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Synthesis, Characterization and Biological Study of New Thiazolidinone Derivatives Containing Oxazole Moiety

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Abstract: *A novel series of 2-amino 4-substituted phenyl oxazole (1a-i), 2-imine substituted phenyl-4-substituted phenyl oxazole (2a-i) 2-(4,-oxo-2 substituted aryl-Thiazolidinyl)-4/ substituted phenyl oxazole. (3a-i) were prepared by the reaction of urea with different acetophenone with excellent yield. Elemental analysis, I.R, H1NMR, C13NMR AND Mass spectral data established. Identification of the compounds (3a-i) was evaluated for their antimicrobial and antifungal activity.*

Keywords: 4-Oxo-Thiazolidines, Thioglycolic Acid, Oxazole, Spectral Data, Antibacterial Activity.

I. INTRODUCTION

Heterocyclic compound plays a vital role in the metabolism of living cells. there are large no of biological active heterocyclic compounds, substituted oxazole derivative are found to be associated with various biological activities antibacterial, antiinflamatory, antitubercular, antidepressant, fluorescent whitening agent and analgesic etc. oxazole are well known as important structural units in a wide variety of biologically active natural as well as synthetic intermediates[57]. oxazole moiety is an area of intense research.

II. RESULT AND DISCUSSION

In view of these observations, it was thought worthwhile to synthesize several compounds in which 2-amino 4-subsituted phenyl oxazole, 2-substituted phenyl imine 4-substituted phenyl oxazole, 2-substituted aryl 3-substituted phenyl oxazole 4-thiazolidinones have been linked oxazole with moiety.

The reaction sequence leading to the formation of desired heterocyclic compounds are outlined in scheme-1.the starting material for 2-amino, 4-substituted phenyl oxazole (1a-i) was prepared by the reaction of substituted acetophenone with urea in presence of Br_2 –H_2o and ethanol. the substituted 2-[4-oxo-2-substituted aryl-thiazolidinyl] 4-substituted phenyl oxazole (3a-i) by the reaction of 2-amine substituted phenyl 4-substituted phenyl oxazole with thioglycolic acid and zinc chloride in presence of benzene the IR, H^1 NMR,C^{13}NMR, Mass spectra of the 2-substituted aryl-3substituted phenyl oxazole 4-thiazoldinones.

III. BIOLOGICAL STUDIES

Comparative study of urea with different acetophenones and (3a-i) has been observed by using Norfloxacine and Griseofulvaline as standards. The enhancement in biological activity of compound (1) as compared with the newly synthesized (3a-i) has been observed.

The synthesized compounds were tested at 100ml concentration against staphylococcus aureus, E-coli, P.vulgaris, A.niger, B.substillis, and C.albicans. For its antibacterial and antifungal screening as shown in Table-I

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Table 1: Antibacterial and antifungal activities of compounds 3a-i.

	Antibacterial activity			Antifungal activity	
compd	**s-aureus**	**B-substills**	**E-coli**	**C-albicans**	**A-niger**
3a	+	+++	+	++	++
3b	++	++	+++	+++	++
3c	+	++	+++	++	++
3d	_	+++	+	+++	+++
3e	+++	++	++	+++	++
3f	++	+++	_	++	++
3g	+++	_	+	_	+++
3h	++	+	+++	++	_
3i	++	_	+	++	+++
SM	+++	+++	++++		
GF				++++	+++

SM(streptomycin) and GF(Griesofulvin). The inhibition diameter in Mm (-)< 6,(+)7-9,(++) 10-15,(+++)16-22,(++++)23-28.

IV. EXPERIMENTAL

Melting point was taken in open capillary tubes and is uncorrected. IR spectra were run in KBr pellets on a perkin-Elmer 157 spectrometer. H NMR spectra were recorded in a CDCL3 on a Bruker_variah 300MHz FT NMR spectrometer using TMS as internal standard. Purity of the compounds was checked by TLC on silica gel G plates and the spots were located by exposure to iodine vapours'. The characterization data of the compounds is given in table-II.

