chemistry proceedings

MDPI

*Proceeding Paper*

# In Silico Studies of Khellin and Related Furochromenes by Modified POM Analysis †

**Renata Gašparová**

Department of Chemistry, Institute of Chemistry and Environmental Science, Faculty of Natural Sciences, University of St. Cyril and Methodius in Trnava, Nám. J. Herdu 2, SK-917 01 Trnava, Slovakia; renata.gasparova@ucm.sk

† Presented at The 28th International Electronic Conference on Synthetic Organic Chemistry (ECSOC 2024), 15–30 November 2024; Available online: https://sciforum.net/event/ecsoc-28.

**Abstract:** POM (Petra/Osiris/Molinspiration) analysis and related in silico tools are well-established methods used to evaluate the potential of molecules to become drug candidates by predicting their biological activity, calculating various physicochemical properties, ADME parameters or toxicity. Khellin **1** is well-known component of *Ammi visnaga* (khella) plant used for centuries in the folk medicine for treatment urinary tract pain associated with kidney stones. Modern medicine has found importance of khellin in the treatment of psoriasis, angina pectoris or vitiligo. However, the oral use of khellin is limited by its potential adverse effects, such as dizziness, constipation, headache, itching, or lack of appetite. Many natural or synthetic furopyrrole derivatives have been extensively studied and reported to possess numerous biological effects, including anticancer, anti-inflammatory or antimicrobial. The present in silico study is aimed at revealing the most promising drug candidates based on favorable pharmacokinetic parameters and toxicological characteristics. A modified POM analysis of sixteen furochromenes was performed using Molinspiration, Osiris and SwissADME softwares. Studied structures were selected due to the modifications of the khellin skeleton. Substitution of the furan or pyran ring, modification of one or both methoxy groups or hydrogenation of one or both heterocyclic rings were included. The results of this preliminary in silico investigations suggest all furopyrroles have good oral bioavailability high level of gastrointestinal absorption. The bioactivity score prediction shows their ability to act predominantly as ion channel modulators or enzyme inhibitors. All compounds exhibit low risk of being irritants, nine of them exhibit low risk of being mutagenic, tumorigenic or to have reproductive effect.

**Keywords:** furochromene; khellin; biological activity; Molinspiration; Osiris; SwissADME

**Citation:** Gašparová, R. In Silico Studies of Khellin and Related Furochromenes by Modified POM Analysis. *Chem. Proc.* **2024**, *6*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s): Name

Published: 15 November 2024

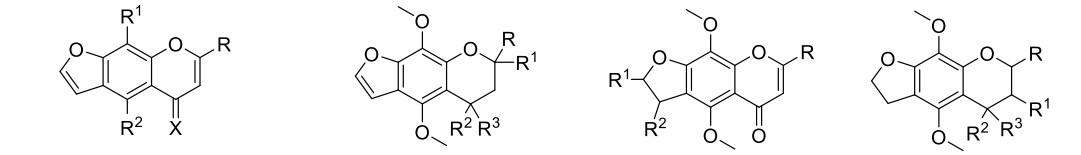


## 1. Introduction

Khellin **1** (Figure 1) is one of furochromenes obtained from fruits and seeds of wild plant *Ammi visnaga* L. (khella), used for many centuries in Egyptian folk medicine to relieve renal colic [1]. Further studies had reported the use of extract of *A. visnaga* for the treatment of psoriasis [2], angina pectoris [3] or vitiligo [4]. However the oral use of khellin is limited by its potential adverse effects, such as dizziness, constipation, headache, itching, insomnia, and lack of appetite [5].

Many in silico tools have been developed to predict physicochemical properties or pharmacokinetic properties (absorption, distribution, metabolism, and excretion—ADME) of molecular structure or to prevent its unwanted effects (toxicity or hazards) on the organism [6]. In silico tools are also important in the druglikeness determination. Druglikeness is estimated from the structure and physico-chemical properties of the chemical structure [7] and represents a term used in drug design to find out the molecule suitable for oral use and therefore promising drug candidate [8]. POM analysis (Petra, Osiris and Molinspiration) represents well-established in silico tool to access the

pharmacokinetic profile of the synthesized molecules [9]. Modified POM analysis [11–13] enables to replace Petra software [10] by swissADME [7] when the prediction of pharmacological parameters is a priority. The aim of this preliminary research is to present in silico evaluation of physicochemical properties, pharmacokinetic parameters and toxicity potential of khellin **1** and related compounds **2–16** (Figure 1) with the intention to find the structure with improved pharmacokinetic properties and low toxicity.



