Racemic and Diastereoselective Synthesis of Aryl and Heteroaryl Tetrahydroisoquinolines *via* the Pictet-Spengler Reaction

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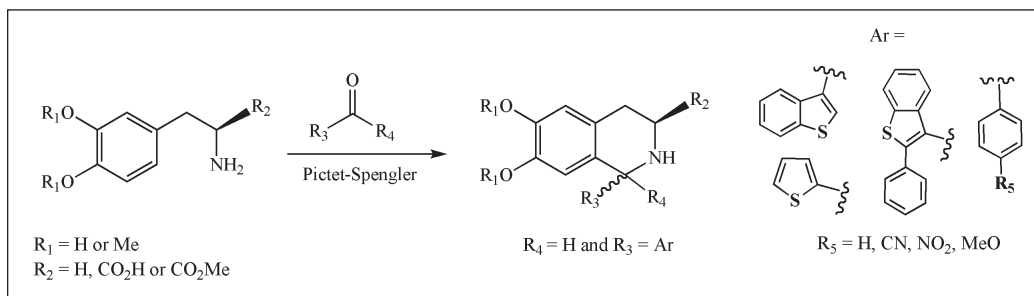
New tetrahydroisoquinolines were synthesized by the Pictet-Spengler reaction. Influence of a wide range of aryl and heteroaryl aldehydes, was investigated in the cyclization step with 3,4-dimethoxyphenylethyl-amine **1**, L-DOPA **2** and L-3,4-dimethoxyphenylalanine methyl ester **3**. Compounds **2** and **3** served as probes to assess the efficiency of two Pictet-Spengler reactions with respect to their diastereoselectivity, in order to obtain optically active diastereoisomers. *Cis-* and *trans-*diastereoisomers were obtained in short reaction times with moderate to good isolated yields (20-79%). Both nmr and X-ray analyses confirmed the expected diastereoisomer configurations.

Introduction.

The synthesis of tetrahydroisoquinolines has received particular attention in the field of medicinal chemistry due to their biological activity [1-4]. Tetrahydroisoquinolines were essentially studied as neurotoxic compounds, and are proven to be involved in some pathologies of the central nervous system [5-8]. This family of compounds is also used in a number of cardiovascular diseases, for the treatment of cardiac ischemia or pulmonary embolism, and plays a role as a venous and arterial antithrombotic agent [9]. One of the most promising methods for the synthesis of many tetrahydroisoquinoline derivatives is the Pictet-Spengler cyclization [10-12].
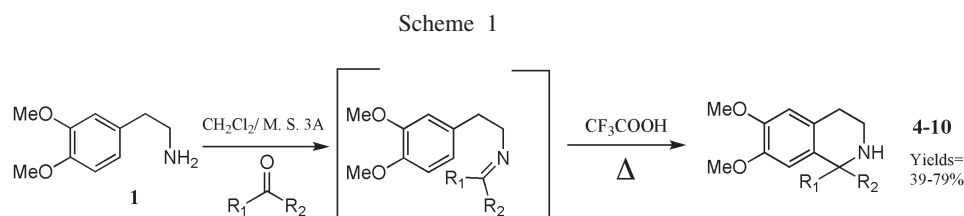
The Pictet-Spengler reaction has been widely investigated with tetrahydro-β-carbolines [13-20] and tetrahydroisoquinolines [21-51], especially in the asymmetric series [42]. The knowledge and synthetic applications of this reaction were pioneered and extensively studied by Kametani and co-workers [21-29] who extended its use to many heterocyclic systems. More recently, Jacobsen [19] reported the asymmetric synthesis of tetrahydro-β-carbolines with a thiourea as chiral ligand. Ohwada [43,44] developed a diastereoselective process based on the Pictet-Spengler reaction in superacidic conditions with several 2-alkyl-*N*-benzylidene-2-phenylethylamines as substrates. Koomen [45,46] described the preparation of enantiopure terahydroisoquinolines *via* a chiral *N*-sulfinyl Pictet-Spengler cyclization in a two-step procedure. More recently, Liu [32] described the phenolic condensation of aldehydes and L-DOPA methyl ester with NaOAc in AcOH as a highly diastereoselective method to prepare chiral tetrahydroisoquinolines. Due to their interesting structures, 3,4-dimethoxyphenylethylamine **1**, L-DOPA **2** and L-3,4-dimethoxyphenylalanine methyl ester **3** allowed the preparation of numerous achiral and chiral building blocks for the synthesis of bioactive compounds. Starting from these materials, we propose here the synthesis of new tetrahydroisoquinolines incorporating substituted aromatic moieties and different heterocyclic units such as thiophene, benzo[*b*]thiophene and pyrrole. Although tetrahydroisoquinoline structures incorporating indole subunits have already been obtained from 1,2,3,4-tetrahydro-2-aryl-isoquinoline [51], the direct introduction of heterocyclic structures from 3,4-dimethoxyphenylethylamine **1** by the Pictet-Spengler reaction at the C(1) position has not yet been assessed. Moreover, the diastereoselectivity of the Pictet-Spengler reaction starting from chiral L-DOPA **2** and L-3,4-dimethoxyphenylalanine methyl ester **3** was evaluated and pure *cis-* and *trans-*adducts could be obtained in good yields.

Results and Discussion.

The Pictet-Spengler cyclization usually involves the condensation of β-arylethylamines and carbonyl deriva-

tives, *via* an intramolecular electrophilic cyclization to afford tetrahydroisoquinolines and their derivatives. The Pictet-Spengler reaction is carried out in protic solvents [21-32] or in acidic conditions [43-50] through imine intermediates. Although the use of 3-activated β-arylethylamines, such as dopamine, allowed a direct cyclization [21-32] through phenolic condensation, a two-step procedure was required when 3,4-dimethoxyphenylethylamine **1** was used. This result can be explained by the lower electron-donating effect of the methoxy groups compared to the hydroxy groups of the dopamine. Thus, the tetrahydroisoquinolines **4-10** were obtained using Ohwada's procedure [43,44] *via* the formation of imine intermediates

With L-DOPA **2** and benzaldehyde, the Pictet-Spengler cyclization, performed in various polar solvents, led selectively to the corresponding *cis-* and *trans-*1-phenyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids **11a** and **11b** (Scheme 3). When the reaction was carried out in water at room temperature, a quantitative conversion and a *cis/trans* ratio of 80/20 were obtained. A selective precipitation provided the *cis*-diastereoisomer **11a** in 60% yield (Table 2). When the reaction was performed in methanol at room temperature, a *cis/trans* mixture of 70/30 was obtained (Table 2). The selective precipitation of this mixture only provided the *trans*-diastereoisomer **11b** in 20% yield: this may be caused by
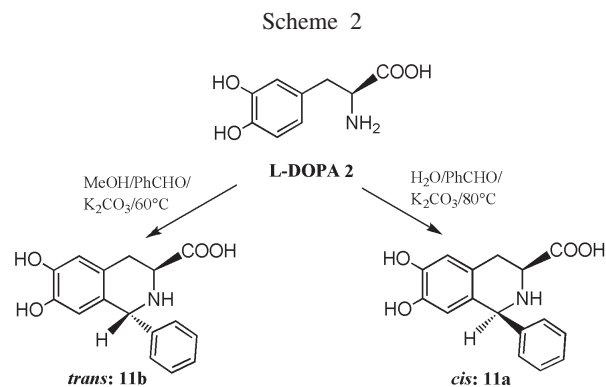
Scheme 1

and cyclization in trifluoroacetic acid (scheme 1). The nature of the functional group on the aromatic ring of the aldehyde exerted a strong influence on the reaction time. An increase of the reaction rate was observed with electron-withdrawing groups in the *p*-position of arylaldehydes, in comparison with the unsubstituted phenyl. However, the presence of a methoxy electron-donating group decreased both the rate and the yield of the cyclization. This phenomenon was also observed in the case of benzo[*b*]thiophene and 2-phenyl benzo[*b*]thiophene (Table 1). When oxo-phenyl-acetic acid ethyl ester was condensed with **1** followed by the cyclization in trifluoroacetic acid, the yield decreased dramatically (39%), probably due to the incomplete conversion of **1** into the imine intermediate, as determined by TLC. Because of its instability, the mixture was used immediately in the cyclization step and the 1,1-disubstituted compound **10** was purified by column chromatography.

Scheme 2

the lesser polarity of the solvent. When the same reactions were refluxed, the cyclization was significantly accelerated (Table 2). When the reaction was conducted in ethanol at 60 °C both diastereoisomer precipitation occurred (Table 2).

Table 1

Synthesis of some new racemic tetrahydroisoquinolines

Compound	R$_1$	R$_2$	Time (h)	Yield (%) [a]
4	C$_6$H$_5$ [44,58]	H	1.5	73
5	4-NC-C$_6$H$_5$	H	0.75	75
6	4-O$_2$N-C$_6$H$_5$ [59,60]	H	0.75	79
7	4-MeO-C$_6$H$_5$ [58]	H	6	65
8	3-benzo[*b*]thiophene	H	3	68
9	3-(2-C$_6$H$_5$-benzo[*b*]thiophene)	H	8	62
10	C$_6$H$_5$	COOEt	3	39

[a] Isolated yields.

Table 2

Experimental Conditions of the Pictet-Spengler Reaction with L-DOPA **2** and Benzaldehyde

Conditions	Time (h)	Ratio *cis/trans* [a]	Isolated Yield [b] (%)
H$_2$O/20 °C	4	80/20	60 (*cis*)
H$_2$O/80 °C	0.25	75/25	56 (*cis*)
MeOH/20 °C	4	70/30	20 (*trans*)
MeOH/60 °C	0.25	65/35	22 (*trans*)
EtOH/60 °C	0.25	70/30	25 (*cis/trans* : 70/30)

[a] Determined by ^{1}H NMR experiments; [b] Obtained by precipitation.

