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DESIGN AND SYNTHESIS OF FUSED TETRAHYDROISOQUINOLINE- IMINOIMIDAZOLINES

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Abstract

In the aim of identifying new privileged structures, we describe the 5-steps synthesis of cyclic guanidine compounds “tetrahydroisoquinoline-iminoimidazolines” derived from tetrahydroisoquinoline-hydantoin core. In order to evaluate this new minimal structure and the impact of replacing a carbonyle by a guanidine moiety, their affinity towards adenosine receptor A_{2A} was evaluated and compared to those of tetrahydroisoquinoline-hydantoin compounds.

KEYWORDS: guanidines, A_{2A} receptor, privileged structure, iminoimidazoline

Abbreviations: Tic-H, tetrahydroisoquinoline hydantoin; $A_{2A}R$, adenosine A_{2A} receptor.

1. Introduction

In the field of medicinal chemistry, privileged structures are considered as a promising source of ligands able to interact with various targets.¹⁻³ In fact, these minimal structures constitute a powerful starting point to identify original compounds by playing with the nature of their substituents. They constitute an anchor point enabling to orientate substituents in various positions, giving access to potentially promising structures and to modulate their affinity and activity. Therefore, identification of novel privileged structures appears as an interesting challenge.

Our group described a series of tetrahydroisoquinoline-hydantoin (Tic-H **1**, Figure 1) derived compounds with potent affinity for the sigma-1 receptor in the nanomolar range ensuing various therapeutical *in vivo* applications.⁴⁻⁹ This heterocycle presents an interesting hydrogen bond acceptor group on the hydantoin cycle and is amenable to various decorations. In this study we proposed to identify a new potential privileged structure and decided to evaluate the consequence of replacing the hydantoin's (**1**) hydrogen bond acceptor by a hydrogen bond donor group resulting in the guanidine moiety of compound **2** (Figure 1). This new heterocycle could be the central core for the design of new active compounds. Guanidines are present in a large variety of natural products with potent biological activities in many fields¹⁰⁻¹³ and more specifically in the central nervous system area.^{14,15}

This approach was exemplified by preparing the guanidine derivative "Tic-guanidine" and its derivatives (**2** to **13**) in order to evaluate the affinity of this new series on the adenosine receptor A_{2A}R.¹⁶ In fact, in addition to its affinity towards sigma-1 receptor, Tic-H **1** showed a promising affinity constant towards adenosine receptor A_{2A} ($K_i = 44 \mu\text{M}$). This receptor is widely expressed in the central nervous system. Expressed at different levels (neurons, astrocytes, microglial cells),¹⁷⁻²¹ it acts at various levels of regulation.²²⁻²⁵ Therefore, A_{2A}Rs are viewed as promising targets in various neurodegenerative diseases, mainly Parkinson's and Alzheimer's diseases.²⁶⁻²⁸

Docking studies, based on the crystal structure of A_{2A} bound to the high affinity antagonist (ZM241385),²⁹ showed that Tic-guanidine restored hydrogen bonds that were missing for Tic-H leading us to expect a better affinity of these compounds.³⁰

We therefore aim to develop a new series of Tic-guanidine compound. We set up an original and efficient chemical synthesis allowing pharmacomodulations. These latter concern the

nature of the substituents on the original tricyclic structure Tic-guanidine (series A, figure 1) but also modifications by opening of the central cyclic core (series B, figure 1).

Figure 1.

2. Results and discussion

2.1. Modeling studies

Jaakola *et al.* published in 2008 a crystal structure of A_{2A}R with the high affinity antagonist ZM241385.²⁹ Tic-H and Tic-guanidine were both docked in A_{2A}R's binding site. Results showed both molecules place in a same manner as ZM241385 does (Figure 2). Mainly, important hydrogen bonds with Glu¹⁶⁹ and Asn²⁵³ missing in the case of Tic-H are being restored with the guanidine function. Finally, upper carbonyl moiety of Tic-H was not maintained, as it doesn't seem to play an essential role in the interactions with amino acids of the binding site.

Figure 2.

Supported by our docking studies, pharmacomodulations were envisaged: various *N*-substituents on the guanidine core (series A, figure 1) and opening of the central tricyclic core (series B, figure 1). Series A enables to evaluate the effect of the modification of the benzyl group in the hydrophobic upper pocket of the binding site. On the other hand, series B was prepared in order to evaluate the importance of the central core's nature and especially how its geometry impacts compounds' affinity. We wanted to establish whether a planar conformation was essential as described in many A_{2A}'s antagonists **ref** or if less restricted structures could improve affinity as compared to already published non planar A_{2A} antagonists **ref**. Finally, B series would bring additional informations on structure activity relationships of our Tic-guanidine compounds.

2.2. Chemical synthesis

Synthesis of Tic-guanidine derivatives of series A and B was achieved thanks to a unique chemical pathway as depicted in Scheme 1. This enabled us to access desired compounds starting from commercially available amino acids and therefore to easily access various

pharmacomodulations. We optimized the synthetic pathway of compound **2** starting from commercially available Boc-protected L-tetrahydroisoquinoline carboxylic acid **I** whose chemistry is well mastered in our group.^{7,9,31} Key step of this synthesis was the final formation of the cyclic guanidine. Various methods are described in the literature to access guanidines¹² and cyclic guanidines³²⁻³⁴ but could not be applied to our strategy. Indeed, we previously described the synthesis of Tic-thiohydantoins, which could be an interesting intermediate for the synthesis of these Tic-guanidines. But their chemical and enantiomeric instability precluded their use in this study.³⁵ For final formation of guanidine cycle, direct cyclisation of the free diamine in the presence of cyanogen bromide³⁶⁻⁴² was unsuccessful. Some adjustments were then required and we finally chose to maintain Boc-protection in order to selectively functionalize the free amine of compounds **2b-13b** with cyanogene bromide.⁴³ Expected guanidines were obtained after Boc-deprotection and subsequent cyclization of intermediate.

Synthesis of series A started from Boc-protected L-tetrahydroisoquinoline carboxylic acid **I**. Corresponding aldehyde was obtained *via* reduction of Weinreb amide **II**^{44,45} using LiAlH₄ in THF at 0°C.⁴⁴ Reductive amination with appropriate amine in the presence of sodium triacetoxyborohydride in CH₂Cl₂ gave expected Boc-monoprotected derivatives **2b-6b**.⁴⁶ Free amine of this last compound was then functionalized using cyanogen bromide in ethanol to give corresponding nitrile derivatives.⁴³ Finally, guanidine cyclization was achieved thanks to acidic deprotection of the carbamate and *in situ* cyclization of the intermediate diamine compound with yields from 46 to 88%.

Scheme 1.

Figure 3.

Depending on the nature of the amine in the reductive amination step, compounds **2** to **6** were first obtained (scheme 1), as depicted in figure 3. On the other hand, opening of the upper part of the central cycle while maintaining *N*-benzyl substitution of the guanidine (scheme 2) core resulted from modification of starting amino acid (compounds **7-13**, Figure 4). Compound **12**, derived from tyrosine, was prepared from Boc-Tyr(*t*Bu)-OH. The tert-butyl protection was removed in the final cyclisation step.

Scheme 2.

Figure 4.

Structure of final compounds was confirmed by various analysis methods. LC-MS gave expected mass, discarding the formation of the dimer. FT-IR indicated the disappearance of the nitrile band ($2260\text{--}2240\text{ cm}^{-1}$) and appearance of the guanidine C=NH bond ($1690\text{--}1640\text{ cm}^{-1}$) confirming cyclisation of the compound (see supporting informations). Finally, 1D and 2D ^1H and ^{13}C NMR showed appropriate signals and correlations, especially the guanidine C=NH bond.

Some of our compounds were able to crystallize. X-ray spectroscopy thus enabled us to confirm the structure and enantiopurity of compounds **2** and **3** (figure 5) but also compounds **7**, **9** and **11** whose absolute configuration was maintained.⁴⁷

On the other hand, crystallographic data showed compound **8** was present as a racemic mixture (for details, see supplementary informations). This compound differs from the other ones, as it is *N*-methylated. *N*-methylation was achieved following a protocol described in the literature to be a non-epimerizing route.⁴⁸ However, in our case, the basic conditions of methylation led to a complete racemization.

Figure 5.

Figure 6.

2.3. Affinity of Tic-guanidine compounds

Affinity of our compounds was evaluated on human A_{2A} receptor membranes stably expressed in HEK293 cells. Results (table 1) showed no improvement of binding compared to initial Tic-H compound **1** ($K_i = 44\text{ }\mu\text{M}$) except for the tricyclic guanidine substituted with phenylbutylamine **5** ($K_i = 35\text{ }\mu\text{M}$). More specifically, affinity was drastically decreased for open guanidines.

Table 1.

Except compound **5** ($35\text{ }\mu\text{M}$) that gives an affinity comparable to the one of Tic-H **1** ($44\text{ }\mu\text{M}$), binding was not improved with our Tic-guanidine compounds. For sure, rigid tricyclic structures are necessary to bind the $A_{2A}\text{R}$ receptor as open structures (**7** to **13**) showed no affinity at all. X-ray analysis helped understanding this observation. In fact, as shown in

figure 5, open Tic-guanidine structures adopt a curved conformation that does not allow the binding of the molecule in the pocket of the receptor whereas tricyclic structures keep a flat conformation.⁴⁹

Concerning the tricyclic structures (**2** to **6**), we therefore assume the replacement of carbonyl moiety of **1** by a hydrogen bond donor does not give us expected improved affinity for the A_{2A}R.