**1** R = $CH_3$, $R^1$ = $R^2$ = $OCH_3$, X = O
**2** R = $CH_3$, $R^1$ = $OCH_3$, $R^2$ = OH, X = O
**3** R = $CH_3$, $R^1$ = $R^2$ = OH, X = O
**4** R = $CH_3$, $R^1$ = $R^2$ = $OCH_3$, X = S
**5** R = $CH_3$, $R^1$ = H, $R^2$ = $OCH_3$, X = O
**6** R = $C_2H_5$, $R^1$ = $R^2$ = $OCH_3$, X = O
**7** R = H, $R^1$ = $R^2$ = $OCH_3$, X = O

**8** R = $CH_3$, $R^1$ = OH, $R^2R^3$ = O
**9** R = $CH_3$, $R^1$ = $R^2$ =H, $R^3$ = OH
**10** R = COOH, $R^1$ =H, $R^2R^3$ = O

**11** R = COOH, $R^1$ = $R^2$ = H
**12** R = $CH_3$, $R^1$ = $R^2$ = OH

**13** R = $CH_3$, $R^1$ = $R^2$ = OH, $R^3$ = H
**14** R = COOH, $R^1$ = H, $R^2R^3$ = O
**15** R = $CH_3$, $R^1$ = H, $R^2R^3$ = O
**16** R = $CH_3$, $R^1$ = $R^2$ = $R^3$ = H

**Figure 1.** Khellin **1** and related furochromenes **2–16**.

## 2. Material and Methods

Structures of furochromene derivatives **2–16** (Figure 1) were selected from the SciFinder database [14] due to the modifications of the khellin 1 skeleton. Substitution on the furan or pyran ring, modification of one or both methoxy groups or hydrogenation of one or both heterocyclic rings were included.

Molinspiration [15] was used for the calculation of molecular properties (logP, TPSA, number of H-bond donors and acceptors) and prediction of bioactivity score for the most important drug targets (GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease or enzyme inhibitor). SwissADME software [16] was used for the pharmacokinetic parameters calculations such as gastrointestinal absorption, blood-brain barrier permeation, skin permeation, the assessment of whether a compound is a substrate of P-gp, the interactions of the molecule with the cytochrome P450 or the skin permeability (Log Kp). The druglikeness score using five different methods (Lipinski, Ghose, Veber, Egan and Muegge) was calculated. The bioavailability score predicts the probability of the oral bioavailability of the compound. PAINS and Brenk structural alerts are used for the identification of potentially problematic fragments—responsible for positive biological output or putatively toxic, chemically reactive or metabolically unstable. Finally, leadlikeness and synthetic accessibility of structure can be predicted. The toxicity risk based on the mutagenicity, tumorigenicity, irritating effects and reproductive effects of studies compounds is reported using Osiris property Explorer [17]. The results are given as a semaphore light colors.

## 3. Results and Discussion

### *3.1. Molinspiration*

According to the Lipinski's rule [18]. only a molecule with MW ≤ 500, LogP ≤ 5, number of H-donors (OH,NH) ≤ 5 and number of H-acceptors (O,N) ≤ 10 could be a good drug candidate. According to the Verber's rule [19] compounds with TPSA ≤ 140 Å and nROTB ≤ 10 have good oral bioavailability. All furochromenes **1–16** are in the accordance with both Lipinski's and Verber's rules (Table 1).

