Reviews

Molecular modeling in synthesis: from statistical methods to quantum chemistry and practical applications*

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The review gives a retrospective of methods for molecular modeling of the structures, mechanisms of chemical reactions, and properties of organic compounds. The development and advancement of the ideology of preliminary modeling of the structures and formation mechanisms of reaction products in the planning of any synthesis is a relevant task in this field of science. Some results of the practical application of this paradigm are considered.

Key words: molecular modeling, targeted synthesis, quantum chemistry.

Modeling and activity evaluation methods for biologically active compounds

The basic principles of preliminary structural modeling

Molecular modeling in synthetic chemistry has a single basic application, that is, to switch from the synthesis of plenty of compounds one of which might possess a desired property to the targeted synthesis of a model structure determined in advance by theoretical prediction of reaction mechanisms and products.

It is evident that this prediction provides

— resource intensity of chemical experiment, which reduces the cost of the experiment by a factor of several tens;

— considerable cost saving for testing of the activity and efficacy of the products;

— departure from the common practice of total synthesis, which results in obtaining inefficacious materials and limits the search for new non-infring-

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ing structures with specified properties. Certainly, the experience in synthetic chemistry is still priceless, as well as literature survey, because mathematical methods and artificial intelligence in chemistry are only tools for theoretical optimization of the preparation of target compounds, and they cannot replace the synthetic chemist.

The approach pursued at the Laboratory of Molecular Modeling and Targeted Synthesis, N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences (ZIOC RAS), biologically active compounds are considered as compound—therapeutic target (ligand—target) complexes. In addition, static and dynamic interactions in homogeneous and heterogeneous catalysis are evaluated relying on the similarity of theoretical approaches to the molecular modeling of these processes.

The ideology of primary modeling in the design of synthesis of a target product and similarity of the methods and results of molecular modeling for the targeted synthesis of both biologically active compounds and other products not related to biology are described in our previous review.[1]

Thus, the basic scientific problem addressed in the present review consists of several parts.

First, the development and synthetic application of molecular modeling, which make it possible to:

— predict the structures of products for targeted synthesis;

— establish reaction mechanisms;

— determine the key electronic and spatial effects that control the synthesis and determine the activity of both single molecules and promising classes of compounds and their complexes;

— calculate the target properties of compounds for the subsequent screening of the most promising structures and giving recommendations for targeted synthesis.

Second, this is the practical validation of methods for the predictive modeling of the structure and preparation of biologically active compounds with properties specified in the modeling using homogeneous and heterogeneous catalysis, in particular with new types of heterogeneous catalysts produced by additive manufacturing methods.

The implementation of these statements changes the principles of targeted synthesis from the use of preliminary molecular modeling to the experimental research work with corrective feedback (according to modern terminology, machine learning). Ideally, a complete plan for the development of a new compound involving preliminary molecular modeling should look in the following way:

(i) prediction of the structure of a compound possessing the desired property;

(ii) synthesis of this compound;

(iii) experimental verification of the predictive efficiency;

(iv) scaling-up of the experimental results for extensive application.

This work takes at least two years and currently costs no less than 2—5 million rubles per compound and requires contributions from computer persons and synthetic chemists and validation experiments. Meanwhile, termination of the work at the first (finding the structure) or second stage (synthesis), which makes it simpler, would cancel out its practical value.

Here will consider this problem and ways to solve it for biologically active compounds.

The activity of a compound is manifested, by definition, towards a compound that responds to this activity. The former compound is called a ligand and the latter one is a target. We will consider the methods for calculating the degree of binding, *i.e.*, the degree of complementarity of one compound to the other. For both calculation of the activity of an unknown compound and modeling of the structure of this compound on the basis of a predictive property model, there exist two options, namely, the structure of the target may be either unknown or known.

The first option: the structure of the target is unknown. In this case, which corresponds to the conventional quantitative structure—activity relationship (QSAR) algorithms, it is possible to collect a critical number of ligands that possess the required property, define descriptors for this property, statistically process the digitized set, build the structure—property model, and then either design a new structure based on statistical modeling or add an (n+1)th structure with unknown property to the model and decide about its synthesis considering the degree of coincidence of the results (Fig. 1).

Within this modeling paradigm, there are quite a few protocols (both for the selection of factors determining the property and for statistical processing) [2] that are able to predict, to a certain extent, the properties of a target product.

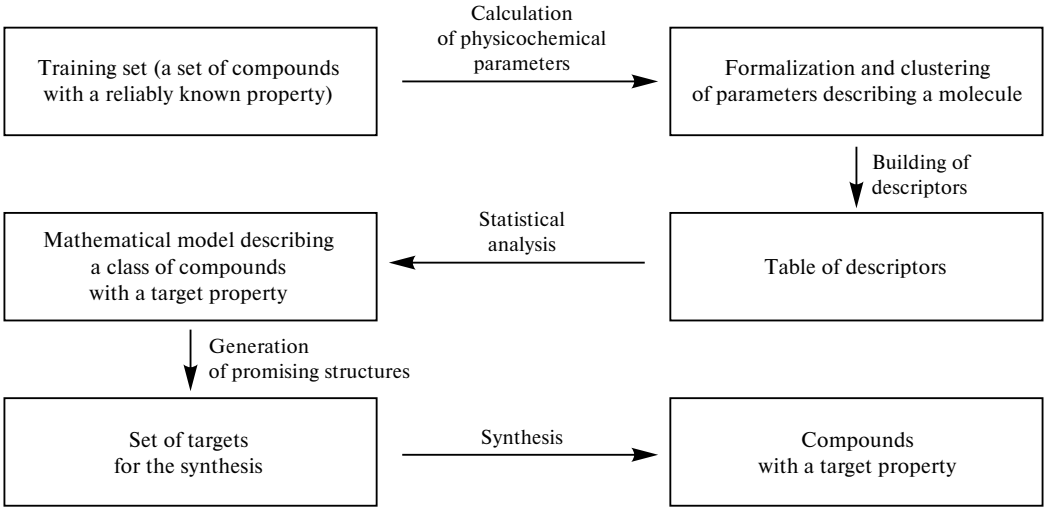


Fig. 1. Sequence of actions and intermediate results in the modeling of new structures on the basis of statistical analysis of available data.

The key factor determining the efficacy of an approach (and, hence the prediction quality) is digitization of the initial (training) set. We have no doubt that any intermolecular interactions are determined by the electrostatic nature of the molecules, *i.e.*, by interaction of the electric fields generated by the molecules.

An electrostatic field has a vector nature; for visualization and calculations, the interacting fields should be discretized.

Case 1. An integrated vector field is considered as a graph of two, three, or more interacting charged groups of atoms[3] (Fig. 2).

Case 2. The electrostatic configuration of a molecule is represented as a scalar cross-section of the vector electrostatic field either at a particular distance from atoms or at a distance equal to the averaged van der Waals radius of the molecule.[4] In this case, the property is modeled by the maximum density of the overlap of the molecular surfaces of training set structures, for example (3D special case), the common points on the superimposed surfaces are the key points defined by the procedure proposed previously[5] (Fig. 3).

