Arh.farm. 2015;65: 287 – 303 *Pregledni rad/ Review article*

Polypharmacology of dopamine D_1-like receptor antagonists

Katarina Nikolic*, Slavica Filipic, Danica Agbaba

University of Belgrade - Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Vojvode Stepe 450, 11221 Belgrade, Serbia

* Corresponding author:
Katarina Nikolic, PhD, University of Belgrade - Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Vojvode Stepe 450, 11221 Belgrade, Serbia
tel: +381-11-3951-259, fax: +381-11-3974-349
e-mail adresa: knikolic@pharmacy.bg.ac.rs

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 D_1-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 D_2/D_3

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 (Aβ)-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, Aβ 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 D_1-like receptor antagonists

Five distinct GPCRs (D_1-D_5 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 D_1-like (D_1, D_5) and D_2-like (D_2, D_3, D_4) receptors [33].

Dopamine D_1 receptor is predominantly found in the direct pathway of the striato-nigral neurons [48, 49]. The main physiological function of the D_1 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 D_1 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 D_1 agonists and antagonists is in agreement with the previous findings [33].

Since D_1 and D_5 receptors possess about 80% homology in their transmembrane domains these two receptors are grouped as D_1-like receptors. Pathophysiology of schizophrenia and related diseases is mainly based on dysfunctions in dopamine, serotonin, and glutamate, [33, 53, 54]. However, selective D_1 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 D_2-like receptors (D_2 and D_4 receptors) and other related aminergic receptors [33]. Blockade of dopamine D_2 and serotonin 5-HT_{2A} receptors is mainly responsible for antipsychotic effect [57], while interaction with various dopamine (D_1, D_3, D_4), serotonin (5-HT_{1A}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}), and histamine H_3 receptors may produce additional antipsychotic or procognitive effects [54, 58, 59]. Moderate antagonistic activity at D_1-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 D_1 specific dopamine antagonist, has initiated development of novel benzazepines for selective targeting D_1 receptor. The pharmacological characterization of **1 (SCH 23390)** [60], which has become the prototype of D_1 antagonist, was followed by development of its conformationally restricted analogue **2** (**SCH 39166)** [61] and fused analogues and their derivatives (Figure 1) [62].

