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SYNTHESIS AND IN SILICO ADME PROFILING OF NOVEL PYRROLE DERIVATIVES

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The development of orally bioavailable drug candidates is a key aspect of pharmaceutical research, emphasizing the need for robust physicochemical properties that support efficient absorption and therapeutic efficacy. This article examines two distinct molecules, $C_{13}H_{11}NO$ and $C_{15}H_{16}N_2O_2$, which demonstrate favorable characteristics for oral bioavailability based on various pharmacokinetic parameters.

By systematically analyzing the pharmacokinetic properties of these compounds, this article aims to provide insight into their suitability for further pharmacological optimization and therapeutic application, highlighting the importance of molecular design in advancing drug discovery efforts.

Keywords: Swiss ADME, chalcones, pyrrole aldehyde, ketones, Lipinski's rule

INTRODUCTION

Pyrroles are an important class of organic compounds that play a key role in various biological processes and chemical reactions. They consist of a five-membered aromatic ring containing one nit-rogen atom. Due to their structure, pyrroles actively participate in the formation of complex molecules, such as hemoglobin, and are used as building blocks for the synthesis of various pharmaceutical and biologically active substances [1, 2].

Analyses using Swiss ADME (Swiss Absorption, Distribution, Metabolism, and Excretion) allow for the assessment of the pharmacokinetic properties of pyrroles and their derivatives. This tool provides predictions about solubility, permeability across cell membranes, metabolizability, and toxicity of compounds, which is crucial in the development of new drugs. Swiss ADME utilizes vari-ous algorithms and databases related to the chemical structure of the compound to evaluate its potential biological activity and safety [3,4,5].

Literature sources emphasize that pyrroles and their derivatives exhibit a wide range of biological activity, including antimicrobial, anti-inflammatory, and anti-cancer properties. The deve-lopment of new compounds based on pyrrole remains a relevant topic in scientific research, and the application of Swiss ADME can significantly accelerate the process of discovering and optimizing new drugs [6,7,8,9,10].

EXPERIMENTAL

Synthesis of (2E)-1-phenyl-3-(1H-pyrrol-2-yl)prop-2-en-1-one (1)

Equimolar amounts of pyrrole-2-carboxaldehyde (1.0 g, известно as 0.012 mol*) and

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acetophenone (1.4 g, 0.012 mol) were dissolved in ethanol (20 mL), following a literature-reported procedure. The reaction mixture was placed in a refrigerator and maintained under cooling conditions. After 2 h, potassium hydroxide was added, and the mixture was kept in the refrigerator for an additional 24 h. Formation of white crystalline precipitates was observed. The resulting solid was collected by filtration and dried.

^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.23 (t, 1H, CH_{pyr}), 6.73 (d, 1H, CH_{pyr}), 6.75 (t, 1H, CH_{pyr}), 7.15 (d, 1H, =CH), 7.52–7.62 (m, 5H, CH_{ar}), 8.03 (d, 1H, =CH), 11.76 (d, 1H, NH).

^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 111.12 (CH_{pyr}), 115.06 (CH_{pyr}), 116.96 (CH_{pyr}), 124.63 (=CH), 128.41–133.00 (CH_{ar}), 134.80 (=CH), 138.77 ($C_{quart.}$), 188.96 (C=O).

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

Pyrrole-2-carboxaldehyde (1.0 g, 10 mmol) and acetoacetanilide (1.77 g, 10 mmol) were dissolved in 20 mL of an 80% ethanol solution. Methylpiperazine (3-4 drops) was added as a catalyst, and the reaction mixture was stirred at room temperature for 2 h. The mixture was then left to stand overnight. The precipitated crystals were separated by filtration and recrystallized from an ethanol/water mixture (1:1). The reaction afforded the product in 69% yield, with a melting point of 240-241 °C.

^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.34 (s, 3H, CH_3), 6.21 (d, 1H, CH_{pyr}), 6.57 (d, 1H, CH_{pyr}), 7.10 (t, 1H, CH_{pyr}), 7.14 (t, 1H, CH_{ar}), 7.35 (m, 2H, $2CH_{ar}$), 7.57 (s, 1H, CH), 7.70 (d, 2H, $2CH_{ar}$), 10.41 (s, 1H, NH), 11.52 (s, 1H, NH).

