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Microwave-Assisted Synthesis and Cytotoxicity Evaluation of Some Novel Pyrazole Containing Imidiazoles, Pyrazoles, Oxazoles, Thiadiazoles and Benzochromene Derivatives

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A SERIES of novel pyrazole derivatives bearing pyran, pyridine, pyrazole, imidazol, 1,3 oxazole and 1,3,4-thiadiazole 4a,b, 5a,b, 6, 8, 9 and 14a-g have been synthesized. 2-Amino-4-(3-methyl-1-phenyl-1H-pyrazol-4-yl)-4H-benzo[g]chromene-3-carbonitrile derivative 15 was synthesized under microwave irradiation. Also compound 15 was used for the synthesis of benzo[g]chromene derivatives 16 & 17 and benzo [g] chromene [2,3-d] pyrimidine derivative 19. The structure of the newly synthesized compounds was elucidated on the basis of analytical and spectral analyses. All the synthesized compounds screened for the anticancer activity against three tumor cell lines using doxorubicin as standard. Compounds 5b (IC_{50} =0.36, 0.28, 0.32 μmol L^{-1}) and 14b (IC_{50} =0.38, 0.32, 0.22 μmol L^{-1}) has excellent cytotoxic agents against the three tumor cell lines, which is more potent than the activity of doxorubicin.

Keywords: Pyrazole derivatives, Microwave irradiation, Imidazolylpyrazole derivative, 1,3,4-thiadiazole, Antitumor.

Introduction

In the new millennium, cancer became one of the most common diseases, which is the second cause of mortality in the world. Traditional chemotherapeutic agents are cytotoxic by means of interfering with cell division but cancer cells vary widely in their susceptibility to these agents. So it clearly underlies the urgent need for developing novel chemotherapeutic agents with more potent antitumor activities. Recently, pyrazole derivatives have attracted a great attention due to their several chemicals and pharmacological importance [1-3]. Moreover, many pyrazole derivatives exhibit a wide range of therapeutic activities including anticonvulsant [4], analgesic, anti-inflammatory [5-7], antimicrobial [8], anticoagulant activity [9], antioxidant [10], antiamoebic [11,12], Antidepressant [13], antihyperglycemic [14], anti-histaminic [15], anti-viral [16], anti-HIV [17], and anticancer [18-22]. (Fig. 1).

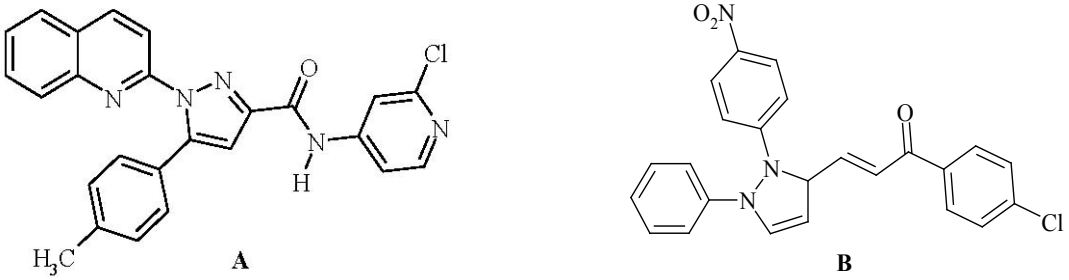

Fig. 1. Antiproliferative agents containing pyrazole moiety.

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Various five membered heterocycles like 1,3,4-thiadiazole derivatives attracted a great attention due to their wide range of biological activities such as antimicrobial [23], antituberculosis [24], antifungal [25], diuretic agents [26], and anticancer [27]. Microwave assisted technique has attracted a great attention of chemists in current organic synthesis [28, 29] due to its unique advantages, such as higher yields, reduced pollution, shorter reaction times and low cost.

In the past few decades, five membered heterocyclic structure containing two or more than one heteroatoms in its ring (O, S, N) is the core skeleton in the synthesis of anticancer drugs. Such heterocyclic rings are pyrazole, imidiazole, oxazole, 1,3,4 thiadiazole which improved anticancer activities when introduced it in the pyrazole skeleton [30].

Therefore, by considering all of the above biological importance of pyrazole derivatives, and in continuation of our ongoing work [31-34]. We can say that pyrazole ring has been used for prospective development of new drug against cancer cell, so we designed and synthesized a series of novel pyrazole derivatives bearing imidiazole, pyrazole, oxazole, thiadiazole, benzo-chromene ring under microwave irradiation in the hope of obtaining novel antiproliferative agents. Their biological activities in vitro are evaluated and the structure activity relationships (SAR) are also discussed.

Experimental

Materials

All melting points were measured on an Electrothermal 9100 series digital melting point apparatus (Shimadzu, Tokyo, Japan). Microanalytical data were gathered with a Vario Elementar apparatus (Shimadzu). Elemental analyses of all compounds were within ± 0.4% of the theoretical values. The IR spectra (KBr) were recorded on a Perkin Elmer 1650 spectrometer (Shelton, CT, USA). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL EX-300 and JEOL ECA-500 (Shimadzu, Tokyo, Japan). Chemical shifts were expressed in ppm relative to $SiMe_4$ as internal standard in DMSO-d_6 as a solvent. Mass spectra were recorded on a 70eV Finnigan SSQ 7000 spectrometer (Thermo-Instrument System Incorporation, Columbia, MD, USA). The purity of the compounds was checked on aluminum plates coated with silica gel (Merck, Darmstadt, Germany). Chemicals and solvents (Analar ≥ 99%) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Doxorubicin disks were supplied by the Pasteur Laboratory (Giza, Egypt).

General Procedure for the synthesis of 3-(3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-substituted prop-2-en-1-one (3a,b)

A solution of acetophenone 2a or 2-acetylthiophene **2b** (10 mmol) in alcoholic NaOH solution (10 %, 30 mL), a solution of 3-methyl-1-phenyl-1*H*-pyrazole-4- carboxaldehyde 1 (1.86 g,10 mmol) was added gradually. The mixture was irradiated in a CEM Discover Focused Synthesizer (160 W, 70 °C, 200 psi, 180-300 Sec), the progress of the reaction was monitored by TLC after every 30 sec. The mixture was cooled to room temperature and the obtained solid was filtrated off, washed with cold EtOH (15 mL), and dried, and crystallized from ethanol.

3-(3-Methyl-1-phenyl-1H-pyrazol-4-yl)-1-phenylprop-2-en-1-one (3a)

White crystal in 60% yield; mp. 140-142 °C; IR (KBr, cm^{-1}): υ 3060 (CH arom.); 2975, 2870 (CH aliph.); 1654 (C=O); 1610 (C=N); 1585 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.43 (s, 3H, CH_3), 6.94 (d, 1H, J = 18.90 Hz, CH=CH), 7.06- 8.15 (m, 10H, Ar-H), 8.89 (s, 1H, C=CH of the pyrazole ring); ^{13}CNMR (DMSO-d_6): δ 13.80 (CH_3), 123.06, 124.01, 125.10, 126.10, 127.40, 128.30, 128.40, 129.00, 131.00, 131.90, 137.30, 138.10, 139.05, 141.80, 145.30, 147.40, 148.80 (C=N of the pyrazole), 168.90 (C=O); Its MS (m/z), 288 (M^+, 79%); $C_{19}H_{16}N_2O$ (288.34); calcd; % C: 79.14, % H: 5.59, % N: 9.72; Found; % C: 79.11, % H: 5.55, % N: 9.70.

