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Reaction of hydrazinoquinolines with trifluoromethyl-β-diketones: structural and mechanistic studies

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Abstract

Reaction of 2-hydrazino-4-methylquinoline with a series of trifluoromethyl-β-diketones gives 3-substituted-5-hydroxy-1-(4-methylquinolin-2-yl)-5-trifluoromethyl-4,5-dihydropyrazoles and, in some cases, 5-substituted-1-(4-methylquinolin-2-yl)-3-trifluoromethylpyrazoles, depending on the substitution of the diketone. Dehydration of the hydroxydihydropyrazoles can be effected with sulphuric acid in acetic acid to give the regioisomeric 3-substituted-1-(4-methylquinolin-2-yl)-5-trifluoromethylpyrazoles. In contrast, the reaction of two 4-hydrazinoquinolines with 1,1,1-trifluoropentane-2,4-dione afforded a different isolable intermediate, the corresponding hydrazone formed at the 4-carbonyl. Dehydration gave the 1-(substituted-quinolin-4-yl)-3-methyl-5-trifluoromethylpyrazoles. The regioisomeric identity of the pyrazoles was established using ^{19}F NMR. © Elsevier Science S.A.

Keywords: Pyrazole; Hydrazinoquinoline; Trifluoromethyl-β-diketone; Cyclisation; ^{19}F NMR

1. Introduction

Recent investigations from our laboratory have shown that the products obtained by treating 2- and 4-hydrazinoquinolines with β-dicarbonyl compounds are the pyrazoles [1,2], instead of the erroneously reported diazepines [3,4]. In continuation of this work, we focused our attention on the reaction of these hydrazines with trifluoromethyl 1,3-diketones. Such a study assumes greater significance in view of the current interest in the development and application of compounds bearing trifluoromethyl groups as pharmaceuticals and agrochemicals [5–7].

2. Results and discussion

In general, the reaction of a monosubstituted hydrazine with unsymmetrical β-diketones can result in the formation of isomeric pyrazoles, depending on the site of initial nucleophilic attack [8–10]. In the first part of the present study, the reaction of 2-hydrazino-4-methylquinoline **1** with the aliphatic trifluoromethyl-β-diketones **2a,b** was investigated. The sole products were identified as the 5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazoles **3a,b**, respectively. However, similar treatment of the aryl trifluoromethyl-β-diketones **2c,d** with **1** in refluxing ethanol gave a mixture of the corresponding 5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazoles **3c,d** and the 3-trifluoromethylpyrazoles **4c,d** (Scheme 1). No traces of **4a,b** were detected in the reaction mixtures. The hydroxydihydropyrazoles **3a–d** were only converted to the aromatic pyrazoles **5a–d** on treatment with sulphuric acid in acetic acid at elevated temperature. These observations, which raise questions of the initial site of nucleophilic attack on the diketone and rate of dehydration/aromatisation of the pyrazole, can be rationalised as follows.

As it is unlikely that the initial nucleophilic attack involves the secondary nitrogen of the hydrazinoquinoline, the first approach must be as shown in Scheme 2. It has been shown [11,12] that **2a–d** exist substantially in the enol form and that the direction of enolisation is largely towards $COCF_3$. Furthermore, there have been reports that these unsymmetrical diketones **2a–d** react with water [13], alcohols [13,14], ethanethiol [15] and pyrrolidine [15] to give the adducts at the $COCF_3$ carbonyl, probably through addition to the appropriate enol. It is therefore likely that, in the present study, the reaction proceeds via conjugate addition of the terminal nitrogen of the hydrazinoquinoline into the two enols, as shown in Scheme 2. Subsequent cyclisation affords the isomeric dihydroxytetrahydropyrazoles. One molecule of water is then eliminated to give the hydroxydihydropyrazoles; further

