© 2019 IJSRST | Volume 6 | Issue 2 | Print ISSN: 2395-6011 | Online ISSN: 2395-602X
Themed Section: Science and Technology
DOI : https://doi.org/10.32628/IJSRST

Studies on Triazolo-Thiadiazine Containing Furan Moiety Fused Heterocycles

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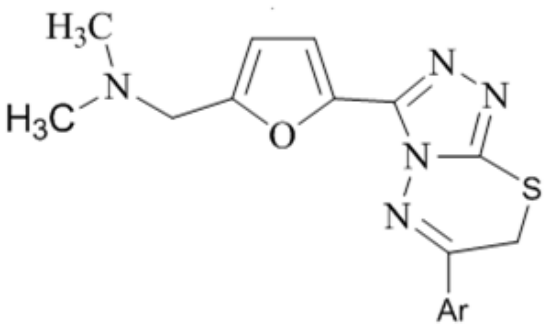
ABSTRACT

Methyl-5-(N,N-dimethyl amino methyl)-2-furoate(1) was on hydrazinolysis to afford acid hydrazide (2).Treatment of (2) with CS_2 yield 4-amino-5-[-(N,N-dimethylamino methyl) furan-2-yl]-4H-1,2,4-triazole-3-thiol(3). The –SH and $–NH_2$ adjacent group in this compound may entail formation of fused heterocycle i.e. triazolo-thiazine. Thus, condensation of (3) with various phenacyl bromides(4a-f), yield triazolo-thiazines(5a-f). All the novel fused compounds (5a-f) were characterized by C, H, N, S analysis and spectral data. The antimicrobial activities of all the compounds were also evaluated by using common microbes. The compounds showed good activities.

Keywords : Antibacterial Activities and Antifungal Activities, Furan, Spectral Studies, Triazolo-Thiadiazine

Graphical Abstract



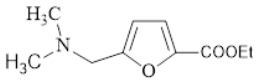
fused triazolo-thiazine derivatives

I. INTRODUCTION

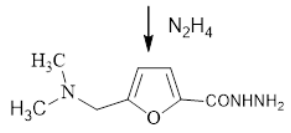
Nitrogen containing heterocyclic compounds are present in natural resources widely and they are more active pharmaceutically.[1]. The development of new N-heterocycles with wide structural variation is one of recent interest of researcher[2-4]

In current era, a concentration of fused derivatives based on 4-amino-5-marcapto-1,2,4-triazole has expected remarkable consideration because of their biological significance. Compounds having triazole or thiadiazole as a moiety are represented for wide range of pharmacological properties for example anticancer, anti-inflammatory, antimicrobial, antibacterial, antifungal, insecticidal and herbicidal[5-15]. Patel et al. reported some triazolo-thiazine fused heterocycles based on 4-amino-3-aryl-5-marcapto-1,2,4-triazole[16]. The present author reported recently the furan ring containing triazolo-

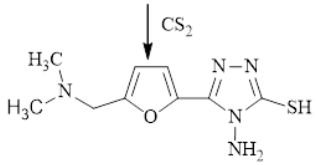
thiazine derivatives [17]. In continuous of our work[17] the present communication comprises the synthesis of N-N-dimethyl-1-[5-(6-aryl-7H-[1,2,4] triazolo[3,4-b] [1,3,4] thiadiazin-3-yl)furan-2-yl]methanamine (2a-f).The synthetic approach is shown in scheme-1.



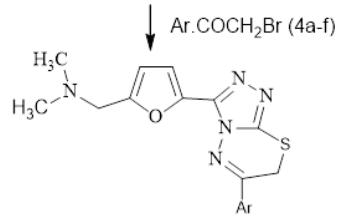
Methyl-5-(N,N-dimethyl amino methyl)-2-furoate**(1)**



Methyl-5-(N,N-dimethyl amino methyl)furan-2-carbohydrazide **(2)**



4-amino-5-[-(N,N-dimethylamino methyl) furan-2-yl]-4H-1,2,4-triazole-3-thiol**(3)**



N-N-dimethyl-1-[5-(6-aryl-7H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazin-3-yl)furan-2-yl] methanamine **(5a-f)**

Where, Ar=(a) C_6H_5, (b) 4-ClC_6H_4, (c) 4-Br-C_6H_4, (d) 3-$NO_2C_6H_4$ (e) 2,4-$Cl_2C_6H_3$ (f) 4-FC_6H_4