3-*(3-Methyl-1-phenyl-1H-pyrazol-4-yl)-1-(thiophen-2-yl)prop-2-en-1-one (3b)*

Yellow crystal in 65% yield; mp. 159-161 °C; IR (KBr, cm^{-1}): υ 3057 (CH arom.); 2980, 2867 (CH aliph.); 1655 (C=O); 1604 (C=N); 1575 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.42 (s, 3H, CH_3), 6.95 (d, 1H, J = 18.90 Hz, CH=CH), 7.19–7.92 (m, 8H, Ar-H , thiophene-H), 8.90 (s, 1H, C=CH of the pyrazole ring); ^{13}CNMR (DMSO-d_6): δ 14.00 (CH_3), 124.32, 125.10, 126.10, 127.36, 128.31, 128.40, 130.50, 131.84, 132.19, 132.94, 137. 30, 141.80, 145.50, 148.80(C=N of the pyrazole), 160.61(thiophene-C), 170.90 (C=O); Its MS (m/z), 294 (M^+, 65%); $C_{17}H_{14}N_2OS$ (294.37); calcd; % C: 69.36, % H: 4.79, % N: 9.52; Found; % C: 69.33, % H: 4.75, % N: 9.49.

General Procedure for the synthesis of Ethyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-

oxo- 6-substituted- 2H-pyran-3-carboxylate derivatives (4a,b)

A mixture of 3a,b (10 mmol) and ethyl cyanoacetate (1.13 mL, 10 mmol) in absolute ethanol(30 mL) in the presence of piperidine was stirred at room temperature for 10 h. The solid formed was filtered off, washed with ethanol, dried and crystallized from dioxane.

Ethyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-oxo-6-phenyl-2H-pyran-3-carboxylate (4a)

Gray powder in 55 % yield; mp. 182-184 °C; IR (KBr, cm^{-1}): υ 3045 (CH arom.); 2980, 2868 (CH aliph.); 1682, 1730 (2C=O); 1610 (C=N), 1590 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 1.36 (t, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.38 (q, 2H, CH_2), 7.30 (s, 1H, pyran H-5), 7.50–7.98 (m, 10H, Ar-H), 8.86 (s, 1H, C=CH of the pyrazole ring); ^{13}CNMR (DMSO-d_6): δ 14.08, 15.00, 24.45, 26.33, 52.70, 62.70, 114.30, 116.05, 123.40, 124.05, 125.17, 127.40, 128.40, 128.60, 129.30, 131.00, 133.70, 137.30, 145.30, 147.40, 148.80 (C=N of the pyrazole), 166.80 (C=O), 195.40 (C=O ester); Its MS (m/z), 400 (M^+, 69%); $C_{24}H_{20}N_2O_4$ (400.42); calcd; % C: 71.99, % H: 5.03, % N: 7.00; Found; % C: 71.97, % H: 5.01, % N: 6.58.

Ethyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-oxo-6-(thiophen-2-yl)- 2H-pyran-3-carboxylate (4b)

White powder in 80% yield; mp. 186-188 °C; IR (KBr, cm^{-1}): υ 3050 (CH arom.); 2965, 2874 (CH aliph.); 1670, 1735 (2C=O); 1604 (C=N); 1589 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 1.34 (t, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.35 (q, 2H, CH_2), 7.35 (s, 1H, pyran H-5), 7.43–8.09 (m, 8H, Ar-H & thiophene-H), 8.84 (s, 1H, C=CH of the pyrazole ring); ^{13}CNMR (DMSO-d_6): δ 14.05, 15.04, 24.65, 27.00, 52.60, 62.00, 115.40, 117.08, 123.40, 125.20, 127.40, 128.34, 128.60, 131.00, 133.70, 137.30, 145.30, 147.40, 148.00 (C=N of the pyrazole), 161.09 (thiophene-C) 166.00 (C=O), 194.90 (C=O ester); Its MS (m/z), 406 (M^+, 71%); $C_{22}H_{18}N_2O_4S$ (406.45); calcd; % C: 65.01, % H: 4.46, % N: 6.89; Found; % C: 65.00, % H: 4.42, % N: 6.87.

General Procedure for the synthesis of ethyl-1-amino-4-(3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-oxo-6-(phenyl and\ or thiophenyl)-1,2-dihydro-pyridine-3-carboxylate (5a, b)

A mixture of 4a, b (10 mmol) and hydrazine hydrate (10 mmol) in absolute ethanol (30 mL) was heated under reflux for 9h. The solid formed was filtered off, dried and crystallized from ethanol.

Ethyl-1-amino-4-(3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carboxylate (5a)

Orange crystals in 75 % yield; mp. 210-212 °C; IR (KBr, cm^{-1}): υ 3400, 3350 (NH_2); 1660, 1710 (2C=O); 1605 (C=N); 1588 (C=C) ; ^{1}H NMR (DMSO-d_6, δ, ppm): 1.45 (t, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.41 (q, 2H, CH_2), 5.45 (s, 2H, D_2O exchangeable, NH_2), 6.90–7.98 (m, 10H, Ar-H), 8.24 (s, 1H, pyridone ring), 8.80 (s, 1H, C=CH of the pyrazole ring); ^{13}CNMR (DMSO-d_6): δ 15.80, 17.00, 24.50, 26.40, 52.70, 62.64, 114.20, 116.60, 123.50, 125.10, 126.17, 127.60, 128.40, 129.40, 131.00, 132,05, 133.70, 135.01, 136.30, 145.30, 147.50, 148.70 (C=N of the pyrazole), 150.80 (C=O), 165.00 (C=O ester); Its MS (m/z), 414 (M^+, 69%); $C_{24}H_{22}N_4O_3$ (414.45); calcd; % C: 69.55, % H: 5.35, % N: 13.52; Found; % C: 69.51, % H: 5.32, % N: 13.50.

Ethyl-1-amino-4-(3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-oxo-6-(thiophene-2-yl)-1,2-dihydro -pyridine-3- carboxylate (5b)

Yellow powder in 70% yield; mp. 218-220 °C; IR (KBr, cm^{-1}): υ 3390, 3309 (NH_2); 1669, 1695 (2C=O); 1600 (C=N); 1593 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 1.46 (t, 3H, CH_3), 2.54 (s, 3H, CH_3), 4.44 (q, 2H, CH_2), 5.40 (s, 2H, D_2O exchangeable, NH_2), 7.00–8.14 (m, 8H, Ar-H & thiophene-H), 8.20 (s, 1H, pyridone ring), 8.79 (s, 1H, C=CH of the pyrazole ring); Its MS (m/z), 420 (M^+, 65%); $C_{22}H_{20}N_4O_3S$ (420.48); calcd; % C: 62.84, % H: 4.79, % N: 13.32; Found; % C: 62.80, % H: 4.76, % N: 13.29.

3'-Methyl-1',5-diphenyl-3,4-dihydro-1'H,2H-3,4'-bipyrazole (6)

A solution of the chalcones **3a** (2.88 g, 10 mmol), 0.3 g (60 mmol) of hydrazine hydrate was refluxed in ethanol for 8 hours and cooled. The precipitate filtered off, and then washed with ethanol and crystallized from diethyl ether as yellow crystal in 88 % yield; mp. 197-199 °C; IR (KBr, cm^{-1}): 3346 (NH); υ 3050 (CH arom.); 2980, 2864 (CH aliph.); 1606 (C=N); 1589 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.40 (s, 3H, CH_3), 3.43 (d, 2H, CH_2), 4.82 (t, 1H, CH), 7.23-7.45 (m, 5H, Ar-H), 7.61, 7.98 (m, 6H, Ar-H +NH), 8.85 (s, 1H, C=CH of the pyrazole ring); ^{13}CNMR (DMSO-d_6): δ 14.05, 40.6, 63.7, 118.06, 123.05, 125.20, 126.60, 127.10, 128.50, 129.09, 131.90, 137.20, 138.10, 139.40, 141.80, 143.00, 145.30, 147.40, 148.80 (C=N of the pyrazole); Its MS (m/z), 300 (M^+, 100%); $C_{19}H_{16}N_4$ (300.37); calcd; % C: 75.96, % H: 5.36, % N: 18.65; Found;

% C: 75.91, % H: 5.34, % N: 18.61.