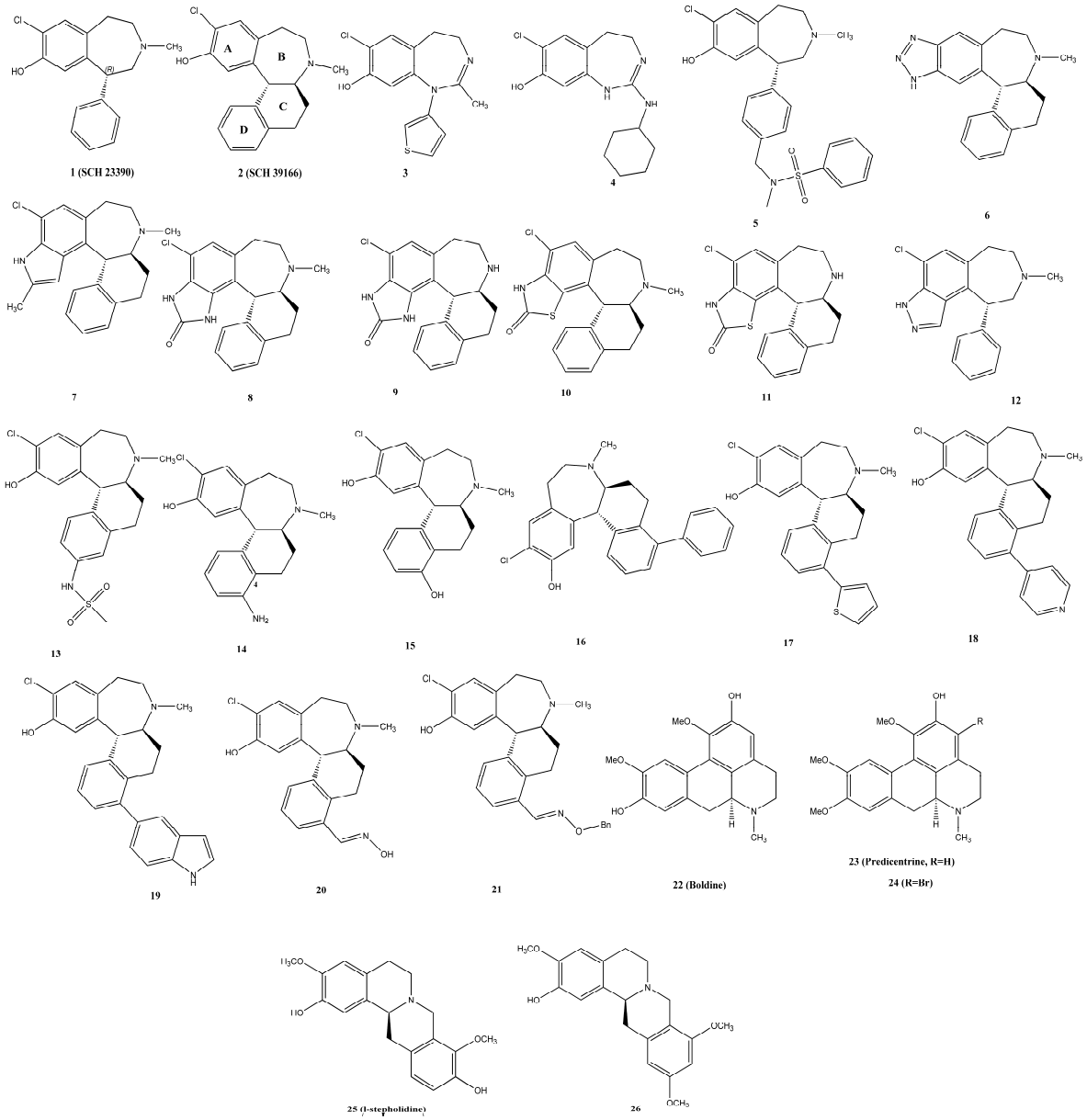

Figure 1. Structural formulas of dopamine D_1-receptor antagonists.

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 D_1-like receptor antagonist with K_i of 0.2 and 0.3nM for the D_1 and D_5 receptors, respectively [63, 64]. The C1-position is a chiral center and activity originates from the *R* enantiomer. Besides its high D_1-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-HT_1 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 D_1 and D_5 antagonistic activity, moderately high binding affinity of **1 (SCH 23390)** to the 5-HT_2 and 5-HT_1 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 D_1 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 D_1 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 D_1 receptor ligands possessing phenyltetrahydrobenzazepines scaffold have been synthesized and analyzed. In particular, D_1 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 D_1 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 D_1 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 D_1 receptor binding affinity **4** (Figure 1) [75], K_i = 129 nM) [74]**.**

A highly potent D_1/D_5 antagonists **5** [75]) possessing subnanomolar D_1 affinity and high selectivity over D_2 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 D_1 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-*5H*-benzo [*d*] naphtho [2,l- *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 D_1 receptor affinity and selectivity over the D_2 receptor. From this investigation were derived highly selective D_1 receptor antagonist which (-)-6a*S*,13b *R* isomer (**2 (SCH 39166)**) has the highest D_1 affinity (K_i = 1.9 nM for D_1 and 514 nM for D_2). This finding is consistent with the fact that the D_1 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 D_1-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 D_1/D_5 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 D_1 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 D_1 receptor. Further optimization of the hydrogen bond donating properties of different heterocyclus 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 D_1/D_5 antagonists, benzimidazolone analogue (**8** [68], K_i = 7 nM for D_1 and 4.2 nM for D_5) and its corresponding NH benzazepine (**9** [68], K_i = 16.5 nM for D_1 and 2.4 nM for D_5) 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 (-NH_2, -$NHCOC_3H_5$, -$NHSO_2CH_3$, -$NHSO_2CH_2CH_3$, -$NHCONHCH_2CH_3$, -NHCONH-2.6-$Cl_2C_6H_3$, -$NHCO_2CH_2CH_3$), 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, -CH_2OH, -CN, -CO_2Me, -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 μg/mL, C_{max} = 72 ng/mL, T_{max} = 0.5 h) showed 2-thienyl derivative, **17** [81] (AUC = 353 h μg/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 D_1/D_5 ligand [68]. Lead compound **2** has been in human clinical trials for a variety of diseases, including schizophrenia, cocaine addiction, and obesity [68].

