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Synthesis and vasodilator activity of 3,4-dihydropyrimidin-2(*1H*)-ones bearing urea, thiourea and sulfonylurea moieties

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Abstract

A series of novel 3,4-dihydropyrimidin-2(1*H*)-ones bearing urea, thiourea and sulfonylurea moieties were synthesized and pharmacologically evaluated as vasodilator agents. The most interesting vasodilators were the thiourea derivatives **6a** and **6b**, and the urea derivatives **6f-i** and **7f-h**, although the ureas were relatively more active than thioureas. Twenty fold more active than diazoxide, the urea **6k** was the most potent vasodilator (EC_{50} = 0.983 ± 0.061 μM), and proved to act as a voltage-gated calcium channel blocker. The lack of activity of sulfonylureas, **6k** and **7j**, could be attributed to their partial ionization at the physiological pH, because of their acidic character. It should be interesting to investigate a larger number of compounds, including N-methylated sulfonylureas, in order to increase the vasodilator activity and to explore other biological models.

Keywords: 3,4-dihydropyrimidin-2(1*H*)-ones, voltage-gated calcium channel blockers, vasodilator activity, urea, thiourea, sulfonylurea.

Introduction

Voltage-gated calcium channel blockers (VGCCBs) belong to a large class of drugs used in the treatment of cardiovascular diseases, such as arterial hypertension, angina pectoris and cardiac arrhythmias.[1] Such drugs inhibit Ca^{2+} influx into the heart muscles by blocking the slow inward Ca^{2+} channels or inhibiting Ca^{2+} influx into vascular smooth muscle.[2] VGCCBs are classified as dihydropyridines or non-dihydropyridines. The dihydropyridines include amlodipine, felodipine, nicardipine, and nifedipine, whereas non-dihydropyridines comprise agents such as diltiazem and verapamil (Fig. 1).[3]

The dihydropyrimidine cycle is an isostere of the dihydropyridine cycle, which is featured by a very good calcium channel blocking activity, making them usable as antihypertensive drugs.[4-6] The pyrimidine nucleus is a fundamental constituent of nucleic acids and is present in numerous drugs with various pharmacological activities. Pyrimidine derivatives are reported as antibacterial agents,[7-9] antifungal agents,[9] anticancer drugs,[10] anti-inflammatory drugs,[8,11] kinase inhibitors,[12] analgesics,[11] cyclin-dependent kinases 1 and 2 inhibitors,[13] calcium channel antagonists,[5,14] anti-histaminic agents,[15] antitubercular drugs,[16] and adenosine receptor antagonists.[17] Batzelladine **A** and **B** derived from 3,4-dihydropyrimidin-2 (1*H*)-imines were isolated by Ashok D. Patil et. al. from a marine plant and have shown promising anti-HIV activity, making them potential candidates for the treatment of AIDS (Fig. 2). [18] Indeed, these low molecular weight natural

products inhibit the binding of HIV envelope gp120 glycoprotein to CD4 receptors.[18] The limited availability of these natural products makes them attractive targets for total synthesis, but also for the synthesis of simpler analogues with similar properties.

According to this later strategy, Zaesung No et al. synthesized 3,4-dihydropyrimidin-2 (1H) -ones (DHPMs), some of which were selected because of a significant inhibition of HIV-1 replication in vitro, with a good security profile (Fig. 3). [19]

In the present work, we describe the synthesis and pharmacological evaluation of new 3,4-dihydropyrimidin-2(1*H*)-one derivatives bearing sulfonylurea, urea and thiourea groups, linked to the para or meta positions (compounds **6a-k** (series **6**) and **7a-j** (series **7**) respectively) of the 4-phenyl group (Fig. 4).

To evaluate their vasodilator activity, the target compounds were tested *in vitro* on rat aortic rings precontracted with 30 mM KCl. The experiments were repeated on rat aortic rings, on the one hand, precontracted with 30 mM KCl in the presence of 10 μM glibenclamide and, on the other hand, precontracted with 80 mM KCl, in order to determine their mechanism of action.

Chemistry

The synthetic pathway to 3,4-dihydropyrimidin-2(1*H*)-ones bearing urea, thiourea or sulfonylurea moieties (**6a-k**, **7a-j**) is described in Scheme 1. Key intermediates (**4a-b**) were prepared according to multicomponent Biginelli's reaction, by refluxing the appropriate nitrobenzaldehyde (**1**), the appropriate β-dicarbonyl compound (**2**) and urea (**3**) in acetonitrile in the presence of a catalytic amount of $Zn_{0.9}Ni_{0.1}Al_2O_4$.[20] The nitro group of **4a-b** was catalytically reduced to give the amines **5a-b**, using hydrogen and Pd/C (5%) under pressure (10 bars) at 65 °C, in anhydrous THF. The 3,4-dihydropyrimidin-2(1H)-one derivatives **6a-k** and **7a-j** were obtained by reacting an aryl isocyanate, an aryl isothiocyanate or an arylsulfonyl isocyanate with amines **5a-c** in

anhydrous THF at room temperature. All compounds of series **6** (**6a-k**) and **7** (**7a-j**) were recrystallized and characterized by IR, ^{1}HNMR, ^{13}C NMR and elemental analysis, prior to be used in pharmacological evaluation.

Results and Discussion

Contractile activity of rat aorta rings

The newly synthesized compounds, 3,4-dihydropyrimidin-2(1*H*)-ones, bearing urea, thiourea and sulfonylurea moieties (**6a-k** and **7a-j**) were pharmacologically evaluated for their ability to relax isolated rat aorta rings pre-contracted with 30 mM KCl. The VGCCB nifedipine and the potassium channel opener diazoxide were used a reference vasodilators. The results obtained with the target compounds and the reference drugs were expressed as the EC_{50} values, which corresponded to the drug concentrations provoking 50% relaxation of the pre-contracted smooth muscle preparation.

The EC_{50} values of compounds **6a-k** and **7a-j** are depicted in Table 1. The results showed that the sulfonylurea derivatives **6k** (*para* derivative) and **7j** (*meta* derivative) showed very weak vasodilator activity on rat aorta rings (EC_{50} > 150 μM), compared to the urea and thiourea derivatives. It can be observed in series **6** that all compounds presented a marked vasodilator activity, in particular the thiourea derivatives **6a** and **6b**, and urea derivatives **6f-i**. Indeed, some of the latters were found to be more active than diazoxide, among which compound **6g** (EC_{50} = 0.983 ± 0.061 μM) was the most active ($p < 0.05$). In terms of structure-activity relationships, groups with a mesomeric electron-donating effect, occupying the para position of phenylureido group, were found to be the most favourable groups for expressing a marked vasodilator activity, as it was the case for **6g** and **6h** (OCH_3 and Cl respectively). The transfer of the methoxy group (OCH_3) to the ortho-position decreased the vasodilator activity by almost twenty-one fold

compared to that of the para position (**6g** *vs* **6f**). This trend can also be observed with the series **7** compounds. Indeed, the most active compounds of this series bear a mesomeric electron-donating group (OCH_3 or Cl or F) at the para-position (**7f-h**) and are all urea derivatives. However, compared to their analogues of series **6** compounds, they were generally found to be relatively less active (**7f** *vs* **6g** and **7g** *vs* **6h**), in particular **6g**, which was 17 fold more active than **7f**. The inactiveness of sulfonylurea derivatives (**6k**, **7j**) could be due to their weak acidic character, since they have a labile hydrogen atom belonging to the NH group confined between the electron-withdrawing groups, SO_2 and C=O, of the sulfonylurea moiety. This fact means that they could mainly exist as negative ionized species at physiological pH, and that the active form should be neutral. Such a phenomenon has been also observed with other series of compounds possessing urea, thiourea and sulfonylurea moieties, where the latters were also found to be inactive.[21-23]

In order to determine the mechanism of action of the target compounds, the most active one, the urea derivative **6g**, was tested again with 30 mM KCl in the presence of 10 μM glibenclamide, an ATP-dependent potassium channel blocker, and with 80 mM KCl. Indeed, the vasodilator activity can be provoked either directly by blocking voltage-gated Ca^{2+} channels, or indirectly by opening ATP-dependent potassium channels, which hyperpolarizes the membrane cells and causes the blockade of voltage-gated Ca^{2+} channels and, consequently, the relaxation process. Therefore, pure potassium channel openers are able to suppress smooth muscle contractions induced by 30 mM KCl (or less), but not high depolarizing K^+ concentrations (80 mM). At 80 mM KCl, the potassium equilibrium potential and the cell membrane potential are so close that the hyperpolarization induced by K^+ channel opening is too weak to close voltage-operated Ca^{2+} channels.[24-26]

As indicated by table 2 and figure **5**, there was no significant change in the vasodilator activity of compound **6g**, in the presence of 10 μM glibenclamide or 80 mM KCl ($p > .05$). It means that this compound is probably a voltage-gated calcium channel blocker (nifedipine-like), and certainly not an ATP-dependent potassium channel opener (non diazoxide-like).

