Synthesis and dopaminergic activity of a series of new 1-aryl tetrahydroisoquinolines and 2-substituted 1-aryl-3-tetrahydrobenzazepines

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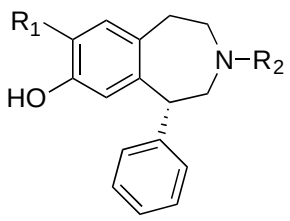
Abstract. A series of new 1-aryl-6,7-dihydroxy tetrahydroisoquinolines with several substitution patterns in the 1-aryl group at C-1 were prepared in good yields. The influence of each substituent on the affinity and selectivity for D_1 and D_2 dopaminergic receptors was studied. Moreover, *N*-alkyl salts of these tetrahydroisoquinolines were used as starting material to synthesize a series of new 1-aryl-7,8-dihydroxy 3-tetrahydrobenzazepines derivatives with electron-withdrawing substituents at C-2 position by the diastereoselective Stevens rearrangement. The structure-activity relationship of these compounds was explored to evaluate the effect of the functional group at C-2 in benzazepines and the modification in the aryl group at the isoquinoline C-1 position towards the affinity and selectivity for the mentioned receptors. The 1-aryl-6,7-dihydroxy tetrahydroisoquinoline **4c** shows significant affinity towards D_2 receptor, with K_i value of 31 nM. This significant affinity can be attributed to the presence of a thiomethyl group, and it is the most active 1-aryl-6,7-dihydroxy tetrahydroisoquinoline derivative reported to date.

Keywords: tetrahydroisoquinolines / 3-tetrahydrobenzazepines / Stevens rearrangement / dopamine receptors / binding

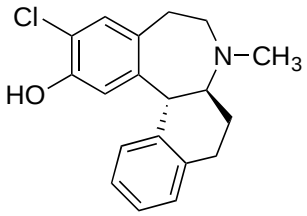
1. Introduction

Dopamine is a significant neurotransmitter present in the central nervous system of mammals that regulates several biological functions, such as coordination, motivation, emotion, learning and memory. Based on their pharmacology, dopaminergic receptors can be considered as two G-protein-coupled receptor families: the D_1-like receptors, including D_1 and D_5 receptor subtypes, which activate adenylyl cyclase enzyme; and the D_2-like receptors, containing D_2, D_3 and D_4 receptor subtypes, which inhibit the mentioned enzyme.[1] During the last few decades, dopaminergic ligands have remained a very active area of research for the development of pharmaceutical products.[2]

The 1-substituted 3-tetrahydrobenzazepines are known to act as dopamine receptor agonists and antagonists.[2,3] These compounds show activity in animal models against several neurological illnesses, such as Parkinson`s[4] and Alzheimer`s[5] diseases. In fact, the discovery of SCH 23390,[6] one of the first selective dopamine D_1-like receptor antagonist, and the ethylene bridged restricted tetrahydrobenzazepine (THB) derivative, SCH 39166,[7] represented a great advance in the dopaminergic receptor studies (Figure 1).



SCH 23390 R_1=Cl, R_2=CH_3
SCH 24518 R_1=Cl, R_2=H
SKF 75670 R_1=OH, R_2=CH_3
SKF 38393 R_1=OH, R_2=H

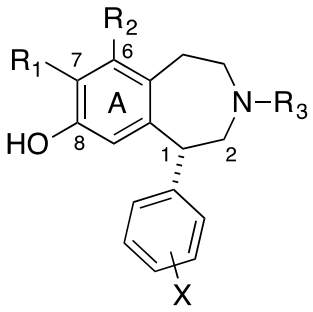


SCH 39166

Figure 1: Structures of active 3-tetrahydrobenzazepines

SCH 39166, also known as ecopipam, improve the overall pharmacological profile of SCH 23390, maintaining similar affinity and selectivity as D_1/D_5 antagonist, however both of them have low oral bioavailability.[8] These two compounds are reference for the design of novel dopaminergic ligands as possible new drugs, and a variety of analogues, such as SCH 24518,[9] SKF 75670[10] and SKF 38393,[11] have been developed, the latter being considered as the model for new D_1 receptor agonist.

Regarding the structure-activity relationship (SAR), isosteres of catecholic 1-aryl-3-tetrahydrobenzazepines, a convenient substitution at the nitrogen atom and/or in C-6 position, the substitution pattern on the 1-phenyl group, and the presence of an azepine ring, are structural modifications that modulate selectivity and improve affinity of this family of compounds towards dopaminergic receptors (see Figure 2).[2,3,12]



R_1= -OH, -Cl, -Br
R_2= -F, -Cl, -Br, -Aryl
R_3= -H, -Me, -Allyl, -Alkyl
X= -NH_2,-NHMe, -Me, -Cl, -Br, -OH

Figure 2: Reported 1-aryl-3-tetrahydrobenzazepine structure requirements for high activity

For example, the absence of a methyl group at nitrogen atom in the SCH 24518 (*nor*-SCH 23390)9 or the presence of a bromophenyl moiety at C-1[13] increase the D_2 receptor affinity, compared with the prototype SCH 23390 (Figure 1). However, the change of chloride for bromine in C-7 position improved the affinity for D_1 receptors.[14] In the case of the 7,8-dihydroxy-1-phenyl-3-tetrahydrobenzazepine SKF 38393 (Figure 1), the absence of the methyl group at nitrogen causes a decrease of the activity against both receptors.[15]

Moreover, other compounds containing the phenylethylamine skeleton as part of their structure are potent and selective ligands for dopaminergic receptors (Figure 3).[16] 1-Substituted tetrahydroisoquinolines (THI), ring-contracted derivatives of tetrahydrobenzazepines, have been evaluated for their ability to inhibit the dopamine transporter and to display affinity at dopaminergic receptors binding sites in rat brain tissue.[17] The presence of phenolic hydroxyl groups in the ring A is necessary for a better binding of this type of compounds to dopaminergic receptors.[18] However, most of the reported structural modifications for THI are located at nitrogen (*N*-alkyl or *nor* derivatives) or at C-1 position (1-phenyl, 1-alkyl or 1-benzyl compounds),[17,19] and the majority of the synthesized THI presents a 6-chloro-7-hydroxy tetrahydroisoquinoline core, being selective for D_1 receptors.[19a] On the other hand, 1-butyl and 1-benzyl derivatives present high affinity for D_2-like receptors due to the flexibility of these substituents.[19c] Consequently, the substitution pattern at the C-1 position, is an essential factor.

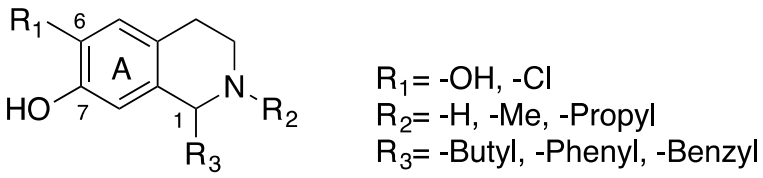


Figure 3: Reported structure-activity tetrahydroisoquinoline requirements to modulate dopaminergic activity.

In addition, regarding the activity of this family of compounds, 7,8-dihydroxy-1-aryl tetrahydroisoquinoline analogues have also been reported as anti-HIV compounds.[20]

In this paper, we describe the synthesis of new 1-aryl tetrahydroisoquinolines and 1-aryl-3-tetrahydrobenzazepines with catecholic hydroxyl groups at ring A, and different substituents, such as hydroxyl, nitro, amino, dimethylamino and methylthio groups, at the C-1 aryl group, together with additional electron-withdrawing substituents at the C-2

of the 3-tetrahydrobenzazepines. The binding affinity and selectivity of these compounds at the dopamine receptors are studied to analyze the influence of the substitution pattern.

2. Results and Discussion

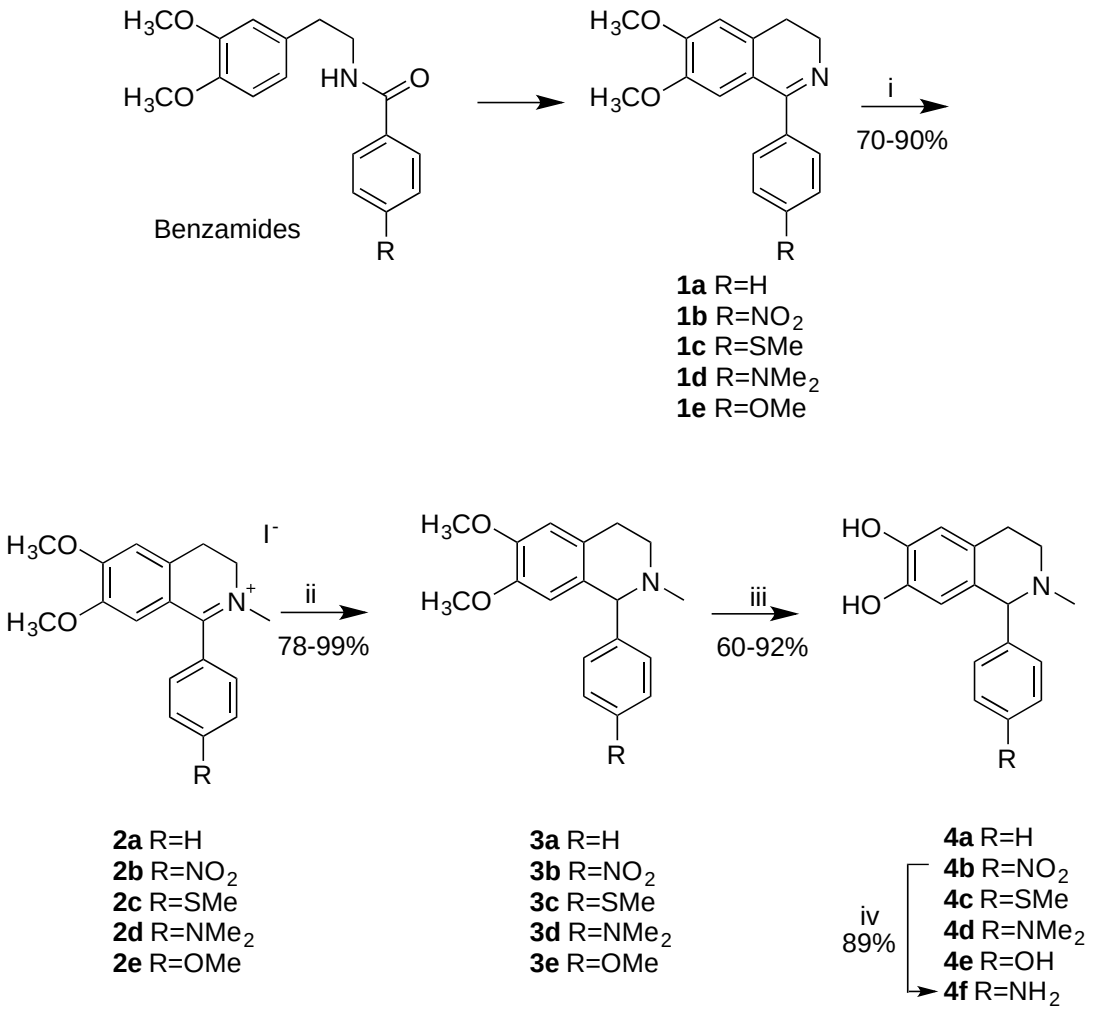
2.1. Synthesis

We have previously described the synthesis of 3-tetrahydrobenzazepines by Stevens rearrangement by using 1-aryl tetrahydroisoquinolinium salts as starting materials.[21] This strategy provides a number of advantages: good yields and mild reaction conditions; a regio- and diastereoselective control of the reaction; broad applicability and versatility to incorporate different groups in the molecule.

Based on these results, new 1,2-disubstituted tetrahydrobenzazepines are synthesized starting from the corresponding benzamide, being intermediate compounds the corresponding 1-aryl tetrahydroisoquinoline derivatives (see Schemes 1 and 2). Starting benzamides were prepared by condensation of 2-(3,4-dimethoxyphenyl)ethylamine and the appropriately substituted arylcarbonyl halide.[22] Then, the ring expansion reaction *via* Stevens rearrangement of a tetrahydroisoquinolinium salt allow the azepine ring construction. The posterior demethylation provides the catecholic structure at ring A, thus complying the requirements previously established for the dopaminergic activity.[18] To avoid side reactions due to the presence of the catechol group on the phenylethylamine moiety, we decided to work with dimethoxy derivatives and to carry out the *O*-demethylation for both structures (R_1= CH_3 → R_1= H, Scheme 1) in the last step of the synthesis.

