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Synthesis, spectral studies and biological profile of some new substituted diphenyl isoxazole derivatives

Ritu Kataria[1]*, Sachdev Yadav[2] and Devender Pathak[2]

[1]Hindu College of Pharmacy, Sonepat, -131001, Haryana, India.
[2]Department of Pharmaceutical Chemistry, Rajiv Academy for Pharmacy, Mathura-281001, Uttar Pradesh, India.

ABSTRACT

Aromatic aldehydes upon reaction with aromatic ketones in presence of sodium hydroxide yield Chalcones (1a-l) which upon bromination in presence of glacial acetic acid formed chalcone dibromide (2a-l), which undergoes a subsequent cyclization on reaction with hydroxalamine hydrochloride in presence of TEA affording substituted diphenyl isoxazoles (3a-l) in high yield. These compounds were characterized by UV, FTIR, ^{1}HNMR, mass spectral data and elemental analysis. All the novel compounds were screened for their anti-inflammatory activity.

Keywords: Chalcone, chalcone dibromide, isoxazole, triethanolamine

Corresponding author

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INTRODUCTION

Isoxazole derivatives constitute huge and diverse groups of compounds used in drug design. Many of them have found practical applications in clinical therapy [1, 2, 3]. A study of literature shows enormous interest in these molecules as potential drugs for various disorders. Their chemical properties have been studies over years and have served as a versatile building block in organic synthesis. In view of this, interest to synthesise some novel derivatives bearing isoxazole moiety and to study their anti-inflammatory activity were undertook. Chalcone being a very good synthon [4], variety of novel heterocycles like isoxazole can be designed with good pharmacological profile. Chalcones are potential biocides, as they owe their biological activity due to α, β- unsaturated carbonyl group.

RESULT AND DISCUSSION

The synthesized compounds were evaluated for their anti-inflammatory activity by using carrageenan induced rat paw oedema method by Winter *et al* [5],. Acute oedema in the hind paws of rat was induced by the injection of freshly prepared, 1% w/v carrageenan in saline solution. Oedema was determined immediately and 30, 60, 120 and 180 minutes after the injection, using a plethysmograph.

Different 5 mg/kg, 10 mg/kg and 20 mg/kg doses of test compounds and the standard drug (Indomethacin) 10 mg/kg were administered 1 hr before the carrageenan injection. The results were expressed as percent inhibition of the oedema as compare to the control.

In-vivo anti-inflammatory activity, determined using the carrageenan induced rat paw oedema assay, showed that the compounds **3a, 3b, 3g, 3h, 3k and 3l** at 20mg/kg i. p. dose inhibited inflammation by 64-85% at 3hrs post drug administration, relative to the reference drug indomethacin (82% inhibition at 3hrs for 10mg/kg). Compounds 3b, 3l were found to be more potent having ED_{50} 6.3mg/kg, 6.6mg/kg respectively. Compounds 3h, 3k were found to be moderate potent having ED_{50} 7.9mg/kg, 7.1mg/kg respectively. Compounds 3a, 3g were found to be least potent having ED_{50} 10mg/kg, 10.1mg/kg respectively.

EXPERIMENTAL

Chalcones (1a-l) were synthesized by reaction of aromatic aldehydes with aromatic ketones, chalcone dibromides (2a-l) were prepared by bromination of chalcone in presence of glacial acetic acid [6]. Compounds (2a-l) on cyclization with hydroxylamine hydrochloride in presence of triethanolamine furnished substituted diphenyl isoxazoles [7]. The compounds were purified by recrystallization using absolute ethanol. Melting points of the newly synthesized compounds were determined by open capillary method using the melting point apparatus and were uncorrected. Thin layer chromatographic analysis on silica gel G coated glass plates was performed to access the reaction and purity of compounds. The structures of the compounds were established by spectral (FTIR, ^{1}HNMR, MASS) and elemental analysis. These studies provide information about various functional groups and protons in the

