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Cyclization of biologically active furan derivatives

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ABSTRACT

The present work involved cyclization of imines by reaction with chloro-methylene chloride using 1,4-dioxane as solvent (2a-2c) . The cyclic derivatives were found to be associated with various diverse pharmacological activity such as antimicrobial. Prior to determination of the pharmacological activity LD_{50} was determined. The pharmacological data obtained were tested for statistical significance.

Keywords: Furfuraldehyde, Imines, Column chromatography, Azatidines, Antimicrobial, Analgesic.

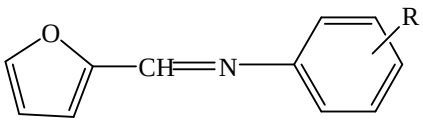
INTRODUCTION

Organic compounds containing five-membered aromatic heterocyclic rings are widely distributed in nature and often play an important role in various biochemical processes. As a result they are incorporated into new chemical entities by medicinal chemists [1]. Furans the most representative five-membered heterocycle, are common structural motifs in many biologically active molecules and pharmaceutical substances, being also widely employed as versatile building blocks in synthetic organic chemistry [2]. The prospect of exciting research activity in the chemistry of furfural derived compounds such as 5-hydroxymethylfurfural (HMF), 2,5-furandicarbaldehyde and 2,5-furan-dicarboxylic acid prompted the writing of this article. As the field of application of these compounds is really enormous, it is no wonder that research in this area, starting at the end of 19th century, is still being developed. Numerous important scientific groups are carrying out studies on the synthesis, and applications of HMF and its derivatives [3]. As furan the least aromatic, and therefore the most pronouncedly dienic, of the five-membered aromatic heterocycles, its tendency to participate in Diels–Alder (DA) cycloaddition reactions as a diene has been studied extensively[4] . Recently Gandini *et al.*[5,6,7] have used bisdienophiles in DA reactions to crosslink polymer chains containing

furanic moieties and have assessed the relative thermal stability of the resulting products. The emergence of multi-resistant strains of bacteria in recent years has driven the search for new therapeutic compounds with novel modes of action to supplement existing anti-microbials[8]. Traditional antibiotics impose selective pressure on bacteria, leading to drug resistance [9]. A new key strategy is to target the various regulatory systems in bacteria that control the expression of virulence. Bacteria communicate with each other *via* small intercellular signal compounds and this regulatory system is known as quorum sensing (QS) [10.11]. Quorum sensing is critical for bacterial biofilm formation and the expression of virulent phenotypes. *N*-Acyl-L-homoserine lactones (AHL) are the most widely studied class of QS mediators and they are used by many pathogenic Gram-negative bacteria species [12].

MATERIALS AND METHODS

The synthesis of the titled compound is given in scheme-1. All the melting points were determined in concord apparatus in ◦C. The UV spectra were recorded on Shimadzu UV-1201 spectrophotometer. The IR spectra of the compounds were recorded in BX-II FTIR Perkin Elmer. The 1H-NMR was determined on 500 MHz JEOL. MS spectra were recorded on MS-MASS FIGGEAN



N-(Furan-yl-methylene)-benzamine derivatives

R = P-$ClC_6H_4NH_2$,
P-$NO_2C_6H_4NH_2$,
P-$BrC_6H_4NH_2$

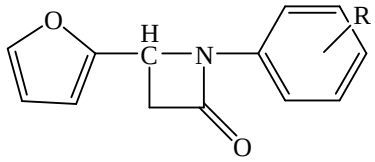
\+

$ClCH_2COCl$

Chloro-methyl chloride

Stirring 2-4 hour
Reflux 3-4 hour

1-4,Dioxane



1-(4-Phenyl)-4-(furan-2-yl)-azetidine-2-one derivatives

Synthesis of Azetidine Derivatives and It's Schiff's Bases

The various imines derivatives obtained [13] was treated with 1, 4- dioxane as solvent followed by 1 meq. of chloro methyl chloride. The reaction mixtures were stirred for 1 hr followed by 6hr reflux in water bath. The completion of the reactions were determined by TLC and record the RF value further the purification of the compound was done by the column chromatography using petroleum ether and ethyl acetate as the solvent.

