

Polypharmacology of dopamine D₁-like receptor antagonists

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Abstract

Drug discovery based on development of selective ligands for a specific target intended to modulate its activity and revert pathophysiological process is now recognized as too simplistic to design effective agent for complex multifactorial diseases, characterized by diverse physiological dysfunctions caused by deregulations of complex networks of proteins. Major challenge in modern drug discovery is to rationally design multitarget drugs able to specifically modulate only a group of desired targets while minimizing interactions with off-targets. Multifactorial cerebral mechanisms implicated in mental (psychiatrics) and neurodegenerative diseases and interactions of the neurotransmitter systems are two main reasons for applying polypharmacology („multi-target”) strategy in drug discovery for these complex brain diseases. In this paper we review polypharmacological profile and potential therapeutic application of dopamine D₁-like receptor antagonists.

Keywords: polypharmacology, multitarget drugs, dopamine receptors

Polypharmacology

Modern drug design of multitarget ligands able to specifically modulate complex networks of proteins and show unique polypharmacological profiles is becoming increasingly important in drug discovery for complex brain diseases [1-5].

The most significant advantages of use of multitarget drugs over the other therapeutic strategies is based on: improved efficacy as result of synergistic or additive effects caused by simultaneous and specific interactions with chosen palette of biological targets; better distribution in target tissue for simultaneous action on multiple targets; accelerated therapeutic efficacy in terms of initial onset and achievement of full effect; treatment of broader therapeutic range of symptoms; predictable pharmacokinetic profile and mitigated drug-drug interactions; lower incidence of molecule-based side effects; increased therapeutic interval of doses; better quality of treatment; improved patient compliance and tolerance; and lower incidence of developing target-based resistance as result of modulation of multiple targets [1, 6, 7].

Designed Multiple Ligands (DMLs) contain the primary pharmacophore elements for each target which could be separated by linker (conjugate DMLs), touched at one point (fused) or combined by using commonalities in the structures of underlying pharmacophores (merged) [7, 8]. Relatively rigid and small structures of highly merged DMLs result in better physicochemical, pharmacokinetic and pharmacological profile [7, 8].

Based on the predicted activities on the targets and estimated pharmacokinetic profiles of designed multipotent ligands are selected the most promising candidates for further study [8-12].

Multifactorial cerebral mechanisms and deregulation of very complex networks of proteins implicated in mental (schizophrenia) [13, 14] and neurodegenerative disorders [15], such as Parkinson's [16, 17] and Alzheimer's diseases [18]), have generated intense interest in developing efficient multipotent CNS drugs [19-21]. Interactions of the neurotransmitter systems, such as the dopamine-glutamate interaction in pathogenesis of schizophrenia and Parkinson's disease [22, 23] and the serotonin-dopamine interaction in pathogenesis of various disorders including schizophrenia, depression, Parkinson's disease and drug abuse [24, 25, 26], are very important factors in design of multitargeted ligands with optimized pharmacological effects.

Therefore, a more efficient polypharmacology strategy for treatment of complex mental/neurodegenerative diseases is based on specific interactions on set of targets with minimal side effects arising from interaction with defined antitargets [1, 27].

As a result of multitarget approach [1, 7, 28, 29] many efficient CNS drugs have been developed. Monoamine reuptake inhibitors with serotonin 5-HT_{2C} antagonistic properties were developed as novel class of antidepressants [6, 30]. Dopamine D₂/D₃

antagonists, with 5-HT_{2A} antagonistic and 5-HT_{1A} partial agonistic activities were proposed as drug candidates for therapy of schizophrenia [19, 31, 32].

While many neurotransmitter systems contribute to the complex pathology of schizophrenia, dopamine dysfunction is considered as the basis of this disorder. The dopamine hypothesis of schizophrenia is supported by the characteristics of the drugs used to treat this disorder: all antipsychotics used clinically have high affinity for dopamine receptors [33].

