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Synthesis and Biological Evaluation of Some New Pyrazoline Derivatives of Vanillin Analogue

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Abstract:
Some new 3-Aryl-5-[4'-(o-chlorobenzyloxy)-3'-methoxyphenyl]-4,-5-dihydro-1H-pyrazoles 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: *Chalcone, Pyrazoline , antimicrobial activities*

1. Introduction

The chemistry of chalcones[1-3] containing an active keto-ethylenic linkage has been assumed important because of their versatility in the synthesis of many heterocyclic compounds. The presence of reactive α ,β –unsaturated keto function in chalcones is found to be responsible for their antibacterial[4-7] and antifungal activity[8-9]. Chalcones constitute an important group of natural products and some of them possess a wide range of biological activity such as antibacterial, antitubercular[10-11,] anticancer[12-13,] antitumour[14-16] etc. Pyrazoline derivative[17-20] have been found to possess a wide range of therapeutic activity such as anticonvulsant[21-22,] analgesic[23-24,] antibacterial, antifungal, anticancer, etc.

Chalcones and pyrazolines have proved to be the most useful framework for biological activities, Both have attracted attention of medicinal chemists for both with regard to heterocyclic chemistry and the pharmacological activities associated with them. This inspired us to synthesize 1-Aryl-3-[4'-(o- chlorobenzyloxy) -3'-methoxyphenyl] -propenones (1a-l) and 3-Aryl-5-[4'-(o-chlorobenzyloxy) -3'-methoxyphenyl] -4, -5-dihydro-1H-pyrazoles (2a-l).

The structure of synthesized compounds was 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 [25] by measuring the zone of inhibition in mm. All the compounds were screened in vitro for their antimicrobial activities[26] 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).

2. Results and Discussion

The synthesis of 1-Aryl-3-[4'-(o- chlorobenzyloxy)-3'-methoxyphenyl]-propenones (1a-l) and 3-Aryl-5-[4'-(o-chlorobenzyloxy)-3'-methoxyphenyl]-4,-5-dihydro-1H-pyrazoles (2a-l) was carried out in two steps, first by the condensation of 4-[(2-chlorobenzyl)oxy]-3-methoxy benzaldehyde (1) with different aromatic acetophenone by Claisen-shmidt condensation in presence base catalyst to give chalcone derivatives (1a-l), which in next step were refluxed with hydrazine hydrate to yield pyrazoline derivatives (2a-l). (scheme-1).

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

3. 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 (1a),(1i),(2c),(2g) against S.aureus. The significant activity was observed in compounds (1b),(1e),(2b),(2f) against B.subtillis. The maximum activity was displayed by the compounds (1e),(1j),(2b),(2d), against E.coli. The compounds (1c),(1h),(2f), and (2g) were comparatively more effective against P.vulgaris.

4. Antifungal Activity

The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds (1g),(1h),(1l),(2c),(2e),(2k), against A.niger.

The antibacterial activity was compared with standard drug viz. Ampicillin, Amoxicillin, Norfloxacin, Penicillin and antifungal activity was compared with standard drug viz. Griseofulvin.

5. Experimental Section

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 (300MHz) using TMS as an internal standard, chemical shift in δ ppm.

General procedure for the preparation of 1-Aryl-3-[4'-(o-chlorobenzyloxy)-3'-methoxyphenyl]-propenones (1a-l) :

Take a mixture of 4-[(2-chlorobenzyl)oxy]-3-methoxy benzaldehyde (1) (0.01M) and 4-methoxy acetophenone (0.01) in methanol, add a NaOH (0.002M) to the reaction mixture . The reaction mixture was magnetically stirred for 12 hrs and then left overnight. After it was pour over ice and neutralised with dil.HCl and ethanol is added for crystallisation.

