Journal of Fluorine Chemistry 135 (2012) 278–284

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Regioselective synthesis of trifluoromethylated 3-(pyrazolyl)indoles on the basis of 6-(trifluoromethyl)comanic acid

Boris I. Usachev *, Dmitrii L. Obydennov, Vyacheslav Ya. Sosnovskikh

Department of Chemistry, Ural Federal University, pr. Lenina 51, 620083 Ekaterinburg, Russia

ARTICLE INFO

Article history:
Received 23 August 2011
Received in revised form 10 December 2011
Accepted 14 December 2011
Available online 22 December 2011

Keywords:
6-(Trifluoromethyl)comanic acid
3-(Pyrazolyl)indoles
Trifluoromethylated heterocycles
Fischer reaction
Regioselectivity

ABSTRACT

A number of trifluoromethylated 3-(pyrazolyl)indoles was synthesized from 2-(trifluoromethyl)comanic acid, its ethyl ester and amide via intermediate isomeric 5(3)-[3,3,3-trifluoro-2-(phenylhydrazono)-propyl]pyrazole-3(5)-carboxylic acids and their derivatives.

1. Introduction

Trifluoromethylated indoles are not a widely distributed group of compounds and attract attention due to two pharmacophoric fragments: the indole moiety and the trifluoromethyl group. 2-(Trifluoromethyl)indole and its 3-substituted derivatives have been synthesized via various approaches [1–20]. Most pertinent to the present research are the reactions involving phenylhydrazones of α-trifluoromethyl ketones [18–20].

The synthesis of trifluoromethylated indoles is of great significance in medicinal chemistry, because it is known, that some representatives of this group of compounds possess antidiabetic activity [21]. Moreover, various 3-(pyrazolyl)indoles, which were synthesized earlier using different approaches [22–34], exhibit a broad spectrum of biological activity [24–35], but 4-[5-(indol-3-yl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide is the most potent inhibitor of PDK-kinase among other investigated 4-[5-hetaryl-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamides [36,37].

Recently we have found [38] that the reactions of non-symmetrically substituted polyelectrophilic substrates such as 6-(trifluoromethyl)comanic acid and its derivatives **1** [39], with phenylhydrazine were exclusively selective based on the nature of the solvent. Treatment of these pyrones with $PhNHNH_2$ in a polar protic solvent gave 5-[3,3,3-trifluoro-2-(phenylhydrazono)propyl]-1-phenyl-1*H*-pyrazole-3-carboxylic acid derivatives **2**, whereas in an aprotic solvent the reaction afforded the derivatives of the regioisomeric 3-[3,3,3-trifluoro-2-(phenylhydrazono)propyl]-1-phenyl-1*H*-pyrazole-5-carboxylic acid **3**.

Two approaches pointed above allow preparation of some CF_3-indoles by the Fischer reaction using phenylhydrazones of α-trifluoromethyl ketones as the substrates and either $MeSO_3H$ (in AcOH) [18] or *p*-TsOH (in toluene) [19,20] as promotors. However, when we tried to use these approaches for **2a** to prepare the corresponding trifluoromethylated 3-(pyrazolyl)indole, only trace amounts of the expected indole were detected by ^1H and ^{19}F NMR.

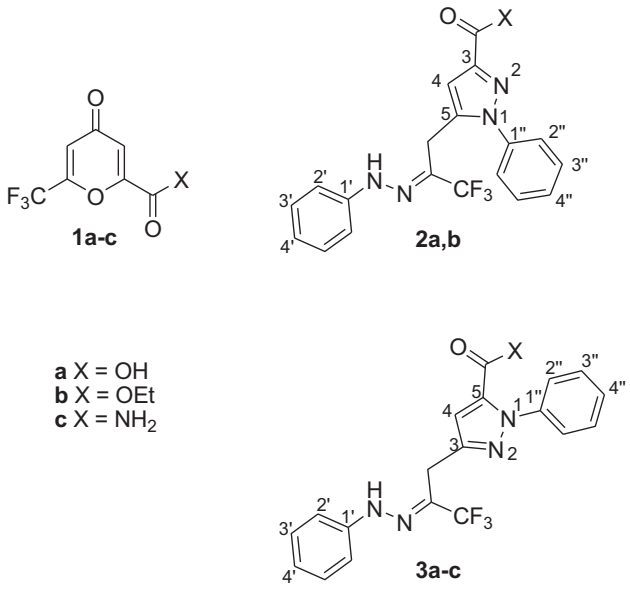
In this paper, we describe our results concerning the regioselective synthesis of some trifluoromethylated 3-(pyrazolyl)indoles from phenylhydrazones **2** and **3**, and show a wide variety of novel compounds, which can be obtained by using only one, the base structure, 6-(trifluoromethyl)comanic acid **1a**. 2-Trifluoromethyl-3-(pyrazolyl)indoles are described for the first time (Scheme 1).

