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Der Pharma Chemica, 2012, 4 (2):639-643
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis, characterrization and biological evaluation of 2,6-diphenyl-3-(4-(3-phenyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)phenyl)-2*H*-1,3,5-oxadiazine-4(3*H*)-thione

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ABSTRACT

4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol ***(1)*** *prepared by treating benzoic acid hydrazide successively with CS_2,-KOH and NH2.NH2,give the nitrogen bridge head fused heteocycles* ***(3)*** *on reacting with N-acetyl-p-Amino benzoic acid followed by hydrolysis. It was on facile condensation reaction with various substituted aromatic aldehydes yields Schiff bases/anils/Azomethines* ***(4a-h).*** *These anils on cyclo- addition reaction with benzoyl isothiocyanate afforded 1,3,5-Oxadiazine* ***(5a-h).*** *These compounds were screened for activities against bacterial and fungal strains.*

Keywords: Schiff bases, *1,3,5-Oxadiazine*, Cyclo-addition reaction, facile condensation, Anti microbial activity.

INTRODUCTION

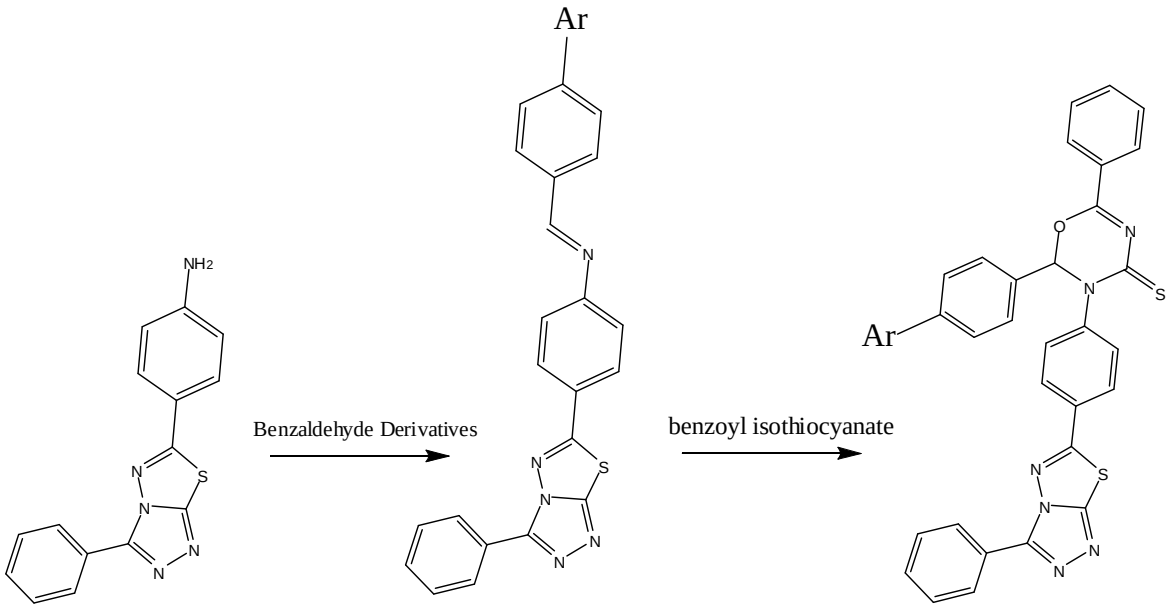
Literature survey reveals that 1,2,4-triazole nucleus is associated with diverse pharmacological activities such as anti-inflammatory[1], diuretic[2], antiviral[3], antihypertensive[4], anthalmentic[5], bactericidal[6], anticonvulsant[7], herbicidal[8], insecticidal and acaricidal[9], fungicidal[10], antimicrobial[11], anticancer and anti-HIV[12], plant growth regulator[13], antiieishmanial[14], antitumor[15], antidepressant and anxiolytic[16],anti-tuberculosis[17], mycobacterial activity[18], A2A receptor antagonists[19], corrosion inhibitor[20], analgesic[21] and antifungal activity[22]. Atsuo have reported triazoles as antiheumatic agents[23]. Monammad has also reported anti-inflammatory activity of 1,2,4-triazole derivatives[24]. Jag mohan have synthesized thiazolo triazoles and studied their antimicrobial activity[25].