The synthesis of tetrahydroisoquinolines has been performed as an outline in Scheme 1.[21] The classical Bischler-Napieralski cyclodehydration reaction was used to obtain the dihydroisoquinolines **1a-e**, which by *N*-methylation and reduction afforded the tetrahydroisoquinolines **3a-e**. Finally, the *O*-demethylation of the synthesized

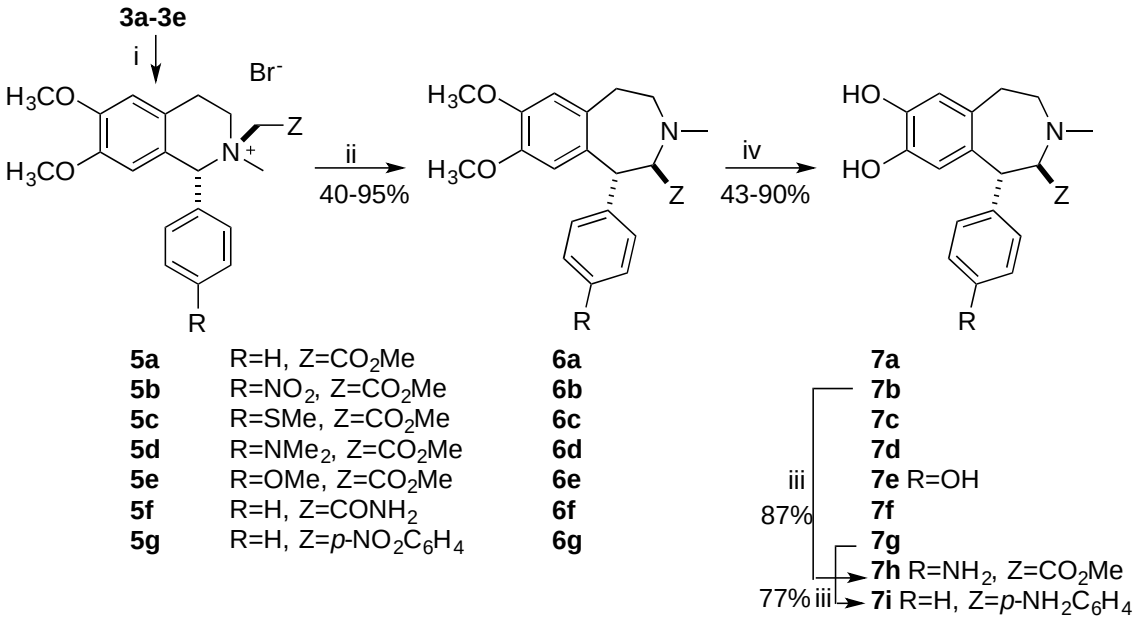
tetrahydroisoquinolines was performed by treatment with 47% HBr aqueous solution followed by basification to pH=8 with sodium bicarbonate, to obtain the resulting phenolic compounds **4a-e**. The compound **4f** was obtained by catalytic hydrogenation of **4b** in good yield.



Scheme 1: Synthesis of **4a-f**: (i) CH_3I/acetone, reflux; for compound **2b** was carried out in CH_3CN; (ii) $NaBH_4$/MeOH, room temperature; (iii) HBr 47%, heat 2 hours to 100ºC; (iv) H_2/ Pd/C/MeOH

The synthesis of 1-aryl-3-tetrahydrobenzazepine analogues is described in Scheme 2 as the result of the Stevens rearrangement of the 1-aryl tetrahydroisoquinolinium salts **5a-g**. The regioselectivity of the ylide formation may be problematic if there is more than one acidic site in the precursor salt. Two prevent this point we observed that electron-withdrawing groups as Z substituent in tetrahydroisoquinolinium salt

exclusively yields 3-tetrahydrobenzazepines, avoiding secondary reactions.[21a] As a consequence, here we used methoxycarbonyl, carbamoyl, *p*-nitrophenyl or *p*-aminophenyl electron-withdrawing groups as *N*-alkylating agents to prepare the tetrahydroisoquinolinium salts **5a-g**.



Scheme 2: Synthesis of **5a-g**, **6a-g** and **7a-i**: (i) $BrCH_2Z$/acetone, room temperature; for **5b**, reflux 168 hours in acetonitrile; for **5f**, $ClCH_2CONH_2$/NaI/acetone; (ii) DBU/CH_3CN, room temperature; (iii) H_2/ Pd/C/MeOH; (iv) BBr_3/CH_2Cl_2, room temperature. The entire compounds **5**, **6** and **7** named in this scheme present *trans* configuration

N-alkylation of compounds **3a-c** and **3f,g** only yielded *trans* diastereoisomer salts, while **5d** and **5e** were obtained as a mixture of diastereoisomers in a *cis:trans* ratio of 1:20 and 1:5, respectively. The relative configuration between H-1 and *N*-methyl group was established by comparison with the previously described NMR data for similar tetrahydroisoquinolinium salts.[21] It should be noted that in the case of **5b** a much longer period of time and reflux in acetonitrile was necessary to complete the *N*-alkylation reaction. The salts **5a**, **5f** and **5g** precipitated from the reaction medium and were obtained in excellent yields. However, all the attempts to isolate the remaining salts invariably failed, so we used the reaction crude directly in the next step.

The application of optimized conditions for the Stevens rearrangement to the salts **5a-g**, *i.e.* 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile at room temperature, afforded the **6a-g** with high regio- and diastereoselectivity. As expected, 3-tetrahydrobenzazepines **6d** and **6e** were obtained in a ratio similar to the *cis/tran* ratio of the starting salts **5d** and **5f**, which is in concordance with the stereochemical control of the Stevens rearrangement. The mixture of diasteroisomers **6d** and **6e** was separated by silica-gel chromatography to obtain the pure *trans* diastereoisomers (**6d**-*trans* and **6e**-*trans*). The relative configuration between H-1 and H-2 in **6a-h** was determined by ^{1}H NMR coupling constants values ($J_{1,2trans}$ 6-8 Hz, $J_{1,2cis}$ <1 Hz), in concordance to data previously reported for other 1,2-disubstituted 3-tetrahydrobenzazepines.[21]

Finally, the demethylation step was carried out using the isomers **6**-*trans* in all the cases. Removal of the *O*-methyl group by refluxing in 47% HBr aqueous solution, under the same reaction conditions used for THI structures, failed and only complexes reaction crudes were obtained. However, the final *O*-demethylation step was achieved by treating **6**-*trans* compounds with BBr_3 in CH_2Cl_2, to obtain 3-tetrahydrobenzazepines **7a-f**-*trans* in good yields. Compounds **7h**-*trans* and **7i**-*trans* were obtained by catalytic hydrogenation of **7b**-*trans* and **7g**-*trans,* respectively (Scheme 2).

2.2. Binding affinities for dopamine receptors

It is known that the 1-aryltetrahydroisoquinolines[17b,17e,19c] and 3-tetrahydrobenzazepines[2,3,11,12] with protected phenolic groups show a lower affinity for D_1 and D_2 dopaminergic receptors than their corresponding catechol derivatives: catechol fragment is an essential feature for effective binding. For this reason, the catechol tetrahydroisoquinolines **4a-f** and 3-tetrahydrobenzazepines **7a-i**-*trans*, were exclusively tested for their ability to displace the selective radioligands of D_1 and D_2 dopaminergic receptors (Figure 4). *In vitro* activity was analyzed on rat striatal

membranes by using [^{3}H]-SCH 23390 and [^{3}H]-Raclopride as radioligands for D_1 and D_2 receptors. The affinities of these compounds towards D_1 and D_2 dopaminergic receptors were determined in competition receptor binding studies.

Previously to study the competition receptor binding experiments, a screening was carried out (at 10^{-6} M concentration) in order to determine the ability to displace the selective radioligand of D_1 and D_2 dopaminergic receptor of each compound **4a-f** and **7a-i**-*trans*.

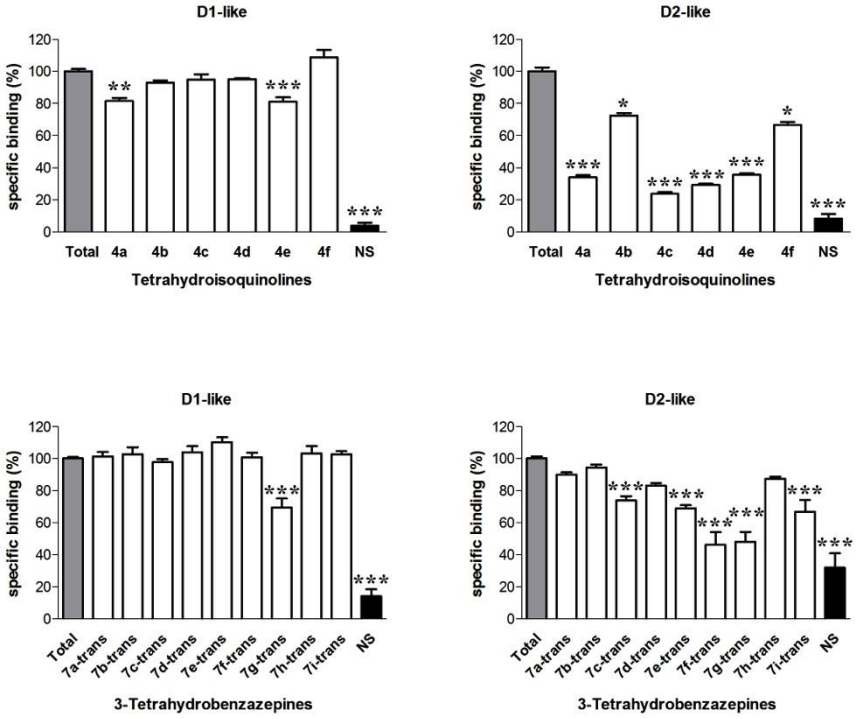


Figure 4: Screening assay to identify tetrahydroisoquinoline and 3-tetrahydrobenzazepine derivative compounds with potential affinity for D_1-like and D_2-like receptors using [^{3}H] SCH 23390 (1 nM) and [^{3}H] raclopride (1 nM), respectively. Data shown are mean values of three independent experiments each performed in duplicates ± SEM, and they are expressed as percentages of total binding (grey bars). Non-specific binding (black bars) was determined in the presence SCH 23390 (50 nM) or butaclamol (50 nM). Differences were set by one-way ANOVA followed by *post hoc* Bonferroni *t* test. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ *vs*. total binding.

As can be seen in Figure 4, the tetrahydroisoquinolines **4b-e**, which are analogues of **4a** with different substituents at *para* position of the 1-aryl group, show similar activity

for D_1 receptor, and some of them **4c**, **4d** and **4e** seems to improve their activity against D_2 receptor.

Taking into account this screening, we carried out competition experiments for those compounds that displaced more than 50% to radioligand in the range of 0.1 mM to 0.1 nM (compounds **4a, 4c**-**e,** Figure 5), to determine their affinity and selectivity towards D_1 and D_2 dopaminergic receptor. Binding affinities for D_1 and D_2 dopaminergic receptors are summarized in Table 1, illustrating some general trends of the structure-activity relationship.

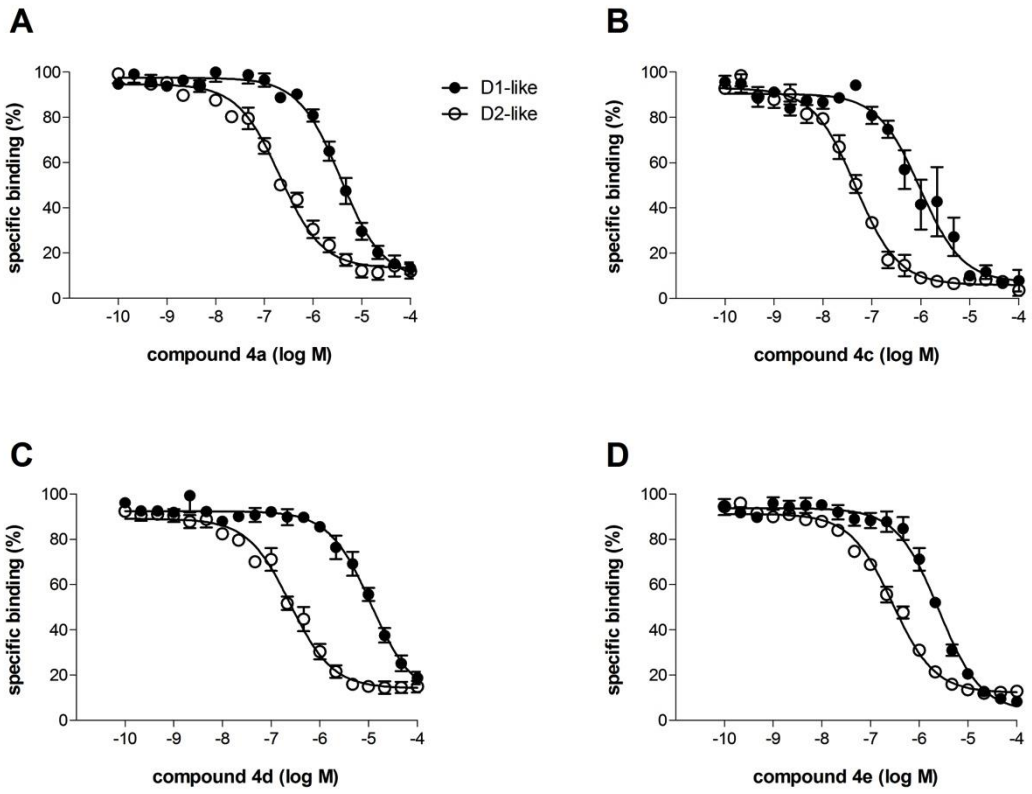


Figure 5: Tetrahydroisoquinoline binding assays. Competition inhibition curves of the tetrahydroisoquinolines 4a (**A**), 4c (**B**), 4d (**C**) and 4e (**D**) *vs.* the D_1-like receptor antagonist [^{3}H] SCH 23390 (●) and the D_2-like receptor antagonist [^{3}H] raclopride (○) in rat striatal membrane preparation.

