applied sciences

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An Efficient Synthesis of Novel Pyrazole-Based Heterocycles as Potential Antitumor Agents

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Received: 22 July 2017; Accepted: 31 July 2017; Published: 3 August 2017

Abstract: A new series of pyrazolylpyridines was prepared by reaction of ethyl-3-acetyl-1,5-diphenyl-1*H*-pyrazole-4-carboxylate with the appropriate aldehyde, malononitrile, or ethyl acetoacetate and an excess of ammonium acetate under reflux in acetic acid. Similarly, two novel bipyridine derivatives were prepared by the above reaction using terephthaldehyde in lieu of benzaldehyde derivatives. In addition, a series of 1,2,4-triazolo[4,3-*a*]pyrimidines was synthesized by a reaction of 6-(pyrazol-3-yl)pyrimidine-2-thione with a number of hydrazonoyl chlorides in dioxane and in the presence of triethylamine. The structure of the produced compounds was established by elemental analyses and spectral methods, and the mechanisms of their formation was discussed. Furthermore, the pyrazolyl-pyridine derivatives were tested as anticancer agents and the results obtained showed that some of them revealed high activity against human hepatocellular carcinoma (HEPG2) cell lines.

Keywords: pyrazoles; pyridines; multicomponent reactions; pyrazolyl-pyridines; antitumor activity

1. Introduction

A literature survey revealed that compounds, including the pyrazole nucleus, are extensively used as a precursor for the synthesis of compounds presenting many applications, such as electrolyte additives in batteries [1], catalysis [2], photographic materials [3], agrochemicals [4], and dyes [5]. The chemical versatility of the pyrazole and its analogues has attracted interest because it allows a range of applications in the pharmaceutical industry. Many pyrazole-derived compounds are known to exhibit anticancer [6–10], antimicrobial [11,12], antiviral [13], antiparasitic [14], anti-inflammatory [15,16], antipyretic [17], analgesic [18], anticoagulant [19], and anti-obesity [20] biological activities. The pyridine nucleus is a key constituent, present in a range of bioactive compounds, occurring both synthetically and naturally with wide range of biological applications [21,22]. Among the successful examples as drug candidates possessing pyridine nuclei are streptonigrin, streptonigrone, and lavendamycin, which are described in the literature as anticancer drugs. Some pyridine derivatives were studied for their topoisomerase inhibitory activity and cytotoxicity against several human cancer cell lines for the development of novel anticancer agents. As a result, it has been reported that various pyridine derivatives, as bioisosteres of α-terthiophene (potent protein kinase C inhibitor) [23], have significant topoisomerase I and/or II inhibitory activity, and cytotoxicity against several human cancer cell lines [24–28]. Early reports on the ability of α-terpyridine to form metal complexes [29] and to

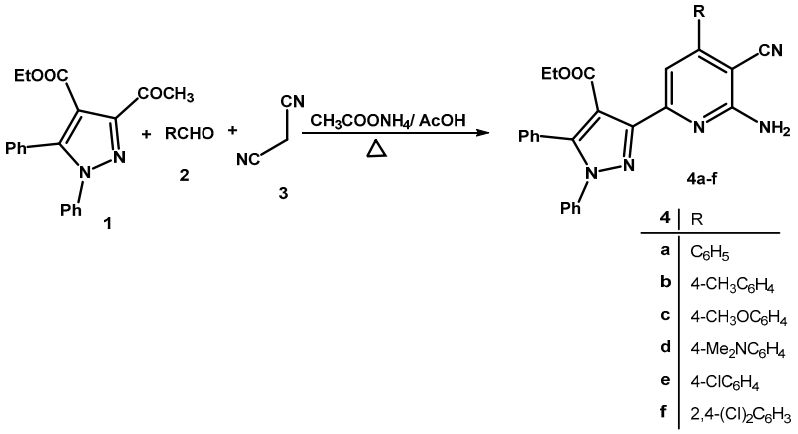
bind with DNA/RNA [30] have been the base for the study on pyridine derivatives as antitumor agents. On the other hand, multicomponent reactions (MCRs) are powerful tools in modern medicinal chemistry, facilitating the lead generation by providing access to drug-like compounds, helping in drug discovery [31–33]. Additionally, the utility of MCR under microwave irradiation in the synthesis of heterocyclic compounds enhanced the reaction rates and improved the regioselectivity [34,35]. Over the last decade, several research groups adopted a hybridization approach for the design of pyrazole-pyridine hybrid analogs and illuminated their synthetic and medicinal importance [36–42].

In light of the above findings and in continuation of our efforts to synthesize new anticancer compounds [43–52], the aim of presented report is to synthesize a new series of pyrazolyl-pyridines via multicomponent reactions which are expected to be active as antitumor agents.