4-[(2-chlorobenzyl)oxy]-3-methoxy benzaldehyde (1) :

Yield 90%, m.p. 58 ^{0}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.:$C_{15}H_{13}O_3Cl$

1-Aryl-3-[4'-(o-chlorobenzyloxy)-3'-methoxyphenyl]-propenones (1a-l) :

Yield 72%, m.p. 70^{0}C; IR(KBr) : ν 2951,2874,1466 (Alkane,-CH_3), 1260 (-OCH_3) ,640 (-C-Cl); 1235 (Ar-O-C) , 1672 (C=O) , 1583 (C=C) ,3061,1506,1163,818 (Aromatic) ,cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 3.88, (s,6H,-OCH_3) , 6.86 & 7.73 (d,2H,-CH=CH-), 5.15(s,2H,-O-CH_2-) ,6.96-8.03(m,11H, ArH) , .Mass m/z 408.5 .M.F.:$C_{24}H_{21}O_4Cl$.

General procedure for the preparation of 3-Aryl-5-[4'-(o-chlorobenzyloxy)-3'-methoxyphenyl]-4,-5-dihydro-1H-pyrazoles (2a-l) :

A mixture of Hydrazine hydrate (0.01M) , 1-Aryl-3-[4'-(o- chlorobenzyloxy)-3'-methoxyphenyl]-propenones (1a-l) (0.01M) and NaOH (0.01M) in methanol was refluxed with stirring about (6-8 hrs) untiill complete the reaction which was monitored by formation of precipitation of pyrazoline products.

3-Aryl-5-[4'-(o-chlorobenzyloxy)-3'-methoxyphenyl]-4,-5-dihydro-1H-pyrazoles (2a-l) :

Yield 67%, m.p. 140 ^{0}C; IR(KBr) : ν 2951,1458 (Alkane,-CH_3), 1242 (-OCH_3) ,793 (-C-Cl); 1255 (Ar-O-C) , 1608 (C=N) , 3035,1517,1097,835 (Aromatic), 2310 (-NH-), cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 3.12, 3.68 (dd,2H,-CH_2-pyr) , 5.51 (dd,1H,-CH-,pyr), 5.02 (s,2H,-O-CH_2-) ,6.68-7.70 (m,12H, ArH) ,3.94 (s,6H,-OCH_3) .Mass m/z 422.5 . M.F.:$C_{24}H_{23}N_2O_3Cl$.

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

compd no.	R	Molecular Formula	Mole.Wt.	M.P. (^{0}C)	Nitrogen %	
					Found	Calcd
1a	-C_6H_5	$C_{23}H_{19}ClO_3$	378.5	88	-	-
1b	-4-NH_2-C_6H_4	$C_{23}H_{20}ClNO_3$	393.66	122	3.51	3.56
1c	-4-Br-C_6H_4	$C_{23}H_{18}BrClO_3$	457.54	146	-	-
1d	-4-Cl-C_6H_4	$C_{23}H_{18}Cl_2O_3$	413	128	-	-
1e	-2,4-(Cl_2)- C_6H_3	$C_{23}H_{17}Cl_3O_3$	447.53	110	-	-
1f	-2-OH- C_6H_4	$C_{23}H_{19}ClO_4$	394.5	104	-	-
1g	-3-OH- C_6H_4	$C_{23}H_{19}ClO_4$	394.5	50	-	-
1h	-4-OH- C_6H_4	$C_{23}H_{19}ClO_4$	394.5	60	-	-
1i	-4-OCH_3- C_6H_4	$C_{24}H_{21}ClO_4$	408.5	70	-	-
1j	-4-CH_3- C_6H_4	$C_{24}H_{21}ClO_3$	392.68	100	-	-
1k	-3-NO_2- C_6H_4	$C_{23}H_{18}ClNO_5$	423.65	110	3.30	3.31
1l	-4-NO_2- C_6H_4	$C_{23}H_{18}ClNO_5$	423.65	168	3.29	3.31
2a	-C_6H_5	$C_{23}H_{21}ClN_2O_2$	392.5	90	7.14	7.13
2b	-4-NH_2-C_6H_4	$C_{23}H_{22}ClN_3O_2$	407.5	>200	10.27	10.31
2c	-4-Br-C_6H_4	$C_{23}H_{20}BrClN_2O_2$	471.5	120	5.93	5.94
2d	-4-Cl-C_6H_4	$C_{23}H_{20}Cl_2N_2O_2$	427	72	6.52	6.56
2e	-2,4-(Cl_2)- C_6H_3	$C_{23}H_{19}Cl_3N_2O_2$	461.5	124	6.05	6.07
2f	-2-OH- C_6H_4	$C_{23}H_{21}ClN_2O_3$	408.5	96	6.82	6.85
2g	-3-OH- C_6H_4	$C_{23}H_{21}ClN_2O_3$	408.5	180	6.84	6.85

