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Microwave-assisted one pot three-component synthesis of some novel pyrazole scaffolds as potent anticancer agents

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Abstract

Background: Pyrazoles, thiazoles and 1,3,4-thiadiazoles have been reported to possess various pharmacological activities.

Results: An efficient and a novel approach for the synthesis of some novel pyrazole based-azoles are described via multi-component reaction under controlled microwave heating conditions. The structures of the synthesized compounds were assigned on the basis of elemental analysis, IR, ¹H NMR and mass spectral data. All the synthesized compounds were tested for in vitro activities against two antitumor cell lines, human lung cancer and human hepatocellular carcinoma compared with the employed standard antitumor drug (cisplatin).

Conclusions: All the newly synthesized compounds were evaluated for their anticancer activity against human lung cancer and human hepatocellular carcinoma cell lines using MTT assay. The results obtained exploring the high potency of six of the tested compounds compared with cisplatin.

Keywords: Acetylpyrazoles, Enaminones, Hydrazonoyl chlorides, Thiazoles, Thiadiazoles, Anticancer activity

Background

Multi-component reactions (MCR) are one-pot processes with at least three components to form a single product, which incorporates most or even all of the starting materials [1–6]. The huge interest for such multi-component reactions during the last years has been oriented towards developing combinatorial chemistry procedures, because of their high efficiency and convenience of these reactions in comparison with multistage procedures. Also, the utility of MCR under microwave irradiation in synthesis of heterocyclic compounds enhanced the reaction rates and improve the regioselectivity [7–12].

On the other hand, pyrazole and its derivatives have drawn considerable attention of the researchers in the past few decades owing to their high therapeutic values. Some of the drugs, possessing pyrazole as basic moiety,

like celecoxib [13], deracoxib [14], etoricoxib and atorivodine [15] are already booming in the market. Pyrazole derivatives possess an extensive range of pharmacological activities such as antiinflammatory, antipyretic, analgesic, antimicrobial, sodium channel blocker, antitubercular, antiviral, antihypertensive, antiglaucoma, antioxidant, antidepressant, anxiolytic, neuroprotective and antidiabetic activity [16–23]. Furthermore, pyrazole prodrugs have also been reported to possess significant anticancer activities [24–30]. Keeping this in mind, and in continuation of our previous work on the synthesis of new anticancer agents [31–40], we herein present an efficient regioselective synthesis of novel 4-heteroaryl-pyrazoles, which have not been reported *hitherto* in a multicomponent synthesis under microwave irradiation and to assess their anticarcinogenic effects against hepatocellular carcinoma (HepG-2) and human lung cancer (A-549) cell lines.

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Results and discussion

Chemistry

Multi-component reaction of acetyl pyrazole **1** [41], dimethylformamide dimethylacetal (DMF–DMA) **2** and nitrileimine **4a–d** (generated in situ from **3a–d** with triethylamine) in toluene under conventional heating for 10–15 h or under microwave irradiation at 150 °C for 4–10 min. afforded compound **6a–d** rather than its isomeric structure **8a–d** in 66–70 and 84–90%, respectively (Scheme 1; Table 1). The structure of **6a–d** was confirmed by their spectral data (IR, MS and ¹H-NMR) and elemental analyses. For example, the IR spectra of products **6** revealed in each case two absorption bands in the regions ν 1638–1676 and 1682–1724 cm⁻¹ due to the two carbonyl groups. The ¹HNMR spectra showed, in addition to the expected signals for the aromatic protons, three singlet signals at δ ~2.34, 2.55 and 8.92 revealed to the two methyl groups and the pyrazole-H5, respectively. The mass spectra of products **6a–d** revealed a molecular ion peak for each one which is consistent with the respective molecular weight. These data are much closer to those reported in literature on similar work [42–44].

Compound **6a** was alternatively synthesized by reacting enaminone **9** (prepared separately via condensation of acetyl pyrazole **1** with DMF–DMF) with 2-oxo-*N*-phenylpropanehydrazonoyl chloride (**3a**) in toluene containing catalytic amount of TEA under MWI. The obtained product was found to be identical with **6a** in all respects (TLC, mp and IR spectrum) which affords further evidence to all structures **6a–d**. The latter products were assumed to be formed via initial 1,3-dipolar cycloaddition of the nitrileimines **4a–d** to the activated double bond in enaminone **9** to afford the non-isolable cycloadducts **5** which underwent loss of dimethylamine yielding the final pyrazole derivatives **6a–d**.

The results obtained Table 1 indicate that, unlike classical heating, microwave irradiation results in higher yields and shorter reaction times for all the carried reactions. Microwave irradiation facilitates the polarization of the molecules under irradiation causing rapid reaction to occur. This is consistent with the reaction mechanism, which involves a polar transition state [45].

By the same way reaction of acetyl pyrazole **1** with nitrile-oxide **11a, b** (derived from reaction of hydroxymoyl chloride **10a, b** with TEA) and DMF–DMA in toluene under microwave irradiation at 150 °C gave isoxazoles **13a, b** (Scheme 2; Table 1). The ¹H NMR spectrum of the product revealed a singlet signal at 9.67 ppm assigned for isoxazole-5H proton not isoxazole-4H proton [42–44, 46] which consistent with the isomeric structure **13** rather than the isomeric structure **15**. Moreover, the mass spectrum of **13a** and **13b** revealed a molecular

ion peaks at $m/z = 506$ and 446 , respectively, which is consistent with their molecular weights.

Furthermore, alternative synthesis of compound **13a** was achieved via reaction enaminone **9** with *N*-hydroxy-2-naphthimidoyl chloride (**10a**) under the same reaction condition to yield authentic product **13a** (Scheme 2).

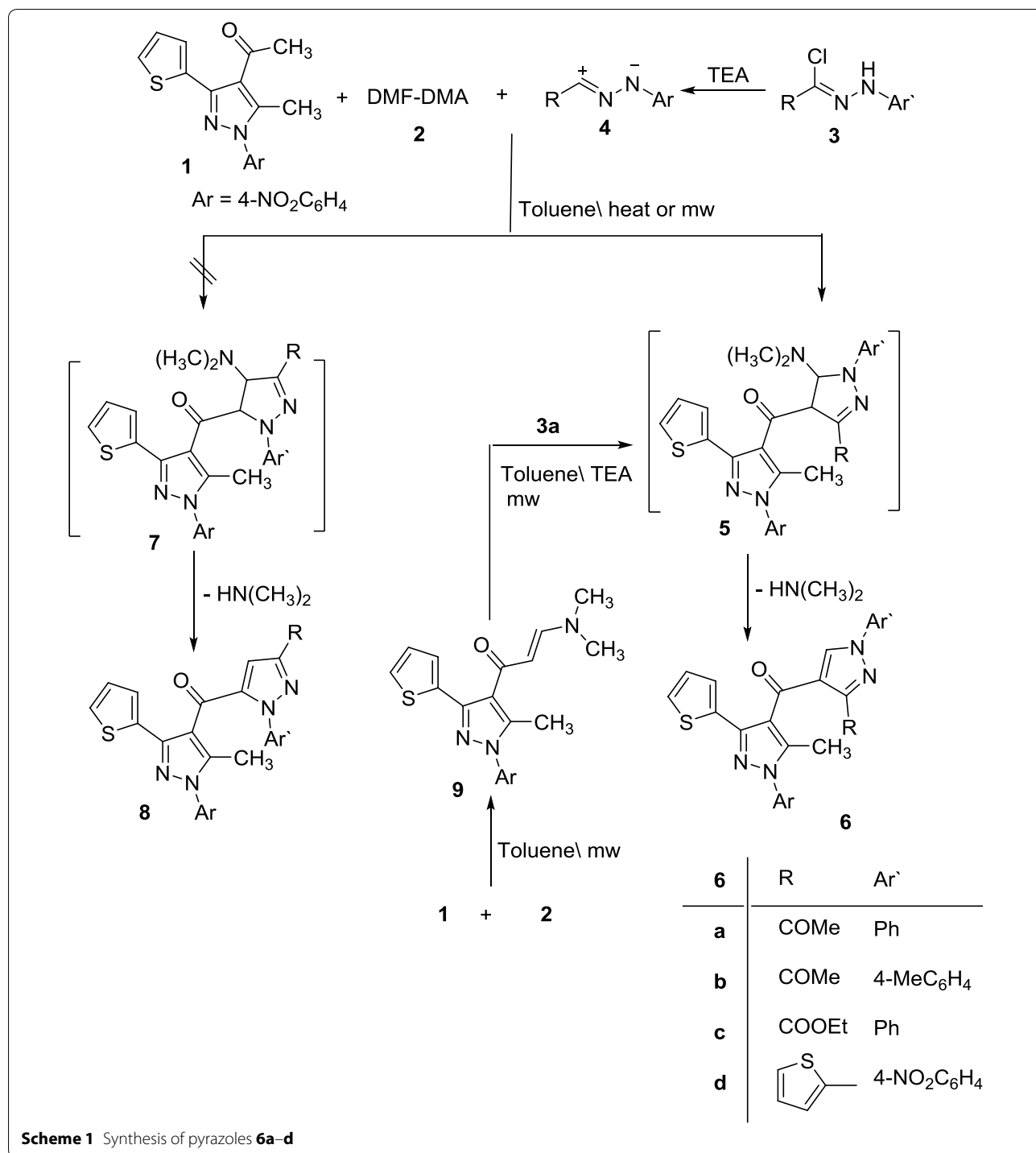
Next, our study was extended to investigate the reactivity of compound **1** towards thiosemicarbazide and various hydrazonoyl halides aiming to synthesize new pyrazole based—1,3-thiazoles and 1,3,4-thiadiazoles. Thus, acetyl pyrrole **1**, thiosemicarbazide **2** and α -keto hydrazonoyl halides **3a, b, e** were allowed to react in a one-pot three-component reaction in dioxane containing catalytic amount of TEA under MWI to afford the arylazothiazole derivatives **18a–c**, respectively (Scheme 3; Table 1). The reaction goes in parallel to literature [32, 35–37].

