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Design, synthesis, spectral analysis & antibacterial activity of thiazol-pyrimidine 5-carboxamide derivatives

GhazalaYasmeen*[1] S.Imam Pasha[2]

[1]*Department of Pharmaceutical Chemistry, Sultan-Ul-Uloom College of Pharmacy, India.*

[2]*Department of Pharmaceutical Analysis & Quality Assurance Sultan-Ul-Uloom College of Pharmacy, India.*

***Corresponding Author: GhazalaYasmeen**

E.mail: ghazalay19@gmail.com

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-thiazol-pyrimidine-5-carboxamidewere synthesized by condensation reaction of thiazolidinone derivatives with phenyl hydrazine in presence of glacial acetic acid. Furthermore the antibacterial of newly synthesized fused heterocyclic compounds was examined against various microbial strains.

Keyword: Thiazolidinone

INTRODUCTION

Thiazolidinone Derivatives

Thiazolidinones[1] are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring. A lot of research work on thiazolidinones has been done in the past. The nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities[2]. Numbers of methods for synthesis by using various agents are available in the references.

Thiazolidinones and their derivatives display a large variety of activities such as antibiotic, diuretic, organoleptic, tuberculostatic, antileukaemic and antiparasitical[3]. As far as literature is concerned, little is known about thiazolidinones and their bioactivities.

EXPERIMENTAL SECTIONCHEMICALS AND REAGENT

The chemicals and reagents used in the present project were of AR and LR grade, procured from Aldrich, Hi-media, Lancaster, Loba, Merck, NR CHEM. Qualigens, Rolex, Reachchem, S.D-Fine Chem. Ltd, and Sigma.

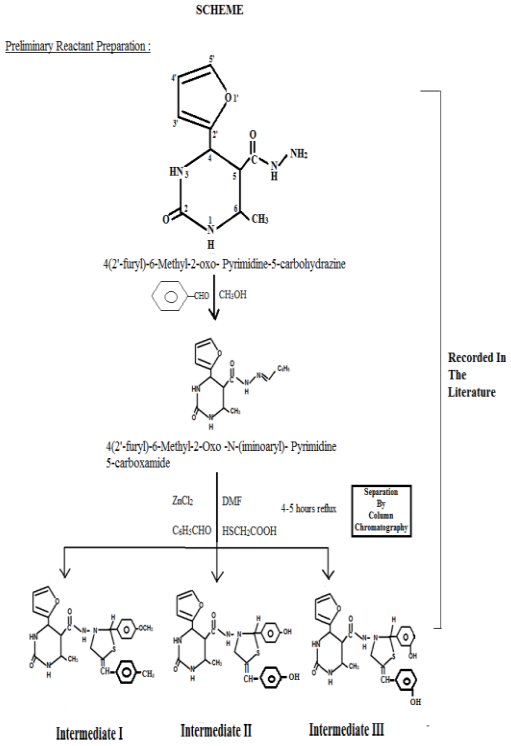
Table-1: List of chemicals and reagents

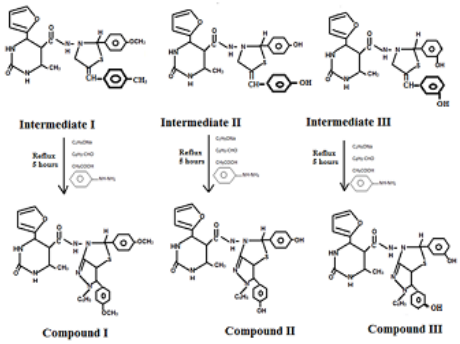
Zinc chloride	DMF
glacial acetic acid	Methanol
Methanol	sodium ethoxide
Benzaldehyde	Phenyl hydrazine

Analytical Techniques

1. **Physical data:** Melting points of the synthesized compounds were recorded using open capillary tubes[4].
2. **Thin Layer Chromatography[5] (TLC) and Column Chromatography[6].**
3. **Instrumentation:** The techniques employed for the characterization of the synthesized compounds were IR, ^{1}H-NMR and Mass spectral analysis[7].

