European Journal of Medicinal Chemistry 44 (2009) 1997–2001

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

*N*1-Alkylated 3,4-dihydropyrimidine-2(1*H*)-ones: Convenient one-pot selective synthesis and evaluation of their calcium channel blocking activity

Kamaljit Singh [a,*], Divya Arora [a], Elizabeth Poremsky [b], Jazmyne Lowery [b], Robert S. Moreland [b]

[a] *Organic Synthesis Laboratory, Department of Applied Chemical Sciences and Technology, Guru Nanak Dev University, Amritsar 143 005, India*
[b] *Department of Pharmacology and Physiology, Drexel University College of Medicine, Philadelphia, PA 19102, USA*

ARTICLE INFO

Article history:
Received 31 March 2008
Received in revised form
22 September 2008
Accepted 2 October 2008
Available online 11 October 2008

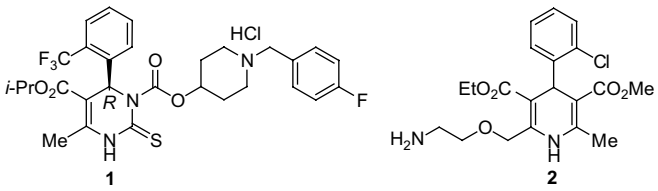
Keywords:
Phase transfer catalysis
N-Alkylation
Biginelli dihydropyrimidinones
Regioselective
Tetrabutylammonium hydrogen sulfate
Vascular smooth muscle

ABSTRACT

It has been found that selective *N*1-alkylation of 3,4-dihydropyrimidine-2(1*H*)-ones can be achieved under solvent-less, mild phase transfer catalytic (PTC) conditions with tetrabutylammonium hydrogen sulfate and 50% aqueous NaOH as the catalyst and base, respectively. The procedure is tolerant to substitutional variation at key diversity points on the pyrimidinone moiety.

1. Introduction

Drugs of three different chemical categories – 1,4-dihydropyridines (DHP) (e.g., nifedipine), phenylalkylamines (e.g., verapamil) and benzothiazepines (e.g., diltiazem) represent the most studied organic calcium channel blockers and are used in the treatment of cardiovascular disorders including hypertension [1]. They are known to bind to three different, but allosterically linked, sites on the α_1 subunit of the calcium channel. The biological activity of these compounds, in particular symmetrical 1,4-DHPs bearing equivalent substituents at C-2/C-6 and esters at C-3/C-5, arises due to the structural features such as an axial aromatic ring at C-4, the plane of which bisects the boat conformation of the DHP ring. A similar binding model has been proposed [2] for a closely related, unsymmetrical dihydropyrimidinones (DHPMs) (Fig. 1), which possess an inherent chiral centre at C-4 by virtue of unsymmetrical substituent modifications. A variety of DHPM have been synthesized and examined for their calcium channel blocking properties using various synthetic routes. In general accord with structure–activity relationships, established for 1,4-DHP calcium channel blockers [3,4], it has been found that *N*3-(alkyl, acyl, carbamate, sulfonyl, ureido) [5–9] substituted-2-hetero (S > O > N)-1,4-dihydropyrimidines [5] (Fig. 2) mimic the activity of 1,4-DHPs. Also it has been found that *ortho* and/or *meta* aromatic substitution, ester alkyl group were major determinants of in vitro potency. DHPM **1** has been identified as a lead with *R*-enantiomer [8] both more potent as well as long lasting and compares most favorably with the long-acting DHP derivative amlodipine **2**, in spontaneously hypertensive rats.



1 **2**

Intrigued by such investigations, we undertook synthetic manipulation of C-6, N-3 and C-4 positions of DHPMs [10–12], as well as investigations of the calcium channel binding properties of a number of these derivatives. Investigations in the calcium channel binding properties of the *N*-1 substituted DHPM derivatives which bear a close similarity with some biologically active molecules [13,14] has not thus far been undertaken. Herein, we report a general route to *N*-1 substituted DHPMs as well as

* Corresponding author. Tel.: +91 183 2258853; fax: +91 183 2258819/20.
E-mail address: kamaljit19in@yahoo.co.in (K. Singh).

0223-5234/$ – see front matter © 2008 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2008.10.002

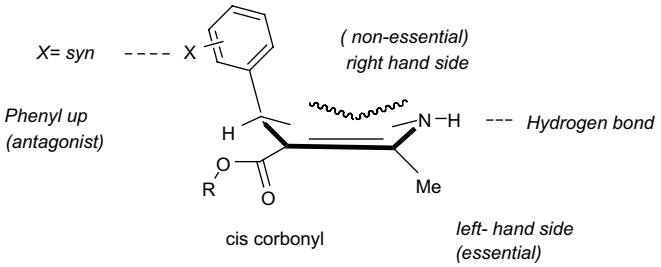


Fig. 1. Proposed receptor-bound dihydropyrimidine conformation (antagonist).

screening results of some of the representative compounds for their calcium channel blocking activity.

