Novel 1, 4-dihydropyridines for L-type calcium channel as antagonists for cadmium toxicity

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Supporting Information:

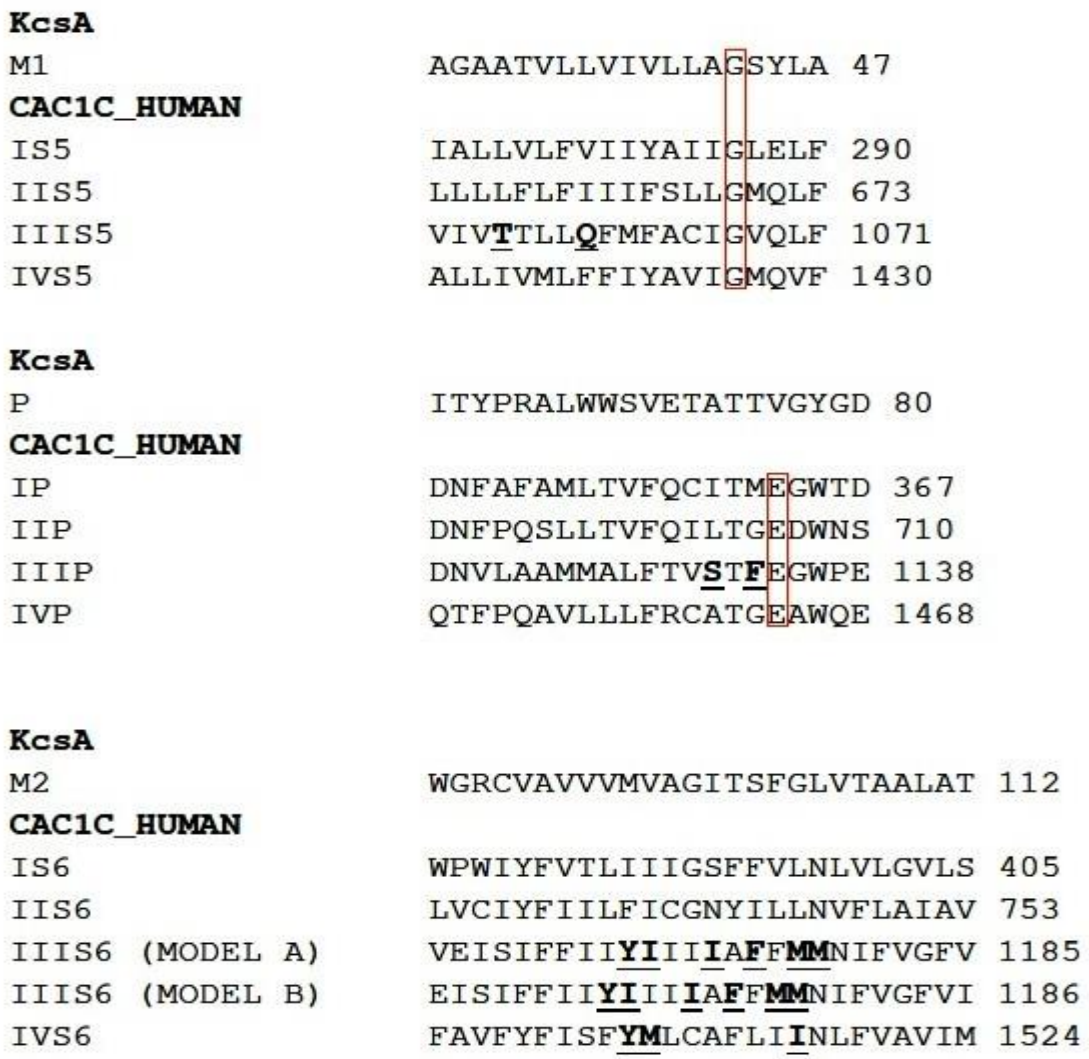


Figure S1: Pairwise alignment of CAC1C_HUMAN and KcsA sequences. The conserved key residues used to align the sequences are shown in red boxes. Residues reported to affect DHPs antagonist binding and underscored and highlighted in bold.