II. RESULTS AND DISCUSSION

It was observed that N-N-dimethyl-1-[5-(6-aryl-7H-[1,2,4]triazolo[3,4-b] [1,3,4] thiadiazin-3-yl)furan-2-yl]methanamine (5a-f) have been synthesized by the reaction of 4-amino-5-(5-((dimethylamino)methyl)furan-2-yl)-4H-1,2,4-triazole-3-thiol (3) with various phenacyl bromide(4a-f). The structures of (5a-f) were confirmed by elemental analysis and IR(KBr,cm^{-1}) spectra showing an absorption band at 3020-3075 (C–H aromatic st.),1675 (C=N st.),1530 (C=C–st.),1235 (–N–N=C– st.),1145(C-O) 690 (C–S–C), 2815-2850,1375(CH_3,CH_2), 1120(C-N), 1080(C-Cl),680(C-Br), 1540,1370 (NO_2), 1360 (C-F). The IR spectrum of 5a–f showed the most relevant peaks of triazolo-thiadiazine ring. The band at about 1675 cm^{-1} and 1530 cm^{-1} corresponding to –C=N stretching and –C=C– stretching. The band at about 1235 cm^{-1} and 690 cm^{-1} corresponding to –N–N=C– stretching and –C–S–C– stretching indicating the formation of triazolo-thiadiazine derivatives.

^{1}H NMR (DMSO–d_6,δ ppm): 6.36- 7.20 (m, 2H, furan), 7.60–8.18 (m, 5H, Ar–H),2.38 (s, 6H, –CH_3),3.80(s,2H,-CH_2),4.46(s,2H,-CH_2). The C, H, N analysis data of all compounds are presented in Table -1.

The structures of 3 were confirmed by elemental analysis and IR(KBr,cm^{-1}) spectra showing an absorption band at 3075 (–C–H aromatic st.), 1675 (–C=N st.), 1530 (–C=C– st.), 1235 (–N–N=C– st.),1145(C-O),690 (–C–S–C– triazolo-thiadiazole),2815-2850 cm^{-1}(CH_3),2544(-SH),671(-C-S),3380(-NH_2). ^{1}H NMR (DMSO–d_6,δ ppm): 6.36 - 7.20(m,2H,furan),2.46 (s,6H,CH3),3.80 (s,2H, CH_2), 5.85(s,2H,-NH_2), 12.32(s, 1H, SH).

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in Scheme-1. The IR data also direct for assignment of the predicted structure. LC-MS data of compounds shows the molecular ion peak, which is consistent with their corresponding molecular weight.

III. EXPERIMENTAL

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR spectra were acquired at 400 MHz on a Bruker NMR spectrometer using DMSO–d_6 as a solvent as well as TMS an internal reference standard. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046.

Preparation of 4-amino-5-(5-((dimethylamino) methyl) furan-2-yl)-4H-1,2,4-triazole-3-thiol (3)

4-amino-5-(5-((dimethylamino) methyl) furan-2-yl)-4H-1,2,4-triazole-3-thiol (1) prepared by our earlier reported method.[17] 5-((dimethylamino)methyl)furan-2-carbohydrazide (2) (0.1 mol) was dissolved in 200 mL absolute alcohol containing potassium hydroxide (0.1 mol) at room temperature carbon disulfide was added in parts and was stirred for 18 hours at room temperature. 100 mL of diethyl ether was added and stirred for further 2 h. Hydrazine hydrate (0.1 mol) was added gradually to the above salt dissolved in 100 mL water with stirring and was refluxed for 9 h during which hydrogen sulphide gas evolved and the colour of the reaction mixture changed. It was then cooled and acidified with hydrochloric acid. The solid was isolated by filtration and recrystallised from ethanol to give compound (3).

Preparation of N-N-dimethyl-1-[5-(6-aryl-7H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazin -3-yl)furan-2-yl] methanamine (5a-f)

A mixture of 4-amino-5-(5-((dimethylamino)methyl)furan-2-yl)-4H-1,2,4-triazole-3-thiol (1) (0.01 mol) and various phenacyl bromide (a-f) (0.01mol) in anhydrous ethyl alcohol (30 mL) was reflux for 6-7 hrs. Then reaction mixture was cooled under tap water, then poured into cold H_2O. The solid product which precipitated was collected by filtration, washed with solid product with water, dried and crystallized from ethyl alcohol. The yields, melting points and other characterization data of these compounds are given in Table -1.

