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Synthesis of some new C2 substituted dihydropyrimidines and their electrophysiological evaluation as L-/T-type calcium channel blockers

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ABSTRACT

Drugs targeting different calcium channel subtypes have strong therapeutic potential for future drug development for cardiovascular disorders, neuropsychiatric diseases and cancer. This study aims to design and synthesize a new series of C2 substituted dihydropyrimidines to mimic the structure features of third generation long acting dihydropyridine calcium channel blockers and dihydropyrimidines analogues. The target compounds have been evaluated as blockers for $Ca_V1.2$ and $Ca_V3.2$ utilizing the whole-cell patch clamp technique. Among the tested compounds, compound **7a** showed moderate calcium channel blockade activity against $Ca_V3.2$. Moreover, the predicted physicochemical properties and pharmacokinetic profiles of the target compounds recommend that they can be considered as drug-like candidates. The results highlight some significant information for the future design of lead compounds as calcium channel blockers.

1. Introduction

Recent studies showed that various calcium channel isoforms have been associated with many disorders ranging from cardiovascular and neuronal diseases [1,2] to cancer development and progression [3]. Hence, they are considered new attractive molecular targets for therapeutic intervention for such disorders. Within this approach, the design of selective calcium channel modulators is currently in progress. Over the last few years, many calcium channel blockers (CCBs) with varying channel isoform selectivity have been reported [4–8]. Among different CCBs, selective T-type (Ca_V3) blockers are emerging as non-traditional therapeutic avenues for different neuropsychiatric disorders such as Parkinson disease, epilepsy, pain, autism, anxiety and addiction [2,9]. Furthermore, there is a growing body of evidence that selective T-type calcium channel blockers can specifically affect calcium homeostasis and signaling in cancer cells, without harming normal tissues thus supporting normal cell proliferation, survival, and resistance to treatment [3]. This may provide new insights in cancer therapy especially in cases in which currently available treatments are limited due to serious side effects or resistance [10]. In cardiovascular system, T-type calcium channels upregulation triggers increased aldosterone secretion [11]. Clinical studies also reported that combined L- and T-types calcium channel blockade avoids cardio-renal injuries associated with traditional L-type CCBs [12]. Accordingly, T-type calcium channel modulation hold promise for better hypertension management [13,14] than traditional L-type CCBs which are still recommended by the 2018 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) Guidelines for the management of arterial hypertension [15].

Along these lines, diverse molecules targeting various calcium channel isoforms have been reported [4–8,16,17]. Structure activity relationships were studied to understand their respective activity and selectivity profiles. Among different CCBs, dihydropyridines (DHPs) are the best known class with well-established structure activity relationship data. Since the introduction of nifedipine [18]; the prototype DHP, the 1,4-DHP scaffold has been modified at almost every position introducing higher generations with improved potency, pharmacokinetic and safety profiles to the market [19–23]. Among various structural modifications, C2-substitution attracted considerable interest to confer optimized activity and desirable pharmacokinetics. Structure activity relationship studies of DHPs showed systematic modifications at C2 leading to the third generation long acting DHP CCB; amlodipine [20]

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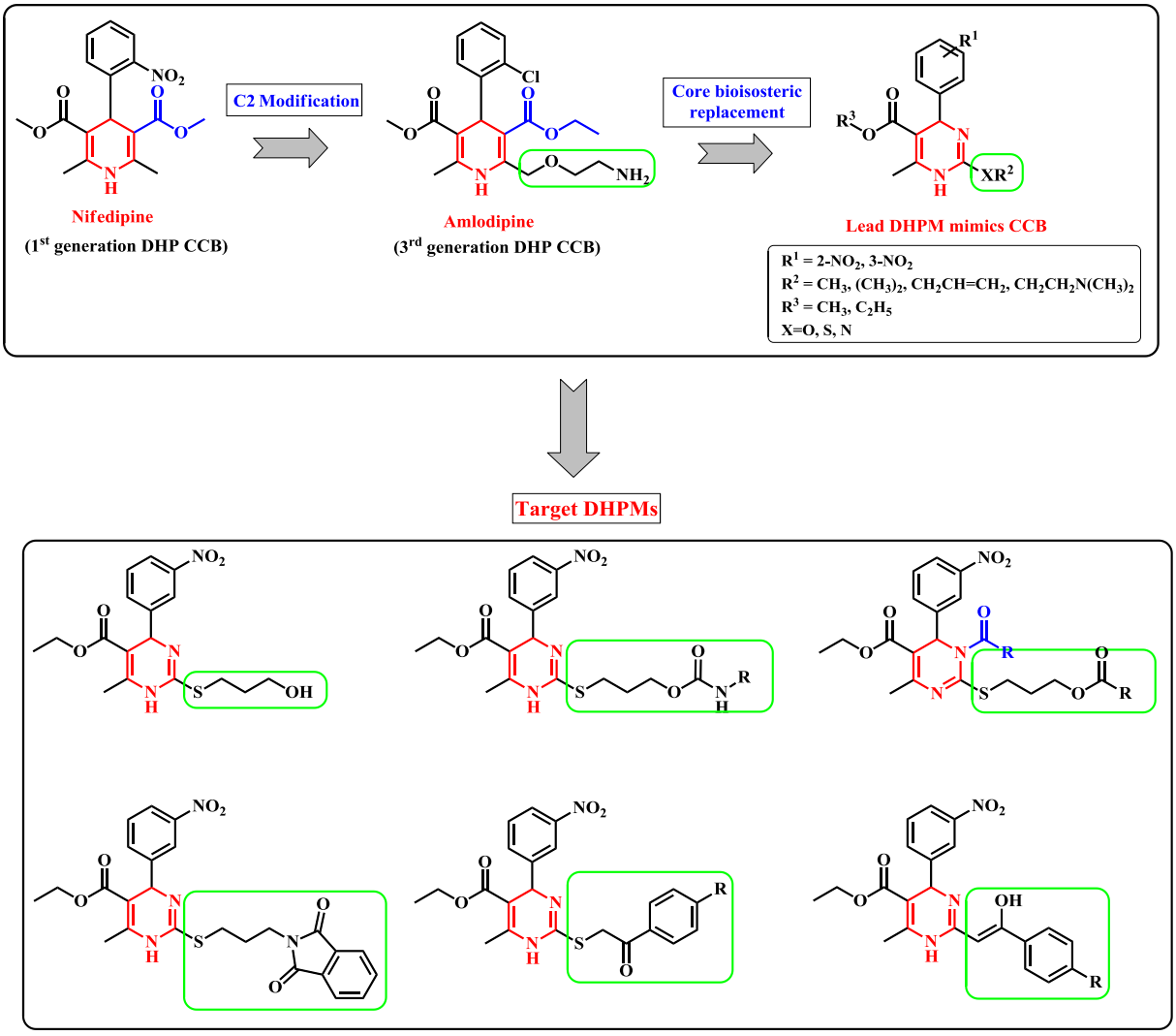


Fig. 1. DHPs in clinical use, lead C2 substituted DHPM mimics and target DHPMs.

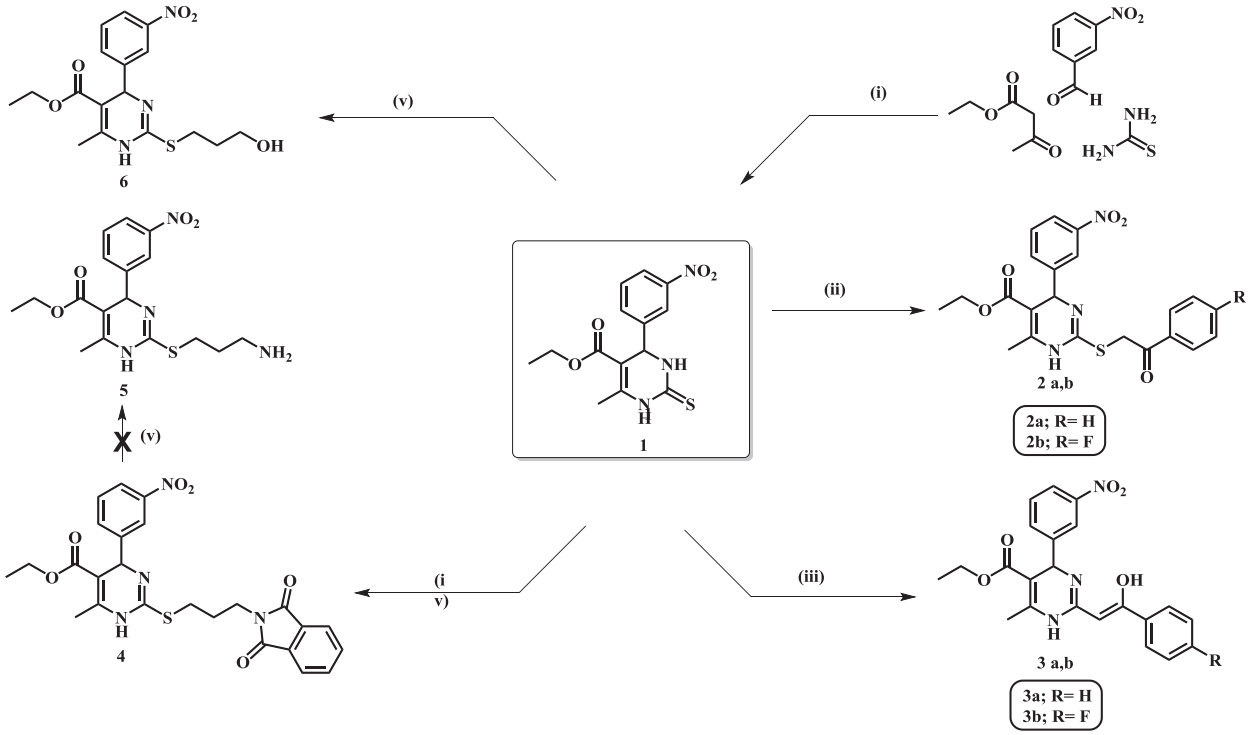
(Fig. 1). Furthermore, bioisosteric replacement of the dihydropyridine core leads to potent dihydropyrimidne (DHPM) mimics adopting similar molecular conformation [24]. This modification eventually paved the way for further exploration of more potent DHPM analogs. Numerous valuable reviews described the importance of DHPMs as CCBs [25–27] (Fig. 1).

