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ABSTRACT
of the dissertation for the degree of Doctor of Philosophy

SYNTHESIS AND STUDY OF KETOHYDRAZONES AND OPTICALLY ACTIVE 4H-PYRANS BASED ON METHYLENE-ACTIVE COMPOUNDS

Specialty: 2306.01 – Organic Chemistry

Field of Science: Chemistry

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GENERAL CHARACTERISTICS OF THE WORK

Relevance and degree of development of the topic. It is well-known that methylene-active compounds, which play a significant role in organic synthesis, and their transformation products are widely used as biologically active compounds.

Ketohydrazones and their derivatives, synthesized based on methylene-active compounds, also possess broad application areas as biologically active substances. In recent years, the complexes of these compounds with metals have garnered significant attention from researchers. Studies have demonstrated that ketohydrazones and their derivatives have found extensive use as reagents, as well as chelates. Additionally, diazepines, seven-membered heterocyclic compounds obtained from ketohydrazones, are widely utilized due to their pharmacological properties. Diazepines and benzodiazepines have diverse therapeutic applications. Many members of the diazepine family are used as antispasmodic, sedative and antidepressant. Benzodiazepine derivatives are also employed as dyes for acrylic fibers. Furthermore, benzodiazepines serve as valuable precursors for the synthesis of triazolo-, oxodiazolo-, oxazino-, and furanbenzodiazepine ring structures.

In recent years, multicomponent reactions have become one of the most notable and significant methods in organic chemistry, largely due to their compliance with the principles of green chemistry. Polyfunctional substituted 4H-pyrans synthesized via this method constitute a class of biologically and pharmacologically important heterocyclic compounds. In medicine, many drugs containing the 4H-pyran moiety are used in the treatment of hypertension, asthma, ischemia, and spastic disorders, as well as for their antibacterial and antimicrobial properties. Heterocyclic compounds containing a 4H-pyran ring also exhibit beneficial properties in treating diseases such as Alzheimer's and schizophrenia, and they are components of antidepressant, antiepileptic, and sedative drugs. Considering the critical properties of 4H-pyrans containing multiple functional groups, it is natural to develop numerous synthetic methods to achieve the desired targets

using more efficient approaches in organic synthesis. Given the broad application areas of these compounds, the enantioselective synthesis of their optical isomers has become one of the pressing issues in contemporary research.

Object and subject of the research

The research focuses on the synthesis of halogen-substituted ketohydrazones based on methylene-active compounds, their transformations, and the study of their physiological properties. Additionally, optically active 4H-pyrans were synthesized via multicomponent condensation of methylene-active compounds in the presence of chiral organic catalysts, and their various application areas were explored.

Objectives and tasks of the research

The primary goal of this dissertation is the synthesis of halogen-substituted ketohydrazones through the reaction of various aromatic halogen-substituted amines with methylene-active compounds, as well as the synthesis of optically active 4H-pyrans via multicomponent condensation in the presence of chiral organic catalysts. The structures of the synthesized compounds were confirmed, and their application areas were investigated.

To achieve this goal, the following tasks were carried out:

- Investigation of the reaction between halogen-substituted aromatic amines and methylene-active compounds, and confirmation of the structure of the resulting compounds;
- Study of the reaction of the synthesized halogen-substituted ketohydrazones with ethylenediamine;
- Examination of multicomponent condensation reactions involving various aromatic aldehydes, malononitrile, and methylene-active compounds in the presence of α-amino acids as chiral organic catalysts;
- Determination of the specific optical rotation of the synthesized optically active 4H-pyrans using the AUTOPOL III polarimeter;
- Investigation of the application areas of the synthesized compounds.

Research methods.

The research work was conducted at the “Organic Chemistry”

Laboratory of BSU. The ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER-300 spectrometer (300 MHz ^{1}H and 75 MHz ^{13}C). Samples were analyzed in the 4000–400 cm^{-1} infrared range.

The RSA method was studied on a "Bruker APEX II CCD" diffractometer.

The chemical purity of the obtained compounds was controlled by thin-layer chromatography (TLC). The specific rotation angles of the compounds we synthesized were determined on an AUTOPOL III polarimeter.

Autodock 4 və Autodock vina dokinqi AMDock proqramının köməyi ilə həyata keçirilmişdir. Some synthesized compounds were molecular docking. For this purpose, the energy values of these compounds, the number of H bonds, and the docking poses were visually inspected in Maestro (Schrödinger 18-1, USA). Various parameters were designed to select the best docking structure for each ligand and the Glide GScore program, iGemDock, Autodock 4, Glide, Autodock vina, etc. were used. Autodock 4 and Autodock vina docking were performed with the help of AMDock program.

ADMET and SwissADME studies were also performed for some of the synthesized compounds. Gas phase density functional theory (DFT) studies were performed using B3LYP to elucidate the relationship between the internal electronic properties and chemical reactivity (biological activities) of some of the obtained compounds.

Hirshfeld surface analysis was performed using the Crystal Explorer 17.5 software using the cif file.

Key propositions for defense:

- Synthesis of ketohydrazones based on methylene-active compounds, some transformations, and studying the structure of the obtained compounds by the RQA method;
- Investigation of multicomponent condensation reactions of methylene-active compounds with malononitrile and various aromatic aldehydes;
- Styding the structure of optically active 4H-pyrans synthesized in the presence of chiral organic catalysts (L-glutamine, L-cysteine, L-arginine) and determination of their specific optical rotation using the AUTOPOL III polarimeter;

- Examination of the properties of ketohydrazone derivatives and optically active 4H-pyrans synthesized from methylene-active compounds.

Scientific novelty of the research.

- Various ketohydrazones (both new and known from the literature) were synthesized from the interaction of halogen-substituted aromatic amines with methylene-active compounds, and their structures were confirmed by X-ray crystallography (RSA).

- The biological activity of the synthesized 2-(2-(4-fluorophenyl)hydrazone)-5,5-dimethylcyclohexan-1,3-dione (V) and 2-(2-(2-trifluoromethylphenyl)hydrazone)-5,5-dimethylcyclohexan-1,3-dione (VI) compounds against COX-2 was studied using molecular docking, molecular dynamics, and DFT methods. These compounds were found to possess strong anti-COX-2 (cyclooxygenase) inhibitor properties. Hirshfeld surface analysis, energy framework, and ADMET studies were also conducted.

- The reactions of ketohydrazones with ethylenediamine were investigated. It was shown that ketohydrazones synthesized from dibenzoylmethane lead to the formation of 6-(2-(4-halogenphenyl) hydrazono)-5,7-diphenyl-3,6-dihydro-2H-1,4-diazepines. The reaction product of the ketohydrazone synthesized from 5,5-dimethylcyclohexan-1,3-dione with ethylenediamine was identified as (5E,5′E,6Z,6′Z)-6,6′-[ethan-1,2-diylbis(azanililiden)] bis{5-[2-(4-fluorophenyl) hydrazone]-3,3-dimethylcyclohexanone} 2.5-hydrate and its structure were confirmed by RSA.

- Synthesis of Optically Active 4H-Pyrans: Optically active 4H-pyran derivatives were synthesized through a multicomponent condensation reaction involving methylene-active compounds, malonitrile, and various aromatic aldehydes in the presence of chiral organic catalysts. The structures of these compounds were confirmed using RSA and NMR methods, and specific rotation angles were measured with the AUTOPOL III polarimeter. The effects of optically active 4H-pyrans on acetylcholinesterase (AChE), butyrylcholinesterase (BChE), β-glucosidase enzymes, and carbonic anhydrase I and II isoenzymes were studied. Additionally, these optically active 4H-pyrans were tested as antioxidants in fuel,

demonstrating strong antioxidant properties.

- For the first time, the multicomponent condensation reaction of benzaldehyde acetoacetic ester and malonitrile in the presence of trichloroacetic acid was investigated. As a result, the condensation occurred in a new direction depending on the conditions, leading to the synthesis of the previously unknown ethyl 3,3,5,5-tetracyan-2-hydroxy-2-methyl-4,6-diphenylcyclohexan-1-carboxylate (XXV).

