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Facile and expedient synthesis and anti-proliferative activity of diversely pyrrolones bearing 1,3-diphenylpyrazole moiety

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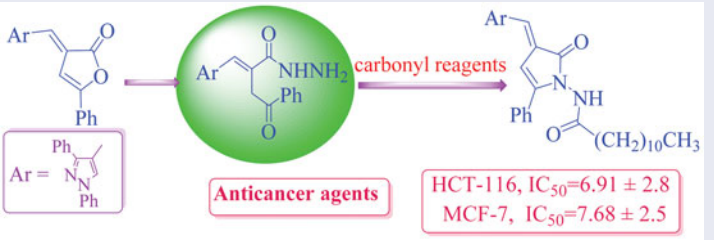
ABSTRACT

A series of some pyrrolone derivatives were synthesized from the acid hydrazide, derived from a pyrazolyl-2(3*H*)-furanone, through treating with some carbonyl reagents such as 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde, formic acid, lauroyl chloride, succinoyl chloride, propionic anhydride, as well as, ethoxymethylene malononitrile. All compounds were obtained in good yields and characterized by their microanalytical and spectral data. The synthesized products were evaluated for their *in vitro* antitumor activity against two human carcinoma cell lines (HCT-116 and MCF7) using doxorubicin as a reference drug by MTT assay. The results revealed that some compounds exhibited significant potency. Noteworthy, the *N*-propionyl hydrazide derivative was the most potent against both cell lines.

GRAPHICAL ABSTRACT



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Cytotoxic; antitumor; acid hydrazide; pyrrolones; pyrazoles

Introduction

The development of new anticancer therapeutic agents is one of the fundamental goals in medicinal chemistry. Cytotoxicity of the anticancer drugs to the normal cells represent major problems in cancer therapy.[1] The pyrazole scaffolds, double nitrogen-containing heterocyclic aromatic organic compounds, have attracted significant attention for their fascinating physiological and pharmacological applications. They have remarkable and valuable biological properties such as anti-H_5N_1 activities, antiviral, antitumor,

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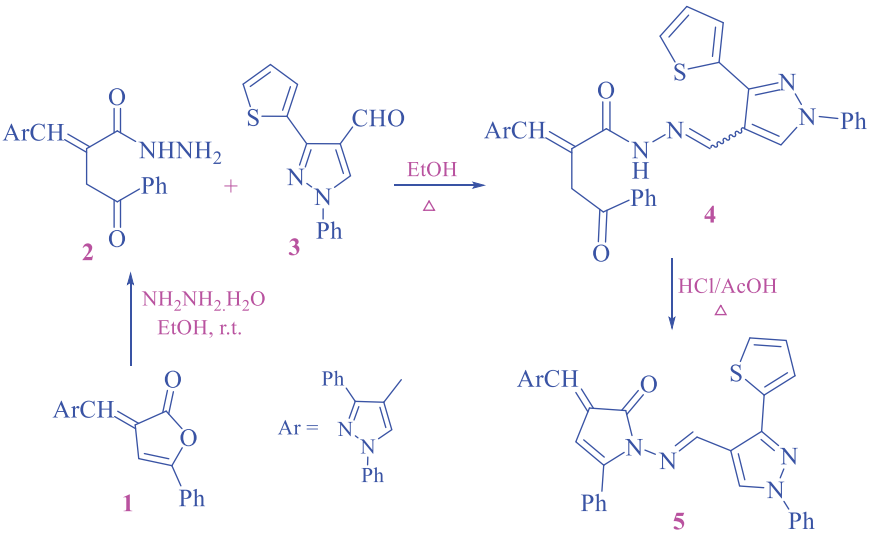
antimicrobial, antihistaminic, antidepressant, antioxidant and anticonvulsant.[2–14] In turn, 2(3*H*)-furanones were easily transformed into a wide variety of nitrogen heterocycles of synthetic and pharmacological prominence e.g. antiviral, anti-inflammatory, antitumor, antimalarial, antimicrobial and herbicidal activities.[15–22] The ability of these products to contribute to cancer therapy has been evidenced by numerous *in vitro* as well as *in vivo* studies. Therefore, extensive researches are still needed to improve and enhance their properties and to reduce their adverse effects. Thus, in the present work, 2(3*H*)-furanone incorporating a pyrazole moiety was readily synthesized and efficiently utilized for the construction of some *N*-heterocycles to examine them as potential antitumor agents.