2.4. Cytotoxicity of Tic-guanidine compounds

Cytotoxicity assays have been conducted on SY5Y cells and showed no toxicity of our compounds at 100 μ M (Table 1).

3. Conclusion

As Tic-H core was of interest for the design of various biologically active compounds, we proposed the Tic-guanidine core as a new privileged structure. This work therefore presented a new and efficient synthesis of guanidine cycles derived from amino acids. We applied this concept to the design of A_{2A}R ligands. Unfortunately, binding results established that our initial hypothesis was not confirmed: replacement of the hydrogen bond acceptor moiety carbonyl of compound **1** by the hydrogen bond donor guanidine did not improve the affinity for A_{2A}R. Other decorations are needed to improve the affinity for A_{2A}R. Of particular importance is the lack of cytotoxicity of this new scaffold. Thus valorization of this new scaffold for other receptors is currently under evaluation.

4. Experimental section

4.1. General information

Chemicals and solvents were obtained from commercial sources, and used without further purification unless otherwise noted. Reactions were monitored by TLC performed on Macherey-Nagel Alugram® Sil 60/UV₂₅₄ sheets (thickness 0.2mm). Purification of products was carried out by either column chromatography or thick layer chromatography. Column chromatography was carried out on using Macherey-Nagel silica gel (230-400 mesh). Thick layer chromatography was performed on glass plates coated with Macherey-Nagel Sil/UV₂₅₄ (thickness 2 mm), from which the pure compounds were extracted with the following solvent system: DCM/MeOH(NH₃), 90:10. NMR spectra were recorded on a Bruker DRX 300 spectrometer (operating at 300 MHz for ¹H and 75 MHz for ¹³C). Chemical shifts are

expressed in ppm relative to either tetramethylsilane (TMS) or to residual proton signal in deuterated solvents. Chemical shifts are reported as position (δ in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = double doublet, br = broad and m = multiplet), coupling constant (J in Hz), relative integral and assignment. The attributions of protons and carbons were achieved by analysis of 2D experiments (COSY, HSQC and HMBC). Mass spectra were recorded on a Varian triple quadrupole 1200W mass spectrometer equipped with a non-polar C18 TSK-gel Super ODS (4.6 x 50 mm) column, using electrospray ionization and a UV detector (diode array). HRMS-ESI spectra were recorded on a Thermo Scientific Exactive spectrometer. The purity of final compounds was verified by two types of high pressure liquid chromatography (HPLC) columns: C18 Interchrom UPTISPHERE and C4 Interchrom UPTISPHERE. Analytical HPLC was performed on a Shimadzu LC-2010AHT system equipped with a UV detector set at 254 nm and 215 nm. Compounds were dissolved in 50 μ L methanol and 950 μ L buffer A, and injected into the system. The following eluent systems were used: buffer A ($\text{H}_2\text{O}/\text{TFA}$, 100:0.1) and buffer B ($\text{CH}_3\text{CN}/\text{H}_2\text{O}/\text{TFA}$, 80:20:0.1). HPLC retention times (HPLC t_R) were obtained at a flow rate of 0.2 mL/min for 35 min using the following conditions: a gradient run from 100% of buffer A over 1 min, then to 100% of buffer B over the next 30 min. The melting point analyses were performed on Barnstead Electrothermal Melting Point Series IA9200 and are uncorrected. Infrared spectra were performed on Bruker FT-IR spectrometer model α . Preparative HPLC were performed using a Varian ProStar system using an OmniSphere 10 column C18 250 mm $\times$ 41.4 mm Dynamax from Varian, Inc. A gradient starting from 20% $\text{CH}_3\text{CN}/80\%$ $\text{H}_2\text{O}/0.1\%$ formic acid and reaching 100% $\text{CH}_3\text{CN}/0.1\%$ formic acid at a flow rate of 80 mL/min was used. Optical rotations were measured at 20°C on a Perkin-Elmer 343 polarimeter.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication 1401476, 1401477, 1401478, 1401480, 1401481 and 1401479. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or email: deposit@ccdc.cam.ac.uk).

4.2. Preparation of Weinreb amide compounds.

4.2.1. General method 1. To a solution of appropriate amino protected carboxylic acid derivative (1 eq.) dissolved in a mixture of CH_2Cl_2 and CH_3CN (1:1, 3,7 mL/mmol of carboxylic acid), EDC (1.3 eq.), HOBt (1.3 eq.), NMM (6.5 eq.) and $\text{HN}(\text{Me})\text{OMe}.\text{HCl}$ (2.1

eq.) were added. The mixture was stirred at room temperature over 24-72 h and then evaporated. The resulting crude product was dissolved in CH₂Cl₂, washed three times with saturated NaHCO₃ solution, three times with 1M HCl and once with brine. Organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. Purification via flash chromatography was performed.

4.2.2. *tert-butyl (3S)-3-[methoxy(methyl)carbamoyl]-3,4-dihydro-1H-isoquinoline-2-carboxylate (II)*. According to general method 1, **II** was obtained as a colorless oil (5.13g, 61%). ¹H NMR (CDCl₃, 300 MHz), δ (ppm) indicates the presence of 2 conformers: 7.15-7.20 (m, 4H); 5.23 and 4.86 [X part of ABX system (ft, J = 6.0 Hz, 0.5H) and (ft, J = 7.5 Hz, 0.5H)]; 4.70 and 4.69 [(AB system, J = 16.5 Hz, 1H, $\Delta\nu$ = 36 Hz) and (AB system, J = 16.5 Hz, 1H, $\Delta\nu$ = 123 Hz)]; 3.85 and 3.78 (2s, 3H); 3.19 and 3.16 (2s, 3H); 3.19-2.94 (unresolved AB part of ABX system, m, 2H); 1.51 and 1.45 (2s, 9H). ¹³C NMR (CDCl₃, 75 MHz), δ (ppm) indicates the presence of 2 conformers: 175.6, 174.9, 173.0, 155.3, 154.9, 154.7, 135.5, 134.7, 134.2, 133.9, 133.0, 132.9, 132.9, 132.7, 132.1, 129.9, 129.4, 128.8, 127.9, 127.7, 127.6, 127.1, 125.8, 83.9, 81.6, 80.4, 61.7, 61.5, 61.3, 54.8, 53.5, 53.2, 52.3, 50.7, 45.4, 44.5, 43.4, 32.7, 32.5, 32.2, 30.9, 30.4, 30.1, 29.8, 28.4, 28.3, 28.1. MS (ESI⁺): m/z = 321.1 [M,H]⁺ found; C₁₇H₂₅N₂O₄ calculated m/z = 321.2[M,H]⁺.

4.2.3. *tert-butyl N-[(1S)-1-benzyl-2-[methoxy(methyl)amino]-2-oxo-ethyl]carbamate (7a)*. According to general method 1, **7a** was obtained as a brown oil (0.94 g, 66%). ¹H NMR (CDCl₃, 300 MHz), δ (ppm): 7.29-7.12 (m, 5H); 5.18 and 5.03-4.86 [X part of ABX system (d, J = 6.0 Hz, 0.5H) and (m, 0.5 H)]; 3.65 (s, 3H); 3.16 (s, 3H); 2.95 [AB part of ABX system (dd, J = 12.0 and 6.0 Hz, 1H) and (dd, J = 15.0 and 9.0 Hz, 1H), $\Delta\nu$ = 60 Hz]; 1.39 (s, 9H).⁵⁰

4.2.4. *tert-butyl N-[(1S)-1-benzyl-2-[methoxy(methyl)amino]-2-oxo-ethyl]-N-methylcarbamate (8a)*. According to general method 1, **8a** was obtained as a yellow oil (0.942 g, 86%). ¹H NMR (CDCl₃, 300 MHz), δ (ppm): indicates the presence of 2 conformers. 7.27-7.16 (m, 5H); 5.64-5.07 [unresolved X part of ABX system, m, 1H]; 3.64 and 3.61 (2s, 3H); 3.16 and 3.19 (2s, 3H); 3.06-2.87 [unresolved AB part of ABX system, m, 2H]; 2.85 (s, 3H); 1.35 and 1.23 (2s, 9H). ¹³C NMR (CDCl₃, 75 MHz), δ (ppm): indicates the presence of 2 conformers. 171.5, 155.6, 154.9, 138.0, 137.5, 129.4, 129.2, 128.4, 128.2, 126.4, 79.8, 61.3, 57.2, 54.7, 34.9, 30.2, 29.8, 28.2, 26.8. MS (ESI⁺): m/z = 323.0 [M,H]⁺ found; C₁₇H₂₆N₂O₄ calculated m/z = 323.2[M,H]⁺.