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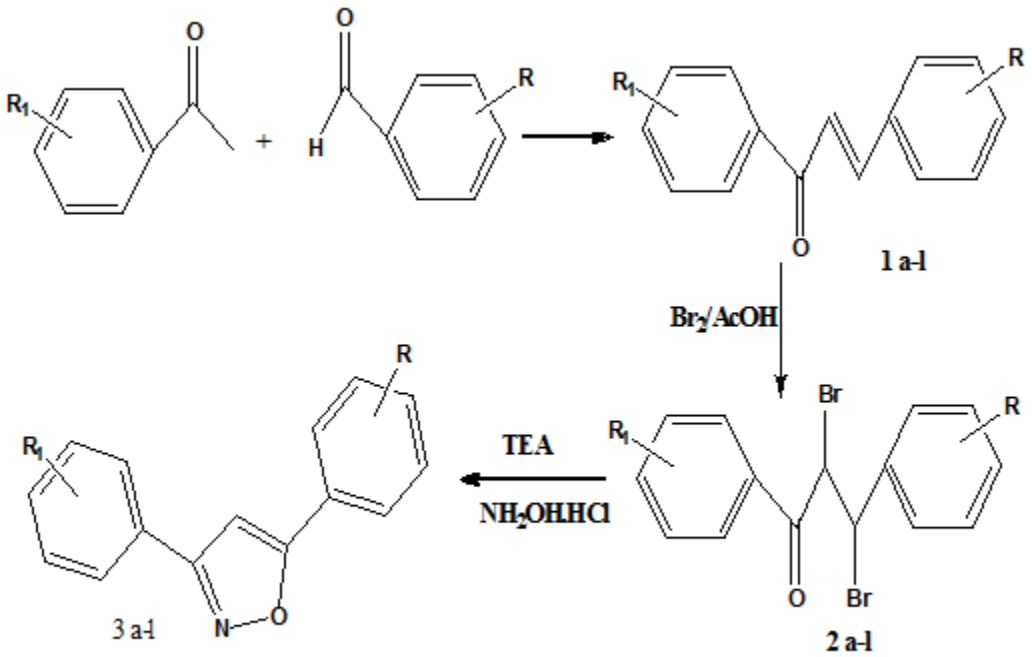
compounds, to help in confirmation of their structures. IR spectra were recorded on Perkin Elmer Spectrum RXI FTIR system by using potassium bromide pellets and noteworthy absorption levels (cm^{-1}) are listed. ^1H NMR Spectra of compounds was recorded on Bruker Avance II 400 NMR using TMS as an internal standard (Chemical shift δ in ppm). Mass spectra of the compounds were obtained by using LC-MS (SHIMADZU-2010AT, Software class VP).

General procedure for the preparation of isoxazoles 3a-l from chalcone dibromide 2a-l.

Chalcone dibromide 2a-l (0.005 mole) and hydroxylamine hydrochloride (0.01 mole) were heated with triethanolamine 15 ml until bumping was started (10-15 min.) reaction mixture was cooled, filtered, dried and recrystallized from absolute ethanol to give 3a-l (**Scheme I**) and physical constants of compounds 3a-l tabulated in **Table I.**



Scheme I

3a : 3, 5-Diphenyl isoxazole : Yield 80.2% ; m.p.183-184ºC ; Calcd for $C_{15}H_{11}NO$: C,81.43; H,5.01; N, 6.33 ; Found : C,81.41; H,5.00; N, 6.30 % ; FTIR (KBr, cm^{-1}) 3047.95 (Aromatic C-H stretching), 1570.67 (C=N stretching),1488.94 (C=C stretching), 1404.08 (N-O stretching), 912.27 (C-C stretching), 687.39 cm^{-1}(Monosubstituted C-H def.);^{1}HNMR (DMSO) δ 6.562 (s, 1H, =CH), 7.342-7.826 ppm (m, 10H, Ar-H);ESI-MS: m/z (%) 222.24[18], 221.25[100], 144.24[26], 77.11[39], 69.02[12].