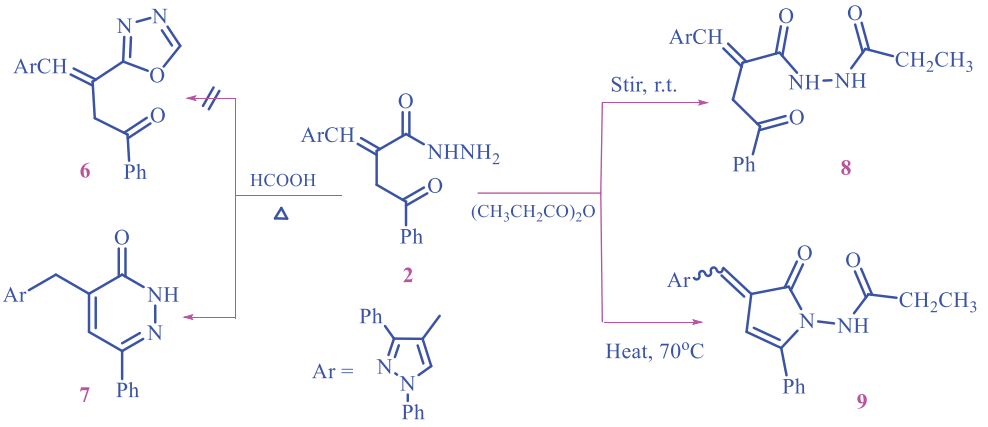
Results and discussion

Synthesis

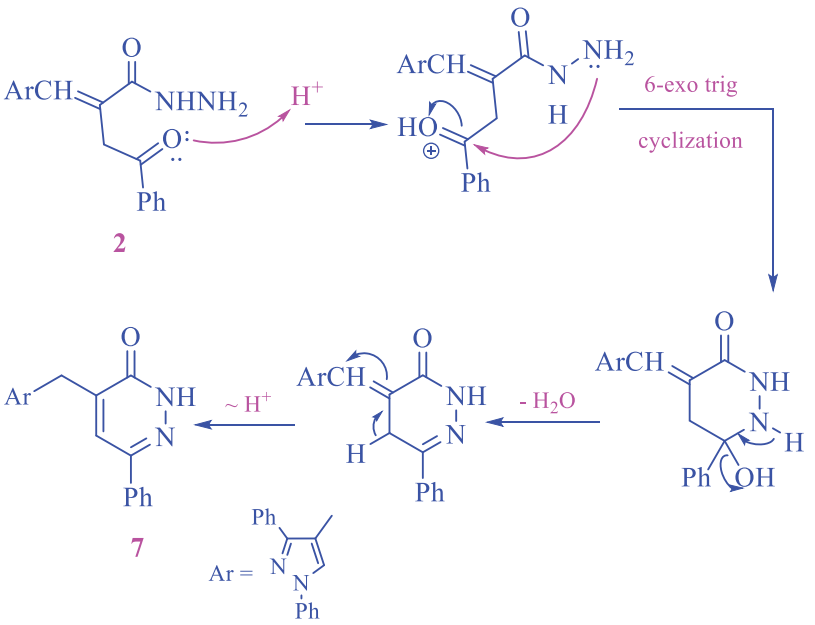
The requisite acid hydrazide **2** was previously prepared from hydrazinolysis of pyrazolyl-2(3*H*)-furanone **1** with hydrazine hydrate,[18] and submitted to react with some carbonyl reagents (Schemes 1 and 2). Indeed, condensation of the hydrazide **2** with the pyrazole aldehyde namely, 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde[23] **(3)** afforded the corresponding hydrazone **4** as yellow crystals which was easily transformed into the pyrrolone derivative **5** in a good yield by refluxing in an equimolar mixture of HCl/CH_3COOH (1:1) for 1 h (Scheme 1). The chemical structures of compounds **4** and **5** were substantiated from their spectral data. The IR spectrum of hydrazone **4** revealed the absence of NH_2 absorption band and the appearance of the absorption bands for NH, carbonyl of ketonic and amide as well as C=N groups at ν 3286, 1694, 1659, and 1622 cm^{-1}, respectively. The ^{1}H-NMR spectrum of compound **4** confirmed its existence as a mixture of two geometrical *Syn*- and *Anti*-isomers in an equal ratio as it showed two singlet signals of equal integration for CH=N proton. In



Scheme 1. Condensation of hydrazide **2** with pyrazole aldehyde **3**.



Scheme 2. Reaction of hydrazide **2** with formic acid and propionic anhydride.



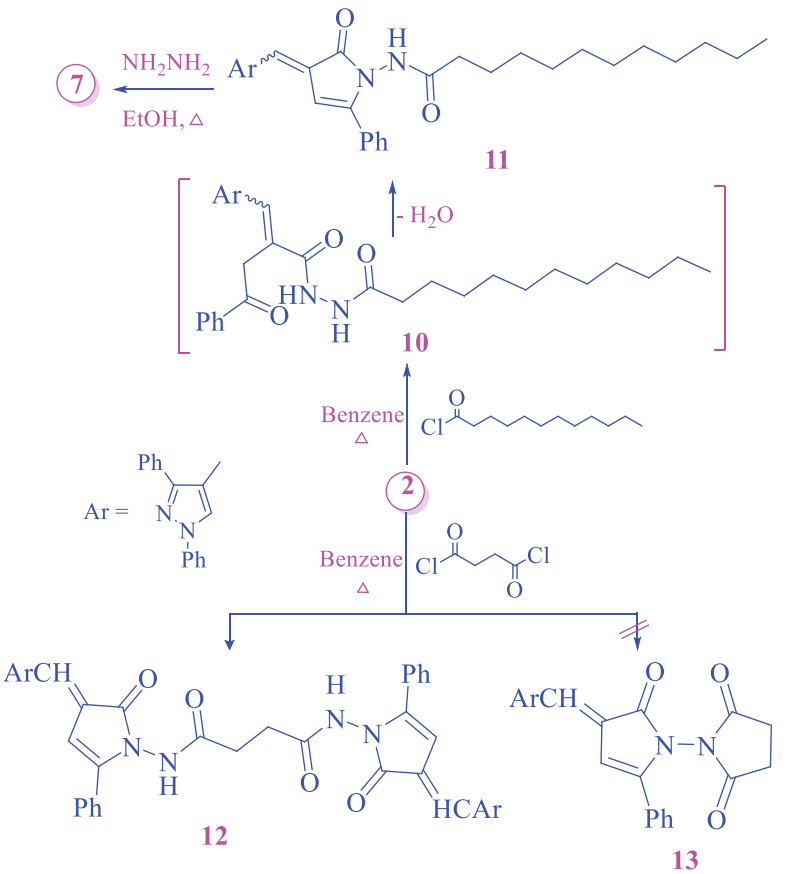
Scheme 3. A suggested mechanistic pathway for the formation of pyridazinone **7**.

turn, the ^{1}H-NMR spectrum of compound **5** was devoid from the singlet signals of NH and CH_2 protons (cf. Experimental). Formation of pyrrolone **5** could be visualized to occur via acid catalyzed 5-exo trig cyclization.

