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ABSTRACT
of the dissertation for the degree of Doctor of Philosophy

SYNTHESIS AND TRANSFORMATIONS OF DI-, TRI-, AND TETRA-SUBSTITUTED PYRROLES

Speciality: 2306.01- Organic chemistry

Field of science: Chemistry

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GENERAL CHARACTERİSTİCS OF WORK

The relevance of the topic and degree of elobaration. Due to their high biological activity, pyrrole and its derivatives are considered fundamental building blocks in organic synthesis. At present, the pharmaceutical industry widely employs multifunctional substituted drugs containing a pyrrole ring. Owing to these properties, the synthesis of pyrrole and its derivatives remains a focal point of research.

It should be noted that various studies dedicated to the synthesis of pyrrole derivatives can be found in the literature. Pyrroles can be obtained using different synthetic methods. In addition to the classical reaction of aldehydes with alkyl isocyanoacetates, examples of pyrrole synthesis include the Knorr, Hantzsch, Paal-Knorr, Barton-Zard, and Trofimov methods.

It has been proven that the structural similarity of certain 2-phenylpyrrole derivatives to CB1 and CB2 "cannabimimetic" receptors is responsible for their high physiological activity. The results of these studies have given new significance to the synthesis of 2-phenylpyrroles.

Against this background, the main challenge for organic chemists is to develop synthetic approaches for new pyrrole derivatives with beneficial properties, as well as to enhance the efficiency of known synthesis methods.

In the literature, various methods have been developed for the synthesis of 3,5-dialkyl(phenyl)-pyrrol-2-ethylcarboxylates. Researchers have carried out the cyclization of β-enamines into pyrrole derivatives using different approaches and in the presence of various catalysts.

β-Enaminones are important synthons for a wide range of biologically active compounds, including inhibitors, dopamine autoreceptor agonists, anticonvulsants, oxytocin antagonists, and others. Moreover, enamines are widely used in the synthesis of highly substituted pyrroles, other heterocycles, and various colored pigments.

Alkoxy derivatives of pyrroles have a wide range of applications as optically active compounds. In recent years, the enantioselective synthesis of compounds containing chiral carbon has attracted significant interest. The limited study of optically active pyrrole derivatives has provided a foundation for expanding research on the synthesis of such compounds.

Polymers such as polyaniline, polypyrrole, and polythiophene have attracted significant research interest due to their unique electrophysical and optical properties. These materials exhibit electrochromic behavior when exposed to ultraviolet radiation. In modern technology, they are widely used as key raw materials for manufacturing anticorrosion coatings, biochemical sensors, transistors, and diodes. Their electrochromic properties enable their application in membranes, light-emitting diodes, optical displays, and sensors.

Semiconducting electrochromic polymers can exhibit different color variations under the influence of low electrical energy. Among them, polypyrrole and polythiophene derivatives are highly conductive semiconductors. Due to their superior electrical conductivity and stability, polythiophenes are often used in copolymers with polypyrrole to enhance material performance.

The presence of a pyrrole core in benzoporphyrins and naphthoporphyrins imparts semiconducting properties to these compounds, enabling their application in optical materials, photostabilizers, and photodynamic therapy (PDT) materials.

Since 4,5-dihydroisomers are chemically pyrrole derivatives, the second position of the pyrrole ring undergoes highly selective electrophilic substitution. This property facilitates the development of various tricyclic derivatives containing functionalized pyrrole rings.

Functionalized nitrogen-containing heterocycles are unique compounds with a broad range of applications due to their biological activity. Substances containing these heterocycles are commonly found in various industrial fields. Among the important representatives of functionalized pyridines, imidazopyridines exhibit extensive biological activity and are utilized in the development of antimicrobial, anticancer, anti-ulcer, anti-inflammatory, and antipyretic pharmaceutical agents.

Taking the aforementioned factors into account, the focus of the research has been on the synthesis of new derivatives of 2-phenylpyrroles, 3,5-dialkyl(phenyl) pyrroles, 2,3- and 2,5-dithienyl pyrroles, as well as various functionally substituted pyrroles.

The object and subject of the research. The object of the research consists of di-, tri-, and tetrasubstituted pyrrole derivatives, certain

optically active pyrrole representatives, as well as various functionally substituted pyrrole derivatives exhibiting biological activity.

The subject of the research focuses on studying the properties of di-, tri-, and tetrasubstituted pyrroles and investigating their signi-ficance in pharmaceutical applications.

The goals and objectives of the research.The primary objective of this study was to synthesize di-, tri-, and tetrasubstituted pyrroles, investigate their transformations, enhance yields using various catalysts based on green chemistry principles, confirm the structures of the obtained compounds through various physical research methods, and explore their potential applications.

To achieve these objectives, tasks like investigation of the reaction of 1,3-dicarbonyl compounds with amines, study of the reaction between tetramethoxytetrahydrofuran and optically active amines, as well as the determination of the specific optical rotation of the synthesized compounds, examination of the condensation reaction of 2,2'-thionine with enamines, investigation of the reaction between 2-propargyl-α-tetralone and various primary amines, synthesis of dihydroimidazo-[1,2-a]pyridine, pyrido[1,2-a]pyrimidine, and novel functionally substituted pyridine derivatives containing a pyrrole ring, structural confirmation of newly synthesized compounds using ^{1}H and ^{13}C NMR spectroscopy and X-ray crystallographic analysis, execution of Hirshfeld surface analysis, assessment of the inhibitory effects of selected compounds on acetylcholinesterase, carbonic anhydrase, and α-glucosidase enzymes, molecular docking studies to evaluate potential interactions with biological targets, antimicrobial activity assays against various bacterial strains, evaluation of anticancer activity of the synthesized compounds were carried out.

Research methods. The syntheses were carried out using appropriate methodologies in the "Organic Chemistry" department. The crystal structures of the synthesized compounds were confirmed using a Bruker APEX II CCD diffractometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer using chloroform ($CDCl_3$) and dimethyl sulfoxide (DMSO) as solvents. Thin-layer chromatography (TLC) was performed on silufol plates (UV-254), and the resulting spots were observed under UV light. Column chromatography was conducted

using Merck silica gel, with hexane and ethyl acetate as eluents for TLC and column chromatography separations.

The main provisions defended. Efficient synthesis of phenyl tetrasubstituted pyrroles; synthesis of 3,5-dialkyl (phenyl)-pirrol-2-ethyl-carboxylates via a convenient route in a superbasic environment (t-BuOK/t-BuOH); synthesis of optically active new alkoxypyrroles with molecular iodine; synthesis of new derivatives of 2,3-dithiophenyl pyrrole; synthesis of some tricyclic compounds containing pyrrole ring; synthesis of new derivatives of dihydroimidazo[1,2-a]pyridine and pyrido[1,2-a]pyrimidine; synthesis of new pyridinone derivatives; application of synthesized compounds as inhibitors of human carbonic anhydrases (HCAs), acetylcholinesterase (AChE), and α-glucosidase (AG), their anticancer properties, and molecular docking analysis.

Scientific novelty of the research:A new synthetic route has been developed by applying the $Y(OTf)_3$ catalyst, which is considered advantageous, for the reaction of enamines with 1,3-dicarbonyl compounds and the HCl salt of glycine ethyl ester.

The enamine cyclization under acidic conditions and in the presence of dimethylformamide (DMFA), with t-BuOK/t-BuOH as a base, led to the synthesis of 3,5-dialkyl(phenyl)-pirrol-2-carboxylates. This approach offers a novel and efficient method for the preparation of these compounds.

