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Der Pharmacia Lettre, 2011, 3(3): 378-382
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Synthesis, characterization and anti-inflammatory activity of some novel isoxazoles

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ABSTRACT

The novel isoxazole derivatives were synthesized from various unstable Chalcones. The synthesized isoxazoles were characterized by IR, ^{1}HNMR and Mass spectral techniques and evaluated for their anti-inflammatory activity. Compounds I_3, I_5, I_6 and I_{11} showed significant activity when compared to standard Diclofenac sodium.

Keywords: Isoxazole, Anti-inflammatory activity, Lipophilicity.

INTRODUCTION

Isoxazoles are unique in their chemical behavior not only among heterocyclic compounds in general, but also among related azoles. This is because isoxazole possesses the typical properties of the aromatic system, which are in fact rather pronounced in these derivatives, together with the high liability of the ring under certain conditions, particularly at the nitrogen-oxygen bond. From a purely formal point of view isoxazole can be considered as an analogue of pyridine just as furan is an analogue of benzene. Such a formal analogy is to some extent valid, isoxazole resembles pyridine more than other heterocyclic compounds as far as chemical properties are concerned. It differs from pyridine in undergoing more readily electrophilic substitution reactions and possessing a more liable ring; this relationship thus resembles that between furan and benzene[1]. Isoxazoles are reported to show potent anti-tuberculosis[2], anti-microbial[3] and anti-inflammatory[4] activities. In the view of various biological activity, we planned to synthesize new isoxazoles **(scheme-1)** from various unstable Chalcones and screened for their anti-inflammatory activity.

MATERIALS AND METHODS

All the melting points were determined on Micro-controller based melting point apparatus CL 725/726 and were uncorrected. Chloro and nitro benzaldehydes were purchased from Techno chemicals, Bangalore. Other chemicals like hydroxyl amine hydrochloride and sodium acetate

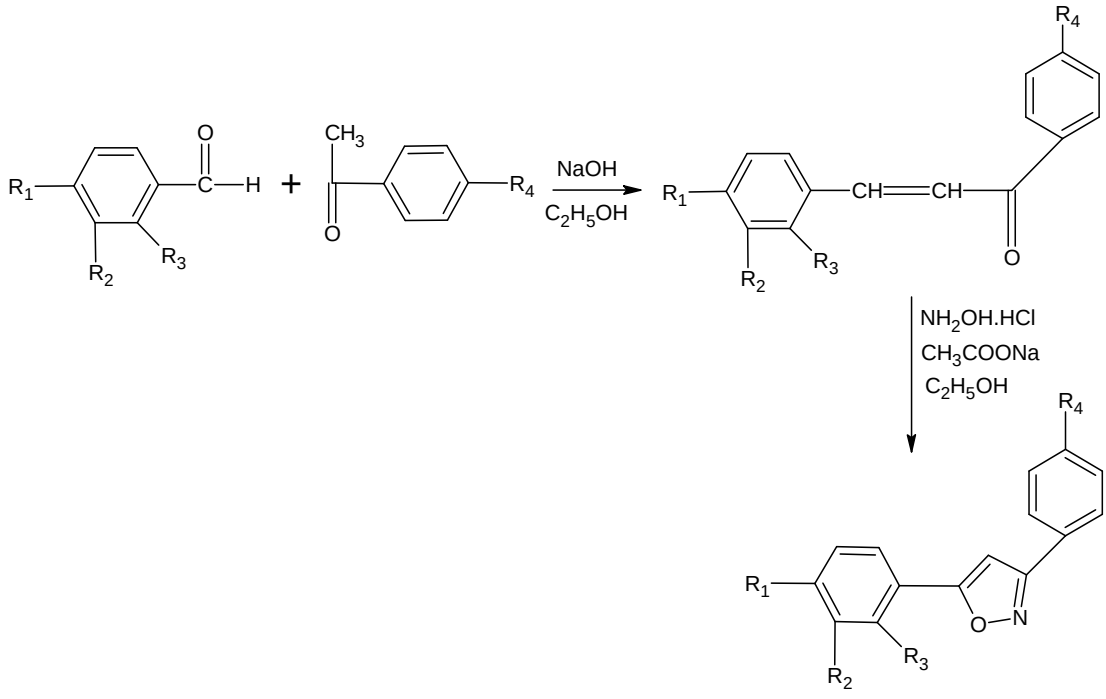
were purchased from S.D. Fine chemicals, Bangalore. Silica gel G plates (3x8cm) were used for TLC and spots were located by UV or in iodine chamber. The IR spectra (KBr) were determined on FTIR 8400S, SHIMADZU Spectrometer and the values were expressed in cm^{-1}. ^{1}H-NMR were recorded in either $CDCl_3$ or DMSO-d_6 solvents using TMS as an internal reference standard at IIT Chennai and IISc Bangalore.

