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A new series of thiazolyl pyrazoline derivatives linked to benzo[1,3]dioxole moiety: Synthesis and evaluation of antimicrobial and anti-proliferative activities

Eman Mansour, Asmaa Aboelnaga, Ekhlass M. Nassar, and Safaa I. Elewa

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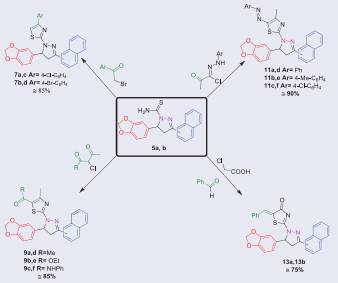
ABSTRACT

2-(5-(Benzo[d][1,3]dioxol-5-yl)-3-(naphthalen-1-yl)-4,5-dihydro-1H-pyrazol-1-yl)-4-(4-substituted phenyl)thiazole **(7)** and thiazole derivatives **(9)** were synthesized *via* reaction of 4,5-dihydro-1H-pyrazoles (**5a,b)** with substituted phenacyl bromide and a number of α-halo-compounds respectively. Also, (E)-2-(5-(benzo[d][1,3]dioxol-5-yl)-3-(naphthalen-1-yl)-4,5 dihydro-1H-pyrazol-1-yl)-4-methyl-5-(substituted phenyldiazenyl)thiazole **(11)** were prepared through reactions of carbothioamide (**5a,b)** with hydrazonoyl halides. In addition, thioamides (**5a–b)** were used as starting materials for preparation of thiazoles (**12a–b)** and benzylidene thiazoles **(13a–b)**. Most of synthesized compounds show interesting biological properties as antimicrobial and antiproliferative activities, the results of minimum inhibitory concentration showed that pyrazole derivative **7c** (MIC: 0.23 mg/mL) showed better results when compared with **11c** and **12a** (MIC: 0.1–0.125 mg/mL) as obtained from their MIC values. On the other hand, 2-(5-(benzo[d][1,3]dioxol-5-yl)-3-(naphthalen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)-4-(4-chlorophenyl) thiazole (**7c**) can be considered as the most promising anti-proliferative agent against **HCT-116** cancer cells owing to its notable inhibitory effect on **HCT-116** cells with an IC_{50} value of 6.19 μM.

GRAPHICAL ABSTRACT



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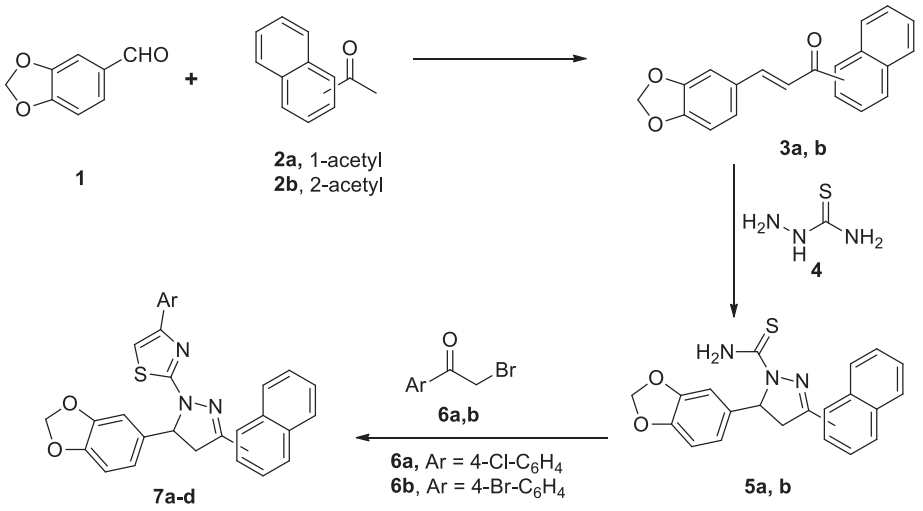
Introduction

