OPHTHALMOLOGY

VIRTUAL AND EXPERIMENTAL SCREENING OF NEW MELATONIN BIOISOSTERES FOR THE TREATMENT OF GLAUCOMA

Babkov D.A.[1],
Taran A.S.[1, 2],
Shevchenko A.A.[2],
Naumenko L.V.[1],
Zhukovskaya O.N.[3],
Efremov A.M.[4],
Bezsonova E.N.[4],
Lozinskaya N.A.[4],
Spasov A.A.[1,2]

[1] Volgograd State Medical University (Pavshikh Bortsov square 1, Volgograd 400131, Russian Federation)
[2] Volgograd Medical Scientific Center (Pavshikh Bortsov square 1, Volgograd 400131, Russian Federation)
[3] Research Scientific Institute of Physical and Organic Chemistry, Southern Federal University (Stachki Ave. 194/2, Rostov-on-Don 344090, Russian Federation)
[4] Lomonosov Moscow State University (Leninskie Gory 1, Moscow 119991, Russian Federation)

Corresponding author:
Denis A. Babkov,
e-mail: dababkov@volgmed.ru

ABSTRACT

Background. *Melatonin is an endogenous regulator of intraocular pressure (IOP), but its effectiveness as a drug for glaucoma treatment is limited.*
The aim of the study. *To develop and to validate a virtual screening method to identify bioisosteric analogs of melatonin that are promising for study as agents that reduce intraocular pressure.*
Results. *A database containing structural and experimental affinity information for 48 individual reference compounds was created. Risk assessments for mutagenic, carcinogenic, irritant and reproductive toxicity were performed in DataWarrior based on substructural analysis and identification of fragments that are markers of relevant toxicity. A virtual screening of 2457 structures was carried out and 25 compounds from the selected ones were experimentally studied for their effect on intraocular pressure (IOP) in intact rats. 10 of the 25 prioritized compounds were found to significantly reduce IOP; compound RU-398 reduced IOP by 40 %, K-165 – by 40.9 %, and RU-615 reduced glaucoma by 33.3 %.*
Conclusion. *The effectiveness of virtual screening after experimental validation was 40 %. The identified active compounds are promising for further study and development as the agents for the treatment of glaucoma.*

Key words: *isostere, melatonin, glaucoma, intraocular pressure, virtual screening*

Received: 12.05.2023
Accepted: 15.01.2024
Published: 26.03.2024

For citation: Babkov D.A., Taran A.S., Shevchenko A.A., Naumenko L.V., Zhukovskaya O.N., Efremov A.M., Bezsonova E.N., Lozinskaya N.A., Spasov A.A. Virtual and experimental screening of new melatonin bioisosteres for the treatment of glaucoma. *Acta biomedica scientifica*. 2024; 9(1): 116-128. doi: 10.29413/ABS.2024-9.1.12

ВИРТУАЛЬНЫЙ И ЭКСПЕРИМЕНТАЛЬНЫЙ СКРИНИНГ НОВЫХ БИОИЗОСТЕРОВ МЕЛАТОНИНА ДЛЯ ЛЕЧЕНИЯ ГЛАУКОМЫ

Бабков Д.А.[1], Таран А.С.[1,2], Шевченко А.А.[2], Науменко Л.В.[1], Жуковская О.Н.[3], Ефремов А.М.[4], Безсонова Е.Н.[4], Лозинская Н.А.[4], Спасов А.А.[1,2]

[1] ФГБОУ ВО «Волгоградский государственный медицинский университет» Минздрава России (400131, г. Волгоград, пл. Павших Борцов, 1, Россия)

[2] ГБУ «Волгоградский медицинский научный центр» (400131, г. Волгоград, пл. Павших Борцов, 1, Россия)

[3] Научно-исследовательский институт физической и органической химии, ФГАОУ ВО «Южный федеральный университет» (344090, г. Ростов-на-Дону, просп. Стачки, 194/2, Россия)

[4] ФГБОУ ВО «Московский государственный университет имени М.В. Ломоносова» (119991, г. Москва, Ленинские горы, 1, Россия)

Автор, ответственный за переписку:
Бабков Денис Александрович,
e-mail: dababkov@volgmed.ru

РЕЗЮМЕ

Обоснование. *Мелатонин является эндогенным регулятором внутриглазного давления (ВГД), но эффективность его применения в качестве лекарственного средства при глаукоме ограничена.*

Цель исследования. *Разработка и валидация метода виртуального скрининга для выявления биоизостерических аналогов мелатонина, перспективных для изучения в качестве средств, снижающих внутриглазное давление.*

Результаты. *Была создана база данных, содержащая информацию о структуре и экспериментальном сродстве 48 отдельных эталонных соединений. Оценка риска мутагенной, канцерогенной, раздражающей и репродуктивной токсичности была выполнена в DataWarrior на основе подструктурного анализа и идентификации фрагментов, которые являются маркерами соответствующей токсичности. Был проведён виртуальный скрининг 2457 структур и 25 соединений из числа отобранных были экспериментально изучены на предмет их влияния на ВГД у интактных крыс. Было обнаружено, что 10 из 25 приоритизированных соединений способны значимо снижать ВГД; соединение RU-398 снижало уровень ВГД на 40 %, K-165 – на 40,9 %, а RU-615 снижало глаукому на 33,3 %.*

Заключение. *Результативность виртуального скрининга после экспериментальной валидации составила 40 %. Выявленные активные соединения являются перспективными для дальнейшего изучения и разработки в качестве средств для лечения глаукомы.*

Ключевые слова: *изостер, мелатонин, глаукома, внутриглазное давление, виртуальный скрининг*

