Asian Journal of Chemistry Vol. 22, No. 7 (2010), 5588-5594

Synthesis and Medicinal Properties of 4-Benzylidene-1-phenyl-2-(substituted styryl)imidazolin-5-ones

K. MADHAVI*, K.V.S.R.G. PRASAD and K. BHARATHI
Institute of Pharmaceutical Technology, Sri Padmavati Mahila Visvavidyalayam, Tirupati-517 502, India
E-mail: kuchanamadhavi@yahoo.co.in

A series of 4-benzylidene-1-phenyl-2-(substituted styryl)imidazolin-5-ones have been synthesized by the interaction of 4-benzylidene-2-methyloxazol-5-one with different Schiff bases, prepared by simple condensation of aniline and various substituted benzaldehydes. The title compounds were evaluated for antiinflammatory activity in carrageenan foot paw edema model and *in vitro* antioxidant activity. Among the 14 compounds synthesized, dimethyl amino derivative and sterically hindered phenolic derivatives were found to possess good antiinflammatory activity which also exhibited antioxidant properties.

Key Words: Imidazolin-5-one, Styryl heterocycle, Antiinflammatory activity, Antioxidant activity.

INTRODUCTION

The nonsteroidal antiinflammatory drugs (NASIDs) are of huge therapeutic benefit in the treatment of various inflammatory conditions such as rheumatoid arthritis and osteoarthritis. However, currently available NSAIDs possess certain type of mechanism based side effects including dyspepsia, gastrointestinal ulceration and nephrotoxicity. These side effects limit the clinical use of NSAIDs. Hence, an intense research is needed towards the discovery of new antiinflammatory agents without any side effects.

During the last few decades, several heterocylic compounds having styryl group with sterically hindered phenolic substituents have been evaluated as cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) dual inhibitors[1-3]. Further, substituted imidazolones received wide attention in the field of inflammation[4,5]. These reports prompted us to synthesize derivatives of various title compounds and to evaluate them for their antiinflammatory and antioxidant activities.

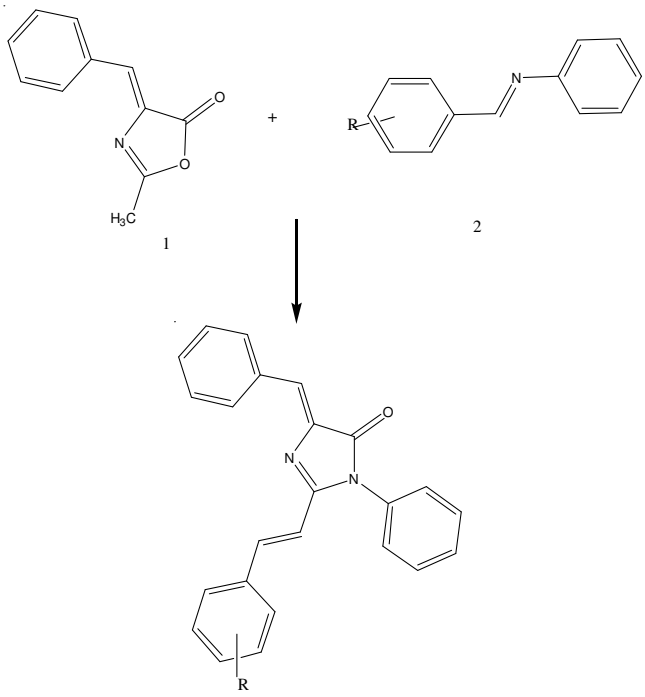
EXPERIMENTAL

All the melting points reported were determined in open capillaries, using Tempo melting point apparatus and are uncorrected. TLC was performed using glass plates coated with silica gel G and spots were detected by iodine vapour. IR spectra of the compounds were recorded on Perkin-Elmer infrared spectrophotometer in Nujol/KBr and expressed in cm^{-1}. Mass spectra of the compounds were recorded by EI

technique on Shimadzu QP 2010 PLUS. The ^{1}H NMR spectra were recorded using AVANCE-300 MHz and the values were expressed in δ ppm. Elemental analysis was carried out by using Herus CHNS rapid analysis.