Biological Activity

Antibacterial activity [14]

All the newly synthesized (2a-2c) were screened in-vitro for their antibacterial activity against *Staphylococcus aureus, Escherichia coli, Bacillus subtitles and Salmonella typhus* by the disc-plate technique using concentrations of 50 mg/ml. Nutrient agar was employed as culture media and DMF was used as solvent control for anti-bacterial activity.

Antifungal activity [15]

The compounds (2a-2c) synthesized were screened for their antifungal activity against *Aspegillus niger, Candida albicans, Cryptococcus neoformans and Thielaviopsis paradoxa* by paper-disc diffusion method at concentration of mg/ml. nutrients agar was employed as culture media and DMF was used as solvent control for antifungal activity .

The known compounds such as amphotericin B, amoxicillin, streptomycin, DMSO.

RESULTS AND DISCUSSION

The compound 1a,1b & 1c was prepared according to literature procedure [13] .The product obtained were further ranned for cyclization reaction .The reactions were ranned with chloro acetyl chloride in the presence of solvent 1,4-dioxan as solvent .The reaction was completed within 6 hours at 100^0c Further purification of the compound was done by column chromatography usuing ethyl acetoacetate and n-hexen as mobile phase. In view of the establishment of the structure it was decided to prove the removal of C=N and formation of the ring and on this regard spectral study was done. The peaks at delta value 5.08ppm(doublet) , 5.07ppm(doublet) and 5.01ppm(doublet) indicates presence of –CH-N- and complete cyclization was confirmed by peaks at 3.24-3.22ppm(doublet), 3.22-3.20ppm(doublet) and 3.20-3.18 ppm(doublet) indicates the presence of –CH-CH_2-C=O and shows the coupling effect due to the neighbouring hydrogen on azatidine ring Further IR spectroscopy proves the presence of –C=O due to the formation of peak at 1673.44 cm-1, 2367.39cm-1and 1785.22 respectively . The molecular mass value indicates the formation of azetidine-2-one and based on the structural conformation the compounds were named as 1-(4-chlorophenyl)-4-(furan-2-yl)-azetidine-2-one, 1-(4-nitrophenyl)-4-(furan-2-yl)-azetidine-2-one, 1-(4-bromophenyl)-4-(furan-2-yl)-azetidine-2-one respectively.

In view of establishment of biological signifance the antimicrobial study was determined due presence of azetidine nucleus and structural similarity with betalactum nucleuses at the dose of 50 mg/ml for all the compounds against different strain of bacterias and fungues and all the compounds shows potent anti- microbial activity .

Table-1 Physical Data of Compounds

Comp. No.	Melting Point(°C)	Color	R_f Value*	%Yield	Solubility
2a	95-96	Dark Brown	0.70	81%	Ethenol & Chloroform
2b	80-84	Greenish	0.86	88%	Ethenol & Chloroform
2c	115-118	Dark Brown	0.74	83%	Ethenol & Chloroform

Determined in TLC taking Ethyl Acetate and Petroleum Ether (1:1) as mobile phase and iodine as spot detecting agent

Table -2 Electronic Transitions of U.V. Visible Spectra

COMPOUND No.	λmax	Absorbance	Types of Peaks	Transitions	Transition due to
2a	372	0.655	Weak-intense band	n-π*- π -π*	C-N
2b	372	0.575	Band-intense	n-π*- π -π*	**C-N**
2c	254	0.656	Band-intense	n-π*- π -π*	**C-N**