Статья поступила: 12.05.2023
Статья принята: 15.01.2024
Статья опубликована: 26.03.2024

Для цитирования: Бабков Д.А., Таран А.С., Шевченко А.А., Наменко Л.В., Жуковская О.Н., Ефремов А.М., Безсонова Е.Н., Лозинская Н.А., Спасов А.А. Виртальный и экспериментальный скрининг новых биоизостеров мелатонина для лечения глакомы. *Acta biomedica scientifica*. 2024; 9(1):116-128. doi: 10.29413/ABS.2024-9.1.12

INTRODUCTION

Glaucoma is a multifactorial chronic progressive optical neuropathy characterised by damage to the optic nerve and retinal nerve fibre layer, which can lead to irreversible loss of peripheral or central vision [1]. Currently, glaucoma is a collective term for a group of neurodegenerative processes affecting the entire visual pathway, characterised by progressive, irreversible destruction and death of retinal ganglion cells [2].

One promising class to look for antiglaucoma drugs is melatonin analogues. Melatonin is the hormone responsible for regulating circadian and seasonal rhythms. This molecule was first discovered and described in the pineal gland, but it is now known to be synthesised in many tissues of the body, including the eye and ocular structures, particularly the retina, iris, ciliary body, lens and lacrimal gland, where it regulates important processes. Its effect on intraocular pressure (IOP) is mediated through MT_1, MT_2 and the putative melatonin receptor MT_3 located in the ciliary body, resulting in a decrease in chloride outflow from non-pigmented epithelial cells by increasing cyclic adenosine monophosphate. A decrease in this outflow causes a decrease in the production of aqueous moisture and finally a decrease in IOP [3].

The search for new melatonin analogues with greater metabolic stability and duration of action is an active area of ongoing study. Compounds of various structures with affinity for melatonin receptors have been described [4].

THE AIM

To develop and to validate a virtual screening method to identify bioisosteric analogs of melatonin that are promising for study as agents that reduce intraocular pressure.

METHODS

Compliance with Ethical Standards

The experimental work was carried out in accordance with the requirements of GOST ISO/IEC 17025-2009, GOST R ISO 5725-2002 and the rules of laboratory practice in conducting preclinical studies in the Russian Federation in accordance with GOST R 33044–2014 'Principles of Good Laboratory Practice' and Order of the Ministry of Health of the Russian Federation № 199n dated April 1, 2016 «About the approval of the rules of good laboratory practice», in compliance with Directive 2010/63/EU of the European Parliament and Council of the European Union of September 22, 2010 concerning the protection of animals used for scientific purposes.

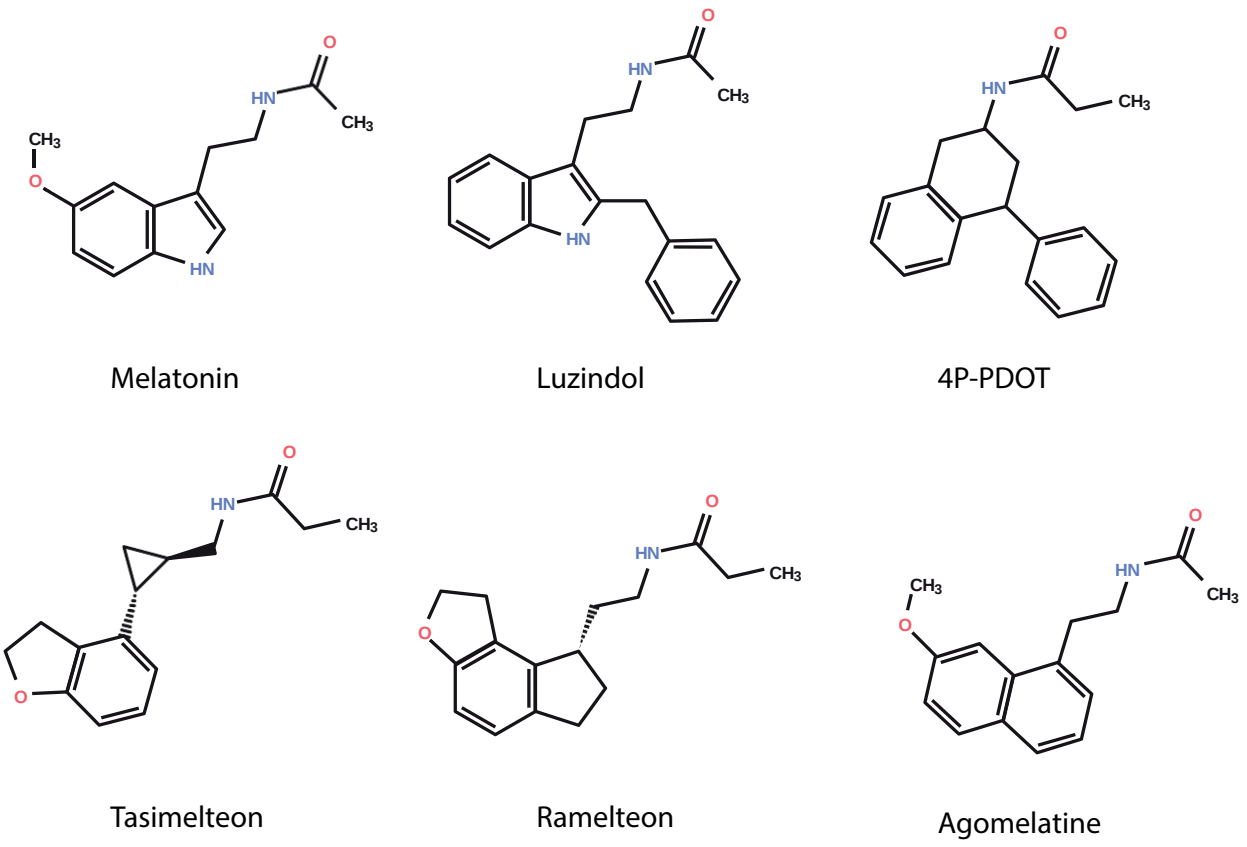


FIG. 1.
Melatonin and some of its bioisosters

Data preparation

In the preparation of the structure database of compounds available for study, duplicates, salt residues were removed and structures were standardised. A database containing 2457 investigated compounds was created.