**Table 1.** Physiochemical properties of **1–16** calculated using Molinspiration software.

| No. | logP | TPSA | n | MW | nON | NHOH | viol | rot | vol |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 2.29 | 61.82 | 19 | 260.25 | 5 | 0 | 0 | 2 | 221.80 |
| **2** | 2.01 | 72.81 | 18 | 246.22 | 5 | 1 | 0 | 1 | 204.27 |
| **3** | 1.74 | 83.81 | 17 | 232.17 | 5 | 2 | 0 | 0 | 186.74 |
| **4** | 2.63 | 44.75 | 19 | 276.61 | 4 | 0 | 0 | 2 | 230.68 |
| **5** | 2.30 | 52.59 | 17 | 230.22 | 4 | 0 | 0 | 1 | 196.25 |
| **6** | 2.86 | 61.82 | 20 | 274.27 | 5 | 0 | 0 | 3 | 238.60 |
| **7** | 2.06 | 61.82 | 18 | 246.22 | 5 | 0 | 0 | 2 | 205.24 |
| **8** | 1.64 | 78.14 | 20 | 278.26 | 6 | 1 | 0 | 2 | 235.71 |
| **9** | 1.88 | 61.07 | 19 | 264.28 | 5 | 1 | 0 | 2 | 233.87 |
| **10** | 1.08 | 95.21 | 21 | 292.24 | 7 | 1 | 0 | 3 | 238.45 |
| **11** | 1.60 | 95.21 | 21 | 292.24 | 7 | 1 | 0 | 3 | 238.43 |
| **12** | 0.36 | 98.37 | 21 | 294.26 | 7 | 2 | 0 | 2 | 244.07 |
| **13** | 0.69 | 77.39 | 20 | 282.29 | 6 | 2 | 0 | 2 | 248.10 |
| **14** | 0.81 | 91.31 | 21 | 294.26 | 7 | 1 | 0 | 3 | 244.64 |
| **15** | 1.94 | 54.01 | 19 | 264.28 | 5 | 0 | 0 | 2 | 234.20 |
| **16** | 2.84 | 36.94 | 18 | 250.29 | 4 | 0 | 0 | 2 | 232.02 |

LogP—Octanol-water partition coefficient; TPSA—topological polar surface area; MW—molecular weight; nON—number of hydrogen bond acceptors; nOHNH—number of hydrogen bond donors; viol—number of Lipinski's rule of five violations; rot—number of rotatable bonds.

A compound with a bioactivity score greater than 0.00 is likely to exhibit considerable bioactivity [20]. Results of Molinspiration bioactivity score prediction suggest that studied furochromenes should exhibit considerable bioactivity as indicated in Table 2. Studied derivatives **1–16** are predicted to be active as ion channel modulators (except **5**, **12** and **15**). Calculated ICM scores of **2**, **7–9** reached high values (0.23–0.30). Hydrogenation of one or both heterocyclic rings led to high values of score as enzyme inhibitors (EI) especially for structures **10–16** (0.22–0.43). Moreover, the calculated scores of carboxylic acid **14** reached high values (0.33) also as the GPCR ligand and nuclear receptor ligand, respectively.

**Table 2.** Bioactivity scores of **1–16** calculated using Molinspiration software.

| No. | GPCR | ICM | KI | NRL | PI | EI |
|---|---|---|---|---|---|---|
| **1** | −0.36 | 0.16 | −0.51 | −0.51 | −0.64 | −0.07 |
| **2** | −0.39 | 0.23 | −0.64 | −0.49 | −0.77 | 0.01 |
| **3** | −0.43 | 0.17 | −0.71 | −0.53 | −0.81 | −0.03 |
| **4** | −0.41 | 0.03 | −0.54 | −0.41 | −0.54 | 0.02 |
| **5** | −0.55 | −0.06 | −0.79 | −0.79 | −0.92 | −0.28 |
| **6** | −0.10 | 0.19 | −0.32 | −0.29 | −0.50 | 0.08 |
| **7** | −0.20 | 0.30 | −0.46 | −0.60 | −0.71 | 0.10 |
| **8** | −0.25 | 0.27 | −0.45 | −0.18 | −0.57 | 0.10 |
| **9** | −0.03 | 0.30 | −0.65 | −0.15 | −0.57 | 0.18 |
| **10** | 0.08 | 0.20 | −0.59 | 0.10 | −0.33 | 0.22 |
| **11** | 0.02 | 0.04 | −0.35 | −0.12 | −0.46 | 0.31 |
| **12** | −0.21 | −0.14 | −0.47 | −0.28 | −0.39 | 0.23 |
| **13** | 0.15 | 0.06 | −0.31 | −0.07 | −0.26 | 0.34 |
| **14** | 0.33 | 0.03 | −0.41 | 0.33 | −0.13 | 0.43 |
| **15** | 0.08 | −0.06 | −0.52 | −0.01 | −0.45 | 0.28 |
| **16** | 0.27 | 0.15 | −0.41 | 0.09 | −0.28 | 0.39 |

GPCR—GPCR ligand; ICM—ion channel modulator; KI—kinase inhibitor; NRL—nuclear receptor ligand; PI—protease inhibitor; EI—enzyme inhibitor.

