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Synthesis and characterization of new 3,5-disubstituted-4,5-dihydro-1*H*-pyrazole and their carbothioamide derivatives

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ABSTRACT

A new series of substituted pyrazolines (**6**-**10**) were synthesized in moderate to excellent yield by treatment of chalcones (**1**-**5**) with hydrazine monohydrate. The carbothioamide compounds (**11**-**14**) were obtained in 65% to quantitative yield by treatment of chalcones (**2**, **4**, and **5**) either with thiosemicarbazide or with phenylisothiocyanate. All new compounds were characterized by various spectroscopic methods such as ^{1}H NMR, ^{13}C NMR, DEPT, COSY, HSQC spectroscopy, elemental analysis, and high resolution mass spectroscopy. The obtained compounds are currently under biological investigations, and the results will be reported elsewhere.

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1. Introduction

Chalcones are a class of important organic compounds. They are the main precursors for the synthesis of a wide range of a biologically active heterocyclic compounds such as pyrazoles [1-5], isoxazoles [4,5], oxazines [6], pyrimidines [7,8], thiazine derivatives, and many other heterocycles [9]. Chalcone substructure is also well-known for the biosynthesis of flavonoids and isoflavonoids that have high therapeutic and preventive potential of many diseases [10-13]. Moreover, chalcones themselves exhibit various interesting biological activities such as; antimicrobial [14], antimalarial [15], antileishmanial [15], anti-diabetic [16], anti-inflammatory [17], anticancer [18,19], antioxidant [20,21], and many other activities [22,23].

Pyrazolines are important heterocyclic compounds due to their potential applications in medicinal chemistry. They have been reported to posses activities such as; EGFR-TK inhibitors [24], anticancer [24-27], MAO-B inhibitors [28,29], anti-microbial [30-32], anti-inflammatory [33], and antidepressant [34-37], along with other biological activities [38,39].

Also, carbothioamide derivatives were found to have significant pharmacological activities such as antitubercular [40], anti-cancer [41], and anticonvulsant [42]. Therefore, this work reports the synthesis of a variety of 4,5-dihydro-1*H*-pyrazoles and pyrazolines containing carbothioamide moiety derived from chalcones.

2. Experimental

2.1. Instrumentation

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance (300 or 400 MHz) spectrometer. Chemical shifts are expressed in ppm with reference to TMS as internal standard. Mass spectra were obtained from a Micromass Zabtec or Finnigan MAT 95 XP instrument. Elemental analysis was performed on a Euro Vector Euro EA 3000 Elemental Analyzer. Thin layer chromatography (TLC) was carried out on ALUGRAM® SIL G/UV254 (Macherey-Nagel) and visualized by UV. Flash column chromatography was performed using silica gel 60M (Macherey-Nagel). Melting points were determined on an Electrothermal-9002 apparatus. IR spectra were recorded as thin films on a Varian IR-660 spectrometer. For analyses, all new compounds were further purified on preparative TLC silica-gel plates using chloroform as eluent.

2.2. Material

Aldehydes were purchased from Aldrich. 2,5-Dichloro

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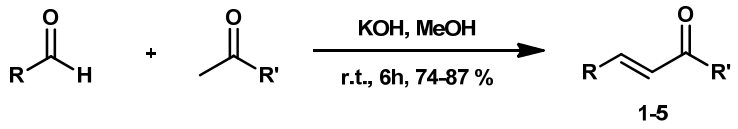
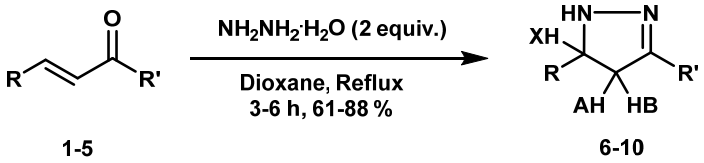


Scheme 1



Scheme 2

thiophene was purchased from Acros. The hydrazines, used in this study, were purchased from Fluka. 3-Acetyl-2,5-dichloro thiophene was prepared according to literature procedure [43].

