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Synthesis and biological evaluation of new heterocyclic moiety N-(2-furylmethyleneamino)-3,4-dihydro-1H-pyrimidine-5-carboxamide derivatives

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ABSTRACT

Six new 3,4-Dihydro-1H-pyrimidine-5-carbohydrazide Derivatives (3a-f) have been synthesized in a three step reaction. In first step 5-(Ethoxycarbonyl)-6-methyl-4-substitutedaryl-3,4-dihydropyrimidin-2(1H)-ones obtained (1a-f) and in second step 4-Substitutedaryl-6-methyl-2-pyrimidinone-5-Carbohydrazides (2a-f). Third step involves synthesis of 4-Substitutedaryl-6-methyl-2-pyrimidinone-5-(N-p-tosyl) Carbohydrazides (3a-f). Their structures are confirmed by IR, ¹H- NMR, C¹³NMR 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 3c, 3e, 3f and 2 b, 2c, 2f showed excellent results on evaluation by direct method. Test compounds 3c, 3e and 2f 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 3b, 3c and 3e showed low ulcerogenic activity.

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KEYWORDS

DOCA-salt hypertension;
Non-invasive tail-cuff
method;
Carotid artery cannulation;
Antihypertensive activity;
Anti-inflammatory activity;
Ulcerogenic activity;
Nifedipine;
Schiff base.

INTRODUCTION

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

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amount of hydrochloric acid at reflux temperature. The product of this novel one pot, three-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 anti-hypertensive 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.

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 : Chloroform : methanol (6:3:1). The absorbance maxima (λ_{max}) and absorbance of synthesized compounds was found in methanol Shimadzu 1700 UV-Visible spectrophotometer. Infrared absorption spectra of synthesized compounds were obtained by preparing KBr pellet, using Shimadzu-3200 FTIR

Spectrophotometer. ¹H-NMR studies on Shimadzu FTNMR spectrophotometer, 300MHz. and Bruker DRX-300 (300 MHz FT NMR) using CDCl₃ and DMSO and Mass spectra were recorded on Joel SX-120 mass spectrophotometer.

CHEMISTRY

Schemes

Chemistry^[11-28]

Synthesis of 5-(Ethoxycarbonyl)-6-methyl-4-substitutedaryl-3,4-dihydropyrimidin-2(1H)-ones (1a-f); following scheme I

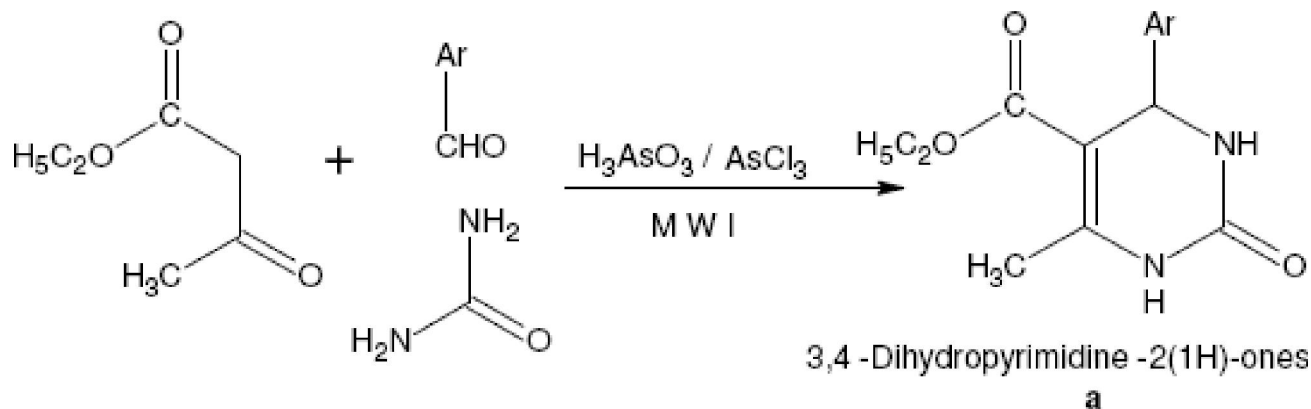
General procedure

Firstly preparation of Arsenious acid solution; sodium hydroxide (2g) in mixture of water (4-5ml) and alcohol (20ml) addition of Arsenic trioxide (0.7g) followed by two drops of phenolphthalein and Conc. HCl is added to acidify the solution or pink color disappears.