The structure of the products **18a–c** was assigned based on the spectral data and elemental analyses. For example mass spectrum of compound **18a** revealed molecular ion peak at m/z 542 and its ¹H NMR spectrum exhibited four characteristic singlet signals at 2.32, 2.36, 2.48 and 10.47 assignable to three CH₃ groups and NH protons, respectively, in addition to an aromatic multiplet in the region 6.99–7.93 ppm equivalent to 12 protons. Its IR spectra showed one NH group band at 3396 cm⁻¹.

The structure of products **18** was further confirmed by an alternative method. Thus, reaction of acetylpyrazole **1** with thiosemicarbazide **16** under MWI in ethanol containing drops of concentrated HCl led to the formation of product **19**. Compound **19** was then react with 2-oxo-*N*-phenylpropanehydrazonoyl chloride (**3a**) in dioxane containing catalytic amount of TEA under MWI to give a product identical in all respects (IR, mp and mixed mp.) with **18a** (Scheme 3).

In a similar manner, when acetyl pyrazole **1** was allowed to react with thiosemicarbazide **2** and ethyl (*N*-arylhydrazono)-chloroacetates **3c, f** in dioxane in the presence of triethylamine under MWI, it afforded in each case a single isolable product, namely, 2-(2-(1-(5-methyl-1-(4-nitrophenyl)-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl) ethylidene) hydrazinyl)-5-(2-arylhydrazono) thiazol-4(5*H*)-one **21a, b** (Scheme 4; Table 1). Structure **21** was confirmed by elemental analysis, spectral data (IR, ¹H NMR, and mass), and alternative synthesis route. Thus, thiosemicarbazone **19** was reacted with ethyl-2-chloro-2-(2-phenylhydrazono)acetate (**3c**) in dioxane in the presence of TEA under MWI afforded a product identical in all aspects (mp, mixed mp, and spectra) with **21a** (Scheme 4).

Finally, the reactivity of acetylpyrazole **1** towards hydrazonoyl halides, be bereft of α -keto group, was



examined. In the present study, we have established that reaction of acetylpyrazole **1** with *N*-thiosemicarbazide **16** and aryl carbohydrazonoyl chlorides **3d, g** gave the respective 1,3,4-thiadiazoles **23a, b** as the end products (Scheme 5; Table 1). The structures of compounds

23a, b were confirmed on the bases of spectral data and elemental analyses (see [Experimental](#) part). The reaction proceeded via *S*-alkylation, with removal of hydrogen chloride, to give *S*-alkylated intermediates **22** followed by intramolecular Michael type addition under

Table 1 Comparative data of conventional (A) and MW (B) methods for the synthesis of compounds 6a–d, 13a, b, 18a–c, 21a, b and 23a, b

Compound no.	Conventional method (A)		Microwave method (B)	
	Time (h)	Yield (%)	Time (min)	Yield (%)
6a	12	66	4	84
6b	15	68	10	85
6c	10	70	8	88
6d	8	69	5	90
13a	12	67	6	82
13b	10	70	6	89
18a	8	66	7	90
18b	6	68	10	88
18c	4	67	7	90
21a	6	69	8	86
21b	5	64	6	92
23a	8	72	10	81
23b	8	67	9	83

the employed reaction conditions, followed by elimination of ammonia, afforded the final product **23** [36, 47] (Scheme 5).

Cytotoxic activity

The in vitro growth inhibitory activity of the synthesized compounds **6a–d**, **9**, **13a, b**, **18a–c**, **19**, **21a, b** and **23a, b** was investigated against two carcinoma cell lines: human lung cancer (A-549) and human hepatocellular carcinoma (HepG-2) in comparison with the well-known anticancer standard drug (cisplatin) under the same conditions using colorimetric MTT assay. Data generated were used to plot a dose response curve of which the concentration of test compounds required to kill 50% of cell population (IC_{50}) was determined. The results revealed that all the tested compounds showed inhibitory activity to the tumor cell lines in a concentration dependent manner. Interestingly, the results represented in Table 2 and Fig. 1 showed that compounds **13a**, **13b** and **21a** were the most active compounds (IC_{50} value of 4.47 ± 0.3 , 3.46 ± 0.6 , 3.10 ± 0.8 $\mu\text{g/mL}$, respectively) against the lung carcinoma cell line (A549), compared with cisplatin reference drug with IC_{50} value of 0.95 ± 0.23 $\mu\text{g/mL}$. Moreover, the order of activity against A549 cell line was **18c** > **18b** > **19** > **9** > **6a** > **6c** > **23b** > **6d** > **18a** > **21b** > **6b**.

On the other hand, compounds **6a**, **9**, **13b**, **23b** were the most active compounds (IC_{50} value of 5.60 ± 0.8 , 5.67 ± 1.2 , 4.47 ± 0.9 and 5.67 ± 1.2 $\mu\text{g/mL}$, respectively) against liver carcinoma cell line (HepG2) cell line while the rest compounds have moderate activities.

Experimental

Chemistry

General

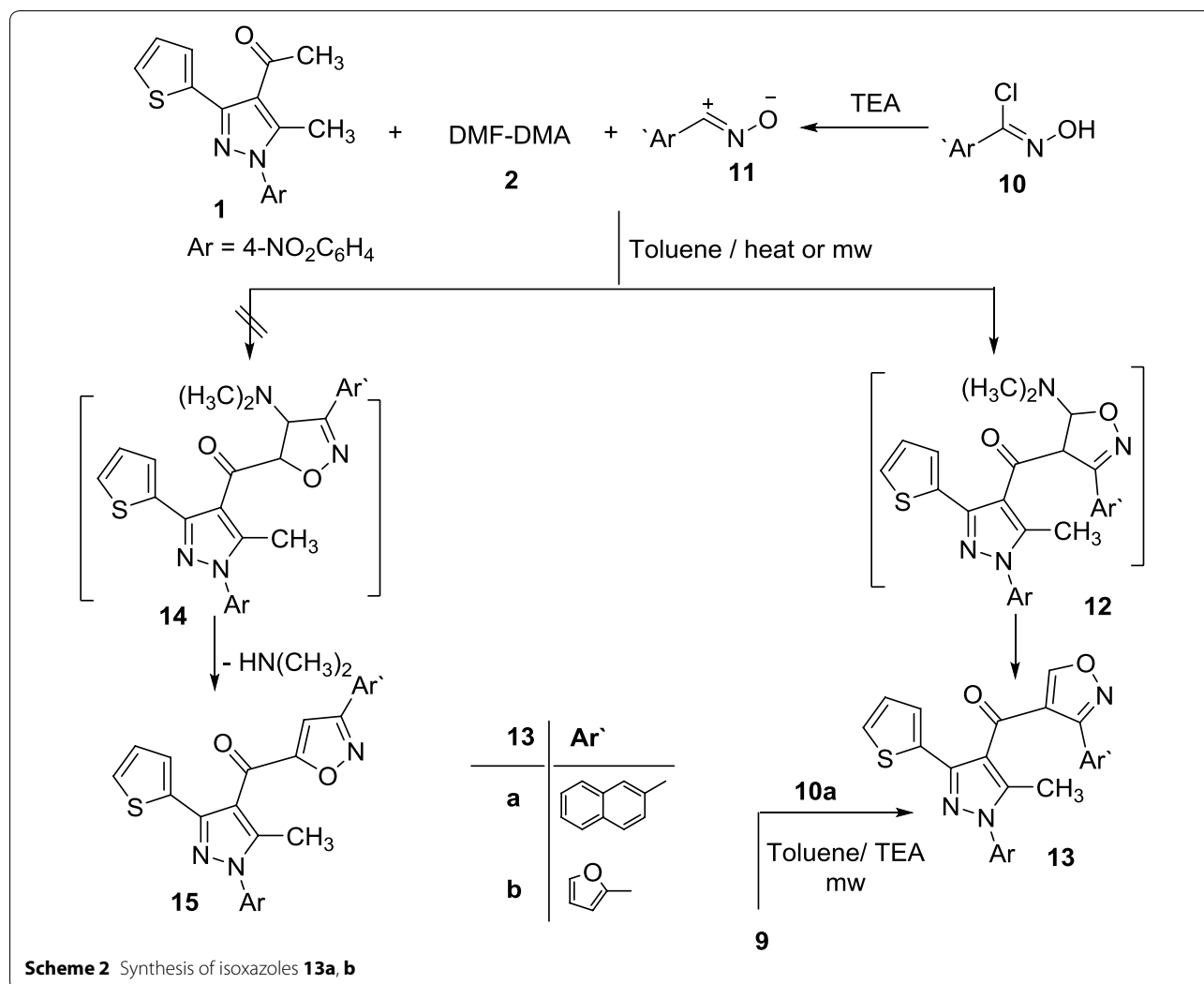
Melting points were measured on an Electrothermal IA 9000 series digital melting point apparatus (Bibby Sci. Lim. Stone, Staffordshire, UK). IR spectra were measured on PyeUnicam SP 3300 and Shimadzu FTIR 8101 PC infrared spectrophotometers (Shimadzu, Tokyo, Japan) in potassium bromide discs. NMR spectra were measured on a Varian Mercury VX-300 NMR spectrometer (Varian, Inc., Karlsruhe, Germany) operating at 300 MHz ($^1\text{H-NMR}$) and run in deuterated dimethylsulfoxide ($\text{DMSO-}d_6$). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer (Tokyo, Japan) at 70 eV. Elemental analyses were measured by using a German made Elementarvario LIII CHNS analyzer. Antitumor activity of the products was measured at the Regional Center for Mycology and Biotechnology at Al-Azhar University, Cairo, Egypt. Hydrazonoyl halides **3a–g** were prepared following literature method [41, 48].