2. Results and discussion

We have found that phenylhydrazones **2** as well as **3** can be transformed into the first representatives of 2-CF_3-3-(pyrazolyl)indoles, regioisomeric compounds **4** and **5**, respectively in 25–73% yield by heating in $MeSO_3H$ in the presence of P_4O_{10} (15%). 3-(Pyrazolyl)indoles **5**, derivatives of pyrazol-5-carboxylic acid, were synthesized by both approaches, via using $MeSO_3H/AcOH$[18] and $MeSO_3H/P_4O_{10}$ (Scheme 2). The structures of indoles **4** and **5** were confirmed by NMR and IR spectroscopies, and elemental analysis.

* Corresponding author. Tel.: +7 343 261 6824; fax: +7 343 261 5978.
E-mail address: boris.usachev@mail.ru (B.I. Usachev).

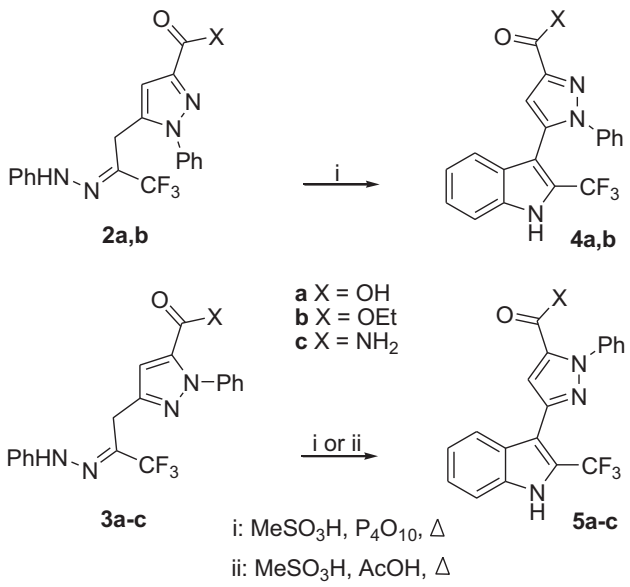
0022-1139/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2011.12.008



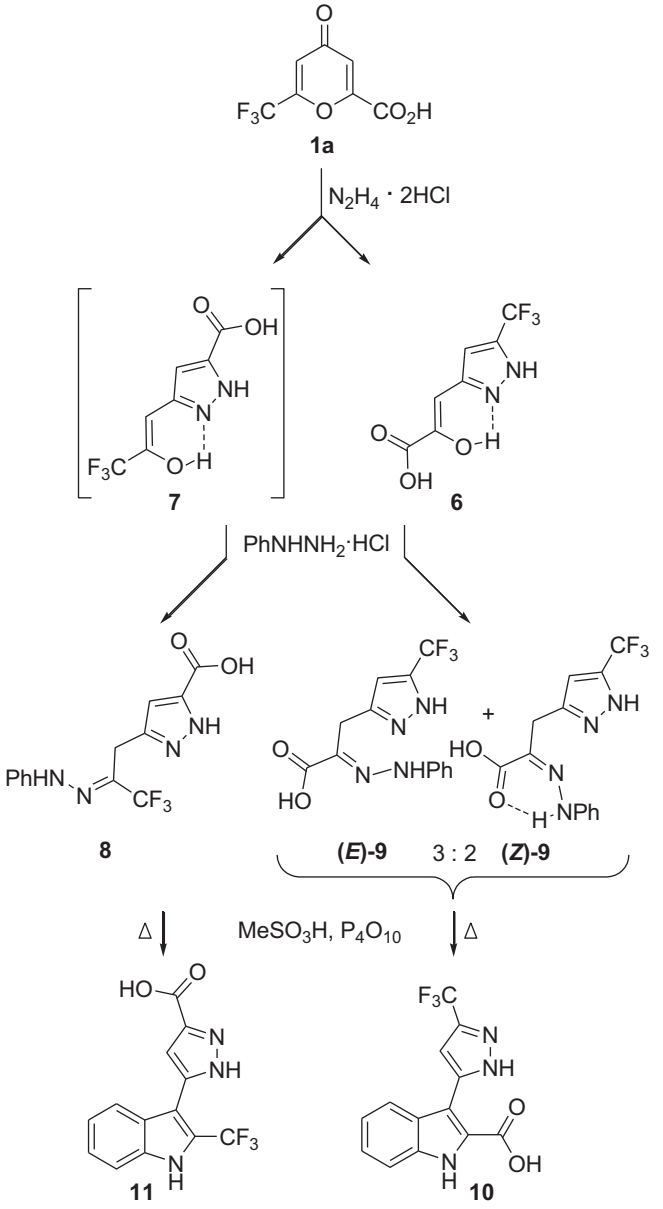
Scheme 1. Starting compounds for the synthesis of trifluoromethylated 3-(pyrazolyl)indoles.