Acknowledgement

The study was supported by the Ministry of Education and Science of the Republic of Serbia, Contract #172033.

References

1. Anighoro A, Bajorath J, Rastelli G. Polypharmacology: Challenges and Opportunities in Drug Discovery. J Med Chem. 2014; 57: 7874-87.
2. Hopkins AL. Network Pharmacology: The Next Paradigm in Drug Discovery. Nat Chem Biol. 2008; 4: 682-90.
3. Boran ADW, Iyengar R. Systems Approaches to Polypharmacology and Drug Discovery. Curr Opin Drug Discovery Dev. 2010; 13: 297-309.
4. Mestres J, Gregori-Puigjané E. Conciliating Binding Efficiency and Polypharmacology. Trends Pharmacol Sci. 2009; 30: 470-4.
5. Peters JU. Polypharmacology-Foe or Friend? J Med Chem. 2013; 56: 8955-71.
6. Millan MJ. Multi-target strategies for the improved treatment of depressive states: conceptual foundation and neuronal substrates, drug discovery and therapeutic application. Pharmacol Ther. 2006; 110: 135-370.
7. Millan MJ. On 'polypharmacy' and multi-target agents, complementary strategies for improving the treatment of depression: a comparative appraisal. International Journal of Neuropsychopharmacology 2014; 17: 1009-37.
8. Besnard J, Ruda GF, Setola V, Abecassis K, Rodriguiz RM, Huang XP, Norval, S, Sassano MF, Shin AI, Webster LA, Simeons FRC, Stojanovski L, Prat A, Seidah NG, Constam DB, Bickerton GR, Read KD, Wetsel WC, Gilbert IH, Roth BL, Hopkins AL. Automated Design of Ligands to Polypharmacological Profiles. Nature 2012; 492: 215-20.
9. Hajjo R, Grulke CM, Golbraikh A, Setola V, Huang XP, Roth BL, Tropsha A. Development, Validation, and Use of Quantitative Structure−Activity Relationship Models of 5-

Hydroxytryptamine (2B) Receptor Ligands To Identify Novel Receptor Binders and Putative Valvulopathic Compounds among Common Drugs. J Med Chem. 2010; 53: 7573-86.

