STUDIES ON SYNTHESIS AND TOXICITY TO FISH OF SOME NEWLY SYNTHESIZED CHALCONES

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ABSTRACT: Twelve new chalcones were synthesized by claisen-schmidid condensation and studies for their toxicity to fish. Some of the chalcones have exhibited moderate activity. The structures of synthetic compounds have been characterized by analytical and spectral data.

Keywords: Substituted benzaldehydes, substituted acetophenones, Chalcones, toxicity to fish.

INTRODUCTION

α, β unsaturated ketones, chalcones and several naturally occurring flavonoids have been found to possess a wide range of pharmacological properties.

Chalcones reported to possess a analgesic[1], antimalerial[2], antiviral[3], antibacterial[4], antifungal[5], antimitotic[6], cytotoxic[7], insect-antifeedant[8], anti-inflammatory[9], antileshmanal[10], antitumar[11], anticancer[12], antimicrobial[13], antinociceptive agent[14] and insecticidal[15].

Considering wide range of bioactivity of chalcones, new chalcones were synthesized from substituted acetophenones and 2- benzyloxy, 3-benzyloxy-4-methoxy, 4-benzyloxy-3-methoxy benzaldehyde. Various substituted chalcones and flavones have been studies for their toxicity. Various methods available for the evaluation of biological activity of compounds. The uses of fish as a test animal have been reported as a method of measure toxicity[16]. Since a wide range of pharmacological properties are found in these types of compounds, it appeared worth while screening these compounds with regard to their toxicity to fish.

RESULT AND DISCUSSION

We have synthesized and evaluated twelve new chalcones by claisen-schmidt condensation. The structures of newly synthesized compounds have been confirmed on the basis of elemental analysis and spectral data and studies for their toxicity to fish. Loss of equilibrium and time of death of *B. ticto* are reported in table-2. It is clear that compounds containing benzyloxy group at 4-position are more toxic as compared to benzyloxy group at 2-position and at 4-position.

Materials and methods:

Melting points were determined in open glass capillaries and are uncorrected. The purity of compounds was checked by TLC. The IR spectra of all compounds were recorded on perkin-Elmer-1420 spectrometer, ^{1}H NMR spectra ($CDCl_3$) on a Varian 300 MHz spectrometer using TMS as internal standard (δ ppm) and mass spectra were recorded on a Jeol SX 102/Da -600 spectrometer. Elemental analysis was performed on a Perkin Elmer 240 chn elemental analyzer.

General procedure for synthesis of chalcones (3a-l):

Equimolar quqntites of substituted acetophenone (0.01mole) and 2- benzyloxy, 3-benzyloxy-4-methoxy, 4-benzyloxy-3-methoxy benzaldehyde (0.01mole) were dissolved in ethanol (15ml) under stirring and aqueous KOH (50% 10ml) was added dropwise. The reaction mixture was stirred at room temperature and kept for 14-16 hr. The reaction mixture was diluted with water and acidified with 10% HCl. The separated solid was filtered and recrystallised from glacial acetic acid to give compounds (3a-3l).

(1) **3-(3-Benzyloxy-4-methoxy-phenyl)-1-(2,3,4-trichloro-phenyl)-propenone(3a): IR ν max (KBr) Cm^{-1}**: 1638 (C=O), 1596 CH=CH), 1260 (Ar-O), 1023 (O-CH_3), 696, 731 (monosubstitued benzene). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 3.95 (s, 2H, OCH_2), 5.20 (s, 3H, OCH_3), 6.95 (d, 1H, =CH_α), 7.35 (d, 1H, =CH_β), 7.1-7.6 (m, 10H, Ar-H). **MS (m/z):** 447 (M^+), 446, 327, 289, 267, 265, 207, 193, 154, 136, 123, 107, 91.

