Bull. Pharm. Sci., Assiut University, Vol. 34, Part 2, December 2011, pp. 159-179.

SYNTHESIS OF SUBSTITUTED DIHYDROPYRIMIDINES AS HYPOTENSIVE AGENTS

Salah A. Abdel-Aziz[1], Nawal A. El-Koussi[2], Hoda Y. Hassan[2], Adel F. Youssef[2] and Magda M. Yousri[3]

[1]*Department of Pharmaceutical Medicinal Chemistry, Faculty of Pharmacy, Al-Azhar University*
[2]*Department of Medicinal Chemistry, Faculty of Pharmacy, Assiut University*
[3]*Department of Pharmacology, Faculty of Medicine, Assiut University*

تم تحضير سلسلة (**I-IV**) من الدايهيدروبيريميدين بالمستبدلات المختلفة لأربعة مواقع فى نواة البيريميدين واختبارها كمغلقات لقنوات الكالسيوم وتأثيرها المخفض للضغط باستخدام أملوديبين كعقار مرجعى وأظهرت النمذجة الجزيئية العلاقة المباشرة بين الملائمة والارتخاء للفائفى الفار. وتم عمل فارماكوفور للمركبات التى لها تاثير مخفض للضغط و، أو مغلقا لقنوات الكالسيوم. وأظهرت السلسلة **IV** تأثيرا مخفضا للضغط ومضادا لتاثير الكالسيوم. بينما السلسلة **I, II** أظهرت تأثيرا مضادا للكالسيوم بدون تأثير مخفضا للضغط. أما السلسلة III فخالية من أيا من التاثيرين.

*A series of Dihydropyrimidines (DHPMs) with variable substituents at four positions in pyrimidine nucleus (**I-IV**), were prepared and tested for their calcium channel blocker and hypotensive effect using amlodipine as a reference compound. Molecular alignment revealed a direct correlation between fitting and in-vitro rat ileum relaxation. A pharmacophore was developed for compounds with hypotensive and/or calcium channel blocking activity. Series **IV** showed hypotensive and calcium antagonist effect, while series **I** and **II** showed calcium antagonist activity without hypotensive action. Series **III** were devoid of either effect.*

INTRODUCTION

Chemistry of 4-aryltetrahydropyrimidine-5-carboxylate of Biginelli type reaction have been attracting widespread attention in recent years. The present popularity of these tetrahydropyrimidines is mainly due to their close structural relationship to the clinically important dihydropyridine calcium channel blockers (DHPs)[1-7]. Dihydropyrimidines (DHPMs) and their analogues possess anti-inflammatory[8-11,] analgesic[11], antitumor[12&13], antibacterial[14-16], antifungal[17], antioxidant[18], α-1a-antagonist[19-23], and FATP4 inhibitory effects[24]. Some marine natural products containing the dihydropyrimidinone-5-carboxylate scaffold have been found to be potent HIV inhibitors[25-27].

The target of the present work was to extend variation of substituents at 1,2,5 and 6 positions of the dihydropyrimidine to mimic the DHP skeleton acting as calcium channel blockers. The present work was supported by the study of the conformational alignment of the prepared compounds with amlodipine as a reference molecule and correlating the alignement data with the biological response. The prepared DHPMs were challenged with the elaborated pharmacophoric features of DHPs and correlation in silico data with their biological activity.

EXPERIMENTS

Melting points were determined on an electrothermal melting point apparatus (Stuart Scientific Co.) and were uncorrected. Elemental microanalyses were performed at the microanalytical center, Faculty of Science, Cairo University, and Assiut University Central Lab, Assiut. Percentage of water was performed on Karl Fisher Titrino 701 in T3A company, Assiut. ^{1}H-NMR spectra were run on Varain Em-360L NMR spectrophotometer (60 MHz) (Varian USA) at the Faculty of Pharmacy, Assiut University. IR spectra were recorded as KBr disks on Shimadzue IR 200-91527 Spectrophotometer at the Faculty of Pharmacy, Assiut University. Mass spectra were performed with JEOL JMS600, Microanalytical center, Cairo University, Cairo. Biological screening was carried out at

Received in 12/9/2011 & Accepted in 21/12/2011

the Department of Pharmacology, Faculty of Medicine, Assiut University. Ethyl acetoacetate was purchased from Adwic Co., 2-chlorobenzaldehyde and isopropyl acetoacetate, isobutyl chloroformate, chloroacetylchloride were purchased from Fluca Co., ethyl chloroformate is purchased from Aldrich Co., while 2-fluorobenzaldehyde purchased from Merk Co. Amlodipine besylate is curtsy of El Amyria Co. All other chemicals and solvents are of reagent grade.

A. Chemistry

General procedure for synthesis of alkyl 6-methyl-4-phenyl (subtituted phenyl) 2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Ia-f)

A mixture of pure aldehyde (0.1 mole), alkyl acetoacetate (0.1 mole), and thiourea (10.0 g, 0.131 mole) in glacial acetic acid (100 mL) was heated at 110°C for 1 hr, then the temperature was raised to 140°C and maintained for 45 min at this temperature. The residue was cooled, crystallized from methanol.

Synthesis of ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Ia)[28]

A mixture of pure benzaldehyde (10.6 g, 0.1 mole), ethyl acetoacetate (13.0 g, 0.1 mole), and thiourea (10.0 g, 0.131 mole) was refluxed for 1 hr in absolute ethanol (100 mL) containing hydrochloric acid (1 mL). The reaction mixture was cooled, filtered under suction and crystallized from methanol to give (16.6 g, 60%) of the product, m.p. 203°C. IR (KBr) 3150, 1660, 1562; ^{1}H-NMR ($CDCl_3$) δ 8.55 (1H, s, N3H); 7.90 (1H, s, N1H); 7.66-7.33 (5H, m, CH Ar.); 5.53 (1H, s, C4H); 4.40-3.93 (2H, q, $\underline{CH_2}CH_3$); 2.50-2.30 (3H, bs, CH_3); 1.50-1.00 (3H, t, $CH_2\underline{CH_3}$).

Isopropyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Ib)

Yield (20.33 g, 70%), m.p. 198-200°C. IR (KBr) 3150, 1692, 1640, 1584; ^{1}H-NMR ($CDCl_3$) δ 9.35 (1H, s, N3H); 8.70 (1H, s, N1H); 8.00-7.56 (5H, m, CH Ar.); 5.80 (1H, s, C4H); 5.60-5.10 (1H, m, $\underline{CH}(CH_3)_2$); 2.56 (3H, s, CH_3); 1.50-1.30 (3H, d, $CH(\underline{CH_3})_2$; 1.30-1.00 (3H, d, $CH(\underline{CH_3})_2$. Anal. Calcd. for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65. Found: C, 61.61; H, 6.28; N, 9.57.

Ethyl 4-(2-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Ic)[29]

Yield (26.42 g, 85%), m.p. 168-170°C. IR (KBr) 3160, 1700, 1642, 1559; ^{1}H-NMR ($CDCl_3$) δ 8.96 (1H, s, N3H); 7.76 (1H, s, N1H); 7.66-7.33 (4H, m, CH Ar.); 6.05 (1H, s, C4H); 4.40-3.83 (2H, q, $\underline{CH_2}CH_3$); 2.46 (3H, s, CH_3); 1.60-0.83 (3H, t, $CH_2\underline{CH_3}$).

Isopropyl 4-(2-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Id)

Yield (24.37 g, 75%), m.p. 239-241°C; IR (KBr) 3155, 1701, 1644, 1568; ^{1}H-NMR ($CDCl_3$) δ 9.40 (1H, s, N3H); 8.20 (1H, s, N1H); 8.10-7.60 (4H, m, CH Ar.); 6.33 (1H, s, C4H); 5.60-5.00 (1H, m, $\underline{CH}(CH_3)_2$); 2.63 (3H, s, CH_3); 1.50-1.30 (3H, d, $CH(\underline{CH_3})_2$; 1.30-0.80 (3H, d, $CH(\underline{CH_3})_2$. $M^{+\bullet}$: m/e 324. Anal. Calcd. for $C_{15}H_{17}ClN_2O_2S$: C, 55.46; H, 5.28; N, 8.62. Found: C, 55.19; H, 5.27; N, 8.52. MS (70eV, EI): m/z (%): 326 ($M^{+\bullet}$ + 2, 18.6); 325 ($M^{+\bullet}$ + 1, 16.9); 324 ($M^{+\bullet}$, 47.8); m/z 237 ($M^{+\bullet}$ - $[CO_2C_3H_7]^+$, 35); m/z 213 ($M^{+\bullet}$ - $[C_6H_4Cl]^+$, 60.5).

Ethyl 4-(2-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Ie)

Yield (20.65 g, 70%), m.p. 169-171°C. IR (KBr) 3160, 1699, 1642, 1575; ^{1}H-NMR ($CDCl_3$) δ 9.00 (1H, s, N3H); 8.06 (1H, s, N1H); 7.80-7.20 (4H, m, CH Ar.); 5.86 (1H, s, C4H); 4.40-4.00 (2H, q, $\underline{CH_2}CH_3$); 2.50 (3H, s, CH_3); 1.40-1.00 (3H, t, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{14}H_{15}FN_2O_2S$: C, 57.13; H, 5.14; N, 9.25. Found: C, 56.83; H, 5.16; N, 9.04.

Isopropyl 4-(2-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (If)

Yield (13.88 g, 45%), m.p. 210-212°C; IR (KBr) 3160, 1695, 1643, 1570; ^{1}H-NMR ($CDCl_3$) δ 9.50 (1H, s, N3H); 8.50 (1H, s, N1H); 8.10-7.40 (4H, m, CH Ar.); 6.15 (1H, s, C4H); 5.60-5.00 (1H, m, $\underline{CH}(CH_3)_2$); 2.63 (3H, s, CH_3); 1.60-1.30 (3H, d, $CH(\underline{CH_3})_2$; 1.30-0.90 (3H, d, $CH(\underline{CH_3})_2$. Anal. Calcd. for $C_{15}H_{17}FN_2O_2S$: C, 58.42; H, 5.56; N, 9.08. Found: C, 58.76; H, 5.85; N, 9.00.

General procedure for synthesis of alkyl 6-methyl-2-methylthio-4-phenyl(substituted phenyl)-1,4-dihydropyrimidine-5-carboxylate (IIa-f)

A mixture of the appropriate alkyl 6-methyl-4-phenyl (substituted phenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **Ia-f** (0.1 mole) and dimethylsulfate (37.84 g, 0.3 mole) was refluxed in absolute ethanol (150 mL) for 1 hr, then cooled, diluted with water (300 mL), and filtered. The clear filtrate was alkalinized by gradual addition of concentrated ammonium hydroxide solution, and the mixture was refrigerated for 2 hrs. The formed precipitate was filtered off, washed with water and crystallized from suitable solvent (**IIa,c,e** (ethanol/water); **IIb,d,f** (DMF/water)).

Ethyl 6-methyl-2-methylthio-4-phenyl-1,4-dihydropyrimidine-5-carboxylate (IIa)[28]

Yield (27.58 g, 95%), m.p. 165°C; IR (KBr) 3380, 3205, 1692, 1636; ^{1}H-NMR ($CDCl_3$) δ 7.66-7.30 (5H, s, CH Ar.); 5.80 (1H, s, C4H); 4.50-4.10 (2H, q, $\underline{CH_2}CH_3$); 2.60 (3H, s, $S\underline{CH_3}$); 2.50 (3H, s, C6$\underline{CH_3}$); 1.50-1.10 (3H, t, $CH_2\underline{CH_3}$).

Isopropyl 6-methyl-2-methylthio-4-phenyl-1,4-dihydropyrimidine-5-carboxylate (IIb)

Yield (28.92 g, 95%), m.p. 142-144°C; IR (KBr) 3450, 3295, 1644; ^{1}H-NMR ($CDCl_3$) δ 8.10-7.60 (5H, m, CH Ar.); 6.04 (1H, s, C4H); 5.60-5.10 (1H, m, $\underline{CH}(CH_3)_2$); 2.60 (3H, s, $S\underline{CH_3}$); 2.50 (3H, s, C6$\underline{CH_3}$); 1.50-1.30 (3H, d, $CH(\underline{CH_3})_2$); 1.30-1.00 (3H, d, $CH(\underline{CH_3})_2$. Anal. Calcd. for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20. Found: C, 62.77; H, 6.57; N, 9.11.

Ethyl 4-(2-chlorophenyl)-6-methyl-2-methylthio-1,4-dihydropyrimidine-5-carboxylate (IIc)

Yield (29.14 g, 85%), m.p. 71-73°C; IR (KBr) 3445, 1660, 1631; ^{1}H-NMR ($CDCl_3$) δ 7.70-7.23 (4H, m, CH Ar.); 6.15 (1H, s, C4H); 4.33-3.90 (2H, q, $\underline{CH_2}CH_3$); 2.50 (3H, s, $S\underline{CH_3}$); 2.40 (3H, s, C6$\underline{CH_3}$); 1.30-0.90 (3H, t, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{15}H_{17}ClN_2O_2S.H_2O$: C, 52.55; H, 5.59; N, 8.17; H_2O, 5.25. Found: C, 52.69; H, 5.86; N, 8.10; H_2O, 5.32.

Isopropyl 4-(2-chlorophenyl)-6-methyl-2-methylthio-1,4-dihydropyrimidine-5-carboxylate (IId)

Yield (33.19 g, 93%), m.p. 71-73°C; IR (KBr) 3480, 3160, 1632 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.20-7.60 (4H, m, CH Ar.); 6.50 (1H, s, C4H); 5.60-5.00 (1H, m, $\underline{CH}(CH_3)_2$); 2.66 (3H, s, $S\underline{CH_3}$); 2.53 (3H, s, C6$\underline{CH_3}$); 1.50-1.30 (3H, d, $CH(\underline{CH_3})_2$; 1.30-0.80 (3H, d, $CH(\underline{CH_3})_2$. Anal. Calcd. for $C_{16}H_{19}ClN_2O_2S.H_2O$: C, 53.85; H, 5.93; N, 7.85; H_2O, 5.04. Found: C, 53.43; H, 5.79; N, 7.81; H_2O, 5.00.

