Synthesis of Different Bioactive Polyfunctionally substituted Fused Azole Derivatives and Studying Their Chemical and Photochemical Reactivity

A Thesis Presented by

Ahmed Ali El-Sayed Ali

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تشييد و دراسة النشاط الكيميائى و الضوء كيميائى للآزولات المختلفة متعددة المجموعات الفعالة النشطة بيولوجيا و مشتقاتهم الملتحمة

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أحمد على السيد على

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عنـــــــــوان الرســـــــالـــــــة

"تشييد و دراسة النشاط الكيميائى و الضوء كيميائى للآزولات المختلفة متعددة المجموعات الفعالة النشطة بيولوجيا و مشتقاتهم الملتحمة"

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Facile synthesis of fused nitrogen containing heterocycles as anticancer agents

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Abstract

One pot three components reaction of the pyrazol-5-one **1** with different aromatic aldehydes and malononitrile was carried out in the presence of Ammonium acetate to furnish the corresponding pyrazolopyridines **2a-g**. Carrying out the same reactions in the presence of piperydine yielded the pyranopyrazoles **4a-c**. Facile formation of the pyrazolopyridopyrimidines **5a-c** and **6a,b** was occurred via boiling of the adducts **2a,b,e** in Formic acid or chloroacetic acid. Treatment of adduct **2a** with triethyl orthoformat yielded the pyrazolopyrrolopyridine derivative **7**. Compound **2a** was also reacted with DMFDMA to form the corresponding adduct **8**. Pyrazol-5-one **1** underwent three different component reactions using a variety of active methylene reagents. The utility ethylbenzoyl acetate and benzoyl acetonitrile yielded the products **9a-e** and **10** respectively. Using of ethylacetoacetate and ethyl cyano acetate reagents led to the formation of adducts **11** and **12a-c**, respectively. On the other hand, diethylmalonate and acetylacetone produced the corresponding products **13** and **14**. The bioactivity of the compounds (**2c, 2e, 2d, 4a, 4b, 9c, 9e, 11, 12b, 12c**) as antitumor agents against liver carcinoma was examined.

Keywords: Pyrazoles, Pyridopyrazoles, Pyrazolopyridopyrimidine, Pyranopyrazoles, Antihepatocellular Carcinoma (HCC).

