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Der Pharmacia Lettre, 2010, 2(3): 209-215
(http://scholarsresearchlibrary.com/archive.html)

Der Pharmacia Lettre
Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

Evaluation of Antibacterial Activity of Some Substituted Phenyl Benzaldimine Derivatives

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Abstract

A series of Phenylbenzaldimine derivatives were derived from 3-chloro-4-fluoroaniline as the central molecule with different substituted aromatic benzaldehydes as the side chain. Their structures have been characterized by IR, ^{1}H -NMR, ^{13}C-NMR, Mass spectra in addition to the elemental analysis. The antibacterial activity was studied against Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa and Escherichia coli .These strains were procured from Department of Microbiology, Assam Medical College, Dibrugarh. The determination of the antibacterial activity was done using the disc diffusion method and MIC was determined by broth dilution method. The antibacterial activity was evaluated in polar solvent, Dimethyl sulfoxide (DMSO).

Keywords: Phenylbenzaldimine derivatives, Antibacterial activity

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INTRODUCTION

Day by day Schiff bases are more frequently applied for the betterment of human welfare. Schiff bases are characterized by the –N=CH– (imine) group which is important in elucidating the mechanism of trans-amination and racemisation reactions in biological systems. Literature survey shows that Schiff bases have both bacteriostatic and bactericidal activity. Sahu *et al* reported fungi toxicity of some Schiff bases [1]. Gawad *et al* synthesized some Schiff bases and observed high antimicrobial activities [2].

Antibacterial, antifungal, antitumor and anticancer activity has been reported and they are also active against a wide range of organisms, e.g. *C. albicans, E. coli, S.aureus, B. polymyxa, P. viticola, etc*[6-18]. The antibacterial and antitumor activity of schiff's bases has been attributed to their ability to chelate with traces of transition metals. Piperazines and substituted piperazines are important pharmacophores that can be found in many marketed drugs, such as the Merck HIV protease inhibitor Crixivan, and durgs under development. Piperazinyl-Linked Ciprofloxacin dimmers reported as potent antibacterial agents against resistant strains, a novel

class of mixed D2/D4 receptor antagonist, dual calcium antagonist, antimalarial agents and potential antipsychotic agents. In view of these observations a new series of compounds bearing N-methylpiperazine and aromatic aldehyde Schiff's bases were undertaken with the objective of obtaining new biologically active compounds.

The required parent compounds were prepared by the reaction of 3-chloro-4-fluoroaniline with aromatic aldehydes. Title compounds SD1- SD4 were obtained by treating schiff's bases with N-Methylpiperazine in acetonitrile in presence of pyridine.

The structures of the newly synthesized compounds were characterized by IR, ^{1}H -NMR, ^{13}C-NMR, Mass spectra in addition to the elemental analysis. The physical data of these compounds are also given in table below.

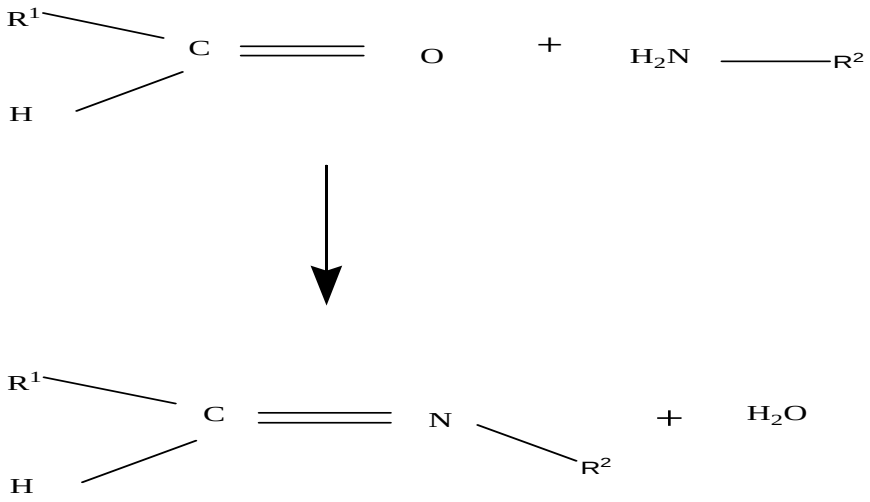
MATERIALS AND METHODS

All reagents for synthesis and analyses were of commercially available analytical grade and were used as received without further purification. All melting points were determined in open capillary in liquid paraffin bath and are uncorrected. The purity of all compounds was checked by TLC.