A simple one pot reaction, which involves interaction of benzylideneimines and 4-benzylidene-2-methyl oxazol-5-one, has been used for the preparation of 4-benzylidene-1-phenyl-2-(substituted styryl)imidazolin-5-ones[6,7]. The starting material, 4-benzylidene-2-methyl-oxazol-5-one was prepared according to the available literature. The Schiff bases were prepared by condensation of various substituted benzaldehydes with aniline in presence of methanol and few drops of glacial acetic acid.

General method for Synthesis of 4-benzylidene-1-phenyl-2-(substituted styryl) imidazolin-5-ones (3a-3n, Scheme-I)[6,7]: To a solution of 4-benzylidene-2-methyl-oxazol-5-one (0.01 mol) in 10 mL glacial acetic acid was added the required Schiff base (0.01 mol) in acetic acid and heated on water bath for 0.5 h to 4 h to get a clear solution. The progress of reaction was monitored by TLC. The reaction mixture was cooled and the crystalline compound that separated was filtered, washed with few drops of alcohol. The crude compounds were purified by recrystallization with suitable solvent. Using the above procedure 14 such compounds (**3a-3n**)were prepared and characterized. The physical data was presented in Table-1 and spectral data are as follows:



Scheme-I

TABLE-1
PHYSICAL DATA OF 4-BENZYLIDENE-1-PHENYL-2-(SUBSTITUTED STYRYL) IMIDAZOLIN-5-ONES

Compound	R	m.p. (ºC)	Yield (%)	m.f.	m.w.
3a	4-H	240 (lit-237)[6]	52	$C_{24}H_{18}N_2O$	350
3b	4-Cl	238 (lit-238)[6]	34	$C_{24}H_{17}N_2OCl$	384
3c	4-CH_3	228 (lit-232)[6]	52	$C_{25}H_{20}N_2O$	364
3d	4-OCH_3	216 (lit-204)[6]	38	$C_{25}H_{20}N_2O_2$	380
3e	4-OH	230	36	$C_{24}H_{18}N_2O_2$	366
3f	2-OH	221	33	$C_{24}H_{18}N_2O_2$	366
3g	4-N $(CH_3)_2$	232	46	$C_{26}H_{23}N_3O$	393
3h	4-CH $(CH_3)_2$	211	32	$C_{27}H_{24}N_2O$	392
3i	3,4-$(OCH_3)_2$	118	53	$C_{26}H_{22}N_2O_3$	410
3j	3,4,5-($OCH_3)_3$	184	51	$C_{27}H_{24}N_2O_4$	440
3k	3-OCH_3, 4-OH	210	45	$C_{25}H_{20}N_2O_3Br$	396
3l	3-OCH_3, 4-OH, 5-Br	220	39	$C_{25}H_{19}N_2O_3$	475
3m	3,5-$(OCH_3)_2$, 4-OH	230	41	$C_{26}H_{22}N_2O_4$	426
3n	3,5-{$[C(CH_3)_3]$}$_2$, 4-OH	162 (lit-147)[7]	48	$C_{32}H_{32}N_2O_2$	476

3a: UV λ_{max} 293 nm; IR (KBr, ν_{max}, cm^{-1}): 2918 (C-H stretching), 1710 (C=O stretching), 1624 (C=C stretching), 1506 (C=N stretching), 1210 (C-N stretching), 970 (H-C=C- H bending); Mass m/z 350 M^+.

3b: UV λ_{max} 295 nm; IR (KBr, ν_{max}, cm^{-1}): 3052 (C-H stretching), 1712 (C=O stretching), 1625 (C=C stretching), 1511 (C=N stretching), 1215 (C-N stretching), 967 (H-C=C- H bending).

