

One-pot and multi-step syntheses of new 2-(4,5-dihydro-1H-pyrazol-1-yl) thiazole derivatives

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Abstract: β -Ketoester and ethanone derivatives, potentially functional molecules, containing the pyrazole/thiazole scaffolds were synthesized. The structures of the synthesized novel compounds were confirmed by FTIR, ¹H NMR and ¹³C NMR spectroscopy and elemental analysis. The NMR spectra of the synthesized compounds are analyzed. Furthermore, ABX systems in pyrazole ring were studied in detail and the coupling constants of the diastereotopic protons.

Keywords: Pyrazole; thiazole; β -ketoester, ethanone; diastereotopic protons. ©2018 ACG Publication. All right reserved.

1. Introduction

Heterocyclic compounds contain at least two different elements in their cyclic structures. These compounds have received great interest in the design of pharmacologically active molecules and advanced organic materials¹⁻³. Among heterocyclic compounds, pyrazole and thiazole scaffolds are very popular because of their versatility in use. The pyrazole derivatives possess an extensive range of biological activities such as anxiolytic⁴, antimicrobial⁵, antihypertensive⁶, antiinflammatory⁷, antipyretic⁸, analgesic⁹, antioxidant¹⁰, anticancer¹¹, sodium channel blocker¹², antiviral¹³, antidepressant¹⁴ and antidiabetic activity¹⁵, while the thiazole derivatives which is found in the structure of many compounds naturally found in nature have antiinflammatory¹⁶, antibacterial¹⁷, antifungal¹⁸, antithrombotic¹⁹, antiHIV²⁰, antihypertensive²¹, hypnotic²², analgesic²³, neuroleptic²⁴, and antimalarial effects²⁵. Also, pyrazole and thiazole compounds having a five atomic ring structure are used in the synthesis of many condensed hetero structures. For example, some pyrazole and thiazole derivatives previously synthesized by our research group are seen in Figure 1²⁶⁻³⁰. These compounds are heterocyclic structures in which pyrazole and thiazole nuclei are integrated with acyl thiourea, benzoxazine, coumarin and benzodiazepine rings.

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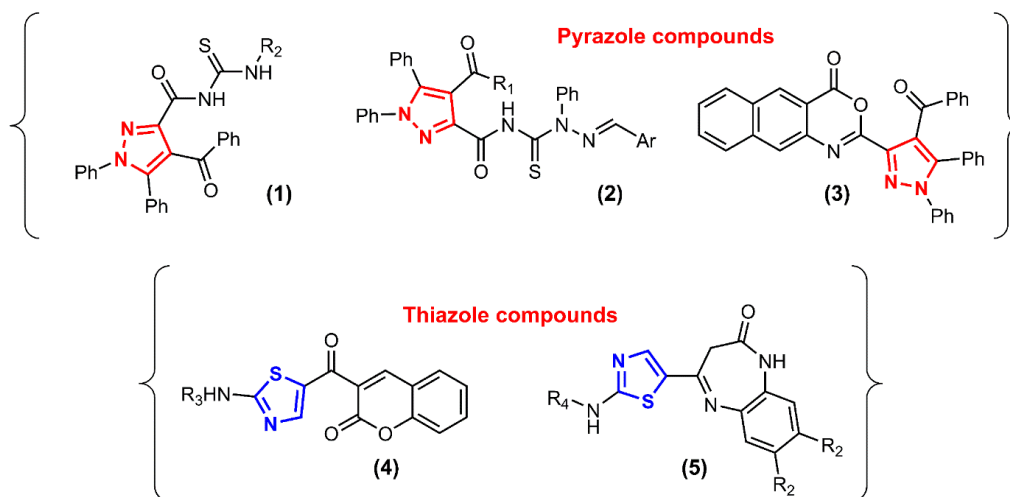


Figure 1. Some pyrazole and thiazole derivatives previously synthesized by our research group ²⁶⁻³⁰.

In this work, we achieved the synthesis and characterization studies about hybrid molecules that including pyrazole and thiazole rings. The molecular formulas of the synthesized compounds (**C1-C4**, **D1-D4**) are given in Figure 2.

The compounds **C** contain β -ketoester group. Also, these compounds are multi-coupling reagents containing both electrophilic carbonyl and nucleophilic carbon ³¹. The compounds **D** are ethanone derivatives which are containing acetyl groups and used as precursors in organic chemistry syntheses ³²⁻³⁴. Due to the above-mentioned reasons, the compounds **C** and **D** are an important reactive molecules for the synthesis and design of new the heterocyclic compounds. The structures of target compounds (**C**, **D**) were characterized by FT-IR, ¹H NMR, ¹³C NMR spectroscopy and elemental analysis techniques.

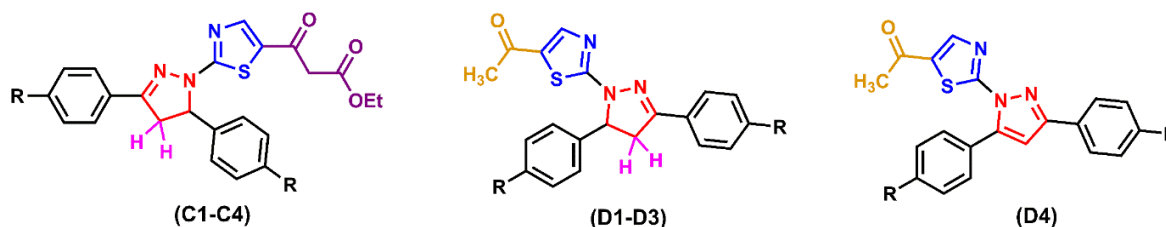


Figure 2. The molecular structures of the target compounds

2. Experimental

Solvents and all other chemical reagents were obtained from Merck and Sigma Aldrich, and were used without further purification. Melting points were determined in open capillary tubes on an Electrothermal 9200 melting point apparatus. FT-IR spectra were recorded in the spectral range of 4000–400 cm^{-1} with a Perkin Elmer Spectrum Two Model FT-IR Spectrometer using ATR method (Bozok University-Department of Chemistry). Elemental analyses were performed using Leco-932 CHNS-O Elemental Analyzer (Bozok University-Department of Chemistry). The ¹H NMR (300 or 400 MHz) and ¹³C NMR (75 or 100 MHz) were run on a Bruker Ultrashield NMR spectrometer using CDCl_3 and $\text{DMSO}-d_6$ as a solvent. All the ¹H NMR and ¹³C NMR experiments were reported in δ units, parts per million (ppm) relative to TMS as internal standard and coupling constants (*J*) were given in Hertz (Hz).

2.1. General Procedure for the Synthesis of Compound A

Starting compounds (**A**) were synthesized from the reaction of chalcones³⁵ (R= Ph, *p*-CH₃-C₆H₄, *p*-Cl-C₆H₄, *p*-OCH₃-C₆H₄) with thiosemicarbazide according to literature^{36,37}.

2.2. General Procedure for the Synthesis of Compound B

A mixture of the compound **A** (5 mmol) and dimethyl formamide dimethyl acetal (DMF-DMA) (6 mmol) in dichloromethane (40 mL) were refluxed for 6 h until the reaction was completed (followed by TLC). The solvent was removed under reduced pressure. Then, the obtained crude product was treated with diethyl ether. Yellow crude product which precipitated was filtered off and used directly without further purification for the next step reaction.

2.3. General Procedure for the Synthesis of Compound C

A mixture of the compound **B** (1 mmol) and ethyl 4-chloro-3-oxo butanoate (1.2 mmol) in ethanol (30 mL) was heated to boiling temperature and stirred for 7h. The solvent was removed under reduced pressure. Then, the obtained residue oil was treated with diethyl ether. Yellow crude product which precipitated was filtered off and purified by recrystallization from isopropyl alcohol to get compounds **C**.

