Synthesis and anticancer activity of 3-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes

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ABSTRACT

The generation of heterocycles containing 1,2,3-triazole and pyrazole moieties has been explored. The synthesis of these heterocycles is of interest because they are components of important compounds ranging from agrochemicals to pharmaceuticals. Particularly interesting are their potential cancer cell anti-proliferation properties. Three 3-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes, where the aryl substituent is phenyl, 4-methoxyphenyl, or 4-nitrophenyl, have been used as precursors for the synthesis of new heterocycles. 1*H*-1,2,3-triazoles containing dithiols, acrylates, isoxazol-5(4*H*)-one, hydrazone, and *bis*-thiocarbohydrazone were synthesized in good yields from the precursors using simple procedures. The in vitro assessment of the activity of the resultant heterocycles against human cancer cells (HCT-116, HepG2, and MCF-7) and a human healthy cell line (BJ-1) was performed using the lactate dehydrogenase assay. Thiocarbohydrazone was the most active heterocycle, and its cytotoxic activity was comparable to that obtained for doxorubicin as a reference. The other heterocycles showed moderate cytotoxic activities.

1. Introduction

Cancer has a high mortality rate globally [1]. Treatment includes the use of various nitrogen-containing heterocycles for, for instance, gastrointestinal stromal tumors, advanced renal cell carcinoma, and pancreatic cancer [2,3]. Other drugs act as growth inhibitors for tumors (e.g., breast cancer) and renal cell carcinoma [4–10].

Heterocyclic compounds containing nitrogen (e.g., 1,2,3-triazoles and pyrazoles) are important components of agrochemicals and pharmaceuticals [11,12]. The 1,2,3-triazole ring system is commonly produced from 1,3-dipolar cycloaddition reactions of azides and alkynes in the presence of a copper catalyst [13–15]. The 1,2,3-triazole moiety is a salient structural backbone in many natural and synthetic biologically active molecules which display a wide range of pharmacological activities, acting as antioxidant, antitubercular, anticancer, anti-inflammatory, antimicrobial, and antidiabetic agents [16–25]. 1,2,3-Triazoles have anticancer activities by inhibiting enzymes, carbonic anhydrases, tryptophan, 2,3-dioxygenase, aromatase, thymidylate synthase, and others [26–31].

Pyrazoles act as antioxidant, antifungal, anticancer, antitubercular, antimalarial, and anti-inflammatory agents [32–37]. They are essential components in a range of drugs, including betazole (a histamine H2 receptor agonist), fezolamine (an anti-depressant), rimonabant (an anorectic anti-obesity), celecoxib (an anti-inflammatory), and 3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (an anti-psychotic) [38–41].

Heterocycles containing both pyrazole and triazole units have been synthesized through cyclization of thiosemicarbazides or carbodithioate, the reaction of triazolylhyrazine and 1,3-diketone or β-ketoester, acetylenic pyrazoles and azides, and pyrazolylazides and acetylenes [42–50]. Pyrazole-3(4)-carbaldehydes can be synthesized through the Vilsmeier-Haack reaction of corresponding hydrazones [51]. In furtherance of our work towards new heterocycles [52–56], the current research aimed to synthesize several heterocycles containing 1*H*-1,2,3-triazole and 1*H*-pyrazole moieties generated from 3-(5-methyl-1-(aryl)-1*H*-1,2,

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3-triazol-4-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes and assess their anticancer activity. The target heterocycles were obtained in high yields using simple procedures. In addition, their anticancer activity against human cancer cells was evaluated and compared to those obtained for the chemotherapy drug doxorubicin as a reference.

2. Experimental

2.1. General

Analytical or HPLC grades of solvents and reagents were sourced from Merck and used as received. Melting points (m.p.) were determined using an Electrothermal melting point apparatus. A JASCO FT/IR-4600 spectrometer was used to record the IR spectra. The NMR spectra were obtained in deuterated dimethyl sulfoxide (DMSO-d_6) using a JEOLNMR 500 MHz spectrometer at 125 MHz and 500 MHz for ^{13}C and ^{1}H NMR measurements, respectively. The coupling constant was recorded in Hz, and the chemical shift was reported in ppm. Confirmation of exchangeable signals in the ^{1}H NMR spectra was achieved by adding deuterated water (D_2O). Compounds **1a–c** [57], **12** [58], and **13** [59] were produced using literature procedures.

Merck supplied the Roswell Park Memorial Institute (RPMI) 1640 medium. Fetal bovine serum (FBS) and fetal calf serum (FCS) were obtained from Gibco. Human liver carcinoma (HepG-2), human colorectal carcinoma (HCT116), human breast adenocarcinoma (MCF-7), and normal human skin fibroblast (BJ-1) cell lines were purchased from the American Type Culture Collection. The cell lines were maintained in RPMI-1640 medium, supplemented with 10% heat-inactivated FBS, 100U/mL penicillin, and 100U/mL streptomycin. The cells were grown in a humidified atmosphere of CO_2 (5%) at 37 °C. The experiments were conducted in triplicate (n =3), providing averages and standard deviations (SD). The significant differences between the means of the values of the IC_{50} were determined using the SPSS software.

2.2. Synthesis of dithiols 2–4

To a solution of thiophenol (2.5 mmol, 0.30 g) and **1a–c** (1 mmol) in DCM (15 mL), I_2 (2.5 mol, 0.32 g) was added, followed by stirring for 4 h at room temperature. The mixture was diluted with $Na_2S_2O_3$ (0.06 M) solution, and the layers were separated. Anhydrous Na_2SO_4 was used to dry the organic layer, and reduced pressure was used to remove the DCM. The solid was purified through recrystallization using dimethylformamide (DMF) to give the corresponding dithiol **2, 3**, or **4**, respectively.

2.2.1. 4-[3-(bis(Phenylthio)methyl)-1-phenyl-1H-pyrazol-5-yl]-5-methyl-1-phenyl-1H-1,2,3-triazole (2)

Yield: 75%, m.p. 166–168 °C. IR (KBr, ν cm^{-1}): 3074 (CH), 1672 (C=N), 1596 (C=C). ^{1}H NMR: 2.47 (s, 3H, Me), 6.95 (s, 1H, CH), 7.22 (d, 7.6 Hz, 2H, Ar), 7.27–7.31 (m, 5H, Ar), 7.42 (d, 7.2 Hz, 4H, Ar), 7.48 (d, 7.6 Hz, 1H, Ar), 7.60–7.67 (m, 5H, Ar), 7.87 (d, 7.2 Hz, 2H, Ar), 7.92 (br, 1H, Ar), 8.66 (s, 1H, pyrazolyl). ^{13}C NMR: 10.5, 49.3, 118.7, 121.8, 125.6, 125.8, 127.1, 128.1, 129.0, 129.6, 130.1, 130.2, 131.7, 132.6, 135.0, 136.3, 138.6, 139.6, 142.5, 162.8. Anal. Calcd. for $C_{31}H_{25}N_5S_2$ (531.69): C, 70.03; H, 4.74; N, 13.17. Found: C, 70.28; H, 4.85; N, 13.28%.

