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«QSPR PREDICTION OF INTESTINAL ABSORPTION OF ACTIVE PHARMACEUTICAL INGREDIENTS»

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CONTENTS

LIST OF SYMBOLS AND ABBREVIATIONS

QSPR	quantitative structure–property relationship
K_a	human intestinal absorption rate constants
API	active pharmaceutical ingredient
%HIA	human intestinal absorption
R^2	coefficient of determination

INTRODUCTION

Actuality. Prediction of intestinal absorption is an important stage in modern drug development because oral administration remains the most widely used route for pharmaceutical therapy. The effectiveness of orally administered active pharmaceutical ingredients largely depends on their ability to be absorbed through the intestinal epithelium and reach systemic circulation in sufficient concentrations. Poor intestinal absorption may significantly reduce bioavailability and limit the therapeutic efficacy of drug candidates.

Experimental determination of human intestinal absorption is often expensive, time-consuming and ethically limited due to the need for in vivo studies. Therefore, the development of computational approaches capable of predicting absorption properties at early stages of pharmaceutical research has become highly relevant. Among these approaches, Quantitative Structure–Property Relationship (QSPR) modeling is considered one of the most promising tools because it allows the establishment of mathematical relationships between molecular structure and pharmacokinetic behavior.

QSPR prediction of intestinal absorption enables rapid screening of active pharmaceutical ingredients based on molecular descriptors such as lipophilicity, polarity, molecular size and hydrogen bonding capacity. The application of such models can reduce the number of experimental studies, optimize the selection of promising compounds and decrease the overall cost and duration of drug development.

The relevance of this topic is further supported by the growing importance of computer-assisted methods in pharmaceutical sciences, medicinal chemistry and pharmacokinetics. Development of reliable QSPR models for predicting human intestinal absorption contributes to rational drug design and improves understanding of the relationship between molecular structure and oral bioavailability of active pharmaceutical ingredients.

Aim and tasks of research. The aim of this study was to develop a QSPR model for predicting the intestinal absorption of active pharmaceutical ingredients based on their chemical structure.

Tasks of research:

− to determine the optimal set of molecular descriptors for the development of a QSPR model for intestinal absorption prediction;

− to develop a QSPR model for predicting the intestinal absorption of active pharmaceutical ingredients based on the selected descriptors;

− to evaluate the accuracy and predictive performance of the developed model using training and test datasets.

Object of the study. The object of the study was active pharmaceutical ingredients with known experimental values of human intestinal absorption.

Subject of the study. The subject of the study was the relationship between molecular descriptors of active pharmaceutical ingredients and their intestinal absorption properties.

Research methods: correlation analysis, multiple linear regression analysis and statistical evaluation of modeling results.

The software package MATLAB R2025b (trial license) and ChemDes were used in this work.

Novelty and significance of the results. The scientific novelty of this study is associated with the development of a QSPR model for predicting human intestinal absorption of active pharmaceutical ingredients using molecular structure descriptors. The study provides a systematic analysis of the relationship between physicochemical and structural characteristics of pharmaceutical compounds and their intestinal absorption behavior. An optimized subset of informative and statistically independent molecular descriptors was selected from a large initial descriptor pool, allowing reduction of data redundancy and improvement of model interpretability and predictive performance.

Unlike traditional experimental approaches for evaluating intestinal absorption, the developed model enables prediction of absorption properties

directly from molecular structure information. The proposed QSPR approach integrates descriptors related to molecular polarity, hydrogen bonding capacity, charge distribution and structural complexity, which are known to play important roles in passive intestinal permeation. The obtained regression model demonstrates statistically significant relationships between molecular descriptors and experimental values of intestinal absorption and confirms the applicability of computational methods for pharmacokinetic prediction.

The practical significance of the study lies in the possibility of applying the developed model for early-stage evaluation of active pharmaceutical ingredients during drug discovery and pharmaceutical development. Prediction of intestinal absorption is critically important because oral administration remains the most common route of drug delivery and insufficient absorption may significantly reduce bioavailability and therapeutic effectiveness. Experimental determination of intestinal absorption is often labor-intensive, expensive and ethically restricted; therefore, computational prediction methods represent an important alternative tool in modern pharmaceutical research.

The developed QSPR model can be used for preliminary screening of compounds, identification of potentially poorly absorbed molecules and optimization of molecular structures before experimental testing. Application of such computational approaches may reduce the number of required *in vitro* and *in vivo* experiments, decrease research costs and accelerate the development of new pharmaceutical compounds. In addition, the study contributes to a better understanding of the relationship between molecular structure and pharmacokinetic properties, which is an important aspect of rational drug design and modern medicinal chemistry.

Approbation of research results. The results of this work were presented at VII International Conference «Current issues in the development of branches of science», April 24, 2026, Bila Tserkva.

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Structure of work: 44 pages, 2 sections, supplementary information, 27 references.

1. LITERATURE REVIEW

1.2. Drug absorption after oral administration

For an orally administered drug to be effective, it must be adequately absorbed from the gastrointestinal tract. Although the stomach has a relatively large surface area and a thick mucosal lining, it plays a limited role in drug absorption. In contrast, the small intestine, due to its extensive villous surface area, is the primary site of absorption for most drugs.

The proportion of the administered dose that reaches the systemic circulation unchanged, referred to as bioavailability, results from a sequence of processes in which the drug must: (1) dissolve and remain stable within the gastrointestinal tract, (2) permeate the intestinal epithelium without degradation, and (3) pass through the liver without significant metabolism. Bioavailability is primarily influenced by drug solubility, permeability and stability toward metabolizing enzymes.

The rate of intestinal drug absorption is mainly determined by dissolution and permeability across the intestinal membrane. Drug transport across the intestinal epithelium occurs via passive diffusion, carrier-mediated transport and active transport mechanisms. In addition, efflux transporters can reduce intracellular drug accumulation and limit overall absorption [1, 2].

1.2. Mechanisms of intestinal drug permeation

The primary mechanisms of intestinal drug absorption include: (1) passive transcellular diffusion through epithelial cells; (2) paracellular diffusion through intercellular pores; (3) carrier-mediated active transport [3-7].

In passive transcellular and paracellular diffusion, molecules move along a concentration gradient, whereas active transport may occur against this gradient.

Multiple transport mechanisms can operate simultaneously, making it difficult to determine the dominant pathway for a given compound.

