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A convenient synthesis of 3- and 5-amino-1*H*-pyrazoles via 3(5)-amino-4-(ethylsulfinyl)-1*H*-pyrazole desulfinylation

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Abstract

Syntheses of 5-amino-3-aryl- and 3-amino-5-aryl-1*H*-pyrazoles from β-bromo-α-(ethylsulfanyl)cinnamonitrile are described. The β-bromo-α-(ethylsulfanyl)cinnamonitriles were oxidized with H_2O_2 to the corresponding β-bromo-α-(ethylsulfinyl)cinnamonitriles. Subsequent treatment of the resulting sulfoxides with hydrazine hydrate or methylhydrazine followed by hydrochloric acid hydrolysis afforded 5-amino-3-aryl- and 3-amino-5-aryl-1*H*-pyrazoles, respectively, in good yields.

Keywords: biological evaluation; desulfinylation; hydrazine; pyrazole; pyrazolo[1,5-a]pyrimidines; sulfoxide.

Introduction

Pyrazoles belong to the most representative five-membered heterocyclic systems (Katritzky, 1985; Eicher et al., 2003). Phenyl-substituted 3(5)-amino-1*H*-pyrazoles and their derivatives exhibit high biological activities and are used as intermediates in the synthesis of pyrazolo-fused heterocycles, such as pyrazolo[1,5-*a*]pyrimidines (Fraley et al., 2002a,b; Compton et al., 2004) and pyrazolopyridines (Straub and Alonso-Alija, 2001).

Synthesis of 3(5)-aminopyrazoles has been extensively investigated in the past, and the different studies were recently reviewed (Anwar and Elnagdi, 2009). These scaffolds can be obtained by reaction between hydrazine and 3-oxoalkanenitriles (Pask et al., 2006; Riyadh et al., 2008), arylalkynenitriles (Rama Rao et al., 2006) or α,β-unsaturated nitriles (Ege et al., 1982; Sadek et al., 1993; Nenaidenko et al., 2004; Cai et al., 2006) as depicted in Scheme 1.

A β-bromo leaving group has been employed for the syntheses of different aza-heterocycles (Pochat, 1980a,b, 1983) including pyrazoles (Pochat, 1979a,b) from β-bromo-α-(ethylsulfanyl)cinnamonitriles but, to our knowledge, β-bromo-α-(ethylsulfinyl)cinnamonitriles have never been used for this purpose. In the present paper, we report the results of our investigation into the synthetic potential of β-bromo-α-(ethylsulfinyl)cinnamonitriles as precursors in 3(5)-aminopyrazole synthesis. Finally, some starting products and fused pyrimidines that were synthesized were evaluated for their bactericidal and cytotoxic activities.

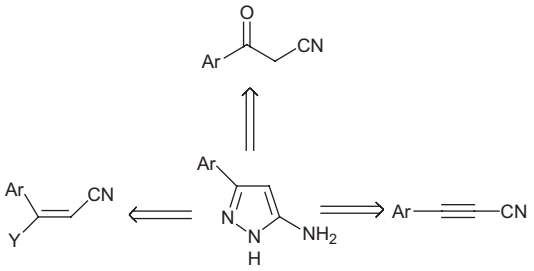
Results and discussion

To our knowledge, no reaction has been described between β-bromo-α-(ethylsulfinyl)cinnamonitriles **2** and hydrazine. The phenyl-substituted aminopyrazoles **3** and **5** were obtained, as outlined in Table 1, in two steps from the β-bromo-α-(ethylsulfanyl)cinnamonitriles **1**.

As previously described (Pochat, 1979b), compounds **1a–f** were readily obtained as *Z/E* mixtures in two steps from aromatic aldehydes and ethyl thioacetonitrile followed by bromination. Several methods were reported to oxidize sulfides to sulfoxides (Kaya et al., 1981; Hirano et al., 1997; Mohanakrishnan and Ramesh, 2005). However, the experiment showed that the β-bromo-α-(ethylsulfanyl)cinnamonitriles **1** can be smoothly oxidized with hydrogen peroxide in acetic acid to produce the corresponding sulfoxides **2** as *Z/E* mixtures in good yields (Table 1, entries 1–6) without epoxide formation.

Compounds **2a–f** were then treated with hydrazine or methylhydrazine in a protic solvent to afford the 5-amino-3-aryl- and 3-amino-5-aryl-1*H*-pyrazoles **3** and **5** in good yields after acidic hydrolysis (Table 1, entries 1–6). The use of methylhydrazine gave the 1-methyl-1*H*-pyrazoles **4** and **5** with high regioselectivity (Table 1, entries 3–5), while phenylhydrazine did not react under the same reaction conditions (Table 1, entries 1 and 2), a result probably due to unfavorable steric interactions. In the case of methylhydrazine, the reaction proceeds exclusively via initial attack of the methyl-substituted amino group to afford an intermediate pyrazole sulfoxide **4** that is transformed into aminopyrazole **5** after a subsequent C–S bond cleavage using aqueous hydrochloric acid. In the case of hydrazine, it proved impossible to isolate an intermediate sulfoxide, and the aminopyrazole **3** was formed after acidic hydrolysis.