2.2.2. 4-[4-(bis(Phenylthio)methyl)-1-phenyl-1H-pyrazol-3-yl]-1-(4-methoxyphenyl)-5-methyl-1H-1,2,3-triazole (3)

Yield: 77%, m.p. 161–162 °C. IR (KBr, ν cm^{-1}): 3064 (CH), 1654 (C=N), 1593 (C=C). ^{1}H NMR: 2.54 (s, 3H, Me), 3.83 (s, 3H, OMe), 6.97 (s, 1H, CH), 7.15 (d, 8.6 Hz, 2H, Ar), 7.22 (t, 7.6 Hz, 2H, Ar), 7.26–7.31 (m, 5H, Ar), 7.43 (d, 7.6 Hz, 4H, Ar), 7.47 (t, 7.6 Hz, 2H, Ar), 7.58 (d, 8.6 Hz, 2H, Ar), 7.86 (d, 8.6 Hz, 2H, Ar), 8.65 (s, 1H, pyrazolyl). ^{13}C NMR: 10.4, 49.2, 56.1, 115.3, 118.7, 121.0, 121.8, 127.1, 127.3, 128.1, 129.0, 129.1, 129.6, 130.1, 131.7, 132.7, 135.0, 138.4, 139.6, 142.6, 160.6. Anal. Calcd. for $C_{32}H_{27}N_5OS_2$ (561.72): C, 68.42; H, 4.85; N, 12.47. Found: C, 68.52; H, 4.89; N, 12.33%.

2.3. 4-[3-(bis(Phenylthio)methyl)-1-phenyl-1H-pyrazol-5-yl]-5-methyl-1-(4-nitrophenyl)-1H-1,2,3-triazole (4)

Yield: 78%, m.p. 158–160 °C. IR (KBr, ν cm^{-1}): 3127 (CH), 1666 (C=N), 1596 (C=C). ^{1}H NMR: 2.66 (s, 3H, Me), 6.92 (s, 1H, CH), 7.20–7.31 (m, 7H, Ar), 7.42–7.49 (m, 6H, Ar), 7.86 (d, 7.7 Hz, 2H, Ar), 8.01 (d, 9.0 Hz, 2H, Ar), 8.44 (d, 9.0 Hz, 2H, Ar), 8.67 (s, 1H, pyrazolyl). ^{13}C NMR: 10.6, 49.3, 118.8, 120.0, 122.0, 125.7, 127.3, 128.2, 129.1, 129.6, 130.1, 131.9, 134.9, 139.2, 139.6, 141.1, 142.1, 148.1, 162.1. Anal. Calcd. for $C_{31}H_{24}N_6O_2S_2$ (576.69): C, 64.56; H, 4.19; N, 14.57. Found: C, 64.67; H, 4.27; N, 14.71%.

2.4. Synthesis of acrylates 6 and 7

A mixture of **1a** or **1b** (2 mmol) and **5** (0.38 g, 2 mmol) in dry EtOH (15 mL) containing piperidine (0.1 mL) was refluxed for 5 h. The mixture was left to cool, and the solid produced was collected by filtration. Crystallization of the crude solids using DMF gave either **6** or **7**, respectively.

2.4.1. Ethyl 2-benzoyl-3-(5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-pyrazol-4-yl)acrylate (6)

Yield: 82%, m.p. 139–140 °C. IR (KBr, ν cm^{-1}): 3059 (CH), 1687 (C=O), 1666 (C=O), 1596 (C=C). ^{1}H NMR: 1.08 (t, 7.2 Hz, 3H, Me), 2.47 (s, 3H, Me), 4.17 (q, 7.2 Hz, 2H, CH_2), 7.32 (t, 7.6 Hz, 1H, Ar), 7.44–7.52 (m, 3H, Ar), 7.61–7.69 (m, 9 H, Ar), 7.94 (d, 7.2 Hz, 2H, Ar), 8.02 (s, 1H, pyrazolyl), 8.72 (s, 1H, CH). ^{13}C NMR: 10.4, 14.5, 61.6, 115.7, 119.4, 119.5, 125.9, 128.1, 128.4, 129.3, 129.7, 130.2, 130.3, 130.5, 133.8, 134.8, 136.2, 136.4, 138.0, 138.8, 138.9, 145.8, 154.5, 165.0, 195.9. Anal. Calcd. for $C_{30}H_{25}N_5O_3$ (503.56): C, 71.56; H, 5.00; N, 13.91. Found: C, 71.69; H, 5.08; N, 14.11%.

2.4.2. Ethyl 2-benzoyl-3-(5-(1-(4-methoxyphenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-pyrazol-4-yl)acrylate (7)

Yield: 84%, m.p. 162–163 °C. IR (KBr, ν cm^{-1}): 3159 (CH), 1708 (C=O), 1666 (C=O), 1612 (C=C). ^{1}H NMR: 1.08 (t, 7.2 Hz, 3H, Me), 2.47 (s, 3H, Me), 3.83 (s, 3H, OMe), 4.17 (q, 7.2 Hz, 2H, CH_2), 7.15 (d, 9.1 Hz, 2H, Ar), 7.32 (t, 7.6 Hz, 1H, Ar), 7.44–7.53 (m, 4H, Ar), 7.58–7.63 (m, 5H, Ar), 7.93 (d, 8.1 Hz, 2H, Ar), 8.01 (s, 1H, pyrazolyl), 8.72 (s, 1H, CH). ^{13}C NMR: 10.4, 14.5, 56.2, 61.5, 115.3, 115.7, 119.4, 119.4, 127.4, 128.1, 128.4, 129.1, 129.3, 129.7, 130.3, 130.5, 133.9, 133.9, 134.8, 136.2, 137.7, 138.9, 160.6, 165.0, 195.9. Anal. Calcd. for $C_{31}H_{27}N_5O_4$ (533.58): C, 69.78; H, 5.10; N, 13.13. Found: C, 69.88; H, 5.19; N, 13.22%.

