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Synthesis of Schiff's base Derivatives of Oxazine from Chalcones and Evaluation of their Antiinflammatory Activity.

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Abstract

Chalcone is a generic term given to compounds bearing the 1,3-diphenyl-2-propen-1-one framework. Oxazine heterocycles have special interest because they constitute an important class of natural and non natural products and show useful biological activities. Its increasing importance in pharmaceutical and biological field, we are planned to synthesize oxazine derivatives for their biological activities. We planned to synthesize Schiff base oxazine derivatives from chalcones and evaluate for anti-inflammatory activity. The synthesized compounds were confirmed structurally by means of IR, 1HNMR, Mass spectral analysis. Further, the synthesized compounds ($5a_1$, $5a_2$, $5a_3$, $5a_4$, $5a_5$, $5b_1$, $5b_2$, $5b_3$, $5b_4$, $5b_5$) were screened for anti-inflammatory activity by using carrageenan – induced rat paw edema method using Diclofenac sodium as standard. The results showed that, compound $5b_2$ was significantly reduced the inflammation there by showed a promising anti-inflammatory activity; whereas the compounds $5b_4$, $5b_5$ moderately reduced the inflammation.

KEY WORDS: Antiinflammatory activity, Chalcones, IR, 1HNMR, Mass Spectroscopy, Oxazine.

INTRODUCTION

Many heterocyclic analogous of chalcones have been synthesized and subsequently demonstrated to possess biological and pharmacological activities, which may possibly result in chemotherapeutic agents. In the view of the varied biological and pharmacological application, we synthesized some heterocyclic derivatives of chalcones [1]. Chalcones found to possess various activities like antimicrobial [2], anti-inflammatory [3], analgesic [4], anticancer [5], antimalarial [6], antiviral [7], antileishmanial [8], antioxidant [9], antitubercular [10], antiulcer [11], antihyperglycemic [12]. In recent years, attention has increasingly been given to the synthesis of oxazine derivatives as a source of new antimicrobials. The synthesis of novel oxazine derivatives remain a main focus of medicinal research. Oxazine derivatives have been reported to posses antifungal [13], antibacterial [14], cytotoxic [15], antiviral [16], and analgesic activity [17]. Oxazine derivatives have played a crucial role in the theoretical development of heterocyclic chemistry and are also used extensively in organic synthesis. Due to the rapid development of bacterial resistant to antibacterial agents, it is vital to discover novel scaffold for the design and synthesis of the new antibacterial agents to help in the battle against pathogenic microorganisms. Much research has been carried out with the aim to discover the therapeutic value of chalcones.

MATERIALS AND METHODS

All the reagents and solvents used were of laboratory grade. The melting points of synthesized compounds were determined by open capillaries using cintex melting point apparatus, expressed in °C and were uncorrected. The IR spectra of the compounds were recorded using KBR pellets on perkin Elmer 337 spectrophotometer. 1HNMR spectra were recorded on Avance - 300 MHz spectrophotometer using DMSO as solvent and TMS as an internal standard (chemical shifts in δ, ppm). Mass spectra were recorded on liquid chromatography Mass Spectrophotometer.

SYNTHESIS AND CHARACTERIZATION OF COMPOUNDS

Synthesis of Chalcones 3(a-b)

Equimolar mixture of Benzaldehyde/Anisaldehyde (0.01 mol) and Acetophenone (0.01 mol) were dissolved in minimum amount of alcohol. Sodium hydroxide(0.02 mol) was added slowly and the mixture stirred for 2 hr until 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 recrstallised from ethanol and the completion of the reaction was monitored by TLC.

Synthesis of Oxazine Derivatives 4(a-b)

A mixture of 3a/3b (0.02 mol), urea (0.02 mol) were dissolved in ethanolic sodium hydroxide(10 ml) 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 42 hours. The precipitate obtained was filtered, washed and recrystallised and the completion of the reaction was monitored by TLC.

Synthesis of Schiff base Derivatives 5(a_1-a_5, & b_1-b_5)

A mixture of Oxazine derivatives 4a/4b (0.1 mol) and appropriate aromatic aldehydes (0.1 mol) in ethanol and 2-3 drops of $TiCl_4$ was added to it and refluxed for 3 hours. The resulting clear solution was cooled and poured in ice-cold water. The separated solid was filtered and recrystalized from DMF and the completion of the reaction was monitored by TLC.
The physical data of these Schiff base Oxazine derivatives were given in table 1.