Considering the principles of green chemistry, new 3,4-methoxy N-substituted pyrrole derivatives were synthesized by the reaction of tetramethoxydihydrofuran with optical amines in the presence of molecular iodine. The reaction was studied with various amounts of catalyst. An efficient one-step, two-component reaction was successfully developed for the synthesis of these new compounds.

Using microwave irradiation, 2,5-di-(2-thienyl)-1,4-butadione underwent the Paal-Knorr reaction to synthesize 2,5-di(2-thienyl)-1H-pyrrole derivatives, while 2,2'-thionine was used to synthesize 2,3-di-(2-thienyl)-1H-pyrrole derivatives. The modifications of the reactions and their efficiency were thoroughly investigated, leading to the successful

and effective synthesis of these new pyrrole derivatives.

For the first time, we synthesized some tricyclic compounds containing a pyrrole fragment through the reaction of 2-propargyl-α-tetralone with various primary amines in the presence of $BF3{\cdot}O(C_2H_5)_2$.

2-((1H-pyrrol-2-yl)methylene)malononitrile and 2-((1-methyl-1H-pyr rol-2-yl)methylene)malonitrile underwent a one-step, three-component reaction with ethylenediamine, leading to the synthesis of pyrrole-substituted dihydroimidazo[1,2-a]pyridine and pirido[1,2-a]pyrimidine derivatives when reacted with diaminopropane.

For the first time, the reaction of 2-((1H-pyrrol-2-yl)methylene)malo-nitrile with acetoacetanilide and benzoylacetone (methylene-active compounds) in the presence of methylpiperazine led to the synthesis new piridinone compounds.

The anticancer effects of dihydroimidazo[1,2-a]pyridine and dihydropyrido[1,2-a]pyrimidine derivatives were investigated, determining their activity against five different malignant tumor cell lines: MCF7 and MDA (breast cancer), C6 (glioma), HT29 (colon cancer), and L929 (fibroblast cells).

The synthesized compounds, ethyl (Z)-4-oxo-1,3-diphenylprop-1-en-1-ylglycine and ethyl-3,5-diphenyl-1H-pyrrole-2-carboxylate, were found to exhibit inhibitory effects against carbonic anhydrase (CAs), α-glucosidase (AG), and acetylcholinesterase (AChE) enzymes. Molecular docking analysis of these compounds revealed that they align with Lipinski, Qoxe, Veber, Egan, and Muegge rules, indicating that they possess a favorable pharmacokinetic profile. Some of the synthesized compounds demonstrated antimicrobial activity against S. aureus, E. coli, C. albicans, P. aeruginosa, B. anthracis, and K. pneumoniae microbes.

Theoretical and practical significance of research. The synthesized alkoxypyrroles, N-substituted dithiolene pyrroles, 2,3-dithiophene pyrroles, pyrrole fragment-containing tricyclic compounds, and derivatives of imidazopyridines and pyridopyrimidines have been tho-

roughly studied for their antimicrobial properties and biological activities. The findings on their biological activity contribute significantly to their potential practical applications.

The results from this research may be valuable for young scientists and researchers in their future work and could open new avenues for further study in the field of medicinal chemistry and drug design.

Approbation and publicating of work. 22 scientific works has been published on the subject of dissertation. 11 of them, are articles (2 single-authored), and 11 are theses (10 of which are international). 8 of the articles are indexed in the 'Web of Science' database. The dissertation work has primarily been presented at scientific conferences held in Italy, Russia, Ukraine, and Azerbaijan. European School of Medicinal Chemistry(42nd Advanced Course of Medicinal Chemistry and "E.Duranti Seminar for PhD Students)-Urbino (2023), VI international (XVI Ukranian) scientific conference for students and young scientists-Vinnytsia (2023), İnternational Congress on Heterocyclic Chemistry"Kost-2015"- Moscow (2015), 3rd International Turkic World Conference on Chemical Sciences and Technologies- Baku (2017), The Republican Scientific Conference on "Macromolecular Chemistry, Organic Synthesis, and Composite Materials" dedicated to the 50th anniversary of the establishment of the Institute of Polymer Materials – Baku (2016), The 3rd International Scientific Conference on "Ecology: Problems of Nature and Society" dedicated to the 110th anniversary of Academician Hasan Aliyev – Baku (2017), The 12th International Scientific Conference on "Current Issues in Chemistry" for doctoral students, master's students, and young researchers, dedicated to the 95th anniversary of the birth of National Leader Heydar Aliyev – Baku (2018), The 13th International Scientific Conference on "Current Issues in Chemistry" for doctoral students, master's students, and young researchers, dedicated to the 96th anniversary of the birth of National Leader Heydar Aliyev – Baku (2019), The 14th International Scientific Conference on "Current Issues in Chemistry" for doctoral students, master's students, and young researchers, dedicated to the 98th anniversary of the birth of National Leader Heydar Aliyev – Baku (2021), The Republican Scientific Conference on "Chemistry and Chemical

Technology" for doctoral students, master's students, and young researchers, dedicated to the 99th anniversary of the birth of National Leader Heydar Aliyev – Baku (2022). İnternational Conference Modern Problems of Theoretical & Experimental Chemistry Devoted to the 90th Anniversary Academician Rafiga Aliyeva - Baku (2022).

The name of the institution where the dissertation work was performed. The presented dissertation work was carried out in accordance with the research topic of the "Fine Organic Synthesis" scientific-research laboratory operating under the Department of "Organic Chemistry" at Baku State University (State Registration No. 01101 Az 0048).

Total volume of the dissertation with a sign indicating the volume of the structural sections of the dissertation separatly. The dissertation consists of an introduction, four chapters, a conclusion, and a references section, which includes 184 cited sources. Excluding the references section, as well as 13 tables and 30 figures representing the results, the total volume of the dissertation amounts to 161,348 characters.

Introduction (14,345 characters): Provides information on the relevance of the research topic, its objectives and tasks, scientific novelty, theoretical and practical significance.

The first chapter (29,365 characters): Reviews literature data on the synthesis of pyrrole derivatives.

The second chapter (68,097 characters): Discusses the obtained results regarding the synthesis and investigation of certain properties of di-, tri-, and tetrasubstituted pyrroles.

The third chapter (25,692 characters): Elaborates on the applications of some derivatives of di-, tri-, and tetrasubstituted pyrroles.

The fourth chapter (23,849 characters): Provides details on the experimental aspects of the conducted research.

The applicant's personal contribution to the research conducted. The candidate actively participated in formulating the research problem, reviewing and summarizing local and foreign literature sources during the dissertation research, conducting experiments, preparing articles for publication, and solving other essential research-related tasks.

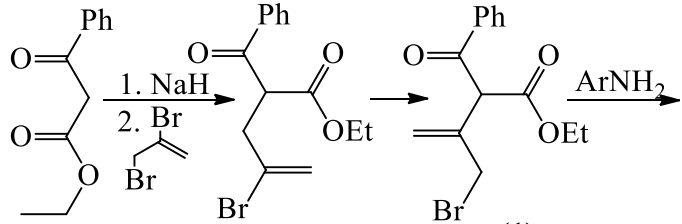
THE MAİN CONTENT OF THE WORK

The literature provides extensive information on the synthesis of pyrrole derivatives. However, there is still a need for scientific research in this field. Pyrrole is a fundamental component of many natural compounds, including pharmaceuticals, catalysts, and a range of natural macrocycles such as vitamin B12, bile pigments (bilirubin and biliverdin), blood pigment (heme), chlorophyll, chlorins, bacteriochlorins, and porphyrinogens. Considering these aspects, the presented dissertation is dedicated to solving essential issues related to the synthesis, reaction mechanisms, and biological activity of di-, tri-, and tetrasubstituted pyrroles.