2.5. Synthesis of ethyl 2-((2-(2,4-dinitrophenyl)hydrazineylidene)(phenyl)methyl)-3-(5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-pyrazol-4-yl)acrylate (9)

A mixture of **6** (1 mmol, 0.50 g) and **8** (1 mmol, 0.20 g) in dry EtOH (15 mL) containing concentrated HCl (0.1 mL) was refluxed for 3 h. The mixture was then cooled, and the solid obtained was filtered off and recrystallized from DMF to give **9** in 88% yield, m.p. 258–260 °C. IR (KBr, νcm^{-1}): 3288 (NH), 3059 (CH), 1695 (C=O), 1609 (C=C). ^{1}H NMR: 1.34 (t, 7.2 Hz, 3H, Me), 2.47 (s, 3H, Me), 4.52 (q, 7.2 Hz, 2H, CH_2), 7.39 (t, 7.7 Hz, 1H, Ar), 7.43 (s, 1H, pyrazolyl), 7.50 (d, 7.6 Hz, 2H, Ar), 7.54–7.64 (m, 9H, Ar), 7.67 (d, 7.6 Hz, 2H, Ar), 7.83 (d, 7.6 Hz, 2H, Ar), 8.34 (s, 1H, CH), 8.46 (d, 9.5 Hz, 1H, Ar), 8.77 (s, 1H, Ar), 11.00 (s, D_2O exch, 1H, NH). ^{13}C NMR (ppm): 10.3, 14.7, 62.2, 116.4, 117.0,

119.4, 123.3, 125.8, 126.6, 127.7, 127.9, 128.9, 129.8, 130.2, 130.4, 130.5, 130.6, 130.9, 131.2, 133.0, 133.3, 136.2, 137.9, 138.3, 138.5, 139.3, 144.1, 145.2, 154.8, 168.3. Anal. Calcd. for $C_{36}H_{29}N_9O_6$ (683.68): C, 63.24; H, 4.28; N, 18.44. Found: C, 63.32; H, 4.32; N, 18.56%.

2.6. Synthesis of 3-methyl-4-((3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)isoxazol-5(4H)-one (11)

A mixture of **1a** (2 mmol, 0.66 g), $H_2NOH.HCl$ (2 mmol, 0.14 g), **10** (2 mmol, 0.26 g), and K_2CO_3 (2 mmol, 0.27 g) in aqueous DMF (1:1; 15 mL) was refluxed for 8 h. The mixture was cooled, and ice water (100 mL) was added. The solid obtained was filtered off, dried, and recrystallized from DMF to give **11** in 77% yield, m.p. 245–246 °C. IR (KBr, νcm^{-1}): 3140 (CH), 1744 (C=O), 1617 (C=C). ^{1}H NMR: 2.25 (s, 3H, Me), 2.64 (s, 3H, Me), 7.64 (t, 7.7. Hz, 1H, Ar), 7.59–7.68 (m, 7H, Ar), 7.88 (d, 7.6 Hz, 2H, Ar), 8.79 (s, 1H, pyrazolyl), 9.88 (s, 1H, CH). Anal. Calcd. for $C_{23}H_{18}N_6O_2$ (410.43): C, 67.31; H, 4.42; N, 20.48. Found: C, 67.43; H, 4.51; N, 20.54%.

2.7. Synthesis of N′-(1-(5-methyl-1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)ethylidene)-2-[(3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-pyrazol-4-yl)methylene]hydrazine-1-carbothiohydrazide (14)

A mixture of **1a** (2 mmol, 0.66 g) and **12** (2 mmol, 0.20 g) in dry EtOH was refluxed for 5 min. 1,2,3-Triazole **13** (2 mmol, 0.49 g) was added, and the mixture refluxed for 2 h. After cooling, the solid was filtered and recrystallized from DMF to give **14** in 77% yield, m.p. 218–220 °C. IR (KBr, ν cm^{-1}): 3239 (NH), 3120 (CH), 1596 (C=C), 1237 (C=S). ^{1}H NMR: 2.46 (br s, 6H, 2 Me), 2.47 (s, 3H, Me), 7.39 (t, 7.7 Hz, 1H, Ar), 7.56–7.67 (m, 8H, Ar), 7.89–8.03 (m, 4H, Ar), 8.45 (d, 9.1 Hz, 2H, Ar), 8.89 (s, 1H, CH), 10.64 (s, D_2O exch, 1H, NH), 12.07 (s, D_2O exch, 1H, NH). ^{13}C NMR: 10.4, 11.3, 118.3, 118.9, 119.2, 125.6, 125.7, 125.9, 126.9, 127.7, 128.4, 129.9, 130.2, 130.4, 132.9, 133.3, 134.3, 136.3, 138.3, 139.5, 141.0, 143.3, 144.5, 148.3, 163.0. Anal. Calcd. for $C_{31}H_{27}N_{13}O_2S$ (645.70): C, 57.66; H, 4.21; N, 28.20. Found: C, 57.72; H, 4.31; N, 28.33%.

2.8. Crystal structure determination

An Agilent SuperNova Dual Atlas diffractometer using mirror monochromated Mo Kα or Cu Kα radiation was used to collect the single crystal diffraction data. The structures were solved by direct methods using SHELXT [60] and refined by full-matrix least-squares methods on F^2 with SHELXL [61]. In the crystal structure of **6**, the ethoxy group was modeled as disordered with two components of occupancy 0.61(1)/0.39 (1). The ethoxy group of molecule **7** was also disordered with two components of occupancy 0.76(2)/0.24(2). Crystal and structure refinement data are shown in Table 1. The X-ray crystallographic data for compounds **4, 6, 7**, and **14** have been deposited in the Cambridge Crystallographic Data Center with CCDC reference numbers 2268247–2268250.

2.9. Lactate dehydrogenase (LDH) assay

An LDH release assay was used to test the newly synthesized heterocycles on membrane permeability in the HepG2, MCF-7, HCT-116, and BJ-1 normal cell lines [62,63]. The cells were seeded in 24-well culture plates (density = 1 × 10^4 cells/well in a volume of 500 µL) and allowed to grow for 18 h. After treatment with heterocycles and doxorubicin® (positive control), the plates were incubated for 48 h. A supernatant (40 µL) was transferred to a new 96-well plate to determine the LDH release. Triton X-100 (6%; 40 µL) was added to the original plate to determine the total LDH. An aliquot of potassium phosphate buffer (0.1 M; 100 µL, pH 7.5) containing pyruvic acid (4.6 mM) was mixed with the supernatant using repeated pipetting. Potassium phosphate buffer (0.1 M; 100 µL, pH 7.5) containing a reduced β-NADH (0.4 mg/mL) was added to the wells. The kinetic changes were read for 1 min
using the ELISA microplate reader in absorbance (wavelength = 340 nm). The procedure was repeated with the total cell lysate (40 µL) to determine the total LDH. The LDH percentage was determined by dividing the LDH released into the media by the total LDH following cell lysis in the same well.

Table 1
Crystal structure solution and refinement data.

