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ISSN: 0973-4945; CODEN ECJHAO
E-Journal of Chemistry
2010, **7(2),** 617-623

Synthesis and Studies of Novel Optically Active Schiff's Base Derivatives and their Antimicrobial Activities

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Received 15 October 2009; Accepted 5 December 2009

Abstract: Several new Schiff's base derivatives were prepared by condensing various substituted benzaldehyde with 1-(4-aminophenyl)-2-{4-[(*S*)-(4-chlorophenyl)(phenyl) methyl]-1-piperazinyl}ethanone in presence of acid catalyst under reflux condition. All the compounds were characterized by elemental analysis and spectral studies. The newly synthesized compounds were evaluated for their antibacterial and antifungal activity.

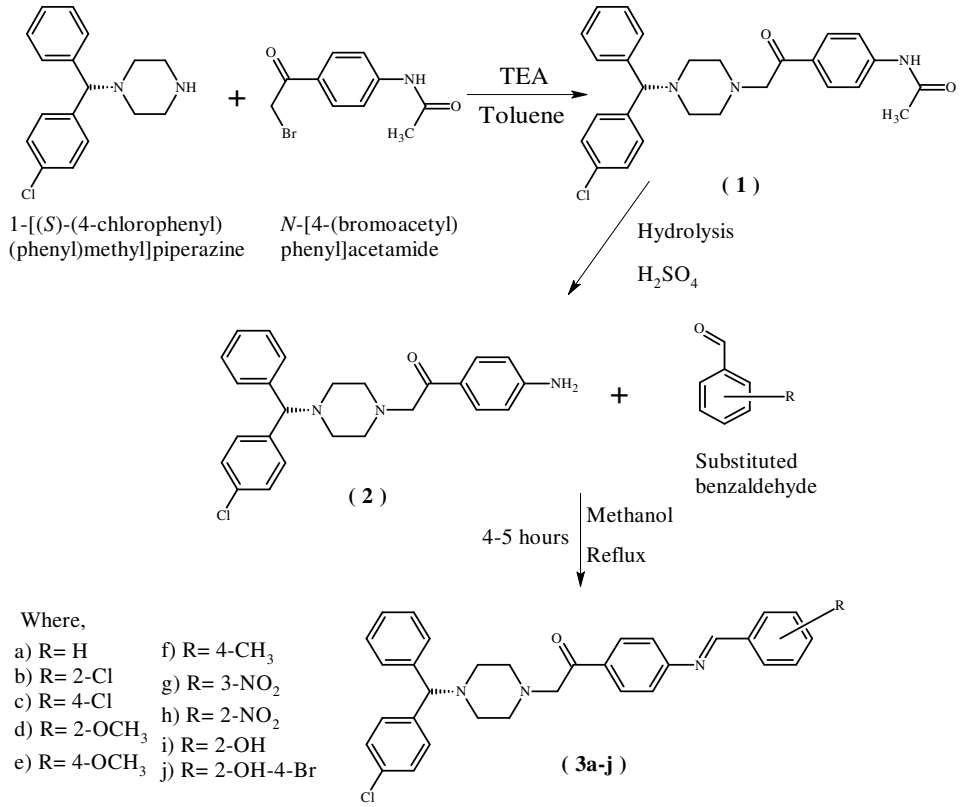
Keywords: Schiff's base, Optically active, Chiral, Spectral studies, Specific optical rotation, Antibacterial activity and Antifungal activity.

Introduction

Schiff's base is a functional group or type of chemical compound containing a carbon-nitrogen double bond with the nitrogen atom connected to an aryl group or an alkyl group but not hydrogen[1]. A Schiff's base (or azomethine) names after Hugo Schiff[2]. Schiff's bases can be synthesized from an aromatic amine and a carbonyl compound in a nucleophilic addition to a hemiaminal followed elimination of water to the imine[3]. Schiff's base ligands derived from salicylaldehyde and chiral amines have been widely applied in enantioselective cyclopropanation of styrenes[4], asymmetric aziridination of olefins[5], enantioselective epoxidation[6], enantioselective ring opening of epoxides[7], asymmetric oxidation of methyl phenyl sulfide[8], enantioselective oxidation of silyl enol[9] and trimethylsilylcyanation of benzaldehydes[10]. Schiff's base containing heterocycles have attracted much attention due to their diverse biological activity such as anticancer[11], antiviral[12-13], fungicidal[14], bactericidal[15] and anti-HIV[16].

