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Synthesis and characterization of new 4,5-dihydropyrazol-1-yl derivatives

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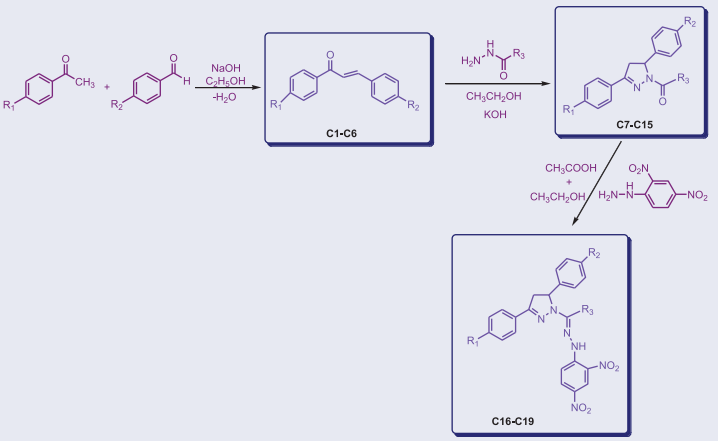
ABSTRACT

In this study, first, a series of chalcone compounds **S1–S6** were synthesized from various acetophenone derivatives (acetophenone, *p*-methyl acetophenone, and *p*-methoxy acetophenone) and aromatic aldehyde derivatives (benzaldehyde, *p*-methyl benzaldehyde, and *p*-methoxy benzaldehyde) by the Claisen–Schmidt condensation reaction. These **S1–S6** compounds were then used in the preparation of 4,5-dihydropyrazol-1-yl derivatives **S7–S15**. Finally, four new compounds **S16–S19** were synthesized from compound (**S7**, **S8**, **S9**, and **S12**) and 2,4-dinitrophenylhydrazine. Therefore, three known and ten new heterocyclic compounds were synthesized and completely characterized using ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis.

GRAPHICAL ABSTRACT



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Introduction

Chalcones, which are compounds with 1,3-diphenyl-2-propen-1-one nucleus in their structural framework, are one of the major classes of natural products and are considered as precursors of isoflavonoids and flavonoids.[1] These type of compounds have a wide spectrum of biological activity such as anticancer,[2] antiviral,[3] antibacterial,[4] antifungal,[5] antiulcer,[6] antimalarial,[7] anti-inflammatory,[8] anti-diabetes,[9] as potential treatment agents of Alzheimer's disease,[10] leishmanicidal,[11] trypanocidal effects,[11] etc. Therefore, many studies have been done on chalcones by researchers.[12–17]

Heterocyclic compounds containing nitrogen elements have an important place in chemistry due to their medical and pharmaceutical properties.[18] For example, there is great research interest in benzimidazole,[19] imidazole,[20] pyrrole,[21] pyridine,[22] pyrazine[23] and indole,[24] which are known significant classes of heterocyclic compounds due to their varying biological activities. Pyrazolines, which are a five-membered ring including two nitrogen atoms and a double bond, are biologically active molecules.[25–28] In this study, due to the immense bioactive significance of heterocyclic compounds, we decided to synthesis and characterize thirteen compounds based on 4,5-dihydropyrazol-1-yl.

Results and discussion

Spectral characterization of compounds

In this study, three known and ten new heterocyclic compounds were synthesized in considerable good yields, which ranged from 57% to 84% (Schemes 1–3). Synthesis of the chalcone derivatives **S1–S6** was conducted in one step. Using the prepared **S1–S6** compounds, the pyrazoline derivatives **S7–S15** and **S16–S19** were synthesized in two and three steps, respectively. The confirmation of molecular structures of **S7–S19** was vindicated by ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis. Yields, melting points, and elemental analysis results of compounds **S7–S19** are given in Table 1.

The aromatic protons of compounds **S7–S19** were obtained within the range of δ 6.80 and 8.83 ppm in ^{1}H NMR spectra. In ^{13}C NMR spectra, the carbon signal belonging to the carbonyl group (C=O) was obtained in a lower area, compared to other

Table 1. Selected properties of synthesized compounds.

