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Synthesis and Calcium Channel Blocking Activity of 1, 2, 3, 4,-Tetrahydropyrimidine Derivatives Containing Carbamates and Carbamides

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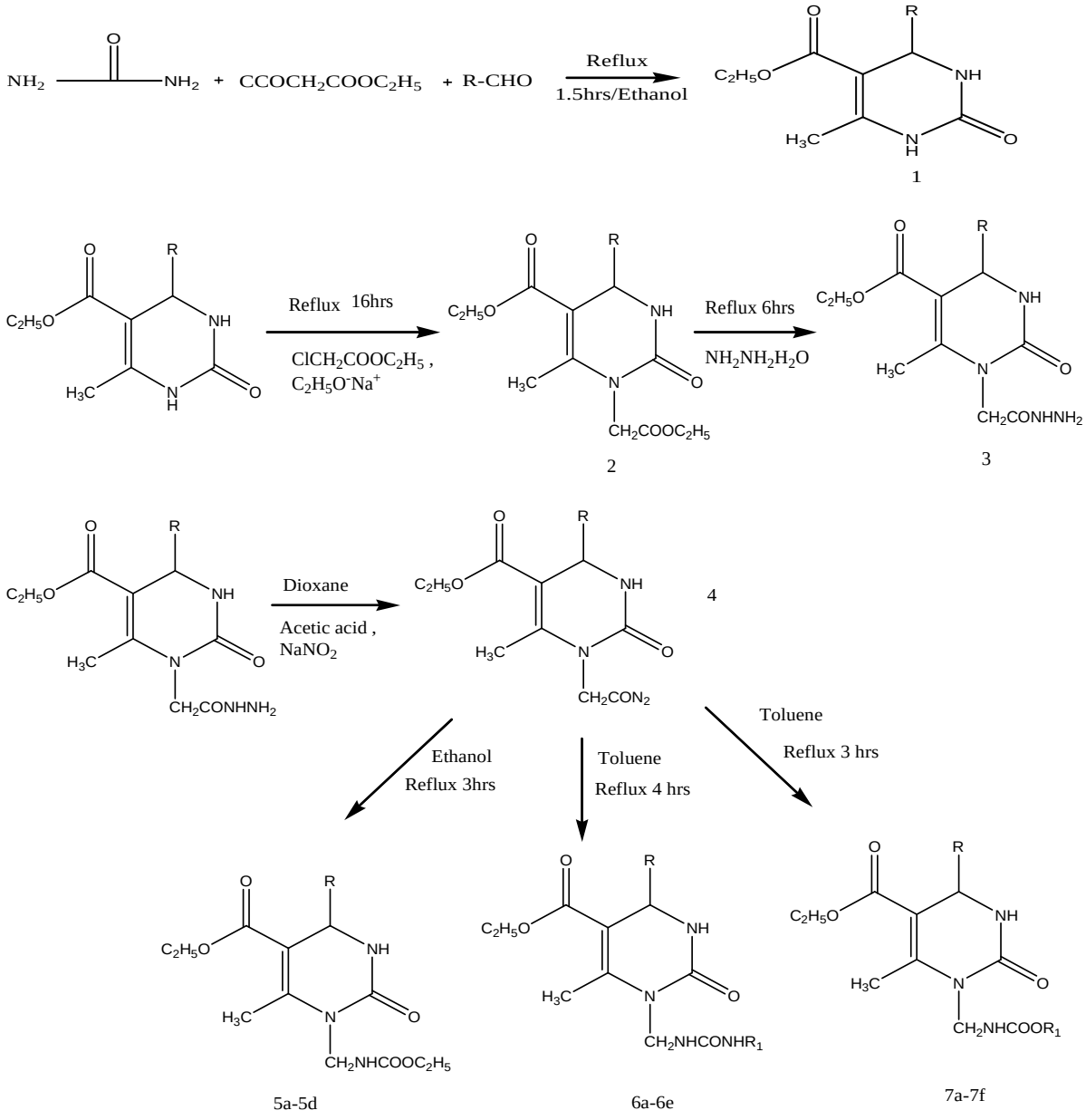
Abstract: Literature survey reveals that partially reduced pyridine and pyrimidine derivatives are known to have antihypertensive property. Most of the clinically used calcium channel blockers like nifedipine, amlodipine have 1, 4-dihydropyridine ring system containing methylcarboxylate side chain at 3rd position. In the present investigation calcium channel blocker effect of containing carbamate and carbamide side chain has been studied. The key starting material diethyl -4- methyl -2- oxo -6- phenyl -3,6-dihydropyrimidine -1,5-dicarboxylate (2) was synthesized as per literature and ethyl carboxylate side chain present at 1st position was exploited without affecting the same chain at 5th position. Compound (2) was treated with hydrazine hydrate to form ethyl-1-[(hydrazinooxy) carbonyl] -6- methyl -2- oxo -4- phenyl -1, 2, 3, 4-tetrahydropyrimidine -5-carboxylate (3). Transformation of compound (3) to ethyl –3- (azidocarbonyl) –6– methyl –2– oxo –4– phenyl -1, 2, 3, 4- tetrahydropyrimidine carboxylate (4) on treating with sodium nitrite in dioxane and acetic acid was indicated in IR spectra at 2361 cm^{-1}. Compound (4) was subjected to Curtius rearrangement on treating with ethyl alcohol / appropriate phenol / appropriate amine to yield the title compounds. Success of the reaction was readily seen in the IR spectra by the absence of peak at 2361cm^{-1}.
Key words: Carbamates, Carbamides, Calcium channel, antihypertensive activity.

Introduction

1,2,3,4-Tetrahydropyrimidine (DHPM) calcium channel blockers are important class of drugs which induce relaxation of vascular smooth muscle, preferentially in arteries, and display a negative inotropic effect on isolated cardiac muscle[1]. They exert these effects by binding to a high affinity binding site in L-type voltage dependent Ca^{2+} channels[2]. So, this class of drug is effective in the treatment of hypertension, angina pectoris and other cardiovascular disorder[3]. DHPMs may lead to other beneficial effects such as regression of left ventricular pressure

and vascular hypertrophy, renal protection, weak anti-platelet, anti-ischemic and anti- atherogenic activity[4-7]. The term cardio protection refers to techniques used to prevent or delay the development of myocardial injury, particularly during ischemia. Ischemia and reperfusion produce profound effects on the function of molecules involved in the control of calcium homeostasis, leading to increased free cystolic Ca^{2+} concentration. Calcium overload is one of the crucial alterations responsible for ischemia and reperfusion injury. Calcium overload can trigger several injurious mechanisms. Many ATP-consuming enzymes require Ca^{2+} for activity, so that calcium overload increases ATP consumption and exacerbates the unbalance between energy supply and demand, which is the metabolic hallmark of ischemia[8]. In recent years, acid-catalyzed cyclocondensation of acetoacetate with aldehyde and ureas, known as the Biginelli reaction, has attracted significant attention[9-17]. The resultant dihydropyrimidines (DHPMs) have been reported to have antibacterial[18], antiviral[19], anti-inflammatory[20], and analgesic, antihypertensive as well as calcium channel blocker[21-22] and antioxidant[23] activities. In the present work, we propose to synthesize a series of Ethyl -6- methyl -2- oxo -4- phenyl -1, 2, 3, 4-tetrahydropyrimidine -5-carboxylate -1- carbamides and carbamates, confirm their structures by spectral analysis, molecular docking studies of the title compounds to ascertain their calcium channel blocking activity[24].



