Article

Synthesis, characterization of 3,5-disubstitutedaryl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide derivatives and evaluation of their antioxidant activity

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Abstract: The pyrazolines are nitrogen-containing heterocyclic structures with five members that are used in the production of pharmaceuticals and organic materials. The goal of this work was to preparation and characterization a novel series of derivatives of 3,5-disubstitutedaryl-4,5-dihydro-1H-pyrazole-1-carbothioamide. Two steps were taken in the synthesis of the novel derivatives from chalcones: the first step chalcones was prepared from reaction of {3,4-(methylenedioxy) acetophenone or para methoxy acetophenone} with various aldehydes (previously prepared) in Claisen-Schmidt condensation at room temperature. seven novel 3,5-disubstitutedaryl-4,5-dihydro-1H-pyrazole-1-carbothioamide derivatives were made in the second step by cyclization reaction of a variety substituted chalcone derivatives with thiosemicarbazide in ethanol. The structures of the newly derivatives are characterized via: ^{1}H-NMR, FT-IR and Mass spectra, then screened for their antioxidant activity.

Key words: Chalcone, Pyrazoline, Antioxidant

1. Introduction: Heterocyclic compounds are regards as an extraordinarily significant class of substance that is crucial for the development of drug design. Chalcones exhibit a variety of biological actions, additionally they are well known intermediate for synthesize diverse of heterocyclic compounds including pyrazolines. Pyrazolines are heterocyclic compounds having molecular formula ($C_3H_4N_2$) with a five membered ring that have some structural characteristics with two nitrogen atoms adjacent to each other. They are also known as azoles [1], [2]. The pyrazoline system and its derivatives are rare in nature and serve as an important heterocyclic template. The difficulty of (N-N) bond formation reactions in live creatures is the cause of these systems' scarcity [3]. Antioxidants are molecules that have the ability to scavenge free radicals during donating or accepting electrons. The levels of free radicals must be controlled, as when their level increases they have detrimental effect on cell component such as lipids, protein and DNA & RNA because they are very small species and highly reactive. Pyrazoline compounds found to be associated with various biological activities such as: antimicrobial [4], analgesic [5], antiplatelet & antifungal [6], [7], antioxidant [8], anticancer [9],[10] anti-inflammatory [11], [12] and inhibiters of human ChK1 kinase [13],[14]. The current research including synthesize a new chalcone derivatives and considered as a base compounds to synthesize a new tri-substituted pyrazoline

derivatives. The newly derivatives were screened for their antioxidant and exhibited excellent to good results.

2. Experimental

2.1. Chemistry

This study's starting ingredients and solvents were all obtained from commercial providers, and they were all used without being purified. An electro-thermal capillary device was used to determine the uncorrected melting points of the produced compounds. The infrared spectrum (FT-IR) was measured using (ALPHA II FTIR Spectrometer-PLATINUM-ATR) (Bruker) in the range (400-4000cm^{-1}). Mass spectrum was measured using (Shimadzu model GCMS-QP2010 PLUS). ^{1}H-NMR spectra of the prepared compounds were recorded using a (Bruker Avance Neo 400MHz) NMR spectrometer (Germany).

2.2. Synthesis

2.2.1. Synthesis of 5-Arylfuran-2-carbaldehyde derivatives (1a-1d):

A solution of [conc. HCl (33.7mL) and distilled water (22.5mL)] was used to dissolve aniline derivatives (0.136mol), cooled to (0-5°C) then add a mixture consisting of [sodium nitrite (9.5gm, 0.138mol) dissolved in distilled water (25mL)] progressively with continuous stirring for (10min) to produced diazonium salt. The solution filtered and then furan-2-carboxyldehyde (15.4gm, 0.16mol) in distilled water (50mL) and 5gm, 0.04mol solution of ($CuCl_2.2H_2O$) dissolved in distilled water (25mL) was added and stirred at 10-15°C. The temperature was gradually raised to (40°C) and the mixture stirred for 4 h. The reaction progress was monitored by TLC using hexane:ethyl acetate(1:1). The precipitate formed was filtered and washed with ($NaHCO_3$) (5%) solution and distilled water for several times, then dried and recrystallized from ethanol [15].

2.2.2. Synthesis of Chalcones (2a-2h):

The preparation of chalcone derivatives accomplished by using the procedure described in published literature [16]. To a solution of methyl ketone (0.001mol) {3,4-(Methylenedioxy)acetophenone or 4-Methoxy acetophenone} in ethanol (10mL), after adding 40%, 1 mL of sodium hydroxide, the reaction liquid was stirred for 30 minutes. (0.001mol) of aromatic aldehyde (previously prepared) (1a-1d) was added then stirred for 12 h. The completion of the reaction was checked by TLC using hexane:ethyl acetate as eluent (1:1). Crushed ice was used to create the precipitate, which was subsequently filtered, dried, and recrystallized from ethanol.

2.2.3. Synthesis of 3,5-disubstitutedaryl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide derivatives (3a-3g):

The modified method in the published reference [17] was followed to synthesis these derivatives. To a solution of chalcone derivatives (0.001mol) in absolute ethanol (10mL), Thiosemicarbazide (0.0015mol) was mixed with 1 mL of 40% NaOH aqueous solution. Refluxed for six hours,

observed by TLC using a 1:1 hexane:ethyl acetate ratio. The solid product was precipitated from the reaction mixture by adding it to crushed ice. It was filtered, washed with distilled water, dried then using ethanol for recrystallization the product.

2.3. Evaluation of Antioxidant activity

The antioxidant activity was quantitatively determined using Spectrophotometric method (DPPH assay):

- **Preparation of standard solution:** Stock solutions of the standard were made using the M. A. Mahdi, *et al.* method [18] by creating a stock solution with a concentration of 1 mg/mL by dissolving 1 milligram of ascorbic acid with 1 milliliter of methanol. Ascorbic acid was produced in various concentrations (5, 25, 50, 100, 150, and 200 µg/mL) using a stock solution of 1 mg/mL as the standard solution.
- **Test sample preparation:** A stock solution containing a concentration of 1 mg/mL was made by dissolving 10 mg of each test compounds **(2b, 2g, 2h, 3e, and 3f)** in 10 milliliters of methanol.
- **Making the DPPH solution:** 3.9 mg of DPPH and 3 mL of methanol were combined, and the liquid was covered with aluminum foil and kept out of the light by using a dark container.
- **A protocol for calculating the amount of DPPH scavenging activity**

1. 1. After adding 150µL of DPPH solution to 3 mL of methanol, the absorbance was measured right away at 517 nm to get the control reading.
2. From the stock solution different concentration of sample (10, 25, 50, 100, 150 and 200µg/mL) were prepared and withdrawn 250µL from each one and diluted with methanol up to 1.75mL.
3. A 250µL DPPH solution volume was introduced into every test tube.
4. After 30 minutes, absorbance was measured using methanol as a blank at 517 nm in a UV-visible spectrophotometer.
5. 5. A volume of 250µL of ascorbic acid (10, 25, 50, 100, 150, and 250µL) was taken out and diluted to a maximum of 1.75 mL with methanol.
6. Each test tube received a 250µL amount from the DPPH solution.
7. Using methanol as a blank, absorbance was measured at 517 nm in a UV-visible spectrophotometer after 30 minutes.
8. Free radical scavenging activity (% scavenging activity) was calculated by using the following equation:

$$\textbf{DPPH scavening effect}\ (\%) = \frac{\boldsymbol{A0 - A1}}{\boldsymbol{A0}} \times \mathbf{100}$$

Were:

$\mathbf{A_0}$: Is the absorbance of control reaction (containing all reagent except sample).

$\mathbf{A_1}$: Is the absorbance of the sample or standard.

