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Synthesis of carbamate and sulfonamide derivatives of amlodipine and their antimicrobial activity

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ABSTRACT

An efficient synthesis of two series of novel carbamate and sulfonamide derivatives of amlodipine, 3-ethyl 5-methyl 2-(2-aminoethoxy)-4-(2-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Amlodipine) ***1*** *was accomplished. Various chloroformates* ***2(a-e)*** *and sulfonyl chlorides* ***4(a-e)*** *on reaction with* ***1*** *in the presence of N,N–dimethylpiperazine as a base in THF at 50-55 ^{0}C yielded the corresponding title compounds* ***3(a-e)*** *and* ***5(a-e)*** *in high yields. The structures of the title compounds* ***3(a-e)*** *and* ***5(a-e)*** *were established by spectral (^{1}H, ^{13}C NMR, mass) and elemental analysis. The title compounds were screened for their antimicrobial activity against bacterial and fungal strains and compared their activities with standards like ciprofloxacin and clotrimazole. The title compounds exhibited moderate to high antimicrobial activity due to the presence of different substituted functional groups at carbamate and sulfonamide moieties of amlodipine.*

Key words: Amlodipine, Carbamates/Sulfonamides, N,N-dimethyl piperazine, antibacterial, antifungal activity.

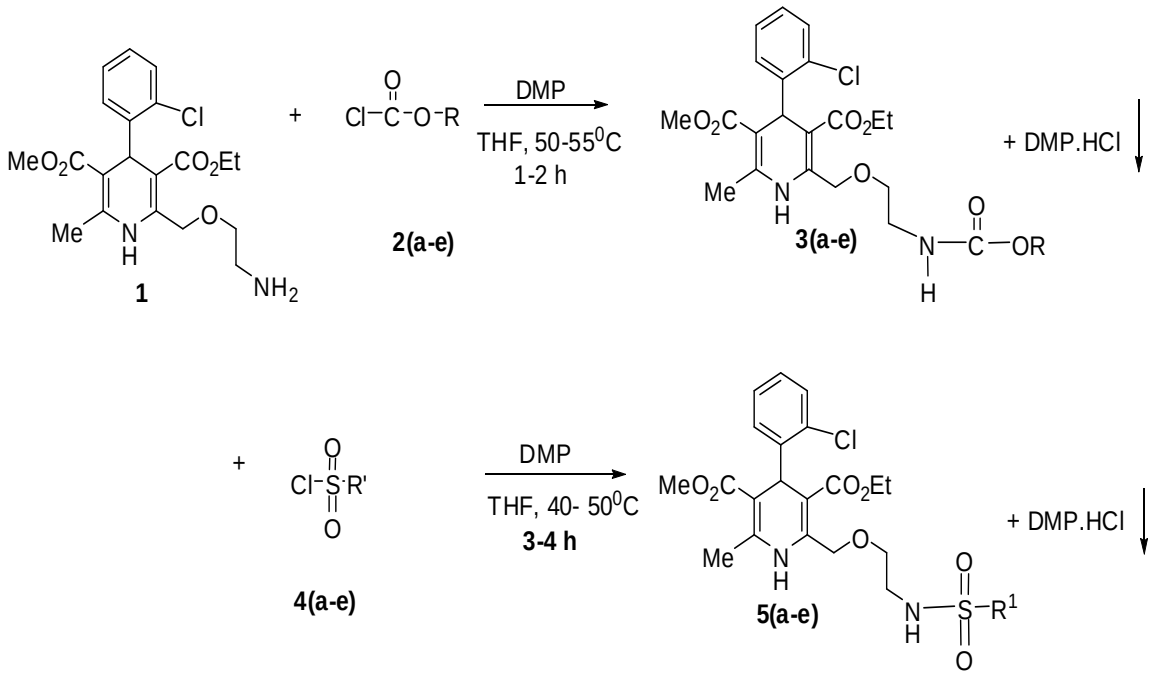
INRTODUCTION

Carbamates are important intermediates in the synthesis of compounds in pharmaceutical, medical, agrochemical and polymer chemistry, which possess biologically potent properties such as inhibitors of HIV, anticancer, anticonvulsants, antibacterials, antiepileptics and enzyme inhibitors [1–6]. Researchers focused on synthesis of carbamate derivatives of drugs, for example gemcitabine carbamate derivatives have potential antiimmunochemotherapeutic and its cytotoxic anti-neoplastic activity against chemotherapeutic-resistant SKBr-3 mammary carcinoma [7]. Chlorphenesin carbamate derivatives were used for the treatment of pain associated with skeletal muscle trauma (strains, sprains), inflammation, spasms, or other muscular conditions [8]. Carbazole-linked carbamates and thiocarbamates are inhibiting the NO production in LPS-activated macrophages [9]. Phenyl N'-(3-cyclopentyloxy-2-hydroxypropyl) carbamates exhibited