Research Article

Synthesis and Antimicrobial Evaluation of Some Novel Schiff's Base Derivatives Containing Piperazine Moiety

Mayank T. Champaneriya*, Dr. Geeta C. Desai, Dr. Shailesh J. Parmar
Department of Chemistry, Sir P. T. Sarvajanik College of Science, Surat, Gujarat, India.
***Corresponding author's E-mail:** mayankch711@gmail.com

Accepted on: 04-05-2014; **Finalized on:** 30-06-2014.

ABSTRACT

In the present study, a novel series of piperazine schiff's base analogs [3a-f] have been synthesized by condensing various aldehydes with piperazine acetohydrazide derivative by using methanol as a solvent in presence of acid catalyst under reflux condition. Structure of the synthesized compound has been confirmed by spectral data (IR, ^{1}H NMR) & elemental analysis. All the newly synthesized compounds have been evaluated for their antimicrobial activities.

Keywords: Antimicrobial activities, Piperazine acetohydrazide, Reflux, Schiff's base, Spectral data.

INTRODUCTION

A big challenge facing academia and industry is the relationship of modern societies to the environment that requires reinventing the manufacture and use of materials. Synthetic methodologies now a day should be designed to use and generate substances that possess little or no toxicity to human health and the environment.The condensation products of primary amines with carbonyl compounds were first reported by Schiff in 1864 and the products are also referred to as Schiff's bases. Schiff's bases are compounds contain azomethine group (>C=N) having general formula $R_1N=C-R_2$ where R_1 and R_2 are aryl, alkyl, cycloalkyl or heterocyclic groups which may be variously substituted. They are also referred as anils, imines or azomethines. Several studies[1-5] showed that the presence of a lone pair of electrons in an sp2 hybridized orbital of nitrogen atom of the azomethine group is of considerable chemical and biological importance. Schiff's bases form a significant class of compounds in medicinal and pharmaceutical chemistry with several biological applications that include antibacterial,[6-10] antifungal[7-10] and antitumor activity.[11-12] Schiff's base complexes play a vital role in designing metal complexes related to synthetic and natural oxygen carriers.[13] Metal complexes make these compounds effective as stereospecific catalysts towards oxidation, reduction, hydrolysis, biological activity and other transformations of organic and inorganic chemistry.[14]

Keeping in view the above facts, various biological and pharmacological activities associated with Schiff's base derivatives, it was our interest to synthesize some new Schiff's base derivatives. Antimicrobial activities of these compounds were also studied.

The synthesis of the title compound is given in Scheme – 1. Condensation of methyl bromo(2-chlorophenyl)acetate with 1–[(4–chlorophenyl)(phenyl)methyl]piperazine gave2–(2–chlorophenyl)–2–{4–[(4–chlorophenyl) (phenyl) methyl]piperazin–1–yl}acetate**[1]** in a very good yield. This condensed product **[1]**, further, on condensation with hydrazine hydrate gives2–(2–chlorophenyl)–2–{4–[(4–chlorophenyl)(phenyl)methyl]piperazin–1–yl} acetohydrazide **[2]**,which, on reaction with various aldehydes gives 2–(2–chlorophenyl)–2–{4–[(4–chlorophenyl)(phenyl)methyl]piperazin–1–yl}–N'–(substitutedphenylmethylidene) acetohydrazide **[3a-f]**.

The structures of the synthesized compounds were assigned on the basis of elemental analysis, IR, ^{1}H NMR data. All new synthesized compounds were characterized and evaluated for their *in vitro* antibacterial and antifungal activities against different strains of microorganisms.

MATERIALS AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. All the products have been characterized by elemental analysis, IR and ^{1}H NMR studies. IR spectra were recorded on PerkinElmer 100 spectrophotometer in KBr disc and noteworthy absorption levels (cm^{-1}) listed. ^{1}H NMR spectra were recorded on Bruker spectrometer (400 Mhz) using TMS as an internal standard, chemical shift in δ ppm.

*General procedure for the synthesis of 2–(2–chlorophenyl)–2–{4–[(4–chlorophenyl)(phenyl) methyl]piperazin–1–yl}acetate***[1]**:

A solution of methyl bromo (2–chlorophenyl)acetate (10.54 gm, 0.04 mol) in methylenedichlorie (MDC) (20 ml) was added to the solution of 1–[(4–chlorophenyl)(phenyl)methyl]piperazine(11.46 gm, 0.04 mol) in methylenedichlorie (20 ml). Into this, Triethyl amine (4.05 gm, 0.04 mol) was added drop wise below 15˚C. The mixture was refluxed for 6-8 hours. After completion of reaction (monitored by TLC Toluene : Methanol :: 9 : 1), it was cooled, washed with water and then washed with 10% $NaHCO_3$ solution. The organic mass dried over sodium sulphate. Solvent was removed.