Reference structures

Information from the IUPHAR pharmacological database was used as a source of validated ligands with affinity for human type 1 and type 2 melatonin receptors (MT_1 and MT_2) [5].

Molecular properties calculation

For each compound, characteristics related to drug similarity were calculated, including molecular weight *M*, lipophilicity index *ClogP*, number of donors and acceptors of hydrogen bonds H_{donors} and $H_{acceptors}$, number of halogen atoms $N_{halogens}$, number of heavy atoms N_{heavy}, polar surface area *PSA* (polar surface area). All the described calculations were performed using the OSIRIS DartaWarrior program (Idorsia Inc., Switzerland) [6].

Assessment of substructural markers of specific toxicity

Risk assessment of mutagenic, carcinogenic, irritant properties and reproductive toxicity was performed in DataWarrior based on substructural analysis and identification of fragments known to be markers of relevant types of toxicity.

DrugScore integral measure of drug eligibility

DrugScore is an integral index including substructural drug similarity, lipophilicity, solubility, molecular weight and risk of specific toxicity (carcinogenicity, mutagenicity, local irritant and reproductive toxicity). The calculation was performed according to [6].

Calculation of corneal permeability to compounds

The calculation of the corneal permeability index for *LogPapp* compounds was performed according to two previously published QSAR models [7, 8] using Eqs:

$$LogPapp_1 = -4{,}002 - 0{,}169 \times (H_{acceptors} + H_{donors}) + 0{,}265 \times LogP;$$

$$LogPapp_2 = 4{,}6823 - 0{,}767 \times (Log(PSA)) - 0{,}1346 \times H_{donors} + 3{,}0024 \times N_{halogens}/N_{heavy};$$

$$LogPapp = (LogPapp_1 + LogPapp_2)/2.$$

Molecular similarity calculation

DataWarrior *Flexophore* 3D pharmacophore descriptor was used as molecular descriptor for molecular similarity calculation. Computation of the *Flexophore* descriptor begins by creating a representative set of up to 250 conformers using a self-organisation-based algorithm to construct small rigid fragments of the molecule, which are then joined by considering the likely torsional angles. Atoms of the molecule that could potentially interact with the protein atoms in some way are then detected and classified. The extended MM2 atom typing is used to describe atoms as interaction points. The Tanimoto coefficient served as a quantitative metric of similarity between the studied compounds and the reference compounds. For each compound, the maximum revealed coefficient of molecular similarity according to the pharmacophore descriptor *Max* (*Flexophore*) was considered.

Calculation of the overall prospectivity index

The integral prospectivity score of compound *F* was calculated based on *DrugScore*, calculated *LogPapp* corneal permeability and maximum pharmacophore similarity to *Max*(*Flexophore*) reference standards converted between 0 and 1 with the inflection point of the sigmoid curve at a given parameter boundary value and curve slope and parameter weight according to the table and formula (Table 2):

$$p = 1/[1 + e^{(a \times p + b)}].$$

Intraocular pressure measurement

The study of the effect upon intraocular pressure was performed on mongrel intact rats of both sexes weighing 220–400 g, aged 2 months (Rappolovo husbandry, Leningrad region). All animals were divided into experimental and comparison drug groups with 6 animals in each group. At 9:00 am, baseline IOP in both eyes was measured in animals of all groups. The veterinary tonometer ICARE TonoVet (Finland) for early diagnosis of glaucoma in veterinary medicine was used to determine IOP [9, 10]. After the measurement, the animals of the experimental groups were instilled with 0.4 % aqueous solutions of the studied compounds in the volume of 50 µl into the right eye (test eye). Animals of the comparison drug groups had melatonin (Sigma, USA; pharmaceutical standard) instilled into the test eye. The left eye (control, collateral eye) served to determine the possible resorptive effect. Follow-up IOP measurements in the test and collateral eyes were performed after 60, 120, 180 min.

Data analysis

Chemoinformatic calculations were performed in DataWarrior software (Idorsia Inc., Switzerland). The computational data processing was performed in RStudio 2022.07.1. Statistical processing of experimental data was performed using MS Office software (Microsoft Corp., USA) and Prism 7.0 (GraphPad Software, USA) with Student's *t*-test.

RESULTS

Reference compounds

As a result of searching and processing information of the IUPHAR pharmacological database [5], a database containing information about the structure and experimental affinity of 48 individual reference melatonin isoster compounds was created. These structures were subjected to pharmacophore analysis and used as references in the evaluation of the molecules under investigation as described below.

Search algorithm

The general scheme for assessing the prospectivity of compounds is depicted in Figure 2. In total, the analyzed database contained 2457 individual compounds (Fig. 3). The calculated values of physicochemical characteristics were used to evaluate drug similarity and bioavailability for topical application as eye drops (Fig. 4, 5). Substructural analysis was used to identify markers of specific toxicity (Table 1). Compounds were ranked according to the likelihood of mutagenic, carcinogenic, locally irritating properties and reproductive toxicity into three levels: no risk, low risk and high risk which was considered in the calculation of the *DrugScore* integral drug prospectivity index along with drug similarity characteristics.