Ethyl 4-(2-fluorophenyl)-6-methyl-2-methylthio-1,4-dihydropyrimidine-5-carboxylate (IIe)

Yield (25.90 g, 84%), m.p. 71-72°C; IR (KBr) 3450, 3295, 1643 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.00-7.60 (4H, m, CH Ar.); 6.45 (1H, s, C4H); 4.70-4.20 (2H, q, $\underline{CH_2}CH_3$); 2.80-2.40 (6H, bs, $S\underline{CH_3}$, C6$\underline{CH_3}$); 1.50-1.10 (3H, t, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{15}H_{17}FN_2O_2S$: C, 58.42; H, 5.56; N, 9.08. Found: C, 57.89; H, 5.04; N, 8.87.

Isopropyl 4-(2-fluorophenyl)-6-methyl-2-methylthio-1,4-dihydropyrimidine-5-carboxylate (IIf)

Yield (30.64 g, 90%), m.p. 74-75°C; IR (KBr) 3465, 3125, 1667, 1634 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.10-7.60 (4H, m, CH Ar.); 6.46 (1H, s, C4H); 5.60-5.00 (1H, m, $\underline{CH}(CH_3)_2$); 2.63 (3H, s, $S\underline{CH_3}$); 2.55 (3H, s, C6$\underline{CH_3}$); 1.46-1.30 (3H, d, $CH(\underline{CH_3})_2$; 1.30-0.86 (3H, d, $CH(\underline{CH_3})_2$. Anal. Calcd. for $C_{16}H_{19}FN_2O_2S.H_2O$: C, 56.45; H, 6.22; N, 8.23; H_2O, 5.29. Found: C, 56.44; H, 6.10; N, 8.26; H_2O, 5.40.

General procedure for synthesis of ethyl 6-methyl-4-phenyl (substituted phenyl)-2-(2-substituted aminoethylthio)-1,4-dihydro-pyrimidine-5-carboxylate (IIg-r)

A mixture of the appropriate ethyl 6-methyl-4-phenyl (substituted phenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **Ia**, **Ic**, and **Ie** (1.0 mmole), 2-chloroethylamine (cyclic amine) hydrochloride (1.1 mmole), and sodium hydroxide (1 M, 2.5 mL) in absolute ethanol (20 mL) was refluxed for 1 hr, concentrated to the half volume, cooled, poured onto water (100 mL). The pH was adjusted to

4-5 by hydrochloric acid 2 M, filtered, and the clear filtrate was alkalinized to pH 10-12 by adding sodium hydroxide 5 M, the mixture was refrigerated overnight. The formed precipitate was filtered off, washed twice with cold water and crystallized from suitable solvent **(IIg,k,l,o,p** (ethanol/water); **IIh,i,j,m,n,q,r** (dissolve in HCl and ppt. with NaOH)).

Ethyl 6-methyl-4-phenyl-2-(2-piperidino-ethylthio)-1,4-dihydropyrimidine-5-carboxylate (IIg)

Yield (0.292 g, 72%), m.p. 80°C; IR (KBr) 3110, 1692, 1636; ^{1}H-NMR ($CDCl_3$) δ 7.70-7.30 (5H, m, CH Ar.); 5.60 (1H, s, C4H); 4.50-3.90 (2H, q, $\underline{CH_2}CH_3$); 3.20-2.30 (11H, bm, $\underline{SCH_2}$-$\underline{CH_2}$, C6$\underline{CH_3}$, C2,6-H piperidine); 1.80-1.50 (6H, m, C3,4,5-H piperidine); 1.50-1.00 (3H, t, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{21}H_{29}N_3O_2S.H_2O$: C, 62.19; H, 7.70; N, 10.36; H_2O, 4.44. Found: C, 61.95; H, 7.81; N, 10.19; H_2O, 4.69.

Ethyl 6-methyl-2-(2-morpholinoethylthio) 4-phenyl-1,4-dihydropyrimidine-5-carboxylate (IIh)

Yield (0.234 g, 60%), m.p. sticky; IR (KBr) 3265, 1679, 1642; ^{1}H-NMR ($CDCl_3$) δ 8.00-7.60 (5H, m, CH Ar.); 6.00 (1H, s, C4H); 4.80-4.16 (2H, q, $\underline{CH_2}CH_3$); 4.16-3.80 (2H, m, C2,6 H morpholine); 3.50-3.00 (2H, m, $\underline{SCH_2}CH_2$); 2.96-2.40 (9H, m, $SCH_2\underline{CH_2}$, C6$\underline{CH_3}$, C3,5-H morpholine); 1.50-1.10 (3H, t, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{20}H_{27}N_3O_3S$: C, 61.67; H, 6.99; N, 10.79. Found: C, 61.42; H, 7.24; N, 10.26.

Ethyl 6-methyl-4-phenyl-2-[2-(pyrrolidin-1-yl)ethylthio]-1,4-dihydropyrimidine-5-carboxylate (IIi)

Yield (0.274 g, 70%), m.p. 64-66°C; IR (KBr) 3205, 1692, 1637; ^{1}H-NMR ($CDCl_3$) δ 7.90-7.40 (5H, m, CH Ar.); 5.75 (1H, s, C4H); 4.50-4.00 (2H, q, $\underline{CH_2}CH_3$); 3.10-2.84 (4H, m, $\underline{SCH_2}$-$\underline{CH_2}$); 2.76-2.44 (4H, m, C2,5H pyrrolidine); 2.35 (3H, s, C6$\underline{CH_3}$); 1.90-1.56 (4H, m, C3,4 H pyrrolidine); 1.30-0.90 (3H, t, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{20}H_{27}N_3O_2S.H_2O$: C, 61.35; H, 7.47; N, 10.73; H_2O, 4.60. Found: C, 61.06; H, 7.22; N, 10.62; H_2O, 4.28.

Ethyl 2-[2-(dimethylamino)ethylthio]-6-methyl-4-phenyl-1,4-dihydropyrimidine-5-carboxylate (IIj)

Yield (0.207 g, 58%), m.p. sticky; IR (KBr) 3255, 1682, 1638; ^{1}H-NMR ($CDCl_3$) δ 8.00-7.50 (5H, m, CH Ar.); 6.13 (1H, s, C4H); 4.66-4.10 (2H, q, $\underline{CH_2}CH_3$); 3.30-2.93 (2H, m, $\underline{SCH_2}$-CH_2); 2.93-2.60 (2H, m, SCH_2-$\underline{CH_2}$); 2.60-1.76 (9H, m, C6$\underline{CH_3}$, CH_2CH_2-N($\underline{CH_3}$)$_2$; 1.46-0.90 (3H, t, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{18}H_{25}N_3O_2S.½H_2O$: C, 60.73; H, 7.36; N, 11.80; H_2O, 2.52. Found: C, 61.15; H, 7.50; N, 11.28; H_2O, 2.29.

Ethyl 4-(2-chlorophenyl)-6-methyl-2-(2-piperidinoethylthio)-1,4-dihydropyrimidine-5-carboxylate (IIk)

Yield (0.308 g, 70%), m.p. 74-75°C; IR (KBr) 3120, 1703, 1648; ^{1}H-NMR ($CDCl_3$) δ 7.60-7.30 (4H, m, CH Ar.); 6.10 (1H, s, C4H); 4.30-3.90 (2H, q, $\underline{CH_2}CH_3$); 3.20-2.30 (11H, bm, $\underline{SCH_2}$-$\underline{CH_2}$, C6$\underline{CH_3}$, C2,6-H piperidine); 1.70-1.40 (6H, m, C3,4,5-H piperidine); 1.28-0.90 (3H, t, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{21}H_{28}ClN_3O_2S.H_2O$: C, 57.32; H, 6.87; N, 9.55; H_2O, 4.09. Found: C, 56.84; H, 6.83; N, 9.38; H_2O, 3.80. MS (70eV, EI): m/z (%): 423 ($M^{+\bullet}$+2, 0.3); 422 ($M^{+\bullet}$ +1, 0.9); m/z 310 ($M^{+\bullet}$ - $[C_6H_4Cl]^+$, 60.5); 111 ($C_5H_{10}NCH{=}CH_2$, 100).

Ethyl 4-(2-chlorophenyl)-6-methyl-2-(2-morpholinoethylthio) 1,4-dihydro-pyrimidine-5-carboxylate (II*l*)

Yield (0.332 g, 75%), m.p. 72-74°C; IR (KBr) 3100, 1697, 1638, 1593; ^{1}H-NMR ($CDCl_3$) δ 7.60-7.31 (4H, m, CH Ar.); 6.20 (1H, s, C4H); 4.40-4.00 (2H, q, $\underline{CH_2}CH_3$); 4.00 (4H, m, C2,6 H morpholine); 3.30-3.00 (2H, m, $\underline{SCH_2}CH_2$); 2.90-2.00 (9H, m, $SCH_2\underline{CH_2}$, C6$\underline{CH_3}$, C3,5H morpholine); 1.30-0.90 (3H, t, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{20}H_{26}ClN_3O_3S.H_2O$: C, 54.35; H, 6.39; N, 9.51; H_2O, 4.07. Found: C, 54.19; H, 6.62; N, 9.48; H_2O, 4.02.

Ethyl 4-(2-chlorophenyl)-6-methyl-2-[2-(pyrrolidin-1-yl)ethylthio]-1,4-dihydro-pyrimidine-5-carboxylate (IIm)

Yield (0.222 g, 52%), m.p. 83-85°C; IR (KBr) 3110, 1680, 1634; ^{1}H-NMR ($CDCl_3$) δ 7.2-7.00 (4H, m, CH Ar.); 6.13 (1H, s, C4H); 4.33-3.90 (2H, q, $\underline{CH_2}CH_3$); 3.20-2.40 (11H, m, $\underline{SCH_2}$-$\underline{CH_2}$, C6$\underline{CH_3}$, C2,5H pyrrolidine); 2.00-

1.70 (4H, m, C3,4 H pyrrolidine); 1.35-0.90 (3H, t, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{20}H_{26}ClN_3O_2S.H_2O$: C, 56.39; H, 6.63; N, 9.86; H_2O, 4.23. Found: C, 56.46; H, 5.94; N, 9.51; H_2O, 4.71.

Ethyl 4-(2-chlorophenyl)-2-[2-(dimethyl-amino)ethylthio]-6-methyl-1,4-dihydro-pyrimidine-5-carboxylate (IIn)

Yield (0.216 g, 54%), m.p. 62-64°C; IR (KBr) 3125, 1689, 1637; ^{1}H-NMR ($CDCl_3$) δ 7.80-7.60 (4H, m, CH Ar.); 6.13 (1H, s, C4H); 4.50-4.10 (2H, q, $\underline{CH_2}CH_3$); 3.20-1.90 (13H, m, $\underline{SCH_2}$-$\underline{CH_2}N(\underline{CH_3})_2$, C6$\underline{CH_3}$); 1.35-0.90 (3H, t, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{18}H_{24}ClN_3O_2S.H_2O$: C, 54.06; H, 6.55; N, 10.51; H_2O, 4.50. Found: C, 53.76; H, 6.11; N, 10.34; H_2O, 4.45.

Ethyl 4-(2-fluorophenyl)-6-methyl-2-(2-piperidinoethylthio)-1,4-dihydropyrimidine-5-carboxylate (IIo)

Yield (0.283 g, 66%), m.p. 78-79°C; IR (KBr) 3180, 1693, 1630; ^{1}H-NMR ($CDCl_3$) δ 8.00-7.40 (4H, m, CH Ar.); 6.30 (1H, s, C4H); 4.55-4.10 (2H, q, $\underline{CH_2}CH_3$); 3.23-2.96 (4H, m, $\underline{SCH_2}$-$\underline{CH_2}$); 2.90-2.40 (7H, m, C6$\underline{CH_3}$, C2,6-H piperidine); 1.90-1.40 (6H, m, C3,4,5-H piperidine); 1.40-1.00 (3H, t, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{21}H_{28}FN_3O_2S.1¼H_2O$: C, 58.92; H, 7.18; N, 9.82; H_2O, 5.26. Found: C, 59.44; H, 6.97; N, 9.81; H_2O, 5.75.

Ethyl 4-(2-fluorophenyl)-6-methyl-2-(2-morpholinoethylthio) 1,4-dihydro-pyrimidine-5-carboxylate (IIp)

Yield (0.353 g, 83%), m.p. 72-74°C; IR (KBr) 3390, 3210, 1697, 1641; ^{1}H-NMR ($CDCl_3$) δ 8.20-7.60 (4H, m, CH Ar.); 6.45 (1H, s, C4H); 4.70-4.20 (2H, q, $\underline{CH_2}CH_3$); 4.20-3.90 (4H, m, C2,6 H morpholine); 3.50-3.20 (4H, t, $S\underline{CH_2}\underline{CH_2}$); 3.10-2.50 (7H, m, C6$\underline{CH_3}$, C3,5H morpholine); 1.50-1.10 (3H, t, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{20}H_{26}FN_3O_3S.H_2O$: C, 56.45; H, 6.63; N, 9.88; H_2O, 4.23. Found: C, 56.15; H, 6.61; N, 9.77; H_2O, 4.52.