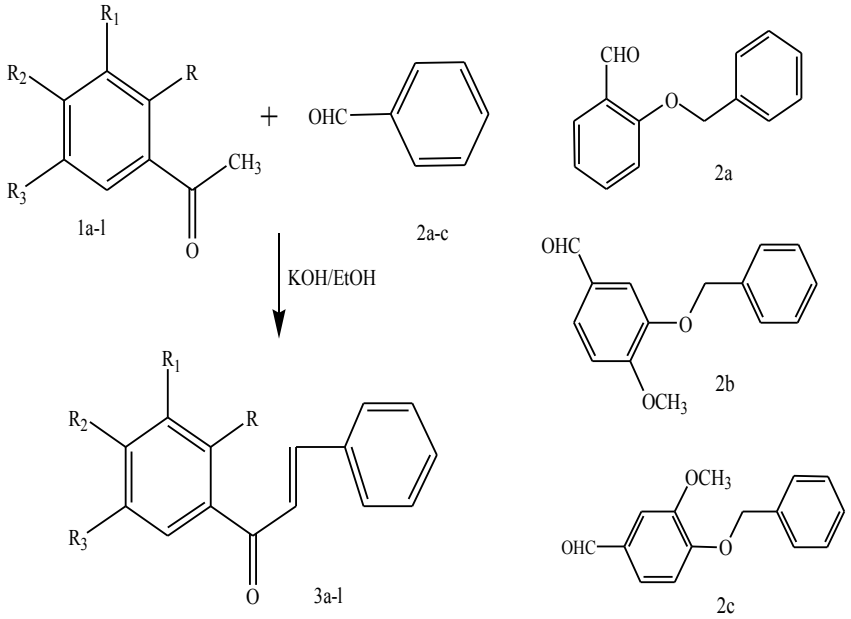
(2) **3-(3-Benzyloxy-4-methoxy phenyl)-1-(2,4-dichloro-1-phenyl)-propenone(3b): IR ν max (KBr) Cm^{-1}**: 1640 (C=O), 1592 (CH=CH), 1264 (Ar-O), 1023 (O-CH_3), 696, 737 (monosubstitued benzene). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 3.95 (s, 2H, O-CH_2), 5.22 (s, 3H, OCH_3), 6.92 (d, 1H,=CH_α), 7.28 (=CH_β), 7.1-7.5 (m, 11H, Ar-H). **MS (m/z):** 413 (M^+), 391, 373, 307, 289, 173, 154, 136, 123, 107, 91.

(3) **1-Benzo-(1,3)-dioxol-5-yl-3-(4-benzyloxy-3-methoxy phenyl)-propenone(3j): IR ν max (KBr) Cm^{-1}**: 1654 (C=O), 1582 (CH=CH), 1262 (Ar-O), 1040 (O-CH_3), 702, 742 (monosubstitued benzene). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 3.95 (s, 2H, OCH_2), 5.20 (s, 3H, OCH_3), 6.12 (s, 2H, OCH_2-O) 6.92 (d, 1H, =CH_α), 7.33 (d, 1H, =CH_β), 7.1-7.8 (m, 10H, Ar-H). **MS (m/z):** 388 (M^+), 389, 307, 297, 289, 267, 154, 136, 119, 107, 91.

(4) **1-Benzo-(1,3)-dioxol-5-yl-3-(3-benzyloxy-4-methoxy phenyl)-propenone(3l): IR ν max (KBr) Cm^{-1}**: 1650 (C=O), 1584 (CH=CH), 1264 (Ar-O), 1036 (O-CH_3), 696, 746 (monosubstitued benzene). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 3.93 (s, 2H, OCH_2), 5.22 (s, 3H, OCH_3), 6.14 (s, 2H, OCH_2-O) 6.94 (d, 1H, =CH_α), 7.35 (d, 1H, =CH_β), 7.1-8.2 (m, 11H, Ar-H). **MS (m/z):** 388 (M^+), 389, 307, 297, 297, 289, 267, 154, 136, 119, 107, 91.

(5) **3-(3-Benzyloxy-4-methoxy-phenyl)-1-(3,5-bis-benzyloxy-phenyl)-propenone(3k): IR ν max (KBr) Cm^{-1}**: 1658 (C=O), 1580 (CH=CH), 1260 (Ar-O), 1032 (O-CH_3), 698, 742 (monosubstitued benzene). **^{1}H NMR (300 MHz, $CDCl_3$):** δ 3.95 (s, 2H, OCH_2), 5.22 (s, 3H, OCH_3), 5.22 (s, 2H, OCH_2-O) 6.92 (d, 1H, =CH_α), 7.35 (d, 1H, =CH_β), 7.1-8.2 (m, 23H, Ar-H). **MS (m/z):** 556 (M^+), 557, 467, 391, 317, 307, 289, 174, 136, 123, 95, 91.

