Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2016, 8(1):750-754

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis, characterization and biological studies of novel fused thiazolidinone derivatives

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ABSTRACT

*Several fused heterocycles based on thiazolidinone derivatives were synthesized and characterized using physical properties, elemental analysis, IR and other spectral studies. New ligands i.e. 4-(2-furyl)-6-methyl-2-oxo- N-(3,5-diaryl-2- phenyl-3,3a- dihydro-2H- pyrazolo [3,4-d][1,3] thiazol-6(5H)-yl)-1,2,3,4-tetrahydro pyrimidine-5-carboxamide **(5a-h)** were synthesized by condensation reaction of thiazolidinone derivatives with phenyl hydrazine in presence of glacial acetic acid. Furthermore the antibacterial and antifungal activity of newly synthesized fused heterocyclic compounds was examined against various microbial strains.*

Keywords: Fused heterocycles, Thiazolidinone derivatives, Spectral studies, Antibacterial activity, Antifungal activity.

INTRODUCTION

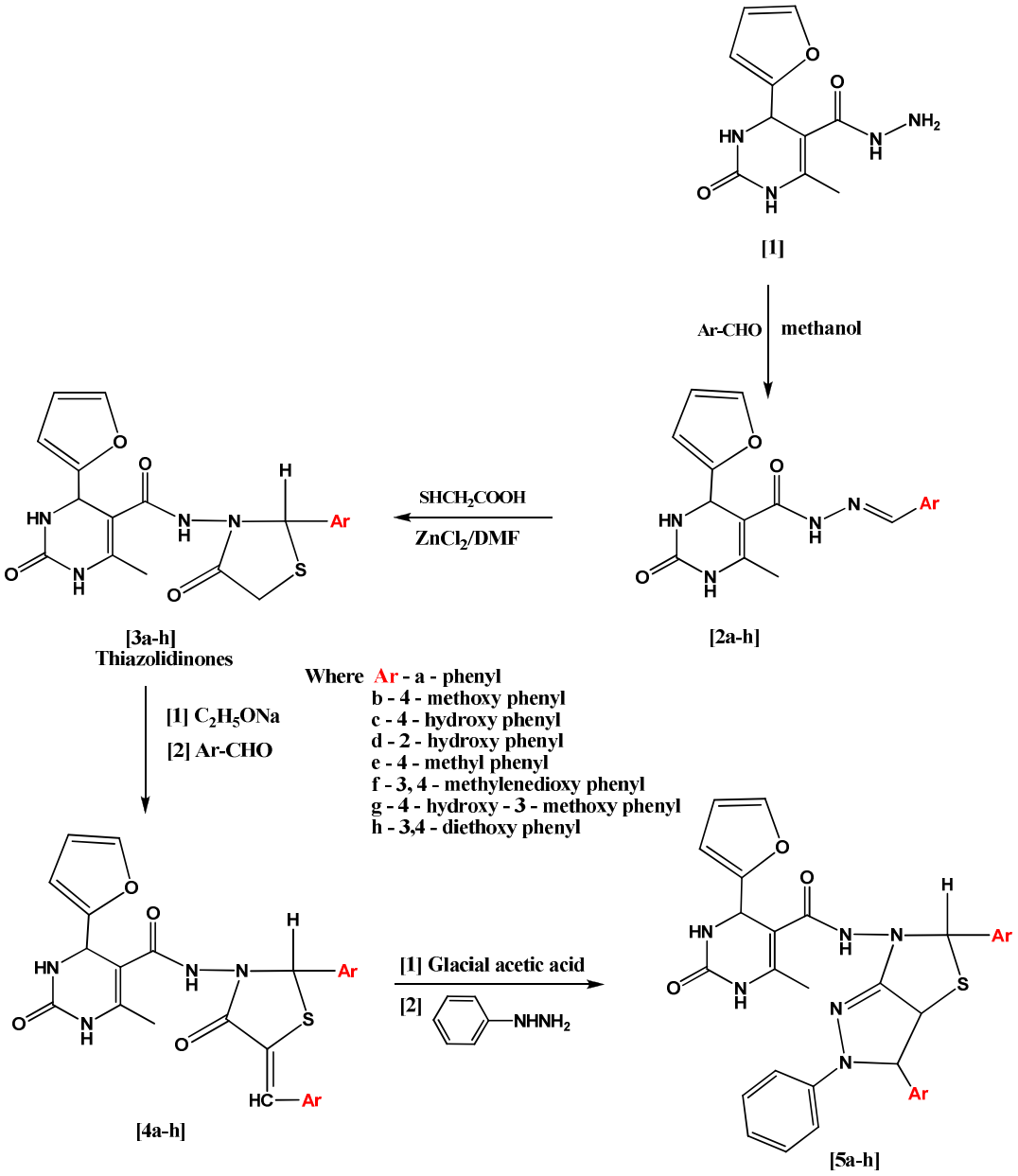
A large number of thiazolidinone compounds have been incorporated into a wide variety of therapeutically active drug applicants [1,2]. Among these thiazolidinones, the 4-substituted thiazolidinones have been studied extensively and also diverse biological applications have been reported so far such as antibacterial, antifungal, anti-inflammatory, antitubercular and anticancer activities [3-6]. In the last few decades, the chemistry of fused heterocyclic derivatives has received considerable attention due to their synthesis and effective biological activities [7-9]. In addition, thiazolidinones are the useful precursors for the synthesis of several fused compounds [10-12]. Heterocyclic compounds containing tetrahydropyrimidine are acquiring more importance in recent years because of broad spectrum of biological as well as pharmacological activities [13-15].

