Derivatives of N-[2-(dimethylamine)ethyl]-N-(2-phenylethyl) aniline as potential polypharmacological ligands of SERT/5-HT$_6$/5-HT$_7$

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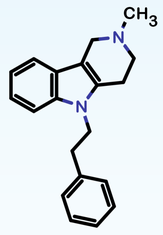
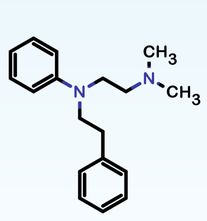
Concept

- Presented series of compounds emerged from a bioisostere **2** genereated on a known 5-HT$_6$/5-HT$_7$ ligand **1**.
- The bioisostere generation protocol utilized two programs: Pipeline Pilot (Accelrys) and vBrood (OpenEye).
- In total 2 965 bioisisteres were obtained out of which one (**2**) was selected for synthesis.

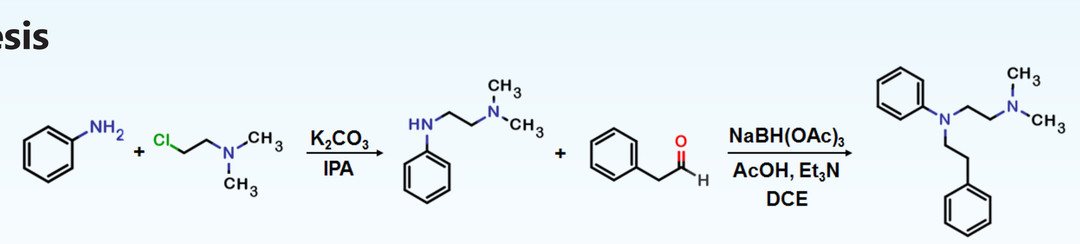


1

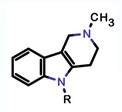
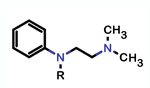
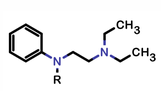
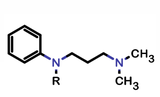
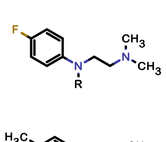
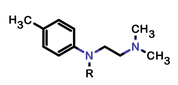
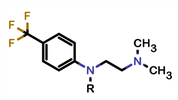
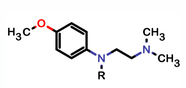
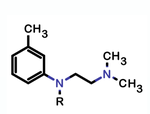
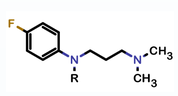
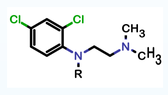


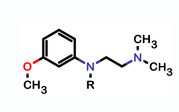
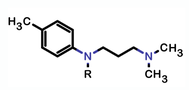
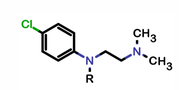
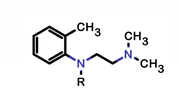
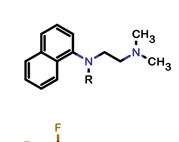
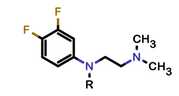
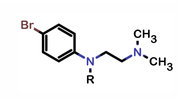
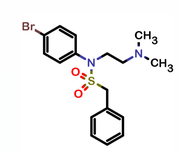
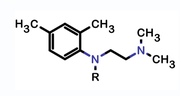
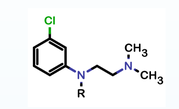
2

