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SYNTHESIS AND BIOLOGICAL STUDIES OF SOME NOVEL 2-AZETIDINONES

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Abstract: Pyridine-3-carboxylic acid hydrazide **(1)** on condensation with substituted aromatic aldehydes in alcohol, in presence of glacial acetic acid yielded the Schiff bases **(3a-j).** These Schiff bases on Cyclocondensation with chloroacetyl chloride in presence of triethylamine afforded the title compounds Azetidinones **(4a-j)**. The structures of the newly synthesized compounds were established on the basis of IR, ^{1}H-NMR and MASS spectral data. All the newly synthesized compounds were screened for their *In-vitro* growth inhibitory activity against several microbes.
Key words: Schiff bases, Cyclocondensation reaction, Azetidinones, Antibacterial activity.

Introduction

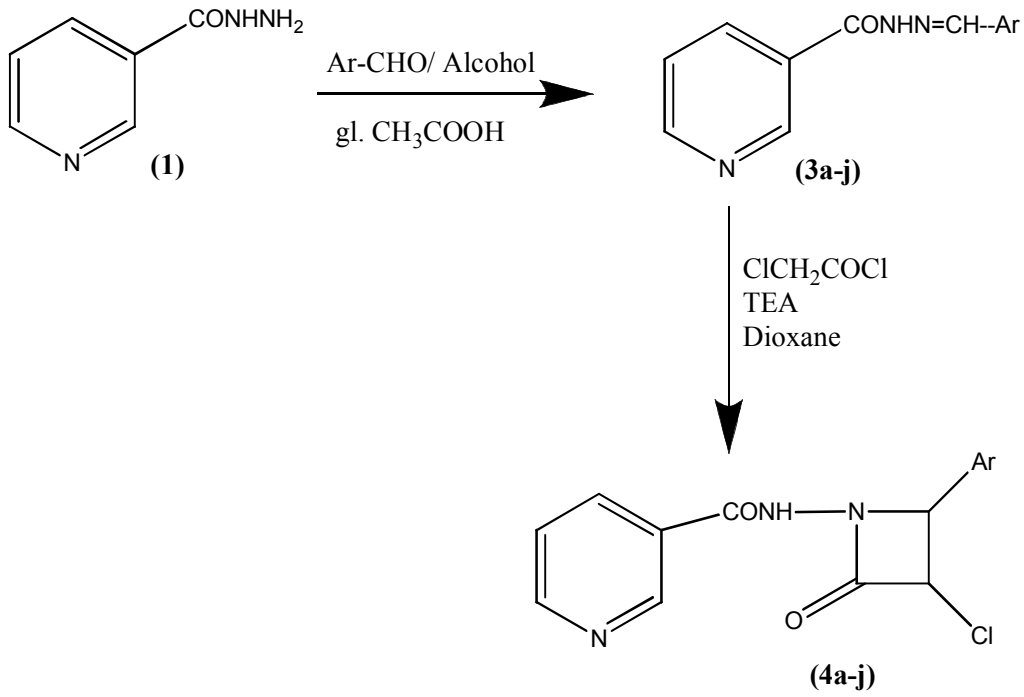
Pyridine is a six membered heterocyclic compound and after its discovery it gained attraction by researchers due to their diversified biological and pharmacological activities exhibited by them. The presence of pyridine moiety is observed in Vitamin B complex, Antidiabetic drugs (Pioglitazone, Rosiglitazone), Neonicotinoids (eg. Imidacloprid, Acetamiprid). Nicotinic acid and its amide (Niacin) are part of the vitamin B complex.

Azetidinones, a very well known compound for the medicinal chemist, since it forms a part of the antibiotic molecules. The earliest use was in the form of antibacterials known as β-lactum drugs. The most widely used antibiotics such as Penicillins, Nocardicins, Cephalosporins, contains the β-lactum ring. Azetidinones are known to exhibit antibacterial[1], anti-tubercular[2], antifungal[3], anticonvulsant[4], anti-inflammatory[4], analgesic[5], and CNS depressant[6] activity.