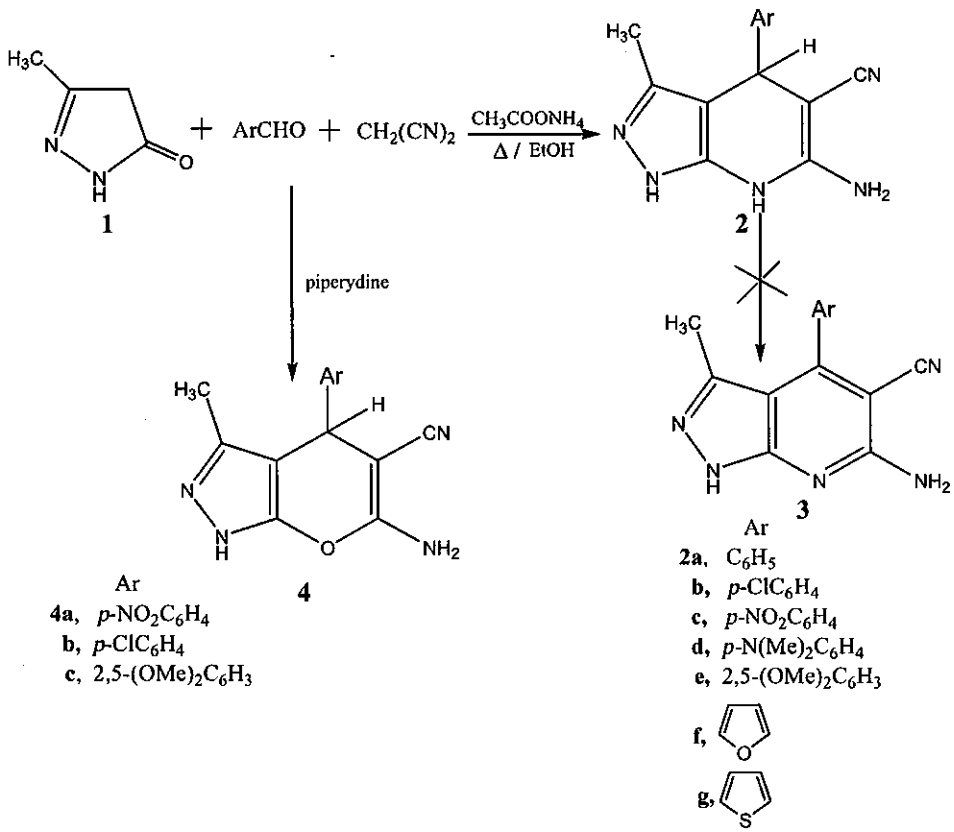
Introduction

Multicomponent reactions (MCRs) by virtue of their ease of execution and generally high yields of products have attracted considerable attention from the point of view organic synthesis[1-3]. Over the last few years, there has been a large development in the three-component reactions and great efforts to afford new and effective (MCRs)[4-6]. In addition, fused heterocycles systems like pyrazolopyridines, pyranopyrazoles and pyrazolopyrido - pyrimidines present interesting biological properties such as anticancer[7], fungicidal[8], bactericidal[9] and vasodilatory activities[10]. A considerable attention has been focused on the development of new methodologies to synthesize many kinds of these Nitrogen containing heterocycles[11,12]. Many of the previous multicomponent reactions for the

synthesis of pyrazolopyridopyrimidines were based on utilizing amino pyrazole or amino pyrimidine as starting materials with different catalysts[5,13]. Aiming to synthesize these important candidates with low cost starting materials and facile tools, we have prepared different fused derivatives *via* simple pyrazole (5-methyl-2,4-dihydro-3H-pyrazol-3-one) as starting material. Facile conversion of the pyrazolopyridines into pyrazolopyridopyrimidines has been reported. As for the multifocal nature of liver Carcinoma, the chemotherapy is the main choice for the liver cancer patient's treatment, so developing new therapeutic agents becomes an urgent need for liver cancer patients. Encouraged by this information and continuation to our previous work[14,15]. We have prepared in this report the formation of different derivatives of Nitrogen containing heterocycles and have evaluated their efficiency as an antihepatocellular *Carcinoma*.

Results and Discussion

A mixture of 5-methyl-2,4-dihydro-3H-pyrazol-3-one **1**, malononitrile and different aromatic aldehydes was heated in Ethanol containing Ammonium acetate under reflux to afford the corresponding 6-aminopyrazolo[3,4-b]pyridine-5-carbonitrile systems **2**. The reaction proceeded via the formation of the benzylidene adducts at first followed by the addition of malononitrile and cyclization *via* loss of water. It was explained previously that the formed adduct may undergo aromatization *via* loss of Hydrogen to produce structure **3**[16]. The ^{1}H-NMR spectrum of the all newly synthesized adducts revealed the presence of Hydrogen proton at C_4 at δ 4.6 ppm. This excluded structure **3** and supported the formation of the adduct **2**. Further more the X-ray of compound **2** was in accordance with the suggested structure (Scheme 1).



(Scheme 1)

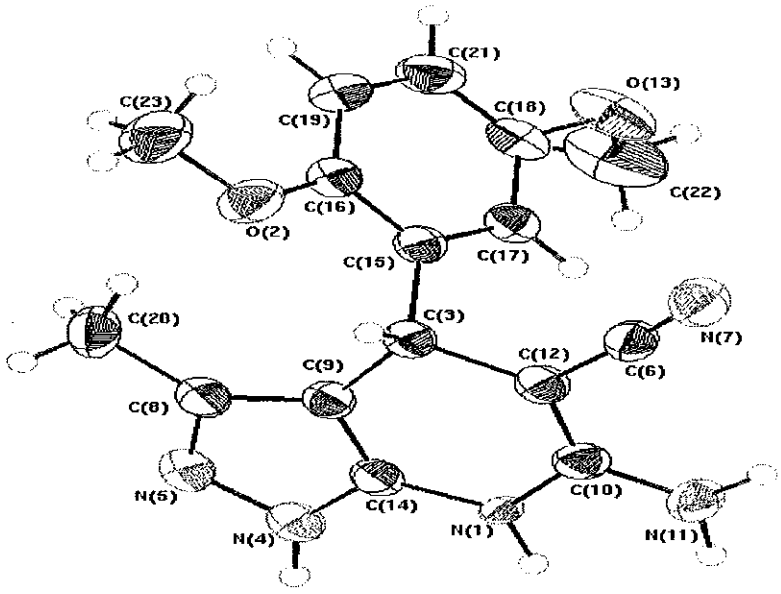


Figure 1

Molecular structure of the product **2** in the crystal; the crystallographic numbering doesn't represent the systematic numbering. Intermolecular bond lengths and bond angles. Selected bond lengths [A°] and bond angles [°] limits use covalent radii + 0.020 A°.