2.3. Synthesis

2.3.1. General procedure for the synthesis of chalcones 1-5

A solution of the corresponding acetylethiophene (2.0 mmol) in methanol (5.0 mL) was added dropwise to a solution containing of the corresponding aldehyde (2.0 mmol) and sodium hydroxide (4.0 mmol, 2 equiv.) in methanol (20 mL). The reaction mixture was stirred for 6 h at room temperature until completion of the reaction. The precipitate formed, filtered off, washed with cold methanol, and dried. The solid product was recrystallized from methanol. The progress of all reactions was monitored by thin layer chromatography (TLC) (Scheme 1).

(E)-1-(2, 5-Dichlorothiophen-3-yl)-3-phenylprop-2-en-1-one (**1**): Color: Yellow solid. Yield: 74% (Lit. 83%) [44]. M.p.: 52-54 °C (Lit. 53-54 °C) [44]. FT-IR (KBr, ν, cm^{-1}): 3046 (C-H), 1659 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.24 (s, 1H, thiophene-*H*), 7.32 (d, 1H, *J* = 15.4 Hz, -CO-C*H*=CH), 7.39-7.58 (m, 5H, Ar-*H*), 7.65 (d, 1H, *J* = 15.4 Hz, -CO-CH=C*H*). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 124.8, 125.5, 126.9, 127,1, 127.4, 128.5, 128.7, 132.1, 132.3, 133.5, 136.9, 143.2, 183.8. MS (EI, *m/z* (%)): 283 (M^+, 100). Anal. calcd. for $C_{13}H_8Cl_2OS$: C, 55.14; H, 2.85. Found: C, 54.91; H, 2.65%.

(E)-3-(4-Bromophenyl)-1-(2, 5-dichlorothiophen-3-yl)prop-2-en-1-one (**2**): Color: Yellow solid. Yield: 87%. M.p.: 106-108 °C. FT-IR (KBr, ν, cm^{-1}): 3048 (C-H), 2941 (C-H), 1653 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.18 (s, 1H, thiophene-*H*), 7.35 (d, 1H, *J* = 15.7 Hz, -CO-C*H*=CH), 7.45 (d, 2H, *J* = 8.4 Hz, Ar-*H*), 7.60 (d, 2H, *J* = 8.6 Hz, Ar-*H*), 7.66 (d, 1H, *J* = 15.7 Hz, -CO-CH=C*H*). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 124.1, 125.3, 127.1, 127.2, 129.9, 131.4, 132.3, 133.4, 137.7, 143.9, 183.6. MS (EI, *m/z* (%)): 361 (M^+, 100). Anal. calcd. for $C_{13}H_7BrCl_2OS$: C, 43.12; H, 1.95. Found: C, 43.23; H, 1.93%.

(E)-1-(5-Chlorothiophen-2-yl)-3-phenylprop-2-en-1-one (**3**): Color: Yellow solid. Yield: 82% (Lit. 89%) [46]. M.p.: 89-92 °C (lit. 91-93 °C) [46]. FT-IR (KBr, ν, cm^{-1}): 3115 (C-H), 1648 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 6.92 (d, 1H, *J* = 4.2 Hz, thiophene-*H*), 7.33 (d, 1H, *J* = 15.2 Hz, -CO-C*H*=CH), 7.35-7.44 (m, 5H, Ar-*H*), 7.63 (d, 1H, *J* = 4.2 Hz, thiophene-*H*), 7.75 (d, 1H, *J* = 15.2 Hz, -CO-CH=C*H*). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 124.4, 125.8, 126.2, 127.3, 128.4, 130.9, 131.4, 132.1, 141.2, 143.4, 143.9, 181.2. MS (EI, *m/z* (%)): 248 (M^+, 100). Anal. calcd. for $C_{13}H_9ClOS$: C, 62.78; H, 3.65. Found: C, 62.27; H, 3.49%.

