Synthesis, computational and pharmacological evaluation of novel *N*-{4-[2-(4-aryl-piperazin-1-yl)ethyl]phenyl}-arylamides

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Abstract: Serotonin, or 5-hydroxytryptamine (5-HT), is a biogenic amine most noted as a neurotransmitter, an activator of the utmost subtype family of G-protein-coupled receptors (GPCR). Drugs targeting 5-HT1A and other 5-HT receptors treat central nervous system diseases such as schizophrenia and depression. Recent advances in serotonin receptor structure research gave us several crystal 5-HT1A receptor structures, most notably 5-HT1A bound to the antipsychotic drug aripiprazole (Abilify®). This discovery prompted us to evaluate a series of newly synthesized ligands for serotonergic activity since those arylpiperazine derivatives share minimal general structure with aripiprazole. The results of molecular docking analysis of unsubstituted starting substances encouraged us to propound further modifications of the tail and head parts of the parent molecules to maximize receptor binding affinity. Intrigued by the results of molecular analysis, all foreseen derivatives were synthesized. The pharmacological activity of all nine (**5a** and **6a** are synthesized previously) compounds was assessed by the *in vitro* tests and *in silico* pharmacokinetics predictions for the most promising candidates. All tested ligands have improved affinity compering to parent compounds (**10a** and **11a**), **8b** and **9b** expressed the best pharmacological profile with an improved binding affinity toward serotonin 5-HT1A receptors (*K*i 12.1 and 4.8 nM, respectively).

Keywords: 5-HT1A; aripiprazole; arylpiperazines; molecular docking; binding assay.

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INTRODUCTION

Serotonin (5-HT) mediates a plethora of physiological effects through at least 14 different receptor subtypes: 13 belong to the G-protein-coupled or seven transmembrane-spanning receptor family, and only one is a ligand-gated ion channel. Based on molecular, pharmacological and functional criteria, 5-HT receptors have been classified into seven discrete families (5-HT1-7).[1] The 5-HT1A receptors are connected with mood disorders (anxiety, depression), cognition and pain modulation. After decades of research in this field, there is continuing interest in developing new chemical entities capable of 5-HT1A receptor activation or blockade.[2] 5-HT1A receptors are also a promising target for alleviating extrapyramidal side effects (EPS) and cognitive/affective disorders caused by either antipsychotic or Parkinson's disease therapy.[3]

N-Arylpiperazine-containing ligands are a large class of chemical compounds with various biological activities, such as antimicrobial, antiviral and anticancer properties and adrenergic and serotonin receptor inhibition.[4-8] Arylpiperazine derivatives are known to bind monoamine receptors, including 5-HT receptors. The general formula is Ar–piperazine–linker–terminal fragment, and suitable modifications of either Ar, linker or terminal segment, can lead to selective or nonselective compounds.[9] The high affinity of these systems to 5-HT receptors stems from the basic nitrogen atom of the piperazine, which can form strong interactions with the conserved acidic amino acids in the GPCR transmembrane domain of these proteins.[10] Chained arylpiperazines (CAPs) have established their position as favourable scaffolds for 5-HT1A receptor binding. Further CAP studies evaluated the length and flexibility of the alkyl chain at the *N*4. In contrast, the influence of introduced amide group is controversial. One study suggests that amide group can stabilize the ligand-receptor complex, whereas others suggest little or no impact on receptor binding.[11,12]

The design of CAPs became the standard approach in drug development, especially for diseases with complex pathophysiology. An aryl group attached to the nitrogen atom of piperazine is substituted phenyl or a heteroaromatic system. The other terminus often contains an amide or has an imide function, but it may be phenyl or another aromatic group. In many series of arylpiperazine ligands, the alkyl chain consists of two to four methylene units; however, groups other than methylene ones (heteroatoms, carbonyl, an amide fragment or multiple bonds) have also been introduced to the spacer. Therefore, investigations within active compounds consist of structural modifications of all the ligand fragments.[13]

