Preparation and Antimicrobial Studies of Pyrazolo-Thiazole Fused Heterocyclic Compounds

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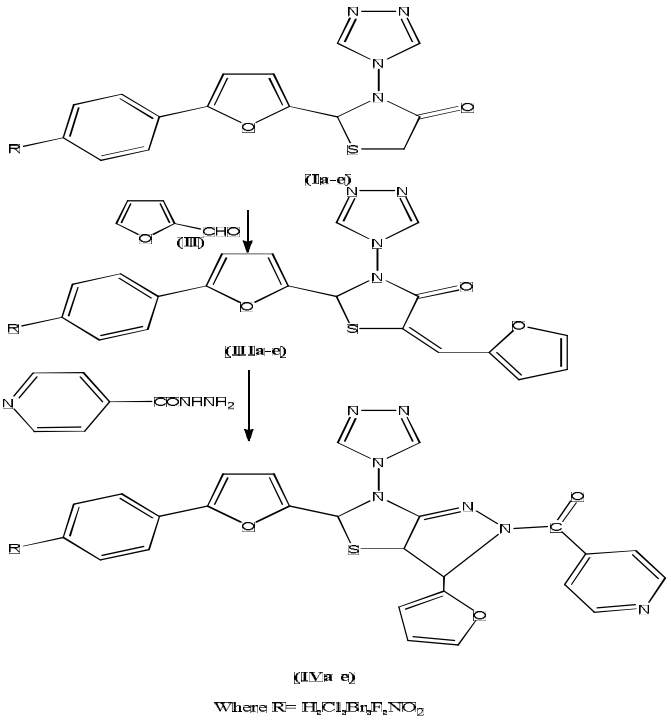
ABSTRACT
2-[5-(4-Ary)furan-2-y]-3-(4H-1,2,4-triazol-4-yl)thiazolidin-4-one (Ia-e) compounds [1] reacted with furfural in the presence of sodium hydroxide affords, 5-[(furan-2-yl)methylen]-2-[5-(4-alkylphenyl)furan-2-y]-3-(4H-1,2,4-triazol-4-yl)thiazolidin-4-one (IIIa-e). These (IIIa-e) compounds reacted with Isoniazide yield [3-(furan-2-yl)-5-[5-(4-alkylphenyl)furan-2-yl]-6-(4H-1,2,4-triazol-4-yl)3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazol-2-yl](pyridin-4-yl) methanone (IVa-e). The molecular structures of all these novel heterocyclic derivatives were confirmed by elemental content and FTIR-NMR spectral features. The antimicrobial activity of all these derivatives were monitored.

***Keywords*:** Thiazolidine, Pyrazole, FTIR-NMR, Antimicrobial activity.

I INTRODUCTION

We reported recently the 4-Thiazolidinone derivatives based on Schiff base of 5-Aryl furfural and 4-Amino-1,2,4-triazole[1]. In continuous of our work[1], the present paper comprises the fused heterocycles i.e. pyrazol-thiazole. For this the furylidine derivatives of 5-[(furan-2-yl)methylene]-2-[5-(4-alkylphenyl)furan-2-yl]-3-(4*H*-1,2,4-triazol-4-yl)thiazolidin-4-one(IIIa-e) were prepared and condensed with isoniazide considering with the potential pharmaceutical activity of these derivatives.[2-7] All the final products [3-(Furan-2-yl)-5-[5-(4-alkylphenyl)furan-2-yl]-6-(4*H*-1,2,4-triazol-4-yl)-3,3a,5,6-tetrahydro-2*H*-pyrazolo [3,4-d] thiazol-2-yl] (pyridin-4-yl)methanone (IVa-e) were characterized duly. The synthetic route is as follows.

Scheme – 1



II EXPERIMENTAL

(a) Materials - All chemicals used were of laboratory grade. 2-[5-(4-alkylphenyl)furan-2-yl]-3-(4*H*-1,2,4-triazol-4-yl) thiazolidin-4-one (Ia-e) prepared by our earlier research work[1].

