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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF SCHIFF'S BASE AND 4-THIAZOLIDINONE DERIVATIVES OF VANILLIN

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ABSTRACT

In the present investigation, it was our interest to synthesize some new derivatives containing 4-(o-Chlorobenzyloxy)-3-methoxybenzaldehyde moiety incorporated with different biologically active heterocycles such as Schiff's base and Thiazolidinones derivatives. Schiff's base of N-Aryl-1,-4-(o-chlorobenzyloxy)-3-methoxyphenyl-1-yl-azomethines and N-Aryl-1,4-(o-chlorobenzyloxy)-3-methoxyphenyl-1-yl-4-thiazolidinones were prepared. All the prepared compounds were characterized by their spectral (I.R., N.M.R., Mass) data and screened for their antimicrobial activities.

Key words: Schiff's base, Thiazolidinones, Antimicrobial activities.

INTRODUCTION

Schiff's base and Thiazolidinone 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.

Thiazolidinones, which belong to an important group of heterocyclic compounds have been extensively explored for their applications in the field of medicine. 4-Thiazolidinone[20-25] derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activities, such as significant *in vitro* activity against DNA and RNA viruses including polioviruses, hypnotic, sedative, analgesic[26], diuretic, antitubercular, anticonvulsant[27], antifungal[28], antibacterial activity etc. These valid observations led us to synthesize some new N-Aryl-4-(o-chlorobenzyloxy)-3-methoxyphenyl-1-yl-azomethines (1a-l) and N-Aryl-1,4-(o-chlorobenzyloxy)-3-methoxyphenyl-1-yl-4-thiazolidinones **(2a-l)** have been synthesized by the heterocyclization of Schiff's bases of **(1a-l)** with thioglycolic acid.

The structure of synthesized compounds were assigned based on Elemental analysis, I.R. ^{1}H-NMR and Mass spectral data. The antimicrobial[29,30] activity was assayed by using the cup-plate agar diffusion

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method[31] by measuring the zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activities 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 1).

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

Compd.	R	Molecular formula	Mole. Wt.	M.P. (^oC)	Nitrogen %	
					Calcd.	Found
1a	-C_6H_5	$C_{21}H_{18}ClNO_3$	351.5	75	3.98	3.94
1b	-$C_{10}H_7$	$C_{25}H_{20}ClNO_2$	401.5	96	3.49	3.44
1c	-4-Br-C_6H_4	$C_{21}H_{17}BrClNO_2$	430.5	110	3.25	3.22
1d	-3-Cl-C_6H_4	$C_{21}H_{17}Cl_2NO_2$	386.0	60	3.63	3.61
1e	-4-Cl-C_6H_4	$C_{21}H_{17}Cl_2NO_2$	386.0	102	3.63	3.62
1f	-4-F-C_6H_4	$C_{21}H_{17}ClFNO_2$	369.5	85	3.79	3.62
1g	-2-OCH_3-C_6H_4	$C_{22}H_{20}ClNO_3$	381.5	125	3.67	3.64
1h	-4-OCH_3-C_6H_4	$C_{22}H_{20}ClNO_3$	381.5	110	3.67	3.66
1i	-2-CH_3-C_6H_4	$C_{22}H_{20}ClNO_2$	365.5	52	3.83	3.80
1j	-4-CH_3-C_6H_4	$C_{22}H_{20}ClNO_2$	365.5	60	3.83	3.81
1k	-3-NO_2-C_6H_4	$C_{21}H_{17}ClN_2O_4$	396.5	125	7.06	7.00
1l	-4-NO_2-C_6H_4	$C_{21}H_{17}ClN_2O_4$	396.5	150	7.06	7.02
2a	-C_6H_5	$C_{23}H_{20}ClNO_3S$	425.5	100	3.29	3.27
2b	-$C_{10}H_7$	$C_{27}H_{22}ClNO_3S$	475.5	68	2.94	2.90
2c	-4-Br-C_6H_4	$C_{23}H_{19}BrClNO_3S$	504.5	140	2.76	2.75
2d	-3-Cl-C_6H_4	$C_{23}H_{19}Cl_2NO_3S$	460.0	115	3.04	3.01
2e	-4-Cl-C_6H_4	$C_{23}H_{19}Cl_2NO_3S$	460.0	105	3.04	3.00
2f	-4-F-C_6H_4	$C_{23}H_{19}ClFNO_3S$	443.5	120	3.16	3.12
2g	-4-OCH_3-C_6H_4	$C_{24}H_{22}ClNO_4S$	455.5	142	3.07	3.04
2h	-2-CH_3-C_6H_4	$C_{24}H_{22}ClNO_3S$	439.5	138	3.19	3.19
2i	-3-CH_3-C_6H_4	$C_{24}H_{22}ClNO_3S$	439.5	125	3.19	3.17
2j	-4-CH_3-C_6H_4	$C_{24}H_{22}ClNO_3S$	439.5	82	3.19	3.16
2k	-3-NO_2-C_6H_4	$C_{23}H_{19}ClN_2O_5S$	470.5	132	5.95	5.94
2l	-4-NO_2-C_6H_4	$C_{23}H_{19}ClN_2O_5S$	470.5	118	5.95	5.93

