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Biomimetic Total Synthesis of *Dysoxylum* Alkaloids

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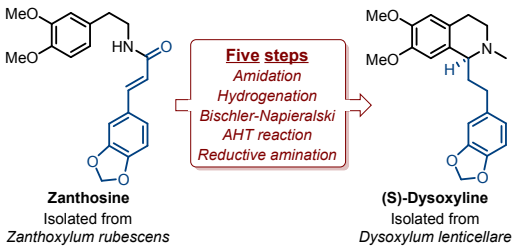


Abstract: A five-step total synthesis of *Dysoxylum* alkaloids has been achieved using a biomimetic approach from zanthoxylamide protoalkaloids. The synthesis featured a direct amidation and a Bischler-Napieralski reaction to form the dihydroisoquinoline ring, which was then subjected to a Noyori asymmetric transfer hydrogenation to establishing the stereogenic center at C-1. Our synthetic sequence provides an important perspective on the biosynthetic origin of *Dysoxylum* alkaloids, since six natural alkaloids and twelve synthetic analogues were obtained with high enantioselectivity and in overall yields up to 68 %. In addition, we describe the acute toxicity toward zebrafish embryos of *Dysoxylum* alkaloids, comparing their toxicity with their corresponding zanthoxylamide protoalkaloids and establishing an enantioselectivity-toxicity relationship.

Introduction

Dysoxylum alkaloids are a family of 1-phenethyl-tetrahydroisoquinolines with seven members having identified to date: (*S*)-dysoxyline,[1] (*S*)-autumnaline,[2] (*S*)-homolaudanosine,[1] (+)-colchiethanamine,[3] (+)-colchiethine,[3] (-)-isoautumnaline[4] and (*S*)-(+)-*O*,*O*-dimethyl-autumnaline (Figure 1).[5]

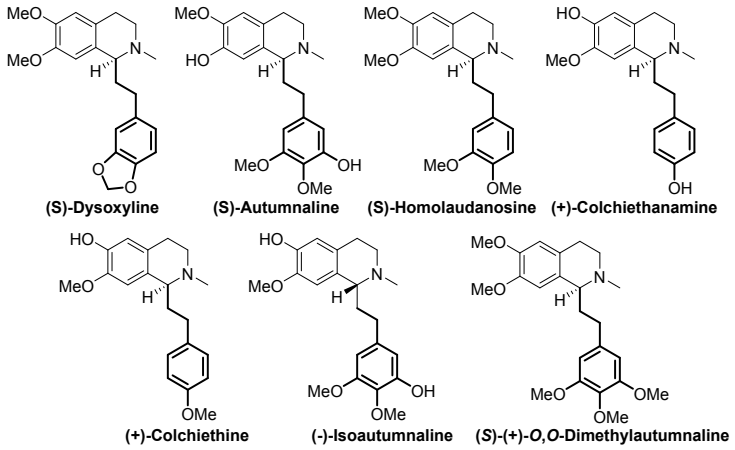


Figure 1. Representative *Dysoxylum* alkaloids.

These alkaloids are known since Leary isolated (*S*)-dysoxyline (0.01 %) and (*S*)-homolaudanosine (0.03 %) from the leaves of *Dysoxylum lenticellare* in 1983,[1] and their medical interest started when Ilesanmi reported their cardiac activity in 1986.[6] However, the very low content of these compounds in natural sources has been the major drawback during the exploration of their pharmacological profile. Thus, the responsibility of preparing these alkaloids at multi-gram scale in a laboratory lays on the organic chemistry. (*S*)-Homolaudanosine was the first synthetized derivative of this family (1987),[7] and although several elegant works have been reported during the last nine years for the total synthesis of *Dysoxylum* alkaloids,[8] none of them were attempted to mimic their biosynthesis, so these approaches involved many synthetic steps, were directed to obtain one or a few compounds and resulted in poor overall yields (Table 1).[9-15]

Table 1. Strategies developed for the total synthesis of *Dysoxylum* alkaloids.

Year	Alkaloid(s)	Strategy	Steps	Overall yield [%]
2011	(*S*)-Homolaudanosine	Asymmetric Allylation[9]	8	30
2012	(*S*)-Dysoxyline	Julia-Kocienski reaction[10]	18	17
	(+)-Colchiethanamine		17	12
	(+)-Colchiethine		17	14
2014	(*S*)-Dysoxyline	A^3 coupling alkynylation[11]	5	39
2014	(*R*)-(+)-Colchiethine	Pictet-Spengler Reaction[12]	7	24
2015	(±)-Homolaudanosine	Mukaiyama-Mannich[13]	6	41
2016	(±)-Dysoxyline	Lithiation[14]	3	42
2019	(±)-Homolaudanosine	Double alkylation[15]	5	49
	(±)-Dysoxyline			33

To the best of our knowledge, the biosynthetic pathway for (*S*)-dysoxyline and their related *Dysoxylum* alkaloids has not been reported so far, but they stand as one of the key intermediates in the biosynthesis of complex alkaloids like homoaporphines,[16] colchicine[17] and (−)-melanthioidine.[18] Thereby, and based on the biosynthetic pathway of reticuline and coclaurine,[19] simple tetrahydroisoquinoline alkaloids, where *N*-phenethyl-2-phenylacetamides are the pivotal intermediates of their biogenesis. We suspected that a specific family of amides could be involved in the biosynthetic origins of *Dysoxylum* alkaloids, and during the course of our synthetic study of zanthoxylamide protoalkaloids,[20] the structural relationship of these natural compounds with the *Dysoxylum* alkaloids were clearly determined.

Keeping the above considerations in mind, our biogenetic hypothesis was focused in the chemical transformation of zanthoxylamide protoalkaloids, into the more complex *Dysoxylum* alkaloids, supporting our proposal in some recognized facts that could established the biosynthetic pathway for (*S*)-dysoxyline and their related alkaloids. First, tyrosine and phenylalanine are the natural building blocks during the biosynthesis of *N*-phenylethyl cinnamamides,[21] the isoquinoline scaffold is prepared in nature by several enzymes (strictosidine synthase or "Pictet-Spenglerase") and this process resembles the Bischler-Napieralski reaction (BNR),[22] and finally, acyclic and cyclic imines are reduced by NAD(P)H-dependent enzymes found in several plant alkaloid biosynthetic pathways, which is moreover similar to the Asymmetric Transfer Hydrogenation (ATH) reaction or Noyori reduction.[23,24]

Herein, we report the total synthesis of the representative members of the *Dysoxylum* alkaloid family, including six natural alkaloids and twelve synthetic analogues, with (*S*)- and (*R*)-configuration. Furthermore, we describe the *in vivo* toxicological profile of these compounds and its relationship with the stereogenic center at C-1 of the tetrahydroisoquinoline scaffold.

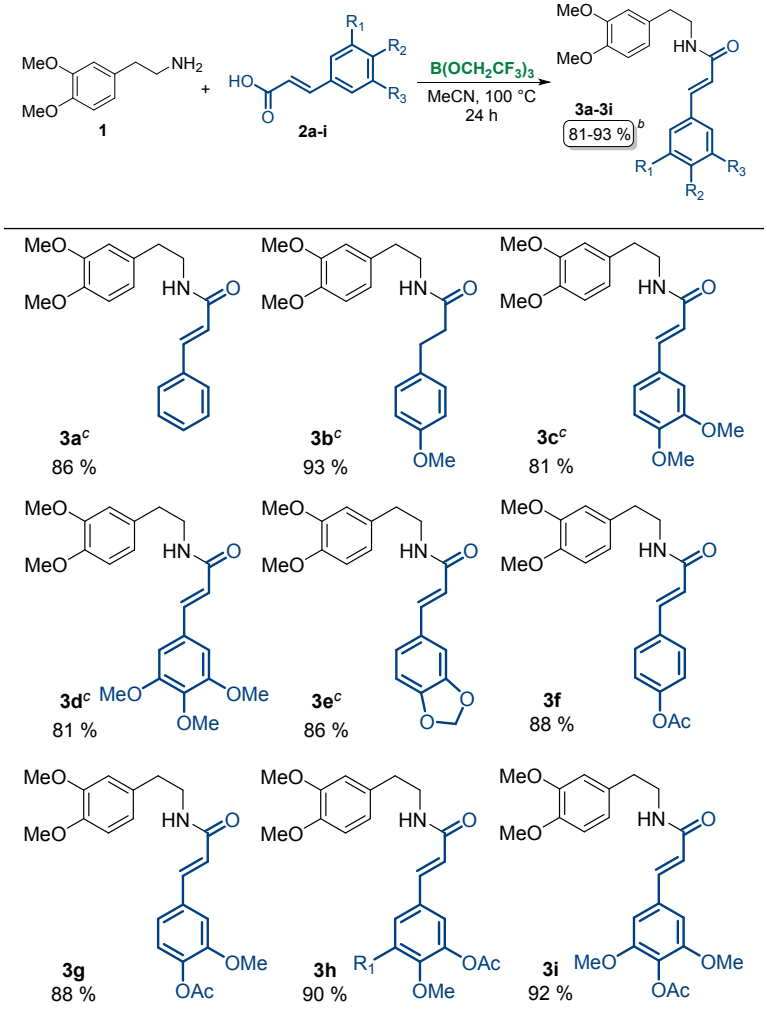
Results and discussion

Biomimetic Total Synthesis of *Dysoxylum* Alkaloids

To test our biogenetic hypothesis, we selected a library of nine zanthoxylamide protoalkaloids **3a-i**, easily prepared from commercially available phenylethylamines **1** and cinnamic acids **2a-i** under the catalysis of *tris*-(2,2,2-trifluoroethyl) borate ($B(OCH_2CF_3)_3$) based on our previous report (Table 2).[20] This series of compounds **3a-i** were obtained in good to excellent yields and under mild reaction conditions. Despite that our main goal is to

report the synthesis of *Dysoxylum* alkaloids from zanthoxylamides, we also focused our efforts in offers a possible scale-up synthesis of 1-phenethyl-tetrahydroisoquinolines for further pharmaceutical purposes in four steps by starting from the propanamide **3b**. This compound was easily obtained from the respective 3-(4-methoxyphenyl) propionic acid **2b** (93 %), demonstrating that our amidation process is suitable for the synthesis of amides from more commercially available, structural diversity, and in some cases, cheaper propionic acid derivatives (Table 2).

Table 2. Synthesis of zanthoxylamide protoalkaloids **3a-i** mediated by $B(OCH_2CF_3)_3$.[a]

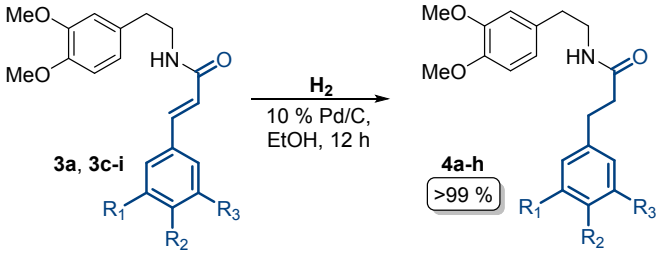


[a] Reaction conditions: phenylethylamine **1** (2 mmol), cinnamic acid **3a-i** (2 mmol), $B(OCH_2CF_3)_3$ (0.5 equiv), CH_3CN (0.5 M), 100 °C, 24 h. [b] Isolated yield after column chromatography (SiO_2). [c] Compounds previously reported under this approach.[20]

The relevance of the last statement is that in principle, compounds **3a-i** could be used as precursors of the BNR to furnished the desired 3,4-dihydroisoquinoline core. However, in a previous study,[25] our group found that the α,β-unsaturation present in the *N*-phenylethyl cinnamamides **3a-i** unfavored the cyclization reaction under the common reaction conditions of the BNR, forcing the use of the ionic liquid [bmim]PF_6 as a solvent which lead the formation of the desired 3,4-dihydroisoquinolines as PF_6-salts, derivatives that resulted to be unreactive toward the ATH reaction conditions.

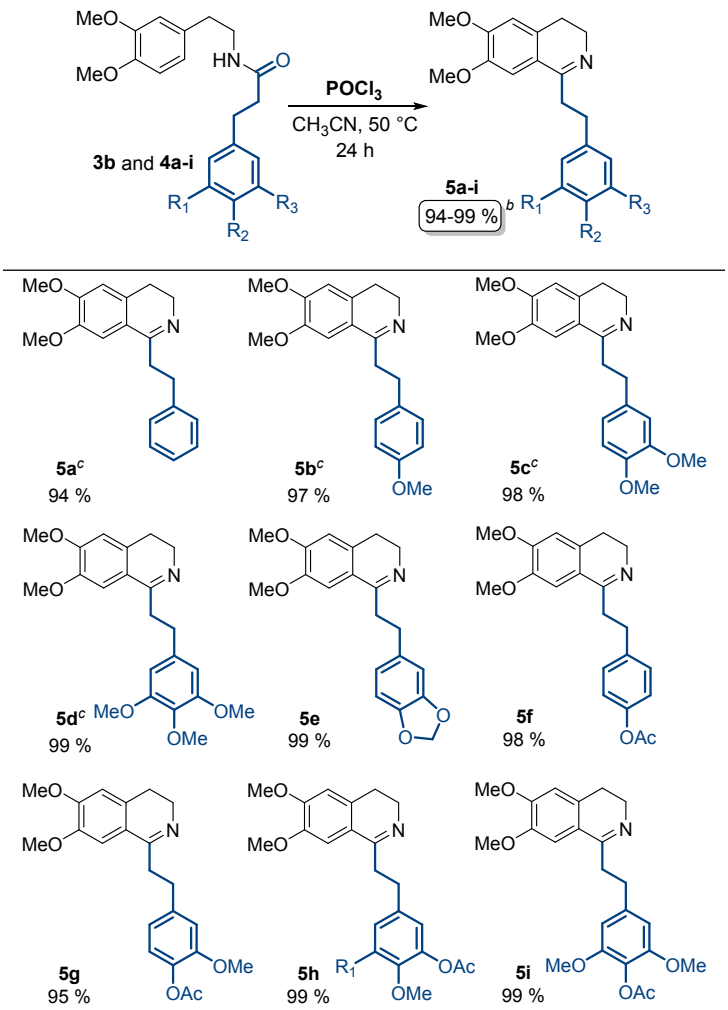
Thus, our strategy demanded the reduction of the C=C bond of α,β-cinnamamides **3a-i** prior to the cyclization process. Fortunately, this step was performed in almost quantitative yields through the Pd/C-catalyzed hydrogenation reaction under atmospheric H_2, furnishing the corresponding *N*-phenethyl-3-phenylpropanamides **4a-h** which were used in the next step without further purification (Scheme 1).

Scheme 1. Synthesis of *N*-phenethyl-3-phenylpropanamides **4a-h**



Thereby, the amides **3b** and **4a-h** were used as starting materials of the BNR, where the optimal reaction conditions were found to be $POCl_3$ (1.5 equiv) at 50 °C in acetonitrile as a solvent to furnish the respective 1-phenethyl-3,4-dihydroisoquinolines **5a-i** in excellent yields (94-99 %) and as free-bases (Table 3).

Table 3. Biomimetic strategy for the construction of isoquinoline scaffold **5a-i**.[a]

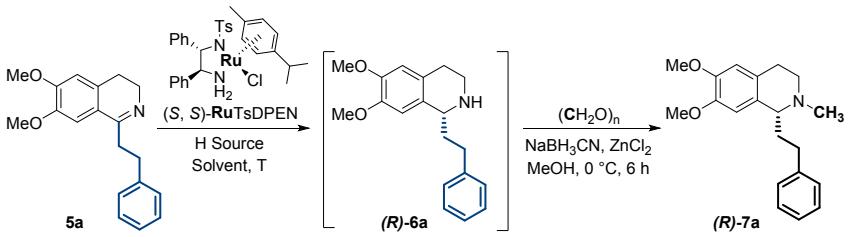


[a] Reaction conditions: propanamides **4a-i** (1.5 mmol), $POCl_3$ (2.25 mmol, 1.5 equiv), and CH_3CN (0.3 M), 50 °C, 24. [b] Isolated yield after column chromatography (SiO_2). [c] Known compounds (see Experimental Section for details).

With 1-phenethyl-3,4-dihydroisoquinolines **5a-i** in hand, we then focused our efforts in check our biogenetic hypothesis by studying the transfer hydrogenation of 3,4-dihydroisoquinolines **5a-i** into the desired chiral tetrahydroisoquinolines. Transfer hydrogenation is one of the most effective reactions for obtaining chiral secondary amines,[26] and as far as we know, this powerful tool has not been used for the synthesis *Dysoxylum* alkaloids.

In order to study the Ru-catalyzed ATH reaction, we employed the dihydroisoquinoline **5a** as a model substrate, however this reaction will lead to the corresponding tetrahydroisoquinoline **6a**, which we found early that could be an unstable intermediate.[25] Thereby, guided by the work of Ma and co-workers,[11] who studied the racemization in the *N*-methylation step during the total synthesis of (*S*)-dysoxyline, and demonstrated that the enantiopurity of intermediate **6a** will be retained if the *N*-methylation was performed a 0°C, we decided to perform an ATH reaction/reductive amination sequence to obtain the desired alkaloid **7a**, without the isolation of **6a** due to its poor stability and the fact that the obtained enantioselectivity of the ATH reaction will be the same of the global process (Table 4).

