Regioselective synthesis of 5-aminopyrazoles from reactions of amidrazones with activated nitriles. NMR investigation and X-ray structural analysis

Ashraf A Aly,*[a] Mohamed Ramadan,[b] Mohamed Abd El-Aziz,[c] Stefan Bräse,[d] Alan B. Brown,[e] Hazem M. Fathy,[b] and Martin Nieger[f]

[a] *Chemistry Department, Faculty of Science, Minia University, 61519 El-Minia, A. R. Egypt.*
[b] *Department of Organic Chemistry, Faculty of Pharmacy, Al-Azhar University, Assiut Branch, Egypt.*
[c] *Medicinal Department, Faculty of Pharmacy, Minia University, 61519 El Minia, Egypt.*
[d] *Institute of Organic Chemistry, Karlsruhe Institute of Technology, Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany.*
[e] *Chemistry Department, Florida Institute of Technology, Melbourne, FL 32901, USA*
[F] *(A. I. Virtasen aukio 1), FI-00014 University of Helsinki, Finland, University of Helsinki, P.O. Box 55*

N-Arylbenzamidrazones and ethyl 2-cyano-3-ethoxybut-2-enoate reacted together in ethanol and catalysed by triethylamine (Et_3N) to give 5-amino-3-methyl-1-(aryl(phenylimino)methyl)-1*H*-pyrazole derivatives. Reaction of the target amidrazones with bis-(methylthio)methylidene)malononitrile in EtOH/Et_3N/DMF mixture proceeded to give the corresponding 5-aminopyrazoles. The structure of the obtained products was proved by IR, mass, and NMR spectra and elemental analyses. Two-dimensional NMR spectroscopy and x-ray structural analyses were used to differentiate the assigned structures from other possible ring systems and regioisomers. The reaction mechanism is discussed.

Keywords: Amidrazones, Activated nitriles, *E*-aminopyrazoles, Conjugate addition, NMR, X-ray structure analyses

1. Introduction

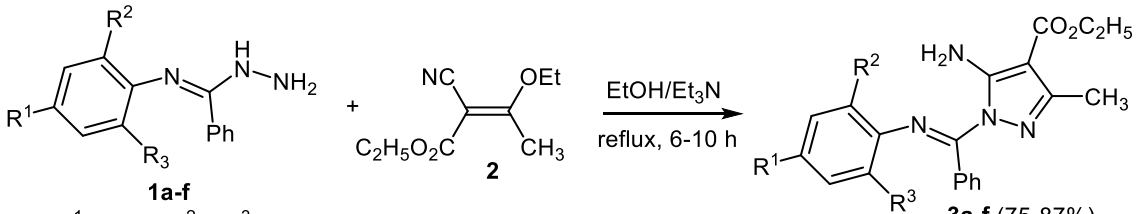
Amidrazones are class of compounds that have biological and pharmaceutical activity. They exhibit antibacterial and antifungal (Mamolo, *et al.*; 1992, Mamolo, 1993; and Ranft, *et al.*), antitumor (Modzelewska-Banachiewic, *et al.* 1999), or antitubercular (Abdel-Jalil, *et al.*, 2010) activities. Amidrazones are also found to be effective herbicides (Dean *et al.*, 2008). We have reported that amidrazones react with 1,4-benzoquinone or 1,4-naphthoquinone to give annulated 1,2,4-triazines (Aly *et al.*, 2007), but with 2,3,5,6-tetrachloro-1,4-benzoquinone and 2,3-dichloro-1,4-naphthoquinone to afford indazole derivatives (Aly *et al.*, 2007). We also reported that reaction of amidrazones with 1,4-dioxo-1,4-dihydronaphthalene-2,3-dicarbonitrile gave a variety of 1,2,4-triazepines (Aly *et al.*, 2008). On the other hand, reaction of amidrazones with 1,4-diphenyl-2-butyne-1,4-dione led to conjugate addition *via* the outermost nitrogen atom, without ring closure (Nour El-Din and Aly, 2007). Recently, we have reported

that amidrazones reacted with phthaloyl chloride and diaminomaleonitrile (DAMN) to give triazolium chlorides (Aly *et al.*, 2016) and *N*-4-amino-5-iminopyrazoles, respectively (Aly *et al.*, 2016). Reaction of amidrazones with ethyl 2-cyano-3,3-bis(methylthio)acrylate led to conjugate addition, followed by ring closure with loss of methanethiol, to afford a series of mercapto pyrazoles (Aly *et al.*, 2015).

Pyrazoles represent a key motif in heterocyclic chemistry and occupy a leading place in medicinal, pesticide and agrochemical industry (Liu *et al.*, 2014) due to their potential to reveal a broad range of bioactivities such as anti-inflammatory (Kumar *et al.*, 2009) antidepressant (Abdel-Aziz, *et al.*, 2009), anti-microbial (Manna K, Agrawal Y. K., 2009), antiviral (i.e. anti-influenza) (Shih, *et al.*, 2010), anti-cancer (Balbi *et al.*, 2011), anti-platelet (Rehse *et al.*, 2009), anticonvulsant (Viveka *et al.*, 2015), anti-biotic (Zhao *et al.*, 2009) and CNS regulatory (O'Connor and Lysz, 2008). The pyrazole products are amidrazones themselves, of unusual stereochemistry. The central $C^2=N^2$ bond of the amidrazone moiety N^1-$N^2=C^2(Ar)$-N^3Ar', has been reported to have an *E*-configuration (Frohberg *et al.*, 2012).[23] There are few examples of amidrazones in the *Z*-configuration, especially when the structure contains heterocyclic instead of aryl substituents (Bhat *et al.*, 2016 and Mazur *et al.*, 2012). Therefore it becomes interesting to investigate the selectivity of amidrazones towards activated alkenes. Moreover, the appealing generality of this method is somewhat vitiated by the severe reaction conditions or the multistep sequences usually required to access the starting materials (Elguero *et al.*, 1996). Therefore, both amidrazones and pyrazoles can be considered as potential drugs; in this paper, we report an efficient method for the synthesis of pyrazoles containing at N^1 an aryliminobenzyl group.

2. Results and Discussion

Amidrazones **1a-f** reacted with ethyl 2-cyano-3-ethoxybut-2-enoate (**2**) in absolute EtOH containing a 0.5 ml of triethylamine (Et_3N), compounds **3a-f** (70-85%) were obtained, after chromatographic purification and recrystallization (Scheme 1).



a; $R^1 = CH_3$, $R^2 = R^3 = H$
b; $R^2 = CH_3$, $R^1 = R^3 = H$
c; $R^2 = R^3 = CH_3$, $R^1 = H$
d; $R^1 = Cl$, $R^2 = R^3 = H$
e; $R^1 = Br$, $R^2 = R^3 = H$
f, $R^1 = NO_2$, $R^2 = R^3 = H$

3a (78%); **3b** (87%); **3c** (81%); **3d** (77%); **3e** (76%); **3f** (75%)