It has been reported that hydrazine undergoes a nucleophilic addition to a nitrile triple bond with the formation of an intermediate hydrazide (Rama Rao et al., 2006). In the case of the β-bromo-α-(ethylsulfinyl)cinnamonitriles **2**, nucleophilic



Scheme 1 Retrosynthetic access to 3(5)-aminopyrazoles

addition followed by elimination reaction also furnished the cyclized products.

Although we have not established the mechanism of this unexpected reaction experimentally, a putative mechanism for the formation of compounds **3**, **4** and **5** starting from compound **2** is depicted in Scheme 2 and Scheme 3. It is suggested that the addition of hydrazine to the isomers of compound **2** would lead to an equilibrated mixture of ene-hydrazines **A** and hydrazones **B**, allowing free rotation around of the C3–C4 bond (Pochat, 1979b). Hydrolysis of the sulfoxides **C** to the phenyl-substituted 3(5)-aminopyrazoles **3** would occur under acidic catalysis with elimination of ethylsulfinic acid (Scheme 2).

Addition of methylhydrazine to isomeric mixture **2** would give the intermediates **D** through two forms justifying the rotation around the C3–C4 bond (Scheme 3). Then a cyclization, as discussed above, could lead to compound **4**. A subsequent desulfinylation could provide compound **5**.

Product **4d** was unambiguously identified by X-ray diffraction data of suitable crystals (Figure 1).

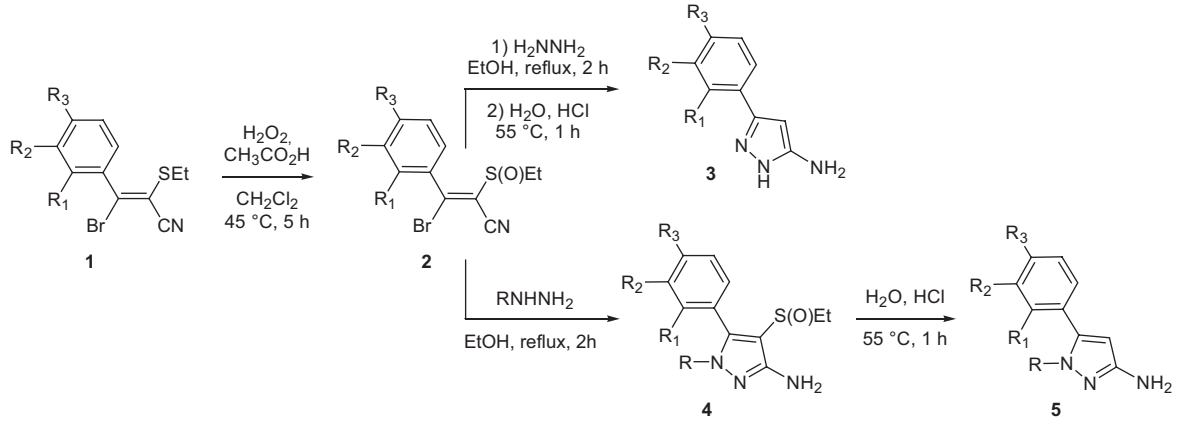
Finally, according to the procedure described in Rama Rao et al. (2006), some of the aminopyrazoles **3** were treated with hexafluoroacetylacetone to afford the corresponding 2-aryl-5,7-bis(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidines **6** in yields ranging from 70 to 86% (Scheme 4).

Pharmacology

Applying the agar plate diffusion technique (Bauer et al., 1966), the **4d** and **4e** compounds synthesized were screened *in vitro* for their bactericidal activity against Gram-positive (*Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*), and for their fungicidal activity against *Fusarium oxysporium* and *Aspergillus niger*. Nevertheless, none of the compounds proved active when compared with cibrofloxacin and nystin, respectively (Table 2).

