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REVIEW ARTICLE

Design Strategies, Chemistry and Therapeutic Insights of Multi-target Directed Ligands as Antidepressant Agents

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Abstract: Depression is one of the major disorders of the central nervous system worldwide and causes disability and functional impairment. According to the World Health Organization, around 265 million people worldwide are affected by depression. Currently marketed antidepressant drugs take weeks or even months to show anticipated clinical efficacy but remain ineffective in treating suicidal thoughts and cognitive impairment. Due to the multifactorial complexity of the disease, single-target drugs do not always produce satisfactory results and lack the desired level of therapeutic efficacy. Recent literature reports have revealed improved therapeutic potential of multi-target directed ligands due to their synergistic potency and better safety. Medicinal chemists have gone to great extents to design multi-target ligands by generating structural hybrids of different key pharmacophores with improved binding affinities and potency towards different receptors or enzymes. This article has compiled the design strategies of recently published multi-target directed ligands as antidepressant agents. Their biological evaluation, structural-activity relationships, mechanistic and *in silico* studies have also been described. This article will prove to be highly useful for the researchers to design and develop multi-target ligands as antidepressants with high potency and therapeutic efficacy.

Keywords: CNS disorders, depression, antidepressants, multi-target directed ligands, structure-activity relationship, inhibitor.

1. INTRODUCTION

Depression is at the forefront of the major CNS disorders affecting more than 264 million people worldwide [1]. The rate of depression is more prevalent in the Middle East, South Asia, North Africa and America compared to the other countries [2]. It is one of the leading causes of decreased productivity, disability, and dependent care. It is recognised as a chronic and recurrent affective disorder with multiple etiology, and its symptoms include stress, low emotion, poor social skills, decreased energy, and cognitive impairment [3-5]. MDD (Major Depression Disorder) is one of the key risk factors for suicide, the tenth leading cause of death worldwide, and linked to various co-morbidities, such as heart disease, diabetes, stroke, and cancer [3, 6]. It is ubiquitous in all regions of the world while the prevalence of this disorder varies in accordance with the geographic location and country. It is especially common in patients with other health problems, and these patients are at a much higher risk for developing depression than the general population [7, 8]. Comorbid depression has pronounced clinical effects, like depression and chronic illness, having additive or even synergistic negative effects on the general health [9, 10]. The Center for Disease Control and Prevention (CDC) estimated that about 8.1% of American adults aged 20 and over were suffering from depression in 2013-2016. It was notable that women (10.4%) were almost twice as likely to be depressed than men (5.5%) [11]. The trend of prevalence of depression did not differ much between age groups [12, 13], and it was found to be lower in non-Hispanic Asian adults (3.1%) than the Hispanic-origin (8.2%) population. There was an interesting observation that the occurrence of depression in adults decreased as the level of family income increased. Adults who were above the federal poverty line (FPL) exhibited a depression rate of 3.5%, while the adults lying below the FPL were found to have a 15.8% depression rate [11].

Despite medical advances and effective mental health treatments, about 76-85% of the population in middle and low-income countries is not well treated either due to lack of adequate skilled health care or resources, and ignorance of the patient and the general public [14]. One of the main symptoms associated with depression is anhedonia which refers to a loss of interest or pleasure in certain activities that people generally enjoy [15-17]. Various types of depressions cause a variety of symptoms, among which some affect your mood and some affect your body [11, 18]. Symptoms can also be continuous or may come and go. Harsh conditions in childhood, such as grief, neglect, mental abuse, physical abuse, sexual abuse, or unequal parental treatment of siblings, can lead to depression in adulthood [19, 20]. In

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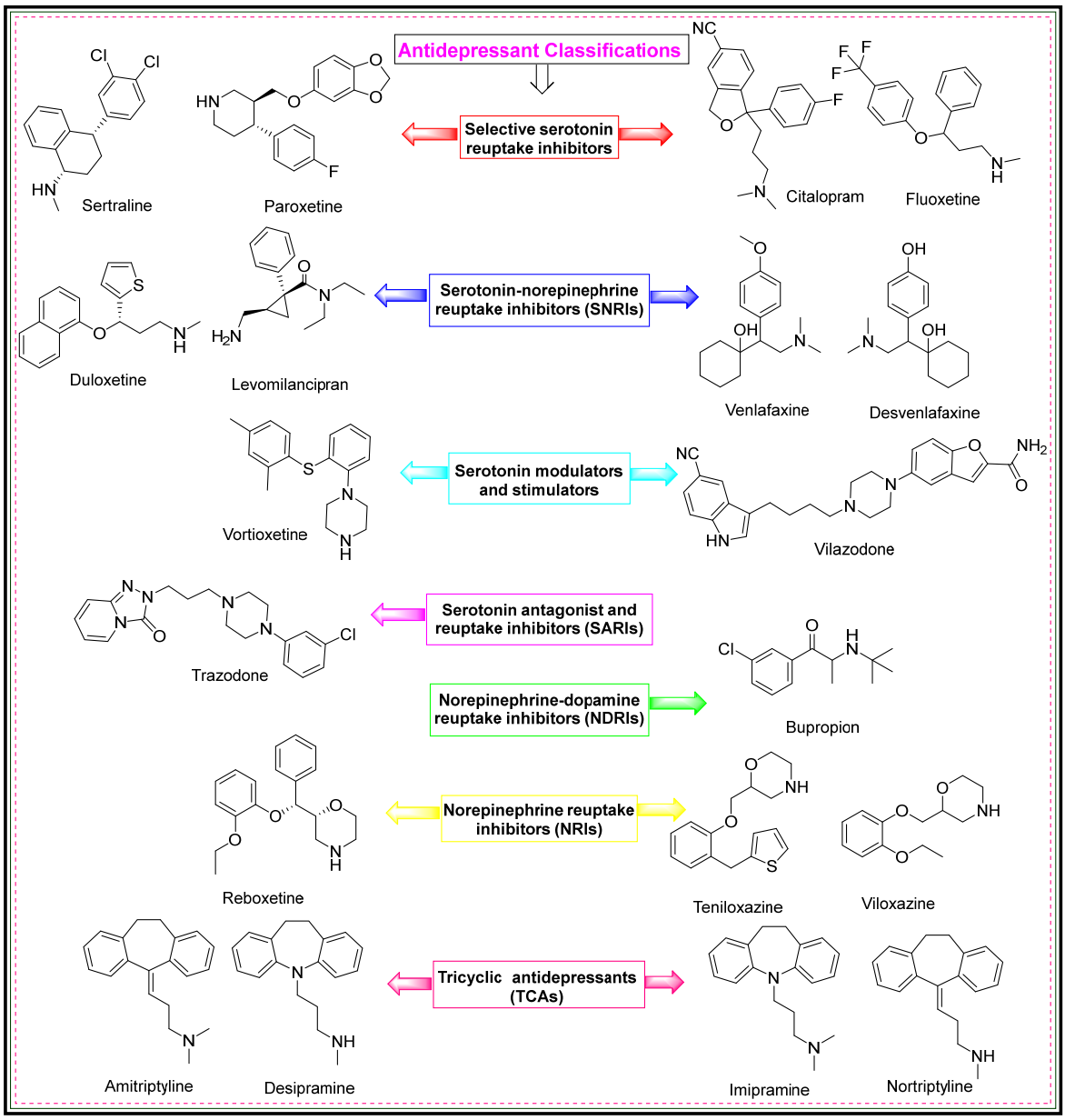
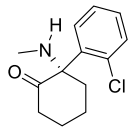
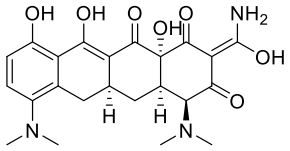
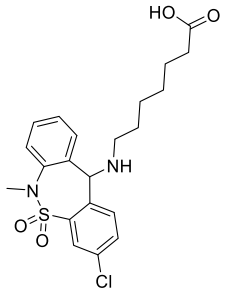
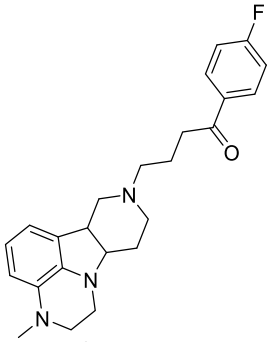
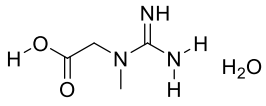
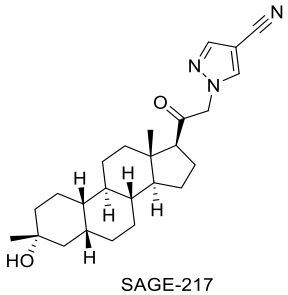


Fig. (1). Antidepressant drugs in clinical use.

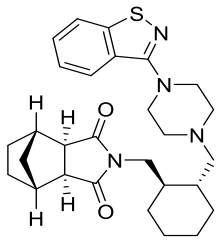
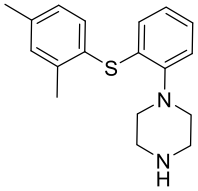
particular, physical or sexual abuse in childhood correlates significantly with the likelihood of suffering from depression during the victim's lifetime [21, 22]. Conditions, such as bullying, natural disaster, rape, jealousy, loss of loved one, separation, relationship troubles, medical diagnosis (HIV, cancer, *etc.*), unemployment, stress (due to work, family, education, living conditions), childbirth, menopause, *etc.*, also lead to depression [23-25]. The age of the adolescent is also prone to mood swings [26, 27]. Depression can be diagnosed based on the symptoms and psychological parameters, such as moods, appetite, sleep pattern, activity level, and thoughts [28-31]. The lack of dopamine in prefrontal areas [32-34], exhaustion of the catecholamines such as norepinephrine [35, 36], and the decrease in the concentration of SAM (S-adenosyl-L-methionine) [37, 38] are the prime causes of depression. Moreover, it is well established that decreased concentration of serotonin in the brain is also associated with the progression of depression [39, 40]. The development of depression might be associated with the availability of fewer serotonin receptors or disability of receptors to receive serotonin and increased serotonin breakdown through MAO-A [41, 42]. Beyond this, another mechanism associated with depression is the overactivity of the hypothalamic-pituitary-adrenal (HPA) axis. HPA is responsible for the handling of normal stress reactions, and any fluctuation in this system leads to the development of depression [43, 44]. Along with this, hyperactivity of NMDA receptors is also considered as one of the prominent causes of depression [45, 46].

There are several therapeutic agents that belong to different structural classes available in the market for the treatment of depression (Fig. **1**); they work by either inhibiting or modifying the above-mentioned mechanism(s) of depression [47]. For example, MAO-A inhibitors like Moclobemide and clorgyline [48, 49], Serotonin reuptake inhibitors (SSRI) like imipramine and nortriptyline, Selective serotonin reuptake

Table 1. Antidepressant drugs under different phases of clinical trials along with their mechanism of action and therapeutic indication.

S. No.	Compound Name and Structure	Clinical Trial Status and Indication	Mechanism of Action	Clinical Trial No.
1	 Eskitamine	Phase Ii; Recruiting, Treatment Resistant Depression	Inhibits the Dopamine Transporter and Increases The Dopamine Activity [59, 60].	NCT04476446
2	 Minocycline	Phase III; recruiting, Treatment Resistant Depression	The Exact Mechanism is not Clear.	NCT03947827
3	 Tianeptine Sodium	Phase IV; recruiting, treatment resistant depression	inhibition of glutamate receptor activity (AMPA and NMDA receptor) [61, 62], and modestly enhances the release of dopamine [63].	NCT04249596
4	 Lumateperone	Phase III; recruiting, bipolar depression, major depressive disorder	Antagonizes the 5-HT_{2A} and dopamine receptor subtypes (D_1, D_2 and D_3) [64, 65].	NCT04285515
5	 Creatine Monohydrate	Phase IV; recruiting, major depressive disorder	Elevates the plasma dopamine level [66, 67].	NCT03202095
6	 SAGE-217	Phase III; recruiting, depression	Positive Allosteric modulator of the $GABA_A$ receptor [68, 69].	NCT0444503

(Table 1) contd….

S. No.	Compound Name and Structure	Clinical Trial Status and Indication	Mechanism of Action	Reference
7	 Lurasidone	Phase III; Recruiting, Bipolar Disorder	Antagonizes the Dopamine D_2 and D_3 Receptor, and Serotonin 5-HT_{2A} AND 5-HT_7, Whereas Partial Agonist of 5-HT_{1A} Receptor [70, 71].	NCT04383691
8	 Vortioxetine	Phase II; Recruiting, Bipolar Disorder	Upregulates the serotonin by inhibiting the reuptake in the synapse [72, 73].	NCT03598868

inhibitors like fluoxetine [50] and sertraline [51], and noradrenaline reuptake inhibitors (NRI) like desipramine, *etc.*, are used to improve serotonin and NA levels in the brain, which in turn leads to an antidepressant-like effect in the patients suffering from depression. The major issue which limits the therapeutic utility of these drugs is that they show little effect in major depression, post-traumatic disorder, obsessive-compulsive disorder and anxiety disorder [52-54]. These drugs follow the trend of one-drug-one-target and are not able to effectively manage the complex pathophysiology of depression. Further, research efforts have led to the discovery of various drug candidates which are under different phases of clinical developmental pipeline, as shown in Table **1**. On the other hand, a few drugs are available in the market for the treatment of depression that work via multi-target ligand drug therapy and are capable of achieving an appropriate proportion of desired activities with improved pharmacokinetics profile, good selectivity, low dose and reduced side effects. For example, serotonin-norepinephrine reuptake inhibitors like duloxetine [55] and venlafaxine [56], and norepinephrine-dopamine reuptake inhibitors like viloxazine [57] and reboxetine [58], are the representative examples of drugs acting on multiple biological targets involved in the pathophysiology of diseases. Hence, the design and development of new therapeutic candidates capable of interacting or interfering and/or modifying more than one biological target of therapeutic interest will be a better choice for the treatment of such complicated disorders.

Recently, several research groups have focused their attention on the design and development of multi-target directed ligands (MTDLs) for the treatment of depression. In this regard, the concept of molecular hybridization or fragment-based drug design (FBDD), which includes clubbing two or more molecular scaffolds into a single molecular entity, represents an excellent approach to developing MTDLs [74, 75]. The designed molecules thus have the tendency to work by acting on multiple targets or pathways. Heterocyclic compounds have shown remarkable potential for the design and development of antidepressant agents belonging to diverse structural classes [76-80]. Various excellent review articles have been published in the past few years describing the recent developments in the medicinal and biological perspectives of antidepressants agents [81-83]. Siddiqui *et al.* and Singh *et al.* reviewed the antidepressant potential of nitrogen-containing heterocyclic moieties [83, 84], while the antidepressant perspective of piperazine derivatives has been compiled by Moreira *et al.* [85]. Further, SAR and medicinal chemistry of indole-based antidepressant agents have been reviewed by Garg *et al.* [86]. These reviews are more entity-oriented and cover limited aspects related to the medicinal and design perspectives of multi-target ligands. Although a number of breakthrough studies have highlighted the therapeutic exploration and medicinal attributes of multi-target ligands over the past few years [87-90], a comprehensive review of the scientific literature describing the potential of MTDLs as a promising class of antidepressant agents is extremely required to give an overview of the rapidly emerging area. This review has compiled the design strategies of MTDLs reported by various researchers in past decade (2011-2020) as a promising class of anti-depressant agents (Fig. **2**). Further, recent advancements in the medicinal chemistry of different heterocyclic scaffolds with strong emphasis on the exploration of their chemical diversity, their biological evaluation *(in vitro* and *in vivo* studies), structure-activity relationships, and *in silico* findings are also described in this manuscript. We hope that this review will serve as a useful reference for the organic and medicinal chemists involved in the design and development of new potent and efficacious antidepressant agents (Table **2**).

2. VARIOUS CLASSES OF MULTI-TARGET DIRECTED LIGANDS AGAINST DEPRESSION

Recent advances in the medicinal chemistry of various MTDLs as a promising class of antidepressant agents are discussed below.

2.1. Indole Appended Piperazine/Piperidine Derivatives

Indole is a bicyclic heterocyclic molecule containing a six-membered benzene ring fused with a five-membered nitrogen-containing pyrrole ring. Literature survey highlights

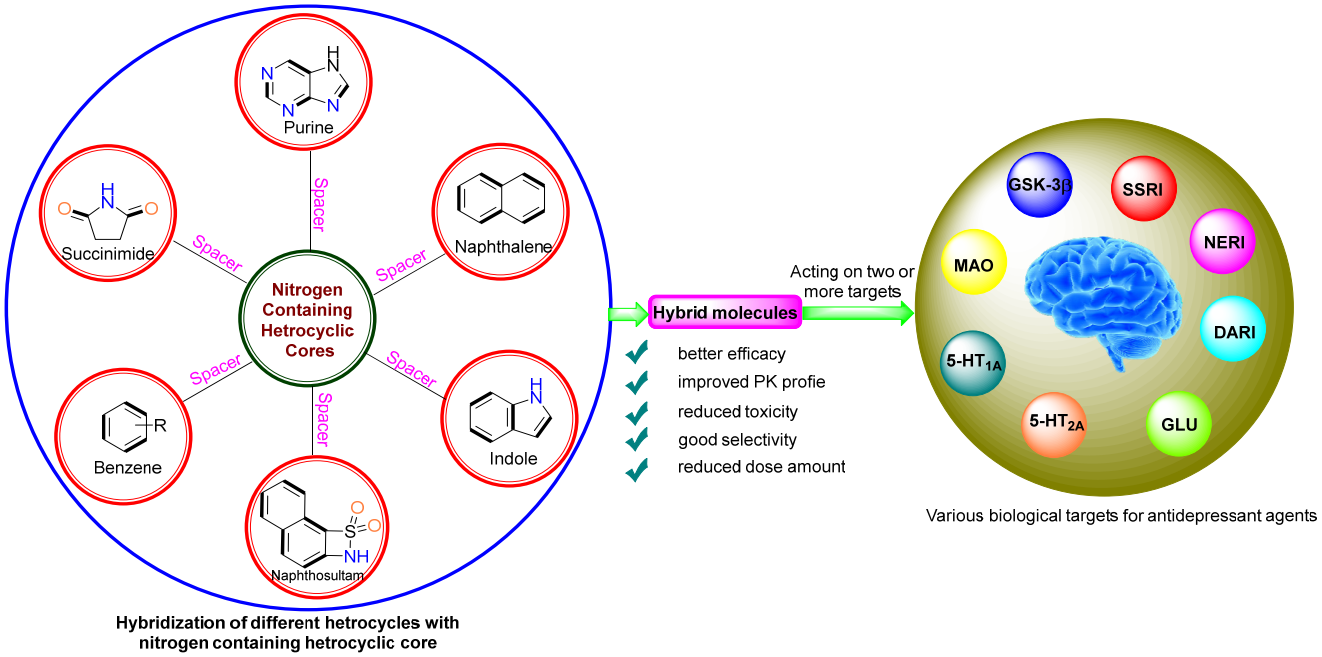


Fig. (2). MTDLs as a promising class of antidepressant agents.

Table 2. List of filed patents on multi-target ligands that display various biological activities.

S. No.	Title	Inventor	Status	References
1	Indole and Indoline Derivatives for Neurodegenerative or Neuropsychiatric Disorders	Michael R. Schrimpf, Chih-Hung Lee, Tao Li, Gregory gfesser, kathleen mortell, ramin faghih, Diana l. Schmidt, Kevin Sippy, William H. Bunnelle, Marc Scanio, Lei Shi, Murali Gopalakrishnan, Diana L. Donnelly-roberts, Min Hu	Active	US9983218B2 [91]
2	Multi-target Compounds for the Treatment of Alzheimer's Disease	Muñoz-torrero López-ibarra, Vázquez Cruz, Pont Masanet, Codony Gisbert	Active	WO2020193448 [92, 93]
3	Neuroprotective Multi-target Directed Drugs that Target the Ache, Buche and Monoamine Oxidase (mao) A And B	Gerard Esteban, Mercedes Unzeta, Tsutomu Inokuchi, José Luis Marco-Contelles, Abdelouahid Samadi, Isabel Iriepa, Masaki Ojima, Wang li	Withdrawn	EP2727916A1 [94]
4	Dual Inhibitor Compounds for Use in the Treatment of Neurodegenerative Disorders and Alzheimer's Disease	Andrea Cavalli, Federica Prati, Giovanni Bottegoni, Angelo Danilo Favia, Daniela Pizzirani, Rita Scarpelli, Maria Laura Bolognesi	Active	EP3154953A1

(Table 2) contd….

S. No.	Title	Inventor	Status	Reference
5	Dual Targeting Compounds for the Treatment of Alzheimer's Disease	Andrea Cavalli, Michela Rosini, Elena simoni, Angelo M. Reggiani, Carlo Melchiorre	-	WO2013160728A1
6	Tapentadol for Preventing and Treating Depression and Anxiety	Steigerwald Ilona, Janel Ulrichtschen Thomas	Active	JP6445637B2
7	Combination of an Nmda Receptor Antagonist and a Selective Serotonin Reuptake Inhibitor for the Treatment of Depression and Other Mood Disorders	Sandeep Gupta, Gary Samoriski	Expired	CA2528622C

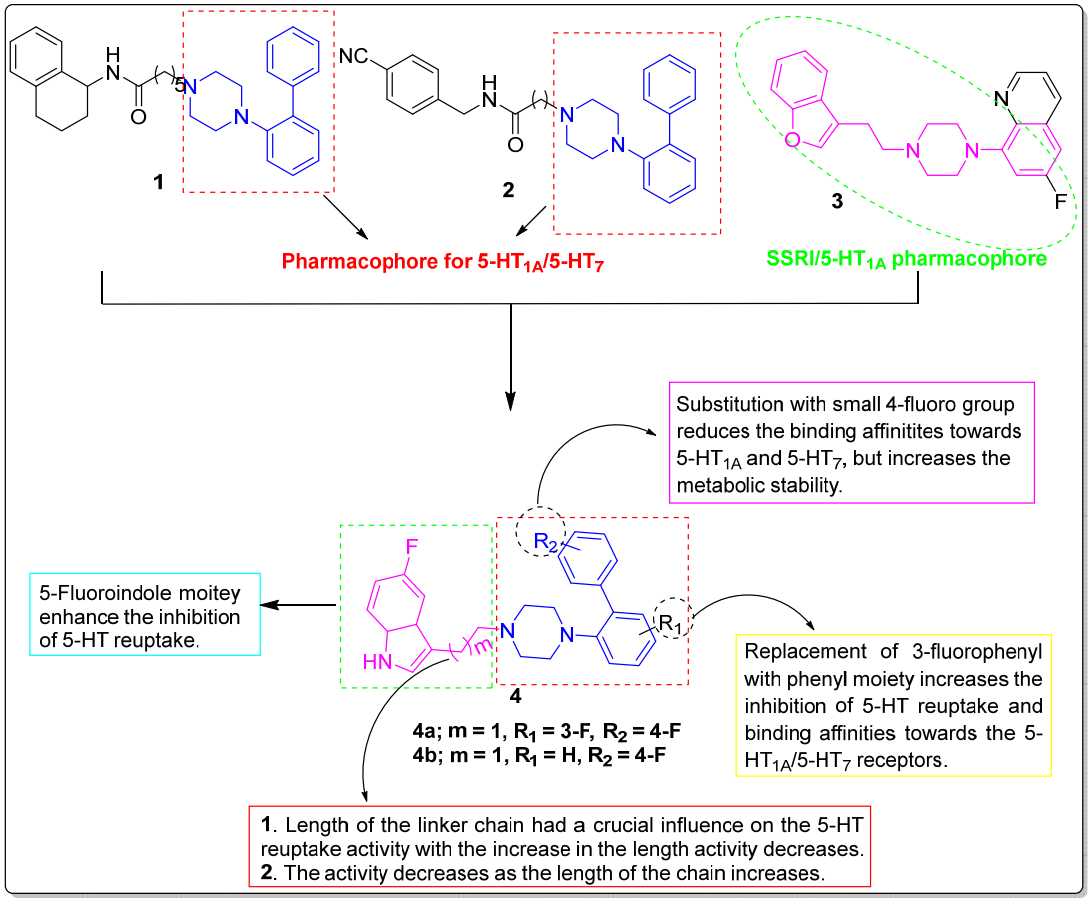


Fig. (3). Strategy and SAR of indole appended piperazine derivatives.

its medicinal significance and acceptance as a privileged pharmacophore due to its broad spectrum of biological activities [95-97]. With respect to the development of antidepressants, various medicinal chemists have reported various indole clubbed piperazine hybrids as potential CNS active molecules with multi-targeting properties for the treatment of CNS-related disorders [98-101]. Indole clubbed piperazine derivatives have been reported to exhibit good binding affinities towards the 5-HT_{1A} receptors and SERT [102]. While 2-biphenylpiperazine derivatives have shown high affinity towards 5-HT_{1A} and 5-HT_7 receptors [47]. These proteins have also been identified as the potential targets for the antidepressant drug discovery.