In the ^{1}H NMR spectra (DMSO-d_6) the signals of the indole protons were similar to those observed for other 2-trifluoromethylindoles [14,18–20]. The pyrazole proton in derivatives of 1-phenylpyrazole-3-carboxylic acid **4** appeared as a singlet in a little higher field (δ 7.01–7.11) than the same proton in derivatives of 1-phenylpyrazole-5-carboxylic acid **5** (δ 7.16–7.24). In the ^{19}F NMR spectra (DMSO-d_6, C_6F_6) of **4** and **5** the signal at about δ 105–106 corresponding to the trifluoromethyl group at the C-2 atom of the indole moiety was observed [14]. In the ^{13}C NMR spectra of compound **4b**, atoms C-2 and C-3 of the indole ring appeared as characteristic quartets at δ 123.0 ($^2J_{C,F}$ = 36.7 Hz) and 105.0 ($^3J_{C,F}$ = 2.8 Hz). The carbon atom of the trifluoromethyl group appeared as quartet at δ 121.0 ($^1J_{C,F}$ = 269.7 Hz).

There are no data in the literature on the reaction of non-annulated 2-trifluoromethyl-4-pyrones with hydrazine. We have investigated the reaction of **1a** with N_2H_4 under various conditions and found that the use of hydrazine as a free base led to a complex mixture of products, whereas the use of N_2H_4·2HCl (2.2 equiv) in water according to ^{1}H NMR spectra gave a mixture of regioisomeric pyrazoles **6** and **7** (Scheme 3). Insoluble in water isomer **6** was easily separated from the reaction mixture by filtration (30% yield) and soluble isomer **7** was not isolated, but transformed rapidly to phenylhydrazone **8** by treatment of the residue, prepared after evaporation of water from the filtrate, with excess phenylhydrazine hydrochloride (56% yield). Analogously, compound **6** was transformed into the corresponding phenylhydrazone **9** (63% yield) by treatment with excess $PhNHNH_2$·HCl. The stable enol form of ketone **6** (according to the ^{1}H NMR spectrum) can be explained by the formation of strong intramolecular hydrogen bond (IHB) between the enol OH group and pyrazole nitrogen atom. In the ^{1}H NMR spectra of **6** singlets due to the vinyl (δ 6.39) and pyrazole (δ 6.82) protons were observed. The labile protons appeared as broad signals at δ 9.55 and 13.30. In the ^{19}F NMR spectrum of compound **6**, the trifluoromethyl group appeared as a singlet at δ 101.5 confirming that this compound belongs to class of CF_3-pyrazoles [40,41]. Phenylhydrazones of α-trifluoromethyl ketones such as **2**, **3** and **8** are the *E*-isomers (CF_3 is a more bulky



Scheme 2. Synthesis of regioisomeric trifluoromethylated 3-(pyrazolyl)indoles.



Scheme 3. Synthesis of N-unsubstituted trifluoromethylated 3-pyrazolylindoles.

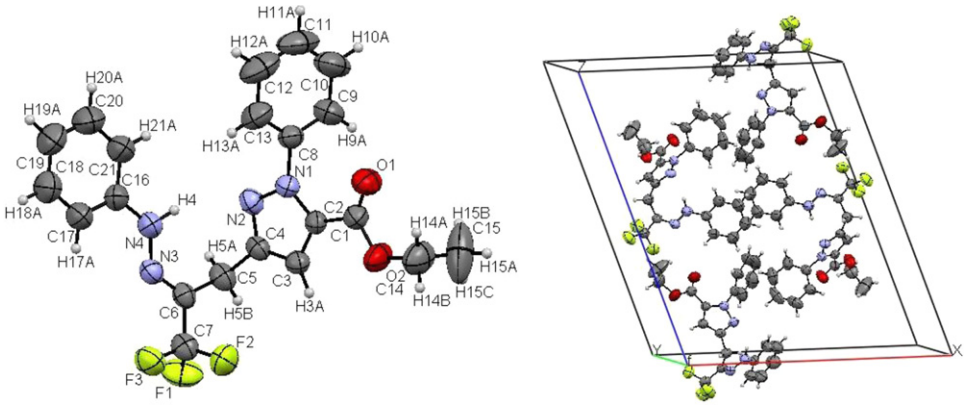
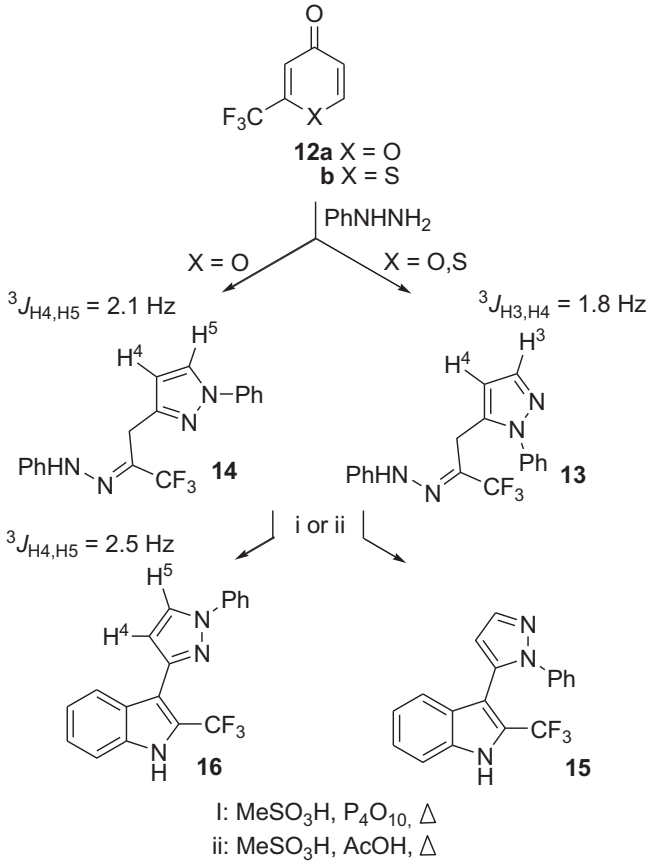