2.3.1. Ethyl 3-(2-(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-5-yl)-3-oxopropanoate (C1): Color: Yellow, Yield 0.344 g, 82%, mp 158-159 °C, FT-IR (ATR, cm⁻¹): ν_{\max} 3093-3034 (Ar-H); 2989-2901 (aliphatic C-H), 1726 (C=O, ester); 1641 (C=O, ketone); 1566-1489 (C=N and C=C). ¹H-NMR (300 MHz; CDCl₃, ppm): δ 7.81 (s, CH, thiazole); 7.79-7.26 (m, 10H, Ar-H); 5.74-5.69 (dd, $J_{\text{trans}} = 5.0$ Hz, $J_{\text{cis}} = 11.7$ Hz, 1H, C₅H-pyrazole); 4.18 (q, $J = 7.1$ Hz, 2H, OCH₂CH₃); 4.01-3.91 (dd, $J_{\text{gem}} = 17.7$ Hz, $J_{\text{cis}} = 11.8$ Hz, 1H, C₄H-pyrazole); 3.74 (s, 2H, CH₂); 3.38-3.30 (dd, $J_{\text{gem}} = 17.7$ Hz, $J_{\text{trans}} = 5.1$ Hz, 1H, C₄H-pyrazole); 1.25 (t, $J = 7.1$ Hz, 3H, OCH₂CH₃). ¹³C-NMR (75 MHz; CDCl₃, ppm): δ 183.2 (C=O, ketone); 166.6 (C=O, ester); 161.3; 155.0; 148.9; 140.6; 130.7; 129.1; 128.9; 128.8; 128.2; 126.9; 126.8; 125.7 (C=C and C=N); 63.7 (C₅-pyrazole); 61.5 (OCH₂); 45.8 (CH₂); 43.9 (C₄-pyrazole); 14.1 (CH₃). Calcd. for C₂₃H₂₁N₃O₃S (419.50): C, 65.85; H, 5.05; N, 10.02; S, 7.64. Found: C, 65.94; H, 5.01; N, 9.78; S, 7.33 %.

2.3.2. Ethyl 3-(2-(3,5-dip-tolyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-5-yl)-3-oxopropanoate (C2): Color: Yellow, Yield 0.353 g, 79%, mp 145-146 °C, FT-IR (ATR, cm⁻¹): ν_{\max} 3092, 3030 (Ar-H); 2984-2868 (aliphatic C-H), 1741 (C=O, ester); 1635 (C=O, ketone); 1612-1500 (C=N and C=C). ¹H-NMR (300 MHz; CDCl₃, ppm): δ 7.81 (s, CH, thiazole); 7.67-7.15 (m, 8H, Ar-H); 5.68-5.62 (dd, $J_{\text{trans}} = 5.0$ Hz, $J_{\text{cis}} = 11.7$ Hz, 1H, C₅H-pyrazole); 4.18 (q, $J = 7.1$ Hz, 2H, OCH₂CH₃); 3.96-3.86 (dd, $J_{\text{gem}} = 17.6$ Hz, $J_{\text{cis}} = 11.7$ Hz, 1H, C₄H-pyrazole); 3.74 (s, 2H, CH₂); 3.33-3.26 (dd, $J_{\text{gem}} = 17.6$ Hz, $J_{\text{trans}} = 5.0$ Hz, 1H, C₄H-pyrazole); 2.40 and 2.32 (s, 6H, 2 x Ar-CH₃); 1.25 (t, $J = 7.1$ Hz, 3H, OCH₂CH₃). ¹³C-NMR (75 MHz; CDCl₃, ppm): δ 183.1 (C=O, ketone); 170.0 (C=O, ester); 167.2; 155.2; 149.1; 141.2; 137.9; 137.8; 129.8; 129.6; 129.4; 127.9; 126.8; 125.7 (C=C and C=N); 63.4 (C₅-pyrazole); 61.5 (OCH₂); 45.8 (CH₂); 44.0 (C₄-pyrazole); 21.6; 21.1 (2 x Ar-CH₃); 14.1 (CH₃). Calcd. for C₂₅H₂₅N₃O₃S (447.55): C, 67.09; H, 5.63; N, 9.39; S, 7.16. Found: C, 67.02; H, 5.33; N, 9.08; S, 7.40 %.

2.3.3. Ethyl 3-(2-(3,5-bis (4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-5-yl)-3-oxopropanoate (C3): Color: Yellow, Yield 0.346 g, 71%, mp 135-137 °C, FT-IR (ATR, cm⁻¹): ν_{\max} 3064-3003 (Ar-H); 2981-2936 (aliphatic C-H), 1737 (C=O, ester); 1642 (C=O, ketone); 1596-1487 (C=N and C=C). ¹H-NMR (300 MHz; CDCl₃, ppm): δ 7.79 (s, CH, thiazole); 7.69 (d, part A of the system AB, $J = 8.5$ Hz, 2H, H-2), 7.41 (d, part B of the system AB, $J = 8.5$ Hz, 2H, H-3), 7.32 (d, part A of the system AB, $J = 8.4$ Hz, 2H, H-3'), 7.21 (d, part B of the system AB, $J = 8.5$ Hz, 2H, H-2'); 5.71-5.65 (dd, $J_{\text{trans}} = 5.2$ Hz, $J_{\text{cis}} = 11.8$ Hz, 1H, C₅H-pyrazole); 4.19 (q, $J = 7.1$ Hz, 2H, OCH₂CH₃); 3.98-3.88 (dd, $J_{\text{gem}} = 17.7$ Hz, $J_{\text{cis}} = 11.8$ Hz, 1H, C₄H-pyrazole); 3.75 (s, 2H, CH₂); 3.30-3.22 (dd, $J_{\text{gem}} = 17.7$ Hz, $J_{\text{trans}} = 5.3$ Hz, 1H, C₄H-pyrazole); 1.25 (t, $J = 7.1$ Hz, 3H, OCH₂CH₃). ¹³C-NMR (75 MHz; CDCl₃, ppm): δ 183.3 (C=O, ketone); 170.0 (C=O, ester); 167.0; 153.7; 148.6; 139.0; 136.9; 134.1; 130.2;

129.4; 129.2; 128.9; 128.0; 127.2 (C=C and C=N); 63.3 (C₅-pyrazole); 61.6 (OCH₂); 45.8 (CH₂); 43.6 (C₄-pyrazole); 14.1 (CH₃). Calcd. for C₂₃H₁₉Cl₂N₃O₃S (488.39): C, 56.56; H, 3.92; N, 8.60; S, 6.57. Found: C, 56.23; H, 3.97; N, 8.62; S, 6.35 %.

2.3.4. Ethyl 3-(2-(3,5-bis(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-5-yl)-3-oxopropanoate (C4): Color: Yellow, Yield 0.354 g, 74%, mp 117-118 °C, FT-IR (ATR, cm⁻¹): ν_{max} 3074-2841 (Ar-H and aliphatic C-H); 1734 (C=O, ester); 1633 (C=O, ketone); 1607-1463 (C=N and C=C), 1248 (C-O). ¹H-NMR (400 MHz; CDCl₃, ppm): δ 7.83 (s, CH, thiazole); 7.73 (d, part A of the system AB, *J*=8.9 Hz, 2H, H-2), 7.22 (d, part A of the system AB, *J*=8.7 Hz, 2H, H-3'), 6.97 (d, part B of the system AB, *J*=8.9 Hz, 2H, H-3), 6.88 (d, part B of the system AB, *J*=8.7 Hz, 2H, H-2'); 5.67-5.62 (dd, *J*_{trans}= 4.9 Hz, *J*_{cis}= 11.6 Hz, 1H, C₅H-pyrazole); 4.20 (q, *J*=7.1 Hz, 2H, OCH₂CH₃); 3.96-3.86 (dd, *J*_{gem}= 17.6 Hz, *J*_{cis}= 11.6 Hz, 1H, C₄H-pyrazole); 3.76 (s, 2H, CH₂); 3.34-3.26 (dd, *J*_{gem}= 17.6 Hz, *J*_{trans}= 4.9 Hz, 1H, C₄H-pyrazole); 1.27 (t, *J*=7.1 Hz, 3H, OCH₂CH₃). ¹³C-NMR (100 MHz; DMSO-*d*₆, ppm): δ 184.3 (C=O, ketone); 169.1 (C=O, ester); 168.0; 161.8; 159.2; 157.1; 151.1; 133.5; 129.2; 128.8; 127.7; 123.2; 114.9; 114.6 (C=C and C=N); 63.2 (C₅-pyrazole); 61.1 (OCH₂); 55.9 and 55.5 (2 x OCH₃); 45.1 (CH₂); 44.1 (C₄-pyrazole); 14.4 (CH₃). Calcd. for C₂₅H₂₅N₃O₅S (479.55): C, 62.61; H, 5.25; N, 8.76; S, 6.69. Found: C, 62.44; H, 5.37; N, 8.83; S, 6.51 %.

