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Research paper

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.

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 varying 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-hydantoins (Tic-H **1**, Fig. 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** (Fig. 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 fields [10–13]

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

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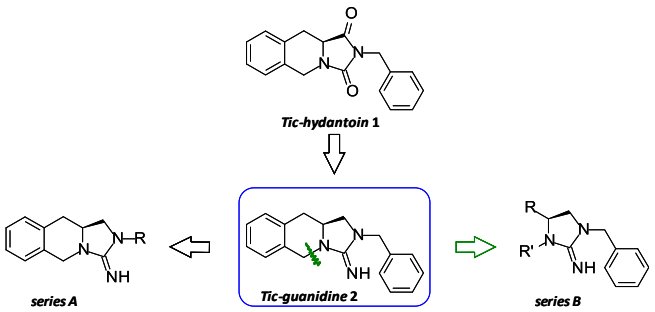


Fig. 1. Tic-guanidine derivatives of series A and B.

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**–**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} (Ki = 44 μM). 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 that concern the nature of the substituents on the original tricyclic structure Tic-guanidine (series A, Fig. 1) but also modifications by the central cyclic core's opening (series B, Fig. 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 (Fig. 2). Mainly, important hydrogen bonds with Glu^{169} and Asn^{253} 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.

Supported by our docking studies, pharmacomodulations are presented: various *N*-substituents on the guanidine core (series *A*, Fig. 1) and the central tricyclic core's opening (series *B*, Fig. 1). Series *A* enables us 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 for many A_{2A}'s antagonists [16,28,31] or if less restricted structures could improve affinity as compared to already published non planar A_{2A} antagonists [16,28,31,32]. 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 [7,9,33]. Key step of this synthesis was the final formation of the cyclic guanidine. Various methods are described in the literature to access guanidines [12] and cyclic guanidines [34–36] 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. However their chemical and enantiomeric instability precluded their use in this study [37]. For final formation of guanidine cycle, direct cyclization of the free diamine in the presence of cyanogen bromide [38–44] 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 [45]. 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** [46,47] using $LiAlH_4$ in THF at 0 °C [46]. Reductive amination with appropriate amine in the presence of sodium triacetoxyborohydride in CH_2Cl_2 gave expected Boc-monoprotected derivatives **2b**–**6b** [48]. Free amine of this last compound was then functionalized by cyanogen bromide in ethanol to give corresponding nitrile derivatives [45]. 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%.

Depending on the nature of the amine in the reductive amination step, compounds **2** to **6** were first obtained (Scheme 1), as depicted in Fig. 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**, Fig. 4). Compound **12**, derived from tyrosine, was prepared from Boc-Tyr(*t*Bu)-OH. The *tert*-butyl protection was removed in the final cyclization step.

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 (2260–2240 cm^{-1}) and appearance of the guanidine C=NH bond (1690–1640 cm^{-1}) confirming cyclization of the compound (see Supporting information). Finally, 1D and 2D ^{1}H 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 not only the structure and enantiopurity of compounds **2** and **3** (Fig. 5) but also compounds **7**, **9** and **11** whose absolute configuration was maintained (Fig. 6) [49].

On the other hand, crystallographic data showed compound **8** was present as a racemic mixture (for details, see Supporting information). 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 [50]. However, in our case, the basic conditions of methylation afforded complete racemization (Fig. 6).