Fig. 1. Molecular structure of **3b** and its packing diagram (X-ray data, CCDC 822163).

group than CH_2), and this postulate was confirmed earlier for phenylhydrazones of other α-trifluoromethyl ketones, bearing an α′-CH_2 group [20]. The *E*-isomeric structure of such phenylhydrazones of α-trifluoromethyl ketones was unambiguously confirmed by X-ray crystallographic analysis of phenylhydrazone **3b** (Fig. 1, CCDC 822163). In contrast to **8**, phenylhydrazone **9** is a mixture of the *E*- and *Z*-isomers (ratio 3:2, ^{1}H NMR data). Both of these isomers were isolated from the mixture separately in analytically pure forms. In the ^{1}H NMR spectrum of **9** two sets of signals of (*E*)-**9** and (*Z*)-**9** were observed. The characteristic NH proton of the phenylhydrazonic moiety in major isomer (*E*)-**9** appeared as a singlet at δ 10.26 confirming the *E*-isomeric structure (almost the same values have phenylhydrazones **2** and **3**) [38]. The value of 10.26 indicates that even the substitution of the CF_3 group in the phenylhydrazonic moiety by the CO_2H group has almost no influence on the chemical shift of the NH proton. The methylene and pyrazole protons in (*E*)-**9** appeared as singlets at δ 4.05 and 6.26, respectively. Minor isomer (*Z*)-**9** was presented in the ^{1}H NMR spectrum by singlets of the methylene and pyrazole protons at δ 3.84 and 6.44, respectively, and a very low-field signal of the phenylhydrazonic NH proton (δ 12.2) due to the formation of the IHB between NH and C=O. The same low-field signal of the NH proton was observed in the spectra of a structurally similar dicarboxylic acid, bearing at the α-position a phenylhydrazonic substituent (δ 12.1) [38]. Heating the mixture of (*E*)-**9** and (*Z*)-**9** in $MeSO_3H/P_4O_{10}$ afforded 3-[3-(trifluoromethyl)pyrazol-5-yl]indole-2-carboxylic acid **10** in 35% yield. Regioisomeric indole **11** was prepared from **8** in 39% yield using the same approach. The use as a reaction medium $MeSO_3H$/AcOH do not allow preparation of **10** or **11** even in a smaller yields due to resinification of the reaction mixtures. The structures of the regioisomeric indoles **10** and **11** were confirmed by spectral methods and elemental analysis.

Thus, it has been shown, that the consecutive interaction of 6-(trifluoromethyl)comanic acid as a CF_3-pyrone with hydrazine as a binucleophile, and then with phenylhydrazine, and treatment of the intermediates under the conditions of the Fischer reaction gives 3-[3-(trifluoromethyl)-5-yl]indole-2-carboxylic acid **10** and regioisomeric 5-[2-(trifluoromethyl)indol-3-yl]-1*H*-pyrazole-3-carboxylic acid **11**. These reactions can be considered as a novel approach for the regioselective synthesis of various trifluoromethylated 3-(hetaryl)indoles on the basis of 2-CF_3-4-pyrones. The use in this approach of other binucleophiles (instead of hydrazine) could give a lot of new CF_3-indoles functionalized in position-3 with various heterocycles.