3c: UV λ_{max} 296 nm; IR (KBr, ν_{max}, cm^{-1}): 3048 (C-H stretching), 1710 (C=O stretching), 1622 (C=C stretching), 1502 (C=N stretching), 1203 (C-N stretching), 971 (H-C=C- H bending). ^{1}H NMR ($CDCl_3$) δ 2.3 (s, 3H, CH_3) 6.5 (d, 1H, H-C=C-H), 8.0 (d, 1H, H-C=C-H), 7.2-8.6 (m, 14H, aromatic and 1H, Ph-CH=) ppm; mass m/z 364 M^+.

3d: UV λ_{max} 299 nm; IR (KBr, ν_{max}, cm^{-1}): 2918 (C-H stretching), 1706 (C=O stretching), 1621 (C=C stretching), 1513 (C=N stretching), 1259 (C-O-C asymmetric), 1210 (C-N stretching), 1026 (C-O-C symmetric), 970 (H-C=C- H bending); mass m/z 380 M^+.

3e: UV λ_{max} 300 nm; IR (KBr, ν_{max}, cm^{-1}): 3416 (O-H stretching), 2920 (C-H stretching), 1719 (C=O stretching), 1623 (C=C stretching), 1514 (C=N stretching), 1329 (C-O stretching), 975 (H-C=C- H bending). ^{1}H NMR ($CDCl_3$) δ 5.1 (s, 1H, OH) 6.4 (d, 1H, H-C=C-H), 6.8 (d, 1H, H-C=C-H), 7.2-7.6 (m, 14H, aromatic), 8.1 (d, 1H, PhH-C=) ppm; mass m/z 366 M^+.

3f: UV λ_{max} 296 nm; IR (KBr, ν_{max}, cm^{-1}): 3388 (O-H stretching), 3058 (C-H stretching), 1716 (C=O stretching), 1632 (C=C stretching), 1526 (C=N stretching), 1329 (C-O stretching), 966 (H-C=C- H bending).

3g: UV λ_{max} 293 nm; IR (KBr, ν_{max}, cm^{-1}): 2918 (C-H stretching), 1711 (C=O stretching), 1638 (C=C stretching), 1526 (C=N stretching), 1230 (C-N stretching),

965 (H-C=C-H bending); ^{1}H NMR ($CDCl_3$) δ 5.6 (d, 1H, H-C=C-H), 6.6 (d, 1H, H-C=C-H), 7.0-7.6 (m, 14H, aromatic), 8.0 (d, 1H, PhH-C=) ppm; mass m/z 394 M^+ + 1; elemental analysis $C_{26}H_{23}N_2O_3$: N (7.07) 6.65, C (75.75) 75.34, H (5.05) 4.69.

3h: IR (KBr, ν_{max}, cm^{-1}): 3036 (C-H stretching), 1718 (C=O stretching), 1621 (C=C stretching), 1502 (C=N stretching), 1210 (C-N stretching), 969 (H-C=C-H bending).

3i: IR (KBr, ν_{max}, cm^{-1}): 2920 (C-H stretching), 1706 (C=O stretching), 1624 (C=C stretching), 1523 (C=N stretching), 1262 (C-O-C asymmetric), 1204 (C-N stretching), 1038 (C-O-C symmetric), 971 (H-C=C- H bending).

3j: UV λ_{max}: 304 nm; 2912 (C-H stretching), 1706 (C=O stretching), 1624 (C=C stretching), 1517 (C=N stretching), 1224 (C-O-C asymmetric), 1209 (C-N stretching), 1032(C-O-C symmetric), 974 (H-C=C- H bending).

3k: UV λ_{max}: 297 nm; IR (KBr, ν_{max}, cm^{-1}): 3402 (O-H stretching), 2919 (C-H stretching), 1712 (C=O stretching), 1624 (C=C stretching), 1507 (C=N stretching), 1252 (C-O-C asymmetric stretching), 1206 (C-N stretching), 1036 (C-O-C symmetric stretching), 969 (H-C=C-H bending); ^{1}H NMR ($CDCl_3$) δ 3.9 (s, 3H, CH_3), 5.9 (s, 1H, OH), 6.4 (d, 1H, H-C=C-H), 7.1 (d, 1H, H-C=C-H), 7.0-7.6 (m, 13H, aromatic), 8.0 (d,1H, PhH-C=) ppm; mass m/z 396 M^+; elemental analysis $C_{25}H_{19}N_3O$: N (10.68) 10.49, C(79.38) 78.88, H (5.8) 5.6.