Elemental analyses were performed on a Perkin-Elmer 2400 series II CHNS/O analyzer. UV spectra were recorded on *Shimadzu UV-1700* in DMSO. IR spectra were measured on a Perkin-Elmer RX-I FT-IR spectrometer with KBr pellets in the range 4000-400cm–1. ^{1}H NMR spectra were recorded on *Bruker Avance II 400 NMR Spectrophotometer* and ^{13}C NMR spectra were recorded on *Bruker Avance II 100 NMR Spectrophotometer*. Chemical shifts are expressed as δ values (ppm), downfield from tetramethylsilane (TMS) used as internal standard.

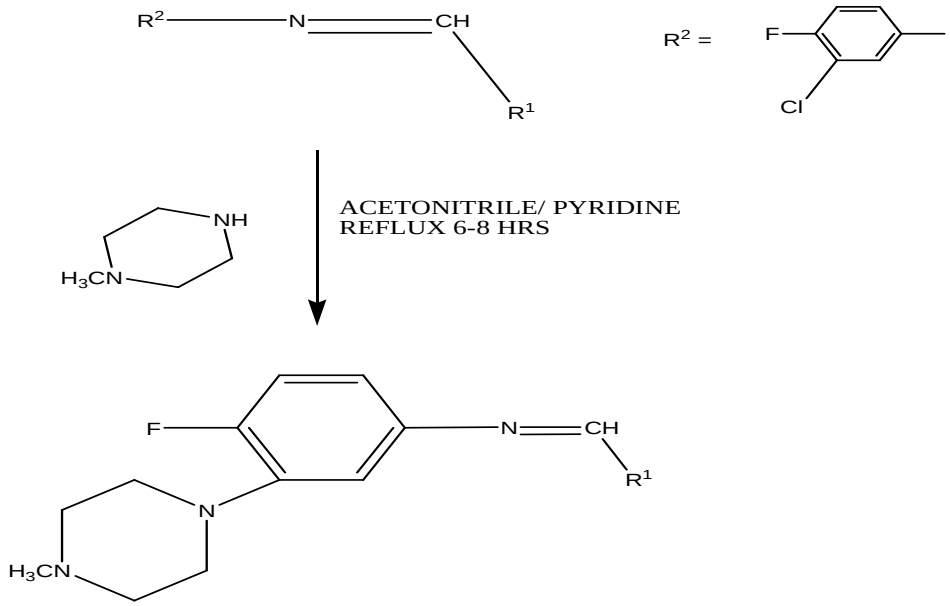
General method of synthesis:

Step-I : Synthesis of the Schiffs bases: The aromatic amine and the respective aldehydes are to be mixed in equimolar quantity. The mixture is to be heated at 80^{0}C for 45 minutes; the viscous liquid so obtained is to be kept overnight allowing solidification. The crude product after washing with ethanol is to be recrystallized using methanol, water mixture [3].



Synthesis of Schiff base

Step-II: Synthesis of the final compounds by substituting with N- Methylpiperazine:
In this step the phenylbenzaldimine derivative, anhydrous N-methylpiperazine in acetonitrile and few drops of pyridine are to be taken in a round bottom flask, refluxed for 6-8 hrs, followed by cooling in ice cold water. The separated solid is filtered, dried, and recrystallized. The completion of reaction is to be monitored by TLC. It is desirable to carry out the reaction in presence of an acid-acceptor in a molar ratio of 1.0 to1.2 mole of acid-acceptor per mole of the donor [4].