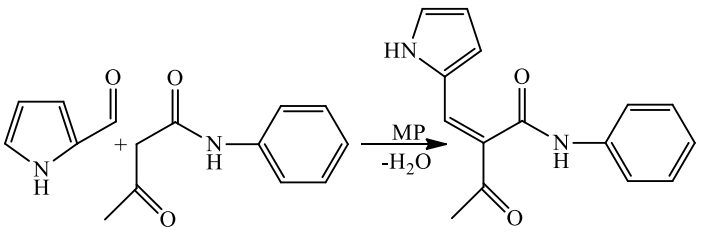
^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 26.45 (CH_3), 112.12 (CH_{pyr}), 114.66 (CH_{pyr}), 119.74 ($2CH_{ar}$), 124.08 (CH_{pyr}), 126.70 (CH_{ar}), 129.37 ($2CH_{ar}$), 130.66 (C_{pyr}), 136.83 (CH), 139.58 ($C_{quart.}$), 139.70 ($C_{quart.}$), 166.74 (C=O), 195.29 (C=O).

RESULTS AND DISCUSSION

To synthesize a variety of novel heterocyclic compounds containing a pyrrole ring, different transformations of 2-acetoxypyrrole, pyrrole-2-carboxaldehyde, and 1-methylpyrrole-2-carboxaldehyde were carried out.

As is well known, carbonyl and aldehyde functional groups are among the most reactive moieties in organic chemistry. The presence of a strong electron-accepting group (the C=O group) enables their wide application in diverse synthetic transformations. A survey of the scientific literature reveals that reactions involving such functional groups constitute a broad and actively investigated field within organic synthesis. From this perspective, we proposed that the application of various synthetic approaches to pyrrole aldehydes and ketones would allow the preparation of new pyrrole derivatives [11, 12].

For the synthesis of pyrrole-containing cyclic compounds, Knoevenagel condensation reactions of pyrrole aldehydes with malononitrile and acetoacetanilide were initially performed. The resulting inter-mediates were subsequently employed as starting materials for further investigations [13,14].



In the continuation of our studies, the same reaction was carried out using acetoacetanilide. As in the case of malononitrile, the reaction proceeds via an identical mechanism. Specifically, due to the acidity of the methylene hydrogen, it is abstracted under basic conditions, and the resulting anion attacks the carbonyl carbon, leading to the formation of (2Z)-3-oxo-N-phenyl-2-[(1H-pyrrol-2-yl)methylidene]butanamide. Single-crystal X-ray diffraction analysis revealed that the obtained compound crystallizes in the monohydrate form. This reaction was performed for the first

time by our research group, resulting in the synthesis of a novel compound, whose structure was unambiguously confirmed by X-ray crystallographic and nuclear magnetic resonance (NMR) analyses [15].

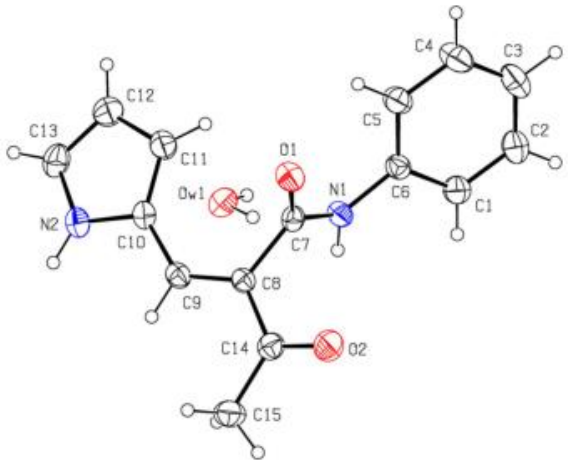
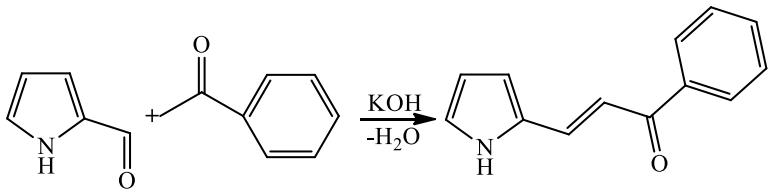