Table 4. Screening of the reaction conditions for the Ru-catalyzed ATH reaction/reductive amination sequence to obtain **7a**.[a]



Entry	H Source (ratio/equiv)	Solvent (M/ratio)	T (°C)	Yield (%)[b]	ee %[c]
1	$H_{2(g)}$ (1 atm)	MeOH	25	N.R.[d]	-
2	HCO_2H/Et_3N (1.1/1)	MeOH	60	78	62
3	HCO_2H/Et_3N (2.5/1)	MeOH	60	81	91
4	HCOONa (5)	H_2O/MeOH (1/3)	60	80	87
5	HCOONa (5)	H_2O/DMF (1/3)	60	86	88
6	HCOONa (5)	H_2O/DMF (1/3)	40	89	93
7	HCOONa (5)	H_2O/DMF (1/1)	40	92	95
8	HCOONa (5)	H_2O/DMF (1/1)	25	64	89

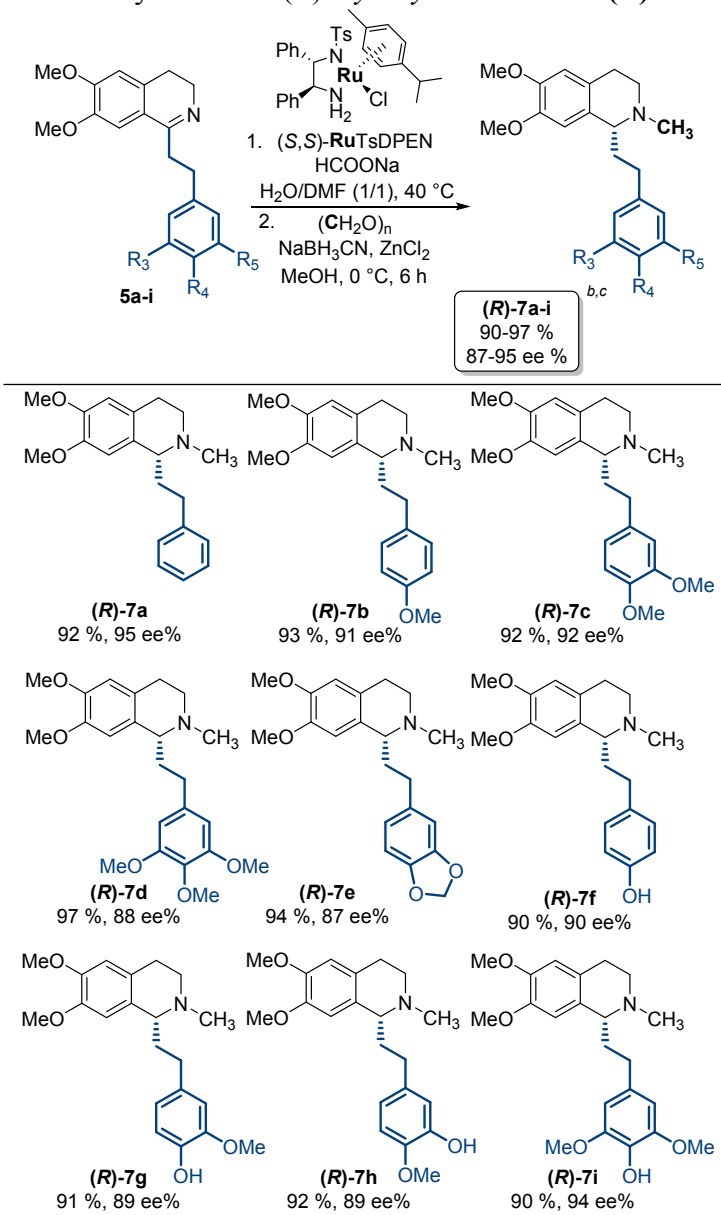
[a] *ATH reaction:* **5a** (0.5 mmol), (*S,S*)-RuTsDPEN (2 mol %), H source, solvent (3 mL), temperature. *Reductive amination:* **(*R*)-6a** (0.5 mmol), $(CH_2O)_n$ (1.5 mmol), $NaBH_3CN$ (0.55 mmol), $ZnCl_2$ (0.25 mmol), MeOH (10 mL). [b] Isolated yield after two steps and after column chromatography. [c] The ee% value of **7a** was determined by HPLC equipped with a column with chiral stationary phase. [d] N.R. No Reaction.

Our first attempt was based on the report that molecular hydrogen could be used as a hydrogen source in ATH reactions,[27] however, under atmospheric pressure and at room temperature, the reaction did not proceed (Table 4, entry 1). Therefore, we screened for better hydrogen sources that could also provide the desired product and mediate the asymmetric proton transfer. Among these, the formic acid (HCO_2H) and triethylamine Et_3N) azeotropic system,[28] in different ratios, furnished the desired tetrahydroisoquinoline **7a**, after the high-yield methylation step, in moderate yield and good ee% (Table 4, entries 2 and 3). Next, we turned to sodium formate (HCOONa) as an alternative hydrogen source,[29] allowing to perform the reaction under aqueous media with an organic co-solvent. After screening between methanol (MeOH) and dimethylformamide (DMF) as organic solvents, we noted that at 60 °C compound **7a** was obtained with better yield and ee% when H_2O/DMF mixture was used as a solvent system in a 1/3 ratio (Table 4, entries 4 and 5).[30] However, when the reaction temperature was lowered to 40 °C to control the energy of the transition state,[31] a considerable increase in the enantioselectivity of **7a** resulted, and in order to favored the dissolution of HCOONa,[32] the solvent system H_2O/DMF was then established in a 1/1 ratio, furnishing to our delight, the 1-phenethyl-tetrahydroisoquinoline **7a** after to steps in 92 % yield and 95 ee% (Table 4, entry 7). Finally, carrying out the reaction at room temperature gave **7a** with lower yield and ee% (Table 4, entry 8). It is worth to noted that these results can be compared with the first approach developed by Noyori and coworkers, in which the corresponding 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **6c** could be isolated using the same catalyst but with different hydrogen sources with 72 % yield and 77 ee%.[26c]

To date, the synthetic and biological studies regarding *Dysoxylum* alkaloids have been focused exclusively on the (*S*)-enantiomers, nevertheless, one member of this family, the (-)-isoautumnaline, exhibits a *R*-configuration at C-1, but its biological properties, as well as

for the other members with this configuration (*e.g.* (*R*)-dysoxyline), are completely unknown. Fortunately, one of the main features of our biomimetic strategy is the possibility to obtain both (*R*)- and (*S*)-enantiomers of *Dysoxylum* alkaloids from the same precursor. Thus, using the chiral catalyst (*S,S*)-RuTsDPEN under the established optimized reaction conditions (Table 4, entry 7), a library of nine alkaloids with (*R*)-configuration **(*R*)-7a-i** were obtained in excellent yields (90-97 %) and enantioselectivities (87-95 ee%), including the alkaloid (−)-isomethylautumnaline **(*R*)-7i** with 81 % overall yield (Table 5).

Table 5. Biomimetic total synthesis of (*R*)-*Dysoxylum* alkaloids **(*R*)-7a-i**.[a]



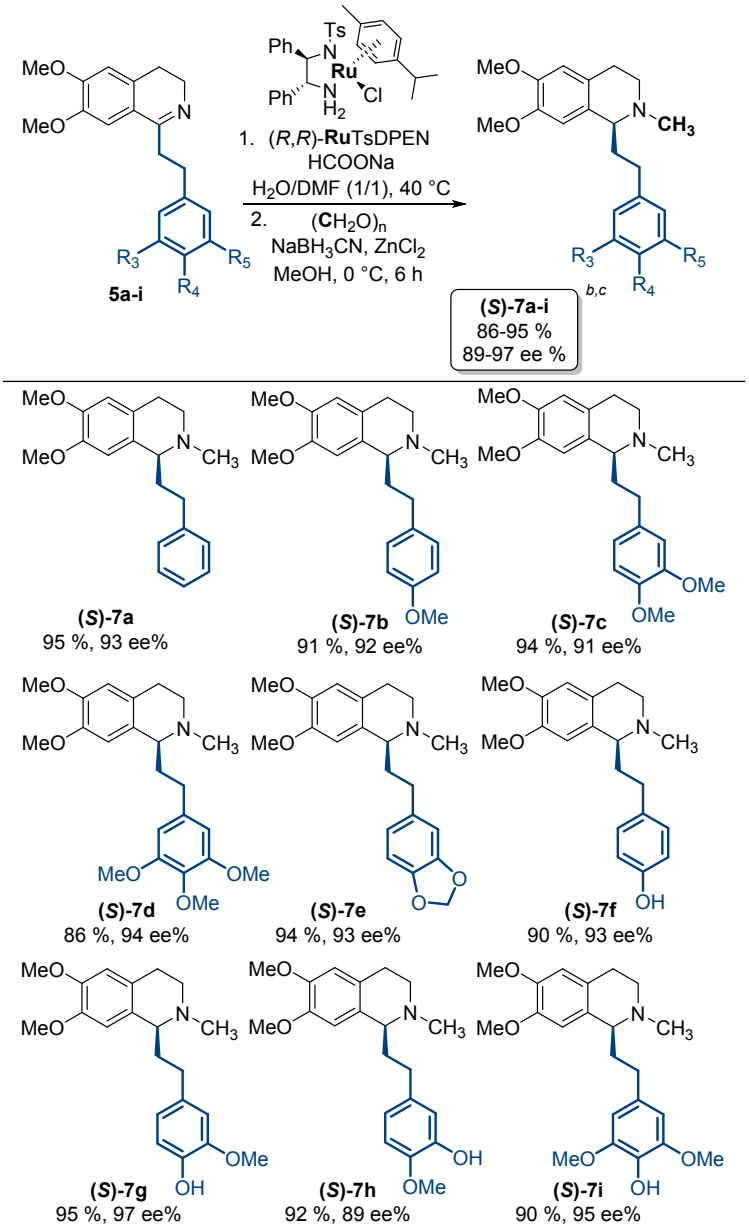
[a] *ATH reaction:* **5a-i** (0.5 mmol), (*S,S*)-RuTsDPEN (2 mol %), HCOONa (2.5 mmol), (H_2O/DMF) (3 mL, 1/1), 40 °C, 12 h. *Reductive amination:* **(*R*)-6a-i** (0.5 mmol), $(CH_2O)_n$ (1.5 mmol), $NaBH_3CN$ (0.55 mmol), $ZnCl_2$ (0.25 mmol), MeOH (10 mL), 6 h. [b] Isolated yield after two steps and after column chromatography. [c] The ee% value of **(*R*)-7a-i** was determined by HPLC equipped with a chiral column.

These results allow to establish that either the electronic or steric effects of the substituents in both aromatic rings, affected the course of the reaction or the asymmetric hydrogen transfer

to the C=N bond, whereas the sequence of the last synthetic step, without the isolation of **(*R*)-6a-i**, did not induce the racemization of these intermediates (Table 5).

Finally, the total synthesis of the main members of the *Dysoxylum* alkaloid family, along with other synthetic alkaloids, **(*S*)-7a-i** was achieved using the chiral catalyst (*R,R*)-RuTsDPEN in good to excellent yields (86-95 %) and enantioselectivities (86-97 ee%) (Table 6). Remarkably, the enantiomerically enriched (*S*)-homolaudanosine **(*S*)-7c**, (*S*)-(+)-*O*,*O*-dimethyl-autumnaline **(*S*)-7d** and (*S*)-dysoxyline **(*S*)-7e** were obtained in five steps with 73 %, 68 % and 79 % overall yield, respectively. Whereas the wide structural diversity of cinnamic acids **2a-l**, enable the synthesis of (*S*)-*O*-methylcolchiethine ***(S)*-7c** and (+)-methylcolchiethanamine **(*S*)-7f** with 82 and 68 % overall yield, respectively, from the respective zanthoxylamide protoalkaloids (Table 6).

Table 6. Biomimetic total synthesis of (*S*)-*Dysoxylum* alkaloids **(*S*)-7a-i**.[a]

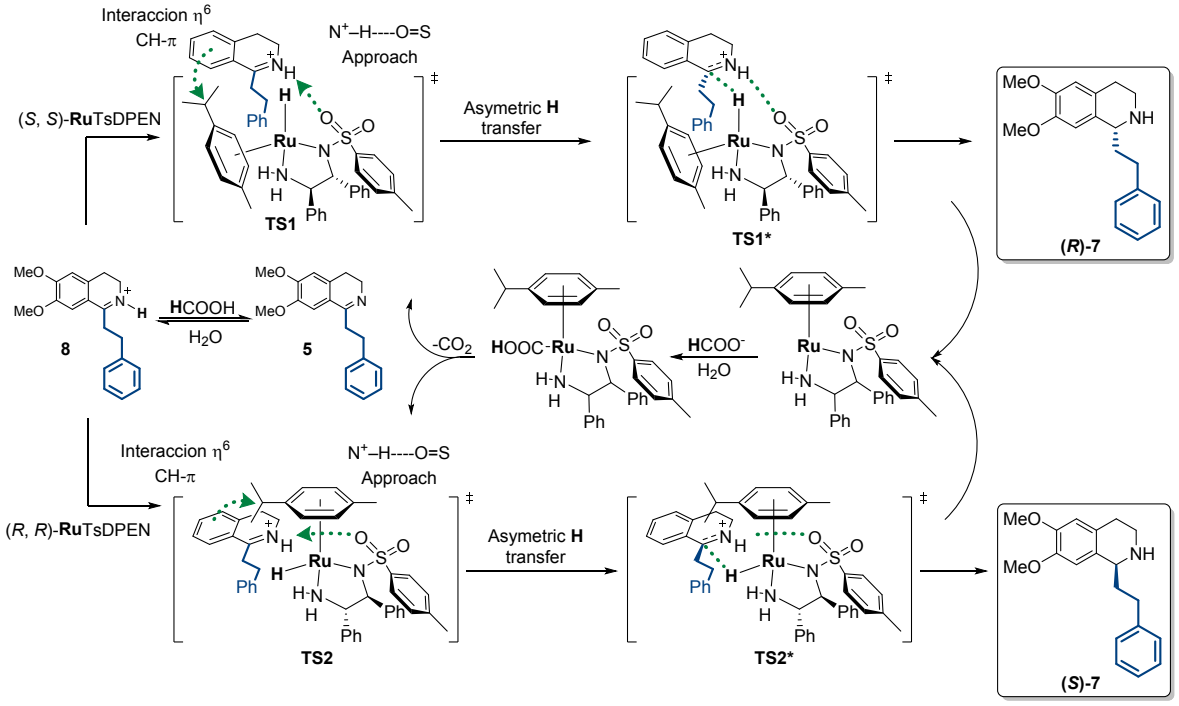


[a] *ATH reaction:* **5a-i** (0.5 mmol), (*R,R*)-RuTsDPEN (2 mol %), HCOONa (2.5 mmol), (H_2O/DMF) (3 mL, 1/1), 40 °C, 12 h. *Reductive amination:* **(*S*)-6a-i** (0.5 mmol), $(CH_2O)_n$ (1.5 mmol), $NaBH_3CN$ (0.55 mmol), $ZnCl_2$ (0.25 mmol), MeOH (10 mL), 6 h. [b] Isolated yield after two steps and after column chromatography. [c] The ee% value of **(*S*)-7a-i** was determined by HPLC equipped with a chiral column.

The mechanism of the ATH reaction of cyclic imines has been extensively investigated, and taken these works under consideration, a mechanistic proposal for the generation of the

chiral centre in both (*R*)- and (*S*)-enantiomers of *Dysoxylum* alkaloids is proposed (Scheme 2). Firstly, one of the main role of HCOONa, besides activate the pre-catalyst RuTsDPEN into the real catalyst, the hydride complex H-RuTsDPEN,[33] is to form formic acid under the aqueos medium to protonate the dihydroisoquinoline **5** since this substrate enters into the catalytic cycle as an iminium species **8** (Scheme 2). Then, **8** approaches to the ruthenium central atom through the N^{+}-H···O=S hydrogen bond with the sulfonyl group of the tosyl moiety present in the TsDPEN ligand, which is also guided by the CH-π interaction between the η^6-arene ligand (*p*-cymene) and the aromatic ring of the dihydroisoquinoline ion **8**, the synergy of these both processes are the responsible for the origin of the enantioselectivity throughout the ATH reaction, by generating the respective transition states **TS1** and **TS2** accordingly to the configuration of the catalyst RuTsDPEN (Scheme 2).[34] Finally, the hydrogen atom is asymmetrically transferred from the ruthenium complex to the electron-withdrawing carbon C-1 of the dihydroisoquinoline ion **8**, through the respective transition states **TS1*** and **TS2***, to furnishing the corresponding **(*R*)-7** and **(*S*)-7** enantiomers (Scheme 2).