In view of the above-mentioned findings, and as a continuation of our effort [6–8] to identify new potent calcium channel blockers, the current study aimed at designing and synthesizing DHPM derivatives with various functionalities at C2 linked to the DHPM core *via* variable spacer nature and size. Most of the synthesized compounds were evaluated as blockers for $Ca_V1.2$ and $Ca_V3.2$ by applying the whole-cell patch clamp technique.

2. Results and discussion

2.1. Chemistry

The synthetic strategies adopted for the synthesis of the intermediate and target compounds are depicted in Schemes 1 and 2. In Scheme 1, the 1,4-Dihydropyrimidinethione **1** was synthesized by multi-components one-pot Biginelli reaction of thiourea, 3-nitrobenzaldehyde and ethyl acetoacetate in boiling ethanol containing 37% HCl [28]. Conversion of the 2(3*H*)-thioxo derivative **1** to the corresponding 2-aroylmethylsulfanyl derivatives **2a, b** was achieved *via* stirring with phenacyl bromides in dry acetone at reflux temperature. IR spectra of **2a, b** showed new stretching absorption band for ketone C═O of the aroyl side chain. The 2-aryl-2-hydroxyvinyl derivatives **3a, b** were prepared according to the method reported by Eschenmoser which illustrated that the thione derivative **1** readily underwent sulfide contraction through selective alkylation of the C^2 sulfur with α-bromoketones followed by subsequent elimination of the bridged sulfur assisted by addition of a thiophilic agent (triphenylphosphine) to furnish the desired C═C coupled products **3a,b** [29]. IR spectra showed the expected OH stretching absorption band at 3314–3309 cm^{-1}, beside usual bands assigned for NH, ester C═O, C═N, NO_2 and C—O—C detected at their expected frequencies. Reaction of **1** with *N*-(3-bromopropyl)phthalimide under mild basic conditions afforded the corresponding 1,3-dioxoisoindolin-2-ylpropylsulfanyl derivative **4** in a good yield (75%). IR spectrum lacked the NHC═S stretching absorption bands characteristic for its precursor **1** and showed an additional C═O stretching absorption band at 1768 cm^{-1} corresponding to the isoindolinyl carbonyl groups. Attempts to prepare the free amino derivative **5** by cleavage of the phthalimido intermediate (4) with methylamine were unsuccessful [20]. Compound **1** was also alkylated under mild basic conditions with 3-bromopropanol to the corresponding 3-hydroxypropylsulfanyl derivative **6**. Structure of the obtained product was confirmed by spectral data. Its IR spectrum lacked the NHC═S stretching absorption bands originally present in its precursor **1** and showed a new OH stretching absorption band at 3150 cm^{-1}. ^1H NMR



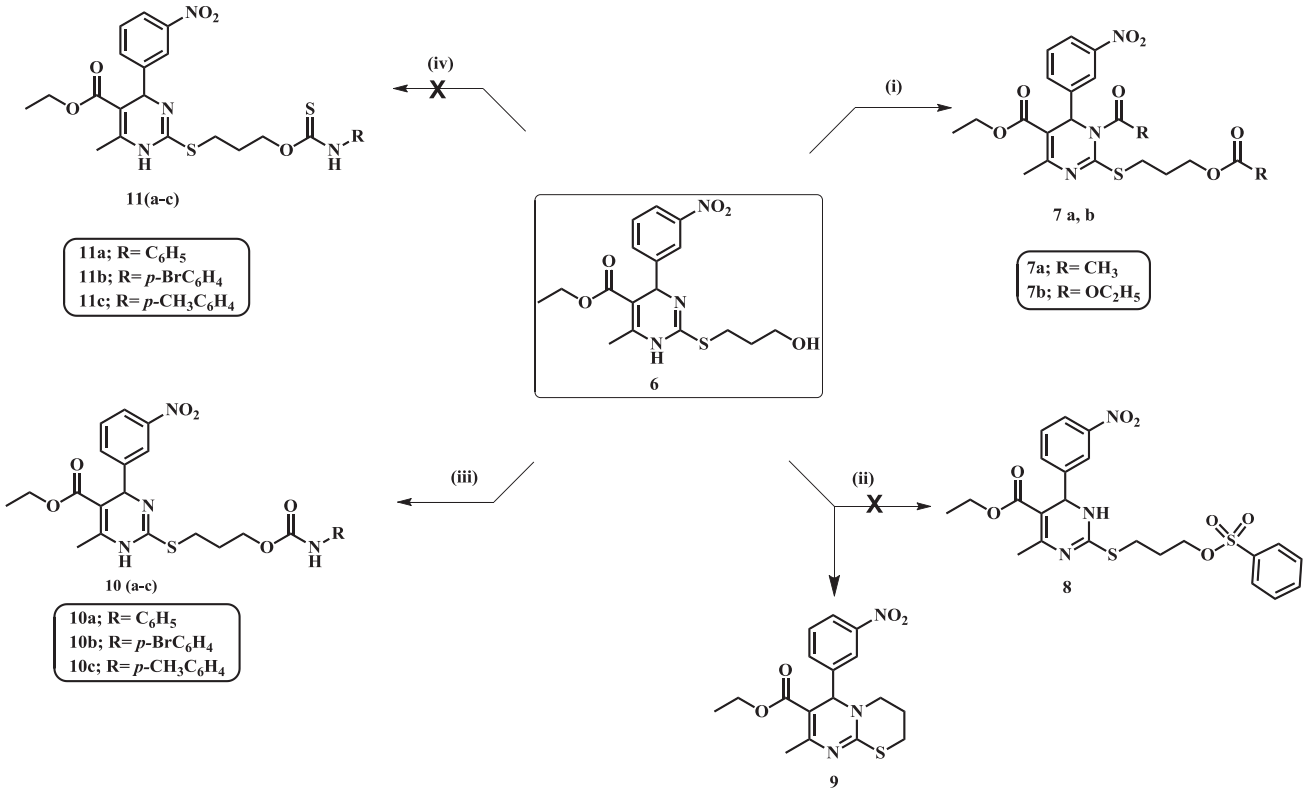
Scheme 1. Synthetic pathways for compounds 1–6. Reagents: (i) HCl, ethanol, reflux; (ii) appropriate phenacyl bromide, acetone, reflux; (iii) K_2CO_3, acetone, appropriate phenacyl bromide, stirring at R.T., then PPh_3, reflux; (iv) K_2CO_3, KI, *N*-(3-bromopropyl)phthalimide, reflux (v) methylamine; (vi) K_2CO_3, 3-Bromopropanol, reflux.

spectrum of **6** displayed two characteristic D_2O-exchangeable broad singlets assigned for OH and N—H at 4.93 and 6.97 ppm respectively.

In Scheme 2, Stirring a solution of the alcohol derivative **6** in anhydrous pyridine with acetyl chloride at room temperature afforded the corresponding acetyl derivative **7a** [30,31]. Carbonate **7b** was also synthesized by treating **6** with 1.2 equivalent of ethyl chloroformate under similar reaction conditions [32]. Structures of **7a,b** were confirmed by spectral data and by HMBC for **7a** (Fig. 2) and by X-ray crystallography for **7b** (Fig. 3). IR spectra of **7a,b** lacked the high frequency OH and NH stretching absorption bands present in their precursor alcohol **6** and showed a new C=O stretching absorption band attributed to side chain carbonyl of carbonate and amide. N^3 acylation regioselectivity was unequivocally established by HMBC of compound **7a** and X-ray crystallography of compound **7b.** HMBC of compound **7a** showed a correlation between C^4-H of the DHPM core at 6.58 ppm and the carbonyl carbon of the acetamido group at 170.88 ppm (Fig. 2) confirming direct connectivity between N^3 and the acetyl group. Stirring a mixture of alcohol **6** and benzenesulfonyl chloride in dry pyridine overnight at room temperature didn't afford the expected phenylsulfonate ester derivative **8**, the ethyl 8-methyl-6-(3-nitrophenyl)-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazine-7-carboxylate **9** was obtained instead. The spectral analysis of this purified product indicated that the intermediate sulfonate ester underwent *in situ* cyclization. Spectral data (IR, ^{1}H NMR, ^{13}C NMR) lacked the ring core N*H* and the side chain phenylsulfonate moiety confirming the cyclic structure. The structure of the compound **9** obtained in the above reaction was confirmed by X-ray crystallography (Fig. 4) and HMBC spectral data (Fig. 5). Cyclization regioselectivity of compound **9** was unequivocally established by HMBC. As evidenced from the spectrum, the methine C^6-H of the DHPM core at 5.31 ppm showed interaction with the side chain methylene carbon NCH_2 at 48.96 ppm confirming structure **9** (Fig. 5). Carbamates are known to be readily prepared by treating the appropriate alcohol with different isocyanates under neutral reaction conditions [33]. Herein, stirring a mixture of the alcohol derivative **6** and the substituted isocyanate derivative in anhydrous dichloromethane at room temperature afforded the corresponding carbamates **10a-c**. Unexpectedly, attempts to synthesize the corresponding thiocarbamates **11a-c** following the same reaction conditions utilizing the appropriate isothiocyanates were unsuccessful. Structures of the obtained products **10a-c** were confirmed by spectral analyses. IR spectra lacked the high frequency OH stretching absorption band and showed new NH and C=O stretching absorption bands attributed to side chain carbamate ester at 3296–3294 and 1699–1679 cm^{-1} respectively. ^{1}H NMR of **10a-c** showed two downfield D_2O-exchangeable singlets at 7.20–9.75 and 8.77–9.83 ppm which were attributed to carbamate-NH and N^1-H protons respectively.