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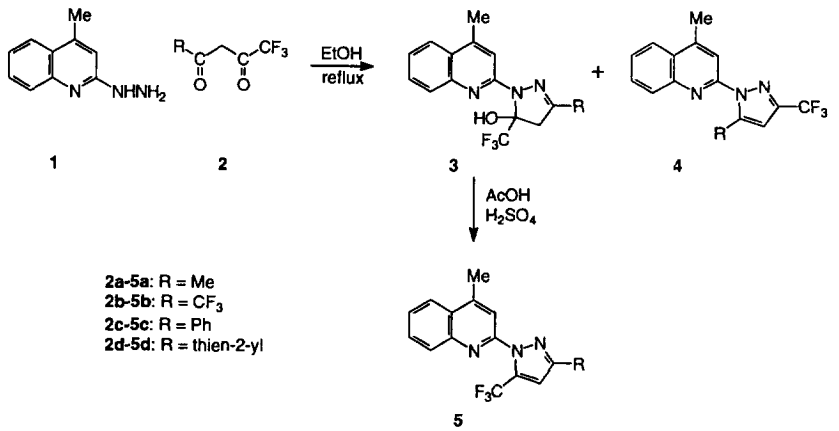
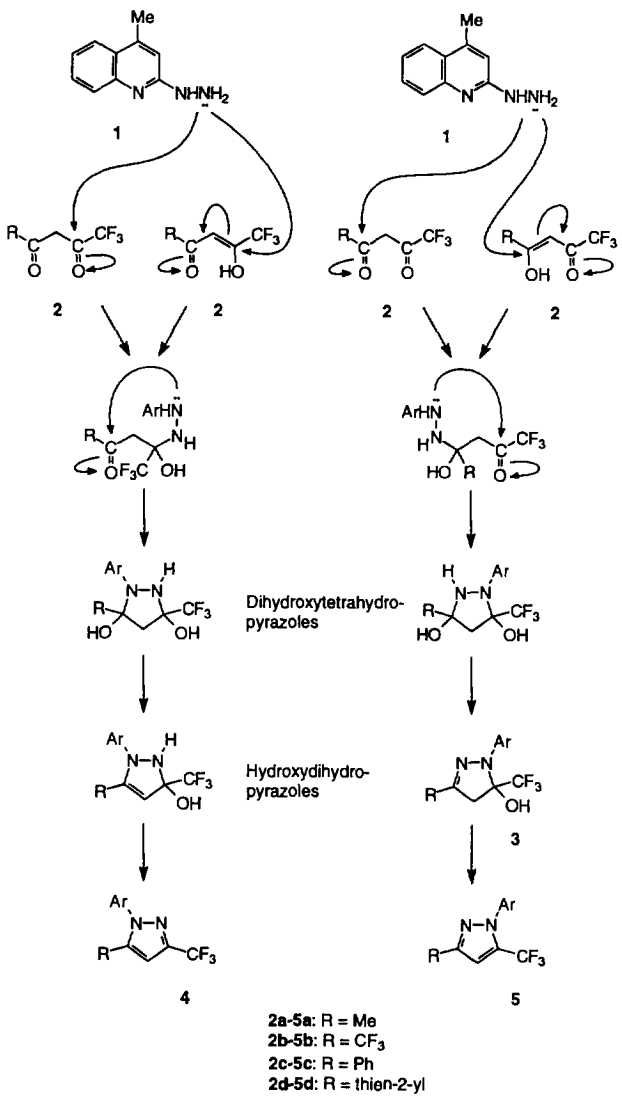


Scheme 1. Reaction of 2-hydrazino-4-methylquinoline **1** with trifluoromethyl β-diketones **2a–d**.

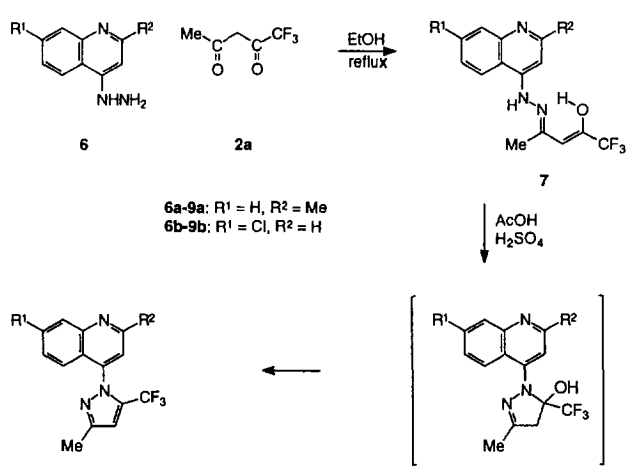


Scheme 2. Possible mechanistic routes for the reaction of 2-hydrazino-4-methylquinoline **1** with trifluoromethyl β-diketones **2a–d**.

elimination of water yields the aromatic pyrazoles **4** and **5**. The ratio of yields of these two regioisomers depends on the proportion of the two enols at equilibrium. For β-diketone **2a**, where R is aliphatic, the $COCF_3$ carbonyl is predominantly enolised, leading eventually to products **3a** and **5a**. In contrast, where R is aromatic (**2c,d**), this enol is cross-conjugated between the C=C and the arene, whereas the alternative enol is fully conjugated in the system Ar–C=C–C=O. Thus, there is now a significant amount of the minor enol present in the reaction mixture and attack can take place, leading to significant amounts of the regioisomer **4**. It should be noted that this effect runs counter to steric influences.

The hydroxydihydropyrazoles **3** can be isolated as stable crystalline solids from the initial reaction mixture but the regioisomeric hydroxydihydropyrazoles are converted directly in boiling ethanol to the pyrazoles **4**. These observations must reflect the relative ease of elimination of the second molecule of water in the overall condensation. Presumably, as the OH or OH_2 leaves, positive charge builds up at C-5 and the electron-withdrawing trifluoromethyl group destabilises this build-up. This effect has been noted [16] for the reaction of 1,1,1,5,5,5-hexafluoropentane-2,4-dione **2b** with other aryl and acyl hydrazines.

