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REVIEW

Designing multi-target drugs for the treatment of major depressive disorder

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ABSTRACT

Introduction: Major depressive disorders (MDD) pose major health burdens globally. Currently available medications have their limitations due to serious adverse effects, long latency periods as well as resistance. Considering the highly complicated pathological nature of this disorder, it has been suggested that multitarget drugs or multi-target-directed ligands (MTDLs) may provide long-term therapeutic solutions for the treatment of MDD.

Areas covered: In the current review, recent lead design and lead modification strategies have been covered. Important investigations reported in the last ten years (2013–2022) for the preclinical development of MTDLs (through synthetic medicinal chemistry and biological evaluation) for the treatment of MDD were discussed as case studies to focus on the recent design strategies. The discussions are categorized on the basis of pharmacological targets. Based on these important case studies, the challenges involved in different design strategies were discussed in detail.

Expert opinion: Even though large variations were observed in the selection of pharmacological targets, some potential biological targets (NMDA, melatonin receptors) are required to be explored extensively for the design of MTDLs. Similarly, apart from structure activity relationship (SAR), in silico techniques such as multitasking cheminformatic modeling, molecular dynamics simulation and virtual screening should be exploited to a greater extent.

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Major depressive disorder; multitarget drugs; drug design; synthetic medicinal chemistry; structure activity relationship; cheminformatics; *in silico* techniques

1. Introduction

Major depressive disorder (MDD) is a highly prevalent chronic and recurrent central nervous system (CNS) disorder prompted by complex interplay of genetic, developmental, situational, and environmental factors. The MDD is characterized by a number of psychological and physical changes including anhedonia (i.e. lack of interest in pleasurable activities), worthlessness, energy loss, weight changes (gain or loss), sleep changes (insomnia or hypersomnia) and more importantly, suicidal thoughts. The MDD in fact poses major risks for suicide globally [1–3]. In 2019, suicide appeared as 15th and 14th leading causes of deaths worldwide for two age groups: (a) 5–14 years and (b) greater than 70 years [4]. World Health Organization (WHO) warned that MDD would affect up to 20% of the world population by 2025 [5]. A study indicated that MDD accounted for around 3% of disability-adjusted life-years [6]. Other than increasing the risks of suicide, heterogeneous nature of MDD leads to a range of comorbidities, among which diabetes, cancer and cardiovascular disorders are the most common. Apart from these, anxiety, insomnia, dementia, drug abuse, sexual dysfunction, and even chronic pain are also associated with MDD [7–9]. Similarly, MDD is frequently observed in patients suffering from other health disorders. This disorder is found in all geographic locations, genders, ages, and races, though its prevalence may vary [10,11]. For example, it has been revealed that people from Middle East, South Asia, North Africa, and America are more prone to this disorder, whereas women are currently more vulnerable than men.

Exact etiology of MDD is yet to be disclosed. However, it is evident that a number of developmental and societal factors (e.g. rape, sexual abuse, relationship problems, joblessness, extreme mental stress, childbirth, and menopause) may lead to this disorder [12]. Despite the availability of a range of medications to tackle MDD, the patients of low-income countries are often deprived of utilizing such facilities due to inadequate resources or simply because of ignorance [13]. Increasing number of research reports insinuated that recent COVID-19 pandemic has led to a significant increase in the number of MDD cases globally [14]. For example, the COVID-19 Mental Disorders Collaborators reported a 27·6% increase in cases of major depressive disorders during 2020 (https://www.thelancet.com/journals/lancet/article/PIIS0140–6736(22)00187–8/fulltext).

Some currently available antidepressants are listed in Table 1 with their mechanism(s) of action. The MDD is clinically diagnosed based on the symptoms and psychological parameters, such as appetite, sleep pattern, social activity, and thought patterns [11,15,16]. This disorder is associated with several factors such as reduction or depletion of neurotransmitters (e.g. dopamine, serotonin and norepinephrine) in the specific areas of brain, decrease in the level of SAM (S-adenosyl-L-methionine), and hyperactivity of the hypothalamic-pituitary adrenal (HPA) axis as well as abnormal

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Article highlights

- Major depressive disorders (MDD) are a major global health burden.
- Multi-target-drug ligands (MTDLs) can offer promising strategies to address MDD with reduced resistance and long-lasting latency period.
- The majority of previous research on designing MTDLs has focused on targeting serotonin receptors (5-HTs) in combination with MAO, NMDA, AChE, and D2.
- Less researched targets, such as neurotrophins (BDNF, GDNF, IGF), the kynurenine pathway, and TrkB, have been identified and should be considered when developing MTDLs.
- Although techniques like multitasking QSAR, virtual screening, and molecular dynamics simulations have not been extensively explored, they hold the potential to offer improved design strategies for drug discovery in the treatment of MDD.

activation of N-methyl D-aspartate (NMDA) receptors. Reduced level of monoamines such as serotonin may be associated with the hyperactivity of monoamine oxidase-A (MAO-A) enzyme that is responsible for the breakdown of these neurotransmitters. This is why the first generation of antidepressants included tricyclic antidepressants and MAO inhibitors that primarily act on serotonin and norepinephrine. However, these antidepressants possessed a range of adverse effects such as dry mouth, blurred vision, constipation, sexual problems, etc [17]. The second generation of antidepressants include selective serotonin reuptake inhibitors (SSRIs), norepinephrine reuptake inhibitors (NRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) with improved safety and tolerability as well as wider therapeutic window. The SSRIs (fluoxetine, fluvoxamine, sertraline, citalopram, etc.) still remain the first line medication for treating depression, even though numerous adverse effects including nausea, insomnia, sexual dysfunction, and somnolence are frequently observed. Besides, complications related to long onset of action and moderate patient response lower their therapeutic reliability [18]. The overall efficacy of SNRIs is similar to SSRIs and these are also considered to be less tolerable than SSRIs [19].

Overall, two major shortcomings of clinically available antidepressants are long-lasting adaptive process (or long latency period) and resistance, especially toward refractory MDD [20]. In fact, refractory MDD is a severe, recurrent, and long-lasting depression that is not cured by multiple long-lasting therapies [21]. For example, 65% of patients showed efficacy with antidepressants therapy, whereas 15% of them demonstrate insignificant response these therapeutic agents. Additionally, the therapeutic efficacy appear only after 2–4 weeks from the starting of antidepressant therapy [20,22]. In order to counter these drawbacks, several new compounds have been proposed and a number of compounds entered clinical trials as potential antidepressant agents in recent years. In Table 2, some of these selected compounds are listed with their reported mechanism(s) of action. Evidently, as far as the discovery of new antidepressants is concerned, significant efforts have been invested toward the design of multitarget ligands or multi-target-directed ligands (MTDLs).

The MTDLs (also termed as 'promiscuous' drugs or multi-target ligands) simultaneously interact with more than one bio-macromolecular targets in a bid to cure complex pathological diseases [31]. It has been suggested that targeting a single receptor may be insufficient for the treatment of MDD due to its pathological complexities. Therefore, a paradigm shift has been observed in recent years in antidepressant therapy where the search for MTDLs has increased rapidly. Vilazodone has been approved for MDD treatment in 2011 as a 5-HT_{1A} partial agonist that also demonstrates SSRI like activity. Other examples include agomelatine (a melatonergic MT_1 and MT_2 receptors agonist and a selective serotonergic 5-HT_{2B} and 5-HT_{2C} antagonist) and aripiprazole (partial agonism/antagonism at D_2 and 5-HT_{1A} receptors with antagonism at 5-HT_{2A}) [32–35]. The current review discusses the recent trends of designing MTDLs aimed for MDD treatment. We focused on the research articles published in the last ten years (2013–2023) to extract information regarding latest lead design and/or lead modification strategies. We started with some important case studies based on major pharmacological targets for which MTDLs were designed, synthesized and biologically evaluated. It is to be noted that a detailed discussion regarding the mechanisms of each target of interest is out of scope but a short description of the same is provided in each section. Furthermore, we observed that the majority of case studies focused mainly on serotonergic receptors and in Table 3, a summary of these receptors is thus outlined [36]. Considering these case studies, we included discussions regarding current opportunities and challenges as well as less explored areas that may pave way to future scopes for more productive preclinical research outcomes.

Table 1. List of different categories of currently available traditional or commonly prescribed antidepressant drugs.

Sl.	Categories	Mechanism of action	Example
1	Selective serotonin reuptake inhibitors (SSRIs)	Selectively inhibits 5-HT (serotonin)	Sertraline, Citalopram
2	Selective noradrenaline inhibitors (SNRIs)	Selectively inhibits noradrenaline over 5-HT uptake	Maprotiline
3	Classical tricyclic antidepressants (TCAs)	Inhibits uptake of noradrenaline and 5-HT	Imipramine, Amitriptyline
4	Mixed serotonin/noradrenaline reuptake inhibitors	Non-selective noradrenaline and 5-HT inhibitor	Duloxetine
5	Monoamine receptor antagonists	Blocks different sub-types of 5-HT receptors along with other adrenergic receptors	Mirtazapine, Trazodone
6	Monoamine oxidase inhibitors (MAO-I) a. Irreversible, non-competitive inhibitors b. Reversible MAO-A selective antagonists	Inhibits MAO-A and MAO-B enzymes	Phenelzine, Selegiline Meclobemide
7	Melatonin agonist	MT_1 and MT_2 receptors agonist	Agomelatine
8	Norepinephrine and dopamine reuptake inhibitors	Inhibit reuptake of norepinephrine and dopamine	Bupropion

Table 2. List of selected compounds that entered clinical trial as antidepressant agents [23–30].

