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SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF BENZAMIDE DERIVATIVES AS POTENT AND SELECTIVE SIGMA-1 PROTEIN LIGANDS

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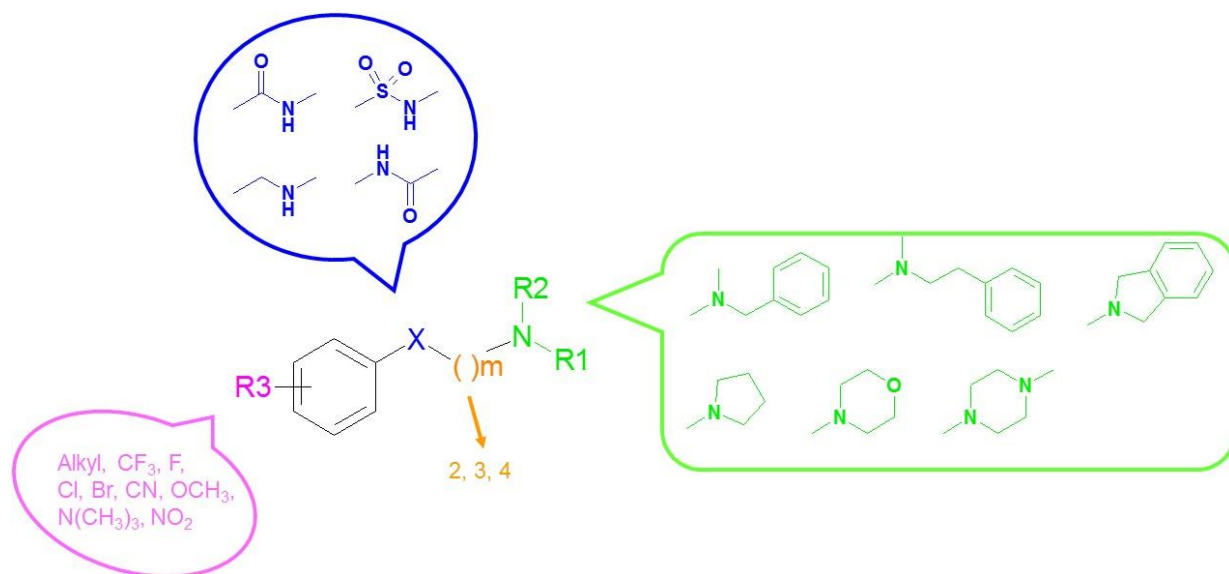
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Graphical Abstract



A series of benzamide-derived compounds was synthesized, evaluated *in vitro* toward their S1R, S2R affinities and cytotoxic effects on SY5Y cells and selectivities on a panel of 40 receptors.

ABSTRACT

A series of novel benzamide-derived compounds was designed, synthesized and pharmacologically evaluated. Among all 37 synthesized compounds, two series were developed with the modulation of the nature, the position of atoms or groups on the benzamide scaffold, but also the nature of the amine group separated from the benzamide with 2, 3 or 4 methylene groups. *In vitro* competition binding assays against sigma proteins (sigma-1 S1R and sigma-2 S2R) revealed that most of them conferred S2R/S1R selectivity toward without cytotoxic effects on SY5Y cells, especially with the first series with compounds **7a-z**. Some selected compounds were also evaluated for their agonist and antagonist activities on a panel of 40 receptors. Results showed the importance of the nature and the position with halogeno atom on the benzamide scaffold, the length chain but also the contribution of the hydrophobic part on the amine group. Among them, compounds **7i, w, y** with Cl, CN or NO₂ groups at the 4-position of the benzamide scaffold showed excellent affinity for S1R ($K_i = 1.2$ to 3.6 nM), selectivity for S2R (K_i up to 1400 nM) and high selectivity index ($IC_{50(SY5Y)}/K_i (S1R)$ ratio from $28\ 000$ to $83\ 000$). Furthermore, these compounds presented an excellent safety profile over 40 other receptors. These derivatives will be selected for further biological investigations.

Key words: benzamide, sigma protein, CNS

1. Introduction

More than 40 years after their discovery and due to their involvement in various CNS pathologies, the sigma proteins continue to be widely studied [1-3]. These proteins have been first described as opioid receptors [4] and then classified in the literature as distinct sigma-1 and sigma-2 receptors (S1R and S2R) differing from their pharmacologically and ligand binding profile, anatomical distribution, function and molecular size [5-8]. The protein S2R has not been cloned from any species, while the S1R protein was cloned from various mouse [9], rat [10] and human [11] tissues.

The S1R have been identified as a small-ligand regulated chaperone protein. They are located at the interface between endoplasmic reticulum (ER) and mitochondria called mitochondria associated membrane (MAM) [12,13]. They modulate the Ca^{2+} homeostasis under conditions of cellular stress [13,14], but also the K^+ and Cl^- channels [15,16]. Additionally, S1R have been shown to regulate the cholinergic [17,18], adrenergic [19,20], dopaminergic [21,22], glutamatergic [21] and serotonergic [23] neurotransmissions.

S1R are involved in the regulation of numerous neurotransmitter systems, the signal transduction pathway is not completely understood but S1R pharmacological modulators have been shown to modulate several CNS diseases such as pain [24,25], depression [26] or schizophrenia [27,28], but also neurodegenerative disorders like Alzheimer's and Parkinson's diseases [29-31]. Thus, the synthesis of such S1R ligands represents a promising strategy to develop novel treatments for various CNS diseases or even cancers [32-33]. Many drugs described in the literature show affinity for S1R, and some of them have undergone clinical trials, but no selective S1R ligands have so far been marketed [34]. A phase 2 study is ongoing to evaluate Anavex 2-73 – a mixed muscarinic and S1R agonist - in patients with Alzheimer's disease [35,36].

Numerous studies described the synthesis, as well as the biological and pharmacological activities of S1R ligands that exhibit K_i values in the nanomolar range, Among them, previous work of our laboratory underlines a first series of tetrahydroisoquinoline-hydantoin (tic-hydantoin) compounds (Figure 1) as efficient S1R ligands ($K_i = 4.5$ to 7.1 nM), with low affinity for S2R ($K_i = 500$ to 1000 nM) and therefore high S2R/S1R selectivity (100 to 140). These S1R ligands were evaluated in different pharmacological models. One derivative increased cocaine-induced locomotor stimulation and sensitisation in anti-cocaine evaluation [37], an other one brought about a 57% decrease of infarct volume in an ischaemia model [38]. These compounds were described as neuroprotective agents by their strong anti-inflammatory and neuroprotective effects in an experimental model of multiple sclerosis [39]. Despite chemical stability of tic-hydantoin derivatives in neutral and acidic media, they demonstrated a low metabolic stability, preventing from the perspective of drug development.

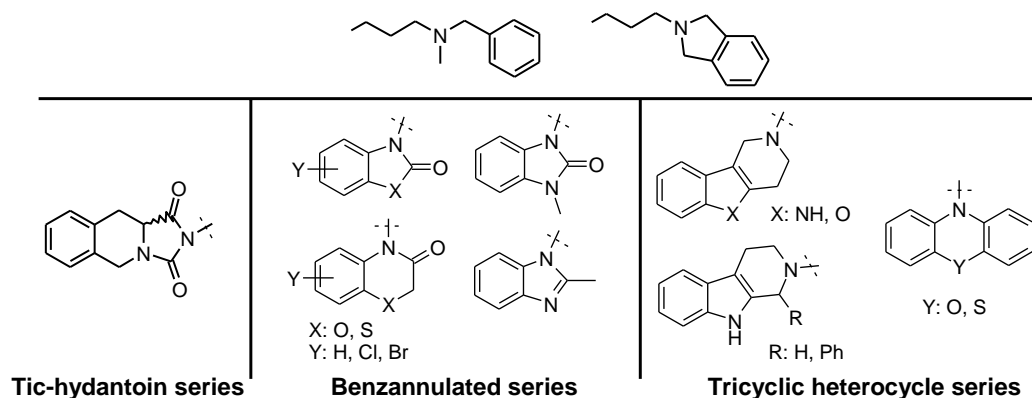


Figure 1: Tic-hydantoin, benzannulated and tricyclic series with propyl-N-methyl-N-benzylamine or isoindoline chains

Continuing our efforts in the synthesis of S1R ligands to solve this problem of metabolic stability, other works (Figure 1) were dedicated to replacement of the tic-hydantoin moieties with different tricyclic heterocycles [40] or benzannulated scaffold [41]. Though the S1R affinity was maintained for most of the compounds ($K_i = 0.6$ to 30 nM), but the S2R/S1R selectivity remained low (< 30).

Thus we report here our efforts to simplify the structure and replace the different heterocycle moieties by benzamide scaffold with a length chain of 2, 3 or 4 methylene functions separated from the amine part with benzylmethylamine to afford compounds **7a-z** (Figure 2) [42]. The design of these compounds could be compared to 4-IBP [43], which was recently cocrystallized with S1R [44]. In a first series, numerous substitutions on the benzamide scaffold were adopted by varying the nature and the position of halogeno atoms (Cl, Br) and groups (alkyl, CF_3 , OCH_3 , NO_2 , $N(CH_3)_2$, CN). Considering the good results with compounds **7a-z**, we developed a second series of derivatives **8a-h** where we kept the 4-chlorobenzamide moieties and modulated the nature of the amine part with N-phenylethyl-N-methylamine, isoindoline, pyrrolidine, morpholine and methylpiperazine (Figure 2). In this second series, compounds **8a-h** were synthesized with length chain of 2 or 3 methylene groups between the benzamide and the functionalized amine. In this series, we also evaluated the importance of the hydrophobic part with the phenyl ring and the hydrophilic part with morpholine and piperazine moieties. In a third series, analogues of the promising compound **7i** were prepared while modifying the linker. On the benzamide scaffold (**7i**), the amide function was changed by sulfamide function to give compound **9**, the benzamide was reduced in benzylamine to furnish derivative **10** and the retroamide was also synthesized with compound **13** (Figure 2).

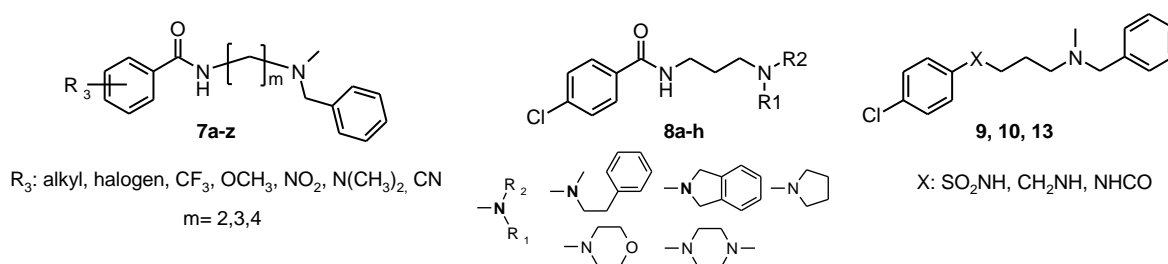
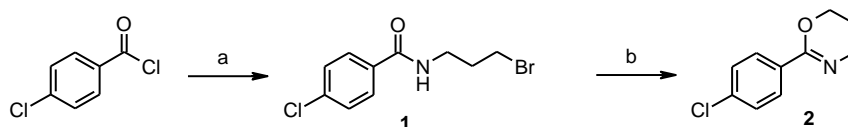


Figure 2: Structure of final compounds **7a-z**, **8a-h**, **9**, **10**, **13**

2. Chemistry

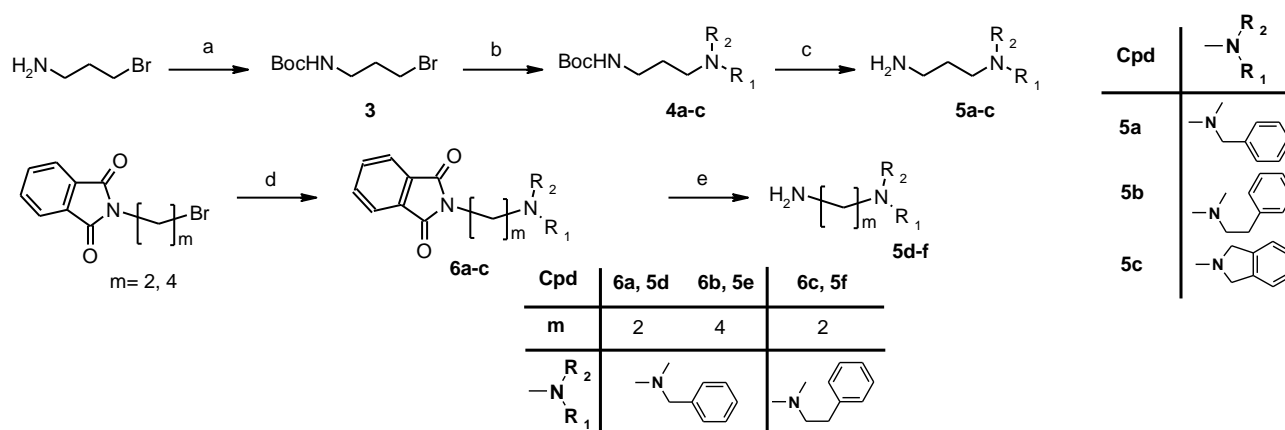
To synthesize final compounds **7a-z**, a first attempt was realized in two steps starting from commercially available 4-chlorophenylacetyl chloride (Scheme 1). Reaction with 3-bromopropylamine in dichloromethane with 4-chlorophenylacetyl chloride gave the intermediate **1**. Nucleophilic substitution in DMF with potassium carbonate and isoindoline as reagent, as the second step, did not afford the corresponding isoindoline compound but derivative **2** obtained by cyclization of bromo compound **1**.



Scheme 1: attempt to synthesized final compounds

Reagents and conditions: (a): 3-bromopropylamine, CH_2Cl_2 , 12h, 0°C to rt, 65%; (b): isoindoline, potassium carbonate, DMF, 12h, 70°C , 70%.