compd no.	R	Molecular Formula	Mole.Wt.	M.P. (^{0}C)	Nitrogen %	
					Found	Calcd
2h	-4-OH- C_6H_4	$C_{23}H_{21}ClN_2O_3$	408,5	164	6.83	6.85
2i	-4-OCH_3- C_6H_4	$C_{24}H_{23}ClN_2O_3$	422.5	140	6.64	6.63
2j	-4-CH_3- C_6H_4	$C_{24}H_{23}ClN_2O_2$	406.5	163	6.88	6.89
2k	-3-NO_2- C_6H_4	$C_{23}H_{20}ClN_3O_4$	437.5	75	9.4	9.6
2l	-4-NO_2- C_6H_4	$C_{23}H_{20}ClN_3O_4$	437.5	110	9.3	9.6

Table 1

compd no.	Antibacterial activity (zone of inhibition in mm)				Antifungal activity
	S.aureus	B.subtillis	E.coli	P.vulgaris	A.niger
1a	18	16	16	15	14
1b	14	18	12	16	16
1c	10	14	12	17	15
1d	10	15	14	10	14
1e	12	16	18	12	13
1f	17	14	13	14	15
1g	15	15	16	15	17
1h	14	13	14	16	16
1i	18	16	13	14	15
1j	13	12	18	12	15
1k	10	14	15	16	13
1l	12	15	14	14	16
2a	12	15	14	16	15
2b	16	20	20	14	13
2c	17	16	15	16	17
2d	15	17	18	13	16
2e	10	16	18	14	19
2f	16	18	16	20	15
2g	18	14	17	21	13
2h	14	16	15	19	16
2i	15	18	14	14	14
2j	16	13	12	17	15
2k	12	14	13	13	17
2l	14	16	17	16	12
Amoxicillin	28	24	28	22	-
Ampicillin	24	26	22	20	-
Penicillin	16	26	22	12	-
Norfloxacin	21	38	28	25	-
Griseofulvin	-	-	-	-	16

Table 2

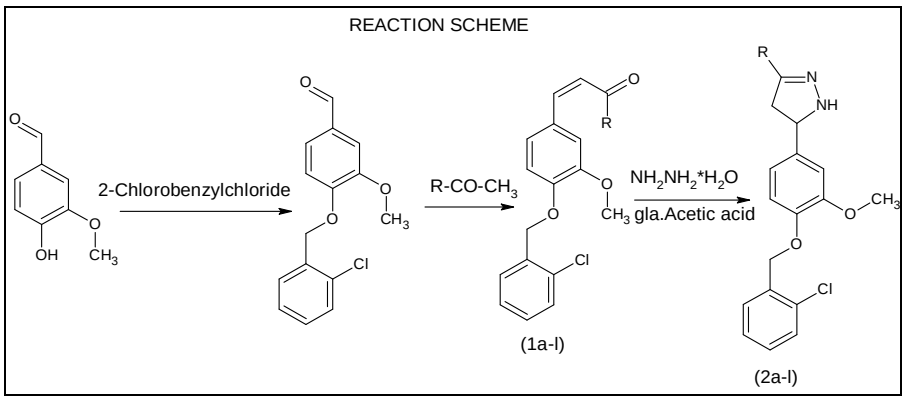

Figure 1

6. 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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8. References

