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Der Pharmacia Lettre, 2013, 5 (1):199-204
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USA CODEN: DPLEB4

Synthesis, spectral characterization and antimicrobial activity of thiourea/urea derivatives of amlodipine

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ABSTRACT

*Amlodipine is one of the calcium channel blockers havingdihydropyridine group, used as an antihypertensive drug.A series of novel ureaandthioureaderivativesofamlodipine(**1**) were prepared by reacting (**1**) with various substituted isocyanates/isothiocyanates in the presence of triethylamine in THF at 50 °C. Their structures were established by IR, ^{1}H, ^{13}CNMR, Mass spectral data and C, H, N elemental analysis. Their antimicrobial activity was evaluated and the title compounds exhibited moderate antimicrobial activity.*

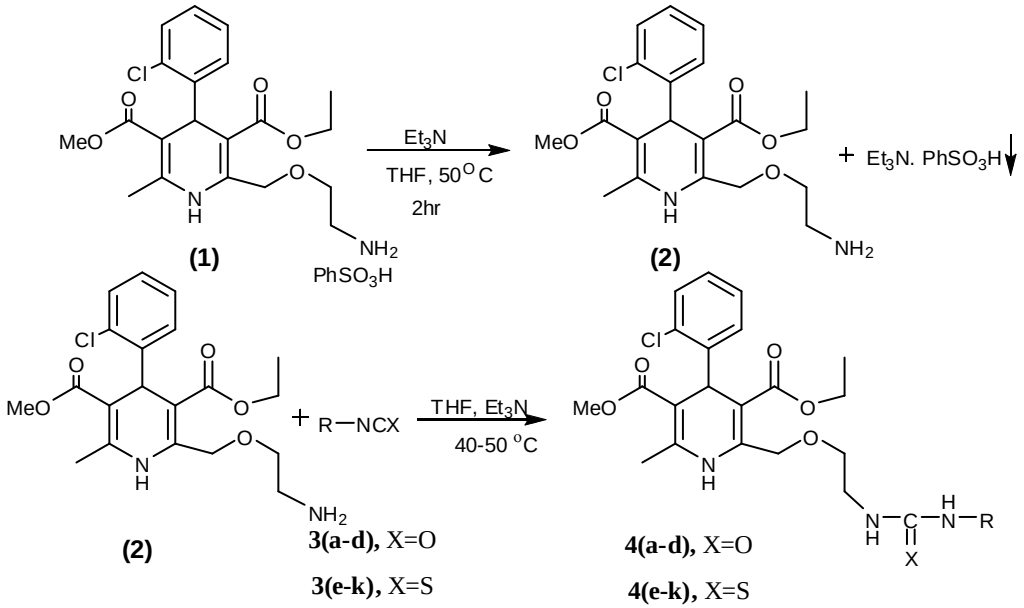
Key words: Amlodipine, Urea and thiourea derivatives, Antimicrobial activity.