(E)-3-(4-Bromophenyl)-1-(5-chlorothiophen-2-yl)prop-2-en-1-one (**4**): Color: White solid. Yield: 77%. M.p.: 147-148 °C. FT-IR (KBr, ν, cm^{-1}): 3028 (C-H), 2941 (C-H), 1668 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.15 (d, 1H, *J* = 4.1 Hz, thiophene-*H*), 7.30 (d, 1H, *J* = 15.5 Hz, -CO-C*H*=CH), 7.49 (d, 2H, *J* = 8.6 Hz, Ar-*H*), 7.56 (d, 2H, *J* = 8.6 Hz, Ar-*H*), 7.64 (d, 1H, *J* = 4.1 Hz, thiophene-*H*), 7.76 (d, 1H, *J* = 15.6 Hz, -CO-CH=C*H*). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 120.8, 125.1, 127.8, 129.9, 131.3, 132.5, 133.4, 140.1, 143.1, 144.0, 180.8. Anal. calcd. for $C_{13}H_8BrClOS$: C, 47.66; H, 2.46. Found: C, 47.35; H, 2.28%.

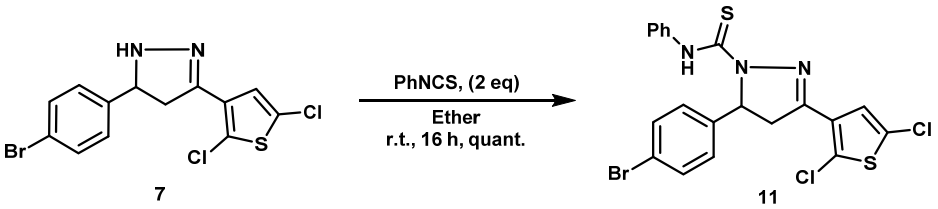
(E)-1-(5-Chlorothiophen-2-yl)-3-(furan-2-yl) prop-2-en-1-one (**5**): Color: Brown solid. Yield: 82% (Lit. 94%) [47]. M.p.: 90-92 °C (lit. 100.3 °C) [47]. FT-IR (KBr, ν, cm^{-1}): 3038 (C-H), 2943 (C-H), 1664 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 6.50 (dd, 1H, *J* = 3.4 Hz, *J* = 1.8 Hz, furan-*H*), 6.71 (d, 1H, *J* = 3.4 Hz, furan-*H*), 6.97 (d, 1H, *J* = 4.1 Hz, thiophene-*H*), 7.20 (d, 1H, *J* = 15.2 Hz, -CO-C*H*=CH), 7.51 (d, 1H, *J* = 1.5 Hz, furan-*H*), 7.56 (d, 1H, *J* = 15.3 Hz, -CO-CH=C*H*), 7.60 (d, 1H, *J* = 4.1 Hz, thiophene-*H*). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 112.8, 116.8, 117.8, 127.7, 130.2, 131.0, 139.6, 144.4, 145.1, 151.3, 180.7. MS (EI, *m/z* (%)): 238 (M^+, 100). Anal. calcd. for $C_{11}H_7ClO_2S$: C, 55.35; H, 2.96. Found: C, 55.18; H, 2.67%.

2.3.2. General procedure for the synthesis of pyrazolines 6-10

A mixture of chalcone (0.50 mmol) and hydrazine hydrate (1.00 mmol, 2 equiv.) was dissolved in dioxane (25 mL) and refluxed for 3-6 hrs. The reaction mixture was then cooled, the precipitate formed, filtered off, washed with cold methanol, and dried. The solid product was recrystallized from methanol. The progress of all reactions was monitored by thin layer chromatography (TLC) (Scheme 2).

3-(2, 5-Dichlorothiophen-3-yl)-5-phenyl-4, 5-dihydro-1H-pyrazole (**6**): Color: Yellow solid. Yield: 74%. M.p.: 100-102 °C. FT-IR (KBr, ν, cm^{-1}): 3218 (N-H), 3049 (C-H), 1558 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.73 (dd, 1H, J_{AB} = 16.4 Hz, J_{AX} = 10.6 Hz, A-*H*), 3.38 (dd, 1H, J_{AB} = 16.3 Hz, J_{BX} = 10.6 Hz, B-*H*), 4.85 (td, 1H, J_{AX} = 2.8 Hz, J_{BX} = 10.6 Hz, X-*H*), 7.24 (s, 1H, thiophene-*H*), 7.18-7.37 (m, 5H, Ar-*H*), 7.65 (d, 1H, *J* = 2.8 Hz, N*H*). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 40.3, 62.8, 124.9, 125.4, 126.2, 127.4, 130.1, 131.2, 136.4, 142.1, 143.4. MS (EI, *m/z* (%)): 298 ([M+H], 100). Anal. calcd. for $C_{13}H_{10}Cl_2N_2S$: C, 52.54; H, 3.39; N, 9.43; S, 10.79. Found: C, 52.19; H, 3.22; N, 9.31; S, 10.74%.