Recently, we investigated the synthesis of some thiazolidinones derivatives [16]. It was thought of interest to prepared fused heterocycles of these thiazolidinones which may enhance the biologiocal activity of compound to some extent and or they might possess some of the above mentioned biological activities. Hence the present communication comprises the synthesis, characterization and biological activities of 4-(2-furyl)-6-methyl-2-oxo-N-(3,5-diaryl-2-phenyl-3,3a-dihydro-2H-pyrazolo[3,4-d][1,3] thiazol-6(5H)-yl)-1,2,3,4-tetrahydro pyrimidine-5-carboxamide **(5a-h)**. **Scheme-1** summarizes synthetic approach to the various phases of our work.

EXPERIMENTAL SECTION

All common reagents and solvents were used of analytical grade and were used without further purification. Alumina supported pre-coated silica gel 60 F254 thin layer chromatography (TLC) plates were purchased from the E. Merck (India) Limited, Mumbai and were used to check purity of compounds and, to study the progress of the reaction whereby TLC plates were illuminated under Ultraviolet light (254 nm), evaluated in I_2 vapors and visualized by spraying with Draggendorff's reagent. Infrared spectra (FT-IR) were obtained from KBr pellets in the range of 4000–400 cm^{-1} with a Nicolet 400D spectrometer (FT-IR) instrument. ^1H 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 the selected samples were taken on LC-MSD-Trap-SL-01046. Micro analytical (C, N, H) data was obtained by using a Perkin–Elmer 2400 CHN elemental analyzer. Melting points were determined in open capillary tubes and were found uncorrected. Thiazolidinone derivatives **(3a-h)** were prepared as per reported method [16].



Scheme-1 Synthesis of fused heterocycles based on Thiazolidinones (5a-h)

Synthesis of 4-(2-furyl)-6-methyl-2-oxo-N-[5-arylidene-4-oxo-2-aryl-1,3-thiazolidin-3-yl]-1,2,3,4-tetrahydro pyrimidine -5-carboxamide (4a-h)

A mixture of 4-(furan-2-yl)-6-methyl-2-oxo-N-(4-oxo-2-arylthiazolidin-3-yl)-1,2,3,4-tetrahydro pyrimidine-5-carboxamide **(3a-h)** (0.25mole) and aromatic aldehydes (0.25mole) in glacial acetic acid (50ml) was refluxed on a water bath for 4-5 hrs. 10 % (10 ml) Sodium ethoxide was used as a catalyst. The solid separated was collected by filtration, dried and recrystallized from Ethanol. The yields, melting points and other characterization data of these compounds are given in **Table-1**.