Synthesis of 2-phenyl-tetrasubstituted pyrroles

The goal was to synthesize 2-phenyl-tetrasubstituted pyrroles based on 1,3-dicarbonyl compounds and 2,3-dibromoprop-1-ene. The primary objective was to study how the nature of the aromatic fragment affects the course and direction of the reaction, as well as the yield of the resulting products (scheme1).

As seen from the reaction scheme, the synthesis proceeds in three stages. Initially, the regiospecific alkylation of ethyl-3-oxo-3-phenylpropanoate with 2,3-dibromopropene leads to the formation of 2-benzoyl-4-bromoethylpent-4-carboxylate. In the presence of para-toluenesulfonic acid (PTSA) in a benzene medium, the reaction of aro-matic amines with 2-benzoyl-4-bromoethylpent-4-carboxylate results in the formation of enamines (2–4) with a yield of 83–95%. In the next stage, the corresponding pyrrole derivatives are synthesized using a strong basic medium consisting of a t-BuOK/DMSO mixture in t-BuOH (scheme 1).



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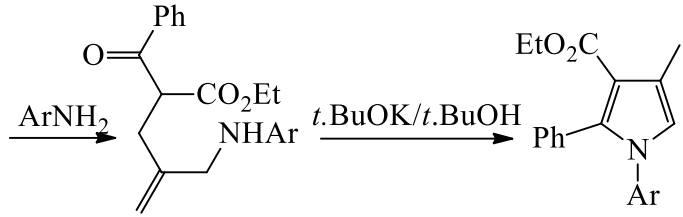
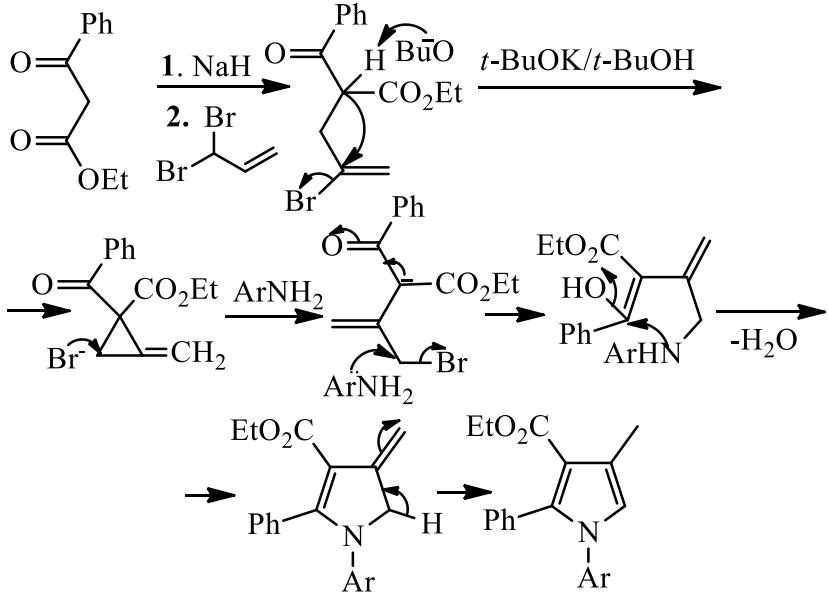


Ar= C_6H_5 (5), C_6H_5 -CH_2 (6), C_6H_5 (CH_3)CH (7)

Scheme 1. Synthesis of 2-phenyl-tetrasubstituted pyrroles

The reaction mechanism is described in the following scheme (scheme2).

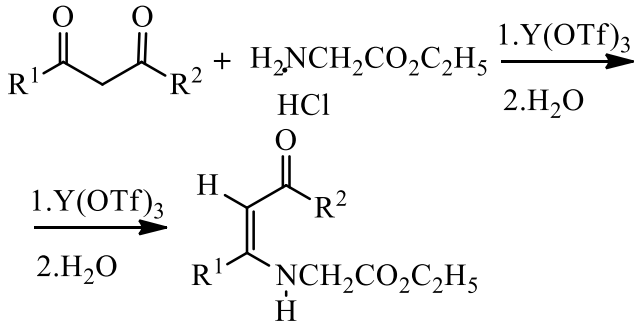


Scheme 2. Mechanism of the synthesis of 2-phenyl-tetrasubstituted pyrroles

According to the proposed reaction mechanism, the process begins with the elimination of HBr, facilitated by sodium hydride, through the interaction of the methylene group's mobile proton in the 1,3-dicar-

bonyl compound with the bromine atom of 2,3-dibromopropene. The resulting carbanion attacks the carbocation, leading to the formation of an intermediate compound. In the presence of a strong base, cyclization occurs, followed by an attack of the released Br^- anion on the cycle, leading to rearrangement. The nucleophilic attack of an arylamine on the intermediate product results in the formation of an enamine, which undergoes various transformations to yield the corresponding β-substituted pyrrole derivatives.

Synthesis of pyrrole-2-carboxylate-3,5-dialkyl (phenyl) derivatives. To obtain new 2,3,5-substituted pyrrole derivatives, enamines were first synthesized via the classical Paal-Knorr reaction, utilizing the reaction of different dicarbonyl compounds with the HCl salt of glycine. The reaction was carried out in an aqueous medium in the presence of $Y(OTf)_3$.



(8-10)

$R^1=R^2=CH_3$ (8) ; $R^1=CH_3$, $R^2=C_6H_5$ (9);
$R^1=R^2=C_6H_5$ (10).

Scheme 3. The reaction between 1,3-dicarbonyl compounds and ethyl glycinate hydrogen chloride salt

As is well known, this reaction takes place in an acidic medium. As mentioned earlier, the presence of a Lewis acid initially activates the carbonyl carbon, facilitating the nucleophilic attack of the amine group. This is then followed by the formation of the corresponding enamine derivatives (scheme 3).

Ethyl-(Z)-(4-oxo-4-phenylbut-2-en-2-yl)glycinate (9) was confirmed by X-ray crystallography (figure 1) and NMR spectroscopy(figure 1).

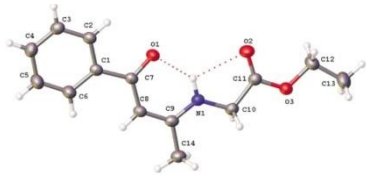
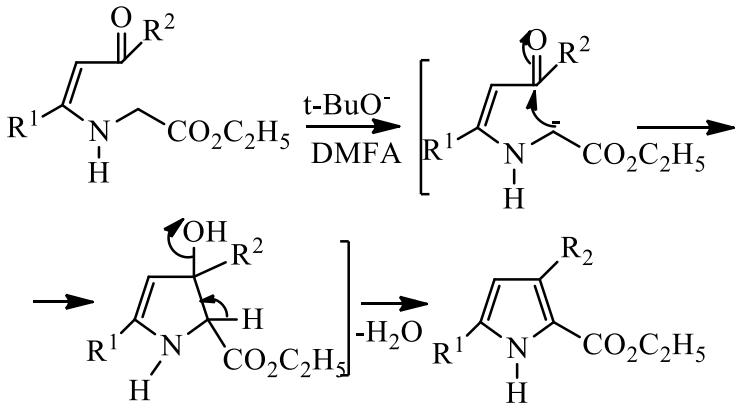


Figure 1. The molecular structure of ethyl-(Z)-(4-oxo-4-phenylbut-2-en-2-yl)glycinate

The newly synthesized enamines (8-10) undergo cyclization in a DMFA medium with t-BuOK/t-BuOH, resulting in the formation of the corresponding pyrrole derivatives (11-13).

