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Short communication

Affinity of 1-aryl-1,2,3,4-tetrahydroisoquinoline derivatives to the ion channel binding site of the NMDA receptor complex

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Abstract

A series of 1-aryl-1,2,3,4-tetrahydroisoquinoline and 8-methyl-1-aryl-1,2,3,4-tetrahydroisoquinoline derivatives was evaluated for affinity to the PCP binding site of the NMDA receptor complex. The (*S*)-configurated tetrahydroisoquinoline derivative (*S*)-**4e·HCl** bearing a 2-methylphenyl substituent in position 1 of the heterocyclic ring system and a methyl group in position 8 was found to exhibit the highest affinity among the derivatives with a K_i-value of 0.0374 μM. In addition, this compound shows a remarkable enantioselectivity of binding by being almost 90 times more potent than the corresponding (*R*)-enantiomer (*R*)-**4e·HCl**. Additionally, a convenient and efficient synthetic approach to racemic 1-aryl-1,2,3,4-tetrahydroisoquinoline derivatives is described.

Keywords: N-Methyl-D-aspartate receptor; PCP binding site; MK-801; Tetrahydroisoquinolines

1. Introduction

Most excitatory synapses in the brain use the neurotransmitter glutamate to pass on impulses between neurons. Glutamatergic pathways are ubiquitous throughout the brain and physiological short-term glutamate release is crucial to synaptic plasticity and higher brain functions such as learning and memory [1]. Excessive exposure to glutamate, conversely, causes overstimulation of the various glutamate receptors leading to localized vulnerability of neurons and triggering neuronal cell death. This excitotoxicity resulting from glutamate exceeding physiological levels is one of the key factors contributing to acute and chronic neuropathological processes, such as ischemia, traumatic brain injury, epilepsy, Parkinson's, Huntington's, and Alzheimer's disease, whereas deficient glutamatergic neurotransmission might be connected with schizophrenia [2]. Modulation of the excitatory synaptic neurotransmission by antagonizing the ionotropic L-glutamate receptor *N*-methyl-D-aspartate (NMDA) limits cascades of neurotoxicity thereby impeding neuronal damage. A blockade of the NMDA receptor complex also efficiently suppresses central sensitization to pain occurring due to prolonged firing of C-fiber nociceptors and enhanced release of glutamate [3]. Since NMDA antagonists have been found to effectively counteract opioid tolerance, they are potentially advantageous as coanalgesics in combination with opioids [4].

Antagonism of receptor mediated processes can be achieved pharmacologically by interaction with the various binding sites of the NMDA receptor complex, i.e. the glutamate-binding site, the glycine co-agonist site, the polyamine binding site, and the redox modulatory site(s) [5]. Lodge et al. identified phencyclidine (PCP) as a noncompetitive NMDA antagonist binding to a previously unknown discrete site located within the cation channel thereby impeding ion passage through the open-channel [6]. The discovery laid the foundation for intensive research towards so called open-channel blockers acting at this PCP binding site. MK801 (**1**), one of the most potent ligands, serves as an excellent probe for the evaluation of novel NMDA channel blockers (Fig. 1). Efforts to develop NMDA antagonists have been plagued by the need to weigh the clin-

Abbreviations: CC, column chromatography; GP, general procedure; NMDA, *N*-methyl-D-aspartate; PCP, phencyclidine; S.E.M., standard error of the means.

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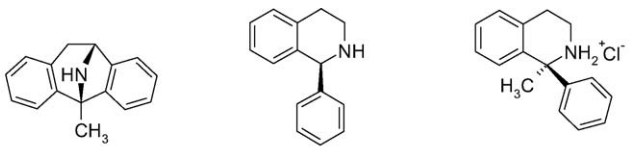


MK801 (**1**)	(1*S*)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline (**2**)	FR115427 (**3**)
K_i = 1.26±0.18 nM	1.38±0.07 μM [8]	0.0354±0.0038 nM [9]

Fig. 1. Structures of representative known NMDA receptor antagonists acting at the PCP binding site.

ical benefits against possible side effects. The therapeutic value of a range of NMDA antagonists is compromised by side effects including psychosis, agitation, and disorientation. Approved open-channel blockers include memantine, amantadine, budipine, ketamine and dextromethorphane. Gray et al. [7] discovered that 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**2**) displays high affinity to the PCP binding site. As demonstrated in our group, binding of the (*S*)-enantiomer is 27-fold greater than that of the (*R*)-enantiomer (Fig. 1) [8]. Consistently, the potency of the (*S*)-configurated close analogue FR115427 (**3**) was found to differ from its enantiomer exceeding it by a factor of 100 (Fig. 1) [9].

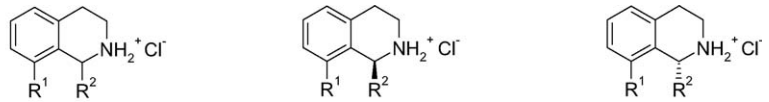
Herein we report the biological evaluation of the 1-aryl-1,2,3,4-tetrahydroisoquinolines **4a**–**c·HCl** and the corresponding 8-methyl derivatives **4d**–**f·HCl** in their racemic form and, for most though not all of the compounds, their enantiomerically pure form as well (Fig. 2). The conceptual rationale for the introduction of a methyl substituent in position 8 was to utilize the $A^{(1,3)}$ strain [10] to change the conformation of the corresponding compound. Based on a conformational analysis performed for closely related isoquinoline derivatives [11] it is reasonable to assume that the preferential conformation adopted by tetrahydroisoquinoline **4a** is one where the heterocyclic ring exists as a half chair and the phenyl ring is disposed in a pseudo equatorial position. But this conformation is likely to change when a methyl group is introduced in position 8 of the isoquinoline nucleus. The severe increase in of the $A^{(1,3)}$ strain between the substituents in positions 1 and 8 of the tetrahydroisoquinoline nucleus resulting from the newly introduced methyl substituent can be expected to force the phenyl group present in position 1 out of the plane of the heterocyclic ring system into a pseudo axial position. Of course, the extent of the allylic strain and thereby the position of the conformational equilibrium will also depend on the steric demand of the substituent present in position 1. Therefore, when the 1-phenyl group in **4a** and **4d** is replaced by sterically more demanding residues, as in **4b**–**c** and **4e**–**f**, this should also affect the position of the conformational equilibria and raise the amount of the conformer with the 1-aryl substituent adopting a pseudo axial position.