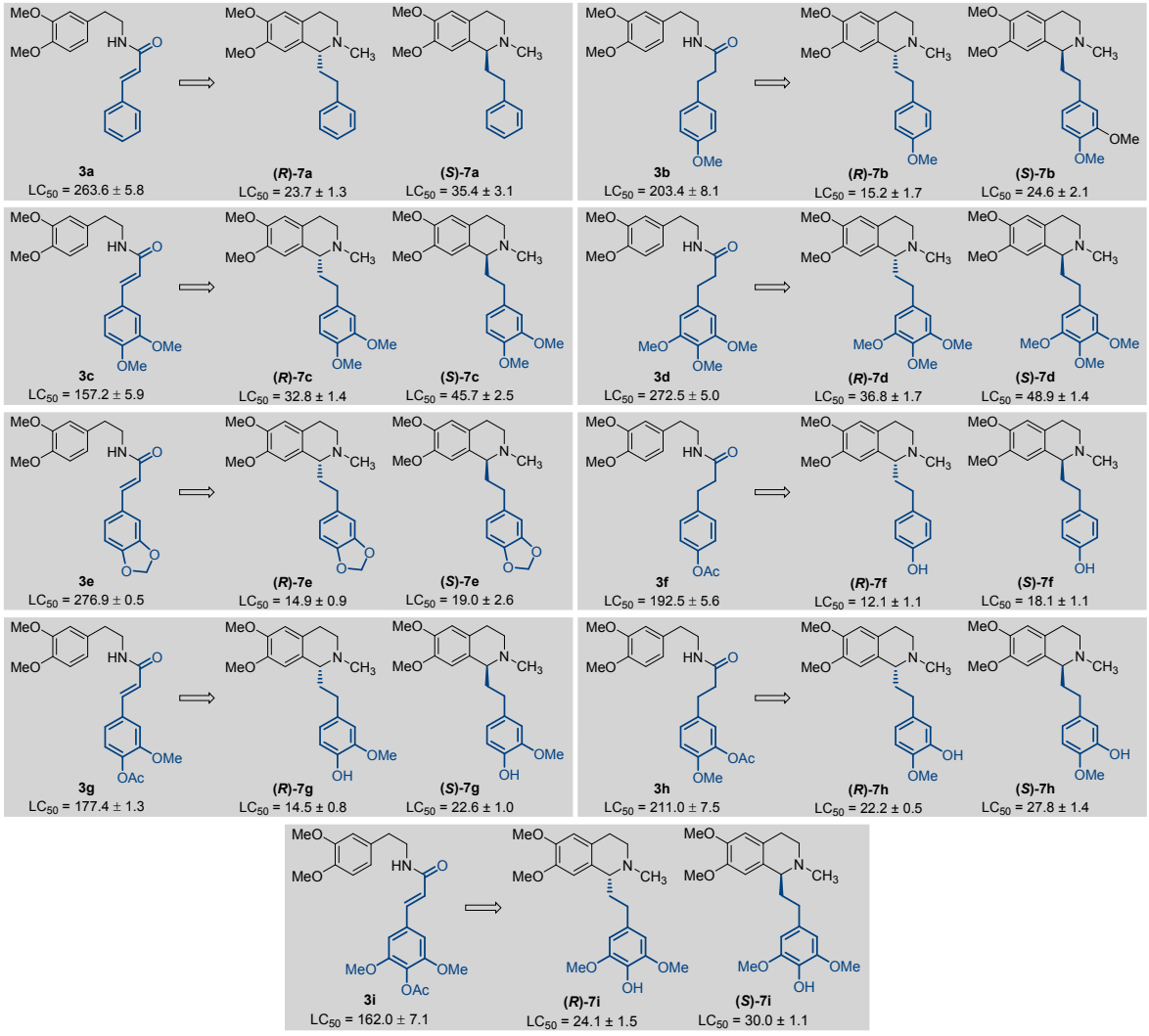
Scheme 2. Proposed reaction mechanism for the ATH reaction during the biomimetic synthesis of *Dysoxylum* alkaloids.



In vivo toxicity assessment in zebrafish embryos

The zebrafish embryo model is one of the well-established protocols in modern *in vivo* studies for rapidly assessing the toxicity of diverse natural and synthetic molecules of interest.[35-39] Moreover, this biological tool has been successfully used to identify and study the different biological and toxicological activities of chiral compounds, referred as enantioselective toxicity.[40] Thereby, this approach was adapted in our laboratory, with some modifications, for the toxicological assessment of both (*R*)- and (*S*)-enantiomers of *Dysoxylum* alkaloids, comparing their toxicity with the previous LC_{50} values reported for their corresponding zanthoxylamide protoalkaloids (Table 7).[20]

Table 7. Zebrafish embryo LC_{50} values determined for both (*R*)- and (*S*)-enantiomers of *Dysoxylum* alkaloids and their corresponding zanthoxylamide protoalkaloids.[a]



[a] LC_{50} values are the mean ± SEM of three different experiments in triplicate.

From the results depicted in Table 7, it is important to mention in first place that zanthoxylamide protoalkaloids **3a-i** (avg. LC_{50} = 217 μM) resulted to be 20-fold less toxic to zebrafish embryos than *Dysoxylum* alkaloids **7a-i** (avg. LC_{50} = 25 μM); and within this series of tetrahydroisoquinolines, the (*R*)-enantiomers (avg. LC_{50} = 21 μM) resulted to be slightly toxic in comparison with the (*S*)-enantiomers (avg. LC_{50} = 30 μM).

It was found that independent of the configuration of the stereogenic centre at C-1, the inclusion of hydroxyl groups at the aromatic ring of the phenyl ethyl motif, enhance the

toxicity of both (*R*)- and (*S*)-enantiomers, **(*R*)-7f** (LC_{50} = 12.1 μM) and **(*S*)-7f** (LC_{50} = 18.1 μM) (Table 7). However, the inclusion of one, two, or three, methoxy groups at this ring reduces the toxicity as was observed for derivatives **(*R*)-7d** (LC_{50} = 36.8 μM) and **(*S*)-7d** (LC_{50} = 48.9 μM), the less toxic compounds among the series of *Dysoxylum* alkaloids (Table 7).

Finally, the most representative member of the *Dysoxylum* family, the (*S*)-dysoxyline **(*S*)-7e**, which previously exhibited a significant *in vivo* cardioactivity,[6] showed a moderate toxicity (LC_{50} = 19.0 μM), contributing to reveal its pharmacological profile.

Conclusions

In conclusion, we have accomplished the total synthesis of *Dysoxylum* alkaloids by developing a biomimetic approach for the first time from zanthoxylamide protoalkaloids. Our strategy involved five synthetic and efficient steps, where the sequence: amidation, hydrogenation and Bischler-Napierlaski reaction allowed the construction of the isoquinoline core, that enable the later study the ATH reaction/reductive amination sequence. For the purposes of our study, these key steps were readily extended to the asymmetric synthesis of both (*R*)- and (*S*)-enantiomers of *Dysoxylum* alkaloids, furnishing the synthetic **(*R*)-7a-i** and natural **(*S*)-7a-i** derivatives that will lead further biological studies in order to explore their cardiac activity and the effect of the stereochemistry of C-1 carbon, since these alkaloids are low-abundance natural products and most of them possess the (*S*)-configuration at C-1. Nevertheless, the access to cyclic amines **(*R*)-6a-i** and **(*S*)-6a-i** could be of great interest in the synthesis of more complex compounds and deserves a deep study. Finally, the brevity, high efficiency and high stereoselectivity of our biomimetic hypothesis afford a potentially

evidence of the biosynthesis of *Dysoxylum* alkaloids and revealed for the first time their toxicological profile for further pharmacological studies.

Experimental section

General information. Unless otherwise noted, all reactions have been carried out with distilled and dried solvents and under atmosphere pressure. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Aldrich and Merck) in air. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F254 precoated plates (0.25 mm). Column chromatography was performed using spherical silica gel 70Å, 40-75 μm or on a Biotage® Automated Liquid Chromatography System Isolera One® using Biotage® SNAP Ultra 25 μm HP-Sphere 10 g silica gel cartridges.

Infrared (FT-IR) spectra were recorded on a Lumex Infralum FT-02 spectrometer, and the wave numbers of the absorption peaks are listed in cm^{-1}. Peaks/Bands are characterized according to the functional group. ^{1}H NMR spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm; DMSO-d_6: δ 2.50 ppm). Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, br = broad, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from solvent resonance as the internal standard ($CDCl_3$: δ 77.00 ppm; DMSO-d6: δ 40.45 ppm). On DEPT-135 spectra, the signals of CH_3 and CH carbons are shown with positive phase (+), while CH_2 carbons are shown with negative phase (-). Quaternary carbons are not shown. HPLC analyses were performed on a Hitachi L-2000 pump and Hitachi L-2420 UV/Vis detector. The enantiomeric excesses (ee) were determined using a Kromasil® 5-Amycoat™ (250 × 4.6 mm) column. Optical rotations were measured with an Optical ActivityTD Series 19-79-38/A digital polarimeter with 1-dm-long cell. High resolution mass spectra (HRMS) were measured on a Thermo Scientific LTQ Orbitrap XL apparatus. Melting points were measured on a Fisher Johns melting point apparatus and are uncorrected.

General procedure and characterization data of zanthoxylamide protoalkaloids 3a-i. In a 50 mL vial equipped with a magnetic stir bar was added the respective cinnamic acid **2a-i** (2 mmol), the vial was sealed and the air was evacuated establishing an Argon atmosphere and anhydrous MeCN (8 mL, 0.5 M) was added. Then, $B(OCH_2CF_3)_3$ (1 mmol, 0.5 equiv.) was added dropwise into the

stirred solution at room temperature. After 10 minutes, the corresponding 3,4-dimethoxyphenylethylamine **1** was added in one portion and the reaction mixture was stirred at 100 °C in an oil bath for 24 hours. After cooling to room temperature, the mixture was extracted with AcOEt (3 x 20 mL). The organic layers were combined, dried over with Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (20-30% AcOEt in petroleum ether) to furnished the desired zanthoxylamide protoalkaloids **3a-i**.

*N-(3,4-Dimethoxyphenylethyl) cinnamamide (***3a***)*. Following general procedure, compound **3a** was obtained as a white solid 0.53 g (1.72 mmol, 86 %); R_f [hexane-EtOAc, 1:1] = 0.64; m.p. = 122-124 ºC (lit. 119-120 °C[41]); IR (KBr Disk): 3317 $\nu_{(NH)}$, 3070 $\nu_{(CH2\text{-}Ar)}$, 2962 $\nu_{(OCH3)}$, 1651$\nu_{(C=O)}$, 1619 $\nu_{(C=C)}$, 1542 $\nu_{(NH)}$, 1326 $\nu_{(CH2\text{-}Ar)}$, 1234 $\nu_{(C\text{-}N)}$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.61 (1H, d, *J* = 15.6 Hz, =C*H*Ph), 7.47-7.44 (2H, m, 6 and 7-H_{Ar}), 7.34-7.31 (3H, m, 6', 7' and 8'-H_{Ar}), 6.80 (1H, d, *J* = 7.9 Hz, 10-H_{Ar}), 6.74 (2H, d, *J* = 8.8 Hz, 5' and 9'-H_{Ar}), 6.36 (1H, d, *J* = 15.6 Hz, =C*H*CO), 5.94 (1H, t, *J* = 6.7 Hz, N*H*), 3.84 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.62 (2H, q, *J* = 6.7 Hz, -CH_2NH), 2.83 (2H, t, *J* = 6.9 Hz, -CH_2Ph). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 166.0, 149.0, 147.7, 141.0 (+), 134.8, 131.4, 129.7 (+), 128.8 (+, 2C), 127.8 (+, 3C), 120.7 (+), 111.9 (+), 111.4 (+), 55.9 (+), 55.9 (+), 41.0 (-), 35.2 (-). HRMS (ESI): calcd. for $C_{19}H_{22}NO_3$ $[M+H]^+$: 312.1594, found: 312.1589.

*N-(3,4-Dimethoxyphenethyl)-3-(4-methoxyphenyl)propanamide (***3b***)*. Following general procedure, compound **3b** was obtained as a white solid 0.64 g (1.86 mmol, 93 %) from 3-(4-methoxyphenyl)propanoic acid and 3,4-dimethoxyphenylethylamine **1**; R_f [hexane-EtOAc, 1:1] = 0.66; m.p. = 118-120 ºC; IR (KBr Disk): 3301 $\nu_{(NH)}$, 3070 $\nu_{(CH2\text{-}Ar)}$, 2931 $\nu_{(OCH3)}$, 1635 $\nu_{(C=O)}$, 1542 $\nu_{(NH)}$, 1511 $\nu_{(C\text{-}N)}$, 1234 $\nu_{(C\text{-}N)}$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.08 (2H, d, *J* = 8.5 Hz, 6' and 8'-H_{Ar}), 6.80 (2H, d, *J* = 8.6 Hz, 5' and 9'-H_{Ar}), 6.76 (1H, d, *J* = 8.1 Hz, 9-H_{Ar}), 6.66-6.59 (2H, m 6 and 10-H_{Ar}), 5.46 (1H, t, *J* = 6.8 Hz, N*H*), 3.85 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.44 (2H, q, *J* = 6.8 Hz, -CH_2NH), 2.87 (2H, t, *J* = 7.6 Hz, -CH_2CO), 2.68 (2H, t, *J* = 7.0 Hz, -CH_2Ph), 2.87 (2H, t, *J* = 7.6 Hz, -CH_2Ph). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 172.2, 158.0, 149.0, 147.6, 132.9, 131.3, 129.3 (2C, +), 120.6 (+), 113.9 (2C, +), 111.8 (+), 111.2 (+), 55.9 (+), 55.9 (+), 55.3 (+), 40.7 (-), 38.8 (-), 35.3 (-), 30.9 (-). HRMS (ESI): calcd. for $C_{20}H_{26}NO_4$ $[M+H]^+$: 344.1856, found: 344.1853. Spectral data were in accordance with those reported in the literature.[42]

*N-(3,4-Dimethoxyphenylethyl)-3,4-dimethoxycinnamamide (***3c***)*. Following general procedure, compound **3c** was obtained as a white solid 0.60 g (1.62 mmol, 81 %); R_f [hexane-EtOAc, 1:1] = 0.44; m.p. = 123-125 ºC; IR (KBr Disk): 3301 $\nu_{(NH)}$, 2931 $\nu_{(OCH3)}$, 1650 $\nu_{(C=O)}$, 1619 $\nu_{(C=C)}$, 1511 $\nu_{(C\text{-}N)}$, 1265 $\nu_{(C\text{-}N)}$, 1141 $\nu_{(C\text{-}O)}$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.52 (1H, d, *J* = 15.5 Hz, =C*H*Ph),

7.00 (1H, dd J = 8.3, 1.8 Hz, 9-H_{Ar}), 6.95 (1H, d, J = 1.9 Hz, 6-H_{Ar}), 6.76 (2H, dd, J = 8.5, 4.3 Hz, 8' and 9'-H_{Ar}), 6.72-6.69 (2H, m, 10 and 5'-H_{Ar}), 6.24 (1H, d, J = 15.5 Hz, =C*H*CO), 6.02 (1H, t, J = 6.9 Hz, N*H*), 3.84 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.80 (6H, s, 2xOCH_3), 3.59 (2H, q J = 6.9 Hz, -CH_2NH), 2.80 (2H, t, J = 7.0 Hz, -CH_2Ph). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 166.2, 150.5, 149.0, 149.0, 147.6, 140.7 (+), 131.4, 127.7, 121.9 (+), 120.6 (+), 118.6 (+), 112.0 (+), 111.4 (+), 111.0 (+), 109.6 (+), 55.9 (2C, +), 55.8 (+), 55.8 (+), 40.9 (-), 35.2 (-). HRMS (ESI): calcd. for $C_{21}H_{26}NO_5$ $[M+H]^+$: 372.1805, found: 372.1800. Spectroscopy data agree with those reported in the literature.[43]

*N-(3,4-Dimethoxyphenylethyl)-3,4,5-trimethoxycinnamamide (**3d**)*. Following general procedure, compound **3d** was obtained as a white solid 0.65 g (1.62 mmol, 81 %); R_f [hexane-EtOAc, 1:1] = 0.36; m.p. = 128-130 ºC (lit. 127-128 °C[44]); IR (KBr Disk): 3286 $\nu_{(NH)}$, 2931 $\nu_{(OCH3)}$, 1650 $\nu_{(C=O)}$, 1619 $\nu_{(C=C)}$, 1511 $\nu_{(C-N)}$, 1265 $\nu_{(C-N)}$, 1141 $\nu_{(C-O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.52 (1H, d, J = 15.5 Hz, =C*H*Ph), 6.82 (1H, d J = 8.0 Hz, 9-H_{Ar}), 6.77-6.73 (2H, m, 6 and 10-H_{Ar}), 6.70 (2H, s, 5' and 9'-H_{Ar}), 6.23 (1H, d, J = 15.5 Hz, =C*H*CO), 5.68 (1H, t, J = 6.8 Hz, N*H*), 3.86 (12H, s, 4xOCH_3), 3.85 (3H, s, OCH_3), 3.64 (2H, q, J = 6.8 Hz, -CH_2NH), 2.83 (2H, t, J = 6.8 Hz, -CH_2Ph). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 165.9, 153.5 (3C), 149.2, 147.8, 141.1 (+), 131.4, 130.4, 120.8 (+), 120.0 (+), 112.1 (+), 111.5 (+), 105.0 (2C, +), 61.0 (+), 56.2 (2C, +), 56.0 (+), 56.0 (+), 40.9 (-), 35.2 (-). HRMS (ESI): calcd. for $C_{22}H_{28}NO_6$ $[M+H]^+$: 402.1911, found: 402.1915.