Scheme 1. Synthesis of pyrazoles **3a-f**

Table 1. NMR assignment of compound **3b**

^{1}H NMR (DMSO-d_6)	^{1}H-^{1}H COSY	Assignment
7.75 (bs; 2H)		NH_2
7.29 (m; 3H)	7.24	H-*p, m/o*
7.24 (m; 2H)	7.29	H-*o/m*
7.10 (d, *J* = 7.3; 2H)	6.91, 6.85, *2.19*	H-6‘
6.91 (t, *J* = 7.3; 2H)	7.10, 6.85, 6.54, *2.19*	H-*m’*
6.85 (t, *J* = 7.3; 1H)	7.10, 6.91, 6.54	H-5’
6.54 (d, *J* = 7.6; 1H)	6.91, 6.85, *2.19*	H-3’
4.24 (q, *J* = 7.1; 2H)	1.30	H-4b
2.19 (s; 3H)	7.10, 6.91, 6.54	H-2a’
2.15 (s;3H)		H-3a
1.30 (t, *J* = 7.1; 3H)	4.24	H-4c

^{13}C NMR (DMSO-d_6)	HSQC	HMBC	Assignment
163.80		4.24, *2.15*	C-4a
157.17		7.29, 7.24	C-α
153.81			C-5
149.66		2.15	C-3
145.63		7.10, 6.91, 6.85, 6.54	C-2’
131.21		7.29	C-*i*
129.82	7.10	6.91, *2.19*	C-6’
129.29	7.29	7.29, 7.24	C-*p*
128.73[b]	7.24	7.29, 7.24	C-*o/m*
128.48		6.85, 6.54, 2.19	C-1’
127.52[b]	7.29	7.29, 7.24	C-*m/o*
125.86	6.91	7.10, *2.19*	C-4’
123.60	6.85	6.54	C-5’
120.87	6.54	6.91, 6.85, 2.19	C-3’
92.40		2.15	C-4
58.99	4.24	1.30	C-4b
18.03	2.19	7.10, *6.54*	C-2a’
18.30	2.04	6.91, 6.81	Ar-CH_3
14.41	2.15		C-3a
14.36	1.30	4.24	C-4c

^{15}N NMR (DMSO-d_6)	HSQC	HMBC	Assignment
277.4		2.15	N-2
71.4	7.75		NH_2

Elemental analyses and IR, NMR (^{1}H, ^{13}C, and ^{15}N) and mass spectra were in good agreement with the assigned product structures. For example, compound **3b** is the product of reaction between 2 and *N*-(*o*-tolyl)benzamidrazone (**1b**). The *o*-tolyl ring gives four discrete ^{1}H signals, two doublets and two "triplets" (double-doublets with equal *J)*. Three of the four give weak COSY correlation with the tolyl methyl signal at δ_H = 2.19; the "triplet" at δ_H = 6.85 does not, and is assigned as the most distant proton, H-5'. The attached carbon at δ_C = 123.60 gives HMBC correlation with a doublet at δ_H = 6.54, assigned as H-3'; this would be a three-bond correlation. Similarly, correlations are observed between the other doublet at δ_H = 7.10, the other "triplet" at δ_H = 6.91, and their attached carbons. In the phenyl ring, protons H-*m/o* and their attached carbons cannot be differentiated. In the pyrazole ring, a set of ethoxycarbonyl resonances is evident, and there is no nitrile carbon, indicating that *N*-1 attacks the nitrile carbon of **2** not the ester carbonyl. Methyl protons H-3a appear at δ_H = 2.15, and the attached carbon appears at δ_C = 14.41. Protons H-3a give HMBC correlation with a carbon at δ_C = 92.40, assigned as C-4, and a nitrogen at δ_N = 277.4, assigned as *N*-2; these are both three-bond correlations. The correlation between H-3a and *N*-2 proves the regioselectivity of the reaction. Nitrogens were detected indirectly, *via* HSQC or HMBC experiments; the nitrile nitrogen, *N*-β, and *N*-1 were

not observed. Spectroscopic data appear in Table 1; the structure assignment of **3b** is unambiguously confirmed by an X-ray crystal structure (Figure 1). Amidrazones **1a,d-g** reacted with [bis(methylthio)methylidene]-malononitrile (**4**) in ethanol catalyzed by trimethylamine (0.5 ml) and containing enough DMF to dissolve the starting compounds, to furnish pyrazoles **5a,d-g** in 65-76% yields (Scheme 2). Here again, we chose amidrazones bearing both electron-withdrawing and electron-donating substituents, to probe the effect of electron demand on the reaction.

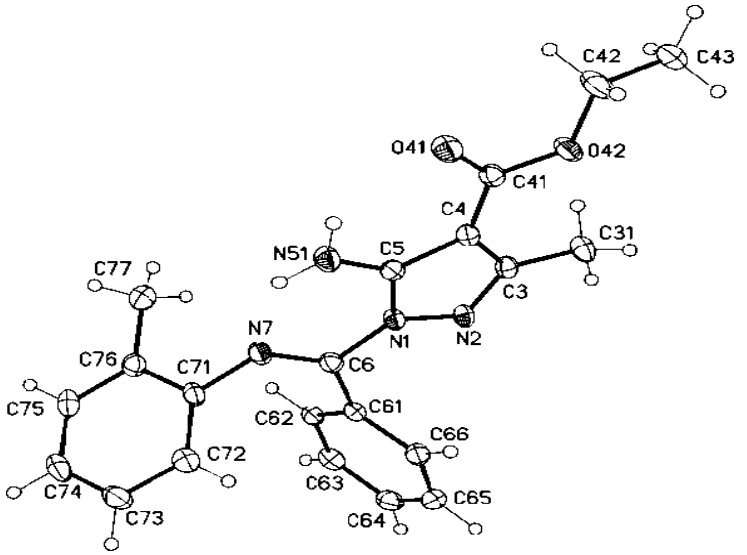
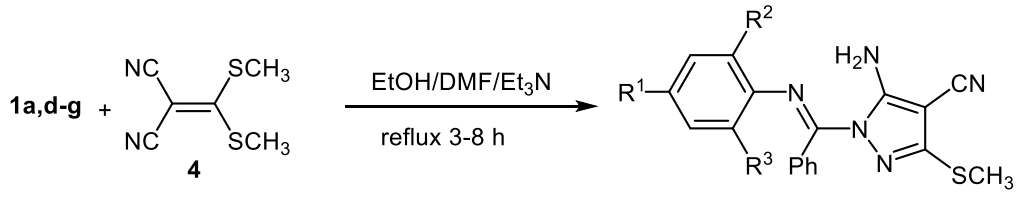


Figure 1. Molecular structure of **3b** (displacement parameters are drawn at 50% probability level).



a: $R^1 = R^2 = R^3 = H$
d: $R^1 = H$, $R^2 = R^3 = CH_3$
e: $R^1 = Cl$, $R^2 = R^3 = H$
f: $R^1 = Br$, $R^2 = R^3 = H$
g: $R^1 = NO_2$, $R^2 = R^3 = H$

5a,**d-g** (65-76%)
5a (75%); **5d** (77%); **5e** (73%); **5f** (76%); **5g** (71%)

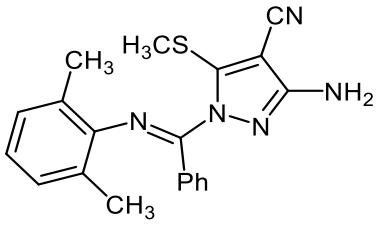
Scheme 2. Reaction of amidrazones **1a,d-g** with 2-(bismethylthio)methylene)malononitrile (**4**). Synthesis of *E*-5-amino-pyrazoles **5a,d-g**

