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Synthesis and Biological evaluation of some heterocyclic derivatives of Chalcones

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Abstract

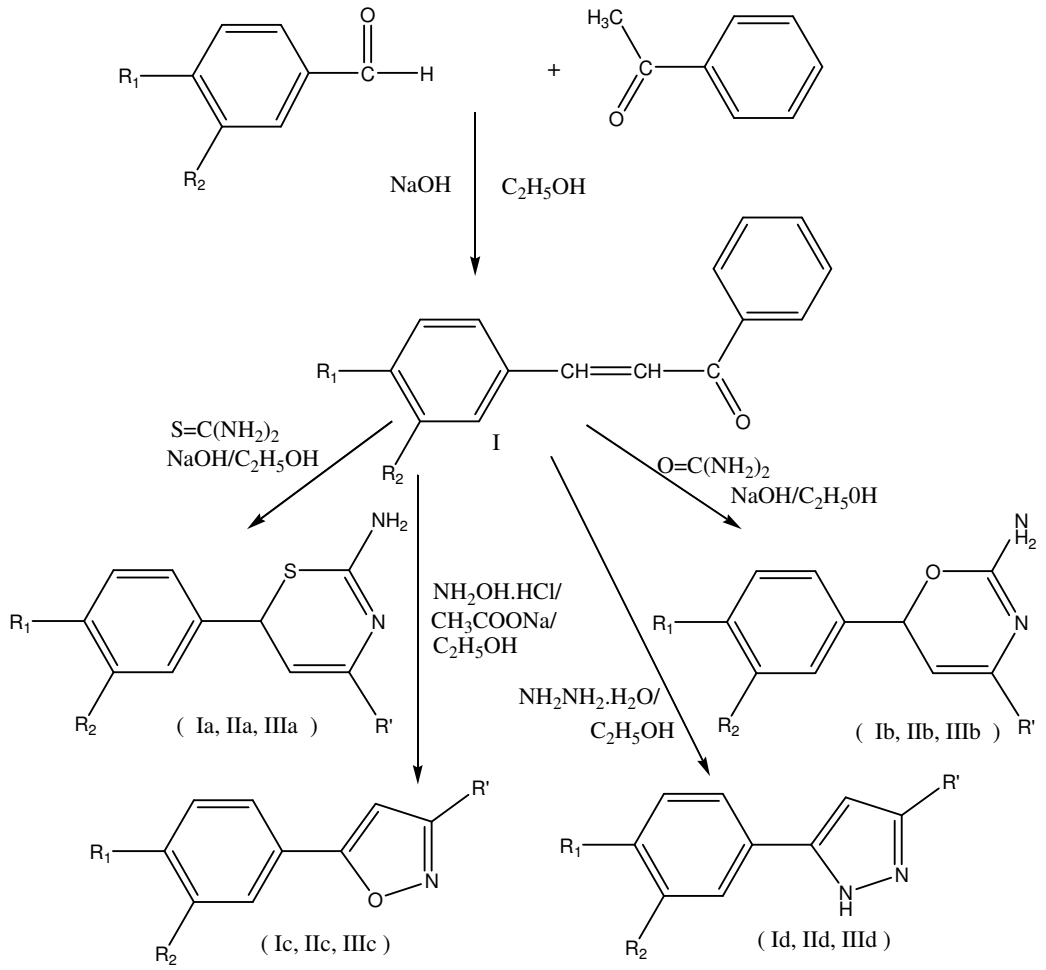
Some novel heterocyclic derivatives such as Thazines, Oxazines, Isoxazoles and Pyrazoles (Ia-d, IIa-d, IIIa-d) were synthesized from various Chalcones. The synthesized compounds have been characterized by TLC, Elemental analysis, IR and ^{1}H.NMR Spectroscopy. These compounds were screened for their Anti inflammatory, Anti Bacterial and Anti fungal activities.