10. Hajjo R, Setola V, Roth BL, Tropsha A. Chemocentric Informatics Approach to Drug Discovery: Identification and Experimental Validation of Selective Estrogen Receptor Modulators as Ligands of 5-Hydroxytryptamine-6 Receptors and as Potential Cognition Enhancers. J Med Chem. 2012; 55: 5704-19.
11. Zhang L, Fourches D, Sedykh A, Zhu H, Golbraikh A, Ekins S, Clark J, Connelly MC, Sigal M, Hodges D, Guiguemde A, Guy RK, Tropsha A. Discovery of Novel Antimalarial Compounds Enabled by QSAR-Based Virtual Screening. J Chem Inf Model. 2013; 53: 475-92.
12. Nikolic K, Agbaba D, Stark H. Pharmacophore modeling, drug design and virtual screening on multi-targeting procognitive agents approaching histaminergic pathways. Journal of the Taiwan Institute of Chemical Engineers 2015; 46: 15–29.
13. Humbert-Claude M, Morisset S, Gbahou F, Arrang JM. Histamine H3 and dopamine D2 receptor-mediated [35S]GTPγ[S] binding in rat striatum: Evidence for additive effects but lack of interactions. Biochem Pharmacol. 2007; 73: 1172-81.
14. Garduno-Torres B, Trevino M, Gutierrez R, Arias-Montano JA. Presynaptic histamine H3 receptors regulate glutamate, but not GABA release in rat thalamus. Neuropharmacology 2007; 52: 527–35.
15. Dai H, Fu Q, Shen Y, Hu W, Zhang Z, Timmerman H, Leurs R, Chen Z. The histamine H3 receptor antagonist clobenpropit enhances GABA release to protect against NMDA induced excitotoxicity through the cAMP/protein kinase A pathway in cultured cortical neurons. Eur J Pharmacol. 2007; 563: 117–23.
16. Gemkow MJ, Davenport AJ, Harich S, Ellenbroek BA, Cesura A, Hallett D. The histamine H3 receptor as a therapeutic drug target for CNS disorders. Drug Discovery Today 2009; 14: 509-15.
17. Threlfell S, Cragg SJ, Imre K, Turi GF, Coen CW, Greenfield SA. HistamineH3 receptors inhibit serotonin release in substantia nigra pars reticulata. J Neurosci. 2004; 24: 8704–10.
18. Goedert M, Spillantini MGA. A century of Alzheimer's disease. Science 2006; 314: 777−81.
19. Roth BL, Sheffler DJ, Kroeze WK. Magic Shotguns versus Magic Bullets: Selectively Non-Selective Drugs for Mood Disorders and Schizophrenia. Nat Rev Drug Discovery 2004; 3: 353−9.
20. Lipina TV, Wang M, Liu F, Roder JC. Synergistic Interactions between PDE4B and GSK-3: DISC1 Mutant Mice. Neuropharmacology 2012; 62: 1252−62.
21. Lipina TV, Palomo V, Gil C, Martinez A, Roder JC. Dual Inhibitor of PDE7 and GSK-3-VP115 Acts as Antipsychotic and Cognitive Enhancer in C57BL/6J Mice. Neuropharmacology 2013; 64: 205−14.
22. Carlsson M, Carlsson A. Interactions between glutamatergic and monoaminergic systems within the basal ganglia - implications for schizophrenia and Parkinson 's disease. Trends Neurosci. 1990; 13: 272-6.
23. Millan MJ. N-Methyl-d-aspartate receptors as a target for improved antipsychotic agents: Novel insights and clinical perspectives. Psychopharmacology 2005; 179: 30-53.