4.2.5. *tert-butyl N-[(1S)-1-[(4-fluorophenyl)methyl]-2-[methoxy(methyl)amino]-2-oxo-ethyl]carbamate (9a)*. According to general method 1, **9a** was obtained as a colorless oil (0.810 g, 70%). ¹H NMR (CDCl₃, 300 MHz), δ (ppm): 7.18-7.09 (m, 2H); 7.02-6.90 (m, 2H);

5.28-5.17 (d, $J = 12.1$ Hz, 1H), 5.00-4.82 (unresolved X part of ABX system, m, 1H); 3.67 (s, 3H); 3.16 (s, 3H); 2.87 [AB part of ABX system (dd, $J = 12.2$ and 6.3 Hz, 1H) and (dd, $J = 12.1$ and 6.6 Hz, 1H), $\Delta\nu = 60$ Hz]; 1.38 (s, 9H). ^{13}C NMR (CDCl_3 , 75 MHz), δ (ppm): 172.0, 163.5, 160.2 ($J_{\text{C-F}} = 234$ Hz); 155.1, 132.3, 131.0, 130.9, 115.3, 115.0, 79.6, 61.6, 51.5, 38.1, 32.0, 28.3. MS (ESI^+): $m/z = 327.1$ $[\text{M,H}]^+$ found; $\text{C}_{16}\text{H}_{24}\text{FN}_2\text{O}_4$ calculated $m/z = 327.2$ $[\text{M,H}]^+$.

4.2.6. *tert*-butyl (2*S*)-2-[methoxy(methyl)carbamoyl]piperidine-1-carboxylate (**10a**). According to general method 1, **10a** was obtained as a yellow oil (0.986 g, 83%). ^1H NMR (CDCl_3 , 300 MHz), δ (ppm): 5.18-4.87 (m, 1H); 4.10-3.84 (m, 1H); 3.76 (s, 3H); 3.58-3.39 (m, 1H); 3.18 (s, 3H); 2.01 (d, $J = 15.0$ Hz, 1H); 1.75-1.57 (m, 3H); 1.44 (s, 9H); 1.34-1.20 (m, 2H). ^{13}C NMR (CDCl_3 , 75 MHz), δ (ppm): 173.5, 156.2, 79.7, 61.3, 50.8, 42.3, 32.2, 29.7, 28.5, 26.5, 19.6. MS (ESI^+): $m/z = 273.1$ $[\text{M,H}]^+$ found; $\text{C}_{13}\text{H}_{25}\text{N}_2\text{O}_4$ calculated $m/z = 273.2$ $[\text{M,H}]^+$.

4.2.7. *tert*-butyl *N*-[(1*S*)-2-(methoxy(methyl)amino)-1-methyl-2-oxo-ethyl]carbamate (**11a**). According to general method 1, **11a** was obtained as a yellow oil (0.566 g, 64%). Analyses similar to literature description.⁵¹

4.2.8. *tert*-butyl *N*-[(1*S*)-1-[(4-*tert*-butoxyphenyl)methyl]-2-[methoxy(methyl)amino]-2-oxo-ethyl]carbamate (**12a**). According to general method 1, **12a** was obtained as a yellow solid (0.722 g, 76%). Analyses similar to literature description.⁵²

4.2.9. *tert*-butyl *N*-[(1*S*)-2-[methoxy(methyl)amino]-1-methyl-2-oxo-ethyl]carbamate (**13a**). According to general method 1, **13a** was obtained as a yellow solid (0.225 g, 48%). Analyses similar to literature description.⁵³

4.3. Preparation of amine compounds 2b-13b.

4.3.1. *General method 2*. To a solution of Weinreb amide (1 eq.) in THF was added LiAlH_4 (0.9 eq. of commercial solution 1M in THF) dropwise under N_2 at 0°C and stirred for 1 h at 0°C . Then saturated KHSO_4 solution was added dropwise. THF was evaporated off. The resulting crude product was dissolved in CH_2Cl_2 , washed twice with saturated NaHCO_3 solution, twice with 1M HCl , once with brine. Organic layer was dried over MgSO_4 , filtered and concentrated *in vacuo*. No further purification was performed. To a solution of resulting aldehyde (1 eq) in CH_2Cl_2 , benzylamine (1.2 eq) was added under N_2 . The mixture was stirred at room temperature for 30 min, $\text{NaBH}(\text{OAc})_3$ (3 eq) was added portion wise (at least for 10 min). The mixture was stirred overnight, diluted with CH_2Cl_2 (3 mL) and saturated NaHCO_3

solution (3 mL) was added. The mixture was stirred for 10 min. The organic layer was separated and the aqueous phase washed twice with CH₂Cl₂ (15 mL). Combined organic layers were dried over MgSO₄, filtered and evaporated *in vacuo*. Purification via flash chromatography was performed.

4.3.2. *tert-butyl (3S)-3-[(benzylamino)methyl]-3,4-dihydro-1H-isoquinoline-2-carboxylate (2b)*. According to general method 2, **2b** was obtained as a colorless oil (0.55g, 95%). ¹H NMR (CDCl₃, 300 MHz), δ (ppm): 7.36-7.21 (m, 5H); 7.20-7.03 (m, 4H); 5.53 (s, 1H); 4.92-4.45 (m, 2H); 4.22 and 4.17 (2s, 1H); 3.85 (dd, J = 19.5 Hz and 13.4 Hz, 2H); 2.93 [AB part of ABX system (dd, J = 18.0 and 6.0 Hz, 1H) and (dd, J = 15.0 and 3.0 Hz, 1H), $\Delta\nu$ = 90 Hz]; 2.72-2.58 (unresolved AB part of ABX system, m, 2H); 1.49 (s, 9H). ¹³C NMR (CDCl₃, 75 MHz), δ (ppm): 155.4, 140.5, 132.9, 129.1, 128.4, 128.0, 126.9, 126.6, 126.1, 79.9, 53.5, 50.1, 50.1, 48.3, 43.1, 31.1, 28.5. MS (ESI⁺): m/z = 353.3 [M,H]⁺ found; C₂₂H₂₉N₂O₂ calculated m/z = 353.2 [M,H]⁺.

4.3.3. *tert-butyl (3S)-3-[[2-(2-pyridyl)ethylamino]methyl]-3,4-dihydro-1H-isoquinoline-2-carboxylate (3b)*. According to general method 2, **3b** was obtained as a light brown oil (0.386g, quantitative). ¹H NMR (CDCl₃, 300 MHz), δ (ppm): 8.53 (s, 1H); 7.69-6.78 (m, 8H); 5.01-4.63 (unresolved AB system, m, 2H); 4.39-4.13 (m, 1H); 3.32-2.64 (m, 8H); 1.45 (s, 9H). ¹³C NMR (CDCl₃, 75 MHz), δ (ppm): 159.4, 136.8, 132.6, 132.0, 129.1, 126.7, 126.38, 123.5, 121.6, 80.5, 49.3, 48.6, 47.8, 31.4, 29.0, 28.6, 28.1, 27.7. MS (ESI⁺): m/z = 368.2 [M,H]⁺ found; C₂₂H₃₀N₃O₂ calculated m/z = 368.2 [M,H]⁺.

4.3.4. *tert-butyl (3S)-3-[(2-morpholinoethylamino)methyl]-3,4-dihydro-1H-isoquinoline-2-carboxylate(4b)*. According to general method 2, **4b** was obtained as a colorless oil (0.428 g, 99%). ¹H NMR (CDCl₃, 300 MHz), δ (ppm): 7.22-7.08 (m, 4H); 4.83-4.49 (unresolved AB system, m, 2H); 4.25 [X part of ABX system (d, J = 18.0 Hz, 1H, CH_(b)); 3.70 (ft, J = 3.0 Hz, 4H); 2.92 [AB part of ABX system (dd, J = 16.4 and 6.7 Hz, 1H) and (d, J = 12.0 Hz, 1H), $\Delta\nu$ = 96 Hz]; 2.75-2.68 (m, 2H); 2.44-2.42 (m, 8H); 1.51 (s, 9H). ¹³C NMR (CDCl₃, 75 MHz), δ (ppm): 155.3, 133.1, 129.1, 126.6, 126.2, 79.9, 67.0, 58.3, 53.7, 53.4, 50.8, 45.9, 42.7, 31.1, 28.5. MS (ESI⁺): m/z = 376.1 [M,H]⁺ found; C₂₁H₃₄N₃O₃ calculated m/z = 376.2 [M,H]⁺.

4.3.5. *tert-butyl (3S)-3-[(4-phenylbutylamino)methyl]-3,4-dihydro-1H-isoquinoline-2-carboxylate (5b)*. According to general method 2, **5b** was obtained as a colorless oil (0.416 g, 92%). ¹H NMR (CDCl₃, 300 MHz), δ (ppm): 8.19 (br s, 1H); 7.30-7.10 (m, 9H); 4.65 (m, 2H); 4.30 [X part of ABX system (d, J = 15.0 Hz, 1H); 3.12-2.59 (m, 8H); 1.70-1.52 (m, 4H); 1.49 (s, 9H). ¹³C NMR (CDCl₃, 75 MHz), δ (ppm): 156.0, 154.9, 141.8, 132.8, 132.4, 128.9, 128.3, 127.0, 126.6, 126.1, 125.8, 80.8, 50.4, 49.3, 48.1, 47.8, 43.9, 42.7, 35.4, 31.7,

28.4, 27.6, 27.0, 22.7. MS (ESI⁺): m/z = 395.2 [M,H]⁺ found; C₂₅H₃₅N₂O₂ calculated m/z = 395.3 [M,H]⁺.