***Synthesis of* 4-(2-furyl)-6-methyl-2-oxo-N-(3,5-diaryl-2-phenyl-3,3a-dihydro-2H-pyrazolo[3,4-d][1,3]thiazol-6(5H)-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (5a-h)**

A mixture of compounds **(4a-h)** (0.0025 mole) and Phenyl hydrazine (0.005 mole) was dissolved in glacial acetic acid (50 ml). The reaction mixture was then refluxed for 5 hours and left at room temperature. The resultant mixture was concentrated, cooled, poured into ice-cold water, and then air-dried. The product thus obtained was

recrystallization using ethanol gave desire fused thiazolidinones **(5a-h)**, which were obtained in 60-66% yield. The analytical and spectral data of compounds **(5a-h)** are described. The yields, melting points and other characterization data of these compounds are given in **Table-2**.

BIOLOGICAL SCREENING

Antibacterial activity

Compounds **5a–h** were screened for *in vitro* antibacterial activity against Gram-positive bacterial strains (*Bacillus subtilis* [BS] and *Staphylococcus aureus* [SA]) and Gram-negative bacterial strains (*klebsiella promioe* [KP] and *Escherichia coli* [EC]) utilizing the agar diffusion assay. The wells were dug in the media with the help of a sterile metallic borer. Recommended concentration of the test sample (50µg/mL in DMSO) was introduced in the respective wells. A methanol system was used as control in this method. Reference antibacterial drug, tetracycline was served as positive controls. 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. The antibacterial activity data of fused heterocycles **(5a-h)** and standard compound tetracycline is shown in **Table-3**.

Table-1 Analytical Data and Elemental Analysis of Compounds (4a-h)

Compd.	Molecular formula	M. Wt.	Yield	M.P.* ^{0}C	Elemental Analysis							
					%C		%H		%N		%S	
					Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
4a	$C_{26}H_{22}N_4O_4S$	486	71	230-231	64.1	64.18	4.5	4.56	11.5	11.52	6.5	6.59
4b	$C_{28}H_{26}N_4O_6S$	546	67	222-223	61.5	61.53	4.7	4.79	10.2	10.25	5.8	5.87
4c	$C_{26}H_{22}N_4O_6S$	518	70	225-226	60.2	60.22	4.2	4.28	10.7	10.80	6.1	6.18
4d	$C_{26}H_{22}N_4O_6S$	518	65	230-232	60.1	60.22	4.2	4.28	10.8	10.80	6.1	6.18
4e	$C_{28}H_{26}N_4O_4S$	514	68	227-228	65.3	65.35	5.0	5.09	10.8	10.89	6.2	6.23
4f	$C_{28}H_{22}N_4O_8S$	574	69	228-230	58.5	58.53	3.8	3.86	9.7	9.75	5.5	5.58
4g	$C_{28}H_{26}N_4O_8S$	578	67	226-228	58.1	58.12	4.5	4.53	9.6	9.68	5.5	5.54
4h	$C_{34}H_{38}N_4O_8S$	662	70	218-221	61.6	61.62	5.7	5.78	8.4	8.45	4.8	4.84

***** *Uncorrected*

Table-2 Analytical Data and Elemental Analysis of fused heterocycles (5a-h)

Compd.	Molecular formula	M. Wt.	Yield	M.P.* ^{0}C	Elemental Analysis							
					%C		%H		%N		%S	
					Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
5a	$C_{32}H_{28}N_6O_3S$	576	65	235-237	66.6	66.65	4.8	4.89	14.5	14.57	5.5	5.56
5b	$C_{34}H_{32}N_6O_5S$	636	62	227-229	64.1	64.14	5.0	5.07	13.1	13.20	5.0	5.04
5c	$C_{32}H_{28}N_6O_5S$	608	66	230-231	63.1	63.14	4.6	4.64	13.7	13.81	5.2	5.27
5d	$C_{32}H_{28}N_6O_5S$	608	60	240-242	63.1	63.14	4.6	4.64	13.7	13.81	5.2	5.27
5e	$C_{34}H_{32}N_6O_3S$	604	62	232-233	67.5	67.53	5.3	5.33	13.8	13.90	5.2	5.30
5f	$C_{34}H_{28}N_6O_7S$	664	61	230-231	61.4	61.44	4.2	4.25	12.6	12.64	4.8	4.82
5g	$C_{34}H_{32}N_6O_7S$	668	63	230-232	61.0	61.07	4.7	4.82	12.5	12.57	4.7	4.79
5h	$C_{40}H_{44}N_6O_7S$	752	65	224-226	63.7	63.81	5.8	5.89	11.1	11.16	4.2	4.26