Synthesis



Compounds

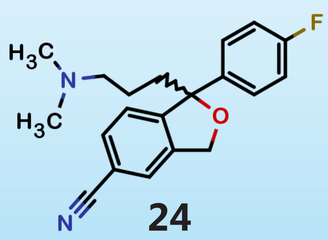
No.	Structure R =	K_i [nM] 5-HT$_6$	5-HT$_7$	5-HT$_{1A}$	5-HT$_{2A}$	D$_2$
1		**22**	**8**	217	N.D.	77
2		**63**	**121**	1682	N.D.	476
3		**51**	**205**	7614	N.D.	266
4		**67**	**623**	4486	N.D.	55
5		**23**	**31**	5707	58	37
6		**25**	**10**	482	70	33
7		**61**	**30**	5341	809	274
8		**234**	**141**	46010	863	1147
9		**264**	**2253**	605	777	N.D.
10		**38**	**38**	8969	27	80
11		**64**	**748**	44480	312	594
12		**597**	**387**	46560	472	1176

No.	Structure R =	K_i [nM] 5-HT$_6$	5-HT$_7$	5-HT$_{1A}$	5-HT$_{2A}$	D$_2$
13		**355**	**4512**	27040	721	1738
14		**83**	**24**	2140	204	108
15		**24**	**4**	5960	212	N.D.
16		**380**	**1040**	48770	348	N.D.
17		**137**	**2037**	4749	621	N.D.
18		**21**	**114**	41880	79	N.D.
19		**90**	**19**	N.D.	265	505
20		**4901**	**2369**	N.D.	359	25400
21		**79**	**10**	N.D.	372	691
22		**347**	**597**	N.D.	518	1751
23		**150**	**353**	N.D.	311	675

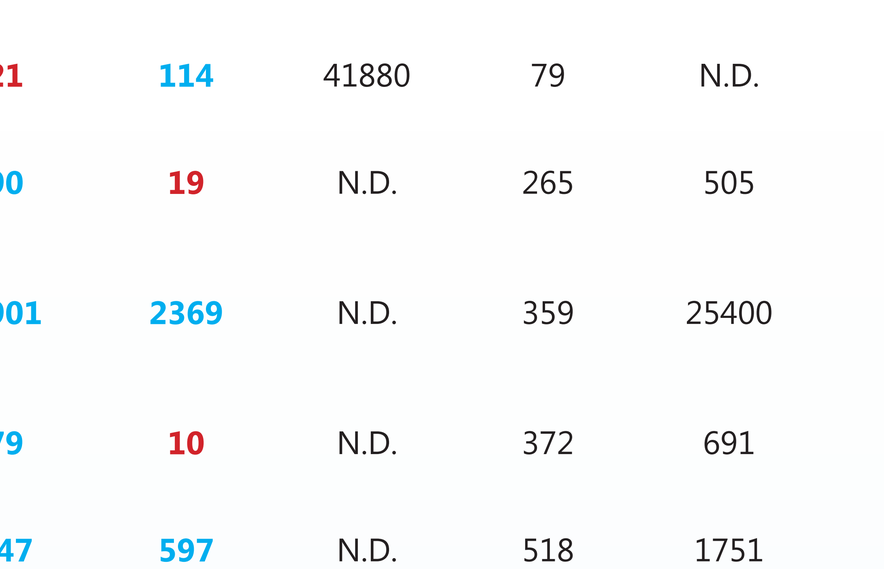
From the obtained series of compounds special attention should be paid to: **5**, **15**, **19** and **21**. These compounds possess different halogen atoms at 4 position of aniline ring - F, Cl, Br and I respectively, with chlorine derivative being the most active both at 5-HT$_6$ and 5-HT$_7$ receptors. Similar affinity values were obtained for compound **6** with methyl group at 4 position of aniline ring, but at the cost of reduced selectivity for 5-HT$_{1A}$ and 5-HT$_{2A}$.

Molecular modelling

Docking of the synthesized structures together with known SERT ligand revealed their similar orientation in the SERT binding pocket (binding poses of **12** together with Citalopram (**24**) presented on the right).



24



Conclusions

It was found that several compounds possess high affinity for 5-HT$_6$ and 5-HT$_7$ receptors. This outcome, together with promising results of molecular modelling studies, suggest their potential as polipharmacological ligands acting at 5-HT$_6$, 5-HT$_7$ receptors and SERT.

Acknowledgments

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