5-(4-Bromophenyl)-3-(2, 5-dichlorothiophen-3-yl)-4, 5-dihydro-1H-pyrazole (**7**): Color: Pale-yellow solid. Yield: 88%. M.p.: 74-76 °C. FT-IR (KBr, ν, cm^{-1}): 3210 (N-H), 3052 (C-H), 1542 (C=N).



Scheme 3

^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.89 (dd, 1H, J_{AB} = 16.6 Hz, J_{AX} = 10.7 Hz, A-*H*), 3.55 (dd, 1H, J_{AB} = 16.6 Hz, J_{BX} = 10.8 Hz, B-*H*), 4.85 (td, 1H, J_{AX} = 2.9 Hz, J_{BX} = 10.8 Hz, X-*H*), 7.30 (s, 1H, thiophene-*H*), 7.32 (d, 2H, *J* = 8.3 Hz, Ar-*H*), 7.54 (d, 2H, *J* = 8.3 Hz, Ar-*H*), 7.86 (d, 1H, *J* = 2.8 Hz, N*H*). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 41.7, 63.2, 120.3, 120.9, 125.4, 126.5, 128.9, 131.3, 131.7, 142.1, 142.5. HRMS (ESI) Calc. for $C_{13}H_8BrCl_2N_2S$: 372.89631 [M-H]; Found: 372.89673. Anal. calcd. for $C_{13}H_9BrCl_2N_2S$: C, 41.52; H, 2.41; N, 7.45; S, 8.53. Found: C, 41.95; H, 2.43; N, 7.61; S, 8.49%.

3-(5-Chlorothiophen-2-yl)-5-phenyl-4, 5-dihydro-1H-pyrazole (**8**): Color: Yellow solid. Yield: 61%. M.p.: 97-99 °C. FT-IR (KBr, ν, cm^{-1}): 3198 (N-H), 3041 (C-H), 1557 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.81 (dd, 1H, J_{AB} = 16.2 Hz, J_{AX} = 10.7 Hz, A-*H*), 3.41 (dd, 1H, J_{AB} = 16.3 Hz, J_{BX} = 10.8 Hz, B-*H*), 4.84 (td, 1H, J_{AX} = 3.0 Hz, J_{BX} = 10.7 Hz, X-*H*), 6.98 (d, 1H, *J* = 3.9 Hz, thiophene-*H*), 7.07 (d, 1H, *J* = 3.9 Hz, thiophene-*H*), 7.25-7.35 (m, 5H, Ar-*H*), 7.65 (d, 1H, *J* = 2.8 Hz, N*H*). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 40.7, 63.9, 125.6, 126.6, 127.3, 127.4, 127.9, 128.5, 136.2, 142.5, 144.2. MS (EI, *m/z* (%)): 263 ([M+H], 100). Anal. calcd. for $C_{13}H_{11}ClN_2S$: C, 59.43; H, 4.22; N, 10.66; S, 12.20. Found: C, 59.84; H, 4.12; N, 10.07; S, 12.28%.