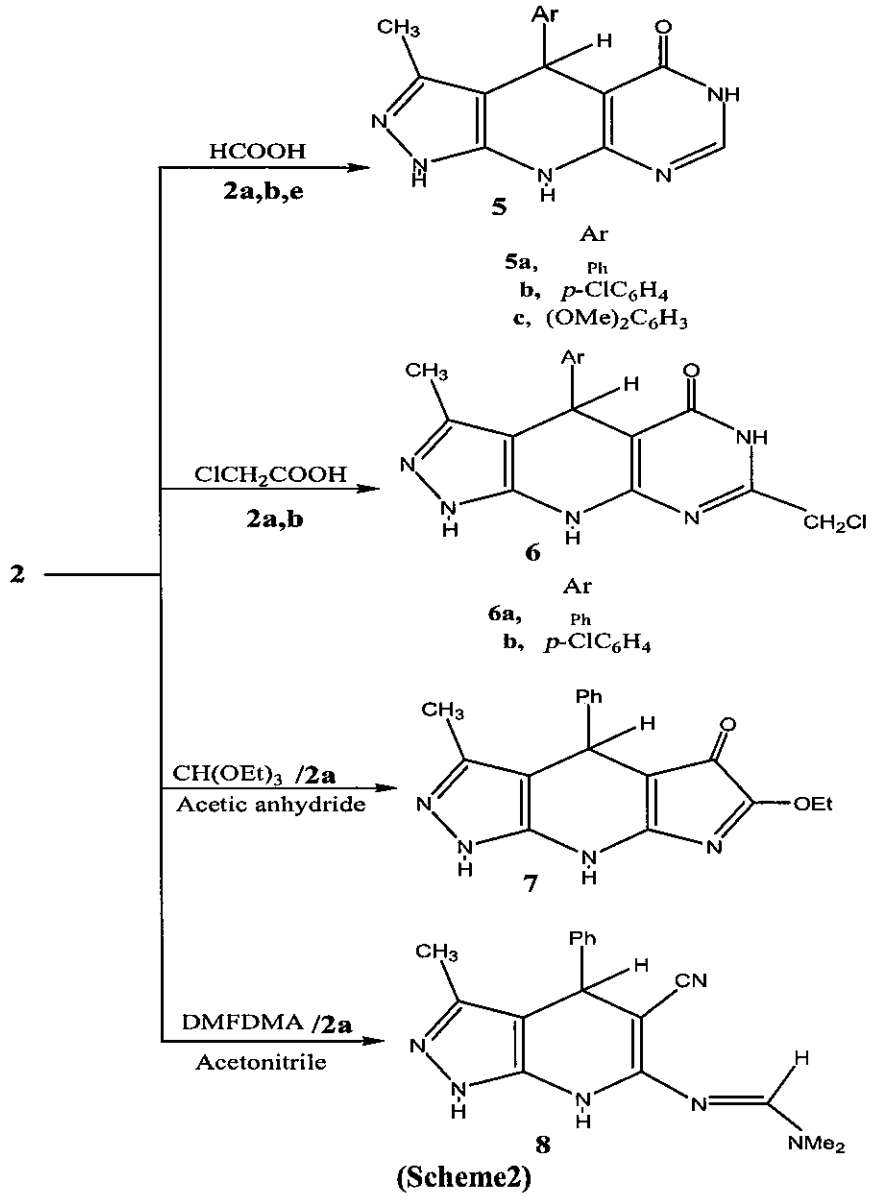
Bond length

[N(1)-C(10) 1.379(4)]; [N(1)-C(14) 1.377(4)]; [O(2)-C(16) 1.361(4)]; [O(2)-C(23)1.427(4)];[C(3)-C(9)1.504(4)];[C(3)-C(12)1.531(4)];[C(3)-C(15) 1.537(5)]; [N(4)-N(5) 1.367(4)]; [N(4)-C(14) 1.308(4)]; [N(5)-C(8) 1.344(4)]; [C(6)-N(7) 1.153(4)]; [C(6)-C(12)1.406(4)]; [C(8)-C(9)1.385(4)]; [C(8)-C(20) 1.499(5)]; [C(9)-C(14) 1.383(4)]; [C(10)-N(11)1.328(4)]; [C(10)-C(12) 1.367(4)]; [O(13) - C(18) 1.388(4)]; [O(13)-C(22) 1.363(5)]; [C(15)-C(16) 1.406(4)]; [C(15) - C(17) 1.388(4)]; [C(16)-C(19)1.387(5)];[C(17)-C(18)1.370(5)]; [C(18)-C(21) 1.378(5)]; [C(19)-C(21) 1.377(5)]; [N(1)- H(1) 0.960(2)]; [C(3)- H(3) 0.960(3)].

