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Research Paper

Correlating Side Effects and Properties of Analgesics with Disance- and Degree-Based Topological Indices

Petra Žigert Pleteršek[1,2*] and Zoja Pleteršek[3]

[1]Faculty of Natural Sciences and Mathematics, University of Maribor, Slovenia
[2]Faculty of Chemistry and Chemical Engineering, University of Maribor, Slovenia
[3]Leiden University College, Leiden University, Netherlands

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Abstract

This study investigates the relationship between the structural properties of 22 analgesic molecules, including opioids and non-steroidal anti-inflammatory drugs (NSAIDs), and their physico-chemical properties and side effects. Opioids are effective for managing moderate to severe pain but carry risks of addiction and dependence, while NSAIDs are widely used for their analgesic, antipyretic, and anti-inflammatory properties, with risks primarily linked to gastrointestinal and cardiovascular complications. Using graph theoretical approaches, we modeled these molecules as molecular graphs, calculating ten distance- and degree-based topological indices. The analysis aims to identify structural patterns that correlate with the drugs' therapeutic effects and adverse reactions. By leveraging computational tools such as Sage, we explore how molecular topology can influence the pharmacological properties of analgesics, offering insights into the design of new analgesics with optimized efficacy and safety profiles. The results provide insight into connections between molecular structure and clinical outcomes, contributing to more effective and safer approaches to pain management.

1 Introduction

In the search for more effective and safer medications, particularly in pain management, it is essential to understand the relationships between the molecular structure of drugs and their biological, chemical, and physical properties. Analgesics or painkillers represent a diverse class of compounds that alleviate pain through various mechanisms, including opioid receptor binding and cyclooxygenase inhibition. While their therapeutic efficacy is well established, adverse

*Corresponding author
E-mail addresses: petra.zigert@um.si (P. Žigert Pleteršek), z.pletersek@umail.leidenuniv.nl (Z. Pleteršek)
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side effects, such as opioid addiction or gastrointestinal complications from non-steroidal anti-inflammatory drugs (NSAIDs) and variability in individual responses, remain significant concerns. This underscores the importance of exploring molecular properties that influence not only the pharmacological properties of these drugs but also their toxicological and side effects profiles, see [1, 2] for example.

A promising method for investigating these relationships lies in the application of topological indices-quantitative descriptors that encapsulate the structural properties of molecules by treating them as mathematical graphs. In graph theoretical terms, molecules can be represented as molecular graphs, where atoms (excluding hydrogen) correspond to vertices, and chemical bonds are modeled as edges. Topological indices derived from these molecular graphs have been shown to correlate with a wide range of physico-chemical properties, including molecular size, shape, polarity, and reactivity, as well as biological activities like toxicity and drug efficacy [3]. These indices, based on properties such as the connectivity between atoms (degree-based indices) or distances between pairs of atoms (distance-based indices), provide a means of quantifying molecular structure for mathematical analysis. The earliest example of this is the Wiener index, which was first established by Wiener in 1947 to correlate the boiling points of alkanes with the molecular structure [4]. This pioneering work laid the foundation for the use of topological indices in Quantitative Structure Activity Relationships (QSAR) and Quantitative Structure Property Relationships (QSPR), which have since been extensively applied in drug development.

In this investigation, we focus on 22 commonly used analgesic molecules, aiming to explore potential connections between their topological indices and their corresponding physico-chemical properties and known side effects, see Tables 1 and 2. By computing and analyzing a set of ten distance- and degree-based topological indices for each molecule, we seek to identify structural patterns that could shed light on how molecular topology influences both the therapeutic effects and adverse reactions associated with these drugs. The ability to predict side effects or optimize therapeutic outcomes based on molecular structure is crucial in addressing issues such as opioid misuse or NSAID-induced gastrointestinal toxicity [5].

This study leverages graph theoretical approaches and computational tools, such as SageMath, to provide a detailed quantitative analysis of the structural features of these analgesics. Our findings are expected to enhance the understanding of the molecular mechanisms that govern drug efficacy and safety. Additionally, this analysis could contribute to the rational design of new analgesics with optimized therapeutic profiles and reduced risks, advancing efforts in safer pain management strategies.

2 Preliminaries

The management of pain, both acute and chronic, remains a cornerstone of medical treatment. To address varying levels of pain severity, analgesic medications are classified into several categories, with one of the most important distinctions being opioids or non-steroidal anti-inflammatory drugs (NSAIDs) [6]. This introduction provides a concise overview of the analgesics, included in this study, their chemical compositions, and their clinical indications.

Opioids are a class of drugs primarily used for pain relief, acting on the central nervous system (CNS) to alleviate moderate to severe pain [7]. They can be derived naturally from the opium poppy or synthesized in laboratories. Opioids are highly effective but carry the risk of addiction, tolerance, and dependence. The opioids included in this study are presented in Table 1 and in Figures 1 and 2.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are approved for their antipyretic, anti-inflammatory, and analgesic effects. They work by inhibiting the enzyme cyclooxygenase

Molecule	**Molecular formula**	**Description**
Oxycodone	$C_{18}H_{21}NO_4$	semisynthetic opioid derived from thebaine used for moderate to severe pain (Xtampza ER)
Fentanyl	$C_{22}H_{28}N_2O$	potent synthetic opioid for breakthrough pain in cancer patients (Subsys)
Hydrocodone	$C_{18}H_{21}NO_3$	semi-synthetic opioid derived from codeine, used for pain or cough (Tussionex Pennkinetic)
Methadone	$C_{21}H_{27}NO$	synthetic opioid for severe pain and opioid dependency, sold as Methadone Hydrochloride
Morphine	$C_{17}H_{19}NO_3$	natural opiate for chronic and severe pain with high addiction potential
Codeine	$C_{18}H_{21}NO_3$	mild opioid for treating mild to moderate pain (PennTuss, Tuzistra XR)
Tramadol	$C_{16}H_{25}NO_2$	synthetic pain reliever with (non)-opioid effects used to moderate severe pain
Hydromorphone	$C_{17}H_{19}NO_3$	potent derivative of morphine for severe pain (Dilaudid)
Buprenorphine	$C_{29}H_{41}NO_4$	used for opioid dependence, often combined with naloxone, available in sublingual tablets
Oxymorphone	$C_{17}H_{19}NO_4$	semi-synthetic opioid for moderate to severe pain, marketed as Opana (Opana ER)
Meperidine	$C_{15}H_{21}NO_2$	synthetic opioid for moderate severe and postoperative pain, known as Demerol
Alfentanil	$C_{21}H_{30}N_6O_3$	synthetic opioid for postoperative pain and g eneral anesthesia maintenance
Tapentadol	$C_{14}H_{23}NO$	newer opioid analgesic for severe, long-term pain management
Butorphanol	$C_{21}H_{29}NO_2$	synthetic opioid for moderate to severe pain, including migraines and as anesthesia adjunct
Diamorphine	$C_{21}H_{23}NO_5$	known as Heroin, used for severe pain in terminally ill patients with high addiction risk

Table 1: Overview of the opioids included in the study [8].