The influence of various aryl and heteroaryl aldehydes on the chirality of the Pictet-Spengler cyclization with preliminary synthesized L-3,4-dimethoxyphenylalanine methyl ester trifluoroacetate salt **3** (see the experimental section) was then studied. Depending on the nature of the substituents on the aromatic moieties and the heterocyclic units, the derivatives **12**-**19** were obtained (Scheme 3) with *cis/trans* ratios ranging from 30/70 to 87/13 (Table 3). When electron-donating groups, such as methoxy, are incorporated

Both *cis*- and *trans*-diastereoisomers were isolated, separated by chromatography and characterized by ^{1}H nmr and ^{13}C nmr spectra. *Cis*- and *trans*-isomers displayed distinctive features in terms of polarity and spectroscopic data. In the present series of tetrahydroisoquinolines **12**-**19,** the *cis*-isomer is less polar than the *trans*-isomer, as indicated by the TLC *Rf* values [52]. The signal assignments were made on the basis of NOESY and HSQC 2D experiments. For the conformational determination of
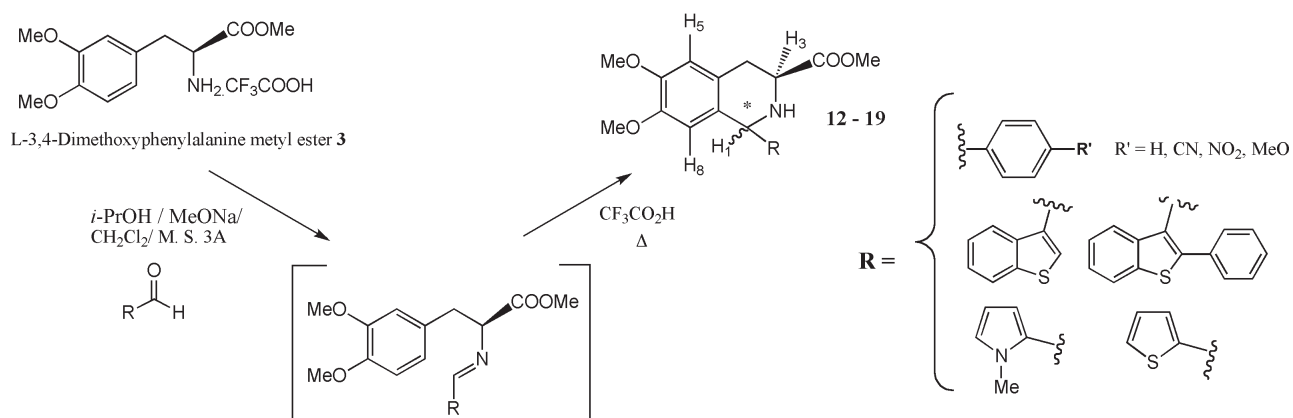
at the *p*-position of the aromatic aldehyde or the benzo[*b*]thiophene-3-carboxaldehyde structure, the electronic delocalisation, lead to a 50/50 ratio. However, arylaldehydes bearing electron-withdrawing groups (cyano, nitro) at the *p*-position, led to an increase in the ratio in favour of the *cis*-adducts. Moreover, a predominant *cis*-ratio was obtained when 2-phenyl-benzo[*b*]thiophene-3-carboxaldehyde was used, certainly due to steric hindrance. With benzaldehyde or thiophene-2-carboxaldehyde, *cis/trans* ratios of 75/25 (Table 3) and 30/70 (Table 3) were obtained respectively. Thus in the latter case, a ratio in favour of the *trans*-adducts was observed. On the other hand, no cyclization occurred with 1-methylpyrrole-2-carboxaldehyde.

compounds **12**-**19**, the NOESY [53-55] experiment displayed correlation peaks which correspond to a typical interaction between both H(1) and H(3) protons. This confirmed the expected *cis*-structures of the compounds **12a** and **13a**. Thus, the two resonance signals at 5.01 ppm and 3.76 ppm correlated by a cross-peak were attributed to the H(1) and H(3) protons of the *cis*-compound **12a**. In the *trans*-isomer **12b**, the H(1) and H(3) protons were characterized by a singlet at 5.19 ppm and a doublet-doublet at 3.72 ppm respectively, without NOE correlation. More generally, we noticed that the chemical shifts of the three singlets corresponding to the signals of H(1), H(5) and H(8) of the *cis*-isomers were upfield relative to the assign-

Table 3

Results of the Pictet-Spengler reaction with the *O*-methylated analogue of L-DOPA **3**

Compound	R	Time (h) [a]	Ratio [b] *cis/trans*	Overall yield (%) [c]	Isolated yield *cis* (%)	Isolated yield *trans* (%)
12a, 12b	C_6H_5	1.5	75/25	74	56	12
13a, 13b	4-NC-C_6H_5	0.75	87/13	79	70	0
14a, 14b	4-O_2N-C_6H_5	0.75	84/16	76	58	10
15a, 15b	4-MeO-C_6H_5	6	50/50	69	31	30
16a, 16b	3-(benzo[*b*]thiophene)	2	50/50	72	34	31
17a, 17b	3-(2-C_6H_5-benzo[*b*]thiophene)	12	85/15	49	36	8
18a, 18b	2-(thiophene)	2	30/70	70	18	45
19	2-(1-methylpyrrole)	24	-	traces	-	-

[a] Determined by TLC after complete consumption of the imine intermediate; [b] Determined by ^{1}H NMR experiment; [c] Isolated yield.

Table 4

Chemical shift of H(1), H(5), H(8), C(1), C(3) resonance signals

Compound	δ (ppm) H(1)	δ (ppm) H(5)	δ (ppm) H(8)	δ (ppm) C(1)	δ (ppm) C(3)
11a (*cis*)	4.87	6.41	5.88	59.1	62.3
11b (*trans*)	5.09	6.51	6.15	52.6	58.8
12a (*cis*)	5.01	6.56	6.09	56.9	63.2
12b (*trans*)	5.19	6.59	6.28	52.5	59.3
13a (*cis*)	5.08	6.57	5.97	56.5	62.7
14a (*cis*)	5.20	6.60	6.00	56.5	62.4
14b (*trans*)	5.32	6.66	6.22	52.6	58.4
15a (*cis*)	5.03	6.62	6.18	57.0	62.6
15b (*trans*)	5.23	6.64	6.34	52.4	58.6
16a (*cis*)	5.57	6.71	6.34	56.9	57.9
16b (*trans*)	5.71	6.70	6.57	52.5	53.8
17a (*cis*)	5.54	6.68	6.22	56.3	57.2
17b (*trans*)	5.63	6.72	6.25	52.4	55.2
18a (*cis*)	5.37	6.54	6.32	56.9	58.3
18b (*trans*)	5.41	6.54	6.47	51.8	55.0

Figure 2. Crystal structure of **13a**.

ments of the *trans*-diastereoisomers (Table 4). Conversely, the signals of the C(1) and C(3) for carbon atoms in *cis*-isomers appeared at a lower field in the nmr spectra than those of the corresponding *trans*-isomers, as already described by Cook and co-workers [19,52] for the tetrahydro-β-carboline analogues. Conformational analysis [56] and examination of molecular models showed two possible half chair conformations (A or B, Figure 1) for the *cis*-isomer **13a**. Conformer A should represent the structure of the more stable species due to the unfavoured interactions between both the axial methyl ester and *p*-cyano-phenyl groups in the conformer B.
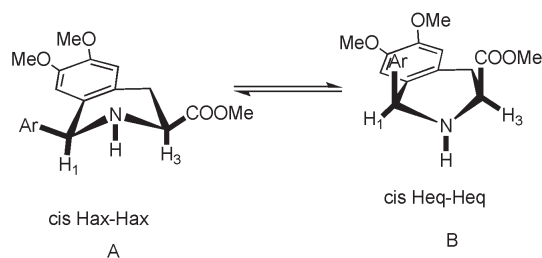

Figure 1. NOE effect observed in the *cis*-isomer.

In order to confirm these structural hypotheses, the solid state structure of compound **13a** was determined by X-ray [57] crystallography (Figure 2). The tetrahydroisoquinoline crystallizes in a half-chair conformation. As expected, it presents a *cis*-configuration with the same axial orientation of C(1)-H(1) and C(3)-H(3) bonds and pseudo equatorial positions for the ester and *p*-cyanophenyl substituents. A similar tetrahydro-β-carboline structure was previously reported by Bailey and co-workers [16].
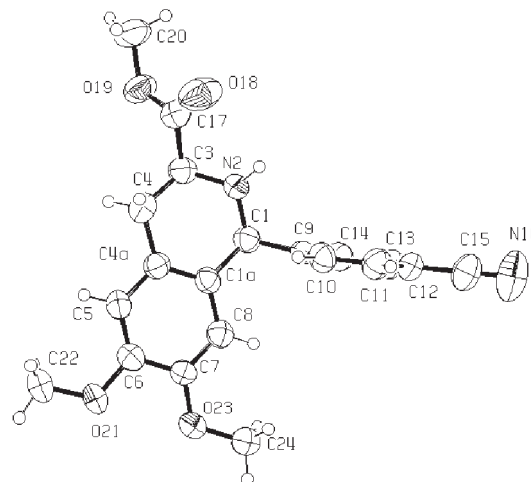
To conclude, the Pictet-Spengler reaction was extended to the synthesis of new tetrahydroisoquinolines. From 3,4-dimethoxyphenylethylamine **1** and several aryl and heteroaryl aldehydes the desired tetrahydroisoquinolines were isolated as racemic mixtures. Whatever the nature of the substituent on the aromatic or heterocyclic subunit (electron-donating or electron-withdrawing groups) cyclization occurred with good yields. This reaction was also extended to chiral tetrahydroisoquinolines by a diastereoselective procedure from chiral L-DOPA **2** and L-3,4-dimethoxy-phenylalanine methyl ester **3** with aryl and heteroaryl aldehydes structures with a better selectivity towards the *cis*-configuration. This study could now be applied to a wide range of targets with a methodological interest in the construction of polycyclic structures incorporating heterocycles.