General Procedure for the synthesis of 4-[(substituted)-1H-imidazol-2-yl]-3-methyl-1-phenyl-1H-pyrazole (8a,b)

A mixture of compound 1 and 1,2-diketones (7a, b) (10 mmol), ammonium acetate (10 equiv) and acetic acid (20mL) was heated at 180 °C under microwave irradiation condition for (10-13) minutes. The completion of reaction was monitored by using TLC, after completion of reaction, the reaction mixture was diluted with water and the precipitate was filtrated off, dried and recrystallized from diethyl ether.

4-[4,5-difuran-2-yl)-1H-imidazol-2-yl]-3-methyl-1-phenyl-1H-pyrazole (8a)

Obtained from 1, 2-difuran- 2-yl-ethane-1,2-dione **7a** (1.9 g, 10 mmol) as white yellowish crystal in 90 % yield; mp. 217-219 °C; IR (KBr, cm^{-1}): 3340 (NH); υ 3080 (CH arom.); 2979, 2884 (CH aliph.); 1604 (C=N); 1589 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.35 (s, 3H, CH_3), 6.13–6.18 (dd, J=7.5 Hz, 2H, furanyl), 6.85–6.89 (d, J=8 Hz, 2H, furanyl), 7.18 (s, 2H, furanyl), 7.22–7.48 (m, 5H, Ar-H), 8.80 (s, 1H, C=CH of the pyrazole ring), 12.42 (brs, 1H, NH); Its MS (m/z), 356 (M^+, 100%); $C_{21}H_{16}N_4O_2$ (356.37); calcd; % C: 70.77, % H: 4.52, % N: 15.72; Found; % C: 70.73, % H: 4.51, % N: 15.69.

4-(4,5-Diphenyl-1H-imidazol-2-yl)-3-methyl-1-phenyl-1H-pyrazole (8b)

Obtained from 1,2-diphenyl -ethane-1,2-dione (**7b**) (2.1 g, 10 mmol) as pale yellow crystal in 93 % yield; mp. 202-204 °C; IR (KBr, cm^{-1}): υ 3343 (NH); 3087 (CH arom.); 2980, 2879 (CH aliph.);1610 (C=N); 1590 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.33 (s, 3H, CH_3), 7.42–8.12 (m, 15H, Ar-H), 8.79 (s, 1H, C=CH of the pyrazole ring), 12.61 (brs, 1H, NH); Its MS (m/z), 376 (M^+, 91%); $C_{25}H_{20}N_4$ (376.4); calcd; % C: 79.76, % H: 5.35, % N: 14.88; Found; % C: 79.73, % H: 5.33, % N: 14.84.

2-(3-Methyl-1-phenyl-1H-pyrazol-4-yl)-4,5-dihydro-1,3-oxazole (9)

3-Methyl-1-phenyl-1*H*-pyrazole-4-carboxaldehyde 1 (1 equiv) and pyridinium hydrobromide perbromide (catalyst; 0.02 equiv) were heated to 150 °C. After the addition of 2-aminoethanol (6 equiv), the resulting suspension was stirred at 150 °C for 24 h. the reaction mixture was cooled to room temperature and chloroform was added. The organic phase was washed 3 times with water and dried. Filtration and evaporation of the solvent under reduced pressure gave a crude product, which was purified by column chromatography (SiO_2, dichloromethane: ethylacetate 4:1, 1% NEt_3), as brown powder in 60 % yield; mp. 230-232 °C; IR (KBr, cm^{-1}): υ 3053 (CH arom.); 2975, 2864 (CH aliph.); 1610 (C=N); 1585 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.41 (s, 3H, CH_3), 4.08 (t, 2H, CH_2), 4.45 (t, 2H, CH_2), 6.92–7.40 (m, 5H, Ar-H), 8.84 (s, 1H, C=CH of the pyrazole ring); ^{13}CNMR (DMSO-d_6): δ 14.05, 55.07, 67.90, 127.71, 129.04, 130.03, 130.90, 135.80, 143.00, 145.30, 148.83; Its MS (m/z), 227 (M^+, 71%); $C_{13}H_{13}N_3O$ (227.26); calcd; % C: 68.70, % H: 5.77, % N: 18.49; Found; % C: 68.70, % H: 5.75, % N: 18.46.

Methyl-2-[(3- methyl-1-phenyl-1H-pyrazol-4-yl) methylidene] hydrazine carbodithoate (10)

A mixture of compound **1** (1.86 g,10 mmol) in ethanol and methyl hydrazinecarbodithioate (1.22 g, 10 mmol) was stirred at room temperature for 5 h. The solid product was filtered off, recrystallized from ethanol as a yellow powder in 75 % yield; mp: 159–161°C; IR (KBr, cm^{-1}): υ 3198 (NH); 2993, 2918 (CH aliph.); 1601 (C=N); 1590 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.30 (s, 3H, CH_3), 2.67 (s, 3H, SCH_3), 6.20 (s, 1H, HC=N), 7.56–7.69 (5H, m, Ar-H), 8.28 (s, 1H, NH), 8.84 (s, 1H, C=CH of the pyrazole ring); ^{13}CNMR (DMSO-d_6): δ 14.90, 21.00, 116.40, 125.80, 129.60, 129.80, 132.40, 133.10, 134.70, 135.01, 148.60, 164.60, 191.30; Its MS (m/z), 290 (M^+, 59%); $C_{13}H_{14}N_4S_2$ (290.40); calcd; % C: 53.77, % H: 4.86, % N: 19.29; Found; % C: 53.74, % H: 4.83, % N: 19.24.

General Procedure for synthesis of 2-[(3-methyl-1-phenyl-1H-pyrazol-4-yl)- methyl- idene] -hydrazinylidene}-3-(4-substituted-phenyl)-5-(substituted)-2,3-dihydro-1,3,4-thia-diazole (14a-g)

A mixture of compound **10** (2.9 g,10 mmol) and the appropriate hydrazonoyl halides 11a–g (10 mmol) in dry chloroform (40 mL) and 5 drops of triethylamine, was stirred under reflux for 6 h. The solid product was washed three times with 30 mL methanol and recrystallized from DMF to produce 14a–g.

2-[(3-Methyl-1-phenyl-1H-pyrazol-4-yl) methylidene]hydrazinylidene}-3,5-diphenyl-2,3-dihydro-1,3,4-thiadiazole (14a)

Orange powder in 70 % yield; mp: 210–212°C; IR (KBr, cm^{-1}): υ 3058 (CH arom.); 2954, 2895 (CH aliph.); 1603 (C=N); 1595 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.49 (s, 3H, CH_3),

6.18 (s,1H, HC=N), 7.10–7.95 (m, 15H, Ar-H), 8.79 (s, 1H, C=CH of the pyrazole ring); ^{13}CNMR (DMSO-d_6): δ 16.90 (CH_3), 116.00, 116.20, 117.30, 118.20, 118.60, 119.30, 119.60, 120.00, 120.20, 120.60, 122.30, 127.00, 128.50, 128.80, 132.40. 139.00, 147.70, 148.50, 151.40; Its MS (m/z), 436 (M^+, 70%); $C_{25}H_{20}N_6S$ (436.53); calcd; % C: 68.78, % H: 4.62, % N: 19.25; Found; % C: 68.72, % H: 4.58, % N: 19.21.