Recently we described a simple synthesis of 2-(trifluoromethyl)-4-pyrone **12a** and -thiopyrone **12b** from **1a** [42]. We have explored the reaction of **12** with phenylhydrazine and found that pyrone **12a** gave a mixture of phenylhydrazones of 1,1,1-trifluoro-3-(1-phenylpyrazol-5-yl)propan-2-one (**13**) (16%) and 1,1,1-trifluoro-5-(1-phenylpyrazol-3-yl)propan-2-one (**14**) (21%), whereas thiopyrone **12b** led to the formation only compound **13** in 14% yield (no isomer **14** was detected in a crude sample of compound **13** prepared from **12b**) (Scheme 4). Compounds **13** and **14** could be easily recognized using as an indicator the values of the vicinal coupling constants between H^3–H^4 and H^4–H^5 in the ^{1}H NMR spectra. According to literature, in case of **13** the value of $^3J_{H3,H4}$ has to be 1.6–2.0 Hz, whereas in case of **14** the value of $^3J_{H4,H5}$ should be >2.0 Hz [22,23]. The observed value of the coupling constant of 1.8 Hz for **13** and 2.1 Hz for **14** proves these structures. Heating **13** in $MeSO_3H$ in the presence of P_4O_{10} gave 3-(1-phenylpyrazol-5-yl)-2-(trifluoromethyl)indole **15** in 60% yield. The same reaction conducted in $MeSO_3H$/AcOH afforded **15** in 65%



Scheme 4. Synthesis of regioisomeric trifluoromethylated 3-(pyrazolyl)indoles using 2-(trifluoromethyl)-4H-pyran-4-one and -4H-thiopyran-4-one.

Table 1
Trifluoromethylated pyrazole and indole derivatives.

Entry	Reagent	Product	Yield %	Mp °C	δ_F ppm (DMSO-d_6, C_6F_6)
1	**1a**	**2a**	64	230–232	96.7
2	**1b**	**2b**	58	199–200	96.7
3	**1a**	**3a**	30	222–223	96.6
4	**1b**	**3b**	34	106	96.6
5	**1c**	**3c**	19	201–203	96.6
6	**2a**	**4a**	45[a]	242–243	105.3
7	**2b**	**4b**	40[a]	205–206	105.3
8	**3a**	**5a**	73[a], 46[b]	240–241	106.2
9	**3b**	**5b**	65[a], 71[b]	152–153	106.2
10	**3c**	**5c**	60[a,b]	207–208	106.2
11	**1a**	**6**	30	231–232	101.5
12	**1a**	**8**	56	166–167	96.5
13	**6**	**9**	80	170–190	102.2, 102.3
14	**6**	(*E*)-**9**	37	196–197	102.2
15	**6**	(*Z*)-**9**	28	172–173	102.3
16	**9**	**10**	35[a]	256–257	102.6
17	**8**	**11**	39[a]	222–224	106.2
18	**12a,b**	**13**	16[c], 14[d]	166–167	96.7
19	**12a**	**14**	21	67–68	96.6
20	**13**	**15**	60[a], 65[b]	192–193	105.3
21	**14**	**16**	60[a], 58[b]	214–215	106.2

[a] The reaction was conducted in $MeSO_3H/P_4O_{10}$.
[b] The reaction was conducted in $AcOH/MeSO_3H$.
[c] Prepared from **12a**.
[d] Prepared from **12b**.

yield. Isomeric indole **16** was synthesized in 60% ($MeSO_3H/P_4O_{10}$) and 58% ($MeSO_3H$/AcOH) yields.

The results of the syntheses of the CF_3-compounds as well as their δ_F values are given in Table 1. The ^{19}F NMR spectroscopy is a good method to determine the regiochemistry of CF_3-3-(pyrazolyl)indoles. The table data show that the fluorines of the trifluoromethyl group at the second position of 3-(pyrazolyl)indoles tend to appear at about δ 105–106. In the case of the starting regioisomeric phenylhydrazones, the δ_F values for **2** are similar to those observed for **3** (96.7 versus 96.6), whereas the $\Delta\delta_F$ value between the corresponding regioisomeric indoles **4** and **5** reaches 0.9 (105.3 versus 106.2).

3. Conclusion

Thus, we have managed to achieve regiocontrolled synthesis of trifluoromethylated indoles based on 6-(trifluoromethyl)comanic acid, which are of interest for medicinal chemistry. The first representatives of 2-CF_3-3-(pyrazolyl)indoles were prepared.

4. Experimental

4.1. General

^1H, ^{19}F and ^{13}C NMR spectra were recorded on Bruker AVANCE DRX-400 spectrometer. Chemical shifts for ^1H NMR spectra are reported in parts per million (ppm) downfield from TMS, shifts for ^{19}F NMR spectra are reported in ppm downfield from internal C_6F_6. Coupling constants (*J*) are given in Hertz (Hz). The terms s, d, t, q, m refer to singlet, doublet, triplet, quartet, multiplet; br refers to a broad signal. Infrared spectra (IR) were recorded on Nicolet 6700 spectrometer, equipped with attenuated total reflection accessory (ATR), absorbance frequencies are given at maximum of intensity in cm^{-1}. Elemental analyses were performed with PE 2400 instrument. High resolution mass spectra were obtained on a MAT-8200 spectrometer, using EI at 70 eV. Single-crystal XRD was performed with graphite-monochromatic Mo K_α radiation (λ = 0.71073 Å) on a Bruker X8 APEX II CCD diffractometer at T = 295(2) K.