Refluxing the hydrazide **2** with formic acid led to the construction of pyridazinone **7** instead of the oxadiazole derivative **6** (Scheme 2). The structure of compound **7** was supported from its spectral data and by direct comparison with an authentic sample prepared by refluxing the hydrazide **2** in HCl/CH_3COOH mixture (1:1), where they were identical in all respects (mp, mixed mp, TLC, and IR). The driving force behind the formation of pyridazinone **7** could be explained via protonation of the ketonic carbonyl oxygen by formic acid pursued by 6-exo-trig cyclization as depicted in Scheme 3.

On the other hand, acylation of the acid hydrazide **2** using propionic anhydride under different reaction conditions was investigated. Indeed, stirring the hydrazide **2** with propionic anhydride at room temperature furnished the *N*-propionyl hydrazide derivative **8** as pale-yellow crystals in 82% yield. While the pyrrolone derivative **9** was obtained as canary yellow crystals upon conveying this reaction under heating at 70 °C (Scheme 2). The structures of compounds **8** and **9** were corroborated by spectroscopic data. The ^{1}H-NMR spectrum of compound **8** exhibited a singlet signal for CH_2 protons, quartet and triplet signals for $-CH_2CH_3$ group as well as two exchangeable broad singlet signals attributable for two NH protons. Meanwhile, the ^{1}H-NMR spectrum of compound **9** provided duplicate signals of different integrations which represent good evidence for its existence as a mixture of two geometrical *E*- and *Z*-stereoisomers in a ratio of 2:1, respectively. The higher percentage of the *E*-isomer as compared with the *Z*-counterpart may be attributed to the steric interference between carbonyl group of pyrrolone and the bulky substituted pyrazolyl moiety in *Z*-isomer. The formation of pyrrolone **9** could be visualized to occur *via* 5-exo-trig cyclization of the *N*-propionyl hydrazide derivative **8**.

When the hydrazide **2** was subjected to react with dodecanoyl chloride in refluxing benzene, the pyrrolone **11** was obtained as orange crystals in 78% yield (Scheme 4). The IR spectrum exhibited the stretching absorption bands for C=O of pyrrolone at



Scheme 4. Reaction of hydrazide **2** with dodecanoyl chloride and succinoyl chloride.

ν 1705 cm^{-1} and NH at ν 3310 cm^{-1}. Its ^{1}H-NMR spectrum was in a good agreement with the assigned structure as it displayed signals for protons of $-(CH_2)_{10}CH_3$ moiety. Also, the ^{1}H-NMR spectrum displayed its existence as a mixture of *E*- and *Z*-isomer in a ratio of 55:45%, respectively, as it showed two singlet signals for each of CH olefinic, pyrazolyl and pyrrolonyl protons (cf. Experimental). Formation of pyrrolone **11** could be interpreted to occur *via* nucleophilic attack of the terminal NH_2 group of hydrazide on the –COCl group of dodecanoyl chloride to give the *N*-dodecanoyl hydrazide derivative **10** as a non-isolable intermediate which *in situ* underwent 5-exo-trig cyclization to eliminate water molecule (cf. Scheme 4).

It was fortunate that, hydrazinolysis of the pyrrolone **11** in boiling ethanol achieved the pyridazinone **7** which was supported by direct comparison with the product obtained from reaction of hydrazide **2** with formic acid (cf. Scheme 4). The heterocyclic transformation of pyrrolone **11** into pyridazinone **7** could be represented *via* ring opening of pyrrolone by nucleophilic attack of hydrazine which subsequently underwent 6-exo-trig cyclization followed by elimination of dodecanoyl hydrazide (Scheme 5).