1-[4-(4-Chlorophenyl)-5-[(3-methyl-1-phenyl-1H-pyrazol-4-yl)methylidene] hydrazinyl idene} -4,5-dihydro-1,3, 4-thiadiazol-2yl] ethanone (14b)

Pale yellow powder in 82 % yield; mp. 240–242°C; IR (KBr, cm^{-1}): υ 3062(CH arom.); 2921, 2857 (CH aliph.); 1676 (C=O); 1607 (C=N); 1560 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.49 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 6.22 (s,1H, HC=N), 6.90 (d, 2H, J = 8.1 Hz, Ar-H), 7.20 (d, 2H, J = 8.1 Hz, Ar-H), 7.34-7.80 (m, 5H, Ar-H) 8.81 (s, 1H, C=CH of the pyrazole ring); ^{13}CNMR (DMSO-d_6): δ 13.67 (CH_3), 16.90 (CH_3), 115.00, 116.50, 117.30, 118.60, 119.30, 119.60 , 120.30, 122.30, 123,40, 124.05, 127.00, 128.60, 128.90, 132.40. 139.00, 147.70, 148.50, 151.40, 166.90; Its MS (m/z), 436 (M^+, 78 %), 437 (M^++1, 29 %); $C_{21}H_{17}ClN_6OS$ (436.91); calcd; % C: 57.73, % H: 3.92, % N: 19.23; Found; % C: 57.70, % H: 3.89, % N: 19.20.

1-[4-(4-Bromophenyl)-5-[(3-methyl-1-phenyl-1H-pyrazol-4-yl)methylidene]-hydrazinylidene} -4,5-dihydro -1,3,4-thiadiazol-2yl]ethanone (14c)

Orange powder in 69 % yield; mp: 281–283°C; IR (KBr, cm^{-1}): υ 3064 (CH arom.); 2983, 2860 (CH aliph.), 1668 (C=O); 1608 (C=N); 1595 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.46 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 6.24 (s,1H, HC=N), 6.87 (d, 2H, J = 8.0 Hz, Ar-H), 7.25 (d, 2H, J = 8.0 Hz, Ar-H), 7.40- 7.97 (m, 5H, Ar-H) 8.80 (s, 1H, C=CH of the pyrazole ring); Its MS (m/z), 483 (M^+ +2, 36), 481 (M+, 75); $C_{21}H_{17}BrN_6OS$ (481.36); calcd; % C: 52.40, % H: 3.56, % N: 17.46; Found; % C: 52.35, % H: 3.55, % N: 17.42.

Ethyl-1-[(3-methyl-1-phenyl-1H-pyrazol-4-yl)methylidene]hydrazinylidene}-3-phenyl -2,3-dihydro-1,3,4-thiadiazole-5-carboxylate (14d)

Orange powder in 70 % yield; mp: 185–187°C; IR (KBr, cm^{-1}): υ 3064 (CH arom.); 2984, 2870 (CH aliph.); 1708 (C=O); 1605 (C=N); 1595 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 1.33 (t, 3H, *J* = 7.2, CH_3) 2.39 (s, 3H, CH_3), 4.38 (q, 2H, *J* = 7.2, CH_2), 6.22 (s,1H, HC=N), 7.38–8.01 (m, 10H, Ar-H), 8.84 (s, 1H, C=CH of the pyrazole ring); Its MS (m/z), 432 (M^+, 76%); $C_{22}H_{20}N_6O_2S$ (432.49); calcd; % C: 61.10, % H: 4.66, % N: 19.43; Found; % C: 61.08, % H: ;4.62, % N: 19.40.

Ethyl-1-[(3-methyl-1-phenyl-1H-pyrazol-4-yl)methylidene]-hydrazinylidene}-3-(4-tollyl)-2,3-dihydro-1,3,4- thiadiazole-5-carboxylate (14e)

Orange powder in 70 % yield; mp: 185–187°C; IR (KBr, cm^{-1}): υ 3060 (CH arom.); 2980, 2868 (CH aliph.); 1715 (C=O); 1601 (C=N); 1596 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 1.40 (t, 3H, *J* = 7.2, CH_3), 2.24 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.14 (q, 2H, *J* = 7.2, CH_2), 6.24 (s,1H, HC=N), 6.92 (d, 2H, *J* =8.1 Hz, Ar-*H*), 7.32 (d, 2H, *J* =8.1 Hz, Ar-*H*), 7.50- 7.88 (m, 5H, Ar-H), 8.80 (s, 1H, C=CH of the pyrazole ring); ^{13}CNMR (DMSO-d_6): δ 13.67, 14.50, 16.90, (CH_3), 65.20 (CH_2), 114.00, 115.50, 117.30, 118.40, 119.20, 119.60, 120.30, 122.30, 123,50, 124.30, 126.00, 128.09, 128.90, 131.40. 139.09, 148.50, 168.90; Its MS (m/z), 446 (M^+, 65%); $C_{23}H_{22}N_6O_2S$ (446.52); calcd; % C: 61.87, % H: 4.97, % N: 18.82; Found; % C: 61.84, % H: 4.95, % N: 18.79.

2-[(3-Methyl-1-phenyl-1H-pyrazol-4-yl) methylidene]-hydrazinylidene}-3-phenyl-5-(naphthalen-2-yl)-2,3- dihydro-1,3,4-thiadiazole (14f)

Red powder in 68 % yield; mp: 190–192°C; IR (KBr, cm^{-1}): υ 3070 (CH arom.); 2960, 2853 (CH aliph.); 1610 (C=N); 1595 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.45 (s, 3H, CH_3), 6.25 (s,1H, HC=N), 7.18–7.85 (m, 16H, ArH's), 8.12 (s, 1H, naphthalene-H1), 8.75 (s, 1H, C=CH of the pyrazole ring); Its MS (m/z), 486 (M^+, 59%); $C_{29}H_{22}N_6S$ (486.59); calcd; % C: 71.58, % H: 4.56, % N: 17.27; Found; % C: 71.54, % H: 4.55, % N: 17.24.

2-[(3-Methyl-1-phenyl-1H-pyrazol-4-yl) methylidene]-hydrazinylidene}-3-phenyl-5-(thiophen-2-yl)-2,3-dihydro-1,3,4-thiadiazole (14g)

Pale red powder in 70 % yield; mp: 212–214°C; IR (KBr, cm^{-1}): υ 3059 (CH arom.); 2953, 2880 (CH aliph.); 1605 (C=N); 1599 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.40 (s, 3H, CH_3), 6.21 (s,1H, HC=N), 7.00–8.14 (m, 13H, Ar-H & thiophene-H), 8.79 (s, 1H, C=CH of the pyrazole ring); Its MS (m/z), 442 (M^+, 68%); $C_{23}H_{18}N_6S_2$ (442.55); calcd; % C: 62.42, % H: 4.10, % N: 18.99; Found; % C: 62.38, % H: 4.08, % N: 18.96.

2-Amino-4-(3-methyl-1-phenyl-1H -pyrazol-4-yl)-4H-benzo[g]chromene-3-carbonitrile (15)

Compound **1** (1.86 g,10 mmol), malononitrile (0.66 g, 10 mmol), β-naphthol(1.44 g, 10 mmol) and sodium carbonate (1.06 g, 10 mmol) were mixed using a mortar and pestle. The resulting mixture was heated at 150 °C under microwave irradiation condition for 10 minutes. After cooling, the reaction mixture was washed with water and recrystallization from DMF, as pale brown powder in 89 % yield; mp. 243-245 ºC; IR (KBr, cm^{-1}): υ 3445, 3327 (NH_2); 3050 (CH arom.); 2928, 2849 (CH aliph.); 2195 (C≡N); 1610 (C=N); 1595 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.38 (s, 3H, CH_3), 4.90 (s, 2H, NH_2, D_2O exchangeable), 5.06 (s, 1H, pyran), 7.30–8.20 (m, 11H, Ar-H), 8.78 (s, 1H, C=CH of the pyrazole ring); Its MS (m/z), 378 (M^+, 61%); $C_{24}H_{18}N_4O$ (378.42); calcd; % C: 76.17, % H: 4.79, % N: 14.81; Found; % C: 76.15, % H: 4.75, % N: 14.80.