2.2. Electrophysiology

Most of the synthesized compounds were evaluated for their calcium channel blocking activities by a whole-cell patch clamp recording assay using $Ca_V1.2$ and $Ca_V3.2$ channels (Fig. 6). Currents from tsA-201 cells transiently transfected with rat $Ca_V1.2$ (L-type) and ancillary calcium channel β1b and α2δ subunit cDNA were recorded, and % inhibition by each test compound (at a concentration of 10 mM) was determined to measure the resting state block. (Fig. 6a) shows that compounds mediated less than 50% block. Results recorded from similar experiments with cells transfected with the $Ca_V3.2$ (T-type) α1



Reagents: (i) acetyl chloride or ethyl chloroformate, anhydrous pyridine, stirring at R.T., under N_2 atmosphere; (ii) benzenesulphonyl chloride, anhydrous pyridine; (iii) appropriate phenylisocyanate, anhydrous DCM, stirring at R.T.; (iv) appropriate phenylisothiocyanate, anhydrous DCM, stirring at R.T.

Scheme 2. Synthetic pathways for compounds 7–10. Reagents: (i) acetyl chloride or ethyl chloroformate, anhydrous pyridine, stirring at R.T., under N_2 atmosphere; (ii) benzenesulphonyl chloride, anhydrous pyridine; (iii) appropriate phenylisocyanate, anhydrous DCM, stirring at R.T.; (iv) appropriate phenylisothiocyanate, anhydrous DCM, stirring at R.T.

subunit are represented in (Fig. 6b). Compound **7a** showed moderate blockade, the remainder of the test compounds were less active.

2.3. In silico prediction of physicochemical properties and drug-likeness data for the new compounds

Oral bioavailability represents important role in the generation of bioactive molecules into therapeutic agents [34]. So, it was essential to apply a computational study to assess whether our compounds possess the right parameters to exhibit drug-likeness or not. *Molinspiration* [35] online software was used to calculate molecular descriptors that were used by Lipinski in formulating his rule of five [36] (Table 1). *Molsoft* software [37] was applied to predict drug likeness and solubility parameters (Table 2) in order to analyze their overall potential to meet the requirements for a drug and to also compare them to the reference drug; amlodipine. Lipinski's rule of five [36] states that cell permeability and oral bioavailability are likely to occur if at least three of the following rules are obeyed: molecular weight (M.W) ≤ 500 Da, *n*-octanol–water partition coefficient (log P) ≤ 5, number of hydrogen bond acceptors (HBA) ≤ 10, number of hydrogen bond donors (HBD) ≤ 5. The results revealed that five compounds **(2a, 6, 7a, 9** and **10a)** are in full accordance to Lipinski's rule of five with no single violation. Two compounds **(3a** and **4)** showed one violation. Other compounds displayed additional violations. Moreover, the number of rotatable bonds (NROTB) and topological polar surface area (TPSA) have been reported as very good descriptors of oral bioavailability of drugs [38]. Also, it has been stated that compounds with TPSA < 140 $Å^2$ are predicted to have good oral bioavailability [39,40]. Results showed that TPSA of all compounds were in the acceptable range (below 150 $Å^2$). Besides, TPSA was used to calculate percentage of absorption (%ABS = 109–0.345 TPSA). All the tested compounds displayed reasonable %ABS in the range of 57.39–78.73% indicating a good predicted oral bioavailability. *In silico* physicochemical properties data are listed in Table 1.

It was reported that 80% of drugs in the market have predictable solubility above 0.0001 mg/L. The results illustrated that all tested compounds accomplished the solubility requirement. Drug-likeness model score is expressed by a numerical value which determines whether a particular molecule can behave as a drug or not the more positive the numerical value the more it is likely for a compound to act as a drug [41]. As shown in (Table 2), all compounds have positive drug likeness values which indicates that they have good predicted drug-likeness prospective. Finally, compounds **(2a, 6, 7a, 9** and **10a)** can be considered as drug-like candidates as they presented reasonable physicochemical properties with good predicted drug-likeness values.

3. Conclusion

This study deals with the synthesis of dihydropyrimidine derivatives with various functionalities at C2 linked to the dihydropyrimidine core *via* variable spacer nature and size. The newly synthesized compounds

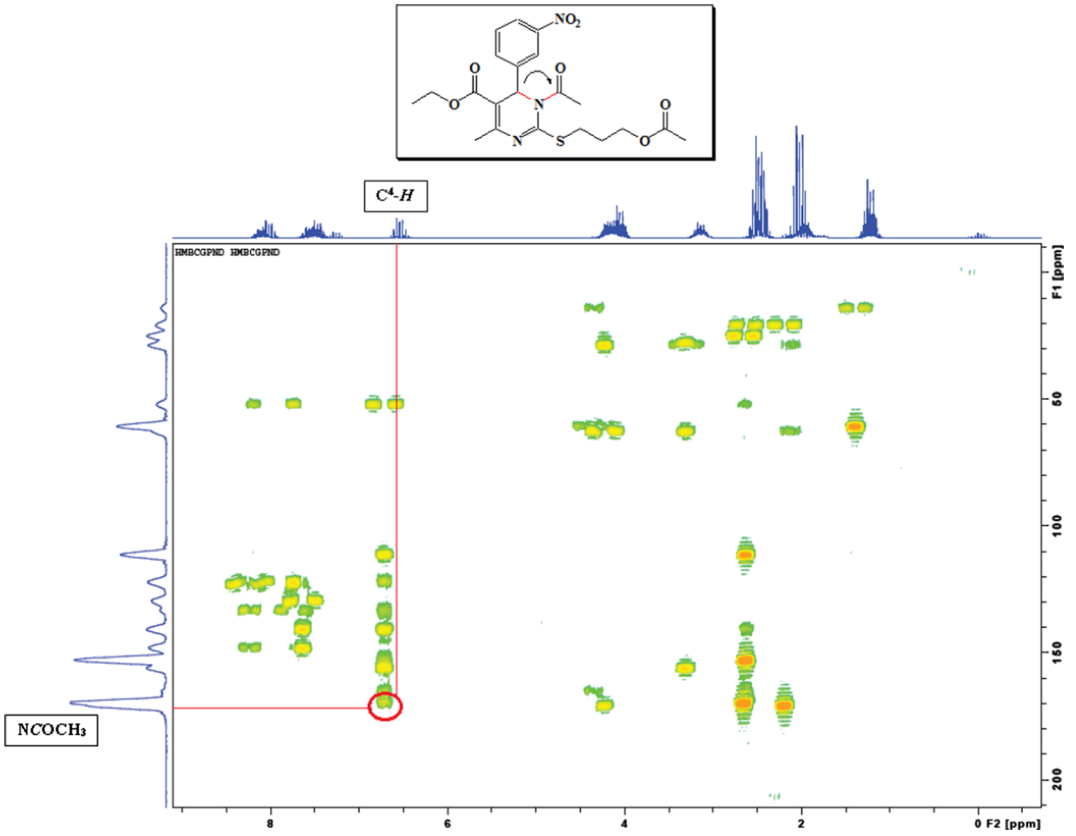


Fig. 2. HMBC spectrum of Compound **7a**.

have been evaluated as blockers for $Ca_V1.2$ and $Ca_V3.2$ utilising the whole-cell patch clamp technique. Among the tested compounds, compound **7a** showed moderate calcium channel activity against $Ca_V3.2$. Additionally, the physicochemical properties and pharmacokinetic profiles of the target compounds were predicted using *Molinspiration* and *Molsoft* softwares. Computational results showed that such type of compounds could be considered as drug-like candidates. Compound **7a** showed an aqueous solubility (S^a) value of 43.95 and a "Drug-likeness model score" value of 0.21. These results may have a value in guiding further structural modification of C2 substituted dihydropyrimidine to develop potent calcium channel blockers.

4. Experimental

4.1. Chemistry

All chemicals were purchased from commercial sources. Flash column chromatography separation was performed using Acros organics silica gel 40–60 μm, 60 Å using combination of ethyl acetate and hexanes. Preparative thin layer chromatography was performed using UNIPLATE™1500μm silica gel plates with UV 254 preparative layer. Whatman and sigma TLC plates were utilized for thin layer chromatography and visualization was done using UV fluorescence at 254 nm.

