**2** on reaction with carbon disulfide with methanolicpotassium hydroxide affords the corresponding intermediate potassium dithiocarbazinate**3**. The required 4-amino-5-substituted phenyl-4H-1,2,4-triazole-3-thiol **4** was synthesized by refluxing compound **3** with excess of hydrazine hydrate. Condensation of **4** with various aromatic acids in the presence of phosphorus oxy chloride yielded 3,6-disubstituted-1,2,4-triazolo-[3,4b][1,3,4]thiadiazole**5a-5b** and with various aroylthiocynate in ethanol under reflux condition gives N,3-disubstituted-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazol-6-amine **6a-6b**. The structure assignments of new compounds were based on their analytical and spectral data. The IR spectra of the compound **4** showed a characteristic weak absorption band at 2665 cm^{-1} attributed to SH group, disappeared in the compounds **5a-5b** and **6a-6b** indicated the formation of triazolothiadiazole ring system. Further the ^{1}H NMR spectra of the synthesized triazoles**4** showed two characteristic broad singlet at δ 13.8 and 5.8, due to SH proton and NH_2 groups respectively. The absence of these absorption due to SH and NH_2 in compounds **5a-5b** and **6a-6b** established that the triazoles had converted to triazole-thiadiazole by reacting with –COOH groups of various acids and with various aroylthiocyanates. In summary all the synthesized compounds exhibited satisfactory spectral data consistent with their structures.

Table 1. Antifungal activity of target compounds

Code	Ar'	Ar"	*A.foeniculum*	*A.niger*	*P.chrysogenum*
			Minimum inhibitory concentration (MIC) in µg/ml/ Zone of Inhibition		
3a	Phenyl	Phenyl	>100	80/10	>100
3b	4-nitrophenyl	Phenyl	>100	>100	>100
4a	Phenyl	Phenyl	57.14/14	>100	>100
4b	4-nitrophenyl	Phenyl	100/8	>100	>100
5a	Phenyl	Phenyl	>100	>100	>100
5b	4-nitrophenyl	Phenyl	>100	80/10	>100
6a	Phenyl	Phenyl	100/8	>100	>100
6b	4-nitrophenyl	Phenyl	>100	>100	>100
Ketoconazole	-	-	2/10	2.5/8	2/10

All the Synthesized compounds**(3-6)** were screened for their antigungal activity against three fungal strains viz. *Aspergillusfoeniculum*, *Aspergillusniger*, *Penicilliumchrysogenum* in dimethyl sulfoxide (DMSO).

Scheme 1: Synthesis of target compounds



Most active compound among all the synthesized compounds is **4a** (4-amino-5-phenyl-4H-1, 2, 4-triazole-3-thiol). This compound inhibited the growth of *A.foeniculum*(MIC 57.14 µg/ml and Zone of inhibition 14 mm) followed by **3a** and **5b** (dithiocarbazinate of benzoic acid hydrazide and3-(4-nitrophenyl)-6-phenyl-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole). These compounds inhibit the growth of *A.niger* (MIC 80µg/ml and Zone of inhibition 10 mm). Compound **6a** (N,3-diphenyl-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazole-6-amine) also showed activity against *A. foeniculum* (MIC 100 µg/ml, Zone of inhibition 8 mm.).

From these studies it has been revealed that *A.foeniculum*, on cyclization shows activity and A. niger shows activity in both non cyclized and in cyclized form,while*P. chrysogenum*may show activity but only above 100µg/ml.