Based on the literature findings, James *et al*. combined both the pharmacophores in a single moiety and synthesized a series of indole piperazine hybrids (Fig. **3**). All the synthesized compounds were investigated for serotonin reuptake inhibitory (RUI) activity and 5-HT_{1A}/5-HT_7 receptor binding affinities. Among them, compounds **4a** and **4b** were found to be most potent and showed RUI with IC_{50} values of 31 and 25 nM, respectively. These compounds possessed good

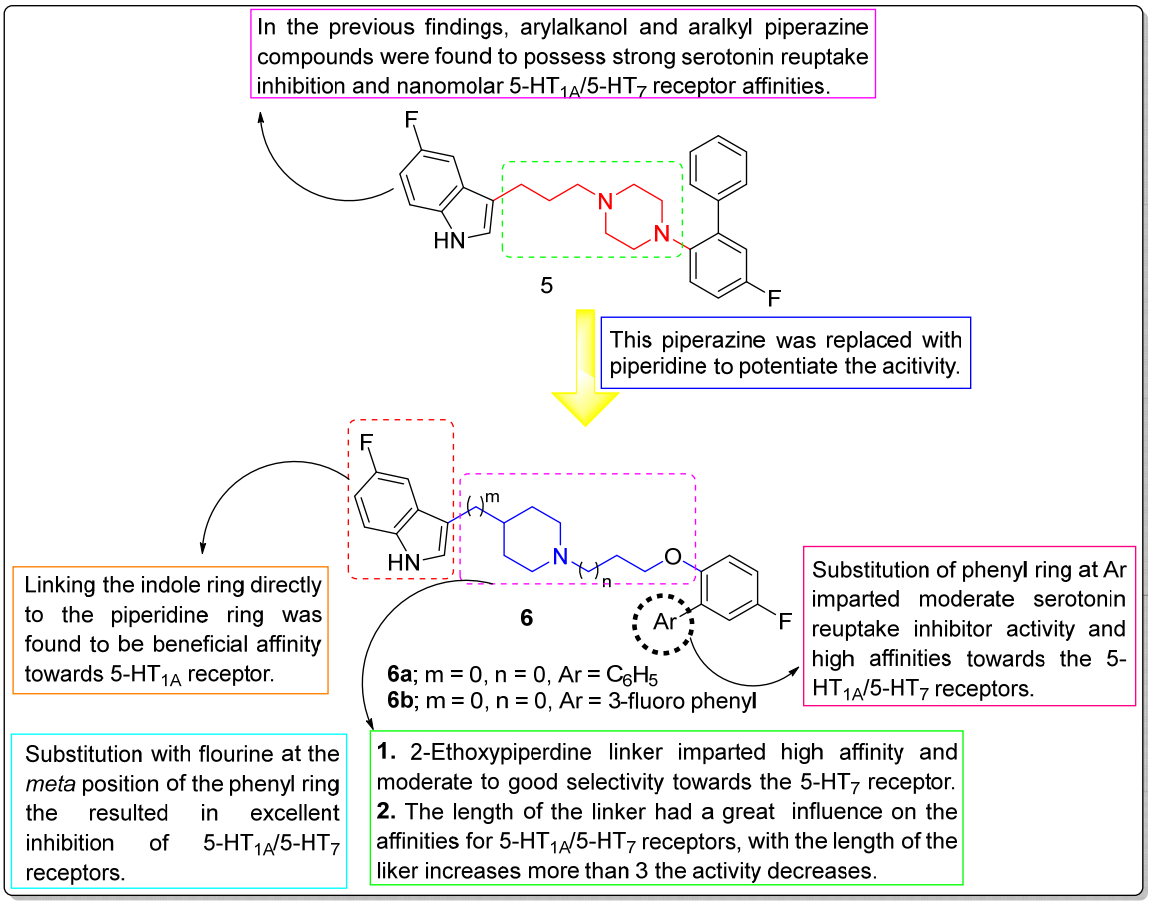


Fig. (4). Design strategy and SAR of multi-targeted alkoxy-piperidines as antidepressants.

binding affinities towards 5-HT_{1A}, with *Ki* values of 62 and 28 nM, while their K*i* values were found to be 12 and 3.3 nM for the 5-HT_7 receptor, respectively. These promising compounds were evaluated for antidepressant-like activity by using FST and TST tests. Results of *in vivo* studies revealed that compounds **4a** and **4b** significantly reduced the immobility time in a dose-dependent manner (20 and 40 mg/kg) similar to vortioxetine (40 mg/kg). Compound **4b** also showed an acceptable hERG profile with an IC_{50} value of 16.66 µM in the hERG binding assay [103]. Structural insights into the synthesized compounds provided a good structure-activity relationship, as discussed in Fig. (**3**), which also includes the design strategy of these compounds.

To elevate the biological potency of the compounds, Wang *et al*. synthesized a series of alkoxy-piperidine substituted indole derivatives by replacing the piperazine moiety with the piperidine ring. All the synthesized derivatives were investigated for their binding affinities towards the 5-HT_{1A}/5-HT_7 receptors and serotonin reuptake inhibition properties. Among them, compounds **6a** and **6b** were found to be the most active members of the series. Compounds **6a** and **6b** showed serotonin reuptake inhibition with IC_{50} values of 177 and 85 nM, respectively, and promising binding affinities towards 5-HT_{1A} with K_i values of 12 and 17 nM as well as 5-HT_7 receptor (K_i values of 25 and 35 nM, respectively). These potent compounds were evaluated *in vivo* by using the forced swim test (FST) and tail suspension test (TST). Results indicated that two compounds significantly reduced the immobility time at the dose of 40 mg/kg as compared to vortioxetine (reference), and exhibited potent antidepressant-like activity. Metabolic stability assay was performed on the rat liver in which the compounds **6a** and **6b** displayed a half-life of 34.5 and 22.9 min, which was higher than the standard drug vortioxetine [104]. The design strategy and SAR studies of these compounds are shown in Fig. (**4**).

Literature survey highlighted that indolylpropyl-piperazine derivatives act as potent serotonin transporter (SERT) ligands [105, 106], while morpholine and benzoxazinone cores act as potent dopamine D_2 receptor modulators and MAOIs [107]. Considering this, Cerda-Cavieres *et al.* clubbed indole moiety with morpholine and benzoxazinone and synthesized two series of 2,3-dihydro-benzo[1,4]oxazin-4-yl)-2-[4-[3-(1H-3indolyl)-propyl]-1-piperazinyl]-ethanamides and (2-(4-[3-(1H-3-indolyl)-propyl]-1-piperazinyl)-acetylamine)-N-(2-morfolin-4-yl-ethyl)-fluorinated benzamides. Binding affinities of all the synthesized compounds were evaluated towards serotonin transporter (SERT), dopamine D_2, and monoamine oxidase-A (MAO-A). Compounds **10a** and **11a** showed potent affinities towards SERT with K_i values 5.63 ± 0.82 nM and 6.85 ± 0.19 nM, respectively. Compounds **10b** and **10c** showed the highest binding affinities towards the D_2 receptor with K_i values of 307 ± 6 nM and 593 ± 62 nM, respectively. Compound **10b** displayed dual affinities towards the SERT and D_2 receptor with the ratio of 3.6, and compound **10b** was considered as a multi-target ligand candidate. None of the tested compounds

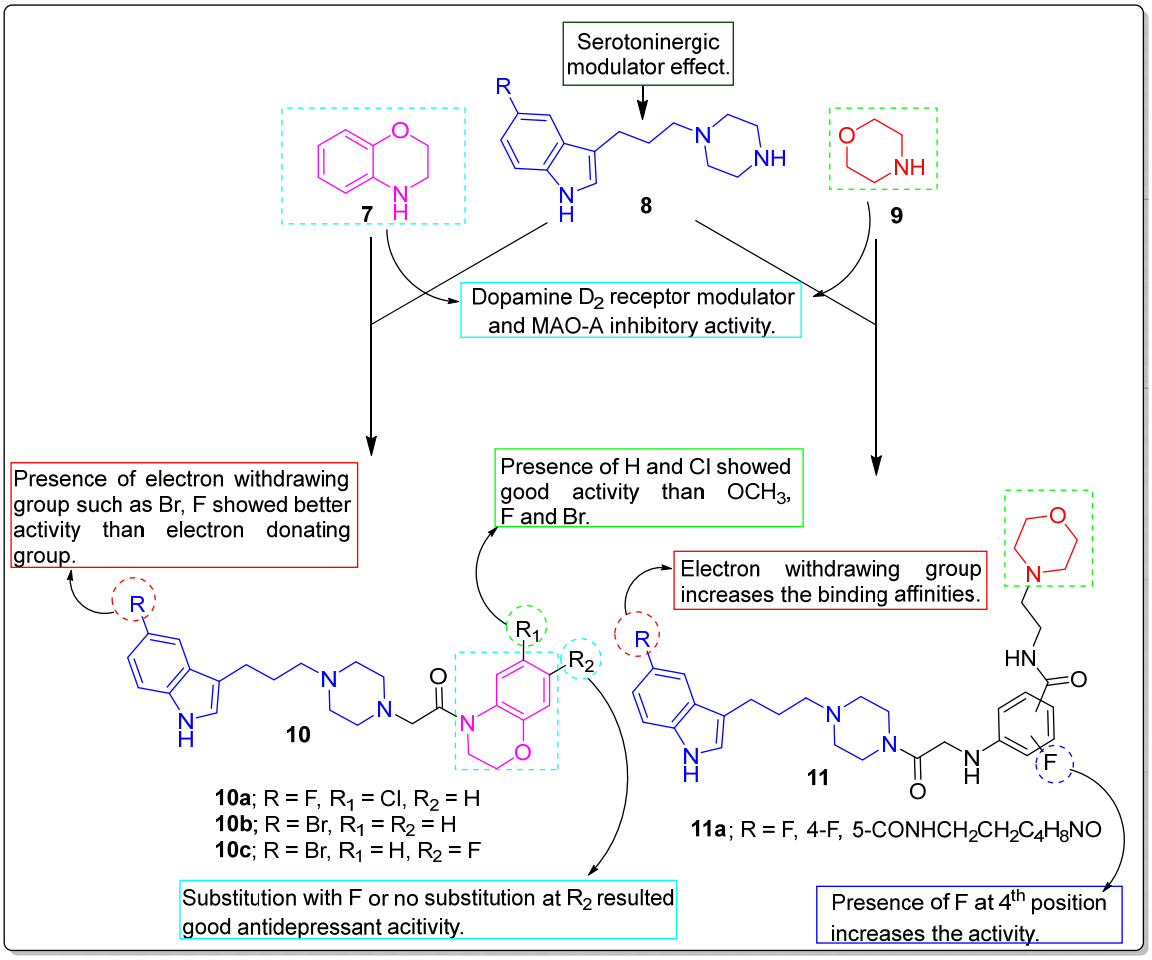


Fig. (5). Design and SAR of indole clubbed morpholine/benzoxazinone derivatives.

inhibited the MAO-A with high binding affinity. Further, docking studies were performed against human SERT and the findings highlighted that compounds **10a**, **10b**, **10c** and **11a** exhibited pi-pi interaction between the indole ring and pi-donor aromatic residue Tyr176 residue. Protonated piperazine displayed coulombic interaction with Asp98 and pi-cation interaction with Try95 [108]. The designing scheme and SAR studies of the current series are demonstrated below in Fig. (**5**).

Long-chain substituted arylpiperazines are promising scaffolds with good 5-HT_{1A} receptor bindings [109]. Buspirone is a prototype drug belonging to this class [110, 111]. Literature studies reveal that pyrrolidine-2,5-dione derivatives have been found to possess good binding affinities towards the 5-HT_{1A} receptor and SERT [112]. In order to retain the binding affinity towards the SERT and to enhance the binding affinity for 5-HT_{1A} receptors, Wróbel *et al.* selected 1-[4-[4-(1*H*-indol-3-yl)-3,6-dihydro-2*H*-pyridin-1-yl] butyl]-3-(1*H*-indol-3-yl) pyrrolidine-2,5-dione **(AC015)** as the reference compound and replaced the 3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole moiety with arylpiperazines. The newly designed and synthesized 4-butyl-arylpiperazine-3-(1*H*-indol-3-yl)pyrrolidine-2,5-dione derivatives (Fig. **6**) were screened for 5-HT_{1A}/D_2 receptor binding affinities and serotonin reuptake inhibition in the *in vitro* studies by using radioligand assay techniques. From the entire series, compound **12a** was found to possess most promising multi-target properties and showed the affinities towards the 5-HT_{1A}, SERT and D_2 receptors with K_i value of 1.3 ± 0.3, 64 ± 7.6, and 182 ± 18 nM, respectively. The SAR studies highlighted that the substitution with electronegative groups at the phenyl ring linked to the piperazine moiety imparted better activities towards 5-HT_{1A} and SERT [113].

In previous studies, arylalkanol and aralkyl piperazine derivatives with the indole and dichlorophenyl ring were found to possess good binding affinities towards the SSRI/5-HT_{1A}/5-HT_7. In the literature survey, it was observed that the compounds substituted with dichlorophenyl moiety displayed a suitable oral pharmacokinetic profile along with antidepressant-like activity. From structure-activity relationship studies, it was concluded that substitution with 3-propylindole moiety imparted good serotonin reuptake inhibition while the biphenyl piperazine group showed good binding affinities towards the 5-HT_{1A}/5-HT_7 receptors [114]. Further, to improve the metabolic stability of such compounds, Gu *et al*. introduced the fluoro group at the *para* position of the piperazine ring, and the biphenyl moiety was replaced with various aromatic substituents. The synthesized aralkyl piperazine and piperidine derivatives were screened for inhibition of serotonin reuptake and their binding affinities towards the 5-HT_{1A}/5-HT_7 receptors. Among them, compound **15a** displayed the most balanced multi-target

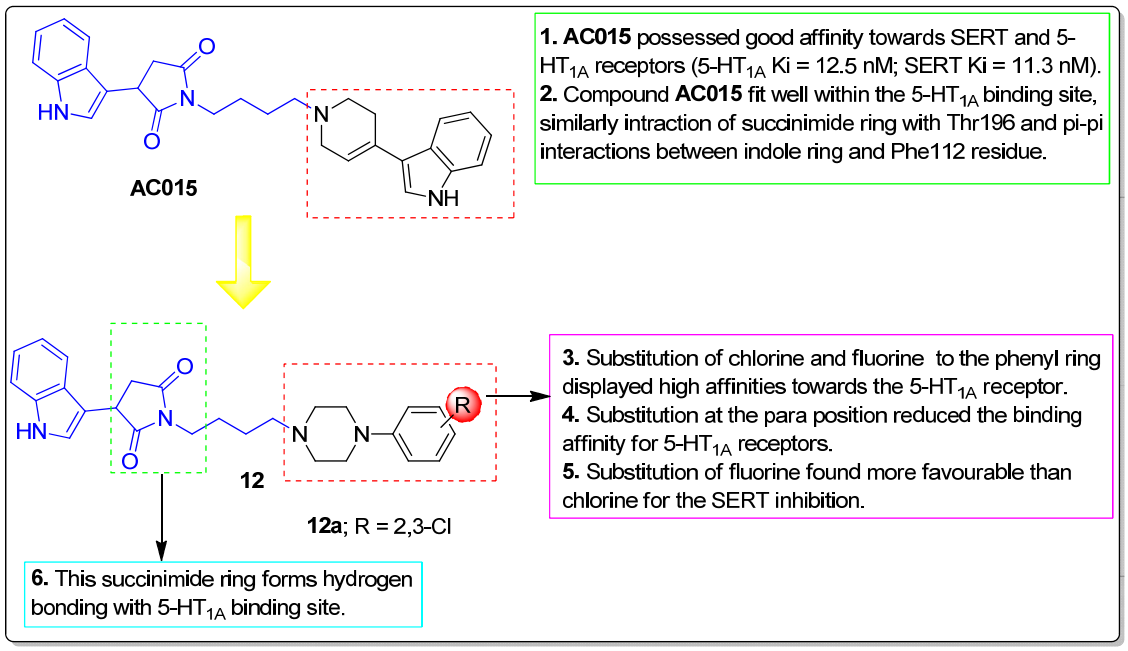


Fig. (6). Arylpiperazines as a promising class of multi-target ligands and their SAR.

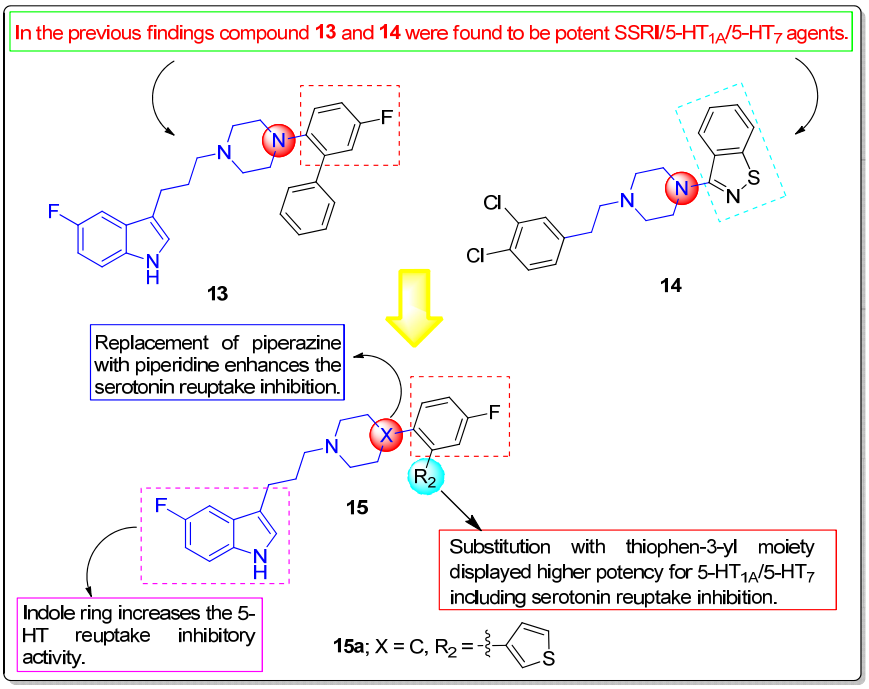


Fig. (7). Design strategy and SAR of multi-targeting aralkyl piperazine/piperidine derivatives.

profile. It showed potent binding affinities towards the 5-HT_{1A} and 5-HT_7 receptors with K_i values of 12 and 3.2 nM, respectively, along with good serotonin reuptake inhibitory activity with an IC_{50} value of 14 nM. It was further subjected to FST and TST studies to evaluate the antidepressant-like activity. Results of *in vivo* studies revealed that the compound **15a** significantly reduced the immobility time in a dose-dependent manner at 20 and 40 mg/kg dose levels, respectively. Metabolic stability studies were performed by using rat and human microsomal liver in which compound **15a** showed a $t_{1/2}$ value of 48.6 and 49.93 min, respectively. SAR studies revealed that the replacement of piperazine ring with a piperidine ring was effective in enhancing the inhibition of serotonin reuptake (Fig. **7**) [115].

Based on the concept that multiple target compounds are more efficacious and safer, Pessoa-Mahana *et al*. designed and synthesized a series of 3-indolylpropyl derivatives with a dual-targeting profile against 5-HT transporter (SERT) and serotonin-1A receptors subtype (5-HT_{1A}R). Results of *in vitro* studies identified compounds **18a** and **19a** as the most

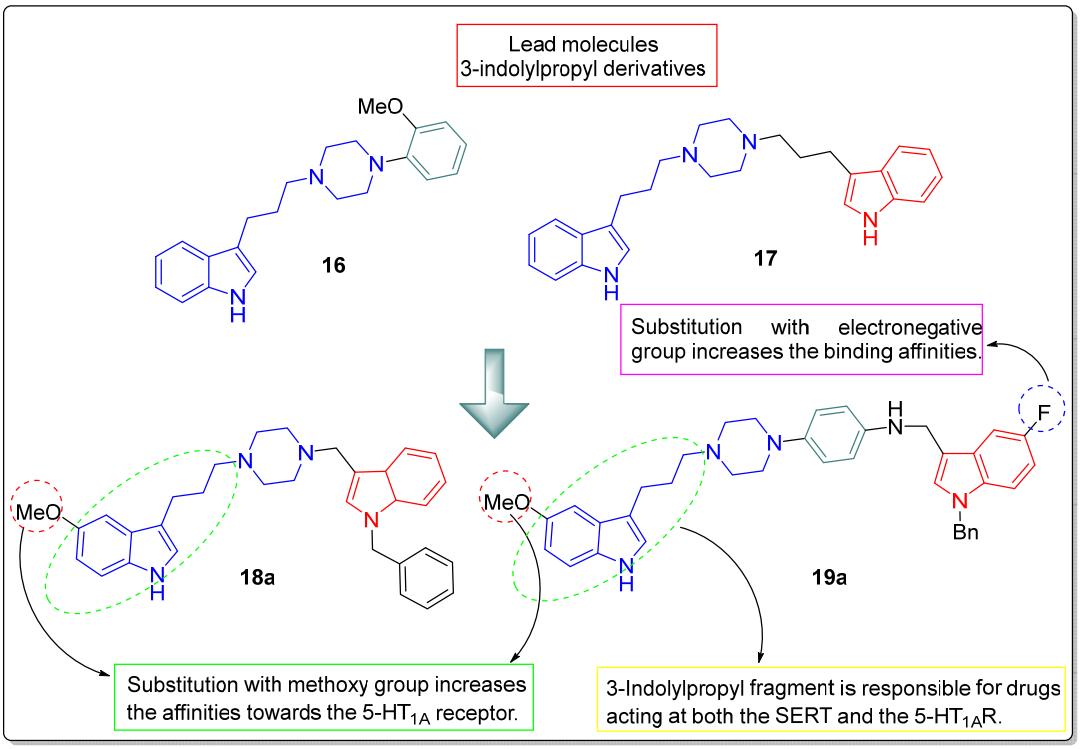


Fig. (8). 3-Indolylpropyl clubbed piperazine derivatives as dual-targeting antidepressants.

balanced dual-targeting agents. Compounds **18a** and **19a** showed the highest affinities towards the 5-HT_{1A}R with K_i values of 43 and 56 nM, respectively, while >10000 and 365 nM, respectively, towards the SERT. SAR studies highlighted that the 3-indolylpropyl fragment was responsible for the SERT inhibition and 5-HT_{1A}R activity. Substitution with a methoxy group at the indole ring increases the binding affinities towards the 5-HT_{1A}R **(**Fig. **8**). Molecular docking studies highlighted that the presence of a methoxy group at the indole ring favoured the aromatic interactions. Compound **19a** adopted the bend confirmations and displayed coulombic interactions with Asp116. It also showed hydrophobic interactions between the aromatic ring of the ligand and aromatic part Trp538, Phe361 and Try195 residues [105].