anti-arrhythmic and ani-hypertensive properties [10]. Piperazinyl carbamates are known to inhibit the fatty acid amide hydrolase (FAAH) and transient receptor potential (TRP) channel dual ligands (TRPV1 antagonists) [11]. The substituted (2'-(1H-tetrazol-5-yl)-biphenyl-4-yl) carbamate derivatives are used as selective antagonists of nonpeptide angiotensin II type 1 (AT1) receptors for treatment of hypertension [12]. The sulfonamide group containing drugs used as broad spectrum of synthetic bacteriostatic antibiotics and inhibit the gram positive and gram negative organisms, some fungi and certain protozoa1 infections [13]. They are also used as anti-inflammatory [14], analgesic [15], antimalarial [16], Alzheimer's disease [17], inhibitors of t-RNA synthetases [18] and anticancer agents [19] . The heterocyclic sulfonamide derivatives act as antimicrobial agents and have been transition state mimetics of peptide hydrolysis, and particularly used for potent irreversible inhibitors of cysteine proteases [20]. The applications of sulfonamides have been greatly extended to antitumor [21], hypoglycemic [22], anti-thyroid [23], anti-carbonic anhydrase [24], diuretic [25], insulin releasing [26] and anti-thyroid [27]. Keeping this in view, we herein report the synthesis of 3-

ethyl-5-methyl 2-(2-aminoethoxy)-4-(2-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate carbamate and sulfonamide derivatives and evaluated their antimicrobial activity.

MATERIALS AND METHODS

Chemicals were purchased from Sigma -Aldrich, Merck and Lancaster, and were used as such without further purification. All solvents used for spectroscopic and other physical studies were reagent grade and were further purified by literature methods [28]. IR spectra were recorded as KBr pellets on a Perkin-Elmer 283 unit. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C, were recorded in $CDCl_3$ and referenced to TMS (^{1}H & ^{13}C) and LC-MS spectra were recorded on a Jeol SX 102 DA/600 Mass spectrometer. Elemental analyses were performed on a Thermo Finnigan Instrument at University of Hyderabad, Hyderabad, India.



Compound	R
3a	O_2N–C$_6$H$_4$–CH_2–
3b	O_2N–C$_6$H$_4$–
3c	Cl_3C-CH_2–
3d	CH_3-CH_2–
3e	Me_2-CH-CH_2–

Compound	R'
5a	O_2N–C$_6$H$_4$–
5b	Br–C$_6$H$_4$–
5c	Cl, O_2N–C$_6$H$_3$–
5d	F, Cl–C$_6$H$_3$–
5e	F_3C–

Scheme 1.