*N-(3,4-Dimethoxyphenylethyl)-3,4-methylenedioxycinnamamide (**3e**)*. Following general procedure, compound **3e** was obtained as a white solid 0.61 g (1.72 mmol, 86 %); R_f [hexane-EtOAc, 1:1] = 0.39; m.p. = 165-167 ºC (lit. 159-161 °C[44]); IR (KBr Disk): 3301 $\nu_{(NH)}$, 3070 $\nu_{(CH2-Ar)}$, 2977 $\nu_{(OCH3)}$, 2900 $\nu_{(-OCH2O-)}$, 1650 $\nu_{(C=O)}$, 1619 $\nu_{(C=N)}$, 1542 $\nu_{(NH)}$, 1326 $\nu_{(CH2-Ar)}$, 1249 $\nu_{(C-N)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.51 (1H, d, J = 15.3 Hz, =C*H*Ph), 6.94 (2H, d, J = 7.8 Hz, 7 and 10-H_{Ar}), 6.81-6.76 (2H, m, 8' and 9'-H_{Ar}), 6.74 (2H, d, J = 9.7 Hz, 5' and 6-H_{Ar}), 6.16 (1H, d, J = 15.4 Hz, =C*H*CO), 5.96 (2H, s, -OCH_2O-), 5.84 (1H, t, J = 6.3 Hz, N*H*), 3.84 (6H, s, 2xOCH_3), 3.60 (2H, q, J = 6.3 Hz, -CH_2NH), 2.81 (2H, t, J = 6.7 Hz, -CH_2Ph). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 166.1, 149.1, 149.0, 148.2, 147.7, 140.8 (+), 131.4, 129.2, 123.9 (+), 120.7 (+), 118.7 (+), 111.9 (+), 111.4 (+), 108.5 (+), 106.3 (+), 101.5 (-), 55.9 (+), 55.9 (+), 41.0 (-), 35.3 (-). HRMS (ESI): calcd. for $C_{20}H_{22}NO_5$ $[M+H]^+$: 356.1492, found: 356.1488.

*N-(3,4-Dimethoxyphenylethyl)-4-acetoxycinnamamide (**3f**)*. Following general procedure, compound **3f** was obtained as a white solid 0.65 g (1.76 mmol, 88 %); R_f [hexane-EtOAc, 1:1] = 0.31; m.p. = 143-145 ºC; IR (KBr Disk): 3301 $\nu_{(NH)}$, 3070 $\nu_{(CH2-Ar)}$, 2931 $\nu_{(OCH3)}$, 1758 $\nu_{(C=O)}$, 1650 $\nu_{(C=O)}$, 1619 $\nu_{(C=C)}$, 1542 $\nu_{(NH)}$, 1203 $\nu_{(C-N)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.55 (1H, d, J = 15.6 Hz, =C*H*Ph), 7.44 (2H, d, J = 8.6 Hz, 6' and 8'-H_{Ar}), 7.05 (2H, d, J = 8.6 Hz, 5' and 9'-H_{Ar}), 6.79

(1H, d, J = 8.7 Hz, 10-H_{Ar}), 6.74-6.72 (2H, m, 6 and 9-H_{Ar}), 6.28 (1H, d, J = 15.6 Hz, =C*H*CO), 5.98 (1H, t, J = 6.9 Hz, N*H*), 3.84 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.60 (2H, q, J = 6.9 Hz, -CH_2NH), 2.81 (2H, t, J = 7.0 Hz, -CH_2Ph), 2.28 (3H, s, CH_3). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 169.3, 166.1, 151.7, 149.1, 147.8, 140.1 (+), 132.5, 131.3, 128.9 (2C, +), 122.1 (2C, +), 120.7 (+), 120.7 (+), 112.0 (+), 111.5 (+), 56.0 (+), 55.9 (+), 41.1 (-), 35.2 (-), 21.2 (-). HRMS (ESI): calcd. for $C_{21}H_{24}NO_5$ $[M+H]^+$: 370.1649, found: 370.1653.

*N-(3,4-Dimethoxyphenylethyl)-4-acetoxy-3-methoxycinnamamide (**3g**)*. Following general procedure, compound **3g** was obtained as a white solid 0.70 g (1.76 mmol, 88 %); R_f [hexane-EtOAc, 1:1] = 0.22; m.p. = 78-80 ºC; IR (KBr Disk): 3440 $\nu_{(NH)}$, 3008 $\nu_{(CH2\text{-}Ar)}$, 2900 $\nu_{(OCH3)}$, 1697 $\nu_{(C=O)}$, 1666 $\nu_{(C=O)}$, 1619 $\nu_{(C=C)}$, 1511 $\nu_{(NH)}$, 1419 $\nu_{(CH2\text{-}Ar)}$, 1280 $\nu_{(C\text{-}N)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.54 (1H, d, J = 15.6 Hz, =C*H*Ph), 7.06-7.01 (2H, m, J = 8.6 Hz, 5' and 9'-H_{Ar}), 6.99 (1H, d, J = 8.1 Hz, 8'-H_{Ar}), 6.80 (1H, d, J = 8.3 Hz, 10-H_{Ar}), 6.75-6.72 (2H, m, 6 and 9-H_{Ar}), 6.26 (1H, d, J = 15.6 Hz, =C*H*CO), 5.85 (1H, t, J = 6.8 Hz, N*H*), 3.84 (6H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.61 (2H, q, J = 6.8 Hz, -CH_2NH), 2.81 (2H, t, J = 7.0 Hz, -CH_2Ph), 2.30 (3H, s, CH_3). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 169.0, 165.8, 151.3, 149.1, 147.8, 140.9, 140.4 (+), 133.9, 131.4, 123.2 (+), 121.0 (+), 120.7 (+), 120.6 (+), 112.0 (+), 111.5 (+), 111.4 (+), 56.0 (+), 55.9 (+), 55.9 (+), 41.0 (-), 35.2 (-), 20.7 (+). HRMS (ESI): calcd. for $C_{22}H_{26}NO_6$ $[M+H]^+$: 400.1755, found: 400.1751.

*N-(3,4-Dimethoxyphenylethyl)-3-acetoxy-4-methoxycinnamamide (**3h**)*. Following general procedure, compound **3h** was obtained as a white solid 0.71 g (1.80 mmol, 90 %); R_f [hexane-EtOAc, 1:1] = 0.25; m.p. = 126-128 ºC; IR (KBr Disk): 3317 $\nu_{(NH)}$, 3070 $\nu_{(CH2\text{-}Ar)}$, 2931 $\nu_{(OCH3)}$, 1758 $\nu_{(C=O)}$, 1650 $\nu_{(C=O)}$, 1604 $\nu_{(C=C)}$, 1265 $\nu_{(C\text{-}N)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.49 (1H, d, J = 15.5 Hz, =C*H*Ph), 7.29-7.26 (1H, m, J = 8.6 Hz, 8'-H_{Ar}), 7.16 (1H, d, J = 2.1 Hz, 5'-H_{Ar}), 6.90 (1H, d, J = 8.6 Hz, 9'-H_{Ar}), 6.79 (1H, d, J = 8.7 Hz, 10-H_{Ar}), 6.74-6.71 (2H, m, 6 and 9-H_{Ar}), 6.18 (1H, d, J = 15.5 Hz, =C*H*CO), 5.95 (1H, t, J = 6.8 Hz, N*H*), 3.83 (6H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.58 (2H, q, J = 6.8 Hz, -CH_2NH), 2.81-2.76 (2H, m, -CH_2Ph), 2.28 (3H, s, CH_3). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 166.1, 162.6, 152.3, 149.1, 147.7, 139.9, 139.7 (+), 131.5, 128.0, 127.4 (+), 121.5 (+), 120.7 (+), 119.4 (+), 112.3 (+), 112.0 (+), 111.4 (+), 56.0 (+), 55.9 (+), 55.9 (+), 41.0 (-), 35.2 (-), 20.6 (+). HRMS (ESI): calcd. for $C_{22}H_{26}NO_6$ $[M+H]^+$: 400.1755, found: 400.1750.

*N-(3,4-Dimethoxyphenylethyl)-4-acetoxy-3,5-dimethoxycinnamamide (**3i**)*. Following general procedure, compound **3i** was obtained as a white solid 0.79 g (1.84 mmol, 92 %); R_f [hexane-EtOAc, 1:1] = 0.17; m.p. = 133-135 ºC; IR (KBr Disk): 3363 $\nu_{(NH)}$, 3070 $\nu_{(CH2\text{-}Ar)}$, 2931 $\nu_{(OCH3)}$, 1758 $\nu_{(C=O)}$, 1666 $\nu_{(C=O)}$, 1604 $\nu_{(C=C)}$, 1511 $\nu_{(NH)}$, 1203 $\nu_{(C\text{-}N)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.51 (1H, d, J = 15.5 Hz, =C*H*Ph), 6.80 (1H, d, J = 8.1 Hz, 10-H_{Ar}), 6.75-6.73 (2H, m, 6 and 9-H_{Ar}), 6.69 (2H, s, 5' and 9'-H_{Ar}), 6.26 (1H, d, J = 15.5 Hz, =C*H*CO), 5.82 (1H, t, J = 6.8 Hz, N*H*), 3.85 (6H, s, OCH_3),

3.80 (6H, s, OCH_3), 3.61 (2H, q, J = 6.8 Hz, -CH_2NH), 2.81 (2H, t, J = 6.9 Hz, -CH_2Ph), 2.32 (3H, s, OAc). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 168.7, 165.7, 152.4 (2C), 149.1, 147.8, 140.7 (+), 133.2, 131.4, 129.9, 121.0 (+), 120.7 (+), 112.0 (+), 111.5 (+), 104.4 (2C, +), 56.2 (2C, +), 56.0 (+), 55.9 (+), 40.9 (-), 35.2 (-), 20.5 (+). HRMS (ESI): calcd. for $C_{23}H_{28}NO_7$ $[M+H]^+$: 430.1860, found: 430.1864.

General procedure and characterization data of *N*-phenethyl-3-phenylpropanamides 4a-h. In a 25 mL vial equipped with a magnetic stir bar was added the respective zanthoxylamide protoalkaloids **3a-i** (1.5 mmol), Pd/C (10 wt-%, 50 mg, 5 mg Pd, 0.05 mmol) the vial was sealed and the air was evacuated establishing a hydrogen atmosphere for 10 min. Then, EtOH (10 mL) was added in one portion and the reaction mixture was stirred at room temperature for 12 hours. The mixture was passed through a pad of celite, washed with EtOH (2 x 10 mL) and the combined filtrate was concentrated in a rotary evaporator to yield the pure *N*-phenethyl-3-phenylpropanamides **4a-i** in quantitative yield.

*N-(3,4-Dimethoxyphenethyl)-3-phenylpropanamide (**4a**)*. Following general procedure, compound **4a** was obtained as a white solid 0.47 g (1.5 mmol, >99 %); R_f [hexane-EtOAc, 2:1] = 0.65; m.p. = 120-122 ºC; IR (KBr Disk): 3301 $\nu_{(NH)}$, 3070 $\nu_{(CH2\text{-}Ar)}$, 2931 $\nu_{(OCH3)}$, 1635 $\nu_{(C=O)}$, 1542 $\nu_{(C\text{-}N)}$, 1326 $\nu_{(CH2\text{-}Ar)}$, 1234 $\nu_{(C\text{-}C)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.20 (2H, t, J = 7.3 Hz, 5' and 9'-H_{Ar}), 7.11 (3H, dd, J = 12.0, 7.1 Hz, 6', 7' and 8'-H_{Ar}), 6.69 (1H, d, J = 8.1 Hz, 10-H_{Ar}), 6.58 (1H, s, 6-H_{Ar}), 6.54 (1H, d, J = 8.1 Hz, 9-H_{Ar}), 5.41 (1H, br. s, NH), 3.78 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.38 (2H, q, J = 6.6 Hz, -CH_2NH), 2.86 (2H, t, J = 7.6 Hz, 2'-CH_2), 2.61 (2H, t, J = 7.0 Hz, -CH_2Ph), 2.35 (2H, t, J = 7.7 Hz, 3'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 172.1, 149.0, 147.6, 140.9, 131.3, 128.5 (2C, +), 128.4 (2C, +), 126.3 (+), 120.6 (+), 111.7 (+), 111.2 (+), 55.9 (+), 55.9 (+), 40.7 (-), 38.5 (-), 35.2 (-), 31.7 (-). HRMS (ESI): calcd. for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1751, found: 314.1755. Spectral data were in accordance with those reported in the literature.[42]

*N-(3,4-Dimethoxyphenethyl)-3-(3,4-dimethoxyphenyl)propanamide (**4b**)*. Following general procedure, compound **4b** was obtained as a white solid 0.56 g (1.5 mmol, >99 %); R_f [hexane-EtOAc, 2:1] = 0.43; m.p. = 84-86 ºC (lit. 95-96 °C[45]); IR (KBr Disk): 3332 $\nu_{(NH)}$, 3054 $\nu_{(CH2\text{-}Ar)}$, 2931 $\nu_{(OCH3)}$, 1635 $\nu_{(C=O)}$, 1589 $\nu_{(C\text{-}N)}$, 1465 $\nu_{(CH2\text{-}Ar)}$, 1234 $\nu_{(C\text{-}C)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.76 (2H, d, J = 8.1 Hz, 9 and 8'-H_{Ar}), 6.71-6.68 (2H, m, 5' and 9'-H_{Ar}), 6.66 (1H, d, J = 1.9 Hz, 6-H_{Ar}), 6.60 (1H, dd, J = 8.1, 1.9 Hz, 10-H_{Ar}), 5.44 (1H, t, J = 6.8 Hz, NH), 3.84 (3H, s, OCH_3), 3.83 (9H, s, OCH_3), 3.45 (2H, q, J = 6.8 Hz, -CH_2NH), 2.88 (2H, t, J = 7.6 Hz, 2'-CH_2), 2.68 (2H, t, J = 6.9 Hz, -CH_2Ph), 2.40 (2H, t, J = 7.6 Hz, 3'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 172.2, 149.0, 148.9, 147.7, 147.4, 133.5, 131.3, 120.6 (+), 120.2 (+), 111.7 (+), 111.6 (+), 111.2 (+), 111.2 (+), 55.9 (+), 55.9 (2C, +), 55.8 (+), 40.7 (-), 38.9 (-), 35.3 (-), 31.4 (-). HRMS (ESI): calcd. for $C_{21}H_{28}NO_5$

[M+H]$^+$: 374.1962, found: 374.1958. Spectral data were in accordance with those reported in the literature.[46]

*N-(3,4-Dimethoxyphenethyl)-3-(3,4,5-trimethoxyphenyl)propanamide (**4c**)*. Following general procedure, compound **4c** was obtained as a white solid 0.61 g (1.5 mmol, >99 %); R_f [hexane-EtOAc, 2:1] = 0.35; m.p. = 111-113 ºC; IR (KBr Disk): 3301 $\nu_{(NH)}$, 3070 $\nu_{(CH2\text{-}Ar)}$, 2931 $\nu_{(OCH3)}$, 1650 $\nu_{(C=O)}$, 1589 $\nu_{(C\text{-}N)}$, 1542 $\nu_{(NH)}$, 1342 $\nu_{(CH2\text{-}Ar)}$, 1249 $\nu_{(C\text{-}N)}$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.76 (1H, d, J = 8.1 Hz, 9-H_{Ar}), 6.66 (1H, d, J = 1.9 Hz, 6-H_{Ar}), 6.60 (1H, dd, J = 8.1, 1.9 Hz, 10-H_{Ar}), 6.39 (2H, s, 5' and 9'-H_{Ar}), 5.46 (1H, t, J = 6.9 Hz, NH), 3.84 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.81 (6H, s, 2xOCH_3), 3.79 (3H, s, OCH_3), 3.45 (2H, q, J = 6.9 Hz, -CH_2NH), 2.87 (2H, t, J = 7.6 Hz, 2'-CH_2), 2.69 (2H, t, J = 7.0 Hz, -CH_2Ph), 2.40 (2H, t, J = 7.6 Hz, 3'-CH_2). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 172.0, 153.2 (2C), 149.0, 147.7, 136.8, 136.3, 131.27, 120.6 (+), 111.8 (+), 111.3 (+), 105.2 (2C, +), 60.9 (+), 56.1 (2C, +), 55.9 (+), 55.9 (+), 40.7 (-), 38.8 (-), 35.3 (-), 32.2 (-). HRMS (ESI): calcd. for $C_{22}H_{30}NO_6$ [M+H]$^+$: 404.2068, found: 404.2065.

*N-(3,4-Dimethoxyphenethyl)-3-(3,4-methylendioxyphenyl)propanamide (**4d**)*. Following general procedure, compound **4d** was obtained as a white solid 0.53 g (1.5 mmol, >99 %); R_f [hexane-EtOAc, 2:1] = 0.38; m.p. = 151-153 ºC; IR (KBr Disk): 3270 $\nu_{(NH)}$, 3085 $\nu_{(CH2\text{-}Ar)}$, 2931 $\nu_{(OCH3)}$, 2894 $\nu_{(\text{-}OCH2O\text{-})}$, 1635 $\nu_{(C=O)}$, 1558 $\nu_{(C\text{-}N)}$, 1425 $\nu_{(CH2\text{-}Ar)}$, 1234 $\nu_{(C\text{-}C)}$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.78 (1H, d, J = 8.1 Hz, 9-H_{Ar}), 6.70 (1H, d, J = 7.9 Hz, 8'-H_{Ar}), 6.67-6.65 (2H, m, 10 and 5'-H_{Ar}), 6.64-6.60 (2H, m, 6 and 9'-H_{Ar}), 5.90 (2H, s, -OCH_2O-), 5.42 (1H, br. s., NH), 3.85 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.45 (2H, q, J = 6.9 Hz, -CH_2NH), 2.85 (2H, t, J = 7.6 Hz, 2'-CH_2), 2.69 (2H, t, J = 7.0 Hz, -CH_2Ph), 2.37 (2H, t, J = 7.6 Hz, 3'-CH_2). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 172.1, 149.1, 147.7 (2C), 146.0, 134.7, 131.3, 121.2 (+), 120.6 (+), 111.8 (+), 111.3 (+), 108.9 (+), 108.1 (+), 100.9 (-), 56.0 (+), 55.9 (+), 40.7 (-), 38.8 (-), 35.3 (-), 31.5 (-). HRMS (ESI): calcd. for $C_{20}H_{24}NO_5$ [M+H]$^+$: 358.1649, found: 358.1653.