Scheme 1: Synthesis of Ethyl-6-methyl-2-oxo-4-substituted-1, 2, 3, 4 tetrahydropyrimidine-5-carboxylate-1-carbamides and carbamates.

Experimental Section:

Melting points were determined in open capillaries and were uncorrected. All compounds were characterized by elemental analysis, IR, 1H NMR spectra & Mass spectroscopy. The IR spectra were recorded on a Bruker FT-IR spectrometer, using ATR technology. The 1H NMR spectra were obtained on Mercury plus 300 MHz NMR spectrometer. Mass spectra was obtained on 410 Prostar binary LC with 500 MS ITPDA detector.

General procedure for synthesis of compounds (1a-d):

To a mixture of urea (0.15 mol), substituted aldehydes (0.1mol) and ethylacetoacetate (0.1 mol) in ethanol (75 ml), 4 drops of concentrated hydrochloric acid was added and heated for 1.5 hr at 70ºC. The reaction mixture was poured into ice water (100 ml) with stirring and left overnight at room temperature. Filtered and residue was dried at room temperature, recrystallised from ethanol.

General procedure for synthesis of compounds (2a-d):

The compound 1 (0.1mol) was dissolved in a solution prepared by reacting Na (0.1mol) with 200ml of absolute ethanol. The solution was refluxed with stirring and ethyl chloroacetate (0.1mol) was added in three portions over a period of 0.5 hr. After heating under reflux for 16 hr, the reaction mixture was filtered while hot to remove precipitated sodium chloride; the solvent was removed on a rotary vaccum evaporator. The crude product was collected and recrystallised from ethanol. Compound (2) were prepared in this manner.

General procedure for synthesis of compounds (3a-d):

A mixture of the appropriate compound (2) (0.1mol), hydrazine hydrate (0.25mol), and 30ml of 95% ethanol was heated under reflux for 6h. The solvent was removed on a rotary vaccum evaporator and the residue was poured into 200ml of cold water. The solid that formed was collected, washed with ice-cold water, and recrystallized from ethanol.

General procedure for synthesis of compounds (4a-d):

Compound (3) (0.1mol) was suspended in a mixture of dioxane(30ml) and acetic acid(30ml) and cooled to 0^o in freezing mixture. An ice cold solution of sodium nitrite (2.12g) in water (10ml) was introduced into it in small portions with vigorous stirring. The temp of the reaction mixture was maintained below 2^o. After the complete addition, the reaction mixture was allowed to stay at room temp for 30min and the pale yellow solid that separated was collected, washed with cold

water.

General procedure for synthesis of compounds (5a-5d):

A suspension of compound (4) in absolute ethanol was refluxed on a steam bath for 3hr. the reaction mixture was concentrated under reduced pressure and then diluted with water. The product that separated was collected and crystallized from benzene-pet ether (60-80).

General procedure for synthesis of compounds (6a-e):

A mixture of compound (4) and appropriate amine in anhydrous toluene was heated under gentle reflux (120ºC) in an oil bath for 4hr. the crystalline product that separated out from the reaction mixture was collected and washed with toluene and pet ether. The analytical sample was obtained by crystallization from benzene-pet ether (60-80).

General procedure for synthesis of compounds (7a-f):

Compound (4) was suspended in anhydrous toluene and heated in an oil bath at 70-80ºC till the evolution of nitrogen gas stopped (nearly 1hr). Then the appropriate phenol in toluene was added and the reaction mixture was heated at 110-120ºC for 3hr. After the removal of toluene under reduced pressure, the residue was dissolved in ether, the ethereal solution was washed with 10% aq sodium hydroxide solution to remove any unreacted phenol and finally with water. The organic layer was dried over anhydrous calcium chloride. The removal of the

solvent furnished resinous mass which solidified on cooling. Further purification was achieved by crystallization from benzene-pet.ether (60-80). Summary of all synthesized compounds are mentioned in table 1.

Pharmacological Activity:

Procedure:

Rats of either sex weighing 180-200g are sacrificed and the descending thoracic aorta from the level of the aortic arch to the level of the diaphragm is rapidly removed. Eight rings of 4–5 mm width are obtained and each is mounted in a 20 ml tissue bath which contains the oxygenated warmed Krebs solution. Initial tension is set at 1.0 g. The tissue is allowed to incubate over a period of 2 h, during which time the Krebs solution is changed every 15 min. Just prior to the end of the 2 h equilibration period, the Krebs solution is changed again and the tissue is allowed to stabilize at 1.0 g tension. A sustained contraction is then generated by addition of either 40 mM KCl or 2.9 × 10–3 mM norepinephrine. Twenty min after addition of the agonist, the test drug is added so that the final concentration in the bath is 1 × 10–5 M. The percent relaxation reading is taken 30 min after addition of the test drug. Contraction of aorta rings is induced by adding potassium chloride to organ bath containing slightly modified Kreb's biocarbonate. Test drug & standard drugs tests for calcium channel blocking activity for relaxing effect[25].

Evaluation:

Active tension is calculated for the tissue at the time point just prior to the addition of the test compound and also at the point 30 min after the addition of each concentration of test compound. Active tension is defined as the difference between the generated tension and the baseline tension. The percent relaxation from the pre drug, precontracted level is calculated for each concentration of test compound. A number of 5 experiments constitute a dose range.

Preparation of standard solutions:

Nifedipine used as standard, were dissolved in ethanol to 100 mmol/lit stock solution. Stock solutions were diluted to reach 10 mmol/lit solutions in ethanol. Final organ bath concentration of ethanol did not exceed 0.54%. Same procedure was taken for preparation of solution of synthesized compounds. Experiments with vehicle were run in parallel. Vehicle showed no relaxant response.

Data analysis:

Data are presented as mean ± S.E.M. and number of animals used is indicated by n. Antagonist potencies were expressed as pEC_{50} values (negative logarithm to base 10 of the molar concentration of the agonist producing 50% of the maximum response). Maximal responses were expressed as E_{max} values (percentage of the maximum contractile response to KCl). Multiple comparisons between treatment groups were performed using the analysis of variance (ANOVA) followed by a Tukey's test. All other statistical evaluations were carried out using Student's t-test (unpaired for comparison of means between independent experiments, paired for comparison of means between experiment and control) after checking the homogeneity of variances by F- test. P values <0.05 were considered to be significant[26-27].

The calcium channel blocking activity of 1,2,3,4 – tetrahydropyrimidine derivatives (5a to 7f) was determine on isolated rat aorta.