In contrast (Scheme 3), when the hydrazine was translocated to the 4-position of the quinoline and substrates **6a,b** were allowed to react with **2a** under the standard conditions (boiling ethanol), the stable crystalline hydrazones **7a,b** were



Scheme 3. Reaction of 4-hydrazinoquinolines **6a,b** with 1,1,1-trifluoropentane-2,4-dione **2a**.

isolated. Elimination of the second molecule of water was effected only by treatment with sulphuric acid in hot acetic acid, reflecting again the relative difficulty of this elimination from a 5-hydroxy-5-trifluoromethyldihydropyrazole. These observations indicate that elimination of the first molecule of water precedes the cyclisation with these substrates **6**. As expected from the studies with **1** and **2a**, there was no evidence of formation of other regioisomers. We were unable to isolate the corresponding hydroxydihydropyrazoles **8a,b** from the reactions, although it is unclear why the point of attachment to the quinoline should have such an effect on the course of the reaction. Hydrazones related to **7** are rarely reported in the literature [17,18] and only those too without direct spectroscopic evidence for their structure.

The structures of the pyrazoles and the intermediates were deduced from their NMR spectra. For example, the ^{1}H NMR spectrum of **3a** displays the signal for the pyrazole 3-Me at δ 2.09 and the methylene protons resonate as an AB system at δ 3.17 and δ 3.34, with a geminal coupling constant ^2J 18.6 Hz. In the regioisomeric hydroxydihydropyrazole (leading to **4a**), the methyl group would resonate at δ ca. 1.5. The same pattern was evident for the analogues **3b–d**. We have previously shown this AB pattern to be characteristic in a series of 5-hydroxy-3,5-bis(trifluoromethyl)-4,5-dihydropyrazoles [16]. Structures **3a–d** were confirmed by mass spectroscopic studies in which molecular ions were observed corresponding to the hydroxydihydropyrazoles, rather than the dihydroxytetrahydropyrazoles or pyrazoles. Further support for the regioisomeric identity of **3a–d** was given by ^{13}C NMR (Table 1). The presence of the trifluoromethyl group makes assignment of the signals straightforward. For example, for **3a**, pyrazole C-3 (sp^2) resonates as a singlet at δ 151.37, C-4 as a singlet at δ 47.90 and C-5 as a quartet ($^2J_{C-F}$ 34.1 Hz) at δ 93.09. In **3b**, which contains two trifluoromethyl groups, pyrazole C-3 appears as a quartet ($^2J_{C-F}$ 39.7 Hz) at δ 140.31, a chemical shift which is appropriate for a sp^2 carbon. Thus the trifluoromethyl group must be attached to the sp^3 carbon in **3a** and the regioisomer must be as shown.

For the hydrazones **7a,b**, the ^{1}H NMR data lend support to the acyclic hydrazone–enol structure as follows. Firstly, no signal is seen at δ 3.5 but rather a singlet from the enol =CH– appears at δ 5.42 for **7a**, ruling out a hydrazone–ketone structure. Secondly, the NH and OH protons of **7a** resonate at δ 11.40 and δ 14.32, respectively, which indicate both that an OH is present and that there is strong intramolecular hydrogen-bonding. Similar observations were recorded for **7b**. The enol form of the hydrazones **7a,b** was further suggested by

Table 1
^{13}C NMR data for hydroxydihydropyrazoles **3a–d**

Carbon atom	**3a**	**3b**	**3c**	**3d**
Pyrazole carbons				
C-3	151.37	140.31 (q, $^2J_{C-F}$ = 39.7 Hz)	150.19	146.07
C-4	47.90	41.95	44.14	44.74
C-5	93.09 (q, $^2J_{C-F}$ = 34.1 Hz)	94.62 (q, $^2J_{C-F}$ = 34.2 Hz)	93.51 (q, $^2J_{C-F}$ = 33.1 Hz)	93.50 (q, $^2J_{C-F}$ = 33.0 Hz)
Quinoline carbons				
C-2	155.54	154.39	155.24	155.03
C-3	112.90	112.53	112.79	112.75
C-4	144.82	144.43	144.79	144.72
C-5	123.83	125.02	124.02	124.04
C-6	123.70	123.83	123.78	123.76
C-7	126.96	127.37	129.83	128.24
C-8	129.70	130.19	130.02	129.82
C-4a	124.45	125.21	124.62	124.62
C-8a	146.65	147.87	146.84	146.91
Other carbons				
quinoline-CH_3	18.87	18.90	19.04	18.99
pyrazole-CF_3	123.97	123.34	123.95	123.86
	(q, $^1J_{C-F}$ = 287.6 Hz)	(q, $^1J_{C-F}$ = 287.5 Hz)	(q, $^1J_{C-F}$ = 287.7 Hz)	(q, $^1J_{C-F}$ = 288.8 Hz)
pyrazole 3-R	15.53 (Me)	119.82 (q, $^1J_{C-F}$ = 269.9 Hz) (CF_3)	130.97 (Ph C-1)	134.43 (thiophene C-2)
			126.14 (Ph C-2,6)	128.00 (thiophene C-3)
			128.75 (Ph C-3,5)	126.98 (thiophene C-4)
			127.05 (Ph C-4)	127.60 (thiophene C-5)

the ^{13}C NMR data, in contrast to the isomeric hydroxydihydropyrazoles **8a,b**. Characteristic signals were seen for **7a** at δ 169.60 ($^{2}J_{C-F}$ 31.2 Hz, =C–CF_3), δ 118.54 ($^{1}J_{C-F}$ 286.6 Hz, CF_3) and δ 87.84 (=CH–). No CH_2 signals were seen in the 135 DEPT spectrum, ruling out hydrazone–ketone and hydroxydihydropyrazole structures. The pattern of chemical shifts and multiplicities for the C-5 unit are very similar to those reported [19] for the enol form of 1,1,1-trifluoropentane-2,4-dione **2a**.