- The structure of the synthesized ethyl 3,3,5,5-tetracyan-2-hydroxy-2-methyl-4,6-diphenylcyclohexan-1-carboxylate compound was confirmed by RSA. Molecular docking studies were performed with the DNA of Dana Timus, and pharmacological properties were identified.

Theoretical and practical significance of the research. Ketohydrazones and optically active 4H-pyrans with broad applications in medicine were synthesized based on methylene-active compounds, and some transformations were studied.

Using molecular docking methods, certain synthesized ketohydrazones were identified to exhibit strong anti-COX-2 inhibitory properties. Optically active 4H-benzopyrans were found to have antiepileptic, antidiabetic, and anticholinergic activities.

The optically active 4H-pyrans were tested as fuel additives with antioxidant properties, demonstrating superior antioxidant activity compared to previously known antioxidants.

The optically active 4H-pyrans were tested as fuel additives with antioxidant properties, demonstrating superior antioxidant activity compared to previously known antioxidants.

Certain synthesized compounds were tested as antimicrobial agents against Gram-positive and Gram-negative microorganisms, paving the way for their potential application as effective antimicrobial drugs in medicine.

The results provide a theoretical basis for researchers working in this field and expand the scope of practical applications.

Approval and application. A total of 22 scientific papers were published on the dissertation topics: 14 articles (7 in impact-factor journals, 1 as sole author), 8 abstracts. Seven of the articles were published in high-impact journals indexed in Web of Science

and Scopus, including: (Archiv der pharmazie İF=4.3, Bioengineering İF=3.8, Applied Biochemistry and Biotechnology İF=3.1, Journal of Structural Chemistry İF=1.2, Russian Journal of Organic Chemistry İF=0.8, Applied Petrochemical Research İF=0.7, Acta Crystallographica Section E: Crystallographic Communications İF=0.5). The results of the research were presented and discussed at the following international and national scientific conferences:

- I All-Russian Youth School-Conference "Achievements in Synthesis and Complexation" Moscow, RUDN, April 25–28, 2016- X Republican Scientific Conference "Actual Problems of Chemistry," Baku, 2016.
- International Scientific Conference dedicated to the 85th anniversary of Academician R. Aliyeva, Baku, 2017.
- International scientific and technical conference "Petrochemical synthesis and catalysis in complex condensed systems", Baku, 2017.
- "Kimyanın Aktual Problemləri" XIII Beynalxalq Elmi Konfransı, Bakı 2019.

Name of the organization where the dissertation work was performed. The dissertation was carried out at the "Organic Chemistry" Research Laboratory of the Department of Organic Chemistry at Baku State University.

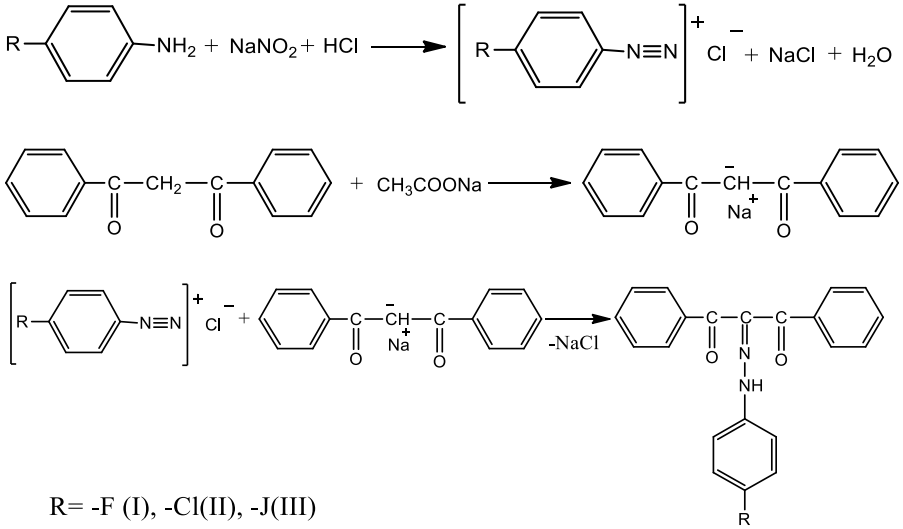
Volume and structure of the dissertation. The dissertation consists of an introduction, three chapters, a conclusion, and a bibliography, comprising a total of 180 pages (A4 format). The main part of the work (excluding 53 figures, 42 schemes, 23 tables and 231 list of literature) has 195795 marks (including introduction – 10877, chapter I – 62505, chapter II – 102353, chapter III – 18063, conclusion – 1994). The list of used literature includes 228 sources cited in the dissertation.

Personal contribution of the applicant. The determination of the research objectives and tasks, experimental procedures, analysis, and generalization of the obtained results were directly performed by the author.

MAIN CONTENT OF THE WORK

Synthesis and investigation of ketohydrazones based on methylene-active compounds

It is well known that methylene-active compounds and their transformation products have broad applications as biologically active substances. Considering this, the aim of this work is to study the reaction of various halogen-containing aromatic amines with methylene-active compounds and to investigate the structure of the obtained compounds. The research results indicate that the reaction of various halogen-substituted aromatic amines with dibenzoylmethane leads to the formation of 2-(2-(4-halogen-substituted phenyl) hydrazone)-1,3-diphenylpropane-1,3-diones (I-III), Scheme 1:



R= -F (I), -Cl(II), -J(III)

(I- III)

Yield: 73%, 72%, 70%

Scheme 1. Synthesis of 2-(2-(4-halogen-substituted phenyl) hydrazone)-1,3-diphenylpropane-1,3-diones.

The progress of the reaction and the purity of the obtained compounds were monitored using thin-layer chromatography (TLC).

The molecular structure of the compound (I), investigated by X-ray diffraction analysis (RSA) (CCDC 1468118), is as follows (Figure 1):

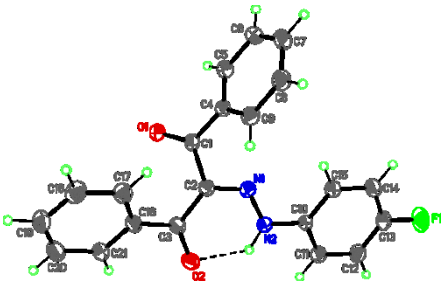
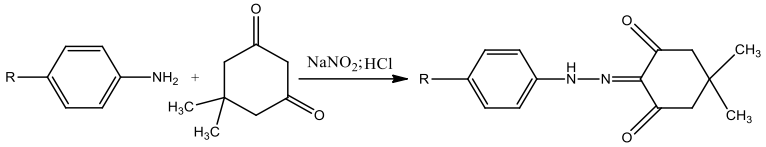


Figure 1. Molecular structure of compound (I)

As part of the ongoing research, we investigated the reaction of various aromatic amines with dimedone, Scheme 2:



R= H(IV), F(V). Yield= 69%, 74%

Scheme 2. Synthesis of 5,5-dimethyl-2-(2-phenylhydrazone) cyclo hexane-1,3-dione (IV) and 2-(2-(4-fluorophenyl) hydrazone)-5,5-dimethylcyclohexane-1,3-dione (V).

Molecular structure of compound (V) is as follows (Figure 2):

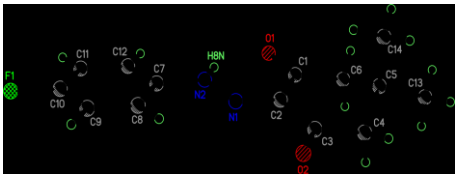
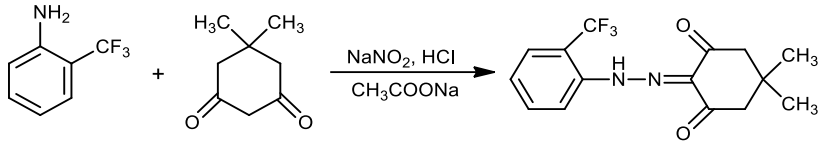


Figure 2. The molecular structure of 2-(2-(4-fluorophenyl) hydrazone)-5,5-dimethylcyclohexane-1,3-dione (V)

Continuing the research in this direction, a reaction with 2-(trifluoromethyl) aniline was also carried out, leading to the synthesis of the previously unknown compound 2-(2-(2-trifluoromethyl-phenyl) hydrazone)-5,5-dimethylcyclohexane-1,3-dione (VI) (CCDC 1475293), Figure 3, Scheme 3.



