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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW SCHIFF BASE DERIVATIVES CONTAINING 4,4'-METHYLENE BIS 3-NITRO ANILINE

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ABSTRACT

In this study, a series of new Schiff base derivatives were synthesised from 4,4'-methylene bis 3-nitro aniline. All of the synthesised compounds have been confirmed by elemental analysis, IR and ^{1}H NMR spectral data. Antimicrobial properties of Schiff base derivatives were investigated against two Gram positive bacteria (*Staphylococcus aureus*, *Streptococcus pyogenes*), two Gram negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*) and three strains of fungi (*Candida albicans, Aspergillus niger, Aspergillus clavatus*) using broth micro dilution method.

INTRODUCTION

Schiff's bases are an important class of organic compounds[1]. They were first reported by Hugo Schiff in 1864[2]. Schiff's bases are condensation products of primary amines with carbonyl compounds. The common structural feature of these compounds is the azomethine group with the general formula RHC = N-R', where R and R' are alkyl, aryl, cycloalkyl, or heterocyclic groups[3-8]. Structurally, a Schiff's base (also known as imine or azomethine) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (>C = O) is replaced by an imine or azomethine group. Schiff's bases have also been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, anti-inflammatory, antiviral, and anti-pyretic properties[9-11]. Imine or azomethine groups are present in various natural, naturally derived, and non natural compounds. The imine group present in such compounds has been shown to be critical to their biological activities[12-14]. These bases are an important class of compounds because of the wide variety and potential applications of their industrial, analytical, medicinal, pharmaceutical and catalytical applications[15-20].

MATERIALS AND METHODS

Experimental

The purity of the compounds was checked by using pre-coated TLC plates (E-MERCK, 60 F_{254}) using ethyl acetate: toluene (3:7) solvent system. The developed chromatographic plates were visualized under UV at 254nm. IR spectra were recorded using KBr on 'F.T.Infra-Red Spectrophotometer Model RZX' (Perkin Elmer Spectrum 400). ^{1}H NMR spectra were recorded on a Bruker Avance II 400 NMR spectrometer instrument using TMS as internal standard.

Step I : Synthesis of 4,4'-methylene bis 3-nitro aniline

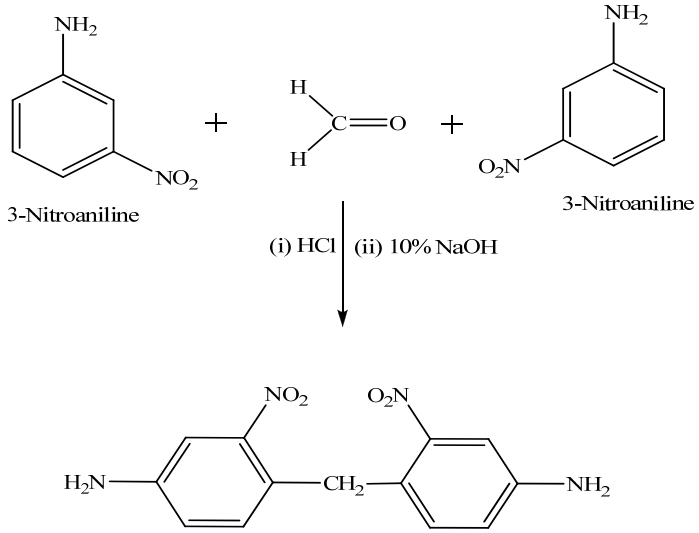
3-Nitro aniline (13.8 g, 0.1 mol) was dissolved in water (125 ml) and 36.5% hydrochloric acid (25 ml) at 50 °C. The reaction mixture was then reacted with 3% aqueous formaldehyde (35 ml) solution at 60°C with stirring for 1hr and neutralized with 10% sodium hydroxide solution. The white precipitates obtained were filtered,washed with hot water, dried and recrystallized from acetic acid. Yield 85%, m.p. 218°C-220°C.

Step II : Synthesis of 4,4'-methylene bis *N*- substituted benzylidine-3-nitro aniline

4,4'-Methylene bis *N*- substituted benzylidine-3-nitro aniline was synthesised by reacting one mole of 4,4'-methylene bis 3-nitro aniline and two moles of various substituted aromatic