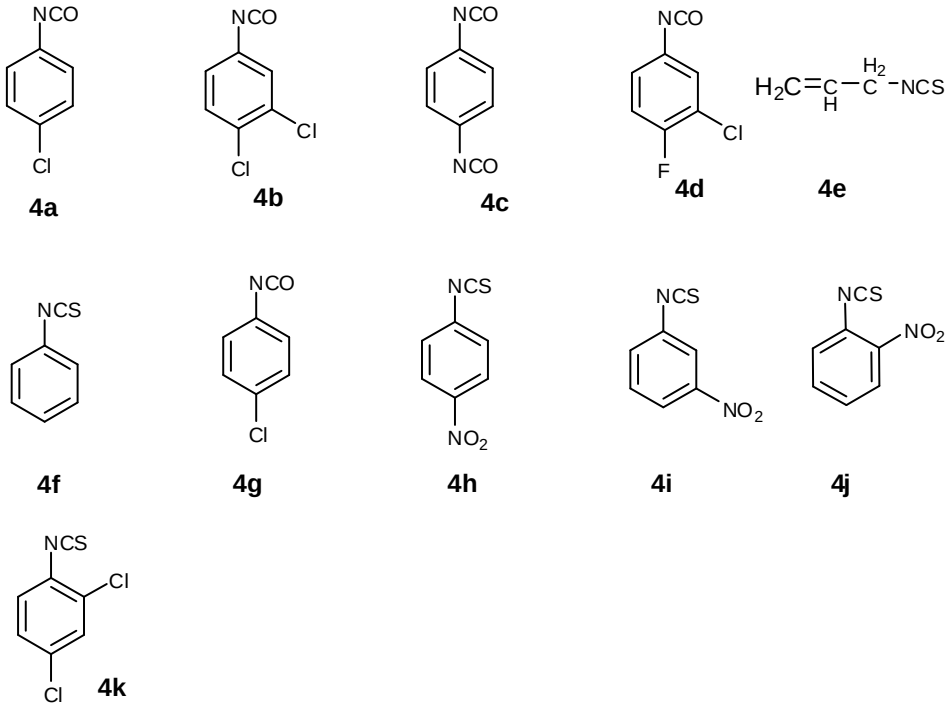
INTRODUCTION

Amlodipine (3-ethyl-5-methyl(±) 2-((2-aminoethoxy) methyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate), commercially available as Norvasc® is a long acting calcium channel blocker used as an anti-hypertensive drug[1] and the mechanism involved in it is a dihydropyridine calcium antagonist that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle [2]. The contractile process of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ion into these cells through specific ion channels [3]. It inhibits calcium ion influx across cell membrane selectively, with a greater effect on vascular smooth muscle than on cardiac muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure [4].

Urea and thiourea derivatives possess potent anticancer properties [5-7]. Thiourea derivatives display a wide range of biological activity including antibacterial, anti-fungal, antitubercular, antihelmintic, rodenticidal, insecticidal, herbicidal and plant growth regulatory properties [8-10]. The importance of such work lies in the possibility of the thiourea derivatives might be more efficacious as antimicrobial and anticancer agents. However, a thorough investigation relating tothe structure and the activity of the thiourea derivatives as well as their stability under biological conditions is required. These detailed investigations could be helpful in designing more potent antimicrobial agents for the therapeutic use. Since varying substituent on abasic structural frame work is a common method for drug design in medicinal chemistry and a useful medical value of substituted thiourea derivatives.

Based on the importance of amlodipine, it is designed and synthesized a series of novel urea and thiourea derivatives of amlodipine in high yield.





MATERIALS AND METHODS

Chemistry: All the chemicals were purchased from Sigma-Aldrich and used without further purification. TLC was performed on pre-coated plates with silica gel 60F254 (Merck). Column chromatography was performed on silica gel (0.040-.063 mm, Macherey, Nagel). Melting points were recorded on Buchi R-535 (Flawil, Switzerland) apparatus and are uncorrected. IR Spectra were recorded on JASCO Japan FT/IR -5300. ^{1}H, and ^{13}C NMR spectra were recorded on Bruker A VIII 500 MHz NMR spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C .NMR data were recorded in DMSO-$d_6$and were referenced to TMS (^{1}H and ^{13}C). Mass spectra were recorded on

LC-MS 2010A Shimadzu(Japan), spectrometer at University of Hyderabad, Hyderabad. Elementary analyses were performed using EA 1112 Thermo Finnigan(France), instrument at University of Hyderabad, Hyderabad, India.

SYNTHESIS:

General synthetic procedure of synthesis of 4a-k.

A solution of Amlodipine benzene sulfonic acid (1.57 g, 0.003 mole) in 20 mL of dry THF was treated with triethyl amine (0.9 mL, 0.003 mole) in 25 mL of THF at 10 ^{o}C. After stirring for 2h at 50^{o}C, formation of **2**(free base) was ascertained by TLC analysis run in a 3:7 mixture of ethylacetate and hexane and the average R_f value observed was 0.75. $Et_3N.PhSO_3H$ was removed by filtration. The filtrate containing **2**was used for the next reaction step without further purification.