SCHEME OF SYNTHESIS





Intermediate I : 4(2'-Furyl)-6-Methyl-2-Oxo- N-(5-arylidine-4-oxo-2-p-di methoxy)-aryl thiazolidine-3yl)-pyrimidine-5-carboxamide

Intermediate II : 4(2'-Furyl)-6-Methyl-2-Oxo- N-(5-arylidine-4-oxo-2-p-di hydroxy)-aryl thiazolidine-3yl)-pyrimidine-5-carboxamide

Intermediate III : 4(2'-Furyl)-6-Methyl-2-Oxo- N-(5-arylidine-4-oxo-2-m-di hydroxy)-aryl thiazolidine-3yl)-pyrimidine-5-carboxamide

Compound I: 4(2'-Furyl)-6-Methyl-2-Oxo- N -(para di methoxy phenyl,4,5-pyrazolo-1,3-thiazol)-pyrimidine-5-carboxamide

Compound II: 4(2'-Furyl)-6-Methyl-2-Oxo- N -(para di hydroxy phenyl,4,5-pyrazolo-1,3-thiazol)-pyrimidine-5-carboxamide

Compound III: 4(2'-Furyl)-6-Methyl-2-Oxo- N -(meta di hydroxy phenyl, 4,5-pyrazolo-1,3-thiazol)-pyrimidine-5-carboxamide

GENERAL PROCEDURE

Synthesis of 4-(2-furyl)-6-methyl-2-oxo-N-[iminoaryl]-pyrimidine-5-carboxamide derivatives

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 (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[46] from Ethanol.

Synthesis of 4-(2-furyl)-6-methyl-2-oxo-thiazol-pyrimidine-5-carboxamide derivatives

A mixture of compounds (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, which were obtained in 60-66% yield. The analytical and spectral data of compounds are described. The yields, melting points and other characterization data of these compounds are given in Table-2.

SPECTRAL INTERPRETATION

Compound (1)

Physical data

Solubility : Ethyl acetate
Melting point : 108-110
TLC solvent : ethanol methanol (9:1)
% Yield : 82%

Spectral data

Spectral interpretation

^{1}HNMR

(DMSO-d_6, 500 MHz) δppm: 4.21 (s, 2H, NHN$\underline{H_2}$), 6.05 (s, 2H, NH_2), 7.65 (d, J=8.54 Hz, 1H, Ar-H), 8.51 (d, J=8.54 Hz, 1H, Ar-H), 9.13 (br., s, 1H, NH).

ESI-MS

ESI-MS: 221 (M+1).

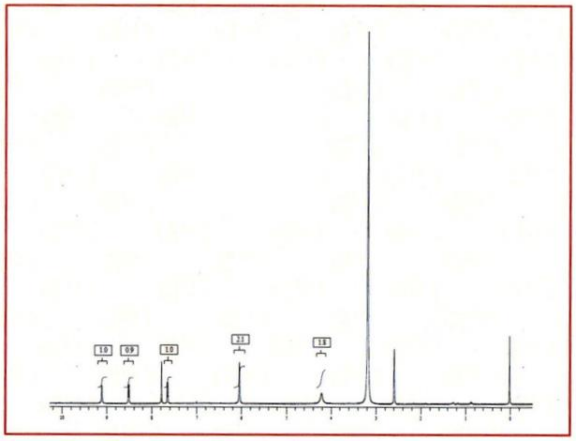
IR

(KBr) cm^{-1}: 3482, 3290 (NH, NH_2), 1650 (amide, CO), 1577 (C=N), 1525 (C=C).

