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Synthesis, Characterization and Antimicrobial Studies of Triazole - Thiazolidine Clubbed Heterocyclic Compounds

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Abstract: 4-Amino-1,2,4-traizol (I) on condensation with 5-Phenyl substituted-2- furan carboxaldehyde (IIa-e) yield schiff bases namely N-[(5-Arylfuran-2-yl)methylen]-4H-1,2,4-triazol-4-amine (IIIa-e). Each of schiff base on cyclization with Thioglycolic acid afforded 2-(5-Arylfuran-2-yl)-3-(4H-1,2,4-triazol-4-yl) thiazolidin-4-one (IVa-e). Following this mannich base reaction of each IVa-e with Formaldehyde and Piperidine give 2-(5-Arylfuran-2-yl)-5-(piperidin-1-yl methyl)-3-(4H-1,2,4-triazol-4-yl)thiazolidin-4-one (Va-e). All the compounds of each series were characterized by spectral features and elemental contents. The compounds were also screened for their antimicrobial behavior.

Key words: Triazole, Schiff base, 4-Thiazolidine, Spectral Studies, Antibacterial and Antifungal Activities

I. INTRODUCTION

Recently considerable interest adopted to synthesis of 1,2,4-Triazole derivatives having prominent pharmaceutical activities[1-6]. 4-Thiazolidinones and their derivatives are also reported industrially for their antitubercular, antibacterial, antifungal, anticonvulsant activities[7-8]. One of the heterocyclic compound i.e. Furfural is an agricultural waste material have various reaction properties for production of polymers, drugs, dyes etc.[9-12]. The literature survey reveals that no such work reported in this direction, hence the present communication deals with the synthesis, characterization and antimicrobial activity of novel heterocyclic having 1,2,4-Traizol-4-thiazolidinone merged system. the work will be scanned in the following scheme.

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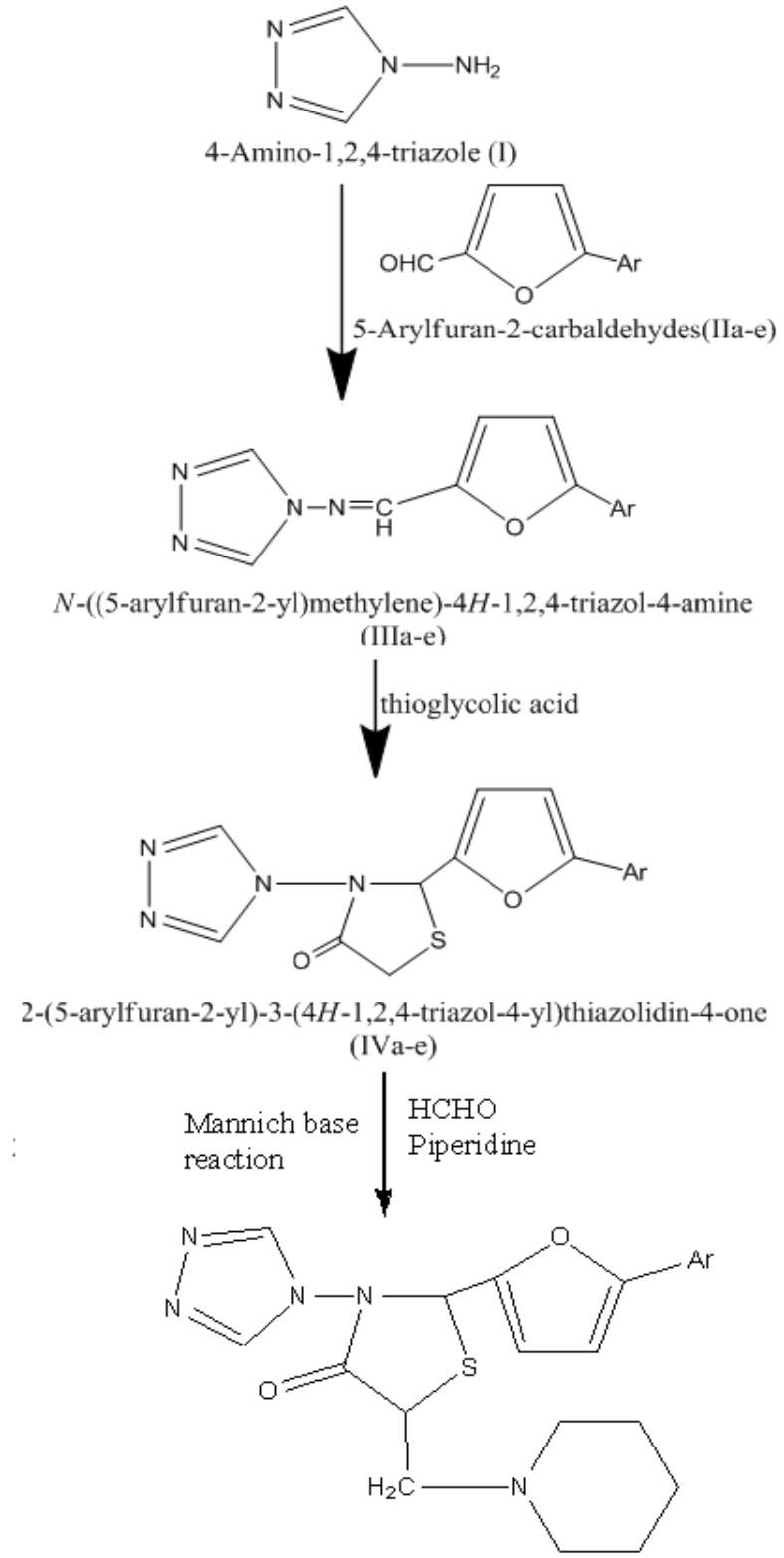