24. Di Giovanni G, Di Matteo V, Pierucci M, Esposito E. Serotonin-dopamine interaction: electrophysiological evidence. Prog Brain Res. 2008; 172: 45-71.
25. Di Matteo V, Di Giovanni G, Pierucci M, Esposito E. Serotonin control of central dopaminergic function: focus on in vivo microdialysis studies. Prog Brain Res. 2008; 172: 7-44.
26. Youdim MBH, Buccafusco JJ. Multi-Functional Drugs for Various CNS Targets in the Treatment of Neurodegenerative Disorders. Trends Pharmacol Sci. 2005; 26: 27−35.
27. Lu JJ, Pan W, Hu YJ, Wang YT. Multi-Target Drugs: The Trend of Drug Research and Development. PLoS One 2012; 7: e40262.
28. León R, Garcia AG, Marco-Contelles J. Recent advances in the multitarget-directed ligands approach for the treatment of Alzheimer's disease. Med Res Rev 2013; 33: 139-189.
29. Morphy R, Rankovic Z. Designed Multiple Ligands An Emerging Drug Discovery Paradigm. J Med Chem. 2005; 48: 6523−43.
30. Quesseveur G, Nguyen HT, Gardier AM, Guiard BP. 5-HT2 ligands in the treatment of anxiety and depression. Expert. Opin Investig Drugs 2012; 21: 1701–25.
31. Meltzer HY, Huang M. In vivo actions of atypical antipsychotic drug on serotonergic and dopaminergic systems. Progress in Brain Research. 2008; 172: 177–97.
32. Millan MJ, Loiseau F, Dekeyne A, Gobert A, Flik G, Cremers TI, Rivet JM, Sicard D, Billiras R, Brocco M. S33138 (N-[4-[2-[(3aS,9bR)-8-cyano-1,3a,4,9b-tetrahydro[1] benzopyrano[3,4-c]pyrrol-2(3H)-yl)-ethyl]phenyl-acetamide), a preferential dopamine D3 versus D2 receptor antagonist and potential antipsychotic agent: III. Actions in models of therapeutic activity and induction of side effects. J Pharmacol Exp Ther. 2008; 324:1212-26.
33. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Ed. by Laurence Brunton (Editor), Bruce Chabner (Associated Editor), Bjorn Knollman (Associated Editor) Copyright © 2011 by The McGraw-Hill Companies, Inc.
34. Zheng, H., Fridkin, M., Youdim, M.B.H. Site-Activated Chelators Derived from Anti-Parkinson Drug Rasagiline as a Potential Safer and More Effective Approach to the Treatment of Alzheimer's Disease. Neurochem Res 2010; 35: 2117–2123.
35. Bautista-Aguilera OM, Esteban G, Bolea I, Nikolic K, Agbaba D, Moraleda I, Iriepa I, Samadi A, Soriano E, Unzeta M, Marco-Contelles J. Design, synthesis, pharmacological evaluation, QSAR analysis, molecular modeling and ADMET of novel donepezil–indolyl hybrids as multipotent cholinesterase/monoamine oxidase inhibitors for the potential treatment of Alzheimer's disease. Eur J Med Chem. 2014; 75: 82-95.
36. Bautista-Aguilera OM, Esteban GM, Chioua M, Nikolic K, Agbaba D, Moraleda I, Iriepa I, Soriano E, Samadi A, Unzeta M, Contelles JM. Multipotent cholinesterase/monoamine oxidase inhibitors for the treatment of Alzheimer's disease: design, synthesis, biochemical evaluation, ADMET, molecular modeling, and QSAR analysis of novel donepezil-pyridyl hybrids. Drug Design, Development and Therapy 2014; 8: 1893-910.
37. Bautista-Aguilera OM, Samadi A, Chioua M, Nikolic K, Filipic S, Agbaba D, Soriano E, Andrés L, Rodríguez-Franco MI, Alcaro S, Ramsay RR, Ortuso F, Yañez M, Contelles JM. N-Methyl-N-

((1-methyl-5-(3-(1-(2-methylbenzyl)piperidin-4-yl)propoxy)-1H-indol-2-yl)methyl)prop-2-yn-1-amine, a New Cholinesterase and Monoamine Oxidase Dual Inhibitor. J Med Chem. 2014; 57: 10455-63.