Piperonal is a suitable compound for many products of commercial importance and it is an organic compound which has high interesting biological and pharmacological activities of several heterocyclic compounds[1] such as benzimidazoles[2–5] benzoxazoles[6–9] and pyrazoles.[10,11] Furthermore, most of the compounds synthesized from piperonal have high anti-proliferative, anti-microbial, anti-inflammatory, anti-neoplastic and fungicidal activity.[12,13] We interested in this work to synthesis piperonal derivatives containing pyrazole moiety. In addition, naphthalene nucleus is present in a wide variety in the field of medicinal chemistry as they used in drug synthesis as nafcillin, naftifine, terbinafine[14] which play important role in microbial infection.[15] We interested in the present work to synthesize chalcones that can be found in natural products. Chalcones have been synthesized in order to develop drugs which act against cancer and malaria,[16,17] so the combination of chalcone, naphthalene, and benzodioxole moiety in one entity seemed promising.[18] Chalcones and their derivatives were recognized as biologically active compounds[19–21] and anticancer.[17,22] Pyrazoles also have been attracting a great deal of interest due to their pharmaceutical application,[23] in addition, compounds containing pyrazole and thiazole moiety possess abroad spectrum as biologically active compounds as antifungal, antibacterial and anti-inflammatory[4,24–29] and anticancer.[30–36] In our studies we deal with the utility of hydrazonyl halides for the synthesis of biologically active polyheterocylic compounds containing either pyrazole or pyrazoline thiazole heterocycles.[33,37] Furthermore, the hybridization of pyrazolyl thiazole with naphthalene revealed potent anti-cancer. According to the aforementioned data, the principle point of this work relies up on the synthesis of new naphthalene derivatives containing either pyrazole or pyrazoline thiazole heterocycles as pharmacophoric moieties.[38]

Results and discussion

Chemistry

In the present work, two novel chalcones were synthesized by condensing the naphthyl ketone with pipronal in ethanol using basic condition at room temperature. The products obtained from the reaction mixture in a pure state and high yield to give prop-2-en-1-ones **3a** and **3b**. The structures of the new chalcones **3a** and **3b** were confirmed by spectroscopic data as well as elemental analysis. Infrared spectra of chalcones revealed absorption bands in the region 1640–1690 cm^{-1} corresponding to the conjugated carbonyl system in chalcones. In the 400 MHz, ^{1}H-NMR spectra of **3a, 3b** exhibit the presence of doublet signals at $\delta = 7.25–7.69$ ppm due to the olefinic hydrogen in chalcones (Scheme 1), when compound **3a** and **3b** were treated with thiosemicarbazide in refluxing ethanol in presence of NaOH afforded thioamide derivatives **5a** and **5b** (Scheme 1). The mechanism of the reaction involved the formation of hydrazones and addition of NH on the olephinic bond. The IR spectra of the latter compounds showed absorption bands at 1598 cm^{-1} corresponding to C=N group and at 1256–1249 cm^{-1} stretching band of C=S group, and the absorption band of NH_2 group at 3412–3255 cm^{-1}. Its ^{1}H-NMR spectrum showed the signals of H_a, H_b, and H_c of pyrazole ring as multiplet in the region 3.26–3.30 ppm



7	Ar
a	4-Cl-C_6H_4
b	4-Br-C_6H_4
c	4-Cl-C_6H_4
d	4-Br-C_6H_4

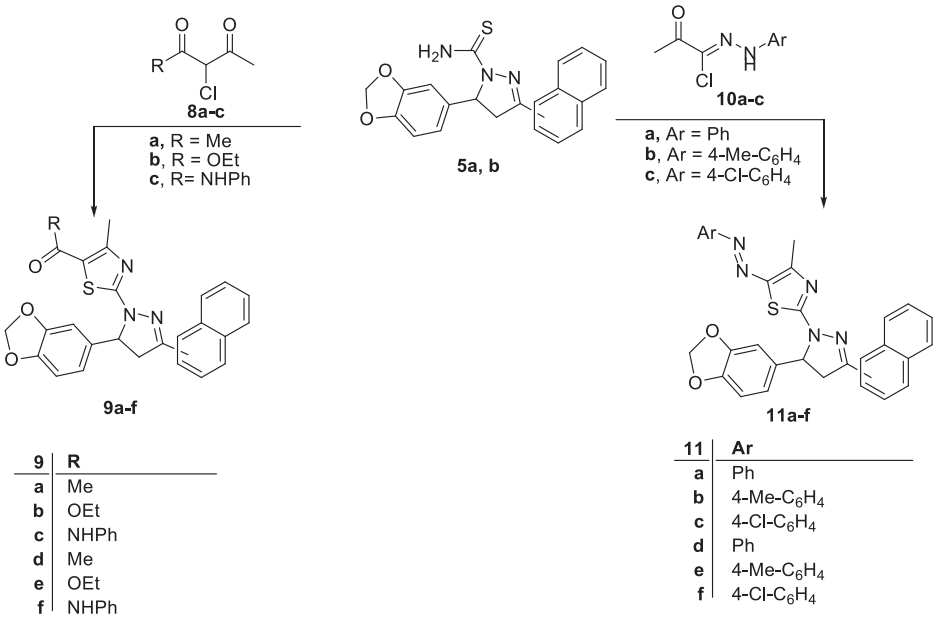
Scheme 1. Synthesis of thiazolyl-pyrazolines **7a–d**.

