Current computer-aided drug design methodologies in discovery of novel drug candidates for neuropsychiatric and inflammatory diseases

Milica Radan, Jelena Bošković, Vladimir Dobričić, Olivera Čudina, and Katarina Nikolić*

University of Belgrade - Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Vojvode Stepe 450, 11000 Belgrade, Serbia

*Corresponding author: Katarina Nikolic, e-mail: knikolic@pharmacy.bg.ac.rs

Abstract

Drug discovery and development is a very challenging, expensive and time-consuming process. Impressive technological advances in computer sciences and molecular biology have made it possible to use computer-aided drug design (CADD) methods in various stages of the drug discovery and development pipeline. Nowadays, CADD presents an efficacious and indispensable tool, widely used in medicinal chemistry, to lead rational drug design and synthesis of novel compounds. In this article, an overview of commonly used CADD approaches from hit identification to lead optimization was presented. Moreover, different aspects of design of multi-target ligands for neuropsychiatric and anti-inflammatory diseases were summarized. Apparently, designing multi-target directed ligands for treatment of various complex diseases may offer better efficacy, and fewer side effects. Antipsychotics that act through aminergic G protein-coupled receptors (GPCRs), especially dopamine D_2 and serotonin 5-HT$_{2A}$ receptors, are the best option for treatment of various symptoms associated with neuropsychiatric disorders. Furthermore, multi-target directed cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) inhibitors are also a successful approach to aid the discovery of new anti-inflammatory drugs with fewer side effects. Overall, employing CADD approaches in the process of rational drug design provides a great opportunity for future development, allowing rapid identification of compounds with the optimal polypharmacological profile.

Keywords: CADD, 5-HT2A, D2, COX-2, 5-LOX

Introduction

The process of drug discovery and development requires a lot of effort, time and costs. On average, it is assessed that getting a drug into the market takes 10-15 years and costs $2.6 billion (1). Therefore, there is a great need to accelerate the drug discovery process to find new therapeutics, as well as discovery methodologies. During this process, intensive research has to be done to find good drug candidates that will successfully get into preclinical and clinical trials (2). There are several main steps that are carried out during drug discovery. The first one is to identify and validate potential targets for a specific disease (3). After that, the next step is the identification of lead compound – a promising molecule which exhibits the desired biological or pharmacological activity. Subsequently, lead compounds selected from initial screening are then optimized to improve their potency, physicochemical and pharmacokinetic properties, as well as to reduce side effects (3, 4).

In recent years, computer-aided drug design (CADD) has become increasingly important in the process of drug discovery and development (Figure 1) (5-8).
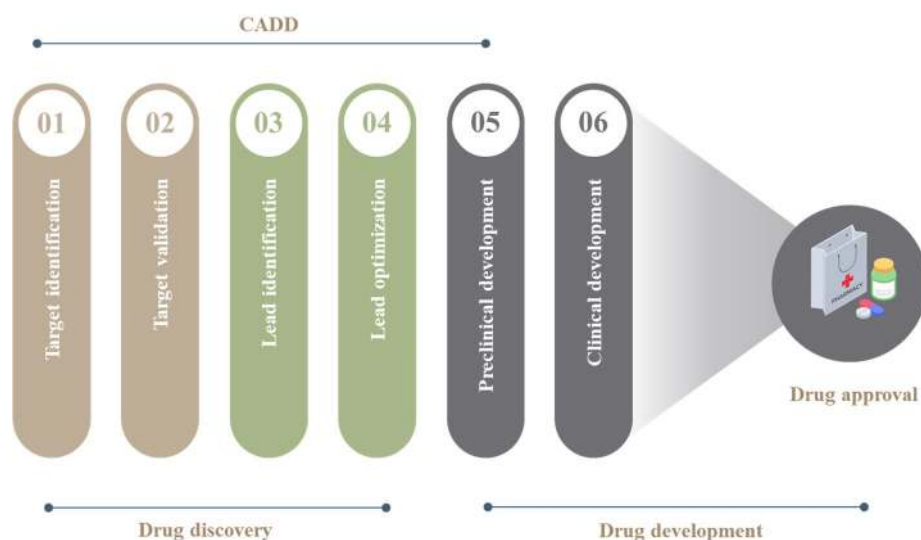

Figure 1.   **The position of CADD in the drug discovery and development pipeline**
**Slika 1.**   **Pozicija CADD u procesu otkrića lekova**

It is based on different *in silico* methods that are used to facilitate rational drug design and synthesis of novel compounds. The application of these methods in early phases of research may reduce the number of experiments that need to be performed, but also enable the handling of a huge amount of data, which are beyond human analytical skills (9). Moreover, the utilization of CADD techniques to identify hits and select the best candidates for further evaluation will greatly decrease time and resource requirements of chemical synthesis and biological testing (10). Different computational methods need to be integrated properly to achieve a comprehensive study, as well as

accurate and effective rational drug design, and thereby to eliminate key risks before making an expensive investment at a late stage (1, 11). Thus, the use of CADD for three main purposes has become a standard practice in modern drug design: (1) filter huge data libraries to select compounds that can be examined experimentally; (2) guide the lead optimization to increase its affinity or optimize physicochemical and pharmacokinetic properties; (3) rational drug design of novel compounds (9).

The introduction of CADD approaches in rational design of potent therapeutics has led to the improved overall efficiency of drug discovery, as well as reduced development times to only 6-8 years (12).

CADD methods in drug design

Depending on the available information about a particular target and ligands, it is possible to utilize different CADD strategies that can be categorized into two groups: structure-based drug design (SBDD) and ligand-based drug design (LBDD) methods (9, 13). Generally, structure-based CADD methods require the 3D structure of the target of interest, and are most commonly used to identify key sites and binding interactions. However, ligand-based CADD approaches are usually based on the study of the structure-activity relationship and are used in the absence of structural information about the target of interest (14). In particular, CADD methods are rapidly improving and new approaches are frequently developing, challenging researchers to be continually updated on the latest knowledge (15). In this review, commonly used CADD methods (Figure 2) will be presented, focusing on those used in our lab for the design of novel anti-inflammatory agents, as well as aminergic GPCR ligands for the treatment of neuropsychiatric disorders.
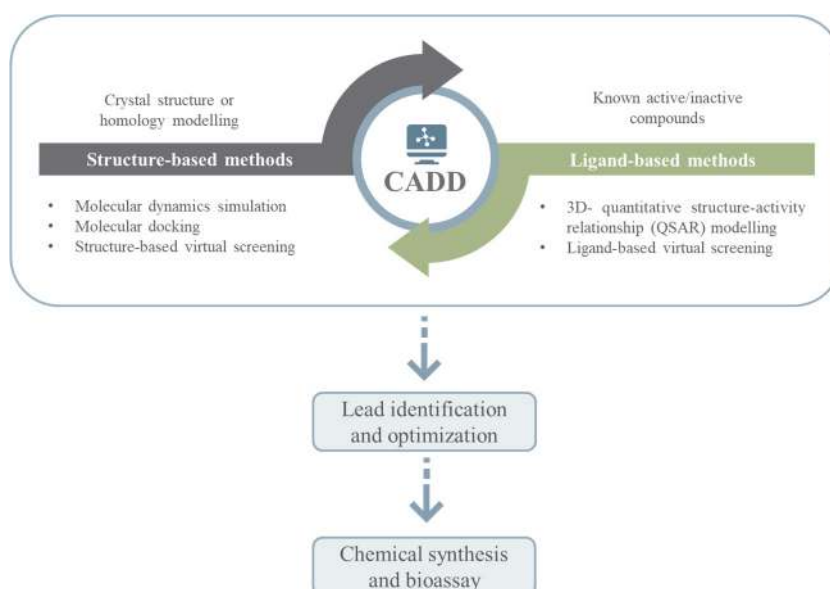
Figure 2.   A summary of commonly used CADD methods
Slika 2.   Prikaz najčešće korišćenih CADD metoda

Structure-based drug design methods

SBDD methods use the known 3D protein structure to assist in the process of rational drug design. Great advances in nuclear magnetic resonance (NMR) techniques and X-ray crystallography have led to the discovery of more than 150,000 3D protein structures available in databases such as Protein Data Bank (PDB) (16, 17). Despite certain limitations, the availability of a large number of solved protein structures enables deeper insights into the ligand and protein complex including analysis of binding conformations, characterization of key intermolecular interactions, as well as identification of unknown binding sites (18). Nevertheless, if the 3D structure of the target of interest is not yet solved, homology modelling is the most reliable method for its prediction. The structure of the known homologous protein is used to generate the 3D structure of protein of interest from a related amino acid sequence. Once the structure is built, the Ramachandran plot is most commonly used for model validation (19). Programs such as MODELLER (20) and an on-line web server such as SWISS-MODEL (21) are the most frequently used for high quality protein structure predictions (22).