Passive transcellular diffusion

Passive transcellular diffusion is the most common mechanism of absorption for orally administered drugs. Compounds undergoing this process cross the apical membrane, diffuse through the cytoplasm and exit via the basolateral membrane into the systemic circulation.

The apical membrane is less fluid and less permeable than the basolateral membrane and therefore represents the rate-limiting barrier for intracellular diffusion. Diffusion through the cytoplasm is generally rapid.

The lipid composition of enterocyte membranes restricts the passage of highly hydrophilic compounds. However, excessively lipophilic compounds may become retained within the apical membrane and fail to traverse the aqueous cytoplasm. Therefore, an optimal balance between lipophilicity and hydrophilicity is required for efficient permeation.

The passage of molecules through the hydrophobic core of the phospholipid bilayer is limited by ionization and increased polarity. Smaller molecules diffuse more readily across membranes due to reduced steric hindrance. In contrast, ionized and highly polar compounds exhibit reduced permeability.

Paracellular transport

Paracellular transport involves the passage of hydrophilic molecules through aqueous pores between epithelial cells. It is generally considered a passive process driven by trans-epithelial concentration gradients.

Molecular charge influences permeability: neutral compounds typically permeate more readily than anions, while negatively charged species pass less efficiently through paracellular pores. Pore size limits this pathway primarily to small and medium-sized molecules.

Paracellular permeability is regulated by tight junction proteins, such as claudins and occludins, which determine pore size and selectivity. Although the overall contribution of this pathway to drug absorption is generally limited, it may

vary across different intestinal regions. Physiological and pathological conditions, such as inflammation or the presence of absorption enhancers, can alter tight junction integrity and increase paracellular permeability.

Active transport

Carrier proteins located in the apical membrane of enterocytes mediate the active transport of endogenous compounds, including ions, vitamins, sugars, amino acids and peptides. This process is energy-dependent and typically applies to drugs structurally similar to endogenous substrates. In addition to uptake transporters that facilitate absorption, enterocytes also express efflux transporters that actively export compounds back into the intestinal lumen.

Intestinal transporters are broadly classified into two major families:

– the solute carrier family (uptake transporters), including peptide transporter 1, organic anion transporting polypeptides and organic cation transporters;

– the ATP-binding cassette family (efflux transporters), including P-glycoprotein, multidrug resistance-associated protein 2 and breast cancer resistance protein.

Since many transporter substrates can also diffuse passively, active transport does not always significantly affect the absorption of sufficiently lipophilic drugs. Furthermore, because active transport is saturable, the relative contribution of passive diffusion increases at higher drug concentrations.

Epithelial structures determining passive intestinal drug permeation

The intestinal epithelium consists of a single layer of epithelial cells organized into villi, which significantly increase the absorptive surface area. Villi are separated by crypts, where epithelial cell renewal occurs. Epithelial cells are connected by intercellular junction complexes that both seal the intercellular space and regulate the movement of ions and solutes. The tight junction, the most apical component of this complex, is the primary determinant of paracellular permeability.

The intestinal epithelium is also covered by a mucus layer, which may act as an additional barrier to drug diffusion. Moreover, the expression of transporters and metabolic enzymes within enterocytes further influences drug permeability and metabolism. Regional variations in epithelial structure and function along the gastrointestinal tract can contribute to variability in drug absorption [8].

Enterocyte membrane

Cell membranes consist of a phospholipid bilayer containing proteins, cholesterol and glycolipids. Their composition varies between cell types and even within different regions of the same cell. Enterocytes exhibit two distinct membrane domains: (1) the apical membrane, facing the intestinal lumen; (2) the basolateral membrane, interfacing with adjacent cells and underlying tissue.

The apical membrane contains higher levels of cholesterol and glycolipids, making it thicker, less fluid and less permeable than the basolateral membrane. Its surface forms microvilli, collectively known as the brush border, which are coated with a glycocalyx layer. Because membrane lipids are amphiphilic, regional differences in polarity and hydrophobicity influence molecular transport across membranes. The asymmetric distribution of lipids and proteins between apical and basolateral membranes contributes to functional differences in permeability and transport [9, 10].

Tight junction pores

The paracellular pathway consists of pores formed by tight junctions within the intercellular space. These structures regulate the movement of ions and solutes and prevent the diffusion of membrane components, thereby maintaining epithelial polarity. Tight junctions are composed of: (1) transmembrane proteins that form continuous strands between adjacent cells; (2) cytoplasmic scaffold proteins that anchor these structures to the cytoskeleton.

Among tight junction proteins, claudins are the most abundant and play a central role in determining barrier properties. Claudins polymerize to form strands that create selective pores, allowing controlled passage of ions and small solutes.

Human perfusion studies have shown that permeability varies along the villus, with the tips being less permeable than the lower regions [11-13].

1.3. QSPR model for predicting intestinal absorption

A systematic strategy was applied for the development and validation of quantitative structure–property relationship models aimed at estimating human intestinal absorption rate constants. Computational approaches play a central role in predicting intestinal drug permeation and oral absorption in modern pharmaceutical research. These models rely on calculated molecular descriptors and are generally classified into two categories: simple qualitative approaches that relate physicochemical properties to bioavailability, and more advanced QSPR models that establish quantitative relationships between molecular structure and absorption properties. Most computational models are designed to describe transcellular permeability, as this is the dominant absorption pathway for the majority of sufficiently lipophilic compounds [14].

Over the past two decades, numerous QSPR models have been developed to predict intestinal drug absorption by correlating structural features with experimental and in vivo endpoints, including cell line permeability, artificial membrane permeability, human jejunal permeability and fraction absorbed in humans. A variety of statistical methods, ranging from linear regression models to artificial neural networks, have been applied to establish quantitative relationships between molecular descriptors and absorption characteristics. The development of a QSPR model typically involves several key steps: compilation of an appropriate dataset, calculation and selection of relevant molecular descriptors, construction of a quantitative model linking descriptors to permeability or absorption and rigorous model validation. The predictive reliability of QSPR models strongly depends on the quality, size and structural diversity of the dataset used [15-19].

Conclusions to section 1

1. Intestinal drug absorption is influenced by multiple physicochemical and biological factors, including solubility, permeability, lipophilicity, molecular size, intestinal epithelial structure and metabolic activity.

2. Passive transcellular diffusion is the predominant mechanism of intestinal permeation for most orally administered drugs, while transport proteins and tight junctions also contribute to drug absorption and bioavailability.