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-(o-Chlorobenzyloxy)-3-methoxybenzaldehyde

The solution of Vanillin (1.53 g, 0.01 M) in D.M.F. (15.0 mL) was heated at 65-70°C with 2-chlorobenzyl 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 92%, M.P. 58°C.

4-(o-chlorobenzyloxy)-3-methoxybenzaldehyde

Yield 92%, M.P. 58°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, ArH) 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-Methoxyphenyl)-1,-4-(o-chlorobenzyloxy)-3-methoxyphenyl-1-yl-azomethine (1a-l)

Mixture of 4-(o-Chlorobezyloxy)-3-methoxybenzaldehyde (2.76 g, 0.01 M) and p-Methoxy aniline (1.23 g, 0.01 M) in methanol was refluxed in presence of glacial acetic acid for 12 hr. The separated solid was filtered out and crystallized from ethanol. Yield 64 %, m.p 110°C. ($C_{22}H_{20}ClNO_3$; Required: C, 69.20; H, 5.24; N, 3.67; Found: C, 69.15; H, 5.20; N, 3.66%. Similarly, other N-Aryl-1,-4-(o-chlorobenzyloxy)-3-methoxyphenyl-1-yl-azomethines were prepared.

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

Yield 64%, M.P. 110°C; IR(KBr): ν 2962.62, 2829.88, 1438.23 (Alkane, -CH_3), 1227.22 (-OCH_3), 759.94 (-C-Cl); 1213.82 (Ar-O-C), 1577.05 (Imine, C=N), 3065.80, 1506.46, 1139.28, 823.21 (Aromatic), cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 3.74, (s, 3H, -OCH_3), 3.93 (s, 3H, -OCH_3), 8.29 (s, 1H, -CH=N-), 5.24 (s, 2H, -O-CH_2-), 6.81-7.56 (m, 11H, Ar-H), Mass m/z 381.5. M.F.: $C_{22}H_{20}ClNO_3$.

General procedure for the preparation of 2-[4-(o-chlorobenzyloxy)-3-methoxyphenyl-1-yl]-N3- (p-chlorophenyl)-1,3-thiazolidin-4-one (2a-l):

A mixture of N-(p-Chlorophenyl)-1,-4-(o-chlorobenzyloxy)-3-methoxyphenyl-1-yl-azomethine (3.81 g, 0.01 M) in benzene (25 mL) was taken, Dean stark apparatus was attached to it and thioglycolic acid (0.92 gm, 0.01 M) in benzene was added slowly. Then it was refluxed for 14 hrs, during the course of the reaction the water was removed continuously. The benzene was distilled off to get the thiazolidinones. The solid product was filtered, dried and recrystallized from absolute alcohol. Yield: 60%, M.P. 105°C. ($C_{23}H_{19}Cl_2NO_3S$; Required: C: 60.0; H: 4.13; N: 3.0; S: 6.95; Found: C:59.95; H: 4.10; N:3.0; S:6.90%), Similarly, other 4-thiazolidinones were prepared.

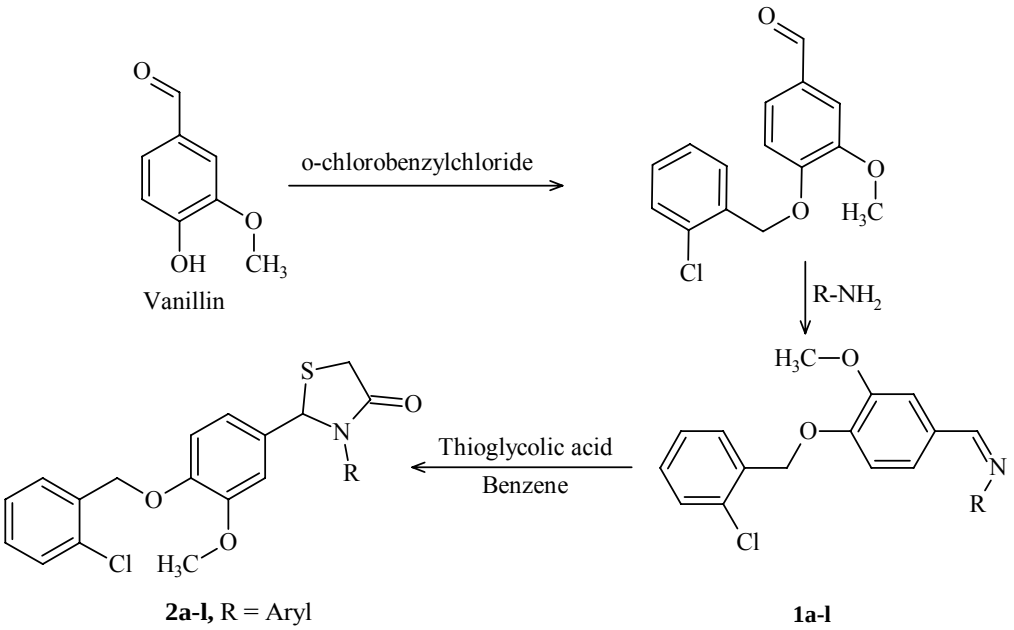
2-[4-(o-chlorobenzyloxy)-3-methoxyphenyl-1-yl]-N3-(p-chlorophenyl)-1,3-thiazolidin-4-one