The pyrazoles **4c,d**, **5a–d** and **9** were characterised by a signal in the range δ 6.63–δ 7.21 for the aromatic pyrazole 4-H. It is interesting to note that the presence of trifluoromethyl at pyrazole C-5 causes the 4-H to resonate further downfield as compared with trifluoromethyl at pyrazole C-3 ($\Delta\delta$ 0.42 for **4c/5c**, $\Delta\delta$ 0.21 for **4d/5d**).

Complete analysis of the ^{13}C spectra of **4c,d**, **5a–d** and **9** (Table 2) was achieved by comparison with reported chemical shifts for pyrazoles [20–22] and quinolines [23] and by DEPT experiments (Table 2). The $\mathbf{C}F_3$ carbons resonated at ca. δ 120 with $^{1}J_{C-F}$ ca. 270 Hz. The $\mathbf{C}$–CF_3 carbons resonated as quartets at δ ca. 143 and δ ca. 133 for pyrazole C-3 and pyrazole C-5, respectively. In the corresponding 1-(quinolin-2-yl)-3,5-dimethylpyrazoles [1], C-3 and C-5 resonate at δ ca. 150 and δ ca. 142, respectively. Thus it can be seen that replacement of CH_3 by CF_3 results in shielding of these ring carbons by ca. 8 ppm.

Finally, ^{19}F NMR has been found to be an elegant method for assigning the trifluoromethyl hydroxydihydropyrazole, hydrazone and pyrazole structures (Table 3). The hydroxydihydropyrazoles **3a–d** exhibited signals at δ ca. −81 for the 5-CF_3, in contrast to δ −67.39 for the 3-CF_3 of **3b**. In contrast, the trifluoromethyl group of the hydrazones **7a,b** resonate at δ ca. −75. Isomeric trifluoromethylpyrazoles can easily be distinguished by their ^{19}F spectra. The 5-CF_3 resonates at δ ca. −58, in contrast to the more upfield resonance of the 3-CF_3 at δ ca. −62.

3. Experimental details

Melting points were determined using open capillaries in a sulphuric acid bath and are uncorrected. ^{1}H NMR spectra were obtained at 270 MHz and 400 MHz, ^{13}C spectra at 67.5 MHz and 100 MHz and ^{19}F spectra at 376 MHz, using Jeol GX270 and Jeol EX400 instruments, using deuteriochloroform as solvent, unless otherwise noted. The internal standard for the ^{19}F spectra was fluorotrichloromethane, setting the $CF^{35}Cl_3$ signal as δ 0.00. ^{13}C and ^{19}F NMR data for **3a–d**, **4c,d**, **5a–d** and **9a,b** are presented in Tables 1–3, respectively. The stationary phase for chromatography was silica gel. High resolution mass spectra were measured in the EI mode on a Kratos MS-50 spectrometer. Elemental analyses were performed at RSIC, Chandigarh, India. 2-Hydrazino-4-methylquinoline **1** [24], 4-hydrazino-2-methylquinoline **6a** [25] and 7-chloro-4-hydrazinoquinoline **6b** [26] were prepared by procedures described in the literature.

3.1. 5-Hydroxy-3-methyl-1-(4-methylquinolin-2-yl)-5-trifluoromethyl-4,5-dihydropyrazole (3a)

1,1,1-Trifluoropentane-2,4-dione **2a** (770 mg, 5 mmol) was boiled under reflux with 2-hydrazino-4-methylquinoline **1** (865 mg, 5 mmol) in ethanol (50 ml) for 3 h. Evaporation of the solvent and recrystallisation (ethanol) provided the hydroxydihydropyrazole **3a** (1.20 g, 78%) as a pale yellow solid, m.p. 113–114 °C. ^{1}H NMR δ: 2.09 (s, 3 H, pyrazole-Me); 2.62 (s, 3 H, quinoline-Me); 3.17 (d, 1 H, J = 18.6 Hz, pyrazole 4-H); 3.34 (d, 1 H, J = 18.6 Hz, pyrazole 4-H); 7.35 (ddd, 1 H, quinoline 6-H); 7.41 (s, 1 H, quinoline 3-H); 7.57 (ddd, 1 H, quinoline 7-H); 7.70 (d, 1 H, quinoline 5-H); 7.82 (d, 1 H, quinoline 8-H) ppm. MS m/z: 309.1092 (M) ($C_{15}H_{14}F_3N_3O$ requires: 309.1089); 291.0991 (M − H_2O) ($C_{15}H_{12}F_3N_3$ requires: 291.0983) (100%). Analysis: Found: N, 13.54%. $C_{15}H_{14}F_3N_3O$ requires: N, 13.59%.