3. QSPR models and drug-likeness rules are important computational tools for predicting intestinal absorption and supporting the early stages of rational drug development.

2. EXPERIMENTAL PART

2.1. Data set

A list of studied active pharmaceutical ingredients (APIs):

1) Adefovir – an antiviral nucleotide analogue used mainly for the treatment of chronic hepatitis B infections;

2) Cidofovir – a broad-spectrum antiviral agent primarily used for the treatment of cytomegalovirus infections;

3) Lactulose – a synthetic sugar used as a laxative and for the treatment of hepatic encephalopathy;

4) Mannitol – an osmotic diuretic commonly used to reduce intracranial pressure and promote urine production;

5) Meropenem – a broad-spectrum carbapenem antibiotic used to treat severe bacterial infections;

6) Pamidronic acid – a bisphosphonate drug used to treat bone disorders such as hypercalcemia and osteoporosis;

7) Pentamidine – an antimicrobial agent used for the treatment of protozoal infections, including Pneumocystis pneumonia;

8) Phthalylsulfathiazole – a poorly absorbed sulfonamide antibacterial used mainly for intestinal infections;

9) Ticarcillin – a broad-spectrum β-lactam antibiotic effective against Gram-negative bacterial infections;

10) AAFC – a pharmaceutical compound or abbreviation requiring additional specification for accurate identification;

11) Amiloride – a potassium-sparing diuretic used in the treatment of hypertension and edema;

12) Bromocriptine – a dopamine receptor agonist used for Parkinson’s disease, hyperprolactinemia and endocrine disorders;

13) Chlorothiazide – A thiazide diuretic used to treat hypertension and fluid retention;

14) Cymarin – a cardiac glycoside with cardiotonic activity traditionally used in heart-related conditions;

15) Flucloxacillin – a β-lactam antibiotic primarily used against penicillinase-producing staphylococcal infections;

16) Fosmidomycin – a phosphonic acid derivative with antibacterial and antimalarial activity;

17) Metaproterenol – a bronchodilator used in the treatment of asthma and bronchospasm;

18) Methyldopa – a centrally acting antihypertensive agent commonly used during pregnancy;

19) Pravastatin – an HMG-CoA reductase inhibitor used to lower cholesterol and reduce cardiovascular risk;

20) Rimiterol – a short-acting bronchodilator used for the relief of bronchospasm;

21) Almotriptan – a selective serotonin receptor agonist used for the acute treatment of migraine attacks;

22) Anagrelide – a platelet-reducing agent used in the treatment of essential thrombocythemia;

23) Atenolol – a selective β1-adrenergic blocker used for hypertension and cardiovascular disorders;

24) Benserazide – a peripheral decarboxylase inhibitor used in combination with levodopa for Parkinson’s disease;

25) Bromhexine – a mucolytic agent used to reduce mucus viscosity in respiratory diseases;

26) Captopril – an angiotensin-converting enzyme inhibitor used for hypertension and heart failure;

27) Cefatrizine – a first-generation cephalosporin antibiotic used to treat bacterial infections;

28) Cycloserine – a second-line antibiotic used in the treatment of tuberculosis;

29) Dipyridamole – an antiplatelet and vasodilator agent used to prevent thromboembolic complications;

30) Eflornithine – an antiparasitic drug used in the treatment of African trypanosomiasis;

31) Ethambutol – a first-line antimycobacterial agent used in tuberculosis therapy;

32) Famciclovir – an antiviral drug used for herpesvirus infections;

33) Fenoterol – a bronchodilator used in asthma and other obstructive airway diseases;

34) Guanabenz – a centrally acting antihypertensive agent that stimulates α2-adrenergic receptors;

35) Hydrochlorothiazide – a thiazide diuretic commonly used for hypertension and edema;

36) Isocarboxazid – a monoamine oxidase inhibitor used in the treatment of depression;

37) Metformin – a first-line oral antidiabetic drug used for type 2 diabetes mellitus;

38) Metolazone – a diuretic used to treat hypertension and fluid retention;

39) Mianserin – a tetracyclic antidepressant used in the treatment of depressive disorders;

40) Mibefradil – a calcium channel blocker formerly used for hypertension and angina;

41) Oxycodone – a potent opioid analgesic used for moderate to severe pain management;

42) Pimozide – a diphenylbutylpiperidine antipsychotic used for Tourette syndrome and chronic psychosis;

43) Propylthiouracil – an antithyroid agent used in the treatment of hyperthyroidism;

44) Pyrbuterol – a short-acting bronchodilator used in asthma therapy;

45) Quetiapine – an atypical antipsychotic used for schizophrenia, bipolar disorder and depression;

46) Ramipril – an angiotensin-converting enzyme inhibitor used for hypertension and cardiovascular protection;

47) Recainam – a class I antiarrhythmic agent investigated for the treatment of cardiac arrhythmias;

48) Reproterol – a bronchodilator used in obstructive airway diseases;

49) Terbutaline – a bronchodilator used for asthma and bronchospasm relief;

50) Tolrestat – an aldose reductase inhibitor formerly investigated for diabetic complications;

51) Acebutolol – a selective β1-adrenergic blocker used in hypertension and arrhythmias;

52) Acetaminophen – an analgesic and antipyretic drug widely used for pain relief and fever reduction;

53) Almitrine – a respiratory stimulant used to improve ventilation in chronic respiratory disorders;

54) Alprenolol – a non-selective β-adrenergic blocker used for cardiovascular conditions;

55) Aminopyrine – a pyrazolone derivative formerly used as an analgesic and antipyretic agent;

56) Amoxicillin – a broad-spectrum β-lactam antibiotic used for bacterial infections;

57) Antipyrine – a pyrazolone compound used as an analgesic and in pharmacokinetic studies;

58) Aspirin – a nonsteroidal anti-inflammatory drug used for pain, inflammation, and antiplatelet therapy;

59) Atropine – an antimuscarinic agent used for bradycardia, poisoning, and ophthalmic applications;

60) Benzydamine – a locally acting anti-inflammatory and analgesic agent used for oral and throat conditions;

61) Betaxolol – a selective β1-adrenergic blocker used in hypertension and glaucoma;

62) Bupropion – an atypical antidepressant also used for smoking cessation therapy;

63) Caffeine – a methylxanthine CNS stimulant used to increase alertness and reduce fatigue;

64) Clofibrate – a fibrate-class drug previously used to reduce blood lipid levels;