Conclusion

In conclusion, we have synthesized and evaluated the vasodilator activity of two series of 3,4-dihydropyrimidin-2(1*H*)-ones (**6** and **7**) bearing urea, thiourea and sulfonylurea moieties, at the *para* (**6a-k**) or *meta* (**7a-j**) positions of the phenyl group at the 4-position of the dihydropyrimidinone ring. Compounds bearing sulfonylurea moieties, belonging to series **6** and **7**, namely **6k** and **7j**, were inactive. The biological results showed that the most interesting compounds are ureas. The most potent vasodilator compounds belong to series **6** such as **6g** and **6h,** where **6g** was found to be twenty fold more active than diazoxide. Further investigations, in the presence of glibenclamide and 80 mM KCl, revealed that compound **6g** was a voltage-gated calcium channel blocker like nifedipine. The inactivity of the sulfonylureas, namely **6k** and **7j**, could be attributed to their partial ionization at the physiological pH, because of their acidic character. Indeed, these compounds possess a labile hydrogen atom on the NH group located between the two electron-attracting C=O and SO_2 groups. This phenomenon was also observed in previous works on other series of compounds, where the sulfonylureas were much less active than urea or thiourea compounds.[22-24] Therefore, it would be interesting to investigate the N-methylated sulfonylureas, because they will not be ionized at physiological pH. Further

biological investigations of urea and thiourea derivatives, including N-methylated sulfonylureas, on other biological models are also suitable to explore a possible tissue-selectivity.

Experimental section

Chemistry

Melting points were determined on a Büchi–Tottoli capillary apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin-Elmer 1750 FT spectrophotometer. The ^{1}NMR spectra were taken on a Bruker (500 MHz) instrument in DMSO-d_6 with tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in term of δ values (ppm) relative to internal TMS. The abbreviation s = singlet, d = doublet, t = triplet, m = multiplet, q = quadruplet, CH_{arom} = aromatic CH and brs = broad singlet, are used throughout. Elemental analyses (C, H, N, S) were realized on a Carlo-Erba EA 1108-elemental analyser and were within ± 0.4% of theoretical. All reactions were checked by TLC on silica gel Merck 60 F_{254}. Column chromatography was performed on a silica gel Merck 60F_{254} using hexane/ ethyl acetate as an eluent system.

General procedure for preparing 4a-b

In a 50 mL flask, the mixture of the appropriate aldehyde (5 mmol), ethyl acetoacetate (5 mmol), urea (7 mmol) and $Zn_{0.9}Ni_{0.1}Al_2O_4$ (20% mass of the aldehyde) in ethanol (10 mL) was stirred under reflux for 4 hours.[20] The product was isolated after filtration of the catalyst on celite and evaporating the solvent. Recrystallization was performed with ethanol to yield pure dihydropyrimidinones **4a-c**. The recovered catalyst was dried in an oven at 200 °C for 24 hours, and reused in subsequent reactions.

5-(Ethoxycarbonyl)-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4a) [28]

Yellow powder (75%). mp 218-220°C. IR (KBr, νcm^{-1}): 3240, 3120, 1710, 1690, 1650, 1590, 1480, 1510, 1350, 1220, 790.^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.35 (s,1H, NH), 8.22 (d, 2H, CH$_{arom,}$ *J* = 8.51 Hz), 7.88 (s, 1H, NH), 7.50 (d, 2H, CH$_{arom}$, *J* =8.51 Hz), 5.27 (d,1H, CH, *J* =2.8 Hz), 3.99 (q, 2H, CH$_{2,}$ *J* =7.5 Hz), 2.27 (s, 3H, CH$_3$), 1.10 (t, 3H, CH$_3$, *J* =7.5 Hz).^{13}C NMR (125 MHz, DMSO-d$_6$) δ 165, 152, 149, 148, 127, 123, 98, 60, 54, 18, 15. Anal. Calcd. $C_{14}H_{15}N_3O_5$ (%): C, 55.08; H, 4.95; N, 13.76. Found C, 54.99; H, 5.01; N, 13.70.

5-(Ethoxycarbonyl)-4-(3-nitrophényl)-6-méthyl-3,4-dihydropyrimidin-2(1H)-one (4b) [29]

Yellow powder (66%). mp 226-228°C. IR (KBr, νcm^{-1}): 3320, 3120, 1720, 1640, 1530, 1350, 1480, 1430, 1380, 1230, 780, 730.^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.36 (s, 1H, N*H*), 8.15-8.13 (m, 1H, C*H$_{arom}$*), 8.08 (s, 1H, CH$_{arom}$), 7.89 (s, 1H, N*H*), 7.71-7.64(m, 2H, CH$_{arom}$), 5.30 (d, 1H, CH, *J* =2.8 Hz),4.00 (m, 2H, CH$_2$), 2.26 (s, 3H, C*H$_3$*), 1.01(t, 3H, C*H$_{3,}$ J* = 7.5Hz).^{13}C NMR (125 MHz, DMSO-d$_6$) δ 165.36, 157.30, 152.18, 148.08, 146.22, 129, 116.5, 114, 113, 99.32, 59.17, 53.5,18,00, 14.00. Anal. Calcd. $C_{14}H_{15}N_3O_5$ (%): C, 55.08; H, 4.95; N, 13.76. Found C, 55.02; H, 5.00; N, 13.83.

General procedure for preparing 5a-b

A solution of **4** (10 mmol) in 40 mL of anhydrous THF was hydrogenated over Pd/C (5%) under pressure (10 bars) at 65 °C for 45 min. After filtration on celite, the organic phase was concentrated under vacuum to get crude products, which were purified by silica gel column chromatography using EtOAc/hexane (70/30).

5-(Methylcarbonyl)-4-(4-aminophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (5a) [28]

White powder (89%). mp 225-227°C. IR (KBr,νcm^{-1}): 3550, 3390, 3220, 3115, 2985, 2915,1700 , 1640,1230.^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9,04 (s,1H, NH), 7,53 (brs, 1H, NH), 6,87 (d, 2H,

CH_{arom}, J=8.51 Hz), 6,47 (d, 2H, CH_{arom}, J=8.51 Hz), 4,99 (s, 2H, NH_2), 4,95 (d, 1H, CH, *J*=2.8 Hz), 3,97 (q, 2H, CH_2, J=7.09 Hz), 2,21 (s, 3H, CH_3), 1,10 (t, 3H, CH_3, J=7.09 Hz).^{13}C NMR (125 MHz, DMSO-d_6) δ 165.48, 152.21, 147.83, 147.33, 132.22, 126.93, 113.48, 99.92, 59.01, 53.49, 17.68, 14.10. Anal. Calcd. $C_{14}H_{17}N_3O_3$ (%): C, 61.08; H, 6.22; N, 15.26. Found C, 60.82; H, 6.35; N, 15.00.

5-(Ethoxycarbonyl)-4-(3-aminophenyl)-6-méthyl-3,4-dihydropyrimidin-2(1H)-one (5b) [29]

White powder (93%). mp 195-197°C. IR (KBr, νcm^{-1}): 3445, 3350, 3240, 3100, 2980, 2935, 1710, 1655, 1230.^{1}H NMR (500 MHz, DMSO-d_6) δ 9.08 (s,1H, NH),7,60 (s, 1H, NH); 6,92 (t, 1H, CH_{arom}, J=7.57 Hz); 6,44-6.37 (m, 3H, CH_{arom}); 5,04 (s, 2H, NH_2), 4,99 (d, 1H, CH, *J*=3.15 Hz) ; 3,987 (q,2H, CH_2, J=7.09 Hz); 2,22 (s, 3H, CH_3); 1,12 (s, 3H, CH_3, J= 7.09 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.44, 152.18, 148.60, 147.73, 145.43, 128.71, 113.81, 112.81, 111.60, 99.43, 59.09, 54.08, 17.75, 14.10. Anal. Calcd. $C_{14}H_{17}N_3O_3$ (%): C, 61.08; H, 6.22; N, 15.26. Found C, 60.83; H, 6.36; N, 15.43.

General procedure for preparing 6a-k and 7a-j

The appropriate aryliso(thio)cyanat or sulfonylisocyanate (2.2 mmol) was added to a solution of **5** (2 mmol) in anhydrous THF (5 mL). The reaction mixture was stirred at room temperature until completion of the reaction monitored by TLC. The solvent was removed under vacuum and the resulting precipitate was collected by filtration, washed with diethyl ether, and dried. The product was recrystallized with acetone/water.

