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Design, Synthesis, and Biological Evaluation of *N*-Phenylpyrazole Derivatives Featuring Nitrogen-Containing Side Chains as Potent Antitumor Agents

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A SERIES of novel N-phenylpyrazole containing acyl derivatives 3a, b, N-methylimidiazole 4, thiazole derivatives 6a-d, benzimidiazole derivatives 7a-c pyrane and pyridine 8, 9a, b, tetrazole 10, pyridodipyrimidine 11, and dihydronaphthaline derivatives 15 have been synthesized. The structure of the newly synthesized compounds was elucidated by IR, ^{1}H NMR, ^{13}C NMR, Mass spectra and Elemental analysis. The newly synthesized compounds were evaluated for their antitumor activity against three tumor cell lines, liver cancer (HepG2), human colonic carcinoma cell line (HCT-116), and human breast adenocarcinoma (MCF-7). Compounds 6d, 7b, c, 9b and 11 exhibited higher antitumor activity compared with the reference drug Doxorubicin.

Keywords: *N*-pyrazolyl derivatives, Hexahydropyridodipyrimidine-4,6-dione, Antitumor activity.

Introduction

Pyrazoles occupy a distinct niche in heterocyclic chemistry, and are one of the most widely specified anti-inflammatory agents with excellent safety profile [1], antitumor [2, 3], and antibacterial activity [4]. Moreover, pyrazole derivatives are well known for their antihyperglycemic [5], anticonvulsant [6], antipyretic [7] antiviral [8], anti-HIV [9], and anticoagulant activities [10]. Recently, arylpyrazoles have huge biological activities and wide application in pesticide and medicinal chemistry [11]. Moreover, arylpyrazole derivatives have non-nucleoside HIV-1 reverse transcriptase inhibitory activity [12]. In addition, pyrazoles have been used for treatment of antiangiogenesis, obesity, thrombopiotinmimetics and type 2 diabetes, because of their kinase inhibitory effects [13]. Furthermore, pyrazole and its synthetic analogs have also been reported to possess antihypertensive [14, 15], and used as human acyl-cholesterol acyltransferase inhibitors [16]. According to the above information's and in continuation of our program of studying the chemistry of phenylpyrazole derivatives incorporated with other biologically active heterocycles such as pyrane, pyridine, imidiazole, benzimidiazole, tetrazole, thiazole and naphthaline was synthesized to see the additive effect of these heterocyclic rings towards the antitumor activities.

Experimental

Materials

All melting points were measured on an Electrothermal 9100 series digital melting point apparatus (Shimadzu, 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 (USA). ^{1}H

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NMR and ^{13}C NMR spectra were recorded on a JEOL EX-300 and JEOL ECA-500 (Shimadzu) instruments. 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 70 eV Finnigan SSQ 7000 spectrometer (Thermo-Instrument System Incorporation, USA). The purity of the compounds was checked on aluminum plates coated with silica gel (Merck, Germany). Chemicals and solvents (Analar ≥ 99%) were purchased from Sigma-Aldrich (USA). Doxorubicin disks were supplied by the Pasteur Laboratory (Egypt).

3-(4-Chlorophenyl)-1-phenyl-*1H*-pyrazol-4-carboxaldhyde (**2)** was achieved by a reported method [17]

*General Procedure for the synthesis of 1-[3-(4-chlorophenyl)-1-phenyl-1H-4-acylpyrazole derivatives (**3a, b**)* A solution of methyl lithium in diethyl ether (5 mL), or vinyl magnesium bromide in THF (3 mL) and compound **2** (2.83 g, 10 mmol) in THF (15 mL) was stirred under liquid nitrogen (-78 ^oC) for 1 h. Then catalytic amount of MnO_2 in chloroform (20 mL) was added and the reaction mixture was stirred at room temperature for appropriate time. The progress of the reaction was monitored by TLC after every 30 min. The mixture was cooled to room temperature and the obtained solid was filtrated off, washed with cold EtOH (15 mL), dried, and crystallized from ethanol.

*1-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl] ethanone (**3a**)*

White crystal in 70% yield; mp. 175-177 ^oC; IR (KBr, cm^{-1}): υ 3085 (CH arom.); 2960, 2890 (CH aliph.); 1686 (C=O); 1612 (C=N); 1580 (C=C); ^1H NMR (DMSO-d_6, δ, ppm): 2.45 (s, 3H, CH_3), 7.06-7.15 (m, 2H, Ar-H), 7.18-7.30 (m, 3H, Ar-H), 7.35 (d, 2H, Ar-H), 7.57 (d, 2H, Ar-H), 8.85 (s, 1H, CH of the pyrazole ring); ^{13}C NMR (DMSO-d_6): δ 15.70 (CH_3), 123.06, 124.08, 126.10, 128.35, 129.10, 131.80, 138.40, 139.05, 141.50, 145.20 (sp^2 carbons) 147.80 (Ar-C=N of the pyrazole), 169.00 (C=O); Its MS (m/z), 296 (M^+, 73%), 298 (M^++2, 19%) ; $C_{17}H_{13}ClN_2O$ (296.75); calcd; % C: 68.81, % H: 4.42, % N: 9.44; Found; % C: 68.80, % H: 4.40, % N: 9.44.

*1-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl] prop-2-en-1-one (**3b**)*

Pale yellow powder in 82% yield; mp. 181-183 ^oC; IR (KBr, cm^{-1}): υ 3090 (CH arom.); 2970, 2898 (CH aliph.); 1690 (C=O); 1610 (C=N); 1590 (C=C); ^1H NMR (DMSO-d_6, δ, ppm): 5.00-5.30 (m, 2H, CH_2), 5.39- 6.20 (m, 1H, CH), 7.01-7.12 (m, 2H, Ar-H), 7.15-7.26 (m, 3H, Ar-H), 7.33 (d, 2H, Ar-H), 7.60 (d, 2H, Ar-H), 8.89 (s, 1H, CH of the pyrazole ring); ^{13}C NMR (DMSO-d_6): δ 95.40 (=CH), 105.01 (=CH_2), 124.50, 125.10, 126.10, 128.30, 129.25, 130.80, 136.38, 138.80, 139.60, 144.25 (sp^2 carbons), 148.80 (Ar-C=N of the pyrazole), 167.00 (C=O); Its MS (m/z), 308 (M^+, 66%), 310 (M^++2, 22%) ; $C_{18}H_{13}ClN_2O$ (308.76); calcd; % C: 70.02, % H: 4.24, % N: 9.07; Found; % C: 70.02, % H: 4.23, % N: 9.04.

*[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl] (1-methyl-1H-imidazol-2-yl)methanone (**4**)*

A solution of 1-methyl imidiazole (3.5 mL), n-butyl lithium (2.5 mL), and compound **2** (2.83 g, 10 mmol) in THF (15 mL) was stirred under liquid nitrogen (-78 ^oC) for 1h. and then catalytic amount of MnO_2 in chloroform (20 mL) was added. The reaction mixture was stirred at room temperature for 6 h. The progress of the reaction was monitored by TLC after every 30 min. The mixture was cooled to room temperature and the obtained solid was filtrated off, washed with cold EtOH (15 mL), dried, and crystallized from ethanol as orange powder in 69% yield; mp. 196-198 ^oC; IR (KBr, cm^{-1}): υ 3087 (CH arom.); 2968, 2860 (CH aliph.); 1686 (C=O); 1615 (C=N); 1593 (C=C); ^1H NMR (DMSO-d_6, δ, ppm): 2.25 (s, 3H, N-CH_3), 6.50 (d, 1H, CH imidazole), 6.95 (d, 1H, CH imidazole), 7.05- 7.15 (m, 2H, Ar-H), 7.25- 7.35 (m, 3H, Ar-H), 7.43 (d, 2H, Ar-H), 7.68 (d, 2H, Ar-H), 8.84 (s, 1H, CH of the pyrazole ring); ^{13}C NMR (DMSO-d_6): δ 21.40 (CH_3) 122.50, 123.70, 125.00, 126.25, 128.48, 129.20, 130.80, 133.40, 136.38, 138.80, 139.45, 141.80, 143.26 (sp^2 carbons), 145.80 (Ar-C=N of the pyrazole), 168.00 (C=O); Its MS (m/z), 362 (M^+, 60%), 364 (M^++2, 13%); $C_{20}H_{15}ClN_4O$ (362.81); calcd; % C: 66.21, % H: 4.17, % N: 15.44; Found; % C: 66.20, % H: 4.16, % N: 15.42.

