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Diaryl substituted pyrrolidinones and pyrrolones as 5-HT$_{2C}$ inhibitors: Synthesis and biological evaluation

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Abstract—Within the continuous quest for the discovery of novel compounds able to treat anxiety and depression, the generation of a pharmacophore model for 5-HT$_{2C}$ receptor antagonists and the discovery of a new class of potent and selective 5-HT$_{2C}$ molecules are reported.

During the last decade, one approach of GSK research in CNS drug discovery was aimed at the discovery of novel chemical entities (NCE) able to modulate the serotoninergic neurotransmission. The 5-HT$_2$ receptor family belongs to the seven-membrane-spanning G-protein-coupled receptor superfamily and represents one of the 7 classes of 5-HT receptors.[1] The 5-HT$_2$ receptor family consists of 5-HT$_{2A}$, 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors that share common primary structure, secondary-messenger system and pharmacological profile.[1,2]

The functional role of the different 5-HT$_2$ receptor subtypes however has not been fully elucidated yet due to the limited availability of selective ligands. Several lines of evidence suggest that selective 5-HT$_{2C}$ antagonists may be useful in the treatment of anxiety and depression.[3–5] More recently, published data have suggested that 5-HT$_{2C}$ antagonists may offer interesting therapeutic opportunities for the treatment of schizophrenia,[6] migraine[7] and Parkinson's disease.[8]

GSK showed a long-standing interest in the 5-HT$_{2C}$ receptor and a number of potent different selective templates were disclosed and investigated.[9–12] With the aim to identify additional NCEs and exploiting the data generated over the years in GSK, a pharmacophore model was developed in house and used both to give priority to the synthesis of different chemical classes and as a filter to screen in silico the compound collection.

This manuscript reports a new and potent class of 5-HT$_{2C}$ antagonists, while the in silico screening activities will be described in a separate manuscript.

Pharmacophore modelling was extensively applied as part of an integrated medicinal and computational chemistry strategy aimed at the identification of novel 5-HT$_{2C}$ antagonists.

At this purpose, a small set of representative structures was selected from the wide in house collection to span the available chemical diversity. All compounds included in the study are endowed with a high affinity in a 5-HT$_{2C}$ binding assay (p$K_i > 8.5$),[4] and are at least 100-fold selective towards 5-HT$_{2A/2B}$. In addition, they were assumed to bind at the 5-HT$_{2C}$ receptors with a common binding mode according to the available SAR data for the selected molecules. Representative examples of compounds included in the study are shown below in Table 1.

All pharmacophore modelling work was performed with program Catalyst 4.6.[13] Ligand conformational searches

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Keywords: Serotonin; 5-HT; 5-HT$_{2C}$; 7-TM; Pharmacophore.

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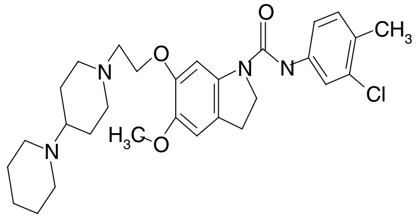
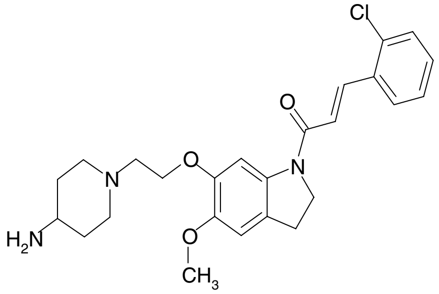
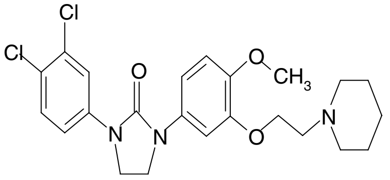
Table 1. Representative compounds included into the pharmacophore modelling exercise

1[9,10]	**2**[11]	**3**[12]
		

were carried out using the BEST routine (max 200 conformations, energy window of 10 Kcal), while common-feature alignments were performed using the HipHop algorithm. Standard catalyst pharmacophore features (H-bond acceptor, positive ionisable, aromatic rings, hydrophobic groups) were selected according to the extensive SAR data available in house for these compound series.

In Figure 1, the best pharmacophore model obtained is shown superimposed to some representative compounds (**3**, **4**, and **5**) included in the study.