Where Ar= (a) C_6H_5 (b)$_4$-ClC_6H_4 (c) 4-BrC_6H_4
(d) 4-$NO_2C_6H_4$ (e) 2,4-$Cl_2C_6H_3$

SCHEME-1

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II. EXPERIMENTAL

Material and Methods

The IR spectra were taken in KBr on a Nicolet 400D spectrometer and ^{1}H NMR spectra were scanned in DMSO solvent on a Bruker spectrometer at 400 MHz. LC-MS of all samples taken on LC-MSD-Trap-SL_01046. 5-Arylfuran-2-carbaldehydes (IIa-e) were prepared according to reported method[13]. All other reagents used were of A.R.grade.

Synthesis of N-[(5-Arylfuran-2-yl)methylene]-4H-1,2,4-triazol-4-amine (IIIa-e)

4-Amino-1,2,4-triazole (I) (0.01mole) and the 5-Arylfuran-2-carbaldehydes (IIa-e) mixed in ethanol (25 ml) and refluxed for 6 hrs. The solid mass was filtered, washed by dry ether and air dried. The details of all these compounds are furnished in Table -1.

Table:-1 Analytical Data Of Compounds (IIIA-E)

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	Yield %	M.P.* ^{0}C	Elemental Analysis		
					%C	% H	%N
					Found (Calcd.)	Found (Calcd.)	Found (Calcd.)
IIIa	$C_{13}H_{10}N_4O$ (238)	240	85	196-197	65.5 (65.54)	4.2 (4.23)	23.5 (23.52)
IIIb	$C_{13}H_9N_4OCl$ (272)	285	82	202-204	57.2 (57.26)	3.3 (3.33)	20.5 (20.55)
IIIc	$C_{13}H_9N_4OBr$ (317)	329	78	198-199	49.2 (49.23)	2.8 (2.86)	17.6 (17.67)
IIId	$C_{13}H_9N_5O_3$ (283)	297	75	204-206	55.1 (55.13)	3.1 (3.20)	24.7 (24.73)
IIIe	$C_{13}H_8N_4OCl_2$ (307)	327	79	197-199	50.8 (50.84)	2.6 (2.63)	18.2 (18.24)

***** Uncorrected

Synthesis of 2-(5-Arylfuran-2-yl)-3-(4H-1,2,4-triazol-4-yl)thiazolidin-4-one (IVa-e)

The compounds (IIIa-e) (0.01 mole) in Tetrahydrofuran (40 ml) and Thioglycolic acid (0.01 mole) with a 20 mg of anhydrous $ZnCl_2$ was heated an at 100°C for 10 hrs. The solvent was removed, the residue obtained was dissolved in toluene and passed through a column of silica gel using toluene: chloroform (7:3 v/v) mixture as an eluent. The eluate was concentrated and the product crystallized from isopropanol to get 4-Thiazolidinones (IVa-e). The details of these compounds are presented in table-2.