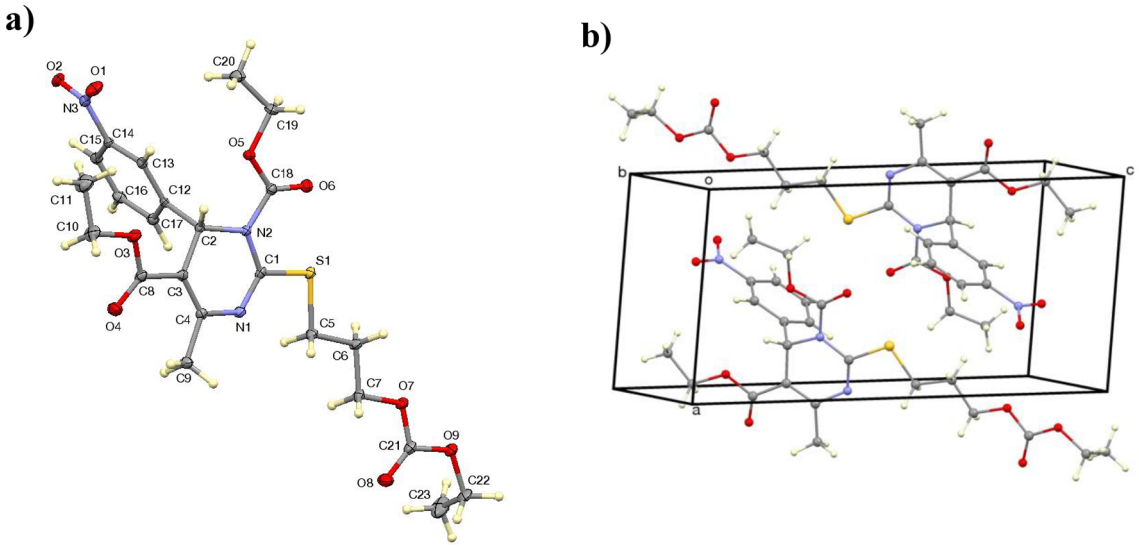


Fig. 3. (a) Compound **7b** with 50% ellipsoids and crystallographic numbering; (b) crystal packing of compound **7b** in the unit cell.

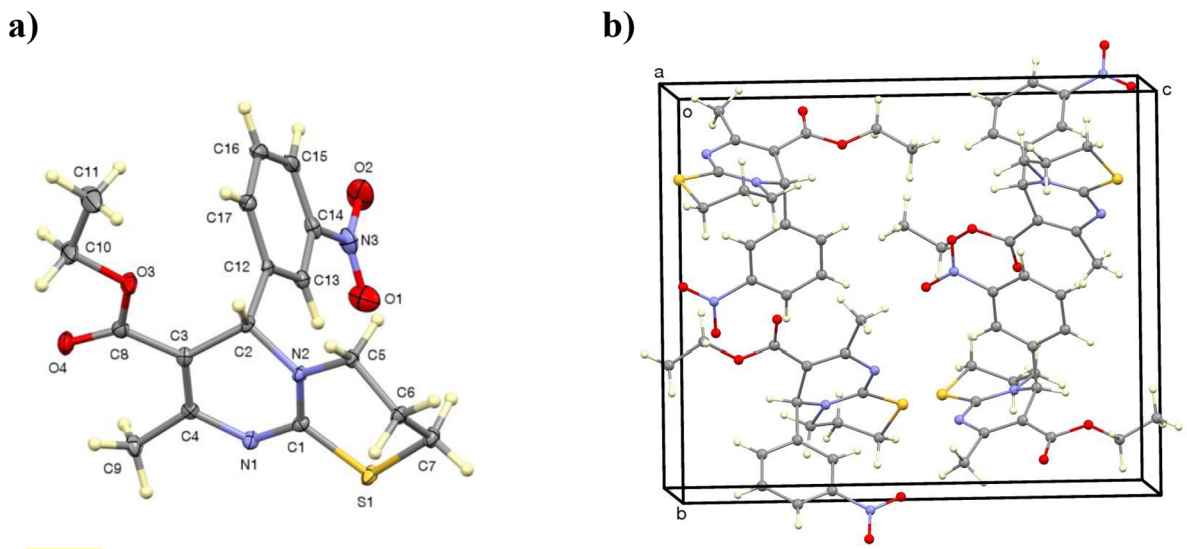


Fig. 4. (a) Compound **9** with 50% ellipsoids and crystallographic numbering; (b) crystal packing of compound 9 in the unit cell.

Melting points were recorded on a Mel-Temp, Laboratory devices, Inc and are uncorrected. %CHN Analyzer by combustion/TCD and %S by O flask combustion/IC were used for elemental analysis of final compounds and performed by Micro Analysis Inc., Wilmington DE, USA and are within 0.4%. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance 400 MHz & 600 MHz instrument using DMSO-d_6 as solvent unless otherwise stated. ^{1}H NMR Spectra are reported in order; multiplicity, number of protons and signals were characterized as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet), br s (broad signal), q (quartet). Chemical shifts are relative to TMS as an internal standard. Mass spectra were recorded on ThermoFinnigan MAT95XL high resolution magnetic sector mass spectrometer, using electrospray ionization method. The IR spectra were recorded on ZnSe crystal at 8 cm^{-1} resolution in Nicolet 380 ATR-FTIR spectrophotometer (Thermo electron Corporation, Madison, WI). 1,4-Dihydropyrimidinethione **(1)** was prepared according to previously published reaction conditions [28].

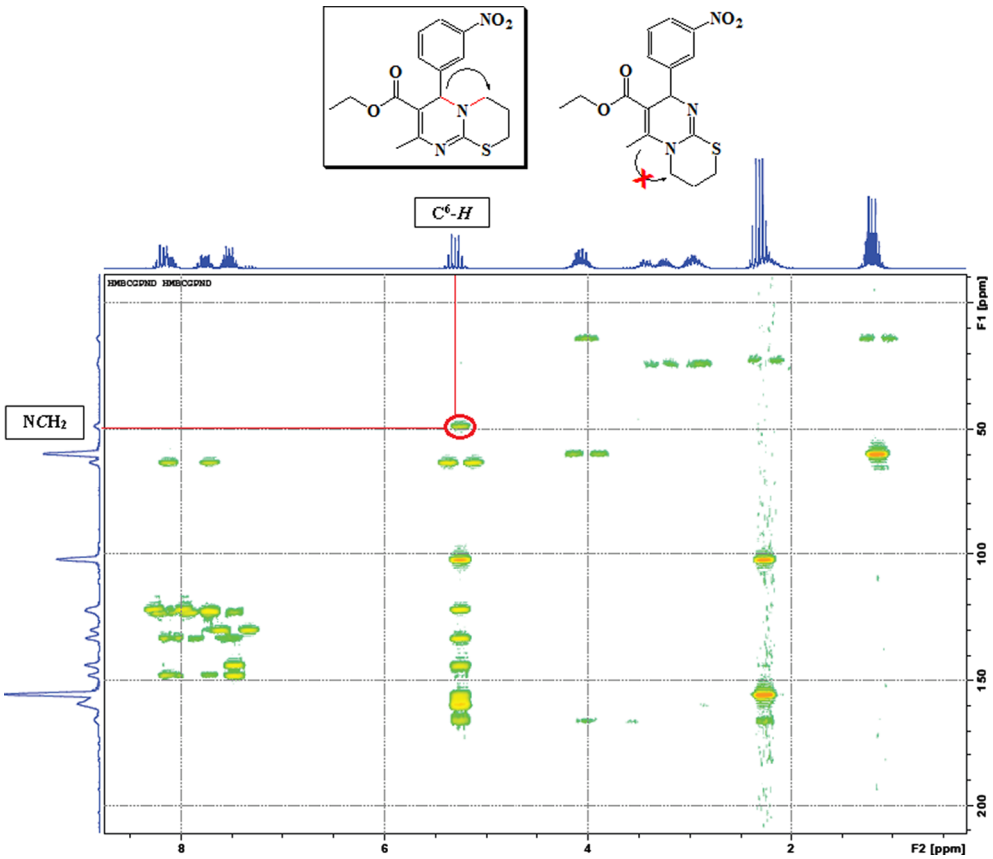


Fig. 5. HMBC spectrum of Compound **9**.

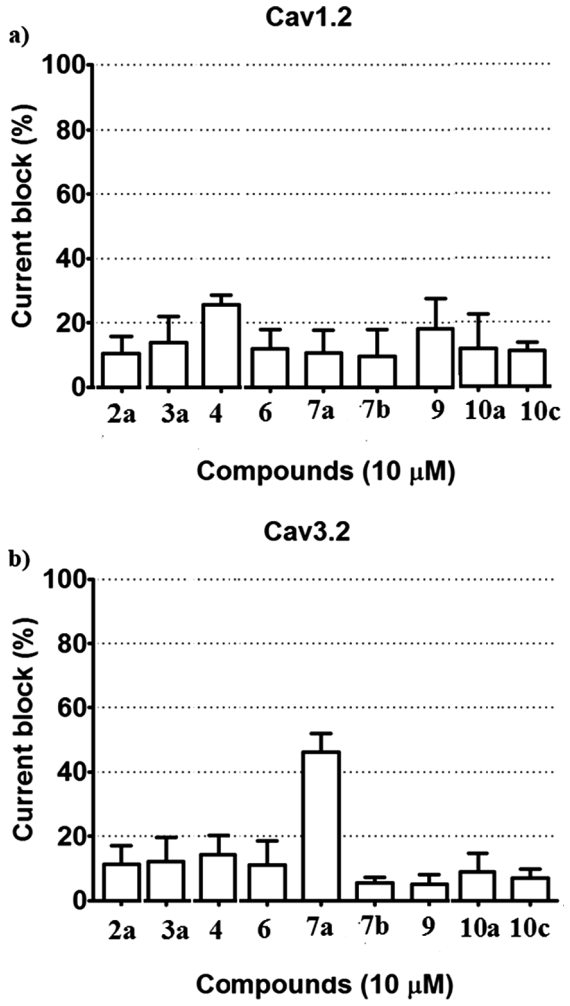


Fig. 6. (a) Tonic block of rat $Ca_v1.2$ (L-type) induced by a 10 μM application of test compounds (n = 4–5 per channel). (b) Tonic block of human $Ca_v3.2$ (T-type) with the same compounds (n = 4–5 per channel, at 10 μM). Error bars reflect standard errors.