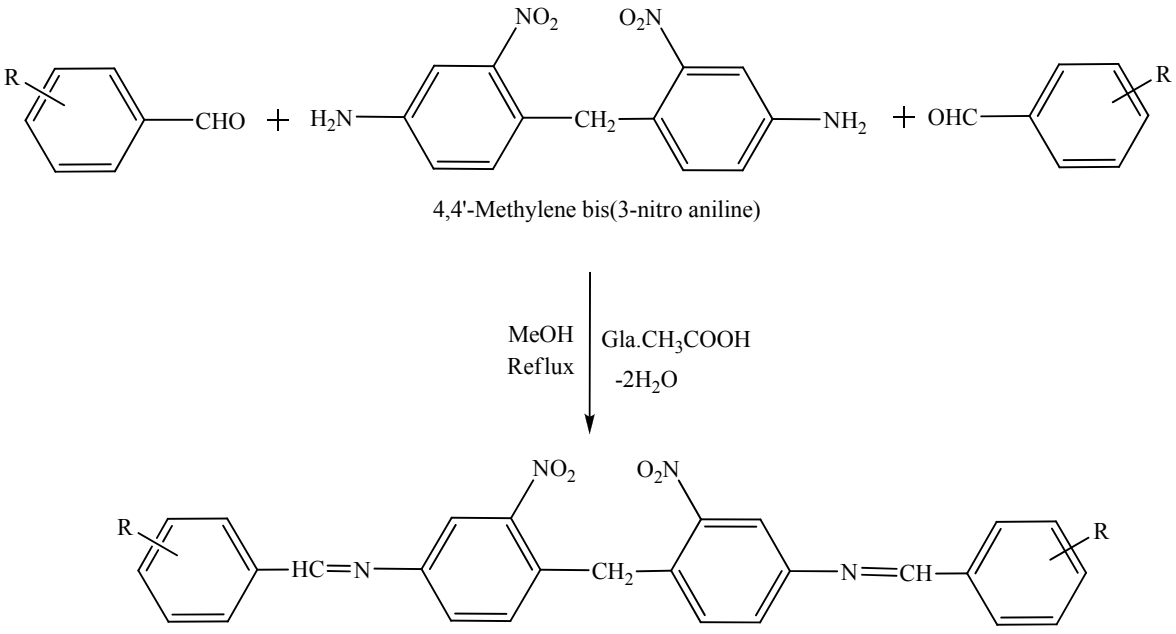
aldehydes. Each reactant was dissolved in a minimum amount of methanol, then mixed together and followed by addition of 0.5 ml glacial acetic acid. The solution was refluxed for 12 hr then cooled to room temperature and poured into ice cold water. The solid product was filtered, dried and recrystallised from ethanol.

Step I : Synthesis of 4,4'-methylene bis 3-nitro aniline



4,4'-Methylene bis(3-nitro aniline)

Step II : Synthesis of 4,4'-methylene bis *N*- substituted benzylidine-3-nitro aniline



