Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Chemica Sinica, 2015, 6(3):15-19

Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Synthesis and biological studies of novel thiazolidinones

[1]Suresh P. Jambu and [2]Yogesh S. Patel*

[1]Chemistry Department, M. B. Patel Science College, Sardar Patel University, Anand, Gujarat, India
[2]Chemistry Department, Government Science College, Gandhinagar, Gujarat, India

---

ABSTRACT

4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (1) undergoes facile condensation with aromatic aldehydes (2a-h) to afford corresponding N-arylidene-4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (3a-h) in good yields. Cyclocondensation of compounds (3a-h) with thioglycolic acid yields 4-(furan-2-yl)-6-methyl-2-oxo-N-(4-oxo-2-arylthiazolidin-3-yl)-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (4a-h). The structures of these compounds were established on the basis of analytical and spectral data. All newly synthesized compounds were evaluated for their antibacterial and antifungal activities.

Keywords: heterocyclic compound; thiazolidine; antibacterial activity.

INTRODUCTION

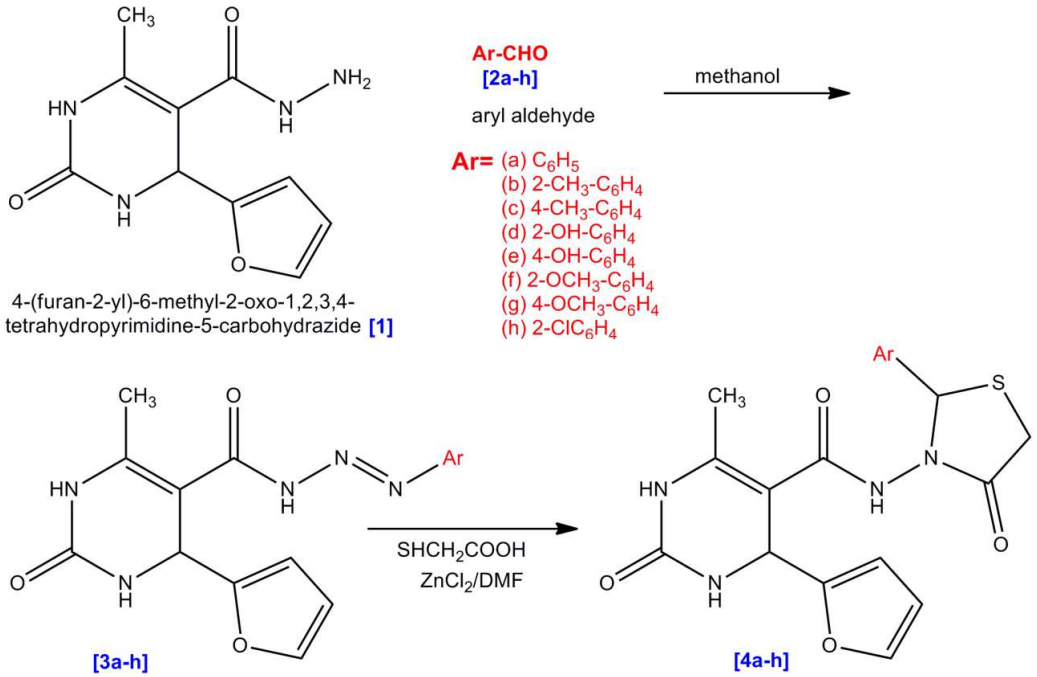
The last few decades have seen a flurry of activity in the synthesis and development of heterocyclic compound because of their important biological properties. Acid hydrazide and their heterocyclised products display diverse biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties. [1-6] These heterocyclic systems find wide use in medicine, agriculture and industry. Some of the acid hydrazides, e.g. salicylhydrazide, isoniazid and their post hetero cyclic products play a vital role in medicinal chemistry. [7, 8] 4-Thiazolidinones and its arylidene compounds give good pharmacological properties. [9-11] They are also known for antitubercular [12], antibacterial [13], antifungal [14] and anticonvulsant activities. Tetrahydropyrimidine is one of the most important heterocyclic compounds, which are widely distributed in nature amongst the plant kingdom. These compounds are containing biological as well as pharmacological activities. [15, 16]

Based on this concept, our main concern was to synthesize such heterocyclic compounds which possess enhance biological activity by introducing thiazolidinone, pyrimidone and hydrazide moieties together in a single molecular framework. Scheme 1 summarize our synthetic approach to the various phases of this work, viz., (i) synthesis of compound 3a-h (ii) synthesis of 4-(furan-2-yl)-6-methyl-2-oxo-N-(4-oxo-2-arylthiazolidin-3-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide derivatives 4a-h. All newly synthesized compounds 4a–h were evaluated for their antibacterial activity against Gram–positive and Gram–negative bacterial strains and antifungal activity against different fungal strains. The details of these procedures and the results obtained are discussed below.