1. S. V. Kostanecki and J. Tambor; Chem. Ber., 32, 1921 (1899).
2. B. S. Holla and S. Y. Ambekar; J. Indian Chem. Soc., 50, 673 (1973); Chem. Abstr., 80, 132961 (1974).
3. K. Kazauki, K. Htayama, S. Yokomor and T. Soki; Japan Kokai 75, 140, 429, (Cl. C07 C A61K) 11 Nov. 1975, Appl. 74, 44, 152, 19 Apr. 1974; 4, p.p.; Chem. Abstr. , 85, 5913 (1976).
4. Y. Inamori et al.; Chem. Pharm. Bull., 39(6), 1604 (1991); Chem. Abstr., 115, 105547c (1991).
5. K. Bowden; P. A. Dal and C. K. Shah; J. Chem. Res. Synop., 12, 2801 (1990); Chem. Abstr., 114, 160570m (1991).
6. P. Desaea; A. Nunrich; M. Carderny and G. Devaux; Eur. J. Med. Chem., 25, 285 (1990).
7. Kalluraya Balakrishna, Chimabalkar R., Rai G., Gururaja R., Shenoy S.; J. Indian Coun. Chemi., 18(2), 39-43 (2001); Chem. Abstr., 138, 238061.
8. V. M. Gaurav and D. B. Ingle; Indian J. Chem. 25B(8), 868 (1986); Chem. Abstr., 103, 17, 39321h (1987).
9. Kalashnikow B. B.; Kalashnikova J. P.; Russ. J. Ger. Chem., 1998; Chem. Abstr., 130, 296596n (1999).
10. A. S. Tomcufak, R. G. Wilkson and R. G. Child; German Patent 2, 502, 490 (1975); Chem. Abstr., 83, 179067 (1975).
11. A. R. Bhatt, R. P. Bhamaria, Mrs. M. R. Patel, R. A. Bellare and C. V. Deliwala; Indian Chem. 10(7), 694 (1972); Chem. Abstr., 78, 119650n (1973).
12. Guo Zongru, Han Rui; CN 1, 13, 909, Chem. Abstr., 125, 103768 (1996).
13. De Vincenzo, R. Seambla G. Panici, P. Benedess, Remelletti F. O.; Anti Cancer Drug Des., 10(6), 481-90 (1995); Chem. Abstr., 124, 247r (1996).
14. Kamei, Hideo, Koide, Tatsurou; Hashimoto Yoko, Kojima et al.; Cancer Biother Radio Pharm. 1997, 12(1), 51-54 (Eng.); Chem. Abstr., 126, 258666v (1997).
15. Tsotitus Andreas, Kalosorooulou Theodara et al.; PCT Int. Appl., WO 99, 54, 278 (1999); Chem. Abstr., 131, 28260z (1999).
16. W. I. Ronald, A. Adriano; Chem. Abstr., 126, 181346f (1997).
17. A. M. Fahmy. M. Hussan, A. A. Khalt; R. A. Ahmedi, Rev. Roum-Chim., 33(7), 755-61 (1988); Chem. Abstr., 111, 77898 (1989).
18. M. Hassaneen Hamdi, A. E. Hamad; Salter Lett., 8(5), 27582 (1989); Chem. Abstr., 111, 57611 (1989).
19. M. A. El. Hashah, M., El-Kady, M. A. Saiyed, A. A. Elsawy; Egypt. J. Chem., 27(6), 715-21 (1985); Chem. Abstr. , 105, 20868u (1986).
20. V. Gohanmukkala, A. Subbaraju, R. Naykula and D. Parmeswara, Indian J. Heterocyclic Chem., 4, 87-92 (1994).
21. Z. Brozozowsk, E. Pormarnacka; Acta. Pol. Pharm., 37(4), 1378, 80 (1980); Chem. Abstr., 25, 80807 (1981).
22. Archana Shrivastava V. K.; Chandra Ramesh, Kumar Ashok; Indian J. Chem., 41B, 2371-75 (2002); Chem. Abstr., 138, 271582 (2003).
23. Delay Francois (Fermenich S. A.) Patent Schrift (Switz); Chem. Abstr., 117, 90276f (1992).
24. Ayses G., Seref D., Gultaze C., Kevser E., Kamil V.; Eur. J. Med. Chem., 35, 359-64 (2002).
25. A. L. Barry; The antimicrobial susceptibility test: Principle and practices, edited by llluslea & Febiger , (Philadelphia), USA, 180; Biol. Abstr., 1977, 64, 25183
26. Panda J. Srinivas S. V., Rao M. E.; J. Indian Chem. Soc., 79(9), 770-1 (2002); Chem. Abstr., 138, 153499n (2003)