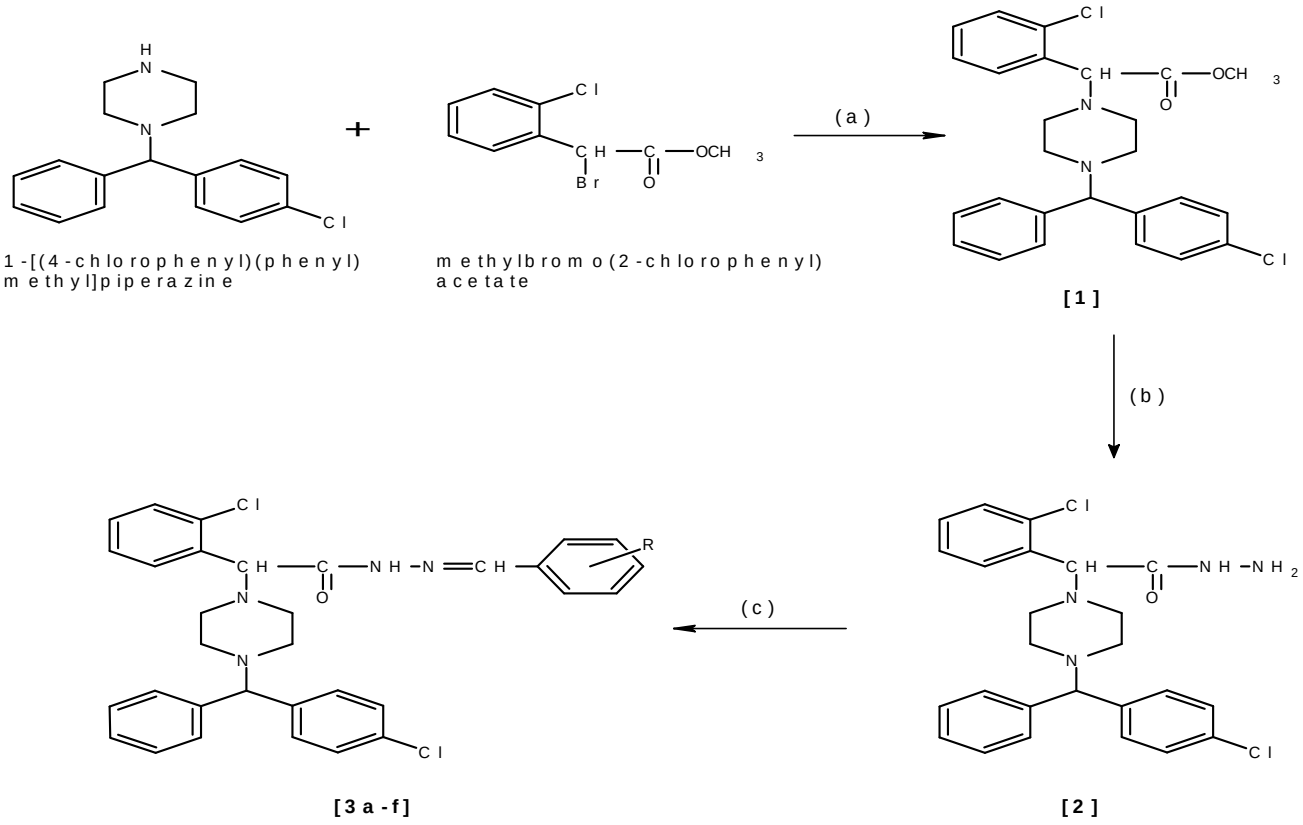
Finally, product was recrystallized from methanol. Yield: 92%. M.P.: 87˚C.