Key words: Chalcones, Thazines, Oxazines, Isoxazoles, Pyrazoles, Anti inflammatory, Anti Bacterial, Anti fungal.

Introduction

Chalcones are prepared by condensing Aryl ketones with aromatic aldehydes in presence of suitable condensing agents. They undergo a variety of chemical reactions and are found useful in synthesis of variety of heterocyclic compounds. Chalcones have been used as intermediate for the preparations of compounds having therapeutic value. Literature review reveals that chalcone derivatives exhibit diverse pharmacological activities[1-9] such as potential cytotoxic agents, antimicrobial agents, antiviral, antiinflammatory, anesthetics, mydriatics etc. Based on the above observation it is worthwhile to prepare newer compounds for their antimicrobial and antiinflammatory activities. In the view of the varied biological and pharmacological application, we synthesized some new Heterocyclic derivatives of Chalcones (Ia-d, IIa-d, IIIa-d, Scheme- I)

SCHEME-I



Compound Code	R_1	R_2	R'
(I), (Ia), (Ib), (Ic) & (Id).	OCH_3	H	C_6H_5
(II), (IIa), (IIb), (IIc) & (IId).	H	Cl	C_6H_5
(III), (IIIa), (IIIb), (IIIc) & (IIId).	H	NO2	C_6H_5

Experimental

Melting points were determined in open capillary tubes and were found uncorrected. IR spectra were recorded on FT-IR spectrometer (Perkin Elmer) using KBr disc method. ^{1}HNMR spectra were recorded on ^{1}H FT-NMR (Brucker AMX 400 MHz) spectrometer in DMSO. The compounds were analyzed for elemental analysis and the percentage of elements were found to be very near that of the calculated values. Physical data of the compounds are recorded in Table-1 and the spectral data are recorded in Table-2.

Table No. 1

Physical Parameters and Elemental Analysis of Synthesized Compounds

Comp.	m. f.	m. w	m.p (^{0}C)	Rf	Yield %	Elemental analysis (Calculated)					
						%C	%H	%N	%O	%S	%Cl
Ia	$C_{17}H_{16}N_2OS$	296.4	77	0.62	57	68.89	5.44	9.45	5.40	10.82	-
Ib	$C_{17}H_{16}N_2O_2$	280.3	72	0.61	61	72.84	5.75	9.99	11.42	-	-
Ic	$C_{16}H_{13}NO_2$	251.3	66	0.68	68	76.48	5.21	5.57	12.73	-	-
Id	$C_{16}H_{14}N_2O$	250.3	54	0.58	52	76.78	5.64	11.2	6.39	-	-
IIa	$C_{16}H_{13}ClN_2S$	300.8	69	0.75	66	63.89	4.36	9.31	-	10.66	11.79
IIb	$C_{16}H_{13}ClN_2O$	284.7	59	0.68	56	67.49	4.60	9.84	5.62	-	12.45
IIc	$C_{15}H_{10}ClNO$	255.7	60	0.78	48	70.46	3.94	5.48	6.26	-	13.87
IId	$C_{15}H_{11}ClN_2$	254.7	58	0.72	45	70.73	4.35	11.0	-	-	13.92
IIIa	$C_{16}H_{13}N_3O_2S$	311.4	129	0.43	59	61.72	4.21	13.5	10.28	10.30	-
IIIb	$C_{16}H_{13}N_3O_3$	295.3	110	0.56	53	65.08	4.44	14.23	16.25	-	-
IIIc	$C_{15}H_{10}N_2O_3$	266.3	118	0.46	49	67.67	3.79	10.52	18.03	-	-
IIId	$C_{15}H_{11}N_3O_2$	265.3	97	0.49	73	67.92	4.18	15.84	12.06	-	-