Wróbel *et al.* synthesized a series of 3-(1*H*-indol-3-yl)pyrrolidine-2,5-dione derivatives with the aim to obtain lead compounds having poly-pharmacological receptor profile. Synthesized compounds were evaluated for binding affinities towards the 5-HT_{1A}/D_2/5-HT_{2A}/5-HT_6/5-HT_7 by using the radioligand assay techniques. From the current series, compounds **22a** and **22b** displayed the highest affinities for the 5-HT_{1A} receptor with K_i values of 2.3 and 3.2 nM, respectively, and against SERT with K_i values of 308.0 and 201.0, respectively. Potent compounds were evaluated for the antidepressant-like activity by using the FST, and results revealed that compounds reduced the immobility time in a dose-dependent manner. The structure-activity relationship indicated that the substitution with electron-withdrawing groups at the indole moiety increased the biological activity (Fig. **9**) [74].

Depression is the most frequent and major complication in AD. Single target-based drugs do not respond effectively due to complex complications. Thus, the molecules need to be designed in such a way that they eliminate the amnesia and depression symptoms of Alzheimer's disease (AD) [116, 117]. Vilazodone acts as dual serotonin reuptake and partial agonist of the 5-HT_{1A} receptor but shows moderate AChE inhibitory activity [118, 119]. To improve the moderate AChE inhibitory activity, Li *et al.* synthesized a series of hybrids of vilazodone and tacrine as potential multi-target ligands for the treatment of depression with AD (Fig. **10**). The synthesized compounds were evaluated using *in vitro* biological assays. Among them, compound **25a** was found to be the most active against acetylcholinesterase enzyme, 5-HT_{1A} receptor and 5-HT reuptake with IC_{50} value of 3.319 ± 0.708 μM, the EC_{50} value of 107 ± 37 nM, and IC_{50} value of 76.3 ± 33 nM. The most potent candidate was also screened for blood-brain barrier permeability assay and hepatotoxicity on HepG2 cells. Results showed that compound **25a** (decreases the viability of the cells at 30 μM concentration) exhibited less cytotoxicity than the marked drug vilazodone (decreases the viability of the cell at the concentration of 20 μM). In the tail suspension test (TST), compound **25a·HCl** was found to be potent and reduced the immobility time at the dose of 30 mg/kg as compared to the reference amitriptyline (10 mg/kg). SAR studies have been summarized in Fig. (**10**) [120].

In continuation, Liu *et al.* designed and synthesized a series of vilazodone-tacrine hybrids and investigated them for multi-target agents against depression with cognitive impairment (Fig. **11**). Tacrine is known for acetylcholinesterase (AChE) inhibition having benzofuran-2-carboxamide moiety, which provides wide opportunities for structural modifications. Thus, a series of hybrid compounds by combining two pharmacophores were synthesized and all the compounds exhibited promising multi-target activities and BBB

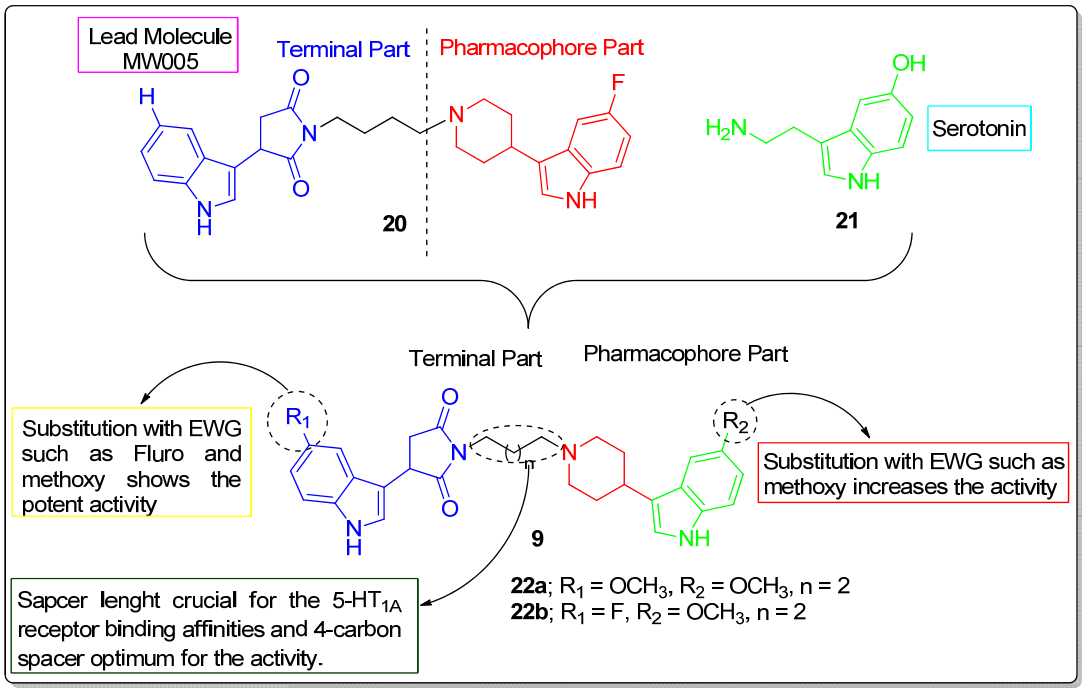


Fig. (9). Designing and SAR of 3-(1*H*-indol-3-yl)pyrrolidine-2,5-dione derivatives.

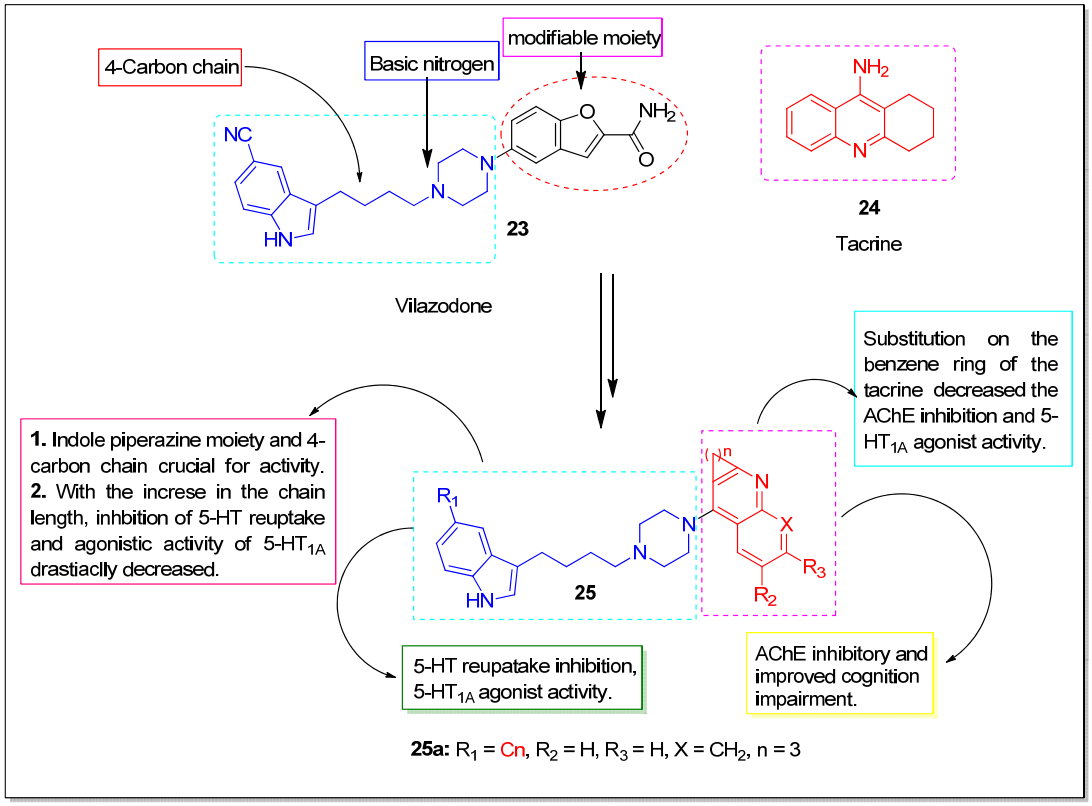


Fig. (10). Design and SAR of vilazodone-tacrine hybrids as multi-target ligands.

(Blood-brain barrier) permeability profile. Compounds **26a** and **26b** were the most active agents as they showed 5-HT reuptake inhibitory activity with IC_{50} values of 20.42 ± 6.60 and 22.10 ± 5.80 nM; 5-HT_{1A} with EC_{50} values of 0.36 ± 0.08 & 0.58 ± 0.14 nM; AChE inhibitory activity with IC_{50} values of 1.72 ± 0.217 and 2.26 ± 0.34 μM, and BuChE inhibition with IC_{50} values of 0.34 ± 0.03 and 0.10 ± 0.01 μM, respectively. The structure-activity relationship has been described in Fig. **(11)** [119]. The multi-target profile of these ligands makes them valuable lead compounds for further development.

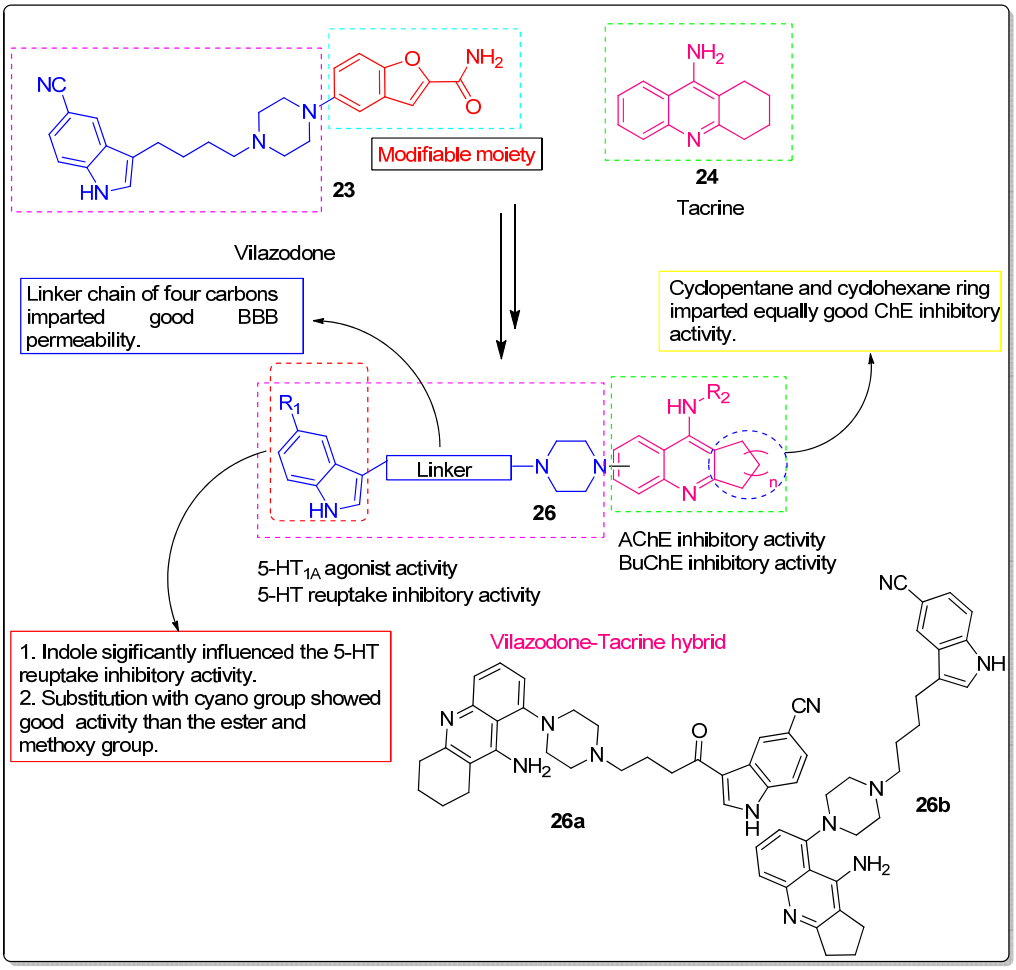


Fig. (11). Design and SAR of vilazodone-tacrine hybrids as multi-target antidepressants.

2.2. Purine Clubbed Piperazine Derivatives

Purine is a heterocyclic organic compound containing nitrogen at 1st, 3rd, 7th and 9th position of 6 membered and 5 membered fused ring systems [121]. 8-Alkoxy-purine-2,6-dione and dihydro[1,3]oxazolo[2,3-f]purinedione belong to the family of the purine. For many years, these purine scaffolds have been exploited as terminal fragments with the long-chain aryl piperazines (LCAPs) for the design and development of novel purine-based antidepressants [122]. Purine derivatives possess diverse pharmacological activities [123, 124], and recent findings show that purine clubbed piperazine derivatives display promising antidepressant profile [124-126].

1,3-Dimethyl-purine-2,6-dione scaffold showed good binding affinities towards the 5-HT_{1A}, 5-HT_{2A}, 5-HT_7 and 5-HT_6 [124] receptors. LCAPs have been reported to possess good binding affinities for 5-HT_{1A}, 5-$HT_{2A,}$ 5-HT_7 and 5-HT_6 receptors [127-129]. Exploring the concept of a multi-target approach, Chłoń-Rzepa *et al.* designed the synthesis of a series of long-chain arylpiperazine derivatives of 8-alkoxy-purine-2,6-dione (**27**) and dihydro[1,3]oxazolo[2,3-f]purinedione (Fig. **12**). All the synthesized compounds were investigated for their antidepressant and antipsychotic effects by targeting the serotonin (5-HT_{1A}, 5-HT_{2A}, 5-HT_6, and 5-HT_7) and dopamine (D_2) receptors. By using the radioligand assay technique, the binding affinities were evaluated. Compounds **28a** and **28b** displayed most promising affinities for 5-HT_{1A} (K_i values 4 nM and 10 nM), 5-HT_{2A} (K_i values 695 nM and 60 nM), 5-HT_7 (K_i values 12 nM and 23 nM) and D_2 (**K**$_i$ values 24 nM and 60 nM) receptors. Compound **28a** was tested further to evaluate the antidepressant-like activity by using the forced swim test, where it failed to show any significant antidepressant activity. Similarly, during the antipsychotic evaluation by using a four-plate test, this compound was unable to show any promising response. Molecular docking supported the outcome of biological findings which highlighted that arylpiperazine occupied the charge-reinforced region by exhibiting hydrogen bond interaction with Asp3.32, pi-pi stacking with Phe6.52 and pi-cation interaction with Lys191 [130]. The design and SAR studies of these compounds are shown below in Fig. (**12**).

In the previous studies, Partyka *et al.* synthesized a series of long-chain arylpiperazine derivatives and evaluated them for antidepressant-like activity [131, 132]. In continuation of earlier studies, the authors reported the design and synthesis of 8-unsubstituted-7-phenylpiperazin-4-yl-alkyl and 7-tetrahydroisoquinolinyl-alkyl derivatives as promising multi-targeting antidepressant agents (Fig. **13**). Synthesized compounds were evaluated for their binding affinities for the 5-HT_{1A}, 5-HT_{2A}, 5-HT_6, 5-$HT_{7,}$ and dopamine D_2 receptors. Among them, compounds **31a**, **31b**, **31c**, and **31d** showed

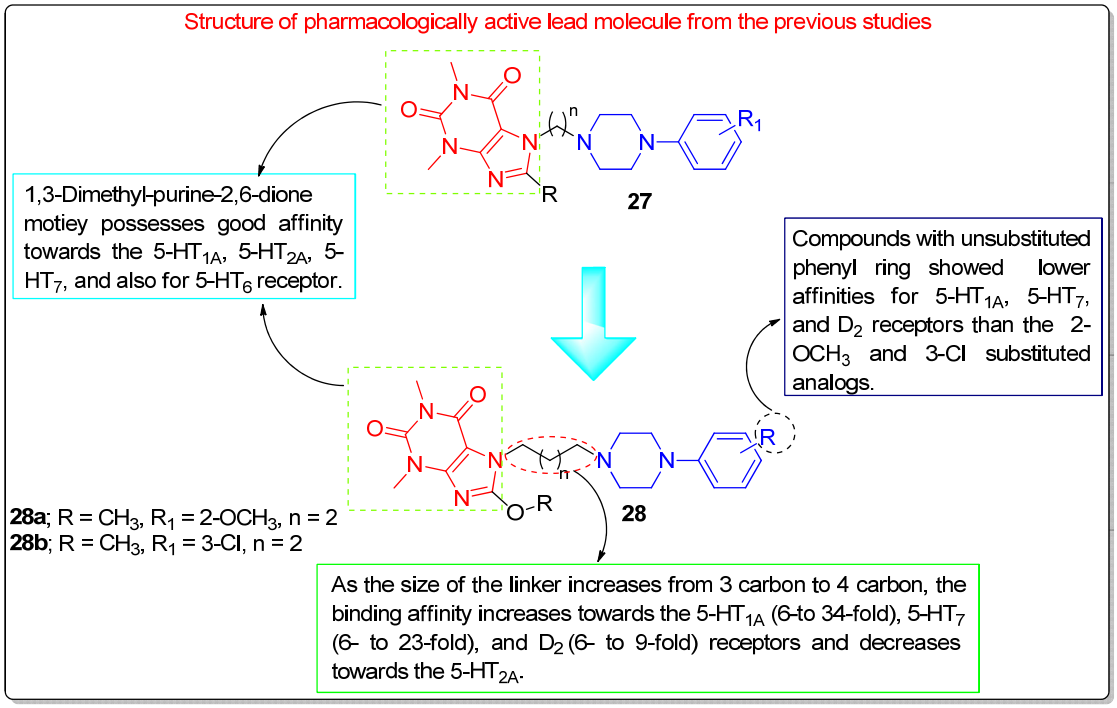


Fig. (12). Purine clubbed piperazine derivatives as multi-targeting antidepressants.

good binding affinity towards the 5-HT_{1A} and moderate affinities for the 5-HT_{2A}, 5-HT_7, and dopamine D_2 receptors. Compounds **31a**, **31b**, **31c**, and **31d** displayed the K_i value of 1 nM, 11 nM, 1 nM, and 5 nM for the 5-HT_{1A}, respectively. Besides, the compounds **31a**, **31b**, and **31c** were found to be potential agonists of pre and/or post-synaptic 5-HT_{1A} receptors, while **31d** turned out to be a potential antagonist of the post-synaptic sites. These potent compounds were further tested for the behavioral studies of antidepressant-like and anti-anxiety-like activity (*in vivo*). The results exposed that except for **31c**, compounds **31a**, **31b**, and **31d** displayed promising anxiolytic activity. In the forced swim test, compounds **31a** and **31c** emerged as the most promising candidates and produced marked antidepressant-like effects which were found to be comparable to the standard drug imipramine [133].

Chłoń-Rzepa *et al.* synthesized a series of 3,7-dimethyl- and 1,3-dimethyl-8-alkoxypurine-2,6-dione derivatives of tetrahydroisoquinolines, perhydroisoquinolines, or arylpiperazines with flexible alkylene spacers. Synthesized compounds were investigated for their binding affinities towards the 5-HT_{1A}/5-HT_7 receptor and also as PDE inhibitors with antidepressant-like activity. Among the series, compounds **32b**, **33a**, and **33b** were found to be most promising and exhibited multi-targeting activity for the 5-HT_{1A}/5-HT_7 receptors. These compounds also displayed antidepressant-like effect in the FST, which was similar to the standard drug citalopram. All the synthesized compounds were found to inhibit phosphodiesterase isoenzyme better than theobromine and theophylline. Compounds **32a** and **32b** showed 51% and 52% inhibition of PDE, respectively. Compound **32b** emerged as the multi-targeting ligand as it showed antidepressant-like effect and PDE inhibition simultaneously. SAR studies revealed that the spacer length of 3-4 carbon atoms was optimum for the 5-HT_{1A} receptor agonistic activity (Fig. **14**). Molecular modeling studies highlighted that the compound **32b** formed a hydrogen bond between the methylxanthine motif of the ligand and Gln443 residue along with pi-pi stacking with the Phe446 [134].

The design and synthesis of another series of 8-aminoalkylamino and 8-arylpiperazinylpropoxy derivatives of 7-substituted 1,3-dimethyl-3,7-dihydropurine-2,6-dione were explored by the same research group. Binding affinities of the synthesised compounds towards the 5-HT_{1A}, 5-HT_{2A}, and 5-HT_7 receptors were determined by using the radioligand assay techniques. Among them, compound **34a** showed a multi-target profile by targeting 5-HT_{1A}, 5-HT_{2A}, and 5-HT_7 simultaneously, with a K_i value of 25, 68, and 65 nM, respectively. The outcome of *in vivo* FST studies showed that compound **34a** significantly decreased the immobility time by 33% at 20 and 30 mg/kg dose, while the reference drug imipramine reduced the immobility time by 52% and 27% at the dose of 10 and 20 mg/kg, respectively. SAR studies indicated that substitution with 3-chloroohenylpiperazine imparted high-to-moderate activity (Fig. **15**) [135].

Chłoń-Rzepa *et al.* reported the synthesis of long chain aryl piperazine derivatves (**35**) as serotonin receptor ligands [131]. In continuation of their previous studies, the design and synthesis of a series of 7-arylpiperazinylalkyl-8-morpholin-4-yl-purine-2,6-dione derivatives and evaluation of their *in vitro* studies for 5-HT_{1A}, 5-HT_{2A}, 5-HT_6 and 5-HT_7 receptors were disclosed by the authors. Among them, compound **35a** showed a potent profile towards the 5-HT_{1A}/5-HT_{2A} with K_i values 22 nM / 21 nM and moderate affinities for the 5-HT_7 and 5-HT_6 with K_i values 207 and 112 nM, respectively (Fig. **15**) [132].