Ethyl 4-(4-{[(4-cyanophenyl)carbamothioyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6a)

White powder (61%). mp 196-196.5°C. IR (KBr, νcm^{-1}): 3425, 3394, 3249, 3104, 2970, 1701, 1639, 1595, 1520, 1427, 1232. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.03 (s,1H, 1NH), 10.01 (s,

1H, 1NH), 9.21 (s, 1H, 1NH), 8.00 (s, 1H, 1NH), 7.76 (m, 2H, CHarom), 7.56 (m, 2H, CH_{arom}), 7.40 (d, 2H, CH_{arom}, J=8.51 Hz), 7.20 (d, 2H, CH_{arom}, J=8.51 Hz), 5.13 (d, 1H, CH, *J*=3.15 Hz), 3.99 (q, 2H, $\underline{CH_2}CH_3$, J=7.09 Hz), 2.25 (s, 3H, CH_3), 1.13 (t, 3H, CH_3 J= 7.5Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.73, 165.33, 152.14, 148.43, 141.27, 140.53, 138.06, 129.68, 126.65, 126.43, 123.83, 118.62, 110.98, 99.18, 59.24, 53.39, 17.80, 14.11. Anal. Calcd. $C_{22}H_{21}N_5O_3S$ (%): C, 60.67; H, 4.86; N, 16.08; S, 7.36. Found C, 60.22; H, 4.90; N, 15.86; S, 7.25.

Ethyl 4-(4-{[(3-cyanophenyl)carbamothioyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6b)

White powder (76%). mp 143.5-144.5°C. IR (KBr, νcm^{-1}): 3362, 3234, 3145, 3106, 2919, 1688, 1649, 1600, 1540, 1552, 1476, 1235. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.11 (s,1H, 1NH), 9.99 (s, 1H, 1NH), 9.20 (s, 1H, 1NH), 8.01 (s, 1H, 1NH), 7.77 (d, 2H, CH_{arom}, J=7.57 Hz), 7.61-7.48 (m, 2H, CH_{arom}), 7.43 (d, 1H, CH_{arom}), 7.34-7.28 (m, 2H, CH_{arom}), 7.04 (d, 1H, CH_{arom}, J=7.57 Hz), 5.14 (d, 1H,CH, *J*=3.15 Hz), 3.99 (q, 2H, CH_2, J = 7.09Hz), 2.24 (s, 3H, CH_3), 1.12 (t, 3H, CH_3, J=7.09 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.27, 152.10, 148.51, 145.34, 140.49, 139.13, 129.68, 128.43, 128.23, 127.67, 125.69, 122.58, 121.07, 118.62, 110.98, 99.00, 59.25, 53.63, 17.79, 14.10. Anal. Calcd. $C_{22}H_{21}N_5O_3S$ (%): C, 60.67; H, 4.86; N, 16.08, S, 7.36. Found C, 60.30; H, 5.01; N, 15.27; S, 6.98.

Ethyl 4-(4-{[(4-fluorophenyl)carbamothioyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6c)

White powder (67%). mp 148.5-150°C. IR (KBr, νcm^{-1}): 3433, 3265, 3226, 3118, 2970, 2870, 1699, 1640, 1552, 1453, 1413, 1225, 810. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.76 (s,1H, 1NH), 9.75 (s, 1H, 1NH), 9.20 (s, 1H, 1NH), 7.75 (s, 1H, 1NH), 7.46-7.39 (m, 4H, CH_{arom}), 7.19-7.14 (m, 4H, CH_{arom}), 5.12 (d, 1H,CH, *J*=3.47 Hz), 3.99 (q,2H, CH_2, J=7.09 Hz), 2.25 (s, 3H, CH3),

1.12 (t, 3H, CH_3, J=7.09 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.92, 165.34, 160.07, 158.14, 152.37, 140.93, 138.39, 135.75, 126.31, 123.65, 119.08, 114.90, 99.21, 59.14, 53.14, 17.79, 14.11. Anal. Calcd. $C_{21}H_{21}FN_4O_3S$ (%): C, 58.86; H, 4.94; N, 13.08; S, 7.48. Found C, 58.79; H, 5.16; N, 12.63; S, 6.69.

Ethyl 6-methyl-4-(4-{[(4-chlorophenyl)carbamothioyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6d)

White powder (88%). mp 144.5-145.5 °C. IR (KBr, νcm^{-1}): 3396, 3252, 3106, 2969, 2870, 1697, 1638, 1521, 1452, 1227 , 826. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.86 (s,1H, 1NH), 9.85 (s, 1H, 1NH), 9.20 (s, 1H, 1NH), 7.74 (s, 1H, 1NH), 7.51 (d, 2H, CH_{arom}, J=8.51 Hz), 7.42-7.35 (m, 4H, CH_{arom}), 7.19 (d, 2H, CH_{arom}, J=8.51 Hz), 5.12 (d, 1H,CH, *J*=3.15 Hz), 4.00 (q, 2H, CH_2, J=7.09 Hz), 2.25 (s, 3H, CH_3), 1.12 (t, 3H, CH_3, J=7.09 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 179.59, 165.33, 152.14, 148.38, 141.00, 138.49, 138.31, 128.45, 128.15, 126.32, 125.19, 123.67, 99.18, 59.22, 53.40, 17.79, 14.10. Anal. Calcd. $C_{21}H_{21}ClN_4O_3S$ (%): C, 56.69; H, 4.76; N, 12.59; S, 7.21. Found C, 57.25; H, 5.18; N, 11.97; S, 6.54.

Ethyl 4-(4-{[(4-methylphenyl)carbamothioyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6e)

White powder (78%). mp 157-159°C. IR (KBr, νcm^{-1}): 3462, 3410, 3266, 3110, 2985, 2935, 1687, 1635, 1600, 1538, 1445, 1400, 1230. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.70 (s,1H, 1NH), 9.66 (s, 1H, 1NH), 9.19 (s, 1H, 1NH), 7.74 (brs, 1H, 1NH), 7.40 (d, 2H, CH_{arom}, J=8.20 Hz), 7.33 (d, 2H, CH_{arom}, J=8.20 Hz), 7.18-7.11 (m, 4H, CH_{arom}), 5.12 (d, 1H,CH, *J*=3.15 Hz), 4.00 (q, 2H, CH_2, J=7.09 Hz), 2.27 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 1.12 (t, 3H, CH_3, J=7.09 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.53, 165.34, 152.15, 148.33, 140.78, 138.56, 136.76, 133.64, 128.87,

126.22, 123.83, 123.64, 99.22, 59.22, 53.42, 20.49, 17.79, 14.11. Anal. Calcd. $C_{22}H_{24}N_4O_3S$ (%): C, 62.27; H, 5.70; N, 13.20; S, 7.55. Found C, 61.97; H, 5.73; N, 12.97; S, 6.92.

Ethyl 4-(4-{[(2-methoxylphenyl)carbamoyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6f)

White powder (82%). mp 250.5-252.5°C. IR (KBr, νcm^{-1}): 3515, 3465, 3308, 3120, 2973, 2835, 1704, 1654, 1605, 1545, 1516, 1457, 1227. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.31 (s,1H, 1NH), 9.16 (s, 1H, 1NH), 8.22 (s, 1H, 1NH), 8.12 (d, 1H, CH_{arom}, J=7.25 Hz), 7.68 (brs, 1H, 1NH), 7.38 (d, 2H, CH_{arom}, J=8.51 Hz), 7.14 (d, 2H, CH_{arom}, J=8.51 Hz), 7.01 (d, 1H, CH_{arom}, J=7.57 Hz), 6.97-6.83 (m, 2H, CH_{arom}), 5.08 (d, 1H,CH, *J*=2.52 Hz), 3.99 (q, 2H, CH_2, J=7.04Hz), 3.87 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 1.11 (t, 3H, CH_3, J=7.04Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.36, 152.23, 152.11, 148.05, 147.56, 138.88, 138.28, 128.88, 128.64, 126.76, 121.72, 120.52, 117.86, 110.67, 99.40, 59.14, 55.73, 53.49, 17.76, 14.11. Anal. Calcd. $C_{22}H_{24}N_4O_5$ (%): C, 62.25; H, 5.70; N, 13.20. Found C, 61.64; H, 6.14; N, 12.54.

