Synthesis and Biological Activity of Furan Containing Azitidinone Compounds

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ABSTRACT
The Schiff's bases (1a-e) based on 5-arylfurfural and Isoniazid prepared by us [1], were condensed with chloro acetyl chloride. The obtained 2-azitidinone derivatives were further treated respectively with sulphamethoxazole and morpholine. The so-called derivatives N-(2-(5-(4-alkylphenyl)furan-2-yl)-3-((4-(N-(isoxazol-3-yl)sulfamoyl) phenyl) amino) -4-oxoazetidin-1-yl) isonicotinamides (3a-e) and N-(2-(5-(4-alkylphenyl)furan-2-yl)-3-morpholino-4-oxoazetidin-1-yl)isonicotinamides (4a-e) and (2-azitidinone) were characterized by elemental content and spectral features. Their antimicrobial activity has also been monitored against common microbes.

Keywords: Isoniazid, furfural, 2-azitidinono, morphine, elemental analysis, spectroscopy and Antibacterial and antifungal activity.

I INTRODUCTION

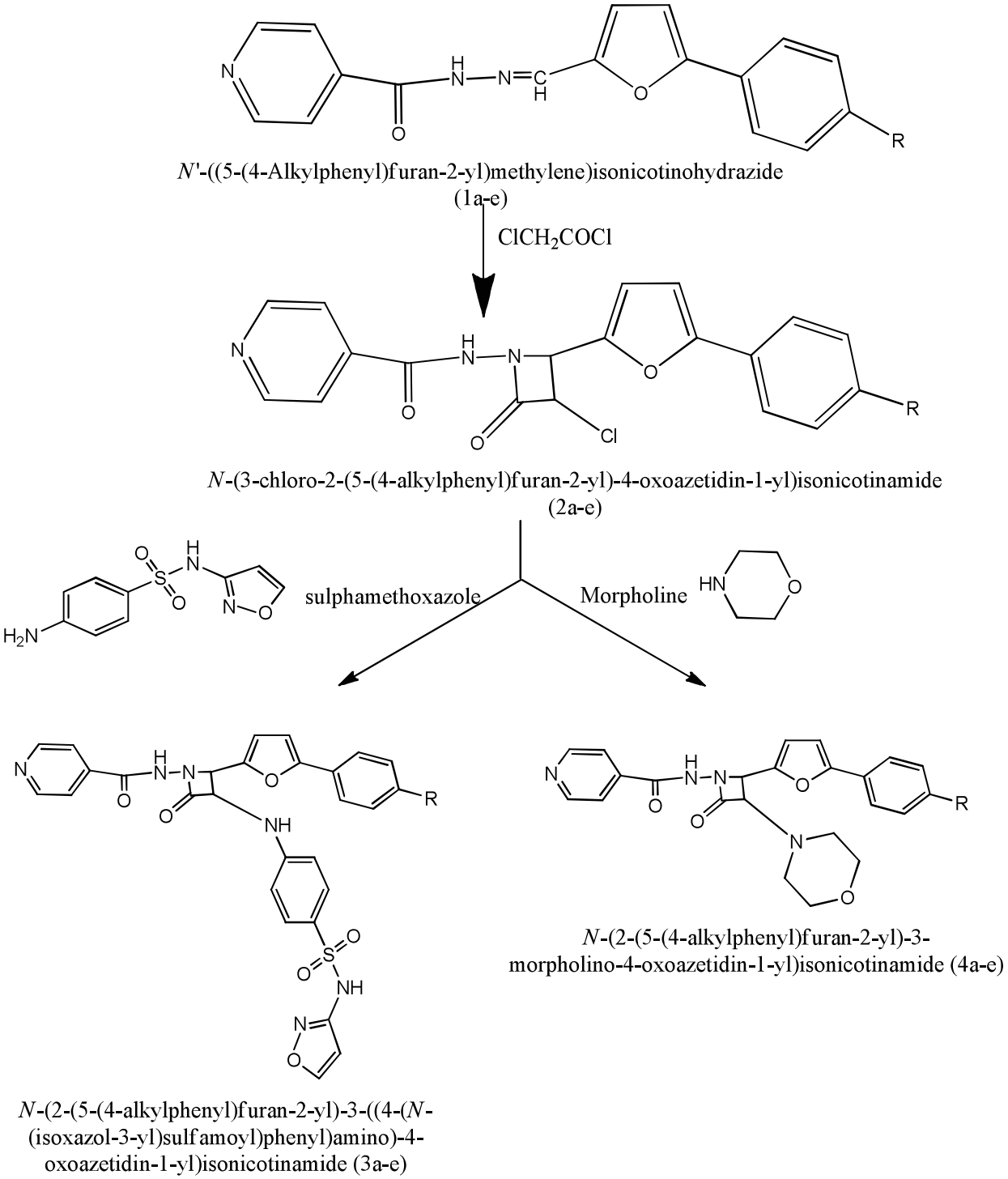
In earlier work of the author [1] 4-thiazolidone derivatives based on Schiff's base of Isoniazid and 5-arylfurfurals was reported. The work was carried out with considering excellent medicinal properties of Isoniazid. In extension of it [1] the present communication comprises the 2-azitidinone derived from same Schiff's bases followed by reaction with sulphamethoxazole and morpholine respectively considering with their important pharmaceutical activities [2-8]. The work is screened at fig. 1.