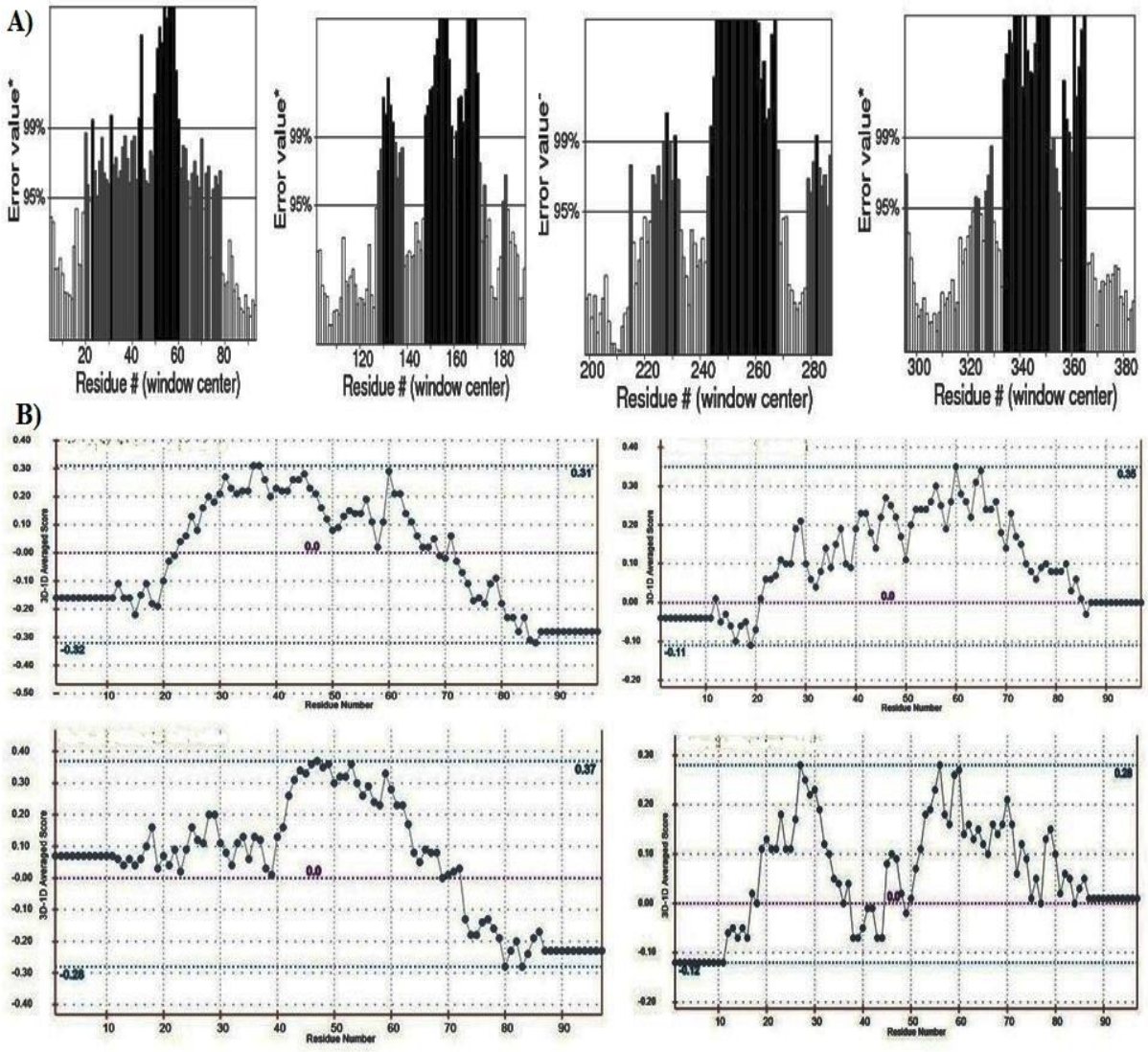


Figure S2: A) ERRAT score of the LCC model (four repeats) **B**) Verify3Dscore profile calculated for LCC model. Scores over 0.2 indicate a high quality model.