*1-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-3-(morpholin-4-yl)propan-1-one (**5**)*

A mixture of compound **3b** (3.08 g, 10 mmol) and morpholine (2.5 mL) was stirred under reflux in ethanol for 4 hours. The solvent was evaporated and the crude product was collected and crystallized from DMF, as a red powder in 65 % yield; mp. 220-222°C; IR (KBr, cm^{-1}): υ 3080 (CH arom.); 2970, 2860 (CH aliph.); 1692 (C=O); 1618 (C=N); 1592 (C=C); ^1H NMR (DMSO-d_6,

δ, ppm): 2.20 (t, 2H, CH_2), 2.36 (t, 2H, CH_2), 3.20 (t, 4H, morpholinyl, $N(CH_2)_2$, *J*=5.0), 3.90 (t, 4H, morpholinyl, $O(CH_2)_2$, *J*=5.0), 6.98-7.12 (m, 2H, Ar-H), 7.20-7.38 (m, 3H, Ar-H), 7.45 (d, 2H, Ar-H), 7.79 (d, 2H, Ar-H), 8.86 (s, 1H, CH of the pyrazole ring); ^{13}C NMR (DMSO-d_6): δ 37.44 ,40.10, 47.16, 68.14 (sp^3 carbons) 125.96, 127.31, 127.54, 129.43, 130.68, 133.44, 136.38, 138.80, 139.75, 141.90, 143.10, 144.12 (sp^2 carbons), 146.08 (Ar-C=N of the pyrazole), 168.60 (C=O); Its MS (m/z), 395 (M^+, 62%), 397 (M^++2. 19%); $C_{22}H_{22}ClN_3O_2$ (395.88); calcd; % C: 66.75, % H: 5.60, % N: 10.61; Found; % C: 66.75, % H: 5.59, % N: 10.60.

*General Procedure for the synthesis of 2-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-3-(4-substituted phenyl)-1,3-thiazolidin -4-one (**6a-d**)*

A mixture of compound **2** (2.83 g, 10 mmol), aniline derivatives (namely 4-methyl aniline, 4-methoxy aniline, 4-nitro aniline and 4-chloroaniline respectively) (10 mmol), thioglycolic acid (10 mmol) was stirred under reflux in ethyl acetate for the appropriate time. Completion of the reaction was indicated by TLC monitoring. The reaction mixture was cooled to ambient temperature, and the crude solid residue was recrystallized from ethanol to afford pure crystals of the proper1,3-thiazolidin-4-one derivatives in 75–86% yields.

*2-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-3-(4-tolyl)-1,3-thiazolidin-4-one (**6a**)*

White powder in 75 % yield; mp: 115-117°C; IR (KBr, cm^{-1}): υ 3068 (CH arom.); 2914, 2878 (CH aliph.); 1675 (C=O); 1615 (C=N); 1565 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.21 (s, 3H, CH_3), 3.23 (s, 2H, CH_2), 6.02 (s, 1H, CH of thiazole), 7.15 (d, 2H, Ar-H, *J* = 8.4), 7.17 (m, 3H, Ar-H), 7.27 (d, 2H, Ar-H, *J*=7.4), 7.29 (m, 2H, Ar-H), 7.33 (d, 2H, Ar-H), 7.38 (d, 2H, Ar-H), 8.84 (s, 1H, CH of the pyrazole ring); ^{13}C NMR (DMSO-d_6): δ 25.20 (CH_3), 33.50, 72.60 (CH_2, CH of thiazole), 120.20, 122.00, 123.6, 126.90, 128.60, 129.20, 130.15, 131.50, 133.40, 136.00, 138.20, 139.20, 142.80, 144.20 (sp^2 carbons), 147.10 (Ar-C=N of the pyrazole),174.20 (C=O); Its MS (m/z), 445 (M^+, 70%), 447 (M^++2, 21%) ; $C_{25}H_{20}ClN_3OS$ (445.96); calcd; % C: 67.33, % H: 4.52, % N: 9.42; Found; % C: 67.30, % H: 4.51, % N: 9.40.

*2-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-3-(4-anisyl)-1,3-thiazolidin-4-one(**6b**)*

White powder in 78 % yield; mp: 119-121°C; IR (KBr, cm^{-1}): υ 3070 (CH arom.); 2925, 2878 (CH aliph.); 1680 (C=O); 1612 (C=N); 1580 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 3.31 (s, 2H, CH_2 of thiazole), 3.55 (s, 3H, OCH_3), 5.88 (s, 1H, CH of thiazole), 7.12 (d, 2H, Ar-H, *J*= 8.2), 7.15 (m, 3H, Ar-H), 7.25 (m, 2H, Ar-H), 7.30 (d, 2H, Ar-H, *J*=7.8), 7.37 (d, 2H, Ar-H *J*=8.1), 7.40 (d, 2H, Ar-H *J*=8.0), 8.87 (s, 1H, CH of the pyrazole ring); Its MS (m/z), 461(M^+, 65%), 463 (M^++2, 18%); $C_{25}H_{20}ClN_3O_2S$ (461.96); calcd; % C: 65.00, % H: 4.36, % N: 9.10; Found; % C: 65.00, % H: 4.34, % N: 9.09.

*2-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-3-(4-nirophenyl)-1,3-thiazolidin-4-one (**6c**)*

White powder in 82 % yield; mp: 109-112°C; IR (KBr, cm^{-1}): υ 3096 (CH arom.); 2910, 2875 (CH aliph.); 1684 (C=O); 1610 (C=N); 1590 (C=C), 1573, 1383 (NO_2); ^{1}H NMR (DMSO-d_6, δ, ppm): 3.28 (s, 2H, CH_2 of thiazole), 5.95 (s, 1H, CH of thiazole), 7.16 (m, 2H, Ar-H), 7.20 (m, 3H, Ar-H), 7.29 (d, 2H, Ar-H, *J*=7.5), 7.35 (d, 2H, Ar-H, *J*=7.5), 7.42 (d, 2H, Ar-H), 7.48 (d, 2H, Ar-H), 8.84 (s, 1H, CH of the pyrazole ring); Its MS (m/z), 476 (M^+, 60%), 478 (M^++2, 19%); $C_{24}H_{17}ClN_4O_3S$ (476.93); calcd; % C: 60.44, % H: 3.59, % N: 11.75; Found; % C: 60.41, % H: 3.58, % N: 11.73.

*3-(4-chlorophenyl)-2-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]- 1,3-thiazolidin-4-one (**6d**)*

White powder in 86 % yield; mp: 122-124°C; IR (KBr, cm^{-1}): υ 3090 (CH arom.); 2884, 2798 (CH aliph.); 1676 (C=O); 1614 (C=N); 1575 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 3.28 (s, 2H, CH_2 of thiazole), 5.78 (s, 1H, CH of thiazole), 7.12 (m, 3H, Ar-H), 7.28 (m, 2H, Ar-H), 7.31 (d, 2H, Ar-H), 7.38 (d, 2H, Ar-H), 7.40 (d, 2H, Ar-H), 7.46 (d, 2H, Ar-H), 8.80 (s, 1H, CH of the pyrazole ring); ^{13}C NMR (DMSO-d_6): 34.80, 65.29, 126.10, 126.60, 127.61, 128.81, 128.92, 129.50, 129.56, 129.59, 129.60, 135.12, 137.73, 138.47, 142.30, 147.10 (sp^2 carbons), 171.20 (C=O); Its MS (m/z), 466 (M^+, 59%), 468 (M^++2, 25%) ; $C_{24}H_{17}Cl_2N_3OS$ (466.38); calcd; % C: 61.81, % H: 3.67, % N: 9.01; Found; % C: 61.79, % H: 3.66, % N: 9.01.

