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Design, synthesis and biological evaluation of novel aminopropylcarboxamide derivatives as sigma ligands

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ABSTRACT

In our continuing effort to develop novel sigma receptor (SR) ligands, we present the design, synthesis and binding studies of a small library of aminopropylcarboxamide derivatives, obtained from a deconstruction of the piperidine ring of previously synthesized piperidine-based compounds. The best results were achieved with benzofuran (**5c**, **5g**) and quinoline (**5a**, **5e**) derivatives. These compounds revealed the highest affinity for both receptor subtypes. In particular, the 3,4-dimethoxyphenyl derivatives **5e** and **5g** showed the highest selectivity profile for S2R, especially the quinoline derivative **5e** exhibited a 35-fold higher affinity for S2R subtype. The cytotoxic activity of aforementioned compounds was evaluated against SKBR3 and MCF7 cell lines, widely used for breast cancer studies. Whereas the potency of **5g** was similar that of Siramesine and Haloperidol in both cell lines, compounds **5a**, **5c** and **5e** exhibited a potency at least comparable to that of Haloperidol in SKBR3 cells. A molecular modelling evaluation towards the S2R binding site, confirmed the strong interaction of compound **5e** thus justifying its highest S2R affinity.

Sigma receptors (SRs) were initially misclassified as class of opioid receptors, but further studies revealed them to be a well-defined class of receptors without any homology with opioid receptors and NMDA receptors.¹ SRs are divided into two subtypes termed Sigma-1 (S1R) and Sigma-2 (S2R).^{2–5} The S1R subtype is a chaperone protein cloned in 1996 from several tissues including human, rat and guinea pig. It has been recently crystallized by Kruse et al., revealing a trimeric protein organization with a single transmembrane domain in each protomer.⁶

At the subcellular level, the S1R subtype is primarily localized in mitochondria-associated membranes (MAMs) of neuronal and peripheral cells, and from there it can also translocate to the plasma membrane or endoplasmic reticulum-membrane. It regulates the activity of several proteins (e.g., NMDA receptors) by modulating different ionic channels

via an IP₃-independent mechanism.^{7–8}

The S1Rs have several physiological central nervous system (CNS) activities ranging from neuroprotection to memory improvement,^{9–10} opioid analgesia modulation,¹¹ as well as having a role in drug addiction.¹² Besides, different studies found S1R overexpression in some cancers.¹³ More recently, it has been found that several high affinity S1R ligands could prevent clinical deterioration in adult outpatients infected with SARS-CoV-2.¹⁴

On the other hand, molecular details concerning the S2R subtype have been puzzling until 2017, when the S2R gene was cloned and identified as the endoplasmic-reticulum-resident transmembrane protein-97 (TMEM97),¹⁵ also known as meningioma-associated protein-30 (MAC-30), implicated in cholesterol homeostasis due to its

Abbreviations: ADME, absorption distribution metabolism excretion; CNS, central nervous system; DAMGO, selective μ -opioid agonist; DOR, δ -opioid receptor; DTG, di-o-tolylguanidine; ER, estrogen receptor; GI, gastrointestinal; Halo, Haloperidol; HER2, tyrosine-protein kinase erb-2; IC₅₀, 50% of maximal cytotoxic concentration; KOR, κ -opioid receptor; MAC-30, meningioma-associated protein-30; MAM, mitochondrion-associated membrane; MOR, μ -opioid receptor; NMDA, N-methyl-D-aspartic acid; NPC1, Niemann-Pick cholesterol transporter type1; p53, cellular tumor antigen p53; PR, progesterone receptor; PTZ, pentazocine; RO5, rule of five; S1R and S2R, sigma-1 receptor and sigma-2 receptor; Srms, Siramesine; TMEM97, transmembrane protein-97; U50488, selective κ -opioid agonist.