Inspired by the above observations of Azetidinones, we planned to synthesize a new series of Azetidinone derviatives containing the pyridine moiety and evaluation for their antibacterial and antifungal activities.

The starting material, Pyridine-3-carboxylic acid ethyl ester was prepared by the esterification of Pyridine-3-carboxylic acid with absolute ethanol in presence of conc. H_2SO_4. Pyridine-3-carboxylic acid hydrazide[7] was prepared by the condensation of hydrazine hydrate with the ester in presence of alcohol. The hydrazide upon reaction with substituted aromatic aldehydes in presence of few drops of glacial acetic acid yielded the schiff bases. The schiff bases upon cyclization with chloroacetyl chloride in presence of triethyl amine will yields the title compounds. The final structures of the compounds have been established on the basis of spectral (IR, ^{1}H NMR and MS) data. The reaction sequence leading to the formation of different title compounds is outlined in **Scheme-01**.

Scheme-01



Experimental

IR spectra were recorded in KBr discs on a SHIMADZU PERKIN ELMER 8201 PC IR SPECTROMETER. ^{1}H NMR spectra were recorded on a BRUKER AVANCE II 400 NMR SPECTROMETER using TMS as internal standard (chemical shifts in δ, ppm) and MASS spectra on a JEOL SX-102/DA-6000 Mass spectrometer operating at 70ev. Purity of the compounds was checked by TLC. Melting points were taken in open capillaries tube method and are uncorrected.

Synthesis of Pyridyl-3-carbohydrazide[7]

A mixture of Pyridine-3-carboxylic acid ethyl ester (0.1 mol), and hydrazine hydrate (99%) (0.1 mol), in absolute alcohol (50ml) was refluxed for about 4 hrs. The excess of solvent was removed and the residue was poured into ice cold water (125ml). The solid which is obtained was recrystallized from ethanol to get white crystalline product. Yield-82%, Mp 162 ^{O}C, IR (KBr): 1612 (C=N), 1670(C=O), 3048 (-CH of pyridyl).

Synthesis of Schiff bases (3a-3l)

The hydrazide (0.01mol) was dissolved in 30 ml of ethanol containing few drops of glacial acetic acid. The reaction mixture was cooled and poured into crushed ice and the solid which is obtained was filtered, washed with water and recrystallized from alcohol. The physical data of the compounds **(3a -j)** is given in table 1.

3i: IR (KBr cms^{-1}): 3218(CH-Ar), 3061 (C-H), 1676 (C=O), 1593(C=C).
^{1}H-NMR ($CDCl_3$) δ ppm: 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3),
6.87-9.1 (m, 9H, Ar-H, Ar-CH), 11.86 (s, 1H, CONH).MS: m/z: 286[M^+]

Synthesis of 2-Azetidinones (4a-j)

General procedure

A mixture of schiff bases (0.01 mol) and triethyl amine (0.02 mol) was dissolved in dioxane (50 ml) and stirred. To this well stirred solution chloroacetyl chloride (0.04 mol) was added drop by drop for a period of 30 min at low teperature. The reacion was further stirred for 6-12 hrs(as monitored from TLC). The reaction mixture is poured into crushed ice and the resultant product was filtered and washed with water, dried and recrystallized from ethanol. The physical data of the compounds **(4a-j)** is given in table 2.

4c: IR (KBr cms^{-1}): 3404(CH-Ar), 2939(C-H), 1718(>C=O), 1641(CONH), 1576 (C=C).**^{1}H-NMR ($CDCl_3$) δ ppm:** 1.28 (d, 1H, C-CH-Cl), 3.10 (d, 1H, N-CH-C), 3.71

(s, 9H, $(OCH_3)_3$), 6.87-8.67 (m, 7H, Ar-H), 12.12 (s,1H,CONH).**MS:** m/z: 391[M^+]