Table 1. Values of affinity constant (K_i, pK_i) and selectivity (ratio K_i D_1/ K_i D_2) determined by binding experiments to D_1 and D_2 dopaminergic receptor[a]

Compound	D_1		D_2		K_i ratio
	K_i, (nM)	pK_i,	K_i (nM)	pK_i	D_1/D_2
4a[19b]	370 ± 82	-	290 ± 36[b]	-	-
4a	476 ± 136	6.48 ± 0.15	148 ± 32	6.83 ± 0.09	3.2
4c	181 ± 52	6.78 ± 0.14	31 ± 2.9	7.50 ± 0.02	5.8
4d	1953 ± 618	5.73 ± 0.14	173 ± 53	6.79 ± 0.13	11.7
4e	416 ± 62	6.38 ± 0.07	178 ± 24	6.74 ± 0.096	2.3
SKF 75670[15a]	1.9	-	1130[c]	-	-
7f-*trans*	1438 ± 304	5.84 ± 0.09	394 ± 93	6.41 ± 0.10	3.6
7g-*trans*	168 ± 45	6.80 ± 0.13	34 8± 210	6.55 ± 0.30	0.5

[a] Specific radioligands are [^{3}H] SCH 23390 and [^{3}H] raclopide for D_1 and D_2 dopamine receptors respectively. [b] Specific radioligand is [^{3}H] spiperone for D_2. [c] Specific radioligand is [^{3}H] spiroperidol for D_2.

In general, all the tested tetrahydroisoquinolines showed a major affinity for D_2 receptor. In our assay, the racemic **4a** showed K_i values of 476 ± 136 nM for D_1 and 148 ± 32 nM for D_2, which are consistent with the results reported in the literature, where the affinity for D_2 is better than for D_1 receptor (K_i 370 ± 82 nM for D_1 and 290 ± 36 nM for D_2 respectively.[19b]

Compared to compound **4a**, the presence of dimethylamino or hydroxyl substituents in the 1-aryl group did not affect the D_2 binding, and the corresponding compounds **4d** and **4e** showed a K_i value of 173 and 178 nM respectively, statistically the same as that of compound **4a** (148 nM). Although the affinity for D_2 receptor did not substantially change, the increase of selectivity towards D_2 receptor is observed in the case of **4d** (Table 1, **4d** *versus* **4a**, **4c** and **4e**), being the most selective of the prepared compounds.

Regarding compound **4c**, the affinity was substantially increased towards D_2 receptor, with K_i values of 31 ± 2.9 nM. This interesting affinity can be attributed to the presence

of a methylthio group, being the most active 6,7-dihydroxi-1-aryl tetrahydroisoquinoline reported to date, with 4.8-fold improvement if compared with **4a**.

We carried out the same procedure for the 1,2-disubstituted 3-tetrahydrobenzazepines (**7a-i**) to study the dopaminergic activity. As reported in the initial screening (Figure 4), the 3-tetrahydrobenzazepines with an additional substituent at C-2 were not significantly active for D_1 receptor, but some of them appeared to displace the radioligand more than 50% for D_2 dopaminergic receptor. The introduction of a substituent such as a CO_2Me (compound **7a**-**7e**, **7h**) implied a lack of activity for D_1 and D_2 dopaminergic receptors, whereas the substituents $CONH_2$ (**7f**) and *p*-C_6H_4-NO_2 (**7g**) appeared to improve the activity at D_2 dopaminergic receptor, so we carried out the competition binding experiments for these compounds (Figure 6, Table 1).

As shown in Table 1, both **7f** and **7g** benzazepine compounds showed an affinity improvement for D_2 (394 and 348 nM, respectively) comparing with SKF 75670 (D_1 K_i 1.9 nM, D_2 K_i 1130 nM).[15a] Surprisingly, regarding the selectivity for both receptors, **7f** shows better activity for D_2 than for D_1, a different behavior to that previously described for the 3-tetrahydrobenzazepines.

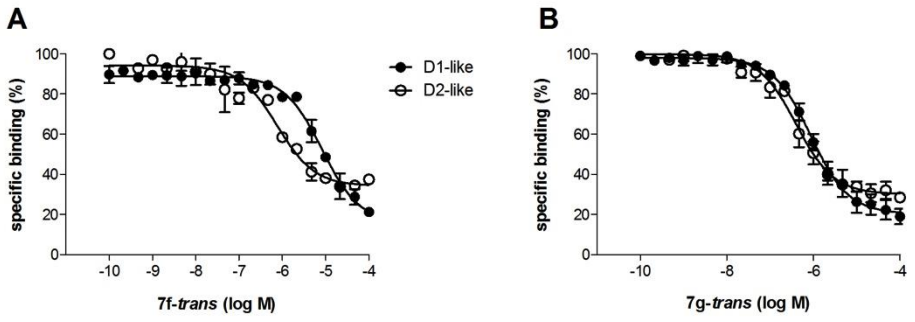


Figure 6: 3-Tetrahydrobenzazepine binding assays. Competition inhibition curves of the 3-tetrahydrobenzazepines **7f**-*trans* (A) and **7g**-*trans* (B) *vs.* the D_1-like receptor antagonist [^{3}H] SCH 23390 (●) and the D_2-like receptor antagonist [^{3}H] raclopride (○) in rat striatal membrane preparation.

3. Conclusions

In summary, a series of new tetrahydroisoquinolines with different substituents at 1-aryl group were synthesized in good yields starting from benzamide derivatives. Salts of the tetrahydroisoquinolines were used as starting material to synthesize a series of new 3-tetrahydrobenzazepines, by using the diastereoselective Stevens rearrangement as the key step of the synthesis. Affinity towards D_1 and D_2 was also analyzed showing the compound **4c**, with a phenyl methylthio ether substituent, a good affinity to D_2 (K_i 31 nM). The other prepared catechol derivatives showed moderate affinities to this receptor.

4. Experimental Section

4.1 General Remarks: Melting points were determined with a Gallenkamp instrument and are uncorrected. EI-MS data were recorded with an HP-MS 5988A spectrometer operating at 70 eV and HMRS data with a VG Autospec spectrometer. NMR spectra were recorded with a Bruker ARX 400 instrument operating at 400 MHz for ^{1}H and 100.6 MHz for ^{13}C NMR spectroscopy. Chemical shifts are given relative to residual $CHCl_3$ (δ = 7.24 ppm) and $CDCl_3$ (δ = 77.0 ppm). All solvents were dried and distilled prior to use. Reaction mixtures were magnetically stirred and monitored by TLC with silica gel 60 F_{254} (Merck) plates. Products were purified by column chromatography with 0.040-0.063 mm silica gel 60.

The compounds 1a,[21a] 1b,[23,24] 1d,[24] 1e,[23b,24,25] 2a,[21a] 3a,[21a] 3e,[26] 4a,[19b] 5a,[21a] 5f,[21a] 5g,[21a] 6a,[21a] 6f,[21a] 6g,[21a] have been prepared by following the reported procedures, and corrected, new or detailed spectroscopic data is included in the supporting information.

4.2. General Procedure for synthesis of 3,4-dihydroisoquinolines (1a-e): A solution of $POCl_3$ (3.7 mL, 40 mmol) in CH_3CN (10 mL) was added dropwise to a solution of the corresponding amide (20 mmol) in CH_3CN (55 mL) under argon. The reaction mixture was heated to reflux for 1 h and concentrated to dryness. The crude material was dissolved in CH_2Cl_2 (50 mL) and washed with a saturated solution of $NaHCO_3$ (3 x 40 mL), NaOH (5%, 2 x 40 mL) and water. The organic layers were dried with anhydrous $MgSO_4$ and concentrated under vacuum to obtain the corresponding isoquinoline.

6,7-Dimethoxy-1-(4-methylthiophenyl)-3,4-dihydroisoquinoline (1c)

Isoquinoline **1c** (2.3 g, 74%) was obtained from the corresponding amide (3.3 g, 10 mmol) as a yellow amorphous solid. M.p. 122-125 ºC. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 7.52 (d, 2H, *J* = 8.5 Hz, H-2´, H-6´), 7.26 (d, 2H, *J* = 8.5 Hz, H-3´, H-5´), 6.77, 6.75 (2 x s, 1H each, H-5, H-8), 3.91, 3.71 (2 x s, 3H each, 2 x OMe), 3.76 (t, 2H, *J* = 7.4 Hz, H-3), 2.70 (t, 2H, *J* = 7.4 Hz, H-4), 2.50 (s, 3H, S-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 166.1 (C-1), 151.0, 147.1 (C-6, C-7), 140.3 (C-4´), 135.5 (C-1´), 132.7 (C-4a), 129.2 (C-2´, C-6´), 125.7 (C-3´, C-5´), 121.3 (C-8a), 111.5, 110.3 (C-5, C-8), 56.1, 55.9 (2 x OMe), 47.4 (C-3), 25.9 (C-4), 15.4 (S-Me) ppm. EI-MS: *m/z* (%) = 314 (20), 313 (M^+, 82), 312 (100), 282 (18), 266 (26). HR-MS: calcd. for $C_{18}H_{20}NO_2S$ $[M + H]^+$ 314.1209*;* found 314.1210.

4.3. *General Procedure for synthesis of N*-methyl-3,4-dihydroisoquinolinium Salts (2a-e): To a solution of the corresponding dihydroisoquinoline (8 mmol) in dry acetone (45 mL) was added CH_3I (3.5 mL, 56 mmol), and the reaction mixture was refluxed for 3 h. After this time, the yellow solid formed was filtered to give the corresponding isoquinolinium salt.

6,7-Dimethoxy-*N*-methyl-1-(4-nitrophenyl)-3,4-dihydroisoquinolinium Iodide (2b)

To a solution of the dihydroisoquinoline **1b** (4.4 g, 14 mmol) in CH_3CN (75 mL) was added dropwise CH_3I (8.2 mL, 131 mmol) and the mixture was heated to reflux for 42 h under argon. After this time, the yellow solid formed was filtered to obtain the isoquinolinium salt **2b** (5.3 g, 83%) as a yellow amorphous solid. M.p. 202-204 ºC. ^{1}H NMR (400 MHz, $CDCl_3$+TFA, 25 ºC): δ = 8.51 (d, 2H, *J* = 8.5 Hz, H-3´, H-5´), 7.82 (d, 2H, *J* = 8.5 Hz, H-2´, H-6´), 6.95 (s, 1H, H-5), 6.28 (s, 1H, H-8), 4.33 (t, 2H, *J* = 8.3 Hz, H-3), 4.03, 3.60 (2 x s, 3H each, 2 x OMe), 3.56 (s, 3H, *N*-Me), 3.41 (t, 2H, *J* = 8.3 Hz, H-4) ppm. ^{13}C NMR (100 MHz, $CDCl_3$+TFA, 25 ºC): δ = 171.8 (C-1), 158.2, 149.9, 148.7 (C-4´, C-6, C-7), 135.4, 134.5 (C-8a, C-1´), 130.2 (C-2´, C6´), 124.7 (C3´, C-5´), 118.8, 111.3 (C-5, C-8), 114.9 (C-4a), 56.9, 56.3 (2 x OMe), 53.0 (C-3), 46.6 (*N*-Me), 25.7 (C-4) ppm. EI-MS: *m/z* (%) = 327 (M^+, 2), 326 (4), 312 (5), 311 (6), 204 (10), 142 (100), 127 (22). HR-MS: calcd. for $C_{18}H_{19}N_2O_4$ $[M - I]^+$ 327.1339*;* found 327.1339.

6,7-Dimethoxy-*N*-methyl-1-(4-methylthiophenyl)-3,4-dihydroisoquinolinium Iodide (2c)

Isoquinolinium salt **2c** (3.3 g, 90%) was obtained from the dihydroisoquinoline **1c** (2.5 g, 8 mmol) as a yellow amorphous solid. M.p. 176-179 ºC. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 7.59 (d, 2H, *J* = 8.4 Hz, H-2´, H-6´), 7.42 (d, 2H, *J* = 8.4 Hz, H-3´, H-5´), 6.87 (s, 1H, H-5), 6.45 (s, 1H, H-8), 4.45 (t, 2H, *J* = 8.0 Hz, H-3), 4.00, 3.77 (2 x s, 3H each, 2 x OMe), 3.62 (s, 3H, *N*-Me), 3.42 (t, 2H, *J* = 8.0 Hz, H-4), 2.55 (s, 3H, S-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 172.9 (C-1), 156.8, 148.2, 145.4 (C-4´, C-6, C-7), 134.2 (C8a), 129.8 (C-2´, C-6´), 125.5 (C-3´, C-5´), 125.2, 119.8 (C-4a, C-1´), 115.6, 111.1 (C-5, C-8), 56.9, 56.2 (2 x OMe), 53.1 (C-3), 47.1 (*N*-Me), 25.9 (C-4), 14.7 (S-Me) ppm. EI-MS: *m/z* (%) = 328 (M^+, 4), 327 (8), 314 (18), 313 (48), 312 (68), 206 (12), 204 (38), 142 (100), 127 (21). HR-MS: calcd. for $C_{19}H_{22}NO_2S$ $[M - I]^+$ 328.1366*;* found 328.1368.