3.95–4.18 ppm and 5.88–5.93 ppm respectively, in addition to the peak signals at 8.2–8.22 ppm and 9.25–9.27 ppm due to NH_2 protons.

The reaction of pyrazole **5a** or **5b** with 1-aryl-2-bromoethanone **6a** or **6b** in ethanol gave thiazolyl-pyrazolines**7a–d** via the nucleophilic sulfur atom of thioamide group to form thiohydrazonate followed by dehydration to give the final product **7a–d**. The ^{1}H-NMR spectrum of the synthesized compounds, the CH_2 protons of pyrazoline ring showed as a multiplet at 3.47–3.63 (H_a), 4.04–4.26 (H_b). The CH (H_c) proton appeared as a multiplet at 5.59–5.97 ppm. The H_5-proton of thiazole was observed as a singlet signal in the region 6.90–7.45 ppm (Scheme 1).

The reaction of carbothioamide derivatives **5a** or **5b** with α-halo compounds **8a–c** in refluxing ethanol in the presence of Et_3N yielded the corresponding condensation products **9a–f**. IR spectra of **9a–f** showed a band at 1630–1720 cm^{-1} due to C=O whereas, the spectra of **9c** and **9f** showed bands at 3235–3251 cm^{-1} due to NH group. ^{1}H-NMR spectra of **9a** and **9d** revealed singlet signals at 2.4–2.5 ppm due to methyl protons of acetyl group, while for **9b** and **9e** showed a triplet-quartet pattern of ethyl protons at 1.24–1.29 and 4.18–4.26 ppm, while the ^{1}H-NMR spectra of **9c** and **9f** elicited exchangeable signals at 9.76 ppm due to NH protons along with aromatic protons at 7.05–7.66 ppm. ^{13}C NMR spectrum of **9e** showed signals due to ethyl carbons at 14.75 and 60.66 ppm with ester carbonyl carbon at 162.29 ppm (Scheme 2).

Next, thioamide **5a** or **5b** were reacted with the appropriate hydrazonyl chloride **10a–c** in EtOH afforded the diazenyl thiazoles **11a–f**. The IR spectra of the obtained compounds showed absorption bands at ν 1576–1592 cm^{-1} due to N=N groups and lack of the band corresponding to NH_2 group. The ^{1}H-NMR spectrum of the synthesized compounds



9	R
a	Me
b	OEt
c	NHPh
d	Me
e	OEt
f	NHPh

11	Ar
a	Ph
b	4-Me-C_6H_4
c	4-Cl-C_6H_4
d	Ph
e	4-Me-C_6H_4
f	4-Cl-C_6H_4

Scheme 2. Synthesis of thiazolyl-pyrazolines **9a–f** and **11a–f**.

showed disappearance of the signal of NH_2 protons and the presence of singlet peak of methyl protons of the thiazole ring at 2.3–2.6 ppm, in addition to the aromatic protons signals at 6.9–7.87 ppm. Also, ^{1}H-NMR spectra of **11b** and **11e** showed additional singlet signals at 2.35–2.37 ppm due the methyl protons of p-tolyl, ^{13}C NMR spectrum of **11f** showed signals at16.61 ppm for CH_3 carbon of the thiazole ring with increase in the number of signals of the aromatic carbons at 101.64–159.62 ppm (Scheme 2).