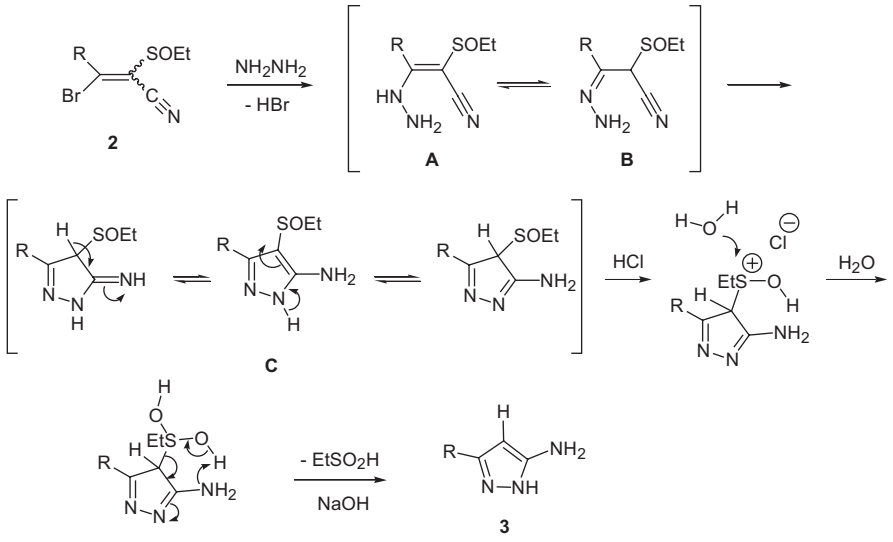
Compounds **2e**, **4d**, **4e**, **6a**, **6b** and **6d** were also tested against a human liver carcinoma cell line (HEPG2), a human breast carcinoma cell line (MCF7), and a human cervix carcinoma cell line (HELA) (Table 3). Compound **2e** was found to be highly active against all the three kinds of carcinoma cell lines, with IC_{50} values below those of the reference drug doxorubicin (IC_{50} is defined as the concentration that results in a 50% decrease in cell number as compared with that of the control structures in the absence of an inhibitor).

Table 1 Synthesis of pyrazoles **3**, **4** and **5** from β-bromo-α-(ethylsulfanyl)cinnamonitriles **1**.



Entry	R_1	R_2	R_3	R	**2**, Yield[a,b]	**3**, Yield[a]	**4**, Yield[a]	**5**, Yield[a]
1	H	H	H	Ph	**2a**, 84%	**3a**, 85%	0%[c]	0%[c]
2	H	H	Cl	Ph	**2b**, 85%	**3b**, 89%	0%[c]	0%[c]
3	H	H	^{t}Bu	Me	**2c**, 86%	**3c**, 90%	**4c**, 90%	**5c**, 90%
4	H	H	OMe	Me	**2d**, 90%	**3d**, 86%	**4d**, 86%	**5d**, 75%
5	H	OCH_2O		Me	**2e**, 86%	**3e**, 85%	**4e**, 95%	**5e**, 70%
6	OMe	H	H	–	**2f**, 80%	**3f**, 88%	–	–

[a]Yields after purification. [b]*Z*/*E* mixtures. [c]Starting material recovered.



Scheme 2 Mechanistic hypothesis to explain the formation of compound **3**.

Conclusion

We have developed a mild, convenient and inexpensive approach for the preparation of 3(5)-aminopyrazoles from β-bromo-α-(ethylsulfinyl)cinnamonitriles **2** through a simple protocol. In comparison, we have established the equivalence between β-bromo-α-(ethylsulfinyl)cinnamonitriles and acetylenic nitrile analogs, and shown that the precursors **2** were good alternatives for the formation of 3(5)-aminopyrazoles without use of potential toxic agents.

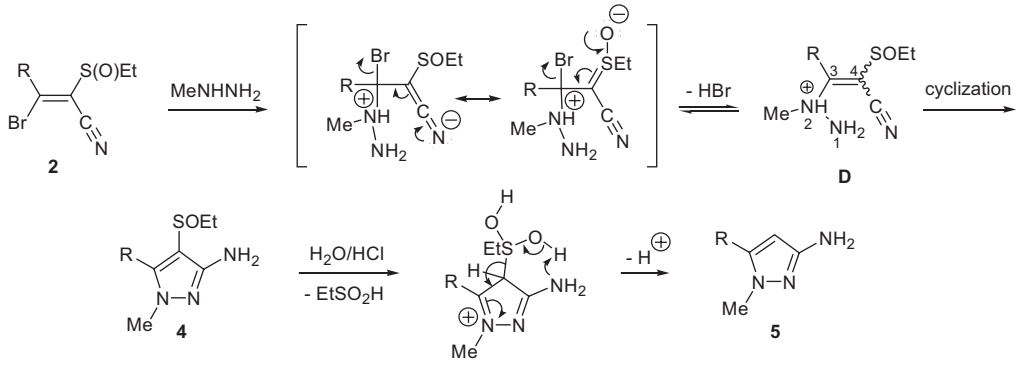
Experimental

General

Liquid chromatography separations were achieved on silica gel (230–400 mesh). The eluent is given in the product description. Melting points were measured using Kofler apparatus. The infrared spectra were obtained using KBr pellets. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III spectrometer at 300 and 75 MHz, respectively, or on a Bruker AC-500 spectrometer at 500 and 125 MHz, respectively. High-resolution mass spectra (HRMS) measurements were performed at the Centre Regional de Mesures Physiques de l'Ouest (CRMPO) in Rennes using either a Waters Q-TOF 2 or a Bruker micrOTOF Q II instrument. Elemental analyses were performed at the CRMPO using a Thermo-Finnigan Flash EA 1112 CHNS analyzer. Hydrazine hydrate, methyl hydrazine and phenyl hydrazine were purchased from Aldrich and used without further purification. (Ethylsulfanyl)acetonitrile and the β-bromo-α-(ethylsulfanyl)cinnamonitriles **1** were prepared according to a procedure described in Dijkstra and Backer (1954; Pochat, 1979a,b).