Parkinson disease (PD), a neurodegenerative disorder of unknown etiology, is characterized by extensive degeneration of dopaminergic neurons within the substantia nigra, resulting in tremor, rigidity, and bradykinesia. One treatment strategy is the use of Dopamine receptor agonists, which act directly on the depleted nigrostriatal dopaminergic system and have fewer undesirable side effects than L-DOPA. Dopamine receptor agonists can be used in conjunction with lower doses of L-DOPA in a combined therapy approach [33].

Pathophysiology of Alzheimer's disease (AD) includes progressive loss of cholinergic neurons, extracellular deposition of amyloid β peptide (A β)-containing plaques, metal dyshomeostasis, neuroinflammation, oxidative stress and increased monoamine oxidase (MAO) enzyme activity. Therefore, multipotent brain permeable drugs affecting few brain targets involved in the disease pathology, such as MAO and ChE enzymes, A β generation/aggregation and iron accumulations were extensively studied as essential therapeutic approach in treatment of AD [28, 34-43].”

Quantitative Structure Activity Relationship (QSAR) modeling and related cheminformatic methods are developed and applied in helping to guide computer-aided-drug-design (CADD) [44, 45] and in polypharmacology for design of ligands with unique polypharmacological profiles [8, 46]. Design of compounds with unique polypharmacology and optimal ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) profile involve several steps such as: formation of chemical analogues of a lead, predicting their binding profiles using a group of ligand-based QSAR models, and synthesizing the most promising candidates with the preferred multitarget activities [8-10].

For example, the MAO A/B and AChE/BuChE inhibiting activities of multitarget donepezil and tacrine hybrids [35, 38, 39, 40, 42, 43, 47] were used in our recent 3D-QSAR and ASS234 optimisation studies [36, 37].

Dopamine D₁-like receptor antagonists

Five distinct GPCRs (D₁-D₅ receptors) have been cloned and determined to mediate the actions of dopamine. The DA receptors are distinct from one another in pharmacology, amino acid sequence, distribution, and physiological function. Based on

their effector-coupling profiles dopamine receptors are organized into two families, the D₁-like (D₁, D₅) and D₂-like (D₂, D₃, D₄) receptors [33].

Dopamine D₁ receptor is predominantly found in the direct pathway of the striato-nigral neurons [48, 49]. The main physiological function of the D₁ receptor is to mediate CNS actions of dopamine to control cognitive function [50] and movement [51, 52].

The physiological processes under dopaminergic control include reward, emotion, cognition, memory, and motor activity. Dysregulation of the dopaminergic system is critical in a number of disease states, including Parkinson disease, Tourette's syndrome, bipolar depression, schizophrenia, attention deficit hyperactivity disorder, and addiction/substance abuse [33]. Dopamine receptor antagonists are a mainstay in the pharmacotherapy of schizophrenia.

Mice lacking the D₁ receptor display deficits in multiple forms of memory, such as impaired spatial memory and deficits in prefrontal cortex-dependent working memory. Therefore the pharmacological evidence that cortical working memory can be modulated with D₁ agonists and antagonists is in agreement with the previous findings [33].

Since D₁ and D₅ receptors possess about 80% homology in their transmembrane domains these two receptors are grouped as D₁-like receptors. Pathophysiology of schizophrenia and related diseases is mainly based on dysfunctions in dopamine, serotonin, and glutamate, [33, 53, 54]. However, selective D₁ antagonism alone is not accepted as effective antipsychotic principle [55, 56]. Therapeutic effects of typical and atypical neuroleptics are mostly mediated by inhibition of dopamine D₂-like receptors (D₂ and D₄ receptors) and other related aminergic receptors [33]. Blockade of dopamine D₂ and serotonin 5-HT_{2A} receptors is mainly responsible for antipsychotic effect [57], while interaction with various dopamine (D₁, D₃, D₄), serotonin (5-HT_{1A}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}), and histamine H₃ receptors may produce additional antipsychotic or procognitive effects [54, 58, 59]. Moderate antagonistic activity at D₁-receptors of atypical antipsychotic clozapine is suggested to be responsible for its effectiveness against treatment-resistant schizophrenia [55].