2. Results and Discussion

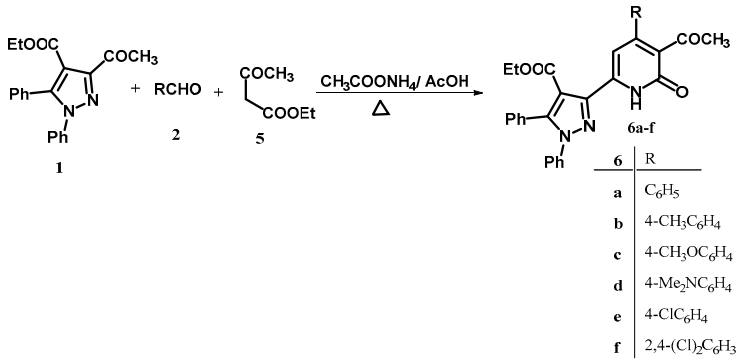
2.1. Chemistry

Ethyl 3-acetyl-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (**1**) [53] was used as the starting compound for the preparation of a number of novel pyrazolyl-pyridine derivatives via one-pot multicomponent reactions. For example, a series of novel 2-amino-3-cyano-6-(pyrazol-3-yl)-pyridines **4a**–**f** was prepared by a one-pot reaction of 3-acetylpyrazole derivative **1** with the appropriate aldehyde **2**, malononitrile **3**, and ammonium acetate under reflux in acetic acid (Scheme 1). Both elemental analyses and spectral data were used to elucidate the structures of the products **4a**–**f**. The IR spectra of compounds **4a**–**f** revealed in each case three absorption bands in the regions υ 3431–3211, 2218–2210, 1715–1709 cm^{-1} attributed to the NH_2, CN and C=O groups. The ^{1}HNMR spectrum of compound **4a** taken as a typical example of the products **4**, revealed two signals at δ = 6.93 (brs, 2H, NH_2) and 8.11 (s, 1H, pyridine-H5), in addition to the expected signals for the aryl and ester protons. Moreover, the mass spectra of product **4** showed in each case the respective molecular ion peak which is consistent with the assigned structure.



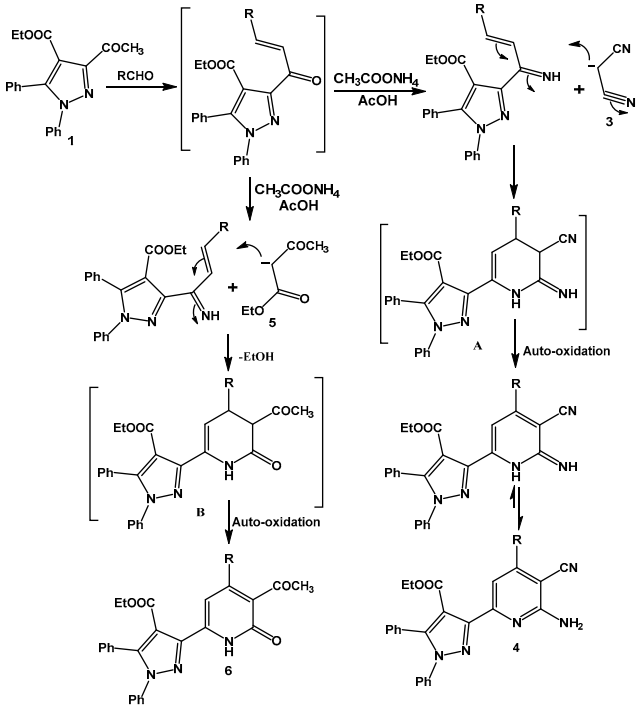
Scheme 1. Synthesis of pyridine derivatives **4a**–**f**.

In a similar manner, another series of pyrazolylpyridines **6a**–**f** was synthesized using ethyl acetoacetate in lieu of malononitrile. Thus, the reaction of 3-acetylpyrazole derivative **1** with the appropriate aldehyde **2**, ethyl acetoacetate **5**, and ammonium acetate in refluxing acetic acid afforded the corresponding products **6a**–**f** (Scheme 2). The structure **6** assigned for the obtained products was established by elemental analyses and spectral (IR, ^{1}HNMR, and MS) data. For example, the IR spectra of products **6a**–**f** revealed, in each case, four absorption bands assigned for the three carbonyl groups and the -NH group of the pyridinone ring (see Section 3). The ^{1}HNMR spectra displayed three singlet signals near δ 2.58, 9.80 and 7.79 ppm attributed to the acetyl, NH and pyridinyl-5H protons, in addition to the expected signals due to the ester and aryl protons (see Section 3).



Scheme 2. Synthesis of pyridine derivatives **6a–f**.

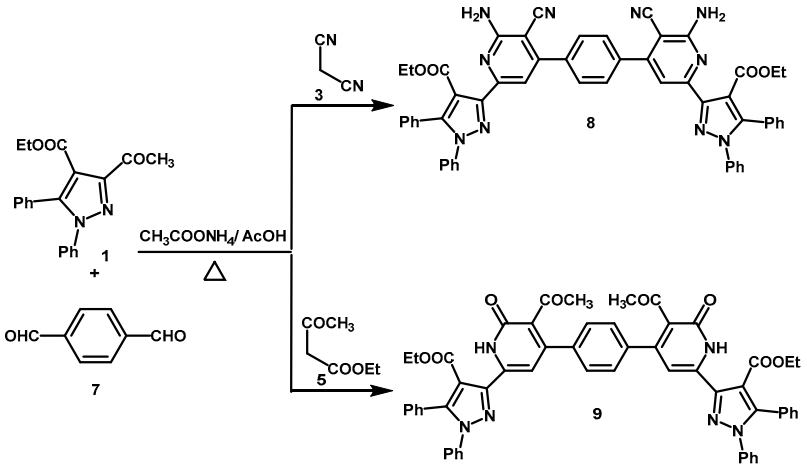
To account for the formation of products **4** and **6**, it was suggested that the reaction proceeds by condensation of the acetyl group of Compound **1** with the aldehyde to give the corresponding chalcone which reacts with ammonium acetate to give the imino derivative, followed by tandem Michael addition of the active methylene group of **3** (or **5**) to afford the non-isolable tetrahydropyridine intermediates **A** (or **B**). The latter undergo in situ auto-oxidation (followed by tautomerization in case of **A**) and formation of the final products **4** (or **6**) (Scheme 3).



Scheme 3. Mechanism of the synthesis of pyridine derivatives **4a–f** and **6a–f**.

