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Synthesis and structural characterization of novel pyrazoline derivatives

Yeni pirazolin türevlerinin sentezi ve yapı karakterizasyonu

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Abstract
Pyrazolines, which are nitrogen including five-membered heterocyclic structures, have been used in the organic and pharmaceutical industries. This study aimed was to synthesize and characterizes new series of 3,5-diphenyl-4,5-dihydro-1H-pyrazole derivatives. The new pyrazoline compounds have been synthesized from chalcones and hydrazine hydrate in two steps. In the first step, chalcones were synthesized from 2-amino acetophenone and various substituted benzaldehyde by Claisen-Schmidt condensation at room temperature. In second step, starting from various substituted chalcones derivatives with hydrazine hydrate and glacial acetic acid in anhydrous ethanol were synthesized six novel 3,5-diphenyl-4,5-dihydro-1H-pyrazole derivatives utilizing intramolecular Michael addition reaction in good yields. The structures of the newly synthesized 3,5-diphenyl-4,5-dihydro-1H-pyrazole derivatives are identified via 1H NMR, 13C NMR, FT-IR, and HRMS.

Keywords: Chalcone, Characterization, Pyrazoline, Synthesis

Öz
Heterosiklik moleküllerin azot içeren 5 halkalı üyesi olan pirazolinler organik ve eczacılık endüstrisinde kullanılırlar. Bu çalışmanın amacı, yeni 3,5-difenil-4,5-dihidro-1H-pirazol türevlerini sentezlemek ve karakterize etmektir. Yeni pirazolin türevleri kalkon ve hidrazin hidrattan iki adımda sentezlendi. İlk adımda, 2-amino asetofenon ve çeşitli substitue benzaldehitlerden oda sıcaklığında Claisen-Schmidt kondenzasyonuyla kalkonlar sentezlendi. İkinci adımda, farklı substitue kalkon türevlerinden başlanarak susuz etanol içinde hidrazin hidrat ile birlikte 6 adet yeni 3,5-difenil-4,5-dihidro-1H-pirazol türevleri molekül içi Michael katılması reaksiyonu kullanılarak iyi verimle sentezlendi. Sentezlenen tüm yeni 3,5-difenil-4,5-dihidro-1H-pirazol türevlerinin yapıları 1H NMR, 13C NMR, FT-IR ve HRMS yardımıyla aydınlatıldı.

***Anahtar kelimeler**: Kalkon, Karakterizasyon, Pirazolin, Sentez*

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1. Giriş

Chalcones are an important functional group for the synthesizing different heterocycles (Karthikeyan et al., 2007). Several chalcone derivatives are of considerable interest in both synthetic organic and medicinal chemistry, act as a precursor for biologically important diverse pharmacological activities (Arslan et al., 2016), such as antiobesity, antioxidant, and anticancer properties (El Sayed Aly et al., 2014).

Pyrazoline is one of the most important five-membered heterocycles, including two nearby nitrogen atoms and an endocyclic double band with the ring (Farooq and Ngaini, 2020). *N*-containing heterocycles such as 2-pyrazoline are essential in medicinal chemistry as a likely scaffold for structural qualification and drug development studies (Patel et al., 2016; Kahriman et al., 2017). Furthermore, 2-pyrazoline is the most popular among the three tautomeric structures of pyrazolines (Lone et al., 2014; Sever et al., 2019). Pyrazolines have been reported to display quality of biological activities as a reactive heterocyclic structure, especially about the anti-tubercular (Ahmad et al., 2016), anti-viral (Yar et al., 2009), anti-bacterial (Solanki et al., 2012), anti-fungal (Hassan, 2013) and anti-cancer (Jainey and Bhat, 2012) activities. Stefans et al. (2019) explored the antileukemic potential against neoplastic cells of pyrazoline derivatives which have been obtained from various chalcones.