In our study on the effect of the introduction of various moieties in *N*-{[2-(4--phenylpiperazin-1-yl)ethyl]phenyl}-arylamides on their binding affinity for the 5-HT1A receptor has been explored.[14] Results of that discovery inspired us to design a series of arylpiperazine derivatives.[15] The main focus of current modifications was on terminal amide moiety (introduction of hydroxyl group) and aryl-

piperazine part (introduction of 2,3-dichloro and methoxy groups) since proposed ligands share minimal general shape with aripiprazole (Fig. 1). Graph representation of the dissection of aripiprazole into four units crucial for the affinity towards 5-HT1A receptor and their incorporation into the structure of the newly synthesized compounds are: a) phenylpiperazine moiety plays a key role in binding at the active site; b) substitution of both electron-withdrawing and electron-donating groups at the ortho position and substitution of chloro group in the meta position of phenyl ring; c) two to five carbon spacer; d) amide group incurporated as part of the terminal fragment. After detailed molecular docking analysis, seven new *N*-{4-[2-(4-aryl-piperazin-1-yl)ethyl]phenyl}-arylamides (**5b** and **c**–**9b**) together with **5a** and **6a** (synthesised previously)[16] are subjected to pharmacological evaluation and *in silico* pharmacokinetics predictions for the most promising candidates.
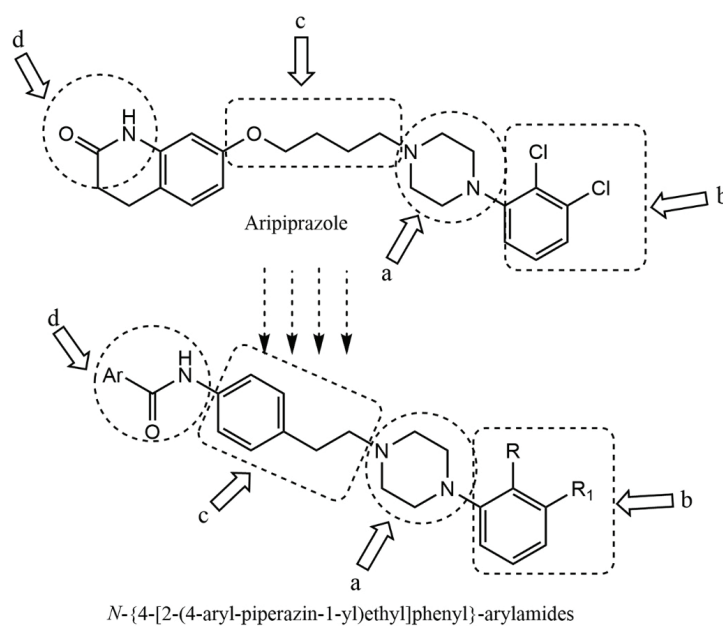

Fig. 1. Rational design of novel arylpiperazines.

EXPERIMENTAL

General information

The reagents and solvents used in this work were obtained from Alfa Aesar or Sigma–Aldrich and used without further purification. Solvents were routinely dried over anhydrous Na_2SO_4 before evaporation. ^{1}H- and ^{13}C-NMR spectra were recorded on: ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz), Gemini 2000 spectrometer; and ^{1}H-NMR (500 MHz) and ^{13}C-NMR (126 MHz), Bruker Avance III spectrometer. Chemical shifts (δ) are reported in ppm from tetramethylsilane (TMS) as an internal standard in deuterated chloroform ($CDCl_3$)

or dimethyl sulfoxide (DMSO-d_6); all coupling constants (*J* values) are reported in Hz; high-resolution mass spectra (HRMS) were obtained with a heated ESI (HESI)-LTQ Orbitrap XL spectrometer. Melting points were obtained by a Boetius PHMK apparatus (VEB Analytic, Dresden, Germany) at a heating rate of 4 °C/min and are uncorrected. IR spectra were recorded using a Thermo Scientific Nicolet 6700 Fourier-transform spectrometer operated in the ATR mode. For analytical thin-layer chromatography (TLC), Polygram SIL G/UV254 plastic-backed thin-layer silica gel plates were used (Macherey-Nagel, Germany).

Analytical and spectral data of the synthesized compounds are given in Supplementary material to this paper.