Thus, the common key points of MEPs of active molecules define the structure—property model. This procedure was used in our studies to determine the odor models: ambergris [6] and musk odors, and neuroleptic properties of bicyclocureas.[7,8]

It is clear that the density of points determines the accuracy of the model and, ideally, the description of the MEP should have been integrated over the whole molecular surface rather than discrete.

One more piece of evidence for the electrostatic nature of interactions is provided by the statistical processing of topological characteristics of electron density obtained by different methods for a model set of bimolecular associates. The method was described by Bader[9] and is successfully used[10] as the basis for modeling of non-covalent binding.

The advent of mathematical methods (machine learning, neural networks, *etc.*) gave a new impetus for the development of approaches to statistical processing of data already known from the literature with the goal to predict the activity of new structures.

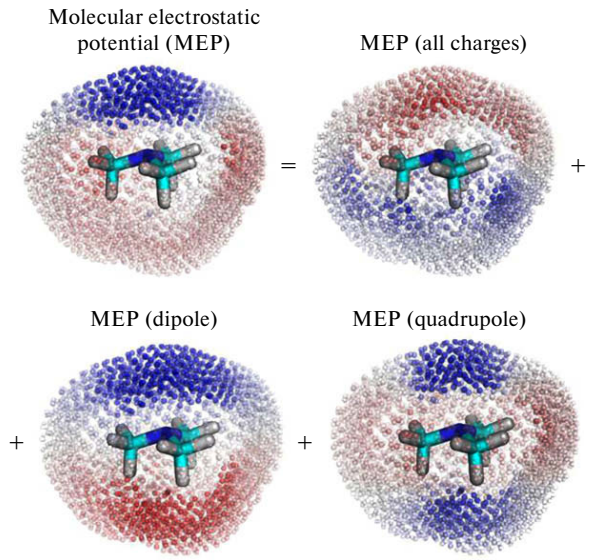


Fig. 2. Modeling of the vector electrostatic field.[3]

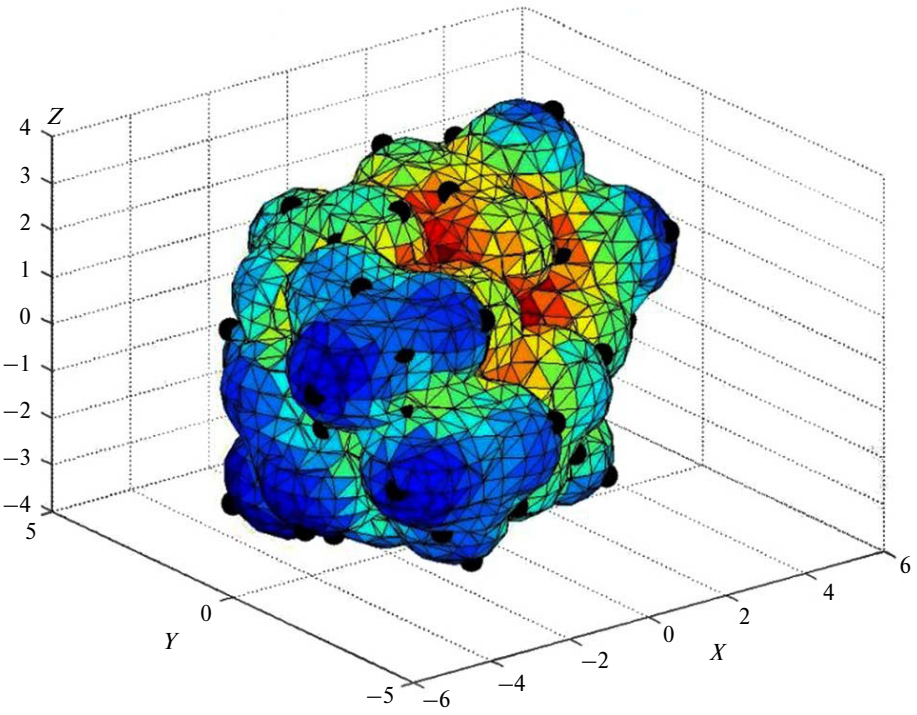
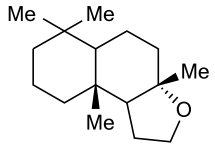


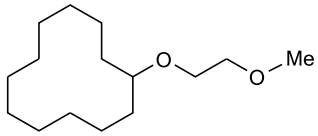
Fig. 3. Molecular surface discretization for calculations: key points of MEP.[4]

Graph neural networks (GNNs) have been used[11] to compose the principal odor map (POM). The authors assert that the odor map they propose is superior in odor prediction to the chemoinformatic models developed earlier. This may indicate that POM successfully encodes the global structure—odor relationship. Models based on the data on fragrance structures available from two data libraries are constructed using machine learning. The resulting models of various odors were validated by human panelists: for 400 control odorants, the odor predicted by the model reproduced quite accurately the actual odor of the test compounds. The authors concluded that the developed method has replaced the human nose.

Of course, this is a far exaggeration. Most often, control odorants are selected among compounds structurally similar to training set compounds and, furthermore, the whole process is based on medium notes where the structure—odor relationships are obvious without neural network training. Our reproduction (as far as this was possible with a similar neural network) of the above-described method for basic amber odorants showed thar neural network training for recognition using control sesquiterpenes with the ambroxide skeleton in no way provides a model for the amber woody odor of macrocycles with an entirely different structure, *e.g.*, ambrolignan.



Ambroxide
(standard)



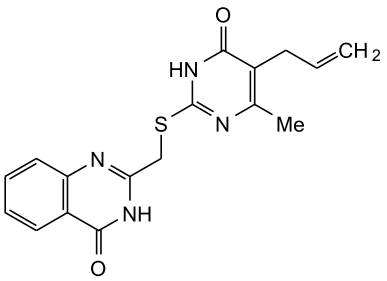
Ambrolignan
(amber woody)

Certainly, comparison of any statistical model with the efficiency of a human nose is all the more an exaggeration: a certified perfumer distinguishes up to 50 thousand scents, and the expertise of a team of perfumers is the most accurate method of identification of this type of biological activity, moreover, requiring no expensive experiments. This is why the theory of odors was the first object for application of computational methods in biological activity modeling, and currently no mechanical nose model has approached the reality.

A fairly subjective approach to the definition system of property descriptors decreases the prediction accuracy of the classical (statistical) QSAR method; because of this drawback, this method is

treated with caution by researchers both engaged in docking (known targets) and quantum chemistry. However, statistical methods are quite applicable as basic methods for preliminary calculations, especially in those cases where the active site of the target is not clearly defined or unknown.