Entry	Compounds	Yield (%)	Melting point (°C)	IR$_{(C=N)}$	Elemental analysis found (calc.)
1	**S7**	79	101–103	1595.14	C: 73.01 (73.45); H: 6.73 (6.16); N: 9.82 (9.52).
2	**S8**	72	97–100	1511.75	C: 77.15 (77.67); H: 6.83 (6.52); N: 10.15 (10.06).
3	**S9**	84	101–103	1594.82	C: 74.15 (74.00); H: 6.89 (6.54); N: 9.14 (9.08).
4	**S10**	78	105–107	1605.92	C: 74.31 (74.00); H: 6.12 (6.54); N: 9.19 (9.08).
5	**S11**	77	110–112	1507.7	C: 78.41 (78.10); H: 6.67 (6.29); N: 7.18 (7.29).
6	**S12**	81	105–108	1512.57	C: 81.73 (81.49); H: 6.23 (6.57); N: 7.38 (7.60).
7	**S13**	67	106–109	1604.61	C: 78.53 (78.10); H: 6.78 (6.29); N: 7.15 (7.29).
8	**S14**	77	108–110	1511.9	C: 81.75 (81.33); H: 6.63 (6.26); N: 7.49 (7.90).
9	**S15**	75	106–109	1493.5	C: 81.69 (81.33); H: 6.95 (6.26); N: 7.61 (7.90).
10	**S16**	64	107–109	1595.9 and 1644.9	C: 60.23 (60.75); H: 4.19 (4.67); N: 17.69 (17.71).
11	**S17**	63	114–117	1511.65 and 1643.52	C: 62.35 (62.87); H: 4.44 (4.84); N: 18.51 (18.33).
12	**S18**	57	112–113	1510.6 and 1644.9	C: 61.83 (61.47); H: 4.35 (4.95); N: 17.05 (17.20).
13	**S19**	63	110–111	1510.9 and 1650.7	C: 67.03 (67.87); H: 5.62 (5.14); N: 15.75 (15.32).

signals, at δ 172.53, 167.78, 168.71, 168.61, 168.92, 168.90, 168.77, 169.00, and 169.00 ppm for **S7–S15**, respectively. The formation of the desired compounds was also confirmed by IR, which showed the presence of stretching bands for the C=N vibrations at 1595.14, 1511.75, 1594.82, 1605.92, 1507.70, 1512.57, 1604.61, 1511.90, 1493.50, 1595.90, 1511.65, 1510.60, and 1510.90 cm^{-1} for compounds **S7–S19**, respectively. However, in the IR spectra, the C=O vibrations were 1642.56, 1643.31, 1643.59, 1654.83, 1636.40, 1654.84, 1649.65, 1654.80, and 1652.30 cm^{-1} for **S7–S15**, respectively.

Conclusion

In the present study, three known and 10 new heterocyclic compounds based on 4,5-dihydropyrazol-1-yl including electron-withdrawing or electron-donating substituents on the positions of the C3 or C5 aryl groups were synthesized and fully characterized by spectroscopic and analytic methods.

Experimental section

Chemical materials used in experimental studies

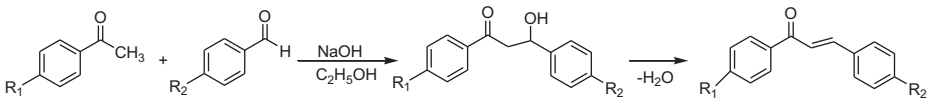
All the chemicals used in the synthesis were purchased from the companies Merck, Carlo Erba, Aldrich, and Fluka. These chemicals are benzaldehyde, 4-methyl benzaldehyde, 4-methoxy benzaldehyde, 4-methyl acetophenone, 4-methoxy acetophenone, 2,4-dinitrophenylhydrazine, sodium hydroxide, acetic acid, ethanol, hexane, and methanol.

Instrumentations

With a Shimadzu FT-IR 8400 spectrophotometer, the FT-IR spectra were recorded from 4000 to 400 cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz Ultra Shield NMR. Elemental analysis was determined using a CHNS-932 LECO apparatus.