For example, compound **5d** is the product of reaction between **4** and *N*-(2,6-dimethylphenyl)benzamidrazone (**1d**) (Table 2). The 2,6-dimethylphenyl ring provides a convenient starting point. The C-methyl protons and their attached carbon are distinctive at $\delta_H = 2.04$ and $\delta_C = 18.30$, respectively. The methyl carbon gives HMBC correlation with a 2H doublet at $\delta_H = 6.91$, assigned as H-*m'*; the attached carbons appear at $\delta_C = 127.69$. H-*m'* gives COSY correlation with a 1H triplet at $\delta_H = 6.81$, assigned as H-*p'*; the attached carbon appears at $\delta_C = 123.46$. H-*m'*, H-*p'*, and $ArCH_3$ all give HMBC correlation with a carbon at $\delta_C = 144.24$, assigned as H-*i'*: this is a three-bond coupling from CH_3 and H-*m'*, and a four-bond coupling from H-*p'*. H-*p'* gives HMBC correlation with a carbon at $\delta_C = 126.60$, assigned as C-o*'*; this is a three-bond coupling. C-*o'* gives no other HMBC correlation; this signal is the only intense carbon signal lacking attached protons. The protons of the mono-substituted phenyl ring barely

separate into a 1H triplet at δ_H = 7.34, a 2H double-doublet at δ_H = 7.26, and a 2H doublet at δ_H = 7.22; these are assigned as H-*p,* H-*m,* and H-*o* respectively. The attached carbons appear at δ_C = 130.08 (C-*p),* 127.32 (C-*m),* and 128.49 (C-*o).* The protons of this ring gives HMBC correlation with a non-protonated carbon at δ_C = 130.95, assigned as C-*i.* H-*m,* H-*o,* and C-CH_3 also give HMBC correlation with one of the two carbon signals at δ_C = 155.67-155.65, assigned as C-α. N-1 is observed, and gives HMBC correlation with the amino protons; this argues for structure **5d**, in which it is a three-bond correlation, over its regioisomer **5d'** in which this correlation would cover four bonds (Figure 2).

Table 2. NMR assignment of compound **5d**

^{1}H NMR (DMSO-d_6)		**^{1}H-^{1}H COSY**	**Assignment**
8.32 (bs; 2H)			NH_2
7.34 (t, *J* = 7.1; 1H)		7.26, 7.22	H-*p*
7.26 (dd, *J* = 7.7, 7.4; 2H)		7.34, 7.22	H-*m*
7.22 (d, *J* = 7.3; 2H)		7.34, 7.26	H-*o*
6.91 (d, *J* = 7.5; 2H)		6.81	H-*m'*
6.81 (t, *J* = 7.5; 1H)		6.91	H-*p'*
2.28 (s; 3H)			SCH_3
2.04 (s; 6H)			$ArCH_3$
^{13}C NMR (DMSO-d_6)	**HSQC**	**HMBC**	**Assignment**
155.67, 155.65		7.26, 7.22, *6.81,* 2.04	C-α, 5
149.58		2.28	C-3
144.24		6.91, 6.81, 2.04	C-*i'*
130.95		7.34-7.22	C-*i*
130.08	7.34	7.34-7.22	C-*p*
128.49	7.22	7.34-7.22	C-*o*
127.69	6.91	6.91, 6.81, 2.04	C-*m'*
127.32	7.26	7.34-7.22	C-*m*
126.72		6.91, 6.81, 2.04	C-*o'*
123.46			C-*p'*
113.38			C-4a
72.86		8.32	C-4
18.30	2,04	6.91, 6.81	C-CH_3
12.81	2.28		SCH_3
^{15}N NMR (DMSO-d_6)	**HSQC**	**HMBC**	**Assignment**
199.7		8.34	N-1
71.8	8.34		NH_2



5d'

Figure 2. Structure of **5d'** as an alternative structural isomer of compound **5d**

In the same series, but with the *N*-aryl ring bearing an electron-withdrawing group, is **5f** (Table 3). This is the reaction product of **4** and *N*-(*p*-bromophenyl)benzamidrazone (**1f**). The *p*-bromophenyl ring gives two ^{1}H doublets at δ_H = 7.34 and 6.75. The upfield of the two is assigned as H-*o'*, because it gives HMBC correlation with a nitrogen at δ_N = 273.3, assigned as *N*-β; therefore, the signal at δ_H = 7.34 is assigned as H-*m'*. The attached carbons appear at δ_C = 123.95 (C-*o'*) and 131.28 (C-*m'*).

Table 3. NMR assignment of compound **5f**

^{1}H NMR (DMSO-*d*$_6$)	**^{1}H-^{1}H COSY**	**Assignment**
8.34 (bs; 2H)		NH_2
7.34 (d, *J* = 8.5; 2H)	6.75	H-*m'*
7.31 (m; 5H)		H-o,*m*,*p*
6.75 (d, *J* = 8.6; 2H)	7.34	H-*o'*
2.25 (s; 3H)		SCH_3

^{13}C NMR (DMSO-*d*$_6$)	**HSQC**	**HMBC**	**Assignment**
157.58		7.31	C-α
155.42			C-5
149.93		2.25	C-3
145.94		7.34, 6.75	C-*i'*
131.28	7.34	7.34	C-*m'*
130.31		7.31	C-*i*
129.69	7.31	7.31	C-*p*
129.44, 127.55	7.31	7.31	C-*o*,*m*
123.95	6.75	6.75	C-*o'*
116.00		7.34, 6.75	C-*p'*
113.37			C-4a
72.69		8.34	C-4
12.78	2.25		SCH_3

^{15}N NMR (DMSO-*d*$_6$)	**HSQC**	**HMBC**	**Assignment**
273.3		6.75	N-β
200.9		8.34	N–1
72.2	8.34		NH_2

The two non-protonated carbons in this ring, at δ_C = 145.94 and 116.00, both give HMBC correlation with both H-*o'* and H-*m';* on chemical-shift grounds, they are assigned as C-*i'* and C-*p'* in that order. In the

phenyl ring, the protons appear as an unresolved envelope at δ_H = 7.31; they give HSQC correlation with two intense ^{13}C signals at δ_C = 129.44 and 127.55, and a shorter line at δ_C = 129.69. The last is assigned as C-*p;* the other two must be C-*o/m*, but cannot be differentiated. In the pyrazole ring, C-3 again gives HMBC correlation with the methyl protons, and *N*-1 with the amino protons. The structure assignment is confirmed by an X-ray crystal structure (Figure 3).