Where, R= 2-OH, 4-OCH_3, 4-CH_3, 4-Cl, 4-OH, 2-NO_2, 2-Cl, 2-F, 4-F, H,

4,4'-Methylenebis(*N*-(2-hydroxybenzylidene)-3-nitroaniline) (Ma) :
IR (KBr cm^{-1}): 3400 (O-H, Ar-OH), 3030 (C-H, Aromatic), 2935,2820 (C-H, -CH_2-), 1635 (C=N, Schiff base), 1585,1490 (C=C, Aromatic), 1525,1350 (N=O, -NO_2), 1220 (C-N, Tertiary amine)
^{1}H-NMR (DMSO-d_6, δ ppm): 3.79 (s, 4H, -S-CH_2-), 6.91-7.39 (m, 14H, Ar-H), 8.72 (s, 2H, -N=CH-), 9.10 (s, 2H, -OH)
4,4'-Methylenebis(*N*-(4-methoxybenzylidene)-3-nitroaniline) (Mb) :
IR (KBr cm^{-1}): 3030 (C-H, Aromatic), 2980,2880 (C-H,-OCH_3), 2935,2820 (C-H, -CH_2-), 1635 (C=N, Schiff base), 1585,1490 (C=C, Aromatic), 1525,1350 (N=O, -NO_2), 1222 (C-N, Tertiary amine)
^{1}H-NMR (DMSO-d_6, δ ppm): 3.88 (s, 4H, -S-CH_2-), 4.00 (s, 6H, -OCH_3), 6.81-7.63 (m, 14H, Ar-H), 8.88 (s, 2H, -N=CH-),
4,4'-Methylenebis(*N*-(4-methylbenzylidene)-3-nitroaniline) (Mc) :
IR (KBr cm^{-1}): 3060 (C-H, Aromatic), 2940,2850 (C-H, -CH_2-), 1630 (C=N, Schiff base), 1575,1480 (C=C, Aromatic), 1522,1345 (N=O, -NO_2), 1210 (C-N, Tertiary amine)
^{1}H-NMR (DMSO-d_6, δ ppm): 2.42 (s, 6H, -CH_3), 3.87 (s, 4H, -S-CH_2-), 6.88-7.69 (m, 14H, Ar-H), 8.82 (s, 2H, -N=CH-)
4,4'-Methylenebis(*N*-(4-chlorobenzylidene)-3-nitroaniline) (Md) :
IR (KBr cm^{-1}): 3060 (C-H, Aromatic), 2940,2850 (C-H, -CH_2-), 1630 (C=N, Schiff base), 1575,1480 (C=C, Aromatic), 1522,1345 (N=O, -NO_2), 1210 (C-N, Tertiary amine)
^{1}H-NMR (DMSO-d_6, δ ppm): 3.92 (s, 4H, -S-CH_2-), 6.79-7.28 (m, 14H, Ar-H), 8.78 (s, 2H, -N=CH-)
4,4'-Methylenebis(*N*-(4-hydroxybenzylidene)-3-nitroaniline) (Me) :
IR (KBr cm^{-1}): 3420 (O-H, Ar-OH), 3050 (C-H, Aromatic), 2940,2825 (C-H, -CH_2-), 1625 (C=N, Schiff base), 1575,1477 (C=C, Aromatic), 1565,1350 (N=O, -NO_2), 1230 (C-N, Tertiary amine)
^{1}H-NMR (DMSO-d_6, δ ppm): 3.85 (s, 4H, -S-CH_2-), 6.86-7.36 (m, 14H, Ar-H), 8.72 (s, 2H, -N=CH-), 9.20 (s, 2H, -OH)
4,4'-Methylenebis(*N*-(2-nitrobenzylidene)-3-nitroaniline) (Mf) :
IR (KBr cm^{-1}): 3096 (C-H, Aromatic), 2930,2840 (C-H, -CH_2-), 1620 (C=N, Schiff base), 1606,1471 (C=C, Aromatic), 1527,1349 (N=O, -NO_2), 1192 (C-N, Tertiary amine)
^{1}H-NMR (DMSO-d_6, δ ppm): 4.02 (s, 4H, -S-CH_2-), 7.10-8.24 (m, 14H, Ar-H), 9.00 (s, 2H, -N=CH-)
4,4'-Methylenebis(*N*-(2-chlorobenzylidene)-3-nitroaniline) (Mg) :
IR (KBr cm^{-1}): 3096 (C-H, Aromatic), 2920,2840 (C-H, -CH_2-), 1621 (C=N, Schiff base), 1590,1495 (C=C, Aromatic), 1520,1346 (N=O, -NO_2), 1190 (C-N, Tertiary amine), 734 (C-Cl, Chloro)
^{1}H-NMR (DMSO-d_6, δ ppm): 4.06 (s, 4H, -S-CH_2-), 7.10-8.14 (m, 14H, Ar-H), 8.93 (s, 2H, -N=CH-)
4,4'-Methylenebis(*N*-(2-fluorobenzylidene)-3-nitroaniline) (Mh) :
IR (KBr cm^{-1}): 3050 (C-H, Aromatic), 2935,2840 (C-H, -CH_2-), 1631 (C=N, Schiff base), 1584,1482 (C=C, Aromatic), 1530,1350 (N=O, -NO_2), 1200 (C-N, Tertiary amine), 1100 (C-F, Chloro)
^{1}H-NMR (DMSO-d_6, δ ppm): 3.98 (s, 4H, -S-CH_2-), 6.90-8.24 (m, 14H, Ar-H), 9.04 (s, 2H, -N=CH-)
4,4'-Methylenebis(*N*-(4-fluorobenzylidene)-3-nitroaniline) (Mi) :
IR (KBr cm^{-1}): 3060 (C-H, Aromatic), 2935,2845 (C-H, -CH_2-), 1626 (C=N, Schiff base), 1580,1475 (C=C, Aromatic), 1540,1355 (N=O, -NO_2), 1210 (C-N, Tertiary amine), 1080 (C-F, Chloro)
^{1}H-NMR (DMSO-d_6, δ ppm): 3.92 (s, 4H, -S-CH_2-), 6.96-8.16 (m, 14H, Ar-H), 8.94 (s, 2H, -N=CH-)
4,4'-Methylenebis(*N*-benzylidene-3-nitroaniline) (Mj) :
IR (KBr cm^{-1}): 3060 (C-H, Aromatic), 2940,2840 (C-H, -CH_2-), 1634 (C=N, Schiff base), 1588,1476 (C=C, Aromatic), 1538,1349 (N=O, -NO_2), 1218 (C-N, Tertiary amine)
^{1}H-NMR (DMSO-d_6, δ ppm): 3.94 (s, 4H, -S-CH_2-), 7.10-8.24 (m, 16H, Ar-H), 9.02 (s, 2H, -N=CH-)

RESULTS AND DISCUSSION

All the synthesized compounds (Ma-Mj) were purified by successive recrystallization method using ethanol. The purity of the synthesized compounds was checked by performing TLC. The structures of the synthesized compounds were determined on the basis of their FT-IR and ^{1}HNMR data.

