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Effect of an Indole-containing Pseudopeptide on Behavioral Despair Models in Mice: Supporting by Molecular Docking and Density Functional Theory Calculations

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ABSTRACT

Aims: *The study refers to application of a synthetic candidate containing an indole scaffold, 5f, in animal models of behavioral despair. Moreover, binding affinity and polarizability of 5f were calculated with molecular docking and density functional theory (DFT) study, respectively.* ***Materials and Methods:*** *To compare, desipramine (DMI) (10 mg/kg, i.p.), a selective serotonin-norepinephrine reuptake inhibitor (SNRI) and fluoxetine (FLX) (10 mg/kg, i.p.), a selective serotonin reuptake inhibitor (SSRI) were employed. The binding affinity of 5f, FLX and DMI to Leu_{Ta}, a leucine tranporter as a homologous protein to monoamine, were evaluated. Also, polarizability of 5f was compared using DFT method. The neuroprotective effect of 5f on behavioral despair was evaluated using forced-swim and tail suspension tests in male mice. The drugs were injected intraperitoneally (i.p.) 30 minutes before the tests.* ***Results:*** *5f (2.5, 5, 10 mg/kg) significantly reduced the immobility behavior in a dose-dependent manner in the behavioral tests. Moreover, no significant changes in locomotor activity of the animals were detected. In addition, in line with the experimental results, docking demonstrated that 5f-$LeuT_{Aa}$ complex has the highest bonding energy comparable with DMI. Moreover, DFT study showed the highest polarizability for 5f. Further, it showed a high lipophilicity. 5f had higher potency in the behavioral tests compared to the antidepressants; however, it was more structurally similar to DMI. 5f was probably capable to reduce behavioral despair lowering the immobility figure.* ***Conclusion:*** *Demonstrating a high polarizability and having the highest bonding energy of docked 5f-$LeuT_{Aa}$ complex comparable with DMI along, 5f probably has the potential to make more serotonin and norepinephrine available.*

Keywords: Indole-containing pseudopeptide, Sodium symporter (NSS) transporter, Forced-swim test, Tail suspension test, Molecular docking, Density functional theory.

INTRODUCTION

Intracellular communication in the central nervous system (CNS) is driven by the controlled release and reuptake of neurotransmitters at the synapses. Extra accumulation or lack of monoamine and amino acid neurotransmitters contributes to many psychiatric and neurological disorders, including Parkinson's disease, Attention Deficiency Hyperactivity Disorder (ADHD) and depression [1,2].

The extent and duration of the released neurotransmitters are tightly regulated by a group of specialized transmembrane neurotransmitter sodium symporter (NSS) transporters localized to the neurons and glial cells. The NSS transporters use the Na^+/Cl^- electrochemical gradient to remove neurotransmitters from the synapse against their concentration gradient [1,2]. NSS is to terminate neurotransmission by rapid removal of neurotransmitters from the synaptic cleft and reuptake them into the presynaptic neurons and/or surrounding glials. The subfamily of NSS responsible for reuptake of monoamines comprises the transporters for dopamine (DAT), noradrenaline (NET), and serotonin (SERT). The 3-dimensional (3D) structure of SERT is not known, however; several 3D structures of a bacterial homologous transporter, the Aquifex aeolicus

leucine transporter ($LeuT_{Aa}$), are available. The first LeuT data revealed a high-resolution occluded structure devoid of water with a single leucine molecule in coordination with two Na^+ ions [3]. A remarkable step forward in understanding structure–function of SLC6 NSS transporters came from the Gouaux laboratory with the determination of the high resolution crystal structure of $LeuT_{Aa}$, a prokaryotic member of the SLC6 NSS family [3]. Given that the structural fold of proteins from the same protein family is generally highly conserved [4], it is not surprising that $LeuT_{Aa}$ has become the established template for studying both prokaryotic and eukaryotic SLC6 transporters, despite sharing only 20%−25% protein sequence identity [5]. The substrate leucine and two Na^+ and one Cl^- ions were also observed in the crystal structure. Out of 22 residues forming the substrate binding site, 18 were direct H bond, ionic or hydrophobic interactions with leucine, and the remaining four coordinated one of the Na^+ ions (Na1) [3]. Models which were constructed from $LeuT_{Aa}$ are now allowing a reasonable approach to further clarify the molecular determinants of NSS transporter–ligand complexes, and potentially the ability to better manipulate drug specificity and affinity. $LeuT_{Aa}$ was also used as template to understand how antidepressants bind to SERT and NET. In fact, the low-affinity interaction sufficed to allow visualizing tricyclic antidepressants (TCAs) in the extracellular vestibule of the transporter [6,7]. TCAs such as desipramine and imipramine, binds to serotonin (5-HT) and norepinephrine (NE) transporters with affinities of nanomolar to tens of nanomolar concentrations and blocks transport activity [8].

