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Synthesis and Evaluation of Substituted Imidazolones for Antiinflammatory and Antioxidant Activities

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A series of 4-substituted benzylidene-2-phenyl-1-substituted phenyl-1*H*-imidazol-5(4*H*)-one were synthesized by condensation of substituted oxazolones with *p*-amino benzoic acid and benzocaine. The chemical structures of synthesized compounds were confirmed by IR, ^{1}H NMR, mass spectral and elemental analysis. The compounds were evaluated for antiinflammatory and antioxidant activities. Out of these series of compounds screened, the compounds **4**, **5**, **14** and **16** showed equipotent activity to the standard drug phenylbutazone. Compounds **8** and **17** showed good antioxidant activity.

Key Words: Imidazolones, Antiinflammatory, Analgesic, Antioxidant.

INTRODUCTION

During the last few decades substituted imidazolones received attention in the filed of inflammation. Many imidazolones and their derivatives are associated with a broad spectrum of biological activities *i.e.*, antiinflammatory[1,2], anticonvulsant[3,4], antibacterial[5], antiparkinsonian[6], antifilarial[7], *etc*. These observations promoted us to synthesize a new series of imidazolones with higher biological activity. 4-Substituted benzylidene-2-phenyl-1-substituted phenyl-1*H*-imidazol-5(4*H*)-ones were prepared by the reaction of 2-phenyl-4-(substituted benzylidene)-oxazol-5-ones with *para*-amino benzoic acid (PABA) and benzocaine. The structures of the various synthesized compounds were assigned on the basis of elemental analysis, IR and ^{1}H NMR spectral data. These compounds were also screened for their antiinflammatory and antioxidant activities.

EXPERIMENTAL

The melting points were determined in an open capillary tube and were uncorrected. Purity of the compounds was checked by using precoated TLC plates (E. Merck Kieselgel 60 F_{254}). The IR spectra were recorded using KBr pellets on a Perkin-Elmer 1760 spectrophotometer (ν_{max}, cm^{-1}). ^{1}H NMR spectra were recorded on GE Omega 400 MHz spectrometer or Bruker Avance (300 MHz) spectrometer using TMS as an internal standard (chemical shift in δ ppm). Mass spectra were recorded on a JEOL-JMS-D-300 spectrometer. Elemental analysis (C, H and N) were undertaken with Perkin-Elmer model 240C analyzer: the found values were within ± 0.4 % of the theoretical values, unless otherwise indicated.

General method of synthesis of 2-phenyl-4-(substituted benzylidene)oxazol-5-ones: (1-9): The various 2-phenyl-4-(substituted benzylidene)-oxazol-5-ones **1-9** were prepared by reported procedure[8].

General procedure for the preparation of imidazolones: A mixture of oxazolone (10 mmol), *p*-amino benzoic acid or [benzocaine (10 mmol)] and sodium acetate (5 g freshly fused) in glacial acetic acid (15 mL) was refluxed for 5 h and cooled. The separated solid was filtered and recrystallized from methanol: water or benzene/pet ether.

Various 4-substituted benzylidene-2-phenyl-1-substituted phenyl-1*H*-imidazol-5(4*H*)-ones **2-18** were prepared in a similar manner.

4-Benzylidene-2-phenyl-1-(4-carboxyphenyl)-1*H*-imidazol-5(4*H*)-one (1): m.p. 170-171 ºC, yield: 76 %, IR (KBr, ν_{max}, cm^{-1}): 1718 (C=O), 1637 (CN), 1604 (C=C). ^{1}H NMR (DMSO-d_6) δ: 7-8 (m, 15H, Ar-H and olefinic), 9.9 (s, 1H COOH). $C_{18}H_{14}N_2O_3$.

4-(4-Chloro-benzylidene)-2-phenyl-1-(4-carboxyphenyl)-1*H*-imidazol-5(4*H*)-one (2): m.p. 175-178 ºC, yield:73 %. IR (KBr, ν_{max}, cm^{-1}): 1719 (C=O), 1636 (CN), 1603 (C=C). ^{1}H NMR (DMSO-d_6) δ: 7.1-8.2 (m, 14H, Ar-H and olefinic), 9.8 (s, 1H, COOH). $C_{18}H_{13}N_2O_3Cl$.