3.2. 3,5-Bis(trifluoromethyl)-5-hydroxy-1-(4-methylquinolin-2-yl)-4,5-dihydropyrazole (3b)

1,1,1,5,5,5-Hexafluoropentane-2,4-dione **2b** (1.04 mg, 5 mmol) was treated with **1** (865 mg, 5 mmol), as for the synthesis of **3a**, to give the hydroxydihydropyrazole **3b** (1.35 g, 75%) as a pale yellow solid, m.p. 135–136 °C. ^{1}H NMR δ: 2.65 (s, 3 H, quinoline-Me); 3.42 (d, 1 H, J = 19.0 Hz, pyrazole 4-H); 3.60 (d, 1 H, J = 19.0 Hz, pyrazole 4-H); 7.42 (s, 1 H, quinoline 3-H); 7.43 (ddd, 1 H, quinoline 6-H); 7.62 (ddd, 1 H, quinoline 7-H); 7.74 (d, 1 H, quinoline 5-H); 7.87 (d, 1 H, quinoline 8-H) ppm. MS m/z: 363.0791 (M) ($C_{15}H_{11}F_6N_3O$ requires: 363.0806); 345.0703 (M − H_2O) ($C_{15}H_9F_6N_3$ requires: 345.0701); 294.0858 (M − CF_3) ($C_{14}H_{11}F_3N_3O$ requires: 294.0854) (100%). Analysis: Found: N, 11.49%. $C_{15}H_{11}F_6N_3O$ requires: N, 11.57%.

3.3. 5-Hydroxy-1-(4-methylquinolin-2-yl)-3-phenyl-5-trifluoromethyl-4,5-dihydropyrazole (3c) and 1-(4-methylquinolin-2-yl)-5-phenyl-3-trifluoromethyl-pyrazole (4c)

1-Phenyl-4,4,4-trifluorobutane-1,3-dione **2c** (1.08 g, 5 mmol) was boiled under reflux with 2-hydrazino-4-methylquinoline **1** (865 mg, 5 mmol) in ethanol (50 ml) for 3 h and the solvent was evaporated. Chromatography (light petroleum (b.p. 60–80 °C):benzene (CAUTION) 4:1) afforded the hydroxydihydropyrazole **3c** (1.15 g, 62%) as an off-white solid, m.p. 137–138 °C. ^{1}H NMR δ: 2.68 (s, 3 H, quinoline-Me); 3.63 (d, 1 H, J = 18.3 Hz, pyrazole 4-H); 3.77 (d, 1 H, J = 18.3 Hz, pyrazole 4-H); 7.24–7.44 (m, 4 H, quinoline 6-H + Ph 3,4,5-H_3); 7.58–7.62 (m, 2 H, quinoline 3,7-H_2); 7.73–7.77 (m, 3 H, quinoline 5-H + Ph 2,6-H_2); 7.86 (d, 1 H, quinoline 8-H) ppm. Analysis: Found: N, 11.42%. $C_{20}H_{16}F_3N_3O$ requires: N, 11.32%. Further elution (light petroleum (b.p. 60–80 °C):benzene 1:1) afforded the