Conformational changes like this can be expected to have a marked influence on the capability of the individual compounds for binding to the target site. Therefore, we thought it quite promising to study the affinity of **4a**–**f** to the PCP binding site of the NMDA receptor.

Additionally, we describe in this paper a highly efficient procedure which provides a straightforward access to the isoquinoline derivatives **4a**–**f·HCl** in racemic form. The procedure is based on *N*-acyliminium ion chemistry and complements earlier efforts directed towards the synthesis of **4a**–**f·HCl** in enantiopure form by a related but asymmetric strategy [12]. For the sake of simplicity the evaluation of the biological activity potencies of **4a**–**f·HCl** at the PCP binding site of the NMDA receptor was based on the racemic compounds, as most but not all of the desired tetrahydroisoquinoline derivatives **4a**–**f·HCl** had been accessible by the aforementioned asymmetric synthesis in enantiopure form.

2. Chemistry

The trapping reaction of *N*-acyliminium ions with nucleophiles is a well established procedure for the construction of α-substituted amides and carbamates as well as their corre-



rac-**4·HCl** (*S*)-**4·HCl*** (*R*)-**4·HCl***

R^1 = H, CH_3 R^2 = Ph, Tol, Xyl

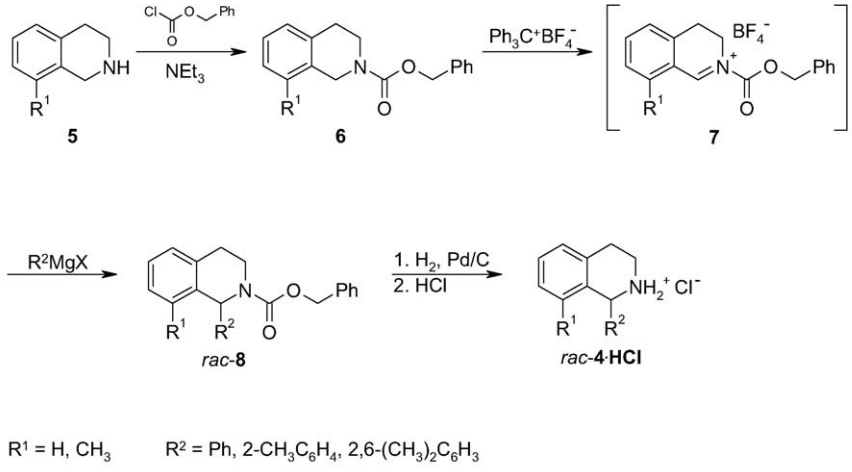
*of note: for R^1 = H and R^2 = 2,6-$(CH_3)_2C_6H_3$ (**4c**) the stereochemical descriptor changes due to the higher priority of the 2,6-$(CH_3)_2C_6H_3$ moiety

Fig. 2. The structures of the target compounds.

sponding amines [13]. We conjectured that this powerful method could be suitable to conveniently provide the racemic 1-aryl-1,2,3,4-tetrahydroisoquinoline derivatives *rac*-**4·HCl** (Scheme 1). Compounds **6**, easily obtained by reaction of tetrahydroisoquinoline derivatives **5** [14] and benzyl chloroformate (yield: 89–95%), proved to be a well-suited precursors for the generation of the isoquinolinium ions **7**. Direct reaction of an imine or an *N*-heterocycle with acylchlorids or chloroformates often suffers from an unfavorable equilibrium. Generation of *N*-acyliminium ions by hydrid abstraction from compounds **6** using $Ph_3C^+BF_4^-$ as oxidizing reagent was found to be advantageous since it is an irreversible process leading to almost complete formation of the key intermediates **7** [8,15,16]. Addition of the respective Grignard reagent (PhMgCl, 2-methylphenylmagnesium bromide, 2,6-dimethylphenylmagnesium bromide) to the *N*-acyliminium ions **7** proceeded with moderate yields (56–71%). The final racemic compounds *rac*-**4a**–**f·HCl** needed for the biological studies were obtained by removal of the carbamate functionality employing catalytic hydrogenolysis (H_2, Pd/C) and subsequent treatment with hydrogen chloride (yields: 46–91%). In addition to these racemic compounds the pure enantiomers (*S*)-**4a·HCl**, (*S*)-**4d**–**f·HCl**, (*R*)-**4a·HCl**, (*R*)-**4c·HCl** and (*R*)-**4e**–**f·HCl** were available to us, too. Their synthesis had been accomplished by an analogous asymmetric synthesis based on chiral *N*-acyliminium ion as mentioned above [12].

3. Results and discussion

The water soluble hydrochloride salts *rac*-**4a**–**f·HCl**, (*S*)-**4a·HCl**, (*S*)-**4d**–**f·HCl**, (*R*)-**4a·HCl**, (*R*)-**4c·HCl** and (*R*)-**4e**–**f·HCl** were screened for their in vitro activity at the PCP site of the NMDA receptor complex using a competitive binding assay at pig frontal cortex preparations with the radioligand [^{3}H]MK-801 that binds to and blocks the channel pore mostly when the receptor is in its active conformation. MK-801 served as reference compounds and exhibited a K_i-value of 1.26 ± 0.18 nM. The biological activities of 1-phenyl-1,2,3,4-tetrahydroisoquinolines (*S*)-**4a·HCl** and (*R*)-**4a·HCl** assessed in a radioreceptor binding assay based on rat frontal cortex were already reported in literature [8] [(*S*)-**4a·HCl**: $K_i = 1.38 \pm 0.07$ μM and (*R*)-**4a·HCl**: $K_i = 37.9 \pm 5.4$ μM]. Using pig frontal cortex we found slightly different K_i values (*rac*-**4a·HCl**: K_i = of 0.921 ± 0.021 μM, (*S*)-**4a·HCl**: $K_i = 0.553 \pm 0.026$ μM, and (*R*)-**4a·HCl**: $K_i = 32.17 \pm 1.24$ μM). Introduction of a methyl group at position 8 of the isoquinoline ring to force the 1-aryl moiety into a pseudo axial position by enhan-