General procedure for synthesis of chalcones and cyclization

Equimolar quantities of different substituted aromatic benzaldehydes (0.01 mol) and substituted aromatic acetophenones (0.01mol) were dissolved in 25 mL of alcohol. Sodium hydroxide solution (0.02mol) was added slowly and the mixture stirred for 12 hours until the entire mixture becomes very cloud formed Chalcones.

The formed unstable Chalcones were further cyclised with 0.015 mol of hydroxylamine hydrochloride and sodium acetate 0.015mol in 25 mL of ethanol was refluxed for 6 hours. The mixture was concentrated by distilling out the solvent under reduced pressure and poured into ice. The precipitate obtained was filtered, washed and recrystallized from acetone.

Scheme-1



I 1-14

I_1: 4-[3-(-4-hydroxyphenyl) isoxazol-5-yl]-2-methoxy phenol

Brown Crystals, Yield: 43%, MP: 81ºC, FTIR (KBr): 3366 (O-H), 1506 (C=N), 3081 (C-H), 1620 (C=C). ^{1}H NMR (DMSOd_6): 6.8-7.6 (m, 7H, Ar-H), 6.3 (s, 1H, CH), 9.45 (d, 2H, OH), 3.8 (s, 3H OCH_3). MS: m/z (%) 283(55%) [M^+]. [Found: C. 67.85, H. 4.66, N. 4.98 $C_{16}H_{13}NO_4$ requires C. 67.84, H. 4.63, N. 4.94%].

I_2: 4-[5-(4-chlorophenyl) isoxazol-3-yl] phenol

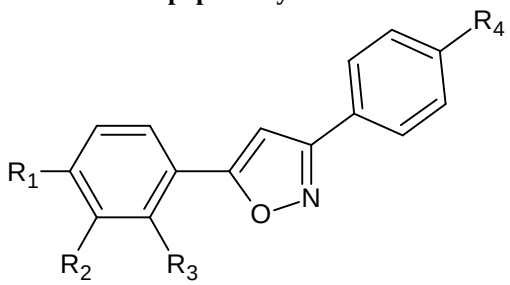
Colour less Crystals, Yield: 36.58%, MP: 88ºC, FTIR (KBr): 3333 (O-H), 1504 (C=N), 3081 (C-H), 1620 (C=C). ^{1}H NMR (DMSOd_6): 6.7-7.6 (m, 8H, Ar-H), 6.3 (s, 1H, CH), 9.5 (s, 1H, OH). MS: m/z (%) 271(55%) [M^+]. [Found: C. 66.34, H. 3.74, N. 5.17 $C_{15}H_{10}ClNO_2$requires C. 66.31, H. 3.71, N. 5.16%].