Discovery of 1-phenyl-benzapine **1 (SCH 23390)** [60], as D₁ specific dopamine antagonist, has initiated development of novel benzazepines for selective targeting D₁ receptor. The pharmacological characterization of **1 (SCH 23390)** [60], which has become the prototype of D₁ antagonist, was followed by development of its conformationally restricted analogue **2 (SCH 39166)** [61] and fused analogues and their derivatives (Figure 1) [62].

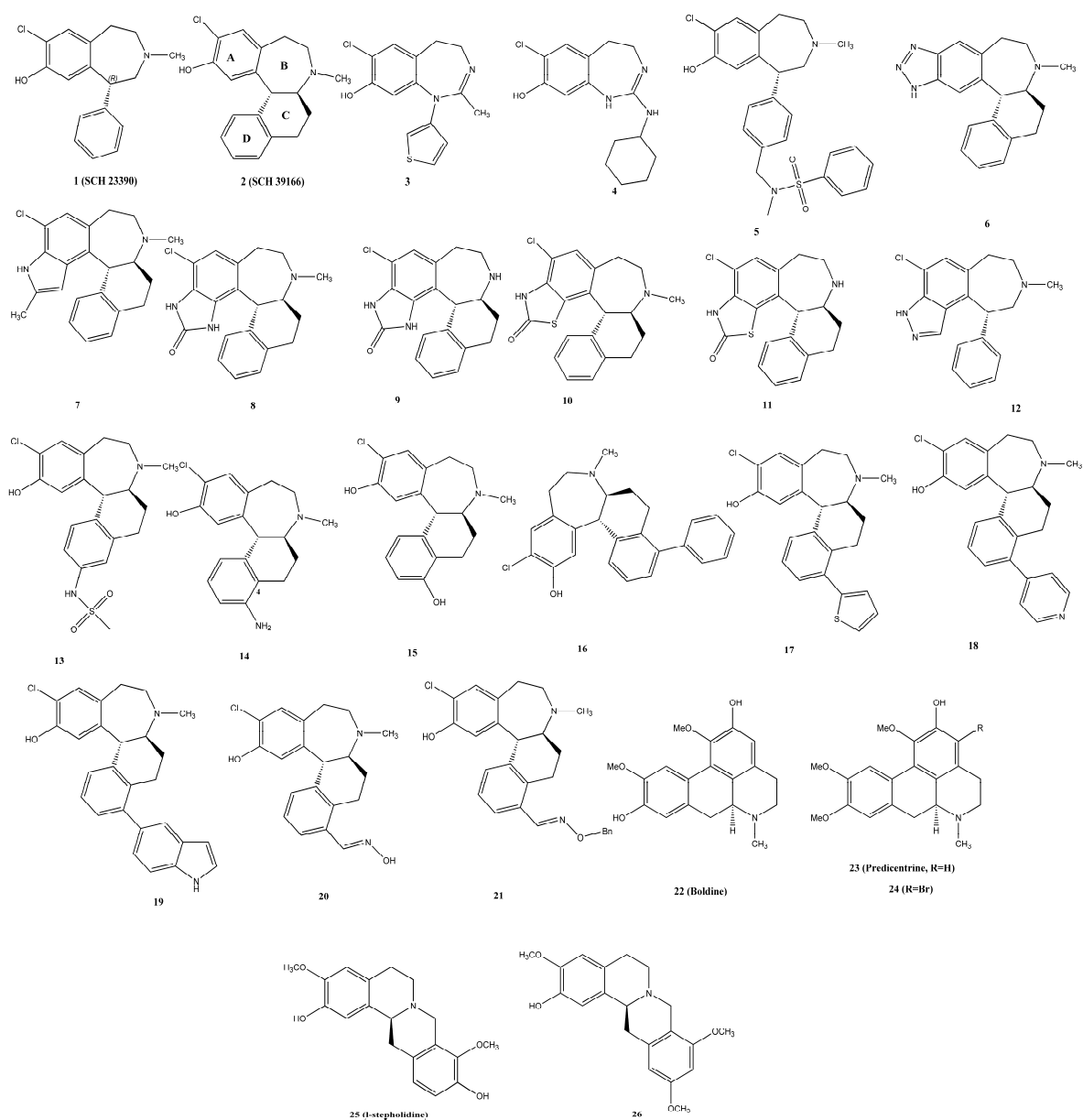


Figure 1. Structural formulas of dopamine D₁-receptor antagonists.

