Indian Journal of Chemistry
Vol. 48B, December 2009, pp. 1738-1748

Synthesis and lipase-catalysed enantioselective acylation studies on ethyl 4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones

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Received and accepted 16 August 2009

A series of different analogs of 4-aryl-3,4-dihydropyrimidin-2(1*H*)-one have been synthesized and their biocatalytic resolution has been carried out using immobilized lipase CAL-L(A) (immobilized on accurel). The systematic one-step procedure is developed for the synthesis of optically enriched ethyl 4-aryl-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylates **8a-d** and acylated ethyl 4-aryl-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylates **9a-e**, **10a-e**, **11b-d** and **12a-e**, by the enantioselective acylation of racemic ethyl 4-aryl-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylates using CAL-L(A).

Keywords: Dihydropyrimidinones, Biginelli condensation, CAL-L(A), enantioselective acylation

Drug discovery since the late 20th century has increasingly focused on the definition and characterization of the molecular scaffolds that serve as targets for drug design. In the area of calcium channel blockers (CCBs: calcium antagonists and calcium channel modulators), structurally diverse groups of organic compounds have been recognized as calcium channel antagonists. There are three classes of CCBs, *e.g.* 1,4-dihydropyridines (1,4-DHPs), phenylalkylamines and benzothiazepines, these differ not only in their basic chemical structures, but also in their relative selectivity towards cardiac *versus* vascular L-type calcium channels. The most smooth muscle selective class of CCBs is the 1,4-DHPs, *e.g.* Nifedipine **1**, (*R*)-Nilvadipine **2**, *etc.* (**Figure 1,** ref. 2,3). Moreover, in the armamentarium of calcium channel blockers, appropriately functionalized 3,4-dihydropyrimidin-2(*1H*)-ones **3** (ref.4,5), have received considerable attention in recent past owing to their structural similarity with 1,4-dihydropyridine based drugs. Particular interest has been devoted to potent orally active antihypertensive agents, such as (*R*)-SQ 32926 **4** and related derivatives.

The inherently asymmetric dihydropyrimidinones have been extensively studied to expand the existing structure-activity relationships (SARs) and to get further insight into molecular interactions at the receptor level.[6-9] Kappe[10] reported the pharmacological studies on uniquely designed single-enantiomer of forty different aryl-3,4-dihydropyrimidinones (DHPMs) and have established that the calcium channel modulation (antagonist *versus* agonist activity) is dependent on the absolute configuration at C-4, whereby the orientation of the C-4 aryl group (*R*- or *S*-configuration) acts as a "molecular switch" between antagonist (aryl-group up) and agonist (aryl-group down) activity. A *cis*-carbonyl ester orientation with respect to the C-5 and C-6 dihydropyrimidine double bond was also found mandatory for optimum calcium channel modulatory activity. Triggle *et al*[11]. reported that the individual enantiomers of DHPMs have opposing pharmacological effects on the calcium channel; access to pure enantiomer of the compound

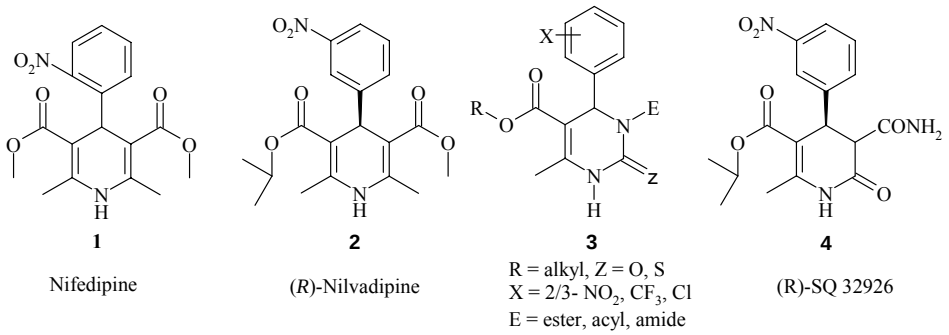


Figure 1

DHPMs is an important requirement for the development of cardiovascular drugs of this structural type. Literature reveals that enantiomerically pure DHPMs can be obtained by resolution of the corresponding racemic 5-carboxylic acids *via* fractional crystallization of diastereoisomeric α-methylbenzyl-ammonium salts[12] .

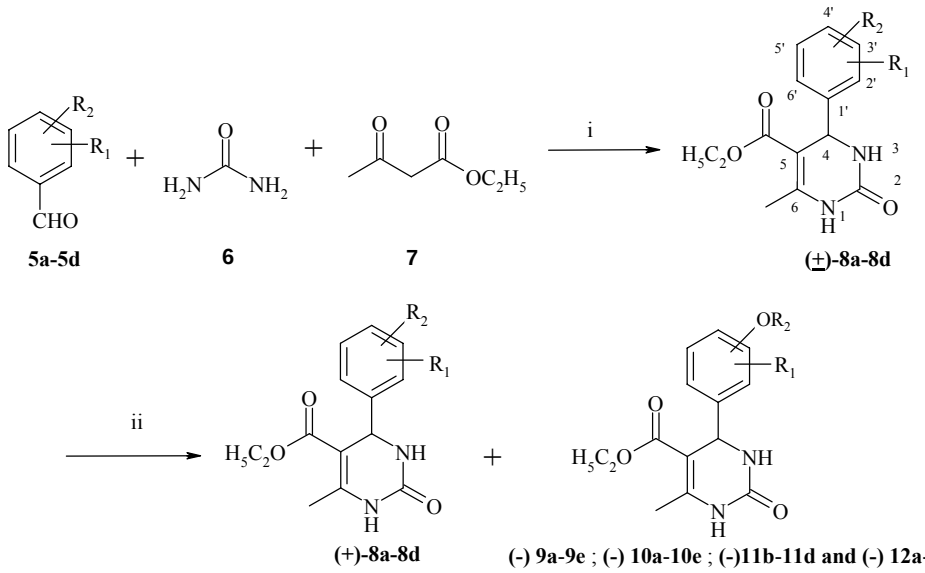
Over the years, we have been actively working in the stimulating area of DHPMs. Earlier we have successfully carried out the Novozyme®-435, an immobilized lipase from *Candida antarctica* mediated enantioselective deacetylation of (±)-4-aryl-6-methyl-3,4-dihyrodpyrimidinones[13]. In the present study, we have developed a direct, efficient CAL-L(A) mediated biocatalytic methodology for the enatioselective acylation of (±)-4-aryl-6-methyl-3,4-dihyrodpyrimidinones and have also optimized the acylation reaction by using different acid anhydrides.

Results and Discussion

The one-pot, three-component synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones has gained great importance in organic and medicinal chemistry as the dihydropyrimidine scaffold displays a facinating array of pharmacological properties ever since this was reported (published by Italian chemist, Pietro Biginelli in 1893, ref.14). Racemic ethyl (±)-4-aryl-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylates **8a-d** were prepared in 70-80% yields by multi-component Biginelli cyclocondensation of ethyl acetoacetate, urea and the corresponding aromatic hydroxyaldehydes **5a-d** in the presence of ferric chloride under microwave conditions, following the modified literature procedure (**Scheme I**, ref. 14,15).

Our past experience[16-19] came handy in the present study with the enzymes where we have successfully demonstrated stereoselective acylation/deacylation, amidation and epoxidation reactions on amines, different polyphenolic compounds, alcohols, dienes, sugars and isoxazolidine derivatives using porcine pancreatic, *Candida antarctica*, *Candida rugosa* or *Pseudomonas* species lipases. Our initial attempt was to screen different lipases, *i.e.* porcine pancreatic lipase (PPL), *Candida rugosa* lipase (CRL), Novozyme-435® (immobilized CAL-B) and CAL-L(A) lipase for enantioselective acylation of ethyl (±)-4-aryl-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylates **8a-d** in different organic solvents. No selectivity was observed on (±)-4-aryl-3,4-dihydropyrimidin-2-ones with PPL or CRL in different solvents at different temperatures. CAL-B in tetrahydrofuran (THF) catalyzed the acylation of ethyl (±)-3,4-dihydropyrimidin-2-ones very slowly. CAL-L(A) showed selectivity towards acylation of ethyl (±)-3,4-dihydropyrimidin-2-ones in THF at 55-60°C.