3l: UV λ_{max}: 304 nm; IR (KBr, ν_{max}, cm^{-1}): 3400 (O-H stretching), 2919 (C-H stretching), 1697 (C=O stretching), 1621 (C=C stretching), 1500 (C=N stretching), 1278 (C-O-C asymmetric stretching), 969 (H-C=C-H bending); ^{1}H NMR ($CDCl_3$) δ 3.9 (s, 3H, CH_3), 6.1 (s, 1H, OH), 6.4 (d, 1H, H-C=C-H), 6.9 (d, 1H, H-C=C-H), 7.2-7.6 (m, 12H, aromatic), 7.9 (d, 1H, PhH-C=) ppm; mass m/z 477 M^+ + 2; elemental analysis $C_{25}H_{19}BrN_2O_3$: N (5.89) 5.42, C(63.15) 62.64, H (4.0) 3.81.

3m: UV λ_{max}: 293 nm; IR (KBr, ν_{max}, cm^{-1}): 2918 (C-H stretching), 1706 (C=O stretching), 1621 (C=C stretching), 1513 (C=N stretching), 1259 (C-O-C asymmetric), 1210 (C-N stretching), 1026 (C-O-C symmetric), 969 (H-C=C- H bending).

3n: UV λ_{max}: 298 nm; IR (KBr, ν_{max}, cm^{-1}): 3415 (O-H stretching), 2921 (C-H stretching), 1713 (C=O stretching), 1613 (C=C stretching), 1532 (C=N stretching), 1203 (C-N stretching), 971 (H-C=C-H bending).

Pharmacological and biochemical studies

Antiinflammatory activity (Carrageenan foot paw edema)[8]: Wistar rats were dosed orally with test compounds (100 mg/kg body weight, in 0.5 % sodium CMC) 1 h before carrangeenan administration. The control group received equivalent amount of vehicle. Foot paw edema was induced by injecting 0.05 mL of carrageenan solution into the plantar region of the right hind paw of each rat. The paw volumes were measured immediately following carrageenan injection and 3 h after carrageenan administration by using water displacement plethysmograph. The paw edema volume in each test group of animals was used to calculate the per cent inhibition of edema achieved by the test compound on comparision with control group.

Antioxidant activity

DPPH scavenging activity[9]: To the ethanolic solution of DPPH (100 µM), an equal amount of test compound (100 µM) dissolved in ethanol, was added in a final volume of 1 mL. An equal volume of ethanol was added to the control. After 20 min, absorbance was recorded at 517 nm in UV-vis spectrophotometer.

Nitric oxide scavenging activity[9]: The reaction mixture containing sodium nitroprusside (10 mM) in phosphate buffer and the test compounds in ethanol was incubated at 25 ºC for 2½ h. After incubation, 0.5 mL of reaction mixture was removed and added to 0.5 mL of Griess reagent. The absorbance of the chromophore formed was evaluated at 546 nm.

Lipid peroxidation in rat brain homogenate[10]: The incubation mixture contained in a final volume of 1.5 mL brain homogenate (0.5 mL. 10 % w/v, KCl, 0.15 M) and ethanol (10 µL) or test compounds dissolved in ethanol. Peroxidation was initiated by adding ferric chloride (100 µM). After incubation for 20 min at 37 ºC the reaction stopped by adding 2 mL ice-cold 0.25 M HCl containing 15 % tricholoro acetic acid, 0.38 % thiobarbituric acid and 0.05 % butylated hydroxyl toluene. Following heating at 80 ºC for 15 min samples were cooled and centrifuged at 1000 g for 10 min and absorbance of the solution was measured at 532 nm. Control experiment without test compound was conducted in an identical manner.