Typical procedure for the preparation of compounds 2a–f

Thirty-five per cent hydrogen peroxide (36.5 mmol) was added to a stirred solution of starting compound **1** (33 mmol) with a mixture of glacial acetic acid (20 ml) and dichloromethane (10 ml) at 40–50°C. After five hours at the same temperature, the mixture was quenched with excess 10% aqueous sodium carbonate, extracted with dichloromethane, dried over Na_2SO_4 and concentrated. Diethyl ether was



Scheme 3 Mechanistic hypothesis to explain the formation of compounds **4** and **5**.

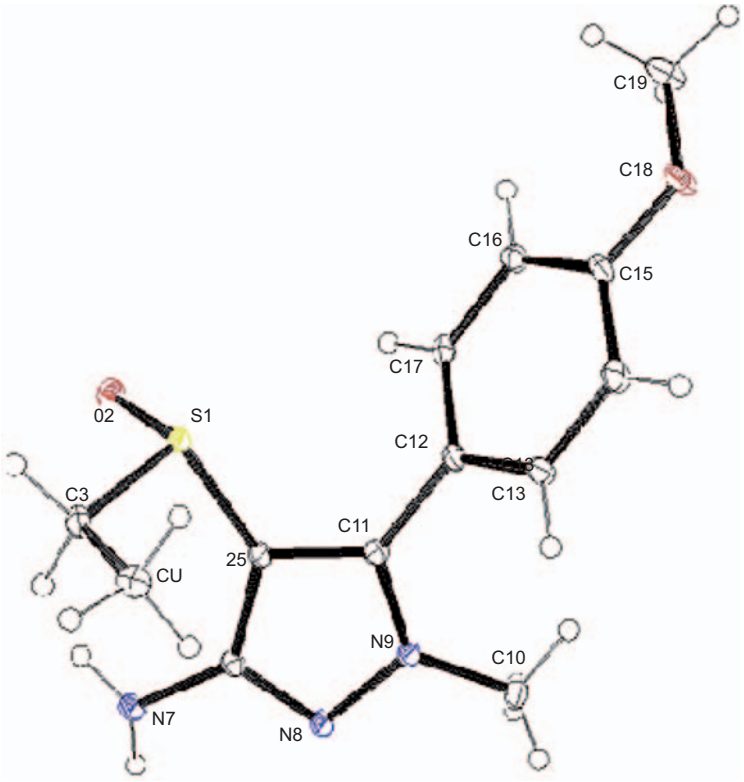
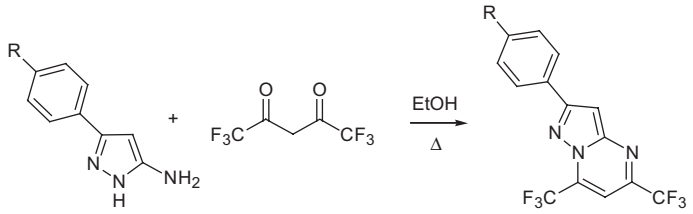


Figure 1 ORTEP diagram (30% probability) of compound **4d**.



Scheme 4 Synthesis of pyrazolo[1,5-*a*]pyrimidine **6** from pyrazole **3**.

added to the oily residue, and the resulting mixture was cooled overnight. The solid was filtered off, yielding the sufficiently pure sulfoxide as a *Z/E* mixture.

3-Bromo-2-(ethylsulfinyl)-3-phenylacrylonitrile (2a) White solid; yield 84%; mp 68–70°C; IR: ν (cm^{-1}) 2217(s); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.29 and 1.42 (2 t, 3H, *J*=7.5 Hz), 2.95 and 3.25 (m, 2H), 7.41 and 7.55 (m, 3H), 7.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 6.9, 7.3, 47.3, 47.9, 112.0, 112.3, 122.8, 124.4, 128.8, 129.0, 129.1, 129.1, 132.3, 132.7, 135.1, 135.7, 148.5, 149.6. HRMS (ESI): analysis calculated for $C_{11}H_{11}BrNOS$ [$(M+H)^{+\bullet}$] 283.97. Found 283.98.