4.2. 5-[3,3,3-Trifluoro-2-(phenylhydrazono)propyl]-1-phenyl-1H-pyrazol-3-carboxylic acid (2a)[38]

A mixture of acid **1a** (1.0 g, 4.8 mmol) and $PhNHNH_2$·HCl (1.53 g, 10.6 mmol) was refluxed in 10% HCl (10 mL) for 10 min. After cooling the mixture to room temperature, the resulting residue was filtered off and washed with water. The crude product was recrystallized from toluene to give **2a** (1.19 g, 64%) as a colorless solid, mp 230–232 °C; δ_F (376.5 MHz, DMSO-d_6) 96.7 (s, CF_3).

4.3. Ethyl 1-phenyl-5-[3,3,3-trifluoro-2-(2-phenylhydrazono)propyl]-1H-pyrazol-3-carboxylate (2b)

Ester **1b** (1.0 g, 4.2 mmol) was added to a solution of freshly distilled phenylhydrazine (1.0 g, 9.3 mmol) in ethanol (5 mL). The reaction mixture was kept at room temperature for 4 days, and then mixed with 20% HCl (2 mL). The residue was filtered off, treated with hot ethanol (20 mL) acidified with HCl (3 drops). After cooling the mixture to ambient temperature the resulting residue was filtered off and washed with ethanol (5 mL) to give **2b** (1.03 g, 58%) as a colourless powder, mp 199–200 °C; ν_{max} (KBr) 3239, 1724, 1622, 1603, 1532, 1501, 1490, 1476 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.27 (3H, t, *J* 7.1 Hz, Me), 4.05 (2H, s, CH_2), 4.27 (2H, q, *J* 7.1 Hz, OCH_2), 6.51 (1H, S, =CH), 6.93 (1H, tt, *J* 7.3, 1.0 Hz, Ar), 7.13–7.32 (4H, m, Ar), 7.50–7.65 (5H, m, Ph), 10.26 (1H, s, NH); δ_F (376.5 MHz, DMSO-d_6) 96.7 (s, CF_3); δ_C (100 MHz, DMSO-d_6, without proton decoupling) 14.10 (qt, Me, ^1J 126.9, ^2J 2.6 Hz), 22.38 (t, CH_2, ^1J 132.2 Hz), 60.45 (tq, OCH_2, ^1J 148.2, ^2J 4.5 Hz), 108.11 (dt, C4, ^1J 179.3, ^3J 3.2 Hz), 113.48 (dt, C2′, C6′, ^1J 160.7, ^2J 5.7 Hz), 121.26 (dt, C4′, ^1J 160.5, ^2J 7.6 Hz), 121.93 (qt, CF_3, $^1J_{C,F}$ 272.6, ^3J 4.3 Hz), 125.10 (ddd, C2″, C6″, ^1J 164.2, ^2J 7.6, 4.9 Hz), 125.61 (qtd, *C*–CF_3, $^2J_{C,F}$ 33.2, ^2J 7.2, ^3J 3.0 Hz), 128.94 (dt, C4″, ^1J 162.5, ^2J 7.3 Hz), 129.15 (dd, C3′, C5′, ^1J 159.4, ^2J 8.2 Hz), 129.44 (dd, C3″, C5″, ^1J 163.8, ^2J 7.7 Hz), 138.24 (q, C5, ^2J 8.4 Hz), 138.47 (td, C1″, ^2J 9.0, ^4J 1.5 Hz), 143.13 (d, C3, ^2J 3.9 Hz), 143.78 (q, C1′, ^2J 8.2 Hz), 161.37 (t, C=O, ^3J 3.3 Hz); [Found: C, 60.47; H, 4.45; N, 13.65. $C_{21}H_{19}F_3N_4O_2$ requires C, 60.57; H, 4.60; N, 13.46%].

4.4. 1-Phenyl-3-[3,3,3-trifluoro-2-(2-phenylhydrazono)propyl]-1H-pyrazole-5-carboxylic acid (3a)[38]

A mixture of acid **1a** (1.0 g, 4.8 mmol) and freshly distilled phenylhydrazine (1.15 g, 10.6 mmol) was refluxed in dry dioxane (30 mL) for 1.5 h. After cooling the reaction mixture to room temperature, the excess solvent was evaporated, the residue was treated with 5% HCl (20 mL). The water layer was decanted, the crude product was triturated with CCl_4, and then filtered off and washed with CCl_4 to give **3a** (0.56 g, 30%) as colourless solid, mp 222–223 °C; δ_F (376.5 MHz, DMSO-d_6) 96.6 (s, CF_3).