Therefore, SBDD methods are widely used for molecular modifications with the aim of improving interactions in the binding site of the target protein and increasing the affinity of new ligands. The most frequently used structure-based methods in the drug discovery process of new drugs are molecular dynamics (MD), molecular docking, and structure-based virtual screening (SBVS) (16).

Molecular dynamics

It is well known that the protein-ligand interactions are followed by significant conformational changes of both molecules. MD simulation is a widely used method for studying the motions of atoms and molecules, providing valuable insights into structure and dynamics (23). It allows a deeper analysis of the protein-ligand interactions over a period of time, in order to reproduce the actual behaviour of all the atoms in a biomolecular system, taking into account the flexibility of structures and the effects of solvents (24). Once the forces exerted on each atom have been calculated, the principles of Newton's laws of motion are used to predict the position of these atoms as a function of time (24, 25). Molecular interaction potentials, which are typically parameterized by quantum chemical calculations combined with experimental data, are used to define the atomic forces that modulate molecular movement (25, 26). These parameters, called the force-field, describe the influence of bonded or non-bonded interactions to the general function (27, 28). Considering the large number of calculations that are required, MD simulations need high performance computing resources, such as multiple GPU based PCs, cluster computing resources or supercomputers, depending on the MD system setup. In addition, if computational resources are limited, in some cases they can be saved by employing the implicit solvent model instead of explicit as it was show to be computationally faster for small systems (29). Although systems without a solvent are inexpensive, they are not realistic, since the solvent plays an important role in protein structure determination. Finally, the obtained trajectory describes the atomic-level

configuration of the simulated system at every point in time, which presents a particular challenge for experimental methods. MD simulations provide valuable information for studying various functional processes such as: conformational changes, ligand binding, or membrane transport. Moreover, they are likely to play an increasingly important role in the lead optimization. Several programmes for MD simulation are available, such as: AMBER (30), CHARMM (31), GROMACS (32), and NAMD (33).

Molecular docking

Molecular docking is a frequently used CADD technique for the analysis of ligand-protein interactions. Starting from the high-resolution X-ray, NMR or homology-modelled structure, it aims to predict the predominant binding mode (conformation/orientation i.e., poses) and free binding energy of small molecules (34, 35). Molecular docking consists of two basic components: sampling algorithm to explore conformations and scoring function to rank each predicted pose (36). There are two major categories of sampling algorithms, systematic and stochastic (37). Scoring functions are used not only to identify the binding pose but also to rank obtained conformations. Additionally, they estimate complex binding energy and can be classified into empirical, force field based, or knowledge based (38). Generally, there are three ways of docking small molecules into the protein structure: (1) rigid docking, where both ligand and protein are treated as rigid, (2) flexible-rigid docking is widely used method where protein conformation is fixed, while the ligand is considered to be flexible, and (3) flexible docking, where conformations of both the ligand and protein are flexible, which is more accurate but challenging (39). Ideally, the obtained results should be in concordance with the experimental binding mode, which could be validated with root mean square deviation (RMSD) (40). Results obtained through a successful molecular docking study can be employed for virtual screening (VS) on large libraries of compounds, structure–activity relationship analysis, or lead optimization. Over the last decades, a large number of programmes for molecular docking have been developed, while the most frequently used ones are AutoDock (41), AutoDock Vina (42), GOLD (43), and GLIDE (44) from the Schrödinger suite (45, 46).

Virtual screening

Virtual screening is a computational method widely applied in the early stages of the drug discovery process. Generally, it is an essential tool for the screening of small molecule libraries in order to identify lead-like compounds with potential biological activity against a target of interest (47). VS techniques can be categorized into two major groups: ligand-based virtual screening (LBVS) and structure-based virtual screening (SBVS). LBVS is mainly used in cases where the 3D structure of the target is unknown. This method relies on a comparison of the chemical structures (similarity search), pharmacophoric features (pharmacophore mapping) or molecular descriptors of the known compounds to those from scanned databases (48, 49). Essentially, it is based on the theory that similar compounds possess a similar behaviour. For the second group of

VS – SBVS, protein 3D structure is the main requirement. This approach involves the docking of each ligand from a database into the protein binding site. Subsequently, the scoring function ranks the selected ligands based on their affinity for the target (49, 50). Therefore, VS makes significant contributions to processes of drug discovery, in particular in hit identification and lead optimization (51).

Ligand-based drug design methods

Ligand-based methods or indirect methods are generally used when the structure of the selected target is unidentified. In this case, the rational design of new compounds is based on the study of 2D or 3D structures of ligands known to interact with a target of interest. One of the commonly employed LBDD techniques is the quantitative structure-activity relationship (QSAR) approach that predicts biological activity from chemical structures (9). In general, it is based on the assumption that compounds with common structures also have similar physicochemical properties and consequently have similar binding modes (52).

Quantitative structure-activity relationship

QSAR modelling is one of the major computational methods, used in medical chemistry for more than 50 years (53). It is based on statistics that form an empirical relationship between the structural features of studied compounds and their experimentally determined biological activity (52). The general workflow of QSAR modelling can be divided into three phases: the first is to collect a group of examined ligands and to calculate molecular descriptors that affect biological activity, then model building, and finally model validation (54). 2D-QSAR and 3D-QSAR are the most common approaches for model building. The first method considers the geometrical and topological properties but excludes 3D conformation of the compound. On the other hand, 3D-QSAR method focuses on the spatial properties of the compound, which may be crucial for distinguishing stereoisomers (55). Nevertheless, the representation of the molecular structure by calculated physicochemical and 3D structural descriptors is a critical step for the further model development for predicting small molecule-receptor interactions (56). Statistical methods are employed to select the most important molecular descriptors, as well as to gain further insights into the key structural features (53, 54). Subsequently, different internal and external validation methods can be utilized to confirm the predictive power and stability of the created QSAR model (57). Finally, the model can be used to modify existing compounds and improve their activities, as well as to predict the activity of newly designed compounds. Therefore, 3D-QSAR is a powerful tool for establishing the relationship between the structure and activity of examined compounds, but it can also be used for database screening to find new active molecules (10, 15).

In silico ADMET (absorption, distribution, metabolism, excretion, toxicity) prediction

In silico ADMET profiling of compounds is one of the most significant steps in the process of drug discovery (58). Having early information on pharmacokinetic properties, metabolism and potential toxicity is crucial in order to avoid the risk of late-stage failures, as well as to guide the lead optimisation by increasing its drug-like properties. Moreover, ADMET data may be analysed by building predictive QSAR models to search for correlations between the activity and a wide variety of ADMET descriptors (58-60). Currently, there are many commercially available as well as free-to-use programmes that can be used for *in silico* ADMET profiling, such as: Swiss-ADME (61), ADMET Predictor (62), Schrodinger-QikProp (63) and many others (58, 59).

Successful application of CADD approaches in the discovery of aminergic GPCR ligands for treatment of neuropsychiatric disorders

GPCRs are the most frequently studied receptors for the discovery of new ligands. A number of successful examples of the application of CADD strategies have been reported in the area of aminergic GPCRs. These receptors belong to rhodopsin like GPCRs, class A, and they are targets for 25% of current drugs (64). In this review, an up-to-date summary of the CADD approaches used in discovery of ligands binding to a specific subfamily of aminergic GPCRs, namely dopamine and serotonin receptor family was provided. Both receptors play an essential role in physiology and pathophysiology of various brain disorders, including depression, schizophrenia, anxiety, Parkinson's disease and many others (65-68). Atypical antipsychotics, generally known as antagonists of dopamine D_2 and serotonin 5-HT_{2A} receptors are used to alleviate the symptoms associated with these conditions (69-71). However, for an effective treatment, a balanced modulation of these receptors and specific activity and selectivity profile of the drug is crucial. Therefore, research and development of new antipsychotics with good efficacy, selectivity, and reduced side effects may present a significant advance in the therapy of neuropsychiatric disorders.

Among all, the aminergic GPCR subfamily is the most extensively studied and many high-resolution crystal structures are available (17, 72). Today, the GPCR database (GPCRdb, http://gpcrdb.org) provides detailed information about the sequence, mutations and structures of GPCRs which could be valuable for various types of analyses (72). The combination of structural analyses with the information of QSAR studies may provide complementary research to gain a deeper insight into the knowledge of receptor-ligand complexes (73-75).

Serotonin 5-HT_{2A} and dopamine D_2 receptors are among the most attractive therapeutic targets for different brain disorders. As mentioned above, structural information is required to gain insights into protein activities, as well as for SBDD study. Many studies have been performed using the homology modelling method to create 3D structures of 5-HT_{2A} and D_2 receptors until their crystal structures were solved (76, 77).