Synthesis of benzalacetophenone derivatives

The synthesis of chalcone compounds **S1–S6** were conducted as illustrated below (Scheme 1). Sodium hydroxide (NaOH) (22 g) was added to a 1 L three-necked flask. 200 mL of water and 140 mL of ethyl alcohol (EtOH) were mixed in the flask and the



			Yield
S1	R_1: H	R_2: OCH_3	83%
S2	R_1: H	R_2: CH_3	88%
S3	R_1: CH_3	R_2: OCH_3	75%
S4	R_1: CH_3	R_2: H	81%
S5	R_1: OCH_3	R_2: CH_3	77%
S6	R_1: CH_3	R_2: CH_3	85%

Scheme 1. Synthesis of chalcone derivatives.

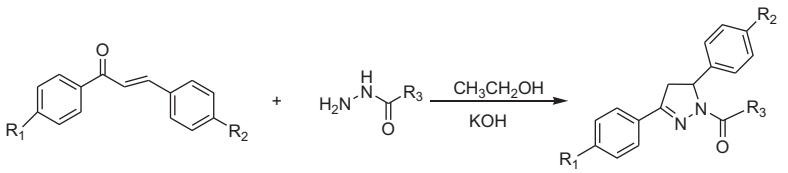
contents were dissolved by mixing in ice with a magnetic stirrer. Then, an acetophenone derivative (acetophenone for **S1** and **S2**, *p*-methyl acetophenone for **S3**, **S4**, and **S6**, *p*-methoxy acetophenone for **S5**) were slowly added drop wise into this mixture with the aid of the dropping funnel. After this process was completed, a benzaldehyde derivative (*p*-methoxy benzaldehyde for **S1** and **S3**, *p*-methyl benzaldehyde for **S2**, **S5**, and **S6**, benzaldehyde for **S4**) was added to the three-necked flask. The reaction was stirred in the salt-ice mixture for 5–6 h. The temperature was kept around (−10 °C). The product was precipitated with the addition of EtOH. The precipitated solid was left in the refrigerator overnight. After filtration of the product in vacuum, the product was washed several times with 200 mL of water + 140 mL of EtOH mixtures. The product was placed in a Petri dish and dried on P_2O_5 in vacuum desiccators for two nights.

3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-one (**S1**), 1-phenyl-3-*p*-tolylprop-2-en-1-one (**S2**), 3-(4-methoxyphenyl)-1-*p*-tolylprop-2-en-1-one (**S3**), 3-phenyl-1-*p*-tolylprop-2-en-1-one (**S4**), 1-(4-methoxyphenyl)-3-*p*-tolylprop-2-en-1-one (**S5**), and 1,3-di-*p*-tolylprop-2-en-1-one (**S6**) were prepared in one step. The colors of the obtained compounds were orange, yellow, yellow, yellow, yellow, yellow for **S1–S6**, respectively. The melting points of the compounds were measured at 72–75 °C, 90–94 °C, 95–98 °C, 72–75 °C, 96–99 °C, and 96–99 °C for **S1–S6**, respectively.

Reactions of chalcones with different hydrazide derivatives

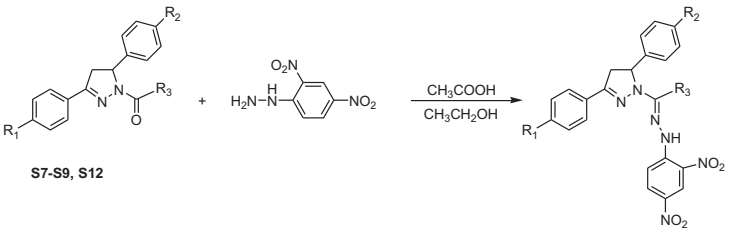
The synthesis of pyrazoline compounds was carried out according to literature procedures.[27,29–31] Chalcone derivatives (**S1–S6**) weighed at the stoichiometric ratio, acetic hydrazide, and KOH were added to a reaction flask and ethyl alcohol was added to the reaction medium as solvent (Scheme 2). It was refluxed for 5 h on a magnetic stirrer. The presence of the new product was checked using TLC, and ice was added to the reaction mixture after 5 h. After the reaction flask was left in the refrigerator for 1 day, the product precipitated, was filtered off, and was crystallized in ethanol. The final product was dried in vacuum desiccators over P_2O_5.