Table No. 2 Spectral Analysis of Synthesized Compounds

Comp.	IR (KBr) ν(cm^{-1})	^{1}H NMR ($CDCl_3$) δ in ppm
Ia	1612.4(1^0NH_2), 2369(C-S-C, St), 1479(Ar-C=C), 1385 (Ar-C-O)	3.73(s,OCH_3),2.3 (s, Ar-NH_2), 6.93(d,Ar-H), 4.64 (s, CH)
Ib	1618.7(1^0NH_2), 1246(C-N, St), 1475(Ar-C=C), 1394 (Ar-C-O)	3.69(s,OCH_3), 2.1 (s, Ar-NH_2), 7.30(t,Ar-H), 4.4 (s, CH)
Ic	1215.7(C-O, St), 1334(C-N, St), 1471(Ar-C=C), 1391 (Ar-C-O)	3.7(s,OCH_3), 7.46 (d, Ar-H), 7.36(d,Ar-H), 4.4 (s, CH)
Id	3407.1(2^0NH , St), 1253(C-N, St), 1469(Ar-C=C), 1387 (Ar-C-O)	3.81(s,OCH_3), 12.6 (NH), 7.35(d, Ar-H), 6.14 (s, CH)
IIa	1611.7(1^0NH_2), 1245(C-S-C, St), 1569(Ar-C=C), 1080 (Ar-Cl)	2.03 (s, Ar-NH_2), 7.65(d,Ar-H), 7.15(d,Ar-H), 5.41 (s, CH)
IIb	1616.5(1^0NH_2), 1253(C-N, St), 1475(Ar-C=C), 1081 (Ar-Cl)	1.98 (s, Ar-NH_2), 7.62(d,Ar-H), 7.18(s,Ar-H), 5.09 (s, CH)
IIc	1219.5(C-O, St) , 1204(C-N, St), 1495(Ar-C=C), 1035 (Ar-Cl)	6.79(s,Ar-H), 7.53(t,Ar-H), 5.17 (s, CH)
IId	1608.1(NH, b), 1294(C-N, St), 1525(Ar-C=C), 1076 (Ar-Cl)	13.6 (NH), 7.48(d,Ar-H), 7.33(t,Ar-H), 6.78 (s, CH)
IIIa	1615.3(1^0NH_2), 2368(C-S-C, St), 1487(Ar-C=C), 1535 (Ar-NO_2)	2.11 (s, Ar-NH_2), 7.62(d,Ar-H), 8.25(s,Ar-H), 5.71 (s, CH)
IIIb	1613.7(1^0NH_2), 1221(C-N, St), 1575(Ar-C=C), 1527 (Ar-NO_2)	1.87 (s, Ar-NH_2), 7.64(d,Ar-H), 7.28(d,Ar-H), 4.9 (s, CH)
IIIc	1223.2(C-O), 1099(C-N, St), 1608(Ar-C=C), 1522 (Ar-NO_2)	7.49(d,Ar-H),8.51(s,Ar-H), 5.17 (s, CH)
IIId	3396(2^0NH), 1215(C-N, St), 1448(Ar-C=C), 1519 (Ar-NO_2)	13.53 (NH),8.48(d,Ar-H), 7.34(d,Ar-H), 6.78 (s, CH)

Synthesis of chalcones [I- III]

Equimolar quantities of Anisaldehyde / 3-Chlorobenzaldehyde/ 3-Nitro benzaldehyde (0.01 mol) and acetophenone (0.01 mol) were dissolved in minimum amount of alcohol. Sodium hydroxide solution (0.02 mol) was added slowly and the mixture stirred for 2hr until the entire mixture becomes very cloud. Then the mixture was poured slowly into 400 ml of water with constant stirring and kept in refrigerator for 24 hours. The precipitate obtained was filtered, washed and recrystallized from ethanol. Finally the compounds synthesized namely, 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (**I),** 3-(3-chlorophenyl)-1-phenylprop-2-en-1-one (**II),** and 3-(3-nitrophenyl)-1-phenylprop-2-en-1-one (**III)** respectively. The completion of the reaction was monitored by TLC.