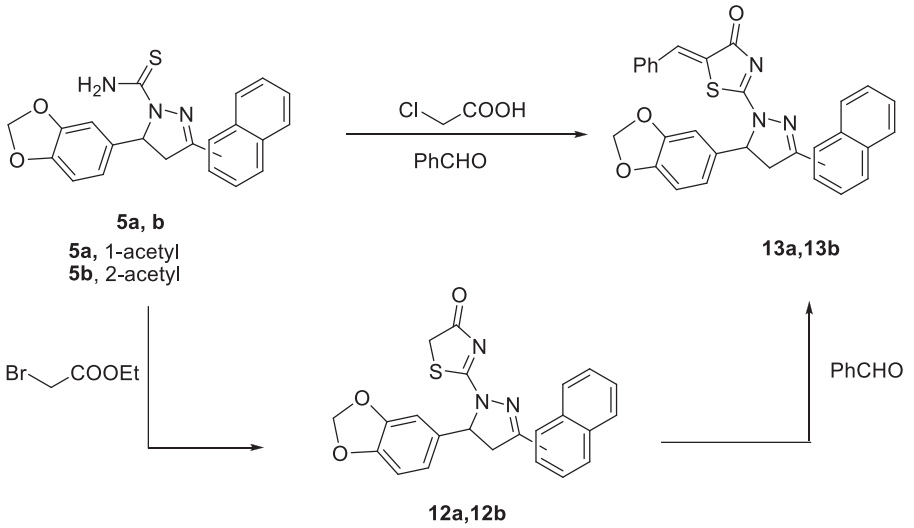
In addition, thioamide derivatives **5a** or **5b** condensed with ethyl bromo acetate in refluxing ethanol afforded thiazoles **12a** and **12b** as shown in (Scheme 3). Its IR spectrum showed absorption bands at 2830–2925 of CH_2 and 1693–1695 cm^{-1} of carbonyl groups. In addition, its ^{1}H-NMR spectrum exhibits the presence of singlet signals at δ 3.96–3.99 ppm due to the thiazolidinone (CH_2) group.

Finally, refluxing thioamide **5a** or **5b** with chloro acetic acid and benzaldehyde in acetic acid afforded benzylidene thiazole derivatives **13a** and **13b**. Compounds **13a** and **13b** were prepared by addition of benzaldehyde to thiazol derivatives **12a** or **12b** as shown in (scheme 3). The structure of the benzylidene thiazole **13a** and **13b** were confirmed from its element and spectral data. The IR spectra showed absorption bands at 1520–1570 cm^{-1} (C=N) and 1681–1694 cm^{-1} (C=O). ^{1}H-NMR showed the disappearance of the singlet peak of CH_2 group and the presence of olefinic proton peaks at 7.45 ppm (Scheme 3).

Biological evaluation

Anti-microbial activity

The antimicrobial activity of the newly synthesized compounds was evaluated against two gram-positive bacteria *Staphylococcus aureus* (*S. a.*) and *Bacillus cereus* (*B. c.*), and gram-negative bacteria species *Klebsiella pneumonia* and *pseudomonas aeruginosa* by



Scheme 3. Synthesis of thiazolyl-pyrazolines **13a** and **13b**.

agar well diffusion method as reported earlier,[39,40] in addition to five different fungus strains namly; *Candida albicans*, *Syncephalastrum racemosum*, *Aspergillus fumigatus, penicillium expansum* and *Aspergillus flavus*.

The anti-bacterial activities of **3a**, **3b**, **5a**, **5b**, **7a–7d**, **9a–9f**, **11a–11f**, **12a**, **12b**, **13a** and **13b** are represented in Table 1. It is noticed that, compounds **3a**, **3b**, **5a**, **7a**, **7c**, **9a**, **9d**, **11a**, **11c**, **11e**, **12a**, **13a** and **13b** revealed a moderate antibacterial activity against *Bacillus subtilis* with inhibition zones 1.6, 1.2, 0.9, 1.8, 1.0, 0.8, 0.9, 0.8, 1.8,0.8,2.0,0.8 and 0.9 mm, respectively, when compared with that of reference drug Amoxicillin (IZ = 3.5 mm), whereas compounds **3a**, **3b**, **5a**, **7a**, **7c, 9a**, **9d**, **11a**, **11c**, **11e**, **12a**, **13a** and **13b** exhibited a moderate antibacterial activity against *Staphylococcus aureus* with inhibition zones in the range of 0.5–2.6 mm when compared with that of reference drug Amoxicillin (IZ = 2.3 mm). Additionally, compounds **3b**, **5b**,**7a**, **7c**, **9a**, **9d**, **11a**, **11c**, **12a**, **13a** and **13b** exhibited good antibacterial activities against gram-negative bacteria *Klebsiella pneumoniae* with inhibition zones in the range of 0.9, 1.5, 1.2, 2.1, 0.5, 0.6, 1.0, 1.9, 0.9, 0.8, 1.2 mm respectively, when compared with that of reference drug Amoxicillin (IZ = 2.4 mm), whereas compounds **3b**, **5b**, **7a**, **7c**, **9d**, **11c**, **12a**, **13b** exhibited moderate antibacterial activities against *Pseudomonas aeruginosa* with inhibition zones in the range of 0.5, 0.9, 1.6, 1.0, 0.5, 2.0, 0.5, 0.8 mm respectively, when compared with that of reference drug Amoxicillin (IZ = 2.2 mm). The anti-fungal activities of pyrazole derivatives **3a**, **3b**, **5a**, **5b**, **7a–7d**, **9a–9f**, **11a–11f**, **12a**, **12b**, **13a** and **13b** are represented in Table 1. It is observed that compounds **5b**, **7c**, **11a**, **11c**, **11e**, **12a** revealed a moderate antifungal action against *C. albicans* with inhibition zones in the range of 1.5, 1.0, 0.9, 2.2, 0.5 and 2.0 mm, respectively, whereas **3a**, **5a**, **5b**, **7c**, **9d**, **11a**, **11c**, **11e**, **12a** and**13b** revealed a moderate antifungal action against *A. fumigatus* with inhibition zones 1, 0.5, 1.2, 2.5, 1.0, 1.8, 2.1, 0.9, 1.5 and 0.8 mm, respectively, when compared with that of reference drug Griseofulvin (IZ = 3.3 mm), respectively. Additionally, compounds **3a**, **3b**, **5b**, **7c**, **9a**, **9c**, **9d**, **11a**, **11c**, **12a** and **12b** exhibited good antifungal activities against