Table-3 FTIR Spectra of the Compounds

COMPOUND No.	Peak at (cm^{-1})	Stretching/Vibration	Group responsible
2a	772.48	Str	C-Cl
	822.10	Str	C-N
	1247.62	Str	C-O
	1673.44	Str	C=O
	3126.23	Str	C-H
2b	3359.59	Str	C-H
	2367.39	Str	C=O
	1496.54	Str, Asymmitric	C-NO2
	1303.91	Str	C-O
	841.01	Str	C-N
2c	498.2	Str	C-Br
	827	Str	C-N
	1493	Str	C-O
	1785.22	Str	C=O

Table-4 NMR (^1H) Spectra of the compounds

COMPOUND No.	δ VALUE (ppm) & J (Hz)	TYPES OF PEAK	POSITION OF THE PROTON RESPOSIBLE
2a	7.20-7.18 (J=10)	doublet	C-O of Furan
	6.14-6.12 (J=10)	multiplet	CH=CH of Furan
	6.03-6.01 (J=10)	doublet	CH=CH-C of Furan
	5.08 (J=10)	Singlet	CH-N- of Azetidine
	3.24-3.21(J=10)	doublet	CH2-C=O of Azetidine
	7-6.98	doublet	Ar-H of phenyl ring
	7.3-7.28 (J=10)	doublet	Ar-H of phenyl ring
2b	7.10-7.08(J=10)	doublet	C-O of Furan
	6.1-5.95(J=10)	multiplet	CH=CH of Furan
	6.06-6.04 (J=10)	doublet	CH=CH-C of Furan
	5.07	singlet	CH-N- of Azetidine
	3.22-3.2 (J=5)	doublet	CH2-C=O of Azetidine
	7.19-7.17	doublet	Ar-H of phenyl ring
	7.28-7.26	doublet	Ar-H of phenyl ring
2c	6.99-6.97 (J=10)	doublet	C-O of Furan
	6.36-6.32 (J=10)	multiplet	CH=CH of Furan

	6.02-6	doublet	CH=CH-C of Furan
	5.01	singlet	CH-N- of Azetidine
	3.20-3.18(J=10)	doublet	CH2-C=O of Azetidine
	7.17-7.15(J=10)	doublet	Ar-H of phenyl ring
	7.21-7.19	doublet	Ar-H of phenyl ring

Table-5 Mass Spectra of the Compounds

COMPOUND NO.	m/e	TYPE OF PEAK (%)
2a	247.04	M+ (100.0 %)
	249.04	M+ (32.40 %)
	248.04	M+1 (14.05%)
2b	258.06	M+ (100 %)
	259.07	M+1 (14.3 %)
	260.07	M+2 (1.8%)
2c	290.99	M+ (100.0 %)
	292.99	M+1 (97.7 %)
	291.99	M+2 (14.5 %)

Table: 6 Antimicrobial activity of the synthesized compounds

Compd.	*B. subtilis*	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. fumigates*
2a	32±0.54	31±0.87	29±0.64	33±0.64	30±0.55	30±0.34
2b	26±0.63	26±0.73	30±0.26	29±0.72	30±0.45	29±0.62
2c	28±0.44	29±0.49	29±0.83	30±0.33	25±0.61	25±0.77
Amoxycillin	23±0.54	26±0.48	28±0.87	28±0.34	-	-
Streptomycin	26.5±0.32	28±0.31	27±0.65	26±0.26	-	-
Amphotericin-B	-	-	-	-	29±0.87	29±0.66
DMSO	NIL	NIL	NIL	NIL	NIL	NIL

[*] *Values are mean inhibition zone (mm±SD) of three replicates*
[@] *DMSO was used as vehicle control*

CONCLUSION

The synthesized compounds named as 1-(4-chlorophenyl)-4-(furan-2-yl)-azetidine-2-one, 1-(4-nitro phenyl)-4-(furan-2-yl)-azetidine-2-one,1-(4-bromo phenyl)-4-(furan-2-yl)-azetidine-2-one shows potent antimicrobial activity due to structural similarity with betalactum antibiotics and presence of azetidine-2-one nucleus

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