*General Procedure for the synthesis of 3-benzyl-6-substituted-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]imidazo[1,2-a]pyridine (7**a-c**)*

A mixture of compound **2** (2.83 g, 10 mmol) and 2-aminopyridine derivatives (10 mmol) was

stirred for 30 min. Water (30 ml) was added, followed by addition of phenyl acetylene (15 mmol). Then, Cu-Mn catalyst (10%) (1: 0.25) was added, and resulting mixture was refluxed at 100 °C for 6 h. Completion of the reaction was monitored by TLC. The reaction mixture was filtered off and the residue washed with water. The product was crystalized from DMF, to obtain the desired products **7a-c**

3-benzyl- [3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]imidazo[1,2-a]pyridine (***7a***)

Brown powder in 76 % yield; mp: 174-176°C; IR (KBr, cm^{-1}): υ3058 (CH arom.); 2940, 2850 (CH aliph.); 1620 (C=N); 1602 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): ^{1}H NMR (DMSO-d_6, δ, ppm): 2.50 (s, 2H, CH_2), 6.91 (t, 1H, *J*=6.8 Hz Ar-H), 7.16-7.20 (m, 6H, Ar-H), 7.27 -7.37 (m, 4H, Ar-H), 7.43 (t, 1H, *J*=6.6 Hz, Ar-H), 7.55 (d, 2H, Ar-H, *J*=7.5), 7.67 (d, 2H, Ar-H), 7.70 (d, 1H, Ar-H), 7.78 (d, 1H, Ar-H), 8.80 (s, 1H, CH of the pyrazole ring); ^{13}C NMR (DMSO-d_6): 29.90 (CH_2), 112.30, 113.80, 115.60 117.50, 117.70, 123.50, 124.30, 126.30, 127.00, 127.70, 127.90, 128.2, 128.70, 129.10, 135.80, 136.7, 140.30, 141.80, 143.00, 144.8, 144.80, 147.20 (sp^2 carbons); Its MS (m/z), 460 (M^+, 59%), 462 (M^++2, 19%); $C_{29}H_{21}ClN_4$ (460.94); calcd; % C: 75.56, % H: 4.59, % N: 12.15; Found; % C: 75.54, % H: 4.56, % N: 12.12.

3-benzyl-6-floro-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]imidazo[1,2-a]pyridine (***7b***)

Pale yellow powder in 62 % yield; mp: 185-186°C; IR (KBr, cm^{-1}): υ 3060 (CH arom.); 2923, 2852 (CH aliph.); 1625 (C=N); 1600 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): ^{1}H NMR (DMSO-d_6, δ, ppm): 2.28 (s, 2H, CH_2), 6.96 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.07 (d, 1H, *J* = 4.0 Hz, Ar-H), 7.15-7.25 (m, 4H, Ar-H), 7.30 (d, 2H, *J* = 7.8, Ar-H), 7.33-7.36 (m, 6H, Ar-H), 7.48(s, 1H, Ar-H), 7.53-7.56 (d, 1H, Ar-H), 8.78 (s, 1H, CH of the pyrazole ring); Its MS (m/z), 478 (M^+, 65%), 480 (M^++2, 18%); $C_{29}H_{20}ClFN_4$ (478.93); calcd; % C: 72.72, % H: 4.21, % N: 11.70; Found; % C: 72.71, % H: 4.21, % N: 11.68.

3-benzyl-6-choro-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]imidazo[1,2-a]pyridine (***7c***)

yellow powder in 65 % yield; mp: 189-201 °C; IR (KBr, cm^{-1}): υ 3069 (CH arom.); 2934, 2867 (CH aliph.); 1622 (C=N); 1598 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): ^{1}H NMR (DMSO-d_6, δ, ppm): 2.26 (s, 2H, CH_2), 6.99 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.09 (d, 1H, *J* = 4.2 Hz, Ar-H), 7.18-7.28 (m, 4H, Ar-H), 7.33 (d, 2H, *J* = 7.8, Ar-H), 7.39-7.42 (m, 6H, Ar-H), 7.53 (s, 1H, Ar-H), 7.62-7.64 (d, 1H, Ar-H), 8.80 (s, 1H, CH of the pyrazole ring); Its MS (m/z), 495 (M^+, 68%), 496 (M^++2, 21%); $C_{29}H_{20}Cl_2N_4$ (495.39); calcd;% C: 70.31, % H: 4.07, % N: 11.31; Found; % C: 70.30, % H: 4.05, % N: 11.29.

*6-amino-4-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-5-cyano-4H-pyran-2-carboxylic acid (**8**)*

A mixture of compound **2** (2.83 g, 10 mmol), pyruvic acid (7 ml, 10 mmol), and malononitrile (12 mmol) was dissolved in ethanol (50 mL). Fe_3O_4 as a catalyst (0.05 g) was then added to this mixture. This mixture was stirred under reflux. The progress of reaction was monitored by TLC (7:3, n-hexane/ethyl acetate). Upon completion of the reaction, the mixture was cooled to room temperature. The remaining solution is concentrated to the product as a crude. This crude was crystallized from ethanol, as a gray powder in 67 % yield; mp: 220-222°C; IR (KBr, cm^{-1}): υ 3390 (NH_2), 3200 (br., OH), 3080 (CH arom.), 2230 (CN), 1715 (C=O), 1622 (C=N); 1600 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 4.95 (br,1H, H-4 of pyran), 6.90 (d,1H, H-3 of pyran), 6.95-7.10 (m, 3H, Ar-H), 7.14 -7.22 (m, 2H, Ar-H), 7.35 (d, 2H, Ar-H), 7.40 (d, 2H, Ar-H), 8.80 (s, 1H, CH of the pyrazole ring), 9.20, 10.15 (2brs, D_2O exchangeable-NH_2), 11.20 (s,1H, OH); ^{13}C NMR (DMSO-d_6); δ 92.4 (CH pyran), 106.50 (CN), 120.40, 125.90, 127.60, 129.20, 131.50, 133.20, 134.30, 136.00, 138.20, 139.20, 142.80, 144.20, 147.10, 149.00, 151.80, 160.00 (sp^2 carbons) 178.10 (C=O); Its MS (m/z), 418 (M^+, 59%), 420 (M^++2, 17%) ; $C_{22}H_{15}ClN_4O_3$ (418.83); calcd; % C: 63.09, % H: 3.61, % N: 13.38; Found; % C: 63.05, % H: 3.60, % N: 13.36.

*General Procedure for the synthesis of 2-amino-4-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-5-(4-substitutedphenyl)pyridine-3-carbonitrile (**9a,b**)*

A mixture of compound **2** (2.83 g, 10 mmol), acetophenone and\or 4-methoxy acetophenone (10 mmol), malononitrile (10 mmol), ammonium acetate (11.2 g, 15 mmol), and Fe_3O_4 (0.05 g) was heated under reflux in ethanol at 90 °C with stirring. The progress of the reaction was monitored by TLC (7:3, n-hexane/ethyl acetate). After completion of the reaction, the mixture was cooled to room temperature. Then the catalyst was separated from this mixture by filtration. The remaining solution is concentrated under reduced pressure to give the product as a crude. This crude

was crystallized from ethanol.

*2-amino-4-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-5-phenylpyridine-3-carbo-nitrile (**9a**)*

White powder in 70% yield; mp: 210-212°C; IR (KBr, cm^{-1}): υ 3386 (NH_2), 3087 (CH arom.), 2225 (CN), 1618 (C=N); 1605 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.12 (d, 2H, Ar-H), 7.18-7.28 (m, 4H, Ar-H), 7.35-7.66 (m, 6H, Ar-H), 7.82 (d, 2H, Ar-H), 8.78 (s, 1H, CH of the pyrazole ring), 8.78 (s, 1H, CH pyridine), 9.53, 10.20 (2brs, D_2O exchangeable-NH_2); Its MS (m/z), 447 (M^+, 60%), 449 (M^++2, 19%) ; $C_{27}H_{18}ClN_5$ (447.91); calcd; % C: 72.40, % H: 4.05, % N: 15.64; Found; % C: 72.38, % H: 4.04, % N: 15.63.

*2-amino-4-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-5-(4-methoxyphenyl) pyridine-3-carbonitrile (**9b**)*

Pale yellow powder in 68% yield; mp: 228-230°C; IR (KBr, cm^{-1}): υ 3390 (NH_2), 3079 (CH arom.), 2963, 2867 (CH aliphatic), 2230 (CN), 1705 (C=O), 1620 (C=N); 1595 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 3.53 (s, 3H, OCH_3), 7.05 (d, 2H, Ar-H), 7.10 (d, 2H, Ar-H), 7.25-7.35 (m, 3H, Ar-H), 7.39-7.42 (m, 2H, Ar-H), 7.56 (d, 2H, Ar-H), 7.70 (d, 2H, Ar-H), 8.82 (s, 1H, CH of the pyrazole ring), 8.98 (s, 1H, CH pyridine), 9.80, 10.60 (2brs, D_2O exchangeable-NH_2); Its MS (m/z), 477 (M^+, 68%), 479 (M^++2, 18%) ; $C_{28}H_{20}ClN_5O$ (477.94); calcd; % C: 70.36, % H: 4.22, % N: 14.65; Found; % C: 70.33, % H: 4.20, % N: 14.65.