Ethyl 4-(4-{[(4-methoxylphenyl)carbamoyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6g)

White powder (95%). mp 167-169°C. IR (KBr, νcm^{-1}): 3505, 3330, 3234, 3116, 2978, 2929, 1699, 1650, 1600, 1550, 1512, 1452, 1226. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (s,1H, 1NH), 8.56 (s, 1H, 1NH), 8.43 (s, 1H, 1NH), 7.68 (s, 1H, 1NH), 7.38-7.31 (m, 4H, CH_{arom}), 7.12 (d, 2H, CH_{arom}, J=8.83 Hz), 6.88-6.83 (m, 2H, CH_{arom}), 5.08 (brs, 1H,CH, *J*=3.15 Hz), 3.99 (q,2H, CH_2, J=7.15Hz), 2.24 (s, 3H, CH_3), 1.11 (t, 3H, CH_3, J=7.15Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.36, 154.40, 152.65, 152.11, 148.03, 138.93, 138.16, 132.67, 126.67, 119.92, 118.03, 113.94, 99.41, 59.14, 55.13, 53.47, 17.75, 14.10. Anal. Calcd. $C_{22}H_{24}N_4O_5$ (%): C, 62.25; H, 5.70; N, 13.20; Found: C, 61.61; H, 6.12; N, 12.57.

Ethyl 4-(4-{[(4-chlorophenyl)carbamoyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6h)

White powder (91%). mp 229-230°C. IR (KBr, νcm^{-1}): 3418, 3330, 3260, 3132, 2985, 2935, 1709, 1640, 1600, 1551, 1491, 1443, 1216, 830. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.17 (brs, 1H,NH), 8.78 (s, 1H,NH), 8.69 (s, 1H,NH), 7.69 (s, 1H,NH), 7.47 (d, 2H, CH$_{arom}$, J=8.83 Hz), 7.37 (d, 2H, CH$_{arom}$, J=8.51 Hz),7.32 (d, 2H, CH$_{arom}$, J=8.83 Hz), 7.14 (d, 2H, CH$_{arom}$, J=8.51 Hz), 5.09 (d, 1H,CH, *J*=3.15 Hz), 3.99 (q, 2H, CH$_2$, J = 7.09 Hz), 2.24 (s, 3H, CH$_3$), 1.11 (t, 3H, CH3 J = 7.09Hz). ^{13}C NMR (125 MHz, DMSO-d$_6$) δ: 165.35, 152.36, 152.10, 148.08, 138.68, 138.54, 128.59, 126.71, 125.24, 119.63, 118.28, 99.36, 59.14, 53.47, 17.75, 14.10. Anal. Calcd. $C_{21}H_{21}ClN_4O_4$ (%): C, 58.81; H, 4.94; N, 13.06. Found. C, 58.76; H, 5.03; N, 12.96.

Ethyl 4-(4-{[(4-fluorophenyl)carbamoyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6i)

White powder (68%). mp 209-211°C. IR (KBr, νcm^{-1}): 3348, 3380, 3310, 3100, 2925, 2872, 1699, 1650, 1600, 1560, 1511, 1435, 1236, 690. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.16 (br.s,1H, 1NH), 8.68 (s, 1H, 1NH), 8.66 (s, 1H, 1NH), 7.68 (brs, 1H, 1NH), 7.44-7.37 (m, 4H, CH$_{arom}$), 7.14-7.09 (m, 4H, CH$_{arom}$), 5.08 (brs, 1H,CH), 3.99 (q,2H, CH$_2$, J=6.62 Hz), 2.24 (s, 3H, CH$_3$), 1.11 (t, 3H, CH$_3$, J= 6.62 Hz). ^{13}C NMR (125 MHz, DMSO-d$_6$) δ: 165.33, 152.54, 152.09, 148.04, 138.69, 138.37, 135.98, 126.67, 119.87, 118.18, 115.31, 115.14, 99.36, 59.12, 53.46, 17.74, 14.08. Anal. Calcd. $C_{21}H_{21}FN_4O_4$ (%): C, 61.12; H, 5.13; N, 13.58. Found C, 60.88; H, 5.28; N, 13.25.

Ethyl 4-(4-{[(2-nitrophenyl)carbamoyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6j)

Yellow powder (68%). mp 261-262°C. IR (KBr, νcm^{-1}): 3326, 3297, 3247, 3120, 2970, 2922, 1682, 1613, 1544, 1495, 1426, 1337 , 1258, 1229. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.84 (s,1H, 1NH), 9.58 (s, 1H, 1NH), 9.16-9.18 (m, 1H, CH_{arom}), 8.30 (m, 1H, CH_{arom}), 8.09 (dd, 1H, CH_{arom}, J=8.35, 1.42 Hz), 7.70 (s, 2H, 2NH), 7.42 (d, 2H, CH_{arom}, J=8.51 Hz), 7.22-7.15 (m, 3H, CH_{arom}), 5.10 (d, 1H,CH, *J*=3.47 Hz) , 4.00 (q, 2H, CH_2, J = 7.09Hz), 3.73 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 1.11 (t, 3H, CH_3, J=7.09 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.33, 152.06, 151.76, 148.14, 139.06, 138.23, 137.56, 134.97, 134.89, 134.73, 126.94, 125.32, 122.72, 118.33, 99.30, 59.14, 53.54, 17.82, 14.08. Anal. Calcd. $C_{21}H_{21}N_5O_6$ (%): C, 57.40; H, 4.86; N, 15.94. Found C, 57.18; H, 4.87; N, 15.75.

Ethyl 6-methyl-4-[4-({[(4-methylphenyl)sulfonyl]carbamoyl}amino)phenyl]-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (6k)

White powder (83%). mp 201-203°C.IR (KBr, νcm^{-1}): 3505, 3347, 3239, 3110, 2983, 2915, 1705, 1676, 1656, 1528, 1460, 1223. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.15 (brs,1H, 1NH), 8.82 (s, 1H, 1NH), 7.84 (d, 2H, CH_{arom}, J=7.88 Hz), 7.67 (s, 1H, 1NH), 7.42 (d, 2H, CH_{arom}, J=7.88 Hz), 7.26 (d, 2H, CH_{arom}, J=8.51 Hz), 7.11 (d, 2H, CH_{arom}, J=8.51 Hz), 5.06 (d, 1H,CH, J=2.84Hz), 3.95 (q, 2H, CH_2, J=6.94 Hz), 2.38 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 1.08 (t, 3H, CH_3, J=6.94 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 165.25, 152.00, 149.24, 148.16, 143.80, 139.80, 137.01, 129.44, 127.44, 126.71, 125.58, 118.97, 99.19, 59.12, 53.43, 21.02, 17.71, 14.06. Anal. Calcd. $C_{22}H_{24}N_4O_6S$ (%): C, 55.92; H, 5.12; N, 11.92; S, 6.79. Found C, 55.25; H, 5.18; N, 11.79; S, 6.54.

Ethyl 4-(3-{[(4-cyanophenyl)carbamothioyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7a)

White powder (61%). mp 189-190°C. IR (KBr, νcm^{-1}): 3362, 3255, 3225, 3127, 2940, 1695, 1644, 1545, 1516, 1447, 1230, 768. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.11 (s,1H, 1NH), 9.99 (s, 1H, 1NH), 9.20 (s, 1H, 1NH), 8.01 (s, 1H, 1NH), 7.79-7.70 (m, 2H, CH_{arom}), 7.58-7.50 (m, 2H, CH_{arom}), 7.43 (d, 1H, CH_{arom}, J=7.88 Hz), 7.34-7.28 (m, 2H, CH_{arom}), 7.04 (d, 1H, CH_{arom}, J=7.57 Hz), 5.14 (brs, 1H,CH, *J*=3.15 Hz), 4.00 (q,2H, CH_2, J = 7.09Hz), 2.24 (s, 3H, CH_3), 1.12 (t, 3H, CH_3, J=7.09 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.57, 165.27, 152.10, 148.51, 145.34, 140.49, 139.13, 129.68, 128.43, 127.67, 126.35, 122.69, 121.07,118.62, 110.98, 99.21, 59.19, 53.98, 17.77, 14.07. Anal. Calcd. $C_{22}H_{21}N_5O_3$ S (%): C, 60.67; H, 4.86; N, 16.08; S, 7.36. Found C, 60.43; H, 4.96; N, 15.81; S; 7.09.

Ethyl 4-(3-{[(3-cyanophenyl)carbamothioyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7b)

White powder (74%). mp 152-153°C. IR (KBr, νcm^{-1}): 3305, 3266, 3128, 2980, 1710, 1641, 1563, 1504, 1445, 1228. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.11 (br.s,1H, 1NH), 9.98 (brs, 1H, 1NH), 9.21 (br.s, 1H, 1NH), 8.01 (brs, 1H, 1NH), 7.78-7.76 (s, 2H, CH_{arom}), 7.64-7.48 (m, 2H, CH_{arom}), 7.43 (d, 1H, CH_{arom}, J=6.94 Hz), 7.20-7.38 (m, 2H, CH_{arom}), 7.04 (d, 1H, CH_{arom}, J=6.94 Hz), 5.14 (s, 1H,CH), 3.99 (q,2H, CH_2, J=6.46 Hz), 2.24 (s, 3H, CH_3), 1.12 (t, 3H, CH_3, J=6.46 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.57, 165.28, 152.11, 148.51, 145.35, 140.39, 139.14, 129.69, 128.44, 128.25, 127.67, 126.37 ,122.70, 122.59, 121.08, 118.63, 110.98, 99.01, 59.23, 53.69, 17.79, 14.11. Anal. Calcd. $C_{22}H_{21}N_5O_3$ S (%): C, 60.67; H, 4.86; N, 16.08; S, 7.36. Found C, 60.37; H, 4.90; N, 15.75; S; 7.28.