6,7-Dimethoxy-*N*-methyl-1-(4-*N*,*N*-dimethylamino)-3,4-dihydroisoquinolinium Iodide (2d)

Isoquinolinium salt **2d** (2.66 g, 70%) was obtained from the dihydroisoquinoline **1d** (2.6 g, 8.4 mmol) as a yellow amorphous solid. M.p. 194-197 ºC. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 7.46 (d, 2H, *J* = 8.8 Hz, H-2´, H-6´), 6.89 (s, 1H, H-5), 6.77 (d, 2H, *J* = 8.8 Hz, H-3´, H-5´), 6.60 (s, 1H, H-8), 4.34 (t, 2H, *J* = 7.8 Hz, H-3), 4.00, 3.86 (2 x s, 3H each, 2 x OMe), 3.66 (s, 3H, *N*-Me), 3.34 (t, 2H, *J* = 7.8 Hz, H-4), 3.10 (s, 6H, *N*-Me_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 172.3 (C-1), 156.1 (C-4´), 152.9, 148.0 (C-6, C-7), 134.5 (C-8a), 132.8 (C-2´, C-6´), 120.4 (C-4a), 116.6 (C-1´), 115.1, 110.8 (C-5, C-8), 110.9 (C-3´, C-5´), 56.8, 56.3 (2 x OMe), 53.1 (C-3), 47.1 (*N*-Me), 40.1 (*N*-Me_2), 26.4 (C-4) ppm. EI-MS: *m/z* (%) = 325 (M^+, 6), 324 (11), 311 (11), 310 (50), 309 (70), 251 (11), 206 (13), 204 (36), 142 (100), 127 (22). HR-MS: calcd. for $C_{20}H_{25}N_2O_2$ $[M - I]^+$ 325.1911*;* found 325.1911.

6,7-Dimethoxy-1-(4-methoxyphenyl)-*N*-methyl-3,4-dihydroisoquinolinium iodide (2e)

Isoquinolinium salt **2e** (3.0 g, 85%) was obtained from the dihydroisoquinoline **1e** (2.4 g, 8 mmol) as a yellow amorphous solid. M.p. 180-183 ºC. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 7.64 (d, 2H, *J* = 8.2 Hz, H-2´, H-6´), 7.09 (d, 2H, *J* = 8.2 Hz, H-3´, H-5´), 6.95 (s, 1H, H-5), 6.43 (s, 1H, H-8), 4.43 (t, 2H, *J* = 7.5 Hz, H-3), 3.99, 3.90, 3.77 (3 x s, 3H each, 3 x OMe), 3.60 (s, 3H, *N*-Me), 3.44 (t, 2H, *J* = 7.5 Hz, H-4) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 173.2 (C-1), 162.6 (C-4´), 156.7, 148.2 (C-6, C-7), 134.2 (C-8a), 131.7 (C-2´, C-6´), 121.3, 120.1 (C-1´, C-4a), 115.1, 110.9 (C-5, C-8), 114.6 (C-3´, C-5´), 56.9, 56.2, 55.7 (3 x OMe), 53.1 (C-3), 47.1 (*N*-Me), 26.0 (C-4) ppm. EI-MS: *m/z* (%) = 312 (M^+, 5), 311 (18), 298 (17), 297 (75), 296 (100), 268 (15), 251 (19), 238 (29), 206 (13), 204 (30), 142 (78), 127 (17). HR-MS: calcd. for $C_{19}H_{22}NO_3$ $[M - I]^+$ 312.1594*;* found 312.1595.

4.4. *General Procedure for synthesis of N*-methyl-1,2,3,4-tetrahydroisoquinolines (3a-e)

To a solution of the corresponding salt (2.6 mmol) in MeOH (80 mL) was added $NaBH_4$ (113 mg, 3 mmol) dropwise over a period of 10 min and the mixture was stirred for 30 min. The solvent was evaporated under vacuum, and the residue obtained was dissolved in CH_2Cl_2 (80 mL) and washed with water. The organic layer was dried with anhydrous $MgSO_4$ and the solvent evaporated under vacuum to obtain the corresponding 1,2,3,4-tetrahydroisoquinoline.

(±)-6,7-Dimethoxy-*N*-methyl-1-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (3b)

Isoquinoline **3b** (520 mg, 80%) was obtained from the salt **2b** (900 mg, 2 mmol) as a yellow amorphous solid. M.p. descomposes. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 8.16 (d, 2H, *J* = 8.9 Hz, H-3´, H-5´), 7.41 (d, 2H, *J* = 8.9 Hz, H-2´, H-6´), 6.61 (s, 1H, H-5), 5.99 (s, 1H, H-8), 4.30 (s, 1H, H-1), 3.83, 3.56 (2 x s, 3H each, 2 x OMe), 3.16 (ddd, 1H, *J* = 15.9, 11.0, 5.4 Hz, H-4ax), 3.06 (ddd, 1H, *J* = 11.0, 5.4, 3.2 Hz, H-3eq), 2.73 (dt, 1H, *J* = 15.9, 3.4 Hz, H-4eq), 2.62 (td, 1H, *J* = 11.0, 3.4 Hz, H-3ax), 2.21 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 151.9 (C-4´), 147.9, 147.3 (C-6, C-7), 130.2 (C-2´, C-6´), 129.9, 128.6, 126.7 (C-1´, C-4a, C-8a), 123.5 (C-3´, C-5´), 111.0 (C-5, C-8), 70.1 (C-1), 55.9, 55.8 (2 x OMe), 51.8 (C-3), 44.2 (*N*-Me), 28.8 (C-4) ppm. EI-MS: *m/z* (%) = 328 (M^+, 10), 327 (8), 207 (15), 206 (100.) HR-MS: calcd for $C_{18}H_{21}N_2O_4$ $[M + H]^+$ 329.1496, found 329.1494.

(±)-6,7-Dimethoxy-*N*-methyl-1-(4-methylthiophenyl)-1,2,3,4-tetrahydroisoquinoline (3c)

Isoquinoline **3c** (1.8 g, 78%) was obtained from the salt **2c** (3.2 g, 7 mmol) as a yellow amorphous solid. M.p. 81-84 ºC. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 7.17 (d, 2H, *J* = 8.8 Hz, H-2´, H-6´), 7.14 (d, 2H, *J* = 8.8 Hz, H-3´, H-5´), 6.57 (s, 1H, H-5), 6.08 (s, 1H, H-8), 4.12 (s, 1H, H-1), 3.81, 3.55 (2 x s, 3H each, 2 x OMe), 3.12 (ddd, 1H, *J* = 15.7, 11.0, 5.4 Hz, H-4ax), 3.04 (ddd, 1H, *J* = 11.0, 5.4, 3.5 Hz, H-3eq), 2.70 (dt, 1H, *J* =

15.7, 3.5 Hz, H-4eq), 2.56 (td, 1H, *J* = 11.0, 3.5 Hz, H-3ax), 2.44 (s, 3H, S-Me), 2.20 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 147.4, 147.0 (C-6, C-7), 140.7 (C-4´), 137.1, 130.1, 126.5 (C-1´, C-4a, C-8a), 129.9 (C-2´, C-6´), 126.4 (C-3´, C-5´), 111.5, 110.8 (C-5, C-8), 70.4 (C-1), 55.8, 55.7 (2 x OMe), 51.9 (C-3), 44.1 (*N*-Me), 28.8 (C-4), 15.7 (S-Me) ppm. EI-MS: *m/z* (%) = 330 (3), 329 (M^+, 15), 328 (9), 207 (12), 206 (100). HR-MS: calcd. for $C_{19}H_{24}NO_2S$ $[M + H]^+$ 330.1522*;* found 330.1522.

(±)-6,7-Dimethoxy-*N*-methyl-1-(4-*N*,*N*-dimethylaminophenyl)-1,2,3,4-tetrahydroisoquinoline (3d)

Isoquinoline **3d** (1.3 g, 78%) was obtained from the salt **2d** (2.3 g, 5 mmol) as a white amorphous solid. M.p. 97-99 ºC. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 7.07 (d, *J* = 8.7 Hz, 2H, H-2´, H-6´), 6.65 (d, 2H, *J* = 8.7 Hz, H-3´, H-5´), 6.57 (s, 1H, H-5), 6.16 (s, 1H, H-8), 4.15 (s, 1H, H-1), 3.82, 3.57 (2 x s, 3H each, 2 x OMe), 3.18-3.06 (m, 2H, H-3eq, H-4ax), 2.91 (s, 6H, *N*-Me_2), 2.74 (dt, 1H, *J* = 15.8, 3.2 Hz, H-4eq), 2.60 (td, 1H, *J* = 10.2, 3.2 Hz, H-3ax), 2.22 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 149.8 (C-4´), 147.3, 147.0 (C-6, C-7), 131.4, 131.1, 126.5 (C-1´, C-4a, C-8a), 130.2 (C-2´, C-6´), 112.3 (C-3´, C-5´), 111.7, 110.7 (C-5, C-8), 70.3 (C-1), 55.9, 55.8 (2 x OMe), 52.0 (C-3), 44.2 (*N*-Me), 40.6 (*N*-Me_2), 28.9 (C-4) ppm. EI-MS: *m/z* (%) = 327 (6), 326 (M^+, 31), 325 (22), 207 (12), 206 (100). HR-MS: calcd. for $C_{20}H_{27}N_2O_2$ $[M + H]^+$ 327.2067*;* found 327.2066.

4.5. *General Procedure for the synthesis of 6,7-dihydroxy-N-methyl-1,2,3,4-tetrahydroisoquinolines (4a-d):* A solution of the corresponding tetrahydroisoquinoline (0.2 mmol) in 47% HBr (2 mL, 43 mmol) was heated at 100 ºC for 2 h. After this time, the reaction crude mixture was basified with a saturated solution of $NaHCO_3$ (5 mL) to pH ~ 8 and then was extracted with $CHCl_3$ (2 x 10 mL). The organic layer was dried with anhydrous $MgSO_4$ and the solvent was concentrated

under vacuum to give the corresponding demethylated tetrahydroisoquinoline in good yield.

(±)-6,7-Dihydroxy-*N*-methyl-1-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (4b)

Tetrahydroisoquinoline **4b** (540 mg, 88%) was obtained from the isoquinoline **3b** (670 mg, 2 mmol) as a pale brown amorphous solid. M.p. 120-123 ºC. ^{1}H NMR (400 MHz, $CDCl_3$+ CD_3OD, 25 ºC): δ = 8.10 (d, 2H, *J* = 8.6 Hz, H-3´, H-5´), 7.39 (d, 2H, *J* = 8.6 Hz, H-2´, H-6´), 6.54 (s, 1H, H-5), 5.93 (s, 1H, H-8), 4.26 (s, 1H, H-1), 3.09-2.98 (m, 2H, H-3, H-4), 2.67-2.53 (m, H-3, H-4), 2.17 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD, 25 ºC): δ = 150.9 (C-4´), 147.2 (C-1´), 143.4, 142.7 (C-6, C-7), 130.4 (C-2´, C-6´), 127.9, 125.8 (C-4a, C-8a), 123.4 (C-3´, C-5´), 114.6 (C-5, C-8), 69.9 (C-1), 51.7 (C-3), 43.9 (*N*-Me), 29.6 (C-4) ppm. EI-MS: *m/z* (%) = 300 (M^+, 10), 299 (7), 179 (16), 178 (100). HR-MS: calcd. for $C_{16}H_{17}N_2O_4$ $[M + H]^+$ 301.1183; found 301.1183.

(±)-6,7-Dihydroxy-*N*-methyl-1-(4-methylthiophenyl)-1,2,3,4-tetrahydroisoquinoline (4c)

Tetrahydroisoquinoline **4c** (55 mg, 60%) was obtained from the isoquinoline **3c** (100 mg, 0.3 mmol) as a yellow amorphous solid. M.p. 174-177 ºC. ^{1}H NMR (400 MHz, CD_3OD, 25 ºC): δ =7.26 (d, 2H, *J* = 7.7 Hz, H-2´, H-6´), 7.18 (d, 2H, *J* = 7.7 Hz, H-3´, H-5´), 6.56 (s, 1H, H-5), 6.01 (s, 1H, H-8), 4.34 (s, 1H, H-1), 3.17-3.05 (m, 2H, H-3, H-4), 2.76-2.61 (m, 2H, H-3, H-4), 2.47 (s, 3H, S-Me), 2.30 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 ºC): δ = 145.4, 144.7 (C-6, C-7), 140.5, 139.8 (C-1´, C-4´), 131.7 (C-2´, C-6´), 129.8, 126.2 (C-4a, C-8a), 127.5 (C-3´, C-5´), 116.1, 115.6 (C-5, C-8), 71.7 (C-1), 53.3 (C-3), 44.2 (*N*-Me), 28.8 (C-4), 15.8 (S-Me) ppm. EI-MS: *m/z* (%) = 302 (10), 301 (M^+, 27), 300 (15), 179 (33), 178 (100), 177 (9). HR-MS: calcd for $C_{17}H_{20}NO_2S$ $[M + H]^+$ 302.1209; found 302.1209.

(±)-6,7-Dihydroxy-*N*-methyl-1-(4-*N*,*N*-dimethylaminophenyl)-1,2,3,4-tetrahydroisoquinoline (4d)

Tetrahydroisoquinoline **4d** (40 mg, 88%) was obtained from the isoquinoline **3d** (50 mg, 0.15 mmol) as a pale brown amorphous solid. M.p. 200-203 ºC. ^{1}H NMR (400 MHz,

$CDCl_3$, 25ºC): δ = 6.99 (d, 2H, *J* = 8.6 Hz, H-2´, H-6´), 6.59 (d, 2H, *J* = 8.6 Hz, H-3´, H-5´), 6.46 (s, 1H, H-5), 6.06 (s, 1H, H-8), 4.72 (s, 1H, H-1), 3.07-2.99 (m, 2H, H-3, H-4), 2.89 (s, 6H, *N*-Me_2), 2.72-2.60 (m, 2H, H-3, H-4), 2.21 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ = 150.5, (C-4´), 145.2, 144.3 (C-6, C-7), 133.8, 125.3 (C-4a, C-8a), 131.3 (C-2´, C-6´), 123.0 (C-1´), 114.8, 114.7 (C-5, C-8), 112.1 (C3´, C-5´), 68.5 (C-1), 49.6 (C-3), 41.8 (*N*-Me), 40.3 (*N*-Me_2), 25.9 (C-4) ppm. EI-MS: *m/z* (%) = 299 (10), 298 (M^+, 46), 297 (26), 254 (18), 179 (14), 178 (100), 177 (27). HR-MS: calcd. for $C_{18}H_{23}N_2O_2$ $[M + H]^+$ 299.1754; found 299.1751.