Table 1 :- Analytical Data and Elemental Analysis of Compounds (5a-f)

Compd.	Molecular formula (Mol.wt.)	Yield %	M.P.˚ ⁰C	Elemental Analysis			
				%C	% H	%N	%S
				Found Calcd.	Found Calcd.	Found Calcd.	Found Calcd.
5a	$C_{17}H_{17}N_5OS$ (339)	82	238	60.16 60.1	5.05 5.0	20.63 20.6	9.45 9.4
5b	$C_{17}H_{16}N_5OSCl$ (373.5)	76	245	54.61 54.6	4.31 4.2	18.73 18.7	8.58 8.5
5c	$C_{17}H_{16}N_5OSBr$ (418)	73	234	48.81 48.8	3.86 3.8	16.74 16.7	7.67 7.6
5d	$C_{17}H_{16}N_6O_3S$ (384)	77	246	53.12 53.1	4.20 4.1	21.86 21.8	8.34 8.3
5e	$C_{17}H_{15}N_5OSCl_2$ (407)	72	248	50.01 49.9	3.70 3.6	17.15 17.1	7.85 7.8
5f	$C_{17}H_{16}N_5OSF$ (357)	76	236	57.13 57.1	4.51 4.4	19.59 19.5	8.97 8.9

IV. BIOLOGICAL SCREENING

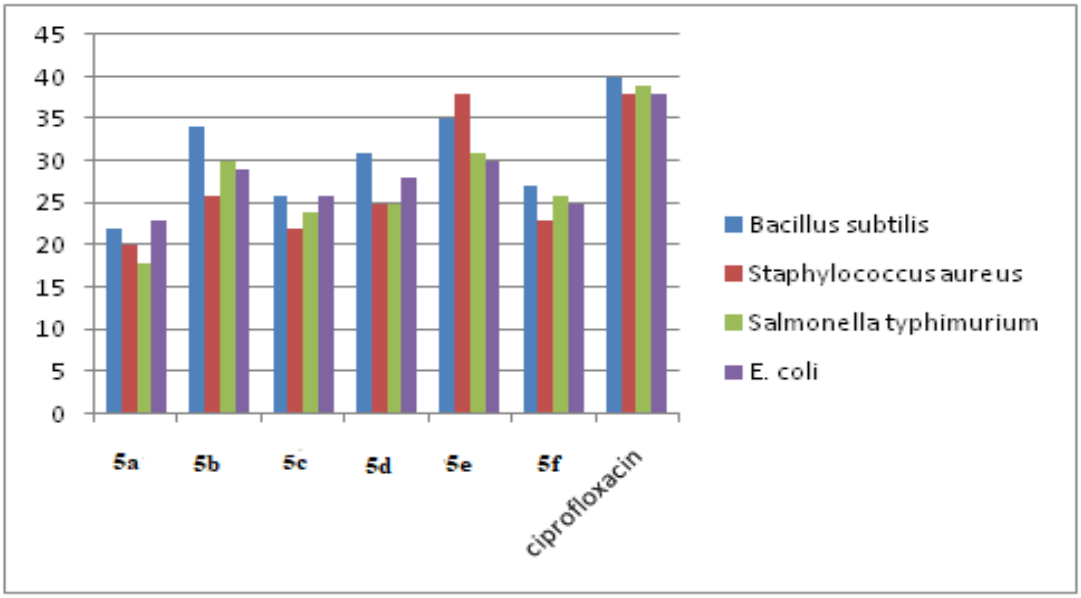
ANTIBACTERIAL ACTIVITIES

The antibacterial activities of all the compounds were studied against gram-positive bacteria (*Staphylococcus aureus and Bacillus subtilis*) and gram-negative bacteria (*E.coli, and Salmonella*

typhimurium) at a concentration of 50µg/ML by agar diffusion assay. The wells were dug in the media with the help of a sterile metallic borer. Recommended concentration (100 µl) of the test sample (1 mg/mL in DMSO) was introduced in the respective wells. Other wells supplemented with DMSO and reference antibacterial drug, ciprofloxacin were served as negative and positive controls, respectively. The plates were incubated immediately at 37˚C for 24 hours. Activity was determined by measuring the diameter of zones showing complete inhibition (mm). Growth inhibition was compared with the standard drug. In order to clarify any participating role of DMSO in the biological screening, separate studies were carried out with the solutions alone of DMSO and they showed no activity against any bacterial strains. The area of inhibition of zone measured in mm. Compounds 5e were found more toxic for microbes. Other compounds found to be less or moderate active shown in Tables -2.