The synthesis of compounds **S7–S15** were completed according to the above mentioned general synthetic procedure. The characterization data of **S7–S15** are given below.



				Yield
S7	R_1: H	R_2: OCH_3	R_3: CH_3	79%
S8	R_1: H	R_2: CH_3	R_3: CH_3	72%
S9	R_1: CH_3	R_2: OCH_3	R_3: CH_3	84%
S10	R_1: OCH_3	R_2: CH3	R_3: CH_3	78%
S11	R_1: CH_3	R_2: OCH_3	R_3: $CH_2C_6H_5$	77%
S12	R_1: CH_3	R_2: CH_3	R_3: $CH_2C_6H_5$	81%
S13	R_1: OCH_3	R_2: CH3	R_3: $CH_2C_6H_5$	67%
S14	R_1: H	R_2: CH3	R_3: $CH_2C_6H_5$	77%
S15	R_1: CH_3	R_2: H	R_3: $CH_2C_6H_5$	75%

Scheme 2. Synthesis of **S7–S15**.



				Yield
S16	R_1: H	R_2: OCH_3	R_3: CH_3	64%
S17	R_1: H	R_2: CH_3	R_3: CH_3	63%
S18	R_1: CH_3	R_2: OCH_3	R_3: CH_3	57%
S19	R_1: CH_3	R_2: CH_3	R_3: $CH_2C_6H_5$	63%

Scheme 3. Schematic diagram of synthesized **S16–S19**.

Reactions of 4,5-dihydro-1H-pyrazole derivatives with 2,4-dinitrophenylhydrazine

Synthesized compounds (**S7**, **S8**, **S9**, and **S12**), 2,4-dinitrophenylhydrazine, and 0.25 mL of acetic acid were put in a reaction flask (Scheme 3). Ethyl alcohol was added to this reaction mixture as solvent. It was refluxed for 8 h on a magnetic stirrer. The presence of the new product was checked using TLC with a sample taken from the reaction medium at intervals of every hour. After 8 h, the reaction mixture was allowed to cool down. Then, the solvent in the reaction medium was removed with a Rotary Evaporator. Hexane was added over oily product, and it was mixed on a magnetic stirrer. The solidified product was filtered and crystallized in hexane. The final product was dried over P_2O_5 in vacuum desiccators.

(E)-1-(1-(3,5-di-p-tolyl-4,5-dihydropyrazol-1-yl)-2-phenylethylidene)-2-(2,4-dinitrophenyl)hydrazine, S19

New compound **S19** ($C_{31}H_{28}N_6O_4$: 548 g/mol) was synthesized from 0.10 g of **S12**, 0.07 g of 2,4-dinitrophenyl hydrazine and 5 drops of acetic acid. The product was crystallized in hexane. Product: 0.07 g, yield: 63%, *m.p.*: 110–111 °C. FT-IR (cm^{-1}): 3027.1 (N–H), 2920.3 (C–H), 1510.9–1650.7 (–C=N), 1322.1–1425.3 (C=C). ^{1}H NMR (δ=ppm): 7.03–7.68 (m, 16H, Ar-H), 5.50–5.55 (d, *J*: 8 Hz, 1H), 4.07–4.19 (q, *J*: 12Hz, aliphatic 2H), 3.10–3.75 (t, *J*: 8 Hz, 2H), 2.30 and 2.42 (s, 6H, CH_3). ^{13}C NMR (δ=ppm): 168.90 (pyrazole C=N), 153.98 (imine C=N), 140.68, 138.91, 137.25, 135.52, 129.61, 129.48, 128.71, 128.31, 126.59, and 125.54 (Ar-C), 59.84 (CH), 42.33, and 41.22 (–CH_2–), 21.54, and 21.09 (–CH_3). Elemental analysis for $C_{31}H_{28}N_6O_4$ (548.59 g/mol) %: Found C: 67.03; H: 5.62; N: 15.75. Anal. Calc. C: 67.87; H: 5.14; N: 15.32.

The characterization data of **S7–S18** were given in supplementary information.

^{1}H NMR, ^{13}C NMR, IR spectra, and full characterization data of all compounds can be found via the "Supplementary Content" section of this article's webpage.'