Table 2. Antibacterial Activity of target compounds

Code	Ar'	Ar''	*H.pylori*	*P.aeroginosa*	*E.coli*	*S.aurius*	MRSA
			Minimum inhibitory concentration (MIC) µg/ml/Zone of Inhibition				
3a	Phenyl	Phenyl	>100	>100	>100	>100	>100
3b	4-nitrophenyl	Phenyl	>100	>100	>100	>100	>100
4a	Phenyl	Phenyl	>100	>100	>100	>100	>100
4b	4-nitrophenyl	Phenyl	>100	>100	>100	>100	>100
5a	Phenyl	Phenyl	>100	>100	100/8	>100	>100
5b	4-nitrophenyl	Phenyl	10/8	>100	13.33/6	66.66/12	57.14/14
6a	Phenyl	Phenyl	>100	>100	>100	100/8	>100
6b	4-nitrophenyl	Phenyl	>100	>100	57.14/14	13.33/6	80/10
Levofloxacin	-	-	0.04/18	0.48/13	0.06/12	1.24/10	3.12/8

The antibacterial activity of synthesized compounds **(3-6)** was screened against five bacteria viz. *Helicobactor pylori*, *Pseudomonasaeroginosa*, *Escherichia coli* (Gram –vestrains) and *Staphylococcus aureus* and Methcyclin Resistant Strain (MRSA) bacteria (Gram +ve strains).

The most potent compound was **5b** (3-(4-nitrophenyl)-6-phenyl-[1, 2, 4]-triazolo [3, 4-b] [1, 3, 4] thiadiazole). This compound inhibited the growth of *H.pylori* (MIC 10µg/ml, Zone of inhibition 8mm),*E.coli* (13.33 µg/ml,Zone of

inhibition 6mm), *S.aurius* (MIC 66.66 µg/ml,Zone of inhibition 12mm) and MRSA (MIC 57.14 µg/ml,Zone of inhibition 14mm).

The compound **6b**(3-(4-nitrophenyl)-6-phenyl-[1, 2, 4]-triazolo [3, 4-b] [1, 3, 4] thiadiazol-6-amine) was also showed good antibacterial activity. This compound inhibited the growth of three bacteria viz. *E.coli* (MIC 57.14 µg/ml,Zone of inhibition 14 mm),*S.aureus*(13.33 µg/ml, Zone of inhibition 6mm), MRSA (80 µg/ml and Zone of inhibition 10mm).

Compound **5a** (3,6-diphenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole) inhibited activity of a bacteria *E.coli* (MIC 100 µg/ml and Zone of inhibition 8 mm).

From the above studies it has been revealed thattriazolothiadiazoles are more potent antibacterial agents than triazoles. And among triazolothiadiazoles compound having nitro substitution at para position of phenyl group (at 3rd position) are more active than the compound having unsubstituted phenyl group.

CONCLUSION

In conclusion, this study has resulted in new antibacterial and antifungal agents.

Acknowledgement
Sincere thanks by the authors to the Director and Head of the Department, Pharmacy Department, Saroj Institute of Technology and Management, Lucknow.