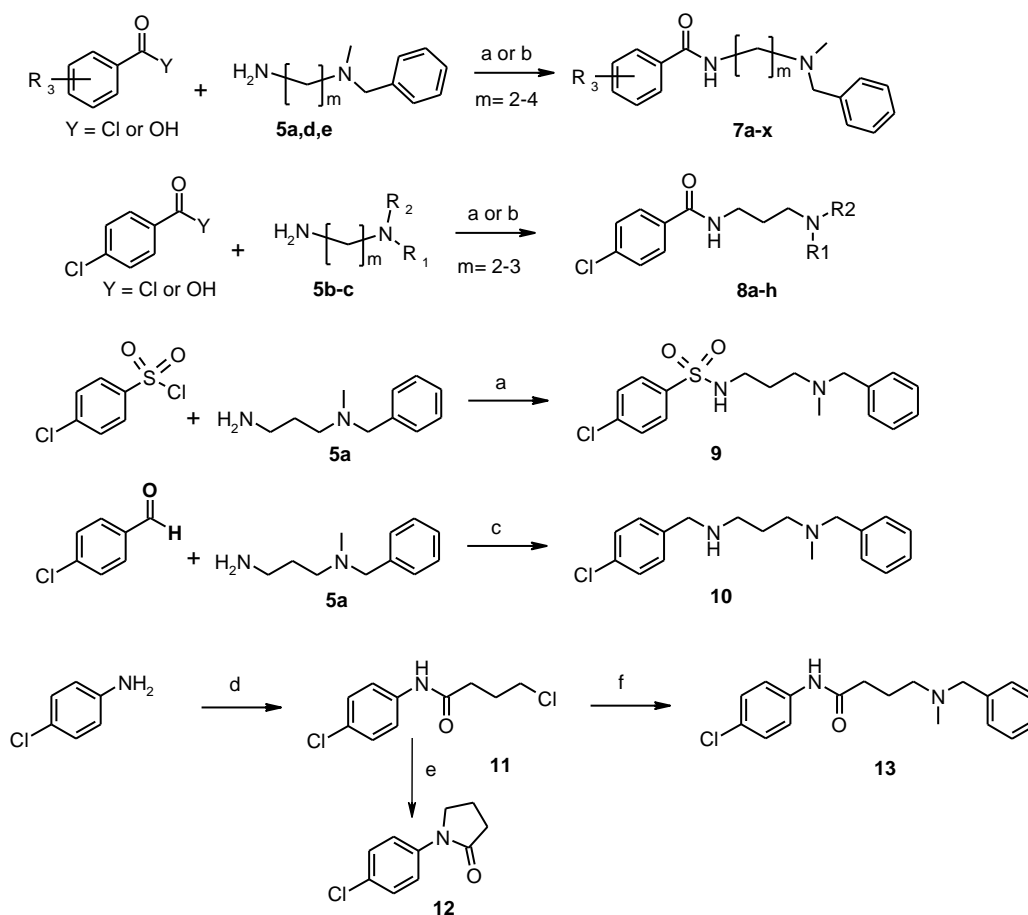
In a first time, diamino compounds **5a-f** were prepared in two or three steps and final compounds **7a-z** were synthesized (Scheme 2). From the first route, diamines **5a-c** were synthesized in three steps. 3-Bromopropylamine was protected with Boc group in CH_2Cl_2 with triethylamine and di-*tert*-butylcarbonate to afford derivative **3**, which reacted with the corresponding substituted amine (HNR_1R_2) in CH_3CN or DMF with potassium carbonate to give compounds **4a-c**. These derivatives **4a-c** were deprotected in 3M HCl in dry dioxane to give compounds **5a-c**. From the second route, the ethyl and butyl analogues of benzylmethylpropane-1,3-diamine (**5a**) were synthesized in two steps (Scheme 2). Starting from bromoalkylphthalimides, substitution reaction in DMF with potassium carbonate and benzylmethylamine afforded compounds **6a-b**, which were deprotected in ethanol with hydrazine to give intermediates **5d-e**. In the series with $m=2$ we also synthesize the superior analogue of compound **5d** with derivative **5f** which contained methylethylbenzylamine group as NR_1R_2 .



Scheme 2: Preparation of diamine compounds **5a-f**

Reagents and conditions: (a): di-*tert*-butylcarbonate, triethylamine, CH_2Cl_2 , 18h, rt, 97%; (b): HNR_1R_2 , potassium carbonate, DMF or CH_3CN , 24h, 70°C , 65-81%; (c): 3M HCl in dry dioxane, 18h, rt, 83-98%; (d): benzylmethylamine, potassium carbonate, DMF, 16h, 90°C , 52-64%; (e): H_2NNH_2 , EtOH 96° , 16h, reflux, 55-73%.

These diamine intermediates **5a,d,e** afforded final compounds **7a-z** (Scheme 3). Compounds **7a-z** were synthesized according two routes, starting from commercially substituted benzoyl acids, in dichloromethane with hydroxybenzotriazole and O-benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate at room temperature or with commercially substituted benzoyl chlorides, in dichloromethane with triethylamine. The SAR study of compounds **7a-z** showed that the substitution of compounds **7h-j** with a chlorine atom in *para* position induced good affinities for S1R, high S2R/S1R selectivities and low cytotoxicities (Table 1). We thus decided to synthesize a second series with 4-chlorobenzamide compounds **8a-h** using the same experimental conditions. We synthesized compounds **9** and **10** respectively as the sulfonyl and reduced analogues of the amide compound **7i** (Scheme 3). Derivative **9** was synthesized starting from the 4-chlorophenyl sulfonyl chloride in dichloromethane with trimethylamine and the diamine intermediate **5a**. Derivative **10** was obtained by a reductive amination of diamine intermediate **5a** in MeOH with 4-chlorobenzaldehyde, followed by the addition of sodium borohydride. We also decided to synthesize the retroamide analogue **13** of compound **7i**. Starting from 4-chloroaniline, reaction in dichloromethane with 4-chlorobutyryl chloride gave compound **11**. This derivative **11** never afforded derivative **13** in DMF with potassium carbonate or in CH₃CN with triethylamine and benzylmethylamine, but gave compound **12** after cyclization. The desired derivative **13** was obtained from compound **11** in benzylmethylamine which reacted both as base and solvent.



Scheme 3: Synthesis of final compounds **7a-x**, **8a-h**, **9**, **10** and **13**

Reagents and conditions: (a): triethylamine, CH₂Cl₂, 12h, 0°C to rt, 7-69%; (b): HOBt, HBTu, DIEA, CH₂Cl₂, 12h, rt, 31-75%; (c): i: MeOH, 18h, rt; ii: NaBH₄, 2h, rt, 35%; (d): 4-chlorobutyryl chloride, CH₂Cl₂, 12h, 0°C to rt, 87%; (e):

benzylmethylamine, potassium carbonate, DMF, 12h, 70°C or Et₃N, CH₃CN, 12h, 50°C; 67% (f): benzylmethylamine, 18h, rt, 37-80%.

3. Results and Discussion

3.1 Biological evaluations and SAR

S1R and S2R affinities were investigated in competition experiments with radioligands according to the methods described by Ganapathy [45]. In the S1R assay, the selective ligand [³H] (+)-pentazocine was employed as the radioligand. Since a selective S2R radioligand was not commercially available, the non-selective ligand [³H]-DTG was employed in the S2R assay, in the presence of an excess of non-tritiated (+)-pentazocine, which selectively occupies S1R. In both assays, Jurkat cell membranes were used as a source of receptors.

The K_i values for S1R and S2R were determined from the corresponding IC₅₀ values for each compounds **7a-z**, **8a-h**, **9**, **10**, and **13**. The S2R/S1R selectivity ratios were also calculated (Table 1).

In the first series, as all compounds **7b-x** exhibited good affinities for S1R ($K_i = 1.1$ to 47 nM) except for derivative **7a** ($K_i > 100$ nM), we could conclude that substitution on the benzamide scaffold was necessary. The substitution with alkyl group, as propyl, butyl and *tert*-butyl for compounds **7b-d** induced excellent affinities for S1R with $K_i = 1.6$ to 7.3 nM and good selectivity toward S2R with a S2R/S1R ratio of 126 especially for derivative **7d**. The modulation of the *tert*-butyl group of compound **7d** by trifluoromethyl group with **7e**, allowed to keep excellent S1R affinity but led to selectivity decrease with a S2R/S1R ratio of 70.

The substitution with one halogen atom, such as Cl or Br, gave high affinities for S1R ($K_i = 1.7$ to 47 nM). On the contrary, the substitution with a fluorine decreased S1R affinity dramatically (compound **7n**). In this series, the best affinities were obtained when benzamide moiety was substituted at the 4 position with a chlorine or bromine atom (**7h**, **7m**). Substitution in *meta* position (for **7g** $K_i = 10$ nM, **7l** $K_i = 3.9$ nM) or *ortho* position (for **7f** $K_i = 47$ nM, **7k** $K_i = 42$ nM) induced a decrease in S1R affinity, but also a meaningful decrease for S2R affinity. Therefore, S2R/S1R selectivities remained modest in the case of substitutions in *meta* or *ortho* position compared to the *para*-substituted compound **7h** with excellent affinity for S1R ($K_i = 3.6$ nM) and selectivity S2R/S1R of 236. According to these results, we decided to introduce two halogens, with two chlorines (compounds **7o-r**) or one fluorine and one bromine (compound **7s**). In this set of compounds **7n-s**, S1R and S2R affinities, and thus selectivities were in the same range. For the last compounds described in table 1 (compounds **7t-x**), the nature and the position of the substituents were modulated with methoxy, dimethylamine, cyano and nitro groups. Substitution with methoxy group (compounds **7t-u**) gave moderate affinities for S1R ($K_i = 37-40$ nM) with a S2R/S1R ratio higher than 27. Compounds **7v-z** with dimethylamine, cyano and nitro groups allowed good affinities for S1R ($K_i = 1.2-24$ nM) and especially derivative **7y** with the best S2R/S1R selectivity ratio of 389. Finally, we also noticed the influence of the length chain between the benzamide scaffold and the

benzylmethylamine. Indeed the decrease in the chain length (from butyl to ethyl) induced a higher selectivity (compare compounds **7h-j**, S2R/S1R = 12 to 236). Moreover, as a comparison, in the case of cyano substitution, a slight modification in the length's chain drastically modified the affinities and selectivity (see compounds **7w** and **7x**).

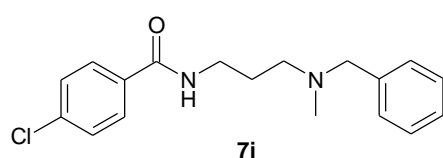
Table 1 : Evaluation of S1R, S2R affinities and cytotoxicity of target compounds **7a-z**

Compounds	R ₃	m	K _i (nM) ^a		K _i (σ ₂)/ K _i (σ ₁)	IC ₅₀ (μM)	IC ₅₀ /K _i (σ ₁)
			σ ₁	σ ₂			
						SY5Y ^b	
7a	H	3	> 100	>> 400 ^a	-	> 100	-
7b	4-Pr	3	3.7	160	43	> 100	> 27 027
7c	4-Bu	3	7.3	49	7	90.2	12 356
7d	4-tBu	3	1.6	200	126	> 100	> 62 500
7e	4-CF ₃	3	1.4	98	70	> 100	> 71 429
7f	2-Cl	3	47	> 1200	> 26	> 100	> 2 128
7g	3-Cl	3	10	340	34	> 100	> 10 000
7h	4-Cl	2	3.6	850	236	> 100	> 27 778
7i	4-Cl	3	3.2	190	60	> 100	> 31 250
7j	4-Cl	4	1.7	20	12	> 100	> 58 824
7k	2-Br	3	42	> 1200	> 29	> 100	> 2 381
7l	3-Br	3	3.9	350	90	> 100	> 25 641
7m	4-Br	3	2.1	160	76	60.2	28 667
7n	4-F	3	20	470	24	> 100	> 5 000
7o	2,3-Cl	3	10	310	31	> 100	> 10 000
7p	2,3-Cl	2	6.5	110	17	> 100	> 15 385
7q	3,4-Cl	3	1.1	59	54	56.6	51 455
7r	3,5-Cl	3	23	48	2	60.0	2 609
7s	2-F-4-Br	3	2.9	200	69	> 100	> 34 483
7t	3-OCH ₃	3	40	> 1200	> 30	> 100	> 2 500
7u	4-OCH ₃	3	37	> 1200	> 27	100.0	2 702
7v	3-N(CH ₃) ₂	3	1.9	321	159	> 100	> 52 632
7w	4-CN	2	1.2	170	142	> 100	> 83 334
7x	4-CN	3	24	> 1200	> 50	> 100	> 4 167
7y	4-NO ₂	2	3.6	1400	389	> 100	> 27 778
7z	4-NO ₂	3	4.3	360	84	> 100	> 23 256

^a Mean K_i values for 2-3 independent experiments are shown with less than 10% deviation.

^b Compound concentration causing 50% of cell death after 24 h treatment.

We then modulated the nature of the amine (HNR₁R₂) and the length's chain with m = 2, 3 between this amine group and the 4-chlorobenzamide. We preserved the chlorine atom at the 4 position, considering the good and maintained affinities and selectivities obtained with compounds **7h-i**. Physicochemical properties of compound **7i** were evaluated and shown the potency of this compound with high LLe, solubility and metabolic stability (Figure 3).



7i

MWt = 316.8
 logD = 2.51 [46]
 LLe = 6.0 [47]
 Solubility (pH7.4) = 173 μM [48]
 Metabolic stability (hLM) = 77% [49]

Figure 3: Physicochemical properties of compound **7i**

The modulation of the nature of the amine group, benzylmethylamine (**7i**) to 2-(phenylethyl)methylamine (**8a**), led to good affinity S1R ($K_i = 4.3$ nM), but low selectivity toward S2R ($K_i = 200$ nM) with a S2R/S1R ratio of 47. The restricted conformation of the benzylmethylamine group with isoindoline moiety for compound **8b** afforded acceptable affinity for S1R ($K_i = 19$ nM) but low selectivity toward S2R ($K_i = 350$ nM) with a S2R/S1R ratio of 16. For compounds **8c-h**, various substituted amine, such as pyrrolidine, morpholine and piperazine, were introduced and we modulated the length's chain with two or three methylene. As expected, the elimination of the phenyl ring with these derivatives **8c-d**, identified as an essential hydrophobic part, and the replacement by morpholine or piperazine for derivatives **8e-h**, as hydrophilic moieties, induced a dramatic lost of affinity for S1R ($K_i \geq 100$ nM).

Table 2 : Evaluation of S1R, S2R affinities and cytotoxicity of target compounds **8a-h**

Compounds	m	-NR ₁ R ₂	K_i (nM) ^a		K_i (σ_2)/ K_i (σ_1)	IC ₅₀ (μ M) SY5Y ^b	IC ₅₀ / K_i (σ_1)
			σ_1	σ_2			
8a	3		4.3	200	47	> 100	> 23 256
8b	3		19	350	16	> 100	> 5 264
8c	2		> 100	> 200	-	> 100	-
8d	3		> 100	> 200	-	> 100	-
8e	2		> 100	> 200	-	> 100	-
8f	3		> 100	> 200	-	> 100	-
8g	2		> 100	> 200	-	> 100	-
8h	3		> 100	> 200	-	> 100	-

^{a-d} see footnotes of Table 1

Starting from **7i**, we decided to replace the amide linker with a sulfonylamide function (**9**), to reduce the amide to amine function (**10**) and to synthesize the retroamide derivative (**13**) (Table 3). These three compounds **9**, **10** and **13** displayed good affinities for S1R ($K_i = 2.9$ - 6.5 nM) but low selectivities toward S2R with a S2R/S1R ratio of 26-35.

Table 3 : Evaluation of S1R, S2R affinities and cytotoxicity of target compounds **9**, **10**, **13**

Compounds	X	K_i (nM) ^a		K_i (σ_2)/ K_i (σ_1)	IC ₅₀ (μ M) SY5Y ^b	IC ₅₀ / K_i (σ_1)
		σ_1	σ_2			
9	SO ₂ NH	5.8	200	35	> 100	> 17 242
10	CH ₂ NH	2.9	95	33	> 100	> 34 483
13	NHCO	6.5	170	26	> 100	> 15 385

^{a-d} see footnotes of Table 1

3.2 Docking study of benzamide 7i

To investigate the potential binding mode of benzamide derivatives, compound **7i** was docked into the binding site of S1R [44]. As illustrated in Figure 3, the representative docking solutions highlighted common interactions of S1R ligands. The benzyl moiety interact with hydrophobic regions of the receptor and the *p*-chlorobenzamide scaffold is stabilized by an aromatic stacking interaction with the Tyr103. In addition, the basic amine of **7i** is engaged in a persistent salt bridge with the carboxylate group of the highly conserved Glu172.