Ethyl 4-(3-{[(4-methylphenyl)carbamothioyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7c)

White powder (91%). mp 135-136°C. IR (KBr, νcm^{-1}): 3478, 3405, 3365, 3249, 3104, 2975, 1701, 1650, 1556, 1484, 1453, 1221. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.73 (s,1H, 1NH), 9.65 (s, 1H, 1NH), 9.19 (s, 1H, 1NH), 7.75 (s, 1H, 1NH), 7.44 (d, 2H, CH_{arom}, J=8.20 Hz), 7.33-7.32 (m, 3H, CH_{arom}), 7.26 (t, 1H, CH_{arom}, J=7.88 Hz), 7.13 (d, 2H, CH_{arom}, J=8.20 Hz), 7.00 (d, 1H, CH_{arom}, J=7.57 Hz), 5.13 (d, 1H,CH, J= 3.47Hz), 4.00 (q, 2H, CH_2, J = 7.09Hz), 2.25 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 1.12 (t, 3H, CH3, J=7.09 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.41, 165.30, 152.11, 148.45, 145.16, 139.61, 136.77, 133.60, 128.85, 128.22, 123.76, 122.42, 122.20, 120.93, 99.05, 59.23, 53.71, 20.50, 17.80, 14.10. Anal. Calcd. $C_{22}H_{24}N_4O_3S$ (%): C, 62.24; H, 5.70; N, 13.20; S, 7.55. Found C, 62.57; H, 5.08; N, 12.74; S, 7.10.

Ethyl 4-(3-{[(4-fluorophenyl)carbamothioyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7d)

White powder (60%). mp 139.5-141.5°C. IR (KBr, νcm^{-1}): 3362, 3255, 3225, 3127, 2940, 1695, 1644, 1545, 1516, 1447, 1230, 768. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.83 (s,1H, 1NH), 9.70 (s, 1H, 1NH), 9.19 (s, 1H, 1NH), 7.75 (brs, 1H, 1NH), 7.48-7.41 (m, 3H, CH_{arom}), 7.33 (s, 1H, CH_{arom}), 7.27 (t, 1H, CH_{arom}, 7.72 Hz), 7.22-7.13 (m, 2H, CH_{arom}), 7.01 (d, 1H, CH_{arom}, J=7.57 Hz), 5.13 (d, 1H, CH, J=3.94 Hz), 3.99 (q, 2H, CH_2, J = 7.09Hz), 2.24 (s, 3H, CH_3), 1.11 (t, 3H, CH_3, J=7.09 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.79, 165.30, 160.03, 158.11, 152.11, 145.22, 139.45, 135.73, 128.31, 126.11, 122.36, 120.98, 115.07, 114.90, 99.04, 59.24, 53.24, 17.80, 14.11. Anal. Calcd.$C_{21}H_{21}FN_4O_3S$ (%): C, 58.86; H, 4.94; N, 13.08; S, 7.48. Found C, 58.68; H, 5.13; N, 12.67; S, 7.45.

Ethyl 4-(3-{[(2-methoxyphenyl)carbamoyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7e)

White powder (80%). mp 150-152°C. IR (KBr, νcm^{-1}): 3397, 3348, 3270, 3110, 2965, 1704, 1655, 1605, 1547, 1487, 1448, 1240. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.82 (s,1H, 1NH), 9.74 (s, 1H, 1NH), 9.19 (s, 1H, 1NH), 7.75 (brs, 1H, 1NH), 7.44 (s, 1H, CH_{arom}, J=8.20 Hz), 7.34 (s, 1H, CH_{arom}), 7.31-7.16 (m, 3H, CH_{arom}), 7.01 (t, 1H, CH_{arom}, J=6.78 Hz), 6.70 (dd, 1H, CH_{arom}, J=8.20, 1.89 Hz), 5.13 (d, 1H,CH, J=3.15 Hz) , 4.00 (q, 2H, CH_2, J = 7.09Hz), 3.73 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 1.12 (t, 3H, CH_3 J=7.09 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.19, 165.30, 159.22, 152.27, 152.09, 148.47, 145.20, 140.54, 139.51, 129.05, 128.40, 122.56, 120.93, 115.57, 109.73, 109.05, 99.05, 59.23, 54.84, 53.54, 17.65, 13.92. Anal. Calcd. $C_{22}H_{24}N_4O_4$ (%): C, 62.25; H, 5.70; N, 13.20. Found C, 61.98; H, 5.79; N, 13.05.

Ethyl 4-(3-{[(4-methoxylphenyl)carbamoyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7f)

White powder (87%). mp 154.5-156°C. IR (KBr, νcm^{-1}): 3330, 3282, 3233, 3135, 2977, 2829, 1688, 1639, 1610, 1560, 1510, 1442, 1225. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (s,1H, 1NH), 8.60 (s, 1H, 1NH), 8.39 (s, 1H, 1NH), 7.73 (brs, 1H, 1NH), 7.41-7.30 (m, 3H, CH_{arom}), 7.27 (s, 1H, CH_{arom}), 7.20 (t, 1H, CH_{arom}, J=7.88 Hz), 6.75-6.90 (m, 3H, CH_{arom}), 5.10 (d, 1H,CH, *J*=3.15 Hz), 4.00 (q,2H, CH_2, J = 7.25Hz), 2.24 (s, 3H, CH_3), 1.13 (t, 3H, CH_3, J=7.25 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.33, 154.41, 152.60, 152.09, 148.19, 145.52, 139.94, 132.66, 128.74, 119.91, 119.61, 116.86, 115.80, 113.96, 99.24, 59.19, 55.13, 53.99, 17.78, 14.08. Anal. Calcd. $C_{22}H_{24}N_4O_5$ (%): C, 62.25; H, 5.70; N, 13.20. Found C, 61.89; H, 5.69; N, 12.75.

Ethyl 4-(4-{[(4-chlorophenyl)carbamoyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7g)

White powder (90%). mp 203-204.5°C. IR (KBr, νcm^{-1}): 3395, 3315, 3235, 3110, 2980, 2940, 1691, 1655, 1600, 1550, 1490, 1430, 1230, 750. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.20 (s,1H,

1NH), 8.73 (s, 2H, 2NH), 7.73 (brs, 1H, NH), 7.47 (d, 2H, CH_{arom}, J=8.83 Hz), 7.40 (d, 1H, CH_{arom}, J=8.83 Hz), 7.31 (m, 3H, CH_{arom}), 7.22 (t, 1H, CH_{arom}, J=7.72 Hz), 7.22 (d, 1H, CH_{arom}, J=8.83 Hz), 5.11 (d, 1H, CH, *J*=3.15 Hz), 4.00 (q,2H, CH_2, J=7.25 Hz), 2.25 (s, 3H, CH_3), 1.13 (t, 3H, CH_3, J=7.25 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.33, 152.30, 152.09, 148.23, 145.59, 139.57, 138.88, 129.05, 128.40, 125.26, 119.79, 119.31, 117.03, 115.90, 99.20, 59.20, 53.87, 17.65, 14.08. Anal. Calcd. $C_{21}H_{21}ClN_4O_4$ (%): C, 58.81; H, 4.94; N, 13.06. Found C, 58.78; H, 5.01; N, 12.98.

Ethyl 4-(3-{[(4-fluorophenyl)carbamoyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7h)

White powder (69%). mp 200-201.5°C. IR (KBr, νcm^{-1}): 3515, 3389, 3250, 3113, 2975, 2935, 1695, 1656, 1557, 1508, 1439, 1223, 790. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (s,1H, 1NH), 8.69 (s, 1H, 1NH), 8.62 (s, 1H, 1NH), 7.73 (brs, 1H, 1NH), 7.50-7.34 (m, 3H, CH_{arom}), 7.29 (s, 1H, CH_{arom}), 7.22 (t, 1H, CH_{arom}, J=7.88 Hz), 7.12 (d, 2H, CH_{arom}, J=8.83 Hz), 6.86 (d, 1H, CH_{arom}, J=7.25 Hz), 5.11 (d, 1H,CH, *J*=2.84 Hz), 4.00 (q, 2H, CH_2, J=7.15 Hz), 2.25 (s, 3H, CH_3), 1.13 (t, 3H, CH_3, J=7.15 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.33, 158.22, 152.49, 152.09, 148.20, 145.55, 139.71, 135.98, 128.76, 119.88, 119.81, 117.04, 115.94, 115.34, 115.17, 99.21, 59.19, 53.98, 17.77, 14.07. Anal. Calcd. $C_{21}H_{21}FN_4O_4$ (%): C, 61.12; H, 5.13; N, 13.58. Found C, 60.75; H, 5.08; N, 13.14.