Pyrazoline compounds have also been reported which have different synthetic methods (Farooq and Ngaini, 2020). The most common synthesis route of pyrazolines used α,β-unsaturated carbonyl compounds (chalcones) as starting compounds. To obtain the pyrazolines, the chalcones have been cyclized in organic solvent using different acid and hydrazine hydrate (Patel et al., 2016; Mishra et al., 2017).

Some bioactive pyrazoline derivatives such as 2-(5-(2-Fluorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenol (**I**) and 2-[-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]pyridine (**II**) were synthesized from chalcones (Figure 1). Compound I had been used as carbonic anhydrase inhibitors in some studies previously (Çelik et al., 2020). Previous significant evidence on compound II gives powerful antimicrobial and antioxidant activity (Lone et al., 2014).

In light of the above finding, here in this study, novel 3,5-diphenyl-4,5-dihydro-1H-pyrazole derivatives (Table 1 and Scheme 3) were synthesized from heterocyclic chalcone for the first time and their structures were characterized by spectroscopic techniques (^{1}H NMR, ^{13}C NMR, FT-IR, and HRMS).

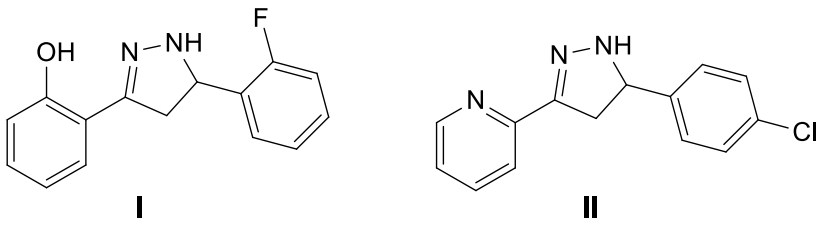

Figure 1. Molecular structure of some bioactive pyrazolines

2. Material and methods

^{1}H, ^{13}C, and APT NMR spectra were measured on an Agilent NMR (nuclear magnetic resonance, 400 MHz) instrument at 25 °C with tetramethylsilane (TMS) and solvent signals allowed as internal standards. Chemical shifts are exhibited in ppm (δ) scale. The high-resolution accurate masses were carried out with Micromass Quattro LC-MS/MS (liquid chromatography and mass spectroscopy) mass spectrometer. All the Fourier Transform Infra-Red (FTIR) spectra were measured on a Perkin Elmer 1600 spectrophotometer. Melting points were taken on the Thermo-var apparatus fitted with a microscope in degrees (°C) and reported as uncorrected.

2.1. General methods for the preparation of chalcone derivatives (3a-3f)

The synthesis of starting compounds 3a-3f has been synthesized from the reported procedure. To a solution mixture of equimolar quantities of 2-amino acetophenone (0.01 mole) and substituted aromatic aldehydes (0.01 mole) in ethanol (30 mL), sodium hydroxide solution (5 mL, 40%) was added with continuous stirring at room temperature for 2-3 h. The reaction mixture was monitored by TLC. When at least one of the starting compounds

finished, the reaction content was poured on ice-water and acidified by HCI (10%). The precipitates obtained was filtered, dried, and recrystallized from ethyl alcohol to obtain compounds 4a-4f (Raghav et al., 2016; Michelini et al., 2018).

2.1.1. General methods for the preparation of 3,5-diphenyl-4,5-dihydro-1H-pyrazole derivatives (4a-4f)

Hydrazine hydrate (80% aqueous solution, 5 mmol) was added to a suspension of 3a-3f (5 mmol) in ethanol 50 mL including 0.5 mL of glacial acetic acid. The obtained mixture was then refluxed 24 h, monitored by TLC (Bano et al., 2015; Çelik et al., 2020). After completion of the reaction, the reaction mixture was cooled at room temperature for 1 h. The mixture was then extracted with chloroform from the one-third concentrated solution. The organic sheet was then evaporated to yield the expected crude 3,5-diphenyl-4,5-dihydro-1H-pyrazole (4a-f) derivatives. Residues received were purified by column chromatography to afford pure compound 4a-4f.