### *3.2. Osiris*

Osiris software was used for prediction of toxicity risks—mutagenicity, irritation, tumorigenicity and reproductive effects. Drug score and drug likeness were also calculated (Table 3). Toxicity risk analysis showed all furochromenes **1–16** exhibit low risk of being irritants. A high risk of mutagenicity was calculated for seven compounds (**1–3**, **6**, **7**, **11** and **12**). Five compounds exhibit high risk to be tumirogenic (**1**, **6**, **7**, **11** and **12**). Only khellin **1** exhibit high risk to be reproductive toxic and three compounds (**2–4**) exhibit moderate reproductive effects. It can be concluded, studied derivatives **5**, **8–10**, **13–16** are low-toxic and safe compounds, while khellin **1** exhibit the high risk in three categories and compounds **2–4**, **6**, **7**, **11** and **12** exhibit high or moderate risk in two categories. Drug score values indicate potential of compound to be a drug. Structures **8**, **9**, **13** and **15** exhibit good drug score values. Moderate values of drug score were calculated for **4**, **5**, **10**, **14** and **16**.

**Table 3.** OSIRIS toxicity risk, druglikeness and drug score calculations of **1–16**.

| No | MUT | TUM | IRR | REP | DL | DS |
|---|---|---|---|---|---|---|
| **1** | ● | ● | ● | ● | −6.87 | 0.09 |
| **2** | ● | ● | ● | ● | −6.79 | 0.2 |
| **3** | ● | ● | ● | ● | −6.98 | 0.21 |
| **4** | ● | ● | ● | ● | −3.77 | 0.34 |
| **5** | ● | ● | ● | ● | −6.84 | 0.41 |
| **6** | ● | ● | ● | ● | 0.47 | 0.22 |
| **7** | ● | ● | ● | ● | −0.55 | 0.21 |
| **8** | ● | ● | ● | ● | 1.38 | 0.76 |
| **9** | ● | ● | ● | ● | 1.02 | 0.76 |
| **10** | ● | ● | ● | ● | −1.55 | 0.51 |
| **11** | ● | ● | ● | ● | −0.21 | 0.24 |
| **12** | ● | ● | ● | ● | −5.88 | 0.16 |
| **13** | ● | ● | ● | ● | 0.66 | 0.77 |
| **14** | ● | ● | ● | ● | −1.74 | 0.52 |
| **15** | ● | ● | ● | ● | 0.51 | 0.72 |
| **16** | ● | ● | ● | ● | −1.28 | 0.53 |

MUT—mutagenicity; TUM—tumorigenicity; IRR—irritant; RE—reproductive effect; DL—druglikeness; DS—drug score.

### *3.3. SwissADME*

SwissADME predictions show that all studied furochromenes **1–16** (Table 4) exhibit high gastrointestinal absorption (GI). The ability to pass through blood-brain barriers (BBB) is predicted for eight structures (**1**, **2**, **5–7**, **9**, **15**, **16**), while furochromenes **3**, **4**, **8**, **10–14** were predicted to be unable to permeat the BBB. P-glycoprotein (P-gp) functions as a biological barrier by extruding toxins and xenobiotics out of cells [21]. Most of studied structures were predicted not to be substrates of Pgp, except compounds **8**, **9** or **13**, **14**. For oral drug administration, inhibiting P-gp can increase drug absorption and bioavailability and thus its therapeutic effects [22]. The cytochromes P450 comprise a family of isoenzymes, important in drug elimination through metabolic processes. They catalyze the oxidative metabolism of a variety of xenobiotic chemicals [23]. The examination of the interactions of CYPs with potential drugs is one of the important steps in drug design [24]. Most of studies compounds are supposed to serve as inhibitors of at least one cytochrome P450 isoenzymes (1A2, 2C19, 2C9, 2D6, 3A4), excluding compound **13** which is expected not to inhibit any of five isoenzymes. Thus, compound **13** is unlikely to have adverse effects and the risk of liver toxicity. Compounds which are potential inhibitors of three (**1–3**, **6**) or four (**4**) P450 isoenzymes are considered less safe with increased toxicity (Table 4).