General procedure for the synthesis of 2-(4-nitrophenyl)-1-(4-arylpiperazin-1-yl)ethane-1-ones (2b and c)

Arylpiperazine (52 mmol), 4-nitrophenylacetic acid (**1**), (52 mmol) and Et$_3$N (57.2 mmol) were dissolved in 170 mL dry *N,N*-dimethylformamide (DMF). The obtained solution was cooled to 10 °C, and propylphosphonic acid anhydride (PPAA) solution (72.7 mmol, 50 % solution in DMF) was added dropwise, and the reaction mixture was stirred for 24 h at room temperature. The reaction was monitored by TLC. The reaction mixture was poured onto ice/water. The pH of the suspension was adjusted to 8 with a 10 % Na$_2$CO$_3$ solution (from the acidic range). The precipitate was filtrated, washed with water, and crystallized from acetone to give the expected product.

General procedure for synthesis 1-(4-nitrophenethyl)-4-arylpiperazines (3b and c)

To a suspension of **2b** or **2c** (46.1 mmol) in 300 mL dry tetrahydrofuran (THF), a diborane solution (1 M in THF, 118 mL, 118 mmol) was added dropwise at 0 °C. When the addition of diborane was completed reaction mixture was progressively heated. After the spontaneous boiling stop, the reaction mixture was refluxed for an additional 2 h. After cooling to room temperature, water (35 mL) was slowly added, followed by 5.5 M HCl (70 mL). The reaction mixture was refluxed for another 60 min and was left to cool down to 25 °C. The reaction mixture was evaporated, and the resulting fluid was treated with 10 % NaHCO$_3$ solution to pH 8. The product was extracted with ethyl acetate, washed with water and brine and evaporated. The resulting 4-nitrophenethyl-piperazines were purified by silica gel column chromatography using a gradient of methanol (0–5 %) in dichloromethane.

General procedure for synthesis 4-(2-(4-arylpiperazin-1-yl)ethyl)anilines (4b and c)

Raney/Ni (195 mg) was added, in portions, to a stirred mixture of hydrazine hydrate (32.5 mm), ethanol (26 mL), (6.5 mm) of compound **3b** or **3c** (6.5 mm), and 1,2-dichloroethane (12mL). Stirring was continued at room temperature until the mixture became colorless and then was heated at 50 °C for 40 min. The resulting mixture was filtrated through Celite, and the solvent was removed under reduced pressure. The resulting anilines were used for further synthesis without purification.

General procedure for synthesis N-(4-(2-(4-phenylpiperazin-1-yl)ethyl)phenyl)arylamides (5b and c–9b)

A solution of **4b** or **4c** (1.77 mmol), triethylamine (4.44 mmol, 0.62 mL), the corresponding carboxylic acid (1.77 mmol), and PPAA (1.95 mmol, 1.14 mL, 50 % solution in DMF) in dry DMF (10mL) was stirred at room temperature overnight. The mixture was poured into ice/water. Organic layers were separated and evaporated. The resulting *N*-{3-[2-(4-arylpiperazin-1-yl)ethyl]phenyl}arylamides were purified by silica gel column chromatography using a gradient of methanol (0–5 %) in dichloromethane.

Binding assays

The affinity of the synthesized compounds towards 5-HT1A was determined by radio-ligand competition binding assays. The assays were performed using crude cell membrane homogenates obtained from HEK cells stably transfected with human 5-HT1A receptor and the 5-HT1A specific radioligand [3H]-8-OH-DPAT (obtained from PerkinElmer, NET929250UC). Membrane suspension was incubated with 1 nM [3H]-OH-DPAT and various concentrations of the test compound in 25 mM Tris-HCl, pH 7.4 buffer containing 120 mM NaCl, 5 mM KCl at room temperature for 60 min. Non-specific binding was determined in the presence of 10 µM of serotonin. The reaction was terminated by rapid filtration using Whatman GF/B glass-fibre filters, pre-soaked in 0.3 % polyethyleneimine, and a 48-channel harvester (Biomedical Research and Development Laboratories, Gaithersburg, MD, USA) followed by washing four times with ice-cold Tris-HCl buffer. Filter-bound radioactivity was quantified by liquid scintillation counting. At least three separate experiments in triplicate were performed to determine inhibitory constant (K_i) values. The data were analyzed by GraphPad Prism, version 4.1 (GraphPad Inc., La Jolla, CA, USA).