3-(2'-Aminophenyl),5-(2'-methoxyphenyl)pyrazoline (4a): Yield: 800 mg. (60%); m.p: 61-63 °C; IR (ATR/FT-IR), ν/cm^{-1}: 3462, 3334 (N-H stretching), 2937, 2835 (aliphatic C-H stretching), 2358, 2331 (NH_2 stretching), 1612, 1600, 1489 (C=C and C=N stretching), 1242, 1026 (C-N and OCH_3 stretching, aromatic C-H in plane bending), 750 (aromatic C-H out of plane bending); for HNMR- 7.4 (d, 1H, *J* = 8 Hz), 7.3 (t, 1H, *J* = 8 Hz), 7.2 (d, *J* = 8 Hz, 1H), 7.1 (t, 1H, *J* = 8 Hz), 6.9 (d, 1H, *J* = 7.8 Hz), 6.9 (m, 1H), 6.7 (m, 2H), 5.1 (dd, 1H, *J* = 9.7/9.6 Hz), 3.9 (s, 3H), 3.55 (dd, 1H, *J* = 15.9/10.2 Hz), 3.05 (dd, 1H, *J* = 15.9/9.1 Hz), for CNMR 156.9, 154.1, 146.7, 130.1, 130.1, 129.2, 128.5, 126.3, 120.7, 115.6, 115.3, 115.3, 110.3, 56.9, 55.4, 40.2; HRMS: MS (ESI, *m/z*) [M+H]$^+$: calcd. For C16H17N3O: 267.3258; Found: 268.1462.

3-(2'-Aminophenyl),5-(3'-methoxyphenyl)pyrazoline (4b): Yield: 734 mg. (55%); m.p: Oil; IR (ATR/FT-IR), ν/cm^{-1}: 3462, 3327 (N-H stretching), 3005 (aromatic C-H stretching), 2937, 2835 (aliphatic C-H stretching), 2358, 2331 (NH_2 stretching), 1610, 1595, 1471 (C=C and C=N stretching), 1257, 1157, 1041(C-N and OCH_3 stretching, aromatic C-H in plane bending), 746 (aromatic C-H out of plane bending); for HNMR-7.3 (m, 2H), 7.2 (m, 2H), δ = 7.0 (m, H), 6.9 (dd, 1H, *J* = 4.0/4.0), 6.7 (m, 2H), 4.8 (dd, 1H, *J* = 10.4/9.0 Hz), 3.9 (s, 3H), 3.55 (dd, 1H, *J* = 16.1/10.5 Hz), 3.15 (dd, 1H, *J* = 16.1/8.9 Hz), for CNMR 159.9, 153.7, 146.7, 144.4, 129.9, 129.4, 128.9, 118.7, 116.4, 115.7, 114.9, 113.1, 111.9, 62.7, 55.3, 42.8; HRMS: MS (ESI, *m/z*) [M+H]$^+$: calcd. For C16H17N3O: 267.3258; Found: 268.1452.

3-(2'-Aminophenyl),5-(4'-methoxyphenyl)pyrazoline (4c): Yield: 600 mg. (45%); m.p: Oil; IR (ATR/FT-IR), ν/cm^{-1}: 3462, 3336 (N-H stretching), 3005 (aromatic C-H stretching), 2935, 2835(aliphatic C-H stretching), 2358, 2322 (NH_2 stretching), 1610, 1450 (C=C and C=N stretching), 1246, 1174, 1029 (C-N and OCH_3 stretching, aromatic C-H in plane bending), 746 (aromatic C-H out of plane bending); for HNMR-7.4 (d, 1H, *J* = 8.6 Hz), 7.3 (t, 1H, *J* = 8.6 Hz), 7.2 (t, 1H, *J* = 7.6 Hz), 7.2 (d, 1H, *J* = 7.7 Hz), 7.2 (d, 1H, *J* = 6.7 Hz), 6.9 (d, 1H, *J* = 8.6 Hz), 6.7 (d, 1H, *J* = 7.4 Hz), 6.7 (d, 1H, *J* = 7.5 Hz,), 4.8 (dd, 1H, *J* = 10.3/8.5 Hz), 3.9 (s, 3H), 3.75 (dd, 1H, *J* = 7.9/5.8 Hz), 3.15 (dd, 1H, *J* = 16.1/8.4 Hz), for CNMR 159.1, 153.9, 146.2, 134.9, 130.0, 129.4, 127.6, 127.6, 116.4, 115.7, 114.1, 114.1, 113.9, 62.2, 55.4, 42.7; HRMS: MS (ESI, *m/z*) [M+H]$^+$: calcd. For C16H17N3O: 267.3258; Found: 268.1441.