Bond Angles

[C(10)-N(1)-C(14) 115.8(2)]; [C(16)-O(2)-C(23) 118.2(3)]; [C(9)-C(3)-C(12) 106.8(2)]; [C(9)-C(3)-C(15) 112.2(3)]; [C(12)-C(3)-C(15) 112.6(3)]; [N(5)-N(4)-C(14) 102.2(3)]; [N(4)-N(5)-C(8) 112.9(3)]; [N(7)-C(6)-C(12) 177.1(3)]; [N(5)-C(8)-C(9) 106.7(3)]; [N(5)-C(8)-C(20) 120.9(3)]; [C(9)-C(8)-C(20)132.4(3)]; [C(3)-C(9)-C(8)134.2(3)];[C(3)-C(9)-C(14)122.8(3)];[C(8)-C(9)-C(14)103.0(3)]; [N(1)-C(10)-N(11) 109.7(3)]; [N(1)-C(10)-C(12) 122.5(3)]; [N(11)-C(10)-C(12) 127.8(3)]; [C(3)-C(12)-C(6) 116.4(3)]; [C(3)-C(12)-C(10) 126.0(3)];[C(6)-C(12)-C(10)117.6(3)]; [C(18)-O(13)-C(22)118.1(3)]; [N(1)-C(14)-N(4) 118.8(3)]; [N(1)- C(14)-C(9) 126.0(3)]; [N(4)-C(14)-C(9) 115.3(3)]; [C(3)-C(15)-C(16) 119.4(3)];[C(3)-C(15)-C(17)122.2(3)];[C(16)-C(15)-C(17) 118.4(3)]; [O(2)-C(16)-C(15) 116.2(3)]; [O(2)-C(16)-C(19) 123.9(3)]; [C(15)-C(16)-C(19) 119.9(3)]; [C(15)-C(17)-C(18) 121.6(3)]; [O(13)-C(18)-C(17) 122.5(3)]; [O(13)-C(18)-C(21) 118.0(3)]; [C(17)-C(18)-C(21) 119.4(3)]; [C(16)-C(19)-C(21) 119.9(3)]; [C(18)-C(21)-C(19) 120.8(3)]; [C(10)-N(1)-H(1) 119.7(2)]; [C(14)-N(1)-H(1)124.6(2)]; [C(9)-C(3)- H(3) 109.4(3)]; [C(12)-C(3)-H(3) 109.3(3)]; [C(15)-C(3)-H(3)106.6(3)].

Carrying out the previous reaction in the presence of piperydine led to the formation of the adducts 6-aminopyrano[2,3-c]pyrazole-5-carbonitrile **4a-c** (Scheme 1). The ^{1}H-NMR spectrum showed the disappearance of the characteristic signal of the NH group of pyridine ring. All the microanalytical and other spectroscopic data were in accordance with the pyranopyrazole structure **4** (c.f. the experimental section).