In a typical reaction, the racemic 3,4-dihydropyrimidin-2-one (**8a-d**, 1 mmole) and acid anhydride (acetic-, propanoic-, butanoic-, valaric- and heptanoic anhydride) were incubated with CAL-L(A) (~150 mg) in THF (20 ml) at 55-60°C. The progress of reaction was monitored periodically by TLC. After about 50% conversion of the starting material into product, the reaction was quenched by filtering off the enzyme and the solvent was removed from the reaction-mixture to get the gummy residue, which was subjected to column chromatography to afford the optically enriched/enzymatically acylated (-)-3,4-dihydropyrimidin-2-ones (**9a-e**, **10a-e**, **11b-d** and **12a-e**) and the unreacted hydroxy (+)-4-aryl-3,4-dihydropyrimidin-2-ones **8a-d** in 54-73% and 30-54 % yields, respectively (**Table I**). The structures of the enzymatically acylated (-)-4-aryl-6-methyl-3,4-dihydropyrimidin-one-5-carboxylates **9a-e**, **10a-e**, **11b-d** and **12a-e** and the recovered, unreacted (+)-4-aryl-3,4-dihydropyrimidin-2-ones **8a-d** were unambiguously established on the basis of their spectral data



Reagents and Conditions: i) microwave 1-2 min, $FeCl_3$, SiO_2; ii) CAL-L(A), THF, acid anhydrides ,10-35 h, 55-60 °C

Compounds 5-12	5 and 8		9		10		11		12	
	R_1	R_2	R_1	R_2 at C-3'	R_1	R_2 at C-4'	R_1 at C-5'	R_2 at C-2'	R_1 at C-3'	R_2 at C-4'
a	H	C-3'OH	H	$COCH_3$	H	$COCH_3$			OC_2H_5	$COCH_3$
b	H	C-4'OH	H	COC_2H_5	H	COC_2H_5	NO_2	COC_3H_7-*n*	OC_2H_5	COC_2H_5
c	C-5' NO_2	C-2'OH	H	COC_3H_7-*n*	H	COC_3H_7-*n*	NO_2	COC_4H_9-*n*	OC_2H_5	COC_3H_7-*n*
d	C-3' OC_2H_5	C-4'OH	H	COC_4H_9-*n*	H	COC_4H_9-*n*	NO_2	COC_6H_{13}-*n*	OC_2H_5	COC_4H_9-*n*
e	-	-	H	COC_6H_{13}-*n*	H	COC_6H_{13}-*n*			OC_2H_5	COC_6H_{13}-*n*

Scheme I

(IR, ^{1}H NMR, ^{13}C NMR and HRMS) analysis. All these reactions, when performed under identical conditions but without adding lipase did not yield any product, thus indicating that CAL-L(A) catalyzes the acylation of (±)-4-aryl-6-methyl-3,4-dihydropyrimidin-2-ones **8a-d** in an enantioselective manner.

From **Table I**, it is quite evident that the rate of acylation of 4-(3-hydrophenyl)-6-methyl-3,4-dihydropyrimidin-one-5-carboxylate **8a** is 1.25-1.91 times faster than the rate of acylation of 4-(4-hydroxyphenyl)-dihydropyrimidinone **8b**, 4-(2-hydroxyphenyl)-5-nitrophenyl)-6-methyl-3, 4 - dihydropyrimidin-one -5-carboxylate **8c** and (±)4-(3-ethoxy-4-hydroxy-3-phenyl-6-methyl-3, 4 -dihydropyrimidin-one-5-carboxylate **8d** which differs only in the position of the hydroxyl group and an extra ethoxy and nitro group at C-4′ position of the C-4 phenyl moiety. Similarly, the rate of acylation with acetic anhydride was much faster than with the other anhydrides and follows the trend acetic- > propanoic- > butanoic- > valeric- > heptanoic anhydride. However, to know the extent of optical enrichment of enzymatically acylated (-)-4-aryl-3,4-dihydropyrimidin-2-ones **9a-e**, **10a-e**, **11b-d** and **12a-e** and the unreacted dihydropyrimidones (+)-**8a-d**, optical rotation values were recorded. These were quite comparable and were of opposite signs **Table II**, thus indicating that the order of enantioselectivity during lipase-catalyzed acylation of (±)-**8a-d** is quite high.

In order to determine the enantiomeric excess (*ee*) values of acylated (-)-4-aryl-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate **9a-e**, **10a-e**, **11b-d** and **12a-e**, and the recovered, unreacted (+)-4-aryl-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate **8a-d**, we attempted the synthesis of *O*-acetylmandelic acid ester of acylated compounds **9a-e**, **10a-e**, **11b-d** and **12a-e** with *S*-(+)-*O*-acetylmandelic acid in dichloromethane according to the procedure of Whitesell and Reynolds[20]. The ^{1}H NMR spectral analysis of the diastereomeric mandelates obtained

Table I — CAL-L(A) mediated enantioselective acylation of ethyl (±) 4-(hydroxyaryl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylates **8a-d** using acid anhydrides[a,b]

Substrate	Time (hr)	Products[c]	Yield (%)[d]
(±)-(**8a**)	12	(+)-(**8a**)	40
		(-)- (**9a**)	70
	18	(+)- (**8a**)	35
		(-)-(**9b**)	60
	24	(+)- (**8a**)	35
		(-)-(**9c**)	65
	22	(+)-(**8a**)	30
		(-)-(**9d**)	60
	22	(+)-(**8a**)	40
		(-)-(**9e**)	57
(±)-(**8b**)	15	(+)-(**8b**)	36
		(-)-(**10a**)	72
	20	(+)-(**8b**)	54
		(-)-(**10b**)	73
	23	(+)-(**8b**)	43
		(-)-(**10c**)	60
	22	(+)-(**8b**)	32
		(-)- (**10d**)	54
	30	(+)-(**8b**)	43
		(-)-(**10e**)	57
(±)-(**8c**)	20	(+)-(**8c**)	50
		(-)-(**11b**)	65
	25	(+)-(**8c**)	32
		(-)-(**11c**)	63
	28	(+)-(**8c**)	35
		(-)-(**11d**)	60
(±)-(**8d**)	19	(+)-(**8d**)	40
		(-)-(**12a**)	71
	23	(+)-(**8d**)	35
		(-)-(**12b**)	68
	26	(+)-(**8d**)	33
		(-)-(**12c**)	62
	22	(+)-(**8d**)	30
		(-)-(**12d**)	60
	30	(+)-(**8d**)	40
		(-)-(**12e**)	57

[a]All these reactions, when performed under identical conditions but without adding lipase did not yield any product. [b]All acylation reactions were stopped by filtering off the enzyme after about 50% conversion of the starting racemic dihydropyrimidin-4-ones to the products, *i.e.* corresponding acetates. [c]Acylated dihydropyrinidin-2-ones and recovered, unreacted hydroxy dihydropyrimidin-2-ones. [d]Yields were calculated by assuming corresponding single enantiomer as 100% in the starting ethyl (±)-4-aryl-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylates **8a-d**.

from esterification of **9a-e**, **10a-e**, **11b-d** and **12a-e** were analyzed to find out the splitting in chemical shift values of diastereomeric protons. Unfortunately, no separation of the signals in the ^{1}H NMR spectra of

Table II — Optical rotation values $[\alpha]^{25}_D$ of (−)-3,4-dihydropyrimidin-2-ones **9a-e**, **10a-e**, **11b-d** and **12a-e** obtained by CAL L(A) catalyzed acylation of (±)-**8a-d** and recovered, unreacted (+)-3,4-dihydropyrimidin-2-ones **8a-d**.