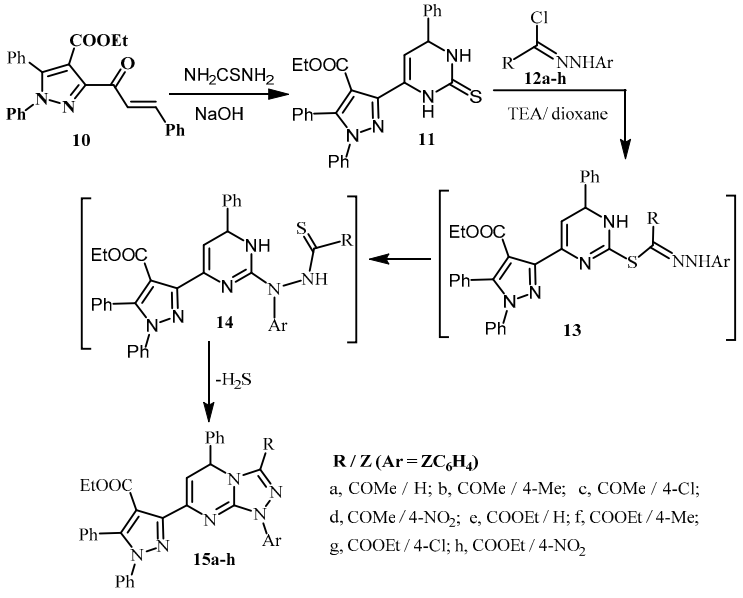
Our study was extended to prepare another new bipyridine derivatives including the pyrazole moiety via multi-component reaction. Thus, the reaction of 3-acetylpyrazole derivative **1** with terephthaldehyde **7**, malononitrile **3**, and ammonium acetate in acetic acid under reflux furnished the bipyridine derivative **8** (Scheme 4).

Similarly, the reaction of compound **1** with terephthaldehyde, ethyl acetoacetate **5**, and ammonium acetate in acetic acid under reflux gave the respective bipyridinone **9** (Scheme 4). The structure of products **8** and **9** were confirmed by elemental analyses and spectral data (IR, ^{1}HNMR, and MS) (see Section 3).



Scheme 4. Synthesis of bipyridine derivatives **8** and **9**.

On the other hand, chalcone **10**, prepared by the reaction of **1** with benzaldehyde in ethanol containing catalytic amounts of NaOH [54], was used for preparation of 6-(pyrazol-3-yl) pyrimidine-2-thione derivative **11** via its reaction with thiourea in ethanol containing a catalytic amount of sodium hydroxide [54]. Reaction of the latter compound **11** with a number of hydrazonoyl chlorides **12a–h** [55] in dioxane in the presence of triethylamine afforded the respective products **15a–h** through the non-isolated intermediates **13** and **14** (Scheme 5). The structure assigned for the products **15** was established via microanalytical and spectral data (see Section 3). For example, the IR spectra of product **15** revealed the absence of the pyrimidinyl-NH groups, and instead showed two absorption bands near υ 1706 and 1649 cm^{-1} assigned for the two carbonyl groups. Additionally, ^{1}HNMR spectra of product **15** showed the absence of the signals attributed to the pyrimidinyl-NH protons and, instead, revealed the signals assigned for the acetyl protons (for **15a–d**) or the ethoxycarbonyl protons (for **15e–h**), in addition to the characteristic signals due to the ester and aromatic protons (see Section 3). The mass spectra of product **15** showed, in each case, the respective molecular ion peak, which is consistent with the assigned structure.

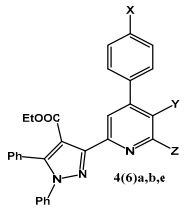


Scheme 5. Synthesis of 1,2,4-triazolo[4,3-*a*]pyrimidines **15a–h**.

2.2. Antitumor Activity

The cytotoxicity of the synthesized pyridines **4a**,**b**,**e** and **6a**,**b**,**e** was evaluated against the human liver carcinoma cell line (HepG2-1) using doxorubicin as a reference drug (IC_{50} value of doxorubicin = 0.08 ± 0.07 nM) and MTT assay. The data generated were used to plot a dose response curve of which the concentration of the tested compounds required to kill 50% of cell population (IC_{50}) was determined. Cytotoxic activity was expressed as the mean IC_{50} of three independent experiments. The results are depicted in Table 1 and Figure 1.

Table 1. IC_{50} values of tested compounds **4** and **6** ± standard deviation against HEPG2-1.

Compound No.	X	Y	Z	IC_{50} (nM)	General Structure
Doxorubicin	-	-	-	0.08 ± 0.07	
4a	H	CN	NH_2	9.7 ± 0.85	
4b	Me	CN	NH_2	1.9 ± 0.16	
4e	Cl	CN	NH_2	17.2 ± 0.83	
6a	H	MeCO	OH	12.3 ± 0.37	
6b	Me	MeCO	OH	2.4 ± 0.29	
6e	Cl	MeCO	OH	22.3 ± 0.36	

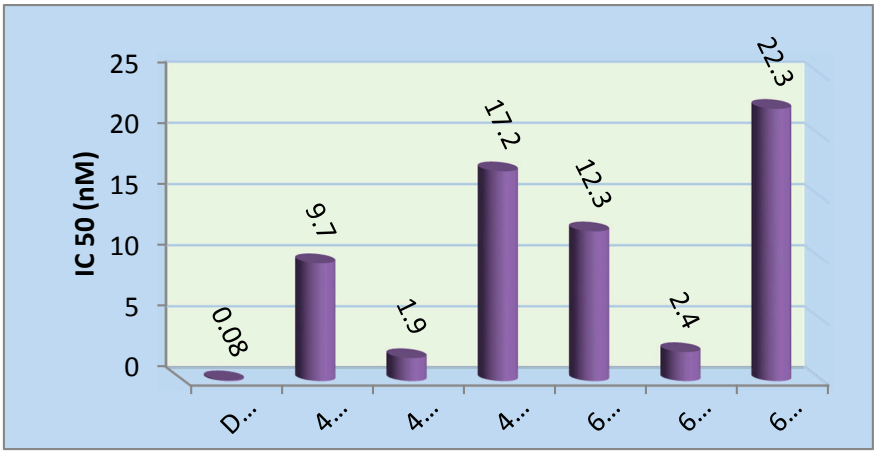


Figure 1. Cytotoxic activities of tested compounds against HEPG2-1.