***** *Uncorrected*

Table-3 Antibacterial Activities of fused heterocycles (5a-h)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	***Bacillus subtilis***	***E.coli***	***Klebsiella promioe***
5a	47	57	62	66
5b	52	60	60	64
5c	50	65	65	67
5d	49	64	64	68
5e	46	62	68	65
5f	49	66	64	69
5g	54	72	69	70
5h	58	75	72	76
Tetracycline	57	76	74	84

Antifungal activity

The fungicidal activity of all the compounds was studied at 1000 ppm concentration *in vitro*. Plant pathogenic organisms used were *Nigrospora Sp* [NS], *Aspergillus niger* [AN], *Botrydepladia thiobromine* [BT], *and Rhizopus nigricum* [RN]**,** *Fusarium oxyporium* [FO]. The antifungal activities of all the compounds **(5a-h)** were measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200g, dextrose 20g, agar 20g and water 1c. Five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120^o C for 15 min. at 15atm. pressure. These

media were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after five days using the formula given below:

$$\text{Percentage of inhibition} = \frac{100(X - Y)}{\text{X}}$$

Where, X = Area of colony in control plate
Y = Area of colony in test plate

The antifungal activity data of fused thiazolidinone derivatives are given in **Table-4**.

Table-4 Antibacterial Activities of fused heterocycles (5a-h)

Compounds	Zone of Inhibition at 1000 ppm (%)				
	Nigrospora Sp.	*Aspergillus Niger*	*Botrydepladia Thiobromine*	*Rhizopus Nigricum*	*Fusarium oxyporium*
5a	60	62	66	65	58
5b	60	61	69	68	59
5c	65	66	71	67	63
5d	59	58	65	72	57
5e	65	64	68	68	58
5f	62	65	69	65	63
5g	70	62	77	71	69
5h	66	70	75	78	66

RESULTS AND DISCUSSION

Condensation of **3a-h** with aromatic aldehydes using sodium ethoxide afforded the corresponding 4-(2-furyl)-6-methyl-2-oxo-N-[5-arylidene-4-oxo-2-aryl-1,3-thiazolidin-3-yl]-1,2,3,4-tetrahydropyrimidine-5-carboxamide**(4a-h).**

The structures of **(4a-h)** were confirmed by elemental analysis and IR spectra showing an absorption band at 1690cm^{-1} (C=O of thiazolidinone ring), 718cm^{-1} (C-S-C of thiazolidinone ring), 3075-3095cm^{-1} (CH_2 of thiazolidinone ring), 3030-3080 cm^{-1} (C-H, of Ar.), 1720,1690 cm^{-1} (-CO,CONH), 3410-3425 (N-H), 1545-1580 (C=C), 1240-1250 (C-O), 2815-2850 cm^{-1} (-OCH_3), 2950, 1370 cm^{-1} (-CH_3).

^{1}H NMR: 7.2 (1H,s,=CH), 5.95-5.97 (1H,s,-CH), 7.48-7.86 (10H,m,Ar-H), 11.8-11.9 (1H,s,-CONH), 2.15 (s,3H,-CH_3), 7.70-5.24 (d,4H,furan ring), 3b; 3.85 (3H,s,-OCH_3), 3c; 5.22 (1H,s,-OH), 3d; 5.17 (1H,s,-OH), 3e; 2.32 (3H,s,CH_3), 3f; 5.82 (2H,s,CH_2), 3g; 5.15 (1H,s,-OH) and 3.82 (3H,s,O-CH_3), 3h; 1.33 (6H-2CH_3) and 3.95 (4H-2CH_2). The C, H, N, S analysis data of all compounds are presented in **Table-1**.

The structures assigned to 4-(2-furyl)-6-methyl-2-oxo-N-(3,5-diaryl-2-phenyl-3,3a-dihydro-2H-pyrazolo[3,4-d][1,3]thiazol-6(5H)-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide **(5a-h)** were supported by the elemental analysis and IR spectra showing an absorption bands at 718cm^{-1} (C-S-C of thiazolidinone ring), 3075-3095cm^{-1} (CH_2 of thiazolidinone ring), 3030-3080 cm^{-1} (C-H, of Ar.), 1720,1690 cm^{-1} (-CO,CONH), 3410-3425 (N-H),1240-1250 (C-O), 1620-1648 (C=N), 3030-3080 cm^{-1} (C-H of Ar.), 2815-2850 cm^{-1} (-OCH_3), 2950, 1370 cm^{-1} (-CH_3). Also, the absence of C=O peak (thiazolidinone ring) supports the fusion of thiazolidinones derivatives **(5a-h)**.