3b:5(4'-Chlorophenyl)3-phenylisoxazole : Yield 73%; m.p.183-184ºC Calcd for $C_{15}H_{10}ClNO$:C,70.46; H,3.94; N, 5.48; Cl, 13.87; Found : C,70.42; H,3.93; N, 5.42; Cl, 13.84%; FTIR (KBr, cm^{-1}) 3062.75 (Aromatic C-H stretching), 1577.09 (C=N stretching), 1487.01(C=C

stretching),1404.08(N-Ostretching), 912.27(C-C stretching), 830.72 (Disubstituted C-H def.), 769.93 (C-Cl stretching), 773.25 cm^{-1} (Monosubstituted C-H def.); ^{1}HNMR (DMSO) δ 6.854 (s, 1H, =CH), 7.374-7.847ppm (m, 9H, Ar-H); ESI-MS : m/z (%) 257.69[36], 255.69[100], 179.05[52], 112.68[19], 77.12[39], 69.02[12].

3c:5-(2'-Chlorophenyl)3-phenylisoxazole : Yield 76.1% ; m.p.182-183ºC; Calcd for $C_{15}H_{10}ClNO$: C,70.46; H,3.94; N, 5.48 Cl, 13.87; Found :C,70.39; H,3.91; N, 5.46 Cl, 13.82; %.; FTIR (KBr, cm^{-1}) 3025.64 (Aromatic C-H stretching), 1545.09 (C=N stretching), 1537.09 (C=C stretching), 1404.08 (N-O stretching), 1002.92 (C-C stretching), 772.28 (Disubstituted C-C def.), 732.69 (C-Cl stretching), 695.81 cm^{-1} (Monosubstituted C-H def.) ^{1}HNMR (DMSO)δ 6.594 (s, 1H, =CH), 7.194-7.942ppm (m, 9H, Ar-H); ESI-MS : m/z (%) 257.65[36], 255.68[100], 179.58[61], 112.70[31], 77.12[39], 69.02[16].

3d:5-(3'-Chlorophenyl)3phenylisoxazole : Yield 69.81% ; m.p.180-181ºC Calcd for $C_{15}H_{10}ClNO$: C,70.46; H,3.94; N, 5.48; Cl, 13.87; Found C,70.43; H,3.92; N, 5.43 ;Cl, 13.86%.; FTIR (KBr, cm^{-1}) 3050.82 (C-H stretching), 1511.72 (C=N stretching), 1467.08(C=C stretching), 1326.93 (N-O stretching), 1227.71(C-C stretching), 797.91 (Disubstituted C-H def.), 719.69 (C-Cl stretching), 675.93 cm^{-1} (Monosubstituted C-H def.); ^{1}HNMR (DMSO)δ 6.744 (s, 1H, =CH), 7.225-7.508 ppm (m, 9H, Ar-H); ESI-MS : m/z (%) 257.67[36], 255.69[100], 179.58[54], 112.69[19], 77.12[39], 69.02[16].

3e:5-(4'-Methoxyphenyl)-3-phenyl-isoxazole : Yield 87.0%; m.p.179-180ºC; Calcd for $C_{16}H_{13}NO_2$: C,76.48; H,5.21; N, 5.57; Found : C,76.47; H,5.20; N, 5.55 %; FTIR (KBr, cm^{-1}) 3017.25 (Aromatic C-H stretching), 2935.40(C-H stretching), 1525.28 (C=N stretching), 1472.21(C=C stretching), 1362.75 (N-O stretching), 1345.57 (C-O stretching), 914.20 (C-C stretching), 807.39 (Disubstituted C-H def.), 750.79 cm^{-1} (Monosubstituted C-H def.); ^{1}HNMR (DMSO)δ 3.731 (s, 3H, $-OCH_3$), 6.181 (s, 1H, =CH), 6.787-7.482ppm (m, 9H, Ar-H); ESI-MS : m/z (%) 252.26[19], 251.27[100], 174.18[21],108.14[28], 77.12[39], 69.02[16].

3f:5-(4´-Fluorophenyl)-3phenylisoxazole : Yield 85.2 % ; m.p.185-186ºC; Calcd for $C_{15}H_{10}FNO$: C, 75.30; H, 4.21; N, 5.85; F,7.94; Found: C, 75.28; H, 4.20; N, 5.83; F,7.91%; FTIR (KBr, cm^{-1}) 3058.19 (Aromatic C-H stretching), 1579.59 (C=N stretching), 1460.01 (C=C stretching), 1398.30 (N-O stretching), 1251.72 (C-F stretching), 1197.71 (C-Cstretching), 804.26 (Disubstituted C-Hdef.), 734.83 cm^{-1} (Monosubstituted C-Hdef.); ^{1}HNMR (DMSO)δ 6.898 (s, 1H, =CH), 7.125-7.489ppm (m, 9H, Ar-H); ESI-MS : m/z (%) 240.24[14], 239.24[100], 162.24[17], 95.09[12], 77.12[39], 69.02[16].