Sl no.	Name	MOA	Current status (Phase)
1	Esketamine	Inhibits dopamine transporter and increases dopamine activity	3
2	Minocycline	Inhibits inflammation-induced depression by kynurenine (KYN) and *p*-38 pathways.	3
3	Tianeptine sodium	Inhibition of glutamate receptor activity (AMPA and NMDA receptor) and modestly increases dopamine release	4
4	Lumateperone	Antagonizes 5-HT_{2A} and dopamine receptor subtypes (D_1, D_2 and D_3)	3
5	Creatine monohydrate	Elevates plasma dopamine level	4
6	SAGE-217	Positive allosteric modulator of $GABA_A$ receptor	3
7	Lurasidone	Antagonizes the dopamine D_2 and D_3 receptor and serotonin 5-HT_{2A}	3
8	Vortioxetine	Up regulates the serotonin by inhibiting the reuptake in the synapse	3
9	Ketamine	Decreases NMDA receptor and increases AMPA receptors	1 2
10	Rapastinel	Partial agonist of the allosteric glycine site of the NMDA receptor	3
11	AV-101	Selective agonist of NMDA receptor glycine binding site	2
12	AGN-241751	Orally administered NMDA receptor modulator	2
13	Dextromethorphan	NMDA receptor agonist. Sigma-1 receptor agonist and inhibitors of serotonin and norepinephrine receptors	4
17	D-cycloserine	Partial NMDA glycine receptor agonist	2
18	Buprenorphine	Partial μ-receptor agonist and κ-receptor antagonist	3
20	Naltrexone	μ-receptor antagonist	2
21	BTRX-246040	Nociception opioid peptide receptor antagonist	2
22	JNJ-67953964	κ-opioid receptor antagonist.	2
23	AZD2327	Selective δ-opioid receptor agonist	2
24	Brexanolone	Allosteric modulator of $GABA_A$ receptor	3
25	Mifepristone	Glucocorticoid receptor antagonist.	3
26	Fludrocortisone	Mineralocorticoid receptor agonist.	1
27	Metyrapone	11-β hydroxylase inhibitor. The enzyme catalyses the conversion of 11-deoxycortisol to cortisol	4
29	Sildenafil	PDE5 antagonist	4
30	SSR149415	Vasopressin 1b receptor antagonist	2
31	MDL100.907	Selective 5-HT_{2A} antagonist	2
32	GSK561679	CRF1 receptor antagonist	2
33	MIJ821	Allosteric modulation of NMDA receptor subtype 2B	2
34	Nitrous oxide	NMDA receptor antagonist	2
35	Psilocybin	5-HT_{2A} agonist	2
36	Ayahuasca	5-HT_{2A} agonist along with MAO inhibitor	2
37	Prasterone	Sigma receptor agonist	3
38	Casopitant	NK receptor antagonist	2
39	Ansofaxine Hydrochloride	Serotonin-norepinephrine-dopamine triple reuptake inhibitor	3
40	BTRX 335,140	Potent and selective κ-opioid receptor antagonist.	2
41	BI 1,358,894	Short transient receptor potential channel 4 & 5 (TRPC4 & 5) blocker	2
42	Hypidone	$5HT_{1A}$ partial agonist and SSRI. Great affinity towards $5HT_6$ receptor.	2
43	JNJ-54175446	P2X7 receptor antagonist	2
44	OPC-64005	Inhibits reuptake of serotonin, dopamine and norepinephrine	2
45	3β-Methoxypregnenolone	Selectively binds to microtubule associated protein type 2	2
47	Esmethadone	Noncompetitive NMDA receptor antagonist	3
48	Apimostinel	Selective antagonist of the glycine allosteric site of the NMDA receptor	2
49	Seltorexant	Selective antagonist of the human orexin-2 receptor (OX2R)	2
50	Brexpiprazole [8]	Dopamine D2 receptor partial agonism and serotonin-modulating activity	3
51	Pimavanserin	Acts as 5-HT_{2A} and 5-HT_{2C} modulators, additionally show low binding to σ1 receptor	3
53	ABT-436	V1B receptor antagonist	2
54	Amitifadine	Triple reuptake inhibitor SNDRI	3

2. Case studies: Design of MTDLs acting on two targets

2.1. 5-HT_{1A}/5-HT_{2A}

The serotonin 1A (5-HT_{1A}) and 5-HT_{2A} receptors are widely distributed in the central nervous system to regulate memory, cognition and mood [37,38]. The 5-HT_{1A} receptors function as presynaptic autoreceptors on the raphe nuclei and its activation reduces the serotonin release. On the other hand, postsynaptic 5-HT_{1A} hetero-receptors act as neuromodulators in different areas of CNS. Crucial role for 5-HT_{1A} heteroreceptors was identified in mediating the behavioral response to antidepressant treatment. The 5-HT_{2A} ligands gained significant attention recently as it has been claimed that 5-HT_{2A} agonists are helpful for the treatment of various types of treatment-resistant forms of depression. The 5-HT_{2A} agonist psilocybin is categorized as a psychedelic and it promotes plasticity in prefrontal cortical neurons causing a 'brain reset' for rapid antidepressant effect. More importantly, 5-HT_{1A} and 5-HT_{2A} ligands may work as complementary to each other since these two receptors share similar distribution patterns but the inhibition of 5-HT_{2A} receptor may improve the biological activity of the second subtype, which will lead to the opening of the G-protein-coupled inwardly rectifying potassium channels inhibition of neuronal firing and hyperpolarization, which is crucial for the treatment of MDD [39–41].

Table 3. Summary of serotonin receptors.

Receptor class	Subtype name	Receptor type	Function
5-HT$_1$	*5-HT$_{1A}$*	G-protein coupled receptor (GPCR)	Inhibitory auto- and hetero-receptor
	5-HT$_{1B}$	GPCR	Inhibitory auto- and hetero-receptor
	5-HT$_{1D}$	GPCR	Inhibitory auto- and hetero-receptor
	5-HT$_{1E}$	GPCR	Inhibitory auto- and hetero-receptor
	5-HT$_{1F}$	GPCR	Inhibitory auto- and hetero-receptor
5-HT$_2$	*5-HT$_{2A}$*	GPCR	Excitatory hetero-receptor
	5-HT$_{2B}$	GPCR	Excitatory hetero-receptor
	5-HT$_{2C}$	GPCR	Excitatory hetero-receptor
5-HT$_3$		Ligand-gated ion channel	Excitatory hetero-receptor
5-HT$_4$		GPCR	Excitatory hetero-receptor
5-HT$_5$	*5-HT$_{5A}$*	GPCR	Inhibitory auto-receptor
	5-HT$_{5B}$		
5-HT$_6$		GPCR	Excitatory hetero-receptor
5-HT$_7$		GPCR	Excitatory hetero-receptor

Nefazodone, which is a potent 5-HT$_{2A}$ ligand with moderate potency toward 5-HT$_{1A}$, may be used for the treatment of patients who are less responsive to other antidepressant drugs [42,43]. Adatanserin and flibanserin, which demonstrate antidepressant activities in animal models, interact with both these receptors. Considering these, Wang et al. synthesized a series of benzoxazole/benzothiazole-2,3-dihydrobenzo[b][1,4]-dioxine derivatives (**C1-C2**, *cf.* Figure S1, Supplemental file) as dual 5-HT$_{1A}$/5-HT$_{2A}$ ligands. The design was based on the fact that structurally similar compounds (lead compounds) had previously been reported as dual 5-HT$_{1A}$/serotonin transporter (SERT) ligands. The most potent derivative (**1**, Figure 1) obtained from such lead modification exhibited low nanomolar and sub-nanomolar affinities for 5-HT$_{1A}$ (Ki = 17 nM) and 5-HT$_{2A}$ (Ki = 0.71 nM), respectively. It is worth mentioning here that forced swim test (FST) and tail suspension test (TST) are the two most common *in vivo* analyses performed to determine antidepressant efficacy. Compound **1** reduced the immobility time and exhibited potent antidepressant-like effects in the FST in an mice model with ED_{50} value of 39 mg/kg. Similarly, TST also depicted considerable antidepressant activity of this compound [44].

2.2. 5-HT$_{1A}$/5-HT$_7$

The 5-HT$_7$R plays significant role in the regulation of sleep, mood, learning, memory, and cognition. More importantly, 5-HT$_{1A}$ and 5-HT$_7$, which share 40% sequence homology with each other, form heterodimers in most brain regions to produce cross-talks that are implicated in MDD. Downregulation of 5-HT$_7$ receptors leads to faster antidepressant responses in rats. Hippocampal 5-HT$_7$ receptors are involved in the interactions between the serotonergic system and the hypothalamus-pituitary-adrenal (HPA) axis. Therefore, compounds acting on both these receptors may have significant therapeutic outcomes [37,38,45,46].