RESULTS AND DISCUSSION

In the present study, Erlenmayer's azalactone synthesis was followed for the synthesis of 4-benzylidene-2-methyl oxazol-5-one (**1**). This on interaction with various substituted benzylideneimines (**2**) was converted to 4-benzylidene-1-phenyl 2-(substituted styryl) imidazolin-5-ones (**3a-3n**). Fourteen compounds were synthesized by following the above simple one step reaction, which facilitates styrylation of 2-methyl group and replacement of oxygen in oxazolone ring by N-phenyl moiety. Out of 14 compounds, the synthesis of 5 compounds was reported but the compounds were not evaluated for biochemical and pharmacological activities. In the earlier reports the reaction mechanism was rationalized as initial nucleophilic attack by the active methyl carbon in compound **1** on the electrophilic carbon in compound **2** and subsequent dehydrative cyclization to yield styryl imidazolone[6,7]. All the compounds were characterized by their melting points, TLC, UV, IR and NMR spectra. The IR spectra of title compounds showed an intense absorption bands at 1719-1697 cm^{-1} assigned to the γ-lactonic carbonyl group. The IR spectra revealed that an intense band at 975-965 cm^{-1} characteristic of bending vibrations of styryl group with E-configuration. Further, the ^1H NMR spectrum of compounds (**3c, 3e, 3g, 3k** and **3l**) revealed the presence of two *trans*-olefinic protons as doublets at δ 5.6-6.6 and 6.6-7.1. The mass spectra of compounds (**3a, 3c, 3d, 3e, 3g, 3i** and **3l**) showed their characteristic molecular ion peaks. The elemental analysis for the compounds **3g**, **3k** and **3l** were carried out and values within limit of ± 0.4 % of theoretical values.

All the synthesized compounds were evaluated for antiinflammatory activity by the carrageenan induced paw edema assay in rats at a dose 100 mg/kg p.o. The data was presented in Table-2. The percentage inhibition of rat paw edema of compound **3a** (unsubstituted derivative) was found to be 33.4 indicating low activity of unsubstituted compound. The structural modification of parent molecule and optimization of biological activity was carried out by substituting the phenyl ring of styryl moiety with electron donating, electron withdrawing and sterically hindered phenolic substituents.

TABLE-2
ANTIINFLAMMATORY ACTIVITY AND ANTIOXIDANT ACTIVITY DATA OF 4-BENZYLIDENE-1-PHENYL-2-(SUBSTITUTED STYRYL) IMIDAZOLIN-5-ONES

Compd.	R	% Inhibition of carrageenan foot paw edema	DPPH scavenging activity	Nitric oxide scavenging activity	% Inhibition of lipid peroxidation
3a	4-H	33.4	NA	27.8	30.9
3b	4-Cl	30.1	NA	24.7	29.3
3c	4-CH_3	31.4	NA	13.4	23.8
3d	4-OCH_3	22.2	NA	11.0	22.9
3e	4-OH	36.9	23.4	19.3	31.2
3f	2-OH	32.1	14.1	17.7	30.1
3g	4-N $(CH_3)_2$	54.9*	36.2	57.5	49.5
3h	4-CH $(CH_3)_2$	26.7	NA	12.6	28.4
3i	3,4-$(OCH_3)_2$	20.8	06.1	10.4	24.1
3j	3,4,5-$(OCH_3)_3$	20.2	NA	07.3	20.9
3k	3-OCH_3, 4-OH	38.2*	31.2	37.1	55.7
3l	3-OCH_3, 4-OH, 5-Br	30.4	27.1	39.4	64.0
3m	3,5-$(OCH_3)_2$, 4-OH	53.3*	34.4	68.0	72.9
3n	3,5-{$[C(CH_3)_3]$}$_2$, 4-OH	42.1*	31.9	53.1	65.1
	Phenylbutazone	72.4	–	–	–
	α-Tocopherol	–	51.2	–	61.4

*: Statistically significant ($p < 0.05$ Mann-Whitney).