For example, prediction of the inhibitory activity of poly(adenine ribose polymerase) (PARP) using 3D QSAR identified six promising drug candidates. Molecular docking showed that one of them, compound **1**, would be inactive. However, this compound, being expected to be inactive according to docking results, showed an activity comparable to those of other compounds in *in vitro* tests.[12]



1

From experience of using different molecular modeling methods, the order of application (and, hence, increase in the accuracy) of methods can be depicted as shown in Fig. 4.[1]

The second option: the structure of the target is known. The selectivity of drug candidates relative to secondary targets is an important feature, which should be taken into account in drug design, apart from the drug efficiency. Preliminary prediction and elimination of the possible off-target activity of compounds may help to avoid side effects that restrict the clinical use of drugs. Owing to the progress in biochemical analysis, a number of companies now offer reliable technologies for compound screening against large kinase panels. However, a drawback of this method is high cost of experiments and large time consumption for the successive optimization stages of compounds to attain the required selectivity. Hence, prediction of the activity of compounds towards secondary targets is a necessary stage of development of safe biologically active compounds. Because of the lack of modern molecular modeling methods in which the error of binding energy determination would be comparable with the error of *in vitro* experiments, a relevant task is to develop a platform for predicting the ligand selectivity to targets corresponding to an unsolved medical problem.

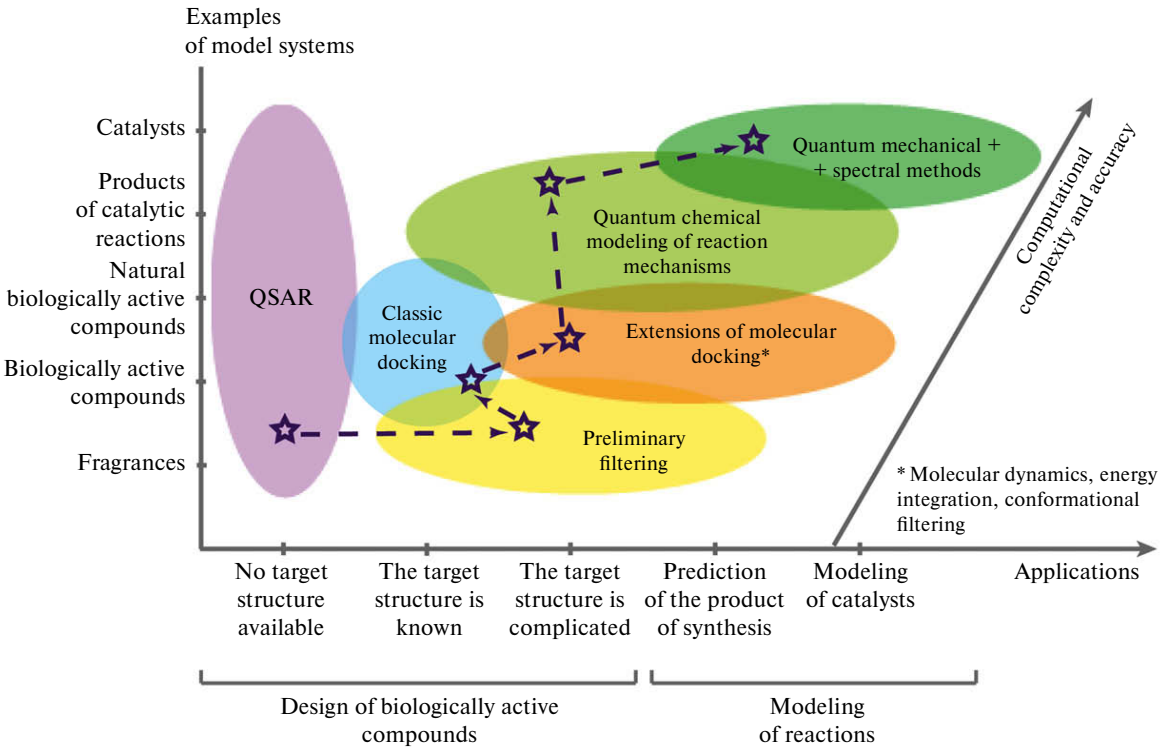


Fig. 4. Application of molecular modeling methods as the problem becomes more complex.[1]

The staff of the Laboratory of Molecular Modeling and Targeted Synthesis of ZIOC RAS has been engaged in the studies of new targets and in the modeling of biologically active compounds for about 15 years. The Lead Finder molecular docking system [13,14] has been developed at the Laboratory and used, in combination with other methods, in several successful drug development projects.

Examples of using original molecular modeling methods in the search for new drugs. The efficacy of Syk kinase inhibition was reliably established for the therapy of two diseases: rheumatoid arthritis and non-Hodgkin lymphoma. The development of an effective Syk kinase inhibitor is highly important for the treatment of socially significant diseases.

Free energy perturbation method, which is the most accurate method for modeling the binding between organic compounds and biomolecules, was used to determine the binding strengths of known Syk kinase inhibitors and to design new effective structures. The accuracy of modeling can be additionally increased by explicit inclusion of the solvent into the protein—ligand system and by detailed analysis of the conformational equilibrium of the inhibitor in the solution.[15] On the basis of predicted activity values, a set of new Syk kinase inhibitors was selected and synthesized. The products effectively inhibited this enzyme in *in vitro* experiments using enzyme preparation as well as non-Hodgkin lymphoma and rheumatoid arthritis cell models in the submicromolar concentration range. The experimental results on the inhibitor efficacy were in excellent agreement with the calculated data (error of <2 kJ mol^{-1}). The synthesized compounds are under clinical trials.[16,17]

The Laboratory staff made a key contribution to the development of the drug PF-114, selective inhibitor of the T315I mutant form of BCR/ABL protein, associated with resistance to the existing drugs used to treat myeloid leukemia;[18] PF-114 is at a final step of clinical trials.[19]

Since 2020, the key studies of the research team have been associated with the development of new approaches to modeling the selectivity of small molecule compounds to homologous protein targets, in particular, kinases that determine socially significant diseases.

Kinases form the largest group of targets for antitumor therapy, since this class of enzymes affects the activity of a significant part of proteins of the body. Cyclin-dependent kinases (CDKs), together with other cell cycle protein kinases such as Aurora, polo-like and checkpoint, have proved themselves as therapeutic targets for the treatment of cancer. The intensive efforts aimed at the development of effective kinase inhibitors resulted in an increase in the number of FDA-approved drug candidates: more than 70 small-molecule kinase inhibitors have now been approved.[20] In addition, according to the results of clinical trials, approximately 110 new kinases are now considered as targets for the therapy of some socially significant diseases. All these targets form only 30% of human kinome, which implies the presence of a large unexplored area for the search and development of new therapeutic agents. Although the discovery and approval of kinase inhibitors have revolutionized the anticancer therapy, the problems of poor efficacy and undesirable toxicity caused by inhibition of off-target kinases are still relevant.

Dozens of non-selective CDK inhibitors entered clinical trials as therapeutic agents against various types of cancer. About a half of the trials were terminated after phase I or II due to poor pharmacokinetic properties and undesirable toxicity associated with side effects.