Ethyl-3-cyano- 4-(3-methyl-1-phenyl-1H -pyrazol -4-yl) benzo[g]chromene-2-(N-sulfamoyl) acetate (16)

A mixture of compound **15** (3.78 g,10 mmol) and ethyl 2-(chlorosulfonyl)acetate (1.86 g,10 mmol) in dichloromethane (50 mL) and 5 drops of triethylamine, was stirred under reflux for 21 h. The solvent was evaporated under reduced pressure. The solid product was washed three times with 30 mL methanol and recrystallized from dioxane to produce **16,** as yellow powder in 60 % yield; mp. 270-272 ºC; IR (KBr, cm^{-1}): υ 3330 (NH); 3020 (CH arom.); 2920, 2850 (CH aliph.); 2200 (C≡N); 1713 (C=O); 1590 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 1.33 (t, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.93 (s, 2H, CH_2), 4.29 (q, 2H, CH_2), 4.98 (s, 1H, pyran), 7.18 (brs, 1H, NH), 7.38–8.25 (m, 11H, Ar-H), 8.90 (s, 1H, C=CH of the pyrazole ring); Its MS (m/z), 528 (M^+, 69%); $C_{28}H_{24}N_4O_5S$ (528.56); calcd; % C: 63.62, % H: 4.57, % N: 10.60; Found; % C: 63.60, % H: 4.54, % N: 10.57.

Methyl-3-[(3-cyano-4-(3-methyl-1-phenyl-5H -pyrazol-4-yl)-4H-benzo[g]chromene-2-yl) amino]-3-oxopropanoate (17)

A mixture of compound 15 (3.78 g,10 mmol) and methyl 3-chloro-3-oxopropionate (1.36 g,10 mmol) in dichloromethane (50 mL) and 5 drops of triethylamine, was stirred under reflux for 16h. The solvent was evaporated under reduced pressure. The solid product was washed three times with 30 mL methanol and recrystallized from dioxane to produce 17, as white powder in 71 % yield; mp. 282-284 ºC; IR (KBr, cm^{-1}): υ 3334 (NH); 3045 (CH arom.); 2954, 2878 (CH aliph.); 2210(C≡N); 1654, 1730(2C=O); 1595 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.39 (s, 3H, CH_3), 3.65 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 4.89 (s, 1H, pyran), 7.40–8.20 (m, 11H, Ar-H), 8.87 (s, 1H, C=CH of the pyrazole ring), 9.25 (brs, 1H, NH); Its MS (m/z), 478 (M^+, 63%); $C_{28}H_{22}N_4O_4$ (478.49); calcd; % C: 70.28, % H: 4.63, % N: 11.71; Found; % C: 70.26, % H: 4.60, % N: 11.71.

Ethyl-4-ethoxy-5-(3-methyl-1-phenyl-5H-pyrazol-4-yl)benzo[g]chromene[2,3-d] pyrimidine-2- carboxylate (19)

A mixture of compound 15 (3.78 g,10 mmol) and diethyl oxalate (1.46 g,10 mmol) in the presence of sodium ethoxide was heated under reflux for 10 h., after cooling to room temperature. The reaction mixture was poured in water, the solid product was filtered off, recrystallized from DMF as yellow powder in 60 % yield; mp: > 300°C; IR (KBr, cm^{-1}): υ 3065 (CH arom.); 2993, 2850 (CH aliph.); 1710 (C=O); 1595 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 1.25 (t, 3H, CH_3), 1.36 (t, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.30 (m, 4H, $2CH_2$), 5.03 (s, 1H, pyran), 7.10–8.15 (m,11H, Ar-H), 8.90 (s, 1H, C=CH of the pyrazole ring); Its MS (m/z), 506 (M^+, 60%); $C_{30}H_{26}N_4O_4$ (506.54); calcd; % C: 71.13, % H: 5.17, % N: 11.06; Found; % C: 71.10, % H: 5.16, % N: 11.02.

In vitro antitumor assay

Human breast adenocarcinoma (MCF-7), human hepatocellular carcinoma (HepG2) and colon cancer (HT29) cell lines were obtained from the National Cancer Institute (Cairo, Egypt). The cells were grown on RPMI-1640 medium supplemented with 10% inactivated fetal calf serum and 50 µg/mL gentamycin (Sigma, USA). The cytotoxicity of the compounds was evaluated on tumor cells using the method of Skehan [35]. The cells were grown as monolayers in growth RPMI-1640. The monolayers of 10^4 cells adhered at the bottom of the wells in a 96-well microtiter plate incubated for 24 h at 37 °C, 5% CO_2, 95 % air and 100 % relative humidity for 24 h prior to addition of experimental drugs to allow attachment of cells to the plate wall. After 24 h, cell line was fixed in situ with TCA (trichloroacetic acid). The mono layers were then washed with sterile phosphate buffered saline (0.01 M, pH 7.2). Simultaneously test compounds were dissolved in DMSO and diluted with saline to the appropriate volume and maintained in RPMI 1640 medium. Different concentrations of each test compound (5, 12.5, 25 and 50 µmol L^{-1}) were added to the

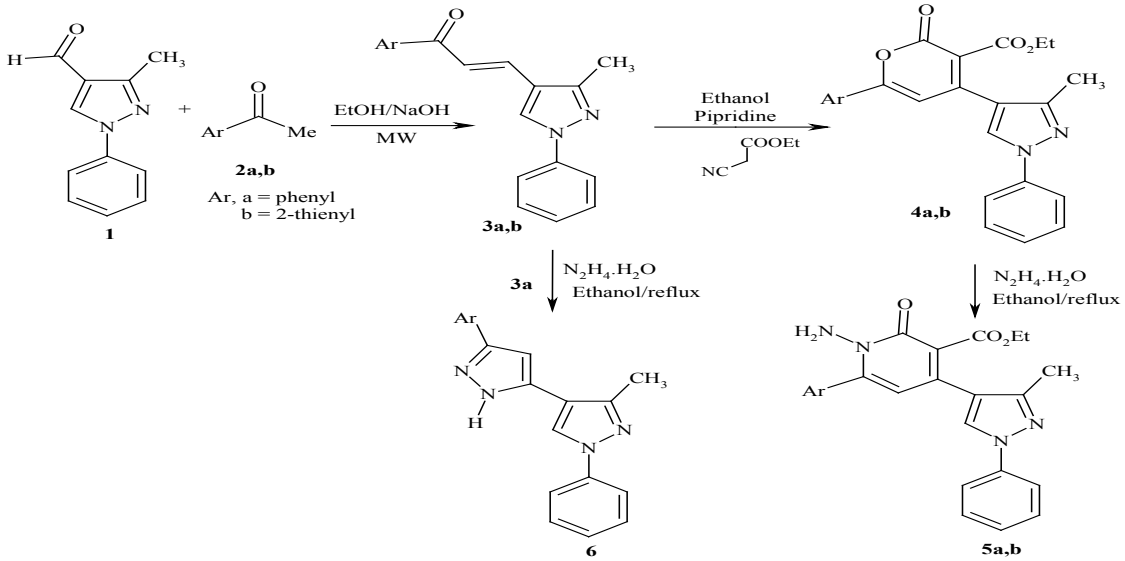
cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h at 37 °C and in an atmosphere of 5 % CO_2. After 48 h, cells were fixed in situ by gentle addition of 50 µL of cold 30 % (*m*/*V*) TCA (final concentration, 10 % TCA) and incubated for 60 min at 4 °C. The supernatant was discarded, the plates were washed five times with tap water and air dried. Sulforhodamine B solution (50 µL) at 0.4 % (*m*/*V*) in 1 % acetic acid was added to each of the wells and plates were incubated for 20 min at room temperature. After staining, unbound dye was removed by four washes with 1 % acetic acid and the attached stain was recovered with Tris-EDTA buffer. Color intensity was measured using an ELISA reader (BMG Labtech, Germany). The relation between the surviving fraction and drug concentration was plotted to get the survival curve for the three tumor cell line after specified time [35]. The molar concentration required for 50 % inhibition of cell viability (IC_{50}) was calculated from the constructed dose response curve using Prism software (Graphpad, Inc., USA) and compared with the reference drug doxorubicin. Results are given in Table 2.