(±)-6,7-Dihydroxy-1-(4-hydroxyphenyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (4e)

A solution of the tetrahydroisoquinoline **3e** (250 mg, 0.8 mmol) in 47% HBr (8 mL) was heated at 100 ºC for 4 h. After this time, the crude reaction mixture was concentrated under vacuum, dissolved in MeOH, stirred with $NaHCO_3$, filtered and concentrated to give the isoquinoline **4e** (200 mg, 92%) as a pale brown amorphous solid. M.p. 232-235 ºC. ^{1}H NMR (400 MHz, CD_3OD, 25 ºC): δ = 7.18 (d, 2H, *J* = 8.5 Hz, H-2´, H-6´), 6.87 (d, 2H, *J* = 8.5 Hz, H-3´, H-5´), 6.66 (s, 1H, H-5), 6.10 (s, 1H, H-8), 5.34 (s, 1H, H-1), 3.70 (ddd, 1H, *J* = 12.2, 5.6, 4.5 Hz, H-3eq), 3.48 (ddd, 1H, *J* = 12.2, 10.2, 4.5 Hz, H-3ax), 3.28-3.20 (m, 1H, H-4ax), 3.00 (dt, 1H, *J* = 17.3, 4.5 Hz, H-4eq), 2.82 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 ºC): δ = 160.0 (C-4´), 146.8, 145.6 (C-6, C-7), 128.6 (C-2´, C-6´), 124.3 (C-1´), 123.8, 123.5 (C-4a, C-8a), 116.9 (C-3´, C-5´), 115.8, 115.6 (C-5, C-8), 70.5 (C-1), 52.3 (C-3), 41.6 (*N*-Me), 25.5 (C-4) ppm. EI-MS: *m/z* (%) = 272 (31), 271 (M^+, 45), 270 (23), 179 (68), 178 (100), 177 (13). HR-MS: calcd. for $C_{16}H_{18}NO_3$ $[M + H]^+$ 272.1281; found 272.1281.

4.6. *General Procedure for synthesis* of *N*-mehyl-1,2,3,4-tetrahydroisoquinolinium salts (5a-g): The appropriate haloderivative (2.4 mmol) was added to a solution of the corresponding tetrahydroisoquinoline (2 mmol) in dry

acetone (25 mL) under argon. The mixture was stirred at room temperature for 24 h and the solvent was concentrated under vacuum to give the corresponding salts.

(±)-*trans*-6,7-Dimethoxy-*N*-[(methoxycarbonyl)methyl]-*N*-methyl-1-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinolinium bromide (5b-*trans*)

A mixture of the isoquinoline **3b** (680 mg, 2.1 mmol) and methyl bromoacetate (0.23 mL, 2.5 mmol) in CH_3CN was refluxed for 168 h. The solvent was evaporated under vacuum and the ^{1}H NMR spectrum of the crude reaction indicated only the presence of the salt **5b**-*trans* (990 mg). The dry crude salt was used to next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 8.11 (d, 2H, *J* = 8.8 Hz, H-3´, H-5´), 7.47 (d, 2H, *J* = 8.8 Hz, H-2´, H-6´), 7.28 (s, 1H, H-1), 6.73 (s, 1H, H-5), 6.31 (s, 1H, H-8), 5.78 (d, 1H, *J* = 17.0 Hz, H-α), 4.49 (d, 1H, *J* = 17.0 Hz, H-α´), 4.40-4.34 (m, 1H, H-3), 3.86, 3.78 (2 x s, 3H each, 2 x OMe), 3.64 (s, 3H, CO*OMe*), 3.60-3.53 (m, 1H, H-3´), 3.30 (s, 3H, *N*-Me), 3.17-2.96 (m, 2H, H-4, H-4´) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ +TFA, 25 ºC): δ = 165.2 (CO), 149.3 (C-4´), 138.6, 138.3 (C-6, C-7), 124.7, 124.4 (C-4a, C-8a), 118.7 (C-1´), 115.9 (C-2´, C-6´), 113.0 (C-3´, C-5´), 110.9, 110.2 (C-5, C-8), 73.1 (C-1), 58.3 (C-α), 56.0 (2 x OMe), 53.7, 53.6 (CO*OMe*, C-3), 47.6 (*N*-Me), 23.5 (C-4) ppm.

(±)-6,7-Dimethoxy-*N*-[(methoxycarbonyl)-methyl]-*N*-methyl-1-(4-methylthiophenyl)- 1,2,3,4-tetrahydroisoquinolinium bromide (5c-*trans*)

According to general procedure, the isoquinoline **3c** (800 mg, 2.4 mmol) and methyl bromoacetate (0.26 mL, 2.9 mmol) gave a reaction crude, which ^{1}H NMR spectrum indicated only the presence of the salt **5c**-*trans* (1.10 g). The dry crude salt was used to next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 7.20-7.14 (m, 4H, H-2´, H-3´, H-5´, H-6´), 6.88 (s, 1H, H-1), 6.66, (s, 1H, H-5), 6.32 (s, 1H, H-8), 5.60 (d, 1H, *J* = 17.5 Hz, H-α), 4.56 (d, 1H, *J* = 17.5 Hz, H-α´), 4.31 (ddd, 1H, *J* = 12.7, 5.8, 2.0 Hz, H-3eq), 3.84, 3.75 (2 x s, 3H each, 2 x OMe), 3.65 (s, 3H, CO*OMe*), 3.63-3.56 (m, 1H, H-3ax), 3.35 (s, 3H, *N*-Me), 3.17 (ddd, 1H, *J* = 18.5, 5.6, 2.0 Hz, H-4eq), 3.10 (ddd, 1H, *J* = 18.5, 11.5, 5.8 Hz, H-4ax), 2.43 (s, 3H, S-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$,

25ºC): δ = 165.6 (CO), 149.6, 149.0 (C-6, C-7), 142.9 (C-4´), 127.8 (C-1´), 125.6, 125.5 (C-2´, C-3´, C-5´, C-6´), 121.1, 120.2 (C-4a, C-8a), 111.1, 110.3 (C-5, C-8), 73.7 (C-1), 57.2 (C-α), 55.9, 55.8 (2 x OMe), 53.1 (CO*OMe*), 51.9 (C-3), 48.0 (*N*-Me), 23.6 (C-4), 14.6 (S-Me) ppm.

(±)-6,7-Dimethoxy-*N*-[(methoxycarbonyl)-methyl]-*N*-methyl-1-(4-*N*,*N*-dimethylaminophenyl)-1,2,3,4-tetrahydroisoquinolinium bromide (5d)

According to general procedure, the isoquinoline **3d** (310 mg, 0.9 mmol) and methyl bromoacetate (0.1 mL, 1.2 mmol) gave a reaction crude, which ^{1}H NMR spectrum indicated the presence of a mixture of stereoisomers **5d** in a *cis*/*trans* ratio of 1:20 (440 mg). The dry crude salt was used to next step without purification.

5d-*trans***.** ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 6.66-6.53 (m, 4H, H-2´, H-3´, H-5´, H-6´), 6.65 (s, 1H, H-1), 6.60 (s, 1H, H-5), 6.26 (s, 1H, H-8), 5.35 (d, 1H, *J* = 17.5 Hz, H-α), 4.56 (d, 1H, *J* = 17.5 Hz, H-α´), 4.24-4.21 (m, 1H, H-3), 3.81, 3.79 (2 x s, 3H each, 2 x OMe), 3.70-3.60 (m, 1H, H-3´), 3.60 (s, 3H, CO*OMe*), 3.31 (s, 3H, *N*-Me), 3.16-3.04 (m, 2H, H-4, H-4´), 2.90 (s, 6H, *N*-Me_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 165.2 (CO), 151.0, 148.9 (C-6, C-7), 148.3 (C-4´), 133.8 (C-2´, C-6´), 121.7 (C-1´), 120.2, 117.3 (C-4a, C-8a), 111.1 (C-3´, C-5´), 110.8, 110.0 (C-5, C-8), 74.6 (C-1), 56.8 (Cα), 55.6, 55.5 (2 x OMe), 52.7 (CO*OMe*), 51.3 (C-3), 47.5 (*N-Me*), 40.0 (*N-*Me_2), 23.5 (C-4) ppm.

(±)-6,7-Dimethoxy-*N*-[(methoxycarbonyl)-mehyl]-1-(4-methoxyphenyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinolinium bromide (5e)

According to general procedure, the isoquinoline **3e** (950 mg, 3.0 mmol) and methyl bromoacetate (0.3 mL, 3.5 mmol) gave a reaction crude, which ^{1}H NMR spectrum indicated the presence of a mixture of stereoisomers **5e** in a *cis*/*trans* ratio of 1:5 (1.35 g). The dry crude salt was used to next step without purification.

5e-*trans***.** ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 6.90-6.68 (m, 4H, H-2´, H-3´, H-5´, H-6´), 6.81 (s, 1H, H-1), 6.66 (s, 1H, H-5), 6.31 (s, 1H, H-8), 5.52 (d, 1H, *J* = 17.7 Hz, H-α), 4.55 (d, 1H, *J* = 17.7 Hz, H-α´), 4.28 (ddd, 1H, *J* = 13.0, 5.7, 1.4 Hz, H-3eq), 3.83,

3.76, 3.74 (3 x s, 3H each, 3 x OMe), 3.63 (s, 3H, CO*OMe*), 3.61-3.51 (m, 1H, H-3ax), 3.31 (s, 3H, *N*-Me), 3.16 (ddd, 1H, *J* = 18.3, 5.1, 1.4 Hz, H-4eq), 3.07 (ddd, 1H, *J* = 18.3, 11.5, 5.7 Hz, H-4ax) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 165.7 (CO), 161.4 (C-4´), 149.7, 149.2 (C-6, C-7), 133.5 (C-2´, C-6´), 123.6, 121.7 (C-4a, C-8a), 123.4 (C-1´), 114.5 (C-3´, C-5´), 111.2, 110.4 (C-5, C-8), 73.8 (C-1), 57.2 (Cα), 56.1 (2 x OMe), 55.4 (OMe), 52.5 (CO*OMe*), 52.1 (C-3), 47.9 (*N*-Me), 23.7 (C-4) ppm.

4.7. General procedure for the Stevens Rearrangement: DBU (0.4 mL, 2.7 mmol) was added to a solution of the corresponding salt (2 mmol) in CH_3CN (90 mL), and the resulting mixture was stirred at room temperature for 1 h. After this time, the solvent was evaporated under vacuum, and the crude reaction mixture was purified by column chromatography to yield the corresponding benzazepine.

(±)-*trans*-7,8-Dimethoxy-2-methoxycarbonyl-*N*-methyl-1-(4-nitrophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6b-*trans*)

Benzazepine **6b**-*trans* (328 mg, 40%) was obtained from the crude salt **5b-*trans*** (990 mg, 2 mmol) after purification by column chromatography (SiO_2, cyclohexane/EtOAc 2:8) as an amorphous solid. M.p. 130-133 ºC. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 8.12 (d, 2H, *J* = 8.9 Hz, H-3´, H-5´), 7.32 (d, 2H, *J* = 8.9 Hz, H-2´, H-6´), 6.62 (s, 1H, H-6), 6.58 (s, 1H, H-9), 4.62 (d, 1H, *J* = 5.6 Hz, H-1), 4.27 (d, 1H, *J* = 5.6 Hz, H-2), 3.86, 3.81 (2 x s, 3H each, 2 x OMe), 3.55 (s, 3H, CO*OMe*), 3.31 (td, 1H, *J* = 10.9, 2.2 Hz, H-4), 2.69-2.62 (m, 2H, H-4´, H-5), 2.56 (s, 3H, *N*-Me), 2.46 (ddd, 1H, *J* = 14.7, 6.0, 2.2 Hz, H-5´) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 172.6 (CO), 148.7 (C-4´), 148.2, 146.3 (C-7, C-8), 147.1 (C-1´), 133.8, 129.5 (C-5a, C-9a), 128.7 (C-2´, C-6´), 123.3 (C-3´, C-5´), 114.7, 113.6 (C-6, C-9), 66.4 (C-2), 56.2, 55.8 (2 x OMe), 51.9 (CO*OMe*), 51.0, 50.3 (C-1, C-4), 46.0 (*N*-Me), 34.8 (C-5) ppm. EI-MS: *m/z* (%) = 400 (M^+, 8), 342 (20), 341 (100), 284 (8). HR-MS: calcd for $C_{21}H_{25}N_2O_6$ $[M + H]^+$ 401.1707, found 401.1704.