Experimental

All melting points were taken in open capillary tubes and are uncorrected. Specific optical rotations (SOR) were taken in Jasco digital polarimeter. Thin layer chromatography was performed on precoated TLC plates with silica gel (Merck 60 F_{254}) and detection was done by UV lamp (254 nm). The IR spectra were obtained on a Simadzu FTIR-8400S spectrophotometer using KBr pellets. The ^{1}H NMR spectra in DMSO-d_6 or $CDCl_3$ were recorded on Bruker WM 400FT MHz spectrometer and chemical shift were reported as parts per million (δ ppm) down field using TMS as internal standard.



Preparation of N-[4-(2-{4-[(S)-(4-chlorophenyl)(phenyl)methyl]-1-piperazinyl} acetyl) phenyl]acetamide(**1**)

A mixture of 1-[(*S*)-(4-chlorophenyl)(phenyl)methyl]piperazine (35 g, 0.122 mol) [SOR:-20.18°] and *N*-[4-(2-bromoacetyl)phenyl]acetamide (32 g, 0.125 mol) was taken in methylene dichloride (140 mL). Triethylamine (12.6 g, 0.125 mol) was added drop wise below 20 °C. The mixture was refluxed for 4-5 h. After completion of reaction, it was cooled and washed with water. The organic mass was dry over sodium sulphate and solvent was removed. The product was recrystalized from methanol.

Yield: 86% MP: 75-76 °C SOR: -9.25° **IR** [ν, cm^{-1}, KBr]: 1666 (C=O), 2956 (-CH_2), 757 (C-Cl). **^{1}H NMR** [400 MHz, δ, ppm, DMSO]: 2.12 (3H, s, –$COCH_3$), 3.36 (2H, s, -$COCH_2$), 10.61 (1H, s, -NH), 5.52 (1H, s, -CH-N), 2.59-4.12 (8H, m, CH_2 piperazine), 7.05-7.94 (13H, m, Ar-H).

Preparation of 1-(4-aminophenyl)-2-{4-[(S)-(4-chlorophenyl)(phenyl)methyl]-1-piperazinyl}ethanone(**2**)

N-[4-(2-{4-[(*S*)-(4-Chlorophenyl)(phenyl)methyl]-1-piperazinyl}acetyl)phenyl]acetamide (40 g, 0.087 mol) was dissolve in methanol (200 mL). Sulfuric acid (22 g, 0.22 mol) was added drop wise by maintaining temperature below 15 °C with constant stirring. The reaction mixture was refluxed for 3 h. After the completion of reaction, solvent was removed and added water (300 mL), made alkaline with concentrated ammonium hydroxide. The solid was separated and recrystalized from methanol.

Yield: 78% MP: 110-112 °C SOR: -5.45° IR [ν, cm^{-1}, KBr]: 1674 (C=O), 3363 (-NH_2), 758 (C-Cl). **^{1}H NMR** [400 MHz, δ, ppm, DMSO]: 3.39 (2H, s,–$COCH_2$), 10.10 (2H, s, –NH_2), 5.51 (1H, –CH-N), 2.56-4.09 (8H, m, CH_2 piperazine), 6.70-8.22 (13H, Ar-H).

*Preparation of 2-{4-[(S)-(4-chlorophenyl)(phenyl)methyl]-1-piperazinyl}-1-(4-{[aryl methylidene]amino}phenyl)ethanone(***3a-j**)

A mixture of 1-(4-aminophenyl)-2-{4-[(*S*)-(4-chlorophenyl)(phenyl)methyl]-1-piperazinyl} ethanone (0.01 mol) and substituted benzaldehyde (0.01 mol) in presence of glacial acetic acid (0.5 mL) in methanol (25 mL) was taken. It was refluxed gently for 4-5 h. The solvent was removed and the product was isolated. It was recrystalized from acetic acid. The remaining compounds **3a-j** was synthesized by using substituted benzaldehyde similarly. Their characterization data were recorded in Table 1.