comp	**R***	**Mol. Formula**	**M. Pt (C^0)**	**RF Value**	**% Yield**	**Analysis found(Cal) %**		
						C	**H**	**N**
3a	H	$C_{18}H_{10}N_2S O_2$	156	0.76	80	74.1 (74.0)	4.45 (4.44)	7.86 7.85
3b	2-OH	$C_{18}H_{12}N_2S O_3$	182	0.82	88	70.5 70.4	4.75 4.74	7.45 7.43
3c	3-OH	$C_{18}H_{12}N_2S O_3$	179	0.85	55	70.8 70.4	4.75 4.74	7.45 7.43
3d	4-OH	$C_{18}H_{12}N_2S O_3$	164	0.88	68	70.5 70.4	4.75 4.74	7.45 7.43
3e	2-NO_2	$C_{18}H_{12}N_3S O_4$	188	0.77	74	72.69 72.68	4.43 4.42	7.08 7.07
3f	3-NO_2	$C_{18}H_{12}N_3SO_4$	172	0.64	64	72.69 72.68	4.43 4.42	7.08 7.07
3g	4-NO_2	$C_{18}H_{12}N_3SO_4$	179	0.66	65	72.69 72.68	4.43 4.42	7.08 7.07

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3h	2-CL	$C_{18}H_{10}N_2SO_2CI$	157	0.76	58	73.3 73.2	4.21 4.20	6.55 6.54
3i	4-CL	$C_{18}H_{10}N_2SO_2CI$	168	0.77	62	73.3 73.2	4.21 4.20	6.55 6.54

* Eluents for TLC: Benzene-acetone (6:4) for 3a-i.
* Solvent for crystallization; aq. ethanol for 3a-i.

General Procedure of Preparation of Compounds:

1. Synthesis of 2-amino, 4-substituted phenyl oxazole

A mixture of substituted acetophenone (0.1mole) urea (0.2mole) in 100ml of ethanol addition of Br_2 –H_2o (0.2mole) was refluxed for overnight and ice was added to it. The reaction mixture was filtered and made alkaline with ammonium hydroxide to obtain 2-amino-4-substituted phenyl oxazole.

2. Synthesis of 2-imine substituted phenyl 4-substituted phenyl oxazole.

A mixture of compound I (0.01mole) and substituted benzaldehyde (0.01mole) were dissolved in absolute ethanol 100ml in presence of few (2-3drops) of conc.H_2SO_4 .The reaction mixture was refluxed for 8hrs. and poured on to crushed ice and resultant solid was washed with ether. Purity checked by TLC.

3. Synthesis of 2-[4 oxo-2-substituted-aryl thiazolidinyl] substituted phenyl oxazole .

A mixture of compound 2(0.01mole) and anhydrous $Zncl_2$ (one pinch) in dry benzene, thioglycolic acid (0.02mole) were added drop wise At 40-50 C temp and the mixtures kept for 2days at room temp and refluxed for 8hrs. The reaction mixture was filtered and dried.

3a:(M.P.165 yield 83), IR(KBr); 3031 (C-H Aromatic stretch)1791.8,1713,1641,1520,C-O-C str 1222,779(C-S) 1685(c=0)of thiazolidinone ring ; H^1NMR(300MHz DMSO) 9.53 (S1H NH) C^{13}NMR(300MHz,DMSO-d_6),14.1,13.1,13.3,23.2,37.9,38.1,34.5,39.1,40.0,58.2,76.6,7.4,111.2,159.0,126.1,137.2,160.2,161.1

3b:(M.P. 172 yield 79), IR(KBr); 2945 (C-H Aromatic stretch), C-O-C str 1224, 3275(OH of phenyl ring) 1639 & 1655 cyclic carbonyl ring,690 (C-S-C linkage of thiazolidinone ring),1152 (c-o str)3209 (N-H Str) 1791.8,1713,1641,1520,779(C-S) 1688(c=0)of thiazolidinone ring; H^1NMR(300MHz DMSO)δ 2.24,4.23,3.56 6.8-7.8(M.8H Aromatic proton)3.5(s,2H,CH_2 thiazolidine ring)C^{13}NMR(300MHz,DMSO-d_6),14.1,13.2,13.61,23.0,37.8,38.2,34.2,39.1,40.2,58.2,72.1,7.3,111.4,159.1,126.1,137.0,160.2,162.0

3c:(M.P. 181 yield 75), IR(KBr); 2945 (C-H Aromatic stretch) C-O-C str 1224 3272(OH of phenyl ring) 1637 & 1653 cyclic carbonyl ring,693(C-S-C linkage of thiazolidinone ring),1151 (c-o str)3208 (N-H Str) 1792.8,1714,1641,1521,779(C-S) 1689(c=0)of thiazolidinone ring ; H^1NMR(300MHz DMSO)δ 2.24,4.21,3.54 6.8-7.8(M.8H Aromatic proton)3.4(s,2H,CH_2 thiazolidine ring C^{13}NMR(300MHz,DMSO-d_6),14.0,13.1,13.1,23.2,37.9,38.2,34.3,39.4,40.1,58.4,76.5,7.3,111.2,159.2,126.2,137.32,160.2,162.2