38. Bolea I, Juárez-Jiménez J, de los Ríos C, Chioua M, Pouplana, R, Javier Luque F, Unzeta M, Marco-Contelles J, Samadi A. Synthesis, Biological Evaluation, and Molecular Modeling of Donepezil and N-[(5-(Benzyloxy)-1-methyl-1H-indol-2-yl)methyl]-Nmethylprop-2-yn-1-amine Hybrids as New Multipotent Cholinesterase/Monoamine Oxidase Inhibitors for the Treatment of Alzheimer's Disease. J Med Chem. 2011; 54: 8251−70.
39. Marco-Contelles J, Leon R, Rıos C, Guglietta A, Terencio J, Lopez MG, Garcıa, AG, Villarroya M. Novel Multipotent Tacrine-Dihydropyridine Hybrids with Improved Acetylcholinesterase Inhibitory and Neuroprotective Activities as Potential Drugs for the Treatment of Alzheimer's Disease. J Med Chem. 2006; 49: No 26.
40. Marco-Contelles J, Leon R, Rıos C, Samadi A, Bartolini M, Andrisano V, Huertas O, Barril X, Luque FJ, Rodrıguez-Franco MI, Lopez B, Lopez MG, Garcıa AG, Carmo Carreiras M, Villarroya M. Tacripyrines, the First Tacrine-Dihydropyridine Hybrids, as Multitarget-Directed Ligands for the Treatment of Alzheimer's Disease. J Med Chem. 2009; 52: 2724–32.
41. Nikolic K, Mavridis L, Aguilera O M B, Contelles JM, Stark H, Carreiras M, Rossi I, Massarelli P, Agbaba D, Ramsay RR, Mitchell JBO. Predicting targets of compounds against neurological diseases using cheminformatic methodology. J Comput Aided Mol Des. 2015; 29: 183-98.
42. Pérez V, Marco-Contelles J, Fernández-Álvarez E, Unzeta M. Relevance of benzyloxy group in 2-indolyl methylamines in the selective MAO-B inhibition. Brit J Pharmacol. 1999; 127: 869-876.
43. Samadi A, Chioua M, Bolea I, de los Ríos C, Iriepa I, Moraleda I, Bastida A, Esteban G, Unzeta M, Gálvez E, Marco-Contelles J. Synthesis, biological assessment and molecular modeling of new multipotent MAO and cholinesterase inhibitors as potential drugs for the treatment of Alzheimer's disease. Eur J Med Chem. 2011; 46: 4665-8.
44. Cherkasov A, Muratov EN, Fourches D, Varnek A, Baskin II, Cronin M, Dearden J, Gramatica P, Martin YC, Todeschini R, Consonni V, KuzMin VE, Cramer R, Benigni R, Yang C, Rathman Jl, Terfloth L, Gasteiger J, Richard A, Tropsha A. QSAR modeling: Where have you been? Where are you going to? J Med Chem. 2014; 57: 4977−5010.
45. Cramer RD. The Inevitable QSAR Renaissance. J Comput-Aided Mol Des. 2012; 26: 35−38.
46. Ning X; Rangwala H; Karypis G. Multi-Assay-Based Structure−Activity Relationship Models: Improving Structure−Activity Relationship Models by Incorporating Activity Information from Related Targets. J Chem Inf Model. 2009; 49: 2444−56.
47. Bolea I, Gella A, Monjas L, Pérez C, Rodríguez-Franco MI, Marco-Contelles J, Samadi A, Unzeta M. Multipotent, permeable drug ASS234 inhibits Aβ aggregation, possesses antioxidant properties and protects from Aβ-induced apoptosis in vitro. Curr Alzheimer Res. 2013; 10: 797–808.
48. Rice ME, Cragg SJ. Dopamine spillover after quantal release: Rethinking dopamine transmission in the nigrostriatal pathway. Brain Res Rev. 2008; 58: 303–13.

49. Fuxe K, Marcellino D, Rivera A, Diaz-Cabiale Z, Filip M, Gago B, Roberts DCS, Langel U, Genedani S, Ferraro L, de la Calle A, Narvaez J, Tanganelli S, Woods A, Agnati LF. Receptor-receptor interactions within receptor mosaics. Impact on neuropsychopharmacology. Brain Res Rev. 2008; 58: 415-52.
50. Previc FH. Dopamine and the origins of human intelligence. Brain Cogn. 1999; 41: 299-350.
51. Carlsson A. On the neuronal circuitries and neurotransmitters involved in the control of locomotor activity. J Neural Transm Suppl. 1993; 40: 1–12.
52. Carlsson A. A paradigm shift in brain research. Science 2001; 294: 1021-24.
53. Witkin JM, Nelson DL. Selective histamine H3 receptor antagonists for treatment of cognitive deficiencies and other disorders of the central nervous system. Pharmacol Ther. 2004; 103: 1-20.
54. Esbenhade TA, Browman KE, Bitner RS, Strakhova M, Cowart MD, Brioni JD. The histamine H3 receptor: An attractive target for the treatment of cognitive disorders. Br J Pharmacol. 2008; 154: 1166-81.
55. Tauscher J, Hussain T, Agid O, Verhoeff NP, Wilson AA, Houle S, Remington G, Zipursky RB, Kapur S. Equivalent occupancy of dopamine D1 and D2 receptors with clozapine: differentiation from other atypical antipsychotics. Am J Psychiatry. 2004; 161: 1620-5.
56. Sedvall GC, Karlsson P. Pharmacological manipulation of D1-dopamine receptor functions in schizophrenia. Neuropsychopharmacol. 2006; 21: S181-8.
57. Remington G. Understanding antipsychotic "atypicality": a clinical and pharmacological moving target. J Psychiatry Neurosci. 2003; 28: 275-84.
58. Coburg Y, Kottke T, Weizel L, Ligneau X, Stark H. Potential utility of histamine H3 receptor antagonist pharmacophore in antipsychotics. Bioorg Med Chem Lett. 2009; 19: 538–42.
59. Reynolds GP. Receptor mechanisms in the treatment of schizophrenia. J Psychopharmacol. 2004; 18: 340-5.
60. Hyttel J. SCH 23390 - the first selective dopamine D-1 antagonist. Eur J Pharmacol. 1983; 91: 153-4.
61. Berger JG, Chang WK, Clader JW, Hou D, Chipkin RE, McPhail AT. Synthesis and Receptor Affinities of Some Conformationally Restricted Analogues of the Dopamine D1 Selective Ligand (5R)-8-Chloro-2,3,4,5-tetrahydro-3-mhetyl-5-ph enyl-1H-3-benzazepin-7-ol. J Med Chem. 1989; 32: 1913-21.
62. Andersen PH, Grønvald FC, Hohlweg R, Hansen LB, Guddal E, Braestrup C, Nielsen EB. NNC-112 l, NNC-687 and NNC-756 l, new selective and highly potent dopamine receptor antagonists. Eur J Pharmacol. 1992; 219: 45-52.
63. Bourne JA, Fosbraey P, Halliday J. SCH 23390 affords protection against soman-evoked seizures in the freely moving guinea-pig: A concomitant neurochemical, electrophysiological and behavioral study. Neuropharmacol. 2001; 40: 279-88.
64. Bourne JA. SCH 23390: The First Selective Dopamine D1-Like Receptor Antagonist. CNS Drug Rev. 2001; 7: 399-414.