Compound	**4**	**6**	**7**	**14**
Formula	$C_{31}H_{24}N_6O_2S_2$	$C_{30}H_{25}N_5O_3$	$C_{31}H_{27}N_5O_4$	$C_{31}H_{27}N_{13}O_2S$
Formula weight	576.68	503.55	533.57	645.71
Temperature (K)	293(2)	296(2)	293(2)	293(2)
Wavelength (Å)	0.71073	1.54184	0.71073	1.54184
Crystal system	Monoclinic	Orthorhombic	Triclinic	Monoclinic
Space group	$P2_1/n$	Pbca	$P\bar{1}$	$P2_1/c$
a (Å)	11.4502(7)	7.1351(2)	7.7683(6)	13.4167(3)
b (Å)	15.8394(10)	25.7615(6)	13.2446(10)	30.2489(9)
c (Å)	15.6728(8)	28.5924(6)	14.3025(11)	7.3795(3)
α (°)	90	90	82.460(6)	90
β (°)	96.693(5)	90	80.792(7)	91.436(3)
γ (°)	90	90	76.226(7)	90
Volume(Å^3)	2823.1(3)	5255.6(2)	1404.15(19)	2993.96(17)
Z	4	8	2	4
Density (calc; Mg/m^3)	1.357	1.273	1.262	1.433
Absorption coeff. (mm^{-1})	0.229	0.684	0.086	1.420
F(000)	1200	2112	560	1344
Crystal size (mm^3)	0.250 × 0.210 × 0.110	0.380 × 0.170 × 0.080	0.360 × 0.090 × 0.060	0.330 × 0.090 × 0.030
Reflections collected	28078	37224	12809	10136
Independent reflections	7036	5225	6642	5332
R(int)	0.1031	0.0261	0.0311	0.0378
Parameters	371	384	403	427
Goodness-of-fit on F^2	1.053	1.047	1.040	1.002
R1 [I>2sigma(I)]	0.0743	0.0457	0.0744	0.0639
wR2 [I>2sigma(I)]	0.1855	0.1437	0.1668	0.1712
Extinction coefficient	–	0.00065(11)	0.0086(19)	–
Largest diff. peak and hole (e.Å^{-3})	0.380 (–0.377)	0.275 (–0.197)	0.190 (–0.157)	0.384 (–0.358)

3. Results and discussion

3.1. Heterocycle synthesis

Thioacetalization of carbonyl compounds occurs if a catalyst is present. Suitable catalysts include nickel(II) dichloride [64], hexabromoacetone [65], lithium perchlorate [66], sulfated zirconia [67], graphene oxide [68], I_2/nanostructured pyrophosphate [69], I_2 supported on natural phosphate [70], H_3NSO_3 [71], H_2O_2–$SOCl_2$ system [72], Cl_3CCO_2H in $NaC_{12}H_{25}SO_4$ micelles [73], cerium triflate [74], I_2 generated in situ from $Fe(NO_3)_3{\cdot}9H_2O$/NaI [75], anhydrous Cu(II) SO_4 [76], and Lewis acids (e.g., $ZnCl_2$, $NiCl_2$, or $CuCl_2$) supported on natural phosphate [77]. In the current work, the catalyst employed for the chemoselective thioacetalization of pyrazole-4-aldehydes was I_2 with dichloromethane (DCM) as the solvent.

Room temperature reactions of 3-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes **1a–c** (R = H, OMe, NO_2) and two-mole equivalents of thiophenol in the presence of I_2 in DCM for 12 h. afforded the corresponding 4-[3-(bis(phenylthio)methyl)-1-aryl-1*H*-pyrazol-5-yl]-5-methyl-1-phenyl-1*H*-1,2,3-triazoles **2–4** in 75–78% yields (Scheme 1).

The ^{1}H NMR spectra of **2–4** showed the CH and pyrazolyl protons as singlets at 6.92–6.97 and 8.65–8.67 ppm, respectively, while the CH carbon appeared at high field (49.2–49.3 ppm) in the ^{13}C NMR spectra.

The structure of **4** was confirmed using single crystal X-ray diffraction. The molecule of **4**, $C_{31}H_{24}N_6O_2S_2$, (Fig. 1) consists of nitrophenyl (**A4**, C1–C6, N1, O1, O2), methyl triazole (**B4**, C7–C9, N2–N4), methyl pyrazole (**C4**, C10–C13, N5, N6), phenyl (**D4**, C26–C31) and benzenethiol ([**E4**, C20–C25, S1], [**F5**, C14–C19) groups. Though not planar, the segment of the molecule closest to planarity comprises groups **A4**–**D4** with twist angles **A4**/**B4** = 36.73(8)°, **B4**/**C4** = 20.41(13)° and **C4**/**D4** = 23.43(11)° in the crystal structure. In contrast, the orientations of the benzenethiol groups **E4** and **F4** deviate more significantly from the **A4**–**D4** segment, with twist angles **C4**/**E4** = 71.38(12) ° and **D4**/**F4** = 69.53(12)°.

Next, we attempted the Claisen-Schmidt condensation reaction of **1**. Condensation of pyrazol-4-carbaldehydes **1a,b** (R = H, OMe) and ethyl benzoylacetate **5** in anhydrous EtOH containing piperidine as catalyst afforded the corresponding enone esters **6** (R= H) and **7** (R= OMe) in 82 and 84% yield, respectively (Scheme 2).

The IR spectra of **6** and **7** showed the presence of two carbonyl groups in the molecule. For example, the IR spectrum of **7** showed two strong absorption bands that appeared at 1666 and 1708 cm^{-1} due to the two carbonyl groups. The ^{1}H NMR spectra of **6** and **7** showed triplet (3H) and quartet (2H) signals at 1.08 and 4.17 ppm due to methyl protons and methylene protons of the ethyl group, respectively. In addition, the CH proton appeared at a high field (8.72 ppm). The ^{13}C NMR spectra of **6** and **7** showed two carbonyl groups at a very low field at 165.0 and 195.9 ppm, while the CH carbon appeared in the aromatic region at 115.7 ppm. The structures of **6** and **7** were confirmed using X-ray diffraction. The molecule of **6**, $C_{30}H_{25}N_5O_3$, (Fig. 2) consists of phenyl ([**A6**, C1–C6)] and [**D**6, C25–C30], methyl triazole (**B6**, C7–C9, N1–N3), pyrazole (**C6**, C10–C12, N4, N5), ethyl butanoate (**E6** (C13–C17, O2, O3) and benzaldehyde (**F6**, C18–C24, O1) groups. In the crystal structure, groups **B6**–**D6** are almost coplanar, with twist angles **B6**/**C6** = 11.51(3)° and **C6**/**D6** = 10.85(5)°. Groups **A6** and **F6** deviate from the plane of **B6**–**D6** with twist angles **A6**/**B6** = 66.95(8)° and **D6**/**F6** = 89.12(7)°. The torsion angle C15–O3–C16–C17 is 100.5(6)°, whereas the rest of the ethyl butanoate group is planar.