As can be seen from the above figure, the pharmacophore model consists of a positive ionisable group (red sphere), which is mapped by the basic nitrogen on the piperidine side chain of compound **3**, a H-bond acceptor (green spheres), mapped by the carbonyl oxygen on the cyclic urea moiety of compound **3**, an aromatic ring (yellow sphere) and 3 hydrophobic groups (cyan spheres). The pharmacophore was validated by means of SARs derived from data available in house, and with the synthesis and testing of a small set of ad hoc compounds (data not shown). As a result of that, it was demonstrated the key role played in particular by both the positive ionisable group and the H-bond acceptor functionality to achieve high 5-HT_{2C} affinity. A second H-bond acceptor functionality, mapped by the ether oxygen on the piperidine side chain of compound **3**, was instead discarded as it is irrelevant in determining the high 5-HT_{2C} affinity.

Considering the wealth of data available and the chemical diversity of the 5-HT_{2C} antagonists available, new chemical templates were rationally designed and evaluated for chemical feasibility. Subsequently, to give the appropriate priority to the synthesis of the possible NCEs, the above-described pharmacophore model was used as a sieve and the best fitting compounds were given a higher priority in the synthetic activities.

The appropriately decorated lactamic scaffolds (**6**, **7**, **8**, **9** and Fig. 2) resulted among the top scorers in terms of fitting to the pharmacophore model as exemplified by the fitting of compound **7a** in Figure 3.

Accordingly, a synthetic strategy was devised for the preparation of both series as outlined in Scheme 1.[14] The alkylation of appropriately substituted phenyl acetic acid was performed by generating the bis anion with 2 mol of lithium HMDSA and with the subsequent quench with allyl iodide. In the next step, the corresponding acid chlorides were prepared with oxalyl chloride and reacted with suitably decorated anilines.

Treatment with $NaIO_4$ and OsO_4 afforded immediately the ring closure to give the 5-hydroxy-1,3-diphenyl-2-pyrrolidinone **16**, a key intermediate to obtain either

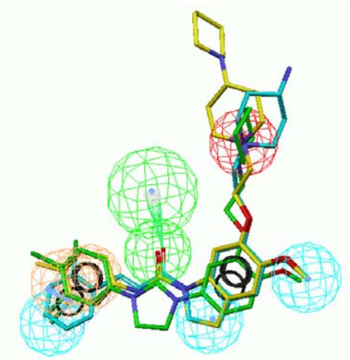


Figure 1. Pharmacophore model for the 5-HT_{2C} ligands. Colour coding of pharmacophoric features: green, H-bond acceptor; red, positive ionisable; cyan, hydrophobic; yellow, aromatic ring.

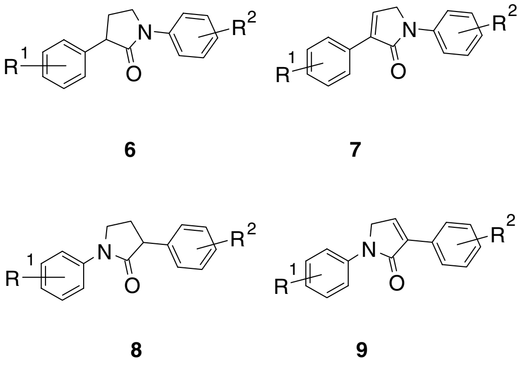


Figure 2. The newly designed 5-HT_{2C} antagonists.

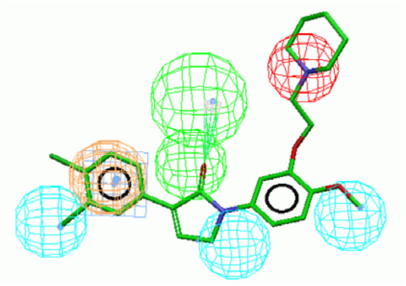
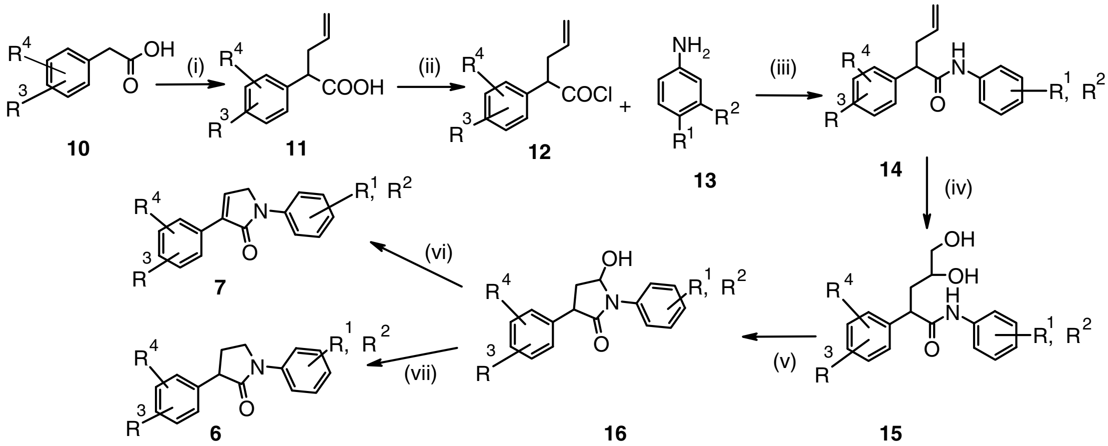