2. Chemistry

The available route of *N*-1 alkylation of DHPMs using *N*-substituted ureas face limitation owing to low yields and the requirement of a number of urea derivatives, which are not available commercially [15]. With the failure of the standard alkylation conditions to show selectivity in *N*-1 alkylation, the use of Mitsunobu-type reaction conditions furnishes *N*-1 alkylated DHPMs, but reagents used are reasonably expensive [16]. But the method is attractive in so far as the formation of mixtures of *N*-1/*N*-3 alkylated DHPMs [17] is avoided.

Recently, we have revealed that Biginelli DHPMs can be regioselectively substituted (acylation and alkoxycarbonylation) [11] at the N-3 position, with a wide variety of electrophiles. Use of a similar methodology through reaction of DHPMs with a base (LDA or *n*-BuLi/−78 °C/THF) followed by quenching with electrophiles such as iodomethane [10,11] or CH-acidic compounds [10,11] such as ethyl bromoacetate or ethyl 2-bromopropionate, resulted in rather indiscriminate attack at C-6 methyl/N-1/N-3 positions resulting in mixture of products. PTC has been established as a versatile method especially for *N*-alkylation reaction of various types of heterocyclic moieties [18]. We have found that a one-pot N1-alkylation of DHPMs **3** could be achieved in high yields, under solvent-free conditions employing tetrabutylammonium hydrogen sulfate and 50% aqueous NaOH as the catalyst and base (Scheme 1), respectively.

The present protocol of *N*-1 alkylation not only preserves the simplicity of synthetic operation but also furnished remarkable selectivity (over *N*-3) in alkylation reaction, furnishing the products in moderate to high yields. The reaction can be performed under relatively simple reaction conditions by stirring together, an appropriate DHPM, electrophile and 50% aqueous sodium hydroxide solution at ambient temperature for specific time (Table 1), without using a solvent. After the reaction is over, the excess electrophile can even be recovered through phase separation and reused. The results presented in Table 1 indicate the scope and generality of the method, which is efficient not only from the point of view of the substituents of the DHPM core, but also with respect to the alkylating agent. Although trace amounts of the corresponding *N*1,*N*3-disubstituted products could be detected in some cases, ethyl-1,2,3-trimethyl-2-oxo-4-(phenyl)-3,4-dihydropyrimidine-5-carboxylate **5** was obtained in 8–10% isolated yield along with **4a**. It has also been found that neither of R^1, R^2, R^3 or R^4 has influenced the regioselectivity or yield of the desired *N*-1 alkylated products.

The structures of the newly synthesized compounds have been established on the basis of elemental analysis and spectroscopic techniques and are presented in Section 5.

3. Biological results and discussion

The study of *N*-1 substituted DHPMs facilitates supplementing information about structure requirements important to biological activity. It also affords to expand the existing structure–activity relationships, and, potentially to discover additional structure modifications consistent with improved biological activity.

The newly synthesized compounds were screened for their calcium channel blocking activity based on their ability to relax a membrane depolarization induced contraction of vascular smooth muscle. Swine carotid arteries were obtained from a local slaughterhouse and transported to the laboratory in an ice-cold MOPS buffered physiological salt solution (PSS). The PSS contained, in mM: 140 NaCl, 4.7 KCl, 1.2 $MgSO_4$, 1.6 $CaCl_2$, 1.2 Na_2HPO_4, 2 3-[*N*-morpholino] propane sulfonic acid (MOPS, pH 7.4), 5 D-glucose, and 0.02 Na_2-ethylenediaminetetraacetic acid (EDTA). Arteries were cleaned of connective tissue, and then dissected free of both intima and adventitia leaving a thin medial layer for experimentation. Intact medial strips of swine carotid artery (7×0.7 mm) were suspended between a Grass FT.03 force transducer and a stationary clip in water-jacketed organ baths. The strips were equilibrated in PSS at 37 °C, pH 7.4 and bubbled with 100% O_2 for 90–120 min. A passive force of ~2 g was applied to all tissues. This passive force sets the muscle at a length that approximates L_o, the length at which maximal active force is generated. During the equilibration period, tissues were maximally contracted with 110 mM KCl (equimolar substitution for NaCl) several times until similar levels of force were attained.

The equilibrated vascular strips were contracted with 110 mM KCl containing PSS, allowed to achieve a stable level of force and then subjected to the cumulative addition of calcium channel blocker (1 μM to 30 mM) or DMSO as a vehicle control. Data are presented (Fig. 3) as a percent of the initial maximal response to 110 mM KCl at each dose of compound.

The calcium channel blockers were compared against nifedipine for their ability to relax a membrane depolarization induced contraction which is almost exclusively dependent on the influx of extra-cellular calcium [19]. The novel compounds and nifedipine were tested across a concentration range of 1 μM to 30 mM. Nifedipine completely relaxed the KCl-induced contraction with an IC_{50} in the 10 μM range. In contrast compounds **4b**–**4g** and **5** maximally relaxed the KCl-induced contractions by only 40% with IC_{50}s ranging from 100 to 300 μM.