*(2E)-3- [3-(4-chlorophenyl) -1- phenyl -1H-pyrazol -4- yl] -2-(1H-tetrazol-5-yl)) prop-2-enenitrile (**10**)*

Fe_3O_4 (0.6 mmol) was added to a mixture of compound **2** (2.83 g, 10 mmol), malononitrile (0.66 g, 10 mmol), and NaN_3 (0.87 g, 12 mmol) in DMF (50 ml) stirred at 90°C for 8 h. After completion of the reaction. Aqueous HCl (2 N, 30 ml) was added to the filtrate with vigorous stirring, causing the product to precipitate. The precipitate was filtered and dried in a drying oven to furnish the tetrazoles. The product was crystallized from ethanol, as a red powder in 65 % yield; mp: 240-242°C; IR (KBr, cm^{-1}): υ 3441 (NH), 3096 (CH arom.), 2225 (CN), 1615 (C=N); 1591 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 3.33 (brs, 1H, NH), 6.52 (s, 1H, CH), 7.16 (m, 2H, Ar-H), 7.19- 7.21 (m, 3H, Ar-H), 7.42-7.44 (d, 2H, J = 8.2, Ar-H), 7.93-7.95 (d, 2H, J = 8.2, Ar-H), 8.84 (s, 1H, CH of the pyrazole ring); ^{13}C NMR (DMSO-d_6); δ 101.9 (CN), 118.20, 120.30, 122.5, 123.00, 129.9, 130.3, 130.4, 132.10, 133.00, 143.5, 148.7, 150.30, 155.8 (sp^2 carbons); Its MS (m/z), 373 (M^+, 59%), 375 (M^++2, 21%); $C_{19}H_{12}ClN_7$ (373.79); calcd; % C: 61.05, % H: 3.24, % N: 26.23; Found; % C: 61.04 % H: 3.24, % N: 26.23.

*5-[3-(4-chlorophenyl)-4-methyl-1-phenyl-1H-pyrazole-4-yl]-2,8-dithioxo-2,3,5,8,9,10 hexahydropyrimido [5',4':5,6] pyrido[2,3-d] pyrimidine-4,6(1H,7H)-dione (**11**)*

A mixture of compound **2** (2.83 g, 10 mmol), 2-thiobarbaturic acid (2.88 g, 10 mmol), ammonium acetate (0.77 g, 10 mmol) and Al_2O_3 (10 mol%) was heated under reflux in ethanol (95%) for 48h. The resulted precipitate was filtered and crystalized from DMF, as a yellow powder in 68 % yield; mp: 260°C decompose; IR (KBr, cm^{-1}): υ 3433 (NH), 3130 (CH arom.), 1630 (C=O) 1612 (C=N); 1538 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 5.91 (s, 1H, CH-pyridine), 6.93-6.98 (m, 2H, Ar-H), 7.06 (d, 2H, Ar-H), 7.19 (m, 3H, Ar-H), 7.57 (d, 2H, Ar-H), 8.89 (s, 1H, CH of the pyrazole ring), 9.90-11.67 (brs, 5H, 5NH); ^{13}C NMR (DMSO-d_6); 71.24 (C-4 pyridine), 117.30, 119.40, 120.17, 122.08, 126.15, 128.70, 130.15, 133.85, 136.56, 144.09, 148.06, 156.50 (sp^2 carbons), 162.94, 165.23 (2C=S), 169.5, 175.52 (2C=O); Its MS (m/z), 534 (M^+, 59%), 536 (M^++2, 17%); $C_{24}H_{16}ClN_7O_2S_2$ (534.01); calcd; % C: 53.98, % H: 3.02, % N: 18.36; Found; % C: 53.95% H: 3.00, % N: 18.35.

*Ethyl (2E)-3-[3-(4-chlorophenyl)- 1-phenyl-1H-pyrazole-4-yl]-2-cyanoprop-2-enoate (**12**)*

To a solution of compound **2** (2.83 g, 10 mmol), ethyl cyanoacetate (1 ml, 7.5 mmol) and acetic acid (1.5 ml, 2.2 mmol) in dry toluene (30 mL) pyrrolidine (0.7 mmol) was added dropwise at room temperature and the mixture was refluxed for 5h . The reaction mixture was cooled to room temperature and the soild product was collected and crystallized from ethanol, as yellow solid in 90% yield mp 179-181 °C; IR (KBr, cm^{-1}): υ 3100 (CH aromatic), 2984, 2899 (CH, alphatic), 2221 (CN), 1721 (C=O) 1612 (C=N); 1592 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): 1.58 (t, 3H, CH_3), 4.35 (q, 2H, CH_2), 6.56 (s, 1H, CH), 7.18 (d, 2H, J = 8.9 Hz, Ar-H), 7.22 (m, 3H, Ar-H), 7.35-7.45 (m, 2H, Ar-H), 7.97 (d, 2 H, J = 8.9 Hz, Ar-H), 8.89 (s, 1H, CH of the pyrazole ring); ^{13}C NMR (DMSO-d_6); 14.10 (CH_3), 62.30 (CH_2), 99.20 (CN), 114.60, 116.10, 124.2, 129.19,

131.00, 133.5, 136.90, 140.10, 144.80, 148.30, 162.90, 163.70 (sp^2 carbons), 168.9 (C=O); Its MS (m/z), 377 (M^+, 72%), 378 (M^++2, 20%); $C_{21}H_{16}ClN_3O_2$ (377.82); calcd; % C: 66.76, % H: 4.27, % N: 11.12; Found; % C: 66.76 % H: 4.25, % N: 11.10.

*Ethyl 2-cyano-3-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-4-phenylbutanoate (**13**)*

To a solution of compound **12** (3.78 mg, 10 mmol) in dry THF (30 mL) benzylmegansium bromide (10.4 mL, 10 mmol) was added and the reaction mixture was stirred under reflux for 6 h at 80 °C. The reaction mixture was cooled to room temperature and the soild product was collected and crystallized from dioxane as a brown powder in 71% yield mp 195-197 °C; IR (KBr, cm^{-1}): υ 3150 (CH aromatic), 2932, 2838 (CH, alphatic), 2231 (CN), 1732 (C=O) 1620 (C=N); 1611 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): ^{1}H NMR (DMSO-d_6, δ, ppm): 1.31 (t, 3H, CH_3), 1.59 (m, 1H, CH), 1.99 (d, 1H, CH), 2.35 (d, 2H, CH_2), 4.05 (q, 2H, OCH_2), 6.86–6.88 (d, 2H, Ar-H J = 8.8 Hz), 7.24-7.26 (m, 4H, Ar-H), 7.30-7.32-7.46 (m, 6H, Ar-H), 7.62-7.65 (d, 2H, J = 8.9 Hz), 8.86 (s, 1H, CH of the pyrazole ring); Its MS (m/z), 469 (M^+, 62%), 471 (M^++2, 16%); $C_{28}H_{24}ClN_3O_2$ (469.94); calcd; % C: 71.56, % H: 5.15, % N: 8.94; Found; % C: 71.53, % H: 5.12,% N: 8.92.

*3-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-3, 4-dihydronaphthalen-1(2H)-one (**15**)*

A suspension of compound **13** (2.28 mg, 5 mmol) in conc. HCl (20 mL) was refluxed for 5 h. The mixture was extracted by dichloromethane (50 mL) and washed with water (30 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. Then the crude **14** was added to trifluoroacetic anhydride (TFAA) (9 mL) at 0 °C. The mixture was stirred at room temperature for 7 h. The solid product crystallized from DMF as a gray powder in 67 % yield mp 105-107 °C; ; IR (KBr, cm^{-1}): υ 3105 (CH aromatic), 2940, 2864 (CH, alphatic), 1675 (C=O) 1620 (C=N); 1599 (C=C); ^{1}H NMR (DMSO-d_6, δ, ppm): ^{1}H NMR (DMSO-d_6, δ, ppm): 2.60 (m, 2H, $COCH_2$), 2.82-2.84 (m, 1H, CH), 3.10 (d, 2H, CH_2), 6.83 (d, 2H, J = 8.4 Hz), 7.07-7.43 (m, 5H, Ar-H), 7.50-7.80 (m, 2H, Ar-H), 7.85-7.92 (d, 2H, Ar-H, J = 8.3 Hz), 7.94- 7.98 (m, 2H, Ar-H), 8.90 (s, 1H, CH of the pyrazole ring); ^{13}C-NMR (DMSO-d_6); 37.80, 41.30, 45.30 (sp^3 carbons), 114.00, 118.50, 120.10, 122.00, 125.15, 125.90, 127.10, 127.70, 128.00, 130.40, 133.20, 133.90, 135.80, 139.30, 143.22, 148.10, 157.80 (sp^2 carbons), 196.80 (C=O); Its MS (m/z), 398 (M^+, 67%), 400 (M^++2, 19%); $C_{25}H_{19}ClN_2O$ (398.88); calcd; % C: 75.28, % H: 4.80, % N: 7.02; Found; % C: 75.26, % H: 4.79, % N: 7.00.

