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SYNTHESIS AND BIOLOGICAL ACTIVITY OF THIAZOLIDINONE DERIVATIVES OF 2-((1H-BENZ[D]IMIDAZOLE-2-YL)THIO)ACETOHYDRAZIDE

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Abstract

2-((1H-benzo[d]imidazol-2-yl)thio)acetohydra zide(1) undergoes facile condensation with various furaldehydes to gives the corresponding 2-[1H-benzo[d] imidazol -2-yl thio] -N'- ((5-subsitutedfuran-2-yl) methylene)acetohydrazide(3a-e) in good yields. Cyclo condensation of compounds (3a-e) with thioglycolic acid yields 2-[1H-benzo [d]imidazol- 2-ylthio] -N-[2-(5-subsituted furan-2-yl)-4-oxothiazolidin-3-yl] acetamide (4a-e). Then (4a-e) on mannich reaction with morpholin and formaldehyde afforded 2-(1H-benzo[d]imidazol-2-ylthio)-N-[2-(5-substitutefuran-2-yl)-5-(morpholine-4-yl) methyl-4-oxotinazolidin-3-yl)] acetamide (5a-e). The structures of all compounds were recognized on the basis of analytical and spectral data. All the newly synthesized compounds were evaluated for their antibacterial and antifungal activities.

Keywords: 2-((1H-benzo[d]imidazol-2-yl)thio)acetohydrazide, thiazolidine, antibacterial activity.

INTRODUCTION

Benzimidazole with wide structural variation have broad spectrum of bioactivity in terms of agriculture,clinical abd veterinary[1]. Many derivatives of benzimidazoles have been approved as important medicines[2-4]. The versatile benzimidazole containing admantane moiety have been reported recently[5] for target drug delivery system. Looking to the good bioproperties of benzimidazole derivatives via introducing hydride group.Hydrazides have been demonstrated to possess various activity like antimicrobial, anticonvulsant, analgesic, antiinflammatory, antiplatelet, antitubercular and antitumoral activities[6-10]. Such hydrazide group introduce benimidazole to be converted into its Schiff base. Schiff base then further condensed in presence of chloro acetyl chloride and thio glycolic acid into 2-Azetidinone and 4-Thiazolidinone derivatives. 4-Thiazolidinones and its arylidene compounds give good pharmacological properties like antitubercular, antibacterial, antifungal and anticonvulsant activities. [11-17]. Hence, it was thought of interest to merge both of thiazolidinone and benzimidazole moieties into one molecule which may enhance the drug activity of compounds to some extent or they might possess some of the above mentioned biological activities. Hence the present communication comprises the synthesis of 2-[1H-benzo[d]imidazol-2-ylthio]-N-[2-(5-subsitut edfuran-2-yl)-4-oxothiazolidin-3-yl]acetamide. The Mannich base products have also been prepared by reaction with Morpholin.The synthetic approach is shown in scheme-1.

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EXPERIMENTAL

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz. LC-MS of selected samples were taken on LC-MSD-Trap-SL_01046. Various 5-aryl furfural derivaties were prepared by reported method.[18] 2[(1H-benzo[d] imidazol -2-yl)thio]acetohydride was by reported in literate[19]. Other chemicals were used of pure grade.

Preparation of 2-(1H-benzo[d] imidazol-2-ylthio)-N'-((5-subsitutedfuran-2-yl) methylene) acetohydrazide(3a-e)

An equimolecular mixture of 2-((1H-benzo [d]imidazol-2-yl) thio) aceto hydrazide (1) (0.01mole) and the various 5-aryl furaldehydes (2a-e) in ethanol was refluxed in a water bath for 1.5 to 2 hrs. 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.

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

Compd.	Molecular formula (Mol.wt.)	Yield	M.P.* ^{0}C	Elemental Analysis							
				%C		% H		%N		%S	
				Found	Calcd.	Found	Found	Found	Calcd.	Found	Calcd.
3a	$C_{20}H_{16}N_4O_2S$ (376)	78	232-233	63.8	63.81	4.2	4.28	14.8	14.88	8.5	8.52
3b	$C_{21}H_{14}N_4O_2S$ (390)	72	239-241	64.5	64.60	4.6	4.65	14.3	14.35	8.2	8.21
3c	$C_{20}H_{15}N_4O_2SCl$ (410)	76	230-231	58.4	58.46	3.6	3.68	13.6	13.64	7.7	7.80
3d	$C_{20}H_{15}N_4O_2SBr$ (455)	73	225-227	52.7	52.76	3.3	3.32	12.2	12.30	7.0	7.04
3e	$C_{20}H_{14}N_4O_2SCl_2$ (444)	76	237-239	53.9	53.94	3.1	3.17	12.5	12.58	7.1	7.20

***** UncorrectedLC-MS data 3c-408,3e-460

Preparation of 2-(1H-benzo[d]imidazol-2-ylthio)-N-(2-(5-subsituted furan-2-yl)-4-oxo thiazolidin-3-yl) acetamide(4a-e)

A mixture 2-(1H-benzo[d]imidazol -2-ylthio) -N'-((5-subsitutedfuran-2-yl) methylene) aceto hydrazide (3a-e) (0.02 mole) in THF (30ML) and thioglycolic acid (0.02 mole) with a pinch of anhydrous $ZnCl_2$ was refluxed for 6hrs. The solvent was then distilled to get a residue, which was dissolved in benzene and passed through a column of silica gel using benzene: chloroform (8:2; v/v) mixture as an eluent. The eluate was concentrated and the product crystallized from ethanol to yield 2-(1H-benzo[d]imidazol-2-ylthio)-N-(2-(5-subsituted furan-2-yl)-4-oxo thiazolidin-3-yl)acetamide (4a-e). The yields, melting points and other characteristic data of all these compounds are given in Table-2.