(a) **Material and Methods -** All the chemicals were used of pure grade. Melting points were estimated by laboratory method and all were uncorrected. The FTIR spectra were taken KBr disc by using Nicolet 400D spectrometer. The proton NMR spectra were as Bruker (400 MHz.) spectrometer using deuterated DMSO. LC-MS of choice compound were scan on LC-MSD-Trap-SL_01046. N'-((5-(Aryl furan-2-yl)methylene) isonicotinohydrazide (1a-e) were prepared by our earlier communication.[1]

II EXPERIMENTAL

Synthesis of N-(3-Chloro-2-(5-(aryl furan-2-yl)-4-oxoazetidin-1-yl) isonicotinamide (2a-e)

A solution of N'-(5-(Arylfuran-2-yl)methylene) isonicotinohydrazide (1a-e) and Triethyl amine (TEA) was prepared in 1,4-dioxane, and cooled with stirring. The equimolor chloroacetyl chloride was added drop wise with stirring. They kept aside for several hours till viscous mass obtained. The so called viscous mass was then added slowly in to crushed ice with vigorous agitation. The precipitation were yielded then filtered, washed by plenty of water then by dry ether. The air dried product finally purified by column chromatography to give gave N-(3-chloro-2-(5-(4-Alkylphenyl)furan-2-yl)-4-oxoazetidin-1-yl)isonicotinamide(2a-e). The details of all these heterocyclic compounds are presented in Table -1.



Where,R = (a) H (b) Cl (c) Br (d) F (e) NO_2

SCHEME - 1

Fig. 1 – Display of Scheme

Table:-1
Analytical Data and Elemental Analysis of Compounds (2a-e)

Compd.	Mol.for. (Mol.wt.)	Product Yield % age	M.P.* ^{0}C	Elemental Analysis in % age					
				C		H		N	
				Calcd.	Obtained	Calcd.	Obtained	Calcd.	Obtained
2a	$C_{19}H_{14}N_3O_3Cl$ (367)	85	185-187	62.05	62.0	3.84	3.8	11.43	11.4
2b	$C_{19}H_{13}N_3O_3Cl_2$ (401)	81	181-182	56.73	56.7	3.26	3.2	10.45	10.4
2c	$C_{19}H_{13}N_3O_3ClBr$ (446.68)	77	194-196	51.09	51.0	2.93	2.9	9.41	9.4
2d	$C_{19}H_{13}N_3O_3ClF$ (385)	79	202-204	59.15	59.1	3.40	3.3	10.89	10.8
2e	$C_{19}H_{13}N_4O_5Cl$ (412)	81	193-195	55.28	55.2	3.17	3.1	13.57	13.5

* Uncorrected LC-MS $M^+$of 2b: 417 ,2d:396

Synthesis of N-(2-(5-(Arylfuran-2-yl)-3-((4-(N-(isoxazol-3-yl)sulfamoyl)phenyl) amino) -4-oxoazetidin-1-yl)isonicotinamide (3a-e)

The mixture of N-(3-Chloro-2-(5-(arylfuran-2-yl)-4-oxoazetidin-1-yl)isonicotinamide (2a-e) and sulphamethoxazole and dilHCl at stoichiometric ratio in Tetrhydrofuran solvent was refluxed for three hrs. the resultant mixture was poured in to ice water, the precipitate were collected , filtered and air dried. The products are designated as N-(2-(5-(Arylfuran-2-yl)-3-((4-(N-(isoxazol-3-yl)sulfamoyl)phenyl)amino)-4-oxoazetidin-1-yl)isonicotinamide (3a-e). The details of all these heterocyclic compounds are presented in Table -2.