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Author's contribution

F. Ö. Güney conducted all experiments under the supervision of İ. Ö. İlhan and S. Akkoç, İ. Ö. İlhan designed the study, and S. Akkoç helped analyze data and wrote the manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] Ghosh, R.; Das, A. Synthesis and Biological Activities of Chalcones and Their Heterocyclic Derivatives: A Review. *World J. Pharm. Pharm. Sci.* **2014**, *3*, 578–595.

[2] Khanapure, S.; Jagadale, M.; Bansode, P.; Choudhari, P.; Rashinkar, G. Anticancer Activity of Ruthenocenyl Chalcones and Their Molecular Docking Studies. *J. Mol. Struct.* **2018**, *1173*, 142–147. DOI: 10.1016/j.molstruc.2018.06.091.

[3] Zhou, D.; Xie, D.; He, F.; Song, B.; Hu, D. Antiviral Properties and Interaction of Novel Chalcone Derivatives Containing a Purine and Benzenesulfonamide Moiety. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 2091–2097. DOI: 10.1016/j.bmcl.2018.04.042.

[4] Ayman, M.; El-Messery, S. M.; Habib, E. E.; Al-Rashood, S. T.; Almehizia, A. A.; Alkahtani, H. M.; Hassan, G. S. Targeting Microbial Resistance: Synthesis, Antibacterial Evaluation, DNA Binding and Modeling Study of New Chalcone-Based Dithiocarbamate Derivatives. *Bioorg. Chem.* **2019**, *85*, 282–292. DOI: 10.1016/j.bioorg.2019.01.001.

[5] Wang, Y.-H.; Dong, H.-H.; Zhao, F.; Wang, J.; Yan, F.; Jiang, Y.-Y.; Jin, Y.-S. The Synthesis and Synergistic Antifungal Effects of Chalcones against Drug Resistant Candida albicans. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3098–3102. DOI: 10.1016/j.bmcl.2016.05.013.

[6] Sashidhara, K. V.; Avula, S. R.; Mishra, V.; Palnati, G. R.; Singh, L. R.; Singh, N.; Chhonker, Y. S.; Swami, P.; Bhatta, R. S.; Palit, G. Identification of Quinoline-Chalcone Hybrids as Potential Antiulcer Agents. *Eur. J. Med. Chem.* **2015**, *89*, 638–653. DOI: 10.1016/j.ejmech.2014.10.068.

[7] Arancibia, R.; Biot, C.; Delaney, G.; Roussel, P.; Pascual, A.; Pradines, B.; Klahn, A. H. Cyrhetrenyl Chalcones: Synthesis, Characterization and Antimalarial Evaluation. *J. Organomet. Chem.* **2013**, *723*, 143–148. DOI: 10.1016/j.jorganchem.2012.08.024.

[8] Ur Rashid, H.; Xu, Y.; Ahmad, N.; Muhammad, Y.; Wang, L. Promising anti-Inflammatory Effects of Chalcones via Inhibition of Cyclooxygenase, Prostaglandin E2, Inducible NO Synthase and Nuclear Factor κb Activities. *Bioorg. Chem.* **2019**, *87*, 335–365. DOI: 10.1016/j.bioorg.2019.03.033.

[9] Cai, C.-Y.; Rao, L.; Rao, Y.; Guo, J.-X.; Xiao, Z.-Z.; Cao, J.-Y.; Huang, Z.-S.; Wang, B. Analogues of Xanthones Chalcones and Bis-Chalcones as α-Glucosidase Inhibitors and anti-Diabetes Candidates. *Eur. J. Med. Chem.* **2017**, *130*, 51–59. DOI: 10.1016/j.ejmech.2017.02.007.

[10] Cong, L.; Dong, X.; Wang, Y.; Deng, Y.; Li, B.; Dai, R. On the Role of Synthesized Hydroxylated Chalcones as Dual Functional Amyloid-β Aggregation and Ferroptosis Inhibitors for Potential Treatment of Alzheimer's Disease. *Eur. J. Med. Chem.* **2019**, *166*, 11–21. DOI: 10.1016/j.ejmech.2019.01.039.