Absorption, distribution, metabolism, excretion and toxicity (ADMET) analysis

To predict absorption, distribution, metabolism and excretion (ADME) qualities of tested ligands, we used the SwissADME webserver (www.swissadme.ch).[17] Toxicology prediction was done through Pro Tox-II virtual lab server for the prediction of toxicities of small molecules (https://tox-new.charite.de/protox_II/index.php?site=home).[18] Ligand structures were provided as SMILES using ChemDraw.

Docking simulations

Docking simulations were done in Maestro Suite software.[19] 3D model of the 5-HT1A receptor with bound aripiprazole (PDB Code 7E2Z) was obtained from the GPCR database.[20] 2D structures of ligands were drawn in ChemDraw software and prepared for docking in Maestro software using default LigPrep procedures.

Induced fit docking (IFD) simulation using standard sampling protocol and default values, was carried out for prepared receptor model and selected ligands.[21] Bind site was defined, based on bound aripiprazole and centered on ASP 116 residue. The inner grid box was set to 10 Å ×10 Å ×10 Å and the outer box size according to the size of each tested ligand. Grid spacing was set to 1 Å. Obtained docking structures were examined and selected for further analysis based on the number of receptor-ligand interactions and calculated post docking MM–GBSA energy.

Molecular dynamics simulations

Molecular dynamics (MD) simulations were performed using the Schrodinger Desmond software package.[19] Docking poses selected for MD were prepared for simulation by embedding the protein–ligand complex into the POPC membrane bilayer using the Desmond system builder module. Protein was oriented in the membrane according to the data from the Orientations of Proteins in Membranes (OPM) server (http://opm.phar.umich.edu/). The entire system was solvated with a TIP3P explicit water model and neutralized *via* counter ions and salt solution of 0.15 M KCl. We used OPLS 2003 forcefield to calculate the interactions between all the atoms. For the calculation of the long-range Coulombic interactions, particle-mesh Ewald (PME) method was used, with the cut-off radius of 9 Å for the short-range van der Waals (VdW) and electrostatic interactions.

During the simulation, a constant temperature of 310 K and a pressure of 1.01235 bar were maintained, using the Nose–Hoover thermostat, and the Martyna Tobias Klein method.

100 ns MD simulation with 2.0 fs step for each complex was performed and the collected trajectory was used in the MD analysis to assess the docking pose and protein-ligand interactions stability.

RESULTS AND DISCUSSION

Chemistry

In Scheme 1, the general synthetic route towards modified derivatives (**5b** and **c**–**9b**) is presented. Briefly, acylation of the appropriate arylpiperazine by 4-nitrophenylacetic acid **1** afforded amides **2b** and **c**, which upon reduction by B_2H_6, provided corresponding amines **3b** and **c**. Further reduction of the nitro group in **3** with Ra/Ni, followed by *N*-acylation of **4** with aryl acids, yielded final products in high overall yields (59–73 %). All compounds were characterized spectroscopically.