Result and Discussion:

Identification and characterization of synthesized compounds:

4-(1–chloro-phenyl) –5- ethoxy carbonyl –6- methyl -3,4 dihydropyrimidine –2 (1H) – one. (1a)

yield: 70%. mp 199-203°C. IR (KBr): v(cm^{-1}) 1648 (amide C=O); 1703 (C=O ester); 3244 (NH). ^{1}H NMR 1.15(t, 3H, CH_3 ester); 2.25 (s, 3H, dihydropyridyl CH_3); 4.05 (q, 2H, CH_2 ester); 6.8(s, 1H, dihydropyridyl -CH); 7.2-7.3 (m, 4H, Ar H) 7.4 (s, 1H, 3 NH); 8.9 (s, 1H, 1 NH). m/e 294.11 (100.0%), 296.11 (32.1), 295.12 (16.5). C, 61.12, H,12.03, Cl,12.03, O,10.86.

4-(1-hydroxyl –2– methyl phenyl) -5- ethoxy carbonyl –6– methyl -3,4 dihydropyrimidine - 2(1H) – one. (1b)

yield: 72%. mp 207-210°C . IR (KBr): v (cm^{-1}) 3283 (-OH), 1648 (amide C=O); 1705 (C=O ester); 3241 (NH); 2950 (CH strech of methyl). ^{1}H NMR 1.13(t, 3H, CH_3 ester); 4.05 (q, 2H, CH_2 ester); 6.9 (s, 1H, dihydropyridyl-CH); 7.2-7.3 (m, 4H, Ar H) 7.3 (s, 1H, 3 NH); 8.6 (s, 1H, 1 NH). m/e 306.16 (100.0%), 307.16 (17.7%), 308.86 (2.4%). C, 62.73, H,7.24, N, 9.14, O,20.89.

4-(3–hydroxyl phenyl) –5- ethoxy carbonyl -6– methyl -3,4–dihydropyrimidine -2 (1H) – one. (1c)

yield: 71%. mp 209-212°C. IR (KBr): v(cm^{-1}) 1648 (amide C=O); 1703 (C=O ester); 3244 (NH); 3284 (-OH). ^{1}H NMR 1.15(t, 3H, CH_3 ester); 2.25 (s, 3H, dihydropyridyl CH_3); 4.05 (q, 2H, CH_2 ester); 6.8(s, 1H, dihydropyridyl-CH); 7.2-7.3 (m, 4H, Ar H) 7.4 (s, 1H, 3 NH); 8.9 (s, 1H, 1 NH). m/e 276.15 (100.0%), 277.15 (16.6%), 278.15 (2.0%). C,65-20, H,7.30, N, 10.14, O,17.34.

4–(3–amino phenyl) –5- ethoxy carbonyl –6– methyl – 3,4 –dihydropyrimidine –2 (1H) – one. (1d)

yield: 74%. mp 215-217°C. IR (KBr): v(cm^{-1}) 1648 (amide C=O); 1703 (C=O ester); 3244 (NH). ^{1}H NMR 1.15(t, 3H, CH_3 ester); 2.25 (s, 3H, dihydropyridyl CH_3); 4.05 (q, 2H, CH_2 ester); 6.8(s, 1H, dihydropyridyl-CH); 7.2-7.3 (m, 4H, Ar H) 7.4 (s, 1H, 3 NH); 8.9 (s, 1H, 1 NH). m/e 275.16 (100.0%), 276.17 (16.5%), 277.17 (1.7%). C,65.43, H, 7.69, N, 15.26, O,11.62.

Ethyl -(2–ethoxy –2– oxo ethyl) –6– methyl –2– oxo –4- (1 –chloro phenyl) 1, 2, 3, 4 –tetrahydropyrimidine –5–carboxylate. (2a)

yield: 75% mp 186-188°C. IR (KBr): v(cm^{-1}) 1648 (CONH), 1701 (C=O of ring carbonyl), 1725 (C=O ester), 2978 (aromatic proton stretching), 3116 (CONH), 3245 (NH stretching); 3088 (C-H stretch of ethyl). ^{1}H NMR 1.1 (t, 6H, CH_3), 2.45 (s, 3H, CH_3), 4.13 (s, 3H, CH_3), 4.2 (q, 4H, CH_2), 4.45 (d, 2H, CH_2), 5.2 (s, H, dihydropyridyl -CH), 7.3-7.4 (m, Ar H), 7.9 (S,1H,NH). m/e 380.15 (100.0%), 382.15 (32.9%), 381.15 (21.4%). C, 59.92, H, 6.62, Cl, 9.31, N,7.36, O, 16.80.

Ethyl -(2–ethoxy –2- oxo ethyl) –6– methyl –2– oxo –4- (1–hydroxyl –3- methoxy phenyl) 1, 2, 3, 4 –tetra hydropyrimidine –5– carboxylate. (2b)

yield: 71%. mp 189-190°C. IR (KBr): v(cm^{-1}) 2950 (methyl C-H stretch); 1648 (CONH), 1701 (C=O of ring carbonyl), 1725 (C=O ester), 2978 (aromatic proton stretching), 3116 (CONH), 3245 (NH stretching); 3088 (C-H stretch of ethyl); 3284 (-OH); 3029 (aromatic C-H stretch). ^{1}H NMR 1.15 (t, 6H, CH_3), 2.44 (s, 3H, CH_3), 4.13 (s, 3H, CH_3), 4.8 (q, 4H, CH_2), 4.45 (d, 2H, CH_2), 5.2 (s, H, dihydropyridyl -CH), 7.3-7.4 (m, Ar H), 7.8 (S, 1H, NH). m/e 392.19 (100.0%), 393.20 (22.2%), 394.20 (3.7%). C,61.21, H,7.19, N, 7.14, O, 24.46.

Ethyl-(2–ethoxy –2- oxo ethyl) –6– methyl –2– oxo –4- (3 -hydroxy phenyl) 1, 2, 3, 4 –tetrahydropyrimidine –5– carboxylate. (2c)

yield: 70 %. mp 185-187°C IR (KBr): v(cm^{-1}) 3091 (C-H stretch of ethyl); 1648 (CONH), 1701 (C=O of ring carbonyl), 1725 (C=O ester), 2978 (aromatic proton stretching), 2998 (aromatic CH stretch); 3116 (CONH), 3245 (NH stretching); 3088 (CH stretch of ethyl); 3284 (-OH). ^{1}H NMR 1.15 (t, 6H, CH_3), 2.44 (s, 3H, CH_3), 4.13 (s, 3H, CH_3), 4.8 (q, 4H, CH_2), 4.45 (d, 2H, CH_2), 5.2 (s, H, dihydropyridyl -CH), 7.3-7.4 (m, Ar H), 7.8 (S, 1H, NH). m/e 362.18 (100.0%), 363.19 (21.0%), 364.19 (3.1%). C,62.97, H,7.23, N,7.73, O,22.07.

Ethyl-(2–ethoxy –2- oxo ethyl) –6– methyl –2– oxo –4- (3 -amino phenyl) 1, 2, 3, 4 –tetrahydropyrimidine – 5– carboxylate. (2d)

yield: 69%. mp 179-182°C . IR (KBr): v(cm^{-1}) 1300 (C-N stretch of primary aromatic amines); 1648 (CONH), 1701 (C=O of ring carbonyl), 1725 (C=O ester), 2978 (aromatic proton stretching), 2950 (methyl C-H stretch); 2998 (aromatic C-H stretch); 3116 (CONH), 3245 (NH stretching); 3088 (C-H stretch of ethyl). ^{1}H NMR 1.1 (t, 6H, CH_3), 2.45 (s, 3H, CH_3), 4.13 (s, 3H, CH_3), 4.8 (q, 4H, CH_2), 4.46 (d, 2H, CH_2), 5.25 (s, H, dihydropyridyl -CH), 7.3-7.4 (m, ArH), 7.8 (S, 1H, NH). m/e 361.20 (100.0%), 362.20 (21.8%), 363.21 (2.1%). C,63.14, H,7.53, N,11.63, O,17.71.