Synthesis

Synthesis of 3-ethyl- 5-methyl- 2-(2-aminoethoxy)-4-(2-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate substituted carbamates **3a-e** and sulfonamide derivatives **5a-e** was achieved in two-steps. In the first step, free base of amlodipine **(1)** was obtained from the amlodipine besylate by treating with N,N-dimethyl piperazine (DMP) as a base in THF at 50-55 ^{0}C. The byproduct salt was removed from the reaction mixture by filtration. Subsequently free base was reacted with various chloroformates **2(a-e)** and sulfonyl chlorides **4(a-e)** in the presence of N,N-dimethyl piperazine at 40-50 ^{o}C to obtain the title compounds **3(a-e)** and **5(a-e)** in 3-4 hr. Purity of the products and completion of the reaction was monitored by TLC using ethyl acetate: hexane (3:2). After completion of the reaction, DMP.HCl was separated by filtration and the solvent was removed in a rota-evaporator and the residue was purified by column chromatography on silica gel (100–200 mesh) using hexane: ethyl acetate (2:1) as an eluent. The resulting title compounds **3(a-e)** and **5(a-e)** were obtained in high yields (68-80%) **(Scheme 1).**

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 ^{o}C. υ_{max} (KBr, cm^{-1}): 3240 (-NH), 1748 (-C=O). ^{1}H-NMR (400 MHz, $CDCl_3$) 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, -OCH_3), 4.16 (2H, q, -OCH_2), 1.42 (3H, t, -CH_3), 4.06 (2H, s, -OCH_2), 3.72 (2H, t, -OCH_2), 3.12 (2H, q, -CH_2-NH), 5.74 (1H, t, -NH-C=O), 5.68 (2H, s, -CH_2-Ar), 7.52 (2H, d, Ar'-H), 8.19 (2H, d, Ar'-H). ^{13}C NMR (100 MHz, $CDCl_3$) 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]$^{+\cdot}$, 589 [65, M+2] $^{+\cdot}$. Anal.cald.for $C_{28}H_{30}ClN_3O_9$: 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 ^{o}C. υ_{max} (KBr, cm^{-1}): 3258 (-NH), 1720 (-C=O). ^{1}H-NMR (400 MHz, $CDCl_3$) 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, -OCH_3), 4.22 (2H, q, -OCH_2), 1.54 (3H, t, -CH_3), 4.15 (2H, s, -OCH_2), 3.64 (2H, t, -OCH_2), 3.24 (2H, q, -CH_2-NH), 5.72 (1H, t, -NH-C=O), 7.58 (2H, d, Ar'-H), 8.26 (2H, d, Ar'-H). ^{13}C NMR (100 MHz, $CDCl_3$) 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]$^{+\cdot}$, 575 [65, M+2] $^{+\cdot}$. Anal.cald.for $C_{27}H_{28}ClN_3O_9$: 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 ^{o}C. υ_{max} (KBr, cm^{-1}): 3236 (-NH), 1760 (-C=O). ^{1}H-NMR (400 MHz, $CDCl_3$) 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, -OCH_3), 4.26 (2H, q, -OCH_2), 1.58 (3H, t, -CH_3), 4.19 (2H, s, -OCH_2), 3.60 (2H, t, -OCH_2), 3.24 (2H, q, -CH_2-NH), 5.78 (1H, t, -NH-C=O), 5.24 (2H, s, -OCH_2). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{23}H_{26}Cl_4N_2O_7$: 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 ^{o}C. υ_{max} (KBr, cm^{-1}): 3230 (-NH), 1756 (-C=O). ^{1}H-NMR (400 MHz, $CDCl_3$) 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, -OCH_3), 4.21 (2H, q, -OCH_2), 1.45 (3H, t, -CH_3), 4.14 (2H, s, -OCH_2), 3.54 (2H, t, -OCH_2), 3.36 (2H, q, -CH_2-NH), 5.78 (1H, t, -NH-C=O), 4.26 (2H, q, -OCH_2), 1.42 (3H, t, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{23}H_{29}ClN_2O_7$: 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 ^{o}C. υ_{max} (KBr, cm^{-1}): 3256 (-NH), 1752 (-C=O). ^{1}H-NMR (400 MHz, $CDCl_3$) 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, -OCH_3), 4.18 (2H, q, -OCH_2), 1.48 (3H, t, -CH_3), 4.26 (2H, s, -OCH_2), 3.62 (2H, t, -OCH_2), 3.32 (2H, q, -CH_2-NH), 5.80 (1H, t, -NH-C=O), 3.72 (2H, t, -