(±)-7,8-Dimethoxy-*2*-methoxycarbonyl-*N*-methyl-1-(4-methylthiophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6c-*trans*)

Benzazepine **6c**-*trans* (460 mg, 57%) was obtained from the crude salt **5c**-*trans* (960 mg, 2 mmol) after purification by column chromatography (SiO_2, cyclohexane/EtOAc 1:1) as a white amorphous solid. M.p. 144-147 ºC. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 7.17 (d, 2H, *J* = 8.2 Hz, H-2´, H-6´), 7.09 (d, 2H, *J* = 8.2 Hz, H-3´, H-5´), 6.62 (s, 1H, H-6), 6.50 (s, 1H, H-9), 4.55 (d, 1H, *J* = 6.5 Hz, H-1), 4.13 (d, 1H, *J* = 6.5 Hz, H-2), 3.85, 3.75 (2 x s, 3H each, 2 x OMe), 3.53 (s, 3H, CO*OMe*), 3.28-3.23 (m, 1H, H-4), 2.78-2.62 (m, 3H, H-4´, H-5, H-5´), 2.50 (s, 3H, S-Me), 2.44 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 172.2 (CO), 147.5, 146.8 (C-7, C-8), 137.3, 135.9, 133.3, 130.7 (C-1´, C-4´, C-5a, C-9a), 128.5 (C-2´, C-6´), 126.4 (C-3´, C-5´), 114.1, 113.1 (C-6, C-9), 67.2 (C-2), 55.9, 55.7 (2 x OMe), 51.1, 50.8 (C-4, CO*OMe*), 50.2 (C-1), 45.6 (*N*-Me), 34.3 (C-5), 15.7 (S-Me) ppm. EI-MS: *m/z* (%) = 402 (5), 401 (M^+, 11), 343 (25), 342 (100), 285 (18). HR-MS: calcd. for $C_{22}H_{28}NO_4S$ $[M + H]^+$ 402.1734*;* found 402.1735.

(±)-7,8-Dimethoxy-*2*-methoxycarbonyl-*N*-methyl-1-(4-*N*,*N*-dimethylaminophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6d)

A mixture of stereoisomers of **6d** were obtained in a *cis*/*trans* ratio 1:20 from the crude salts **5d** (*cis*/*trans* 1:20, 200 mg, 0.4 mmol). Both stereoisomers of **6d** were isolated by column chromatography (SiO_2, cyclohexane/EtOAc, 3:7) to yield **6d**-*trans* (80 mg, 48%) and **6d**-*cis* (4 mg, 2%).

6d-*trans*: orange oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 7.04 (d, 2H, *J* = 8.9 Hz, H-2´, H-6´), 6.67 (d, 2H, *J* = 8.9 Hz, H-3´, H-5´), 6.63 (s, 1H, H-6), 6.52 (s, 1H, H-9), 4.52 (d, 1H, *J* = 7.0 Hz, H-1), 4.05 (d, 1H, *J* = 7.0 Hz, H-2), 3.84, 3.72 (2 x s, 3H each, 2 x OMe), 3.52 (s, 3H, CO*OMe*), 3.22 (ddd, 1H, *J* = 11.5, 7.5, 3.8 Hz, H-4), 2.91 (s, 6H, *N*-Me_2), 2.86-2.71 (m, 2H, H-5, H-5´), 2.68 (ddd, 1H, *J* = 11.5, 6.8, 5.0 Hz, H-4´), 2.46 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 172.7 (CO), 149.2 (C-4´), 147.4, 146.9 (C-7, C-8), 133.1, 131.9, 128.0 (C-1´, C-5a, C-9a), 128.9 (C-2´, C-6´),

113.9, 112.9 (C-6, C-9), 112.6 (C-3´, C-5´), 68.2 (C-2), 56.0, 55.8 (2 x OMe), 50.8 (CO*O*Me), 50.6 (C-4), 50.4 (C-1), 45.6 (*N*-Me), 40.6 (*N*-Me_2), 34.2 (C-5) ppm. EI-MS: *m/z* (%) = 399 (8), 398 (M^+, 26), 340 (26), 339 (100), 282 (48). HR-MS: calcd. for $C_{23}H_{31}N_2O_4$ $[M + H]^+$ 399.2278*;* found 399.2275.

6d-*cis*: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 7.21 (d, 2H, *J* = 8.8 Hz, H-2´, H-6´), 6.72 (d, 2H, *J* = 8.8 Hz, H-3´, H-5´), 6.63 (s, 1H, H-6), 6.29 (s, 1H, H-9), 4.68 (br. s, 1H, H-1), 3.97 (br. s, 1H, H-2), 3.83, 3.57 (2 x s, 3H each, 2 x OMe), 3.52 (s, 3H, CO*OMe*), 3.29 (dd, 1H, *J* = 12.8, 11.6 Hz, H-4), 3.09 (ddd, 1H, *J* = 14.3, 11.6, 1.9 Hz, H-5), 2.93 (s, 6H, *N*-Me_2), 2.82 (ddd, 1H, *J* = 12.8, 6.0, 1.9 Hz, H-4´), 2.72 (dd, 1H, *J* = 14.3, 6.0 Hz, H-5´), 2.47 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 171.0 (CO), 149.2 (C-4´), 146.9, 146.8 (C-7, C-8), 133.8, 132.7, 129.0 (C-1´, C-5a, C-9a), 129.7 (C-2´, C-6´), 112.9, 112.4 (C-6, C-9), 112.5 (C-3´, C-5´), 68.4 (C-2), 56.0, 55.8 (2 x OMe), 51.2, 50.8 (C-1, C-4, CO*OMe*), 44.9 (*N*-Me), 40.6 (*N*-Me_2), 34.9 (C-5) ppm.

(±)-7,8-Dimethoxy-*2*-methoxycarbonyl-1-(4-methoxyphenyl)-*N*-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6e)

A mixture of stereoisomers of **6e** were obtained in a *cis*/*trans* ratio 1:5 from the crude salts **5e** (*cis*/*trans* 1:5, 900 mg, 1.9 mmol). Both stereoisomers of **6e** were isolated by column chromatography (SiO_2, cyclohexane/EtOAc, 4:6) to yield of pure **6e**-*trans* (323 mg, 44%), pure **6e**-*cis* (64 mg, 8%).

6e-*trans*: white amorphous solid: M.p. 114-117 ºC. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 7.10 (d, 2H, *J* = 8.9 Hz, H-2´, H-6´), 6.83 (d, 2H, *J* = 8.9 Hz, H-3´, H-5´), 6.63 (s, 1H, H-6), 6.50 (s, 1H, H-9), 4.54 (d, 1H, *J* = 7.0 Hz, H-1), 4.08 (d, 1H, *J* = 7.0 Hz, H-2), 3.84, 3.77, 3.73 (3 x s, 3H each, 3 x OMe), 3.54 (s, 3H, CO*OMe*), 3.27-3.21 (m, 1H, H-4), 2.81-2.64 (m, 3H, H-4´, H-5, H-5´), 2.48 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 172.6 (CO), 158.1 (C-4´), 147.6, 146.9 (C-7, C-8), 133.3, 132.4, 131.5 (C-1´, C-5a, C-9a), 129.3 (C-2´, C-6´), 114.0, 113.1 (C-6, C-9), 113.7 (C-3´, C-5´), 68.0 (C-2), 56.1, 55.9, 55.2 (3 x OMe), 50.9 (CO*OMe*), 50.8, 50.4 (C-1, C-4), 45.7

(*N*-Me), 34.3 (C-5) ppm. EI-MS: *m/z* (%) = 385 (M^+, 6), 327 (22), 326 (100), 269 (18). HR-MS: calcd. for $C_{22}H_{28}NO_5$ $[M + H]^+$ 386.1962*;* found 386.1958.

6e-*cis*: colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 7.29 (d, 2H, *J* = 8.9 Hz, H-2´, H-6´), 6.86 (d, 2H, *J* = 8.9 Hz, H-3´, H-5´), 6.64 (s, 1H, H-6), 6.20 (s, 1H, H-9), 4.73 (br. s, 1H, H-1), 3.99 (br. s, 1H, H-2), 3.83, 3.80, 3.56 (3 x s, 3H cada, 3 x OMe), 3.52 (s, 3H, CO*OMe*), 3.29 (ddd, 1H, *J* = 13.9, 11.6, 1.6 Hz, H-5), 3.11 (t, 1H, *J* = 11.6 Hz, H-4), 2.82 (ddd, 1H, *J* = 11.6, 5.9, 1.6 Hz, H-4´), 2.73 (dd, 1H, *J* = 13.9, 5.9 Hz, H-5´), 2.48 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 171.3 (CO), 158.1 (C-4´), 147.0, 146.8 (C-7, C-8), 133.8, 133.6, 132.9 (C-1´, C-5a, C-9a), 130.1 (C-2´, C-6´), 113.7 (C-3´, C-5´), 112.8, 112.5 (C-6, C-9), 68.3 (C-2), 56.0, 55.9, 55.2 (3 x OMe), 51.3, 51.1, 50.9 (C-1, C-4, CO*OMe*), 45.1 (*N*-Me), 35.2 (C-5) ppm.

***4.8. General Procedure for synthesis of 7,8-dihydroxy-N-methyl-2,3,4,5-tetrahydro-1H-3-benzazepines (7a-g)*:** A solution of the corresponding benzazepine (**6a-g**, 0.3 mmol) in CH_2Cl_2 (4 mL) was cooled to -78ºC. Subsequently, a solution of Br_3B in CH_2Cl_2 (0.8 mL, 4.6 mmol) was added dropwise. After 15 min, the reaction mixture was warmed up to room temperature and stirred for 3 h. After this period, the reaction was quenched with MeOH and stirred for another 30 min. The solvent was evaporated under vacuum, and the residue obtained was dissolved in EtOAc (2 mL), made alkaline with 25% aqueous NH_4OH to pH 11, and neutralized with 37% HCl to pH 7-8. The aqueous layer was extracted with EtOAc (2 x 10 mL). The organic layer was dried with anhydrous $MgSO_4$, the solvent evaporated under vacuum and the crude reaction was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1 to 8:2) to obtain the corresponding demethylated benzazepine in moderated and good yield.

(±)-*trans*-7,8-Dihydroxy-2-(methoxycarbonyl)-*N*-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7a-*trans*)

Benzazepine **7a**-*trans* (50 mg, 57%) was obtained from the benzazepine **6a**-*trans* (95 mg, 0.27 mmol) as a pale brown amorphous solid. M.p.: 119-122 ºC. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 7.32-7.20 (m, 5H, Ph), 6.53 (s, 1H, H-6), 6.28 (s, 1H, H-9), 4.55 (d, 1H, *J* = 8.0 Hz, H-1), 4.04 (d, 1H, *J* = 8.0 Hz, H-2), 3.54 (s, 3H, CO*OMe*), 3.22-3.17 (m, 1H, H-4), 2.88-2.84 (m, 1H, H-5), 2.72-2.65 (m, 2H, H-4´, H-5´), 2.42 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 172.0 (CO), 143.0, 142.4 (C-7, C-8), 139.5 (C-1´), 131.3, 130.0 (C-5a, C-9a), 128.4, 128.3, 126.6 (CH Ph), 117.1, 116.7 (C-6, C-9), 67.8 (C-2), 51.2 (CO*OMe*), 50.7, 50.1 (C-1, C-4), 45.1 (*N*-Me), 32.8 (C-5) ppm. EI-MS: *m/z* (%) = 327 (M^+, 3), 269 (20), 268 (100), 178 (12). HR-MS: calcd for $C_{19}H_{22}NO_4$ $[M + H]^+$ 328.1543; found 328.1543.

(±)-*trans*-7,8-Dihydroxy-*2*-methoxycarbonyl-*N*-methyl-1-(4-nitrophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7b-*trans*)

Benzazepine **7b**-*trans* (80 mg, 72 %) was obtained from the benzazepine **6b**-*trans* (120 mg, 0.3 mmol) as an orange amorphous solid. M.p. 103-105 ºC. ^{1}H NMR (400 MHz, CDCl3+CD_3OD, 25 ºC): δ = 8.10 (d, 2H, *J* = 8.8 Hz, H-3´, H-5´), 7.32 (d, 2H, *J* = 8.8 Hz, H-2´, H-6´), 6.58, 6.52 (2 x s, 1H each, H-6, H-9), 4.55 (d, 1H, *J* = 5.9 Hz, H-1), 4.20 (d, 1H, *J* = 5.9 Hz, H-2), 3.55 (s, 3H, CO*OMe*), 3.26 (ddd, 1H, *J* = 12.5, 9.8, 3.1 Hz, H-4), 2.66-2.42 (m, 3H, H-4´, H-5, H-5´), 2.52 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD, 25 ºC): δ = 172.2 (CO), 148.9, 146.2, 143.2, 142.3 (C-1´, C-4´, C-7, C-8), 133.2, 129.4 (C-5a, C-9a), 128.9 (C-2´, C-6´), 123.2 (C-3´, C-5´), 117.9, 117.1 (C-6, C-9), 66.7 (C-2), 51.5, 51.1, 50.5 (C-1, C-4, CO*OMe*), 45.8 (*N*-Me), 34.2 (C-5) ppm. EI-MS: *m/z* (%) = 372 (M^+, 5), 314 (29), 313 (100), 267 (12), 178 (9), 176 (14). HR-MS: calcd. for $C_{19}H_{21}N_2O_6$ $[M + H]^+$ 373.1394; found 373.1393.

