Drug Design of molecules binding to the 5-HT receptor using a Bioisosteric approach

Maria Schembri, Claire Shoemake, Lilian Azzopardi
Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida, Malta
email: maria.r.schembri.08@um.edu.mt

Department of Pharmacy

University of Malta

INTRODUCTION

A strategy used to improve a lead compound is based on the concept of bioisosterism. In bioisosterism, the properties of a compound are fine-tuned by the replacement of some groups or fragments in a molecule, without affecting its overall biological activity.[1]

AIMS

- To design molecules binding to the 5-HT receptor using a bioisosteric approach.
- To compare the affinity of the generated bioisosteres to the affinity of the endogenous ligands.

METHOD

- Three Tricyclic Antidepressants (TCAs—amitriptyline, imipramine and clomipramine) and three Selective Serotonin Reuptake Inhibitors (SSRIs—fluoxetine, paroxetine and sertraline) were selected. Molecular modelling of these structures was carried out in SYBYL-X®1.2[2]
- The Structure Activity Relationships (SARs) of each selected molecule were identified from the literature to identify which moieties on these molecules were crucial for binding and for eliciting biological activity.
- Using Spark®V10[3] software and its molecular databases, 4 different fragments were selected to generate novel ligands which are bioisosteric to the original molecules. The top 5 bioisosteres that had the highest BIF (Bio-Isostere Factor) were chosen for each of the 4 fragments. This process was repeated for every SSRI and TCA molecule.
- The ligand binding affinity (p*Kd*) of the bioisosteric structures for the cognate target receptor was measured in Score®[5] and compared to that of the template structure.

Results

Rank	Structure	BIF%	Score	Field Score	Shape Score	MW	SlogP	Rof5	Unstable	Frag ID
1		82	0.978	0.961	0.994	374	5.1	1	false	224
2		80	0.975	0.968	0.983	327	4.7	0	false	289
3		75	0.969	0.976	0.962	341	4.7	0	true	77827
4		75	0.969	0.98	0.957	335	5	0	false	686
5		72	0.965	0.933	0.996	330	5	0	false	343
6		71	0.964	0.977	0.951	337	5.2	1	false	497

Table 1: Top bioisosteric results generated by Spark® when changing a specific fragment.

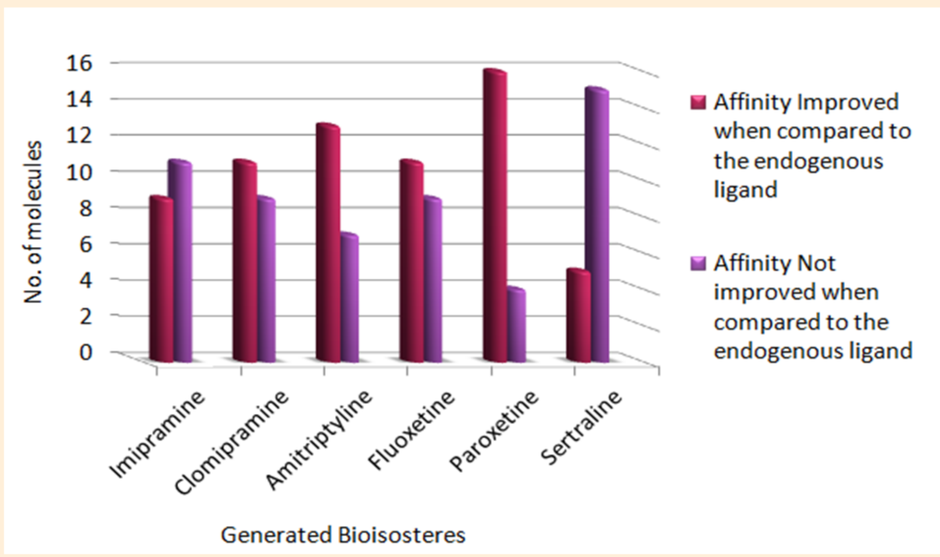
RESULTS

A total of 120 designed bioisosteric molecules were imported to Score® for their affinity to be measured. Table 2 shows the results obtained for one of the fluoxetine fragments. The column showing 'Predicted average –log(kd)' shows the average affinity of the endogenous ligand and its corresponding five bioisosteres. As shown, the endogenous fluoxetine ligand had an average affinity of 5.79 and its bioisosteres show an improved affinity with the highest affinity reaching 6.03.

Rank	Chemical Formula	BIF%	HPScore -log(kd)	HMScore -log(kd)	HSScore -log(kd)	Predicted average -log(kd)	Predicted binding energy kcal/mol
Endogenous ligand	C17H18F3NO	100	5.82	6.06	5.50	5.79	-7.90
1	C16H15NOF3BR	82	5.82	6.38	5.61	5.93	-8.90
2	C17H17N0F4	80	5.81	6.02	5.45	5.76	-7.86
4	C19H20NOF3	75	5.92	6.09	5.82	5.94	-8.10
5	C16H15NOF3Cl	72	5.81	6.25	5.57	5.88	-8.02
6	C19H22N0F3	71	5.90	6.36	5.85	6.03	-8.23

Table 2: A comparison of the affinities of the endogenous ligand and of the generated bioisosteres generated by Score®.

Out of the 120 bioisosteres generated, 65 of the molecules show an improved affinity when compared to their endogenous ligand. The graph below deliniates that clomipramine, amitriptyline, fluoxetine and paroxetine have the highest number of bioisosteres with improved affinities, with paroxetine having 16 out of the 20 molecules with improved binding affinity to the receptor.



Graph 1: A graph of improved affinities for each molecule.

CONCLUSION

The results show that when a bioisosteric approach is used, properties such as the affinity of the ligand binding to the receptor are refined. Further studies can be carried out using other strategies such as *de novo* drug design where analysis of the improvement in affinites of the new ligands designed *de novo* can be made.

REFERENCES

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