Scheme-I



Where;

3a: R, R_1, R_2= Cl, R_3= H, Ar=2b

3b:R,R_2=Cl,R_1,R_1,R_3=H,Ar=2b

3c: R= OH, R_1= H, R_2= CH_3, R_3= Cl, Ar=2b

3d: R, R_3= H, R_1, R_2= Cl, Ar= 2a

3e: R, R_1, R_2= Cl, R_3= H, Ar= 2a

3f: R= H, R_1, R_3= Br, R_2= OH, Ar= 2a

3g: R, R_3= H, R_1, R_2= Cl, Ar= 2b

3h:R,R_1,R_2=Cl,R_3=H,Ar=2c

3i: R=OH, R_1=H, R_2=CH_3, R_3=Cl, Ar=2c

3j: R, R_1, R_2, R_3=H

3k: R, R_1, R_2, R_3=H

3l: R, R_1, R_2, R_3=H

Toxicity to fish:

A fresh water fish, *barbus ticto* was selected as a test animal for determining the toxic effect of chalcones prepared in the laboratory. The fish were collected from the river Manjra near latur. They were about 1 to 1.5″ length and weighed about 2 to 3 gm on an average. Before carrying out the experiment the fish were maintained in a large glass aquarium filled with aerated water for 24 hr. at laboratory condition. Five fish were employed for each experiment.

Table-I: Analytical and physical datd of chalcones (3a-l)

Entry	Molecular formula	M.p (^{0}C)	Yield	Elemental Analysis (%) found (calculated)		
				C	H	X-(Cl,Br,I)
3a	$C_{23}H_{17}O_3Cl_3$	150	79	61.67 (61.64)	3.79 (3.75)	23.49 (23.79)
3b	$C_{23}H_{18}O_3Cl_2$	110	81	66.82 (66.83)	4.35 (4.37)	17.55 (17.19)
3c	$C_{29}H_{21}O_4Cl$	124	62	85.18 (85.00)	5.15 (5.13)	8.69 (8.66)
3d	$C_{22}H_{16}O_2Cl_2$	90	68	68.92 (68.90)	4.17 (4.15)	18.23 (18.53)
3e	$C_{22}H_{15}O_2Cl_2$	42	70	63.23 (63.21)	3.59 (3.58)	25.81 (25.50)
3f	$C_{22}H_{16}O_3Br_2$	40	72	54.09 (54.10)	3.27 (3.29)	32.42 (32.78)
3g	$C_{23}H_{18}O_3Cl_2$	84	65	66.82 (66.84)	4.35 (4.31)	17.5 (17.59)
3h	$C_{23}H_{17}O_3Cl3$	112	83	61.67 (61.65)	3.79 (3.75)	23.45 (23.79)
3i	$C_{29}H_{21}O_4Cl$	162	75	85.18 (85.00)	5.14 (5.11)	8.69 (8.60)
3j	$C_{24}H_{20}O_5$	130	86	74.22 (74.20)	5.15 (5.13)	----------
3k	$C_{37}H_{32}O_5$	102	83	79.85 (79.83)	5.75 (5.73)	----------
3l	$C_{24}H_{20}O_5$	110	79	74.22 (74.23)	5.15 (5.13)	----------

Dioxane solution of the substance under investigation was added (30 mg of each compound dissolved in 1ml of dioxane) to 1 lit. of water in a glass trough and after mixing well five fish were introduced into it. Their movement was observed and the time at which the fish lost their balance and overtoned and the time of death were recorded. The average of the five individual values (which did not differ very greatly) was obtained.

The control experiment conducted by using dioxae showed that a concentration of 1% is harmless to the fish over a period of 24hr.

Loss of equilibrium and time of death of *B.ticto* are represented in table-2.

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Table-2 Toxicity to fish of some chalcones Values are means ± SE of five

Entry	Loss of equilibrium (min)	Death (min)
3a	7 ± 0.08	11 ± 0.22
3b	18 ± 0.26	28 ± 0.29
3c	6 ± 0.09	10 ± 0.012
3d	102 ± 0.16	126 ± 1.66
3e	90 ± 0.08	100 ± 0.12
3f	101 ± 0.16	112 ± 0.12
3g	7 ± 0.08	12 ± 0.12
3h	38 ± 0.89	61 ± 0.26
3i	35 ± 0.41	40 ± 0.16
3j	40 ± 0.08	48 ± 0.17

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