Zagórska *et al.* reported the synthesis of 2-fluoro and 3-trifluoromethylphenylpiperazinylalkyl derivatives of 1*H*-imidazo[2,1-f]purine-2,4(3*H*,8*H*)-dione (**36**). The synthesized

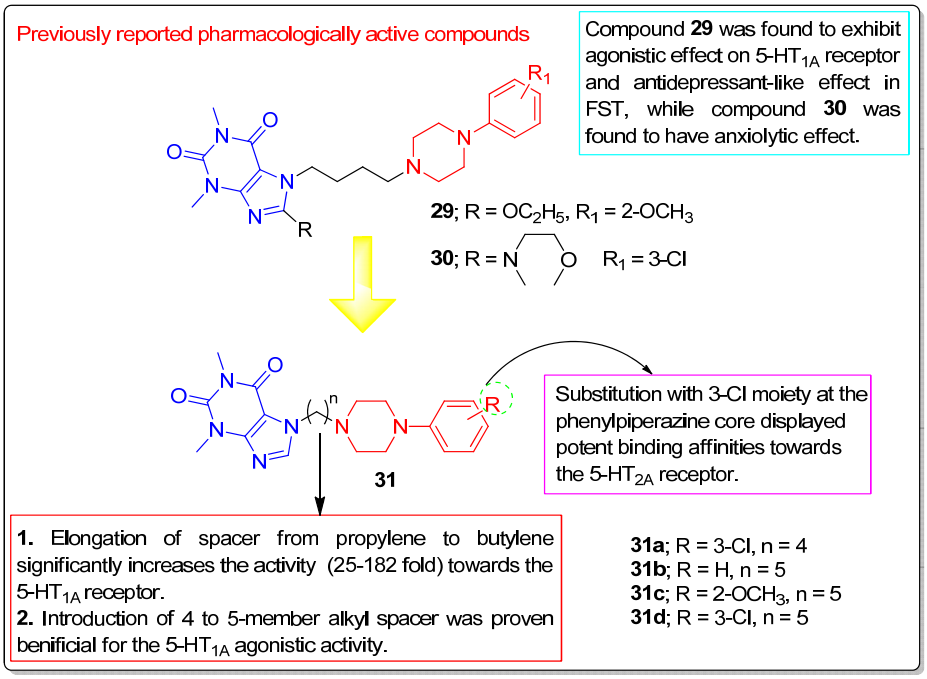


Fig. (13). 7-Phenylpiperazin-4-yl-alkyl and 7-tetrahydroisoquinolinyl-alkyl derivatives as antidepressant agents.

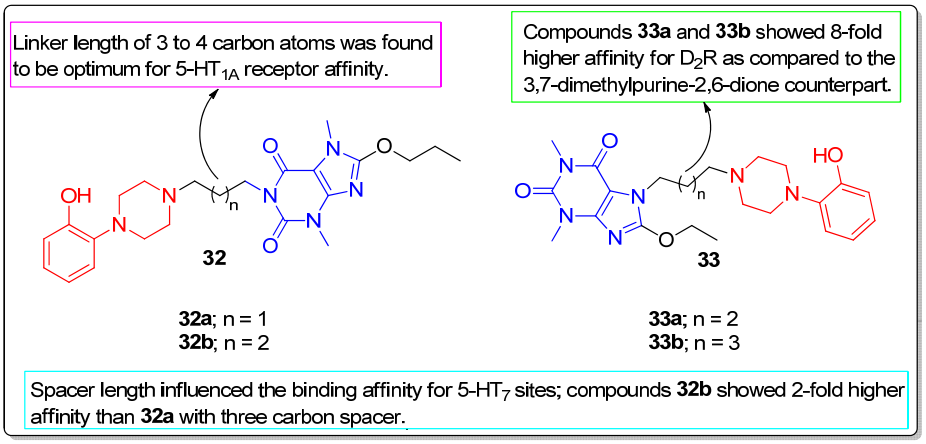


Fig. (14). 3,7-Dimethyl- and 1,3-dimethyl-8-alkoxypurine-2,6-dione appended piperazine derivatives as antidepressants.

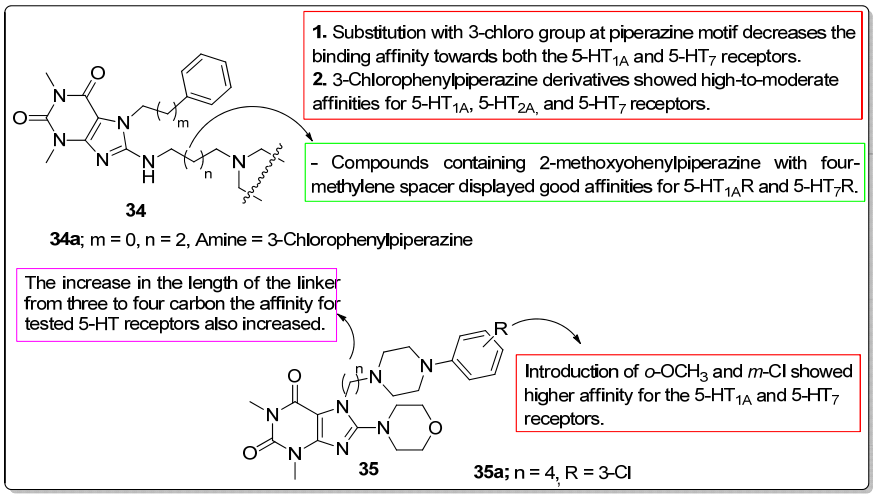


Fig. (15). Dihydropurine-2,6-dione and 8-arylpiperazinyl-purine derivatives as MTDLs.

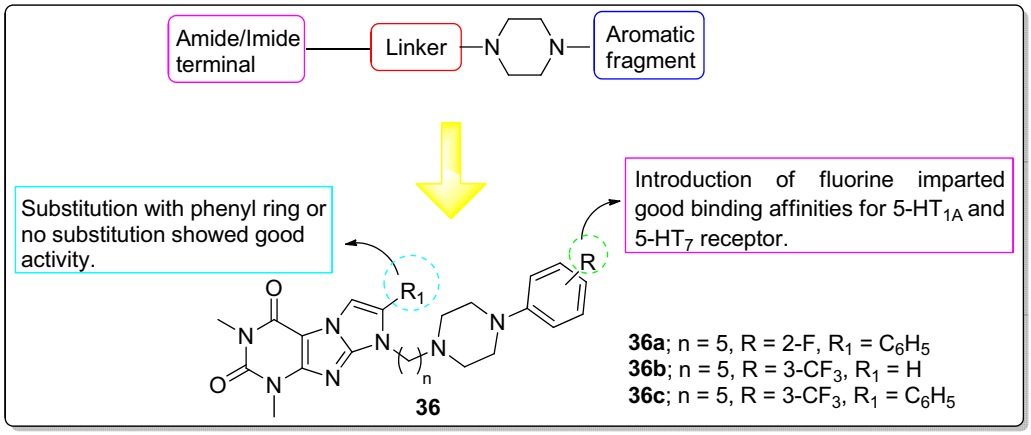


Fig. (16). Design and SAR of fluoromethylphenylpiperazinylalkyl derivatives as antidepressants.

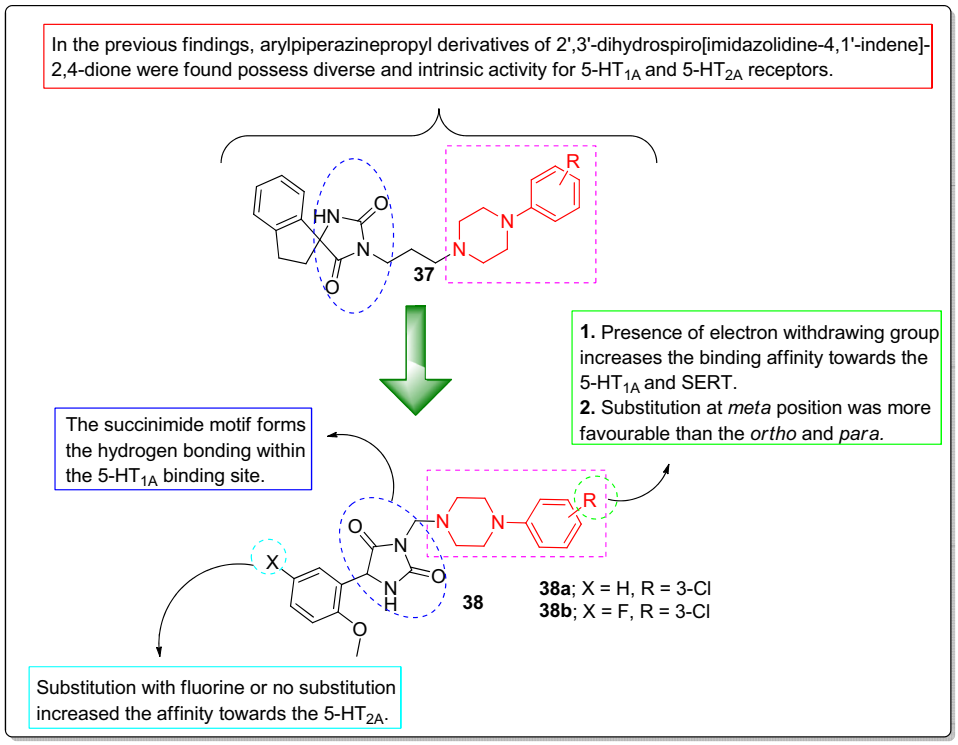


Fig. (17). Mannich bases of the imidazolidine-2,4-diones as promising antidepressants.

compounds were screened for serotonin (5-HT_{1A}/5-HT_7) receptor affinity and phosphodiesterase (PDE10A and PDE4B) inhibition potential. Among them, compounds **36a**, **36b** and **36c** were found to be the most promising candidates for 5-HT_{1A} and 5-HT_7, while they displayed weak inhibitory activity for the phosphodiesterase. Results of *in vivo* evaluation showed that the compound **36a** reduced the immobility time by 21% at the dose of 2.5 and 5 mg/kg, while the standard drug citalopram reduced the immobility time by 28%, 51% and 61% at the dose range of 1.25-5 mg/kg. SAR studies suggested that the introduction of a fluorine group was beneficial for the inhibition of PDE (Fig. **16**). Further, molecular docking studies were performed within the two cavities of the binding sites. Among them, one is constituted by transmembrane helices (TMHs) 3-6 and the other with the TMHs 2 and 7. Compounds displayed charge-reinforced hydrogen bond between the carboxyl group of Asp3.32 and protonated hydrogen, CH-pi interaction between the aromatic amino acid (Phe6.52) and arylpiperazine ring [126].

2.3. Succinimide Piperazine Conjugates

In previous findings, Czopek *et al*. disclosed the synthesis of a series of 5,5-disubstituted and 5-spiro-imidazolidine-2,4-dione derivatives appended with an arylpiperazinylpropyl moiety, and the compounds displayed diversified affinity profile towards 5-HT_{1A} and 5-HT_{2A} receptors [136]. The most potent compounds behaved as 5-HT_{1A}R agonists or partial agonists and exhibited potent antidepressant activity. Considering the therapeutic relevance of compounds with a dual mechanism of action, namely serotonin transporter (SERT) blockers and 5-HT_{1A} ligands, Czopek *et al*. incorporated the structural features of serotonin reuptake inhibitory activity into the profile of compounds interacting with the 5-HT_{1A} receptors. A series of Mannich bases of the arylpipera-

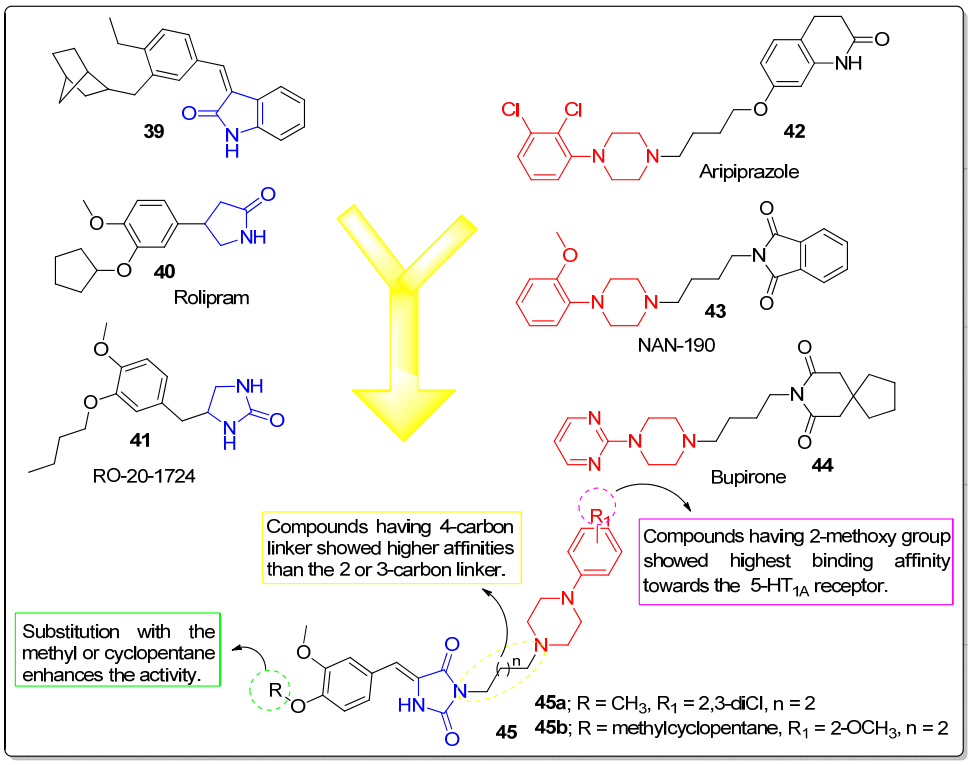


Fig. (18). Piperazine clubbed 5-arylidenehydantoin derivatives as MTDLs.

zinemethylimidazolidine-2,4-diones (Fig. **17**) were designed, synthesized and investigated for their binding affinities towards the SERT, 5-$HT_{1A,}$ and 5-HT_{2A} receptors. From the series, compounds **38a** and **38b** were found to be the most potent candidates for SERT, 5-$HT_{1A,}$ and 5-HT_{2A} receptors with K_i values 0.16, 0.28, 38, 76, 89, and 58 nM, respectively. The agonist assay of the potent compounds (**38a and 38b**) was evaluated, and the EC_{50} value was found to be 157 nM and 4.1 μM, respectively. FST studies revealed that compounds **38a** and **38b** significantly reduced the immobility time in a dose-dependent manner at the dose of 20 and 30 mg/kg compared to the reference drug imipramine. Compound **38b** was found to be less effective due to its sedative effect observed in the locomotor activity. SAR studies confirmed that the presence of an electron-withdrawing group on the phenyl ring linked to the piperazine core enhanced the binding affinities towards the SERT and 5-HT_{1A} receptors [137].

In continuation, the research group has designed new molecules by hybridizing the structural features of serotonin modulators or drugs (buspirone (**44**) [138], NAN-190 (**43**) [139], aripiprazole (**42**) [140]) with the phosphodiesterase 4 inhibitors (RO-20-1724 (**41**) [141], rolipram (**40**) [142]). They synthesized a series of 5-arylidenehydantoin derivatives containing the arylpiperazine fragment. Binding affinities of all the synthesized compounds were determined towards the 5-HT_{1A} and 5-HT_7 (Fig. **18**) receptors. Among them, compounds **45a** and **45b** were found to be most promising with binding affinity values in the low nanomolar range. Compound **45a** showed excellent affinity towards the 5-HT_{1A} and 5-HT_7 with K_i values of 0.2 and 0.8 nM, respectively, whereas compound **45b** showed K_i value of 1.0 and 1.0 nM, respectively. The results of the cytotoxicity assay on cancer and normal cells indicated that the compounds were less toxic than the positive control and the reference drug doxorubicin. To evaluate antidepressant-like activity, FST (*in vivo*) was implemented in which compound **45a** reduced the immobility time by 27% at the dose of 0.625 mg/kg, while compound **45b** reduced the immobility time by 30% approx. at the dose of 0.625, 1.025, and 2.5 mg/kg, respectively. SAR studies demonstrated that substitution with electron-donating groups at the phenyl ring linked to the piperazine moiety enhanced the binding affinities towards the 5-HT_{1A} receptor. Further, docking studies revealed that these compounds exhibited two interactions within the binding site; one involved charge-reinforced hydrogen bond between the carboxyl group of Asp3.32 and protonated nitrogen of the ligand and the other involved CH-pi stacking between arylpiperazine fragment and aromatic ring of Phe6.52 [143].

2.4. Naphthosultam Coupled Piperazine Derivatives

Napthosultam consists of a naphthalene ring fused with a lactam ring at 1- and 8-position. This ring system holds various pharmacological activities. Based on the structure-activity relationship and virtual screening of the long-chain arylpiperazines (LCAP), Zaręba *et al.* synthesized various LCAP derivatives by incorporating the structural features of fananserin via microwave-assisted synthesis (Fig. **19**). Synthesized molecules were evaluated for their binding affinities towards the serotonin and dopamine receptors (5-HT_7, 5-HT_{1A}, D_2) by implementing the radioligand bioassay. Among them, compound **47a** showed a potent multifunctional/multi-target ligand profile and displayed high binding affinities for the 5-HT_{1A}/5-HT_7/D_2 with K_i values of 43, 53 and 75 nM, respectively. On the other hand, compound **47b** exhibited dual action on the 5-HT_{1A}, D_2 receptors with a K_i value of 66

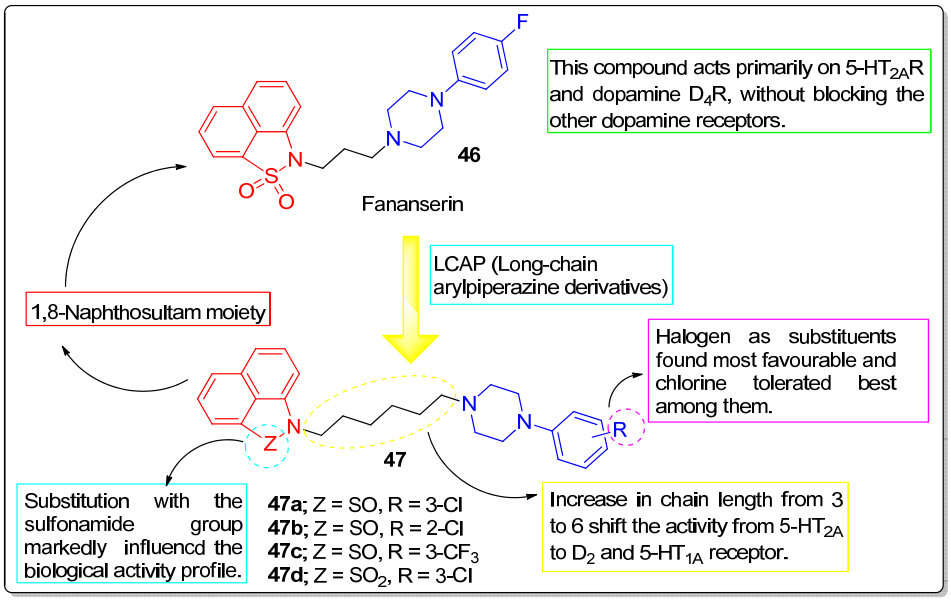


Fig. (19). Fananserin-derived long-chain arylpiperazines as MDTLs for depression.

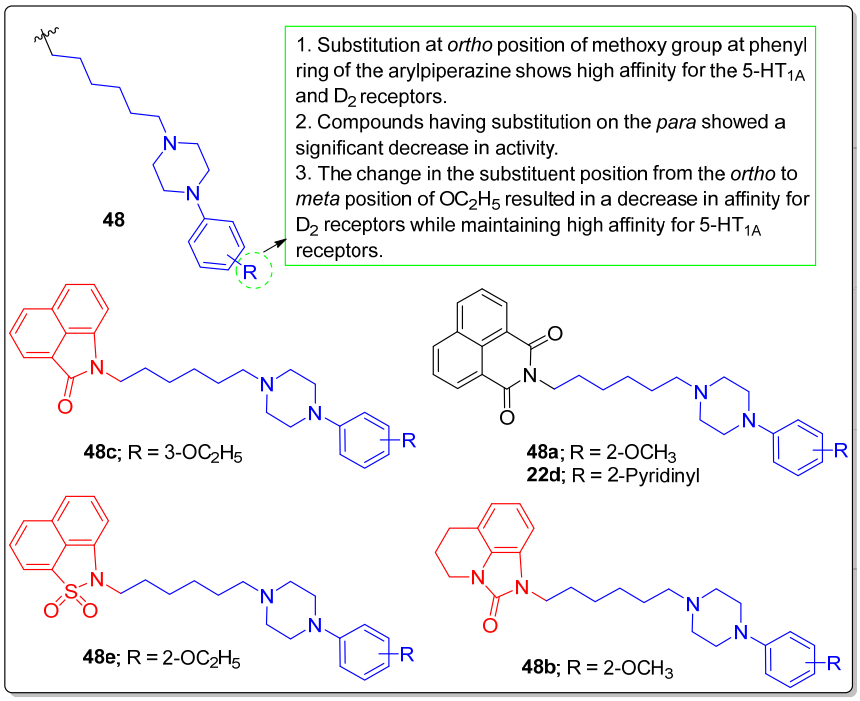


Fig. (20). Structure-activity relationship of hexylarylpiperazine derivatives.

and 58 nM, and compounds **47c** and **47d** demonstrated the selectivity of the 5-HT_{1A} with K_i values of 54 and 46 nM, respectively. SAR studies suggested that the substitution with a halogen atom (most favorable was chlorine) at the phenyl ring linked to the piperazine motif increased the activity [144].

Zaręba *et al*. designed and synthesized a series of bulky hexylarylpiperazine derivatives by using the microwave synthesizer (a green chemistry approach). The synthesized compounds or ligands were examined for their binding affinities towards the 5-HT_{1A}, 5-HT_{2A}, 5-HT_6, 5-HT_7, and D_2 receptors. Compounds **48a**, **48b**, **48c**, **48d**, and **48e** were found to be the most promising candidates for targeting the 5-HT_1A and D_2 receptors and classified as multi-target ligands. Compound **48d** exhibited favorable and high binding affinities towards the 5-HT_7 receptor. The K_i values exhibited by compounds for 5-HT_1A/D_2 were **(48a)** 10 nM, 20 nM, **(48b)** 2 nM, 19 nM, **(48c)** 11 nM, 22 nM, **(48d)** 27 nM, 28 nM, and **(48e)** 30 nM, 48 nM, respectively. SAR studies suggested that the substitution of a methoxy group at the *para* position of the phenyl ring linked to the arylpiperazine motif showed high binding affinities for the 5-HT_{1A} and D_2 receptors. Changing the position of substitution from *para* to *ortho,* the binding affinities decreased significantly (Fig. **20**). The

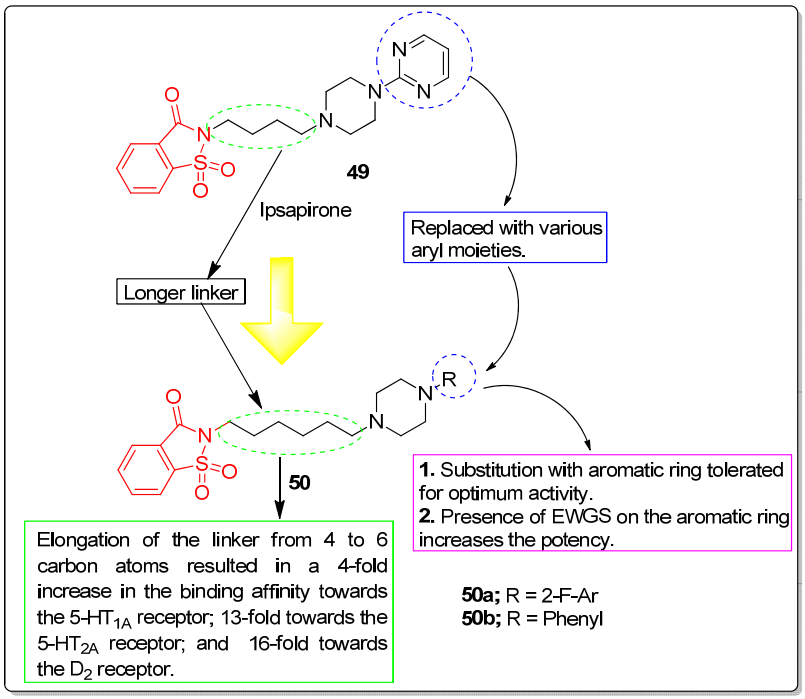


Fig. (21). Design strategy and SAR of hexyl arylpiperazines as MDTLs.