Molecular pharmacophore descriptors served as descriptors of the molecules when assessing similarity to reference melatonin receptor agonists; maximum values were considered (Figs. 3, 5). Compounds that, according to at least one descriptor, had similarity to reference antagonists or inverse agonists of MT_1 and MT_2 receptors were screened out (Fig. 6).

The overall *F* prospectivity score consisted of the maximum pharmacophore similarity to the reference standards (factor weight 1.0), with consideration of *DrugScore* drug suitability index (factor weight 0.25) and the calculated corneal permeability *LogPapp* (factor weight 0.25) to account for topical application as eye drops (Table 2). The *F* indicator can take values from 0 (minimum prospectivity) to 1 (maximum prospectivity).

A visualisation of the contribution of pharmacophore affinity to melatonin analogues and calculated *LogPapp* corneal permeability to the overall *F* prospectivity score of is presented in Figure 7. The compounds with $F > 0.85$, ranked according to the comprehensive prospectivity assessment, are summarized in Table 3. They are distinguished by a set of favourable prognostic characteristics: specific types of toxicity (mutagenic, carcinogenic, locally irritating properties and reproductive toxicity) are not expected; the calculated permeability of the *LogPapp* cornea exceeds -5.43; pharmacophore similarity to the reference compounds ranges from 0.81 to 0.91, according to the Tanimoto coefficient.