OCH_2), 1.92-1.88 (1H, m, -CH), 1.04 (6H, d, -$(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$) 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]$^{+\cdot}$, 410 [65, M+2] $^{+\cdot}$. Anal.cald.for $C_{25}H_{33}ClN_2O_7$: 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 ^{o}C. υ_{max} (KBr, cm^{-1}): 3262 (-NH), 1348 (-S=O). ^{1}H-NMR (400 MHz, $CDCl_3$) 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, -OCH_3), 4.25 (2H, q, -OCH_2), 1.58 (3H, t, -CH_3), 4.19 (2H, s, -OCH_2), 3.52 (2H, t, -OCH_2), 3.28 (2H, q, -CH_2-NH), 3.22 (1H, t, -NH-SO_2), 8.24 (2H, d, Ar'-H), 8.42 (2H, d, Ar'-H). ^{13}C NMR (100 MHz, $CDCl_3$) 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]$^{+\cdot}$, 595 [65, M+2] $^{+\cdot}$. Anal.cald.for $C_{26}H_{28}ClN_3O_9S$: 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 ^{o}C. υ_{max} (KBr, cm^{-1}): 3315 (-NH), 1352 (-S=O). ^{1}H-NMR (400 MHz, $CDCl_3$) 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, -OCH_3), 4.22 (2H, q, -OCH_2), 1.54 (3H, t, -CH_3), 4.20 (2H, s, -OCH_2), 3.56 (2H, t, -OCH_2), 3.22 (2H, q, -CH_2-NH), 3.26 (1H, t, -NH-SO_2), 7.92 (2H, d, Ar'-H), 8.04 (2H, d, Ar'-H). ^{13}C NMR (100 MHz, $CDCl_3$) 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]$^{+\cdot}$, 628 [98, M+2] $^{+\cdot}$. Anal.cald.for $C_{26}H_{28}BrClN_2O_7S$: 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-dihydro pyridine-3,5-dicarboxylate (5c).
Yield 79%. mp 169-171 ^{o}C. υ_{max} (KBr, cm^{-1}): 3354 (-NH), 1375 (-S=O). ^{1}H-NMR (400 MHz, $CDCl_3$) 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, -OCH_3), 4.20 (2H, q, -OCH_2), 1.52 (3H, t, -CH_3), 4.26 (2H, s, -OCH_2), 3.52 (2H, t, -OCH_2), 3.28 (2H, q, -CH_2-NH), 3.25 (1H, t, -NH-SO_2), 8.06 (1H, d, Ar'-H), 8.24 (1H, d, Ar'-H), 8.62 (1H, s, Ar'-H). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{26}H_{27}Cl_2N_3O_9S$: 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 ^{o}C. υ_{max} (KBr, cm^{-1}): 3342 (-NH), 1366 (-S=O). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): ^{1}H-NMR ($CDCl_3$) 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, -OCH_3), 4.26 (2H, q, -OCH_2), 1.62 (3H, t, -CH_3), 4.24 (2H, s, -OCH_2), 3.52 (2H, t, -OCH_2), 3.26 (2H, q, -CH_2-NH), 3.21 (1H, t, -NH-SO_2), 7.96 (2H, d, Ar'-H), 7.52 (2H, d, Ar'-H). ^{13}C NMR ($CDCl_3$) 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 $C_{26}H_{27}Cl_2FN_2O_7S$: 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 ^{o}C. υ_{max} (KBr, cm^{-1}): 3328 (-NH), 1372 (-S=O). ^{1}H-NMR (400 MHz, $CDCl_3$) 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, -OCH_3), 4.42 (2H, q, -OCH_2), 1.68 (3H, t, -CH_3), 4.34 (2H, s, -OCH_2), 3.61 (2H, t, -OCH_2), 3.28 (2H, q, -CH_2-NH), 3.24 (1H, t, -NH-SO_2). ^{13}C NMR (100MHz, $CDCl_3$) 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]$^{+\cdot}$, 542 [65, M+2] $^{+\cdot}$. Anal.cald.for $C_{21}H_{24}ClF_3N_2O_7S$: C, 46.63; H, 4.47; N, 5.18; Found: C, 46.58, H, 4.42; N, 5.12.