3-Bromo-3-(4-chlorophenyl)-2-(ethylsulfinyl)acrylonitrile (2b) Yellow solid; yield 85%; mp 98–100°C; IR: ν (cm^{-1}) 2217 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.31 and 1.44 (2 t, 3H, *J*=7.5 Hz), 3.03 and 3.27 (m, 2H), 7.44–7.69 (dd, 4H, *J*=8.7 and 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 6.8, 7.4, 47.5, 48.8, 111.9, 112.3, 123.5, 125.1, 129.4, 130.5, 133.6, 134.2, 138.9, 139.2, 146.9, 148.2. HRMS (ESI): analysis calculated for $C_{11}H_9BrClNOSNa$ [$(M+Na)^{+\bullet}$] 339.92. Found 339.92.

3-Bromo-3-(*4-tert*-butylphenyl)-2-(ethylsulfinyl)acrylonitrile (2c) White solid; yield 86%; mp 116–118°C; IR: ν (cm^{-1}) 2212 (s); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.32 (s, 9H), 1.42 (t, 3H, *J*=7.5 Hz), 3.00 and 7.27 (m, 2H), 7.48 (dd, 2H, *J*=7.5 and 2.0 Hz), 7.68 (dd, 2H, *J*=7.5 and 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 6.9, 31.0, 35.2, 47.3, 112.3, 121.4, 125.9, 129.1, 132.7, 148.9, 156.8. HRMS (ESI): analysis calculated for $C_{15}H_{18}BrNOSNa$ [$(M+Na)^{+\bullet}$] 362.02. Found 362.02.

3-Bromo-2-(ethylsulfinyl)-3-(4-methoxyphenyl)acrylonitrile (2d) White solid; yield 90%; mp 96–98°C; IR: ν (cm^{-1}) 2212 (s); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.30 and 1.42 (2 t, 3H, *J*=7.5 Hz),

Table 2 Bactericidal and fungicidal activity of compounds **4d** and **4e**, ciprofloxacin and nystin.

Entry	Compound	*Staphylococcus aureus*	*Escherichia coli*	*Aspergillus niger*	*Fusarium oxysporium*
1	**4d**	20 (++)	16 (++)	20 (++)	20 (++)
2	**4e**	21 (++)	17 (++)	21 (++)	20 (++)
3	ciprofloxacin	++++	++++	–	–
4	nystin	–	–	++++	++++

The diameters of zones of inhibition are given in mm. Stock solution: 5 µg in 1 ml of DMF; 1 ml of stock solution in each hole of each paper disk. +: <15 mm; ++: 15–24 mm; +++: 25–34 mm; ++++: 35–44 mm, etc.

2.86 and 3.31 (m, 2H), 3.87 (s, 3H,), 6.95–7.76 (dd, 4H, *J*=9.0 and 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 6.9, 7.4, 47.3, 47.9, 55.6, 112.5, 114.1, 114.2, 119.8, 127.3, 127.7, 131.5, 131.7, 148.6, 150.1, 163.0, 163.2. HRMS (ESI): analysis calculated for $C_{12}H_{12}BrNOSNa$ [$(M+Na)^{+\bullet}$] 335.97. Found 335.97.

3-(1,3-Benzodioxol-5-yl)-3-bromo-2-(ethylsulfinyl)acrylonitrile (2e) Yellow solid; yield 86%; mp 134–136°C; IR: ν (cm^{-1}) 2202 (s); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.31 and 1.41 (2 t, 3H, *J*=7.5 Hz), 2.96 and 3.29 (m, 2H), 6.07 (s, 2H), 6.86 (d, 1H, *J*=8.3 Hz), 7.17 (d, 1H, J=1.9 Hz), 7.33 (dd, 1H, *J*=8.3 and 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 6.9, 7.4, 47.3, 47.9, 102.4, 108.2, 108.4, 109.4, 109.5, 112.3, 120.8, 125.0, 125.2, 128.7, 129.3, 148.0, 148.2, 148.2, 149.4, 151.4, 151.6. HRMS (ESI): analysis calculated for $C_{12}H_{10}BrNO_3SNa$ [$(M+Na)^{+\bullet}$] 349.95. Found 349.95.

3-Bromo-2-(ethylsulfinyl)-3-(2-methoxyphenyl)acrylonitrile (2f) White solid; yield 80%; mp 88–90°C; IR: ν (cm^{-1}) 2213 (s); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.29 and 1.44 (2 t, 3H, *J*=7.5 Hz), 3.04 and 3.27 (m, 2H), 3.86 and 3.91 (s, 3H), 6.82–7.07 (m, 2H), 7.33–7.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 6.6, 7.2, 47.5, 55.7, 111.3, 111.7, 120.8, 125.4, 129.9, 133.3, 144.2, 155.8. HRMS (ESI): analysis calculated for $C_{12}H_{12}BrNOSNa$ [$(M+Na)^{+\bullet}$] 335.97. Found 335.97.

