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Research Article

Cyclization of microbiologically active 4-(furan-2-yl)-1-(pyridine-4-yl)-azetidine-2-one 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&2b). The imines were formed by reaction with furan-2-carboxyldehyde and various substituted heterocyclic amines (1a&1b). The cyclic derivatives were found to be associated with diverse antimicrobial activity.

Keywords: Furfuraldehyde; Imines; Column chromatography; Azetidines; Antimicrobial.

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 *(Dalvie et al., 2002).* One-pot reduction of imines prepared in situ from carbonyl compounds and primary amines is one of the convenient routes to various secondary amines *(Hutchins et.al. 1991).* Furans derivatives belong to aromatic heterocyclic group consequently they are important structural fragment in many pharmaceutical and chemical compounds *(Kagan et al., 1983 Gribble et al., 1984).* Furans compounds have been found to show nematocidal *(Bakker et al., 1979)* insecticidal *(Iyengar, et al., 1987)* antibacterial *(Matsuura et al., 1996)* and antioxidant activity *(Malmstrom et al.,2001*) . Furan-containing congeners of the histamine H_2 receptor antagonist ranitidine were synthesized and tested for improgan-like antinociceptive activity. The most potent ligand of the series, VUF5498 is the most potent improgan like agent described to date (*Hough et.al. 2007*). 1-furan-2-yl-3-pyridin-2-yl-propenone (FPP-3), a synthetic dual inhibitor of COX/5-LOX (*Lee et.al. 2006*). Antiplatelet activity of [5-(2-methoxy-5-chlorophenyl) furan-2-ylcarbonyl] guanidine (KR-32570) have been reported (*Kyung et.al.* 2006). The prospect of exciting research activity in the chemistry of furfural derived compounds such as 5-hydroxymethylfurfural (HMF), 2, 5-furan-dicarbaldehyde and 2, 5-furan-dicarboxylic acid prompted the writing of this article (*Jarosław Lewkowski 2001*). Substituted furan-2-carboxaldehydes type aldehydes which possess a C2 carbonyl group that may act as a reactive centre for various condensation reactions. Many of the published condensation products are biologically active compounds or can be used as intermediates in organic synthesis (*Alžbeta Krutošíková et.al. 2004*)

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EXPERIMENTAL

Materials and methods

The synthesis of the titled compound is given in scheme-1 & 2. 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 MASS FIGGEAN

Synthesis of N-(furan-2-ylmethylene)-pyrimidine imine derivatives

Taken 50 ml of dry ethanol to that added 1gm of furfuraldehyde and stirred for 15 minutes for proper mixing; to the resulting mixtures glacial acetic acid were added and run the reaction for 1hr. After that to the resulting mixture the substituted pyridine anilines were added in different proportions 4-aminopyridine (1.5 meq) and 2-aminopyridine (1.5 meq). Then stirred the reaction for an hour followed by 2-3 hrs refluxes in water bath. At the end of the there was color change takes place. The completions of the reactions were determined by TLC using iodine chamber. Keep the reaction for one night. To the cooled reaction mixture added crushed ice. Formation of precipitate takes place. The purification of the compounds was done by column chromatography using petroleum ether and ethyl acetate as mobile phase.

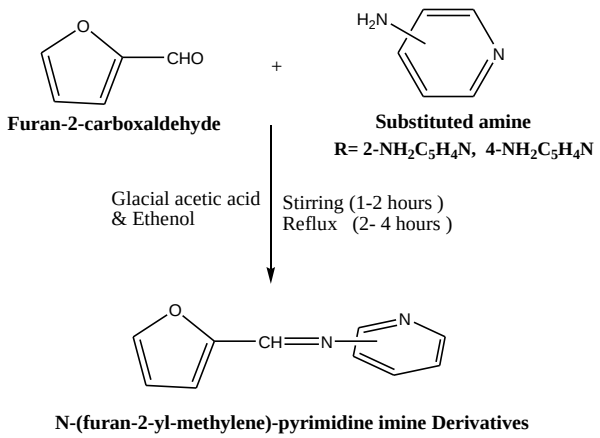

Figure 1: Scheme of Synthesis of N-(furan-2-ylmethylene)-pyrimidine imine derivatives

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

The various imines obtained from the scheme-1 were treated with 1,4-dioxane as solvent followed by addition of 1 meq. chloro-methylene-chloride. The reaction mixtures were stirred for 1 hr followed by 4 hrs reflux in water bath. The completion of the reactions were determined by TLC and recorded the R_f values further the purification of the compound was done by the column chromatography using petroleum ether and ethyl acetate as the solvent.