Ethyl 4-(3-{[(2-nitrophenyl)carbamoyl]amino}phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7i)

Yellow powder(61%). mp 175.5-177°C. IR (KBr, νcm^{-1}): 3340, 3300, 3213, 3105, 2947, 1700, 1648, 1610, 1560, 1500, 1441, 1382, 1245. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.86 (s,1H, 1NH), 9.57 (s, 1H, 1NH), 9.20 (s, 1H, 1NH), 8.10 (dd, 1H, CH_{arom}, J=8.35, 1.42 Hz), 7.746-7.69 (m,

2H, CH_{arom}), 7.43-7.47 (m, 1H, CH_{arom}), 7.33 (s, 1H, 1NH), 7.27-7.19 (m, 3H, CH_{arom}), 6.91 (d, 1H, CH_{arom}, J=7.57), 5.12 (d, 1H,CH, 3.15 Hz) , 4.00 (q, 2H, CH_2, J = 7.15Hz), 2.25 (s, 3H, CH_3), 1.12 (t, 3H, CH_3, J=7.15 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.31, 152.02, 151.72, 148.22, 145.66, 139.26, 137.58, 135.06, 134.88, 128.73, 125.15, 122.72, 122.23, 120.44, 117.68, 116.55, 99.17, 59.21, 54.03, 17.65, 14.24. Anal. Calcd. $C_{21}H_{21}N_5O_6$ (%): C, 57.40; H, 4.82; N, 15.94. Found C, 57.09; H, 4.87; N, 15.68.

Ethyl 6-methyl-4-[3-({[(4-methylphenyl)sulfonyl]carbamoyl}amino)phenyl]-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7j)

White powder (83%). mp 199.5-200.5°C. IR (KBr, νcm^{-1}): 3285, 3255, 3235, 3107, 2979, 2930, 1690, 1631, 1552, 1493, 1444, 1227. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.62 (brs,1H, 1NH), 9.18(s, 1H, 1NH), 8.87(s, 1H, NH), 7.84 (d, 2H, CH_{arom}, J=8.20 Hz), 7.70(s, 1H, NH), 7.42 (d, 1H, CH_{arom}, J=8.20 Hz), 7.32 7.16 (m, 3H, CH_{arom}), 6.89 (d, 1H, CH_{arom}, J=7.25 Hz), 5.08 (d, 1H,CH, *J*=2.84 Hz) , 3.95 (q,2H, CH_2, J=7.09 Hz), 2.39 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 1.07 (t, 3H, CH_3, J=7.09 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.22, 151.99, 148.30, 145.61, 138.20, 131.59, 129.37, 128.82, 128.63, 127.41, 125.58, 120.87, 117.63, 116.76, 99.06, 59.16, 53.84, 21.02, 17.73, 14.00. Anal. Calcd. $C_{22}H_{24}N_4O_6S$ (%): C, 55.92; H, 5.12; N, 11.92; S, 6.79. Found C, 55.32; H, 5.25; N, 11.65; S, 6.33.

Biological assays

Measurement of the contraction of rat aorta rings

Diazoxide and nifedipine were tested as reference compounds. Experiments were performed, as previously described,[22-24] on the aorta, collected from adult female Wistar rats (230–240 g) purchased from Janvier Labs (Le Genest-Saint-Isle, France). After anaesthesia by intraperitoneal injection of pentobarbital (100 mg/kg, i.p.), a section of the thoracic aorta was cleared of adhering

fat and connective tissue, without damaging the endothelium, and cut into transverse rings (2-3mm long). The segments were suspended under 1.5 g tension by means of two steel hooks (one being connected to a tension transducer) in an organ bath containing 10 mL of a Krebs physiological solution of the following composition (in mM): NaCl 118, KCl 5.6, $CaCl_2$ 2.4, $NaHCO_3$ 25, KH_2PO_4 1.2, $MgCl_2$ 1.2, D-glucose 11, pH 7.4. The physiological solution was maintained at 37 °C, and was continuously bubbled with a mixture of O_2-CO_2 (95-5%). Isometric contractions of aortic rings were measured with a force-displacement transducer connected to a PowerLab/8S with Chart software (AD instruments, Paris, France) for recording and analysis. Rings initially stretched at 1.5 g were allowed to equilibrate for 60 min and the Krebs solution was replaced each 15 min. After this period, a final mechanical stretch of 1.5 g was applied to the rings for 15 min before starting the experiment. Aorta ring contraction was induced by replacing the bathing Krebs solution by a hyperpotassic physiological solution (30 or 80mM KCl). The integrity of endothelium layer was checked using 1mM acetycholine, which relaxes aorta rings when this layer is intact. After KCl-induced elevation, the ring tension stabilized and reached a plateau after 15 min, and the tested drugs diluted in dimethylsulfoxide (the maximum final concentration of DMSO <1% v/v) were added to the organ bath in a cumulative manner until maximal relaxation or up to 300 mM. Analogous experiment was performed in the presence of vehicle (same DMSO volume), as control. Some experiments were repeated in the continuous presence of 1 or 10 mM glibenclamide (K_{ATP} channel blocker) in the bathing medium. The stabilization of the organ response towards KCl, tested drugs and reference compounds, was obtained at least after 15 min, the time needed to obtain steady-state contraction or relaxation (plateau). The relaxation response was expressed as the percentage of decrease in the contractile response to KCl. The EC_{50} were calculated by non-linear regression analysis (GraphPad Prism 5 software). Data were expressed as mean ± SEM from 4 experiments (n).

5.2.3. Statistical evaluation

The statistical significance of differences between mean data was assessed by using the ANOVA. The biological results were considered statistically different when $p < .05$.

Supplementary material

^{1}H NMR and ^{13}C NMR data of synthesized compounds are available with the article through the journal Web site.

Acknowledgements

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Fig. 1. Some representative voltage-gated calcium channel blockers.

Fig. 2. Chemical structures of Batzelladine A and B, two natural substances isolated from marine plant.

Fig. 3. Dihydropyrimidinone analogues with HIV-1 replication inhibitory properties.

Fig. 4. General structures of target compounds (series **6** and **7**).

Fig. 5. Concentration-response curves for the myorelaxant effect of **6g** on induced contraction of rat aorta rings incubated in the presence of : Δ 30 mM KCl; ***** 30 mM KCl + 10mM glibenclamide; ■ 80 mM KCl. Data are expressed as mean ± SEM of (n) rat aorta rings.

Scheme 1. Synthetic route to 3,4-dihydropyrimidin-2 (1*H*)-one derivatives (**6a-k)** and (**7a-j**). Reagents: i) $Zn_{0.9}Ni_{0.1}Al_2O_4$ [20], EtOH, reflux, ii) 5% Pd/C, H_2 10 bars, anhydrous THF 65 C°, iii) RNCX (X = O or S, R = Ar or SO_2Ar), anhydrous THF.

Table 1. The effects of compounds **6a-k** and **7a-j** on the contractile activity of rat aorta rings.

[a] EC_{50}: drug concentration giving 50% relaxation of the 30 mM KCl-induced contraction of rat aorta rings (mean± SEM (n)). n refers to the number of samples.[b] Published results.[27]

Table 2. Myorelaxant effects of active compounds **6g** and nifedipine on 30 and 80 mM induced contraction of rat aorta rings incubated in the absence or the presence of 10 μM Glibenclamide [a].

[a] Results are expressed as (mean ± SEM (n)); n number in parentheses refers to the number of samples. ns: non-significant ($p>0.05$). **[b]** Published results. [27]

Table 1. The effects of compounds **6a-k** and **7a-j** on the contractile activity of rat aorta rings.