Yield 60%, M.P. 105°C; IR(KBr): ν 2943.06, 2829.88, 1465.50 (Alkane, -CH_3), 1256.56 (-OCH_3), 745.01 (-C-Cl); 1213.82 (Ar-O-C), 1376.87 (-C-N str.), 1698.39(-C=O str.), 745.01 (C-S-C str.) 3066.77, 1505.39, 1130.95, 823.21 (Aromatic), cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ ppm 3.72, (s, 3H, -O-CH_3), 3.35 (s, 2H, -S-CH_2-CO-), 5.24 (s,1H,-CH-), 5.27 (s, 2H, -O-CH_2-) 7.21-7.63 (m, 11H, Ar-H). Mass m/z 460.0. M.F.:$C_{23}H_{19}Cl_2NO_3S$.

RESULTS AND DISCUSSION

The synthesis of N-Aryl-4-(o-chlorobenzyloxy)-3-methoxyphenyl-1-yl-azomethines Type-**(1a-l)** was prepared by reaction of 4-(o-Chlorobenzyloxy)-3-methoxybenzaldehyde and amine derivatives in presence of glacial acetic acid and N-Aryl-1,4-(o-chlorobenzyloxy)-3-methoxyphenyl-1-yl-4-thiazolidinones Type-

(2a-l) have been prepared by the reaction of N-Aryl-4-(o-chlorobenzyloxy)-3-methoxyphenyl-1-yl-azomethines with Thioglycolic acid in benzene 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.

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. However the maximum activity was observed in compounds **(1d)**, **(1g)**, **(1j)**, **(2b)**, **(2d)**, **(2f)** against *S. aureus*. The significant activity was observed in compounds **(1d)**, **(1e)**, **(1f)**, **(2e)**, **(2g)**, **(2k)** against *B. subtillis*. The maximum activity was displayed by the compounds **(1e)**, **(1g)**, **(1i)**, **(2a)**, **(2d)**, **(2f)**, against *E. coli*. The compounds **(1b)**, **(1d)**, **(1f)**, **(2e)**, **(2i)** and **(2j)** were comparatively more effective against *P. vulgaris*.

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	12	13	15	15	20
1b	14	16	13	18	21
1c	10	19	13	14	19
1d	16	21	14	24	17
1e	10	22	17	18	12
1f	10	20	15	22	18

Cont…

Compd.	Antibacterial activity (zone of inhibition in mm)				Antifungal activity
	S. aureus	***B. subtillis***	***E. coli***	***P. vulgaris***	***A. niger***
1g	19	18	25	14	18
1h	11	18	14	14	16
1i	13	19	27	16	20
1j	16	12	14	15	14
1k	8	14	13	14	12
1l	13	14	20	16	16
2a	20	12	22	17	13
2b	21	12	19	14	16
2c	18	14	16	14	19
2d	23	20	28	16	20
2e	14	22	12	25	14
2f	26	16	23	20	15
2g	14	24	16	18	19
2h	18	14	16	14	16
2i	14	16	14	21	14
2j	16	13	15	22	10
2k	17	23	16	13	16
2l	12	13	14	15	15
Amoxicillin	28	24	28	22	-
Ampicillin	24	26	22	20	-
Penicillin	16	26	22	12	-
Norfloxacin	21	38	28	25	-
Griseofulvin	-	-	-	-	16

Antifungal activity

The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds **(1a), (1b)**, **(1i)**, **(2c)**, **(2d)**, **(2g)** 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.

Future aspect

Future investigation could give some interesting results by changing substitution at various position of thiazolidinone as well as vanillin ring.

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