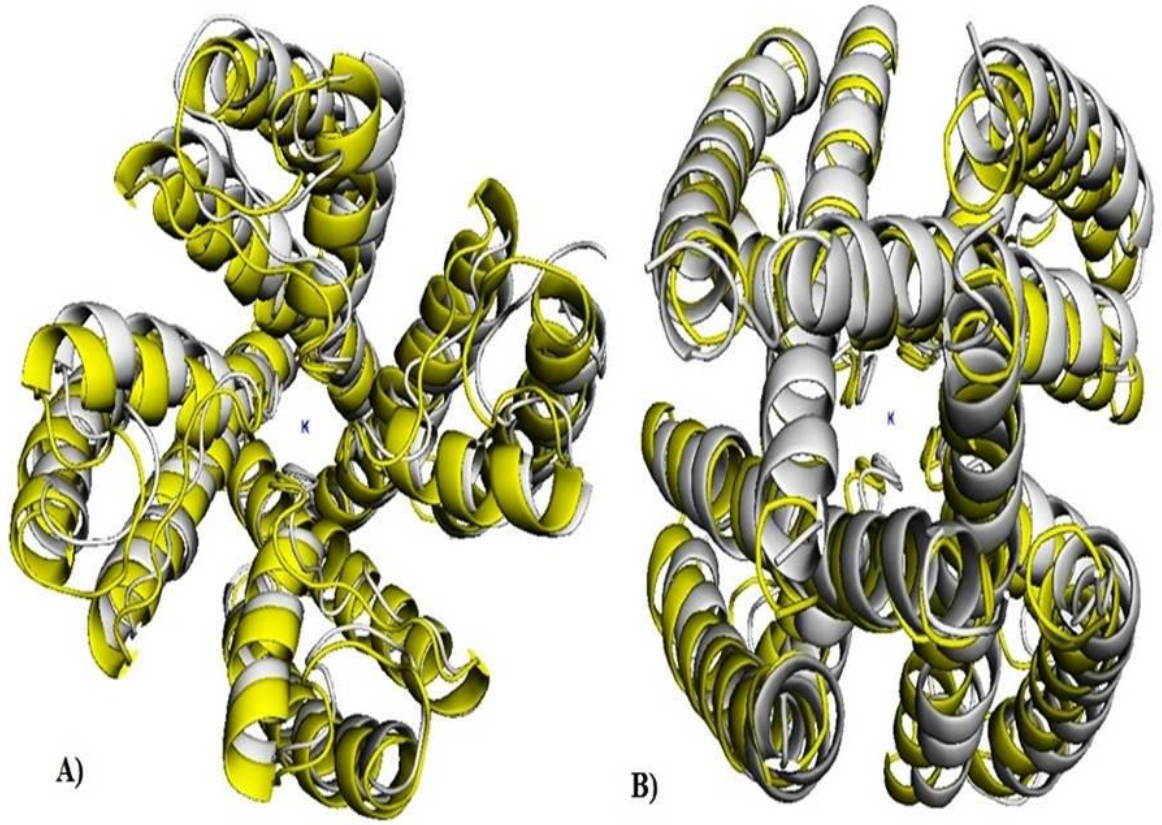
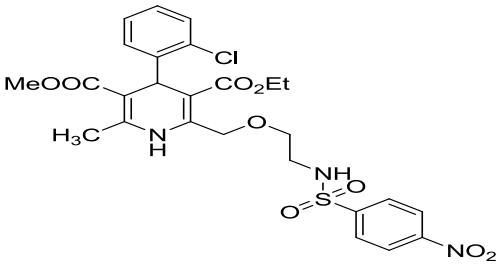
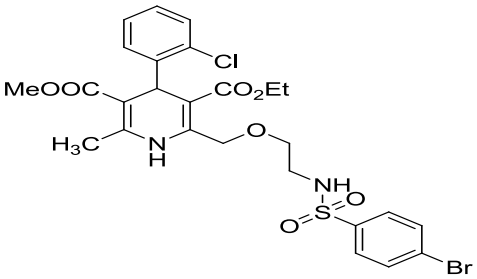


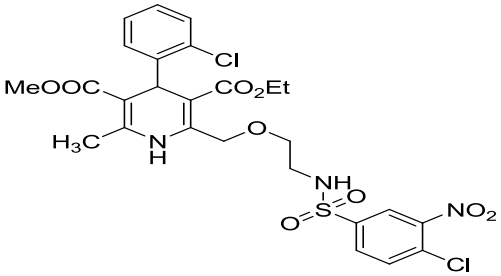
Figure S3: Superimposition of the LCC model (white) and KcsA (yellow) (PDB: 3BPM). (A) Open conformation, (B) Closed conformation.