5-(4-Bromophenyl)-3-(5-chlorothiophen-2-yl)-4, 5-dihydro-1H-pyrazole (**9**): Color: Yellow solid. Yield: 79%. M.p.: 75-77 °C. FT-IR (KBr, ν, cm^{-1}): 3215 (N-H), 3044 (C-H), 1563 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.79 (dd, 1H, J_{AB} = 16.3 Hz, J_{AX} = 10.6 Hz, A-*H*), 3.42 (dd, 1H, J_{AB} = 16.3 Hz, J_{BX} = 10.8 Hz, B-*H*), 4.83 (t, 1H, *J* = 10.7 Hz, X-*H*), 6.98 (d, 1H, *J* = 3.8 Hz, thiophene-*H*), 7.07 (d, 1H, *J* = 3.9 Hz, thiophene-*H*), 7.31 (d, 2H, *J* = 8.4 Hz, Ar-*H*), 7.53 (d, 2H, *J* = 8.3 Hz, Ar-*H*), 7.69 (sb, 1H, N*H*). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 40.6, 63.2, 120.2, 125.8, 127.4, 128.0, 128.9, 131.3, 136.0, 142.0, 144.3. HRMS (ESI) Calc. for $C_{13}H_{11}BrClN_2S$: 342.94881 [M+H]; Found: 342.94705. Anal. calcd. for $C_{13}H_{10}ClBrN_2S$: C, 45.70; H, 2.95; N, 8.20; S, 9.38. Found: C, 45.30; H, 2.75; N, 8.13; S, 9.24%.

3-(5-Chlorothiophen-2-yl)-5-(furan-2-yl)-4, 5-dihydro-1H-pyrazole (**10**): Color: Brown solid. Yield: 72%. M.p.: 80-82 °C. FT-IR (KBr, ν, cm^{-1}): 3208 (N-H), 3053 (C-H), 1544 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.86 (dd, 1H, J_{AB} = 16.4 Hz, J_{AX} = 10.5 Hz, A-*H*), 3.13 (dd, 1H, J_{AB} = 16.4 Hz, J_{BX} = 10.5 Hz, B-*H*), 4.96 (t, 1H, *J* = 10.7 Hz, X-*H*), 6.22 (d, 1H, *J* = 2.9 Hz, furan-*H*), 6.26 (dd, 1H, *J* = 3.0 Hz, furan-*H*), 6.83 (d, 1H, *J* = 3.9 Hz, thiophene-*H*), 6.96 (d, 1H, *J* = 3.9 Hz, thiophene-*H*), 7.48 (d, 1H, *J* = 3.0 Hz, furan-*H*), 7.78 (sb, 1H, N*H*). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 41.4, 56.8, 108.1, 110.2, 128.1, 128.9, 131.0, 133.4, 141.3, 150.9, 154.3. MS (EI, *m/z* (%)): 253 ([M+H], 100). Anal. calcd. for $C_{11}H_9ClN_2OS$: C, 52.28; H, 3.59; N, 11.08; S, 12.69. Found: C, 52.04; H, 3.78; N, 10.94; S, 12.78%.

2.3.3. Procedure for the synthesis of carbothioamide derivative 11

Phenylisothiocyanate (27 mg, 0.02 mmol, 2 equiv.) was added to a solution of pyrazole **7** (38 mg, 0.01 mmol) in ether (5 mL). The reaction mixture was then stirred for 24 h at room temperature until completion of the reaction. The precipitate formed, filtered off, washed with ether, and dried to give carbothioamide **11** as spectroscopically and analytically pure brown solid. The progress of the reaction was monitored by thin layer chromatography (TLC) (Scheme 3).

5-(4-Bromophenyl)-3-(2,5-dichlorothiophen-3-yl)-N-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (**11**): Color: Brown solid. Yield: Quant. M.p.: 182-184 °C. FT-IR (KBr, ν, cm^{-1}): 3405 (N-H), 3058 (C-H), 1584 (C=N), 1345 (C=S). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.21 (dd, 1H, J_{AB} = 18.3 Hz, J_{AX} = 3.9 Hz, A-*H*), 4.05 (dd, 1H, J_{AB} = 18.3 Hz, J_{BX} = 11.7 Hz, B-*H*), 5.97 (dd, 1H, J_{AX} = 3.8 Hz, J_{BX} = 11.6 Hz, X-*H*), 7.13-7.20 (m, 3H, Ar-*H*), 7.34 (t, 2H, *J* = 7.7 Hz, Ar-*H*), 7.48 (d, 2H, *J* = 8.3 Hz, Ar-*H*), 7.50 (d, 2H, *J* = 8.3 Hz, Ar-*H*), 8.01 (s, 1H, thiophene-*H*), 10.19 (s, 1H, N*H*). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 43.1, 63.2, 120.1, 125.3, 125.8, 126.0, 127.0, 127.4, 127.8, 128.1, 129.9, 131.5, 139.2, 141.9, 148.9, 174.0. HRMS (ESI) Calc. for $C_{20}H_{15}BrCl_2N_3S_2$: 509.92623 [M+H]; Found: 509.92695. Anal. calcd. for $C_{20}H_{14}BrCl_2N_3S_2$: C, 46.98; H, 2.76; N, 8.22; S, 12.54. Found: C, 46.52; H, 2.11; N, 7.13; S, 12.13%.