*N-(3,4-Dimethoxyphenethyl)-3-(4-acetoxyphenyl)propanamide (**4e**)*. Following general procedure, compound **4e** was obtained as a white solid 0.55 g (1.5 mmol, >99 %); R_f [hexane-EtOAc, 2:1] = 0.30; m.p. = 125-127 ºC; IR (KBr Disk): 3317 $\nu_{(NH)}$, 3054 $\nu_{(CH2\text{-}Ar)}$, 2931 $\nu_{(OCH3)}$, 1758 $\nu_{(C=O)}$, 1650 $\nu_{(C=O)}$, 1542 $\nu_{(C\text{-}N)}$, 1465 $\nu_{(CH2\text{-}Ar)}$, 1265 $\nu_{(C\text{-}C)}$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.15 (2H, d, J = 8.6 Hz, 6' and 8'-H_{Ar}), 6.96 (2H, d, J = 8.6 Hz, 5' and 9'-H_{Ar}), 6.77 (1H, d, J = 8.1 Hz, 9-H_{Ar}), 6.67 (1H, d, J = 1.9 Hz, 6-H_{Ar}), 6.63 (1H, dd, J = 8.1, 2.0 Hz, 10-H_{Ar}), 5.42 (1H, t, J = 7.0 Hz, NH), 3.84 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.43 (2H, q, J = 7.0 Hz, -CH_2NH), 2.91 (2H, t, J = 7.6 Hz, 2'-CH_2), 2.68 (2H, t, J = 7.1 Hz, -CH_2Ph), 2.39 (2H, t, J = 7.6 Hz, 3'-CH_2), 2.26 (3H, s, CH_3). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 172.0, 169.7, 149.1 (2C), 147.7, 138.5, 131.4, 129.4 (2C, +), 121.6

(2C, +), 120.7 (+), 111.9 (+), 111.4 (+), 56.0 (+), 55.9 (+), 40.7 (-), 38.4 (-), 35.2 (-), 31.1 (-), 21.1 (+). HRMS (ESI): calcd. for $C_{21}H_{26}NO_5$ $[M+H]^+$: 372.1805, found: 372.1808.

*N-(3,4-Dimethoxyphenethyl)-3-(4-acetoxy-3-methoxyphenyl)propanamide (**4f**)*. Following general procedure, compound **4f** was obtained as a white solid 0.59 g (1.5 mmol, >99 %); R_f [hexane-EtOAc, 2:1] = 0.21; m.p. = 108-110 ºC; IR (KBr Disk): 3317 $\nu_{(NH)}$, 3070 $\nu_{(CH2\text{-}Ar)}$, 2931 $\nu_{(OCH3)}$, 1758 $\nu_{(C=O)}$, 1635 $\nu_{(C=O)}$, 1542 $\nu_{(C\text{-}N)}$, 1425 $\nu_{(CH2\text{-}Ar)}$, 1234 $\nu_{(C\text{-}C)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.91 (1H, d, J = 8.0 Hz, 9-H_{Ar}), 6.79-6.76 (2H, m, 5' and 8'-H_{Ar}), 6.72 (1H, dd, J = 8.0, 1.9 Hz, 9'-H_{Ar}), 6.67 (1H, d, J = 1.9 Hz, 6-H_{Ar}), 6.64 (1H, dd, J = 8.1, 2.0 Hz, 10-H_{Ar}), 5.46 (1H, t, J = 7.0 Hz, N*H*), 3.84 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.45 (2H, q, J = 7.0 Hz, -CH_2NH), 2.91 (2H, t, J = 7.6 Hz, 2'-CH_2), 2.69 (2H, t, J = 7.0 Hz, -CH_2Ph), 2.40 (2H, t, J = 7.6 Hz, 3'-CH_2), 2.28 (3H, s, CH_3). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 171.9, 169.3, 151.0, 149.1, 147.7, 140.0, 138.1, 131.3, 122.7 (+), 120.7 (+), 120.4 (+), 112.7 (+), 111.9 (+), 111.4 (+), 56.0 (+), 55.8 (+), 55.9 (+), 40.7 (-), 38.5 (-), 35.3 (-), 31.7 (-), 20.7 (+). HRMS (ESI): calcd. for $C_{22}H_{28}NO_6$ $[M+H]^+$: 402.1911, found: 402.1915.

*N-(3,4-Dimethoxyphenethyl)-3-(3-acetoxy-4-methoxyphenyl)propanamide (**4g**)*. Following general procedure, compound **4g** was obtained as a white solid 0.60 g (1.5 mmol, >99 %); R_f [hexane-EtOAc, 2:1] = 0.24; m.p. = 89-91 ºC; IR (KBr Disk): 3332 $\nu_{(NH)}$, 3008 $\nu_{(CH2\text{-}Ar)}$, 2931 $\nu_{(OCH3)}$, 1758 $\nu_{(C=O)}$, 1650 $\nu_{(C=O)}$, 1511 $\nu_{(C\text{-}N)}$, 1450 $\nu_{(CH2\text{-}Ar)}$, 1265 $\nu_{(C\text{-}C)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.98 (1H, dd, J = 8.4, 1.8 Hz, 9'-H_{Ar}), 6.85-6.83 (2H, m, 5' and 8'-H_{Ar}), 6.77 (1H, d, J = 8.1 Hz, 9-H_{Ar}), 6.67 (1H, d, J = 8.1 Hz, 6-H_{Ar}), 6.63 (1H, dd, J = 8.0, 1.6 Hz, 10-H_{Ar}), 5.53 (1H, t, J = 6.8 Hz, N*H*), 3.84 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.42 (2H, q, J = 6.8 Hz, -CH_2NH), 2.86 (2H, t, J = 7.5 Hz, 2'-CH_2), 2.67 (2H, t, J = 7.0 Hz, -CH_2Ph), 2.36 (2H, t, J = 7.5 Hz, 3'-CH_2), 2.28 (3H, s, CH_3). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 172.0, 169.2, 149.5, 149.1, 147.7, 139.6, 133.5, 131.4, 126.6 (+), 122.8 (+), 120.7 (+), 112.5 (+), 111.9 (+), 111.4 (+), 56.0 (+), 55.9 (+), 55.9 (+), 40.7 (-), 38.5 (-), 35.2 (-), 30.7 (-), 20.7 (+). HRMS (ESI): calcd. for $C_{22}H_{28}NO_6$ $[M+H]^+$: 402.1911, found: 402.1909.

*N-(3,4-Dimethoxyphenethyl)-3-(4-acetoxy-3,5-dimethoxyphenyl)propanamide (**4h**)*. Following general procedure, compound **4h** was obtained as a white solid 0.64 g (1.5 mmol, >99 %); R_f [hexane-EtOAc, 2:1] = 0.16; m.p. = 96-98 ºC; IR (KBr Disk): 3363 $\nu_{(NH)}$, 3008 $\nu_{(CH2\text{-}Ar)}$, 2931 $\nu_{(OCH3)}$, 1758 $\nu_{(C=O)}$, 1666 $\nu_{(C=O)}$, 1511 $\nu_{(C\text{-}N)}$, 1465 $\nu_{(CH2\text{-}Ar)}$, 1265 $\nu_{(C\text{-}C)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.77 (1H, d, J = 8.1 Hz, 9-H_{Ar}), 6.67 (1H, d, J = 1.9 Hz, 6-H_{Ar}), 6.63 (1H, dd, J = 8.1, 1.8 Hz, 10-H_{Ar}), 6.42 (2H, s, 5' and 9'-H_{Ar}), 5.52 (1H, br. s., N*H*), 3.84 (6H, s, OCH_3), 3.76 (6H, s, OCH_3), 3.44 (2H, q, J = 6.9 Hz, -CH_2NH), 2.89 (2H, t, J = 7.6 Hz, 2'-CH_2), 2.69 (2H, t, J = 7.0 Hz, -CH_2Ph), 2.39 (2H, t, J = 7.6 Hz, 3'-CH_2), 2.30 (3H, s, OAc). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 172.0, 169.0,

152.0 (2C), 149.1, 147.7, 139.6, 131.3, 127.0, 120.7 (+), 111.9 (+), 111.4 (+), 105.0 (2C, +), 56.1 (2C, +), 55.9 (+), 55.9 (+), 40.8 (-), 38.6 (-), 35.2 (-), 32.3 (-), 20.5 (+). HRMS (ESI): calcd. for $C_{23}H_{30}NO_7$ $[M+H]^+$: 432.2017, found: 432.2013.

General procedure and characterization data of 1-phenethyl-3,4-dihydroisoquinolines 5a-i. A 10 mL reactor vial equipped with a magnetic stir bar was charged with the corresponding *N*-phenethyl-3-phenylpropanamides **3b** and **4a-h** (1.5 mmol) and anhydrous acetonitrile (CH_3CN) (5 mL). The resulting solution was stirred at room temperature until complete dissolution of the amide and phosphoryl chloride ($POCl_3$) (2.25 mmol, 1.5 equiv) was added in one portion. Then, the system was heated at 50°C in an oil bath for 24 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure and the crude reaction mixture was suspended in crushed ice, treated with aqueous $NaHCO_3$ (1 M) to pH = 8, and then extracted with CH_2Cl_2 (3 x 10 mL). Finally, the combined organic extracts were dried over Na_2SO_4, concentrated, and purified by flash column chromatography on silica gel (10% MeOH in CH_2Cl_2) to afford the desired 1-phenethyl-3,4-dihydroisoquinolines **5a-i**.

*6,7-Dimethoxy-1-phenethyl-3,4-dihydroisoquinoline (***5a***)*. Following general procedure, compound **5a** was obtained as a yellow solid 0.42 g (1.41 mmol, 94 %); R_f [CH_2Cl_2/MeOH 8:1] = 0.52; m.p. = 81-83 ºC; IR (KBr Disk): 2993 $\nu_{(CH2\text{-}Ar)}$, 2838 $\nu_{(OCH3)}$, 1604 $\nu_{(C=N)}$, 1511 $\nu_{(C\text{-}N)}$, 1465 $\nu_{(CH2\text{-}Ar)}$, 1265 $\nu_{(C\text{-}C)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.33-7.28 (2H, m, 5' and 9'-H_{Ar}), 7.27-7.18 (3H, m, 6', 7' and 8'-H_{Ar}), 6.96 (1H, s, 8-H_{Ar}), 6.71 (1H, s, 5-H_{Ar}), 3.92 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.70-3.64 (2H, m, -CH_2N), 3.03-2.97 (4H, m, 2' and 3'-CH_2), 2.65-2.59 (2H, m, -CH_2Ph). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 165.9, 150.7, 147.5, 142.1, 131.5, 128.5 (4C, +), 126.0 (+), 122.0, 110.3 (+), 108.4 (+), 56.2 (+), 56.0 (+), 47.0 (-), 37.9 (-), 33.2 (-), 25.9 (-). HRMS (ESI): calcd. for $C_{19}H_{22}NO_2$ $[M+H]^+$: 296.1645, found: 296.1649. Spectral data were in accordance with those reported in the literature.[43]

*6,7-Dimethoxy-1-(4-methoxyphenethyl)-3,4-dihydroisoquinoline (***5b***)*. Following general procedure, compound **5b** was obtained as a yellow solid 0.47 g (1.45 mmol, 97 %); R_f [CH_2Cl_2/MeOH 8:1] = 0.51; m.p. = 143-145 ºC; IR (KBr Disk): 2915 $\nu_{(CH2\text{-}Ar)}$, 2854 $\nu_{(OCH3)}$, 1650 $\nu_{(C=N)}$, 1511 $\nu_{(C\text{-}N)}$, 1465 $\nu_{(CH2\text{-}Ar)}$, 1280 $\nu_{(C\text{-}C)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.15 (2H, d, J = 8.6 Hz, 6' and 8'-H_{Ar}), 6.95 (1H, s, 8-H_{Ar}), 6.84 (2H, d, J = 8.7 Hz, 5' and 9'-H_{Ar}), 6.70 (1H, s, 5-H_{Ar}), 3.91 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.67-3.61 (2H, m, -CH_2N), 2.97-2.92 (4H, m, 2' and 3'-CH_2), 2.66-2.57 (2H, m, -CH_2Ph). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 166.0, 157.9, 150.7, 147.5, 134.1, 131.5, 129.4 (2C, +), 122.0, 113.9 (2C, +), 110.3 (+), 108.5 (+), 56.2 (+), 56.0 (+), 55.3 (+), 47.0 (-), 38.2 (-), 32.4 (-), 25.9 (-). HRMS (ESI): calcd. for $C_{20}H_{24}NO_3$ $[M+H]^+$: 326.1751, found: 326.1747. Spectral data were in accordance with those reported in the literature.[43]

*6,7-Dimethoxy-1-(3,4-dimethoxyphenethyl)-3,4-dihydroisoquinoline (**5c**)*. Following general procedure, compound **5c** was obtained as a yellow solid 0.52 g (1.47 mmol, 98 %); R_f [CH_2Cl_2/MeOH 8:1] = 0.48; m.p. = 95-97 ºC (lit. 89-91 °C[46]); IR (KBr Disk): 2931 $\nu_{(CH2\text{-}Ar)}$, 2838 $\nu_{(OCH3)}$, 1604 $\nu_{(C=N)}$, 1511 $\nu_{(C\text{-}N)}$, 1465 $\nu_{(CH2\text{-}Ar)}$, 1265 $\nu_{(C\text{-}C)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.96 (1H, s, 8-H_{Ar}), 6.80 (1H, d, J = 8.6 Hz, 8'-H_{Ar}), 6.77-6.74 (2H, m, 5' and 9'-H_{Ar}), 6.70 (1H, s, 5-H_{Ar}), 3.91 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.68-3.62 (2H, m, -CH_2N), 2.98-2.91 (4H, m, 2' and 3'-CH_2), 2.64-2.59 (2H, m, -CH_2Ph). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 166.3, 151.0, 149.0, 147.6, 147.4, 134.6, 131.7, 122.0, 120.3 (+), 112.0 (+), 111.4 (+), 110.5 (+), 108.8 (+), 56.3 (+), 56.1 (+), 56.0 (+), 55.9 (+), 46.8 (-), 38.0 (-), 33.0 (-), 26.0 (-). HRMS (ESI): calcd. for $C_{21}H_{26}NO_4$ $[M+H]^+$: 356.1856, found: 356.1860.

*6,7-Dimethoxy-1-(3,4,5-trimethoxyphenethyl)-3,4-dihydroisoquinoline (**5d**)*. Following general procedure, compound **5d** was obtained as a yellow solid 0.52 g (1.48 mmol, 99 %); R_f [CH_2Cl_2/MeOH 8:1] = 0.42; m.p. = 104-106 ºC; IR (KBr Disk): 2993 $\nu_{(CH2\text{-}Ar)}$, 2838 $\nu_{(OCH3)}$, 1604 $\nu_{(C=N)}$, 1511 $\nu_{(C\text{-}N)}$, 1465 $\nu_{(CH2\text{-}Ar)}$, 1265 $\nu_{(C\text{-}C)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.03 (1H, s, 8-H_{Ar}), 6.77 (1H, s, 5-H_{Ar}), 6.41 (2H, s, 5' and 9'-H_{Ar}), 3.96 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.81 (6H, s, 2xOCH_3), 3.80 (3H, s, OCH_3), 3.74-3.69 (2H, m, -CH_2N), 3.17-3.11 (2H, m, 2'-CH_2), 2.96 (2H, dd, J = 8.7, 6.7 Hz, 3'-CH_2), 2.81-2.75 (2H, m, -CH_2Ph). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 183.2, 153.4 (3C), 148.2, 136.4, 132.9, 123.5 (+), 122.0, 110.7 (+), 110.05 (s), 105.4 (+, 2C), 60.9 (+), 56.4 (+, 2C), 56.1 (+, 2C), 50.0 (-), 37.0 (-), 33.9 (-), 25.7 (-). HRMS (ESI): calcd. for $C_{22}H_{28}NO_5$ $[M+H]^+$: 386.1962, found: 386.1966. Spectral data were in accordance with those reported in the literature.[47]

*6,7-Dimethoxy-1-(3,4-methylendioxyphenethyl)-3,4-dihydroisoquinoline (**5e**)*. Following general procedure, compound **5e** was obtained as a yellow solid 0.50 g (1.48 mmol, 99 %); R_f [CH_2Cl_2/MeOH 8:1] = 0.50; m.p. = 125-127 ºC; IR (KBr Disk): 2915 $\nu_{(CH2\text{-}Ar)}$, 2777 $\nu_{(\text{-}OCH2O\text{-})}$, 1604 $\nu_{(C=N)}$, 1496 $\nu_{(C\text{-}N)}$, 1465 $\nu_{(CH2\text{-}Ar)}$, 1295 $\nu_{(C\text{-}C)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.98 (1H, s, 8-H_{Ar}), 6.79 (1H, s, 5-H_{Ar}), 6.70 (1H, d, J = 1.3 Hz, 5'-H_{Ar}), 6.65 (1H, d, J = 7.8 Hz, 8'-H_{Ar}), 6.61 (1H, dd, J = 7.9, 1.4 Hz, 9'-H_{Ar}), 5.87 (2H, s, -OCH_2O-), 3.98 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.84-3.79 (2H, m, -CH_2N), 3.47 (2H, t, J = 7.6 Hz, 2'-CH_2), 3.06 (2H, t, J = 7.5 Hz, -CH_2Ph), 2.93 (2H, t, J = 7.6 Hz, 3'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 176.2, 156.2, 148.7, 147.9, 146.5, 133.6, 132.3, 121.6 (+), 117.6 (-), 111.3 (+), 111.0 (+), 109.0 (+), 108.5 (+), 101.0 (-), 56.6 (+), 56.4 (+), 40.7 (-), 34.8 (-), 34.5 (-), 25.5 (-). HRMS (ESI): calcd. for $C_{20}H_{22}NO_4$ $[M+H]^+$: 340.1543, found: 340.1539.