Figure 1. Molecular structure of (2Z)-3-oxo-N-phenyl-2-[(1H-pyrrol-2-yl)methylidene]butanamide

In further investigations, various chalcone derivatives were synthesized via the Claisen-Schmidt condensation. N-heterocyclic chalcones, particularly those containing a pyrrole scaffold, are known to exhibit a wide range of biological and pharmacological activities, including antibacterial, antioxidant, antifungal, antileishmanial, anticancer, anti-tubercular, and anti-malarial effects. Based on these findings, the synthesis of chalcones bearing a pyrrole ring and the preparation of new derivatives derived from them constituted the primary objective of this study. Accordingly, a series of synthetic transformations were performed, and further modi-fications of the obtained chalcone derivatives are currently on-going. Future publications will report the synthesis of new compounds derived from these chalcones [16, 17,18,19].



The synthetic strategy was based on the reactions of pyrrole-2-carboxaldehydes with various ketones. One such reaction involved pyrrole-2-carboxaldehyde and acetophenone, resulting in the synthesis of (2E)-1-phenyl-3-(1H-pyrrol-2-yl)prop-2-en-1-one. The structural pa-rameters of the resulting crystals, along with Hirshfeld surface analysis, were thoroughly investigated [20].

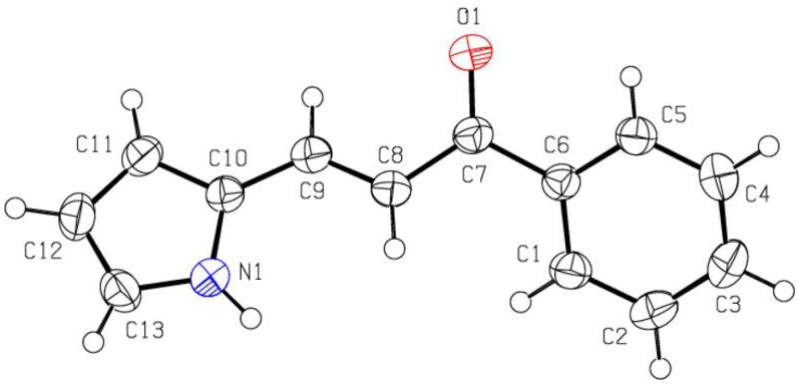


Figure 2. Molecular structure of (2E)-1-phenyl-3-(1H-pyrrol-2-yl)prop-2-en-1-one.

The first investigated compound, $C_{13}H_{11}NO$ (2E)-1-phenyl-3-(1H-pyrrol-2-yl)prop-2-en-1-one (molecular weight 197.23 g/mol), fulfills all principal physicochemical requirements for oral bioavailability. Its moderate lipophilicity (consensus Log P=2.44) falls within the optimal range for passive diffusion across biological membranes, supporting efficient systemic absorption. The low topological polar surface area (TPSA=32.86 Å²), combined with limited structural flexibility (three rotatable bonds), suggests a strong propensity for gastrointestinal uptake and potential blood-brain barrier permeability. The presence of one hydrogen-bond donor and one hydrogen-bond acceptor further contributes to favorable absorption and distribution characteristics. According to ESOL predictions, the compound is classified as soluble (LogS=−2.99), which is advantageous for oral formulation and bioavailability. Collectively, these properties indicate a well-balanced hydrophilic-lipophilic profile, consistent with high membrane permeability and adequate aqueous solubility. Importantly, the molecule fully complies with Lipinski's rule of five, underscoring its drug-like character and suitability for further optimization.