Recently, several high-resolution 3D structures of these receptors complexed with the agonist, inverse agonist or antagonist have been generated (Table I) (78-84). In a relevant number of articles described below, different CADD approaches were successfully employed in order to rationally design novel promising compounds for selected receptors.

Table I Crystal structures of 5-HT$_{2A}$ and D$_2$ receptors from GPCRdb

Tabela I Kristalne strukture 5-HT$_{2A}$ i D$_2$ receptora preuzete iz GPCRdb

	PDB ID	State	Resolution	Ligand name	Function	Reference
5-HT$_{2A}$ receptor	6WHA	Active	3.40	25-CN-NBOH	Agonist	(78)
	6WGT	Inactive	3.40	Lysergide	Agonist	(78)
	6WH4	Inactive	3.40	CHEMBL428892	Inverse agonist	(78)
	6A94	Inactive	2.90	Zotepine	Antagonist	(79)
	6A93	Inactive	3.00	Risperidone	Antagonist	(79)
D$_2$ receptor	7JVR	Active	2.80	Bromocriptine	Agonist	(80)
	7DFP	Inactive	3.10	Spiperone	Antagonist	(81)
	6VMS	Active	3.80	Bromocriptine	Agonist	(82)
	6LUQ	Inactive	3.10	Haloperidol	Antagonist	(83)
	6CM4	Inactive	2.90	Risperidone	Inverse agonist	(84)

In 2017, Lin et al. examined arylpiperazine derivatives as promising 5-HT$_{2A}$ receptor antagonists by an integrated use of 3D-QSAR analysis, molecular docking and MD simulation (85). Firstly, they employed comparative molecular field analyses (CoMFA) and comparative molecular similarity indices analyses (CoMSIA) in a 3D-QSAR study to select the most important structural features that affect their biological activity (85). Even though CoMFA/CoMSIA methods are frequently used in 3D-QSAR modelling, they are largely dependent on the structure alignment, which presents their main limitation. Besides, molecular docking (using GOLD software) followed with MD simulation (using GROMACS software) was used to analyse the binding mode of the examined ligands to the 5-HT$_{2A}$ receptor. The obtained results revealed that H-bonds with D3.32 and S3.36, two π-π stacking interactions with W3.28 and F6.52, and hydrophobic interaction are the most important for high-affinity binding. Lastly, using compound **1 (13)** from Figure 3 as a template, new potential arylpiperazine antagonists were designed based on the obtained results.

1-(13)   2-(D2AAK1)   3-(5)   4-(5.3a)   5-(5.4)

6-(FW01)   7-(9f)   8-(S1)   Lumateperone
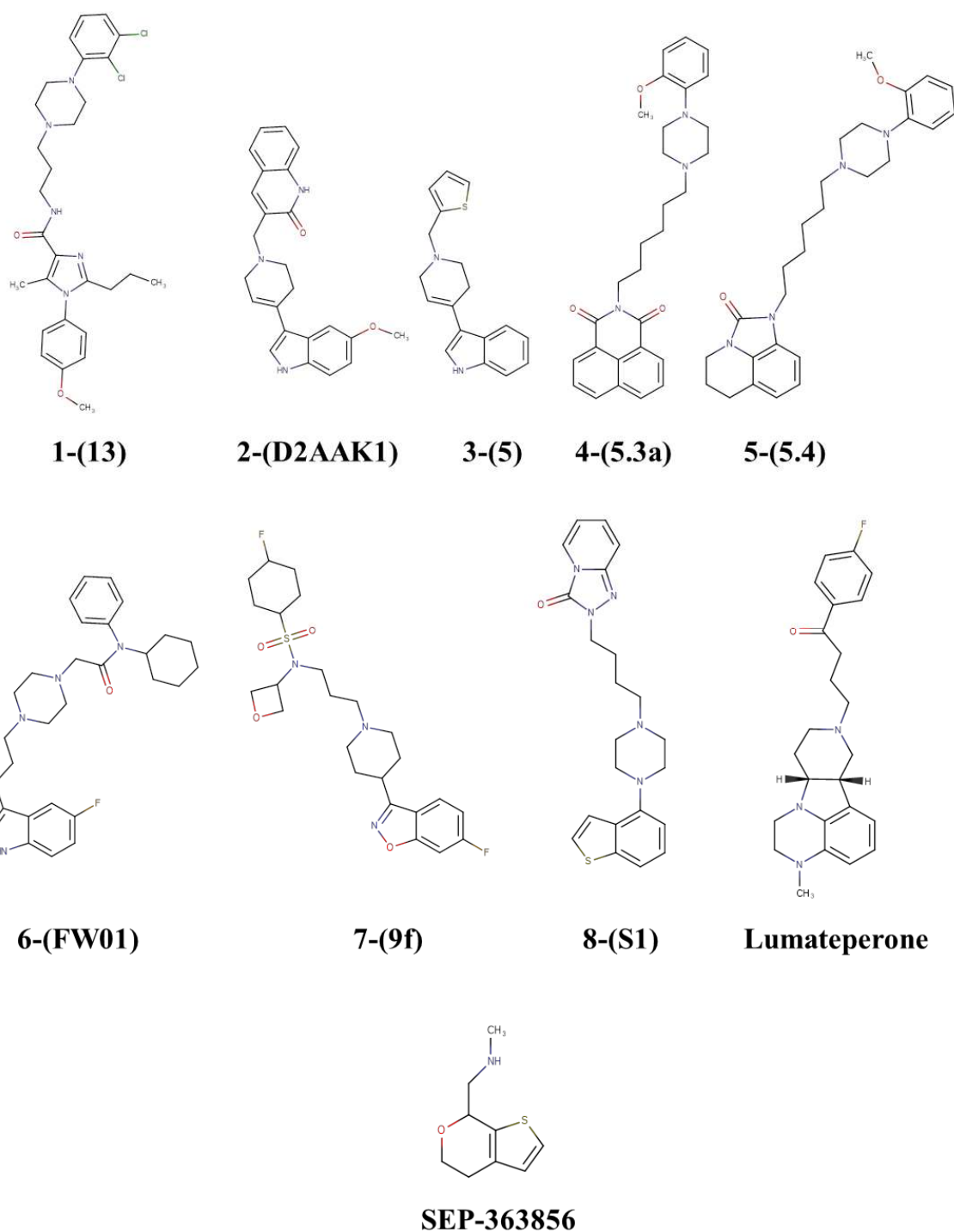
SEP-363856

Figure 3.   **Structures of novel multi-target antipsychotics adopted from references 85 (1), 90 (2), 93 (3), 100 (4, 5), 102 (6, 7), 104 (8), 105 (Lumateperon) and 106 (SEP-363856)**

Slika 3.   **Strukture novih višeciljnih antipsihotika preuzete iz referenci 85 (1), 90 (2), 93 (3), 100 (4, 5), 102 (6, 7), 104 (8), 105 (Lumateperon) and 106 (SEP-363856)**

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More recently, a similar procedure was used to design potent dual antagonists of D_2 and 5-HT$_{2A}$ receptors (86). Zhang et al. used structures of ziprasidone, risperidone, and brexpiprazole to design novel pyridopyrimidinone derivatives (86). In this study, CoMFA, CoMSIA, Topomer CoMFA and HQSAR (hologram quantitative structure activity relationship) models were successfully built and used for further visualization. The obtained results revealed that the modification of region A with bulkier substituents may decrease the activity of studied antagonists, while the introduction of nitrogen atom at position b may lead to an increase in the activity (Figure 4) (86). Afterwards, a molecular docking study performed with SYBYL-X software was used to validate the created models (87). In summary, it demonstrated that the salt bridge with Asp residue (D3.32), as well as hydrogen bonding, Van der Waals, and hydrophobic interactions maintain the stability of both complexes. Additionally, pharmacophore-based VS model was used to search the ZINC12 database to find out new dual antagonists by using the UNITY Flex program (88). Selected compounds were docked into D_2 and 5-HT$_{2A}$ receptors, and four of them were chosen for further optimization. MD simulation was also used to confirm obtained docking results. In conclusion, combining LBVS and molecular docking, as well as 3D-QSAR approach with SBDD methods presents a promising tool for future rational drug design of new compounds and creating new opportunities for innovation in medicinal chemistry.
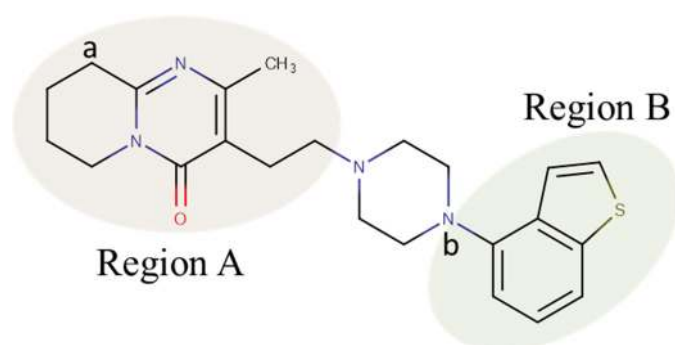
Figure 4. **General structure of compounds used in Zhang et al. study (86)**
Slika 4. **Opšta struktura jedinjenja proučavanih u studiji objavljenoj od strane Zhang et al. (86)**

Kumar et al. also employed LBVS to create a new library of 5-HT$_{2A}$ receptor antagonists using 2D/3D similarity search of ZINC database (InstJChem and Screen3D softwares, ChemAxon Ltd., Budapest, Hungary) (89). All the selected ligands were docked into a 5-HT$_{2A}$ receptor, using GOLD software, whereas MD simulations (GROMACS software) were used to verify the stability of the formed complexes.

