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Synthesis and *in-vitro* screening of novel dihydropyrimidine derivatives as potential calcium channel blockers

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ABSTRACT

Novel dihydropyrimidine derivatives were synthesized and evaluated for their calcium channel blocker activity. Synthesis involves the modification of dihydropyrimidine (DHPM) pharmacophore with thiosemicarbazide, semicarbazide and hydrazide functions. The calcium channel blocker effect was tested on rat ileum by taking cumulative responses of the test compound on KCl (60mM) - induced contracted rat ileum. Among all the synthesized compounds, DHPMs with semicarbazide residue have shown the most significant activity. Among semicarbazides series, compound 6C was found to show potent Calcium channel blocker activity.

Keywords: Thiosemicarbazide, semicarbazide, one-pot synthesis

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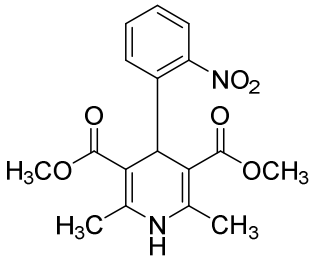
INTRODUCTION

Calcium channel blockers (CCBs) are prescribed for the treatment of hypertension, angina and arrhythmia [1]. The currently available CCBs (mostly dihydropyridines, DHPs) are effective for the treatment, but still many of these drugs have disadvantages such as light sensitivity of DHPs, pharmacokinetic and ADMET problems such as very short plasma half-life, and clinical administration of drugs with negative inotropic activity is not desirable because of their cardiosuppresive effects, especially in patients with a tendency towards heart failure [2]. There is a need for development of promising novel drug candidates free from these detrimental effects. Dihydropyrimidine derivatives are widely used for the variety of pharmacological actions [3,4] and are screened for diverse range of biological activities such as calcium channel blocker [5,6], antitubercular [7], antitumor [4,8], antiepileptic [9], antimalarials [10], antiviral [11], anti-inflammatory [12], analgesic [12,13], and antimicrobial [14] activity. It is not surprising that dihydropyrimidines are often reported as CCBs because dihydropyrimidines are aza- analogs of dihydropyridines which are well established as cardiovascular agents [15]. In fact, they have been found to be bioisosteres of DHPs [16]. 4-Aryl-1, 4-dihydropyridines (DHPs) of the nifedipine and amlodipine type were introduced into clinical medicine in 1975 and they are still the most potent group of calcium channel modulators for the treatment of cardiovascular diseases. Recent articles reported the importance of the DHPM analogues as calcium channel blockers [17, 18]. It is therefore tempting us to examine a closely related structure, i.e. 3, 4-dihydropyrimidines. Thus, DHPMs also serve as an important tool for the design of calcium channel blockers [7]. The present work is devoted to a study of promising dihydropyrimidine derivatives encouraged by the recent investigations in this area and their versatile pharmacological profile.

Many research groups have worked on DHPM moiety to explore its SAR (structural activity relationship). To the best of our knowledge, the modification at ester functionality is studied for the first time. Our group is interested in exploring pharmacological activities of semicarbazides, thiosemicarbazide and hydrazide functions. In our designed molecules, we are introducing these functional groups in the structure by replacing the ester group. The designed molecules are shown in the figure 1.

Figure 1.

Structure 1: Nifedipine



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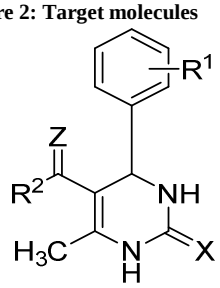
Structure 2: Target molecules



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Where R^1 = -H, m-Cl, p-Cl, Z = $NH_2NHCSNH_2$ / $NH_2NHCONH_2$/O, R^2= -CH_3, $NHNH_2$, X= O, S

MATERIALS AND METHODS

Chemistry:

All chemicals used were of Research-lab fine chem. industries, Mumbai. Solvents and Chemicals were purified wherever required. The completion of reaction was checked by thin layer chromatography (TLC) on silica gel-G coated plates and spots were visualized by exposure to iodine vapors. All the synthesized compounds were purified by recrystallization using suitable solvents before the characterization. All melting points were determined by open cup capillary method and were uncorrected.