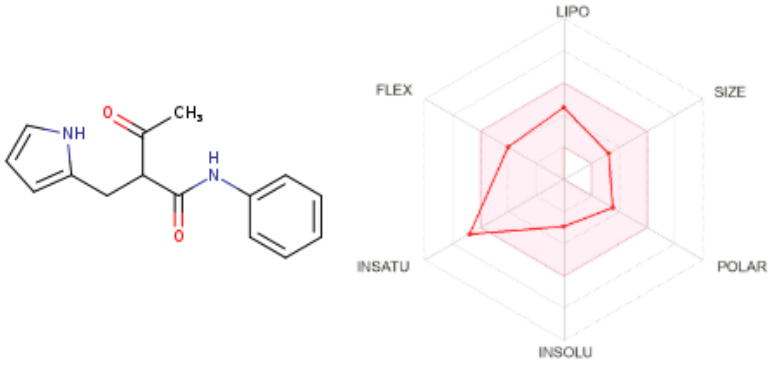


Figure 3. Swiss ADME analysis of (2E)-1-phenyl-3-(1H-pyrrol-2-yl)prop-2-en-1-one

According to the SwissADME BOILED-Egg analysis, the studied compound exhibits a highly favorable pharmacokinetic profile. Its position within the yellow "yolk" region of the BOILED-Egg diagram indicates a high probability of blood–brain barrier (BBB) penetration, while its simultaneous localization within the white region suggests efficient passive human intestinal absorption (HIA). The compound is predicted to be a non-substrate of P-glycoprotein (PGP−), implying a reduced risk of active efflux from both the intestinal epithelium and the central nervous system, which may enhance systemic exposure and brain availability. Overall, the balanced relationship between lipophilicity (WLOGP) and polarity (TPSA) supports good oral bioavailability and central nervous system permeability, underscoring the compound's potential suitability for the development of orally administered CNS-targeted therapeutics.

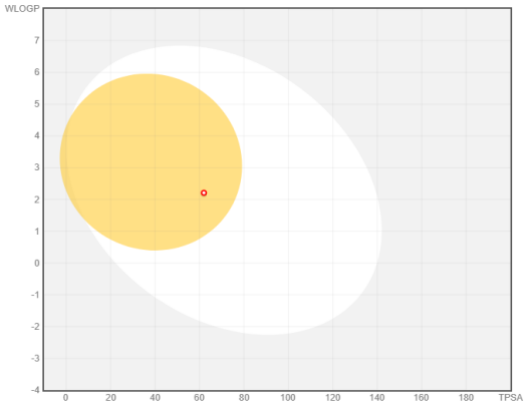


Figure 4. SwissADME BOILED-Egg analysis of (2E)-1-phenyl-3-(1H-pyrrol-2-yl)prop-2-en-1-one

The second compound, $C_{15}H_{16}N_2O_2$ (2Z)-3-oxo-N-phenyl-2-[(1H-pyrrol-2-yl)methylidene]-butanamide (molecular weight 256.30 g/mol), also exhibits physicochemical attributes favorable for oral drug development. It consists of 19 heavy atoms, including 11 aromatic carbons, and displays a TPSA of 61.96 Å² with a fraction Csp^3 of 0.20, indicative of moderate polarity and a predominantly aromatic framework. The presence of six rotatable bonds reflects moderate conformational flexibility, while two hydrogen-bond donors and two acceptors support inter-molecular interactions relevant to absorption. Lipophilicity estimates yielded log $P_o/_p$ values between 1.10 and 2.94, with a consensus Log P of 2.06, suggesting balanced hydrophobicity. Solubility assessments predicted the compound to be soluble (ESOL and Ali models) to moderately soluble (SILICOS-IT), in agreement with its polarity profile [20].