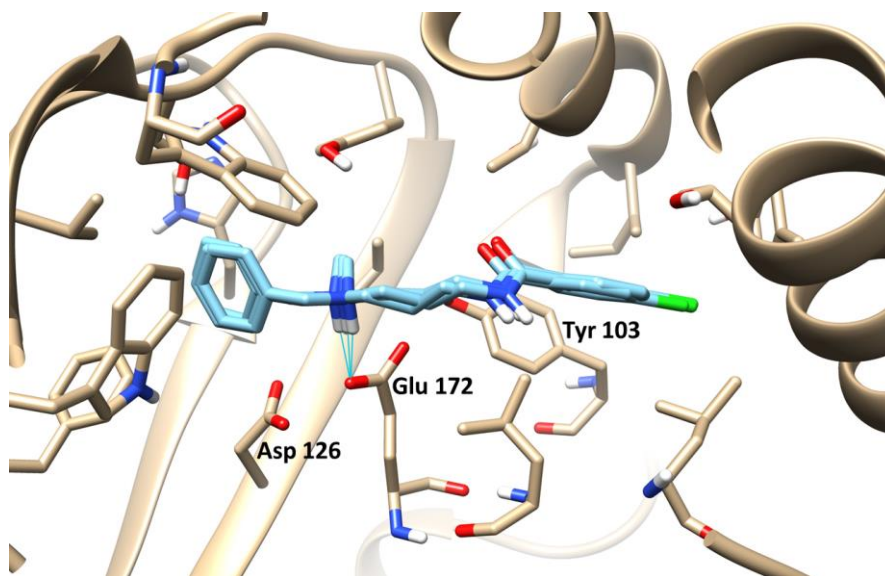


Figure 3: Docking of compound **7i** in the binding site of S1R (PDB Entry: 5HK2)

3.3 Evaluation of cytotoxic effects

To determine the potential cytotoxic effects of our compounds on CNS tissues, a human neuroblastoma cell line was treated with the whole compounds at different concentrations up to 100 μ M. Cell viability was calculated using a colorimetric MTT assay.

All target compounds exhibited very low cytotoxicity (Table 1, 2, 3) with selectivity index between 2 128 and 76 923 ($IC_{50(SY5Y)}/K_i(S1R)$ ratio). In particular, derivatives **7i** and **7p** with high affinities for S1R ($K_i = 1.3-3.6$ nM) and S2R/S1R selectivities (236-238) showed excellent selectivity index of 31 250 and 15 385 respectively. Compound **7y** with the best selectivity for S2R ($S2R/S1R = 389$) also showed excellent selectivity index of 27 778.

3.4 Selectivity profile over a panel of 40 recombinant human receptors

Among these compounds, eleven were selected regarding their affinity, selectivity, ligand efficiency and chemical diversity. Compounds (**7b**, **7e**, **7h**, **7i**, **7l**, **7m**, **7t**, **7u**, **7w**, **7y**, **7z**, **8a**) were tested on their agonist and antagonist activities on 40 receptors relevant for CNS diseases like serotonin, adenosine, adrenergic, cannabinoide, dopamine, histamine, muscarinic and others receptors. They were tested at 10 μ M, in

duplicate, on the Aequorin [50], cAMP HTRFTM [51] and GTP γ ³⁵S [52] binding assays as described in Table 4.

None of the studied compounds provided significant agonist activity at 10 μ M, except compound **8a** which showed an agonist activity on serotonin receptors (5-HT_{2B}, 5-HT_{2C} and 5-HT₇). Significant antagonist activity was observed at 10 μ M for serotonin (5-HT_{2B}, 5-HT_{2C} and 5-HT₃), adrenergic (all subtypes), histamine H1, dopamine D4 and muscarinic M1 receptors for compounds **7b**, **7e**, **7i**, **7l**, **7m**, **8a** with propyl, trifluoromethyl groups or chlorine, bromine atoms. In these cases, the position of the substitution (*meta* or *para*) or the length's chain played a significant part in the antagonist activities of the compounds. For example, 4-bromo benzamide **7m** was more selective than the 3-bromo derivative **7l**, which showed significant antagonist activity on 5-HT_{2B}, 5-HT_{2C}, α _{2A} and H1 receptors. For 4-chlorobenzamide derivatives, propyl chain and benzylmethylamine seemed optimal (compound **7i**) as the decrease from propyl to ethyl (compound **7h**) induced activity on 5-HT_{2A}, 5-HT_{2C} and D2 receptors. In a similar manner, the stretching from benzylamine (compound **7i**) to phenethylamine (compound **8a**) led to an increased activity on 5-HT_{1B}, 5-HT_{2B}, 5-HT_{2C}, 5-HT₃, α _{2A}, α _{2B}, H1 and M2 receptors.

	5-HT _{1A}		5-HT _{1B}		5-HT _{2A}		5-HT _{2B}		5-HT _{2C}		5-HT ₃		5-HT ₄		5-HT _{5a}		5-HT ₆		5-HT ₇		A ₁		A _{2A}		A ₃		Beta ₁		Beta ₂		Alpha _{1a}		Alpha _{1b}		Alpha _{2a}		Alpha _{2b}		AT1		
	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]
7b		55					75	63	94		90																						96	72					54		
7e							66				75																				79	70									
7h				52			66	62	92		51																				96	96									
7i							58																								92	73									
7l							78		54		85																				97	97		57							
7m											79																				93	81									
7t																															82	56									
7u																															52										
7w											75																				56	89									
7y									80																						62	84									
7z																															95	63									
8a				65			92	75	95		62								130												95	98		105	83						

	CB1		CCK1		D1		D2		Eta		H1		H2		M1		M2		M3		M4		NK1		NK2		NMDA		NPY1		Delta		Kappa		Mu		SST4		V1 _a		VPAC1		
	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]	[b]	[a]
7b																98																											
7e																88																											
7h						90										69																				61							
7i																89																											
7l										74						96						58																					
7m																89																											
7t										57																																	
7u																																											
7w								55																														66					
7y																																						60					
7z																85																											
8a										90						86		54																									

Table 4 : [a]: Agonist activity at 10 μ M in duplicate; [b] : Antagonist activity at 10 μ M in duplicate. For the agonist activity, data are expressed as the percentage of the activity of the reference agonist. For the antagonist activity, data are expressed as the percentage of inhibition of the reference agonist activity In green, 0-50%, in white 51-80%, in red 81-100%. Numerical value are indicated over 51%. ND, not determined.

Compounds **7t**, **7u**, **7w**, **7y** could be considered as selective compounds-because they show excellent profil toward all receptors and hight selectivities for S1R. In particular, methoxy derivatives **7t** and **7u** showed no activity upon near all tested receptors at a concentration of 10 μ M. Compounds **7w**, **7y** with cyano and nitro group showed low affinities for H₁, 5-HT₃ and μ opioid receptors. Once again, the length's chain between the benzylmethylamine and the benzamide scaffold was important. When we compared the nitro compounds **7y** and **7z** the elongation of the ethyl (**7y**) to propyl chain (**7z**) induced higher affinities for antagonist activities for α_{1a} and M₁. It is important to emphasize that compound **7y** showed an excellent profil S1R toward S2R (S1R : K_i = 3.6 nM, S2R : K_i > 1400 nM, S2R/S1R= 389) and an excellent profil for agonist and antagonist activities against all the tested receptors.

4. Conclusion

Starting from previous work in our lab and in the literature, we used benzamide moiety as tic-hydantoin surrogate and various modulations were realized. In the first series, we modulated the nature and the position of atoms or groups on the benzamide moiety and kept the benzylmethylamine separated with alkyl chain with 2 to 4 methylene group from the heterocycle, to give compounds **7a-z**. In a second series, 4-chlorobenzamide moiety was kept and the nature of the amine group was modulated (HNR₁R₂) to afford derivatives **8a-h**. Then, three compounds were prepared as the sulfonyl (**9**), reduced (**10**) and retroamide (**13**) analogues of derivative **7i**. The K_i values for S1R and S2R were determined from the corresponding IC₅₀ values for each compound. The modulation with chlorine or bromine atoms gave good affinities for S1R and selectivities toward S2R. The length's chain also played an important part from these 2 parameters. As expected, the introduction of hydrophilic moieties in compounds **8c-h** induced a dramatic lost of affinities for S1R, underlining the major importance of both hydrophobic moieties highlighted in the Glennon's pharmacophore. All together this study underlined the interest of compounds **7i**, **w**, **y** with Cl, CN or NO₂ groups at the 4-position of the benzamide scaffold showed excellent affinity for S1R (K_i = 1.2 to 3.6 nM), selectivity for S2R (K_i up to 1400 nM) and high selectivity index (from 28 000 to 83 000). Physicochemical properties of compound **7i** are very compatible with drug development. Futhermore, these compounds showed a highly selective profile over 40 other receptors. These derivatives will be considered for further biological investigations.

5. Experimental

5.1 Chemistry

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. IR spectra were performed on a Bruker Alpha FT-IR Spectrometer. 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 ionisation and a UV detector (diode array). HRMS experiments were performed on Q Exactive Benchtop LC-MS/MS (Thermo Scientific). 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 (H₂O/TFA, 100:0.1) and buffer B (CH₃CN/H₂O/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.

Preparation of *N*-(3-bromopropyl)-4-chlorobenzamide (1)

To a solution of 3-bromopropylamine hydrobromide (2.86 mmol, 625 mg) in 10 mL of DCM at 0°C was added slowly a solution of 4-chlorobenzoyl chloride (2.86 mmol, 363 μ L) in 5 mL of DCM. The resulting mixture was stirred at room temperature for 12 hours. Then the solution was diluted with DCM and washed successively with HCl (2M) solution, NaHCO₃ saturated solution and NaCl solution. The organic layer was dried over magnesium sulfate and evaporated. The crude product **2.1** was purified by column chromatography (DCM: cyclohexane, 5:5 (v/v)). Yield: 65%. Mp: 84°C. ¹H NMR (300 MHz, CDCl₃), δ : 7.72 (d, J = 9.1 Hz, 2H, H₂, H₆); 7.38 (d, J = 9.2 Hz, 2H, H₃, H₅); 6.69 (br s, 1H, NH); 3.60 (q, J = 7.1 Hz, 2H, H_a); 3.48 (t, J = 7.3 Hz, 2H, H_c); 2.19 (p, J = 7.1 Hz, 2H, H_b). ¹³C NMR (75 MHz, CDCl₃) δ : 166.8 (CO); 137.8 (C_{aro}); 132.7 (C_{aro}); 128.8 (2 C_{aro}); 128.4 (2 C_{aro}); 38.8 (CH₂); 32.0 (CH₂); 31.0 (CH₂). LCMS m/z calc for [M+H⁺]: 275.9, 277.9; found: 276.0; 278.0.

2-(4-Chlorophenyl)-5,6-dihydro-4H-1,3-oxazine (2)

To a solution of isoindoline (20.4 μ L, 0.18 mmol) in 1 mL of DMF was added a 24 mg (0.18 mmol) amount of potassium carbonate. The resulting mixture was stirred at 70°C. After 30 minutes, the 4-chloro- *N*-(3-bromopropyl)-4-chlorobenzamide (50 mg, 0.18 mmol) was added and the reacting mixture was stirred at 70°C overnight. The solvent was removed under reduced pressure and 15 mL of water added to the residue. The crude product was extracted with 3x15 mL of DCM. The combined organic fractions were washed with water and dried over magnesium sulphate. The compound was purified by column chromatography (DCM:MeOH(NH₃), 99:1 (v/v)) and obtained as a colourless oil. Yield: 70%. Mp= 84°C. ¹H NMR (300 MHz, CDCl₃) δ : 7.83 (d, *J* = 9.2 Hz, 2H, H₂, H₆); 7.34 (d, *J* = 9.1 Hz, 2H, H₃, H₅); 4.36 (t, *J* = 6.3 Hz, 2H, CH₂); 3.61 (t, *J* = 6.1 Hz, 2H, CH₂); 1.99 (p, *J* = 6.3 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ : 154.7 (OCN); 136.4 (C_{aro}); 132.6 (C_{aro}); 128.3 (2 C_{aro}); 128.2 (2 C_{aro}); 65.2 (CH₂); 42.6 (CH₂); 21.9 (CH₂). LCMS (ESI⁺): LCMS *m/z* calc for [M+H⁺]: 196.0, 198.0; found: 196.0; 198.0.

2. Preparation of diamine intermediates (5a-e)

tert-Butyl-3-bromopropylcarbamate (3)

3-Bromopropylamine (13.70 mmol, 3.0 g) was dissolved in 80 mL of DCM. After addition of triethylamine (16.4 mmol, 2.32 mL) and di-*tert*-butylcarbonate (13.70 mmol, 3.0 g), the resulting mixture was stirred at room temperature overnight. Then, it was washed with 2 x 60 mL of a citric acid solution (5%) and 50 mL of saturated brine solution. The organic fraction was dried over magnesium sulphate and concentrated to give the desired product as yellow oil of sufficient purity for use without purification in the next step. Yield: 97%. ¹H NMR (300 MHz, CDCl₃) δ : 4.67 (br s, 1H, NH); 3.45 (t, *J* = 7.4 Hz, 2H, CH₂); 3.28 (q, *J* = 7.1 Hz, 2H, CH₂); 2.06 (p, ³*J* = 7 Hz, 2H, CH₂); 1.46 (s, 9H, C(CH₃)₃).

General procedure for the synthesis of substituted compounds 4a-c

To a mixture of *tert*-butyl-3-bromopropylcarbamate **1.2** (5.6 mmol, 1.3 eq, 1.3 g) and *N,N*-disubstituted amine (4.3 mmol, 1 eq) in 30 mL of DMF was added potassium carbonate (13.0 mmol, 3 eq, 1.8 g). The resulting mixture was heated at 70°C for 24 hours. Then, the solvent was removed under reduced pressure and water (80 mL) added to the residue. The crude product was extracted with 3 x 60 mL of DCM. The combined organic fractions were washed with 60 mL of water and dried over magnesium sulphate. The solvent was evaporated and the crude product collected as yellow oil. Purification by column chromatography (DCM: MeOH(NH₃), 9.7:0.3 (v/v)) was performed.

tert-Butyl-3-[benzyl(methyl)amino]propyl carbamate (4a)

Yield: 74%. ¹H NMR (300 MHz, CDCl₃) δ : 7.36-7.19 (m, 5H, H_{aro}); 5.61 (br s, 1H, NH); 3.48 (s, 2H, H_e); 3.20 (q, *J* = 6.4 Hz, 2H, CH₂); 2.45 (t, *J* = 6.3 Hz, 2H, CH₂); 2.17 (s, 3H, CH₃); 1.68 (p, *J* = 6.2 Hz, 2H, CH₂); 1.46 (s, 9H, C(CH₃)₃). ¹³C NMR (75 MHz, CDCl₃) δ : 156.1 (CO); 139.0 (C_{aro}); 129.0 (2 C_{aro});

128.3 (2 C_{aro}); 127.0 (C_{aro}); 78.7 (C(CH₃)₃); 62.7 (CH₂); 56.5 (CH₂); 42.1 (CH₃); 40.1 (CH₂); 28.5 (C(CH₃)₃); 26.6 (CH₂). LCMS *m/z* calc for [M+H⁺]: 279.2; found: 279.1.