**Table 4.** The SwissADME calculations of **1–16**.

| No | GIA | BBB | P-gpS | CYP | Lipinski | Ghose | Veber | Egan | Muegge | PAINS | Brenk | LL | SA | $LogK_p$ | BA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | H | Y | N | Y,N,Y,N,Y | Y | Y | Y | Y | Y | 0 | 0 | Y | 3.16 | −6.28 | 0.55 |
| **2** | H | Y | N | Y,N,N,Y,Y | Y | Y | Y | Y | Y | 0 | 0 | N | 2.97 | −6.03 | 0.55 |
| **3** | H | N | N | Y,N,N,Y,Y | Y | Y | Y | Y | Y | 0 | 1 | N | 2.91 | −6.18 | 0.55 |
| **4** | H | N | N | Y,Y,Y,N,Y | Y | Y | Y | Y | Y | 0 | 1 | Y | 3.19 | −5.95 | 0.55 |
| **5** | H | Y | N | Y,N,N,N,Y | Y | Y | Y | Y | Y | 0 | 0 | N | 2.89 | −6.08 | 0.55 |
| **6** | H | Y | N | Y,Y,Y,N,Y | Y | Y | Y | Y | Y | 0 | 0 | Y | 3.23 | −6.06 | 0.55 |
| **7** | H | Y | N | Y,N,N,N,Y | Y | Y | Y | Y | Y | 0 | 0 | N | 3.17 | −6.46 | 0.55 |
| **8** | H | N | Y | Y,N,N,N,N | Y | Y | Y | Y | Y | 0 | 0 | Y | 3.58 | −7.01 | 0.55 |
| **9** | H | Y | Y | Y,Y,N,N,N | Y | Y | Y | Y | Y | 0 | 0 | Y | 3.83 | −6.53 | 0.55 |
| **10** | H | N | N | Y,N,N,N,N | Y | Y | Y | Y | Y | 0 | 0 | Y | 3.55 | −7.12 | 0.56 |
| **11** | H | N | N | Y,N,N,N,N | Y | Y | Y | Y | Y | 0 | 0 | Y | 3.21 | −7.21 | 0.56 |
| **12** | H | N | N | Y,N,N,N,N | Y | Y | Y | Y | Y | 0 | 0 | Y | 4.05 | −7.93 | 0.55 |
| **13** | H | N | Y | N,N,N,N,N | Y | Y | Y | Y | Y | 0 | 0 | Y | 3.93 | −7.61 | 0.55 |
| **14** | H | N | Y | Y,N,N,N,N | Y | Y | Y | Y | Y | 0 | 0 | Y | 3.42 | −7.42 | 0.56 |
| **15** | H | Y | Y | Y,Y,N,N,N | Y | Y | Y | Y | Y | 0 | 0 | Y | 3.31 | −6.66 | 0.55 |
| **16** | H | Y | Y | Y,N,N,Y,N | Y | Y | Y | Y | Y | 0 | 0 | Y | 3.26 | −5.93 | 0.55 |

**Y**—yes, **N**—no, **GIA**—gastrointestinal absorption, **BBB**—blood brain barrier permeation, **P-gpS**—P-glycoprotein substrate, **CYP**—cytochrome P450 (1A2, 2C19, 2C9, 2D6, 3A4) inhibitors, **PAINS**—pan assay interference structures, **Brenk**—structural alert by Brenk, **LL**—leadlikeness, **SA**—synthetic accessibility, **$LogK_p$**—skin permeation (cm/s), **BA**—bioavailability score.

Calculation of druglikeness showed all compounds **1–16** obey all five filters (Lipinski, Ghose, Weber, Egan and Muegge). The skin permeation (log Kp) values are in the range of −5.93 to −7.93 cm/s, indicating low skin permeability of studied compounds. The bioavailability score (BA) predicts the probability of a compound having at least 10% oral bioavailability in rats or measurable Caco-2 permeability [13]. The BA values of **1–16** are in 0.55–0.56 range. There is 55 or 56% chance for the compounds to have at least 10% bioavailability in rats. Pan assays interference structure (PAINS) and Brenk structural alerts were calculated. Only two compounds (**3**, **4**) were identified by Brenk alert due to the presence of hydroquinone or thiocarbonyl structural units.