Antibacterial activity:
The compounds were assayed for antimicrobial activity against bacterial cultures [29]. The bacteria includes Gram positive (*Staphylococcus aureus* & *Bacillus subtilis*) and Gram negative bacteria (*Klebsiella pneumonia* & *Escherichia coli*). The bacterial cultures were grown in nutrient agar media and sub cultured for the better growth and sub cultured onto the Petri plates for the experiments. The cultures were diluted with sterilized saline to bring the final inoculum's size of approximately 10^5–10^6 CFU/mL. The compounds were diluted in acetone and diethyl ether for biological assays. The bacterial cultures containing discs were placed on the media and incubated at 37 ^oC for 24 h to 72 h for better observation. The zone of inhibition was measured. All the experiments were carried out in triplicates and the results were expressed as Zone of Inhibition in mm. The results were compared with the activity of the standard antibiotic ciprofloxacin (20 µg/mL). In the agar disc diffusion method, the test compound was introduced onto the disc and then allowed to dry. Thus the disc was completely saturated with the test compound. Then the disc was introduced onto the upper layer of the medium with the bacteria. The Petri dishes were incubated overnight at 37 °C for 24 hrs. Bioactivity was determined by measuring Diameter of Inhibition Zones (DIZ) in mm.

Antifungal activity:
The antifungal activity of the newly synthesized compounds was tested against three pathogenic fungi, namely *Fusarium oxysporum*, *Aspergillus niger* and *Aspergillus flavus* by the poison plate technique [30]. Test compounds were dissolved in acetone (10 mL) before mixing with Potato Dextrose Agar (PDA, 90 mL). The final concentration of compounds in the medium was fixed at 50 µg/mL. Three kinds of fungi were incubated in PDA at 25±1 °C for 5 days to get new mycelium for antifungal assay, then a mycelia disk of approximately 0.45 cm diameter was cut from the culture medium and it was picked up with a sterilized inoculation needle and inoculated in the centre of PDA plate. The inoculated plates were incubated at 25±1°C for 5 days. Acetone in sterilized distilled water served as control, while Clotrimazole (50 µg/mL) was used as positive control for each treatment, three replicates were carried out. The radial growth of the fungal colonies was measured on the sixth day. The *in vitro* inhibiting effects of the test compounds on the fungi were calculated by the formula CV =A-B/A, where A represents the diameter of fungi growth on untreated PDA, B represents the diameter of fungi on treated PDA, and CV represents the rate of inhibition.

RESULTS AND DISCUSSION

The chemical structures of all the title compounds **3(a-e)** and **5(a-e)** were established by IR, ^1H and ^{13}C NMR, mass spectral data and elemental analyses and their data are presented in experimental section. IR bands in the regions 1720-1760 and 1340-1375 cm^{-1} are assigned to C=O and S=O stretching vibrations respectively for **3(a-e)** and **5(a-e).** The ^1H NMR spectra exhibited triplet at δ 5.80-5.72, due to carbamate N–H protons and sulfonamide –NH proton gave a triplet at δ 3.26-3.19. The proton signals of Ar-H appeared as a multiplet in the region δ 7.62-6.96. ^{13}C NMR chemical shifts were observed in the region δ 151.2-155.6 for -NH-C=O. All the newly synthesized title compounds **3(a-e)** and **5(a-e)** were screened for their antibacterial and antifungal activities and the results were compared with standard drugs. The title compounds **3e, 3d** and **5a, 5b, 5c** exhibited good antibacterial activity due to the carbamate and sulfonamide derivatives having functional groups such as isobutyl, ethyl, -NO_2, -Br and -Cl, NO_2 groups. The title compounds exhibited moderate to good antifungal activity, the compounds **3a, 3b, 3c** and **5a, 5b, 5c** showed good inhibition against fungi due to the presence of -benzyl –NO_2, NO_2, -Cl, -NO_2, -Br, and Cl, NO_2 groups respectively. The sulfonamide derivatives of amlodipine **(5a-e)** exhibited better antimicrobial activity than that of the carbamate derivatives **(3a-e).**