General procedure for the synthesis of 2–(2–chlorophenyl)–2–{4–[(4–chlorophenyl)(phenyl) methyl] piperazin–1–yl}acetohydrazide **[2]**:

methyl2–(2–chlorophenyl)–2–{4–[(4–chlorophenyl) (phenyl)methyl]piperazin–1–yl}acetate **[1]**(15 gm, 0.032 mol) was dissolved in 40 ml isopropylacohol. To this, Hydrazine hydrate (3.2 gm, 0.065 mol) was added slowly. The mixture was refluxed for 10 hours. After completion of reaction (monitored by TLC Toluene : Methanol :: 9 : 1), it was cooled, solvent was removed and product was washed with water and filtered. Finally, product was recrystallized from methanol. Yield: 86%. M.P: 102˚C.

General procedure for the synthesis of 2–(2–chlorophenyl)–2–{4–[(4–chlorophenyl)(phenyl) methyl] piperazin–1–yl}–N'–(phenylmethylidene) acetohydrazide **[3a]**:

2–(2–chlorophenyl)–2–{4–[(4–chlorophenyl) (phenyl) methyl]piperazin–1–yl}acetohydrazide **[2]**(3 gm, 0.006 mol) and benzaldehyde (0.635 gm, 0.006 mol) were taken in methanol (25 ml). 3-4 drops of Conc. H_2SO_4 added. The mixture was refluxed for 5-6 hours. After completion of reaction (monitored by TLC Toluene : Methanol :: 9 : 1), solvent was removed and product was isolated. Finally, product was recrystallized from methanol. IR (cm^{-1}) 1696 (C=O str), 1571 (C=N str), 756 (C-Cl str), 2950 (CH_2str). ^1H NMR δ ppm in (DMSO-d_6) 5.80 (1H, s, CH-N), 8.38 (1H, s, N=CH), 11.68 (1H, s, NH), 4.61 (1H, s, CH-CO), 2.30-4.23 (8H, m, CH_2 piparazine), 7.06-7.89 (18H, m, Ar-H).



Scheme-1

Reagent & Condition: (a)CH_2Cl_2, Triethylamine, 6-8 hrs reflux; (b) Isopropyl alcohol, Hydrazine hydrate, 10 hr reflux; (c) CH_3OH, 2-3 drops of Conc. H_2SO_4, 5-6 hrs reflux.

Table 1: Physical characterization

Code No.	R	Mole. Wt.	MP (˚C)	Yield (%)	Elementary Analysis (%) Found/Calc.		
					C	H	N
3a	-H	557	130-134	79	68.98/69.00	5.44/5.43	10.07/10.06
3b	2-OH	573	138-140	84	67.08/67.07	5.31/5.28	9.77/9.78
3c	3-NO_2	602	122-125	88	63.86/63.84	4.87/4.86	11.61/11.63
3d	4-OH	573	151-154	75	67.09/67.07	5.27/5.28	9.79/9.78
3e	4-Cl	592	126-128	70	64.93/64.92	5.13/5.11	9.45/9.46
3f	4-OCH_3	587	145-148	64	65.46/65.47	5.48/5.49	9.56/9.54

Table-2:*In vitro* antimicrobial activity of newly synthesized compounds**[3a-f]**

Antibacterial Activity					Antifungal Activity	
Zone Of Inhibition (mm)					Zone Of Inhibition (mm)	
Code No.	*Escherichia coli*	*Klebsiella pneumoniae*	*Staphylococcus aureus*	*Bacillus subtilis*	*Candida albicans*	*Saccheromyces cervecieaceae*
3a	15	16	R	17	22	14
3b	18	19	19	18	18	14
3c	19	18	16	20	16	12
3d	22	18	19	20	R	R
3e	17	14	20	18	15	16
3f	20	16	24	18	17	21
Ref.-1	19	19	18	18	-	-
Ref.-2	-	-	-	-	≥22	≥19

Where R = Resistant, Ref.-1 = Ciprofloxacin, Ref.-2 = Flucanazol.

Other compounds **[3b-f]** were synthesized using various aromatic aldehydes. Their physical characterization data are shown in **Table-1**.

2–(2–chlorophenyl)–2–{4–[(4–chlorophenyl) (phenyl) methyl] piperazin–1–yl}–N'–(2-hydroxy phenylmethylidene) acetohydrazide **[3b]:**IR(cm^{-1}) 1685 (C=O str), 1550 (C=N str), 768 (C-Cl str), 2974 (CH_2str), 3362 (OH str). ^{1}H NMR δ ppm in (DMSO-d_6) 5.41 (1H, s, CH-N), 8.71 (1H, s, N=CH), 11.50 (1H, s, NH), 4.47 (1H, s, CH-CO), 3.89 (1H, s, OH), 2.25-4.32 (8H, m, CH_2 piparazine), 6.80-8.24 (17H, m, Ar-H).