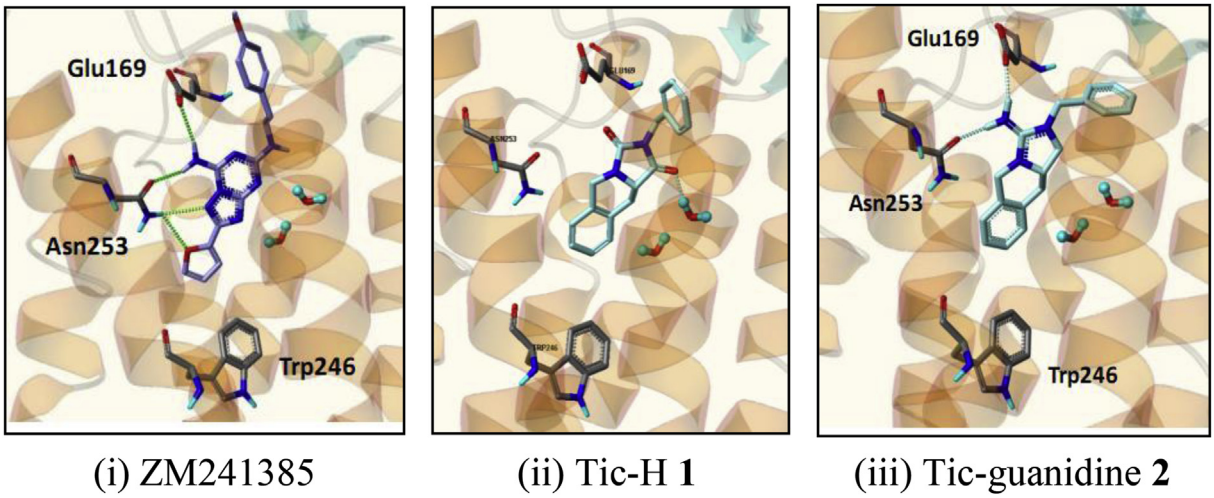
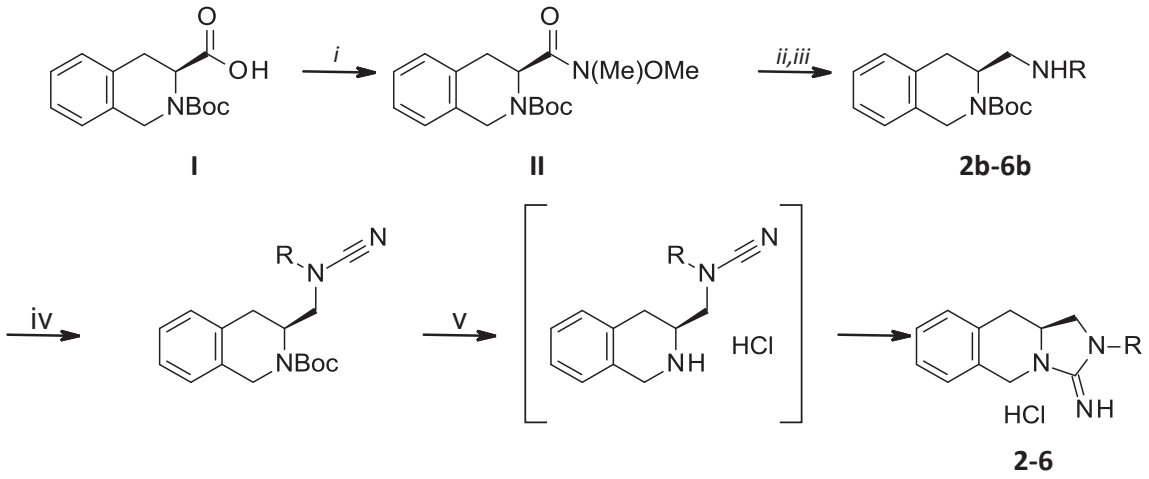


Fig. 2. $A_{2A}R$'s crystal structure with (i) high-affinity antagonist ZM241385, (ii) Tic-H **1** and (iii) Tic-guanidine **2**. Hydrogen bonds with Glu^{169} and Asn^{253} missing with Tic-H (ii) are being restored with the guanidine function (iii).



Scheme 1. *i*) HNMe(OMe)·HCl, EDC, HOBt, NMM, CH_3CN, CH_2Cl_2, 61%; *ii*) $LiAlH_4$, THF 0 °C then aq. $KHSO_4$, 66%; *iii*) R-NH_2, $NaHB(OAc)_3$, CH_2Cl_2 then aq. $NaHCO_3$, 92%-quant; *iv*) BrCN, $NaHCO_3$, EtOH, 54–97%; *v*) HCl, dioxane, 46–88%.