(VI) Yield: 73%

Scheme 3. Synthesis of 2-(2-(2-trifluoromethylphenyl) hydrazone)-5,5-dimethylcyclohexane-1,3-dione (VI)

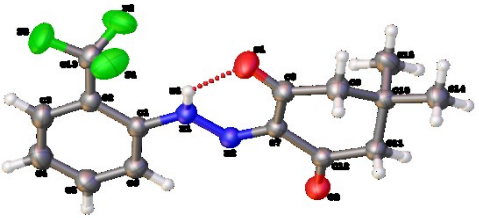
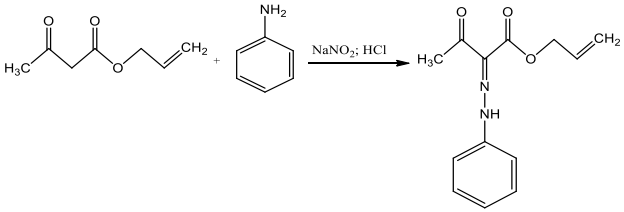


Figure 3. Molecular structure of the (VI) compound

Continuing the research, the synthesis of the new allil 3-oxo-2-(2-phenylhydrazone) butanate (VII), containing various functional groups, was carried out based on the methylene-active compound allyl 3-oxo-butanoate (CCDC 1484656), Scheme 4:



(VII) Yield: 61%

Scheme 4. Synthesis of Allyl 3-Oxo-2-(2-Phenylhydrazone) Butanoate (VII)

The structure of the obtained compound was confirmed by X-ray Crystallography (XRC) and is stored in the Cambridge Crystallographic Data Centre (CCDC 1537217), Figure 4:

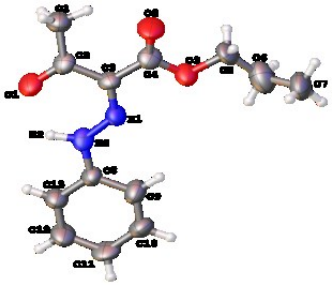


Figure 4. Molecular structure of compound (VII)

Molecular docking of 2-(2-(4-fluorophenyl) hydrazone)-5,5-dimethylcyclohexane-1,3-dione (V) and 2-(2-(2-trifluoromethyl phenyl)hydrazone)-5,5-dimethyltricyclohexane-1,3-dione (VI), along with DFT-B3LYP studies, Hirshfeld surface analysis, and energy framework analysis

The aim of our research was not only the synthesis of ketohydrazones and confirmation of their structures using X-ray crystallographic analysis (RSA), but also the investigation of the biological activities of the newly obtained compounds. Currently, methylene-active compounds and their derivatives are of great interest in research due to their significant biological effects.

It is well known that the anti-inflammatory effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs) is due to their inhibition of the cyclooxygenase enzymes COX-1 and COX-2, which prevent the production of prostaglandins. Considering this, the COX-2 inhibitory properties of the synthesized ketohydrazones (V, VI) were also investigated. However, the inhibitory effect of NSAIDs on cyclooxygenase is a reversible process, which results in weaker effects. Therefore, research focused on COX-2 inhibitors has gained attention as potential replacements for NSAIDs.

Ibuprofen (IBF) is a commonly used NSAID for pain relief, fever reduction, and inflammation control, and it was chosen as the

reference compound to study the COX-2 inhibitory effectiveness of the investigated ketohydrazones (V, VI).

To clarify the relationship between the internal electronic properties and biological activity of complexes (V) and (VI), a gas-phase Functional Density Theory (DFT) study was conducted using the B3LYP functional. The B3LYP-optimized geometry of the complexes (V) and (VI) is depicted in Figure 7.

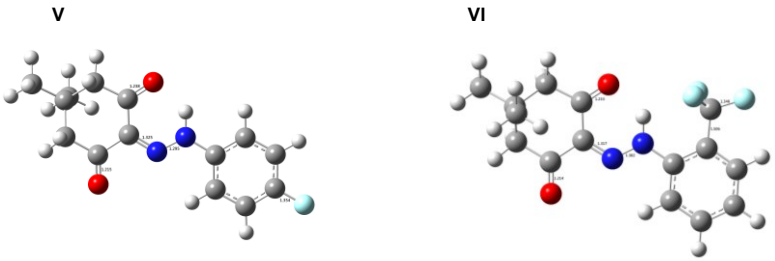


Figure 7. B3LYP-optimized geometries of the studied complexes (V, VI)

An important aspect of frontier molecular orbital theory is its focus on the highest and lowest energy molecular orbitals (HOMO and LUMO). Therefore, in this study, the frontier molecular orbitals of the complexes were separately analyzed (Figure 8).

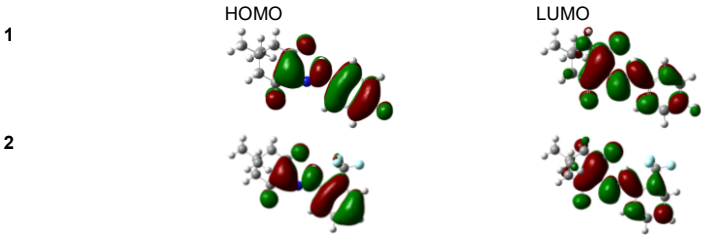


Figure 8. Frontier orbitals of the studied complexes (V, VI)

Molecular electrostatic potentials (MEP) are an important tool for measuring the interaction strength of nearby charges, nuclei, and electrons at a specific position. This allows for the investigation of

charge distribution and related molecular properties. To easily interpret electrostatic potential data, a visual representation with a color scale is used. Regions in red indicate the lowest electrostatic potential values, making them sensitive to electrophilic attacks. In contrast, regions in blue represent the highest electrostatic potential values, making them sensitive to nucleophilic attacks. In this study, the general density matrix was used to obtain the total density of the complexes, and the resulting molecular electrostatic potentials (MEP) were mapped onto their surfaces (Figure 9).

Figure 9. MEPs of the studied complexes (V, VI)

It is well known that Hirshfeld surface analysis plays a crucial role in studying how the interactions are affected when different functional groups are introduced into the crystal structure.

Hirshfeld surface analyses (d_{norm}) of the studied complexes (V) and (VI) are depicted in Figure 10. The 3D d_{norm} surface is used to identify very close intermolecular interactions. When intermolecular contacts are shorter (longer) than the Van der Waals radii, the d_{norm} value becomes negative (positive). D_{norm} values on the Hirshfeld surface are color-coded in red, white, or blue. Red areas indicate closer interactions with negative (negative) d_{norm} values, while blue areas represent longer interactions with positive (positive) d_{norm} values. White areas represent equal interactions corresponding to the Van der Waals bonds and have a zero d_{norm} value. Comparing the shape index and curvature of compound V with those of compound VI, the π-π stacking interaction in the VI crystal is stronger than in the V crystal.