Synthetic procedures

Synthesis of trisubstituted pyrazoles 6a–d and isoxazoles 13a, b *Method A* To a stirred solution of acetyl pyrazole **1** (0.327 g, 1 mmol), dimethylformamide dimethylacetal **2** (1 mmol) and the appropriate hydrazonoyl halides **3a–d** or hydroximoyl chlorides **10a, b** (1 mmol) in dry toluene (15 mL), an equivalent amount of triethylamine (0.5 mL) was added. The reaction mixture was heated under reflux for 10–15 h (monitored through TLC). The precipitated triethylamine hydrochloride was filtered off, and the filtrate was evaporated under reduced pressure. The residue was triturated with MeOH. The solid product, so formed in each case, was collected by filtration, washed with water, dried, and crystallized from the proper solvent to afford the corresponding pyrazole **6a–d** and isoxazole derivatives **13a, b**, respectively.

Method B Repetition of the same reactions of method A with heating in microwave oven at 500 W and 150 °C for 4–10 min., gave products identical in all respects with those separated from method A. The products **6a–d** and **13a, b** together with their physical constants are listed below.

1-(4-(5-Methyl-1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazole-4-carbonyl)-1-phenyl-1H-pyrazol-3-yl)ethanone (6a) Brown solid, mp 208–210 °C; IR (KBr) ν_{max} 1599 (C=N), 1670, 1682 (2C=O), 2924, 3105 (C–H) cm^{-1} ; $^1\text{H NMR}$ ($\text{DMSO-}d_6$) δ 2.34 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 6.98–8.39 (m, 12H, Ar–H), 8.92 (s, 1H, pyrazole-H5); MS m/z (%) 497 (M^+ , 9), 342 (25), 252 (22), 174 (11), 145 (22),

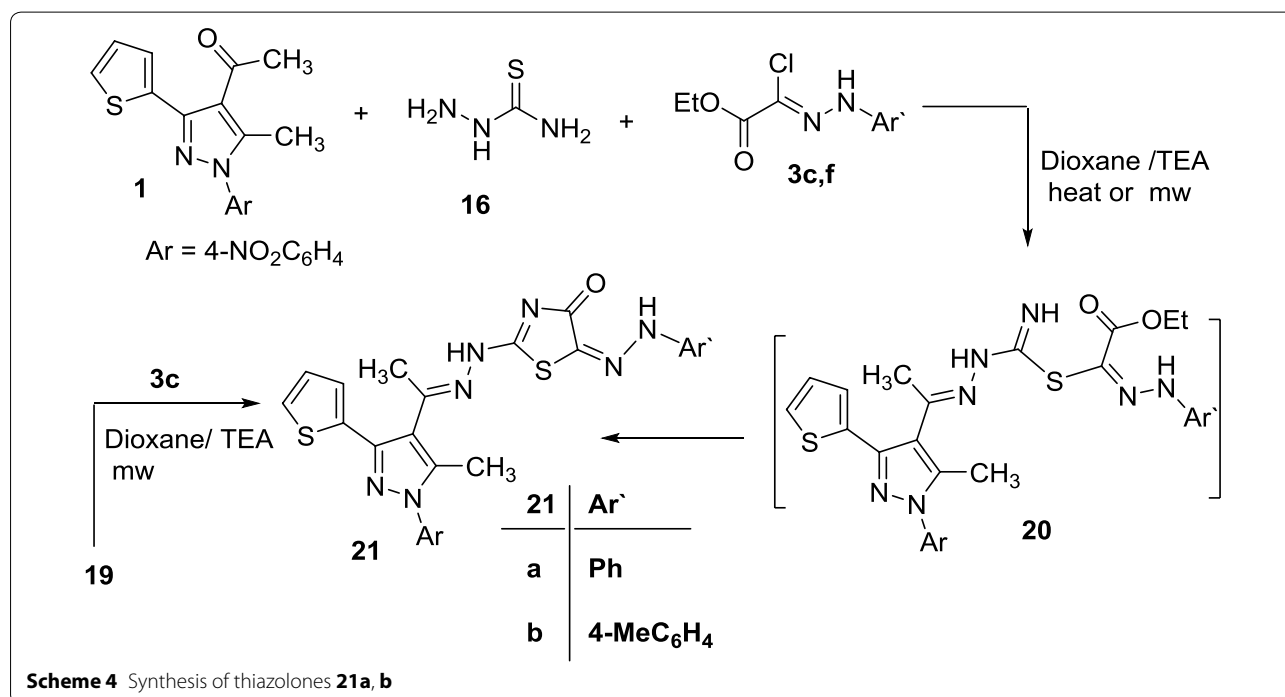
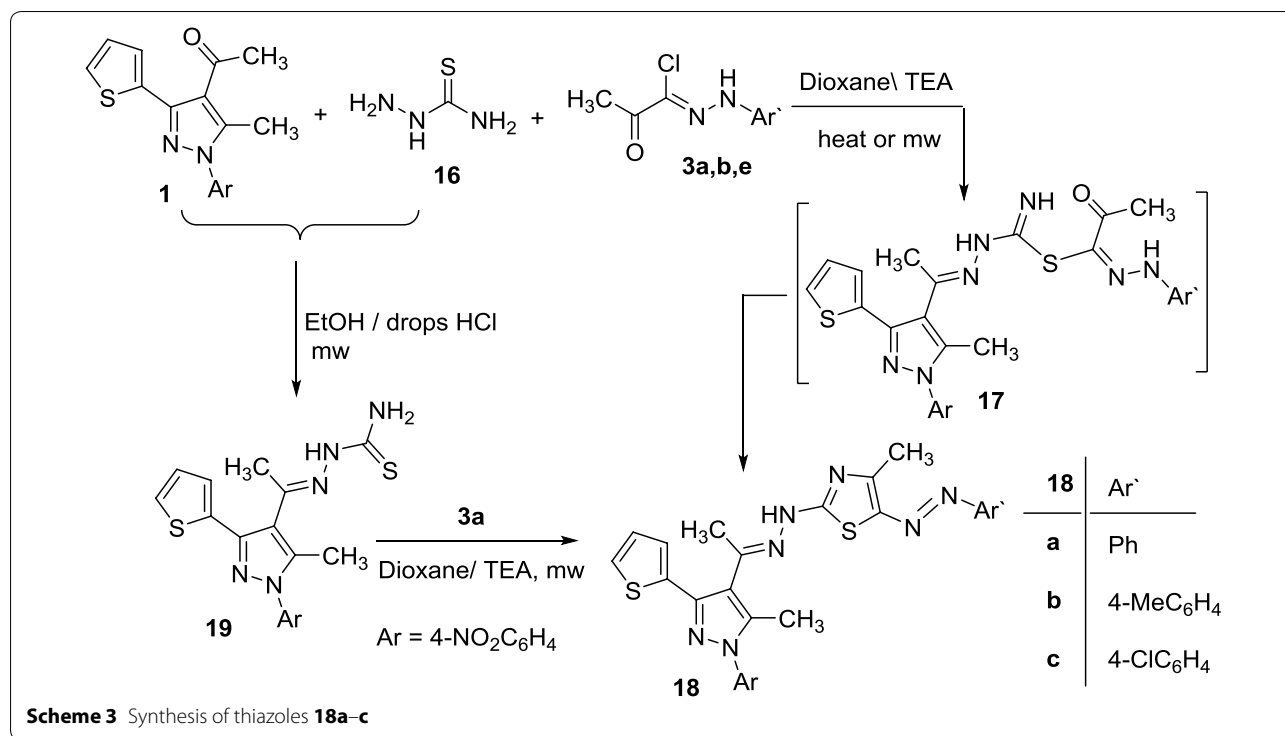


115 (26), 103 (40), 76 (100), 63 (13), 50 (19). Anal. Calcd. for C₂₆H₁₉N₅O₄S (497.53): C, 62.77; H, 3.85; N, 14.08. Found: C, 63.08; H, 3.55; N, 13.70%.

