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Research Article

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Synthesis and characterization of some novel isoxazolyl-1,3-thiazolidin-4-ones

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ABSTRACT

*A series of novel 1,3-thiazolidin-4-ones**(2a-h)** have been synthesiszed from isoxazolyl hydrazide-hydrazone derivatives**(1a-h)**.These hydrazide-hydrazone derivatives undergoes cyclocondensation with mercaptoacetic acid in dioxane in the presence of anhydrous zinc chloride give title compounds in good yields**(Table-I)**. Structure of all the synthesized compounds have been established on the basis of IR, [1]HNMR and Mass spectral data.*

Key words: Isoxazolyl hydrazid- hydrazones,cyclo condensation, mercapto acetic acid, 1,3-thiazolidin-4-ones.

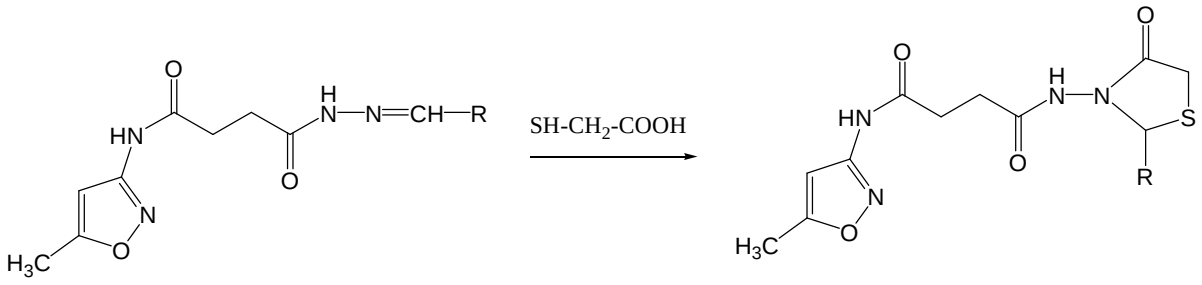
INTRODUCTION

1,3-Thiazolidin-4-ones exhibit a wide range of biological activity [1-9],such as anti tubercular, antithyroid, antimicrobial, anti-inflammatory, analgesic, anticonvulsant, antiviral, anticancer and antidiabetic effects. Isoxazole derivatives shows variety of biological activity[10-14],Such as antitumor, CNS–Active, Analgesic, antimicrobial and chemotherapeutic agents.

Inspired by the biological profile of thiazolidinin-4-ones and isoxazole and their increasing importance in pharmaceutical and biological fields and in connection with our research on the design and synthesis of biologically active and pharmacologically important new isoxazole substituted heterocyclies[15-17].The present investigation reports synthesis and characterization of isoxazolyl 1,3-thiazolidin-4-ones.

EXPERIMENTAL SECTION

All the chemical were purchased from Sigma Aldrich, all the reagents were analytically pure. Melting points were determined on a Cintex melting point apparatus and are uncorrected. The purity of the compounds checked by TLC (Merck precoated) and visualized under U.V. Light. IR Spectra were recorded as a KBr pellet with a Perkin Elmer BX series FT-IR Spectrophotometer, ^{1}HNMR spectra were recorded in DMSO-d_6 with a Verian Gemini of 300 MHz instrument. Chemical Shift values were reported in δ(ppm) using TMS as an internal standard Mass Spectra were recorded using Jeol JMC D-300 spectrometer at 70ev.



1 2

1a/2a: R=C_6H_5; 1b/2b: R=4-ClC_6H_4 ;1c/ 2c: R=4-$OCH_3C_6H_4$; 1d/2d: R=4-OHC_6H_4 ;1e/2eR= 4-FC_6H_4;1f/ 2f: R=3-BrC_6H_4;1g/ 2g: R= 4-$NO_2C_6H_4$; 1h/2h: R=2,4-$Cl_2C_6H_3$

Scheme-I

General procedure for the synthesis of compounds 2a-h: A mixture of compound **1** (0.01mol) and mercaptoacetic acid (0.01 mol) was dissolved in 1,4 dioxane (15 ML) ,catalytic amount of an hydrous zinc chloride was added , and the contents were refluxed for 5-8 h. After completion of the reaction (monitored by TLC) , reaction mixture was allowed to cool down and was poured over crushed ice. The aqueous layer was extracted with ethyl acetate (2X20 ml) Washed with 10 % Sodium bicarbonate solution (1X20 ml) and dried over anhydrous sodium sulphate, the solvent was removed under Vaccum , and the residue was recrystallized from ethyl acetate.