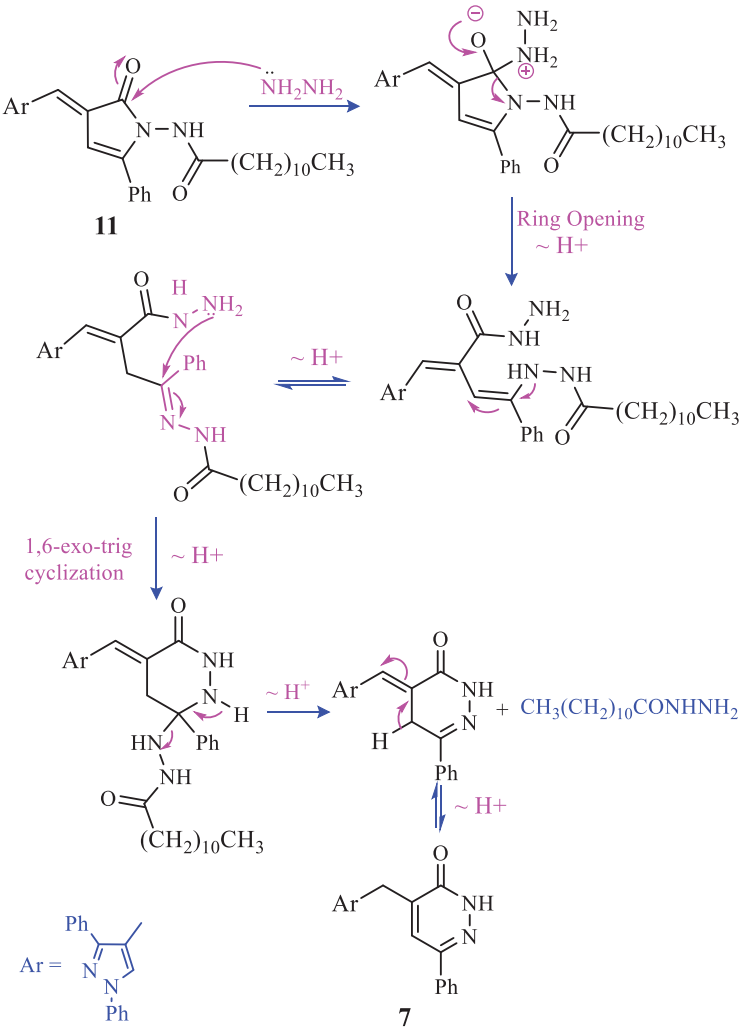
It was interesting that similar treatment of the hydrazide **2** with succinoyl chloride in refluxing benzene prompted the construction of pyrrolone derivative **12** instead of pyrrolylpyrrolidinedione **13** (Scheme 4). The IR spectrum displayed the stretching absorption bands for NH at ν 3262 cm^{-1} and C=O groups at ν 1724 and 1690 cm^{-1}, ruling out the structure **13**. Likewise, its ^{1}H-NMR spectrum displayed an exchangeable broad singlet signal at δ 10.62 ppm which attributed to NH proton and it was in accordance with the proposed structure (cf. Experimental). The formation of compound **12** could be interpreted *via* elimination of two HCl molecules from two hydrazide molecules with both terminal acid chloride moieties in succinoyl chloride followed by 5-exo-trig cyclization. The driving force behind the reaction pathway could be the high reactivity of the acid chloride that will immediately form the dimer **12**.

It was fortunate that, treatment of the hydrazide **2** with ethoxymethylene malononitrile in boiling dioxane led to the construction of pyrrolone **14** instead of the cyanoaminopyrazole derivative **15** (Scheme 6). The IR spectrum was devoid from the absorption bands of C≡N and NH_2 groups, with the appearance of the stretching absorption bands for carbonyl groups at ν 1719 and 1697 cm^{-1}, which excluded the enaminonitrile structure **15** and confirmed the pyrrolone structure **14**. Also, inspection of the ^{1}H-NMR spectrum was completely matched with the assigned structure and revealed the absence of singlet signal for NH_2 protons and showed its existence in the enol form (cf. Experimental). Formation of pyrrolone derivative **14** could be demonstrated to occur as depicted in Scheme 7.

In vitro *antiproliferative activity*

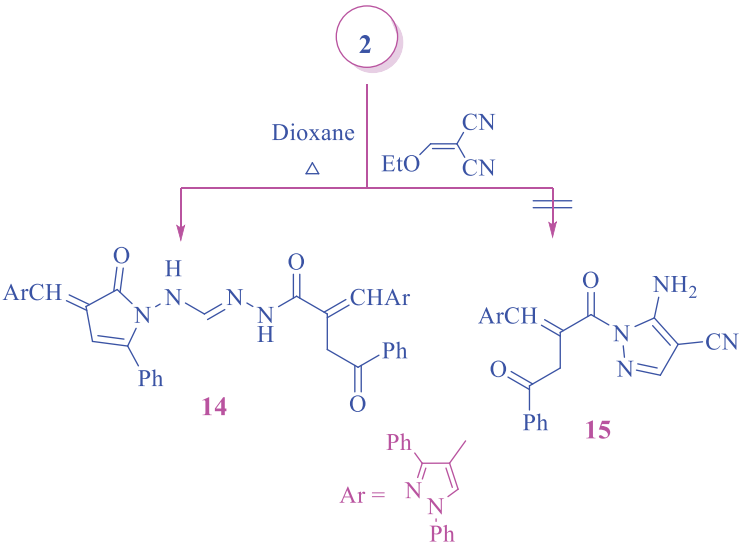
Cytotoxic effect on human cell lines (HCT-116 and MCF7)

In vitro cytotoxic activity was examined by 3-(4,5-dimethylthiazol-2-yl-2,5-diphenyl tetrazolium bromide (MTT assay),[24–26] as this technique represent a reliable method to determine the bioactivity of the products.[27,28] The synthesized compounds were examined against two human carcinoma cell lines namely, colon cancer HCT-116 and