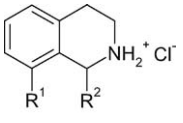
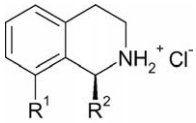
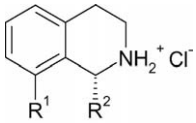
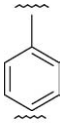
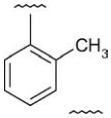
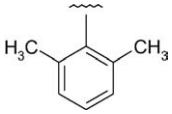
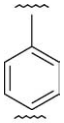
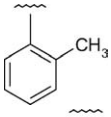
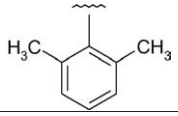


5, 6, 7	a	b
R^1	H	CH_3

4, 8	a	b	c	d	e	f
R^1	H	H	H	CH_3	CH_3	CH_3
R^2	C_6H_5	2-$CH_3C_6H_4$	2,6-$(CH_3)_2C_6H_3$	C_6H_5	2-$CH_3C_6H_4$	2,6-$(CH_3)_2C_6H_3$

Scheme 1. Synthetic approach to racemic 1-aryl-1,2,3,4-tetrahydroisoquinoline derivatives.

Table 1
ESSAI Affinity of compounds **4·HCl** to the PCP binding site of the NMDA receptor complex

		K_i-value (μM)		
				
R^1	R^2			
H		0.921 ± 0.021 (*rac*-**4a·HCl**)	0.553 ± 0.026 ((*S*)-**4a·HCl**)	32.17 ± 1.24 ((*R*)-**4a·HCl**)
		0.514 ± 0.039 (*rac*-**4b·HCl**)	–	–
		7.52 ± 0.20 (*rac*-**4c·HCl**)	5.97 ± 0.29 ((*R*)-**4c·HCl**)[a]	–
CH_3		0.872 ± 0.063 (*rac*-**4d·HCl**)	0.475 ± 0.030 ((*S*)-**4d·HCl**)	–
		0.0827 ± 0.0097 (*rac*-**4e·HCl**)	**0.0374 ± 0.0068** ((*S*)-**4e·HCl**)	3.31 ± 017 ((*R*)-**4e·HCl**)
		1.87 ± 0.25 (*rac*-**4f·HCl**)	1.06 ± 0.06 ((*S*)-**4f·HCl**)	5.81 ± 0.34 ((*R*)-**4f·HCl**)

[a] Of note: for R^1 = H and R^2 = 2,6-$(CH_3)_2C_6H_3$ (**4c**) the stereochemical descriptor changes due to the higher priority of the 2,6-$(CH_3)_2C_6H_3$ moiety.

cing the allylic strain led to higher potencies for compounds *rac*-**4e**–**f·HCl** at the PCP binding site as compared to the 8-unsubstituted derivatives *rac*-**4b**–**c·HCl** (Table 1). *rac*-**4a** and *rac*-**4d** also seem to follow the same trend, but in this case the difference between the K_i values is not significant. Among the series of the racemic mixtures, the 1-tolyl substituted derivatives *rac*-**4b·HCl** and *rac*-**4e·HCl** exhibited the highest affinity, with K_i-values of 0.514 ± 0.039 and 0.0827 ± 0.0097 μM, respectively. In contrast, replacement of the tolyl group by a xylyl moiety was found to be detrimental, leading to a profound loss of affinity with compounds *rac*-**4c·HCl** and *rac*-**4f·HCl** exhibiting the highest K_i values (Table 1).

So far one can only speculate about the origin of the high affinity of rac-**4e·HCl** to the PCP binding site compared to the remaining racemates. However, the presence of a methyl substituent at position 8 of the isoquinoline ring, as for example in *rac*-**4d**–**f·HCl**, will certainly cause a marked change of the conformational equilibrium of these compounds, forcing the aryl substituent at position 1 out of the ring plane into a more pseudo axial orientation. The ortho substituents at the phenyl ring of rac-**4e**–**f·HCl** will, furthermore, effect the rotational isomerism around the single bond between C-1 of the isoquinoline moiety and the quaternary carbon of the aryl ring. The 1-tolyl group in *rac*-**4e** could be capable of favoring a specific conformation that is beneficial for binding to the target whereas the symmetric 1-phenyl and 1-xylyl moieties in *rac*-**4d·HCl** and *rac*-**4f·HCl**, respectively, are not. This could explain the higher potency of *rac*-**4e·HCl** compared to that of *rac*-**4d·HCl** and *rac*-**4f·HCl**, though other phenomena of a more steric origin, an attractive interaction with the target binding site for the first ortho methyl group (in *rac*-**4e·HCl**) and a repulsion of the second (in *rac*-**4f·HCl**) could be responsible as well.

It has consistently been noted that 1-aryl-1,2,3,4-tetrahydroisoquinolines display a distinct enantioselectivity of binding with the (*S*)-configurated enantiomer being more potent than its counterpart [8,9]. This observation is confirmed by the screening data reported here (see Table 1). Overall, methyl substitution at position 8 of the isoquinoline ring, one methyl group in *o*-position of the 1-phenyl moiety and (*S*)-configuration gave the most potent compound (*S*)-**4e·HCl** with a K_i-value of = 0.0374 ± 0.0068 μM. The pharmacological enantioselectivity was determined to be 89/1 ((*S*)-**4e·HCl**/(*R*)-**4e·HCl**) almost reaching the eudismic ratio reported for **3** (100/1) [9].