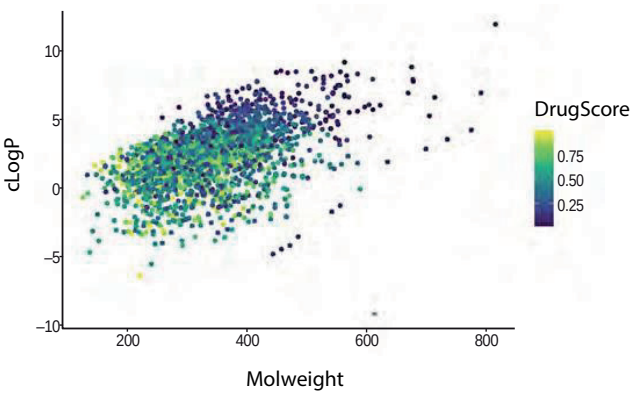


FIG. 3.
Library of analyzed compounds

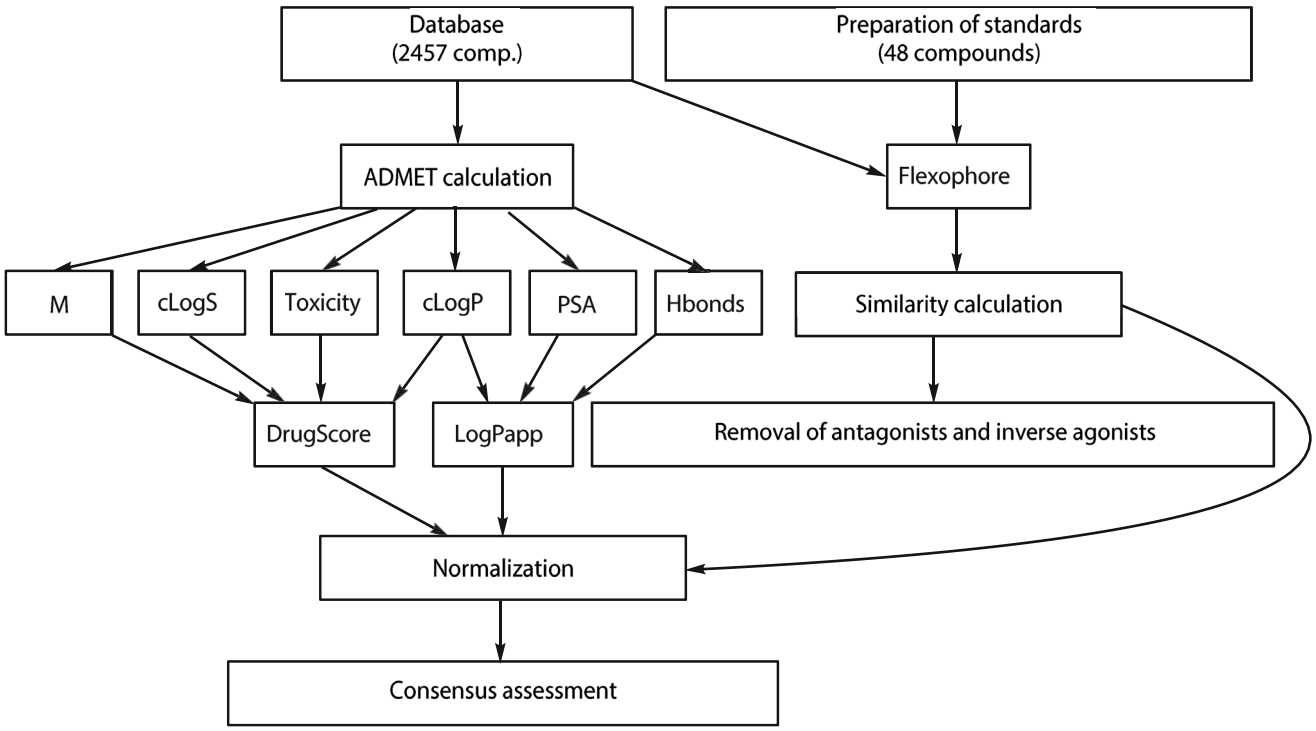


FIG. 2.
Algorithm for evaluating compounds

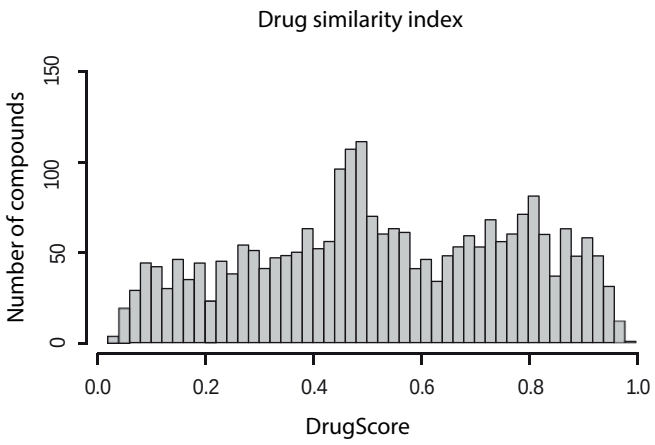


FIG.4.
Drug-like distribution of compounds

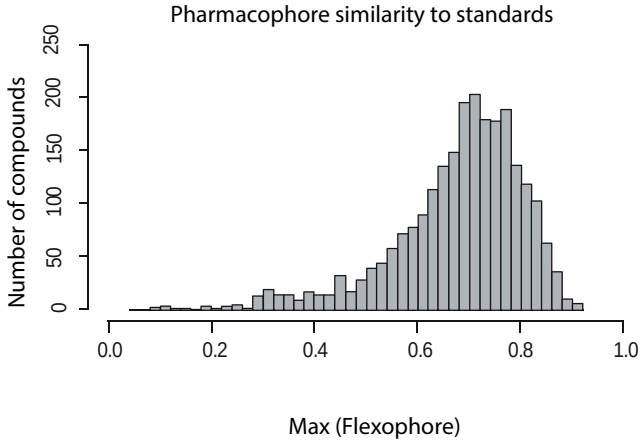


FIG.6.
Distribution of compounds by pharmacophore similarity to standards

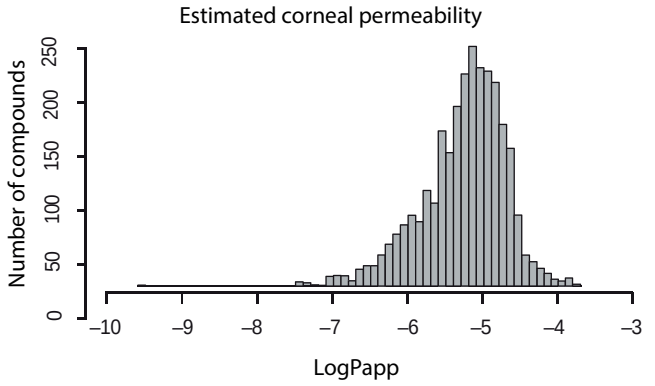


FIG.5.
Distribution of compounds by calculated corneal permeability

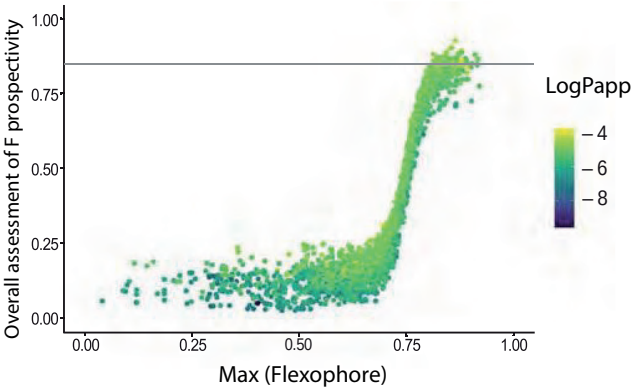


FIG.7.
The contribution of pharmacophore similarity to the Max(Flexophore) standards and the calculated corneal permeability of LOGPPP to the overall F prospectivity score

TABLE 1

RESULTS OF THE SPECIFIC TYPES OF TOXICITY ASSESSMENT FOR THE STUDIED COMPOUNDS

Type of toxicity	Number of compounds (*n*)		
	high risk	low risk	no risk
Mutagenicity	204	60	2193
Carcinogenicity	249	84	2124
Reproductive	135	131	2191
Local irritant effect	333	63	2061

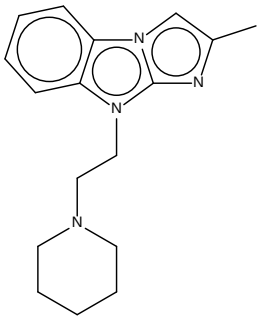
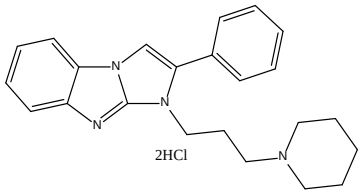
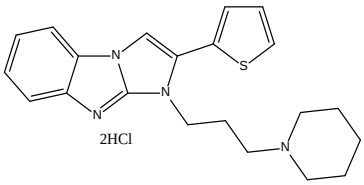
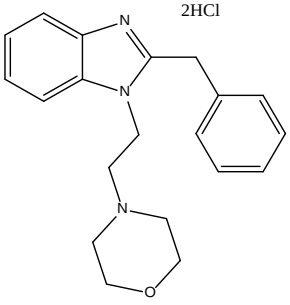
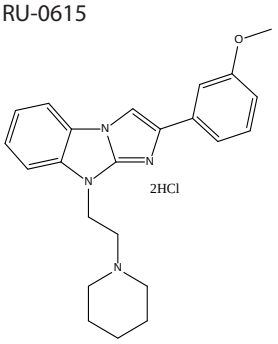
TABLE 2