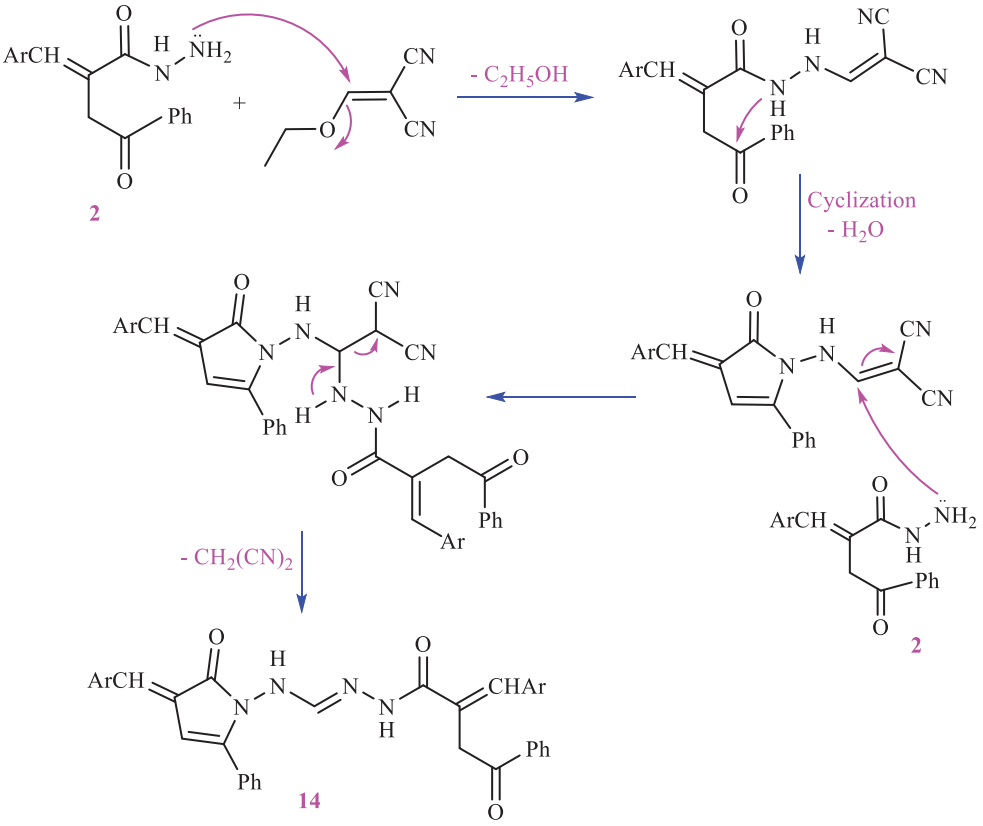


Scheme 5. A plausible pathway for hydrazinolysis of pyrrolone **11**.

mammary gland breast cancer MCF7 cell lines using doxorubicin as a standard anticancer drug. The anticancer activity was expressed as IC_{50} values (the concentration of test compounds required to kill 50% of the cell population). The results of cytotoxic activity of compounds are depicted in Table 1 and Figure 1. The results obtained revealed that the tested compounds exhibited variable degrees of inhibitory activity towards the two tested human tumor cell lines. As for activity against HCT-116, the most potent cytotoxic activity was shown by compounds **8** and **11** which displayed the percentage viability IC_{50} at 6.91 ± 2.8 and $7.49 \pm 1.2\,\mu M$, respectively. Whereas, the strong cytotoxic activity was displayed by compounds **9** and **12** which showed the percentage viability IC_{50} at 18.73 ± 1.2 and $15.47 \pm 2.9\,\mu M$, respectively. While compounds **5** and **14** showed weak activity. On the other hand, the activity against MCF7 cell line revealed that compounds **8** and **11** have the highest percentage viability IC_{50} at 7.68 ± 2.5 and $8.51 \pm 2.3\,\mu M$, respectively. Both compounds **9** and **12** showed good



Scheme 6. Reaction of hydrazide **2** with ethoxymethylene malononitrile.



Scheme 7. A plausible pathway for the formation of compound **14**.

Table 1. *In vitro* Cytotoxic effect on human cancer cell lines (HCT-116 and MCF7).

	In vitro cytotoxicity IC_{50} (μM)	
Compound	HCT-116	MCF7
Doxorubicin	5.23 ± 0.3	4.17 ± 0.2
4	25.51 ± 1.2	31.12 ± 2.3
5	49.21 ± 1.3	52.57 ± 2.4
7	19.46 ± 1.5	28.57 ± 2.3
8	6.91 ± 2.8	7.68 ± 2.5
9	18.73 ± 1.2	21.58 ± 1.5
11	7.49 ± 1.2	8.51 ± 2.3
12	15.47 ± 2.9	13.13 ± 3.2
14	46.64 ± 1.8	50.46 ± 2.1

IC_{50} (μM): 1–10 (very strong); 11–20 (strong); 21–50 (moderate); 51–100 (weak), and >100 (non-cytotoxic).

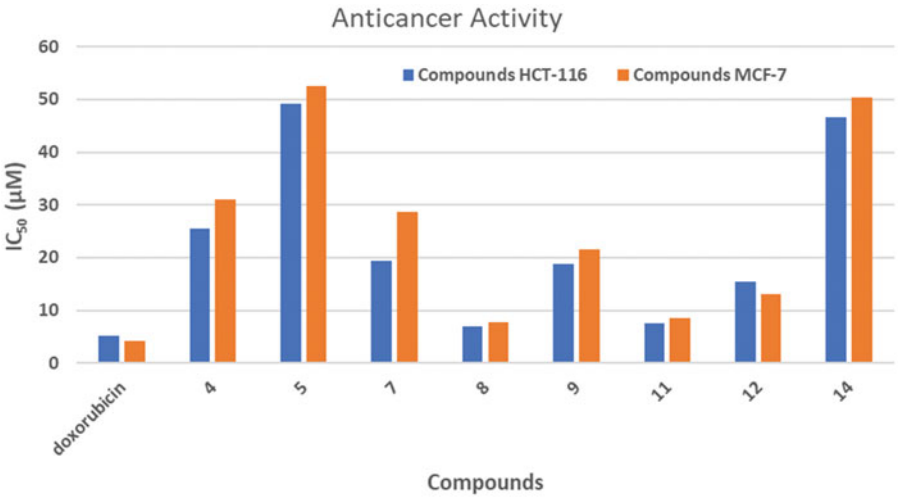


Figure 1. *In vitro* Cytotoxic effect on human cancer cell lines (HCT-116 and MCF7).

activities. Whereas compound **4** showed moderate activity and compound **14** exhibited weak activity.