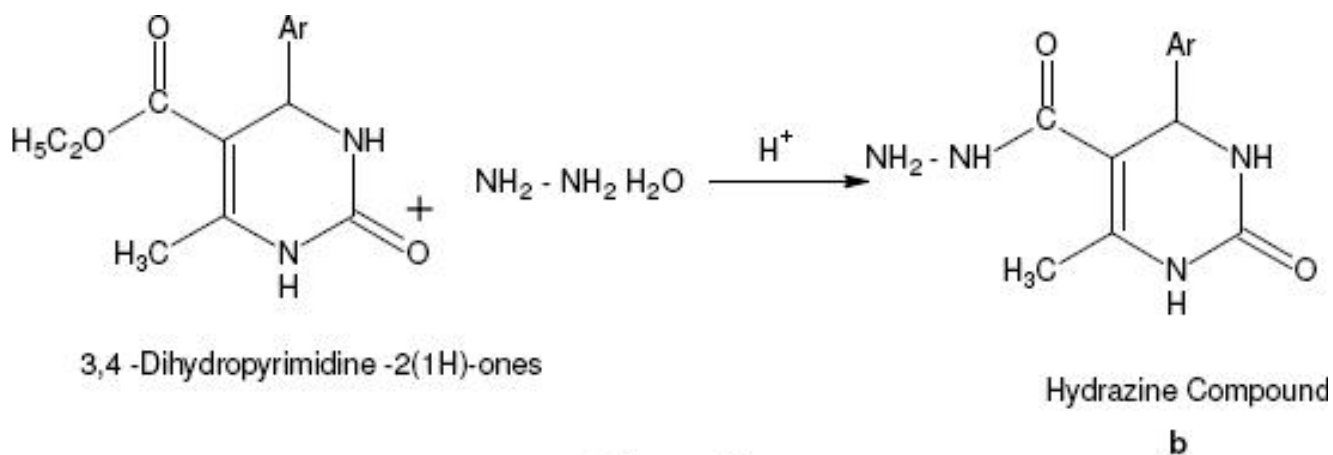
In the first step three component reaction involving ethylacetoacetate, urea and substituted benzaldehydes reacted in presence of ethanol and arsenious acid solution to form the substituted ring nucleus compounds (1a-f). Reaction mixture was heated at 70° for 6-13 h. as per the completion of respective reaction and the completion of reaction was monitored by TLC (ethyl acetate: toluene:: 6:4). After cooling to room temperature, the mixture was diluted with 150 mL of brine and extracted with ether (2 x 150 mL), dried over magnesium sulfate and excess of solvent was removed under reduced pressure. After complete drying product was collected and recrystallized from ethanol. The structure of compounds was confirmed by IR, ¹H-NMR, C¹³ NMR, Mass and elemental analysis.

ethyl 4-(4-dimethylaminophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyrimidine-5-carboxylate (1a).