Table 2
^{13}C NMR data for compounds **4c,d**, **5a–d** and **9a,b**

Carbon atom	**4c**	**4d**	**5a**	**5b**	**5c**	**5d**	**9a**	**9b**
Pyrazole carbons								
C-3	143.71 (q, $^2J_{C-F}$ = 36.8 Hz)	143.58 (q, $^2J_{C-F}$ = 38.6 Hz)	149.47	142.05 (q, $^2J_{C-F}$ = 38.6 Hz)	149.49	147.61	149.99	150.39
C-4	106.72	106.83	111.57	108.36	109.04	108.97	108.35	108.80
C-5	145.82	139.53	133.12 (q, $^2J_{C-F}$ = 40.7 Hz)	133.26 (q, $^2J_{C-F}$ = 42.9 Hz)	133.82 (q, $^2J_{C-F}$ = 41.0 Hz)	133.84 (q, $^2J_{C-F}$ = 40.5 Hz)	134.20 (q, $^2J_{C-F}$ = 38.6 Hz)	134.20 (q, $^2J_{C-F}$ = 40.0 Hz)
Quinoline carbons								
C-2	150.11	149.88	149.65	147.69	151.78	149.27	158.97	151.16
C-3	116.96	117.49	118.17	113.47	114.65	114.62	119.90	119.01
C-4	145.98	145.85	146.10	144.80	146.00	145.98	143.11	142.98
C-5	126.94	126.94	126.36	126.25	125.94	125.43	127.09	124.44
C-6	123.67	123.82	123.64	122.76	123.69	123.71	122.57	128.59
C-7	128.99	129.28	129.56	128.75	128.86	129.56	128.81	136.49
C-8	129.67	130.22	129.91	129.36	129.58	130.02	130.35	129.10
C-4a	127.46	127.42	127.22	126.75	127.35	127.36	123.45	123.52
C-8a	147.92	148.19	147.41	147.40	147.52	147.23	149.11	149.86
Other carbons								
quinoline-CH_3	18.88 (4-CH_3)	18.86 (4-CH_3)	18.86 (4-CH_3)	17.92 (4-CH_3)	18.99 (4-CH_3)	18.99 (4-CH_3)	25.30 (2-CH_3)	
pyrazole 3-CH_3			13.47				13.38	13.38
pyrazole 3-CF_3	121.17 (q, $^1J_{C-F}$ = 270.3 Hz)	121.02 (q, $^1J_{C-F}$ = 268.4 Hz)		118.30 (q, $^1J_{C-F}$ = 268.8 Hz)				
pyrazole 5-CF_3			120.14 (q, $^1J_{C-F}$ = 267.7 Hz)	119.36 (q, $^1J_{C-F}$ = 268.9 Hz)	120.07 (q, $^1J_{C-F}$ = 268.0 Hz)	119.92 (q, $^1J_{C-F}$ = 268.4 Hz)	119.46 (q, $^1J_{C-F}$ = 268.4 Hz)	119.50 (q, $^1J_{C-F}$ = 270.0 Hz)
Ph or thiophene	130.13 (Ph C-1) 128.11 (Ph C-2,6) 130.00 (Ph C-3,5) 128.68 (Ph C-4)	130.00 (thiophene C-2) 129.63 (thiophene C-3) 127.22 (thiophene C-4) 127.79 (thiophene C-5)			131.55 (Ph C-1) 126.49 (Ph C-2,6) 130.00 (Ph C-3,5) 128.81 (Ph C-4)	134.50 (thiophene C-2) 127.68 (thiophene C-3) 126.03 (thiophene C-4) 126.54 (thiophene C-5)		

Table 3
^{19}F NMR data for compounds **3a–d**, **4c,d**, **5a–d** and **9a,b**

	3a	3b	3c	3d	4c	4d	5a	5b	5c	5d	9a	9b
3-CF_3		67.39			62.80	62.87		63.16				
5-CF_3	81.72	81.64	81.63	81.58			58.15	58.49	58.13	58.25	58.94	58.80

pyrazole **4c** (185 mg, 10%) as an off-white solid, m.p. 110–111 °C. ^1H NMR δ 2.72 (d, 3 H, J = 0.9 Hz, quinoline-Me); 6.79 (s, 1 H, pyrazole 4-H); 7.24–7.36 (m, 5 H, Ph-H_5); 7.52–7.69 (m, 4 H, quinoline 3,5,6,7-H_4); 7.98 (d, 1 H, quinoline 8-H) ppm. Analysis: Found: N, 11.86%. $C_{20}H_{14}F_3N_3$ requires: N, 11.90%.

*3.4. 5-Hydroxy-1-(4-methylquinolin-2-yl)-3-(thien-2-yl)-5-trifluoromethyl-4,5-dihydropyrazole (**3d**) and 1-(4-methylquinolin-2-yl)-5-(thien-2-yl)-3-trifluoromethylpyrazole (**4d**)*

1-(Thien-2-yl)-4,4,4-trifluorobutane-1,3-dione **2d** (1.11 g, 5 mmol) was boiled under reflux with 2-hydrazino-4-methylquinoline **1** (865 mg, 5 mmol) in ethanol (50 ml) for 3 h and the solvent was evaporated. Chromatography (light petroleum (b.p. 60–80 °C):benzene (CAUTION) 4:1) afforded the hydroxydihydropyrazole **3d** (1.15 g, 61%) as a pale solid, m.p. 123–124 °C. ^1H NMR δ: 2.66 (d, 3 H, J = 0.7 Hz, quinoline-Me); 3.61 (d, 1 H, J = 18.1 Hz, pyrazole 4-H); 3.77 (d, 1 H, J = 18.1 Hz, pyrazole 4-H); 7.06 (dd, 1 H, thiophene 4-H); 7.20 (dd, 1 H, thiophene 3-H); 7.34–7.41 (m, 2 H, quinoline 6-H + thiophene 5-H); 7.52 (s, 1 H, quinoline 3-H); 7.59 (ddd, 1 H, quinoline 7-H); 7.72 (d, 1 H, quinoline 5-H); 7.84 (d, 1 H, quinoline 8-H); 9.43 (br, 1 H, OH) ppm. Analysis: Found: N, 11.27%. $C_{18}H_{14}F_3N_3OS$ requires: N, 11.14%. Further elution (light petroleum (b.p. 60–80 °C):benzene 1:1) afforded the pyrazole **4d** (150 mg, 8%) as a pale solid, m.p. 75–76 °C. ^1H NMR δ: 2.73 (d, 3 H, J = 0.7 Hz, quinoline-Me); 6.87 (s, 1 H, pyrazole 4-H); 6.97 (dd, 1 H, thiophene 4-H); 7.22 (dd, 1 H, thiophene 3-H); 7.33 (dd, 1 H, thiophene 5-H); 7.57–7.63 (m, 2 H, quinoline 3,6-H_2); 7.72 (ddd, 1 H, quinoline 7-H); 7.96–8.03 (m, 2 H, quinoline 5,8-H_2) ppm. Analysis: Found: N, 11.73%. $C_{18}H_{12}F_3N_3S$ requires: N, 11.70%.