*6,7-Dimethoxy-1-(4-acetoxyphenethyl)-3,4-dihydroisoquinoline (**5f**)*. Following general procedure, compound **5f** was obtained as a yellow solid 0.51 g (1.47 mmol, 98 %); R_f [CH_2Cl_2/MeOH 8:1] = 0.45; m.p. = 132-134 ºC; IR (KBr Disk): 2931 $\nu_{(CH2\text{-}Ar)}$, 2854 $\nu_{(OCH3)}$, 1758 $\nu_{(C=O)}$, 1604 $\nu_{(C=N)}$, 1511 $\nu_{(C\text{-}N)}$, 1465 $\nu_{(CH2\text{-}Ar)}$, 1280 $\nu_{(C\text{-}C)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.23 (2H, d, J = 8.5

Hz, 6' and 8'-H_A), 6.99 (2H, d, J = 8.5 Hz, 5' and 9'-H_A), 6.95 (1H, s, 8-H_{Ar}), 6.70 (1H, s, 5-H_{Ar}), 3.91 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.68-3.61 (2H, m, -CH_2N), 3.00-2.97 (4H, m, 2' and 3'-CH_2), 2.64-2.58 (2H, m, -CH_2Ph), 2.28 (3H, s, OAc). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 169.8, 157.1, 151.1, 149.0, 147.7, 139.6, 131.6, 129.5 (2C, +), 121.8, 121.6 (2C, +), 110.5 (+), 108.6 (+), 56.3 (+), 56.1 (+), 46.8 (-), 37.6 (-), 32.5 (-), 25.9 (-), 21.2 (+). HRMS (ESI): calcd. for $C_{21}H_{24}NO_4$ $[M+H]^+$: 354.1700, found: 354.1704.

*6,7-Dimethoxy-1-(4-acetoxy-3-methoxyphenethyl)-3,4-dihydroisoquinoline (***5g***)*. Following general procedure, compound **5g** was obtained as a yellow solid 0.54 g (1.42 mmol, 95 %); R_f [CH_2Cl_2/MeOH 8:1] = 0.42; m.p. = 119-121 ºC; IR (KBr Disk): 2931 $\nu_{(CH2\text{-}Ar)}$, 2838 $\nu_{(OCH3)}$, 1758 $\nu_{(C=O)}$, 1604 $\nu_{(C=N)}$, 1511 $\nu_{(C\text{-}N)}$, 1465 $\nu_{(CH2\text{-}Ar)}$, 1280 $\nu_{(C\text{-}C)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.96 (1H, s, 8-H_{Ar}), 6.93 (1H, d, J = 8.0 Hz, 8'-H_{Ar}), 6.84 (1H, d, J = 1.8 Hz, 5'-H_{Ar}), 6.79 (1H, dd, J = 8.0, 1.8 Hz, 9'-H_{Ar}), 6.70 (1H, s, 5-H_{Ar}), 3.91 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.68-3.62 (2H, m, -CH_2N), 2.98-2.95 (4H, m, 2' and 3'-CH_2), 2.64-2.59 (2H, m, -CH_2Ph), 2.30 (3H, s, CH_3). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 169.4, 165.9, 151.0, 150.9, 147.7, 141.1, 138.0, 131.6, 122.6 (+), 122.0, 120.6 (+), 112.9 (+), 110.5 (+), 108.6 (+), 56.4 (+), 56.1 (+), 55.9 (+), 46.9 (-), 37.8 (-), 33.1 (-), 25.9 (-), 20.8 (+). HRMS (ESI): calcd. for $C_{22}H_{26}NO_5$ $[M+H]^+$: 384.1805, found: 384.1808.

*6,7-Dimethoxy-1-(3-acetoxy-4-methoxyphenethyl)-3,4-dihydroisoquinoline (***5h***)*. Following general procedure, compound **5h** was obtained as a yellow solid 0.56 g (1.48 mmol, 99 %); R_f [CH_2Cl_2/MeOH 8:1] = 0.43; m.p. = 82-84 ºC; IR (KBr Disk): 2931 $\nu_{(CH2\text{-}Ar)}$, 2838 $\nu_{(OCH3)}$, 1758 $\nu_{(C=O)}$, 1604 $\nu_{(C=N)}$, 1511 $\nu_{(C\text{-}N)}$, 1465 $\nu_{(CH2\text{-}Ar)}$, 1280 $\nu_{(C\text{-}C)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.05 (1H, dd, J = 8.3, 2.1 Hz, 9'-H_{Ar}), 6.95 (1H, s, 8-H_{Ar}), 6.90-6.86 (2H, m, 5' and 8'-H_{Ar}), 6.69 (1H, s, 5-H_{Ar}), 3.90 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.64 (2H, t, J = 7.5 Hz, -CH_2N), 2.97-2.89 (4H, m, 2' and 3'-CH_2), 2.63-2.57 (2H, m, -CH_2Ph), 2.29 (3H, s, CH_3). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 169.2, 166.0, 150.9, 149.3, 147.6, 139.6, 134.6, 131.6, 126.7 (+), 122.8 (+), 121.9, 112.5 (+), 110.4 (+), 108.6 (+), 56.3 (+), 56.0 (+), 46.8 (-), 37.6 (-), 32.1 (-), 25.9 (-), 20.7 (+). HRMS (ESI): calcd. for $C_{22}H_{26}NO_5$ $[M+H]^+$: 384.1805, found: 384.1809.

*6,7-Dimethoxy-1-(4-acetoxy-3,5-dimethoxyphenethyl)-3,4-dihydroisoquinoline (***5i***)*. Following general procedure, compound **5i** was obtained as a yellow solid 0.61 g (1.48 mmol, 99 %); R_f [CH_2Cl_2/MeOH 8:1] = 0.39; m.p. = 104-105 ºC; IR (KBr Disk): 2931 $\nu_{(CH2\text{-}Ar)}$, 2838 $\nu_{(OCH3)}$, 1758 $\nu_{(C=O)}$, 1635 $\nu_{(C=N)}$, 1511 $\nu_{(C\text{-}N)}$, 1465 $\nu_{(CH2\text{-}Ar)}$, 1280 $\nu_{(C\text{-}C)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.01 (1H, s, 8-H_{Ar}), 6.72 (1H, s, 5-H_{Ar}), 6.47 (2H, s, 5' and 9'-H_{Ar}), 3.93 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.77 (6H, s, OCH_3), 3.71-3.66 (2H, m, -CH_2N), 3.21-3.15 (2H, m, 2'-CH_2), 3.00 (2H, dd, J = 9.3, 6.7 Hz, -CH_2Ph), 2.71-2.64 (2H, m, 3'-CH_2), 2.31 (3H, s, CH_3). $^{13}C\{^1H\}$ NMR (101 MHz,

$CDCl_3$): $\delta_{(ppm)}$: 169.1, 169.0, 152.7, 152.1 (2C), 148.1, 139.4, 132.3, 127.1, 120.6, 110.6 (+), 109.5 (+), 105.3 (2C, +), 56.4 (+), 56.2 (+), 44.9 (-), 36.4 (-), 34.1 (-), 25.8 (-), 20.5 (+). HRMS (ESI): calcd. for $C_{23}H_{28}NO_6$ $[M+H]^+$: 414.1911, found: 414.1907.

General procedure and characterization data of (*R*)-7a-i and (*S*)-7a-i *Dysoxylum* alkaloids. In a 10 mL vial equipped with a magnetic stir bar was added the respective 1-phenethyl-3,4-dihydroisoquinoline **5a-i** (0.5 mmol), (*S,S*)- or (*R,R*)-RuTsDPEN (10 µmol, 2 mol %) and HCOONa (2.5 mmol, 5 equiv). The vial was sealed and the air was evacuated establishing an Argon atmosphere. Then, 3 mL of H_2O/DMF (1/1) was added in one portion and the reaction mixture was stirred at 40 °C in an oil bath for 12 hours. After completion of the reaction (TLC), the reaction mixture was cooled, quenched with distilled water and extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, dried over with Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product in quantitative yield. The desired 1-phenethyl-1,2,3,4-tetrahydroisoquinoline **6a-i** was obtained sufficiently pure to be used in the next step without any further purification. A solution of the respective 1,2,3,4-tetrahydroisoquinoline **6a-i** (0.5 mmol), paraformaldehyde ($(CH_2O)_n$) (1.5 mmol) and methanol (4 mL), in a 25 ml round-bottom flask, was added dropwise into a stirred solution of sodium cyanoborohydride ($NaBH_3CN$) (0.55 mmol, 1.1 equiv.), zinc chloride ($ZnCl_2$) (0.25 mmol, 0.5 equiv.) and methanol (4 mL). Then, the mixture was stirred for 6 hours at 0 °C and the reaction was quenched with $NaHCO_3$ (1 M) and extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, dried over with Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (10% MeOH in CH_2Cl_2) to furnished the desired **(*R*)-7a-i** and **(*S*)-7a-i** *Dysoxylum* alkaloids

(R)-6,7-Dimethoxy-N-methyl-1-phenethyl-1,2,3,4-tetrahydroisoquinoline (**(*R*)-7a**). Following general procedure, compound **(*R*)-7a** was obtained as a yellow oil 0.13 g (0.44 mmol, 89 %); R_f [CH_2Cl_2/MeOH 10:1] = 0.65; IR (liquid film): 2931 $\nu_{(CH2\text{-}Ar)}$, 2838 $\nu_{(OCH3)}$, 2792 $\nu_{(N\text{-}C)}$, 1604 $\nu_{(C\text{-}C)}$, 1511 $\nu_{(C\text{-}N)}$, 1218 $\nu_{(CH3)}$, 1110 $\nu_{(C\text{-}O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.29-7.24 (2H, m, 5' and 9'-H_{Ar}), 7.19-7.14 (3H, m, 6', 7' and 8'-H_{Ar}), 6.57 (1H, s, 8-H_{Ar}), 6.54 (1H, s, 5-H_{Ar}), 3.85 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.42 (1H, t, J = 5.3 Hz, CH_a-N), 3.18-3.10 (1H, m, CH_b-N), 2.80-2.67 (4H, m, -CH_2Ph and 3'-CH_2), 2.61-2.52 (1H, m, 1-CH), 2.48 (3H, s, NCH_3), 2.09-2.03 (2H, m, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 147.4, 147.3, 143.1, 129.9, 128.5 (2C, +), 128.4 (2C, +), 126.9, 125.7 (+), 111.4 (+), 110.1 (+), 62.9 (+), 56.1 (+), 55.9 (+), 48.9 (-), 42.8 (+), 36.9 (-), 31.7 (-), 25.7 (-). *ee* value: 95 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 6.06 min (minor, 2.5 %), t_{R2} = 8.36 min (major, 97.4 %), $[\alpha]_D^{25}$ = -11.4 (c = 0.025, EtOH). HRMS (ESI): calcd. for $C_{20}H_{26}NO_2$ $[M+H]^+$: 312.1958, found: 312.1962.

(R)-6,7-Dimethoxy-1-(4-methoxyphenethyl)-N-methyl-1,2,3,4-tetrahydroisoquinoline ***((R)-7b)***. Following general procedure, compound **(*R*)-7b** was obtained as a yellow oil 0.15 g (0.46 mmol, 93 %); R_f [CH_2Cl_2/MeOH 10:1] = 0.61; IR (liquid film): 2931 $\nu_{(CH2\text{-}Ar)}$, 2838 $\nu_{(OCH3)}$, 2792 $\nu_{(N\text{-}C)}$, 1604 $\nu_{(C\text{-}C)}$, 1511 $\nu_{(C\text{-}N)}$, 1249 $\nu_{(CH3)}$, 1033 $\nu_{(C\text{-}O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.12 (2H, d, *J* = 8.7 Hz, 6' and 8'-H_{Ar}), 6.84 (2H, d, *J* = 8.7 Hz, 5' and 9'-H_{Ar}), 6.59 (1H, s, 8-H_{Ar}), 6.56 (1H, s, 5-H_{Ar}), 3.88 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.44 (1H, t, *J* = 5.4 Hz, CH_a-N), 3.22-3.13 (1H, m, CH_b-N), 2.81-2.66 (4H, m, -CH_2Ph and 3'-CH_2), 2.55 (1H, dd, *J* = 15.1, 7.8 Hz, 1-C*H*), 2.49 (3H, s, NCH_3), 2.09-2.00 (2H, m, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 157.6, 147.2, 147.2, 134.9, 129.9, 129.3 (2C, +), 126.7, 113.7 (2C, +), 111.3 (+), 110.0 (+), 62.7 (+), 56.0 (+), 55.8 (+), 55.2 (+), 48.1 (-), 42.6 (+), 37.1 (-), 30.7 (-), 25.4 (-). *ee* value: 91 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 6.88 min (minor, 4.7 %), t_{R2} = 11.07 min (major, 95.3 %), $[\alpha]_D^{25}$ = -5.9 (c = 0.025, EtOH). HRMS (ESI): calcd. for $C_{21}H_{28}NO_3$ $[M+H]^+$: 342.2064, found: 342.2068.

(R)-6,7-Dimethoxy-1-(3,4-dimethoxyphenethyl)-N-methyl-1,2,3,4-tetrahydroisoquinoline ***((R)-7c).*** Following general procedure, compound **(*R*)-7c** was obtained as a yellow oil 0.17 g (0.46 mmol, 92 %); R_f [CH_2Cl_2/MeOH 10:1] = 0.59; IR (liquid film): 2931 $\nu_{(CH2\text{-}Ar)}$, 2838 $\nu_{(OCH3)}$, 2792 $\nu_{(N\text{-}C)}$, 1604 $\nu_{(C\text{-}C)}$, 1511 $\nu_{(C\text{-}N)}$, 1265 $\nu_{(CH3)}$, 1041 $\nu_{(C\text{-}O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.81 (1H, d, *J* = 7.9 Hz, 8'-H_{Ar}), 6.76-6.72 (2H, m, 5' and 9'-H_{Ar}), 6.60 (1H, s, 8-H_{Ar}), 6.56 (1H, s, 5-H_{Ar}), 3.88 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.45 (1H, t, *J* = 5.4 Hz, CH_a-N), 3.21-3.14 (1H, m, CH_b-N), 2.83-2.66 (4H, m, -CH_2Ph and 3'-CH_2), 2.55 (1H, dd, *J* = 14.7, 8.3 Hz, 1-C*H*), 2.50 (3H, s, NCH_3), 2.05 (2H, ddd, *J* = 7.9, 7.0, 3.6 Hz, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 148.8, 147.3, 147.3, 147.1, 135.6, 129.9, 126.8, 120.2 (+), 112.0 (+), 111.4 (+), 111.3 (+), 110.2 (+), 62.7 (+), 56.1 (+), 56.0 (+), 55.9 (2C, +), 48.1 (-), 42.8 (+), 37.1 (-), 31.3 (-), 25.4 (-). *ee* value: 91 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 13.35 min (minor, 4.4 %), t_{R2} = 21.84 min (major, 95.6 %), $[\alpha]_D^{25}$ = -3.9 (c = 0.025, EtOH). HRMS (ESI): calcd. for $C_{22}H_{30}NO_4$ $[M+H]^+$: 372.2169, found: 372.2165.