The *R* isomer of **1** (**SCH 23390**) [60], *R*(+)-7-Chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine, is a highly potent enantioselective dopamine D₁-like receptor antagonist with *K_i* of 0.2 and 0.3nM for the D₁ and D₅ receptors, respectively [63, 64]. The C1-position is a chiral center and activity originates from the *R* enantiomer. Besides its high D₁-like antagonistic activity, some *in vitro*

studies demonstrated moderately high binding affinity of **1 (SCH 23390)** to the 5-HT_{2A}, 5-HT_{2C}, 5-HT₁ serotonin receptors [65-67], α_{2A} adrenergic receptor (AR) and the 5-HT transporter [68].

Conformationally restricted derivative **2 (SCH 39166)** [61] has exerted high D₁ and D₅ antagonistic activity, moderately high binding affinity of **1 (SCH 23390)** to the 5-HT₂ and 5-HT₁ serotonin receptor subtypes [65, 66] and also to the α_{2a} adrenergic receptor and the 5-HT transporter [68].

As a selective antagonist, **1 (SCH 23390)** has been extensively used for the clarification and better understanding of the role of the D₁ receptors in various CNS disorders.

Examination of the pharmacologic profile of **1 (SCH 23390)** covered its effects on motor behavior and memory, as well as *in vivo* anticonvulsant studies. The anticonvulsant properties of **1 (SCH 23390)** indicated on the importance of D₁ dopaminergic receptor in initiation of generalized seizures. The available pharmacokinetic data of this compound suggest that after oral administration it undergoes extensive first-pass metabolism and has short half-life of around 25 minutes following administration of 0.3 mg/kg i.p. in the rat and therefore could not be further developed as a drug [63, 64]. Even the longer acting analogue **2 (SCH 39166)** [61] showed very low oral bioavailability (0.6%). Pharmacokinetic studies has discovered that extensive O-glucuronidation of the phenol and N-dealkylation of the N-Me group of the **1 (SCH 23390)** and **2 (SCH 39166)** may contribute to the poor pharmacokinetic (PK) profile [69-71].

Since the discovery of the **1 (SCH 23390)**, many dopamine D₁ receptor ligands possessing phenyltetrahydrobenzazepines scaffold have been synthesized and analyzed. In particular, D₁ antagonistic activity of this chemical group of compounds is determined by the nature of C-7 substituent, such as chlorine in the **1 (SCH 23390)** or bromine in the **SKF R-83566** [72, 73].

The two series of 1,3-benzodiazepine based D₁ antagonists, the cyclic *N*-aryl amidine and the cyclic *N*-aryl guanidine, was designed following a pharmacophore models derived from catecholamine analog **1 (SCH 23390)**. By replacing benzazepine core with 1,3-benzodiazepine, metabolically labile N3-methyl group presented in **1 (SCH 23390)** was eliminated while basicity of new model systems, with pK_a values of 8-9 and 10-11 for *N*-aryl amidine and *N*-aryl guanidine respectively, stayed within same range as those for the *tert*-azepine nitrogen center in **1 (SCH 23390)**. Among N1-arylbenzodiazepines the highest affinity for D₁ receptor was observed with 3-thienyl substituent **3** [74], K_i = 87 nM) while within cyclic *N*-aryl guanidines stronger basicity did not result in improved D₁ receptor binding affinity **4** (Figure 1) [75], K_i = 129 nM) [74].