General method:

Synthesis of DHPM derivatives by using Biginelli Multicomponent condensation reaction [19] (4 A-C, 7 A-C): Dihydropyrimidine derivatives (4A-C, 7A-C and 9) were prepared according to the earlier reported procedures . Briefly, dihydropyrimidine derivatives were prepared from substituted aryl aldehydes (**1**), thiourea or urea (**2**) and 1, 3-dicarbonyl compounds **(3)** i.e. ethylacetoacetate or acetyl acetone by refluxing together in the presence of catalytic quantity of hydrochloric acid and ethanol as solvent. The dihydropyrimidines thus obtained were recrystallised with ethanol.

1. *General method for Synthesis of DHPM with thiosemicarbazones (5A-C) or semicarbazones (6A-C)* residue:

3 mmole of thiosemicarbazide or semicarbazide in 12 ml ethanol was added to a boiling solution of 2.5 mmole of **4A** in methanol. Few drops of conc. HCl were added as a catalyst, and the reaction mixture was refluxed for 3.5 hr. After the completion of reaction, reaction mixture was cooled in ice-bath. Solid thus separated was filtered, dried and recrystallised form methanol.

2. *General method for Synthesis of DHPM with Hydrazide residue at C_5 ester function (8A-C):*

To 3 mmol (0.14 ml) of boiling solution of hydrazine hydrate (99%), 1mmol of **4A** in ethanol was added drop wise with stirring and mixture was refluxed for 3.5 hr. After the completion of reaction, reaction mixture was cooled to r.t. Separated product was filtered and washed with cold water and recrystallised from methanol.

Characterization data for prototype compounds:

The compounds were analyzed by FT-IR on a Jasco FT-IR spectrophotometer, model-4100 using KBr pellet. Prototype compounds were selected from a series and analyzed for ^{1}H-NMR using BRUKER AVANCE-II 400 NMR spectrophotometer using $CDCl_3$ and DMSO as per the solubility of synthesized compounds. The prototype compound was selected from the series and analyzed for mass spectrometry.

(Compound 5A) 2-[1-(6-methyl-4-phenyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidin-5-yl) ethylidene] hydrazinecarbothioamide: yield 72 %, mp. 216-218°C; FTIR (γmax, cm^{-1}) 3504 & 3414 (1° -NH stretch), 3353, 3264 (2° -NH stretch), 1656 (C=N α, β unsaturated stretch), 1587 (1° NH bend), ~1550 (2° NH bend), 1017, ~1410 (C-N aliphatic stretch), 1131(C=S stretch); ^{1}H NMR (400 MHz, DMSO-d_6)): dH 1.99 (s, 3H, C_6-CH_3), *δ* 2.06 (s, 3H, N=C-CH_3), *δ* 5.26 (d, 1H, *J* 8.5, C_4-H), *δ* 6.98 (s, 1H, N_3-H), *δ* 7.21-7.47 (m, 5H, Ar-H), *δ* 7.99 (s, 1H, N_1-H), *δ* 9.20 (s,1H, -NH-N), *δ* 9.87 (s, 2H,-NH_2). ^{13}C NMR (400 MHz, DMSO-d_6) *δ* 17.08, 52.21, 109.64, 126.59, 127.29, 127.63, 128.28, 128.39, 143.20, 147.42, 154.21,175.94, 178.35. MS calcd. for $C_{14}H_{17}N_5S_2$: 320.09. Found: 320.01 $(M+H)^+$

(Compound 5B) 2-{1-[4-(3-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimi- din-5-yl]ethylidene} hydrazinecarbothioamide: yield 63 %, mp. 212-215°C; FTIR (γmax, cm^{-1}) 3425 (1° NH stretch), 3266 (2° NH stretch), 1534 (1° NH bend), 1524 (2° NH bend), 1600 (C=N α, β unsaturated stretch). 1232 (C=S stretch), 1093,

1429 (C-N aliphatic stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.97 (s, 3H, C_6-CH_3), δ 2.05 (s, 3H, N=C-CH_3), δ 5.24 (d, 1H, *J* 8.5, C_4-H), δ 6.98 (s, 1H, N_3-H), δ 7.18 (d, 1H, Ar-H), δ 7.22 (t, 1H, Ar-H), δ 7.26 (d, 1H, Ar-H), δ 7.39 (s, 1H, Ar-H), δ 7.99 (s, 1H, N_1-H), δ 9.20 (s,1H, -NH-N), δ 9.87 (s, 2H,-NH_2). ^{13}C NMR (400 MHz, DMSO-d_6) δ 17.08, 51.72, 109.92, 126.59, 131.81, 132.78, 135.22, 135.49, 148.20, 149.42, 154.27, 175.94, 178.35. MS calcd for $C_{14}H_{16}ClN_5S_2$: 354.05. Found: 354.18 $(M+H)^+$.