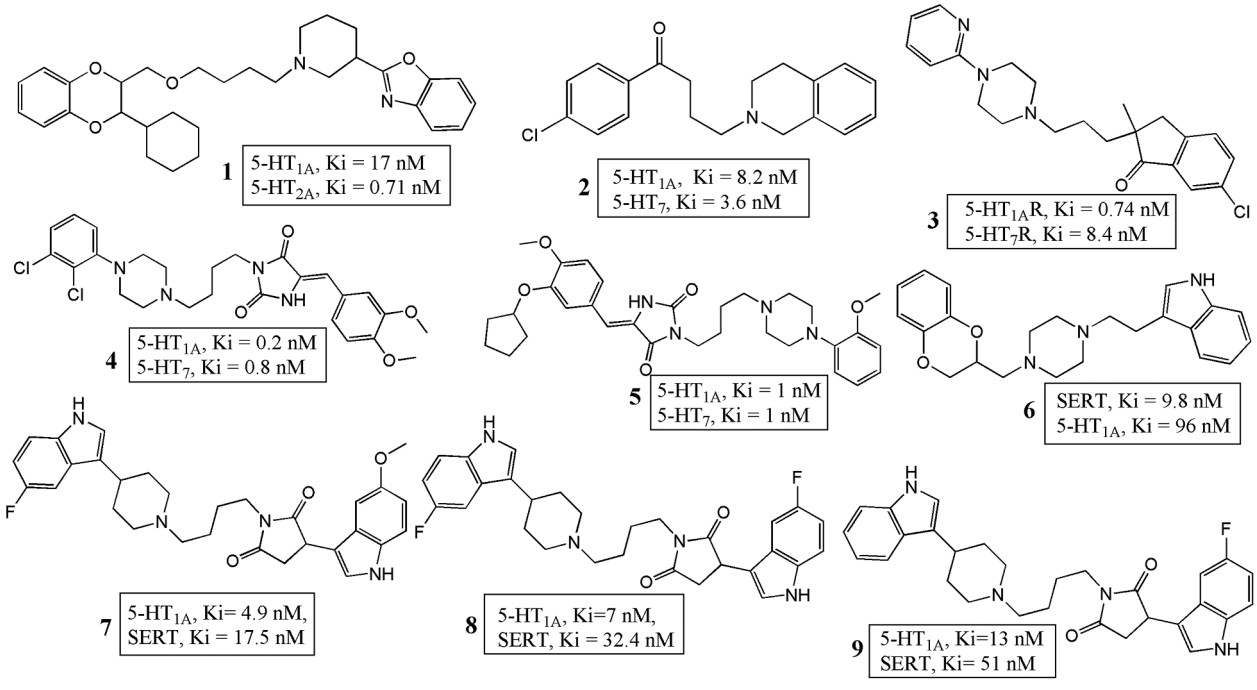

Figure 1. Chemical structures and biological activities of MTDLs (1–9) developed as potential antidepressant agents.

The 1,2,3,4-tetrahydroquinoline (THQ) moiety is found in the well-known antidepressant agent aripiprazole. Since the 1,2,3,4-tetrahydroisoquinoline (THIQ) moiety is a close analogue of THQ, Ofori et al. focused on using different substitutions at the aromatic ring of arylalkyl substituted THIQs (**C3**, cf. Figure S2, Supplemental file). The most potent compound of this series (**2**, Figure 1) depicted binding affinity (Ki) values of 8.2 nM and 3.6 nM for 5-HT_{1A} and 5-HT_7, respectively. Selectivity was obtained for these two targets as compared to other serotonin receptors as well as SERT. These compounds were also tested for dopamine (D_2, D_3 and D_4) receptor, and histamine (H_1) receptor. Among these, the maximum potency (as well as selectivity) was observed toward dopamine 3 (D_3) receptor (i.e. Ki = 17 nM). Therefore, this ligand may also be considered as 5-HT_{1A}/5-HT_7/D_3 ligand [47]. The D_3 receptor antagonists may provide effective antipsychotic treatment with low extrapyramidal adverse effects. Nevertheless, selective blockade of this receptor may not have sufficient antipsychotic potential.

More recently, the same researchers reported another work, where the compounds were designed based on earlier reported dual 5-HT_{1A} and 5-HT_7 ligand **SYA16263** (*cf*. Figure S3, Supplemental file), which is a long-chain arylpiperazine (LCAP) with low nanomolar potency for 5-HT_{1A}. This investigation resulted in a compound (**3**, Figure 1) with sub-nanomolar (5-HT_{1A}R, Ki = 0.74 nM) and a low nanomolar (5-HT_7R, Ki = 8.4 nM) affinity for these receptors. A significant improvement (approximately 10-fold) was achieved for the potency toward 5-HT_7 that led to more balanced activities for both these targets. Compound **3** behaves as a 5-HT_{1A}R agonist and 5-HT_7R antagonist and therefore, it has significant potential as lead compound for MDD [48].

In continuation of a previous work, Czopek and coworkers attempted to hybridize structures of six different serotonin modulators or drugs to propose a series of multitarget 5-arylidenehydantoins with arylpiperazinealkyl fragment (**C4**, *cf*. Figure S4, Supplemental file) as novel antidepressant agents. Among twelve synthesized compounds, the most promising activity was obtained from compound **4** (Figure 1) that showed excellent affinities toward 5-HT_{1A} and 5-HT_7 with Ki values of 0.2 and 0.8 nM, respectively. This compound was however found to have negligible potency for PDE enzyme (5% inhibition at 10^{-5} M) in spite of the fact that a thoughtful hybridization strategy was adopted by incorporating the structural characteristics of antidepressant agent rolipram (a PDE4B inhibitor) in the designed ligands. Nevertheless, this compound was found to be less toxic than doxorubicin. *In vivo* test suggested that the immobility time may be reduced by 27% at the dose of 0.625 mg/kg. Slightly improved *in vivo* activity (30% reduction) was, however, noticed from another compound **5** (Figure 1) with Ki values of 1 nM toward both 5-HT_{1A} and 5-HT_7 [49].

2.3. 5-HT_{1A}/SERT

Pre-clinical studies suggested that the administration of SSRIs with 5-HT_{1A} receptor partial agonists or antagonists may significantly improve the speed and efficacy of antidepressant action in clinical studies [50,51]. Co-administration of SSRI and a 5-HT_{1A} receptor agonist or a partial agonist in fact increases the neurotransmission in the serotonergic system through stimulation of postsynaptic receptors. The release of endogenous serotonin is reduced by a negative feedback mechanism activated by the stimulation of somatodendritic autoreceptors [52].

Waszkielewicz et al. reported design, syntheses and biological evaluation of six 4-substituted 1-(2-methoxyphenyl) piperazine derivatives and save for one, all these compounds were found to be potent dual ligands of 5-HT_{1A}/5-HT_7. The most potent MTDL (10, Figure 1) depicted sub-nanomolar (<1 nM) potency toward 5-HT_{1A} and nanomolar activity for 5-HT_7. Apart from these promising in vitro results, this compound demonstrated strong antidepressant activity in vivo (i.e. TST). With only 2.5 mg/kg dose, over 30% reduction in immobility time was reported. Nevertheless, the same compounds showed sedative activity with ED50 of 17.5 mg/kg and neurotoxicity with TD50 of 53.2 mg/kg [53].

Wang et al. reported 2,3-Dihydrobenzo[b] [1,4]-dioxin- and indolealkylamine derivatives (**C5**, *cf*. Figure S5, Supplemental file). The design was based on linking a 5-HT_{1A} component and SERT component in forms of aryloxyethylamine and 3-indolealkyamine, respectively. To represent aryloxyethylamine, Benzodioxanmethyl piperazine moiety was chosen and after synthesizing twenty-four compounds and evaluating these against multiple biological targets related to depression, the most potent compound (**6**, Figure 1) was identified with Ki values of 9.8 nM and 98 nM toward 5-HT_{1A} and SERT, respectively. Furthermore, most of the synthesized compounds were found to be highly selective toward these two targets as compared to 5-HT_{2A}, 5-HT_{2C}, α_1, α_2 and D_2. With acceptable pharmacokinetic properties, this compound was found to have significant antidepressant activity in both FST and TST based *in vivo* assay [54]. For example, the ED_{50} of compound **6** was reported as 18.6 mg/kg in TST. Locomotor activity test was also conducted to distinguish the false positive effects in the animal models. Compound **6** may therefore be explored as a lead molecule for developing promising antidepressant agent [54].

In 2013, Wrobel et al. described the synthesis and biological evaluation of pyrrolidine-2,5-dione derivatives with significant binding affinities for SERT and 5-HT_{1A} receptors. This investigation yielded **MW005** (*cf*. Supplemental data, Figure S6) as a potent ligand with multi-receptor profile [55]. More recently, Wrobel prepared a series of 3-(1 H-indol-3-yl)-pyrrolidine -2,5-dione derivatives based on previous research that projected **MW005** [56]. In fact, all the newly synthesized 3-(1 H-indol-3-yl)-pyrrolidine-2,5-dione derivatives were tested against 5HT_{1A} and SERT. Two compounds (**7–8**, Figure 1) were identified with the most promising binding affinities for these two targets. Noticeably, the activities toward SERT improved significantly for these compounds. From this series another compound (**9**, Figure 1) was identified, and as compared to **MW005,** demonstrated slightly improved polypharmacological profiles against six different targets (*cf*. Supplemental data, Figure S6). Therefore, compound **9** may be considered as MTDL acting on six biological targets. SAR studies disclosed the importance of (a) the four-methylene spacer and (b) methoxy group for increased affinity toward 5-HT_{1A}. Along with four-methylene spacer, a 5-fluoro-3-piperidin-4-yl-1 H-indole residue was found to impart dual

affinities toward 5-HT_{1A} and SERT. The presence of the fluoro or methoxy group substituents improved the affinity of the compounds for 5-HT_7 [56]. This investigation also demonstrated some interesting pharmacokinetic and *in vivo* results for **MW005**. It reduced immobility time in the FST and decreased activity in the spontaneous locomotor activity test at 10 mg/kg dose. Nevertheless, **MW005** has a high propensity for hERG channel blocking, emphasizing that this compound requires further optimization to improve its permeability, oral pharmacokinetic properties and cardiac safety [56].