(COX), which lowers the production of eicosanoids like thromboxanes, prostaglandins, and prostacyclins and can be used to treat muscle pain, dysmenorrhea, arthritis, fever, gout, migraines, and as opioid alternatives in acute trauma. Unlike opioids, NSAIDs are not associated with the same risks of addiction or dependence but are instead known more for gastrointestinal and cardiovascular risks, for more details see [5]. The NSAIDs included in this study are presented in Table 2 and in Figure 3.

The molecules of analgesics presented must be modeled using a molecular graph, and then their topological indices can be calculated. In order to do that, we need to introduce some graph theory concepts.

Let $G = (V, E)$ be a *connected graph* defined on the set of vertices $V = V(G)$ and the set of edges $E = E(G)$ with at least one edge. Moreover, denote by $d(u, v)$ the standard shortest-path *distance* between vertices $u, v \in V(G)$. In addition, let $\deg(u)$ be the *degree* of vertex u. The distance $d(e, f)$ between edges e and f of graph G is the distance between the corresponding vertices e and f in the line graph $L(G)$ of G. Then the *Wiener index* $W(G)$ [4] and and the

Molecule	Molecular formula	Description
Naproxen	$C_{14}H_{14}O_3$	commonly used for reducing pain, fever, inflammation (EC-Naprosyn)
Diclofenac	$C_{14}H_{11}Cl_2NO_2$	treating pain and inflammation due to arthritis, surgery, or injury (Zorvolex)
Ibuprofen	$C_{13}H_{18}O_2$	common over-the-counter NSAID used for pain relief, fever reduction, and inflammation (Motrin, Advil)
Aspirin	$C_9H_8O_4$	acetylsalicylic acid (ASA), used for pain, fever, and inflammation relief, ommon in over-the-counter forms
Ketorolac	$C_{15}H_{13}NO_3$	used for short-term management of acute pain, often post-operative, nown for low addiction risk
Celecoxib	$C_{17}H_{14}F_3N_3O_2S$	COX-2 inhibitor used for osteoarthritis, rheumatoid arthritis, and acute pain management (Celebrex)
Acetaminiphen	$C_8H_9NO_2S$	used to treat mild to moderate pain and fever reducer

Table 2: Overview of the NSAIDs included in the study [8].

edge-Wiener index $W_e(G)$ [9–11] of a graph G are defined as:

$$W(G) = \sum_{\{u,v\}\subseteq V(G)} d(u,v),$$

$$W_e(G) = \sum_{\{e,f\}\subseteq E(G)} d(e,f).$$

Further, the *first Zagreb index* $M_1(G)$ and the *second Zagreb index* $M_2(G)$ of a graph G are defined as [12]:

$$M_1(G) = \sum_{uv\in E(G)} (\deg(u)+\deg(v)) = \sum_{u\in V(G)} \deg^2(u),$$

$$M_2(G) = \sum_{uv\in E(G)} \deg(u)\deg(v).$$

Randić introduced the *Randić index* $R(G)$ of a graph G, also called the *connectivity index*, as [13]:

$$R(G) = \sum_{uv\in E(G)} \frac{1}{\sqrt{\deg(u)\deg(v)}}.$$

Also a very well-known degree-based topological index is the *atom-bond connectivity index* $ABC(G)$ of a graph G, proposed by Estrada et al. [14]:

$$ABC(G) = \sum_{uv\in E(G)} \sqrt{\frac{\deg(u)+\deg(v)-2}{\deg(u)\deg(v)}}.$$

We will also consider the *Gutman index* $Gut(G)$ [15] and the *Schultz index* $Sc(G)$ [16, 17], that

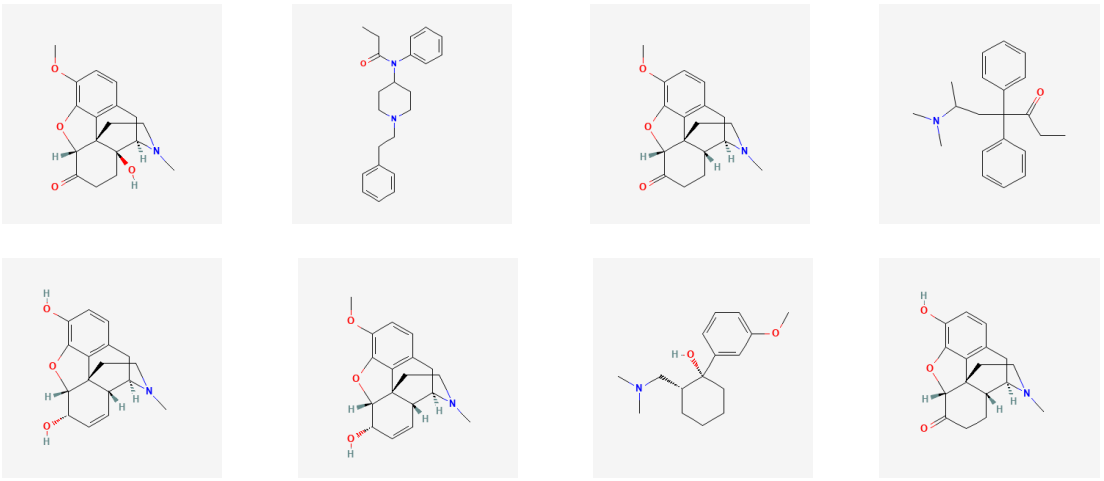

Figure 1: Molecules of opioids Oxycodone, Fentanyl, Hydrocodone, Methadone, Morphine, Codeine, Tramadol, and Hydromorphone.

are defined as:

$$Gut(G) = \sum_{\{u,v\}\subseteq V(G)} \deg(u)\deg(v)d(u,v),$$

$$Sc(G) = \sum_{\{u,v\}\subseteq V(G)} (\deg(u)+\deg(v))d(u,v).$$

For an edge $e = uv \in E(G)$, we introduce the following sets:

$$N_u(e|G) = \{x \in V(G) \mid d_G(u,x) < d_G(v,x)\},$$
$$N_v(e|G) = \{x \in V(G) \mid d_G(v,x) < d_G(u,x)\}.$$