4.3.6. *tert-butyl (3S)-3-[(hexylamino)methyl]-3,4-dihydro-1H-isoquinoline-2-carboxylate (6b)*. According to general method 2, **6b** was obtained as a colorless oil (0.386 g, 97%). ¹H NMR (CDCl₃, 300 MHz), δ (ppm): 7.23-7.10 (m, 4H); 4.88-4.13 (m, 2H); 4.37-4.15 (m, 1H); 3.09 (AB part of ABX system, dd, *J* = 16.2 Hz and 6.9 Hz, 1H); 2.85-2.67 (m, 5H); 2.04 (s, 3H); 1.50 (s, 9H); 1.33-1.23 (m, 6H); 0.87 (t, *J* = 7.5 Hz, 3H). ¹³C NMR (CDCl₃, 75 MHz), δ (ppm): 170.0, 133.0, 132.7, 128.9, 126.9, 126.4, 126.0, 80.5, 50.9, 50.4, 48.3, 39.7, 31.5, 29.6, 28.7, 28.2, 28.0, 22.5, 13.9. MS (ESI⁺): m/z = 347.2 [M,H]⁺ found; C₂₁H₃₅N₂O₂ calculated m/z = 347.3 [M,H]⁺.

4.3.7. *tert-butyl N-[(1S)-1-benzyl-2-(benzylamino)ethyl]carbamate (7b)*. According to general method 2, **7b** was obtained as a brown solid (0.498 g, 90%). Analyses similar to literature description.⁵⁴

4.3.8. *tert-butyl N-[(1S)-1-benzyl-2-(benzylamino)ethyl]-N-methyl-carbamate (8b)*. According to general method 2, **8b** was obtained as a light yellow oil (0.120 g, 52%). ¹H NMR (CDCl₃, 300 MHz), δ (ppm): indicates the presence of 2 conformers. 7.44-7.05 (m, 10H); 4.71-4.34 (unresolved X part of ABX system, m, 1H); 3.89 and 3.71 [AB part of ABX system (d, *J* = 13.1 Hz, 1H) and (m, 1H)]; 2.93-2.55 (m, 7H); 2.00 (br s, 1H); 1.38 and 1.28 (2s, 9H). ¹³C NMR (CDCl₃, 75 MHz), δ (ppm): 156.3, 138.6, 129.0, 128.4, 128.2, 127.1, 126.6, 79.6, 55.6, 53.2, 50.1, 49.6, 36.9, 28.2. MS (ESI⁺): m/z = 355.1 [M,H]⁺ found; C₂₂H₃₀N₂O₂ calculated m/z = 355.2 [M,H]⁺.

4.3.9. *tert-butyl N-[(1S)-1-[(benzylamino)methyl]-2-(4-fluorophenyl)ethyl]carbamate (9b)*. According to general method 2, **9b** was obtained as a light yellow oil (0.510 g, 70%). ¹H NMR (CDCl₃, 300 MHz), δ (ppm): 7.38-7.22 (m, 5H); 7.16-7.08 (m, 2H); 7.01-6.89 (m, 2H); 4.74 (br s, 1H), 3.99-3.85 (unresolved X part of ABX system, m, 1H); 3.77 (AB system, *J* = 12.4 Hz, Δ*ν* = 24 Hz, 2H); 2.90-2.71 (unresolved AB part of ABX system, m, 2H); 2.71-2.54 (unresolved AB part of ABX system, m, 2H); 2.10 (br s, 1H); 1.41 (s, 9H). ¹³C NMR (CDCl₃, 75 MHz), δ (ppm): 163.2, 160.0 (*J*_{C-F} = 242.2 Hz); 155.6, 139.9, 133.8, 130.8, 130.7, 128.5, 128.2, 127.1, 115.3, 115.0, 79.4, 53.7, 51.4, 51.2, 38.3, 28.4. MS (ESI⁺): m/z = 359.0 [M,H]⁺ found; C₂₁H₂₈FN₂O₂ calculated m/z = 359.2 [M,H]⁺.

4.3.10. *tert-butyl (2S)-2-[(benzylamino)methyl]piperidine-1-carboxylate (10b)*. According to general method 2, **10b** was obtained as a yellow oil (0.453 g, 62%). ¹H NMR (CDCl₃, 300 MHz), δ (ppm): 7.37-7.20 (m, 5H); 4.45-4.32 (unresolved X part of ABX system, m, 1H); 4.02-3.87 (m, 1H); 3.83 (AB system, d, *J* = 12.0 Hz, Δ*ν* = 24.2 Hz, 1H); 2.79 [AB part of

ABX system(dd, $J = 12.3$ and 3.1 Hz, 1H) and (dd, $J = 12.0$ and 6.6 Hz, 1H), $\Delta\nu = 81.2$ Hz); 2.73-2.69 (m, 1H); 1.76-1.53 (m, 6H); 1.44 (s, 9H). ^{13}C NMR (CDCl_3 , 75 MHz), δ (ppm): 155.1, 140.4, 128.3, 128.0, 126.9, 124.8, 79.4, 53.4, 49.9, 48.0, 39.3, 28.5, 26.7, 25.4, 19.3. MS (ESI^+): $m/z = 305.0$ $[\text{M},\text{H}]^+$ found; $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_2$ calculated $m/z = 305.2$ $[\text{M},\text{H}]^+$.

4.3.11. *tert-butyl N-[2-(benzylamino)-1-methyl-ethyl]carbamate (11b)*. According to general method 2, **11b** was obtained as a yellow oil (0.286 g, 19%). Analyses similar to literature description.⁵⁵

4.3.12. *tert-butyl N-[(1S)-1-[(benzylamino)methyl]-2-(4-*tert*-butoxyphenyl)ethyl]carbamate (12b)*. According to general method 2, **12b** was obtained as a yellow oil (0.252 g, 58%). ^1H NMR (CDCl_3 , 300 MHz), δ (ppm): 7.33-7.20 (m, 5H); 7.14-6.98 (m, 2H); 6.91-6.82 (m, 2H); 4.98 (br s, 1H); 3.94-3.84 (unresolved X part of ABX system, m, 1H); 3.77 (AB system, $J = 13.1$ Hz, $\Delta\nu = 26.8$ Hz, 2H); 3.12-2.91 (unresolved AB part of ABX system, m, 1H); 2.90-2.69 (unresolved AB part of ABX system, m, 3H); 1.41 and 1.32 (2s, 19H). ^{13}C NMR (CDCl_3 , 75 MHz), δ (ppm): 155.8, 153.7, 139.0, 132.8, 129.7, 128.5, 127.2, 124.1, 79.2, 78.2, 53.2, 51.0, 38.5, 28.8, 28.4. MS (ESI^+): $m/z = 413.1$ $[\text{M},\text{H}]^+$ found; $\text{C}_{25}\text{H}_{37}\text{N}_2\text{O}_3$ calculated $m/z = 413.3$ $[\text{M},\text{H}]^+$.

4.3.13. *tert-butyl N-[(1S)-3-(benzylamino)-1-[(4-methoxyphenyl)methyl]-2-oxopropyl]carbamate (13b)*. According to general method 2, **13b** was obtained as a yellow oil (0.032 g, 22%). ^1H NMR (CDCl_3 , 300 MHz), δ (ppm): 7.31-7.15 (m, 5H); 7.09 (d, $J = 8.6$ Hz, 2H); 6.82 (d, $J = 9.5$ Hz, 2H); 4.74 (br s, 1H); 3.89-3.78 (unresolved X part of ABX system, m, 1H); 3.77-3.68 (m, 5H); 2.80-2.65 (unresolved AB part of ABX system, m, 2H); 2.63-2.57 (unresolved AB part of ABX system, m, 2H); 1.75-1.66 (m, 1H, NH); 1.43 (s, 9H). ^{13}C NMR (CDCl_3 , 75 MHz), δ (ppm): 158.2, 155.7, 140.2, 130.3, 130.1, 128.4, 128.2, 127.0, 113.8, 79.8, 55.2, 53.8, 51.33, 42.9, 38.2, 28.4. MS (ESI^+): $m/z = 371.2$ $[\text{M},\text{H}]^+$ found; $\text{C}_{22}\text{H}_{31}\text{N}_2\text{O}_3$ calculated $m/z = 371.2$ $[\text{M},\text{H}]^+$.

4.4. Preparation of guanidine compounds 2-13.

4.4.1. *General method 3*. To a solution of appropriate secondary amine (1 eq) in EtOH (1.6 mL/mmol of amine), NaHCO_3 (3 eq) and BrCN (1.1 eq) were added. The mixture was stirred at room temperature for 5 h. The mixture was diluted with H_2O and extracted twice with CH_2Cl_2 . Combined organic layers were dried under MgSO_4 . The solution was filtered and evaporated *in vacuo*. No further purification was performed unless specified. The nitrile compound (1 eq) was dissolved in 3M HCl/dioxane (0.08 M) and stirred at room temperature

overnight. Dioxane was evaporated *in vacuo*. Purification via flash chromatography was performed.