Example: dinaciclib is a small-molecule *pan*CDK inhibitor, which inhibits CDK1, CDK2, CDK5, and CDK9 with IC50 being in the range from 1 to 4 nmol L^{-1}. The intravenous administration of dinaciclib once a week caused, in 60% of cases, grade 3 or 4 side effects, including nausea, vomiting, increased liver enzyme levels, hyperbilirubinemia, and hematological disorders (neutropenia, anemia).[21] Due to the side effects, the clinical trials were terminated despite the obvious antitumor activity of dinaciclib. Generally, a similar situation was typical of clinical investigations of some other non-selective CDK inhibitors, such as SNS-032, RGB-286638, ZK-304709, AG-024322, and P1446A-05.[22]

Unfortunately, automatic computational docking is now unable to describe all ligand—target interactions with sufficient accuracy. Therefore, the original Lead Finder system uses an expert visual adjustment

of the ligand position with respect to various target functionals.

Docking specification and extensions: free energy perturbation (FEP) method, over-the-hood docking, and quantum chemical modeling (QM/MM)

The prediction of ligand selectivity to secondary targets is a key and a challenging aspect of drug modeling, because most inhibitors bind to the highly conserved ATP binding site, which is common to the greater part of protein kinases. Since the error of the selectivity prediction depends on the error of prediction of the change in the affinity to two or more targets, the overall error may impose limitations on the use of the existing modeling methods for a particular problem. For example, the minimum root-mean-square error for free energy calculation by the free energy perturbation (FEP) method, which is currently used most widely to predict the relative binding energy of the ligand to the target, is ~1.0 kcal mol^{-1}.[23] Meanwhile, the difference in the free binding energy of 1.4 kcal mol^{-1} corresponds to a tenfold change in the binding constant.

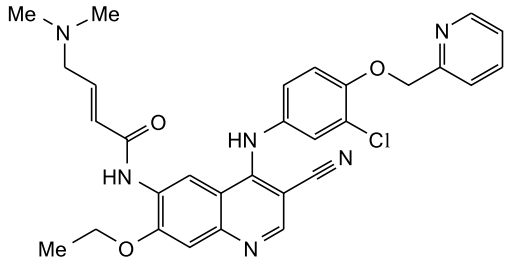
A significant challenge is to model binding to proteins with either weak or undescribed active binding sites. In this case, there are two operating concepts:

— synthesis of multi-pharmacophore agents that combine several basic structural groups (scaffolds) from various neuroactive compounds in one molecule, *i.e.*, synthesis of ligands possessing multiple binding sites;[24]

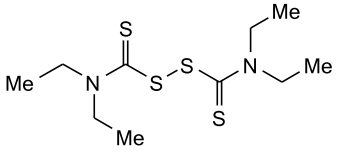
— search for the active site over the whole surface of the target followed by targeted synthesis of a potentially active compound with a single active site. The over-the-hood docking method that we developed provides a considerable gain of accuracy (from 77 to 91%) compared to the standard docking into the active site and requires only 30 runs for each ligand.[25] This is caused by the difference between the ligand binding energy to one active site and the binding energy of same ligand to all possible sites of the protein.

Shaimardanov *et al.*[26] concluded that non-complementary ligand—target interactions and intermolecular interactions should additionally be taken into account to increase the accuracy of determination of free binding energy in the ligand—receptor complex.

The use of over-the-hood docking for the search of SARS-CoV-2 main protease inhibitors resulted in identification of two potential anti-COVID-19 drugs: neratinib and disulfiram.[27]



Neratinib



Disulfiram

According to laboratory studies of these compounds, neratinib has almost no activity against the target virus, while disulfiram, which has been used in the medical practice for more than 70 years, inhibits this virus fairly actively. In the experts′ opinion, in the search for all possible binding sites, the differences between the activities of compounds are most likely determined by the partially covalent nature of interaction with 3CL^{pro}.

Dynamic modeling

The system of docking extensions is used rather widely. The FEP method makes it possible to take account of the dynamic conformational filtering in the formation of the ligand—target complex (Fig. 5).

The multiple ligand—target—solvent can also be used for non-biological objects to model asymmetric synthesis. An example is modeling of the Diels—Alder reaction by comparing the binding energy of the chiral auxiliary to each of the two reaction products: the product that is more efficiently stabilized by the chiral auxiliary is formed predominantly. In this case, it is the (*R*,*R*,*R*,*S*) isomer (Scheme 1).[28]

Using a computational protocol based on non-equilibrium thermodynamics (NEQ), imidazole-4-*N*-acetamide derivatives were studied at ZIOC RAS as scaffolds for new cyclin-dependent kinase 2 (CDK2) inhibitors.[29] The developed protocol provided an accurate prediction of the change in the free

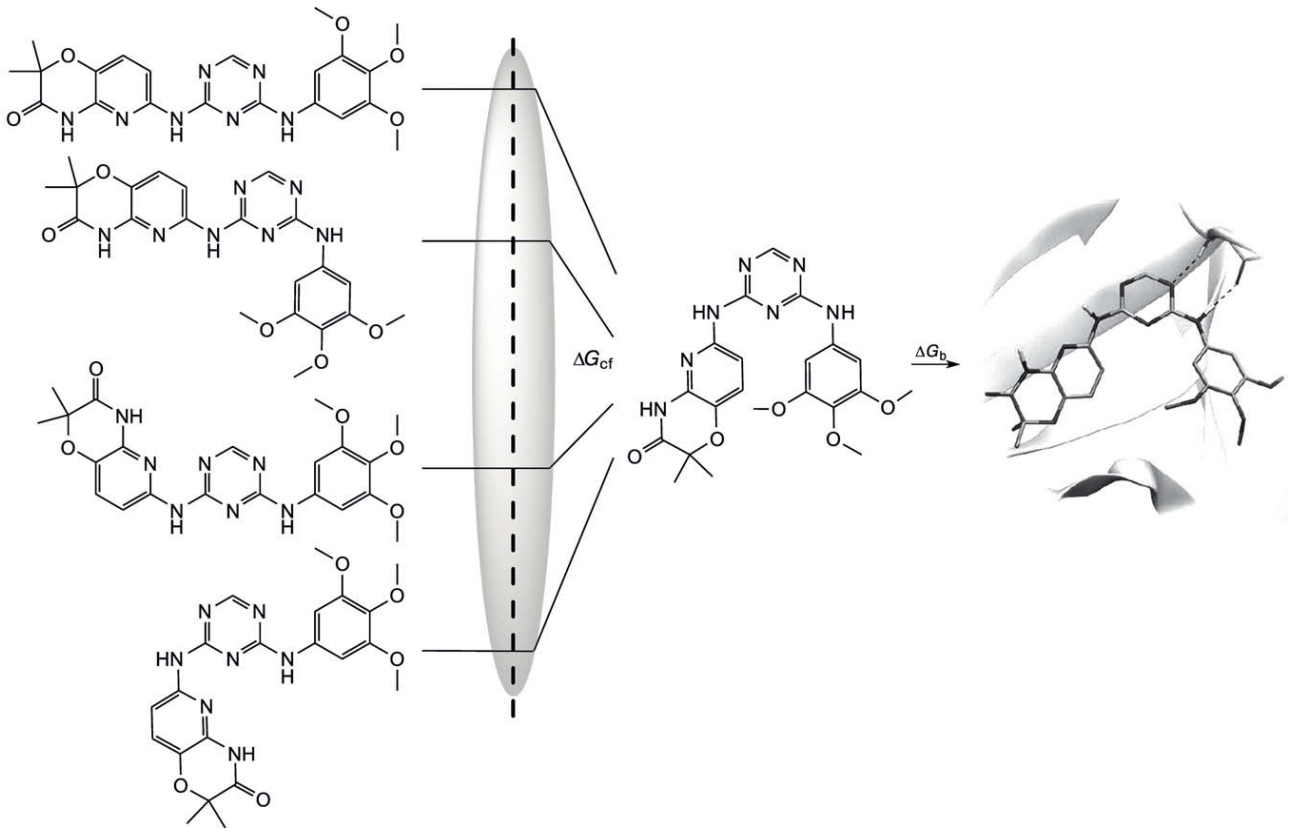
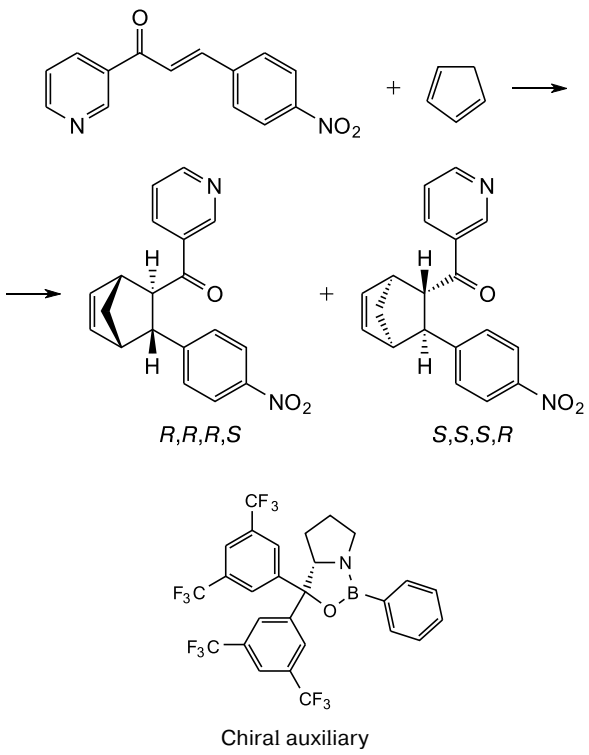