1-(4-(5-Methyl-1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazole-4-carbonyl)-1-(p-tolyl)-1H-pyrazol-3-yl)ethanone (6b) Yellow solid, mp 222–224 °C; IR (KBr) ν_{\max} 1597 (C=N), 1676, 1688 (2C=O), 2919, 3118 (C–H) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 2.24 (s, 3H, CH₃), 2.34 (s, 3H, CH₃), 2.56 (s, 3H, CH₃), 7.12 (t, *J* = 1.2 Hz, 1H, thiophene-H), 7.31 (d, *J* = 1.2 Hz, 1H, thiophene-H), 7.33 (d, *J* = 1.2 Hz, 1H, thiophene-H), 7.55 (d, *J* = 4.4 Hz, 2H, Ar–H), 7.63 (d, *J* = 4.4 Hz, 2H, Ar–H), 7.88 (d, *J* = 8.8 Hz, 2H, Ar–H), 8.39 (d, *J* = 8.8 Hz, 2H, Ar–H), 10.58 (s, 1H, pyrazole-H5); ¹³C-NMR (DMSO-*d*₆): δ 13.3, 20.8, 25.7 (CH₃), 115.3, 117.6, 118.9, 121.37, 122.7, 125.2, 126.7, 128.1, 129.4, 130.1, 132.2, 133.8, 138.1, 140.6, 143.43, 144.4, 146.8, 147.2 (Ar–C and C=N), 188.2, 194.9 (C=O);

MS *m/z* (%) 511 (M⁺, 2), 406 (10), 266 (6), 219 (11), 168 (7), 147 (7), 125 (11), 104 (25), 98 (17), 83 (93), 79 (44), 69 (35), 54 (53), 44 (100). Anal. Calcd. for C₂₇H₂₁N₅O₄S (511.55): C, 63.58; H, 4.14; N, 13.69. Found: C, 63.78; H, 4.05; N, 13.29%.

Ethyl 4-(5-methyl-1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazole-4-carbonyl)-1-phenyl-1H-pyrazole-3-carboxylate (6c) Yellow solid, mp 207–209 °C; IR (KBr) ν_{\max} 15,984 (C=N), 1660, 1724 (2C=O), 2931, 2974 (C–H) cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.18 (t, *J* = 7.6 Hz, 3H, CH₃CH₂), 2.34 (s, 3H, CH₃), 4.27 (q, *J* = 7.1 Hz, 2H, CH₂CH₃), 6.96–8.43 (m, 12H, Ar–H), 8.99 (s, 1H, pyrazole-H5); MS *m/z* (%) 527 (M⁺, 6), 484 (22), 366 (26), 328 (33), 268 (50), 226 (35), 210 (37), 151 (49), 124 (78), 115 (61), 75 (100), 42 (45). Anal. Calcd. for C₂₇H₂₁N₅O₅S (527.55): C, 61.47; H, 4.01; N, 13.28. Found: C, 61.77; H, 3.75; N, 12.94%.



(5-Methyl-1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazol-4-yl)(1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazol-4-yl)methanone (**6d**) Orange solid, mp 219–220 °C; IR (KBr) ν_{\max} 1595 (C=N), 1638 (C=O), 2924, 3105 (C–H)

cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.34 (s, 3H, CH₃), 6.98–8.52 (m, 14H, Ar–H), 9.28 (s, 1H, pyrazole-H5); ^{13}C -NMR (DMSO- d_6): δ 26.9 (CH₃), 113.1, 113.3, 115.0, 115.6, 122.5, 122.6, 123.1, 123.6, 126.5, 126.7, 128.4, 131.1, 131.7, 132.1,

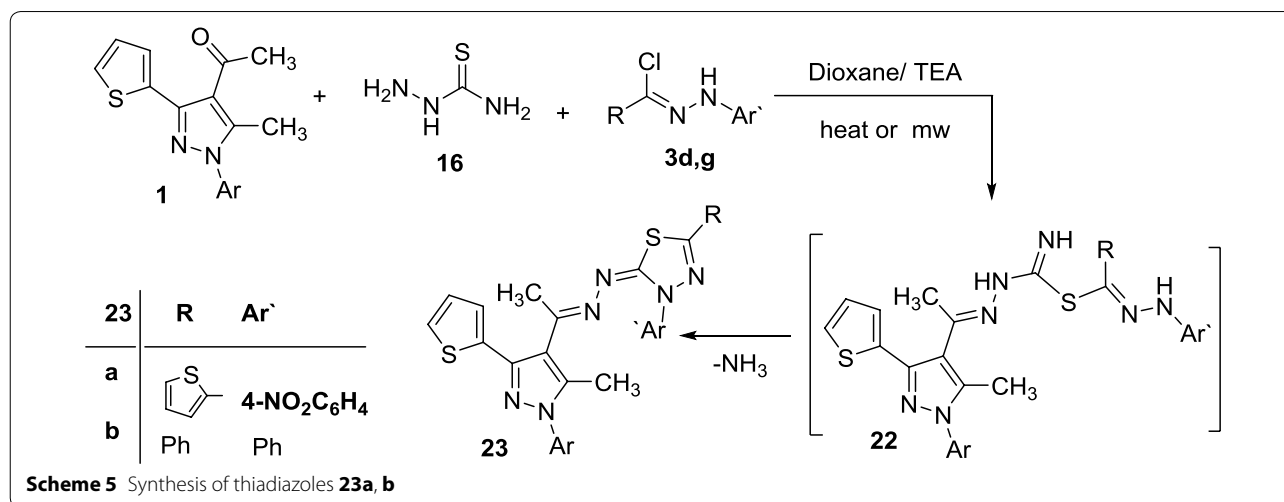
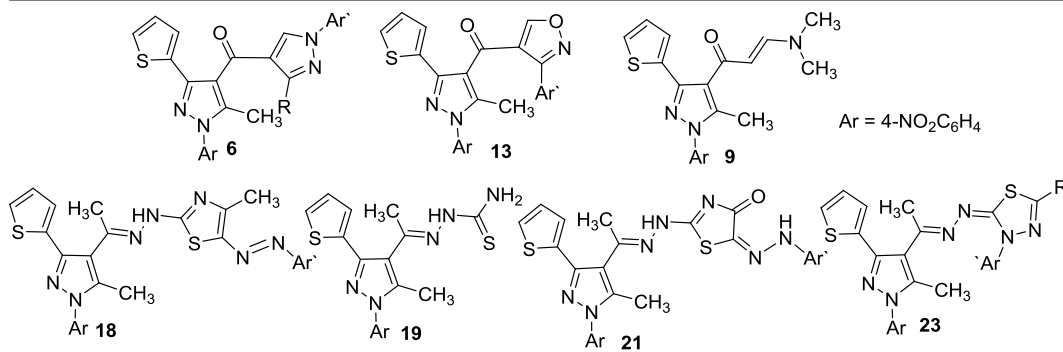
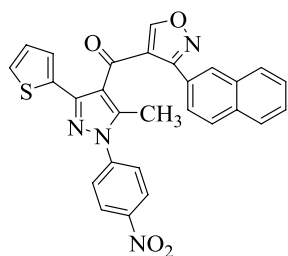
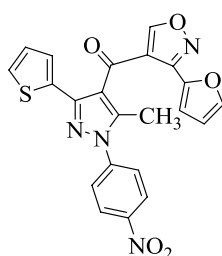
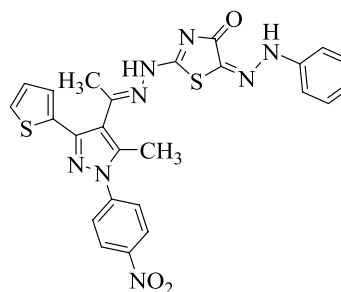
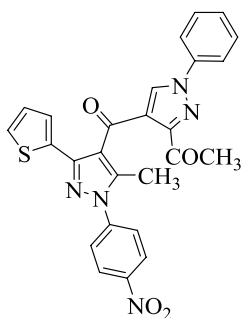
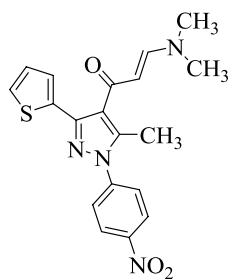
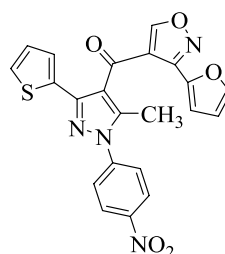
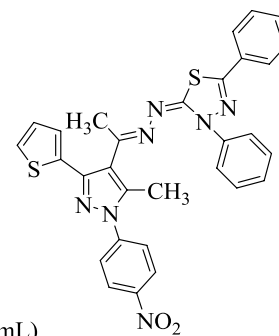