b: R=OCH₃, R₁=H;
c: R=Cl, R₁=Cl.
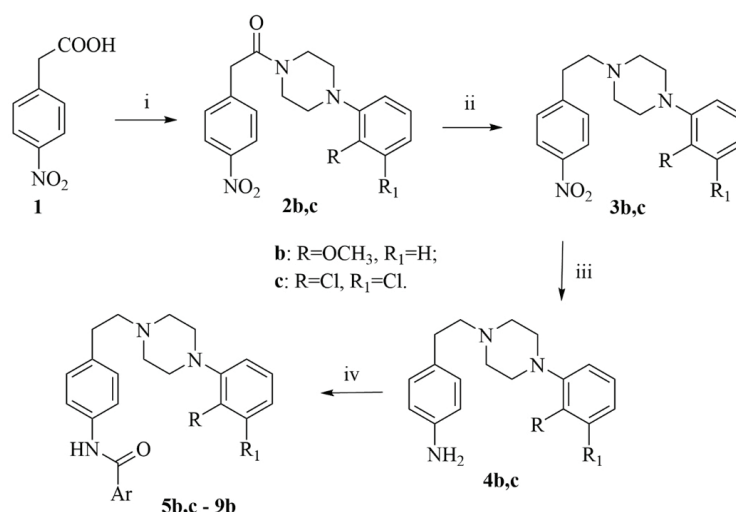
Scheme 1. Reagents and conditions for the synthesis: *i*) arylpiperazine, Et₃N, PPAA, DMF, r.t.; *ii*) B_2H_6, THF, 0 °C for 6 h, r.t. for 1 h, then reflux for 2 h; *iii*) Ra/Ni, NH₂NH₂, EtOH, 1,2-dichloroethane; *iv*) ArCO₂H, Et₃N, PPAA, DMF, r.t. (ArCO₂H: 2-hydroxynicotinic acid for the preparation of **5b** and **c**; 6-hydroxynicotinic acid for the preparation of **6b** and **c**; 2-(4-hydroxyphenyl)acetic acid for the preparation of **7b**; 3-hydroxybenzoic acid for the preparation of **8b**; 4-hydroxybenzoic acid for the preparation of **9b**).
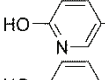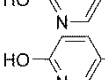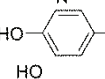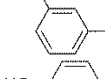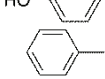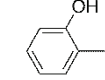
Detailed spectral data for all synthesized compounds are given in the Supplementary material to this paper (Figs. S-1–S-22; for phenyl precursors and ligands **5a** and **6a**, please see ref. 14 and 16).

Biological evaluation

The affinity of the compounds, depicted in Table I, towards 5-HT1A was determined in radioligand competition binding assays using [³H]-8-OH-DPAT.

As presented in Table I, all nine ligands (**5a–c–9b**) had an enhancement in affinity for 5-HT1A receptors compared to parent compounds (**10a** and **11a**). Scrutiny of the obtained experimental affinity values revealed that the most pronounced increase was recorded with ligand **9b**, followed by **8b**, **5b** and **7b**. For other ligands, the enhancement of the affinity is from temperate to slight (compared to hydroxy ligand **11a**, the more active of the two parent compounds), and the decreasing order is **6b** > **5a** > **5c** > **6c** > **6a**. Analyzing the relationship between the experimental affinity values of the new ligands and aripiprazole, ligand **9b** stood out with affinity in the same range as a commercial drug.

TABLE I. 5-HT1A affinity for newly synthesized and parent compounds and commercial drug, aripiprazole; data for parent compounds **10a** and **11a** taken from Ref. 14; data for aripiprazole taken from Ref. 22

No.	Ar	R	R_1	$Ki\pm SEM$ / nM
5a		H	H	182.3±7.0
5b		OCH_3	H	24.2±3.1
5c		Cl	Cl	392.6±9.2
6a		H	H	453.9±8.0
6b		OCH_3	H	117.3±4.3
6c		Cl	Cl	286.6±5.1
7b		OCH_3	H	46.8±1.9
8b		OCH_3	H	12.1±1.2
9b		OCH_3	H	4.8±0.5
10a		H	H	2662
11a		H	H	575
Aripiprazole				5.6±0.8

The Ki values indicate that the influence of substitution on phenyl piperazine on the 5-HT1A receptors binding affinity is pronounced (compared to parent compounds **10a** and **11a**).

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The introduction of 2,3-dichloro and methoxy group and hydroxyl group (regardless of the position) in the amide group led to an increase in the affinity of the 5-H1A receptor, especially pronounced in the case of ligands with sizeable affinity gains, **8b** and **9b**.

Docking simulations and molecular dynamics

Docking analysis was done using aripiprazole-bound 5-HT1A receptor-Gi protein complex receptor model (PDB: 7E2Z)[20] and selected ligands (Table I). Receptor binding site was determined using bound aripiprazole position. All ligands were protonated at physiological pH 7.4. Induced fit docking procedure using standard sampling procedure was carried out and results were sorted based on docking score and number of key receptor-ligand interactions.