Table:-2 Analytical Data of Compounds (IVa-e)

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	Yield %	M.P.* ^{0}C	Elemental Analysis			
					%C	%H	%N	%S
					Found (Calcd.)	Found (Calcd.)	Found (Calcd.)	Found (Calcd.)
IVa	$C_{15}H_{12}N_4O_2S$ (312)	314	68	231-232	57.6 (57.68)	3.8 (3.87)	17.9 (17.94)	10.2 (10.27)
IVb	$C_{15}H_{11}N_4O_2SCl$ (346)	329	62	214-215	51.9 (51.95)	3.1 (3.20)	16.0 (16.16)	9.2 (9.25)
IVc	$C_{15}H_{11}N_4O_2SBr$ (391)	406	63	226-228	46.0 (46.05)	2.8 (2.83)	14.3 (14.32)	8.1 (8.20)
IVd	$C_{15}H_{11}N_5O_4S$ (357)	371	68	219-220	50.4 (50.42)	3.0 (3.10)	19.5 (19.60)	8.9 (8.97)
IVe	$C_{15}H_{10}N_4O_2SCl_2$ (381)	395	63	224-226	47.2 (47.26)	2.6 (2.64)	14.6 (14.70)	8.3 (8.41)

*****Uncorrected

Mannich base formation of 2-(5-Arylfuran-2-yl)-5-(piperidin-1-yl methyl)-3-(4H-1,2,4-triazol-4-yl) thiazolidin-4-one (Va-e)

The each of above 4-Thiazolidinone derivatives (IVa-e) was refluxed with piperidine and formaldehyde (≈37%w/w) solutions at stoichiometric ratio in 1,4-dioxane. The product was filtered, washed by ethanol and air-dried. The analytical data are given in Table-3.

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Table:-3 Analytical Data of Compounds (Va-e)

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	Yield %	M.P.* ^{0}C	Elemental Analysis			
					%C	%H	%N	%S
					Found (Calcd.)	Found (Calcd.)	Found (Calcd.)	Found (Calcd.)
Va	$C_{21}H_{23}N_5O_2S$ (409)	422	70	180-181	61.5 (61.59)	5.6 (5.66)	16.9 (17.10)	7.8 (7.83)
Vb	$C_{21}H_{22}N_5O_2SCl$ (443)	458	65	196-198	56.8 (56.81)	4.9 (4.99)	15.7 (15.78)	7.2 (7.22)
Vc	$C_{21}H_{22}N_5O_2SBr$ (488)	503	66	203-204	51.6 (51.64)	4.5 (4.54)	14.3 (14.34)	6.5 (6.57)
Vd	$C_{21}H_{22}N_6O_4S$ (454)	468	64	211-212	55.4 (55.49)	4.8 (4.88)	14.0 (14.08)	7.0 (7.05)
Ve	$C_{21}H_{21}N_5O_2SCl_2$ (477)	495	61	215-217	52.7 (52.72)	4.4 (4.42)	14.6 (14.64)	6.6 (6.70)

*****Uncorrected

III. 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[14]. A methanol system was used as control in this method. Similar conditions using tetracycline as a control was used standard for comparison. The results in terms of percentage area of inhibition growth of bacteria are given in table- 4 to 6. The results show that compounds IIIe, IVe and Ve are more toxic for bacteria.

Table:-4 Antibacterial Activity of Compounds (IIIa-e)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	Bacillus subtilis	E.coli	Klebsiella promioe
IIIa	54	53	56	48
IIIb	56	53	51	56
IIIc	57	55	65	54
IIId	63	58	59	53
IIIe	68	67	77	61

Table:-5 Antibacterial Activity of Compounds (IVa-e)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	Bacillus subtilis	E.coli	Klebsiella promioe
IVa	56	54	58	51
IVb	58	58	59	56
IVc	60	59	67	54
IVd	64	60	69	53
IVe	71	72	77	66

Table:-6 Antibacterial Activity of Compounds (Va-e)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	Bacillus subtilis	E.coli	Klebsiella promioe
Va	58	55	59	53
Vb	60	59	60	57
Vc	61	61	68	55
Vd	66	63	70	54
Ve	73	74	78	68

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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 (IIIa-e), (IVa-e) and (Va-e) were measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. The PDA media were poured into sterile petri plates having 100 mg sample, then the Petri dishes were kept inside for 5 days, 5 days culture (i.e. fungi) was inoculated into Petri plates. All the plates were kept aside per 5 days, the percentage inhibition for growth of fungi was calculated as follows

Percentage of inhibition = 100(X-Y) / X

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

The results of various compounds (IIIa-e), (IVa-e) and (Va-e) is shown in Tables-7,8 and 9.