Ethyl 4-(2-fluorophenyl)-6-methyl-2-[2-(pyrrolidin-1-yl)ethylthio]-1,4-dihydro-pyrimidine-5-carboxylate (IIq)

Yield (0.340 g, 83%), m.p. 66-68°C; IR (KBr) 3375, 3210, 1689, 1634; ^{1}H-NMR ($CDCl_3$) δ 7.80-7.10 (4H, m, CH Ar.); 6.03 (1H, s, C4H); 4.40-3.90 (2H, q, $\underline{CH_2}CH_3$); 3.20-2.90 (4H, m, $\underline{SCH_2}$-$\underline{CH_2}$); 2.90-2.56 (4H, m, C2,5H pyrrolidine); 2.50-2.30 (3H, s, C6$\underline{CH_3}$); 2.10-1.70 (4H, m, C3,4H pyrrolidine); 1.40-0.96 (3H, t, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{20}H_{26}FN_3O_2S.H_2O$: C, 58.66; H, 6.89; N, 10.26; H_2O, 4.40. Found: C, 59.20; H, 6.33; N, 9.59; H_2O, 4.28.

Ethyl 2-[2-(dimethylamino)ethylthio]-4-(2-fluorophenyl)-6-methyl-1,4-dihydro-pyrimidine-5-carboxylate (IIr)

Yield (0.192 g, 50%), m.p. 70-71°C; IR (KBr) 3380, 3225, 1693, 1639; ^{1}H-NMR ($CDCl_3$) δ 8.00-7.33 (4H, m, CH Ar.); 6.40 (1H, s, C4H); 4.66-4.16 (2H, q, $\underline{CH_2}CH_3$); 3.33-3.10 (2H, m, $\underline{SCH_2}$-CH_2); 3.10-2.73 (2H, m, SCH_2-$\underline{CH_2}$); 2.73-2.20 (9H, m, C6$\underline{CH_3}$, CH_2CH_2-N($\underline{CH_3}$)$_2$; 1.53-0.90 (3H, t, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{18}H_{24}FN_3O_2S$. H_2O: C, 56.38; H, 6.83; N, 10.96; H_2O, 4.69. Found: C, 56.68; H, 7.00; N, 11.31; H_2O, 4.64.

General procedure for synthesis of diethyl 4-methyl-2-methylthio-6-phenyl (substituted phenyl)-1,6-dihydropyrimidine-1,5-dicarboxylate (IIIa, IIIe and IIIi)

A mixture of the appropriate ethyl 6-methyl-2- methylthio-4-phenyl (substituted phenyl)-1,4-dihydropyrimidine-5-carboxylate **IIa**, **IIc**, and **IIe** (20 mmole), pyridine (5.54 g, 70 mmole) and ethyl chloroformate (6.5 g, 60 mmole) in acetonitrile (100 mL) was refluxed for 1 hr, cooled, poured onto water (500 mL) with vigorous shaking. The formed precipitate was filtered off and crystallized from methanol.

Diethyl 4-methyl-2-(methylthio)-6-phenyl-1,6-dihydropyrimidine-1,5-dicarboxylate (IIIa)[30]

Yield (6.16 g, 85%), m.p. 87-89°C; IR (KBr) 1722, 1694, 1629, 1508 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.60-7.40 (5H, bs, $\underline{CH}$ Ar.); 6.45 (1H, s, C6H); 4.70-4.05 (4H, m, 2($\underline{CH_2}CH_3$); 2.70-2.40 (6H, bs, $S\underline{CH_3}$, C4$\underline{CH_3}$); 1.60-1.10 (6H, q, 2($CH_2\underline{CH_3}$).

Diethyl 6-(2-chlorophenyl)-4-methyl-2-methylthio-1,6-dihydropyrimidine-1,5-dicarboxylate (IIIe)

Yield (5.56 g, 70%), m.p. 105-108°C; IR (KBr) 1715, 1694, 1602, 1512 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.70-7.20 (4H, m, CH Ar.); 6.83

(1H, s, C6H); 4.63-4.03 (4H, m, 2($\underline{CH_2}CH_3$); 2.53 (6H, bs, S$\underline{CH_3}$, C4$\underline{CH_3}$); 1.60-1.10 (6H, q, 2($CH_2\underline{CH_3}$). Anal. Calcd. for $C_{18}H_{21}ClN_2O_4S$: C, 54.47; H, 5.33; N, 7.06. Found: C, 54.48; H, 5.44; N, 7.00.

Diethyl 6-(2-fluorophenyl)-4-methyl-2-methylthio-1,6-dihydropyrimidine-1,5-dicarboxylate (IIIi)

Yield (4.56 g, 60%), m.p. 126-128°C; IR (KBr) 1724, 1695, 1606, 1513 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.00-7.30 (4H, s, CH Ar.); 6.94 (1H, s, C6H); 4.80-4.13 (4H, m, 2($\underline{CH_2}CH_3$); 2.80-2.40 (6H, bs, S$\underline{CH_3}$, C4$\underline{CH_3}$); 1.60-1.10 (6H, q, 2($CH_2\underline{CH_3}$). Anal. Calcd. for $C_{18}H_{21}FN_2O_4S$: C, 56.53; H, 6.06; N, 7.32. Found: C, 56.72; H, 5.43; N, 7.34.

General procedure for synthesis of dialkyl 4-methyl-2-methylthio-6-phenyl(substituted phenyl)-1,6-dihydropyrimidine-1,5-dicarboxylate (IIIb,c,d, IIIf,g,h and IIIj,k,l)

A mixture of the appropriate alkyl 6-methyl-2-methylthio-4-phenyl(substituted phenyl)-1,4-dihydropyrimidine-5-carboxylate **IIa-f** (5.0 mmole), pyridine (1.38 g, 17.5 mmole) and alkyl chloroformate (15.0 mmole) in chloroform (30 mL) and acetonitrile (20 mL) was refluxed for 1 h, and the solvents were evaporated under reduced pressure. The residue was dissolved in dimethylsulfoxide (10 mL), poured onto cold water (100 mL) with vigorous shaking. The mixture was refrigerated for 3 hrs, carefully decanted, and the residue was dissolved in methanol (20 mL) and kept in the freezer overnight. The formed precipitate was filtered while cold and dried in air, crystallized from methanol.

5-Ethyl 1-isobutyl 4-methyl-2-(methylthio)-6-phenyl-1,6-dihydropyrimidine-1,5-dicarboxylate (IIIb)

Yield (1.02 g, 52%), m.p. 60°C; IR (KBr) 1719, 1694, 1606, 1505 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.90 (5H, s, CH Ar.); 6.90 (1H, s, C6H); 4.80-4.30 (4H, m, $\underline{CH_2}CH_3$, $\underline{CH_2}CH(CH_3)_2$); 2.70 (6H, bs, S$\underline{CH_3}$, C4$\underline{CH_3}$); 2.40-1.80 (1H, m, $CH_2\underline{CH}(CH_3)_2$); 1.60-1.20 (3H, t, $CH_2\underline{CH_3}$); 1.20-0.96 (6H, d, $CH_2CH(\underline{CH_3})_2$). Anal. Calcd. for $C_{20}H_{26}N_2O_4S$: C, 61.51; H, 6.71; N, 7.17. Found: C, 61.20; H, 6.94; N, 7.12.

1-Ethyl 5-isopropyl 4-methyl-2-(methylthio)-6-phenyl-1,6-dihydropyrimidine-1,5-dicarboxylate (IIIc)

Yield (1.15 g, 61%), m.p. 62°C; IR (KBr) 1720, 1667, 1604, 1504 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.26-7.70 (5H, bs, CH Ar.); 6.84 (1H, s, C6H); 5.70-5.20 (1H, m, $\underline{CH}(CH_3)_2$); 5.00-4.43 (2H, q, $\underline{CH_2}CH_3$); 2.90-2.50 (6H, bs, S$\underline{CH_3}$, C4$\underline{CH_3}$); 1.70-1.10 (9H, m, CH($\underline{CH_3}$)$_2$, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{19}H_{24}N_2O_4S$: C, 60.62; H, 6.43; N, 7.44. Found: C, 60.54; H, 6.31; N, 6.89.

1-Isobutyl 5-isopropyl 4-methyl-2-(methylthio)-6-phenyl-1,6-dihydropyrimidine-1,5-dicarboxylate (IIId)

Yield (0.974 g, 48%), m.p. 52-54°C; IR (KBr) 1717, 1692, 1610, 1504 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.90 (5H, s, CH Ar.); 6.90 (1H, s, C6H); 5.80-5.20 (1H, m, $\underline{CH}(CH_3)_2$); 4.60-4.20 (2H, d, $\underline{CH_2}CH(CH_3)_2$); 2.70 (6H, s, S$\underline{CH_3}$, C4$\underline{CH_3}$); 2.40-1.90 (1H, m, $CH_2\underline{CH}(CH_3)_2$); 1.60-0.90 (12H, m, $CH_2CH(\underline{CH_3})_2$, $CH(\underline{CH_3})_2$). Anal. Calcd. for $C_{21}H_{28}N_2O_4S$: C, 62.35; H, 6.98; N, 6.93. Found: C, 61.95; H, 7.32; N, 6.84.

5-Ethyl 1- isobutyl 6-(2-chlorophenyl)-4-methyl-2-(methylthio)-1,6-dihydro-pyrimidine-1,5-dicarboxylate (IIIf)

Yield (1.34 g, 63%), m.p. 70-2°C; IR (KBr) 1721, 1695, 1600, 1505 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.10-7.70 (4H, m, CH Ar.); 7.30 (1H, s, C6H); 4.80-4.30 (4H, m, $\underline{CH_2}CH_3$, $\underline{CH_2}CH(CH_3)_2$); 2.70 (6H, bs, S$\underline{CH_3}$, C4$\underline{CH_3}$); 2.40-1.80 (1H, m, $CH_2\underline{CH}(CH_3)_2$); 1.60-1.20 (3H, t, $CH_2\underline{CH_3}$); 1.20-0.96 (6H, d, $CH_2CH(\underline{CH_3})_2$). Anal. Calcd. for $C_{20}H_{25}ClN_2O_4S$: C, 56.53; H, 5.93; N, 6.59. Found: C, 56.52; H, 5.82; N, 6.47.

1-Ethyl 5-isopropyl 6-(2-chlorophenyl)-4-methyl-2-(methylthio)-1,6-dihydro-pyrimidine-1,5-dicarboxylate (IIIg)

Yield (1.44 g, 70%), m.p. 62-64°C; IR (KBr) 1723, 1680, 1599, 1510 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.10-7.60 (4H, m, CH Ar.); 7.20 (1H, s, C6H); 5.73-5.13 (1H, m, $\underline{CH}(CH_3)_2$); 4.90-4.40 (2H, q, $\underline{CH_2}CH_3$); 2.90-2.50 (6H, bs, S$\underline{CH_3}$, C4$\underline{CH_3}$); 1.70-1.00 (9H, m, CH($\underline{CH_3}$)$_2$, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{19}H_{23}ClN_2O_4S$: C, 55.54; H, 5.64; N, 6.82. Found: C, 55.31; H, 5.40; N, 6.75.

1-Isobutyl 5-isopropyl 6-(2-chlorophenyl)-4-methyl-2-(methylthio)-1,6-dihydropyrimidine-1,5-dicarboxylate (IIIh)

Yield (1.10 g, 50%), m.p. 54-56°C; IR (KBr) 1721, 1693, 1600, 1507cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.20-7.70 (4H, m, CH Ar.); 7.30 (1H, s, C6H); 5.73-5.20 (1H, m, $\underline{CH}(CH_3)_2$); 4.60-4.20 (2H, d, $\underline{CH_2}CH(CH_3)_2$); 2.70 (6H, s, $S\underline{CH_3}$, $C4\underline{CH_3}$); 2.50-2.00 (1H, m, $CH_2\underline{CH}(CH_3)_2$); 1.60-0.90 (12H, m, $CH_2CH(\underline{CH_3})_2$, $CH(\underline{CH_3})_2$). $M^{+\bullet}$: m/e 438. Anal. Calcd. for $C_{21}H_{27}ClN_2O_4S$: C, 57.46; H, 6.20; N, 6.38. Found: C, 57.70; H, 6.31; N, 6.37. (70eV, EI): m/z (%): 439 ($M^{+\bullet}$ + 1, 12.1); 438 ($M^{+\bullet}$, 11.6); m/z 327 ($M^{+\bullet}$ - $[C_6H_4Cl]^+$, 26.9); m/z 57 ($^{\bullet}C_4H_9$, 100).

5-Ethyl 1-isobutyl 6-(2-fluorophenyl)-4-methyl-2-(methylthio)-1,6-dihydropyrimidine-1,5-dicarboxylate (IIIj)

Yield (1.02 g, 50%), m.p. 64-66°C; IR (KBr) 1697, 1605, 1511 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.10-7.40 (4H, m, CH Ar.); 7.20 (1H, s, C6H); 4.80-4.20 (4H, m, $\underline{CH_2}CH_3$, $\underline{CH_2}CH(CH_3)_2$); 2.70 (6H, bs, $S\underline{CH_3}$, $C4\underline{CH_3}$); 2.43-1.80 (1H, m, $CH_2\underline{CH}(CH_3)_2$)); 1.50-1.13 (3H, t, $CH_2\underline{CH_3}$); 1.13-0.80 (6H, d, $CH_2CH(\underline{CH_3})_2$). Anal. Calcd. for $C_{20}H_{25}FN_2O_4S$: C, 58.81; H, 6.17; N, 6.86. Found: C, 58.84 H, 6.07; N, 6.85.

1-Ethyl 5-isopropyl 6-(2-fluorophenyl)-4-methyl-2-(methylthio)-1,6-dihydropyrimidine-1,5-dicarboxylate (IIIk)

Yield (0.950 g, 48%), m.p. 74°C; IR (KBr) 1720, 1689, 1606, 1504 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.00-7.30 (4H, m, CH Ar.); 7.00 (1H, s, C6H); 5.70-5.10 (1H, m, $\underline{CH}(CH_3)_2$); 4.90-4.33 (2H, q, $\underline{CH_2}CH_3$); 2.90-2.40 (6H, bs, $S\underline{CH_3}$, $C4\underline{CH_3}$); 2.00-1.00 (9H, m, $CH(\underline{CH_3})_2$, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{19}H_{23}FN_2O_4S$: C, 57.85; H, 5.88; N, 7.10. Found: C, 57.82; H, 5.60; N, 7.07.