***tert*-Butyl-3-[*N*-methyl-*N*-(2-phenylethyl)amino] propyl carbamate (4b)**

Yield: 81%. ¹H NMR (300 MHz, CDCl₃), δ: 7.30 (m, 2H, H_{aro}); 7.20 (m, 2H, H_{aro}); 5.66 (br s, 1H, NH); 3.16 (m, 2H, CH₂); 2.79 (m, 2H, CH₂); 2.61 (m, 2H, CH₂); 2.45 (t, *J* = 6.8 Hz, 2H, CH₂); 2.28 (s, 3H, CH₃); 1.65 (q, *J* = 6.6 Hz, 2H, CH₂); 1.47 (s, 9H, C(CH₃)₃). ¹³C NMR (75 MHz, CDCl₃) δ: 156.1 (CO); 140.4 (C_{aro}); 128.7 (2 C_{aro}); 128.4 (2 C_{aro}); 126.0 (C_{aro}); 78.8 (C(CH₃)₃); 59.6 (CH₂); 55.9 (CH₂); 42.1 (CH₃); 39.7 (CH₂); 33.9 (CH₂); 28.5 (C(CH₃)₃); 27.0 (CH₂). LCMS *m/z* calc for [M+H- *tert*But]⁺: 237.1; found: 237.0.

***tert*-Butyl-3-(isoindolin-2-yl)propylcarbamate (4c)**

Yield: 65%. ¹H NMR (300 MHz, CDCl₃), δ: 7.20 (m, 4H, H_{aro}); 5.12 (br s, 1H, NH); 3.96 (s, 4H, 2 CH₂); 3.24 (m, 2H, CH₂); 2.79 (t, *J* = 6.0 Hz, 2H, CH₂); 1.75 (q, *J* = 6.7 Hz, 2H, CH₂); 1.44 (s, 9H, C(CH₃)₃). ¹³C NMR (75 MHz, CDCl₃) δ: 156.1 (CO); 139.7 (2 C_{aro}); 126.8 (2 C_{aro}); 122.3 (2 C_{aro}); 79.1 (C(CH₃)₃); 59.1 (2 CH₂); 54.0 (CH₂); 39.5 (CH₂); 28.7 (CH₂); 28.5 (C(CH₃)₃). LCMS *m/z* calc for [M+H- *tert*But]⁺: 221.2; found: 221.0.

General procedure for the synthesis of substituted compounds 6a-c

To a mixture of *N*-(bromoethyl or bromobutyl)phtalimide (5.9 mmol) and benzylmethylamine (7.1 mmol, 0.8 mL) or 2-phenylethylamine (7.1 mmol, 0.9 mL) in 30 mL of DMF was added potassium carbonate (11.80 mmol, 1.6 g). The resulting mixture was heated at 90°C for 16 hours. Then, inorganics were eliminated by filtration and the solvent was removed under reduced pressure. Purification by column chromatography (DCM: MeOH(NH₃), 9.9:0.1 (v/v)) was performed.

2-[2-(Benzylmethylamino)ethyl]-2,3-dihydro-1H-isoindole-1,3-dione (6a)

Yield 52%. ¹H NMR (300 MHz, CDCl₃), δ: 7.88 (m, 2H, H_{aro}); 7.72 (m, 2H, H_{aro}); 7.09-7.11 (m, 5H, H_{aro}); 3.82 (t, *J* = 6.3 Hz, 2H, CH₂); 3.55 (s, 2H, CH₂); 2.70 (t, *J* = 6.3 Hz, 2H, CH₂); 2.31 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ: 168.3 (2 CO); 138.8 (C_{aro}); 133.8 (2 C_{aro}); 132.3 (2 C_{aro}); 128.9 (2 C_{aro}); 128.1 (2 C_{aro}); 126.9 (C_{aro}); 123.1 (2 C_{aro}); 62.1 (CH₂); 54.5 (CH₂); 42.2 (CH₃); 35.9 (CH₂). LCMS *m/z* calc for [M+H⁺]: 295.1; found: .295.0.

2-[4-(Benzylmethylamino)butyl]-2,3-dihydro-1H-isoindole-1,3-dione (6b)

Yield 53%. ¹H NMR (300 MHz, CDCl₃), δ: 7.82 (m, 2H, H_{aro}); 7.69 (m, 2H, H_{aro}); 7.15-7.32 (m, 5H, H_{aro}); 3.71 (t, *J* = 7.2 Hz, 2H, CH₂); 3.48 (s, 2H, CH₂); 2.41 (t, *J* = 7.2 Hz, 2H, CH₂); 2.18 (s, 3H, CH₃); 1.74 (m, 2H, CH₂); 1.55 (m, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 168.4 (2 CO); 138.9 (C_{aro}); 133.9

(2 C_{aro}); 132.1 (C_{aro}); 129.0 (2 C_{aro}); 128.2 (2 C_{aro}); 126.9 (2 C_{aro}); 123.1 (2 C_{aro}); 62.4 (CH₂); 56.8 (CH₂); 42.1 (CH₃); 37.9 (CH₂); 26.5 (CH₂); 24.6 (CH₂). LCMS *m/z* calc for [M+H⁺]: 323.1; found: 323.0.

2-[2-(N-methyl-N-(2-phenylethyl)amino)ethyl]-2,3-dihydro-1H-isoindole-1,3-dione (6c)

Yield: 64%. ¹H NMR (300 MHz, CDCl₃), δ: 7.85 (m, 2H, H_{aro}); 7.70 (m, 2H, H_{aro}); 7.05-7.20 (m, 5H, H_{aro}); 3.80 (t, *J* = 6.6 Hz, 2H, CH₂); 2.62-2.75 (m, 6H, 3CH₂); 2.38 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ: 168.3 (CO); 140.3 (C_{aro}); 133.8 (C_{aro}); 132.2 (C_{aro}); 128.7 (C_{aro}); 128.2 (C_{aro}); 125.8 (C_{aro}); 123.1 (C_{aro}); 59.4 (CH₂); 54.7 (CH₂); 42.2 (CH₃); 35.8 (CH₂); 33.7 (CH₂). LCMS *m/z* calc for [M+H⁺]: 309.1; found: 309.0.

General procedure for the synthesis of substituted compounds 5a-c

The compound **1.3** (1 eq) was dissolved in 72 mL of 3M HCl in dry 1,4-dioxane. The resulting mixture was stirred at room temperature overnight. Then, the solvent was removed under reduced pressure to give the desired product of sufficient purity for use without purification in the next step.

N¹-Benzyl-N¹-methylpropane-1,3-diamine (5a)

Yield 98%. Mp: 77°C. ¹H NMR (300 MHz, CDCl₃), δ: 11.27 (br s, 1H, NH); 8.37 (br s, 3H, NH); 7.66-7.41 (m, 5H, H_{aro}); 4.27 (m, 2H, CH₂), 3.27-2.28 (m, 4H, 2 CH₂); 2.60 (s, 3H, CH₃); 2.13 (p, *J* = 7.4 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 123.0 (C_{aro}); 130.3 (C_{aro}); 129.9 (2 C_{aro}); 129.2 (2 C_{aro}); 58.6 (CH₂); 52.1 (CH₂); 39.0 (CH₃); 36.7 (CH₂); 22.0 (CH₂). LCMS *m/z* calc for [M+H⁺]: 179.1; found: .179.0

N¹-Benzyl-N¹-(2-phenylethyl)propane-1,3-diamine (5b)

Yield: 88%. ¹H NMR (300 MHz, CDCl₃), δ: 7.38-7.22 (m, 5H, H_{aro}); 6.20 (br s, 2H, NH₂); 3.37-3.24 (m, 4H, CH₂); 3.19-3.01 (m, 4H, 2 CH₂); 2.83 (s, 3H, CH₃); 2.15 (q, *J* = 7.4 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 137.0 (C_{aro}); 128.7 (2 C_{aro}); 128.6 (2 C_{aro}); 126.7 (C_{aro}); 57.6 (CH₂) 39.6 (CH₃); 37.3 (CH₂); 30.6 (CH₂); 22.4 (CH₂). LCMS *m/z* calc for [M+H⁺]: 193.1; found: 193.0.

3-(Isoindolin-2-yl)propan-1-amine (5c)

Yield: 83%. ¹H NMR (300 MHz, CDCl₃), δ: 8.04 (m, 4H, H_{aro}); 5.58 (br s, 2H, NH₂); 4.12 (t, *J* = 7.9 Hz, 2H, CH₂); 3.91 (s, 4H, CH₂), 3.74 (t, *J* = 7.6 Hz, 2H, CH₂); 2.71 (t, *J* = 7.8 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 133.9 (2 C_{aro}); 128.6 (2 C_{aro}); 122.6 (2 C_{aro}); 58.5 (2 CH₂); 51.7 (CH₂); 36.6 (CH₂); 23.7 (CH₂). LCMS *m/z* calc for [M+H⁺]: 177.1; found: 177.0.

General procedure for the synthesis of substituted compounds 5d-f

In 50 mL of ethanol 96°, was added a mixture of 2-[N,N-disubstitutedaminoalkyl]-2,3-dihydro-1H-isoindole-1,3-dione (6.2 mmol) and hydrazine hydrate (62.0 mmol, 3.1 mL). The resulting mixture was

heated at reflux for 16 hours. The solution was removed under reduced pressure. The mineral was eliminated by filtration and washed with ethyl acetate. The filtrate was evaporated under reduced pressure to give an oily residue. Purification by column chromatography (DCM: MeOH(NH₃), 9:1 (v/v)) was performed.

***N*¹-Benzyl-*N*¹-methylethane-1,2-diamine (5d)**

Yield 55%. ¹H NMR (300 MHz, CDCl₃), δ: 7.35-7.30 (m, 5H, H_{aro}); 4.90 (br s, 2H, NH₂); 3.58 (s, 2H, CH₂); 2.91 (t, *J* = 6.3 Hz, 2H, CH₂); 2.60 (t, *J* = 6.2 Hz, 2H, CH₂); 2.22 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ: 138.0 (C_{aro}); 129.0 (2 C_{aro}); 128.0 (2 C_{aro}); 127.0 (C_{aro}); 62.1 (CH₂); 55.9 (CH₂); 40.7 (CH₃); 37.4 (CH₂). LCMS *m/z* calc for [M+H⁺]: 165.1; found: 165.0.

***N*¹-Benzyl-*N*¹-methylbutane-1,4-diamine (5e)**

Yield 73%. ¹H NMR (300 MHz, CDCl₃), δ: 7.35-7.25 (m, 5H, H_{aro}); 3.50 (s, 2H, CH₂); 2.72 (t, *J* = 6.8 Hz, 2H, CH₂); 2.39 (t, *J* = 6.9 Hz, 2H, CH₂); 2.22 (s, 5H, NH₂, CH₃); 1.61-1.45 (m, 4H, 2 CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 139.1 (C_{aro}); 129.10 (2 C_{aro}); 128.2 (2 C_{aro}); 126.9 (C_{aro}); 62.3 (CH₂); 57.2 (CH₂); 42.1 (CH₃); 42.0 (CH₂); 31.4 (CH₂); 24.7 (CH₂). LCMS *m/z* calc for [M+H⁺]: 193.1; found: 193.0.

***N*¹-(2-phenylethyl)-*N*¹-methylethane-1,2-diamine dihydrochloride (5f)**

Yield: 64%. ¹H NMR (300 MHz, CDCl₃), δ: 7.30-7.22 (m, 2H, H_{aro}); 7.20-7.10 (m, 3H, H_{aro}); 2.80-2.70 (m, 4H, 2CH₂); 2.62 (m, 2H, CH₂); 2.47 (t, *J* = 6.0 Hz, 2H, CH₂); 2.26 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ: 140.5 (C_{aro}); 128.7 (C_{aro}); 128.3 (C_{aro}); 125.9 (C_{aro}); 59.7 (CH₂); 59.6 (CH₂); 42.1 (CH₃); 39.2 (CH₂); 33.8 (CH₂). LCMS *m/z* calc for [M+H⁺]: 179.1; found: 179.1.

General procedure E1

A solution of *N,N*-disubstitutedalkyldiamine **5a-f** or commercially available amine (1 eq), and triethylamine (3 eq) in 10 mL of DCM was cooled at 0°C. A solution of substituted benzoylchloride (1 eq) in 5 mL of DCM was added slowly. The resulting mixture was stirred at room temperature overnight. The solution was evaporated under reduced pressure. An aqueous solution of 3% sodium hydroxide (20 mL) was added and the mixture was stirred for 1 hour. The solution was extracted with DCM. The organic layer was dried over magnesium sulphate and concentrated to give an oily product. The residue was purified by thick layer chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) or column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)).

General procedure E2

Reaction was carried out under nitrogen atmosphere. In 10 mL of DCM, benzoic acid (1 eq), HOBt (1.2 eq) and HBTu (1.2 eq) were added and stirred at room temperature for 10 minutes. A solution of *N,N*-

disubstitutedalkyldiamine **5a-f** or commercially available amine (1 eq) and DIEA (15 eq) in DCM was added to the reacting mixture. After stirring at room temperature for 24 hours, the solvent was removed under reduced pressure and DCM was added to the residue. The solution was washed with a solution of NaHCO₃ (5%) then saturated NaCl solution. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The crude product was purified by thick layer chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) or column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)).

N-[3-(N-benzyl-N-methylamino)propyl]benzamide (7a)

Procedure E2. Purification by thick layer chromatography was performed. Yield: 75%. ¹H NMR (300 MHz, CDCl₃), δ: 8.05 (br s, 1H, NH); 7.70 (m, 2H, H₂, H₆); 7.49-7.30 (m, 3H, H₃, H₄, H₅); 7.29-7.22 (m, 5H, H_{aro}); 3.61-3.52 (m, 4H, 2 CH₂); 2.65 (t, *J* = 6.7 Hz, 2H, CH₂); 2.29 (s, 3H, CH₃); 1.84 (p, *J* = 6.8 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 167.3 (CO); 137.8 (C_{aro}); 134.7 (C_{aro}); 131.1 (2 C_{aro}); 129.4 (2 C_{aro}); 128.4 (C_{aro}); 128.4 (2 C_{aro}); 127.4 (C_{aro}); 126.9 (2 C_{aro}); 63.1 (CH₂); 56.9 (CH₂); 41.6 (CH₃); 40.1 (CH₂); 25.3 (CH₂). LCMS *m/z* calc for [M+H⁺]: 283.2; found: 283.1. HPLC (C₄, 35 min): *t*_R 17.5 min, P_{HPLC} 97%; HPLC (C₁₈, 35 min): *t*_R 15.2 min, P_{HPLC} 99%.