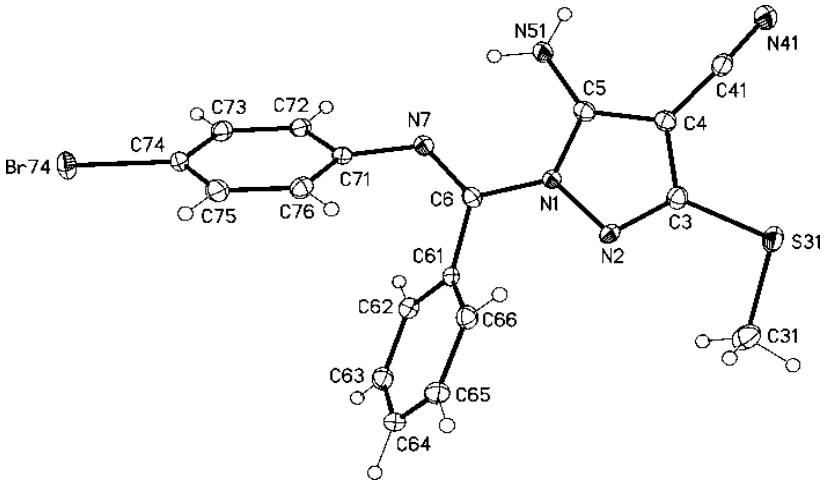


Figure 3. **Molecular structure of** 5f **(displacement parameters are drawn at 50% probability level)**

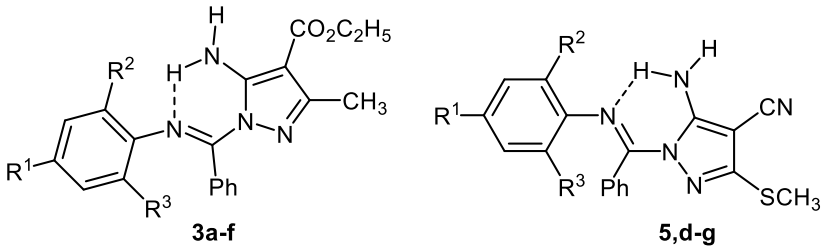
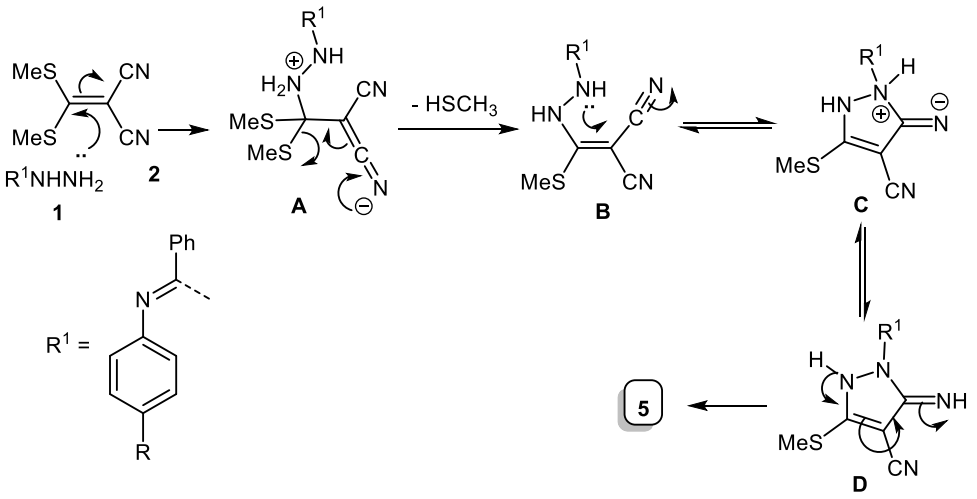


Figure 4. Proposal intramolecular hydrogen bond formation in 5-aminopyrazoles **3a-f** and **5a,d-g**.

The formation of *E*-configuration of the obtained 5-aminopyrazoles **3a-f** and **5a,d-g** might attributed to the proposed hydrogen bond forming between the hydrogen atoms of 5-substituted amino group of pyrazole moiety and the substituted nitrogen of the arylimino group as shown in Figure 4. We propose the mechanism shown in Scheme 3. Conjugate addition of **1** to **2** would give intermediate **A**. Elimination of methanethiol would provide **B**. Successive tautmoerism of **B** would then occur to give **C** and thereafter it would give **D**. Ultimately, aromatization of **D** would give **5** (Scheme 3).



Scheme 3. Proposed mechanism for formation of pyrazoles **5**

3. Conclusion

In this paper, we have unambiguously proved the *E*-form of the structure of 5-aminopyrazoles, in which the amino group is found in the same direction of substituted amino group (i.e. N-7 as in x-ray structure analyses, Figures 1 and 2). Most indicative of this paper is related to the good yields of the obtained products in addition to the simplicity of the method of preparation.

4. Acknowledgments

We thank the DFG (BR 1750) for its financial support for the stay of Professor Aly at the Karlsruhe Institute of Technology, Institute of Organic Chemistry, Germany. The NMR spectrometer at Florida Institute of Technology was purchased with the assistance of the U.S. National Science Foundation (CHE 03 42251).

5. Experimental

NMR spectra were measured on a Bruker AV-400 spectrometer (Bruker BioSpin Corp., Billerica, MA, USA) (400MHz for 1H and 100 MHz for 13C) at Florida Institute of Technology, USA. The ^{1}H and ^{13}C chemical shifts are given relative to internal standard TMS; ^{15}N shifts are reported versus ammonia. For preparative thin layer chromatography (PLC), glass plates (20 x 48 cm) were covered with a slurry of silica gel Merck PF254 and air dried and developed using the solvents listed. Zones were detected by quenching of indicator fluorescence upon exposure to 254 nm UV light. Elemental analyses were carried in the

National Research center, Dokki, Cairo, Egypt. Mass spectrometry was performed by electron impact at 70 eV, with a Finnigan MAT 8430 spectrometer in the National Research center, Dokki, Cairo, Egypt. IR spectra using KBr pellets, were run on a FT-IR (Bruker), Minia University, El-Minia, Egypt. Amidrazones **1a-g** were prepared according to reference (Doyle and Kurzer, 1974). Single crystal X-ray diffraction studies were carried out on Bruker D8 Venture diffractometer with Photon100 detector at 123 K using MoKα radiation (λ = 0.71073 Å). X-Ray structure analyses were carried out in laboratory of Inorganic Chemistry, Department of Chemistry, University of Helsinki, P.O. Box55 (A. I. Virtasenaukio I), 00014, Helsinki, Finland.

General Procedures

Reaction of amidrazones 1a-f with 2. General procedure (Scheme 1)

A 100 mL round-bottom flask was flame-dried. Dry absolute ethyl alcohol (20 mL) containing a mixture of **1a–f** (1 mmol), **2** (1 mmol), and 0.5 mL of Et_3N. The mixture was stirred under reflux for 6–10 h (the reaction was followed by TLC analysis). The solvent was then removed under vacuum and the residue was separated. The products **3a**–**f** were obtained and were recrystallized from the stated solvents.

Ethyl (*E*)-5-amino-1-((4'-methylphenylimino)(phenyl)methyl)3-methyl-1*H*-pyrazole-4-carboxylate (3a). Pale yellow crystals (CH_2Cl_2/MeOH), m.p. 171-172 ºC, yield 0.32 g (78%). IR (KBr, cm^{-1}): 3410-3285 (NH_2), 3063 (CH aromatic), 2971 (CH aliphatic), 1675 (ester C=O), 1637, 1599 (C=N), 1549 (C=C). ^{1}H NMR (DMSO-d_6; 2D): δ_H = 7.71 (bs, 2H; NH_2), 7.30 (m, 3H; H-*m,p*'), 7.24 (m, 2H; H-*o*), 6.95(d, *J* = 7.8, 2H; H-*m'*), 6.64 (d, *J* = 7.9, 2H; H-*o'),* 4.24, (q, *J* = 7.0, 2H; CH_2), 2.17 (s, 3H; Tol-CH_3), 2.14 (s, 3H; H-3a), 1.30 (t, *J* = 7.0, 3H; $CH_2\mathbf{CH_3}$). ^{13}C NMR (DMSO-d_6; 2D): δ_C = 163.8 (C=O), 157.6 (C-α), 153.7 (C-5), 149.6 (C-3), 144.2 (C-*i'*), 132.4 (C-*p'),* 131.2 (C-*i*), 129.2 (C-*m,p),* 129.0 (C-*m'),* 127.6 (C-*o),* 121.5 (C-*o'),* 92.3 (C-4), 59.0 (CH_2), 20.3 (Tol-CH_3), 14.43 (C-3a), 14.35 ($CH_2\mathbf{CH_3}$). ^{15}N NMR (DMSO-d_6; 2D): δ_N = 277.3 (N-2), 71.2 (NH_2). MS: *m/z* (%): 429 (49, M+2), 427 (47, M^+), 225 (100), 179 (33), 76 (45). Calcd for $C_{21}H_{22}N_4O_2$ (362.43): C, 69.59; H, 6.12; N, 15.46. Found: C, 69.65; H, 6.00; N, 15.65.

