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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF SCHIFF'S BASE DERIVATIVES OF VANILLIN ANALOGUE

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ABSTRACT

The chemistry of Schiff's base containing an active Imine linkage has assumed important because of their versatility in the synthesis of many heterocyclic compounds. Schiff's base of N-Aryl-4-(p-chlorobenzyloxy)-3-methoxyphenyl-1-yl-azomethines and Aryl amines of 4-(p-chlorobenzyloxy)-3-methoxybenzylarylamines were prepared. All the prepared compounds were characterized by their spectral (IR, NMR, Mass) data and screened for their antimicrobial activities.

Key words: Schiff's base, Aryl amine, Antimicrobial activities.

INTRODUCTION

Schiff's base derivatives have been found to be potent drug in pharmaceutical industries and possess a wide spectrum of biological activities. Azomethines are also known as Schiff's bases and they are well known intermediate for the preparation[1-11] of azetidinone, thiazolidinone, formazan, arylacetamide and many other derivatives. These are the compounds containing characteristic –C = N– group. Schiff's base derivatives are endowed with different therapeutic activities such as antibacterial[12-16], analgesic, antiviral[17], antiinflammatory[18], antitubercular[19], etc. Azomethines are obtained mainly by heating the aldehyde and aromatic amine together. Aryl amine derivatives have been found to be potent drug in pharmaceutical Industries and possess a wide spectrum of biological activities. Aryl amines exhibit a wide range of pharmacological activities like antifungal[20], antibacterial, antiviral, anti-inflammatory etc. This inspired us to synthesize N-Aryl-4-(p-chlorobenzyloxy)-3-methoxyphenyl-1-yl-azomethines **(1a-l)** and Aryl amines of 4-(p-chlorobenzyloxy)-3-methoxy-benzylarylamines **(2a-l)**.

The structure of synthesized compounds were assigned based on Elemental analysis, I.R. ^{1}H-NMR and mass spectral data. The antimicrobial activity was assayed by using the cup-plate agar diffusion method[21] by measuring the zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activities[22] against varieties of bacterial strains such *Staphylococcus aureus*, *Bacillus subtillis*, *Escherichia coli*, *Proteus vulgaris* and fungi *Aspergillus niger* at 40 µg concentration. Standard drugs like Ampicillin, Amoxicillin, norfloxacin, Benzyl penicillin and Griseofulvin were used for comparison purpose (Table 2).

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EXPERIMENTAL

Melting points were taken in open capillary tubes are uncorrected. IR spectra (cm^{-1}) were recorded on Shimadzu-435-IR Spectrophotometer and, ^{1}H-NMR spectra on Bruker spectrometer (300 MHz) using TMS as an internal standard, chemical shift in δ ppm.

General procedure for the preparation of 4-(p-Chlorobenzyloxy)-3-methoxybenzaldehyde

The solution of Vaniline (1.53 g, 0.01 M) in DMF (7.7 mL) was heated at 50-55^{o}C in presence of 4-chlorobenzoyl chloride (1.75 g, 0.01) and K_2CO_3 (2.76 g, 0.02) for 5 hrs, after 5 hrs product was precipitated by water addition. The separated solid was filtered and leached in methanol. Yield 90%, M.P. 110^{o}C.

4-(p-chlorobenzyloxy)-3-methoxybenzaldehyde

Yield 90%, m.p.110^{o}C; IR (KBr): ν 2922 (-CHO), 1260 (-OCH_3) ,640 (-C-Cl); 1235 (Ar-O-C) cm^{-1}, ^{1}H-NMR ($CDCl_3$): δ 9.86 (s,1H,-CHO), 5.15 (s, 2H, -O-CH_2-) 6.96-8.03 (m, 7H, Ar-H) 3.94 (s, 3H, -OCH_3). Mass m/z 276. M.F.: $C_{15}H_{13}O_3Cl$.

