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Synthesis of 3,4-Dihydropyrimidine-2(1H)-one Derivatives using Microwave for their Biological screening

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Abstract: Eight new 4-Substitutedaryl-6-methyl-2-pyrimidinone-5 - (N-p-tosyl) Carbohydrazides (**c1-8**) have been synthesized in a three step reaction. In first step 5-(Ethoxycarbonyl)-6-methyl-4-substitutedaryl-3,4-dihydropyrimidin-2(1H)-ones obtained (**a1-8**) and in second step 4-Substitutedaryl-6-methyl-2-pyrimidinone-5-Carbohydrazides (**b1-8**). Third step involves synthesis of 4-Substitutedaryl-6-methyl-2-pyrimidinone-5-(N-p-tosyl) Carbohydrazides (**c1-8**). Their structures are confirmed by IR, ^{1}H- NMR, C^{13}NMR and Mass. The compounds were tested for antihypertensive activity by non-invasive tail-cuff, and evaluated by carotid artery cannulation method for determining the diastolic blood pressure. Hypertension was induced by DOCA-salt. Anti-inflammatory activity was carried out by carrageenan induced rat-paw oedema method. Test compounds **c1-8** exerted comparative anti-hypertensive activity at 10 mg/kg dose level compared to nifedipine. Compounds **c2**, **c4** and **c8** showed excellent results on evaluation by direct method. Test compounds **c3, c4** and **c7** exerted moderate to comparative anti-inflammatory activity at the 100 mg/kg dose level compared to indomethacin. Their further investigation for analgesic activity and acute ulcerogenesis was carried out, compounds **c2, c5** and **c8** showed excellent to good analgesic activity and low ulcerogenic activity.

Keywords: DOCA-salt hypertension; Non-invasive tail-cuff method; Carotid artery cannulation; Antihypertensive activity; Anti-inflammatory activity; Analgesic activity; Ulcerogenic activity, nifedipine, Schiff base.

Introduction[1-10]

Similar groups/structures often exhibit similar biological activities. However, they usually exhibit different potency. The traditional structure activity relationship (SAR) is a useful tool in the search for new drugs. However, SAR is usually determined by making minor changes to the structure of the existing compound and assessing the effect on its biological activity. Similarly, structural analogy has played vital role in designing compounds with higher potency. One of such structural analogy is seen between 4-aryl-1,4-dihydropyridines (DHPs) of the nifedipine type and dihydropyrimidines (DHPMs).In 1893 Italian chemist Pietro Biginelli reported on the acid-catalyzed cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea. The reaction was carried out simply by heating a mixture of three components dissolved in ethanol with a catalytic amount of hydrochloric acid at reflux temperature. The product of this novel one pot, tree-component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3, 4-dihydropyrimidine-2(1H)-one.

The synthetic potential of this new heterocyclic synthesis remained unexplored for quite some time. In the 1970s and 1980s interest slowly increased, and the scope of the original cyclocondensation reaction was gradually extended by variation of all three building blocks, allowing access to a large number of multifunctionalized dihydropyrimidines.

In the past decades, a broad range of biological effects, including antiviral , anti tumor, antibacterial and anti-inflammatory activities has been ascribed to these partly reduced pyrimidine derivatives. More recently, DHPMs have emerged as, for e.g., orally active antihypertensive agents. A very recent highlight in this context been the identification of the structurally rather simple DHPM monastrol as a mitotic kinesin motor protein inhibitor and potential new lead for the development of anticancer drugs. Appropriately functionalized DHPM derivatives have emerged as potent calcium channel modulators. Apart from synthetic DHPM derivatives several marine natural products with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have recently been isolated. Most among these are the batzelladine alkaloids A and B which inhibit the binding of HIV envelop protein gp-120 to human CD4 cells and therefore, are potential new leads for AIDs therapy.

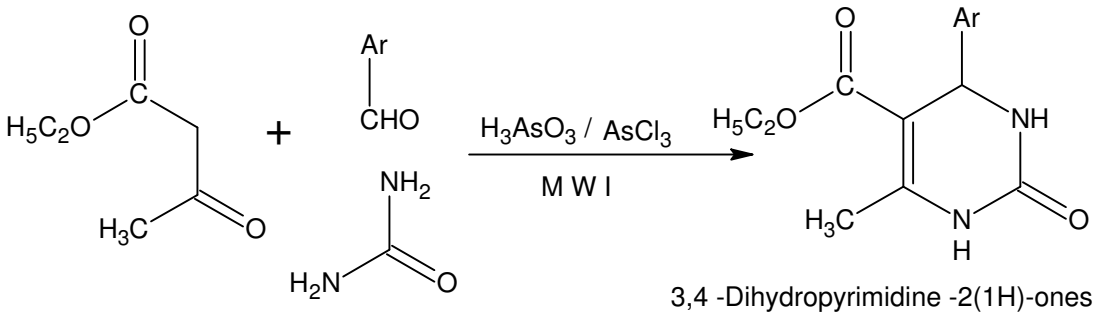
2. Materials and Methods

Melting points were determined in a DBK programmed melting point apparatus and are uncorrected. The TLC of the compounds was performed on silica gel

G coated glass plate with the solvent systems used as: **(a)**Ethylacetate:Toluene (6:4), **(b)** Chloroform:Methanol (8:2), **(c)** Ethylacetate: Chloroform (6:4); **(d)** Benzene : Chlroroform : methanol (6:3:1). The absorbance maxima (λmax) and absorbance of synthesized compounds was found in methnol Shimadzu 1700 UV-Visible pectrophotometer. Infrared absorption spectra of synthesized compounds were obtained by preparing KBr pellet, using Schimdzu-3200 FTIR Spectrophotometer. 1HNMR studies on Schimadzu FTNMR spectrophotometer, 300MHz. and Bruker DRX-300 (300 MHz FT NMR) using $CDCl_3$ and DMSO and Mass spectra were recorded on Joel SX-120 mass spectrophotometer.