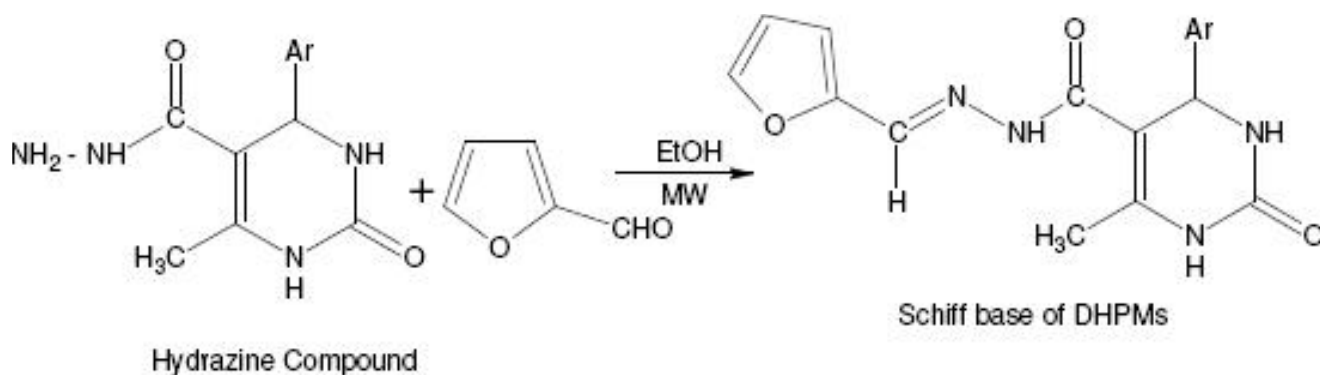
Yield: 84 %, m.p. 256-258 °C. R_f : 0.60 (Ethylacetate:Toluene, 6:4). λ_{max} (ϵ_{max}): 280 (8506). IR (KBr) ν = 784 (-Ar), 1091-1168 (C-O-C), 1220-(N-(CH₃)₂), 1525-1720 (- double bond region), 1525-1620 (- C=O), 1649 (- C=O), 1699 (-C=O chain), 2977-3242 (-N-H). ¹H-NMR (CDCl₃) δ 7.1-7.3 (m, 4H, arom.), 6.9-6.7 (dd, 2H, -NH), 5.35 (d,



Scheme-I



Scheme-II



Scheme - III

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. (C₁₆H₂₁O₃N₃) C, H, N.

ethyl 4-(4-hydroxy-3-methoxy-phenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyrimidine-5-carboxylate (1b).

Yield: 81 %, m.p. 235-238 °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). ¹H-NMR (CDCl₃) 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.

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m/z : 306 (M+); 278 (M-CO) +; 199; 107 (-C₇H₇O); 43 (100%).

Anal. (C₁₅H₁₈O₅N₂) C,H,N.

ethyl 6-methyl-4-(2-nitrophenyl)-2-oxo-3,4-dihydro-1H-pyrimidine-5-carboxylate (1c).

Yield: 83.60 %, m.p. 217-220 °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). ¹H-NMR (CDCl₃) 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. (C₁₄H₁₆N₃O₅) C,H,N.

ethyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyrimidine-5-carboxylate (1d).

Yield: 81.66 %, m.p. 226-229 °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). ¹H-NMR (CDCl₃) 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. (C₁₄H₁₅O₄N₂) C,H,N.

ethyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyrimidine-5-carboxylate (1e).

Yield: 78 %, m.p. 175-178 °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). ¹H-NMR (CDCl₃) 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. (C₁₆H₂₀O₅N₂) C,H,N.

ethyl 6-methyl-2-oxo-4-(E)-styryl]-3,4-dihydro-1H-pyrimidine-5-carboxylate (1f)

Yield: 86 %, m.p. 224-226 °C. 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). ¹H-NMR (CDCl₃) 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. (C₁₆H₁₈O₃N₂) C,H,N.

Synthesis of 4-Substitutedaryl-6-methyl-2-pyrimidinone-5-Carbohydrazides (2a-f); following scheme II

General Procedure

A mixture of 5-(Ethoxycarbonyl)-6-methyl-4-substitutedaryl-3,4-dihydropyrimidin-2(1H)-ones (1a-f) (0.01 mmol), with Hydrazine hydrate (0.01 mmol) were taken in dichloromethane (20 mL) as solvent and pyridine (1.5 mL) as a catalyst. The resultant mixture was refluxed for 7-18 h. as per the completion of respective reaction. Then it was cooled to room temperature and poured on to crushed ice. It was kept overnight and filtered to obtain solid, which was dried and recrystallized from ethanol. The structure of compounds was confirmed by IR, ¹H-NMR, C¹³ NMR, Mass and elemental analysis.

4-(4-dimethylaminophenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyrimidine-5-carbohydrazide (2a).

Yield: 75 %, m.p. 239-242 °C. 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). ¹H-NMR (CDCl₃) 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. (C₁₄H₁₉O₂N₅) C, H, N.

4-(4-hydroxy-3-methoxy-phenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyrimidine-5-carbohydrazide (2b).