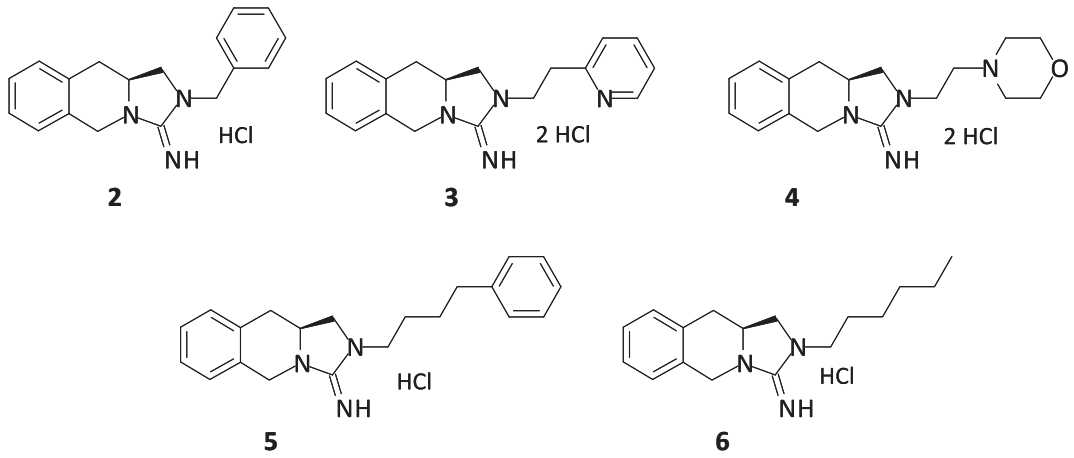
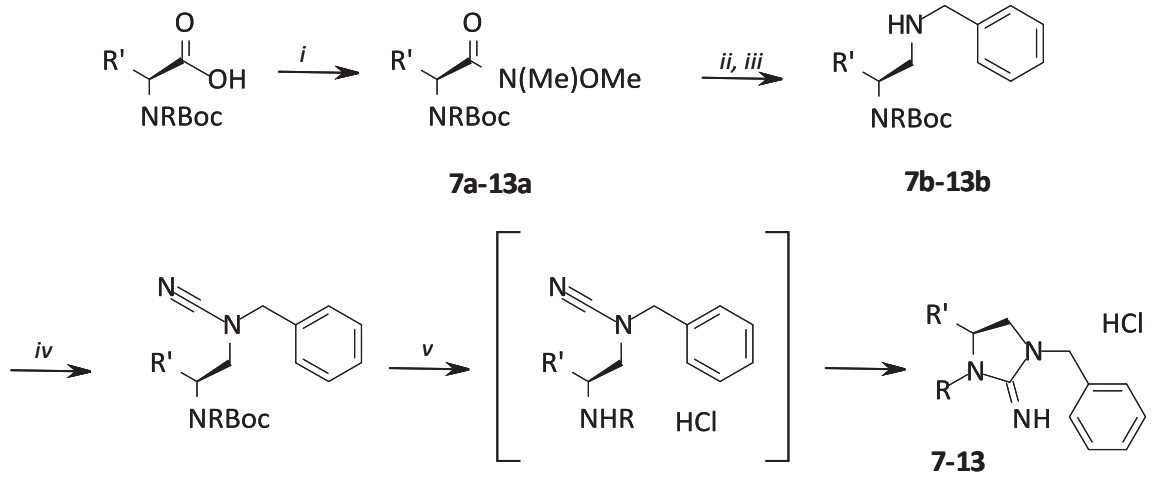


Fig. 3. Pharmacomodulations of compounds **2**–**6** of the Tic-guanidine core using various amines in the reductive amination step.



Scheme 2. *i*) HNMe(OMe)·HCl, EDC, HOBt, NMM, CH_3CN, CH_2Cl_2, 36–86%; *ii*) $LiAlH_4$, THF 0 °C then aq. $KHSO_4$, 20–97%; *iii*) Bn-NH_2, $NaHB(OAc)_3$, CH_2Cl_2 then aq. $NaHCO_3$, 19–99%; *iv*) BrCN, $NaHCO_3$, EtOH, 44–94%; *v*) HCl, dioxane, 23–90%.

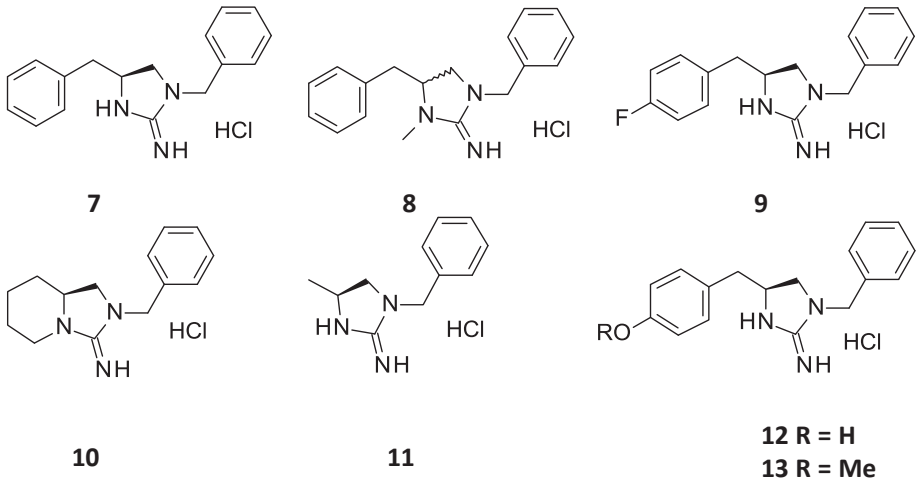


Fig. 4. Opening of the central Tic-guanidine core.