Preparation of thiazine/oxazine derivatives [I-III a, I-III b]

A mixture of Chalcone I, II, III (0.02mol), thiourea/urea (0.02 mol) were dissolved in ethanolic sodium hydroxide (10ml) was stirred about 2-3 hours with a magnetic stirrer. This was then poured into 400 ml of cold water with continuous stirring for an hour and then kept in refrigerator for 24 hours. The precipitate obtained was filtered, washed and recrystallized. The completion of the reaction was monitored by TLC.

Preparation of isoxazole/ pyrazole derivatives[I-III c,I-IIIc]

A mixture of Chalcone I, II, III (0.02 mol), hydroxylamine hydrochloride/ hydrazine hydrate (0.02 mol) and sodium acetate in ethanol (25 ml) was refluxed for 6hr. The mixture was concentrated by distilling out the solvent under reduced pressure and poured into ice water. The precipitate obtained was filtered, washed and recrystallized. The completion of the reaction was monitored by TLC.

In vitro anti –microbial screening [10]

The synthesized compounds were subjected to antimicrobial screening by cup plate method for zone of inhibition. The Antibacterial activity was tested against various gram positive and Gram negative bacteria and anti fungal activity against various fungal stains compared with standard drug (Ampicillin and Ketoconazole) using solvent control. The results were described in the table no -3

Table No. 3

Antimicrobial activity of Synthesized Compounds

Comp. (100µg /ml)	Zone of Inhibition (mm)					
	Gram positive		Gram negative		Anti Fungal	
	B. Subtilis	***S. Aureus***	***K. Pneumonia***	***E. Coli***	***C. albicans***	***A. niger***
I a	17	_	_	15	22	15
I b	_	18	20	_	23	_
I c	_	_	_	_	21	_
I d	18	_	19	_	20	21
II a	_	19	_	19	_	_
II b	_	_	_	_	23	18
II c	21	_	19	_	22	20
II d	_	17	_	18	20	_
III a	20	_	18	_	19	17
IIIb	_	_	_	_	_	18
III c	18	_	18	_	_	_
III d	_	18	_	20	12	18
Std Drug (100µg /ml)	24	20	22	22	26	20
Solvent Control (DMSO)	_	_	_	_	_	_

-- **indicates no activity**

In-vitro anti-inflammatory activity [11]

All the newly synthesized compounds were tested for Anti-inflammatory activity by In-Vitro HRBC Membrane Stabilization method.

The reaction mixtures (4.5 ml) consisted of 2 ml hypotonic saline solution, phosphate buffer (PH 7.4) and 1 ml test solution in normal saline. 0.5 ml of 10 % rabbit RBC in normal saline was added. For control tests, 1 ml of isotonic solution was used instead of test solution while product control tests lacked RBC. The mixtures were incubated at 56^{o}C for 30 min, cooled under running water and centrifuged and the absorbance of the supernatants were read at 560 nm. Percentage membrane stabilizing activity was calculated as follows,

$$\text{Percentage stabilization} = 100 - \frac{(\text{O. D. Of Test} - \text{O.D. of product control})}{\text{O. D. of control}} \times 100$$

The control represents 100 % lysis. The result was compared with STD (100µg/ml) treated samples.

Results and discussion

All the synthesized compounds were characterized by TLC, Melting point, elemental analysis, IR and ^{1}HNMR. Analysis indicated by the symbols of the elements is very close to the theoretical values. The compounds were evaluated for their anti microbial activity by cup-plate method against various Gram positive, Gram negative bacteria and fungal stains. Many of the compounds show comparable activity with that of standard (Ampicillin and Ketoconazole). The compounds were also evaluated for their invitro Anti-inflammatory activity by HRBC membrane stabilization method. All the compounds have highly significant activity when compared with standard drug Ibuprofen, with percentage of inhibition to the inflammatory response ranging from 62% to 75%.

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