3d:(M.P. 188 yield 58), IR(KBr); 2945 (C-H Aromatic stretch) C-O-C str 1224,3274(OH of phenyl ring) 1638 & 1650 cyclic carbonyl ring,691(C-S-C linkage of thiazolidinone ring),1150 (c-o str)3207(N-H Str) 1791.8,1713,1641,1520,779(C-S 1691(c=0)of thiazolidinone ring) ; H^1NMR(300MHz DMSO)δ 2.25,4.20,3.52 6.8-

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7.8(M.8H Aromatic proton)3.3(s,2H,CH_2 thiazolidine ring) C^{13}NMR(300MHz,DMSO-d_6), 14.2,13.0,13.5,23.0, 37.8, 38.2,34.6,39.4,40.0,58.5,76.7,7.3,111.8,159.1,126.1,137.3,160.2,161.1

3e:(M.P.191 yield 54), IR(KBr); 2945 (C-H Aromatic stretch) C-O-C str 1224 ,c1791.8,1713,1641,1520,779(C-S) 1690(c=0)of thiazolidinone ring ; H^1NMR(300MHz DMSO)δ 2.22,4.20,3.51 6.8-7.8(M.8H Aromatic proton)3.3(s,2H,CH_2 thiazolidine ring)(300MHz,DMSO-d_6),14.0,13.1,13.3, 23.1,37.8, 38.2, 34.2, 39.3, 40.0, 58.2, 76.8,7.4,111.2,159.1,126.2,137.1,160.1,162.1

3f:(M.P.192 yield 62), IR(KBr); 2945 (C-H Aromatic stretch) C-O-C str 1224 1791.8,1713,1641,1520,779(C-S) 1691(c=0)of thiazolidinone ring ; H^1NMR(300MHz DMSO)δ 2.20,4.21,3.54m, 6.8-7.8(M.8H Aromatic proton)3.3(s,2H,CH_2 thiazolidine ring) C^{13}NMR(300MHz,DMSO-d_6),14.1,13.1,13.0, 23.1,37.8, 38.2, 34.5, 39.1, 40.0, 58.2,76.9,7.3,111.2,158.1,126.2,136.3,160.2,162.1

3g. :(M.P.189 yield 65), IR(KBr); 2942 (C-H Aromatic stretch) C-O-C str 1224 1791.8,1713,1641,1520,779(C-S) 1692(c=0)of thiazolidinone ring ; H^1NMR(300MHz DMSO)δ 2.24,4.23,3.56 6.8-7.8(M.8H Aromatic proton)3.4(s,2H,CH_2 thiazolidine ring) C^{13}NMR(300MHz,DMSO-d_6),14.0,13.2,13.5,23.2, 37.9,38.1, 34.5,39.3, 40.0, 58.3,76.2,7.3,111.2,159.1,126.2,137.2,160.2,162.1

3h:(M.P.157 yield 49), IR(KBr); 2944 (C-H Aromatic stretch) C-O-C str 1224 1791.8,1713,1641,1520,779(C-S) 1690(c=0)of thiazolidinone ring ; 1689(c=0)of thiazolidinone ringH^1NMR(300MHz DMSO)δ 2.24,4.23,3.56 6.5-7.8(M.8H Aromatic proton)3.3(s,2H,CH_2 thiazolidine ring) C^{13}NMR(300MHz,DMSO-d_6),14.0,13.2,13.5,23.0, 37.9,38.1,34.2,39.2,40.0,58.51,76.2,7.2,111.3,159.1,126.3,137.3,160.2,162.1

3i:(M.P.143 yield 58), IR(KBr); 2941 (C-H Aromatic stretch) C-O-C str 1224,1791.8,1713,1641,1520,779(C-S) 1686(c=0)of thiazolidinone ring ; H^1NMR(300MHz DMSO)δ 2.24,4.23,3.56 6.7-7.8(M.8H Aromatic proton)3.3(s,2H,CH_2 thiazolidine ring) C^{13}NMR(300MHz,DMSO-d_6),14.2,13.2,13.5,23.2,37.9, 38.3,34.5,39.6,40.1, 58.4,76.8,7.2,111.8,159.1,126.3,137.3,160.2,162.1