(R)-6,7-Dimethoxy-1-(3,4,5-trimethoxyphenethyl)-N-methyl-1,2,3,4-tetrahydroisoquinoline ***((R)-7d)***. Following general procedure, compound **(*R*)-7d** was obtained as a yellow oil 0.19 g (0.48 mmol, 97 %); $\mathbf{R_f}$ [CH_2Cl_2/MeOH 10:1] = 0.52; **IR** (liquid film): 2931 $\nu_{(CH2\text{-}Ar)}$, 2838 $\nu_{(OCH3)}$, 2792 $\nu_{(N\text{-}C)}$, 1589 $\nu_{(C\text{-}C)}$, 1511 $\nu_{(C\text{-}N)}$, 1249 $\nu_{(CH3)}$, 1026 $\nu_{(C\text{-}O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.58 (1H, s, 8-H_{Ar}), 6.54 (1H, s, 5-H_{Ar}), 6.39 (2H, s, 5' y 9'-H_{Ar}) 3.85 (3H, s, OCH_3), 3.83 (6H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.43 (1H, t, *J* = 5.5 Hz, CH_a-N), 3.19-3.11 (1H, m, CH_b-N), 2.81-2.64 (4H, m, -CH_2Ph and 3'-CH_2), 2.52 (1H, dd, *J* = 14.5, 7.1 Hz, 1-C*H*), 2.48 (3H, s, NCH_3), 2.05 (2H,

ddd, J = 13.3, 8.2 Hz, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 153.1 (3C), 147.4, 138.8, 136.0, 129.8, 126.9, 111.4 (+), 110.2 (+), 105.4 (2C, +), 62.8 (+), 60.9 (+), 56.1 (+), 56.1 (2C, +), 55.9 (+), 48.1 (-), 42.8 (+), 37.0 (-), 32.1 (-), 25.5 (-). *ee* value: 88 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 12.48 min (minor, 5.9 %), t_{R2} = 20.75 min (major, 94.0 %), $[\alpha]_D^{25}$ = -5.6 (c = 0.025, EtOH). HRMS (ESI): calcd. for $C_{23}H_{32}NO_5$ $[M+H]^+$: 402.2275, found: 402.2271.

*(R)-6,7-Dimethoxy-1-(3,4-methylendioxyphenethyl)-N-methyl-1,2,3,4-tetrahydroisoquinoline (**(R)-7e**)*. Following general procedure, compound **(*R*)-7e** was obtained as a yellow oil 0.16 g (0.47 mmol, 94 %); R_f [CH_2Cl_2/MeOH 10:1] = 0.60; IR (liquid film): 2931 $\nu_{(CH2\text{-}Ar)}$, 2838 $\nu_{(OCH3)}$, 2792 $\nu_{(N\text{-}C)}$, 1604 $\nu_{(C\text{-}C)}$, 1511 $\nu_{(C\text{-}N)}$, 1357, $\nu_{(\text{-}OCH2O\text{-})}$, 1249 $\nu_{(CH3)}$, 1110 $\nu_{(C\text{-}O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.70 (1H, d, J = 7.9 Hz, 8'-H_{Ar}), 6.67 (1H, d, J = 1.5 Hz, 5'-H_{Ar}), 6.62 (1H, dd, J = 7.9, 1.6 Hz, 9'-H_{Ar}), 6.56 (1H, s, 8-H_{Ar}), 6.53 (1H, s, 5-H_{Ar}), 5.88 (2H, s, -OCH_2O-), 3.84 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.41 (1H, t, J = 5.4 Hz, CH_a-N), 3.17-3.08 (1H, m, CH_b-N), 2.79-2.61 (4H, m, -CH_2Ph and 3'-CH_2), 2.52-2.47 (1H, m, 1-CH), 2.46 (3H, s, NCH_3), 2.01 (2H, dt, J = 10.2, 6.6 Hz, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 147.5, 147.3, 147.3, 145.4, 136.7, 129.7, 126.7, 121.1 (+), 111.3 (+), 110.0 (+), 108.9 (+), 108.1 (+), 100.7 (-), 62.6 (+), 56.0 (+), 55.8 (+), 48.1 (-), 42.6 (+), 37.1 (-), 31.4 (-), 25.4 (-). *ee* value: 87 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 7.69 min (minor, 6.3 %), t_{R2} = 11.81 min (major, 93.6 %), $[\alpha]_D^{25}$ = -3.6 (c = 0.025, EtOH). HRMS (ESI): calcd. for $C_{21}H_{26}NO_4$ $[M+H]^+$: 356.1856, found: 356.1852.

*(R)-6,7-Dimethoxy-1-(4-hydroxyphenethyl)-N-methyl-1,2,3,4-tetrahydroisoquinoline (**(R)-7f**)*. Following general procedure, compound **(*R*)-7f** was obtained as a red oil 0.14 g (0.45 mmol, 90 %); R_f [CH_2Cl_2/MeOH 10:1] = 0.47; IR (liquid film): 3455 $\nu_{(OH)}$, 2946 $\nu_{(CH2\text{-}Ar)}$, 2838 $\nu_{(OCH3)}$, 2792 $\nu_{(N\text{-}C)}$, 1604 $\nu_{(C\text{-}C)}$, 1511 $\nu_{(C\text{-}N)}$, 1249 $\nu_{(CH3)}$, 1110 $\nu_{(C\text{-}O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.03 (1H, br. s., -OH), 6.99 (2H, d, J = 8.5 Hz, 6' and 8'-H_{Ar}), 6.70 (2H, d, J = 8.5 Hz, 5' and 9'-H_{Ar}), 6.57 (1H, s, 8-H_{Ar}), 6.53 (1H, s, 5-H_{Ar}), 3.85 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.45 (1H, t, J = 5.6 Hz, CH_a-N), 3.21-3.16 (1H, m, CH_b-N), 2.84-2.62 (4H, m, -CH_2Ph and 3'-CH_2), 2.54 (1H, dd, J = 9.9, 5.3 Hz, 1-CH), 2.46 (3H, s, NCH_3), 2.11-1.93 (2H, m, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 154.3, 147.4, 147.3, 134.2, 129.7, 129.5 (2C, +), 126.3, 115.5 (2C, +), 111.5 (+), 110.4 (+), 62.7 (+), 56.1 (+), 55.9 (+), 47.6 (-), 42.4 (+), 37.3 (-), 31.2 (-), 25.0 (-). *ee* value: 90 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 13.13 min (minor, 5.2 %), t_{R2} = 32.37 min (major, 94.7 %), $[\alpha]_D^{25}$ = -5.1 (c = 0.025, EtOH. HRMS (ESI): calcd. for $C_{20}H_{26}NO_3$ $[M+H]^+$: 328.1907, found: 328.19011.

*(R)-6,7-Dimethoxy-1-(4-hydroxy-3-methoxyphenethyl)-N-methyl-1,2,3,4-tetrahydroisoquinoline (**(R)-7g**)*. Following general procedure, compound **(*R*)-7g** was obtained as a brown oil 0.15 g (0.45 mmol, 91 %); R_f [CH_2Cl_2/MeOH 10:1] = 0.43; IR (liquid film): 3440 $\nu_{(OH)}$, 2931 $\nu_{(CH2\text{-}Ar)}$, 2854 $\nu_{(OCH3)}$, 2792 $\nu_{(N\text{-}C)}$, 1604 $\nu_{(C\text{-}C)}$, 1511 $\nu_{(C\text{-}N)}$, 1265 $\nu_{(CH3)}$, 1110 $\nu_{(C\text{-}O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.81 (1H, d, *J* = 7.7 Hz, 8'-H_{Ar}), 6.76 (1H, br. s., -O*H*), 6.70-6.65 (2H, m, 5' and 9'-H_{Ar}), 6.57 (1H, s, 8-H_{Ar}), 6.52 (1H, s, 5-H_{Ar}), 3.85 (6H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.46 (1H, t, *J* = 4.9 Hz, CH_a-N), 3.23-3.16 (1H, m, CH_b-N), 2.82-2.64 (4H, m, -CH_2Ph and 3'-CH_2), 2.54 (1H, dd, *J* = 10.0, 5.0 Hz, 1-C*H*), 2.49 (3H, s, NCH_3), 2.16-1.95 (2H, m, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 147.5, 147.4, 146.5, 143.7, 134.6, 129.4, 126.3, 120.9 (+), 114.3 (+), 111.4 (+), 111.2 (+), 110.2 (+), 62.7 (+), 56.1 (+), 56.0 (+), 55.9 (+), 47.8 (-), 42.5 (+), 37.2 (-), 31.5 (-), 25.1 (-). *ee* value: 89 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 16.70 min (minor, 5.5 %), t_{R2} = 31.86 min (major, 94.4 %), $[\alpha]_D^{25}$ = -4.3 (c = 0.025, EtOH). HRMS (ESI): calcd. for $C_{21}H_{28}NO_4$ $[M+H]^+$: 358.2013, found: 358.2009.

*(R)-6,7-Dimethoxy-1-(3-hydroxy-4-methoxyphenethyl)-N-methyl-1,2,3,4-tetrahydroisoquinoline (**(R)-7h**)*. Following general procedure, compound **(*R*)-7h** was obtained as a brown oil 0.15 g (0.46 mmol, 92 %); R_f [CH_2Cl_2/MeOH 10:1] = 0.42; IR (liquid film): 3455 $\nu_{(OH)}$, 2931 $\nu_{(CH2\text{-}Ar)}$, 2838 $\nu_{(OCH3)}$, 2792 $\nu_{(N\text{-}C)}$, 1604 $\nu_{(C\text{-}C)}$, 1511 $\nu_{(C\text{-}N)}$, 1265 $\nu_{(CH3)}$, 1126 $\nu_{(C\text{-}O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.98 (1H, br. s., -O*H*), 6.77 (1H, d, *J* = 1.2 Hz, 5'-H_{Ar}), 6.75 (1H, d, *J* = 8.3 Hz, 8'-H_{Ar}), 6.65 (1H, dd, *J* = 7.8, 1.5 Hz, 9'-H_{Ar}), 6.56 (1H, s, 8-H_{Ar}), 6.54 (1H, s, 5-H_{Ar}), 3.85 (6H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.42 (1H, t, *J* = 5.3 Hz, CH_a-N), 3.16-3.10 (1H, m, CH_b-N), 2.80-2.60 (4H, m, -CH_2Ph and 3'-CH_2), 2.50 (1H, dd, *J* = 8.8, 6.6 Hz, 1-C*H*), 2.47 (3H, s, NCH_3), 2.05-1.99 (2H, m, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 147.4, 147.3, 145.6, 144.7, 136.3, 129.9, 126.7, 119.8 (+), 114.8 (+), 111.4 (+), 110.7 (+), 110.1 (+), 62.7 (+), 56.1 (2C, +), 55.9 (+), 48.2 (-), 42.7 (+), 37.0 (-), 31.1 (-), 25.5 (-). *ee* value: 89 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 17.06 min (minor, 5.6 %), t_{R2} = 25.01 min (major, 94.3 %), $[\alpha]_D^{25}$ = -4.0 (c = 0.025, EtOH). HRMS (ESI): calcd. for $C_{21}H_{28}NO_4$ $[M+H]^+$: 358.2013, found: 358.2017.

*(R)-6,7-Dimethoxy-1-(4-hydroxy-3,5-dimethoxyphenethyl)-N-methyl-1,2,3,4-tetrahydroisoquinoline (**(R)-7i**)*. Following general procedure, compound **(*R*)-7i** was obtained as a brown oil 0.16 g (0.45 mmol, 90 %); R_f [CH_2Cl_2/MeOH 10:1] = 0.40; IR (liquid film): 3425 $\nu_{(OH)}$, 2931 $\nu_{(CH2\text{-}Ar)}$, 2854 $\nu_{(OCH3)}$, 2792 $\nu_{(N\text{-}C)}$, 1604 $\nu_{(C\text{-}C)}$, 1511 $\nu_{(C\text{-}N)}$, 1249 $\nu_{(CH3)}$, 1110 $\nu_{(C\text{-}O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.05 (1H, br. s., -O*H*), 6.58 (1H, s, 8-H_{Ar}), 6.50 (1H, s, 5-H_{Ar}), 6.43 (2H, s, 5' and 9'-H_{Ar}), 3.86 (6H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.51 (1H, t, *J* = 5.6

Hz, CH_a-N), 3.28-3.20 (1H, m, CH_b-N), 2.85-2.67 (4H, m, -CH_2Ph and 3'-CH_2), 2.75 (1H, dd, J = 9.6, 4.8 Hz, 1-C*H*), 2.52 (3H, s, NCH_3), 2.21-1.94 (2H, m, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 147.7, 147.5, 147.0 (2C), 133.8 111.4 (+), 110.3 (+), 105.1 (2C, +), 62.7 (+), 56.4 (2C, +), 56.1 (+), 55.9 (+), 45.9 (-), 42.3 (+), 37.1 (-), 32.0 (-), 24.7 (-). *ee* value: 94 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 27.10 min (minor, 3.0 %), t_{R2} = 36.48 min (major, 96.9 %), $[\alpha]_D^{25}$ = -9.3 (c = 0.025, EtOH). HRMS (ESI): calcd. for $C_{22}H_{30}NO_5$ $[M+H]^+$: 388.2118, found: 388.2122.

(S)-6,7-Dimethoxy-N-methyl-1-phenethyl-1,2,3,4-tetrahydroisoquinoline ***((S)-7a)****.* Following general procedure, compound **(*S*)-7a** was obtained as a yellow oil 0.14 g (0.45 mmol, 95 %); R_f [CH_2Cl_2/MeOH 10:1] = 0.65; IR (liquid film): 2931 $\nu_{(CH2-Ar)}$, 2838 $\nu_{(OCH3)}$, 2792 $\nu_{(N-C)}$, 1604 $\nu_{(C-C)}$, 1511 $\nu_{(C-N)}$, 1218 $\nu_{(CH3)}$, 1110 $\nu_{(C-O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.29-7.25 (2H, m, 5' and 9'-H_{Ar}), 7.19-7.16 (3H, m, 6', 7' and 8'-H_{Ar}), 6.57 (1H, s, 8-H_{Ar}), 6.55 (1H, s, 5-H_{Ar}), 3.86 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.43 (1H, t, J = 5.4 Hz, CH_a-N), 3.18-3.11 (1H, m, CH_b-N), 2.81-2.67 (4H, m, -CH_2Ph and 3'-CH_2), 2.61-2.53 (1H, m, 1-C*H*), 2.48 (3H, s, NCH_3), 2.07 (2H, ddd, J = 13.1, 7.4, 5.5 Hz, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 147.4, 147.3, 143.1, 129.9, 128.5 (2C, +), 128.4 (2C, +), 126.8, 125.7 (+), 111.4 (+), 110.1 (+), 62.9 (+), 56.1 (+), 55.9 (+), 48.3 (-), 42.8 (+), 36.9 (-), 31.7 (-), 25.6 (-). *ee* value: 93 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 5.97 min (major, 96.5 %), t_{R2} = 8.33 min (minor, 3.4 %), $[\alpha]_D^{25}$ = +7.9 (c = 0.025, EtOH). HRMS (ESI): calcd. for $C_{20}H_{26}NO_2$ $[M+H]^+$: 312.1958, found: 312.1961.

(S)-6,7-Dimethoxy-1-(4-methoxyphenethyl)-N-methyl-1,2,3,4-tetrahydroisoquinoline ***((S)-7b)****.* Following general procedure, compound **(*S*)-7b** was obtained as a yellow oil 0.15 g (0.45 mmol, 91 %); R_f [CH_2Cl_2/MeOH 10:1] = 0.61; IR (liquid film): 2931 $\nu_{(CH2-Ar)}$, 2838 $\nu_{(OCH3)}$, 2792 $\nu_{(N-C)}$, 1604 $\nu_{(C-C)}$, 1511 $\nu_{(C-N)}$, 1249 $\nu_{(CH3)}$, 1033 $\nu_{(C-O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.10 (2H, d, J = 8.7 Hz, 6' and 8'-H_{Ar}), 6.82 (2H, d, J = 8.7 Hz, 5' and 9'-H_{Ar}), 6.57 (1H, s, 8-H_{Ar}), 6.54 (1H, s, 5-H_{Ar}), 3.85 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.41 (1H, t, J = 5.4 Hz, CH_a-N), 3.18-3.11 (1H, m, CH_b-N), 2.79-2.64 (4H, m, -CH_2Ph and 3'-CH_2), 2.52 (1H, dd, J = 15.0, 8.0 Hz, 1-C*H*), 2.47 (3H, s, NCH_3), 2.05-1.99 (2H, m, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 157.7, 147.4, 147.3, 135.1, 130.0, 129.4 (2C, +), 126.8, 113.8 (2C, +), 111.4 (+), 110.1 (+), 62.8 (+), 56.1 (+), 55.9 (+), 55.3 (+), 48.2 (-), 42.8 (+), 37.2 (-), 30.8 (-), 25.5 (-). *ee* value: 92 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 6.45 min (major, 95.8 %), t_{R2} = 11.05 min (minor, 4.1 %), $[\alpha]_D^{25}$ = +6.3 (c = 0.025, EtOH)- HRMS (ESI): calcd. for $C_{21}H_{28}NO_3$ $[M+H]^+$: 342.2064, found: 342.2060.