Results and Discussion

Chemistry

Applying the typical procedure of Claisene Schmidt condensation for the synthesis of chalcones [36] from 3-methyl-1-phenyl-1*H*-pyrazole-4-carboxaldehyde (1) and acetophenone (2a) or 2-acetyl- thiophene (2b) as our model reaction. Initially, the stirring of an equimolar mixture of both compounds in ethanol, at ambient temperature, in the presence of 10 % aq. NaOH after 16-19 h of stirring afforded the chalcones derivatives **3a**,**b**. The microwave-assisted synthesis and conventional method was also employed in this experiment. NaOH/ EtOH system was applied under microwave irradiation, the best reaction condition is at 70-90 °C for (180-300) Sec. under microwave irradiation synthesis (Table 1).

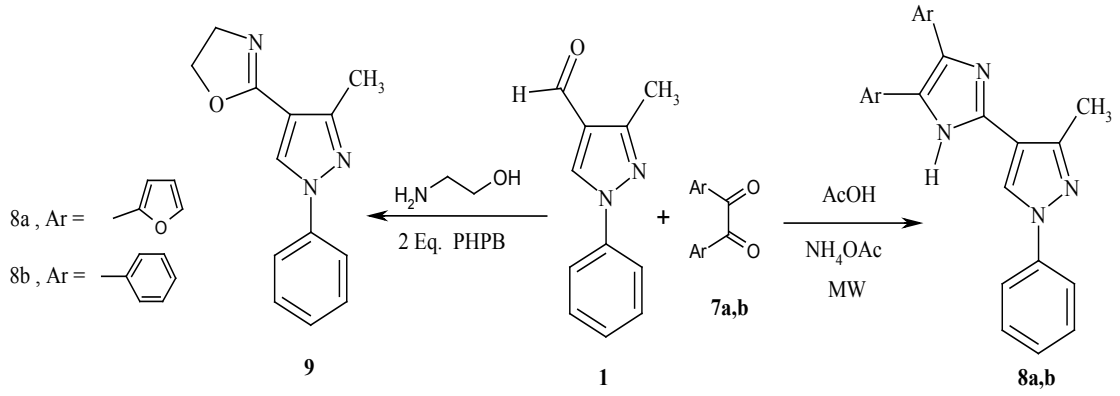
α,β-Unsaturated ketone is a simple substrate to synthesize a variety of heterocycles of known biological interest. pyran-3-carboxylate derivatives 4a,b were synthesized by the treatment of 3a,b with ethyl cyanoacetate in ethanol at room temperature. The structures of compounds 4a,b were established by spectral analyses. The IR spectra show two absorption bands at 1682, 1730 cm^{-1} and 1670, 1735 cm^{-1} for the ester and lactone carbonyl groups, respectively. In addition, the ^{1}H-NMR shows the pyran H-5 at δ 7.30-7.35 ppm and other protons in their expected locations. *N*-Nucleophilic addition reaction of hydrazine at the lactonic carbonyl group of 4a,b gave 1,2-dihydropyridine-3-carboxylate derivatives 5a,b. The IR spectra showed the presence of NH_2 group at υ 3400, 3350 cm^{-1} (5a**)** and at υ 3390, 3309 cm^{-1} (5b**)** as new bands and ^{1}H-NMR showed a singlet signal at 5.40 and 5.45 ppm attributed to amino group of compounds 5a,b respectively. Cyclocondensation of compounds 3a with *N*-nucleophiles under appropriate experimental conditions afforded pyrazoline derivatives 6, the IR spectra showed absence of the carbonyl group



Scheme 1. Synthesis of 4-substituted-3-methyl-1-phenyl-1H-pyrazole derivatives.

and the appearance of NH group at υ 3135 cm^{-1} (Scheme 1).

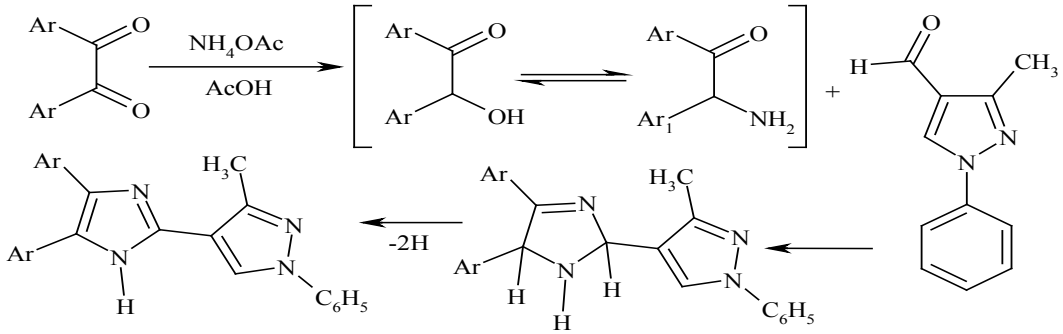
Microwave-assisted technique is a green method in current organic synthesis [37]. It is attractive offering reduced pollution, high yields and low cost. The method can often shorten the reaction time. As a part of an ongoing development of efficient protocols for the preparation of biologically active heterocycles from common intermediates (**1**). 4-Disubstituted imidiazolyl-3-methyl-1-phenyl-1*H*-pyrazole derivatives **8** were synthesized in high yield under microwave irradiation [38] by the reaction of 1,2-diketones such as 1,2-difuran-2-yl-ethane-1,2-dione (7a), 1,2-diphenyl-ethane-1,2-dione (7b) and 3-methyl-1-phenyl-1*H*-pyrazole-4-carboxaldehyde(1) in the presence of ammonium acetate (Table 1). Furthermore, treatment of (**1**) with 2-aminoethanol with pyridinium hydrobromide perbromide as a



Scheme 2. Synthesis of 4-(imdiazolyl and\or [1,3] oxazolyl) -3-methyl-1-phenyl-pyrazole derivatives.

catalyst in water at room temperature afforded 2-(3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-4,5 dihydro-1,3-oxazole (9) (Scheme 2).

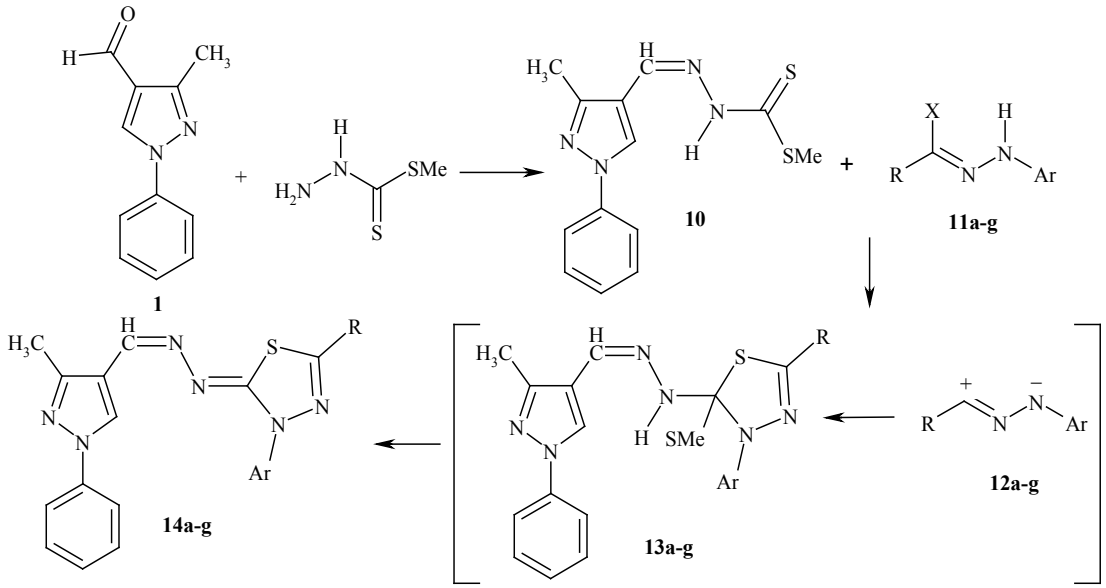
The most probable mechanism of the resulting compound **8**, which is shown in Scheme 3.