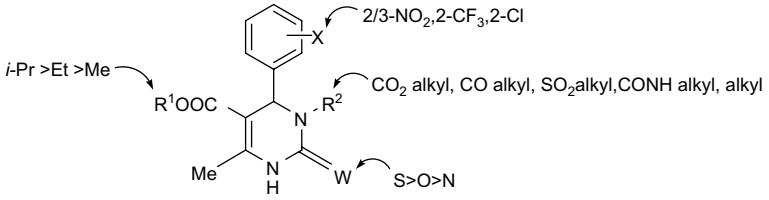
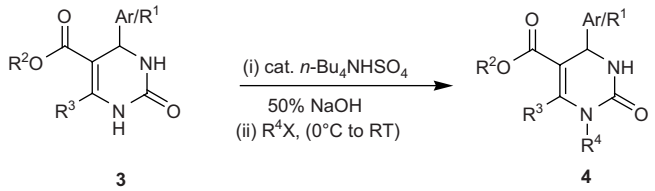


Fig. 2. General structure–activity relationship of 1,4-dihydropyrimidine calcium channel blockers.



Scheme 1. *N*-1 Alkylation of Biginelli DHPMs under phase transfer catalytic conditions.

4. Conclusions

Thus an efficient protocol for the selective *N*1-alkylation of 3,4-dihydropyrimidin-2(1*H*)-ones using PTC, under mild solvent-free reaction conditions is presented. The method holds potential for the preparation of **4** in multi-gram scale as has been achieved in case of **4a** in this investigation. Among the novel compounds tested very minor calcium channel blocking activity was observed as compared to nifedipine in a screen using relaxation of a membrane depolarized vascular tissue as the end-point.

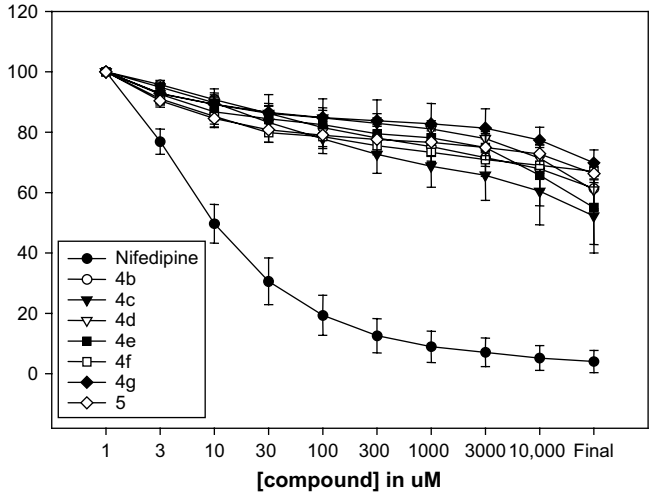


Fig. 3. Medial strips from the swine carotid artery were contracted with 110 mM KCl-PSS and then subjected to the cumulative addition of calcium channel blocker to determine their potential for relaxation. Nifedipine and 6 novel calcium channel blockers (**4b**–**4g** and **5**) were tested.

5. Experimental

Melting points were determined by open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on JEOL FT-NMR AL-300 MHz spectrophotometer using TMS as an internal standard. The mass spectra were recorded on Esquire 3000-00037 mass spectrophotometer. The elemental analysis was done on Thermo Flash EA 112. The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plates using *n*-hexane and ethyl acetate as solvent system. Analyses indicated by the symbols of the elements were within ±0.4% of the theoretical values.

5.1. General procedure for the synthesis of ethyl-1,6-dimethyl-2-oxo-4-(phenyl)-3,4-dihydropyrimidine-5-carboxylate (*4a*–*q*/*5*)

To a mixture of DHPM **3** (5.26 mmol), tetrabutylammonium hydrogen sulfate (5.21 mmol) and an electrophile (0.16 mol) in a round bottomed flask, aqueous NaOH solution (2.0 ml, 50% w/v) was added slowly with stirring at 0 °C. After stirring for half an hour, the reaction mixture was shifted to room temperature and stirred to complete the reaction (TLC). The reaction was neutralized using aqueous hydrochloric acid solution (1 N). Extractive workup with ethyl acetate furnished corresponding **4**/**5** which were further purified using column chromatography on silica gel (60–120 mesh). The characterization data of the compounds is given below.