REFERENCES

[1]D. H. Boschelli,D. T. Connor,D. A.Barnemierer, *J.Med. Chem*, **1993**,36, 1802.
[2] A. Ikizler, E. Uzanali, A. Demirbas, *Indian J .Pharm. Sci* ,**2005**, 5, 289.
[3] F. Malbec, R. Milcent, P.Vicotr, A.M. Bure, *J.Het.Chem*, **1984,** 21, 1769.
[4] M. Barboni, M. Cimpoesu, C. Guran, C.T.Supuran, *Met Based Drugs*, **1996**,3, 5, 227.
[5] G. Turan-Zitouni, A. Ozdemir ,Z.A. Kaplanikli , K. Benkli, P. Chevallet, G. Akalin,*Eur.J.Med.Chem*,**2007**,43,5, 981.
[6] J.T. Wit Koaski, R.K. Robins, R.W.Sidwell, L.N.Simon, *J. Med .Chem*, **1972**, 15, 150.
[7] K. Cooper, J. Steele, E P 329357, *ChemAbstr*, **1990**, 112, 76957.
[8] N.D. Heindel, J.R. Reid, *J. Heterocycl. Chem.*, **1980**, 17**,** 1087.
[9] B.S. Holla, B. Kalluraya, K.R. Sridhar, E. Drake, L.M. Thomas, K.K. Bhandary, M.S. Levine, *Eur. J. Med. Chem*. **(1994)**, 29,301.
[10] V.Mathew, J. Keshavayya, V.P. Vidya, Acharya, B.M. Reddy. *Eur. J. Med. Chem*.,**(2006)**,41, 1048.
[11]B.S. Holla, P.M. Akberali, M.K.Shivananda. *IlFarmaco***2001**, *56*, 919.
[12] D.L. Coffen, R.I. Fryer, U.S. Patent, 3,849,434 1974; Chem. Abstr., 82, 73044v, 1975.
[13] D.R. Abernelly, D.J. Greenblatt, M Divoll, R.I. Shader,*J ClinPscychiatary*,**1983** 44, 8 Pt_2, 45-47.
[14] A. Brucato, A. Coppola, S. Gianguzza, P.M. Provenzano, *Boll. Soc. Ital. Biol. Sper.*,**1978**, 54, 1051.
[15]H.A.Burch, W.O. Smith, *J. Med. Chem*., **1966**, 9, 405.
[16] A. Foroumadi, S. Mansouri, Z. Kiani, A. Rahmani, *Eur. J. med. Chem.*, (**2003**),38, 851.
[17] V.J. Ram, L. Mishra, N.H. Pandey, D.S. Kushwaha, L.A.C. Pieters, A.J. Vlietinck, *J. heterocycl. Chem.*, **1990**, 27, 351.
[18] N. Ergenc, E. Ilhan, G. Ötük, *Pharmazie*, **1992**,47, 59.
[19] B.S. Holla, C.S. Prasannaa, B. Poojary, K.S. Rao, Sridhara, *Indian J. Chem.*,**2006**45B, 2071.
[20] Mithun Ashok, B. SrivaramaHolla, *J. Pharmacol. Toxicol.*,**2007**2, 3, 256-263.
[21] N.Kalyoncuoolu, S.Rollas, D. Sür-Altiner, Y. Ygenoolu, Ö. Ano, *Pharmazie*, **1992**,47, 796.
[22] S.Rollas,N, Kalyoncuoolu, D. Sür-Altiner, Y. Ygenoolu, *Pharmazie*, 1993, 48, 308.
[23] I. Mir, M.T. Siddiqui, A. Comrie, *Tetrahedron*, **1970**,26, 5235.
[24] W. Rudnicka, H. Foks, M. Janowiec, Z. Zwolska-Kwiek, *Acta Pol. Pharm.*,1986,43, 523
[25] B.S. Holla, B. Veerendra, M.K. Shivananda, BojaPoojary, *Eur. J. Med. Chem.*, **2003**,38, 59.
[26] A.Duran, H.N. Dogan, S.Rollas,*Farmaco*, **2002**, 57, 559.
[27] H.L. Yale, J.J. Piala, *J .Med. Chem.*, **1966**,9, 42.
[28] M.H. Shah, M.Y. Mhasalkar, M.V. Palki, C.V. Deliwala, U.K. Sheth, *J.Pharm. Sci.*, 1969, 58, 1398.
[29] M.Y. Mhasalkar, M.H. Shah, S.T. Nikam, K.G. Anantanarayanan, C.V. Deliwala, *J. Med. Chem.*,**1970**,13, 672.
[30] KaliappanIlango,ParthibanValentina. *Eur. J. Chem.* **2010**, 1, 1, 50.
[31] Sun Xiao-Wen, Zhang Yan, Zhang Zi-Yi, Wang Qin, Wang Shu-Fang,*Indian J.Chem.*,**1999**, 38B, 3, 380.
[32] R.H. Udupi, G.V. Suresh, S.R. Setty, A.R. Bhat,*J. Indian Chem. Soc*. **2000**, *77*, 302.

[33] Nizamuddin, M. Gupta, M.H. Khan, M.K. Srivastava,*J. Sci. Ind. Res*. **1999**, 58, 538.
[34] F.P.Invidiata, D. Simoni, F. Scintu, N. Pinna,*Farmaco*. **1996**, *51*, 659.