2.4. General Procedure for the Synthesis of Compound D

The solution of compounds **C** (1 mmol) in acetic acid (25 mL) was refluxed for 24h. After the solvent was removed under reduced pressure, the residue was treated with the diethyl ether to give crude product as a yellow solid. The crude product which precipitated was filtered off and purified by recrystallization from *n*-butanol to get compounds **D**.

2.4.1. 1-(2-(3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)thiazol-5-yl)ethanone (D1): Color: Yellow, Yield 0.291 g, 84%, mp 227-228 °C, FT-IR (ATR, cm⁻¹): ν_{max} 3053-2848 (Ar-H and aliphatic C-H); 1626 (C=O, ketone); 1594-1489 (C=N and C=C). ¹H-NMR (400 MHz; DMSO-*d*₆, ppm): δ 8.03 (s, CH, thiazole); 7.83-7.10 (m, 10H, Ar-H); 5.79-5.74 (dd, *J*_{trans}= 5.0 Hz, *J*_{cis}= 11.7 Hz, 1H, C₅H-pyrazole); 4.13-4.06 (dd, *J*_{gem}= 18.1 Hz, *J*_{cis}= 11.8 Hz, 1H, C₄H-pyrazole); in DMSO-*d*₆ (dd, 1H, C₄H-pyrazole); 2.36 (s, 3H, COCH₃). ¹³C-NMR (100 MHz; DMSO-*d*₆, ppm): δ 189.6 (C=O, ketone); 168.8 (C=N, thiazole); 156.4; 149.4; 141.6; 131.2; 130.8; 130.4; 129.4; 129.3; 128.1; 127.3; 126.3 (C=C and C=N); 63.8 (C₅-pyrazole); 44.0 (C₄-pyrazole); 26.3 (CH₃). Calcd. for C₂₀H₁₇N₃OS (347.43): C, 69.14; H, 4.93; N, 12.09; S, 9.23. Found: C, 69.28; H, 4.99; N, 12.26; S, 9.37 %.

2.4.2. 1-(2-(3,5-dip-tolyl-4,5-dihydro-1H-pyrazol-1-yl)thiazol-5-yl)ethanone (D2): Color: Yellow, Yield 0.285 g, 76%, mp 257-258 °C, FT-IR (ATR, cm⁻¹): ν_{max} 3033-2918 (Ar-H and aliphatic C-H); 1631 (C=O, ketone); 1593-1502 (C=N and C=C). ¹H-NMR (300 MHz; CDCl₃, ppm): δ 7.75 (s, CH, thiazole); 7.66-7.15 m, 8H, Ar-H); 5.67-5.62 (dd, *J*_{trans}= 5.1 Hz, *J*_{cis}= 11.8 Hz, 1H, C₅H-pyrazole); 3.95-3.85 (dd, *J*_{gem}= 17.6 Hz, *J*_{cis}= 11.7 Hz, 1H, C₄H-pyrazole); 3.32-3.24 (dd, *J*_{gem}= 17.6 Hz, *J*_{trans}= 5.1 Hz, 1H, C₄H-pyrazole); 2.40 (s, 6H, Ar-CH₃), 2.31 (s, 3H, COCH₃). ¹³C-NMR (75 MHz; CDCl₃, ppm): δ 189.4 (C=O, ketone); 169.7 (C=N, thiazole); 154.6; 147.9; 141.0; 137.9; 137.8; 130.6; 129.7; 129.5; 128.0; 126.7; 125.7 (C=C and C=N); 63.4 (C₅-pyrazole); 44.0 (C₄-pyrazole); 26.0 (-COCH₃); 21.5 and 21.1 (2x Ar-CH₃). Calcd. for C₂₂H₂₁N₃OS (375.49): C, 70.37; H, 5.64; N, 11.19; S, 8.54. Found: C, 70.62; H, 5.46; N, 11.50; S, 8.69 %.

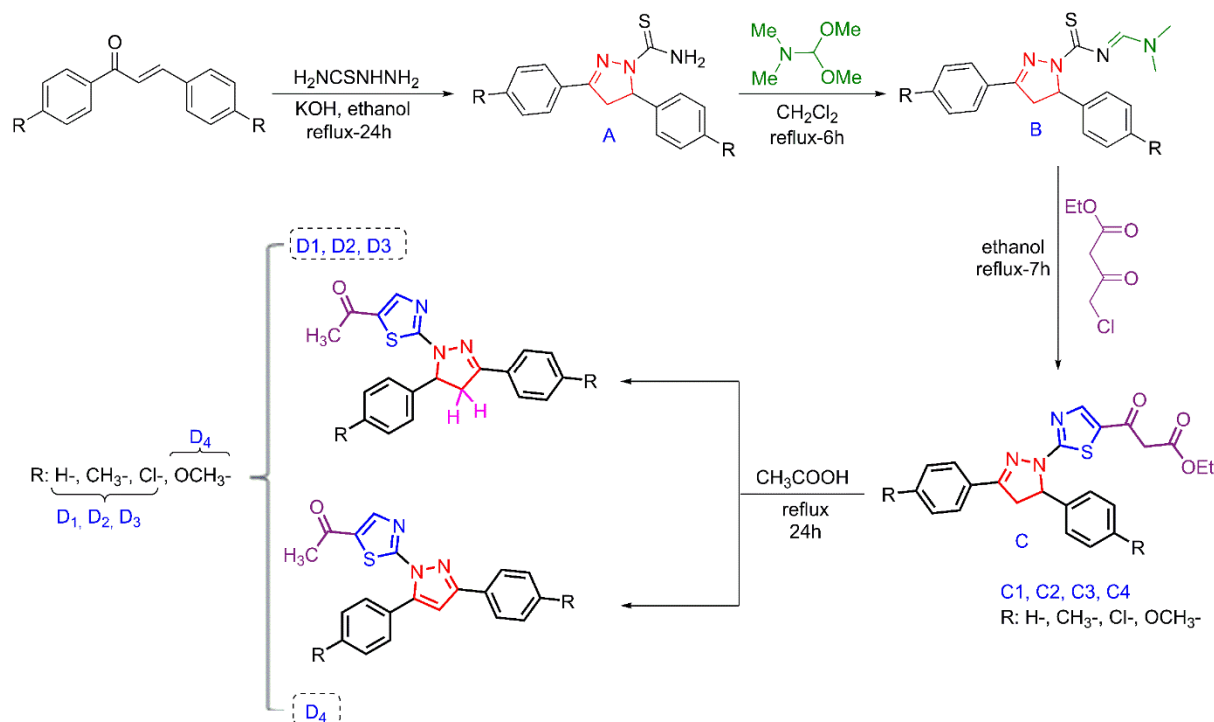
2.4.3. 1-(2-(3,5-bis(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-5-yl)ethanone (D3): Color: Yellow, Yield 0.308 g, 74%, mp 260-261 °C, FT-IR (ATR, cm⁻¹): ν_{max} 3065-2935 (Ar-H and aliphatic C-H); 1631 (C=O, ketone); 1598-1486 (C=N and C=C). ¹H-NMR (400 MHz; CDCl₃, ppm): δ 7.76 (s, CH, thiazole); 7.71-7.21 (m, 8H, Ar-H); 5.72-5.66 (dd, *J*_{trans}= 5.3 Hz, *J*_{cis}= 11.9 Hz, 1H, C₅H-pyrazole); 3.98-3.88 (dd, *J*_{gem}= 17.6 Hz, *J*_{cis}= 11.9 Hz, 1H, C₄H-pyrazole); 3.30-3.23 (dd, *J*_{gem}= 17.6 Hz, *J*_{trans}= 5.4 Hz, 1H, C₄H-pyrazole); 2.43 (s, 3H, Ar-CH₃). ¹³C-NMR (100 MHz; DMSO-*d*₆, ppm): δ 189.7 (C=O, ketone); 168.7 (C=N, thiazole); 155.4; 149.3; 140.5; 135.7; 132.7; 130.7; 129.7; 129.5; 129.2; 129.0; 128.5 (C=C and C=N); 63.4 (C₅-pyrazole); 43.7 (C₄-pyrazole); 26.4 (CH₃). Calcd. for