3. Chemistry:-

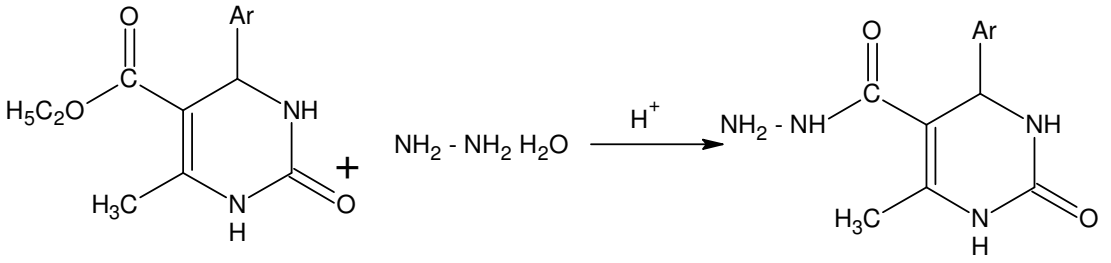
3.1.1. Schemes



3,4 -Dihydropyrimidine -2(1H)-ones

a

Scheme-I

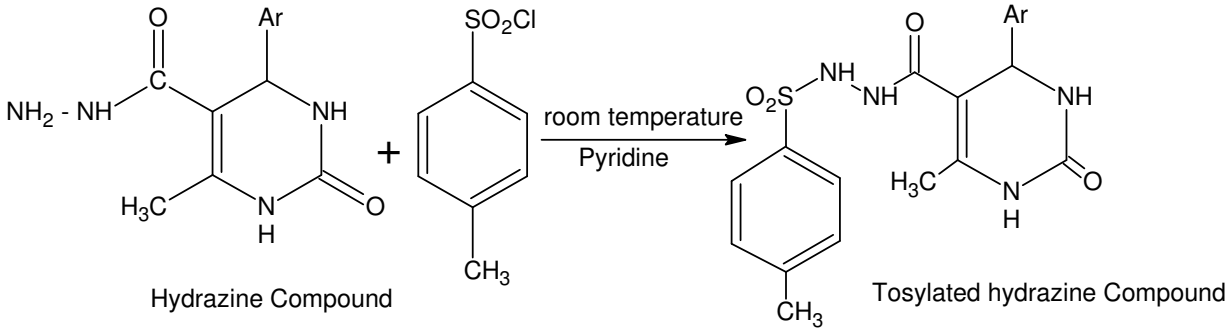


3,4 -Dihydropyrimidine -2(1H)-ones

Hydrazine Compound

b

Scheme-II



Hydrazine Compound

Tosylated hydrazine Compound

c

Scheme – III

3.2. Chemistry[11-28]

3.2.1. Synthesis of 5-(Ethoxycarbonyl)-6-methyl-4-substitutedaryl-3,4-dihydropyrimidin-2(1H)-ones (a1-8); following scheme I

Preparation of Arsenious acid solution

(2g) sodium hydroxide + 4-5ml of water & alcohol (20ml) + 0.7g of Arsenic trioxide + two drops of phenopthalein → Conc.HCl → Pink color disappears (Neutral/Acidic solution)

General procedure :

In the first step three component reaction involving ethylacetoacetate, urea and substituted benzaldehydes reacted in presence of ethanol and arsenious acid solution to form the substituted ring nucleus compounds (**a1-8**). Mixture subjected to stirring for specified hours as given in Table.

3.2.1.1. 5-(Ethoxy Carbonyl)-6-methyl-4-(4-dimethylaminophenyl)-3,4-dihydropyrimidin-2(1H)-one (**a2**).

Yield: 84 %, m.p. 256-258 ^{o}C. R_f : 0.60 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 280 (8506). IR (KBr) ν = 784 (-Ar), 1091-1168 (C-O-C), 1220-(N-(CH3)2), 1525-1720 (– double bond region), 1525-1620 (– C=O), 1649 (– C=O), 1699 (–C=O chain), 2977-3242 (–N-H). ^{1}H-NMR ($CDCl_3$) δ 7.1-7.3 (m,4H, arom.), 6.9-6.7 (dd, 2H, -NH), 5.35 (d, 1H,-CH), 3.9 (q, 2H, OCH2), 2.35 (s, 3H, -OC-CH3), 1.55 (s, 6H,-N(CH3)2), 1.2 (t,3H,-CH3CH2O).
ESMS: m/z (MH^+) 303.
m/z : 303 (M+); 272 (M-CO) +, 253; 183; 120 (-C8H10N); 43 (100%).
Anal. ($C_{16}H_{21}O_3N_3$) C,H,N.

3.2.1.2. 5-(Ethoxy Carbonyl)-6-methyl-4-(4-hydroxy,3-methoxyphenyl-3,4- dihydro pyrimidin-2(1H)-one (**a3**).

Yield: 81 %, m.p. 235-238 ^{o}C. R_f : 0.53 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 282 (12410). IR (KBr) ν = 781-800 (– Ar), 1093-1124 (–C-O-C), 1222 (–acetate (C=O) ester), 1222-1275 (–OCH3), 1515-1697 (– double bond region), 1697 (–C=O), 2975 (–N-H), 3244 (-OH). ^{1}H-NMR ($CDCl_3$) δ 7.25 (m,2H,arom.), 6.85 (m,1H, arom.), 6.73 (Br,2H,-NH), 5.30 (s,1H,-CH), 4 (q,2H,-OCH2CH3), 2.92 (s,3H,OCH3), 2.34 (s,1H,-OH), 1.56 (BrS, EtOH).
ESMS: m/z (MH^+) 306.
m/z : 306 (M+); 278 (M-CO) +; 199; 107 (-C7H7O); 43 (100%).
Anal. ($C_{15}H_{18}O_5N_2$) C,H,N.

3.2.1.3. 5-(Ethoxycarbonyl)-6-methyl-4-(2-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one(**a5**).

Yield: 83.60 %, m.p. 217-220 ^{o}C. R_f : 0.42 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 269 (9150). IR (KBr) ν = 784 (– Ar ring), 1093 – 1137 (– C-O-C), 1521 (–NO2), 1566-1606 (–C=C), 1647 (–C=O), 1699 (–C=O), 3130 (–Ar), 3244 – 3296 (–N-H). ^{1}H-NMR ($CDCl_3$) δ 7.8-7.9 (m, 4H, arom.), 7.4-7.5 (m, 2H, arom.), 6.0 (s,1H, -NH), 5.8 (s,1H,-OH), 3.8-4.0 (d,5H, -C=O-OC2H5), 2.4-2.5 (d, 2H, OCH2), 2.1(s,3H,-C=C-CH3), 1.5 (s,1H, -NH), 0.5-0.6 (s,3H,-CH3).
ESMS: m/z (MH^+) 305.
m/z : 305 (M+); 277 (M-CO) +;260; 122 (-C6H4O2N); 43(100%).
Anal. ($C_{14}H_{16}N_3O_5$) C,H,N.

3.2.1.4. 5-(Ethoxycarbonyl)-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one(**a7**).