Figure 3. Compound **7a** superimposed to the 5-HT_{2C} pharmacophore.

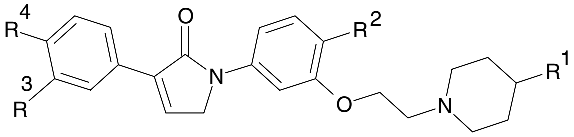
lactams series. The unsaturated lactams **7** were obtained dissolving compounds **16** in neat TFA, while the saturated lactams **6** were isolated when the reaction was performed in presence of Et_3SiH. Biological data for the unsaturated lactams **7** are reported in Table 2 and confirm the working hypothesis.

The key features of the selective 5-HT_{2C} pharmacophore are clearly conserved and this confers high selectivity to all the compounds reported below. Considering compound **7a** as an example of the lactam class, no affinity



Scheme 1. Reagents and conditions: (i) LiHMDS 1 M in THF, allyl iodide, THF, −78 to 0 °C, 78%; (ii) $(COCl)_2$, CH_2Cl_2, DMF (cat.), 0 °C (15 min) to rt, 18 h; (iii) TEA, CH_2Cl_2, 0 °C to rt, 5 h, 84–57%; (iv) OsO_4 (4 wt % soln in H_2O), 4-methyl-morpholine *N*-oxide, acetone/H_2O 8:1, rt, 5 h; (v) $NaIO_4$, THF/H_2O, rt, 2 h, 62% two steps; (vi) TFA, rt, 8 h, 56%; (vii) Et_3SiH, TFA, CH_2Cl_2, 63%.

Table 2. Affinity results associated with class **7**



Compound	R^1	R^2	R^3	R^4	pK_i		
					5-HT_{2C}	5-HT_{2A}	5-HT_{2B}
7a	H	OCH_3	Cl	Cl	9.1	6.2	6.2
7b	H	Cl	Cl	Cl	7.2	<5.9	<5.8
7c	H	OCF_3	Cl	Cl	<5.9	<5.0	<5.5
7d	H	NHAc	Cl	Cl	7.3	<5.8	<5.8
7e	H	CH_3	Cl	Cl	6.9	<5.9	<5.7
7f	H	Pyrrolidine	Cl	Cl	6.7	<5.9	<5
7g	H	OCH_3	F	H	9.1	6.2	6.3
7h	H	OCH_3	CF_3	H	8.3	6.1	<6.1
7i	H	OCH_3	H	F	8.2	6.4	6.0
7j	H	OCH_3	H	CF_3	7.9	<5.9	<6.0
7k	H	OCH_3	H	CH_3	9.5	<6.0	<6.0
7l	H	OCH_3	H	Br	8.9	6.8	6.7
7m	Me	OCH_3	Cl	H	8.3	6.1	6.3
7n	Me	OCH_3	H	Cl	8.2	6.2	<5.8
7o	Me	OCH_3	F	Cl	8.1	<5.9	<5.7
7p	Me	OCH_3	H	F	8.5	6.6	5.9
7q	Me	OCH_3	H	CH_3	8.8	6.2	5.8
7r	Me	OCH_3	H	CF_3	7.9	5.8	<5.0
7s	Me	OCH_3	H	Br	8.4	6.4	<6.2
7t	H	OCH_3	Cl	H	8.6	6.2	6.2
7u	H	OCH_3	H	Cl	8.1	6.0	<5.8

(pK_i < 5.5) was detected on 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_6$ and 5-HT$_7$ receptors. No affinity was also detected on Adr. β$_2$ or DA D$_2$ receptors, while poor affinity was observed for DA D$_3$ (pK_i = 6.34) and Adr. α$_1$ (pK_i = 5.74) receptors.