EXPERIMENTAL

Reactants and solvents were supplied by Aldrich, Acros, Lancaster, Alfa Aeser and Fluka. NMR spectra were recorded either on a Bruker AMX 300 (^{1}H: 300MHz; ^{13}C: 75MHz) or a Bruker DPX 500, (^{1}H: 500MHz; ^{13}C: 100MHz) spectrometer in appropriate deuterated solvents. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion. In the NMR spectra, the nature of the carbon atoms was determined by recording DEPT 135 spectra, and is given in brackets. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, broad, thio = thiophene, benzothio = benzo[*b*]thiophene. Low-resolution mass spectra were recorded using a thermo Finnigan LCQ Advantage instrument using positive electron spray ionization mode. Thin layer chromatography (TLC) was performed with Merck 60 F254 silica gel plates. *Rf* values refer to TLC on Merck 60 F254 silica gel plates. Flash chromatography was performed using Merck Si 60 (40-63μm) silica. Elemental analyses were performed by the 'Service Central d'Analyses du CNRS' (Solaize, France). Optical rotations were measured at 23°C using a Perkin-Elmer 241 polarimeter. Melting points were measured on a

Kofler bench.

General Procedure for the Synthesis of Tetrahydroisoquinolines (4)-(10) from 3,4-Dimethoxyphenylethylamine (1).

To a solution of (**1**) (1mmol) stirred in 3 mL of dichloromethane with 3Å molecular sieves under argon was added aldehyde (1.1 mmol) dissolved in 3 mL of dichloromethane. The solution was then stirred between 0.5 h and 12 h depending on the nature of the aldehyde. The reaction progress was monitored by TLC (diethyl ether/petroleum ether = 2/1). When the reaction was complete the solution was diluted with 5 mL of dichloromethane, filtered, washed with 10 mL of dichloromethane, dried on magnesium sulphate and evaporated. The Schiff base was then engaged in the next step without further purification.

The corresponding Schiff base (1 mmol) solution was suspended in trifluoroacetic acid (100 mmol) and warmed at 72 °C under argon between 0.75 and 8 hours. The reaction was controlled by TLC (ethyl acetate/n-heptane = 5/5). After complete consumption of the Schiff base the solution was diluted with dichloromethane and neutralised with saturated aqueous sodium hydrogen carbonate until pH 9-10. The aqueous phase was then extracted twice with 20 mL of ethyl acetate. The organic layers were then dried on magnesium sulfate, filtered, evaporated and purified on flash chromatography (SiO$_2$, n-heptane/ethyl acetate = 5/5→ ethyl acetate) to provide the racemic mixture of the corresponding amine.

1-Phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4) [44,58].

This compound was obtained as a white solid in 73% yield (196 mg), mp 127-128 °C (ethyl acetate/n-heptane), (lit. mp [44]: 133-134°C, ethanol/n-hexane); ^{1}H nmr (deuteriochloroform): δ 1.89 (br s, 1H, NH, deuterium oxide-exchangeable), 2.63 (dt, 1H, CH_AH$_B$CH$_2$N, J = 4.9, 15.9 Hz), 2.82 (m, 1H, CH$_A$H$_B$CH$_2$N), 2.96 (ddd, 1H, CH$_2$CH_AH$_B$N, J = 4.6, 8, 12.1 Hz), 3.12 (dt, 1H, CH$_2$CH$_A$H$_B$N, J = 5.1, 12 Hz), 3.53 (s, 3H, 7-OCH$_3$), 3.79 (s, 3H, 6-OCH$_3$), 5.00 (s, 1H, 1-H), 6.17 (s, 1H, 8-H), 6.56 (s, 1H, 5-H), 7.12-7.30 (m, 5H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ$_C$ 29.7 (CH$_2$), 42.3 (CH$_2$), 56.2 (2 OCH$_3$), 61.8 (CH), 111.3 (ArCH), 111.8 (ArCH), 127.7 (ArCH), 128.1 (ArC), 128.8 (2ArCH), 129.3 (2ArCH), 130.2 (ArC), 145.3 (ArC), 147.4 (ArC), 148.0 (ArC); ms: m/z 270 ([M+H]$^+$).

Anal. Calcd. for C$_{17}$H$_{19}$NO$_2$. 0.2H$_2$O: C, 74.83; H, 7.11; N, 5.13. Found: C, 74.90; H, 7.30; N, 4.99.

1-(4-Cyanophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5).

This compound was obtained as a white solid in 75% yield (220 mg), mp 127-128 °C (ethyl acetate/n-heptane); ^{1}H nmr (deuteriochloroform): δ 2.02 (br s, 1H, NH deuterium oxide-exchangeable), 2.65 (dt, 1H, J = 4.7, 16 Hz, CH_AH$_B$CH$_2$N), 2.83 (m, 1H, CH$_A$H$_B$CH$_2$N), 2.96 (ddd, 1H, CH$_2$CH_AH$_B$N, J = 4.9, 7.6, 12.4 Hz), 3.05 (dt, 1H, J = 5.7, 12.1 Hz, CH$_2$CH$_A$H$_B$N), 3.54 (s, 3H, 7-OCH$_3$), 3.77 (s, 3H, 6-OCH$_3$), 4.99 (s, 1H, 1-H), 6.07 (s, 1H, 8-H), 6.56 (s, 1H, 5-H), 7.3 (d, 2H, 2'-H, 6'-H, J = 8.3 Hz), 7.51 (d, 2H, 3'-H, 5'-H, J = 8.3 Hz); ^{13}C nmr (deuteriochloroform): δ 29.4 (CH$_2$), 41.9 (CH$_2$), 55.2 (2 OCH$_3$), 61.2 (CH), 111.0 (ArCH), 111.5 (ArC), 112.1 (ArCH), 119.2 (CN), 128.1 (ArC), 128.6 (ArC), 130.1 (2ArCH), 132.5 (2ArCH), 147.5 (ArC), 148.3 (ArC), 150.7 (ArC); ms: m/z 295.1 ([M+H]$^+$).

Anal. Calcd. for C$_{18}$H$_{18}$N$_2$O$_2$. 0.2H$_2$O: C, 72.58; H, 6.11; N, 9.41. Found: C, 72.42; H, 6.18; N, 9.40.

1-(4-Nitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6) [59,60].

This compound was obtained as a pale yellow solid in 79% yield (248 mg), mp 140-141 °C (ethyl acetate/n-heptane); ^{1}H nmr (deuteriochloroform): δ 1.61 (broad s, 1H, NH, deuterium oxide-exchangeable), 2.75 (dt, 1H, J = 4.5, 16 Hz, CH_AH$_B$CH$_2$N), 2.90 (m, 1H, CH$_A$H$_B$CH$_2$N), 3.04 (ddd, 1H, CH$_2$CH_AH$_B$N, J = 4.7, 7.7, 12.2 Hz), 3.11 (dt, 1H, CH$_2$CH$_A$H$_B$N, J = 5.5, 12.2 Hz), 3.61 (s, 3H, 7-OCH$_3$), 3.83 (s, 3H, 6-OCH$_3$), 5.09 (s, 1H, 1-H), 6,12 (s, 1H, 8-H), 6,60 (s, 1H, 5-H), 7.46 (d, 2H, 2'-H, 6'-H, J = 8.8 Hz), 8.15 (d, 2H, J = 8.8 Hz, 3'-H, 5'-H); ^{13}C nmr (deuteriochloroform): δ 29.5 (CH$_2$), 42.0 (CH$_2$), 56.2 (OCH$_3$), 56.3 (OCH$_3$), 61.0 (CH), 111.0 (ArCH), 112.1 (ArCH), 124.0 (2ArCH), 128.1 (ArC), 128.6 (ArC),130.2 (2ArCH), 147.6(ArC), 147.7 (ArC), 148.4 (ArC), 152.7 (ArC); ms: m/z 315.1 ([M+H]$^+$).

Anal. Calcd. for C$_{17}$H$_{18}$N$_2$O$_4$: C, 64.23; H, 5.79; N, 8.81. Found: C, 64.10; H, 5.90; N, 8.58.

1-(4-Methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7) [58].

This compound was obtained as a pale yellow solid in 65% yield (194 mg), mp 95-96 °C (ethyl acetate/n-heptane); ^{1}H nmr (deuteriochloroform): δ 1.90 (broad s, 1H, NH, deuterium oxide-exchangeable), 2.63 (dt, 1H, J = 4.7, 15.7 Hz, CH_AH$_B$CH$_2$N), 2.81 (m, 1H, CH$_A$H$_B$CH$_2$N), 2.92 (ddd, 1H, CH$_2$CH_AH$_B$N, J = 4.7, 7.9, 12.2 Hz), 3.11 (dt, 1H, CH$_2$CH$_A$H$_B$N, J = 5.2, 11.9 Hz), 3.54 (s, 3H, 7-OCH$_3$), 3.77 (s, 3H, 6-OCH$_3$), 4.99 (s, 1H, 1-H), 6.07 (s, 1H, 5-H), 6.56 (s, 1H, 8-H), 7.3 (d, 2H, 3'-H, 5'-H, J = 8.3 Hz,), 7.51 (d, 2H, 2'-H, 6'-H, J = 8.3 Hz,); ^{13}C nmr (deuteriochloroform): δ 29.7 (CH$_2$), 42.4 (CH$_2$), 55.6 (CH$_3$), 56.2 (2 OCH$_3$), 61.3 (CH), 111.3 (ArCH), 111.8 (ArCH), 114.1 (2ArCH), 128.0 (ArC), 130.3 (2ArCH), 130.6 (ArC), 137.5 (ArC), 147.4 (ArC), 147.9 (ArC), 159.2 (ArC); ms: m/z 300.1 ([M+H]$^+$).