SCHEME OF SYNTHESIS

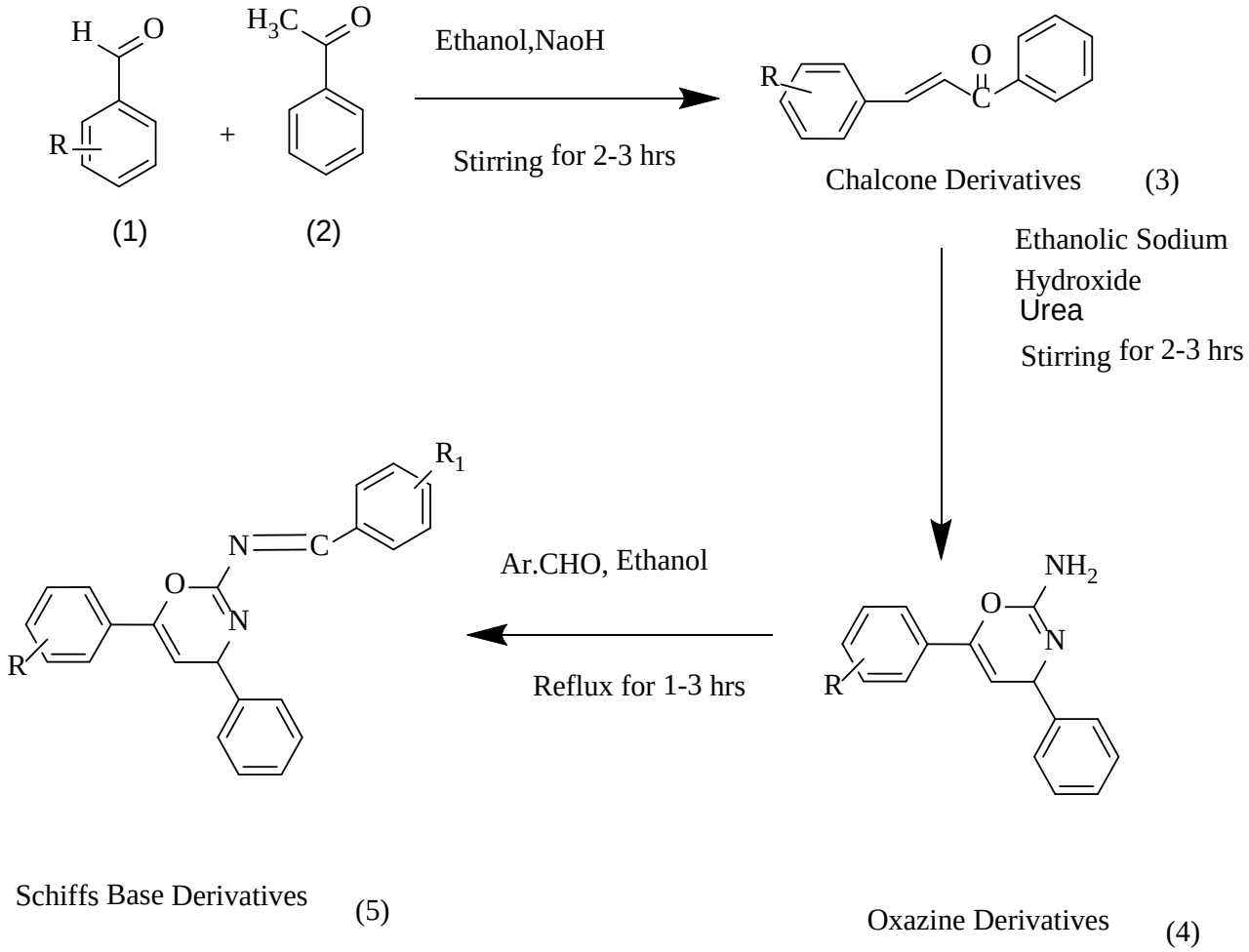

Table 1: Physical Data of Schiff base Oxazine Derivatives

S.No	Compound	R	R'	Mol.Formula	Mol.Weight	M.P in ^{o}C	% yield
1	$5a_1$	H	H	$C_{23}H_{18}N_2O$	338.408	82	70.15
2	$5a_2$	H	2-Cl	$C_{23}H_{17}N_2OCl$	372.85	86	84.7
3	$5a_3$	H	4-Cl	$C_{23}H_{17}N_2OCl$	372.85	92	40.25
4	$5a_4$	H	2-OH	$C_{23}H_{18}N_2O_2$	354.407	110	83.22
5	$5a_5$	H	4-OH	$C_{23}H_{18}N_2O_2$	354.407	91	62.19
6	$5b_1$	OCH_3	H	$C_{24}H_{20}N_2O_2S$	368.433	95	42.4
7	$5b_2$	OCH_3	2-Cl	$C_{24}H_{19}N_2O_2Cl$	402.877	116	65.83
8	$5b_3$	OCH_3	4-Cl	$C_{24}H_{19}N_2O_2Cl$	402.877	129	72.8
9	$5b_4$	OCH_3	2-OH	$C_{24}H_{20}N_2O_3$	384.432	119	41.6
10	$5b_5$	OCH_3	4-OH	$C_{24}H_{20}N_2O_3$	384.432	105	64.92

RESULTS AND DISCUSSION

Compound 5a1

IR (KBR, cm-1): 3384(NH), 2930(CH), 1640(NH), 1627(C=N), 1475, 1559(Ar ring stretching).

1H NMR (DMSO-d6): 7.7(m, 4H, Ar), 7.5(m,4H,Ar), 7.35(m,5H,Ar),
5.3(d, 1H, CH, Oxazine), 1.7(s,1H,CH).

MS (*m/z*): M+ calculated 339, found 338.

Compound 5a2

IR (KBR, cm-1): 3382(NH), 2931(CH), 1630(NH), 1637(C=N), 1465, 1559(Ar ring stretching),
608(Cl).

1H NMR (DMSO-d6): 7.5(m,4H,Ar), 7.2(m,4H,Ar), 7.3(m,5H,Ar),
5.2(d,1H,CH, Oxazine),1.7(s,1H,CH).

MS (*m/z*): M+ calculated 373, found 372.

Compound 5a3

IR (KBR, cm-1): 3385(NH), 2941(CH), 1640(NH), 1617(C=N), 1455, 1549(Ar ring stretching),
610(Cl).

1H NMR (DMSO-d6): 7.6(m,4H,Ar), 7.3(m,4H,Ar), 7.3(m,5H,Ar),