The molecule of **7**, $C_{31}H_{27}N_5O_4$, (Fig. 3) consists of methoxy phenyl ([**A7**, C25–C31, O4)], methyl triazole (**B7**, C22–C24, N3–N5), pyrazole (**C7**, C13–C15, N1, N2), phenyl (**D7**, C16–C21) ethyl butanoate (**E7**, C8–C12, O2, O3) and benzaldehyde (**F7**, C1–C7, O1) groups. In the crystal structure, groups **B7**–**D7** are coplanar, with twist angles **B7**/**C7** = 6.00(10)° and **C7**/**D7** = 7.24(13)°. Groups **A7** and **F7** deviate from the plane of **B7**–**D7** with twist angles **A7**/**B7** = 68.68(13)° and **C7**/**F7** = 86.39(10)°. The ethyl butanoate group is planar, as shown by the torsion angle C9–O3–C10–C11 of 179.7(6)°.

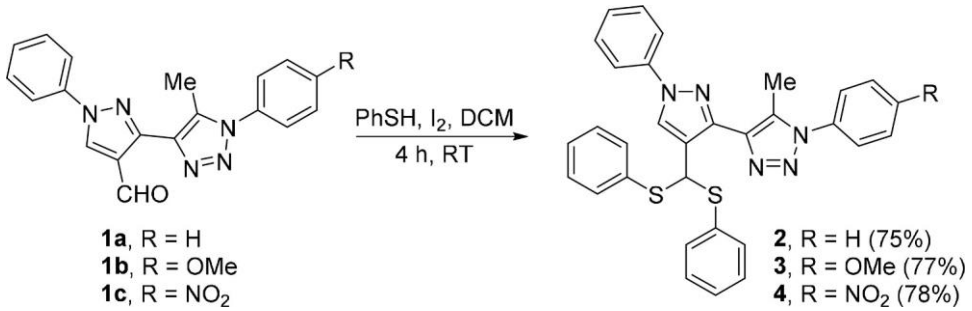
Condensation of **6** and 2,4-dinitrophenylhydrazine (**8**) in EtOH containing concentrated HCl as the catalyst gave the corresponding hydrazone **9** in 88% yield (Scheme 2). The IR spectrum of **9** had absorption bands at 3288 and 1695 cm^{-1} assigned to NH and C=O groups, respectively. After adding D_2O, the ^{1}H NMR spectrum of **9** revealed an exchangeable singlet at 11.00 ppm assigned to the NH proton. CH protons were observed as a singlet at 8.34 ppm. The carbonyl carbon appeared at a low field (168.3 ppm) in the ^{13}C NMR spectrum of **9**.

Isoxazol-5(4*H*)-one **11** was synthesized in 77% yield through a one-pot reaction of equimolar equivalents of **1a**, hydroxylamine hydrochloride, and ethyl acetoacetate (**10**) in a boiling mixture of H_2O and DMF (1:1) in the presence of potassium carbonate (K_2CO_3) for 8 h (Scheme 3). The IR spectrum of **11** showed a strong absorption band at 1744 cm^{-1} due to the C=O group. The ^{1}H NMR spectrum showed the CH proton as a singlet at a low field (9.88 ppm). It should be noted that **11** is highly insoluble in DMSO-d_6, and attempts to record the ^{13}C NMR spectrum failed.

Finally, the one-pot three-component reaction of equimolar equivalents of **1a**, thiocarbohydrazide **12**, and 4-acetyl-1,2,3-triazole **13** in boiling dry EtOH containing concentrated HCl for 2 h gave the corresponding bis-carbothiohydrazone **14** in 77% yield (Scheme 4).

An absorption band due to the NH group was observed at 3239 cm^{-1} in the IR spectrum of **14**. The ^{1}H NMR spectrum showed two exchangeable singlets at 10.64 and 12.07 ppm due to the two NH protons. In addition, the spectrum showed a singlet at 8.89 ppm due to the CH proton. The C=S carbon appeared at a low field (160.3 ppm) in the ^{13}C NMR spectrum of **14**.

Single crystal X-ray diffraction confirmed the structure of **14**. The molecule, $C_{31}H_{27}N_{13}O_2S$, (Fig. 4) comprises phenyl ([**A14**, C1–C6)] and [**D14**, C13–C18], methyl triazole ([**B14**, C7–C9, N1–N3] and [**F14**, C23–C25, N10–N12]), pyrazole (**C14**, C10–C12, N4, N5), ethylidenemethylidenehydrazine-carbothiohydrazide (**E14**, C19–C22, N7–N9, S1) and nitrobenzene (**G14**, C26–C31, N13, O1, O2) groups. In the crystal structure, groups **B14**–**F14** are coplanar, with twist angles **B14**/**C14** = 8.40(11)°, **C14**/**D14** = 4.15(10)°, **C14**/**E14** = 6.07 (8)°, **E14**/**F14** = 4.78 (9)°. The planarity of **E14** is partially stabilized by



Scheme 1. Synthesis of 4-[3-(bis(phenylthio)methyl)-1-aryl-1*H*-pyrazol-5-yl]-5-methyl-1-phenyl-1*H*-1,2,3-triazoles.