Yield: 84.42 %, m.p. 198-201 ^{o}C. R_f : 0.43 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 282.5 (12064). IR (KBr) ν = 781-790 (–Ar), 1089 –1176 (–C-O-C), 1224 (–OCH3), 1504–1614 (–C=C), 1681 (–C=O), 1704 (–C=O), 2956–3242 (-N-H). ^{1}H-NMR ($CDCl_3$) δ 9.14 (s,1H), 7.66(s,1H), 7.14 (d,J=8.4HZ,2H), 6.86 (d,J=8.4HZ,2H), 5.08(d,J=2.8HZ,1H), 3.97 (q,J=7.2HZ,2H), 3.71(s,3H), 2.23(s,3H), 1.09(t,J=7.2HZ,3H).
m/z : 290 (M+); 262 (M-CO) +; 212; 107 (C7H7O); 43 (100%)
ESMS: m/z (MH^+) 274.
Anal. ($C_{15}H_{18}O_4N_2$) C,H,N.

3.2.1.5. 5-(Ethoxycarbonyl)-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-one(**a8**).

Yield: 81.66 %, m.p. 226-229 ^{o}C. R_f : 0.63 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 280 (9450). IR (KBr) ν = 750-827 (–Ar), 1230 (–acetate(C=O) stretch), 1681 (-C=O), 1506 –1614 (– C=C), 1714 (–C-H), 3232 (–N-H), 3274 – (OH). ^{1}H-NMR ($CDCl_3$) δ 9.32 (s,1H), 9.11(s,1H), 7.61(s,1H), 7.02 (d,J=8.4HZ,2H), 6.69 (d,J=8.4HZ,2H), 5.04 (d,J=3.2HZ,1H), 3.97 (q,J=7.2HZ,2H), 2.23 (s,3H), 1.08(t,J=7.2HZ,3H).
ESMS: m/z (MH^+) 275.
m/z : 275 (M+); 247 (M-CO) +; 198; 93 (-C6H5O); 43 (100%).
Anal. ($C_{14}H_{15}O_4N_2$) C,H,N.

3.2.1.6. 5-(Ethoxycarbonyl)-6-methyl-4-(3,4-dimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one(**a9**).

Yield: 78 %, m.p. 175-178 ^{o}C. R_f : 0.55 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 282 (9123). IR (KBr) ν = 781-790 (–Ar), 1095-1139 (–C-O-C), 1234-

1278 (-OCH3), 1234 (–acetate (C=O) stretch), 1506-1681 (–double bond region), 1681 (–C=O), 3114-3247 (– N-H). ^{1}H-NMR ($CDCl_3$) δ 8.33 (br,s,1H), 5.90 (br,s,1H), 6.75-6.90 (m,3H), 5.38 (d,J=3.0HZ,1H), 3.85 (s,6H), 4.09 (q,J=7.5HZ,2H), 2.32 (s,3H), 1.17 (t,7.5HZ,3H).
ESMS: m/z (MH^+) 320.
m/z : 320 (M+); 292 (M-CO) +; 243; 137 (-C8H9O2); 43 (100%).
Anal. ($C_{16}H_{20}O_5N_2$) C,H,N.

3.2.1.7. 5-(Ethoxycarbonyl)-6-methyl-4-(Ethenylphenyl)-3,4-dihydropyrimidin-2(1H)-one(**a10**)

Yield: 86 %, m.p. 224-226 ^oC. R_f : 0.65 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 258.5 (9856). IR (KBr) ν = 742-756 (–aromatic), 1066 (– C-O-C), 1519-1900 (– double bond region), 1650 (–C=O), 1697 (–C=C), 3087 & 3232 (–N-H). ^{1}H-NMR ($CDCl_3$) δ 9.13 (s,1H,NH), 7.53 (d,J=1.9HZ,1H,NH), 7.21-7.46 (m,5H,arom.), 6.37 (d,J=15.9Hz,1H,H-C=CH), 6.20 dd,J=15.86HZ, 1H, CH=CH), 4.74 (d,J=5.80HZ, 1H, CH), 4.09 (m,2H,-OCH2), 2.21 (s,3H,CH3), 1.20 (t, J=7.0HZ, 3H, -CH3).
ESMS: m/z (MH^+) 286.
m/z: 286 (M+); 258 (M-CO) +; 209; 103 (C8H7); 43 (100%).
Anal. ($C_{16}H_{18}O_3N_2$) C,H,N.

3.2.1.8. 5-(Ethoxycarbonyl)-6-methyl-4-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one(**a11**).

Yield: 80 %, m.p. 161-163 ^oC. R_f : 0.63 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 281 (9415). IR (KBr) ν = 783-804 (-Ar), 1095-1134 (–C-O-C), 1224 (–acetate (C=O) stretch), 1504 – 1693 (–double bond region), 1681 (–C=O), 1650 (–C=C), 2954 & 3328 (–N-H). ^{1}H-NMR ($CDCl_3$) δ 8.32 (s, 1H, N_1-H), 8.15 (d, J = 7.9 Hz, 1H, aromatic), 8.11 (s, 1H, aromatic), 7.64 (d, J =7.9 Hz, 1H, aromatic), 7.51 (t, J = 7.9 Hz, 1H, aromatic), 7.32 (m, 5H, aromatic), 5.98, 4.18 (d, J = 5.29 Hz, 2H, benzylic), 6.00 (s, 1H, methine), 4.19 (m, 2H, ethyl ester), 2.39 (s, 3H, methyl) and 1.40-1.70 (d, J = 7.38 Hz, 2H, ethyl ester). ESMS: m/z (MH^+) 350.
Anal. ($C_{17}H_{22}O_6N_2$) C,H,N.

3.2.2. Synthesis of 4-Substitutedaryl-6-methyl-2-pyrimidinone-5-Carbohydrazides (b1-8); following scheme II

General Procedure:
On reaction of DHPM compounds **(a1-8)** with Hydrazine hydrate, to form their respective 4-Substitutedaryl-6-methyl-2-pyrimidinone-5-Carbohydrazides derivatives **(b1-8)**. Mixture subjected to MWI for specified minutes as given in Table.

3.2.2.1. 4-(4-dimethylaminophenyl)-6-methyl-2-pyrimidinone-5-carbohydrazide (**b1**).