As a part of surge of interest in heterocyclic that have been explored for developing pharmaceutically important molecule *1,3,5-Oxadiazine* [26-27] have played an important role in medicinal chemistry. Moreover, they have been studied extensively because of their ready accessibility and broad spectrum of biological activities.

Biological activities
Antibacterial Activity
The Compounds **(5a-h)** were tested for in vitro antibacterial activity against gram -ve bacteria Escherichia.Coli and Peudomonas.Aeruginosa, and gram +ve bacteria, Staphylococcus.Aureus and Bacillus Subtills. The standard drugs used were Ampicillin and tetracycline. The investigation of antibacterial screening is reported in **Table I** revealed that some of the newly synthesized compounds showed moderate to good inhibition at 100 µg/ml in DMF.Compounds **5d, 5e, 5f, 5g, 5h, 5g** exhibited good activity against all the four bacterial strains. Compounds **5f** and **5h** showed good activity against E.Coli and S. Aureus bacterial strains.

Antifungal Activity

The compounds **(5a-h)** were tested for in vitro antifungal activity against Candida. Albicans and Aspergillus. Niger. The standard drug used was Griseofulvin. The investigation antifungal screening is reported in **Table I**. Compound **5d, 5f, 5h** shows good activity against C. Albicans fungal strain. Rest of all compounds not exhibit good activity against both fungal.



(3) (4 a -h) (5 a -h)

where Ar - a)- phenyl
b) - 4 - methoxy phenyl
c) - 4 - Hydroxy phenyl
d)- 2 - hydroxy phenyl
e)- 4 - methyl phenyl
f)- 3,4 - methylenedioxy phenyl
g) - 4 - hydroxy - 3 - methoxy phenyl
h)- 3,4 -diethoxy phenyl

Scheme

MATERIAL AND METHODS

Melting points were determine with Buchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer PE-1600 FTIR Spectrometer in KBr disc. 1H NMR spectra were recorded on a Varian 400 spectrometer in DMSO-d6 as a solvent and TMS as an internal standard. Peak values are shown in δ ppm. EI-MS spectra were measured on a Waters Mass Spectrometer. All of the solvents and materials were reagent grade and purified as required.

Preparation of 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol (**1**), 3-(phenyl)-6-(4-N-acetylamino phenyl) [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (**2**) and 3-(phenyl)-6-(4-amino phenyl) [1,2,4]triazolo[3,4b] [1,3,4]thiadiazole (**3**) were prepared by method reported in literature [28]

Preparation of arylidine – [3,6-(di phenyl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole] (4a-h) were prepared by method reported in literature.[29]

Preparation of 2,6-diphenyl-3-(4-(3-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)phenyl)-2H-1,3,5-oxadiazine-4(3H)-thione (**5 a-h**)

General procedure

A mixture of Schiff bases **(4a-h)** (0.002 mole) and triethyl amine (TEA) (0.004 mole) was dissolved in 1,4-dioxane (50 ml), cooled, and stirred. To this well-stirred cooled solution benzoyl isothiocyanate (0.004 moles) was added

drop wise within a period of 30 minutes. The reaction mixture was then stirred and reflux for an additional 3 hours and left at room temperature for 48 hours. The resultant mixture was concentrated, cooled, poured into ice-cold water, and then air-dried. Recrystallization from absolute ethanol gave 1,3,5-oxadiazine **(5a-h)**, which were obtained in 55-60% yield.

2,6-diphenyl-3-(4-(3-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)phenyl)-2H-1,3,5-oxadiazine-4(3H)-thione (5a)

M.P: 192-194^{o}C; IR(KBr,cm^{-1}): 3030-3080(Aromatic C-H Stretching), 1350 (C=S stretching); ^{1}HNMR(δ ppm): 6.14-7.90 (15H, m, Aromatic) 5.64 (1H, s, 1H for oxadiazine), ^{13}CMR (δppm): 169(C=O), 136-145 (Triazole+ thiadiazole), 156.3 O–C=N , *Anal*. Calcd. For $C_{30}H_{20}N_6OS_2$ (544.65); C,66.16; H,3.70; N,15.43; S,11.77; Found: C,66.01; H,3.50; N,15.43; S,11.47. Yield,60%

2-(4-methoxyphenyl)-6-phenyl-3-(4-(3-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)phenyl)-2H-1,3,5-oxadiazine-4(3H)-thione (5b)