Table-1: Anti-inflammatory activity of compounds I_1-I_{12}

Sl. No	Group	0hr	1hr	2hr	3hr	4hr
1	Control	1.466± 0.1212	1.616± 0.079	1.633± 0.250	1.676± 0.074	1.75± 0.061^{a}
2	Standard	1.616±0.0793	1.45± 0.067	1.35± 0.151	1.45± 0.099	1.283± 0.060
3	I_1	1.55± 0.042	0.983± 0.074^{a**}	0.816± 0.147^{a***}	1.066± 0.042^{a**}	0.816± 0.047^{a,***}
4	I_2	1.45± 0.056	1.016± 0.074^{a*}	1.016± 0.183^{a*}	0.966± 0.066^{a***}	0.866± 0.066^{a,***}
5	I_3	1.533± 0.055	1.366± 0.071	0.916± 0.231^{a*}	1.116± 0.060^{a*}	0.933± 0.055^{a**}
6	I_4	1.5± 0.093	1.366± 0.084	0.933± 0.186^{a*}	1.066± 0.049^{a**}	0.883± 0.047^{a***}
7	I_5	1.5± 0.093	0.983± 0.074^{a**}	0.866± 0.150^{a**}	1.1± 0.063^{a*}	0.933± 0.055^{a**}
8	I_6	1.5± 0.0774	1.05± 0.067^{a*}	0.833± 0.150^{a,**}	1.2± 0.051^{a}	1.000± 0.036^{a*}
9	I_7	1.616± 0.83	0.975± 0.083^{a**}	0.85± 0.164^{a**}	1.083± 0.047^{a**}	0.833± 0.033^{a***}
10	I_8	1.616± 0.94	1.433± 0.0988	0.883± 0.194^{a**}	1.083± 0.0792^{a**}	0.95± 0.076^{a**}
11	I_9	1.583± 0.011	1±0.103^{a*}	1±0.253^{a*}	1.1± 0.056^{a*}	0.883± 0.060^{a***}
12	I_{10}	1.133± 0.088	0.966± 0.080^{a**}	0.966± 0.196^{a**}	1.083± 0.060^{a**}	0.866± 0.066^{a***}
13	I_{11}	1.65± 0.076	1.466± 0.666	0.85± 0.242^{a**}	1.116± 0.060^{a*}	0.916± 0.060^{a**}
14	I_{12}	1.55±0.076	1.4±0.816	0.783± 0.116^{a***}	1.083± 0.060^{a**}	0.9± 0.057^{a***}

All values are expressed as mean ±SEMs, $^{a}p<0.001$ V_s Control, $^{***}p<0.001$, $^{**}p<0.05$, $^{*}p<0.01$ V_s Standard.

Table - 2. Lipophilicity of the Isoxazoles



COMPOUNDS	R_1	R_2	R_3	R_4	$\log_{10}P^a$
I_1	OH	OCH_3	H	OH	3.59
I_2	Cl	H	H	OH	4.76
I_3	H	NO_2	H	OH	3.82
I_4	H	H	Cl	OH	4.81
I_5	H	H	OH	OH	3.54
I_6	OCH_3	H	H	OH	4.09
I_7	H	H	H	OH	4.17
I_8	OH	OCH_3	H	H	4.08
I_9	Cl	H	H	H	5.29
I_{10}	H	H	Cl	H	5.29
I_{11}	H	H	OH	H	4.16
I_{12}	H	H	H	H	4.71

I_3: 4-[5-(3-nitrophenyl) isoxazol-3-yl] phenol

Colour less Crystals, Yield: 40.28%, MP: 86ºC, FTIR (KBr): 3081 (O-H), 1504 (C=N), 3081 (C-H), 1620 (C=C). ^{1}H NMR ($DMSOd_6$): 6.6-7.6 (m, 8H, Ar-H), 6.3 (s, 1H, CH), 9.5 (s, 1H, OH). MS: m/z (%) 271(55%) [M^+]. [Found: C. 66.85, H. 3.56, N. 9.96 $C_{15}H_{10}N_2O_4$ requires C. 66.83, H. 3.57, N. 9.92%].