65) Codeine – a mild opioid used for pain relief and cough suppression;

66) Diclofenac – a potent nonsteroidal anti-inflammatory drug used for pain, inflammation, and musculoskeletal disorders;

67) Disulfiram – a drug used in the treatment of chronic alcohol dependence;

68) Felbamate – an antiepileptic drug used in refractory epilepsy;

69) Fluconazole – a triazole antifungal used to treat systemic and superficial fungal infections;

70) Hydrocortisone – a corticosteroid used for anti-inflammatory and immunosuppressive effects;

71) Ibuprofen – a widely used nonsteroidal anti-inflammatory drug for pain, fever, and inflammation;

72) Ketoprofen – an nonsteroidal anti-inflammatory drug used for pain and inflammatory conditions;

73) Labetalol – a combined α- and β-adrenergic blocker used for hypertension;

74) Lansoprazole – a proton pump inhibitor used to reduce gastric acid secretion;

75) Minoxidil – a potassium channel opener used for hypertension and hair growth stimulation;

76) Moricizine – a class I antiarrhythmic agent used for the treatment of cardiac arrhythmias;

77) Moxonidine – a centrally acting antihypertensive agent that reduces sympathetic nervous system activity;

78) Naproxen – an nonsteroidal anti-inflammatory drug used for pain, inflammation, and fever;

79) Nordiazepam – a long-acting benzodiazepine metabolite with anxiolytic and sedative properties;

80) Saccharin – an artificial sweetener used as a sugar substitute;

81) Timolol – a non-selective β-adrenergic blocker used for glaucoma and cardiovascular conditions;

82) Tolbutamide – an oral hypoglycemic agent used in type 2 diabetes mellitus;

83) Trimethoprim – an antibiotic that inhibits bacterial folate synthesis, often used in urinary tract infections;

84) Foscarnet – an antiviral agent used primarily for cytomegalovirus and herpesvirus infections;

85) Cefpodoxime proxetil – an oral prodrug cephalosporin antibiotic used to treat bacterial infections.

The experimental human intestinal absorption (%HIA) values for 85 organic compounds were collected from the literature and are presented together with the corresponding chemical names in Table 2.1. %HIA represents the percentage of an orally administered drug dose that is absorbed through the human intestinal tract into the systemic circulation. For QSPR modeling purposes, the %HIA values were transformed into logarithmic form using the expression log10 (%HIA + 10) [20].

For QSPR model development, the compounds were divided into training and test sets. The training set was used to construct and optimize the predictive models, whereas the test set was used for external validation and evaluation of model predictive performance on independent compounds. Table 2.1 also includes

the classification of each API according to its assignment to either the training set or the test set.

Table 2.1. List of 85 APIs and experimental values of their %HIA

N	API	%HIA [20]	Set
1	Adefovir	1,342	training
2	Cidofovir	1,114	training
3	Lactulose	1,025	training
4	Mannitol	1,415	training
5	Meropenem	1,000	training
6	Pamidronic acid	1,176	training
7	Pentamidine	1,000	training
8	Phthalylsulfathiazole	1,176	training
9	Ticarcillin	1,176	training
10	AAFC	1,623	training
11	Amiloride	1,778	training
12	Bromocriptine	1,580	training
13	Chlorothiazide	1,528	training
14	Cymarin	1,756	training
15	Flucloxacillin	1,699	training
16	Fosmidomycin	1,602	training
17	Metaproterenol	1,732	training
18	Methyldopa	1,708	training
19	Pravastatin	1,643	training
20	Rimiterol	1,763	training
21	Almotriptan	1,929	training
22	Anagrelide	1,903	training
23	Atenolol	1,785	training
24	Benserazide	1,903	training

25	Bromhexine	1,903	training
26	Captopril	1,892	training
27	Cefatrizine	1,934	training
28	Cycloserine	1,919	training
29	Dipyridamole	1,833	training
30	Eflornithine	1,813	training
31	Ethambutol	1,954	training
32	Famciclovir	1,903	training
33	Fenoterol	1,845	training
34	Guanabenz	1,954	training
35	Hydrochlothiazide	1,875	training
36	Isocarboxazid	1,903	training
37	Metformin	1,799	training
38	Metolazone	1,863	training
39	Mianserin	1,903	training
40	Mibefradil	1,898	training
41	Oxycodone	1,845	training
42	Pimozide	1,903	training
43	Propylthiouracil	1,929	training
44	Pyrbuterol	1,845	training
45	Quetiapine	1,919	training
46	Ramipril	1,845	training
47	Recainam	1,909	training
48	Reproterol	1,845	training
49	Terbutaline	1,857	training
50	Tolrestat	1,881	training
51	Acebutolol	1,999	training
52	Acetaminophen	1,978	training
53	Almitrine	2,000	training

54	Alprenolol	2,016	training
55	Aminopyrine	2,041	training
56	Amoxicillin	2,016	training
57	Antipyrine	2,041	training
58	Aspirin	2,041	training
59	Atropine	2,033	training
60	Benzydamine	1,987	training
61	Betaxolol	2,000	training
62	4Bupropion	1,987	training
63	Caffeine	2,041	training
64	Clofibrate	1,987	training
65	Codeine	2,021	training
66	Diclofenac	2,041	training
67	Disulfiram	2,029	training
68	Felbamate	2,000	training
69	Fluconazole	2,027	training
70	Hydrocortisone	2,004	training
71	Ibuprofen	2,041	training
72	Ketoprofen	2,009	training
73	Labetalol	2,021	training
74	Lansoprazol	1,978	training
75	Minoxidil	2,033	training
76	Moricizine	1,991	test
77	Moxonidine	1,991	test
78	Naproxen	2,037	test
79	Nordiazepam	2,037	test
80	Saccharin	1,991	test
81	Timolol	2,021	test
82	Tolbutamide	1,978	test

83	Trimethoprim	2,029	test
84	Foscarnet	1,431	test
85	Cefpodoximeproxetyl	1,778	test

A total of 170 molecular descriptors were calculated using the ChemDes software [21]. These descriptors represent various structural, physicochemical, topological, geometrical and electronic properties of the molecules that may influence intestinal absorption and permeability. The calculated descriptor set included parameters related to molecular size, lipophilicity, polarity, hydrogen bonding capacity, atom distribution and molecular connectivity.