To a stirred solution of Amlodipine **(2)** in 20 mL dry THF, a solution of 4-chlorophenylisocyanate (**3a**) (0.001mole) in 10 mL of dry THF was added dropwise at room temperature in the presence of triethylamine (0.001 mole). After the completion of the addition, the temperature of the reaction was raised to 40-50 ^{o}C and the reaction mixture was stirred for 3 h. After the completion of the reaction, as indicated by TLC conducted in 3:7 mixture of ethyl acetate and hexane, an average R_f value of 0.60 was observed. It was purified by column chromatography on silica gel (100-200 mesh) eluting with ethyl acetate: hexane, 1:9) to afford the pure compound**4a**. Other urea derivatives **4 (b-d)**and thiourea derivatives **4 (e-k)**were synthesized by adopting the above synthetic procedure.The compounds thus obtained were characterized by elemental analysis, ^{1}H, ^{13}C NMR, mass spectra and elemental analysis.

3-Ethyl-5-methyl-4-(2-chlorophenyl)-2-((2-(3-(4-chlorophenyl)ureido)ethoxy)methyl)-6-methyl-1,4-dihydro pyridine-3,5-dicarboxylate (*4a*):

Yield80%; mp 178-180^{o}C;IR (KBr) (ν_{max} cm^{-1}):1682 (C=O), 1715 (C=O),3368 (NH); ^{1}H-NMR (DMSO- d_6) δ ppm: 1.22 (t, 3H, CH_3, H-12), 2.10 (s, 3H, CH_3, H-15), 3.18 (dd, 2H, CH_2, H-9), 3.30 (s, 3H, OCH_3, H-14), 3.60 (t, 2H, CH_2, H-8), 4.07 (s, 2H, CH_2, H-7),4.23 (m, 2H, CH_2, H-11),4.40 (s, 1H, CH, H-4), 5.90 (t, 1H,NH, H-22), 7.22-7.70 (m, 8H, Ar-H), 8.20 (s, 1H, NH, H-1), 9.21 (s, 1H, H-24); ^{13}C-NMR (DMSO-d_6)δ(ppm): 15.2 (C-12), 18.7 (C-15), 37.2 (C-4), 39.0 (C-9), 54.0 (C-14), 60.2 (C-11), 67.8 (C-7), 68.0 (C-8), 103.1 (C-5), 103.7 (C-3),121.3 (C-2′&C-6′), 126.1 (C-21), 126.8 (C-20), 127.4 (C-19),128.0 (C-18), 130.4 (C-3′ &C-5′), 131.0 (C-17), 133.8 (C-4′), 136.5 (C-1′) 142.7 (C-6), 144.3 (C-2), 144.6 (C-16), 158.1 (C-23), 166.4 (C-10), 166.5(C-13); LCMSmass m/z (%)562.3 (100%)[M+H]$^{+\cdot}$, 564.2 (65%), 408.5 (60%).Anal.cald.for$C_{27}H_{29}Cl_2N_3O_6$:C 57.66; H 5.20; N 7.47;FoundC 57.60; H 5.16; N 7.41;

3-Ethyl-5-methyl-4-(2-chlorophenyl)-2-((2-(3-(3,4-dichlorophenyl)ureido)ethoxy)methyl)- 6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (*4b*)