Biological screening

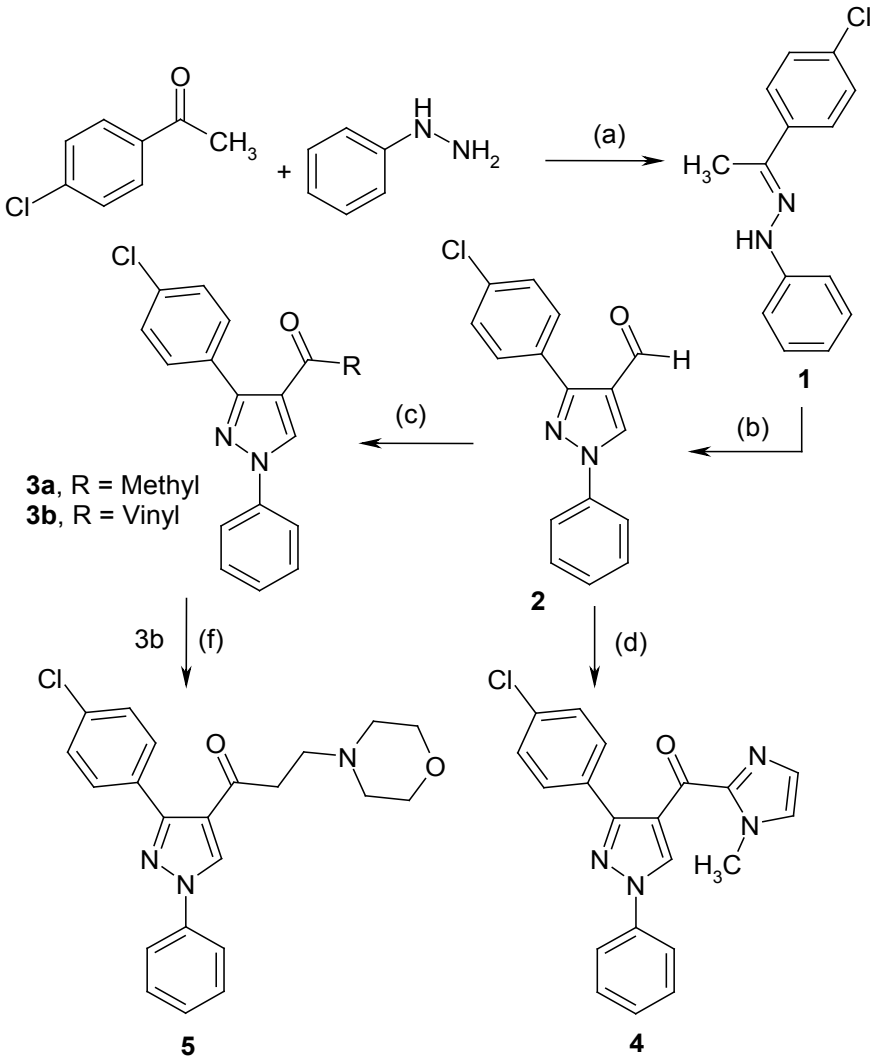
In vitro anticancer activity. We evaluated the activity of newly synthesized compounds against the liver cancer (HepG2), human colonic carcinoma cell line (HCT-116), and human breast adenocarcinoma cell line (MCF-7) using the sulforhodamine B assay [18]. The three human cancer cell lines were provided by the National Cancer Institute (NCI, Cairo, Egypt). Continuous drug exposure for 48 h was the method used. All the cell lines were cultured in Dulbecco's modified Eagle's medium containing 10 % fetal bovine serum (FBS) (in a humidified atmosphere with 5 % CO_2 at 37 °C). Their growth as a monolayer was maintained in RPMI-1640 medium supplemented with 5 % heat inactivated FBS, 2 mmol L^{-1} glutamine and antibiotics (penicillin 100 U mL^{-1}, streptomycin 100 μg mL^{-1}). The effect of compounds on the in vitro growth of human tumor cell lines was evaluated using sulforhodamine B (SRB) as protein binding dye to assess cell growth. Cells growing in 96-well plates were obtained by plating 1.5×10^5 cells mL^{-1}. The microtiter plates were incubated at 37 °C for 24 h prior to addition of experimental drugs and were incubated for 48 h with five different concentrations of each compound (0.01, 0.1, 1, 10, 100 μg mL^{-1}), which were dissolved in DMSO and diluted with saline to the mentioned concentration, starting from a maximum concentration of 100 μg mL^{-1}. After 48 h, the cell monolayers were fixed by addition of 10 % (m/V) trichloroacetic acid and incubated at 4 °C for 1 h, and then stained for 30 min with 0.4 % (m/V) sulforhodamine B in 1 % acetic acid. Excess of unbound dye was removed by four washes with 1 % acetic acid and the attached stain was recovered with Tris-EDTA buffer. Absorbance was measured and growth inhibition of 50 % (GI_{50}) was calculated [19]. Table 1 displays GI_{50} values of each compound for the above listed three cell lines. Doxorubicin was used as a reference compound. The influence of solvent, DMSO, on the growth of cell lines was evaluated in all experiments (negative control). This was performed by exposing untreated control cells to the maximum concentration of DMSO used in each assay (0.5 %).