Physical properties

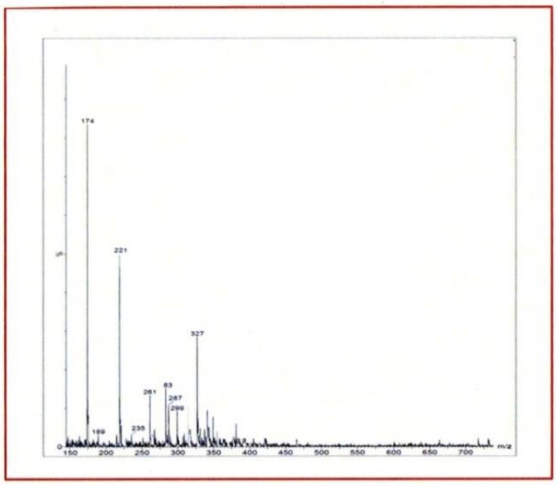
Yield: 82% (Yellow solid); m.p. 108-110 °C

^{1}H NMR



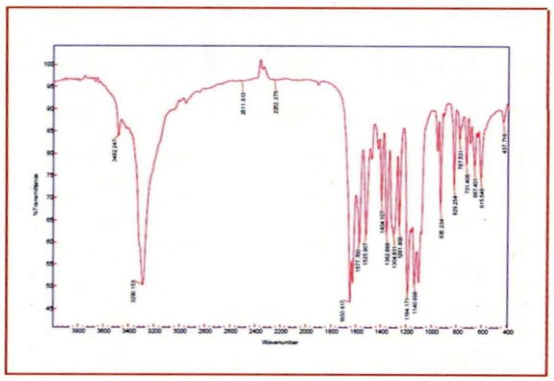
PROTON NMR OF COMPOUND (I)

ESI-MS



ES MS OF COMPOUND (I)

IR-Spectrum



IR SPECTRA OF Compound (I)

COMPOUND (II)

Physical data

Solubility : Ethyl acetate
Melting point : 170-172
TLC solvent : Ethanol
% Yield : 93%

Spectral interpretation

^{1}HNMR

1.49 (t, 3H, CH_3), 4.40-4.49 (q, 2H, OCH_2, Ar-H), 7.86 (d, 2H, J = 8.30 Hz, Ar-H), 8.26 (s, 1H, N=CH), 8.59 (d, 1H, J = 8.30 Hz, Ar-H), 8.75 (s, 1H, Ar-H).

ESI-MS

287 (M+1).

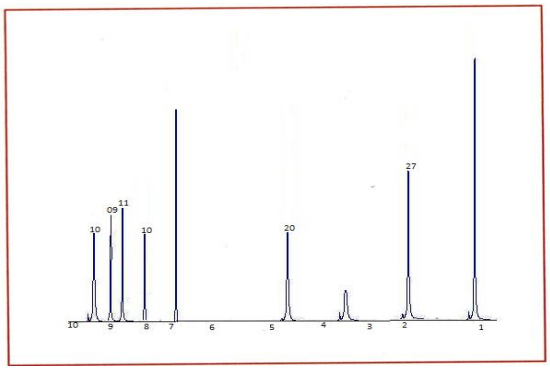
IR

(KBr) cm^{-1}: 1682 (amide, CO), 1607 (C=N), 1501 (C=C).

Physical properties

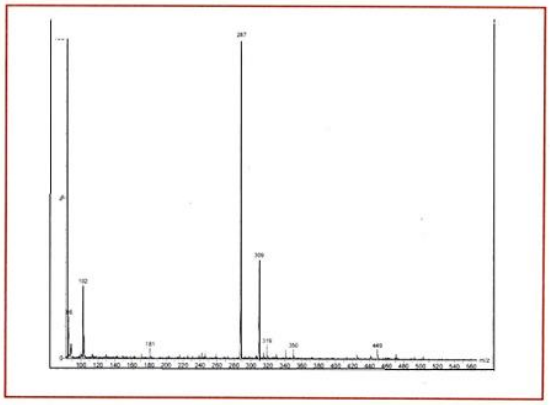
Yield: 93% (Off white solid); m.p. 170-172 °C.