General procedure for the preparation of N-(p-Thiomethoxyphenyl)-1,-4-(p-chlorobenzyloxy)-3-methoxyphenyl-1-yl-azomethine (1a-l)

A mixture of 4-(p-Chlorobenzyloxy)-3-methoxybenzaldehyde (2.76 g, 0.01 M) and p-Thiomethoxy-aniline (1.39 g, 0.01 M) in ethanol (10v) was refluxed in presence of glacial acetic acid for 10 hr. The separated solid was filtered out and crystallized from ethanol. Yield 48%, M.P. 160^{o}C. $C_{22}H_{20}ClNO_2S$; Similarly, other N-Aryl-1,-4-(p-chlorobenzyloxy)-3-methoxyphenyl-1-yl-azomethines were prepared.

N-(p-Thiomethoxyphenyl)-1,4-(p-chlorobenzyloxy)-3-methoxyphenyl-1-yl-azomethine

Yield 48%, M.P. 160^{o}C; IR (KBr): ν 2961.12, 2867.6, 1465.33 (Alkane, -CH_3), 1230.46 (-OCH_3), 750.94 (-C-Cl); 1214.35 (Ar-O-C), 1574.2 (Imine, C=N) , 3074.75, 1508, 1109.44, 826.46 (Aromatic), cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.5, (s, 3H, -OCH_3), 3.98 (s, 3H, -S-CH_3), 8.35 (s, 1H, -CH=N-), 5.18 (s, 2H,-O-CH_2-), 7.14-7.62 (m, 11H, Ar-H), Mass m/z 397.5, M.F.: $C_{22}H_{20}ClNO_2S$.

General procedure for the preparation of 4-(p-Chlorobenzyloxy)-3-methoxy-N-(p-thiomethoxy-phenyl)-benzylamine (2a-l)

A solution of N-(p-Thiomethoxyphenyl)-1,-4-(p-chlorobenzyloxy)-3-methoxyphenyl-1-yl-azomethine (3.97 g, 0.01M) and Sodiumcyanoborohydride (1.25 g, 0.02 M) in ethanol (40 mL) was stirred for 10 hrs. The separated solid was filtered out and crystallized from ethanol. Yield 55%, M.P 140^{o}C. $C_{22}H_{22}ClNO_2S$; Similarly, other 4-(p-Chlorobenzyloxy)-3-methoxy-benzylarylamines were prepared.

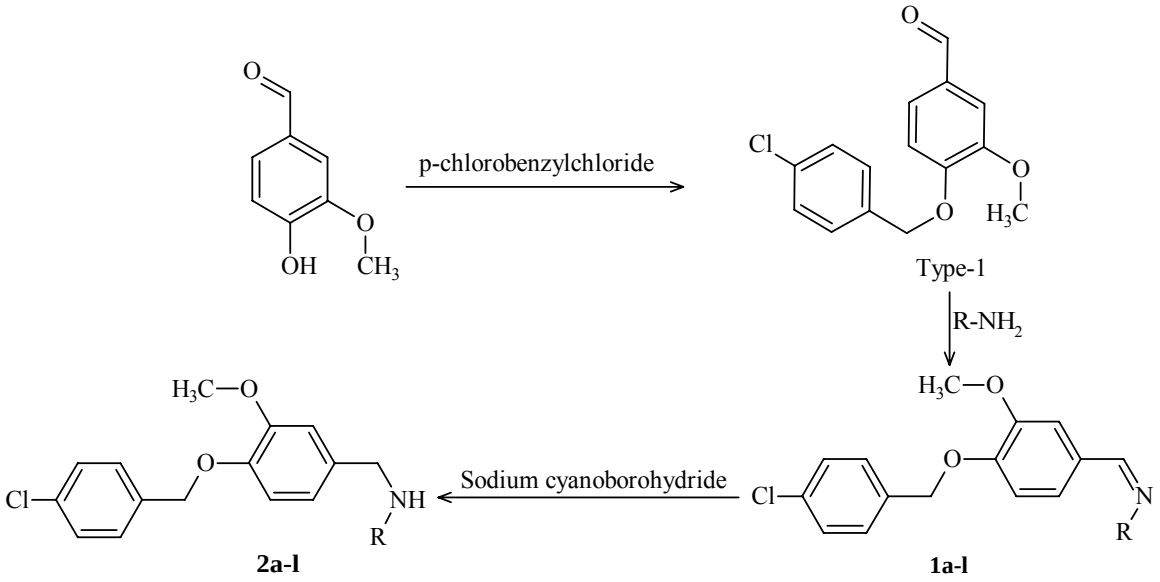
4-(p-Chlorobenzyloxy)-3-methoxy-N-(p-thiomethoxyphenyl)-benzylamine