Table 2 The *in vitro* inhibitory activity of tested compounds against tumor cell lines expressed as IC₅₀ values (μg/mL) ± standard deviation from three replicates



Tested compounds	R	Ar'	Tumor cell lines	
			A-549	HepG2
6a	COCH ₃	Ph	22.9 ± 0.9	5.60 ± 0.8
6b	COCH ₃	4-MeC ₆ H ₄	38.5 ± 1.2	44.4 ± 1.3
6c	COOEt	Ph	23.3 ± 0.9	22.4 ± 0.9
6d	2-Thienyl	4-NO ₂ C ₆ H ₄	30.6 ± 1.1	35.9 ± 1.4
9	–	–	22.6 ± 0.8	5.67 ± 1.2
13a	–	2-Naphthyl	4.47 ± 0.3	8.03 ± 1.1
13b	–	2-Furyl	3.46 ± 0.6	4.67 ± 0.9
18a	–	Ph	32.7 ± 1.2	22.4 ± 1.1
18b	–	4-MeC ₆ H ₄	19.1 ± 1.1	6.67 ± 1.3
18c	–	4-ClC ₆ H ₄	18.2 ± 0.9	21.8 ± 0.9
19	–	–	21.3 ± 0.8	23.1 ± 1.1
21a	–	Ph	3.10 ± 0.8	23.9 ± 1.1
21b	–	4-MeC ₆ H ₄	33.6 ± 0.9	43.4 ± 0.8
23a	2-Thienyl	4-NO ₂ C ₆ H ₄	27.9 ± 1.1	34.4 ± 0.9
23b	Ph	Ph	23.4 ± 1.2	5.67 ± 1.7
Cisplatin	–	–	0.95 ± 0.23	1.4 ± 0.37

For the lung carcinoma cell line (A-549):**13a** ($IC_{50} = 4.47 \pm 0.3 \mu\text{g/mL}$)**13b** ($IC_{50} = 3.46 \pm 0.6 \mu\text{g/mL}$)**21a** ($IC_{50} = 3.10 \pm 0.8 \mu\text{g/mL}$)**For the liver carcinoma cell line (HepG2):****6a** ($IC_{50} = 5.60 \pm 0.8 \mu\text{g/mL}$)**9** ($IC_{50} = 5.67 \pm 1.2 \mu\text{g/mL}$)**13b** ($IC_{50} = 4.47 \pm 0.9 \mu\text{g/mL}$)**23b** ($IC_{50} = 5.67 \pm 1.2 \mu\text{g/mL}$)**Fig. 1** Cytotoxic activities of the most active compounds against HEPG2 and A-549 cell lines

132.3, 136.5, 137.1, 141.5, 141.6, 142.4, 142.6, 142.8 (Ar–C and C=N), 197.2 (C=O); MS m/z (%) 582 (M^+ , 6), 532 (12), 383 (16), 286 (11), 219 (21), 135 (49), 79 (16), 83 (27), 76 (67), 60 (28), 45 (100). Anal. Calcd. for $C_{28}H_{18}N_6O_5S_2$ (582.61): C, 57.72; H, 3.11; N, 14.42. Found: C, 57.99; H, 2.80; N, 14.12%.

Synthesis of 3-(dimethylamino)-1-(5-methyl-1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazol-4-yl)prop-2-en-1-one (9). A mixture of acetyl pyrazole **1** (3.27 g, 10 mmol) and dimethylformamide–dimethylacetal (DMF–DMA) (10 mmol) in dry toluene (20 mL) was refluxed in microwave oven at 500 W and 150 °C for 5 min., then left to cool to room temperature. The precipitated product was filtered off, washed with light petroleum (40–60 °C), and dried. Recrystallization from benzene afforded enaminone **1** as orange solid, mp 250–252 °C; IR (KBr) ν_{max} 1642 (C=O), 2920, 3080 (C–H) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.34 (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 3.06 (s, 3H, CH_3), 5.24 (d, $J = 12.8$ Hz, 1H, N–CH=), 7.05 (t, $J = 1.2$ Hz, 1H, thiophene-H), 7.14 (d, $J = 1.2$ Hz, 1H, thiophene-H), 7.50 (d, $J = 1.2$ Hz, 1H, thiophene-H), 7.65 (d, $J = 12.8$ Hz, 1H, =CH–CO), 7.90 (d, $J = 8.8$ Hz, 2H, Ar–H), 8.37 (d, $J = 8.8$ Hz, 2H, Ar–H); ^{13}C -NMR (DMSO- d_6): δ 12.4, 36.1, 44.0 (CH_3), 120.4, 124.3, 124.4,

125.8, 127.0, 127.1, 128.4, 134.0, 142.5, 143.5, 145.4, 145.8, 146.3 (Ar–C and C=N), 194.0 (C=O); MS m/z (%) 382 (M^+ , 3), 300 (11), 286 (11), 189 (9), 132 (7), 104 (100), 77 (58), 64 (16), 51 (13), 43 (12). Anal. Calcd. for $C_{19}H_{18}N_4O_3S$ (382.44): C, 59.67; H, 4.74; N, 14.65. Found: C, 59.58; H, 4.44; N, 14.39%.

(5-Methyl-1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazol-4-yl)(3-(naphthalen-2-yl)isoxazol-4-yl)methanone (13a) Yellow solid, mp 203–205 °C; IR (KBr) ν_{max} 1597 (C=N), 1660 (C=O), 2976, 3117 (C–H) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.31 (s, 3H, CH_3), 7.13–8.45 (m, 14H, Ar–H), 9.67 (s, 1H, isoxazole-H5); ^{13}C -NMR (DMSO- d_6): δ 26.9 (CH_3), 110.0, 113.3, 115.0, 115.1, 115.5, 122.5, 123.3, 124.5, 125.0, 126.5, 126.7, 128.4, 130.8, 133.6, 135.4, 136.9, 137.0, 141.5, 141.6, 142.6, 148.8, 152.4, 160.0 (Ar–C and C=N), 188.3 (C=O); MS m/z (%) 506 (M^+ , 2), 435 (9), 412 (14), 379 (45), 214 (12), 142 (10), 105 (26), 93 (21), 77 (51), 65 (62), 60 (52), 43 (100). Anal. Calcd. for $C_{28}H_{18}N_4O_4S$ (506.53): C, 66.39; H, 3.58; N, 11.06. Found: C, 66.04; H, 3.21; N, 10.86%.

(3-(Furan-3-yl)isoxazol-4-yl)(5-methyl-1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazol-4-yl)methanone (13b) Orange solid, mp 209–211 °C; IR (KBr) ν_{max} 1598

(C=N), 1664 (C=O), 2925, 3107 (C-H) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.34 (s, 3H, CH₃), 7.13–8.61 (m, 10H, Ar-H), 9.23 (s, 1H, pyrazole-H5); MS m/z (%) 446 (M⁺, 2), 392 (100), 349 (43), 317 (23), 285 (11), 234 (16), 191 (16), 172 (20), 130 (26), 102 (26), 77 (69). Anal. Calcd. for C₂₂H₁₄N₄O₅S (446.44): C, 59.19; H, 3.16; N, 12.55. Found: C, 59.50; H, 2.80; N, 12.17%.

Alternate synthesis of 6a and 13a Equimolar amounts of enaminone **9** (0.382 g, 1 mmol) and hydrazonoyl halide **3a** or hydroximoyl chloride **10a** (1 mmol) in dry toluene (15 mL) containing an equivalent amount of triethylamine (0.5 mL) was refluxed in microwave oven at 500 W and 150 °C for 6 min., gave products identical in all respects (mp, mixed mp and IR spectra) with compounds **6a** and **13a**, respectively.

Synthesis of thiazoles 18a–c and 21a, b and thiadiazoles 23a, b: Method A To a stirred solution of acetyl pyrazole **1** (0.327 g, 1 mmol), thiosemicarbazide **16** (0.091 g, 1 mmol) and the appropriate hydrazonoyl halides **3a, b, e** or **3c, f** or **3d, g** (1 mmol) in dioxane (15 mL), an equivalent amount of triethylamine (0.05 mL) was added. The reaction mixture was heated under reflux for 4–8 h (monitored through TLC). Excess of solvent was removed under reduced pressure and the reaction mixture was triturated with MeOH. The product separated was filtered, washed with MeOH, dried and recrystallized from the proper solvent to give thiazoles **18a–c** and **21a, b** and thiadiazoles **23a, b**, respectively.