MATERIALS AND METHODS

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 vapours 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. ^{1}H NMR and ^{13}C 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. 4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide was prepared as per the reported method. [17]



Scheme 1 Synthesis of compounds 3a-h and 4a-h

Synthesis of N-arylidene-4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine -5-carbohydrazide (3a-h)

A mixture of 4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbo hydrazide (1) (0.25mole) and the aromatic aldehydes (2a-h) (0.25mole) in ethanol (15ml) was refluxed on a water bath for 1.5-3 hrs. The solid separated was collected by filtration, dried and recrystallized from Ethanol: H_2O (1:1). The yields, melting points and other characterization data of these compounds are given in Table -1.

Synthesis of 4-(furan-2-yl)-6-methyl-2-oxo-N-(4-oxo-2-arylthiazolidin-3-yl)-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (4a-h)

An equimolar mixture N-arylidene-4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carbohydrazide (3a-h) in THF (30ml) and thioglycolic acid with a pinch of anhydrous $ZnCl_2$ was refluxed for 7-8 hrs. The solvent was then removed to get a residue, which was dissolved in benzene and passed through a column of silica gel using p-xylene: chloroform (6:4) mixture as eluent. The eluate was concentrated and the product crystallized from alcohol to give 4-(furan-2-yl)-6-methyl -2-oxo- N-(4-oxo- 2-aryl thiazolidin -3-yl)-1,2,3,4-tetrahydro pyrimidine -5-carboxamide (4a-h), which were obtained in 64-69% yield. The yields, melting points and other characterization data of these compounds are given in Table -2.

BIOLOGICAL SCREENING

Antibacterial activity (in vitro)

Compounds **4a–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.

Antifungal activity (in vitro)

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 (4a-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:

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

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

RESULTS AND DISCUSSION

It was observed that 4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (1), on condensation with aromatic aldehydes, yields N-arylidene-4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (3a-h). The structures of (3a-h) were confirmed by elemental analysis and IR spectra showing an absorption band at 3410-3425(N-H),1240-1250 (C-O), 3030-3080 cm^{-1} (C-H of Ar.), 1720,1690 cm^{-1} (-CO,CONH), 2815-2850 cm^{-1} (-OCH_3), 2950, 1370 cm^{-1} (-CH_3). ^{1}H NMR: 7.48 –7.86 (5H,m,Ar - H),11.8-11.9 (1H, s,-CONH), 8.43-8.8 (1H,s,-N=CH), 1.92 (s,3H,–CH3), 7.72-5.25 (d,4H, furan ring), 3b; 2.28(3H,s,-CH_3), 3c; 2.30(3H,s,CH_3), 3d; 5.12(1H,s,-OH), 3e; 5.19(1H,s,-OH),3f; 3.82(3H,s,-OCH_3), 3g; 3.87(3H,s,-OCH_3).The C, H, N analysis data of all compounds are presented in Table 1.

Table: 1 Analytical Data and Elemental Analysis of Compounds (3a-h)

	Molecular formula	*M. Wt.*	*Yield*	*M.P.* ^0C	*Elemental Analysis*					
					%C		*% H*		*%N*	
					Found	*Calcd.*	*Found*	*Calcd.*	*Found*	*Calcd.*
3a	$C_{17}H_{16}N_4O_3$	324	82	218-219	62.93	62.95	4.95	4.97	17.26	17.27
3b	$C_{18}H_{18}N_4O_3$	338	79	223-224	63.88	63.89	5.34	5.36	16.54	16.56
3c	$C_{18}H_{18}N_4O_3$	338	77	208-211	63.87	63.89	5.35	5.36	16.55	16.56
3d	$C_{17}H_{16}N_4O_4$	340	79	213-215	59.97	59.99	4.72	4.74	16.43	16.46
3e	$C_{17}H_{16}N_4O_4$	340	80	211-213	59.97	59.99	4.73	4.74	16.44	16.46
3f	$C_{18}H_{18}N_4O_4$	354	83	208-210	61.00	61.01	5.10	5.12	15.79	15.81
3g	$C_{18}H_{18}N_4O_4$	354	75	216-218	60.99	61.01	5.11	5.12	15.80	15.81
3h	$C_{17}H_{15}N_4O_3Cl$	358.5	78	212-214	56.90	56.91	4.20	4.21	15.60	15.62