I_4: 4-[5-(2-chlorophenyl) isoxazol-3-yl] phenol

Colour less Crystals, Yield: 39.4%, MP: 87ºC, FTIR (KBr): 3081 (O-H), 1521 (C=N), 3081 (C-H), 1620 (C=C). ^{1}H NMR ($DMSOd_6$): 6.5-8.1 (m, 8H, Ar-H), 6.3 (s, 1H, CH), 8.9 (s, 1H, OH). MS: m/z (%) 271(60%) [M^+]. [Found: C. 66.30, H. 3.74, N. 5.17 $C_{15}H_{10}N_2O_4$ requires C. 66.31, H. 3.71, N. 5.16%].

I_5: 2-[3-(4-hydroxyphenyl) isoxazol-5-yl] phenol
Colour less Crystals, Yield: 46.29%, MP: 84ºC, FTIR (KBr): 3366 (O-H), 1506 (C=N), 3081 (C-H), 1620 (C=C). ^{1}H NMR (DMSOd_6): 6.8-7.6 (m, 8H, Ar-H), 6.3 (s, 1H, CH), 9.4 (d, 2H, OH). MS: m/z (%) 253(55%) [M^+]. [Found: C. 71.15, H. 4.40, N. 5.55 $C_{15}H_{11}NO_3$ requires C. 71.14, H. 4.38, N. 5.53%].

I_6: 4-[5-(4-methoxyphenyl) isoxazol-3-yl] phenol
Colourless Crystals, Yield: 46.29%, MP: 82ºC, FTIR (KBr): 3366 (O-H), 1506 (C=N), 3081 (C-H), 1620 (C=C). ^{1}H NMR (DMSOd_6): 6.8-7.6 (m, 7H, Ar-H), 6.3 (s, 1H, CH), 9.45 (s, 1H, OH), 3.5 (s, 3H OCH_3). MS: m/z (%) 255 (55%) [M^+]. [Found: C. 71.89, H. 4.91, N. 5.25 $C_{15}H_{13}NO_3$ requires C. 71.90, H. 4.90, N. 5.24%].

I_7: 4-(5-phenylisoxazol-3-yl) phenol
Colourless Crystals, Yield: 46.29%, MP: 89ºC, FTIR (KBr): 3366 (O-H), 1506 (C=N), 3081 (C-H), 1620 (C=C). ^{1}H NMR (DMSOd_6): 6.8-7.6 (m, 9H, Ar-H), 6.3 (s, 1H, CH), 9.45 (s, 1H, OH). MS: m/z (%) 237 (55%) [M^+]. [Found: C. 75.97, H. 4.69, N. 5.92 $C_{15}H_{11}NO_2$ requires C. 75.94, H. 4.67, N. 5.90%].

I_8: 2-methoxy-4-(3-phenylisoxazol-5-yl) phenol
Brown crystals, Yield: 34.28%, MP: 80ºC, FTIR (KBr): 3366 (O-H), 1506 (C=N), 3081 (C-H), 1620 (C=C). ^{1}H NMR (DMSOd_6): 6.8-7.6 (m, 8H, Ar-H), 6.3 (s, 1H, CH), 9.45 (s, 1H, OH), 3.5 (s, 3H OCH_3). MS: m/z (%) 267 (55%) [M^+]. [Found: C. 75.93, H. 4.68, N. 5.92 $C_{16}H_1NO_2$ requires C. 75.94, H. 4.67, N. 5.90%].

I_9: 5-(4-chlorophenyl)-3-phenylisoxazole
Colourless Crystals, Yield: 39.4%, MP: 98ºC, FTIR (KBr): 1521 (C=N), 3081 (C-H), 1620 (C=C). ^{1}H NMR (DMSOd_6): 6.6-7.5 (m, 9H, Ar-H), 6.3 (s, 1H, CH). MS: m/z (%) 255 (60%) [M^+]. [Found: C. 70.50, H. 3.97, N. 5.91 $C_{15}H_{10}ClNO$ requires C. 70.46, H. 3.94, N. 5.90%].