Yield: 78 %, m.p. 230-232 °C. *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). ¹H-NMR (CDCl₃) δ 7.1-7.3 (m, 4H, arom.), 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. (C₁₃H₁₆O₄N₄) C, H, N.

6-methyl-4-(2-nitrophenyl)-2-oxo-3,4-dihydro-1H-pyrimidine-5-carbohydrazide (2c).

Yield: 77 %, m.p. 234-238 °C. *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). ¹H-NMR (CDCl₃) 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. (C₁₂H₁₃O₄N₅) C, H, N.

4-(4-hydroxyphenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyrimidine-5-carbohydrazide (2d).

Yield: 76 %, m.p. 178-181 °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). ¹H-NMR (CDCl₃) 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. (C₁₂H₁₄O₃N₄) C, H, N.

4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyrimidine-5-carbohydrazide (2e).

Yield: 70 %, m.p. 200-203 °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). ¹H-NMR (CDCl₃) 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. (C₁₄H₁₈O₄N₄) C, H, N.

6-methyl-2-oxo-4-[(Z)-styryl]-3,4-dihydro-1H-pyrimidine-5-carbohydrazide (2f).

Yield: 73 %, m.p. 139-141 °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). ¹H-NMR (CDCl₃) 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. (C₁₄H₁₄O₂N₄) C, H, N.

Synthesis of N-(2-furylmethyleneamino)-6-methyl-2-oxo-4-substitutedaryl-3,4-dihydro-1H-pyrimidine-5-carboxamide (3a-f); following scheme III

General procedure

A mixture of 4-Substitutedaryl-6-methyl-2-pyrimidinone-5-Carbohydrazides (2a-f) (0.01 mmol), with p-toluene sulphonyl chloride (0.01 mmol) were taken in ethanol (20 mL) as solvent and pyridine (6 mmol) as a catalyst. The resultant mixture was refluxed for 5-10 h. as per the completion of respective reaction. Then it was cooled to room temperature and poured on to crushed ice. It was kept overnight and filtered to obtain solid, which was dried and recrystallized from ethanol. The structure of compounds was confirmed by IR, ¹H-NMR, C¹³ NMR, Mass and elemental analysis.

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4-(4-dimethylaminophenyl)-6-methyl-2-oxo-N'-(p-tolylsulfonyl)-3,4-dihydro-1H-pyrimidine-5-carbohydrazide (3a).

Yield: 76 %, m.p. 229-231 °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. $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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. ($\text{C}_{15}\text{H}_{20}\text{O}_5\text{N}_4$) C, H, N.

4-(4-hydroxy-3-methoxy-phenyl)-6-methyl-2-oxo-N'-(p-tolylsulfonyl)-3,4-dihydro-1H-pyrimidine-5-carbohydrazide (3b).

Yield: 76 %, m.p. 229-231 °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. $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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. ($\text{C}_{15}\text{H}_{20}\text{O}_5\text{N}_4$) C, H, N.

6-methyl-4-(2-nitrophenyl)-2-oxo-N'-(p-tolylsulfonyl)-3,4-dihydro-1H-pyrimidine-5-carbohydrazide (3c).

Yield: 76 %, m.p. 229-231 °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). $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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. ($\text{C}_{15}\text{H}_{20}\text{O}_5\text{N}_4$) C, H, N.

3.2.3.5. 4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-N'-(p-tolylsulfonyl)-3,4-dihydro-1H-pyrimidine-5-carbohydrazide (3d).

Yield: 76 %, m.p. 229-231 °C. 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). $^1\text{H-NMR}$ (CDCl_3) δ 7.2 (s, 3H, arom.), 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). $^{13}\text{C-NMR}$ (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. ($\text{C}_{15}\text{H}_{20}\text{O}_5\text{N}_4$) C, H, N.

4-(4-hydroxyphenyl)-6-methyl-2-oxo-N'-(p-tolylsulfonyl)-3,4-dihydro-1H-pyrimidine-5-carbohydrazide (3e).

Yield: 76 %, m.p. 229-231 °C. 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). $^1\text{H-NMR}$ (CDCl_3) δ 7.2 (s, 3H, arom.), 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). $^{13}\text{C-NMR}$ (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. ($\text{C}_{15}\text{H}_{20}\text{O}_5\text{N}_4$) C, H, N.