Recovered, unreacted dihydropyrimidinones (+)-**8a-d** (°)	Dihydropyrimidinones (-)-**9a-e**, (-)-**10a-e**, (-)-**11b-d** and (-)-**12a-e** obtained by enzymatic acylation of (±)-**8a-d** (°)
(+)-**8a**: +12.5	(-)-**9a**: -10.5
(+)-**8a**: +7.5	(-)-**9b**: - 9.0
(+)-**8a**: +18.2	(-)-**9c**: -15.2
(+)-**8a**: +8.9	(-)-**9d**: -10.9
(+)-**8a**: +14.2	(-)-**9e**: -18.2
(+)-**8b**: +20.2	(-)-**10a**: -16.2
(+)-**8b**: +15.4	(-)-**10b**: -12.5
(+)-**8b**: +16.0	(-)-**10c**: -20.2
(+)-**8b**: +12.5	(-)-**10d**: -16.5
(+)-**8b**: +16.0	(-)-**10e**: -15.2
(+)-**8c**: +12.5	(-)-**11b**: -16.0
(+)-**8c**: +10.2	(-)-**11c**: -13.4
(+)-**8c**: +20.0	(-)-**11d**: -25.2
(+)-**8d**: +16.0	(-)-**12a**: -10.2
(+)-**8d**: +14.5	(-)-**12b**: -16.0
(+)-**8d**: +14.5	(-)-**12c**: -13.4
(+)-**8d**: +7.5	(-)-**12d**: -12.5
(+)-**8d**: +12.5	(-)-**12e**: -16.0

diastereomeric mandelates was observed, thus enantiomeric excess values of acylated, optically enriched (-)-4-aryl-3, 4 -dihydropyrimidin-2-one-5-carboxylate **9a-e**, **10a-e**, **11b-d** and **12a-e**, and recovered, unreacted (+)-4-aryl-3,4-dihydropyrimidin-2-ones **8a-d** could not be determined by NMR techniques.

The melting points and spectral data of all the recovered, unreacted optically enriched samples of (+)-**8a-d** (**Table I**) compared well with the corresponding melting points and spectral data of the starting racemic compounds (±)-**8a-d**, thus establishing the identity of these optically enriched compounds (**Tables I** and **II**).

Materials and Methods

Microwave reactions were performed in a domestic microwave oven of 850 W 1.2 Cft (33L, infodisplay, Sharp Carosel). Column chromatography was carried out using silica gel (100-200 mesh). Melting points were determined using H_2SO_4-bath and are uncorrected. Analytical TLCs were performed on precoated Merck silica gel $60F_{254}$ plates; the spots were detected either using UV light

or charring with 4% alcoholic H_2SO_4. The IR spectra were recorded on a Perkin-Elmer model 2000 FT-IR spectrophotometer and spectrometric UV was recorded using Beckman DU-64 spectrophotometer. The optical rotations were measured with Bellingham-Stanley AD 220 polarimeter. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Advance-300 spectrometer at 300 and 75.5 MHz, respectively. The chemical shift values are reported as δ (ppm) relative to TMS used as internal standard and the coupling constants (*J*) are measured in Hz. The FAB-HRMS spectra of all the compounds were recorded on a JEOL JMS-AX505W high-resolution mass spectrometer in positive ion mode using the matrix NaHEDS (*bis*hydroxyethylsulphide) doped with sodium acetate. CAL-L(A) was a gift from Novozyme A/S (Copenhagen, Denmark), whereas *Candida rugosa* lipase (CRL) and porcine pancreatic lipase (PPL) were purchased from Sigma Chemical Co. (USA). These lipases were used after storing *in vacuo* over P_2O_5 for 24 hr. The chiral derivatising agent (*S*)-(+)-*O*-acetylmandelic acid and all acid anhydrides were purchased from Aldrich Chemical Co. (USA). The organic solvent THF was used after drying and distillation over sodium pieces.

Experimental Section

General procedure for the preparation of ethyl (±)-4-aryl-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylates 8a-d

To a mixture of hydroxy aldehyde (**5a-d**, 50 mmole), urea (**6**, 150 mmole), ethyl acetoacetate (**7**, 55 mmole), ferric chloride.hexahydrate (25 mmole) and silica gel (100 g) was added to make a thick paste. The resulting mixture was irradiated in a microwave oven for 1-2 min until TLC showed completion of reaction. The crude product was purified by column chromatography over silica gel using a gradient solvent system of chloroform-methanol to obtain the pure ethyl (±)-4-aryl)-3,4-dihyropyrimidin-2-one-5-carboxylates **8a-d** in 70-85% yields. The melting points reported by Fu *et al.*[21] for **8a** (163-65°C) and **8b** (230-32°C) are different than the melting points of our samples of **8a** (210-12°C) and **8b** (193-95°C). Fu *et al*.[21] had reported only the ^1H NMR spectral data of **8a** and **8b** (^{13}C NMR, CHN, HRMS and IR spectra not reported). The compounds **8c** and **8d** are not reported so far in literature. We have fully characterized all the four carboxylates **8a-d** on the basis of their ^1H and ^{13}C NMR, HRMS and IR spectra.

General procedure for enzymatic acylation of (±)-ethyl 4-aryl-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylates 8a-d

To a solution of ethyl (±)-4-aryl-3,4-dihydropyrimidin-2-one-5-carboxylate **(8a-d**, 1 mmole) in anhydrous THF (10 mL), acid anhydride was added, followed by CAL-L(A) (150 mg). The suspension was stirred at 55-60°C in an incubator shaker and the progress of the reaction was monitored periodically by analytical TLC. After about 50% conversion of the starting material into the product, the reaction was quenched by filtering off the enzyme and the solvent evaporated to dryness *in vacuo* to afford a gummy residue, which was purified by column chromatography over silica gel using a gradient solvent system of chloroform-methanol to afford optically enriched acetates of (-)-ethyl 4-aryl-3,4-dihydropyrimidin-2-one-5-carboxylates **9a-e**, **10a-e**, **11b-d** and **12a-e**. All these reactions, when performed under identical conditions but without adding the lipase did not yield any product.

Ethyl (±)-4-(3′-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 8a

It was obtained as a light yellow solid in 70% yield. m.p. 210-12°C; IR (Nujol): 3409 (OH), 3315 (NH), 3217 (NH), 1693 (CO), 1653 (CO), 1461, 1356, 1228, 1087, 1032, and 757 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.13 (3H, t, *J*=6.9 Hz, $COOCH_2CH_3$), 2.34 (3H, s, C-6 CH_3), 4.09 (2H, q, *J* = 6.9 Hz, $COOCH_2CH_3$), 5.42 (1H, s, C-4H), 5.92 (1H, s, N-1H/N-3H), 6.95 (2H, m, C-5′ and C-2′H), 7.11 (1H, m, C-4′H), 7.28 (1H, m, C-6′H), 8.35 (1H, s, OH) and 9.60 (1H, s, N-3H/N-1H); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 14.25 ($COOCH_2CH_3$), 18.90 (C-6 CH_3), 52.71 (C-4), 61.22 ($COOCH_2CH_3$), 101.10 (C-5), 119.90, 121.22, 123.98, 129.70 (C-2′, C-4′, C-5′ and C-6′), 144.61 (C-6), 147.01 (C-1′), 151.07 (C-3′), and 153.39 and 169.20 (2×CO); HRMS: *m/z* Calcd for $[C_{14}H_{16}N_2O_4+H]^+$ 277.1144. Obsd 277.0756.