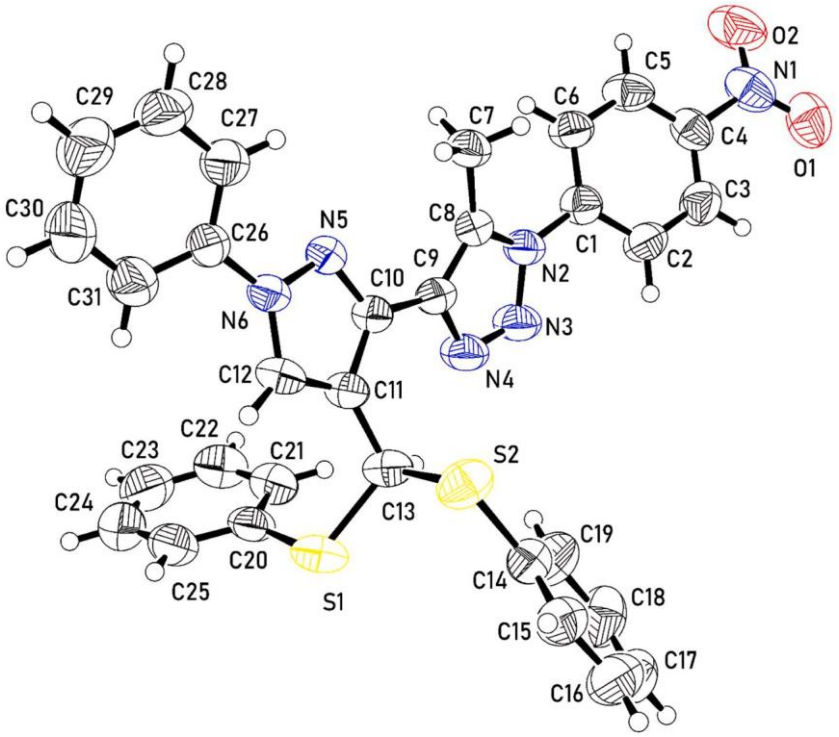
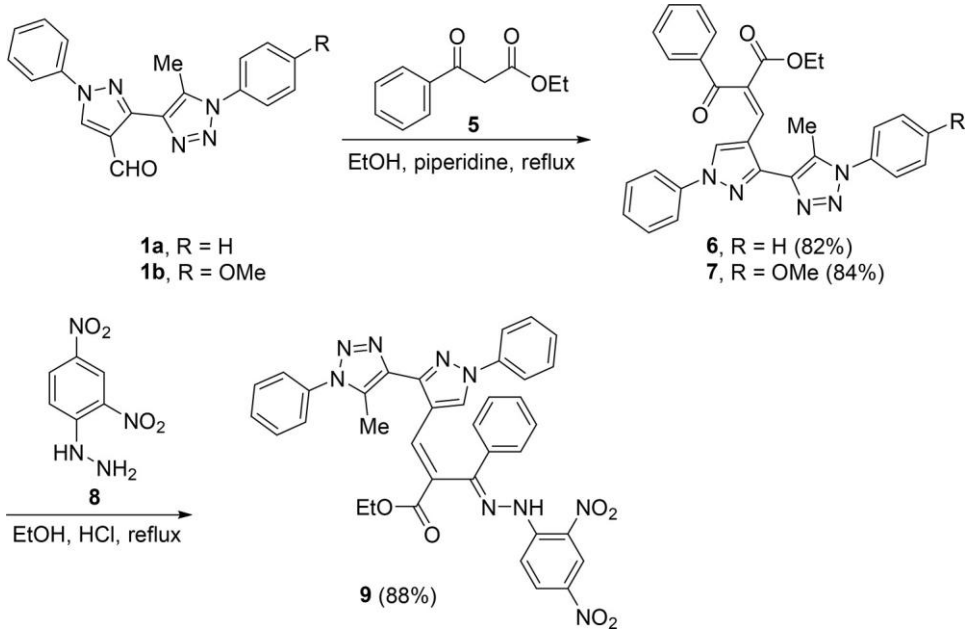


Fig. 1. An ortep representation of 4-[3-(bis(Phenylthio)methyl)-1-phenyl-1*H*-pyrazol-5-yl]-5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazole showing 50% probability atomic displacement ellipsoids.



Scheme 2. Synthesis of acrylate containing heterocycles.

intramolecular C–H...N and N–H...N contacts with geometry [C(19–H(19)...N(3) = 121.2°, C(19)...N(3) = 3.152(4)Å,] and [N(8)–H(8)...N(10) = 136.0°, N(8)...N(10) = 2.688(3) Å]. Groups **A14** and **G14** deviate from the plane of **B14**–**F14**, with twist angles **A14**/**B14** = 42.7(1)° and **E14**/**F14** = 46.6(1)°. An intermolecular N–H...O hydrogen bond with geometry (N(7)–H(7)...O(1) = 154.8°, N(7)...O(1) = 3.416(4) Å occurs in the crystal structure.

The molecules generated, including those characterized by single crystal diffraction (**4, 6, 7**, and **14**) contain the 5-methyl-1-phenyl-4-(1-phenyl-1*H*-pyrazol-3-yl)-1*H*-1,2,3-triazole fragment. Several compounds containing the fragment have also been reported (Supplementary Table S1). In the structures of **6, 7**, and **14**, the three-ring 5-methyl-4-(1-phenyl-1*H*-pyrazol-3-yl)-1*H*-1,2,3-triazole groups are planar with twist angles between linked rings of less than 12°, as already discussed. In each case, the phenyl group attached to the triazole group is twisted from this plane more significantly (> 36°). The geometry with a planar methyl triazole-pyrazole fragment with the phenyl ring attached to the triazole group being twisted from this plane is also seen in other related crystal structures [for example, PUWCOC [78], QEGROM [79], RAPLEC [80] as well as most of the others in Table S1].

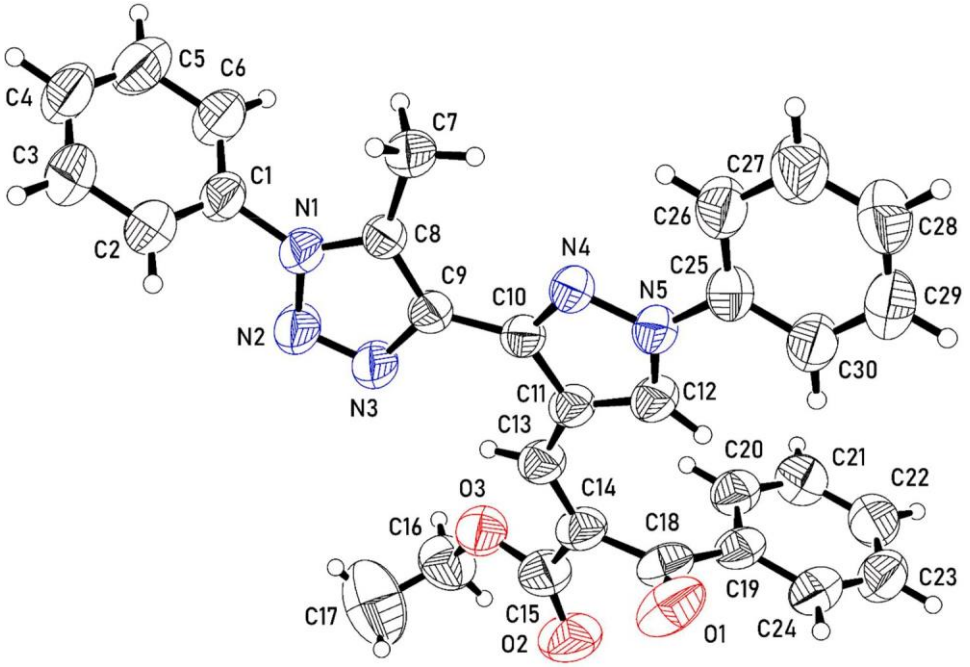


Fig. 2. An ortep representation of ethyl 2-benzoyl-3-(5-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-4-yl)acrylate showing 50% probability atomic displacement ellipsoids for the major disorder component.