Method B Repetition of the same reactions of method A with heating in microwave oven at 500 W and 150 °C for 4–10 min., gave products identical in all respects with those separated from method A. The products **18a–c**, **21a, b** and **23a, b** together with their physical constants are listed below.

4-Methyl-2-(2-(1-(5-methyl-1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazol-4-yl)ethylidene)hydrazinyl)-5-(phenyldiazenyl)thiazole (18a) Orange solid, mp 219–220 °C; IR (KBr) ν_{max} 1600 (C=N), 2974 (C-H), 3396 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.32 (s, 3H, CH₃), 2.36 (s, 3H, CH₃), 2.48 (s, 3H, CH₃), 6.99–7.93 (m, 12H, Ar-H), 10.65 (s, 1H, NH); ^{13}C -NMR (DMSO- d_6): δ 9.2, 12.5, 24.6 (CH₃), 114.5, 121.4, 123.1, 125.2, 126.3, 127.0, 127.9, 128.1, 128.5, 128.9, 135.3, 140.4, 140.9, 143.1, 144.1, 145.3, 145.79, 153.3, 163.4 (Ar-C and C=N); MS m/z (%) 542 (M⁺, 6), 432 (16), 253 (13), 138 (11), 106 (69), 90 (12), 78 (100), 64 (11), 51 (34). Anal. Calcd. for C₂₆H₂₂N₈O₂S₂ (542.64): C, 57.55; H, 4.09; N, 20.65. Found: C, 57.87; H, 3.70; N, 20.35%.

4-Methyl-2-(2-(1-(5-methyl-1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazol-4-yl)ethylidene)hydrazinyl)-5-(p-tolyldiazenyl)thiazole (18b) Orange solid, mp 226–228 °C; IR (KBr) ν_{max} 1600 (C=N), 2924 (C-H), 3438 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.17 (s, 3H, CH₃), 2.32 (s, 3H, CH₃), 2.36 (s, 3H, CH₃), 2.47 (s, 3H, CH₃), 6.99–7.89 (m, 11H, Ar-H), 10.65 (s, 1H, NH); ^{13}C -NMR (DMSO- d_6): δ 12.0, 14.3, 15.7, 26.8 (CH₃), 105.3, 111.5, 114.9, 116.3, 117.9, 119.8, 120.8, 122.2, 126.4, 126.6, 127.9, 128.1, 131.9, 132.6, 137.6, 141.7, 142.1, 142.3, 170.2 (Ar-C and C=N); MS m/z (%) 556 (M⁺, 18), 431 (18), 314 (25), 251 (43), 193 (32), 166 (29), 152 (43), 136 (20), 119 (45), 104 (67), 90 (68), 75 (100), 62 (55), 52 (28), 41 (41). Anal. Calcd. for C₂₇H₂₄N₈O₂S₂ (556.66): C, 58.26; H, 4.35; N, 20.13. Found: C, 58.58; H, 4.05; N, 19.80%.

5-((4-Chlorophenyl)diazenyl)-4-methyl-2-(2-(1-(5-methyl-1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazol-4-yl)ethylidene)hydrazinyl)thiazole (18c) Orange solid, mp 232–235 °C; IR (KBr) ν_{max} 1598 (C=N), 2922 (C-H), 3436 (NH) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.32 (s, 3H, CH₃), 2.36 (s, 3H, CH₃), 2.47 (s, 3H, CH₃), 6.99–7.93 (m, 11H, Ar-H), 10.65 (s, 1H, NH); ^{13}C -NMR (DMSO- d_6): δ 12.2, 19.1, 24.7 (CH₃), 120.3, 125.1, 125.3, 125.4, 127.0, 127.1, 127.2, 128.2, 128.4, 134.3, 140.3, 140.4, 143.9, 144.1, 144.2, 145.5, 146.3, 146.4, 170.4 (Ar-C and C=N); MS m/z (%) 579 (M⁺+2, 2), 577 (M⁺, 5), 548 (7), 378 (14), 333 (11), 271 (100), 211 (20), 181 (20), 153 (18), 118 (16), 104 (66), 94 (36), 77 (52), 69 (36), 57 (37). Anal. Calcd. for C₂₆H₂₁N₈ClO₂S₂ (577.08): C, 54.11; H, 3.67; N, 19.42. Found: C, 54.44; H, 3.35; N, 19.12%.

Synthesis of 2-(1-(5-methyl-1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazol-4-yl)ethylidene)hydrazinecarbothioamide (19) A mixture of acetyl pyrazole **1** (3.27 g, 10 mmol) and thiosemicarbazide **16** (0.91 g, 10 mmol) in ethanol (20 mL) containing catalytic amounts of concentrated HCl was refluxed in microwave oven at 500 W and 150 °C for 6 min., then left to cool to room temperature. The precipitated product was filtered off, washed with ethanol, and dried. Recrystallization from acetic acid afforded thiosemicarbazone **19** as yellow solid, (78% yield), mp 212–215 °C; IR (KBr) ν_{max} 1596 (C=N), 2926 (C-H), 3157, 3241, 3388 (NH and NH₂) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.17 (s, 3H, CH₃), 2.34 (s, 3H, CH₃), 7.10 (t, J = 1.2 Hz, 1H, thiophene-H), 7.23 (d, J = 1.2 Hz, 1H, thiophene-H), 7.56 (d, J = 1.2 Hz, 1H, thiophene-H), 7.86 (d, J = 8.8 Hz, 2H, Ar-H), 8.20 (s, 2H, NH₂), 8.38 (d, J = 8.8 Hz, 2H, Ar-H), 10.28 (s, 1H, NH); MS m/z (%) 400 (M⁺, 8), 322 (21), 284 (30), 211 (18), 176 (24), 150 (26), 130 (25), 112 (29), 105 (71), 97 (40), 83 (45), 69 (63), 57 (62), 43 (100). Anal. Calcd. for C₁₇H₁₆N₆O₂S₂ (400.48): C, 50.98; H, 4.03; N, 20.98. Found: C, 51.30; H, 3.73; N, 20.65%.

2-(2-(1-(5-Methyl-1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazol-4-yl)ethylidene)hydrazinyl)-5-(2-phenylhydrazono)thiazol-4(5H)-one (**21a**) Orange solid, mp 203–205 °C; IR (KBr) ν_{\max} 1600 (C=N), 1680 (C=O), 2932 (C–H), 3211, 3420 (2NH) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.24 (s, 3H, CH₃), 2.42 (s, 3H, CH₃), 7.12–7.92 (m, 12H, Ar–H), 9.82 (s, 1H, NH), 10.27 (s, 1H, NH); ^{13}C -NMR (DMSO- d_6): δ 12.1, 23.2 (CH₃), 112.6, 120.9, 125.3, 125.6, 125.9, 127.0, 127.3, 127.8, 128.2, 128.4, 134.3, 140.2, 140.4, 143.1, 144.7, 145.2, 155.5, 160.1 (Ar–C and C=N), 175.4 (C=O); MS m/z (%) 544 (M⁺, 3), 367 (18), 267 (15), 194 (17), 177 (18), 129 (25), 115 (29), 102 (38), 91 (39), 79 (35), 72 (93), 60 (100), 43 (71). Anal. Calcd. for C₂₅H₂₀N₈O₃S₂ (544.61): C, 55.13; H, 3.70; N, 20.58. Found: C, 55.44; H, 3.40; N, 20.25%.

2-(2-(1-(5-Methyl-1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazol-4-yl)ethylidene)hydrazinyl)-5-(2-(*p*-tolyl)hydrazono)thiazol-4(5H)-one (**21b**) Orange solid, mp 201–203 °C; IR (KBr) ν_{\max} 1596 (C=N), 1675 (C=O), 2920, 2978 (C–H), 3272, 3419 (2NH) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.28 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 2.48 (s, 3H, CH₃), 6.94–8.43 (m, 11H, Ar–H), 10.51 (s, 1H, NH), 10.54 (s, 1H, NH); ^{13}C -NMR (DMSO- d_6): δ 13.5, 14.5, 21.1 (CH₃), 112.0, 114.9, 116.3, 117.5, 119.5, 122.2, 125.3, 126.6, 128.0, 129.8, 136.5, 137.4, 138.4, 142.1, 148.2, 151.8, 154.5, 160.1 (Ar–C and C=N), 173.5 (C=O); MS m/z (%) 558 (M⁺, 2), 536 (11), 457 (61), 423 (12), 396 (27), 284 (44), 212 (45), 187 (51), 158 (22), 145 (36), 115 (57), 95 (41), 65 (100), 51 (28). Anal. Calcd. for C₂₆H₂₂N₈O₃S₂ (558.63): C, 55.90; H, 3.97; N, 20.06. Found: C, 56.20; H, 3.65; N, 19.70%.