Table 1. Characterization data of compounds **(3a-j).**

Comp. No.	R	Molecular Formula, (M.Wt)	MP °C	SOR $[\alpha]_d$ °	Yield %	Elementary Analysis % Found (Calculated)		
						% C	% H	% N
1a	H	$C_{32}H_{30}ClN_3O$ (508)	138-139	-1.96	74	75.61 (75.65)	5.92 (5.95)	8.25 (8.27)
1b	2 - Cl	$C_{32}H_{29}Cl_2N_3O$ (542)	204-205	-2.15	79	70.83 (70.85)	5.32 (5.39)	7.84 (7.75)
1c	4 - Cl	$C_{32}H_{29}Cl_2N_3O$ (542)	125-126	-1.90	73	70.81 (70.85)	5.38 (5.39)	7.80 (7.75)
1d	2 - OCH_3	$C_{33}H_{32}ClN_3O_2$ (538)	179-180	-2.08	71	73.69 (73.66)	5.95 (5.99)	7.85 (7.81)
1e	4 - OCH_3	$C_{33}H_{32}ClN_3O_2$ (538)	148-150	-2.19	66	73.65 (73.66)	5.98 (5.99)	7.80 (7.81)
1f	4 - CH_3	$C_{33}H_{32}ClN_3O$ (522)	141-142	-3.10	75	75.90 (75.92)	5.17 (6.18)	8.01 (8.05)
1g	3 - NO_2	$C_{32}H_{29}ClN_4O_3$ (553)	146-147	-3.58	72	69.45 (69.49)	5.26 (5.29)	10.09 (10.1)
1h	2 - NO_2	$C_{32}H_{29}ClN_4O_3$ (553)	171-172	-3.27	76	69.47 (69.49)	5.22 (5.77)	10.02 (10.1)
1i	2 - OH	$C_{32}H_{30}ClN_3O_2$ (524)	133-134	-1.89	69	73.31 (73.34)	5.78 (5.29)	8.00 (8.02)
1j	4 - OH 3 - Br	$C_{32}H_{29}BrClN_3O_2$(603)	156-158	-2.45	74	60.30 (60.32)	4.60 (4.62)	6.15 (6.21)

*2-{4-[(S)-(4-Chlorophenyl)(phenyl)methyl]-1-piperazinyl}-1-(4-[phenylmethylidene]amino} phenyl)ethanone(***3a**)

IR [ν, cm^{-1}, KBr]: 1672 (C=O), 1593 (–C=N), 757 (C-Cl). **^{1}H NMR** [400 MHz, δ, ppm, DMSO]: 3.31 (2H, s, $–COCH_2$), 8.71 (1H, s, –CH=N), 5.48 (1H, s, –CH-N), 2.54-4.11 (8H, m, CH_2 piperazine), 7.04-7.89 (18H, m, Ar-H).

*1-(4-{[(2-Chlorophenyl)methylidene]amino}phenyl)-2-{4-[(S)-(4-chlorophenyl)(phenyl) methyl]-1-piperazinyl}ethanone(***3b**)

IR [ν, cm^{-1}, KBr]: 1681 (C=O), 1595 (–C=N), 774 (C-Cl). **^{1}H NMR** [400 MHz, δ, ppm, DMSO]: 3.33 (2H, s, $–COCH_2$), 8.80 (1H, s, –CH=N), 5.42 (1H, s, –CH-N), 2.58-4.17 (8H, m, CH_2 piperazine), 7.05-7.85 (17H, m, Ar-H).

*1-(4-{[(4-Chlorophenyl)methylidene]amino}phenyl)-2-{4-[(S)-(4-chlorophenyl)(phenyl) methyl]-1-piperazinyl}ethanone(***3c***)*

IR [ν, cm^{-1}, KBr]: 1678 (C=O), 1597 (–C=N), 768 (C-Cl). **^{1}H NMR** [400 MHz, δ, ppm, DMSO]: 3.38 (2H, s, $–COCH_2$), 8.78 (1H, –CH=N), 5.44 (1H, s, –CH-N), 2.59-4.18 (8H, m, CH_2 piperazine), 7.00-7.82 (17H, m, Ar-H).

2-{4-[(S)-(4-Chlorophenyl)(phenyl)methyl]-1-piperazinyl}-1-(4-{[(2-methoxyphenyl) methylidene]amino}phenyl)ethanone(**3d**)

IR [ν, cm^{-1}, KBr]: 1667 (C=O), 1594 (–C=N), 2827 (Ar-OCH_3), 756 (C-Cl). **^{1}H NMR** [400 MHz, δ, ppm, DMSO]: 3.70 (3H, s, $–OCH_3$), 3.35 (2H, s, $–COCH_2$), 8.68 (1H, -CH=N), 5.51 (1H, s,-CH-N), 2.57-4.16 (8H, m, CH_2 piperazine), 6.96-7.85 (17H, m, Ar-H).