Anal. Calcd. for C$_{17}$H$_{18}$N$_2$O$_4$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.00; H, 7.21; N, 4.49.

1-(Benzo[b]thiophene-3-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8).

This compound was obtained as a white solid in 68% yield (221 mg), mp 51-52 °C (ethyl acetate/n-heptane); ^{1}H nmr (deuteriochloroform): δ 1.94 (broad s, 1H, NH, deuterium oxide-exchangeable), 2.86 (m, 2H, CH_AH$_B$CH$_2$N, CH$_A$H$_B$CH$_2$N), 3.05 (dt, 1H, CH$_2$CH_AH$_B$N, J = 5.6, 12.2 Hz), 3.14 (ddd, 1H, J = 5.3, 7.1, 12.2 Hz, CH$_2$CH$_A$H$_B$N), 3.57 (s, 3H, 7-OCH$_3$), 3.82 (s, 3H, 6-OCH$_3$), 5.45 (s, 1H, 1-H), 6.35 (s, 1H, 8-H), 6.60 (s, 1H, 5-H), 6.94 (s, 1H, 2'-H), 7.36 (m, 2H, 5'-H, 6'-H), 7.86 (m, 2H, 4'-H, 7'-H); ^{13}C nmr (deuteriochloroform): δ 29.6 (CH$_2$), 41.4 (CH$_2$), 55.7 (CH), 56.3 (2 OCH$_3$), 111.0 (ArCH), 111.9 (ArCH), 122.9 (ArCH), 122.9 (ArCH), 124.6 (ArCH), 124.8 (ArCH), 125.8 (CH$_{benzothio}$), 128.0 (ArC), 129.2 (ArC), 138.4 (C$_{benzothio}$), 139.7 (ArC), 141.4 (ArC), 147.6 (ArC), 148.2 (ArC); ms: m/z 326.1 ([M+H]$^+$).

Anal. Calcd. for C$_{19}$H$_{19}$NO$_2$S: C, 70.12; H, 5.88; N, 4.30. Found: C, 70.02; H, 5.85; N, 4.26.

1-(2-Phenyl-benzo[b]thiophene-3-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9).

This compound was obtained as a white solid in 62% yield (248 mg), mp 80-81 °C (ethyl acetate/n-heptane); ^{1}H nmr (deu-

teriochloroform): δ 1.70 (broad s, 1H, NH, deuterium oxide-exchangeable), 2.72 (m, 1H, $CH_AH_BCH_2N$), 3.07 (ddd, 1H, $CH_AH_BCH_2N$, J = 4.1, 8.1, 11.8 Hz), 3,17 (m, 1H, $CH_2CH_AH_BN$), 3.38 (m, 1H, $CH_2CH_AH_BN$), 3.52 (s, 3H, 7-OCH_3), 3.86 (s, 3H, 6-OCH_3), 5.49 (s, 1H, 1-H), 6.27 (s, 1H, 8-H), 6.66 (s, 1H, 5-H), 7.14 (ddd, 1H, 5'-H, J = 1.2, 7.5, 8.1 Hz), 7.24 (ddd, 1H, 6'-H, J = 1.3, 7.5, 7.9 Hz), 7.40-7.50 (m, 5H, phenyl protons), 7.62 (dd, 1H, 4'-H, J = 1.3, 8.1 Hz), 7.78 (d, 1H, 7'-H, J = 7.9 Hz); ^{13}C nmr (deuteriochloroform): δ 30.0 (CH_2), 44.9 (CH_2), 56.1 (CH), 56.3 (2 OCH_3), 110.3 (ArCH), 112.2 (ArCH), 122.4 (ArCH), 124.4 (ArCH), 124.5 (ArCH), 125.3 (ArCH), 127.7 (ArC), 128.9 (ArCH), 129.2 (2ArCH), 130.1 (2ArCH), 130.3 ($C_{benzothio}$), 133.6 (ArC), 134.7 (ArC), 139.1($C_{benzothio}$), 139.8 (ArC), 142.4 (ArC), 147.8 (ArC), 148.0 (ArC); ms: m/z 402.1 ([M+H]$^+$).

Anal. Calcd. for $C_{25}H_{23}NO_2S$. $0.1H_2O$: C, 74.46; H, 5.76; N, 3.46. Found: C, 74.38; H, 5.78; N, 3.30.

1-Phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Ethyl Ester (**10**).

This compound was obtained as a colourless oil in 39% yield (133 mg); Rf = 0.2 (ethyl acetate/*n*-heptane = 1/1); ^{1}H nmr (deuteriochloroform): δ 1.19 (t, 3H, CH_3CH_2O, J = 7.2 Hz), 2.54 (broad s, 1H, NH, deuterium oxide-exchangeable), 2.63 (dt, 1H, $CH_AH_BCH_2N$, J = 4.5, 15.8 Hz), 2.82 (m, 1H, $CH_AH_BCH_2N$), 2.92 (m, 1H, $CH_2CH_AH_BN$), 3.11 (dt, 1H, $CH_2CH_AH_BN$, J = 4.5, 12.9 Hz), 3.59 (s, 3H, 7-OCH_3), 3.79 (s, 3H, 6-OCH_3), 4.21 (q, 1H, J = 7.2 Hz, 0.5 OCH_2CH_3), 4.22 (q, 1H, J = 7.2 Hz, 0.5 OCH_2CH_3), 6.53 (s, 1H, 8-ArH), 6.64 (s, 1H, 5-ArH), 7.15 (m, 5H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 14.6 (CH_3), 29.6 (CH_2), 40.8 (CH_2), 56.1 (OCH_3), 56.3 (OCH_3), 62.1 (OCH_2), 70.0 (C), 111.3 (ArCH), 113.8 (ArCH), 127.6 (ArC), 127.8 (ArCH), 128.3 (2ArCH), 128.5 (2ArCH), 129.1 (ArC), 145.4 (ArC), 146.9 (ArC), 148.6 (ArC), 174.7 (C=O); ms: m/z 342 ([M+H]$^+$).

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.38; H, 6.74; N, 4.10. Found: C, 70.25; H, 6.89; N, 3.82.

General Procedure for the Synthesis of Tetrahydroisoquinolines (**11a**), (**11b**) from L-DOPA (**2**).

Benzaldehyde (0.116 g, 1.1 mmol) was added to a solution of L-DOPA (**2**) (0.197 g, 1 mmol) dissolved in 2 mL of water, methanol or ethanol and potassium carbonate (0.152 g, 1.1 mmol) preliminary added at 0 °C under argon. The mixture was stirred at room temperature or at reflux between 0.25 and 4 hours. The reaction was stopped when the precipitation of the corresponding amino-acid occurred. Then the product was collected by filtration and washed with 5 ml of cold reaction solvent.

cis-1-Phenyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (**11a**).

This compound was obtained as a white solid in 60% yield (171 mg), mp 280-281 °C (water/isopropyl alcohol); $[\alpha]_D^{23}$ -16.2 (c 0.5, 0.01 *M* sodium hydroxide); ^{1}H nmr (deuterium oxide/sodium deuteroxide): δ 2.77 (m, 2H, CH_AH_BCHN, CH_AH_BCHN), 3.43 (dd, 1H, 3-H, J = 4.9, 11.7 Hz), 4.87 (s, 1H, 1-H), 5.88 (s, 1H, 8-H), 6.41 (s, 1H, 5-H), 7.32 (m, 5H, phenyl protons); ^{13}C nmr (deuterium oxide/sodium deuteroxide): δ 32.4 (CH_2), 59.1 (CH), 62.3 (CH), 114.0 (ArCH), 116.0 (ArCH), 125.1 (ArC), 126.3 (ArC), 128.2 (ArCH), 129.1 (2ArCH), 129.4 (2ArCH), 144.4 (ArC), 148.0 (ArC), 150.6 (ArC), 181.0 (C=O);

ms: m/z 286 ([M+H]$^+$).

Anal. Calcd. for $C_{16}H_{15}NO_4$. 0.4 H_2O: C, 65.70; H, 5.40; N, 4.79. Found: C, 65.51; H, 5.22; N, 4.79.

trans-1-Phenyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (**11b**).

This compound was obtained as a white solid in 20% yield (57 mg), mp 270-272 °C (methanol); $[\alpha]_D^{23}$ -11.0 (c 0.5, 0.01 *M* sodium hydroxide); ^{1}H nmr (deuterium oxide/sodium deuteroxide): δ 2.68 (dd, 1H, CH_AH_BCHN, J = 10, 16.5 Hz), 2.89 (dd, 1H, CH_AH_BCHN, J = 4.7, 16.2 Hz), 3.41 (dd, 1H, 3-H, J = 4.7, 10 Hz), 5.09 (s, 1H, 1-H), 6.15 (s, 1H, 8-H), 6.51 (s, 1H, 5-H), 7.20-7.32 (m, 5H, phenyl protons); ^{13}C nmr (deuterium oxide/sodium deuteroxide): δ 31.3 (CH_2), 52.5 (CH), 58.7 (CH), 115.3 (ArCH), 115.8 (ArCH), 123.2 (ArC), 123.3 (ArC), 127.7 (ArCH), 128.8 (2ArCH), 129.2 (2ArCH), 145.4 (ArC), 151.7 (ArC), 153.3 (ArC), 181.6 (C=O); ms: m/z 286 ([M+H]$^+$).