4.4.2. (10a*S*)-2-benzyl-1,5,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-3-imine monohydrochloride (**2**). According to general method 2, **2** was obtained (chromatography, CH₂Cl₂/methanol 94/6) as a white powder (0.13g, 46%). ¹H NMR (CD₃OD, 300 MHz), δ (ppm): 7.41-7.36 (m, 5H); 7.26-7.18 (m, 4H); 4.72-4.54 (m, 4H); 4.11-4.01 (m, 1H); 3.61 [AB part of ABX system (t, *J* = 9.0 Hz, 1H) and (t, *J* = 6.0 Hz, 1H), Δ*ν* = 144 Hz]; 2.95 [AB part of ABX system (dd, *J* = 18.0 and 9.0 Hz, 1H) and (dd, *J* = 15.0 and 9.0 Hz, 1H), Δ*ν* = 72 Hz]. ¹³C NMR (CD₃OD, 75 MHz), δ (ppm): 156.7, 134.4, 132.0, 129.9, 129.1, 128.8, 128.1, 127.7, 127.0, 126.8, 126.2, 53.2, 51.7, 48.5, 43.9, 33.4. HRMS (ESI⁺): *m/z* = 278.16548 [M,H]⁺ found; C₁₈H₁₉N₃ calculated *m/z* = 278.16517 [M,H]⁺. Mp: 198.5°C. α_D (20°C, CH₃OH) = – 0.548° (0.500 mg/mL). IR, ν (cm^{–1}): 3089, 1660 (C=N). HPLC: C₄ column: *t_R* = 11.7 min, purity > 99% C₁₈ column: *t_R* = 20.5 min, purity > 99%.

4.4.3. (10a*S*)-2-[2-(2-pyridyl)ethyl]-1,5,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-3-imine dihydrochloride (**3**). According to general method 2, **3** was obtained (chromatography, CH₂Cl₂/methanol 90/10) as a white powder (0.10 g, 67%). ¹H NMR (CD₃OD, 300 MHz), δ (ppm): 8.84 (d, *J* = 6.0 Hz, 1H); 8.64 (t, *J* = 9.0 Hz, 1H); 8.23 (d, *J* = 6.0 Hz, 1H); 8.04 (t, *J* = 9.0 Hz, 1H); 7.23 (s, 4H); 4.67 (AB system, *J* = 15.0 Hz, Δ*ν* = 75 Hz, 2H); 4.15-3.91 (m, 4H); 3.63 [AB part of ABX system (t, *J* = 9.0 Hz, 1H) Δ*ν* = 114 Hz]; 3.56 (t, *J* = 8.0 Hz, 2H); 2.99 [AB part of ABX system (d, *J* = 15.0 Hz, 1H) and (t, *J* = 9.0 Hz, 1H), Δ*ν* = 51 Hz]. ¹³C NMR (CD₃OD, 75 MHz), δ (ppm): 156.6, 152.9, 147.1, 141.4, 131.9, 129.7, 129.1, 128.1, 127.0, 126.8, 126.1, 125.7, 53.4, 52.6, 43.8, 44.2, 33.4. HRMS (ESI⁺): *m/z* = 293.17595 [M,H]⁺ found; C₁₈H₂₀N₄ calculated *m/z* = 293.17607 [M,H]⁺. Mp: 123.8°C. α_D (20°C, CH₃OH) = – 0.449° (0.500 mg/mL). IR, ν (cm^{–1}): 3039, 1668 (C=N). HPLC: C₄ column: *t_R* = 6.7 min, purity > 99% C₁₈ column: *t_R* = 12.9 min, purity 98%.

4.4.4. (10a*S*)-2-(2-morpholinoethyl)-1,5,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-3-imine dihydrochloride (**4**). According to general method 2, **4** was obtained (chromatography, CH₂Cl₂/methanol 90/10) as a brown oil (0.282 g, 69%). ¹H NMR (CD₃OD, 300 MHz), δ (ppm): 7.34-7.18 (m, 4H); 4.66 (AB system, *J* = 16.0 Hz, Δ*ν* = 70 Hz, 2H); 4.17-3.99 (m, 1H); 3.71 (t, *J* = 4.6 Hz, 4H); 3.67-3.48 (m, 4H); 3.03 [AB part of ABX system (dd, *J* = 15.0 and 3.7 Hz, 1H) and (dd, *J* = 15.4 and 10.3 Hz, 1H), Δ*ν* = 51 Hz]; 2.69 (t, *J* = 5.8 Hz, 2H); 2.60 (t, *J* = 4.5 Hz, 4H). ¹³C NMR (CD₃OD, 75 MHz), δ (ppm): 157.4, 132.0, 129.9, 129.1, 127.0, 126.8, 126.0, 66.4, 55.7, 53.5, 53.2, 43.7, 42.3, 30.7. HRMS (ESI⁺): *m/z* = 301.20265

[M,H]⁺ found; C₁₇H₂₅N₄O calculated m/z = 301.20229 [M,H]⁺. HPLC: C₄ column: t_R = 12.3 min, purity > 94% C₁₈ column: t_R = 4.7 min, purity 97%.

4.4.5. (10a*S*)-2-(4-phenylbutyl)-1,5,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-3-imine hydrochloride (**5**). According to general method 2, **5** was obtained (chromatography, CH₂Cl₂/methanol 94/6) as a light brown oil (0.206 g, 82%). ¹H NMR (CD₃OD, 300 MHz), δ (ppm): 7.29-7.13 (m, 9H); 4.62 ([AB system (dd, *J* = 18.0 Hz, Δ*ν* = 81 Hz, 2H); 4.03-3.97 [unresolved X part of ABX system (m, 1H)]; 3.87 and 3.46-3.32 [AB part of ABX system (t, *J* = 9.0 Hz, 1H) and (m, 1H), Δ*ν* = 144 Hz]; 3.46-3.39 (m, 2H); 2.95 [AB part of ABX system (dd, *J* = 15.0 and 3.0 Hz, 1H) and (dd, *J* = 15.0 and 9.0 Hz, 1H), Δ*ν* = 72 Hz]; 2.69 (t, *J* = 9.0 Hz, 2H); 1.83-1.60 (m, 4H). ¹³C NMR (CD₃OD, 75 MHz), δ (ppm): 156.6, 141.8, 132.0, 129.9, 129.7, 128.8, 128.0, 127.3, 126.9, 126.8, 126.1, 125.5, 124.8, 53.1, 51.9, 45.4, 43.3, 35.0, 33.3, 28.0, 26.1. HRMS (ESI⁺): m/z = 320.21259 [M,H]⁺ found; C₂₁H₂₆N₃ calculated m/z = 320.21212 [M,H]⁺. α_D (20°C, CH₃OH) = − 0.499° (0.500 mg/mL). IR, ν (cm^{−1}): 2929, 1664 (C=N). HPLC: C₄ column: t_R = 12.7 min, purity 98% C₁₈ column: t_R = 23.7 min, purity 98%.

4.4.6. *tert*-butyl (3*S*)-3-[(hexylamino)methyl]-3,4-dihydro-1*H*-isoquinoline-2-carboxylate (**6**). According to general method 2, **6** was obtained (chromatography, CH₂Cl₂/methanol 85/15) as an orange oil (228 mg, 88%). ¹H NMR (CD₃OD, 300 MHz), δ (ppm): 7.29-7.14 (m, 4H); 4.68 (AB system, *J* = 15.7 Hz, Δ*ν* = 90.6 Hz, 2H); 4.03-3.94 (m, 2H); 3.64-3.32 (m, 3H); 2.97 [AB part of ABX system (dd, *J* = 15.5 and 2.7 Hz, 1H) and (dd, *J* = 15.5 and 10.0 Hz, 1H), Δ*ν* = 87.7 Hz]; 1.66 (quin, *J* = 6.9 Hz, 2H); 1.49-1.31(m, 6H); 0.93 (t, *J* = 6.2 Hz, 3H). ¹³C NMR (CD₃OD, 75 MHz), δ (ppm): 156.6, 132.1, 130.1, 129.1, 127.0, 126.8, 126.2, 53.2, 52.0, 44.9, 43.9, 33.4, 31.3, 26.6, 25.9, 22.3, 13.1. HRMS (ESI⁺): m/z = 272.21249 [M,H]⁺ found; C₁₇H₂₆N₃ calculated m/z = 272.21212 [M,H]⁺. HPLC: C₄ column: t_R = 3.3 min, purity 98% C₁₈ column: t_R = 26.9 min, purity 97%.

4.4.7. (4*S*)-1,4-dibenzylimidazolidin-2-imine hydrochloride (**7**). According to general method 2, **7** was obtained (chromatography, CH₂Cl₂/methanol 95/5) as a white powder (19 mg, 27%). ¹H NMR (CD₃OD, 300 MHz), δ (ppm): 7.38-7.22 (m, 6H); 7.21-7.10 (m, 4H); 4.35 (dd, *J* = 28.9 and 13.5 Hz, 2H); 4.29-4.21 (unresolved X part of ABX system, m, 1H); 3.61 and 3.33-3.27 [AB part of ABX system (ft, *J* = 9.6 Hz, 1H) and (m, 1H), Δ*ν* = 93 Hz]; 2.87 (d, *J* = 5.9 Hz, 2H). ¹³C NMR (CD₃OD, 75 MHz), δ (ppm): 157.9, 135.7, 134.2, 129.2, 128.8, 128.4, 127.9, 127.4, 126.7, 53.8, 51.1, 48.5, 39.9. HRMS (ESI⁺): m/z = 266.16529 [M,H]⁺ found; C₁₇H₂₀N₃ calculated m/z = 266.16517 [M,H]⁺. Mp: 196.1°C. α_D (20°C, CH₃OH) = − 0.006°

(0.500 mg/mL). IR, ν (cm^{-1}): 3060, 1668 (C=N). HPLC: C₄ column: t_R = 13.1 min, purity > 99% C₁₈ column: t_R = 24.7 min, purity > 99%.