N^1-(5-methylisoxazol-3-yl)-N^4-(4-oxo-2-phenylthiazolidin-3-yl)succinamide2a:IR(KBr): 1700(-C=O), 1220(C-S) cm^{-1}, ^{1}HNMR(DMSO-d_6), δ2.35 (s, 3H, isoxazole-CH_3), 2.80(t, 2H, CH_2-CH_2, J=7Hz), 3.11(t, 2H, CH_2-CH_2, J=7Hz), 3.88(s, 2H, thiazolidinone ring-CH_2), 5.60(s, 1H, thiazolidinone ring-H), 6.08(s, 1H, isoxazole-H), 7.30—7.38(m, 5H, Ar-H), 9.22(bs, 1H, NH, D_2O exchangeable); MS: m/z(M^++1)375.

N^1-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-N^4-(5-methylisoxazol-3-yl)succinamide2b: IR(KBr): 1702(-C=O), 1222(C-S) cm^{-1}; ^{1}HNMR(DMSO-d_6): δ 2.39(s, 3H, isoxazole-CH_3), 2.98(t, 2H, CH_2-CH_2, J=7Hz), 3.18(t, 2H, CH_2-CH_2, J=7Hz), 3.90(s, 2H, thiazolidinone ring-CH_2), 5.62(s, 1H, thiazolidinone ring-H), 6.20(s, 1H, isoxazole-H), 7.20(d, 2H, Ar-H), 7.38(d, 2H, Ar-H), 8.80(bs, 1H, NH, D_2O exchangeable) ; MS: m/z(M^++1)409.

N^1-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-N^4-(5-methylisoxazol-3-yl)succinamide2c: IR(KBr): 1705(-C=O), 1212(C-S) cm^{-1}; ^{1}HNMR(DMSO-d_6): δ 2.40(s, 3H, isoxazole-CH_3), 2.82(t, 2H, CH_2-CH_2, J=7Hz), 3.28(t, 2H, CH_2-CH_2, J=7Hz), 3.75(s, 3H, -OCH_3), 3.95(s, 2H, thiazolidinone ring-CH_2), 5.75(s, 1H, thiazolidinone ring-H), 6.22(s, 1H, isoxazole-H), 6.80(d, 2H, Ar-H), 7.20(d, 2H, Ar-H), 9.02(bs, 1H, NH, D_2O exchangeable); MS: m/z(M^++1)405.

N^1-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)-N^4-(5-methylisoxazol-3-yl)succinamide2d: IR(KBr): 1708(-C=O), 1222(C-S) cm^{-1}; ^{1}HNMR(DMSO-d_6): δ2.44(s, 3H, isoxazole-CH_3), 2.98(t, 2H, CH_2-CH_2, J=7Hz), 3.22(t, 2H, CH_2-CH_2, J=7Hz), 3.90(s, 2H, thiazolidinone ring-CH_2), 5.68(s, 1H, thiazolidinone ring-H), 6.12(s, 1H, isoxazole-H), 6.78(d, 2H, Ar-H), 7.69(d, 2H, Ar-H), 8.130(bs, 1H, NH, D_2O exchangeable), 8.50(bs, 1H, OH, Ar-OH, D_2O exchangeable); MS: m/z(M^++1)391.

N^1-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)-N^4-(5-methylisoxazol-3-yl)succinamide2e: IR(KBr): 1710(-C=O), 1220(C-S) cm^{-1}; ^{1}HNMR(DMSO-d_6): δ2.32(s, 3H, isoxazole-CH_3), 2.85(t, 2H, CH_2-CH_2, J=7Hz), 3.19(t, 2H, CH_2-CH_2, J=7Hz), 3.92(s, 2H, thiazolidinone ring-CH_2), 5.70(s, 1H, thiazolidinone ring-H), 6.08(s, 1H, isoxazole-H), 6.98(d, 2H, Ar-H), 7.25(d, 2H, Ar-H), 9.32(bs, 1H, NH, D_2O exchangeable); MS: m/z(M^++1)393.