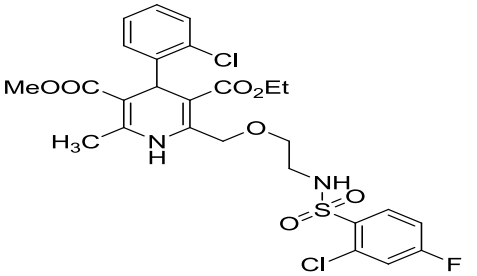
5a



5b



5c



5d

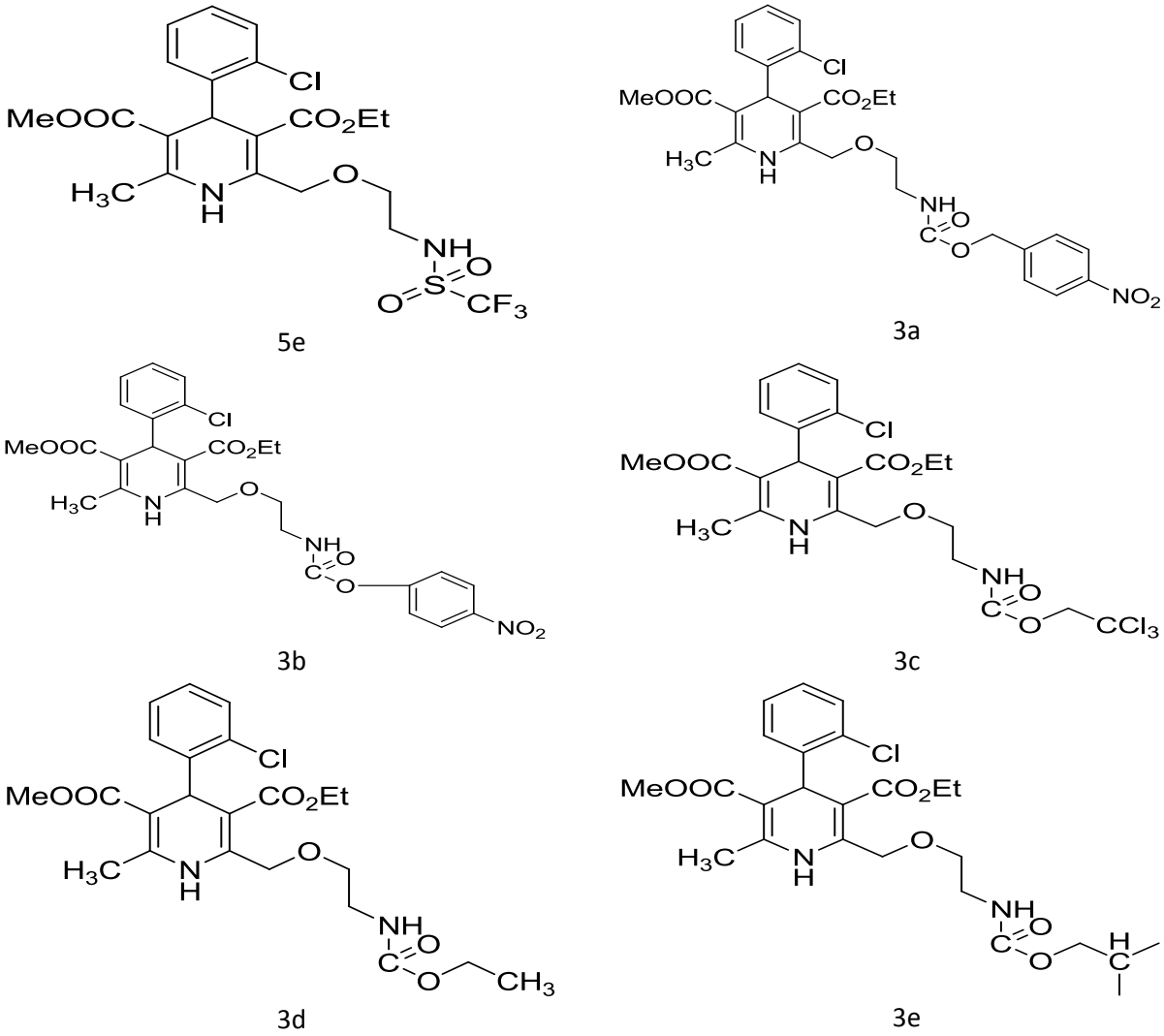


Figure S4: The synthesized calcium channel blocker (CCB) structures were built with standard bond length and angles using ChemSketch.

Spectral data

3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-((2-((4-nitrophenethoxy) carbonylamino) ethoxy) methyl)-1,4-dihydro pyridine-3,5-dicarboxylate (3a).