$C_{22}H_{21}N_3OS$ (416.32): C, 57.70; H, 3.63; N, 10.09; S, 7.70. Found: C, 57.74; H, 3.36; N, 10.28; S, 7.78 %.

2.4.4. 1-(2-(3,5-bis(4-methoxyphenyl)-1*H*-pyrazol-1-yl) thiazol-5-yl)ethanone (**D4**): Color: Yellow, Yield 0.275 g, 68%, mp 167-168 °C, FT-IR (ATR, cm^{-1}): ν_{max} 3112-2839 (Ar-H and aliphatic C-H); 1650 (C=O, ketone); 1614-1455 (C=N and C=C), 1252 (C-O). 1H -NMR (400 MHz; $CDCl_3$, ppm): δ 7.91 (s, 1H, CH-thiazole), 6.68 (s, 1H, CH-pyrazole), 7.87-6.95 (m, 8H, Ar-H), 3.88 and 3.87 (s, 6H, 2 x OCH_3), 2.52 (s, 3H, $COCH_3$). ^{13}C -NMR (100 MHz; $DMSO-d_6$, ppm): δ 191.2 (C=O, ketone); 166.0; 160.6; 160.4; 154.0; 147.4; 146.3; 137.2; 131.4; 127.9; 123.8; 122.0; 114.8; 113.9; 109.4; 55.7 (2 x OCH_3); 27.0 ($COCH_3$). Calcd. for $C_{22}H_{19}N_3O_3S$ (405.47): C, 65.17; H, 4.72; N, 10.36; S, 7.91. Found: C, 65.02; H, 4.85; N, 10.46; S, 8.19 %.

3. Results and Discussion

We report here the synthesis and characterization of novel β -ketoester (**C**) and ethanone derivatives (**D**) containing pyrazole and thiazole rings which are not previously described in the literature. The target compounds (**C**, **D**) were synthesized starting from chalcones as shown in the Scheme 1.

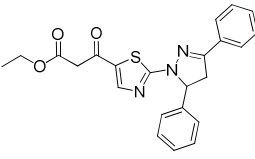
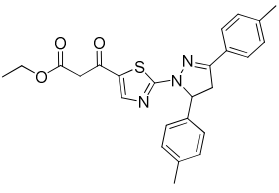
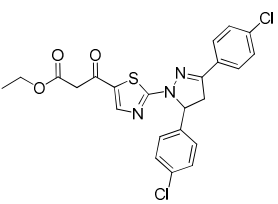
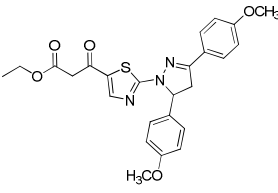


Scheme 1. Synthesis of β -ketoester (**C**) and ethanone (**D**) compounds

While β -ketoester derivatives (**C**) were obtained in a three-steps, ethanone derivatives (**D**) were obtained in the fourth steps by the sequential reaction of compounds **C** as shown in Scheme 1. In the first step, the pyrazole derivatives (**A**) known in the literature were synthesized by reaction of chalcone derivatives with thiosemicarbazide³⁷. These pyrazole derivatives (**A**) contain a thioamide group. Accordingly, the compounds **A** are analogous to a certain thiourea derivative compounds. In a previous work²⁸, thiazolyl- β -ketoester compounds were synthesized by a two step reaction using thiourea derivatives by our group. In this work, pyrazole and thiazole scaffolds were integrated by this method we described earlier. In the second step, the compounds **A** were reacted with *N,N*-Dimethylformamide dimethyl acetal (DMF-DMA) to give dimethylamino imine derivatives (**B**). This reaction was carried out at the boiling point of dichloromethane for 6 hours. In the third step, the compounds **B** were refluxed with ethyl 4-chloro-3-oxobutanoate in ethanol for 7 hours. After

completion of the reaction (checked by TLC), novel β -ketoester compounds containing pyrazole and thiazole rings (**C**) were obtained with reaction yields varying from 82% to 71%. (Table 1). Some properties of four novel β -ketoester compounds (**C1-C4**) are given in the Table 1.

Table 1. Some properties of newly synthesized compounds **C**^{a,b,c}

			
C1 , 82%; 158-159 °C	C2 , 79%; 145-146 °C	C3 , 71%; 135-137 °C	C4 , 74%, 117-118 °C

^aReaction conditions: **B** (1.00 mmol), ethyl 4-chloro-3-oxo butanoate (1.20 mmol), Solvent: ethanol, 7h reflux

^bIsolated yields are shown.

^cMelting points are shown.

The structures of the compounds **C** were confirmed by its elemental analyses and spectroscopic data (FTIR, ¹H and ¹³C NMR). There are two carbonyl groups due to the β -ketoester group in these compounds. Because of these ketone and ester groups have different electronic environment, the infrared spectrums are quite distinctive for determination of these groups. For example, the compound **C2** showed absorption bands at 1741, 1635 cm⁻¹ and in the range of 3092-2868 cm⁻¹ due to ester, ketone groups and aromatic- aliphatic C-H bonds, respectively. In addition, the FTIR spectrum of this compound presented C=N and C=C stretching bands in the range of 1612-1500 cm⁻¹.