Ethyl (±)-4-(4′-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 8b

It was obtained as a white crystaline solid in 72% yield. m.p. 193-95°C; IR (KBr): 3412 (OH), 3340 (NH), 3265 (NH), 1765 (CO), 1699 (CO), 1660, 1464, 1222, 1057, 1024, and 781 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.09 (3H, t, *J* = 7.1 Hz, $COOCH_2CH_3$), 2.24 (3H, s, C-6 CH_3), 3.99 (2H, q, *J* = 7.1 Hz, $COOCH_2CH_3$), 5.05 (1H, s, C-4H), 6.70 (2H, m, C-2′H and C-6′H), 7.02 (2H, brs, C-3′H and

C-5′H), 7.60 (1H, s, N1H/N-3H), 9.03 (1H, s, N-3H/N-1H), and 9.31 (1H, s, OH); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 14.33 (COOCH$_2$*C*H$_3$), 17.97 (C-6 CH$_3$), 53.71 (C-4), 59.34 (COO*C*H$_2$CH$_3$), 100.06 (C-5), 115.24 (C-3′ and C-5′), 127.64 (C-2′ and C-6′), 135.69 (C-6), 147.93 (C-1′), and 152.44 (C-4′), 156.78 and 165.68 (2 × CO); HRMS: *m/z* Calcd for $[C_{14}H_{16}N_2O_4+H]^+$ 277.1144. Obsd 277.0731.

Ethyl (±) –4-(2′-hydroxy-5′-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 8c

It was obtained as a light yellow solid in 75% yield. m.p. 180°C; IR (KBr): 3407 (OH), 3240 (NH), 3120 (NH), 1695 (CO), 1642 (CO), 1491, 1377, 1336, 1293, 1229, 1109 and 755 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.11 (3H, t, *J* = 7.0 Hz, COOCH$_2$C*H*$_3$), 2.39 (3H, s, C-6 CH$_3$), 4.02 (2H, q, *J* = 7.0 Hz, COOC*H*$_2$CH$_3$), 5.59 (1H, s, C-4H), 6.77 (1H, s, N-1H/N-3H), 6.98 (1H, d, *J* = 8.9 Hz, C-3′H), 7.88 (1H, d, *J* = 2.6 Hz, C-6′H), 7.98 (1H, dd, *J* = 2.7 and 6.0 Hz, C-4′H), 9.15 (1H, s, N-1H/N-3H), and 10.5 (1H, s, OH); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 14.12 (COOCH$_2$*C*H$_3$), 18.19 (C-6 CH$_3$), 49.90 (C-4), 59.49 (COO*C*H$_2$CH$_3$), 97.47 (C-5), 115.86 (C-3′),123.53 (C-1′), 124.80 (C-6′), 130.42 (C-4′), 139.86 (C-5′), 149.68 (C-6), 152.78 (C-2′), and 161.51 and 165.57 (2 × CO); HRMS: *m/z* Calcd for $[C_{14}H_{15}N_3O_6+Na]^+$ 344.0859. Found 344.0851.

Ethyl(±)-4-(3′-ethoxy-4′-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 8d

It was obtained as a white crystaline solid in 85% yield. m.p. 185-86°C; IR (KBr): 3234 (NH), 3099 (OH and NH), 1705 (CO), 1685 (CO), 1655, 1518, 1476, 1382, 1324, 1286, 1254, 1229, 1100, 1045, 815, 751 and 720 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 (3H, t, *J* = 7.0 Hz, COOCH$_2$C*H*$_3$), 1.36 (3H, t, *J* = 6.9Hz, OCH$_2$C*H*$_3$), 2.25 (3H, s, C-6 CH$_3$), 3.99 (4H, m, COOC*H*$_2$CH$_3$ and OC*H*$_2$CH$_3$), 5.08 (1H, d, *J* = 2.5 Hz, C-4H), 6.64 (1H, dd, *J* = 1.3 and 8.1 Hz, C-6′H), 6.71 (1H, d, *J* = 8.1 Hz, C-5′H), 6.79 (1H,brs, C-2′H), 7.49 (1H,brs, N-1H/N-3H), 8.58 and 8.99 (2H, 2s, 1H each, OH and N-3H/N-1H); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 15.12 and 15.75 (COOCH$_2$-*C*H$_3$ and OCH$_2$*C*H$_3$), 18.81 (C-6 CH$_3$), 54.83 (C-4), 60.01 (COO*C*H$_2$CH$_3$), 65.07(O*C*H$_2$CH$_3$), 100.89 (C-5), 113.33, 116.23 and 119.65(C-2′, C-5′ and C-6′), 137.03 (C-6), 147.11, 147.28 and 148.54 (C-1′, C-3′ and C-4′), 153.44 (amidic CO) and 166.51(ester CO); HRMS: *m/z* Calcd for $[C_{16}H_{20}N_2O_5]^+$ 320.1372. Found 320.1372.

Ethyl(-)-4-(3′-acetoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 9a

It was obtained as a white crystalline solid in 70% yield. $[\alpha]_D^{25}$ - 10.5° (*c* 0.01 MeOH); m.p. 210-12°C; IR (Nujol): 3310 (NH), 3210 (NH), 1758 (CO), 1699 (CO), 1643 (CO), 1461, 1366, 1218, 1089, 1016 and 787 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.16 (3H, t, *J* = 6.9 Hz, COOCH$_2$C*H*$_3$), 2.28 (3H, s, OCOCH$_3$), 2.33 (3H, s, C-6 CH$_3$), 4.07 (2H, q, *J* = 7.0 Hz, COOC*H*$_2$CH$_3$), 5.39 (1H, s, C-4H), 5.96 (1H, s, N-1H/N-3H), 6.99 (2H, m, C-5′H and C-2′H), 7.17 (1H, m, C-4′H), 7.31 (1H, m, C-6′H), and 8.31(1H, s, NH); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 14.23 (COOCH$_2$-*C*H$_3$), 18.78 (C-6 CH$_3$), 21.26 (OCO*C*H$_3$), 55.46 (C-4), 60.22 (COO*C*H$_2$CH$_3$), 101.10 (C-5), 119.95, 121.27, 124.13, 129.80 (C-2′, C-4′, C-5′ and C-6′), 145.61 (C-6), 146.88 (C-1′), 151.00 (C-3′), and 153.49, 165.66 and 169.41 (3 × CO); HRMS: *m/z* Calcd for $[C_{16}H_{18}N_2O_5+Na]^+$ 341.1113. Found 341.1094.

Ethyl (-)-4-(3′-propanoyloxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 9b

It was obtained as a white crystalline solid in 60% yield. $[\alpha]_D^{25}$ - 9.0° (*c* 0.01 MeOH); m.p. 166-67 °C; IR (Nujol): 3361 (NH), 3109 (NH), 1749 (CO), 1679 (CO), 1649 (CO), 1459, 1376, 1243, 1090, 1016 and 791 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.17 (3H, t, *J* = 6.7 Hz, OCOCH$_2$C*H*$_3$), 1.22 (3H, t, *J* = 7.1Hz, OCOC*H*$_2$CH$_3$), 2.31 (3H, s, C-6 CH$_3$), 2.58 (2H, q, *J* = 7.1 Hz, OCOC*H*$_2$CH$_3$), 4.04 (2H, q, *J* = 7.0 Hz, COOC*H*$_2$CH$_3$), 5.29 (1H, s, C-4H), 6.93 (1H, s, N-1H/N-3H), 7.01 (2H, m, C-5′H and C-2′H), 7.23 (1H, m, C-4′H), 7.29 (1H, m, C-6′H), and 9.01 (1H, s, N-1H/N-3H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ 13.96 (OCOCH$_2$*C*H$_3$), 19.15 (COOCH$_2$*C*H$_3$), 23.24 (C-6 CH$_3$), 32.46 (OCO*C*H$_2$CH$_3$), 59.46 (C-4), 64.50 (COO*C*H$_2$CH$_3$), 104.70 (C-5), 124.81, 125.64, 128.90, 134.15 (C-2′, C-4′, C-5′ and C-6′), 151.68 (C-6), 153.26 (C-1′), 155.73 (C-3′), and 157.85, 170.66 and 177.46 (3 × CO); HRMS: *m/z* Calcd for $[C_{17}H_{20}N_2O_5+Na]^+$ 355.1270. Found 355.1245.