65. Bischoff S, Heinrich M, Sonntag JM, Krauss J. The D-1 dopamine receptor antagonist SCH 23390 also interacts potently with brain serotonin (5-HT2) receptors. Eur J Pharmacol. 1986; 129: 367-70.
66. Skarsfeldt T, Larsen JJ. SCH 23390 - a selective dopamine D-1 receptor antagonist with putative 5-HT 1 receptor agonistic activity. Eur J Pharmacol. 1988; 148: 389-95.
67. Tamagnan G, Baldwin RM, Kula NS, Baldessarini RJ, Innis RB. Cyclopentadienyltricarbonylrheniumbenzazepines: synthesis and binding affinity. Bioorg Med Chem Lett. 2000; 10: 1113-5.
68. Wu WL, Burnett DA, Spring R, Greenlee WJ, Smith M, Favreau L, Fawzi A, Zhang H, Lachowicz JE. Dopamine D1/D5 Receptor Antagonists with Improved Pharmacokinetics: Design, Synthesis, and Biological Evaluation of Phenol Bioisosteric Analogues of Benzazepine D1/D5 Antagonists. J Med Chem. 2005; 48: 680-93.
69. Tedford CE, Coffin VL, Ruperto V, Cohen M, McQuade RD, Johnson R, Kim HK, Lin CC. Determination of plasma and brain concentrations of SCH 39166 and their correlation to conditioned avoidance behavior in rats. Psychophamacol. 1993; 113: 199-204.
70. Tedford CE, Ruperto VB, Coffin VL, Cohen M, Libonati M, Barnett A. SCH 39166, a novel dopamine D1 receptor antagonist: in vitro investigation of its glucuronidation and potential species differences. Drug Dev Res. 1992; 26: 389-403.
71. Tedford CE, Ruperto VB, Barnett A. Characterization of a rat liver glucuronosyltransferase that glucuronidates the selective D1 antagonist, SCH 23390 and other benzazepines. Drug Metab Dispos. 1990; 19: 1152-9.
72. Flaim KE, Gessner GW, Crooke ST, Heys JR, Weinstock J. Regulation of agonist and antagonist binding to striatal D-1 dopamine receptors: Studies using the selective D-1 antagonist [3H]SK&F R-83566. Life Sci. 1986; 38: 2087-96.
73. Ohlstein EH, Berkowitz BA. SCH 23390 and SK&F 83566 are antagonists at vascular dopamine and serotonin receptors. Eur J Pharmacol. 1985; 108: 205-8.
74. Zhu Z, Sun ZY, YeY, McKittrick B, Greenlee W, Czarniecki M, Fawzi A, Zhang H, Lachowicz JE. Design and discovery of 1,3-benzodiazepines as novel dopamine antagonists. Bioorg Med Chem Lett. 2009; 19: 5218–21.
75. Qiang L, Sasikumar TK, Burnett DA, Su J, Tang H, Ye Y, Mazzola RDJr, Zhu Z, McKittrick BA, Greenlee WJ, Fawzi A, Smith M, Zhang H, Lachowicz JE. Discovery of new SCH 39166 analogs as potent and selective dopamine D1 receptor antagonists. Bioorg Med Chem Lett. 2010; 20: 836–40.
76. Astrup A, Greenway FL, Ling W, Pedicone L, Lachowicz J, Strader CD, Kwan R. Randomized Controlled Trials of the D1/D5 Antagonist Ecopipam for Weight Loss in Obese Subjects. Obesity 2007; 15: 1717–31.
77. Haney M, Ward AS, Foltin RW, Fischman MW. Effects of ecopipam, a selective dopamine D1 antagonist, on smoked cocaine self-administration by humans. Psychopharmacology (Berl) 2001; 155: 330-7.