Fig. 5. Conformational filtering (ΔG_{cf} is the energy difference between the conformers) of labile compounds upon ligand coordination to the target (ΔG_b is the final binding energy) in the paradigm of determination of dynamic energy parameters.

Scheme 1



binding energy ($\Delta\Delta G$) of the inhibitors to CDK2 and the change in the selectivity (ΔS) relative to CDK1, CDK5, and CDK9. Prediction of the selectivity for structurally similar targets is the key difficulty in the design of CDK inhibitors. We developed a strategy for an accurate estimation of $\Delta\Delta G$ and selectivity change in the series of homologous targets (ΔS) with a mean absolute error of 0.83 kcal mol^{-1}. The calculations of $\Delta\Delta G$ showed a good agreement with the *in vitro* inhibitory activity of the ligands ($R^2 = 0.7$). The use of non-equilibrium methods for the estimation of $\Delta\Delta G$ reduced the computing time by ~40% compated to classical equilibrium approaches. These results confirm the prospects of this computational approach as a tool for targeted drug discovery. The predicted CDK inhibition profiles and the experimental activity of new compounds *in vitro* demonstrated the potential of a new structural cage for the development of antitumor agents. The primary generation of protein—ligand complexes was based on automatic structural filtering of the molecular docking results. The optimal conformation of the protein—ligand complexes was identified by means of

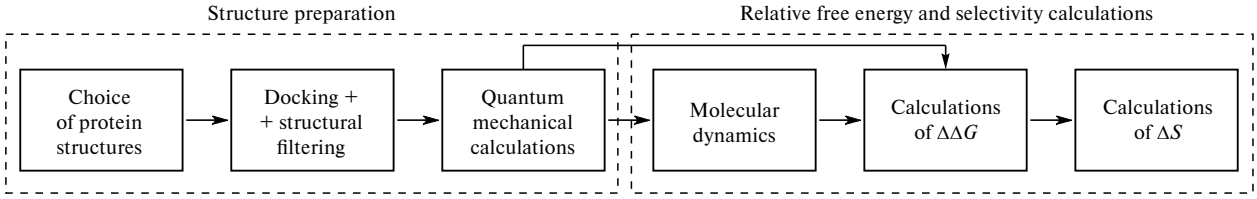


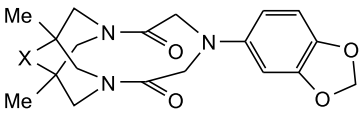
Fig. 6. Block diagram of the computational protocol.

the quantum mechanical (QM) cluster approach. The resulting systems were used to calculate $\Delta\Delta G$ and ΔS (Fig. 6) according to a computational protocol based on NEQ thermodynamics. The Crooks—Gauss intersection (CGI), Jarzynsky (JAR), and Bennet (BAR) methods served as NEQs. The prediction accuracy was evaluated experimentally in *in vitro* enzymatic experiment.

The NEQ-based calculations of the relative free binding energy showed good agreement with the inhibitory activity of the ligands *in vitro*.[29]

The interest of researchers is also attracted by unexpected or disproportional influence of a minor structural change on the biological activity. This issue can be clarified by molecular modeling.

For example, the change of X in the tricyclic bispidine derivative **2** from C=O to CH_2 results in the loss of any type of activity towards the AMPA receptor,[30] while modeling of these tricyclic structures and their subsequent synthesis afford allosteric modulator of glutamate receptors **3**.[31]



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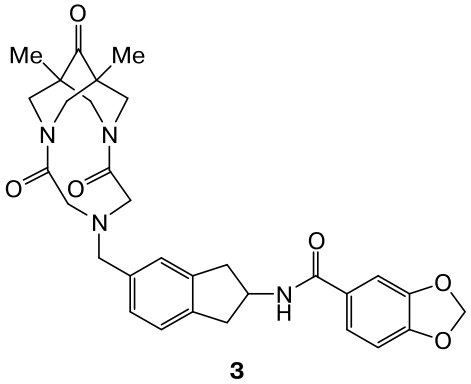
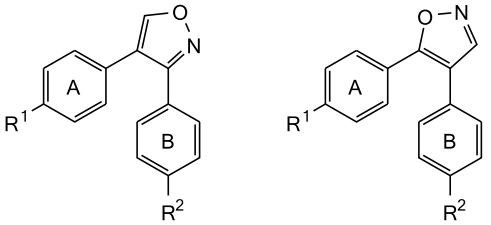


3

The difference between the activities of isomeric monomethoxy-substituted *o*-diphenylisoxazole structures towards the colchicine binding site of tubulin was also unexpected.[32] Compound **4a** showed vity much exceeding the activities of other isomers; the order of decreasing activity was **a** > **c** > **b** > **d**.