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.26; H, 5.30; N, 4.91. Found: C, 67.00; H, 5.29; N, 4.80.

Synthesis of L-3,4-Dimethoxyphenylalanine Methyl Ester (**3**).

L-3,4-Dihydroxyphenylalanine Methyl Ester (**20**) [61-63].

To L-DOPA (**2**) (10 g, 0.0507 mol) in 500 mL of dry methanol stirred at 0 °C was slowly added thionyl chloride (12 g, 0.101 mol) during 1 h. The solution was then refluxed over a period of 24 hours before being cooled and coevaporated with 100 mL of toluene giving amine chlorhydrate (**20**) in 99% yield (12.55 g,) as a white solid, mp 174-175 °C (methanol/dichloromethane), (lit. mp [61]: 172-174 °C, lit. mp [62]: 170-171 °C, lit. mp [63]: 170.5-171.5 °C); $[\alpha]_D^{23}$ +7.9 (c 1, methanol) (lit. $[\alpha]_D^{22}$ [63]: +14.7 (c 12.5, methanol)); ^{1}H nmr (deuterium oxide): δ 3.06 (dd, 1H, CH_AH_BCHN, J = 7.7, 14.6 Hz), 3.18 (dd, 1H, CH_AH_BCHN, J = 5.9, 14.6 Hz), 3.82 (s, 3H, OCH_3), 4.35 (t, 1H, *J* 6.6, CH_2CHN), 6.68 (dd, 1H, 6-H, J = 1.8, 8.1 Hz), 6.78 (d, 1H, 2-H, J = 1.8 Hz), 6.78 (d, 1H, 5-H, J = 8.2 Hz); ^{13}C nmr (deuterium oxide): δ 35.4 (CH_2), 54.0 (OCH_3), 54.8 (CH), 117.1 (ArCH), 117.4 (ArCH), 122.3 (ArCH), 126.6 (ArC), 144.2 (ArC), 144.8 (ArC), 170.6 (C=O); ms: m/z 212 ([M+H]$^+$).

Anal. Calcd. for $C_{10}H_{14}NO_4Cl$: C, 48.48; H, 5.70; N, 5.66. Found: C, 48.24; H, 5.42; N, 5.36.

(L)-N-*tert*-Butoxycarbonyl-3,4-dihydroxyphenylalanine Methyl Ester (**21**) [61,64,65].

To L-3,4-dihydroxyphenylalanine methyl ester (**20**) (12.5 g, 0.0505 mol) in 275 mL of methanol were added triethylamine (0.196 mol, 27.5 cm^3) and di-*tert*-butyl dicarbonate (12.2 g, 0.056 mol) at room temperature. The solution was then stirred during 2 h. After completion (monitored by TLC, ethyl acetate), the solvent was evaporated and the residue was acidified with 1 *M* hydrochloric acid at 0 °C. The solution was then extracted with ethyl acetate (3x50 mL) and the organic layer was dried on magnesium sulfate and evaporated. The crude product was purified by flash chromatography (SiO$_2$, ethyl acetate/*n*-heptane = 9/1) giving (**21**) in 92% yield (14.1 g) as a white solid, mp 134-135 °C (methanol), (lit. mp [61]: 133-135°C, lit. mp [64]: 140-141 °C (methanol/water), lit. mp [65]: 135°C); Rf = 0.4 (ethyl acetate); $[\alpha]_D^{23}$ +6.9 (c 1, methanol), (lit. $[\alpha]_D^{26}$ [61]: +7.6, (c 1.2, methanol), lit. $[\alpha]_D^{25}$ [65]: +7 (c 1, methanol); ^{1}H nmr (deuteriochloroform): δ 1.41 (s, 9H, O(CH_3)$_3$), 2.90 (dd, 1H, CH_AH_BCHN, J = 6.5, 13.9 Hz), 2.99 (dd, 1H, CH_AH_BCHN, J = 5.6,

13.9 Hz), 3.72 (s, 3H, CO$_2$CH$_3$), 4.53 (m, 1H, CH$_2$CHN), 5.08 (d, 1H, NH, deuterium oxide-exchangeable, J =8.2 Hz), 6.50 (d, 1H, 6-H, J = 1.8, 9.9 Hz), 6.66 (broad s, 1H, 2-H), 6.75 (d, 1H, 5-H, J = 8.1 Hz); ^{13}C nmr (deuteriochloroform): δ 28.2 (3CH$_3$), 37.6 (CH$_2$), 52.4 (OCH$_3$), 54.7 (CH), 80.6 (C), 115.4 (ArCH), 116.1 (ArCH), 121.4 (ArCH), 128.1 (ArC), 143.1 (ArC), 144.0 (ArC), 155.6 (NC=O), 172.9 (C=O); ms: m/z 334 ([M+Na]$^+$), 312 ([M+H])$^+$).

Anal. Calcd. for C$_{15}$H$_{21}$NO$_6$. 0.2H$_2$O: C, 57.21; H, 6.74; N, 4.45. Found: C, 57.18; H, 6.96; N, 4.12.

(L)-N-*tert*-Butoxycarbonyl-3,4-dimethoxyphenylalanine Methyl Ester (**22**) [32,66,67].

To a stirred solution of 100 mL of *N*,*N*-dimethylformamide and potassium carbonate (55.9 g, 0.405 mol) were added L-*tert*-butoxycarbonyl-3,4-dihydroxyphenylalanine methyl ester (**21**) (14 g, 0.045 mol) and methyl iodide (27.5 g, 0.202 mol). The mixture was then stirred for 24 hours. Monitoring by TLC (ethyl acetate/ *n*-heptane: 7/3) indicated the disappearance of starting material. The mixture was then filtered, extracted with 60 mL of ether and washed twice with 20 mL of 1 *M* hydrochloric acid. The organic layer was then dried on magnesium sulfate, filtered, evaporated and purified on flash chromatography (SiO$_2$, ethyl acetate/n-heptane = 9/1→7/3) giving (**22**) in 89% yield (13.6 g) as a colourless oil, *Rf* = 0.4 (AcOEt/n-heptane = 1/1); [α]$_D^{23}$ +6.0 (c 1, methanol); ^{1}H nmr (deuteriochloroform): δ 1.34 (s, 9H, O(CH$_3$)$_3$), 2.93 (t, 1H, CH$_A$H$_B$CHN, J = 6 Hz), 2.94 (m, 1H, CH$_A$H$_B$CHN), 3.64 (s, 3H, 4-OCH$_3$), 3.78 (s, 6H, 3-OCH$_3$, CO$_2$CH$_3$), 4.47 (dd, 1H, CH$_2$CHN, J = 6, 13.7 Hz), 4.98 (broad d, 1H, NH, deuterium oxide-exchangeable), 6.56 (m, 2H, 6-H, 2-H), 6.72 (d, 1H, 5-H, J = 9 Hz); δ$_C$(75 MHz, CDCl$_3$) 28.7 (3CH$_3$), 38.2 (CH$_2$), 52.6 (OCH$_3$), 54.8 (CH), 56.1 (OCH$_3$), 56.2 (OCH$_3$), 80.2 (C), 111.6 (ArCH), 112.7 (ArCH), 121.7 (ArCH), 128.8 (ArC), 148.4 (ArC), 149.2 (ArC), 155.4 (NC=O), 172.8 (C=O); ms: m/z 362 ([M+Na]$^+$), 240 ([M+H-CO$_2$t-Bu]$^+$).

Anal. Calcd. for C$_{17}$H$_{25}$NO$_6$: C, 60.16; H, 7.42; N, 4.13. Found: C, 59.84; H, 7.32; N, 4.11.

(L)-3,4-Dimethoxyphenylalanine Methyl Ester Trifluoroacetate (**3**) [68-70].

To (L)-*tert*-butoxycarbonyl-3,4-dimethoxyphenylalanine methyl ester (**22**) (13.6 g, 0.0402 mol) was added 100 mL of a solution of trifluoroacetic acid in dichloromethane (5/95). The resulting mixture was stirred over a period of 5 hours. The mixture was then coevaporated with toluene giving a residual solid which was dissolved in ethyl acetate. A few drops of cyclohexane were added giving (**3**) in 90% yield (11.3 g) as a white solid, mp 150-152 °C (methanol/dichloromethane), (lit. mp [68]: 158-159 °C (ethanol/ether)); [α]$_D^{23}$ +3.2 (c 1, methanol), (lit. [α]$_D^{20}$ [68]: +6.8, (c 2, methanol)); ^{1}H nmr (deuterium oxide): δ 3.19 (dd, 1H, CH$_A$H$_B$CHN, J = 7.6, 14.5 Hz), 3.27 (dd, 1H, CH$_A$H$_B$CHN, J = 5.9, 14.4 Hz), 3.64 (s, 3H, 4-OCH$_3$), 3.80 (s, 6H, 3-OCH$_3$, CO$_2$CH$_3$), 4.38 (dd, 1H, CH$_2$CHN, J = 5.9, 7.6 Hz), 6.82 (dd, 1H, 6-H, J = 1.8, 8 Hz), 6.88 (d, 1H, 2-H, J = 1.8 Hz), 6.97 (d, 1H, 5-H, J= 8 Hz); ^{13}C nmr (deuterium oxide): δ 35.5 (CH$_2$), 53.9 (OCH$_3$), 54.4 (CH), 55.8 (2 OCH$_3$), 111.3 (ArCH), 112.7 (ArCH), 122.5 (ArCH), 126.8 (ArC), 148.1 (ArC), 148.7 (ArC), 170.4 (C=O); ms: m/z 240 ([M+H]$^+$, 223 ([M+H-NH$_3$]$^+$).