Conclusion

A pyrazolyl-2(3*H*)-furanone was easily transformed into some pyrrolone and pyridazinone derivatives encompassing a pyrazole scaffold utilizing the corresponding acid hydrazide. The synthesized compounds were screened for their *in vitro* antitumor activity against two human carcinoma cell lines namely, colon cancer HCT-116 and mammary gland breast cancer MCF7 cell lines. The biological results revealed that some compounds exhibited good activities. Among these compounds, the *N*-propionyl hydrazide derivative was the most potent against the two carcinoma cell lines. Thus, some of these compounds seem to be interesting for pharmaceutical studies.

Experimental

Chemistry

Melting points were measured on a GALLENKAMP electric melting point apparatus and are uncorrected. All reagents and solvents were of analytical grade, obtained from commercial suppliers, purified and dried by standard techniques. The infrared spectra were recorded using potassium bromide disks on IR Thermo Electron Nicolet iS10 (USA) infrared spectrometer and expressed in wave number (ν, cm^{-1}) at Chemistry Department, Faculty of Science, Ain Shams University. The ^{1}H-NMR spectra were run at 300 and 400 MHz on a GEMINI/BRUKER NMR spectrometer using tetramethyl silane (TMS) as internal standard in denudated dimethylsulfoxide (DMSO-d_6) at Faculty of Science, Cairo University, Giza; the Main Defense Chemical Laboratory, Cairo; and Faculty of Pharmacy, Ain Shams University, Cairo, Egypt. Chemical shifts (δ) are quoted in ppm. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. All coupling constant (*J*) values are given in hertz. The mass spectra were recorded on a Shimadzu GC-MS-QP-1000 EX mass spectrometer (Shimadzu Scientific Instruments, Inc., USA) operating at 70 eV at the Regional Center for Mycology and Biotechnology of Al-Azhar University, Nasr City, Cairo, Egypt. The reactions were monitored by thin layer chromatography (TLC) using Merck Kiesel gel 60 F_{254} aluminum backed plates, Fluka, Switzerland. The antitumor activity was performed at the Faculty of Pharmacy, Mansoura University, Mansoura, Egypt.

The acid hydrazide **2** was previously prepared from hydrazinolysis of pyrazolyl-2(3*H*)-furanone **1** with hydrazine hydrate.[18]

Anti/syn-2-((1,3-Diphenyl-1H-pyrazol-4-yl)methylene)-4-oxo-4-phenyl-N′-((1-phenyl-3-(thiophen-2-yl)-1H-pyrazol-4-yl)methylene)butanehydrazide (4)

A solution of hydrazide **2** (2.11 g, 5 mmol) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde **(3)** (1.27 g, 5 mmol) in absolute ethanol (20 mL) was heated under reflux for 2 h. The precipitated solid while hot was collected and recrystallized from ethanol/dioxane mixture (1:1) to afford the corresponding hydrazone **4** as yellow crystals, mp. 300-302 °C, yield 81%. IR (KBr, ν, cm^{-1}): 3286 (NH), 1694 (C=O ketone), 1659 (C=O amide), 1622 (C=N). ^{1}H-NMR (400 *MHz*, DMSO-d_6, δ, ppm): 3.45 (s, 2H, CH_2), 7.01 (s, 1H, CH=), 7.06–7.20 (m, 5H, Aryl-C=N), 7.29–7.67 (m, 10H, two Aryl-N), 7.76–7.92 (m, 5 H, Aryl-C=O), 7.94–8.09 (m, 3 H, Thiophene), 8.78 (s, 1H, C^5–H pyrazole–CH=C), 8.86 (s, 1H, C^5–H pyrazole–CH=N), for *Anti-isomer* (50%), 9.16 (s, 1H, CH=N), 9.56 (*br*.s, 1H, NH, exchangeable); for *Syn-isomer* (50%), 8.92 (s, 1H, CH=N), 9.35 (*br*.s, 1H, NH, exchangeable). MS (*m/z*, %): 658 ($M^{\cdot+}$, 26). Anal. Calcd. For $C_{40}H_{30}N_6O_2S$ (658.22): C, 72.93; H, 4.59; N, 12.76. Found: C, 72.71; H, 4.32; N, 12.71%.

3-((1,3-Diphenyl-1H-pyrazol-4-yl)methylene)-5-phenyl-1-(((1-phenyl-3-(thiophen2-yl)-1H-pyrazol-4-yl)methylene)amino)-1,3-dihydro-2H-pyrrol-2-one (5)

A solution of the hydrazone derivative **4** (1.31 g, 2 mmol) in HCl/CH_3COOH (10 mL, 1:1) was heated under reflux for 1 h. The precipitated solid during heating was collected by filtration and recrystallized from dioxane to furnish the pyrrolone **5** as orange crystals, mp. 272–274 °C, yield 72%. IR (KBr, ν, cm^{-1}): 1688 (C=O), 1658 (C=N). ^{1}H-NMR (400 *MHz*, DMSO-d_6, δ, ppm): 6.99 (s, 1H, C^4–H pyrrole), 7.23 (s, 1H, CH=), 7.91–7.34 (m, 20H, Aryl), 7.93–8.07 (m, 3H, Thiophene), 8.88 (s, 1H, C^5–H pyrazole), 9.26 (s, 1H, C^5–H pyrazole), 9.32 (s, 1H, CH=N). MS (*m/z*, %): 640 (M^+, 13). Anal. Calcd. For $C_{40}H_{28}N_6OS$ (640.20): C, 74.98; H, 4.40; N, 13.12. Found: C, 74.67; H, 4.19; N, 13.08%.