4. Conclusion

In summary, we have developed a new method for the synthesis of 1-aryl-1,2,3,4-tetrahydroisoquinolines. Biological screening showed that a methyl group in position 8 and the *o*-position of the 1-phenyl substituent is beneficiary for binding affinity to the PCP site of the NMDA receptor complex. Our results corroborate previous findings that the potency of 1-aryl-

1,2,3,4-tetrahydroisoquinolines to the PCP binding site is highly enantioselective.

5. Experimental

5.1. Chemistry

5.1.1. General

All reactions were carried out in vacuum dried glassware under nitrogen atmosphere. All reagents were used as commercially available. PhMgCl was purchased from Fluka (1.8 M in THF). 2-Methylphenylmagnesium bromide and 2,6-dimethylphenylmagnesium bromide were prepared from 2-bromotoluene and from 2-bromo-1,3-dimethylbenzene in THF, respectively (1.0 M in THF based on amount of arylhalide employed, metallic magnesium was activated by means of I_2). Solvents were dried and distilled prior to use. CH_2Cl_2 was distilled from CaH_2 and CH_3OH from Mg prior to use. Melting points were determined on a Büchi melting point apparatus no. 510 (Dr. Tottoli) and are uncorrected. IR spectra were recorded with a Perkin Elmer FT-IR spectrophotometer Paragon 1000 or 1600, and NMR spectra were obtained with a JEOL JNM-GX 400 spectrometer (400 MHz for 1H, 100 MHz for 13C) with TMS as internal standard. The NMR spectra were recalculated with NUTS, 2D version 4.35 or 5.097. MS spectra were recorded on a Hewlett Packard 5989 A with 59980 B particle beam LC/MS interface. CHN-analyses were determined with an elemental analysator Rapid (Heraeus). The results of elemental analyses for C, H and N were within ± 0.4% of the theoretical values. LC: Merck 60 F-254. Column chromatography (CC) was performed as flash chromatography with silica gel Merck 60 F-254 (0.040–0.063 mm).

5.1.2. Synthesis of the N-benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinolines (GP1)

Benzyl chloroformate was added to a solution of the respective 1,2,3,4-tetrahydroisoquinoline **5** and NEt_3 in CH_2Cl_2. The reaction mixture was stirred at room temperature. After addition of HCl (2 M in H_2O) the organic solvent was evaporated in vacuo. Following extraction with Et_2O, the organic layers were dried ($MgSO_4$), concentrated in vacuo, and purified by CC.

5.1.3. α-Amidoalkylation via N-benzyloxycarbonyliminium ions (GP2)

$Ph_3C^+BF_4^-$ (1.1 eq, 0.1 M in CH_2Cl_2) was added to a solution of **6** (0.03 M in CH_2Cl_2) at room temperature. After 16 h the reaction mixture was cooled to –78 °C followed by the addition of the respective Grignard reagent. The reaction was quenched with H_2O after 4 h, warmed to room temperature, and acidified with HCl (2 M in H_2O). Following extraction with Et_2O, the combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and purified by CC.

5.1.4. Catalytic hydrogenolysis (GP3)

20% Pd/C (oxidized form, 1.0 w/w) were added to the respective compound **8** (0.2 M in MeOH) in a 3-necked round-bottom flask connected to a gas burette and the reaction mixture was hydrogenated at room temperature and normal pressure for 16 h. Following filtration and evaporation in vacuo, the free amines were obtained. Treatment of the free amines in Et_2O with gaseous HCl and evaporation in vacuo gave the corresponding hydrochlorides **4·HCl**.

5.1.5. N-Benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline (6a)

According to GP1 from benzylchloroformate (5.16 ml, 36.13 mmol), 1,2,3,4-tetrahydroisoquinolinium hydrochloride **5a·HCl**) (4.087 g, 24.09 mmol) and NEt_3 (10.07 ml, 72.27 mmol) in 50 ml CH_2Cl_2; reaction time: 17 h. Purification by CC (EtOAc/*n*-heptane = 20:80). Yield: 5.713 g (89%); colorless oil. TLC: $R_f = 0.42$ (EtOAc/*n*-heptane = 20:80). ^{1}H NMR ($CDCl_3$, 20 °C): $\delta = 2.77–2.95$ (m, 2 H, CH_2CH_2), 3.63–3.81 (m, 2 H, CH_2CH_2), 4.67 (s, 2 H, $C_{ar}CH_2N$), 5.20 (s, 2 H, CH_2O), 7.06–7.24 (m, 4 H, H_{aromat}), 7.30–7.45 (m, 5 H, H_{aromat}).

5.1.6. N-Benzyloxycarbonyl-8-methyl-1,2,3,4-tetrahydroisoquinoline (6b)

According to GP1 from benzylchloroformate (0.87 ml, 6.06 mmol), 8-methyl-1,2,3,4-tetrahydroisoquinoline (**5b**) [14] (1.173 g, 4.04 mmol) and NEt_3 (1.69 ml, 12.13 mmol) in 14 ml CH_2Cl_2; reaction time: 18 h. Purification by CC (EtOAc/*n*-heptane = 15:85). Yield: 1.077 g (95%); colorless oil. TLC: $R_f = 0.40$ (EtOAc/*n*-heptane = 15:85). ^{1}H NMR ($CDCl_3$, 20 °C): $\delta = 2.17–2.29$ (m, 3 H, $C_{ar}CH_3$), 2.85 (br. s, 2 H, CH_2), 3.68–3.76 (m, 2 H, CH_2), 4.55 (s, 2 H, $C_{ar}CH_2N$), 5.20 (s, 2 H, CH_2O), 6.95–7.01 (m, 1 H, H_{aromat}), 7.03 (d, $J = 7.4$ Hz, 1 H, H_{aromat}), 7.09 (t, $J = 7.4$ Hz, 1 H, H_{aromat}), 7.29–7.42 (m, 5 H, H_{aromat}). IR (film): $\tilde{\nu} = 1700$ cm^{-1}, 1429, 1286, 1246, 1219. MS (CI); *m/z* (%): 282 (100) [M + H$^+$], 190 (36), 174 (13), 91 (55). $C_{18}H_{19}NO_2$ (281.36).

