Molecular modeling explains differences in binding affinity of new potent and selective 5-HT$_{1A}$ ligands arylpiperazinylalkylthiobenzoxazole derivatives

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INTRODUCTION

The 5-HT$_{1A}$ serotonin receptor subtype is one of the most studied serotonin receptors and it is generally accepted to be involved, among others, in anxiety and depression.

Long-chain arylpiperazines (LCAP) represent one of the most important classes of 5-HT$_{1A}$R ligands.

A series of new compounds (full or partial 5-HT$_{1A}$ agonists) containing a benzimidazole, benzothiazole, or benzoxazole nucleus bridged to an arylpiperazine by different thioalkyl chains was prepared [1]. They were tested in radioligand binding experiments to evaluate their affinity for 5-HT$_{1A}$ and 5-HT$_{2A}$ serotonergic, $_1$ adrenergic, D1, and D2 dopaminergic receptors [1]. Many of tested compounds showed an interesting binding profile; in particular 36 displayed very high 5-HT$_{1A}$ receptor affinity (Table 1) and selectivity over all the other investigated receptors (data not shown).

Here we present the results of molecular modeling study conducted to rationalize the differences in 5-HT$_{1A}$ receptor binding affinity of benzoxazole derivatives bridged to an arylpiperazine by the thioalkyl spacers of different length.

RESULTS

Apart from principal interactions coming from pharmacophoric arylpiperazine fragment, benzoxazole moiety of 24, 36, and 38 formed H-bonds with Tyr7.43 and/or Asn7.39. Additionally, for the best binder in the group (36), a remarkable - stacking with Phe3.28 was observed (Figure 1C). This last finding could be considered as possible explanation of outstandingly high affinity of this compound. The most visible difference in K_i values characterized compound 18 that was at least 100-fold less active than the others. In the top-scored docking solution for this compound only weak H-bond interaction was present between Tyr7.43 and thioether fragment of the spacer (Figure 1C). In certain number of solutions H-bonds between benzoxazole moiety of 18 and residues on helix 7 were formed (results not shown), but at the cost of weakening interactions from arylpiperazine part. On the other hand, when this pharmacophoric portion of 18 occupied more optimal position (common for the remaining compounds) as it was found, e.g. for the best receptor model 82, benzoxazole fragment has lost its specific interactions with helix 7 and pointed towards the exterior of the binding site (Figures 1A and 2).