Anal. Calcd. for C$_{14}$H$_{18}$ F$_3$NO$_6$: C, 47.60; H, 5.14; N, 3.96. Found: C, 47.81; H, 5.33; N, 4.10.

General Procedure for the Synthesis of Tetrahydroisoquinolines (**12**)-(**18**) from L-3,4-Dimethoxyphenylalanine Methyl Ester (**3**).

At 0 °C, to a solution of amino ester salt (**3**) (1 mmol) stirred in 3 mL of dichloromethane/isopropyl alcohol (2/1) with 3Å molecular sieves under argon were preliminary added sodium methoxide (1.1 mmol) and aldehyde (1.1 mmol) in 3 mL of dichloromethane. The solution was then stirred at room temperature or at reflux between 0.75 h and 12 h depending on the nature of aldehyde. The reaction progress was monitored by TLC (ethyl acetate/*n*-heptane = 3/7). When the reaction was complete the solution was diluted with 5 mL of dichloromethane, filtered, washed with 10 mL of dichloromethane and evaporated. The Schiff base was then engaged in the next step without further purification.

The Schiff base (1 mmol) contained in trifluoroacetic acid (100 mmol) was heated at reflux under argon between 1 and 6 hours. The reaction was controlled by TLC (ethyl acetate/heptane = 1/1). After complete consumption of the Schiff base the solution was diluted with 20 mL of dichloromethane and neutralized with saturated aqueous sodium hydrogen carbonate solution until pH 9-10. The aqueous phase was then extracted twice with 20 mL of ethyl acetate. The organic layers were then dried on magnesium sulfate, filtered, evaporated and purified by flash chromatography (SiO$_2$, *n*-heptane/ethyl acetate = 8/2→6/4) to separate both diastereoisomers.

cis-1-Phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Methyl Ester (**12a**).

This compound was obtained as a white solid in 56% yield (183 mg), mp 120-121 °C (AcOEt ethyl acetate/*n*-heptane); *Rf* = 0.3 (ethyl acetate/*n*-heptane = 7/3); [α]$_D^{23}$ - 1.7 (c 1, chloroform). ^{1}H nmr (deuteriochloroform): δ 2.58 (broad s, 1H, NH, deuterium oxide-exchangeable), 2.99 (m, 2H, CH$_A$H$_B$CHN, CH$_A$H$_B$CHN), 3.50 (s, 3H, 7-OCH$_3$), 3.68 (s, 3H, CO$_2$CH$_3$), 3.76 (m, 1H, 3-H), 3.77 (s, 3H, 6-OCH$_3$), 5.01 (s, 1H, 1-H), 6.09 (s, 1H, 8-H), 6.56 (s, 1H, 5-H), 7.25 (m, 5H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 32.6 (CH$_2$), 52.6 (OCH$_3$), 56.2 (CH), 56.3 (2 OCH$_3$), 56.9 (CH), 63.2 (CH), 110.9 (ArCH), 111.7 (ArCH), 126.4 (ArC), 128.3 (ArCH), 129.0 (2ArCH), 129.4 (2ArCH), 130.5 (ArC), 144.2 (ArC), 147.8 (ArC), 148.1 (ArC), 173.3 (C=O); ms: m/z 328 ([M+H]$^+$).

Anal. Calcd. for C$_{19}$H$_{21}$NO$_4$. 1/6H$_2$O: C, 69.09; H, 6.41; N, 4.24. Found: C, 69.07; H, 6.56; N, 4.28.

trans-1-Phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Methyl Ester (**12b**).

This compound was obtained as a white solid in 12% yield (39 mg), mp 115-116 °C (ethyl acetate/*n*-heptane); *Rf* = 0.15 (ethyl acetate/*n*-heptane = 1/1); [α]$_D^{23}$ -8.2 (c 0.35, chloroform); ^{1}H nmr (deuteriochloroform): δ 2.18 (broad s, 1H, NH, deuterium oxide-exchangeable), 2.94 (dd, 1H, CH$_A$H$_B$CHN, J = 8.6, 16 Hz), 3.08 (dd, 1H, CH$_A$H$_B$CHN, J = 5.1, 16 Hz), 3.61 (s, 3H, CO$_2$CH$_3$), 3.64 (s, 3H, 7-OCH$_3$), 3.72 (dd, 1H, 3-H, J = 5.1, 8.7 Hz), 3.79 (s, 3H, 6-OCH$_3$), 5.19 (s, 1H, 1-H), 6.28 (s, 1H, 8-H), 6.59 (s, 1H, 5-H), 7.11-7.22 (m, 5H, phenyl protons); ^{13}C nmr (deuteriochloroform): δ 31.5 (CH$_2$), 51.7 (OCH$_3$), 52.5 (CH), 56.2 (2OCH$_3$), 59.3 (ArCH), 111.2 (ArCH), 111.5 (ArCH), 128.4 (ArC), 128.7 (ArCH), 129.0 (2ArCH), 129.4 (2ArCH), 130.6 (ArC), 145.0 (ArC), 147.8 (ArC), 148.3 (ArC), 174.3 (C=O); ms: m/z 328 ([M+H]$^+$).

Anal. Calcd. for $C_{19}H_{21}NO_4$. $1/6H_2O$: C, 69.04; H, 6.54; N, 4.10. Found: C, 69.09; H, 6.41; N, 4.24.

cis-1-(4-Cyanophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Methyl Ester (**13a**).

This compound was obtained as a white solid in 70% yield (246 mg), mp 128-129 °C (ethyl acetate/*n*-heptane); *Rf* = 0.3 (ethyl acetate/*n*-heptane = 1/1); $[\alpha]_D^{23}$ -1.9 (c 1.75, chloroform); ^{1}H nmr (deuteriochloroform): δ 2.44 (broad s, 1H, NH, deuterium oxide-exchangeable), 3.00 (m, 2H, CH_AH$_B$CHN, CH$_A$H$_B$CHN), 3.51 (s, 3H, 7-OCH$_3$), 3.69 (s, 3H, CO$_2$CH$_3$), 3.77 (s, 3H, 6-OCH$_3$), 3.74 (m, 1H, 3-H), 5.08 (s, 1H, 1-H), 5.97 (s, 1H, 8-H), 6.57 (s, 1H, 5-H), 7.39 (d, 2H, 2'-H, 6'-H, J = 8.3 Hz), 7.54 (d, 2H, 3'-H, 5'-H, J = 8.2 Hz); ^{13}C nmr (deuteriochloroform): δ 32.4 (CH$_2$), 52.6 (OCH$_3$), 56.2 (CH), 56.3 (2 OCH$_3$), 56.5 (CH), 62.7 (CH), 110.5 (Ar*C*H), 111.8 (Ar*C*H), 112.0 (Ar*C*), 119.2 (CN), 126.6 (Ar*C*), 129.0 (Ar*C*), 130.3 (2Ar*C*H), 132.8 (2Ar*C*H), 147.9 (Ar*C*), 148.4 (Ar*C*), 149.8 (Ar*C*), 173.1 (C=O); ms: m/z 353 ([M+H]$^+$).

Anal. Calcd. for $C_{20}H_{20}N_2O_4$. $0.1H_2O$: C, 67.64; H, 5.69; N, 7.89. Found: C, 67.72; H, 5.67; N, 7.95.

cis-1-(4-Nitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Methyl Ester (**14a**).

This compound was obtained as a pale yellow solid in 58% yield (215 mg), mp 126-127 °C (ethyl acetate/*n*-heptane); *Rf* = 0.2 (ethyl acetate/*n*-heptane = 1/1); $[\alpha]_D^{23}$ -11.2 (c 1, chloroform); ^{1}H nmr (deuteriochloroform): δ 2.12 (broad s, 1H, NH, deuterium oxide-exchangeable), 3.00 (m, 2H, CH_AH$_B$CHN, CH$_A$H$_B$CHN), 3.59 (s, 3H, 7-OCH$_3$), 3.78 (s, 3H, CO$_2$CH$_3$), 3.82 (m, 1H, 3-H), 3.86 (s, 3H, 6-OCH$_3$), 5.20 (s, 1H, 1-H), 6.00 (s, 1H, 8-H), 6.60 (s, 1H, 5-H), 7.53 (d, 2H, 2'-H, 6'-H, J = 8.5 Hz), 8.20 (d, 2H, 3'-H, 5'-H, J = 8.7 Hz); ^{13}C nmr (deuteriochloroform): δ 32.4 (CH$_2$), 52.7 (OCH$_3$), 56.3 (2 OCH$_3$), 56.5 (CH), 62.4 (CH), 110.5 (Ar*C*H), 111.9 (Ar*C*H), 124.2 (2Ar*C*H), 126.6 (Ar*C*), 128.9 (Ar*C*), 130.4 (2Ar*C*H), 147.9 (Ar*C*), 148.0 (Ar*C*), 148.5 (Ar*C*), 151.9 (Ar*C*), 173.1 (C=O); ms: m/z 373.1 ([M+H]$^+$).

Anal. Calcd. for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.02; H, 5.49; N, 7.43.

trans-1-(4-Nitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Methyl Ester (**14b**).