Indole nucleus is found in numerous natural products and pharmaceuticals. It has found that indole compounds, derivatives and complexes have the potential to be used to assist in treatment of human immune and neurological disorders [9-11]. Indole has gained prominence in medicinal chemistry due to its diverse biological properties [12-14]. Many indole derivatives are considered as the most potent scavenger of free radicals [15]. Indoles have analgesic, antipyretic and anti-inflammatory characteristics. They are essential to maintain healthy functioning of the nervous and immune systems. They are often used in synthesis of new pharmaceuticals [9]. Among the large family of indoles, indole carboxamides have recently attracted a great deal of interest from chemists and biologists due largely to their various pharmacological activities such as antioxidant [16], hypocholestrolemic [17], antihistaminic [18] etc. [19-21]. Although functionalized indole ring systems have been found frequently in biologically active compounds, indole derivatives as multi-component reaction (MCR) partners and flexible reactions for the rapid generation of complex molecules with often biologically relevant scaffold structures [22-24], are rather under-represented [25]. The synthesized indole-containing pseudopeptide possesses optimal range of lipophilicity for oral absorption, cell membrane penetration, and blood-brain barrier (BBB) permeation [26].

Peptidomimetics typically are small protein-like molecules designed to mimic natural peptides or proteins. These mimetics whose structures were mainly derived from natural peptides, should have the ability binding to their natural targets in the same way of the natural sequences and hence produce the same biological impacts. It is possible to design these molecules in such a way that they show the same biological influences as their peptide role models, nevertheless, with enhanced properties like higher proteolytic stability and bioavailability and often with improved selectivity or potency [27]. The purpose is to replace as much of the peptide backbone as possible with non-peptide fragments while still maintaining the pharmacophoric groups, usually the amino acid side chains, of the peptide. This makes the compound more lipophilic, and as a result its bioavailability is improved. Replacement of the amide bond with alternative groups prevents proteolysis and promotes metabolic stability [28].

The discovery of new effective drugs still has remained a top priority as depression affects approximately 21% of the world population. Extensive studies have measured antidepressant-like effects of chemical compounds to discover modern drugs [29]. Clinically-used antidepressants have several limitations and drawbacks which demand persistent development of novel, efficient, and safe drugs. Particular attention has been devoted to synthesis of tricyclic structures as potential scaffolds for novel pseudopeptides [30].

Due to the biological importance of the indole nucleus and its presence in the CNS drugs and the similarity between molecular structure of general anti-depression drugs (Figure 1a) and our synthetic compound (Figure 1b), we aim to demonstrate protective effect of a synthesized novel indole-containing pseudopeptide (5f) in mice exposed to inescapable situations to evaluate behavioral despair in animal models. We compare our result with a TCA, desipramine (DMI), and a SSIR, fluoxetine (FLX). Moreover, to compare capability of 5f with DMI and FLX in possible inhibition of 5-HT or NE-reuptake, we model different types of interactions associated with $LeuT_{Aa}$ and the drugs, using molecular docking density functional theory (DFT) method.

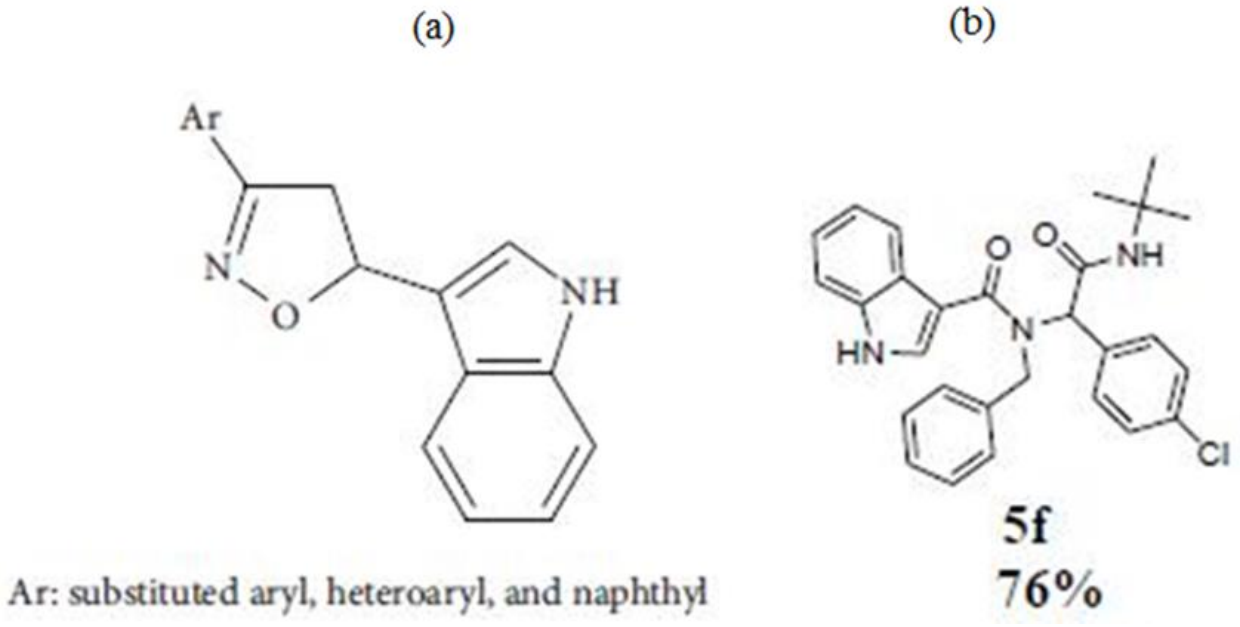

Figure 1: General structure of proposed scaffold as antidepressant agents (a). N-[(tert-Butylcarbamoyl) (4-chlorophenyl) methyl]-Nbenzyl- 1H-indole-3-carboxamide. 76% lipophilicity (b)