Scheme 3.

Treatment of 3-methyl-1-phenyl-1*H*-pyrazol-4-carboxaldehyde **1** with methyl hydrazine carbodithioate in ethanol afforded methyl-2-[(3-methyl-1-phenyl-1*H*-pyrazol-4-yl) methylidene] -hydrazine carbodithioate 10. The 1,3-dipolar cycloadditions of the nitrile imines generated in situ from hydrazonoyl chlorides 11a–g and triethylamine in dry chloroform to 2-(1-(3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-methylidene) hydrazine carbodithioate 10 afforded 2-[(3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-methylidene]-hydrazinylidene}-3-(4-substituted-phenyl)-5-(substituted)-2,3-dihydro-1,3,4-thiadiazole 14a–g in good yields Scheme 4. The mixture of an equimolar of 10, *C*-phenyl-*N*-phenyl hydrazonoyl chloride 11a in dry chloroform in presence of triethylamine was refluxed for 2 h. led to the compound 14a. This cycloaddition occurs only on C=S of 10 furnishing 2-[(3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylidene]hydrazinylidene}-3,5-diphenyl-2,3-dihydro-1,3,4-thiadiazole 14a. The mechanism of the reaction outlined in Scheme

3, which proceed via the electron rich nitrogen adds to the carbon of thione 10. The spectroscopic analyses (IR, NMR, MS), confirmed the structure of 14a. Similarly, treatment of the appropriate 10 with each of 11b-g afforded 14b–g, respectively, in good yield (Scheme 4).



a, Ar= C6H5
b, Ar= C6H4-Cl-4
c, Ar= C6H4-Br-4
d, Ar= C6H5
e, Ar= C6H4-CH3-4
f, Ar= C6H5
g, Ar= C6H5

a, R= C6H5 11,12,14
b, R= COCH3
c, R= COCH3
d, R= COOC2H5
e, R= COOC2H5
f, R= 2-Naphtol
g, R= 2-Thienyl

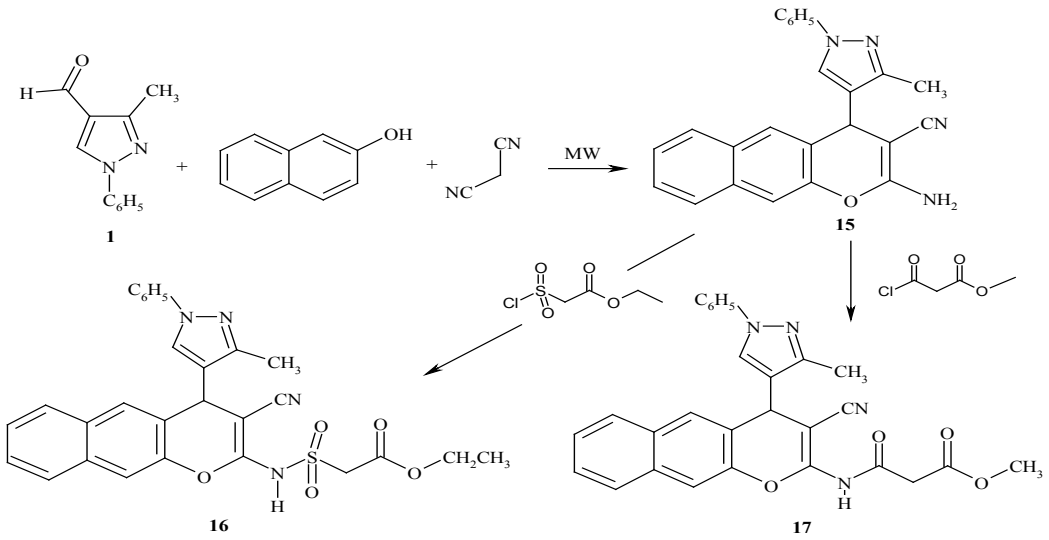
Scheme 4. synthesis of 2-[(3-methyl-1-phenyl-1H-pyrazol-4-yl)-methylidene]-hydrazinylidene}-3-(4- substituted-phenyl)-5-(substituted)-2,3-dihydro-1,3,4-thiadiazole 14a–g.

Solvent-free, catalyst-free and one-pot multi-component condensations are efficient procedures for the synthesis of the target compound 2-Amino-4-(3-methyl-1-phenyl-1H-pyrazol-4-yl)-4H-benzo[g]chromene-3-carbonitrile 15 in which equimolar quantities of 3-methyl-1-phenyl-1*H*-pyrazole -4-carboxaldehyde (1), malononitrile, *β*-naphthol and sodium carbonate were mixed using a mortar and pestle. The resulting mixture was heated at 150 °C under microwave irradiation condition for 10 minutes. The structures of compound 15 were established by both analytical and spectral analyses. The IR spectra show two absorption bands at 3445, 3327 cm^{-1} for NH_2 and 2195 cm^{-1} for (C≡N).

TABLE 1. Comparison of yields of 3a,b through methods with or without microwave irradiation, 8a,b and 15.

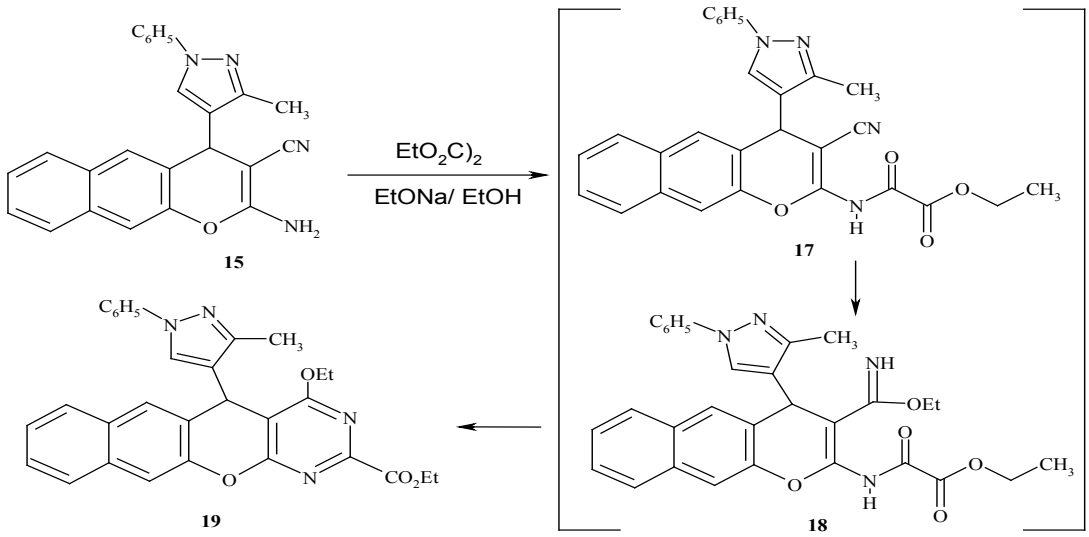
Comp.	Method	Time	Temperature\°C	Yield
3a	No-MW	16h	r.t.	60%
3b	No-MW	19h	r.t.	65%
3a	MW	180 Sec.	70	89%
3b	MW	300 Sec.	90	91%
8a	MW	10 min.	180	90%
8b	MW	13 min.	180	93%
15	MW	10min.	150	89 %

Chlorosulfonylacetic acid ethyl ester was treated with 2-amino-4*H*-chromene-3-carbonitrile derivatives 15 in the presence of triethylamine in DCM to obtain the 3-cyano-chromene-4-sulfamoylacetic acid ethyl ester derivative 16 in good yield. Also the reaction of 15 with methyl-3-chloro-3-oxopropionate in the presence of triethylamine generated methyl-3-[(3-cyano-4-(3-methyl-1-phenyl-1H-pyrazol-4-yl)-4H-benzo[g] chromene-2-yl) amino]-3-oxopropanoate 17 (Scheme 5).