(Compound 5C) 2-{1-[4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrim idin-5-yl]ethylidene} hydrazinecarbothioamide: yield 36 %, mp. 208-210°C; FTIR (γmax, cm^{-1}) 3425 (1° NH stretch), 3266 (2° NH stretch), 1672 (C=N α, β unsaturated stretch), 1571 (1° NH bend), 1529 (2° NH bend), 1090, ~1410 (C-N aliphatic stretch), 1203 (C=S stretch), 828 (C-Cl); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.99 (s, 3H, C_6-CH_3), δ 2.09 (s, 3H, N=C-CH_3), δ 5.27 (d, 1H, *J* 8.5, C_4-H), δ 6.99 (s, 1H, N_3-H), δ 7.28 (d, 2H, Ar-H), δ 7.34 (d, 2H, Ar-H), δ 7.99 (s, 1H, N_1-H), δ 9.20 (s,1H, -NH-N), δ 9.87 (s, 2H,-NH_2). ^{13}C NMR (400 MHz, DMSO-d_6) δ 17.08, 54.63, 109.92, 129.47, 130.27, 133.77, 135.58, 135.92, 149.87, 150.02, 154.27, 175.94, 178.35. MS calcd. for $C_{14}H_{16}ClN_5S_2$: 354.05. Found: 354.18 $(M+H)^+$.

(Compound 6A) 2-[1-(6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethylidene] hydrazine carboxamide: yield 62 %, mp. 210-212°C; FTIR (γmax, cm^{-1})3484 & 3401 (1° NH stretch), 3369 & 3202 (2° NH stretch), 1664 (C=N), ~1630 (amide C=N), 1572 (1°NH bend), 1529 (2°NH bend), 1025, 1443 (C-N aliphatic stretch), 1178 (C=S); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.99 (s, 3H, C_6-CH_3), δ 2.06 (s, 3H, N=C-CH_3), δ 5.26 (d, 1H, *J* 8.5, C_4-H), δ 6.98 (s, 1H, N_3-H), δ 7.21-7.47 (m, 5H, Ar-H), δ 7.99 (s, 1H, N_1-H), δ 7.92 (s,1H, -NH-N), δ 8.53 (s, 2H,-NH_2). ^{13}C NMR (400 MHz, DMSO-d_6) δ 17.08, 52.21, 109.64, 126.59, 127.29, 127.63, 128.28, 128.39, 143.20, 147.42, 154.21, 159.62, 175.94. m/z calcd for $C_{14}H_{17}N_5OS$: 303.12, Found: 303.25 $(M+H)^+$.

(Compound 6B) 2-{1-[4-(3-chlorophenyl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimi- din-5-yl]ethylidene} hydrazinecarboxamide yield 56 %, mp. 212-215°C; FTIR (γmax, cm^{-1}) 3468 (1° NH stretch), 3256 (2° NH stretch), 1688 (amide C=N), 1570 (1°NH bend), 1032 (C-N aliphatic stretch), 1091 (C=S), 837 (C-Cl); . ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.97 (s, 3H, C_6-CH_3), δ 2.05 (s, 3H, N=C-CH_3), δ 5.24 (d, 1H, *J* 8.5, C_4-H), δ 6.98 (s, 1H, N_3-H), δ 7.18 (d, 1H, Ar-H), δ 7.22 (t, 1H, Ar-H), δ 7.26 (d, 1H, Ar-H), δ 7.39 (s, 1H, Ar-H), δ 7.99 (s, 1H, N_1-H), δ 7.92 (s,1H, -NH-N), δ 8.53 (s, 2H,-NH_2). ^{13}C NMR (400 MHz, DMSO-d_6) δ 17.08, 51.72, 109.92, 126.59, 131.81, 132.78, 135.22, 135.49, 148.20, 149.42, 154.27, 159.23, 175.94. MS calcd. for $C_{14}H_{16}ClN_5OS$: 337.05. Found: 337.21 $(M+H)^+$.