4-(4-Methoxy-benzylidene)-2-phenyl-1-(4carboxyphenyl)-1*H*-imidazol-5(4*H*)-one (3): m.p. 150-155 ºC, yield: 80 %, IR (KBr, ν_{max}, cm^{-1}): 1717 (C=O), 1635 (CN), 1604 (C=C). ^{1}H NMR (DMSO-d_6) δ: 3.9 (s, 3H, Ar-OCH_3), 7.1-8.1 (m, 14H, Ar-H and olefinic), 9.9 (s, 1H, COOH). $C_{19}H_{16}N_2O_4$.

4-(4-Methyl-benzylidene)-2-phenyl-1-(4-carboxyphenyl)-1*H*-imidazol-5(4*H*)-one (4): m.p. 65 ºC, yield: 72 %, IR (KBr, ν_{max}, cm^{-1}): 1722 (C=O), 1682 (C=O), 1640 (CN), 1604 (C=C). ^{1}H NMR (DMSO-d_6) δ: 2.1 (s, 3H, Ar-CH_3), 6.9-8.3 (m, 14H, Ar-H and olefinic), 10.0 (s, 1H, COOH). $C_{19}H_{16}N_2O_3$.

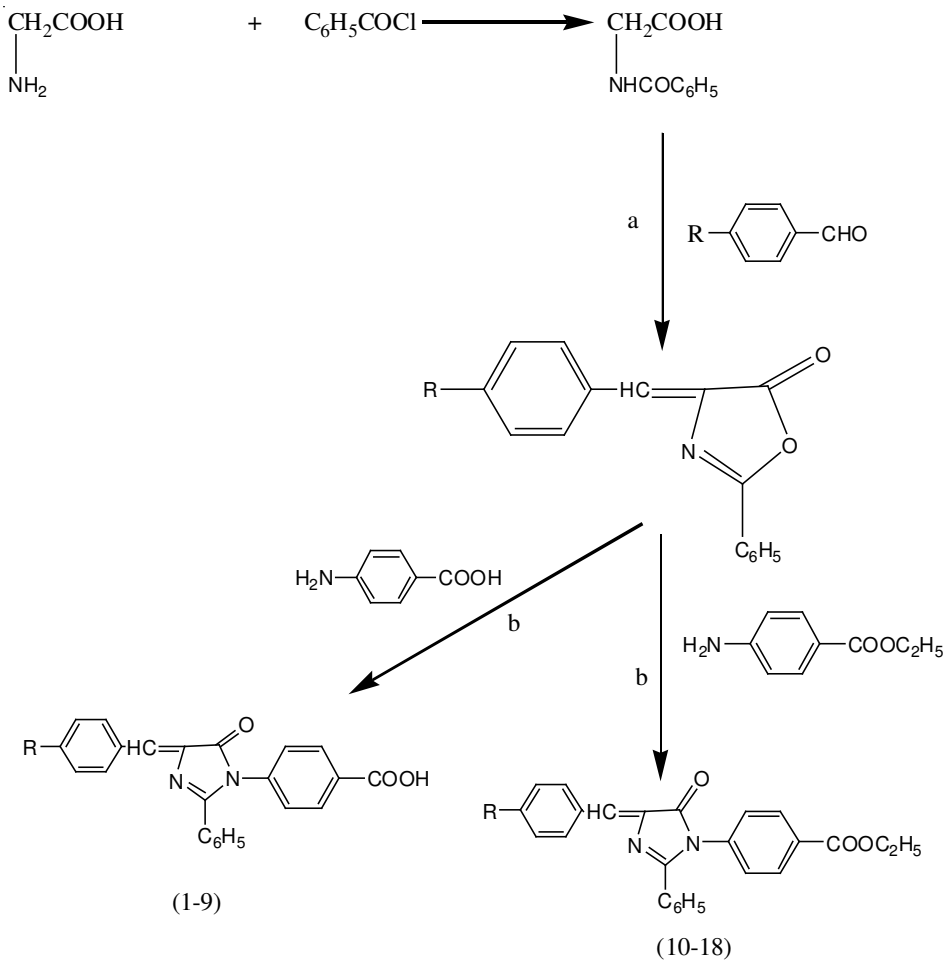
4-(4-Isopropyl-benzylidene)-2-phenyl-1-(4-carboxyphenyl)-1*H*-imidazol-5(4*H*)-one (5): m.p. 85-90 ºC, yield:68 %. ^{1}H NMR (DMSO-d_6) δ: 1.2-1.3 (m, 1H, $\underline{CH}(CH_3)_2$), 2.8 (d, 6H, $CH(\underline{CH_3})_2$), 6.7-8.4 (m, 14H , Ar-H and olefinic), 10.4 (s, 1H, COOH). $C_{21}H_{20}N_2O_3$.