1-Isobutyl 5-isopropyl 6-(2-fluorophenyl)-4-methyl-2-(methylthio)-1,6-dihydropyrimidine-1,5-dicarboxylate (III*l*)

Yield (0.950 g, 45%), m.p. 70°C; IR (KBr) 1723, 1694, 1605, 1505 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.30-7.40 (4H, m, CH Ar.); 7.20 (1H, s, C6H); 5.80-5.20 (1H, m, $\underline{CH}(CH_3)_2$); 4.60-4.30 (2H, d, $\underline{CH_2}CH(CH_3)_2$); 2.70 (6H, s, $S\underline{CH_3}$, $C4\underline{CH_3}$); 2.40-1.90 (1H, m, $CH_2\underline{CH}(CH_3)_2$); 1.60-0.90 (12H, m, $CH_2CH(\underline{CH_3})_2$, $CH(\underline{CH_3})_2$). Anal. Calcd. for $C_{21}H_{27}FN_2O_4S$: C, 59.70; H, 6.44; N, 6.63. Found: C, 59.14 H, 6.19; N, 6.57.

General procedure for synthesis of alkyl 1-(2-chloroacetyl)-6-(2-chlorophenyl)-4-methyl-2-methylthio-1,6-dihydropyrimidine-5-carboxylate (IIIm and IIIn)

A mixture of the appropriate alkyl 4-(2-chlorophenyl)-6-methyl-2-methylthio-1,4-dihydropyrimidine-5-carboxylate **IIc,** and **IId** (20 mmole), pyridine (5.54 g, 70 mmole) and chloroacetylchloride (6.78 g, 60 mmole) in acetonitrile (100 mL) was stirred for 1 hr at room temperature then in ice bath for 20 min. The formed precipitate was filtered off, washed with hexane, dried in air and crystallized from hexane-ethyl acetate mixture.

Ethyl 1-(2-chloroacetyl)-6-(2-chlorophenyl)-4-methyl-2-methylthio-1,6-dihydropyrimidine-5-carboxylate (IIIm)

Yield (6.83 g, 85%), m.p. 154-156°C; IR (KBr) 1696, 1601, 1513 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.10-7.60 (4H, m, CH Ar.); 7.42 (1H, s, C6H); 4.96 (2H, s, $CO\underline{CH_2}Cl$); 4.80-4.26 (2H, q, $\underline{CH_2}CH_3$); 2.70 (6H, s, $S\underline{CH_3}$, $C4\underline{CH_3}$); 1.50-1.10 (3H, t, $CH_2\underline{CH_3}$). $M^{+\bullet}$: m/e 400. Anal. Calcd. for $C_{17}H_{18}Cl_2N_2O_3S$: C, 50.88; H, 4.52; N, 6.98. Found: C, 50.45; H, 4.69; N, 6.83. MS (70eV, EI): m/z (%): 402 ($M^{+\bullet}$ + 2, 7.9); 401($M^{+\bullet}$ + 1, 6.3); 400 ($M^{+\bullet}$, 6.9); m/z 323 ($M^{+\bullet}$ - $[COCH_2Cl]^+$, 19.9); m/z 291 ($M^{+\bullet}$ - $[C_6H_4Cl]^+$, 9.8); m/z 77 ($[COCH_2Cl]^+$, 27.4).

Isopropyl 1-(2-chloroacetyl)-6-(2-chlorophenyl)-4-methyl-2-methylthio-1,6-dihydropyrimidine-5-carboxylate (IIIn)

Yield (6.65 g, 80%), m.p. 128-131°C; IR (KBr) 1682, 1590, 1513 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.10-7.50 (4H, m, CH Ar.); 7.40 (1H, s, C6H); 5.60-5.10 (1H, m, $\underline{CH}(CH_3)_2$); 4.90 (2H, s, $CO\underline{CH_2}Cl$); 2.70 (6H, s, $S\underline{CH_3}$, $C4\underline{CH_3}$); 1.50-1.30 (3H, d, $CH(\underline{CH_3})_2$); 1.30-1.10 (3H, d, $CH(\underline{CH_3})_2$. Anal. Calcd. for $C_{18}H_{20}Cl_2N_2O_3S$: C, 52.05; H, 4.85; N, 6.74. Found: C, 52.47; H, 4.57; N, 6.77.

General procedure for synthesis of alkyl 6-(2-chlorophenyl)-4-methyl-2-methylthio-1-(2-morpholinoacetyl)-1,6-dihydro-pyrimidine-5-carboxylate (IIIo and IIIp)

A mixture of the appropriate alkyl 1-(2-chloroacetyl)-6-(2-chlorophenyl)-4-methyl-2-methylthio-1,6-dihydropyrimidine-5-carboxylate **IIIm**, and **IIIn** (2.0 mmole), pyridine (0.79 g, 10.0 mmole), potassium iodide (100 mg) and morpholine (0.2 g, 2.3 mmole) in dry acetone (20 mL) was stirred for 1 hr at room temperature. The reaction mixture was poured onto ice water (100 mL) with stirring for 15 min, and set aside for 1 hr. The formed precipitate was filtered off, dried in air and crystallized from hexane-ethyl acetate mixture.

Ethyl 6-(2-chlorophenyl)-4-methyl-2-methylthio-1-(2-morpholinoacetyl)-1,6-dihydro-pyrimidine-5-carboxylate (IIIo)

Yield (0.68 g, 75%), m.p. 141-143°C; IR (KBr) 1690, 1592, 1509 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.10-7.50 (4H, m, CH Ar.); 7.30 (1H, s, C6H); 4.70-4.20 (2H, q, $\underline{CH_2}CH_3$); 4.20-3.60 (6H, m, $CO\underline{CH_2}$, C2,6 H morpholine); 3.00-2.40 (10H, m, $S\underline{CH_3}$, $C4\underline{CH_3}$, C3,5 H morpholine); 1.50-1.00 (3H, t, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{21}H_{26}ClN_3O_4S$: C, 55.81; H, 5.80; N, 9.30. Found: C, 56.00; H, 5.93; N, 9.14.

Isopropyl 6-(2-chlorophenyl)-4-methyl-2-methylthio-1-(2-morpholinoacetyl)-1,6-dihydropyrimidine-5-carboxylate (IIIp)

Yield (0.662 g, 71%), m.p. 135°C; IR (KBr) 1692, 1589, 1508 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.10-7.60 (4H, m, CH Ar.); 7.48 (1H, s, C6H); 5.70-5.20 (1H, m, $\underline{CH}(CH_3)_2$); 4.20-3.70 (6H, m, $CO\underline{CH_2}$, C2,6 H morpholine); 3.00-2.30 (10H, m, $S\underline{CH_3}$, $C4\underline{CH_3}$, C3,5H morpholine); 1.60-1.30 (3H, d, $CH(\underline{CH_3})_2$); 1.30-1.00 (3H, d, $CH(\underline{CH_3})_2$). Anal. Calcd. for $C_{22}H_{28}ClN_3O_4S$: C, 56.70; H, 6.06; N, 9.02. Found: C, 56.70; H, 5.69; N, 8.90. MS (70eV, EI): m/z (%): m/z 337 ($M^{+\bullet}$ - $[COCH_2C_4H_8NO]^+$, 10.0); m/z 128 ($[COCH_2C_4H_8NO]^+$, 2.4); 100 ($[C_5H_{10}NO]^+$, 100).

General procedure for synthesis of dialkyl 4-methyl-2-oxo-6-phenyl (substituted phenyl)-1,2,3,6-tetrahydropyrimidine-1,5-dicarboxylate (IVa-l)

A solution of the appropriate dialkyl 4-methyl-2-methylthio-6-phenyl (substituted phenyl)-1,6-dihydropyrimidine-1,5-dicarboxylate **IIIa-l** (5.0 mmole) in ethanol (90.0%, 30 mL) containing hydrochloric acid (2 mL) was refluxed for 3 hrs. The reaction mixture was cooled, poured onto ice water (100 mL), alkalinized with concentrated ammonia solution with shaking, then refrigerated 2 hrs. The formed precipitate was filtered off, dried in air and crystallized from hexane-ethyl acetate mixture.

Diethyl 4-methyl-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-1,5-dicarboxylate (IVa)

Yield (1.23 g, 74%), m.p. 138-140°C; IR (KBr) 3235, 1757, 1697, 1631 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.73 (1H, s, NH); 7.60-7.10 (5H, m, CH Ar.); 6.40 (1H, s, C6H); 4.66-4.00 (4H, m, $2(\underline{CH_2}CH_3)$; 2.40 (3H, s, C4 $\underline{CH_3}$); 1.60-1.10 (6H, m, $2(CH_2\underline{CH_3})$. Anal. Calcd. for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.58; H, 6.19; N, 8.33.

5-Ethyl 1-isobutyl 4-methyl-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-1,5-dicarboxylate (IVb)

Yield (1.352 g, 75%), m.p. 162-164°C; IR (KBr) 3210, 1705, 1634 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.70 (1H, s, NH); 7.93 (5H, s, CH Ar.); 6.90 (1H, s, C6H); 4.80-4.30 (4H, m, $\underline{CH_2}CH_3$, $\underline{CH_2}CH(CH_3)_2$); 2.60 (3H, bs, $C4\underline{CH_3}$); 2.50-1.80 (1H, m, $CH_2\underline{CH}(CH_3)_2$); 1.60-1.20 (3H, t, $CH_2\underline{CH_3}$); 1.20-0.80 (6H, d, $CH_2CH(\underline{CH_3})_2$). Anal. Calcd. for $C_{19}H_{24}N_2O_5$: C, 63.32; H, 6.71; N, 7.77. Found: C, 63.50; H, 6.62; N, 7.76.

1-Ethyl 5-isopropyl 4-methyl-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-1,5-dicarboxylate (IVc)

Yield (1.212 g, 70%), m.p. 180-182°C; IR (KBr) 3210, 1701, 1639 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.43 (1H, s, NH); 8.20-7.70 (5H, bs,

CH Ar.); 6.84 (1H, s, C6H); 5.80-5.20 (1H, m, $\underline{CH}(CH_3)_2$); 5.00-4.43 (2H, q, $\underline{CH_2}CH_3$); 2.90-2.50 (3H, s, C4$\underline{CH_3}$); 1.70-1.06 (9H, m, $CH(\underline{CH_3})_2$, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{18}H_{22}N_2O_5$: C, 62.42; H, 6.40; N, 8.09. Found: C, 62.10; H, 6.77; N, 8.03.

1-Isobutyl 5-isopropyl 4-methyl-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-1,5-dicarboxylate (IVd)

Yield (1.273 g, 68%), m.p. 128-130°C; IR (KBr) 3215, 1707, 1635 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.70 (1H, s, NH); 8.00 (5H, s, CH Ar.); 6.93 (1H, s, C6H); 5.80-5.30 (1H, m, $\underline{CH}(CH_3)_2$); 4.60-4.30 (2H, d, $\underline{CH_2}CH(CH_3)_2$); 2.60 (3H, s, C4$\underline{CH_3}$); 2.40-1.90 (1H, m, $CH_2\underline{CH}(CH_3)_2$); 1.60-0.90 (12H, m, $CH_2CH(\underline{CH_3})_2$, $CH(\underline{CH_3})_2$). Anal. Calcd. for $C_{20}H_{26}N_2O_5$: C, 64.15; H, 7.00; N, 7.48. Found: C, 64.21; H, 6.86; N, 7.52.

Diethyl 6-(2-chlorophenyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-1,5-dicarboxylate (IVe)

Yield (1.376 g, 75%), m.p. 161-162°C; IR (KBr) 3200, 1774, 1696, 1627 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.00 (1H, s, NH); 7.83-7.10 (4H, m, CH Ar.); 6.67 (1H, s, C6H); 4.66-4.06 (4H, m, 2($\underline{CH_2}CH_3$); 2.50 (3H, s, C4 $\underline{CH_3}$); 1.60-1.10 (6H, m, 2($CH_2\underline{CH_3}$). Anal. Calcd. for $C_{17}H_{19}ClN_2O_5$: C, 55.67; H, 5.22; N, 7.64. Found: C, 55.45; H, 5.60; N, 7.59.

5-Ethyl 1-isobutyl 6-(2-chlorophenyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-1,5-dicarboxylate (IVf)

Yield (1.382 g, 70%), m.p. 138-140°C; IR (KBr) 3220, 1699, 1634 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 10.13 (1H, s, NH); 8.40-7.70 (4H, m, CH Ar.); 7.10 (1H, s, C6H); 4.80-4.26 (4H, m, $\underline{CH_2}CH_3$, $\underline{CH_2}CH(CH_3)_2$); 2.62 (3H, s, C4$\underline{CH_3}$); 2.40-1.90 (1H, m, $CH_2\underline{CH}(CH_3)_2$); 1.60-1.20 (3H, t, $CH_2\underline{CH_3}$); 1.20-0.80 (6H, d, $CH_2CH(\underline{CH_3})_2$). Anal. Calcd. for $C_{19}H_{23}ClN_2O_5$: C, 57.80; H, 5.87; N, 7.09. Found: C, 58.01; H, 5.87; N, 7.17.