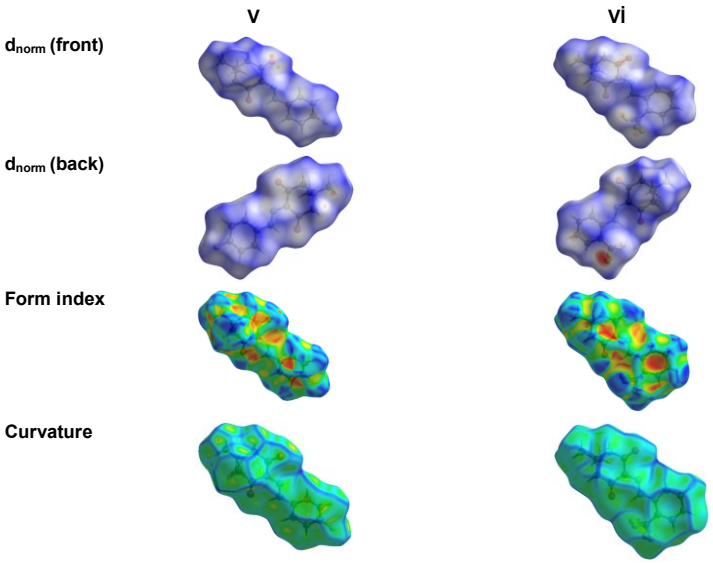
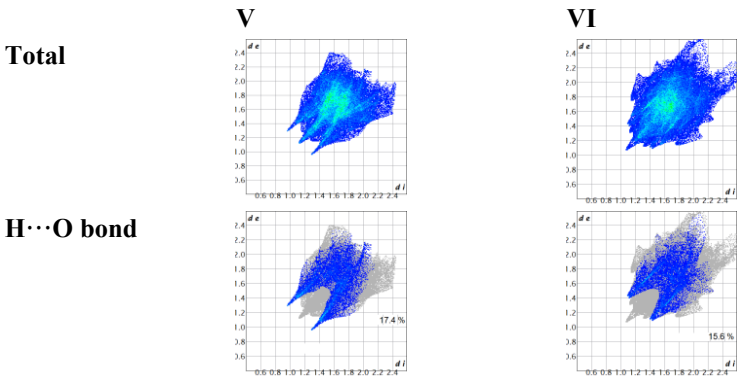


Figure 10. Hirshfeld surface analysis of the studied complexes (V, VI).

2D fingerprint plots highlight the interactions between specific atom pairs and allow the separation of contributions from different types of interactions overlapping in the full fingerprint. The distance scales de and di on the graph axes are obtained using the standard 0.6 - 2.4 Å distance range. In the complexes we studied, we identified that the most important interaction related to hydrogen is the H•••H contact (Figure 11).



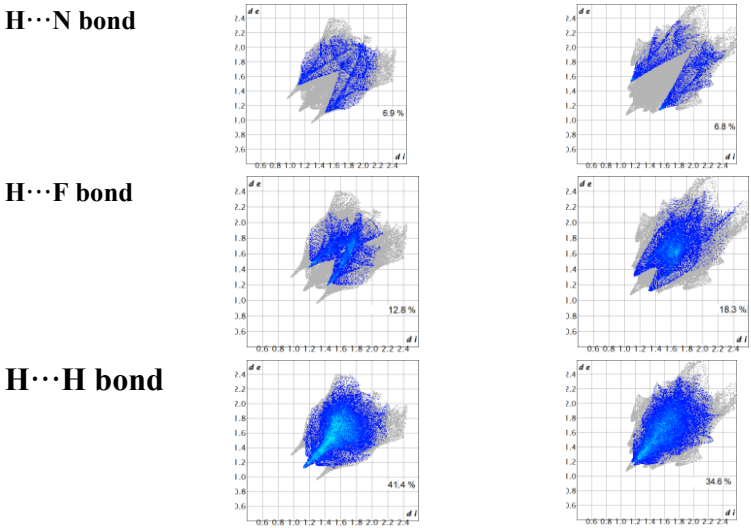
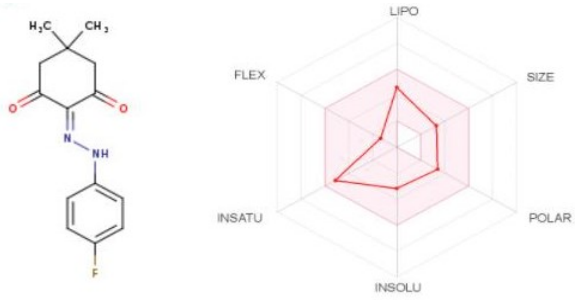


Figure 11. 2D fingerprint plots of the studied complexes (V, VI).

The pharmacokinetic properties of the studied complexes (V, VI), including their drug likeness, were examined using the SwissADME online server.

The drug likeness profile obtained from SwissADME showed that the physical-chemical properties of the complexes are within the desired range.



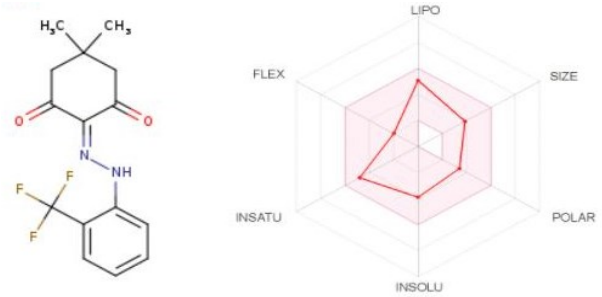
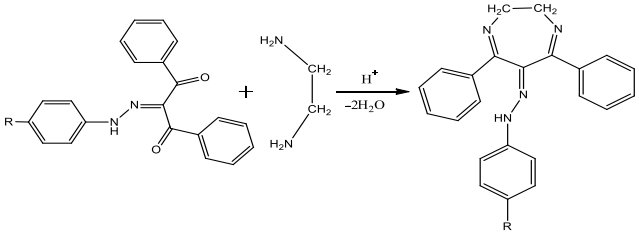


Figure 12. SwissADME drug likeness plots of the complexes

In the drug likeness plots of the complexes obtained from SwissADME, the pink area represents the optimal range for each property.

Synthesis of 6-(2-(4-halogenophenyl)hydrazone)-5,7-diphenyl-3,6-dihydro-2H-1,4-diazepines

Considering the broad applications of seven-membered heterocyclic compounds like diazepines and continuing the research, the reaction of some ketohydrazones we synthesized with ethylenediamine in a 2:1 ratio was investigated, leading to the synthesis of 6-(2-(4-halogenophenyl)hydrazone)-5,7-diphenyl-3,6-dihydro-2H-1,4-diazepines (VIII-X), Scheme 5:



VIII-X

R= F(VIII), Br(IX), J(X). Yield: 73%, 67%, 63%

Scheme 5. Synthesis of 6-(2-(4-halogenophenyl) hydrazone)-5,7-diphenyl-3,6-dihydro-2H-1,4-diazepines (VIII-X)

The structure of the newly synthesized 6-(2-(4-fluorophenyl) hydrazone)-5,7-diphenyl-3,6-dihydro-2H-1,4-diazepine (VIII) was confirmed using the RQA method. The compound has a triclinic structure and has been deposited in the Cambridge Structural Data Centre (CCDC 1481580), Figure 13.

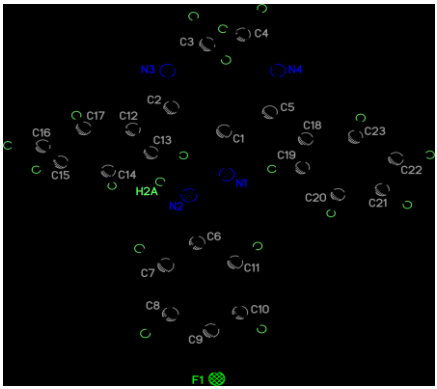
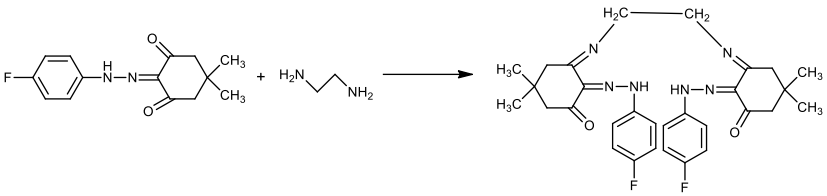


Figure 13. Molecular structure of compound (VIII).

Synthesis of (5E,5′E,6Z,6′Z)-6,6′-[ethane-1,2-diylbis(azanilidene)] bis{5-[2-(4-fluorophenyl)-hydrazone]-3,3-dimethylcyclohexanone} 2.5-hydrate (XI), its crystal structure, Hirshfeld surface analysis, and DFT calculations

To investigate the transformation of the synthesized ketohydrazones and the structure of the obtained compounds, the reaction of 2-(2-(4-fluorophenyl) hydrazone)-5,5-dimethylcyclo hexane-1,3-dione (IV) with ethylenediamine was carried out. The resulting compound was crystallized as a hydrate in the C2/c space group, leading to the new compound (5E,5′E,6Z,6′Z)-6,6′-[ethane-1,2-diylbis(azanilidene)]bis{5-[2-(4-fluorophenyl)-hydrazone]-3,3-dimethylcyclohexanone} 2.5-hydrate (XI), Scheme 6.