General procedure for the preparation of compounds 3a–f, 4c–e, 5c–e

Hydrazine hydrate or methylhydrazine (30 mmol) was added with stirring to a suspension of compound **2** (10 mmol) in absolute ethanol (40 ml) cooled to –5°C. After 20 min at 19–20°C and 2 h under reflux, the mixture was cooled, filtered and concentrated under reduced pressure, affording compound **4**. The solid was dissolved into 6N aqueous hydrochloric acid (5 ml) and heated at 50–60°C for 1 h. After cooling, the mixture was basified using 6N aqueous sodium hydroxide until reaching pH 9 and cooled overnight. The crude solid was rapidly purified either on a silica gel column or by crystallization.

Table 3 *In vitro* cytotoxic activity (IC_{50}) of compounds **2e**, **4d**, **4e**, **6a**, **6b** and **6c** and doxorubicin against a human liver carcinoma cell line (HEPG2), a human breast carcinoma cell line (MCF7) and a human cervix carcinoma cell line (HELA).

Entry	Compound	HEPG2 ($\mu g.ml^{-1}$)	MCF7 ($\mu g.ml^{-1}$)	HeLa ($\mu g.ml^{-1}$)
1	**2e**	0.48	0.63	0.59
2	**4d**	2.92	–	–
3	**4e**	3.62	–	–
4	**6a**	1.58	1.05	1.92
5	**6b**	1.20	1.43	1.62
6	**6c**	1.66	2.80	2.27
7	doxorubicin	0.60	0.70	0.85

5-Amino-3-phenyl-1*H*-pyrazole (3a) White solid (eluent: AcOEt-EtOH 99/1); yield 85%; mp 128–130°C (Rama et al., 2006, mp 126–127°C); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 5.91 (s, 1H), 7.32 (td, 1H, *J*=7.35 and 1.1 Hz), 7.38 (dd, 2H, *J*=7.35 and 1.3 Hz), 7.69 (dd, 2H, *J*=7.15 and 1.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 90.3, 125.5, 128.3, 128.9, 130.4, 145.8, 154.3. HRMS (ESI): analysis calculated for $C_9H_{10}N_3$ [$(M+H)^{+\bullet}$] 160.09. Found 160.09.

5-Amino-3-(4-chlorophenyl)-1*H*-pyrazole (3b) White solid (eluent: AcOEt-EtOH 99/1); yield 89%, mp 172°C (Nenaidenko et al., 2004, mp 172–173°C); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 5.92 (s, 1H), 7.40 (d, 2H, *J*=8.5 Hz), 7.50 (d, 2H, *J*=8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 29.6, 90.7, 126.6, 129.1, 134.2, 145.2, 154.0. HRMS (ESI): analysis calculated for $C_9H_9N_3Cl$ [$(M+H)^{+\bullet}$] 194.05. Found 194.05.

5-Amino-3-(*4-tert*-butylphenyl)-1*H*-pyrazole (3c) White solid (eluent: AcOEt-EtOH 99/1); yield 90%; mp 164–166°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.37 (s, 9H), 5.92 (s, 1H), 7.44 (d, 2H, *J*=8.5 Hz), 7.47 (d, 2H, *J*=8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 31.2, 34.6, 90.6, 125.1, 125.8, 127.3, 145.3, 151.7, 155.0. HRMS (ESI): analysis calculated for $C_{13}H_{18}N_3$ [$(M+H)^{+\bullet}$] 216.15. Found 216.15.

5-Amino-3-(4-methoxyphenyl)-1*H*-pyrazole (3d) White solid (eluent: AcOEt-EtOH 97/3); yield 86%; mp 144°C (Nenaidenko et al., 2004, mp 141–143°C); ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 3.75 (s, 3H), 5.7 (s, 1H), 6.95 (d, 2H, *J*=8.8 Hz), 7.6 (d, 2H, *J*=8.8 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 55.0, 87.0, 113.9, 124.5, 126.0, 144.2, 152.8, 158.5. HRMS (ESI): analysis calculated for $C_{10}H_{12}N_3O$ [$(M+H)^{+\bullet}$] 190.10. Found 190.10.

5-Amino-3-(1,3-benzodioxol-5-yl)-1*H*-pyrazole (3e) Gray solid (eluent: AcOEt-EtOH 99/1); yield 85%; mp 158°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.85 (s, 3H), 5.89 (s, 1H), 6.95 (t, 1H, *J*=7.5 Hz), 7.07 (d, 1H, *J*=8.4 Hz), 7.26 (t, 1H, *J*=7.2 Hz), 7.62 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C (ppm): 55.3, 91.5, 111.7, 114.1, 120.4, 120.4, 127.0, 128.5, 138.7, 155.5. HRMS (ESI): analysis calculated for $C_{10}H_{10}N_3O_2$ [$(M+H)^{+\bullet}$] 204.08. Found 204.08.