(Compound 6C) 2-{1-[4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimi- din-5-yl] ethylidene} hydrazine carboxamide yield 67 %, mp. 200-202°C; FTIR (γmax, cm^{-1}) 3464 (1°NH stretch), 3281 (2°NH stretch), 1670 (C=N), (amide C=O), 1572 (1°NH bend), 1013 (C-N aliphatic stretch), 1091 (C=S stretch) 824 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.99 (s, 3H, C_6-CH_3), δ 2.09 (s, 3H, N=C-CH_3), δ 5.27 (d, 1H, *J* 8.5, C_4-H), δ 6.99 (s, 1H, N_3-H), δ 7.28 (d, 2H, Ar-H), δ 7.34 (d, 2H, Ar-H), δ 7.99 (s, 1H, N_1-H),), δ 7.92 (s,1H, -NH-N), δ 8.53 (s, 2H,-NH_2). ^{13}C NMR (400 MHz, DMSO-d_6) δ 17.08, 54.63, 109.92, 129.47, 130.27, 133.77, 135.58, 135.92, 149.87, 150.02, 154.27, 159.88, 175.94. MS calcd. for $C_{14}H_{16}ClN_5OS$: 337.05. Found: 337.21 $(M+H)^+$

(Compound 8A) 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydra- zide [20] yield 65 %, mp. 205-207°C; FTIR (γmax, cm^{-1}) 3244 (1° NH stretch), 3115 (2° NH stretch), 1592 (2° NH bend), 1186 (C-N aliphatic stretch), 1698 (amide C=O), 1648 (NH_2NH.C=O). ^{1}HNMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H, C_6-CH_3), δ 4.04-4.10 (br, 2H, -NH_2), δ 5.40 (s, 1H, C_4-H), δ 5.72 (s,1H, N_3-H), δ 6.98 (s, 1H, N_1-H), δ 7.26- 7.32 (m, 5H, Ar-H), δ 7.96 (t, 1H, *J* 10.0, -HN-CO-). ^{13}C NMR (400 MHz, DMSO-d_6) 17.60, 60.40, 110.34, 127.55, 128.35, 130.73, 134.47, 142.94, 148.13, 162.12, 167.42, 176.29. MS calcd. for $C_{12}H_{14}N_4O_2$: 247.77. Found: 247.92 $(M+H)^+$.

(Compound 8B) 4-(3-chlorophenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide: yield 88 %, mp. 195-197°C; FTIR (γmax, cm^{-1}) 3228 & 3118 (NH stretch), 1588 (2° NH bend), 1121(C-N aliphatic stretch), 1652 (amide C=O), 1596 (NH_2NH.C=O), 768 (C-Cl). ^{1}HNMR (400 MHz, DMSO): δ 2.32 (s, 3H, C_6-CH_3), δ 4.00-4.09 (br, 2H, -NH_2), δ 5.27 (s, 1H, C_4-H), δ 7.19-7.29 (m, 4H, Ar-H), δ 7.52 (s,1H, N_3-H), δ 7.77 (s, 1H, N_1-H), δ 9.07(1H, -HN-CO-).^{13}C NMR (400 MHz, DMSO-d_6) 17.60, 60.40, 110.34, 127.55, 129.37, 132.35, 134.79, 142.59, 148.22, 162.12, 167.42, 176.29. m/z calcd for C12H13ClN4O2: 281.07. Found: 281.25 $(M+H)^+$.

(Compound 8C) 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide: yield 58 %, mp. 213-215°C; FTIR (γmax, cm^{-1}) 3254, 3124 (NH stretch), 1594 (2° NH bend), 1141 (C-N aliphatic stretch), 1658 (amide C=O), 1602 (NH_2NH.C=O), 776 (C-Cl). ^{1}HNMR (400 MHz, DMSO): δ 2.36 (s, 3H, C_6-CH_3), δ 4.00-4.07 (br, 2H, -NH_2), δ 5.21 (s, 1H, C_4-H), δ 7.31-7.42 (m, 5H, Ar-H), δ 7.71 (s,1H, N_3-H), δ 7.94 (s, 1H, N_1-H), δ 9.56 (1H, -HN-CO-).^{13}C NMR (400 MHz, DMSO-d_6) 17.60, 60.40, 110.34, 127.55, 129.37, 134.25, 136.19, 142.58, 148.22, 162.12, 167.42, 176.29. m/z calcd for C12H12ClN4O2: 281.07. Found: 281.25 $(M+H)^+$.