Table:-2
Analytical Data and Elemental Analysis of Compounds (3a-e)

Compd.	Mol.for. (Mol.wt.)	Product Yield % age	M.P.* ^{0}C	Elemental Analysis in % age							
				C		H		N		S	
				Calcd.	Obtained	Calcd.	Obtained	Calcd.	Obtained	Calcd.	Obtained
3a	$C_{28}H_{22}N_6O_6S$ (570)	65	213-215	58.94	58.9	3.89	3.8	14.73	14.7	5.62	5.6
3b	$C_{28}H_{21}N_6O_6SCl$ (604)	63	210-212	55.58	55.5	3.50	3.4	13.89	13.8	5.30	5.2
3c	$C_{28}H_{21}N_6O_6SBr$ (648)	60	226-227	51.78	51.7	3.26	3.2	12.94	12.9	4.94	4.9
3d	$C_{28}H_{21}N_6O_6SF$ (588)	65	238-239	57.14	57.1	3.60	3.5	14.28	14.2	5.45	5.4
3e	$C_{28}H_{21}N_7O_8S$ (615)	66	221-223	54.63	54.6	3.44	3.4	15.93	15.9	5.21	5.2

*** Uncorrected LC-MS $M^+$of 3b: 620 ,3d:603**

Synthesis of N-(2-(5-(4-alkylphenyl)furan-2-yl)-3-morpholino-4-oxoazetidin-1-yl)isonicotin amide (4a-e)

A mixture N-(3-chloro-2-(5-(4-alkylphenyl)furan-2-yl)-4-oxoazetidin-1-yl)isonicotinamide (2a-e) and Morpholine and dil HCl at stoichiometric ratio was refluxed for 3 day. It was then poured in to ice water ,filtered and, air dried, it was Recrystallization from ethanol-acetone mixture to obtained N-(2-(5-(arylfuran-2-yl)-3-morpholino-4-oxoazetidin-1-yl)isonicotinamide (4a-e). The details of all these heterocyclic compounds are presented in Table -3.

Table:-3
Analytical Data and Elemental Analysis of Compounds (4a-e)

Compd.	Mol. For. (Mol.wt.)	Product Yield % age	M.P.* ^{0}C	Elemental Analysis in % age					
				C		H		N	
				Calcd.	Obtained	Calcd.	Obtained	Calcd.	Obtained
4a	$C_{23}H_{22}N_4O_4$ (429)	60	198-199	66.02	66.0	5.30	5.2	13.39	13.3
4b	$C_{23}H_{21}N_4O_4Cl$ (452)	58	196-197	61.00	60.9	4.67	4.6	12.37	12.3
4c	$C_{23}H_{21}N_4O_4Br$ (496)	54	190-192	55.54	55.5	4.26	4.2	11.27	11.2
4d	$C_{23}H_{21}N_4O_4F$ (436)	57	187-189	63.30	63.2	4.85	4.8	12.84	12.8
4e	$C_{23}H_{21}N_5O_6$ (463)	58	191-192	59.61	59.6	4.57	4.5	15.11	15.1

***** Uncorrected LC-MS $M^+$of 4b: 468,4d:448

III BIOLOGICAL SCREENING

(a) **Antibacterial activities** - Antibacterial and antifungal activity of all three series (2a-e, 3a-e,4a-e) of compounds were evaluated by the method described by us [1] and also earlier report [9]. Both the activities measured by using bacteria and fungi mentioned in table 4 to 9. The similar parameters and type of microbes mentioned in tables 3 to 8 as presented in our communication [1].