The results revealed that the descending order of the antitumor activity of the tested compounds against HEPG2-1cell line is as follow: **4b** > **6b** > **4a** > **6a** > **4e** > **6e**.

The pyridine derivatives **4b** and **6b** (IC_{50} = 1.9 ± 0.16 and 2.4 ± 0.29 nM, respectively) have promising antitumor activity against HEPG2-1. On the other hand, pyridine derivatives **4e** and **6e** have poor inhibitory activity (IC_{50} > 17 nM) compared with doxorubicin which used as reference drug.

Structural Activity Relationship SAR

Examination of the SAR led to the following conclusions:

The activity of the synthesized compounds **4** and **6** against hepatocellular carcinoma depends on the structural skeleton and electronic environment of the molecules. For example, the activity of the tested compounds **4a**,**b**,**e** and **6a**,**b**,**e** were found to be highly related to their structures since replacement of electron-donating groups in the two aryl groups in compounds **4b** and **6b** with electron-withdrawing groups in compounds **4e** and **6e** dramatically decreases their cytotoxicity against HEPG2-1. On the other hand, the cytotoxicity of compounds **4a** and **6a** whose structures contain two phenyl groups (no substituent), is intermediate between the highly-potent and the weakly-potent compounds (See Table 1).

3. Experimental

3.1. Chemistry

Melting points were measured on an Electrothermal IA 9000 series (Bibby Sci. Lim. Stone, Staffordshire, UK) digital melting point apparatus. The IR spectra were recorded in potassium bromide discs on a Pye Unicam SP 3300 (Cambridge, UK) and a Shimadzu FT IR 8101 PC infrared (Shimadzu, Tokyo, Japan) spectrophotometer. ^{1}H-NMR spectra were recorded in deuterated dimethyl sulfoxide (DMSO-d_6) using a Varian Gemini 300 NMR spectrometer (Varian, Inc., Karlsruhe, Germany). Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer (Tokyo, Japan) at 70 eV. Elemental analysis was carried out at the Microanalytical Centre of Cairo University, Giza, Egypt. All reactions were followed by TLC (Silica gel, Merck, Darmstadt, Germany).

3.1.1. Synthesis of Tetra-Substituted Pyridine Derivatives (**4a**–**f** and **6a**–**f**)

General procedure: A mixture of ethyl 3-acetyl-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (**1**) (0.334 g, 1 mmol), the appropriate aldehyde **2a**–**f** (1 mmol) and malononitrile (**3**), or ethyl acetoacetate (**5**) (1 mmol) in glacial acetic acid (20 mL) containing ammonium acetate (0.616 g, 8 mmol) was refluxed for 6–8 h (monitored by TLC). After complete reaction, the mixture was cooled and the precipitated products were filtered, washed with water, dried, and crystallized from ethanol to give the pyridine derivatives **4a**–**f** and **6a**–**f**, respectively**.** Compounds **4a**–**f** and **6a**–**f** together with their physical and spectral data are listed below:

Ethyl 3-(6-amino-5-cyano-4-phenylpyridin-2-yl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (**4a**). Brown solid, (70% yield), mp 169–171 °C; IR (KBr) ν_{max} 3364, 3208 (NH_2), 2218 (CN), 1715 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.02 (t, *J* = 7.2 Hz, 3H, CH_3), 4.13 (q, *J* = 7.2 Hz, 2H, CH_2), 6.93 (s, br, 2H, NH_2), 7.18–7.90 (m, 15H, Ar-H), 8.11 (s, 1H, Pyridine-H5); MS *m*/*z* (%) 485 (M$^+$, 14), 322 (47), 252 (29), 167 (38), 77 (52), 43 (100). Anal. Calcd. for $C_{30}H_{23}N_5O_2$ (485.55): C, 74.21; H, 4.77; N, 14.42. Found: C, 74.05; H, 4.52; N, 14.26%.

Ethyl 3-(6-amino-5-cyano-4-(p-tolyl)pyridin-2-yl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (**4b**). Brown solid, (72% yield), mp 180–182 °C; IR (KBr) ν_{max} 3379, 3211 (NH_2), 2210 (CN), 1712 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.01 (t, *J* = 7.2 Hz, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.12 (q, *J* = 7.2 Hz, 2H, CH_2), 6.92 (s, br, 2H, NH_2), 7.14–7.94 (m, 14H, Ar-H), 8.15 (s, 1H, Pyridine-H5); MS *m*/*z* (%) 499 (M$^+$, 15), 468 (32), 364 (39), 209 (42), 104 (38), 78 (72), 43 (100). Anal. Calcd. for $C_{31}H_{25}N_5O_2$ (499.57): C, 74.53; H, 5.04; N, 14.02. Found: C, 74.37; H, 5.00; N, 13.85%.

Ethyl 3-(6-amino-5-cyano-4-(4-methoxyphenyl)pyridin-2-yl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (**4c**). Pale green solid, (68% yield), mp 154–156 °C; IR (KBr) ν_{max} 3367, 3219 (NH_2), 2210 (CN), 1714 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.02 (t, *J* = 7.2 Hz, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.15 (q, *J* = 7.2 Hz, 2H, CH_2), 6.93 (s, br, 2H, NH_2), 7.18–7.80 (m, 14H, Ar-H), 8.12 (s, 1H, Pyridine-H5); MS *m*/*z* (%) 515 (M$^+$, 9), 452 (42), 316 (100), 234 (51), 182 (37), 118 (50), 76 (66). Anal. Calcd. for $C_{31}H_{25}N_5O_3$ (515.57): C, 72.22; H, 4.89; N, 13.58. Found: C, 72.01; H, 4.77; N, 13.30%.