The different decoration of the scaffold, however, leads to different values in potency. From the exploration, it resulted quite clear that a methoxy group was favoured in position R^2, probably contributing to some specific interaction within the receptor (es **7a**). Actually, its replacement with a trifluoromethoxy group (**7c**) led to a completely inactive compound. The replacement with a neutral group (Me, **7e**) or with an electron-withdrawing group (Cl, **7b**) led to a significative decrease of potency. The introduction of the acetamido group (NHAc, **7d**) where a possible H-bonding acceptor is still present but in a slightly different position still leads to almost 100-fold less potent compound.

The above-reported drop of potency is consistent with the decrease of electron-donating power of the substituents in agreement with the Swain–Lupton parameters, as shown in Figure 4. A clear trend can actually be observed between pK_i on 5-HT$_{2C}$ receptor and Swain and Lupton *R* parameter,[15,16] a measure of the electron donor resonance effect of substituents. Affinity towards 5-HT$_{2C}$ receptor increases as *R* decreases, that is, as the electron donor resonance effect of the substituents increases.

Exploration of the left-handside aromatic portion was well tolerated with respect to the potency and in particular led to very potent and selective compounds (entries **7g** and **7k**).

Nonetheless, the potency of a compound is not the only important factor which leads a medicinal chemistry exploration as other parameters are very important in achieving a drug-like profile in a NCE.

Considering the pharmacokinetic (PK)[17] properties of this class of lactams, it resulted quite clear that the exploration was going in the right direction for a possible CNS drug. Compound **7a**, the starting point, was endowed with a good brain/blood ratio of 3.9 and acceptable bioavailability in rats after oral administration (*F* = 11%), even if this was probably affected by a moderately high plasmatic clearance (59 ml/min/kg). As the exploration was further detailed, it resulted quite evident that the di-chloro substitution pattern on the LH-aromatic moiety proved to be the best compromise in terms of potency and metabolic stability.

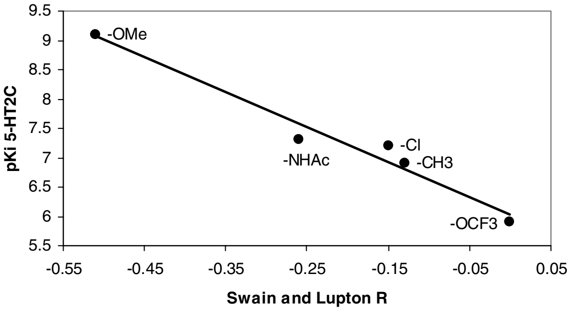
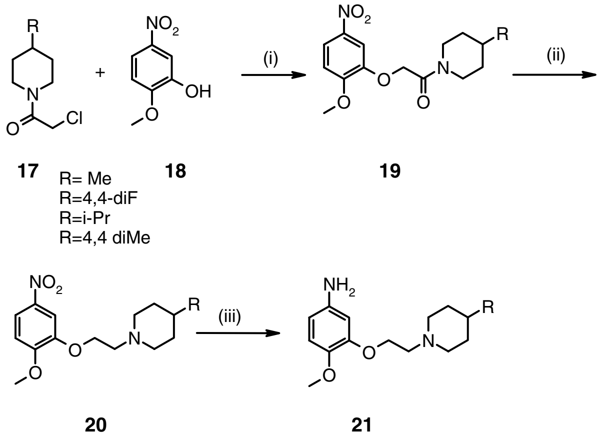


Figure 4. Trend between 5-HT$_{2C}$ pK_i and Swain and Lupton *R* parameter.[15,16]

Unfortunately, some of the selected RH resulted in moderate to high blood clearance suggesting a possible metabolic way of degradation of the scaffold. Accordingly, to match the potency with the appropriate PK parameters, a number of aniline intermediates were prepared according to the Scheme 2 below reported, where alkylation of the phenol **18** with substituted 1-(chloroacetyl)piperidines (or other amides) was followed by reduction of the amide with boranes and completed with the catalytic hydrogenation of the nitro group.

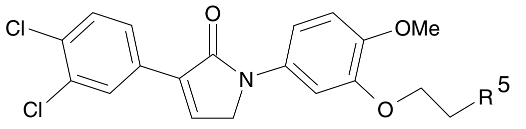
The results of this exploration are reported in Table 3. The piperidine (**7a**) was clearly the best substituent as far as potency was concerned because all the modifications led to slightly less potent compounds.