Moreover, a group of novel potential antipsychotics was identified through a VS approach. Kaczor et al. successfully implemented SBVS of the Enamine compound

database to find dopamine D_2 receptor ligands (90). Multistep VS workflow from the Schrodinger software suite was used for hits docking (91). As a result, 21 compounds were selected as the best candidates for further experimental validation. Ten molecules were identified that have an additional affinity for the 5-HT_{2A} receptor, which made them good starting points for further optimization studies. Compound **2** (**D2AAK1**) was selected as the most promising compound from this VS study (Figure 3). Additional *in silico*, *in vitro* and *in vivo* studies confirmed that **D2AAK1** is a multi-target ligand of aminergic GPCRs, with neuroprotective properties and pro-cognitive activity, therefore providing a new therapeutic option for the treatment of multifactorial brain disorders (92-94). Since *in vitro* studies showed the affinity of **D2AAK1** for dopamine D_1 and D_3 receptors, as well as for serotonin 5-HT_{1A} and 5-HT_{2A} receptors, molecular dynamics (using Desmond) and molecular docking (using GLIDE) studies were used to reveal its interactions and binding poses with these targets at the molecular level. The results of molecular docking were in agreement with the binding mode of aminergic GPCR ligands previously described in literature, while MD simulations were mainly used to examine how **D2AAK1** modulated the inactive conformation of the examined receptors. The obtained results were in concordance with *in vitro* studies, suggesting that this compound is an antagonist or partial agonist at these receptors based on the obtained specific conformations. Overall, this implies that such *in silico* methods may be used for assessment of the intrinsic efficacy of the compounds at GPCRs. Furthermore, the same team designed some new analogues of **D2AAK1**, whereas compound **3** (**5**) from Figure 3 with the most favourable multi-target profile was chosen for further molecular modelling, *in vitro* and *in vivo* studies (93). Finally, it can be concluded that VS plays a prominent role in the drug discovery process for the identification of new bioactive molecules and has already contributed to the compounds on the market (95).

Zięba and co-workers analysed dopamine D_2 receptor antagonists employing the LBDD method (96). Taking into account that molecular alignment presents a crucial factor in CoMFA model building, they performed a 3D-QSAR analysis for structurally unrelated compounds using molecular docking-based alignment. The studied compounds were aligned by electrostatic interaction between the positively charged nitrogen of the ligand and the polar D3.32 residue, as it was described as essential for aminergic receptors, as well as by equivalent substituents of structurally different compounds (97). GLIDE programme from the Schrödinger software was used for the docking study, while the 3D-QSAR CoMFA model was built with SYBYL-X. In this context, the obtained results were used to discuss the structure–activity relationship of the studied ligands based on their interactions with the receptor.

In a recent investigation, Radan et al. integrated a number of CADD methods, including MD simulation, molecular docking, and 3D-QSAR modelling in order to analyse the 3D-structure of the pharmacophore and binding kinetics of structurally different 5-HT_{2A} receptor antagonists (98). Based on chemical structures, dataset compounds were separated into three clusters representing dibenzodiazepine, 1,2-benzoisothiazole and sulfonylpyridine derivatives. Structure-based methods were

used not only to examine how structurally different antagonists bind and modulate activity of this receptor, but also to generate their virtually bioactive conformations. Firstly, a complex of each cluster representative with 5-HT$_{2A}$ receptor was submitted to 50 ns long MD simulation to obtain their inactive, antagonist-bound conformations. The obtained conformations were further used for docking studies in order to generate virtually bioactive conformations of all studied ligands, as well as to investigate their binding modes in the active site of the receptor. MD simulation was performed with the NAMD software, while docking studies were performed with both AutoDock Vina and GOLD programs. Afterward, the predicted bioactive conformers were utilized to develop 3D-QSAR models by using the Pentacle program and therefore to gain further insights into the structural requirements that affect their antagonistic activity on 5-HT$_{2A}$ receptor (99). Overall, the results obtained through performed LBDD and SBDD studies as well as ADMET profiling may provide information that can be used for further optimization of compounds as well as for rational drug design. A summary of the aforementioned process is depicted in Figure 5.
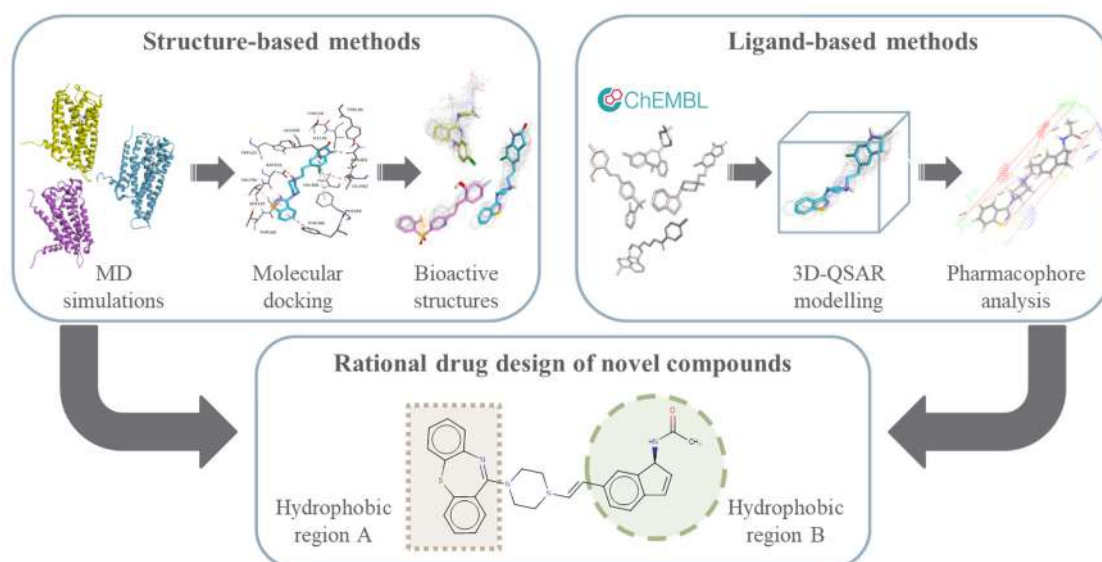
Figure 5. **Overview of Radan et al. study (98)**

Slika 5. **Skicirani prikaz studije objavljene od strane Radan et al. (98)**

In an effort to provide better efficiency and fewer adverse effects of drugs in treatment of complex neuropsychiatric disorders, many studies employed the multi-target approach in drug design and synthesis. It is currently a hot topic in GPCR-oriented research and some examples are described below.

Zaręba et al. reported new bulky analogues of arylpiperazine (LCAP- long chain arylpiperazines) as multi-functional antidepressants (100). The activities of new ligands were assessed both by *in vitro* testing as well as by using the molecular docking method.

Among a number of synthesized compounds, five were classified as dual ligands for D_2 and 5-HT$_{1A}$ receptors, and two of them, compounds **4 (5.3a)** and **5 (5.4)** from Figure 3, showed the most favourable properties. In recent studies, 5-HT$_{1A}$ receptor was described as a promising target of novel antidepressants (101). Through the application of the molecular docking method they aimed to clarify SAR (structure-activity relationship) analysis and concluded that the studied compounds showed very similar binding mode for 5-HT$_{1A}$ receptor, while different conformations were observed in the D_2 receptor binding pocket. Since ligand **5 (5.4)** showed the highest affinity for the D_2 receptor, it was explained by the largest number of hydrophobic interactions in the binding site compared to others.