Table:-7 Antifungal Activity of Compounds (IIIa-e)

Zone of Inhibition of growth at 1000 ppm (%)					
Compounds	**Nigrospora Sp.**	**Aspergillus Niger**	**Botrydepladia Thiobromine**	**Rhizopus Nigricum**	**Fusarium oxyporium**
IIIa	56	50	61	55	67
IIIb	66	67	63	62	68
IIIc	67	66	69	61	66
IIId	69	68	70	74	64
IIIe	70	72	73	75	76

Table:-8 Antifungal Activity of Compounds (IVa-e)

Zone of Inhibition of growth at 1000 ppm (%)					
Compounds	**Nigrospora Sp.**	**Aspergillus Niger**	**Botrydepladia Thiobromine**	**Rhizopus Nigricum**	**Fusarium oxyporium**
IVa	59	53	62	57	69
IVb	67	69	65	66	70
IVc	70	67	71	64	69
IVd	72	70	73	76	66
IVe	72	74	75	77	79

Table:-9 Antifungal Activity of Compounds(Va-e)

Zone of Inhibition of growth at 1000 ppm (%)					
Compounds	**Nigrospora Sp.**	**Aspergillus Niger**	**Botrydepladia Thiobromine**	**Rhizopus Nigricum**	**Fusarium oxyporium**
Va	61	54	63	58	70
Vb	68	70	67	67	72
Vc	71	68	72	65	73
Vd	74	71	74	78	67
Ve	76	75	76	79	80

IV. RESULTS AND DISCUSSION

The 4-Amino-1,2,4-triazole (I) on reaction with 5-Arylfuran-2-carbaldehydes (IIa-e), perform schiff bases N-[(5-Arylfuran-2-yl)methylene]-4H-1,2,4-triazol-4-amine (IIIa-e). The structures of (IIIa-e) were confirmed by elemental analysis and IR spectra bands at 1625-1650 (C=N), 3040-3080 cm^{-1} (C-H, of Ar.),1185(C-O-C), 3385(-OH), 2850 cm^{-1} (-OCH_3), 2950, 1370 cm^{-1} (-CH_3), 1080(-Cl),1555, 1375(-NO_2) and the ^{1}H NMR signals 6.62-9.01 (9H, m, Ar - H), 8.41-8.80 (1H, s,-N=CH). The C, H, N analysis data of all compounds are agree with desired structure.

Similarly 2-(5-Arylfuran-2-yl)-3-(4H-1,2,4-triazol-4-yl)thiazolidin-4-one (IVa-e) shows IR spectra bands at 1680cm^{-1} (C=O of thiazolidinone ring), 720cm^{-1} (C-S-C of thiazolidinone ring), 3080-3090cm^{-1} (CH_2 of thiazolidinone ring), 3040-3080cm^{-1} (C-H, of Ar.), 3450-3560 cm^{-1} (-OH), 1185(C-O-C), 3385(-OH), 2850 cm^{-1} (-OCH_3), 2950, 1370 cm^{-1} (-CH_3), 1080(-Cl),1555, 1375(-NO_2) and ^{1}H NMR signal 3.80-3.90 (2H, s,-CH_2 of the ring), 5.94-5.95 (1H, s,-CH), 6.32-8.44 (9H, m, Ar - H). The C, H, N, S analysis data of all compounds are shown in Table-2.

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The Mannich base products were confirmed structurally by the elemental analysis, IR and NMR spectral features. The bands at 1680cm^{-1} (C=O of thiazolidinone ring), 720cm^{-1} (C-S-C of thiazolidinone ring), 3080-3090cm^{-1} (CH of thiazolidinone ring), 3040-3080cm^{-1} (C-H, of Ar.),2950, 1370 cm^{-1} (-CH_2), 1080(-Cl),1555, 1375(-NO_2). The ^{1}H NMR signal 3.80-3.90 (2H, s,-CH of the ring), 5.94-5.95 (1H, s,-CH), 6.32-8.44 (9H, m, Ar - H),2.54(4H,t,-CH_2),1.55-1.62(6H,m,CH_2). The C, H, N, S analysis data of all compounds are shown in Table-3.

The assessment of elemental analytical data discloses that the elemental contents are consistence with the expected structure shown in Scheme-1. The IR data also express for assignment of the predicted structure. The final structure of all compounds is confirmed by LC-MS. LC-MS data of all compounds are presented in Tables-1,2 and 3.

CONCLUSION

The reaction of 4-Amino-1,2,4-triazole (I) with 5-Arylfuran-2-carbaldehydes (IIa-e) yields Schiff bases of N-[(5-Arylfuran-2-yl)methylene]-4H-1,2,4-triazol-4-amine (IIIa-e), which on reaction with Thioglycolic acid yielded 2-(5-Arylfuran-2-yl)-3-(4H-1,2,4-triazol-4-yl)thiazolidin-4-one (IVa-e) and their Mannich base products (Va-e), their structured were proved by the elemental and spectral analysis. Newly prepared compounds were shows moderate to good antibacterial and antifungal activities.

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