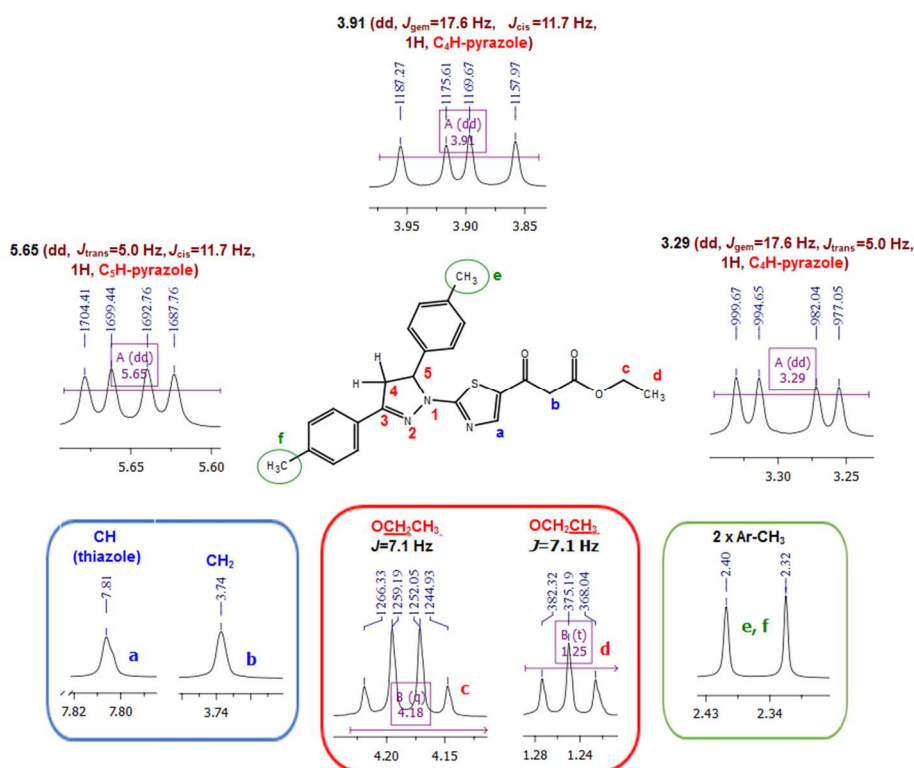
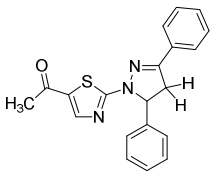
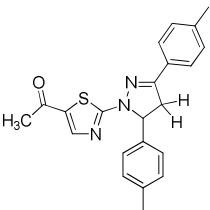
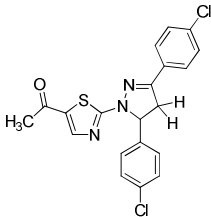
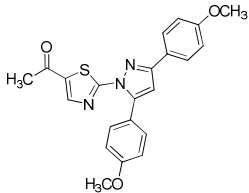


Figure 3. Elucidation of the structure of **C2** with ¹H NMR

The ^1H NMR spectrum of **C2** was recorded in CDCl_3 . In this spectra, the signal of CH proton on the thiazole ring was observed at 7.81 ppm as singlet as shown in Figure 3. In the ^1H NMR spectrum of this compound gave multiplet signal belonging eight of aromatic CH protons in the range of 7.67-7.15 ppm. The ^1H NMR spectrum of **C2** revealed the methylene protons of ethoxy group at 4.18 ppm ($J=7.1$ Hz) as quartet. Characteristic ABX system as three dd, belonging to aliphatic protons of pyrazole ring of **C2** were seen in the range of 5.68-5.62, 3.96-3.86 and 3.33-3.26 ppm. Also the two methyl groups (Ar-CH_3) arised at 2.40 and 2.32 ppm as singlet and the methyl protons of ethoxy group resonated at 1.25 ppm ($J=7.1$ Hz) as triplet signal. In ^{13}C NMR spectrum of **C2**, the signals of ketone and ester groups were observed at 183.1 and 170.0 ppm, respectively. The signals of $\text{C}=\text{C}$ and $\text{C}=\text{N}$ groups belonging to twelve carbon atoms appeared at 167.2-125.7 ppm. The C_5 and C_4 carbons of the pyrazole ring resonated at 63.4 and 44.0 ppm, respectively. While the signals of ethoxy group appeared at 61.5 and 14.1 ppm, the active methylene carbon of β -keto ester group was observed at 45.8 ppm. Besides, the signals of two Ar-CH_3 groups observed at 21.6 and 21.1 ppm. The spectroscopic data of the compounds **C** can be viewed in experimental part and supplementary file.

As shown in Scheme 1, in the last step, β -ketoester derivatives (**C1-C4**) were converted into the corresponding ethanone derivatives (**D1-D4**) containing pyrazole and thiazole scaffolds through the acidic hydrolysis reaction. This reaction was carried out in acetic acid at the boiling temperature for 24 hours. The reaction yields ranged from 68% to 84%. Some properties of four novel ethanone compounds (**D**) are given in the Table 2.

Table 2. Some properties of newly synthesized compounds **D**^{a,b,c}

			
D1 , 84%; 226-227 °C	D2 , 76%; 257-258 °C	D3 , 74%; 260-261 °C	D4 , 68%, 167-168 °C

^aReaction conditions: **C** (1.00 mmol), Solvent: acetic acid, 24h reflux

^bIsolated yields are shown.

^cMelting points are shown.

Looking at Table 2, it appears that the compound **D4** is different from the other ethanone derivatives. In the compounds **D1**, **D2** and **D3**, there are diastereotopic protons in pyrazole ring. These protons have a different chemical environment because the adjacent carbon atom (C_5 -pyrazole) is the chiral center. Hence, these protons signal in different areas in the form of doublet of doublet in ^1H NMR analyzes^{38, 39}. Compound **D4** does not also contain diastereotopic protons in pyrazole ring. For this reason, the pyrazole scaffold in this compound has acquired aromaticity. This situation is easily seen at ^1H NMR analyzes (Figure 4). When the ethanone derivatives (**D**) were synthesized from the β -ketoester compounds (**C**), the ester group disappeared. This condition was very easily diagnosed by FT-IR analysis. There is one carbonyl group due to the ketone group in the compounds **D**. For example, the compound **D2** showed absorption bands at 1631 cm^{-1} and in the range of $3033\text{-}2918\text{ cm}^{-1}$ due to ketone group and aromatic-aliphatic CH bonds, respectively. In addition, the FTIR spectrum of this compound presented $\text{C}=\text{N}$ and $\text{C}=\text{C}$ stretching bands in the range of $1593\text{-}1502\text{ cm}^{-1}$. The ^1H NMR and ^{13}C NMR spectrums of **D2** were recorded in $\text{DMSO-}d_6$. In the ^1H NMR spectra, the signal of CH proton on the thiazole ring was observed at 7.75 ppm as singlet. Compound **D2** gave multiplet signal belonging eight of aromatic CH protons in the range of 7.66-7.15 ppm. H_{4a} , H_{4b} and H_5 of pyrazole ring gave an typical ABX system as three dd. A singlet signal arised at 2.40 pmm due to two methyl group protons attached to the aromatic ring (CH_3). Also, the signal of methyl protons attached to the carbonyl group ($-\text{COCH}_3$) was observed at 2.31 ppm as singlet. The ethoxy group is removed from the structure, while β -ketoester compounds (**C**) are converted into ethanone derivatives (**D**). This is evidenced by the disappearance of triplet and quadruple splits of the ethyl group in the synthesized

compounds **D**. The ^1H NMR data of the compounds **D1**, **D2** and **D3** containing diastereotopic protons are compatible with each other. J values (J_{gem} , J_{trans} , J_{cis}) of these compounds are given in the Table 3. In the ^{13}C NMR spectrum of **D2** was observed the signal of ketone group at 189.4 ppm. The signals of $\text{C}=\text{C}$ and $\text{C}=\text{N}$ groups belonging to twelve carbon atoms appeared in the range of 169.7 -125.7 ppm. In the ^{13}C NMR spectra, the C_5 and C_4 carbons of the pyrazole ring resonated at 63.4 and 44.0 ppm, respectively. Also, the signals of methyl group attached to the carbonyl group ($-\text{COCH}_3$) and two methyl groups attached to the aromatic ring ($2 \times \text{CH}_3$) appeared at 26.0, 21.5 and 21.1 ppm, respectively. In the compounds **D**, the signals of the carbon atoms of the ethyl group and the active methylene group are not observed in ^{13}C NMR analysis.