5-Amino-3-(2-methoxyphenyl)-1*H*-pyrazole (3f) White solid (eluent: AcOEt-EtOH 97/3); yield 88%; mp 94–96°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.85 (s, 3H), 5.89 (s, 1H), 6.95 (t, 1H, *J*=7.5 Hz), 7.07 (d, 1H, *J*=8.4 Hz), 7.26 (t, 1H, *J*=7.2 Hz), 7.62 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 55.3, 91.5, 111.7, 114.1, 120.4, 120.4, 127.0, 128.5, 138.7, 155.5. HRMS (ESI): analysis calculated for $C_{10}H_{12}N_3O$ [$(M+H)^{+\bullet}$] 190.10. Found 190.10.

3-Amino-5-(*4-tert*-butylphenyl)-4-(ethylsulfinyl)-1-methyl-1*H*-pyrazole (4c) The compound was obtained after crystallization from AcOEt-EtOH as a pale yellow solid; yield 90%; mp 186°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.07 (t, 3H, *J*=7.5 Hz), 1.32 (s, 9H), 2.98–3.17 (m, 2H), 3.51 (s, 3H), 5.09 (br s, 2H), 7.32 (d, 2H, *J*=8.7 Hz), 7.52 (d, 2H, *J*=8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 7.9, 30.9, 34.4, 36.3, 45.5, 102.0, 124.7, 125.4, 129.4, 142.8, 151.8, 153.4. HRMS (ESI): analysis calculated for $C_{16}H_{24}N_3OS$ [$(M+H)^{+\bullet}$] 306.16. Found 306.16.

3-Amino-4-(ethylsulfinyl)-5-(4-methoxyphenyl)-1-methyl-1*H*-pyrazole (4d) The compound was obtained after crystallization from AcOEt-EtOH as a yellow solid; yield 86%; mp.174–176°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.05 (t, 3H, *J*=7.5 Hz), 2.94–3.13 (m, 2H), 3.49 (s, 3H), 3.81 (s, 3H), 5.07 (s, 1H), 7.06 (d, 2H, *J*=8.7 Hz), 7.34 (d, 2H, *J*=8.7 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 7.8, 36.1, 45.6, 55.2, 101.9, 114.1, 119.7, 131.1, 142.8, 153.4, 159.9. HRMS (ESI): analysis calculated for $C_{13}H_{18}N_3O_2S$ [$(M+H)^{+\bullet}$] 279.10. Found 279.10.

3-Amino-5-(1,3-benzodioxol-5-yl)-4-(ethylsulfinyl)-1-methyl-1*H*-pyrazole (4e) The compound was obtained after crystallization from AcOEt-EtOH as a white solid; yield 95%; mp 170°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.12 (t, 3H, *J*=6.0 Hz), 3.01–3.19 (m, 2H), 5.15 (br s, 2H), 6.17 (s, 2H), 6.93 (dd, 1H, *J*=9.0 and 3.0 Hz), 7.08–7.12 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 7.9, 36.3, 45.6, 101.6, 102.1, 108.5, 109.9, 121.1, 124.1, 142.6, 147.4, 148.2, 153.5. HRMS (ESI): analysis calculated for $C_{13}H_{16}N_3O_3S$ [$(M+H)^{+\bullet}$] 294.09. Found 294.09.

3-Amino-5-(*4-tert*-butylphenyl)-1-methyl-1*H*-pyrazole (5c) White solid (eluent: AcOEt); yield 90%; mp 140°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.35 (s, 9H), 3.70 (s, 9H), 5.66 (s, 1H), 7.32 (d, 2H, *J*=8.7 Hz), 7.45 (d, 2H, *J*=8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 31.2, 34.6, 36.6, 93.1, 125.5, 127.9, 128.2, 145.0, 151.4, 153.2. HRMS (ESI): analysis calculated for $C_{14}H_{20}N_3$ [$(M+H)^{+\bullet}$] 230.166. Found 230.17.

3-Amino-5-(4-methoxyphenyl)-1-methyl-1*H*-pyrazole (5d) Pale yellow solid (eluent: AcOEt-EtOH 99/1); yield 75%; mp 130°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 3.68 (s, 3H), 3.86 (s, 3H), 5.64 (s, 1H), 6.98 (d, 2H, *J*=6.7 Hz), 7.33 (d, 2H, *J*=6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 36.6, 55.5, 93.0, 114.0, 114.2, 123.3, 129.9, 131.0, 144.9, 153.3, 159.7. HRMS (ESI): analysis calculated for $C_{11}H_{14}N_3O$ [$(M+H)^{+\bullet}$] 204.11. Found 204.11.

3-Amino-5-(1,3-benzodioxol-5-yl)-1-methyl-1*H*-pyrazole (5e) The compound was obtained after crystallization from AcOEt as a pale yellow solid; yield 70%; mp 142–144°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.55 (s, 3H), 5.49 (s, 2H), 6.06 (s, 2H), 6.89 (dd, 1H, J=9.0 and 1.8 Hz), 6.96–7.00 (m, 2H);^{13}C NMR (75 MHz, DMSO-d_6): δ_C 36.3, 92.2, 101.2, 108.4, 108.5, 121.9, 124.5, 143.0, 147.0, 147.4, 154.0. HRMS (ESI): analysis calculated for $C_{11}H_{12}N_3O_2$ [$(M+H)^{+\bullet}$] 218.09. Found 218.09.