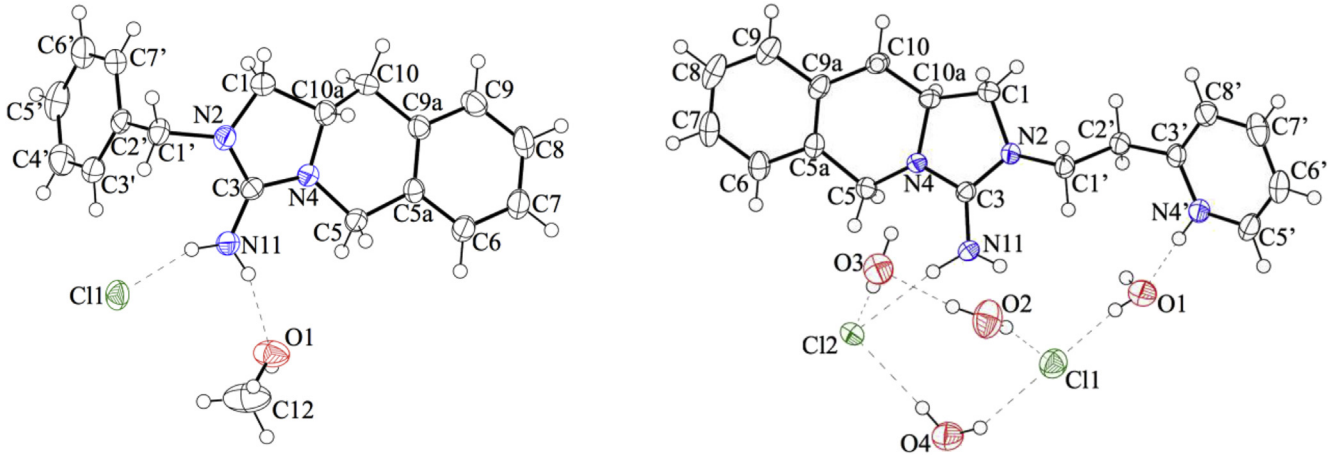


Fig. 5. Thermal ellipsoid drawing [49] (30% probability) of the asymmetric unit of compound **2** (left) and **3** (right) showing the molecular structure and the labeling scheme.