In order to search for potential multi-target antipsychotics, Zhu et al. designed new aryl-piperazine ligands based on **FW01** (compound **6** from Figure 3), which is a potent agonist of the 5-HT$_{1A}$ receptor discovered by dynamic pharmacophore-based VS in their previous study (102, 103). They employed molecular hybridization strategy with the aim of synthesizing new derivatives with dual D_2 and 5-HT$_{2A}$ antagonistic activity. In this context, the D_2 receptor binding pocket was divided into the orthosteric binding site (OBS), and a second binding site (SBS) and new compounds were designed so as to enhance binding interactions compared to the **FW01** compound. The designed compounds were further analysed through an *in vitro* study, and compound **7 (9f)** was selected as a potent dual D_2 and 5-HT$_{2A}$ receptors antagonist, with no activity on 5-HT$_{1A}$ receptor (Figure 3). A molecular docking study (using GOLD software) confirmed the obtained results and revealed strong interactions of compound **7** with D3.32, T3.37 and T7.39 in the D_2 receptor binding site, and with D3.32, T3.37, S5.46 and L45.52 in the 5-HT$_{2A}$ receptor binding site, whereas unfavourable interaction was determined within the 5-HT$_{1A}$ receptor binding site. Overall, this compound makes a good candidate for further optimization and design of novel dual antagonists.

Another series of multi-target ligands was recently investigated by Shi et al. (104). They synthesized triazolopyridinone derivatives and evaluated their affinity for the 5-HT$_{2A}$, 5-HT$_{1A}$ and D_2 receptors through *in vitro* and molecular docking studies. The multi-receptor affinity profile of compound **8 (S1)** from Figure 3 was especially promising and was selected for further preclinical investigation.

In December 2019, the Food and Drug Administration (FDA) approved lumateperone (Figure 3) as potent dual 5-HT$_{2A}$/D_2 receptor antagonists, for the treatment of schizophrenia in adults (105). Also, this drug is under clinical trials for other neurological and neuropsychiatric disorders. An interesting compound, **SEP-363856** (Figure 3), is currently undergoing clinical trials for the treatment of schizophrenia (106). It is a unique compound with a non-D_2/5-HT$_{2A}$ mechanism of action discovered with *in vitro* screening. Even though the mechanism of action is not yet completely revealed, data show that agonism at both TAAR1 and 5-HT$_{1A}$ receptors is essential to its efficacy (107). Trace amine-associated receptors (TAARs) are aminergic GPCRs located in the brain and periphery with an important role in human physiology and pathophysiology (108). Overall, the design of multi-target drugs in a rational way remains a great challenge, due

to the necessity to balance the affinity to all desired targets and reducing affinity to off-targets. Nevertheless, it is currently the best option for the treatment of complex neuropsychiatric disorders.

Successful application of CADD approaches in the discovery of dual COX-2 and 5-LOX inhibitors for treatment of inflammatory diseases

Many inflammatory disorders are caused by the excessive production of arachidonic acid cascade mediators by cyclooxygenase and lipoxygenase pathways. Non-selective non-steroidal anti-inflammatory drugs (NSAIDs) block the activity of both cyclooxygenase-1 and cyclooxygenase-2 enzymes. They are used in the therapy of numerous inflammatory conditions, like temporary pain, osteoarthritis, rheumatoid arthritis (prolonged use). Traditional NSAIDs were associated with a lot of side effects (primarily gastrointestinal); thus, selective COX-2 inhibitors (coxibs) were introduced. Unfortunately, both traditional NSAIDs and coxibs are linked with increased cardiovascular risk. It is assumed that the inhibition of cyclooxygenase pathway could switch the metabolism to LOX pathway and cause an overproduction of inflammatory mediators. Therefore, dual inhibition of COX-2 and 5-LOX enzymes represents a reasonable approach used in the development of safer drugs with anti-inflammatory activity. The available crystal structures of enzyme-ligand complexes provide information about key interactions between the substrate and the active site of enzyme, which are important in computer-aided development of new drugs (Table II) (109-112). The design of dual COX-2 and 5-LOX inhibitors has been performed by the modification of the already known NSAIDs (introducing LOX pharmacophores) or by using computational techniques in order to obtain new scaffolds (113).

Table II   Crystal structures of COX-2 and 5-LOX enzymes from PDB database

Tabela II   Kristalne strukture COX-2 i 5-LOX enzima preuzete iz PDB baze podataka

	PDB ID	**Resolution**	**Ligand name**	**Function**	**Reference**
COX-2 enzyme	5IKV	2.51	Flufenamic acid	Inhibitor	(109)
	6COX	2.80	SC-558	Inhibitor	(110)
	1CX2	3.00	SC-558	Inhibitor	(110)
5-LOX enzyme	3O8Y	2.40	/	/	(111)
	3V99	2.25	Arachidonic acid	Substrate	(112)

The most studied compounds with dual COX-2 and 5-LOX inhibitory activity are di-*tert*-butylphenol derivatives. It was demonstrated that 2,6-di-*tert*-butylphenol which contains a substituent in the C4 position is important scaffold for dual inhibition of COX-2 and 5-LOX enzymes (Figure 6). It was assumed that the phenol moiety, which contains antioxidant properties, was important for anti-inflammatory activity. Considering radical scavenging activity, these compounds could potentially be useful in the therapy of radical-mediated disorders like cancer and allergic conditions. Some compounds were

involved in clinical trials at some point in time (tebufelone, **R-830**, **BF389**, darbufelone (**CI-1004**) and **S2474**) (114-118). Many subsequent studies relied on this information. Some of di-*tert*-butylphenol derivatives that act as COX and 5-LOX dual inhibitors were developed according to performed structure-activity relationship (SAR) studies, such as darbufelone, **S-2474**, tebufelone and others (Figure 6) (115, 118).
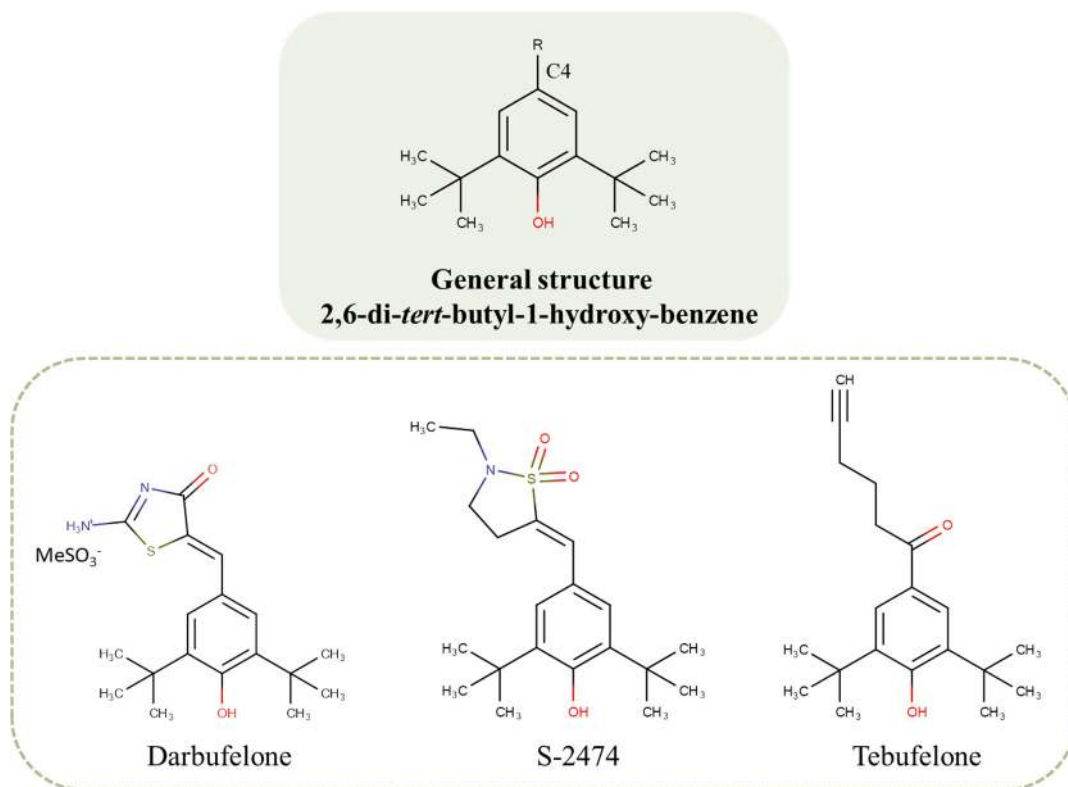

Figure 6. **General structure (2,6-di-*tert*-butyl-1-hydroxy-benzene substituted in the C4 position) and structures of dual COX-2/5-LOX inhibitors (darbufelone (116), S-2474 (117) and tebufelone (114))**