4.4. General procedure for the preparation of the 2-aryl-5,7-bis(trifluoromethyl)pyrazolo[1,5-*a*] pyrimidines 6 according to the procedure described in Rama et al. (2006)

A solution of aminopyrazole **3** (1 mmol) in ethanol (2 ml) was added to an ethanolic solution of hexafluoroacetylacetone (1 mmol). The mixture was heated under reflux for 3 h. The solvent was removed and the crude material was purified by crystallization.

2-Phenyl-5,7-bis(trifluoromethyl)pyrazolo[1,5-a]pyrimidine (6a) The compound was obtained after crystallization from AcOEt-EtOH as yellow crystals; yield 75%; mp 132–134°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.34 (s, 1H), 7.43 (s, 1H), 7.45–7.55 (m, 3H), 8.06 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm): 96.8, 101.8 (m), 119.0 (q, *J*=275 Hz), 120.2 (q, *J*=275 Hz), 127.0, 129.0, 130.1, 131.2, 136.2 (q, *J*=39 Hz), 145.5 (q, *J*=38 Hz), 159.2. Analysis calculated for $C_{14}H_7F_6N_3$: C, 50.77; H, 2.13; N, 12.69%. Found C, 50.33; H, 2.04; N, 12.60%.

2-(4-Chlorophenyl)-5,7-bis(trifluoromethyl)pyrazolo[1,5-*a*] pyrimidine (6b) The compound was obtained after crystallization from EtOH as yellow crystals; yield 70%; mp 164–166°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.31 (s, 1H), 7.43 (s, 1H), 7.46 (d, 2H, *J*=8.7 Hz), 7.99 (d, 2H, *J*=8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 96.8, 102.1 (m), 118.9 (q, *J*=275 Hz), 120.1 (q, *J*=275 Hz), 128.2, 129.2, 129.7, 135.2 (q, *J*=38 Hz), 145.8 (q, *J*=38 Hz), 136.2, 149.4, 158.1. Analysis calculated for $C_{14}H_7ClF_6N_3$: C, 45.99; H, 1.65; N, 11.49%. Found C, 45.70; H, 1.75; N, 11.23%.

2-(*4-tert*-Butylphenyl)-5,7-bis(trifluoromethyl)pyrazolo[1,5-*a*] pyrimidine (6c) The compound was purified by crystallization from EtOH as yellow crystals, yield 86%, mp 116–118°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 7.32 (s, 1H), 7.41 (s, 1H), 7.54 (d, 2H, *J*=8.7 Hz), 8.00 (d, 2H, *J*=8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 31.4, 35.0, 96.8, 101.8 (m), 118.9 (q, *J*=275 Hz), 120.1 (q, *J*=275 Hz), 126.1, 127.0, 128.6, 135.3 (q, *J*=38 Hz), 145.6 (q, *J*=38 Hz), 149.6, 153.7, 159.6. Analysis calculated for $C_{18}H_{15}F_6N_3$: C, 55.82; H, 3.90; N, 10.85%. Found C, 5.72; H, 3.67; N, 10.60%.

Crystallographic data for compound 4d

Crystals of **4d** were obtained from a CH_2Cl_2 solution by slow evaporation of the solvent. The sample was studied with graphite monochromatized $Mo_K\alpha$ radiation (λ=0.71073 Å). X-ray diffraction data were collected at *T*=*T*=100(2) K using APEXII, Bruker-AXS diffractometer. The structure was solved by direct methods using the SIR97 program (Altomare et al., 1999) and then refined with full-matrix least-square methods based on F^2 (SHELXL-97) (Sheldrick, 2008) with the aid of the WINGX program (Farrugia, 1999). All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Nitrogen-linked hydrogen atoms were introduced in the structural model through Fourier difference map analysis. Molecular diagrams were generated by ORTEP-3, version 1.08 (Farrugia, 1997).

Crystal data for 4d $C_{13}H_{17}N_3O_2S$, *M*=279.36 g.mol^{-1}, monoclinic, $P2_1/c$, *a*=8.4546(9), *b*=18.0721(17), *c*=9.1047(9) Å, β=95.676(5)°, *V*=1384.3(2) Å^3, *Z*=4, *d*=1.34 g.cm^{-3}, μ=0.236 mm^{-1}. A final refinement on F^2 with 3088 unique intensities and 181 parameters converged at $\omega R(F^2)$=0.11 (*R*(F)=0.05) for 2143 observed reflections with I >2σ(*I*). Crystallographic data were deposited in CSD under CCDC registration number 809709.

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