Moreover, let

$$n_u(e) = |N_u(e|G)|,$$
$$n_v(e) = |N_v(e|G)|.$$

Then, the *Szeged index* $Sz(G)$ [18] and the *Mostar index* $Mo(G)$ [19] of a graph G are defined as:

$$Sz(G) = \sum_{e=uv\in E(G)} n_u(e)n_v(e) \quad \text{and} \quad Mo(G) = \sum_{e=uv\in E(G)} |n_u(e) - n_v(e)|.$$

3 Computational methods

3.1 Mathematical modeling and calculations

To apply graph theoretical methods to molecular structures, it is essential to represent molecules as molecular graphs denoted by $G = (V, E)$. In its most elementary form, each vertex in V corresponds to an atom within the molecule, excluding hydrogen atoms, while edges in E signify the presence of chemical bonds between the atoms. This simple unweighted model effectively captures the basic connectivity of the molecular structure.

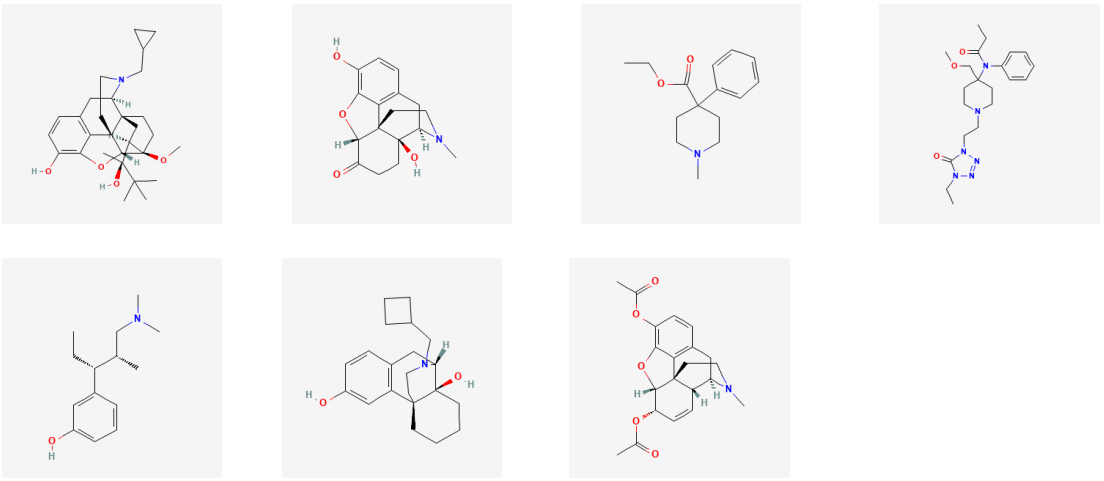

Figure 2: Molecules of opioids Buprenorphine, Oxymorphone, Meperidine, Alfentanil, Tapentadol, Butorphanol, and Diamorphine.

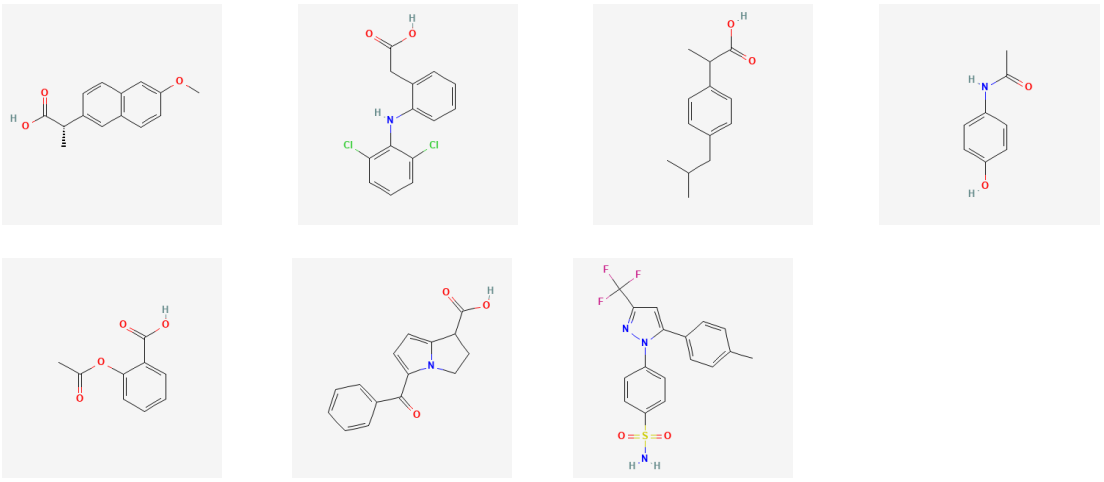

Figure 3: Molecules of NSAIDs Naproxen, Diclofena, Ibuprofen, Acetaminophen, Aspirin, Ketorolac, and Celecoxib.

However, more sophisticated representations involve the use of weighted molecular graphs. In such models, additional information is encoded by assigning weights either to the vertices or the edges or both. For example, weights on the vertices can account for the presence of heteroatoms, reflecting their distinct chemical properties, while edge weights may represent the multiplicity of chemical bonds (i.e., single, double, or triple bonds). Despite the potential richness of this approach, it is infrequently employed in practice. The primary reason for this reluctance is the absence of a standardized, universally accepted method for determining the appropriate weights for molecular graphs. Consequently, the unweighted model remains more common due to its simplicity and ease of implementation.

In this study, we utilized proprietary software to compute ten different topological indices: the Wiener index, the Gutman index, the Schultz index, the edge-Wiener index, the first Zagreb

index, the second Zagreb index, the Randić index, the ABC index, the Szeged index, and the Mostar index. All 22 molecules of analgesics were modeled with a molecular graph and then the corresponding adjacency matrices were used as an input data for the calculation of all ten investigated topological indices. These topological indices were calculated with the aid of the Sage mathematical software system. The comprehensive results of these computations are presented in Table 7, offering valuable insights into the structural properties of the molecules under consideration.

3.2 Data collection

Information regarding the chemical properties of the substances used in the computational analysis was sourced from PubChem, an open chemistry database provided by the National Institutes of Health (NIH) [8]. Specifically, the molecular structure, boiling point, melting point, and $\log P$ (partition coefficient) values were extracted for each substance.