Yield: 75 %, m.p. 239-242 ^oC. R_f : 0.46 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 246 (13183). IR (KBr) ν = 784 (–aromatic), 1226 (–N(CH3)2), 1525 –1710 (– double bond region), 1556(–amide), 1647(–NH2), 1710 (–C=O), 2987 (–NH-NH2), 3112 (–aromatic), 3240 (–NH). ^{1}H-NMR ($CDCl_3$) δ 8.5 (S,4H,arom.), 7.6-7.7 (dd.2H,arom.), 7.1-7.2 (t,2H,-NH-NH2), 6.6-6.7 (m,1H,-NH), 5.1-5.3 (d,1H-CH), 3.0 (d,1H,NH2), 2.33 (s,3H, -C=C-CH3), 1.5 (s,6H,-N(CH3).
Anal. ($C_{14}H_{19}O_2N_5$) C,H,N.

3.2.2.2. 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-pyrimidinone-5-carbohydrazide (**b2**).

Yield: 78 %, m.p. 230-232 ^oC. R_f : 0.65 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 283.5 (11806). IR (KBr) ν = 790 (–aromatic), 1222-1276 (–OCH3), 1515 –1701 (–double bond region), 1645 (–C=O), 1701 (–NH2), 2983 (–NH-NH2), 3004 (–aromatic), 3112 (–N-H). ^{1}H-NMR ($CDCl_3$) δ 7.1-7.3 (m,4H,arm.), 6.9 (m,4H,arom.), 5.59 (br,1H,-NH), 5.35 (Br,2H-NH2), 2.92 (s,3H,OCH3), 2.34 (s,1H,-OH), 1.56 (Br,s,-C2H5OH), 0.89 (t,3H,-CH3).
Anal. ($C_{13}H_{16}O_4N_4$) C,H,N.

3.2.2.3. 4-(2-nitrophenyl)-6-methyl-2-pyrimidinone-5-carbohydrazide (**b3**).

Yield: 77 %, m.p. 234-238 ^oC. R_f : 0.72 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 271.5 (10844). IR (KBr) ν = 784-804 (–aromatic), 1093-1224 (–NH-C=O), 1492 (-C=C), 1523 (–NO2), 1645 (–NH2), 1697 (– C=O), 1712 (–C=O), 2989 (–NH-NH2), 3124 (–aromatic), 3236 & 3367 (–N-H). ^{1}H-NMR ($CDCl_3$) δ 7.6 (s,4H,arom.), 7.4 (s,4H,arom.), 6.7-6.8 (t,1H,-NH-NH2), 6.4 (s,1H,-NH), 5.2 (s,1H,-CH), 4.0-4.1 (s,2H,-NH-NH2), 2.7 (s,3H,-C=C-CH3), 2.3 (s,1H,-NH), 1.15-1.2 (m,3H,-CH3).
Anal. ($C_{12}H_{13}O_4N_5$) C,H,N.

3.2.2.4. 4-(4-metoxyphenyl)-6-methyl-2-pyrimidinone-5-carbohydrazide (**b4**).

Yield: 78 %, m.p. 167-170 ^oC. R_f : 0.55 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 281.5 (6513.5). IR (KBr) ν = 790 (–aromatic), 1026-1095 (–C=O-NH), 1236 (–OCH3), 1519 (–C=C), 1593 (–amide), 1650 (-NH2), 1681 (–C=O), 1703 (–C=O), 2954 (–NH-NH2), 3116 (– aromatic), 3251 (– NH). ^{1}H-NMR ($CDCl_3$) δ 7.2 (s,2H,arom.), 6.8 (m,4H,arom.), 5.6 (s,1H,-NH), 5.3 (d,1H,-CH), 4.0-4.1 (s,1H,-NH-C=O), 2.3 (s,3H,-OCH3), 1.1 (t,3H,-CH3).
Anal. ($C_{13}H_{16}O_3N_4$) C,H,N.

3.2.2.5. 4-(4-hydroxyphenyl)-6-methyl-2-pyrimidinone-5-carbohydrazide (**b5**).

Yield: 76 %, m.p. 178-181 ^{o}C. R_f : 0.45 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 282 (10936). IR (KBr) ν = 781-796 (–aromatic), 1095–1126 (–NH-C=O), 1504 –1589 (– C=C), 1589 (–amide), 1650 (–NH2), 1704 (– C=O), 2975 (– NH-NH2), 3004 (–aromatic), 3099 (–N-H), 3226 (–OH). ^{1}H-NMR ($CDCl_3$) δ 9.32 (s,1H), 9.11(s,1H), 7.61 (s,1H), 7.02 (d,J=8.4HZ,2H), 5.04 (d,J=3.2HZ,1H), 3.97 (q,J=7.2HZ,2H), 2.23 (s,3H), 1.08 (t,J=7.2HZ, 3H).
Anal. ($C_{12}H_{14}O_3N_4$) C,H,N.

3.2.2.6. 4-(3,4-dimethoxyphenyl)-6-methyl-2-pyrimidinone-5-carbohydrazide (**b6**).

Yield: 70 %, m.p. 200-203 ^{o}C. R_f : 0.60 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 283 (10455). IR (KBr) ν = 779-790 (–aromatic), 1234 (–OCH3), 1519-1716 (–double bond reg., 1595 (–amide), 1650 (–NH2),1681 (–C=O), 1716 (–C=O), 3093 (–aromatic), 3112 (–NH-NH2), 3247 (–N-H). ^{1}H-NMR ($CDCl_3$) δ 8.33 (brs 1H), 5.90 (brs,1H), 6.75-6.90 (m,3H), 5.38 (d,J=3.0HZ,1H), 3.85 (s,6H), 4.09 (q,J=7.5HZ,2H), 2.32 (s, 3H), 1.17 (t, 7.5HZ,3H).
Anal. ($C_{14}H_{18}O_4N_4$) C,H,N.

3.2.2.7. 4-(Ethenylphenyl)-6-methyl-2-pyrimidinone-5-carbohydrazide (**b7**).

Yield: 73 %, m.p. 139-141 ^{o}C. R_f : 0.52 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 256.5 (20930). IR (KBr) ν = 779 (–aromatic), 1596 (–amide), 1650 (–C=O), 1703 (–C=C), 1722 (–C=O), 3029 (–aromatic), 3110 (–NH-NH2), 3244 (–NH). ^{1}H-NMR ($CDCl_3$) δ 7.1-7.2 (m,4H, arom.), 6.8 (t, 1H, -NH-NH2), 6.4 (s,1H,-NH), 5.3 (s,1H,-CH), 4.2 (s, 2H, -NH-NH2), 2.7 (s, 3H, - NH), 1.2 (m,3H,-CH3).
Anal. ($C_{14}H_{14}O_2N_4$) C,H,N.

3.2.2.8. 4-(3,4,5-trimethoxyphenyl)-6-methyl-2-pyrimidinone-5-carbohydrazide (**b8**).