The structures assigned to 4-(furan-2-yl)-6-methyl -2-oxo- N-(4-oxo- 2-aryl thiazolidin -3-yl)-1,2,3,4-tetrahydro pyrimidine -5-carboxamide (4a-h) were supported by the elemental analysis and IR spectra showing an absorption bands 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),1240-1250 (C-O), 3030-3080 cm^{-1} (C-H of Ar.), 2815-2850 cm^{-1} (-OCH_3), 2950, 1370 cm^{-1} (-CH_3).for (4a-h) compound.

^{1}H NMR: 3.85-3.95 (2H, s,-CH_2 of the ring), 5.95-5.97 (1H, s,-CH), 7.48 –7.86 (5H,m, Ar - H),11.8-11.9 (1H, s,-CONH), 2.14 (s,3H,–CH3), 7.72-5.25 (d,4H, furan ring), 4b; 2.28 (3H,s,-CH_3), 4c; 2.30(3H,s,CH_3), 4d; 5.12(1H,s,-OH), 4e; 5.19(1H,s,-OH),4f; 3.82(3H,s,-OCH_3), 4g; 3.87(3H,s,-OCH_3). The C, H, N, S analysis data of all compounds are presented in Table-2.

Table: 2 Analytical Data and Elemental Analysis of Compounds (4a-h)

	Molecular formula	*M. Wt.*	*Yield*	*M.P.* ^0C	*Elemental Analysis*							
					%C		*%H*		*%N*		*%S*	
					Found	*Calcd.*	*Found*	*Calcd.*	*Found*	*Calcd.*	*Found*	*Calcd.*
4a	$C_{19}H_{18}N_4O_4S$	398	67	222-225	57.25	57.27	4.53	4.55	14.05	14.06	8.04	8.05
4b	$C_{20}H_{20}N_4O_4S$	412	65	205-207	58.23	58.24	4.87	4.89	13.57	13.58	7.75	7.77
4c	$C_{20}H_{20}N_4O_4S$	412	63	212-214	58.22	58.24	4.88	4.89	13.56	13.58	7.76	7.77
4d	$C_{19}H_{18}N_4O_5S$	414	66	223-224	55.04	55.06	4.36	4.38	13.50	13.52	7.72	7.74
4e	$C_{19}H_{18}N_4O_5S$	414	69	217-219	55.04	55.06	4.37	4.38	13.51	13.52	7.71	7.74
4f	$C_{20}H_{20}N_4O_5S$	428	67	215-217	56.05	56.06	4.69	4.70	13.06	13.08	7.46	7.48
4g	$C_{19}H_{18}N_4O_5S$	414	68	216-218	56.04	56.06	4.68	4.70	13.07	13.08	7.47	7.48
4h	$C_{19}H_{17}N_4O_4SCl$	432.5	63	214-216	52.70	52.72	3.95	3.96	12.92	12.94	7.39	7.41

The examination of elemental analytical data reveals that the elemental contents are consistent with the predicted structure shown in Scheme-1. The IR data also direct for assignment of the predicted structure.

Based on the data from the antibacterial studies against both Gram-positive and Gram-negative bacterial strains, the following observations can be made. Among the analogs 4a–h, compound 4h was identified as a potent antibacterial agent against all Gram-positive and Gram-negative bacterial strains. Compound 4g also had good antibacterial activity against bacterial strains. Other compounds exhibited moderate antibacterial activity (Table 3).

Compounds 4a-h exhibited less antibacterial activity as compared to standard antibiotic drug. Based on the screening data from the antifungal studies, the following observations can be made. All compounds exhibited antifungal activity against different fungal strains (Table 4). Compounds 4h and 4g were found more potent as compare to other compounds.