The reaction mechanism is discussed in detail in the dissertation (scheme 4).

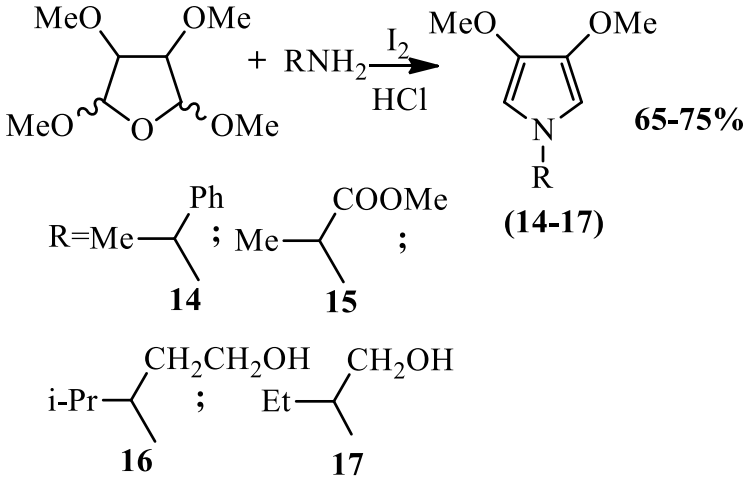


$R^1=R^2=CH_3$ (11); $R^1=CH_3$, $R^2=C_6H_5$(12);
$R^1=R^2=C_6H_5$ (13)

Scheme 4. Synthesis of 3,5-dialkyl(phenyl)-pyrrole-2-ethylcarboxylates in the presence of t-BuOK/t-BuOH

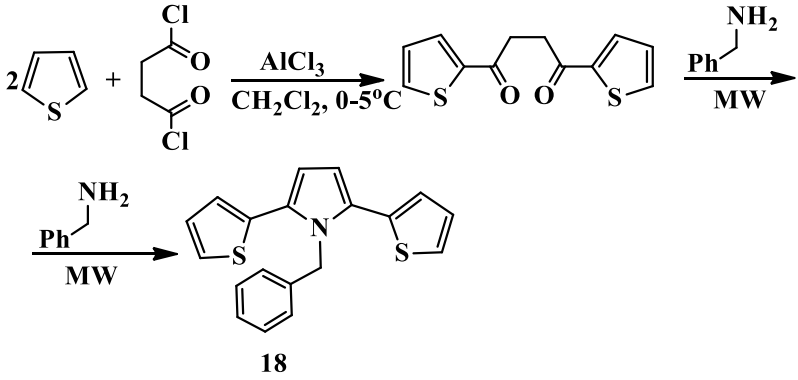
Synthesis of alkoxypyrroles from the reaction of optical amines with tetramethoxytetrahydrofuran in the presence of molecular iodine. Alkoxy derivatives of pyrroles are less studied. Therefore, we decided to synthesize N-substituted 3,4-dimethoxypyrrole derivatives.

For this purpose, new pyrrole derivatives were synthesized by reacting 2,3,4,5-tetramethoxytetrahydrofuran with various optical amines in the presence of molecular iodine (scheme 5).



Scheme 5. Synthesis of 3,4-dimethoxypyrrole derivatives

Synthesis of 2,5- and 2,3-dithiofenyl pyrrole derivatives. To synthesize N-substituted 2,5-di-(2-thienyl)-1H-pyrrole derivatives, 2,5-di(2-thienyl)-1,4-butadione is first obtained through a Friedel-Crafts reaction, based on literature methods (scheme 6).

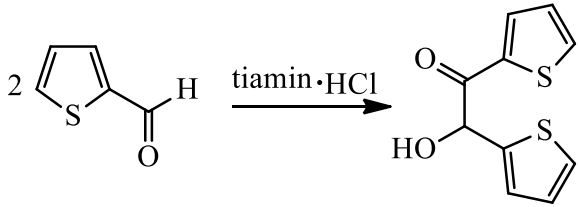


Scheme 6. Synthesis of 2,5-di(2-thienyl)-1H-pyrrole derivative

For this purpose, the synthesis is carried out in a single step using the catalytic effect of the Lewis acid $AlCl_3$ on the reaction of thiophene with succinic acid dichloride. In the next stage, N-substituted-2,5-di-(2-thienyl)-1H-pyrroles are synthesized through the Paal-Knorr reaction between 1,4-di-(2-thienyl)-1,4-butanedione and various amines.

To synthesize 2,5-di-(2-thienyl)-1H-pyrroles, a mixture of 2,5-di-(2-thienyl)-1,4-butanedione and a primary amine is irradiated in a microwave oven. As a result, the Paal-Knorr reaction yields the desired product with an efficiency of 60–65% (scheme 6).

As mentioned earlier, 2,5-dithiophene derivatives have been extensively studied in the literature. Several representatives of these compounds have also been synthesized by our team. However, since no information is available in the literature regarding 2,3-dithiophene derivatives of pyrrole, their synthesis and structural characterization have been of interest to us.

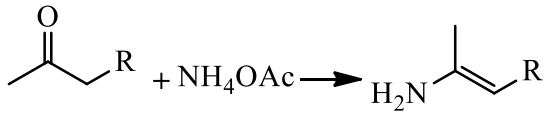


(19)

Scheme 7. Synthesis of 2,2′-thionine

To synthesize 2,3-dithiophene derivatives of pyrrole, condensation of 2,2′-thionine with various enamines at high temperatures was carried out. Initially, the starting material, 2,2′-thionine, was synthesized following a literature-reported method. As illustrated in the scheme below, the synthesis of 2,2′-thionine was achieved through the condensation of thiophene aldehyde with thiamine hydrochloride and triethylamine at room temperature. The reaction yield was optimized by adjusting the catalyst amount (scheme 7).

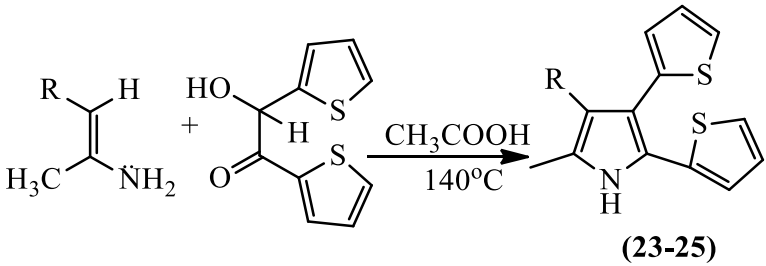
The three enamines we used as starting materials were synthesized according to the following scheme, as in our previous works (scheme 8).



R= Ac (20); $CO_2C_2H_5$ (21); CN (22).

Scheme 8. Synthesis of corresponding enamines

The synthesis was carried out based on the reaction of 2,2′-thionine with various amines to form pyrroles (scheme 9).



(23-25)

R= Ac (20); $CO_2C_2H_5$ (21); CN (22).