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association with the lysosomal transporter NPC1.^{16–17}

The S2R/TMEM97 crystal structure has been now revealed thanks to Kruse and his team,¹⁸ and several pharmacophore models have been proposed so far.^{19–21} It was demonstrated that expression of S2R is mostly increased in breast, lung, brain, gastric, esophageal, lung, ovarian, and prostate cancer,^{22–25} but decreased in meningiomas, pancreatic and renal cancer.^{26–28}

In this context, S2R agonists are of interest for inducing tumour cell death and have been proposed as potential antitumoral agents. Since the S2R are also widely expressed in several CNS tissues such as cerebellum, red nucleus, and substantia nigra, they are also a potential target for the treatment of CNS disorders like neuroleptic-induced acute dystonia and movement disorders.²⁹ In addition, both S1R antagonists and S2R agonists can modulate neuropathic pain.^{30,31}

Long ago, our group synthesized and biologically investigated a variety of piperidine-based compounds for their activity against SRs which yielded some intriguing results, particularly for the S1R subtype.³² Indeed, our compounds showed the best K_i S1R value of 14 nM, whereas the S2R affinity was practically negligible (best K_i S2R = 270 nM). With the aim of improving similar structures, but with increased affinity for the S2R subtype, we planned to synthesize a new set of compounds by replacing the piperidine ring with a more flexible linear chain and by introducing the 3,4-dimethoxyphenyl moiety (Fig. 1).

This kind of substitution pattern is present in several S2R ligands, such as some benzamide derivatives (e.g. RHM-1),³³ and it is apparently associated with enhancement of the selectivity towards this receptor subtype.^{33–34} Additional SAR studies by the authors within this class of benzamide derivatives, revealed that shortening the length of the spacer group between the amide nitrogen and the nitrogen atom of the secondary amine moiety from 4 carbons to 3 and 2 carbons did not alter binding affinity to the S2R (e.g. YUN-234).³³

Therefore, in order to develop new compounds with potential

anticancer activity, associated with their S2R agonist profile, herein we synthesized a library of aminopropylcarboxamide derivatives, and tested them towards both SR subtypes.

The synthetic route was carried out from different aryl chlorides **1a–d** and commercially available 3-bromopropylamine hydrobromide (**2**) to afford the corresponding 3-bromopropyl-2-arene-carboxamides **3a–d**. The latter were reacted with commercial benzylmethylamine (**4a**) or 3,4-dimethoxybenzylmethylamine (**4b**, prepared from 3,4-dimethoxybenzaldehyde and methylamine via reductive amination) to give the final compounds **5a–h** (Scheme 1).

The synthesized compounds were evaluated for affinity towards both S1R and S2R, as well as to opioid receptors μ (MOR), δ (DOR) and κ (KOR), through radioligand binding assay and the results are depicted in Table 1.

A number of considerations on the selectivity (with a potential impact on structure-activity) can be drawn from the binding affinity data shown in Table 1. Concerning the S1R/S2R selectivity, within the series of compounds bearing the unsubstituted phenyl ring (**5a–d**), the most potent molecules resulted quinoline **5a** and benzofuran **5c** derivatives, which showed a pan-affinity against both SR subtypes with K_i S1R of 16 and 12 nM, and K_i S2R of 21 and 9.9 nM, respectively. On the other hand, the 3,4-dimethoxy substituted series **5e–h**, again the quinoline **5e** and benzofuran **5g** derivatives resulted the most interesting compounds, as they showed a strong preference for the S2R subtype with K_i S2R of 16 and 46 nM. The highest selectivity was reached by quinoline derivative with a 35-fold higher selectivity towards S2R with respect to the S1R. Then, the dimethoxy substitution on phenyl ring, present in the sub-series **5e–h**, resulted to be strongly detrimental for the S1R affinity, raising the affinity values by an order of magnitude with respect to the **5a–d** sub-series data. Lastly, the furan derivatives **5d** and **5h** showed K_i values in the high micromolar range.