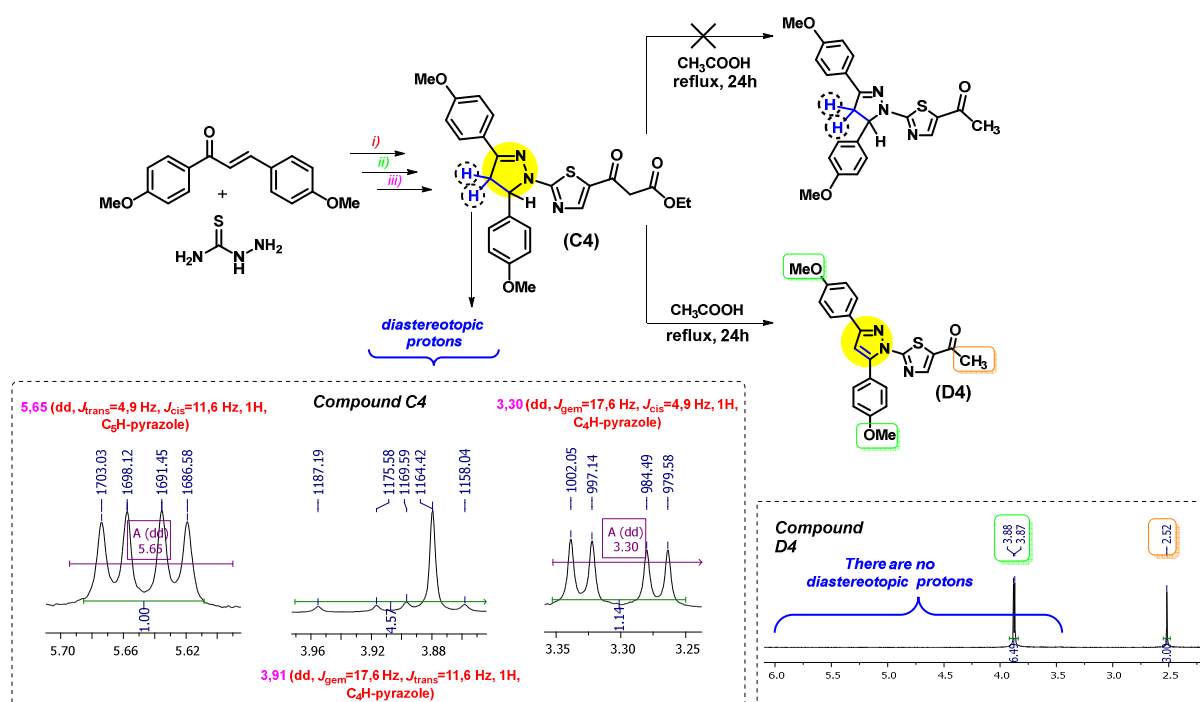


Figure 4. Definition of the diastereotopic protons in the synthesis of the compounds **C4** and **D4**

Table 3. J values of diastereotopic protons (Hz) in the compounds **D1**, **D2** and **D3**

Title	Molecular structure	C_5H -pyrazole (1H)	C_4H -pyrazole (1H)	C_4H -pyrazole (1H)
D1		5,77 (dd, $J_{\text{trans}}=5,0$ Hz, $J_{\text{cis}}=11,7$ Hz)	4,10 (dd, $J_{\text{gem}}=18,1$ Hz, $J_{\text{cis}}=11,8$ Hz)	in DMSO- d_6 (dd, 1H, C_4H -pyrazole)
D2		5,65 (dd, $J_{\text{trans}}=5,1$ Hz, $J_{\text{cis}}=11,8$ Hz)	3,90 (dd, $J_{\text{gem}}=17,6$ Hz, $J_{\text{cis}}=11,7$ Hz)	3,28 (dd, $J_{\text{gem}}=17,6$ Hz, $J_{\text{trans}}=5,1$ Hz)
D3		5,69 (dd, $J_{\text{trans}}=5,3$ Hz, $J_{\text{cis}}=11,9$ Hz)	3,93 (dd, $J_{\text{gem}}=17,6$ Hz, $J_{\text{cis}}=11,9$ Hz)	3,26 (dd, $J_{\text{gem}}=17,6$ Hz, $J_{\text{trans}}=5,4$ Hz)

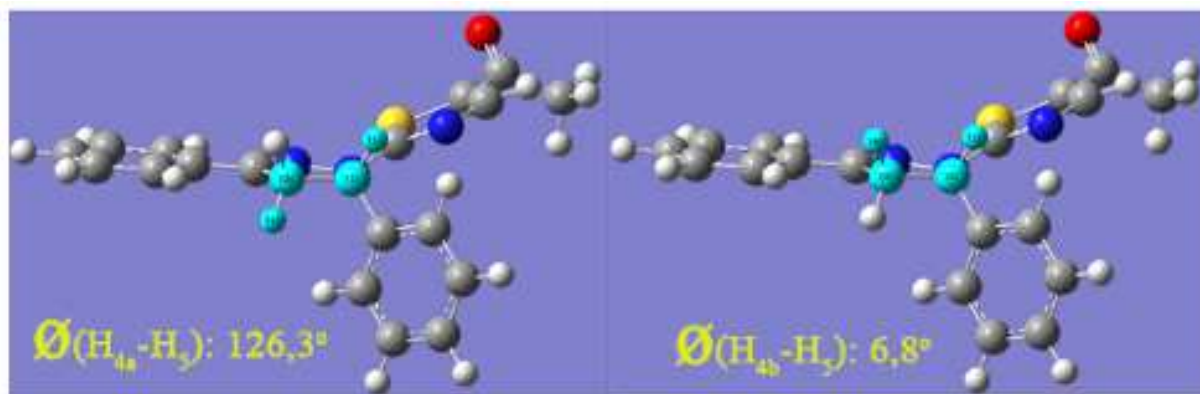
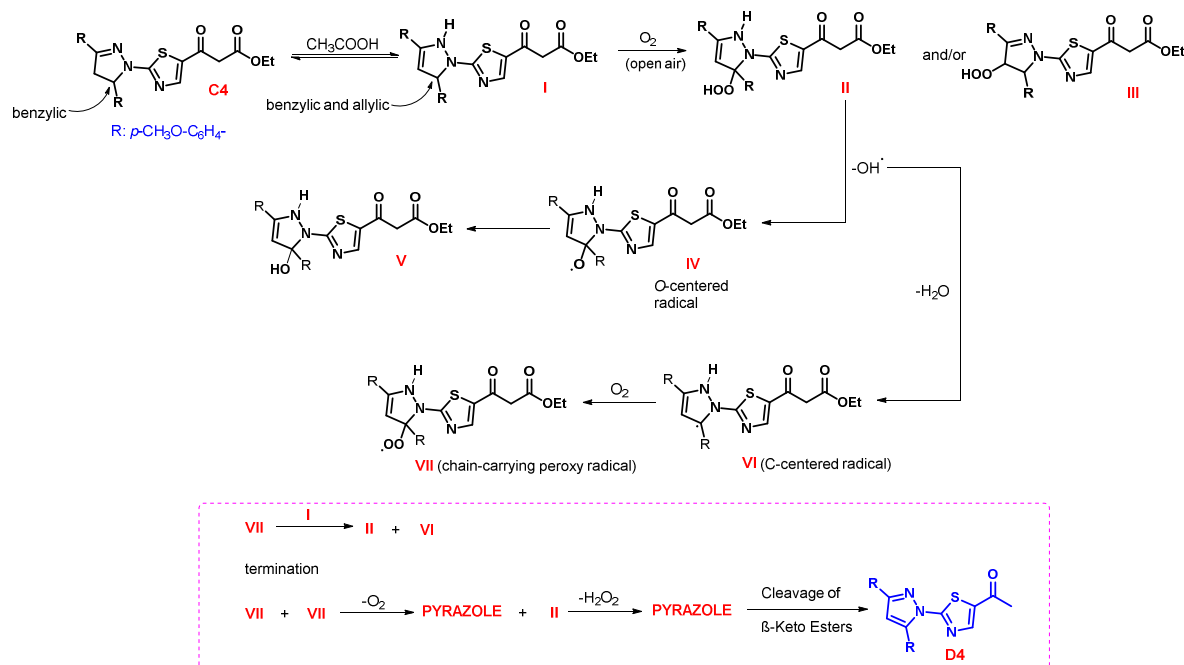


Figure 5. Optimized structure of **D1** calculated by Gaussian 03 software ⁴⁰.