I_{10}: 5-(2-chlorophenyl)-3-phenylisoxazole
Colourless Crystals, Yield: 44.73%, MP: 106ºC, FTIR (KBr): 1521 (C=N), 3081 (C-H), 1620 (C=C). ^{1}H NMR (DMSOd_6): 6.5-7.5 (m, 9H, Ar-H), 6.3 (s, 1H, CH). MS: m/z (%) 255 (60%) [M^+]. [Found: C. 70. 44, H. 3.95, N. 5.47 $C_{15}H_{10}ClNO$ requires C. 70. 43, H. 3.94, N. 5.48%].

I_{11}: 2-(3-phenylisoxazol-5-yl) phenol
Colourless crystals, Yield: 44.73%, MP: 88ºC, FTIR (KBr): 3366 (O-H), 1506 (C=N), 3081 (C-H), 1620 (C=C). ^{1}H NMR (DMSOd_6): 6.8-7.6 (m, 9H, Ar-H), 6.3 (s, 1H, CH), 9.45 (s, 1H, OH). MS: m/z (%) 237 (55%) [M^+]. [Found: C. 75.95, H. 4.66, N. 5.92 $C_{15}H_{11}NO_2$ requires C. 75.94, H. 4.67, N. 5.90%].

I_{12}: 3, 5-diphenylisoxazole
Colourless crystals, Yield: 36.36%, MP: 92ºC, FTIR (KBr): 1506 (C=N), 3081 (C-H), 1620 (C=C). ^{1}H NMR (DMSOd_6): 6.6-7.5 (m, 10H, Ar-H), 6.3 (s, 1H, CH), MS: m/z (%) 237 (55%) [M^+]. [Found: C. 81.44, H. 5.00, N. 6.36 $C_{15}H_{11}NO$ requires C. 81.43, H. 5.01, N. 6.33%].

RESULTS AND DISCUSSION

Anti-inflammatory activity

Isoxazole derivatives were screened for their anti-inflammatory activity by *in vivo* method on rats[5]. The action of synthesized compounds was done on paw of Wister albino rats and compared with Diclofenac sodium as a standard. The paw volumes were recorded within one hour interval time duration and the SEM values are calculated by using SPSS software. The study indicated that compounds **I_3, I_5, I_6** and **I_{11}** exhibited potent anti-inflammatory activity **(Table-1)**.

As expected, isoxazole derivatives exhibited anti-inflammatory activity in which some are good and moderately active like standard employed for comparison. Therefore further a detailed study of toxicity is necessary.

Lipophilicity

The compounds lipophilicity was determined using the software ALOGPS. The efficiency of an anti-inflammatory drug will depend in part on its ability to accumulate in cells. Lipophilicity of compounds plays a vital role in anti-inflammatory effect of the compounds. The isoxazoles are strong bases and able to exist in both charged (protonated) and uncharged (unprotonated) forms. The lipophilicity data of **(I_1-I_{12})** varying from 3.54-5.29 expressed in $\log_{10}P$ are given in **Table-2**. Substitution of aryl group with OCH_3, OH, NO_2 and Cl in positions C-2, C-3 and C-4 resulted in an enhancement in the $\log_{10}P$ values. Analysis of the relationship between $\log_{10}P$ values and the anti-inflammatory activity showed poor correlation. The major outlier in this analysis was **I_9 and I_{10}** with $\log_{10}P$ values (5.29) is comparatively having higher $\log_{10}P$ values than any of other substituted derivatives and not effective at increasing anti-inflammatory activity. In contrast, compounds **I_5** with $\log_{10}P$ values (3.54) did show the maximum activity. Therefore, the degree of lipophilicity of each drug would seem to be important, but it is not the sole determinant for anti-inflammatory activity of isoxazoles.

Acknowledgement:
Authors are thankful to IISC Bangalore and Bharathi college of Pharmacy, Bharathi Nagara for providing the facilities for this work.

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