1-Ethyl 5-isopropyl 6-(2-chlorophenyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-1,5-dicarboxylate (IVg)

Yield (1.334 g, 70%), m.p. 152-154°C; IR (KBr) 3210, 1734, 1697, 1642 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.63 (1H, s, NH); 8.30-7.60 (4H, bs, CH Ar.); 7.10 (1H, s, C6H); 5.70-5.10 (1H, m, $\underline{CH}(CH_3)_2$); 4.90-4.40 (2H, q, $\underline{CH_2}CH_3$); 2.90-2.40 (3H, s, C4$\underline{CH_3}$); 1.70-0.80 (9H, m, $CH(\underline{CH_3})_2$, $CH_2\underline{CH_3}$). $M^{+\bullet}$: m/e 380. Anal. Calcd. for $C_{18}H_{21}ClN_2O_5$: C, 56.77; H, 5.56; N, 7.36. Found: C, 57.12; H, 5.29; N, 7.75. MS (70eV, EI): m/z (%): 383 ($M^{+\bullet}$ + 3, 3.4); 382 ($M^{+\bullet}$ + 2, 10.8); 381 ($M^{+\bullet}$ + 1, 21.7); 380 ($M^{+\bullet}$, 13.9); m/z 309 ($M^{+\bullet}$ - $[CO_2C_2H_5]^+$, 18.5); m/z 269 ($M^{+\bullet}$ - $[C_6H_4Cl]^+$, 7.6); 155 ($M^{+\bullet}$- $[CO_2C_2H_5$ + $(C_6H_4Cl)^+$ + $CH_3CN]$, 100).

1-Isobutyl 5-isopropyl 6-(2-chlorophenyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-1,5-dicarboxylate (IVh)

Yield (1.39 g, 68%), m.p. 134-135°C; IR (KBr) 3210, 1724, 1697, 1633 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 10.05 (1H, s, NH); 8.40-7.70 (4H, s, CH Ar.); 7.20 (1H, s, C6H); 5.80-5.20 (1H, m, $\underline{CH}(CH_3)_2$); 4.60-4.30 (2H, d, $\underline{CH_2}CH(CH_3)_2$); 2.63 (3H, s, C4$\underline{CH_3}$); 2.40-1.90 (1H, m, $CH_2\underline{CH}(CH_3)_2$); 1.60-0.90 (12H, m, $CH_2CH(\underline{CH_3})_2$, $CH(\underline{CH_3})_2$). Anal. Calcd. for $C_{20}H_{25}ClN_2O_5$: C, 58.75; H, 6.16; N, 6.85. Found: C, 58.55; H, 6.10; N, 6.79.

Diethyl 6-(2-fluorophenyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-1,5-dicarboxylate (IVi)

Yield (1.226 g, 70%), m.p. 164-165°C; IR (KBr) 3305, 7156, 1698, 1633 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.20 (1H,s, NH); 8.00-7.13 (4H, m, CH Ar.); 6.77 (1H, s, C6H); 4.80-4.10 (4H, m, 2($\underline{CH_2}CH_3$); 2.53 (3H, s, C4$\underline{CH_3}$); 1.60-1.10 (6H, m, 2($CH_2\underline{CH_3}$). Anal. Calcd. for $C_{17}H_{19}FN_2O_5$: C, 58.28; H, 5.47; N, 8.00. Found: C, 57.94; H, 5.12; N, 8.01.

5-Ethyl 1-isobutyl 6-(2-fluorophenyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-1,5-dicarboxylate (IVj)

Yield (1.230 g, 65%), m.p. 136-138°C; IR (KBr) 3220, 1713, 1634 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.83 (1H, s, NH); 8.20-7.50 (4H, m, CH Ar.); 7.06 (1H, s, C6H); 4.80-4.26 (4H, m, $\underline{CH_2}CH_3$, $\underline{CH_2}CH(CH_3)_2$); 2.60 (3H, s, C4$\underline{CH_3}$); 2.40-1.90 (1H, m, $CH_2\underline{CH}(CH_3)_2$); 1.70-1.20 (3H, m, $CH_2\underline{CH_3}$); 1.20-0.80 (6H, d, $CH_2CH(\underline{CH_3})_2$). Anal. Calcd. for $C_{19}H_{23}FN_2O_5$: C, 60.31; H, 6.13; N, 7.40. Found: C, 60.19; H, 5.86; N, 7.33.

1-Ethyl 5-isopropyl 6-(2-fluorophenyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-1,5-dicarboxylate (IVk)

Yield (1.20 g, 66%), m.p. 148-150°C; IR (KBr) 3215, 1703, 1639 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.36 (1H, s, NH); 8.20-7.30 (4H, bs, CH Ar.); 6.94 (1H, s, C6H); 5.70-5.00 (1H, m, $\underline{CH}(CH_3)_2$); 4.90-4.40 (2H, q, $\underline{CH_2}CH_3$); 2.80-2.40 (3H, s, C4$C\underline{H_3}$); 1.70-0.90 (9H, m, $CH(\underline{CH_3})_2$, $CH_2\underline{CH_3}$). Anal. Calcd. for $C_{18}H_{21}FN_2O_5$: C, 59.33; H, 5.81; N, 7.69. Found: C, 59.69; H, 5.51; N, 8.12.

1-Isobutyl 5-isopropyl 6-(2-fluorophenyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-1,5-dicarboxylate (IV*l*)

Yield (1.26 g, 64%), m.p. 134-137°C; IR (KBr) 3225, 1714, 1635 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.70 (1H, s, NH); 8.30-7.50 (4H, s, CH Ar.); 7.10 (1H, s, C6H); 5.70-5.20 (1H, m, $\underline{CH}(CH_3)_2$); 4.60-4.30 (2H, d, $\underline{CH_2}CH(CH_3)_2$); 2.60 (3H, s, C4$\underline{CH_3}$); 2.36-1.70 (1H, m, $CH_2\underline{CH}(CH_3)_2$); 1.70-0.80 (12H, m, $CH_2CH(\underline{CH_3})_2$, $CH(\underline{CH_3})_2$). Anal. Calcd. for $C_{20}H_{25}FN_2O_5$: C, 61.21; H, 6.42; N, 7.14. Found: C, 61.38; H, 6.65; N, 7.16.

B. Pharmacology

Hypotensive activity

Groups of three Adult Boscat healthy rabbits (1.5-2 Kg) were used. Animals were anaesthetized first with an i.p. injection of urethane solution (25%) in a dose of 1.6 g/Kg. Arterial blood pressure was recorded via the carotid artery; the latter was cannulated to elcomatic EM 751 blood pressure transducer. The tip of the cannula was dipped in heparin to prevent clotting. Blood pressure was recorded by using a universal oscillograph (Harvard apparatus limited, Kent, U.K.). A dose of 2 μmole of the tested compounds in aqueous ethanol 1:3 was injected intravenously through the ear vein. Blood pressure was recorded before and after administration of the dose over a period of 4 hrs.

Calcium channel blocker activity on isolated rat ileum preparation

Test solutions

1) Stock solution A: 0.1 mmole of the tested compound was dissolved in 10 mL absolute ethanol.
2) Diluted stock solution B: 0.1 mL of stock solution A was diluted to 10 mL distilled water.

Method

Male and female albino rats weighing between 150 and 200 g were used in this study. Animals entered the test having fasted overnight. After the animals had been scarified by cervical dislocation, the ileum (10-15 cm terminal portion) was immediately removed, discarding the 5-8 cm segment proximal to the ilio-caecal junction. Segments 1.5-2 cm long were mounted vertically in a 100 mL organ bath containing 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 bath contents were maintained at 37 °C and aerated by 95% O_2 and 5% CO_2. The isometric tension generated by ileum muscle was recorded using a universal oscillograph. After equilibration, 0.25 mL of 1% barium chloride solution was added and the generated contraction was recorded. The rat ileum was washed three times with the Tyrode solution. The substances to be tested were investigated using the single-dose technique. Barium chloride contractions were induced after addition of the test substances at the different concentrations (0.1, 1, 10 μmole) and 5 min exposure time. The responses to the barium chloride in presence and in absence of the tested compounds were recorded and compared. Only one compound was tested in each preparation. Because the solvent effect 100 μmole concentration can not done, the control responses were taken after the addition of the same amount of the solvent free compounds. The responses of the compounds were compared to those of amlodipine besylate.

Acute toxicity

Groups of adult albino mice of either sex, each of six animals (25-30 g) were injected i.p. with graded doses of the tested compounds and the reference drug. The percentage of mortality, in each group of animals, was determined 24 h after the injection. Calculation of the LD_{50} was processed by graphical method.

Molecular modeling

All the molecular modeling studies were carried out on an Intel Pentium 1.6 GHz processor, 512 MB memory with Windows XP operating system using Molecular Operating Environment (MOE 2005.06; Chemical Computing Group, Canada)[31] as the computational software. All the minimizations were performed with MOE until a RMSD gradient of 0.05 $Kcal.mole^{-1}$ $A^{\circ-1}$ with MMFF94X force-field and the partial charges were automatically calculated.

General methodology

Flexible alignment

1) The structures of amlodipine and the DHPM compounds that will be aligned were loaded into MOE page.
2) A collection of similarity field terms is selected as a field of the alignment. However, H-bond donor, H-bond acceptor, atomicity, polar hydrogen are selected as similarity terms.
3) Flexible alignment technique of flexible body type is the choice for the alignment procedure.
4) After finishing of the calculation, load the aligned conformers of the molecule that having the lowest S value with amlodipine.

Pharmacophore searching

i- Generation of 3D structures of tested set and training set molecules

1) The structures of the tested set molecules which include the entire synthesized compounds are loaded into MOE page and from which create tested set database.
2) The structure of the training set molecules that include nifedipine, amlodipine, nitrendipine, nicardipine, nisoldipine, fleodipine, nimodipine, isradipine, elgodipine, and benidipine are loaded into new MOE page.
3) Flexible alignment technique are applied for the chosen training set molecules
4) The best one aligned conformers that having the lowest S value for the aligned training set molecules are browsed into the new MOE page.

ii- Assignment of the pharmacophoric features

5) The pharmacophoric features is generating on the functional groups of the best aligned training set conformers to build pharmacophoric query.
6) The suggested features of the pharmacophoric query are selected as the features of 100% score that expressed as 3D sphere features. The features fields are aromatic ring (Aro), hydrogen donor (Don), hydrogen acceptor (Acc), hydrophobicity (Hyd), and metal ligator (ML). Each Pharmacophoric feature is composed of one or more feature from the feature field.

iii- Conformational searching of databases for new structures matching the generated pharmacophoric features

7) Pharmacophore query is searched in the tested set database that matched the query.
8) When the search is completed the numbers of hit (match) molecules are shown as a database query and from the database query, one of the hit compounds was selected and browse it through the matches.

RESULTS AND DISCUSSION

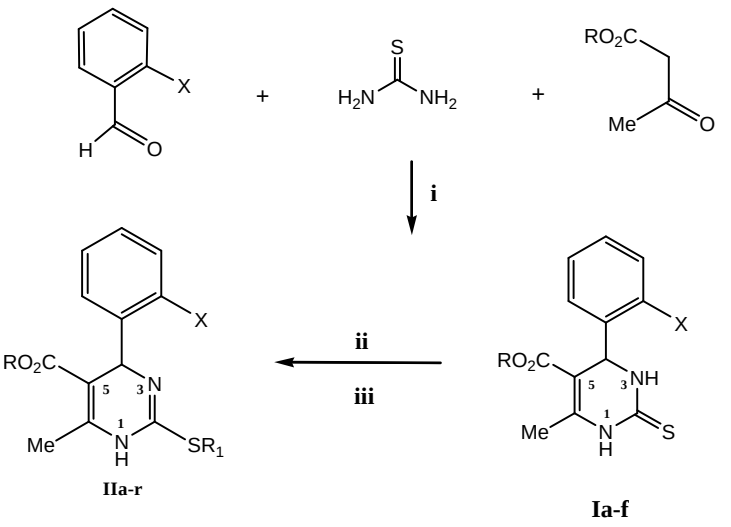
A. Chemistry

The synthones alkyl 6-methyl-4-phenyl(substituted phenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **Ia-f** were synthesized according to Biginelli reaction condition by heating at 105-110°C a mixture of araldehyde, alkyl acetoacetate, and thiourea in glacial acetic acid[30&32] for 1 hr then at 130-140°C for 45 min as depicted by scheme 1.

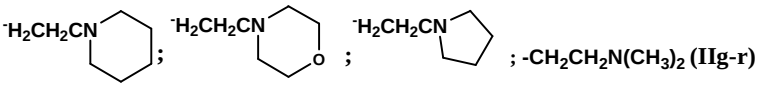
^{1}H-NMR spectra of these compounds showed two singlets attributed to N3H and N1H at δ (9.50-8.55), (8.50-7.76) ppm respectively. The signal of C4-H appeared as singlet at (6.30-5.53) ppm where the chemical shift was affected by *o*-substituent on the phenyl ring. The C6-CH_3 signal appeared at (2.63-2.46) ppm.

S-alkylamines **IIg-r** were prepared by reacting **Ia, Ic** and **Ie** with 2-chloroethylamine(cyclic amines) hydrochloride in presence of sodium hydroxide[28&30] (Scheme 1). The free bases were mostly separated as hydrates.

^{1}H-NMR spectra of these compounds revealed the disappearance of the one NH signals in the parent compound and appearance of ethylamine signals overlapping the C6-CH_3 signal which appeared as multiplet at 3.20-1.50 ppm.



X= H;Cl; F; R = CH_2CH_3; $CH(CH_3)_2$; R_1 = CH_3(IIa-f); R_1 =



i, glacial acetic acid; ii, (1) dimethylsulfate, ethanol, (2) conc ammonia (**IIa-f**); iii, 2-chloroethylamine(cyclic amines) hydrochloride, ethanol, aqueous sodium hydroxide (**IIg-r**)

Scheme 1: Synthetic pathway for DHPMs **I** and **II**.