5.5(d,1H,CH,Oxazine),1.8(s,1H,CH).

MS (*m/z*): M+ calculated 373, found 372.

Compound 5a4

IR (KBR, cm-1): 3386(NH), 2921(CH), 1635(NH), 1607(C=N), 1445, 1559(Ar ring stretching), 3554(OH)

1H NMR (DMSO-d6): 7.6(m,4H,Ar), 7.1(m,4H,Ar), 7.0(m,5H,Ar), 5.1(d,1H,CH,Oxazine),1.7(s,1H,CH), 9.5(s,1H,OH).

MS (*m/z*): M+ calculated 355, found 354.

Compound 5a5

IR (KBR, cm-1): 3372(NH), 2921(CH), 1620(NH), 1617(C=N), 1455, 1549(Ar ring stretching), 3560(OH)

1H NMR (DMSO-d6): 7.2(m,4H,Ar), 7.1(m,4H,Ar), 7.3(m,5H,Ar), 5.0(d,1H,CH,Oxazine),1.7(s,1H,CH), 9.7(s,1H,OH).

MS (*m/z*): M+ calculated 355, found 354.

Compound 5b1

IR (KBR, cm-1): 3392(NH), 2951(CH), 1640(NH), 1657(C=N), 1495, 1579(Ar ring stretching), 2820(CH,OCH_3)

1H NMR (DMSO-d6): 7.5(m,4H,Ar), 7.1(m,4H,Ar), 7.0(m,5H,Ar), 5.1(d,1H,CH,Oxazine),1.8(s,1H,CH), 2.5(s,3H,OCH_3).

MS (*m/z*): M+ calculated 369, found 368.

Compound 5b2

IR (KBR, cm-1): 3372(NH), 2961(CH), 1650(NH), 1667(C=N), 1425, 1579(Ar ring stretching), 2850(CH,OCH_3), 615(Cl).

1H NMR (DMSO-d6): 7.5(m,4H,Ar), 7.1(m,4H,Ar), 7.0(m,5H,Ar), 5.1(d,1H,CH,Oxazine),1.8(s,1H,CH), 2.5(s,3H,OCH_3).

MS (*m/z*): M+ calculated 403, found 402.

Compound 5b3

IR (KBR, cm-1): 3362(NH), 2943(CH), 1645(NH), 1642(C=N), 1428, 1554(Ar ring stretching), 2842(CH,OCH_3), 612(Cl).

1H NMR (DMSO-d6): 7.4(m,4H,Ar), 7.0(m,4H,Ar), 7.2(m,5H,Ar), 5.3(d,1H,CH,Oxazine),1.7(s,1H,CH), 2.5(s,3H,OCH_3).