4a,b **4c,d**

R^1 = OMe, R^2 = H (**a**, **d**); R^1 = H, R^2 = OMe (**b**, **c**)

A general principle for the study of structurally similar compounds is bioisosteric replacement. Bioisosteres are structurally similar molecules with different substituents. Bioisosteric replacements are used to modify the activity and change the metabolism or bioavailability. The prediction of the relative similarity of bioisosteres using standard force fields in the calculations is almost an unsolvable task.

Nevertheless, sets of H → F bioisosteric replacements were correctly calculated using an approach based on the GFN2-xTB semiempirical quantum chemical method.[33] This protocol makes it possible to expand the predicted change in the biological activity upon the bioisosteric replacement of H by F with a standard deviation of 0.60 kcal mol^{-1} exceeding the ChemPLP scoring function (0.83 kcal mol^{-1}) and makes the QM estimate of $\Delta\Delta G$ comparable with ~0.42 kcal mol^{-1} (the error of the *in vitro* experiment). The simplicity of the method and the lack of tunable parameters makes this method applicable in modern drug research.

Quantum chemical methods in the dynamic modeling

Systematic contributions to the calculation error can arise due to the drawbacks of empirical force fields, which represent a molecule as a set of spring-

bound charged atoms and, hence, do not take into account many important effects such as hyperconjugation, charge transfer, and halogen bonds. Their accuracy is sufficient for comparison of the affinities of two absolutely different molecules, *i.e.*, for the search for the scaffold of the future drug candidate or another target product not related to biology. However, this accuracy is insufficient to predict the effects of minor structural changes. Meanwhile, quantum mechanical methods consider all contributions to the energy, and they would be more accurate.

By using FEP in combination with QM/MM, we demonstrated [34] that degradation of the palladium complex in the Suzuki reaction is energetically more favorable when it involves the attack of palladium by the hydrogen rather than oxygen atom of water, as considered in the classical version of the mechanism (Fig. 7).

Quantum chemical methods predominate in the dynamic modeling of reaction mechanisms. An example is the modeling of the mechanisms of reactions in the *N*-NAT8L methyltransferase active site (Scheme 2, Fig. 8).[35]

One more revision of the commonly accepted mechanism is as follows. In the opinion of Fage *et al.*,[36] the formation of the only one natural insecticide catalyzed by the SpnF enzyme follows the standard [4+2]-cycloaddition pathway (Scheme 3, Diels—Alder reaction in the living nature).

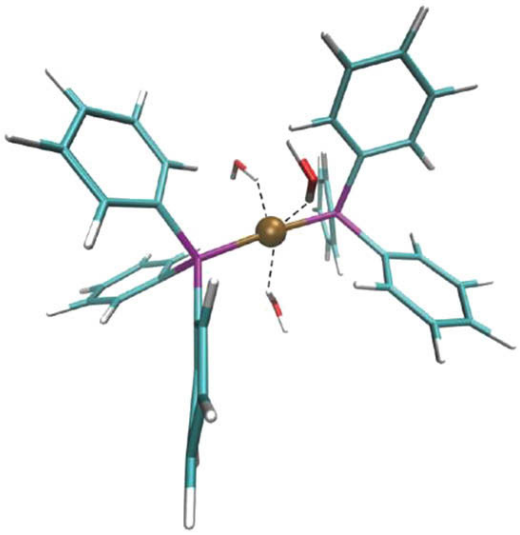
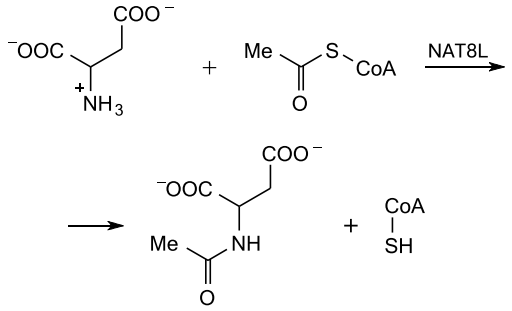


Fig. 7. Formation of Pd...H—O bonds by unshielded Pd atom with water molecules in $Pd(PPh_3)_2$.[34]

Scheme 2



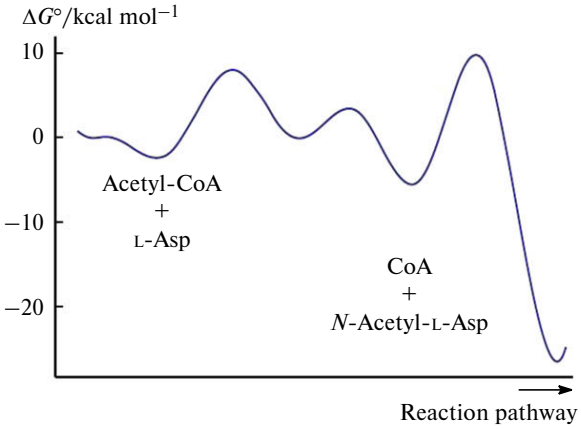
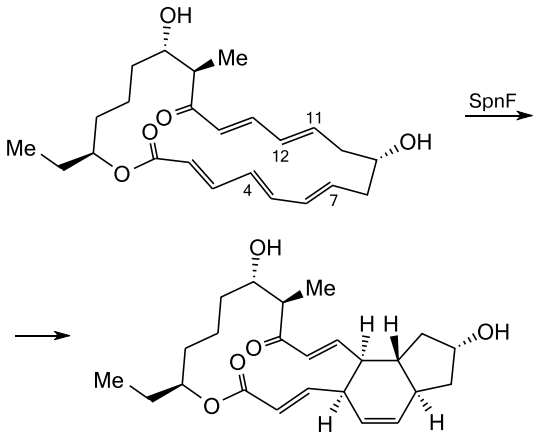
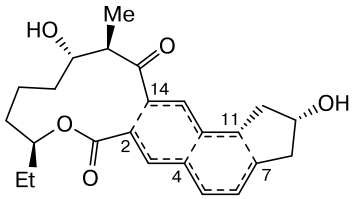


Fig. 8. Example of dynamic modeling of an enzymatic catalysis mechanism (see Scheme 2).

Scheme 3



Having modeled more than 750 transition states for both the basic [4+2]-mechanism and alternative mechanisms, we demonstrated that the transition state of [6+4]-cycloaddition of **5** and the subsequent Cope rearrangement to give the final macrolactone are energetically more favorable.[37]



5

This mechanism implies an absolutely different structure of the enzyme active site.

Thus, methods developed at the laboratory founded by N. S. Zefirov at ZIOC RAS cover the hierarchy of activity predictions for a broad pool of compounds, ranging from statistical processing to quantum mechanical calculations of physical models. In all cases, the final stage of the production cycle is experimental validation of the methods by targeted synthesis according to the model of a property and testing of the resulting product for the specified type of activity.