Yield: 76 %, m.p. 229-231 ^{o}C. R_f : 0.46 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 279.5 (15736). IR (KBr) ν = 754 – 827 – Aromatic ring; 1228 – 1257 – Aryl ethers (OCH3); 1514 – ring C=C; 1645 (–NH2 deformation), 1681 (– C=O ring), 1693 – C=O side chain; 3112 – Aromatic ring; 3224-3242 – NH-NH2; 3280 – NH ring. ^{1}H-NMR ($CDCl_3$) δ 9.2 (s,1H), 8.3 (s,1H), 6.95 (m,3H), 5.8 (d,1H), 4.3 (s,1H,-NH-C=O), 2.3(s,3H,OCH3), 1.1(t,3H,-CH3).
Anal. ($C_{15}H_{20}O_5N_4$) C,H,N.

3.2.3. Synthesis of 4-Substitutedaryl-6-methyl-2-pyrimidinone-5-(N-p-tosyl) Carbohydrazides (c1-8); following scheme III

General Procedure:

To a hydrazine compounds **(b1-8)** (5 mmol) p-toluene sulphonyl chloride(5 mmol) was added in presence of alcohol and pyridine (6 mmol). Formation of tosylated hydrazine compounds **(c1-8)** takes place. Mixture subjected to MWI for specified minutes as given in Table.

3.2.3.1. 4-(4-dimethylaminophenyl)-6-methyl-2-pyrimidinone-5-(N-p-tosyl) carbohydrazide (**c1**).

Yield: 76 %, m.p. 229-231 ^{o}C. R_f : 0.46 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 279.5 (15736). IR (KBr) ν = 772-803 (-aromatic), 1053-1086 (-NH-C=O), 1259-1303 (- S=O stretch), 1520 (-C=O), 1670 (-C=O), 2983 (-N-H), 3104-NH). ^{1}H-NMR ($CDCl_3$) δ 7.2 (s,3H,arom.), 7.1 (d,1H,arom.), 6.6 (d,1H,-NH), 5.2-5.3 (d,1H,-CH), 4.0 (q,1H,-NH), 3.6 (s,1H,-NH-C=O), 2.3 (s,6H,-N(CH3)2, 1.1 (t,3H,-CH3). ^{13}C-NMR (δ): 172-(-C7-O-O-C2H5); 155 (C2=O); 152-(-C5-CO-Oet); 140 (C6-CH3); 132-135 (CH-arm); 102 (C1arm.); 66 (-C8H2); 55.5 (-C4H); 21.66 (-C9H3); 16.6 (-CH3).
ESMS: m/z (MH^+) 369.
Anal. ($C_{15}H_{20}O_5N_4$) C,H,N.

3.2.3.2. 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-pyrimidinone-5-(N-p-tosyl) carbohydrazide(**c2**).

Yield: 76 %, m.p. 229-231 ^{o}C. R_f : 0.46 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 279.5 (15736). IR (KBr) ν = 720-850 (-aromatic), ring; 1082-NH-C=O; 1140-1320 –S=O; 1235-Aryl ethers; 1670 –C=O; 2930 – NH-NH2; 3112-3230-NH-ring. ^{1}H-NMR ($CDCl_3$) δ 7.2 (s,3H,arom.), 6.8 (d,3H,arom.), 5.5 (s,1H,-NH), 5.3 (b,1H,-CH), 3.8 (d,1H,-NH), 3.6 (s,1H,-NH-C=O), 2.3 (bs,1H,-OH), 1.2 (m,3H,-CH3). ^{13}C-NMR (δ): 177-(-C7-O-O-C2H5); 158 (C2=O); 151-(-C5-CO-Oet); 146 (C6-CH3); 129-132 (CH-arm); 101 (C1arm.); 63 (-C8H2); 56.4 (-C4H); 23.33 (-C9H3); 16.2 (-CH3).
ESMS: m/z (MH^+) 371.
Anal. ($C_{15}H_{20}O_5N_4$) C,H,N.

3.2.3.3. 4-(2-nitrophenyl)-6-methyl-2-pyrimidinone-5-(N-p-tosyl) carbohydrazide (**c3**).

Yield: 76 %, m.p. 229-231 ^{o}C. R_f : 0.46 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 279.5 (15736). IR (KBr) ν = 750-790 (-aromatic), 1062 –1123 (-NH-C=O), 1179-1320-(S=O), 1675 (-C=O), 2900 (-NH-NH2), 3117-3260 (-NH). ^{1}H-NMR ($CDCl_3$) δ 7.8 (d,3H,arom.), 7.4-7.6 (m,4H,arom.), 7.2 (s,1H,-NH), 6.4 (B,1H,-NH), 5.7-5.8 (Bs,1H,-CH), 3.9 (s,1H,-NH-C=O), 2.4 (s,2H,-CH=CH-), 0.96 (m,3H,-CH3). ^{13}C-NMR (δ):

170-(-C7-O-O-C2H5); 156 (C2=O); 152-(-C5-CO-Oet); 149 (C6-CH3); 130-133 (CH-arm); 104 (C1arm.); 64 (-C8H2); 58.5 (-C4H); 22.36 (-C9H3); 18.6 (-CH3).
ESMS: m/z (MH^+) 370.
Anal. ($C_{15}H_{20}O_5N_4$) C,H,N.

3.2.3.4. 4-(4-metoxyphenyl)-6-methyl-2-pyrimidinone-5-(N-p-tosyl) carbohydrazide (**c4**).

Yield: 76 %, m.p. 229-231 ^oC. R_f : 0.46 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 279.5 (15736). IR (KBr) ν = 779-790 (–aromatic), 1026–1093 (-NH-C=), 1139 & 1323 (– S=O), 1236 (–OCH3), 1519 (–C=O), 1681 (–C=O), 1708 (– C=O), 2954 (–NH-NH2), 3093 (–aromatic), 3112–3249 (–N-H). ^{1}H-NMR ($CDCl_3$) δ 8.2 (s,3H,arom.), 7.1 (d,1H,arom.), 6.8 (s,1H,-NH), 6.4 (B,1H,-NH), 5.3 (s,1H,-NH), 3.9 (s,1H,-NH-C=O), 2.3 (s,3H,-OCH3), 1.2 (t,3H,-CH3). ^{13}C-NMR (δ): 173-(-C7-O-O-C2H5); 158 (C2=O); 153-(-C5-CO-Oet); 144 (C6-CH3); 133-136 (CH-arm); 103 (C1arm.); 61 (-C8H2); 57.5 (-C4H); 22.36 (-C9H3); 17.5 (-CH3).
ESMS: m/z (MH^+) 353.
Anal. ($C_{15}H_{20}O_5N_4$) C,H,N.