Ethyl(-)-4-(3′-butyryloxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 9c

It was obtained as a white crystalline solid in 65% yield. $[\alpha]_D^{25}$ - 15.2° (*c* 0.01 MeOH); m.p. 147-48°C; IR (Nujol): 3247 (NH), 3115 (NH), 1756 (CO), 1705 (CO), 1654 (CO), 1462, 1377, 1228, 1094 and 774 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.03 (3H, t,

J = 7.4 Hz, $OCOCH_2CH_2CH_3$), 1.16 (3H, t, *J* = 7.1Hz, $COOCH_2CH_3$), 1.77 (2H, m, $OCOCH_2CH_2CH_3$), 2.32 (3H, s, C-6 CH_3), 2.52 (2H, t, *J* 7.3 Hz, $OCOCH_2$-CH_3), 4.08 (2H, m, $COOCH_2CH_3$), 5.38 (1H, s, C-4H), 6.17 (1H, s, N-1H/N-3H), 7.00 (2H, m, C-5′ and 2′H), 7.17 (1H, m, C-4′H), 7.29 (1H, t, *J* = 7.5 Hz, C-6′H), and 8.61(1H, s, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.77 ($OCOCH_2CH_2CH_3$), 14.26 ($COOCH_2CH_3$), 18.54 (C-6 CH_3), 18.71 ($OCOCH_2$-CH_2CH_3), 36.36 ($OCOCH_2CH_3$), 55.42 (C-4), 60.20 ($COOCH_2CH_3$), 101.02 (C-5), 120.00, 121.27, 124.00 (C-2′, C-4′ and C-5′), 129.78 (C-6′), 145.62 (C-6), 146.99 (C-1′), 151.03 (C-3′), and 153.75, 165.69 and 172.11 (3 × CO); HRMS: *m/z* Calcd for $[C_{18}H_{22}N_2O_5+Na]^+$ 369.1426. Found 369.1421.

Ethyl (-) - 4-(3′-pentanoyloxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 9d

It was obtained as a white crystalline solid in 60 % yield. $[\alpha]_D^{25}$ - 10.9° (*c* 0.01 MeOH); m.p. 78-81°C; IR (Nujol): 3210 (NH), 3208 (NH), 1744 (CO), 1696 (CO), 1643 (CO), 1462, 1377, 1217, 1097 and 705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (3H, t, *J* = 7.4 Hz, $OCOCH_2CH_2CH_2CH_3$), 1.17 (3H, t, *J* = 7.0 Hz, $COOCH_2CH_3$), 1.44 (2H, m, $OCOCH_2$-$CH_2CH_2CH_3$), 1.73 (2H, m, $OCOCH_2CH_2CH_2CH_3$), 2.36 (3H, s, C-6 CH_3), 2.54 (2H, t, *J* = 7.4 Hz, $OCOCH_2$), 4.09 (2H, q, *J* = 7.0 Hz, $COOCH_2CH_3$), 5.41 (1H, s, C-4H), 6.23 (1H, s, N-1H/N-3H), 7.02 (2H, m, C-5′H and C-2′H), 7.20 (1H, m, C-4′H), 7.31 (1H, t, *J* = 7.4 Hz, C-6′H), and 8.61(1H, s, N-1H/N-3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.07 ($OCO(CH_2)_3CH_3$), 14.49 ($COOCH_2CH_3$), 18.97 (C-6 CH_3), 22.61 ($OCOCH_2CH_2CH_2CH_3$), 27.32 ($OCOCH_2$-$CH_2CH_2CH_3$), 34.49 ($OCOCH_2$), 55.65 (C-4), 60.54 ($COOCH_2CH_3$), 101.59 (C-5), 120.24, 121.60, 124.25 (C-4′, C-2′ and C-6′), 130.07 (C-5′), 145.58 (C-6), 146.87 (C-1′), 151.34 (C-3′), and 154.48, 165.84 and 171.08 (3 × CO); HRMS: *m/z* Calcd for $[C_{19}H_{24}N_2O_5+Na]^+$ 383.1583. Found 383.1578.

Ethyl (-) - 4-(3′-heptanoyloxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 9e

It was obtained as a white crystalline solid in 57% yield. $[\alpha]_D^{25}$= - 18.2° (*c* 0.01 MeOH); m.p. 106-07°C; IR (Nujol): 3232 (NH), 3108 (NH), 1762 (CO), 1703 (CO), 1653 (CO), 1464, 1378, 1228, 1093 and 803 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (3H, brs, $OCO(CH_2)_5CH_3$), 1.16 (3H, t, *J* = 7.0 Hz, $COOCH_2CH_3$), 1.33 (6H, m, $OCOCH_2CH_2CH_2CH_2$-CH_2CH_3), 1.71 (2H, m, $OCOCH_2(CH_2)_2CH_2CH_3$), 2.33 (3H, s, C-6 CH_3), 2.54 (2H, t, *J* = 7.4 Hz, $OCOCH_2$), 4.07 (2H, m, $COOCH_2CH_3$), 5.39 (1H, s, C-4H), 5.92 (1H, s, N-1H/N-3H), 6.98 (2H, m, C-5′H and C-2′H), 7.20 (1H, m, C-4′H), 7.30 (1H, m, C-6′H), and 8.33 (1H, s, N-1H/N-3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.36 ($OCO(CH_2)_5CH_3$), 14.47 ($COOCH_2CH_3$), 18.95 (C-6 CH_3), 22.83 ($OCOCH_2$-$CH_2CH_2CH_2CH_2CH_3$), 25.20 ($OCOCH_2CH_2CH_2CH_2$ - CH_2CH_3), 30.06 ($OCOCH_2CH_2CH_2CH_2CH_2CH_3$), 31.79 ($OCOCH_2CH_2CH_2CH_2CH_2CH_3$), 34.75 ($OCOCH_2$), 55.70 (C-4), 60.42 ($COOCH_2CH_3$), 101.26 (C-5), 120.22, 121.49, 124.21 (C-4′, C-2′ and C-6′), 130.00 (C-5′), 145.81 (C-6), 147.15 (C-1′), 151.27 (C-3′), and 153.83, 165.88 and 172.49 (3 × CO); HRMS: *m/z* Calcd for $[C_{21}H_{28}N_2O_5+Na]^+$ 411.1896. Found 411.1867.

Ethyl(-)-4-(4′-acetoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 10a

It was obtained as a white crystalline solid in 72% yield. $[\alpha]_D^{25}$ - 16.2° (*c* 0.01 MeOH); m.p. 141-42°C; IR (KBr): 3244 (NH), 3109 (NH), 1758 (CO), 1702 (CO), 1649 (CO), 1461, 1366, 1218, 1089, 1016 and 787 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (3H, t, *J* = 6.9 Hz, $COOCH_2CH_3$), 2.28 (3H, s, C-6 CH_3), 2.32 (3H, s, $OCOCH_3$), 4.07 (2H, q, *J* = 7.0 Hz, $COOCH_2CH_3$), 5.39 (1H, s, C-4H), 6.09 (1H, s, N-1H/N-3H), 7.02 (2H, m, C-2′H and C-6′H), 7.32 (2H, m, C-3′ and 5′H), and 8.53 (1H, s, N-1H/N-3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.30 ($COOCH_2CH_3$), 18.76 (C-6 CH_3), 21.24 ($OCOCH_3$), 55.19 (C-4), 60.19 ($COOCH_2CH_3$), 101.35 (C-5), 121.88 (C-3′ and C-5′), 127.88 (C-2′ and C-6′), 141.51 (C-6), 146.75 (C-1′), 150.36 (C-4′), and 153.74, 165.72 and 169.48 (3 × CO); HRMS: *m/z* Calcd for $[C_{16}H_{18}N_2O_5+Na]^+$ 341.1113. Found 341.1088.