Concerning the selectivity for opioid receptors, all compounds

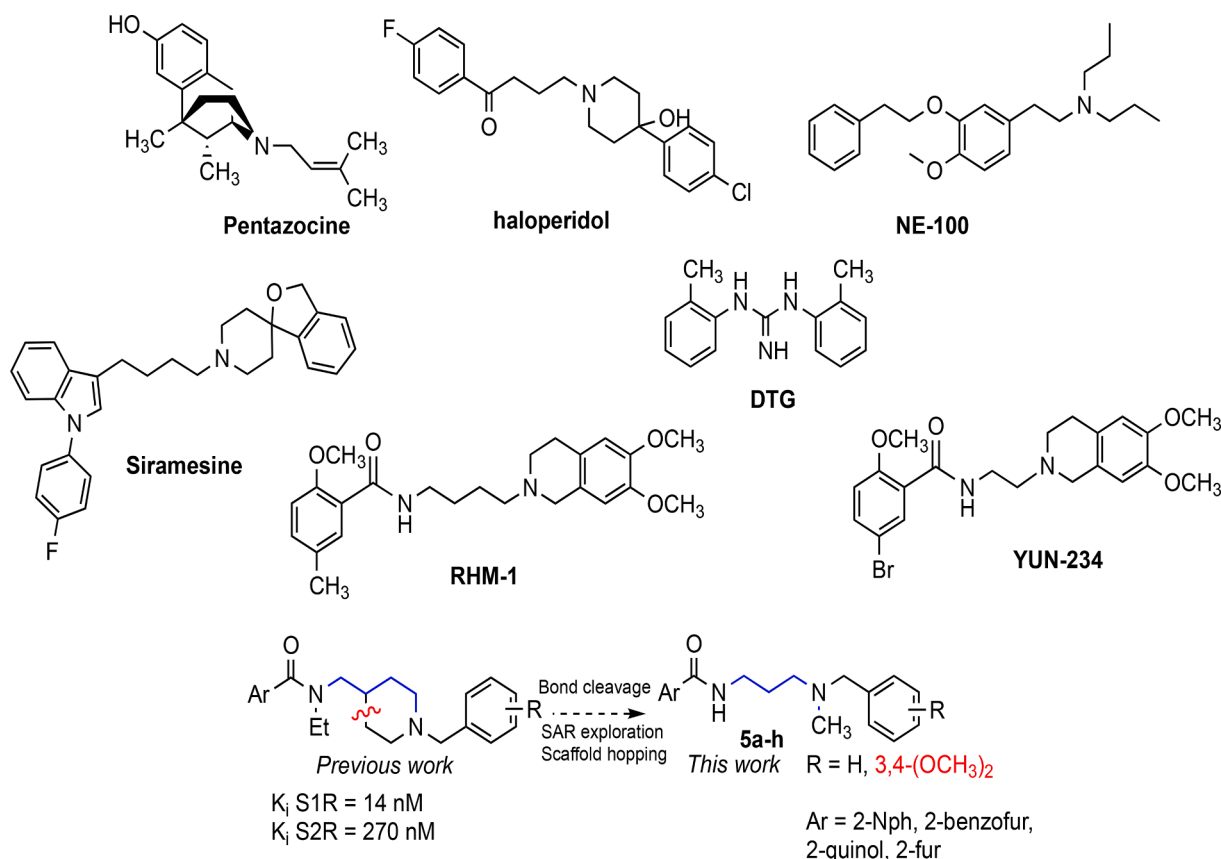
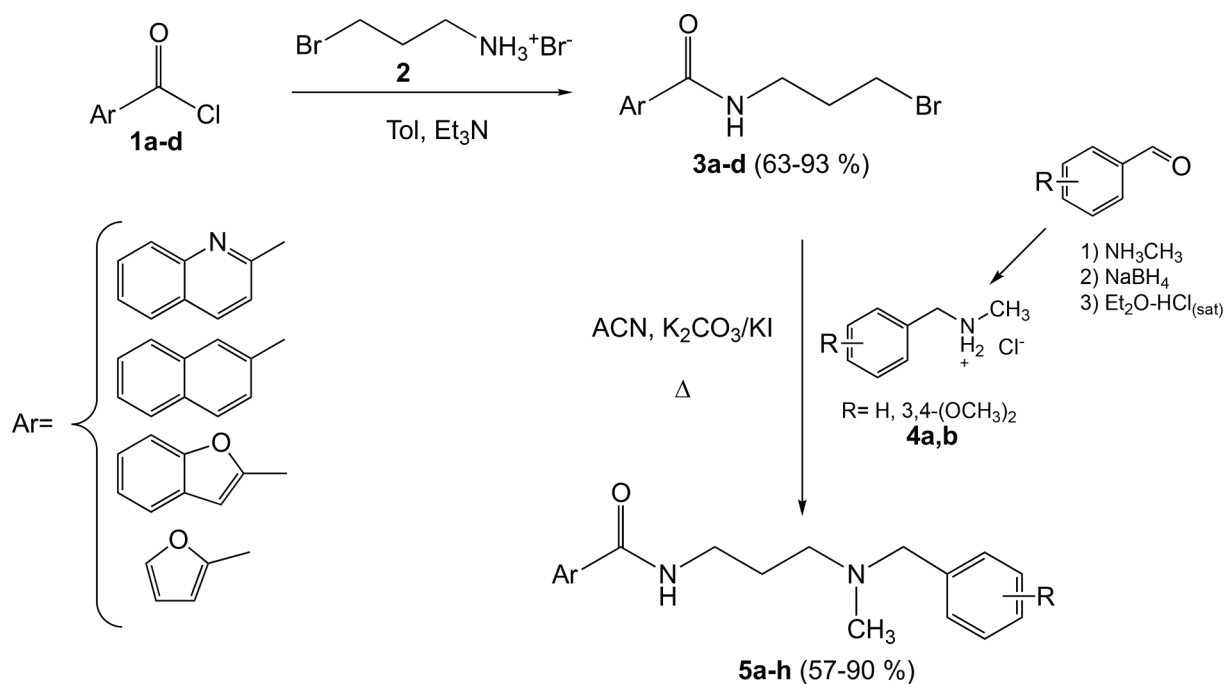