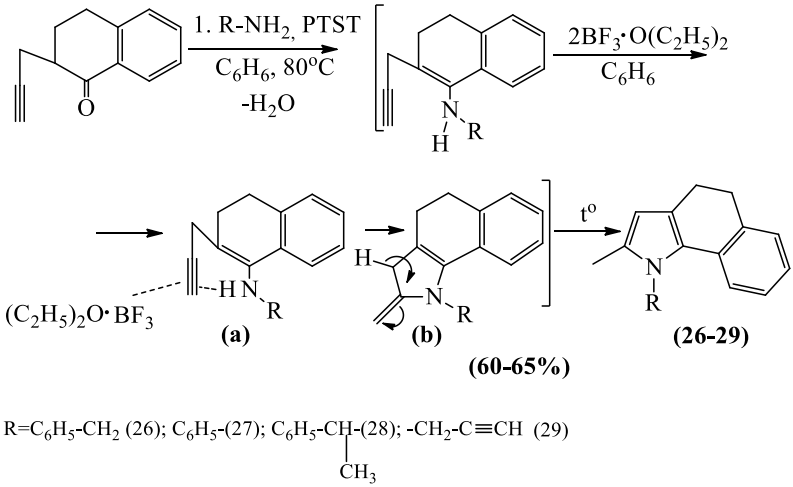
Scheme 9. Synthesis of 2,3-dithiophene-1H-pyrrole derivatives

In the literature, the synthesis of N-substituted-2,5-di-(2-thienyl)-1H-pyrroles is typically carried out in an acidic medium. It is well known that an acidic environment is used when an amine group attacks a carbonyl group. The choice of solvents depends on the pH balance of the medium and the nature of the amine. In reactions with aliphatic amines, acetic and propionic acids are commonly used as solvents. Considering these factors, a condensation reaction was performed at 140°C using ammonium acetate. The reaction lasted for two hours. The obtained compounds were washed with water and dried using $MgSO_4$.

The proposed reaction mechanism is presented in the dissertation. The reaction products were synthesized with a yield of 73–78%. All three compounds are liquids.

The structures of compounds (23–25) were characterized using ^1H and ^{13}C NMR spectroscopy.

Synthesis of some tricyclic compounds containing a pyrrole fragment. As a continuation of this research, new N-substituted derivatives of tricyclic compounds containing a pyrrole fragment were synthesized using the Trofimov reaction. This was achieved through the reaction of 2-propargyl-α-tetralone with various primary amines in the presence of $BF_3 \cdot O(C_2H_5)_2$ as a catalyst (scheme 10).



R=C_6H_5-CH_2 (26); C_6H_5-(27); C_6H_5-CH(-CH_3)-(28); -CH_2-C≡CH (29)

Scheme 10. Synthesis of new N-substituted derivatives of tricyclic compounds containing a pyrrole fragment

In the first stage of the reaction, various enamine derivatives are formed in a benzene medium at 80°C in the presence of para-toluenesulfonic acid (p-TSA). The reaction is assumed to proceed according to the mechanism shown in the scheme above. As described in the earlier part of the dissertation, the synthesis is carried out in the presence of a Lewis acid. Initially, the lone pair of electrons on the oxygen atom of the carbonyl group in 2-propargyl-α-tetralone interacts with the proton of p-TSA, leading to the cleavage of the triple bond and the formation of an electrophilic species. A nucleophilic attack occurs when the lone pair on the nitrogen atom of a primary amine interacts with the electrophilic center, resulting in the elimination of water and the formation of the corresponding enamine derivatives. The boron trifluoride diethyl ether complex ($BF_3 \cdot O(C_2H_5)_2$) activates the –C≡C– triple

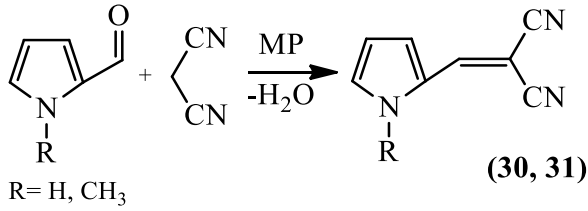
bond of the propargyl group in the enamine, leading to the formation of intermediate (a). The lone pair of electrons on the nitrogen atom in the NH group then attacks the newly formed electrophilic center, breaking the triple bond and forming intermediate (b). The process continues with isomerization under thermal influence, leading to the formation of tricyclic compounds containing a pyrrole ring (scheme 10).

As a result of this one-step reaction, various N-substituted tricyclic compounds containing a pyrrole ring (26–29) were synthesized with a yield of 55–60%. The structures of the synthesized (26–29) compounds were analyzed using IR and NMR spectroscopy.

Synthesis of various cyclic compounds containing a pyrrole ring. To synthesize new heterocyclic compounds containing a pyrrole ring, various transformations of pyrrole-2-carboxaldehyde, 1-methylpyrrole-2-carboxaldehyde, and 2-acetoxypyrrole were carried out.

As is well known carbonyl and aldehyde groups are among the most reactive groups in organic chemistry. The presence of the strong electron-acceptor CO group allows their use in various syntheses. A review of studies in organic synthesis highlights the broad research scope of such transformations. Based on this approach, we aimed to synthesize new pyrrole derivatives through various synthetic modifications of pyrrole-2-carboxaldehyde and 2-acetylpyrrole.

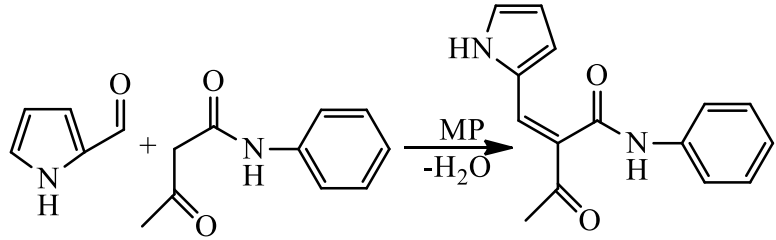
To synthesize various cyclic compounds containing a pyrrole ring, the Knoevenagel condensation was first employed, where pyrrole aldehydes reacted with malononitrile and acetoacetanilide. The obtained starting compounds were then used for further research studies (scheme11).



Scheme 11. The reaction scheme of pyrrole-2-carboxyaldehyde and malonitrile

As seen from the scheme, the reaction follows the mechanism of the well-known Knoevenagel condensation. Due to the basic properties of methyl piperazine, the methylene group of the active compound is activated, allowing the nucleophilic attack of the carbonyl group. As a result, the corresponding pyrrolidene malonitrile derivative is obtained. Methyl piperazine is used in catalytic amounts. Based on the obtained substances, various new cyclic compounds containing a pyrrole ring have been synthesized.

Synthesis of (2Z)-3-oxo-N-phenyl-2-[(1H-pyrrol-2-yl)methylidene] butanamide and its X-Ray investigation. In the continuation of our work, the same reaction was carried out with acetoacetanilide. The reaction follows the same mechanism as with malonitrile. That is, due to the reactivity of the hydrogen of the methylene group, it is cleaved under the influence of the base, and the resulting anion attacks the carbon atom of the carbonyl group, leading to the formation of (2Z)-3-oxo-N-phenyl-2-[(1H-pyrrol-2-yl)methylidene]butanamide. X-ray structure analysis investigations showed that the obtained compound is in the form of a monohydrate. This reaction, for the first time conducted by us, has synthesized a new compound, and the structure of the obtained compound has been confirmed by X-ray crystallography and nuclear magnetic resonance analysis methods (scheme 12).



(32)

Scheme 12. Synthesis of (2Z)-3-oxo-N-phenyl-2-[(1H-pyrrol-2-yl)methylidene]butanamide monohydrate

The structure of (2Z)-3-oxo-N-phenyl-2-[(1H-pyrrol-2-yl)methylidene]butanamide has been confirmed using ^{13}C and ^{1}H NMR spectroscopy methods.

The crystal structure of (2Z)-3-oxo-N-phenyl-2-[(1H-pyrrol-2-yl) methylidene]butanamide monohydrate has been investigated, and Hirshfeld surface analysis has been performed (figure 2).