Table 1
N-1 Alkylation of 3,4-dihydropyrimidinones **3** using PTC.[a]

Product[b]	R^1	R^2	R^3	R^4X	Reaction Time (h)	Yield (%)
4a[c]	C_6H_5	C_2H_5	CH_3	CH_3I	3	90
4b	C_6H_5	C_2H_5	CH_3	C_2H_5Br	3	87
4c	C_6H_5	C_2H_5	CH_3	n-C_3H_7Br	3	92
4d	C_6H_5	C_2H_5	CH_3	n-C_4H_9Br	3	85
4e	C_6H_5	C_2H_5	CH_3	n-C_5H_{11}	3	95
4f	C_6H_5	C_2H_5	CH_3	n-$C_{10}H_{21}Br$	4	85
4g	C_6H_5	C_2H_5	CH_3	CH_2=$CHCH_2Br$	5	80
4h	C_6H_5	C_2H_5	CH_3	$Br(CH_2)_4Br$	5	75
4i	C_6H_5	C_2H_5	CH_3	$Br(CH_2)_5Br$	5	72
4j	C_6H_5	C_2H_5	CH_3	$Br(CH_2)_6Br$	5	77
4k	$C_6H_4OCH_3$	C_2H_5	CH_3	n-C_4H_9Br	4	82
4l	$C_6H_3(OCH_3)_2$	C_2H_5	CH_3	n-C_4H_9Br	4	81
4m	CH_3	C_2H_5	CH_3	n-C_4H_9Br	3	80
4n	C_5H_{11}	C_2H_5	CH_3	n-C_4H_9Br	3	81
4o	C_6H_5	CH_3	CH_3	n-C_4H_9Br	3	79
4p	CH_3	CH_3	CH_3	n-C_4H_9Br	4	83
4q	CH_3	C_2H_5	C_6H_5	n-C_4H_9Br	5	89

[a] Tetrabutylammonium hydrogen sulfate was employed as catalyst. Reactions were considerably slow when tetraethylbenzylammonium chloride was employed.
[b] Trace amounts of *N*1,*N*3-dialkylated products were also formed in some cases.
[c] Corresponding *N*1,*N*3-dimethyl derivative **5** was also isolated in 8–10% yield.

Compound ***4a***. White solid; R_f: 0.5 (45% ethyl acetate/hexane); yield: 90%, mp = 170 °C, ^{1}H NMR ($CDCl_3$) δ: 1.18 (t, 3H, J = 7.2 Hz, ester-CH_3), 2.51 (s, 3H, CH_3), 3.23 (s, 3H, NCH_3), 4.10 (q, 2H, J = 7.2 Hz, ester-CH_2), 5.38 (d, 2H, J = 2.7 Hz, CH), 5.52 (s, NH, exchanged with D_2O), 7.23–7.29 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ: 14.1, 16.4, 30.2, 53.8, 60.1, 104.1, 126.1, 127.7, 128.6, 143.3, 148.5, 153.9 and 166.0. Anal. $C_{15}H_{18}N_2O_3$: C, 65.69; H, 6.56; N, 10.21. Found: C, 65.72; H, 6.96; N, 10.52; MS: m/z 274 (M^+).

Compound ***4b***. White solid; R_f: 0.5 (45% ethyl acetate/hexane); yield: 87%; mp = 118 °C (dichloromethane); ^{1}H ($CDCl_3$) δ: 1.17 (t, 3H, J = 6.9 Hz, ester-CH_3), 1.21 (t, 3H, J = 7.2 Hz, CH_3), 2.53 (s, 3H, CH_3), 3.70–3.94 (m, 2H, NCH_2), 4.08 (q, 2H, J = 6.9 Hz, ester-CH_2), 5.35 (d, 2H, J = 2.7 Hz, CH), 5.63 (s, NH, exchanged with D_2O), 7.21–7.29 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ: 13.6, 14.4, 15.3, 37.1, 53.4, 59.5, 103.8, 125.7, 127.1, 128.0, 143.1, 148.0, 152.9 and 165.6. Anal. $C_{16}H_{20}N_2O_3$: C, 66.66; H, 6.94; N, 9.72. Found: C, 66.94; H, 6.96; N, 9.92; MS: m/z 288 (M^+).

Compound ***4c***. White solid; R_f: 0.5 (45% ethyl acetate/hexane); yield: 92%; mp = 108 °C (dichloromethane); ^{1}H ($CDCl_3$) δ: 0.86 (t, 3H, J = 7.2 Hz, ester-CH_3), 1.15 (m, 3H, CH_3), 1.13–1.19 (m, 2H, CH_2), 2.51 (s, 3H, CH_3), 3.48–3.89 (m, 2H, NCH_2), 4.08 (m, 2H, ester-CH_2), 5.35 (d, 2H, J = 3.0 Hz, CH), 5.86 (s, NH, exchanged with D_2O), 7.22–7.29 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ: 10.9, 14.0, 15.9, 22.9, 44.0, 53.6, 59.9, 104.3, 126.1, 127.4, 128.4, 143.4, 148.7, 153.7 and 166.1. Anal. $C_{17}H_{22}N_2O_3$: C, 67.54; H, 7.28; N, 9.27. Found: C, 67.72; H, 7.38; N, 9.42; MS: m/z 302 (M^+).