*3.5. 3-Methyl-1-(4-methylquinolin-2-yl)-5-trifluoromethylpyrazole (**5a**)*

The hydroxydihydropyrazole **3a** (927 mg, 3 mmol) was boiled under reflux with concentrated sulphuric acid (0.2 ml) in acetic acid (20 ml) for 5 h. The mixture was poured into ice-water and was extracted thrice with dichloromethane. The combined organic extracts were washed with aqueous sodium hydrogen carbonate solution and with water and were dried (sodium sulphate). The solvent was evaporated and the residue was recrystallised from ethanol to give the pyrazole **5a** (788 mg, 85%) as a pale yellow solid, m.p. 103–104 °C. ^1H NMR δ: 2.39 (s, 3 H, pyrazole-Me); 2.74 (s, 3 H, quinoline-Me); 6.70 (s, 1 H, pyrazole 4-H); 7.54 (ddd, 1 H, quinoline 6-H); 7.71 (ddd, 1 H, quinoline 7-H); 7.83 (s, 1 H, quinoline 3-H); 7.97 (d, 1 H, quinoline 5-H); 8.03 (d, 1 H, quinoline 8-H) ppm. MS m/z: 291.0987 (M) ($C_{15}H_{12}F_3N_3$ requires: 291.0983) (100%); 222.1025 (M − CF_3) ($C_{14}H_{12}N_3$ requires: 222.1031). Analysis: Found: N, 14.41%. $C_{15}H_{12}F_3N_3$ requires: N, 14.43%.

*3.6. 3,5-Bis(trifluoromethyl)-1-(4-methylquinolin-2-yl)-pyrazole (**5b**)*

The hydroxydihydropyrazole **3b** was treated with sulphuric acid and acetic acid, as for the synthesis of **5a**, to give the *pyrazole* **5b** (80%) as a pale yellow solid, m.p. 93–94 °C. ^1H NMR δ: 2.76 (s, 3 H, quinoline-Me); 7.15 (s, 1 H, pyrazole 4-H); 7.60 (t, 1 H, quinoline 6-H); 7.74 (t, 1 H, quinoline 7-H); 7.85 (s, 1 H, quinoline 3-H); 8.00 (d, 1 H, quinoline 5-H); 8.04 (d, 1 H, quinoline 8-H) ppm. MS m/z: 345.0692 (M) ($C_{15}H_9F_6N_3$ requires: 345.0700) (100%). Analysis: Found: N, 12.13%. $C_{15}H_9F_6N_3$ requires: N, 12.17%.

*3.7. 1-(4-Methylquinolin-2-yl)-3-phenyl-5-trifluoromethylpyrazole (**5c**)*

The hydroxydihydropyrazole **3c** was treated with sulphuric acid and acetic acid, as for the synthesis of **5a**, to give the pyrazole **5c** (75%) as a pale yellow solid, m.p. 109–110 °C. ^1H NMR δ: 2.76 (d, 3 H, J = 0.9 Hz, quinoline-Me); 7.21 (s, 1 H, pyrazole 4-H); 7.36–7.49 (m, 3 H, Ph 3,4,5-H_3); 7.55 (ddd, 1 H, quinoline 6-H); 7.72 (ddd, 1 H, quinoline 7-H); 7.90–7.98 (m, 4 H, quinoline 3,5-H_2 + Ph 2,6-H_2); 8.05 (d, 1 H, quinoline 8-H) ppm. Analysis: Found: N, 12.02%. $C_{20}H_{14}F_3N_3$ requires: N, 11.90%.

*3.8. 1-(4-Methylquinolin-2-yl)-3-(thien-2-yl)-5-trifluoromethylpyrazole (**5d**)*

The hydroxydihydropyrazole **3d** was treated with sulphuric acid and acetic acid, as for the synthesis of **5a**, to give the pyrazole **5d** (70%) as a pale yellow solid, m.p. 116–117 °C. ^1H NMR δ: 2.76 (d, 3 H, J = 0.7 Hz, quinoline-Me); 7.08–7.11 (m, 2 H, pyrazole 4-H + thiophene 4-H); 7.34 (dd, 1 H, thiophene 5-H); 7.45 (dd, 1 H, thiophene 3-H); 7.55 (ddd, 1 H, quinoline 6-H); 7.72 (t, 1 H, quinoline 7-H); 7.94 (s, 1 H, quinoline 3-H); 7.97 (d, 1 H, quinoline 5-H); 8.04 (d, 1 H, quinoline 8-H) ppm. Analysis: Found: N, 11.82%. $C_{18}H_{12}F_3N_3S$ requires: N, 11.70%.