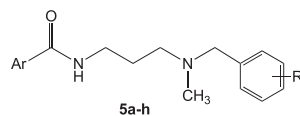
Fig. 1. Some common S1R and S2R ligands and rationale design for the new synthesized derivatives **5a–h**.



Scheme 1. Synthesis of title compounds **5a-h**.

Table 1

S1R, S2R, MOR, DOR and KOR binding assay for compounds **5a-h**.



Cmpd	Ar	R	$K_i \pm \text{SEM}^a$ (nM)					KOR
			S1R	S2R	S1R/S2R	MOR	DOR	
5a		H	16 ± 3	21 ± 4	0.7	2763 ± 25	>10,000	3576 ± 33
5b		H	104 ± 18	106 ± 12	1.0	3433 ± 24	>10,000	>10,000
5c		H	12 ± 3	9.9 ± 0.9	1.2	1770 ± 13	>10,000	2390 ± 24
5d		H	>10,000	1067 ± 295	–	>10,000	>10,000	>10,000
5e		3,4(OCH ₃) ₂	573 ± 91	16 ± 2	35	56 ± 4	>10,000	>10,000
5f		3,4(OCH ₃) ₂	1445 ± 459	126 ± 24	11	1219 ± 12	>10,000	>10,000
5g		3,4(OCH ₃) ₂	375 ± 89	46 ± 7	8.1	2905 ± 18	>10,000	>10,000
5h		3,4(OCH ₃) ₂	>10,000	>5000	–	>10,000	>10,000	4172 ± 4
Halo	–	–	2.5 ± 0.4	16 ± 2	0.1	Nd	nd	nd
(+)-PTZ	–	–	4.7 ± 0.7	1465 ± 224	<0.01	Nd	nd	nd
DTG	–	–	nd ^b	18 ± 1	nd	Nd	nd	nd
DAMGO	–	–	nd	nd	nd	1.49 ± 0.5	nd	nd
Naltrindole	–	–	nd	nd	nd	nd	2.53 ± 0.5	nd
U50488	–	–	nd	nd	nd	nd	nd	1.1 ± 0.2

^a Each value is the mean ± SEM of at least two experiments performed in triplicate (SRs) and duplicate (opioid receptors).

^b Not determined.

showed no affinity for MOR, DOR and KOR receptors, except a slight interaction of the compound **5e** with MOR, confirming a high selectivity of our series of derivatives for SRs.

From the data obtained, it is clear the positive contribution of a bulky bicyclic aromatic moiety, linked to the carboxamide group and preferentially bearing a hetero atom into the cycle. Conversely, the presence of

a small monocyclic ring is strongly detrimental for the affinity towards both SRs (e.g. **5d** and **5h**), whereas the introduction of two methoxy moieties at 3- and 4- position on the phenyl ring confirms the preference for the S2R, by increasing the selectivity towards this receptor subtype. Finally, for what regards the synthesis of new compounds gifted with affinity for both SR subtypes, the methylaminopropyl linker resulted a useful spacer for connecting the two aromatic portions by being more adaptable in the receptor pocket than the rigid piperidine nucleus.

Future developments will concern the synthesis of a larger library of compounds, for instance by replacing the propyl chain with a longer butyl or even pentyl linker and/or by increasing the variety of aromatic substituents, in order to evaluate the eventual increase in the affinity and the selectivity towards both receptor subtypes.