4.1.1. Ethyl 2-(aroylmethylsulfanyl)-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyrimidine-5-carboxylates ***(2a,b)***

The appropriately substituted phenacyl bromide (1.0 mmol) was added to a stirred suspension of the 1,4-dihydropyrimidinethione **1** (0.32 g, 1.0 mmol) in dry acetone (50 mL) and stirring was continued at reflux temperature for 1–3 h. The separated product was filtered, washed with dry acetone and dried without need for further purification.

Table 2
In silico drug-likeness data of the tested compounds as predicted by *Molsoft*.

Code	S[a] (mg/L)	Drug-likeness model score
2a	0.40	0.06
3a	1.18	0.28
4	0.37	0.64
6	57.56	0.24
7a	**43.95**	**0.21**
7b	7.53	0.23
9	8.10	0.27
10a	0.41	0.34
10c	0.15	0.36
Amlodipine	26.53	0.94

S[a] aqueous solubility.

4.1.2. Ethyl 2-(benzoylmethylsulfanyl)-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyrimidine-5-carboxylates ***(2a)***

Yield: 0.3 g (79%); MP: 210–12 °C; IR (KBr, cm^{-1}): 3056 (NH), 1722, 1687 (C═O), 1600 (C═N), 1524, 1323 (NO_2), 1195, 1094 (C—O—C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 0.97–1.10 (m, 3H, $OCH_2\underline{CH_3}$), 2.47 (s, 3H, C^6-CH_3), 3.85–4.25 (m, 4H, SCH_2 & $O\underline{CH_2}CH_3$), 5.38, 5.57 (2 s, 1H, C^4-H), 6.86–7.09 (m, 2H, ArHs), 7.43–8.18 (m, 7H, ArHs), 8.55 (s, br, 1H, NH, D_2O-exchangeable); ^{13}C NMR (DMSO-d_6, 100.63 MHz) δ ppm: 13.61, 17.17, 39.84, 43.46, 55.68, 56.07, 60.73, 97.50, 99.79, 105.33, 122.08, 123.48, 125.85, 127.03, 127.64, 128.96, 129.13, 130.17, 133.82, 142.04, 146.67, 163.32, 166.32; HRMS (ESI) calcd. for $C_{22}H_{22}N_3O_5S$ $[M+1]^{+\cdot}$: 440.1275; Found: 440.1275.

4.1.3. Ethyl 2-(4-fluorobenzoylmethylsulfanyl)-6-methyl-4-(3-nitrophenyl)-1,4-dihydro pyrimidine-5-carboxylates ***(2b)***

Yield: 0.4 g (89%); MP: 218–20 °C; IR (KBr, cm^{-1}): 3069 (NH), 1726, 1673 (C═O), 1596 (C═N), 1523, 1324 (NO_2), 1192, 1089 (C—O—C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 0.92–1.13 (m, 3H, $OCH_2\underline{CH_3}$), 2.45 (s, 3H, C^6-CH_3), 3.86–4.25 (m, 4H, SCH_2 & $O\underline{CH_2}CH_3$), 5.33, 5.56 (2s, 1H, C^4-H), 6.79–8.18 (m, 8H, ArHs), 8.63 (s, br, 1H, NH, D_2O-exchangeable); HRMS (ESI) calcd. for $C_{22}H_{21}FN_3O_5S$ $[M+1]^{+\cdot}$: 458.1180; Found: 458.1189.

4.1.4. Ethyl 2-(2-aryl-2-hydroxyvinyl)-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyrimidine-5-carboxylates ***(3a,b)***

A stirred suspension of the dihydropyrimidinethione **1** (0.32 g,

Table 1
In silico physicochemical properties of the tested compounds as predicted by *Molinspiration*.

Code	LogP[a]	M.Wt[b]	HBA[c]	HBD[d]	Lipinski's Violation	TPSA[e]	%ABS[f]	Volumes $(A)^3$	NROTB[g]
2a	4.24	439.49	8	1	0	113.59	69.81	379.66	9
3a	5.19	407.43	8	2	1	116.75	68.72	361.18	7
4	4.58	508.56	10	1	1	135.60	62.21	434.19	10
6	2.74	379.44	8	2	0	116.75	68.72	330.89	9
7a	**3.04**	**463.51**	**10**	**0**	**0**	**131.11**	**63.76**	**403.32**	**11**
7b	4.27	523.56	12	0	2	149.57	57.39	454.90	15
9	3.47	361.42	7	0	0	87.73	78.73	312.41	5
10a	4.92	498.56	10	2	0	134.85	62.47	434.65	12
10c	5.37	512.59	10	2	2	134.85	62.47	451.21	12
Amlodipine	2.58	408.88	7	3	0	99.89	74.54	363.90	10

[a] LogP: logarithm of compound partition coefficient between *n*-octanol and water.
[b] M.Wt: molecular weight.
[c] HBA: number of hydrogen bond acceptors.
[d] HBD:number of hydrogen bond donors.
[e] TPSA: polar surface area.
[f] %ABS: percentage of absorption.
[g] NROTB: number of rotatable bonds.

1.0 mmol) in dry acetone (50 mL) was treated with K_2CO_3 (0.2 g, 1.5 mmol) and the appropriate phenacyl bromide (1 mmol) at room temperature. After stirring for 30 min (monitored by TLC), triphenylphosphine (0.39 g, 1.5 mol) was added in one portion, and the reaction temperature was raised to reflux. Stirring was continued for additional 10 h for completion of the reaction followed by evaporation of the solvent to dryness under reduced pressure. The obtained residue was purified by flash chromatography or preparative TLC with gradient eluents of 0–90% EtOAc/hexane to produce the desired product.

*4.1.5. Ethyl 2-(2-phenyl-2-hydroxyvinyl)-6-methyl-4-(3-nitrophenyl)-1,4-dihydro pyrimidine-5-carboxylates (**3a**)*

Yield: 0.29 g (71%); MP: oil; IR (KBr, cm^{-1}): 3314 (OH), 3187 (NH), 1682 (C═O), 1630 (C═N), 1525, 1346 (NO_2), 1201, 1057 (C−O−C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 1.11 (t, J = 8.0 Hz, 3H, $OCH_2\underline{CH_3}$), 2.24, 2.31 (2s, 3H, C^6-CH_3), 3.95–4.10 (m, 2H, $OC\underline{H_2}CH_3$), 5.29 (s, 1H, vinylic $\underline{CH}$═C−OH), 5.35, 5.40 (2s, 1H, C^4-H), 7.16–7.34 (m, 4H, Ar-Hs), 7.47 (d, J = 8.0 Hz, 2H, Ar-, 7.52 (d, J = 8.0 Hz, 2H, Ar-H), 7.61 (d, J = 8.0 Hz, 1H, Ar-H), 7.96 (t, J = 6.0, 1H, Ar-H), 8.04 (s, 1H, Ar-H), 8.60 (s, 1H, NH, D_2O-exchangeable), 11.40, 12.79 (2 s, 1H, vinylic OH, D_2O-exchangeable); ^{13}C NMR ($CDCl_3$, 100.63 MHz) δ ppm: 14.18, 18.71, 19.48, 51.99, 52.31, 60.42, 60.50, 78.98, 101.40, 101.84, 121.66, 121.86, 122.83, 126.53, 126.61, 128.23, 128.30, 129.69, 129.92, 130.64, 130.79, 132.83, 132.93, 139.94, 140.20, 145.04, 145.39, 145.82, 146.08, 148.04, 148.30, 154.34, 154.80, 165.07, 165.20, 186.61, 187.02; HRMS (ESI) calcd. for $C_{22}H_{22}N_3O_5$ $[M+1]^{+\cdot}$: 408.1554; Found: 408.1558.

*4.1.6. Ethyl 2-(2-[4-fluorophenyl]-2-hydroxyvinyl)-6-methyl-4-(3-nitrophenyl)-1,4-dihydro pyrimidine-5-carboxylates (**3b**)*

Yield: 0.3 g (70%); MP: oil; IR (KBr, cm^{-1}): 3309 (OH), 3191 (NH), 1701 (C═O), 1630 (C═N), 1527, 1346 (NO_2), 1197, 1058 (C−O−C); ^{1}H NMR (Acetone-d_6, 400 MHz) δ ppm: 1.17–1.24 (m, 3H, $OCH_2\underline{CH_3}$), 2.47, 2.49 (2 s, 3H, C^6-CH_3), 4.04–4.15 (m, 2H, $OC\underline{H_2}CH_3$), 5.61, 5.66 (2s, 1H, C^4-H), 5.73 (s, 1H, vinylic $\underline{CH}$═COH), 7.08–8.26 (m, 8H, ArHs), 9.38 (s, 1H, NH, D_2O-exchangeable), 11.65, 13.14 (2 s, 1H, vinylic OH, D_2O-exchangeable); HRMS (ESI) calcd. for $C_{22}H_{20}FN_3O_5Na$ $[M+Na]^{+\cdot}$: 448.1279; Found: 448.1282.