Substitutions with N-Methylpiperazine

All the final compounds (SD-1 to SD-4) were synthesized by utilizing the procedure described in step-I & step-II of the scheme of synthesis.

Table: 1 List of Synthesized Compounds

Compound Code	R1	R2
SD1	4-Hydroxyphenyl	3-Chloro-4-fluorophenyl
SD2	4-Methoxyphenyl	3-Chloro-4-fluorophenyl
SD3	4-Chlorophenyl	3-Chloro-4-fluorophenyl
SD4	4-Dimethylamino Phenyl	3-Chloro-4-fluorophenyl

Table No: 2 Physical Data

Compound code	Mol. Formula (Molecular Weight)	%Yield.	M.pt (□ C)
SD-1	$C_{18}H_{20}N_3FO$ (313.52)	67	140-143
SD-2	$C_{19}H_{22}N_3FO$ (327.4)	58	76-78
SD-3	$C_{18}H_{19}ClN_3F$ (331.81)	67	115-120
SD-4	$C_{20}H_{25}N_4F$ (340.44)	67	98-102

Table No: 3 Spectral Data

Compound code	FTIR Spectrum	UV λ_{max} (nm) (Chloroform)	Elemental analysis found		
			C%	H%	N%
SD-1	3620.08 (O-H $_{stretch}$), 3084.74, (C-$H_{stretch}$, Aromatic), 1604.59(C=N), 1375.75(C-$O_{stretch}$) , 1167.75 (C-$N_{stretch}$)	238,263, 333	67.99	5.98	12.22
SD-2	3084.74, (C-$H_{stretch}$, Aromatic), 1627.46 (C=N), 1260.03 (C-$O_{stretch}$), 1129.66 (C-$N_{stretch}$), 1499.75(Ar-C=C)	236, 266, 318	68.44	5.56	11.98
SD-3	1572.84(Ar-C=C), 3040.2 (C-$H_{stretch}$, Aromatic), 1627.11(C=N), 1249.36 (C-$N_{stretch}$),	240, 285, 338.	63.15	5.57	12.22
SD-4	1526.94(Ar-C=C), 3030.2(C-$H_{stretch}$,Aromatic), 1603.11 (C=N),1252.71(C-$N_{stretch}$), 1369.73(C-F).	237, 276, 332	70.22	6.88	15.22

Table No: 4 Mass Data

Compound Code	SD-1	SD-2	SD-3	SD-4
m/z	312.9 (M+)	330.2 (M+)	331.2 (M+)	340.5 341.7