4.4.8. (4*S*)-1,4-dibenzyl-3-methyl-imidazolidin-2-imine hydrochloride (**8**). According to general method 2, **8** was obtained (chromatography, CH₂Cl₂/methanol 95/5) a white powder (14 mg, 67%). ¹H NMR (CD₃OD, 300 MHz), δ (ppm): 7.39-7.23 (m, 6H); 7.17-7.04 (m, 4H); 4.39 (AB system, J = 15.7 Hz, $\Delta\nu$ = 38.9 Hz, 2H); 4.23-4.11 (unresolved X part of ABX system, m, 1H); 3.37 [AB part of ABX system (t, J = 9.7 Hz, 1H) and (dd, J = 9.9 and 5.7 Hz, 1H), $\Delta\nu$ = 91.7 Hz]; 3.10 (s, 3H); 2.94 [AB part of ABX system (dd, J = 13.9 and 4.4 Hz, 1H) and (dd, J = 7.1 and 6.8 Hz, 1H), $\Delta\nu$ = 61.9 Hz]. ¹³C NMR (CD₃OD, 75 MHz), δ (ppm): 157.4, 135.3, 134.2, 129.2, 128.7, 128.5, 127.9, 127.3, 126.9, 59.8, 49.4, 48.0 (CH_{2(d)}); 36.8 (CH_{2(a)}); 30.2 (CH₃₍₁₎). HRMS (ESI⁺): m/z = 280.18080 [M,H]⁺ found; C₁₈H₂₂N₃ calculated m/z = 280.18082 [M,H]⁺. Mp: 244.5°C. α_D (20°C, CH₃OH) = -0.098° (0.500 mg/mL). IR, ν (cm^{-1}): 3024, 1664 (C=N). HPLC: C₄ column: t_R = 10.1 min, purity > 99% C₁₈ column: t_R = 4.5 min, purity > 99%.

4.4.9. (4*S*)-1-benzyl-4-[(4-fluorophenyl)methyl]imidazolidin-2-imine hydrochloride (**9**). According to general method 2, **9** was obtained (chromatography, CH₂Cl₂/methanol 90/10) a white powder (217 mg, 90%). ¹H NMR (CD₃OD, 300 MHz), δ (ppm): 7.41-7.28 (m, 3H); 7.26-7.17 (m, 2H); 7.17-7.09 (m, 2H); 7.06-6.95 (m, 2H); 4.44 [AB system, J = 16.1 Hz, $\Delta\nu$ = 41 Hz, 2H]; 4.32-4.19 (unresolved X part of ABX system, m, 1H); 3.62 and 3.34-3.24 [unresolved AB part of ABX system (t, J = 11.2 Hz, 1H) and (m, 1H), $\Delta\nu$ = 108 Hz]; 2.94-2.77 (unresolved AB part of ABX system, m, 2H). ¹³C NMR (CD₃OD, 75 MHz), δ (ppm): 163.7, 160.4 (J_{C-F} = 242.1 Hz); 157.9, 134.2, 131.6, 131.1, 131.0, 128.7; 127.9, 127.5, 115.2, 114.9, 53.7, 50.9, 48.5, 38.8. HRMS (ESI⁺): m/z = 284.15576 [M,H]⁺ found; C₁₇H₁₉FN₃ calculated m/z = 284.15575 [M,H]⁺. Mp: 244.5°C. α_D (20°C, CH₃OH) = -0.072° (0.500 mg/mL). HPLC: C₄ column: t_R = 11.0 min, purity > 99% C₁₈ column: t_R = 19.5 min, purity > 99%.

4.4.10. (8*aS*)-2-benzyl-1,5,6,7,8,8*a*-hexahydroimidazo[1,5-*a*]pyridin-3-imine hydrochloride (**10**). According to general method 2, **10** was obtained (chromatography, CH₂Cl₂/methanol 90/10) a white powder (130 mg, 29%). ¹H NMR (CD₃OD, 300 MHz), δ (ppm): 7.47-7.28 (m, 5H); 4.59 (AB system, d, J = 15.1 Hz, $\Delta\nu$ = 18.7 Hz, 1H); 3.92-3.88 (m, 1H); 3.51 [unresolved AB part of ABX system (dd, J = 12.3 and 9.0 Hz, 1H) and (dd, J = 15.3 and 9.2 Hz, 1H), $\Delta\nu$ = 246 Hz]; 3.87-3.73 (m, 1H); 3.08 (dd, J = 9.0 and 3.1 Hz, 1H); 1.91-1.77 (m, 2H); 1.58-1.30 (m, 4H). ¹³C NMR (CD₃OD, 75 MHz), δ (ppm): 156.0, 134.4, 128.7, 128.0; 127.5, 59.5, 51.5, 47.8, 42.3, 29.7, 24.0, 22.2. HRMS (ESI⁺): m/z = 230.16490 [M,H]⁺ found;

C₁₄H₂₀N₃ calculated $m/z = 230.16517$ [M,H]⁺. Mp: 188.2°C. α_D (20°C, CH₃OH) = +10.6° (0.500 mg/mL). IR, ν (cm⁻¹): 2941, 1660 (C=N). HPLC: C₄ column: $t_R = 9.0$ min, purity 98% C₁₈ column: $t_R = 16.6$ min, purity > 99%.

4.4.11. (4*S*)-1-benzyl-4-methyl-imidazolidin-2-imine hydrochloride (**11**). According to general method 2, **11** was obtained (chromatography, CH₂Cl₂/methanol 90/10) a white powder (42 mg, 53%). ¹H NMR (CD₃OD, 300 MHz), δ (ppm): 7.48-7.27 (m, 5H); 4.59 (br s, 1H); 4.42 (br s, 2H); 4.12-3.99 (unresolved X part of ABX system, m, 1H); 3.71 and 3.14 [AB part of ABX system (dd, $J = 18.9$ and 9.5 Hz, 1H) and (dd, $J = 9.6$ and 6.7 Hz, 1H) $\Delta\nu = 179.9$ Hz]; 1.25 (d, $J = 6.0$ Hz, 3H). ¹³C NMR (CD₃OD, 75 MHz), δ (ppm): 158.0, 134.5, 128.8, 127.9, 127.5, 53.6, 48.9, 19.5. HRMS (ESI⁺): $m/z = 190.13416$ [M,H]⁺ found; C₁₁H₁₆N₃ calculated $m/z = 190.13387$ [M,H]⁺. Mp: 194.9°C. α_D (20°C, CH₃OH) = -0.045° (0.500 mg/mL). IR, ν (cm⁻¹): 3055, 1667 (C=N). HPLC: C₄ column: $t_R = 7.3$ min, purity 98% C₁₈ column: $t_R = 8.0$ min, purity > 99%.

4.4.12. 4-[[*(4S)*-1-benzyl-2-imino-imidazolidin-4-yl]methyl]phenol hydrochloride (**12**). According to general method 2, **12** was obtained (chromatography, CH₂Cl₂/methanol 85/15) a brown solid (53 mg, 73%). ¹H NMR (CD₃OD, 300 MHz), δ (ppm): 7.33 (m, 3H); 7.06 (m, 2H); 6.98 (d, $J = 8.5$ Hz, 2H); 6.72 (d, $J = 8.5$ Hz, 2H); 4.45 (AB system, $J = 15.8$ Hz, 2H, $\Delta\nu = 42.9$ Hz); 4.20 (unresolved X part of ABX system, m, 1H); 3.59 and 3.33-3.27 [AB part of ABX system (t, $J = 9.7$ Hz, 1H) and (m, 1H), $\Delta\nu = 259.7$ Hz]; 2.82-2.66 (unresolved AB part of ABX system, m, 2H). ¹³C NMR (CD₃OD, 75 MHz), δ (ppm): 158.0, 156.3, 134.2, 130.3, 128.7, 127.8, 127.2, 126.0, 115.1, 53.9, 50.9, 47.9, 38.9. HRMS (ESI⁺): $m/z = 282.15985$ [M,H]⁺ found; C₁₇H₂₀N₃O calculated $m/z = 282.16009$ [M,H]⁺. Mp: °C. α_D (20°C, CH₃OH) = -0.014° (0.500 mg/mL). IR, ν (cm⁻¹): 3064, 1670 (C=N). HPLC: C₄ column: $t_R = 10.2$ min, purity 99% C₁₈ column: $t_R = 15.8$ min, purity > 99%.

4.4.13. (4*S*)-1-benzyl-4-[(4-methoxyphenyl)methyl]imidazolidin-2-imine hydrochloride (**13**). According to general method 2, **13** was obtained (chromatography, CH₂Cl₂/methanol 90/10) a brown solid (14 mg, 67%). ¹H NMR (CD₃OD, 300 MHz), δ (ppm): 7.39-7.31 (m, 5H); 7.09 (d, $J = 8.6$ Hz, 2H); 6.83 (d, $J = 6.6$ Hz, 2H); 4.45 (AB system, 2H, $J = 15.8$ Hz, $\Delta\nu = 37.3$ Hz); 4.26-4.19 (unresolved X part of ABX system, m, 1H); 3.79 (s, 3H); 3.61 [AB part of ABX system (ft, $J = 9.7$ Hz, 1H) and (m, 1H), $\Delta\nu = 90$ Hz)]; 2.80 (unresolved AB part of ABX system, m, 2H). ¹³C NMR (CD₃OD, 75 MHz), δ (ppm): 158.9, 157.9, 134.2, 130.2, 128.7, 127.9, 127.4, 127.3, 113.8, 54.3, 53.9, 50.9, 48.4, 48.1, 47.9, 38.9. HRMS (ESI⁺): $m/z = 296.17555$ [M,H]⁺ found; C₁₇H₂₀N₃O calculated $m/z = 296.17574$ [M,H]⁺. Mp: °C. α_D

(20°C, CH₃OH) = -0.045° (0.500 mg/mL). IR, ν (cm⁻¹): 3064, 1670 (C=N). HPLC: C₄ column: t_R = 13.3 min, purity 99% C₁₈ column: t_R = 8.0 min, purity > 99%.