Yield 84%; mp 198-200 ^{o}C;IR (KBr) (ν_{max} cm^{-1}):1677 (C=O), 1718 (C=O),3376 (NH); ^{1}H-NMR (DMSO- d_6) δ ppm: 1.27 (t, 3H, CH_3, H-12), 2.15 (s, 3H, CH_3, H-15), 3.23 (dd, 2H, CH_2, H-9), 3.35 (s, 3H, OCH_3, H-14), 3.65 (t, 2H, CH_2, H-8), 4.12 (s, 2H, CH_2, H-7),4.28 (m, 2H, CH_2, H-11),4.45 (s, 1H, CH, H-4), 5.95 (t, 1H,NH, H-22), 7.28-7.85 (m, 7H, Ar-H), 8.25 (s, 1H, NH, H-1), 9.26 (s, 1H, H-24); ^{13}C-NMR (DMSO-d_6)δ(ppm): 15.25 (C-12), 18.75 (C-15), 37.25 (C-4), 39.05 (C-9), 54.05 (C-14), 60.25 (C-11), 67.85 (C-7), 68.05 (C-8), 103.15 (C-5), 103.75 (C-3),122.4 (C-5′), 125.2 (C-6′), 126.15 (C-21), 126.85 (C-20), 127.45 (C-19),128.05 (C-18), 130.8 (C-3′), 131.3 (C-2′), 131.1 (C-17), 128.9 (C-4′), 135.8 (C-1′),142.8 (C-6), 144.4 (C-2), 144.65 (C-16), 157.9 (C-23), 166.5 (C-10), 166.55(C-13); LCMSmass m/z (%)596.4 (100%)[M+H]$^{+\cdot}$, 598.3 (66%), 408.2 (52%).Anal.cald.for$C_{27}H_{28}Cl_3N_3O_6$:C 54.33; H 4.73; N 7.04;FoundC 54.28; H 4.70; N 7.02;

3-Ethyl-5-methyl-4-(2-chlorophenyl)-2-[(2-[(4-isocyanatoanilino)carbonyl]aminoethoxy)methyl]-6-methyl-1,4-dihydro-3,5-pyridinedicarboxylate(4c)

Yield 73%; mp225-227^{o}C;IR (KBr) (ν_{max} cm^{-1}):1682 (C=O), 1724 (C=O),3385 (NH); ^{1}H-NMR (DMSO- d_6) δ ppm: 1.26 (t, 3H, CH_3, H-12), 2.14 (s, 3H, CH_3, H-15), 3.22 (dd, 2H, CH_2, H-9), 3.34 (s, 3H, OCH_3, H-14), 3.64 (t, 2H, CH_2, H-8), 4.11 (s, 2H, CH_2, H-7),4.27 (m, 2H, CH_2, H-11),4.44 (s, 1H, CH, H-4), 5.94 (t, 1H,NH, H-22), 7.25-7.64 (m, 8H, Ar-H), 8.24 (s, 1H, NH, H-1), 9.15 (s, 1H, H-24); ^{13}C-NMR (DMSO-d_6)δ(ppm): 15.24 (C-12), 18.74 (C-15), 37.24 (C-4), 39.04 (C-9), 54.04 (C-14), 60.24 (C-11), 67.84 (C-7), 68.4 (C-8), 103.14 (C-5), 103.74 (C-3),120.2 (C-2′&C-6′),126.14 (C-21), 126.84 (C-20), 127.44 (C-19),128.04 (C-18), 128.2 (C-7′), 126.2 (C-3′ &C-5′), 129.5 (C-4′), 131.04 (C-17), 136.1 (C-1′), 142.74 (C-6), 144.34 (C-2), 144.64 (C-16), 157.2 (C-23), 166.44 (C-10), 166.54(C-13); LCMSmass m/z (%)569.6 (100%)[M+H]$^{+\cdot}$, 571.5 (64%), 408.4 (72%).Anal.cald.for$C_{28}H_{29}ClN_4O_7$:C 59.10; H 5.14; N 9.85;FoundC 59.05; H 5.08; N 9.80;

3-Ethyl-5-methyl-2-((2-(3-(3-chloro-4-fluorophenyl)ureido)ethoxy)methyl)-4-(2-chlorophenyl)- 6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (*4d*)
Yield 78%; mp 185-187^{o}C;IR (KBr) (ν_{max} cm^{-1}):1675 (C=O), 1721 (C=O),3396 (NH); ^{1}H-NMR (DMSO- d_6) δ ppm: 1.25 (t, 3H, CH_3, H-12), 2.13 (s, 3H, CH_3, H-15), 3.21 (dd, 2H, CH_2, H-9), 3.33 (s, 3H, OCH_3, H-14), 3.63 (t, 2H, CH_2, H-8), 4.10 (s, 2H, CH_2, H-7),4.26 (m, 2H, CH_2, H-11),4.43 (s, 1H, CH, H-4), 5.93 (t, 1H,NH, H-22), 7.24-7.75 (m, 7H, Ar-H), 8.23 (s, 1H, NH, H-1), 9.24 (s, 1H, H-24); LCMSmass m/z (%)580.2 (100%)$[M+H]^{+\cdot}$, 582.5 (65%), 408.5 (68%).Anal.cald.for$C_{27}H_{28}Cl_2FN_3O_6$:C 55.87; H 4.86; N 7.24;FoundC 55.81; H 4.79; N 7.15;