Yield 73%. mp 122-124 ºC. υmax (KBr, cm-1): 3240 (-NH), 1748 (-C=O). 1H-NMR (400 MHz, CDCl3) *δ* (ppm): 8.24 (s, 1H, Ar-NH), 7.58-6.92 (m, 5H, Ar-H), 2.12 (3H, s, -CH3), 3.14 (3H, s, -OCH3), 4.16 (2H, q, -OCH2), 1.42 (3H, t, -CH3), 4.06 (2H, s, -OCH2), 3.72 (2H, t, -OCH2), 3.12 (2H, q, -CH2-NH), 5.74 (1H, t, -NH-C=O), 5.68 (2H, s, - CH2-Ar), 7.52 (2H, d, Ar'-H), 8.19 (2H, d, Ar'-H). 13C NMR (100 MHz, CDCl3) *δ*: 144.5 (C-2), 102.4 (C-3), 37.2 (C-4), 109.4 (C-5), 136.8 (C-6), 19.2 (C-7), 143.2 (C-8), 126.4 (C-9), 127.1 (C-10), 128.4 (C-11), 128.6 (C-12), 131.6 (C-13), 167.4 (C-14), 54.3 (C-16), 167.5 (C-17), 62.4 (C-19), 15.2 (C-20), 70.4 (C-21), 68.6 (C-23), 41.4 (C- 24), 155.4 (C-26), 65.6 (C-27), 141.2 (C-1'), 128.2 (C-2'), 124.2 (C-3'), 146.2 (C-4'). LC MS: m/z (%) 587.17 [100, M]+., 589 [65, M+2] +.. Anal.cald.for C28H30ClN3O9: C, 57.19; H, 5.14; N, 7.15; Found: C, 57.12, H, 5.09; N, 7.11.

3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-((2-((4-nitrophenoxy)carbonylamino) ethoxy) methyl)-1,4-dihydro pyridine-3,5-dicarboxylate (3b).

Yield 72%. mp 132-134 ºC. υmax (KBr, cm-1): 3258 (-NH), 1720 (-C=O). 1H-NMR (400 MHz, CDCl3) *δ* (ppm): 8.16(s, 1H, Ar-NH), 7.54-6.96 (m, 5H, Ar-H), 2.16 (3H, s, -CH3), 3.18 (3H, s, -OCH3), 4.22 (2H, q, -OCH2), 1.54 (3H, t, -CH3), 4.15 (2H, s, -OCH2), 3.64 (2H, t, -OCH2), 3.24 (2H, q, -CH2-NH), 5.72 (1H, t, -NH-C=O), 7.58 (2H, d, Ar'-H), 8.26 (2H, d, Ar'-H). 13C NMR (100 MHz, CDCl3) *δ*: 144.2 (C-2), 101.5 (C-3), 36.6 (C-4), 109.4 (C-5), 136.2 (C-6), 19.4 (C-7), 142.6 (C-8), 127.2 (C-9), 126.9 (C-10), 128.5 (C-11), 129.2 (C-12), 131.4 (C-13), 166.2 (C- 14), 54.5 (C-16), 168.2 (C-17), 61.9 (C-19), 15.8 (C-20), 70.2 (C-21), 68.6 (C-23), 41.2 (C-24), 151.2 (C-26), 156.2 (C-1'), 122.2 (C-2'), 125.2 (C-3'), 144.5 (C-4'). LC MS: m/z (%) 573 [100, M]+., 575 [65, M+2] +.. Anal.cald.for C27H28ClN3O9: C, 56.50; H, 4.92; N, 7.32; Found: C, 56.48, H, 4.86; N, 7.28.

3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-((2-((2,2,2-trichloroethoxy)carbonylamino) ethoxy)methyl)-1,4-dihydro pyridine-3,5-dicarboxylate (3c).