(b) Measurement - Melting points of present novel derivatives were measured by laboratory paraffin method. All m.p were uncorrected.

Preparation of 5-[(5-substituted furan-2-yl) methylene]-2-[5-(4-alkylphenyl)furan-2-yl]-3-(4*H*-1,2,4-triazol-4-yl)thiazolidin-4-one (IIIa-e)

An equimolar solution of 2-[5-(4-alkylphenyl)furan-2-yl]-3-(4*H*-1,2,4-triazol-4-yl)thiazolidin-4-one(Ia-e) and 2-furaldehyde in alkaline 1,4-dioxane 50 ml were boiled for 5 hrs. The 1,4-dioxane was distilled under reduced pressure. The so called obtained derivative was recrystallized from absolute alcohol. It was designated as 5-[(5-substituted furan-2-yl) methylene]-2-[5-(4-alkylphenyl)furan-2-yl]-3-(4*H*-1,2,4-triazol-4-yl) thiazolidin-4-one(IIIa-e). The product yields, m.p. and other data of present novel derivatives are presented in Table-1.

Preparation of [3-(furan-2-yl)-5-[5-(4-alkylphenyl) furan-2-yl]-6-(4*H*-1,2,4-triazol-4-yl)-3,3a,5,6-tetra hydro-2*H*-pyrazolo[3,4-d]thiazol-2-yl](pyridin-4-yl)methanone (IVa-e)

A solution of **(IIIa-e)** (0.01mol) in glacial acetic acid (25 ml) was stirred with isoniazide (0.15 mol) for 5 hours at 70-80°C. The solvent was removed under reduced pressure, and the residue was diluted with water. It was extracted with ether, washed with saturated $NaHCO_3$ solution, water, brine solution and dried. The solvent was removed and the crude product was purified by recrystallization from ethanol. The product yields, m.p. and all the details of present heterocycles are tabulated in Table-2.

Table:-1
Characterization of novel heterocyclic compounds (IIIa-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.
IIIa	$C_{20}H_{14}N_4O_3S$ (390)	70	231-233	61.5	61.53	3.6	3.61	14.3	14.35	8.2	8.21
IIIb	$C_{20}H_{13}N_4O_3SCl$ (424)	67	227-228	56.5	56.54	3.0	3.08	13.1	13.19	7.5	7.55
IIIc	$C_{20}H_{13}N_4O_3SBr$ (467)	72	233-234	51.1	51.18	2.7	2.79	11.9	11.94	6.8	6.83
IIId	$C_{20}H_{13}N_4O_3SF$ (408)	66	239-240	58.8	58.82	3.2	3.21	13.7	13.72	7.8	7.85
IIIe	$C_{20}H_{13}N_5O_5S$ (435)	69	229-230	55.1	55.17	2.9	3.01	16.0	16.08	7.3	7.36

***** Uncorrected LC-MS data of IIIc-469,IIIe-437

Table:-2
Characterization of novel heterocyclic compounds (IVa-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.
IVa	$C_{26}H_{19}N_7O_3S$ (509)	78	241-243	61.2	61.29	3.7	3.76	19.2	19.24	6.2	6.29
IVb	$C_{26}H_{18}N_7O_3SCl$ (543)	72	245-247	57.4	57.41	3.3	3.34	18.0	18.02	5.8	5.89
IVc	$C_{26}H_{18}N_7O_3SBr$ (587)	74	248-249	53.0	53.07	3.0	3.08	16.6	16.66	5.4	5.45
IVd	$C_{26}H_{18}N_7O_3SF$ (527)	63	238-239	59.1	59.20	3.4	3.44	18.5	18.59	6.0	6.08
IVe	$C_{26}H_{18}N_8O_5S$ (554)	73	246-247	56.3	56.31	3.2	3.27	20.2	20.21	5.7	5.78

***** Uncorrected LC-MS data of IVa-512,IVd-529

III BIOLOGICAL SCREENING

(a) Antibacterial activities - The antibacterial properties of all the produced heterocycles were screened against gram +ve and gram -ve bacteria (the bacteria name are given in table). The monitoring such properties was carried out by far process reported in an our earlier communication[1]. Compounds IIIb & IVb were observed as more toxic for bacteria. All compounds found to be less or moderate active shown in Tables -3.