Yield: 59% XI

Scheme 6. Reaction for the synthesis of (5E,5′E,6Z,6′Z)-6,6′-[ethane-1,2-diylbis(azanilidene)]bis{5-[2-(4-fluorophenyl)-hydrazone] -3,3-dimethylcyclohexanone} 2.5-hydrate (XI)

The compound (XI) with a monoclinic structure has been deposited in the Cambridge Crystallographic Data Centre (CCDC 1510185), Figure 14.

Molecule pairs in the crystal are connected by N-H…N hydrogen bonds. The C-F, C-O, and C-N interactions further stabilize the crystal lattice. Hirshfeld surface analysis reveals that in the crystal lattice, H-H (49.1%), H-O (9.1%), O-H (9.9%), and H-C/C-H (6.4%) interactions play significant roles.

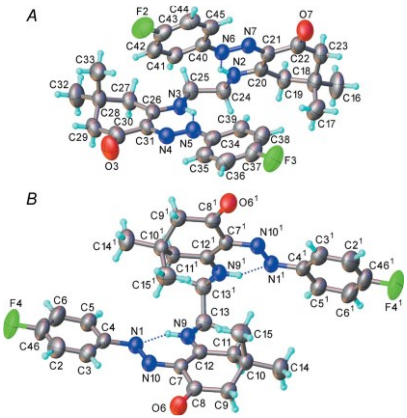


Figure 14. Molecular structure of compound (XI)

The specific torsion angle at the average position of the C24—C25 (symmetry code (1) ½-x, 1/2 - y, 1/2 - z) and N2—C25—C24—N3 dihedral is −59.0 (3) °. This indicates that the molecule has

a book-like structure. The molecule contains two benzene rings, which are stacked on top of each other, Figure 15.

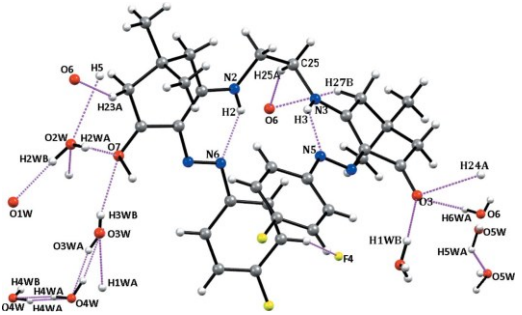


Figure 15. Hydrogen bonds in the crystal of compound (XI)

Red spots represent N-H-N hydrogen bonds, while blue indicates weaker C-H-N intermolecular interactions. A two-dimensional fingerprint plot of the Hirshfeld surface (Figure 16) illustrates the percentage distribution of different interactions on the overall Hirshfeld surface.

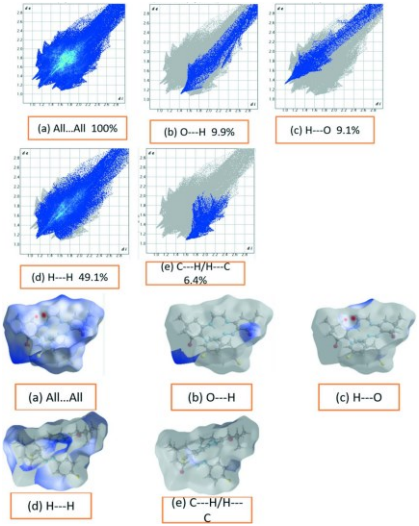


Figure 16. Two-dimensional fingerprint plots of compound (XI)

Fragment molecular orbitals (FMO) play a significant role in the molecule, and the energy gap is an important stability index. Useful information about donor-acceptor interactions can also be derived from the molecular orbital energy. DFT calculations for the fragment molecular orbitals were performed using the 6-311 G(d,p) basis set and the B3LYP method. The ionization potential, electron affinity, electroactivity, hardness, softness, and dipole moment are 4.8164 eV, 3.9894 eV, 0.4135, 2.4183, and 5.0777, respectively. The two-dimensional plots of HOMO and LUMO in the gas phase are shown in Figure 17.

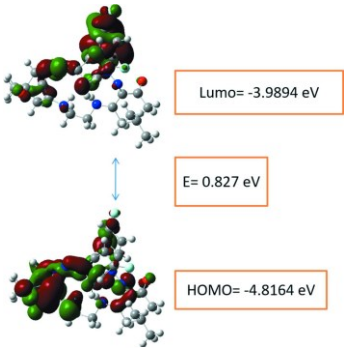


Figure 17. Frontier molecular orbitals of compound (XI).

Synthesis and investigation of optically active 4H-pyrans based on methylene-active compounds

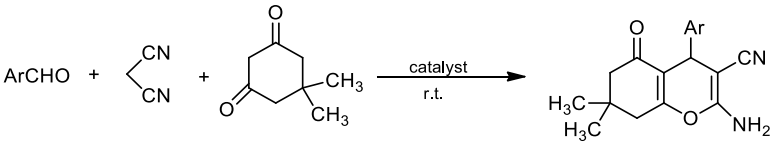
In recent decades, multicomponent reactions have proven to be powerful and efficient methods in organic, combinatorial, and medicinal chemistry, forming strong connections within the context of green chemistry. Considering this, we have conducted the synthesis of 4H-pyrans with broad applications in medicine.

The objective of our study was to synthesize optically active 4H-pyrans with L-glutamic acid, L-cysteine, and L-arginine as chiral organic catalysts, which distinguishes it from previous works. We also aimed to determine their specific rotation angles using an AUTOPOL III polarimeter and study their structure and biological properties.

Enantioselective synthesis of optically active 2-amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromen-3-carbonitriles (XII-XVI)

Multicomponent reactions have become a useful approach in ecological and organic synthesis, which is aligned with green chemistry principles. Polyfunctional substituted 4H-pyrans synthesized through this method belong to a class of biologically and pharmacologically significant heterocyclic compounds. Considering their successful application in medicine, the enantioselective synthesis of their optical isomers remains a key issue.

Few studies have been published on the asymmetric synthesis of optically active pyrans and their derivatives. Therefore, the work presented here focuses on the enantioselective synthesis of optically active 4H-pyrans, with chiral organic catalysts used in the process. The general scheme of the reactions is as follows; Scheme 7:



XII-XVI

Yield: 75%, 72%, 72%, 74%,76%

Ar= C_6H_5 (XII), 2-ClC_6H_4 (XIII), 2-Furanyl (XIV), 4-$MeOC_6H_4$ (XV), 2-OHC_6H_4 (XVI).

Scheme 7. Synthesis of 2-amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromen-3-carbonitriles (XII-XVI)

The specific rotation angles of the synthesized compounds were determined using an AUTOPOL-III polarimeter.

It is known that enantiomers have the ability to rotate the plane of polarization. The specific rotation angle is determined by the following equation:

$$[\alpha]^t_D = \frac{\alpha \cdot 100}{l \cdot c}$$

$[\alpha]^t_D$- specific rotation angle;
α- observed rotation;
l- length of the light path;
c- concentration of the solution.

The specific rotation values of the optically active compounds synthesized with various chiral organic catalysts are provided in the table below (Table 1):

Table 1.
Specific rotation angles of optically active 4H-pyrans

№	Chiral Organic Catalysts	Specific Rotation $[\alpha]_D$, 20^0C, c=1, DMF
XII	L-Glutamic Acid	+25.36
	L-Cysteine	+21.17
	L-Arginine	+24.72
XIII	L-Glutamic Acid	+27.09
	L-Cysteine	+24.63
	L-Arginine	+24.95
XIV	L-Glutamic Acid	+23.81
	L-Cysteine	+22.23
	L-Arginine	+25.61
XV	L-Glutamic Acid	+24.30
	L-Cysteine	+22.91
	L-Arginine	+25.17
XVI	L-Glutamic Acid	+23.36
	L-Cysteine	+22.81
	L-Arginine	+22.84

Biological properties of optically active 2-amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromen-3-carbonitriles (XII-XVI)

The 2-amino-4-(2-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8 -tetrahydro-4H-chromen-3-carbonitrile (XVI) and 2-amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromen-3-carbonit-

rile (XIV) exhibit the strongest inhibitory effects on the hCA I isoform. Their Ki values are 21.33 ± 1.11 and 23.04 ± 6.71 μM, respectively. The clinically used acetazolamide (AZA) preparation showed a Ki value of 44.17 ± 7.91 μM. Therefore, the investigated molecules exhibit better inhibitor profiles compared to the AZA molecule. The results indicate that the 4H-chromenes (XII-XVI) effectively inhibit hCA II. These compounds possess strong hCA II inhibition with Ki values ranging from 28.91 ± 6.51 to 59.97 ± 15.62 μM. The Ki values of the new molecules are better than that of the standard AZA preparation (Ki: 63.15 ± 11.31 μM).