2-((1-(5-Methyl-1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazol-4-yl)ethylidene)hydrazono)-3,5-diphenyl-2,3-dihydro-1,3,4-thiadiazole (**23a**) Orange solid, mp 195–197 °C; IR (KBr) ν_{\max} 1591 (C=N), 2924, 3105 (C–H) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.18 (s, 3H, CH₃), 2.43 (s, 3H, CH₃), 7.09–8.42 (m, 17H, Ar–H); ^{13}C -NMR (DMSO- d_6): δ 12.1, 24.7 (CH₃), 113.6, 120.3, 122.1, 125.3, 125.9, 126.0, 127.5, 127.8, 128.2, 128.4, 130.2, 133.5, 134.3, 135.3, 137.3, 140.4, 143.1, 144.4, 145.5, 146.3, 146.4, 159.4 (Ar–C and C=N); MS m/z (%) 577 (M⁺, 6), 492 (36), 441 (20), 356 (30), 327 (59), 269 (42), 177 (57), 121 (51), 103 (100), 77 (77), 55 (72), 42 (30). Anal. Calcd. for C₃₀H₂₃N₇O₂S₂ (577.68): C, 62.37; H, 4.01; N, 16.97. Found: C, 62.68; H, 3.70; N, 16.62%.

2-((1-(5-Methyl-1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazol-4-yl)ethylidene)hydrazono)-3-(4-nitrophenyl)-5-(thiophen-3-yl)-2,3-dihydro-1,3,4-thiadiazole (**23b**) Orange solid, mp 209–210 °C; IR (KBr) ν_{\max} 1693 (C=N), 2954 (C–H) cm^{-1} ; ^1H NMR (DMSO- d_6) δ 2.18 (s, 3H, CH₃), 2.27 (s, 3H, CH₃), 7.10–8.42 (m, 14H, Ar–H); MS

m/z (%) 628 (M⁺, 7), 561 (11), 510 (31), 441 (20), 360 (26), 313 (24), 284 (78), 270 (52), 190 (26), 152 (100), 105 (63), 89 (30), 63 (39). Anal. Calcd. for C₂₈H₂₀N₈O₄S₃ (628.70): C, 53.49; H, 3.21; N, 17.82. Found: C, 53.81; H, 2.90; N, 17.51%.

Alternate synthesis of thiazole 18a and 21a Equimolar amounts of thiosemicarbazone **19** (0.400 g, 1 mmol) and hydrazonoyl chloride **3a** or **3c** (1 mmol) in dioxane (15 mL) containing an equivalent amount of triethylamine (0.05 mL) was refluxed in microwave oven at 500 W and 150 °C for 3 min., gave product identical in all respects (mp, mixed mp and IR spectra) with compounds **18a** and **21a**, respectively.

Biological activity

Anticancer activity

The cytotoxic evaluation of the synthesized compounds was carried out at the Regional Center for Mycology and Biotechnology at Al-Azhar University, Cairo, Egypt according to the reported method [49].

Conclusion

In our present work, we herein present an efficient regioselective synthesis of novel 4-heteroaryl-pyrazoles, which have not been reported *hitherto* in a multicomponent synthesis under microwave irradiation. The structures of the newly synthesized compounds were established on the basis of spectroscopic evidences and their synthesis by alternative methods. The *in vitro* growth inhibitory activity of the synthesized compounds against hepatocellular carcinoma (HepG-2) and human lung cancer (A-549) cell lines were investigated in comparison with Cisplatin reference drug as a standard drug using MTT assay and the results revealed promising activities of six compounds.

Abbreviations

A-549: human lung cancer; HepG2: human hepatocellular carcinoma; EtOH: ethanol; mp: melting point; TEA: triethylamine; IR: infra-red; ATCC: American type culture collection; TLC: thin layer chromatography.

Authors' contributions

SMG designed research; SMG, ZAM, RAMF and MME performed research and analyzed the data. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Sample availability

Samples of the compounds are available from the authors.

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References

- Murata T, Murai M, Ikeda Y, Miki K, Ohe K (2012) Pd- and Cu-catalyzed one-pot multicomponent synthesis of hetero alpha, alpha'-dimers of heterocycles. *Org Lett* 14:2296–2299
- Lalli C, Bouma MJ, Bonne D, Masson G, Zhu J (2011) Exploiting the divergent reactivity of alpha-isocyanoacetate: multicomponent synthesis of 5-alkoxyoxazoles and related heterocycles. *Chemistry* 17:880–889
- Zhang S, Zhang WX, Xi Z (2010) Efficient one-pot synthesis of N-containing heterocycles by multicomponent coupling of silicon-tethered diynes, nitriles, and isocyanides through intramolecular cyclization of iminoacyl-Zr intermediates. *Chemistry*. 16:8419–8426
- Lopez C, Zougagh M, Algarra M, Rodriguez-Castellon E, Campos BB, Esteves da Silva JC, Jimenez-Jimenez J, Rios A (2015) Microwave-assisted synthesis of carbon dots and its potential as analysis of four heterocyclic aromatic amines. *Talanta* 132:845–850
- Agudelo Mesa LB, Padro JM, Reta M (2013) Analysis of non-polar heterocyclic aromatic amines in beefburguers by using microwave-assisted extraction and dispersive liquid-ionic liquid microextraction. *Food Chem* 141:1694–1701
- Pawelczyk A, Zaprutko L (2009) Microwave assisted synthesis of unsaturated jasmone heterocyclic analogues as new fragrant substances. *Eur J Med Chem* 44:3032–3039
- Jeselnik M, Varma RS, Polanc S, Kocevar M (2001) Catalyst-free reactions under solvent-free conditions: microwave-assisted synthesis of heterocyclic hydrazones below the melting points of neat reactants. *Chemical Commun* 18:1716–1717
- Al-Qalaf F, Mandani F, Abdelkhalik MM, Bassam AA (2009) Synthesis of 5-substituted 3-amino-1H-pyrazole-4-carbonitriles as precursors for microwave assisted regioselective syntheses of pyrazolo[1,5-a]pyrimidines. *Molecules* 14:78–88
- Ezer M, Yildirim LT, Bayro O, Verspohl EJ, Dundar OB (2012) Synthesis and antidiabetic activity of morpholinothiazolyl-2,4-thiazolidindione derivatives. *J Enzyme Inhib Med Chem* 27:419–427
- Zhang K, Yan JF, Tang XM, Liu HP, Fan L, Zhou GM, Yang DC (2011) Synthesis of novel beta-aminoalcohols containing nabumetone moiety with potential antidiabetic activity. *Yaoxue Xuebao* 46:412–421
- Dutt P, Sarkar AK (1993) Alterations in rat intestinal sucrase and alkaline phosphatase activities in alloxan induced experimental diabetes. *Indian J Biochem Biophys* 30:177–180
- Tarach JS (1978) Electronmicroscopic cytochemical studies on lysosomes and peroxisomes of a rat cardiac muscle in the experimental alloxan diabetes. *Acta Histochem* 62:32–43
- Ranatunge RR, Garvey DS, Janero DR, Letts LG, Martino AM, Murty MG, Richardson SK, Young DV, Zemetseva IS (2004) Synthesis and selective cyclooxygenase-2 (COX-2) inhibitory activity of a series of novel bicyclic pyrazoles. *Bioorg Med Chem* 12:1357–1366
- Sakya SM, Cheng H, Lundy KM, De Mello, Shavnya A, Minich ML, Rast B, Dutra J, Li C, Rafka RJ, Koss DA, Li J, Jaynes BH, Ziegler CB, Mann DW, Petras CF, Seibel SB, Silvia AM, George DM, Hickman A, Haven ML, Lynch MP (2006) 5-Heteroatom-substituted pyrazoles as canine COX-2 inhibitors: part 2. Structure-activity relationship studies of 5-alkylethers and 5-thioethers. *Bioorg Med Chem Lett* 16:1202–1206
- Reddy GJ, Pallavi K, Reddy RS, Reddy KS (2005) Synthesis of 1,3-diaryl-4-(pyridine-4-yl)pyrazoles as a new class of pyrazole based diaryl heterocycles. *Indian J Chem* 44:812–814
- Sauzem PD, Sant'Anna GDS, Machado P, Duarte MMMF, Ferreira J, Mello CF, Beck P, Bonacorso HG, Zanatta N, Martins MAP, Rubin MA (2009) Effect of 5-trifluoromethyl-4,5-dihydro-1H-pyrazoles on chronic inflammatory pain model in rats. *Eur J Pharmacol* 61:91–100
- Koca I, Ozgur A, Coskun KA, Tutar Y (2013) Synthesis and anticancer activity of acyl thioureas bearing pyrazole moiety. *Bioorg Med Chem* 21:3859–3865
- Tyagarajan S, Chakravarty PK, Zhou B, Taylor B, Eid R, Fisher MH, Parsons WH, Wyvratt MJ, Lyons KA, Klatt T, Li X, Kumar S, Williams B, Felix J, Priest BT, Brochu RM, Warren V, Smith M, Garcia M, Kaczorowski GJ (2010) Discovery of a novel class of biphenyl pyrazole sodium channel blockers for treatment of neuropathic pain. *Bioorg Med Chem Lett* 20:7479–7482
- Pattan SR, Rabara PA, Pattan JS, Bukitagar AA, Wakale VS, Musmade DS (2009) Synthesis and evaluation of some novel substituted 1,3,4-oxadiazole and pyrazole derivatives for antitubercular activity. *Indian J Chem* 48B:1453–1456
- Shih SR, Chu TY, Reddy G, Tseng SN, Chen HL, Tang WF, Wu MS, Yeh JY, Chao YS, Hsu J, Hsieh HP, Horng JT (2010) Pyrazole compound BPR1P0034 with potent and selective anti-influenza virus activity. *J Biomed Sci* 17:13
- Lo HY, Man CC, Fleck RW, Farrow NA, Ingraham RH, Kukulka A, Proudfoot JR, Betageri R, Kirrane T, Patel U, Sharma R, Hoermann MA, Kabcenell A, Lombaert SD (2010) Substituted pyrazoles as novel sEH antagonist: investigation of key binding interactions within the catalytic domain. *Bioorg Med Chem Lett* 26:6379–6383
- Kasimogullari R, Bulbul M, Arslan BS, Gokçe B (2010) Synthesis, characterization and antiglaucoma activity of some novel pyrazole derivatives of 5-amino-1,3,4-thiadiazole-2-sulfonamide. *Eur J Med Chem* 45:4769–4773
- Padmaja A, Rajasekhar C, Muralikrishna A, Padmavathi V (2011) Synthesis and antioxidant activity of oxazolyl/thiazolylsulfonmethyl pyrazoles and isoxazoles. *Eur J Med Chem* 46:5034–5038
- Xia Y, Dong ZW, Zhao BX, Ge X, Meng N, Shin DS, Miao JY (2007) Synthesis and structure activity relationships of novel 1-arylmethyl-3-aryl-1H-pyrazole-5-carbohydrazide derivatives as potential agents against A549 lung cancer cells. *Bioorg Med Chem* 15:6893–6899
- Daidone G, Maggio B, Raffa D, Plescia S, Schillaci D, Maria V, Raimondi (2004) Synthesis and in vitro antileukemic activity of new 4-triazenopyrazole derivatives. *Farmaco* 59:413–417
- Farghaly AR (2010) Synthesis of some new indole derivatives containing pyrazoles with potential antitumor activity. *ARKIVOC* 11:177–187
- Soliman EA, El-Zahar MI, El-Masry AH, Kamel M, Gohar RS (2010) Synthesis and anticancer evaluation of novel tetrahydronaphthalen-6-ylthiazole heterocycles against human HePG2 and MCF7 cell lines. *Der Pharma Chem*. 2:507–521
- El-Zahar MI, EL-Karim SA, Haiba ME, Khedr MA (2011) Synthesis, antitumor activity and molecular docking study of novel benzofuran-2-yl pyrazole pyrimidine derivatives. *Acta Pol Pharm Drug Res* 68:357–373
- Tanitime A, Oyamada Y, Ofuji K, Terauchi H, Kawasaki M, Wachi M, Yamagishi JI (2005) Synthesis and antibacterial activity of a novel series of DNA gyrase inhibitors: 5-[(E)-2-arylvinyl]pyrazoles. *Bioorg Med Chem Lett* 15:4299–4303
- Dawood KM, Eldebss TMA, El-Zahabi HSA, Yousef MH, Metz P (2013) Synthesis of some new pyrazole-based 1,3-thiazoles and 1,3,4-thiadiazoles as anticancer agents. *Eur J Med Chem* 70:740–749
- Gomha SM, Khali KD, El-Zanate AM, Riyadh SM (2015) A Facile Green Synthesis and anti-cancer activity of bis-arylhydrazonitriles, triazolo[5,1-c][1,2,4]triazine, and 1,3,4-thiadiazoline. *Heterocycles* 87(5):1109–1120
- Gomha SM, Badrey MG, Edrees MM (2016) Heterocyclization of a bis-thiosemicarbazone of 2,5-diacetyl-3,4-disubstituted-thieno[2,3-b]thiophene bis-thiosemicarbazones leading to bis-thiazoles and bis-1,3,4-thiadiazoles as anti-breast cancer agents. *J Chem Res* 40:120–125
- Gomha SM, Kheder NA, AAbdelhamid AO, Mabkhot YN (2016) One pot single step synthesis and biological evaluation of some novel bis(1,3,4-thiadiazole) derivatives as potential cytotoxic agents. *Molecules* 21:15321–15328