5.1.7. N-Benzyloxycarbonyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (rac-8a)

According to GP2 from compound **6a** (1.068 g, 3.00 mmol) and PhMgCl (1.8 M in THF, 6.66 ml, 11.98 mmol). Purification by CC (Et_2O/*n*-heptane = 20:80). Yield: 0.928 g (68%); colorless oil. TLC: $R_f = 0.23$ (Et_2O/*n*-heptane = 20:80). ^{1}H NMR (d_5-nitrobenzene, 140 °C): $\delta = 2.78$ (dt, $J = 16.1$, 5 Hz, 1 H, CH_2CH_2), 2.95 (ddd, $J = 16.1$, 9.7, 5 Hz, 1 H, CH_2CH_2), 3.44 (ddd, $J = 13.2$, 9.7, 4.8 Hz, 1 H, CH_2CH_2), 4.13 (dt, $J = 13.2$, 5 Hz, 1 H, CH_2CH_2), 5.28 (d, $J = 12.7$ Hz, 1 H, CH_2O), 5.35 (d, $J = 12.7$ Hz, 1 H, CH_2O), 6.47 (s, 1 H, CH), 7.05 (d, $J = 7.5$ Hz, 1 H, H_{aromat}), 7.12–7.35 (m, 11 H, H_{aromat}), 7.39–7.44 (m, 2 H, H_{aromat}). IR (film): $\tilde{\nu} = 1698$ cm^{-1}, 1454, 1425, 1293, 1227. MS (CI); *m/z* (%): 344 (100) [M + H$^+$], 266 (12), 252 (22), 208 (5). $C_{23}H_{21}NO_2$ (343.43).

*5.1.8. N-Benzyloxycarbonyl-1-(2-methylphenyl)-1,2,3,4-tetrahydroisoquinoline (**rac-8b**)*

According to GP2 from compound **6a** (0.514 g, 1.92 mmol) and 2-methylphenylMgBr (1.0 M in THF, 5.77 ml, 5.77 mmol). Purification by CC (EtOAc/*n*-heptane = 10:90). Yield: 0.434 g (63%); colorless oil. TLC: $R_f = 0.21$ (EtOAc/*n*-heptane = 10:90). ^{1}H NMR (d_5-nitrobenzene, 140 °C): $\delta = 2.58$ (s, 3 H, CH_3), 2.83 (ddd, $J = 16.4$, 4.2, 2.5 Hz, 1 H, CH_2), 3.06 (ddd, $J = 16.4$, 11.5, 6.2 Hz, 1 H, CH_2), 3.42 (ddd, $J = 13.6$, 11.5, 4.2 Hz, 1 H, CH_2), 4.27 (ddd, $J = 13.6$, 6.2, 2.5 Hz, 1 H, CH_2), 5.23 (d, $J = 12.5$ Hz, 1 H, CH_2O), 5.27 (d, $J = 12.5$ Hz, 1 H, CH_2O), 6.59 (s, 1 H, CH), 6.87 (d, $J = 7.7$ Hz, 1 H, H_{aromat}), 6.91 (d, $J = 7.7$ Hz, 1 H, H_{aromat}), 7.00−7.11 (m, 2 H, H_{aromat}), 7.11−7.21 (m, 4 H, H_{aromat}), 7.22−7.37 (m, 5 H, H_{aromat}). IR (film): $\tilde{\nu} = 1694$ cm^{-1}, 1454, 1416, 1289, 1223. MS (CI); *m/z* (%): 358 (92) [M + H$^+$], 266 (28), 250 (27), 222 (8), 176 (100). $C_{24}H_{23}NO_2$ (357.45).

*5.1.9. N-Benzyloxycarbonyl-1-(2,6-dimethylphenyl)-1,2,3,4-tetrahydroisoquinoline (**rac-8c**)*

According to GP2 from compound **6a** (0.495 g, 1.85 mmol) and 2,6-dimethylphenylMgBr (1.0 M in THF, 5.56 ml, 5.56 mmol). Purification by CC (EtOAc/*n*-heptane = 10:90). Yield: 0.452 g (66%); colorless crystals. TLC: $R_f = 0.19$ (EtOAc/*n*-heptane = 10:90). M.p. 115 °C. ^{1}H NMR (d_5-nitrobenzene, 140 °C): $\delta = 2.24$ (s, 6 H, 2 CH_3), 2.91−3.06 (m, 2 H, CH_2), 3.52 (ddd, $J = 13.1$, 10.0, 4.5 Hz, 1 H, CH_2), 4.56 (dt, $J = 13.1$, 4.1 Hz, 1 H, CH_2), 5.05 (d, $J = 12.4$ Hz, 1 H, CH_2O), 5.10 (d, $J = 12.4$ Hz, 1 H, CH_2O), 6.35 (s, 1 H, CH), 6.63 (d, $J = 7.9$ Hz, 1 H, H_{aromat}), 6.96−7.02 (m, 3 H, H_{aromat}), 7.06 −7.32 (m, 8 H, H_{aromat}). IR (KBr): $\tilde{\nu} = 1707$ cm^{-1}, 1399, 1363, 1239. MS (CI); *m/z* (%): 372 (32) [M + H$^+$], 266 (23), 264 (10), 176 (100). $C_{25}H_{25}NO_2$ (371.48).