N-[3-(benzylmethylamino)propyl]-4-propylbenzamide (7b)

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 61%. ¹H NMR (300 MHz, CDCl₃), δ: 7.90 (br s, 1H, NH) ; 7.60 (d, *J* = 8.2 Hz, 2H, H₂, H₆); 7.29-7.20 (m, 5H, H_{aro}); 7.13 (d, *J* = 8.1 Hz, 2H, H₃, H₅); 3.55 (t, *J* = 6.0 Hz, 2H, CH₂); 3.50 (s, 2H, CH₂); 2.60 (m, 4H, 2 CH₂); 2.23 (s, 3H, CH₃); 1.80 (p, *J* = 6.0 Hz, 2H, CH₂); 1.62 (s, *J* = 7.5 Hz, 2H, CH₂); 0.95 (t, *J* = 7.3 Hz, 2H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ: 167.2 (CO); 146.1 (C_{aro}); 138.4 (C_{aro}); 132.2 (C_{aro}); 129.3 (C_{aro}); 128.5 (C_{aro}); 128.4 (C_{aro}); 127.2 (C_{aro}); 126.9 (C_{aro}); 63.3 (CH₂); 57.1 (CH₂); 42.1 (CH₃); 40.2 (CH₂); 37.9 (CH₂); 25.5 (CH₂); 24.3 (CH₂); 14.2 (CH₃). LCMS *m/z* calc for [M+H⁺]: 325.2; found: 325.0. HRMS: calcd for (C₂₁H₂₈ON₂)H⁺: 325.22744; found: 325.22617. HPLC (C₄, 35 min): *t*_R 16.5 min, P_{HPLC} 96%; HPLC (C₁₈, 35 min): *t*_R 22.5 min, P_{HPLC} 97%.

N-[3-(benzylmethylamino)propyl]-4-butylbenzamide (7c)

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 30%. ¹H NMR (300 MHz, CDCl₃), δ: 7.97 (br s, 1H, NH) ; 7.60 (d, *J* = 8.2 Hz, 2H, H₂, H₆); 7.29-7.23 (m, 5H, H_{aro}); 7.13 (d, *J* = 8.2 Hz, 2H, H₃, H₅); 3.56 (m, 4H, 2CH₂); 2.64 (m, 4H, 2CH₂); 2.28 (s, 3H, CH₃); 1.83 (p, *J* = 6.1 Hz, 2H, CH₂); 1.62 (m, 2H, CH₂); 1.35 (m, 2H, CH₂); 0.97 (t, *J* = 7.1 Hz, 2H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ: 167.7 (CO); 146.7 (C_{aro}); 138.0 (C_{aro}); 132.5 (C_{aro}); 129.8 (2 C_{aro}); 128.8 (4 C_{aro}); 127.9 (C_{aro}); 127.3 (2 C_{aro}); 63.5 (CH₂); 57.1 (CH₂); 41.9 (CH₃); 40.3 (CH₂); 35.9 (CH₂); 33.7 (CH₂); 25.7 (CH₂); 22.6 (CH₂); 14.3 (CH₃). LCMS *m/z* calc for [M+H⁺]: 339.2; found: 339.0. HPLC (C₄, 35 min): *t*_R 16.0 min, P_{HPLC} 96%; HPLC (C₁₈, 35 min): *t*_R 21.9 min, P_{HPLC} 97%.

***N*-[3-(benzylmethylamino)propyl]-4-*tert*-butylbenzamide (7d)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 27%. ¹H NMR (300 MHz, CDCl₃), δ: 8.03 (br s, 1H, NH); 7.63 (d, *J* = 8.5 Hz, 2H, H₂, H₆); 7.37 (d, *J* = 8.5 Hz, 2H, H₃, H₅); 7.29-7.24 (m, 5H, H_{aro}); 3.57 (m, 4H, 2CH₂); 2.63 (t, *J* = 6.0 Hz, 2H, CH₂); 2.28 (s, 3H, NCH₃); 1.84 (p, *J* = 5.9 Hz, 2H, CH₂); 1.32 (s, 9H, 3CH₃). ¹³C NMR (75 MHz, CDCl₃) δ: 167.1 (CO); 154.4 (C_{aro}); 137.8 (C_{aro}); 131.8 (C_{aro}); 129.5 (2 C_{aro}); 128.4 (2 C_{aro}); 127.4 (C_{aro}); 126.8 (2 C_{aro}); 125.3 (2 C_{aro}); 63.1 (CH₂); 56.9 (CH₂); 41.5 (CH₃); 40.1 (CH₂); 34.8 (C); 31.2 (CH₃); 25.3 (CH₂). LCMS *m/z* calc for [M+H⁺]: 339.2; found: 339.0. HPLC (C₄, 35 min): *t*_R 17.2 min, P_{HPLC} 97%; HPLC (C₁₈, 35 min): *t*_R 23.5 min, P_{HPLC} 98%.

***N*-[3-(benzylmethylamino)propyl]-4-trifluoromethylbenzamide (7e)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 57%. ¹H NMR (300 MHz, CDCl₃), δ: 8.50 (br s, 1H, NH); 7.78 (d, *J* = 8.2 Hz, 2H, H₂, H₆); 7.59 (d, *J* = 8.2 Hz, 2H, H₃, H₅); 7.28-7.21 (m, 5H, H_{aro}); 3.63-3.55 (m, 4H, 2 CH₂); 2.68 (t, *J* = 5.8 Hz, 2H, CH₂); 2.30 (s, 3H, CH₃); 1.85 (p, *J* = 5.7 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 165.8 (CO); 138.0 (C_{aro}); 129.5 (2 C_{aro}); 128.5 (2 C_{aro}); 127.7 (C_{aro}); 127.4 (2 C_{aro}); 125.5 (2 C_{aro}); 125.4 (2 C_{aro}); 62.9 (CH₂); 57.1 (CH₂); 41.3 (CH₃); 40.5 (CH₂); 24.8 (CH₂). LCMS *m/z* calc for [M+H⁺]: 351.1; found: 351.0. **HRMS: calcd for (C₁₉H₂₁ON₂F₃)H⁺: 351.16787; found: 351.16663.** HPLC (C₄, 35 min): *t*_R 18.5 min, P_{HPLC} 96%; HPLC (C₁₈, 35 min): *t*_R 25.2 min, P_{HPLC} 97%.

***N*-[3-(benzylmethylamino)propyl]-2-chlorobenzamide (7f)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 46%. ¹H NMR (300 MHz, CDCl₃), δ: 7.52 (dd, *J* = 7.0 Hz, *J* = 1.9 Hz, 1H, H₆); 7.39-7.25 (m, 4H, NH, H₃, H₄, H₅); 7.17-7.09 (m, 5H, H_{aro}); 3.54 (q, *J* = 6.2 Hz, 2H, CH₂); 3.49 (s, 2H, CH₂); 2.58 (t, *J* = 6.3 Hz, 2H, CH₂); 2.21 (s, 3H, NCH₃); 1.83 (p, *J* = 6.2 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 166.7 (CO); 137.9 (C_{aro}); 136.0 (C_{aro}); 130.8 (C_{aro}); 130.7 (C_{aro}); 130.1 (C_{aro}); 129.5 (C_{aro}); 128.9 (2 C_{aro}); 128.3 (2 C_{aro}); 127.2 (C_{aro}); 126.9 (C_{aro}); 62.6 (CH₂); 56.0 (CH₂); 41.8 (CH₃); 39.7 (CH₂); 25.3 (CH₂). LCMS *m/z* calc for [M+H⁺]: 317.1, 319.1; found: 317.0, 319.0. HPLC (C₄, 35 min): *t*_R 12.6 min, P_{HPLC} 95%; HPLC (C₁₈, 35 min): *t*_R 17.1 min, P_{HPLC} 96%.

***N*-[3-(benzylmethylamino)propyl]-3-chlorobenzamide (7g)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 8%. ¹H NMR (300 MHz, CDCl₃), δ: 8.22 (br s, 1H, NH); 7.78 (dd, *J* = 1.5 Hz, *J* = 2.0 Hz, 1H, H₂); 7.68 (d, *J* = 8.0 Hz, 1H, H₆); 7.52 (d, *J* = 7.8 Hz, 1H, H₄); 7.52 (t, *J* = 7.3 Hz, 1H, H₅); 7.32-7.22 (m, 5H, H_{aro}); 3.58-3.51 (m, 4H, 2CH₂); 2.63 (t, *J* = 7.5 Hz, 2H, CH₂); 2.30 (s, 3H, CH₃); 1.84 (p, *J* = 6.4 Hz, 2H,

CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 165.8 (CO); 136.5 (C_{aro}); 134.6 (C_{aro}); 131.2 (C_{aro}); 129.7 (C_{aro}); 129.4 (2 C_{aro}); 128.5 (2 C_{aro}); 127.7 (2 C_{aro}); 127.5 (C_{aro}); 125.0 (C_{aro}); 63.1 (CH₂); 56.7 (CH₂); 41.6 (CH₃); 40.4 (CH₂); 24.8 (CH₂). LCMS *m/z* calc for [M+H⁺]: 317.1, 319.1; found: 317.0, 319.0. HPLC (C₄, 35 min): *t_R* 14.8 min, P_{HPLC} 97%; HPLC (C₁₈, 35 min): *t_R* 20.2 min, P_{HPLC} 97%.

***N*-[3-(2-(*N*-methylbenzyl)amino)ethyl]-4-chlorobenzamide (7h)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 20%. ¹H NMR (300 MHz, CDCl₃), δ: 7.67 (d, *J* = 8.6 Hz, 2H, H₂, H₆); 7.41 (d, *J* = 8.6 Hz, 2H, H₃, H₅); 7.23-7.33 (m, 5H, H_{aro}); 6.78 (br s, 1H, NH); 3.56 (s, 2H, CH₂); 3.51 (q, *J* = 5.2 Hz, 2H, CH₂); 2.62 (t, *J* = 5.9 Hz, 2H, CH₂); 2.31 (s, 3H, NCH₃). ¹³C NMR (75 MHz, CDCl₃) δ: 166.4 (CO); 138.6 (C_{aro}); 137.5 (C_{aro}); 133.1 (C_{aro}); 129.4 (2 C_{aro}); 129.1 (2 C_{aro}); 128.9 (2 C_{aro}); 128.7 (2 C_{aro}); 127.4 (C_{aro}); 62.3 (CH₂); 54.9 (CH₂); 42.1 (CH₃); 37.1 (CH₂). LCMS *m/z* calc for [M+H⁺]: 303.1, 305.1; found: 303.0, 305.0. HRMS: calcd for (C₁₇H₁₉ON₂Cl)H⁺: 303.12531; found: 303.12587. HPLC (C₄, 35 min): *t_R* 14.2 min, P_{HPLC} 97%; HPLC (C₁₈, 35 min): *t_R* 19.3 min, P_{HPLC} 97%.

***N*-[3-(benzylmethylamino)propyl]-4-chlorobenzamide (7i)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 55%. IR (cm⁻¹): 1625 (C=O), 3012 (NH). ¹H NMR (300 MHz, CDCl₃), δ: 8.25 (br s, 1H, NH); 7.60 (d, *J* = 9 Hz, 2H, H₂, H₆); 7.33-7.21 (m, 7H, H₃, H₅, H_{aro}); 3.62-3.51 (m, 4H, 2CH₂); 2.65 (t, *J* = 5.4 Hz, 2H, CH₂); 2.27 (s, 3H, NCH₃); 1.83 (p, *J* = 5.5 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 166.0 (CO); 137.8 (C_{aro}); 137.3 (C_{aro}); 133.1 (C_{aro}); 129.4 (2 C_{aro}); 128.6 (2 C_{aro}); 128.5 (2 C_{aro}); 128.4 (2 C_{aro}); 127.5 (C_{aro}); 63.2 (CH₂); 57.2 (CH₂); 41.5 (CH₃); 40.5 (CH₂); 25.0 (CH₂). LCMS *m/z* calc for [M+H⁺]: 317.1, 319.1; found: 316.9, 318.9. HRMS: calcd for (C₁₈H₂₁ON₂Cl)H⁺: 317.14152; found: 317.14083. HPLC (C₄, 35 min): *t_R* 7.7 min, P_{HPLC} 98%; HPLC (C₁₈, 35 min): *t_R* 18.0 min, P_{HPLC} 98%.

***N*-[4-(benzylmethylamino)butyl]-4-chlorobenzamide (7j)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 25%. ¹H NMR (300 MHz, CDCl₃), δ: 7.60 (d, *J* = 9.2 Hz, 2H, H₂, H₆); 7.41 (br s, 1H, NH); 7.33-7.26 (m, 7H, H₃, H₅, H_{aro}); 3.53 (s, 2H, CH₂); 3.45 (q, *J* = 6.2 Hz, 2H, CH₂); 2.45 (t, *J* = 6.4 Hz, 2H, CH₂); 2.17 (s, 3H, NCH₃); 1.73-1.62 (m, 4H, 2CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 166.6 (CO); 137.7 (C_{aro}); 137.3 (C_{aro}); 133.3 (C_{aro}); 129.3 (2 C_{aro}); 128.6 (2 C_{aro}); 128.5 (2 C_{aro}); 128.4 (2 C_{aro}); 127.4 (C_{aro}); 61.8 (CH₂); 56.7 (CH₂); 42.1 (CH₃); 39.9 (CH₂); 27.1 (CH₂); 24.8 (CH₂). LCMS *m/z* calc for [M+H⁺]: 331.1, 333.1; found: 331.0, 333.0. HPLC (C₄, 35 min): *t_R* 14.8 min, P_{HPLC} 96%; HPLC (C₁₈, 35 min): *t_R* 20.2 min, P_{HPLC} 97%.

***N*-[3-(benzylmethylamino)propyl]-2-bromobenzamide (7k)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 52%. ¹H NMR (300 MHz, CDCl₃), δ: 7.56 (dd, *J* = 7.8 Hz, *J* = 1.3 Hz, 1H, H₆); 7.47 (br s, 1H, NH); 7.37 (dd, *J* = 7.4 Hz, *J* = 2.0 Hz, 1H, H₃); 7.31 (td, *J* = 7.3 Hz, *J* = 1.2 Hz, 1H, H_{aro}); 7.24 (td, *J* = 7.4 Hz, *J* = 1.9 Hz, 1H, H_{aro}); 7.16-7.07 (m, 5H, H_{aro}); 3.52 (q, *J* = 6.2 Hz, 2H, CH₂); 3.48 (s, 2H, CH₂); 2.57 (t, *J* = 6.1 Hz, 2H, CH₂); 2.19 (s, 3H, NCH₃); 1.80 (p, *J* = 6.2 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 167.8 (CO); 138.6 (C_{aro}); 138.0 (C_{aro}); 133.2 (C_{aro}); 130.8 (C_{aro}); 129.0 (2 C_{aro}); 128.9 (2 C_{aro}); 128.3 (C_{aro}); 127.4 (C_{aro}); 127.1 (C_{aro}); 119.5 (C_{aro}); 62.6 (CH₂); 56.1 (CH₂); 41.8 (CH₃); 39.6 (CH₂); 25.3 (CH₂). LCMS *m/z* calc for [M+H⁺]: 361.1; 363.1; found: 360.9; 362.9. HPLC (C₄, 35 min): *t_R* 13.0 min, P_{HPLC} 96%; HPLC (C₁₈, 35 min): *t_R* 17.8 min, P_{HPLC} 96%.

***N*-[3-(benzylmethylamino)propyl]-3-bromobenzamide (7l)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 53%. ¹H NMR (300 MHz, CDCl₃), δ: 8.27 (br s, 1H, NH); 7.82 (t, *J* = 1.8 Hz, 2H, H₂); 7.55 (m, 1H, H₅); 7.28-7.17 (m, 7H, H₄, H₆, H_{aro}); 3.55 (m, 4H, 2CH₂); 2.62 (t, *J* = 6.0 Hz, 2H, CH₂); 2.30 (s, 3H, NCH₃); 1.83 (p, *J* = 5.9 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 165.7 (CO); 137.6 (C_{aro}); 136.7 (C_{aro}); 134.0 (C_{aro}); 130.3 (C_{aro}); 129.9 (C_{aro}); 129.4 (2 C_{aro}); 128.5 (2 C_{aro}); 127.6 (C_{aro}); 125.4 (C_{aro}); 122.6 (C_{aro}); 63.1 (CH₂); 56.8 (CH₂); 41.8 (CH₃); 40.4 (CH₂); 24.9 (CH₂). LCMS *m/z* calc for [M+H⁺]: 361.1; 363.1; found: 360.9; 362.9. HRMS: calcd for (C₁₈H₂₁ON₂Br)H⁺: 361.09100; found: 361.08984. HPLC (C₄, 35 min): *t_R* 14.8 min, P_{HPLC} 98%; HPLC (C₁₈, 35 min): *t_R* 20.2 min, P_{HPLC} 98%.