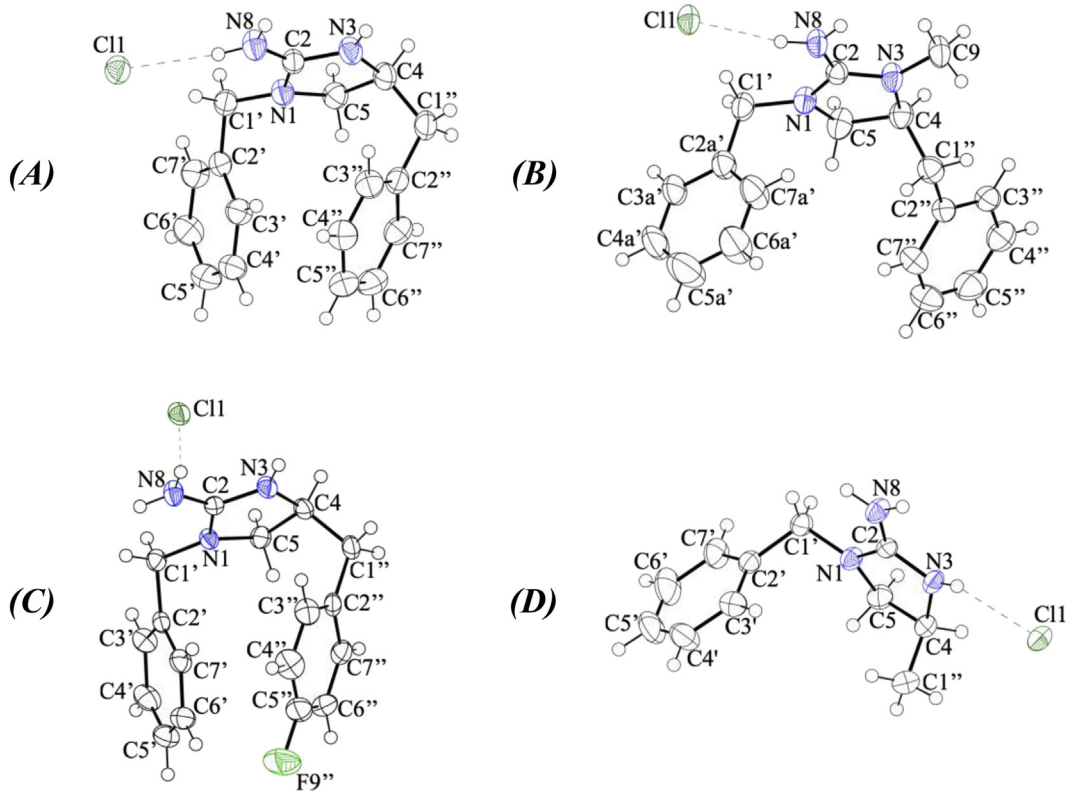


Fig. 6. Thermal ellipsoid drawing [49] (30% probability) of the asymmetric unit of compound **7**–**9** and **11** showing the molecular structure and the labeling scheme.

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** (Ki = 44 μM) except for the tricyclic guanidine substituted with phenylbutylamine **5** (Ki = 35 μM). More specifically, affinity was drastically decreased for open guanidines.

Except compound **5** (35 μM) that gives an affinity comparable to the one of Tic-H **1** (44 μM), binding was not improved with our Tic-guanidine compounds. For sure, rigid tricyclic structures are necessary to bind the A_{2A}R receptor as open structures (**7**–**13**) showed no affinity at all. X-ray analysis helped understanding this observation. In fact, as shown in Fig. 5, open Tic-guanidine from series B 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 [51]. On the other hand, compared to already published non-planar structures [16,28,31,32], our open Tic-guanidines compounds are not aromatic and this could explain the lack of efficacy as regards to the affinity.

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

More generally, low affinities of our Tic-guanidine compounds of both series might be improved by adding functionalized chains likely to favor interactions in the binding site.

Table 1
A_{2A} receptor affinity (Ki) and cytotoxicity assays of compounds **1**–**13**.

Cpd	Ki (μM)[a]	CC_{50} (μM)[b]
1	44	>100
2	64	>100
3	>200	>100
4	>200	>100
5	35	>100
6	>200	>100
7	>200	>100
8	>200	>100
9	>200	>100
10	>200	>100
11	>200	>100
12	>200	>100
13	>200	>100

[a] A_{2A}R's agonist CGS-21680 used as a reference (Ki = 0.503 μM). Displacement of specific [^{3}H]-ZM 241385 binding in membranes obtained from hA_{2a} receptor stably expressed in HEK293 cells.
[b] Cytotoxicity assays on SY5Y cells.

2.4. Cytotoxicity of Tic-guanidine compounds

Cytotoxicity assays have been conducted on SY5Y cells and showed no toxicity of our compounds at 100 μM.

3. Conclusion

As Tic-H core was a structure 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. The lack of cytotoxicity

of this new scaffold constitutes a major advantage. 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/UV_{254} sheets (thickness 0.2 mm). Purification of products was carried out by either column chromatography or thick layer chromatography. Column chromatography was carried out using Macherey–Nagel silica gel (230–400 mesh). Thick layer chromatography was performed on glass plates coated with Macherey–Nagel Sil/UV_{254} (thickness 2 mm), from which the pure compounds were extracted with the following solvent system: DCM/MeOH (NH_3), 90:10. NMR spectra were recorded on a Bruker DRX 300 spectrometer (operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C). 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 × 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 μL methanol and 950 μL buffer A, and injected into the system. The following eluent systems were used: buffer A (H_2O/TFA, 100:0.1) and buffer B (CH_3CN/H_2O/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 × 41.4 mm Dynamax from Varian, Inc. A gradient starting from 20% CH_3CN/80% H_2O/0.1% formic acid and reaching 100% CH_3CN/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 HN(Me)OMe.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 CH_2Cl_2, washed three times with saturated $NaHCO_3$ solution, three times with 1 M HCl and once with brine. Organic layer was dried over $MgSO_4$, 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 (5.13 g, 61%). ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 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; $C_{17}H_{25}N_2O_4$ 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%). ^{1}H NMR ($CDCl_3$, 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, 0.5H)]; 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) [52].

4.2.4. tert-Butyl N-[(1S)-1-benzyl-2-[methoxy(methyl)amino]-2-oxo-ethyl]-N-methyl-carbamate (***8a***)

According to general method 1, **8a** was obtained as a yellow oil (0.942 g, 86%). *^{1}H NMR* (*$CDCl_3$*, *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). *^{13}C NMR* (*$CDCl_3$*, *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; $C_{17}H_{26}N_2O_4$ 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%). ^{1}H NMR ($CDCl_3$, 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_{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 [M,H]$^+$ found; $C_{16}H_{24}FN_2O_4$ calculated m/z = 327.2 [M,H]$^+$.