Ethyl 3-(6-amino-5-cyano-4-(4-(dimethylamino)phenyl)pyridin-2-yl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (**4d**). Dark yellow solid, (73% yield), mp 150–152 °C; IR (KBr) ν_{max} 3431, 3212 (NH_2), 2210 (CN), 1709 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.01 (t, *J* = 7.2 Hz, 3H, CH_3), 2.97 (s, 6H, $2CH_3$), 4.11 (q, *J* = 7.2 Hz, 2H, CH_2), 6.82 (s, br, 2H, NH_2), 7.14–7.82 (m, 14H, Ar-H), 8.10 (s, 1H, Pyridine-H5); MS *m*/*z* (%) 528 (M$^+$, 14), 416 (80), 212 (100), 170 (27), 105 (48), 76 (63). Anal. Calcd. for $C_{32}H_{28}N_6O_2$ (528.62): C, 72.71; H, 5.34; N, 15.90. Found: C, 72.59; H, 5.30; N, 15.73%.

Ethyl 3-(6-amino-4-(4-chlorophenyl)-5-cyanopyridin-2-yl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (**4e**). Dark yellow solid, (76% yield), mp 181–183 °C; IR (KBr) ν_{max} 3362, 3218 (NH_2), 2213 (CN), 1712 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.02 (t, *J* = 7.2 Hz, 3H, CH_3), 4.14 (q, *J* = 7.2 Hz, 2H, CH_2), 6.98 (s, br, 2H, NH_2), 7.17–7.84 (m, 14H, Ar-H), 8.17 (s, 1H, Pyridine-H5); MS *m*/*z* (%) 521 (M$^+$, 23), 519 (M$^+$, 8), 397 (32), 316

(60), 191 (55), 127 (51), 85 (47), 57 (100). Anal. Calcd. for $C_{30}H_{22}ClN_5O_2$ (519.99): C, 69.30; H, 4.26; N, 13.47. Found: C, 69.16; H, 4.18; N, 13.28%.

Ethyl 3-(6-amino-5-cyano-4-(2,4-dichlorophenyl)pyridin-2-yl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (**4f**). Yellow solid, (75% yield), mp 197–199 °C; IR (KBr) ν_{max} 3367, 3215 (NH_2), 2214 (CN), 1714 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.04 (t, J = 7.2 Hz, 3H, CH_3), 4.15 (q, J = 7.2 Hz, 2H, CH_2), 7.06 (s, br, 2H, NH_2), 7.28–7.85 (m, 13H, Ar-H), 8.14 (s, 1H, Pyridine-H5); MS m/z (%) 554 (M^+, 100), 316 (77), 281 (41), 193 (71), 105 (33), 58 (72). Anal. Calcd. for $C_{30}H_{21}Cl_2N_5O_2$ (554.43): C, 64.99; H, 3.82; N, 12.63. Found: C, 64.80; H, 3.61; N, 12.44%.

Ethyl 3-(5-acetyl-6-oxo-4-phenyl-1,6-dihydropyridin-2-yl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (**6a**). Brown solid, (68% yield), mp 186–188 °C; IR (KBr) ν_{max} 3367 (NH), 1722, 1690, 1657 (3C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.03 (t, J = 7.2 Hz, 3H, CH_3), 2.58 (s, 3H, CH_3), 4.12 (q, J = 7.2 Hz, 2H, CH_2), 7.24–7.49 (m, 15H, Ar-H),), 7.77 (s, 1H, Pyridine-H5), 9.63 (s, br, 1H, NH); MS m/z (%) 503 (M^+, 48), 458 (27), 334 (52), 232 (46), 99 (54), 57 (68), 43 (100). Anal. Calcd. for $C_{31}H_{25}N_3O_4$ (503.56): C, 73.94; H, 5.00; N, 8.34. Found: C, 73.73; H, 4.86; N, 8.17%.

Ethyl 3-(5-acetyl-6-oxo-4-(p-tolyl)-1,6-dihydropyridin-2-yl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (**6b**). Brown solid, (66% yield), mp 134–136 °C; IR (KBr) ν_{max} 3409 (NH), 1718, 1681, 1662 (3C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.02 (t, J = 7.2 Hz, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 4.11 (q, J = 7.2 Hz, 2H, CH_2), 7.19–7.49 (m, 14H, Ar-H),), 7.79 (s, 1H, Pyridine-H5), 9.81 (s, br, 1H, NH); MS m/z (%) 517(M^+, 23), 385 (33), 294 (38), 147 (50), 120 (100), 76 (62). Anal. Calcd. for $C_{32}H_{27}N_3O_4$ (517.59): C, 74.26; H, 5.26; N, 8.12. Found: C, 74.20; H, 5.14; N, 8.03%.

Ethyl 3-(5-acetyl-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridin-2-yl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (**6c**). Pale brown solid, (67% yield), mp 141–143 °C; IR (KBr) ν_{max} 3423 (NH), 1715, 1687, 1660 (3C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.00 (t, J = 7.2 Hz, 3H, CH_3), 2.57 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.01 (q, J = 7.2 Hz, 2H, CH_2), 7.16–7.54 (m, 14H, Ar-H),), 7.74 (s, 1H, Pyridine-H5), 9.80 (s, br, 1H, NH); MS m/z (%) 533 (M^+, 14), 423 (37), 313 (51), 279 (100), 105 (36), 76 (43). Anal. Calcd. for $C_{32}H_{27}N_3O_5$ (533.58): C, 72.03; H, 5.10; N, 7.88. Found: C, 71.85; H, 5.02; N, 7.63%.