Development of a new quantum chemistry method

It is known that modern quantum chemistry methods are restricted by the difficulty of solving the Schrödinger equation for multi-electron systems. An approach[38,39] developed at the Laboratory of Mathematical Chemistry and Computer Synthesis (since 2019, Laboratory of Molecular Modeling and Targeted Synthesis) of ZIOC RAS uses mathematically rigorous separation of spin and spatial variables to solve the Schrödinger equation for N-electron systems ($N > 2$). This eliminates, to a certain extent, the limitations of existing quantum chemical methods and substantially increases the calculation accuracy. This was possible owing to investigation of the topological structure of multidimensional configuration spaces, particularly for excited states.

It is known that the Pauli exclusion principle (PEP) was initially formulated as a prohibition for two electrons in an atom to have the four quantum numbers equal. Heisenberg formulated PEP as the requirement of antisymmetry of the wave functions, and all known quantum chemistry methods use this requirement as a necessary condition for solution of the Schrödinger equation. This actually results in the situation that, although the Hamiltonian is not spin-dependent, the spin and coordinate variables are not separated for $N > 2$. This issue defines one of the main difficulties in finding the wave functions for a system of identical particles.

In our quantum chemical method, the requirement of the wave function antisymmetry is replaced by the requirement of zero wave function on the nodal surfaces separating $N!$ regions of the configuration space. The distinction of the developed method (called the method of multi-electron wave functions, MWF) is that the basis functions in direct variational methods include the necessary boundary conditions, while the functions defined for one region can, as mentioned above, have an arbitrary symmetry or even no symmetry. This allows for shortening of the calculation procedure by a factor of $N!$ and increases the calculation accuracy and efficiency.

The possibility of existence of superstable states of helium atoms and obtaining the corresponding energy levels in strong and superstrong magnetic fields was demonstrated on the basis of proposed theoretical approach and performed calculations.[40]

Modeling of structure and properties of energetic materials

Smolenskii *et al.*[41] presented original methodological materials and summarized the research results on the modeling of processes and physicochemical characterization of various energy sources, including natural (hydrocarbons) and chemical (energetic materials) sources. It was noted that the use of QSPR methods brings about a significant question of why the structure—property relationships for some properties are rather simple and have been established long ago (for example, molecular refraction and enthalpy of formation of compounds), while for other properties, these relationships are complex and poorly formalized, despite numerous attempts to reveal them. To answer this question, the authors proposed to quantitatively estimate physicochemical properties by "complexity" depending on the structure of compounds and ranging from 0 to 1. It was shown that the complexity of establishing structure—property relationships for any physicochemical property is a measure of scatter of experimental value of this property among structural isomers. For example, for alkanes, the complexity of molecular refraction is 0.017, while that of melting point is 0.997. This means that a model for estimation of structure—property relationships using, for example, topological indices (descriptors defined only by structural formulas, without taking into account the real geometry of molecules) can be constructed for molecu-

lar refraction, while for the melting point this is virtually impossible. As regards, for example, the standard enthalpy of formation ($\Delta H°_f$) of compounds in the liquid state, an estimation of the complexity of these relationships on the basis of published/experimental data for alkanes with the number of carbon atoms $n < 9$ gives a value of 0.019. This means that it is possible to build computational models for determining the enthalpy with an accuracy close to the experimental one. Using the identified structure—property relationships for hydrocarbons with various spatial structures, compounds with high (in absolute value) enthalpies of formation were found.

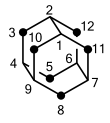
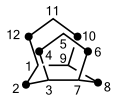
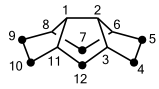
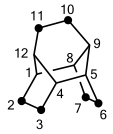
A large series of works to develop a *strategy for elucidating the structures of high-density energetic (HDE) molecular crystals* was carried out at the Laboratory.

It is known that in the early 1990s, cage nitramines aroused great interest among synthetic chemists, and the currently known most potent energetic compound, 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane (CL-20), was synthesized. We applied the search strategy for HDE materials that we developed to identify the most effective cage compounds of various series. Using pre-optimized molecular formulas of energetic compounds, we generated molecular graphs that were subsequently converted to 3D structures.[42] The application of the MOLGEO software developed at the Laboratory of Mathematical Chemistry and Computer Synthesis of ZIOC RAS[43] afforded structural isomers of wurzitane and adamantane. Then, relying on the statement that molecules with higher intrinsic symmetry form closer packings, six nitro or nitramine groups were introduced into the molecular cages in positions that ensured the retention of the intrinsic symmetry of the molecules. Further, we modeled the crystal structures of the resulting hexanitro- and hexaazanitro derivatives of the adamantane and wurtzitane analogs in the statistically most realistic space groups of symmetry using quantum chemistry and atom—atom potential (AAP) methods and evaluated the physicochemical characteristics of the compounds.[41] Table 1 presents the results of calculations of molecular crystal density, enthalpy of formation, and detonation characteristics of the resulting compounds.

Analysis of the results leads to the conclusion that, regarding the set of detonation characteristics, structural isomer **6** (2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazawurtzitane) rather than widely known CL-20 (isomer **7**) is the most efficient among the considered substituted cage derivatives.

Then the main statements of the crystal structure modeling were developed[44,45] and relevant software was devised. This made it possible to predict the

Table 1. Calculated physicochemical characteristics of cage isomers: density of molecular crystals (d), enthalpy of formation (ΔH_f), detonation velocity (D), heat of explosion (Q_{ex}), detonation pressure at the Chapman—Jouguet point (P_{CJ}), and the accelerating ability I (relative specific impulse)

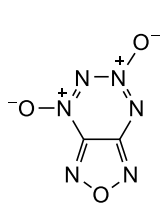
Compound	d/g cm^{-3}	ΔH_f/kcal mol^{-1}	D/m s^{-1}	Q_{ex}/cal mol^{-1}	P_{CJ}/kbar	I
 (**6**)	2.04	94.10	9765	1467	466	139.4
 (**7**)	2.00 (2.04)	90.00 (90.02)	9575	1453	443	135.9
 (**8**)	1.96	118.67	9512	1507	430	134.7
 (**9**)	1.94	152.56	9548	1575	429	135.4

Note. Dots indicate the positions of NNO_2 groups in the hydrocarbon cages. Experimental values are given in parentheses.

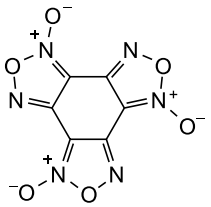
structure and evaluate the properties of energetic crystals for a broad range of compounds belonging to various chemical classes: furoxano-1,2,3,4-tetrazine 1,3-dioxides,[46] bifurazano[3,4-*b*:3′,4′-*f*]furoxano[3",4"-*d*]oxacyclo-heptatriene (BFFO),[47] tetrazinotetrazine tetroxide (TTTO),[48] [1,2,5]oxadiazolo[3,4-*e*][1,2,3,4]tetrazine 4,6-dioxide (FTDO),[49] benzotrifuroxan (BTF),[50] and other compounds.