Full tables and spectroscopic data can be found in Supplemental files.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] Aydemir, N.; Bilaloğlu, R. Genotoxicity of Two Anticancer Drugs, Gemcitabine and Topotecan, in Mouse Bone Marrow *in Vivo*. *Mutat. Res.* **2003**, *537*, 43. DOI: 10.1016/s1383-5718(03)00049-4.

[2] Ramadan, S. K.; Sallam, H. A. Synthesis, Spectral Characterization, Cytotoxic, and Antimicrobial Activities of Some Novel Heterocycles Utilizing 1,3-Diphenylpyrazole-4-Carboxaldehyde Thiosemicarbazone. *J. Heterocyclic Chem.* **2018**, *55*, 1942. DOI: 10.1002/jhet.3232.

[3] Shejale, S. R.; Rajput, C. G.; Bansode, S. S.; Kondawar, M. S. Synthesis, Characterisation, Evaluation of Antimicrobial and Antifungal Activity of Novel Pyrazolopyrimidine and Pyrazolopyridine Derivatives. *Internat. J. Pharmaceutical Chem.* **2017**, *7*, 144.

[4] Ragavan, R. V.; Vijayakumar, V.; Kumari, N. S. Synthesis and Antimicrobial Activities of Novel 1,5-diaryl pyrazoles . *Eur. J. Med. Chem.* **2010**, *45*, 1173. DOI: 10.1016/j.ejmech.2009.12.042.

[5] Kim, D.; Lee, Y.; Lee, Y. W.; Dewang, P. M.; Sheen, Y. Y.; Kim, Y. W.; Park, H.; Yoo, J.; Lee, H. S.; Kim, Y. Synthesis and Biological Evaluation of 4(5)-(6-Methylpyridin-2-yl)Imidazoles and Pyrazoles as Transforming Growth Factor-β Type 1 Receptor Kinase Inhibitors. *Bioorg. Med. Chem.* **2010**, *18*, 4459. DOI: 10.1016/j.bmc.2010.04.071.

[6] Tantawy, A. S.; Nasr, M. N. A.; El-Sayed, M. A. A.; Tawfik, S. S. Synthesis and Antiviral Activity of New 3-Methyl-1,5-Diphenyl-1*H*-Pyrazole Derivatives. *Med. Chem. Res.* **2012**, *21*, 4139. DOI: 10.1007/s00044-011-9960-2.

[7] Franchini, M. C.; Bonini, B. F.; Camaggi, C. M.; Gentili, D.; Pession, A.; Rani, M.; Strocchi, E. Design and Synthesis of Novel 3,4-Disubstituted Pyrazoles for Nanomedicine Applications against Malignant Gliomas. *Eur. J. Med. Chem.* **2010**, *45*, 2024. DOI: 10.1016/j.ejmech.2010.01.014.

[8] Riyadh, S. M. Enaminones as Building Blocks for the Synthesis of Substituted Pyrazoles with Antitumor and Antimicrobial Activities. *Molecules.* **2011**, *16*, 1834. DOI: 10.3390/molecules16021834.

[9] Rashad, A. E.; Hegab, M. I.; Abdel-Megeid, R. E.; Micky, J. A.; Abdel-Megeid, F. M. E. Synthesis and Antiviral Evaluation of Some of New Pyrazole and Fused Pyrazolopyrimidine Derivatives. *Bioorg. Med. Chem.* **2008**, *16*, 7102. DOI: 10.1016/j.bmc.2008.06.054.

[10] Allan, G. M.; Bubert, C.; Vicker, N.; Smith, A.; Tutill, H. J.; Purohit, A.; Reed, M. J.; Potter, B. V. L. Novel, Potent Inhibitors of 17β-Hydroxysteroid Dehydrogenase Type 1. *Molecul. Cell Endocrin.* **2006**, *248*, 204. DOI: 10.1016/j.mce.2005.10.021.

[11] Rathelot, P.; Azas, N.; El-Kashef, H.; Delmas, F.; Giorgio, C. D.; Timon-David, P.; Maldonado, J.; Vanelle, P. 1,3-Diphenylpyrazoles: synthesis and Antiparasitic Activities of Azomethine Derivatives. *Eur. J. Med. Chem.* **2002**, *37*, 671. DOI: 10.1016/S0223-5234(02)01388-0.

[12] Rangaswamy, J.; Kumar, H. V.; Harini, S. T.; Naik, N. Synthesis, Antitubercular and Antimicrobial Evaluation of 3-(4-Chlorophenyl)-4-Substituted Pyrazole Derivatives. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4773. DOI: 10.1016/j.bmcl.2012.05.061.

[13] Abdel-Sayed, M. A.; Bayomi, S. M.; El-Sherbeny, M. A.; Abdel-Aziz, N. I.; El-Tahir, K. H.; Shehatou, G. S.; Abdel-Aziz, A. A. Synthesis, anti-Inflammatory, Analgesic, COX-1/2 Inhibition Activities and Molecular Docking Study of Pyrazoline Derivatives. *Bioorg. Med. Chem.* **2016**, *24*, 2032. DOI: 10.1016/j.bmc.2016.03.032.