3-Ethyl-5-methyl-2-((2-(3-allylthioureido)ethoxy)methyl)-4-(2-chlorophenyl)- 6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (*4e*)
Yield 75%; mp207-209^{o}C;IR (KBr) (ν_{max} cm^{-1}): 1363 (C=S), 1673 (C=O), 3321 (NH);^{1}H-NMR (DMSO- d_6) δ ppm: 1.24 (t, 3H, CH_3, H-12), 2.12 (s, 3H, CH_3, H-15), 3.20 (dd, 2H, CH_2, H-9), 3.32 (s, 3H, OCH_3, H-14), 3.62 (t, 2H, CH_2, H-8), 4.09 (s, 2H, CH_2, H-7), 4.25 (m, 2H, CH_2, H-11),4.42 (s, 1H, CH, H-4), 4.9-5.6 (m, 5H, -CH_2-CH=CH_2), 5.92 (t, 1H,NH, H-22), 7.00-7.90 (m, 4H, Ar-H), 8.22 (s, 1H, NH, H-1), 9.23 (s, 1H, H-24); ^{13}C-NMR (DMSO-d_6)δ(ppm): 15.22 (C-12), 18.72 (C-15), 37.22 (C-4), 39.02 (C-9), 40.4 (C-1′), 54.02 (C-14), 60.22 (C-11), 67.82 (C-7), 68.02 (C-8), 103.12 (C-5), 103.72 (C-3),118.6 (C-3′), 126.12 (C-21), 126.82 (C-20), 127.42 (C-19),128.02 (C-18), 131.02 (C-17), 134.8 (C-2′), 142.72 (C-6), 144.32 (C-2), 144.62 (C-16), 166.42 (C-10), 166.52(C-13), 185.7 (C-23); LCMSmass m/z (%)508.3 (100%)$[M+H]^{+\cdot}$, 510.5 (65%), 408.5 (58%). Anal.cald. for$C_{24}H_{30}ClN_3O_5S$: C56.74; H 5.95; N 8.27;FoundC 56.68; H 5.90; N 8.21;

3-Ethyl-5-methyl-4-(2-chlorophenyl)-2-((2-(3-phenylthioureido)ethoxy)methyl)-6-methyl-1,4-dihydropyridine -3,5-dicarboxylate (*4f*) :
Yield 73%; mp 189-191^{o}C;IR (KBr) (ν_{max} cm^{-1}):1355 (C=S), 1668 (C=O), 3268 (NH);^{1}H-NMR (DMSO- d_6) δ ppm: 1.23 (t, 3H, CH_3, H-12), 2.11 (s, 3H, CH_3, H-15), 3.19 (dd, 2H, CH_2, H-9), 3.31 (s, 3H, OCH_3, H-14), 3.61 (t, 2H, CH_2, H-8), 4.08 (s, 2H, CH_2, H-7),4.24 (m, 2H, CH_2, H-11),4.41 (s, 1H, CH, H-4), 5.91 (t, 1H,NH, H-22), 6.93-7.62 (m, 9H, Ar-H), 8.21 (s, 1H, NH, H-1), 9.22 (s, 1H, H-24); ^{13}C-NMR (DMSO-d_6)δ(ppm): 15.2 (C-12), 18.7 (C-15), 37.2 (C-4), 39.1 (C-9), 54.1 (C-14), 60.2 (C-11), 67.8 (C-7), 68.1 (C-8), 103.1 (C-5), 103.7 (C-3),126.2 (C-2′&C-6′),126.1 (C-21), 126.8 (C-20), 127.4 (C-19), 127.6 (C-4′), 128.01 (C-18), 129.2 (C-3′ &C-5′), 131.01 (C-17), 137.3 (C-1′), 142.71 (C-6), 144.31 (C-2), 144.61 (C-16), 166.41 (C-10), 166.5(C-13), 182.2 (C-23); LCMSmass m/z (%)544.2 (100%)$[M+H]^{+\cdot}$, 546.5 (33%), 408.2 (66%).Anal.cald.for$C_{27}H_{30}ClN_3O_5S$:C 59.61; H 5.56; N 7.72;FoundC 59.54; H 5.51; N 7.65;