Slika 6. **Opšta struktura (2,6-di-*terc*-butil-1-hidroksi-benzen supstituisan u položaju C4) i strukture dualnih COX-2/5-LOX inhibitora (darbufelon (116), S-2474 (117) i tebufelon (114))**

Ghatak et al. reported that newly designed di-*tert*-butyl phenol derivatives (di-*tert*-butyl phenylhydrazone based compounds: **DTPSAL**, **DTPBHZ**, **DTPINH** and **DTPNHZ**; Figure 7) showed a significant inhibition of COX-2 and 5-LOX enzymes and demonstrated cytotoxicity against human colorectal cancer (CRC) cell lines (119). Molecular docking studies were performed with the aim of obtaining information about interactions with protein residues within the active sites of COX-2 and 5-LOX enzymes and for the evaluation of the efficacy of synthesized dual inhibitors. For this purpose, AutoDock Vina software was used. As a result, compounds **DTPBHZ** and **DTPSAL** showed the best fit in the protein pocket of COX-2 enzyme with binding energies -10.1

Kcal/mol and -9.7 Kcal/mol, respectively. Compound **DTPSAL** exhibited binding energy of -8.2 Kcal/mol when docked to 5-LOX enzyme (PDB ID: 3O8Y) and this value was lower than the binding energy of darbufelone (already known dual inhibitor, -7.73 Kcal/mol). It can be concluded that all novel di-*tert*-butyl phenol compounds have high binding affinities for COX and LOX active sites, which is in compliance with *in vitro* results.
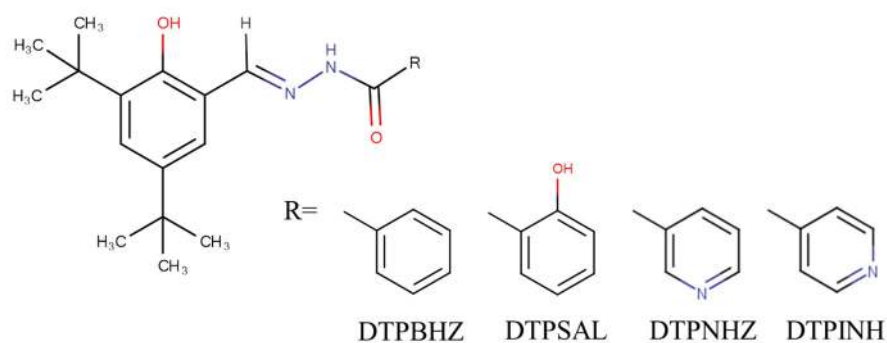

Figure 7. **Structures of di-*tert*-butyl phenylhydrazone ligands: DTPBHZ, DTPSAL, DTPNHZ and DTPINH adopted from refrence 119**

Slika 7. **Strukture di-*terc*-butil fenilhidrazon liganada: DTPBHZ, DTPSAL, DTPNHZ and DTPINH preuzete iz reference 119**

Lino et al. developed new dual COX and 5-LOX inhibitor LQFM-091 (di-*tert*-butylphenol compound) obtained from darbufelone and nimesulide (Figure 8) (120). A colorimetric screening assay and molecular docking study were performed with the aim of explaining the underlying mechanism of action. COX-1, COX-2 and 5-LOX crystal structures were obtained from the PDB database. Avogadro was used for structure drawing, Gaussian (MP2) for the calculation of partial charges and AutoDockTools4 for final structure preparation (121, 122). The molecular docking study was performed using DockThor and Vina (123). Both programs succeeded to pose **LQFM-091** near or in the active sites of enzymes. A visual comparison between the best-ranked **LQFM-091** poses and poses of darbufelone and nimesulide was carried out using PyMOL (The PyMOL Molecular Graphics System, version 1.8). LigPlot[+] v1.4.5 was used for the estimation of interactions between the protein and ligand (124). Darbufelone, nimesulide and **LQFM-091** were similarly docked into the active sites of enzymes. In conclusion, the molecular docking study revealed that **LQFM-091** interacted with important residues for the catalytic activity of all tested enzymes in a similar manner as darbufelon and nimesulide. In addition, *in vitro* studies showed that **LQFM-091** is a dual COX and 5-LOX inhibitor, which confirmed the molecular docking results.
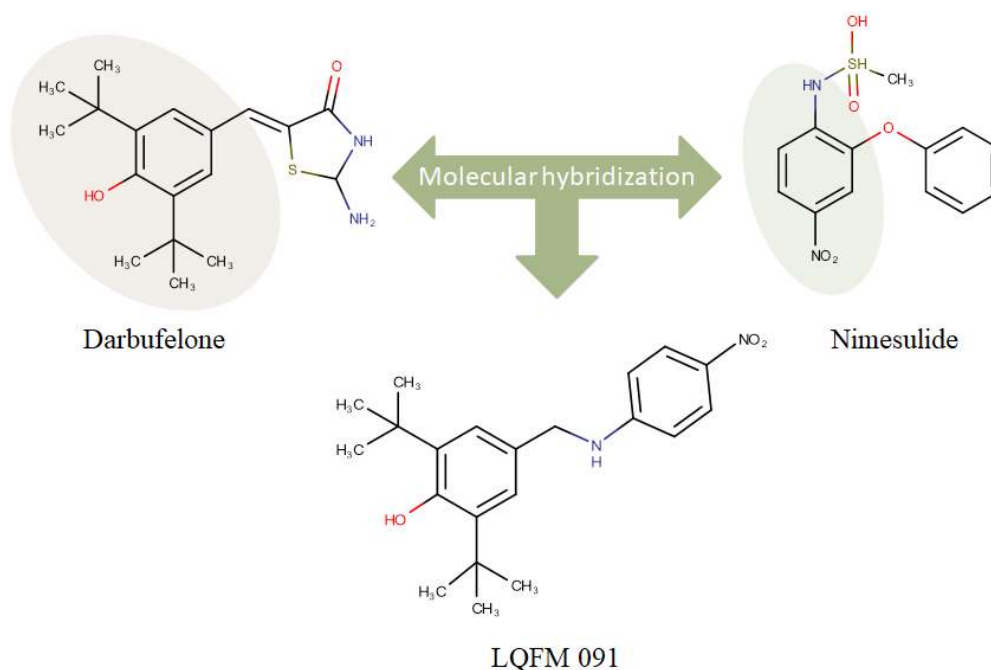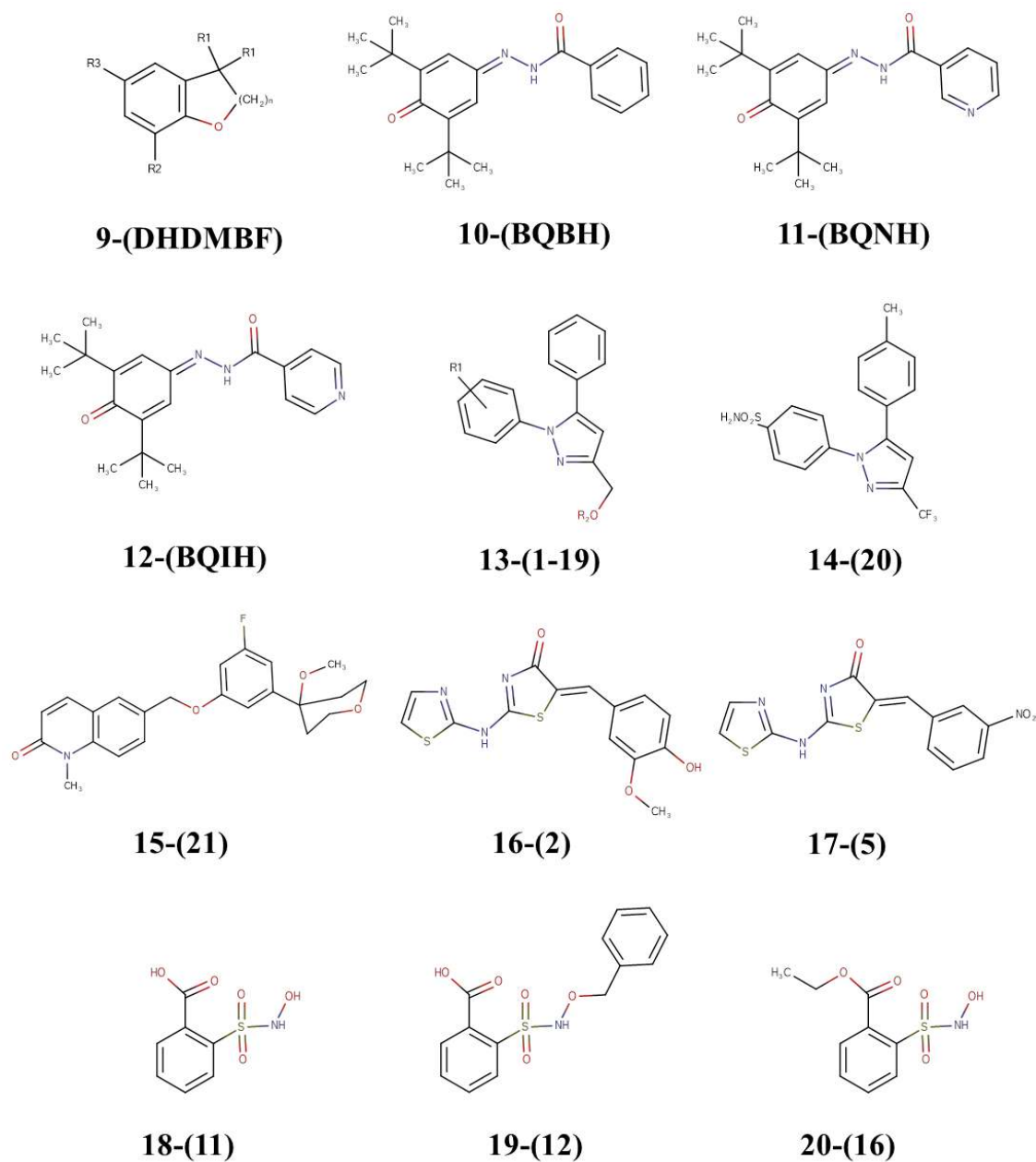
Figure 8. **Design of di-tert-butylphenol compound LQFM 091 from darbufelone and nimesulide adopted from reference 120**