On the other hand, when considering the overall profile of the molecule, including its PK properties, the intro-



Scheme 2. Reagents and conditions: (i) K_2CO_3, DMF, rt, 58–64%; (ii) BH_3, THF, reflux, then HCl 6N, 80 °C; (iii) Pd/C (10% Pd) (cat), CH_3OH, rt, H_2, 1 atm.

Table 3. Affinity values for the class **7** where the right-hand-side chain was modified



Compound	R^5	pK_i		
		5-HT$_{2C}$	5-HT$_{2A}$	5-HT$_{2B}$
7a	Piperidine	9.1	6.2	6.2
7v	Morpholine	8.2	5.4	<5.8
7w	Pyrrolidine	8.4	6.2	<5.8
7x	4,4-DiF-piperidine	8.1	<5.3	<5.3
7y	4-Me-Piperidine	8.5	6.1	<6.1
7z	4,4-DiMe-piperidine	8.4	<5.2	6.5
7aa	4-*i*-Pr-piperidine	7.9	<6.1	<6.0

duction of a group on the position 4 of the piperidine (e.g., **7y**) led to significative achievements. The slightly reduced potency was actually matched with a reduced plasma clearance in rat, leading to higher bioavailability and to a more balanced profile as reported in Table 4.

A further step in the investigation of the unsaturated lactams was related to the presence of the double bond which was decorated as reported in Figure 5. As clearly reported in Table 5, the introduction of the methyl group on the double bond brings to a slightly reduced potency at the receptor, with a complete abolishment of the 5-HT$_{2A}$ and 5-HT$_{2B}$ activity for compound **22**. On the other hand, the PK profile was superimposable with the unsubstituted system, and no further reduction of the plasmatic clearance was achieved with the introduction of the gem dimethyl group which was extremely detrimental to the desired pharmacological activity (**22b** and **22c**).

As far as the saturated lactams **6** are concerned, it can clearly be appreciated by Table 6, that the potency on the desired target was not as good as the previously described class. Moreover, when analyzed from the PK point of view, a clear reduction of bioavailability was observed.

Through studies of metabolite ID, it was possible to clearly relate this to a specific metabolic pathway associated to the hydroxylation of the saturated lactam.

As illustrated in Table 7, the introduction of a α methyl group was neutral in terms of pK_i; nonetheless, the working hypothesis was proved as compound **24** showed a dramatic increase in bioavailability. Finally, to fully complete the exploration, the corresponding 'inverted' lactams were prepared like in Scheme 1, but inverting the acidic moieties with the anilines.

As reported in Tables 8 and 9, compounds belonging to these classes were endowed with similar, but not 'superimposable' profiles when compared with their counterparts **6** and **7**, showing a reduced affinity and a comparable PK profile. This might probably be linked to some specific key interactions within the receptor; currently both receptor modelling studies as well as SDM studies are in progress to fully evaluate this point.

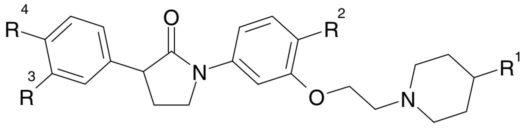
Table 4. Head to head PK comparison between compounds **7y** and **7a**

	7y	7a
Clp (ml/min/kg)	11	59
V_{dss} (L)	4.0	10.7
$T_{1/2}$ (h)	4.5	2.8
F (%)	52	11
B/P	7.2	3.9
Brain concn 5′ (ng/g)	1058	320

Table 5. Affinity data for substituted lactams

Compound	R^1	R^2	pK_i		
			5-HT$_{2C}$	5-HT$_{2A}$	5-HT$_{2B}$
22	Cl	H	8.1	<6.2	<6.4
22a	H	H	8.0	5.9	<6.0
22b	Cl	CH$_3$	6.4	<6.1	<6.1
22c	H	CH$_3$	<5.8	<5.9	<5.1

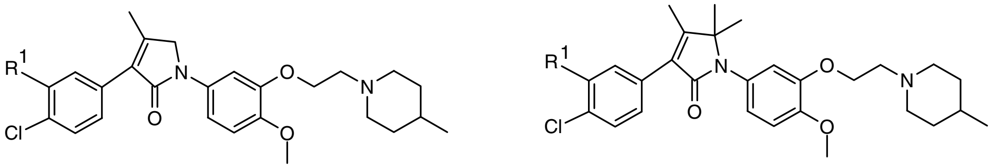
Table 6. Affinity data for the saturated lactams class 6