4d: IR (KBr cms^{-1}): 3203(CH-Ar), 3029 (C-H), 1735(>C=O), 1664 (CONH), 1600(C=C).**^{1}H-NMR ($CDCl_3$) δ ppm:** 1.97(d, 1H, C-CH-Cl), 2.80 (d, 1H, N-CH-C), 3.08 (s, 6H, $(CH_3)_2$), 7.44-8.56 (m, 8H, Ar-H), 12.06(s, 1H, CONH).**MS:** m/z: 344[M^+]

4h: IR (KBr cms^{-1}): 3380(CH-Ar), 2975(C-H), 1726(>C=O), 1658(CONH), 1564(C=C).**^{1}H-NMR ($CDCl_3$) δ ppm:** 1.76(d, 1H, C-CH-Cl), 3.32 (d, 1H, N-CH-C),
7.10-8.45 (m, 9H, Ar-H), 12.42 (s, 1H, CONH).**MS:** m/z: 346[M^+]

Antimicrobial activity

The antimicrobial activity was assayed by using the cup-plate agar diffussion method[8], by measurig the zone of inhibition in mm. All the compounds were screened *In-vitro* for their antimicrobial activity against *S.aureus, B.Subtilis, P.aeruginosa, E.coli* and fungi *A.niger* and *C.albicans.* The activities of these compounds were tested at a conc. of 100 µg/ml. Ampicillin and Flucanazole were used as standard drugs for the comparison purpose. DMSO was used as solvent control. The antimicrobial activity data is reported in table-3.

Results and discussion

In the present work, a new series of Schiff bases were synthesized from Pyridine-3-carboxylic acid hydrazide with substituted aromatic aldehydes in presence of catalytic amount of glacial acetic acid. The resulted schiff bases undergoes cyclocondensation reaction with chloroacetyl chloride in presence of trietyl amine under cold conditions will yields the title compounds.The purity of the compounds is checked by TLC. The final synthesized compounds were established on the basis of spectral data. All the new compounds were screened for their antibacterial and antifungal activity. In the antibacterial activity, compounds **4a, 4e, 4b, 4j** have shown maximum activity against all the four pathogenic micro-organisms. But most of the compounds are moderately active against *S.aureus* and *B.subtilis* In the antifungal study, compounds **4a, 4c,4j** have shown highest activity against both the fungi. In overall, most of the synthesized compounds have shown moderate activity against both the strains.

Table: 1 Physical data of Compounds (3a-j)

Compound	Ar-CHO	% yield	Melting point (^{o}C)
3a	C_6H_5	68	148
3b	4-OCH_3	66	107
3c	3,4,5- $(0CH_3)_3$	70	187
3d	4- $(CH_3)_2N$	68	138
3e	Furfural	64	156
3f	4-F	61	161
3g	3-Br	62	112
3h	4-NO_2	70	175
3i	3,4- $(OCH_3)_2$	69	132
3j	2-thiophene	62	143

Table: 2 Physical data of Compounds (4a-j)

Compound	Ar-CHO	% yield	Melting point (^{o}C)
4a	C_6H_5	54	222-224
4b	4-OCH_3	58	192-194
4c	3,4,5- $(OCH_3)_3$	61	228-230
4d	4- $(CH_3)_2N$	61	205-207
4e	Furfural	59	186-188
4f	4-F	60	210-212
4g	3-Br	66	179-181
4h	4-NO_2	54	232-234
4i	3,4- $(OCH_3)_2$	57	198-200
4j	2-thiophene	61	166-168

Table: 3 Antimicrobial and Antifungal Data of Compounds 4a-j

Comp	Diameter of zone of inhibition. (mm)					
	P.aeruginosa	***S.aureus***	***E.coli***	***B.subtilis***	***C.albicans***	***A. niger***
4a	10	13	10	11	10	12
4b	10	11	11	13	11	10
4c	09	11	08	11	11	11
4d	08	11	11	12	10	11
4e	12	11	11	13	09	10
4f	08	12	08	13	09	10
4g	09	11	11	10	09	09
4h	10	08	12	11	10	09
4i	11	11	09	12	10	10
4j	10	10	12	12	11	11
DMSO	-	-	-	-	-	-
Ampicillin	19	20	21	22	-	-
Flucanazole	-	-	-	-	21	22

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