*4.1.7. Ethyl 2-(3-(1,3-dioxoisoindolin-2-yl)propylsulfanyl)-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyrimidine-5-carboxylate (**4**)*

A suspension of the dihydropyrimidinethione **1** (0.32 g, 1.0 mmol) in dry acetone (50 mL) was treated with K_2CO_3 (0.2 g, 1.5 mmol) and stirred at room temperature for 30 min. KI (40 mg) and *N*-(3-bromopropyl)phthalimide (0.3 g, 1.2 mmol) were then added in one portion and the reaction temperature was raised to reflux. Stirring was continued for additional 5–6 h until completion of the reaction followed by evaporation of the solvent to dryness under reduced pressure. The obtained residue was purified by flash chromatography with gradient eluents of 0–90% EtOAc/hexane to offer the desired product. Yield: 0.38 g (75%); MP: 150–2 °C; IR (KBr, cm^{-1}): 3272 (NH), 1768, 1693 (C═O), 1647 (C═N), 1531, 1349 (NO_2), 1163, 1100 (C−O−C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 1.22 (t, J = 6.0 Hz, 3H, $OCH_2\underline{CH_3}$), 1.97 (quint, J = 8.0 Hz, 2H, $SCH_2\underline{CH_2}CH_2$), 2.34 (s, 3H, C^6-CH_3), 2.94, 3.09 (2 quint, J = 8.0 Hz, 2H, SCH_2), 3.71, (t, J = 6.0 Hz, 2H, CH_2N), 4.12 (q, J = 8.0 Hz, 2H, $OC\underline{H_2}CH_3$), 5.69 (s, 1H, C^4-H), 6.64 (s, 1H, NH, D_2O-exchangeable), 7.43 (t, J = 8.0 Hz, 1H, Ar-H), 7.61 (d, J = 8.0, 1H, Ar-H), 7.69–7.74 (m, 2H, Ar-Hs), 7.79–7.86 (m, 2H, Ar-Hs), 8.04 (d, J = 8.0, 1H, Ar-H), 8.08 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100.63 MHz) δ ppm: 14.25, 18.80, 28.03, 28.70, 36.67, 59.21, 60.06, 99.80, 121.99, 123.25, 123.32, 129.17, 131.96, 133.44, 134.03, 145.34, 146.25, 146.84, 148.22, 150.00, 166.36, 168.33; HRMS (ESI) calcd. for $C_{25}H_{25}N_4O_6S$ $[M+1]^{+\cdot}$: 509.1489; Found: 509.1491.

*4.1.8. Ethyl 2-(3-hydroxypropylsulfanyl)-6-methyl-4-(3-nitrophenyl)-1,4-dihydro pyrimidine-5-carboxylate (**6**)*

A suspension of the dihydropyrimidinethione **1** (0.32 g, 1.0 mmol) in dry acetone (50 mL) was treated with K_2CO_3 (0.2 g, 1.5 mmol) and stirred at RT for 30 min. 3-Bromoethanol (0.16 g, 0.11 mL, 1.2 mmol) was then added in one portion and the reaction temperature was raised to reflux. Stirring was continued for additional 20 h until completion of the reaction followed by evaporation of the solvent to dryness under reduced pressure. The obtained residue was diluted with H_2O, extracted with EtOAc (3 × 50 mL), washed with H_2O and brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The obtained residue was purified by flash chromatography with gradient eluents of 0–90% EtOAc/hexane to afford the desired product. Yield: 0.37 g (97%); MP: 107–9 °C; IR (KBr, cm^{-1}): 3150 (OH), 3113 (NH), 1696 (C═O), 1638 (C═N), 1532, 1355 (NO_2), 1191, 1079 (C−O−C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 1.22 (t, J = 8.0 Hz, 3H, $OCH_2\underline{CH_3}$), 1.63–1.73 (m, 1H, $S\text{-}CH_2\underline{CH_2}CH_2$), 1.90–1.98 (m, 1H, $S\text{-}CH_2\underline{CH_2}CH_2$), 2.37 (s, 3H, C^6-CH_3), 3.05–3.11 (m, 1H, SCH), 3.19–3.27 (m, 1H, SCH), 3.57–3.74 (m, 2H, $C\underline{H_2}$-OH), 4.08–4.16 (m, 2H, $OC\underline{H_2}CH_3$), 4.93 (s, br, 1H, OH, D_2O-exchangeable), 5.77 (s, 1H, C^4-H), 6.97 (s, br, 1H, NH, D_2O-exchangeable), 7.48 (t, J = 6.0 Hz, 1H, Ar-H), 7.67 (d, J = 8.0 Hz, 1H, Ar-H), 8.10–8.17 (m, 2H, Ar-H); HRMS (ESI) calcd. for $C_{17}H_{22}N_3O_5S$ $[M+1]^{+\cdot}$: 380.1275; Found: 380.1277.

*4.1.9. Ethyl 2-(3-substituted propylsulfanyl)-3-acetyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidine-5-carboxylate (**7a,b**)*

A mixture of DHPM alcohol **5** (0.38 g, 1.0 mmol) and acetyl chloride (0.09 g, 1.2 mmol) or ethyl chloroformate (0.13 g, 1.2 mmol) in anhydrous pyridine (3 mL) was stirred overnight at room temperature under N_2 atmosphere. The reaction mixture was diluted with H_2O (100 mL), extracted with ethyl acetate (3 × 100 mL) and the combined organic layers were washed with H_2O and brine, dried over anhydrous sodium sulphate and evaporated under reduced pressure. The pure compounds were isolated by flash chromatography utilizing gradient eluents of 0–90% EtOAc/hexane.

*4.1.10. Ethyl 2-(3-acetoxypropylsulfanyl)-3-acetyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidine-5-carboxylate (**7a**)*

Yield: 0.32 g (70%); MP: oil; IR (KBr, cm^{-1}): 1738, 1693 (C═O), 1609 (C═N), 1527, 1349 (NO_2), 1227, 1077 (C−O−C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 1.25 (t, J = 6.0 Hz, 3H, $OCH_2\underline{CH_3}$), 1.94–2.02 (m, 2H, $S\text{-}CH_2\underline{CH_2}CH_2$), 2.05 (2 s, 3H, C^6-CH_3), 2.49 (s, 3H, $OCOCH_3$), 2.52 (s, 3H, $NCOCH_3$), 3.18 (t, J = 8.0 Hz, 2H, $S\text{-}C\underline{H_2}$), 4.07–4.13 (m, 2H, $OC\underline{H_2}CH_3$), 4.21 (t, J = 8.0 Hz, 2H, $C\underline{H_2}$-$OCOCH_3$), 6.58 (s, 1H, C^4-H), 7.50 (t, J = 8.0 Hz, 1H, Ar-H), 7.61 (t, J = 8.0 Hz, 1H, Ar-H,), 8.06 (s, dist, 1H, Ar-H), 8.14 (d, J = 8.0 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100.63 MHz) δ ppm: 14.21, 20.87, 20.97, 25.00, 27.89, 28.65, 52.15, 60.79, 62.71, 111.49, 121.97, 123.23, 129.65, 133.35, 140.66, 148.41, 153.02, 156.29, 165.49, 169.89, 170.88; HRMS (ESI) calcd. for $C_{21}H_{26}N_3O_7S$ $[M+1]^{+\cdot}$: 464.1486; Found: 464.1491.

*4.1.11. Ethyl 2-(3-ethoxycarbonyloxypropylsulfanyl)-3-ethoxycarbonyl-6-methyl-4- (3-nitrophenyl)-3,4-dihydropyrimidine dicarboxylate (**7b**)*

Yield: 0.38 g (73%); MP: 70–2 °C; IR (KBr, cm^{-1}): 1744, 1732, 1708 (C═O), 1623 (C═N mixed with C═C Ar), 1506–1495 (C═C Ar), 1535, 1349–1356 (NO_2), 1193, 1254, 1072, 1014 (C−O−C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 1.26 (t, J = 8.0 Hz, 3H, $OCH_2\underline{CH_3}$,), 1.31 (t, J = 8.0 Hz, 3H, $NCOOCH_2\underline{CH_3}$), 1.39 (t, 3H, J = 8.0 Hz, $OCOOCH_2\underline{CH_3}$), 1.96–2.09 (m, 2H, $S\text{-}CH_2\underline{CH_2}CH_2$), 2.45 (s, 3H, C^6-CH_3), 3.07, 3.24 (2 quint, J = 7.0 Hz, 2H, $S\text{-}CH_2$), 4.16–4.24 (m, 6H, $OC\underline{H_2}CH_3$, carbamate $NCOOC\underline{H_2}CH_3$ & carbonate $CH_2C\underline{H_2}OCO$), 4.34 (q, 2H, J = 8.0 Hz, carbonate $OCOOC\underline{H_2}CH_3$), 6.33 (s, 1H, C^4-H), 7.50 (d, J = 8.0 Hz, 1H, Ar-H), 7.60 (d, J = 8.0 Hz, 1H, Ar-H), 8.13–8.16 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 100.63 MHz) δ ppm: 14.22, 14.27, 21.61, 28.01, 28.33, 54.16, 60.74, 64.02, 64.14, 66.25, 109.63, 122.22, 123.29, 129.68, 133.15, 141.76, 148.38, 152.60, 152.88, 155.06,

157.12, 165.70; HRMS (ESI) calcd. for $C_{23}H_{30}N_3O_9S$ $[M+1]^{+\cdot}$: 524.1697; Found: 524.1698.