3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-((2-(3-(4-chlorophenyl)thioureido)ethoxy)methyl)- 6-methyl-1,4-dihydro pyridine-3,5-dicarboxylate (*4g*)
Yield 80%; mp 194-196^{o}C;IR (KBr) (ν_{max} cm^{-1}): 1348 (C=S), 1668 (C=O), 3274 (NH); ^{1}H-NMR (DMSO- d_6) δ ppm: 1.17 (t, 3H, CH_3, H-12), 2.05 (s, 3H, CH_3, H-15), 3.13 (dd, 2H, CH_2, H-9), 3.25 (s, 3H, OCH_3, H-14), 3.55 (t, 2H, CH_2, H-8), 4.02 (s, 2H, CH_2, H-7),4.18 (m, 2H, CH_2, H-11),4.35 (s, 1H, CH, H-4), 5.85 (t, 1H,NH, H-22), 6.75-7.59 (m, 8H, Ar-H), 8.15 (s, 1H, NH, H-1), 9.16 (s, 1H, H-24); ^{13}C-NMR (DMSO-d_6)δ(ppm): 15.15 (C-12), 18.65 (C-15), 37.15 (C-4), 39.95 (C-9), 53.95 (C-14), 60.15 (C-11), 67.75 (C-7), 67.95 (C-8), 103.05 (C-5), 103.65 (C-3),126.05 (C-21), 126.75 (C-20), 127.35 (C-19),127.95 (C-18), 130.8 (C-3′&C-5′), 130.8 (C-17), 131.2 (C-2′&C-6′), 132.9 (C-4′), 135.2 (C-1′), 142.65 (C-6), 144.25 (C-2), 144.55 (C-16), 166.35 (C-10), 166.45(C-13), 183.4 (C-23); LCMSmass m/z (%)578.2 (100%)$[M+H]^{+\cdot}$, 579.8 (65%), 408.5 (54%).Anal.cald.for$C_{27}H_{29}Cl_2N_3O_5S$:C 56.06; H 5.05; N 7.26;FoundC 56.02; H 5.01; N 7.19;

3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-((2-(3-(4-nitrophenyl)thioureido)ethoxy)methyl)- 6-methyl-1,4-dihydro pyridine-3,5-dicarboxylate (*4h*)
Yield 85%; mp215-217^{o}C;IR (KBr) (ν_{max} cm^{-1}): 1346 (C=S), 1669 (C=O), 3275 (NH);^{1}H-NMR (DMSO- d_6) δ ppm: 1.18 (t, 3H, CH_3, H-12), 2.06 (s, 3H, CH_3, H-15), 3.14 (dd, 2H, CH_2, H-9), 3.26 (s, 3H, OCH_3, H-14), 3.56 (t, 2H, CH_2, H-8), 4.03 (s, 2H, CH_2, H-7),4.19 (m, 2H, CH_2, H-11),4.36 (s, 1H, CH, H-4), 5.86 (t, 1H,NH, H-22), 7.71-7.98 (m, 8H, Ar-H), 8.16 (s, 1H, NH, H-1), 9.17 (s, 1H, H-24); LCMSmass m/z (%)589.7 (100%)$[M+H]^{+\cdot}$, 591.5 (33%), 408.2 (48%).Anal.cald.for$C_{27}H_{29}ClN_4O_7S$:C 55.05; H 4.96; N 9.51;FoundC 55.01; H 4.89; N 9.42;