We calculated the optimized structure of **D1** by Gaussian 03 software ⁴⁰ (Figure 4). It easily seen that from the Figure 5, dihedral angle of H_{4a}-H₅ is 126.3° and H_{4b}-H₅ is 6.8°. The relationship between the dihedral angle (ϕ) of the groups in the compounds and the coupling constant ($^3J_{H-H}$) is expressed by Martin Karplus ^{41,42}. According to Karplus curve, J_{cis} vicinal proton-proton coupling constants is higher than J_{trans} in our synthesized compound.

Experimental conditions are completely identical in the synthesis of ethanone derivatives (**D1-D4**) from β -ketoester compounds (**C1-C4**). However, the synthesized compound **D4** differs from the compounds **D1**, **D2** and **D3**. This situation is thought to originate from the starting compounds **C**. Looking at the compounds **C1-C4**, there are four different substituent groups in the aromatic rings attached to the pyrazole scaffold. These are the groups H, CH₃, Cl and OCH₃, respectively. When looking at the compound **C4**, there is a methoxy group which is *p*-substituted group. While the methoxy group increases the electron density of the ring aromatic more than H and CH₃, the chlorine group reduces the electron density of the aromatic ring ⁴³.



Scheme 2. A suggested mechanism for the formation of **D4**

The reaction was accomplished under open air condition. The presence of the methoxy group allows the aerobic oxidation of the pyrazole ring to elimination. The reaction proceeded via a

mechanism which proposed by Jin Yu et al.⁴⁴. Furthermore, the aromatic structure (**D4**) is a more stable form than the pyrazoline ring.

4. Conclusion

We herein developed a simple method for the synthesis of novel hybrid compounds containing pyrazole and thiazole ring giving excellent yields of the products (68-84%) under reflux conditions. Structures of the synthesized compounds were confirmed through elemental analysis, FTIR and NMR techniques. These compounds are important reactive molecules that can be used in the synthesis of new heterocyclic compounds with their functional groups. While the compounds **C** contain a ketoester group, the compounds **D** are a derivative of ethanone containing acetyl group. Therefore, β -ketoester compounds (**C**) are important compounds used in ring closure reactions. The compounds also can react in a number of ways via the methyl group. It is also an advantage that the target molecules contain biologically active pyrazole and thiazole scaffolds. As a result, the compounds **C** and **D** which are novel and functional molecules can be used easily through continued reactions in the synthesis and design of new biologically active compounds.

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Supporting Information

Supporting information accompanies this paper on <http://www.acgpubs.org/OC>

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References

- [1] Martins, P.; Jesus, J.; Santos, S.; Raposo, L. R.; Roma-Rodrigues, C.; Baptista, P. V; Fernandes, A. R., Heterocyclic anticancer compounds: recent advances and the paradigm shift towards the use of nanomedicine's tool box. *Molecules* **2015**, *20*, 16852-16891.
- [2] Mukhtyar, S. S.; Aran, K.; Jaya, D.; Rakesh, S. A Review; Biological significances of heterocyclic compounds. *Inter. J. Pharma Sci. Res.* **2013**, *4*, 66-77.
- [3] Sobhi, M. G.; Khaled, K.; Hassan, A.; Mohamed, A. Synthesis and antihypertensive α -blocking activity evaluation of thiazole derivatives bearing pyrazole moiety. *Heterocycles* **2015**, *91*, 1763-1773.

- [4] Brito, A. F.; Fajemiroye, J. O.; Neri, H. F. S.; Silva, D. M.; Silva, D. P. B.; Sanz, G.; Vaz, B. G.; De Carvalho, F. S.; Ghedini, P. C.; Liao, L. M.; Menegatti, R.; Costa, E. A.; Anxiolytic-like effect of 2-(4-((1-phenyl-1*H*-pyrazol-4-yl)methyl)piperazin-1-yl)ethan-1-ol is mediated through the benzodiazepine and nicotinic pathways. *Chem. Biol. Drug Des.* **2017**, *90*(3), 432-442.
- [5] Demir, G.; Gürdere, M. B.; Ceylan, M.; Budak, Y. Synthesis and anti-bacterial activity of novel 1,3-phenylene-bis-*N*-acetyl- and *N*-phenylpyrazole derivatives. *Org. Commun.*, **2017**, *10*(2), 90-98.
- [6] Khan M. F.; Alam M. M.; Verma G.; Akhtar W.; Akhter M.; Shaquiquzzaman M. The therapeutic voyage of pyrazole and its analogs: A review. *Eur. J. Med. Chem.*, **2016**, *120*(14), 170-201.
- [7] Samir M. E.; Flora F. B.; Hamdy, M. A.; Adel, A.M. Synthesis and anti-inflammatory activity of some pyrazole derivatives. *Med. Chem. Res.* **2012**, *21*, 1722-1733.
- [8] Malvar, D. C.; Ferreira, R. T.; De Castro, R. A.; De Castro, L. L.; Freitas, A. C. C.; Costa, E. A.; Florentino, I. F.; Mafra, J. C.-; De Souza, Gloria E. P.; Vanderlinde, Frederico A. Antinociceptive, anti-inflammatory and antipyretic effects of 1,5-diphenyl-1*H*-Pyrazole-3-carbohydrazide, a new heterocyclic pyrazole derivative. *Life Sci.* **2014**, *95*, 81-88.
- [9] Alam, M. J.; Alam, O.; Khan S. A.; Naim, M. J.; Islamuddin, M.; Deora, G. S. Synthesis, anti-inflammatory, analgesic, COX1/2-inhibitory activity, and molecular docking studies of hybrid pyrazole analogues. *Drug Des. Dev. Ther.* **2016**, *10*, 3529-3543.
- [10] Abrigach, F.; Khoutoul, M.; Merghache, S.; Oussaid, A.; Lamsayah, M.; Zarrouk, A.; Benchat, N.; Touzani, R. Antioxidant activities of *N*-((3,5-dimethyl-1*H*-pyrazol-1-yl)methyl)pyridin-4- amine derivatives. *Pharma Chem.* **2014**, *6*, 280-285.
- [11] Nitulescu, G. M.; Draghici, C.; Missir, A. V. Synthesis of new pyrazole derivatives and their anticancer evaluation. *Eur. J. Med. Chem.* **2010**, *45*, 4914-4919.
- [12] Tyagarajan, S.; Chakravarty, P. K.; Zhou, B.; Taylor, B.; Fisher, M. H.; Wyvratt, M. J.; Lyons, K.; Klatt, T.; Li, X.; Kumar, S.; Williams, B.; et. al. Substituted biaryl pyrazoles as sodium channel blockers. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5480-5483.
- [13] Aymn E. R., Mohamed, I. H, Randa, E. A., Jehan, A., Farouk, M. E. A. Synthesis and antiviral evaluation of some new pyrazole and fused pyrazolopyrimidine derivatives. *Bioorg. Med. Chem.* **2008**, *16*, 7102-7106.
- [14] Naim, M. J.; Alam, O.; Nawaz, F.; Alam, M. J.; Alam, P. Current status of pyrazole and its biological activities. *J. Pharm. Bioallied Sci.* **2016**, *8*(1), 2-17.
- [15] Datar, P. A.; Jadhav, S. R. Design and synthesis of pyrazole-3-one derivatives as hypoglycaemic agents. *Int. J. Med. Chem.* **2015**, *2015*, 670181, 10 pages.
- [16] Deb, P. K.; Kaur, R.; Chandrasekaran, B.; Bala, M.; Gill, D.; Kaki, V. R.; Akkinepalli, R. R.; Mailavaram, R. Synthesis, anti-inflammatory evaluation, and docking studies of some new thiazole derivatives. *Med. Chem. Res.* **2014**, *23*, 2780-2792.
- [17] Khalil, A. M.; Berghot, M. A.; Gouda; M. A. Synthesis and antibacterial activity of some new thiazole and thiophene derivatives. *Eur. J. Med. Chem.* **2009**, *44*, 4434-4440.
- [18] Song, Y. L.; Liu, X. M.; Yang, N.; Yang, G. L. Synthesis and antifungal activity of some thiazole derivatives. *Asian J. Chem.* **2013**, *25*, 1849-1852.
- [19] Wong, P. C.; Pinto, D. J. P.; Knabb, R. M. Nonpeptide factor Xa inhibitors: DPC423, a highly potent and orally bioavailable pyrazole antithrombotic agent. *Cardiovasc. Drug Rev.* **2002**, *20*, 137-152.
- [20] Khan, M. H.; Hameed, S.; Akhtar, T.; Al-Masoudi, N. A.; Al-Masoudi, W. A.; Jones, P. G.; Pannecouque, C. Synthesis, crystal structure, anti-HIV, and antiproliferative activity of new oxadiazole and thiazole analogs. *Med. Chem. Res.* **2016**, *25*, 2399-2409.
- [21] Rouf, A.; Tanyeli, C.. Bioactive thiazole and benzothiazole derivatives. *Eur. J. Med. Chem.* **2015**, *97*, 911-927.
- [22] Ergenç, N.; Capan G.; Günay, N. S; Ozkirimli, S.; Güngör, M.; Ozbey, S.; Kendi, E. Synthesis and hypnotic activity of new 4-thiazolidinone and 2-thioxo-4,5-imidazolidinedione derivatives. *Arch. Pharm. (Weinheim)* **1999**, *332*, 343-347.