Results and Discussion

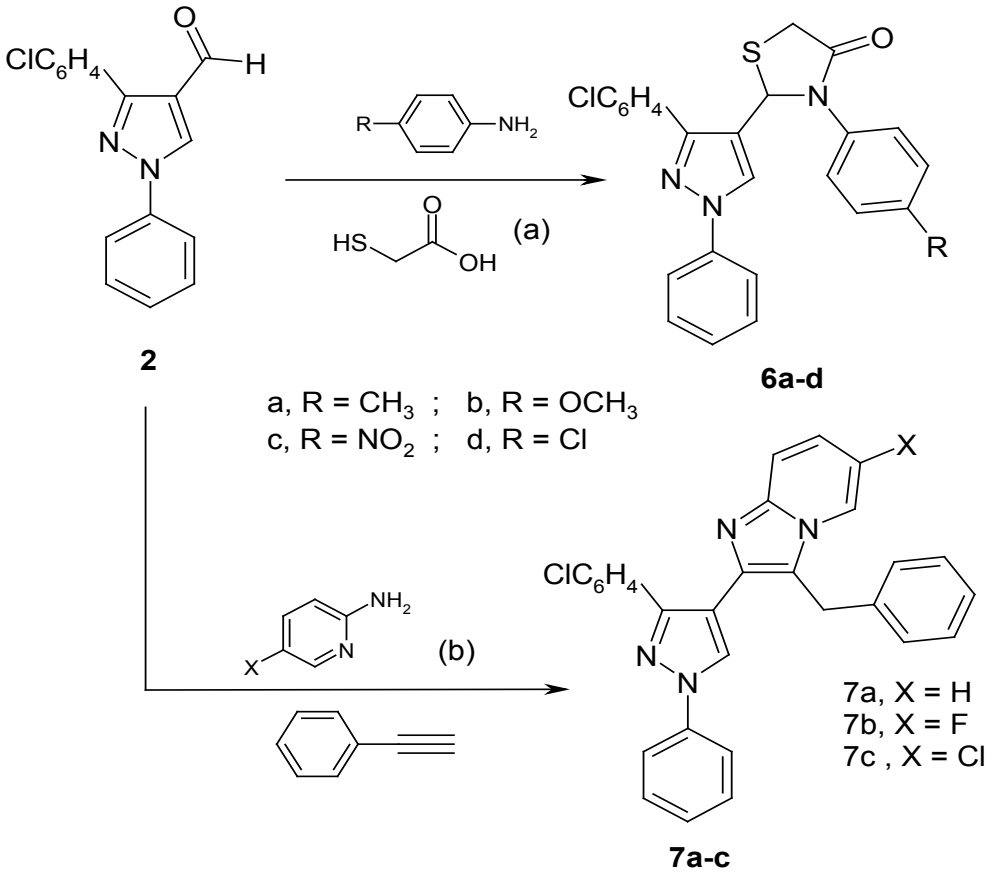
Chemistry

The synthetic routes of the target compounds are outlined in Schemes 1-4. 3-(4-chlorophenyl)-1-phenyl -*1H*- pyrazol -4- carboxaldhyde **2** were prepared via acid condensation of 4-chloroacetophenone with phenylhydrazine hydrochloride afforded hydrazone derivative **1** which underwent cyclization following procedures applied in literature [17] to afford compound **2** in good yield which used as key intermediate for the synthesis of novel pyrazole derivatives. 4-Acylpyrazole derivatives **3a**,**b** and **4** were obtained by addition of the corresponding metal reagents such as [methyl lithium & vinyl magnesium bromide and (1-methylimidiazole in n-butyl lithium)] respectively to the aldehyde group of **2** followed by oxidation with MnO_2. On the other hand, the addition of moropholine to 4-acryloylpyrazole **3b** afforded 1-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-3(moropholin-4-yl) propan-1-one **5 (**Scheme 1).

2-[3-(4- chlorophenyl))-1-phenyl-1*H*-pyrazol-4-yl]-3-(4-substitutedphenyl)-1,3-thiazolidin-4-one **6a-d** have been synthesized by one pot reaction of pyrazole carboxyaldhyde derivatives **2** with thioglycolic acid and aniline derivatives in ethyl acetate under reflux for 8h. In addition, using bimetallic heterogeneous Cu-Mn spinel oxide as a catalyst the reaction of key intermediate **2**,



Scheme 1. Reagents and conditions: (a) Glacial acetic acid, dry ethanol, reflux 5 h; (b) $POCl_3$, DMF, 90 °C; (c) (i) MeLi, Et_2O, THF, -78 °C or vinylmagnasium bromide, THF, -78 °C (ii) MnO_2, $CHCl_3$, r.t.(2 steps) (d) (i) 1- methylimidazole, n-BuLi, THF, -78 °C, (ii)MnO_2, $CHCl_3$, r.t.(2 steps); (f) morpholine, EtOH.



Scheme 2. Reagents and conditions: (a) ethylacetate, reflux, 8h; (b) 20 mol % Cu: Mn (1 :0.25), ethanol, 6h

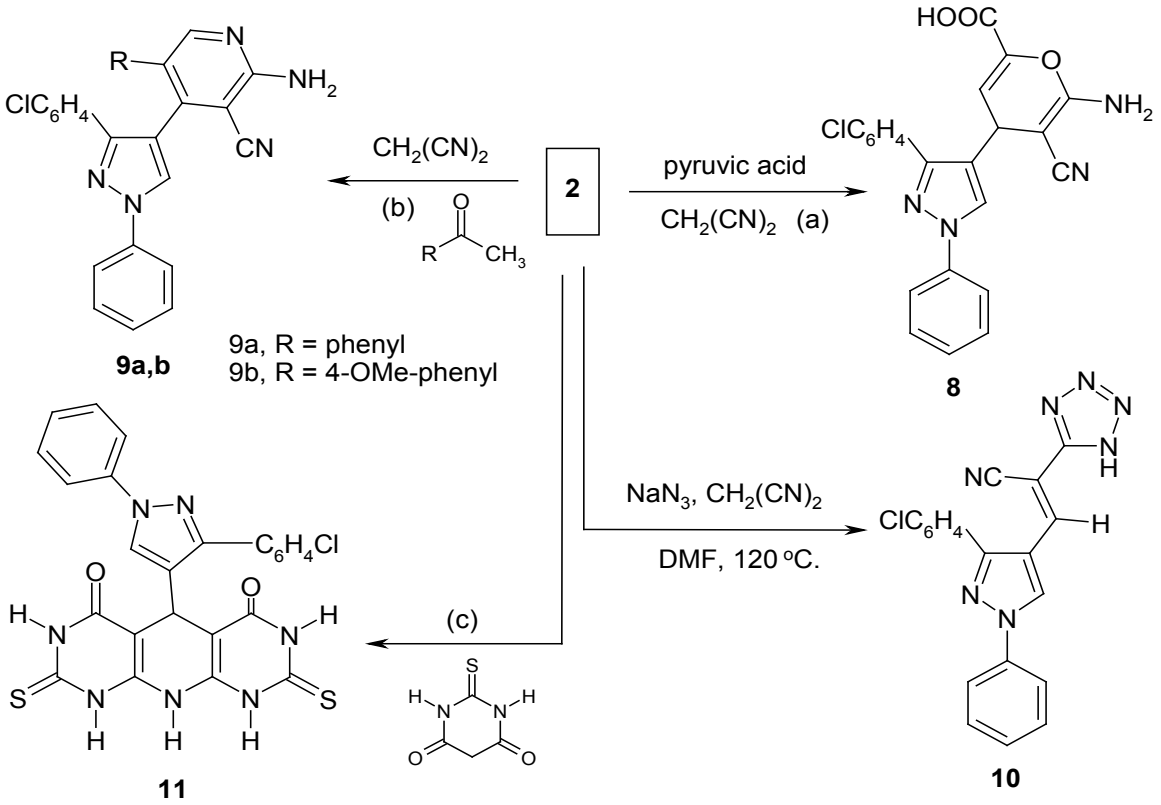
phenylacetylene and 2-aminopyridine derivatives in ethanol afforded imidiazo[1,2-a]pyridinyl derivatives **7a-c** in good yield, The structure of compound **7a-c** was confirmed by IR which revealed the disappearance of carbonyl group (Scheme 2).

In order to synthesize various of heterocyclic ring, using malononitrile and bulk Fe_3O_4 as a catalyst with different reagents. Reaction of 3-(4-chlorophenyl)-1-phenyl-*1H*-pyrazol-4-carboxaldhyde **2** with malononitrile and keto acid such as pyruvic acid in the presence of bulk Fe_3O_4 as a catalyst give 6-amino-4-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-5-cyano-4*H*-pyran-2-carboxylic acid **8**. Also, on the other hand, one pot reaction of pyrazole carboxyaldhyde derivatives **2** with malononitrile, acetophenone derivatives and ammonium acetate in the presence of bulk Fe_3O_4 as a catalyst afforded 4-pyridinyl-pyrazole derivatives **9a, b**.

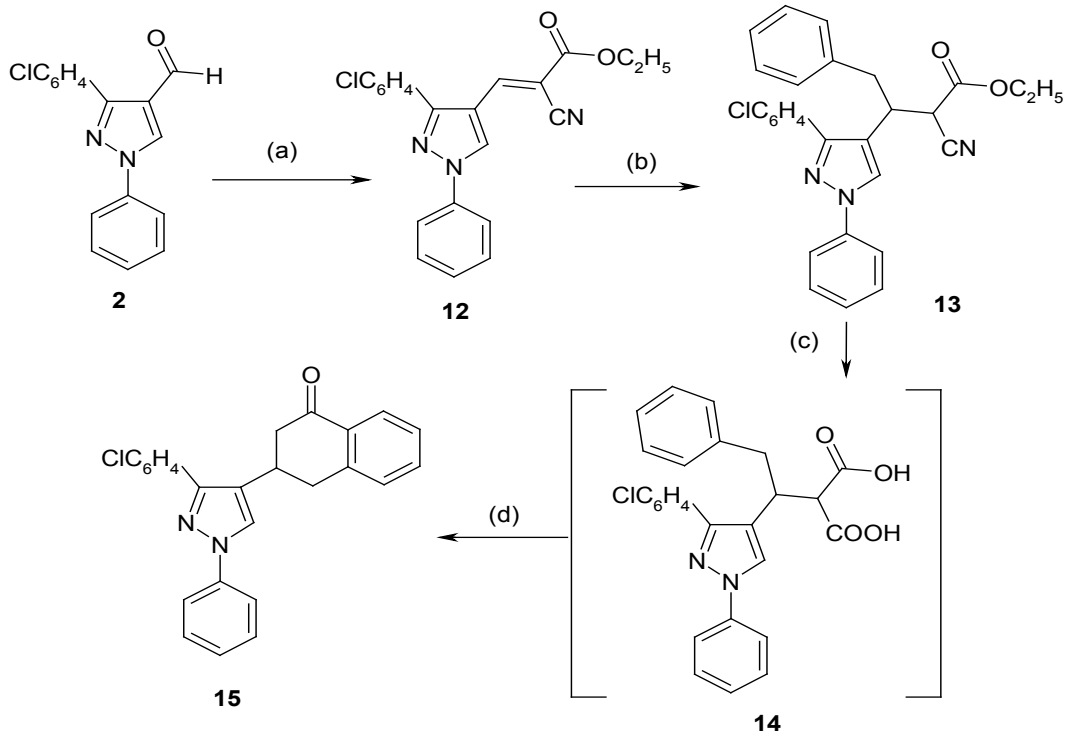
Following our program to synthesize 5-substituted 1*H*-tetrazolyl pyrazole derivatives via 1,3-dipolar cycloaddition reaction of malononitrile, sodium azide and pyrazole carboxyaldhyde derivatives **2** and catalytic amount of in Fe_3O_4 DMF afforded **10**.