Table: 3 Antibacterial Activities of Compounds 4a-h

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	*Bacillus subtilis*	*E.coli*	*Klebsiella promioe*
4a	42	54	60	68
4b	48	58	59	67
4c	46	62	64	70
4d	45	60	62	72
4e	42	59	67	69
4f	47	64	64	72
4g	51	69	68	74
4h	53	73	70	78
Tetracycline	57	76	74	84

Table: 4 Antifungal Activities of Compounds 4a-h

	Zone of Inhibition at 1000 ppm (%)				
Compounds	*Nigrospora Sp.*	*Aspergillus Niger*	*Botrydepladia Thiobromine*	*Rhizopus Nigricum*	*Fusarium oxyporium*
4a	67	67	67	59	61
4b	61	62	65	62	60
4c	67	67	67	65	64
4d	60	59	66	67	62
4e	68	68	68	68	63
4f	63	64	66	64	65
4g	70	68	71	65	73
4h	69	70	69	72	68

CONCLUSION

Novel compounds N-arylidene-4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carbohydrazide (3a-h) and 4-(furan-2-yl)-6-methyl-2-oxo-N-(4-oxo-2-arylthiazolidin-3-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4a-h) have been synthesized successfully. The structures of these compounds were established on the basis of analytical and spectral data. All newly synthesized compounds were evaluated for their antibacterial and antifungal activities.

Acknowledgements
S. P. Jambu is greatly thankful to the authorities of M. B. Patel Science College, Sardar Patel University, Anand for providing necessary research facilities.

REFERENCES

[1] Patel YS, Patel PN, Patel HS, *International Research Journal of Pure & Applied Chemistry*, **2014**, 4(3), 315.
Patel GK, Patel YS, Patel HS, *International Journal of Chemtech Applications*, **2014**, 3(3), 1.
[2] Gursoy E, Guzeldemirci-Ulusoy N, *Eur J Med Chem* **2007**, 42, 320.
[3] Shah PJ, Patel HS, Patel BP, *Journal of Saudi Chemical Society*, **2013,** 17, 307.
[4] Janin Y, *Bioorg Med Chem*, **2007**, 15, 2479.
[5] Kalsi R, Shrimali M, Bhalla TN, Barthwal JP, *Indian J Pharm Sci*, **2006**, 41, 353.
[6] Shah PJ, Patel HS, Patel BP, *Bulgarian Chemical Communications*, **2010**, 42(4), 474.
[7] Al- Mawsawi LQ, Dayam R, Taheri L, Witvrouw M, Debyser Z, Neamati N, *Bioorg Med Chem Lett*, **2007**, 17(23), 6472.
[8] Plasencia C, Daym R, Wang Q, Pinski J, Burke TR Jr, Quinn DI, Neamati N, *MolCancer Ther*, **2005**, 4(7), 1105.

[9] Iqbal KM, Khan AY, Kalashetti MB, Belavagi NS., Gong YD, Khazi IAM, *Eur J Med Chem*,**2012**, 53, 308.
[10] Pareek D, Chaudhary M, Pareek PK, Kant R, Ojha KG, Pareek A, *Der Chemica Sinica*, **2010**, 1(3), 22.
[11] Pareek D, Chaudhary M, Pareek PK, Kant R, Ojha KG, Pareek A, *Der Pharmacia Sinica*, **2011**, 2(1), 170.
[12] Havrylyuk D, Kovach N, Zimenkovsky B, Vasylenko O, Lesyk R, *Arch Pharm* **2011,** 344**,** 514.
[13] Patel HS, Mistry HJ, *Phosphorous Sulfur and Silicon*, **2004,** 179, 1085.
[14] Singh T, Khobragade DS, *Unique Journal Of Pharmaceutical And Biological Sciences*, **2014**, 2(1), 13.
[15] Alper-Hayta S, Arisoy M, Temiz-Arpaci O, Yildiz I, Aki E, *Eur J Med Chem*, **2008**, XX, 1.
[16] Kirilmis C, Ahmedzade M, Servi S, Koca M, Kizirgil A, *Eur J Med Chem*, **2008**, 43, 300.
[17] Vaidya VP, Agasimundin YS, *Indian J Chem*, **1983,** 22(B), 432.