Compound ***4d***. White solid; R_f: 0.5 (45% ethyl acetate/hexane); yield: 85%; mp = 110 °C (dichloromethane); ^{1}H ($CDCl_3$) δ: 0.91 (t, 3H, J = 7.2 Hz, ester-CH_3), 1.17 (t, 3H, J = 7.2 Hz, CH_3), 1.29 (m, 2H, CH_2), 1.55 (m, 2H, CH_2), 2.56 (s, 3H, CH_3), 3.53–3.96 (m, 2H, NCH_2), 4.09 (q, 2H, J = 7.2 Hz, ester-CH_2), 5.35 (d, 1H, J = 2.7 Hz, CH), 5.42 (s, NH, exchanged with D_2O), 7.23–7.29 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ: 13.7, 14.0, 16.0, 19.9, 25.6, 37.8, 54.1, 60.1, 126.2, 128.6, 143.1, 143.4 and 194.3. Anal. $C_{18}H_{24}N_2O_3$: C, 68.35; H, 7.59; N, 8.86. Found: C, 68.17; H, 7.38; N, 8.52; MS: m/z 316 (M^+).

Compound ***4e***. White solid; R_f: 0.5 (45% ethyl acetate/hexane); yield: 95%; mp = 121 °C (dichloromethane); ^{1}H ($CDCl_3$) δ: 0.88

(t, 3H, $J = 7.2$ Hz, ester-CH_3), 1.76 (t, 3H, $J = 7.2$ Hz, CH_3), 1.27 (m, 4H, $2 \times CH_2$), 2.52 (s, 3H, CH_3), 3.58–3.91 (m, 2H, NCH_2), 4.09 (q, 2H, $J = 6.9$ Hz, ester-CH_2), 5.30 (s, NH, exchanged with D_2O), 5.35 (s, 1H, CH), 7.26–7.30 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ: 13.9, 14.1, 16.0, 22.3, 28.8, 29.5, 42.6, 54.0, 60.1, 104.4, 126.2, 127.7, 128.6, 143.4, 148.7, 153.4 and 166.1. Anal. $C_{19}H_{26}N_2O_3$: C, 69.09; H, 7.87; N, 8.48. Found: C, 69.38; H, 7.96; N, 8.71; MS: m/z 330 (M^+).

Compound ***4f***. White solid; R_f: 0.5 (45% ethyl acetate/hexane); yield: 85%; mp = 103 °C (dichloromethane); ^{1}H ($CDCl_3$) δ: 0.88 (t, 3H, $J = 6.9$ Hz, ester-CH_3), 1.17 (t, 3H, $J = 7.2$ Hz, CH_3), 1.25 (s, 16H, $8 \times CH_2$), 2.52 (s, 3H, CH_3), 3.52–3.95 (m, 2H, NCH_2), 4.08 (q, 2H, $J = 7.2$ Hz, ester-CH_2), 5.35 (s, 1H and NH, exchanged with D_2O), 7.23–7.29 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ: 14.1, 16.1, 22.6, 29.2, 29.8, 31.8, 42.7, 60.1, 67.1, 90.3, 126.2, 128.6, 148.7, 165.8, 175.7 and 180.7. Anal. $C_{24}H_{36}N_2O_3$: C, 72.00; H, 9.00; N, 12.00. Found: C, 72.15; H, 9.17; N, 12.11; MS: m/z 400 (M^+).

Compound ***4g***. White solid; R_f: 0.5 (45% ethyl acetate/hexane); yield: 80%; mp = 122 °C (dichloromethane); ^{1}H ($CDCl_3$) δ: 1.16 (t, 3H, $J = 7.2$ Hz, ester-CH_3), 2.50 (s, 3H, CH_3), 4.09 (q, 2H, $J = 7.2$ Hz, ester-CH_2), 4.40 (q, 2H, $J = 21.3$ Hz, CH_2), 5.13 (t, 2H, $J = 18.0$ Hz, CH_2), 5.39 (s, 1H, CH), 5.69 (broad, NH, exchanged with D_2O), 5.79–5.91 (m, 1H, CH), 7.27–7.29 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ: 14.0, 15.9, 44.8, 53.9, 60.1, 104.2, 116.0, 126.2, 127.6, 128.5, 133.9, 143.3, 148.8 and 166.0. Anal. $C_{17}H_{20}N_2O_3$: C, 68.00; H, 6.66; N, 9.33. Found: C, 68.14; H, 6.44; N, 9.11; MS: m/z 300 (M^+).

Compound ***4h***. White solid; R_f: 0.5 (45% ethyl acetate/hexane); yield: 75%; mp = 140 °C (dichloromethane); ^{1}H ($CDCl_3$) δ: 1.17 (t, 3H, $J = 7.2$ Hz, ester-CH_3), 1.69–1.80 (m, 4H, $2 \times CH_2$), 2.54 (s, 3H, CH_3), 3.38 (t, 2H, $J = 6.3$ Hz, CH_2Br) 3.62–3.97 (m, 2H, NCH_2), 4.10 (q, 2H, $J = 6.9$ Hz, ester-CH_2), 5.37 (s, 1H and NH, exchanged with D_2O), 7.23–7.31 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ: 14.0, 15.9, 28.2, 29.5, 33.0, 41.3, 53.5, 60.1, 104.8, 126.0, 127.6, 128.5, 143.2, 148.3, 153.7 and 166.0. Anal. $C_{18}H_{23}N_2O_3Br$: C, 54.68; H, 5.82; N, 7.08. Found: C, 54.38; H, 5.82; N, 7.01; MS: m/z 395 (M^+).