Among these compounds, 4-dimethyl amino derivative exhibited highest activity (54.9 %). Thus dimethyl amino group at 4th position on the phenyl ring is an interesting substitution for optimization of activity of parent compound. Compounds with sterically hindered phenolic substitution, 3,5-dimethoxy-4-hydroxy derivative and 3,5-di-*tert*-butyl-4-hydroxy derivative (**3m, 3n**) also exhibited good activity. (53.3 %, 42.1 %, respectively). These results were in good agreement with the earlier reports on various compounds containing sterecally hindered phenolic moiety which were found to possess promising antiinflammatory activity. Compound **3k**, 3-methoxy-4-hydroxystyryl derivative also possess significant activity. Further, it is evident from the activity data of compounds **3b** and **3l**, introduction of halogen atom on phenyl ring of styryl moiety lowers the activity.

All the synthesized compounds were evaluated for *in vitro* antioxidant activity in three different models *viz*. reduction of DPPH free radical, scavenging of nitric oxide free radical and ferric ion induced lipid peroxidation using rat brain homogenate as lipid source. The activity data was presented in Table-2. The activity data reveals that compounds **3m** and **3n** possess highest antioxidant activity in all the three *in vitro* models. Greater activity of these compounds may be attributed to the steric hindrance of phenolic hydroxyl group. The activity data also reveals that 4-dimethyl-aminostyryl derivative (**3g**) also possess good antioxidant activity. Interestingly, compounds which showed antiinflammatory activity also exhibited good *in vitro* antioxidant properties. The ability of these compounds to scavenge free radicals may be partially responsible for antiinflammatory activity. The antiinflammatory activity of this series of compounds was found to be less than the standard compound phenylbutazone. However, the antioxidant activity of **3m** and **3n** was greater than α-tocopherol in ferric ion induced lipid peroxidation.

In conclusion, electron donating groups especially 4-dimethyl amino and sterically hindered phenolic groups on styryl moiety were necessary for the antiinflammatory and antioxidant activities. This observation was in agreement with earlier reports[2,4,10], where similar substitution of styryl moiety resulted in optimization of antiinflammatory and antioxidant activities.

REFERENCES

1. E.S. Lazer, Hin-Chor Wong, G.J. Possanza, A.G. Graham and P.R. Farina *J. Med. Chem*., **32**, 100 (1989).
2. D.L. Flynn, T.R. Belliotti, A.M. Boctor, D.T. Connor, C.R. Kostlan, D.E. Nies, D.F. Ortwine, D.J. Schrier and J.C. Sircar, *J. Med. Chem*., **34**, 518 (1991).
3. M.D. Mullican, M.W. Wilson, D.T. Connor, C.R. Kostlan, D.J. Schrier and R.D. Dyer, *J. Med. Chem*., **36**, 1090 (1993).
4. A. Kumar, M. Verma, A.K. Saxena and K. Shanker, *Indian J. Chem*., **27B**, 301 (1988).
5. K. Pande, P. Tandon, T.N. Bhalla and J.P. Barthwal, *Indian Drugs*, **23**, 13 (1985).
6. M.S. Reddy, P. Hanumanthu and C.V. Ratnam, *Indian J. Chem*., **21B**, 646 (1982).
7. V.I. Kelarev, M.A. Silin and O.A. Borisova, *Chem. Heterocycl. Comp.*, **39**, 729 (2003).
8. C.A. Winter, E.A. Risley and G.W. Nuss, *Proc. Soc. Exp. Biol. N.Y*., **11**, 544 (1962).
9. M.S. Baliga, G.C. Jagetia, P. Venkatesh, R. Reddy and J.N. Ulloor, *Br. J. Radiology*, **77**, 1027 (2004).
10. N. Sreejayan and M.N.A. Rao, *J. Pharm. Pharmcol*., **46**, 1013 (1994).

(*Received*: 19 November 2009; *Accepted*: 31 March 2010) AJC-8594