Calcium channel blocker activity:
Wistar Albino rats of either sex weighing 120-200 g were used as experimental animals. The animals were maintained at an ambient temperature, in a group of 4 per cage under the standard laboratory conditions, receiving standard laboratory chow and water ad libitum. A 12h: 12h light and dark cycle was maintained throughout the experimental studies. All the tests have been performed in accordance with the guidelines laid by the Institutional Animal Ethics Committee (1329/AC/10/CPCSEA). For the in-vitro animal testing, all the protocols were followed according to guidelines of CPCSEA. Nifedipine was used as standard drug. All the test compounds were dissolved in DMSO. Calcium channel blocker activity was done on isolated rat ileum.

Method:
Animals were scarified and the ileum (10-15 cm terminal portion) was immediately removed, discarding the 5-8 cm segment proximal to the ileocaecal junction. Segments 1.5-2 cm long were mounted vertically in organ bath containing freshly prepared tyrode solution of the following composition / liter: NaCl (8.0 g), KCl (0.2 g), $CaCl_2$ (0.2 g), $NaHCO_3$ (1.0 g), $MgCl_2.6H_2O$ (0.1 g), NaH_2PO_4 (0.05 g), and Glucose (1.0 g). The organ bath containing tyrode solution maintained at 32-35^oC and bubbled with air. A tension of 0.5g was applied and the tissue was allowed to equilibrate for 30 min before adding drugs to the organ bath. The effect of calcium channel blocker on isolated rat ileum was determined for all synthesized compounds (500 µg mL^{-1}) and compared these responses with Nifedipine (200 µg mL^{-1}) as a standard drug. This procedure was repeated 3 times and mean of % height of response was taken from 3 CRC plotted for each compound which was then plotted against doses of the compound.