Compound ***4i***. White solid; R_f: 0.5 (45% ethyl acetate/hexane); yield: 72%; mp = 122 °C (dichloromethane); ^{1}H ($CDCl_3$) δ: 1.17 (t, 3H, $J = 7.2$ Hz, ester-CH_3), 1.37–1.87 (m, 6H, $3 \times CH_2$), 2.52 (s, 3H, CH_3), 3.35 (t, 2H, $J = 6.9$ Hz, CH_2Br), 3.57–3.91 (m, 2H, NCH_2), 4.10 (q, 2H, $J = 7.2$ Hz, ester-CH_2), 5.36 (s, 1H and NH, exchanged with D_2O), 7.23–7.30 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ: 14.0, 16.0, 25.1, 28.8, 32.2, 33.2, 42.1, 53.5, 60.1, 104.7, 126.1, 127.5, 128.5, 143.4, 148.5, 153.6 and 166.0. Anal. $C_{19}H_{25}N_2O_3Br$: C, 55.74; H, 6.11; N, 6.84. Found: C, 55.88; H, 6.02; N, 6.94; MS: m/z 409 (M^+).

Compound ***4j***. White solid; R_f: 0.5 (45% ethyl acetate/hexane); yield: 77%; mp = 128 °C (dichloromethane); ^{1}H ($CDCl_3$) δ: 1.17 (t, 3H, $J = 7.2$ Hz, ester-CH_3), 1.22–1.84 (m, 8H, $4 \times CH_2$), 2.52 (s, 3H, CH_3), 3.38 (t, 2H, $J = 6.9$ Hz, CH_2Br), 3.59–3.91 (m, 2H, NCH_2), 4.10 (q, 2H, $J = 6.9$ Hz, ester-CH_2), 5.37 (s, 1H and NH, exchanged with D_2O), 7.23–7.33 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ: 14.0, 15.9, 25.7, 27.6, 29.4, 32.4, 33.6, 42.2, 53.3, 60.0, 104.5, 126.0, 127.4, 128.4, 143.3, 148.6, 153.7 and 166.0. Anal. $C_{20}H_{27}N_2O_3Br$: C, 56.73; H, 6.38; N, 6.61. Found: C, 56.79; H, 6.37; N, 6.66; MS: m/z 423 (M^+).

Compound ***4k***. White solid; R_f: 0.5 (45% ethyl acetate/hexane); yield: 82%; mp = 120 °C (dichloromethane); ^{1}H ($CDCl_3$) δ: 0.92 (t, 3H, $J = 7.2$ Hz, ester-CH_3), 1.17 (t, 3H, $J = 7.0$ Hz, CH_3), 1.26–1.61 (m, 4H, $2 \times CH_2$), 2.51 (s, 3H, CH_3), 3.58–3.90 (m, 2H, NCH_2), 3.78 (s, 3H, OCH_3), 4.08 (q, 2H, $J = 7.0$ Hz, ester-CH_2), 5.31 (s, 1H, CH), 5.34 (broad, NH, exchanged with D_2O), 6.81 (d, 2H, $J = 8.6$ Hz, ArH), 7.16 (d, 2H, $J = 8.8$ Hz, ArH); ^{13}C NMR ($CDCl_3$) δ: 13.7, 14.1, 16.0, 19.9, 31.8, 42.3, 53.4, 55.2, 60.0, 104.7, 113.8, 127.4, 135.8, 148.3, 153.5, 159.0 and 166.2. Anal. $C_{19}H_{26}N_2O_4$: C, 65.89; H, 7.51; N, 8.09. Found: C, 66.00; H, 7.37; N, 8.25; MS: m/z 346 (M^+).

Compound ***4l***. White solid; R_f: 0.5 (45% ethyl acetate/hexane); yield: 81%; mp = 105 °C (dichloromethane); ^{1}H ($CDCl_3$) δ: 0.88 (t, 3H, $J = 7.2$ Hz, ester-CH_3), 1.11 (t, 3H, $J = 6.9$ Hz, CH_3), 1.22–1.54 (m, 4H, $2 \times CH_2$), 2.60 (s, 3H, CH_3), 3.44–4.01 (m, 2H, NCH_2), 3.73 (s, 1H, OCH_3), 3.78 (s, 1H, OCH_3), 4.06 (q, 2H, $J = 7.2$ Hz, ester-CH_2), 5.56 (d, 1H, CH), 5.64 (broad, NH, exchanged with D_2O), 6.35 (dd, 1H, $J = 6.0$ Hz, ArH), 6.45 (d, 1H, $J = 2.1$ Hz, ArH), 6.99 (d, 1H, $J = 8.4$ Hz, ArH); ^{13}C NMR ($CDCl_3$) δ: 13.6, 14.0, 15.9, 19.8, 32.0, 42.1, 48.0, 55.2, 59.9, 98.6, 102.3, 103.4, 122.1, 126.8, 150.0, 154.0, 157.8, 160.4 and 166.2. Anal. $C_{20}H_{28}N_2O_5$: C, 63.82; H, 7.44; N, 7.44. Found: C, 63.75; H, 7.37; N, 7.66; MS: m/z 376 (M^+).