4.5. *In vitro* testing.

4.5.1. *Displacement binding assays.* Competition binding curves of the A_{2A} receptor antagonist [³H]-ZM24135 by the designed A_{2A} antagonists described above, were performed as before⁵⁶ in Human HEK293 A_{2A}R membranes (Perkin Elmer). 0.5 μ L of membranes (0.5U of A_{2A}R) were incubated with [³H]-ZM24135 (2 nM) and increasing concentrations of the designed A_{2A}R antagonists (0 to 600 nM) in a final volume of 300 μ L in the presence of 1U/mL of adenosine deaminase (Roche). All samples were assayed in duplicate. Non-specific binding was determined for each assay in the presence of the antagonist ZM-24135 (8.3nM). Microplates were incubated for 1 hour at room temperature and the reaction was stopped by vacuum filtration with a Skatron semi-automatic cell harvester with chilled incubation solution (pH 7.4, Tris 50mM MgCl 10mM) to filtermats 1.5 μ m (Molecular Devices). 3 mL of scintillation cocktail (OptiPhase 'HiSafe' 2, PerkinHelmer) were added and radioactivity bound to the filters was determined after 12 hours with an efficiency of 55-60% for 2 minutes. Displacement reference curves were performed with ZM-24135 (0 to 6nM in 6%, 40% or 60% of DMSO) and CGS241680 (0 to 6nM).

4.5.2. *Cell culture and cytotoxicity assay.* The human neuroblastoma cell line (SY5Y) was cultured in DMEM (Dulbecco's Modified Eagle Medium) (Gibco) supplemented with 2 mM L-glutamine, 100 μ g/ml streptomycin, 100 IU/mL penicillin, 1 mM non-essential amino acids and 10% (v/v) heat-inactivated foetal bovine serum (Sigma Aldrich), and grown at 37°C in a humidified incubator with 5% CO₂.

Cells were seeded at 2,000 cells per well onto 96-well plates in DMEM medium. Cells were starved for 24 hours to obtain synchronous cultures, and were then incubated in culture medium that contained various concentrations of test compounds, each dissolved in less than 0.1% DMSO. After 72 hours of incubation, cell growth was estimated by the colorimetric MTT (thiazolyl blue tetrazolium bromide) assay.

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List of captions

Table 1. ^aYield of the cyclization step. ^bA_{2a}R's agonist CGS-21680 used as a reference (K_i = 0.503 μ M). Displacement of specific [³H]-ZM 241385 binding in membranes obtained from hA_{2a} receptor stably expressed in HEK293 cells. ^cCytotoxicity assays on SY5Y cells. ^c K_i > 450 μ M.

Figure 1.

Figure 2. A_{2A}R's crystal structure with **(i)** high-affinity antagonist ZM241385, **(ii)** Tic-H **1** and **(iii)** Tic-guanidine **2**. Hydrogen bonds with Glu¹⁶⁹ and Asn²⁵³ missing with Tic-H **(ii)** are being restored with the guanidine function **(iii)**.

Figure 3. Pharmacomodulations of compounds **2-6** of the Tic-guanidine core using various amines in the reductive amination step.

Figure 4. Opening of the central Tic-guanidine core.

Figure 5. Thermal ellipsoid drawing⁴⁷ (30% probability) of the asymmetric unit of compound **2** (left) and **3** (right) showing the molecular structure and the labeling scheme.

Figure 6. Thermal ellipsoid drawing⁴⁷ (30% probability) of the asymmetric unit of compound **7-9** and **11** showing the molecular structure and the labeling scheme.

Scheme 1. **i)** HNMe(OMe).HCl, EDC, HOBT, NMM, CH₃CN, CH₂Cl₂, 61%; **ii)** LiAlH₄, THF 0°C then aq. KHSO₄, 66%; **iii)** R-NH₂, NaHB(OAc)₃, CH₂Cl₂ then aq. NaHCO₃, 92%-quant; **iv)** BrCN, NaHCO₃, EtOH, 54-97%; **v)** HCl, dioxane, 46-88%.

Scheme 2. **i)** HNMe(OMe).HCl, EDC, HOBT, NMM, CH₃CN, CH₂Cl₂, 36-86%; **ii)** LiAlH₄, THF 0°C then aq. KHSO₄, 20-97%; **iii)** Bn-NH₂, NaHB(OAc)₃, CH₂Cl₂ then aq. NaHCO₃, 19-99%; **iv)** BrCN, NaHCO₃, EtOH, 44-94%; **v)** HCl, dioxane, 23-90%.

Entry	Cpd	Yield ^a	Ki (μ M) ^b	CC ₅₀ (μ M) ^c
1	1	/	44	>100
2	2	46%	64	>100
3	3	67%	>200	>100
4	4	69%	>200	>100
5	5	82%	35	>100
6	6	88%	>200	>100
7	7	27%	>200	>100
8	8	67%	>200	>100
9	9	90%	>200	>100
10	10	29%	>200	>100
11	11	53%	>200	>100
12	12	73%	>200	>100
13	13	67%	>200	>100

Table 1.

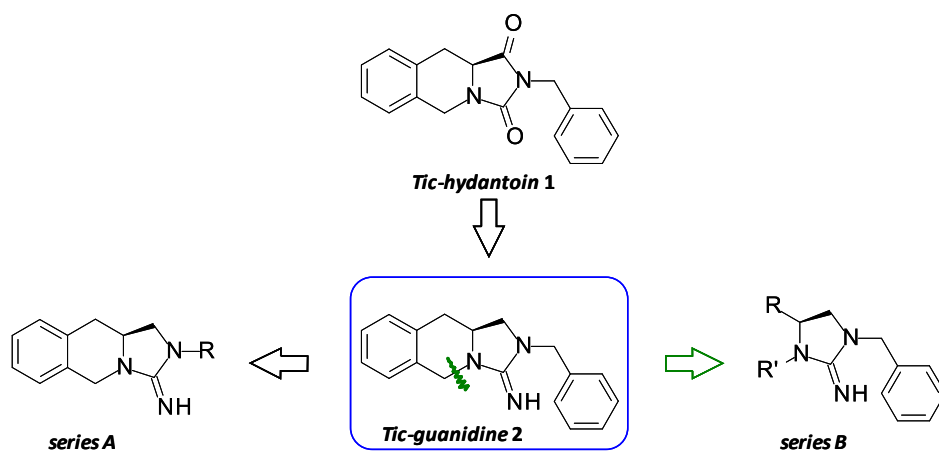


Figure 1.

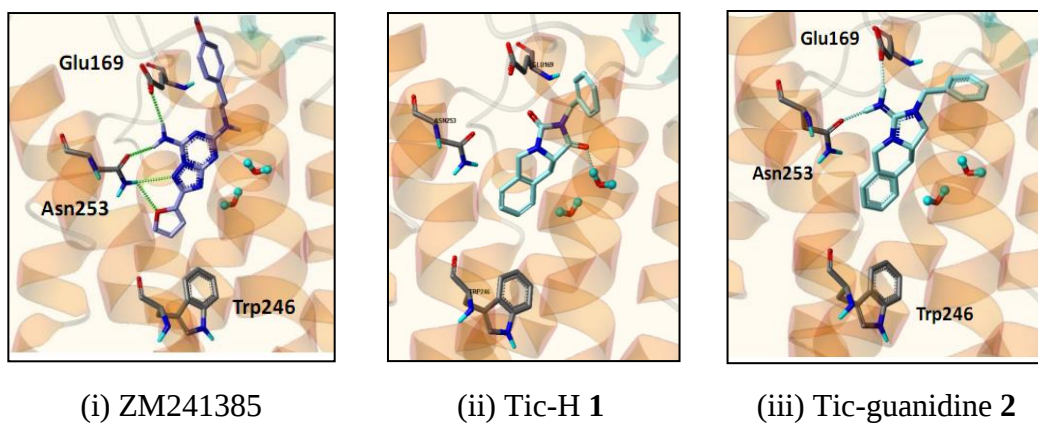


Figure 2.