M.P: 198-200^{o}C; IR(KBr,cm^{-1}): 3030-3080(Aromatic C-H Stretching), 1350 (C=S stretching); ^{1}HNMR(δ ppm): 6.14-7.90 (15H, m, Aromatic) 5.64 (1H, s, 1H for oxadiazine), ^{13}CMR (δppm): 169(C=O), 136-145 (Triazole+ thiadiazole), 156.3 O–C=N, 46 (-OCH_3); *Anal*. Calcd. For $C_{31}H_{22}N_6O_2S_2$ (574.88); C,64.79; H,3.86; N,14.62; S,11.17. Found: C,64.67; H,3.56; N,14.7; S,11.10. Yield,65%

2-(4-hydroxyphenyl)-6-phenyl-3-(4-(3-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)phenyl)-2H-1,3,5-oxadiazine-4(3H)-thione (5c)

M.P: 189-191^{o}C; IR(KBr,cm^{-1}): 3030-3080(Aromatic C-H Stretching), 1350 (C=S stretching); ^{1}HNMR(δ ppm): 6.14-7.90 (15H,m,Aromatic) 5.64 (1H, s, 1H for oxadiazine), ^{13}CMR (δppm):169(C=O), 136-145 (Triazole+ thiadiazole), 156.3 O–C=N, 119(-C-O-H); *Anal*. Calcd. For $C_{30}H_{20}N_6O_2S_2$(560.65); C,64.27;H,3. 60; N,14.99; S,11.44. Found: ; C,64.17; H,3. 56; N,14.79; S,11.37. Yield,55%

2-(2-hydroxyphenyl)-6-phenyl-3-(4-(3-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)phenyl)-2H-1,3,5-oxadiazine-4(3H)-thione (5d)

M.P: 188-190^{o}C; IR(KBr,cm^{-1}): 3030-3080(Aromatic C-H Stretching), 1350 (C=S stretching); ^{1}HNMR(δ ppm): 6.14-7.90 (15H,m,Aromatic) 5.64 (1H, s, 1H for oxadiazine), ^{13}CMR (δppm): 169(C=O), 136-145 (Triazole+ thiadiazole), 156.3 O–C=N, 135(-C-O-H); *Anal*. Calcd. For $C_{30}H_{20}N_6O_2S_2$(560.65); C,64.27; H,3. 60; N,14.99; S,11.44. Found: ; C,64.11; H,3. 50; N,14.80 ; S,11.30.Yield,55%

6-phenyl-3-(4-(3-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)phenyl)-2-p-tolyl-2H-1,3,5-oxadiazine-4(3H)-thione (5e)

M.P: 194-195^{o}C; IR(KBr,cm^{-1}): 3030-3080(Aromatic C-H Stretching), 1350 (C=S stretching); ^{1}HNMR(δ ppm): 6.14-7.90 (15H,m,Aromatic) 5.64 (1H , s, 1H for oxadiazine), ^{13}CMR (δppm):169(C=O), 136-145 (Triazole+thiadiazole), 156.3 O–C=N,; *Anal*. Calcd. For $C_{31}H_{22}N_6OS_2$(558.68); C,66.65; H,3.97; N,14.99; S,11.48;. Found: C,66.55; H,3.87; N,14.77; S,11.38. Yield,65%

2-(benzo[d][1,3]dioxol-5-yl)-6-phenyl-3-(4-(3-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)phenyl)-2H-1,3,5-oxadiazine-4(3H)-thione (5f)

M.P: 182-183^{o}C; IR(KBr,cm^{-1}): 3030-3080(Aromatic C-H Stretching), 1350 (C=S stretching),1200 (Aryl-alkyl ether); ^{1}HNMR(δ ppm): 6.14-7.90 (14H,m,Aromatic) , 5.64 (1H , s, 1H for oxadiazine),5.8 (2H of –O-CH_2-O-) ;^{13}CMR (δ,ppm):169(C=O), 136-145 (Triazole+thiadiazole),91 (–O-CH_2-O-);*Anal*.Calcd.For $C_{31}H_{20}N_6O_3S_2$ (588.66)C,63.25;H,3.42;N,14.28;S,10.89;.Found: C,63.10;H,3.40;N,14.20;S,10.80.Yield,55%

2-(4-hydroxy-3-methoxyphenyl)-6-phenyl-3-(4-(3-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)phenyl)-2H-1,3,5-oxadiazine-4(3H)-thione (5g)