Ethyl 3-(5-acetyl-4-(4-(dimethylamino)phenyl)-6-oxo-1,6-dihydropyridin-2-yl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (**6d**). Brown solid, (69% yield), mp 141–143 °C; IR (KBr) ν_{max} 3425 (NH), 1721, 1682, 1657 (3C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.00 (t, J = 7.2 Hz, 3H, CH_3), 2.58 (s, 3H, CH_3), 2.99 (s, 6H, $2CH_3$), 4.11 (q, J = 7.2 Hz, 2H, CH_2), 6.78–7.39 (m, 14H, Ar-H), 7.72 (s, 1H, Pyridine-H5), 9.73 (s, br, 1H, NH); MS m/z (%) 546 (M^+, 14), 406 (36), 349 (55), 241 (49), 121 (36), 76 (30), 43 (100). Anal. Calcd. for $C_{33}H_{30}N_4O_4$ (546.63): C, 72.51; H, 5.53; N, 10.25. Found: C, 72.39; H, 5.38; N, 10.02%.

Ethyl 3-(5-acetyl-4-(4-chlorophenyl)-6-oxo-1,6-dihydropyridin-2-yl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (**6e**). Brown solid, (68% yield), mp 170–172 °C; IR (KBr) ν_{max} 3366 (NH), 1720, 1680, 1663 (3C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.06 (t, J = 7.2 Hz, 3H, CH_3), 2.58 (s, 3H, CH_3), 4.14 (q, J = 7.2 Hz, 2H, CH_2), 7.24–7.59 (m, 14H, Ar-H), 7.78 (s, 1H, Pyridine-H5), 10.06 (s, br, 1H, NH); MS m/z (%) 540 (M^+ + 2, 1), 538 (M^+, 3), 368 (53), 214 (100), 120 (55), 40 (79). Anal. Calcd. for $C_{31}H_{24}ClN_3O_4$ (538.00): C, 69.21; H, 4.50; N, 7.81. Found: C, 69.46; H, 4.35; N, 7.66%.

Ethyl 3-(5-acetyl-4-(2,4-dichlorophenyl)-6-oxo-1,6-dihydropyridin-2-yl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (**6f**). Brown solid, (69% yield), mp 197–199 °C; IR (KBr) ν_{max} 3414 (NH), 1720, 1683, 1659 (3C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.09 (t, J = 7.2 Hz, 3H, CH_3), 2.61 (s, 3H, CH_3), 4.15 (q, J = 7.2 Hz, 2H, CH_2), 7.26–7.52 (m, 13H, Ar-H), 7.76 (s, 1H, Pyridine-H5), 10.24 (s, br, 1H, NH); MS m/z (%) 572 (M^+, 12), 388 (64), 256 (44), 207 (67), 125 (50), 83 (42), 55 (100). Anal. Calcd. for $C_{31}H_{23}Cl_2N_3O_4$ (572.44): C, 65.04; H, 4.05; N, 7.34. Found: C, 65.24; H, 4.02; N, 7.16%.

3.1.2. Synthesis of Bipyridine Derivatives **8** and **9**

A mixture of 3-acetylpyrazole derivative **1** (0.668 g, 2 mmol), terephthalaldehyde **7** (0.134 g, 1 mmol), and malononitrile **3** or ethyl acetoacetate **5** (2 mmol) in acetic acid (30 mL) containing ammonium acetate (1.232 g, 16 mmol) was refluxed for 8 h. After cooling the reaction mixture it was poured into an ice-water mixture, the formed a precipitate that was collected by filtration, then crystallized from dioxane to give the bipyridine products **8** and **9**, respectively.

Diethyl 3,3′-(1,4-phenylenebis(6-amino-5-cyanopyridine-4,2-diyl))bis(1,5-diphenyl-1H-pyrazole-4-carboxylate) (**8**). Brown solid, (68% yield), mp 187–189 °C; IR (KBr) ν_{max} 3378, 3201 (NH_2), 2211 (CN), 1709 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.03 (t, *J* = 7.2 Hz, 6H, $2CH_3$), 4.14 (q, *J* = 7.2 Hz, 4H, $2CH_2$), 6.93 (s, br, 4H, $2NH_2$), 7.18–7.49 (m, 20H, Ar-H), 7.85 (s, 4H, Ar-H), 8.10 (s, 2H, 2Pyridine-H3); MS *m*/*z* (%) 892 (M^+, 39), 724 (48), 622 (63), 368 (39), 82 (60), 76 (57), 43 (100). Anal. Calcd. for $C_{54}H_{40}N_{10}O_4$ (892.98): C, 72.63; H, 4.52; N, 15.69. Found: C, 72.69; H, 4.36; N, 15.47%.

Diethyl 3,3′-(1,4-phenylenebis(5-acetyl-6-oxo-1,6-dihydropyridine-4,2-diyl))bis(1,5-diphenyl-1H-pyrazole-4-carboxylate) (**9**). Brown solid, (66% yield), mp 207–209 °C; IR (KBr) ν_{max} 3423 (NH), 1723, 1677, 1653 (3C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.11 (t, *J* = 7.2 Hz, 6H, $2CH_3$), 2.58 (s, 6H, $2CH_3$), 4.14 (q, *J* = 7.2 Hz, 4H, $2CH_2$), 7.24–7.48 (m, 20H, Ar-H),), 7.77 (s, 2H, 2Pyridine-H3), 7.81 (s, 4H, Ar-H), 10.06 (s, br, 2H, 2NH); MS *m*/*z* (%) 929 (M^+, 17), 776 (41), 509 (37), 386 (55), 267 (40), 148 (32), 77 (100), 43 (68). Anal. Calcd. for $C_{56}H_{44}N_6O_8$ (929.00): C, 72.40; H, 4.77; N, 9.05. Found: C, 72.17; H, 4.62; N, 9.01%.