^{1}H NMR



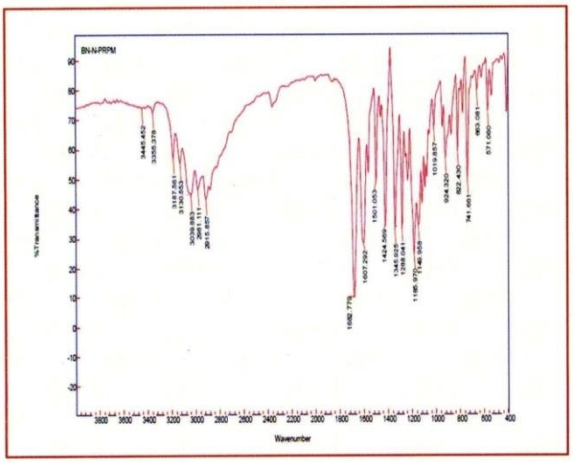
PROTON NMR OF COMPOUND (II)

ESI-MS



ESI MS OF COMPOUND (II)

IR-SPECTRUM



IR SPECTRUM OF COMPOUND (II)

Compound (III)

Physical data

Solubility : Ethyl acetate
Melting point : 142-144
TLC solvent : ethanol
% Yield : 78%

Spectral interpretation

^{1}H NMR

($CDCl_3$, 300 MHz): δ 1.46 (t, 3H, CH_3), 1.92 (s, 3H, CH_3), 2.53 (t, 3H, CH_3), 4.46-4.50 (q, 2H, OCH_2), 7.83 (d, 1H, J = 8.30 Hz, Ar-H), 8.57 (d, 1H, J = 8.30 Hz, Ar-H).

ESI-MS

315 (M+1).

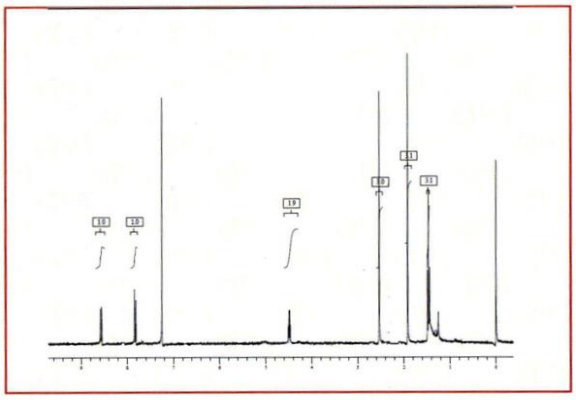
IR

(KBr) cm^{-1}: 1678 (amide, CO), 1618 (C=N), 1438 (C=C)

Physical properties

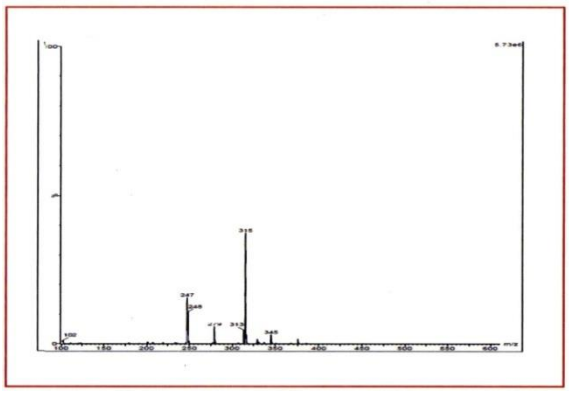
Yield: 78% (Off white solid); m.p. 142-144 °C.

^{1}H NMR



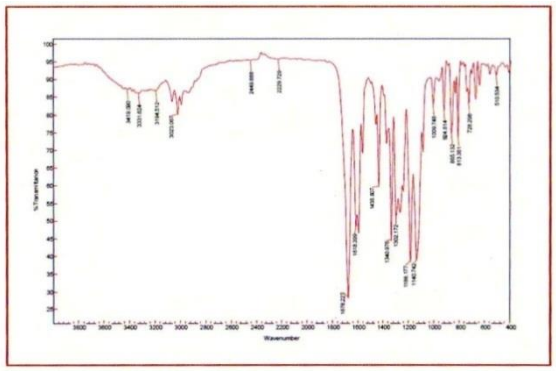
PROTON NMR OF COMPOUND (III)

ESI-MS



ESI MS COMPUND (III)

IR-SPECTRUM



IR SPECTRUM OF COMPOUND (III)

ANTIBACTERIAL ACTIVITY

Antibacterial Activities of all the compounds were studied against gram-positive bacteria (Staphylococcus aureus and Bacillus subtilis) and gram-negative bacteria (E.coli, and klebsiellapneumoniae) at a concentration of 50µg/ml by agar cup plate method. Methanol system was used as control in this method. Under similar condition using tetracycline as a standard for comparison carried out control experiment. The area of inhibition of zone measured in mm. The anti bacterial activity data of fused thiazolidinone derivatives are given in Table-3

RESULTS AND DISCUSSION

Condensation of intermediatewith 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**(**compound I,II,III**).**

The structures of compound I,II,IIIwere 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 (CH2 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 (-OCH3), 2950, 1370 cm-1 (-CH3).