2.2. Building a QSPR model

Since the initially calculated pool of molecular descriptors was highly multidimensional and included a large number of structurally and statistically interrelated variables, a systematic descriptor selection procedure was performed before QSPR model development. In studies involving molecular modeling, the use of excessively large descriptor sets may negatively affect model quality because redundant or weakly informative variables can introduce statistical noise, decrease model stability and reduce predictive performance. Therefore, the main objective of the descriptor selection stage was to reduce the dimensionality of the original dataset, eliminate non-informative and highly correlated descriptors and retain only those molecular characteristics that provide meaningful information about the pharmacokinetic behavior of the studied compounds.

At the first stage of descriptor preprocessing, the relationship between each individual molecular descriptor and the experimental values of the %HIA was evaluated. For this purpose, the coefficient of determination (R^2) was calculated for every descriptor. The R^2 value reflects the strength of the linear relationship between descriptor values and the experimental pharmacokinetic parameter and indicates how well variation in the descriptor explains variation in the observed

human intestinal absorption. Descriptors with R^2 values below 0.05 were considered weakly informative because they demonstrated minimal contribution to the explanation of experimental variability. Such descriptors were excluded from further analysis. This filtering step allowed the removal of variables that had little practical significance for model construction and reduced the influence of irrelevant information on the statistical analysis.

Following the elimination of poorly informative variables, multicollinearity analysis was performed among the remaining descriptors. Multicollinearity is a common problem in QSPR studies because many molecular descriptors describe similar structural or physicochemical properties and therefore may be strongly correlated with one another. The presence of highly correlated descriptors can lead to unstable regression coefficients, reduced robustness of the model and difficulties in interpretation of the obtained relationships. To detect multicollinearity, pairwise correlation coefficients between descriptors were calculated. For each pair of highly correlated descriptors, only the descriptor showing the higher R^2 values with the experimental %HIA values was retained, whereas the less informative descriptor was removed from the dataset. This approach ensured that the final descriptor pool contained variables with the greatest explanatory power while minimizing redundancy [22, 23].

As a result of the performed descriptor selection procedure, a reduced and optimized set of informative molecular descriptors was obtained. These descriptors retained the essential information describing the relationship between molecular structure and the pharmacokinetic behavior of the compounds while simultaneously decreasing noise and redundancy in the dataset.

From the initial set of 170 calculated descriptors, only 5 descriptors remained after application of the described filtering and selection criteria. The reduction of the descriptor space substantially improved the suitability of the dataset for statistical modeling and created favorable conditions for the development of a stable, interpretable and predictive QSPR model.

After establishing the optimized subset of informative and statistically independent descriptors, these variables were used for QSPR model construction in the MATLAB software environment [24]. Regression analysis techniques [25-27] were applied to establish quantitative relationships between the selected molecular descriptors and the experimental values of the %HIA. These statistical methods make it possible to identify how variations in molecular structure influence the investigated pharmacokinetic parameter and to generate mathematical models capable of predicting the distribution behavior of new compounds based solely on their structural characteristics.

The developed QSPR model for predicting human intestinal absorption of active pharmaceutical ingredients is represented by the following equation:

$$\%HIA = 2{,}3087 + 0{,}04768 \cdot count.HBA2 - 0{,}002211 \cdot WINSA\text{-}2 - 0{,}00442 \cdot types.PolarSurfaceArea - 0{,}017096 \cdot PPSA\text{-}3 - 3{,}918 \cdot SCH\text{-}4 \quad (2.1)$$

This equation describes the quantitative relationship between selected molecular descriptors and the predicted intestinal absorption of pharmaceutical compounds. Each coefficient reflects the contribution and direction of influence of the corresponding descriptor on the absorption process.

The constant term (2,3087) represents the intercept of the regression equation and corresponds to the theoretical baseline value of %HIA when all descriptor values are equal to zero.

The descriptor *count.HBA2* corresponds to the number of hydrogen bond acceptors in the molecule. The positive coefficient associated with this descriptor (+0,04768) indicates that an increase in the number of hydrogen bond acceptors contributes positively to intestinal absorption within the analyzed dataset. This may reflect the role of hydrogen bonding interactions in improving solubility and molecular interactions with the intestinal environment.

The descriptor *WINSA-2* is a weighted partial negatively charged surface area descriptor. It characterizes the distribution of negatively charged surface

regions within the molecule. The negative coefficient (−0,002211) suggests that an increase in negatively charged surface area decreases intestinal absorption. Molecules with extensive negatively charged regions generally exhibit reduced membrane permeability due to unfavorable transport across the hydrophobic lipid bilayer of enterocyte membranes.

The descriptor *types.PolarSurfaceArea* represents the polar surface area of the molecule, which reflects the total surface occupied by polar atoms, mainly oxygen and nitrogen atoms and their attached hydrogens. The negative regression coefficient (−0,00442) indicates that compounds with larger polar surface areas tend to show lower intestinal absorption. This observation is consistent with established principles of drug absorption, since highly polar compounds typically possess reduced passive membrane permeability.

The descriptor *PPSA-3* refers to the partial positively charged surface area and characterizes the positively polarized regions of the molecular surface. Its negative coefficient (−0,017096) demonstrates that increased positively charged surface area may also negatively affect intestinal permeation. Excessive molecular polarity or charge distribution can hinder diffusion through the lipophilic intestinal membrane.

The descriptor *SCH-4* is a topological molecular descriptor associated with molecular branching and structural complexity. The large negative coefficient (−3,918) indicates that increased structural complexity or branching has a pronounced negative effect on intestinal absorption. More structurally complex molecules often exhibit reduced flexibility and lower membrane permeability, which may limit their absorption in the gastrointestinal tract.

Overall, the developed QSPR equation demonstrates that intestinal absorption is influenced by a balance between hydrogen bonding capacity, molecular polarity, charge distribution and structural complexity. Descriptors associated with increased polarity and charged surface areas negatively affect absorption, whereas moderate hydrogen bond acceptor capacity may contribute positively to the absorption process. The obtained model reflects the fundamental

physicochemical principles governing passive intestinal permeation of active pharmaceutical ingredients.

Table 2.2. presents the predicted %HIA values and calculated informative descriptors for the 85 studied APIs.

The quality of the developed QSPR model for predicting %HIA values was evaluated by comparing the experimental intestinal absorption values with the calculated values obtained using Equation (2.1). For this purpose, plots of «predicted %HIA versus experimental %HIA» were constructed for both the training and test sets in order to visually assess the agreement between the experimental and model-predicted data.