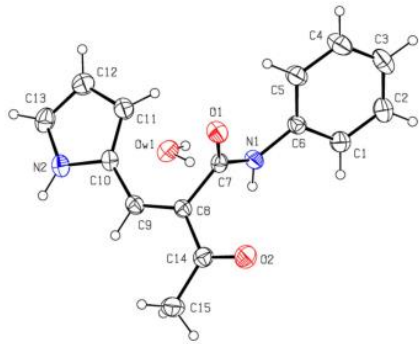
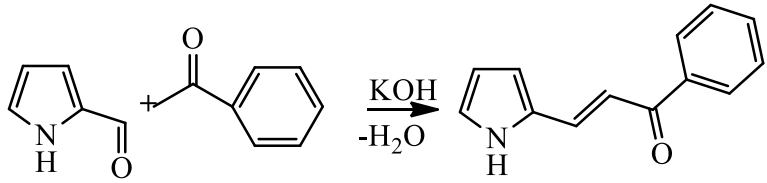


Figure 2. The molecular structure of (2Z)-3-oxo-N-phenyl-2-[(1H-pyrrol-2-yl)methylidene]butanamide monohydrate

Investigation of the crystal structure of 2(E)-1-phenyl-3-(1H-pyrrol-2-yl)prop-2-en-1-one. In the continuation of our research, various chalcone derivatives were synthesized based on the Claisen-Schmidt condensation. The syntheses were based on the reactions of pyrrole-2-carboxyaldehydes with different ketones. These reactions was carried out between pyrrole-2-carboxyaldehyde and acetophenone, resulting in the synthesis of (2E)-1-phenyl-3-(1H-pyrrol-2-yl)prop-2-en-1-one. The crystal structure parameters of the obtained compound, as well as Hirshfeld surface analysis, have been investigated (figure 3). The reaction scheme is shown below (scheme 13).



(33)

Scheme 13. The synthesis of 2(E)-1-phenyl-3-(1H-pyrrol-2-yl)prop-2-ene-1-one

The studied $C_{13}H_{11}NO$ compound is in the E configuration due to the presence of a C=C double bond.

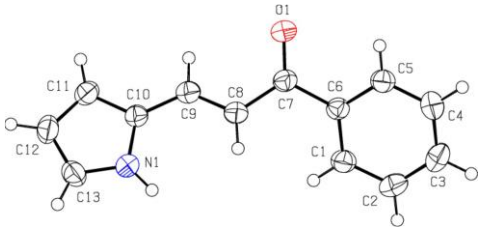
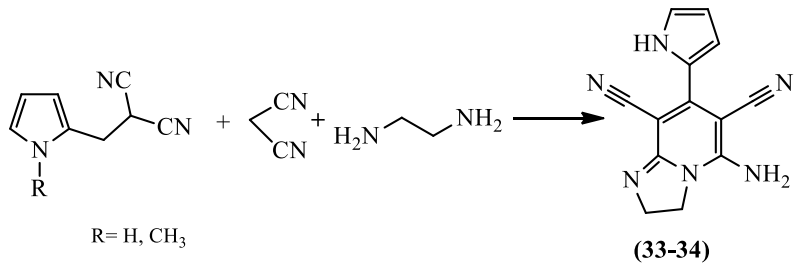


Figure 3. The molecular structure 2(E)-1-phenyl-3-(1H-pyrrol-2-yl)prop-2-ene-1-one

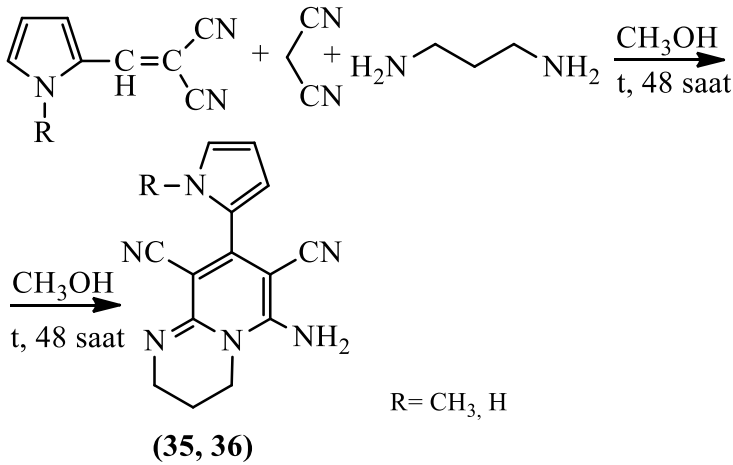
A three-component, one-step reaction between pyrrolidine malononitrile, malononitrile, and amines. 2-((1H–pyrrol-2-yl) methylene)malononitrile and 2-((1-methyl-1H–pyrrol-2-yl)methylene) malononitrile were synthesized by reacting pyrrole-2-carboxyaldehyde with malononitrile in ethanol and water, using a known method from the literature. This synthesis, based on the Knoevenagel reaction, was carried out in an ethanol medium at room temperature. As a result of the reaction, pyrrolidinemalononitriles were obtained, and imidazo[1,2-a]pyridine derivatives containing a pyrrole ring were synthesized from these compounds. For this, a three-component reaction was carried out between 2-((1H-pyrrol-2-yl)methylene)malononitrile and 2-((1-methyl-1H–pirrol-2-yl)methylene) malononitrile with ethylenediamine and malononitrile (scheme 14).



Scheme 14. Synthesis of imidazopyridine derivatives containing a pyrrole ring

During the analysis of nuclear magnetic resonance spectra, a nuance was noticed: when synthesizing from 2-((1H-pyrrol-2-yl)methylene)malononitrile, a dihydroimidazo[1,2-a]pyridine derivative was obtained, where as when synthesizing from 2-((1-methyl-1H-pyrrol-2-yl)methylene)malononitrile, a tetrahydroimidazo[1,2-a]pyridine derivative was obtained. The reason for this is

assumed to be that the second compound is resistant to oxidation. As a result, it can be concluded that, without using a catalyst, tetrahydroimidazo(dihydroimidazo)[1,2-a]pyridine compounds were synthesized for the first time by us in a methanol medium under reflux (scheme 15). The structure of the obtained compounds has been studied using ^{1}H and ^{13}C NMR spectroscopy.



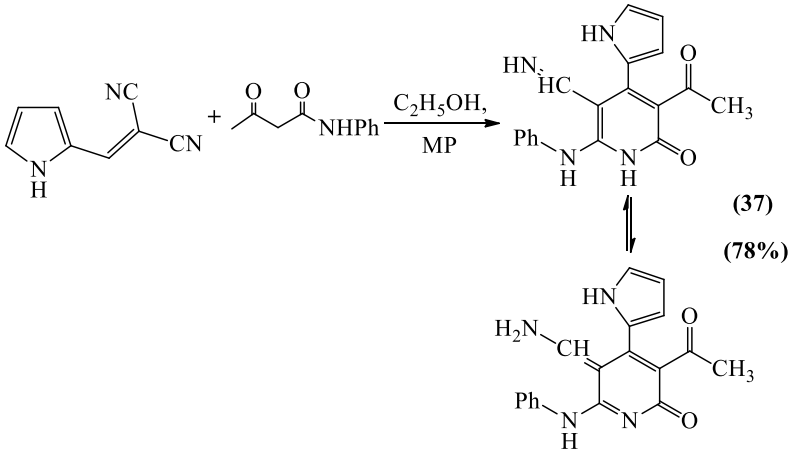
(35, 36)

Scheme 15. Synthesis of pyrido[1,2-a]pyrimidine derivatives containing a pyrrole scaffold

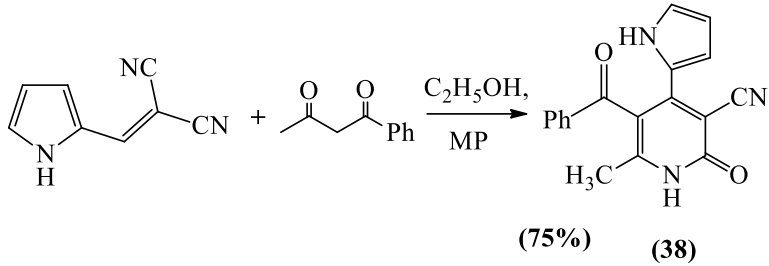
As a continuation of this research, we also performed the three-component one-step synthesis of pyrrolidinemalononitrile derivatives, malononitrile, and 1,3-diaminopropane under the same conditions. However, it was observed that the reaction did not proceed at room temperature.