Information on the adverse effects of the drugs were gathered from two sources: Drugs.com [20] and Medscape [21]. Drugs.com, which is sourced by agents such as the American Society of Health-System Pharmacists (ASHP), FDA, Truven Health Analytics, Harvard Health and Cerner Multum, provided peer-reviewed, and independent data for the following substances: Ketorolac, Naproxen, Fentanyl, Tramadol, Codeine, Hydromorphone, and Acetaminophen. Medscape, a global platform regulated and updated by staff pharmacists and its Advisory Board, using a Literature Survey Process to review key medical journals, FDA announcements, and practice guidelines, was used to obtain side effect data for Celecoxib, Butorphanol, Alfentanil, Oxycodone, Morphine, Oxymorphone, Diclofenac, Ibuprofen, Buprenorphine, and Tapentadol. We have to mention that the data for the side effects is not available for every drug in the studied set of 22 analgesics. For example, for Diamorphine (also known as Heroin) and Meperidine, we did not find any numerical data on side effects in the mentioned sources. Also, some numerical values are given in a range, in which case we have taken the arithmetic mean as the numerical value for statistical analysis. For all the data, see Tables 8 and 9.

3.3 Statistical analysis

Once the data was extracted and topological indices computed, the remaining statistical analysis was conducted using RStudio. A preliminary examination of all independent variables was performed to assess potential multicollinearity. A threshold for multicollinearity was set at a correlation coefficient 0.8 or higher. Variables exceeding this threshold are considered to exhibit significant multicollinearity, leading to the removal of one variable from each highly correlated pair/cluster. The Schultz index is not well correlated with other topological indices and was therefore included in the cluster. All other topological indices show relatively high correlations. The correlation ability is an important factor in analyzing graph invariants, but it is not subtle enough to provide deeper insights. The discrimination power, which measures the ability to structurally distinguish graphs, is an important property of topological indices and note that correlated topological indices do not necessarily have the same discrimination power [22]. Therefore three other topological indices were included in the investigated cluster: the Randić index, one of the most investigated indices, the Mostar index, the recently introduced topological index, which has gained much popularity among researchers in the chemical graph theory, and lastly the ABC index, which proves effective in correlating with a variety of molecular properties.

Following variable selection, two multilinear linear regression models were created. The models used R^2 values to quantify the proportion of variance in the dependent variables -

molecular properties and side effects, both explained by the selected topological indices. The first model focused on molecular properties, including boiling point, melting point, and $\log P$, while the second model analyzed the various side effects considered in this study.

After that, the topological indices were normalized by dividing them by the number of vertices in order to eliminate the effect of molecular size. Subsequently, all the statistical analysis were re-run to assess any potential changes in the results.

The initial statistical analysis was performed on the set of 22 molecules of analgesic drugs. They can be classified into two groups, the opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Finally, the statistical analysis was implemented separately for both sets and R^2 values were calculated to quantify the proportion of variance in the molecular properties analysis and side effects analysis.

4 Results

First, we calculate the correlation coefficients between the topological indices and the properties and then also between the topological indices and the side effects of the analgesic molecules under consideration for each topological index individually. The highest correlation coefficient within the properties is obtained for the boiling point, $R = 0.48$, and for the side effects the highest correlation coefficient is $R = 0.62$. As these are not the best results, we performed the multilinear regression with 10 topological indices. Due to the intercorrelations between them, four of them were determined in the factor analysis: the Schultz index, the Randić index, the ABC index and the Mostar index. The results are visualized in the heat-maps in Figure 4, in which the R^2 values for each combination of the four topological indices are displayed in relation to the properties of the 22 molecules analyzed and the associated side effects. The best results are obtained for the property $\log P$, where all 4 indices together give the coefficient of determination $R^2 = 0.44$. The same combination of indices also gives the highest value for the boiling point and the melting point, but R^2 values is lower in these two cases. The situation is similar with the coefficient of determination for the side effects. The highest R^2 values are achieved when all 4 topological indices are encountered. Top correlations are obtained for the headache, where $R^2 = 0.49$, and for the nausea with $R^2 = 0.29$. For other side effects the R^2 values are even lower.

The statistical analysis was then carried out again using the normalized topological indices, where each index was normalized with the order of the underlying molecular graph. However, the results did not significantly change, so we continue the analysis with the standard topological indices.

The 22 drugs considered in this study can be divided into two subgroups. The first group consists of 15 opioids and the second of 7 NSAIDs. The multilinear regressions were again performed on each of those two subsets separately.

In the case of opioids, the best results are again achieved when all four indices are combined, see Figure 5. For the property $\log P$, the R^2 value increases significantly from 0.44 for the entire set of 22 molecules to $R^2 = 0.70$ for the subset of 15 opioids. The R^2 values for the boiling point and melting point are also significantly higher at 0.36 and 0.44, respectively. When looking at the results for the correlation between topological indices and side effects of opioids, we need to be careful in the interpretation. Indeed, when all four indices are combined, the R^2 for the side effect hypertension is equal to 1 (see Figure 5, right side). However, due to the lack of data, the analysis for this side effect is only performed on the basis of 5 molecules and is therefore not statistically very significant. High R^2 values are then obtained for vomiting ($R^2 = 0.46$) and headache ($R^2 = 0.38$), where the multilinear regressions with four topological indices are

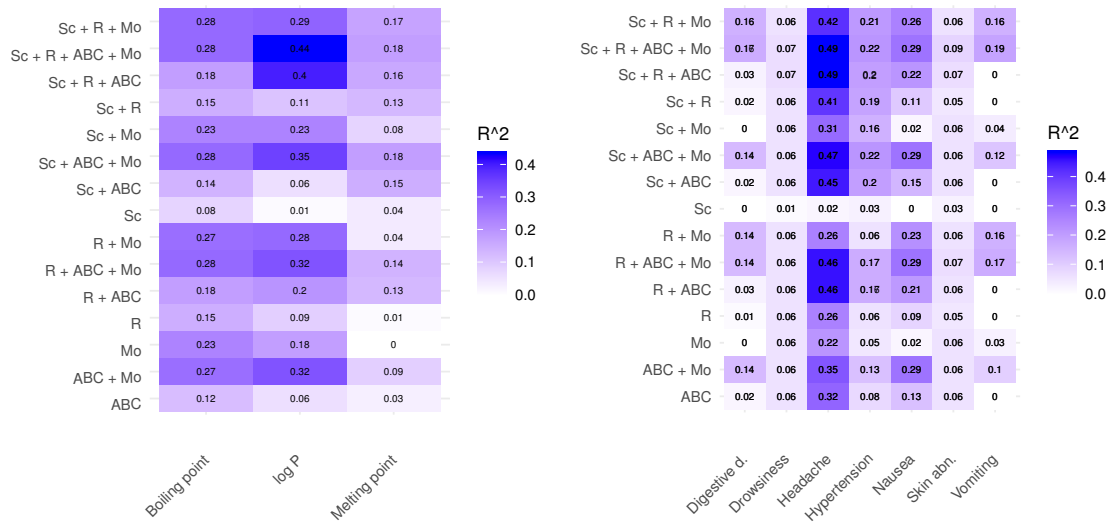

Figure 4: Heat-maps of R^2 values for the combinations of selected topological indices in relation to molecular properties (left) and side effects (right) for all 22 molecules.

performed on the set of 13 and 8 molecules, respectively. For other side effects correlations are lower.