## 4. Conclusions

The modified POM analysis (SwissAdme/Osiris/Molinspiration) of sixteen furopyrrole derivatives was accomplished to identify the drug-likeness score, bioactivity, toxicity and ADME parameters. Molinspiration calculations results show all studied structures are predicted to possess good oral bioavailability. Most of the studied structures show significant drug scores as ion channel modulators. Furopyrroles with hydrogenated one or both heterocyclic rings express good score as enzyme inhibitors. SwissADME calculations indicated the most promising 4,9-dimethoxy-7-methyl-2,3,6,7-tetrahydro-5*H*-furo[2,3-*g*]chromen-5,6-diol **13** is expected to express high intestinal absorption, is unable to permeat the BBB and is a non-inhibitor of CYP450 isoenzymes. However, compound **13** is predicted to be Pgp substrate. Toxicity risk analysis calculated using Osiris software, showed compounds **8**, **9**, **13** and **15** exhibit not only low toxicity risk, but also good drug score and druglikeness values.

**Funding:** This work was supported by the Slovak Research Agency: VEGA 1/0086/21.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** Author declares no conflicts of interest.

## References


1. Khalil, N.; Bishr, M.; Desouky, S.; Salama, O. *Ammi visnaga* L., a Potential Medicinal Plant: A Review. *Molecules* **2020**, *25*, 301. https://doi.org/10.3390/molecules25020301.
2. Abdel-Fattah, A.; Aboul-Enein, M.N.; Wassel, G.; El-Menshawi, B. Preliminary report on the therapeutic effect of khellin in psoriasis. *Dermatologica* **1983**, *167*, 109–110. https://doi.org/10.1159/000249760.
3. Hultgren, H.N.; Robertson, H.S.; Stevens, L.E. Clinical and experimental study of use of khellin in treatment of angina pectoris. *J. Am. Med. Assoc.* **1952**, *148*, 465–469. https://doi.org/10.1001/jama.1952.62930060006013.
4. Ortel, B.; Tanew, A.; Hönigsmann, H. Treatment of vitiligo with khellin and ultraviolet A. *J. Am. Acad. Dermatol.* **1988**, *18*, 693–701. https://doi.org/10.1016/s0190-9622(88)70092-4.
5. Bhagavathula, A.S.; Al-Khatib, A.J.M.; Elnour, A.A.; Al Kalbani, N.M.S.; Shehab, A. *Ammi Visnaga* in treatment of urolithiasis and hypertriglyceridemia. *Pharmacogn. Res.* **2015**, *7*, 397–400. https://doi.org/10.4103/0974-8490.167894.
6. Madden, J.C.; Enoch, S.J.; Paini, A.; Cronin, M.T.D. A Review of In Silico Tools as Alternatives to Animal Testing: Principles, Resources and Applications. *Altern. Lab. Anim.* **2020**, *48*, 146–172. https://doi.org/10.1177/0261192920965977.
7. Daina, A.; Michielin, O.; Zoete, V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci. Rep.* **2017**, *7*, 42717. https://doi.org/10.1038/srep42717.
8. Ursu, O.; Rayan, A.; Goldblum, A.; Oprea, T.I. Understanding drug-likeness. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2011**, *1*, 760–781. https://doi.org/10.1002/wcms.52.
9. Jarrahpour, A.; Motamedifar, M.; Zarei, M.; Youssoufi, M.H.; Mimouni, M.; Chohan, Z.H.; Ben Hadda, T. Petra, Osiris, and Molinspiration Together as a Guide in Drug Design: Predictions and Correlation Structure/Antibacterial Activity Relationships of New N-Sulfonyl Monocyclic β-Lactams. *Phosphorus Sulfur Silicon Relat. Elem.* **2010**, *185*, 491–497. https://doi.org/10.1080/10426500902953953.