34. Gomha SM, Ahmed SA, Abdelhamid AO (2015) Synthesis and cytotoxicity evaluation of some novel thiazoles, thiadiazoles, and pyrido[2,3-d][1, 2, 4]triazolo[4,3-a]pyrimidin-5(1*H*)-one incorporating triazole moiety. *Molecules* 20:1357–1376
35. Gomha SM, Khalil KD (2012) A convenient ultrasound-promoted synthesis and cytotoxic activity of some new thiazole derivatives bearing a coumarin nucleus. *Molecules* 17:9335–9347
36. Gomha SM, Riyadh SM, Mahmmoud EA, Elaasser MM (2015) Synthesis and anticancer activity of arylazothiazoles and 1,3,4-thiadiazoles using chitosan-grafted-poly(4-vinylpyridine) as a novel copolymer basic catalyst. *Chem Heterocycl Compd* 51:1030–1038
37. Gomha SM, Riyadh SM, Abbas IM, Bauomi MA (2013) Synthetic utility of ethylenedithio-semicarbazide: synthesis and anti-cancer activity of 1,3-thiazines and thiazoles with imidazole moiety. *Heterocycles* 87:341–356
38. Gomha SM, Abdel-aziz HM (2015) Synthesis and antitumor activity of 1,3,4-thiadiazole derivatives bearing coumarine ring. *Heterocycles* 91:583–592
39. Abbas IM, Gomha SM, Elaasser MM, Bauomi MA (2015) Synthesis and biological evaluation of new pyridines containing imidazole moiety as antimicrobial and anticancer agents. *Turk J Chem* 39:334–346
40. Gomha SM, Salah TA, Abdelhamid AO (2015) Synthesis, characterization and pharmacological evaluation of some novel thiadiazoles and thiazoles incorporating pyrazole moiety as potent anticancer agents. *Monatsh Chem* 146:149–158
41. Hassaneen HM, Mousa AH, Abeer NM, Shawali AS (1988) Chemistry of C-Heteroarylhydrazidoyl Halides. Synthesis and reactions of *N*-(*p*-Nitrophenyl)-*C*-(2-thienyl)-formohydrazidoyl Halides. *Heterocycles* 27:695–706
42. Al-Bogam AS, Mekky AEM (2016) Microwave-assisted regioselective synthesis of novel bis (azoles) and bis(azoloazines). *J Heterocycl Chem* 53:1554–1562
43. Zaki YH, Sayed AR, Elroby SA (2016) Regioselectivity of 1,3-dipolar cycloadditions and antimicrobial activity of isoxazoline, pyrrolo[3,4-d]isoxazole-4,6-diones, pyrazolo[3,4-d]pyridazines and pyrazolo[1,5-a]pyrimidines. *Chem Central J.* 10:17(1–13)
44. Eldebss TMA, Gomha SM, Abdulla MM, Arafa RK (2015) Novel pyrrole derivatives as selective CHK1 inhibitors: design, regioselective synthesis and molecular modeling. *Med Chem Commun* 6:852–859
45. Gaber HM, Bagley MC, Muhammad ZA, Gomha SM (2017) Recent developments in chemical reactivity of *N,N*-dimethylenamino ketones as synthons for various heterocycles. *RSC Adv* 7:14562–14610
46. Gomha SM, Shawali AS, Abdelhamid AO (2014) Convenient method for synthesis of various fused heterocycles via utility of 4-acetyl-5-methyl-1-phenyl-pyrazole as precursor. *Turk J Chem* 38:865–879
47. Gomha SM, Abdelrazek FM, Abdelrahman AH, Metz P (2016) Synthesis of some novel thiazole, thiadiazole and 1,4-phenylene-bis-thiazole derivatives as potent antitumor agents. *Heterocycles* 92:954–967
48. Shawali S, Gomha SM (2000) A new entry for short and regioselective synthesis of [1,2,4]triazolo[4,3-b][1,2,4]-triazin-7(1*H*)-one. *Adv Synth Catal* 342:599–604
49. Gomha SM, Riyadh SM, Mahmmoud EA, Elasser MM (2015) synthesis and anticancer activities of thiazoles, 1,3-thiazines, and thiazolidine using chitosan-grafted-poly(vinylpyridine) as basic catalyst. *Heterocycles* 91:1227–1243

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