3.9. 4-(N'-(3-Hydroxy-1-methyl-4,4,4-trifluorobut-2-enylidine))hydrazino-2-methylquinoline (7a)

1,1,1-Trifluoropentane-2,4-dione **2a** (770 mg, 5 mmol) was boiled under reflux with **6a** (865 mg, 5 mmol) in ethanol (50 ml) for 6 h. Evaporation of the solvent and recrystallisation (methanol) afforded the hydrazone **7a** (1.10 g, 70%) as a yellow solid, m.p. 239–240 °C. ^{1}H NMR ($(CD_3)_2SO$) δ: 2.32 (s, 3 H, =CMe); 2.36 (s, 3 H, quinoline-Me); 5.42 (s, 1 H, =CH); 5.90 (s, 1 H, quinoline 3-H); 7.24 (t, 1 H, quinoline 7-H); 7.34 (d, 1 H, quinoline 5-H); 7.53 (ddd, 1 H, quinoline 6-H); 8.15 (dd, 1 H, quinoline 8-H); 11.40 (s, 1 H, NH); 14.32 (s, 1 H, OH) ppm. ^{13}C NMR δ: 87.84 (–CH=); 118.54 (q, $^1J_{C-F}$ = 286.6 Hz, CF3); 169.60 (q, $^2J_{C-F}$ = 31.2 Hz, CCF3) ppm. ^{19}F NMR δ: −74.79 (s) ppm. Analysis: Found: N, 13.52%. $C_{15}H_{14}F_3N_3O$ requires: N, 13.59%.

3.10. 7-Chloro-4-(N'-(3-Hydroxy-1-methyl-4,4,4-trifluorobut-2-enylidine))hydrazinoquinoline (7b)

1,1,1-Trifluoropentane-2,4-dione **2a** (770 mg, 5 mmol) was treated with **6b** (965 mg, 5 mmol), as for the synthesis of **7a**, to afford the hydrazone **7b** (1.18 g, 72%) as a yellow solid, m.p. 255–256 °C. ^{1}H NMR δ: 2.38 (s, 3 H, =CMe); 5.51 (s, 1 H, =CH); 6.11 (d, 1 H, quinoline 3-H); 7.31 (dd, 1 H, quinoline 6-H); 7.40 (d, 1 H, quinoline 5-H); 7.74 (d, 1 H, quinoline 2-H); 8.20 (dd, 1 H, quinoline 8-H); 11.49 (s, 1 H, NH); 14.30 (s, 1 H, OH) ppm. ^{13}C NMR δ ((CD3)2SO): 87.79 (–CH=); 118.35 (q, $^1J_{C-F}$ 286.4 Hz, CF3); 170.23 (q, $^2J_{C-F}$ 30.8 Hz, CCF3) ppm. ^{19}F NMR δ: −74.37 (s) ppm. MS m/z: 331/329 (M). Analysis: Found: N, 12.71%. $C_{14}H_{11}ClF_3N_3O$: N, 12.73%.

3.11. 3-Methyl-1-(2-methylquinolin-4-yl)-5-trifluoromethylpyrazole (9a)

The hydrazone **7a** (927 mg, 3 mmol) was boiled under reflux in acetic acid (30 ml) for 4 h. Evaporation of the solvent and recrystallisation (ethanol) afforded the pyrazole **9a** (650 mg, 75%) as a pale yellow solid, m.p. 135–136 °C. ^{1}H NMR δ: 2.37 (s, 3 H, pyrazole-Me); 2.72 (s, 3 H, quinoline-Me); 6.63 (s, 1 H, pyrazole 4-H); 7.25 (s, 1 H, quinoline 3-H); 7.29 (d, 1 H, quinoline 5-H); 7.41 (t, 1 H, quinoline 6-H); 7.65 (t, 1 H, quinoline 7-H); 8.03 (d, 1 H, quinoline 8-H) ppm. Analysis: Found: N, 14.38%. $C_{15}H_{12}F_3N_3$ requires: N, 14.43%.

3.12. 1-(7-Chloroquinolin-4-yl)-3-methyl-5-trifluoromethylpyrazole (9b)

The hydrazone **7b** (988 mg, 3 mmol) was boiled under reflux in acetic acid (30 ml) for 4 h. Evaporation of the solvent and recrystallisation from ethanol afforded the pyrazole **9b** (670 mg, 72%) as a pale yellow solid, m.p. 78–79 °C. ^{1}H NMR δ: 2.43 (s, 3 H, pyrazole-Me); 6.74 (s, 1 H, pyrazole 4-H); 7.44 (d, 1 H, quinoline 3-H); 7.46 (d, 1 H, quinoline 5-H); 7.53 (dd, 1 H, quinoline 6-H); 8.23 (d, 1 H, quinoline 8-H); 9.04 (d, 1 H, quinoline 2-H) ppm. MS m/z 311/313 (M). Analysis: Found: N, 13.42%. $C_{14}H_9ClF_3N_3$ requires: N, 13.46%.

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