10. Gasteiger, J. Empirical Methods for the Calculation of Physicochemical Data of Organic Compounds. In *Physical Property Prediction in Organic Chemistry*; Jochum, C., Hicks, M.G., Sunkel, J., Eds.; Springer: Heidelberg, Germany, 1988; pp. 119–138. https://doi.org/10.1007/978-3-642-74140-1_11.
11. Maliar, T.; Maliarová, M.; Purdešová, A.; Jankech, T.; Gerhardtová, I.; Beňovič, P.; Dvořáček, V.; Jágr, M.; Viskupičová, J. The Adapted POM Analysis of Avenanthramides In Silico. *Pharmaceuticals* **2023**, *16*, 717. https://doi.org/10.3390/ph16050717.
12. Živković J. V., Kalauzović, S.G., Milosavljević, M.R., Kalauzović, K.G. In silico evaluation of selected benzimidazole derivatives in the discovery of new potent antimicrobial agents. *Acta Med. Median.* **2019**, *58*, 106–115. https://doi.org/10.5633/amm.2019.0115.
13. Apan, A.; Casoni, D.; Leonte, D.; Pop, C.; Iaru, I.; Mogosan, C.; Zaharia, V. Heterocycles 52: The Drug-Likeness Analysis of Anti-Inflammatory Thiazolo [3,2-b][1,2,4]triazole and Imidazo [2,1-b][1,3,4]thiadiazole Derivatives. *Pharmaceuticals* **2024**, *17*, 295. https://doi.org/10.3390/ph17030295.
14. Available online: https://scifinder-n.cas.org / (accessed on 2 April 2024).
15. Molinspiration Chemoinformatics Software. Available online: https://www.molinspiration.com/ (accessed on 24 April 2024).
16. SwissADME Software. Available online: http://www.swissadme.ch/ (accessed on 2 May 2024).
17. *OSIRIS Property Explorer*; Actelion Pharmaceuticals Ltd.: Allschwil, Switzerland, 2010. Available online: http://www.organic-chemistry.org/prog/peo/ (accessed on 12 May 2024).
18. Lipinski, C.A.; Lombardo, F.; Dominy, B.W.; Feeney, P.J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* **1997**, *23*, 3–25. https://doi.org/10.1016/s0169-409x(00)00129-0.
19. Veber, D.F.; Johnson, S.R.; Cheng, H.Y.; Smith, B.R.; Ward, K.W.; Kopple, K.D. Molecular Properties That Influence the Oral Bioavailability of Drug Candidates. *J. Med. Chem.* **2002**, *45*, 2615–2623. https://doi.org/10.1021/jm020017n.
20. Husain, A.; Ahmad, A.; Khan, S.A.; Asif, M.; Bhutani, R.; Al-Abbasi, F.A. Synthesis, molecular properties, toxicity and biological evaluation of some new substituted imidazolidine derivatives in search of potent anti-inflammatory agents. *Saudi Pharm. J.* **2016**, *24*, 104–114. https://doi.org/10.1016/j.jsps.2015.02.008.
21. Lin, J.H.; Yamazaki, M. Role of P-Glycoprotein in Pharmacokinetics. *Clin. Pharmacokinet.* **2003**, *42*, 59–98. https://doi.org/10.2165/00003088-200342010-00003.
22. Nguyen, T.T.; Duong, V.A.; Maeng, H.J. Pharmaceutical Formulations with P-Glycoprotein Inhibitory Effect as Promising Approaches for Enhancing Oral Drug Absorption and Bioavailability. *Pharmaceutics* **2021**, *13*, 1103. https://doi.org/10.3390/pharmaceutics13071103.
23. Sharma, R.; Williams, I.S.; Gatchie, L.; Sonawane, V.R.; Chaudhuri, B.; Bharate, S.B. Khellinoflavanone, a Semisynthetic Derivative of Khellin, Overcomes Benzo[a]pyrene Toxicity in Human Normal and Cancer Cells That Express CYP1A1. *ACS Omega* **2018**, *3*, 8553–8566. https://doi.org/10.1021/acsomega.8b01088.

24. Šestić, T.L.; Ajduković, J.J.; Marinović, M.A.; Petri, E.T.; Savić, M.P. In silico ADMET analysis of the A-, B- and D-modified androstane derivatives with potential anticancer effects. *Steroids* **2023**, *189*, 109147. https://doi.org/10.1016/j.steroids.2022.109147.