6-methyl-2-oxo-N'-(p-tolylsulfonyl)-4-[(E)-styryl]-3,4-dihydro-1H-pyrimidine-5-carbohydrazide (3f).

Yield: 76 %, m.p. 229-231 °C. 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). $^1\text{H-NMR}$

(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). $^{13}\text{C-NMR}$ (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. ($\text{C}_{15}\text{H}_{20}\text{O}_5\text{N}_4$) C,H,N.

TABLE 1 : 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
2a	225±4	222±8	221±9	195±2	180±4	175±8	172±6	165±4	160±6	158±3	155±3
2b	226±8	224±5	210±5	193±4	178±5	161±4	142±4	138±6	131±7	125±5	122±8
2c	226±8	224±5	210±5	193±4	178±5	161±4	142±4	138±6	131±7	125±5	122±8
2d	225±4	222±8	220±9	190±2	178±4	172±8	167±6	160±4	158±6	152±3	145±3
2e	225±6	223±5	210±6	195±8	180±5	160±8	145±3	140±6	135±7	125±5	125±7
2f	226±3	224±6	210±3	193±5	178±7	161±2	142±5	134±6	130±7	125±5	121±8
3a	225±4	222±8	221±9	195±2	180±4	175±8	172±6	165±4	160±6	158±3	155±3
3b	226±4	222±8	220±9	193±2	185±4	175±8	170±6	165±4	161±6	155±3	150±3
3c	226±8	220±5	200±5	193±4	170±5	161±4	142±4	138±6	130±7	125±5	122±8
3d	225±8	220±0	200±5	191±4	170±0	161±7	142±2	135±6	130±7	125±0	122±2
3e	222±3	220±6	210±3	193±5	178±7	161±2	140±5	131±6	128±7	123±5	121±8
3f	228±3	220±6	210±3	183±5	170±7	161±2	140±5	131±6	128±7	113±5	110±5
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 2 : Anti-hypertensive activity data percentage inhibition

Compound	Inhibition (%)										
	0	15	30	60	120	180	240	300	360	420	480
2a	0.8	0.59	1.43	12.98	19.61	21.56	23.33	26.3	28.69	29.43	31.04
2b	0.71	0.7	6.49	13.78	20.46	27.98	36.74	38.24	41.52	45.0	46.48
2c	0.1	1.0	6.49	13.78	20.46	27.98	36.80	38.30	41.60	45.1	46.48
2d	0.8	0.91	1.87	15.21	20.5	22.9	25.62	28.35	29.7	32.1	35.57
2e	0.1	0.27	6.45	12.71	19.57	28.25	35.46	37.35	39.75	44.05	44.19
2f	0.1	0.1	6.58	13.74	20.37	28.07	36.76	40.02	42.0	44.05	46.06
3a	0.8	0.27	1.43	12.71	19.61	21.56	23.33	26.3	28.0	29.43	31.04
3b	0.5	0.59	1.87	13.74	17.38	27.98	36.80	38.30	41.97	44.05	45.48
3c	0.1	1.61	11.09	13.78	24.02	28.0	36.80	39.50	41.97	44.0	45.74
3d	0.8	0.91	1.87	15.21	20.5	22.9	25.62	28.35	29.7	32.1	35.57
3e	0.1	1.82	11.09	14.67	24.0	28.1	36.90	39.58	41.97	44.05	46.30
3f	0.9	1.57	6.58	13.74	20.36	28.0	36.0	41.35	42.85	44.98	45.91
Control	-	-	-	-	-	-	-	-	-	-	-
Nifedipine	0.4	1.29	4.44	12.92	19.69	24.98	35.49	44.20	44.51	45.51	46.58

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Anti-hypertensive activity

Non-invasive tail-cuff method

The newly synthesized compounds were subjected for antihypertensive activity studies. Norwegian strain of inbred 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.