Slika 8. **Dizajn di-*terc*-butilfenol jedinjenja LQFM 091, iz darbufelona i nimesulida, preuzeto iz reference 120**

Dihydrodimethylbenzofuran (**DHDMBF**) is metabolite of di-*tert*-butylphenol tebufelone which showed an anti-inflammatory activity comparable to tebufelone. It was demonstrated that 5-keto-substituted **DHDMBF**s have *in vitro* COX-2 and 5-LOX inhibitory activity and potent *in vivo* analgesic and anti-inflammatory activity when administered orally (125). The general structure of **DHDMBF** (compound **9**) analogues is presented in Figure 9.

9-(DHDMBF) **10-(BQBH)** **11-(BQNH)**

12-(BQIH) **13-(1-19)** **14-(20)**

15-(21) **16-(2)** **17-(5)**

18-(11) **19-(12)** **20-(16)**

Figure 9. Structures of novel dual COX-2 and 5-LOX inhibitors adopted from references 125 (9), 125 (10, 11, 12), 131 (13, 14, 15), 137 (16, 17) and 140 (18, 19, 20)

Slika 9. Strukture novih dualnih COX-2 and 5-LOX inhibitora preuzete iz referenci 125 (9), 125 (10, 11, 12), 131 (13, 14, 15), 137 (16, 17) and 140 (18, 19, 20)

Zheng et al. performed homology modelling and MD simulations of 5-LOX enzyme, as well as 3D-QSAR studies and molecular docking on **DHDMBF**s analogues

(COX-2 and 5-LOX dual inhibitors) in order to reveal a common binding mode in COX-2 and 5-LOX enzymes, explain conclusions from SAR studies and create highly predictive QSAR models which could be used in the development of new compounds that act as dual inhibitors (126). They created a homology model of the human 5-LOX enzyme by using the X-ray structure of the 15-LOX enzyme as a prototype. MODELLER was used for the creation of ten 5-LOX models. Further optimization of these models was performed via a conjugate gradient minimization scheme, followed by a restrained simulated annealing MD simulation (127). Based on the obtained results, a representative 5-LOX model was selected. COX-2 crystal structure was downloaded from PDB (PDB ID: 6COX). Further equilibration of the 3D model was performed using the AMBER 7.0 program (4-ns MD simulation). As a result, iron ligand residues, which are important for the 5-LOX activity, were precisely aligned. High reliability of the created final 5-LOX model was indicated by the high score. Twenty-seven **DHDMBF**s analogues from literature were docked into the active sites of both enzymes. The prediction of binding free energies of the docked compounds was performed by using the Auto Dock 3.0.3. programme, after structure optimization. The predicted binding free energies (both enzymes) for all compounds were in a good correlation with the experimental inhibitory activities (-logIC50). Twenty-one **DHDMBF** analogues were selected for CoMFA and CoMSIA studies, according to the binding conformations acquired from the performed molecular docking study. These studies were carried out with the aim of creating models which could be used for the design of new dual inhibitors. In conclusion, the performed modelling provided an explanation of binding modes of **DHDMBF** analogues within COX-2 and 5-LOX enzymes, while the 3D-QSAR study provided models that could be used in the development of novel potent dual inhibitors.

It was found that darbufelone acts as an inhibitor of growth of non-small cell lung cancer cell lines. Despite this discovery, di-*tert*-butyl phenols and their prodrugs di-*tert*-butyl benzoquinones remained incompletely investigated. Misra et al. synthesized three di-*tert*-butyl benzoquinone inhibitors attached to hydrazide side chain, named **BQBH**, **BQNH** and **BQIH** (compounds **10**, **11** and **12,** respectively in Figure 9) (128). These derivatives were docked into COX-2 and 5-LOX enzymes. They were also evaluated for inhibitory activities on both enzymes and cytotoxicity against colon cancer cell lines. The crystal structures for COX-2 and 5-LOX enzymes were downloaded from PDB site (PDB ID COX-2: 6COX; 5-LOX: 3O8Y). The AutoDock-Vina was used to dock **BQBH**, **BQNH**, **BQIH** and darbufelone in the active sites of targeted enzymes. In the case of docking to the COX-2 enzyme, calculated binding energies were in the range from -6.8 to -7.2 Kcal/mol and the best result was obtained for **BQNH**. For the 5-LOX enzyme, calculated binding energies for **BQNH**, **BQIH**, darbufelone and **BQBH** were in the range from -7.0 to -8.4 Kcal/mol, respectively. The molecular docking study indicated that all the tested compounds interact with amino acid residues within the active sites of both enzymes. Compound **BQNH** expressed the highest binding energy in both enzymes. *In vitro* tests confirmed that di-*tert*-butyl benzoquinones analogues are effective COX and 5-LOX inhibitors (128).

Ruiz et al. tested the dual COX and 5-LOX inhibitory activity of 24 mono-, 2,6-di-*tert*-butyl and unsubstituted phenols taken from the literature (115). Twenty compounds were di-*ortho* substituted phenols (*tert*-butyl groups in *ortho* positions), which is an essential scaffold for antioxidant activity, while various substituents were introduced in *para* position of the phenol. The remaining four compounds, with mono or unsubstituted *ortho* positions (*tert*-butyl or methyl groups), were also considered in order to test the effect of *tert*-butyl groups in *ortho* positions. The conformational variability of the compounds was investigated. A conformational study was carried out after molecular mechanics (MM) calculations (for building up initial geometries) and it was performed using semi-empirical AM1 method (incorporated in MOPAC 6.0 ESP program). Geometry optimization of minimum energy conformations (HF/6-31G(d) ab initio level) was performed using GAUSSIAN-94 program (129). The possible active conformations were selected using molecular superimposition between minimum energy conformations and the optimized conformations of active dual inhibitor tebufelone. According to the performed conformational analysis, molecular flexibility could be important for the modulation of COX and 5-LOX inhibitory activity. MEPMIN program was used for the drawing of molecular electrostatic potential maps (MEP) (130). GRID program was used for the representation of favorable interaction regions for each compound. For this purpose, various probes such as hydrophobic (DRY), water (OH2), ferric and ferrous iron cation (Fe^{3+} and Fe^{2+}) were used. It can be concluded that di-*tert*-butyl phenol analogues can occupy four common minimum energy conformations that show a correct fit with the structure of tebufelone. The presence of electron-donating substituents (*tert*-butyl group in ortho positions of the phenol ring) favours phenoxyl radical formation and the hydrophobic interactions within the active sites of COX and LOX enzymes according to the performed QSAR studies. High EHOMO (energy of the highest-occupied molecular orbital) and low ferric cation interaction energies were calculated for the most active dual inhibitors, which indicates a probable Fe redox mechanism for LOX inhibition. The predictive ability of the suggested QSAR equations was tested with selective dual COX and 5-LOX inhibitors.

Pommery et al. synthesized and *in vitro* tested diarylpyrazole derivatives for COX-2 and 5-LOX inhibitory activity (131). They also performed molecular modelling approach and proposed a set of SAR data important for further investigations of this group of compounds.