4-(4-Dimethylamino-benzylidene)-2-phenyl-1-(4-carboxyphenyl)-1*H*-imidazol-5(4*H*)-one (6): m.p. 220-222 ºC, yield: 88 %, IR (KBr, ν_{max}, cm^{-1}): 1702 (C=O), 1637 (CN), 1598 (C=C). ^{1}H NMR (DMSO-d_6) δ: 2.9 (s, 6H, $(CH_3)_2$, N), 7-8 (m, 14H, Ar-H and olefinic), 9.9 (s, 1H, COOH). $C_{20}H_{19}N_3O_3$.

4-(4-Hydroxy-benzylidene)-2-phenyl-1-(4-carboxyphenyl)-1*H*-imidazol-5(4*H*)-one (7): m.p. 175-180 ºC, yield: 60 %, IR (KBr, ν_{max}, cm^{-1}): 1680 (C=O), 1640 (CN), 1605 (C=C). ^{1}H NMR (DMSO-d_6) δ: 6.6-7.9 (m, 14H, Ar-H and olefinic), 9.6 (s, 1H, Ar-OH), 10.0 (s, 1H, COOH). $C_{18}H_{14}N_2O_4$.

4-(4-Hydroxy-3-methoxy-benzylidene)-2-phenyl-1-(4-carboxyphenyl)-1*H*-imidazol-5(4*H*)-one (8): m.p. 210-215 ºC, yield: 75 %. $C_{19}H_{16}N_2O_5$.

4-(4-Nitro-benzylidene)-2-phenyl-1-(4-carboxyphenyl)-1*H*-imidazol-5(4*H*)-one (9): m.p. 180-185 ºC, yield: 62 %. $C_{18}H_{13}N_3O_5$.



(1-9) (10-18)

a) $(CH_3CO)_2O/CH_3COONa$
b) CH_3COOH/CH_3COONa

Scheme-I

4-Benzylidene-2-phenyl-1-(4-carbethoxyphenyl)-1*H*-imidazol-5(4*H*)-one (10): m.p. 148-149 ºC, yield: 90 %, IR (KBr, ν_{max}, cm^{-1}): 1713 (C=O), 1645 (CN), 1601 (C=C). ^1H NMR (DMSO-d_6) δ: 1. 2-1.4 (t , 3H, -$CH_2\underline{CH_3}$), 4.2-4.4 (q, 2H, -$\underline{CH_2}CH_3$) 7.1-8.5 (m, 15H, Ar-H and olefinic). $C_{20}H_{18}N_2O_3$.

4-(4-Chloro-benzylidene)-2-phenyl-1-(4-carbethoxyphenyl)-1*H*-imidazol-5(4*H*)-one (11): m.p. 150-155 ºC, yield: 71 %. $C_{20}H_{17}N_2O_3Cl$.

4-(4-Methoxybenzylidene)-2-phenyl-1-(4-carbethoxyphenyl)-1*H*-imidazol-5(4*H*)-one (12): m.p. 111-115 ºC, yield: 64 %, ^1H NMR (DMSO-d_6) δ: 1.2-1.4 (t , 3H, -$CH_2\underline{CH_3}$), 3.9 (s, 3H, Ar-OCH_3), 4.2-4.4 (q, 2H, -$\underline{CH_2}CH_3$) 7.1-8.5 (m, 14H, Ar-H and olefinic). $C_{21}H_{20}N_2O_4$.