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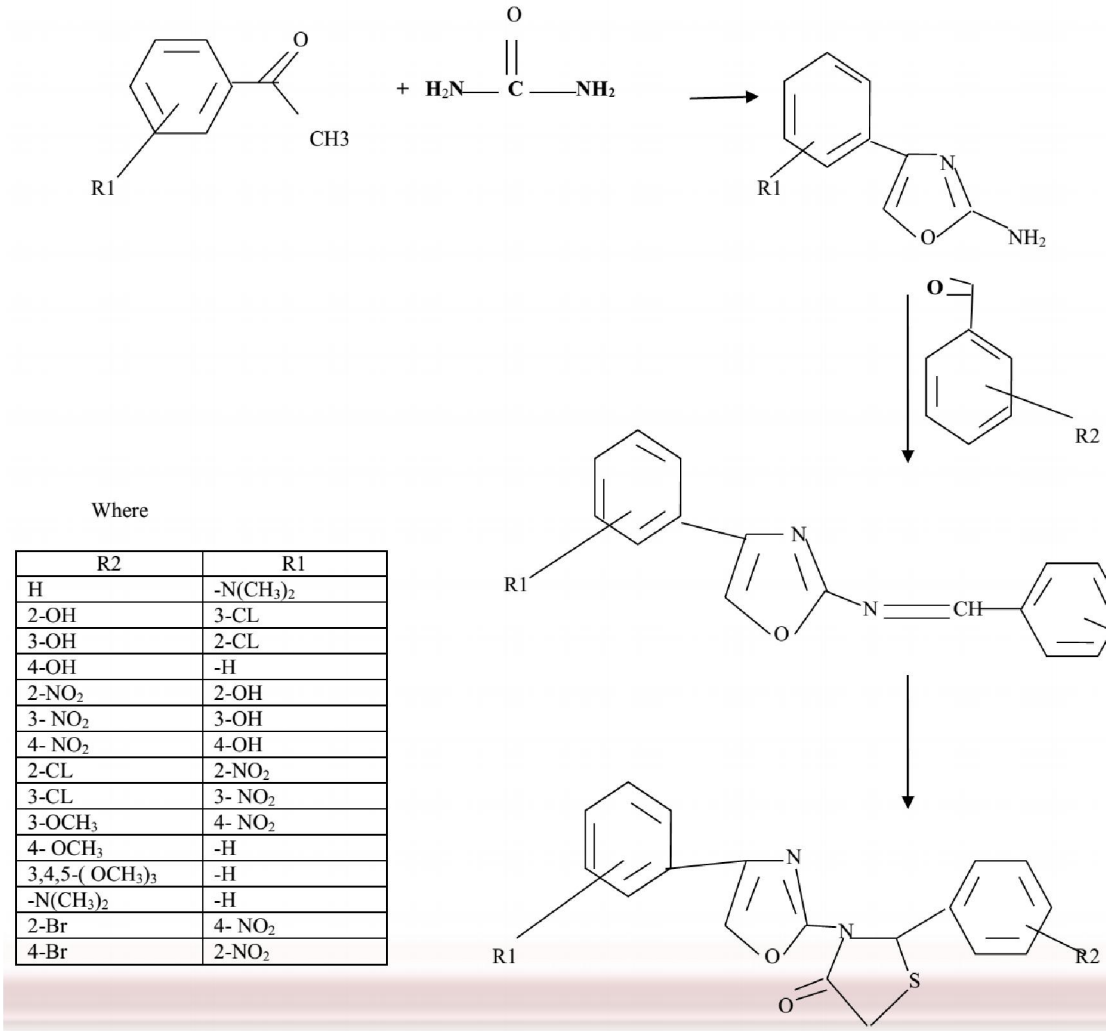

Where

R2	R1
H	-N(CH$_3$)$_2$
2-OH	3-CL
3-OH	2-CL
4-OH	-H
2-NO$_2$	2-OH
3- NO$_2$	3-OH
4- NO$_2$	4-OH
2-CL	2-NO$_2$
3-CL	3- NO$_2$
3-OCH$_3$	4- NO$_2$
4- OCH$_3$	-H
3,4,5-(OCH$_3$)$_3$	-H
-N(CH$_3$)$_2$	-H
2-Br	4- NO$_2$
4-Br	2-NO$_2$

V. CONCLUSION

An efficient method for synthesis of (3a-i) with excellent yield has been developed. The result for this study indicate that present synthetic method is a simple efficient in expensive and easy synthesis of biologically active compound (3a-i) these compound showing good result tested at 100 mg conc against E-coli, S-aureus,P-Vulgaris, A-niger , C-albicans.

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