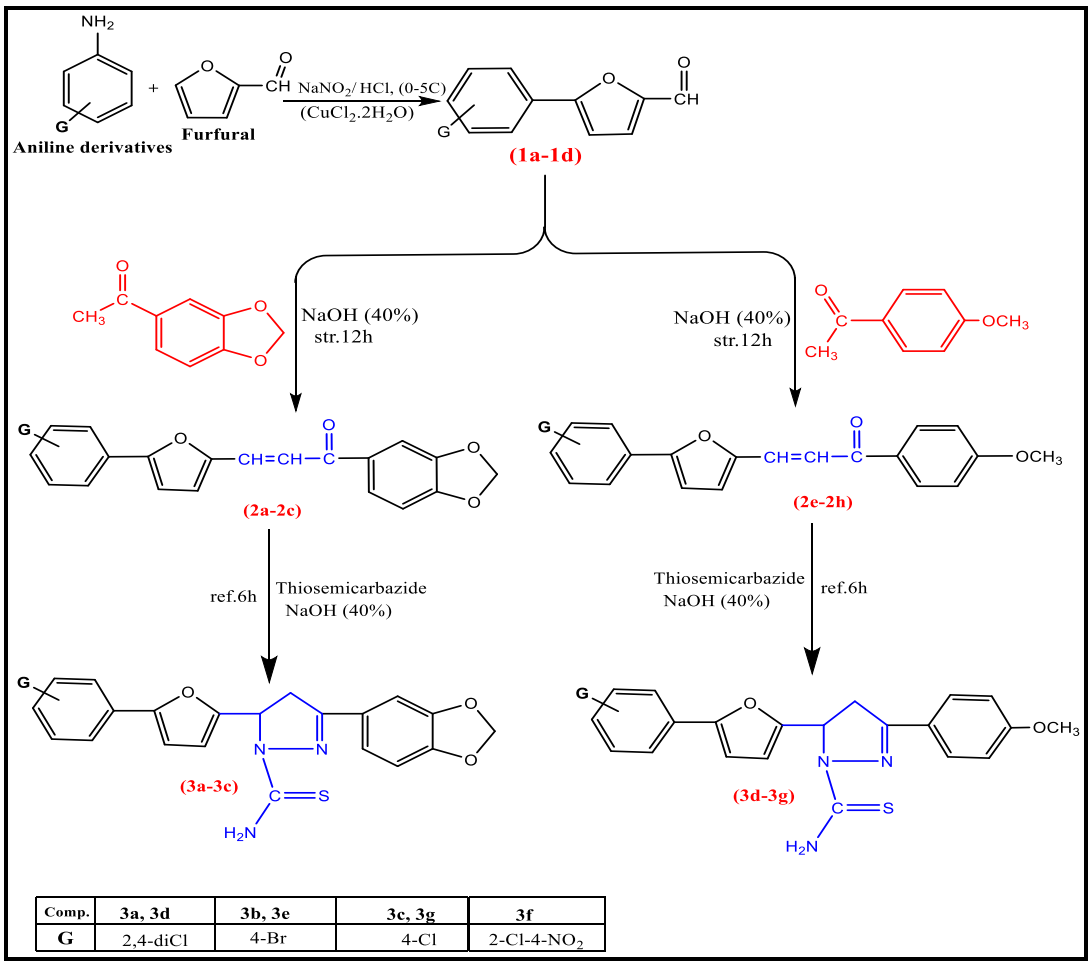
In order to determine the IC_{50}, the DPPH scavenging effect results (%) were plotted against the scavenger concentration.

3. Result and Discussions

(Note): The 1H-NMR spectra display signs for the solvents DMSO-d6 and CDCl3 at δ 2.5 and 7.26 ppm, respectively.

Chalcone derivatives **(2a-2h)** were created using a Claisen-Schmidt condensation reaction analogous approach. In brief, acetophenone derivatives reacted with the corresponding 5-Arylfuran-2-carbaldehyde derivatives in ethanol in the presence of aqueous sodium hydroxide, latterly the resulting chalcones cyclized with thiosemicarbazide to produced 3,5-disubstitutedaryl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide derivatives **(3a-3g)**. In order to characterize the synthesized derivatives, their FT-IR, 1H-NMR, and GC-Mass spectra were recorded. The results of FTIR spectrum of compound **1a (Figure 1)** displayed weak, sharp band at 2842 cm^{-1} attributed to CO-H aldehyde, while a strong sharp band at 1677 cm^{-1} belongs to the stretching vibration of carbonyl group for aldehyde compound. C=C aromatic stretching vibration of furan ring appears as sharp strong band at 1663 cm^{-1} while the C=C group of aromatic ring appears as medium strong band at 1585 cm^{-1}. The ^{1}H-NMR data of **1a (Figure 2)** summarized doublet signal at 7.32 ppm due to one proton of aromatic ring, two doublet signals at 7.37 & 7.50 ppm which belongs to (CH-CH) of furan ring, and proton of aromatic ring appears as doublet signal at 7.96 ppm and the other aromatic proton appears as singlet signal at 7.53ppm as well as the presence of singlet signal at 9.70 ppm due to proton CO-H aldehyde. The Mass spectrum of aldehyde compounds **1a (Figure 3)** giving *m/z*: **240** which representing the molecular ion **(M^{+})** for **($C_{11}H_6Cl_2O_2$)**. FTIR spectrum of chalcone **2a (Figure 4)** showed characteristic bands at 1645 cm^{-1} belongs to C=O chalcone, 1606 cm^{-1} due to CH=CH chalcone and disappeared the CO-H aldehyde band. The ^{1}H-NMR data of **2a (Figure 5)** summarized singlet signal at 6.18 ppm due to -O-CH_2-O, doublet signal at 7.11 ppm belongs to aromatic ring proton. The two doublet signals appeared at 7.26 ppm & 7.40 ppm related to (CH-CH) furan, the singlet signal at 7.56 related to one proton of aromatic ring, while the multiplet signal at 7.58-7.64 ppm belongs to CH=CH-CO chalcone and one aromatic proton. The doublet signal at 7.76 ppm related to other proton of CH=CH-CO chalcone. The doublet signal at 7.80 ppm belongs to aromatic proton and finally the two doublet signals at 7.85 ppm and 8.23 ppm belongs to aromatic rings protons. The molecular ion in GC-Mass spectrum **(Figure 6)** showed *m/z*: **387(M^{+})** strongly confirmed the structures **($C_{20}H_{12}Cl_2O_4$)** of the prepared chalcone **2a**. The FT-IR spectrum of compound **3a (Figure 7)** showed characteristic absorption bands at: 3431, 3264cm^{-1} related to NH_2 group, 3093cm^{-1} due to CH aromatic and at 2981cm^{-1} due to CH aliphatic. The C=N group was associated with the absorption band at 1595 cm-1, whereas the C=C aromatic and C=S groups were appear at 1577 and 1349 cm-1, respectively. The ^{1}H-NMR spectrum of compound **3a (Figure 8)** summarized two doublet of doublet signals appeared at 3.49 ppm (*J*=4.0, 20.0Hz) and 3.77 ppm (*J*=8.0, 16.0Hz) belongs to Ha & Hb protons of pyrazoline ring, and the proton Hx of pyrazoline ring showed up as doublet of doublet signal at 6.03 ppm (*J*=4.0, 12.0 Hz). The singlet signal at 6.11 ppm related to CH_2 of methylenedioxy ring. The two doublet signals at 7.15 ppm (*J*=4.0Hz) and 7.34 ppm (*J*=4.0Hz) belongs to the two protons for furan ring. The multiplet signal at the range 7.51-7.54 ppm due to one proton of aromatic ring. The doublet signal at 7.76 ppm (*J*=4.0Hz) due to aromatic ring proton. The multiplet signal appeared as broad singlet at 7.87 ppm belongs to aromatic ring proton while the singlet signal at 8.00 ppm belongs to an aromatic ring proton. The doublet signal at 8.07 ppm (*J*=8.0Hz) due to one proton of the aromatic ring. The multiplet signal appeared as broad singlet at 8.37 ppm and the singlet signal appeared at 11.61 ppm belongs to one

aromatic ring proton and NH_2 protons respectively. The molecular ion *m/z*: **460(M^+)** in GC-Mass spectrum **(Figure 9)** strongly confirmed the molecular weight for the synthesized derivative **3a**.



Comp.	3a, 3d	3b, 3e	3c, 3g	3f
G	2,4-diCl	4-Br	4-Cl	2-Cl-4-NO_2

Scheme 1: Synthetic route of all synthesized compounds

Structure analysis data of the prepared compounds:

Compound (1a) {5-(2,4-dichlorophenyl)furan-2-carbaldehyde}

Brown & powder, (Output ratio 79%), (melting point 148-150°C) [15]; FTIR data: 3158 (CH furan), 3079 (CH aromatic), 2842 (CH aldehyde), 1740 (C=O), 1663 (C=C furan ring), 1585(C=C aromatic ring), 1034 (C-Cl).The ^{1}HNMR signs (400MHz, $CDCl_3$) in δ(ppm): 7.32(d,1H,Ar-H, *J*=12.0 Hz), 7.37(d,1H,CH furan *J*=4.0 Hz), 7.50(d,1H,CH furan *J*=4.0 Hz), 7.96(d,1H,Ar-H, *J*=12.0 Hz), 7.35(s,1H,Ar-H), 9.70(s,1H, CO-H aldehyde). Mass *m/z* : 240 (M^+) for ($C_{11}H_6Cl_2O_2$).

Compound (1b) {5-(4-bromophenyl)furan-2-carbaldehyde}

Brown & powder, (Output ratio 65%), (melting point 143-145°C) [20]; FTIR data: 3110 (CH furan), 3056 (CH aromatic), 2858 (CH aldehyde), 1672 (C=O), 1660 (C=C furan ring), 1595 (C=C aromatic ring), 1039 (C-Br).The ^{1}HNMR signs (400MHz, $CDCl_3$) in δ(ppm): 6.84(d,1H,CH furan, *J*=4.0Hz), 7.32(d,1H,CH furan, *J*= 4.0Hz), 7.57(d,2H,Ar-H, *J*=8.0Hz), 7.68(d,2H,Ar-H, *J*=8.0Hz), 9.65(s,1H,CO-H aldehyde). Mass *m/z* : 250 (M^+) for ($C_{11}H_7BrO_2$).