For the training set, a satisfactory correlation was observed between the experimental and predicted %HIA values, with $R^2 = 0,6123$. This result indicates that the developed QSPR model explains approximately 61% of the variability in the experimental %HIA values within the training set. The obtained relationship demonstrates that the selected molecular descriptors are significantly associated with intestinal absorption properties of the studied API.

For the test set, the developed model demonstrated a stronger correlation between predicted and experimental %HIA values, with $R^2 = 0,7732$. This result indicates good predictive ability of the model for external compounds that were not included in the model development stage. The higher R^2 value obtained for the test set suggests that the developed QSPR equation possesses acceptable robustness and predictive performance for estimating intestinal absorption of API based on molecular structure descriptors.

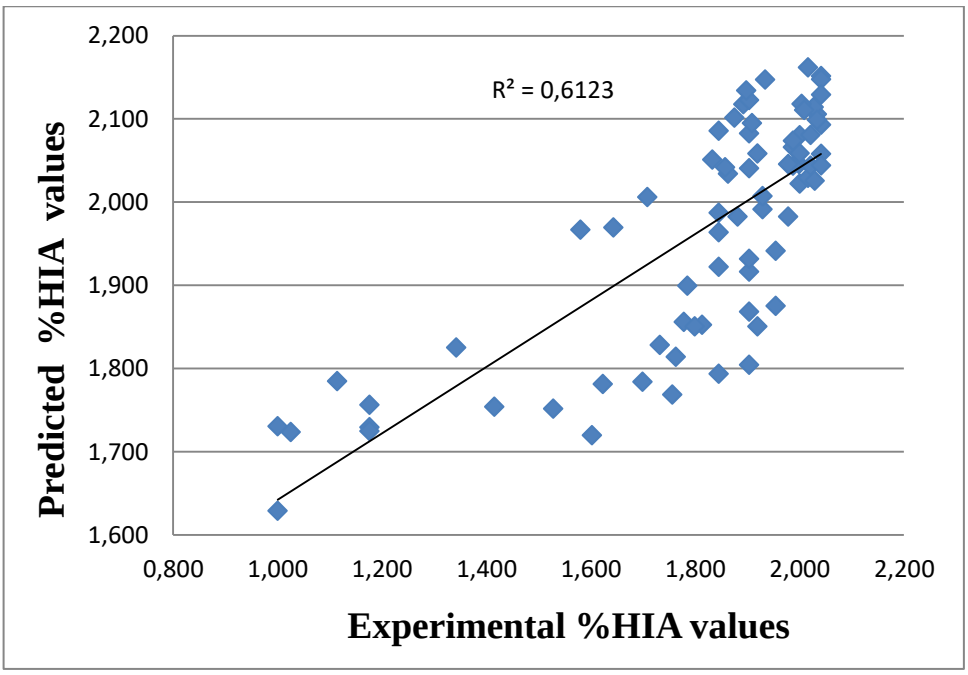

Figure 2.1. Dependence of predicted %HIA values on experimental %HIA values of active pharmaceutical ingredients of the training set

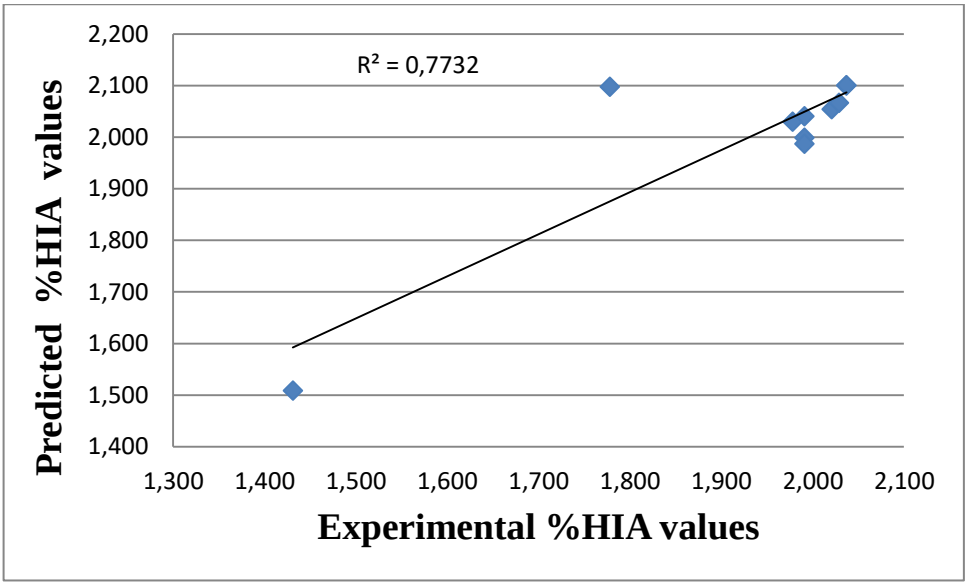

Figure 2.2. Dependence of predicted %HIA values on experimental %HIA values of active pharmaceutical ingredients of the test set

Table 2.2. Predicted values of %HIA and calculated descriptors for studied 85 APIs

N	API	Predicted values of %HIA	Descriptor				
			count. HBA2	*WINSA-2*	*types. PolarSurfaceArea*	*PPSA-3*	*SCH-4*
1	Adefovir	1,825	9,000	-293,172	162,700	49,220	0,000
2	Cidofovir	1,785	7,000	-310,078	148,090	51,970	0,000
3	Lactulose	1,724	5,000	-84,845	101,150	32,976	0,000
4	Mannitol	1,754	5,000	-72,664	101,150	29,636	0,000
5	Meropenem	1,731	9,000	-299,720	157,930	31,383	0,111
6	Pamidronic acid	1,757	10,000	-326,461	215,270	46,744	0,000
7	Pentamidine	1,629	5,000	-73,504	118,010	32,703	0,000
8	Phthalylsulfathiazole	1,730	4,000	-60,351	119,210	22,015	0,000
9	Ticarcillin	1,725	5,000	-86,249	101,150	33,100	0,000
10	AAFC	1,781	5,000	-87,655	101,150	29,975	0,000
11	Amiloride	1,856	9,000	-287,247	157,930	22,417	0,111
12	Bromocriptine	1,967	6,000	-200,220	124,830	30,350	0,000
13	Chlorothiazide	1,752	7,000	-292,939	191,500	40,456	0,000
14	Cymarin	1,769	4,000	-111,546	114,170	27,640	0,000
15	Flucloxacillin	1,784	10,000	-300,921	215,270	41,831	0,000