78. Karlsson P, Smith L, Farde L, Härnryd C, Sedvall G, Wiesel FA. Lack of apparent antipsychotic effect of the D1-dopamine receptor antagonist SCH39166 in acutelyill schizophrenic patients. Psychopharmacology (Berl). 1995; 121: 309-16.
79. Barnett A, McQuade RD, Tedford C. Highlights of D1 dopamine receptor antagonist research. Neurochem Int 20 (Suppl) 1992; 119S-122S.
80. Sasikumar TK, Burnett DA, Greenlee WJ, Smith M, Fawzi A, Zhang H, Lachowicz JE. Remote functionalization of SCH 39166: Discovery of potent and selective benzazepine dopamine D1 receptor antagonists. Bioorg Med Chem Lett. 2010; 20: 832–5.
81. Asencio M, Delaquerrière B, Cassels BK, Speisky H, Comoy E, Protais P. Biochemical and Behavioral Effects of Boldine and Glaucine on Dopamine Systems. Pharmacol Biochem Behav. 1999; 62: 7–13.
82. Asencio M, Hurtado-Guzmán C, López JJ, Cassels BK, Protais P, Chagraoui A. Structure–affinity relationships of halogenated predicentrine and glaucine derivatives at D1 and D2 dopaminergic receptors: halogenation and D1 receptor selectivity. Bioorg Med Chem. 2005; 13: 3699-704
83. Sobarzo-Sánchez EM, Arbaoui J, Protais P, Cassels BK. Halogenated Boldine Derivatives with Enhanced Monoamine Receptor Selectivity. J Nat Prod. 2000; 63: 480-4.
84. Qian W, Lu W, Sun H, Li Z, Zhu L, Zhao R, Zhang L, Zhou S, Zhou Y, Jiang H, Zhen X, Liu H. Design, synthesis, and pharmacological evaluation of novel tetrahydroprotoberberine derivatives: Selective inhibitors of dopamine D1 receptor. Bioorg Med Chem. 2012; 20: 4862–71.

Polifarmakologija antagonista dopaminskih D_1-receptora

Katarina Nikolić*, Slavica Filipić, Danica Agbaba

Univerzitet u Beogradu - Farmaceutski fakultet, Katedra za farmaceutsku hemiju, Vojvode Stepe 450, 11221 Beograd, Srbija

* Autor za korespondenciju:

Doc. dr. Katarina Nikolić, Univerzitet u Beogradu - Farmaceutski fakultet, Katedra za farmaceutsku hemiju, Vojvode Stepe 450, 11221 Beograd, Srbija
tel: +381-11-3951-259, fax: +381-11-3974-349
e-mail: knikolic@pharmacy.bg.ac.rs

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 D_1 familiji dopaminskih receptora.

Ključne reči: polifarmakologija, multitarget lekovi, dopaminski receptori

---