Yield 80%. mp 154-156 ºC. υmax (KBr, cm-1): 3236 (-NH), 1760 (-C=O). 1H-NMR (400 MHz, CDCl3) *δ* (ppm): 8.26(s, 1H, Ar-NH), 7.62-6.90 (m, 5H, Ar-H), 2.24 (3H, s, -CH3), 3.21 (3H, s, -OCH3), 4.26 (2H, q, -OCH2), 1.58 (3H, t,-CH3), 4.19 (2H, s, -OCH2), 3.60 (2H, t, -OCH2), 3.24 (2H, q, -CH2-NH), 5.78 (1H, t, -NH-C=O), 5.24 (2H, s, - OCH2). 13C NMR (100 MHz, CDCl3) *δ*: 144.6 (C-2), 102.4 (C-3), 36.8 (C-4), 109.8 (C-5), 136.6 (C-6), 19.2 (C-7), 142.8 (C-8), 127.5 (C-9), 127.2 (C-10), 128.6 (C-11), 129.6 (C-12), 131.6 (C-13), 166.6 (C-14), 54.8 (C-16), 168.8 (C-17), 61.2 (C-19), 15.6 (C-20), 70.5 (C-21), 66.4 (C-23), 41.5 (C-24), 153.4 (C-26), 71.2 (C-1'), 96.2 (C-2'). Anal.cald.for C23H26Cl4N2O7: C, 47.28; H, 4.49; N, 4.79; Found: C, 47.23, H, 4.45; N, 4.72.

3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-((2-(ethoxy carbonylamino) ethoxy)methyl)-1,4-dihydropyridine-3,5- dicarboxylate (3d).

Yield 78%. mp 142-144 ºC. υmax (KBr, cm-1): 3230 (-NH), 1756 (-C=O). 1H-NMR (400 MHz, CDCl3) *δ* (ppm): 8.32(s, 1H, Ar-NH), 7.48-7.02 (m, 5H, Ar-H), 2.20 (3H, s, -CH3), 3.32 (3H, s, -OCH3), 4.21 (2H, q, -OCH2), 1.45 (3H, t, -CH3), 4.14 (2H, s, -OCH2), 3.54 (2H, t, -OCH2), 3.36 (2H, q, -CH2-NH), 5.78 (1H, t, -NH-C=O), 4.26 (2H, q, - OCH2), 1.42 (3H, t, -CH3); 13C NMR (100 MHz, CDCl3) *δ*: 144.2 (C-2), 103.2 (C-3), 36.4 (C-4), 109.6 (C-5), 136.4(C-6), 19.5 (C-7), 142.5 (C-8), 127.2 (C-9), 126.8 (C-10), 127.8 (C-11), 129.4 (C-12), 131.2 (C-13), 166.9 (C-14), 54.4 (C-16), 168.2 (C-17), 61.6 (C-19), 15.2 (C-20), 71.2 (C-21), 66.5 (C-23), 40.6 (C-24), 155.6 (C-26), 61.2 (C- 1'), 13.7 (C-2'). Anal.cald.for C23H29ClN2O7: C, 57.44; H, 6.08; N, 5.82; Found: C, 57.38, H, 6.02; N, 5. 78.

3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-((2-(isobutoxycarbonylamino)ethoxy)methyl)-1,4-dihydropyridine-3,5-dicarboxylate (3e).

Yield 74%. mp 166-168 ºC. υmax (KBr, cm-1): 3256 (-NH), 1752 (-C=O). 1H-NMR (400 MHz, CDCl3) *δ* (ppm): 8.28(s, 1H, Ar-NH), 7.58-7.06 (m, 5H, Ar-H), 2.08 (3H, s, -CH3), 3.36 (3H, s, -OCH3), 4.18 (2H, q, -OCH2), 1.48 (3H, t, -CH3), 4.26 (2H, s, -OCH2), 3.62 (2H, t, -OCH2), 3.32 (2H, q, -CH2-NH), 5.80 (1H, t, -NH-C=O), 3.72 (2H, t, - OCH2), 1.92-1.88 (1H, m, -CH), 1.04 (6H, d, -(CH3)2). 13C NMR (100 MHz, CDCl3) *δ*: 145.2 (C-2), 102.5 (C-3),36.1 (C-4), 109.2 (C-5), 136.6 (C-6), 19.7 (C-7), 142.4 (C-8), 127.4 (C-9), 126.2 (C-10), 127.4 (C-11), 129.2 (C-12),131.4 (C-13), 166.3 (C-14), 54.2 (C-16), 167.4 (C-17), 61.2 (C-19), 15.6 (C-20), 71.4 (C-21), 66.5 (C-23), 40.6 (C-24), 152.8 (C-26), 71.2 (C-1'), 26.7 (C-2'), 20.1 (C-3'). LC MS: m/z (%) 508 [100, M]+., 410 [65, M+2] +..Anal.cald.for C25H33ClN2O7: C, 58.99; H, 6.53; N, 5.50; Found: C, 58.92, H, 6.48; N, 5.42.