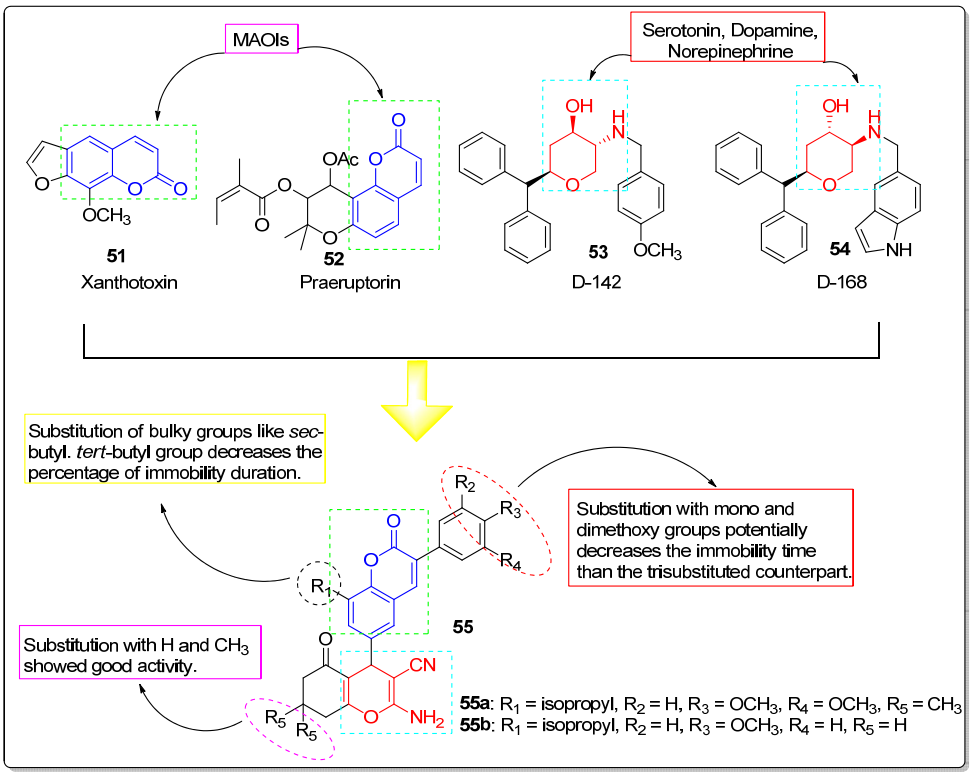


Fig. (22). Coumarin clubbed aminopyran derivatives as potent antidepressants.

docking studies demonstrated that ligands formed a hydrogen bond between the basic nitrogen atom of the arylpiperazine ring and Asp3.32 within the 5-HT_{1A} receptor binding pocket [145].

Kułaga *et al.* designed and synthesized a series of new hexyl arylpiperazine derivatives (**50**) from the saccharin moiety. The synthesized compounds were estimated for their binding affinities towards the serotonin and dopamine receptors. Among them, compounds **50a** and **50b** displayed the highest selectivity towards the 5-HT_{1A}R and D_2R receptors. Compound **50a** showed a K_i value of 12 nM for 5-HT_{1A} and 24 nM for D_2, while compound **50b** showed a K_i

value of 48 nM for 5-HT_{1A} and 48 nM for D_2, respectively. Both the compounds emerged as the promising multi-target ligands having antidepressant-like effect. SAR studies revealed that substitution of the aromatic ring with electron-withdrawing groups at the 4th position of the piperazine ring increased the activity (Fig. **21**) [146].

2.5. Coumarin Conjoined Aminopyran Derivatives

Coumarins belong to the class of benzopyrenes and have been reported to exhibit antidepressant activity [147-149]. Xanthotoxin (**51**) and praeruptorin (**52**) represent the new generation of coumarin-based MAOIs with potent antidepressant activity [150]. Aminopyran containing compounds (**53**, **54**) have been reported to exhibit promising antidepressant activity via triple reuptake inhibitor mechanism (dopamine, serotonin, and norepinephrine) [151]. To further potentiate their biological potency and selectivity, Sashidhara *et al*. clubbed coumarin and aminopyran fragments by utilizing molecular hybridization strategy and synthesized their structural hybrids **(55**, Fig. **22)**. All the synthesized compounds were evaluated for antidepressant effect by using forced swim test and tail suspension test in swiss albino mice. Among them, compounds **55a** and **55b** were found to be the most potent which reduced the immobility time by 86.5% and 69.7% at the dose of 0.5 mg/kg, respectively, as compared to the standard drug fluoxetine (69.8 % at the dose of 20 mg/kg) and control. These compounds were further tested at the lower dose in the forced swim test. Results revealed that compound **55a** was able to attenuate the immobility time by 41%, whereas **55b** was unable to reduce the immobility time at the lower dose. In the tail suspension test, compound **55a** decreased the immobility time at a dose of 0.5 mg/kg. Neurotoxicity studies revealed the compounds to be non-toxic at the dose of 1.0 mg/kg. [152].

Bashir *et al.* designed and synthesised a series of dibenzylidene ketone derivatives, *i.e.*, (2*E*, 6*E*)-2,6-dibenzylidene cyclohexanone (**57a**) and (1*E*,4*E*)-5-(2,3-dichlorophenyl)-1-(4-methoxyphenyl)-2-methylpenta-1,4-diene-3-one (**58a**), inspired from the potential biological profile of the natural lead molecule curcumin (**56,** Fig. **23**). Synthesized molecules were evaluated for antidepressant-like activity by using forced swim test, tail suspension test, and open field test, and for evaluation of their anti-Alzheimer activity, Y-maze test and morris water maze test have been performed. Two compounds, **57a** and **58a**, decreased the immobility time significantly in the dose-dependent manner (0.1-1 mg/kg) in the tail suspension test and forced swim test. Compounds **57a** and **58a** increased the number of ambulations and rearings in the open-field test. Toxicity studies indicated that the compounds were devoid of any toxicity up to the dose of 10 mg/kg. Furthermore, results of the molecular docking studies supported the outcome of biological findings wherein compound **57a** exhibited good affinity towards the biological targets involved in the depression, while compound **58a** exhibited significant binding affinity towards the biological targets involved in Alzheimer's [153].

2.6. Miscellaneous

Gu *et al*. substituted the benzo[b][1,4]oxazine unit with the 3,4-dichlorophenyl unit and the 2-methioxyphenyl unit with other aromatic rings in the lead molecule **59** to improve their pharmacokinetic and selectivity profile and synthesized a series of arylalkanol and aralkyl piperazine derivatives (Fig. **24**). The synthesised compounds were screened for binding affinities towards the 5-HT_{1A}/5-HT_7 receptors and serotonin reuptake inhibitory proficiencies. Among them, compound **60a** was found to be most energetic with a multi-target profile and displayed high binding affinity towards 5-HT_{1A}/5-HT_7 receptors with K_i values of 0.84 and 12 nM, respectively. However, it possessed moderate inhibitory activity for serotonin reuptake transporter with an IC_{50} value of 100 nM. The potent compound was further evaluated for antidepressant-like activity by using FST, in which compound **60a** significantly reduced the immobility time in a dose-dependent manner. Metabolic stability of compounds was investigated, and results specified that compound **60a** showed $t_{1/2}$ of 5.3 min. The designed analogues were found to possess improved pharmacokinetic profile as compared to parent lead molecule (**59**), and can be explored as a valuable tool for the development of more potent and effective SSRI/5-HT_{1A}/5-HT_7 targeting agents. [114].

In recent years, researchers have developed a number of 5-HT_{1A}/5-HT_7 receptor ligands based on long-chain arylpiperazines possessing purine-2,6-dione scaffold as the terminal section [131, 133, 154]. Considering this, Jankowska *et al.* synthesized a series of anilide and benzylamide derivatives of ω-(4-(2-methoxyphenyl)piperazin-1-yl)alkanoic acids (Fig. **25**) and evaluated them for 5-HT_{1A}/5-HT_7 affinity as well as for phosphodiesterase (PDE4B and PDE7A) inhibition profile. Compound **64a** was found to possess the most promising multifunctional/multi-target profile. It showed 5-HT_{1A} receptor antagonistic properties with K_i value of 8 nM and K_b value of 0.04 nM; 5-HT_7 antagonistic activity with K_i value of 451 nM and K_b value of 460 nM. It also displayed significant PDE4B/PDE7A inhibitory activity with IC_{50} values 80.4 and 151.3 μM, respectively. These potent compounds were further investigated for *in vitro* ADME as well as metabolic studies, and results showed that compound **64a** exhibited good penetration through the biological membranes and was found to possess high metabolic stability. Compound **64a** significantly reduced the immobility time by 34 % at the dose of 10 mg/kg in the FST. The structure-activity relationship studies showed that substitution with the branched alkyl group at the phenyl ring was more favorable than the ester, hydroxy, and amide (Fig. **25**) group. Further, molecular docking revealed that the phenyl ring of the phenylpiperazine moiety exhibited pi-pi stacking with the Phe416 residue while the protonated nitrogen of the piperazine ring formed a hydrogen bond with the water molecule [155].

GSK-3β inhibitors are ATP-competitive and non-ATP competitive inhibitors which find applications in the treatment of various human illnesses, including neurodegenerative and psychiatric disorders [156]. The first GSK-3β inhibitor was lithium, a mood stabilizer, and has been long used for the treatment of bipolar (manic-depressive) disorders [157, 158]. GSK-3β has attracted the attention of various researchers around the globe to develop compounds which selectively target GSK-3β and produce antidepressant-like effects. In this regard, derivatives of 1,2,3-triazole and 2-substituted pyrimidin-4-ones have been reported to possess various biological activities, including antidepressant activity

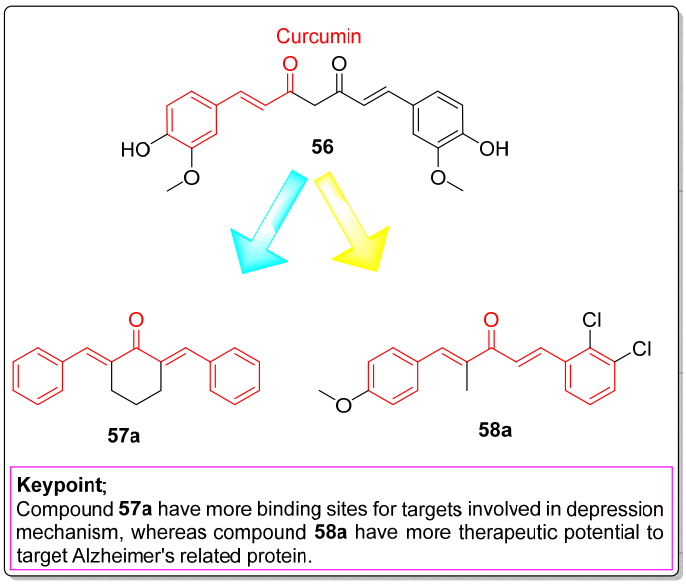


Fig. (23). Dibenzylidene ketone derivatives as multi-target directed antidepressant agents.

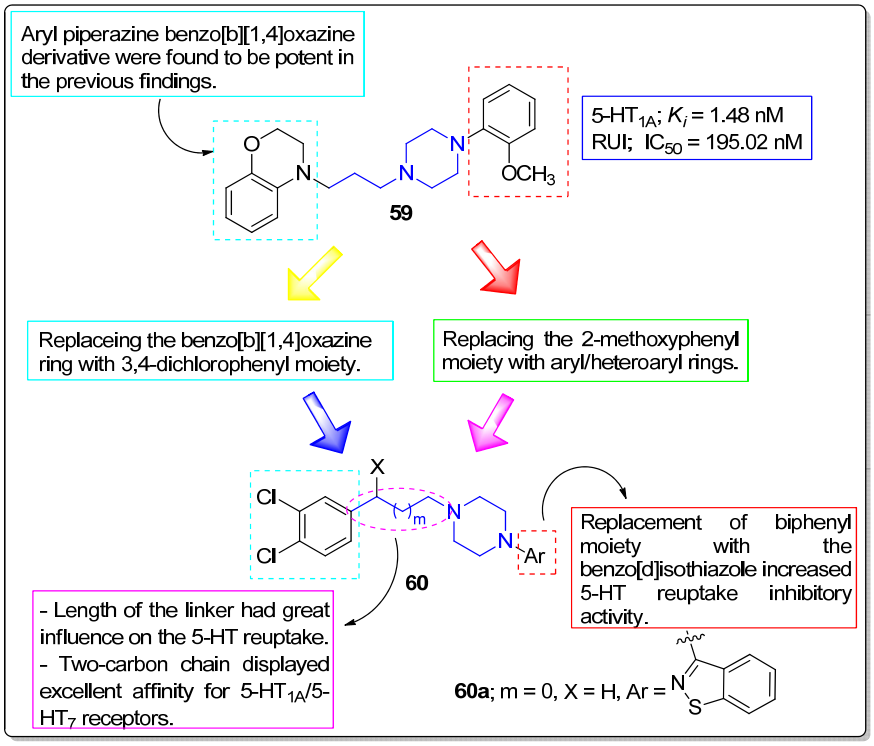


Fig. (24) Arylalkanol and aralkyl piperazine derivatives as MDTLs for depression.

[159, 160]. With the aim to improve the GSK-3β inhibition and antidepressant-like activity, Khan *et al.* synthesized a series of conjugates by introducing the triazole ring at the C-2 position of the pyrimidine core (Fig. **26**), and investigated them as GSK 3β inhibitors. Among them, compound **67a** was found to be the most active GSK-3β inhibitor with an IC_{50} value of 82 nM. Results of the *in vivo* antidepressant-like activity revealed that the compound **67a** significantly reduced the immobility time at the dose of 50 mg/kg in both the tests, *i.e.*, TST as well as FST. Molecular docking was performed against the protein GSK-3β, and it was observed that the potent compounds formed hydrogen bonds and exhibited hydrophobic interactions with various amino acid residues present in the binding site. Compound **67a** exhibited a glide score of -7.10 and formed a hydrogen bond with Val-135 residue [161].

Monoamine transporters play an important role in the mechanism of depression [162, 163]. However, monoamine reuptake inhibitors (**68-70**) having the cationic amphiphilic structures possess some problems, such as hERG inhibition of CYP2D6 inhibition [164], phospholipidosis, *etc.* [165]. To eliminate these drawbacks, Honda *et al.* hypothesized that the compounds restricted to one aromatic ring and having a

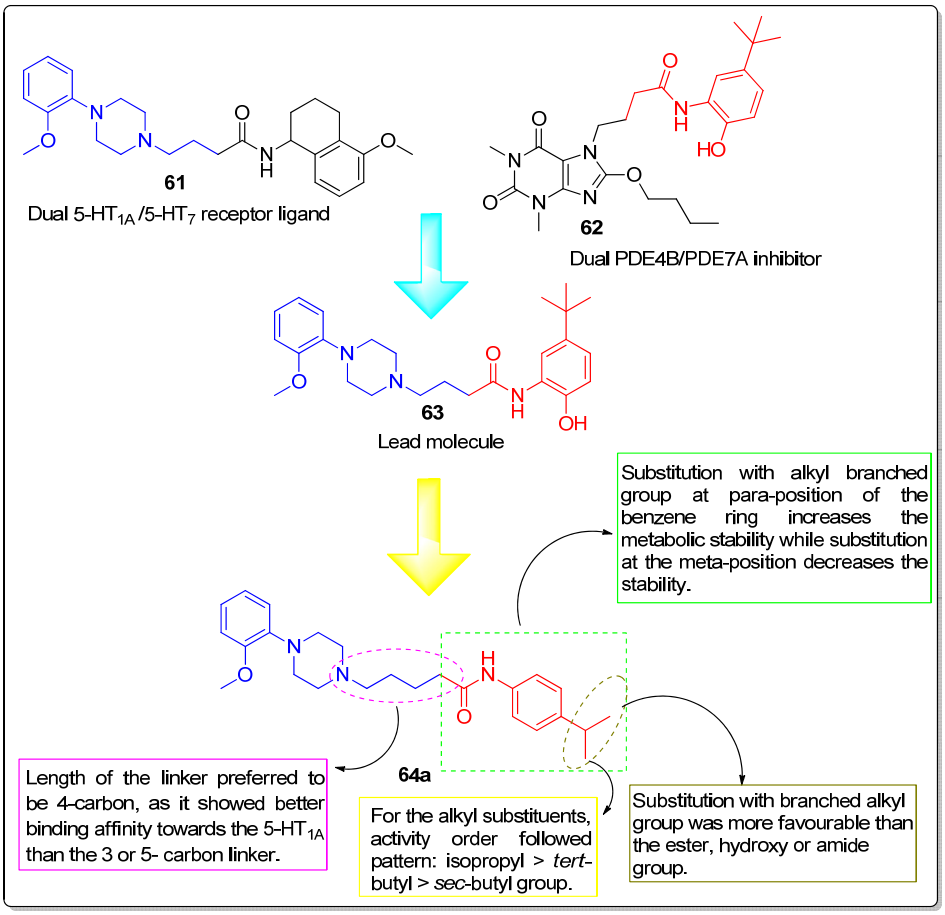


Fig. (25). Design and SAR of ω-(4-(2-methoxyphenyl)piperazin-1-yl)alkanoic acid derivatives as MDTLs for depression.

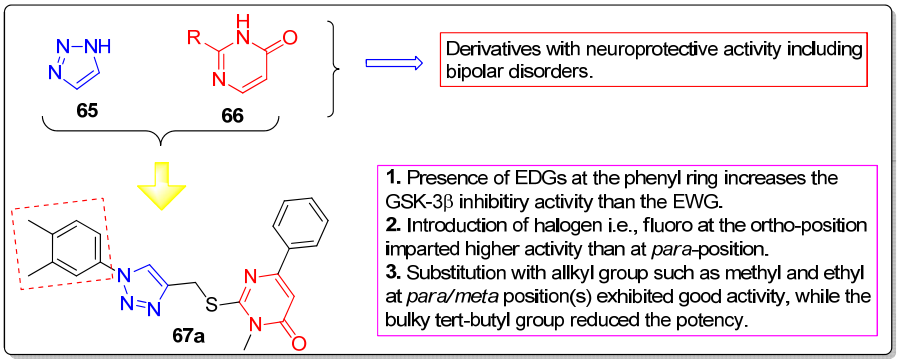


Fig. (26). Pyrimidine-triazole hybrids as antidepressants with GSK-3β inhibitory activity.

molecular weight less than 300 daltons possess less complications. Hence, they designed and synthesized 1-aryl-1,4-diazepan-2-one derivatives (Fig. **27**) as triple reuptake inhibitors (a multi-target ligand approach). Synthesized compounds were investigated to determine their inhibitory potential for serotonin reuptake, norepinephrine transporter, and dopamine transporter. Compound **71a** was found to possess a potent activity profile with poor metabolic stability. The compound showed inhibition of serotonin reuptake with a K_i value of 50 nm, norepinephrine with a K_i value of 13 nM, and dopamine with a K_i value of 420 nM. Potent compounds were evaluated for antidepressant-like activity *in vivo,* and results revealed that compound **71a** reduced the immobility time significantly in a dose-dependent manner. Additional studies showed compound **71a** to be safe and devoid of CYP2D6 and hERG inhibitory activity [166].

Based on the previous studies [167] and in a quest to discover potential lead(s) for antidepressant-like activity, Wen *et al*. designed and synthesized a series of arylamidine derivatives (Fig. **28**) as dual reuptake inhibitors of serotonin and norepinephrine. Synthesized compounds were investigated for binding affinities towards serotonin (5-HT) and norepinephrine (NE). Among them, compound **72a** was found to be the most promising candidate with potent 5-HT and NE inhibitory profiles having IC_{50} values 620 and 10 nM, respectively. Results of *in vivo* studies showed that compound **72a**

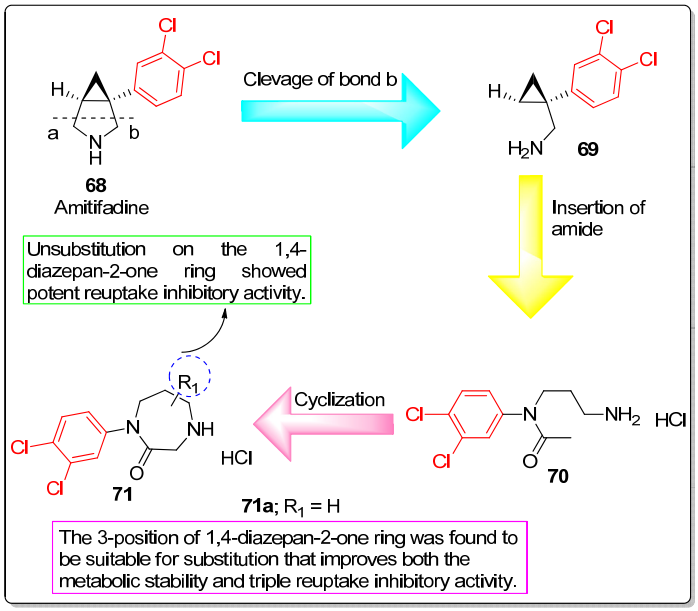


Fig. (27). Design and SAR of 1-aryl-1,4-diazepan-2-ones as MDTLs for depression.

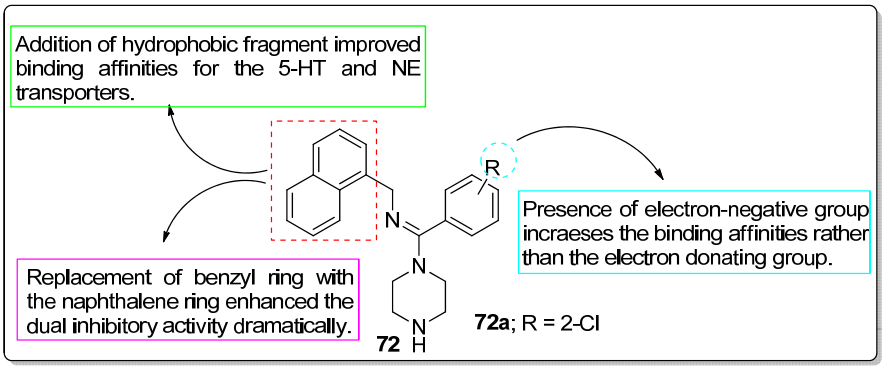


Fig. (28). Arylamidine derivatives as dual reuptake inhibitors.