Ethyl -1- (2–hydrazine –2- oxo ethyl) –6– methyl –2– oxo -4– (1–chloro phenyl) - 1, 2, 3, 4 –tetrahydro pyrimidine –5- carboxylate. (3a)

yield: 72% . mp 227-230°C . IR (KBr): v(cm^{-1}) 1608 (amideC=O), 1647 (ester C=O), 1706 (carbohydrazide C=O), 3238 (-NH). ^{1}H NMR 1.14 (t, 3H, CH_3 of C_2H_5), 1.5 (s, 3H, dihydropyridyl CH_3), 4.04 (q, 2H, CH_2 of C_2H_5) 5.4 (s, 2H, NH_2); 5.6 (d, 1H, NH); 7.22-7.3 (m, ArH), 7.8 (s, 1H, 1 NH). m/e 366.15 (100.0%), 368.14 (32.0%), 367.15 (18.8%). C,55.66, H,6.32, Cl,9.66, N,15.27, O,13.08.

Ethyl -1- (2–hydrazine –2- oxo ethyl) –6– methyl –2– oxo -4– (1–hydroxyl –2 methoxy phenyl) - 1, 2, 3, 4 – tetrahydropyrimidine –5– carboxylate. (3b)

yield: 73 %. mp 223-226°C . IR (KBr): v(cm^{-1}) 1608 (amideC=O), 1647 (ester C=O), 1706 (carbohydrazide C=O), 2833 (C-H Stretch of methyl); 3238 (-NH); 3287 (O-H). ^{1}H NMR 1.12 (t, 3H, CH_3 of C_2H_5), 1.55 (s, 3H, dihydropyridyl CH_3), 4.07 (q, 2H, CH_2 of C_2H_5) 5.4 (s, 2H, NH_2); 5.66 (d, 1H, NH); 7.22-7.3 (m, ArH), 7.8 (s, 1H, 1 NH). m/e 378.19 (100.0%), 379.19 (21.1%), 380.20 (1.9%). C,57.13, H,6.93, N,14.81, O,21.14.

Ethyl -1- (2–hydrazine –2- oxo ethyl) –6– methyl –2– oxo -4– (3–hydroxyl phenyl) - 1, 2, 3, 4 –tetrahydro pyrimidine –5– carboxylate. (3c)

yield: 68 %. mp 222-224°C. IR (KBr): v(cm^{-1}) 1608 (amideC=O), 1647 (ester C=O), 1706 (carbohydrazide C=O), 3044 (aromatic C-H stretch); 3238 (-NH); 3287 (O-H). ^{1}H NMR 1.12 (t, 3H, CH_3 of C_2H_5), 1.57 (s, 3H, dihydropyridyl CH_3), 4.07 (q, 2H, CH_2 of C_2H_5) 5.45 (s, 2H, NH_2); 5.65 (d, 1H, NH); 7.22-7.3 (m, ArH), 7.8 (s, 1H, 1 NH). m/e 348.18 (100.0%), 349.18 (20.0%), 350.19 (1.7%). C,58.61, H,6.94, N,16.08, O,18.37.

Ethyl -1- (2–hydrazine –2- oxo ethyl) –6– methyl –2– oxo -4– (3 – amino phenyl) - 1, 2, 3, 4 –tetrahydro pyrimidine –5– carboxylate. (3d)

yield:70 %. mp 226-228°C. IR (KBr): v(cm^{-1}) 1265 (aromatic amines C-N stretch); 1608 (amideC=O), 1647 (ester C=O), 1706 (carbohydrazide C=O), 3044 (aromatic C-H stretch); 3238 (-NH); 3287 (O-H). ^{1}H NMR 1.1 (t, 3H, CH_3 of C_2H_5), 1.57 (s, 3H, dihydropyridyl CH_3), 4.10 (q, 2H, CH_2 of C_2H_5) 5.43 (s, 2H, NH_2); 5.6 (d, 1H, NH); 7.22-7.3 (m, ArH), 7.83 (s, 1H, 1NH). m/e 347.20 (100.0%), 348.20 (18.8%), 349.20 (2.6%). C,58.77, H,7.25, N,20.16, O,13.82.

Ethyl -1- (2–azido –2- oxo ethyl) –6– methyl –2– oxo –4– (1 – chloro phenyl) - 1, 2, 3, 4 –tetrahydro pyrimidine -5– carboxylate. (4a)

yield: 69%. mp 219-224°C. IR (KBr): v(cm^{-1}) 1549 (CO of CON_3), 1603 (C=O of ring carbonyl), 1641 (C=O ester), 2361 (azide bond), 3424 (NH). ^{1}H NMR 1.14 (t, 3H, CH_3), 2.3 (s, 3H, CH_3), 4.3 (q, 2H, CH_2), 4.52 (s, 2H, CH_2), 5.7 (s, 1H, dihydropyridyl -CH) , 7.23-7.36 (m, Ar H),7.77 (s, 1H, NH). m/e 351.12 (100.0%), 353.12 (32.2%), 352.13 (17.63%). C,52.53, H,5.51, Cl,9.69, N,15.93, O,13.12.

Ethyl -1- (2–azido –2- oxo ethyl) –6– methyl –2– oxo –4– (1 – hydroxyl –2– methoxy phenyl) - 1, 2, 3, 4 – tetrahydropyrimidine -5– carboxylate. (4b)

yield: %. mp 218-221°C . IR (KBr): v(cm^{-1}) 1549 (CO of CON_2), 1603 (C=O of ring carbonyl), 1641 (C=O ester), 2361 (azide bond), 2947 (C-H stretch of methyl); 3289 (O-H stretch); 3424 (NH). ^{1}H NMR 1.15 (t, 3H, CH_3), 2.3 (s, 3H, CH_3), 4.34 (q, 2H, CH_2), 4.54 (s, 2H, CH_2), 5.74 (s, 1H, dihydropyridyl -CH) , 7.23-7.36 (m, ArH),7.75 (s, 1H, NH). m/e 366.17 (100.0%), 364.17 (18.8%), 365.17 (2.9%). C,56.19, H,6.38, N,15.42, O,22.01.

Ethyl -1- (2–azido –2- oxo ethyl) –6– methyl –2– oxo –4– (3 – hydroxyl phenyl) - 1, 2, 3, 4 –tetrahydro pyrimidine -5– carboxylate. (4c)

yield: %. mp 219-220°C. IR (KBr): v(cm^{-1}) 1549 (CO of CON_2), 1603 (C=O of ring carbonyl), 1641 (C=O ester), 2361 (azide bond), 2997 (Aromatic C-H stretch); 3289 (O-H stretch); 3424 (NH). ^{1}H NMR 1.11 (t, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.32 (q, 2H, CH_2), 4.53 (s, 2H, CH_2), 5.74 (s, 1H, dihydropyridyl -CH) , 7.23-7.36 (m, ArH),7.78 (s, 1H, NH). m/e 333.16 (100.0%), 334.16 (19.3%), 335.17 (1.5%). C,55.32, H,6.09, N, 15.16, O,18.42.