5-HT1A receptor binding site can be divided into two distinctive parts. Orthosteric binding site (OBS) that is located deep inside the binding cavity, between transmembrane helices 3 and 5 and extended bind pocket (EBP) bordering extracellular space and formed in part by receptor extracellular loops. OBS is responsible for binding of arylpiperazine part of the ligand and correct ligand orientation in the receptor bind site.

Docking results and MD simulations of compounds **5a** and **6a** showed well--established pattern of aryl-piperazine binding to the 5-HT1A receptor. The aryl part of the ligand binds to the OBS inside the receptor binding cavity and the linker–terminal part fits into the EBP bordering extracellular space. Key interactions in the OBS, with Asp116 (salt bridge) and Phe361 and 362 (aromatic, edge--to-face, C–H···π), provide correct ligand orientation inside the receptor binding cavity and binding of linker–terminal part in the EBP.

Key interactions in the EBP depend on linker–terminal length, shape, size and flexibility, and can further amplify (or diminish) ligand affinity. In the case of compound **5a**, key interactions in the EBP are with Tyr96, Gln97, Asn386 and Asn387, while **6a** forms interaction with Tyr96 and Asn100 (for details, see the Supplementary material, Fig. S-22).

The introduction of 2-methoxy and 2,3-dichloro groups in the aryl part of starting compounds should lead to an increase in receptor affinity through the amplification of existing aromatic interactions with Phe361 and 362 and the establishment of new interactions with various amino acid residues in OBS.[23]

Experimental results show an increase in affinity in compounds **5b**, **6b** and **6c**, while compound **5c** had a slight affinity drop. Docking and MD results revealed that in the case of **5b**, **6b** and **6c**, original key interactions were preserved, and additional interactions were formed, with Gln97 and Asn386 (for **6b** and **c**) and Tyr390 (for **5b**). However, compound **5c** didn't perform as expected. Obviously, the addition of two chlorine atoms in the aryl part of the molecule and an intermolecular hydrogen bond in the linker–terminal fragment caused increased

ligand rigidity and size that led to a decrease in binding affinity (for details, see the Supplementary material, Figs. S-23 and S-24).

Since in both series (**5a**–**c** and **6a**–**c**), ligands with 2,3-dichloro substituent performed worse than expected, compared to 2-methoxy counterparts, the decision was to keep 2-methoxy moiety fixed for further synthesis, but to alter linker–terminal part, to obtain compounds with increased receptor affinity. With that in mind, compounds **7b**, **8b** and **9b** were synthesized and tested.

Molecular docking and dynamics gave us the following results. In the case of compound **8b**, we have key interactions with Asp116, Phe361, 362 and Cys120 in the OBS, together with Tyr96, Gln97 and Asn386 in the EBP. Interactions of **9b** formed in OBS are the same as **8b**. In the EBP, key interactions are with Tyr96, Gln97, Asn100 and Asn386 (Figs. 2 and 3). The indicated makes **9b** the best receptor affinity compound among newly synthesized compounds, followed by **8b** and **5b**. Compound **7b** shows a drop in affinity because the elongation of the linker-terminal part reached the maximum allowed length that can bind in EBP (for details, see the Supplementary material, Fig. S-25).
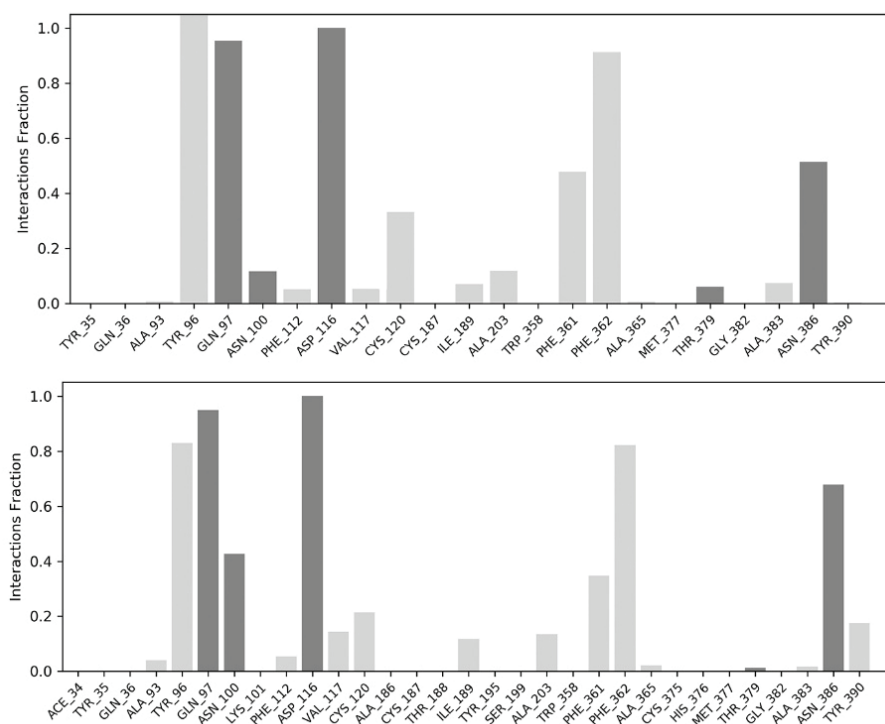

