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DESIGN, PRELIMINARY QSAR STUDY AND DRUG-LIKENESS SCORE OF ISOBENZOFURAN ANALOGUES

C. IYYAPPAN[1], C. PRAVEEN[2], K. HEMALATHA[1] AND K. GIRIJA*[1]

[1]Department of Pharmaceutical Chemistry, Mother Theresa Post Graduate and Research Institute of Health Sciences, (A Govt. of Puducherry Institution), Puducherry, India.
[2]Organic Chemistry division, Central Leather Research Institute, Chennai, India.

Corresponding author girijanarashimhan66@gmail.com

ABSTRACT

In order to create novel antidepressants without oxidative tissue damage, less side effects and good bioavailability, structurally simple selective serotonin reuptake inhibitors with a isobenzofuran skeleton were designed based on the SAR of the target molecule - Citalopram and Talopram. As a result, designed molecules obey the Lipinski rule of 5 and also give moderate to good druglikness score.

KEY WORD

Isobenzofuran, Ligand based drug design, Selective Serotonin Reuptake Inhibitor, Citalopram, Talopram, Druglikeness,

INTRODUCTION

We are living in an era of computer where everything is measured in terms of bits. Drugs have become an essential thing in our life. The conventional way of synthesizing drugs is a tedious process. It consumes several years, huge man power, and several dollars to come up with single effective drug. It can be done efficiently with the help of computers (*in silico*).
Drugs can be designed computationally by using two strategies:

1. Structure or target based drug designing (SBDD).
2. Analogue or ligand based drug designing (LBDD).

In the method (1), the structure of the receptor or the target is known. From the knowledger of the active sites and site points in the receptor, ligands are designed, whereas in the case of method (2), there is no knowledge of the receptor or the target, drugs can be designed in this case with the help of the geometry of already known ligands. This is particularly useful in the case of protein targets which are not crystallizable and for which the 3D structure is unknown.

DEPRESSION AND ANTIDEPRESSANTS

Depression, according to the WHO, is projected to be the second largest global health problem by 2010[1]. Already, depression is the leading cause of disability measured as years lived with disease. Pharmacological treatment of depression still suffers from

- Latency periods of 3-4 weeks,

- A high percentage of non responding patients, and
- An ensemble of side effects,[2]

all warranting research in the design of novel antidepressant medicine. Rational design of more effective drugs, however, is currently impeded by the minimal understanding of the molecular basis of affinity and selectivity.

The serotonin transporter (SERT) and the norepinephrine transporter (NET) are integral membrane proteins that facilitate the reuptake of the neurotransmitters 5-hydroxytryptamine (5-HT, serotonin) and norepinephrine (NE), respectively, from the extracellular space into neurons[3]. SERT and NET are important drug targets for treatment of psychiatric diseases such as depression and anxiety[4]. In particular, the development of selective serotonin reuptake inhibitors (SSRIs) and combined serotonin/norepinephrine reuptake inhibitors (SNRIs) has resulted in important drugs used in the treatment of depression.

In the search for novel antidepressants, the ring structure from tricyclic antidepressants (TCAs) was replace by bicyclic ring structures (e.g., indanes, indenes, and phtalanes) at H. Lundbeck A/S (Valby, Denmark) in the 1960s [5, 6]. The phenyl substituted phtalanes were found to be the most potent antidepressant especially citalopram[7].

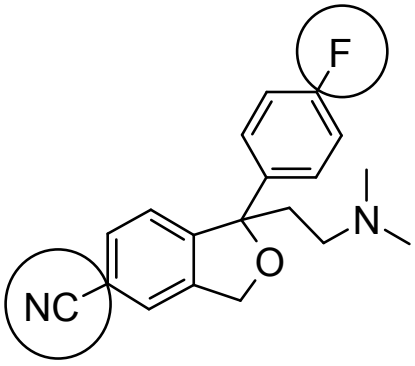
SAR OF TARGET MOLECULE (CITALOPRAM & TALOPRAM)

The development of a drug is a costly and time-consuming process. It is therefore of greater importance to have satisfactory tools and models as a basis for drug design and development. Structure activity relationships (SAR) are a major component in the drug development process.

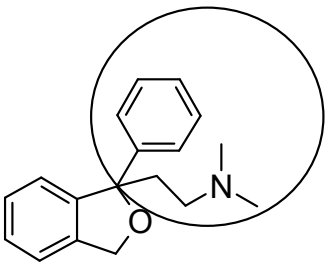
Citalopram & Talopram, these two compounds are structurally close related. They have very distinct pharmacological profiles. Citalopram is a potent, selective inhibitor of SERT[8] hereas talopram is a potent, selective inhibitor of NET [5, 9]. The two compounds have the same phenyl substituted phthalane skeleton, as well as a propylamine moiety, and they differ in four positions only.