Acetylcholinesterase inhibitors (AChEIs) are prescribed for the symptomatic treatment of mild and moderate Alzheimer's disease. Currently, only five drugs are approved for the clinical treatment of Alzheimer's disease, four of which are AChEIs. Only one acts as an N-methyl-D-aspartate receptor antagonist, preventing the excessive release of neurotoxic glutamate. The inhibitory effect of the compounds we synthesized on the AChE enzyme is shown in Table 2.

Table 2.

Results of inhibition of human carbonic anhydrase I and II (hCA I and II), acetylcholinesterase (AChE), and α-glucosidase (α-Gly) enzymes by new 4H-chromenes (XII-XVI)

	IC_{50}							(μM)
Compounds	**hCA I**	**r^2**	**hCA II**	**r^2**	**AchE**	**r^2**	**α-Gly**	**r^2**
XII	27,98	0,9761	33,62	0,9714	45,31	0,9782	38,67	0,9792
XIII	28,14	0,9852	50,94	0,9602	62,34	0,9764	32,76	0,9513
XIV	29,58	0,9891	44,73	0,9823	41,41	0,9892	42,71	0,9723
XV	29,72	0,9712	33,91	0,9932	59,30	0,9862	37,23	0,9662
XVI	25,97	0,9853	44,30	0,9984	38,10	0,9921	38,96	0,9631
AZA[a]	54,81	0,9683	65,22	0,9488	-	-	-	-
TAC[b]	-	-	-	-	131,23	0,9054	-	-
ACR[c]	-	-	-	-	-	-	22800	-

K_i (μM)

Compounds	hCA I	hCA II	AchE	α-Gly
XII	32.38 ± 0.83	59.97±15.62	8.68 ± 0.93	27.42 ± 1.43
XIII	40.24±10.78	33.11 ± 4.97	26.43 ± 9.28	23.07 ± 9.95
XIV	23.04 ± 6.71	41.78 ± 2.18	102.61±24.96	18.16 ± 3.18
XV	29.64 ± 1.86	29.43 ± 3.70	35.24 ± 15.08	66.57 ± 1.36
XVI	21.33 ± 1.11	28.91 ± 6.51	17.66 ± 2.43	31.14 ± 1.88
AZA[a]	44.17 ± 7.91	63.15±11.31	-	-
TAC[b]	-	-	104.12±14.80	-
ACR[c]	-	-	-	12600 ± 78

[a]Acetazolamide (AZA) was used as a control for hCA I and II.
[b]Tacrine (TAC) was used as a control for the AChE enzyme.
[c]Acarbose (ACR) was used as a control for the α-glucosidase enzyme.

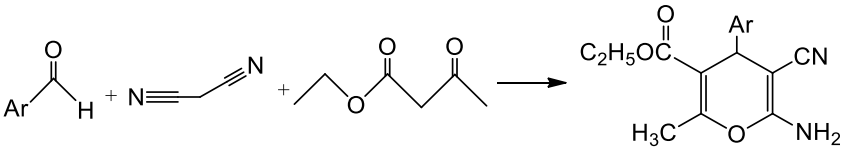
There are several therapeutic mechanisms for the management of diabetes. The inhibition process of the enzyme depends on its ability to bind to the carbohydrate component. For this metabolic enzyme, the 4H-chromenes (XII-XVI) exhibit IC50 values ranging from 32.76 to 42.71 and Ki values ranging from 18.16 ± 3.18 to 66.57 ± 1.36 μM. The results clearly show that all 4H-chromenes (XII-XVI) are more effective inhibitors of α-glucosidase compared to acarbose (IC50: 22.80 μM).

The newly synthesized compounds studied in this research may serve as effective drugs for the treatment of diseases such as epilepsy, gastric and duodenal ulcers, glaucoma, mountain sickness, osteoporosis, or neurological disorders, similar to CAIs. As a result, all the synthesized compounds are effective inhibitors at micromolar levels for various metabolic enzymes such as α-glucosidase, hCA I, hCA II, and AChE.

Synthesis of optically active ethyl 6-amino-5-cyano-2-methyl-4-aryl-4H-pyran-3-carboxylates (XVII-XXIV)

It should be noted that there is limited research in the literature on the asymmetric synthesis of optically active 4H-pyrans and their derivatives. Considering this, we focused more on the enantioselective synthesis of optically active 4H-pyrans in the presented work. As the research object, aromatic aldehydes,

malonitrile, and a methylene-active compound, such as acetosyringe ether, were chosen, with L-glutamic acid, a more affordable and easily obtainable optically active α-amino acid, used as the catalyst.



(XVII-XXIX)

Ar= C_6H_5 (XVII), p-$CH_3C_6H_4$ (XVIII), p-$CH_3OC_6H_4$ (XIX), p-FC_6H_4 (XX), o-ClC_6H_4 (XXI), p-BrC_6H_4 (XXII), p-OHC_6H_4 (XXIII), p-$NO_2C_6H_4$ (XXIV);

Catalyst = L-glutamic acid.

Scheme 8. Synthesis of optically active ethyl 6-amino-5-cyano-2-methyl-4-aryl-4H-pyran-3-carboxylates (XVII-XXIV)

Investigation of the antioxidant properties of synthesized optically active ethyl 6-amino-5-cyano-2-methyl-4-aryl-4H-pyran-3-carboxylates (XVII-XXIV)

Oxidation resistance is one of the key operational characteristics of fuels and lubricants. In this study, we investigated a series of synthesized, previously unknown ethyl-6-amino-5-cyano-2-methyl-4-aryl-4H-pyran-3-carboxylates as potential multifunctional compounds, including fuel additives. Their mechanism of action was explored, and the relationship between their structure and antioxidant activity was assessed.

When selecting compounds for the study, two types of antioxidant properties were considered. The first was their ability to effectively break oxidation chains by peroxyl radicals and reaction pathways, while the second was their capacity to decompose hydroxides.

The synthesized 4H-pyrans are important multifunctional heterocyclic compounds. The study of the auto-oxidation of cumene with the involvement of the XVII-XXIV compounds demonstrated that they efficiently inhibit this process. The kinetic curves of the

automatic oxidation of cumene with the participation of the XVII-XXIV compounds are shown in the Figure18, Table 3.

Table 3.

Time values for the induction of the auto-oxidation of cumene in the presence of synthesized XVII-XXIV compounds, as well as their kinetic parameters for the reaction with cumene peroxyl radicals and cumene hydroperoxides.

Compound	Induction Time of Cumene Auto-Oxidation (in min.)	Reaction with RO_2-RO_2		Reaction with CHP-CHP	
		F	$K_7 \cdot 10^{-4}$ *l/mol·s*	*K, l/mol ·s*	Y
XVII	250	2.6	3.6	15	12000
XVIII	220	2.2	3.2	13	10000
XIX	130	1.59	1.92	8	6000
XX	210	1.81	2.88	-	-
XXI	260	2.73	3.84	6	4500
XXII	280	4.24	4.32	10	7000
XXIII	200	1.97	3.12	11	8000
XXIV	170	1.72	2.04	-	-
İonol	150	2.10	2.00	-	-

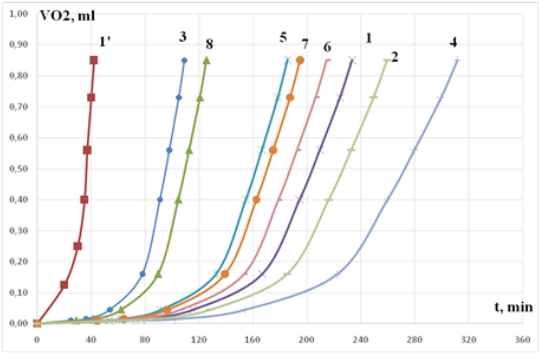


Figure 18. Kinetic Curves of Cumene with the Participation of Synthesized Compounds:T = 110°C, VO_2 volume of oxygen (ml), τ time (min); [InH] = 0 (1I), [InH] = **1-2-3-4-5-6-7-8** = $5 \cdot 10^{-4}$ mol/l.