Table:-3 Antibacterial Activity of Compounds (5a-f)

Compounds	Gram +Ve		Gram –Ve	
	Bacillus subtilis	*Staphylococcus aureus*	*Salmonella typhimurium*	*E. coli*
5a	22	20	18	23
5b	34	26	30	29
5c	26	22	24	26
5d	31	25	25	28
5e	35	38	31	30
5f	27	23	26	25
ciprofloxacin	40	38	39	38



V. Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Penicillium expansum, Botryodiplodia theobromae, Nigrospora sp., Trichothesium sp.* The antifungal drug, ketoconazole was used as a positive control. Antifungal screening for compounds (5a-f) and positive control was performed at a recommended concentration. The fungal strains were grown and maintained on potato dextrose agar plates. The cultures of the fungi were purified by single spore isolation technique. Each compound (5a–f) in DMSO solution was prepared for testing against spore germination of each fungus. The fungal culture plates were inoculated and incubated at 25± 2˚C for 48 h. The plates were then observed and the diameters of the zone of inhibition (in mm) were measured. The percentage inhibition for fungi was calculated after five days using the formula given below:

Percentage of inhibition =100(X-Y) / X

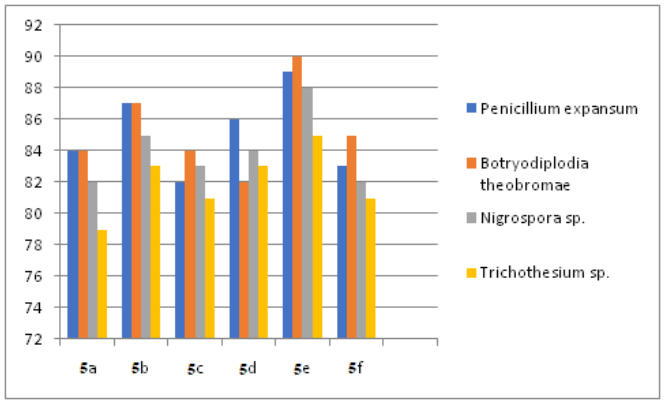
Where, X = Area of colony in control plate

Y = Area of colony in test plate

The fungicidal activity displayed by various compounds (5a-f) is shown in Tables-3.

Table 3 :- Antifungal Activity of Compounds (5a-f)

Zone of Inhibition at 1000 ppm (%)				
Compounds	*Penicillium expansum*	*Botryodiplodia theobromae*	*Nigrospora sp.*	*Trichothesium sp.*
5a	84	84	82	79
5b	87	87	85	83
5c	82	84	83	81
5d	86	82	84	83
5e	89	90	88	85
5f	83	85	82	81



VI. CONCLUSION

The novel fused heterocyclic ligand ,N-N-dimethyl-1-[5-(6-aryl-7H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazin-3-yl)furan-2-yl] methanamine (5a-f) synthesised by condensation of 4-amino-5-[-(N,N-dimethylamino methyl) furan-2-yl]-4H-1,2,4-triazole-3-thiol(3)with various phenacyl bromides(4a-f).The structures of fused compounds (5a-f) were characterized by C, H, N, S analysis and spectral data, which are consistent with predicted structure. The antimicrobial activities of all the compounds were showed good activities.

VII. ACKNOWLEDGMENT

The authors are thankful to Principal, Sheth M. N. Patel Science College, Patan for providing laboratory facilities for work.

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Cite this article as :

Venkataramana Kondepati, R. I. Patel, P. J. Vyas, " Studies on Triazolo-Thiadiazine Containing Furan Moiety Fused Heterocycles", International Journal of Scientific Research in Science and Technology(IJSRST), Print ISSN : 2395-6011, Online ISSN : 2395-602X, Volume 6, Issue 2, pp.885-890, March-April-2019.

Journal URL : https://ijsrst.com/IJSRST2183166