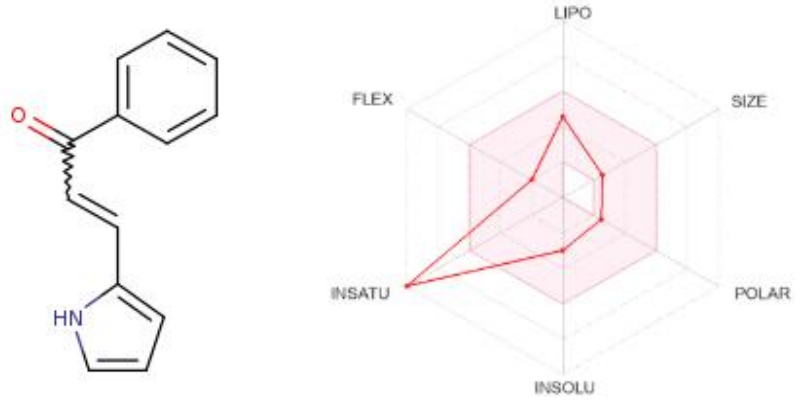


Figure 5. Swiss ADME analysis of 2Z)-3-oxo-N-phenyl-2-[(1H-pyrrol-2-yl)methylidene]butanamide

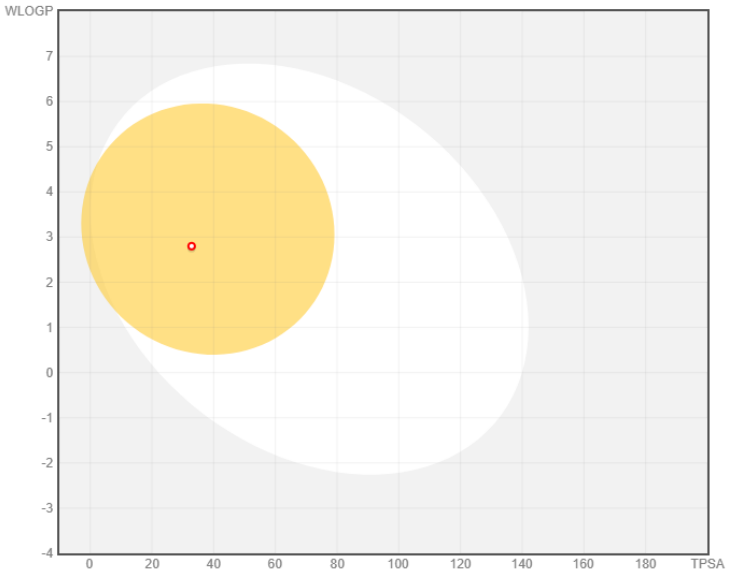


Figure 6. SwissADME BOILED-Egg analysis (2Z)-3-oxo-N-phenyl-2-[(1H-pyrrol-2-yl)methylidene]butanamide

Based on the SwissADME BOILED-Egg model, the compound demonstrates highly favo-rable pharmacokinetic properties. The molecule is positioned within the yellow region of the BOILED-Egg diagram, indicating a high probability of blood-brain barrier (BBB) permeation, while simultaneously falling within the white region, which is predictive of efficient passive human intestinal absorption (HIA). The compound is classified as a non-substrate of P-glycoprotein (PGP−), suggesting a low likelihood of active efflux from the intestinal

epithelium or central nervous system, thereby supporting sustained systemic and cerebral exposure. Overall, the balanced lipophilicity (WLOGP) and moderate polarity (TPSA) of the molecule are consistent with good oral bioavailability and effective central nervous system penetration, highlighting its potential suitability for the development of orally administered CNS-active therapeutic agents.In silico pharmacokinetic analysis predicted high gastrointestinal absorption and negligible blood-brain barrier permeability, indicating suitability for oral administration without central nervous system exposure. The compound was not identified as a substrate of P-glycoprotein, reducing the likelihood of efflux-related bioavailability limitations. Cytochrome P450 interaction profiling indicated potential inhibition of CYP1A2, while no inhibitory effects were predicted for CYP2C19, CYP2C9, CYP2D6, or CYP3A4. Furthermore, the predicted skin permeation coefficient (log Kp ≈ −5.7 cm/s) suggests minimal transdermal absorption.

CONCLUSION

Based on a comprehensive physicochemical evaluation of both compounds, it is evident that they possess favorable properties for the development of oral pharmaceutical agents. The first compound, $C_{13}H_{11}NO$, demonstrates an optimal balance between lipophilicity and hydrophilicity, as reflected by its consensus Log P value of 2.44 and a TPSA of 32.86 Å². These characteristics, together with compliance with Lipinski's rule of five, indicate a strong potential for efficient oral bioavailability and permeability across biological membranes, including the blood-brain barrier.