Fig. 2. Diagram of key receptor – **8b** (top) and **9b** (bottom) interactions observed during 100 ns molecular dynamics. Aromatic interactions are shown light gray, while hydrogen bonds are dark gray. Interactions maintained for 20 % or more of total MD time are considered crucial.
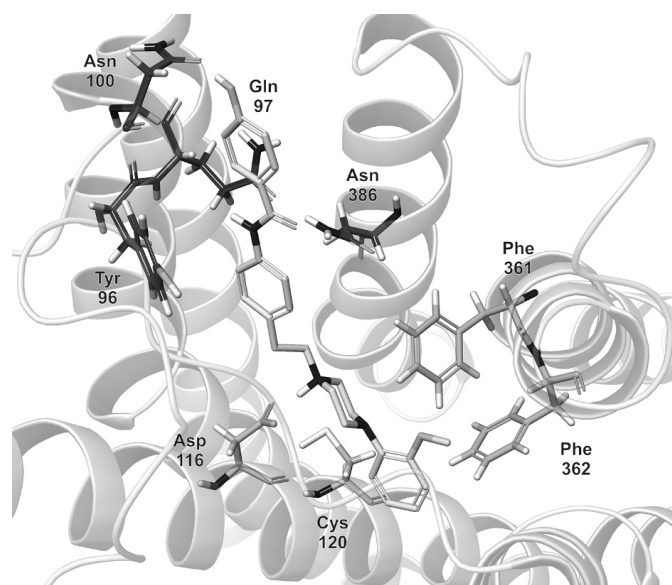
Fig. 3. 3D model of compound **9b** (light gray) docked into 5-HT1A bind site. Only key OBS (light gray) and EBP (dark gray) amino acid residues are shown for clarity.

ADMET prediction

Rejection of potential drugs at later stages of drug development may cause substantial financial loss; therefore, it is reasonable that pharmacokinetic studies have been highlighted as early predictors of important potential drug parameters. To account for these characteristics, we used ADMET prediction. Results of the most promising compounds, **8b** and **9b**, together with aripiprazole, are displayed (Fig. 4). Predicted ADME results are favorable and show no potential problems. Solubility, gastrointestinal absorption and crossing the blood–brain barrier (BBB) are on par with aripiprazole.
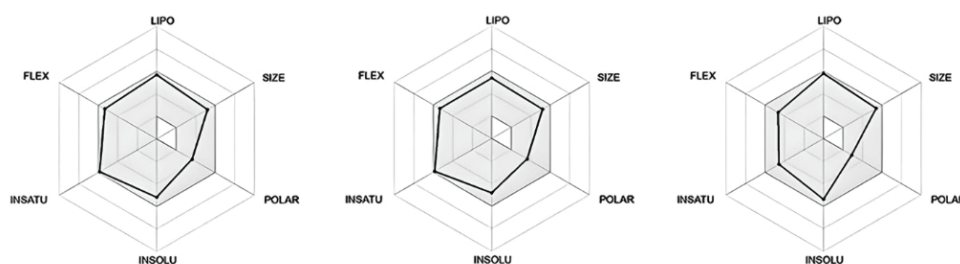

Fig. 4. Radar representation of ADME properties for compounds **8b** (left), **9b** (middle) and aripiprazole (right). For details, see the Supplementary material, Figs. S-26–S-28.