3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-((2-(4-nitrophenylsulfonamido)ethoxy)methyl)-1,4-dihydropyridine-3,5-dicarboxylate (5a).

Yield 75%. mp 142-144 ºC. υmax (KBr, cm-1): 3262 (-NH), 1348 (-S=O). 1H-NMR (400 MHz, CDCl3) δ (ppm): 8.28(s, 1H, Ar-NH), 7.62-7.12 (m, 5H, Ar-H), 2.12 (3H, s, -CH3), 3.12 (3H, s, -OCH3), 4.25 (2H, q, -OCH2), 1.58 (3H, t,-CH3), 4.19 (2H, s, -OCH2), 3.52 (2H, t, -OCH2), 3.28 (2H, q, -CH2-NH), 3.22 (1H, t, -NH-SO2), 8.24 (2H, d, Ar'-H), 8.42 (2H, d, Ar'-H). 13C NMR (100 MHz, CDCl3) δ: 143.2 (C-2), 100.6 (C-3), 35.4 (C-4), 108.2 (C-5), 135.5(C-6), 18.8 (C-7), 141.8 (C-8), 126.4 (C-9), 125.2 (C-10), 127.2 (C-11), 128.5 (C-12), 130.2 (C-13), 165.4 (C-14),54.2 (C-16), 162.4 (C-17), 62.4 (C-19), 15.6 (C-20), 69.1 (C-21), 68.4 (C-23), 41.6 (C-25), 152.4 (C-1'), 128.2 (C-2'), 124.2 (C-3'), 150.6 (C-4'). LC MS: m/z (%) 593 [100, M]+., 595 [65, M+2] +.. Anal.cald.for C26H28ClN3O9S: C,52.57; H, 4.75; N, 7.07; Found: C, 52.52, H, 4.70; N, 7.01.

3-Ethyl 5-methyl 2-((2-(4-bromophenylsulfonamido)ethoxy)methyl)-4-(2-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (5b).

Yield 76%. mp 156-158 ºC. υmax (KBr, cm-1): 3315 (-NH), 1352 (-S=O). 1H-NMR (400 MHz, CDCl3) δ (ppm): 8.20(s, 1H, Ar-NH), 7.56-7.02 (m, 5H, Ar-H), 2.06 (3H, s, -CH3), 3.14 (3H, s, -OCH3), 4.22 (2H, q, -OCH2), 1.54 (3H,t, -CH3), 4.20 (2H, s, -OCH2), 3.56 (2H, t, -OCH2), 3.22 (2H, q, -CH2-NH), 3.26 (1H, t, -NH-SO2), 7.92 (2H, d, Ar'-H), 8.04 (2H, d, Ar'-H). 13C NMR (100 MHz, CDCl3) δ: 144.5 (C-2), 101.6 (C-3), 37.2 (C-4), 107.4 (C-5), 136.2(C-6), 18.6 (C-7), 142.4 (C-8), 126.8 (C-9), 124.3 (C-10), 128.4 (C-11), 128.2 (C-12), 131.5 (C-13), 166.5 (C-14),55.4 (C-16), 163.2 (C-17), 63.5 (C-19), 16.2 (C-20), 68.6 (C-21), 65.6 (C-23), 41.4 (C-25), 144.2 (C-1'), 129.4 (C-2'), 130.4 (C-3'), 128.2 (C-4'). LC MS: m/z (%) 626 [100, M]+., 628 [98, M+2] +.. Anal.cald.for C26H28BrClN2O7S:C, 49.73; H, 4.49; N, 4.46; Found: C, 49.68, H, 4.43; N, 4.42.

3-Ethyl 5-methyl 2-((2-(4-chloro-3-nitrophenylsulfonamido)ethoxy)methyl)-4-(2-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (5c).