2.3.4. General procedure for the synthesis of carbothioamide derivatives **12-14**

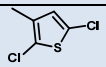
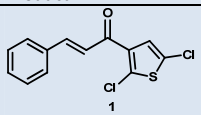
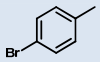
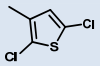
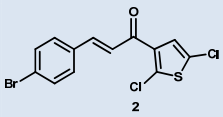
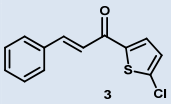
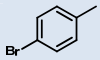
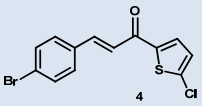
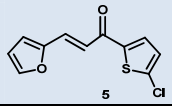
The appropriate chalcone (**2**, **4** and **5**) (0.5 mmol) was added to a solution of KOH (56 mg, 1.0 mmol, 2 equiv.) in ethanol (5.0 mL). Then thiosemicarbazide (91 mg, 1.0 mmol, 2 equiv.) was added at room temp. The resulting mixture was left to stirred and reflux for 5 h. Upon cooling, the solid product precipitated, filtered off then crystallized from ethanol (Scheme 4).

5-(4-Bromophenyl)-3-(2, 5-dichlorothiophen-3-yl)-4, 5-dihydro-1H-pyrazole-1-carbothioamide (**12**): Color: Brown solid. Yield: 71%. M.p.: 135-137 °C. FT-IR (KBr, ν, cm^{-1}): 3473 (N-H), 3054 (C-H), 1573 (C=N), 1324 (C=S). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.11 (dd, 1H, J_{AB} = 18.3 Hz, J_{AX} = 3.8 Hz, A-*H*), 3.99 (dd, 1H, J_{AB} = 18.3 Hz, J_{BX} = 11.7 Hz, B-*H*), 5.85 (dd, 1H, J_{AX} = 3.0 Hz, J_{BX} = 11.6 Hz, X-*H*), 7.07 (d, 2H, *J* = 8.3 Hz, Ar-*H*), 7.50 (d, 2H, *J* = 8.3 Hz, Ar-*H*), 7.79 (s, 1H, thiophene-*H*), 8.00 (s, 1H, N*H*), 8.19 (s, 1H, N*H*). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 42.6, 62.5, 120.0, 126.0, 126.5, 127.2, 127.7, 129.9, 131.5, 142.2, 145.3, 176.3. HRMS (ESI) Calc. for $C_{14}H_{11}BrCl_2N_3S_2$: 433.89493 [M+H]; Found: 433.89426. Anal. calcd. for $C_{14}H_{10}BrCl_2N_3S_2$: C, 38.64; H, 2.32; N, 9.66; S, 14.74. Found: C, 38.92; H, 2.50; N, 9.14; S, 14.47%.