However, the results for the opioid subset exhibit stronger correlations than those for the entire dataset, as anticipated due to the clustering of structurally similar molecules. The primary limitation of this approach is the reduced sample size, which may yield results with limited statistical significance.
Multilinear regression analysis was also conducted for the NSAIDs subset. The resulting R^2 values are presented in Figure 6, with values for properties on the left and side effects on the right. Although the R^2 values are notably high, the original set includes only 7 molecules, and incomplete data for certain side effects (drowsiness and nausea) limited the analysis to just 4 molecules in these cases. Consequently, these results lack statistical robustness. For the remaining side effects, the subset consisted of 5 to 6 molecules, further underscoring the need for cautious interpretation. In the multilinear regression analysis the coefficient of the determination R^2 always increases when more predictors are added to the model, regardless of whether those predictors improve the model. The adjusted R^2 value adjusts the R^2 value to account for the number of predictors in the model. It penalizes the addition of unnecessary predictors that do not improve the model significantly. Therefore we also calculate the adjusted R^2 values for the set of all 22 molecules, see Table 3 for molecular properties and Table 4 for molecular side effects. Regarding the molecular properties the highest adjusted $R^2 = 0.30$ value is obtained for the property $\log P$, when considering all four topological indices. Unfortunately, this values is quite low, so the linear regression model based of this topologicel indices can not be considered as a good predictor. When considering the adjusted R^2 for molecular side effects, the highest value is obtained for the headache, where the adjusted $R^2 = 0.35$.

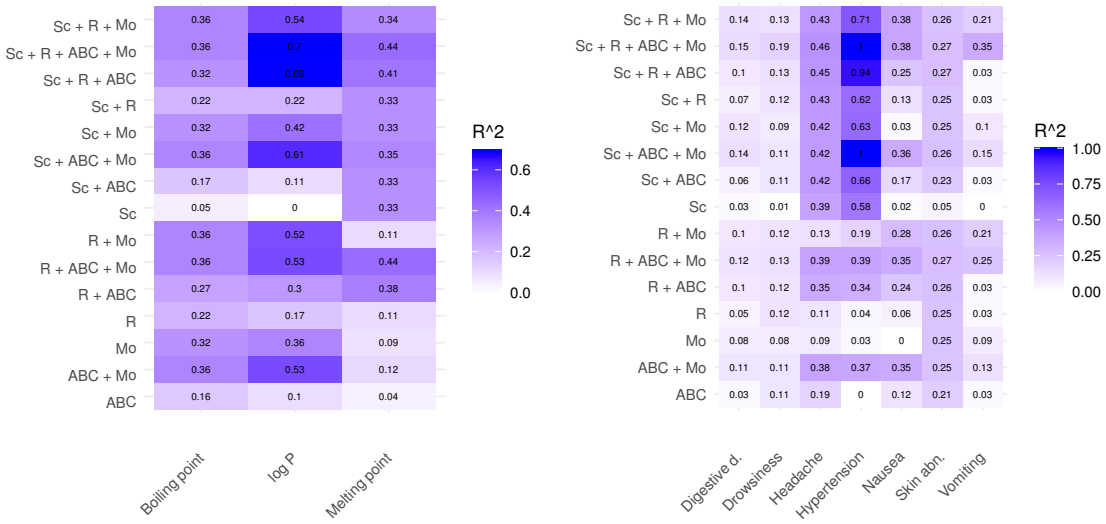

Figure 5: Heat-maps of R^2 values for the combinations of selected topological indices in relation to molecular properties (left) and side effects (right) for 15 opiods.

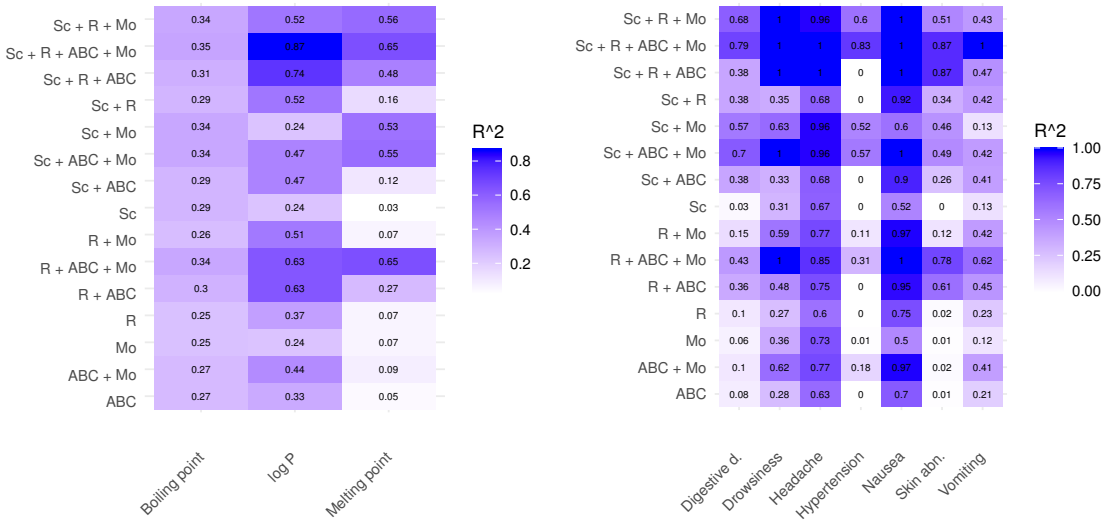

Figure 6: Heat-maps of R^2 values for the combinations of selected topological indices in relation to molecular properties (left) and side effects (right) for 7 NSAIDs.