4.2.6. tert-Butyl (2S)-2-[methoxy(methyl)carbamoyl]piperidine-1-carboxylate (***10a***)

According to general method 1, **10a** was obtained as a yellow oil (0.986 g, 83%). ^{1}H 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^+): $m/z = 273.1$ $[M,H]^+$ found; $C_{13}H_{25}N_2O_4$ calculated $m/z = 273.2$ $[M,H]^+$.

*4.2.7. tert-Butyl N-[(1S)-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 [53].

*4.2.8. tert-Butyl N-[(1S)-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 [54].

*4.2.9. tert-Butyl N-[(1S)-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 [55].

*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 1 M 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 1 M 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, $NaBH(OAc)_3$ (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 CH_2Cl_2 (15 mL). Combined organic layers were dried over $MgSO_4$, 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 (0.55 g, 95%). ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 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; $C_{22}H_{29}N_2O_2$ 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 (0.386 g, quantitative). ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 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; $C_{22}H_{30}N_3O_2$ 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%). ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 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; $C_{21}H_{34}N_3O_3$ 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%). ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 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; $C_{25}H_{35}N_2O_2$ 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%). ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 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; $C_{21}H_{35}N_2O_2$ 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 [56].

*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%). ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 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; $C_{22}H_{30}N_2O_2$ 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%). ^{1}H NMR ($CDCl_3$, 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, $\Delta\nu = 24$ 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). ^{13}C NMR ($CDCl_3$, 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; $C_{21}H_{28}FN_2O_2$

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%). ^{1}H NMR ($CDCl_3$, 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, $\Delta\nu = 24.2$ 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^+): $m/z = 305.0$ $[M,H]^+$ found; $C_{18}H_{28}N_2O_2$ calculated $m/z = 305.2$ $[M,H]^+$.

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 [57].

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%). ^{1}H 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^+): $m/z = 413.1$ $[M,H]^+$ found; $C_{25}H_{37}N_2O_3$ calculated $m/z = 413.3$ $[M,H]^+$.

4.3.13. tert-Butyl N-[(1S)-3-(benzylamino)-1-[(4-methoxyphenyl)methyl]-2-oxo-propyl]carbamate (**13b**)

According to general method 2, **13b** was obtained as a yellow oil (0.032 g, 22%). ^{1}H 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^+): $m/z = 371.2$ $[M,H]^+$ found; $C_{22}H_{31}N_2O_3$ calculated $m/z = 371.2$ $[M,H]^+$.

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 3 M 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. (10aS)-2-Benzyl-1,5,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-3-imine monohydrochloride (**2**)

According to general method 2, **2** was obtained (chromatography, CH_2Cl_2/methanol 94/6) as a white powder (0.13 g, 46%). ^{1}H NMR (CD_3OD, 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), $\Delta\nu = 144$ 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), $\Delta\nu = 72$ Hz]. ^{13}C NMR (CD_3OD, 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; $C_{18}H_{19}N_3$ calculated $m/z = 278.16517$ $[M,H]^+$. Mp: 198.5 °C. α_D (20 °C, CH_3OH) = −0.548° (0.500 mg/mL). IR, ν (cm^{-1}): 3089, 1660 (C=N). HPLC: C_4 column: $t_R = 11.7$ min, purity >99% C_{18} column: $t_R = 20.5$ min, purity >99%.

4.4.3. (10aS)-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, CH_2Cl_2/methanol 90/10) as a white powder (0.10 g, 67%). ^{1}H NMR (CD_3OD, 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, $\Delta\nu = 75$ Hz, 2H); 4.15–3.91 (m, 4H); 3.63 [AB part of ABX system (t, $J = 9.0$ Hz, 1H) $\Delta\nu = 114$ 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), $\Delta\nu = 51$ Hz). ^{13}C NMR (CD_3OD, 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; $C_{18}H_{20}N_4$ calculated $m/z = 293.17607$ $[M,H]^+$. Mp: 123.8 °C. α_D (20 °C, CH_3OH) = −0.449° (0.500 mg/mL). IR, ν (cm^{-1}): 3039, 1668 (C=N). HPLC: C_4 column: $t_R = 6.7$ min, purity >99% C_{18} column: $t_R = 12.9$ min, purity 98%.