Compound (1c) {5-(2-chloro-4-nitrophenyl)furan-2-carbaldehyde}

Orange & powder, (Output ratio 75%), (melting point 124-126°C); FTIR data:3105 (C-H furan ring), 3034 (C-H aromatic ring), 2832 (C-H of aldehyde), 1680 (C=O), 1664 (C=C furan ring), 1582(C=C aromatic ring), $1341_{sym.}$,$1513_{asym.}(No_2)$, 1034 (C-Cl).The 1HNMR signs(400MHz, $CDCl_3$) in δ(ppm): 7.41(d,1H,CH furan, *J*=4.0Hz), 7.56(d,1H,CH furan, *J*=4.0Hz), 8.22(d,1H,Ar-H, *J*=8.0Hz), 8.25(d,1H,Ar-H, *J*=8.0Hz), 8.38(s,1H,Ar-H), 9.77 (s,1H,CO-H aldehyde). Mass *m*/*z*: 251 (M^+)for ($C_{11}H_6ClNO_4$).

Compound (1d) {5-(4-chlorophenyl)furan-2-carbaldehyde}

Deep brown & powder, (Output ratio 64%), (melting point 114-116°C) [15]; FTIR data: 3110 (C-H furan ring), 3059 (CH aromatic ring), 2834 (CH of aldehyde group), 1741 (C=O), 1661 (C=C furan ring), 1589 (C=C aromatic ring), 1010 (C-Cl).The 1HNMR signs(400MHz, $CDCl_3$) in δ(ppm): 6.83(d,1H,CH furan, *J*=4.0Hz), 7.32(d,1H, CH furan ring, *J*=4.0Hz), 7.41(d,2H,Ar-H, *J*=8.0Hz), 7.75(d,2H,Ar-H, *J*=8.0Hz), 9.65(s,1H,CO-H aldehyde). Mass *m*/*z*: 206 (M^+) for ($C_{11}H_7ClO_2$).

Compound (2a) {1-(benzo[d] [1,3]dioxol-5-yl)-3-(5-(2,4-dichlorophenyl)furan-2-yl)-prop-2-en-1-one}

Yellow & powder, (Output ratio 75%), (melting point 158-160 in°C); FTIR data: 3111 (C-H Ar.), 2900 (C-H alph.), 1645 (C=O chalcone), 1606 (CH=CH chalcone), 1576 (C=C aromatic), 1024 (C-Cl).The1HNMR signs in δ(ppm): 6.18(s,2H,O-CH_2-O), 7.11(d,1H,Ar-H, *J*=8.0Hz), 7.26 (d,1H,CH furan ring, *J*=4.0Hz), 7.40 (d, 1H, CH furan ring, *J*=4.0Hz), 7.56(s,1H,Ar-H), 7.58-7.64(d,1H,CH=CH-CO chalcone & 1H,Ar-H), 7.76(d,1H,CH=CH-CO chalcone, *J*=16.0Hz), 7.80(d,1H,Ar-H, *J*=4.0Hz), 7.85(d,1H,Ar-H, *J*=8.0Hz), 8.23(d,1H,Ar-H, *J*=8.0Hz). GC-mass *m*/*z*: 387 (M^+)for ($C_{20}H_{12}Cl_2O_4$).

Compound (2b) {1-(benzo[d] [1,3]dioxol-5-yl)-3-(5-(4-bromophenyl)furan-2-yl)-prop-2-en-1-one}

Yellow & powder, (Output ratio 68%), (melting point 180-182 in°C); FTIR data: 3106 (C-H Ar.), 2937 (C-H alph.), 1643 (C=O chalcone), 1602 (CH=CH chalcone), 1581 (C=C aromatic), 1022 (C-Br).The ^{1}HNMR signs in δ(ppm): 6.18 (s,2H,O-CH_2-O), 7.11(d,1H,Ar-H, *J*=8.0Hz), 7.20(d,1H,CH furan, *J*=4.0Hz), 7.27(d,1H,CH furan, *J*=4.0Hz), 7.55(d,2H,Ar-H, *J*=16.0Hz), 7.67(d,1H,CH=CH-CO chalcone, *J*=12.0Hz), 7.70(s,1H,Ar-H), 7.72(d,2H,Ar-H, *J*=16.0Hz),7.86(d,1H,Ar-H,*J*=8.0Hz), 7.92(d,1H,CH=CH-CO chalcone, *J*=12.0Hz). GC-mass *m*/*z*: 397 (M^+)for ($C_{20}H_{13}BrO_4$).

Compound (2c) {1-(benzo[d] [1,3]dioxol-5-yl)-3-(5-(2-chloro-4-nitrophenyl)furan-2-yl)-prop-2-en-1-one}

Yelow & powder, (Output ratio 78%), (melting point 211-213 in°C); FTIR data: 3105 (C-H Ar.), 2911 (C-H alph.), 1650 (C=O chalcone), 1607 (CH=CH chalcone), 1586 (C=C aromatic), $1352_{sym.}$, $1477_{asym.}(NO_2)$, 1036 (C-Cl). The 1HNMR signs in δ(ppm): 6.19 (s,2H,O-CH_2-O), 7.13 (d,1H,,Ar-H, *J*=8.0Hz), 7.34(d,1H,CH furan, *J*=4.0Hz), 7.61(d,1H,CH=CH-CO chalcone, *J*=16.0Hz), 7.56(d,1H,Ar-H, *J*=4.0Hz), 7.69(d, 1H,CH furan, *J*=4.0 Hz), 7.86 (d,1H,CH=CH-CO chalcone, *J*=16.0Hz)), 8.29-8.52(m,3H,Ar-H). GC-mass *m*/*z*: 397 (M^+)for ($C_{20}H_{12}ClNO_6$).

Compound (2d) {1-(benzo[d] [1,3]dioxol-5-yl)-3-(5-(4-chlorophenyl) furan-2-yl)-prop-2-en-1-one}

Yellow & powder, (Output ratio 73%), (melting point 165-167 in^{o}C); FTIR data: 3108 (C-H Ar.), 2902 (C-H alph.), 1644 (C=O chalcone), 1603 (CH=CH chalcone), 1580 (C=C aromatic), 1042 (C-Cl).The1HNMR signs in δ(ppm): 6.18(s,2H,O-CH_2-O), 7.12(d,1H,Ar-H, *J*=8.0Hz), 7.20 (d,1H,CH furan, *J*=4.0Hz), 7.26(d,1H,CH furan, *J*=4.0Hz), 7.55 (d,2H,Ar-H, *J*=4.0Hz), 7.57(d,2H,Ar-H, *J*=4.0Hz), 7.65(d,1H,Ar-H, *J*=4.0Hz), 7.70(s,1H,Ar-H), 7.86 (d,1H,CH=CH-CO chalcone, *J*=8.0Hz), 7.98 (d,1H,CH=CH-CO chalcone, *J*=8.0Hz). GC-mass *m*/*z*: 352 (M^+)for $(C_{20}H_{13}ClO_4)$.

Compound (2e) {3-(5-(2,4-dichlorophenyl) furan-2-yl)-1-(4-methoxyphenyl)-prop-2-en-1-one}

Yellow & powder, (Output ratio 84%),(melting point 114-116 in^{o}C); FTIR data: 3112 (C-H Ar.), 2836 (C-H alph.), 1648 (C=O chalcone), 1603 (CH=CH chalcone), 1583 (C=C Ar.), 1023 (C-Cl).The1HNMR signs in δ(ppm): 3.88(s,3H,-OCH_3), 7.11(d,2H,Ar-H, *J*=8.0Hz), 7.25(d,1H,CH furan, *J*=4.0Hz) 7.39(d,1H,CH furan, *J*=4.0Hz), 7.56-7.80(m,1H,CH chalcone & 1H,Ar-H), 8.15(d,2H,Ar-H, *J*=8.0Hz), 8.20(d,1H,CH=CH-CO chalcone, *J*=8.0Hz). GC-mass *m*/*z*: 373 (M^+)for $(C_{20}H_{14}Cl_2O_3)$.

Compound (2f) {3-(5-(4-bromophenyl) furan-2-yl)-1-(4-methoxyphenyl)-prop-2-en-1-one}

Yellow & powder, (Output ratio 76%), (melting point 185-187 in^{o}C); FT-IR data: 3109 (C-H Ar.), 2939 (C-H alph.), 1646 (C=O chalcone), 1599 (CH=CH chalcone), 1587 (C=C aromatic), 1029 (C-Br).The 1HNMR signs in δ(ppm): 3.88(s,3H,-OCH_3), 7.11(d,2H,Ar-H, *J*=8.0Hz), 7.20(d,1H,CH furan, *J*=4.0Hz), 7.27(d,1H,CH furan, *J*=4.0Hz), 7.56(d,1H,CH=CH-CO chalcone, *J*=16.0Hz), 7.69(d,2H,Ar-H, *J*=8.0Hz), 7.75(d,1H,CH=CH-CO chalcone, *J*=16.0Hz), 7.91 (d,2H,Ar-H, *J*=8.0Hz), 8.16(d,2H,Ar-H, *J*=8.0Hz). GC-mass *m*/*z* : 383 (M^+)for $(C_{20}H_{15}BrO_3)$.