3-(2'-Aminophenyl),5-(2'-nitrophenyl)pyrazoline (4d): Yield: 705 mg. (50%); m.p: 88-90 °C; IR (ATR/FT-IR), ν/cm^{-1}: 3462, 3336 (N-H stretching), 2933, 2843 (aliphatic C-H stretching), 2358, 2341 (NH_2 stretching), 1614, 1521, 1465, 1348 (C=C, C=N and NO_2 stretching), 1246, 1161, 1031(C-N and aromatic C-H in plane bending), 750 (aromatic C-H out of plane bending); for HNMR-8.5 (dd, 1H, *J* = 8.1/7.9 Hz), 8.05 (dd, 1H, *J* = 18.0/9.3 Hz), 7.9 (t, 1H, *J* = 8.0 Hz), 7.8 (m, 1H), 6.7 (m, 1H), 7.4 (t, 1H, *J* = 7.4 Hz), 7.4 (t, 1H, *J* = 7.3 Hz), 7.2 (m, 1H), 6.0 (brs, 3H), 5.3 (t, 1H, *J* = 10.0 Hz), 3.85 (dd, 1H, *J* = 16.4/10.7 Hz), 3.15 (dd, 1H, *J* = 16.4/9.6 Hz), for CNMR 153.6, 146.6, 138.0, 134.3, 133.8, 129.7, 128.9, 127.2, 124.6, 118.8, 116.9, 116.5, 115.7, 58.2, 42.8; HRMS: MS (ESI, *m/z*) [M+H]$^+$: calcd. For C15H14N4O2: 282.2974; Found: 283.1152.

3-(2'-Aminophenyl),5-(3'-nitrophenyl)pyrazoline (4e): Yield: 775 mg. (55%); m.p: 165-167 °C; IR (ATR/FT-IR), ν/cm^{-1}: 3460, 3327 (N-H stretching), 2358, 2330 (NH_2 stretching), 1612, 1523, 1508, 1452, 1346 (C=C, C=N and NO_2 stretching), 1161, 1083 (C-N and aromatic C-H in plane bending), 752 (aromatic C-H out of plane bending); for HNMR-8.3 (s, 1H), 8.2 (d, 1H, *J* = 7.8 Hz), 7.8 (d, 1H, *J* = 7.3 Hz), 7.5

(t, 1H, *J* = 7.8 Hz), 7.2 (m, 2H), *δ* = 6.7 (m, 1H), 6.0 (brs, 3H), 5.0 (t, 1H, *J* = 10.1 Hz), 3.65 (dd, 1H, *J* = 16.0/10.8 Hz), 3.05 (dd, 1H, *J* = 16.0/10.0 Hz), for CNMR 153.5, 148.4, 146.7, 144.8, 132.7, 129.9, 129.7, 128.8, 122.7, 121.8, 115.7, 115.7, 114.3, 62.1, 43.2; HRMS: MS(ESI, *m/z*) $[M+H]^+$: calcd. For $C_{15}H_{14}N_4O_2$: 282.2974; Found: 283.1222.