4-(4-Methyl-benzylidene)-2-phenyl-1-carbethoxyphenyl-1*H*-imidazol-5(4*H*)-one (13): m.p. 189-191 ºC, yield: 57 %, ^{1}H NMR (DMSO-d_6) δ: 1.2-1.4 (t , 3H, -$CH_2\underline{CH_3}$), 2.1 (s, 3H, Ar-CH_3), 4.2-4.4 (q, 2H, -$\underline{CH_2}CH_3$) 7. 1-8.5 (m, 14H, Ar-H and olefinic). $C_{21}H_{20}N_2O_3$.

4-(4-Isopropyl-benzylidene)-2-phenyl-1-(4-carbethoxyphenyl)-1*H*-imidazol-5(4*H*)-one (14): m.p. 148-149 ºC, yield: 90 %, IR (KBr, ν_{max}, cm^{-1}): 1713 (C=O), 1639 (CN). ^{1}H NMR (DMSO-d_6) δ: 1.1-1.2 (t, H, -$CH_2\underline{CH_3}$), 1.3-1.4 (m, 1H, $\underline{CH}(CH_3)_2$) 2.8 (d, 6H, $CH(\underline{CH_3})_2$), 4.2-4.4 (q, 2H, -$\underline{CH_2}CH_3$), 6.7-8.4 (m, 14H , Ar-H and olefinic), 10.4 (s, 1H, COOH). $C_{23}H_{24}N_2O_3$.

4-(4-Dimethylamino-benzylidene)-2-phenyl-1-(4-carbethoxyphenyl)-1*H*-imidazol-5(4*H*)-one (15): m.p. 198-202 ºC, yield: 79 %, IR (KBr, ν_{max}, cm^{-1}): 1702 (CO), 1637 (CN), 1598 (C=C), ^{1}H NMR (DMSO-d_6) δ: 1.2-1.4 (t, 3H, -$CH_2\underline{CH_3}$), 2.9 (s, 6H, $(CH_3)_2$, N), 4.2-4.4 (q, 2H, -$\underline{CH_2}CH_3$) 7.1-8.5 (m, 14H, Ar-H and olefinic). $C_{22}H_{23}N_3O_3$.

4-(4-Hydroxy-benzylidene)-2-phenyl-1-(4-carbethoxyphenyl)-1*H*-imidazol-5(4*H*)-one (16): m.p. 101-105 ºC, yield: 63 %, IR (KBr, ν_{max}, cm^{-1}): 1640 (CN), 1559 (C=C), ^{1}H NMR (DMSO-d_6) δ: 1.3 (t, 3H, $CH_2\underline{CH_3}$), 4.3 (q, 2H, -$\underline{CH_2}CH_3$), 7.2-8.2 (m, 14H, Ar-H and olefinic), 10.5 (s, 1H, COOH). $C_{20}H_{18}N_2O_4$.

4-(4-Hydroxy-3-methoxy-benzylidene)-2-phenyl-1-(4-carbethoxyphenyl)-1*H*-imidazol-5(4*H*)-one (17): m.p. 105-107 ºC, yield: 61 %. $C_{21}H_{20}N_2O_5$.

4-(4-Nitro-benzylidene)-2-phenyl-1-(4-carbethoxyphenyl)-1*H*-imidazol-5(4*H*)-one (18): Yield: 60 %. $C_{20}H_{17}N_3O_5$.

Antiinflammatory activity: The method of Winter *et al.*[9] was followed. The compounds were given orally to groups of male albino rats (150-180 g, wistar strain) 1 h before injection of 0.05 mL of 1 % suspension of carrageenan into the subplantar region of the rat hind paw. Additional groups were similarly treated with 100 mg/kg of phenylbutazone (positive controls) or 10 mL/kg of 0.5 % sodium carboxy methylcellulose (vehicle controls). The volume of the injected paw was measured by water displacement in a plethysmograph immediately after carrageenan injection. The paw volume was again measured after 3 h. The results were expressed as the per cent edema inhibition which was calculated using the following formula.

$$\text{Edema inhibition (\%)} = 100\ (1 - V_t/V_c)$$

where, V_c = volume of the edema in the control group. V_t = volume of the edema in the treated group.