The treatment of compound **2** with 2-thiobarbaturic acid, and ammonium acetate with (1:2:1 mol ratio) in the presence of Al_2O_3 gave dithioxo-hexahydropyrido[2,3-d:6,5-d-d`] dipyrimidine-4,6-dione **11** in moderate yield **(**Scheme 3).

Knoevenagel condensation [20] of 3-(4-chlorophenyl)-1-phenyl-*1H*-pyrazol-4-carboxaldhyde **2** with ethyl cyanoacetate in the presence of pyrrolidine and acetic acid generated a ketoester **12** in excellent yield. The treatment of compound **12** with benzylmagnesium bromide in dry THF afford Ethyl 2-cyano-3-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-4-phenylbutanoate **13**, which undergo oxidation in acidic medium to afford dicarboxylic acid **14**.



Scheme 3. Reagents and conditions: (a) bulk Fe_3O_4, ethanol, reflux, 8h; (b) NH_4OAc, bulk Fe_3O_4, ethanol, reflux, 6h; (c) NH_4OAc, Al_2O_3, ethanol, reflux, 48h.



Scheme 4. Synthesis of 3- [3-(4-chlorophenyl) -1- phenyl -1H-pyrazol-4-yl] -3,4- dihydro - napthalene -1- (2H)-one 15 Reagents and conditions: (a) ethylcyanoacetate, AcOH, Pyrroliden, Toluene, reflux 5 h; (b) benzylmagnesium bromide, THF, 6 h at 80 °C; (c-d) conc. HCl, reflux 5 h; and then TFAA, r.t., 7 h

Finally, the monoacid was accomplished by decarboxylation of **14** in situ with hydrochloric acid, which then underwent an intramolecular cyclization by using trifluoroacetic anhydride (TFAA) to give 3-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-3,4-dihydronapthalene-1-(2*H*)-one **15** (Scheme 4).

Antitumor activity and structure activity relationship

The antitumor activity of the newly synthesized compounds was evaluated against three tumor cell lines namely liver cancer (HepG2), human colonic carcinoma cell line (HCT-116), and human breast adenocarcinoma cell line (MCF-7) after continuous exposure for 48 h. The results summarized in Table 1 show that most of the newly synthesized compounds exhibited significant antitumor activity compared to doxorubicin.

Pyrazole bearing 4-chlorophenyl thiazolidone **6d** with GI_{50} value of (0.01, 0.04 and 0.08 μmol L^{-1}), and hexapyridodipyrimidine **11** moieties with GI_{50} value of (0.01, 0.03 and 0.05 μmol L^{-1}) exhibited higher antitumor activity than doxorubicin (GI_{50} = 0.04, 0.05 and 0.09 μmol L^{-1}) against three tumor cell lines. Compound **6b** exhibited good activity, while compounds **6a**, **c** exhibited moderate activity the variation in activities may be due to the type of the substituent on the phenyl ring attached to thiazolidone moiety.

In addition, 4-fluorobenzyl-benzimidiazole **7b** with GI_{50} value of (0.01, 0.05 and 0.06 μmol L^{-1}) exhibited higher antitumor activity than doxorubicin, the presence of stronger electron-withdrawing substituents (fluoro) in the para-position of the phenyl ring might be responsible for enhancing the growth inhibition activity, while 4-chlorobenzyl-benzimidiazole **7c** with GI_{50} value of (0.05, 0.08 and 1.02 μmol L^{-1}) is almost as active as doxorubicin. The absence of substituent in the phenyl ring as in compound **7a** exhibited moderate activity. Compound **9b** with GI_{50} value of (0.09, 1.05 and 0.09 μmol L^{-1}) revealed slightly lower activity than that of doxorubicin.

TABLE 1. The effect of synthesized compounds on the growth of cervical carcinoma cell line (HeLa), human colonic carcinoma cell line (HCT-116), and human breast adenocarcinoma cell line (MCF-7).

Compd.	GI_{50} (μmol L^{-1})		
	HepG2	**HCT-116**	**MCF-7**
3a	28.14 ± 5.75	23.45 ± 7.56	20.50 ± 1.89
3b	12.07 ± 1.89	12.86 ± 1.51	15.09 ± 3.71
3c	2.95 ± 0.74	4.64 ± 0.68	5.84 ± 2.05
4	7.23 ± 2.36	8.05 ± 2.09	6.28 ± 0.65
5	9.80 ± 1.08	7.45 ± 1.67	20.25 ± 3.12
6a	15.09 ± 3.71	17.09 ± 2.3	15.23 ± 2.75
6b	1.06 ± 0.51	2.95 ± 0.74	1.80 ± 0.59
6c	10.20 ± 2.05	8.05 ± 2.04	12.07 ± 1.89
6d	0.01 ± 0.006	0.04 ± 0.01	0.08 ± 0.02
7a	5.38 ± 2.44	7.02 ± 2.40	7.25 ± 1.45
7b	0.01 ± 0.004	0.05 ± 0.006	0.06 ± 0.002
7c	0.05 ± 0.007	0.08 ± 0.005	1.02 ± 0.03
8	12.80 ± 2.51	10.80 ±1.50	17.03 ± 2.30
9a	15.20 ± 1.44	12.87 ± 1.31	8.50 ± 2.01
9b	0.09 ± 0.006	1.05 ± 0.006	0.09 ± 0.007
10	10.20 ± 2.04	12.25 ± 1.10	12.63 ± 2.22
11	0.01 ± 0.006	0.03 ± 0.004	0.05 ± 0.007
12	15.75 ± 1.82	10.47 ± 1.06	10.23 ± 2.03
15	12.45 ± 1.85	17.09 ± 2.3	15.20 ± 2.05
Doxorubicin	0.04 ± 0.009	0.05 ± 0.008	0.09 ± 0.005

GI_{50} – concentrations that cause 50 % cell growth inhibition after continuous exposure for 48 h.
Mean ± SEM of three independent experiments performed in duplicate.

On the other hand, compounds **3c** exhibited moderate activity due to the presence of *N*-methyl imidiazole moiety. Furthermore, compounds **3b**, **4**, **5**, **8**, **9a**, **10**, **12** and **15** exhibited moderate to low antitumor activity on the three tumor cell lines, while compounds **3a** exhibited very low antitumor activity.

Conclusions

We have synthesized novel pyrazole bearing thiazolyl, pyridinyl, imidiazolyl, tetrazolyl, and hexapyridodipyrimidine moieties, and were investigated for their anticancer activity.

Compounds **6d**, **7b**, **c**, **9b** and **11** exhibited higher antitumor activity compared with Doxorubicin, while the other compounds showed good to moderate antitumor activity. The activity of these compounds are dependent on the pyrazole ring, the nature of heterocyclic ring, and the type of the substituent on the phenyl ring attached to these heterocyclic ring.

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References

1. Ranatunge, R.R., Earl, R.A., Garvey, D.S., Janero, D.R., Letts, L.G., Martino, A.M., Murty, M.G., Richardson, S.K., Schwalb, D.J., Young, D.V., Zemtseva, I.S., 3-(2-Methoxy-tetrahydro- furan-2-yl) pyrazoles: a novel classof potent, selective cyclooxygenase-2 (COX-2) inhibitors. *Bioorg. Med. Chem. Lett.* **14**, 6049-6052 (2004).