*5.1.10. N-Benzyloxycarbonyl-8-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**rac-8d**)*

According to GP2 from compound **6b** (0.399 g, 1.42 mmol) and PhMgCl (1.8 M in THF, 2.50 ml, 4.26 mmol). Purification by CC (EtOAc/*n*-heptane = 10:90). Yield: 0.284 g (56%); colorless oil. TLC: $R_f = 0.15$ (CH_2Cl_2/*n*-heptane = 50:50). ^{1}H NMR (d_5-nitrobenzene, 140 °C): $\delta = 2.04$ (s, 3 H, CH_3), 2.73 (dt, $J = 16.4$, 5 Hz, 1 H, CH_2), 2.96 (ddd, $J = 16.4$, 9.8, 6.6 Hz, 1 H, CH_2), 3.30 (ddd, $J = 13.0$, 9.8, 5 Hz, 1 H, CH_2), 4.05 (dddd, $J = 13.0$, 6.6, 5, 0.7 Hz, 1 H, CH_2), 5.32 (d, $J = 12.6$ Hz, 1 H, CH_2O), 5.37 (d, $J = 12.6$ Hz, 1 H, CH_2O), 6.67 (s, 1 H, CH), 7.00 (d, $J = 7.4$ Hz, 1 H, H_{aromat}), 7.03 (d, $J = 7.4$ Hz, 1 H, H_{aromat}), 7.14 (t, $J = 7.4$ Hz, 1 H, H_{aromat}), 7.19−7.29 (m, 6 H, H_{aromat}), 7.30−7.36 (m, 2 H, H_{aromat}), 7.43−7.47 (m, 2 H, H_{aromat}). IR (film): $\tilde{\nu} = 1694$ cm^{-1}, 1426, 1319, 1201. MS (CI); *m/z* (%): 358 (100) [M + H$^+$], 280 (11), 266 (25), 222 (17). $C_{24}H_{23}NO_2$ (357.45).

*5.1.11. N-Benzyloxycarbonyl-8-methyl-1-(2-methylphenyl)-1,2,3,4-tetrahydroisoquinoline (**rac-8e**)*

According to GP2 from compound **6b** (0.469 g, 1.67 mmol) and (2-methylphenyl)MgBr (1.0 M in THF, 5.00 ml, 5.00 mmol). Purification by CC (CH_2Cl_2/*n*-heptane = 80:20). Yield: 0.441 g (71%); colorless crystals. TLC: $R_f = 0.14$ (CH_2Cl_2/*n*-heptane = 80:20). M.p. 140 °C. ^{1}H NMR (d_5-nitrobenzene, 140 °C): $\delta = 1.93$ (s, 3 H, CH_3), 2.59 (s, 3 H, CH_3), 2.71−2.79 (m, 1 H, CH_2CH_2), 3.08−3.27 (m, 2 H, CH_2CH_2), 4.09−4.17 (m, 1 H, CH_2CH_2), 5.27−5.35 (m, 2 H, CH_2O), 6.69 (d, $J = 7.9$ Hz, 1 H, H_{aromat}), 6.79 (s, 1 H, CH), 6.92−7.05 (m, 3 H, H_{aromat}), 7.09−7.34 (m, 6 H, H_{aromat}), 7.41 (d, $J = 7.9$ Hz, 2 H, H_{aromat}). IR (KBr): $\tilde{\nu} = 1698$ cm^{-1}, 1436, 1412, 1214, 1104. MS (CI); *m/z* (%): 372 (56) [M + H$^+$], 280 (27), 236 (8), 167 (100). $C_{25}H_{25}NO_2$ (371.48).

*5.1.12. N-Benzyloxycarbonyl-1-(2,6-dimethylphenyl)-8-methyl-1,2,3,4-tetrahydroisoquinoline (**rac-8f**)*

According to GP2 from compound **6b** (0.680 g, 2.42 mmol) and 2,6-dimethylphenylMgBr (1.0 M in THF, 7.25 ml, 7.25 mmol). Purification by CC (EtOAc/*n*-heptane = 10:90). Yield: 0.453 g (69%); colorless oil. TLC: $R_f = 0.18$ (CH_2Cl_2/*n*-heptane = 50:50). ^{1}H NMR (d_5-nitrobenzene, 140 °C): $\delta = 1.93$ (s, 3 H, CH_3), 2.15 (br. s, 6 H, 2 × CH_3), 2.72−2.84 (m, 1 H, CH_2), 3.24−3.37 (m, 2 H, CH_2), 4.13−4.25 (m, 1 H, CH_2), 5.27 (s, 2 H, CH_2O), 6.80 (s, 1 H, CH), 6.91−7.00 (m, 4 H, H_{aromat}), 7.04−7.11 (m, 2 H, H_{aromat}), 7.22−7.33 (m, 3 H, H_{aromat}), 7.35−7.40 (m, 2 H, H_{aromat}). IR (film): $\tilde{\nu} =$ 1694 cm^{-1}, 1463, 1410, 1212. MS (CI); *m/z* (%): 386 (100) [M + H$^+$], 294 (15), 280 (34), 91 (10). $C_{26}H_{27}NO_2$ (385.51).

*5.1.13. 1-Phenyl-1,2,3,4-tetrahydroisoquinoline (**rac-4a**) and 1-phenyl-1,2,3,4-tetrahydroisoquinolinium chloride (**rac-4a·HCl**)*

According to GP3 from compound ***rac*-8a** (1.082 g, 3.15 mmol).

***rac*-4a**: Yield: 0.602 g (91%); colorless crystals. TLC: R_f = 0.19 (EtOAc/*n*-heptane = 20:80 + 2% $EtMe_2N$). M.p. 94 °C (lit.: 94–96 °C [16]). ^{1}H NMR ($CDCl_3$, 20 °C): $\delta = 1.91$ (br. s, 1 H, NH), 2.80−2.90 (m, 1 H, CH_2), 3.01−3.15 (m, 2 H, CH_2), 3.25−3.34 (m, 1 H, CH_2), 5.12 (s, 1 H, CH), 6.77 (d, $J = 7.8$ Hz, 1 H, H_{aromat}), 7.02−7.09 (m, 1 H, H_{aromat}), 7.13 −7.19 (m, 2 H, H_{aromat}), 7.26−7.37 (m, 5 H, H_{aromat}). IR (KBr): $\tilde{\nu} = 2922$ cm^{-1}, 1492, 1453. MS (CI); *m/z* (%): 210 (100) [M + H$^+$], 132 (8). $C_{15}H_{15}N$ (209.29).