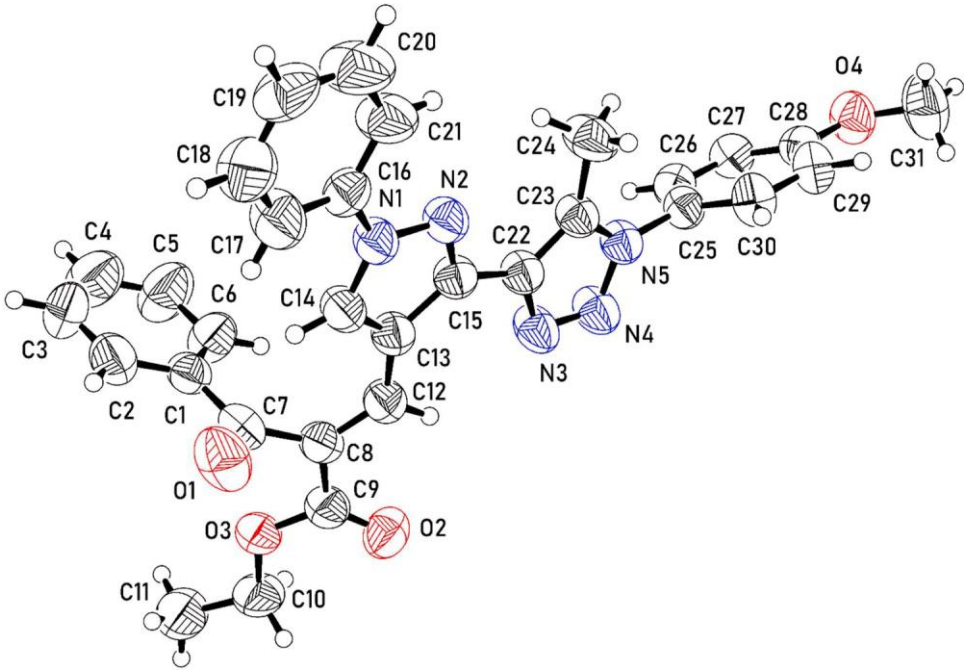
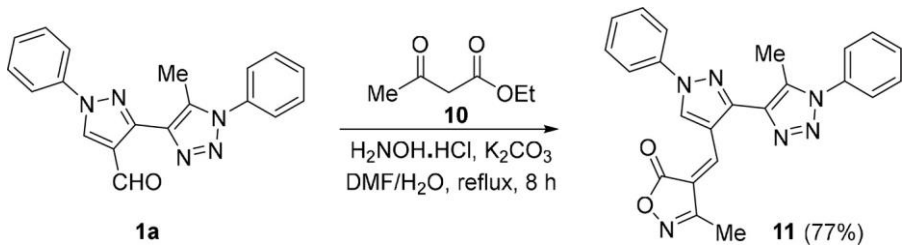


Fig. 3. An ortep representation of ethyl 2-benzoyl-3-(5-(1-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-4-yl)acrylate showing 50% probability atomic displacement ellipsoids for the major disorder component.

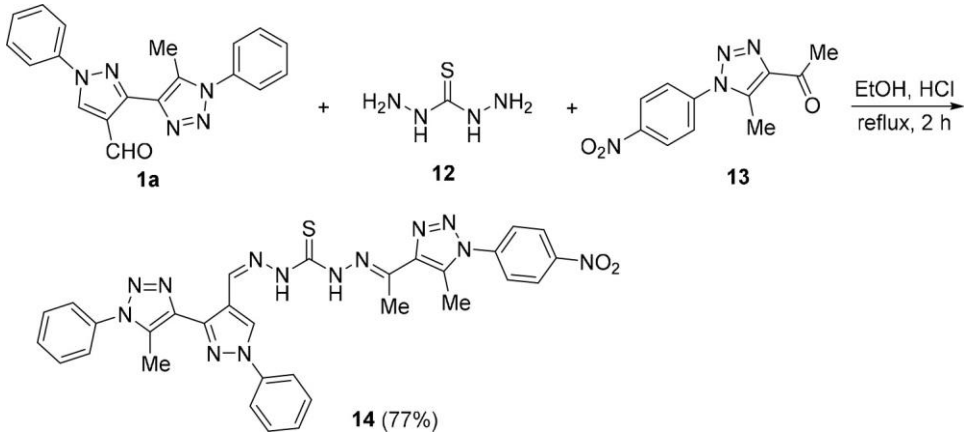
In the structure of **4**, however, the methyl triazole-pyrazole fragment shows less planarity, with a twist angle of 20°. A similar twist (25°) is also observed in a related QEGSAZ structure [79]. This exaggerated twist between the linked 1,2,3-triazole and pyrazole, the heterocyclic groups of interest, is rarer in the reported structures (Table S1). However, the twist indicates structural flexibility in the solution allowing conformational adaptability that may influence their biological activity.

3.2. In vitro antiproliferative activity

The new heterocycles were tested *in vitro* for their antiproliferative properties. Their activity against HCT-116, HepG2, and MCF-7 human cancer cells and the human healthy cell line (BJ-1) was assessed using the LDH assay. The antiproliferative activity (IC_{50}) of the synthesized heterocycles was calculated and compared to that of doxorubicin as a control (Table 2). The tests revealed that the heterocycles were safe against the non-cancer (BJ) cell line. Additionally, all heterocycles suppressed the three cancer cells (HCT-116, HepG2, and MCF-7) in a



Scheme 3. Synthesis of 3-methyl-4-((3-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)isoxazol-5(4*H*)-one.



Scheme 4. Synthesis of *N′*-(1-(5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)ethylidene)-2-[(3-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene]hydrazine-1-carbothiohydrazide.