Ethyl -1- (2–azido –2- oxo ethyl) –6– methyl –2– oxo –4– (3 – amino phenyl) - 1, 2, 3, 4 –tetrahydro pyrimidine -5– carboxylate. (4d)

yield: %. mp 223-2225°C. IR (KBr): v(cm^{-1}) 1254 (C-N of aromatic amine); 1549 (CO of CON_2), 1603 (C=O of ring carbonyl), 1641 (C=O ester), 2361 (azide bond), 2997 (Aromatic C-H stretch); 3424 (NH). ^{1}H NMR 1.14 (t,3H,CH_3), 2.37 (s, 3H, CH_3), 4.32 (q, 2H, CH_2), 4.54 (s, 2H, CH_2), 5.74 (s, 1H, dihydropyridyl -CH), 7.23-7.36 (m, Ar H),7.77 (s, 1H, NH). m/e 332.18 (100.0%), 333.18 (17.7%), 334.18 (2.5%). C,55.4, H,6.40, N,16.26, O,13.86.

Ethyl - (5-(ethoxy carbonyl) –4- (4–chloro phenyl) -3, 4 –dihydro –6– methyl –2– oxopyrimidin - 1(2H) - yl) methylcarbamate. (5a)

yield: 89 %. mp 207-213°C. IR (KBr): v(cm^{-1}) 1648 (CONH), 1701 (C=O of ring carbonyl), 1724 (C=O ester), 2978 (aromatic proton stretching), 3116 (CONH), 3245 (NH stretching). ^{1}H NMR 1.14 (t, 3H, CH_3), 1.6(s, 1H, CH of dihydropyridyl), 2.45 (s, 3H, CH_3), 4.0 (q, 2H, CH_2), 5.3 (d, 2H, CH_2), 5.6 (s, 1H, NH of NHCO), 7.2-7.3 (m, 10 Ar H),7.8 (s, 1H, NH). m/e: 395.12 (100.0%), 397.12 (32.0%), 396.13 (19.9%), 398.13 (6.7%), 397.13 (3.1%), 396.12 (1.1%). C, 54.62; H, 5.60; Cl, 8.96; N, 10.62; O, 20.21

Ethyl - (5-(ethoxycarbonyl) -3, 4– dihydro –4- (4– hydroxyl –3- methoxyphenyl) –6– methyl –2– oxopyrimidin - 1(2H) - yl) methylcarbamate. (5b)

yield: 75 %. mp 211-213°C. IR (KBr): v(cm^{-1}) 1648 (CONH), 1701 (C=O of ring carbonyl), 1724 (C=O ester), 2833 (methyl C-H stretch); 2978 (aromatic proton stretching), 3116 (CONH), 3245 (NH stretching). 3288 (O-H); ^{1}H NMR 1.11 (t, 3H, CH_3), 1.65 (s, 1H, CH of dihydropyridyl), 2.43 (s, 3H, CH_3), 4.0 (q, 2H, CH_2), 5.35 (d, 2H, CH_2), 5.6 (s, 1H, NH of NHCO), 7.2-7.3 (m, 10 Ar H),7.78 (s, 1H, NH). m/e: 407.17 (100.0%), 408.17 (21.9%), 409.18 (2.1%), 409.17 (1.7%). C, 56.01; H, 6.18; N, 10.31; O, 27.49

Ethyl - (5-(ethoxycarbonyl) -3, 4– dihydro –4- (2 -hydroxyphenyl) –6– methyl –2 – oxopyrimidin - 1(2H) - yl) methylcarbamate (5c)

yield: 77 %. mp 209-210°C. IR (KBr): v(cm^{-1}) 1648 (CONH), 1701 (C=O of ring carbonyl), 1724 (C=O ester), 2833 (methyl C-H stretch); 2978 (aromatic proton stretching), 3056 (Aromatic C-H stretch); 3116 (CONH), 3245 (NH stretching). 3289 (O-H); ^{1}H NMR 1.17 (t, 3H, CH_3), 1.6(s, 1H, CH of dihydropyridyl), 2.43 (s, 3H, CH_3), 4.04 (q, 2H, CH_2), 5.3 (d, 2H, CH_2), 5.6 (s, 1H, NH of NHCO), 7.2-7.3 (m, 10 Ar H),7.78 (s, 1H, NH). m/e: 377.16 (100.0%), 378.16 (21.1%), 379.17 (1.9%), 379.16 (1.5%). C, 57.29; H, 6.14; N, 11.13; O, 25.44

Ethyl - (5 - (ethoxycarbonyl) –4- (2 - aminophenyl) –3, 4 – dihydro –6– methyl –2– oxopyrimidin - 1(2H) - yl) methylcarbamate (5d)

yield: 68 %. mp 212-214°C. IR (KBr): v(cm^{-1}) 1248 (C-N stetch of primary amines); 1648 (CONH), 1701 (C=O of ring carbonyl), 1724 (C=O ester), 2833 (methyl C-H stretch); 2978 (aromatic proton stretching), 3056 (Aromatic C-H stretch); 3116 (CONH), 3245 (NH stretching). ^{1}H NMR 1.17 (t, 3H, CH_3), 1.64 (s, 1H, CH of dihydropyridyl), 2.44 (s, 3H, CH_3), 4.04 (q, 2H, CH_2), 5.32 (d, 2H, CH_2), 5.6 (s, 1H, NH of NHCO), 7.2-7.3 (m, 10Ar H),7.77 (s, 1H, NH). m/e: 376.17 (100.0%), 377.18 (19.9%), 378.18 (3.2%), 377.17 (1.5%). C, 57.44; H, 6.43; N, 14.88; O, 21.25

Ethyl –6– methyl –2– oxo – 4 [4 – chloro – phenyl –1– (methyl –3– phenyl urea)] – 1, 2, 3, 4, - tetrahydropyrimidine –5– carboxylate (6a)

yield: 50 %. mp 220-223°C. IR (KBr): ν(cm^{-1}) 1648 (CONH), 1701 (C=O of ring carbonyl), 1725 (C=O ester), 2927 (aromatic proton stretching), 3117 (CONH), 3245 (NH stretching). 1H NMR 1.14 (t, 3H CH_3), 1.5 (s,1H, CH of dihydropyridyl), 2.45 (s,3H CH_3), 4.0 (q,2H CH_2), 5.4 (d,2H CH_2), 5.5 (d,1H NH),), 7.2-7.3 (m,Ar H), 7.71 (s,1H NH). m/e: 442.14 (100.0%), 444.14 (32.3%), 443.14 (25.4%), 445.14 (7.8%), 444.15 (3.6%), 446.14 (1.2%). C, 59.66; H, 5.23; Cl, 8.00; N, 12.65; O, 14.45.