Table No: 5 ^{1}H- NMR -and ^{13} C- NMR Spectral Data

Compound Code	^{1}H- NMR -and ^{13} C- NMR spectral data
SD-1	**^{1}H NMR (400 MHz, $CDCl_3$):** δ,ppm: 8.348 (s,1H,HC=N), 7.284-7.084 (m,14H, Ar-H) , 9.821 (s, OH) , 2-035 (s,3H,-N-CH_3) ,2.393-2.372 (m,4H-N-Methylpiperazine), 3.884(s,4H,N-Methylpiperazine).; **^{13} C NMR (100 MHz, $CDCl_3$):** δ, ppm: 161.629(1C, HC=N), 160.990, 159.524, 157.523, 132.491, 131.238, 131.108, 122.665, 122.615, 120.924, 116.995, 116.771, 116.002(12C-Aromatic), 77.339, 77.022(4C, N-Methylpiperazine), and 76.704(1C, CH_3).
SD-2	**^{1}H NMR (400 MHz, $CDCl_3$):** δ,ppm: 8.309(s,1H,HC=N), 7.833-7.812 (d,Ar-H) 7.249-7.045(m,12H,Ar-H), 2.089-2.193(-N-CH_3), 3.863 (s,3H,OCH_3); **^{13} C NMR (100 MHz, $CDCl_3$):** δ, ppm: 160.567(1C, HC=N), 157.383, 154.933, 148.963, 148.930, 130.709, 128.734, 122.605, 121.243, 121.060, 120.870, 120.800, 116.888, 116.670, 114.264(12C-Aromatic), 77.444, 77.126(4C, N-Methylpiperazine), 76.810(1C,CH_3), and 55.416.
SD-3	**^{1}H NMR (400 MHz, $CDCl_3$):** δ,ppm: 8.379 (s,1H,HC=N), 7.286-7.083 (m,14H,Ar-H), 1.745(s,3H,-N-CH_3), 2.394-2.383 (m,4H,N-Methylpiperazine); **^{13} C NMR (100 MHz, $CDCl_3$):** δ, ppm: 159.491(1C, HC=N), 157.802, 155.341, 148.179, 137.845, 134.194, 130.065, 129.182, 122.680, 121.491, 121.305, 120.921, 120.851, 117.031, 116.812(12C-Aromatic), 77.363, 77.046(4C, N-Methylpiperazine) and 76.730(1C,CH_3).
SD-4	**^{1}H NMR (400 MHz, $CDCl_3$):** δ,ppm: 8.252 (s,1H,HC=N), 7.141-7.054 (m,6H,Ar-H) , 3.045 [s,-N-$(CH_3)_2$] , 2.393-2.306(m, 4H-piperazine); **^{13} C NMR (100 MHz, $CDCl_3$):** δ, ppm: 160.877(1C, HC=N), 156.998, 154.557, 152.709, 149.677, 149.644, 130.687, 123.766, 122.563, 121.058, 120.889, 116.787, 116.570, 111.513, 110.993(12C-Aromatic), 77.492, 77.176(4C, N-Methylpiperazine), 76.856(1C,CH_3), 40.105, and 40.049[2C,-N$(CH_3)_2$].

Antibacterial activity

The synthesized compounds were tested for their in vitro inhibitory activity against two Gram positive strains (*Bacillus subtilis, Staphylococcus aureus)* and two Gram negative strains (*Pseudomonas aeruginosa, Escherichia coli)* of bacteria. Disc diffusion method for antimicrobial susceptibility testing was carried out according to the standard method by Kirby and Bauer to assess the presence of antibacterial activities of the test compounds [5]. The discs impregnated with a series of test compounds were placed on the Mueller- Hinton agar surface. Each test plate comprised of four discs. One positive control, which is a standard commercial antibiotic disc, one negative control, and rest treated discs. The standard antibiotic disc was Ofloxacin 5 µg. The negative control was DMSO (100%). The plate was then incubated at 37°C for 24 hours. After the incubation, the plates were examined for inhibition zone. The zones of inhibition were recorded in mm and are given in table 6 .The tests were repeated three times to ensure reliability.

Table No: 6 Mean zone of inhibition against different organisms

SL. No.	Compound Code	Mean zone of inhibition in (mm)			
		***Bacillus subtilis* (G+ve)**	***Staphylococus aureus* (G+Ve)**	***Pseudomonas aeruginosa* (G-ve)**	***Escherichia coli* (G-ve)**
1	SD1	NA	NA	NA	NA
2	SD2	NA	NA	NA	NA
3	SD3	8	16	16	18
4	SD4	NA	14	12	12
5	ofloxacin	16	21	23	25
6	DMSO	NA	NA	NA	NA

RESULTS AND DISCUSSION

Out of the four compounds (SD1to SD4) two (SD3and SD4) exhibited a moderate antibacterial activity against both gram (+ve) and gram (-ve) organisms. The test compound SD-3 has shown promising antibacterial activity against gram -ve bacteria *E.coli*.and *Pseudomonas aeruginosa* when compare to standard drug ofloxacin. SD-3 has also shown activity against *S.aureus* and *B.subtilis*. Compounds SD-4 showed moderate activity against *Staphylococcus aureus* when compare to standard drug ofloxacin but none of them showed greater activity than the standard.

CONCLUSION

The results of antibacterial screening reveals that compound SD-3 with para-chlorophenyl azo moiety exhibited potent antibacterial activity against gram+ve organism as compared to other p-substitued derivatives.

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