Ethyl (*E*)-5-amino-1-((2'-methylphenylimino)(phenyl)methyl)-3-methyl-1*H*-pyrazole-4-carboxylate (3b). Pale yellow crystals (CH_2Cl_2/MeOH), m.p. 139-140 ˚C; yield 0.35 g (87%). IR (KBr, cm^{-1}): 3454-

3329 (NH_2), 3050 (CH aromatic), 2976 (CH aliphatic), 1682 (ester C=O), 1643, 1600 (C=N), 1576 (C=C). NMR: see Table 1. MS: *m/z* (%): 362 (M^+, 20), 193 (100), 90 (20). Calcd for $C_{21}H_{22}N_4O_2$ (362.43): C, 69.59; H, 6.12; N, 15.46. Found: C, 69.70; H, 6.24; N, 15.66.

Ethyl (*E*)-5-amino-1-((2',6'-dimethylphenylimino)(phenyl)-methyl)3-methyl-1*H*-pyrazole-4-carboxylate (3c). Pale yellow crystals (CH_2Cl_2/ MeOH), m.p 172-173 °C; yield 0.30 g (81%). IR (KBr, cm^{-1}): 3441-3318 (NH_2), 3010 (CH aromatic), 2978 CH aliphatic), 1674 (ester C=O), 1642, 1601(C=N), 1543 (C=C). ^{1}H NMR (DMSO-d_6; 2D): δ_H = 7.67 (bs, 2H; NH_2), 7.33 (t, *J* = 7.2, 1H; H-*p*), 7.27 (dd, *J* = 7.6, 7.1, 2H; H-*m*), 7.18 (d, *J* = 7.2, 2H; H-*o*), 6.91 (d, *J* = 7.5, 1H; H-*p'*), 4.25 (q, *J* = 7.1, 2H; CH_2), 2.16 (s, 3H; H-3a), 2.04 (s, 6H; Ar-CH_3), 1.30 (t, *J* = 7.1, 3H; CH_2**CH_3**). ^{13}C NMR (DMSO-d_6; 2D): δ_C = 163.8 (C=O), 156.4 (C-α), 153.9 (C-5), 149.6 (C-3), 144.5 (C-*i'*), 131.5 (C-*i*), 129.8 (C-*p*), 128.2 (C-*o*), 127.7 (C-*m'*), 127.4 (C-*m*), 126.6 (C-*o'*), 123.3 (C-*p'*), 92.5 (C-4), 59.0 (CH_2), 18.3 (Ar-CH_3), 14.43 (C-3a), 14.39 (CH_2**CH_3**). ^{15}N NMR (DMSO-d_6; 2D): δ_N = 277.5 (N-2), 71.3 (NH_2). MS: *m/z* (%): 376 (M^+, 11), 207 (100), 104 (15). Calcd for $C_{22}H_{24}N_4O_2$ (376.46): C, 70.19; H, 6.43; N, 14.88. Found: C, 70.00; H, 6.32; N, 15.05.

Ethyl (*E*)-5-amino-1-((4'-chlorophenylimino)(phenyl)-methyl)-3-methyl-1*H*-pyrazole-4-carboxylate (3d). White crystals (EtOH), m.p 166-167 °C; yield 0.33 g (77%). IR (KBr, cm^{-1}): 3429-3298 (NH_2), 3015 (CH aromatic), 2967 (CH aliphatic), 1673 (ester C=O), 1637, 1592 (C=N), 1544(C=C). ^{1}H NMR (DMSO-d_6; 2D): δ_H = 7.70 (bs, 2H; NH_2), 7.32 (m, 3H; H-*p,m/o),* 7.26 (m, 2H; H-*o/m),* 7.20 (d, *J* = 8.4, 2H; H-*m'),* 6.79 (d, *J* = 8.4, 2H; H-*o'),* 4.24 (q, *J* = 7.1, 2H; CH_2), 2.14 (s, 3H; H-3a), 1.29 (t, *J* = 7.1, 3H; CH_2**CH_3**). ^{13}C NMR (DMSO-d_6; 2D): δ_C = 163.8 (C=O), 158.2 (C-α), 153.8 (C-5), 149.9 (C-3), 145.9 (C-*i'),* 130.8 (C-*p'),* 129.4 (C-*p),* 129.2 (C-*m/o),* 128.4 (C-*m'),* 127.65 (C-*o/m),* 127.60 (C-*i),* 123.5 (C-*o'),* 92.3 (C-4), 59.0 (CH_2), 14.4 (C-3a), 14.3 (CH_2**CH_3**). ^{15}N NMR (DMSO-d_6; 2D): δ_N = 277.0 (N-2), 272.2 (N-β). MS: *m/z* (%): 384 (M+2, 9), 382 (M^+, 27), 213 (100), 153 (16), 110 (14). Calcd for $C_{20}H_{19}ClN_4O_2$ (382.85): C, 62.75; H, 5.00; N, 14.63. Found: 62.62; H, 5.15; N, 14.56.

(*E*)-Ethyl 5-amino-1-((4'-bromophenylimino)(phenyl)methyl)3-methyl-1*H*-pyrazole-4-carboxylate (3e). Pale yellow crystals (MeOH), m.p. 150-151 °C; yield 0.32 g (76%). IR (KBr, cm^{-1}): 3429-3297 (NH_2),

3020 (CH aromatic), 2968 (CH aliphatic), 1673 (ester C=O), 1637, 1590 (C=N), 1543 (C=C). ^{1}H NMR (DMSO-d_6; 2D): δ_H = 7.70 (bs, 2H; NH_2), 7.33 (m, 5H; H-*p,m,m'),* 7.28 (m, 2H; H-*o),* 6.74 (d, *J* = 8.5, 2H; H-*o'),* 4.24 (q, *J* = 7.1, 2H; CH_2), 2.14 (s, 3H; H-3a), 1.30 (t, *J* = 7.1, 3H; $CH_2\mathbf{CH_3}$). ^{13}C NMR (DMSO-d_6; 2D): δ_C = 163.8 (C=O), 158.1 (C-α), 153.8 (C-5), 149.9 (C-3), 146.3 (C-*i'),* 131.3 (C-*m),* 130.8 (C-*i),* 129.4 (C-*p),* 129.2 (C-*o),* 127.6 (C-*m'),* 123.9 (C-*o'),* 115.8 (C-*p'),* 92.3 (C-4), 59.0 (CH_2), 14.4 (C-3a), 14.3 ($CH_2\mathbf{CH_3}$). ^{15}N NMR (DMSO-d_6; 2D): δ_N = 276.9 (N-2), 272.2 (N-β). MS: *m/z* (%): 429 (M+2, 49), 427 (M^+, 47), 225 (100), 179 (33), 76 (45). Calcd for $C_{20}H_{19}BrN_4O_2$ (427.30): C, 56.22; H, 4.48; N, 13.11. Found: C, 56.06; H, 4.40; N, 13.06.