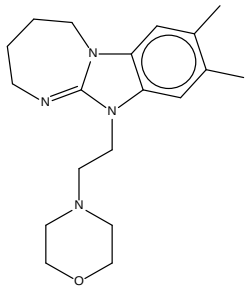
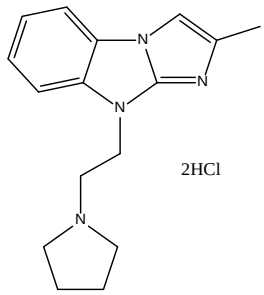
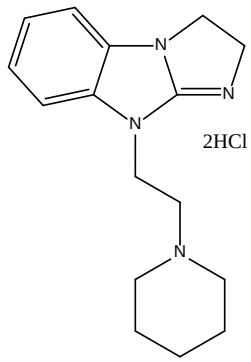
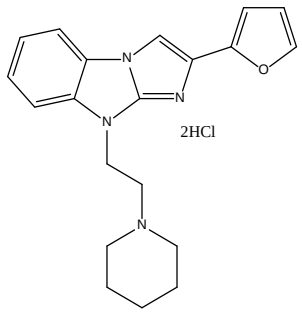
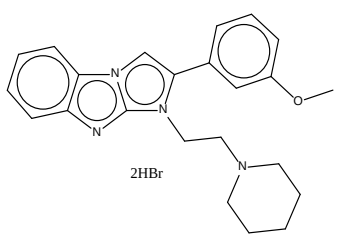
SELECTING THE DECISIVE RULE PARAMETERS

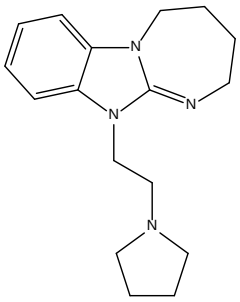
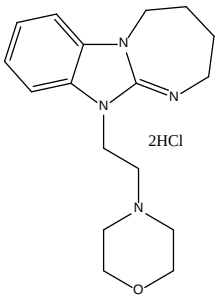
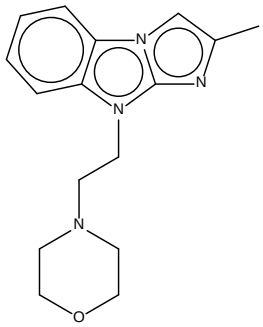
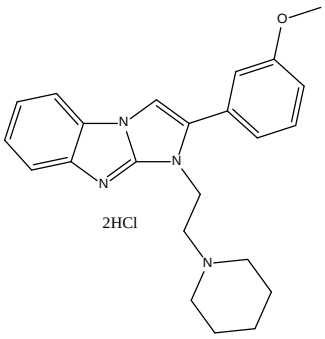
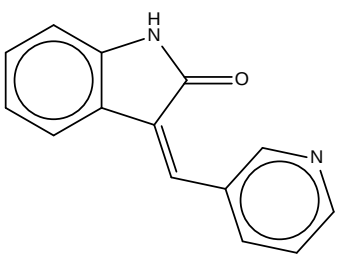
Indicator, *p*	Condition, *a*	Slope of the curve, *b*	Weight, *k*
DrugScore	> 0.5	0.1	0.25
LogPapp	≥ 5	0.35	0.25
Max(*Flexophore*)	> 0.75	1.0	1.0

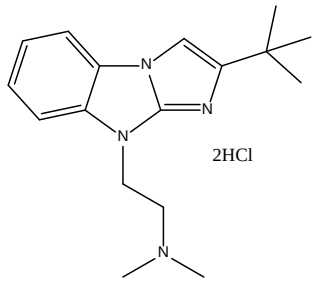
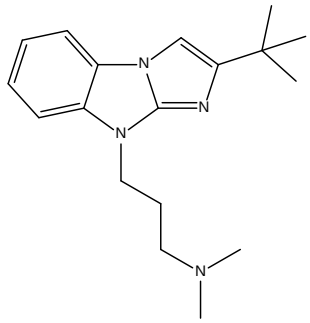
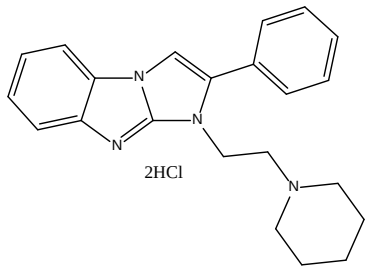
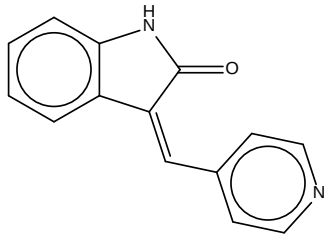
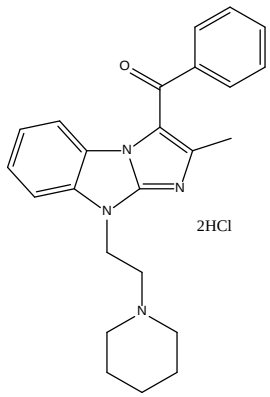
TABLE 3

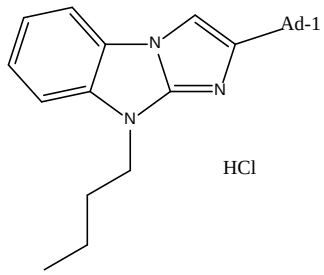
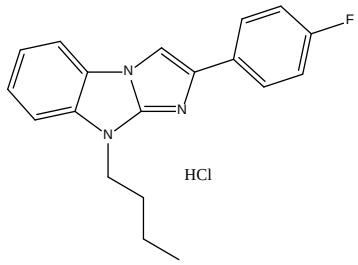
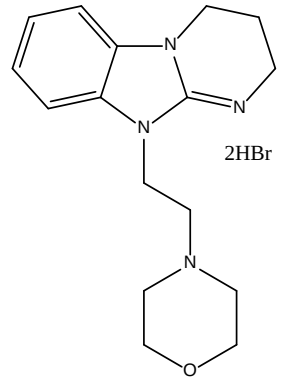
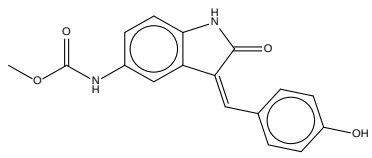
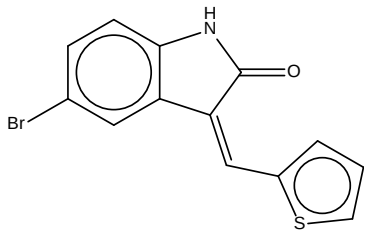
COMPOUNDS WITH MAXIMUM PROSPECTIVITY AND THEIR IOP-LOWERING ACTIVITY