3g: 3-(3´-Phenylisoxazol-5-yl) phenol: Yield 78.1%; m.p.175-176ºC; Calcd for $C_{15}H_{11}NO_2$: C,76.17; H,5.59; N, 5.55; Found: C,76.13; H,5.58; N, 5.54 %; FTIR (KBr, cm^{-1}) 3577.26 (O-H stretching), 3060.82 (Aromatic C-H stretching), 1596.40 (C=N stretching), 1475.44 (C=C stretching), 1410.80 (N-O stretching, 1253.64 (C-O stretching), 1099.65 (C-C stretching), 781.12 (Disubstituted C-H def.), 740.81 cm-^{1} (Monosubstitued C-Hdef.); ^{1}HNMR (DMSO)δ 5.019 (s, 1H, -OH, D_2Oexchangable), 6.754 (s, 1H, =CH), 6.868-7.484ppm (m, 9H, Ar-H); ESI-MS : m/z (%) 238.24[14], 237.25[100], 160.12[24], 93.18[8], 77.12[39], 69.02[16].

3h:5-(3´-Methoxyphenyl)-3-phenyl-isoxazole: Yield 68.1%; m.p.178-179ºC; Calcd for $C_{16}H_{13}NO_2$: C,76.48; H,5.21; N, 5.57; Found : C,76.45; H,5.19; N, 5.52 %; FTIR (KBr, cm^{-1}) 3073.77 (Aromatic C-H stretching), 2896.88 (C-H stretching), 1573.81 (C=N stretching), 1485.09 (C=C stretching), 1352.88 (C-O stretching), 1325.88 (N-O stretching), 1031.49 (C-C stretching), 773.40 (Disubstituted C-Hdef.), 698.90 cm^{-1} (Monosubstituted C-Hdef.); ^{1}HNMR (DMSO)δ 3.732 (s, 3H, -OCH_3), 6.243 (s, 1H, =CH), 6.733-7.487ppm (m, 9H, Ar-H); ESI-MS: m/z (%)252.27[18], 251.27[100], 174.15[22],108.14[12],77.12[39], 69.02[16].

3i:3-(4'-Bromophenyl)-5-phenyl-isoxazole: Yield 81.8%; m.p.210-211ºC; Calcd for $C_{15}H_{10}BrNO$: C,60.02; H,3.36; N,4.67;Br, 26.62 ;Found :C,60.00; H,3.35; N,4.65; Br, 26.60 %; FTIR (KBr, cm^{-1})3053.40 (Aromatic C-H stretching), 1508.81 (C=N stretching), 1487.01 (C=C stretching), 1404.08 (N-O stretching), 1195.78 (C-Cstretching), 840.19 (Disubstituted C-Hdef.), 700.78 (Monosubstituted C-Hdef.), 565.10 cm^{-1} (C-Br stretching); ^{1}HNMR (DMSO)δ 6.594 (s, 1H, =CH), 7.117-7.823ppm (m, 9H, Ar-H);ESI-MS : m/z (%):- 302.15[98], 300.15[100], 224.03[34], 156.02[19], 77.12[39], 69.01[16].

3j:N,N-dimethyl-4-(3'-phenylisoxazol-5yl)aniline: Yield 64.1%; m.p.187-188ºC; Calcd for $C_{17}H_{16}N_2O$: C,77.25; H,6.16; N,10.60; Found : C,77.24; H,6.12; N,10.58%; FTIR (KBr, cm^{-1}) 3039.33 (Aromatic C-H stretching), 2933.53 (C-H stretching), 1545.65 (C=N stretching), 1465.01(C=C stretching), 1404.08 (N-O stretching), 1326.93 (C-N stretching), 1251.72 (C-C stretching), 800.17 (Disubstituted C-Hdef.), 735.31 cm^{-1}(Monosubstituted C-Hdef.);^{1}HNMR(DMSO)δ 2.859 (s, 6H, -$N(CH_3)_2$, 6.582 (s, 1H, =CH), 6.651 -7.413ppm (m, 9H, Ar-H); ESI-MS: m/z (%)265.31[12], 264.32[34], 187.20[18], 118.19[22], 77.12[39], 69.01[16].