^{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,-CH3), 7.70-5.24 (d,4H,furan ring), 3b; 3.85 (3H,s,-OCH3), 3c; 5.22 (1H,s,-OH), 3d; 5.17 (1H,s,-OH), 3e; 2.32(3H,s,CH3), 3f; 5.82 (2H,s,CH2), 3g; 5.15 (1H,s,-OH) and 3.82 (3H,s,O-CH3), 3h; 1.33 (6H-2CH3) and 3.95 (4H-2CH2). The C, H, N, S analysis data of all compounds are presented in Table-2.

The structures assigned to 4-(2-furyl)-6-methyl-2-oxo-thiazol-N-(Phenyl, 4,5-pyrazolo-1,3-thiazo)-pyrimidine-5-carboxamide. Synthesizedcompound

(I,II,III) 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 **(**compound I,II,III**)**.

^{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,-CH3), 7.72-5.23 (d,4H, furan ring), 3b; 3.82 (3H,s,-OCH3), 3c; 5.14 (1H,s,-OH), 3d; 5.10(1H,s,-OH), 3e; 2.29 (3H,s,CH3), 3f; 5.80 (2H,s,CH2), 3g; 5.17 (1H,s,-OH) and 3.78 (3H,s,O-CH3), 3h; 1.36 (6H-2CH3) and 3.97 (4H-2CH2). The C, H, N, S analysis data of all compounds are presented in Table-2

Table-2. Analytical Data and Elemental Analysis of fused heterocycles (Compound I,II,III)

Compd.	Molecular formula	M. Wt.	Yield	M.P.* ^{0}C	%C Found	%H Found	%N Found	%S Found
I	$C_{35}H_{29}N_6O_5S$	635	62	227	64.1	5.0	13.1	5.0
II	$C_{33}H_{25}N_6O_5S$	617	66	230	63.1	4.6	13.7	5.2
III	$C_{33}H_{25}N_6O_5S$	617	60	240	63.1	4.6	13.7	5.2

The anti bacterial data of fused thiazolidinone derivatives are given in Table-2.

Table-3. Antibacterial Activities of fused heterocycles (Compound I,II,III)

S. No.	Staphylococcus aureus(G Positive) mm	Bacillus Subtilis (G Positive) mm	E.Coli(G .negative) mm	klebsiella pneumoniae (G .negative) mm
Intermediate-I	45	56	58	59
Intermediate-II	47	58	59	63
Intermediate--III	46	54	56	61
Compound-I	52	60	60	64
Compound-II	50	65	65	67
Compound-III	49	64	64	68
Tetracycline	57	76	74	84

(Staphylococcus aureus and Bacillus subtilis) and gram-negative bacteria (E.coli, and klebsiellapneumoniae) at a concentration of 50µg/ml by agar cup plate method. Methanol system was used as control in this method. Under similar condition using Tetracycline as a standard for comparison carried out control experiment. The area of inhibition of zone measured in mm. The anti bacterial activity data of fused thiazolidinone derivatives are given in Table-3

CONCLUSION

The yield of the synthesized compound was found to be in the range from 60-66%. All these molecules were characterized by IR, along with physical data. ^{1}HNMR and mass spectral analysis was done for the compounds I, II, III**.** The functional groups in the title compounds were indicated by their IR spectra. The number of protons in the compounds was confirmed by their ^{1}HNMR spectra. The structure of title compounds were confirmed by their Mass Spectra. Compounds (I, II, III) shows relatively same extent of antibacterial activity compared to Intermediate compounds and standard Tetracycline.

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