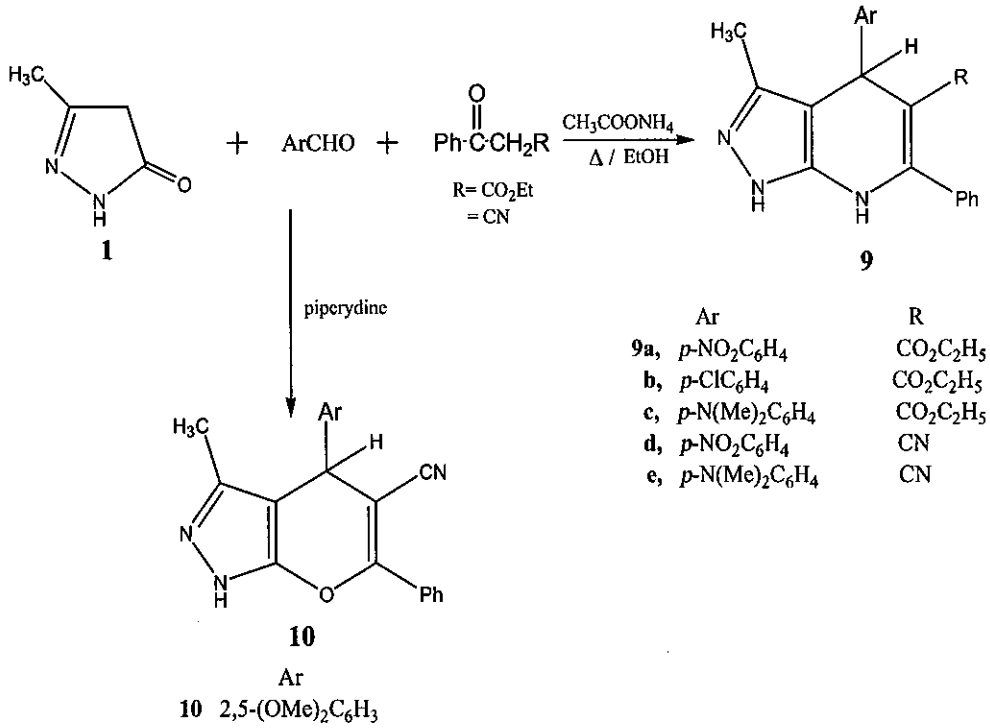


(Scheme2)

The pyrazolopyridopyrimidines **5a-c** and **6a,b** were formed easily *via* boiling of the pyrazolopyridines **2a,b,e** in organic acids e.g. Formic acid or Chloroacetic acid . It is believed that the nitrile group was converted at first into that amide group that was followed by cyclization. Dimorth rearrangement took place to furnish the final fused pyrazolopyrido-pyrimidine[17-18]. Treatment of the pyrazolopyridine **2a** with triethylor-thoformate in Acetic anhydride yielded the corresponding pyrazolopyrro-lopyridine adducts **7** (Scheme 2). The IR spectrum revealed the pyrrole carbonyl band at ν 1738 cm^{-1} and the ^{1}H-NMR showed the characteristic ethyl protons signals at δ 1.23 (t, 3H, CH_3); 4.30 (q, 2H, CH_2) ppm., besides the other signals that elucidate the suggested structure (c.f. the experimental section). In addition,

compound **2a** was allowed to react with DMFDMA in acetonitrile to form the open structure **8** (Scheme 2). ^{1}H-NMR confirmed the structure by revealing the signal corresponding to the sp^2 CH at δ 8.32 ppm and the singlet signal of the Me_2N at δ 3.13 ppm. The IR spectrum proved the presence of CN group band at ν 2188 cm^{-1} that supported the suggested structure (c.f. the experimental section).

In order to synthesize different types of pyrazolopyridine and pyranopy-razole; different active methylene reagents were utilized. The use of ethylbenzoylacetate and benzoylacetonitrile under the same previous conditions furnished the corresponding 6-phenylpyrazolo[3,4-b]pyridine-5-carboxylate **9** and 6-phenyl-pyrano[2,3-c]pyrazole-5-carbonitrile **10** (Scheme 3). The ^{1}H-NMR of **9a** taken as an example revealed the presence of a triplet at δ 1.03 ppm and quartet at δ 3.56 ppm characteristic of the ethyl ester protons. In addition, the appearance of the other signals characteristic of the aromatic protons at δ 7.37-8.41 ppm and NH exchangeable singlet signal at δ 12.15 ppm were present. On the other hand the IR spectrum showed the carbonyl ester band at ν 1728 cm^{-1} and the characteristic band of the CN group present in **9e** at ν 2221 cm^{-1} (c.f. the experimental section).



	Ar	R
9a,	*p*-$NO_2C_6H_4$	$CO_2C_2H_5$
b,	*p*-ClC_6H_4	$CO_2C_2H_5$
c,	*p*-$N(Me)_2C_6H_4$	$CO_2C_2H_5$
d,	*p*-$NO_2C_6H_4$	CN
e,	*p*-$N(Me)_2C_6H_4$	CN

(Scheme 3)

Similarly, we examined the three component reaction of the pyrazolone **1** with the use of ethylacetoacetate and ethylcyanoacetate. In this case the reaction yielded the corresponding pyrazolopyridine adducts **11** and **12a-c** (Scheme 4). In addition, the use of diethylmalonate and acetylacetone produced the adducts **13, 14,** respectively (Scheme 4). Elucidation of the structure of all synthesized compounds was based on the microanalytical and the spectroscopic data.