Biological activity
Antibacterial activity:
The newly synthesized title compounds **3(a-e)** and **5(a-e)** were screened for their antibacterial activity. The title compounds were screened against the Gram positive bacteria *Bacillus subtilis* and *Enterococcus faecalis* and Gram negative bacteria *Klebsiella pneumoniae* and *Escherichia coli* and ciprofloxacin is used as a reference standard. The activity was measured at two different concentrations for all the title compounds at 20 µg/mL and 40 µg/mL. The title compounds (**3a-e)** and **(5a-e)** exhibited good inhibiting activities, due to the attachment of different pharmacophoric functional groups in the carbamate and sulfonamide derivatives of amlodipine. The final results are presented in **Table 1. [Insert Table 1]**

Antifungal activity:
The title compounds **3(a-e)** and **5(a-e)** were screened against *Fusarium oxysporum*, *Aspergillus flavus* and *Aspergillus niger*. The title compounds concentration was taken 50 µg/mL and anti fungal activity was evaluated and their activities were compared with the standard clotrimazole. The title compounds (**3a-e)** and **(5a-e)** showed good antifungal activities and the results are presented in **Table 2.** This may be due to the attachment of different bioactive functional groups to the carbamate and sulfonamide derivatives of amlodipine. **[Insert Table 2]**

Table 1. Antibacterial activity of carbamate and sulfonamide derivatives of amlodipine (3a-e) and (5a-e).

Compound	*Staphylococcus aureus*		*Bacillus subtilis*		*Klebsiella pneumoniae*		*Escherichia coli*	
Concentration (µg/mL)	**20**	**40**	**20**	**40**	**20**	**40**	**20**	**40**
3a	4	8	5	12	8	11	6	13
3b	5	10	4	8	6	14	5	8
3c	5	12	6	12	5	12	8	10
3d	7	14	7	16	5	10	7	16
3e	8	18	6	12	8	13	8	18
5a	12	20	8	18	5	12	10	19
5b	8	14	6	14	4	12	6	12
5c	5	10	8	17	6	13	6	12
5d	4	9	5	9	6	10	6	10
5e	4	8	4	8	5	9	5	12
Ciprofloxacin (20 *µg*/mL)	22	--	24	--	25	--	22	--

Table 2. Anti fungal activity carbamate and sulfonamide derivatives of amlodipine (3a-e) and (5a-e).

Compound[a]	***Fusarium oxysporum***	***Aspergillus flavus***	***Aspergillus niger***
3a	11.4	10.2	11.0
3b	11.8	12.2	13.8
3c	12.5	12.2	10.5
3d	14.8	12.7	12.4
3e	12.0	16.0	14.8
5a	15.5	16.6	15.2
5b	6.4	5.2	8.5
5c	5.6	5.8	13.6
5d	6.8	5.7	6.6
5e	5.0	4.8	4.2
Clotrimazole (50 *µg*/mL)	17.3	16.7	18.2

[a] *Concentration 50 µg/mL.*

CONCLUSION

The synthesis of carbamate **(3a-e)** and sulfonamide **(5a-e)** derivatives of 3-ethyl 5-methyl2-(2-aminoethoxy)-4-(2-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (amlodipine) was accomplished high yields. The structures were established by elemental analysis and spectral data (IR, ^{1}H, ^{13}C and LC- mass). The title compounds **3e, 3d** and **5a, 5b, 5c** exhibited high antibacterial activity and **3a, 3b, 3c** and **5a, 5b, 5c** showed good antifungal activities when compared to reference standards like Ciprofloxacin and Clotrimazole.

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