No.	Cipher and structure	*DrugScore*[1]	Consensus assessment *F*	IOP change, % of baseline
1	RU-1331 	0.889	0.895	–20.3 ± 3.54*
2	RU-0721 	0.724	0.890	–8.9 ± 9.62
3	RU-0882 	0.732	0.877	–17.2 ± 14.29
4	RU-0536 	0.860	0.874	–8.3 ± 7.54
5	RU-0615 	0.751	0.874	–33.3 ± 4.40*

No.	Cipher and structure	*DrugScore*[1]	Consensus assessment *F*	IOP change, % of baseline
6	DAB-0034 	0.799	0.873	–24.5 ± 4.44*
7	RU-0026 	0.743	0.872	–11.9 ± 7.83
8	RU-0255 	0.865	0.872	–12.4 ± 8.60
9	RU-0155 	0.823	0.871	–2.5 ± 2.12
10	RU-0580b 	0.751	0.871	–10.1 ± 1.70

No.	Cipher and structure	*DrugScore*[1]	Consensus assessment *F*	IOP change, % of baseline
11	DAB-0021 	0.677	0.870	–17.3 ± 2.40*
12	DAB-0023 	0.861	0.870	–20.5 ± 1.43*
13	RU-1332 	0.930	0.870	–24.3 ± 4.60*
14	RU-0580 	0.751	0.869	–16.7 ± 8.33
15	OIP-H-0003 	0.903	0.866	–5.6

No.	Cipher and structure	*DrugScore*[1]	Consensus assessment *F*	IOP change, % of baseline
16	RU-0470 	0.804	0.865	–10.26 ± 10.26
17	RU-0398 	0.819	0.864	–40.0 ± 4.15*
18	RU-0354 	0.771	0.863	–27.0 ± 5.18*
19	OIP-H-0004 	0.903	0.862	–26.11 ± 3.15*
20	RU-0514 	0.722	0.862	–2.5 ± 6.75

No.	Cipher and structure	*DrugScore*[1]	Consensus assessment *F*	IOP change, % of baseline
21	RU-0012 	0.576	0.861	–6.1 ± 3.09
22	RU-1256 	0.541	0.858	–15.71 ± 17.93
23	RU-0837 	0.909	0.856	–5.8 ± 3.02
24	K-00165 	0.298	0.856	–40.9 ± 3.52*
25	OIP-Br-S-1 	0.734	0.851	–13.8 ± 9.09

Note. [1] is an integral indicator that takes into account drug similarity, solubility, the risk of mutagenic, carcinogenic, irritating properties and reproductive toxicity; * – $p < 0.05$ relative to baseline IOP (*t*–test; $n = 6$).

Validation by *in vivo* experiment

After virtual screening of 2457 structures, 25 selected compounds with maximum *F* prospectivity score were experimentally studied to determine the effect on intraocular pressure of intact rats. 10 compounds were identified that statistically significantly reduced the IOP of intact rats. It was revealed that new bioisosters of melatonin – compounds RU-398 and K-165 – were superior to melatonin itself in their ability to reduce IOP, and compound RU-615 was not inferior to melatonin in its activity. Specifically, substance RU-398 reduced IOP by 40 %, K-165 by 40.9 %, and RU-615 and melatonin by 33.3 %. Compounds RU-398 and RU-615 also resulted in IOP reduction in the control eye, which may indicate a possible systemic action of the compounds, which was not detected for substance K-165.

DISCUSSION

Multiparametric optimisation is one of the central and most challenging problems in the development of new drugs. To have a chance to reach the stage of clinical trials, the molecule must have a number of optimal characteristics determined by its structure - not only affinity to the biological target, but also selectivity of action, sufficient solubility, ability to penetrate tissue barriers, metabolic stability, low toxicity. The approach offered in this study is characterised by simplicity, accessibility, and flexibility. Using chemoinformatics methods, compounds with low calculated toxicity, high drug similarity and permeability through the cornea of the eye and primarily pharmacophore close to known modulators, melatonin receptor agonists, are prioritised, followed by validation by experimental screening.

The limitations of the present study include the limited sample library of source structures for the study. Additionally, experimental validation was performed by phenotypic screening for the ability to reduce intraocular pressure. Non-verification of the effect against melatonin receptors itself does not exclude the possibility of other mechanisms of action of the active compounds, different from the mechanism of action of melatonin itself.

CONCLUSION

A flexible computational approach for prioritisation of compounds with high drug similarity, low computational toxicity and similarity to a target-oriented library of reference compounds is proposed. The effectiveness of the proposed search system was confirmed by the identification of new chemical classes and scaffolds of melatonin bioisosters promising for further study as antiglaucoma agents.

Funding

The research was performed within the framework of the regional project of the Russian Science Foundation dated March 25, 2022 № 22-15-20025 «Synthesis and study of the efficacy of melatonin bioisosters».