4.4.4. (10aS)-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, CH_2Cl_2/methanol 90/10) as a brown oil (0.282 g, 69%). ^{1}H NMR (CD_3OD, 300 MHz), δ (ppm): 7.34–7.18 (m, 4H); 4.66 (AB system, $J = 16.0$ Hz, $\Delta\nu = 70$ 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), $\Delta\nu = 51$ Hz]; 2.69 (t, $J = 5.8$ Hz, 2H); 2.60 (t, $J = 4.5$ Hz, 4H). ^{13}C NMR (CD_3OD, 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; $C_{17}H_{25}N_4O$ calculated $m/z = 301.20229$ $[M,H]^+$. HPLC: C_4 column: $t_R = 12.3$ min, purity >94% C_{18} column: $t_R = 4.7$ min, purity 97%.

4.4.5. (10aS)-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, CH_2Cl_2/methanol 94/6) as a light brown oil (0.206 g, 82%). ^{1}H NMR (CD_3OD, 300 MHz), δ (ppm): 7.29–7.13 (m, 9H); 4.62 ([AB system (dd, $J = 18.0$ Hz, $\Delta\nu = 81$ 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), $\Delta\nu = 144$ 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), $\Delta\nu = 72$ Hz]; 2.69 (t, $J = 9.0$ Hz, 2H); 1.83–1.60 (m, 4H). ^{13}C NMR (CD_3OD, 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; $C_{21}H_{26}N_3$ calculated $m/z = 320.21212$ $[M,H]^+$. α_D (20 °C, CH_3OH) = −0.499° (0.500 mg/mL). IR, ν (cm^{-1}): 2929, 1664 (C=N). HPLC: C_4 column: $t_R = 12.7$ min, purity 98% C_{18} column: $t_R = 23.7$ min, purity 98%.

4.4.6. tert-Butyl (3S)-3-[(hexylamino)methyl]-3,4-dihydro-1H-isoquinoline-2-carboxylate (**6**)

According to general method 2, **6** was obtained (chromatography, CH_2Cl_2/methanol 85/15) as an orange oil (228 mg, 88%). ^{1}H

NMR (CD_3OD, 300 MHz), δ (ppm): 7.29–7.14 (m, 4H); 4.68 (AB system, J = 15.7 Hz, $\Delta\nu$ = 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), $\Delta\nu$ = 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). ^{13}C NMR (CD_3OD, 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; $C_{17}H_{26}N_3$ calculated m/z = 272.21212 [M,H]$^+$. HPLC: C_4 column: t_R = 3.3 min, purity 98% C_{18} column: t_R = 26.9 min, purity 97%.

4.4.7. (4S)-1,4-Dibenzylimidazolidin-2-imine hydrochloride (**7**)

According to general method 2, **7** was obtained (chromatography, CH_2Cl_2/methanol 95/5) as a white powder (19 mg, 27%). ^{1}H NMR (CD_3OD, 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), $\Delta\nu$ = 93 Hz]; 2.87 (d, J = 5.9 Hz, 2H). ^{13}C NMR (CD_3OD, 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; $C_{17}H_{20}N_3$ calculated m/z = 266.16517 [M,H]$^+$. Mp: 196.1 °C. α_D (20 °C, CH_3OH) = −0.006° (0.500 mg/mL). IR, ν (cm^{-1}): 3060, 1668 (C=N). HPLC: C_4 column: t_R = 13.1 min, purity >99% C_{18} column: t_R = 24.7 min, purity >99%.

4.4.8. (4S)-1,4-Dibenzyl-3-methyl-imidazolidin-2-imine hydrochloride (**8**)

According to general method 2, **8** was obtained (chromatography, CH_2Cl_2/methanol 95/5) a white powder (14 mg, 67%). ^{1}H NMR (CD_3OD, 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]. ^{13}C NMR (CD_3OD, 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 ($CH_{3(1)}$). HRMS (ESI$^+$): m/z = 280.18080 [M,H]$^+$ found; $C_{18}H_{22}N_3$ calculated m/z = 280.18082 [M,H]$^+$. Mp: 244.5 °C. α_D (20 °C, CH_3OH) = −0.098° (0.500 mg/mL). IR, ν (cm^{-1}): 3024, 1664 (C=N). HPLC: C_4 column: t_R = 10.1 min, purity >99% C_{18} column: t_R = 4.5 min, purity >99%.

4.4.9. (4S)-1-Benzyl-4-[(4-fluorophenyl)methyl]imidazolidin-2-imine hydrochloride (**9**)

According to general method 2, **9** was obtained (chromatography, CH_2Cl_2/methanol 90/10) a white powder (217 mg, 90%). ^{1}H NMR (CD_3OD, 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). ^{13}C NMR (CD_3OD, 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; $C_{17}H_{19}FN_3$ calculated m/z = 284.15575 [M,H]$^+$. Mp: 244.5 °C. α_D (20 °C, CH_3OH) = −0.072° (0.500 mg/mL). HPLC: C_4 column: t_R = 11.0 min, purity >99% C_{18} column: t_R = 19.5 min, purity >99%.

