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Synthesis, spectroscopic and biological study of 3-(furan-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives

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ABSTRACT

A novel heterocyclic compounds N-(benzo[d]thiazol-2-yl)-2-(3-(furan-2-yl)-[1,2,4] triazolo [3,4-b][1,3,4]thiadiazol-6-yl)benzamide derivatives 5a–g have been synthesized by the reaction of 4-amino-5-(furan-4-yl)-4H-1,2,4-triazole-3-thiol 3 and 2-(benzo[d]thiazol-2-ylcarbamoyl) benzoic acid derivatives 4a–g. All the Synthesized compounds were characterized by elemental analysis, ^{1}H NMR, ^{13}C NMR, FT–IR and LC-MS spectral studies. Antibacterial activities were studied against gram positive and gram negative bacteria and antifungal activities of all the compounds were studied against various fungi.

KEYWORDS

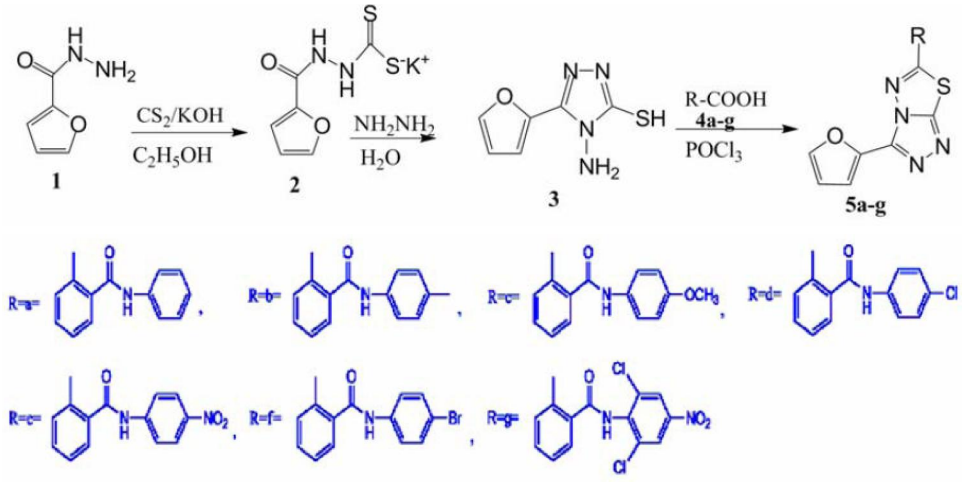
Heterocyclic compound;
Furan-2-carbohydrazide;
Amino-1,2,4-triazoles;
Spectral studies;
Antibacterial activities and antifungal activities.

INTRODUCTION

The last few decades have seen a flurry of activity in the synthesis and development of heterocyclic compound because of their important biological properties. Heterocyclic compounds bearing 1,2,4-triazole nucleus and their triazolothiadiazole derivatives have shown a broad spectrum of pharmacological properties such as antimicrobial[1-2], anti-inflammatory[3-4], anticonvulsant[5], anticancer[6-9], antitubercular[10] and antitumor activities[11]. Looking to the pharmacological importance, our main concern was to prepare such heterocyclic compounds which possess comparable biological activity by introducing amino-1,2,4-triazoles and triazolothiadiazoles segments together. Literature survey reveals that, not a single report was found in which compound 3 was reacted with 2-(benzo[d]thiazol-2-ylcarbamoyl) benzoic acid derivatives 4a–g to produce compound 5a–g. Hence the present communication comprises the synthesis of N-(benzo[d]thiazol-2-yl)-2-(3-(furan-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl) benzamide derivatives. The synthetic approach is shown in scheme-1.

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 and ^{13}C NMR spectra were



scheme 1

acquired at 400 MHz on a Bruker NMR spectrometer using DMSO–d6 (residual peak at δ ~2.5 or ~39.5 ppm,300æ%K) as a solvent as well as TMS an internal reference standard.. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046. Compound 1, 2 and 3 are reported. Compounds 4a-g was prepared by the reported method[12]. Compounds 5a-g synthesized by the method given below.