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

Compd.	Molecular formula (Mol.wt.)	Yield	M.P.* ^{0}C	Elemental Analysis							
				%C		%H		%N		%S	
				Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
4a	$C_{22}H_{18}N_4O_3S_2$ (450)	70	207 -209	58.6	58.65	4.0	4.03	12.4	12.44	14.2	14.23
4b	$C_{23}H_{20}N_4O_3S_2$ (464)	65	211 -213	59.4	59.46	4.3	4.34	12.0	12.06	13.7	13.80
4c	$C_{22}H_{17}N_4O_3S_2Cl$ (484)	62	195 -197	54.4	54.48	3.5	3.53	11.5	11.55	13.2	13.22
4d	$C_{22}H_{17}N_4O_3S_2Br$ (527)	64	199 -200	49.9	49.91	3.2	3.24	10.5	10.58	12.0	12.11
4e	$C_{22}H_{16}N_4O_3S_2Cl_2$ (518)	66	202 -203	50.8	50.87	3.0	3.10	10.7	10.79	12.3	12.35

***** Uncorrected LC-MS data 4a-466,4d-544

Synthesis of 2-(1H-benzo [d] imidazol -2-yl thio)-N-[2-(5-substitutefuran-2-yl)-5-morpholine -4-yl) methyl-4-oxo tin azolidin-3-yl)] acetamide (5a-e) (Synthesis of Manich base)

The above 4a-e thiazolidinone derivatives were reacted with morphholin and 37% w/w formalin at stoichiametric ratio in 1,4-dioxane under refluxed condition for 3hrs.The products were checked by TLC. The yields, melting points and other characterization data of these compounds are given in Table -3.

Table: 3 Analytical Data and Elemental Analysis of Compounds (5a-e)

Compd.	Molecular formula (Mol.wt.)	Yield	M.P.* ^{0}C	Elemental Analysis							
				%C		%H		%N		%S	
				Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
5a	$C_{27}H_{27}N_5O_4S_2$ (549)	78	242 -243	58.9	59.00	4.9	4.95	12.7	12.74	11.6	11.67
5b	$C_{27}H_{26}N_6O_6S_2$ (594)	69	238 -239	54.5	54.53	4.4	4.41	14.1	14.13	10.7	10.78
5c	$C_{27}H_{26}N_5O_4S_2Cl$ (584)	66	215 -217	55.5	55.52	4.4	4.49	11.9	11.99	10.9	10.98
5d	$C_{27}H_{26}N_5O_4S_2Br$ (627)	68	225 -226	51.5	51.59	4.1	4.17	11.1	11.14	10.1	10.20
5e	$C_{27}H_{25}N_5O_4S_2Cl_2$ (617)	70	253 -255	51.4	52.43	4.0	4.07	11.3	11.32	10.3	10.37

***** Uncorrected LC-MS data 5b-613,5e-633

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BIOLOGICAL SCREENING

Antibacterial activities

The antibacterial activities of all the compounds were studied against gram-positive bacteria (*Staphylococcus aureus and Bacillus subtilis*) and gram-negative bacteria (*E.coli, and klebsiella promioe*) at a concentration of 50µg/ML by agar cup plate method. A methanol system was used as control in this method. Similar conditions using tetracycline as a control was used standard for comparison.[20,21] The % area of inhibition of zone measured in mm. Compounds 3e,4e and 5e were found toxic for microbes shown in Tables -4,5 and 6.

Table: 4 Antibacterial Activity of Compounds (3a-e)

Compounds	Gram +Ve		Gram –Ve	
	Staphylococcus aureus	***Bacillus subtilis***	***E.coli***	***Klebsiella promioe***
3a	44	53	60	70
3b	46	56	57	75
3c	49	57	59	69
3d	47	59	68	72
3e	52	68	71	79

Table: 5 Antibacterial Activity of Compounds (4a-e)

Compounds	Gram +Ve		Gram –Ve	
	Staphylococcus aureus	***Bacillus subtilis***	***E.coli***	***Klebsiella promioe***
4a	55	58	68	66
4b	66	60	59	63
4c	79	69	77	76
4d	56	60	71	80
4e	69	73	80	63

Table: 6 Antibacterial Activity of Compounds (5a-e)

Compounds	Gram +Ve		Gram –Ve	
	Staphylococcus aureus	***Bacillus subtilis***	***E.coli***	***Klebsiella promioe***
5a	55	58	68	66
5b	66	60	59	63
5c	79	69	77	76
5d	56	60	71	80
5e	69	73	80	63

Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Nigrospora Sp, Aspergillus niger, Botrydepladia thiobromine, and Rhizopus nigricum, Fusarium oxyporium.* The antifungal activity of all the compounds 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 fungicidal activity displayed by various compounds is shown in Tables-7,8 and 9.