3.2.3.5. 4-(4-hydroxyphenyl)-6-methyl-2-pyrimidinone-5-(N-p-tosyl) carbohydrazide (**c5**).

Yield: 76 %, m.p. 229-231 ^oC. R_f : 0.46 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 279.5 (15736). IR (KBr) ν = 1018 – 1037 (–NH-C=O), 1062–1134 (– SO2 sym.stret.), 1504 (–C=N), 1640 (–C=O), 2991 (–N-H), 3008–3045(– aromatic), 3076–3085 (–N-H), 3120-3310 (-OH). ^{1}H-NMR ($CDCl_3$) δ 7.2 (s,3H, arm.), 7.1 (m,5H,arom.), 5.3 (s,1H,-NH), 4.2 (d,1H,-NH), 3.6 (s,1H,-NH-C=O), 2.3 (s, 6H, -N(CH3)2, 1.1 (t,3H,-CH3). ^{13}C-NMR (δ): 176-(-C7-O-O-C2H5); 152 (C2=O); 150-(-C5-CO-Oet); 146 (C6-CH3); 129-133 (CH-arm); 100 (C1arm.); 61 (-C8H2); 54.3 (-C4H); 20.24 (-C9H3); 16.8 (-CH3).
ESMS: m/z (MH^+) 340.
Anal. ($C_{15}H_{20}O_5N_4$) C,H,N.

3.2.3.6. 4-(3,4-dimethoxyphenyl)-6-methyl-2-pyrimidinone-5-(N-p-tosyl) carbohydrazide (**c6**).

Yield: 76 %, m.p. 229-231 ^oC. R_f : 0.46 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 279.5 (15736). IR (KBr) ν = 781 – 790 (–aromatic), 1085 (–NH-C=O), 1178–1332 (–S=O), 1220-1278 (–OCH3), 1514 (–C=C), 1612 (–amide), 1643 (–NH2), 1703 (–C=O), 1726 (–C=O), 3105 (–aromatic), 3172-3240 (–N-H). ^{1}H-NMR ($CDCl_3$) δ 7.2 (s,3H,aromat.), 6.8 (m,3H,aromatic), 5.8 (s,1H,-NH), 5.3 (s,1H,-CH), 4.0 (q,1H,-NH), 3.6 (s,1H,NH-C=O), 2.3 (s,1H,-OCH3), 1.18 (t,3H,-CH3). ^{13}C-NMR (δ): 176-(-C7-O-O-C2H5); 155 (C2=O); 153-(-C5-CO-Oet); 150 (C6-CH3); 131-134 (CH-arm); 105 (C1arm.); 65 (-C8H2); 59.1 (-C4H); 23.22 (-C9H3); 17.2 (-CH3).
ESMS: m/z (MH^+) 384.
Anal. ($C_{15}H_{20}O_5N_4$) C,H,N.

3.2.3.7. 4-(Ethenylphenyl)-6-methyl-2-pyrimidinone-5-carbohydrazide (**c7**).

Yield: 76 %, m.p. 229-231 ^oC. R_f : 0.46 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 279.5 (15736). IR (KBr) ν = 756 – 779 (-aromatic), 1091 (–NH-C=O), 1170-1336 (–S=O), 1643 (–amide), 1693 (–C=O), 1712 (–C=O), 3029 (–aromatic ring), 2977 & 3242 (–N-H), 3110 (–N-H). ^{1}H-NMR ($CDCl_3$) δ 7.2 (s,3H,aromatic), 6.5 (m,5H,aromatic), 6.4 (m,2H,aroma.), 5.3 (s,1H,-NH), 4.9 (s,1H,-CH), 3.7 (s,1H,-NH-C=O), 1.5 (s,2H,-CH=CH-), 1.2 (t,3H,-CH3). ^{13}C-NMR (δ): 176-(-C7-O-O-C2H5); 158 (C2=O); 151-(-C5-CO-Oet); 146 (C6-CH3); 128-131 (CH-arm); 105 (C1arm.); 63 (-C8H2); 57.8 (-C4H); 23.71 (-C9H3); 16.2 (-CH3).
ESMS: m/z (MH^+) 350.
Anal. ($C_{15}H_{20}O_5N_4$) C,H,N.

3.2.3.8. 4-(3,4,5-trimethoxyphenyl)-6-methyl-2-pyrimidinone-5-carbohydrazide (**c8**).

Yield: 76 %, m.p. 229-231 ^oC. R_f : 0.46 (Ethylacetate:Toluene, 6:4). λ max, (ε max): 279.5 (15736). IR (KBr) ν = 783-802 (–aromatic), 1095-1132 (–NH-C=O), 1132 & 1315 (–S=O), 1224-1292 (–OCH3), 1504-1593 (–C=C), 1593 (–amide), 1693 (–C=O), 2952 (–N-H), 3107 (–aromatic), 3213 & 3320 (–N-H). ^{1}H-NMR ($CDCl_3$) δ 8.2 (s,3H,arom.), 7.2 (s,5H,arom.), 6.5 (s,2H,arom.), 5.8 (s,1H,-NH), 5.3 (s,1H,-CH), 3.6 (s,1H,-NH-C=O), 2.3 (s,3H,-OCH3), 1.2 (t,3H,-CH3). ^{13}C-NMR (δ): 173-(-C7-O-O-C2H5); 156 (C2=O); 152-(-C5-CO-Oet); 145 (C6-CH3); 130-133 (CH-arm); 104 (C1arm.); 66 (-C8H2); 56.5 (-C4H); 23.44 (-C9H3); 16.2 (-CH3).
ESMS: m/z (MH^+) 413.

Table1: MWI reaction time:

Scheme- I		Scheme- II		Scheme- III	
Compound	MWI (min)	Compound	MWI (min)	Compound	MWI (min)
a1	6	b1	13	c1	5
a2	5	b2	7	c2	6
a3	8	b3	7	c3	6
a4	6	b4	7	c4	5
a5	9	b5	5	c5	6
a6	6	b6	10	c6	7
a7	5	b7	7	c7	6
a8	8	b8	5	c8	5
a9	7				
a10	5				
a11	7				
a12	5				
a13	8				

4. Pharmacology[29-46]

4.1. Anti-hypertensive activity

Non-invasive tail-cuff method

The newly synthesized compounds were subjected for antihypertensive activity studies. Norwegian strain of inbreed albino rats (male) weighing 200-250 g, were used in experiment. Nifedipine was used as standard drug. All rats were housed in a temperature and humidity controlled room with 12-hour light/dark cycle. All rats were allowed free access to regular food and tap water. The drinking water was replaced by 1% w/v sodium chloride aqueous solution for rats used in DOCA experiments. All experimental work was carried out in accordance with the guidelines provided by the Committee for the Purpose of Control and Supervision of Experiments in Animal (CPCSEA), India.