Michael addition reaction of 2-((1H-pyrrol-2-yl)methylene)malononitrile with benzoylacetone and acetoacetanilide. A two-component, one-step reaction was carried out between 2-((1H-pyrrol-2-yl)methylene)malononitrile and methylene-active compounds such as acetoacetanilide and benzoylacetone. The interaction of these substances in a methanol medium, under the catalytic influence of methyl piperazine, led to the synthesis of corresponding pyrrole-substituted pyridine derivatives. The reactions were carried out by refluxing the

system equipped with a condenser (scheme 16,17).



Scheme 16. Synthesis of pyridinone derivatives containing an acetyl group

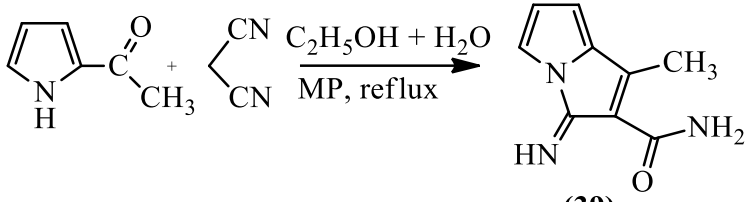


Scheme 17. Synthesis of pyridinone derivatives containing a benzoyl group

During the reaction with benzoylacetone, 5-benzoyl-6-methyl-2-oxo-4-(1H-pyrrol-2-yl)-1,2-dihydropyridine-3-carbonitrile was synthesized. With acetoacetanilide, in an imine-amine tautomeric state, 3-acetyl-5-(imino-methyl)-6-(phenylamino)-4-(1H-pyrrol-2-yl)pyridin-2(1H)-one and 3-acetyl-5-(aminomethyl)-6-(phenylamino)-4-(1H-pyrrol-2-yl)pyridin-2(1H)-one were synthesized .

The structure of the newly obtained compounds has been confirmed through NMR spectroscopy.

Reaction between 2-acetylpyrrole and malononitrile. As mentioned earlier, pyrrol-2-carboxyaldehyde reacts with malononitrile to synthesize corresponding pyrrolidinemalononitrile derivatives. In the literature, the reaction between 2-acetylpyrrole and malonitrile has also been reported to yield pyrrolidinemalonitrile derivatives. However, when we carried out the reaction between 2-acetylpyrrole and malonitrile, we encountered different results. 3-Imino-1-methyl-3H-pyrrolizine-2-carboxamide was obtained upon heating a mixture of 2-acetylpyrrole and malonitrile in ethanol and water with the presence of methyl piperazine under reflux (scheme 18).



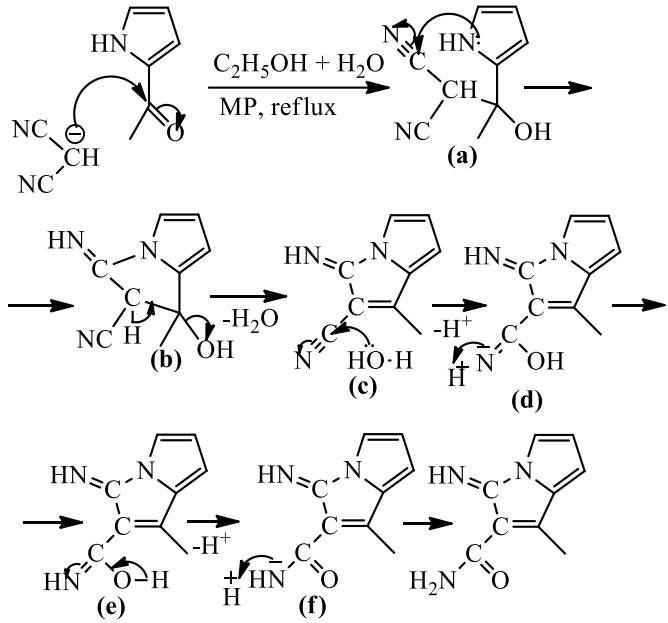
(39)

Scheme 18. Synthesis of 3-imino-1-methyl-3h-pyrrolizine-2-carboxamidine

The probable mechanism of the reaction is shown in the scheme below. It is assumed that methylpiperazine acts as a base, abstracting a proton from malononitrile, thereby converting it into a nucleophilic species. The resulting nucleophile attacks the electrophilic center of 2-acetylpyrrole, leading to the formation of intermediate (a). In the next step, the electron density shifts towards the nitrogen in the cyano group, generating a new electrophilic center. As a result, the nitrogen of the pyrrole ring attacks this center with its lone pair, yielding intermediate (b).

As the reaction progresses, water is eliminated, leading to the formation of intermediate (c). Subsequently, another shift of electron density towards the nitrogen in the second cyano group creates a new electrophilic center, which is then attacked by the oxygen of water through its lone pair, resulting in intermediate (d). Further electron rearrangements and the attack of nitrogen on a proton lead to the formation of

intermediates (e) and (f). In the final step, the reaction concludes with the formation of 3-imino-1-methyl-3H-pyrrolizine-2-carboxamidine (scheme 19).



Scheme 19. Mechanism of the synthesis reaction of 3-imino-1-methyl-3H-pyrrolizine-2-carboxamidine

The ^{1}H and ^{13}C NMR spectra of the obtained compounds were studied using a Bruker Avance 300-MHz spectrometer.

İnhibitory effects of the newly synthesized compounds on carbonic anhydrase, acetylcholinesterase, and α-glucosidase enzymes. In this study, the inhibitory effects of new enamine and pyrrole derivatives on acetylcholinesterase (AChE), hCA I and II isoenzymes, and α-glucosidase enzyme activity were investigated. (Z)-ethyl-2-(3-oxo-1,3-diphenylprop-1-enylamino)acetate (10) and ethyl-3,5-diphenyl-1H-pyrrole-2-carboxylate (14) were found to effectively inhibit hCA I and II isoenzymes, α-glucosidase, and AChE enzymes at the micromolar level. Therefore, both compounds could be considered promising drug candidates for the treatment of epilepsy, diabetes, duodenal and gastric ulcers,

glaucoma, altitude sickness, Alzheimer's disease, neurological disorders, and osteoporosis.

Molecular docking and molecular dynamics simulations of (Z)-ethyl-2-(3-oxo-1,3-diphenylprop-1-enylamino)acetate (10).and ethyl-3,5-diphenyl-1H-pyrrole-2-carboxylate (14) In addition to experimental studies on α-glucosidase and acetylcholinesterase enzyme activity, molecular docking studies were performed using AutoDock 4.2.5 software to determine the most suitable binding interactions of these compounds with the crystal structures of the respective enzymes

In this context, (Z)-ethyl-2-(3-oxo-1,3-diphenylprop-1-enylamino)acetate (10) and ethyl-3,5-diphenyl-1H-pyrrole-2-carboxylate (14) were formed strong interactions with AChE and α-glucosidase enzymes, leading to highly stable complexes. The compounds exhibit good drug-like properties and possess a favorable pharmacokinetic profile.