(±)-*trans*-7,8-Dihydroxy-*2*-methoxycarbonyl-*N*-methyl-1-(4-methylthiophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7c-*trans*)

Benzazepine **7c**-*trans* (40 mg, 43 %) was obtained from the benzazepine **6c**-*trans* (100 mg, 0.25 mmol) as a pale brown amorphous solid. M.p. 114-117 ºC. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 7.17 (d, 2H, *J* = 8.5 Hz, H-2´, H-6´), 7.13 (d, 2H, *J* = 8.5 Hz, H-3´, H-5´), 6.57 (s, 1H, H-6), 6.34 (s, 1H, H-9), 4.49 (d, 1H, *J* = 7.8 Hz, H-1), 4.05 (d, 1H, *J* = 7.8 Hz, H-2), 3.53 (s, 3H, CO*OMe*), 3.25-3.19 (m, 1H, H-4), 2.84-2.79 (m, 1H, H-5), 2.74-2.66 (m, 2H, H-4´, H-5´), 2.45 (s, 3H, S-Me), 2.44 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 172.3 (CO), 142.7,142.3 (C-7, C-8), 136.6, 136.5 (C-1´, C-4´), 131.4, 130.5 (C-5a, C-9a), 129.1 (C-2´, C-6´), 126.5 (C-3´, C-5´), 116.9, 116.8 (C-6, C-9), 67.8 (C-2), 51.3 (CO*OMe*), 50.3, 49.9 (C-1, C-4), 45.0 (*N*-Me), 32.7 (C-5), 15.7 (S-Me) ppm. EI-MS: *m/z* (%) = 373 (M^+, 7), 315 (27), 314 (100), 257 (9), 178 (14), 176 (14). HR-MS: calcd. for $C_{20}H_{24}NO_4S$ $[M + H]^+$ 374.1421; found 374.1421.

(±)-*trans*-7,8-Dihydroxy-*2*-methoxycarbonyl-1-(4-*N*,*N*-dimethylaminophenyl)-*N*-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7d-*trans*)

Benzazepine **7d**-*trans* (15 mg, 81 %) was obtained from the benzazepine **6d**-*trans* (20 mg, 0.05 mmol) as a yellow amorphous solid. M.p. 125-128 ºC. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 7.07 (d, 2H, *J* = 8.3 Hz, H-2´, H-6´), 6.67 (d, 2H, *J* = 8.3 Hz, H-3´, H-5´), 6.61 (s, 1H, H-6), 6.39 (s, 1H, H-9), 4.44 (d, 1H, *J* = 7.8 Hz, H-1), 4.03 (d, 1H, *J* = 7.8 Hz, H-2), 3.51 (s, 3H, CO*OMe*), 3.28-3.23 (m, 1H, H-4), 2.88 (s, 6H, *N*-Me_2), 2.83-2.70 (m, 3H, H-4´, H-5, H-5´), 2.46 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 172.2 (CO), 149.4 (C-4´), 142.7, 142.3 (C-7, C-8), 131.2, 131.1, 127.4 (C-1´, C-5a, C-9a), 129.3 (C-2´, C-6´), 116.7, 116.5 (C-6, C-9), 112.8 (C-3´, C-5´), 68.4 (C-2), 51.3 (CO*OMe*), 50.6, 49.6 (C-1, C-4), 45.1 (*N*-Me), 40.7 (*N*-Me_2), 29.6 (C-5) ppm. EI-MS: *m/z* (%) = 371 (7), 370 (M^+, 30), 312 (26), 311 (100), 254 (34), 178 (13), 176 (16). HR-MS: calcd. for $C_{21}H_{27}N_2O_4$ $[M + H]^+$ 317.1965; found 317.1966.

(±)-*trans*-7,8-Dihydroxy-1-(4-hydroxyphenyl)-*2*-methoxycarbonyl-*N*-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7e-*trans*)

A solution of the benzazepine **6e**-*trans* (100 mg, 0.3 mmol) and Br_3B (1.2 mL, 7 mmol) in CH_2Cl_2 (4 mL) was stirred to room temperature for 3 h. After this time, the reaction

was terminated by addition of MeOH and the crude reaction mixture was concentrated under vacuum to obtain the benzazepine **7e**-*trans* (80 mg, 90%) as a pale brown amorphous solid. M.p. 209-212 ºC. ^{1}H NMR (400 MHz, CD_3OD, 25 ºC): δ = 7.05 (d, 2H, *J* = 8.1 Hz, H-2´, H-6´), 6.81 (d, 2H, *J* = 8.1 Hz, H-3´, H-5´), 6.70 (s, 1H, H-6), 6.49 (s, 1H, H-9), 4.82 (d, 1H, *J* = 5.9 Hz, H-1), 4.65 (d, 1H, *J* = 5.9 Hz, H-2), 3.59 (s, 3H, CO*OMe*), 2.98-2.84 (m, 4H, H-4, H-4´, H-5, H-5´), 2.68 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 ºC): δ = 171.0 (CO), 157.7 (C-4´), 145.7, 145.1 (C-7, C-8), 131.5, 130.6, 129.7 (C-1´, C-5a, C-9a), 130.6 (C-2´, C-6´), 119.3, 118.4 (C-6, C-9), 116.8 (C-3´, C-5´), 69.5 (C-2), 53.6 (C-1), 52.9, 51.3 (C-4, CO*OMe*), 45.8 (*N*-Me), 32.9 (C-5) ppm. EI-MS: *m/z* (%) = 343 (M^+, 2), 285 (43), 284 (68), 283 (43), 228 (25), 227 (32), 179 (22), 178 (100), 177 (26). HR-MS: calcd. for $C_{19}H_{22}NO_5$ $[M + H]^+$ 344.1493; found 344.1493.

(±)-*trans*-2-Carbamoyl-7,8-dihydroxy-*N*-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7f-*trans*)

Benzazepine **7f**-*trans* (40 mg, 44%) was obtained from the benzazepine **6f**-*trans* (100 mg, 0.3 mmol) as a yellow amorphous solid. M.p. 200-202 ºC. ^{1}H NMR (400 MHz, CD_3OD, 25 ºC): δ = 7.31-7.18 (m, 5H, Ph), 6.58 (s, 1H, H-6), 6.30 (s, 1H, H-9), 4.63 (d, 1H, *J* = 8.0 Hz, H-1), 3.83 (d, 1H, *J* = 8.0 Hz, H-2), 3.16-3.10 (m, 1H, H-4), 3.04-2.96 (m, 1H, H-5), 2.78-2.68 (m, 2H, H-4´, H-5´), 2.33 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 ºC): δ = 176.8 (CO), 144.8, 144.4 (C-7, C-8), 142.7 (CPh), 132.4, 131.9 (C-5a, C-9a), 130.4, 129.5, 127.7 (CH Ph), 118.4, 117.6 (C-6, C-9), 70.5 (C-2), 52.2 (C-4), 51.7 (C-1), 45.2 (*N*-Me), 33.6 (C-5) ppm. EI-MS: *m/z* (%) = 312 (M^+, 2), 270 (25), 269 (79), 268 (100), 178 (15). HR-MS: calcd for $C_{18}H_{21}N_2O_3$ $[M + H]^+$ 313.1547; found 313.1547.

(±)-*trans*-7,8-Dihydroxy-*N*-methyl-*N*-2-(4-nitrophenyl)-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7g-*trans*)

Benzazepine **7g**-*trans* (130 mg, 70 %) was obtained from the benzazepine **6g**-*trans* (200 mg, 0.5 mmol) as a yellow amorphous solid. M.p. 140-143 ºC. ^{1}H NMR (400 MHz,

$CDCl_3$+CD_3OD, 25 ºC): δ = 8.04 (d, 2H, *J* = 8.5 Hz, H3´, H-5´), 7.35 (d, 2H, *J* = 8.5 Hz, H-2´, H-6´), 7.19-7.08 (m, 5H, Ph), 6.75 (s, 1H, H-6), 6.32 (s, 1H, H-9), 4.55-4.48 (m, 2H, H-1, H-2), 3.13-2.82 (m, 4H, H-4, H-5), 2.13 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD, 25 ºC): δ = 147.4, 146.9, 142.4, 140.4 (C-1´, C-4´, C-7, C-8), 140.3 (CPh), 131.4, 130.8 (C-5a, C-9a), 130.0 (C-2´, C-6´), 129.1, 128.3, 126.6 (CH Ph), 123.1 (C-3´, C-5´), 116.8, 116.5 (C-6, C-9), 70.4 (C-2), 53.6 (C-1), 50.8 (C-4), 44.8 (*N*-Me), 32.8 (C-5) ppm. EI-MS: *m/z* (%) = 391 (20), 390 (M^+, 80), 300 (21), 299 (100), 268 (7), 211 (37), 178 (64), 177 (33), 165 (45). HR-MS: calcd for $C_{23}H_{23}N_2O_4$ $[M + H]^+$ 391.1652; found 391.1652.

4.9. Preparation of amine derivatives from nitro derivatives via catalytic hydrogenation

A mixture of the corresponding nitroderivative (0.3 mmol) and Pd/C (approx. 3 mg) in MeOH (20 mL) was saturated with hydrogen and stirred at 20 ºC for 3 h under hydrogen. After this period, the crude reaction was filtered through celite and the solvent was evaporated under vacuum to give the corresponding amino derivative.

(±)-1-(4-Aminophenyl)-6,7-dihydroxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (4f)

Tetrahydroisoquinoline **4f** (80 mg, 89%) was obtained from the isoquinoline **4b** (100 mg, 0.33 mmol) as a brown amorphous solid. M.p. 190-192 ºC. ^{1}H NMR (400 MHz, CD_3OD, 25 ºC): δ = 6.96 (d, 2H, *J* = 8.5 Hz, H-2´, H-6´), 6.69 (d, 2H, *J* = 8.5 Hz, H-3´, H-5´), 6.52 (s, 1H, H-5), 6.06 (s, 1H, H-8), 4.16 (s, 1H, H-1), 3.12-3.00 (m, 2H, H-3, H-4), 2.72-2.60 (m, 2H, H-3´, H-4´), 2.22 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 ºC): δ = 148.5, 145.2, 144.6 (C-4´, C-6, C-7), 132.4, 130.4, 126.1 (C-1´, C-4a, C-8a), 132.0 (C-2´, C-6´), 116.4 (C-3´, C-5´), 115.5 (C -5, C-8), 71.7 (C-1), 53.2 (C-3), 44.1 (*N*-Me), 28.8 (C-4) ppm. EI-MS: *m/z* (%) = 271 (7), 270 (M^+, 27), 269 (18), 179 (19), 178 (100), 177 (15). HR-MS: calcd. for $C_{16}H_{19}N_2O_2$ $[M + H]^+$ 271.1441; found 271.1443.

(±)-*trans*-1-(4-Aminophenyl)-7,8-dihydroxy-*2*-methoxycarbonyl-*N*-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7h-*trans*)

Benzazepine **7h**-*trans* (40 mg, 87%) was obtained from the benzazepine **7b**-*trans* (50 mg, 0.13 mmol) as a pale brown amorphous solid. M.p. decomposes. ^{1}H NMR (400 MHz, CD_3OD, 25 ºC): δ = 6.95 (d, 2H, *J* = 8.2 Hz, H-2´, H-6´), 6.71 (d, 2H, *J* = 8.2 Hz, H-3´, H-5´), 6.59 (s, 1H H-6), 6.45 (s, 1H H-9), 4.50 (d, 1H, *J* = 7.2 Hz, H-1), 4.37 (d, 1H, *J* = 7.2 Hz, H-2), 3.56 (s, 3H, CO*OMe*), 3.48-3.37 (m, 2H, H-4, H-5), 2.84-2.71 (m, 2H, H-4´, H-5´), 2.58 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 ºC): δ = 170.4 (CO), 147.1 (C-4´), 145.6, 145.0 (C-7, C-8), 132.5, 131.6, 130.4 (C-1´, C-5a, C-9a), 130.2 (C-2´, C-6´), 119.2, 118.2 (C-6, C-9), 117.0 (C-3´, C-5´), 69.5 (C-2), 53.3 (C-1), 52.6 (C-4), 51.4 (CO*OMe*), 45.7 (*N*-Me), 33.1 (C-5) ppm. EI-MS: *m/z* (%) = 343 (3), 342 (M^+, 10), 284 (32), 283 (100), 240 (14), 226 (20), 178 (11), 176 (9). HR-MS: calcd. for $C_{19}H_{23}N_2O_4$ $[M + H]^+$ 343.1652; found 343.1652.

(±)-*trans*-*N*-2-(4-Aminophenyl)-7,8-dihydroxy-*N*-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7i-*trans*)

Benzazepine **7i**-*trans* (50 mg, 77%) was obtained from the benzazepine **7g**-*trans* (70 mg, 0.18 mmol) as a pale brown amorphous solid. M.p. 170-173 ºC. ^{1}H NMR (400 MHz, CD_3OD, 25 ºC): δ = 7.26-7.13 (m, 5H, Ph), 7.08 (d, 2H, *J* = 8.5 Hz, H-2´, H-6´), 6.75 (s, 1H, H-6), 6.63 (d, 2H, *J* = 8.5 Hz, H-3´, H-5´), 6.75 (s, 1H, H-6), 6.35 (s, 1H, H-9), 4.72 (d, 1H, *J* = 9.5 Hz, H-1), 4.47 (d, 1H, *J* = 9.5 Hz, H-2), 3.28-3.26 (m, 1H, H-5), 3.20 (dt, 1H, *J* = 11.8, 4.8 Hz, H-4), 3.10-2.99 (m, 1H, H-5'), 2.94 (td, 1H, *J* = 11.8, 4.8 Hz, H-4'), 2.25 (s, 3H, *N*-Me) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 ºC): δ = 149.5 (C-4´), 145.6, 145.5 (C-8, C-7), 141.8 (CPh), 132.3, 130.4, 127.8 (CH Ph), 131.9, 131.2 (C-5a, C-9a), 129.5 (C-2´, C-6´), 129.4 (C-1´), 118.5, 118.0 (C-6, C-9), 116.2 (C-3´, C-5´), 72.1 (C-2), 54.6 (C-1), 52.5 (C-4), 44.5 (*N*-Me), 32.2 (C-5) ppm. EI-MS: *m/z* (%) = 269 (7), 268 (11), 254 (16), 253 (22), 211 (9), 195 (28), 179 (26), 178 (100), 177 (13). HR-MS: calcd for $C_{23}H_{25}N_2O_2$ $[M + H]^+$ 361.1911; found 361.1906.