***rac*-4a·HCl**: Colorless crystals. M.p. 223 °C (lit.: 227–229 °C [17]). ^{1}H NMR (d_4-MeOH, 20 °C): $\delta = 3.10$ −3.38 (m, 2 H, CH_2), 3.46−3.61 (m, 2 H, CH_2), 5.78 (s, 1 H, CH), 6.85 (d, $J = 7.8$ Hz, 1 H, H_{aromat}), 7.19−7.26 (m, 1 H, H_{aromat}), 7.33−7.41 (m, 2 H, H_{aromat}), 7.48−7.53 (m, 5 H, H_{aromat}). IR (KBr): $\tilde{\nu} = 2888$ cm^{-1}, 2754, 2620, 2537, 1577, 1496, 1453. MS (CI); *m/z* (%): 210 (100) [M – HCl + H$^+$], 132 (4). $C_{15}H_{16}ClN$ (245.75).

*5.1.14. 1-(2-Methylphenyl)-1,2,3,4-tetrahydroisoquinoline (**rac-4b**) and 1-(2-methylphenyl)-1,2,3,4-tetrahydroisoquinolinium hydrochloride (**rac-4b·HCl**)*

According to GP3 from compound ***rac*-8b** (107 mg, 0.30 mmol).

***rac*-4b**: Yield: 53 mg (79%); colorless oil. TLC: $R_f = 0.29$ (EtOAc/*n*-heptane = 20:80 + 2% $EtMe_2N$). ^{1}H NMR ($CDCl_3$, 20 °C): $\delta = 1.75$ (br. s, 1 H, NH), 2.42 (s, 3 H, CH_3), 2.80

−2.88 (m, 1 H, CH_2), 3.02−3.16 (m, 2 H, CH_2), 3.28−3.35 (m, 1 H, CH_2), 5.35 (s, 1 H, CH), 6.70 (d, J = 7.7 Hz, 1 H, H_{aromat}), 7.00−7.08 (m, 2 H, H_{aromat}), 7.10−7.23 (m, 5 H, H_{aromat}). IR (Film): $\tilde{\nu}$ = 1491 cm^{-1}, 1453. MS (CI); *m/z* (%): 224 (100) [M + H^+], 132 (17). $C_{16}H_{17}N$ (223.32).

rac*-4b·*HCl: Colorless crystals. M.p. 123 °C. ^{1}H NMR (d_4-MeOH, 20 °C): δ = 2.55 (s, 3 H, CH_3), 3.21 (dt, J = 17.5, 5.3 Hz, 1 H, CH_2), 3.37 (dd, J = 17.5, 7.5 Hz, 1 H, CH_2), 3.56−3.64 (m, 2 H, CH_2), 6.01 (s, 1 H, CH), 6.74 (d, J = 7.9 Hz, 1 H, H_{aromat}), 7.05 (d, J = 7.8 Hz, 1 H, H_{aromat}), 7.17−7.42 (m, 6 H, H_{aromat}). IR (KBr): $\tilde{\nu}$ = 3423 cm^{-1}, 2920, 2754, 1584, 1494, 1456, 1420. MS (CI); *m/z* (%): 224 (100) [M – HCl + H^+], 132 (8). $C_{16}H_{18}ClN$ (259.78).

*5.1.15. (2,6-Dimethylphenyl)-1,2,3,4-tetrahydroisoquinoline (**rac-4c**) and (2,6-dimethylphenyl)-1,2,3,4-tetrahydroisoquinolinium chloride (**rac-4c·HCl**)*

According to GP3 from compound ***rac*-8c** (163 mg, 0.44 mmol).

***rac*-4c**: Yield: 80 mg (77%); colorless crystals. TLC: R_f = 0.40 (EtOAc/*n*-heptane = 20:80 + 2% $EtMe_2N$). M.p. 70 °C. ^{1}H NMR ($CDCl_3$, 20 °C): δ = 1.75 (br. s, 1 H, NH), 1.99 (s, 3 H, CH_3), 2.52 (s, 3 H, CH_3), 2.75−2.85 (m, 1 H, CH_2), 3.11 −3.23 (m, 2 H, CH_2), 3.39−3.48 (m, 1 H, CH_2), 5.62 (s, 1 H, CH), 6.63 (d, J = 7.8 Hz, 1 H, H_{aromat}), 6.95−7.04 (m, 2 H, H_{aromat}), 7.05−7.15 (m, 4 H, H_{aromat}). IR (KBr): $\tilde{\nu}$ = 2919 cm^{-1}, 2771, 1586, 1455. MS (CI); *m/z* (%): 238 (100) [M – HCl + H^+], 132 (20). $C_{17}H_{19}N$ (237.34).

rac*-4c·*HCl: Colorless crystals. M.p. 275 °C. ^{1}H NMR (d_4-MeOH, 20 °C): δ = 1.84 (s, 3 H, CH_3), 2.61 (s, 3 H, CH_3), 3.19 (dt, J = 17.4, 3.1 Hz, 1 H, CH_2), 3.26−3.41 (m, 1 H, CH_2), 3.65−3.75 (m, 2 H, CH_2), 6.23 (s, 1 H, CH), 6.72 (d, J = 8.0 Hz, 1 H, H_{aromat}), 7.11 (d, J = 7.1 Hz, 1 H, H_{aromat}), 7.17−7.22 (m, 1 H, H_{aromat}), 7.24−7.35 (m, 4 H, H_{aromat}). IR (KBr): $\tilde{\nu}$ = 2919 cm^{-1}, 2771, 1586, 1455. MS (CI); *m/z* (%): 238 (100) [M – HCl + H^+], 132 (20). $C_{17}H_{20}ClN$ (273.81).

*5.1.16. 8-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**rac-4d**) and 8-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolinium chloride (**rac-4d·HCl**)*

According to GP3 from compound ***rac*-8d** (195 mg, 0.55 mmol). Purification by CC (EtOAc/*n*-heptane = 20:80 + 2% $EtMe_2N$).