DOCA-salt hypertension

Rats were anesthetized by injecting pentobarbital injection administered intraperitonialy in a dose of 50 mg/kg body wt. It was placed on a heated surgical surface maintained at 37 ^{o}C. A flank incision was made to expose the left kidney, which was ligated and removed. This procedure of removing either of the kidneys is called as uninephrectomy. The incision was sutured. One week after uninephrectomy, rats were administered subcutaneously with injection of DOCA (30-50 mg/kg/week) and drinking water was replaced by 1% w/v sodium chloride aqueous solution. Control group of rats were uninephrectomized, injection of DOCA-salt was not administered to them and received vehicle injections and tap water.

Antihypertensive activity carried out by the non-invasive method gave the systolic blood pressure (SBP), from which the observations are summarized in the Table . For structure activity studies we choose the aromatic substitutions that are commonly employed in dihydorpyridines. Methoxy derivative **c2, c4, c5** and **b2, b4, b7, b8** has remarkable antihypertensive activity and **b2, b4, b7, b8** moderate activity than others. Data are presented as means ± S.E.M. a repeated measures analysis of variance was use to obtain the statistical significance between and within groups. Differences were considered statistically significant at a P level lower than 0.05 and F value for all compounds are F: 22.33±0.5. Their results for percentage inhibition are as shown in Fig. 1 and table 3 respectively.

Table 2: Anti-hypertensive activity data

Compound (10mg/kg)	Average Systolic Blood Pressure (mm Hg) at time (min.)										
	0	15	30	60	120	180	240	300	360	400	460
b1	225±4	222±8	221±9	195±2	180±4	175±8	172±6	165±4	160±6	158±3	155±3
b2	226±8	224±5	210±5	193±4	178±5	161±4	142±4	138±6	131±7	125±5	122±8
b3	226±8	224±5	210±5	193±4	178±5	161±4	142±4	138±6	131±7	125±5	122±8
b4	225±4	222±8	220±9	190±2	178±4	172±8	167±6	160±4	158±6	152±3	145±3
b5	225±6	223±5	210±6	195±8	180±5	160±8	145±3	140±6	135±7	125±5	125±7
b6	226±3	224±6	210±3	193±5	178±7	161±2	142±5	134±6	130±7	125±5	121±8
b7	224±4	222±8	220±9	190±2	175±4	172±8	162±6	160±4	154±6	150±3	145±3
b8	226±2	224±3	210±8	190±4	172±5	160±4	142±4	135±6	130±7	125±5	122±8
c1	225±4	222±8	221±9	195±2	180±4	175±8	172±6	165±4	160±6	158±3	155±3
c2	226±4	222±8	220±9	193±2	185±4	175±8	170±6	165±4	161±6	155±3	150±3
c3	226±8	220±5	200±5	193±4	170±5	161±4	142±4	138±6	130±7	125±5	122±8
c4	225±8	220±0	200±5	191±4	170±0	161±7	142±2	135±6	130±7	125±0	122±2
c5	222±3	220±6	210±3	193±5	178±7	161±2	140±5	131±6	128±7	123±5	121±8
c6	228±3	220±6	210±3	183±5	170±7	161±2	140±5	131±6	128±7	113±5	110±5
c7	226±8	224±5	210±5	193±4	178±5	161±4	142±4	138±6	131±7	125±5	122±8
c8	226±3	220±6	210±3	190±5	175±7	160±2	140±5	128±6	125±7	120±5	115±8
Control	225±2	224±1	225±1	224±3	224±4	224±1	225±1	224±4	225±2	224±3	225±2
Nifedipine	225±1	221±2	215±1	195±3	180±2	168±1	145±2	125±2	125±1	122±2	120±3

Table 3: Anti-hypertensive activity data percentage inhibition

Compound	Inhibition (%)										
	0	15	30	60	120	180	240	300	360	420	480
b1	0.8	0.59	1.43	12.98	19.61	21.56	23.33	26.3	28.69	29.43	31.04
b2	0.71	0.7	6.49	13.78	20.46	27.98	36.74	38.24	41.52	45.0	46.48
b3	0.1	1.0	6.49	13.78	20.46	27.98	36.80	38.30	41.60	45.1	46.48
b4	0.8	0.91	1.87	15.21	20.5	22.9	25.62	28.35	29.7	32.1	35.57
b5	0.1	0.27	6.45	12.71	19.57	28.25	35.46	37.35	39.75	44.05	44.19
b6	0.1	0.1	6.58	13.74	20.37	28.07	36.76	40.02	42.0	44.05	46.06
b7	0.36	0.59	1.87	15.21	21.84	23.0	27.77	28.53	31.35	33.0	35.48
b8	0.9	1.0	6.36	15.12	23.13	28.43	36.73	39.58	41.97	44.05	45.48
c1	0.8	0.27	1.43	12.71	19.61	21.56	23.33	26.3	28.0	29.43	31.04
c2	0.5	0.59	1.87	13.74	17.38	27.98	36.80	38.30	41.97	44.05	45.48
c3	0.1	1.61	11.09	13.78	24.02	28.0	36.80	39.50	41.97	44.0	45.74
c4	0.8	0.91	1.87	15.21	20.5	22.9	25.62	28.35	29.7	32.1	35.57
c5	0.1	1.82	11.09	14.67	24.0	28.1	36.90	39.58	41.97	44.05	46.30
c6	0.9	1.57	6.58	13.74	20.36	28.0	36.0	41.35	42.85	44.98	45.91
c7	0.9	1.57	6.58	18.19	23.82	28.0	36.0	41.35	42.85	49.39	51.90
c8	0.9	1.57	6.58	15.06	21.59	27.8	36.0	40.1	41.85	46.51	48.57
Control	-	-	-	-	-	-	-	-	-	-	-
Nifedipine	0.4	1.29	4.44	12.92	19.69	24.98	35.49	44.20	44.51	45.51	46.58