Gomółka et al. prepared a series of 4-aryl-pyrido[1,2-c]pyrimidines containing a 1-(2- quinoline)piperazine moiety based on the previously reported compounds with binding affinities toward 5-HT_{1A} and SERT [57]. This work was also a continuation of previous investigations that highlighted 4-aryl-pyrido[1,2-c]-pyrimidines as a promising scaffold and its presence along with long-chain arylpiperazine (LCAP) residue may improve potency toward some important biological targets related to depression. Therefore, starting from the structures of some previously reported derivatives, the authors were interested in exploring different quinoline derivatives (**C6**, *cf*. Supplemental data, Figure S7). The major objectives of the work were (a) to insert the quinoline moiety to improve the potencies, (b) to understand the role of the degree of unsaturation of pyrido[1,2-c]-pyrimidine and (c) to assess different types and location of substituents in the 4-aryl-pyrido[1,2-c]-pyrimidine moiety on the affinity for 5-HT_{1A}R, 5-HT_{2A}R and SERT. This investigation identified two different lead molecules (**10 and 11**, Figure 2) with less than 100 nM Ki values for both 5-HT_{1A} and SERT [57]. However, in another work [58], it was found that retention of the indole moiety attached to piperidine (**C7**, *cf*. Supplemental data, Figure S7) may lead to more potent and balanced affinities toward these two targets. Even though this investigation resulted in multiple promising dual 5-HT_{1A}/SERT, one compound (**12**, Figure 2) depicted Ki values of 68 nM and 22 nM for SERT and 5-HT_{1A}, respectively.

From this experience, it was realized that it is important to retain the fragment of 3-(piperidin-3-yl)-1 H-indole as pharmacophore part whereas pyrido[1,2-c]-pyrimidine fragment or its aromatic substitution should rather be modified. This idea resulted in a new series of new 5,6,7,8-tetrahydropyrido [1,2-c]pyrimidine derivatives (**C8**, *cf*. Supplemental data, Figure S8) with rigidized tryptamine moiety [59]. Even though this work helped in identifying seven potent dual 5-HT_{1A}/SERT ligands, the researchers focused on two compounds (**13** and **14**; Figure 2) that along with having nanomolar potencies toward these two targets also showed good metabolic stabilities as well as selectivity as compared to D_2, 5-HT_{2A}, 5-HT_6 and 5-HT_7. Significantly, **14** did not affect the immobility time in the FST in mice. Finally, further *in vivo* studies on compounds **13** and **14** revealed that they behaved as moderate presynaptic 5-HT_{1A} receptor antagonists [59].

2.4. 5-HT_{1A}/D_2

Dopamine-2 (D2) receptors are present in postsynaptic dopaminergic target neurons and these also act pre-synaptically as autoreceptors. The D_2 receptors are associated with Go and Gi proteins that inactivate adenylyl cyclase, decreasing cytosolic cAMP levels. Binding of DA to D_2-like receptors inhibits the cAMP/PKA signaling pathway, ultimately affecting the CREB phosphorylation [60]. Olanzapine, a D_2 receptor antagonist, demonstrates a much stronger antidepressant effect in combination with Fluoxetine [53,54]. Additionally, aripiprazole acts as a partial agonist of D_2 and 5-HT_{1A} receptors and at the same time, it is a 5-HT_{2A} receptor antagonist [61]. Several investigations depicted that D_2 receptor partial agonists are indeed useful adjuncts for the treatment of MDD since these significantly improve the efficacy of selective SSRIs [61–63]. Additionally, drugs like buspirone, aripiprazole, ipsapirone, and brexpiprazole may be categorized as dual 5-HT_{1A}/D_2

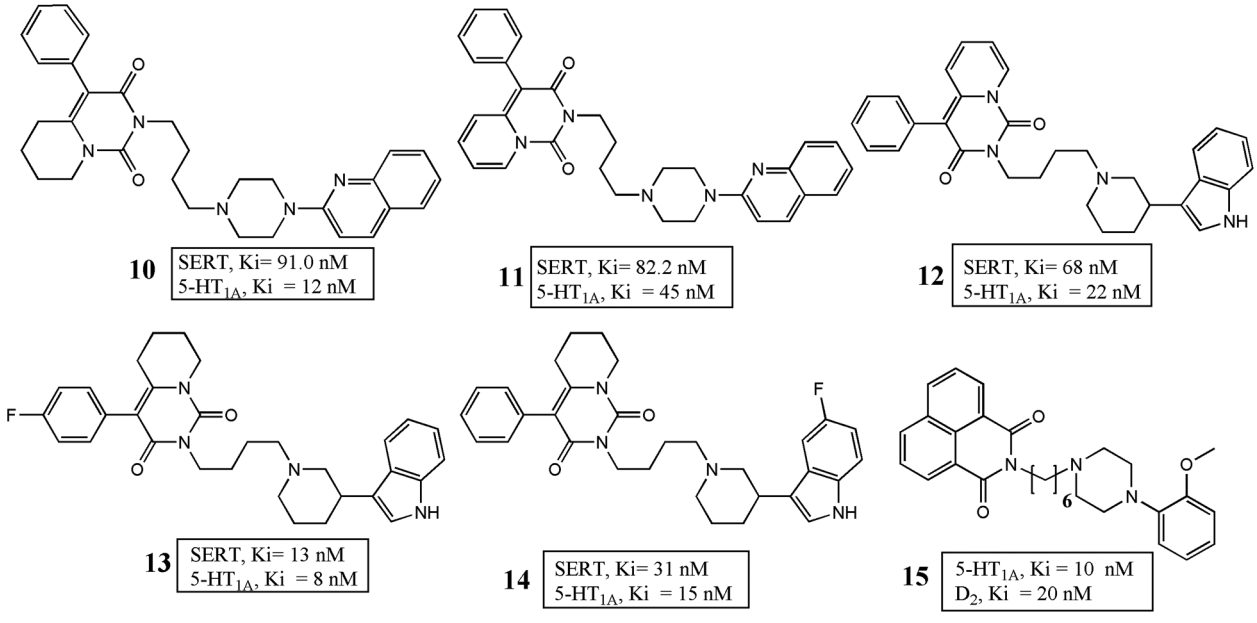

Figure 2. Chemical structures and biological activities of MTDLs (10–15) developed as potential antidepressant agents.

ligands [64]. Nevertheless, the rationale behind the benefit of combining the effects of these two receptors are not well understood. However, it is observed that it is the balance between the properties of these two receptors that may have a profound influence on the pathophysiology of depression. In addition, these two receptors may form constitutive heterodimers, the bio-functional mechanism of which is different from each protein [65].

Zareba et al. designed and synthesized a series of bulky hexylarylpiperazine derivatives (**C9**, *cf*. Supplemental data, Figure S9) and the synthesized compounds were evaluated against 5-HT_{1A}, 5-HT_{2A}, 5-HT_6, 5-HT_7 and D_2 receptors. A number of compounds showed selective potencies toward $5HT_{1A}$ and D_2 receptors. For example, one compound (**15**, Figure 2) depicted Ki values of 10 nM and 20 nM for 5-HT_{1A} and 5-HT_7[63].

3. Case studies: MTDLs acting on three targets

3.1. 5-HT_{1A}/$5HT_7$/SERT

The significance of 5-HT_{1A}, 5-HT_7 and SSRIs in the treatment of MDD has been described above. The possible relationship between SSRIs (which act on SERT) and 5-HT_{1A} agonists has been revealed. The SSRIs, which provide the first line treatment of MDD, may gradually desensitize presynaptic 5-HT_{1A} autoreceptors that leads to postsynaptic binding of serotonin with 5-HT_{1A} hetero-receptors, enhancing the antidepressant activity of SSRIs. Therefore, there may be a long term-benefit in combining 5-HT_{1A} agonists with SSRIs. Besides, the inhibition of 5-HT_7 has also been found to improve the efficacy of SSRIs [40,41]. Vortioxetine is a recently approved antidepressant agent that exhibits potent serotonin reuptake inhibition and high 5-HT_{1A}/5-HT_7 receptor affinities [66]. Gu et al. synthesized a series of arylalkanol and arylalkyl derivatives containing aryl piperazine benzo[b] [1,4] oxazine moieties [67]. One previously reported dual 5-HT_{1A}/SERT derivative **S1** (*cf*. Supplemental data, Figure S10) was used as a template structure and its benzo[b] [1,4]-oxazine moiety was replaced with aromatic 3,4-dichlorophenyl as the latter moiety is frequently present in a number of known SSRI antidepressants [68]. Furthermore, the 2-methoxyphenyl moiety of **S1** was replaced with different aromatic or heteroaromatic groups for the design of new multitarget agents. All sixteen synthesized compounds depicted >80% binding affinity toward $5HT_{1A}$ and $5HT_7$ at 10 µM concentration though serotonin reuptake inhibition by these compounds varied to a considerable extent at the same concentration. Two highly active multitarget agents of this series (**16 and 17**, Figure 3) were identified. The most potent compound **17** depicted satisfactory binding affinities toward all these targets with binding affinity (Ki) values of 0.84 nM and 12 nM toward $5HT_{1A}$ and $5HT_7$ respectively, whereas its serotonin reuptake inhibition