3.1.3. Synthesis of 1,5-Diphenyl-1,5-dihydro-[1,2,4]triazolo[4,3-*a*]pyrimidine derivatives **15a**–**h**

General procedure: Triethylamine (0.14 mL, 1 mmol) was added to a mixture of equimolar amounts of thione **11** (0.480 g, 1 mmol) and the appropriate hydrazonoyl halides **12a**–**h** (1 mmol) in dioxane (20 mL) at room temperature. The reaction mixture was then refluxed for 10–15 h until all hydrogen sulfide gas stopped evolving. The solid that formed after concentration of the reaction mixture was filtered and crystallized from the proper solvent to give the products **15a**–**h**, respectively.

Ethyl 3-(3-acetyl-1,5-diphenyl-1,5-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (**15a**). Yellow solid, (74% yield), mp 233–235 °C (DMF); IR (KBr) ν_{max} 3026, 2956 (C-H), 1706, 1649 (2C=O), 1595 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.15 (t, *J* = 7.2 Hz, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.19 (q, *J* = 7.2 Hz, 2H, CH_2), 5.33 (d, *J* = 4 Hz, 1H, CH), 6.62 (d, *J* = 4Hz, 1H, CH), 7.03–7.80 (m, 20H, Ar-H); MS *m*/*z* (%) 606 (M^+, 5),406 (36), 287 (29), 247 (75), 194 (37), 92 (71), 65 (60), 43 (100). Anal. Calcd. for $C_{37}H_{30}N_6O_3$ (606.69): C, 73.25; H, 4.98; N, 13.85. Found: C, 73.07; H, 4.84; N, 13.67%.

Ethyl 3-(3-acetyl-5-phenyl-1-(p-tolyl)-1,5-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (**15b**). Yellow solid, (72% yield), mp 211–213 °C (DMF); IR (KBr) ν_{max} 3030, 2951 (C-H), 1697, 1642 (2C=O), 1597 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.04 (t, *J* = 7.2 Hz, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.16 (q, *J* = 7.2 Hz, 2H, CH_2), 5.32 (d, *J* = 4 Hz, 1H, CH), 6.61 (d, *J* = 4Hz, 1H, CH), 7.05–7.73 (m, 19H, Ar-H); MS *m*/*z* (%) 620 (M^+, 7), 498 (27), 390 (35), 285 (60), 105 (41), 77 (100), 43 (92). Anal. Calcd. for $C_{38}H_{32}N_6O_3$ (620.71): C, 73.53; H, 5.20; N, 13.54. Found: C, 73.39; H, 5.38; N, 13.36%.

Ethyl 3-(3-acetyl-1-(4-chlorophenyl)-5-phenyl-1,5-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (**15c**). Yellow solid, (74% yield), mp 242–244 °C (DMF/EtOH); IR (KBr) ν_{max} 3028, 2963 (C-H), 1707, 1641 (2C=O), 1597 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.02 (t, *J* = 7.2 Hz, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.15 (q, *J* = 7.2 Hz, 2H, CH_2), 5.36 (d, *J* = 4 Hz, 1H, CH), 6.69 (d, *J* = 4Hz, 1H, CH), 7.27–7.70 (m, 19H, Ar-H); MS *m*/*z* (%) 643 (M^+ + 2, 4), 641 (M^+, 13), 499 (57), 322 (39), 180 (28), 105 (35), 77 (100). Anal. Calcd. for $C_{37}H_{29}ClN_6O_3$ (641.13): C, 69.32; H, 4.56; N, 13.11. Found: C, 69.19; H, 4.51; N, 13.00%.

Ethyl 3-(3-acetyl-1-(4-nitrophenyl)-5-phenyl-1,5-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (**15d**). Yellow solid, (75% yield), mp 204–206 °C (EtOH); IR (KBr) ν_{max} 3031, 2950

(C-H), 1712, 1656 (2C=O), 1598 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.02 (t, *J* = 7.2 Hz, 3H, CH_3), 2.47 (s, 3H, CH_3), 4.15 (q, *J* = 7.2 Hz, 2H, CH_2), 5.39 (d, *J* = 4 Hz, 1H, CH), 6.72 (d, *J* = 4Hz, 1H, CH), 7.24–8.52 (m, 19H, Ar-H); MS *m*/*z* (%) 651 (M^+, 26), 484 (48), 400 (71), 252 (39), 179 (42), 105 (100), 57 (83). Anal. Calcd. for $C_{37}H_{29}N_7O_5$ (651.68): C, 68.19; H, 4.49; N, 15.05. Found: C, 68.04; H, 4.33; N, 14.92%.

Ethyl 7-(4-(ethoxycarbonyl)-1,5-diphenyl-1H-pyrazol-3-yl)-1,5-diphenyl-1,5-dihydro-[1,2,4]triazolo[4,3-a] pyrimidine-3-carboxylate (**15e**). Yellow solid, (72% yield), mp 180–182 °C (DMF/EtOH); IR (KBr) ν_{max} 3056, 2973 (C-H), 1713, 1679 (2C=O), 1596 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.04 (t, *J* = 7.2 Hz, 3H, CH_3), 1.26 (t, *J* = 7.6 Hz, 3H, CH_3), 4.14 (q, *J* = 7.2 Hz, 2H, CH_2), 4.26 (q, *J* = 7.6 Hz, 2H, CH_2), 5.46 (d, *J* = 4 Hz, 1H, CH), 6.47 (d, *J* = 4Hz, 1H, CH), 6.96–7.79 (m, 20H, Ar-H); MS *m*/*z* (%) 636 (M^+, 9), 394 (51), 283 (33), 235 (49), 194 (62), 83 (53), 57 (100). Anal. Calcd. for $C_{38}H_{32}N_6O_4$ (636.71): C, 71.68; H, 5.07; N, 13.20. Found: C, 71.62; H, 5.01; N, 13.03%.