Ethyl (*E*)-5-amino-1-((4'-nitrophenylimino)(phenyl)methyl)-3-methyl-1*H*-pyrazole-4-carboxylate (3f). Yellow crystals (CH_2Cl_2/cyclohexane), m.p. 183-184 °C; yield 0.29 g (75%). IR (KBr, cm^{-1}): 3444-3329 (NH_2), 3104 (CH aromatic), 2983 (CH aliphatic), 1688 (ester C=O), 1642, 1603 (C=N), 1547 (C=C). ^{1}H NMR (DMSO-d_6; 2D): δ_H = 8.05 (d, *J* = 8.6, 2H; H-*m'*), 7.68 (bs, 2H; NH_2), 7.32 (m, 5H; H-*o.m.p),* 7.03 (d, *J* = 8.7, 2H; H-*o'*), 4.25 (q, *J* = 7.0, 2H; H-4b), 2.15 (s, 3H; H-3a), 1.30 It, *J* = 7.0, 3H; H-4c). ^{13}C NMR (DMSO-d_6; 2D): δ_C = 163.8 (C-4a), 158.0 (C-α), 153.8, 153.6 (C-*p'*, 5), 150.4 (C-3), 143.1 (C-*i'*), 130.6 (C-*i),* 129.7 (C-*p*), 129.2, 127.7 (C-*o,m*), 124.3 (C-*m'*), 122.6 (C-*o'*), 92.4 (C-4), 59.1 (C-4b), 14.5 (C-3a), 14.3 (C-4c). ^{15}N NMR (DMSO-d_6; 2D): δ_N = 277.0 (N-2), 72.2 (NH_2). MS: m/z (%):393 (M^+, 25), 224 (100), 178 (16), 88 (14). Calcd for $C_{20}H_{19}N_5O_4$ (393.40): C, 61.06; H, 4.87; N, 17.80. Found: C, 65.85; H, 4.80; N, 17.70.

Reaction of amidrazones 1a,d-g with 4 (Scheme 2)

General procedure

A 100 mL round-bottom flask was flame-dried. Dry absolute ethyl alcohol (20 mL) containing a mixture of **1a,d-g** (1 mmol) and **4** (1 mmol) was added. The suspension solution was allowed to be dissolved by adding 0.5 mL of dimethylformamide (DMF). The mixture was stirred under reflux for 3–8 h (the reaction was followed by TLC analysis). The solvent was then removed under vacuum and the residue was separated. The products **5a,d**–**g** were obtained and were recrystallized from the stated solvents.

(*E*)-3-Amino-1-((phenylimino)(phenyl)methyl)-5-(methylthio)-1*H*-pyrazole-4-carbonitrile (5a).

Yellow crystals (CH_2Cl_2/cyclohexane), m.p. 233-234 °C; yield 0.25 g (75%). IR (KBr, cm^{-1}): 3380-3260 (NH_2), 2215 (CN), 1650, 1560 (C=N), 1490 (C=C). ^{1}H-NMR (DMSO-d_6; 2D): δ_H = 7.81 (bs, 2H; NH_2), 7.31 (m, 5H; H-*o,m,p)*, 7.18 (dd, *J* = 7.8, 7.5, 2H; H-*m'),* 6.96 (t, *J* = 7.3, 1H; H-*p'),* 6.80 (d, *J* = 7.8, 2H; H-*o'),* 4.26 (q, *J* = 7.0, 2H; CH_2), 2.09 (s, 3H; SCH_3), 1.31 (t, *J* = 7.1, 3H; C-CH_3). ^{13}C NMR (DMSO-d_6; 2D): δ_C = 162.9 (C=O), 157.4 (C-α), 154.0 (C-5), 149.8 (C-3), 146.8 (C-*i'),* 130.7 (C-*i)*, 129.5 (C-*o)*, 129.4 (C-*p),* 128.5 (C-*m'*), 127.3 (C-*m),* 123.6 (C-*p'),* 121.7 (C-*o'),* 91.8 (C-4), 59.2 (CH_2), 14.4 (C-**CH_3**), 11.9 (SCH_3). ^{15}N NMR (DMSO-d_6; 2D): δ_N = 72.3 (NH_2). MS: *m/z* (%): 333 (M^+, 20), 256 (100), 77 (21). Calcd. For $C_{18}H_{15}N_5S$ (333.41): C, 64.84; H, 4.53; N, 21.01. Found: C, 64.70; H, 4.50; N, 21.12.

(*E*)-3-Amino-1-((2',6'-dimethylphenylimino)(phenyl)methyl)-5-(methylthio)-1*H*-pyrazole-4-carbonitrile (5d). Yellow crystals (EtOH), m.p. 244-245 °C; yield 0.28 g (77%). IR (KBr, cm^{-1}): 3427-3358(NH_2), 3000 (CH aromatic), 2972 (CH aliphatic), 2213 (CN), 1649, 1612 (C=N), 1533 (C=C). NMR: Table 2. MS: *m/z* (%): 315 (20, M^+), 214 (100). Calcd. For $C_{20}H_{19}N_5S$ (361.47): C, 66.46; H, 5.30; N, 19.38. Found: C, 66.32; H, 5.22; N, 19.52.

(*E*)-3-Amino-1-((4'-chlorophenylimino)(phenyl)methyl)-5-(methylthio)-1*H*-pyrazole-4-carbonitrile (5e). White crystals (CH_3CN), m.p. 257-258 °C; yield 0.27 g (73%). IR (KBr, cm^{-1}): 3384-3258 (NH_2), 3015 (CH aromatic), 2928 (CH aliphatic), 2206 (CN), 1655, 1607 (C=N), 1540 (C=C). ^{1}H-NMR (DMSO-d_6; 2D): δ_H = 7.78 (bs, 2H; NH_2), 7.31 (m, 5H; H-*p,m,o)*, 7.21 (d, *J* = 8.5, 2H; H-*m'),* 6.81 (d, *J* = 8.5, 2H; H-*o'),* 4.24 (q, *J* = 7.0, 2H; CH_2), 2.07 (s, 3H; H-3a), 1.29 (t, *J* = 7.1, 3H; CH_2**CH_3**). ^{13}C NMR (DMSO-d_6; 2D): δ_C = 162.9 (C=O), 158.0 (C-α), 154.1 (C-5), 150.1 (C-3), 145.8 (C-*i'),* 130.5 (C-*p'),* 129.52, 129.50 (C-*i,p),* 128.4 (C-*m'),* 127.7, 127.4 (C-*m,o),* 123.5 (C-*o'),* 91.8 (C-4), 59.3 (CH_2), 14.4 (CH_2**CH_3**), 11.9 (SCH_3). ^{15}N NMR (DMSO-d_6; 2D): δ_N = 270.5 (N-β). MS: m/z (%): 369 (M+2, 7), 367 (M^+, 21), 214 (100), 111 (38), 77 (22). Calcd. For $C_{18}H_{14}ClN_5S$ (367.86): C, 58.77; H, 3.84; N, 19.04. Found: C, 58.62; H, 3.75; N, 18.88.