***N*-[3-(benzylmethylamino)propyl]-4-bromobenzamide (7m)**

Procedure E2. Purification by thick layer chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 67%. ¹H NMR (300 MHz, CDCl₃), δ : 8.29 (br s, 1H, NH); 7.54 (d, *J* = 9.1 Hz, 2H, H₂, H₆); 7.46 (d, *J* = 9.2 Hz, 2H, H₃, H₅); 7.33-7.20 (m, 5H, H_{aro}); 3.65-3.47 (m, 4H, 2 CH₂); 2.66 (t, *J* = 5.9 Hz, 2H, CH₂); 2.29 (s, 3H, CH₃); 1.84 (p, *J* = 5.8 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 166.2 (CO); 137.5 (C_{aro}); 133.5 (C_{aro}); 131.6 (2 C_{aro}); 129.5 (2 C_{aro}); 128.6 (2 C_{aro}); 128.5 (2 C_{aro}); 127.7 (C_{aro}); 125.7 (C_{aro}); 63.0 (CH₂); 57.0 (CH₂); 41.4 (CH₃); 40.3 (CH₂); 24.9 (CH₂). LCMS *m/z* calc for [M+H⁺]: 361.1; 363.1; found: 360.9; 362.9. HRMS: calcd for (C₁₈H₂₁ON₂Br)H⁺: 361.09100; found: 361.08948. HPLC (C₄, 35 min): *t_R* 8.8 min, P_{HPLC} >99%; HPLC (C₁₈, 35 min): *t_R* 18.4 min, P_{HPLC} >99%.

***N*-[3-(benzylmethylamino)propyl]-4-fluorobenzamide (7n)**

Procedure E2. Purification by thick layer chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 58%. ¹H NMR (300 MHz, CDCl₃), δ : 8.20 (br s, 1H, NH); 7.66 (m, 2H, H₂ and H₆); 7.28-7.24 (m, 5H, H_{aro}); 7.00 (t, ³*J*_{3-F} = 9 Hz, 2H, H₃ and H₅); 3.60-3.52 (m, 4H, H_a et H_e); 2.65 (t, ³*J* = 6 Hz, 2H, H_c); 2.28 (s, 3H, H_d); 1.83 (p, ³*J* = 6 Hz, 2H, H_b). ¹³C NMR (75 MHz, CDCl₃) δ: 166.1 (CO); 164.5 (d, ¹*J*_{4-F} = 250 Hz, C₄); 137.6 (C_{aro}); 130.8 (d, ⁴*J*_{1-F} = 3 Hz, C₁); 129.5 (2 C_{aro}); 129.2 (d, ³*J*_{2-F} = 9 Hz, C₂ and C₆);

128.5 (2 C_{aro}); 127.6 (C_{aro}); 115.3 (d, ²J_{3-F} = 20 Hz, C₃ and C₅); 63.1 (CH₂); 57.1 (CH₂); 41.4 (CH₃); 40.3 (CH₂); 25.0 (CH₂). LCMS *m/z* calc for [M+H⁺]: 301.2; found: 301.1. HPLC (C₄, 35 min): *t_R* 8.4 min, P_{HPLC} >99%; HPLC (C₁₈, 35 min): *t_R* 16.3 min, P_{HPLC} >99%.

***N*-[3-(benzylmethylamino)propyl]-2,3-dichlorobenzamide (7o)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 66%. ¹H NMR (300 MHz, CDCl₃), δ: 7.58 (br s, 1H, NH); 7.51 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1H, H₆); 7.32 (dd, *J* = 7.7 Hz, *J* = 1.6 Hz, 1H, H₄); 7.25 (m, 1H, H₅); 7.17-7.07 (m, 5H, H_{aro}); 3.55 (q, *J* = 6.7 Hz, 2H, CH₂); 3.48 (s, 2H, CH₂); 2.58 (t, *J* = 5.9 Hz, 2H, CH₂); 2.21 (s, 3H, NCH₃); 1.82 (p, *J* = 6.0 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 166.2 (CO); 138.6 (C_{aro}); 137.8 (C_{aro}); 133.7 (C_{aro}); 131.3 (C_{aro}); 128.9 (C_{aro}); 128.3 (2 C_{aro}); 127.6 (2 C_{aro}); 127.5 (C_{aro}); 127.3 (C_{aro}); 127.0 (C_{aro}); 62.7 (CH₂); 56.0 (CH₂); 41.8 (CH₃); 39.7 (CH₂); 25.1 (CH₂). LCMS *m/z* calc for [M+H⁺]: 351.1, 353.1, 355.1; found: 351.0, 353.0, 355.0. HPLC (C₄, 35 min): *t_R* 14.7 min, P_{HPLC} 98%; HPLC (C₁₈, 35 min): *t_R* 20.0 min, P_{HPLC} 98%.

***N*-[2-(benzylmethylamino)ethyl]-2,3-dichlorobenzamide (7p)**

Procedure E1. Purification by thick layer chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 18%. ¹H NMR (300 MHz, CDCl₃), δ: 7.60 (d, *J* = 8.3 Hz, 1H, H_{aro}); 7.44 (d, *J* = 2.0 Hz, 1H, H_{aro}); 7.32 (dd, *J* = 8.4 Hz, *J* = 2.0 Hz, 1H, H_{aro}); 7.30-7.25 (m, 1H, H_{aro}); 6.90 (br s, 1H, NH); 3.59-3.52 (m, 4H, 2 CH₂); 2.63 (d, *J* = 5.6 Hz, 2H, CH₂); 2.26 (s, 3H, NCH₃). ¹³C NMR (75 MHz, CDCl₃) δ: 165.3 (CO); 138.4 (C_{aro}); 136.6 (C_{aro}); 133.5 (C_{aro}); 131.6 (C_{aro}); 131.4 (C_{aro}); 130.0 (C_{aro}); 129.0 (2 C_{aro}); 128.4 (2 C_{aro}); 127.4 (C_{aro}); 127.3 (C_{aro}); 62.4 (CH₂); 55.0 (CH₂); 41.6 (CH₃); 37.3 (CH₂). LCMS *m/z* calc for [M+H⁺]: 337.1; 341.1; found: 337.0; 341.0. HPLC (C₄, 35 min): *t_R* 15.0 min, P_{HPLC} 97%; HPLC (C₁₈, 35 min): *t_R* 20.5 min, P_{HPLC} 97%.

***N*-[3-(benzylmethylamino)propyl]-3,4-dichlorobenzamide (7q)**

Procedure E2. Purification by thick layer chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 31%. ¹H NMR (300 MHz, CDCl₃), δ: 8.44 (br s, 1H, NH); 7.82 (d, *J* = 2.0 Hz, 1H, H₂); 7.47 (dd, *J* = 8.2 Hz, *J* = 2.0 Hz, 1H, H₆); 7.38 (d, *J* = 8.3 Hz, 1H, H₅); 7.31-7.22 (m, 5H, H_{aro}); 3.60 (s, 2H, CH₂); 3.56 (q, *J* = 6.1 Hz, 2H, CH₂); 2.68 (t, *J* = 6.1 Hz, 2H, CH₂); 2.33 (s, 3H, CH₃); 1.86 (p, *J* = 6.2 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 164.9 (CO); 135.4 (C_{aro}); 134.5 (C_{aro}); 132.9 (C_{aro}); 130.4 (2 C_{aro}); 129.5 (2 C_{aro}); 129.3 (C_{aro}); 128.6 (2 C_{aro}); 127.8 (C_{aro}); 126.1 (C_{aro}); 62.8 (CH₂); 56.7 (CH₂); 41.4 (CH₃); 40.3 (CH₂); 24.7 (CH₂). LCMS *m/z* calc for [M+H⁺]: 351.1, 353.1, 355.1; found: 350.9, 352.9, 354.9. HPLC (C₄, 35 min): *t_R* 15.6 min, P_{HPLC} >99%; HPLC (C₁₈, 35 min): *t_R* 19.8 min, P_{HPLC} >99%.

***N*-[3-(benzylmethylamino)propyl]-3,5-dichlorobenzamide (7r)**

Procedure E2. Purification by thick layer chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 34%. ¹H NMR (300 MHz, CDCl₃), δ: 8.42 (br s, 1H, NH) ; 7.55 (m, 2H, H₂, H₆); 7.44 (m, 1H, H₄); 7.28-7.20 (m, 5H, H_{aro}); 3.57-3.51 (m, 4H, 2 CH₂); 2.63 (t, *J* = 6.1 Hz, 2H, CH₂); 2.32 (s, 3H, CH₃); 1.82 (p, *J* = 6.0 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 164.6 (CO); 137.7 (C_{aro}); 137.5 (C_{aro}); 135.3 (C_{aro}); 130.9 (2 C_{aro}); 129.3 (2 C_{aro}); 128.5 (2 C_{aro}); 127.6 (C_{aro}); 125.7 (2 C_{aro}); 63.0 (CH₂); 56.7 (CH₂); 41.8 (CH₃); 40.7 (CH₂); 24.8 (CH₂). LCMS *m/z* calc for [M+H⁺]: 351.1, 353.1, 355.1; found: 350.9, 352.9, 354.9. HPLC (C₄, 35 min): *t_R* 21.9 min, P_{HPLC} >99%; HPLC (C₁₈, 35 min): *t_R* 20.3 min, P_{HPLC} >99%.

***N*-[3-(benzylmethylamino)propyl]-4-bromo-2-fluorobenzamide (7s)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 22%. ¹H NMR (300 MHz, MeOD), δ: 7.60 (d, *J* = 8.2 Hz, 1H, H₆); 7.50 (m, 1H, H_{aro}); 7.44 (m, 1H, H_{aro}); 7.22-7.34 (m, 5H, H_{aro}); 3.59 (s, 2H, CH₂); 3.43 (t, *J* = 6.7 Hz, 2H, CH₂); 2.56 (t, *J* = 7.1 Hz, 2H, CH₂); 2.28 (s, 3H, CH₃); 1.85 (p, *J* = 7.0 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 162.5 (CO); 132.9 (C_{aro}); 129.5 (C_{aro}); 128.7 (C_{aro}); 128.4 (2 C_{aro}); 128.1 (2 C_{aro}); 125.1 (C_{aro}); 119.8 (C_{aro}); 119.4 (C_{aro}); 62.4 (CH₂); 55.3 (CH₂); 41.4 (CH₃); 29.7 (CH₂); 25.4 (CH₂). LCMS *m/z* calc for [M+H⁺]: 379.1; 381.1 found: 379.0; 381.0 HPLC (C₄, 35 min): *t_R* 15.1 min, P_{HPLC} >99%; HPLC (C₁₈, 35 min): *t_R* 20.6 min, P_{HPLC} >99%.

***N*-[3-(benzylmethylamino)propyl]-3-methoxybenzamide (7t)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 35%. ¹H NMR (300 MHz, CDCl₃), δ: 8.10 (br s, 1H, NH); 7.35 (m, 1H, H₂); 7.28-7.14 (m, 7H, H₅, H₆, H_{aro}); 7.11 (m, 1H, H₄); 3.78 (s, 3H, OCH₃); 3.55 (m, 4H, 2CH₂); 2.63 (t, *J* = 6.2 Hz, 2H, CH₂); 2.28 (s, 3H, NCH₃); 1.83 (p, *J* = 6.4 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 165.3 (CO); 159.7 (C_{aro}); 137.6 (C_{aro}); 136.2 (C_{aro}); 129.4 (3 C_{aro}); 128.4 (2 C_{aro}); 127.4 (C_{aro}); 118.8 (C_{aro}); 117.6 (C_{aro}); 112.1 (C_{aro}); 63.0 (CH₂); 56.8 (CH₂); 55.3 (OCH₃); 41.5 (NCH₃); 40.2 (CH₂); 25.2 (CH₂). LCMS *m/z* calc for [M+H⁺]: 313.2; found: 313.0. HRMS: calcd for (C₁₉H₂₄O₂N₂)H⁺: 313.19105; found: 313.18948. HPLC (C₄, 35 min): *t_R* 13.8 min, P_{HPLC} 98%; HPLC (C₁₈, 35 min): *t_R* 18.8 min, P_{HPLC} 98%.

***N*-[3-(benzylmethylamino)propyl]-4-methoxybenzamide (7u)**

Procedure E2. Purification by thick layer chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 73%. ¹H NMR (300 MHz, CDCl₃), δ: 7.97 (br s, 1H, NH) ; 7.67 (m, 2H, H₂, H₆); 7.32-7.24 (m, 5H, H_{aro}); 6.84 (m, 2H, H₃, H₅); 3.84 (s, 3H, OCH₃); 3.60-3.52 (m, 4H, 2 CH₂); 2.65 (t, *J* = 6.0 Hz, 2H, CH₂); 2.29 (s, 3H, CH₃); 1.85 (p, *J* = 6.1 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 166.9 (CO); 162.0 (C_{aro}); 137.2 (C_{aro}); 129.6 (2 C_{aro}); 128.8 (2 C_{aro}); 128.5 (2 C_{aro}); 127.7 (C_{aro}); 125.0 (C_{aro}); 113.6 (2 C_{aro}); 62.9 (CH₂); 56.7 (CH₂); 55.4 (OCH₃); 41.4 (CH₃); 39.9 (CH₂); 25.3 (CH₂). LCMS *m/z* calc for [M+H⁺]:

313.2; found: 313.0. HRMS: calcd for (C₁₉H₂₄O₂N₂)H⁺: 313.19105; found: 313.18976. HPLC (C₄, 35 min): *t_R* 18.1 min, P_{HPLC} >99%; HPLC (C₁₈, 35 min): *t_R* 16.2 min, P_{HPLC} 98%.

***N*-[3-(benzylmethylamino)propyl]-3-dimethylaminobenzamide (7v)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 11%. ¹H NMR (300 MHz, CDCl₃), δ: 7.90 (br s, 1H, NH); 7.28-7.24 (m, 5H, H_{aro}); 7.22-7.19 (m, 2H, H₂, H₅); 6.92 (d, *J* = 7.5 Hz, 1H, H₆); 6.82 (dd, *J* = 8.1 Hz, *J* = 2.2 Hz, 1H, H₄); 3.62-3.51 (m, 4H, 2 CH₂); 2.95 (s, 6H, 2 CH₃); 2.64 (t, *J* = 6.0 Hz, 2H, CH₂); 2.31 (s, 3H, CH₃); 1.85 (p, *J* = 5.8 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 162.4 (CO); 138.5 (C_{aro}); 133.1 (2 C_{aro}); 129.0 (2 C_{aro}); 128.2 (2 C_{aro}); 128.0 (2 C_{aro}); 127.1 (C_{aro}); 119.7 (C_{aro}); 119.4 (C_{aro}); 63.0 (CH₂); 55.9 (CH₂); 50.9 (CH₂); 41.9 (3 CH₃); 39.9 (CH₂); 25.6 (CH₂). LCMS *m/z* calc for [M+H⁺]: 326.2; found: 326.0. HPLC (C₄, 35 min): *t_R* 14.5 min, P_{HPLC} >99%; HPLC (C₁₈, 35 min): *t_R* 19.8 min, P_{HPLC} >99%.