The compound with the highest affinity and selectivity towards S2R, namely **5e**, was computationally investigated. The human S2R was constructed by homology technique, employing the corresponding bovine receptor as structural template.¹⁸ The structure was minimized, and compound **5e** was docked into the receptor. Optimum complexes were then minimized once again allowing for induced fit, and compound **5e** was docked to the receptor once again and further minimized. The analysis of the lowest energy pose (Fig. 2a) revealed the ligand assuming a similar position and orientation as that previously observed for the

Roluperidone, with the bovine receptor.¹⁸ A closer analysis revealed that the nitrogen atom of the quinoline ring forms a hydrogen bond with Tyr 147 (Fig. 2b) and is located into a polar cavity orthogonal to the protein helices (Fig. 2c). It is interesting to note that the cavity, while being capable of accommodating larger substituents, presents charged residues of opposite charge. This aspect explains why, among all docked poses, we also found some poses with the 3,4-dimethoxyphenyl ring at this position as its shape and size are compatible with that of the cavity. However, due to electrostatic repulsion, these were higher energy conformations. Indeed, the 3,4-dimethoxyphenyl ring was more often found filling a hydrophobic surface exposed pocket (Fig. 2d). The molecule is further stabilized by a hydrogen bond between Asp29 and the nitrogen atom of the secondary amine moiety (Fig. 2b).

We have chosen the four best candidates of our series (**5a**, **5c**, **5e** and **5g**) in order to evaluate the cytotoxic response towards two commonly used human breast cancer cell lines (SKBR3 and MCF7) compared to that of Siramesine (Srms), a commonly accepted S2R agonist, and Haloperidol (Halo), a well-known S1R antagonist.

The characteristics of the human breast cancer cell lines used in this study are presented in Table 2, showing SR density as previously determined by Vilner et al.³⁵ and Crawford and Bowen;³⁶ information about HER2, Estrogen receptor (ER), and Progesterone receptor (PR) status, was obtained from ref.^{37,38} whereas information about p53 status was obtained from ref.³⁹⁻⁴³ S2Rs are expressed at high levels in both cell lines. The cytotoxic potency of the four compounds was tested by using a resazurin assay (Supplementary Material).

The human breast cancer cell lines SKBR3 and MCF7 were treated with various concentrations of the indicated S2R ligands (Supplementary Material). The percentages of toxicity against both cell lines are reported in Table 3 (Figs. S1a-b Supplementary Material) and are expressed in terms of cytotoxicity concentrations (IC₅₀).

In SKBR3 cells, the compounds **5a** and **5c** exhibited approximately 50% of toxicity at the highest tested concentrations (100 μ M and 200 μ M), while for **5e** and **5g** the toxicity raised up to 60%, compared to 48% and 98% of cell death induced by Halo and Srms, respectively.

In MCF7 cells, at 100 μ M concentration, the compound **5a** exhibited the lowest percentage of toxicity (approximately 30%), which raised up to 50% for the derivatives **5e** and **5c** and up to 60% for **5g**, in comparison to 79% and 96% of cell death induced by Halo and Srms, respectively.

In these experiments, whose results are shown in Table 3, all compounds showed micromolar-potency inhibition (IC₅₀) for a 48-h exposure to drug and values were determined by curve-fitting (Fig. S1a-b Supplementary Material). On one hand, the potency of **5g** was similar in both cell lines (35 vs 36 μ M, in SKBR3 and MCF7, respectively) and substantially comparable to that of Srms (14 and 13 μ M, in SKBR3 and MCF7, respectively) and that of **5e** (88 and 251 μ M) and of **5c** (52 and 86 μ M) was similar to that of Halo (131 and 68 μ M in SKBR3 and MCF7, respectively). On the other hand, the IC₅₀ of the compound **5a** was higher than that of the reference-compounds in both cell lines.

Thus, although the comparison with the IC₅₀ of Srms suggests that the differences in cytotoxic potency observed in the two cell lines cannot be ascribed just to their HER2/ER/PR/p53 status, at least for SKBR3 cells, the antiproliferative effects of the compound **5g** and **5e** are substantially comparable to those of Srms and Halo, respectively.