[11] Espinoza-Hicks, J. C.; Chacón-Vargas, K. F.; Hernández-Rivera, J. L.; Nogueda-Torres, B.; Tamariz, J.; Sánchez-Torres, L. E.; Camacho-Dávila, A. Novel Prenyloxy Chalcones as Potential Leishmanicidal and Trypanocidal Agents: Design, Synthesis and Evaluation. *Eur. J. Med. Chem.* **2019**, *167*, 402–413. DOI: 10.1016/j.ejmech.2019.02.028.

[12] Maragatham, G.; Selvarani, S.; Rajakumar, P.; Lakshmi, S. Structure Determination and Quantum Chemical Analysis of Chalcone Derivatives. *J. Mol. Struct.* **2019**, *1179*, 568–575. DOI: 10.1016/j.molstruc.2018.11.048.

[13] Reeta, Vinoth, R.; Rangarajan, T. M.; Ayushee, Singh, R. P.; Singh, M. Synthesis of Novel Chalcones through Palladium-Catalyzed CO Cross-Coupling Reaction of Bromo-Chalcones with Ethyl Acetohydroxamate and Their Antiplasmodial Evaluation against Plasmodium Falcipuram in Vitro. *Bioorg. Chem.* **2019**, *86*, 631–640. DOI: 10.1016/j.bioorg.2019.02.016.

[14] Kotlyar, V. M.; Kolomoitsev, O. O.; Nikolaievskyi, D. V.; Pedan, P. I.; Chumak, A. Y.; Orlov, V. D.; Shishkina, S. V.; Doroshenko, A. O. Photoreactive Fused Aziridinylpiperazines on the Background of 4-Substituted Chalcones and Their Benzimidazolic Analogs. *J. Mol. Struct.* **2019**, *1180*, 741–746. DOI: 10.1016/j.molstruc.2018.12.015.

[15] Borge, V. V.; Patil, R. M. Syntheses and Characterization of Copper Metal Complexes Prepared from Chalcone Derivatives. *Microchem. J.* **2019**, *145*, 456–459. DOI: 10.1016/j.microc.2018.11.001.

[16] Tajudeen Bale, A.; Mohammed Khan, K.; Salar, U.; Chigurupati, S.; Fasina, T.; Ali, F.; Kanwal, Wadood, A.; Taha, M.; Sekhar Nanda, S.; Ghufran, M.; Perveen, S. Chalcones and Bis-Chalcones: As Potential α-Amylase Inhibitors; Synthesis, in Vitro Screening, and Molecular Modelling Studies. *Bioorg. Chem.* **2018**, *79*, 179–189. DOI: 10.1016/j.bioorg.2018.05.003.

[17] Burmaoglu, S.; Yilmaz, A. O.; Polat, M. F.; Kaya, R.; Gulcin, İ.; Algul, O. Synthesis and Biological Evaluation of Novel Tris-Chalcones as Potent Carbonic Anhydrase, Acetylcholinesterase, Butyrylcholinesterase and α-Glycosidase Inhibitors. *Bioorg. Chem.* **2019**, *85*, 191–197. DOI: 10.1016/j.bioorg.2018.12.035.

[18] Stefanes, N. M.; Toigo, J.; Maioral, M. F.; Jacques, A. V.; Chiaradia-Delatorre, L. D.; Perondi, D. M.; Ribeiro, A. A. B.; Bigolin, Á.; Pirath, I. M. S.; Duarte, B. F.; et al. Synthesis of Novel Pyrazoline Derivatives and the Evaluation of Death Mechanisms Involved in Their Antileukemic Activity. *Bioorg. Med. Chem.* **2019**, *27*, 375–382. DOI: 10.1016/j.bmc.2018.12.012.

[19] Akkoç, S. Derivatives of 1-(2-(Piperidin-1-yl)Ethyl)-1H-Benzo[d]Imidazole: Synthesis, Characterization, Determining of Electronic Properties and Cytotoxicity Studies. *ChemistrySelect* **2019**, *4*, 4938–4943.

[20] Gök, Y.; Akkoç, S.; Akkurt, M.; Tahir, M. N. Imidazole, Pyrimidine and Diazepine Containing Heteroaryl-Substituted Heterocyclic Salts as Efficient Ligand Precursors for Mizoroki–Heck Coupling Reaction: synthesis, Structural Characterization and Catalytic Activities. *J. Iran. Chem. Soc.* **2014**, *11*, 1767–1774. DOI: 10.1007/s13738-014-0449-z.