***N*-[2-(benzylmethylamino)ethyl]-4-cyanobenzamide (7w)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 33%. ¹H NMR (300 MHz, CDCl₃), δ: 8.00 (d, 2H, *J* = 7.3 Hz, 2H, H_{aro}); 7.57 (d, 2H, *J* = 7.4 Hz, 2H, H_{aro}); 7.30-7.24 (m, 5 H, H_{aro}); 6.71 (br s, 1H, NH); 3.53 (s, 2H, CH₂); 3.00 (t, 2H, *J* = 5.5 Hz, CH₂); 2.65 (t, 2H, *J* = 5.7 Hz, CH₂); 2.18 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ: 171.4 (CO); 137.5 (C_{aro}); 131.7 (2 C_{aro}); 129.8 (2 C_{aro}); 129.0 (2 C_{aro}); 128.5 (2 C_{aro}); 127.5 (C_{aro}); 118.7 (C_{aro}); 114.0 (C_{aro}); 62.2 (CH₂); 54.7 (CH₂); 41.6 (CH₃); 37.0 (CH₂). LCMS *m/z* calc for [M+H⁺]: 294.1; found: 294.0. HRMS: calcd for (C₁₈H₁₉ON₃)H⁺: 294.16009; found: 294.15906. HPLC (C₄, 35 min): *t_R* 12.7 min, P_{HPLC} 97%; HPLC (C₁₈, 35 min): *t_R* 17.3 min, P_{HPLC} 97%.

***N*-[3-(benzylmethylamino)propyl]-4-cyanobenzamide (7x)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 7%. ¹H NMR (300 MHz, CDCl₃), δ: 8.61 (br s, 1H, NH); 7.71 (d, *J* = 8.2 Hz, 2H, H₃, H₅); 7.61 (d, *J* = 8.3 Hz, 2H, H₂, H₆); 7.30-7.20 (m, 5H, H_{aro}); 3.62 (q, *J* = 6.4 Hz, 2H, CH₂); 3.55 (s, 2H, CH₂); 2.69 (t, *J* = 5.8 Hz, 2H, CH₂); 2.27 (s, 3H, CH₃); 1.84 (p, *J* = 6.0 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 165.3 (CO); 138.4 (C_{aro}); 136.8 (C_{aro}); 132.2 (2 C_{aro}); 129.6 (2 C_{aro}); 128.6 (2 C_{aro}); 127.7 (2 C_{aro}); 118.2 (C_{aro}); 114.6 (C_{aro}); 63.3 (CH₂); 57.6 (CH₂); 41.5 (CH₃); 40.9 (CH₂); 25.1 (CH₂). LCMS *m/z* calc for [M+H⁺]: 308.1; found: 308.0. HPLC (C₄, 35 min): *t_R* 13.2 min, P_{HPLC} 98%; HPLC (C₁₈, 35 min): *t_R* 18.0 min, P_{HPLC} >99%.

***N*-[2-(benzylmethylamino)ethyl]-4-nitrobenzamide (7y)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 52%. ¹H NMR (300 MHz, CDCl₃), δ: 8.30 (d, *J* = 8.8 Hz, 2H, H_{aro}); 7.85 (d, *J* = 8.7 Hz, 2H, H_{aro});

7.34-7.28 (m, 5H, H_{aro}); 6.85 (br s, 1H, NH); 3.58 (s, 2H, CH₂); 3.53 (q $J = 4.9$ Hz, 2H, CH₂); 2.64 (t, $J = 5.6$ Hz, 2H, CH₂); 2.34 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ : 165.2 (CO); 149.5 (C_{aro}); 140.3 (C_{aro}); 138.6 (C_{aro}); 129.1 (2 C_{aro}); 128.8 (2 C_{aro}); 128.5 (2 C_{aro}); 127.5 (C_{aro}); 123.8 (2 C_{aro}); 62.3 (CH₂); 54.6 (CH₂); 42.2 (CH₃); 37.3 (CH₂). LCMS (ESI⁺): calc for [M+H⁺]: 314.1; found: 314.1. HRMS: calcd for (C₁₇H₁₉O₃N₃)H⁺: 314.14992; found: 314.14905. HPLC (C₄, 35 min): t_R 15.1 min, P_{HPLC} >99%; HPLC (C₁₈, 35 min): t_R 20.6 min, P_{HPLC} >99%.

***N*-[3-(benzylmethylamino)propyl]-4-nitrobenzamide (7z)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 50%. ¹H NMR (300 MHz, CDCl₃) δ : 8.68 (br s, 1H, NH); 8.17 (d, $J = 8.8$ Hz, 2H, H₃, H₅); 7.79 (d, $J = 8.8$ Hz, 2H, H₂, H₆); 7.32-7.22 (m, 5H, H_{aro}); 3.65-3.56 (m, 4H, 2CH₂); 2.72 (t, $J = 5.6$ Hz, 2H, CH₂); 2.32 (s, 3H, NCH₃); 1.88 (p, $J = 5.7$ Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ : 166.7 (CO); 149.3 (C_{aro}); 140.1 (C_{aro}); 137.1 (C_{aro}); 129.6 (2 C_{aro}); 128.6 (2 C_{aro}); 128.1 (2 C_{aro}); 127.8 (C_{aro}); 123.6 (2 C_{aro}); 63.5 (CH₂); 57.6 (CH₂); 41.7 (CH₃); 41.1 (CH₂); 25.0 (CH₂). LCMS m/z calc for [M+H⁺]: 328.1; found: 328.0. HRMS: calcd for (C₁₈H₂₁O₃N₃)H⁺: 328.16557; found: 328.16388. HPLC (C₄, 35 min): t_R 13.6 min, P_{HPLC} 96%; HPLC (C₁₈, 35 min): t_R 18.6 min, P_{HPLC} 96%.

***N*-[3-(*N*-methyl-2-phenylethylamino)propyl]-4-chlorobenzamide (8a)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 69%. ¹H NMR (300 MHz, CDCl₃) δ : 8.25 (br s, 1H, NH); 7.58 (d, $J = 8.3$ Hz, 2H, H₂, H₆); 7.34 (d, $J = 8.4$ Hz, 2H, H₃, H₅); 7.26-7.12 (m, 5H, H_{aro}); 3.53 (q, $J = 6.2$ Hz, 2H, CH₂); 2.82 (m, 2H, CH₂); 2.75 (m, 2H, CH₂); 2.66 (t, $J = 6.0$ Hz, 2H, CH₂); 2.35 (s, 3H, NCH₃); 1.80 (p, $J = 5.9$ Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ : 165.9 (CO); 139.5 (C_{aro}); 137.2 (C_{aro}); 133.1 (C_{aro}); 128.6 (4 C_{aro}); 128.5 (2 C_{aro}); 128.3 (2 C_{aro}); 126.3 (C_{aro}); 59.6 (CH₂); 57.1 (CH₂); 41.7 (CH₃); 40.4 (CH₂); 33.3 (CH₂); 24.3 (CH₂). LCMS m/z calc for [M+H⁺]: 331.1, 333.1; found: 331.0, 333.0. HRMS: calcd for (C₁₉H₂₃ON₂Cl)H⁺: 331.15717; found: 331.15601. HPLC (C₄, 35 min): t_R 15.5 min, P_{HPLC} >99%; HPLC (C₁₈, 35 min): t_R 21.2 min, P_{HPLC} >99%.

***N*-[3-(isoindolin-2-yl)methylamino]propyl]-4-chlorobenzamide (8b)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 36%. ¹H NMR (300 MHz, CDCl₃) δ : 9.00 (br s, 1H, NH); 7.48 (d, $J = 8.6$ Hz, 2H, H₂, H₆); 7.31-7.21 (m, 4H, H_{aro}); 7.03 (d, $J = 8.5$ Hz, 2H, H₃, H₅); 4.02 (s, 4H, 2CH₂); 3.63 (q, $J = 5.0$ Hz, 2H, CH₂); 3.05 (t, $J = 5.8$ Hz, 2H, CH₂); 1.89 (p, $J = 5.8$ Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ : 165.6 (CO); 139.2 (2 C_{aro}); 137.1 (C_{aro}); 132.6 (C_{aro}); 128.4 (2 C_{aro}); 128.2 (2 C_{aro}); 127.2 (2 C_{aro}); 122.4 (2 C_{aro}); 58.6 (2 CH₂); 55.3 (CH₂); 40.8 (CH₂); 25.9 (CH₂). LCMS m/z calc for [M+H⁺]: 315.1, 317.1; found: 315.0, 317.0. HPLC (C₄, 35 min): t_R 14.6 min, P_{HPLC} 97%; HPLC (C₁₈, 35 min): t_R 20.0 min, P_{HPLC} 98%.

***N*-[2-pyrrolidinylethyl]-4-chlorobenzamide (8c)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 22%. ¹H NMR (300 MHz, CDCl₃), δ: 7.82 (d, *J* = 8.5 Hz, 2H, H₂, H₆); 7.51 (br s, 1H, NH); 7.48 (d, *J* = 8.5 Hz, 2H, H₃, H₅); 3.63 (q, *J* = 6.1 Hz, 2H, CH₂); 2.91 (t, *J* = 6.0 Hz, 2H, CH₂); 2.78 (m, 4H, 2CH₂); 1.90 (m, 4H, 2CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 165.6 (CO); 137.6 (C_{aro}); 132.6 (C_{aro}); 128.7 (4 C_{aro}); 54.9 (CH₂); 54.0 (2 CH₂); 37.9 (CH₂); 23.4 (2 CH₂). LCMS *m/z* calc for [M+H⁺]: 253.1, 255.1; found: 253.0, 255.0. HPLC (C₄, 35 min): *t_R* 12.1 min, P_{HPLC} >99%; HPLC (C₁₈, 35 min): *t_R* 16.5 min, P_{HPLC} >99%.

***N*-[3-pyrrolidinylpropyl]-4-chlorobenzamide (8d)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 7%. ¹H NMR (300 MHz, CDCl₃), δ: 8.48 (br s, 1H, NH); 7.96 (d, *J* = 8.8 Hz, 2H, H₂, H₆); 7.39 (d, *J* = 8.8 Hz, 2H, H₃, H₅); 3.77 (m, 2H, CH₂); 3.63 (m, 2H, CH₂); 3.18 (q, *J* = 6.1 Hz, 2H, CH₂); 2.84 (m, 2H, CH₂); 2.37-1.88 (m, 6H, 3 CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 166.7 (CO); 137.8 (C_{aro}); 131.9 (C_{aro}); 129.3 (2 C_{aro}); 129.1 (2 C_{aro}); 54.1 (2 CH₂); 53.0 (CH₂); 36.7 (CH₂); 25.6 (CH₂); 23.6 (2 CH₂). LCMS *m/z* calc for [M+H⁺]: 267.1, 269.1; found: 267.0, 269.0. HPLC (C₄, 35 min): *t_R* 12.7 min, P_{HPLC} 98%; HPLC (C₁₈, 35 min): *t_R* 17.3 min, P_{HPLC} 98%.

***N*-[2-morpholinethyl]-4-chlorobenzamide (8e)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 35%. ¹H NMR (300 MHz, CDCl₃), δ: 7.66 (d, *J* = 8.6 Hz, 2H, H₂, H₆); 7.32 (d, *J* = 8.6 Hz, 2H, H₃, H₅); 6.99 (br s, 1H, NH); 3.65 (m, 4H, 2CH₂); 3.45 (q, *J* = 6.0 Hz, 2H, CH₂); 2.53 (t, *J* = 6.2 Hz, 2H, CH₂); 2.42 (m, 4H, 2CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 166.4 (CO); 137.5 (C_{aro}); 132.9 (C_{aro}); 128.7 (2 C_{aro}); 128.4 (2 C_{aro}); 66.9 (2 CH₂); 56.9 (CH₂); 53.3 (2 CH₂); 36.2 (CH₂). LCMS *m/z* calc for [M+H⁺]: 269.1, 271.1; found: 269.0, 271.0. HPLC (C₄, 35 min): *t_R* 12.2 min, P_{HPLC} 98%; HPLC (C₁₈, 35 min): *t_R* 16.6 min, P_{HPLC} 98%.

***N*-[3-morpholinpropyl]-4-chlorobenzamide (8f)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 42%. ¹H NMR (300 MHz, CDCl₃), δ: 8.09 (br s, 1H, NH); 7.73 (d, *J* = 8.6 Hz, 2H, H₂, H₆); 7.48 (d, *J* = 8.6 Hz, 2H, H₃, H₅); 3.67 (m, 4H, 2CH₂); 3.52 (q, *J* = 6.1 Hz, 2H, CH₂); 2.58-2.43 (m, 6H, 3CH₂); 1.76 (p, *J* = 6.1 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 166.8 (CO); 137.8 (C_{aro}); 133.5 (C_{aro}); 129.1 (2 C_{aro}); 128.8 (2 C_{aro}); 67.2 (2 CH₂); 58.7 (CH₂); 54.4 (2 CH₂); 40.8 (CH₂); 24.5 (CH₂). LCMS *m/z* calc for [M+H⁺]: 283.1, 285.1; found: 283.0, 285.0. HPLC (C₄, 35 min): *t_R* 11.5 min, P_{HPLC} 98%; HPLC (C₁₈, 35 min): *t_R* 15.7 min, P_{HPLC} 99%.

***N*-[2-piperazinylethyl]-4-chlorobenzamide (8g)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 42%. ¹H NMR (300 MHz, CDCl₃), δ: 7.72 (d, *J* = 7.9 Hz, 2H, H₂, H₆); 7.37 (d, *J* = 7.9 Hz, 2H, H₃, H₅); 6.94 (br s, 1H, NH); 3.54 (q, *J* = 5.5 Hz, 2H, CH₂); 2.67-2.48 (m, 10H, 5CH₂); 2.32 (s, 3H, NCH₃). ¹³C NMR (75 MHz, CDCl₃) δ: 166.3 (CO); 137.6 (C_{aro}); 132.9 (C_{aro}); 128.7 (2 C_{aro}); 128.4 (2 C_{aro}); 56.2 (CH₂); 54.8 (2 CH₂); 52.5 (2 CH₂); 45.8 (CH₃); 36.4 (CH₂). LCMS *m/z* calc for [M+H⁺]: 282.1, 284.1; found: 282.0, 284.0. HPLC (C₄, 35 min): *t*_R 13.0 min, P_{HPLC} 96%; HPLC (C₁₈, 35 min): *t*_R 17.8 min, P_{HPLC} 96%.