Compound (2g) {3-(5-(2-chloro-4-nitrophenyl) furan-2-yl)-1-(4-methoxyphenyl)-prop-2-en-1-one}

Orange & powder, (Output ratio 80%), (melting point 164-166 in^{o}C); FT-IR data: 3110 (C-H aromatic), 2838 (C-H alph.), 1648 (C=O chalcone), 1605 (CH=CH chalcone), 1583 (C=C aromatic), $1339_{sym.}$, $1510_{asym.}$(NO_2), 1019 (C-Cl).The ^{1}HNMRsigns in δ(ppm): 3.88(s,3H,-OCH_3), 7.11(d,2H,Ar-H, *J*=8.0Hz), 7.31(d,1H,CH furan, *J*=4.0Hz), 7.59(d,1H,CH=CH-CO chalcone, *J*=16.0Hz), 7.65(d,1H,CH furan, *J*=4.0Hz), 7.84(d,1H,CH=CH-CO chalcone, *J*=16.0Hz), 8.15(d,2H,Ar-H, *J*=8.0Hz), 8.25-8.46(m,3H,Ar-H). GC-mass *m*/*z* : 384 (M^+)for $(C_{20}H_{14}ClO_5)$.

Compound (2h) {3-(5-(4-chlorophenyl) furan-2-yl)-1-(4-methoxyphenyl)-prop-2-en-1-one}

Yellow & powder, (Output ratio 75%), (melting point 169-171 in^{o}C); FT-IR data: 3109 (C-H Ar.), 2839 (C-H aliphatic), 1646 (C=O chalcone), 1603 (CH=CH chalcone), 1587 (C=C Ar.), 1031 (C-Cl).The ^{1}H-NMR in δ(ppm): 3.89(s,3H,O-CH_3), 7.11(d,2H,Ar-H, *J*=8.0Hz), 7.19(d,1H,CH furan, *J*=4.0Hz), 7.24(d,1H,CH furan, *J*=4.0Hz), 7.54-7.58(m,2H,Ar-H & 1H,CH chalcone), 7.73(d,1H,CH=CH-CO chalcone, *J*=16.0Hz), 7.96(d,2H,Ar-H, *J*=8.0Hz), 8.15(d,2H,Ar-H, *J*=8.0Hz). GC-mass *m*/*z* : 338 (M^+)for $(C_{20}H_{15}ClO_3)$.

Compound (3a) {3-(benzo[d] [1,3]dioxol-5-yl)-5-(5-(2,4-dichlorophenyl)-furan-2-yl) 4,5-dihydro-1H-pyrazol-1- carbothioamide}

Pale yellow & powder, (Output ratio 70%), (melting point 90-92 in^{o}C); FTIR data: 3431, 3264 (NH_2 thioamide), 3093 (CH aromatic), 2981(CH aliphatic), 1595(C=N), 1349(C=S thioamide),

1034(C-Cl).The 1HNMR in δ(ppm): 3.49(d*d,1H, Ha pyrazoline ring, *J*=4.0, 20.0 Hz), 3.77 (d*d,1H, Hb pyrazoline ring, J=8.0, 16.0 Hz), 6.03(d*d,1H, Hx pyrazoline ring, *J*=4.0, 12.0 Hz), 6.11 (s,2H,O-CH_2-O), 7.15(d,1H,CH furan, *J*=4.0 Hz), 7.34(d,1H,CH furan, *J*=4.0 Hz), 7.49(dd,1H,Ar-H, *J*=4.0, 8.0 Hz), 7.53(dd,1H,Ar-H, *J*=4.0, 8.0 Hz), 7.76 (d,1H,Ar-H, *J*=4.0 Hz), 8.07(d,1H,Ar-H, *J*=8.0 Hz), 8.00, 8.36(s, 2H,NH_2), 11.59(s,1H,NH). GC-mass (EI) *m*/*z*: 460 (M^+)for ($C_{21}H_{15}Cl_2N_3O_3S$).

Compound (3b) {3-(benzo[d] [1,3]dioxol-5-yl)-5-(5-(4-bromophenyl) furan-2-yl) 4,5-dihydro-1H-pyrazol-1-carbothioamide}

Beige & powder, (Output ratio 62%), (melting point 93-95 in^oC); FTIR data: 3274, 3230 (NH_2 thioamide), 3143 (CH aromatic), 2955(CH aliphatic), 1671(C=N), 1351(C=S thioamide), 1037(C-Br).The 1HNMR in δ(ppm): 3.46(d*d,1H,Ha pyrazoline ring, *J*=4.0, 20.0 Hz), 3.76(d*d,1H,Hb pyrazoline ring, *J*=12.0, 16.0 Hz), 6.02(d*d,1H,Hx pyrazoline ring, *J*=12.0, 16.0 Hz), 6.11(s,2H,O-CH_2-O), 7.00(d,1H,Ar-H, *J*=8.0 Hz), 7.08(d,1H,CH furan, *J*=4.0 Hz), 7.19(d,1H,CH furan, *J*=4.0 Hz), 7.32(dd,1H,Ar-H, *J*=4.0, 8.0 Hz), 7.63(d,2H,Ar-H, *J*=8.0 Hz), 7.79 (d,2H,Ar-H, *J*=8.0 Hz), 7.97,8.32(s,2H,NH_2), 11.54(s,1H,NH). GC-mass (EI) *m*/*z*: 470 (M^+) for ($C_{21}H_{16}BrN_3O_3S$).

Compound (3c) {3-(benzo[d] [1,3]dioxol-5-yl)-5-(5-(4-chlorophenyl)furan-2-yl) -4,5-dihydro-1H-pyrazole-1-carbothioamide}

Pale yellow & powder, (Output ratio 66%), (melting point 79-81 in^oC); FTIR data: 3428, 3269 (NH_2 thioamide), 2981 (CH aromatic), 2900(CH aliphatic), 1668(C=N), 1349(C=S thioamide), 1036(C-Cl). GC-mass (EI) *m*/*z*: 425 (M^+) for ($C_{21}H_{16}ClN_3O_3S$).

Compound (3d) {5-(5-(2,4-dichlorophenyl) furan-2-yl)-3-(4-methoxyphenyl) -4,5-dihydro-1H-pyrazol-1-carbothioamide}

Pale orange & powder, (Output ratio 73%), (m.p 95-97 in^oC); FTIR data: 3492, 3266 (NH_2 thioamide), 3068 (CH aromatic), 2962(CH aliphatic), 1653(C=N), 1348(C=S thioamide), 1024(C-Cl The ^{1}HNMR in δ(ppm): 3.49(d*d,1H,Ha-pyrazoline, *J*=4.0, 12.0 Hz), 3.75-3.85(m,1H,Hb-pyrazoline), 3.81(s,3H,OCH_3), 6.03(d*d,1H,Hx-pyrazoline, *J*=4.0, 8.0 Hz), 7.02 (d,2H,Ar-H, *J*=12.0 Hz), 7.07 (d,1H,CH furan, *J*=4.0Hz), 7.14(d,1H,CH furan, *J*=4.0 Hz), 7.32(d,1H,Ar-H, *J*=4.0 Hz), 7.47(dd,1H,Ar-H, *J*=2.0, 8.0 Hz), 7.74(d,1H,Ar-H, *J*=2.0 Hz), 8.05(d,H,Ar-H, *J*=8.0 Hz), 7.98, 8.34 (s,2H,NH_2), 11.58(s,1H,NH).GC-mass (EI) *m*/*z*: 446 (M^+) for ($C_{21}H_{17}Cl_2N_3O_2S$).

Compound (3e) {5-(5-(4-bromophenyl) furan-2-yl)-3-(4-methoxyphenyl) -4,5-dihydro-1H-pyrazole-1- carbothioamide}

Pale yellow & powder, (Output ratio 62%), (melting point 81-83 in^oC); FTIR data: 3425, 3267 (NH_2 thioamide), 2960(CH aromatic), 2932(CH aliphatic), 1665(C=N), 1346(C=S thioamide), 1072(C-Cl).The ^{1}HNMR in δ(ppm): 3.48(d*d,1H,Ha pyrazoline ring, *J*=4.0, 12.0 Hz), 3.77(d*d,1H,Hb pyrazoline ring, *J*=8.0, 20.0 Hz), 6.01(d*d,1H,Hx pyrazoline ring, *J*=4.0, 12.0Hz), 7.08(d,1H,CH furan, *J*=4.0Hz), 7.19(d,1H,CH furan, *J*=4.0 Hz), 7.55(d,2H,Ar-H, *J*=12.0 Hz), 7.63(d,2H,Ar-H, *J*=8.0Hz), 7.97(d,2H,Ar-H, *J*=8.0 Hz), 7.85(d,2H,Ar-H, *J*=12.0 Hz),7.97(s,2H,NH_2), 11.56(s,1H,NH). GC-mass (EI) *m*/*z*: 456.3 (M^+) for ($C_{21}H_{18}BrN_3O_2S$).