A highly potent D₁/D₅ antagonists **5** [75]) possessing subnanomolar D₁ affinity and high selectivity over D₂ receptor were synthesized by introducing a series of bulky substituents at the *para* position of the pendant phenyl ring in **1** (SCH 23390). The obtained results indicate that the *para* position has a high steric tolerance for substitution [75].

Despite of their cyclic structure the benzazepines possess a considerable degree of conformational mobility and it is considered that equatorial orientation of the phenyl ring is optimal for interaction with the D₁ receptor [61].

The preparation of conformationally restricted analogues of the **1** (SCH 23390) resulted in new series of 6,6a,7,8,9,13b- hexahydro-5*H*-benzo [*d*] naphtho [2,1- *b*] azepines having the B and C rings junction in two possible configurations, B/C-*cis* and B/C-*trans*. Binding studies of the B/C-*cis* and B/C-*trans* series of compounds clearly demonstrated that conformationally rigid *trans* series, where the D ring is unequivocally fixed in an equatorial orientation, possess significantly higher D₁ receptor affinity and selectivity over the D₂ receptor. From this investigation were derived highly selective D₁ receptor antagonist which (-)-6*aS*,13*bR* isomer (**2** (SCH 39166)) has the highest D₁ affinity ($K_i = 1.9$ nM for D₁ and 514 nM for D₂). This finding is consistent with the fact that the D₁ receptor activity in the 1-phenyl-1*H*-3-benzazepine series is associated with the *R*-enantiomers [61]. **2** (SCH 39166), also known as ecopipam, has been in clinical trials for several diseases including obesity [76], cocaine addiction [77] schizophrenia [78]. Although **2** (SCH 39166) possess high D₁-like selectivity with reduced affinity for serotonin receptors and longer duration of action in primates in comparison to **1** (SCH 23390), both compounds displayed low oral bioavailability [79].

Various **1** (SCH 23390) and **2** (SCH 39166) analogues were synthesized and evaluated as selective dopamine D₁/D₅ receptor antagonists. Some of these trials include investigation of the phenol bioisosteric analogues of **1** (SCH 23390) and **2** (SCH 39166), such as benzotriazole, indole, benzimidazole, benzimidazolone and benzothiazolone. The designed corresponding heterocyclic systems, containing an N-H hydrogen bond donor group, retained the characteristic of the phenol group that are thought to be responsible for interaction with the receptor. Benzotriazole analogue of **2** (SCH 39166), **6** (Figure 1) [68], displayed very low affinity for D₁ receptor ($K_i = 583$ nM) suggested that conformer A was not the active binding conformer. In comparison with **6** [68], indole analogue of **2** (SCH 39166) **7** [68] displayed appreciable affinity for D₁ receptor. Further optimization of the hydrogen bond donating properties of different heterocyclous analogues of conformer B also indicated the preference of conformation B over A, whereby hydrogen-bond donating directionality has been established. Among the designed compounds highly selective D₁/D₅ antagonists, benzimidazolone analogue (**8** [68], $K_i = 7$ nM for D₁ and 4.2 nM for D₅) and its corresponding NH benzazepine (**9** [68], $K_i = 16.5$ nM for D₁ and 2.4 nM for D₅) together with benzothiazolone analogue

(**10** [68], $K_i = 2.1$ nM for D_1 , 2.8 nM for D_5) and its corresponding NH benzazepine (**11** [68], $K_i = 6.5$ for D_1 and 1.7 for D_5) were of particular interest in terms of their overall profiles (Figure 1). Improved pharmacokinetic profiles of heterocyclic isosteres demonstrated by rats plasma levels is associated with higher metabolic stability with respect to O-glucuronidation. In contrast, biological evaluation of phenol bioisosteric analogues of **1** (**SCH 23390**) revealed huge decrease in the D_1 binding affinity with exception of **12** [68] which was identified as a potent D_1/D_5 ligand in this series but without significant improvement in pharmacokinetic profile compared to **1** (**SCH 23390**). This finding indicated that molecular rigidity might play important role in improving the pharmacokinetic properties [68].