Interestingly, there seems to be a correlation between S2R binding affinities and cytotoxicity. In fact, compounds **5c**, **5e** and **5g**, which are among those with best S2R binding affinities (K_i S2R = 9.9, 16 and 46

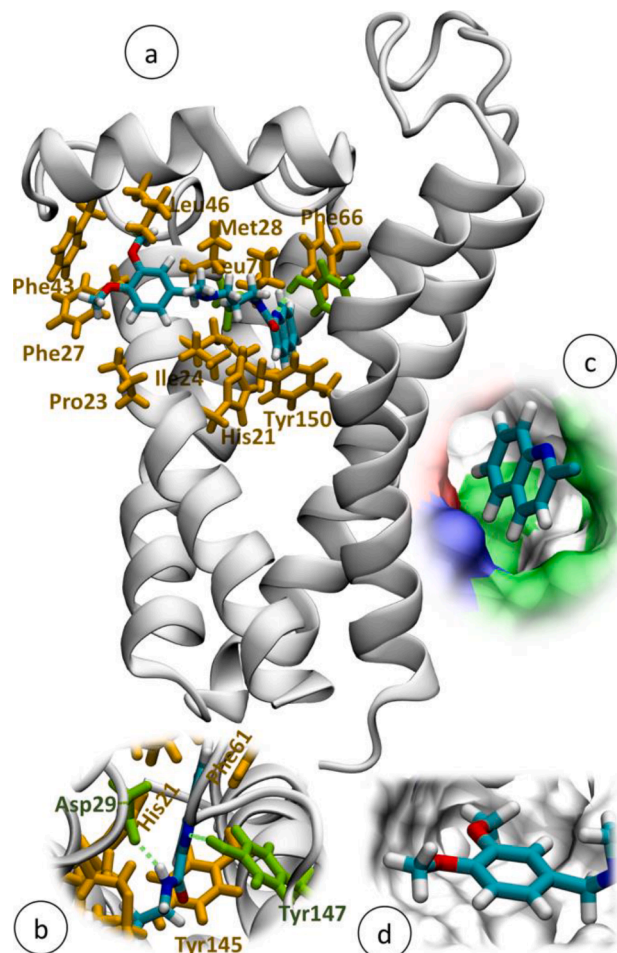


Figure 2. S2R modelling results for compound **5e**: (a) representative docked pose, (b) detail of the hydrogen bonds, (c-d) shape complementarity between ligand moieties and receptor cavities. In (a-b) protein residues interacting with all compounds by van der Waals interactions are highlighted in yellow, residues involved in hydrogen bonds in green. In (c-d) the receptor surface is colour coded as follows: non-polar residues (white), basic residues (blue), acidic residues (red) and polar residues (green).

Table 2

Features of SKBR3 and MCF7 cell lines and S2R density (Bmax, fmol/mg protein) values.

Cell line	HER2	ER	PR	p53	S2R density
SKBR3	+	-	-	Wild-type	2071 $\pm$ 734
MCF7	-	+	+	R175H	2826 $\pm$ 309

Table 3

Values of IC₅₀ (μM) of selected test compounds **5a**, **5c**, **5e** and **5g**, in SKBR3 and MCF7 cell lines. Values are averages of three to four experiments ± SEM.

Cmpd	IC ₅₀ (μM)	
	SKBR3	MCF7
5a	169 ± 20	1637 ± 196
5c	52 ± 7	86 ± 12
5e	88 ± 11	251 ± 30
5g	35 ± 5	36 ± 4
Halo	131 ± 18	68 ± 10
Srms	14 ± 3	13 ± 2

nM, respectively), display higher levels of toxicity in both cell lines.

In conclusion, in this work, we synthesized and tested for their SR affinity a library of new aminopropylcarboxamide derivatives, derived from a piperidine-based deconstruction of previously synthesized compounds. The new molecules showed affinity for both SRs in low nanomolar range. In particular, four out of eight derivatives (**5a**, **5c**, **5e** and **5g**) showed high affinity for S2R subtype and were tested for their potential antiproliferative activity towards two cancer cell lines.

Compounds **5a-h** were also *in-silico* scored for molecular descriptors related to drug likeness (ADME).⁴⁴ None of the derivatives violate the Lipinski's RO5 and all of them were predicted to be highly absorbed from GI tract (Supplementary Materials, Table S1).

These finding can be useful to design new compounds based on aminopropylcarboxamide spacer in order to enhance the selectivity for the S2R subtype.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bmcl.2022.128860>.

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