Compound (3f) {5-(5-(2-chloro-4-nitrophenyl)furan-2-yl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1- carbothioamide}

Deep & orange powder, (Output ratio 70%), (melting point 131-133 in^{o}C); FT-IR data: 3431, 3326 (NH_2 thioamide), 3107(CH aromatic), 2959(CH aliphatic), 1648(C=N), 1343(C=S thioamide), $1305_{sym.}$, $1462_{asym.}$ (NO2), 1020(C-Cl). GC-mass (EI) *m/z*: 456.9 (M^+)for ($C_{21}H_{17}ClN_4O_4S$).

Compound (3q) {5-(5-(4-chlorophenyl)furan-2-yl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1- carbothioamide}

Beige & powder, (Output ratio 65%), (melting point 78-80 in^{o}C); FT-IR data: 3430, 3257 (NH_2 thioamide), 2971(CH aromatic), 2835(CH aliphatic), 1668(C=N), 1346(C=S thioamide), 1091(C-Cl).The ^{1}HNMR in δ(ppm): 3.47(d*d,1H,Ha-pyrazoline, *J*=4.0, 16.0 Hz), 3.74-3.85(m,H,1H,Hb-pyrazoline), 6.00 (d*d,1H,Hx-pyrazoline, *J*=4.0, 12.0 Hz), 6.39(d,1H,CH furan, *J*=4.0 Hz), 6.91(d,1H,CH furan, *J*=4.0 Hz), 7.02(d,2H,Ar-H, *J*=8.0 Hz), 7.42(d,2H,Ar-H, *J*=8.0 Hz), 7.58(d,2H,Ar-H, *J*=8.0 Hz), 7.86(d,2H,Ar-H, *J*=8.0 Hz), 8.04,8.31(s,2H,NH_2), 11.54 (s,1H,NH). . GC-Mass (EI) *m/z*: 411 (M^+) for ($C_{21}H_{18}ClN_3O_2S$).