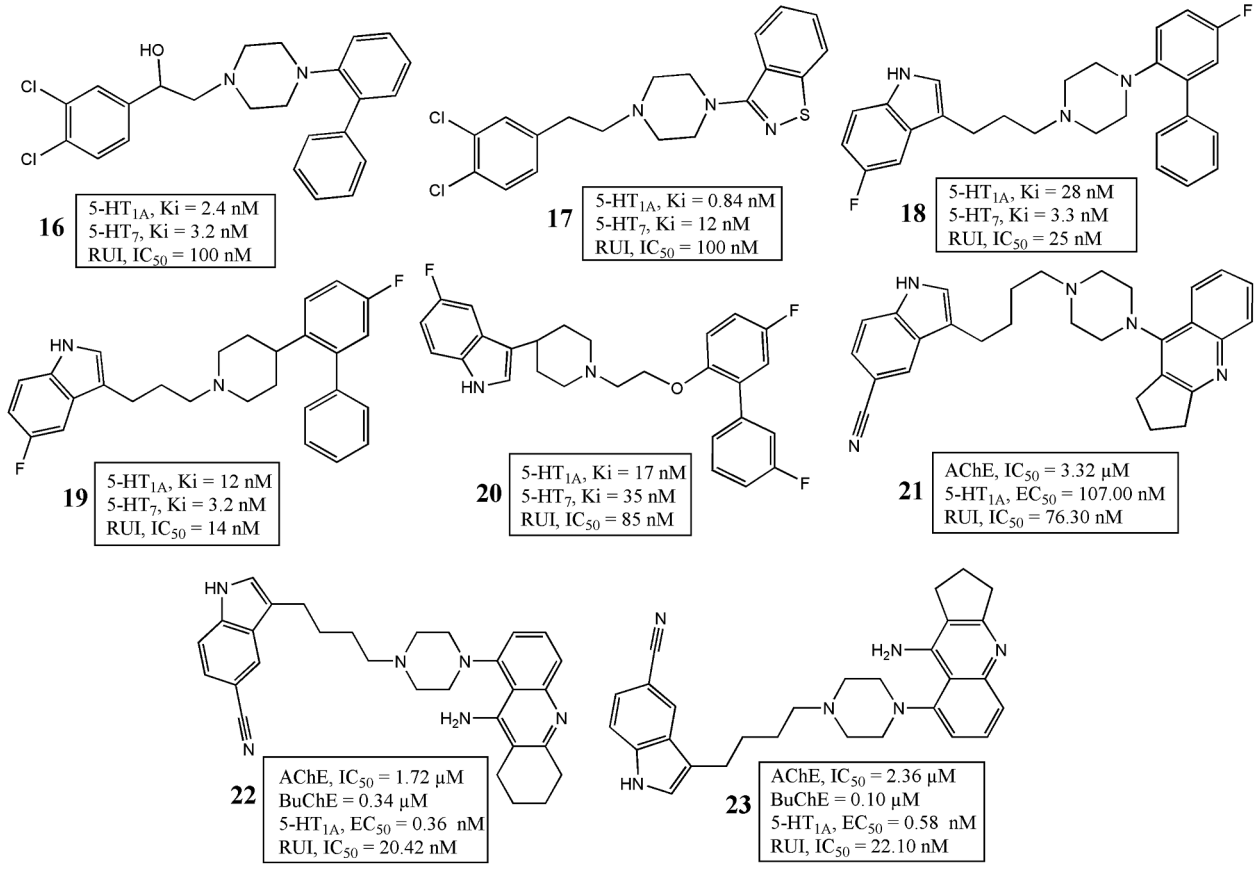

Figure 3. Chemical structures and biological activities of MTDLs (16–23) developed as potential antidepressant agents.

activity (expressed as IC_{50}) was 100 nM. Both the compounds **16** and **17** depicted shorter half-lives than vortioxetine. Furthermore, both these compounds showed significant antidepressant activity in the FST model (21–26% at a dose of 20 mg/kg and 30–45% at a dose of 40 mg/kg). Based on the *in vitro* and *in vivo* results, the authors proposed compound **16** as a promising MTDL for the treatment of depression. The SAR revealed that length of the linker between 3,4-dichlorophenyl and piperazine moieties as well as the presence of benzoisothiazole moiety strongly influence the reuptake inhibition (RUI) activity. Two carbon chain linker was found to be optimal for the higher affinity toward $5HT_{1A}$ and $5HT_7$ [67].

In continuation of this research, Gu et al. reported a series of arylalkyl piperazine derivatives in 2018 and these were tested for serotonin reuptake inhibition as well as binding affinity toward 5-HT_{1A} and 5-HT_7. It should be noted that the design of this series of compounds was influenced by a number of previously reported multitarget agents but the most significant one was found to be compound **S2** (*cf.* Supplemental data, Figure S11) containing benzofuran, piperazine and quinoline moieties that was reported by Venkatesan et al. with potent binding affinities toward 5-HT_7 and SERT. The most potent compound of this series (**18**, Figure 3) was found to have satisfactory nanomolar activity for all three targets. Additionally, apart from having satisfactory oral bioavailability, compound **18** showed potent antidepressant activity *in vivo* in FST and TST. More importantly, with improved reuptake inhibition, the *in vivo* antidepressant activity was also enhanced (at 40 mg/kg the immobility time was reduced to 52%). Furthermore, compound **18** possessed satisfactory oral pharmacokinetic properties and acceptable cardiac safety [69].

More recently, the same group of researchers reported additional aralkyl piperazine and piperidine derivatives (**C12** and **C13**) in two different reports and the design of these new derivatives was based on compound **18** (*cf.* Supplemental data, Figure S12). From one investigation, one potent piperidine derivative **19** (Figure 3) was identified with more balanced activity for all these three targets (i.e. 5-HT_{1A}, 5-HT_7 and serotonin RUI). The Ki values for 5-HT_{1A} and 5-HT_7 were found as 12 nM and 3.2 nM, respectively, whereas the IC_{50} value serotonin reuptake inhibition of this compound was reported as 14 nM. Additionally, compound **19** depicted agonistic property with EC_{50} of 1180 nM at 5-HT_{1A}R and antagonist property with IC_{50} of 650 nM at 5-HT_7R in *in vitro* functional activity assays. *In vivo* assay (i.e. FST) showed that **19** reduces the immobility time to about 35% and 47% at doses of 20 and 40 mg/kg, respectively. Another *in vivo* TST also showed satisfactory antidepressant activity [70]. In another investigation, however, no significant improvement in the activities was observed, and one of the most potent derivatives (**20**, Figure 3) of the series was reported with Ki values of 17 nM and 35 nM for 5-HT_{1A} and 5-HT_7. The IC_{50} value of serotonin reuptake inhibition was reported as 85 nM. Significantly, *in vivo* FST and TST studies revealed that **20** is able to reduce the immobility times (27% and 15%, respectively) in animals and at 40 mg/kg dose [71].

3.2. 5-HT_{1A}/SERT/AChE

Vilazodone is a compound that exhibits partial agonistic activity for 5-HT_{1A} and serotonin reuptake inhibition but at the same time, it also possesses AChE inhibition. Since AChE is one of the most promising targets for the treatment of Alzheimer's disease (AD), MTDLs acting on these three biological targets may be utilized in the depression related to AD [72–74]. Considering this hypothesis, Li et al. designed vilazodone-tacrine hybrids (*cf.* Supplemental data, Figure S13) as multitarget-directed potential anti-AD agents [74]. Tacrine was used not only because it is a well-known AChE inhibitor but also because of its structural simplicity and structure-modifying accessibility. Among thirty synthesized hybrid compounds, the most potent compound (**21**, Figure 3) depicted the most balanced activities among AChE inhibition (IC_{50} = 3.319 μM), 5-HT_{1A} agonism (EC_{50} = 107 nM) and serotonin reuptake inhibition (IC_{50} = 76.3 nM). SAR analyses indicated that indolebutylpiperazine fragment is crucial and modification of the 4-carbon chain and the piperazine moiety is detrimental for 5-HT_{1A} agonist and 5-HT reuptake inhibition. Furthermore, substitution in the benzene ring of **21** decreases the AChE inhibition properties. Compound **21** showed less cytotoxicity as compared to Vilazodone. *In vivo* analyses performed with TST method revealed that **21** is potent antidepressant agent [74].

In continuation to this investigation, another series of vilazodone-tacrine hybrids (*cf.* Supplemental data, Figure S14) were designed and synthesized [75]. In this work, the linker between indole and piperazine scaffolds were varied with different size of aliphatic linkers. At the same time, the tacrine and indole moieties were also modified. Along with AChE, the biological activity was also assessed for BuChE. This investigation helped in identifying two potent multitargets agents (**22** and **23**, Figure 3) that showed micromolar and sub-micromolar activities toward AChE and BuChE. These compounds also depicted nanomolar potencies for 5-HT_{1A} as well as for serotonin reuptake inhibition. Additionally, these compounds showed good blood-brain barrier permeability [75].

3.3. 5-HT_{1A}/5-HT_7/PDE

Phosphodiesterases (PDEs) are group of enzymes that degrade cAMP and/or cGMP by hydrolysis of phosphodiester bonds. There are eleven different PDE families (PDE1-PDE11) and each family has multiple isoforms and splice variants. Elevated intracellular cAMP levels are associated with antidepressant and antipsychotic effects. Inhibition of two PDE subtypes PDE4 and PDE10A was found to be highly effective in the treatment of depression because of their presence in the areas of the brain associated with the site of action of antidepressant drugs [76–78]. Therefore, compounds possessing PDE inhibitory potential may be used as antidepressant agents.