Yield 79%. mp 169-171 ºC. υmax (KBr, cm-1): 3354 (-NH), 1375 (-S=O). 1H-NMR (400 MHz, CDCl3) δ (ppm): 8.32(s, 1H, Ar-NH), 7.56-6.92 (m, 5H, Ar-H), 2.14 (3H, s, -CH3), 3.15 (3H, s, -OCH3), 4.20 (2H, q, -OCH2), 1.52 (3H, t,-CH3), 4.26 (2H, s, -OCH2), 3.52 (2H, t, -OCH2), 3.28 (2H, q, -CH2-NH), 3.25 (1H, t, -NH-SO2), 8.06 (1H, d, Ar'-H), 8.24 (1H, d, Ar'-H), 8.62 (1H, s, Ar'-H). 13C NMR (100 MHz, CDCl3) δ: 145.2 (C-2), 102.4 (C-3), 38.6 (C-4),108.2 (C-5), 138.2 (C-6), 18.5 (C-7), 140.4 (C-8), 128.2 (C-9), 125.4 (C-10), 128.4 (C-11), 128.6 (C-12), 132.4 (C-13), 168.2 (C-14), 55.6 (C-16), 163.4 (C-17), 63.2 (C-19), 16.6 (C-20), 68.2 (C-21), 65.4 (C-23), 41.5 (C-25), 138.2(C-1'), 134.6 (C-2'), 130.4 (C-3'), 132.5 (C-4'), 146.2 (C-5'), 125.2 (C-6'). Anal.cald.for C26H27Cl2N3O9S: C, 49.69;H, 4.33; N, 6.69; Found: C, 49.64, H, 4.29; N, 6.62.

3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-((2-(4-fluorophenylsulfonamido) ethoxy)methyl) -1,4-dihydropyridine-3,5-dicarboxylate (5d).

Yield 70%. mp 176-178 ºC. υmax (KBr, cm-1): 3342 (-NH), 1366 (-S=O). 1H-NMR (400 MHz, CDCl3) δ (ppm): 1HNMR(CDCl3) δ (ppm): 8.28 (s, 1H, Ar-NH), 7.58-6.95 (m, 5H, Ar-H), 2.17 (3H, s, -CH3), 3.24 (3H, s, -OCH3),4.26 (2H, q, -OCH2), 1.62 (3H, t, -CH3), 4.24 (2H, s, -OCH2), 3.52 (2H, t, -OCH2), 3.26 (2H, q, -CH2-NH), 3.21(1H, t, -NH-SO2), 7.96 (2H, d, Ar'-H), 7.52 (2H, d, Ar'-H). 13C NMR (CDCl3) δ: 144.2 (C-2), 102.4 (C-3), 37.5 (C-4), 107.2 (C-5), 136.6 (C-6), 18.8 (C-7), 142.8 (C-8), 126.6 (C-9), 124.8 (C-10), 127.6 (C-11), 127.8 (C-12), 131.2(C-13), 166.2 (C-14), 56.2 (C-16), 164.4 (C-17), 63.2 (C-19), 16.5 (C-20), 68.2 (C-21), 65.4 (C-23), 41.3 (C-25),141.2 (C-1'), 130.8 (C-2'), 115.4 (C-3'), 166.5 (C-4'). Anal.cald.for C26H27Cl2FN2O7S: C, 51.92; H, 4.52; N, 4.66;Found: C, 51.88, H, 4.48; N, 4.61.

3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-((2-(trifluoromethylsulfonamido) ethoxy)methyl) -1,4-dihydropyridine-3,5-dicarboxylate (5e).

Yield 68%. mp 181-183 ºC. υmax (KBr, cm-1): 3328 (-NH), 1372 (-S=O). 1H-NMR (400 MHz, CDCl3) δ (ppm): 8.32(s, 1H, Ar-NH), 7.52-6.94 (m, 5H, Ar-H), 2.15 (3H, s, -CH3), 3.38 (3H, s, -OCH3), 4.42 (2H, q, -OCH2), 1.68 (3H, t,-CH3), 4.34 (2H, s, -OCH2), 3.61 (2H, t, -OCH2), 3.28 (2H, q, -CH2-NH), 3.24 (1H, t, -NH-SO2). 13C NMR(100MHz, CDCl3) δ: 145.2 (C-2), 103.5 (C-3), 38.2 (C-4), 108.2 (C-5), 137.2 (C-6), 19.0 (C-7), 143.5 (C-8), 127.2(C-9), 125.2 (C-10), 128.2 (C-11), 129.2 (C-12), 134.4 (C-13), 167.2 (C-14), 57.2 (C-16), 166.4 (C-17), 64.4 (C-19),16.7 (C-20), 69.4 (C-21), 65.6 (C-23), 41.8 (C-25), 150.2 (C-1'). LC MS m/z (%) 540 [100, M]+., 542 [65, M+2] +..Anal.cald.for C21H24ClF3N2O7S: C, 46.63; H, 4.47; N, 5.18; Found: C, 46.58, H, 4.42; N, 5.12.