Compd.	X	R	EC_{50} (μM)[a] aortic rings	Compd.	X	R	EC_{50} (μM)[a] aortic rings
6a	**S**	**4-CNC$_6$H$_4$**	24.73± 2.86 (4)	**7a**	**S**	**4-CNC$_6$H$_4$**	49.54 ± 5.93 (4)
6b	**S**	**3-CNC$_6$H$_4$**	22.92 ± 2.97 (4)	**7b**	**S**	**3-CNC$_6$H$_4$**	27.64 ± 3.11 (4)
6c	**S**	**4-FC$_6$H$_4$**	42.66 ± 2.66 (4)	**7c**	**S**	**4-MeC$_6$H$_4$**	65.55 ± 4.24 (4)
6d	**S**	**4-ClC$_6$H$_4$**	79.26 ± 9.33 (4)	**7d**	**S**	**4-FC$_6$H$_4$**	63.23 ± 5.52 (4)
6e	**S**	**4-MeC$_6$H$_4$**	48.21 ± 2.00 (4)	**7e**	**O**	**2-OMeC$_6$H$_4$**	48.20 ± 3.70 (4)
6f	**O**	**2-OMeC$_6$H$_4$**	20.47 ± 1.43 (4)	**7f**	**O**	**4-OMeC$_6$H$_4$**	17.04 ± 1.43(4)
6g	**O**	**4-OMeC$_6$H$_4$**	0.983±0.061 (4)	**7g**	**O**	**4-ClC$_6$H$_4$**	11.96 ± 0.95 (4)
6h	**O**	**4-ClC$_6$H$_4$**	5.08 ± 0.36 (4)	**7h**	**O**	**4-FC$_6$H$_4$**	17.98 ± 1.40 (4)
6i	**O**	**4-FC$_6$H$_4$**	16.54 ± 1.03 (4)	**7i**	**O**	**2-NO$_2$C$_6$H$_4$**	38.49 ± 1.0 (4)
6j	**O**	**2-NO$_2$C$_6$H$_4$**	35.18 ± 1.04 (4)	**7j**	**O**	**4-MeC$_6$H$_4$SO$_2$**	> 150 (4)
6k	**O**	**4-MeC$_6$H$_4$SO$_2$**	> 150 (4)	**Nifedipine**	////	//////////////////	0.029 ± 0.002 (4)
Diaz	/////	//////////////	19.5 ± 2.7 (6)[b]	//////////////////	////	//////////////////	//////////////////

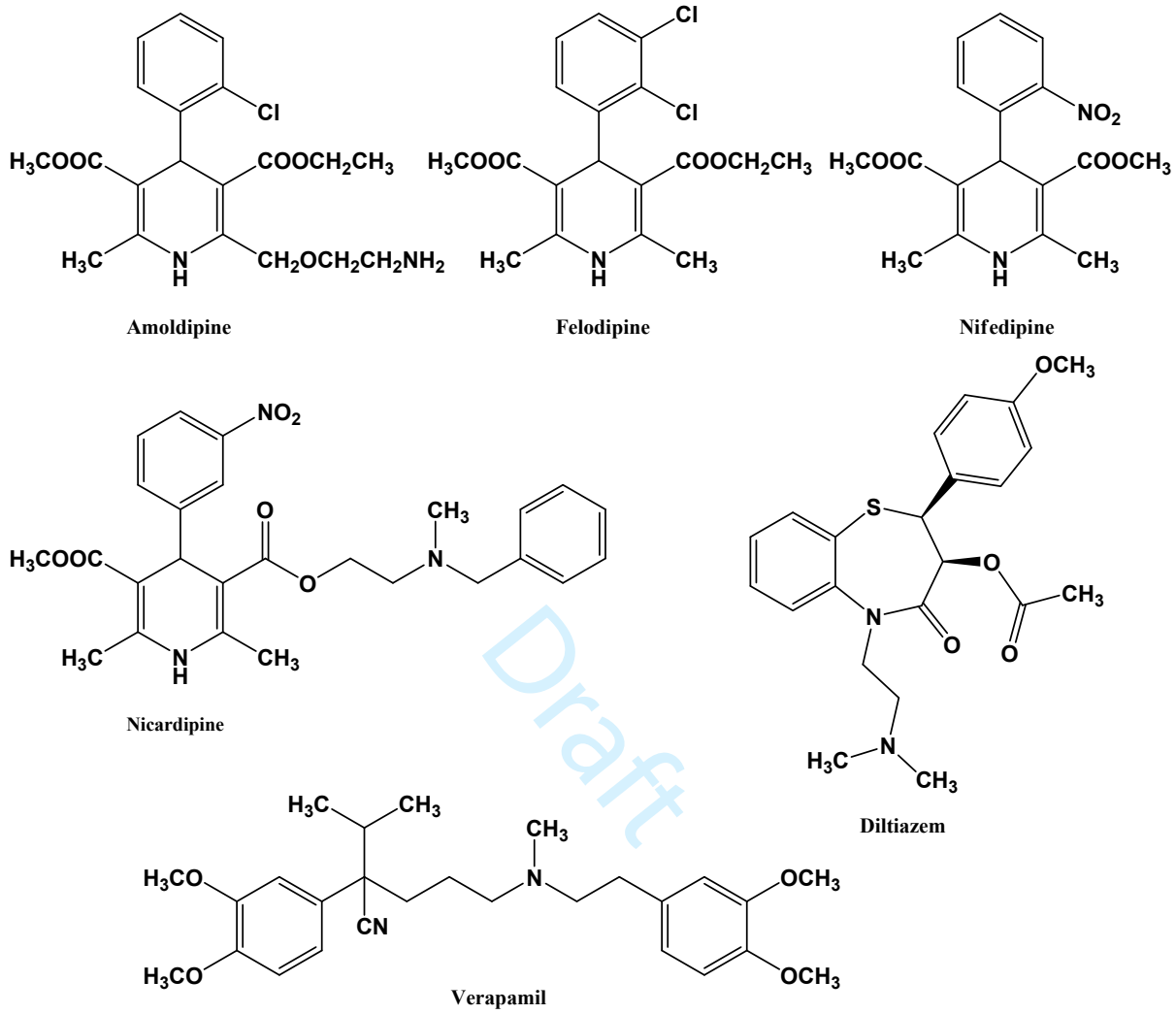
[a] EC_{50}: drug concentration giving 50% relaxation of the 30 mM KCl-induced contraction of rat aorta rings (mean± SEM (n)). n refers to the number of samples. [b] Published results.[27]

Table 2. Myorelaxant effects of active compounds **6g** and nifedipine on 30 and 80 mM induced contraction of rat aorta rings incubated in the absence or the presence of 10 µM Glibenclamide[a].

Compound	Myorelaxant activity 30 mM KCl EC_{50} (µM)		Myorelaxant activity 80 mM KCl EC_{50} (µM)
	0 µM Glib	10 µM Glib	-
6i	0.983 ± 0.061 (4)	1.096 ± 0.059[ns] (4)	1.184 ± 0.106[ns] (4)
Nifedipine	0.029 ± 0.002 (4)	0.031 ± 0.003[ns] (4)	0.040 ± 0.005[ns] (4)
Diazoxide	19.5 ± 2.7 (6)[b]	163.4 ± 41.2 (6)[b]	>300 (6)[b]

[a] Results are expressed as (mean ± SEM (n)); n number in parentheses refers to the number of samples. ns: non-significant ($p>0.05$). [b] Published results.[27]

Fig. 1. Some representative voltage-gated calcium channel blockers.



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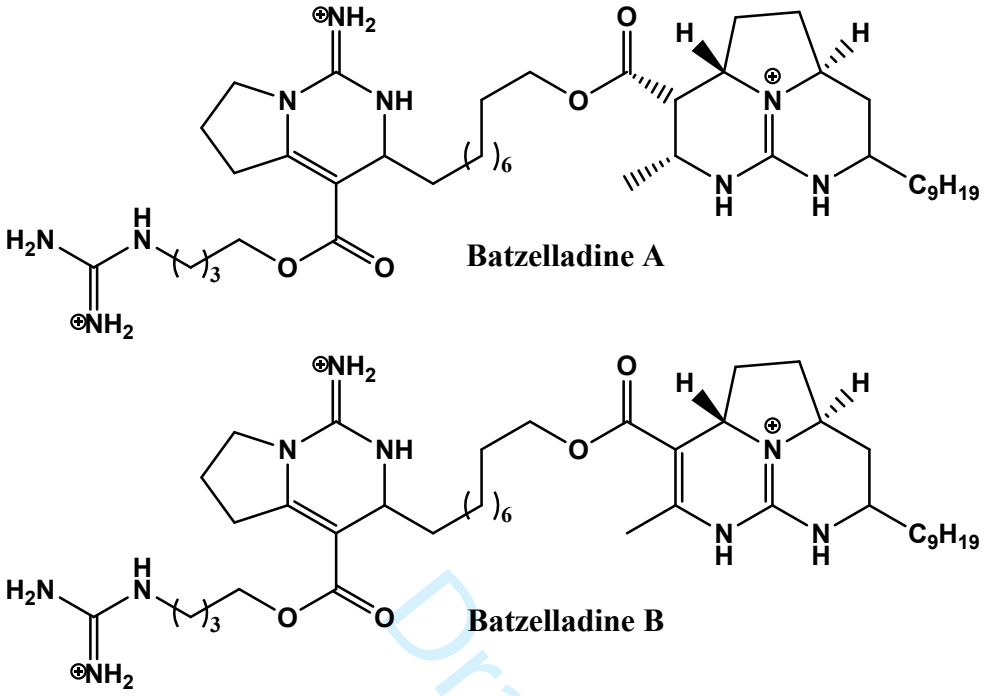