Yield 55%, M.P. 140^{o}C; IR(KBr): ν 2968.35, 2863.6, 1468.83 (Alkane, -CH_3), 1233.43 (-OCH_3), 755.95 (-C-Cl); 1214.33 (Ar-O-C) , 1574.2 (Imine, C=N), 3079.35, 1518, 1103.43, 827.17 (Aromatic), cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ ppm 2.4, (s, 3H, -O-CH_3), 3.86 (s, 3H, -S-CH_3), 5.09 (s, 2H, -O-CH_2-), 6.56-7.37 (m, 11H, Ar-H), 3.99 (s, 1H, -CH_2-NH-), 4.22 (s, 2H, -CH_2-NH-). Mass m/z 399.10, M.F.: $C_{22}H_{22}ClNO_2S$.

RESULTS AND DISCUSSION

The synthesis of N-Aryl-4-(p-chlorobenzyloxy)-3-methoxyphenyl-1-yl-azomethines **(1a-l)** was prepared by reaction of 4-(p-Chlorobenzyloxy)-3-methoxybenzaldehyde (Type-I) and Amine derivatives in presence of glacial acetic acid and 4-(p-Chlorobenzyloxy)-3-methoxy-benzylarylamines of type **(2a-I)** have

been prepared by the reduction of N-Aryl-1,-4-(p-chlorobenzyloxy)-3-methoxyphenyl-1-yl-azomethines with sodium cyanoborohydride in methanol at ambient temperature (**Scheme 1**).



Scheme 1

The formulas of selected compounds were confirmed by the elemental analysis and their structures were determined by IR, ^{1}H-NMR and mass spectral data.

Table 1: Characterization data of the compounds (1a-l) and (2a-l)

Compd.	R	Molecular formula	Mole. wt.	M.P. (^{o}C)	Nitrogen %	
					Calcd.	Found
1a	4-SCH_3-C_6H_4	$C_{22}H_{20}ClNO_2S$	397.5	160	3.52	3.55
1b	-3-Cl-C_6H_4	$C_{21}H_{17}Cl_2NO_2$	386.0	162	3.63	3.60
1c	-3-Br-C_6H_4	$C_{21}H_{17}BrClNO_2$	430.5	180	3.25	3.20
1d	-C_6H_5	$C_{21}H_{18}ClNO_2$	351.5	174	3.98	4.10
1e	-3,5-$(Cl)_2$-C_6H_3	$C_{21}H_{16}Cl_3NO_2$	420.5	190	3.33	3.40
1f	-4-CH_3-C_6H_4	$C_{22}H_{20}ClNO_2$	365.5	155	3..83	3.80
1g	-4-F-C_6H_4	$C_{21}H_{17}ClFNO_2$	369.5	174	3.79	3.85
1h	-4-Cl-C_6H_4	$C_{21}H_{17}Cl_2NO_2$	386.0	185	3.63	3..58
1i	-2,4-$(Cl)_2$-C_6H_3	$C_{21}H_{16}Cl_3NO_2$	420.5	210	3.33	3.41
1j	-2,6-$(Cl)_2$-C_6H_3	$C_{21}H_{16}Cl_3NO_2$	420.5	220	3.33	3.35
1k	-2,5-$(OCH_3)_2$-C_6H_3	$C_{23}H_{22}ClNO_4$	411.5	196	3.40	3.45
1l	-3-F-C_6H_4	$C_{21}H_{17}ClFNO_2$	369.5	174	3.79	3.83
2a	4-SCH_3-C_6H_4	$C_{22}H_{22}ClNO_2S$	399.5	140	3.50	3.55
2b	-3-Cl-C_6H_4	$C_{21}H_{19}Cl_2NO_2$	388.0	156	3.61	3.65
2c	-3-Br-C_6H_4	$C_{21}H_{19}BrClNO_2$	432.5	165	3.24	3.30