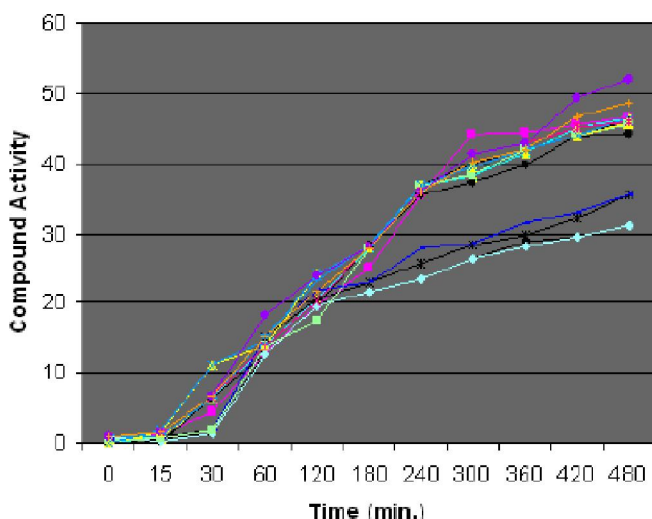


Figure 1 : Graph showing (%) decrease in Systolic Blood Pressure (SBP)

DOCA-salt hypertension

Rats were anesthetized by injecting pentobarbital injection administered intraperitoneally in a dose of 50 mg/kg body wt. It was placed on a heated surgical surface maintained at 37 °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

TABLE 3 : Anti-inflammatory activity data

Com pound (10 mg /kg)	Average paw volume				% Inhibition			
	0 h	1 h	3 h	5 h	0 h	1 h	3 h	5 h
2a	1.15± 0.01	1.12± 0.02	1.10± 0.02	1.10± 0.01	38.09	39.83	41.03	42.05
2b	1.20± 0.02	1.18± 0.02	1.15± 0.02	1.10± 0.02	35.57	36.62	38.36	42.0
2c	1.20± 0.01	1.17± 0.01	1.15± 0.01	1.10± 0.01	35.62	37.09	38.41	42.65
2d	1.15± 0.02	1.12± 0.02	1.10± 0.02	1.10± 0.01	38.25	39.83	41.03	42.05
2e	1.14± 0.01	1.12± 0.02	1.10± 0.02	1.10± 0.01	38.82	39.83	41.03	42.05
2f	1.21± 0.02	1.17± 0.02	1.14± 0.02	1.0± 0.02	35.83	37.15	38.76	47.26
3a	1.18± 0.01	1.16± 0.02	1.15± 0.02	1.14± 0.01	36.62	37.63	38.25	39.94
3b	1.17± 0.01	1.16± 0.01	1.16± 0.01	1.16± 0.01	39.09	37.78	37.85	38.89
3c	1.15± 0.02	1.12± 0.02	1.10± 0.02	1.10± 0.01	35.83	37.15	38.76	47.26
3d	1.21± 0.02	1.17± 0.02	1.14± 0.02	1.0± 0.02	37.15	38.82	39.83	42.05
3e	1.16± 0.02	1.14± 0.02	1.12± 0.02	1.10± 0.01	36.62	38.82	40.55	52.63
3f	1.18± 0.01	1.14± 0.02	1.11± 0.01	0.9	35.83	37.78	39.48	42.0
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
Indome thacin	1.11± 0.01	1.04± 0.01	0.91± 0.02	0.93± 0.01	38.09	39.83	41.03	42.05

TABLE 4 : 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 5 : 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
3a	100	3.82±0.33
3b	100	Nil
3c	100	Nil
3d	100	2.32±0.42
3e	100	Nil
3f	100	1.51±0.47

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 dihydropyridines. Methoxy derivative 3c, 3e, 3f and 2b, 2c, 2f has remarkable antihypertensive activity and 2d moderate activity than others. Data are presented as means \pm S.E.M. a repeated measures analysis of variance was used 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 \pm 0.5. Their results for percentage inhibition are as shown in Figure 1 and TABLE 2 respectively.

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:

$$\text{Anti-inflammatory activity (\% Inhibition)} = [1 - (Dt/Dc) \times 100]$$

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.

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 received 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.

RESULT AND DISCUSSION

All the synthesized compounds are characterised by TLC. These derivatives were obtained from the two step synthesis, their structures were 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 compounds 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 acute ulcerogenesis studies.

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