3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-((2-(3-(3-nitrophenyl)thioureido)ethoxy)methyl)- 6-methyl-1,4-dihydro pyridine-3,5-dicarboxylate (*4i*)
Yield 70%; mp208-210^{o}C;IR (KBr) (ν_{max} cm^{-1}): 1349 (C=S), 1662 (C=O), 3277 (NH);^{1}H-NMR (DMSO-d_6) δ ppm: 1.19 (t, 3H, CH_3, H-12), 2.07 (s, 3H, CH_3, H-15), 3.15 (dd, 2H, CH_2, H-9), 3.27 (s, 3H, OCH_3, H-14), 3.57 (t, 2H,

CH_2, H-8), 4.04 (s, 2H, CH_2, H-7),4.18 (m, 2H, CH_2, H-11),4.35 (s, 1H, CH, H-4), 5.85 (t, 1H,NH, H-22), 6.94-7.75 (m, 8H, Ar-H), 8.15 (s, 1H, NH, H-1), 9.16 (s, 1H, H-24); LCMSmass m/z (%)589.7 (100%)$[M+H]^{+\cdot}$, 591.5 (33%), 408.3 (50%).Anal.cald.for$C_{27}H_{29}ClN_4O_7S$: C 55.05; H 4.96; N 9.51; FoundC 55.01; H 4.89; N 9.42;

3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-((2-(3-(2-nitrophenyl)thioureido)ethoxy)methyl)- 6-methyl-1,4-dihydro pyridine-3,5-dicarboxylate (*4j*)

Yield 83%; mp211-213^{o}C;IR (KBr) (ν_{max} cm^{-1}): 1351 (C=S), 1663 (C=O), 3266 (NH);^{1}H-NMR (DMSO- d_6) δ ppm: 1.20 (t, 3H, CH_3, H-12), 2.08 (s, 3H, CH_3, H-15), 3.16 (dd, 2H, CH_2, H-9), 3.28 (s, 3H, OCH_3, H-14), 3.58 (t, 2H, CH_2, H-8), 4.05 (s, 2H, CH_2, H-7),4.21 (m, 2H, CH_2, H-11),4.38 (s, 1H, CH, H-4), 5.88 (t, 1H,NH, H-22), 7.22-7.90 (m, 8H, Ar-H), 8.18 (s, 1H, NH, H-1), 9.19 (s, 1H, H-24); LCMSmass m/z (%)589.7 (100%)$[M+H]^{+\cdot}$, 591.5 (33%), 408.2 (52%).Anal.cald.for$C_{27}H_{29}ClN_4O_7S$: C 55.05; H 4.96; N 9.51;FoundC 55.01; H 4.89; N 9.42;

3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-((2-(3-(2,4-dichlorophenyl)thioureido)ethoxy)methyl)- 6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (*4k*)

Yield 75%; mp 193-195^{o}C;IR (KBr) (ν_{max} cm^{-1}):1345 (C=S), 1658 (C=O),3259 (NH); ^{1}H-NMR (DMSO- d_6) δ ppm: 1.21 (t, 3H, CH_3, H-12), 2.11 (s, 3H, CH_3, H-15), 3.17 (dd, 2H, CH_2, H-9), 3.31 (s, 3H, OCH_3, H-14), 3.61 (t, 2H, CH_2, H-8), 4.06 (s, 2H, CH_2, H-7),4.22 (m, 2H, CH_2, H-11),4.41 (s, 1H, CH, H-4), 5.91 (t, 1H,NH, H-22), 7.31-7.96 (m, 7H, Ar-H), 8.21 (s, 1H, NH, H-1), 9.20 (s, 1H, H-24); LCMSmass m/z (%)612.4 (100%)$[M+H]^{+\cdot}$, 614.5 (33%), 408.6 (69%).Anal.cald.for$C_{27}H_{28}Cl_3N_3O_5S$:C 52.91; H 4.60; N 6.86;FoundC 52.82; H 4.54; N 6.79;