Cont…

Compd.	R	Molecular formula	Mole. wt.	M.P. (^oC)	Nitrogen %	
					Calcd.	Found
2d	$-C_6H_5$	$C_{21}H_{20}ClNO_2$	353.5	163	3.96	4.10
2e	$-3,5-(Cl)_2-C_6H_3$	$C_{21}H_{20}Cl_3NO_2$	422.5	169	3.31	3.40
2f	$-4-CH_3-C_6H_4$	$C_{22}H_{22}ClNO_2$	367.5	186	3.81	3.90
2g	$-4-F-C_6H_4$	$C_{21}H_{19}ClFNO_2$	371.5	175	3.77	3.85
2h	$-4-Cl-C_6H_4$	$C_{21}H_{19}Cl_2NO_2$	388.0	160	3.61	3.75
2i	$-2,4-(Cl)_2-C_6H_3$	$C_{21}H_{18}Cl_3NO_2$	422.5	173	3.31	3.40
2j	$-2,6-(Cl)_2-C_6H_3$	$C_{21}H_{18}Cl_3NO_2$	422.5	182	3.31	3.42
2k	$-2,5-(OCH_3)_2-C_6H_3$	$C_{23}H_{24}ClNO_4$	413.5	183	3.38	3.35
2l	$-3-F-C_6H_4$	$C_{21}H_{19}ClFNO_2$	371.5	175	3.77	3.65

Table 2: Antibacterial and antifungal activity of compounds (1a-l) and (2a-l)

Compd.	Antibacterial activity (zone of inhibition in mm)				Antifungal activity
	S. aureus	***B. subtillis***	***E. coli***	***P. vulgaris***	***A. niger***
1a	14	20	20	11	20
1b	13	19	16	14	15
1c	15	12	18	12	20
1d	11	14	12	13	18
1e	13	15	19	20	10
1f	14	11	22	18	20
1g	19	11	10	16	12
1h	16	18	23	17	16
1i	18	22	17	12	17
1j	14	17	15	12	15
1k	18	12	16	18	12
1l	11	14	22	13	19
2a	18	18	15	18	20
2b	12	14	18	14	15
2c	15	12	20	19	18
2d	18	18	21	22	22
2e	14	13	14	20	10
2f	16	17	19	17	20
2g	12	20	22	12	17
2h	20	14	14	14	15

Cont…

Compd.	Antibacterial activity (zone of inhibition in mm)				Antifungal activity
	S. aureus	*B. subtillis*	*E. coli*	*P. vulgaris*	*A. niger*
2i	20	18	15	11	16
2j	15	18	17	16	13
2k	12	15	21	14	17
2l	14	12	18	11	14
Ampicillin	20	24	22	21	0
Amoxicillin	21	24	25	25	0
Norfloxacin	18	17	24	25	0
Benzyl penicillin	20	18	18	15	0
Griseofulvin	0	0	0	0	24

Antibacterial activity

It has been observed from the microbiological data that all compounds **(1a-l)** and **(2a-l)** were found to be mild to moderately active against Gram positive and Gram negative bacterial strains. How ever the maximum activity was observed in compounds **(1g)**, **(1l)**, **(2h)**, **(2l)** against *S. aureus*. The significant activity was observed in compounds **(1a)**, **(1l)**, **(2g)**, **(2j)** against B.subtillis. The maximum activity was displayed by the compounds **(1f)**, **(1h)**, **(2g)**, **(2k)**, against *E. coli*. The compounds **(1e)**, **(1f)**, **(2c)**, and **(2e)** were comparatively more effective against *P.vulgaris*.