Citalopram has two aromatic substituents, a fluorine and a cyano group, whereas talopram has no aromatic substituents. On the other hand, talopram has two methyl substituents on the dihydro-isobenzofuran moiety while citalopram has no substituents in that position.

In a SAR study of citalopram and talopram analogues it was demonstrated that the aromatic substituents and the substituents on the dihydro isobenzofuran moiety were important for inhibitory activity at SERT[7] and inhibitory activity at NET respectively.



Citalopram (1)



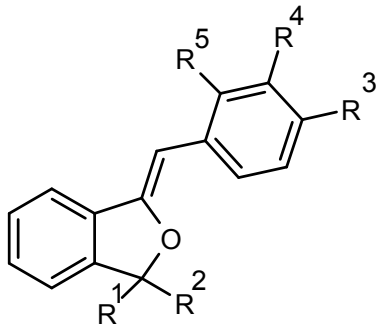
Talopram (2)

DESIGNING OF ANTI-DEPRESSANTS – TARGET BASED DRUG DESIGN

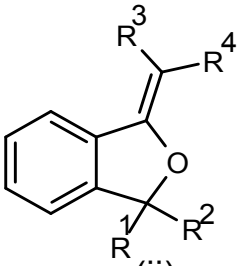
From the SAR studies of Citalopram and Talopram the aromatic substituents and the substituents on the dihydro isobenzofuran moiety are responsible for selective serotonin reuptake inhibitory & selective norepinephrine receptor reuptake inhibitory actions respectively.

Based on these results we planed to design some novel isobenzofuran derivatives have both aromatic substituents as well as substituent on dihydro isobenzofuran moiety.

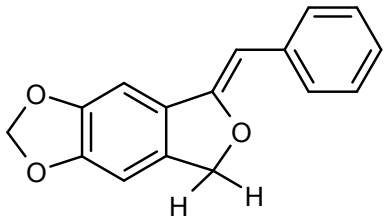
We have designed three different isobenzofuran scaffolds (i, ii, iii) with some modification of substituents.



(i)



(ii)

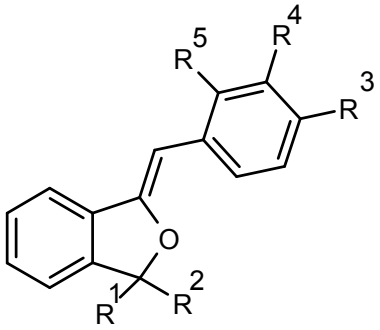


(iii) - 3a

Table: 1
Designed Molecules containing Isobenzofuran Scaffold (i)

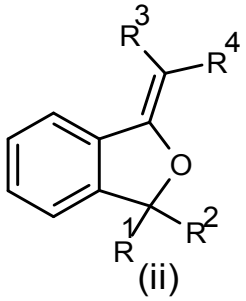
Compounds	R^1	R^2	R^3	R^4	R^5
1a	H	H	H	H	H
1b	H	H	$-CH_3$	H	H
1c	H	H	H	$-CH_3$	H
1d	H	H	$-OCH_3$	H	H
1e	$-C_2H5$	$-C_2H_5$	H	H	H
1f	H	$-C_4H_9$	H	H	H
1g	H	H	H	H	$-OCH_3$

Designed Molecules containing Isobenzofuran scaffold (i)



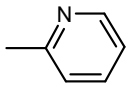
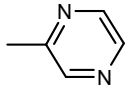
(i)

Designed Molecules containing Isobenzofuran scaffold (ii)



(ii)

Table: 2

Compounds	R^1	R^2	R^3	R^4
2a	$-C_2H5$	$-C_2H_5$	H	$-C_4H_9$
2b	H	H	-C=O	$-CH_3$
2c	H	$-CH_2NH_2$	H	H
2d	H	$-CH_3$	H	H
2e	H	H	H	H
2f	H	H	H	
2g	H	H	H	

Designed Molecules containing Isobenzofuran Scaffold (ii)

PRELIMINARY QSAR STUDY OF DESIGNED MOLECULES

The designed molecules were performed for preliminary QSAR study and drug likeness score by using Molinspiration software.

Preliminary QSAR studies include log P value, Molar Volume, number of rotatable bonds Topological Polar surface area.