Table 1 Antifungal activity of compounds 4a-j

Compound	Zone of inhibition (in mm)			
	Colletotrichumgloeosporioides		*Aspergillusniger*	
	250 (µg/disc)	500 (µg/disc)	250 (µg/disc)	500 (µg/disc)
4a	6	11	7	12
4b	8	14	8	15
4c	7	13	7	14
4d	6	11	9	19
4e	7	12	8	12
4f	8	14	8	15
4g	10	16	8	14
4h	7	12	10	20
4i	8	15	11	18
4j	9	14	9	16
Griseofulvin	20	-	20	-

Table 2 Antibacterial activity of compounds 4a-j

Compound	Zone of inhibition(in mm)							
	S aureus		*B subtilis*		*E coli*		*K pneumoniae*	
	250 (µg/disc)	500 (µg/disc)	250 (µg/disc)	500 (µg/disc)	250 (µg/disc)	500 (µg/disc)	250 (µg/disc)	500 (µg/disc)
4a	7	12	9	11	7	12	7	12
4b	11	20	11	10	8	13	8	12
4c	7	11	8	12	9	14	10	15
4d	8	14	11	19	8	12	7	11
4e	13	22	9	12	8	12	8	13
4f	10	14	8	14	9	14	10	14
4g	7	11	8	13	10	17	7	11
4h	12	17	8	14	9	11	9	14
4i	9	14	8	14	7	15	7	11
4j	10	17	9	12	9	13	11	16
Penicillin	22	--	22	--	22	--	22	--

Antimicrobial activity

Susceptibility of test organisms to the title compounds **4(a-k)** was determined by employing the standard disc diffusion technique [11]. All the compounds **4(a-k)** were tested for their antifungal activity against the growth of *Colletotrichumgleosorioides and Aspergillusniger*along with the standard fungicide Griseofulvin at concentrations of 250 and 500 µg/disc, according to the reported procedure [12].(**Table1**). Title compounds **4(a-k)**were also screened for their anti-bacterial activity against the growth of *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia*

coli and *Klebsiellapeumoniae*along with the standard Penicillin at concentrations of 250 and 500 µg/disc according to the reported method [13].(**Table2**). The results revealed that the title compounds exhibited moderate anti-fungal and good anti-bacterial activity against the tested species.

RESULTS AND DISCUSSION

Synthesis of a series of urea/thiourea derivatives **4(a-k**) was accomplished through a single-step process. Benzene sulfonic acid was removed from Amlodipine by treating with Et_3N in THF at 50 ^oC. Then Amlodipine was reacted with different isocyanates/isothiocyanates in the presence of Et_3N in THF at 40-50$^oC$to form **4(a-k)**. The progress of the reaction was monitored by TLC analysis at different time intervals and the crude products obtained after removing the solvent were purified by column chromatography on silica gel using ethylacetate and hexane (2:3) as step grade mixtures as eluents. The structures of **4(a-k)** were established by elemental analysis, IR, ^1H, ^{13}C NMR and mass spectral data (Scheme 1). The synthetic and analytical data of title compounds **4(a-k**) are given in the experimental part. All the compounds**4(a-k**) exhibited absorption bands for C=O and -NH in the regions 1675-1682 and 3260-3340 cm^{-1}. In the ^1H NMR spectra (400 MHz) of **4(a-k),** aromatic protons resonated as multipletsin the region 6.81-7.95 ppm. The –NH proton signals were observed in the region 7.90-9.40 ppm as singlets. The ^{13}C NMR spectra for a few compounds were recorded and the data are given in the experimental part. The C=O and C=S carbons gave signals in the regions 157.2-158.1and 182.2-185.7ppmrespectively. The remaining carbon signals are observed in the expectedregions. The LC-MS of a few of the title compounds were recorded and the data are given in the experimental part.

CONCLUSION

Amlodipine was treated with differentisocyanates/isothiocyanates to form urea/thiourea derivatives with high yields75-85%. Modification of Amlodipine as its urea/thiourea derivatives exhibited good antibacterial activity against two Gram positive and two Gram negative bacteria andmoderate antifungal activity against two different fungi.

Acknowledgements
The authors express their grateful thanks to UGC, New Delhi, for giving financial assistance through BSR fellowship.

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