4.5. Ethyl 1-phenyl-3-[3,3,3-trifluoro-2-(2-phenylhydrazono)propyl]-1H-pyrazole-5-carboxylate (3b)

A mixture of ester **1b** (1.0 g, 4.2 mmol) and freshly distilled phenylhydrazine (1.07 g, 9.3 mmol) was refluxed in toluene (8 mL) for 12 h. The excess solvent was then evaporated (rest volume ~ 5 mL) and the residue was mixed with CCl_4 (5 mL). The resulting solution was cooled to 0 °C, the residue was recrystallized from toluene to give **3b** (0.59 g, 34%) as colourless crystals, mp 106 °C; ν_{max} (KBr) 3293, 1736, 1604, 1542, 1528, 1504 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.1 Hz, Me), 3.82 (2H, s, CH_2), 4.22 (2H, q, *J* 7.1 Hz, OCH_2), 6.90 (1H, s, =CH), 6.92 (1H, tt, *J* 7.5, 1.0 Hz, Ar), 7.02–7.06 (2H, m, Ar), 7.21–7.25 (2H, m, Ar), 7.35–7.39 (2H, m, Ph–pyraz.), 7.45–7.49 (3H, m, Ph–pyraz.), 9.56 (1H, s, NH); δ_F (376.5 MHz, $CDCl_3$) 92.9 (s, CF_3); δ_H (400 MHz, DMSO-d_6) 1.14 (3H, t, *J* 7.1, Me), 4.03 (2H, s, CH_2), 4.16 (2H, q, *J* 7.1 Hz, OCH_2), 6.88 (1H, s, =CH), 6.90 (1H, tt, *J* 7.3, 1.0 Hz, Ar), 7.16–7.20 (2H, m, Ar), 7.25–7.30 (2H, m, Ar), 7.40–7.49 (5H, m, Ph), 10.28 (1H, s, NH); δ_F (376.5 MHz, DMSO-d_6) 96.6 (s, CF_3); δ_C (100 MHz, $CDCl_3$) 13.95 (Me), 24.27 (CH_2), 61.41 (OCH_2), 111.47 (C4), 113.56 (C2′, C6′), 121.60 (C4′), 121.84 (q, CF_3, $^1J_{C,F}$ 272.0 Hz), 125.93 (C2″, C6″), 128.03 (q, *C*–CF_3, $^2J_{C,F}$ 34.1 Hz), 128.63 (C3′, C5′), 128.97 (C4″), 129.20 (C3″, C5″), 135.06 (C5), 139.80 (C1″), 143.75 (C1′), 146.45 (C3), 158.61 (C=O); δ_C (100 MHz, DMSO-d_6) 13.72 (Me), 23.11 (CH_2), 60.98 (OCH_2), 111.31 (C4), 113.32 (C2′, C6′), 120.99 (C4′), 122.12 (q, CF_3, $^1J_{C,F}$ 272.5 Hz), 125.61 (C2″, C6″), 127.67 (q, *C*–CF_3, $^2J_{C,F}$ = 32.5 Hz), 128.43 (C4″), 128.57 (C3′, C5′), 129.14 (C3″, C5″), 133.82 (C5), 139.70 (C1″), 144.00 (C1′), 146.43 (C3), 158.24; [Found: C, 60.57; H, 4.61; N, 13.53. $C_{21}H_{19}F_3N_4O_2$ requires C, 60.57; H, 4.60; N, 13.46%]; the structure was solved from X-ray data by direct method with SHELXS-97 program and refined by full matrix least-squares on F2 with SHELXL-97 program [43]. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were located and included at their calculated position. The CCDC deposition number is 822163. Unit cell parameters: *a* = 21.788(2), *b* = 4.4981(3), *c* = 23.391(3). The crystal system is monoclinic, space group P21/c.

4.6. 1-Phenyl-3-[3,3,3-trifluoro-2-(2-phenylhydrazono)propyl]-1H-pyrazole-5-carboxamide (3c)

A mixture of amide **1c** (0.50 g, 2.4 mmol) and freshly distilled phenylhydrazine (0.58 g, 5.7 mmol) in ethanol (2.5 mL) was refluxed for 7 h. Then the reaction mixture was diluted with water (15 mL) and conc. HCl (2 mL), and the water layer was decanted. The residue was triturated with CCl_4 (5 mL) to give a yellow precipitate, which was filtered off and recrystallized from toluene to give **3c** (0.18 g, 19%) as a colourless solid, mp 201–202 °C; ν_{max} (KBr) 3282, 1710, 1614, 1555, 1528, 1501 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 4.00 (2H, s, CH_2), 6.74 (1H, s, =CH), 6.89 (1H, tt, *J* 7.3 Hz, Ar), 7.17–7.30 (4H, m, Ar), 7.34–7.47 (5H, m, Ph), 7.54 (1H, s, CONHH), 8.07 (1H, s, CONHH), 10.29 (1H, s, NNH); δ_F (376.5 MHz, DMSO-d_6) 96.6 (s, CF_3); *m/z* (EI, 70 eV) 387 (100, M^+), 291 (20), 252 (25); HRMS (EI, 70 eV): M^+, found 387.13114. $C_{19}H_{16}F_3ON_5$ requires 387.13070; [Found: C, 58.80; H, 4.27; N, 18.13. $C_{19}H_{16}F_3N_5O$ requires C, 58.91; H, 4.16; N, 18.08%].