3-(2'-Aminophenyl),5-(4'-nitrophenyl)pyrazoline (4f): Yield: 564 mg. (40%); m.p: 93-95 °C; IR (ATR/FT-IR), ν/cm^{-1}: 3462, 3327 (N-H stretching), 2927, 2854 (aliphatic C-H stretching), 2360(NH_2 stretching) , 1612, 1516, 1452, 1344, 1215 (C=C, C=N and NO_2 stretching), 1161, 1014 (C-N and aromatic C-H in plane bending), 750 (aromatic C-H out of plane bending); for HNMR-8.2 (d, 2H, *J* = 7.2 Hz), *δ* = 7.6 (d, 2H, *J* = 7.2 Hz), 7.3 (s, 1H), *δ* = 7.2 (m, 2H), 6.7 (m, 1H), 6.0 (brs, 3H), 4.9 (t, 1H, *J* = 9.0 Hz), 3.65 (dd, 1H, *J* = 16.0/8.6 Hz), 3.05 (dd, 1H, *J* = 15.6/9.6 Hz), for CNMR 150.1, 146.7, 129.8, 128.9, 127.5, 127.0, 127.5, 126.1, 124.1, 124.1, 122.9, 116.4, 115.8, 62.2, 43.2; HRMS: MS (ESI, *m/z*) $[M+H]^+$: calcd. For $C_{15}H_{14}N_4O_2$: 282.2974; Found: 283.1204.

3. Results and discussion

The general synthesis route of chalcones (3a-3f) and 3,5-diphenyl-4,5-dihydro-1H-pyrazole derivatives (4a-4f) are given in Table 1 and Figure 2. Firstly, the chalcones were synthesized by Claisen-Schmidt condensation among the aromatic aldehydes and the substituted acetophenone utilizing reported methods in the literature (Abdel-Halim et al., 2020; Çelik, 2020). Secondly, for compounds 4a-4f, chalcones have been converted into pyrazoline molecules by intramolecular Michael addition with hydrazine hydrate in refluxing ethanol and acetic acid as a catalyst (Table 1 and Figure 2)(Li et al., 2017; Çelik et al., 2020; Dofe et al., 2020; Farooq and Ngaini, 2020). Finally, six novel pyrazolines were synthesized with high yield for the first time in this work. All the synthesized compounds gave satisfactory spectroscopic data (^{1}H NMR, ^{13}C NMR, FT-IR, and HRMS), which were in the whole accordance with their described structures.

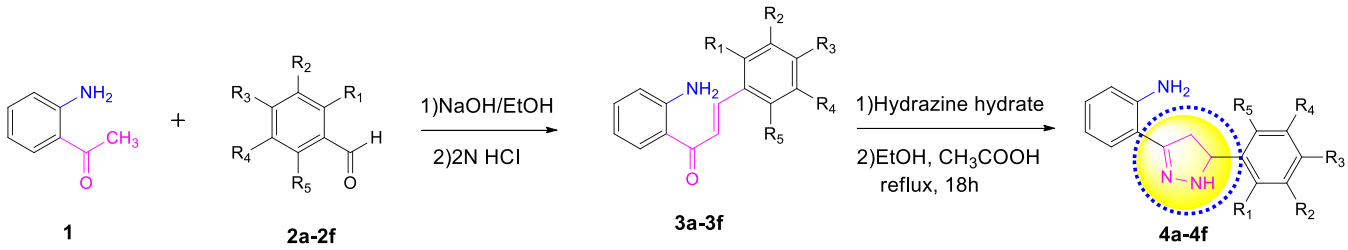

Figure 2. The general route for the preparation of 3,5-diphenyl-4,5-dihydro-1H-pyrazole derivatives (4a-4f)

Table 1. 3,5-diphenyl-4,5-dihydro-1H-pyrazole derivatives (4a-4f)

Compounds	R_1	R_2	R_3	R_4	R_5
4a	OCH_3	H	H	H	H
4b	H	OCH_3	H	H	H
4c	H	H	OCH_3	H	H
4d	NO_2	H	H	H	H
4e	H	NO_2	H	H	H
4f	H	H	NO_2	H	H