(*E*)-3-Amino-1-((4'-bromophenylimino)(phenyl)methyl)-5-(methylthio)-1*H*-pyrazole-4-carbonitrile (5f). Yellow crystals (CH_2Cl_2/MeOH), m.p. 251-252 °C; yield 0.31 g (76%). IR (KBr, cm^{-1}): 3363-3260(NH_2), 3010 (CH aromatic), 2935 (CH aliphatic),2218 (CN), 1633, 1613 (C=N), 1547 (C=C). NMR:

Table 3. MS: *m/z* (%): 413 (M+2, 30), 411 (M^+, 29), 306 (41), 259 (68), 153 (100), 136 (61), 106 (15). Calcd for $C_{18}H_{14}BrN_5S$ (412.31): C, 52.44; H, 3.42; N, 16.99. Found: C, 52.32; H, 3.35; N, 17.18.

(*E*)-3-Amino-5-(methylthio)-1-((4'-nitrophenylimino)(phenyl)methyl)-1*H*-pyrazole-4-carbonitrile (5g). Yellow crystals (CH_2Cl_2/MeOH), m.p. 231-232 °C; yield 0.27 g (71%). IR (KBr, cm^{-1}): 3396-3265 (NH_2), 3015 (CH aromatic), 2982 (CH aliphatic), 2203 (CN), 1648, 1612 (C=N), 1587 (C=C). ^{1}H-NMR (DMSO-d_6; 2D): δ 8.06 (d, J = 8.7, 2H; H-*m'*), 7.75 (b, 2H: NH_2), 7.34 (m, 5H: H-*o,m,p),* 7.04 (d, J = 8.8, 2H; H-*o'),* 4.24 (q, J = 7.0, 2H; CH_2), 2.08 (s, 3H; SCH_3), 1.29 (t, J = 7.0; C-CH_3). ^{13}C NMR (DMSO-d_6; 2D): δ 162.9 (C=O), 157.7 (C-α), 154.1, 153.6 (C-5, *i'),* 150.6 (C-*p'*), 143.1 (C-*p'),* 130.2, 129.9 (C-*i, p),* 129.5, 127.5 (C-*o, m),* 124.4 (C-*m'),* 122.7 (C-*o'),* 91.8 (C-4), 59.3 (CH_2), 14.4 (C-**CH_3**), 12.0 (SCH_3). ^{15}N NMR (DMSO-d_6; 2D): δ 73.1 (NH_2). MS: *m/z* (%): 378 (M^+, 15), 225 (100), 179 (33), 76 (45). Calcd. For $C_{18}H_{14}N_6O_2S$ (378.41): C, 57.13; H, 3.73; N, 22.21. Found: 57.00; H, 3.65; N, 22.21.

Single Crystal X-ray Structure Determinations of 3b and 5f:

Single crystal X-ray diffraction studies were carried out on Bruker D8 Venture diffractometer with Photon100 detector at 123 K using MoKα radiation (λ = 0.71073 Å). Direct methods (**3b**) or Patterson Methods (**5f**) (Sheldrick, 2008) were used for the structure solution, and refinement was carried out using the method in Sheldrick, 2015 (full-matrix least-squares on F^2). Hydrogen atoms were localized using a difference Fourier synthesis map and refined using a riding model [H (N) free]. Semi-empirical absorption correction were applied. For **3b** an extinction correction was applied.

Compound **3b**: $C_{21}H_{22}N_4O_2$, Mr = 362.42 g mol^{-1}, colorless blocks, size 0.55 × 0.30 × 0.25 mm, monoclinic, P2/c (no.13), a = 11.3918(7) Å, b = 9.4638(6) Å, c = 18.3880(11) Å, β = 105.218(2)°, V = 1912.9(2) $Å^3$, Z = 4, D_{calcd} = 1.258 Mg m^{-3}, F (000) = 768, μ = 0.083 mm^{-1}, T = 123 K, 54567 measured reflections ($2\theta_{max}$ = 55.2 °), 4405 independent [R_{int} = 0.031], 253 parameters, 2 restraints, R_1 [for 3846 I › 2σ (I)] = 0.036, *w*R_2 (for all data) = 0.093, S = 1.04, largest diff. peak and hole = 0.326 e$Å^{-3}$ / - 0.180 e $Å^{-3}$.

Compound **5f**: $C_{18}H_{14}BrN_5S$, Mr = 412.31 g mol^{-1}, yellow plates, size 0.30 × 0.05 × 0.05 mm, triclinic, P-1 (no.2), a = 6.1213(3) Å, b = 7.9546(4) Å, c = 18.2014(8) Å, α = 86.045(2)°, β = 85.577(2)°, γ = 88.466(2)°, V = 881.32(7) $Å^3$, Z = 2, D_{calcd} = 1.554 Mg m^{-3}, F (000) = 416, μ = 2.461 mm^{-1}, T = 123 K, 18037

measured reflections ($2\theta_{max}$ = 55°), 4037 independent [R_{int} = 0.034], 233 parameters, 2 restraints, R_1 [for 3622 I › 2σ (I)] = 0.027, wR_2 (for all data) = 0.057, S = 1.08, largest diff. peak and hole = 0.356 e Å^{-3}/ -0.350 e Å^{-3}.

CCDC 1476346 (**3b**), and 1476347 (**5f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

6. References

Abdel-Aziz , M., Gamal El-Din A. Abuo-Rahma, G. El. D., Hassan, A. A. (2009). Synthesis of novel pyrazole derivatives and evaluation of their antidepressant and anticonvulsant activities. *Eur. J. Med. Chem. 44*, 3480–487. Doi: org/10.1016/j.ejmech.2009.01.032

Abdel-Jalil, R.; J., Al Momani, E., Hamad, M., Voelter, W., Mubarak, M. S., Smith, B. H., Peters, D. G. (2010). Synthesis, antitumor activity, and electrochemical behavior of some piperazinyl Amidrazones. *Monatshefte fuer Chemie 141*, 251–258. Doi: 10.1007/s00706-009-0241-4.

Aly, A. A., Gomaa, A.-M. M., Nour-El-Din, A. M., Fahmy, M. S. (2007). Reactions of amidrazones with 1,4-quinones, *Arkivoc xvi*, 41-50. Doi: org/10.3998/ark.5550190.0008.g04

Aly, A. A.; Nour El-Din, A. M.; Gomaa, M. A.-M.; Fahmi, M. S. (2008). Rapid and Facile Synthesis of 4-Aryl-5-imino-3-phenyl-1*H*-naphtho[2,3-*f*]-1,2,4-triazepine-6,11-diones *via* the Reaction of Amidrazones with Dicyanonaphthoquinone. *Z. Naturforsch. 63B*, 223-228. Doi:10.1515/znb-2008- 0217.

Aly, A. A., Hassan, A. A., Bräse, S., Gomaa, M. A.-M., Nemr, F. M. (2016). Reaction of Amidrazones with Phthaloyl Chloride—Synthesis of 1,2,4-Triazolium Salts (Part I). *J. Heterocylc. Chem.* (in press). DOI: 10.1002/jhet.2643

Aly, A. A., Hassan, A. A., Gomaa, M. A.-M., Bräse, S., Nemr, F. M. (2016). Reaction of Amidrazones with Diaminomaleonitrile: Synthesis of 4-Amino-5-Iminopyrazoles. *J. Heterocyclic Chem.* (in press). DOI: 10.1002/jhet.2607.