4.4.10. (8aS)-2-Benzyl-1,5,6,7,8,8a-hexahydroimidazo[1,5-a] pyridin-3-imine hydrochloride (**10**)

According to general method 2, **10** was obtained (chromatography, CH_2Cl_2/methanol 90/10) a white powder (130 mg, 29%). ^{1}H NMR (CD_3OD, 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). ^{13}C NMR (CD_3OD, 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; $C_{14}H_{20}N_3$ calculated m/z = 230.16517 [M,H]$^+$. Mp: 188.2 °C. α_D (20 °C, CH_3OH) = +10.6° (0.500 mg/mL). IR, ν (cm^{-1}): 2941, 1660 (C=N). HPLC: C_4 column: t_R = 9.0 min, purity 98% C_{18} column: t_R = 16.6 min, purity >99%.

4.4.11. (4S)-1-Benzyl-4-methyl-imidazolidin-2-imine hydrochloride (**11**)

According to general method 2, **11** was obtained (chromatography, CH_2Cl_2/methanol 90/10) a white powder (42 mg, 53%). ^{1}H NMR (CD_3OD, 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). ^{13}C NMR (CD_3OD, 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; $C_{11}H_{16}N_3$ calculated m/z = 190.13387 [M,H]$^+$. Mp: 194.9 °C. α_D (20 °C, CH_3OH) = −0.045° (0.500 mg/mL). IR, ν (cm^{-1}): 3055, 1667 (C=N). HPLC: C_4 column: t_R = 7.3 min, purity 98% C_{18} 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, CH_2Cl_2/methanol 85/15) a brown solid (53 mg, 73%). ^{1}H NMR (CD_3OD, 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). ^{13}C NMR (CD_3OD, 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; $C_{17}H_{20}N_3O$ calculated m/z = 282.16009 [M,H]$^+$. Mp: °C. α_D (20 °C, CH_3OH) = −0.014° (0.500 mg/mL). IR, ν (cm^{-1}): 3064, 1670 (C=N). HPLC: C_4 column: t_R = 10.2 min, purity 99% C_{18} column: t_R = 15.8 min, purity >99%.

4.4.13. (4S)-1-Benzyl-4-[(4-methoxyphenyl)methyl]imidazolidin-2-imine hydrochloride (**13**)

According to general method 2, **13** was obtained (chromatography, CH_2Cl_2/methanol 90/10) a brown solid (14 mg, 67%). ^{1}H NMR (CD_3OD, 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). ^{13}C NMR (CD_3OD, 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; $C_{17}H_{20}N_3O$ calculated m/z = 296.17574 [M,H]$^+$. Mp: °C. α_D (20 °C, CH_3OH) = −0.045° (0.500 mg/mL). IR, ν (cm^{-1}): 3064, 1670 (C=N). HPLC: C_4 column: t_R = 13.3 min, purity 99% C_{18} 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 [^{3}H]-ZM24135 by the designed A_{2A} antagonists described above, were performed as before [58] in Human HEK293 A_{2A}R membranes (Perkin Elmer). 0.5 μL of membranes (0.5 U of A_{2A}R) were incubated

with [^{3}H]-ZM24135 (2 nM) and increasing concentrations of the designed A_{2A}R antagonists (0–600 nM) in a final volume of 300 μL in the presence of 1 U/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 (8.3 nM). Microplates were incubated for 1 h 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 50 mM MgCl 10 mM) to filtermats 1.5 μm (Molecular Devices). 3 mL of scintillation cocktail (OptiPhase 'HiSafe' 2, PerkinHelmer) were added and radioactivity bound to the filters was determined after 12 h with an efficiency of 55–60% for 2 min. Displacement reference curves were performed with ZM-24135 (0–6 nM in 6%, 40% or 60% of DMSO) and CGS241680 (0–6 nM).

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 μg/ml streptomycin, 100 IU/mL penicillin, 1 mM non-essential amino acids and 10% (v/v) heat-inactivated fetal bovine serum (Sigma Aldrich), and grown at 37 °C in a humidified incubator with 5% CO_2.

Cells were seeded at 2000 cells per well onto 96-well plates in DMEM medium. Cells were starved for 24 h 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 h of incubation, cell growth was estimated by the colorimetric MTT (thiazolyl blue tetrazolium bromide) assay.

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Appendix A. Supporting information

Supporting information related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.10.030.

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