Antifungal activity

The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds **(1a)**, **(1c)**, **(1f)**, **(2a)**, **(2e)**, **(2f)**, against *A. niger*. The antibacterial activity was compared with standard drug viz. Ampicillin, Amoxicillin, Norfloxacin, Benzyl penicillin and antifungal activity was compared with standard drug viz. Griseofulvin.

CONCLUSION

The present study leads to a convenient synthetic method for the synthesis of new compounds. Which show significant antibacterial and antifungal activity. Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products.

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REFERENCES

1. R. Neustadt Bernard and Liu Hong, Chem. Abstr., **139(2)**, 22227v (2003).
2. Nettekoven Matthias, Heinrich, Schmitt and Sebastien, Chem. Abstr., **138(21)**, 321280e (2003).
3. Krueger Martin, Petrov Orlin, Thierauch Karl Heinz and Siemeister Gerhard, Chem. Abstr., **138(1)**, 4620t (2003)

4. S.K. Shrivastava and Soumya Shrivastava and S. D. Shrivastava, Indian J. Chem., **41B(9)**, 1937 (2002).

5. Lattman Rene and Waldmeier Felix, Chem. Abstr., **138 (25)**, 385430m (2003).

6. H. Heindel Ned, Laskin Jeffery D Heck Diene E.; Guillon and D. Rapp Robert, Chem. Abstr., **139(6)**, 85356g (2003).

7. Sobin, Bachmann, J. Am. Chem Soc., **57**, 2458 (1935).

8. M. S. Murray, Chemical Review, **26**, 297 (1940).

9. Strache, Bre., **21**, 2361 (1888).

10. Van Alphen, Dec. Tran. Chim., **54**, 93 (1935).

11. Oddo and Tognacchini, Gazz. Chim. Ital., **52(II)**, 347 (1922).

12. R. H. Mehta, Sonal Shah and Rajeev Vyas, J. Indian Chem. Cos., **69(9)**, 590 (1992).

13. Chohan, Zahid Hussain, Kusuar, Somina, Chem. Pharm., Bull., **41(5)**, 951 (1993).

14. Solankee Anjani, Mistry Pankaj, Patel V. M., Orient J. Chem., **13(30)**, 289 (1997).

15. Yousif Ali, Al-Rawi, Annis, A1-Rawi Muna S, Dirasat Nat., Eng. Sct., **25(1)**, 94 (1998).

16. B. S. Holla and R. Gonzalves, Boll. Chim. Farm., **137(11)**, 467 (1998).

17. Wang, Yangang, Ye, Wenfa, Yang Jun, Lou, Aihong, Wuhan Daxue Xuebao and Ziran Kexueban, 191-194 (1996) (Ch.), Chem. Abstr. 125(13), 167488b (1996).

18. Cascaval Alexandru, Stocia, Gheorghe-Zaharia, Berdan, Ioan, Rom. RO., 106, 403, (C1. CO7D 231/04), (1993), Appl. 143, 707. 15 (1990).

19. Smalders, Robert Rene, Brunin. Dominique, Sarten, Frederic, Bull. Soc. Chim. Belg., **97(11-12)**, 941 (1988).

20. Ergenc Nedime, Uinsoy, Nuray, Capangultate, Soruis, Aulten o tuk; Kiraz, Mnammer, Arch. Pharm., **329(8-9)**, 427 (1996).

21. A. L. Barry, The Antimicrobial Susceptibility Test: Principle and Practices, Edited by Llluslea & Febiger, (Philadelphia), USA, 180, Biol. Abstr., **64**, 25183 (1977).

22. J. Panda, S. V. Srinivas and M. E. Rao, J. Indian Chem. Soc., **79(9)**, 770 (2002).