Aly, A. A., Brown, A. B., Hassan, A. A., Gomaa, M. A.-M., Nemr, F. M. (2015). Reaction of ethyl 2-cyano-3,3-bis(methylthio)acrylate with amidrazones; synthesis of new mercapto pyrazoles and NMR investigation. *J. Sulfur Chem. 36,* 502-510. Doi: org/10.1080/17415993.2015.1064929

Balbi, A., Anzaldi, M., Maccio, M., Aiello, C., Mazzei, M., Gangemi, R., Castagnola, P., Miele, M., Rosano, C., Viale, M. (2011). Synthesis and biological evaluation of novel pyrazole derivatives with anticancer activity. *Eur. J. Med. Chem. 46,* 5293-5309. Doi: 10.1016/j.ejmech.2011.08.014

Bhat, M. A., Al-Rashood, K. A., Abdel-Aziz, H. A. (2016). Unexpected Configuration in Stereoselectively Synthesis of Some Novel (1*Z*)-1-(morpholin-1-yl)-N^2-Arylamidrazones. *Lett. Org. Chem. 9,* 487-492. Doi: 10.2174/157017812802139636

Dean, G. S., S. G. Rhodes, M. Coad, A. O. Whelan, P. Wheeler, B. Villareal-Ramos, E. Mead, L. Johnson, D. J. Clifford, R. G. Hewinson, and H. M. Vordermeier. (2008). Isoniazid treatment of Mycobacterium bovis in cattle as a model for human tuberculosis. *Tuberculosis* (Edinb.) 88, 586-594. Doi: org/10.1016/j.tube.2008.01.004

Doyle, K. M.; Kurzer F. (1974). Synthesis of Unsubstituted Amidrazones. *Synthesis* 583-584. Doi: 10.1055/s-1974-23385

Elguero, J. K. A., Rees C. W., Scriven, E. F. V. (1996). *In Comprehensive Heterocyclic Chemistry II:* Pyrazoles eds; Pergamon Press, Oxford: UK, Vol. 3. Doi: org/10.3998/ark.5550190.0003.815

Frohberg, P., Schulze, I., Donner, C., Krauth, F. (2012). Remarkable stereoselectivity switch in synthesis of carbonyl substituted N^2-arylamidrazones with low lipophilicity. *Tetrahedron Lett. 53,* 4507-4509. Doi: org/10.1016/j.tetlet.2012.06.032

Kumar, A. S., Ilango, K., Manikandan, R. S., Ramalakshmi N. (2009). Synthesis and anti-inflammatory activity of some novel pyrazole derivatives of gallic acid, *E. J. Chem. 6,* 123-128. Doi: org/10.1155/2009/128586.

Liu, X. R., Wu, H.; He, Z. Y., Ma, Z. Q., Feng, J. T., Zhang, X. (2014). Design, Synthesis and Fungicidal Activities of Some Novel Pyrazole Derivatives. *Molecules 19,* 14036-14051.

Mamolo, M. G., Vio, L., Banfi, E., Predominato, M., Fabris, C., & Asaro, F. (1992). Synthesis and antimycobacterial activity of some 2-pyridinecarboxyamidrazone derivatives. *IL Farmaco, 47,* 1055-1066. PMID: 1445613.

Mamolo, M. G., Vio, L, Banfi, E., Predominato, M., Fabris, C., & Asaro, F. (1993). Synthesis and antimycobacterial activity of some 4-pyridinecarboxyamidrazone derivatives. *IL Farmaco 48*, 529-538. PMID: 8357468

Manna K, Agrawal Y. K (2009) Microwave assisted synthesis of new indophenazine 1,3,5-trisubstituted pyrazoline derivatives of benzofuran and their antimicrobial activity. *Bioorg Med Chem Lett.* 19, 2688–2692. org/10.1016/j.bmcl.2009.03.161

Mazur, L., Modzelewska-Banachiewicz, B., Paprocka, R.; Zimecki, M., Wawrzyniak, U. E., Kutkowska, J., Ziółkowska, G. J. (2012). Synthesis, crystal structure and biological activities of a novel amidrazone derivative and its copper(II) complex — A potential antitumor drug. *Inorg. Biochem. 114*, 55-64. Doi: org/10.1016/j.tetlet.2012.06.032

Modzelewska-Banachiewic, B., Matysiak, J., Niewiadomy, A (2001). Synthesis and mycological activity of the compounds obtained in the reaction of N^3-substituted amidrazones with sulphinyl-bis-2,4-dihydroxybenzenethioyl. *Eur. J. Med. Chem. 36*, 75–80. Doi: org/10.1016/S0223-5234(00)-01176-4

Nour El-Din, A. M.; Aly, A. A. (2007). Reaction of amidrazones with 1,4-diphenylbut-2-yne-1,4-dione. *J. Chem. Res.* 665-667. Doi: org/10.3184/030823407X268340

O'Connor, J. P., Lysz, T. (2008). Celecoxib, NSAIDs and the skeleton. Drugs Today (Barc). *44*, 693-709. Doi: 10.1358/dot.2008.44.9.1251573.

Ranft, D., Seyfarth, T., Schaper, K. J., Lehwark-Yvetot, G., Bruhn, C. B. (1999). A. New N^1-Hetarylmethylene-Substituted Amidrazones with Potential Antimycobacterial Activity. *Archive Der Pharmacy Pharm. Med. Chem. 332*, 427-430. Doi: 10.1002/(SICI)1521-4184.

Rehse, K.; Kotthaus, J.; Khadembashi, L. (2009). New 1*H*-pyrazole-4-carboxamides with antiplatelet activity. *Arch. Pharm.* (Weinheim). *342*, 27-33. Doi: 10.1002/ardp.200800181.

Sheldrick, G. M. (2008). A short history of SHELX. *Acta Crystallogr.* 2008, *A64*, 112-122. Doi: org/10.1107/S0108767307043930

Sheldrick, G. M. (2015). Crystal structure refinement with SHELXL**.** *Acta Crystallogr. C71*, 3-8. Doi: 10.1107/S2053229614024218

Shih, S. R., Chu, T.-Y., Reddy, G. R., Tseng, S.-N., Chen, H.-L., Tang, W.-F., Wu, M. S., Yeh, J.-Y., Chao, Y. S., Hsu, J. T. A., Hsieh, H. P (2010). Pyrazole compound BPR1P0034 with potent and selective anti-influenza virus activity. *J. Biomed. Sci. 17*, 13-20. Doi: 10.1186/1423-0127-17-13.

Viveka, S., Dinesha, Shama, P., Naveen, S., Lokanath, N. K., Nagaraja, G. K. (2015). Design, synthesis, anticonvulsant and analgesic studies of new pyrazole analogues: a Knoevenagel reaction approach. *RSC Adv. 5*, 94786-94795. Doi: 10.1039/C5RA17139C.

Zhao, Y., Bacher, A., Illarionov, B., Fischer, M., Georg, G., Qi-Zhuang, Ye, Fanwick, P. E., Franzblau, S. G., Wan, B., Cushman, M. (2009). Discovery and Development of the Covalent Hydrates of Trifluoromethylated Pyrazoles as Riboflavin Synthase Inhibitors with Antibiotic Activity against *Mycobacterium tuberculosis. J. Org. Chem. 74*, 5297-5303. Doi: 10.1021/jo900768c.