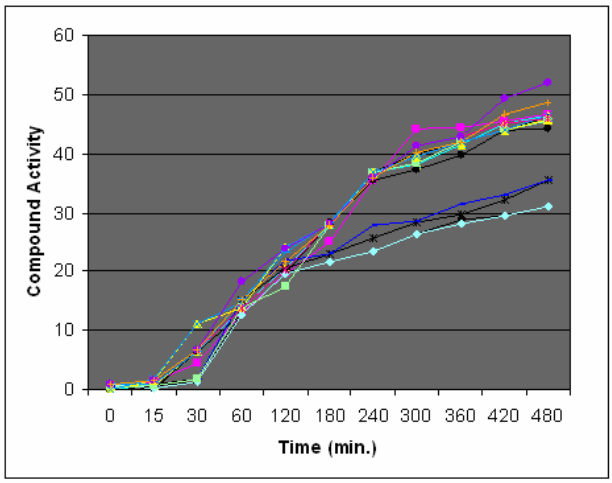


Fig. 1. Graph showing (%) decrease in Systolic Blood Pressure (SBP)

4.2. Anti-inflammatory activity

The method of Winter et al was employed with some modifications. All test samples were administered to animals at a 100 mg/kg dosage, as suspension in 0.5% carboxymethyl cellulose and administered orally. After 60 min of drug dose, the injection of 0.1 ml of solution of carrageenan (0.5 mg/25 mL) was injected into the sub-plantar tissue of the left hind paw of each rat. Out of this, one group was treated with indomethacin as standard (100 mg/kg). The initial volume of paw was measured within 30 sec. after carrageenan injection. Later on paw volume were measured after 1-5 h respectively. The relative increase in the paw volume was calculated in the individual animal of the control, test, and standard groups respectively. The % inhibition of oedema was calculated as follows:

Anti-inflammatory activity
(% Inhibition) = [1 – (Dt/Dc) x 100]

Where Dt is mean relative change in a paw volume in test group and Dc is mean relative change in paw volume in control group.

The experiment was repeated at two different dose level (25 and 50 mg/kg) for compounds which showed significant statistical differences between the test and the control group. ANOVA was employed as the statistical method.

Table 4: Anti-inflammatory activity data:

Compound (10 mg/kg)	Average paw volume				% Inhibition			
	0 h	1 h	3 h	5 h	0 h	1 h	3 h	5 h
b1	1.15±0.01	1.12±0.02	1.10±0.02	1.10±0.01	38.09	39.83	41.03	42.05
b2	1.20±0.02	1.18±0.02	1.15±0.02	1.10±0.02	35.57	36.62	38.36	42.0
b3	1.20±0.01	1.17±0.01	1.15±0.01	1.10±0.01	35.62	37.09	38.41	42.65
b4	1.15±0.02	1.12±0.02	1.10±0.02	1.10±0.01	38.25	39.83	41.03	42.05
b5	1.14±0.01	1.12±0.02	1.10±0.02	1.10±0.01	38.82	39.83	41.03	42.05
b6	1.21±0.02	1.17±0.02	1.14±0.02	1.0±0.02	35.83	37.15	38.76	47.26
b7	1.14±0.01	1.12±0.02	1.10±0.02	1.10±0.01	38.84	39.83	40.91	42.05
b8	1.20±0.01	1.18±0.02	1.14±0.02	1.10±0.01	35.62	36.62	38.76	42.05
c1	1.18±0.01	1.16±0.02	1.15±0.02	1.14±0.01	36.62	37.63	38.25	39.94
c2	1.17±0.01	1.16±0.01	1.16±0.01	1.16±0.01	39.09	37.78	37.85	38.89
c3	1.15±0.02	1.12±0.02	1.10±0.02	1.10±0.01	35.83	37.15	38.76	47.26
c4	1.21±0.02	1.17±0.02	1.14±0.02	1.0±0.02	37.15	38.82	39.83	42.05
c5	1.16±0.02	1.14±0.02	1.12±0.02	1.10±0.01	36.62	38.82	40.55	52.63
c6	1.18±0.01	1.14±0.02	1.11±0.01	0.9	35.83	37.78	39.48	42.0
c7	1.21±0.02	1.16±0.02	1.13±0.02	1.10±0.02	35.80	37.70	39.83	47.2
c8	1.21±0.01	1.16±0.01	1.12±0.01	1.0±0.01	-	-	-	-
Control	1.86±0.02	1.86±0.01	1.86±0.02	1.86±0.01	41.0	46.38	51.84	52.63
Indomethacin	1.11±0.01	1.04±0.01	0.91±0.02	0.93±0.01	38.09	39.83	41.03	42.05

4.4 Acute ulcerogenesis

Acute ulcerogenesis test was done according to Cioli et al. Albino rats (150-200 g) were divided into different groups consisting of six animals in each group. Ulcerogenic activity evaluated after p.o. administration of test compounds or ibuprofen at the dose of 50 mg/kg. Control rat's recived p.o.administration of vehicle (suspension of 1% methyl cellulose). Food but not water was removed 24 h before administration of the test compounds. After the drug treatment, the rats were fed normal diet for 17 h and then sacrificed. The stomach was removed and opened along the greater curvature, washed with distilled water and opened along the greater curvature, washed with distilled water and cleaned gently by dipping in saline. The gastric mucosa of the rats was examined by means of a 4x binocular magnifier. The lesions were counted and divided into large (greater than 2mm in diameter), small (1-2 mm) and punctiform (less than 1 mm). For each stomach the severity of mucosal damage was assessed according to the following scoring system. The mean score of each treated group minus the mean score of the control group was considered the 'ulcer index' of gastric damage.

5. Result and Discussion

All the synthesized compounds are characterised by TLC. These derivatives were obtained from the two step synthesis, their structures was confirmed by IR, NMR, C^{13} NMR and MS. All synthesized derivatives were screened for their biological activity. Antihypertensive activity was carried out initially for all the test compounds. Those compound which were found out to show significant activity by non-invasive (Tail-cuff method) technique were further evaluated. Anti-inflammatory activity was carried out followed by analgesic and acute ulcerogenesis studies.

Table 5: scoring of Gastric Ulcers:

Sr.No.	Ulcerogenic response	Score
1	Ulcers less than 1 mm	1
2	Ulcers less than 1-2 mm	2
3	Ulcers less than 2-3 mm	3
4	Ulcers less than 3-4 mm	4
5	Ulcers less than 4-5 mm	5
6	Ulcers less than 5 mm	10
7	Perforated lesions	25

Table 6: Results of Ulcerogenic Activity

Compound	Dose mg/kg	Ulcer index ± S.D.
Control 1% gum acacia, p.o.	-	10.78±0.40
Standard	50	18.51±0.47
C1	100	3.82±0.33
C2	100	Nil
C3	100	Nil
C4	100	Nil
C5	100	Nil
C6	100	2.32±0.42
C7	100	Nil
C8	100	1.51±0.47

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