Compound	R^1	R^2	R^3	R^4	pK_i		
					5-HT$_{2C}$	5-HT$_{2A}$	5-HT$_{2B}$
6a	H	OCH$_3$	Cl	Cl	7.9	6.3	5.8
6b	H	Cl	Cl	Cl	7.0	<6.0	<5.8
6c	CH$_3$	OCH$_3$	Cl	Cl	7.9	6.4	5.7
6d	H	OCF$_3$	Cl	Cl	6.1	5.5	5.8
6e	H	NHAc	Cl	Cl	6.5	<5.5	<5.8
6f	H	OCH$_3$	Cl	H	7.6	<6.0	<6.0
6g	H	OCH$_3$	H	F	7.0	<5.6	<5.3
6h	H	CH$_3$	Cl	Cl	6.4	<5.8	<5.8
6i	DiCH$_3$	OCH$_3$	Cl	Cl	7.9	6.4	<6.0
6j	*i*-Pr	OCH$_3$	Cl	Cl	7.6	6.4	<6.0
6k	H	OCH$_3$	F	H	7.0	<5.1	<5.8

A pharmacophore model was generated to predict antagonist recognition site on the 5-HT$_{2C}$ receptor.

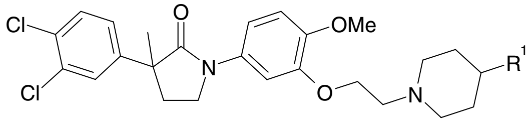
New scaffolds were filtered through this newly designed tool and ranked according to the overall quality of their fitting. The synthesis of the best fitting compounds led to the identification of a new class of potent and selective 5-HT$_{2C}$ antagonists. In particular, compound **7y** represented the best compromise between the potency/selectivity and the PK properties. This compound has nanomolar affinity for the 5-HT$_{2C}$ receptor. Its PK profile is encouraging to allow future tests in different models of anxiety and depression. Finally, further classes were identified through the screening of the corporate database using the pharmacophore model and will the subject of further communications in due time.



22, 22a **22b, 22c**

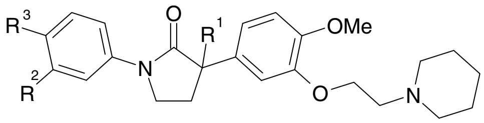
Figure 5. Substituted double bond derivatives.

Table 7. Affinity data for the α substituted saturated lactams



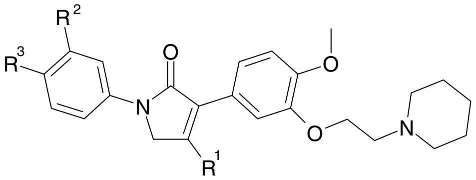
Compound	R^1	pK_i			F (%)	B/P	Cl (ml/min/kg)
		$5\text{-}HT_{2C}$	$5\text{-}HT_{2A}$	$5\text{-}HT_{2B}$			
23	H	8.3	6.2	6.0	13	5	65
24	CH_3	8.3	<6.3	<6.1	50	1.8	20

Table 8. Affinity data for the inverted saturated lactams class **8**



Compound	R^1	R^2	R^3	pK_i		
				$5\text{-}HT_{2C}$	$5\text{-}HT_{2A}$	$5\text{-}HT_{2B}$
8a	H	H	OCH_3	7.0	<5.0	<5.0
8b	H	Cl	OCH_3	7.7	<5.7	5.8
8c	H	F	OCH_3	7.8	<6.0	<5.8
8d	H	Cl	Cl	8.0	6.1	6.4
8e	CH_3	Cl	Cl	8.0	6.3	<6.3
8f	H	F	H	7.7	<5.9	<6.1

Table 9. Affinity data for the inverted unsaturated lactams class **9**



Compound	R^1	R^2	R^3	pK_i		
				$5\text{-}HT_{2C}$	$5\text{-}HT_{2A}$	$5\text{-}HT_{2B}$
9a	H	Cl	Cl	8.3	5.9	6.9
9b	H	H	OCH_3	8.0	<5.3	<5.7
9c	H	Cl	OCH_3	8.3	<5.2	<6.4
9d	H	F	OCH_3	8.2	<5.5	<5.8
9e	H	F	H	8.2	6.0	6.3
9f	CH_3	H	Cl	6.7	6.4	6.3
9g	CH_3	Cl	Cl	6.9	6.3	6.7

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bmcl.2006.05.034.

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