Ethyl 7-(4-(ethoxycarbonyl)-1,5-diphenyl-1H-pyrazol-3-yl)-5-phenyl-1-(p-tolyl)-1,5-dihydro-[1,2,4]triazolo [4,3-a]pyrimidine-3-carboxylate (**15f**). Yellow solid, (73% yield), mp 172–174 °C (EtOH); IR (KBr) ν_{max} 3052, 2955 (C-H), 1710, 1699 (2C=O), 1595 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.02 (t, *J* = 7.2 Hz, 3H, CH_3), 1.23 (t, *J* = 7.6 Hz, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.10 (q, *J* = 7.2 Hz, 2H, CH_2), 4.26 (q, *J* = 7.6 Hz, 2H, CH_2), 5.39 (d, *J* = 4 Hz, 1H, CH), 6.45 (d, *J* = 4Hz, 1H, CH), 7.12–7.76 (m, 19H, Ar-H); MS *m*/*z* (%) 650 (M^+, 6), 439 (44), 361 (30), 244 (57), 104 (100), 91 (48), 43 (60). Anal. Calcd. for $C_{39}H_{34}N_6O_4$ (650.74): C, 71.98; H, 5.27; N, 12.91. Found: C, 71.75; H, 5.19; N, 12.74%.

Ethyl 1-(4-chlorophenyl)-7-(4-(ethoxycarbonyl)-1,5-diphenyl-1H-pyrazol-3-yl)-5-phenyl-1,5-dihydro-[1,2,4] triazolo[4,3-a]pyrimidine-3-carboxylate (**15g**). Yellow solid, (75% yield), mp 188–190 °C (DMF/EtOH); IR (KBr) ν_{max} 3037, 2966 (C-H), 1713, 1667 (2C=O), 1597 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.05 (t, *J* = 7.2 Hz, 3H, CH_3), 1.19 (t, *J* = 7.6 Hz, 3H, CH_3), 4.13 (q, *J* = 7.2 Hz, 2H, CH_2), 4.24 (q, *J* = 7.6 Hz, 2H, CH_2), 5.42 (d, *J* = 4 Hz, 1H, CH), 6.47 (d, *J* = 4Hz, 1H, CH), 7.25–7.79 (m, 19H, Ar-H); MS *m*/*z* (%) 673 (M^+ + 2, 11), 671 (M^+, 36), 387 (100), 324 (68), 278 (50), 105 (42), 78 (83). Anal. Calcd. for $C_{38}H_{31}ClN_6O_4$ (671.15): C, 68.00; H, 4.66; N, 12.52. Found: C, 68.25; H, 4.40; N, 12.46%.

Ethyl 7-(4-(ethoxycarbonyl)-1,5-diphenyl-1H-pyrazol-3-yl)-1-(4-nitrophenyl)-5-phenyl-1,5-dihydro-[1,2,4] triazolo[4,3-a]pyrimidine-3-carboxylate (**15h**). Brown solid, (71% yield), mp 206–208 °C (EtOH); IR (KBr) ν_{max} 3030, 2948 (C-H), 1713, 1644 (2C=O), 1593 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.07 (t, *J* = 7.2 Hz, 3H, CH_3), 1.25 (t, *J* = 7.6 Hz, 3H, CH_3), 4.12 (q, *J* = 7.2 Hz, 2H, CH_2), 4.27 (q, *J* = 7.6 Hz, 2H, CH_2), 5.46 (d, *J* = 4 Hz, 1H, CH), 6.49 (d, *J* = 4Hz, 1H, CH), 7.25–8.42 (m, 19H, Ar-H); MS *m*/*z* (%) 681 (M^+, 31), 577 (73), 390 (66), 327 (95), 115 (100), 83 (52). Anal. Calcd. for $C_{38}H_{31}N_7O_6$ (681.71): C, 66.95; H, 4.58; N, 14.38. Found: C, 66.77; H, 4.42; N, 14.23%.

3.2. Cytotoxic 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 [56].

4. Conclusions

Two series of functionalized pyrazolyl-pyridines were prepared by multi-component reaction of 3-acetylpyrazole derivative with the appropriate aldehyde, malononitrile (or ethyl acetoacetate) in acetic acid in the presence of excess ammonium acetate. The mechanism of formation of the novel products was also discussed. Additionally, two novel bipyridine derivatives were synthesized by the above described reaction and under the same reaction conditions using terephthaldehyde in lieu of benzaldeyde derivatives. Another series of 1,2,4-triazole[4,3-*a*]pyrimidines, including a pyrazole moiety, was prepared by the reaction of a pyrazolylpyrimidine-2-thione derivative with a variety of hydrazonoyl chlorides under reflux in dioxane in the presence of triethylamine. The assigned structure for the products was elucidated based on elemental analyses and spectral data (IR, ^{1}HNMR, MS).

Moreover, the novel pyrazolyl-pyridines were tested for their reactivity as antitumor agents and the results obtained revealed high potency of some of them against HEPG2-1 compared with doxorubicin used as the reference drug.

Acknowledgments: The authors extend their sincere appreciation to the Deanship of Scientific Research at the King Saud University for its funding this Prolific Research group (PRG-1437-29).

Author Contributions: Magda A. Abdallah, Sobhi M. Gomha, and Ikhlass M. Abbas designed research; Mariam S. H. Kazem, Seham S. Alterary and Yahia N. Mabkhot performed the research, analyzed the data, wrote the paper, and approved the final manuscript.

Conflicts of Interest: The authors declare no conflict of interests.

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