Table: 7 Antifungal Activity of Compounds (3a-e)

Zone of Inhibition at 1000 ppm (%)					
Compounds	***Nigrospora Sp.***	***Aspergillus Niger***	***Botrydepladia Thiobromine***	***Rhizopus Nigricum***	***Fusarium oxyporium***
3a	68	62	64	59	64
3b	60	64	60	66	66
3c	69	68	69	64	68
3d	67	67	63	72	70
3e	70	72	71	75	73

Table: 8 Antifungal Activity of Compounds (4a-e)

Zone of Inhibition at 1000 ppm (%)					
Compounds	***Nigrospora Sp.***	***Aspergillus Niger***	***Botrydepladia Thiobromine***	***Rhizopus Nigricum***	***Fusarium oxyporium***
4a	70	67	67	61	63
4b	67	69	64	64	61
4c	71	66	62	65	65
4d	65	72	68	66	66
4e	78	74	72	71	70

Table: 9 Antifungal Activity of Compounds (5a-e)

Zone of Inhibition at 1000 ppm (%)					
Compounds	***Nigrospora Sp.***	***Aspergillus Niger***	***Botrydepladia Thiobromine***	***Rhizopus Nigricum***	***Fusarium oxyporium***
5a	70	67	67	61	63
5b	67	69	64	64	61
5c	71	66	62	65	65
5d	65	72	68	66	66
5e	78	74	72	71	70

RESULTS AND DISCUSSION

It was observed that 2-((1H-benzo[d]imidazol-2-yl)thio)acetohydrazide(1) on condensation with furaldehydes, yields 2-(1H-benzo[d]imidazol-2-ylthio)-N'-((5-subsitute

dfuran-2-yl) methylene) acetohydrazide(3a-e). The structures of 3a-e were confirmed by elemental analysis and IR spectra showing an absorption band at 1620-1640 (C=N), 3030-3080 cm^{-1} (C-H of Ar.), 1720-1750 cm^{-1} (-CO), 738 cm^{-1} (C-S),2950, 1370 cm^{-1} ($-CH_3$), 735 (C-Cl),590 (C-Br). ^{1}H NMR : 6.20 – 7.70 (13H, m, Ar – H), 11.80-11.81 (1H, s,-CONH), 8.43-8.80 (1H, s,-N=CH), 4.05(2H,s,CH_2), 2.41 (3H, s,-CH_3). The C, H, N analysis data of all compounds are presented in Table -1.

The structures assigned to 2-(1H-benzo[d]imidazol-2-ylthio)-N-(2-(5-subsitut ed furan-2-yl)-4-oxothiazolidin-3-yl)acetamide(4a-e) were supported by the elemental analysis and IR spectra showing an absorption bands at1690cm^{-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.),1660-1670 cm^{-1} (-CONH), 738 cm^{-1} (C-S), 2950, 1370 cm^{-1} ($-CH_3$), 735 (C-Cl),590 (C-Br) for (4a-e) compounds.^{1}H NMR: 3.85-3.95 (2H, s,-CH_2 of the ring), 5.95-5.96(1H, s,-CH), 6.10 – 7.70 (13H, m, Ar – H), 11.80-11.81 (1H, s,-CONH), 4.05(2H,s,CH_2), 2.41 (3H, s,-CH_3). The C, H, N, S analysis data of all compounds are presented in Table-2.

The structures assigned to 2-(1H-benzo [d] imidazol-2-ylthio) -N-[2-(5-substitutefuran-2-yl) -5-morpholine -4-yl) methyl-4-oxotinazolidin-3-yl)] acetamide (5a-e) were supported by the elemental analysis and IR spectra showing an absorption bands at1690cm^{-1} (C=O of thiazolidinone ring), 718cm^{-1} (C-S-C of thiazolidinone ring), 3030-3080 cm^{-1} (C-H, of Ar.),1660-1670 cm^{-1} (-CONH), 738 cm^{-1} (C-S), 2950, 1370 cm^{-1} ($-CH_3$), 735 (C-Cl),590 (C-Br) for (5a-e) compounds.^{1}H NMR: 3.20-2.90 (2H, s,-CH_2), 3.72-3.76(1H,s,CH),5.95-5.96(1H, s,-CH), 6.10 – 7.70 (12H, m, Ar – H), 11.80-11.81 (1H, s,-CONH), 4.05(2H,s,CH_2), 2.75-3.80 (8H, t,-CH_2). The C, H, N, S analysis data of all compounds are presented in Table-3.

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.LC-MS data of selected compounds shows the molecular ion peak, which is consistent with their corresponds molecular weight.

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