Similarly, the second compound, $C_{15}H_{16}N_2O_2$, with a molecular weight of 256.30 g/mol and a TPSA of 61.96 Å², also exhibits promising features for drug development. Its moderate conformational flexibility and favorable hydrogen-bonding capacity highlight its potential in absorption and distribution processes. The balanced lipophilicity, reflected by a consensus Log P of 2.06, together with predicted solubility profiles, further supports its viability as an orally administered therapeutic agent.

In conclusion, both compounds represent well-defined scaffolds for further optimization in pharmaceutical development. Their physicochemical profiles are well aligned with the requirements for systemic absorption and therapeutic efficacy, making them suitable candidates for advanced drug development initiatives. Future studies may focus on their biological activity and potential clinical applications to fully elucidate their therapeutic potential.

REFERENCES

[1] Bhardwaj, V.; Gumber, D.; Abbot,V.; Dhimana, S.; Sharmaa, P. Pyrrole: a resourceful small molecule in key medicinal hetero-aromatics, *RSC Adv.*, **2015,** 5, pp.15233-15238, https://doi.org/10.1039/C4RA15710A

[2] Borah, B.; Dwivedi, K.D.; Chowhan, L.R. Recent approaches in the organocatalytic synthesis of pyrroles, *RSC Advances*, **2021,** 11(22), pp.13585-13601, https://doi.org/10.1039/D1RA01690C

[3] Daina, D.; Michielin, O.; Zoete, V. Swiss ADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules, *Scientific Reports*, **2017**, 7, pp.42717-42730, https://doi.org/10.1038/srep42717

[4] Saczewski, J.; Popenda, L.; Fedorowicz, J. In silico SwissADME analysis of antibacterial NHC-silver acetates and halides complexes, *Applied Sciences-Basel,* **2023,** 14(19), pp.8865-8881, https://doi.org/10.3390/app14198865

[5] Khizr, M.; Sahoo, S.C.; Khan, M.M. Synthesis, characterization, X-ray crystallographic study and in silico ADME predictions of functionalized nitropyrrole derivatives, *Journal of Molecular Structure,* **2022,** 1250(1), pp.131655-131665, https://doi.org/10.1016/j.molstruc.2021.131655

[6] Ozcan, H. Pyrrole-Based Schiff-Bases: Synthesis, Fluorescent Properties, Molecular docking and in silico ADME/Tox profiling studies, *Chemistry Select*, **2023,** 8(11), pp. e202204168-202204180, https://doi/org/10.1002/slct.202204168

[7] Pereira, F.; Bedda, L.; Tammam, M.A.; Alabdullah, A.K.; Arafa, R.; El-Demerdash, A. Investigating the antiviral therapeutic potentialities of marine polycyclic lamellarin pyrrole alkaloids as promising inhibitors for SARS-CoV-2 and Zika main proteases (Mpro), *Journal Of Biomolecular Structure & Dynamics*, **2023**, 42(8), pp.3983-4001, https://doi/org/10.1080/07391102.2023.2217513

[8] Chapan, I.; Gumush, M.; Gokche, H.; Chetin, H.; Sert, Y.; Koca, I. Synthesis, dielectric properties, molecular docking and ADME studies of pyrrole-3-ones, *Journal of Biomolecular Structure & Dynamics,* **2022**, 40(19), pp.8655-8671, https://doi.org/ 10.1080/07391102.2021.1914174

[9] Ke, W.; Soon, H.K.; Xuhan, Z. Overcoming challenges in small-molecule drug bioavailability: A review of key factors and approaches, *International. Journal of Molecular Science,* **2024**, *25*(23), pp.13121, https://doi.org/10.3390/ijms252313121

[10] Abd El-Hameed, R.H; Sayed, A.I.; Mahmoud, A.S.; Mosa, A.M.; Khoder, Z.M.; Fatahala, S.S. Synthesis of novel pyrroles and fused pyrroles as antifungal and antibacterial agents, *Journal of Enzyme Inhibition and Medicinal Chemistry*, **2021,** 36(1), pp.2183–2198, https://doi.org/10.1080/14756366.2021.1984904