Compound ***4m***. White solid; R_f: 0.5 (45% ethyl acetate/hexane); yield: 80%; mp = 85 °C (dichloromethane); ^{1}H ($CDCl_3$) δ: 0.94 (t, 3H, $J = 6.9$ Hz, ester-CH_3), 1.20–1.65 (m, 7H, CH_3 and $2 \times CH_2$), 2.46 (s, 3H, CH_3), 3.46–3.98 (m, 2H, NCH_2), 4.14–4.22 (m, 2H, ester-CH_2), 4.30–4.33 (m, 1H, CH), 5.04 (broad, NH, exchanged with D_2O); ^{13}C NMR ($CDCl_3$) δ: 13.7, 14.2, 15.7, 19.9, 23.1, 31.9, 42.0, 45.9, 59.8, 106.0, 148.4, 154.4 and 166.1. Anal. $C_{13}H_{22}N_2O_3$: C, 61.41; H, 8.66; N, 11.02. Found: C, 61.15; H, 8.79; N, 10.95; MS: m/z 254 (M^+).

Compound ***4n***. White solid; R_f: 0.5 (45% ethyl acetate/hexane); yield: 81%; mp = 70 °C (dichloromethane); ^{1}H ($CDCl_3$) δ: 0.90 (m, 6H, $2 \times CH_3$), 1.22–1.63 (m, 15H, $6 \times CH_2$ and CH_3), 2.45 (s, 3H, CH_3), 3.43–3.95 (m, 2H, NCH_2), 4.13–4.22 (m, 3H, ester-CH_2 and CH), 5.17 (s, NH, exchanged with D_2O); ^{13}C NMR ($CDCl_3$) δ: 13.6, 13.8, 14.1, 15.8, 19.9, 22.4, 24.0, 31.3, 31.8, 36.6, 42.0, 49.8, 59.8, 105.1, 148.6, 154.5 and 166.2. Anal. $C_{17}H_{29}N_2O_3$: C, 66.01; H, 9.38; N, 9.06. Found: C, 66.00; H, 9.27; N, 9.10; MS: m/z 309 (M^+).

Compound ***4o***. White solid; R_f: 0.5 (45% ethyl acetate/hexane); yield: 79%; mp = 97 °C (dichloromethane); ^{1}H ($CDCl_3$) δ: 0.90 (t, 3H, $J = 7.2$ Hz, ester-CH_3), 1.23–1.59 (m, 4H, $2 \times CH_2$), 2.52 (s, 3H, CH_3), 3.56–3.92 (m, 2H, NCH_2), 3.63 (s, 3H, OCH_3), 5.35 (d, 1H, $J = 3.0$ Hz, CH), 5.71 (broad, NH, exchanged with D_2O), 7.22–7.33 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ: 13.6, 15.9, 19.7, 31.7, 42.1, 51.1, 53.2, 104.1, 125.9, 127.4, 128.4, 143.2, 149.1, 153.9 and 166.5. Anal. $C_{17}H_{22}N_2O_3$: C, 67.54; H, 7.28; N, 9.27. Found: C, 67.52; H, 7.39; N, 9.10; MS: m/z 302 (M^+).

Compound ***4p***. White solid; R_f: 0.5 (45% ethyl acetate/hexane); yield: 83%; mp = 72 °C (dichloromethane); ^{1}H ($CDCl_3$) δ: 0.94 (t, 3H, $J = 7.0$ Hz, ester-CH_3), 1.22 (d, 3H, $J = 7.0$ Hz, CH_3), 1.29–1.58 (m, 4H, $2 \times CH_2$), 2.46 (s, 3H, CH_3), 3.46–3.93 (m, 2H, NCH_2), 3.71 (s, 3H, OCH_3), 4.29–4.34 (m, 1H, CH), 5.69 (broad, NH, exchanged with D_2O); ^{13}C NMR ($CDCl_3$) δ: 13.5, 15.6, 19.7, 22.8, 31.7, 41.8, 45.5, 50.9, 105.5, 148.6, 154.3 and 166.4. Anal. $C_{12}H_{20}N_2O_3$: C, 60.00; H, 8.33; N, 11.66. Found: C, 60.13; H, 8.19; N, 11.59; MS: m/z 240 (M^+).