*2–(2–chlorophenyl)–2–{4–[(4–chlorophenyl) (phenyl) methyl] piperazin–1–yl}–N'–(3-nitrophenylmethylidene) acetohydrazide***[3c]:**IR(cm^{-1}) 1683 (C=O str), 1565 (C=N str), 751 (C-Cl str), 2968 (CH_2str), 1354 (C-N str). ^{1}H NMR δ ppm in (DMSO-d_6) 5.48 (1H, s, CH-N), 8.80 (1H, s, N=CH), 11.20 (1H, s, NH), 4.78 (1H, s, CH-CO), 2.35-4.46 (8H, m, CH_2 piparazine), 6.78-7.95 (17H, m, Ar-H).

*2–(2–chlorophenyl)–2–{4–[(4–chlorophenyl)(phenyl) methyl] piperazin–1–yl}–N'–(4-hydroxy phenylmethylidene) acetohydrazide***[3d]:** IR(cm^{-1}) 1688 (C=O str), 1595 (C=N str), 764 (C-Cl str), 2962 (CH_2str), 3375 (OH str). ^{1}H NMR δ ppm in (DMSO-d_6) 5.33 (1H, s, CH-N), 8.75 (1H, s, N=CH), 11.58 (1H, s, NH), 4.62 (1H, s, CH-CO), 3.92 (1H, s, OH), 2.33-4.28 (8H, m, CH_2 piparazine), 6.97-8.02 (17H, m, Ar-H).

*2–(2–chlorophenyl)–2–{4–[(4–chlorophenyl)(phenyl) methyl]piperazin–1–yl}–N'–(4-chlorophenyl methylidene) acetohydrazide***[3e]:**IR(cm^{-1}) 1697 (C=O str), 1585 (C=N str), 772 (C-Cl str), 2928 (CH_2str). ^{1}H NMR δ ppm in (DMSO-d_6) 5.62 (1H, s, CH-N), 8.56 (1H, s, N=CH), 11.07 (1H, s, NH), 4.57 (1H, s, CH-CO), 2.57-4.63 (8H, m, CH_2 piparazine), 7.02-8.14 (17H, m, Ar-H).

*2–(2–chlorophenyl)–2–{4–[(4–chlorophenyl)(phenyl) methyl]piperazin–1–yl}–N'–(4-methoxyphenyl methylidene) acetohydrazide***[3f]**:IR(cm^{-1}) 1690 (C=O str), 1558 (C=N str), 755 (C-Cl str), 2972 (CH_2str), 2823 (OCH_3 str). ^{1}H NMR δ ppm in (DMSO-d_6) 5.86 (1H, s, CH-N), 8.88 (1H, s, N=CH), 11.72 (1H, s, NH), 4.92 (1H, s, CH-CO), 3.63 (3H, s, OCH_3), 2.97-4.47 (8H, m, CH_2 piparazine), 6.73-7.70 (17H, m, Ar-H).

Antimicrobial activity

The antimicrobial assay has been determined by using Kirby-Bauer disc diffusion method. In this method, reference drugs and the compounds to be tested were dissolved in dimethyl sulfoxide (DMSO) and disc was prepared with whatman filter papers. Plates were prepared with Mueller-Hinton agar medium for rapidly growing organisms. Inoculum was prepared with the broth culture diluted with sterile saline and turbidity was adjusted to 0.5 McFarland turbidity standards, which is roughly equivalent to 150 million cells per mL. Then, by using aseptic technique, sterile cotton swab was dipped into the broth culture of specific organisms and excess of liquid was removed by gently pressing or rotating the swab against the inside of the tube. The swab was streaked three times over the dried surface of Mueller-Hinton agar plate and allowed the inoculums to dry for 5-15 minutes with lid in place. Discs were applied to the plates and incubated the plates at 35-37˚Covernight. After that, zones showing complete inhibition were measured and recorded.

RESULTS AND DISCUSSION

The compounds of Scheme – 1[3a-f] have been successfully synthesized and tested for their efficacy as antibacterial and antifungal *in vitro* against two gram-negative (*Escherichia Coli*, *Klebsiella Pneumoniae*), gram-positive (*Staphylococcus Aureus*, *Bacillus Subtilis*) bacteria as well as two fungal (*Candida Albicans*, *Sachheromyces Cervecieaceae*) strains using Kirby-Bauer method by measuring the inhibition zones in mm as recommended by National Committee for Clinical Laboratory Standards (NCCLS).[15] The summery of antimicrobial activities is shown in Table-2. It reveals comparable activity with standard drugs. Most of the compounds showed moderate to good antibacterial activity and the same compounds showed promising antifungal activity against the strains used.