N^1-(2-(3-bromophenyl)-4-oxothiazolidin-3-yl)-N^4-(5-methylisoxazol-3-yl)succinamide2f:IR(KBr): 1704(-C=O), 1218(C-S) cm^{-1}; ^{1}HNMR(DMSO-d_6): δ 2.28(s, 3H, isoxazole-CH_3), 2.96(t, 2H, CH_2-CH_2, J=7Hz), 3.29(t, 2H, CH_2-CH_2, J=7Hz), 3.96(s, 2H, thiazolidinone ring-CH_2), 5.52(s, 1H, thiazolidinone ring-H), 6.15(s, 1H, isoxazole-H), 7.10-7.50(m, 4H, Ar-H), 9.45(bs, 1H, NH, D_2O exchangeable); MS: m/z(M^++1)453.

N^1-(5-methylisoxazol-3-yl)-N^4-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)succinamide2g: IR(KBr): 1711(-C=O), 1210(C-S) cm^{-1}; ^{1}HNMR(DMSO-d_6): δ 2.26(s, 3H, isoxazole-CH_3), 2.95(t, 2H, CH_2-CH_2, J=7Hz), 3.26(t, 2H, CH_2-CH_2, J=7Hz), 3.98(s, 2H, thiazolidinone ring-CH_2), 5.72(s, 1H, thiazolidinone ring-H), 6.21(s, 1H, isoxazole-H), 7.40(d, 2H, Ar-H), 8.18(d, 2H, Ar-H), 9.22(bs, 1H, NH, D_2O exchangeable); MS: m/z(M^++1)420.

N^1-(2-(2,4-dichlorophenyl)-4-oxothiazolidin-3-yl)-N^4-(5-methylisoxazol-3-yl)succinamide2h: IR(KBr): 1710(-C=O), 1212(C-S)cm^{-1}; ^{1}HNMR(DMSO-d_6): δ 2.22(s, 3H, isoxazole-CH_3), 2.99(t, 2H, CH_2-CH_2, J=7Hz), 3.32(t, 2H, CH_2-CH_2, J=7Hz), 4.02(s, 2H, thiazolidinone ring-CH_2), 6.30(s, 1H, thiazolidinone ring-H), 6.18(s, 1H, isoxazole-H), 7.30(m, 2H, Ar-H), 7.55(m, 1H, Ar-H), 9.08(bs, 1H, NH, D_2O exchangeable), MS: m/z(M^++1)443.

Table I-The physicochemical characteristics of the newly synthesized compounds 2a-h

Compound	Ar	Mol. Formula	Mol. Weight	Yield(%)	m.p(°C)
3a	C_6H_5	$C_{17}H_{18}N_4O_4S$	374	72	145
3b	4-ClC_6H_4	$C_{17}H_{17}ClN_4O_4S$	408	75	152
3c	4-$OCH_3C_6H_4$	$C_{18}H_{20}N_4O_5S$	404	75	148
3d	4-OHC_6H_4	$C_{17}H_{18}N_4O_5S$	390	70	150
3e	4-FC_6H_4	$C_{17}H_{17}FN_4O_4S$	392	72	153
3f	3-BrC_6H_4	$C_{17}H_{17}BrN_4O_4S$	452	73	155
3g	4-$NO_2C_6H_4$	$C_{17}H_{18}N_5O_6S$	419	75	159
3h	2,4-$Cl_2C_6H_4$	$C_{15}H_{15}FN_4O_3$	442	76	160

RESULTS AND DISCUSSION

The synthetic route of the title compounds (**2a-h)** is shown in scheme -I .The starting compounds(**1a-h)** have been synthesized from 4-hydrazinyl-N-(5-methylisoxazol-3-yl)-4-oxobutanamide[18].The hydrazide-hydrazone derivatives (**1a-h**) undergoes cyclocondensation with mercaptoacetic acid in dioxane in the presence of anhydrous zinc chloride give title compounds in good yields**(Table-I).**

Structure of newly synthesized compounds were established on the basis of their spectroscopic data (IR,^{1}HNMR and Mass). All the compounds exhibit characteristic signals appropriately (see experimental section). This can be illustrated with compound **2a,** in the IR spectrum, strong absorption at1700cm^{-1} corresponding to the CO group,1220cm^{-1} stretching vibration of C-S bond. A singlet at δ 3.88 observed in the ^{1}HNMR spectrum corresponding to methylene proton of thiazolidinone ring and another singlet appeared at δ 5.60 due to the methyne proton of the thiazolidinone ring. All other aliphatic and aromatic protons were observed at the expected region. The mass spectra showed (M^++1) peak at 375.The Physicochemical data of compounds (**2a-h)** are presented in **Table-I**

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