Chlon-Rzepa et al. synthesized a new series of 3,7-dimethyl- and 1,3-dimethyl-8-alkoxypurine-2,6-dione derivatives of arylpiperazines, perhydroisoquinolines, or tetrahydroisoquinolines (**C14**, *cf.* Supplemental data, Figure S15) with flexible alkylene

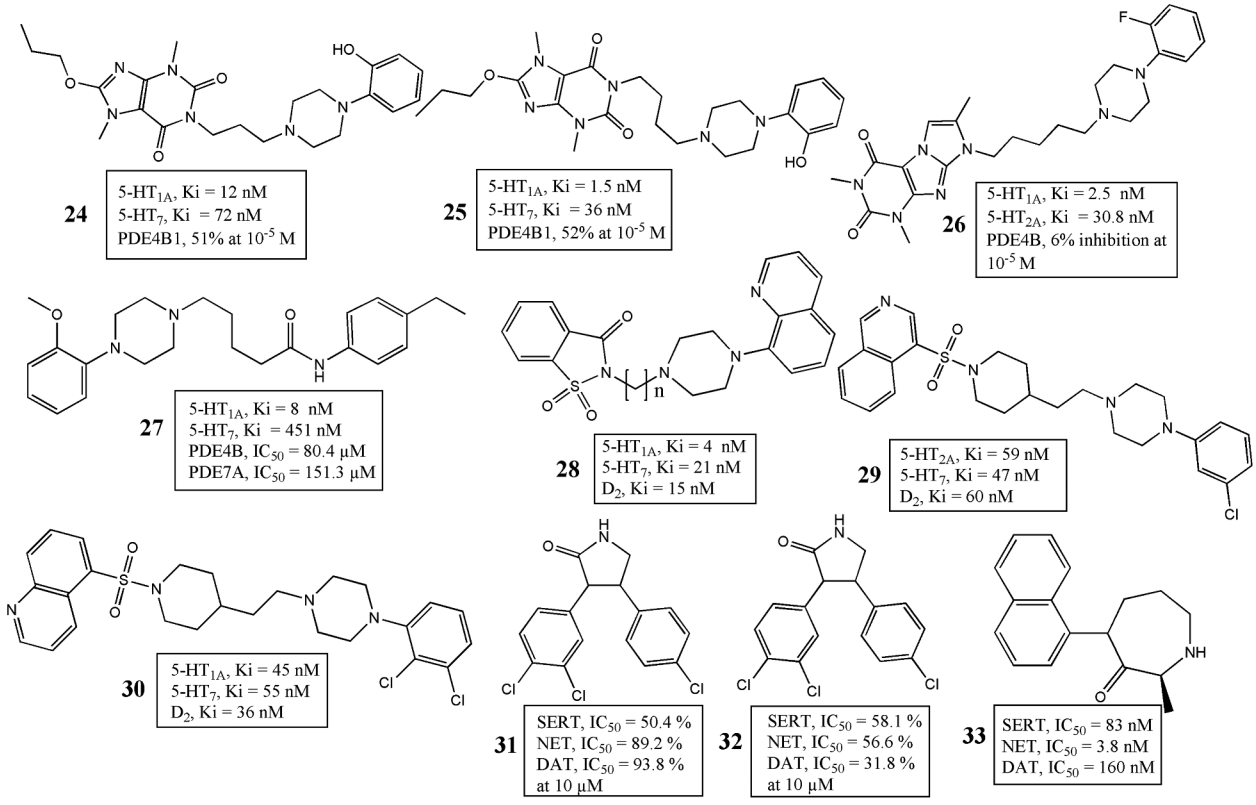

Figure 4. Chemical structures and biological activities of MTDLs (24–33) developed as potential antidepressant agents.

spacers. These compounds were evaluated for 5-HT_{1A}/5-HT_7 receptor affinities as well as PDE4B1 and PDE10A inhibitory properties. In animal models, elevated intracellular cAMP levels have shown to possess antidepressant effects which can be achieved by inhibition of PDE4 and PDE10A subtypes. Two compounds (**24** and **25**, Figure 4) depicted the most balanced properties toward all these enzymes since along with having nanomolar potentials toward 5-HT_{1A} and 5-HT_7, these also showed 51% and 52% inhibition of PDE4B1 at 10^{-5} M concentration. This study also revealed that strong antagonistic activity toward 5-HT_{1A}/5-HT_7 as well as PDE4B1 inhibition may lead to antidepressant-like effect [79].

With an aim to design and develop 5-HT_{1A}/5-HT_7/PDE ligands, Zagorska et al. reported the syntheses of 2-fluoro and 3-trifluoromethylphenylpiperazinylalkyl derivatives of 1 H-imidazo-[2,1-f]-purine-2,4(3 H,8 H)-dione (**C15**, *cf.* Supplemental data, Figure S16). Even though three compounds were identified with nanomolar potencies for 5-HT_{1A} and 5-HT_7, weak inhibitory potential was obtained against PDE4B and PDE10A. Only 6% inhibition was noticed against PDE4B in a one compound (**26**, Figure 4) that could be considered for the most balanced activity toward both serotonin and PDE receptors. This compound was, however, found as a potential antidepressant, and significantly reduced the immobility time of mice in that test by 21% only at 5 mg/kg dose. Additionally, as compared to diazepam, greater antianxiety effects were found in this compound [80].

By hybridizing the structures of previously reported dual 5-HT_{1A}/5-HT_7 receptor ligands and dual PDE4B/PDE7A inhibitors, Jankowska et al. designed anilide and benzylamide derivatives of arylpiperazinylalkanoic acids (**C16**, *cf.* Supplemental data, Figure S17) as potential multifunctional ligands. After synthesizing thirty designed compounds, one compound (**27**, Figure 4) showed maximum balanced potencies toward 5-HT_{1A} (Ki = 8 nM), 5-HT_7 (Ki = 451 nM) and PDE4B/PDE7A inhibitory activity (PDE4B IC_{50} = 80.4 µM; PDE7A IC_{50} = 151.3 µM). Apart from having satisfactory membrane penetrating properties as well as metabolic stability, **27** reduced the immobility time of the animals to 34% at a dose of 10 mg/kg [81].

3.4. 5-HT_{1A}/5-HT_7/D_2 receptors

Kułaga et al. designed a series of new hexyl arylpiperazine derivatives (**C17**, *cf.* Supplemental data, Figure S18) from the saccharin moiety (i.e. 1,1-dioxo-1,2-benzothiazol-3-one). The authors were also interested to explore the LCAPs for the design of MTDLs considering the potential of such structural residues to function as 5-HT_{1A} inhibitors and linked these to saccharin [64]. Note that one of the inspirations of designing saccharin-based compounds came from ipsapirone, a 1,1-dioxo-1,2-benzothiazol-3-one containing compound with dual 5-HT_{1A}/D_2 activity. However, the authors increased the 4-carbon linker and explored hexyl alkyl chain. After synthesizing seventeen compounds, one compound (**28**, Figure 4) was obtained with nanomolar potencies (5-HT_{1A} = 4 nM and D_2 = 15 nM) toward both 5-HT_{1A} and D_2 receptors. However, when tested against other receptors, this compound

was also found to be highly active toward 5-HT_7 as well and a Ki value of 21 nM was obtained. Therefore, this compound may be projected as *5-HT_{1A}/5-HT_7/D_2* ligand. This investigation clearly pointed out that extension of the carbon chain from 4 to 6 atoms lead to 4-fold increase in 5-HT_{1A} activity; a 13-fold increase in 5-HT_{2A} activity and a 16-fold increase in D_2 activity. The preliminary *in silico* parameters of ADME predicted that the ligands have CNS drug-like potential [64].

Partyka et al. pointed out that several antipsychotics block D_2 receptors to reverse positive symptoms of schizophrenia. It was also argued that 5-HT_7 antagonism and partial agonism at 5-HT_{1A}Rs may assist in reducing the social withdrawal. The authors designed a series of azinesulfonamides with different arylpiperazines separated by an alkylene spacer (**C18**, *cf*. Supplemental data, Figure S19) [82]. The design was partially based on previously reported compound by Zajdel et al. in which one compound (**29**, Figure 4) was reported to possess nanomolar potencies toward 5-HT_{2A}, 5-HT_7 and D_2 [83]. Further structural modifications of **29** was aimed to understand the role of azinesulfonamide fragment as well as to verify the halogen substitution of phenyl piperazine moiety. The activities of the newly synthesized compounds were evaluated against D_2, 5-HT_{1A}, 5-HT_{2A}, 5-HT_6 and 5HT_7. One compound (**30**, Figure 4) was reported with low nanomolar potencies toward 5-HT_{1A} (Ki = 45 nM), 5-HT_7 (Ki = 55 nM) and D_2 (Ki = 36 nM). Compound **30** behaved as D_2, 5-HT_{1A} and 5-HT_7 receptor antagonist and *in vivo* FST ensured that this compound exhibits antidepressant-like effect with minimum effective dose (MED) of 0.625 mg/kg [82].

3.5. Triple reuptake inhibitors (SERT/NET/DAT)

A triple reuptake inhibitor (TRI), which are also known as serotonin – norepinephrine–dopamine reuptake inhibitor (SNDRI), is a type of drug that acts as reuptake inhibitors of three different monoamine neurotransmitters – serotonin, norepinephrine, and dopamine. Recently, clinical trials of several TRIs like Amitifadine (EB-1010, formerly DOV-21,947) and GSK372475 (NS-2359) were carried out as antidepressants. These TRIs are expected to provide more rapid onset of action with improved therapeutic efficacy for the treatment of refractory MDD [84,85]. Park et al. designed a series of 3,4-diarylpyrrolidin-2-one derivatives (**C19**, *cf*. Supplemental data, Figure S20) as TRIs for antidepressant agents that may act on hSERT, hNET and hDAT. The design of these compounds was based on previously investigated compounds and known triple reuptake inhibitors amitifadine and JZAD-IV-22. From twenty-two synthesized derivatives, two compounds (**31** and **32**, Figure 4) were identified with maximum balanced affinities (>50% inhibition for each target at 10 μM) for all these three targets [86].