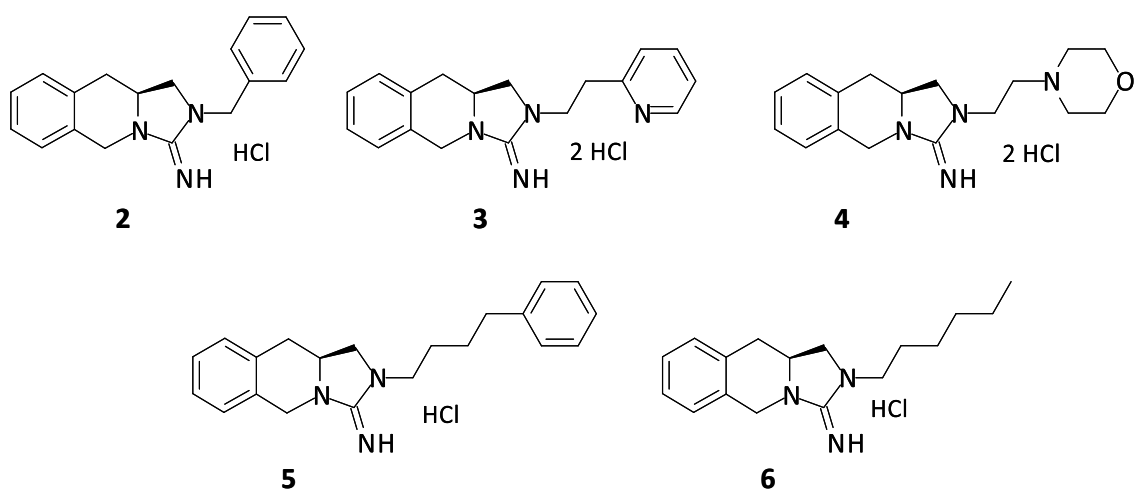


Figure 3.

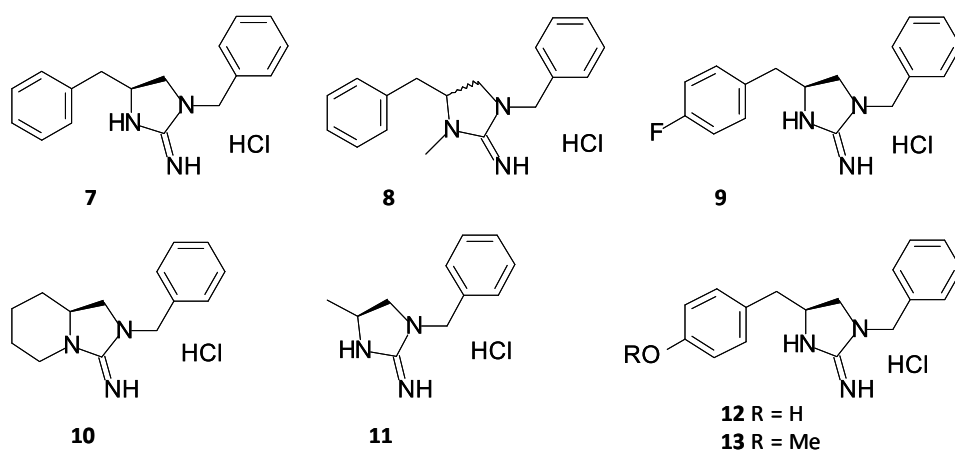


Figure 4.

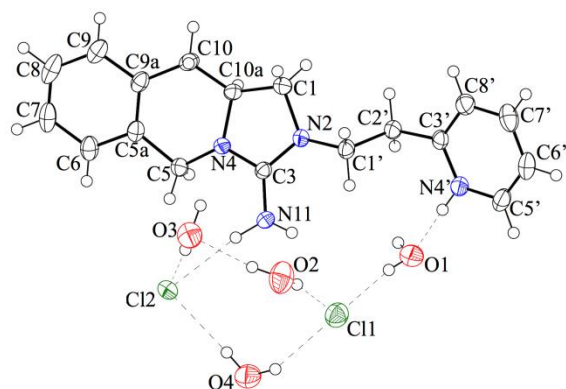
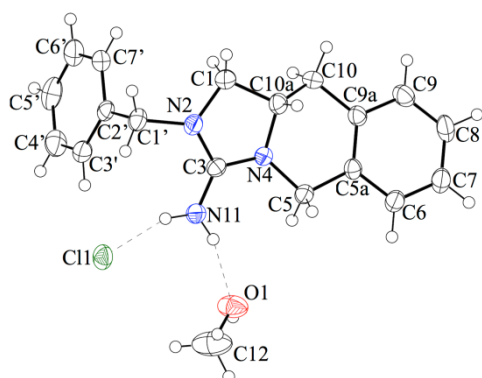


Figure 5.

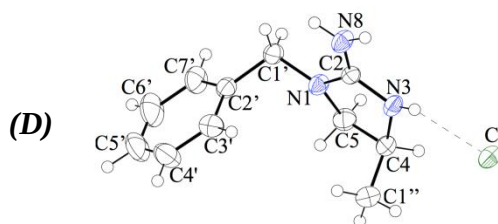
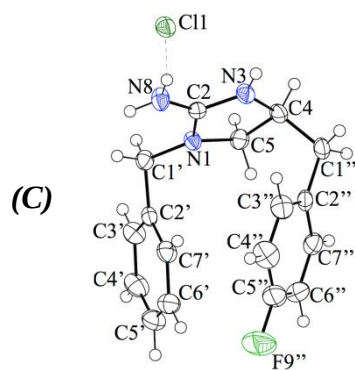
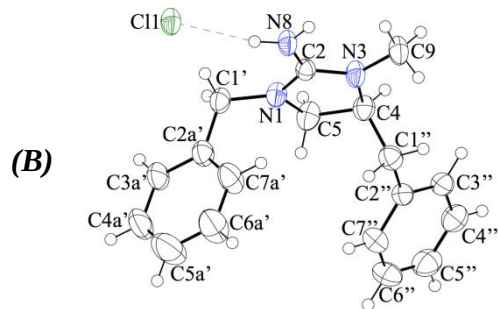
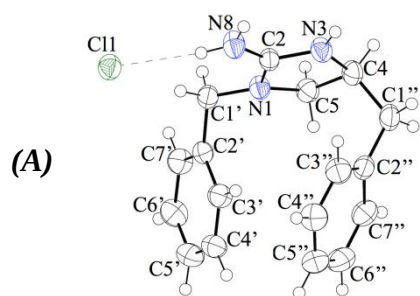
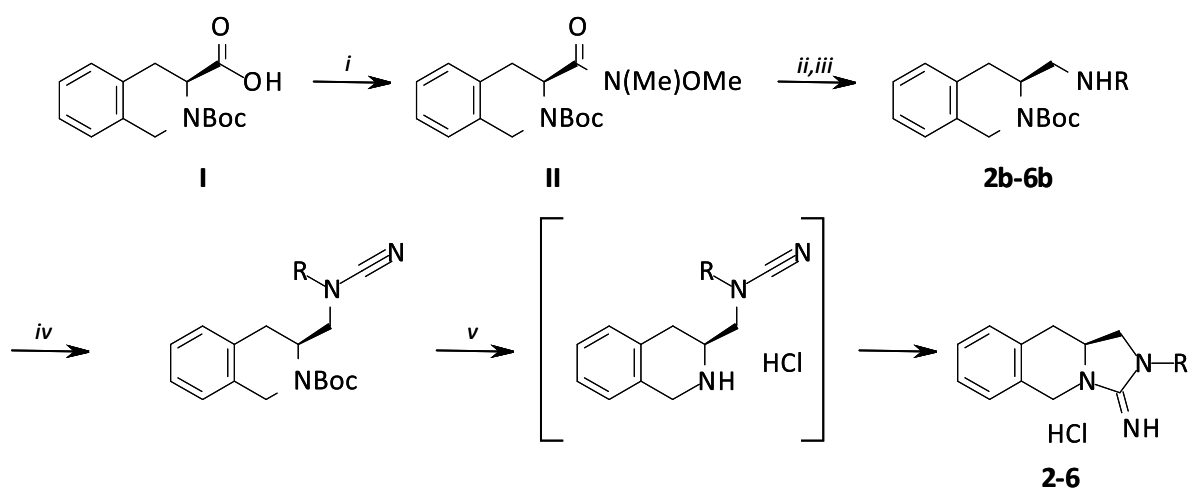
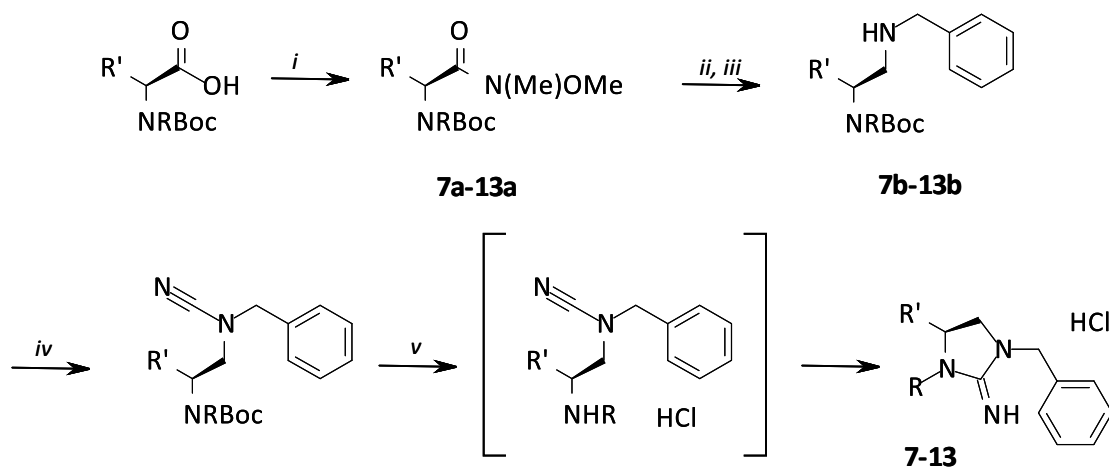


Figure 6.



Scheme 1.



Scheme 2.