- [23] Thore, S. N.; Gupta, S. V.; Baheti, K. G. Docking, synthesis, and pharmacological investigation of novel substituted thiazole derivatives as non-carboxylic, anti-inflammatory, and analgesic agents. *Med. Chem. Res.* **2013**, *22*, 3802-3811.
- [24] Hirota, S.; Kawashima, N.; Chaki, S.; Okuyama, S. Neuropharmacological profile of an atypical antipsychotic, NRA0562. *CNS Drug Rev.* **2003**, *9*, 375-388.
- [25] Bueno, J. M.; Carda, M.; Crespo, B.; Cunat, A. C.; De Cozar, C.; Leon, M. L.; Marco, J. A.; Roda, N.; Sanz-Cervera, J. F. Design, synthesis and antimalarial evaluation of novel thiazole derivatives. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3938-3944.
- [26] Gümüş, M.; Özgür, A.; Tutar, L.; Dişli, A.; Koca, İ.; Tutar, Y. Design, synthesis, and evaluation of heat shock protein 90 inhibitors in human breast cancer and its metastasis. *Current Pharm. Biotechnol.* **2016**, *17*, 1231-1245.
- [27] Koca, İ.; Gümüş, Mehmet; Gökbas, L.; Er, M. One-pot synthesis of pyrazole ring attached novel thiosemicarbazone derivatives. *Phospho. Sulfur* **2015**, *190*, 1489-1497.
- [28] Koca, İ.; Gümüş, M.; Özgür, A.; Dişli, A.; Tutar, Y. A novel approach to inhibit heat shock response as anticancer strategy by coumarine compounds containing thiazole skeleton. *Anti-Cancer Agents Med. Chem.* **2015**, *15*, 916-930.
- [29] Koca, İ.; Özgür, A.; Coskun, K. A.; Tutar, Y. Synthesis and anticancer activity of acyl thioureas bearing pyrazole moiety. *Bioorg. Med. Chem.* **2013**, *21*, 3859-3865
- [30] Sert, Y.; Gümüş, M.; Kamacı, V.; Gökçe, H.; Kani, İ.; Koca, İ. Spectroscopic investigation of 2-(4-Benzoyl-1,5-Diphenyl-1H-Pyrazol-3-yl)-4H-Naphto[2,3-d][1,3] oxazin-4-one molecule. *J. Theo. Comp. Chem.* **2017**, *16*, 1750039, 22 pages.
- [31] Chang, M. Q.; Gao, F.; Li, Y.; Gao, W. T. Synthesis and keto-enol tautomerism of ethyl 4-oxo-3,4-dihydro-1H-pyrano[3,4-b]quinoline-3-carboxylate. *Chem. Pap.* **2013**, *67*, 437-443.
- [32] Bain, R.-M.; Pulliam, C. J.; Raab, S. A.; Cooks, R. G. Chemical synthesis accelerated by paper spray: The haloform reaction. *J. Chem. Edu.* **2016**, *93*, 340-344.
- [33] Baruah, B.; Dasu, K.; Vaitilingam, B.; Vanguri, A.; Casturi, S. R.; Yeleswarapu, K. R. 1,2-Diaryl-1-ethanone and pyrazolo [4,3-c] quinoline-4-one as novel selective cyclooxygenase-2 inhibitors. *Bioorgan. Med. Chem. Lett.* **2004**, *14*, 445-448.
- [34] Salem, M. E.; Darweesh, A. F.; Farag, A. M.; Elwahy, A. H. M. 2-Bromo-1-(1H-pyrazol-4-yl)ethanone: versatile precursors for novel mono-, bis- and poly{6-(1H-pyrazol-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines. *Tetrahedron* **2016**, *72*, 712-719.
- [35] Wani, M. Y.; Bhat, A. R.; Azam, A.; Lee, D. H.; Choi, I.; Athar, F. Synthesis and in vitro evaluation of novel tetrazole embedded 1,3,5-trisubstituted pyrazoline derivatives as Entamoeba histolytica growth inhibitors. *Eur. J. Med. Chem.* **2012**, *54*, 845-854.
- [36] Gurdere, M. B.; Kamo, E.; Budak, Y.; Yaglioglu, A. S.; Ceylan, M. Synthesis and anticancer and cytotoxic effects of novel 1,4-phenylene-bis-N-thiocarbamoylpyrazole and 1,4-phenylene-bis-pyrazolylthiazole derivatives, *Turkish J. Chem.* **2017**, *41*(2), 179-189.
- [37] Chimenti, F.; Carradori, S.; Secci, D.; Bolasco, A.; Bizzarri, B.; Chimenti, P.; Granese, A.; Yanez, M.; Orallo, F. Synthesis and inhibitory activity against human monoamine oxidase of N1-thiocarbamoyl-3,5-di(hetero)aryl-4,5-dihydro-(1H)-pyrazole derivatives, *Eur. J. Med. Chem.* **2010**, *45*, 800-804.
- [38] Khatab, T. K.; El-Bayouki, K. A. M.; Basyouni, W. M. An efficient synthesis of β -acylureas via a three-component, one-pot synthesis using TCS/ZnCl₂. *Tetrahedron Lett.* **2011**, *52*, 1448-1451.
- [39] Balci, M. *Basic ¹H- and ¹³C-NMR Spectroscopy*. Elsevier : ISBN: 0-444-51811-8, **2005**, 174-175 pages.
- [40] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery Jr, J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewsk, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Fox, D. J.; Keith, T.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian 03, Revision C.02, Gaussian, Inc., Wallingford, CT, **2004**.

- [41] Karplus, M. Contact electron-spin coupling of nuclear magnetic moments. *J. Chem. Phys.* **1959**, *30*, 11-15.
- [42] Karplus, M. Vicinal proton coupling in nuclear magnetic resonance. *J. Am. Chem. Soc.* **1963**, *85*, 2870-2871.
- [43] Bhasin, S. K.; Khare, R.; Gupta, R. *Pharmaceutical Organic Chemistry*, Elsevier Health Sciences: ISBN: 9788131232675, **2012**.
- [44] Yu J.; Kim K. H.; Moon H. R.; Kim J. N. Facile One-Pot Synthesis of 1,3,5-Trisubstituted Pyrazoles from α,β -Enones. *Bull. Korean Chem. Soc.* **2014**, *35*, 1692-1696.

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