[14] Abdel-Wahab, B. F.; Abdel-Gawad, H.; Awad, G. E. A.; Badria, F. A. Synthesis, Antimicrobial, Antioxidant, anti-Inflammatory, and Analgesic Activities of Some New 3-(2′-Thienyl)Pyrazole-Based Heterocycles. *Med. Chem. Res.* **2012**, *21*, 1418. DOI: 10.1007/s00044-011-9661-x.

[15] Husain, A.; Khan, S. A.; Iram, F.; Iqbal, M. A.; Asif, M. Insights into the Chemistry and Therapeutic Potential of Furanones: A Versatile Pharmacophore. *Eur. J. Med. Chem.* **2019**, *171*, 66. DOI: 10.1016/j.ejmech.2019.03.021.

[16] Ramadan, S. K.; Abou-Elmagd, W. S. I. Synthesis and anti H_5N_1 Activities of Some Novel Fused Heterocycles Bearing Pyrazolyl Moiety. *Synth. Commun* **2018**, *48*, 2409. DOI: 10.1080/00397911.2018.1491995.

[17] Abou-Elmagd, W. S. I.; El-Ziaty, A. K.; Elzahar, M. I.; Ramadan, S. K.; Hashem, A. I. Synthesis and Antitumor Activity Evaluation of Some *N*-Heterocycles Derived from Pyrazolyl-Substituted 2(3*H*)-Furanone. *Synth. Commun* **2016**, *46*, 1197. DOI: 10.1080/00397911.2016.1193755.

[18] Hashem, A. I.; Youssef, A. S. A.; Kandeel, K. A.; Abou-Elmagd, W. S. I. Conversion of Some 2(3*H*)-Furanones Bearing a Pyrazolyl Group into Other Heterocyclic Systems with a Study of Their Antiviral Activity. *Eur. J. Med. Chem* **2007**, *42*, 934. DOI: 10.1016/j.ejmech.2006.12.032.

[19] El-Ziaty, A. K.; Abou-Elmagd, W. S. I.; Ramadan, S. K.; Hashem, A. I. Synthesis and Biological Screening of Some Chromonyl-Substituted Heterocycles Derived from 2(3*H*)-Furanone Derivative. *Synth. Commun* **2017**, *47*, 471. DOI: 10.1080/00397911.2016.1271896.

[20] Hashem, A. I.; Abou-Elmagd, W. S. I.; El-Ziaty, A. K.; Ramadan, S. K. Ring Transformation of a 2(3H)-Furanone Derivative into Oxazinone and Pyrimidinone Heterocycles. *J. Heterocyclic Chem.* **2017**, *54*, 3711. DOI: 10.1002/jhet.2937.

[21] Ramadan, S. K.; El-Helw, E. A. E. Synthesis and Antimicrobial Activity Evaluation of Some Novel Heterocycles Derived from Chromonyl-2(3*H*)-Furanone. *J. Chem. Res.* **2018**, *42*, 332. DOI: 10.3184/174751918X15295796734379.

[22] Abou-Elmagd, W. S. I.; Hashem, A. I. Conversion of Some 2(3H)-Furanones into Pyrrolinotriazine and Oxazolopyrimidine Derivatives. *J. Heterocyclic Chem.* **2012**, *49*, 947. DOI: 10.1002/jhet.889.

[23] Kiyani, H.; Albooyeh, F.; Fallahnezhad, S. Synthesis of New Pyrazolyl-1,3-Diazabicyclo[3.1.0]Hexe-3-Ene Derivatives. *J. Mol. Struct.* **2015**, *1091*, 163. DOI: 10.1016/j.molstruc.2015.02.069.

[24] Mosmann, T. Rapid Colorimetric Assay for Cellular Growth and Survival: Application to Proliferation and Cytotoxicity Assays. *J. Immunol Methods.* **1983**, *65*, 55. DOI: 10.1016/0022-1759(83)90303-4.

[25] Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. New Colorimetric Cytotoxicity Assay for Anticancer-Drug Screening. *J. Natl. Cancer Inst.* **1990**, *82*, 1107. DOI: 10.1093/jnci/82.13.1107.

[26] Mauceri, H. J.; Hanna, N. N.; Beckett, M. A.; Gorski, D. H.; Staba, M. J.; Stellato, K. A.; Bigelow, K.; Heimann, R.; Gately, S.; Dhanabal, M.; et al. Combined Effects of Angiostatin and Ionizing Radiation in Antitumor Therapy. *Nature.* **1998**, *394*, 287. DOI: 10.1038/28412.

[27] Griffith, D.; Cecco, S.; Zangrando, E.; Bergamo, A.; Sava, G.; Marmion, C. J. Ruthenium (III) Dimethyl Sulfoxide Pyridinehydroxamic Acid Complexes as Potential Antimetastatic Agents: synthesis, Characterisation and *In Vitro* Pharmacological Evaluation. *J. Biol. Inorg. Chem.* **2008**, *13*, 511. DOI: 10.1007/s00775-007-0337-4.

[28] Abu-Bakr, Sh, M.; Abu-Zied, K. M.; Youns, M.; Hashim, A.; El-Diwan, H. I. Novel Synthesis and anti-Tumour Activity of 2-Hydrazino-1H-Benzimidazoles. *Res. J. Pharm. Biol. Chem. Sci.* **2013**, *4*, 1350.