Honda et al. described the design, synthesis, and biological activities of novel 1-aryl-1,4-diazepan-2-one derivatives (**C20** and **C21**, *cf*. Supplemental data, Figure S21) as potent TRIs. The proposed compounds were designed from milnacipran and amitifadine, considering that both these reuptake inhibitors possess relatively rigid structures and relative distance between aromatic ring and basic amino group was important for TRI activities. Additionally, milnacipran demonstrates a relatively lower risk of CYP2D6 and hERG inhibition. The amide moiety of Milnacipran is unique among antidepressants, and it may help in avoiding the common liabilities of cation amphiphilic drugs due to its low hydrophobicity. Compound **33** (Figure 4) was found to be a potent TRI with satisfactory ADME-Tox profile. Oral administration of **33** significantly enhanced norepinephrine, dopamine, and serotonin levels in the mouse prefrontal cortex and depicted significant antidepressant-like activity in TST in mice [87].

3.6. 5-HT_{2A}/5-HT_{2C}/SERT

5-HT_{2A} and 5-HT_{2C} are two subtypes of the 5-HT_2 receptor that mediate excitatory neurotransmission through interaction with endogenous serotonin and therefore, their antagonists have antidepressant effects. It has been suggested that trazodone may act through inhibition of 5-HT_{2A}, 5-HT_{2C} and SERT. In one work, scaffold hopping technique was explored by Kim et al. to design phthalazinone-based compounds (**C22**, *cf*. Supplemental data, Figure S22) as inhibitors of 5-HT_{2A}, 5-HT_{2C}, and SERT. Two most potent derivatives (**34** and **35**, Figure 5) depicted strong potencies toward 5-HT_{2A} and 5-HT_{2C} receptors but their binding affinities toward SERT was found to be weak, as compared to fluoxetine. Nonetheless, compounds **34** and **35** depicted significant antidepressant affect in *in vivo* FST. At 25 mg/kg, **34** caused 40% reduction in the immobility time whereas **35** had similar *in vivo* efficacy as fluoxetine at 50 mg/kg. These results implicated that these compounds may be developed to help the treatment of MDD [88].

4. MTDLs acting on more than three targets

4.1. α_1/α_2/5-HT_{1A}/5-HT_{2A}/5-HT_7

Matetic et al. reported a systematic review on the role of α-adrenergic receptors in the pathophysiology and treatment of MDD. It has been reported that the α_1 receptors are desensitized in the brains of patients suffering from MDD. On the other hand, affinity and density of inhibitory α_2-receptors are elevated in the locus coeruleus and prefrontal cortex of patients receiving antidepressant agents indicating a resistance of α_2 receptors to the effect of antidepressants. Therefore, α_1 and α_2-receptors may be considered as potential therapeutic targets for treatment of patients suffering from severe MDD with suicidal thoughts [89].

In a previous investigation, published in 2007, Chłoń-Rzepa et al. identified two 1,3-dimethyl-3,7- dihydropurine-2,6-dione derivatives (**36** and **37**, Figure 5) as multitarget agents with nanomolar binding affinity toward 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 [90]. In 2014, the authors further investigated these two compounds with three other 8- alkoxy-purine-2,6-dione derivatives as multitarget antidepressant agents acting on 5 receptors that are α_1, α_2, 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 [91]. All five compounds were found to be highly active 5-HT_{2A} receptor (Ki 15–28 nM) and α1 adrenoceptor (Ki 21–89 nM) ligands. However, the most potent multitarget agent (**38**) depicted the low nanomolar potencies against five biological targets. On the basis of *in vivo* assays (i.e. FST), all these compounds were projected as good antidepressant agents [91].

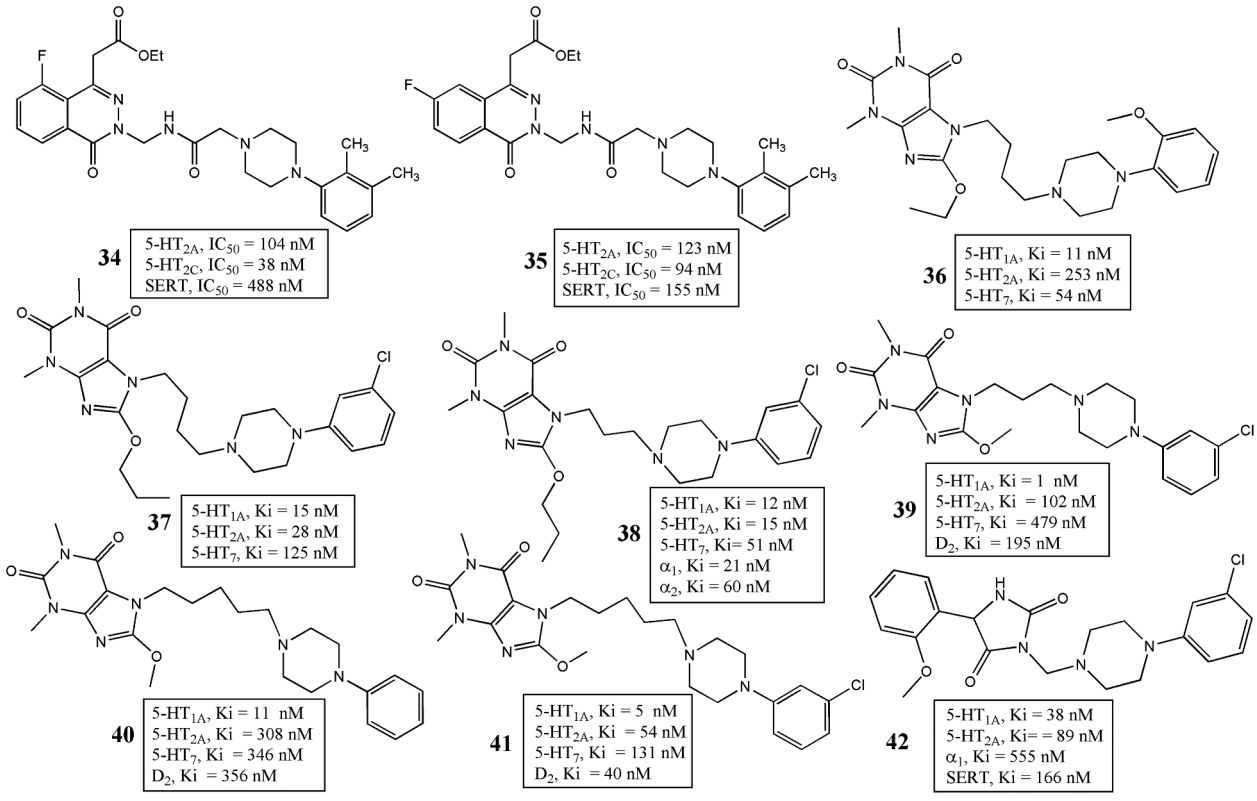

Figure 5. Chemical structures and biological activities of MTDLs (34–42) developed as potential antidepressant agents.

4.2. 5-HT$_{1A}$/5-HT$_{2A}$/5-HT$_7$/D$_2$ receptors

Chłon-Rzepa and coworkers investigated a number of long-chain arylpiperazines (LCAPs) as multitarget antidepressant agents [90,92]. In one investigation [93], they reported syntheses and biological evaluation of thirteen purine-2,6-dione derivatives (**C24-C25**, Figure S24) based on their previous findings. Three compounds were identified in this work, all having nanomolar potencies toward 5HT$_{1A}$, 5HT$_{2A}$, 5-HT$_7$ and D$_2$. These showed relatively poor binding potential for 5-HT$_6$. Among these, three compounds (**39–41**, Figure 5) depicted promising *in vivo* anxiolytic properties. However, compound **41 achieved the most balanced potencies for all these targets**. These three compounds demonstrated different mechanisms of action since **39** and **40** showed features of agonists of pre- and/or postsynaptic 5-HT$_{1A}$ receptors, whereas **41** was found as an antagonist of postsynaptic sites [93].

4.3. 5-HT$_{1A}$/5-HT$_{2A}$/SERT/α$_1$

Czopek and coworkers designed and developed 5-Arylimidazolidine-2,4-dione derivatives with dual 5-HT$_{1A}$ receptor and SERT affinity based on molecular modeling results [94]. In previous studies, these researchers reported the syntheses of 5,5- disubstituted- and 5-spiro-imidazolidine -2,4-diones with arylpiperazinyl propyl moieties exhibited diversified affinity and intrinsic activity for serotonin 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors (5-HT$_{2A}$R). The most interesting compound (**42**, Figure 5) behaved like agonists or partial agonists of 5-HT$_{1A}$Rs and they showed antidepressant activity. Based on molecular docking analyses, 5-phenylimidazolidine-2,4-dione derivatives with an arylpiperazinemethyl fragment were proposed. Two compounds were selected through higher binding potentials toward four receptors (i.e. 5-HT$_{1A}$, 5-HT$_{2A}$, SERT and α$_1$) for further studies. Compound **42**, tested in the forced swim test in mice, exhibited a favorable antidepressant-like profile without affecting spontaneous locomotor activity [94].