Compound ***4q***. White solid; R_f: 0.5 (45% ethyl acetate/hexane); yield: 89%; mp = 118 °C (dichloromethane); ^{1}H ($CDCl_3$) δ: 0.68–0.86 (m, 6H, ester-CH_3 and CH_3), 1.00–1.13 (m, 2H, CH_2), 1.25–1.44 (m, 5H, CH_3 and CH_2), 2.89–3.71 (m, 2H, NCH_2), 3.83 (q, 2H, $J = 7.0$ Hz, ester-CH_2), 4.39–4.43 (m, 1H, CH), 5.37 (broad, NH, exchanged with D_2O), 7.20–7.41 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ: 13.4, 13.5, 19.6, 23.3, 31.6, 43.3, 46.5, 59.6, 107.3, 127.9, 128.1, 128.5, 129.0, 134.6, 149.8, 154.4 and 165.4. Anal. $C_{18}H_{24}N_2O_3$: C, 68.35; H, 7.59; N, 8.86. Found: C, 68.17; H, 7.44; N, 8.70; MS: m/z 316 (M^+).

Compound ***5***. White solid; R_f: 0.5 (60% ethyl acetate/hexane); yield: 10%; mp = 55 °C (dichloromethane); ^{1}H ($CDCl_3$) δ: 1.23 (t, 3H, $J = 7.2$ Hz, ester-CH_3), 2.47 (s, 3H, CH_3), 2.91 (s, 3H, NCH_3), 3.26 (s, 3H, NCH_3), 4.12 (q, 2H, $J = 7.2$ Hz, ester-CH_2), 5.24 (s, 1H, CH), 7.21–7.31 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ: 14.1, 16.5, 30.9, 34.3, 60.0, 60.7, 103.5, 126.5, 127.7, 128.5, 140.9, 141.1, 153.7 and 165.9. Anal. $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.92; H, 7.13; N, 10.25; MS: m/z 288 (M^+).

Acknowledgements

Financial support from CSIR (01(1960)/04/EMR-II) and UGC (31-53/2005/SR), New Delhi is gratefully acknowledged. DA thanks CSIR, New Delhi for research fellowship. This study was also supported in part by funds from National Institutes of Health grants HL 37945 and DK 57252 to RSM.

References

[1] D.J. Triggle, J. Cardiovasc. Pharmacol. 18 (1991) S1–6.
[2] W.M.F. Fabian, M.A. Semones, C.O. Kappe, J. Mol. Struct. (Theochem) 432 (1998) 219–228.
[3] R. Rodenkircken, R. Bayer, R. Steiner, F. Bossert, H. Meyer, E. Moller, Naunyn-Schiedeberg's Arch. Pharmacol. 310 (1979) 69–78.
[4] F. Bossert, H. Meyer, E. Wehnger, Angew. Chem., Int. Ed. Engl. 20 (1981) 762–769.
[5] K.S. Atwal, G.C. Rovnyak, B.C. O'Reilly, J. Schwartz, J. Org. Chem. 54 (1989) 5898–5907.
[6] K.S. Atwal, G.C. Rovnyak, S.D. Kimball, D.M. Floyd, S. Moreland, B.N. Swanson, J.Z. Gougoutas, J. Schwartz, K.M. Smillie, M.F. Malley, J. Med. Chem. 33 (1990) 2629–2635.
[7] K.S. Atwal, B.N. Swanson, S.E. Unger, D.M. Floyd, S. Moreland, A. Hedberg, B.C. O'Reilly, J. Med. Chem. 34 (1991) 806–811.
[8] G.C. Rovnyak, K.S. Atwal, A. Hedberg, S.D. Kimball, S. Moreland, J.Z. Gougoutas, B.C. O'Reilly, J. Schwartz, M.F. Malley, J. Med. Chem. 35 (1992) 3254–3263.
[9] K.S. Atwal, S. Moreland, Bioorg. Med. Chem. Lett. 1 (1991) 291–294.
[10] K. Singh, S. Singh, A. Mahajan, J. Org. Chem. 70 (2005) 6114–6117.
[11] K. Singh, S. Singh, Tetrahedron Lett. 47 (2006) 8143–8146.
[12] K. Singh, D. Arora, S. Singh, Tetrahedron Lett. 48 (2007) 1349–1352.
[13] C.M. Wright, R.J. Chovatiya, N.E. Jameson, D.M. Turner, G. Zhu, S. Werner, D.M. Huryn, J.M. Pipas, B.W. Day, P. Wipf, J.L. Brodsky, Bioorg. Med. Chem. 16 (2008) 3291–3301.
[14] S. Wisen, J. Androsavich, C.G. Evans, L. Chang, J.E. Gestwicki, Bioorg. Med. Chem. Lett. 18 (2008) 60–65.
[15] A. Stadler, C.O. Kappe, J. Comb. Chem. 3 (2001) 624–630.
[16] D. Dallinger, C.O. Kappe, Synlett 11 (2002) 1901–1903.
[17] E.L. Khanina, M.B. Andaburskaya, G. Duburs, R.M. Zolotoyabko, Latv. PRS Zinat. Akad. Vestis, Kim. Ser. (1978) 197;
Chem. Abstr. 89 (1978) 43319r.
[18] E.V. Dehmlow, S.S. Dehmlow, Phase-Transfer Catalysis, third ed. Verlag Chemie, Weinheim 1993.
[19] S. Moreland, R.S. Moreland, Am. J. Physiol. 252 (1987) H1049–H1058.