2-Methylthio derivatives **IIa-f** were synthesized by reaction of the synthones **Ia-f** with excess dimethylsulfate[33]. The formed compounds were precipitated by addition of dilute ammonium hydroxide. This method afforded better yields than the reported method in which alkylation occurs by alkyl halide in the presence of base[30] or by addition of equivalent amount of dimethylsulfate in presence of sodium hydroxide. N1 alkylation can occur if the dimethylsulfate is more than the equivalent amount and in presence of excess base[28]. In our case SCH_3 derivative was obtained in quantitative yield in presence of excess dimethylsulfate and absence of a base.

^{1}H-NMR spectra of these compounds revealed the disappearance of the one NH signals and the appearance of SCH_3 singlet at (2.63-2.50) ppm.

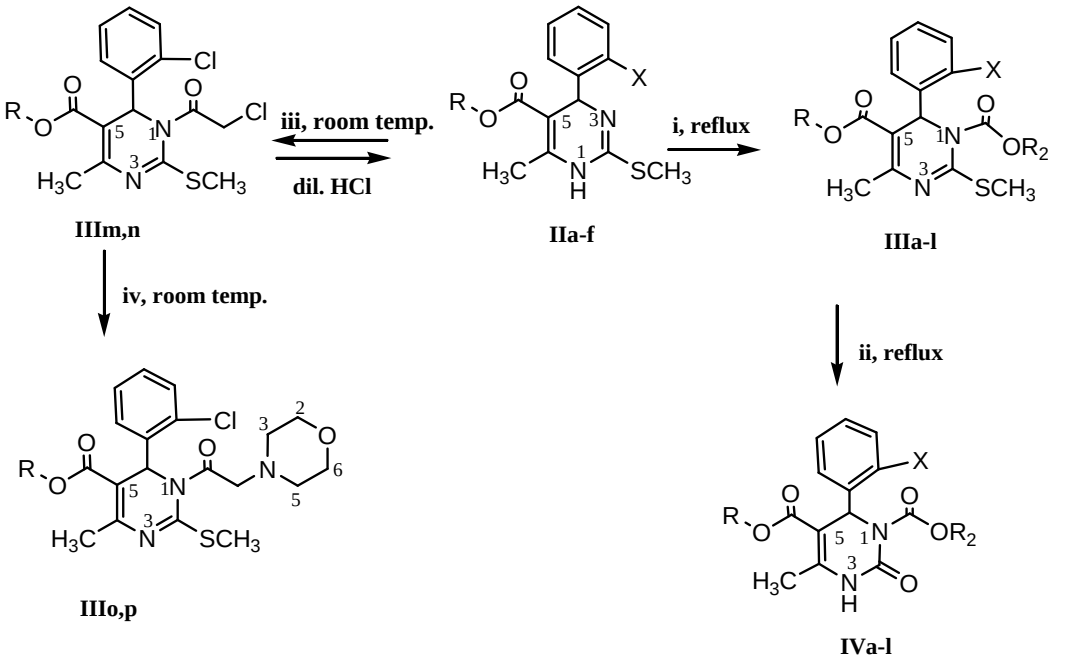
The N1 carbamoylation[2,28&30] was undertaken through reaction of compounds **IIa-f** with excess alkyl chloroformate in presence of pyridine to yield **IIIa-l** (Scheme 2). Most of these compounds were separated as oily residues that solidified from methanolic solution at freezer temperature overnight.

^{1}H-NMR spectra of these compounds revealed the most characteristic difference from the precursors **IIa-f** where the signals of SCH_3 and C4-CH_3 appeared as singlet at (3.00-2.40) ppm, in addition to the signals of the two alkyl esters.

Reaction of compounds **IIc** and **IId** with chloroacetylchloride[28,30&34] in presence of pyridine yielded the chloroacetyl derivatives **IIIm** and **IIIn** (Scheme 2).

^{1}H-NMR spectra of these compounds revealed the deshielding effect of the chloroacetyl group on C6-H that appeared as singlet at 7.40 ppm; and signal of CH_2Cl appeared as singlet at 4.90 ppm.

Next step was the trial to replace the chlorine in 2-chloroacetyl moiety with different primary or secondary aliphatic (or aromatic) amines. All the trials were unsuccessful except with morpholine that easily reacted at room temperature with **IIIm** and **IIIn** in dry acetone in presence of excess pyridine and a crystal of potassium iodide to give alkyl 1-(2-morpholinoacetyl) derivatives **IIIo** and **IIIp**.



X = H, Cl, F: R = CH_2CH_3; $CH(CH_3)_2$, R_2 = CH_2CH_3; $CH_2CH(CH_3)_2$

i, alkylchloroformate, pyridine, acetonitrile; ii, hydrochloric acid, ethanol; iii, chloroacetylchloride, pyridine, acetonitrile; iv, morpholine, KI, pyridine, dry acetone.

Scheme 2: Synthetic pathway for DHPMs **III** and **IV**.

On the other hand reaction of **IIIm** and **IIIn** with amines like triethylamine, yielded the deacetyled product **IIc** and **IId** (Scheme 2).

^{1}H-NMR spectra of morpholino derivatives **IIIo,p** revealed a multiplet at 4.20-3.60 ppm integrated by 6 protons assigned to C2 and C6 morpholine plus NCH_2CO protons. An upfield multiplet at 3.00-2.40 ppm integrated by 10 protons was attributed to SCH_3,C4-CH_3 and four protons of C3 and C5 in morpholine nucleus.

Desulforization[28&30] of compounds **IIIa-l** by refluxing in ethanol containing hydrochloric acid gave the 2-oxo compounds of **IVa-l** (Scheme 2).

^{1}H-NMR spectra of series IV were differentiated from their precursors **III** by the appearance of NH signal at 10.13-8.73 ppm and the disappearance of SCH_3 signal.

Attempted desulforization of compounds **IIIm-p** with hydrochloric acid, was unsuccessful since deacylatoin took place and **IIc** and **IId** were regenerated.

EI-Mass spectra of the 4-(2-chlorophenyl) compounds **Id, IIk, IIIh, IIIm, IIIp,** and **IVg**, exhibited the characteristic bond cleavage sites[35-39]. In addition to other fragments related to each individual compound according to nature of substituents[35,36&39].

B. Pharmacology

Hypotensive activity

Thirty compounds, **IIg-r**, **IIIe,m,o**, **IIIh,n,p** and **IVa-l** were evaluated for hypotensive effect in comparison to amlodipine besylate according to the reported method[1&2]. The assessment of the hypotensive activity for the aforementioned compounds was carried out by measuring the percentage decrease in the mean blood pressure of anesthetized normotensive rabbits after i.v. injection of 2 µmol/kg dose in aqueous ethanol (1:1 for the compounds **IIIe,m,o** and **IIIh,n,p** and 1:2 for the other compounds). Only 2-oxo-tetrahydropyrimidine-1,5-dicarboxylate **IVa-l** showed hypotensive effect with different potencies and duration of action.

A strong and transient high onset of action that faded within 5-30 min was the common pattern showed by the four members in the series **IVa-d** (Table 1).

Uneven distribution of bulkiness of the ester groups at N1 and C5 as in **IVb** (CO_2Et, CO_2i-Bu) and **IVc** (CO_2i-Pr, CO_2Et) was accompanied by relative decrease in the onset of action that was still higher than that of amlodipine. On the other hand balanced bulkiness of both carboxylates as in **IVa** (CO_2Et, CO_2Et) and **IVd** (CO_2i-Pr, CO_2i-Bu) showed the relative high onset that reached twice the value shown by amlodipine.

Compounds **IVe-h** revealed an onset of action pattern similar to that noticed in **IVa-d** (Table 2). In other words it is the extent of matched bulkiness attached to the carboxylates that played the main impact on the onset of hypotensive potential. Thus **IVh** (CO_2i-Pr, CO_2i-Bu) and **IVe** (CO_2Et, CO_2Et) showed higher decrease in blood pressure (twice that of amlodipine), while the unbalanced distribution in **IVf** (CO_2Et, CO_2i-Bu) and **IVg** (CO_2i-Pr, CO_2Et) elicited less activity than the other compounds in this series.

It seem worthy to comment on the behavior of the most active compound **IVg** (CO_2i-Pr, CO_2Et). Under our experimental conditions the obseved hypotensive effect matched that of amlodipine at the first 60 min and continued to decrease blood pressure to reach more than 1.5 times that of amlodepine at the end of the experiment at 240 min. The other three compounds **IVe**, **IVf**, **IVh** are much less active than amlodipine and showed rapid decline of the hypotensive effect that abolished completely after 30-60 min.

Pattern of onset of action of members **IVi-l** was not much different from that revealed by **IVa-d** and **IVe-h**. Compounds **IVi,j,l** showed an onset of action that faded rapidly to reach a sustained maximum value that continued for additional 3 hrs (Table 3).

An exception was compound **IVk** that displayed a weak and short hypotensive effect that completely abolished at 60 min.

Calcium channel blocker activity

The calcium channel blocker effect on the isolated contracted rat ileum was done for all the synthesized compounds in a dose of 1, 10 μmole/liter in comparison to amlodipine besylate as a reference drug[3,4&40].

All the tested compounds including amlodipine besylate don't show any relaxant effect on the isolated contracted rat ileum in a dose of 1 μmole. On the other hand most of the tested compounds including amlodipine besylate were able to depress the rat ileum contraction at a dose level 10 μmole. The derivatives **IIIa-l**, and **IIIo** and **IIIp** were exception since they did not show appreciable depression of contracted rat ileum at this dose level **(**Fig. 1).

Acute toxicity

Acute toxicity of the most active compounds; **IVg**, and **IVl** was determined by calculating their median lethal dose (LD_{50}) using graphical method[41]. Solutions of **IVg**, and **IVl** in 0.1 mL DMSO were used in our test. The dosed amount of DMSO did not elicit appreciable effect on the animal's control. LD_{50} of compounds **IVg** and **IVl** were found to be 45 and 60 mg/kg, respectively (Table 4, Fig. 2), while LD_{50} of amlodipine besylate in the same solvent at the same condition was found to be 37.5 mg/kg (reported 31 mg/kg)[42].

Molecular modeling

Flexible alignment

Conformational analyses of automated flexible alignments between amlodipine and the entire synthesized compounds of series **I-IV** have been performed with the MOE 2005.06 software suite.

A collection of similarity field beside the energy strain is selected as parameters in the alignment.

However, H-bond donor, H-bond acceptor, aromaticity, polar hydrogen are selected as similarity terms.

The output of flexible alignment containing the following data: **U**, the average strain energy of the molecules in the alignment in kcal/mole; **F**, the total mutual similarity score, –kTlogF, of the configuration; **S**, the alignment score of the configuration. This is calculated as –kTlogF + U, the flexible alignment experiment was carried to investigate degree of molecular superimposition of the synthesized compounds on amlodipine. It was observed that the aromatic ring 4-phenyl (or substituted phenyl) is placed in a plane perpendicular to the dihydropyrimidine ring, that was already acknowledged for amlodipine and DHP congeners (Fig. 3a-c are representative examples).

Table 1: Decrease in B.P. by time induced by compounds **IVa-d** in normotensive rabbits in a dose 2 µmole/Kg body weight.

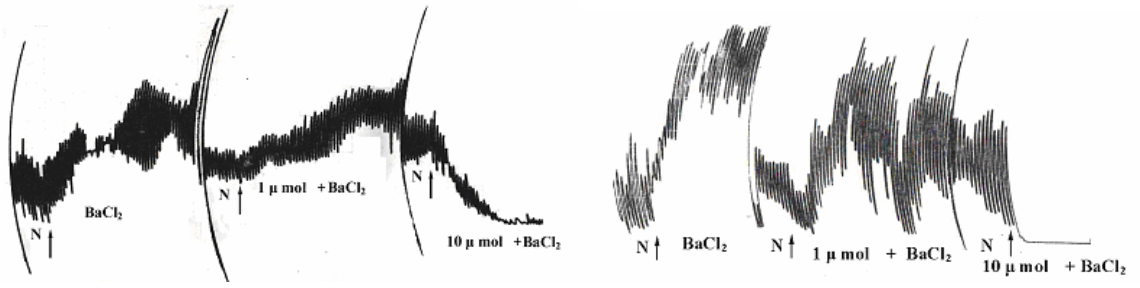
Time (min)	Mean decrease in blood pressure (%)				
	IVa	**IVb**	**IVc**	**IVd**	Amlodipine
1	36.60 ± 0.60	27.60 ± 2.20	18.35 ± 0.25	31.10 ± 1.20	15.16 ± 2.27
5	13.70 ± 0.90	10.95 ± 0.95	11.55 ± 0.95	13.62 ± 0.98	17.97 ± 1.88
15	0	10.4 0± 0.90	0	12.85 ± 0.55	17.97 ± 1.88
30		10.40 ± 0.90		0	17.17 ± 1.35
60		0			17.17 ± 1.35
120					17.17 ± 1.35
180					15.67 ± 1.27
240					12.78 ± 0.95

Table 2: Decrease in B.P. by time induced by compounds **IVe-h** in normotensive rabbits in a dose 2 µmole/Kg body weight.

Time (min)	Mean decrease in blood pressure (%)				
	IVe	**IVf**	**IVg**	**IVh**	Amlodipine
1	30.10 ± 1.90	18.50 ± 1.80	20.53 ± 2.10	32.40 ± 2.10	15.16 ± 2.27
5	13.46 ± 0.84	12.90 ± 0.60	15.4 0± 0.80	13.55 ± 0.25	17.97 ± 1.88
15	13.46 ± 0.84	12.90 ± 0.60	16.90 ± 0.78	12.95 ± 0.85	17.97 ± 1.88
30	10.70 ± 0.90	0	18.63 ± 0.90	12.65 ± 0.55	17.17 ± 1.35
60	6.0 ± 0.10		18.30 ± 1.0	0	17.17 ± 1.35
120	0		19.20 ± 1.59		17.17 ± 1.35
180			20.93 ± 2.02		15.67 ± 1.27
240			22.13 ± 2.13		12.78 ± 0.95

Table 3: Decrease in B.P. by time induced by compounds **IVi-l** in normotensive rabbits in a dose 2 µmole/Kg body weight.