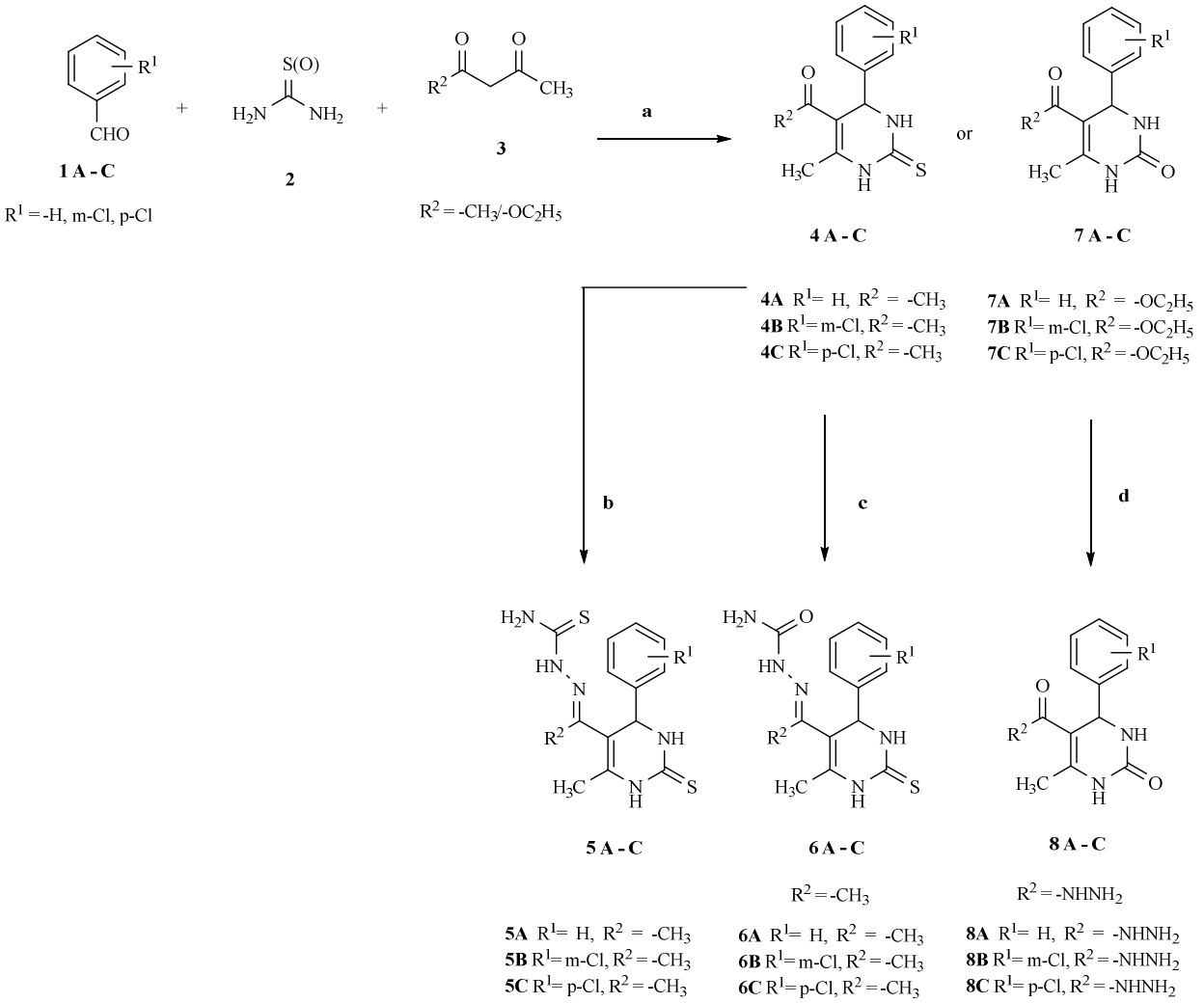
RESULTS AND DISCUSSION

Chemistry
To obtain our designed molecules (Figure 1), first we synthesized DHPM scaffold by using Biginelli multicomponent reaction [19] of aldehydes, urea/thiourea, 1,3-dicarbonyl compounds. In the second step, target molecules were synthesised by modifying DHPM pharmacophore with a second pharmacophore such as semicarbazide or thiosemicarbazide or hydrazide. This was accomplished by treating DHPM with semicarbazide, thiosemicarbazide and hydrazine hydrate respectively. Figure 2 represents the synthesis of the target molecules.

The spectroscopic data (IR, PMR, CMR, Mass) were consistent with the structures. All the compounds are showing characteristic NH stretching and peak for C=O or C=S in IR spectroscopy. The ^1H NMR spectrum revealed that the -CH_3 proton attached to pyrimidine ring showed a singlet at δ= 1.99 ppm. Pyrimidine -N_3H and –N_1H protons showed singlet at 6.98 and 7.99 respectively. -NH-N and NH_2 protons showed singlet at 9.2 and 9.87 ppm. Aromatic protons were observed in the region of 7.21-7.47 ppm. In carbon NMR, methyl carbon attached to pyrimidine ring and thiosemicarbazide chain showed δ values at 17.08 and 27.43. C=S in pyrimidine ring and thiosemicarbazide showed δ values at 175.94 and 178.35 respectively. Enamine carbon showing characteristics δ value at 154.21. All the aromatic carbon showed δ values in between 126.59-143.20. In mass spectrometry, compounds are showing M+1 ion peak. All this data supported the synthesis of the molecules.

Pharmacology
All newly synthesized DHPM derivatives were screened for their calcium channel blocker (CCB) activity on isolated rat ileum. All synthesized compounds were dissolved in DMSO [21] (500 µg mL^{-1}) and their effect of calcium channel blocker on isolated rat ileum was determined and compared these responses with Nifedipine (200 µg mL^{-1}) as a standard drug [22]. Nifedipine was used as standard drug for screening of calcium channel blocker because, nifedipine and test compounds both have similar bioisosteric nucleus (Figure 1). Table 1 represents activity of the synthesized compounds. To determine the CCB activity, % height of the response was calculated from the concentration response curve (CRC) for each compound. The graph of % response of the compound (%) versus dose of the compound (µg mL^-1) were plotted from each CRC and from this graph EC50 was determined.

Figure 2. Synthesis of Target molecules



Reagents and conditions: (a) Ethanol, HCl, 1.5 hr, reflux; (b) $NH_2NHCSNH_2$, methanol, HCl, 3.5 hr, reflux; (c) $NH_2NHCONH_2$, methanol, HCl, 3.5 hr, reflux; (d) $NH_2NH_2.H_2O$ (99%), ethanol, 3.5 hr reflux

Table 1: EC50 value of target molecules

Sr. No.	Compound Code	EC_{50} value
1.	5A	1.69×10^{-6} M
2.	5B	5.37×10^{-7} M
3.	5C	2.83×10^{-7} M
4.	6A	3.03×10^{-7} M
5.	6B	2.10×10^{-7} M
6.	6C	1.78×10^{-7} M
7.	8A	4.88×10^{-7} M
8.	8B	2.67×10^{-7} M
9.	8C	2.32×10^{-7} M
10.	Nifedipine	7.51×10^{-8} M

The concentration required to relax the tissue to 50% was calculated by using graphical interpolation method. In our study, the CCB activity was measured by calculating EC50 value and can be expressed in molar concentration.