3k:3(4'-Bromophenyl)-5-(3"-chloro phenyl)isoxazole: Yield 63.7%; m.p.196-197ºC; Calcd for $C_{15}H_9BrClNO$: C,53.84; H,2.71; N,4.19; Br,23.88; Cl,10.60; Found : C,53.83; H,2.69; N,4.17; Br,23.86; Cl,10.61%; FTIR (KBr, cm^{-1}) 3049.51(Aromatic C-H stretching), 1572.60 (C=N stretching), 1489.78 (C=C stretching), 1404.08(N-O stretching), 1082.71 (C-C stretching), 837.18 (Disubstituted C-Hdef.), 780.10 (C-Cl stretching), 625.62 cm^{-1} (C-Br stretching) ; ^{1}HNMR (DMSO)δ 6.617 (s, 1H, =CH), 7.079-7.469ppm (m, 8H, Ar-H); ESI-MS : m/z (%)335.61[19], 334.61[100], 180.45[18], 154.15[33], 111.45[42], 69.02[16].

3l:3-(4'-Chlorophenyl)-5-(4"-methoxy-phenyl)isoxazole: Yield 64.6% m.p.191-192ºC; Calcd for $C_{16}H_{12}ClNO_2$: C,67.89; H,5.03; N,4.66; Cl,11.79; Found : C,67.86; H,5.00; N,4.64; Cl,11.77%; FTIR (KBr, cm^{-1}) 3021.19 (Aromatic C-H stretching), 2962.64 (C-H stretching), 1596.95 (C=N stretching), 1517.87 (C=C stretching) , 1436.86 (N-O stretching), 1365.51(C-O stretching), 1178.43 (C-Cstretching), 817.76 (Disubstituted C-Hdef.), 754.12 cm^{-1} (C-Cl stretching);^{1}HNMR (DMSO)δ 3.730(s, 3H, -OCH_3), 6.171(s, 1H, =CH), 6.874-7.468ppm (m, 8H, Ar-H); ESI-MS : m/z (%) 286.70[18], 285.72[100], 174.27[24], 111.45[42], 105.27[29], 69.02[16].

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Table I – Physical constants of compounds 3a-l

Compound	R	R_1	Molecular formula	Log P	Log ε	Parachor (cm^3)	Rf*
3a	H	H	$C_{15}H_{11}NO$	4.04	4.16	502.1±4.0	0.54
3b	*p*-Cl	H	$C_{15}H_{10}ClNO$	4.59	4.18	537.9±4.0	0.83
3c	*o*-Cl	H	$C_{15}H_{10}ClNO$	4.59	4.18	537.9±4.0	0.77
3d	*m*-Cl	H	$C_{15}H_{10}ClNO$	4.59	4.18	537.9±4.0	0.74
3e	*p*-OCH_3	H	$C_{16}H_{13}NO_2$	3.91	4.19	558.7±4.0	0.73
3f	*p*-F	H	$C_{15}H_{10}FNO$	4.19	4.21	509.2±4.0	0.8
3g	*m*-OH	H	$C_{15}H_{11}NO_2$	3.65	4.22	517.1±4.0	0.57
3h	*m*-OCH_3	H	$C_{16}H_{13}NO_2$	3.91	4.19	558.7±4.0	0.67
3i	H	*p*-Br	$C_{15}H_{10}BrNO$	4.87	4.32	552.6±4.0	0.77
3j	$N(CH_3)_2$	H	$C_{17}H_{16}N_2O$	4.32	4.41	604.1±4.0	0.72
3k	*m*-Cl	*p*-Br	$C_{15}H_9BrClNO$	5.42	4.33	588.4±4.0	0.66
3l	*p*-OCH_3	*p*-Cl	$C_{16}H_{12}ClNO_2$	4.47	4.34	594.6±4.0	0.58

*Mobile phase- Chloroform:Methanol :1:1
ε- Extinction coefficient

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