5. Design strategies adopted for MTDL

From the above-mentioned discussions, it is evident that a number of design strategies have been adopted so far for the discovery of novel MTDLs for the treatment of MDD. The researchers often relied on previously obtained compounds developed in the same research group to improve the activity toward multiple targets of interest or to improve activity toward a new target of interest through lead modifications [44,57,59,67,69,70]. In-depth SAR analyses reveals crucial structural attributes to direct further design of new compounds with improved affinities [56,67,74,80]. Another widely used strategy is to design novel compounds from the clinically active known compounds. The study of Kułaga et al. is one important example where the increase in the length of the carbon-chain linker of ipsapirone improved the affinities toward multiple targets [64]. Similarly, Zareba et al. started with the structure of fananserin (which is a dual 5-HT$_{2A}$/D$_4$ ligand, clinically useful in schizophrenia treatment) to design some MTDLs with multifunctional 5-HT$_{1A}$/5-HT$_7$/D$_2$ ligand and

dual 5- HT_{1A}/D_2 ligand [95]. More importantly, structures of antipsychotic or other CNS agents may also be used as a starting point to design novel MTDLs aimed for MDD treatment. Hybridization of multiple structures with well-known biological activity also remained a common strategy to design compounds for the treatment of MDD or to find MTDLs that may act on multiple CNS disorders [49,74,75,87]. Noticeably, *in silico* modeling, especially structure-based molecular modeling played an important role in several investigations to design new compounds or to study crucial drug-receptor interaction to rationalize the activity toward various targets of interest [49,81,94,96]. For example, the structure-based drug design approach by Jankowska et al. played a crucial role in the design of novel anilide and benzylamide derivatives of ω-(4-(2-methoxyphenyl)-piperazin-1-yl)-alkanoic acids as combined $5\text{-}HT_{1A}/5\text{-}HT_7$ receptor ligands and phosphodiesterase PDE4B/PDE7A inhibitors. From molecular docking analysis, the authors pointed out that the two major anchoring interactions of phenylpiperazine fragment is common for both these receptors and these are salt bridges to aspartic acid residues and π-π stackings interaction with phenylalanine residues of these receptors [81]. Similar anchoring interactions were noticed by Chłoń-Rzepa et al. and Zagórska et al. with $5\text{-}HT_{1A}$ and $5\text{-}HT_7$ when they designed MTDLs for the treatment of depression [79,80]. While designing monoamine neurotransmitter reuptake inhibitors, Paudel et al. chose to select the naphthyl moiety as an aromatic group due to the fact that molecular docking analyses predicted its interactions with the hydrophobic amino acid residues at ligand binding site of hSERT. It is a common practice to evaluate the pharmacokinetic profiles of the designed MTDLs experimentally [64,87]. However, *in silico* prediction often helps in predicting pharmacokinetic properties of MTDLs considering the fact that certain physicochemical parameters such as blood-brain barrier crossing is crucial for determining the therapeutic outcomes of such agents [96]. Even though a majority of investigations performed structure-based modeling, the significance of ligand-based *in silico* modeling should not be overlooked. A recent investigation reported by Cerda-Cavieres et al. may be taken into consideration. The authors designed and synthesized some indole derivatives targeting serotonin transporter, dopamine D_2 Receptor, and MAO-A Enzyme as antidepressant agents. Apart from utilizing molecular docking, the dataset containing the SERT activity was utilized to develop 3D-quantitative structure activity relationship (3D-QSAR) models to understand the structural requirements required for higher binding interactions [97]. As far as ligand-based drug design is concerned, it is worth mentioning here that multi-tasking 2D-QSAR analyses with large datasets have been suggested to be highly useful due to remarkable advancements in machine learning methods, computation efficacy as well as big-data-handling techniques [98–100]. Our group recently conducted multitarget QSAR modeling with more than 5,000 MAO-A and MAO-B inhibitors to achieve linear and non-linear 2D-QSAR models with significantly high accuracies (>95%). Noticeably, for the development of the model only one types of descriptors, namely, 2D Geary autocorrelations were utilized [101]. Virtual screening remained another area that is required to be explored more for the design of MTDLs.

6. Expert opinion

MDD is one of the most complex CNS diseases, pathophysiology of which is yet to be disclosed properly. The major identified mediators such as serotonin, dopamine and norepinephrine have multiple and diverse receptor subtypes with complex interplay among these. Therefore, considering the complex nature of this disease, it is important to design compounds that may simultaneously interact with multiple mediators of interests while sparing off-targets or anti-targets. Ideally, design of MTDL is a tricky and challenging since excessive promiscuity leads to serious adverse effects. Therefore, design of such ligands requires understanding about the pathophysiology of the disease. From the above discussions, it is clear that the biological targets that have been frequently explored include $5\text{-}HT_{1A}$, $5\text{-}HT_{2A}$, $5\text{-}HT_7$, D_2, and SERT. Among these, $5\text{-}HT_{1A}$ was found in maximum investigation as a prime target of interest. Interestingly, some important targets such as MAO, NMDA and melatonin receptors have not been explored much. Previously, Olumuyiwa John Fasipe mentioned that more research is required to be conducted on NMDA-glutamatergic ionoceptor blockers as new member classes of the antidepressant agents [35]. Similarly, melatonin receptors must be studied extensively as melatonergic MT_1 and MT_2 receptor agonist agomelatine (which is also a $5\text{-}HT_{2C}$ receptors antagonist) is used as an antidepressant agent. Furthermore, it is imperative that MTDLs are designed focusing on the subtypes of MDD with different pathophysiological substrates, such as monoamines, glutamatergic, neuroimmune, and neuroplasticity [102,103]. It is also noteworthy that proinflammatory cytokines also play a significant role in the pathophysiology of MDD through affecting HPA axis and enhancing glucocorticoid resistance. Kynurenine (KYN) pathway alteration and HPA axis anomaly also elevate glutamate synthesis in extracellular space along with glutamate neurotransmission diminishing hippocampal neurogenesis [104]. Thus, one such strategy may involve preventing conversion of Tryptophan into KYN through the inhibition of indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). 3-hydroxy kynurenine is converted into quinolinic acid by kynurenic acid monooxygenase (KMO) which subsequently leads to neurodegeneration and cell death, making KMO another potential target for therapy. Additionally, role of neurotrophins in enhancing synaptic plasticity has been well established through MAPK/ERK, PI3-K and PLCγ pathways. Neurotrophins activate these pathways and in turn, enhances neuroplasticity, neuronal transmission and neuronal growth and survival. Neurotrophins like brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), glial-cell line derive neurotrophic factor (GDNF), insulin like growth factor 1 (IGF-1) and fibroblast growth factor (FGF) are the major

neurotrophins which are capable of inducing synaptic plasticity through the aforementioned pathways [103,105]. Furthermore, an extremely viable therapeutic approach may include activation of the neurotrophins through Tropomyosin receptor kinase B (TrkB) modulation. TrkB agonists like 7,8-dihydroxyflavone, gedunin have been extensively investigated with promising outcomes [103,106,107].

It is evident that often researchers face challenges to design MTDLs for highly different biological targets. For example, Pessoa-Mahana et al. pointed out that design of dual SERT/5-HT_{1A}R may be difficult since 5-HT_{1A}R is G-protein-coupled receptor (GPCR) whereas the other is plasma membrane protein [108]. However, since these two proteins have a common substrate (i.e. serotonin), it leaves the scope to design MTDLs active for both targets. When more than two targets are considered, the task becomes more challenging. For example, in two different investigations, Zagorska et al. [80] and Czopek et al. [49] aimed to design *5-HT_{1A}/5-HT_7/PDE* ligands but ended up with weak activity for the PDE, even though strong binding potentials were obtained for the other targets. In constrast, while developing dual *5-HT_{1A}/5-HT_7* ligands, Ofori et al. obtained high potency for the compounds toward dopamine D_3 receptor and as triple inhibitors these are likely to provide antipsychotic activity along with being antidepressant agents [40].

Research with MTDLs helps in understanding the functionalities of different targets in the pathophysiology of MDD. Ślifirski et al. obtained nanomolar potencies for one compound toward 5-HT_{1A} and SERT. Yet, this compound did not exhibit *in vivo* antidepressant activity and the authors suggested that this ligand should be acting as a presynaptic antagonist [59]. On the other hand, Wrobel at al identified a compound **MW005** with significant affinities toward multiple targets (i.e. 5-HT_{1A}, 5-HT_{2A}, D_2 and 5-HT_6) and obtained satisfactory *in vivo* results. However, **MW005** was found to possess cardiac risk. The authors mentioned that it is the high affinity toward both the 5-HT_{1A} and α_1 receptors (Ki = 7.5 nM and Ki = 30 nM, respectively) that leads to the adverse effects such as hypotension [56]. Such examples clearly point out the complications and challenges involved in the design of MTDLs for the treatment of MDD but in-depth analyses definitely assist in proper lead modifications for the development of better therapeutic agents.

Noticeably, several investigations relied on *in silico* analyses, especially molecular docking. On the other hand, ligand-based *in silico* modeling and molecular dynamics simulations are rarely explored for the same purpose. These analyses may further improve the drug design strategies. Secondary structure analyses performed with the trajectories obtained from MD simulation may help recognizing agonistic and antagonistic properties of the ligands for the receptors of interest. Another area that should be explored extensively is multitasking cheminformatic modeling with large datasets containing structurally diverse compounds having activity for multiple bio-macromolecular targets of interest [99,100]. The scope of developing machine learning-based predictive cheminformatic models has expanded with the increasing number of data points available in the literature and chemical databases such as ChEMBL and Binding Database. Cheminformatics models such as 2D-quantitative structure activity relationship (2D-QSAR) help identifying a quantitative relationship between the structural features and biological activity, but conventional QSAR models rely on a single target or the same experimental assay conditions. Multitasking QSAR or mt-QSAR, performed with the Box-Jenkins moving average approach, can integrate data obtained from various targets measured at diverse experimental conditions to generate unique models that can be highly useful for retrieving MTDLs with desired potencies. Similarly, virtual screening may serve as another important strategy to help in retrieving new lead compounds acting on multiple targets and such strategy may help in drug repurposing [109,110].

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