4.1.12. Ethyl 8-methyl-6-(3-nitrophenyl)-3,4-dihydro-2H,6H-pyrimido [2,1-b][1,3]thiazine-7-carboxylate (9)

A mixture of DHPM alcohol **5** (0.38 g, 1.0 mmol) and benzenesulfonyl chloride (0.35 g, 0.25 mL, 2.0 mmol) in dry pyridine (5 mL) was stirred at room temperature for an overnight. The reaction mixture was diluted with H_2O and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with H_2O and brine, dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue left was purified by preparative TLC with gradient eluent of 0–90% EtOAc/hexane to give the desired product. Yield: 0.3 g (83%); MP: 126–8 °C; IR (KBr, cm^{-1}): 1685 (C═O), 1589 (C═N), 1526, 1347 (NO_2), 1227, 1075 (C−O−C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 1.23 (t, J = 8.0 Hz, 3H, $OCH_2C\underline{H}_3$), 2.05–2.20 (m, 1H, S-$CH_2C\underline{H}_2CH_2$), 2.24–2.30 (m, 1H, S-$CH_2C\underline{H}_2CH_2$), 2.35 (s, 3H, C^6-CH_3), 2.92–3.04 (m, 2H, S-$C\underline{H}_2$), 3.21–3.28 (m, 1H, N-$C\underline{H}_2$), 3.40–3.45 (m, 1H, N-$C\underline{H}_2$), 4.05–4.15 (m, 2H, $OC\underline{H}_2CH_3$), 5.31 (s, 1H, C^4-H), 7.54 (t, J = 8.0 Hz, 1H, Ar-H), 7.79 (d, J = 8.0 Hz, 1H, Ar-H), 8.16 (d, J = 8.0 Hz, 1H, Ar-H), 8.20 (s, dist, 1H, Ar-H); ^{13}C NMR (DMSO-d_6, 100.63 MHz) δ ppm: 14.29, 22.90, 24.36, 27.03, 48.96, 59.93, 63.40, 102.29, 122.03, 123.26, 130.17, 133.37, 144.12, 148.14, 155.82, 160.02, 166.18; HRMS (ESI) calcd. for $C_{17}H_{20}N_3O_4S$ $[M+1]^{+\cdot}$: 362.1169; Found: 362.1165.

4.1.13. Ethyl 2-(3-arylcarbamoyloxypropylsulfanyl)-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyrimidine-5-carboxylates (10a-c)

A solution of DHPM alcohol **5** (0.38 g, 1.0 mmol) in anhydrous dichloromethane (5 mL), was treated with the appropriate isocyanate derivative (1.0 mmol). After overnight stirring at room temperature, the reaction was concentrated under reduced pressure and the residue left was purified by flash chromatography using gradient eluents of 0–90% EtOAc/hexane to afford the pure carbamates.

4.1.14. Ethyl 2-(3-phenylcarbamoyloxypropylsulfanyl)-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyrimidine-5-carboxylates (10a)

Yield: 0.35 g (70%); MP: oil; IR (KBr, cm^{-1}): 3294 (NH), 1702, 1679 (C═O), 1650 (C═N), 1526, 1347 (NO_2), 1218, 1087 (C−O−C); ^{1}H NMR (Acetone-d_6, 400 MHz) δ ppm: 1.19 (t, J = 6.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.94–2.06 (m, 2H, S-$CH_2C\underline{H}_2CH_2$), 2.36 (s, 3H, C^6-CH_3), 3.01–3.19 (m, 2H, S-CH_2), 4.03–4.23 (m, 4H, $OC\underline{H}_2CH_3$ & $\underline{CH}_2OCONH$), 5.80 (s, 1H, C^4-H), 7.01 (t, J = 8.0 Hz, 1H, Ar-H), 7.28 (t, J = 8.0 Hz, 2H, Ar-Hs), 7.54–7.58 (m, 3H, Ar-H), 7.77 (d, J = 8.0 Hz, 1H, Ar-H), 8.07 (d, J = 8.0 Hz, 1H, Ar-H,), 8.18 (s, 1H, Ar-H), 8.59, 8.77 (2 s, 2H, NH & carbamate NH, D_2O-exchangeable); ^{13}C NMR (acetone-d_6, 100.63 MHz) δ ppm: 14.54, 18.11, 20.83, 27.38, 59.88, 60.23, 63.71, 99.47, 119.09, 122.32, 123.35, 129.53, 130.35, 134.26, 140.11, 147.32, 148.63, 149.10, 151.57, 154.30, 166.87, 170.94; HRMS (ESI) calcd. for $C_{24}H_{27}N_4O_6S$ $[M+1]^{+\cdot}$: 499.1646; Found: 499.1649.

4.1.15. Ethyl 2-(3-[4-bromophenyl]carbamoyloxypropylsulfanyl)-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyrimidine-5-carboxylates (10b)

Yield: 0.3 g (52%); MP: oil; IR (KBr, cm^{-1}): 3296 (NH), 1700, 1679 (C═O), 1650 (C═N), 1526, 1347 (NO_2), 1216, 1077 (C−O−C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 1.14 (2 t, J = *4.0 Hz,* 3H, $OCH_2C\underline{H}_3$), 1.87–1.99 (m, 2H, S-$CH_2C\underline{H}_2CH_2$), 2.26 (s, 3H, C^6-CH_3), 2.96–3.13 (m, 2H, S-CH_2), 3.96–4.24 (m, 4H, $\underline{CH}_2OCOAr$& $OC\underline{H}_2CH_3$), 5.65 (s, 1H, C^4-H), 7.41–7.50 (m, 4H, ArHs), 7. 59 (t, J = *8.0 Hz,* 1H, Ar-H,), 7.67 (d, J = *8.0 Hz,* 1H, Ar-H,), 8.02 (s, 1H, Ar-H), 8.07 (d, J = *8.0 Hz,* 1H, Ar-H,), 9.75, 9.83 (2 s, 2H, NH & OCONHAr, D_2O-exchangeable); HRMS (ESI) calcd. for $C_{24}H_{26}BrN_4O_6S$ $[M+1]^{+\cdot}$: 577.0751; Found: 577.0735. $C_{24}H_{26}[81]BrN_4O_6S$ $[M+1]^{+}$: 579.0730; Found: 579.0738.

4.1.16. Ethyl 2-(3-[p-tolyl]carbamoyloxypropylsulfanyl)-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyrimidine-5-carboxylates (10c)

Yield: 0.4 g (78%); MP: oil; IR (KBr, cm^{-1}): 3296 (NH), 1702, 1679 (C═O), 1651 (C═N), 1526, 1347 (NO_2), 1160, 1092 (C−O−C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 1.21 (t, J = 8.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.89–1.92 (m, 2H, S-$CH_2C\underline{H}_2CH_2$), 2.27 (s, 3H, tolyl-CH_3), 2.29 (s, 3H, C^6-CH_3), 2.94–3.15 (m, 2H, S-CH_2,), 4.07–4.17 (m, 4H, $OC\underline{H}_2CH_3$ & CH_2OCOAr), 5.79 (s, 1H, C^4-H), 7.06 (d, J = 8.0 Hz, 2H, Ar-Hs), 7.20–7.28 (m, 3H, Ar-H & NH, D_2O-exchangeable), 7.41 (t, J = 8.0 Hz, 1H, Ar-H), 7.64–7.66 (m, 2H, Ar-H & OCONHAr, D_2O-exchangeable), 8.03 (d, J = *8.0 Hz,* 1H, Ar-H), 8.16 (s, 1H, Ar-H); HRMS (ESI) calcd. for $C_{25}H_{29}N_4O_6S$ $[M+1]^{+\cdot}$: 513.1802; Found: 513.1780.

4.2. Calcium channel antagonism

4.2.1. Chemicals

Stock solutions of 10 or 30 mM concentrations of the test compounds were prepared in DMSO. The stock solutions were diluted before the experiments so that the concentration of DMSO was 0.1% or less in the final dilution. Calcium channel currents are not affected by a concentration of 0.1% DMSO or less.

4.2.2. Cell culture and transient transfection

Human embryonic kidney cells (HEK) tsA-201 cells were grown to 80–90% confluence at 37 °C (5% CO2) in Dulbecco's modiEed Eagle's medium (Life Technologies, Grand Island, NY). They were supplemented with 10% (vol/vol) fetal bovine serum (HyClone, Thermo Scientific, Pittsburgh, PA), 200 U/ml penicillin, and 0.2 mg/mL streptomycin (Life Technologies, Grand Island, NY). Cells were then suspended with 0.25% trypsin/ethylenediaminetetraacetic acid and plated onto glass coverslips in 10-cm culture dishes (Corning, Corning, NY) at 10% confluence 6 h before transfection. Calcium channel (5 μg) and green fluorescent protein marker (0.5 μg) DNAs were transfected into the cells with calcium phosphate. For $Ca_V1.2$, the additional $Ca_V\beta1b$ (5 μg) and $Ca_V\alpha2\delta1$ (5 μg) subunits were co-expressed. Cells were then transferred to 30 °C 16–18 h later following transfection and stored for two days before recording.

4.2.3. Electrophysiology

Cells on a glass coverslip were transferred into an external bath solution of 20 mM $BaCl_2$, 1 mM $MgCl_2$, 40 mM TEACl, 65 mM CsCl, 10 mM HEPES, 10 mM glucose, pH 7.4. Borosilicate glass pipettes (Sutter Instrument Co., Novato, CA, 3e5 MU) were filled with internal solution containing 140 mM CsCl, 2.5 mM $CaCl_2$,1mM $MgCl_2$, 5 mM EGTA, 10 mM HEPES, 2 mM Na-ATP and 0.3 mM Na-GTP, pH 7.3. Whole-cell patch clamp recordings were carried out using an EPC 10 amplifier (HEKA Elektronik, Bellmore, NY) linked to a personal computer equipped with Pulse (V8.65) software (HEKA Elektronik, Bellmore, NY). After seal formation, the membrane beneath the pipette was ruptured and the pipette solution was allowed to dialyze into the cell for 2–5 min before recording. Voltage-dependent currents were leak corrected with an online P/4 subtraction paradigm. Data were recorded at 10 kHz and filtered at 2.9 kHz. T-type calcium currents were produced by depolarization from a holding potential of −110 mV to a test potential of −20 mV. L-type calcium currents were produced by depolarization from a holding potential of −90 mV to a test potential of +20 mV, with an inter-pulse interval of 20 s. The duration of the test pulse typically was 100 ms.