Time (min)	Mean decrease in blood pressure (%)				
	IVi	**IVj**	**IVk**	**IVl**	Amlodipine
1	23.40 ± 2.34	13.90 ± 0.80	19.10 ± 1.72	39.17 ± 2.07	15.16 ± 2.27
5	12.23 ± 0.55	14.75 ± 0.45	12.40 ± 0.25	20.30 ± 2.05	17.97 ± 1.88
15	10.87 ± 0.69	13.55 ± 0.45	9.57 ± 0.52	14.70 ± 1.08	17.97 ± 1.88
30	10.70 ± 0.46	14.21 ± 0.15	10.07 ± 0.87	13.46 ± 1.23	17.17 ± 1.35
60	13.77 ± 1.19	16.25 ± 0.75	0	17.23 ± 1.56	17.17 ± 1.35
120	13.77 ± 1.19	14.75 ± 0.75		17.23 ± 1.56	17.17 ± 1.35
180	14.13 ± 1.48	16.25 ± 0.75		16.93 ± 1.60	15.67 ± 1.27
240	17.93 ± 1.54	16.25 ± 0.75		17.62 ± 1.80	12.78 ± 0.95



Ia **Amlodipine**

Fig. 1: Representative illustration of the Ia and amlodipine on the contraction of the isolated rat ileum muscle in a dose of 1 and 10 µmole/liter organ bath concentration.
• Chart speed = 0.5 mm/sec. for all the experiments, • N: Normal muscle contraction

Table 4: Acute toxicity of **IVg, IVl**, and amlodipine.

Drug concentration ((mg/kg mice)	Percentage of mortality (%)		
	IVg	**IVl**	Amlodipine
10	-	-	0
20	0	0	16
30	16	16	33
45	50	33	67
60	67	50	100
80	83	83	-
100	100	100	-

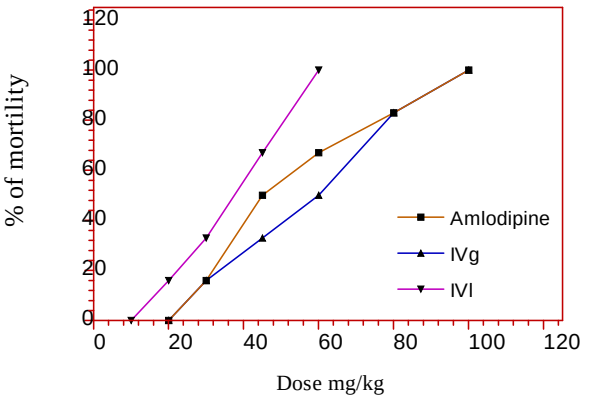
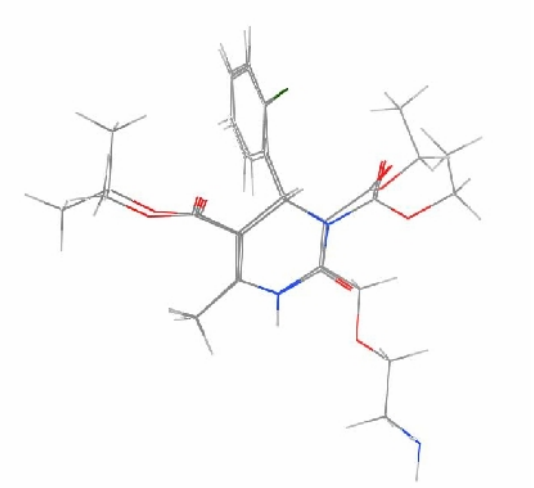
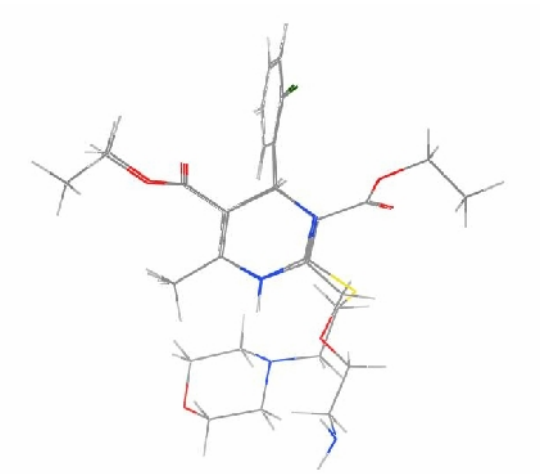


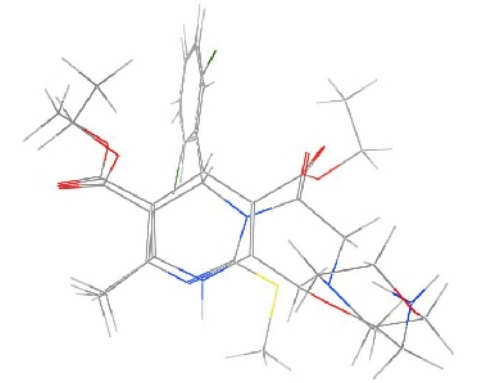
Fig. 2: Acute toxicity of **IVg, IVl** and Amlodipine besylate.



a) **IVg** (S= 148.54)



b) **Ill** (S= 176.78)



c) **IIIo** (S= 226.92)

Fig. 3a-c: Illustration of conformational alignment of representatives **IVg, Ill** and **IIIo** with amlodipine.

According to goodness of molecular alignment with amlodipine it was possible to classify the tested set of compounds into three categories. Namely compounds with the least S range values 142-150, were those found for series **IV**, those of moderate range 155-177, were series **I**, and **II**, while series **III** showed the highest range 192-226. A clear correlation between the three ranges of alignments and the observed pharmacological activity can be established. Thus the most aligned series **IV** revealed hypotensive and calcium antagonist effect, while members of series **I** and **II** with the moderate alignment range revealed only calcium antagonist activity without hypotensive action. Finally series **III** with highest alignment score were devoid of either effect. Compounds **IIIm** and **IIIn** with high alignment score (200-205) were exceptional since they demonstrated calcium antagonist effect.

Pharmacophore search

Pharmacophore query is 3D arrangement of molecular features. These features are electrostatic and steric features of different compounds that have the same biological target structure. In the absence of receptor information, pharmacophore query try to relate the feature geometries to the biological response of these compounds and also relate the bound conformation of the actives and the receptor.

There are continual steps for the computerized pharmacophore building (Fig. 4).

Ten DHP derivatives that have reported remarkable calcium channel antagonist and hypotensive effects are used to create the pharmacophore query namely nifedipine, amlodipine, nitrendipine, nicardipine, nisoldipine, fleodipine, nimodipine, isradipine, elgodipine, and benidipine. These compounds were aligned together and from the conformers with lowest S value, initial pharmacophore query was created by MOE program. Six pharmacophoric features were assigned, hydrogen acceptor and metal ligator (Acc & ML), aromatic ring (Aro), hydrophobicity (Hyd), hydrogen acceptor and metal ligator (Acc & ML), hydrophobicity and hydrogen donor (Hyd/Don), and metal ligator, hydrophobicity, and hydrogen acceptor (ML/Hyd/Acc). To examine the initial pharmacophore query, the synthesized compounds of the series **I-IV** were challenged as test set and were searched to investigate the number of hit compounds with the query. At first the results of search did not agree with the results from the biological experiments, and modifications of the query were practiced to obtain the consensus query. Our trials yielded two consensus pharmacophore queries A and B.

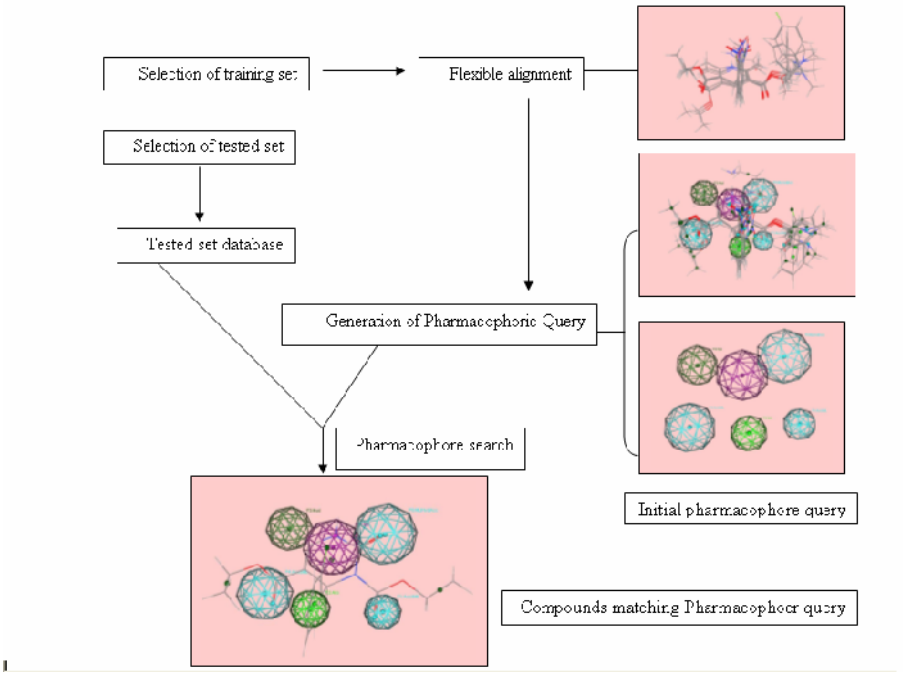


Fig. 4: General steps of Pharmacophore building.

Consensus query A with six pharmacophoric features hit 12 compounds that possess calcium channel blocker with hypotensive effect (Fig. 5). While the consensus query B with the pharmacophoric features Aro, Hyd, Acc & ML, Don, and ML/Hyd/Acc hit 36 compounds (Fig. 6) eventually possess calcium channel blocker activity with probable hypotensive effect. In the other words consensus query B can be considered the general pharmacophore query for the calcium channel blocker effect. The two exceptions **IIIm** and **IIIn** didn't hit the query B although they possess calcium antagonist effect only.

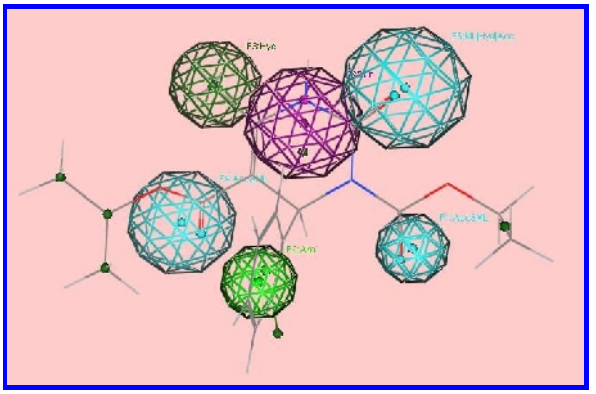


Fig. 5: Matching of compound **IVg** with consensus query A.

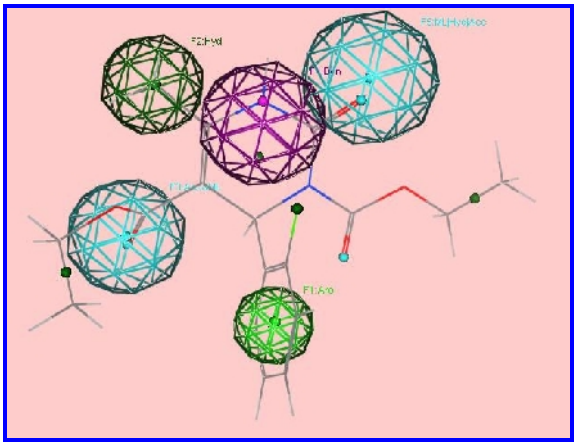


Fig. 6: Matching of compound **IVi** with consensus query B.

Conclusion

Mono and dicarboxylic acid esters of DHPMs were prepared through variation at 2- and 6-positions in addition to tuned bulkiness of the alkyl ester moiety. Their activities as hypotensive and Ca^{+2} channel blockers were challenged using normotensive rabbits and rat elium tests. The most active compounds in the series **IVg** and **IVl** revealed hypotensive activity more than that of amlodepine mesylate over a scaning period of 4 hrs. Acute toxicity estimated by determination of LD50 were found 45 and 60 mg/kg body weight of rats. Developed pharmacophore A outlined by six features hit 12 compounds that possessed hypotensive and Ca^{+2} channel blocking activities. On the other hand the pharmacophore B outlined by five features hit 36 compounds eventually possess Ca^{+2} channel blocking activity.

Two derivatives **IIIm,n** did not fit the pharmacophore B in spite of their prominent Ca^{+2} channel blocking activity. This apparent anomaly can be attributed to the readily eliminated N1-chloroacetyl moiety leaving monocarboxylated derivatives.

REFERENCES

1- H. Cho, M. Ueda, K. Shima, A. Mizuno, M. Hayashimatsu, Y. Ohnaka, Y. Takeuchi, M. Hamaguchi, K. Aisaka, T. Hidaka, M. Kawai, M.Takeda, T. Ishihara, K. Funahashi, F. Satoh, M. Morita and T. Noguchi, "Dihydropyrimidines: novel calcium antagonists with potent and long-lasting vasodilative and antihypertensive activity", J. Med. Chem., 32, 2399 (1989).

2- G. C. Rovnyak, K. S. Atwal, A. Hedberg, S. D. Kimball, S. Moreland, J. Z. Gougoutas, B. C. O'Reilly, J. Schwartz and M. F. Malley, "Dihydropyrimidine calcium channel blockers. 4. Basic 3-substituted-4-aryl-1,4-dihydropyrimidine-5-carboxylic acid esters potent antihypertensive agents", ibid., 35, 3254 (1992).