Revathi et al. perfomed a QSAR study on 1,5-diarylpyrazoles in order to obtain information about the structural features important for COX-2 and 5-LOX inhibitory activity (132). The inhibitory activities of 1,5-diarylpyrazole derivatives (compounds **13** and **14,** Figure 9) on COX-1, COX-2 and 5-LOX enzymes were taken from literature (131). CS ChemOffice version 8.0 (133) and Dragon program (134) were used for modelling the study (structures drawing and computation of molecular descriptors), while VALSTAT (135) was used for regression analysis. At first, the structures were optimized using molecular mechanics (MM2), then re-optimized via Austin model-1 (AM1) method

using MOPAC and the geometry optimization of the lowest energy structure was performed using the EF routine. Molecular descriptors were calculated in the Dragon program. The obtained data were further transferred to VALSTAT to find a correlation between independent (molecular descriptors) and dependent variables (pIC50 values) using the sequential multiple linear regression analysis method. As a result of the performed QSAR study, important information about structural insights was obtained. Hy (hydrophilic factor) and Mor17v (3D molecular representation of structure based on electron diffraction code) are the descriptors essential for the development of more selective COX-2 and 5-LOX dual inhibitors.

Thiazole and thiazolidinone scaffolds can be found in many of pharmacologically active compounds. Liaras et al. explored the effects of thiazole and thiazolidinone derivatives on COX and LOX enzymes (136). According to the performed study, these compounds could be an encouraging initial point for the future development of potent and safer COX and LOX inhibitors.

In a study performed by Geronikaki et al. (137), CADD approach (PASS software (138)) was used in order to predict the biological activity of 573 *in silico* designed compounds (thiazole/benzothiazoles and benzoisothiazoles) and the obtained results were further analyzed by the Pharma Expert software (139). Anti-inflammatory activity was predicted for thirty-one compounds, while twenty-two were nonspecific COX and specific 5-LOX inhibitors. These twenty-two compounds were 2-(thiazole-2-ylamino)-5-phenylidene-4-thiazolidinone derivatives. Nine of them were selected for biological assays and eight derivatives expressed anti-inflammatory activity in *in vitro* experiments (Figure 7). According to the results of the performed *in vitro* experiments, compounds **16** (**2**) and **17** (**5**) from Figure 9 showed the highest anti-inflammatory activity. The most active compounds were docked to COX-2 and 15-LOX enzymes with the aim of obtaining information about binding modes. GOLD 3.0.1 software was used for the molecular docking study. Goldscore (GS), ChemScore (CS), PLP 1 and 2, LigScore 1 and 2 and PMF scoring functions were used in order to find the best pose. The docking results provided a good explanation about the inhibitory activity of the most active compounds.

Kaur et al. designed and synthesized analogues of aspirin in order to evaluate dual COX-2 and 5-LOX inhibitory activity (140). The design was based on the assumption that the replacement of acetoxy moiety of aspirin with a sulfohydroxamic moiety (SO$_2$NHOR: R=H, CH$_2$Ph, Me) would lead to the development of new compounds with a more potent activity. It was presumed that sulfohydroxamic moiety acts as a COX-2 pharmacophore (similar to celecoxib, a selective COX-2 inhibitor), 5-LOX pharmacophore (similar to 5-LOX inhibitors - iron chelators) and nitric oxid (NO) donor, inducing vascular smooth-muscle relaxation. According to *in vitro* studies, compounds **18** (**11**), **19** (**12**) and **20** (**16**) act as selective and highly potent COX-2 inhibitors, while compounds **18** (**11**) and **20** (**16**) also expressed high 5-LOX inhibitory activity (Figure 9). Compounds **18** (**11**) and **20** (**16**) with unsubstituted SO$_2$NHOH moiety appeared to be good NO donors. In order to explore the interactions into active sites of COX-1, COX-2 and 5-LOX enzymes (PDB ID: COX-1: 1EQG, COX-2: 6COX, 5-LOX: 3O8Y),

molecular docking studies were performed. The ArgusLab 4.0.1 software was used for structure building, structure geometry optimization (using semiempirical quantum mechanical method PM3) and docking (141). Active sites of selected monomeric structures of enzymes were defined around the ligand. Docking was based on a grid-based algorithm and a simulation was performed between flexible ligand parts and the enzyme. The shape scoring function determined ligand orientation, while final positions were ranked according to the lowest energy values. Discovery studio 3.0. was used for visual inspection of interactions within the active region of the 5-LOX enzyme (142). The results of the performed molecular docking studies were in accordance with the experimental biological data.

Just a few dual COX-2 and 5-LOX inhibitors were involved in clinical trials as anti-inflammatory agents; among them, only licofelone entered phase III, while tenidap was withdrawn due to hepatotoxicity (143). Although these compounds have not been registered yet, they might represent a worthy therapeutic alternative to classical NSAIDs in the treatment of various inflammatory conditions and a wide variety of diseases.

Conclusion

Nowadays, CADD approaches form an integral part of the drug discovery process. In general, they are divided into ligand-based and structure-based drug design approaches, while their integration may provide more extensive information in the design of novel therapeutics. LBVS methods are usually combined with molecular docking to identify potential lead molecules from huge compound libraries as promising starting points for further ligand optimization studies. MD simulations offer valuable insights into protein structure and dynamics, therefore providing a variety of information for further LBDD and SBDD methods. Since the protein undergoes conformational changes upon binding different classes of ligands, utilizing MD simulation may be crucial in defining the appropriate biding site for a molecular docking study. Furthermore, the integration of 3D-QSAR and molecular docking methods in rational drug design presents a beneficial strategy for the development of highly predictive models. 3D-QSAR models are generated on the basis of virtually predicted bioactive conformations, enabling more trustworthy results of the structure-activity relationship analysis. Finally, the results obtained through applications of various CADD methods may be used for structural modification and design of novel compounds, as well as for guiding experimental studies. Both computational and experimental methods are complementary approaches which have important roles in drug discovery. The rationalization of the drug design process combining these methods will result in deeper and more innovative research of novel potential therapeutics. This review provided a brief introduction to computational approaches and their uses to identify potential drug candidates that might be used as future therapeutics for neuropsychiatric and inflammatory diseases.

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Metode kompjuterski potpomognutog dizajniranja lekova u istraživanju novih potencijalnih terapeutika za neuropsihijatrijske i inflamatorne bolesti

Milica Radan, Jelena Bošković, Vladimir Dobričić, Olivera Čudina i Katarina Nikolić*

Univerzitet u Beogradu - Farmaceutski fakultet, Katedra za farmaceutsku hemiju, Vojvode Stepe 450, 11000 Beograd, Srbija

Autor za korespodenciju: dr Katarina Nikolić, e-mail: knikolic@pharmacy.bg.ac.rs

Apstrakt

Proces otkrića i razvoja lekova je veoma zahtevan, skup i dugotrajan. Veliki tehnološki napredak u molekularnoj biologiji i kompjuterskim naukama je omogućio primenu metoda kompjuterski potpomognutog dizajniranja lekova (CADD) u različitim fazama procesa otkrića i razvoja lekova. Danas CADD predstavlja efikasnu i nezamenljivu alatku, koja se široko koristi u medicinskoj hemiji za racionalni dizajn i sintezu novih jedinjenja. U ovom preglednom radu biće prikazani CADD pristupi koji se najčešće koriste od procesa identifikacije *hit* jedinjenja do optimizacije *lead* jedinjenja. Pored toga, biće predstavljeni različiti aspekti u dizajnu višeciljnih liganada za neuropsihijatrijske i inflamatorne bolesti. Pokazano je da su ova jedinjenja veoma efikasna u lečenju složenih bolesti zbog veće efikasnosti i manje neželjenih efekata koje izazivaju. Antipsihotici koji deluju preko aminergičnih G-protein spregnutih receptora (GPCR), posebno preko dopaminskih D_2 i serotoninskih $5\text{-}HT_{2A}$ receptora, predstavljaju najbolju opcija za lečenje različitih simptoma povezanih sa neuropsihijatrijskim poremećajima. Pored toga, dizajn i sinteza dualnih inhibitora ciklooksigenaze-2 (COX-2) i 5- lipoksigenaze (5-LOX) takođe predstavlja uspešan pristup u otkrivanju novih antiinflamatornih lekova sa manje neželjenih efekata. Na kraju se može zaključiti da primena CADD metoda u procesu racionalnog dizajniranja lekova pruža značajnu priliku za dalji napredak jer omogućava brzu identifikaciju jedinjenja sa optimalnim polifarmakološkim profilom.

Ključne reči: CADD, 5-HT2A, D2, COX-2, 5-LOX