Functionalization of the D-ring of **2** (**SCH 39166**) with the special focus on the C-3 and C-4 positions have been also examined [75, 80]. Several **2** (**SCH 39166**) analogs substituted on the C-3 and C-4 positions with amino, amido and sulfonamido groups (-NH₂, -NHCOC₃H₅, -NHSO₂CH₃, -NHSO₂CH₂CH₃, -NHCONHCH₂CH₃, -NHCONH-2,6-Cl₂C₆H₃, -NHCO₂CH₂CH₃), showed strong D_1 antagonistic activity [75, 80]. Results of the study indicated on far more significant substitution on C-3 (**13** [75]) than on C-4 (**14** [75]) position of **2** (**SCH 39166**) ligands for strong and selective D_1 receptor antagonism. In addition, high selectivity over D_2 receptor was achieved with C-3 derivatisation while moderate selectivity over D_2 was observed in C-4 series. The most representative compound, sulfonamido D_1 antagonist (**13** [75]) showed even higher affinity to D_1 receptor ($K_i = 0.5$ nM) and selectivity over D_2 , D_4 , 5HT_{2a} and α_{2a} receptors compare to parent drug **2** (**SCH 39166**) while D_5 affinity was somewhat lower. This compound also posses improved pharmacokinetic profile and bioavailability compared to **2** (**SCH 39166**) (rat AUC: 2486 ng/mL.hr and 156 ng/mL.hr for **13** [75] and **2** (**SCH 39166**) respectively; rat bioavailability: 29% and 0.6% for **13** [70] and **2** (**SCH 39166**) respectively [75]). On the other side the position 4 of D-ring can tolerate a wide variety of functional groups such as -CHO, -CH₂OH, -CN, -CO₂Me, -OH and pyrrolidine-2-one wherein in addition to high D_1 antagonistic activity, selectivity over D_2 receptor is also retained (**15** [80]) (Figure 1). However, the most potent dopamine D_1 antagonists from C-4 series were obtained by the introduction of an aromatic group at the position 4 of the D-ring of **2** (**SCH 39166**). Almost every aromatic group including phenyl (**16** [80] D_1 $K_i = 0.2$ nM), 2-thienyl (**17** [80] D_1 $K_i = 0.9$ nM), piridinyl (**18** [80] D_1 $K_i = 0.3$ nM) and indolyl (**19** [80] D_1 $K_i = 0.6$ nM) are well tolerated at the 4-position. Regarding the D_2 selectivity it was observed that unsubstituted phenyl derivative **16** [80], as well as 1*H*-Indol-5-yl (**19** [80]) and 2-thienyl (**17** [80]) derivatives possess significant affinities for D_2 receptor (Figure 1). Among tested compounds improved pharmacokinetic profile compared to **2** (**SCH 39166**) (AUC = 156 h μ g/mL, $C_{max} = 72$ ng/mL, $T_{max} = 0.5$ h) showed 2-thienyl derivative, **17** [81] (AUC = 353 h μ g/mL, $C_{max} = 90$ ng/mL, $T_{max} = 2$ h). Oxime analogs are also well tolerated in the

position 4 (**20** [80] and **21** [80]). The most potent compound in this series is the *O*-benzyl oxime **21** [80] with D_1 K_i of 0.2 nM and notably higher D_2 K_i of 69 nM [80].

Besides this series of benzodiazepines, derivatives of alkaloids such as **boldine**, **predicentrine** and *l*-(**S**)-**stepholidine** have been synthesized and examined as potential D_1 -ligands [81,83].