On the basis of the developed theoretical principles for modeling the structure of one-component compounds, we elaborated a unique technique for modeling the structure of cocrystals with various component ratios, which can be used to predict the complex formation of conformers. The optimized point charges approximating MEP were derived from *ab initio* calculations. The best models were subsequently used to calculate the crystal packings of molecules in the framework of the AAP method with corrected parameters of the Lennard-Jones potential (6—12) using optimization of the unit cell parameters in the most widely encountered space groups ($P2_1/c$, $P2_12_12_1$, $P\bar{1}$, $P2_1$, $Pbca$, $C2/c$, $Pna2_1$, $Pca2_1$, Cc, $P1$, $Pbcn$, $Pccn$) and identification of the corresponding minima of potential energy surfaces (PES).

We will illustrate the structural search for the optimal packings in relation to FTDO and BTF cocrystals in 1 : 1, 2 : 1, and 3 : 1 component ratios.



FTDO



BTF

The PES minima were determined by the PMC (packing of molecules in crystals) software.[44] The number of starting molecules was markedly reduced by taking account of both the symmetry of the space group and the point group of symmetry of the molecules. The optimal crystal structures were selected using the CRYCOM software.[51]

According to calculations, the cocrystal with 3 : 1 component ratio is thermodynamically the most stable (Fig. 9) and, hence, it is more preferable for cocrystallization. Indeed, we successfully obtained the cocrystal only for 3 : 1 component ratio.[52] The cocrystal was characterized by X-ray diffraction and vibrational spectroscopy.

Baraboshkin *et al.*[53] performed structural search for the optimal packings and determined the crystal structure of FTDO cocrystals with nitrobenzenes (nitrobenzene, *o*-, *m*-, and *p*-dinitrobenzenes, 1,3,5-trinitrobenzene, and hexanitrobenzene) in 1 : 1 ratio. The energies of formation and cocrystallization were estimated. The results indicate that the formation of FTDO—NB (1 : 1), FTDO—1,4-DNB (1 : 1), and FTDO—TNB (1 : 1) cocrystals is energetically favorable, which makes these compounds the best choice for experimental preparation.

The methodical work on the prediction of the cocrystal structures and physicochemical characteristics are summarized in a review.[54]

Khakimov and Pivina [55] described an original technique for estimating the enthalpy of salt formation surpassing in accuracy all currently known computational protocols. The method is based on conceptually new model in which cocrystals are represented as a mixture of $[AH]^+$ cation and $[B]^-$ anion with a quasi-salt formed by neutral components (molecules A and HB), with the enthalpy of formation (ΔH_f) being calculated as the mean of the enthalpies of formation of these two structural parts (ΔH_{subl} is the enthalpy of sublimation):

$$\Delta H_f(\text{salt}) = 0.5 \cdot (\Delta H_f([AH]^+[B]^-) + \Delta H_f([A][HB])),$$

$$\Delta H_f^\circ([AH]^+[B]^-) =$$
$$= \Delta H_f^\circ(\text{gas}[AH]^+) + \Delta H_f^\circ(\text{gas}[B]^-) - \Delta H_{subl}([AH]^+[B]^-),$$

$$\Delta H_f^\circ([A][HB]) =$$
$$= \Delta H_f^\circ(\text{gas}[A]) + \Delta H_f^\circ(\text{gas}[HB]) - \Delta H_{subl}([A][HB]).$$

The composition of the salt may be different, not necessarily 1 : 1. Therefore, this procedure is also suitable for calculation of 1 : 2, 2 : 1, or 2 : 2 compounds.

While developing the method, we proceeded from the fact that the sublimation of salts does not always follows the cation + anion pathway, but a variety of processes take place during heating preceding the sublimation, *e.g.*, lattice restructuring, component mixing, and the subsequent decomposition of components; in other words, sublimation is a complex

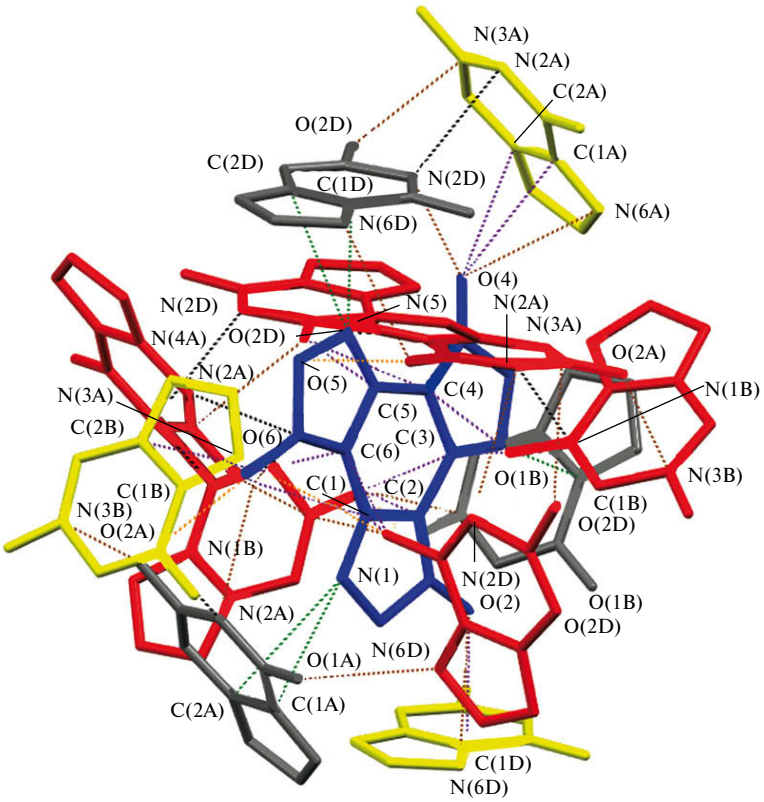


Fig. 9. Shortest contacts in the FTDO cocrystal with BTF (3 : 1). The BTF molecule is shown in blue and FTDO molecules are red, yellow, and gray. The atoms of a symmetrically independent FTDO molecule are designated by A, B, and D. The violet dashed lines indicate C...O contacts, orange lines show O...O contacts, brown lines are N...O contacts, black lines are N...N contacts, and green lines are C...N contacts.[52]

process. Thus, unlike the known correlation and additive schemes, the developed method is based on the construction of a real physical model of the salt crystal in which the molecular geometry of ions and neutral salt components is preliminarily optimized by quantum chemistry methods. The results are used to build the initial crystal lattice models in statistically most probable structural classes, which are subsequently optimized by the AAP method. For some compounds of various chemical classes (formamidine salts,[56] nitrates and perchlorates[57]), this method for estimating the enthalpy of salts was found to surpass known methods in the calculation accuracy.

Thus, effective methods and appropriate software for modeling the structure and evaluating the activity/efficiency of organic compounds of various chemical classes were developed at the Laboratory of Mathematical Chemistry and Computer Synthesis (currently, Laboratory of Molecular Modeling and Targeted Synthesis) of ZIOC RAS. The physicochemical characteristics of the compounds were determined, recommendations were formulated, models for the targeted synthesis of the most effective compounds were developed, and some of them were implemented.

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Animal Testing and Ethics

No human or animal subjects were used in this research.

Conflict of Interest

The authors declare no competing interests.

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