Table:-4
Antibacterial behaviors of Compounds (2a-e)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	Bacillus subtilis	E.coli	Klebsiella promioe
2a	58	56	54	45
2b	59	51	49	53
2c	61	52	63	49
2d	65	57	55	48
2e	72	66	75	56

Table:-5
Antibacterial behaviors of Compounds (3a-e)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	Bacillus subtilis	E.coli	Klebsiella promioe
3a	64	60	48	37
3b	65	47	43	45
3c	67	48	57	41
3d	71	53	49	40
3e	78	62	69	48

Table:-6
Antibacterial behaviors of Compounds (4a-e)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	Bacillus subtilis	E.coli	Klebsiella promioe
4a	61	58	51	41
4b	62	49	46	49
4c	64	50	60	45
4d	68	55	52	44
4e	75	64	72	52

Table:-7
Antifungal behaviors of Compounds (2a-e)

% age of growth of Zone of Inhibition of fungus				
Compounds	Nigrospora Sp.	Aspergillus Niger	Botrydepladia Thiobromine	Rhizopus Nigricum
2a	67	62	45	33
2b	68	45	40	41
2c	70	46	54	37
2d	74	51	46	36
2e	75	60	66	44

Table:-8
Antifungal behaviors of Compounds (3a-e)

% age of growth of Zone of Inhibition of fungus				
Compounds	Nigrospora Sp.	Aspergillus Niger	Botrydepladia Thiobromine	Rhizopus Nigricum
3a	73	66	39	25
3b	74	41	34	33
3c	76	42	48	29
3d	78	47	40	28
3e	79	56	60	36

Table:-9
Antifungal behaviors of Compounds (4a-e)

% age of growth of Zone of Inhibition of fungus				
Compounds	Nigrospora Sp.	Aspergillus Niger	Botrydepladia Thiobromine	Rhizopus Nigricum
4a	70	64	42	29
4b	71	43	37	37
4c	73	44	51	33
4d	77	49	43	32
4e	78	58	63	40

IV RESULTS AND DISCUSSION

It was observed that Schiff bases [1a-e] on condensation with Chloroacetyl chloride afford 2-Azetidine derivatives namely 5-Arylfuran-2-carbaldehydes (2a-e). These on further on neucleophilic substituted reactions respectively sulphamethoxazole and morpholine yieldthe compound namely N'-((5-Arylfuran-2-yl)methylene)isonicotinohydrazide (3a-e) and N-(4-oxo-2-(5-Arylfuran-2-yl)thiazolidin-3-yl) isonicotinamide(4a-e) all the series compounds determined and furnishes tables 1 to 3. The results of these values

The Infra-red (IR) spectra of all the these series are identical in most of aspects. All the spectra complies the the bands due to aromatic ring at 3030 and 1600,1500 cm^{-1}, C=O of azetidinone around 1690 cm^{-1} due to amide group. However the discernible differences in the spectra of 3a-e and 4a-e are observed. The bands due to sulfonamide at 3300, 3230,1340,1190,920 cm^{-1} observed in spectra of 3a-e and the bands due to CH_2 groups, around 2920,2850 and 1470 cm^{-1} observed in the spectra of (4a-e) from morpholine ring .

NMR spectra of all the series of compound comprise following common features.

The signal due to aromatic proton appeared in the range of 6.9 to 8.1 ppm depending upon the number of protons.

The signal due to –CONH amide proton arised around 8.1-8.2 ppm.

The signals due to proton of azetidine ring are appeared in the range of 3.3 to 3.5 ppm.

The NMR spectra of (3a-e) compound have additional signal due to proton of –NH and $-SO_2NH_2$ group. These are appeared respectively the 6.1-6.31 and 9.03-9.2 ppm .

The NMR spectra of (4a-e) compound deals with the prominent signal due to 4-CH_2 groups the more intensive signal with C_6H_5 arised around 2.1 ppm .

The LC-MS data of selected compound (Shown as footnote in tables 1 to 3) indicate for molecular weight of compound.

V CONCLUSION

The reaction of Schiff bases (1a-e) with Chloroacetyl chloride yield 2-azetidine derivatives. The post reactions of 2-Azetidines (2a-e) respectively with Sulphamethoxazole and morpholine afforded (chlorine replaced products 5-Arylfuran-2-carbaldehydes (2a-e), N'-((5-Arylfuran-2-yl)methylene)isonicotinohydrazide (3a-e) and N-(4-oxo-2-(5-Arylfuran-2-yl)thiazolidin-3-yl) isonicotinamide (4a-e). There structure confirmed by spectra analytical data. The antibacterial and antifungal activities of all these componds are more or less depending upon the nature of compound.

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