3- S. Sarac, M. Yarim, M. Ertan, S. Boydag and K. Erol, "Synthesis, chemical and pharmacological properties of some 4-aryl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-diones", Pharmazie, 53, 91 (1998).

4- M. Yarima, S. Sarac, F. S. Kilic and K. Erol, "Synthesis and *in-vitro* calcium antagonist activity of 4-aryl-7,7-dimethyl/1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione derivatives", Il Farmaco, 58, 17 (2003).

5- G. C. Rovnyak, S. D. Kimball, B. Beyer, G. Cucinotta, J. D. DiMarco, J. Z. Gougoutas, A. Hedberg, M. F. Malley, J. P. McCarthy, R. Zhang and S. Moreland, "Calcium entry blockers and activators: Conformational and structural determinants of dihydropyrimidine calcium channel modulators", J. Med. Chem., 38, 119 (1995).

6- K. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Moreland, A. Hedberg and B. O'Reilly, "Dihydropyrimidine calcium channel blockers. 3. 3-Carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl-5-pyrimidine-carboxylic acid esters as orally effective antihypertensive agents", ibid., 34, 806 (1991).

7- K. S Atwal, G. C Rovnyak, S. D Kimball, D. M Floyd, S. Moreland, B. N. Swanson, J. Z. Gougoutas, J. Schwartz, K. M. Smillie and M. F. Malley, "Dihydropyrimidine calcium channel blockers. 2. 3-Substituted-4-aryl-1,4-dihydro-6-methyl-5-pyrimidine carboxylic acid esters as potent mimics of dihydropyridines", ibid., 33, 2629 (1990).

8- Y. S. Sadanandem, M. M. Shetty and P. V. Diwan, "Synthesis and biological evaluation of new 3,4-dihydro-6-methyl-5-n-methylcarbamoyl-4-(substituted phenyl) 2(1H) pyrimidinones and pyrimidinethiones", Eur. J. Med. Chem., 27, 87 (1992).

9- B. Tozkoparan, M. Ertan, P. Kelicen and R. Demirdamar, "Synthesis and anti-inflammatory activities of some thiazolo[3,2-a]pyrimidine derivatives", Il Farmaco, 54, 588 (1999).

10- D. Bozsing, P. Sohar, G. Gigler and G. Kovacs, "Synthesis and pharmacological study of new 3,4-dihydro-2H,6H-pyrimido-[2,1-b][1,3]thiazines", Eur. J. Med. Chem., 31, 663 (1996).

11- S. S. Bahekar and D. B. Shinde, "Synthesis and anti-inflammatory activity of some [4,6-(4-substituted aryl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]-acetic acid derivatives", Bioorg. Med. Chem. Lett., 14, 1733 (2004).

12- Z. Maliga, T. M. Kapoor and T. Mitchison, "Evidence that monastrol is an allosteric inhibitor of the mitotic kinesin Eg5", Chem. Bio., 9, 989 (2002).

13- D. Russowsky, R. F. S. Canto, S. A. A. Sanches, M. G. M. D'Oca, A. de Fatima, R. A. Pilli, L. K.Kohn, M. A.Antonio and J. E. de Carvalho, "Synthesis and differential antiproliferative activity of biginelli compounds against cancer cell lines: monastrol, oxo-monastrol and oxygenated analogues", Bioorg. Chem., 34, 173, (2006).

14- N. Foroughifar, S. M. Shariatzadeh, A. M. Khaledi, E. Khasnavi and M. Masoudnia, "Synthesis, characterization, and microbial activity of some 4-aryl-6-methyl-2-thioxo(or oxo)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid derivatives", Ultra Scientist of Phys. Sciences, 12, 277 (2000), through Chem. Abs. 135, 242198 (2001).

15- N. Foroughifar, A. Mobinikhaledi, S. M.Shariatzadeh and M. Masoudnia, "A convenient synthesis by microwave assisted high-speed and antibacterial activity of ethyl 4-aryl-6-methyl-2-oxo(or thioxo)-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives without solvent", Asian J. Chem., 14, 782 (2002).

16- M. M. Ghorab, Y. A Mohamed, S. A. Mohamed and Y. A. Ammar, "Synthesis and radiation stability of novel thiazolopyrimidines with expected antifungal activity", Phosphorus, Sulfur Silicon Relat. Elem., 108, 249 (1996), through Chem. Abs. 125, 195563 (1996).

17- A. K. Chhillar, P. Arya, C. Mukherjee, P. Kumar, Y. Yadav, A. K. Sharma, V. Yadav, J. Gupta, R. Dabur, H. N. Jha, A. C. Watterson, V. S. Parmar, A. K. Prasad and G. L. Sharma, "Microwave-assisted synthesis of antimicrobial dihydro-pyridines and tetrahydropyrimidin-2-ones: Novel compounds against aspergillosis", Bioorg. Med. Chem., 14, 973 (2006).

18- H. A. Stefani, C. B. Oliveira, R. B. Almeida, C. M. P. Pereira, R. C. Braga, R. Cella, V. C. Borges, L. Savegnago and C. W. Nogueira, "Dihydropyrimidin-(2H)-ones obtained by ultrasound irradiation: a new class of potential antioxidant agents", Eur. J. Med. Chem., 41, 513 (2006).

19- D. Nagarathnam, S. W. Miao, B. Lagu, G. Chiu, J. Fang, T. G. Murali, J. Zhang, S. Tyagarajan, M. R. Marzabadi, F. Zhang, W. C. Wong, W. Sun, D. Tian, J. M

Wetzel, C. Forray, R. S. L. Chang, T. P. Broten, R. W. Ransom, T. W. Schorn, T. B. Chen, S. O'Malley, P. Kling, K. Schneck, R. Bendesky, C. M. Harrel, K. P. Vyas and C. Gluchowski, "Design and synthesis of novel α1a adrenoceptor-selective antagonists. 1. Structure-activity relationship in dihydropyrimidinones", J. Med. Chem. 42, 4764 (1999).

20- T. G. M. Dhar, D. Nagarathnam, M. R. Marzabadi, B. Lagu, W. C. Wong, G. Chiu, S. Tyagarajan, S. W. Miao, F. Zhang, W. Sun, D. Tian, Q. Shen, J. Zhang, J. M. Wetzel, C. Forray, R. S. L. Chang, T. P. Broten, T. W. Schorn, T. B. Chen, S. O'Malley, R. Ransom, K. Schneck, R Bendesky, C. M. Harrel, K. P. Vyas,. K. Zhang, J. Gilbert, D. J. Pettibone, M. A. Patane, M. G. Bock, R. M. Freidinger and C. Gluchowski, "Design and synthesis of novel α1a adrenoceptor-selective antagonists. 2. Approaches to eliminate opioid agonist metabolites via modification of linker and 4-methoxycarbonyl-4-phenylpiperidine moiety", ibid., 42, 4778 (1999).

21- B. Lagu, D. Tian, D. Nagarathnam, M. R. Marzabadi, W. C. Wong, S. W. Miao, F. Zhang, W. Sun, G. Chiu, J. Fang, C. Forray, R. S. L. Chang, R. Ransom, T. B. Chen, S. O'Malley, K. Zhang, K. P Vyas and C. J. Gluchowski, "Design and synthesis of novel α1a adrenoceptor-selective antagonists. 3. Approaches to eliminate opioid agonist metabolites by using substituted phenylpiperazine side chains", ibid., 42, 4794 (1999).

22- W. C. Wong, W. Sun, B. Lagu, D. Tian, M. R. Marzabadi, F. Zhang, D. Nagarathnam, S. W. Miao, J. M. Wetzel, J. Peng, C. Forray, R. S. Chang, T. B. Chen, R. Ransom, S. O'Malley, T. P. Broten, P. Kling, K. P. Vyas, K. Zhang and C. Gluchowski, "Design and synthesis of novel α1a adrenoceptor-selective antagonists. 4. Structure-activity relationship in the dihydropyrimidine series", ibid., 42, 4804 (1999).

23- J. C. Barrow, P. G. Nantermet, H. G. Selnick, K. L. Glass, K. E. Rittle, K. F. Gilbert, T. G. Steele, C. F. Homnick,. R. M. Freidinger, R. W. Ransom, P. Kling, D. Reiss, T. P. Broten, T. W. Schorn, R. S. Chang, S. S. O'Malley, T.V. Olah, J. D. Ellis, A. Barrish, K. Kassahun, P. Leppert, D. Nagarathnam and C. Forray, "*In-vitro* and *in-vivo* evaluation of dihydropyrimidinone C-5 amides as potent and selective r1A receptor antagonists for the treatment of benign prostatic hyperplasia), ibid., 43, 2703 (2000).

24- C. Blackburn, B. Guan, J. Brown, C. Cullis, S. M. Condon, T. J. Jenkins, S. Y. Peluso, Y. Ye, R. E. Gimeno, S. Punreddy, Y. Sun, H. Wu, B. Hubbard, V. Kaushik, P. Tummino, P. Sanchetti, D. Y Sun, T. Daniels, E. Tozzo, S. K. Balanic and P. Ramana, "Identification and characterization of 4-aryl-3,4-dihydropyrimidin-2(1H)-ones as inhibitors of the fatty acid transporter FATP4", Bioorg. Med. Chem. Lett., 16, 3504 (2006).

25- L. E. Overman, M. H. Rabinowitz and P. A. Renhowe, "Enantioselective total synthesis of (-)-ptilomycalin", J. Am. Chem. Soc., 117, 2657 (1995).

26- D. S. Coffey, A. I. McDonald, L. E. Overman and F. Stappenbeck, "Enantioselective total synthesis of 13, 14, 15-isocrambescidin 800", ibid., 121, 6944 (1999).

27- A. D. Patil, N. V. Kumar, W. C. Kokke, M. F. Bean, A. J. Freyer, C. De Brosse, S. Mai, A. Truneh, D. J. Faulkner, B. Carte, A. L. Breen, R. P. Hertzberg, R. K. Johnson, J. W. Westley and B. C. M. Potts, "Novel alkaloids from the sponge batzella sp.: Inhibitors of HIV gp 120-human CD4 binding", J. Org. Chem., 60, 1182 (1995).

28- B. Kumar, B. Kaur, J. Kaur, A. Parmar, R. D. Anand and H. Kumar, "Thermal/microwave assisted synthesis of substituted tetrahydropyrimidines as potent calcium channel blockers", Indian J. Chem., 41B, 1526 (2002).

29- P. Shanmugam, G. Annie and P. T. Perumal, "Synthesis of novel 3,4-dihyropyrimidineones on water soluble solid support catalyzed by indium triflate", J. Heterocycl. Chem., 40 879 (2003).

30- C. O. Kappe and P. Roschger, "Synthesis and reactions of Biginelli compounds. Part I", ibid., 26, 55 (1989).

31- Molecular Operating Environment (MOE), version 2005.06. Chemical Computing Group, Inc. Montreal, Quebec, Canada, 2005, http://www.chemcomp.com.
32- H. Chun, D. Licheng, X. Guying, X. Yutain and W. Shengfu, Zhong-guo Yaown Huaxue Zazhi, 11, 255 (2001), through Chem. Abstr. 137, 169475s (2002).
33- P. R. Shildneck, W. Widus, H. Gilman, W. F. Schulz and Ed. A. H. Blatt, "Org. Synthesis" Collective Vol. 2, John Wiley and Sons, Inc., New York London Sydney 1921, p. 411.
34- M. M. F. Ismail, N. A. M. El-Sayed, H. S. Rateb, M. Ellithey and Y. A. Ammar, "Synthesis and evaluation of some 1,2,3,4-tetrahydropyrimidine-2-thione and condensed pyrimidine derivatives as potential antihypertensive agents", Arzneimittel-Forsch, 56, 322 (2006).
35- R. M. Silverstein and F. X. Webster, "Spectrometric Identification of Some Organic Compounds", 6th ed, Jhon Wiley and Sons, Inc, New York, Toronto, Singapore, 1998, p. 27.
36- E. Pretsch, W. Simon and T. Clerc, 'Tables of Spectral Data for Structure Determination of Organic Compounds ^{13}C-NMR ^{1}H-NMR IR Ms UV/Vis", K. Trs. Biemann, Springer-Verlag Berlin Heidelberg, New York, Tokyo, 1983, p. B225.
37- Q. N. Porter, "Mass Spectrometry of Heterocyclic Compounds", 2nd ed, Jhon Wiley and Sons, Inc, New York, Toronto, Singapore, 1985, p. 728.
38- D. J. Brown, "The Mass Spectra of Pyrimidines", Comprehensive Hetero-cyclic Chemistry, Vol. 3, Part 2B, Ed. Katritzky, A. R, Pergamon Press, Oxford, New York, Paris Frankfurt, 1984, p. 57.
39- H. Budzikiewicz, C. Djerassi and D. H. Willaims, "Interpretation of Mass Spectra of Organic Compounds", Holden-Day, Inc, San Francisco, 1965, p. 100.
40- I. S. Zorkun, S. Sarac, S. Celebi and K. Erol, "Synthesis of 4-aryl-3,4-dihydropyrimidin-2(1H)-thione derivatives as potential calcium channel blockers", Bioorg. Med. Chem., 14, 8582 (2006).
41- A. A. Bekhit and H. T. Fahmy, "Design and synthesis of some substituted 1H-pyrazolyl-oxazolidines or 1H-pyrazolyl-thiazolidines as anti-inflammatory-antimicrobial agents", Arch. Pharm. Pharm. Med. Chem., 336, 111 (2003).
42- NIIRDN, "Drugs in Japan", (Ethical Drugs), Yakugyo Jiho Co., Ltd., Tokyo, Japan, 1995, p. 71.