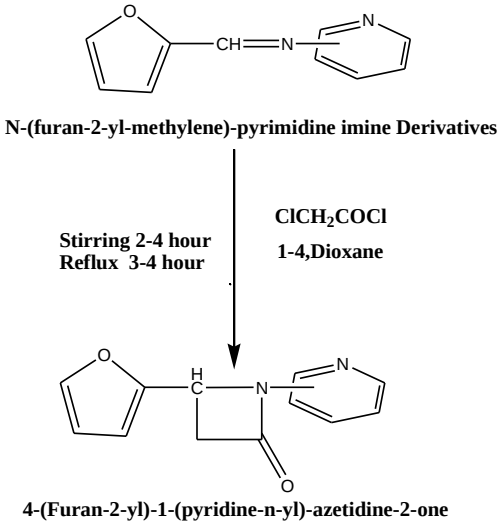

Figure 2: Scheme of Synthesis of Azetidine Derivatives and It's Schiff's Bases

BIOLOGICAL ACTIVITY

Antibacterial activity (*Collins et.al.1984*,)

All the newly synthesized (2a and 2b) 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 *(Seely et.al.1981)*

The compounds (2a and 2b) synthesized were screened for their antifungal activity against *Candida albicans , A.fumigates* 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 were used as standard drugs.

Characterization of Compounds

N-(furan-2-yl-methylene)-pyrimidine-4-imine

^{1}HNMR (500 MHz , δ value in ppm ,DMSO-d_6) – 8.82-8.8 (d , 2H , J=10 Hz ,CH-N=CH of pyridine ring) ; 7.5-7.48 (d , 2H , J=10Hz , =CH-O-C= , of furan ring) ; 7.46-7.44(d , 2H, J=10Hz , Ar-H of pyridine ring) ; 6.29-6.27 (d , 2H ,J=10Hz , Ar-H of furan ring) ; 5.49 (s , 1H , CH=N- of imine) ; **IR (KBr ,Cm^{-1})** – 1600.01 (C=N , str ,-CH=N-) ; 1293 (C-H , str , -CH=N-) ; 836 (C-N , vib ,=C-N=CH-) : **MS (m/e %) Acetonitrile** – 173.07 (10.07%) ; 172.06 (100%).

N-(furan-2-yl-methylene)-pyrimidine-2-imine

^{1}HNMR (500 MHz , δ value in ppm ,DMSO-d_6) – 8.6-8.58 (d , 2H , J=10 Hz ,-CH-N=CH- , of pyridine ring) ; 7.82-7.8 (d , 2H , J=10Hz , Ar-H of pyridine ring) ; 7.39 (s , 1H , CH=N- , of imine) ; 7.26-7.24 (d , 2H , J=10Hz ,=CH-O-C= , of furan ring) ; 7.1 (s , 1H , Ar-H of pyridine ring) ; 7.1-6.69 (d , 1H , Ar-H of pyridine ring) ; 6.62-6.60 (d , 2H , J=10Hz , Ar-H of furan ring) ; **IR (KBr ,Cm^{-1})** – 1660.01 (C=N , str , -CH=N-) ; 1295 (C-H , str , -CH=N-) ; 833 (C-N , vib ,=C-N=CH-) ; **MS (m/e %) Acetonitrile** – 173.09 (12.07%) , 172.18 (100%).

4-(furan-2-yl)-1-(pyridine-4-yl)-azetidine-2-one

^{1}HNMR (500 MHz , δ value in ppm ,DMSO-d_6) – 7.37-7.35 (d , 2H , J=10Hz , =CH-O-C= , of furan ring) ; 7.21-7.19 (d , 2H , J=10Hz , Ar-H of pyridine ring) ; 7.10-7.8 (d , 2H , J=10 Hz , -CH-N=CH- of pyridine ring) ; 5.2 (d, 1H ,-CH-N- , of azetidine ring) ; 3.24-3.22 (d,2H , J=10 Hz ,-CH-CH_2-C=O , of azetidine ring) ; 6.21-6.19 (d , 2H, J=10Hz , Ar-H of furan ring) ; **IR (KBr ,Cm^{-1})** – 2990.82 (C-H , str , Ar-H) ; 1725.61 (C=O , str ,-CH_2-C=O, of azetidine ring) ; 833.62 (C-N , str , HC-N- ,of azetidine ring); **MS (m/e %) Acetonitrile** – 216.08(14.5%), 215.08 (97.7 %) , 214.22 (100%).

4-(furan-2-yl)-1-(pyridine-2-yl)-azetidine-2-one

^{1}HNMR (500 MHz , δ value in ppm ,DMSO-d_6) – 7.91-7.89 (d , 1H , J=10Hz , Ar-H of pyridine ring) ; 7.58-7.56 (d , 2H , J=10 Hz , -CH-N=CH-CH= , of pyridine ring) ; 7.59-7.57 (d , 1H , J=10Hz , Ar-H of pyridine ring) ; 6.9-6.88 (d , 1H , J=10 , -CH-N- , of azetidine ring) ; 7.38-7.36 (d , 2H , J=10Hz , =CH-O-C= , of furan ring) ; 3.49-3.47 (d , 2H , J=10 Hz ,-CH-CH_2-C=O , of azetidine ring); 6.20-6.18 (d , 2H , J=10Hz , Ar-H of furan ring) ; **IR (KBr, Cm^{-1})** – 3001.12 (C-H , str , Ar-H) ; 1685.91 (C=O , str ,-