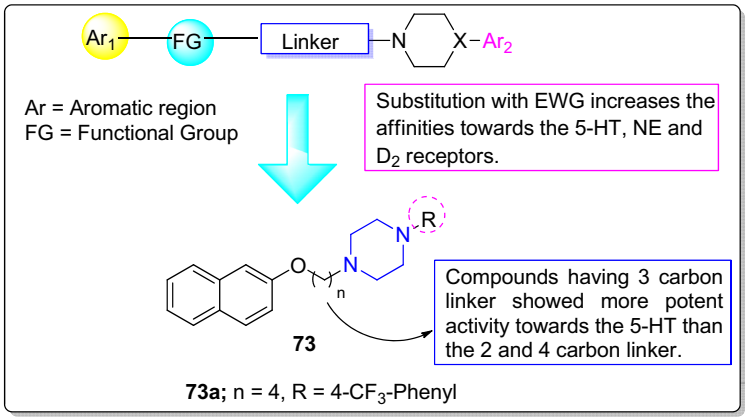


Fig. (29). 4-Arylpiperazine and 4-benzylpiperidine naphthyl ethers as multi-target ligands.

significantly reduced the immobility time, which was found to be similar to the standard duloxetine. Acute toxicity studies were performed at the dose of 200 and 400 mg/kg after 20h and results demonstrated that compound **72a** exhibited low toxicity with LD_{50} value >400 mg/kg. SAR studies suggested that the substitution with electron-withdrawing groups at the phenyl ring increased the binding affinities, whereas that of electron-donating groups decreased the affinities [167].

Paudel *et al.* designed molecules based on the docking models of reported monoamine neurotransmitters reuptake inhibitors and their SAR studies [168]. A series of 4-arylpiperazine and 4-benzylpiperidine naphthyl ethers were

synthesized (Fig. **29**) and evaluated for serotonin, norepinephrine, and monoamine neurotransmitters reuptake inhibition properties. Among the various tested compounds, **73a** was found to be the most active candidate that showed an antidepressant-like effect via a multi-target approach. Compound **73a** showed an IC_{50} value of 0.68 μM for 5-HT and 20.5 μM for the norepinephrine receptor. Molecular docking studies were implemented for the potent compound **73a**, and the results exposed the compound to possess ideal interactions within the binding site of the hSERT. SAR studies recommended that the substitution with electron-withdrawing groups at the 4- position of the piperazine moiety increased the inhibitory potential towards the serotonin, norepinephrine, and dopamine reuptake. Molecular docking studies showed that compound **73a** interacted with the hSERT in a similar mode as paroxetine. The naphthalene ring of the ligand displayed hydrophobic interactions with Ile172 and Try176 residues [169].

CONCLUSION

The progression of depression is not only mediated by serotonin, but glutamate, histamine, noradrenaline and other receptors as well as their subtypes are also responsible for causing depression. The drugs targeting only one target/mechanism are not enough to treat and manage this complicated disease. Moreover, these single target medications are likewise connected with various side effects and toxicities. The great advancements in the health sector have led to the development of several therapeutic agents which work through different mechanisms and counteract depression up to different extents. The complex pathophysiology of depression still is an obstacle in the way of these agents as they are based upon the traditional one-drug-one-target strategy. Multi-target directed ligands (MTDLs) layout method is an appealing technique for recent drug development strategies aiming at issues related to the complicated pathological mechanisms, including depression. MTDLs approach is one of the rationales and validated approaches for the antidepressant drug discovery. The growing benefits of MTDL derivatives are more likely as these are present in various marketed drugs, like teniloxazine, viloxazine, *etc.*, and will serve as potential weapons for the treatment of depression with the goal to address multiple targets. In this review, design strategies for MTDLs, their structural-activity relationships, biological evaluation, including both *in vitro* and *in vivo* findings, as well as *in silico* considerations, have been discussed. A thorough study of cited literature has revealed that the compound(s) possessing two or more active pharmacophores connected with an optimum spacer are likely to act upon more than one biological target. The piperazine ring plays a crucial role in the development of novel antidepressants using a fragment-based drug design approach. Substituted piperazine derivatives have been found to be active on multiple targets and to show remarkable affinity towards 5-HT_{1A}, 5-HT_7, norepinephrine and serotonin receptors. In particular, hybrids of substituted piperazine with indole or purine linked with an optimum spacer generate potent molecules with multi-target ligand profile, promising biological activity, better efficacy, and low toxicity. These compounds have displayed remarkable binding affinities towards different receptors involved in the pathophysiology of the disease, and these results have been further supported by *in vivo* and *in silico* studies. This compilation may be helpful to the medicinal chemists and drug developers in obtaining ideas regarding important structural features responsible for the biological activity which may be employed for rational drug design related to depression. Researchers can utilize these results as supporting evidences for the development of more efficient, potent and safe molecules to tackle depression-like complex disorders.

LIST OF ABBREVIATIONS

CNS	=	Central nervous system
MDD	=	Major depression disorder
CDC	=	Center for diseases control and prevention
FPL	=	Federal poverty line
HPA	=	Hypothalamic pituitary adrenal axis
NMDA receptor	=	N-methyl-D-aspartic acid receptor
MTDLs	=	Multi-target directed ligands
FBDD	=	Fragment based drug design
AMPA receptor	=	Alpha-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid receptor
TST	=	Tail suspension test
FST	=	Forced swim test
SSRI	=	Selective serotonin reuptake inhibitor
SNRIs	=	Serotonin and norepinephrine reuptake inhibitors
TCAs	=	Tricyclic antidepressants
MAOIs	=	Monoamine oxidase inhibitors
SERT	=	Serotonin transporter
GSK-3β	=	Glycogen synthase kinase 3β
5-HT	=	Serotonin
NE	=	Norepinephrine
DAT	=	Dopamine transporter
DA	=	Dopamine
SI	=	Selectivity index
SAR	=	Structure-activity relationship
NA	=	Noradrenaline
hMAO	=	Human monoamine oxidase
NDRIs	=	Inhibitors of norepinephrine and dopamine
BuChE	=	Butyrylcholinesterase
AChE	=	Acetylcholinesterase

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Jablensky, A.; Johnson, R.; Bunney, W.; Cruz, M.; Durkin, M.; Familusi, J. *Neurological, psychiatric, and developmental disorders; meeting the challenge in the developing world*; National Academy Press, **2001**.

[2] Ferrari, A.J.; Charlson, F.J.; Norman, R.E.; Patten, S.B.; Freedman, G.; Murray, C.J.; Vos, T.; Whiteford, H.A. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med.,* **2013**, *10*(11), e1001547. http://dx.doi.org/10.1371/journal.pmed.1001547 PMID: 24223526

[3] Subbaiah, M.A.M. Triple reuptake inhibitors as potential therapeutics for depression and other disorders: design paradigm and developmental challenges. *J. Med. Chem.,* **2018**, *61*(6), 2133-2165. http://dx.doi.org/10.1021/acs.jmedchem.6b01827 PMID: 28731336

[4] Ouyang, G.; Pan, G.; Liu, Q.; Wu, Y.; Liu, Z.; Lu, W.; Li, S.; Zhou, Z.; Wen, Y. The global, regional, and national burden of pancreatitis in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *BMC Med.,* **2020**, *18*(1), 388. http://dx.doi.org/10.1186/s12916-020-01859-5 PMID: 33298026

[5] Hellerstein, D.J.; Flaxer, J. Vilazodone for the treatment of major depressive disorder: an evidence-based review of its place in therapy. *Core Evid.,* **2015**, *10*, 49-62. http://dx.doi.org/10.2147/CE.S54075 PMID: 25945081

[6] Fiske, A.; Wetherell, J.L.; Gatz, M. Depression in older adults. *Annu. Rev. Clin. Psychol.,* **2009**, *5*, 363-389. http://dx.doi.org/10.1146/annurev.clinpsy.032408.153621 PMID: 19327033

[7] Gold, S.M.; Köhler-Forsberg, O.; Moss-Morris, R.; Mehnert, A.; Miranda, J.J.; Bullinger, M.; Steptoe, A.; Whooley, M.A.; Otte, C. Comorbid depression in medical diseases. *Nat. Rev. Dis. Primers,* **2020**, *6*(1), 69. http://dx.doi.org/10.1038/s41572-020-0200-2 PMID: 32820163

[8] DE Hert, M.; Correll, C.U.; Bobes, J.; Cetkovich-Bakmas, M.; Cohen, D.; Asai, I.; Detraux, J.; Gautam, S.; Möller, H.J.; Ndetei, D.M.; Newcomer, J.W.; Uwakwe, R.; Leucht, S. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World Psychiatry,* **2011**, *10*(1), 52-77. http://dx.doi.org/10.1002/j.2051-5545.2011.tb00014.x PMID: 21379357

[9] Moussavi, S.; Chatterji, S.; Verdes, E.; Tandon, A.; Patel, V.; Ustun, B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet,* **2007**, *370*(9590), 851-858. http://dx.doi.org/10.1016/S0140-6736(07)61415-9 PMID: 17826170

[10] Bartels, H.; Middel, B.L.; van der Laan, B.F.; Staal, M.J.; Albers, F.W. The additive effect of co-occurring anxiety and depression on health status, quality of life and coping strategies in help-seeking tinnitus sufferers. *Ear Hear.,* **2008**, *29*(6), 947-956. http://dx.doi.org/10.1097/AUD.0b013e3181888f83 PMID: 18941410

[11] Brody, D.J.; Pratt, L.A.; Hughes, J.P. *Prevalence of depression among adults aged 20 and over*; United States, **2018**, pp. 2013-2016.

[12] Ettman, C.K.; Abdalla, S.M.; Cohen, G.H.; Sampson, L.; Vivier, P.M.; Galea, S. Prevalence of depression symptoms in US adults before and during the COVID-19 pandemic. *JAMA Netw. Open,* **2020**, *3*(9), e2019686. http://dx.doi.org/10.1001/jamanetworkopen.2020.19686 PMID: 32876685

[13] Weissman, M.M.; Bland, R.; Joyce, P.R.; Newman, S.; Wells, J.E.; Wittchen, H-U. Sex differences in rates of depression: cross-national perspectives. *J. Affect. Disord.,* **1993**, *29*(2-3), 77-84. http://dx.doi.org/10.1016/0165-0327(93)90025-F PMID: 8300980

[14] Wang, P.S.; Aguilar-Gaxiola, S.; Alonso, J.; Angermeyer, M.C.; Borges, G.; Bromet, E.J.; Bruffaerts, R.; de Girolamo, G.; de Graaf, R.; Gureje, O.; Haro, J.M.; Karam, E.G.; Kessler, R.C.; Kovess, V.; Lane, M.C.; Lee, S.; Levinson, D.; Ono, Y.; Petukhova, M.; Posada-Villa, J.; Seedat, S.; Wells, J.E. Use of mental health services for anxiety, mood, and substance disorders in 17 countries in the WHO world mental health surveys. *Lancet,* **2007**, *370*(9590), 841-850. http://dx.doi.org/10.1016/S0140-6736(07)61414-7 PMID: 17826169

[15] Gilbert, P. Psychotherapy and counselling for depression. *Sage,* **2007**.

[16] Watson, R.; Harvey, K.; McCabe, C.; Reynolds, S. Understanding anhedonia: a qualitative study exploring loss of interest and pleasure in adolescent depression. *Eur. Child Adolesc. Psychiatry,* **2020**, *29*(4), 489-499. http://dx.doi.org/10.1007/s00787-019-01364-y PMID: 31270605

[17] Treadway, M.T.; Zald, D.H. Reconsidering anhedonia in depression: lessons from translational neuroscience. *Neurosci. Biobehav. Rev.,* **2011**, *35*(3), 537-555. http://dx.doi.org/10.1016/j.neubiorev.2010.06.006 PMID: 20603146

[18] Higgins, E.T.; Klein, R.; Strauman, T. Self-concept discrepancy theory: A psychological model for distinguishing among different aspects of depression and anxiety. *Soc. Cogn.,* **1985**, *3*(1), 51-76. http://dx.doi.org/10.1521/soco.1985.3.1.51

[19] Cawson, P.; Wattam, C.; Brooker, S.; Kelly, G. *Child maltreatment in the United Kingdom: A study of the prevalence of abuse and neglect*; NSPCC: London, **2000**.

[20] Springer, K.W.; Sheridan, J.; Kuo, D.; Carnes, M. The long-term health outcomes of childhood abuse. An overview and a call to action. *J. Gen. Intern. Med.,* **2003**, *18*(10), 864-870. http://dx.doi.org/10.1046/j.1525-1497.2003.20918.x PMID: 14521650

[21] Heim, C.; Newport, D.J.; Mletzko, T.; Miller, A.H.; Nemeroff, C.B. The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology,* **2008**, *33*(6), 693-710. http://dx.doi.org/10.1016/j.psyneuen.2008.03.008 PMID: 18602762

[22] Pillemer, K.; Suitor, J.J.; Pardo, S.; Henderson, C., Jr Mothers' differentiation and depressive symptoms among adult children. *J. Marriage Fam.,* **2010**, *72*(2), 333-345. http://dx.doi.org/10.1111/j.1741-3737.2010.00703.x PMID: 20607119

[23] Schmidt, P.J. Mood, depression, and reproductive hormones in the menopausal transition. *Am. J. Med.,* **2005**, *118*(12)(Suppl. 12B), 54-58. http://dx.doi.org/10.1016/j.amjmed.2005.09.033 PMID: 16414327

[24] Rashid, T.; Haider, I. Life events and depression. *Ann. Punjab Med. College,* **2008**, *2*(1), 11-16.

[25] Mata, D.A.; Ramos, M.A.; Bansal, N.; Khan, R.; Guille, C.; Di Angelantonio, E.; Sen, S. Prevalence of depression and depressive symptoms among resident physicians: a systematic review and meta-analysis. *JAMA,* **2015**, *314*(22), 2373-2383. http://dx.doi.org/10.1001/jama.2015.15845 PMID: 26647259

[26] Davey, C.G.; Yücel, M.; Allen, N.B. The emergence of depression in adolescence: development of the prefrontal cortex and the representation of reward. *Neurosci. Biobehav. Rev.,* **2008**, *32*(1), 1-19. http://dx.doi.org/10.1016/j.neubiorev.2007.04.016 PMID: 17570526

[27] Larson, R.; Csikszentmihalyi, M.; Graef, R. Mood variability and the psychosocial adjustment of adolescents. *J. Youth Adolesc.,* **1980**, *9*(6), 469-490. http://dx.doi.org/10.1007/BF02089885 PMID: 24318310

[28] Mitchell, A.J.; Vaze, A.; Rao, S. Clinical diagnosis of depression in primary care: a meta-analysis. *Lancet,* **2009**, *374*(9690), 609-619. http://dx.doi.org/10.1016/S0140-6736(09)60879-5 PMID: 19640579

[29] Beck, A.T.; Steer, R.A.; Beck, J.S.; Newman, C.F. Hopelessness, depression, suicidal ideation, and clinical diagnosis of depression. *Suicide Life Threat. Behav.,* **1993**, *23*(2), 139-145. http://dx.doi.org/10.1111/j.1943-278X.1993.tb00378.x PMID: 8342213

[30] Gotlib, I.H.; Lewinsohn, P.M.; Seeley, J.R. Symptoms *versus* a diagnosis of depression: differences in psychosocial functioning. *J. Consult. Clin. Psychol.,* **1995**, *63*(1), 90-100. http://dx.doi.org/10.1037/0022-006X.63.1.90 PMID: 7896995

[31] Kumar, K.S.; Srivastava, S.; Paswan, S.; Dutta, A.S. Depression-symptoms, causes, medications and therapies. *Pharma Innov.,* **2012**, *1*(3, Part A), 37.

[32] Diamond, A. Evidence for the importance of dopamine for prefrontal cortex functions early in life. *Philos. Trans. R. Soc. Lond. B Biol. Sci.,* **1996**, *351*(1346), 1483-1493. http://dx.doi.org/10.1098/rstb.1996.0134 PMID: 8941960

[33] Bymaster, F.P.; Katner, J.S.; Nelson, D.L.; Hemrick-Luecke, S.K.; Threlkeld, P.G.; Heiligenstein, J.H.; Morin, S.M.; Gehlert, D.R.; Perry, K.W. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology,* **2002**, *27*(5), 699-711. http://dx.doi.org/10.1016/S0893-133X(02)00346-9 PMID: 12431845

[34] Seamans, J.K.; Yang, C.R. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Prog. Neurobiol.,* **2004**, *74*(1), 1-58. http://dx.doi.org/10.1016/j.pneurobio.2004.05.006 PMID: 15381316

[35] Lambert, G.; Johansson, M.; Ågren, H.; Friberg, P. Reduced brain norepinephrine and dopamine release in treatment-refractory depressive illness: evidence in support of the catecholamine hypothesis of mood disorders. *Arch. Gen. Psychiatry,* **2000**, *57*(8), 787-793. http://dx.doi.org/10.1001/archpsyc.57.8.787 PMID: 10920468

[36] Molinoff, P.B.; Axelrod, J. Biochemistry of catecholamines. *Annu. Rev. Biochem.,* **1971**, *40*(1), 465-500. http://dx.doi.org/10.1146/annurev.bi.40.070171.002341 PMID: 4399447

[37] Papakostas, G.I. Evidence for S-adenosyl-L-methionine (SAM-e) for the treatment of major depressive disorder. *J. Clin. Psychiatry,* **2009**, *70*(Suppl. 5), 18-22. http://dx.doi.org/10.4088/JCP.8157su1c.04 PMID: 19909689

[38] Mischoulon, D.; Fava, M. Role of S-adenosyl-L-methionine in the treatment of depression: a review of the evidence. *Am. J. Clin. Nutr.,* **2002**, *76*(5), 1158S-1161S. http://dx.doi.org/10.1093/ajcn/76.5.1158S PMID: 12420702

[39] Owens, M.J.; Nemeroff, C.B. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clin. Chem.,* **1994**, *40*(2), 288-295. http://dx.doi.org/10.1093/clinchem/40.2.288 PMID: 7508830

[40] Dantzer, R.; O'Connor, J.C.; Lawson, M.A.; Kelley, K.W. Inflammation-associated depression: from serotonin to kynurenine. *Psychoneuroendocrinology,* **2011**, *36*(3), 426-436. http://dx.doi.org/10.1016/j.psyneuen.2010.09.012 PMID: 21041030

[41] Dorszewska, J.; Florczak-Wyspianska, J.; Kowalska, M.; Stanski, M.; Kowalewska, A.; Kozubski, W. Serotonin in neurological diseases. *Serotonin: A Chemical Messenger Between All Types of Living Cells,* **2017**, *219.* http://dx.doi.org/10.5772/intechopen.69035

[42] Ramsay, R.R. Monoamine oxidases: the biochemistry of the proteins as targets in medicinal chemistry and drug discovery. *Curr. Top. Med. Chem.,* **2012**, *12*(20), 2189-2209. http://dx.doi.org/10.2174/156802612805219978 PMID: 23231396

[43] Bosch, O.J.; Müsch, W.; Bredewold, R.; Slattery, D.A.; Neumann, I.D. Prenatal stress increases HPA axis activity and impairs maternal care in lactating female offspring: implications for postpartum mood disorder. *Psychoneuroendocrinology,* **2007**, *32*(3), 267-278. http://dx.doi.org/10.1016/j.psyneuen.2006.12.012 PMID: 17337328

[44] Dickens, M.J.; Pawluski, J.L. The HPA axis during the perinatal period: implications for perinatal depression. *Endocrinology,* **2018**, *159*(11), 3737-3746. http://dx.doi.org/10.1210/en.2018-00677 PMID: 30256957

[45] Adell, A. Brain NMDA receptors in schizophrenia and depression. *Biomolecules,* **2020**, *10*(6), 947. http://dx.doi.org/10.3390/biom10060947 PMID: 32585886

[46] Szakacs, R.; Janka, Z.; Kalman, J. The "blue" side of glutamatergic neurotransmission: NMDA receptor antagonists as possible novel therapeutics for major depression. *Neuropsychopharmacol. Hung.,* **2012**, *14*(1), 29-40. PMID: 22427468

[47] Kumar, R.R.; Sahu, B.; Pathania, S.; Singh, P.K.; Akhtar, M.J.; Kumar, B. Piperazine, a key substructure for antidepressants: its role in developments and structure-activity relationships. *ChemMedChem,* **2021**, *16*(12), 1878-1901. http://dx.doi.org/10.1002/cmdc.202100045 PMID: 33751807

[48] Kumar, B.; Mantha, A.K.; Kumar, V. Recent developments on the structure–activity relationship studies of MAO inhibitors and their role in different neurological disorders. *RSC Advances,* **2016**, *6*(48), 42660-42683. http://dx.doi.org/10.1039/C6RA00302H

[49] Kumar, B.; Gupta, V.P.; Kumar, V. A perspective on monoamine oxidase enzyme as drug target: challenges and opportunities. *Curr. Drug Targets,* **2017**, *18*(1), 87-97. http://dx.doi.org/10.2174/1389450117666151209123402 PMID: 26648064

[50] Benfield, P.; Heel, R.C.; Lewis, S.P. Fluoxetine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness. *Drugs,* **1986**, *32*(6), 481-508. http://dx.doi.org/10.2165/00003495-198632060-00002 PMID: 2878798

[51] Murdoch, D.; McTavish, D. Sertraline. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depression and obsessive-compulsive disorder. *Drugs,* **1992**, *44*(4), 604-624. http://dx.doi.org/10.2165/00003495-199244040-00007 PMID: 1281075

[52] Cassano, G.B.; Baldini Rossi, N.; Pini, S. Psychopharmacology of anxiety disorders. *Dialogues Clin. Neurosci.,* **2002**, *4*(3), 271-285. http://dx.doi.org/10.31887/DCNS.2002.4.3/gcassano PMID: 22033867

[53] Locher, C.; Koechlin, H.; Zion, S.R.; Werner, C.; Pine, D.S.; Kirsch, I.; Kessler, R.C.; Kossowsky, J. Efficacy and safety of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and placebo for common psychiatric disorders among children and adolescents: a systematic review and meta-analysis. *JAMA Psychiatry,* **2017**, *74*(10), 1011-1020. http://dx.doi.org/10.1001/jamapsychiatry.2017.2432 PMID: 28854296

[54] Puetz, T.W.; Youngstedt, S.D.; Herring, M.P. Effects of pharmacotherapy on combat-related PTSD, anxiety, and depression: a systematic review and meta-regression analysis. *PLoS One,* **2015**, *10*(5), e0126529. http://dx.doi.org/10.1371/journal.pone.0126529 PMID: 26020791

[55] Knadler, M.P.; Lobo, E.; Chappell, J.; Bergstrom, R. Duloxetine: clinical pharmacokinetics and drug interactions. *Clin. Pharmacokinet.,* **2011**, *50*(5), 281-294. http://dx.doi.org/10.2165/11539240-000000000-00000 PMID: 21366359

[56] Holliday, S.M.; Benfield, P. Venlafaxine. A review of its pharmacology and therapeutic potential in depression. *Drugs,* **1995**, *49*(2), 280-294. http://dx.doi.org/10.2165/00003495-199549020-00010 PMID: 7729333

[57] Protti, M.; Mandrioli, R.; Marasca, C.; Cavalli, A.; Serretti, A.; Mercolini, L. New-generation, non-SSRI antidepressants: Drug-drug interactions and therapeutic drug monitoring. Part 2: NaSSAs, NRIs, SNDRIs, MASSAs, NDRIs, and others. *Med. Res. Rev.,* **2020**, *40*(5), 1794-1832. http://dx.doi.org/10.1002/med.21671 PMID: 32285503

[58] Massana, J.; Möller, H.J.; Burrows, G.D.; Montenegro, R.M. Reboxetine: a double-blind comparison with fluoxetine in major depressive disorder. *Int. Clin. Psychopharmacol.,* **1999**, *14*(2), 73-80.

http://dx.doi.org/10.1097/00004850-199903000-00003 PMID: 10220121

[59] Nishimura, M.; Sato, K. Ketamine stereoselectively inhibits rat dopamine transporter. *Neurosci. Lett.,* **1999**, *274*(2), 131-134. http://dx.doi.org/10.1016/S0304-3940(99)00688-6 PMID: 10553955