Ethyl –6– methyl –2– oxo –4 [4 – chloro – phenyl –1– (methyl –3– p - tolyurea)] – 1, 2, 3, 4, - tetrahydro pyrimidine –5– carboxylate (6b)

yield:81%. mp 214-217°C. IR (KBr): ν(cm^{-1}) 1648 (CONH), 1701 (C=O of ring carbonyl), 1725 (C=O ester), 2927 (aromatic proton stretching), 3068 (Aromatic C-H stretch); 3117 (CONH), 3245 (NH stretching). 1H NMR 1.11 (t,3H CH_3), 1.5(s,1H, CH of dihydropyridyl), 2.44 (s,3H CH_3), 4.04 (q,2H CH_2), 5.4 (d,2H CH_2), 5.54 (d,1H NH),), 7.2-7.3 (m,ArH), 7.71 (s,1H NH). m/e: 456.16 (100.0%), 458.15 (32.0%), 457.16 (25.3%), 459.16 (8.4%), 458.16 (4.2%), 457.15 (1.5%), 460.16 (1.3%). C, 60.46; H, 5.51; Cl, 7.76; N, 12.26; O, 14.01

Ethyl –6– methyl –2– oxo – 4 [4 – hydroxyl –3– methoxy phenyl –1– (methyl –3– p - tolyurea)] – 1, 2, 3, 4, - tetrahydropyrimidine –5– carboxylate (6c)

yield:66 %. mp 235-237°C. IR (KBr): ν(cm^{-1}) 1648 (CONH), 1701 (C=O of ring carbonyl), 1725 (C=O ester), 2927 (aromatic proton stretching), 2950 (methyl C-H stretch); 3068 (Aromatic C-H stretch); 3117 (CONH), 3245 (NH stretching); 3288 (O-H stretch). 1H NMR 1.14 (t, 3H CH_3), 1.5(s, 1H, CH of dihydropyridyl),2.47 (s, 3H CH_3), 4.04 (q, 2H CH_2), 5.45 (d, 2H CH_2), 5.5 (d, 1H NH),), 7.2-7.3 (m, ArH), 7.70 (s, 1H NH). m/e: 452.21 (100.0%), 453.21 (26.5%), 454.21 (4.7%), 453.20 (1.5%). C, 63.70; H, 6.24; N, 12.38; O, 17.68

Ethyl –6– methyl –2– oxo – 4 [2 – hydroxy phenyl –1– (4 – chloro phenyl) –3– methyl urea] – 1, 2, 3, 4, - tetrahydropyrimidine –5– carboxylate (6d)

yield: 70%. mp 239-242°C. IR (KBr): ν(cm^{-1}) 1648 (CONH), 1701 (C=O of ring carbonyl), 1725 (C=O ester), 2927 (aromatic proton stretching), 2960 (methyl C-H stretch); 3060 (Aromatic C-H stretch); 3117 (CONH), 3245 (NH stretching); 3288 (O-H stretch). 1H NMR 1.14 (t, 3H CH_3), 1.5(s, 1H, CH of dihydropyridyl), 2.47 (s, 3H CH_3), 4.04 (q, 2H CH_2), 5.45 (d, 2H CH_2), 5.5 (d, 1H NH),), 7.2-7.3 (m, Ar H), 7.70 (s, 1H NH). m/e: 458.14 (100.0%), 460.13 (32.0%), 459.14 (24.2%), 461.14 (8.1%), 460.14 (4.1%), 459.13 (1.5%), 462.14 (1.2%). C, 57.58; H, 5.05; Cl, 7.73; N, 12.21; O, 17.43

Ethyl –6– methyl –2– oxo – 4 [2 – amino phenyl –1– (4 – chloro phenyl) –3– methyl urea] – 1, 2, 3, 4, - tetra hydropyrimidine –5– carboxylate (6e)

yield:79%. mp 247-249°C. IR (KBr): ν(cm^{-1}) 1260 (C-N of aromatic amines); 1648 (CONH), 1701 (C=O of ring carbonyl), 1725 (C=O ester), 2927 (aromatic proton stretching), 2965 (methyl C-H stretch); 3060 (Aromatic C-H stretch); 3117 (CONH), 3245 (NH stretching); 3287 (O-H stretch). 1H NMR 1.14 (t, 3H CH_3), 1.5(s, 1H, CH of dihydropyridyl), 2.47 (s, 3H CH_3), 4.04 (q, 2H CH_2), 5.45 (d, 2H CH_2), 5.5 (d, 1H NH),), 7.2-7.3 (m, Ar H), 7.70 (s, 1H NH). m/e: 457.15 (100.0%), 459.15 (32.4%), 458.16 (24.2%), 460.15 (8.3%), 459.16 (3.6%), 458.15 (1.8%). C, 57.70; H, 5.28; Cl, 7.74; N, 15.29; O, 13.98

Ethyl –6– methyl –2– oxo –1 - [(3 – phenoxy carbonyl amino) methyl] –4– (4 – chloro phenyl) - 1, 2, 3, 4, - tetrahydropyrimidine –5– carboxylate (7a)

yield: 82%. mp 264-266°C. IR (KBr): ν(cm^{-1}) 1648 (CONH), 1702 (C=O of ring carbonyl), 1725 (C=O ester), 2978 (aromatic proton stretching), 3118 (CONH), 3245 (NH stretching). 1H NMR 1.14 (t, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.0 (q, 2H, CH_2), 5.3 (d, 2H, CH_2), 5.6 (s, NH, of NHCOOR), 7.2-7.3 (m, ArH), 7.77 (s, 1H, NH),7.9 (d, 1H, NH). m/e: 443.12 (100.0%), 445.12 (32.0%), 444.13 (24.2%), 446.13 (8.2%), 445.13 (4.1%), 447.13 (1.2%), 444.12 (1.1%). C, 59.53; H, 5.00; Cl, 7.99; N, 9.47; O, 18.02

Ethyl –6– methyl –2– oxo –1- [(3 – {4 – nitro phenyl }carbonyl amino) methyl] –4– (4 – hydroxyl –3– methoxy phenyl) - 1, 2, 3, 4, - tetrahydropyrimidine –5– carboxylate (7b)

yield: 80%. mp 278-280°C. IR (KBr): v(cm^{-1}) 852 C-N stretch for Ar-NO_2); 1523 (N=O stretch); 1648 (CONH), 1702 (C=O of ring carbonyl), 1725 (C=O ester), 2978 (aromatic proton stretching), 3060 (Aromatic C-H stretch); 3118 (CONH), 3245 (NH stretching); 3288 (O-H Stretch). 1H NMR 1.14 (t, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.0 (q, 2H, CH_2), 5.3 (d, 2H, CH_2), 5.65 (s, NH, of NHCOOR), 7.2-7.3 (m, ArH), 7.75 (s, 1H, NH),7.92 (d, 1H, NH). m/e: 500.15 (100.0%), 501.16 (25.5%), 502.16 (5.0%), 501.15 (1.5%). C, 55.20; H, 4.83; N, 11.20; O, 28.77