Table 1. The anti-microbial activity of the newly synthesized compounds against 9 microbial species.

	Inhibition ZONE (IZ, mm)								
	Antibacterial activity*				Antifungal activity*				
Comp. (conc. 5 mg/mL)	*S. aureus*	*B. subtilis*	*K. pnumonia*	*P. aeruginosa*	*A. fumigatus*	*A. flavus*	*S. racemosum*	*P. expansum*	*C. albicans*
3a	2.0	1.6	–	–	1.0	1.5	0.5	0.3	–
3b	1.0	1.2	0.9	0.5	–	0.5	–	0.9	–
5a	1.8	0.9	–	–	0.5	–	–	–	–
5b	–	–	1.5	0.9	1.2	1.0	1.2	0.9	1.5
7a	2.0	1.8	1.2	1.6	–	–	–	–	–
7b	–	–	–	–	–	–	–	–	–
7c	1.4	1.0	2.1	1.0	2.5	1.8	1.9	0.5	1.0
7d	–	–	–	–	–	–	–	–	–
9a	1.2	0.8	0.5	–	–	0.9	1.0	–	–
9b	–	–	–	–	–	–	–	–	–
9c	–	–	–	–	–	0.5	–	0.8	–
9d	1.0	0.9	0.6	0.5	1.0	0.8	–	0.8	–
9e	–	–	–	–	–	–	–	–	–
9f	–	–	–	–	–	–	–	–	–
11a	0.5	0.8	1.0	–	1.8	1.5	1.8	2.0	0.9
11b	–	–	–	–	–	–	–	–	–
11c	2.6	1.8	1.9	2.0	2.1	2.3	1.9	0.8	2.2
11d	–	–	–	–	–	–	–	–	–
11e	1.0	0.8	–	–	0.9	–	0.8	–	0.5
11f	–	–	–	–	–	–	–	–	–
12a	1.9	2.0	0.9	0.5	1.5	0.5	–	2.3	2.0
12b	–	0.8	–	–	–	0.9	–	1	–
13a	1.0	–	0.8	–	–	–	0.7	–	–
13b	1.0	0.9	1.2	0.8	0.8	–	0.5	–	–
	2.3	3.5	2.4	2.2	3.3	2.4	2.1	2.8	*3*

'–' Indicates bacteria were resistant to the compound.
*Antibacterial reference drug = Amoxicilline and Antifungal reference drug = Griseofulvin.

A. flavus with inhibition zones in the range of 1.5, 0.5, 1.0, 1.8, 0.9, 0.5, 0.8, 1.5, 2.3, 0.5, 0.9 mm, respectively, when compared with IZ = 2.4 mm of reference drug Griseofulvin. Compounds **3a**, **5b**, **7c**, **9a**, **11a**, **11c**, **11e**, **13a** and **13b** revealed a good antibacterial activity against *Syncephalastrum racemosum* with inhibition zones in the range of 0.5–1.9 mm when compared with Griseofulvinas a reference (IZ = 2.1 mm) whereas **3a**, **3b**, **5b**, **7c**, **9c**, **9d**, **11a**, **11c**, **12a**, **12b** and **13b** revealed a moderate antifungal action against *Penicillium expansum* in the range of 0.3–2.3 mm comparing Griseofulvin drug as a reference (IZ = 2.8 mm). From the data, it is observed that compounds **7c** and **11c** and **12a** showed good anti-microbial activity which showed the role of chloro group on acquiring their anti-microbial activities.

