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Journal of Chemical and Pharmaceutical Research, 2012, 4(8):3909-3913

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis of some new derivatives of N-phenyl-2-chloro-9*H*-pyrido[2,3-b]indole-3-ylmethanimines using Vilsmeier–Haack reagent

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ABSTRACT

In this paper, a number of new derivatives N-phenyl-2-chloro-9H-pyrido[2,3-b]indole-3-ylmethanimine were synthesized using of the Vilsmeier–Haack reagent (DMF+ $POCl_3$). To this end ,the initial composition of 1H-2-indolamine after the acquisition of a group methyl- ketone (1) , gave the fused pyridine ring by cyclization and a free aldehyde group is made (2) . Finally , after using aryl-amine derivatives one type, made imine bond connection to the 2-chloro- 9H-pyrido[2,3-b]indole (3) . final products were supported by FTIR , ^{1}H NMR and Mass spectroscopic measurements and possess moderate to good antifungal and antibacterial activities.

Keywords: pyrido[2,3-b], indole, antifungal

INTRODUCTION

The effect of the phytonutrient on the immune system has been researched and it was noted that indoles do offer certain benefits[1-3]. Commonly present in high amounts in cruciferous vegetables, indole supplements are proposed to have anti-cancer, antioxidant and anti-atherogenic properties. Phytonutrients such as indole may exert such effects either by direct or indirect methods[4-7].

The supplementation of indole in autoimmune disorders such as lupus may improve the survival rates of affected individuals[8-12]. Autoimmune disorders are generally characterized by an abnormal increase in the activity of immune cells[13-15]. The immune cells begin to attack healthy cells and cause the release of various chemicals that result in inflammation[16-18].

The administration of indole supplements may help individuals suffering from severe types of autoimmune disorders by reducing the severity of the symptoms and regulating the adverse effects of inflammation[19-22].

In such sequence of study it has seen that the activity of such nucleus may be due to the presence of fused pyridine because other literature also shown such derivatives which give such activities in the presence of pyridine in their structure. In literature review the indole also been reported as potent antimicrobial activity[23-27]. After these thorough studies of literature, it has been postulated that the fusion of pyridine nucleus with the indole may also give some potent antimicrobial derivatives[28-31].

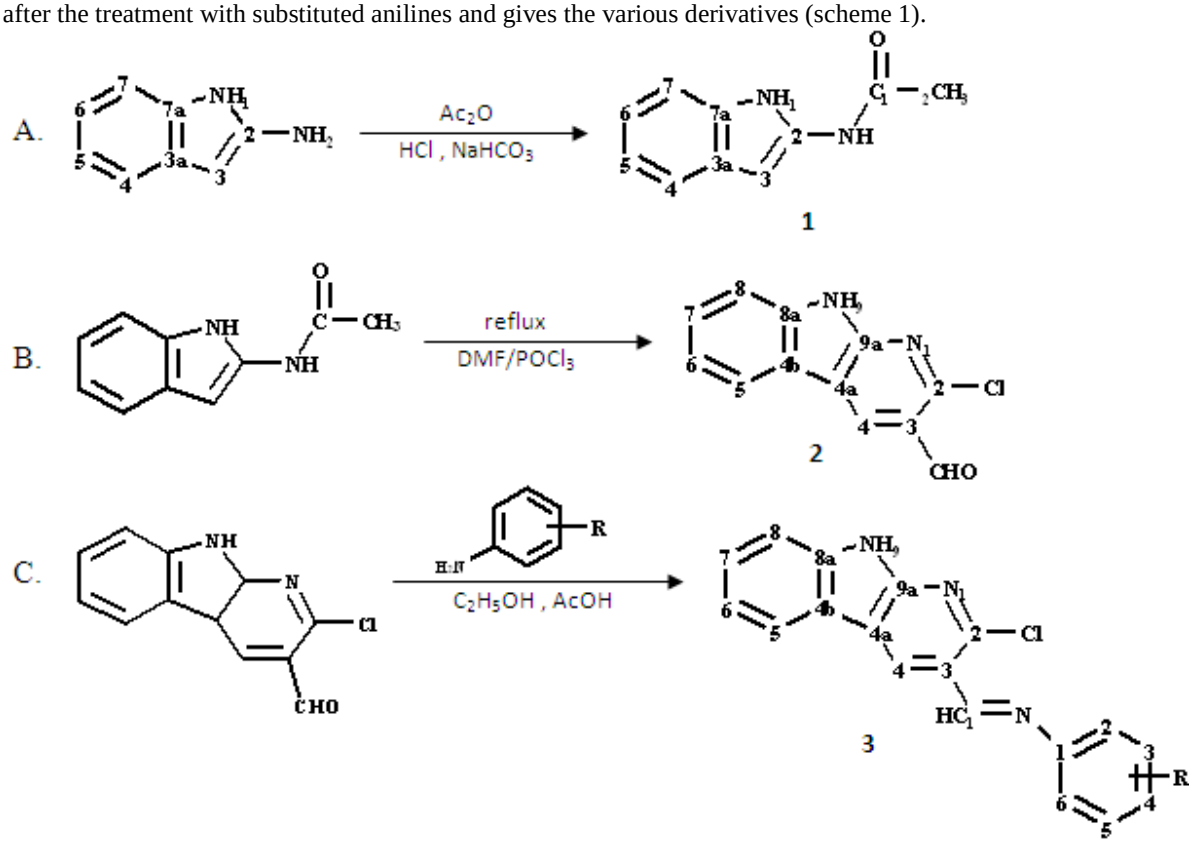
The different substituted schiff bases were prepared to enhance the antimicrobial activity of fused indole derivatives. In the present study the schiff base was used because schiff bases are more frequently used for the preparation of such derivatives which produce various biological activities due to its versatile nature[32-33].