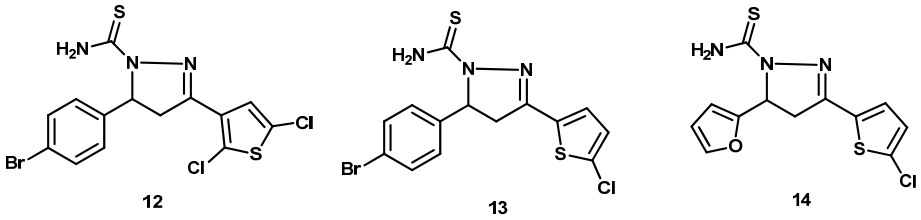
5-(4-Bromophenyl)-3-(5-chlorothiophen-2-yl)-4, 5-dihydro-1H-pyrazole-1-carbothioamide (**13**): Color: Brown solid. Yield: 65%. M.p.: 204-205 °C. FT-IR (KBr, ν, cm^{-1}): 3478 (N-H), 3056 (C-H), 1571 (C=N), 1328 (C=S). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.13 (dd, 1H, J_{AB} = 19.6 Hz, J_{AX} = 4.3 Hz, A-*H*), 3.86 (dd, 1H, J_{AB} = 17.9 Hz, J_{BX} = 11.5 Hz, B-*H*), 5.92 (dd, 1H, J_{AX} = 3.3 Hz, J_{BX} = 11.4 Hz, X-*H*), 7.07 (d, 2H, *J* = 8.3 Hz, Ar-*H*), 7.19 (d, 1H, *J* = 4.0 Hz, thiophene-*H*), 7.34 (d, 1H, *J* = 4.0 Hz, thiophene-*H*), 7.51 (d, 2H, *J* = 8.3 Hz, Ar-*H*), 7.68 (s, 1H, N*H*), 8.10 (s, 1H, N*H*). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 42.8, 63.0, 121.6, 127.1, 127.2, 129.5, 132.0, 132.3, 135.0, 140.4, 150.3, 176.3. HRMS (ESI) Calc. for $C_{14}H_{12}BrClN_3S_2$: 399.93391 [M+H]; Found: 399.93350. Anal. calcd. for $C_{14}H_{11}BrClN_3S_2$: C, 41.96; H, 2.77; N, 10.49; S, 16.00. Found: C, 41.74; H, 2.72; N, 10.14; S, 15.78%.

3-(5-Chlorothiophen-2-yl)-5-(furan-2-yl)-4, 5-dihydro-1H-pyrazole-1-carbothioamide (**14**): Color: Brown solid.

Table 1. Scope of chalcones and their yields.

Entry	R	R'	Product	Yield (%)[a]
a			 1	74
b			 2	87
c			 3	82
d			 4	77
e			 5	82

[a] Yield after crystallization.



Scheme 4

Yield: 80%. M.p.: 156-157 °C. FT-IR (KBr, ν, cm^{-1}): 3481 (N-H), 3049 (C-H), 1583 (C=N), 1321 (C=S). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.30 (dd, 1H, J_{AB} = 17.8 Hz, J_{AX} = 3.0 Hz, A-*H*), 3.74 (dd, 1H, J_{AB} = 17.8 Hz, J_{BX} = 11.5 Hz, B-*H*), 6.00 (dd, 1H, J_{AX} = 2.8 Hz, J_{BX} = 11.2 Hz, X-*H*), 6.28 (d, 1H, *J* = 2.8 Hz, furan-*H*), 6.37 (d, 1H, *J* = 3.0, furan-*H*), 7.18 (d, 1H, *J* = 3.9 Hz, thiophene-*H*), 7.39 (d, 1H, *J* = 3.9 Hz, thiophene-*H*), 7.51 (sb, 1H, furan-*H*), 7.58 (s, 1H, N*H*), 8.02 (s, 1H, N*H*). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 43.8, 56.9, 107.7, 110.6, 128.2, 131.1, 132.4, 132.9, 142.3, 150.6, 152.8, 175.8. HRMS (ESI) Calc. for $C_{12}H_{11}ClN_3OS_2$: 312.00165 [M+H]; Found: 312.00266. Anal. calcd. for $C_{12}H_{10}ClN_3OS_2$: C, 46.22; H, 3.23; N, 13.48; S, 20.57. Found: C, 46.09; H, 3.22; N, 13.57; S, 20.92%.

3. Results and discussion

3.1. Preparation of chalcones

Chalcones **1**-**5** (Scheme 1, Table 1) were prepared by Claisen-Schmidt condensation of appropriate acetylethiophene with the corresponding aldehydes in presence of potassium hydroxide in methanol at room temperature. Although chalcones **1**, **3**-**5** have been reported previously [44-47], their pyrazoles **6**-**10** and their carbothioamide derivatives **11**-**14** have not been reported in the literature.