16	Fosmidomycin	1,720	4,000	-55,842	119,210	21,988	0,000
17	Metaproterenol	1,828	3,000	-107,562	88,330	27,545	0,000
18	Methyldopa	2,006	4,000	-155,237	97,200	23,794	0,000
19	Pravastatin	1,969	4,000	-73,777	80,590	19,706	0,000
20	Rimiterol	1,814	3,000	-100,904	88,330	27,517	0,000
21	Almotriptan	1,991	0,000	-49,222	20,230	19,692	0,000
22	Anagrelide	1,916	1,000	-41,248	28,680	23,654	0,000
23	Atenolol	1,900	3,000	-93,773	72,090	25,778	0,000
24	Benserazide	1,868	6,000	-168,066	118,640	33,543	0,000
25	Bromhexine	2,083	1,000	-70,447	30,460	17,249	0,000
26	Captopril	2,118	5,000	-98,955	99,240	12,246	0,000
27	Cefatrizine	2,147	3,000	-128,651	53,600	20,590	0,000
28	Cycloserine	1,851	3,000	-41,984	65,970	23,528	0,000
29	Dipyridamole	2,051	10,000	-413,891	143,060	59,493	0,000
30	Eflornithine	1,852	2,000	-57,280	67,770	22,148	0,000
31	Ethambutol	1,875	1,000	-56,991	53,450	21,682	0,000
32	Famciclovir	1,804	6,000	-134,058	101,980	37,197	0,000
33	Fenoterol	1,794	3,000	-101,183	88,330	28,744	0,000

34	Guanabenz	1,941	3,000	-84,426	61,900	24,762	0,000
35	Hydrochlothiazide	2,101	6,000	-179,764	114,300	22,554	0,000
36	Isocarboxazid	2,041	5,000	-120,572	81,260	24,194	0,000
37	Metformin	1,851	5,000	-52,622	91,490	23,886	0,000
38	Metolazone	2,034	5,000	-94,257	73,910	23,078	0,000
39	Mianserin	2,123	2,000	-44,420	20,040	17,015	0,000
40	Mibefradil	2,134	5,000	-130,737	53,470	27,227	0,000
41	Oxycodone	1,964	4,000	-223,676	54,210	24,189	0,096
42	Pimozide	1,932	3,000	-58,077	41,130	27,287	0,000
43	Propylthiouracil	2,007	3,000	-71,353	70,140	17,084	0,000
44	Pyrbuterol	1,922	2,000	-53,524	57,070	20,354	0,000
45	Quetiapine	2,058	5,000	-107,703	58,100	27,486	0,000
46	Ramipril	2,086	6,000	-205,583	128,210	23,205	0,000
47	Recainam	2,095	2,000	-77,054	33,540	19,379	0,000
48	Reproterol	1,987	3,000	-118,641	66,300	25,364	0,000
49	Terbutaline	2,042	3,000	-137,796	66,300	24,659	0,000
50	Tolrestat	1,983	3,000	-51,049	78,170	13,821	0,000
51	Acebutolol	2,046	2,000	-101,639	46,070	22,195	0,000

52	Acetaminophen	1,983	3,000	-74,317	49,330	24,301	0,000
53	Almitrine	2,022	2,000	-63,706	39,690	20,298	0,000
54	Alprenolol	2,029	2,000	-115,457	57,070	22,094	0,000
55	Aminopyrine	2,152	5,000	-65,083	57,690	16,637	0,000
56	Amoxicillin	2,162	9,000	-375,585	176,380	36,641	0,000
57	Antipyrine	2,148	5,000	-59,191	57,690	16,109	0,000
58	Aspirin	2,129	4,000	-99,021	66,430	17,279	0,000
59	Atropine	2,106	1,000	-14,415	13,670	12,987	0,000
60	Benzydamine	2,044	4,000	-167,345	66,580	31,068	0,000
61	Betaxolol	2,080	2,000	-121,536	46,070	22,732	0,000
62	4Bupropion	2,066	3,000	-69,823	49,330	18,832	0,000
63	Caffeine	2,093	3,000	-67,397	33,460	21,041	0,000
64	Clofibrate	2,074	3,000	-70,725	34,890	22,238	0,000
65	Codeine	2,044	2,000	-113,167	42,090	24,817	0,000
66	Diclofenac	2,058	3,000	-79,046	49,360	20,483	0,000
67	Disulfiram	2,026	6,000	-85,366	121,260	12,980	0,000
68	Felbamate	2,059	7,000	-214,768	115,560	32,023	0,000
69	Fluconazole	2,114	3,000	-82,222	27,050	23,384	0,000

70	Hydrocortisone	2,118	3,000	-103,995	57,530	18,082	0,000
71	Ibuprofen	2,044	2,000	-85,732	40,130	21,758	0,000
72	Ketoprofen	2,111	2,000	-60,581	40,130	14,620	0,000
73	Labetalol	2,081	3,000	-120,878	56,760	22,651	0,000
74	Lansoprazol	2,046	3,000	-81,975	38,690	24,340	0,000
75	Minoxidil	2,099	0,000	-30,339	4,440	15,049	0,000
76	Moricizine	2,040	1,000	-80,2539	37,3	19,2366	0,000
77	Moxonidine	1,999	3,000	-64,5507	53,43	21,0405	0,000
78	Naproxen	2,100	2,000	-107,074	40,13	21,2823	0,000
79	Nordiazepam	2,100	0,000	-24,3268	4,44	14,1833	0,000
80	Saccharin	1,986	4,000	-78,571	71,62	21,6468	0,000
81	Timolol	2,054	3,000	-158,868	66,3	26,6747	0,000
82	Tolbutamide	2,029	3,000	-69,3046	78,17	13,4636	0,000
83	Trimethoprim	2,066	4,000	-68,164	39,94	23,8344	0,000
84	Foscarnet	1,508	5,000	-77,355	113,130	41,510	0,000
85	Cefpodoximeproxetyl	2,097	6,000	-316,488	107,220	42,325	0,000

Conclusions to section 2

The developed QSPR model appears to be physically meaningful and pharmacokinetically reasonable because the selected molecular descriptors and the directions of their effects are consistent with the known mechanisms of intestinal drug absorption.