[11] Safarova, A.S; Maharramov, A.M.; Asadov, Kh.A.; Naghiyev, F.N.; Huseynov, E.Z. Recent advances in the synthesis and structural elucidation of tetrasubstituted pyrroles under su-perbasic condition, *Baku State University Journal of Chemistry and Material Sciences*, **2025**, 1(2), pp.38-42, https://doi.org/10.30546/209501.201.2025.1.02.081

[12] Guchhait, T.; Roy, S.; Jena, P. Mannich reaction: An alternative synthetic approach for vario-us pyrrole-based anion receptors and chelating ligands, *European Journal of Organic Che-mistry*, **2022**, 2022(34), pp. e202200578-202200588, https://doi.org/10.1002/ejoc.202200578

[13] Quan, H.; Wang, L.; Wang, Z.; Mei, X.; Ning, J.; She, D. Alkylacylimidazoles in Claisen-Schmidt and Knoevenagel Condensations, *Russian Journal of Organic Chemistry*, **2020,** 56(8), pp.1462-1467, https://doi.org/10.1134/S1070428020080187

[14] Naghiyev, F.N. Research into one-step three component reaction of some ylidenecyanoacetamides (or ylidenemalononitriles), malononitrile and 1,3-diaminopropane, *Chemical Problems*, **2019,** 2(17), pp.275-281, https://doi.org/10.32737/2221-8688-2019-2-275-281

[15] Safarova, A.S.; Khalilov, A.N.; Akkurt, M.; Brito, I.; Bhattarai, A.; Naghiyev, F.N.; Mamedov, I.G.; Meervelt, L.V. Crystal structure and Hirshfeld surface analysis of (2Z)-3-oxo-N-phenyl-2-[(1H-pyrrol-2-yl)methylidene]butanamide monohydrate, *Acta Crystallographica Section E,* **2023**, 234(12), pp.1142-1146, https://doi.org/10.1107/S2056989023009799

[16] Shahverdiyeva, K.S; Ismayilova, S.A; Huseynzada, A.E.; Hasanova, U.A.; Yusubov, N.N.; Ismayilov, V.A. Halogen-containing chalcones as versatile bioactive agents: A review, *Baku State University Journal of Chemistry and Material Sciences*, **2025,** 2(3), pp.23-32, https://doi.org/10.30546/209501.201.2025.2.003.008

[17] Tiwari, A.; Bendi, A.; Bhathiwal, A.S An overview on synthesis and biological activity of chalcone derived pyrazolines, *Chemistry Select,* **2021**, 6(45), pp.12757-12795 https://doi.org/10.1002/slct.202103779

[18] Kurbanova, M.M.; Maharramov, A.M.; Huseyinov, E.Z.; Lai, C.H.; Weng, Y.C. Synthesis, structure, density functional theory study and in silico investigation of the biological activity of a newly synthesized hexahydroquinoline derivative, *Journal Of Computational Biophy-sics and Chemistry,* **2025**, pp.1-20, https://doi.org/10.1142/S2737416525501212

[19] Maharramov, A.M.; Kurbanova, M.M.; Taslimi, P.; Sujayev, A.; Alwasel, S.; Gulchin, I. Synthesis, characterization, crystal structure and bioactivities of novel enamine and pyrrole derivatives endowed with acetylcholinesterase, α-glycosidase and human carbonic anhydrase inhibition effects, *Organic Communications*, **2021**, 14(2), pp.144-156,

https://doi.org/10.25135/acg.oc101.21.04.2029

[20] Safarova, A.S.; Khalilov, A.N.; Akkurt, M.; Bhattarai, A.; Maharramov, A.M.; Naghiyev, F.N.; Mamedov, I.G. Crystal structure and Hirshfeld surface analysis of (2E)-1-phenyl-3-(1H-pyrrol-2-yl)propen-1-one, *Acta Crystallographia Section E*, **2024,** 80(2), pp.191-195, https://doi.org/10.1107/S2056989024000495