TI	Boiling point		Melting point		log$P$	
	R^2	R^2-adj.	R^2	R^2-adj.	R^2	R^2-adj.
Sc	0.0823	0.0364	0.0393	-0.0087	0.0071	-0.0426
R	0.1499	0.1074	0.0101	-0.0394	0.0894	0.0439
ABC	0.1248	0.081	0.0255	-0.0232	0.0566	0.0095
Mo	0.2326	0.1942	0.0014	-0.0485	0.1839	0.1431
Sc + R	0.1518	0.0625	0.1332	0.042	0.1117	0.0182
Sc + ABC	0.1358	0.0448	0.1487	0.059	0.0605	-0.0384
Sc + Mo	0.2326	0.1518	0.0769	-0.0203	0.2296	0.1485
R + ABC	0.1766	0.09	0.1343	0.0431	0.197	0.1125
R + Mo	0.2724	0.1958	0.0392	-0.0619	0.2814	0.2058
ABC + Mo	0.2749	0.1986	0.0931	-0.0024	0.3181	0.2463
Sc + R + ABC	0.182	0.0457	0.163	0.0235	0.3969	0.2964
Sc + R + Mo	0.278	0.1577	0.1746	0.037	0.2935	0.1757
Sc + ABC + Mo	0.2751	0.1543	0.1821	0.0458	0.3529	0.2451
R + ABC + Mo	0.2756	0.1549	0.1383	-0.0053	0.3219	0.2089
Sc + R + ABC + Mo	0.2781	0.1082	0.1822	-0.0103	0.4363	0.3036

Table 3: R^2 and adjusted R^2 for the properties of all 22 molecules.

TI	Hypertension		Vomiting		Drowsiness		Nausea	
	R^2	R^2-adj.	R^2	R^2-adj.	R^2	R^2-adj.	R^2	R^2-adj.
Sc	0.0271	-0.0810	0.0000	-0.0625	0.0088	-0.0620	0.0029	-0.0636
R	0.0576	-0.0472	0.0012	-0.0612	0.0617	-0.0053	0.0932	0.0327
ABC	0.0848	-0.0169	0.0012	-0.0612	0.0583	-0.0090	0.1346	0.0769
Mo	0.0548	-0.0503	0.0282	-0.0325	0.0607	-0.0064	0.0238	-0.0413
Sc + R	0.1924	-0.0095	0.0022	-0.1309	0.0637	-0.0804	0.1136	-0.0130
Sc + ABC	0.1976	-0.0030	0.0018	-0.1313	0.0583	-0.0866	0.1490	0.0274
Sc + Mo	0.1592	-0.0510	0.0408	-0.0871	0.0615	-0.0828	0.0246	-0.1147
R + ABC	0.1650	-0.0437	0.0012	-0.1319	0.0617	-0.0826	0.2082	0.0951
R + Mo	0.0576	-0.1780	0.1576	0.0452	0.0630	-0.0812	0.2307	0.1208
ABC + Mo	0.1298	-0.0877	0.1029	-0.0167	0.0627	-0.0815	0.2887	0.1870
Sc + R + ABC	0.1983	-0.1453	0.0027	-0.2110	0.0661	-0.1674	0.2222	0.0427
Sc + R + Mo	0.2138	-0.1231	0.1576	-0.0229	0.0647	-0.1691	0.2584	0.0873
Sc + ABC + Mo	0.2161	-0.1198	0.1168	-0.0724	0.0633	-0.1709	0.2887	0.1246
R + ABC + Mo	0.1722	-0.1825	0.1731	-0.0040	0.0630	-0.1713	0.2892	0.1251
Sc + R + ABC + Mo	0.2186	-0.3023	0.1890	-0.0606	0.0662	-0.2734	0.2894	0.0525

TI	Digestive distress		Headache		Skin abnormalities	
	R^2	R^2-adj.	R^2	R^2-adj.	R^2	R^2-adj.
Sc	0.0001	-0.0624	0.0208	-0.0682	0.0253	-0.0397
R	0.0119	-0.0499	0.2624	0.1953	0.0531	-0.0100
ABC	0.0171	-0.0443	0.3236	0.2621	0.0565	-0.0064
Mo	0.0011	-0.0613	0.2201	0.1491	0.0618	-0.0007
Sc + R	0.0168	-0.1143	0.4113	0.2936	0.0537	-0.0815
Sc + ABC	0.0219	-0.1085	0.4474	0.3369	0.0586	-0.0759
Sc + Mo	0.0011	-0.1320	0.3129	0.1755	0.0625	-0.0714
R + ABC	0.0336	-0.0952	0.4616	0.3539	0.0568	-0.0780
R + Mo	0.1419	0.0275	0.2632	0.1158	0.0619	-0.0721
ABC + Mo	0.1379	0.0230	0.3466	0.2159	0.0627	-0.0712
Sc + R + ABC	0.0336	-0.1735	0.4864	0.3152	0.0651	-0.1507
Sc + R + Mo	0.1638	-0.0154	0.4250	0.2333	0.0628	-0.1535
Sc + ABC + Mo	0.1417	-0.0422	0.4692	0.2922	0.0634	-0.1528
R + ABC + Mo	0.1446	-0.0387	0.4619	0.2825	0.0703	-0.1443
Sc + R + ABC + Mo	0.1650	-0.0919	0.4906	0.2359	0.0923	-0.2103

Table 4: R^2 and adjusted R^2 for the side effects of all 22 molecules.

Similarly as in the R^2 analysis we continue with the adjusted R^2 analysis separately on the subset of 15 opioids and then on the subset of of 7 NSAIDs. First we consider the subset of opioids, see Table 5 for molecular properties and Table 6 for molecular side effects. When considering the molecular properties of the opioids, the adjusted R^2 value is the higher again for the $\log P$. For the multilinear regression on three topological indices: the Schultz index, the Randić index and the ABC index, the adjusted $R^2 = 0.60$. Since the difference between $R^2 = 0.69$ in the adjusted R^2 is relatively small, all three mentioned topological indices contribute meaningful information to the prediciton of $\log P$.
For the molecular side effects, the higher value for the adjusted R^2 is achieved for the hypertension, but as mentioned above, the data set consists of only 5 molecules due to the lack of data. The best result is therefore obtained for the side effect headache, where the adjusted $R^2 = 0.29$ in the linear regression on Schultz index. Note that the R^2 value is the highest when all four topological indices were considered, but then the adjusted R^2 value was lower compared to the regressions on other combinations of topological indices. Therefore, the added indices do not improve the regression model.
The adjusted R^2 was also calculated for the subset of 7 NSAIDs. Since the model is highly likely to overfit due to the small number of observations the results ara trivial and are not included.