Toxicity calculations were negative for compound **9b**, but **8b** has a 0.6 chance of being immunotoxic. Compared to aripiprazole, this is not the reason for automatic exclusion as a potential drug candidate because aripiprazole shows the same result, with a greater probability (0.98, for details, see the Supplementary material, Figs. S-26–S-28).

CONCLUSION

In summary, we used computer-aided rational drug design to amplify the receptor affinity of starting compounds to levels comparable with aripiprazole. From nine tested *N*-{4-[2-(4-aryl-piperazin-1-yl)ethyl]phenyl}-arylamides, **9b** had Ki = 4.7 nM, closely followed by **8b** (Ki = 12.06nM). Both compounds are 2-OMe derivatives of the parent phenyl ligands with lower receptor affinity. Introduction of the 2-OMe group in the aryl part of the ligand strengthens aromatic interactions with Phe361 and 362 residues, establishing additional hydrogen bond with Cys120. The linker–terminal part of the compound is a material segment in obtaining high receptor affinity ligands because of the additional interaction with the key amino acid residues of EBP. According to our findings, Gln97 and Tyr96 are the key residues in EBP, shared between all tested compounds (and aripiprazole) and followed by Asn386 and Asn100. Flexible ligands had better affinity than rigid ones. The initial size of the compounds was well judged as elongation of the molecule in the case of **7b** caused a drop in affinity compared with **9b**. Predicted ADMET characteristics for both compounds show a preferable profile for drug candidates.

The results for the most active compound from series **9b** and aripiprazole (4.8 and 5.6 nM) suggest that the presented modification strategies resulted in candidates that confirm the effectiveness of the predictive-experimental correlation approach and in our opinion compound **9b** presents a good candidate for further testing.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/12577, or from the corresponding author on request.

ИЗВОД

СИНТЕЗА, КОМПЈУТЕРСКА АНАЛИЗА И ФАРМАКОЛОШКА ЕВАЛУАЦИЈА НОВИХ
N-{4-[2-(4-АРИЛПИПЕРАЗИН-1-ИЛ)ЕТИЛ]ФЕНИЛ}-АРИЛАМИДА

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Серотонин, 5-хидрокситриптамин (5-HT), је биогени амин који је најпознатији као
неуротрансмитер, активатор највеће породице подтипова G-протеин-куплованих рецеп-
тора (GPCR). Лекови, чије су мете 5-HT1A и други 5-HT рецептори, се користе у лечењу
болести централног нервног система, као што су шизофренија и депресија. Недавни
напредак у истраживању структуре серотонинских рецептора се огледа у неколико крис-
талних 5-HT1A рецепторских структура, од којих је најзначајнија она код које је за
5-HT1A везан антипсихотични лек, арипипразол. Ово откриће нас је мотивисало да про-
ценимо серотонергичку активност серије новосинтетизованих лиганада, пошто ти дери-
вати арилпиперазина са арипипразолом деле минималну општу структуру. Резултати
молекулске анализе пристајања несупституисаних лиганада подстакли су нас да предло-
жимо даље модификације репа и делова главе полазних молекула, како би афинитет
везивања за рецептор био израженији. Заинтригирани резултатима молекулске анализе,
сви предвиђени деривати су и синтетисани. Фармаколошка активност свих девет једи-
њења је процењена *in vitro* тестовима, док је за најперспективнија једињења урађено *in
silico* фармакокинетичко предвиђање. Сва тестирана једињења имају побољшани афини-
тет у поређењу са полазним (**10а** и **11а**), док се **8б** и **9б** истичу најбољим фармако-
лошким профилом и афинитетом везивања према серотонинским 5-HT1A рецепторима
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