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We thank the staff of the Laboratory of Organic Synthesis of the Scientific Research Institute of Physical and Organic Chemistry Kuzmenko T.A. and Divaeva L.N. for providing the DAB series compounds.

REFERENCES

1. Stein JD, Khawaja AP, Weizer JS. Glaucoma in adults – screening, diagnosis, and management: A review. *JAMA*. 2021; 325(2): 164. doi: 10.1001/jama.2020.21899

2. Rieck J. The pathogenesis of glaucoma in the interplay with the immune system. *Invest Ophthalmol Vis Sci*. 2013; 54(3): 2393. doi: 10.1167/iovs.12-9781

3. Martínez-Águila A, Martín-Gil A, Carpena-Torres C, Pastrana C, Carracedo G. Influence of circadian rhythm in the eye: Significance of melatonin in glaucoma. *Biomolecules*. 2021; 11(3): 340. doi: 10.3390/biom11030340

4. Boutin JA, Witt-Enderby PA, Sotriffer C, Zlotos DP. Melatonin receptor ligands: A pharmaco-chemical perspective. *J Pineal Res*. 2020; 69(3): e12672. doi: 10.1111/jpi.12672

5. Cardinali DP, Delagrange P, Dubocovich ML, Jockers R, Krause DN, Markus RP, et al. Melatonin receptors (version 2019.3) in the IUPHAR/BPS guide to pharmacology database. *IUPHAR/BPS Guide to Pharmacology CITE*. 2019; 2019(3). doi: 10.2218/gtopdb/F39/2021.3

6. López-López E, Naveja JJ, Medina-Franco JL. DataWarrior: An evaluation of the open-source drug discovery tool. *Exp Opin Drug Discov*. 2019; 14(4): 335-341. doi: 10.1080/17460441.2019.1581170

7. Ekinci D, Karagoz L, Ekinci D, Senturk M, Supuran CT. Carbonic anhydrase inhibitors: *In vitro* inhibition of α isoforms (hCA I, hCA II, bCA III, hCA IV) by flavonoids. *J Enzyme Inhib Med Chem*. 2013; 28(2): 283-288. doi: 10.3109/14756366.2011.643303

8. Thombre AG, Himmelstein KJ. Quantitative evaluation of topically applied pilocarpine in the precorneal area. *J Pharmaceut Sci*. 1984; 73(2): 219-222. doi: 10.1002/jps.2600730219

9. Spasov A, Ozerov A, Vassiliev P, Kosolapov V, Gurova N, Kucheryavenko A, et al. Synthesis and multifaceted pharmacological activity of novel quinazoline NHE-1 inhibitors. *Sci Rep*. 2021; 11(1): 24380. doi: 10.1038/s41598-021-03722-w

10. Marcus AJ, Iezhitsa I, Agarwal R, Vassiliev P, Spasov A, Zhukovskaya O, et al. Data on the effects of imidazo[1,2-a]benzimidazole and pyrimido[1,2-a]benzimidazole compounds on intraocular pressure of ocular normotensive rats. *Data Brief*. 2018; 18: 523-554. doi: 10.1016/j.dib.2018.03.01

Information about the authors

Denis A. Babkov – Cand. Sc. (Chem.), Senior Research Officer at the Laboratory of Metabotropic Agents of the Scientific Centre for Innovative Drugs, Volgograd State Medical University, e-mail: dababkov@volgmed.ru, https://orcid.org/0000-0002-9645-3324

Alena S. Taran – Cand. Sc. (Med.), Senior Research Officer at the Laboratory of Toxicology of the Scientific Centre for Innovative Drugs, Volgograd State Medical University; Junior Research Officer at the Laboratory of Experimental Pharmacology, Volgograd Medical Scientific Center, e-mail: alena-beretta-taran@mail.ru, https://orcid.org/0000-0001-8477-254X

Alina A. Shevchenko – Postgraduate at the Department of Pharmacology and Bioinformatics, Volgograd State Medical University, e-mail: alina.shew4enko2014@yandex.ru

Lyudmila V. Naumenko – Dr. Sc. (Med.), Professor at the Department of Pharmacology and Bioinformatics, Volgograd State Medical University, e-mail: milanaumenko@mail.ru, https://orcid.org/0000-0002-2119-4233

Olga N. Zhukovskaya – Cand. Sc. (Chem.), Senior Research Officer at the Laboratory of Organic Synthesis, Research Scientific Institute of Physical and Organic Chemistry, Southern Federal University, e-mail: zhukowskaia.ol@yandex.ru, https://orcid.org/0000-0001-9928-694X

Alexander M. Efremov – Postgraduate at the Department of Medicinal Chemistry and Fine Organic Synthesis, Lomonosov Moscow State University, e-mail: sashka.e@yandex.ru, http://orcid.org/0000-0002-1777-7081

Elena N. Bezsonova – Postgraduate at the Department of Medicinal Chemistry and Fine Organic Synthesis, Lomonosov Moscow State University, e-mail: elena.bezsonova@chemistry.msu.ru, https://orcid.org/0000-0002-9804-5447

Natalia A. Lozinskaya – Cand. Sc. (Chem.), Associate Professor at the Department of Medicinal Chemistry and Fine Organic Synthesis, Lomonosov Moscow State University, e-mail: natalylozinskaya@mail.ru, https://orcid.org/0000-0003-2518-3694

Alexander A. Spasov – Dr. Sc. (Med.), Head of the Department of Pharmacology and Bioinformatics, Volgograd State Medical University; Head of the Department of Pharmacology, Head of the Laboratory of Experimental Pharmacology, Volgograd Medical Scientific Center, e-mail: aspasov@mail.ru, https://orcid.org/0000-0002-7185-4826