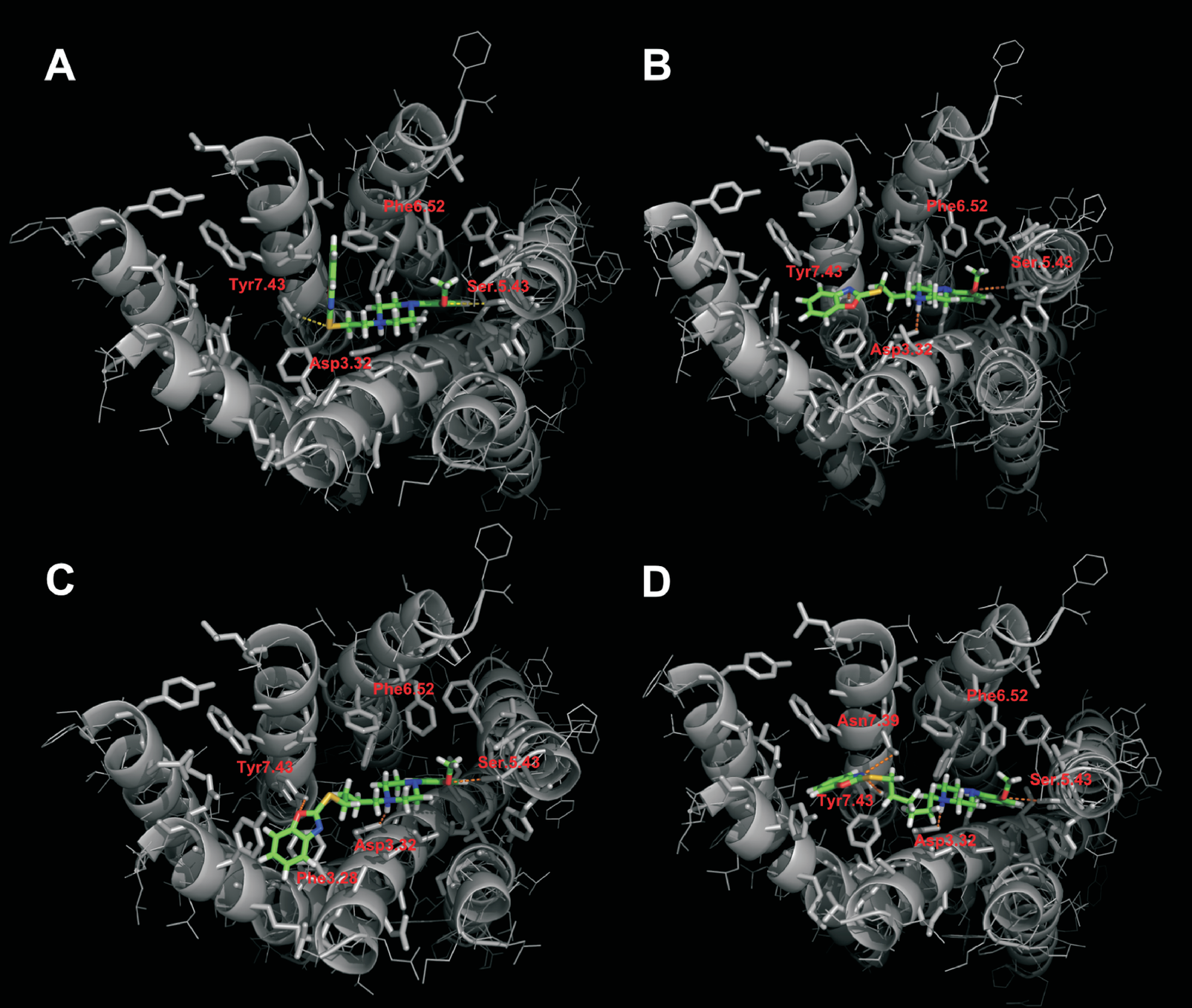

Fig. 1. Top scored ligand-receptor complexes for compounds studied by means of ligand-receptor docking. A: 18; B: 24; C: 36; D: 38. Helical bundle is presented from the extracellular side. Sticks representation depicts residues used as "active site" in FlexX docking. Amino acids forming specific interactions with ligands were labelled. Dashed yellow line shows H-bonding.

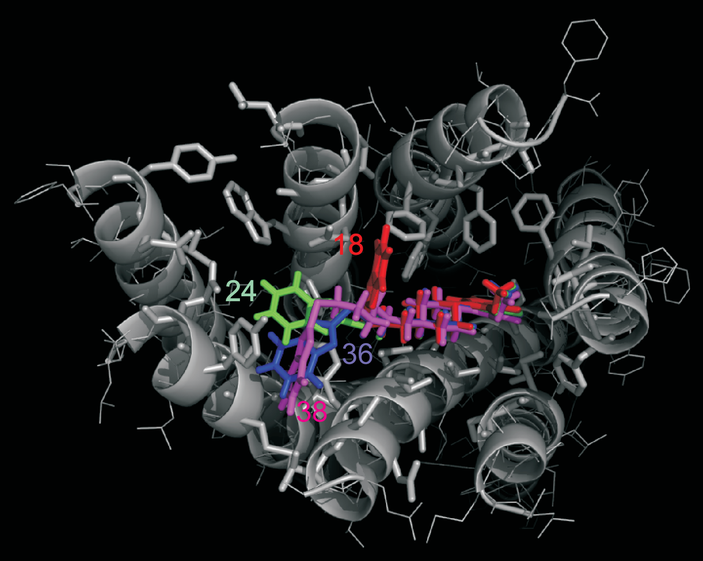

Fig.2 . The best receptor model (no 82) with top scored poses of all four ligands. Arylpiperazine part was constrained to interact with Phe6.62, Ser5.43, and Asp3.32.

Table 1. 5-HT$_{1A}$R experimental binding affinity; PMF score for (a) the top solutions of the entire set of receptor models and for (b) the receptor model 82 [a].

Compd	K_i 5-HT$_{1A}$ (nM)	Top solution		Receptor model no 82[a]	
		PMF score	Receptor model no.	PMF score	Rank[b]
18	67.22	-85.8	82	-85.8	1
24	0.55	-106.2	67	-106.0	3
36	0.094	-110.9	82	-110.9	1
38	0.52	-111.0	23	-102.5	28

[a] The best receptor model identified according to the lowest value of summed PMF

Among all the docked poses the extended conformations predominated, and no folded arrangements were found. For the 3-unit spacer compound, however, a partly bent (hockey stick-like) conformations were also observed, since even one torsion angle in synclinal position caused such shape of a molecule. It has to be stressed that in all the best-scored complexes, the analyzed molecules existed in extended conformations (Figure 1) what is in general agreement with NMR experimental data as well as with results of conformational analysis (results not shown on poster, presented in [1]).

REFERENCES

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