(S)-6,7-Dimethoxy-1-(3,4-dimethoxyphenethyl)-N-methyl-1,2,3,4-tetrahydroisoquinoline ***((S)-7c)***. Following general procedure, compound **(*S*)-7c** was obtained as a yellow oil 0.18 g (0.47 mmol, 94 %); R_f [CH_2Cl_2/MeOH 10:1] = 0.59; IR (liquid film): 2931 $\nu_{(CH2\text{-}Ar)}$, 2838 $\nu_{(OCH3)}$, 2792 $\nu_{(N\text{-}C)}$, 1604 $\nu_{(C\text{-}C)}$, 1511 $\nu_{(C\text{-}N)}$, 1265 $\nu_{(CH3)}$, 1041 $\nu_{(C\text{-}O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.79 (1H, d, *J* = 7.8 Hz, 8'-H_{Ar}), 6.74-6.71 (2H, m, 5' and 9'-H_{Ar}), 6.57 (1H, s, 8-H_{Ar}), 6.54 (1H, s, 5-H_{Ar}), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.42 (1H, t, *J* = 5.5 Hz, CH_a-N), 3.18-3.11 (1H, m, CH_b-N), 2.81-2.64 (4H, m, -CH_2Ph and 3'-CH_2), 2.56-2.49 (1H, m, 1-C*H*), 2.47 (3H, s, NCH_3), 2.07-2.00 (2H, m, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 148.9, 147.4 (2C), 147.1, 135.6, 129.9, 126.8, 120.2 (+), 112.0 (+), 111.4 (+), 111.3 (+), 110.2 (+), 62.7 (+), 56.1 (+), 56.0 (+), 55.9 (2C, +), 48.0 (-), 42.7 (+), 37.1 (-), 31.4 (-), 25.4 (-). *ee* value: 91 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 12.51 min (major, 95.4 %), t_{R2} = 23.52 min (minor, 4.5 %), $[\alpha]_D^{25}$ = +4.7 (c = 0.025, EtOH) (lit. $[\alpha]_D^{18}$ = +10.5 (c = 0.16, EtOH)).[9] HRMS (ESI): calcd. for $C_{22}H_{30}NO_4$ $[M+H]^+$: 372.2169, found: 372.2173.

(S)-6,7-Dimethoxy-1-(3,4,5-trimethoxyphenethyl)-N-methyl-1,2,3,4-tetrahydroisoquinoline ***((S)-7d)***. Following general procedure, compound **(*S*)-7d** was obtained as a yellow oil 0.17 g (0.43 mmol, 86 %); R_f [CH_2Cl_2/MeOH 10:1] = 0.52; IR (liquid film): 2931 $\nu_{(CH2\text{-}Ar)}$, 2838 $\nu_{(OCH3)}$, 2792 $\nu_{(N\text{-}C)}$, 1589 $\nu_{(C\text{-}C)}$, 1511 $\nu_{(C\text{-}N)}$, 1249 $\nu_{(CH3)}$, 1026 $\nu_{(C\text{-}O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.58 (1H, s, 8-H_{Ar}), 6.54 (1H, s, 5-H_{Ar}), 6.39 (2H, s, 5' and 9'-H_{Ar}) 3.85 (3H, s, OCH_3), 3.83 (6H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.44 (1H, t, *J* = 5.4 Hz, CH_a-N), 3.19-3.12 (1H, m, CH_b-N), 2.80-2.64 (4H, m, -CH_2Ph and 3'-CH_2), 2.52 (1H, dd, *J* = 15.0, 7.8 Hz, 1-C*H*), 2.48 (3H, s, NCH_3), 2.05 (2H, dt, *J* = 13.1, 6.7 Hz, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 153.0 (2C), 147.3, 147.2, 138.7, 135.9, 129.7, 126.7, 111.3 (+), 110.1 (+), 105.3 (2C, +), 62.7 (+), 60.8 (+), 56.0 (2C, +), 56.0 (+), 55.8 (+), 47.9 (-), 42.7 (+), 36.8 (-), 32.0 (-), 25.3 (-). *ee* value: 94 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 13.07 min (major, 97.0 %), t_{R2} = 21.18 min (minor, 2.9 %), $[\alpha]_D^{25}$ = +8.7 (c = 0.025, EtOH) (lit. $[\alpha]_D^{25}$ = +6.1 (c = 0.92, MeOH)).[5] HRMS (ESI): calcd. for $C_{23}H_{32}NO_5$ $[M+H]^+$: 402.2275, found: 402.2278.

(S)-6,7-Dimethoxy-1-(3,4-methylendioxyphenethyl)-N-methyl-1,2,3,4-tetrahydroisoquinoline ***((S)-7e)***. Following general procedure, compound **(*S*)-7e** was obtained as a yellow oil 0.16 g (0.47 mmol, 94 %); R_f [CH_2Cl_2/MeOH 10:1] = 0.60; IR (liquid film): 2931 $\nu_{(CH2\text{-}Ar)}$, 2838 $\nu_{(OCH3)}$, 2792 $\nu_{(N\text{-}C)}$, 1604 $\nu_{(C\text{-}C)}$, 1511 $\nu_{(C\text{-}N)}$, 1357, $\nu_{(\text{-}OCH2O\text{-})}$, 1249 $\nu_{(CH3)}$, 1110 $\nu_{(C\text{-}O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.71 (1H, d, *J* = 7.9 Hz, 8'-H_{Ar}), 6.67 (1H, d, *J* = 1.4 Hz, 5'-H_{Ar}), 6.62 (1H, dd, *J* = 7.9, 1.6 Hz,

9'-H_{Ar}), 6.56 (1H, s, 8-H_{Ar}), 6.53 (1H, s, 5-H_{Ar}), 5.90 (2H, s, -OCH_2O-), 3.85 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.40 (1H, t, J = 5.5 Hz, CH_a-N), 3.16-3.09 (1H, m, CH_b-N), 2.79-2.61 (4H, m, -CH_2Ph and 3'-CH_2), 2.52-2.47 (1H, m, 1-CH), 2.46 (3H, s, NCH_3), 2.01 (2H, dt, J = 13.0, 6.7 Hz, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 147.6, 147.4, 147.3, 145.5, 136.9, 129.9, 126.8, 121.2 (+), 111.4 (+), 110.1 (+), 109.0 (+), 108.2 (+), 100.8 (-), 62.7 (+), 56.1 (+), 55.9 (+), 48.2 (-), 42.8 (+), 37.2 (-), 31.4 (-), 25.5 (+). *ee* value: 93 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 7.83 min (major, 96.6 %), t_{R2} = 12.85 min (minor, 3.3 %), $[\alpha]_D^{25}$ = +6.4 (c = 0.025, EtOH) (lit. $[\alpha]_D^{25}$ = +21.3 (c = 0.37, EtOH)).[11] HRMS (ESI): calcd. for $C_{21}H_{26}NO_4$ $[M+H]^+$: 356.1856, found: 356.1853.

(S)-6,7-Dimethoxy-1-(4-hydroxyphenethyl)-N-methyl-1,2,3,4-tetrahydroisoquinoline ***((S)-7f)***. Following general procedure, compound **(*S*)-7f** was obtained as a red oil 0.14 g (0.45 mmol, 90 %); R_f [CH_2Cl_2/MeOH 10:1] = 0.47; IR (liquid film): 3455 $\nu_{(OH)}$, 2946 $\nu_{(CH2-Ar)}$, 2838 $\nu_{(OCH3)}$, 2792 $\nu_{(N-C)}$, 1604 $\nu_{(C-C)}$, 1511 $\nu_{(C-N)}$, 1249 $\nu_{(CH3)}$, 1110 $\nu_{(C-O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.03 (1H, br. s., -OH), 6.99 (2H, d, J = 8.4 Hz, 6' and 8'-H_{Ar}), 6.70 (2H, d, J = 8.5 Hz, 5' and 9'-H_{Ar}), 6.57 (1H, s, 8-H_{Ar}), 6.53 (1H, s, 5-H_{Ar}), 3.85 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.45 (1H, t, J = 5.5 Hz, CH_a-N), 3.22-3.15 (1H, m, CH_b-N), 2.83-2.62 (4H, m, -CH_2Ph y 3'-CH_2), 2.54 (1H, dd, J = 9.9, 5.3 Hz, 1-CH), 2.47 (3H, s, NCH_3), 2.11-1.93 (2H, ddd, m, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 154.3, 147.5, 147.3, 134.2, 129.6, 129.5 (2C, +), 126.3, 115.5 (2C, +), 111.5 (+), 110.4 (+), 62.7 (+), 56.1 (+), 55.9 (+), 47.5 (-), 42.4 (+), 37.2 (-), 31.2 (-), 25.0 (-). *ee* value: 93 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 13.21 min (major, 96.6 %), t_{R2} = 32.23 min (minor, 3.3 %), $[\alpha]_D^{25}$ = +6.9 (c = 0.025, EtOH). HRMS (ESI): calcd. for $C_{20}H_{26}NO_3$ $[M+H]^+$: 328.1907, found: 328.19011.

(S)-6,7-Dimethoxy-1-(4-hydroxy-3-methoxyphenethyl)-N-methyl-1,2,3,4-tetrahydroisoquinoline ***((S)-7g)***. Following general procedure, compound **(*S*)-7g** was obtained as a brown oil 0.16 g (0.47 mmol, 95 %); R_f [CH_2Cl_2/MeOH 10:1] = 0.43; IR (liquid film): 3440 $\nu_{(OH)}$, 2931 $\nu_{(CH2-Ar)}$, 2854 $\nu_{(OCH3)}$, 2792 $\nu_{(N-C)}$, 1604 $\nu_{(C-C)}$, 1511 $\nu_{(C-N)}$, 1265 $\nu_{(CH3)}$, 1110 $\nu_{(C-O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.80 (2H, dd, J = 7.4, 4.8 Hz, 5' and 8'-H_{Ar}), 6.76 (1H, br. s., -OH), 6.66 (1H, dd, J = 8.0, 1.5 Hz, 9'-H_{Ar}), 6.59 (1H, s, 8-H_{Ar}), 6.45 (1H, s, 5-H_{Ar}), 3.85 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.44-3.35 (1H, m, CH_a-N), 3.09-2.99 (1H, m, CH_b-N), 2.91-2.74 (4H, m, -CH_2Ph and 3'-CH_2), 2.65 (1H, dd, J = 9.1, 5.6 Hz, 1-CH), 2.46 (3H, s, NCH_3), 2.07-1.91 (2H, m, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 148.3, 147.8, 146.8, 144.1, 133.0, 126.1, 123.9, 120.9 (+), 114.5 (+), 111.4 (+), 111.3 (+), 110.3 (+), 62.7 (+), 56.1 (+), 56.1 (+), 55.9 (+), 46.4 (-), 41.3 (+), 36.7 (-), 31.6 (-), 23.5 (-). *ee* value: 97 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 16.53 min

(major, 98.2 %), t_{R2} = 31.15 min (minor, 1.7 %), $[\alpha]_D^{25}$ = +14.9 (c = 0.025, EtOH). HRMS (ESI): calcd. for $C_{21}H_{28}NO_4$ $[M+H]^+$: 358.2013, found: 358.2016.

*(S)-6,7-Dimethoxy-1-(3-hydroxy-4-methoxyphenethyl)-N-methyl-1,2,3,4-tetrahydroisoquinoline (**(S)-7h**)*. Following general procedure, compound **(*S*)-7h** was obtained as a brown oil 0.15 g (0.46 mmol, 92 %); R_f [CH_2Cl_2/MeOH 10:1] = 0.42; IR (liquid film): 3455 $\nu_{(OH)}$, 2931 $\nu_{(CH2\text{-}Ar)}$, 2838 $\nu_{(OCH3)}$, 2792 $\nu_{(N\text{-}C)}$, 1604 $\nu_{(C\text{-}C)}$, 1511 $\nu_{(C\text{-}N)}$, 1265 $\nu_{(CH3)}$, 1126 $\nu_{(C\text{-}O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 6.98 (1H, br. s., -O*H*), 6.77 (1H, d, *J* = 2.0 Hz, 5'-H_{Ar}), 6.75 (1H, d, *J* = 8.2 Hz, 8'-H_{Ar}), 6.65 (1H, dd, *J* = 8.2, 2.0 Hz, 9'-H_{Ar}), 6.56 (1H, s, 8-H_{Ar}), 6.54 (1H, s, 5-H_{Ar}), 3.85 (6H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.42 (1H, t, *J* = 5.4 Hz, CH_a-N), 3.17-3.10 (1H, m, CH_b-N), 2.79-2.60 (4H, m, -CH_2Ph and 3'-CH_2), 2.50 (1H, dd, *J* = 8.8, 6.3 Hz, 1-C*H*), 2.47 (3H, s, NCH_3), 2.06-1.98 (2H, ddd, m, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 147.4, 147.3, 145.6, 144.7, 136.3, 129.9, 126.7, 119.8 (+), 114.8 (+), 111.4 (+), 110.7 (+), 110.1 (+), 62.7 (+), 56.1 (2C, +), 55.9 (+), 48.2 (-), 42.7 (+), 37.0 (-), 31.1 (-), 25.5 (-). *ee* value: 89 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 16.67 min (major, 94.6 %), t_{R2} = 26.48 min (minor, 5.3 %), $[\alpha]_D^{25}$ = +4.0 (c = 0.025, EtOH). HRMS (ESI): calcd. for $C_{21}H_{28}NO_4$ $[M+H]^+$: 358.2013, found: 358.2017.

*(S)-6,7-Dimethoxy-1-(4-hydroxy-3,5-dimethoxyphenethyl)-N-methyl-1,2,3,4-tetrahydroisoquinoline (**(S)-7i**)*. Following general procedure, compound **(*S*)-7i** was obtained as a brown oil 0.16 g (0.45 mmol, 90 %); R_f [CH_2Cl_2/MeOH 10:1] = 0.40; IR (liquid film): 3425 $\nu_{(OH)}$, 2931 $\nu_{(CH2\text{-}Ar)}$, 2854 $\nu_{(OCH3)}$, 2792 $\nu_{(N\text{-}C)}$, 1604 $\nu_{(C\text{-}C)}$, 1511 $\nu_{(C\text{-}N)}$, 1249 $\nu_{(CH3)}$, 1110 $\nu_{(C\text{-}O)}$ cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_{(ppm)}$: 7.05 (1H, br. s., -O*H*), 6.58 (1H, s, 8-H_{Ar}), 6.52 (1H, s, 5-H_{Ar}), 6.41 (2H, s, 5' and 9'-H_{Ar}), 3.86 (6H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.46 (1H, t, *J* = 5.7 Hz, CH_a-N), 3.24-3.16 (1H, m, CH_b-N), 2.85-2.64 (4H, m, -CH_2Ph and 3'-CH_2), 2.54 (1H, dd, *J* = 9.8, 4.8 Hz, 1-C*H*), 2.50 (3H, s, NCH_3), 2.05 (2H, tdd, *J* = 23.2, 16.2 Hz, 2'-CH_2). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_{(ppm)}$: 147.5, 147.5, 147.0 (2C), 143.2, 133.8, 132.8, 126.3, 111.4 (+), 110.3 (+), 105.1 (2C, +), 62.7 (+), 56.4 (2C, +), 56.1 (+), 55.9 (+), 47.7 (-), 42.5 (+), 37.2 (-), 32.0 (-), 25.0 (-). *ee* value: 95 % (HPLC conditions: KROMASIL® 5-CelluCoat 4.6 x 250 mm, elute: hexane/*i*-PrOH = 90/10, 0.1 % DEA, λ = 254 nm, flow rate: 1.0 mL/min, 25 °C); t_{R1} = 24.58 min (major, 97.5 %), t_{R2} = 36.19 min (minor, 2.4 %), $[\alpha]_D^{25}$ = +10.2 (c = 0.025, EtOH). HRMS (ESI): calcd. for $C_{22}H_{30}NO_5$ $[M+H]^+$: 388.2118, found: 388.2115.

Toxicity assessment of (*R*)-7a-i and (*S*)-7a-i *Dysoxylum* alkaloids using the zebrafish embryo model. Wild-type adult zebrafish of both sexes were separated in two tanks (30 L each), according to their gender, at 26 ± 2 °C under natural light-dark photoperiods. Fishes were feed twice daily and the water quality was recorded weekly, in order to acclimate the fishes for at least two weeks before

experiments begin. For the reproduction of the adult fishes, small breeding tanks were set up in the evening previous to experiment, each containing three males and one female specimen. The tanks were isolated until next morning when the lights switch on and the natural mating occurs, without any perturbation.

The adult fishes were returned to their corresponding tank and the embryos were collected, pooled and washed with E3 medium and transferred into a 92 mm glass Petri dish. Further, dead, delayed, malformed and unfertilized embryos were identified under a dissecting microscope and removed by select aspiration with a pipette. This last procedure was repeated at 12 and 20 hpf in order to remove the unfit embryos. Throughout this period of time, the embryos were kept at 28 ± 2 °C in an incubator under natural light-dark photoperiods.

The selected embryos of 24 hpf from the Petri dish were gently distributed into 96-well plates, placing a single embryo and 200 μL of E3 medium per well.

Adult zebrafish were care and used according to the Guide of the National Institute of Health for Care and Use of Laboratory Animals, keep them healthy and free of any signs of disease. The Ethics and Research Committee of the Heart Institute of Bucaramanga approved the protocol under the Acta Number 050 of May 26 of 2012.

Determination of zebrafish embryo LC_{50}. For this experiment, in total 72 embryos were required per sample in order to run three independent experiments in three different plates, and each compound was evaluated three times in the same plate, allowing the evaluation of four samples peer plate. In the range of concentrations established by a geometric series, starting from 12.5 and finishing in 1250 μM, the determination of the LC_{50} (expressed in μmol of compound/L of solution) was based on the cumulative mortality after 72 hours of chemical exposure (96 hpf). Each embryo was examined under a dissecting microscope and the statistical analysis was made using Regression Probit analysis with *SPSS* for windows version 19.0. Data are expressed as the standard error of the mean (SEM) of three different experiments in triplicate.

ASSOCIATED CONTENT

The supporting information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.xxxxxxx

Copies of ^{1}H NMR, $^{13}C\{^{1}H\}$ NMR and DEPT-135 spectra of all synthetized compounds and copies of chiral HPLC chromatograms of *Dysoxylum* alkaloids.

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