Ethyl(-)-4-(4′-propanoyloxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 10b

It was obtained as a white crystalline solid in 73% yield. $[\alpha]_D^{25}$ - 12.5° (*c* 0.01 MeOH); m.p. 163°C; IR (KBr): 3249 (NH), 3120 (NH), 1754 (CO), 1706 (CO), 1652 (CO), 1461, 1377, 1227, 1096, 1016 and 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (3H, t, *J* = 6.7 Hz, $OCOCH_2CH_3$), 1.26 (3H, t, *J* = 7.1 Hz, $COOCH_2CH_3$), 2.34 (3H, s, C-6 CH_3), 2.57 (2H, q, *J* = 7.1 Hz, $OCOCH_2$), 4.07 (2H, q, *J* = 7.0 Hz, $COOCH_2CH_3$), 5.40 (1H, s, C-4H), 5.77 (1H, s, N-1H/N-3H), 7.03 (2H, m, C-2′H and C-6′H), 7.33 (2H,

m, C-3′H and C-5′H), and 8.11 (1H, s, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 9.40 ($OCOCH_2CH_3$), 14.54 ($COOCH_2CH_3$), 18.94 (C-6 CH_3), 28.11 ($OCOCH_2$ - CH_3), 55.37 (C-4), 60.41 ($COOCH_2CH_3$), 101.54 (C-5), 122.08 (C-3′ and C-5′), 128.08 (C-2′ and 6′), 141.65 (C-1′), 147.05 (C-6), 150.67 (C-4′), and 154.18, 165.98 and 173.22 (3 × CO); HRMS: *m/z* Calcd for $[C_{17}H_{20}N_2O_5+Na]^+$ 355.1270. Found 355.1267.

Ethyl (-)-4-(4′-butanoyloxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 10c

It was obtained as a white crystalline solid in 60% Yield. $[\alpha]_D^{25}$ - 20.2° (*c* 0.01 MeOH); m.p. 125-27°C; IR (KBr): 3248 (NH), 3118 (NH), 1748 (CO), 1705 (CO), 1650 (CO), 1461, 1367, 1227, 1095 and 776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (3H, t, *J* = 7.4 Hz, $OCOCH_2CH_2CH_3$), 1.17 (3H, t, *J* = 7.0 Hz, $COOCH_2CH_3$), 1.76 (2H, m, $OCOCH_2CH_2CH_3$), 2.33 (3H, s, C-6 CH_3), 2.52 (2H, t, *J* = 7.4 Hz, $OCOCH_2$), 4.08 (2H, q, *J* = 7.3 Hz, $COOCH_2CH_3$), 5.39 (1H, s, C-4H), 6.02 (1H, s, N-1H/N-3H) 7.01 (2H, m, C-2′H and C-6′H), 7.31 (2H, m, C-3′H and C-5′H), and 8.47 (1H, s, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.76 ($OCOCH_2CH_2CH_3$), 14.31 ($COOCH_2CH_3$), 18.58 (C-6 CH_3), 18.75 ($OCOCH_2CH_2CH_3$), 36.37 ($OCOCH_2$), 55.21 (C-4), 60.19 ($COOCH_2CH_3$), 101.36 (C-5), 121.89 (C-3′ and C-5′), 127.86 (C-2′ and C-6′), 141.40 (C-1′), 146.73 (C-6), 150.45 (C-4′), and 153.76, 165.73 and 173.17 (3 × CO); HRMS: *m/z* Calcd for $[C_{18}H_{22}N_2O_5+Na]^+$ 369.1426. Found 369.1412.

Ethyl(-)-4-(4′-pentanoyloxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 10d

It was obtained as a white crystalline solid in 54% yield. $[\alpha]_D^{25}$ - 16.5° (*c* 0.01 MeOH); m.p. 115°C; IR (KBr): 3250 (NH), 3119 (NH), 1749 (CO), 1705 (CO), 1650 (CO), 1462, 1378, 1226, 1095 and 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, t, *J* = 7.3 Hz, $OCOCH_2CH_2CH_2CH_3$), 1.17 (3H, t, *J* = 7.0 Hz, $COOCH_2CH_3$), 1.42 (2H, m, $OCOCH_2$ - $CH_2CH_2CH_3$), 1.73 (2H, m, $OCOCH_2CH_2CH_2CH_3$), 2.34 (3H, s, C-6 CH_3), 2.55 (2H, t, *J* = 7.4 Hz, $OCOCH_2$), 4.07 (2H, q, *J* = 7.2 Hz, $COOCH_2CH_3$), 5.41 (1H, s, C-4H), 5.76 (1H, s, N-1H/N-3H), 7.02 (2H, m, C-2′H and C-6′H), 7.32 (2H, m, C-3′H and C-5′H), and 8.11 (1H, s, N-1H/N-3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.08 ($OCOCH_2(CH_2)_2CH_3$), 14.54 ($COOCH_2CH_3$), 18.94 (C-6 CH_3), 22.61 ($OCOCH_2$-$CH_2CH_2CH_3$), 27.34 ($OCOCH_2CH_2CH_2CH_3$), 34.48 ($OCOCH_2$), 55.36 (C-4), 60.41 ($COOCH_2CH_3$), 101.54 (C-5), 122.10 (C-3′ and C-5′), 128.08 (C-2′ and C-6′), 141.64 (C-1′), 147.06 (C-6), 150.66 (C-4′), and 154.20, 165.98 and 172.59 (3 × CO); HRMS: *m/z* Calcd for $[C_{19}H_{24}N_2O_5+Na]^+$ 383.1583. Found 383.1565.

Ethyl(-)-4-(4′-heptanoyloxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 10e

It was obtained as a white crystalline solid in 57% yield. $[\alpha]_D^{25}$ - 15.2° (*c* 0.01 MeOH); m.p. 90-91°C; IR (KBr): 3228 (NH), 3113 (NH), 1760 (CO), 1704 (CO), 1654 (CO), 1463, 1378, 1223, 1091 and 804 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (3H, brs, $OCOCH_2(CH_2)_4CH_3$), 1.16 (3H, brs, $COOCH_2CH_3$), 1.33 (6H, brs, $OCOCH_2CH_2CH_2CH_2CH_2CH_3$), 1.74 (2H, brs, $OCOCH_2(CH_2)_3CH_2CH_3$), 2.34 (3H, s, C-6 CH_3), 2.54 (2H, brs, $OCOCH_2$), 4.07 (2H, m, $COOCH_2CH_3$), 5.40 (1H, s, C-4H), 5.85 (1H, s, N-1H/N-3H), 7.02 (2H, m, C-2′H and C-6′H), 7.29 (2H, m, C-3′H and C-5′H) and 8.30 (1H, s, N-1H/N-3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.36 ($OCOCH_2$-$(CH_2)_4CH_3$), 14.53 ($COOCH_2CH_3$), 18.94 (C-6 CH_3), 22.83 ($OCOCH_2(CH_2)_3CH_2CH_3$), 25.25 ($OCOCH_2$-$CH_2CH_2CH_2CH_2CH_3$), 29.13 ($OCOCH_2CH_2CH_2CH_2$-CH_2CH_3), 31.79 ($OCOCH_2CH_2(CH_2)_3CH_3$), 34.76 ($OCOCH_2$), 55.40 (C-4), 60.40 ($COOCH_2CH_3$), 101.56 (C-5), 122.10 (C-3′ and C-5′), 128.07 (C-2′ and C-6′), 141.63 (C-1′), 147.01 (C-6), 150.69 (C-4′), and 154.11, 165.96 and 172.56 (3 × CO); HRMS: *m/z* Calcd for $[C_{21}H_{28}N_2O_5+Na]^+$ 411.1896. Found 411.1882.

Ethyl (-)-4-(2′-propanoyloxy-5′-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 11b

It was obtained as a white crystalline solid in 65% yield. $[\alpha]_D^{25}$ - 16.0° (*c* 0.01 MeOH); m.p. 180-82°C; IR (KBr): 3229 (NH), 2972 (NH), 1773 (CO), 1700 (CO), 1640 (CO), 1462, 1344, 1226, 1098, 1017, 936 and 757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (3H, t, *J* = 6.7 Hz, $OCOCH_2CH_3$), 1.31 (3H, t, *J* = 7.1 Hz, $COOCH_2CH_3$) 2.43 (3H, s, C-6 CH_3), 2.70 (2H, q, *J* = 7.0 Hz, $OCOCH_2CH_3$), 4.02 (2H, m, $COOCH_2$-CH_3), 5.54 (1H, s, C-4H), 5.82 (1H, s, N-1H/N-3H), 7.26 (1H, m, C-3′H), 8.17 (2H, m, C-4′H and C-6′H), and 8.35 (1H, s, N-1H/N-3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 9.31 ($OCOCH_2CH_3$), 14.37 ($COOCH_2$-CH_3), 18.09 (C-6 CH_3), 28.11 ($OCOCH_2CH_3$), 50.87 (C-4), 60.62 ($COOCH_2CH_3$), 98.79 (C-5), 123.91,

124.52 and 124.72 (C-3′, C-4′ and C-5′), 137.50 (C-1′), 146.32 (C-6), 148.86 (C-6′), 152.82 (C-2′), and 152.97, 165.26 and 172.89 (3 × CO); HRMS: Calcd for $[C_{17}H_{19}N_3O_7+Na]^+$ 400.1121. Found 400.1119.