The neuroleptic-like behavior of aporphine alkaloid **22** (**boldine**) suggested that it may act as dopamine receptors antagonist. In vitro binding studies showed micromolar nonselective D_1 - and D_2 -activity of **22** (**boldine**) while *in vivo* central antidopaminergic activity was negligible (Figure 1) [81, 82]. Unlike apomorphine which typical agonist activity is associated with *R* configuration at C-6a position, **22** (**boldine**) and its 9-*O*-methylated analogue of **23** (**predicentrine**) share the *S* configuration and shows antagonistic properties. The lack of **22** (**boldine**) activity *in vivo* could be related to its unfavorable pharmacokinetics such as short plasma half-life of only few minutes (Figure 1) [83]. Contrary, halogenated derivatives of **22** (**boldine**) and **23** (**predicentrine**) showing higher lipophilicity displayed increased affinity for the D_1 -like receptors and higher selectivity over the D_2 -like receptors. The highest affinity for D_1 receptor and selectivity over D_2 receptor among brominated, chlorinated and iodinated **22** (**boldine**) derivatives showed **3-iodo-boldine** (D_1 , $K_i = 2$ nM, K_i ratio $D_2/D_1 = 34$) [82, 83]. Similar behavior was noticed among halogenated **23** (**predicentrine**) derivatives where **3-iodo-predicentrine** [82] (D_1 , $K_i = 6$ nM) displayed the highest affinity as well as selectivity over D_2 -like receptors, being 140-fold more selective for D_1 -like receptors. Unlike **3-bromo-boldine** derivative, **24** (**3-bromo-predicentrine**) [82] possesses higher affinity and selectivity but lower than **3-iodo-predicentrine** (Figure 1) [82].

Removing of hydroxy group and introducing methoxy group in benzene moiety of **25** (*l*-(**S**)-**stepholidine**) resulted in greater affinity and reversed function (from agonistic to antagonistic) at D_1 receptor (**26** [84]). These results were in accordance with molecular docking studies at human D_1 receptor [84]. The compound **26** [84] displayed 2.5-fold higher affinity for the D_1 receptor ($K_i = 2.53$ nM) compared to **25** (*l*-(**S**)-**stepholidine**) (D_1 , $K_i = 6.23$ nM) and binding affinities for D_2 , 5-HT_{1A}, and 5-HT_{2A} receptors (Figure 1) [84].

Conclusion

Based on the results of the studies novel selective D_1/D_5 antagonists, **8**, **9**, **10**, **11**, and **12** [68], were of particular interest in terms of their overall binding profiles for dopamine D_1/D_5 receptors and α_{2A} -AR, improved pharmacokinetic properties compared to their leads **1** (**SCH 23390**) and **2** (**SCH 39166**), and moderate binding affinity to the

5-HT transporter ($K_i = 540$ nM, 6220 nM, 842 nM, 2950 nM, and 137 nM, respectively [68]. The indazole compound **12** in this series was identified as a potent D₁/D₅ ligand [68]. Lead compound **2** has been in human clinical trials for a variety of diseases, including schizophrenia, cocaine addiction, and obesity [68].

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Polifarmakologija antagonista dopaminskih D₁-receptora

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Kratak sadržaj

Istraživanje novih lekova koji deluju kao selektivni ligandi za određeno ciljno mesto i tako usporavaju ili zaustavljaju patofiziološki process danas se smatra nedovoljno efikasnim u razvoju lekova za kompleksna oboljenja nastala usled više patofizioloških procesa i promena u nekoliko signalnih puteva. Najveći izazov predstavlja razvoj lekova koji specifično modifikuju aktivnost nekoliko izabranih ciljnih mesta dejstva, a istovremeno minimalno stupaju u interakciju sa ostalim biomolekulima. Kompleksni patofiziološki procesi psihijatrijskih i neurodegenerativnih oboljenja i interakcija neurotransmiterskih sistema su dva ključna razloga za primenu strategije polifarmakologije (strategije multiplih ciljnih mesta) u razvoju efikasnih lekova koji deluju na centralni nervni sistem. U ovom radu dat je pregled polifarmakoloških profila i potencijalne terapijske primene antagonista receptora koji pripadaju D₁ familiji dopaminskih receptora.

Ključne reči: polifarmakologija, multitarget lekovi, dopaminski receptori