Inhibition of lipid peroxidation in rat brain homogenate: Albino wistar rats (180-200 g) of either sex were used for study. Decapitated and removed the brain and perfused transcardially with ice-cold normal saline to prevent contamination of brain tissue with blood. Tissue was weighed and homogenate (10 % w/v) was prepared in 0.15 M KCl and centrifuged at 800 g for 10 min. The supernatant was used immediately for the study of *in vitro* lipid peroxidation. The incubation mixture contained in a final volume of 1.5 mL, brain homogenate (0.5 mL), KCl (0.15 M)

and ethanol (10 µL) or test compound dissolved in ethanol. Peroxidation was initiated by adding, ferric chloride (100 µM) to give the final concentration stated. After incubating for 20 min at 37 °C, reactions were stopped by adding 2 mL of ice-cold 0.25 M HCl containing 15 % trichloroacetic 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. The absorbance of the supernatant was measured at 532 nm[10]. Percentage inhibition of TBARS formed by test compound was calculated by comparing with vehicle only experiments. Control experiments without test compound were conducted in an identical manner.

Interaction with stable free radical DPPH: DPPH assay was performed as described[11]. Solutions of various drugs at 100 µM concentration were added to 100 µM DPPH in 95 % ethanol and tubes were kept at an ambient temperature for 20 min and absorbance was measured at 517 nm[11]. Ethanol was used as blank and DPPH solution in ethanol served as the control.

RESULTS AND DISCUSSION

Antiinflammatory activity: Antiinflammatory activity of all the 12 compounds were screened by carrageenan induced hind paw edema model in rats (dose 100 mg/kg). The data is given in Table-1. Compounds **1-18** have been tested for their

TABLE-1
PHARMACOLOGICAL AND BIOCHEMICAL DATA OF 4-SUBSTITUTED BENZYLIDENE-2-PHENYL-1-SUBSTITUTED PHENYL-1*H*-IMIDAZOL-5(4*H*)-ONES

Compound	R	Edema inhibition (%)	Reduction of DPPH (%)	Inhibition of lipid peroxidation (%)
1	H	26.00	22.0	20.0
2	4-Cl	22.00	11.0	30.0
3	4-OCH_3	31.00	16.0	30.0
4	4-CH_3	**56.00**	15.0	48.0
5	4-$(CH_2)_2CH_3$	58.00	16.0	38.0
6	4-$N(CH_3)_2$	29.00	22.0	20.0
7	4-OH	48.00	30.0	45.0
8	4-OH, 3-OCH_3	40.00	40.0	50.0
9	4-NO_2	10.00	10.0	20.0
10	H	26.00	26.0	25.0
11	4-Cl	NA	20.0	22.0
12	4-OCH_3	32.00	23.0	35.0
13	4-CH_3	49.00	11.0	37.0
14	4-$(CH_2)_2CH_3$	**59.00**	11.0	12.0
15	4-$N(CH_3)_2$	27.20	12.0	47.0
16	4-OH	54.00	32.0	39.0
17	4-OH, 3-OCH_3	43.00	46.0	55.0
18	4-NO_2	15.00	10.0	10.0
Phenyl butazone	–	53.08	–	–
Tocopherol	–	–	43.6	51.6

antiinflammatory activity at the dose of 100 mg/kg p.o. of varying degree from 20.16-59.23 % and biological results are given in Table-1. Among these, compounds **4**, **5**, **14**, **16** exhibited activity which is equipotent to phenylbutazone. Compounds **7**, **8**, **13**, **17** showed moderated activity. It is observed that compounds with electron withdrawing groups such as chloro and nitro showed less activity in the series.

Antioxidant activity

Interaction with stable free radical DPPH: Compounds **7** and **16** showed significant antioxidant activity. Compounds **8** and **17** showed good antioxidant activity which is comparable to α-tocopherol. These results agree with earlier work indicating that the antioxidant efficiency of monophenols is strongly enhanced by the introduction of one or two methoxy substitutions in position *ortho* to the phenolic group[12].

Inhibition of lipid peroxidation: Compounds **4**, **5**, **7**, **12**, **13**, **15** and **16** exhibited significant activity. The compounds **8** and **17** showed activity which is comparable to α-tocopherol.

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