CONCLUSION

The substituted piperazine moieties are already known for different biological activities. As per the results of the screening described in Table-2, it is clearly indicated that the compounds of the scheme are good antibacterial and antifungal agent's equipotent with the standard drugs. Form the above results; one can establish that the synthesized substituted piperazines can be rich source for the exploitation. Therefore in search of new generation of the active compounds, it may be worthwhile to explore the possibility in this area by making or introducing different functional groups as substitutions. Which may results into better pharmacological agents.

REFERENCES

1. Elmali A, Kabak M, Elerman Y, Keto-enol tautomerism, conformations and structure of N-(2-hydroxy-5-methylphenyl), 2-hydroxybenzaldehydeimine, J. Mol. Struct., 477, 1999, 151-158.
2. Patel PR, Thaker BT, Zele S, Preparation and characterization of some lanthanide complexes involving a heterocyclic β – diketone, Indian J. Chem., 38A, 1999, 563-567.
3. Valcarcel M, Laque de Castro MD, Flow-Through Biochemical Sensors, Elsevier, Amsterdam, 1994.
4. Spichiger-Keller U, Chemical Sesors and Biosensors for Medical and Biological Applications, Wiley-VCH, Weinheim, 1998.
5. JF Lawrence, RW Frei, "Chemical Derivatization in Chromatography", Elsevier, Amsterdam, 1976.
6. Sithambaram Karthikeyan M, Jagadesh Prasad D, Poojary B, Subramanya Bhat K, Synthesis and biological activity of Schiff and Mannich bases bearing 2,4-dichloro-5-fluorophenyl moiety, Bioorg. Med. Chem., 14, 2006, 7482-7489.
7. Singh K, Barwa MS, Tyagi P, Synthesis, characterization and biological studies of Co(II), Ni(II), Cu(II) and Zn(II) complexes with bidentate Schiff bases derived by heterocyclic ketone Eur. J. Med. Chem., 41, 2006, 147-153.
8. Pannerselvam P, Nair RR, Vijayalakshmi G, Subramanian EH, Sridhar SK, Synthesis of Schiff bases of 4-(4-aminophenyl)-morpholine as potential antimicrobial agents, Eur. J. Med. Chem., 40, 2005, 225-229.
9. Sridhar SK, Saravan M, Ramesh A, Synthesis and antibacterial screening of hydrazones, Schiff and Mannich bases of isatin derivatives, Eur. J. Med. Chem., 36, 2001, 615-625.
10. Pandeya SN, Sriram D, Nath G, Declercq E, Synthesis, antibacterial, antifungal and anti-HIV activities of Schiff and Mannich bases derived from isatin derivatives and N-[4-(4′-chlorophenyl)thiazol-2-yl] thiosemicarbazide., Eur. J. Pharmacol., 9, 1999, 25-31.
11. Mladenova R, Ignatova M, Manolova N, Petrova T, Rashkov I, Preparation, characterization and biological activity of Schiff base compounds derived from 8-hydroxyquinoline-2-carboxaldehyde and Jeffamines ED®, Eur. Polym. J., 38, 2002, 989-999.
12. Walsh OM, Meegan MJ, Prendergast RM, Nakib TA, Synthesis of 3-acetoxyazetidin-2-ones and 3-hydroxyazetidin-2-ones with antifungal and antibacterial activity, Eur. J. Med. Chem., 31, 1996, 989-1000.
13. Thangadurai TD, Gowri M, Natarajan K, Synthesis and characterization of ruthenium(iii) complexes containing monobasic bidentate schiff bases and their biological activities, Synth. React. Inorg. Met.-Org. Chem., 32, 2002, 329-343.
14. Ramesh R, Sivagamasundari M, Synthesis, spectral and antifungal activity of Ru(II) mixed-ligand complexes, Synth. React. Inorg. Met.-Org. Chem., 33, 2003, 899-910.
15. National Committee for Clinical Laboratory Standards. Standard methods for antimicrobial susceptibility test for bacteria. PA: NCCLS, 1982, 242.

Source of Support: Nil, **Conflict of Interest:** None.