Table 1: Physical Data of Compounds

Comp. No.	Melting Point(°C)	Color	R_f Value*	%Yield	Solubility
1a	175-178	Dark pink	0.62	85	DMSO
1b	127-130	Brown	0.68	65	$CHCl_3$
2a	135-138	Brown	0.77	70	DMSO
2b	180-184	Light red	0.62	55	$CHCl_3$

*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
1a	321	0.625	Band intense	n -π*	C-N
1b	312	0.611	Band intense	n -π*	C-N
2a	378	0.827	Band intense	n-π*	C-N
2b	370	0.727	Band intense	n-π*	C-N

Table 3: Antimicrobial activity of the synthesized compounds

Zone of inhibition (mm±SD)* 50 mg/mL						
Compd.	***B.subtilis***	***S. aureus***	***E. coli***	***P. aeruginosa***	***C. albicans***	***A. fumigates***
2a	27±0.54	28±0.87	27±0.64	27±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
Amoxycillin	25±0.54	22±0.48	26±0.87	26±0.34	-	-
Streptomycin	23±0.32	25±0.31	24±0.65	28±0.26	-	-
Amphotericin-B	-	-	-	-	29±0.87	28±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

CH_2-C=O , of azetidine ring) ; 838.62 (C-N ,str, HC-N- ,of azetidine ring) .

DISCUSSION

The compounds 1a and 1b were prepared by reaction of furfuraldehyde and substituted heterocyclic anilines. In this case pyridine-n-amines (Where n= position of amine on pyridine ring) is selected as the starting material. The reactions were ranned in the presence of lewis acid and formation of imine taken place. The formation of the respective compounds were characterized by formation of singlet peak at 5.49 ppm (singlet) and 1600 cm^{-1} (stretching) which were taken place due to –CH=N- in case of the compound 1a and formation of 1b were due to characteristic peak at7.89 ppm (singlet) and 1600.07 cm^{-1} (stretching) further compounds were confirmed by m/e 172.06 and 172.26 respectively. The value λ_{max} 321 & 312 were shown due to non-bonding electron on nitrogen atom. From the physical data it was found that percentage yield is less in case of 2– amino pyridine which indicates the increased electron density around imine nitrogen create steric effect and reduce the feasibility of the reaction. The presence of steric effect was associated due to variation in delta value of CH=N which were found to be 5.49 in case of 1a and where as the value was increased to 7.39 due to deshielding effect of pyridine nitrogen which induces the steric effect by lone pair of nitrogen atom on the pyridine nucleus Based on the above discussion the compound can be named as 4-N-(furan-2-yl-methylene)-pyrimidine-4- imine and 4-N-(furan-2-yl-methylene)-pyrimidine-2-imine.

The products obtained in scheme-1 were further ranned for cyclization reaction. The reactions were ranned with chloro methylene chloride in the presence of solvent 1, 4-dioxan. The reaction was completed within 4 hours at 100°C. Further purification of the compound was done by column chromatography using 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 were done . The peaks at delta value 5.2 ppm (doublet) and 6.39 ppm (doublet) indicates presence of –CH-N- and complete cyclization were confirmed by peaks at 3.24-3.22 ppm (doublet) and 3.49-3.47 ppm (doublet) indicates the presence of –CH-CH_2-C=O and also characterized due to the coupling effect of neighboring hydrogen on azetidine ring . Further IR spectroscopy proves the presence of –C=O due to the formation of peak at 1725.61 cm-1 and 1685.31cm-1. The molecular mass value indicates the formation of azatidine-2one and based on the structural conformation the compounds were named as 4-(furan-2-yl)-1-(pyridine-4-yl)-

azatidine-2-one,4-(furan-2-yl)-1-(pyridine-2-yl)-azatidine-2-one .

Due to the structural similarity with betalactum antibiotics and azetidine nucleus it was decided to determine the antimicrobial proficasy against different strains of bacteria and funguses at different concentration comparing with standards. It was found that at 50mg/ml all the compound shown maximum inhibitory concentration. In view of study for the basic part of the moiety responsible for the activity was determine on all the compounds including intermediate 1a and 1b, but the potency were more in case of the compound 2a and 2b . Which indicated azetidine nucleus is more responsible rather than furan nucleus for antimicrobial activity.

CONCLUSION

The synthesized compounds namedsd as 4-(furan-2-yl)-1-(pyridine-4-yl)-azatidine-2-one, 4-(furan-2-yl)-1-(pyridine-2-yl)-azatidine-2-one shows potent antimicrobial activity due to structural similarity with betalactum antibiotics and presence of azatidine-2-one nucleus

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