This compound was obtained as a pale yellow solid in 58% yield (37 mg), mp 118-119 °C (ethyl acetate/*n*-heptane); *Rf* = 0.1 (ethyl acetate/*n*-heptane = 1/1); $[\alpha]_D^{23}$ -19.8 (c 0.9, chloroform); ^{1}H nmr (deuteriochloroform): δ 2.45 (broad s, 1H, NH, deuterium oxide-exchangeable), 2.94 (dd, 1H, CH_AH$_B$CHN, J = 7.7, 16.2 Hz), 3.10 (dd, 1H, CH$_A$H$_B$CHN, J = 5.1, 16 Hz), 3.66 (s, 3H, CO$_2$CH$_3$), 3.70 (s, 3H, 7-OCH$_3$), 3.76 (dd, 1H, 3-H, J = 5.2 ,8.9 Hz), 3.86 (s, 3H, 6-OCH$_3$), 5.32 (s, 1H, 1-H), 6.22 (s, 1H, 8-H), 6.66 (s, 1H, 5-H), 7.33 (d, 2H, 2'-H, 6'-H, J = 8.7 Hz), 8. 07 (d, 2H, 3'-H, 5'-H, J = 8.7 Hz); ^{13}C nmr (deuteriochloroform): δ 31.2 (CH$_2$), 52.6 (OCH$_3$), 52.2 (CH), 56.3 (2 OCH$_3$), 58.4 (CH), 110.8 (Ar*C*H), 111.8 (Ar*C*H), 124.3 (2Ar*C*H), 127.0 (Ar*C*), 128.0 (Ar*C*), 130.0 (2Ar*C*H), 147.6 (Ar*C*), 148.1 (Ar*C*), 148.7 (Ar*C*), 152.4 (Ar*C*), 174.0 (C=O); ms: m/z 373.1 ([M+H]$^+$).

Anal. Calcd. for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.11; H, 5.48; N, 7.51.

cis-1-(4-Methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Methyl Ester (**15a**).

This compound was obtained as a white solid in 31% yield (111 mg), mp 129-130 °C (ethyl acetate/*n*-heptane); *Rf* = 0.2 (ethyl acetate/heptane = 1/1); $[\alpha]_D^{25}$ -20.5 (c 0.6, chloroform); ^{1}H nmr (deuteriochloroform): δ 2.37 (broad s, 1H, NH, deuterium oxide-exchangeable), 3.07 (m, 2H, CH_AH$_B$CHN, CH$_A$H$_B$CHN), 3.59 (s, 3H, 7-OCH$_3$), 3.75 (s, 3H, CO$_2$CH$_3$), 3.80 (s, 3H, 4'-OCH$_3$), 3.83 (m, 1H, 3-H), 3,85 (s, 3H, 6-OCH$_3$), 5.03 (s, 1H, 1-H), 6.18 (s, 1H, 8-H), 6.62 (s, 1H, 5-H), 6.86 (d, 2H, 3'-H, 5'-H, J = 8.5 Hz), 7.24 (d, 2H, 2'-H, 6'-H, J = 8.5 Hz); ^{13}C nmr (deuteriochloroform): δ 32.6 (CH$_2$), 52.5 (OCH$_3$), 55.6 (CH), 56.3 (2 OCH$_3$), 56.9 (OCH$_3$), 62.6 (CH), 110.9 (Ar*C*H), 111.6 (Ar*C*H), 114.3 (2Ar*C*H), 126.4 (Ar*C*), 130.5 (2Ar*C*H), 130.9 (Ar*C*), 136.5 (Ar*C*), 147.7 (Ar*C*), 148.1 (Ar*C*), 159.5 (Ar*C*), 173.4 (C=O); ms: m/z (ESI) 358 ([M+H).

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.22; H, 6.44; N, 3.92. Found: C, 67.43; H, 6.51; N, 3.92.

trans-1-(4-Methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Methyl Ester (**15b**).

This compound was obtained as a white solid in 30% yield (107 mg), mp 119-120 °C (ethyl acetate/*n*-heptane); *Rf* = 0.1 (ethyl acetate/*n*-heptane = 1/1); $[\alpha]_D^{23}$ -34.3 (c 0.6, chloroform); ^{1}H nmr (deuteriochloroform): δ 2.15 (broad s, 1H, NH, deuterium oxide-exchangeable), 2.99 (dd, 1H, CH_AH$_B$CHN, J = 8.5, 16.2 Hz), 3.10 (dd, 1H, CH$_A$H$_B$CHN, J = 5.1, 16 Hz), 3.67 (s, 3H, CO$_2$CH$_3$), 3.72 (s, 3H, 7-OCH$_3$), 3.78 (m, 1H, 3-H), 3.79 (s, 3H, 4'-OCH$_3$), 3,88 (s, 3H, 6-OCH$_3$), 5.23 (s, 1H, 1-H), 6.34 (s, 1H, 8-H), 6.64 (s, 1H, 5-H), 6.82 (d, 2H, 3'-H, 5'-H, J = 8.6 Hz), 7.09 (d, 2H, 2'-H, 6'-H, J = 8.6 Hz); ^{13}C nmr (deuteriochloroform): δ 31.4 (CH$_2$), 51.7 (OCH$_3$), 52.4 (CH), 55.6 (OCH$_3$), 56.2 (2 OCH$_3$), 58.6 (CH), 111.2 (Ar*C*H), 111.5 (Ar*C*H), 114.1 (2Ar*C*H), 126.0 (Ar*C*), 128.8 (Ar*C*), 130.2 (2Ar*C*H), 137.2 (Ar*C*), 147.8 (Ar*C*), 148.2 (Ar*C*), 159.2 (Ar*C*), 174.3 (C=O); m/z (ESI) 358 ([M+H]$^+$, 100%).

Anal. Calcd. for $C_{20}H_{23}NO_5$. $0.1H_2O$: C, 67.22; H, 6.44; N, 3.92. Found: C, 66.74; H, 6.54; N, 3.77.

cis-1-(Benzo[*b*]thiophen-3-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Methyl Ester (**16a**).

This compound was obtained as a pale yellow solid in 34% yield (130 mg), mp 66-67 °C (ethyl acetate/*n*-heptane); *Rf* = 0.5 (ethyl acetate/*n*-heptane = 1/1); $[\alpha]_D^{23}$ -10.9 (c 1, chloroform); ^{1}H nmr (deuteriochloroform): δ 2.53 (broad s, 1H, NH, deuterium oxide-exchangeable), 3.15 (dd, 1H, CH_AH$_B$CHN, J = 4.2, 15.5 Hz), 3.21(dd, 1H, CH$_A$H$_B$CHN, J = 11, 15.4 Hz), 3.53 (s, 3H, 7-OCH$_3$), 3.74 (s, 3H, CO$_2$CH$_3$), 3.88 (s, 3H, 6-OCH$_3$), 3.92 (dd, 1H, J = 4.1, 10.7 Hz, 3-H), 5.57 (s, 1H, 1-H), 6.34 (s, 1H, 8-H), 6.71 (s, 1H, 5-H), 7.25 (dd, 1H, 5'-H, J = 7.6, 7.9 Hz), 7.30 (dd, 1H, 6'-H, J = 7.6, 8.2 Hz), 7.45 (s, 1H, 2'-H), 7.69 (d, 1H, 4'-H, J = 8.2 Hz), 7.85 (d, 1H, 7'-H, J = 7.9 Hz); ^{13}C nmr (deuteriochloroform): δ 32.5 (CH$_2$), 52.6 (OCH$_3$), 56.2 (OCH$_3$), 56.3 (OCH$_3$), 57.9 (CH), 56.9 (CH), 110.1 (Ar*C*H), 111.8 (Ar*C*H), 123.2 (C$_{benzothio}$H), 124.0 (Ar*C*H), 124.4 (Ar*C*H), 124.8 (Ar*C*H), 125.9 (Ar*C*H), 126.2 (Ar*C*), 129.3 (Ar*C*), 138.0 (C$_{benzothio}$), 138.5 (Ar*C*), 141.4 (Ar*C*), 148.0 (Ar*C*), 148.3 (Ar*C*), 173.3 (C=O); ms: m/z (ESI) 384.1 ([M+H]$^+$).

Anal. Calcd. for $C_{21}H_{21}NO_4S$: C, 65.78; H, 5.52; N, 3.65. Found: C, 66.09; H, 5.63; N, 3.59.

trans-1-(Benzo[*b*]thiophen-3-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Methyl Ester (**16b**).

This compound was obtained as a pale yellow solid in 31% yield (119 mg), mp 69-70 °C (ethyl acetate/*n*-heptane); *Rf* = 0.3 (ethyl

acetate/*n*-heptane = 1/1); $[\alpha]_D^{23}$ +20.9 (c 1, chloroform); ^{1}H nmr (deuteriochloroform): δ 2.47 (broad s,1H, NH, deuterium oxide-exchangeable), 2.92 (dd, 1H, C*H*$_A$*H*$_B$CHN, J = 9.4, 16.2 Hz), 3.08 (dd, 1H, CH$_A$*H*$_B$CHN, J = 4.8, 16 Hz), 3.71 (s, 6H, CO$_2$CH$_3$, 7-OCH$_3$), 3.80 (dd, 1H, 3-H, J = 4.9, 9.4 Hz), 3.91 (s, 3H, 6- OCH$_3$), 5.71 (s, 1H, 1-H), 6.57 (s, 1H, 8-H), 6.70 (s, 1H, 5-H), 6.82 (s, 1H, 2'-H), 7.40 (ddd, 1H, 5'-H, J = 1.3, 7.2, 8.3 Hz), 7.46 (ddd, 1H, 6'-H, J = 1.3, 7.2, 7.9 Hz), 7.89 (ddd, 1H, 4'-H, J = 0.8, 1.2, 7.9 Hz), 7.98 (ddd, 1H, 7'-H, J = 0.8, 1.1, 8.1 Hz); ^{13}C nmr (deuteriochloroform): δ 31.7 (CH$_2$), 52.0 (OCH$_3$), 52.5 (CH), 53.8 (CH), 56.3 (OCH$_3$), 56.5 (OCH$_3$), 111.0 (Ar*C*H), 111.6 (Ar*C*H), 122.4 (CH$_{benzothio}$), 123.5 (Ar*C*H), 124.8 (Ar*C*H), 125.0 (Ar*C*), 126.1 (2Ar*C*H), 127.8 (Ar*C*), 138.3 (*C*$_{benzothio}$), 139.5 (Ar*C*), 141.4 (Ar*C*), 147.9 (Ar*C*), 148.5 (Ar*C*), 174.1 (C=O); ms: m/z (ESI) 384.1 ([M+H]$^+$).

