INFLUENCE OF FUNCTIONAL GROUPS ON THE PHYSICOCHEMICAL PROPERTIES OF SMALL MOLECULES

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The study analyzes the influence of various functional groups on the physicochemical properties of small molecules with a benzene core. Key properties such as solubility, partition coefficient, molecular weight, the number of hydrogen bonds, and rotatable bonds were calculated, while pKa values were determined using computational methods. The obtained data revealed patterns in how functional groups affect molecular properties, which is crucial for predicting bioavailability and designing pharmaceutical compounds.

Keyword: small molecules; physicochemical properties; functional group; solubility; partition coefficient; Lipinski's Rule of Five

ВЛИЯНИЕ ФУНКЦИОНАЛЬНЫХ ГРУПП НА ФИЗИКО-ХИМИЧЕСКИЕ СВОЙСТВА МАЛЫХ МОЛЕКУЛ

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В исследовании проанализировано влияние различных функциональных групп на физико-химические свойства малых молекул с бензольным кольцом. Для оценки свойств были рассчитаны растворимость, коэффициент распределения, молекулярная масса, число водородных связей и вращаемых связей, а значения pKa определены с помощью вычислительных методов. Полученные данные позволили выявить закономерности влияния функциональных групп на свойства молекул, что важно для прогнозирования их биодоступности и разработки лекарственных соединений.

Ключевые слова: малые молекулы; физико-химические свойства; функциональная группа; растворимость; коэффициент распределения; правило пяти Липинского

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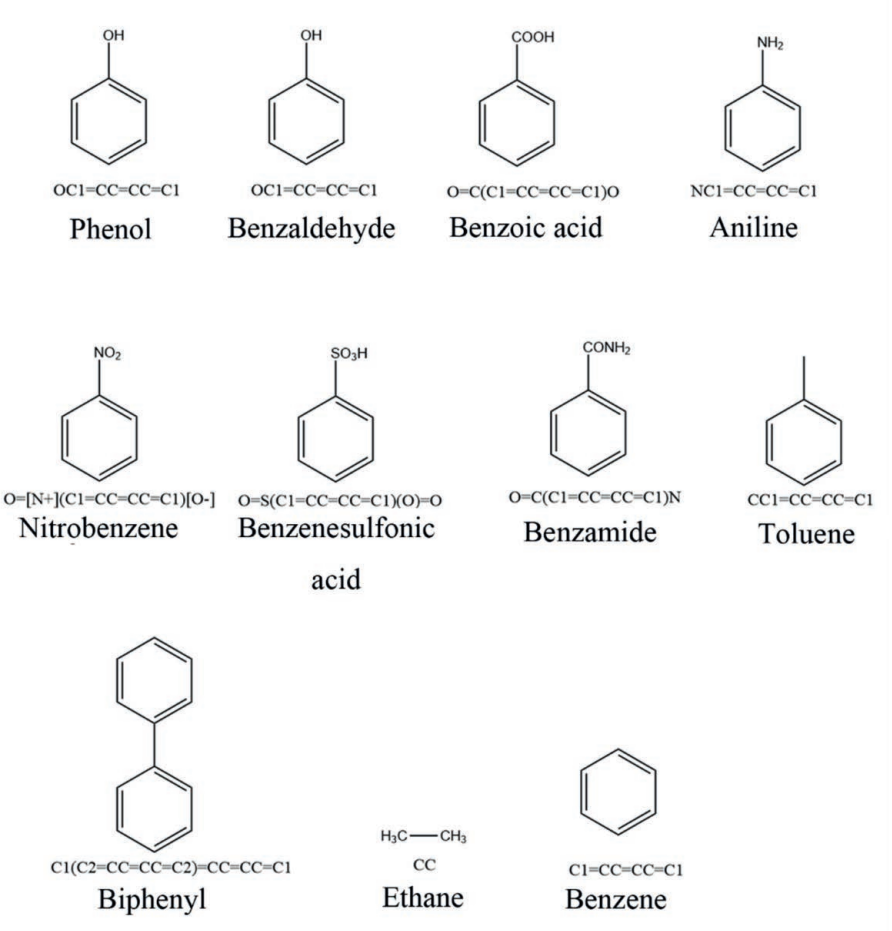
This study investigates the impact of different functional groups on small molecules with a benzene core. Eleven structurally similar molecules were designed, each incorporating distinct functional groups such as hydroxyl, methoxy, nitro, and amino. Chemical structures were drawn, and SMILES representations were generated. Key physicochemical properties were calculated using SwissADME [1] (http://www.swissadme.ch) and Chemaxon (https://chemaxon.com), including pKa, solubility, rotatable bonds, partition coefficient, molecular mass, and hydrogen bonding capacity.

By analyzing and comparing the collected data, the study identifies specific trends in how functional groups affect molecular properties. The findings contribute to a deeper understanding of how structural modifications influence drug-like properties, providing insights into the rational design of bioactive molecules.

By entering the SMILES representation of each small molecule (figure 1), key physicochemical properties, including solubility, the number of rotatable bonds, the distribution coefficient (LogP), molecular weight, and hydrogen bond acceptors/donors, were successfully calculated using SwissADME. Additionally, the pKa values of ionizable small molecules were determined using the Chemaxon online calculator.



Small molecules structures

The data of these small molecules were calculated and statistically analyzed using the above method, and the data were summarized into a table. The following table is a data table of the pKa and solubility of these small molecules.