^{1}H NMR: 3.89,4.54 (2H,s,-CH of the fused ring), 5.95-5.97 (1H,s,-CH), 6.80-7.86 (15H,m, Ar - H), 11.8-11.9 (1H, s,-CONH), 2.17 (s,3H,-CH_3), 7.72-5.23 (d,4H, furan ring), 3b; 3.82 (3H,s,-OCH_3), 3c; 5.14 (1H,s,-OH), 3d; 5.10 (1H,s,-OH), 3e; 2.29 (3H,s,CH_3), 3f; 5.80 (2H,s,CH_2), 3g; 5.17 (1H,s,-OH) and 3.78 (3H,s,O-CH_3), 3h; 1.36 (6H-2CH_3) and 3.97 (4H-2CH_2). The C, H, N, S analysis data of all compounds are presented in **Table-2**.

CONCLUSION

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structures as shown in **Scheme-1**. The IR data also direct for assignment of the predicted structure. The final structure of all compounds is also confirmed by LC-MS and NMR spectral data of all compounds. Some compounds shows good antibacterial activity compared to standard Tetracycline. The fungal activity data suggest that the % age of fungus is inhibited in the range of 57 to 78% depending upon the biospecies.

Acknowledgement
The authors are thankful to authorities of Department of Chemistry, for providing laboratory facilities.

REFERENCES

[1] V. Khurana, V. Lakshika, Int. J. Res. Pharm. Sci., **2011**, 1, 17.
[2] Y. K. Agrawal, H. G. Bhatt, H. G. Raval, P. M. Oza, H. B. Vaidya, *J. Sci. Indust. Res.*, **2007**, 66, 191.
[3] H. Zhou, S Wu, S Zhai, A Liu, Y Sun, R Li, Y Zhang, S Ekins, P. W. Swaan, B Fang, B Zhang, B Yan, *J. Med. Chem.*, **2008**, 51, 1242-1251.
[4] F. C. Brown, *Chem. Rev.*, **1961**, 61, 463-521.
[5] S. P. Singh, S. S. Parmar, K. Raman, V. I. Stenberg, *Chem. Rev.*, **1981**, 81, 175.
[6] M. Abhinit, M. Ghodke, N. A. Pratima, *Int. J. Pharm. Pharma. Sci.*, **2009**, 1, 47.
[7] Z. EL-Gendy, R. M. Abdel-Rahman, M. M. Fawzy, M. B. Mahmoud. *ChemInform.*, **2010**, 23, 212.
[8] B. Singh, A. Maheshwari, G. Dak, K. Sharma, G. L. Talesara, *Ind. J. Pharm. Sci.*, **2010**, 72, 607.
[9] F. Aydogan, N. Ocal, Z. Turgut, C. Yolacan, *Bull. Korean Chem. Soc.*, **2001**, 22, 476.
[10] M. A. Badawya, N. H. Metwallya, D. S. Okpya, *J. Sulfur Chem.*, **2015**, 36, 511.
[11] S. K. Patil, B. P. Langi, H. P. Deokar, *Ind. Am. J. Pharm. Res.*, **2015**, 5, 578.
[12] R. Gupta, *J. Heterocyclic Chem.*, **2015**, doi: 10.1002/jhet.2476.
[13] A. Bari, M. K. Parvez, A. A. Khan, A. M. Alanazi, S. A. Syed, M. S. Al-Dosari, A. M. Alobaid, *J. Heterocyclic Chem.*, **2015**, doi: 10.1002/jhet.2400.
[14] S. Kaping, R. Nongkynrih, L. I. Singh, J. N. Vishwakarm, *Med. Chem. Res*., **2015**, 24, 2742.
[15] M. N. Bhoi, M. A. Borad, E. A. Pithawala, S. Modi, H. D. Patel, *Int. Lett. Chem. Phy. Astro.*, **2015**, 56, 82.
[16] S. P. Jambu, Y. S. Patel, *Der Chem. Sin.*, **2015**, 6, 15.