3.2. Preparation of pyrazoline derivatives

Pyrazoline **6**-**10** derivatives were obtained in moderate to good yield by refluxing the appropriate chalcones with two equivalents of hydrazine monohydrate for 3 to 6 hours in dioxane, (Scheme 2, Table 2).

The treatment of the pyrazoline **7** with phenyliso thiocyanate (2 equiv.) in ether at room temperature afforded the corresponding carbothioamide derivative **11** in quantitative yield, Scheme 3.

A series of 3,5-disubstituted pyrazole-1-carbothioamides **12**-**14** were prepared in good yields by cyclocondensation of chalcones **2**, **4** and **5** with thiosemicarbazide in ethanolic solution of potassium hydroxide for 6 to 12 h. The results of these reactions are shown in Scheme 4.

All compounds **1**-**14** were characterized by different spectroscopic techniques including IR, ^{1}H NMR, ^{13}C NMR, DEPT, COSY, HSQC spectroscopy, and Mass spectrometry along with elemental analysis.

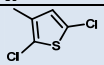
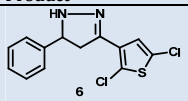
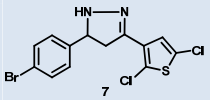
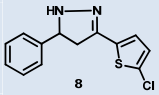
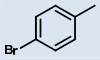
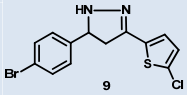
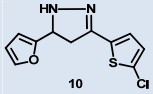
The MS spectra display the correct molecular ion peaks as suggested by their molecular formulas as M^+ or M^++1. In the IR spectra of chalcones **1**-**5**, a characteristic strong absorption bands was observed in the region 1648-1659 cm^{-1} which might be attributed to the carbonyl group.

The IR spectra of compounds **6**-**10** showed the characteristic bands for NH at 3198-3218 cm^{-1}. The IR spectra of the thiocarboamides derivatives, **11**-**14**, showed the characteristic C=S and NH bands in the ranges 1321-1345 cm^{-1} and 3405-3481 cm^{-1}, respectively.

The ^{1}H NMR spectra of compounds **1**-**5** showed the olfenic protons *α*- and *β*-H as two doublets in the region δ 7.20-7.76 ppm, with a coupling constant value of ^3J = 15.2-15.7 Hz in agreement with the formation of the *E* isomers.

In chalcones **1** and **2**, the 4′-H of thienyl moiety appeared as a singlet at 7.24 and 7.18 ppm, respectively, while it is appeared in the region 7.24-8.01 ppm for pyrazoles **6**, **7**, and carbothioamides **11** and **12**.

Table 2. Scope of 4,5-dihydro-1*H*-pyrazoles and their yields.

Entry	R	R'	Product	Yield (%)[a]
a			 **6**	74
b			 **7**	88
c			 **8**	61
d			 **9**	79
e			 **10**	72

[a] Yield after crystallization.

The two dd peaks at the region 2.73-3.55 ppm are assigned to the 4-H protons of the pyrazoles **6-10** with a germinal coupling constant value of ^{3}J = 16.2-16.6 Hz and the other low field peaks which appeared in the region 4.83-4.96 assigned to the 5-H protons for the same compounds. For carbothioamide derivatives **11-14**, the 4-H and 5-H protons shifted to a lower field and appeared in the regions 3.11-4.05 ppm and 5.85-6.00 ppm, respectively.

The ^{13}C NMR spectra of chalcones **1-5** showed the carbonyl carbon at the region δ 180.7-193.6 ppm. The ^{13}C NMR spectra of pyrazoles **6-10** showed absorption in the range 141.3-142.5 ppm corresponding to the C=N carbon. The absorption appeared in the range 174.0-176.3 ppm in the spectra of carbothioamides **11-14** attributed to the C=S carbon.

4. Conclusion

In this study, a series of 3,5-disubstituted-4,5-dihydro-1*H*-pyrazole and their pyrazolines containing carbothioamide moiety were successfully synthesized. All compounds were characterized by standard spectroscopic techniques. The obtained compounds are currently under biological investigations, and the results will be reported elsewhere.

Acknowledgements

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