To evaluate the ability of the investigated compounds (XVII-XXIV) to break oxidation chains by reacting with cumene peroxyl radicals, the oxidation of cumene was initiated at 60°C with the presence of these inhibitors and azodiisobutyronitrile, and it was found that they effectively inhibited the oxidation of cumene (Figure 19).

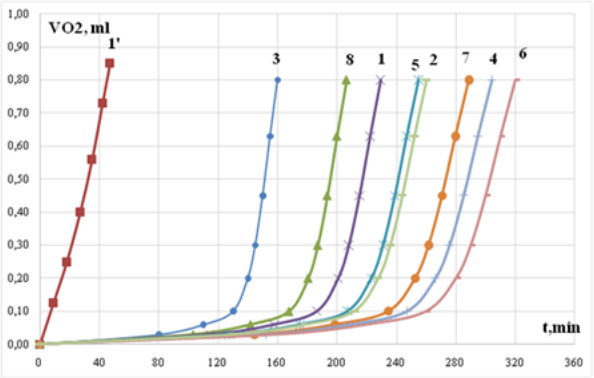


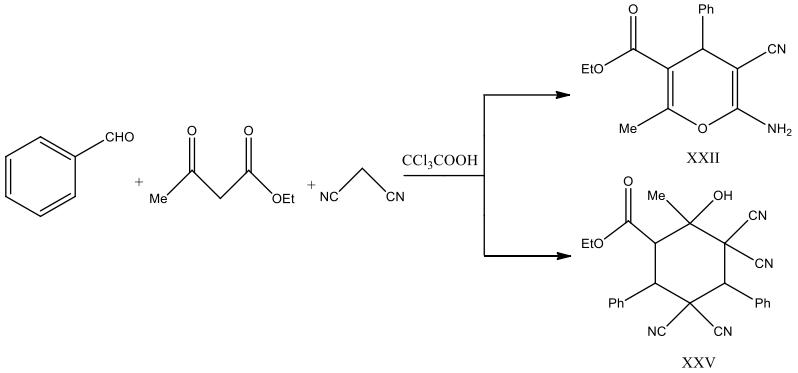
Figure 19. Kinetic curves of initial cumene oxidation with the participation of synthesized compounds (XVII-XXIV):T = 60°C; VO_2 volume of oxygen (ml), τ time (min); [InH] = 0 (1'), [InH] = $5 \cdot 10^{-4}$ mol/l = 17-24.

Based on the experiments conducted, the investigated compounds, except for compound XXIV, exhibited very high antioxidant properties, surpassing well-known antioxidants such as ionol (2,5-di-ter-butyl-4-methylphenol) in terms of antioxidant activity.

Synthesis and structure of ethyl 3,3,5,5-tetrasian-2-hydroxy-2-methyl-4,6-diphenylcyclohexan-1-carboxylate (XXV)

A major direction of modern organic chemistry is the development of methods and approaches that allow the synthesis of compounds with practical and valuable properties, using minimal reagents, solvents, energy, and time. This approach, based on more efficient multicomponent reactions, is eco-friendly and economically

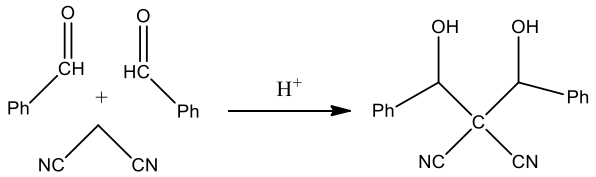
viable in organic synthesis. Multicomponent reactions provide access to heterocyclic systems that are difficult or impossible to obtain using traditional methods. As a continuation of our research, we studied the three-component condensation of benzaldehyde with acetosyringe ether and malonitrile in the presence of trichloroacetic acid (Scheme 9).

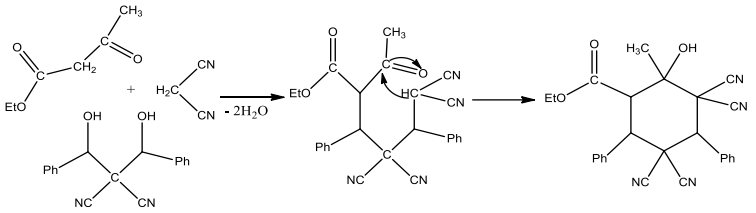


Scheme 9. Three-component condensation reaction

It has been established that under certain conditions, with the participation of CCl_3COOH, the condensation product is the expected product, ethyl 6-amin-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate (XVII), and the previously unknown ethyl-3,3,5,5-tetrasian-2-hydroxy-2-methyl-4,6-diphenylcyclohexan-1-carboxylate (XXV).

The possible mechanism for the synthesis of the new ethyl-3,3,5,5-tetrasian-2-hydroxy-2-methyl-4,6-diphenylcyclohexan-1-carboxylate, which was not previously known in the literature, is proposed as follows, Scheme 10:





Scheme 10. Synthesis of ethyl-3,3,5,5-tetrasian-2-hydroxy-2-methyl-4,6-diphenylcyclohexan-1-carboxylate (XXV)

The progress of the reaction was monitored using the TLC method. The structure of the synthesized new compound (XXV) was confirmed by the RSA method (CCDC 1839026), Figure 20.

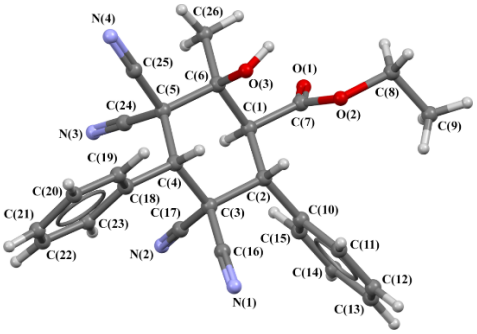


Figure 20. Molecular structure of compound (XXV)

Hirschfeld analysis, quantum chemical calculation analysis, molecular docking of ethyl 3,3,5,5-tetracyano-2-hydroxy-2-methyl-4,6-diphenylcyclohexane-1-carboxylate (XXV)

The strong red surface observed in the nitrile and hydroxyl groups on the d_{norm} surface indicates the presence of O-H···N type hydrogen bonding in the crystalline phase, while the small red spots indicate the presence of C–H···N type weak hydrogen bonding interactions around the molecules. Strong white and blue surfaces in the 3D d_{norm}-based Hirshfeld surface maps distinguish the sum of Van der Waals radii and short contact distances (Figure 21).

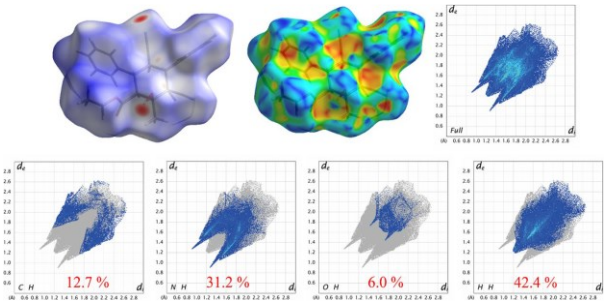


Figure 21. Hirshfeld Surface Analysis of the Molecule; d_{norm} (top left), shape index (top center), and fingerprint 2D plots (top right and bottom) in percentage values

To understand the relationship between structure, stability, and global chemical reactivity, the reactive descriptors of the compound can be derived from conceptual density functional theory. The ionization potential and electron density are related to the energy of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), Figure 22.