Scheme 5. Synthesis of 2-Amino-4-(3-methyl-1-phenyl-1H -pyrazol-4-yl)-4H-benzo[g]chromene-3-carbonitrile derivatives 15-17.

Finally compound 15 react with diethyl oxalate in the presence of sodium ethoxide to give ethyl-4-ethoxy-5-(3-methyl-1-phenyl-1*H*-pyrazol-4-yl)benzo[g] chromene[2,3-d] pyrimidine-2-carboxylate (19) by successive *N*-acylation, the formation of imidate 18, and cyclization into pyrimidine derivatives 19 (Scheme 6).



Scheme 6. Synthesis of ethyl-4-ethoxy-5-(3-methyl-1-phenyl-1H-pyrazol-4-yl)benzo[g] chromene[2,3-d] pyrimidine -2- carboxylate 19.

Antitumor activity and SAR

In vitro the cytotoxic activity against the human breast adenocarcinoma (MCF-7), liver cancer (HepG2) and colon cancer (HT29) tumor cell lines of the newly synthesized compounds were investigated in comparison with the well-known anticancer standard drug doxorubicin Table 2. From the results of the study, it is inferred that among the new heterocyclic synthesized compounds in the present research work, exhibited significant activity compared to doxorubicin.

TABLE 2. The *in vitro* inhibitory activity of tested compounds against human breast adeno- carcinoma (MCF-7), hepatocellular carcinoma (HepG2) and colon cancer (HT29) cell lines expressed as IC_{50} values (µmol L^{-1}) ± standard deviation from three replicates.

Compd.	Tumor Cell Lines IC_{50} (µmol L^{-1})		
	MCF-7	HepG2	HT29
4a	22.40 ± 0.20	29.11 ± 0.21	25.42 ± 0.21
4b	29.41± 0.07	23.42 ± 0.21	20.1 ± 0.12
5a	4.35 ± 0.47	5.59 ± 0.37	4.06 ± 0.38
5b	0.36 ± 0.22	0.28 ± 0. 09	0.32 ± 0.01
6	10.71 ± 0.27	15.72 ± 0.24	13.71 ± 0.28
8a	0.94 ± 0.09	0.68 ± 0.11	0.90 ± 0.15
8b	0.82 ± 0.14	0.64 ± 0.19	1.02 ± 0.20
9	27.94 ± 0.13	37.7 ± 0.11	32.8 ± 0.14
14a	22.5 ± 0.24	27.90 ± 0.24	21.72 ± 0.14
14b	0.38 ± 0.03	0.32 ± 0.09	0.22 ± 0.04
14c	1.19 ± 0.07	0.94 ± 0.20	1.10 ± 0.23
14d	15.70 ± 0.25	13.72 ± 0.20	10.71 ± 0.27
14e	10.71 ± 0.27	15.72 ± 0.24	13.71 ± 0.28
14f	16.13 ± 0.21	14.40 ± 0.20	19.72 ± 0.20
14g	4.35 ± 0.47	5.59 ± 0.37	4.06 ± 0.38
15	43.43 ± 0.19	38.21 ± 0.16	34.50 ± 0.13
16	18.67 ± 0.30	17.90 ± 0.25	17.72 ± 0.18
17	20.1 ± 0.12	22.5 ± 0.24	25.42 ± 0.21
19	5.34 ± 0.18	2.94 ± 0.12	4.67 ± 0.30
Doxorubicin	0.46 ± 0.21	0.42 ± 0.22	0.38 ± 0.02

6-Thieonyl-*N*-aminopyridine derivatives attached to pyrazole **5b** exhibited excellent antitumor activity, which is more potent than doxorubicin, while 6- phenyl-*N*-aminopyridine derivatives **5a** exhibited promising inhibitory activity. Also, it was found that pyrazoles containing biologically active 1,3,4-thiadiazole derivatives exhibited promising activities, compound **14b** with IC_{50} values of (0.38, 0.32, 0.22 µmoL^{-1}) has excellent cytotoxic agents against the three tumor cell lines, which is more potent than the activity of doxorubicin with IC_{50} values of (0.46 , 0.42 and 0.38 µmoL^{-1}), also 4-Cl substituted attached to 1,3,4-thiadiazole derivative is most favorable in imparting antitumor activity. In addition, introduction of stronger electron-withdrawing substituent (Cl > Br) in the para-position of the benzene ring might assist in enhancing antitumor activity. So the growth inhibition activity of **14b** is higher than 14c which contain 4-Br substituted, **14g** 2-thieonyl attached to 1,3,4-thiadiazole derivatives exhibited good inhibition activity while the other 1,3,4-thiadiazole derivatives **14d-f** exhibited moderate activities (Table 1). Compounds **8a,b** exhibited high growth inhibition activity which was nearly as the activity of the doxorubicin. This activity may be attributed to the presence of 4,5 difuroimidazolyl **8a** and 4,5-diphenylimidazolyl **8b** attached to the pyrazole ring. pyrimidinyl chromene derivatives **19** showed promising inhibitory activity against the three tumor cell lines while the other compounds **4a,b, 5a, 6, 9, 14a, 15-17** exhibited moderate activity.

Conclusions

A series of novel pyrazole derivatives has been synthesized starting from 3-methyl-1- phenyl-1*H*-pyrazole-4-carboxaldehyde and evaluated for their antitumor activities. In vitro anticancer evaluation of the synthesized compounds showed moderate to excellent anticancer activities against the three tumor cell lines. Ethyl-1-amino-4-(3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-oxo-6-(thiophen-2-yl)-1,2-dihydropyridine-3-carboxylate **5b** with

IC_{50} values of (0.36, 0.28, 0.32 µmol L^{-1}) and 4-(4-chlorophenyl)-5- [(3-methyl-1-phenyl-1*H*-pyrazol-4yl) methyl -idene]hydrazin-ylidene}-4,5-dihydro-1,3,4-thiadiazol-2yl]ethanone **14b** with IC_{50} values of (0.38, 0.32, 0.22 µmol L^{-1}) were more potent than doxorubicin. The presence of 6-thieonyl-*N*-aminopyridine, 1,3,4-thiadiazole and imidazole derivatives incorporating pyrazole moieties is responsible for excellent anticancer activities.

Acknowledgments

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تشييد بعض مركبات البيرازول الفريدة المحتوية على الايميدايزول، البيرازول، الإوكسازول، الثيازول و مشتقات البنزوكرومين بتقنية الميكروويف و تقييم النشاط المضاد للسمية الخلوية

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تم تشييد متسلسلة من مشتقات البيرازول الفريدة التى تحمل البيران، البريدين، البيرازول، الايميدازول، 1,3أوكسازول و -1,3,4ثيادايازول 4a-g. تم تخليق مشتق -2 أمينو4--(-3 ميثيل1--فينيل1H-- بيرازول-4-يل)4H-- بنزوكرومين3--كاربونيتريل 15 تحت تأثير أشعة الميكروويف. أيضا مركب 15 تم إستخدامة فى تشييد مشتقات البنزوكرومين 16& 17 و مشتق البنزوكرومين[2,3-d]بيريميدين 19. تم إثبات المركبات الجديدة التى تم تشييدها بأستخدام التحاليل الدقيقة و الاطياف الضوئية المختلفة. تم إجراء مسح لجميع المركبات التى تم تحضيرها كمضاد للنشاط السرطانى تجاه ثلاث خلايا من الاورام وأستخدام الدكسوروبسين كمادة قياسية مضادة للسرطان. وأظهرت المركبات 5b (IC50 =0.36, 0.28, 0.32 & و 14b (IC50 =0.36, 0.28, 0.32) فاعلية مضادة للسرطان بالمقارنة بالدكسوروبسين.