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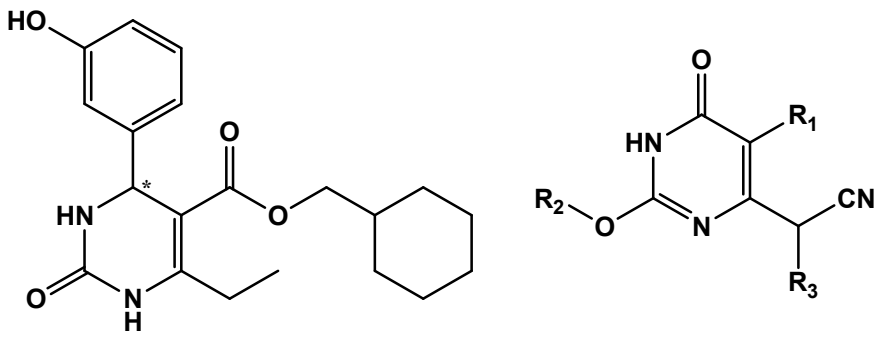
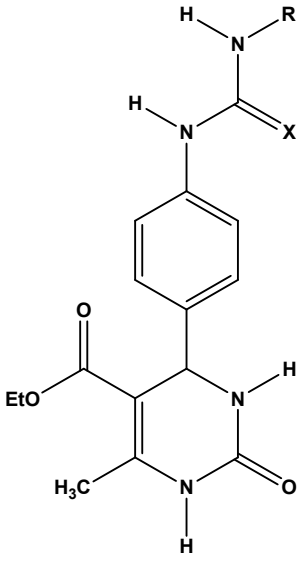
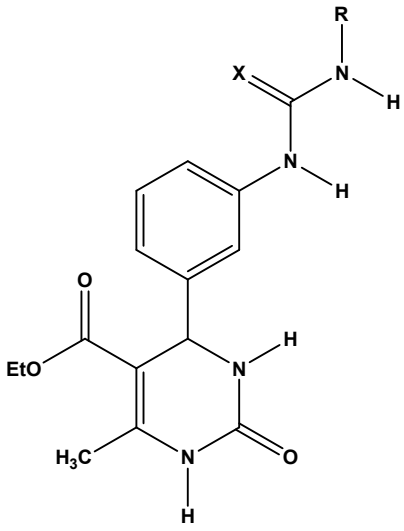


Fig. 4. General structures of target compounds (series **6** and **7**).



Series 6



Series 7

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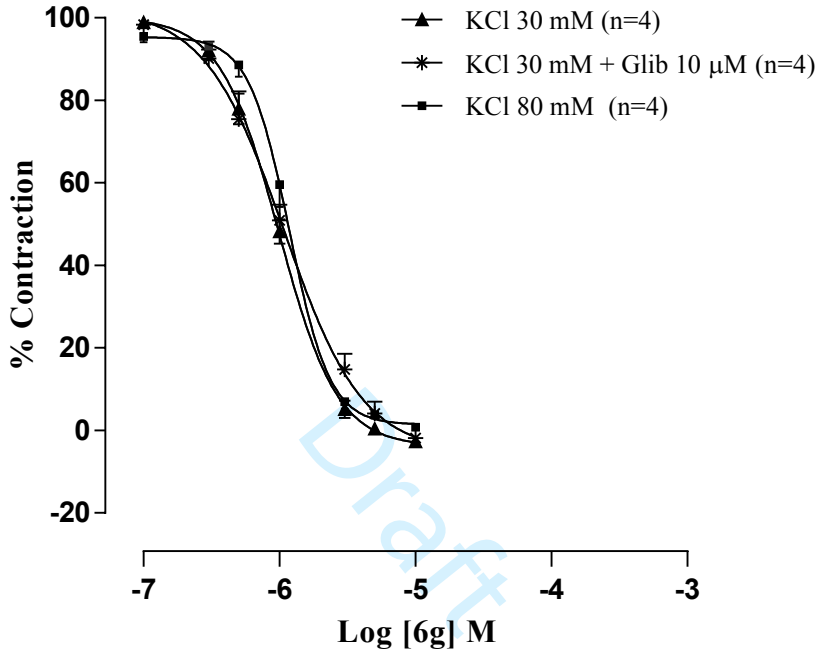

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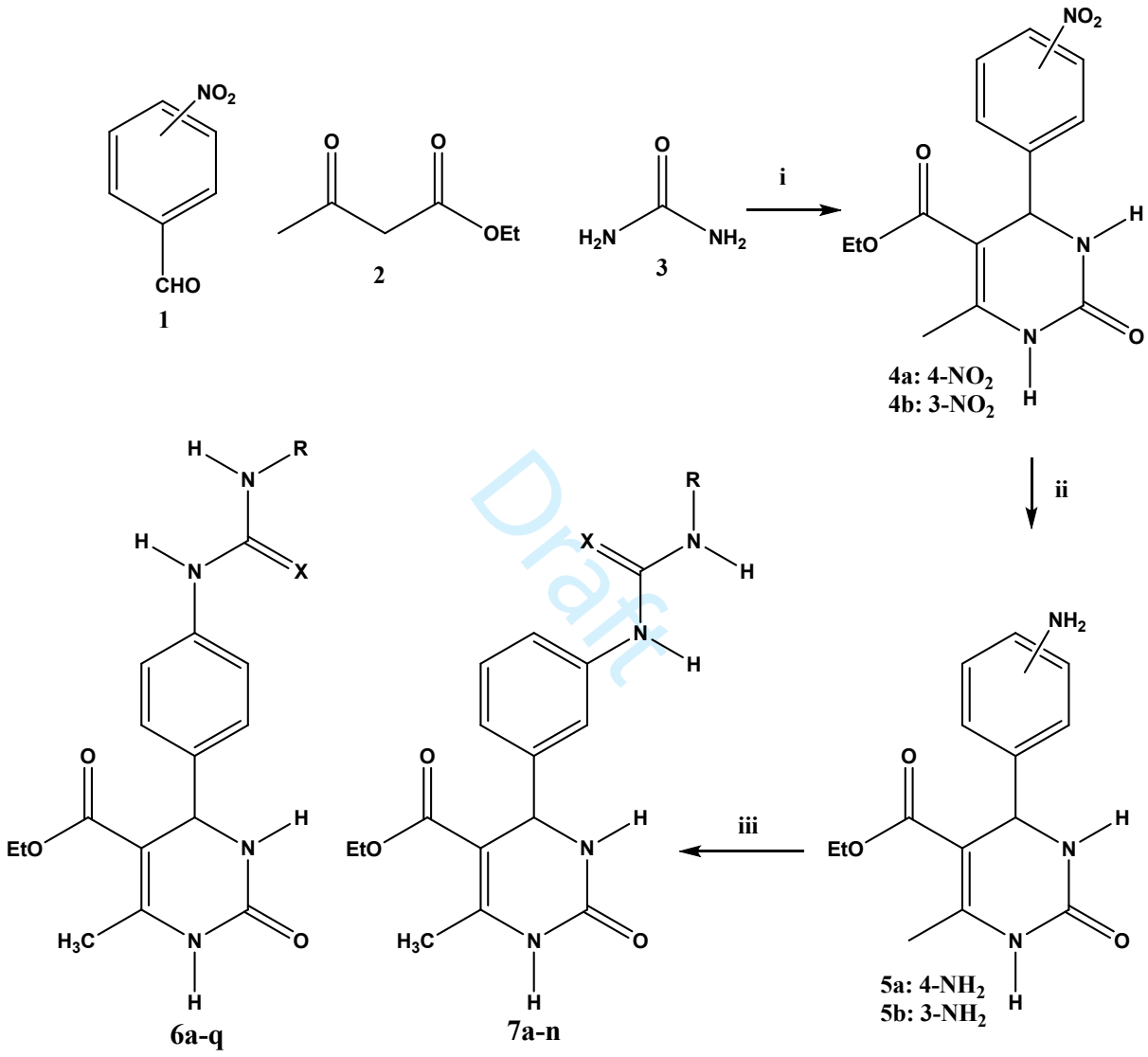

Synthesis and vasodilator activity of 3,4-dihydropyrimidin-2(1*H*)-ones bearing urea, thiourea and sulfonylurea moieties

Tahir Habila [1,2], Mebrouk Belghobsi [1], Mohamed-Zakaria Stiti [1,2], Eric Goffin [2], Pascal de Tullio[2], Gilles Faury [3], Bernard Pirotte [2] and Smail Khelili [1] *

Graphical Abstract