The CRC of most potent compound 6C and standard drug Nifedipine is compared in Figure 3 and 4. The series from T1, T2, T3, T4 in the graphs show the cumulative doses of test substance in ml. The experiment was repeated 3 times to study constant effect of each compound on contracted tissue.

Graph of % response vs dose of the compound plotted for compound 6C and Nifedipine is shown in Figure 5 and 6 respectively.

Figure 3: CRC of Compoud 6C

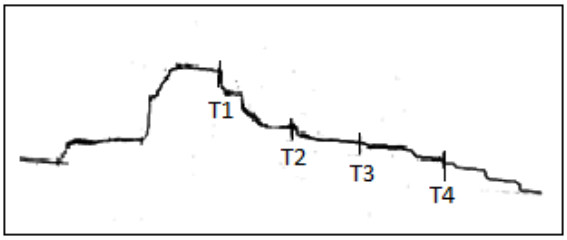


Figure4: CRC of Nifedipine

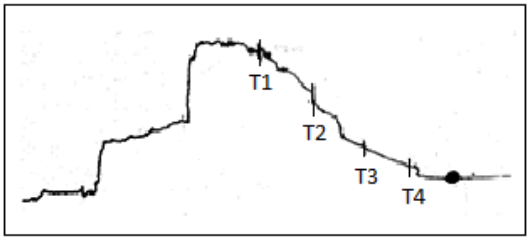


Figure 5: Graph of compound 6C

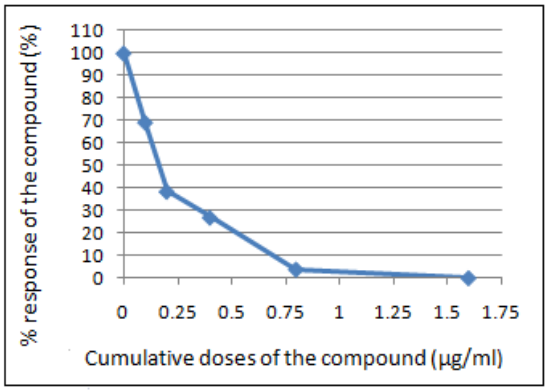
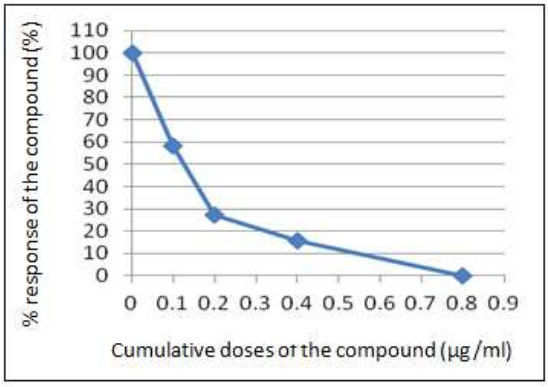


Figure 6: Graph of Nifedipine



Rovnyak proposed that a substituent on N3 of the DHPM ring is a must for activity [3, 17, 23]. However, our series of DHPMs are without N3 substituents, (Table 2) and they appeared to be active CCB compounds. When we compared activity of all three series, it was found that semicarbazones (6A – 6C) are more potent than thiosemicarbazone (5A- 5C) and hydrazide (8A – 8C) series. In regards to substitution of chloro group on phenyl ring, it was found that in all series para position (5C, 6C, and 8C) showed good activity as compared to the unsubstituted and meta substituted compounds. Overall, 6C was the most active compound among all synthesized compound.

CONCLUSION

In conclusion, we have identified a series of dihydropyrimidine based CCB blockers on isolated rat ileum. The potential of this novel class of CCB blockers is being explored. DHPMs enriched with a second pharmacophore offer rich potential as CCBs. Our approach opens up new horizons for DHPM moiety with insertion of new pharmacophore.

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