TI	Boiling point		Melting point		log$P$	
	R^2	R^2-adj.	R^2	R^2-adj.	R^2	R^2-adj.
Sc	0.0492	-0.0239	0.3274	0.2757	0.0002	-0.0767
R	0.2164	0.1561	0.1089	0.0403	0.1730	0.1094
ABC	0.1552	0.0902	0.0366	-0.0375	0.1007	0.0315
Mo	0.3228	0.2707	0.0950	0.0253	0.3606	0.3114
Sc + R	0.2164	0.0858	0.3311	0.2196	0.2190	0.0888
Sc + ABC	0.1652	0.0261	0.3275	0.2154	0.1094	-0.0390
Sc + Mo	0.3229	0.2100	0.3345	0.2236	0.4233	0.3272
R + ABC	0.2706	0.1491	0.3847	0.2821	0.2964	0.1791
R + Mo	0.3550	0.2476	0.1089	-0.0397	0.5203	0.4403
ABC + Mo	0.3626	0.2563	0.1185	-0.0285	0.5288	0.4503
Sc + R + ABC	0.3210	0.1358	0.4081	0.2467	0.6869	0.6015
Sc + R + Mo	0.3578	0.1827	0.3363	0.1553	0.5366	0.4102
Sc + ABC + Mo	0.3630	0.1893	0.3496	0.1722	0.6053	0.4977
R + ABC + Mo	0.3626	0.1887	0.4409	0.2884	0.5342	0.4072
Sc + R + ABC + Mo	0.3638	0.1093	0.4409	0.2172	0.6980	0.5772

Table 5: R^2 and adjusted R^2 for the properties of 15 opioids.

TI	Hypertension		Vomiting		Drowsiness		Nausea	
	R^2	R^2-adj.	R^2	R^2-adj.	R^2	R^2-adj.	R^2	R^2-adj.
Sc	0.5762	0.4349	3e-04	-0.0906	0.0051	-0.0943	0.0168	-0.0726
R	0.0393	-0.2810	0.0263	-0.0623	0.1169	0.0286	0.0611	-0.0243
ABC	0.0001	-0.3332	0.0266	-0.0619	0.1075	0.0183	0.1219	0.0421
Mo	0.0272	-0.2971	0.0908	0.0082	0.0845	-0.0071	0.0043	-0.0862
Sc + R	0.6230	0.2461	0.0295	-0.1646	0.1229	-0.0720	0.1265	-0.0482
Sc + ABC	0.6556	0.3111	0.0270	-0.1676	0.1075	-0.0908	0.1671	0.0005
Sc + Mo	0.6304	0.2607	0.1002	-0.0797	0.0856	-0.1176	0.0309	-0.1629
R + ABC	0.3425	-0.3151	0.0269	-0.1677	0.1170	-0.0793	0.2397	0.0877
R + Mo	0.1855	-0.6289	0.2061	0.0473	0.1239	-0.0708	0.2811	0.1373
ABC + Mo	0.3711	-0.2578	0.1305	-0.0434	0.1076	-0.0907	0.3520	0.2224
Sc + R + ABC	0.9442	0.7769	0.0302	-0.2931	0.1346	-0.1899	0.2492	-0.0010
Sc + R + Mo	0.7116	-0.1535	0.2062	-0.0584	0.1317	-0.1940	0.3782	0.1709
Sc + ABC + Mo	0.9998	0.9992	0.1488	-0.1349	0.1077	-0.2270	0.3552	0.1403
R + ABC + Mo	0.3867	-1.4532	0.2450	-0.0066	0.1256	-0.2022	0.3526	0.1369
Sc + R + ABC + Mo	1.0000	NA	0.3506	0.0259	0.1917	-0.2702	0.3782	0.0673

TI	Digestive distress		Headache		Skin abnormalities	
	R^2	R^2-adj.	R^2	R^2-adj.	R^2	R^2-adj.
Sc	0.0312	-0.0657	0.3933	0.2921	0.0528	-0.0524
R	0.0480	-0.0472	0.1124	-0.0356	0.2519	0.1688
ABC	0.0277	-0.0696	0.1922	0.0576	0.2055	0.1172
Mo	0.0832	-0.0085	0.0941	-0.0568	0.2473	0.1636
Sc + R	0.0728	-0.1332	0.4264	0.1970	0.2534	0.0667
Sc + ABC	0.0610	-0.1477	0.4220	0.1909	0.2289	0.0361
Sc + Mo	0.1159	-0.0806	0.4213	0.1898	0.2517	0.0646
R + ABC	0.0959	-0.1050	0.3467	0.0854	0.2639	0.0799
R + Mo	0.0966	-0.1041	0.1282	-0.2206	0.2575	0.0718
ABC + Mo	0.1090	-0.0891	0.3828	0.1359	0.2488	0.0610
Sc + R + ABC	0.0976	-0.2408	0.4450	0.0288	0.2706	-0.0420
Sc + R + Mo	0.1443	-0.1766	0.4302	0.0029	0.2595	-0.0579
Sc + ABC + Mo	0.1392	-0.1836	0.4221	-0.0113	0.2551	-0.0642
R + ABC + Mo	0.1159	-0.2156	0.3936	-0.0613	0.2655	-0.0493
Sc + R + ABC + Mo	0.1461	-0.3418	0.4602	-0.2594	0.2708	-0.2153

Table 6: R^2 and adjusted R^2 for the side effects of 15 opioids.

5 Discussion

Overall, the study demonstrates the potential of combining multiple topological indices for analysing the relationship between molecular structure and properties, but also highlights the limitations posed by small sample sizes and the need for further refinement of the models. Thus, the models with multiple regression on topological indices indicate potential predictive power, so this line of research can be continued and improved with the use of more independent topological indices. For example, recently introduced root-indices [22–24] might be considered as well.

The analysis of the relationship between topological indices and the side effects of analgesics provides valuable insights into potential patterns dictated by the molecular structures of these compounds. Despite the moderate correlations observed and the limitations posed by the available data, the results remain noteworthy. It is important to highlight that these analysis were performed using real life data, which means that the correlations identified are directly linked to the actual physico-chemical properties and side effects of the drugs in clinical practice.