2. Hafez, H. N., Microwave-Assisted Synthesis and Containing Imidiazole, Pyrazole, Oxazole, Thiadiazole and Benzochromene Derivatives. *Egypt. J. Chem.* **60**, 1015 – 1028 (2017).

3. Li, X., Lu, X., Xing, M., Yang, X., Zhao, T., Gong, H., Zhu, H., Synthesis, biological evaluation, and molecular docking studies of N,1,3-triphenyl-1Hpyrazole-4-carboxamide derivatives as anticanceragents. *Bioorg. Med. Chem. Lett.* **22**, 3589– 3593 (2012).

4. Hafez, H.N., El-Gazzar, A.B.A., Synthesis and Biological Evaluation of N- Pyrazolyl Derivatives and Pyrazolopyrimidine Bearing a Biologically Active Sulfonamide Moiety as Potential Antimicrobial Agent. *Molecules* **21**, 1156 (2016).

5. S.R. Stauffer, C. J. Coletta, R. Tedesco, G. Nishiguchi, K. Carison, J. Sun, B .S. Katzenellenbogen, J. A. Katzenellenbogen, Pyrazole ligands: structure - affinity/activity relationships and estrogen receptor-alpha-selective agonists. *J. Med. Chem.* **43**, 4934-4947(2000).

6. Ozdemir, Z., Gumusel, H. B. B., Calis, U., Bilgin, A. A., Synthesis and studies on antidepressant and anticonvulsant activities of some 3-(2-furyl)-pyrazoline derivatives. *Eur. J. Med. Chem.* **42**, 373-379 (2007).

7. El-Hawash, S. A.M., Badawey, E.A.M., El-Ashmawey, I. M., Nonsteroidal anti-inflammatory Agents- part 2 antiinflammatory, analgesic and antipyretic activity of some substituted 3- pyrazolin-5-ones and 1,2,4,5,6,7-3H-hexahydroindazol-3-ones. *Eur. J. Med. Chem.* **41**, 155–165 (2006).

8. Genin, M. J., Biles, C., Keiser, B. J., Poppe, S. M., Swaney, S. M., Tarpley, W. G., Yagi, Y., Romero, D. L., Novel 1,5-diphenylpyrazole nonnucleoside HIV-1 reverse transcriptase inhibitors with enhanced activity versus the delavirdine-resistant P236L mutant: lead identification and SAR of 3- and 4-substituted derivatives. *J. Med. Chem.* **43**, 1034-1040 (2000).

9. Mowbray, C. E., Burt, C., Corbau, R., Gayton, S., Hawes, M., Perros, M., Tran, I., Price, D. A., Quinton, F. J., Selby, M. D., Stupple, P. A., Webster, R., Wood, A., Pyrazole NNRTIs 4: Selection of UK453,061 (lersivirine) as a Development Candidate. *Bioorg. Med. Chem. Lett.* **19**, 5857–5860 (2009).

10. Jia, Z. J., Wu, Y., Huang, W., Zhang, P., Song, Y., Woolfrey, J., Sinha, U., Arfsten, A. E., Edwards, S.T., Hutchaleelaha, A., Hollennbach, S. J., Lambing, J. L., Scarborough, R. M., Zhu, B.-Y., 1-(2-Naphthyl)- 1H-pyrazole-5-carboxylamides as potent factor Xa inhibitors. Part 3: Design, synthesis and SAR of orally bioavailable benzamidine-P4 inhibitors. *Bioorg. Med. Chem.*

Lett. **14**, 1229–1234 (2004)

11. Lyga, J.W., Patera, R.M., Plummer, M. J., Halling, B. P., Yuhas, D.A., Synthesis, mechanism of action, and QSAR of herbicidal 3-substituted-2-aryl-4,5,6,7- tetrahydroindazoles. *Pesticide Science.,* **42,** 29-36 (1994).

12. Genin, M.J., Biles, C., Keiser, B. J., Poppe, S. M., Tarpley, W. G., Yagi, Y., Romero, D.L. Novel1,5-diphenylpyrazole nonnucleoside HIV-1 reverse transcriptase inhibitors with enhanced activity versus the delavirdine-resistant P236L mutant: lead identification and SAR of 3- and 4-substituted derivatives. *J. Med. Chem.* **43,** 1034- 1040 (2000).

13. Yang, L., Okuda, F., Kobayashi, K., Nozaki, K., Tanabe, Y., Ishii, Y., Haga, M. Syntheses and phosphorescent properties of blue emissive iridium complexes with tridentate pyrazolyl ligands. *Inorg. Chem.* **47,** 7154-7165 (2008).

14. El-Hawash, S. A.M., Badawey, E.A.M., El-Ashmawey, I. M., Nonsteroidal anti-inflammatoryagents—part 2 antiinflammatory, analgesic and antipyretic activity of some substituted 3- pyrazolin-5- ones and 1,2,4,5,6,7-3H-hexahydroindazol-3-ones. *Eur. J. Med. Chem.* **41,** 155–165 (2006).

15. Arya, V. P., Grewal, R. S., Kaul, C. L., Ghate, S. P., Mehta, D. V., George, T., Antihypertensive agents II: Synthesis and hypotensive activity of certain 1,4,5-Trisubstituted pyrazoles, *Journal of Pharmaceutical Sciences*. **58,** 432-440 (1969).

16. Te-Sook, J., Kyung, S. K., So-Jin, A., Kyung-Hyun, C., Sangku, L., Woo, S. L., Novel 3,5-diaryl pyrazolines as human acyl-CoA:cholesterol acyltransferase Inhibitors. *Bioorg. Med. Chem. Lett.* **14,** 2715-2717 (2004).

17. Shetty, S.C., Bhagat, V.C., Synthesis and Pharmacological Activities of 3-(4-Substituted phenyl)-1- phenyl-1H-pyrazole 4-carboxaldehyde and Its Aldimines Derivatives. *Asian J. Chem.* **20,** 5037- 5045 (2008).

18. Skehan, P., Storeng, R., Scudiero, D., Monks, A., McMahon, J., Vistica, D., Warren, J. T.,Bokesch, H., Kenny, S., Boyd, M. R., New colorimetric cytotoxicity assay for anti-cancer drug screening. *J. Natl. Cancer Inst.* **82**, 1107–1112 (1990).

19. Monks, A., Scudiero, D., Skehan, P., Shoemaker, R., Paul, K., Vistica, D., Hose, C., Langley, J., Cronise, P., Vaigro-Wolff, A., Gray-Goodrich, M., Campbell, H., Mayo, J., Boyd, J. M., Feasibility of a high-flux anticancer drug screen using a diverse panel of cultured human tumor cell lines. *J. Natl. Cancer Inst.* **83**, 757–766 (1991).

20. Benfatti, F., Cardillo, G., Gentilucci, L., Mosconi, E., Tolomelli, A. Enzymatic resolution of ethyl 3-hydroxy-2-(1'-substituted-methylidene) butyrate by Pseudomonas cepacia lipase catalyzed acetylation. *Tetrahedron Asymmetry* **18,** 2227–2232 (2007).

التصميم والتشييد والتقييم الحيوي لمشتقات N - فينيل بيرازول التي تحتوي على سلاسل جانبية تحتوي على النيتروجين كعوامل مضادة للأورام

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تم تشييد متسلسلة فريدة من N - فينيل بيرازول المحتوية على مشتقات الأسيل(N، (3a, b – ميثيل إيميدازول (4)، مشتقات الثيازول (6a-d)، مشتقات البنزإيميدازول (7a-c)، مشتقات البيران و البيريدين8, 9a, b ، التترازول (10)، البيريدوبيريميدين (11)، و مشتقات الداي هيدرونفثالين (15). تم إثبات المركبات الجديدة التى تم تشييدها باستخدام التحاليل الدقيقة و الاطياف الضوئية المختلفة. وتم أختبار النشاط المضاد للأورام تجاه ثلاث خلايا من الاورام واستخدام الدكسوروبسين كمادة قياسية مضادة للسرطان. و أظهرت المركبات 6d, (7b, c), 9b, 11 فاعلية عالية مضادة للسرطان بالمقارنة بالدكسوروبسين.