***rac*-4d**: Yield: 74 mg (61%); colorless crystals. TLC: R_f = 0.19 (EtOAc/*n*-heptane = 20:80 + 2% $EtMe_2N$). M.p. 79 °C. ^{1}H NMR ($CDCl_3$, 20 °C): δ = 1.85 (br. s, 1 H, NH), 1.89 (s, 3 H, CH_3), 2.74−2.84 (m, 2 H, CH_2), 2.84−3.04 (m, 2 H, CH_2), 5.19 (s, 1 H, CH), 6.97 (d, J = 7.3 Hz, 1 H, H_{aromat}), 7.06 (d, J = 7.6 Hz, 1 H, H_{aromat}), 7.07−7.12 (m, 2 H, H_{aromat}), 7.14 (t, J = 7.5 Hz, 1 H, H_{aromat}), 7.21−7.32 (m, 3 H, H_{aromat}). IR (KBr): $\tilde{\nu}$ = 1459 cm^{-1}, 1448, 1257, 1028. MS (CI); *m/z* (%): 224 (100) [M + H^+], 194 (39), 146 (9). $C_{16}H_{17}N$ (223.32).

rac*-4d·*HCl: Colorless crystals. M.p. 233 °C. ^{1}H NMR (d_4-MeOH, 20 °C): δ = 1.93 (s, 3 H, CH_3), 3.12−3.38 (m, 4 H, CH_2CH_2), 5.91 (s, 1 H, CH), 7.13 (d, J = 7.3 Hz, 1 H, H_{aromat}), 7.23 (d, J = 7.6 Hz, 1 H, H_{aromat}), 7.25−7.29 (m, 2 H, H_{aromat}), 7.31 (t, J = 7.5 Hz, 1 H, H_{aromat}), 7.43−7.49 (m, 3 H, H_{aromat}). IR (KBr): $\tilde{\nu}$ = 3448 cm^{-1}, 2920, 2696, 2633, 1577, 1473, 1452. MS (CI); *m/z* (%): 224 (100) [M – HCl + H^+], 146 (6). $C_{16}H_{18}ClN$ (259.78).

*5.1.17. 8-Methyl-1-(2-methylphenyl-1,2,3,4-tetrahydroisoquinoline (**rac-4e HCl**)*

According to GP3 from compound ***rac*-8e** (0.449 g, 1.21 mmol). Purification by CC (EtOAc/*n*-heptane = 20:80 + 2% $EtMe_2N$). TLC: R_f = 0.26 (EtOAc/*n*-heptane = 20:80 + 2% $EtMe_2N$).

***rac*-4e·*HCl*:** Yield: 152 mg (46%); colorless crystals. M.p. 260 °C. ^{1}H NMR (d_4-MeOH, 20 °C): δ = 1.86 (s, 3 H, CH_3), 2.65 (s, 3 H, CH_3), 3.18−3.30 (m, 2 H, CH_2), 3.37−3.43 (m, 2 H, CH_2), 5.99 (s, 1 H, CH), 6.76 (dd, J = 7.8, 1.0 Hz, 1 H, H_{aromat}), 7.11 (br. d, J = 7.4 Hz, 1 H, H_{aromat}), 7.18 (td, J = 7.5, 1.2 Hz, 1 H, H_{aromat}), 7.23 (d, J = 7.7 Hz, 1 H, H_{aromat}), 7.29 (d, J = 7.6 Hz, 1 H, H_{aromat}), 7.36 (td, J = 7.5, 1.3 Hz, 1 H, H_{aromat}), 7.42 (br. d, J = 7.5 Hz, 1 H, H_{aromat}). IR (KBr): $\tilde{\nu}$ = 2917 cm^{-1}, 2724, 1581, 1472, 1433. MS (CI); *m/z* (%): 238 (100) [M – HCl + H^+], 146 (9). $C_{17}H_{20}ClN$ (273.81).

*5.1.18. 8-Methyl-1-(2,6-dimethylphenyl)-1,2,3,4-tetrahydroisoquinolinium chloride (**rac-4f·HCl**)*

According to GP3 from compound ***rac*-8f** (0.643 g, 1.67 mmol).

rac*-4f·*HCl: Yield: 409 mg (85%); colorless crystals. M.p. > 300 °C. TLC: R_f = 0.45 (EtOAc/*n*-heptane = 20:80 + 2% $EtMe_2N$). ^{1}H NMR (d_4-MeOH, 20 °C): δ = 1.68 (s, 3 H, CH_3), 1.74 (s, 3 H, CH_3), 2.67 (s, 3 H, CH_3), 3.17 (dt, J = 17.4, 4.0 Hz, 1 H, CH_2), 3.24−3.34 (m, 1 H, CH_2), 3.50 (ddd, J = 12.3, 10.7, 4.3 Hz, 1 H, CH_2), 3.58 (ddd, J = 12.3, 5.2, 4 Hz, 1 H, CH_2), 6.19 (s, 1 H, CH), 7.01–7.05 (1 M, 1 H, H_{aromat}), 7.07 (d, J = 7.7 Hz, 1 H, H_{aromat}), 7.16 (d, J = 7.6 Hz, 1 H, H_{aromat}), 7.23 (d, J = 7.4 Hz, 1 H, H_{aromat}), 7.24−7.27 (m, 2 H, H_{aromat}). IR (KBr): $\tilde{\nu}$ = 2968 cm^{-1}, 2771, 2655, 2478, 1581, 1466, 1444, 1428. MS (CI); *m/z* (%): 252 (100) [M – HCl + H^+], 146 (18). $C_{18}H_{22}ClN$ (287.83).

5.1.19. Radioreceptor assay

The binding assay was performed as described previously in [18]. K_i values for test compounds were calculated from competition experiments with at least six concentrations of test compounds, by the use of InPlot 4.0 (GraphPad Software, San Diego, CA). Data are expressed as mean ± standard error of the means (S.E.M.) of three experiments, each carried out in triplicate.

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