***N*-[3-piperazinylpropyl]-4-chlorobenzamide (8h)**

Procedure E1. Purification by column chromatography (DCM:MeOH(NH₃), 9:1 (v/v)) was performed. Yield: 43%. ¹H NMR (300 MHz, CDCl₃), δ: 8.28 (br s, 1H, NH); 7.78 (d, *J* = 8.5 Hz, 2H, H₂, H₆); 7.39 (d, *J* = 8.5 Hz, 2H, H₃, H₅); 3.56 (q, *J* = 5.5 Hz, 2H, CH₂); 2.62 (t, *J* = 5.7 Hz, 2H, CH₂); 2.58 -2.42 (m, 8H, 4CH₂); 2.32 (s, 3H, NCH₃); 1.81 (p, *J* = 5.8 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 166.3 (CO); 137.4 (C_{aro}); 133.1 (C_{aro}); 128.6 (4 C_{aro}); 57.9 (CH₂); 54.7 (2 CH₂); 52.9 (2 CH₂); 45.9 (CH₃); 40.5 (CH₂); 24.1 (CH₂). LCMS *m/z* calc for [M+H⁺]: 296.1, 298.1; found: 296.0, 298.0. HPLC (C₄, 35 min): *t*_R 11.6 min, P_{HPLC} 95%; HPLC (C₁₈, 35 min): *t*_R 15.9 min, P_{HPLC} 95%.

***N*-[3-(benzylmethylamino)propyl]-4-chlorobenzensulfonamide (9)**

Procedure E1. Purification by column chromatography (petroleum ether:DCM:MeOH(NH₃), 5:4:1 (v/v)) was performed. Yield: 60%. IR (cm⁻¹): 1323 and 1156 (SO₂). ¹H NMR (300 MHz, CDCl₃), δ: 7.76 (d, *J* = 9.1 Hz, 2H, H₂, H₆); 7.47(d, *J* = 9.2 Hz, 2H, H₃, H₅); 7.36-7.22 (m, 5H, H_{aro}); 3.46 (s, 2H, CH₂); 3.05 (t, *J* = 7.2 Hz, 2H, CH₂); 2.45 (t, *J* = 7.1 Hz, 2H, CH₂); 2.18 (s, 3H, CH₃); 1.67 (p, *J* = 7.0 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 138.8 (C_{aro}); 138.7 (C_{aro}); 137.9 (C_{aro}); 129.3 (2 C_{aro}); 129.0 (2 C_{aro}); 128.6 (2 C_{aro}); 128.5 (2 C_{aro}); 127.4 (C_{aro}); 62.8 (CH₂); 56.8 (CH₂); 44.0 (CH₃); 41.9 (CH₂); 24.7 (CH₂). LCMS *m/z* calc for [M+H⁺]: 353.1, 355.1; found: 353.0, 355.0. HRMS: calcd for (C₁₇H₂₁O₂N₂ClS)H⁺: 353.10850; found: 353.10782. HPLC (C₄, 35 min): *t*_R 13.8 min, P_{HPLC} >99%; HPLC (C₁₈, 35 min): *t*_R 18.6 min, P_{HPLC} >99%.

***N*-(4-chlorobenzyl)-3-(benzylmethylamino)propanamine (10)**

A solution of 4-chlorobenzaldehyde (0.55 mmol, 77 mg) and *N*¹-benzyl-*N*¹-methylpropane-1,3-diamine **5a** (0.55 mmol, 100 mg) in MeOH (10 mL) was stirred at room temperature for 16 hours. Then, sodium borohydride (0.82 mmol, 32 mg) was added and the reaction media was stirred for 3 hours. The mixture was quenched with water (5 mL) and evaporated under reduce pressure. The crude product was purified by thick layer chromatography (DCM:MeOH(NH₃), 9:1 (v/v)). Yield: 35%. IR (cm⁻¹): 2950 (NH). ¹H

NMR (300 MHz, CDCl₃), δ : 7.80 (br s, 1H, NH); 7.48 (d, J = 8.4 Hz, 2H, H₂, H₆); 7.33 (d, J = 8.5 Hz, 2H, H₃, H₅); 7.30-7.26 (m, 3H, H_{aro}); 7.13 (m, 2H, H_{aro}); 4.00 (s, 2H, CH₂); 3.53 (s, 2H, CH₂); 2.94 (t, J = 6.5 Hz, 2H, CH₂); 2.60 (t, J = 6.3 Hz, 2H, CH₂); 2.27 (s, 3H, CH₃); 2.02 (p, J = 6.2 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ : 136.5 (C_{aro}); 135.3 (C_{aro}); 131.2 (2 C_{aro}); 130.3 (C_{aro}); 129.4 (2 C_{aro}); 129.3 (2 C_{aro}); 128.6 (2 C_{aro}); 127.8 (C_{aro}); 62.2 (CH₂); 55.4 (CH₂); 50.9 (CH₂); 47.3 (CH₂); 41.5 (CH₃); 22.6 (CH₂). LCMS m/z calc for [M+H⁺]: 303.1, 305.1; found: 303.0, 305.0. HRMS: calcd for (C₁₈H₂₃N₂Cl)H⁺: 303.16225; found: 303.16180. HPLC (C₄, 35 min): t_R 12.4 min, P_{HPLC} 95%; HPLC (C₁₈, 35 min): t_R 21.1 min, P_{HPLC} 95%.

4-Chloro-*N*-(4-chlorophenyl)butyramide (**11**)

To a solution of 4-chloroaniline (7.8 mmol, 1.0 g) in 15 mL of DCM at 0°C was added slowly a solution of 4-chlorobutyryl chloride (7.8 mmol, 878 μ L) in 5 mL of DCM. The resulting mixture was stirred at room temperature for 12 hours. Then the reaction was quenched with 25 mL of water and the product extract with 3 x 25 mL of DCM. The combined organic layers were dried over magnesium sulphate and concentrated to give the desired product **2.2** with sufficient purity to be used without purification in the next step. Yield: 87%. Mp = 98°C. ¹H NMR (300 MHz, CDCl₃), δ : 7.75 (br s, 1H, NH); 7.46 (d, J = 9.1 Hz, 2H, H₂, H₆); 7.26 (d, J = 9.0 Hz, 2H, H₃, H₅); 3.65 (t, J = 6.2 Hz, 2H, CH₂); 2.55 (t, J = 7.3 Hz, 2H, CH₂); 2.18 (p, J = 6.3 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ : 170.0 (CO); 136.2 (C_{aro}); 129.4 (C_{aro}); 129.0 (2 C_{aro}); 121.1 (2 C_{aro}); 44.4 (CH₂); 34.1 (CH₂); 27.8 (CH₂). LCMS m/z calc for [M+H⁺]: 232.0, 234.0, 236.0; found: 232.0, 234.0, 236.0.

1-(4-Chlorophenyl)pyrrolidin-2-one (**12**)

To a solution of *N*-methyl-*N*-benzylamine (106 μ L, 0.82 mmol) in 10 mL of DMF was added a 340 mg (2.46 mmol) amount of potassium carbonate. The resulting mixture was stirred at 70°C. After 30 minutes, the 4-chloro-*N*-(4-chlorophenyl)butyramide **11** (210 mg, 0.91 mmol) was added and the reacting mixture was stirred at 70°C overnight. The solvent was removed under reduced pressure and 15 mL of water added to the residue. The crude product was extracted with 3x15 mL of DCM. The combined organic layers were washed with water and dried over magnesium sulphate. Purification by column chromatography (DCM:MeOH(NH₃), 99:1 (v/v)) was performed. Yield: 67%. Mp = 98°C. ¹H NMR (300 MHz, CDCl₃), δ : 7.63-7.55 (m, 2H, H₂ and H₆); 7.36-7.29 (m, 2H, H₃, H₅); 3.84 (t, J = 7.3 Hz, 2H, CH₂); 2.62 (t, J = 8.5 Hz, 2H, CH₂); 2.16 (p, J = 7.3 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ : 174.2 (CO); 138.0 (C_{aro}); 129.4 (C_{aro}); 128.8 (2 C_{aro}); 120.9 (2 C_{aro}); 48.6 (CH₂); 32.6 (CH₂); 17.8 (CH₂).

4-(benzylmethylamino)-*N*-(4-chlorophenyl)butanamide (**13**)

A solution of compound **11** (1.29 mmol) in *N*-benzylmethylamine (7.75 mmol, 1 mL) was stirred at room temperature for 12 hours. A 5 mL amount of hexane was added and the white solid, identified as

disubstitutedamine hydrochloride, was filtered. The filtrate was concentrated and purified by thick layer chromatography (cyclohexane: ethyl acetate: MeOH(NH₃), 4.5:4.5:1 (v/v)) to afford compound **13**. Yield: 70%. IR (cm⁻¹): 1686 (C=O). ¹H NMR (300 MHz, CDCl₃), 9.63 (br s, 1H, NH); 7.45 (d, *J* = 9.1 Hz, 2H, H₂, H₆); 7.34-7.27 (m, 5H, H_{aro}); 7.21 (d, *J* = 9.0 Hz, 2H, H₃, H₅); 3.69 (s, 2H, CH₂); 2.62 (t, *J* = 6.2 Hz, 2H, CH₂); 2.51 (t, *J* = 7.0 Hz, 2H, CH₂); 2.35 (s, 3H, CH₃); 1.96 (p, *J* = 6.1 Hz, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 171.4 (CO); 137.2 (C_{aro}); 135.9 (C_{aro}); 129.7 (2 C_{aro}); 128.8 (2 C_{aro}); 128.7 (2 C_{aro}); 128.5 (2 C_{aro}); 128.0 (C_{aro}); 120.8 (C_{aro}); 62.2 (CH₂); 56.5 (CH₂); 41.4 (CH₃); 36.2 (CH₂); 22.2 (CH₂). LCMS *m/z* calc for [M+H⁺]: 317.1, 319.1; found: 317.2, 319.2. HRMS: calcd for (C₁₈H₂₁ON₂Cl)H⁺: 317.14152; found: 317.14026. HPLC (C₄, 35 min): *t*_R 8.6 min, P_{HPLC} >99%; HPLC (C₁₈, 35 min): *t*_R 20.3 min, P_{HPLC} >99%.

5.2 *In vitro* testing

5.2.1 Assay for binding to sigma receptors

The binding assays were performed by CEREP (Poitiers, France), according to Ganapathy [43]. Rapidly, the S1R binding assay was carried out by incubating Jurkat cell membranes (10-20 mg protein per tube) with [³H](+)-pentazocine (15 nM) and a range of concentrations of test compounds, at 37°C for 2 hours, in 5 mM Tris/HCl buffer (pH = 7.4). The S2R binding assay was performed by incubating Jurkat cell membranes (10-20 mg protein per tube) with [³H]-DTG (25 nM) in the presence of (+)-pentazocine (1 μM) to saturate S1R, and a range of concentrations of test compounds, at room temperature for 1 hour in 5 mM TrisHCl buffer (pH = 7.4). Bound radioactivity was measured using liquid scintillation counting. Nonspecific binding was determined, in both assays, under similar conditions, but in the presence of 10 μM unlabelled haloperidol. Inhibition constants (*K_i*) were calculated from the IC₅₀ values according to the method of Cheng and Prusoff [53].

5.2.2 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 foetal bovine serum (Sigma Aldrich), and grown at 37°C in a humidified incubator with 5% CO₂.

Cells were starved for 24 hours to obtain synchronous cultures, and were then incubated in culture medium that contained various concentrations of test compounds (100, 50, 10, 5, 1, 0.5, 0.1, 0.05 μM), 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.

5.2.3 Physicochemical properties

Standardised ADME experiments were performed by CEREP (Paris, France). Bioavailability-related profile was measured according to Lipinski et al. for aqueous solubility in PBS (pH 7.4, [48]); Sangster et al. [45] for partition coefficient (logD, n-octanol-PBS, pH 7.4) and Kuhnz and Gieschen [49] for metabolic stability (human liver microsomes). The LC/MS system for microsomal stability and metabolites identification consisted of an Orbitrap Exactive instrument (Thermo) equipped with an electrospray ionization source used in positive mode ($M+H^+$). The apparatus was managed with Xcalibur software.

5.2.4 Selectivity profile (agonist and antagonist activities) over a panel of 40 recombinant human receptors

Rapidly, the tests were performed by Euroscreen (www.ogeda.com) with recombinant human G coupled receptor expressing cell lines using aequorin functional assays for serotonin 5-HT_{2A}, 2B, 2C, 3 and 5A, adrenergic alpha_{1a} and 1b, angiotensin AT₁, cholestokinin CCK₁, endothelin ETA, histamine H₁, muscarinic M₁ and 3, neurokinin NK₁ and 2, vasopressin V_{1a} and vasoactive intestinal peptide VPAC₁ receptor analysis [50]. cAMP HTRFTM assays were used to analyse serotonin 5-HT_{1A}, 4E, 6 and 7, adenosine A₁, 2A and 3, adrenergic beta₁ and 2, cannabinoid CB₁, dopamine D₁, histamine H₂ and neuropeptide Y NPY receptors [51]. GTP γ S³⁵ assays were used to analyse serotonin 5-HT_{1B}, adrenergic alpha_{2a} and b, dopamine D_{2L}, muscarinic M₂ and 4, opioid delta, kappa and mu, and somatostatin STT₄ receptor [52].

Agonist and antagonist activities of the test compound are expressed as the percentage of the activity of the reference agonist at its EC₁₀₀ concentration or the percentage of inhibition of the reference agonist activity at its EC₈₀ concentration, respectively.

For the aequorin assays, different cell lines coexpressing the receptors were grown in specific culture media and incubated for 4 hours with coelenterazine h. For agonist testing, cell suspensions were mixed with test or reference agonist in a 96-well plate. For antagonist testing, reference agonist at its EC₈₀ (final concentration) was injected to the mix containing cells and tested compound. The resulting emission of light was recorded using Hamamatsu Functional Drug Screening System 6000 [50].

For the cAMP HTRFTM assays, different cell lines coexpressing the receptors were grown in specific culture media and resuspended in assay buffer. For agonist testing on G_s coupled receptor, the tested compound was added at increasing concentrations. For antagonist testing, the tested compound and the reference agonist at its EC₈₀ (final concentration) were added. For agonist and antagonist testing on G_i coupled receptor, forskolin was added to the reagents listed above. After incubation, cells were lysed and cAMP concentrations were estimated with the HTRF kit, according to the manufacturer specifications [51].

For the GTP γ S scintillation proximity assay, optimized specific conditions were determined for each receptor. Membrane extracts were prepared from different cell lines coexpressing the receptors, mixed with GDP and incubated on ice. For agonist testing, the tested compound or the reference agonist, GDP mix and GTP γ [³⁵S] were added. For antagonist testing, the tested compound or the reference antagonist, the reference agonist at historical EC80, GDP mix and GTP γ [³⁵S] were added. GTP concentrations were estimated with PerkinElmer TopCount reader [52].

5.2 Molecular docking

The compound was built using the ChemBiodraw 3D module and minimized. Docking simulation was then performed into S1R (RCSB Protein Data Bank 5HK2) with the automated GOLD program. The active site was defined around 4-IBP.

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Conflict of Interest:

The authors declare no competing financial interests. All authors have approved the final article.

Authors contribution

Marion Donnier-Marechal : Contributed to the compounds synthesis

Pascal Carato : Contributed to the design of the study and wrote the manuscript

Paul-Emmanuel Larchanché : Contributed to the compounds synthesis

Amélie Barczyk : Contributed to the cytotoxicity assays

Bénédictte Oxombre : Contributed to the analyses of biological data and wrote the manuscript

Patrick Vermersch : Contributed to the design of the study

Patricia Melnyk : Contributed to the design of the study and wrote the manuscript

Reference

NMR and mass spectra of compounds **7a-z**, **8a-h**, **9**, **10** and **13** are available as supplementary data.

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