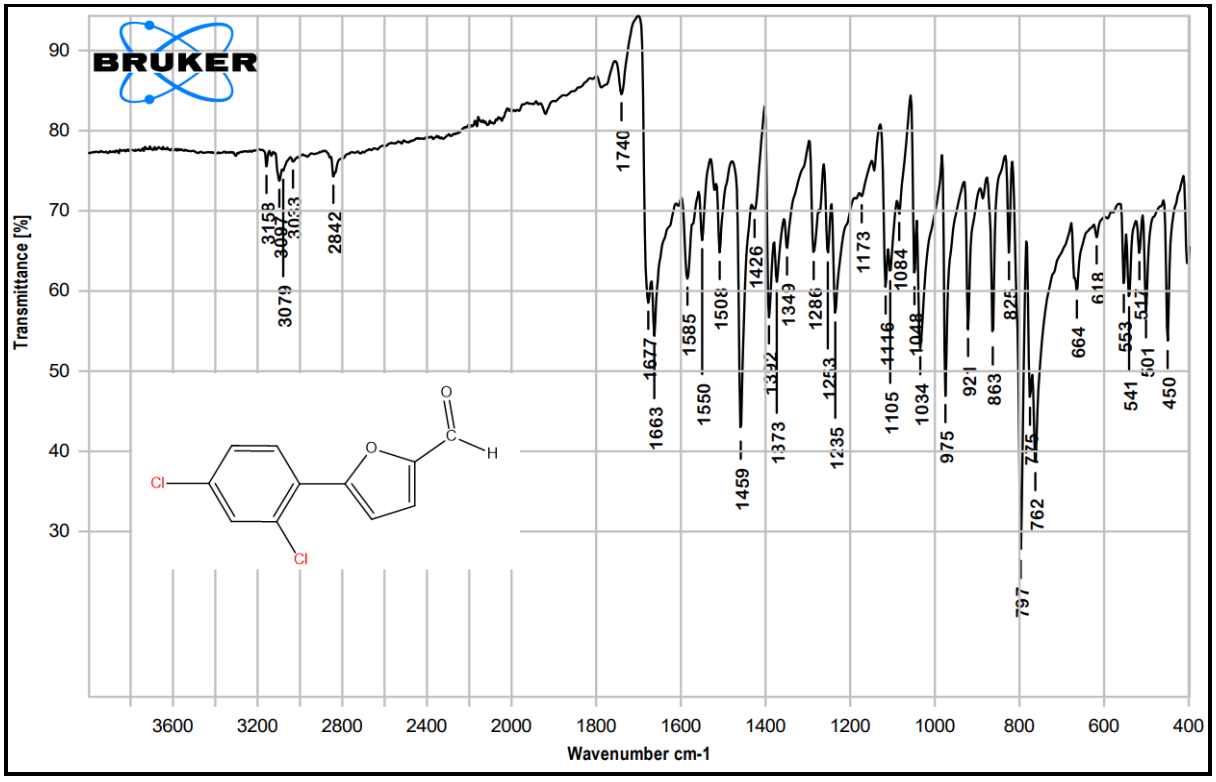


Figure-1: FTIR spectrum for 1a

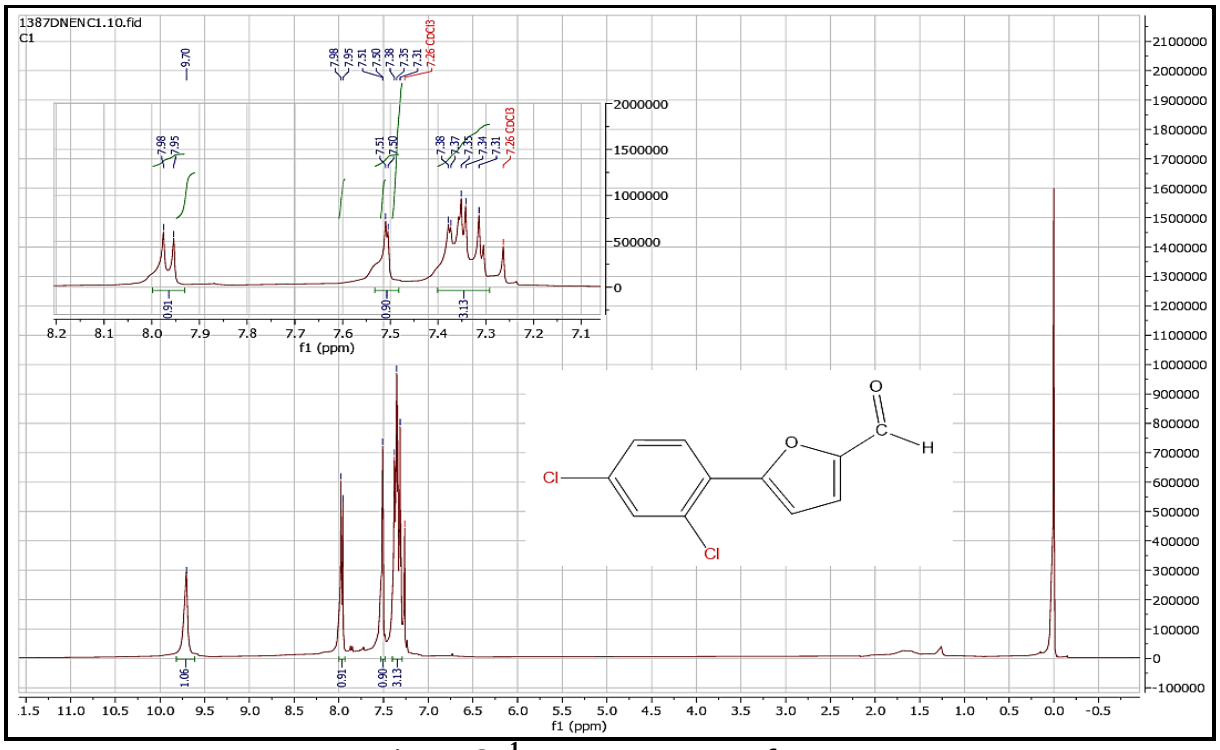


Figure-2: ^{1}HNMR spectrum for 1a

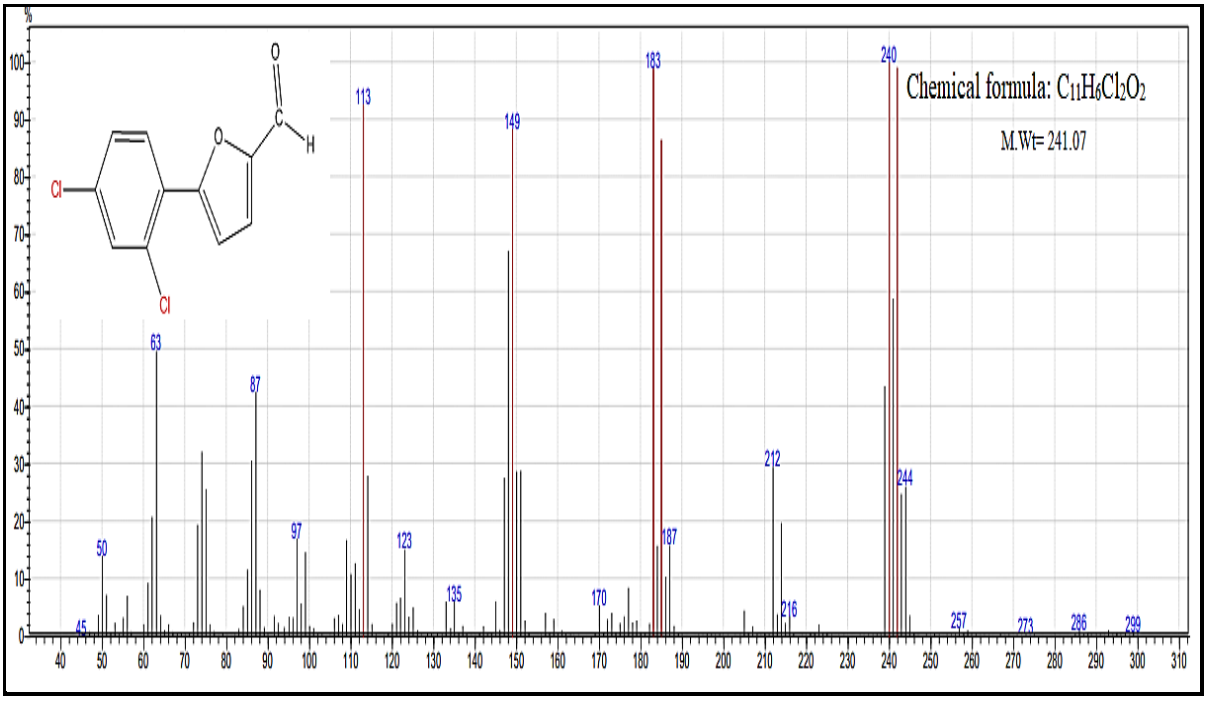


Figure-3: Mass spectrum for 1a

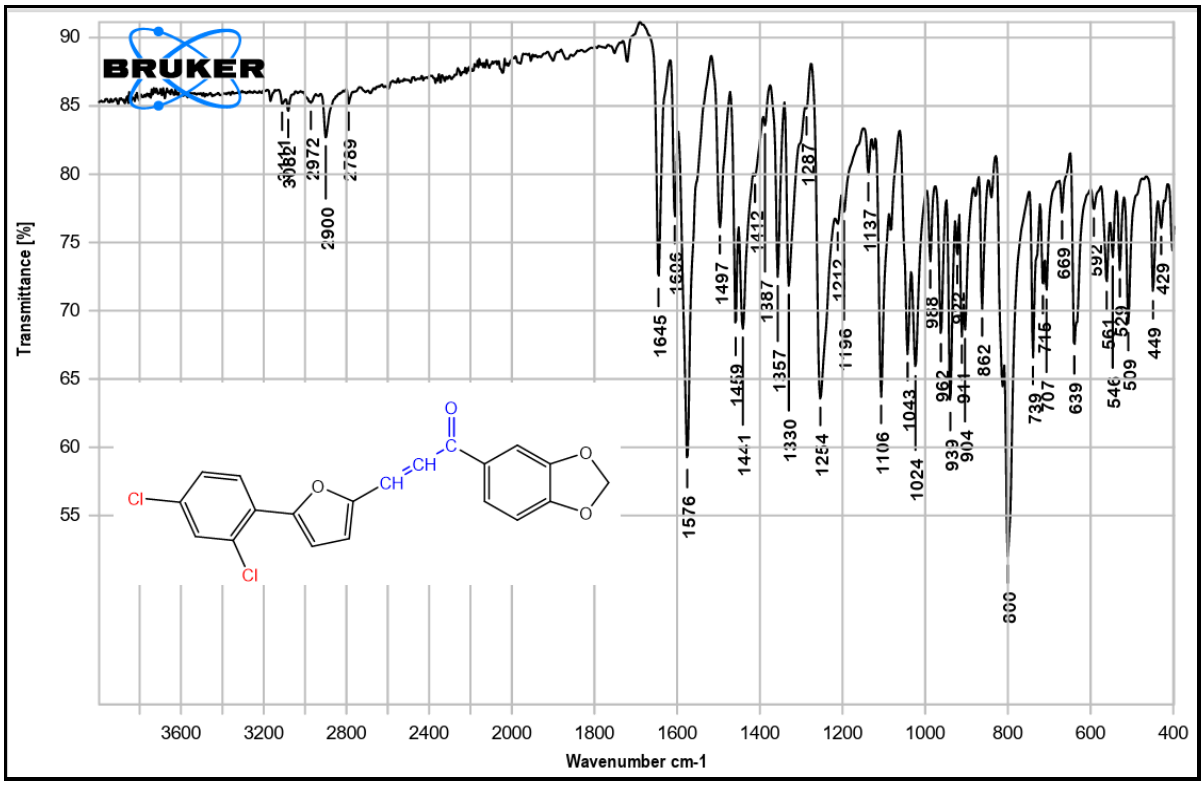


Figure-4: FTIR spectrum for 2a

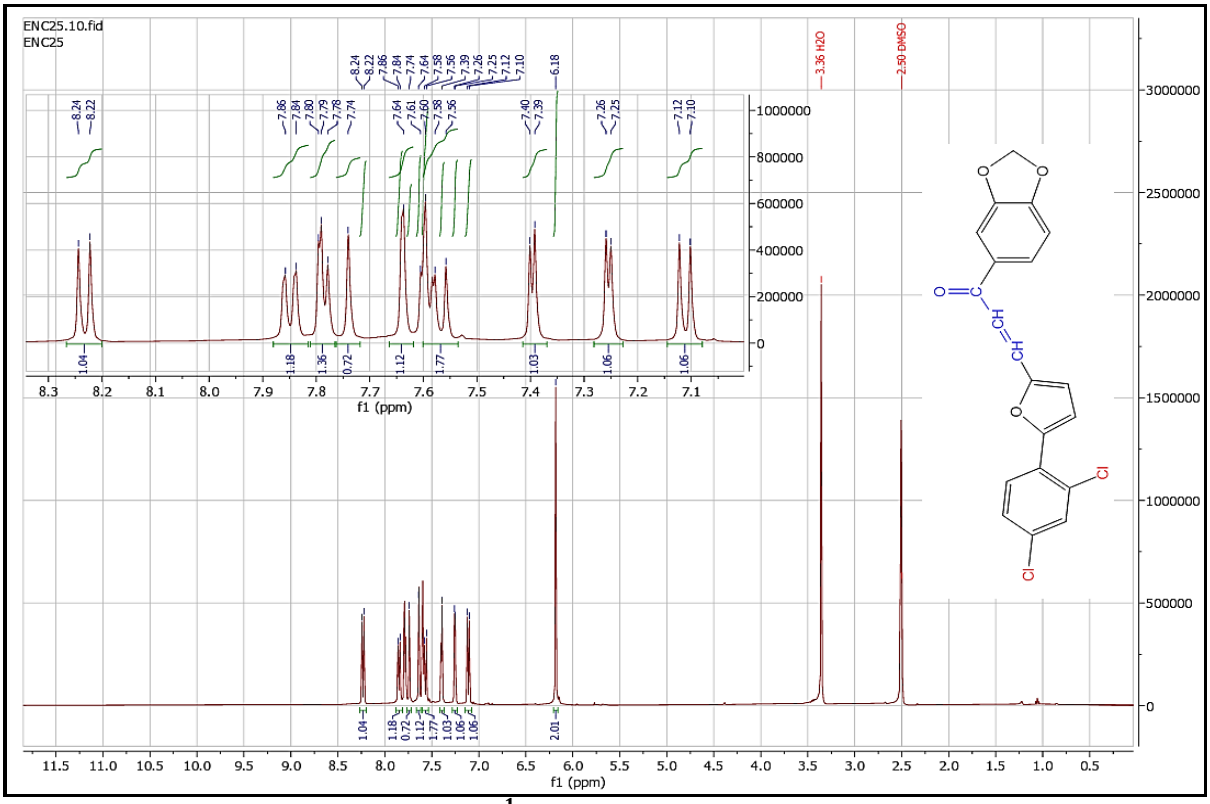


Figure-5: ^{1}HNMR spectrum for 2a

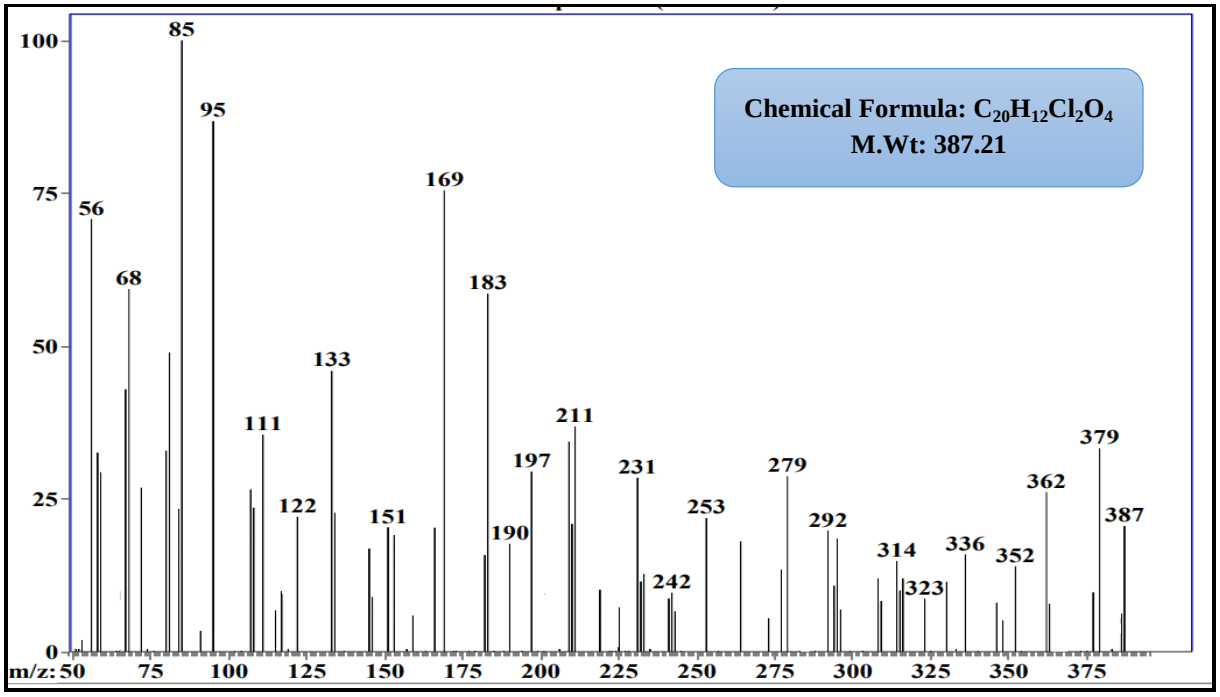


Figure-6: GC-mass spectrum for 2a

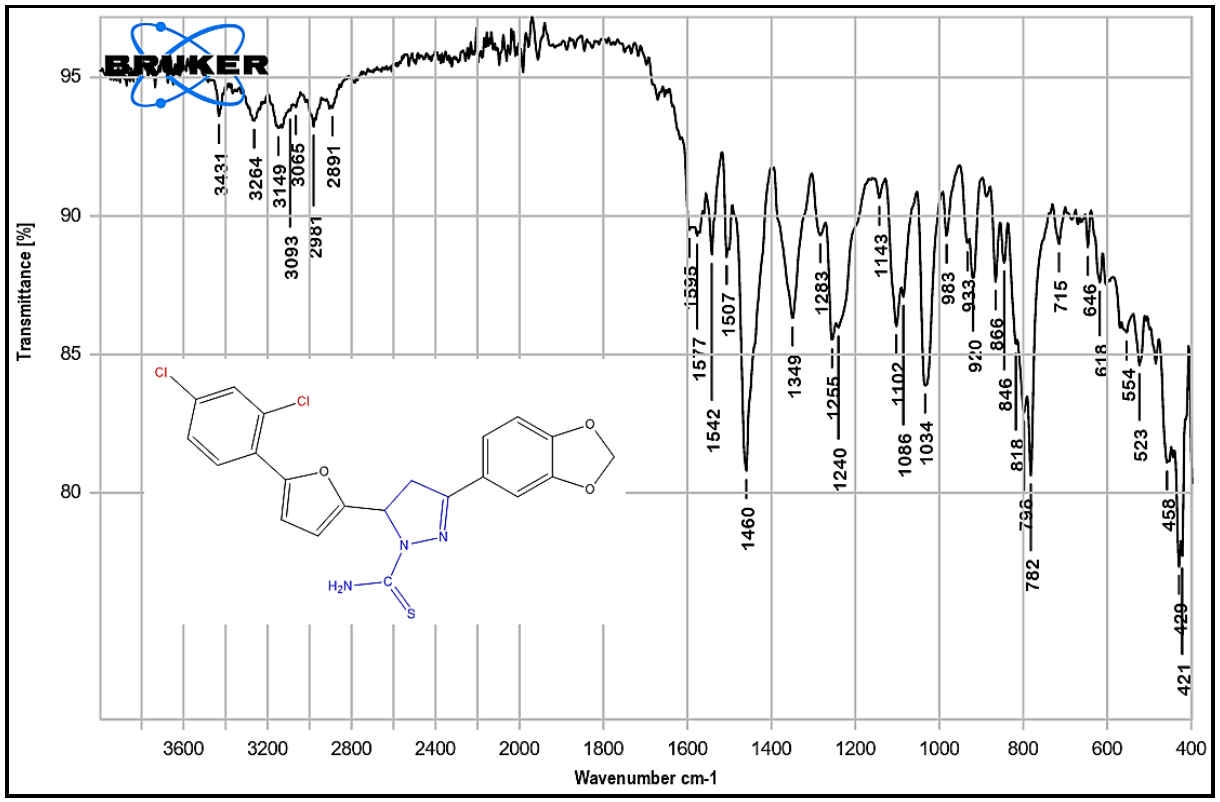


Figure-7: FTIR spectrum for 3a

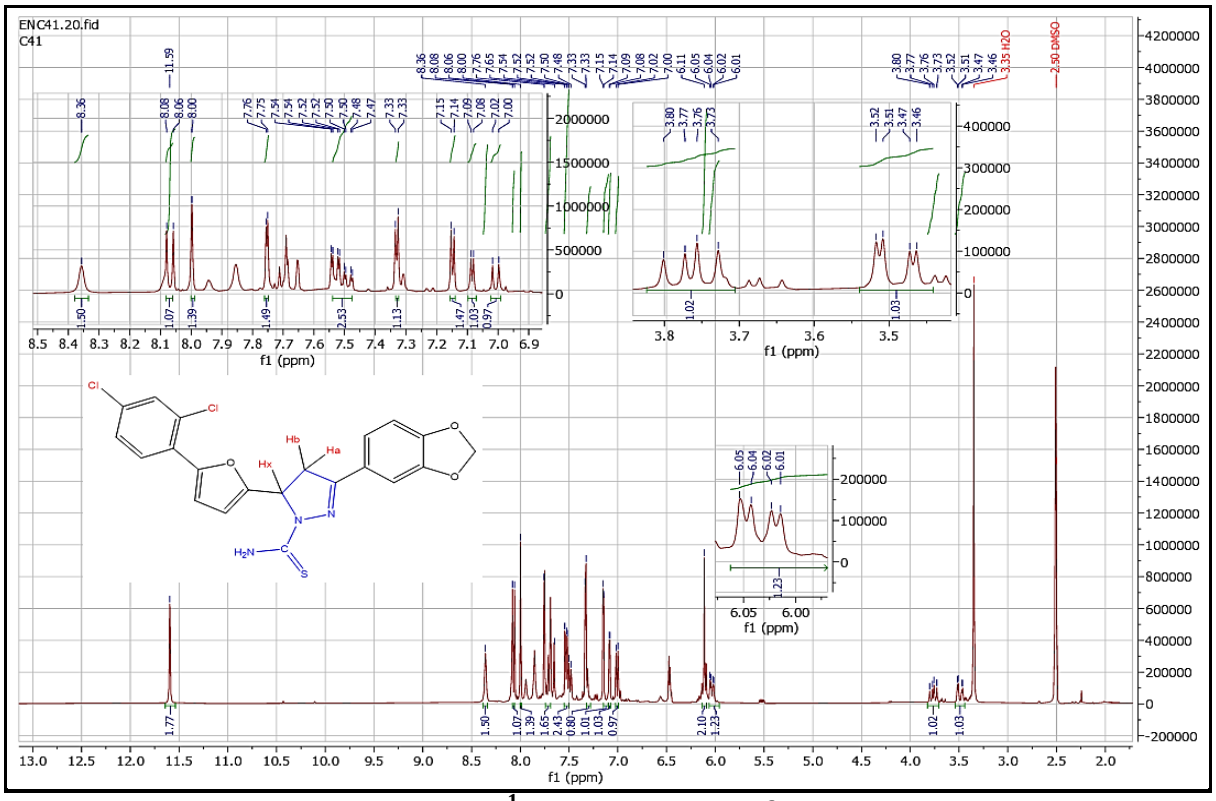


Figure-8: ^{1}HNMR spectrum for 3a

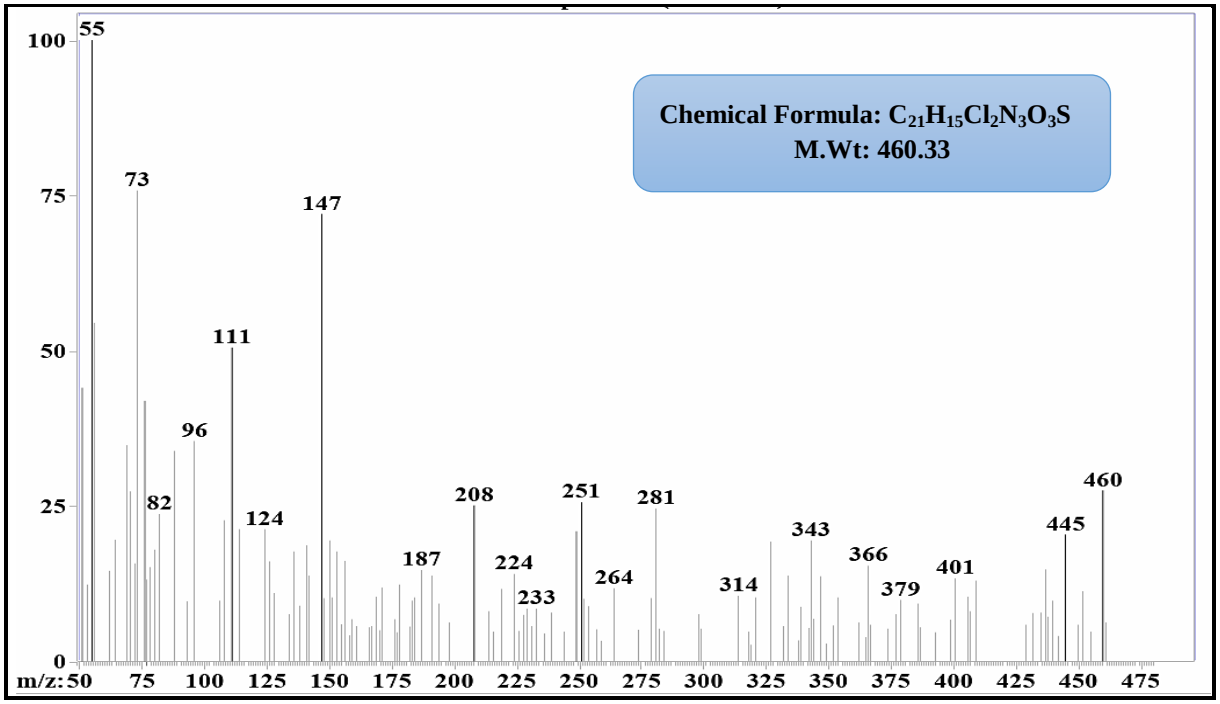


Figure-9: GC-mass spectrum for 3a

Biological study

The *in vitro* results of antioxidant activity for the synthesized compounds were estimated depending on the concentration of specific compound which inhibit 50% of DPPH free radical (IC_{50}). The