Minimum inhibitory concentration (MIC). For MIC test, Figure 1 showed different minimum inhibition concentrations of **7c**, **11c** and **12a**. It is already known that as the inhibition, bactericidal or fungicidal concentrations decreases this implies the highest efficacy, i.e., the tested compound possesses a high toxicity so that low concentration is sufficient to cause inhibition, bactericidal or fungicidal effects.

Pyrazole derivative **7c** (MIC: 0.25 mg/mL) showed better results when compared with **11c** and **12a** (MIC: 0.1–0.125 mg/mL) as obtained from their MIC values.

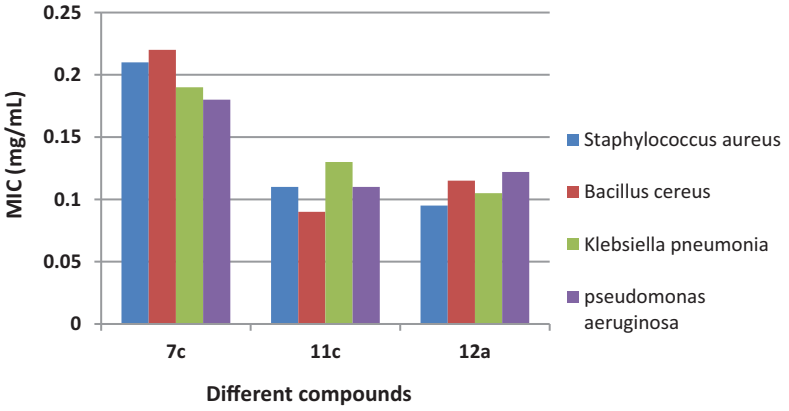


Figure 1. MIC (mg/mL) of compounds **7c**, **11c** and **12a**.

Table 2. The 50% inhibitory concentration (IC_{50}) of **7c**, **11c** and **12a** against **HTC-116, BHK, HEP-G2** and **MCF-7** cell lines.

	IC_{50} (μM)				IC_{50} (μM) of Human normal liver
Compounds	**HCT116**	**BHK**	**HEP-G2**	**MCF-7**	HL-7702
7c	6.19 ± 0.02	7.08 ± 0.92	6.71 ± 0.51	6.52 ± 0.02	123.05 ± 1.0
11c	9.82 ± 0.12	7.71 ± 0.31	7.49 ± 0.22	6.94 ± 0.21	279.94 ± 1.02
12a	12.91 ± 0.03	10.76 ± 0.71	19 ± 1.04	9.1 ± 0.08	328.56 ± 1.04

Anti-proliferative activity

*Determination of anti-proliferative activities against **HCT-116, BHK, HEP G2** and **MCF-7** cell lines.* On the bases of the concept of broad pharmacological activity of thioimide, pyrazole compounds we carried out the anti-proliferative activity for the newly synthesized compounds **7c**, **11c** and **12a** against four cancer cell lines **HCT-116** (colon carcinoma) and **BHK** (baby hamster kidney), **HEP G2** (human liver cell line) and **MCF-7** (breast cell line). As control cell, the human normal liver cell line **HL-7702** was employed to discern an unspecific cytotoxicity of newly synthesized compounds (Table 2). All cell lines were gotten from the VACSERA Tissue Culture Unit. The effect of new compounds on the cell was calculated and the microplate reader (SunRise, TECAN, Inc, USA) was utilized to gauge the optical density and to determine the number of viable cells and the percentage of viability which calculated as $[1 - (ODt/ODc)] \times 100\%$ where ODt is the mean Optical Density of wells dealed with the tested sample and ODc is the mean Optical Density of untreated Cells.

SAR. From the results presented in Table 3, it was reported that all the tested compounds have been made visible anti proliferative. Among them, compound **7c,** which had IC_{50} values of is the more effective one followed by **11c** and **12a**, this may be attributed to the presence of pyrazole and thiazole rings in these compounds. Among them, compound **7c**, which had IC_{50} values of 7.90, 7.08, 6.71 and 6.52 μM against HCT116, BHK, HepG2 and, MCF-7, respectively, displayed the most potent anti-proliferative activity. These results suggested that compound **7c** is more potent than the other compounds overall. Presence of halogen substituent was performed to

Table 3. Anti-proliferative activities of compounds (μm/mL) against four tumor cell lines (survival %) and IC_{50} of dose which reduces survival to 50%.