Investigation of the Antimicrobial Properties of New Pyrrole Derivatives. Five newly synthesized chemical compounds were submitted for antimicrobial activity studies to the "Medical Microbiology and Immunology" department of the Azerbaijan Medical University.

The disk diffusion method was used to assess the initial antibacterial and antifungal effects of the submitted compounds. Based on the conducted studies and initial results, among the tested compounds, (ethyl-(Z)-4-oxo-1,3-diphenylprop-1-enyl)glycinate exhibited the highest antimicrobial activity.

Anticancer properties of pyrrole-substituted imidazo[1,2-a]pyridine and pyrido[1,2-a]pyrimidine derivatives. As previously mentioned, imidazo[1,2-a]pyridine and pyrido[1,2-a]pyrimidine derivatives are used as pharmaceutical agents in medicine. Based on this information, we investigated the biological activity of our newly synthesized compounds.

The anticancer activity of these compounds was studied against various cancer cell lines, including human breast adenocarcinoma (MDA-MB-231 and MCF7), rat glioma (C6), human colorectal cancer (HT29), and normal fibroblast cells (L929), obtained from the American Type Culture Collection (ATCC).

. The tested compounds were found to exhibit biological activity against tumor cells.

CONCLUSION

1) New derivatives of optically active 3,4-dimethoxypyrroles were synthesized through the interaction of molecular iodine with optically active amines and 2,3,4,5-tetramethoxyhydrofuran [1].

2) For the first time, N-substituted derivatives of new pyrrole-containing tricyclic compounds were synthesized via the reaction of 2-propargyl α-tetralone with various amines in the presence of a $BF_3 \cdot O(C_2H_5)_2$ catalyst [2,3].

3) The synthesis of new derivatives of 2,3-dithiophene pyrrole based on 2,2'-thionine was performed for the first time [4].

4) Novel pyrrole derivatives were synthesized for the first time using various amines and 2-((1H-pyrrol-2-yl)methylene)malononitrile, as well as 2-((1-methyl-1H-pyrrol-2-yl)methylene)malononitrile [9,10].

5) New pyridinone derivatives were synthesized via a one-step, two-component condensation reaction of methylene-active compounds and 2-((1H-pyrrol-2-yl)methylene)malononitrile [11].

6) The crystal structures of several synthesized compounds were studied, and Hirshfeld surface analysis was performed, revealing interactions such as C–H···π, π–π, and many others [5,12,13].

7) The inhibitory properties of (Z)-ethyl-2-(3-oxo-1,3-diphenylprop-1-enylamino)acetate and ethyl-3,5-diphenyl-1H-pyrrole-2-carboxylate on hCA I and II isoenzymes, α-glucosidase, and AChE enzymes were examined, and molecular docking analyses were conducted. These compounds were identified as potential inhibitor drug candidates for counteracting the excessive activity of these enzymes [6,7].

8) The anticancer properties of synthesized imidazo[1,2-a] pyridine and pyrido[1,2-a]pyrimidine derivatives were investigated, demonstrating significant biological activity against tumor cells [9].

The main results of the dissertation were expressed in the following publications:

1. Akhmedov, I.M. Catalytic effect of molecular iodine in the pyrrolization of tetramethoxytetrahydrofuran with optically active amines / I.M. Akhmedov, E.Z. Guseinov, A.S. Safarova [et al.] // Russian Journal of Organic Chemistry, – 2016. vol. 52, iss. 12, – p. 1849-1850.
2. Əhmədov, İ.M. Məhərrəmov, A.M., Səfərova, A.Ş., Qurbanova, M.M. Yarımkeçirici polimer monomerlərin yeni metodla sintezi // Polimer Materialları Institutunun yaradılmasının 50 illik yubileyinə həsr olunmuş "Makromolekullar Kimyası, Üzvi sintez və Kompozit Materiallar" mövzusunda Respublika elmi konfransı, – Bakı, – 20 – 21 oktyabr, – 2016, – s. 20
3. Safarova, A.S. Synthesis of new derivatives of 4,5-dihydro-1H-benzo[g]indol // Chemical Problems, – 2019. №3(17), – p. 413-416
4. Safarova, A.S. Synthesis of 1-benzyl-2,5-di(tiophen-2-yl)-1H-pyrrole under microwave irradiation // Journal of Baku Engineering University, – 2019. vol. 3, №2, – p. 140-144.
5. Safarova, A.S. Crystal structure of ethyl (Z)-(4-oxo-4-phenyl-but-2-en-2-yl) glycinate, $C_{14}H_{17}NO_3$ / A.S. Safarova, I. Brito, J. Cisterna [et al.] // Zeitschrift Fur Kristallographie-New Crystal Structures, – 2019. vol. 234, iss. 6, – p. 1183-1185
6. Maharramov, A. Synthesis, characterization, crystal structure and bioactivities of novel enamine and pyrrole derivatives endowed with acetylcholinesterase, α-glucosidase and human carbonic anhydrase inhibition effects / A. Maharramov, M. Kurbanova, P. Taslimi, [et al.] // Organic Communications, – 2021. 14(2), – p. 144-156.
7. Kurbanova, M. Molecular docking study and molecular dynamics simulation of ethyl-3,5-diphenyl-1H-pyrrole-2-carboxylate and (Z)-ethyl-2-(3-oxo-1,3-diphenylprop-1-enylamino)acetate / M. Kurbanova, A. Maharramov, A. Safarova [et al.] // Journal of Biochemical and Molecular Toxicology, – 2022. vol. 36, iss. 5,

– p. e23013

8. Safarova, A.S., Huseynov, E.Z. Synthesis of new dihydro-1H-benzo[g]indol derivatives // İnternational conference of Modern Problems of Theoretical and Experimental Chemistry, – Baku, – 29 – 30 September, – 2022, – p. 282.
9. Safarova, A.S. The synthesis of some new biological active pyrrole derivatives on the base of 2-carboxyaldehydepyrrole // European School of Medicinal Chemistry (42 nd Advanced Course of Medicinal Chemistry and "E. Duranti" Seminar for PhD Students) – Urbino – 2 – 6 July, – 2023, – p. 132.
10. Safarova, A.S., Naghiyev, F.N., Mamedov, I.G. Synthesis of pyrido-pyrimidine and imidazo-pyridine derivatives // VI international (XVI Ukranian) scientific conference for students and young scientists “Current Chemical Problems”, – Vinnytsia, – 21 – 23 March, – 2023, – p. 60.
11. Safarova, A.S., Naghiyev, F.N., Mamedov, I.G. Synthesis of new derivatives of pyrroles // VI international (XVI Ukranian) scientific conference for students and young scientists “Current Chemical Problems”, – Vinnytsia, – 21 – 23 March, – 2023, – p. 59.
12. Safarova, A.S. Crystal structure and Hirshfeld surface analysis of (2Z)-3-oxo-N-phenyl-2-[(1H-pyrrol-2-yl)methylidene]butanamide monohydrate / A.S. Safarova, A.N. Khalilov, M. Akkurt [et al.] // Acta Crystallographica Section E, – 2023. vol. 234, iss. 12, – p. 1142-1146.
13. Safarova, A.S. Crystal structure and Hirshfeld surface analysis of (2E)-1-phenyl-3-(1H-pyrrol-2-yl)propen-1-one / A.S. Safarova, A.N. Khalilov, M. Akkurt // Acta Crystallographia E, – 2024. vol. 80, part 2, – p. 191-195.

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