Synthesis of N-(benzo[d]thiazol-2-yl)-2-(3-(furan-2-yl)-[1,2,4] triazolo [3,4-b][1,3,4] thiadiazol-6-yl)benzamide derivatives 5a–g

An equimolar mixture (0.10 mol) of 4-amino-5-(furan-4-yl)-4H-1,2,4-triazole-3-thiol 3 and 2-(benzo[d]thiazol-2-ylcarbamoyl)benzoic acid derivatives 4a–g in phosphorus oxychloride (10 mL) was refluxed for 7 h. The reaction mixture was cooled to room temperature and then gradually poured onto crushed ice with stirring. The mixture was allowed to stand for few hours. The solid precipitates separated out was filtered, treated with dilute sodium hydroxide solution and washed thoroughly with cold water. The compound obtained was air dried and recrystallized from ethanol. Products were designated as 5a–g. The yields, melting points and other characterization data of these compounds are given in TABLE -1.

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[13]. 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 37ÚC 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 5g were found more toxic for microbes. Other compounds found to be less or moderate active shown in TABLE-2.

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–g) and positive control was performed at a recommended concen-

TABLE 1 : Analytical data and elemental analysis of compounds (5a-g)

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	Yield	M.P.* ^{0}C	Elemental Analysis							
					%C		% H		%N		%S	
					Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
5a	$C_{21}H_{12}N_6O_2S_2$ (444)	465	66	241	56.7	56.74	2.7	2.72	18.9	18.91	14.4	14.43
5b	$C_{22}H_{14}N_6O_2S_2$ (458)	478	65	238	57.6	57.63	3.0	3.08	18.3	18.33	13.9	13.99
5c	$C_{22}H_{14}N_6O_3S_2$ (474)	489	64	239	55.6	55.69	2.9	2.97	17.7	17.71	13.5	13.51
5d	$C_{21}H_{11}N_6O_2S_2Cl$ (478)	496	68	236	52.6	52.66	2.3	2.32	17.5	17.55	13.3	13.39
5e	$C_{21}H_{11}N_7O_4S_2$ (489)	505	70	234	51.5	51.53	2.2	2.27	20.0	20.03	13.1	13.10
5f	$C_{21}H_{11}N_6O_2S_2Br$ (521)	545	65	231	48.1	48.19	2.1	2.12	16.0	16.06	12.2	12.25
5g	$C_{21}H_9N_7O_4S_2Cl_2$ (556)	574	63	237	45.1	45.17	1.6	1.62	17.5	17.56	11.4	11.49

*** Uncorrected**

TABLE 2 : Antibacterial activity of compounds (5a-g)

Compounds	Gram +Ve		Gram –Ve	
	Bacillus subtilis	Staphylococcus aureus	Salmonella typhimurium	E. coli
5a	26	27	27	29
5b	29	26	27	29
5c	31	29	29	31
5d	38	35	34	36
5e	33	30	31	33
5f	36	32	32	35
5g	39	36	38	36
ciprofloxacin	40	38	39	38

tration. 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–g) in DMSO solution was prepared for testing against spore germination of each fungus. The fungal culture plates were inoculated and incubated at 25± 2ÚC 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-g) is shown in TABLES-3.

RESULTS AND DISCUSSION

It was observed that have been synthesized by the reaction of and. 4-amino-5-(furan-4-yl)-4H-1,2,4-triazole-3-thiol 3, on reaction with 2-(benzo[d]thiazol-2-ylcarbamoyl)benzoic acid derivatives 4a–g, yields novel heterocyclic compounds N-(benzo[d]thiazol-2-yl)-2-(3-(furan-2-yl)-[1,2,4] triazolo [3,4-b][1,3,4]thiadiazol-6-yl) benzamide derivatives 5a–g. The structures of (5a-g) were confirmed by elemental analysis and IR(KBr,cm^{-1}) spectra showing an absorption band at 3071 (–C–H aromatic st.), 1680 (–C=N st.), 1530 (–C=C– st.), 1230 (–N–N=C– st.), 690 (–C–S–C– triazolo-thiadiazole),2815-2850 cm^{-1} (-OCH_3),850(C-Cl),1350(C-NO_2),680(C-Br). The FTIR spectrum of 5a–g showed the most relevant peaks of triazolo-thiadiazole ring. The band at about 1680 cm-1 and 1533 cm-1 corresponding to –C=N stretching and –C=C– stretching. The band at about 1230 cm-1 and 688 cm-1 corresponding to –N–N=C– stretching and –C–S–C– stretching indicating the formation of triazolo-thiadiazole derivatives.