	HCT-116			BHK			HEPG2			MCF-7		
No.	**7c**	**11c**	**12a**	**7c**	**11c**	**12a**	**7c**	**11c**	**12a**	**7c**	**11c**	**12a**
Conc.												
0.0	100	100	100	100	100	100	100	100	100	100	100	100
1.0	80	92	98	86	85	98	83	92	95	92	95	83
2.5	54	84	95	65	70	84	72	85	78	85	78	72
5.0	46	70	93	54	62	76	59	76	55	76	55	59
10.0	35	59	88	42	50	63	42	68	38	41	38	42

explore the structure-activity relationships of this compound. Also, Compound **11c** bearing one chloro group at the para-position in the phenyl ring showed strong anti-proliferative activity (the IC_{50} values of **7c** and **11c**: 6.52 and 6.94 μM against MCF-7 cells) than compound **12a** (the IC_{50} value: 9.1 μM against MCF-7 cells) which possess thiazolone ring.

Conclusion

In summary, new thiazolyl pyrazoline derivatives linked to benzo[1,3]dioxole moiety were synthesized and their structures were established by different spectral data, then these compounds were examined for their antibacterial, antifungal activities and anti-proliferative activity against four different cell lines. In particular, compound **7c** was the most promising antifungal derivative against A. funigatus with inhibition zone 2.5 mm. Also, compound **11c** had got high activity against S. aureus with MIC value of 0.115 mg/mL. Furthermore, compound **7c** can be identified as the most promising anti-cancer agent owing to its anti-proliferative effect on all tested cell lines and nontoxic towards human normal liver HL-7702.

Experimental

Chemistry

General

Gallenkamp melting point device used to measure the melting points. Infrared (IR) Spectra were recorded as KBr disks using the Perkin Elmer FT-IR Spectrum BX apparatus. Mass spectral data are given as *m/z* (Intensity %) and measured on GCQ Finnigan MAT. Nuclear Magnetic Resonance Spectra were recorded on a Bruker NMR spectrometer, 1H spectrum was run at 300 MHz and the ^{13}C NMR spectrum was run at 125 MHz in deuterated DMSO, the chemical shift in δ, ppm and the coupling constant (*J*) values in Hertz.[41] Mass spectrum was carried out on direct probe controller inlet part to single quadro-pole mass analyzer in (thermo scientific gcms) model (isq lt) using thermo x-calibur software at the regonal center for mycology and biotechnology (rcmb) al-azhar university, Naser City, Cairo. Reaction courses and product mixtures were monitored by thin layer chromatography (TLC) on silica gel plates. All the chemicals were purchased from Sigma–Aldrich.

*Synthesis of prop-2-en-1-ones **3a** and **3b**.* To a solution of benzo[*d*][1,3]dioxole-5-carbaldehyde (piperonal) (**1**) (10 mmol) and 1-acetylnaphthalene (**2a**) or 2-acetylnaphthalene (**2b**) (1.82 g, 10 mmol), in absolute ethanol (50 mL), sodium hydroxide solution (5 mL, 20%) was added portion-wise. The mixture was stirred for 4 h. The solid product was collected by filtration, washed with water, dried and finally recrystallized from ethanol to give compounds **3a** and **3b**, respectively.

*(E)-3-(benzo[d][1,3]dioxol-5-yl)-1-(naphthalen-1-yl)prop-2-en-1-one (**3a**).* Yellow crystals (8.8 mmol), m.p. 176–78 °C; IR (KBr, ν cm^{-1}): 1640 (C = C) and 1680 (C=O); ^{1}H NMR (DMSO-d_6) δppm: 6.12 (s, 2 H, CH_2 of dioxole), 6.96–6.98 (d, 1 H, J = 8 Hz, H-4 of benzodioxole), 7.25–7.27 (dd, 2 H, J = 8 Hz, olefinic hydrogens), 7.55–7.57 (d, 2 H, J = 8 Hz, H-6 and H-7 of benzodioxole), 7.59–8.32 (m,7H, naphthalene Hs); MS: m/z = 302.24$[M]^+$. Anal.Calcd for $C_{20}H_{14}O_3$: C, 79.46; H, 4.67. Found: C, 79.36; H, 4.50.