In the ^{1}H NMR spectra of the 3,5-diphenyl-4,5-dihydro-1H-pyrazole derivatives (4a-4f), the three hydrogen atoms connected to the C-4 and C-5 carbon atoms of the heterocyclic ring provided an ABX spin system (Figure 3). This form an ABX spin system of a set of three doublets of doublets peaks was seen, which appeared due to *geminal-vicinal* coupling with the non-equivalent protons of the methylene group H_a and H_b at the C-4 and methine proton H_X at C-5 of the pyrazole ring (Çelik et al., 2020; Delgado et al., 2020). In these compounds (4a-4f) H_A appeared as a doublet of doublets (J_{AB} = 15.6-16.4 Hz, J_{AX} = 8.4-10.0 Hz) at 3.0-3.2 ppm. The H_B protons were recognized as a doublet of doublets at 3.5-3.9 ppm (J_{BA} = 7.9-16.4 Hz, J_{BX} = 5.8-10.8 Hz), whereas the H_X protons resonated as a doublet of doublets (J_{AX} = 8.5-9.6 Hz, J_{BX} = 9.3-10.4 Hz) or triplet (*J* = 9.0-10.1 Hz) at 4.8-5.3 ppm. Sun et al. (2013) reported, the characteristic methylene protons related to the AB

system of the pyrazoline ring were observed at 1.72-2.60 ppm (J= 13.6 Hz). The protons of the methoxy group appeared as a singlet at 3.9 ppm. Other aromatic protons were located in the predicted regions. Besides, the -NH- and -NH_2 groups of pyrazoline assigned to a signal as broad at 5.9-6.2 ppm. According to the previous reports, the formation of pyrazoline scaffold in the final compounds was confirmed, in which N-H protons determined at 7.89 ppm by broad singlet (Sever et al., 2020). The ^{13}C NMR spectra were further supported all structures which gave the chemical shift values of carbon atoms of pyrazoline ring C-3 at 150.1-153.9 ppm, C-4 at 40.2-43.2 ppm, and C-5 at 56.9-62.7 ppm. Similarly, previous studies reported that pyrazoline scaffold carbons of the C-3, C-4, and C-5 were exhibited 152.38-153.65 ppm, 42.62-43.73 ppm, and 63.68-63.93 ppm (Sever et al., 2020; Rana et al., 2021). In the proton-decoupled ^{13}C NMR, the methoxy group between 55.3-55.4 ppm and aromatic carbons recorded the signal in the region δ 111.9-156.9 ppm. Other aromatic carbons were detected in expected regions. The IR spectra of 4a-4f exhibited for N-H a broad stretching was observed a common at 3327-3462 cm^{-1} which absorption band. The stretching band for C-N and C-C groups showed in the regions 1489-1614 cm^{-1}. Besides, absorption bands for a functional group like -NO_2 were also observed at 1516-1523 cm^{-1} and 1344-1348 cm^{-1}. Besides, the high-resolution mass spectrometry (HRMS) spectra of compounds 4a-4f confirmed the molecular weight of all compounds with their molecular formulas.

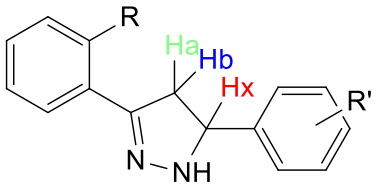

Figure 3. ABX system of pyrazoline ring

4. Conclusion

In the present study, six novel 3,5-diphenyl-4,5-dihydro-1H-pyrazole derivatives were synthesized from cyclization of substituted chalcones by intramolecular Michael addition, and chemical structures have been identified by ^{1}H NMR, ^{13}C NMR, FT-IR, and HRMS techniques. Furthermore, the reported derivatives bearing 3,5-diphenyl-4,5-dihydro-1H-pyrazole derivatives are biologically privileged scaffolds. The compounds can be considered for the development of novel bioactive molecules.

Acknowledgements

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