1H NMR (DMSO–d6,δ ppm): 9.30(s,1H,–NH),

TABLE 3 : Antifungal activity of compounds (5a-g)

	Zone of Inhibition at 1000 ppm (%)			
Compounds	**Penicillium expansum**	**Botryodiplodia theobromae**	**Nigrospora sp.**	**Trichothesium sp.**
5a	34	30	34	30
5b	33	32	32	29
5c	34	31	33	31
5d	39	36	36	34
5e	35	32	33	31
5f	38	35	35	33
5g	39	40	39	37
ketoconazole	41	42	40	39

6.86- 8.10 (m, 3H, furan), 7.20–8.18 (m, 8H, Ar–H),5b; 2.43 (s, 3H, –CH3),5c; 3.82(s, 3H, –OCH3). ^{13}C NMR (DMSO–d6, δ ppm): 173.3 (–N=C–S–), 167.1 (–N=C–S–), 165.2 (–C=O), 152.8 (–N=C–N–), 109-145.6(furan), 121.4-136.2(Ar–H). The C, H, N analysis data of all compounds are presented in TABLE -1.

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. The final structure of all compounds is confirmed by LC-MS. LC-MS data of all compounds are presented in TABLES-1.

REFERENCES

[1] T.Karabasanagouda, A.V.Adhikari, N.S.Shetty; European Journal of Medicinal Chemistry, **42**, 521–529 **(2007)**.

[2] M.F.El-Shehry, A.A.Abu-Hashem, E.M.El-Telbani; European Journal of Medicinal Chemistry, **45(11)**, 1906–1911 **(2010)**.

[3] G.Chawla, U.Kumar, S.Bawa, J.Kumar; Journal of Enzyme Inhibition and Medicinal Chemistry, **27**, 658–665 **(2012)**.

[4] A.Husain, M.A.Naseer, M.Sarafroz; Acta Poloniae Pharmaceutica.Drug Research, **66(2)**, 135–140 **(2009)**.

[5] A.Kamal, M.N.A.Khan, K.S.Reddy, Y.V.V.Srikanth, B.Sridhar; Chemical Biology & Drug Design, **71**, 78–86 **(2008)**.

[6] P.L.Zhao, A.N.Duan, M.Zou, H.K.Yang, W.W.You, S.G.Wu; Bioorganic & Medicinal Chemistry Letters, **22**, 4471–4474 **(2012)**.

[7] D.Sunil, A.M.Isloor, P.Shetty, K.Satyamoorthy, A.S.Bharath Prasad; Arabian Journal of Chemistry, **3**, 211–217 **(2010)**.

[8] M.Rashid, A.Husain, A.A.Siddiqui, R.Mishra; European Journal of Medicinal Chemistry, **62**, 785–798 **(2013)**.

[9] S.D.Joshi, H.M.Vagdevi, V.P.Vaidya, G.S.Gadaginamath; European Journal of Medicinal Chemistry, **43(9)**, 1989–1996 **(2008)**.

[10] D.A.Ibrahim; European Journal of Medicinal Chemistry, **44(7)**, 2776–2781 **(2007)**.

[11] S.J.Gilani, S.A.Khan, O.Alam, N.Siddiqui; Acta Poloniae Pharmaceutica & Drug Research, **68(2)**, 205–211 **(2011)**.

[12] S.Alam; Journal of Chemical Sciences, **166(6)**, 325–331 **(2004)**.

[13] M.J.Pelzar, E.C.S.Chan, N.R.Krieg; 'Antibiotics and other chemotherapeutic agents in microbiology',5th Edition, Blackwell Science, New York, **(1998)**.