[60] Molero, P.; Ramos-Quiroga, J.A.; Martin-Santos, R.; Calvo-Sánchez, E.; Gutiérrez-Rojas, L.; Meana, J.J. Antidepressant efficacy and tolerability of ketamine and esketamine: a critical review. *CNS Drugs,* **2018**, *32*(5), 411-420. http://dx.doi.org/10.1007/s40263-018-0519-3 PMID: 29736744

[61] McEwen, B.S.; Chattarji, S.; Diamond, D.M.; Jay, T.M.; Reagan, L.P.; Svenningsson, P.; Fuchs, E. The neurobiological properties of tianeptine (Stablon): from monoamine hypothesis to glutamatergic modulation. *Mol. Psychiatry,* **2010**, *15*(3), 237-249. http://dx.doi.org/10.1038/mp.2009.80 PMID: 19704408

[62] McEwen, B.S.; Olié, J.P. Neurobiology of mood, anxiety, and emotions as revealed by studies of a unique antidepressant: tianeptine. *Mol. Psychiatry,* **2005**, *10*(6), 525-537. http://dx.doi.org/10.1038/sj.mp.4001648 PMID: 15753957

[63] Invernizzi, R.; Pozzi, L.; Garattini, S.; Samanin, R. Tianeptine increases the extracellular concentrations of dopamine in the nucleus accumbens by a serotonin-independent mechanism. *Neuropharmacology,* **1992**, *31*(3), 221-227. http://dx.doi.org/10.1016/0028-3908(92)90171-K PMID: 1630590

[64] Kumar, B; Kuhad, A. Lumateperone: a new treatment approach for neuropsychiatric disorders. *Drugs of Today (Barcelona, Spain: 1998),* **2018**, *54*(12), 713-719. http://dx.doi.org/10.1358/dot.2018.54.12.2899443

[65] Blair, H.A. Lumateperone: First approval. *Drugs,* **2020**, *80*(4), 417-423. http://dx.doi.org/10.1007/s40265-020-01271-6 PMID: 32060882

[66] McMorris, T.; Harris, R.C.; Swain, J.; Corbett, J.; Collard, K.; Dyson, R.J.; Dye, L.; Hodgson, C.; Draper, N. Effect of creatine supplementation and sleep deprivation, with mild exercise, on cognitive and psychomotor performance, mood state, and plasma concentrations of catecholamines and cortisol. *Psychopharmacology (Berl.),* **2006**, *185*(1), 93-103. http://dx.doi.org/10.1007/s00213-005-0269-z PMID: 16416332

[67] Cunha, M.P.; Machado, D.G.; Capra, J.C.; Jacinto, J.; Bettio, L.E.; Rodrigues, A.L.S. Antidepressant-like effect of creatine in mice involves dopaminergic activation. *J. Psychopharmacol.,* **2012**, *26*(11), 1489-1501. http://dx.doi.org/10.1177/0269881112447989 PMID: 22674968

[68] Martinez Botella, G.; Salituro, F.G.; Harrison, B.L.; Beresis, R.T.; Bai, Z.; Blanco, M-J.; Belfort, G.M.; Dai, J.; Loya, C.M.; Ackley, M.A.; Althaus, A.L.; Grossman, S.J.; Hoffmann, E.; Doherty, J.J.; Robichaud, A.J. Neuroactive steroids. 2. 3α-Hydroxy-3β-methyl-21-(4-cyano-1 H-pyrazol-1′-yl)-19-nor-5β-pregnan-20-one (SAGE-217): a clinical next generation neuroactive steroid positive allosteric modulator of the (γ-aminobutyric acid) A receptor. *J. Med. Chem.,* **2017**, *60*(18), 7810-7819. http://dx.doi.org/10.1021/acs.jmedchem.7b00846 PMID: 28753313

[69] Kleinman, R.A.; Schatzberg, A.F. Understanding the clinical effects and mechanisms of action of neurosteroids. *Am. J. Psychiatry,* **2021**, *178*(3), 221-223. http://dx.doi.org/10.1176/appi.ajp.2020.20020134 PMID: 33138631

[70] Ishibashi, T.; Horisawa, T.; Tokuda, K.; Ishiyama, T.; Ogasa, M.; Tagashira, R.; Matsumoto, K.; Nishikawa, H.; Ueda, Y.; Toma, S.; Oki, H.; Tanno, N.; Saji, I.; Ito, A.; Ohno, Y.; Nakamura, M. Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT7) and 5-HT1A receptor activity. *J. Pharmacol. Exp. Ther.,* **2010**, *334*(1), 171-181. http://dx.doi.org/10.1124/jpet.110.167346 PMID: 20404009

[71] Ishiyama, T.; Tokuda, K.; Ishibashi, T.; Ito, A.; Toma, S.; Ohno, Y. Lurasidone (SM-13496), a novel atypical antipsychotic drug, reverses MK-801-induced impairment of learning and memory in the rat passive-avoidance test. *Eur. J. Pharmacol.,* **2007**, *572*(2-3), 160-170. http://dx.doi.org/10.1016/j.ejphar.2007.06.058 PMID: 17662268

[72] Bang-Andersen, B.; Ruhland, T.; Jørgensen, M.; Smith, G.; Frederiksen, K.; Jensen, K.G.; Zhong, H.; Nielsen, S.M.; Hogg, S.; Mørk, A.; Stensbøl, T.B. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. *J. Med. Chem.,* **2011**, *54*(9), 3206-3221. http://dx.doi.org/10.1021/jm101459g PMID: 21486038

[73] Sanchez, C.; Asin, K.E.; Artigas, F. Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. *Pharmacol. Ther.,* **2015**, *145*, 43-57. http://dx.doi.org/10.1016/j.pharmthera.2014.07.001 PMID: 25016186

[74] Wróbel, M.Z.; Chodkowski, A.; Herold, F.; Marciniak, M.; Dawidowski, M.; Siwek, A.; Starowicz, G.; Stachowicz, K.; Szewczyk, B.; Nowak, G.; Belka, M.; Bączek, T.; Satała, G.; Bojarski, A.J.; Turło, J. Synthesis and biological evaluation of new multi-target 3-(1H-indol-3-yl)pyrrolidine-2,5-dione derivatives with potential antidepressant effect. *Eur. J. Med. Chem.,* **2019**, *183*, 111736. http://dx.doi.org/10.1016/j.ejmech.2019.111736 PMID: 31586817

[75] Khan, A. Vilazodone, a novel dual-acting serotonergic antidepressant for managing major depression. *Expert Opin. Investig. Drugs,* **2009**, *18*(11), 1753-1764. http://dx.doi.org/10.1517/13543780903286396 PMID: 19764890

[76] Verma, R.; Bhatia, R.; Singh, G.; Kumar, B.; Mehan, S.; Monga, V. Design, synthesis and neuropharmacological evaluation of new 2,4-disubstituted-1,5-benzodiazepines as CNS active agents. *Bioorg. Chem.,* **2020**, *101*, 104010. http://dx.doi.org/10.1016/j.bioorg.2020.104010 PMID: 32615464

[77] Dhiman, P.; Arora, N.; Thanikachalam, P.V.; Monga, V. Recent advances in the synthetic and medicinal perspective of quinolones: A review. *Bioorg. Chem.,* **2019**, *92*, 103291. http://dx.doi.org/10.1016/j.bioorg.2019.103291 PMID: 31561107

[78] Nehra, B.; Rulhania, S.; Jaswal, S.; Kumar, B.; Singh, G.; Monga, V. Recent advancements in the development of bioactive pyrazoline derivatives. *Eur. J. Med. Chem.,* **2020**, *205*, 112666. http://dx.doi.org/10.1016/j.ejmech.2020.112666 PMID: 32795767

[79] Rulhania, S.; Kumar, S.; Nehra, B.; Gupta, G.; Monga, V. An insight into the medicinal perspective of synthetic analogs of imidazole. *J. Mol. Struct.,* **2021**, 129982. http://dx.doi.org/10.1016/j.molstruc.2021.129982

[80] Alhaider, A.A.; Abdelkader, M.A.; Lien, E.J. Design, synthesis, and pharmacological activities of 2-substituted 4-phenylquinolines as potential antidepressant drugs. *J. Med. Chem.,* **1985**, *28*(10), 1394-1398. http://dx.doi.org/10.1021/jm00148a004 PMID: 4045918

[81] Faquih, A.E.; Memon, R.I.; Hafeez, H.; Zeshan, M.; Naveed, S. A review of novel antidepressants: a guide for clinicians. *Cureus,* **2019**, *11*(3), e4185. http://dx.doi.org/10.7759/cureus.4185 PMID: 31106085

[82] Molenaar, N.M.; Kamperman, A.M.; Boyce, P.; Bergink, V. Guidelines on treatment of perinatal depression with antidepressants: An international review. *Aust. N. Z. J. Psychiatry,* **2018**, *52*(4), 320-327. http://dx.doi.org/10.1177/0004867418762057 PMID: 29506399

[83] Singh, K.; Pal, R.; Khan, S.A.; Kumar, B.; Akhtar, M.J. Insights into the structure activity relationship of Nitrogen-containing heterocyclics for the development of antidepressant compounds: An updated review. *J. Mol. Struct.,* **2021**, 130369. http://dx.doi.org/10.1016/j.molstruc.2021.130369

[84] Siddiqui, N.; Andalip, S.B.; Bawa, S.; Ali, R.; Afzal, O.; Akhtar, M.J.; Azad, B.; Kumar, R. Antidepressant potential of nitrogen-containing heterocyclic moieties: An updated review. *J. Pharm. Bioallied Sci.,* **2011**, *3*(2), 194-212. http://dx.doi.org/10.4103/0975-7406.80765 PMID: 21687347

[85] Moreira, L.K.D.S.; de Brito, A.F.; da Silva, D.M.; Siqueira, L.; da Silva, D.P.B.; Cardoso, C.S.; Florentino, I.F.; de Carvalho, P.M.G.; Ghedini, P.C.; Menegatti, R.; Costa, E.A. Potential antidepressant-like effect of piperazine derivative LQFM212 in mice: Role of monoaminergic pathway and brain-derived neurotrophic factor. *Behav. Brain Res.,* **2021**, *401*, 113066. http://dx.doi.org/10.1016/j.bbr.2020.113066 PMID: 33333109

[86] Garg, V.; Maurya, R.K.; Thanikachalam, P.V.; Bansal, G.; Monga, V. An insight into the medicinal perspective of synthetic analogs of indole: A review. *Eur. J. Med. Chem.,* **2019**, *180*, 562-612. http://dx.doi.org/10.1016/j.ejmech.2019.07.019 PMID: 31344615

[87] Zhou, J.; Jiang, X.; He, S.; Jiang, H.; Feng, F.; Liu, W.; Qu, W.; Sun, H. Rational design of multitarget-directed ligands: strategies and emerging paradigms. *J. Med. Chem.,* **2019**, *62*(20), 8881-8914. http://dx.doi.org/10.1021/acs.jmedchem.9b00017 PMID: 31082225

[88] Bolognesi, M.L.; Simoni, E.; Rosini, M.; Minarini, A.; Tumiatti, V.; Melchiorre, C. Multitarget-directed ligands: innovative chemical probes and therapeutic tools against Alzheimer's disease. *Curr. Top. Med. Chem.,* **2011**, *11*(22), 2797-2806. http://dx.doi.org/10.2174/156802611798184373 PMID: 22039879

[89] Zhang, P.; Xu, S.; Zhu, Z.; Xu, J. Multi-target design strategies for the improved treatment of Alzheimer's disease. *Eur. J. Med. Chem.,* **2019**, *176*, 228-247. http://dx.doi.org/10.1016/j.ejmech.2019.05.020 PMID: 31103902

[90] Bhatia, R.; Rawal, R.K. Coumarin Hybrids: Promising Scaffolds in the Treatment of Breast Cancer. *Mini Rev. Med. Chem.,* **2019**, *19*(17), 1443-1458. http://dx.doi.org/10.2174/1389557519666190308122509 PMID: 30854961

[91] Schrimpf, M.R.; Lee, C-h.; Li, T.; Gfesser, G.; Mortell, K.; Faghih, R. *Indole and indoline derivatives and methods of use thereof*; Google Patents, **2018**.

[92] Muñoz-torrero lópez-ibarra VC, Pont Masanet, Codony Gisbert, inventor Multitarget compounds for the treatment of Alzheimer's disease; 2020.

[93] Bortolami, M.; Rocco, D.; Messore, A.; Di Santo, R.; Costi, R.; Madia, V.N.; Scipione, L.; Pandolfi, F. Acetylcholinesterase inhibitors for the treatment of Alzheimer's disease - a patent review (2016-present). *Expert Opin. Ther. Pat.,* **2021**, *31*(5), 399-420. http://dx.doi.org/10.1080/13543776.2021.1874344 PMID: 33428491

[94] Andrisano, V.; Naldi, M.; De Simone, A.; Bartolini, M. A patent review of butyrylcholinesterase inhibitors and reactivators 2010-2017. *Expert Opin. Ther. Pat.,* **2018**, *28*(6), 455-465. http://dx.doi.org/10.1080/13543776.2018.1476494 PMID: 29757691

[95] Manna, K.; Agrawal, Y.K. Microwave assisted synthesis of new indophenazine 1,3,5-trisubstruted pyrazoline derivatives of benzofuran and their antimicrobial activity. *Bioorg. Med. Chem. Lett.,* **2009**, *19*(10), 2688-2692. http://dx.doi.org/10.1016/j.bmcl.2009.03.161 PMID: 19395261

[96] Shibinskaya, M.O.; Lyakhov, S.A.; Mazepa, A.V.; Andronati, S.A.; Turov, A.V.; Zholobak, N.M.; Spivak, N.Y. Synthesis, cytotoxicity, antiviral activity and interferon inducing ability of 6-(2-aminoethyl)-6H-indolo[2,3-b]quinoxalines. *Eur. J. Med. Chem.,* **2010**, *45*(3), 1237-1243. http://dx.doi.org/10.1016/j.ejmech.2009.12.014 PMID: 20056519

[97] Palluotto, F.; Carotti, A.; Casini, G.; Campagna, F.; Genchi, G.; Rizzo, M.; De Sarro, G.B. Structure-activity relationships of 2-aryl-2,5-dihydropyridazino [4,3-b]indol-3(3H)-ones at the benzodiazepine receptor. *Bioorg. Med. Chem.,* **1996**, *4*(12), 2091-2104. http://dx.doi.org/10.1016/S0968-0896(96)00220-9 PMID: 9022974

[98] Heinrich, T.; Böttcher, H.; Schiemann, K.; Hölzemann, G.; Schwarz, M.; Bartoszyk, G.D.; van Amsterdam, C.; Greiner, H.E.; Seyfried, C.A. Dual 5-HT1A agonists and 5-HT re-uptake inhibitors by combination of indole-butyl-amine and chromenonyl-piperazine structural elements in a single molecular entity. *Bioorg. Med. Chem.,* **2004**, *12*(18), 4843-4852. http://dx.doi.org/10.1016/j.bmc.2004.07.014 PMID: 15336263

[99] Dhar, A.K.; Mahesh, R.; Jindal, A.; Bhatt, S. Piperazine analogs of naphthyridine-3-carboxamides and indole-2-carboxamides: novel 5-HT3 receptor antagonists with antidepressant-like activity. *Arch. Pharm. (Weinheim),* **2015**, *348*(1), 34-45. http://dx.doi.org/10.1002/ardp.201400293 PMID: 25581677

[100] Sravanthi, T.V.; Manju, S.L. Indoles - A promising scaffold for drug development. *Eur. J. Pharm. Sci.,* **2016**, *91*, 1-10. http://dx.doi.org/10.1016/j.ejps.2016.05.025 PMID: 27237590

[101] Zhou, D.; Zhou, P.; Evrard, D.A.; Meagher, K.; Webb, M.; Harrison, B.L.; Huryn, D.M.; Golembieski, J.; Hornby, G.A.; Schechter, L.E.; Smith, D.L.; Andree, T.H.; Mewshaw, R.E. Studies toward the discovery of the next generation of antidepressants. Part 6: Dual 5-HT1A receptor and serotonin transporter affinity within a class of arylpiperazinyl-cyclohexyl indole derivatives. *Bioorg. Med. Chem.,* **2008**, *16*(14), 6707-6723. http://dx.doi.org/10.1016/j.bmc.2008.05.075 PMID: 18571421

[102] Kumar, D.; Sharma, S.; Kalra, S.; Singh, G.; Monga, V.; Kumar, B. Medicinal Perspective of Indole Derivatives: Recent Developments and Structure-Activity Relationship Studies. *Curr. Drug Targets,* **2020**, *21*(9), 864-891. http://dx.doi.org/10.2174/1389450121666200310115327 PMID: 32156235

[103] James, S.L.; Abate, D.; Abate, K.H.; Abay, S.M.; Abbafati, C.; Abbasi, N. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet,* **2018**, *392*(10159), 1789-1858. http://dx.doi.org/10.1016/S0140-6736(18)32279-7 PMID: 30496104

[104] Wang, W-T.; Qian, H.; Wu, J-W.; Chen, X-W.; Li, J-Q. Synthesis and antidepressant-like activity of novel alkoxy-piperidine derivatives targeting SSRI/5-HT_{1A}/5-HT_7. *Bioorg. Med. Chem. Lett.,* **2019**, *29*(24), 126769. http://dx.doi.org/10.1016/j.bmcl.2019.126769 PMID: 31699607

[105] Pessoa-Mahana, H.; Silva-Matus, P.; Pessoa-Mahana, C.D.; Chung, H.; Iturriaga-Vásquez, P.; Quiroz, G.; Möller-Acuña, P.; Zapata-Torres, G.; Saitz-Barría, C.; Araya-Maturana, R.; Reyes-Parada, M. Synthesis and docking of novel 3-indolylpropyl derivatives as new polypharmacological agents displaying affinity for 5-HT_{1A} R/SERT. *Arch. Pharm. (Weinheim),* **2017**, *350*(1), e1600271. http://dx.doi.org/10.1002/ardp.201600271 PMID: 27981607

[106] Pessoa-Mahana, H.; González-Lira, C.; Fierro, A.; Zapata-Torres, G.; Pessoa-Mahana, C.D.; Ortiz-Severin, J.; Iturriaga-Vásquez, P.; Reyes-Parada, M.; Silva-Matus, P.; Saitz-Barría, C.; Araya-Maturana, R. Synthesis, docking and pharmacological evaluation of novel homo- and hetero-bis 3-piperazinylpropylindole derivatives at SERT and 5-HT1A receptor. *Bioorg. Med. Chem.,* **2013**, *21*(24), 7604-7611. http://dx.doi.org/10.1016/j.bmc.2013.10.036 PMID: 24262884

[107] Mathew, B.; Baek, S.C.; Thomas Parambi, D.G.; Lee, J.P.; Mathew, G.E.; Jayanthi, S.; Vinod, D.; Rapheal, C.; Devikrishna, V.; Kondarath, S.S.; Uddin, M.S.; Kim, H. Potent and highly selective dual-targeting monoamine oxidase-B inhibitors: Fluorinated chalcones of morpholine *versus* imidazole. *Arch. Pharm. (Weinheim),* **2019**, *352*(4), e1800309. http://dx.doi.org/10.1002/ardp.201800309 PMID: 30663112

[108] Cerda-Cavieres, C.; Quiroz, G.; Iturriaga-Vásquez, P.; Rodríguez-Lavado, J.; Alarcón-Espósito, J.; Saitz, C.; Pessoa-Mahana, C.D.; Chung, H.; Araya-Maturana, R.; Mella-Raipán, J.; Cabezas, D.; Ojeda-Gómez, C.; Reyes-Parada, M.; Pessoa-Mahana, H. Synthesis, docking, 3-D-qsar, and biological assays of novel indole derivatives targeting serotonin transporter, dopamine D2 receptor, and mao-a enzyme: In the pursuit for potential multitarget directed ligands. *Molecules,* **2020**, *25*(20), 4614. http://dx.doi.org/10.3390/molecules25204614 PMID: 33050524

[109] Modica, M.N.; Intagliata, S.; Pittalà, V.; Salerno, L.; Siracusa, M.A.; Cagnotto, A.; Salmona, M.; Romeo, G. Synthesis and binding properties of new long-chain 4-substituted piperazine derivatives as 5-HT1A and 5-HT7 receptor ligands. *Bioorg. Med. Chem. Lett.,* **2015**, *25*(7), 1427-1430. http://dx.doi.org/10.1016/j.bmcl.2015.02.042 PMID: 25759032

[110] Oh, S.J.; Ha, H-J.; Chi, D.Y.; Lee, H.K. Serotonin receptor and transporter ligands - current status. *Curr. Med. Chem.,* **2001**, *8*(9), 999-1034. http://dx.doi.org/10.2174/0929867013372599 PMID: 11472239

[111] Bojarski, A.J.; Mokrosz, M.J.; Duszyńska, B.; Kozioł, A.; Bugno, R. New imide 5-HT1A receptor ligands - modification of terminal fragment geometry. *Molecules,* **2004**, *9*(3), 170-177. http://dx.doi.org/10.3390/90300170 PMID: 18007421

[112] Wróbel, M.Z.; Chodkowski, A.; Herold, F.; Gomółka, A.; Kleps, J.; Mazurek, A.P.; Pluciński, F.; Mazurek, A.; Nowak, G.; Siwek, A.; Stachowicz, K.; Sławińska, A.; Wolak, M.; Szewczyk, B.; Satała, G.; Bojarski, A.J.; Turło, J. Synthesis and biological evaluation of novel pyrrolidine-2,5-dione derivatives as potential antidepressant agents. Part 1. *Eur. J. Med. Chem.,* **2013**, *63*, 484-500. http://dx.doi.org/10.1016/j.ejmech.2013.02.033 PMID: 23524160

[113] Wróbel, M.Z.; Chodkowski, A.; Marciniak, M.; Dawidowski, M.; Maksymiuk, A.; Siwek, A.; Nowak, G.; Turło, J. Synthesis of new 4-butyl-arylpiperazine-3-(1H-indol-3-yl)pyrrolidine-2,5-dione de-

rivatives and evaluation for their 5-HT_{1A} and D_2 receptor affinity and serotonin transporter inhibition. *Bioorg. Chem.,* **2020**, *97*, 103662.
http://dx.doi.org/10.1016/j.bioorg.2020.103662 PMID: 32086055

[114] Gu, Z-S.; Xiao, Y.; Zhang, Q-W.; Li, J-Q. Synthesis and antidepressant activity of a series of arylalkanol and aralkyl piperazine derivatives targeting SSRI/5-HT_{1A}/5-HT_7. *Bioorg. Med. Chem. Lett.,* **2017**, *27*(24), 5420-5423.
http://dx.doi.org/10.1016/j.bmcl.2017.11.007 PMID: 29138029

[115] Gu, Z-S.; Wang, W-T.; Qian, H.; Zhou, A-N.; Sun, H-B.; Zhang, Q-W.; Li, J.Q. Synthesis and antidepressant effect of novel aralkyl piperazine and piperidine derivatives targeting SSRI/5-HT_{1A}/5-HT_7. *Bioorg. Med. Chem. Lett.,* **2019**, *29*(23), 126703.
http://dx.doi.org/10.1016/j.bmcl.2019.126703 PMID: 31627993