Therefore in the present study we have prepared some fused derivatives by combining these potent organic fragments which have reported for their antimicrobial activity to produce more potent derivatives.

EXPERIMENTAL SECTION

Chemicals and Instrumentation:
The pyrido[2,3-b]indole nucleus was prepared by the method reported in the literature[34-35]. In which the primary aryl amine was taken as starting compound and its acetylation occurs by the treatment with the acetic anhydride.

The resulting aryl acetamide is further cyclized by the treatment with the Vilsmeier–Haack reagent (DMF+ $POCl_3$) which results the pyrido[2,3-b]indole nucleus with primary aldehyde. This aldehyde group is turned to schiff base after the treatment with substituted anilines and gives the various derivatives (scheme 1).



scheme 1

Melting points were determined with open capillary and are uncorrected. Proton NMR spectra were taken in $CDCl_3$ and recorded at 300 MHz in Bruker DRX-300. Chemical shifts (δ) were measured in ppm with respect to TMS. FTIR spectra recorded on instrument simadzu 2100 S and Perkin Elmer BX. Mass were obtained on a JEO JMC-300 instrument. Elemental analysis performed on Elementar Vario EL III.

Synthesis of N-(1H-2-indolyl)methanamide (1) :
1H-2-indolamine (10 mmol) was added into the water (50 ml) to produce heterogenous suspension which becomes homogenous after addition of 6N HCl (5 ml) with continuous stirring. The resulting homogenous solution was cooled in an ice bath. In the above solution acetic anhydride (10 mmol) was added followed by the addition of solid sodium bicarbonate until there was no effervescence. The precipitated product filtered and dried and finally dried in a vacuum desicator.

Synthesis of 2-choloro-9H-pyrido[2,3-b]indole-3-carbaldehyde (2) :
The $POCl_3$ (7 ml) was added drop wise to a stirring solution of the acetamide solution (1) in ice cooled DMF (2 ml) and the resulting mixture was heated at 130°C for 2 hrs, the solution was cooled and poured on to ice-water (150 ml) to precipitate synthesized fused pyridine compound.

Synthesis of N-phenyl-2-chloro-9H-pyrido[2,3-b]indole-3- ylmethanimine (3)
Cyclized pyridine compound was dissolved in 30 ml of ethanol containing few drops of glacial acetic acid. The substituted aniline (10 mmol) was added into the above mixture. The reaction mixture was refluxed for 5 hrs at 700C. The reaction mixture was cooled and poured in crushed ice. The solution was filtered and purified by recrystallization from ethanol.

SPECTROSCOPIC DATA OF COMPOUNDS
3a. N-(4-chlorophenyl)-2-chloro-9H-pyrido[2,3-b]indole-3- ylmethanimine:
mp 154-158°C, FTIR (KBr) cm^{-1}: 3345.06(Ar-C-H), 728.53(C-Cl), 1654.64(C=C), 1533.43 (Ar C-C), 1654.21(C=Ns), 1001.64(C-N), ^1H NMR ($CDCl_3$) : 7.1-7.8(9H, Ar-H), 10.04(1H, -NCH-), MS (m/z): 340.

3b. 4-[(E)-1-(2-chloro-9H-pyrido[2,3-b]indole-3- yl)methylideneamino]phenple :
mp 108-110°C, FTIR (KBr) cm^{-1}: 3045.06(Ar-C-H), 763.28(C-Cl), 1451.45(C=C), 1345.43 (Ar C-C), 1623.21(C=N), 1109.64(C-N), 3403.27(O-H), ^1H NMR ($CDCl_3$) : 7.1-7.7(10H, Ar-H), 10.84(1H, -NCH-), 3.6-4.5(1H,-OH), MS (m/z): 322.