Table 1 : Physical data of synthesized compounds (Ma to Mj)

Sr. No.	R	M.F M.W. (g)	Yield %	m.p ^{o}C	Elemental analysis		
					% C	% H	% N
Ma	2-OH	$C_{27}H_{20}N_4O_6$ 496.47	62	221	65.38 (65.32)	4.02 (4.06)	11.34 (11.29)
Mb	4-OCH_3	$C_{29}H_{24}N_4O_6$ 524.52	69	140	66.48 (66.41)	4.56 (4.61)	10.72 (10.68)
Mc	4-CH_3	$C_{29}H_{24}N_4O_4$ 492.52	81	150	70.80 (70.72)	4.86 (4.91)	11.42 (11.38)
Md	4-Cl	$C_{27}H_{18}Cl_2N_2O_4$ 533.36	79	120	60.86 (60.80)	3.34 (3.40)	10.55 (10.50)
Me	4-OH	$C_{27}H_{20}N_4O_6$ 496.47	74	200	65.38 (65.32)	4.00 (4.06)	11.33 (11.29)
Mf	2-NO_2	$C_{27}H_{18}N_6O_8$ 454.46	89	220	58.54 (58.49)	3.22 (3.27)	15.20 (15.16)
Mg	2-Cl	$C_{27}H_{18}Cl_2N_2O_4$ 533.36	82	175	60.84 (60.80)	3.35 (3.40)	10.52 (10.50)
Mh	2-F	$C_{27}H_{18}F_2N_2O_4$ 500.45	86	238	64.86 (64.80)	3.61 (3.63)	11.24 (11.20)
Mi	4-F	$C_{27}H_{18}F_2N_2O_4$ 500.45	79	189	64.84 (64.80)	3.60 (3.63)	11.25 (11.20)
Mj	H	$C_{27}H_{20}N_2O_4$ 464.47	72	129	69.88 (69.82)	4.30 (4.34)	12.14 (12.06)

Note: ( ) Indicated calculated value.

TABLE – 2: Antibacterial activity of compounds Ma to Mj :

Compound	Minimal Bactericidal Concentration (µg/ml)			
	Gram positive organisms		Gram negative organisms	
	S. aureus	*S. pyogenes*	*E. coli*	*P. aeruginosa*
Ma	1000	250	500	250
Mb	250	500	1000	500
Mc	250	250	500	1000
Md	1000	500	1000	500
Me	500	500	1000	1000
Mf	1000	500	250	250
Mg	500	1000	100	125
Mh	250	62.5	500	250
Mi	500	1000	250	1000
Mj	1000	250	500	250
Norfloxacin	50	50	50	50
Ciprofloxacin	50	50	50	50
Chloramphenicol	50	50	50	50
Ampicillin	50	50	50	50

TABLE – 3: Antifungal activity of compounds MC_1 to MC_{10} :

Compound	Minimal Fungicidal Concentration (µg/ml)		
	C. albicans	*A. niger*	*A. clavatus*
Ma	1000	1000	1000
Mb	1000	1000	1000
Mc	500	1000	1000
Md	1000	1000	1000
Me	1000	1000	1000
Mf	500	500	500
Mg	500	1000	1000
Mh	1000	1000	1000
Mi	1000	500	250
Mj	500	1000	1000
Nystatin-B	100	100	100
Gresiofulvin	100	100	100

Antimicrobial activity

The antimicrobial activity of all the synthesized compounds (Ma -Mj) were examined against two Gram positive bacteria (*Staphylococcus aureus*, *Streptococcus pyogenes*), two Gram negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*) and three strains of fungi (*Candida albicans, Aspergillus niger, Aspergillus clavatus*). The antimicrobial activity was performed by broth micro dilution method. Norfloxacin, Ciprofloxacin, Chloramphenicol and Ampicillin were used as standard drug for antibacterial activity at a concentration of 50µg/ml. Nystatin-B and Gresiofulvin were used as standard drug for antifungal activity at a concentration of 100µg/ml. Results of the antimicrobial activity are shown in Table 2 and 3.

CONCLUSIONS

In the present investigation, new Schiff bases have been synthesised by reacting 3-nitro aniline with formaldehyde in acidic medium and then condensed with various aromatic aldehyde in methanol in presence of acetic acid. Synthesized compounds exhibited promising antibacterial activity against *S. aureus, E. coli, P. aeruginosa and S. pyogenes* organisms, while antifungal activity against *C. albicans, A. niger and A. clavatus* organisms. compound MB_7 showed highly active against gram negative organisms and compound MB_8 showed more active against *S. pyogenes*. Rest of compounds showed good to moderate activity. The antifungal results of this series indicated that compound MB_9 showed more active against *A. clavatus*. Rest of the compounds showed moderate to good activity.

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