MS (*m/z*): M+ calculated 403, found 402.

Compound 5b4

IR (KBR, cm-1): 3262(NH), 2993(CH), 1675(NH), 1660(C=N), 1417, 1454(Ar ring stretching), 2851(CH,OCH_3), 3552(OH).

1H NMR (DMSO-d6): 7.2(m,4H,Ar), 7.1(m,4H,Ar), 7.3(m,5H,Ar), 5.1(d,1H,CH,Oxazine),1.7(s,1H,CH), 2.5(s,3H,OCH_3), 9.7(s,1H,OH).

MS (*m/z*): M+ calculated 385, found 384.

Compound 5b5

IR (KBR, cm-1): 3271(NH), 2951(CH), 1652(NH), 1653(C=N), 1417, 1454(Ar ring stretching), 2850(CH,OCH_3), 3562(OH).

1H NMR (DMSO-d6): 7.0(m,4H,Ar), 6.1(m,4H,Ar), 7.1(m,5H,Ar), 5.1(d,1H,CH,Oxazine),1.8(s,1H,CH), 2.5(s,3H,OCH_3), 9.8(s,1H,OH).

MS (*m/z*): M+ calculated 385, found 384.

ANTI – INFLAMMATORY ACTIVITY

Carrageenan-Induced Rat Paw Edema Method [18]

Wister strain albino rats weighing between 180-250gm, were housed in clean polypropylene cages and kept under room temperature (25±2°C) fasted 24 hours before the test, divided into eight groups of five animals each. Acute inflammation was produced by sub plantar injection of 0.1ml of 1% suspension of carrageenan with 2% gum acacia in normal saline, in the right hind paw of rats. The volume of the right hind paw was measured using a plethysmometer. This constituted the initial reading. Compounds were tested in the dose of 100mg/kg body weight. Diclofenac 20mg/kg was used as standard. The compounds were administered as suspensions in sodium CMC (0.1%w/v) intraperitonially 1 hr before the

injection of carrageenan. Control group of animals received a suspension of sodium CMC only. 0.1ml of 1.0%w/v carrageenan suspension in normal saline was injected into the plantar region (aponeurosis) of the right hind paw. The swelling produced after injection of the phlogistic agent was measured at hourly intervals for 4 hrs. Percentage inhibition of edema was calculated and the results were presented in table 2.

All the newly synthesized oxazine derivatives were evaluated for anti inflammatory activity by using diclofenac sodium as standard for the period of four hours with one hour interval. The activity of the test compounds is comparable with the activity of the standard diclofenac sodium.

The most potent compound was found to be $5b_2$ (R= OCH_3, R'=2Cl) with 77.28 percent inhibition of paw edema after one hour of administration. Compounds $5b_4$, $5b_5$, $5a_2$, $5a_4$, $5a_5$, $5b_3$, $5b_1$, $5a_1$, $5a_3$ were in the next order of inhibition of paw edema after an hour of administration.

Table 2: Anti-inflammatory activity of 2-Mercapto-N-(substituted arylidene) benzoxazole-5- carbohydrazide

S.No	Compound 50mg/kg	R	R'	% Inhibition of paw oedema			
				1Hr	2Hr	3Hr	4Hr
1	$5a_1$	H	H	45.34	45.90	44.12	44.42
2	$5a_2$	H	2-Cl	52.45	52.72	51.35	51.05
3	$5a_3$	H	4-Cl	45.22	45.10	46.23	45.21
4	$5a_4$	H	2-OH	50.23	50.89	51.23	50.11
5	$5a_5$	H	4-OH	49.21	49.76	48.78	46.23
6	$5b_1$	OCH_3	H	46.76	46.88	45.72	45.12
7	$5b_2$	OCH_3	2-Cl	77.28	78.05	65.35	68.12
8	$5b_3$	OCH_3	4-Cl	46.89	47.23	46.76	45.21
9	$5b_4$	OCH_3	2-OH	66.12	67.33	68.86	67.10
10	$5b_5$	OCH_3	4-OH	56.31	57.11	57.09	56.06
11	Standard	Diclofenac sod.		80.21	79.03	67.56	69.63

CONCLUSION

From the above results we can conclude that Schiff base Oxazine derivatives showed promising anti-inflammatory activity. The most potent anti-inflammatory compound was found to be $5b_2$ (R= OCH_3, R'=2Cl) with high percentage inhibition of paw edema..

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