3c. 4-[(E)-1-(2-chloro-9H-pyrido[2,3-b]indole-3- yl)methylideneamino]benzoic acid :
mp 132-138°C, FTIR (KBr) cm^{-1}: 3154.67(Ar-C-H), 699.75(C-Cl), 1567.75(C=C), 1132.43 (Ar C-C), 1540.21(C=N), 985.64(C-N), 1685.64(C=O), ^1H NMR ($CDCl_3$) : 7.3-7.8(9H, Ar-H), 10.48(1H, -NCH-), 11.54(1H, COOH), MS (m/z): 350.

3d. 4-[(E)-1-(2-chloro-9H-pyrido[2,3-b]indole-3- yl)methylideneamino]benzensulfonamide :
mp 148-152°C, FTIR (KBr) cm^{-1}: 3334.67(Ar-C-H), 709.75(C-Cl), 1677.75(C=C), 1012.43 (Ar C-C), 1540.21(C=N), 1085.64(C-N), 1128.53(S=O), ^1H NMR ($CDCl_3$) : 6.8-7.9(9H, Ar-H), 11.76(1H, -NCH-),4.3-4.7(2H,-NH2), MS (m/z): 353.
3e. N-(4-methoxyphenyl)-2-chloro-9H-pyrido[2,3-b]indole-3- ylmethanimine :
mp 118-120°C, FTIR (KBr) cm^{-1}: 3334.67(Ar-C-H), 709.75(C-Cl), 1677.75(C=C), 1012.43(Ar C-C), 1540.21(C=N), 1085.64(C-N), 1229.66(C-O, OCH3), ^1H NMR ($CDCl_3$) : 7.1-7.7(9H, Ar-H), 10.84(1H, -NCH-),3.6-4.5(1H, -(OCH3), MS (m/z): 336.

3f. N-(4-nitrophenyl)-2-chloro-9H-pyrido[2,3-b]indole-3- ylmethanimine :
mp 122-124°C, FTIR (KBr) cm^{-1}: 3135.45(Ar-C-H), 820.31(C-C), 1730.31(C=C str), 1003.73(Ar C-Cstr), 1710.21(C=N), 971.64(C-N), 1444.34(N=O, NO2), ^1H NMR ($CDCl_3$) : 7.37-8.74 (9H, Ar-H), 10.23(1H, -NCH-), MS (m/z): 351.

RESULTS AND DISCUSSION

Table 1 shows the efficiencies obtained from the derivatives of 3 compound . As can be seen , The highest and lowest yields, respectively, is Pertain to the compounds **3a** and **3c**.

The spectral data of synthesized compounds are evident and showed that all the proposed compounds are synthesized properly and the common mechanism of synthesis of pyridine nucleus can be used to produce pyrido[2,3-b]indole (3). After substitution of schiff base in the heterocyclic nucleus give easier way to compare the antimicrobial activity. The antimicrobial activity of all the synthesized compounds showed that the pyrido[2,3-b]indole compounds are moderately active against all used bacterial strain . So The **6a**, **6c** and **6d** are revealed good antimicrobial activity [36-38]. All the compounds synthesized still not significant against microbes under investigation but the further purification and modification in the synthesized derivatives give scope for further development in the same heterocyclic nucleus.

Table 1 . synthesis of N-phenyl-2-chloro-9H-pyrido[2,3-b]indole-3- ylmethanimine derivatives

Compound	R	Molecular formula	Yield value(%)
3a	4-Cl	$C_{18}H_{11}Cl_2N_3$	89
3b	4-OH	$C_{18}H_{12}ClN_3O$	83
3c	4-COOH	$C_{19}H_{12}ClN_3o_2$	72
3d	4-SO_2NH_2	$C_{18}H_{13}ClN_4O_2S$	77
3e	4-OCH_3	$C_{19}H_{14}ClN_3O$	81
3f	4-NO_2	$C_{18}H_{11}ClN_4O_2$	80

CONCLUSION

In the current research some substituted -N-((2-chloro-9H-pyrido[2,3-b]indol-3-yl) methylene)benzenamine (3) have been synthesized . From the above results, it can be conclude that pyrido[2,3-b]indole compounds are moderately active against all used bacterial strain .

Although the compounds synthesized are not much significant against microbes under investigation but the further purification and modification of synthesized derivatives give scope for further development in the same heterocyclic nucleus.

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