4.2.4. Data analysis and statistics

Data analysis was carried out using online analysis built-in Pulse software (HEKA Elektronik, Bellmore, NY). All graphs were prepared using GraphPad Prism 5 (GraphPad Software, La Jolla, CA). All data are given as mean values ± standard errors.

4.3. X-ray crystallography

The crystal structure of **7b** was determined using X-ray data collected at 90 K with MoKα radiation (λ = 0.71073 Å), on a Bruker Kappa Apex-II DUO diffractometer. $C_{23}H_{29}N_3O_9S$, triclinic space group *P*-1, a = 8.1914(9), b = 9.4010(9), c = 16.1918(16) Å, α = 95.372(6), β = 96.356(6), γ = 93.378(6)°, Z = 2, D_{calcd} = 1.413 g cm^{-3}. A total of 16,372 data was collected at to θ = 28.7°, R = 0.039 for 4842 data with I > 2σ(I) of 6200 unique data (R_{int} = 0.025) and 329 refined parameters. The CIF has been deposited at the Cambridge Crystallographic Data Centre, CCDC 1885031.

The crystal structure of **9** was determined using X-ray data collected at 90 K with MoKα radiation (λ = 0.71073 Å), on a Bruker Kappa Apex-II DUO diffractometer. $C_{17}H_{19}N_3O_4S$, orthorhombic space group $P2_12_12_1$, a = 7.7908(5), b = 13.5778(9), c = 16.0974(10) Å, Z = 4, D_{calcd} = 1.410 g cm^{-3}. A total of 18,313 data was collected at to θ = 30.6°, R = 0.041 for 4404 data with I > 2σ(I) of 5208 unique data (R_{int} = 0.050) and 229 refined parameters. The CIF has been deposited at the Cambridge Crystallographic Data Centre, CCDC 1885032.

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References

[1] C.J. Doering, G.W. Zamponi, J. Bioenergy Biomembr. 35 (6) (2003) 491–505.
[2] G.W. Zamponi, J. Striessnig, A. Koschak, A.C. Dolphin, Pharmacol. Rev. 67 (4) (2015) 821–870.
[3] B. Dziegielewska, L.S. Gray, J. Dziegielewski, Pflügers Archiv-Eur. J. Phys. 466 (4) (2014) 801–810.
[4] B. Cosimelli, E. Severi, E. Novellino, A. Cavaccini, M. Cataldi, R. Budriesi, M. Micucci, A. Chiarini, P. Ioan, J. Med. Chem. 54 (15) (2011) 5597–5601.
[5] L. Remen, O. Bezencon, L. Simons, R. Gaston, D. Downing, J. Gatfield, C. Roch, M. Kessler, J. Mosbacher, T. Pfeifer, C. Grisostomi, M. Rey, E.A. Ertel, R. Moon, J. Med. Chem. 59 (18) (2016) 8398–8411.
[6] M. Teleb, F.X. Zhang, A.M. Farghaly, O.M. Wafa, F.R. Fronczek, G.W. Zamponi, H. Fahmy, Eur. J. Med. Chem. 134 (2017) 52–61.
[7] M. Teleb, F.X. Zhang, H. Junting, M.G. Vinicius, A.M. Farghaly, O.M. Wafa, G.W. Zamponi, H. Fahmy, Bioorg. Med. Chem. 25 (2017) 1926–1938.
[8] M. Teleb, O.H. Rizk, F.X. Zhang, F.R. Fronczek, G.W. Zamponi, H. Fahmy, Bioorg. Chem. 83 (2019) 354–366.
[9] G.W. Zamponi, Nat. Rev. Drug Discov. 15 (1) (2016) 19–34.
[10] S.M. Todorovic, V. Jevtovic-Todorovic, Channels 1 (4) (2007) 238–245.
[11] X.L. Chen, D.A. Bayliss, R.J. Fern, P.Q. Barrett, Am. J. Physiol. Renal Physiol. 276 (5) (1999) F674–F683.
[12] E. Yamamoto, K. Kataoka, Y.F. Dong, T. Nakamura, M. Fukuda, H. Nako, H. Ogawa, S. Kim-Mitsuyama, J. Hypertens. 28 (6) (2010) 1321–1329.
[13] T. Oshima, R. Ozono, Y. Yano, Y. Higashi, H. Teragawa, N. Miho, T. Ishida, M. Ishida, M. Yoshizumi, M. Kambe, Hypertens. Res. 28 (11) (2005) 889–894.
[14] E. Perez-Reyes, A.L. Van Deusen, I. Vitko, J. Pharmacol. Exp. Ther. 328 (2) (2009) 621–627.
[15] E. Perez-Reyes, A.L. Van, Eur. Heart J. 39 (33) (2018) 3021–3104.
[16] G.W. Zamponi, R.J. Lewis, S.M. Todorovic, S.P. Arneric, T.P. Snutch, Brain Res Rev. 60 (2009) 84–89.
[17] W. Choe, R.B. Messinger, E. Leach, V.S. Eckle, A. Obradovic, R. Salajegheh, V. Jevtovic-Todorovic, S.M. Todorovic, Mol. Pharmacol. 80 (2011) 900–910.
[18] W. Vater, G. Kroneberg, F. Foffmeister, H. Kaller, K. Meng, A. Oberdorf, W. Puls, K. Schiossmann, K. Stoepel, Arzneim.-Forsch 22 (1972) 1–14.
[19] T. Takenaka, S. Usuda, T. Nomura, H. Maeno, T. Sado, Arzneim.-Forsch 26 (1976) 2172–2178.
[20] J.E. Arrowsmith, S.F. Campbell, P.E. Cross, J.K. Stubbs, R.A. Burges, D.G. Gardiner, K.J. Blackburn, J. Med. Chem. 29 (1986) 1696–1702.
[21] A. Leonardi, G. Motta, R. Penninia, R. Testab, G. Sironi, A. Cattoc, A. Cerrid, M. Zappa, G. Bianchif, D. Nardig, Eur. J. Med. Chem. 33 (1998) 399–420.
[22] K. Meguro, M. Aizawa, T. Sohda, Y. Kawamatsu, A. Nagaoka, Chem. Pharm. Bull. 33 (1985) 3787–3797.
[23] C.C. Chang, S. Cao, S. Kang, L. Kai, X. Tian, P. Pandey, S.F. Dunne, Chi-Hao Luan, D.J. Surmeier, R.B. Silverman, Bioorg. Med. Chem. 18 (2010) 3147–3158.
[24] K.S. Atwal, G.C. Rovnyak, J. Schwartz, S. Moreland, A. Hedberg, J.Z. Gougoutas, M.F. Malley, D.M. Floyd, J. Med. Chem. 33 (1990) 1510–1515.
[25] A. de F_atima, T.C. Braga, L.D.S. Neto, B.S. Terra, B.G.F. Oliveira, D.L. da Silva, L.V. Modolo, J. Adv. Res. 6 (2015) 363–373.
[26] C.O. Kappe, Molecules 3 (1998) 1–9.
[27] C.O. Kappe, Eur. J. Med. Chem. 35 (12) (2000) 1043–1052.
[28] N.P. Tale, A.V. Shelke, B.Y. Bhong, N.N. Karade, Monatsh. Chem. 144 (7) (2013) 981–986.
[29] S. Singh, A. Schober, M. Gebinoga, A. GroB, Tetrahedron Lett. 50 (2009) 1838–1843.
[30] T.W. Greene, P.G.M. Wutz, Greene's Protective Groups in Organic Synthesis, fourth ed., Wiley and Sons, New York, 2007.
[31] J.B. Van Tol, D.E. Kraayveld, J.A. Jongejan, J.A. Duine, Biocatal. Biotransform. 12 (1995) 119–136.
[32] W. Jin, Q. Yang, P. Wu, J. Chen, Z. Yu, Adv. Syn. Cat. 356 (2014) 2097–2102.
[33] Y. Takano, F. Shiga, J. Asano, N. Ando, H. Uchiki, K. Fukuchi, T. Anraku, Bioorg. Med. Chem. 13 (2005) 5841–5863.
[34] Y.H. Zhao, M.H. Abraham, J. Lee, A. Hersey, C.N. Luscombe, G. Beck, B. Sherborne, I. Cooper, Pharm. Res. 19 (2002) 1446–1457.
[35] Molinspiration Cheminformatics. www.molinspiration.com.
[36] C.A. Lipinski, F. Lombardo, B.W. Dominy, P.J. Feeney, Adv. Drug Deliv. Rev. 46 (2001) 3–26.
[37] http://molsoft.com/mprop/.
[38] D.F. Veber, S.R. Johnson, H.-Y. Cheng, B.R. Smith, K.W. Ward, K.D. Kopple, J. Med. Chem. 45 (2002) 2615–2623.
[39] A. Polinsky, The Practice of Medicinal Chemistry, second ed., Academic Press, London, 2003, pp. 147–155.
[40] P. Ertl, B. Rohde, P. Selzer, J. Med. Chem. 43 (2000) 3714–3717.
[41] M.A. Bakht, M.S. Yar, S.G. Abdel-Hamid, S.I. Al Qasoumi, A. Samad, Eur. J. Med. Chem. 45 (12) (2010) 5862–5869.