Ethyl (-)-4-(2′-butanoyloxy-5′-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 11c

It was obtained as a white crystalline solid in 63% yield. $[\alpha]_D^{25}$ - 13.4° (*c* 0.01 MeOH); m.p. 145°C; IR (KBr): 3229 (NH), 2961 (NH), 1771 (CO), 1701 (CO), 1644 (CO), 1460, 1347, 1226, 1094, 933 and 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.09 (6H, t, *J* = 7.3 Hz, $OCOCH_2CH_2CH_3$ and $COOCH_2CH_3$), 1.83 (2H, m, $OCOCH_2CH_2CH_3$) 2.43 (3H, s, C-6 CH_3), 2.67 (2H, t, *J* = 7.1 Hz, $OCOCH_2CH_3$), 4.02 (2H, q, *J* = 7.2 Hz, $COOCH_2CH_3$), 5.53 (1H, s, C-4H), 5.85 (1H, s, N-1H/N-3H), 7.24 (1H, m, C-3′H), 8.16 (2H, m, C-4′H and C-6′H), and 8.35 (1H, s, N-1H/N-3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.96 ($OCOCH_2CH_2CH_3$), 14.36 ($COOCH_2CH_3$), 18.71 (C-6 CH_3), 19.02 ($OCOCH_2CH_2CH_3$), 36.46 ($OCOCH_2$), 50.82 (C-4), 60.60 ($COOCH_2CH_3$), 98.77 (C-5), 123.88, 124.44 and 124.73 (C-3′, C-4′ and C-5′), 124.73 (C-1′), 137.57 (C-6), 146.38 (C-6′), 148.89 (C-2′), and 152.82, 165.23 and 172.08 (3 × CO); HRMS: *m/z* Calcd for $[C_{18}H_{21}N_3O_7+Na]^+$ 414. 1277. Found 414.1272.

Ethyl(-)-4-(5′-nitro-2′-pentanoyloxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 11d

It was obtained as a white crystalline solid in 60% yield. $[\alpha]_D^{25}$ - 25.2° (*c* 0.01 MeOH); m.p. 129-30°C; IR (KBr): 3404 (NH), 2962 (NH), 1771 (CO), 1701 (CO), 1645 (CO), 1460, 1347, 1226, 1093, 933 and 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (3H, t, *J* = 7.3 Hz, $OCOCH_2CH_2CH_2CH_3$), 1.09 (3H, t, *J* = 7.1 Hz, $COOCH_2CH_3$), 1.47 (2H, m, $OCOCH_2CH_2CH_2CH_3$), 1.77 (2H, m, $OCOCH_2CH_2CH_2CH_3$), 2.43 (3H, s, C-6 CH_3), 2.68 (2H, t, *J* = 7.4 Hz, $OCOCH_2$), 4.02 (2H, q, *J* = 7.1 Hz, $COOCH_2CH_3$), 5.53 (1H, s, C-4H), 5.86 (1H, s, N-1H/N-3H), 7.23 (1H, s, C-3′H), 8.16 (2H, m, C-4′H and C-6′H), and 8.52 (1H, s, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.02 ($OCOCH_2(CH_2)_2CH_3$), 14.38 ($COOCH_2CH_3$), 18.11 (C-6 CH_3), 18.98 ($OCOCH_2CH_2CH_2CH_3$), 27.19 ($OCOCH_2CH_2CH_2CH_3$), 34.51 ($OCOCH_2$), 50.79 (C-4), 60.61 ($COOCH_2CH_3$), 98.75 (C-5), 123.88, 124.47 and 124.74 (C-3′, C-4′ and C-5′), 137.54 (C-1′), 146.35 (C-6), 148.95 (C-6′), 152.79 (C-2′) and 153.05, 165.23 and 172.25 (3 × CO); HRMS: *m/z* Calcd for $[C_{19}H_{23}N_3O_7+Na]^+$ 428.1434. Found 428.1416.

Ethyl(-)-4-(4′-acetoxy-3′-ethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 12a

It was obtained as a white crystalline solid in 71% yield. $[\alpha]_D^{25}$ - 10.2° (*c* 0.01 MeOH); m.p. 171-72°C; IR (KBr): 3248 (NH), 3110 (NH), 1765 (CO), 1710 (CO), 1689 (CO), 1508, 1430, 1372, 1280, 1246, 1094, 1042 and 791 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (3H, t, *J* = 7.0 Hz, $OCOCH_3$), 1.36 (3H, t, *J* = 6.9 Hz, $COOCH_2CH_3$), 2.29 and 2.33 (6H, 2s, 3H each, C-6 CH_3 and OCH_2CH_3), 4.02 (4H, m, 2H each, OCH_2CH_3 and $COOCH_2CH_3$), 5.39 (1H, s, C-4H), 5.69 (1H, s, N-1H/N-3H), 6.82 (3H, m, C-2′H, C-5′H and C-6′H) and 7.95 (1H, s, N-1H/N-3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.56 ($COOCH_2CH_3$), 15.04 (OCH_2CH_3), 19.16 (C-6 CH_3), 20.94 ($OCOCH_3$), 55.81 (C-4), 60.40 (OCH_2CH_3), 64.80 ($COOCH_2CH_3$), 101.82 (C-5), 110.46, 118.99 and 123.19 (C-2′, C-5′ and C-6′), 142.76 (C-6), 143.63 (C-1′), 145.86 (C-3′), 150.91 (C-4′) and 153.51, 166.42, and 169.33 (3 × CO); HRMS: *m/z* Calcd for $[C_{18}H_{22}N_2O_6+Na]^+$ 385.1376. Found 385.1330.

Ethyl(-)-4-(3′-ethoxy-4′-propanoyloxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 12b

It was obtained as a white crystalline solid in 68% yield. $[\alpha]_D^{25}$- 16.0° (*c* 0.01 MeOH); m.p. 155-56°C; IR (KBr): 3291 (NH), 3177 (NH), 1712 (CO), 1695 (CO), 1651 (CO), 1522, 1438, 1369, 1276, 1221, 1095, 1037 and 791 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (3H, t, *J* = 7.0 Hz, $OCOCH_2CH_3$), 1.27 (3H, t, *J* = 7.5 Hz, $COOCH_2CH_3$), 1.35 (3H, t, *J* = 6.8 Hz, OCH_2CH_3), 2.33 (3H, s, C-6 CH_3), 2.56 (2H, q, *J* = 7.2 Hz, $OCOCH_2CH_3$), 4.00 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 4.10 (2H, q, *J* = 7.1 Hz, $COOCH_2CH_3$), 5.39 (1H, s, C-4H), 5.88 (1H, s, N-1H/N-3H), 6.89 (3H, m, C-2′H, C-5′H and C-6′H) and 8.23 (1H, s, N-1H/N-3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 9.57 ($OCOCH_2CH_3$), 14.46 ($COOCH_2CH_3$), 14.96 (OCH_2CH_3), 18.97 (C-6 CH_3), 27.69 ($OCOCH_2CH_3$), 55.69 (C-4), 60.36 ($COOCH_2CH_3$), 64.66 (OCH_2CH_3), 101.56 (C-5), 112.18, 118.89 and 123.07 (C-2′, C-5′ and C-6′), 142.58 (C-6), 146.60 (C-1′), 150.81 (C-3′), 153.64 (C-4′), and 155.66, 165.89, and 172.77 (3 × CO); HRMS: *m/z* Calcd for $[C_{19}H_{24}N_2O_6+Na]^+$ 399.1532. Found 399.1511.