*(E)-3-(benzo[d][1,3]dioxol-5-yl)-1-(naphthalen-2-yl)prop-2-en-1-one (**3b**).* Yellow crystals (9.1 mmol), m.p. 148–150 °C; IR (KBr, ν cm^{-1}): 1655 (C = C) and 1690 (C=O); ^{1}H NMR (DMSO-d_6) δppm: 6.13 (s, 2 H, CH_2 of dioxole), 7.01–7.03 (d, 1 H, J = 8 Hz, H-6 of benzodioxole), 7.37–7.38 (d, 1 H, J = 4 Hz, H-7 of benzodioxole), 7.62–7.65 (t, 2 H, J = 12 Hz, H-6 and H-7 of naphthalene), 7.67–7.69 (dd, 2 H, J = 8 Hz, olefinic hydrogens), 7.78 (s, 1 H, H-4 of dioxole), 8.01–8.07(m, 3 H, olefinic hydrogens, H-3 and H-4), 8.13–8.17 (m, 2 H, H-5 and H-8); MS: m/z = 302.24$[M]^+$. Anal.Calcd for $C_{20}H_{14}O_3$: C, 79.46; H, 4.67. Found: C, 79.26; H, 4.52.

Synthesis of 4,5-dihydro-1H-pyrazoles 5a and 5b

To a solution of NaOH (1 g, 0.025 mol) and chalcone **3a** or **3b** (10 mmol) in ethanol (50 mL), thiosemicarbazide (**4**) (10 mmol) was added. The reaction mixture was refluxed for 8 h. The resulting solid was filtered, washed with water, dried and recrystallized from EtOH/DMF to give pyrazole derivatives **5a** and **5b**, respectively.

*5-(benzo[d][1,3]dioxol-5-yl)-3-(naphthalen-1-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**5a**).* Off white crystals (8.3 mmol), m.p. 170–172 °C; IR (KBr, ν cm^{-1}): 3417–3255 (NH_2) 1598 (C=N) and 1256 (C=S); ^{1}H NMR (DMSO-d_6) δppm: 3.27–3.3 (m, 1 H, H_a of pyrazole), 4.11–4.18 (m, 1 H, H_b of pyrazole), 5.88–5.89 (m, 1 H, H_c of pyrazole), 5.91 (d, J = 3.6 Hz, 2 H, CH_2 of dioxole), 6.64–6.68 (m, 2 H, H-6 and H-7 of benzodioxole), 6.86 (d, J = 8 Hz, 1 H, H-4 of benzodioxole), 7.52–7.63 (t, J = 12 Hz, 2 H, H-6 and H-7 of naphthalene), 7.68–7.23 (t, J = 8 Hz,1H, H-3 of naphthalene), 7.77–7.78 (d, J = 4 Hz, 2 H, H-5 and H-8 of naphthalene), 7.99–8.04 (m, 2 H, H-2 and H-4 of naphthalene), 8.2 (s, 1 H, NH), 9.25–9.27 (d, J = 8 Hz, 1 H, NH); MS: m/z = 375.28$[M]^+$. Anal.Calcd for $C_{21}H_{17}N_3O_2S$: C, 67.18; H, 4.56; N, 11.19. Found: C, 67.29; H, 4.58; N, 11.03.

*5-(benzo[d][1,3]dioxol-5-yl)-3-(naphthalen-2-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**5b**).* Pale yellow crystals(8.9 mmol), m.p. 239–240 °C; IR (KBr, ν cm^{-1}): 3412–3234 (NH_2) and 1598 (C=N) and 1249 (C=S); ^{1}H NMR (DMSO-d_6) δppm:

3.26–3.3 (m, 1 H, H_a of pyrazole), 3.93–4.0 (m, 1 H, H_b of pyrazole), 5.90–5.93 (m, 1 H, H_c of pyrazole), 5.93 (d, $J = 3.6$ Hz, 2H, CH_2 of dioxole), 6.64–6.61 (m, 2 H, H-6 and H-7 of benzodioxole), 6.85 (d, $J = 8.2$ Hz,1H, H-4 of benzodioxole), 7.54–7.60 (m, 2 H, H-6 and H-7 of naphthalene), 7.94–7.99 (m, 4 H, naphthalene Hs), 8.09 (s,1H, NH), 8.21(s, 1 H, H-1 of naphthalene),8.22 (s, 1 H, NH).^{13}C NMR (DMSO-d_6) δppm: 42.89 ($\underline{C}H_2$), 63.24 ($\underline{C}H$), 101.40, 106.41, 108.74, 118.94, 124.08, 127.30, 127.87, 128.20, 128.48, 128.61, 128.90, 129.03, 133.13, 134.21, 137.47, 146.58, 147.78, 155.50, 176.64; MS: $m/z = 375.28[M]^+$. Anal.Calcd for $C_{21}H_{17}N_3O_2S$: C, 67.18; H, 4.56; N, 11.19. Found: C, 67.19; H, 4.55; N, 11.05.

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