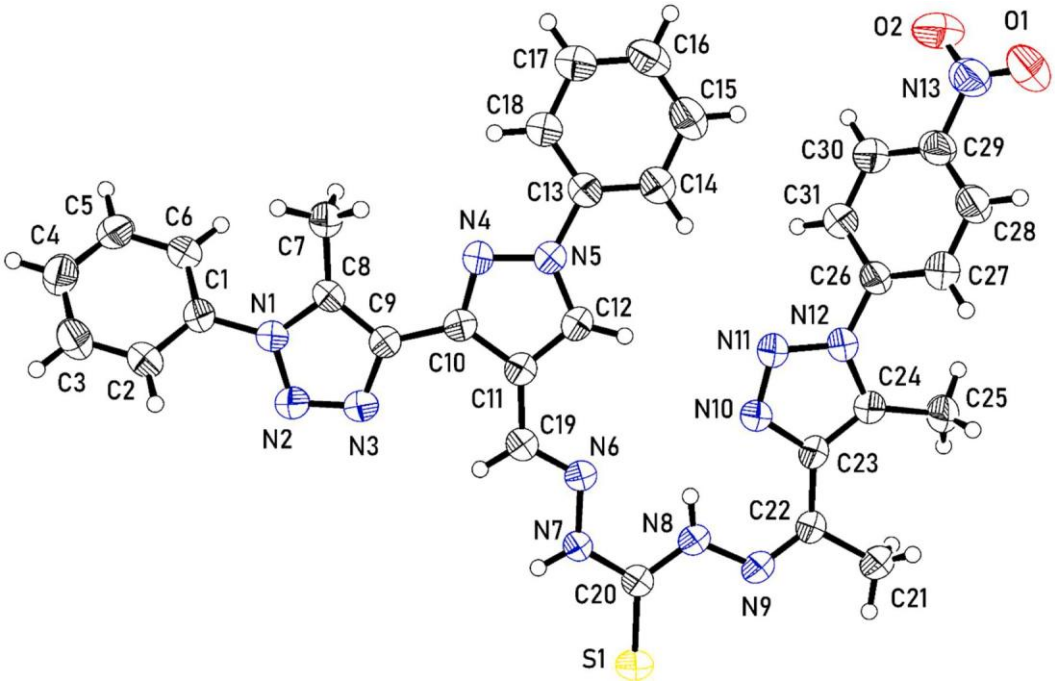


Fig. 4. An ortep representation of a molecule of *N′*-(1-(5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)ethylidene)-2-[(3-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene]hydrazine-1-carbothiohydrazide showing 50% probability atomic displacement ellipsoids.

dose-dependent manner. In the case of HCT-116 human colorectal carcinoma cells, all the synthesized heterocycles except **2** showed mild antiproliferation properties (IC_{50} = 19.1–33.4 μM). The *bis*-thiocarbohydrazone **14** has cytotoxic activity (12.5 ± 2.2 μM) comparable to doxorubicin (11.8 1.5μM). Heterocycles **3, 4, 7, 6, 9**, and **11** have moderate cytotoxic activities, while heterocycle **2** has low cytotoxic activity compared to doxorubicin. In the case of MCF-7 human breast cancer cells, **2, 3, 7, 9, 11**, and **14** have moderate cytotoxic activities, and **4** and **6** have weak activities compared to the reference drug. In the case of HepG2 human liver cancer cells, the tested heterocycles showed promising antiproliferation properties with IC_{50} ranging from 2.3 to 2.6 μM compared to 2.1 μM for doxorubicin. In the case of the non-tumor

Table 2
The antiproliferative (IC_{50}) for the newly synthesized heterocycles against cancer cell lines.

Heterocycle	IC_{50} (μM) ± SD			
	HCT-116	HepG-2	MCF-7	BJ-1
2	56.5 ± 4.5	2.3 ± 0.1	23.3 ± 2.1	17.6 ± 2.1
3	33.4 ± 2.9	2.4 ± 0.1	33.8 ± 3.2	17.6 ± 2.1
4	32.4 ± 3.9	2.4 ± 0.3	45.9 ± 4.1	17.2 ± 1.9
6	19.1 ± 2.3	2.3 ± 0.2	42.7 ± 3.1	19.9 ± 2.1
7	25.6 ± 3.1	2.4 ± 0.1	26.2 ± 2.6	18.9 ± 1.7
9	25.2 ± 1.9	2.3 ± 0.2	21.6 ± 1.8	16.4 ± 1.6
11	28.8 ± 3.1	2.6 ± 0.2	30.5 ± 2.9	17.2 ± 1.5
14	12.5 ± 2.2	2.5 ± 0.2	25.4 ± 3.2	28.8 ± 2.2
Doxorubicin	11.8 ± 1.5	2.1 ± 0.2	6.2 ± 0.5	17.7 ± 1.8

fibroblast-derived cell line, heterocycles **2, 3, 4, 9**, and **11** showed potentially higher potent cytotoxic activities than the control. Compounds **6** and **7** had cytotoxic activities only slightly higher than the reference drug, while, on the other hand, **14** had weak cytotoxic activity against the healthy cells.

Based on the observed antiproliferation properties, the structure-activity relationship can be assigned. In the case of the dithiols **2**–**4**, the unsubstituted derivative **2** (R = H, IC_{50} = 2.3 μM) has higher antiproliferation properties than **3** containing 4-methoxyphenyl (C_{50} = 2.4 μM) and **4** having 4-nitrophenyl (IC_{50} = 2.4 μM). A similar observation has been made for heterocycle **6** containing a phenyl group (IC_{50} = 2.3 μM) and **7** having the 4-methoxyphenyl unit (IC_{50}=2.4μM). In the case of the MCF-7 human breast cancer cells, only **2, 9**, and **14** displayed moderate cytotoxic activity with IC_{50} ranging from 21.6 to 25.4 μM compared to only 6.2 μM for the reference drug.

In conclusion, the newly synthesized agents show promising antiproliferative properties against the human liver cancer cell line (HepG-2). Heterocycles **14** displayed good antiproliferative properties against the colon anticancer cell line (HCT-116). It does not show any significant cytotoxic activity on the normal cells.

4. Conclusions

Several new heterocycles containing 1*H*-1,2,3-triazole and 1*H*-pyrazole moieties have been synthesized. The procedures were simple, and heterocycles were produced in good yields. The chemical structures of the synthesized heterocycles have been established, and their anticancer activities against three types of human cancer cells were assessed. The newly synthesized heterocycles show promising antiproliferative properties against the human liver cancer cell line. The heterocycle containing *bis*-thiocarbohydrazone showed the highest anticancer activity (e.g., against the colon anticancer) compared to the others. The anticancer activities of *bis*-thiocarbohydrazone were comparable to those obtained for the reference drug doxorubicin. The results obtained provide support for the future design of new heterocycles based on *bis*-thiocarbohydrazone and assessment of their anticancer activity with the aim of finding effective treatment against malignant cells.

CRediT authorship contribution statement

Bakr F. Abdel-Wahab: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Benson M. Kariuki:** Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Hanan A. Mohamed:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Mohamed S. Bekheit:** Formal analysis, Writing – original draft, Writing – review & editing. **Hanem M. Awad:** Formal analysis, Writing – original draft, Writing – review & editing. **Gamal A. El-Hiti:** Formal analysis, Conceptualization, Methodology, Investigation, Funding acquisition, Writing – review & editing, Writing – original draft.

Declaration of Competing Interest

There are no conflicts of interest to declare.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2023.136528.

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