Ethyl –6– methyl –2– oxo –1- [(3 – (4 – nitro phenyl }carbonyl amino) methyl] –4– (2 – hydroxy phenyl) - 1, 2, 3, 4, - tetrahydropyrimidine –5– carboxylate (7c)

yield: 72 %. mp 270-273. IR (KBr): v(cm^{-1}) 850 (C-N stretch for Ar-NO_2); 1525 (N=O stretch); 1648 (CONH), 1702 (C=O of ring carbonyl), 1725 (C=O ester), 2978 (aromatic proton stretching), 3060 (Aromatic C-H stretch); 3118 (CONH), 3245 (NH stretching); 3289 (O-H Stretch). 1H NMR 1.14 (t, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.04 (q, 2H, CH_2), 5.35 (d, 2H, CH_2), 5.65 (s, NH, of NHCOOR), 7.2-7.3 (m, ArH), 7.77 (s, 1H, NH),7.90 (d, 1H, NH). m/e: 470.14 (100.0%), 471.15 (24.4%), 472.15 (4.5%), 471.14 (1.5%). C, 56.17; H, 4.71; N, 11.91; O, 27.21

Ethyl –6– methyl –2– oxo –1- [(3 – phenoxy carbonyl amino) methyl] –4– (2 – amino phenyl) - 1, 2, 3, 4, - tetrahydropyrimidine –5– carboxylate (7d)

yield: 66%. mp 261-263°C. IR (KBr): v(cm^{-1}) 1335 (C-N for aromatic amines); 1648 (CONH), 1702 (C=O of ring carbonyl), 1725 (C=O ester), 2978 (aromatic proton stretching), 3068 (Aromatic C-H stretch); 3118 (CONH), 3245 (NH stretching). 1H NMR 1.14 (t, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.0 (q, 2H, CH_2), 5.35 (d, 2H, CH_2), 5.66 (s, NH, of NHCOOR), 7.2-7.3 (m, ArH), 7.77 (s, 1H, NH), 7.92 (d, 1H, NH). m/e: 424.17 (100.0%), 425.18 (24.3%), 426.18 (4.2%), 425.17 (1.5%). C, 62.25; H, 5.70; N, 13.20; O, 18.85

Ethyl –6– methyl –2– oxo –1- [(3 – phenoxy carbonyl amino) methyl] –4– (4 – hydroxyl –3– methoxy phenyl) - 1, 2, 3, 4, -tetrahydropyrimidine –5– carboxylate. (7e)

yield: 65 %. mp 255-256°C. IR (KBr): v(cm^{-1}) 1648 (CONH), 1702 (C=O of ring carbonyl), 1725 (C=O ester), 2835 (methyl C-H stretch); 2978 (aromatic proton stretching), 3028 (N-H stretch); 3068 (Aromatic C-H stretch); 3118 (CONH), 3245 (NH stretching); 3289 (OH stretch). 1H NMR 1.14 (t, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.0 (q, 2H, CH_2), 5.35 (d, 2H, CH_2), 5.66 (s, NH, of NHCOOR), 7.2-7.3 (m, ArH), 7.77 (s, 1H, NH),7.92 (d, 1H, NH). m/e: 455.17 (100.0%), 456.17 (26.3%), 457.18 (3.1%), 457.17 (1.7%). C, 60.65; H, 5.53; N, 9.23; O, 24.59

Ethyl –6– methyl –2– oxo –1- [(3 – {4 – nitro phenyl }carbonyl amino) methyl] –4– (4 – chloro phenyl) - 1, 2, 3, 4, - tetrahydropyrimidine –5– carboxylate. (7f)

yield: 61%. mp 272-274°C. IR (KBr): v(cm^{-1})) 850 C-N stretch for Ar-NO_2); 1525 (N=O stretch); 1648 (CONH), 1702 (C=O of ring carbonyl), 1725 (C=O ester), 2978 (aromatic proton stretching), 3060 (Aromatic C-H stretch); 3118 (CONH), 3245 (NH stretching). 1H NMR 1.14 (t, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.04 (q,2H, CH_2), 5.35 (d, 2H, CH_2), 5.65 (s, NH, of NHCOOR), 7.2-7.3 (m,Ar H), 7.78 (s, 1H, NH), 7.90 (d,1H, NH). m/e: 488.11 (100.0%), 490.11 (33.8%), 489.11 (25.5%), 491.11 (7.8%), 490.12 (2.8%), 492.11 (1.5%). C, 54.05; H, 4.33; Cl, 7.25; N, 11.46; O, 22.91.

Discussion:

The prepared compounds are white crystalline solids and soluble at room temperature in ethanol, by heating in benzene, toluene and water. The structure, molecular formula, molecular weight, melting points, yield and R_f values of new derivatives are presented in table 1.

The results shows that the molecular weight of the prepared compounds were ranged between 377g to 500g , the melting points between 207^0 to 224^0c and yield of synthesized compounds were obtained between 61 to 89%.

Pharmacological Activity:

Whereas compounds 6b to 6d, 7b to 7e failed to show any blocking activity in the isolated rat aorta assay. Compounds 5a to 5d, 6a, 6e, 7a, 7f were found to be active in different degrees in table 2. The results indicated

that both compounds 5a and 6e were most actively showed calcium channel blocking potency of 102±5 and 99±1 respectively. The observed results compared with standard calcium channel blocker Nifedipine which exhibited a blocking potency of 7.46±0.05. On the other hand the maximal antagonistic effect expressed as a percentage E_{max} value of 101±1 by Nifedipine was not achived by all derivatives. The highest E_{max} value was found by 5a in both compounds 5a and 6e respectively. The obtained results indicated that addition of carbamate and carbamide side chain on 1st position shows good calcium channel blocking activity compared with Nifedipine. Structure activity relationships observed in present study that presence of amide and esters substitutions at third position led to completely inactive molecule whereas substitution at first position led to good activity.

Since compounds 5a (graph 1) and 6e were moderate to high potent in relaxing effect in rat aorta, a cumulative concentration-response curves for both compounds were established to further investigation to check a competitive antagonism is present or not. The antagonist potencies and maximal responses are summarized in table 2.

Graph-1: A typical graph showing A1 (5a) on relaxation response in KCl induced pre contracted rat aorta.