[21] Wan, S.-H.; Liu, S.-T. Functionalized Pyrroles from Vinylaziridines and Alkynes via Rhodium-Catalyzed Domino Ring-Opening Cyclization Followed by CC Bond Migration. *Tetrahedron* **2019**, *75*, 1166–1170. DOI: 10.1016/j.tet.2019.01.022.

[22] Song, Y.-L.; Tian, C.-P.; Wu, Y.; Jiang, L-h.; Shen, L.-Q. Design, Synthesis and Antitumor Activity of Steroidal Pyridine Derivatives Based on Molecular Docking. *Steroids* **2019**, *143*, 53–61. DOI: 10.1016/j.steroids.2018.12.007.

[23] Kim, J.; Park, M.; Choi, J.; Singh, D. K.; Jeong Kwon, H.; Kim, S. H.; Kim, I. Design, Synthesis, and Biological Evaluation of Novel Pyrrolo[1,2-a]Pyrazine Derivatives. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 1350–1356. DOI: 10.1016/j.bmcl.2019.03.044.

[24] Demurtas, M.; Baldisserotto, A.; Lampronti, I.; Moi, D.; Balboni, G.; Pacifico, S.; Vertuani, S.; Manfredini, S.; Onnis, V. Indole Derivatives as Multifunctional Drugs: Synthesis and Evaluation of Antioxidant, Photoprotective and Antiproliferative Activity of Indole Hydrazones. *Bioorg. Chem.* **2019**, *85*, 568–576. DOI: 10.1016/j.bioorg.2019.02.007.

[25] Ozmen Ozgun, D.; Gul, H. I.; Yamali, C.; Sakagami, H.; Gulcin, I.; Sukuroglu, M.; Supuran, C. T. Synthesis and Bioactivities of Pyrazoline Benzensulfonamides as Carbonic Anhydrase and Acetylcholinesterase Inhibitors with Low Cytotoxicity. *Bioorg. Chem.* **2019**, *84*, 511–517. DOI: 10.1016/j.bioorg.2018.12.028.

[26] Ahmad, A.; Husain, A.; Khan, S. A.; Mujeeb, M.; Bhandari, A. Synthesis, Antimicrobial and Antitubercular Activities of Some Novel Pyrazoline Derivatives. *J. Saudi Chem. Soc.* **2016**, *20*, 577–584. DOI: 10.1016/j.jscs.2014.12.004.

[27] Ilhan, I. O.; Caglayan, A.; Onal, Z.; Akkoc, S.; Cadır, M. Reactions of Some Pyrazole-3-Carboxylic Acids and Carboxylic Acid Chlorides with Various O- and N- Nucleophiles. *Loc.* **2013**, *10*, 602–610. DOI: 10.2174/15701786113109990025.

[28] Kadi, A. A.; Yin, W.; Rahman, A. F. M. M. In-Vitro Metabolic Profiling Study of Potential Topoisomerase Inhibitors 'Pyrazolines' in RLMs by Mass Spectrometry. *J. Chromatogr. B* **2019**, *1114–1115*, 125–133. DOI: 10.1016/j.jchromb.2019.03.026.

[29] Levai, A.; Jeko, J. Synthesis of Carboxylic Acid Derivatives of 2-Pyrazolines. *Arkivoc* **2007**, *(i)*, 134–145.

[30] İlhan, İÖ.; Çadir, M.; Saracoglu, M.; Kandemirli, F.; Kökbudak, Z.; Akkoç, S. The Reactions and Quantum Chemical Calculations of Some Pyrazole-3- Carboxylic Acid Chlorides with Various Hydrazides. *Chem. Sci. Rev. Lett.* **2015**, *4*, 838–850.

[31] Ilhan, I. O.; Demirkol, K.; Önal, Z.; Akkoç, S.; Çadır, M. Functionalization Reactions of Various Pyrazole-3-Carboxylic Acid Chlorides with Some Ureas. *Asian J. Chem.* **2014**, *26*, 2365–2368. DOI: 10.14233/ajchem.2014.16000.