results exhibited that the derivatives **3e** and **3f** revealed as the most potent antioxidant activity against DPPH compared with Ascorbic acid (standard) as shown in Table 3-1, **(Figure 10)**. Chalcone derivatives **2b, 2g** and **2h** exhibited a good antioxidant activity compared to Ascorbic acid because of the nitro and carbonyl groups that are present in their structures as well as aromatic rings that make a resonance system which capture the electrons for more time and decreased the free radicals activity [19]. Finally the tri-substituted pyrazolines **3e** & **3f** revealed excellent antioxidant activity, generally most of carbothioamide derivatives displayed a high antioxidant activity may be due to presence of thiol atom (S) which reported as a good radical scavenger [20] as well as the presence of nitro group and aromatic rings that enhanced the resonance in their structures.

Table 3-1: Antioxidant activity for some of the synthesized compounds (IC_{50} µg/mL)

No. of compounds	IC_{50} µg/mL
Ascorbic acid	32.57
2b	112.72
2g	156.33
2h	120.45
3e	54.81
3f	57.06

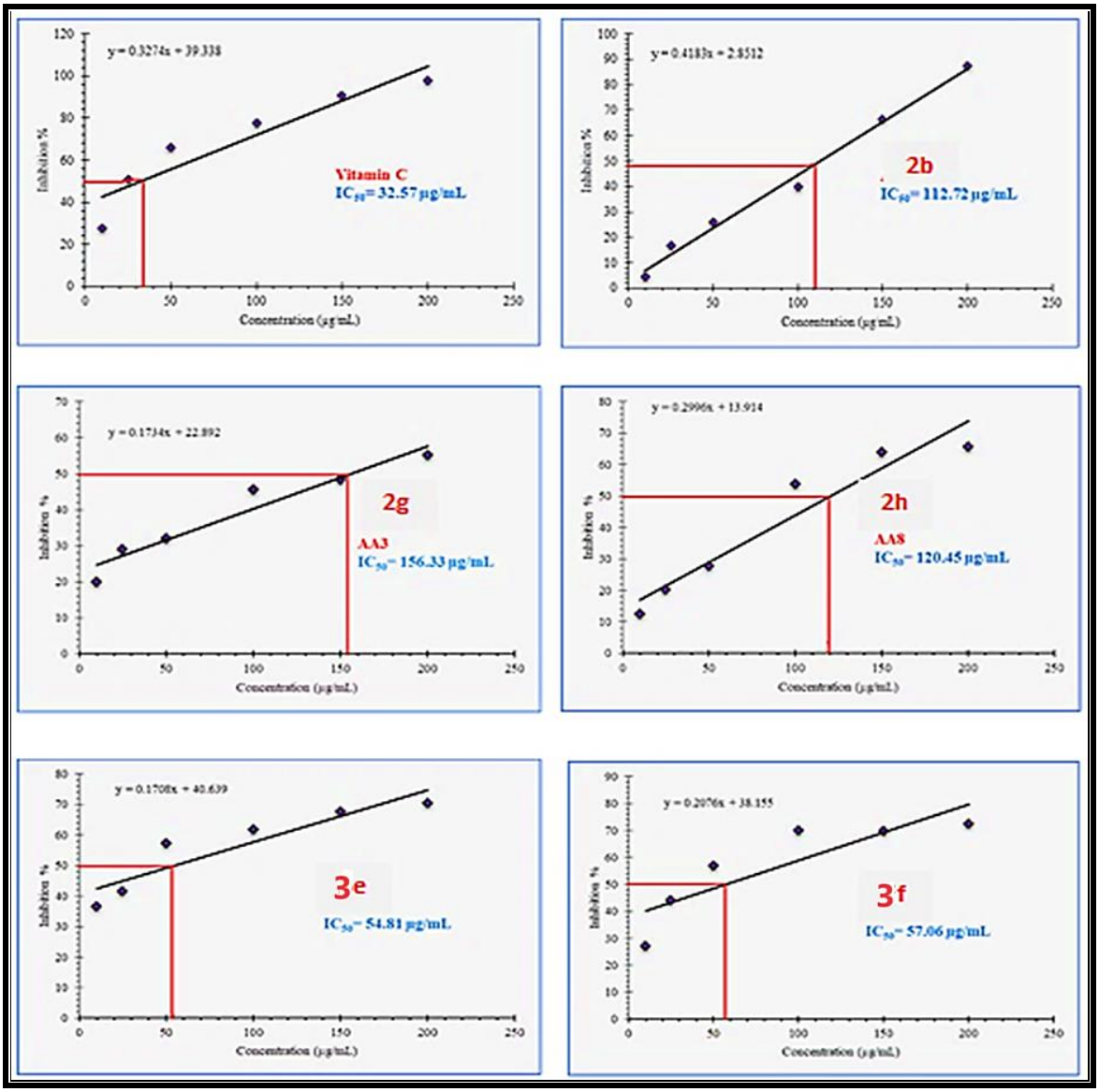


Figure 10: The percentage of inhibition against concentration of Ascorbic acid and the potent antioxidant compounds 2b, 2g, 2h, 3e and 3f

Conclusion:

This project led to synthesis of new chalcone compounds in order to create new active tri-substituted pyrazoline derivatives, the produced compounds were confirmed via spectroscopic technique FTIR, ^{1}H-NMR & GC-Mass spectroscopy. The antioxidant activity was evaluated for new derivatives and exhibited excellent to good activity. As a result, depending on the IC_{50} values compounds **3e** and **3f** can be classified as newly discovered antioxidants.

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