Anal. Calcd. for C$_{21}$H$_{21}$NO$_4$S. 0.2H$_2$O : C, 65.16; H, 5.53; N, 3.62. Found: C, 65.12; H, 5.56; N, 3.52.

cis-1-(2-Phenyl-benzo[b]thiophen-3-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Methyl Ester (**17a**).

This compound was obtained as a white solid in 36% yield (165 mg), mp 70-72 °C (ethyl acetate/*n*-heptane); *Rf* = 0.3 (ethyl acetate/*n*-heptane = 3/7); $[\alpha]_D^{23}$ +94 (c 0.5, chloroform); ^{1}H nmr (deuteriochloroform): δ 2.54 (broad s, 1H, NH,deuterium oxide-exchangeable), 3.14 (m, 2H, C*H*$_A$*H*$_B$CHN, CH$_A$*H*$_B$CHN), 3.54 (s, 3H, 7-OCH$_3$), 3.76 (s, 3H, CO$_2$CH$_3$), 3.83 (dd, 1H, 3-H, J = 4.5, 8.8 Hz), 3.85 (s, 3H, 6-OCH$_3$), 5.54 (s, 1H, 1-H), 6.22 (s, 1H, 8-H), 6.68 (s, 1H, 5-H), 7.13 (m, 1H, 5'-H), 7.23 (m, 1H, 6'-H), 7.34 (m, 3H, phenyl protons), 7.46 (m, 1H, 4'-H), 7.54 (m, 2H, phenyl protons), 7.68 (d, 1H, J = 7.9, 7'-H); ^{13}C nmr (deuteriochloroform): δ 32.5 (CH$_2$), 52.5 (OCH$_3$), 56.3 (CH), 56.4 (2 OCH$_3$), 57.2 (CH), 110.2 (Ar*C*H), 112.2 (Ar*C*H), 122.3 (Ar*C*H), 124.3 (Ar*C*H), 124.5 (2Ar*C*H), 126.2 (Ar*C*), 128.9 (Ar*C*H), 129.1 (2Ar*C*H), 129.7 (Ar*C*), 130.1 (2Ar*C*H), 132.6 (C$_{benzothio}$), 134.6 (C$_{benzothio}$), 138.9 (Ar*C*), 139.8 (Ar*C*), 142.8 (Ar*C*), 148.13 (Ar*C*), 148.4 (Ar*C*), 173.3 (C=O); ms: m/z 460 ([M+H]$^+$).

Anal. Calcd. for C$_{27}$H$_{25}$NO$_4$S: C, 70.57; H, 5.48; N, 3.05. Found: C, 70.42; H, 5.73; N, 2.84.

trans-1-(2-Phenyl-benzo[b]thiophen-3-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Methyl Ester (**17b**).

This compound was obtained as a white solid in 8% yield (37 mg), mp 72-74 °C (ethyl acetate/*n*-heptane); *Rf* 0.3 (ethyl acetate/*n*-heptane = 3/7); $[\alpha]_D^{23}$ -52.6 (c 1, chloroform); ^{1}H nmr (deuteriochloroform): δ 2.50 (broad s, 1H, NH, deuterium oxide-exchangeable), 3.16 (m, 1H, C*H*$_A$*H*$_B$CHN), 3.26 (m, 1H, CH$_A$*H*$_B$CHN), 3.50 (s, 3H, CO$_2$CH$_3$), 3.58 (s, 3H, 7-OCH$_3$), 3.86 (s, 3H, 6-OCH$_3$), 4.10 (dd, 1H, 3-H, J = 4.1, 8.6 Hz), 5.67 (s, 1H, 1-H), 6.25 (s, 1H, 8-H), 6.72 (s, 1H, 5-H), 7.15 (ddd, 1H, 5'-H, J = 1.3, 7.2, 8.3 Hz,), 7.25 (ddd, 1H, 6'-H, J = 1.3, 7.2, 8.0 Hz), 7.46 (m, 3H, phenyl protons), 7.54 (m, 1H, 4'-H), 7.63 (m, 2H, phenyl protons), 7.80 (ddd 1H, 7'-H, J = 0.8, 1.1, 8.1 Hz); ^{13}C nmr (deuteriochloroform): δ 30.3 (CH$_2$), 51.6 (OCH$_3$), 52.4 (CH), 55.2 (CH), 56.2 (OCH$_3$), 56.3 (OCH$_3$), 110.0 (Ar*C*H), 111.6 (Ar*C*H), 122.4 (Ar*C*H), 124.4 (Ar*C*H), 124.5 (Ar*C*H), 125.0 (Ar*C*), 125.1 (Ar*C*H), 128.5 (Ar*C*), 128.9 (Ar*C*H), 129.0 (2Ar*C*H), 130.2 (2Ar*C*H), 133.3 (C$_{benzothio}$), 134.5 (C$_{benzothio}$), 139.0 (Ar*C*), 139.8 (Ar*C*), 143.0 (Ar*C*), 148.0 (Ar*C*), 148.1 (Ar*C*), 174.5 (C=O); ms: m/z 460 ([M+H]$^+$).

Anal. Calcd. for C$_{27}$H$_{25}$NO$_4$S: C, 70.57; H, 5.44; N, 3.05. Found: C, 70.39; H, 5.63; N, 2.81.

cis-1-(Thiophen-2-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroiso-quinoline-3-carboxylic Acid Methyl Ester (**18a**).

This compound was obtained as a pale yellow oil in 18% yield (60 mg); *Rf* = 0.3 (ethyl acetate/*n*-heptane = 1/1); $[\alpha]_D^{23}$ -65.5 (c 1, chloroform); ^{1}H nmr (deuteriochloroform): δ 2.50 (broad s, 1H, NH, deuterium oxide-exchangeable), 2.99 (m, 2H, C*H*$_A$H-$_B$CHN, CH$_A$*H*$_B$CHN), 3.59 (s, 3H, 7-OCH$_3$), 3.70 (s, 3H, CO$_2$CH$_3$), 3.78 (m, 1H, 3-H), 3.80 (s, 3H, 6-OCH$_3$), 5.37 (s, 1H, 1-H), 6.32 (s, 1H, 8-H), 6.54 (s, 1H, 5-H), 6.80 (dd, 1H, 4'-H, J = 3.4, 4.9 Hz), 7.06 (d, 1H, J = 3.4 Hz, 3'-H), 7.20 (d, 1H, 5'-H J = 4.9 Hz); ^{13}C nmr (deuteriochloroform): δ 32.3 (CH$_2$), 52.6 (OCH$_3$), 56.3 (2 OCH$_3$), 56.9 (CH), 58.3 (CH), 110.5 (Ar*C*H), 111.6 (Ar*C*H), 125.9 (Ar*C*), 126.1 (C*thio*H), 126.5 (C*thio*H), 126.6 (C*thio*H), 130.0 (Ar*C*), 147.8 (C*thio*), 147.9 (Ar*C*), 148.4 (Ar*C*), 173.0 (C=O); ms: m/z 334.1 ([M+H]$^+$).

Anal. Calcd. for C$_{17}$H$_{19}$NO$_4$S. 0.4H$_2$O: C, 59.54; H, 5.81; N, 4.11. Found: C, 59.77; H, 5.86; N, 3.86.

trans-1-(Thiophen-2-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroiso-quinoline-3-carboxylic Acid Methyl Ester (**18b**).

This compound was obtained as a pale yellow oil in 45% yield (150 mg); *Rf* = 0.2 (ethyl acetate/*n*-heptane = 1/1); $[\alpha]_D^{23}$ -17.8 (c 2.25, chloroform); ^{1}H nmr (deuteriochloroform): δ$_H$(300 MHz, CDCl$_3$) 2.46 (broad s, 1H, NH, deuterium oxide-exchangeable), 2.85 (dd, 1H, C*H*$_A$*H*$_B$CHN, J = 9.4, 16 Hz), 2.98 (dd, 1H, CH$_A$*H*-$_B$CHN, J = 5.1, 16.2 Hz), 3.64 (s, 3H, CO$_2$CH$_3$), 3.67 (s, 3H, 7-OCH$_3$), 3.77 (s, 3H, 6-OCH$_3$), 3.81 (dd, 1H, 3-H, J = 4.9, 9.5 Hz), 5.41 (s, 1H, 1-H), 6.47 (s, 1H, 8-H), 6.54 (s, 1H, 5-H), 6.80 (d, 1H, 3'-H, J = 3.3 Hz), 6.82 (dd, 1H, 4'-H, J = 3.6, 4.9 Hz), 7.13 (d, 1H, 5'-H, J = 4.9 Hz); ^{13}C nmr (deuteriochloroform): δ 31.4 (CH$_2$), 51.8 (CH), 52.5 (OCH$_3$), 55.0 (CH), 56.2 (OCH$_3$), 56.3 (OCH$_3$), 111.1 (Ar*C*H), 111.6 (Ar*C*H), 125.5 (Ar*C*), 125.6 (C*thio*H), 126.4 (C*thio*H), 126.8 (C*thio*H), 128.3 (Ar*C*), 147.7 (C*thio*), 148.5 (Ar*C*), 149.6 (Ar*C*), 174.0 (C=O); m/z 334.1 ([M+H]$^+$).

Anal. Calcd. for C$_{17}$H$_{19}$NO$_4$S. 0.3H$_2$O: C, 60.26; H, 5.79; N, 4.13. Found: C, 60.19; H, 5.95; N, 3.84.

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