Ethyl(-)-4-(4′-butanoyloxy-3′-ethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 12c

It was obtained as a white crystalline solid in 62% yield. $[\alpha]_D^{25}$ - 13.4° (*c* 0.01 MeOH); m.p. 115°C; IR (KBr): 3251 (NH), 3123 (NH), 1764 (CO), 1703

(CO), 1654 (CO), 1510, 1459, 1384, 1279, 1259, 1093, 1043 and 792 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.05 (3H, t, *J* = 7.2 Hz, $OCOCH_2CH_2CH_3$), 1.17 (3H, t, *J* = 6.8 Hz, $COOCH_2CH_3$), 1.35 (3H, t, *J* = 6.7 Hz, OCH_2CH_3), 1.80 (2H, m, $OCOCH_2CH_2CH_3$) 2.32 (3H, s, C-6 CH_3), 2.53 (2H, t, *J* = 7.1 Hz, $OCOCH_2$), 3.99 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 4.05 (2H, q, *J* = 7.1 Hz, $COOCH_2CH_3$), 5.38 (1H, s, C-4H), 5.89 (1H, s, N-1H/N-3H), 6.88 (3H, m, C-2′H, C-5′H and C-6′H) and 8.26 (1H, s, N-1H/N-3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.93 ($OCOCH_2CH_2CH_3$), 14.46 ($COOCH_2CH_3$), 14.95 (OCH_2CH_3), 18.87 (C-6 CH_3), 18.96 ($OCOCH_2CH_2CH_3$), 36.19 ($OCOCH_2$), 55.68 (C-4), 60.35 ($COOCH_2CH_3$), 64.62 (OCH_2CH_3), 101.56 (C-5), 112.10, 118.86, 123.13 (C-2′, C-6′ and C-5′), 142.59 (C-6), 146.61 (C-1′), 150.84 (C-3″ 152.89 (C-4′), and 153.67, 165.89 and 171.87 (3 × CO); HRMS: *m/z* Calcd for $[C_{20}H_{26}N_2O_6+Na]^+$ 413.1689. Found 413.1693.

Ethyl(-)-4-(3′-ethoxy-4′-pentanoyloxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate, 12d

It was obtained as a white crystalline solid in 60% yield. $[\alpha]_D^{25}$ - 12.5° (*c* 0.01 MeOH); m.p. 104-05°C; IR (KBr): 3264 (NH), 3125 (NH), 1767 (CO), 1714 (CO), 1683 (CO), 1508, 1441, 1369, 1273, 1242, 1094, 1040 and 785 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (3H, t, *J* = 7.1 Hz, $OCOCH_2(CH_2)_2CH_3$), 1.17 (3H, t, *J* = 6.9 Hz, $COOCH_2CH_3$), 1.35 (3H, t, *J* = 6.8 Hz, OCH_2CH_3), 1.47 (2H, m $OCOCH_2CH_2CH_2CH_3$), 1.74 (2H, m, $OCOCH_2CH_2CH_2CH_3$), 2.33 (3H, s, C-6 CH_3), 2.55 (2H, t, *J* = 7.4 Hz, $OCOCH_2$), 4.01 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 4.07 (2H, q, *J* = 7.2 Hz, $COOCH_2CH_3$), 5.38 (1H, s, C-4H), 5.89 (1H, s, N-1H/N-3H), 6.90 (3H, m, C-2′H, C-5′H and C-6′H), and 8.28 (1H, s, N-1H/N-3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.96 ($OCOCH_2(CH_2)_2CH_3$), 14.46 ($COOCH_2CH_3$), 14.95 (OCH_2CH_3), 18.94 (C-6 CH_3), 22.47 ($OCOCH_2CH_2CH_2CH_3$), 27.44 ($OCOCH_2CH_2CH_2CH_3$), 34.04 ($OCOCH_2$), 55.69 (C-4), 60.35 ($COOCH_2CH_3$), 64.62 (OCH_2CH_3), 101.55 (C-5), 112.09, 118.86 and 123.13 (C-2′, C-6′ and C-5′), 139.93 (C-6), 142.59 (C-1′), 146.62 (C-3′), 150.85 (C-4′), and 153.69, 165.88 and 172.03 (3 × CO); HRMS: *m/z* Calcd for $[C_{21}H_{28}N_2O_6+Na]^+$ 427.1845. Found 427.1818.

Ethy (-)-4-(3′-ethoxy-4′-heptanoyloxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate 12e

It was obtained as a white crystalline solid in 57% yield. $[\alpha]_D^{25}$ - 16.0° (*c* 0.01 MeOH); m.p. 91-93°C; IR (KBr): 3234 (NH), 3109 (NH), 1767 (CO), 1724 (CO), 1706 (CO), 1514, 1462, 1377, 1283, 1224, 1095, 1041 and 788 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (3H, brs, $OCOCH_2(CH_2)_4CH_3$), 1.17 (3H, t, *J* = 7.0 Hz, $COOCH_2CH_3$), 1.33 (3H, t, *J* = 6.6 Hz, OCH_2CH_3), 1.40 (6H, t, *J* = 7.6 Hz, $OCOCH_2CH_2CH_2CH_2CH_2CH_3$), 1.75 (2H, m, $OCOCH_2(CH_2)_3CH_2CH_3$), 2.33 (3H, s, C-6 CH_3), 2.55 (2H, t, *J* = 7.2 Hz, $OCOCH_2$), 4.00 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 4.10 (2H, q, *J* = 7.0 Hz, $COOCH_2CH_3$), 5.39 (1H, s, C-4H), 5.84 (1H, s, N-1H/N-3H), 6.90 (3H, m, C-2′H, C-5′H and C-6′H), and 8.18 (1H, s, N-1H/N-3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.29 ($OCOCH_2(CH_2)_4CH_3$), 14.46 ($COOCH_2CH_3$), 14.96 (OCH_2CH_3), 18.98 (C-6 CH_3), 22.74 ($OCOCH_2(CH_2)_3CH_2CH_2CH_3$), 25.33 ($OCOCH_2(CH_2)_2CH_2CH_2CH_3$), 29.03 ($OCOCH_2CH_2CH_2(CH_2)_2CH_3$), 31.73 ($OCOCH_2CH_2(CH_2)_3CH_3$), 34.33 ($OCOCH_2$), 55.69 (C-4), 60.36 ($COOCH_2CH_3$), 64.61 ($OCH_2CH_3$), 101.56 (C-5), 111.69, 112.09 and 118.86 (C-2′, C-6′ and C-5′), 123.12 (C-6), 142.57 (C-1′), 146.58 (C-3′), 150.85 (C-4′) and 153.61, 165.88 and 172.03 (3 × CO); HRMS: *m/z* Calcd for $[C_{23}H_{32}N_2O_6+Na]^+$ 455.2158. Found 455.2160.

Conclusion

We have developed a systematic one-step procedure for the preparation of optically enriched / pure (+)-ethyl 4-aryl-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylates **8a-d** and acylated (-)-ethyl 4-aryl-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylates **9a-e**, **10a-e**, **11b-d** and **12a-e**, which belong to a class of compounds exhibiting interesting biological activities, in particular calcium channel modulation. This is the environment-friendly report of lipase-catalyzed resolution of 4-aryl-6-methyl-3,4-dihydropyrimidin-2-ones involving hydroxyl group in the C-4 aryl moiety of the molecule as remote handle. This lipase-catalyzed methodology developed for the resolution of 4-aryldihydropyrimidinones is simple and efficient because it is one-step process for the preparation of optically enriched products. The enzymatic resolution reported herein may find applications in the synthesis of optically enriched compounds of this class.

Acknowledgements

Authors thank the Department of Scientific and Industrial Research (DSIR, New Delhi) and the Defense Research and Development Organization (DRDO, New Delhi) for financial support.

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