LogP (octanol/water partition coefficient): Octanol-water partition coefficient logP is used in QSAR studies and rational drug design as a measure of molecular hydrophobicity. Hydrophobicity affects drug absorption, bioavailability, hydrophobic drug-receptor interactions, metabolism of molecules, as well as their toxicity. LogP has become also a key parameter in studies of the environmental fate of chemicals.

Molecular Polar Surface Area (TPSA)[10]: Molecular polar surface area (PSA) is a very useful parameter for prediction of drug transport properties. Polar surface area is defined as a sum of surfaces of polar atoms (usually oxygens, nitrogens and attached hydrogens) in a molecule. This parameter has been shown to correlate very well with the human intestinal absorption, Caco-2 monolayers permeability, and blood-brain barrier penetration.

Molecular Volume: Molecular volume determines transport characteristics of molecules, such as intestinal absorption or blood-brain barrier penetration. Volume is therefore often used in QSAR studies to model molecular properties and biological activity. Various methods may be used to calculate molecular volume, including methods requiring generation of 3D molecular geometries, or fragment contribution methods such as McGowan volume approximation.

Number of Rotatable Bonds – nrotb*:* This simple topological parameter is a measure of molecular flexibility. It has been shown to be a very good descriptor of oral bioavailability of drugs [11]. Rotatable bond is defined as any single non-ring bond, bounded to nonterminal heavy (i.e., non-hydrogen) atom. Amide C-N bonds are not considered because of their high rotational energy barrier.

Table 3
Preliminary QSAR Study of Designed molecules

S.No	Compounds	M.W	Log P	TPSA	n rotb	M.V
1	1a	208.26	3.755	9.234	1	197.8
2	1b	222.29	4.203	9.234	1	214.4
3	1c	222.29	4.179	9.234	1	214.4
4	1d	238.29	3.812	18.468	2	223.4
5	1e	264.37	5.570	9.234	3	264.2
6	1f	264.37	5.685	9.234	4	264.8
7	1g	238.29	3.584	18.468	2	223.4
8	2a	244.38	5.918	3.234	5	259.8
9	2b	174.20	1.468	26.305	1	161.9
10	2c	161.21	0.840	35.257	2	154.8
11	2d	146.19	2.411	9.234	0	143.3
12	2e	132.16	2.048	9.234	0	126.7
13	2f	209.25	2.405	22.126	1	193.7
14	2g	210.24	2.108	35.018	1	189.5
15	3a	252.27	3.621	27.702	1	221.7

M.W – Molecular Weight
TPSA – Topological Polar Surface Area
n rotb – Number of Rotatable bonds
M.V – Molar Voume

DRUGLIKENESS SCORE OF DESIGNED MOLECULES

The Molinspiration virtual screening is fast (100,000 molecules may be screened in about 30 minutes) and therefore allows processing of very large molecular libraries. Validation tests performed on various target classes (including kinase inhibitors, various GPCR targets, different enzymes etc.,) show 10 to 20- fold increases in hit rate in comparison with standard / random selection of molecules for screening.

Table 4
Druglikeness Score of the Designed Moleucules

S.No	Compound	GPCR Ligand Score	Ion channel modulator score	Kinase inhibitor score	Nuclear receptor ligand score
1	1a	-0.09	-0.49	-0.37	-0.67
2	1b	-0.12	-0.55	-0.35	-0.65
3	1c	-0.11	-0.55	-0.37	-0.63
4	1d	-0.05	-0.53	-0.27	-0.44
5	1e	-0.18	-0.29	-0.42	-0.18
6	1f	-0.14	-0.20	-0.49	-0.25
7	1g	-0.18	-0.52	-0.29	-0.42
8	2a	-0.31	-0.24	-0.49	-0.28
9	2b	-0.67	-0.71	-0.88	-1.29
10	2c	-0.11	-0.10	-0.62	-1.38
11	2d	-0.58	-0.56	-1.06	-1.47
12	2e	-0.45	-0.87	-0.87	-1.74
13	2f	-0.17	-0.41	-0.25	-0.92
14	2g	-0.04	-0.39	-0.17	-0.92
15	3a	-0.06	-0.42	-0.27	-0.46

RESULT AND DISCUSSION

The designed molecules were evaluated for the drug likeness score using Molinspiration software. The designed molecules were act as a ligand for various receptors like G-Protein Coupled Receptor (GPCR), Ion Channel Modulator, Kinase receptor and neuron receptor. The results were within the limits (-3 to 3) (Table 4). The designed molecules obey the Lipinski rule of five. So the designed molecules may useful as a lead compound for various diseases like depression, cancer and some infectious diseases also.

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