2-{4-[(S)-(4-Chlorophenyl)(phenyl)methyl]-1-piperazinyl}-1-(4-{[(4-methoxyphenyl) methylidene]amino}phenyl)ethanone(**3e**)

IR [ν, cm^{-1}, KBr]: 1675 (C=O), 1588 (–C=N), 2822 (Ar-OCH_3), 755 (C-Cl). **^{1}H NMR** [400 MHz, δ, ppm, DMSO]: 3.74 (3H, s, $–OCH_3$), 3.32 (2H, s, $–COCH_2$), 8.79 (1H, s, -CH=N), 5.49 (1H, s, –CH-N), 2.57-4.10 (8H, m, CH_2 piperazine), 6.90-7.87 (17H, m, Ar-H).

2-{4-[(S)-(4-Chlorophenyl)(phenyl)methyl]-1-piperazinyl}-1-(4-{[(4-methylphenyl) methylidene]amino}phenyl)ethanone(3f)

IR [ν, cm^{-1}, KBr]: 1672 (C=O), 1596 (–C=N), 1332 (Ar-CH_3), 757 (C-Cl). **^{1}H NMR** [400 MHz, δ, ppm, DMSO]: 2.25 (3H, s, $–CH_3$), 3.34 (2H, s,$–COCH_2$), 8.71 (1H, –CH=N), 5.56 (1H, s,–CH-N), 2.55-4.13 (8H, m, CH_2 piperazine), 7.01-7.85 (17H, m, Ar-H).

2-{4-[(S)-(4-Chlorophenyl)(phenyl)methyl]-1-piperazinyl}-1-(4-{[(3-nitrophenyl) methylidene]amino}phenyl)ethanone(**3g)**

IR [ν, cm^{-1}, KBr]: 1692 (C=O), 1587 (–C=N), 1344 (Ar-NO_2), 756 (C-Cl). **^{1}H NMR** [400 MHz, δ, ppm, DMSO]: 3.36 (2H, s, $–COCH_2$), 8.64 (1H, s, –CH=N), 5.52 (1H, s, -CH-N), 2.54-4.20 (8H, m, CH_2 piperazine), 7.04-7.98 (17H, m, Ar-H).

2-{4-[(S)-(4-Chlorophenyl)(phenyl)methyl]-1-piperazinyl}-1-(4-{[(2-nitrophenyl) methylidene]amino}phenyl)ethanone(**3h**)

IR [ν, cm^{-1}, KBr]: 1695 (C=O), 1583 (–CH=N), 1349 (Ar-NO_2), 752 (C-Cl). **^{1}H NMR** [400 MHz, δ, ppm, DMSO]: 3.37 (2H, s, $–COCH_2$), 8.68 (1H, s, –CH=N), 5.53 (1H, s, –CH-N), 2.56-4.17 (8H, m, CH_2 piperazine), 7.02-8.08 (17H, m, Ar-H).

1-(4-{[(2-Hydroxyphenyl)methylidene]amino}phenyl)-2-{4-[(S)-(4-chlorophenyl)(phenyl) methyl]-1-piperazinyl}ethanone(**3i**)

IR [ν, cm^{-1}, KBr]: 1681 (C=O), 1595 (–C=N), 3374 (-OH), 754 (C-Cl). **^{1}H NMR** [400 MHz, δ, ppm, DMSO]: 3.35 (2H, s, $–COCH_2$), 4.50 (1H, s, -OH), 8.86 (1H, s, –CH=N), 5.50 (1H, s, –CH-N), 2.59-4.15 (8H, m, CH_2 piperazine), 6.92-7.84 (17H, m, Ar-H).

1-(4-{[(3-Bromo-4-hydroxyphenyl)methylidene]amino}phenyl)-2-{4-[(S)-(4-chlorophenyl) (phenyl)methyl]-1-piperazinyl}ethanone(**3j**)

IR [ν, cm^{-1}, KBr]: 1678 (C=O), 1591 (–C=N), 3364 (-OH), 763 (C-Cl), 687 (C-Br). **^{1}H NMR** [400 MHz, δ, ppm, DMSO]: 3.41 (2H, s, $–COCH_2$), 4.46 (1H, s, -OH), 8.69 (1H, s, –CH=N), 5.40 (1H, s, –CH-N), 2.59-4.15 (8H, m, CH_2 piperazine), 6.95-7.98 (16H, m, Ar-H).