Table:-3
Antibacterial Activity of Compounds (IIIa-e) and (IVa-e)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	*Bacillus subtilis*	*E.coli*	*Klebsiella promioe*
IIIa	42	61	59	68
IIIb	50	75	69	80
IIIc	49	74	66	77
IIId	45	67	64	74
IIIe	46	64	61	70
IVa	43	63	60	68
IVb	51	76	70	81
IVc	51	74	67	82
IVd	46	67	65	75
IVe	46	66	63	71

(b) Antifungal Activities - The antifungal activities of all the new derivatives were measured as process reported by us earlier[1]. The fungicidal activity displayed by various compounds (IIIa-e) and (IVa-e) is shown in Tables-4.

Table:-4
Antifungal Activity of Compounds (IIIa-e) and (IVa-e)

Compounds	*Nigrospora Sp.*	*Aspergillus Niger*	*Botrydepladia Thiobromine*	*Rhizopus Nigricum*
IIIa	54	53	58	59
IIIb	67	72	68	66
IIIc	66	69	72	68
IIId	62	67	59	61
IIIe	56	56	60	63
IVa	55	54	60	61
IVb	67	74	69	67
IVc	65	70	66	67
IVd	64	69	60	62
IVe	57	57	61	64

IV RESULTS AND DISCUSSION

The IR spectra of 5-[(5-substituted furan-2-yl)methylene]-2-([-(4-alkylphenyl)furan-2-yl]-3-(4*H*-1,2,4-triazol-4-yl) thiazolidin-4-one(IIIa-e) showing an absorption bands at 1680cm^{-1}(C=O of thiazolidinone ring), 720cm^{-1} (C-S-C of thiazolidinone ring), 3040-3080cm^{-1} (C-H, of Ar.), 1185(C-O-C),1080(-Cl),1555,1375(-NO_2),710(C-Br),1255(C-F), 1625cm^{-1}(-C=CH-Ar). ^{1}H NMR: 7.76(1H,s,-CH), 6.50-8.20(12H,m,Ar-H), 6.50(1H,s,CH). The C, H, N, S analysis data of all compounds are presented in Table-1. The IR spectra of (IVa-e) are almost identical with those of the corresponding (IIIa-e). Only the difference appeared that the new bands (but not strong) at 1640cm^{-1} (-C=N) and 1045 cm^{-1}(N-N) are observed in all the spectra of (IVa-e). ^{1}HNMR:6.50-8.92(16H,m,Ar-H),5.36(1H,s,CH), 5.50(1H,s,CH). The C, H, N, S analysis data of all compounds are presented in Table-2. LC-MS of selected samples IIIc and IV d show the peak respectively at 469 and 529 which assign the molecular weight of compound, The inspection of elemental content of all the new derivatives suggest that the values are agree wrt proposed structure illustrated in Scheme-1. The FTIR also confirm the proposed structure and further in 1,4-dioxane with little NaOH were heated to boiling for 4 hrs. The solvent was distilled under vacuum and the resultant derivative was recrystallized from R.Spirit are mostly identical those of corresponding (IIIa-e). Only noticeable change observed that the new medium band around 1642 cm^{-1} (-C=) appeared in all FTIR spectral scans (IVa-e).

V CONCLUSION

The [3-(furan-2-yl)-5-[5-(4-alkylphenyl)furan-2-yl] -6-(4H-1,2,4-triazol-4-yl)3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d] thiazol-2-yl](pyridin-4-yl) methanone (IVa-e) was synthesized by reaction of 5-[(furan-2-yl)methylene]-2-[5-(4-alkylphenyl)furan-2-yl]-3-(4H-1,2,4-triazol-4-yl) thiazolidin-4-one (IIIa-e) with Isoniazide. The structures of all synthesized compounds

were characterized by elemental and spectral data. All the synthesized compounds showed moderate to good antibacterial and antifungal activities.

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