Most descriptors included in the equation are related to molecular polarity, charge distribution, hydrogen bonding ability and structural complexity, which are well-established factors influencing membrane permeability and oral absorption. The negative contribution of descriptors associated with polar surface area and charged molecular surfaces is consistent with the fundamental principle that highly polar or highly charged compounds generally exhibit reduced passive diffusion through the lipophilic intestinal membrane. Similarly, the negative effect of the structural complexity descriptor suggests that larger or more topologically complex molecules may have lower permeability, which also agrees with established absorption theories.

CONCLUSIONS

1. An optimized set of informative molecular descriptors suitable for QSPR modeling of intestinal absorption was identified. The model includes hydrogen bond acceptor capacity, polar surface area, charged molecular surface distribution and topological structural complexity, which collectively represent key physicochemical factors influencing intestinal permeation of active pharmaceutical ingredients.

2. A QSPR model for predicting intestinal absorption of active pharmaceutical ingredients was successfully developed using multiple linear regression analysis. The obtained model established quantitative relationships between molecular descriptors and experimental values of intestinal absorption.

3. The predictive performance of the developed model was evaluated using training and test datasets. The obtained results demonstrate satisfactory accuracy and indicate that the model can be used for preliminary prediction of intestinal absorption and computer-assisted screening of active pharmaceutical ingredients.

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SUPPLEMENTARY INFORMATION

СЕРТИФІКАТ

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«АКТУАЛЬНІ ПИТАННЯ РОЗВИТКУ ГАЛУЗЕЙ НАУКИ»

СЕКЦІЯ XXV.
ФАРМАЦІЯ ТА ФАРМАКОТЕРАПІЯ

PHYSICOCHEMICAL AND BIOLOGICAL DETERMINANTS OF INTESTINAL DRUG ABSORPTION

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Oral administration remains the most widely used route for drug delivery due to its convenience, patient compliance and cost-effectiveness. However, the efficiency of oral drug therapy is limited by incomplete intestinal absorption, which directly affects bioavailability and therapeutic efficacy. Intestinal drug absorption is a complex, multifactorial process governed by the interplay of physicochemical properties of drug molecules, biological transport mechanisms and physiological conditions of the gastrointestinal tract [1].

Drug transport across the intestinal epithelium occurs via three primary mechanisms: passive transcellular diffusion, paracellular diffusion and carrier-mediated active transport. Passive transcellular diffusion is the dominant pathway for most lipophilic drugs and is governed by Fick's law, where the rate of diffusion depends on the concentration gradient, membrane surface area and permeability coefficient. This mechanism is strongly influenced by lipophilicity, as well as by the ionization state of the drug. Only the unionized form of a drug can readily diffuse through the hydrophobic core of the phospholipid bilayer [2].

Paracellular transport, on the other hand, involves the movement of hydrophilic molecules through aqueous pores between epithelial cells. This pathway is generally limited to small molecules and is regulated by tight junction proteins such as claudins and occludins. Although its overall contribution to drug absorption is relatively minor, it can become significant

under certain physiological or pathological conditions. Active transport involves carrier proteins located in the apical membrane of enterocytes and is particularly important for compounds structurally similar to endogenous substrates such as amino acids, peptides and sugars. Physicochemical properties of drug molecules critically determine their ability to permeate biological membranes. Lipophilicity enhances membrane permeability, but excessive hydrophobicity may result in membrane retention. Molecular size is another key factor, as smaller molecules generally diffuse more easily. Polarity and ionization reduce permeability by limiting passage through the nonpolar membrane core [3, 4].

In summary, intestinal drug absorption is governed by a complex interaction of physicochemical, biological and physiological factors. Understanding these determinants is essential for optimizing drug design and improving oral bioavailability.

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SUMMARY

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QSPR PREDICTION OF INTESTINAL ABSORPTION OF ACTIVE PHARMACEUTICAL INGREDIENTS

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Keywords: molecular descriptors, pharmacy, chemoinformatics, quantitative structure–property relationship, active pharmaceutical ingredient.

Introduction. Prediction of intestinal absorption is an important stage in modern drug development because oral administration remains the most widely used route for pharmaceutical therapy. The effectiveness of orally administered active pharmaceutical ingredients largely depends on their ability to be absorbed through the intestinal epithelium and reach systemic circulation in sufficient concentrations. Poor intestinal absorption may significantly reduce bioavailability and limit the therapeutic efficacy of drug candidates. Experimental determination of human intestinal absorption is often expensive, time-consuming and ethically limited due to the need for in vivo studies. Therefore, the development of computational approaches capable of predicting absorption properties at early stages of pharmaceutical research has become highly relevant. Among these approaches, Quantitative Structure–Property Relationship modeling is considered one of the most promising tools because it allows the establishment of mathematical relationships between molecular structure and pharmacokinetic behavior. The aim of this study was to develop a QSPR model for predicting the intestinal absorption of active pharmaceutical ingredients based on their chemical structure.

Materials and methods. Data set includes total 85 active pharmaceutical ingredients and 170 descriptors. Research methods: correlation analysis, multiple linear regression analysis and statistical evaluation of modeling results.

Results. From the initial set of 170 calculated descriptors, only 5 descriptors remained after application of the described filtering and selection criteria. The reduction of the descriptor space substantially improved the suitability of the dataset for statistical modeling and created favorable conditions for the development of a stable, interpretable and predictive QSPR model. The developed QSPR model appears to be physically meaningful and pharmacokinetically reasonable because the selected molecular descriptors and the directions of their effects are consistent with the known mechanisms of intestinal drug absorption.

Conclusions. An optimized set of informative molecular descriptors suitable for QSPR modeling of intestinal absorption was determined. The final descriptor set included parameters associated with hydrogen bond acceptor capacity, polar surface area, charged molecular surface distribution and topological structural complexity, all of which are important factors influencing intestinal permeation of active pharmaceutical ingredients.

A QSPR model for predicting intestinal absorption of active pharmaceutical ingredients was successfully developed using multiple linear regression analysis. The obtained model established quantitative relationships between molecular descriptors and experimental values of intestinal absorption. The selected descriptors demonstrated statistically significant associations with the absorption properties of the studied compounds and reflected important physicochemical factors affecting intestinal permeation.

The predictive ability and accuracy of the developed QSPR model were evaluated using both training and test datasets. The obtained results indicate satisfactory predictive performance of the model and support its potential application in preliminary pharmacokinetic screening and computer-assisted drug design.