4.10. Pharmacological *in vitro* assays

Animals

Male Sprague-Dawley rats (Charles River, Barcelona, Spain) (n= 5) weighing 200-220 g were used. Animals were maintained on a standard light/dark cycle (12/12 h), constant room temperature (20 ± 2 ºC) and relative humidity (40 ± 5%). Food and water were available *ad libitum*. Animal care and procedures described in the present study were conducted in accordance with protocols passed by the Ethical Committee of the University of Málaga and in keeping with the European (Directive 2010/63/UE) and Spanish (Real Decreto 53/2013) guidelines.

Binding experiments

The experiments were performed on striatal membranes. Rats were sacrificed by decapitation and the striatal samples were dissected from the brain, frozen in isopentane (-40 ºC) and stored at -80 ºC until use. Each striatum was homogenized in 10 volumes (w/v) of ice-cold Tris-HCl (50 mM, pH 7.4) with EDTA (1 mM) and centrifuged at 20,000 rpm for 20 min at 4 ºC. The supernatant was discarded and the pellet resuspended in 10 mL of Tris-HCl (50 mM, pH 7.4) and centrifuged again. The final pellet was resuspended in Tris-HCl (50 mM, pH 7.4) containing NaCl (120 mM), KCl (2 mM) and $MgCl_2$ (1 mM) to a final protein concentration of 2.5 mg/mL.

The ability of each compound to bind D_1-like or D_2-like was evaluated in a preliminary experiment. Striatal membranes were incubated for 1 h at 25 ºC with either the dopamine D_1-like antagonist [^{3}H]SCH 23390 (1 nM) (PerkinElmer) or the D_2-like antagonist [^{3}H]raclopride (1 nM) (PerkinElmer) and one of the compounds (10^{-6} M). Non-specific binding was determined in the presence of SCH 23390 (50 mM) or butaclamol (50 mM) (Sigma-Aldrich). The incubation was stopped by fast filtration through a glass-fibre (GF/B, Whatman) followed by washing three times with 5 mL of Tris-HCl (50 mM, pH 7.4) with an automatic cell harvester (Brandel). The radioactivity content of the filters was detected by liquid scintillation spectrometry.

Those compounds that displaced at least 50% of the radioligand were used for competition experiments. In this case, the striatal membranes were incubated for 1 h at 25ºC with [^{3}H]SCH 23390 (1 nM) or [^{3}H]raclopride (1 nM) and various concentrations of the competitive compound selected (10^{-4} M to 10^{-10} M). Non-specific binding was determined in the presence of SCH 23390 (50 mM) or butaclamol (50 mM) (Sigma-Aldrich). The incubation was stopped by fast filtration through a glass-fibre (GF/B, Whatman) followed by washing three times with 5 mL of Tris-HCl (50 mM, pH 7.4) with an automatic cell harvester (Brandel). The radioactivity content of the filters was detected by liquid scintillation spectrometry. Data were analyzed by Prim (Graph Pad Software, San Diego, CA, U.S.A.), and K_i values were determined using K_D value for [^{3}H]SCH 23390 of 0.2 nM and for [^{3}H]Raclopride of 1.8 nM. Values are expressed as the mean ± SEM of three independent experiments performed in duplicated.

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1 (a) H. H. M. Van Tol, J. R. Buznow, H. C. Guan, R. K. Sunahara, P. Seeman, H. B. Niznik and O. Civelli, *Nature*, 1991, **350**, 610–614. (b) P. Sokoloff, B. Giros, M. P. Martres, M. L. Bouthenet and J. C. Schwartz, *Nature*, 1990, **347**, 146–151. (c) R. K. Sunahara, H. C. Guan, B. F. O'Dowd, P. Seeman, L. G. Laurier, G. Ng, S. R. George, J. Torchia, H. H. M. Van Tol and H. B. Niznik, *Nature*, 1991, **350**, 614–619. (d) K. Negash, D. E. Nichols, V. J. Watts, R. B. Mailman, *J. Med. Chem.*, 1997, **40**, 2140–2147. (e) R. M. Huff, *Cell Signal.,* 1996, ***8***, 453-459.

2 A. Zhang, J. L. Neumeyer and R. J. Baldessarini, *Chem. Rev.*, 2007, **107**, 247-302.

3 J. Zhang, B. Xiong, X. Zhen and A. Zhang*, Med. Res. Rev.*, 2009, **29**, 272-294.

4 K. K. Gnanalingham, A. J. Hunter, P. Jenner and C. D. Marsden, *Psychopharmacology*, 1995, **117**, 403–412.

5 A. D. Medhurst, A. R. Atkins, I. J. Beresford, K. Brachenborough, M. A. Briggs, A. R. Calver, J. Cilia, J. E. Cluderay, B. Crook, J. B. Davis, R. K. Davis, R. P. Davis, L. A. Dawson, A. G. Foley, J. Gartlon, M. I. Gonzalez, T. Heslop, W. D. Hirst, C. Jennings, D. N. C. Jones, L. P. Lacroix, A. Martyn, S. Ociepka, A. Ray, C. M. Regan, J. C. Roberts, J. Schogger, E. Southam, T. O. Stean, B. K. Trail, N. Upton, G. Wadsworth, J. A. Wald, T. White, J. Witherington, M. L. Woolley, A. Worby and D. M. Wilson, *J. Pharmacol. Exp. Therap*., 2007, **321**, 1032–1045.

6 a) E. H. Gold and W. K. Chang, U. S. Patent 4284555, 1981. b) L. C. Iorio, A. Barnett, F. H. Leitz, V. P. Houser and C. A. Korduba, *Pharmacology*, 1983, **226**, 462–468; c) J. A. Bourne, *CNS Drug Rev.*, 2001, **7**, 399-414.

7 J. G. Berger, W. K. Chang, J. W. Clader, D. Hou, R. E. Chipkin and A. T. McPhail, *J. Med. Chem*., 1989, **32**, 1913–1921.

8 A. Barnett, R. D. McQuade and C. Tedford, *Neurochem. Int*., 1992, **20**, 119S–122S.

9 P. S. Charifson, S. D. Wyrick, A. J. Hoffman, R. M. A. Simmons, J. P. Bowen, D. L. McDougald and R. B. Mailman, *J. Med. Chem.*, 1988, **31**, 1941-1946.

10 S. D. Gleason and J. M. Witkin, *Psycopharmacology*, 2006, **186**, 25-31.

11 J. Zhang, X. Chen, L. Yu, X. Zhen and A. Zhang, *Bioorg. Med. Chem.*, 2008, **16**, 9425-9431.

12 J. Neumeyer, N. S. Kula, J. Bergman and R. J. Baldessarini, *Eur. J. Pharm*., 2003, **474**, 137-140.

13 G. Tamagnan, R. M. Baldwin, N. S. Kula, R. J. Baldessarini and R. B. Innis, *Bioorg. Med. Chem.*, 2000, **10**, 1113-1115.

14 V. Bakthavachalam, N. Baindur, B. K. Madras and J. L. Neumeyer, *J. Med. Chem.*, 1991, **34**, 3235-3241.

15 a) P. H. Andersen and J. A. Jansen, *Eur. J. Pharmacol.*, 1990, **188**, 335-347. b) J. L. Conroy, R. B. Free and D. R. Sibley, *ACS Chem. Neurosci.*, 2015, **6**, 681-692.

16 a) N. Cabedo, I. Berenguer, B. Figadere and D. Cortes, *Curr. Med. Chem.*, 2009, **16**, 2441-2467. b) A. Bermejo, P. Protais, M. A. Blazquez, K. S. Rao, M. C. Zafra-Polo and D. Cortes, *Nat. Prod. Lett.*, 1995, **6**, 57-62. c) P. Protais, J. Arbaoui, E. H. Bakkali, A. Bermejo and D. Cortes, *J. Nat. Prod*., 1995, **58**, 1475-1484. d) J. Parraga, N. Cabedo, S. Andújar, L. Piqueras, L. Moreno, A. Galan, E. Angelina, R. D. Enriz, M. D. Ivorra, M. J. Sanz and D. Cortes, *Eur. J. Med. Chem.*, 2013, **68**, 150-166. e) L. Moreno, N. Cabedo, M. D. Ivorra, M. J. Sanz, A. Lopez-Castel, M. C. Alvarez and D. Cortes, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 4824-4827. f) J. Parraga, A. Galán, M. J. Sanz, N. Cabedo and D. Cortes, *Eur. J. Med. Chem.*, 2015, **90**, 101-106. g) E. Angelina, S. Andujar, L. Moreno, F. Garibotto, J. Párraga, N. Peruchena, N. Cabedo, M. Villecco, D. Cortes and R. D. Enriz, *Mol. Inf.*, 2015, **34**, 28-43.

17 a) N. Cabedo, P. Protais, B. K. Cassels and D. Cortes, *J. Nat. Prod.*, 1998, **61**, 709-712. b) I. Andreu, D. Cortes, P. Protais, B. K. Cassels, A. Chagraoui and N. Cabedo, *Bioorg. Med. Chem.*, 2000, **8**, 889-895. c) N. Cabedo, I. Andreu, M. C. Ramírez de Arellano, A. Chagraoui, A. Serrano, A. Bermejo, P. Protais and D. Cortes, *J. Med. Chem.*, 2001, **44**, 1794-1801. d) I. Andreu, N. Cabedo, G. Torres, A. Chagraoui, M. C. Ramírez de Arellano, S. Gil, A. Bermejo, M. Valpuesta, P. Protais and D. Cortes, *Tetrahedron*, 2002, **58**, 10173-10179. e) N. El Aouad, I. Berenguer, V. Romero, P. Marín, A. Serrano, S. Andujar, F. Suvire, A. Bermejo, M. D. Ivorra, R. D. Enriz, N. Cabedo and D. Cortes, *Eur. J. Med. Chem.*, 2009, **44**, 4616-4621. f) S. Andujar, F. Suvire, I. Berenguer, N. Cabedo, P. Marín, L. Moreno, M. D. Ivorra, D. Cortes and R. D. Enriz, *J. Mol. Model.*, 2012, **18**, 419-431. g) O. Parravicine, M. L. Bogado, S. rojas, E. L. Angelina, S. A. Andujar, L. J. Gutierrez, N. Cabedo, M. J. Sanz, M. P. López-Gresa, D. Cortes and R. D. Enriz, *J. Mol. Model.*, 2017, **23**, 1-14.

18 a) F. D. Suvire, I. Andreu, A. Bermejo, M. A. Zamora, D. Cortes and R. D. Enriz, *J. Mol. Struct. (Teochem.)*, 2003, **666**, 109-116. b) F. D. Suvire, N. Cabedo, A. Chagraoui, M. A. Zamora, D. Cortes and R. D. Enriz, *J. Mol. Struct. (Teochem.)*, 2003, **666**, 455-467.

19 a) B. Hoffman, S. J. Cho, W. Zheng, S. Wyrick, D. E. Nichols, R.B. Mailman and A. Tropsha, *J. Med. Chem*., 1999, **42**, 3217-3226. b) D. L. Minor, S. D. Wyrick, P. S. Charifson, V. J. Watts, D. E. Nichols and R. B. Mailman, *J. Med. Chem.*, 1994, **37**, 4317-4328. c) I. Berenguer, N. El Aouad, S. Andujar, V. Romero, F. Surive, T. Freret, A. Bermejo, M. D. Ivorra, R.D. Enriz, M. Boulouard, N. Cabedo and D. Cortes, *Bioorg. Med. Chem.*, 2009, **17**, 4968-4980.

20 P. Cheng, N. Huang, Z. Jiang, Q. Zhang, Y. Zheng, J. Chen, X. Zhang and Y. Ma, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2475-3478.

21 a) M. Valpuesta, M. Ariza, A. Díaz and R. Suau, *Eur. J. Org. Chem.*, 2010, **23**, 4393-4401. b) M. Ariza, A. Díaz, R. Suau and M. Valpuesta, *Eur. J. Org. Chem.*, 2011, **32**, 6507-6518.

22 M. Valpuesta, M. Ariza, A. Díaz, G. Torres and R. Suau, *Eur. J. Org. Chem.*, 2010, **4**, 638-645.

23 a) B. Zhao, Y. Yang and S. Eguchi, *Org. Prep. Proced. Int.*, 1997, **29**, 185-194. b) S. Hati and S. Sen, *Eur. J. Org. Chem.*, 2017, **9**, 1277-1280.

24 K. Neuvonen, F. Fulop, H. Neuvonen, A. Koch, E. Kleinpeter and K. Pihlaja, *J. Org. Chem.,* 2005, **70**, 10670-10678.
25 a) K. Jia, D. Yang, S. Zhang and J. Cheng, *Org. Lett*., 2009, **11**, 4716-4719. b) M. Chaitanya, D. Yadagiri and P. Anbarasan, *Org. Lett.*, 2013, **15**, 4960-4963.
26 M. Kaur, E. Sharma, A. Singh, P. Singh and K. N. Singh, *Eur. J. Org. Chem.*, 2016, **24**, 4159-4170.