Results and Discussion

The structures of substituted Schiff's base **3a-j** were confirmed by elemental analysis, IR and ^{1}H NMR spectra. IR spectra showed absorption band at 1596 cm^{-1} indicated the stretching vibration of -CH=N (Schiff's base) which confirming the condensation of reactants. C-H stretching vibration of $-CH_2$ appeared at 2956 cm^{-1} and –C=O stretching appeared at 1666 cm^{-1} indicated which confirming the condensation of reactants. The other peaks of IR spectra prove the structure of Schiff's base derivatives. ^{1}H NMR spectrum displayed signals for the presence of one imine proton (-CH=N) at 8.70 ppm (1H, s), one ketone group ($-CO-CH_2$) at 3.39 ppm (2H, s), which also confirms the condensation of reactants.

Biological screening

Antibacterial activities

Antibacterial activities of all the compounds were studied against gram-positive bacteria [*Staphylococcus aureus* (MTCC96), *Streptococcus pyogenes* (MTCC442)] and gram-negative bacteria [*Escherichia coli* (MTCC443), *Pseudomonas aeruginosa* (MTCC424)] by the broth dilution method. Stock solutions of the series of compounds were prepared in DMSO. Each synthesized drug was diluted obtaining 2000 microgram/mL concentration, as a stock solution. Serial dilutions were prepared in primary and secondary screening. In primary screening 500 µg/mL, 250 µg/mL and 125 µg/mL concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 100 µg/mL, 50 µg/mL, 25 µg/mL, 12.5 µg/mL, 6.250 µg/mL, 3.125 µg/mL and 1.5625 µg/mL concentrations. Under similar condition using Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin, and Norfloxacin as a standard for comparison control experiment was carried out.

An examination of the data reveals that all compounds showed antibacterial activity. The compounds **3e, 3j,** were highly active against all four organisms employed. The compounds **3a, 3c, 3d, 3e, 3f, 3g** and **3i** were highly active against *Escherichia coli* (MTCC443) and *Staphylococcus aureus* (MTCC96). Results were presented in Table 2.

Antifungal activities

The compounds **3a-j** were also screened for their antifungal activity against *Candida albicans* (MTCC227), *Aspergillus niger* (MTCC282) and *Aspergillus clavatus* (MTCC1323) at 2000 µg/mL concentration using broth dilution method. As shown in Table 2, the antifungal

activity data clearly showed that the compound **3a-j** having a good activity against *Candida albicans* but less active against *Aspergillus niger* and *Aspergillus clavatus.* The antifungal activity was compared with the known standard drugs greseofulvin, nystatin and the results were presented in Table 2.

Table 2. Antimicrobial activity of compounds (**3a-j).**

Comp.	Antibacterial activity				Antifungal activity		
	Minimum bactericidal concentration μg/mL				Minimum fungicidal concentration μg/mL		
	S.a[a]	S.p[b]	E.c[c]	P.a[d]	C.a[g]	A.n[e]	A.c[f]
3a	50	250	250	250	250	500	1000
3b	250	500	500	500	100	1000	1000
3c	62.5	500	250	250	500	1000	1000
3d	100	100	100	500	250	500	1000
3e	200	250	62.5	125	500	1000	1000
3f	250	500	100	125	250	250	1000
3g	50	500	250	250	500	1000	1000
3h	500	50	500	250	100	1000	1000
3i	250	500	100	125	500	1000	1000
3j	100	125	500	250	>1000	1000	>1000
Gentamycin	0.05	1	0.25	0.5	-	-	-
Ampicillin	100	100	250	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Ciprofloxacin	25	25	50	50	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Greseofulvin	-	-	-	-	500	100	100

S.a[a] - Staphylococcus aureus(MTCC96), S.p[b]- Streptococcus pyogenes(MTCC442), E.c[c]- Escherichia coli(MTCC443), P.a[d]- Pseudomonas aeruginosa(MTCC441), A.n[e]- Aspergillus niger(MTCC282), A.c[f]- Aspergillus clavatus(MTCC1323), C.a[g]- Candida albicans(MTCC227).

Conclusion

The antimicrobial activity of **3a-j** carried out against some strain bacteria. The results show that the prepared compounds were toxic against the bacteria. The comparison of the antibacterial and antifungal activity of these compounds with standard drugs show that the presence of nitro, methoxy and halogen (-Cl) group in the phenyl ring increases the activity.

Acknowledgments

Authors are thankful to the Principal, Sir P.T. Sarvajanik College of Science, Surat for providing research facilities. Authors are also thankful to Praveen Laboratory Pvt. Ltd, Jolwa, Surat for providing chemicals. Thanks are also due to Cadila Healthcare Limited, Baroda and Microcare Laboratory, Surat for providing spectral data, elemental analysis and antimicrobial activity.

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