Table 1

Molecular pKa and solubility data table

name	pKa	Water Solubility		
	acid	Log S (ESOL)	Solubility	Class
Phenol	10.2	-1.98	1.05e-02 mol/l	Very soluble
Benzaldehyde	none	-1.92	1.20e-02 mol/l	Very soluble
Benzoic acid	4.08	-2.2	6.27e-03 mol/l	Soluble
Aniline	4.64	-1.62	2.41e-02 mol/l	Very soluble
Nitrobenzene	none	-2.2	6.37e-03 mol/l	Soluble
Benzenesulfonic acid	2.36	-1.2	6.24e-02 mol/l	Very soluble
Benzamide	14.56	-1.42	3.79e-02 mol/l	Very soluble
Toluene	none	-2.77	1.72e-03 mol/l	Soluble
Biphenyl	none	-3.98	1.05e-04 mol/l	Soluble
Ethane	none	-0.85	1.43e-01 mol/l	Very soluble
Benzene	NONE	-2.41	3.92e-03 mol/l	Soluble

From the table 1, we can see that Phenol, Benzoic acid, Aniline, Benzenesulfonic acid and Benzamide are acidic, and the Benzenesulfonic acid has the lowest pKa, indicating that it is the most acidic. Other molecules without pKa have no ionizable molecules. Among them, the sulfonic acid group has the greatest impact on acidity, while the amide group of Benzamide has the least impact on acidity.

At the same time, based on the solubility of benzene and ethane, the effects of functional groups on solubility can be compared and ranked from high to low: Benzene ring > Methyl group > Benzene ring > Carboxyl group > Nitro group > Hydroxyl group > Aldehyde group > Amino group > Amide group > Sulfonic acid group.

However, the methyl group alone does not have strong solubility. It needs to be present with a soluble functional group to have better solubility.

The following five data charts pertain to Lipinski's Rule of Five, a key criterion for assessing the quality of designed drug compounds.

Table 2

Lipinski's Rule of Five Data Table

name	RO5				
	Molecular weight	H-bond acceptors	H-bond donors	Log Po/w (iLOGP)	Num. rotatable bonds
Phenol	94.11 g/mol	1	1	1.24	0
Benzaldehyde	106.12 g/mol	1	1	1.36	1
Benzoic acid	122.12 g/mol	2	1	1.11	1
Aniline	93.13 g/mol	0	1	1.2	0
Nitrobenzene	123.11 g/mol	2	0	1.33	1
Benzenesulfonic acid	158.18 g/mol	3	1	0.46	1
Benzamide	121.14 g/mol	1	1	1.08	1
Toluene	92.14 g/mol	0	0	1.85	0
Biphenyl	154.21 g/mol	0	0	2.26	1
Ethane	30.07 g/mol	0	0	1.47	0
Benzene	78.11 g/mol	0	0	1.58	0

By comparing and analyzing the data from Table 2, the impact of different functional groups on lipophilicity can be ranked from highest to lowest as follows: Benzene ring > Methyl group > Carboxyl group > Nitro group > Hydroxyl group > Aldehyde group > Amino group > Amide group > Sulfonic acid group. Since ethane and benzene lack hydrogen bond acceptors, donors, and rotatable bonds, any changes in these parameters are solely attributed to the effects of functional groups.

The data analysis for all tested molecules has been completed and summarized as follows:

– *Hydroxyl group*: Increases molecular weight by 16 g/mol, adds 1 hydrogen bond acceptor, 1 hydrogen bond donor, 0 rotatable bonds; decreases lipid solubility, increases water solubility; ionizable, weakly acidic.

– *Aldehyde group*: Increases molecular weight by 28.01 g/mol, adds 1 hydrogen bond acceptor, 1 hydrogen bond donor, 1 rotatable bond; decreases lipid solubility, increases water solubility; non-ionizable.

– *Carboxyl group*: Increases molecular weight by 44.01 g/mol, adds 2 hydrogen bond acceptors, 1 hydrogen bond donor, 1 rotatable bond; decreases lipid solubility, increases water solubility; ionizable, acidic.

– *Amino group*: Increases molecular weight by 15.01 g/mol, adds 0 hydrogen bond acceptors, 1 hydrogen bond donor, 0 rotatable bonds; decreases lipid solubility, increases water solubility; ionizable, acidic.

– *Nitro group*: Increases molecular weight by 45 g/mol, adds 2 hydrogen bond acceptors, 0 hydrogen bond donors, 1 rotatable bond; decreases lipid solubility, increases water solubility; non-ionizable.

– *Sulfonic acid group*: Increases molecular weight by 80.07 g/mol, adds 3 hydrogen bond acceptors, 1 hydrogen bond donor, 1 rotatable bond; significantly decreases lipid solubility, greatly increases water solubility; ionizable, strong acid.

– *Amide group*: Increases molecular weight by 43.03 g/mol, adds 1 hydrogen bond acceptor, 1 hydrogen bond donor, 1 rotatable bond; decreases lipid solubility, increases water solubility; ionizable, weakly acidic.

– *Methyl group*: Increases molecular weight by 14.03 g/mol, adds 0 hydrogen bond acceptors, 0 hydrogen bond donors, 0 rotatable bonds; increases lipid solubility, decreases water solubility; non-ionizable.

– *Benzene ring*: Increases molecular weight by 14.03 g/mol, adds 0 hydrogen bond acceptors, 0 hydrogen bond donors, 1 rotatable bond; increases lipid solubility, decreases water solubility; non-ionizable.

This summary provides valuable insights into how each functional group influences molecular properties, aiding in drug design while adhering to Lipinski's Rule of Five. Additionally, areas for improvement in the experiment were identified, such as expanding the range of functional groups, incorporating different substrates for the same functional group to reduce variability, and including more physicochemical properties for further analysis.

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