Even though the findings are limited by the sample size, their significance lies in contributing to a deeper understanding of the structure-property relationships and offering a solid basis for future studies with larger datasets.

Molecule	W	Gut	Sc	W_e	MM_1	MM_2	R	ABC	Sz	Mo
Fentanyl	1680	7469	7091	1865	124	142	12.28	19.08	2538	379
Tramadol	670	2640	2670	658	96	112	9.06	14.4	1038	234
Butorphanol	1145	5776	5152	1447	144	183	11.62	19.77	2612	340
Meperidine	568	2263	2276	564	90	106	8.69	13.53	871	220
Alfentanil	2599	10985	10702	2756	152	180	14.54	22.62	3604	580
Codeine	824	4108	3694	1045	136	178	10.66	18.18	2007	258
Oxycodone	907	4423	4022	1124	144	191	11.03	18.99	2189	296
Morphine	530	2112	2126	527	132	173	10.13	17.58	934	132
Hydromorphone	712	3631	3227	925	132	173	10.13	17.58	1790	231
Hydrocodone	824	4108	3694	1045	136	178	10.66	18.18	2007	258
Oxymorphone	788	3922	3529	998	140	186	10.49	18.39	1958	267
Buprenorphine	2624	12998	1172	3300	220	293	16.02	28.47	5957	728
Methadone	1044	4052	4128	1010	114	135	11.02	17.18	1404	406
Tapentadol	448	1578	1690	392	74	82	7.54	11.67	583	158
Heroin	1548	7157	6689	1811	160	203	12.91	22.04	3268	427
Naproxen	530	2112	2126	527	86	100	8.11	12.93	934	132
Ketorolac	693	3091	2935	787	102	123	9.18	14.93	977	209
Celecoxib	1654	6909	6780	1736	142	166	12.05	20.62	2432	440
Diclofenac	706	2840	2840	708	94	107	9.08	14.46	1054	228
Aspirin	246	851	921	211	60	66	6.11	9.55	348	93
Ibuprofen	404	1417	1521	352	70	77	7	11.07	572	101
Acetaminophen	166	589	629	146	50	53	5.18	8.11	250	53

Table 7: Topological indices of all 22 considered analgesics molecules.

6 Conclusions

Software tools like SageMath have enabled the calculation of a wide range of topological indices, facilitating large-scale screening of drug candidates. These tools have allowed researchers to handle molecular data computationally, but the connection between these indices and clinical outcomes remains an ongoing challenge. Molecular dynamics simulations and quantum chemistry calculations are often used in conjunction with graph theoretical approaches to refine predictions of molecular behavior.

There is growing interest in integrating machine learning with graph theoretical methods, where topological indices are used as features in predictive models. This is particularly relevant for personalized medicine and the development of safer analgesics with reduced side effects. The exploration of multi-objective optimization in drug design is also becoming more common, where multiple properties (efficacy, safety, pharmacokinetics) are optimized simultaneously, using graph theoretical models to quantify molecular features.

Despite advancements in the application of topological indices to drug design, there remains a gap in directly linking these indices to clinical side effects for analgesics, particularly opioids and NSAIDs. The lack of a standardized method for defining weights in molecular graphs and the complexity of capturing dynamic molecular behaviors (e.g., conformational changes) limit

Molecule	Boiling point $[C^\circ]$	Melting point $[C^\circ]$	$\log P$
Oxycodone	501.6	219	0.70
Fentanyl	466	85.2	4.05
Hydrocodone	461.4	198	1.20
Methadone	423.7	235	3.93
Morphine	190	255	0.87
Codeine	250	157.5	1.39
Tramadol	388.1	180	1.34
Hydromorphone	475	266	1.06
Buprenorphine	570.1	217	4.98
Oxymorphone	190	248	0.83
Meperidine	390.4	270	2.72
Alfentanil	511.8	140.8	2.16
Tapentadol	323.5	203.5	2.87
Butorphanol	507.3	273	3.30
Diamorphine	273	173	1.58
Naproxen	403.9	155	3.14
Diclofenac	412	284	4.51
Ibuprofen	319.6	76	3.97
Aspirin	140	139	1.18
Acetaminophen	500	170	0.46
Ketorolac	493.2	163	2.10
Celecoxib	529	158	3.53

Table 8: Properties of all 22 considered analgesics molecules.

the predictive power of these indices. A more comprehensive integration of bioactivity data, pharmacokinetics, and toxicology with topological models is needed to enhance the utility of these approaches in real-world drug design. So far, graph theoretical methods, particularly topological indices, have been useful in analyzing the structural properties of analgesics and other drugs. However, while some progress has been made, especially in predicting physicochemical properties, there is still substantial room for further research to connect molecular topology with specific clinical outcomes, such as side effects and safety profiles. This remains an active area of exploration, with future studies likely focusing on refining these models and integrating them with more advanced computational and machine learning techniques.

Conflicts of Interest. The authors declare that they have no conflicts of interest regarding the publication of this article.

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Molecule	Hypert.	Vomit.	Drows.	Nausea	Dig. d.	Headache	Skin abn.
Oxycodone	NA	13	NA	25	15.5	14	1
Fentanyl	0.5	10	10	18	10	5	5
Hydrocodone	NA	4	5	8.5	9.5	5	3
Methadone	NA	10	5	10	5	NA	5
Morphine	NA	38.5	5.5	7.5	17.5	22	5.5
Codeine	NA	2	5.5	5.5	5.5	1	0.5
Tramadol	NA	6.4	37.2	42.6	23.4	NA	NA
Hydromorphone	NA	15	14	15	28	31	12
Buprenorphine	0.5	6.4	0.5	11.8	9.4	29.6	0.5
Oxymorphone	0.5	9	9	19	4	7	8
Meperidine	NA	NA	NA	NA	NA	NA	NA
Alfentanil	18	18	1	28	NA	NA	0.5
Tapentadol	NA	18	15	30	8	NA	5
Butorphanol	10	10	49	10	10	NA	NA
Diamorphine	NA	NA	NA	NA	NA	NA	NA
Naproxen	19	9.1	18	6.1	6.1	3	NA
Diclofenac	5.5	NA	NA	NA	10	NA	30
Ibuprofen	23	2	6	NA	2	2	6
Aspirin	NA	NA	NA	NA	NA	NA	0.5
Acetaminophen	5.5	15	NA	34	5.5	5.5	5.5
Ketorolac	5	5	5	10	10	10	5
Celecoxib	13	6	2	3.5	5.6	13	2.2

Table 9: Side effects of all 22 considered analgesics molecules.

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