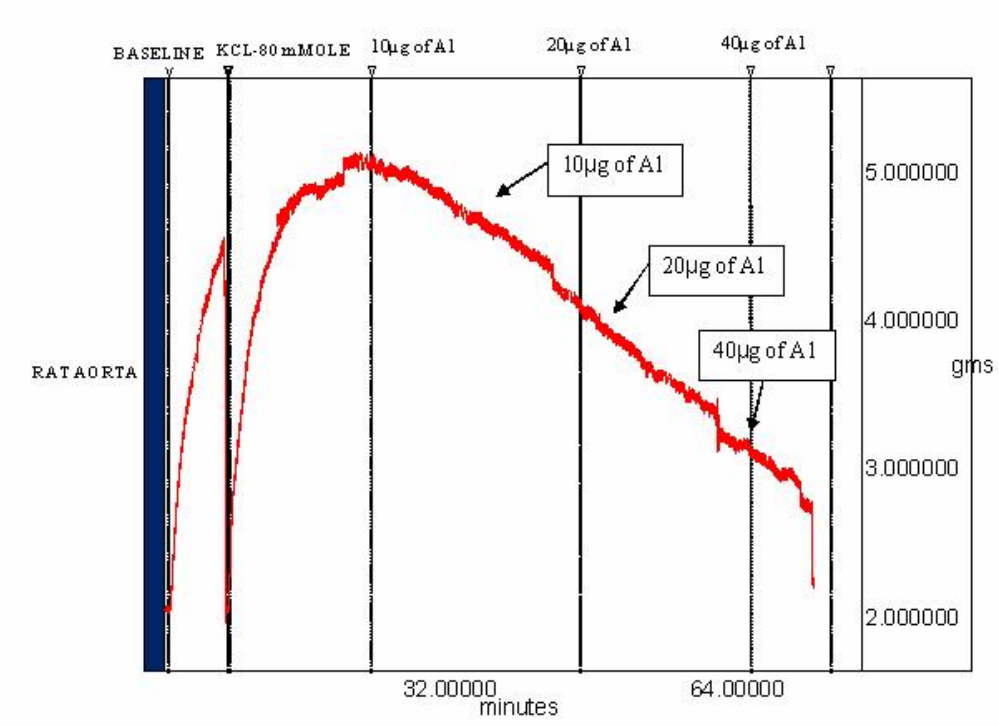


Table 1 characteristic of the new compounds **(5a-7f)**

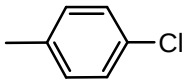
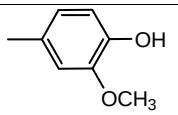
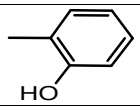
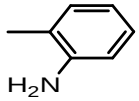
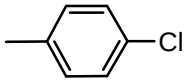
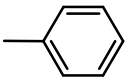
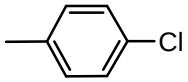
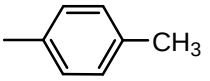
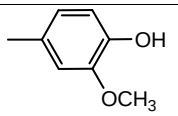
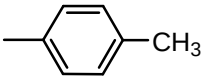
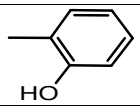
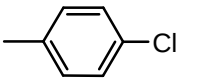
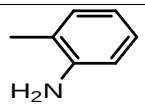
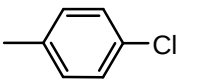
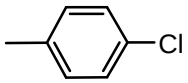
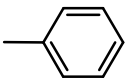
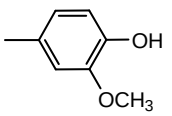
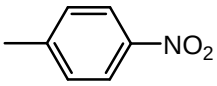
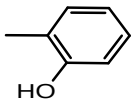
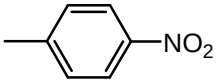
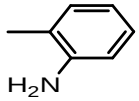
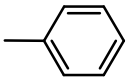
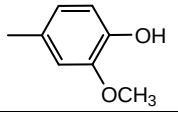
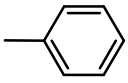
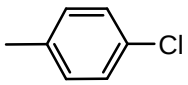
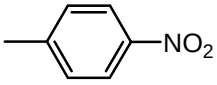
Compound	R	R_1	Mol. Formula	Mol. Weight	M.P. °C	% Yield	R_f value
5a		----	$C_{18}H_{22}ClN_3O_5$	**395**	**207**	**89**	**0.75**
5b		-----	$C_{19}H_{25}N_3O_7$	**407**	**210**	**75**	**0.78**
5c		-----	$C_{18}H_{23}N_3O_6$	**377**	**209**	**77**	**0.77**
5d		-----	$C_{18}H_{24}N_4O_5$	**376**	**230**	**68**	**0.79**
6a			$C_{22}H_{23}ClN_4O_4$	**442**	**220**	**50**	**0.82**
6b			$C_{23}H_{25}ClN_4O_4$	**456**	**214**	**81**	**0.86**
6c			$C_{24}H_{28}N_4O_5$	**452**	**218**	**66**	**0.77**
6d			$C_{22}H_{23}ClN_4O_5$	**458**	**215**	**70**	**0.82**
6e			$C_{22}H_{24}ClN_5O_4$	**457**	**218**	**79**	**0.78**
7a			$C_{22}H_{22}ClN_3O_5$	**443**	**212**	**82**	**0.72**
7b			$C_{22}H_{24}N_4O_9$	**500**	**215**	**80**	**0.77**
7c			$C_{22}H_{22}N_4O_8$	**470**	**220**	**72**	**0.81**
7d			$C_{22}H_{24}N_4O_5$	**424**	**218**	**66**	**0.88**
7e			$C_{23}H_{25}N_3O_7$	**455**	**224**	**65**	**0.74**
7f			$C_{22}H_{21}ClN_4O_7$	**488**	**222**	**61**	**0.71**

Table 2 Observed calcium channel blocking activities for synthesized compounds

Compound	R	R^1	pEC_{50}±SEM	E_{max} (%) ± SEM	n
5a	**4-chlorophenyl**	**_**	**6.86 ± 0.10**	**102 ± 5**	**5**
5b	**4–hydroxyl–3-methoxyphenyl**	**_**	**5.38 ± 0.10**	**99 ± 1**	**5**
5c	**2-hydroxyphenyl**	**_**	**4.37 ± 0.10**	**99 ± 1**	**5**
5d	**2-aminophenyl**	**_**	**4.31 ± 0.07**	**92 ± 5**	**3**
6a	**4-chlorophenyl**	**Phenyl**	**5.32 ± 0.10**	**92 ± 7**	**4**
6b	**4-chlorophenyl**	**4-methyl phenyl**	**No effect**	**_**	**3**
6c	**4–hydroxyl–3-methoxyphenyl**	**4-methyl phenyl**	**No effect**	**_**	**4**
6d	**2-hydroxyphenyl**	**4-chloro phenyl**	**No effect**	**_**	**4**
6e	**2-aminophenyl**	**4-chloro phenyl**	**6.97 ±0.10**	**99 ± 1**	**5**
7a	**4-chlorophenyl**	**Phenyl**	**4.33 ± 0.10**	**94 ± 1**	**3**
7b	**4–hydroxyl–3-methoxyphenyl**	**4-nitro phenyl**	**No effect**	**_**	**3**
7c	**2-hydroxyphenyl**	**4-nitro phenyl**	**No effect**	**_**	**4**
7d	**2-aminophenyl**	**Phenyl**	**No effect**	**_**	**3**
7e	**4–hydroxyl–3-methoxyphenyl**	**Phenyl**	**No effect**	**_**	**3**
7f	**4-chlorophenyl**	**4-nitro phenyl**	**No effect**	**_**	**4**
Nifedipine	**_**	**_**	**7.46 ± 0.05***	**101 ± 1***	**_**

***(Moritz et al., 2006)**

R= Substituted aldehydes

R^1 for Compound 6a-6e = Substituted aromatic amines

R^1 for Compound 7a-7f = Substituted aromatic phenols

Conclusion:

The obtained results reveal that a introduction of ester moiety at first position which was converted to carbohydrazine on treating hydrazine hydrate and then to azide, which was converted to carbamate and carbamide on treating with ethanol/ phenols/ amines. Synthesized compounds shows calcium channel blocking activity on rat aorta. Although some of the developed compounds show maximal response comparable to Nifedipine. As we know amides are more stable to metabolic enzymes than others. The developed compounds in the present study will predicatively show on increased metabolic stability and consequently longer duration of action as compared to Nifedipine. Therefore further optimization to be needed for new class of antihypertensive agents.

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