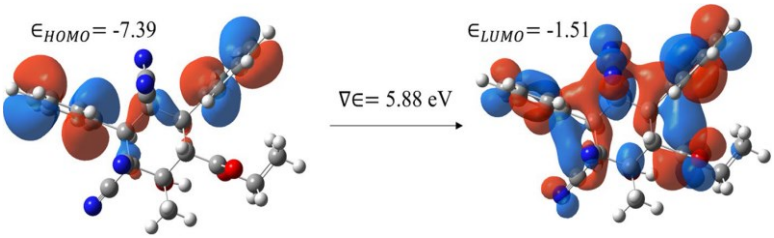


Figure 22. HOMO and LUMO Interaction of Etil 3,3,5,5-Tetrasian-2-hidroksi-2-metil-4,6-difeniltsikloheksan-1-karboksilat Molecule (XXV)

The molecular docking score of the compound is −12.14 kcal/mol, indicating its binding to the minor groove of DNA. To determine the receptor's interaction with the DNA molecule and the stability of the binding mode, molecular dynamics simulations were carried out over 100 ns at the location where the drug interacts with the receptor (Figure 23).

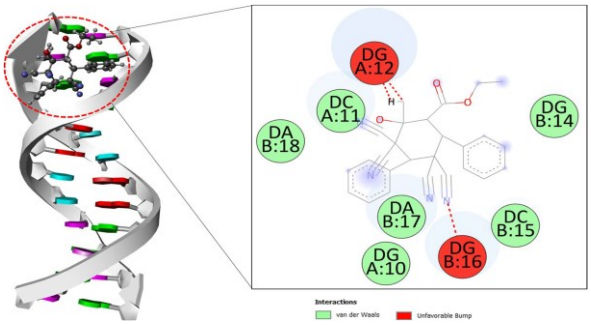


Figure 23. Conformation of macromolecule in DNT (Top and Stick Representation). Chemical interactions between the drug molecule and DNA are observed.

One of the main characteristics of a successful drug-like molecule is its good absorption in the body over a period of time. This supports the effective distribution of the compound and its arrival at the target area at the highest concentration for optimal activity.

Thus, computer-aided drug analysis demonstrates that the compound binds well to the DNA molecule and exhibits better drug-like properties and pharmacokinetic profiles.

Study of antimicrobial properties of some synthesized compounds

As we know, the production of antibiotics is a leading sector in the pharmaceutical industry. Antibiotics consist of various antimicrobial agents. Although a sufficient number of antimicrobial agents have been synthesized, there is always a need for new ones. In light of this, the antimicrobial properties of some synthesized compounds (VII, VI, I, XII, XIII, XIV) have been studied.

The antimicrobial effects of these compounds have been compared to widely used substances like alcohol, furacilin, and nitrofungin. The test cultures included Gram-positive microorganisms such as Staphylococcus aureus, Gram-negative

bacteria like Escherichia coli, pigment-producing Pseudomonas aeruginosa, and fungi from the Candida genus such as Candida albicans. The synthesized substances are generally antimicrobial and the results are shown in Table 4 below:

Table 4.

Antimicrobial effects of synthesized substances

Test kulturalar	Ekspozisiya müddəti (dəq)	Müayinə olunan maddələr																							
		Maddə I				Maddə VI				Maddə VII				Maddə XII				Maddə XIII				Maddə XIV			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
St. aureus	10	-	-	+	+	-	-	+	+	-	-	+	+	-	-	-	+	-		+	+	-	-	+	+
	20	-	-	+	+	-	-	+	+	-	-	+	+	-	-	-	+	-	-	+	+	-	-	+	+
	40	-	-	+	+	-	-	+	+	-	-	+	+	-	-	-	+	-	-	-	+	-	-	+	+
	60	-	-	+	+	-	-	+	+	-	-	+	+	-	-	-	+	-	-	-	+	-	-	+	+
Ps.aerugi noza	10	-	+	+	+	-	+	+	+	-	+	+	+	-	-	-	+	-	-	+	+	-	-	-	+
	20	-	+	+	+	-	+	+	+	-	-	+	+	-	-	-	+	-	-	+	+	-	-	-	+
	40	-	+	+	+	-	+	+	+	-	-	+	+	-	-	-	+	-	-	+	+	-	-	-	+
	60	-	-	+	+	-	+	+	+	-	-	+	+	-	-	-	+	-	-	+	+	-	-	-	+
E.coli	10	-	+	+	+	-	+	+	+	-	-	+	+	-	-	-	+	-	-	+	+	-	-	+	+
	20	-	+	+	+	-	+	+	+	-	-	+	+	-	-	-	+	-	-	+	+	-	-	+	+
	40	-	-	+	+	-	+	+	+	-	-	+	+	-	-	-	+	-	-	+	+	-	-	+	+
	60	-	-	+	+	-	+	+	+	-	-	-	+	-	-	-	+	-	-	+	+	-	-	+	+
Cand. albicans	10	-	-	+	+	-	-	+	+	-	-	+	+	-	-	+	+	-	-	+	+	-	-	+	+
	20	-	-	+	+	-	-	+	+	-	-	+	+	-	-	-	+	-	-	+	+	-	-	+	+
	40	-	-	-	+	-	-	+	+	-	-	-	+	-	-	-	+	-	-	-	+	-	-	+	+
	60	-	-	-	+	-	-	+	+	-	-	-	+	-	-	-	-	-	-	-	+	-	-	+	

CONCLUSION

1.Methylenactive compounds were synthesized through interaction with various halogen-substituted aromatic amines, and the structures of the obtained compounds were confirmed by RQA and RSA methods [1,2,9,11].

2.Molecular docking, molecular dynamics, and DFT were used to investigate the biological activity against COX-2 for the synthesized new ketohydrazones. Hirshfeld surface analysis, energy frameworks, and ADMET studies were conducted. Based on the

molecular docking results, the synthesized compounds were identified as strong anti-COX-2 inhibitors [12, 14].

3.The reaction of synthesized ketohydrazones with ethylenediamine was studied, revealing that ketohydrazones based on benzoylacetophenone led to the synthesis of 6-(2-(4-halogenphenyl)hydrazone-5,7-diphenyl-3,6-dihydro-2H-1,4-diazepines. The reaction product of ketohydrazones based on 5,5-dimethylcyclohexane-1,3-dione with ethylenediamine was determined as (5E,5′E,6Z,6′Z)-6,6′-[ethane-1,2-dibis (azanilidene)] bis{5-[2-(4-fluorophenyl)-hydrazone]-3,3-dimethyl cyclohexanone} 2.5-hydrate. The structures of the synthesized compounds were confirmed by RSA and NMR methods [3,13].

4.Optically active 4H-pyran derivatives were synthesized through multicomponent condensation of methylenactive compounds with α-amino acids, malonitrile, and various aromatic aldehydes. Their structures were confirmed using RSA methods and NMR spectroscopy, and specific optical rotation angles were determined using an AUTOPOL III polarimeter [4].

5.The optical active 4H-benzopyrans were studied for their inhibition properties against acetylcholinesterase (AChE), butyrylcholinesterase (BChE), β-glucosidase enzymes, and carbonic anhydrase I and II isoenzymes. It was found that they possess antiepileptic, antidiabetic, and anticholinergic potential. Additionally, optically active 4H-pyrans were investigated as antioxidant additives to fuels, and it was determined that these compounds have high antioxidant properties [8,10].

6.For the first time, a new compound, ethyl 3,3,5,5-tetrasian-2-hydroxy-2-methyl-4,6-diphenylcyclohexane-1-carboxylate, was synthesized via the condensation of benzaldehyde, acetosuccinic ester, and malonitrile with trichloroacetic acid, a previously unknown compound in the literature. Its structure was confirmed using RSA methods, and molecular docking analysis, along with Dana Timus DNA interaction calculations, was performed. Pharmacological properties were determined [5, 7].

7.Some synthesized compounds were tested as antimicrobial agents against Gram-positive and Gram-negative microorganisms.

They demonstrated more effective antimicrobial properties than several commonly used drug preparations [6].

The main results of this dissertation work are reflected in the following publications:

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