[116] Kumar, B.; Kumar, V.; Prashar, V.; Saini, S.; Dwivedi, A.R.; Bajaj, B.; Mehta, D.; Parkash, J.; Kumar, V. Dipropargyl substituted diphenylpyrimidines as dual inhibitors of monoamine oxidase and acetylcholinesterase. *Eur. J. Med. Chem.,* **2019**, *177*, 221-234.
http://dx.doi.org/10.1016/j.ejmech.2019.05.039 PMID: 31151057

[117] Kumar, B.; Dwivedi, A.R.; Sarkar, B.; Gupta, S.K.; Krishnamurthy, S.; Mantha, A.K.; Parkash, J.; Kumar, V. 4, 6-Diphenylpyrimidine derivatives as dual inhibitors of monoamine oxidase and acetylcholinesterase for the treatment of Alzheimer's disease. *ACS Chem. Neurosci.,* **2019**, *10*(1), 252-265.
http://dx.doi.org/10.1021/acschemneuro.8b00220 PMID: 30296051

[118] Frampton, J.E. Vilazodone: in major depressive disorder. *CNS Drugs,* **2011**, *25*(7), 615-627.
http://dx.doi.org/10.2165/11207550-000000000-00000 PMID: 21699273

[119] Liu, W.; Wang, H.; Li, X.; Xu, Y.; Zhang, J.; Wang, W.; Gong, Q.; Qiu, X.; Zhu, J.; Mao, F.; Zhang, H.; Li, J. Design, synthesis and evaluation of vilazodone-tacrine hybrids as multitarget-directed ligands against depression with cognitive impairment. *Bioorg. Med. Chem.,* **2018**, *26*(12), 3117-3125.
http://dx.doi.org/10.1016/j.bmc.2018.04.037 PMID: 29729987

[120] Li, X.; Wang, H.; Xu, Y.; Liu, W.; Gong, Q.; Wang, W.; Qiu, X.; Zhu, J.; Mao, F.; Zhang, H.; Li, J. Novel Vilazodone-Tacrine Hybrids as Potential Multitarget-Directed Ligands for the Treatment of Alzheimer's Disease Accompanied with Depression: Design, Synthesis, and Biological Evaluation. *ACS Chem. Neurosci.,* **2017**, *8*(12), 2708-2721.
http://dx.doi.org/10.1021/acschemneuro.7b00259 PMID: 28872831

[121] Rosemeyer, H. The chemodiversity of purine as a constituent of natural products. *Chem. Biodivers.,* **2004**, *1*(3), 361-401.
http://dx.doi.org/10.1002/cbdv.200490033 PMID: 17191854

[122] Zagórska, A.; Kołaczkowski, M.; Bucki, A.; Siwek, A.; Kazek, G.; Satała, G.; Bojarski, A.J.; Partyka, A.; Wesołowska, A.; Pawłowski, M. Structure-activity relationships and molecular studies of novel arylpiperazinylalkyl purine-2,4-diones and purine-2,4,8-triones with antidepressant and anxiolytic-like activity. *Eur. J. Med. Chem.,* **2015**, *97*, 142-154.
http://dx.doi.org/10.1016/j.ejmech.2015.04.046 PMID: 25965777

[123] Haesslein, J.L.; Jullian, N. Recent advances in cyclin-dependent kinase inhibition. Purine-based derivatives as anti-cancer agents. Roles and perspectives for the future. *Curr. Top. Med. Chem.,* **2002**, *2*(9), 1037-1050.
http://dx.doi.org/10.2174/1568026023393291 PMID: 12171570

[124] Wang, S-B.; Deng, X-Q.; Liu, D-C.; Zhang, H-J.; Quan, Z-S. Synthesis and evaluation of anticonvulsant and antidepressant activities of 7-alkyl-7 H-tetrazolo [1, 5-g] purine derivatives. *Med. Chem. Res.,* **2014**, *23*(10), 4619-4626.
http://dx.doi.org/10.1007/s00044-014-1030-0

[125] Pawlowski, M.; Katlabi, J.; Drabczynska, A.; Duszynska, B.; Charakchieva-Minol, S.; Deren-Wesolek, A. New 9-or 10-arylpiperazinoalkyl substituted pyrimido-or diazepino [2, 1-f] purines with partial or full 5-HT1A agonistic activity. *Eur. J. Med. Chem.,* **1999**, *34*(2), 167-175.
http://dx.doi.org/10.1016/S0223-5234(99)80050-6

[126] Zagórska, A.; Bucki, A.; Kołaczkowski, M.; Siwek, A.; Głuch-Lutwin, M.; Starowicz, G. Synthesis and biological evaluation of 2-fluoro and 3-trifluoromethyl-phenyl-piperazinylalkyl derivatives of 1 H-imidazo [2, 1-f] purine-2, 4 (3 H, 8 H)-dione as potential antidepressant agents. *J. Enzyme Inhib. Med. Chem.,* **2016**, *31*(sup3), 10-24.

[127] Magli, E.; Kędzierska, E.; Kaczor, A.A.; Bielenica, A.; Severino, B.; Gibuła-Tarłowska, E.; Kotlińska, J.H.; Corvino, A.; Sparaco, R.; Esposito, G.; Albrizio, S.; Perissutti, E.; Frecentese, F.; Leśniak, A.; Bujalska-Zadrożny, M.; Struga, M.; Capasso, R.; Santagada, V.; Caliendo, G.; Fiorino, F. Synthesis, docking studies, and pharmacological evaluation of 2-hydroxypropyl-4-arylpiperazine derivatives as serotoninergic ligands. *Arch. Pharm. (Weinheim),* **2021**, *354*(5), e2000414.
http://dx.doi.org/10.1002/ardp.202000414 PMID: 33543794

[128] Chłon, G.; Pawłowski, M.B. Duszyn ska, A. Szaro, E. Tatarczyn ska, A. Kłodzin ska, E. Chojnacka-Wójcik. *Pol. J. Pharmacol.,* **2001**, *53*, 359.
PMID: 11990082

[129] Pawłowski, M.; Chłoń, G.; Obniska, J.; Zejc, A.; Charakchieva-Minol, S.; Mokrosz, M.J. Synthesis, 5-HT1A and 5-HT2A receptor affinity of new 1-phenylpiperazinylpropyl derivatives of purine-2,6- and pyrrolidine-2,5-diones. *Farmaco,* **2000**, *55*(6-7), 461-468.
http://dx.doi.org/10.1016/S0014-827X(00)00069-0 PMID: 11204747

[130] Chłoń-Rzepa, G.; Zagórska, A.; Bucki, A.; Kołaczkowski, M.; Pawłowski, M.; Satała, G.; Bojarski, A.J.; Partyka, A.; Wesołowska, A.; Pękala, E.; Słoczyńska, K. New arylpiperazinylalkyl derivatives of 8-alkoxy-purine-2,6-dione and dihydro[1,3]oxazolo[2,3-f]purinedione targeting the serotonin 5-HT1A /5-HT2A /5-HT7 and dopamine D2 receptors. *Arch. Pharm. (Weinheim),* **2015**, *348*(4), 242-253.
http://dx.doi.org/10.1002/ardp.201500015 PMID: 25773907

[131] Chłoń-Rzepa, G.; Żmudzki, P.; Zajdel, P.; Bojarski, A.J.; Duszyńska, B.; Nikiforuk, A.; Tatarczyńska, E.; Pawłowski, M. 7-Arylpiperazinylalkyl and 7-tetrahydroisoquinolinylalkyl derivatives of 8-alkoxy-purine-2,6-dione and some of their purine-2,6,8-trione analogs as 5-HT(1A), 5-HT(2A), and 5-HT(7) serotonin receptor ligands. *Bioorg. Med. Chem.,* **2007**, *15*(15), 5239-5250.
http://dx.doi.org/10.1016/j.bmc.2007.05.017 PMID: 17517514

[132] Chłoń-Rzepa, G.; Żmudzki, P.; Pawłowski, M.; Wesołowska, A.; Satała, G.; Bojarski, A.J. New 7-arylpiperazinylalkyl-8-morpholin-4-yl-purine-2, 6-dione derivatives with anxiolytic activity–Synthesis, crystal structure and structure–activity study. *J. Mol. Struct.,* **2014**, *1067*, 243-251.
http://dx.doi.org/10.1016/j.molstruc.2014.03.018

[133] Partyka, A.; Chłoń-Rzepa, G.; Wasik, A.; Jastrzębska-Więsek, M.; Bucki, A.; Kołaczkowski, M.; Satała, G.; Bojarski, A.J.; Wesołowska, A. Antidepressant- and anxiolytic-like activity of 7-phenylpiperazinylalkyl-1,3-dimethyl-purine-2,6-dione derivatives with diversified 5-HT1A receptor functional profile. *Bioorg. Med. Chem.,* **2015**, *23*(1), 212-221.
http://dx.doi.org/10.1016/j.bmc.2014.11.008 PMID: 25435254

[134] Chłoń-Rzepa, G.; Zagórska, A.; Żmudzki, P.; Bucki, A.; Kołaczkowski, M.; Partyka, A.; Wesołowska, A.; Kazek, G.; Głuch-Lutwin, M.; Siwek, A.; Starowicz, G.; Pawłowski, M. Aminoalkyl Derivatives of 8-Alkoxypurine-2,6-diones: Multifunctional 5-HT_{1A} /5-HT_7 Receptor Ligands and PDE Inhibitors with Antidepressant Activity. *Arch. Pharm. (Weinheim),* **2016**, *349*(12), 889-903.
http://dx.doi.org/10.1002/ardp.201600260 PMID: 27869315

[135] Chłoń-Rzepa, G.; Żmudzki, P.; Satała, G.; Duszyńska, B.; Partyka, A.; Wróbel, D.; Jastrzębska-Więsek, M.; Wesołowska, A.; Bojarski, A.J.; Pawłowski, M.; Zajdel, P. New 8-aminoalkyl derivatives of purine-2,6-dione with arylalkyl, allyl or propynyl substituents in position 7, their 5-HT1A, 5-HT2A, and 5-HT7 receptor affinity and pharmacological evaluation. *Pharmacol. Rep.,* **2013**, *65*(1), 15-29.
http://dx.doi.org/10.1016/S1734-1140(13)70960-5 PMID: 23563020

[136] Czopek, A.; Byrtus, H.; Kołaczkowski, M.; Pawłowski, M.M. Dybała, G. Nowak, E. Tatarczyńska, A. Wesołowska, E. Chojnac ka-Wójcik. *Eur. J. Med. Chem.,* **2010**, *45*, 1295-1303.
http://dx.doi.org/10.1016/j.ejmech.2009.11.053 PMID: 20060623

[137] Czopek, A.; Kołaczkowski, M.; Bucki, A.; Byrtus, H.; Pawłowski, M.; Siwek, A.; Bojarski, A.J.; Bednarski, M.; Wróbel, D.; Wesołowska, A. Novel mannich bases, 5-arylimidazolidine-2,4-dione derivatives with dual 5-HT(1A) receptor and serotonin transporter affinity. *Arch. Pharm. (Weinheim),* **2013**, *346*(2), 98-109.
http://dx.doi.org/10.1002/ardp.201200378 PMID: 23288448

[138] Jann, M.W. Buspirone: an update on a unique anxiolytic agent. *Pharmacotherapy,* **1988**, *8*(2), 100-116.

http://dx.doi.org/10.1002/j.1875-9114.1988.tb03543.x PMID: 3041384

[139] Rydelek-Fitzgerald, L.; Teitler, M.; Fletcher, P.W.; Ismaiel, A.M.; Glennon, R.A. NAN-190: agonist and antagonist interactions with brain 5-HT1A receptors. *Brain Res.,* **1990**, *532*(1-2), 191-196. http://dx.doi.org/10.1016/0006-8993(90)91759-A PMID: 2282513

[140] Casey, A.B.; Canal, C.E. Classics in chemical neuroscience: aripiprazole. *ACS Chem. Neurosci.,* **2017**, *8*(6), 1135-1146. http://dx.doi.org/10.1021/acschemneuro.7b00087 PMID: 28368577

[141] Halene, T.B.; Siegel, S.J. Antipsychotic-like properties of phosphodiesterase 4 inhibitors: evaluation of 4-(3-butoxy-4-methoxybenzyl)-2-imidazolidinone (RO-20-1724) with auditory event-related potentials and prepulse inhibition of startle. *J. Pharmacol. Exp. Ther.,* **2008**, *326*(1), 230-239. http://dx.doi.org/10.1124/jpet.108.138586 PMID: 18420599

[142] Huai, Q.; Wang, H.; Sun, Y.; Kim, H-Y.; Liu, Y.; Ke, H. Three-dimensional structures of PDE4D in complex with roliprams and implication on inhibitor selectivity. *Structure,* **2003**, *11*(7), 865-873. http://dx.doi.org/10.1016/S0969-2126(03)00123-0 PMID: 12842049

[143] Czopek, A.; Bucki, A.; Kołaczkowski, M.; Zagórska, A.; Drop, M.; Pawłowski, M.; Siwek, A.; Głuch-Lutwin, M.; Pękala, E.; Chrzanowska, A.; Struga, M.; Partyka, A.; Wesołowska, A. Novel multitarget 5-arylidenehydantoins with arylpiperazinealkyl fragment: Pharmacological evaluation and investigation of cytotoxicity and metabolic stability. *Bioorg. Med. Chem.,* **2019**, *27*(18), 4163-4173. http://dx.doi.org/10.1016/j.bmc.2019.07.046 PMID: 31383628

[144] Zaręba, P.; Jaśkowska, J.; Czekaj, I.; Satała, G. Design, synthesis and molecular modelling of new bulky Fananserin derivatives with altered pharmacological profile as potential antidepressants. *Bioorg. Med. Chem.,* **2019**, *27*(15), 3396-3407. http://dx.doi.org/10.1016/j.bmc.2019.06.028 PMID: 31253535

[145] Zaręba, P.; Jaśkowska, J.; Śliwa, P.; Satała, G. New dual ligands for the D_2 and 5-HT_{1A} receptors from the group of 1,8-naphthyl derivatives of LCAP. *Bioorg. Med. Chem. Lett.,* **2019**, *29*(16), 2236-2242. http://dx.doi.org/10.1016/j.bmcl.2019.06.029 PMID: 31253532

[146] Kułaga, D.; Jaśkowska, J.; Satała, G. Design, synthesis and biological evaluation of novel serotonin and dopamine receptor ligands being 6-bromohexyl saccharine derivatives. *Bioorg. Med. Chem. Lett.,* **2019**, *29*(21), 126667. http://dx.doi.org/10.1016/j.bmcl.2019.126667 PMID: 31547945

[147] Peng, X-M.; Damu, G.L.; Zhou, C. Current developments of coumarin compounds in medicinal chemistry. *Curr. Pharm. Des.,* **2013**, *19*(21), 3884-3930. http://dx.doi.org/10.2174/1381612811319210013 PMID: 23438968

[148] Patil, P.O.; Bari, S.B.; Firke, S.D.; Deshmukh, P.K.; Donda, S.T.; Patil, D.A. A comprehensive review on synthesis and designing aspects of coumarin derivatives as monoamine oxidase inhibitors for depression and Alzheimer's disease. *Bioorg. Med. Chem.,* **2013**, *21*(9), 2434-2450. http://dx.doi.org/10.1016/j.bmc.2013.02.017 PMID: 23517722

[149] Abdel-Latif, N.A. Synthesis and antidepressant activity of some new coumarin derivatives. *Sci. Pharm.,* **2005**, *73*(4), 193-216. http://dx.doi.org/10.3797/scipharm.aut-05-15

[150] Huong, D.T.L.; Choi, H.C.; Rho, T.C.; Lee, H.S.; Lee, M.K.; Kim, Y.H. Inhibitory activity of monoamine oxidase by coumarins from Peucedanum japonicum. *Arch. Pharm. Res.,* **1999**, *22*(3), 324-326. http://dx.doi.org/10.1007/BF02976373 PMID: 10403141

[151] Dutta, A.K.; Gopishetty, B.; Gogoi, S.; Ali, S.; Zhen, J.; Reith, M. The novel trisubstituted pyran derivative D-142 has triple monoamine reuptake inhibitory activity and exerts potent antidepressant-like activity in rodents. *Eur. J. Pharmacol.,* **2011**, *671*(1-3), 39-44. http://dx.doi.org/10.1016/j.ejphar.2011.09.162 PMID: 21963455

[152] Sashidhara, K.V.; Modukuri, R.K.; Singh, S.; Bhaskara Rao, K.; Aruna Teja, G.; Gupta, S.; Shukla, S. Design and synthesis of new series of coumarin-aminopyran derivatives possessing potential anti-depressant-like activity. *Bioorg. Med. Chem. Lett.,* **2015**, *25*(2), 337-341. http://dx.doi.org/10.1016/j.bmcl.2014.11.036 PMID: 25488839

[153] Bashir, M.A.; Khan, A.U.; Badshah, H.; Rodrigues-Filho, E.; Din, Z.U.; Khan, A. Synthesis, characterization, molecular docking evaluation, antidepressant, and anti-Alzheimer effects of dibenzylidene ketone derivatives. *Drug Dev. Res.,* **2019**, *80*(5), 595-605. http://dx.doi.org/10.1002/ddr.21537 PMID: 30964563

[154] Zygmunt, M.; Sapa, J.; Chłoń-Rzepa, G.; Zagórska, A.; Siwek, A.; Pawłowski, M.; Nowak, G. 7-3-Chlorophenypiperazinylalkyl derivatives of 8-alkoxy-purine-2,6-dione as a serotonin receptor ligands with potential antidepressant activity. *Pharmacol. Rep.,* **2014**, *66*(3), 505-510. http://dx.doi.org/10.1016/j.pharep.2013.12.014 PMID: 24905531

[155] Jankowska, A.; Satała, G.; Kołaczkowski, M.; Bucki, A.; Głuch-Lutwin, M.; Świerczek, A.; Pociecha, K.; Partyka, A.; Jastrzębska-Więsek, M.; Lubelska, A.; Latacz, G.; Gawalska, A.; Bojarski, A.J.; Wyska, E.; Chłoń-Rzepa, G. Novel anilide and benzylamide derivatives of arylpiperazinylalkanoic acids as 5-HT_{1A}/5-HT_7 receptor antagonists and phosphodiesterase 4/7 inhibitors with procognitive and antidepressant activity. *Eur. J. Med. Chem.,* **2020**, *201*, 112437. http://dx.doi.org/10.1016/j.ejmech.2020.112437 PMID: 32673902

[156] Kramer, T; Schmidt, B; Lo Monte, F. Small-molecule inhibitors of GSK-3: structural insights and their application to Alzheimer's disease models. *Int J Alzheimers Dis.,* **2012**, *2012*, 381029. http://dx.doi.org/10.1155/2012/381029 PMID: 22888461

[157] Klein, P.S.; Melton, D.A. A molecular mechanism for the effect of lithium on development. *Proc. Natl. Acad. Sci. USA,* **1996**, *93*(16), 8455-8459. http://dx.doi.org/10.1073/pnas.93.16.8455 PMID: 8710892

[158] Silva, T.; Reis, J.; Teixeira, J.; Borges, F. Alzheimer's disease, enzyme targets and drug discovery struggles: from natural products to drug prototypes. *Ageing Res. Rev.,* **2014**, *15*, 116-145. http://dx.doi.org/10.1016/j.arr.2014.03.008 PMID: 24726823

[159] Journet, M.; Cai, D.; Kowal, J.J.; Larsen, R.D. Highly efficient and mild synthesis of variously 5-substituted-4-carbaldehyde-1, 2, 3-triazole derivatives. *Tetrahedron Lett.,* **2001**, *42*(52), 9117-9118. http://dx.doi.org/10.1016/S0040-4039(01)01923-2

[160] Sanghvi, Y.S.; Bhattacharya, B.K.; Kini, G.D.; Matsumoto, S.S.; Larson, S.B.; Jolley, W.B.; Robins, R.K.; Revankar, G.R. Growth inhibition and induction of cellular differentiation of human myeloid leukemia cells in culture by carbamoyl congeners of ribavirin. *J. Med. Chem.,* **1990**, *33*(1), 336-344. http://dx.doi.org/10.1021/jm00163a054 PMID: 2296029

[161] Khan, I.; Tantray, M.A.; Hamid, H.; Alam, M.S.; Kalam, A.; Hussain, F.; Dhulap, A. Synthesis of pyrimidin-4-one-1,2,3-triazole conjugates as glycogen synthase kinase-3β inhibitors with antidepressant activity. *Bioorg. Chem.,* **2016**, *68*, 41-55. http://dx.doi.org/10.1016/j.bioorg.2016.07.007 PMID: 27454617

[162] Charney, D.S. Monoamine dysfunction and the pathophysiology and treatment of depression. *J. Clin. Psychiatry,* **1998**, *59*(14), 11-14. PMID: 9818625

[163] Hamon, M.; Blier, P. Monoamine neurocircuitry in depression and strategies for new treatments. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2013**, *45*, 54-63. http://dx.doi.org/10.1016/j.pnpbp.2013.04.009 PMID: 23602950

[164] Skinner, M.H.; Kuan, H.Y.; Pan, A.; Sathirakul, K.; Knadler, M.P.; Gonzales, C.R.; Yeo, K.P.; Reddy, S.; Lim, M.; Ayan-Oshodi, M.; Wise, S.D. Duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers. *Clin. Pharmacol. Ther.,* **2003**, *73*(3), 170-177. http://dx.doi.org/10.1067/mcp.2003.28 PMID: 12621382

[165] Fischer, H.; Kansy, M.; Bur, D. CAFCA: a novel tool for the calculation of amphiphilic properties of charged drug molecules. *CHIMIA International Journal for Chemistry.,* **2000**, *54*(11), 640-645.

[166] Honda, E.; Ishichi, Y.; Kimura, E.; Yoshikawa, M.; Kanzaki, N.; Nakagawa, H.; Terao, Y.; Suzuki, A.; Kawai, T.; Arakawa, Y.; Ohta, H.; Terauchi, J. Design, synthesis, and biological activities of 1-aryl-1,4-diazepan-2-one derivatives as novel triple reuptake inhibitors. *Bioorg. Med. Chem. Lett.,* **2014**, *24*(16), 3898-3902. http://dx.doi.org/10.1016/j.bmcl.2014.06.046 PMID: 25017029

[167] Wen, H.; Qin, W.; Yang, G.; Guo, Y. Design and Synthesis of Arylamidine Derivatives as Serotonin/Norepinephrine Dual Reuptake Inhibitors. *Molecules,* **2019**, *24*(3), 497. http://dx.doi.org/10.3390/molecules24030497 PMID: 30704101

[168] Paudel, S.; Sun, N.; Khadka, D.B.; Yoon, G.; Kim, K-M.; Cheon, S.H. Design, synthesis and docking study of 4-arylpiperazine car-

boxamides as monoamine neurotransmitters reuptake inhibitors. *Bioorg. Med. Chem.,* **2018**, *26*(14), 4127-4135. http://dx.doi.org/10.1016/j.bmc.2018.06.043 PMID: 30007567

[169] Paudel, S.; Min, X.; Acharya, S.; Khadka, D.B.; Yoon, G.; Kim, K-M.; Cheon, S.H. Design, synthesis, and systematic evaluation of 4-arylpiperazine- and 4-benzylpiperidine napthyl ethers as inhibitors of monoamine neurotransmitters reuptake. *Bioorg. Med. Chem.,* **2018**, *26*(20), 5538-5546. http://dx.doi.org/10.1016/j.bmc.2018.09.033 PMID: 30293797