M.P: 198-199^{o}C; IR(KBr,cm^{-1}): 3030-3080(Aromatic C-H Stretching), 1350 (C=S stretching), 1200 (Aryl-alkyl ether); ^{1}HNMR(δ ppm): 6.14-7.90 (14H,m,Aromatic) 5.64 (1H , s, 1H for oxadiazine),4.3 (3H,s,-OCH_3), 3.36(1H,s, OH) ;^{13}CMR (δ,ppm):169(C=O), 136-145 (Triazole+thiadiazole), 46 (-OCH_3), 135(-C-OH); *Anal*. Calcd. For $C_{31}H_{22}N_6O_3S_2$ (590.67); C,63.03; H,3.75; N,14.23; S,10.86;. Found: C,63.93; H,3.65; N,14.10; S,10.70. Yield,55%

2-(3,4-diethoxyphenyl)-6-phenyl-3-(4-(3-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)phenyl)-2H-1,3,5-oxadiazine-4(3H)-thione (5h)

M.P: 190-191^{o}C; IR(KBr,cm^{-1}): 3030-3080(Aromatic C-H Stretching), 1350 (C=S stretching), 1200 (Aryl-alkyl ether); ^{1}HNMR(δ ppm): 6.14-7.90 (14H,m,Aromatic) 5.64 (1H , s, 1H for oxadiazine),2.9 (4H,q,-2CH_2-), 2.5(6H,d, -2CH_3) ;^{13}CMR (δ ppm): 169(C=O), 136-145 (Triazole+thiadiazole),135(-C-OH);*Anal*. Calcd. For$C_{34}H_{26}N_6O_3S_2$ (632.75);C,64.54;H,4.46;N,13.28;S,10.14.Found: C,64.54;H,4.46;N,13.28;S,10.14.Yield,53%

TABLE I Antibacterial Activity and Anti fungal activity of compounds (**5 a-h**)

	Antibacterial Activity				Anti fungal activity	
	Zone of Inhibition (in mm)					
	Gram +ve		Gram -ve			
Compounds	B.Subtillis	S.Aureus	E.Coli	P's.Aeruginosa	C. Albicans	A. Niger
5a	9	13	10	12	11	12
5b	16	10	12	8	8	14
5c	11	9	7	10	12	9
5d	15	12	18	15	16	17
5e	18	13	14	9	7	12
5f	19	18	16	21	15	16
5g	15	15	14	12	10	14
5h	14	14	17	22	14	15
Ampicillin	19	15	20	21	-	-
Tetracyclin	20	20	15	18	-	-
DMF	6	5	5	5	-	-
Griseofulvin	-	-	-	-	22	24

RESULTS AND DISCUSSION

preparation of 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol (**1**) of potassium-benzoic acid hydrazide dithiocarbamate reaction with hydrazine hydrate in presence of acetic acid were prepared according to the literature procedure[28] The structure of (**1**) was established by spectroscopic evidence. The compound (1) was reaction with N-Acetyl-p-amino benzoic acid in the presence of $POCl_3$ to get corresponding 3-(phenyl)-6-(4-N-acetylamino phenyl) [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (**2)** by the reported method[28]it can be hydrolyzed to 3-(phenyl)-6-(4-amino phenyl) [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole(**3)** by ethanol/HCl. It is characterized by elemental analysis, IR Spectral studies, and NMR Spectral studies. The IR Spectra of the compound (**3)** show the bands at 3362 cm^{-1} for NH_2 group.

This hydrolyzed compound (**3)** was reacted with various aromatic aldehydes in the presence of acetic acid to yields Schiff bases (**4a-h)** by the reported method [30] were then characterized by the elemental analysis, IR Spectral studies, and NMR Spectral studies. The IR Spectra of Schiff bases show the prominent band at 1630cm^{-1} for the anils (CH=N) group.

These Schiff bases on cyclo addition reaction with benzoyl isothiocyanate in the presence of tri ethyl amine afforded 1,3,5-oxadiazine (**5a-h)**. The structure of these compounds has been confirmed by the elemental analysis, IR Spectral studies, and NMR Spectral studies. These compounds show the bands at 1620, 1350 cm-1 for C=N , C=S group. All the compounds show the NMR signals for different kinds of protons at their respective positions.

Acknowledgment

We are thankful to the department of chemistry, Himchandracharya North Gujarat University, patan, Gujarat (India) for providing the necessary facilities for the research work.

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