4.7. (Z)-3-[5-(Trifluoromethyl)-1H-pyrazol-3-yl]-2-hydroxyacrylic acid (6)

A mixture of acid **1a** (1.0 g, 4.8 mmol) and N_2H_4·2HCl (0.52 g, 5.0 mmol) was heated in water (10 mL) at 60 °C for 4 h. The precipitated residue was filtered off, washed with water (3 mL) and dried to give **6** (0.32 g, 30%) as white solid, mp 231–232 °C; ν_{max} (ATR) 3414, 1701, 1659 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 6.39 (1H, s, =CH), 6.82 (1H, s, =CH–pyraz.), 9.55 (1H, s, NH), 10.50–11.28 (1H, br s, OH), 13.27 (1H, br s, CO_2H); δ_F (376.5 MHz, DMSO-d_6) 101.5 (s, CF_3); [Found: C, 37.71; H, 2.23; N, 12.62. $C_7H_5F_3N_2O_3$ requires C, 37.85; H, 2.27; N, 12.61%].

4.8. 3-[2-(Phenylhydrazono)-3,3,3-trifluoropropyl]-1H-pyrazole-5-carboxylic acid (8)

A mixture of the residue, isolated after evaporation of water from the filtrate from **6** (0.70 g, mp 205–215 °C) and PhNHNH$_2$·HCl (0.29 g, 2.0 mmol) was heated at 70 °C for 1 h. The resulting residue was filtered off and recrystallized from toluene to give **8** (0.51 g, 56%) as a colourless solid, mp ~167 °C; ν_{max} (ATR) 3466, 1716, 1665, 1615 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 3.96 (2H, s, CH_2), 6.53 (1H, s, =CH), 6.90 (1H, t, *J* 7.3 Hz, Ph), 7.18 (2H, d, *J* 7.7 Hz, Ph), 7.28 (2H, dd, *J* 7.3, 7.7 Hz, Ph), 10.24 (1H, s, NH), 13.40 (1H, br s, CO_2H); δ_F (376.5 MHz, DMSO-d_6) 96.54 (c, CF_3); [Found: C, 50.24; H, 3.46; N, 17.55. $C_{13}H_{11}F_3N_4O_2$ requires C, 50.00; H, 3.55; N, 17.94%].

4.9. (E)- and (Z)-2-(2-Phenylhydrazono)-3-[5-(trifluoromethyl)-1H-pyrazol-3-yl]propanoic acid (9)

A mixture of ketone **9** (250 mg, 1.1 mmol) and PhNHNH$_2$·HCl (180 mg, 1.2 mmol) in ethanol (4 mL) was heated at 50 °C for 4 h. Then the reaction mixture was diluted with water (10 mL), the precipitate was filtered off to give a mixture of (*E*)-**9** and (*Z*)-**9** (3:2) (280 mg, 80%) as a colourless powder, mp 170–190 °C; [Found: C, 50.18; H, 3.37; N, 17.65. $C_{13}H_{11}F_3N_4O_2$ requires C, 50.00; H, 3.55; N, 17.94%].

4.10. (E)-2-(2-Phenylhydrazono)-3-[5-(trifluoromethyl)-1H-pyrazole-3-yl]propanoic acid ((E)-9)

A mixture of (*E*)-**9** and (*Z*)-**9**, prepared as described above, was heated in toluene (10 mL) until the toluene boiled. The hot mixture was filtered to give (*E*)-**9** (130 mg, 37%) as a colourless solid, mp 196–197 °C; ν_{max} (ATR) 3229, 1720, 1603, 1577, 1499 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 4.05 (2H, s, CH_2), 6.26 (1H, s, =CH), 6.92 (1H, t, *J* 6.9 Hz, Ph), 7.29 (2H, t, *J* 7.2 Hz, Ph), 7.34 (2H, d, *J* 7.2 Hz, Ph), 10.26 (1H, s, NNH), 12.2 (1H, br s, NH-pyraz.), 13.49 (1H, s, CO_2H); δ_F (376.5 MHz, DMSO-d_6) 102.2 (c, CF_3).

4.11. (Z)-2-(2-Phenylhydrazono)-3-[5-(trifluoromethyl)-1H-pyrazol-3-yl]propanoic acid ((Z)-9)

The filtrate from (*E*)-**9** was collected in a glass, the solvent was evaporated, and the resulting residue was recrystallized from AcOH–H_2O (1:1) to give (*Z*)-**9** (0.10 g, 28%) as a colourless solid, mp 172–173 °C; ν_{max} (ATR) 3273, 1664, 1649, 1541, 1535 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 3.84 (2H, s, CH_2), 6.44 (1H, s, =CH), 6.92 (1H, t, *J* 6.9 Hz, Ph), 7.18 (2H, d, *J* 8.0 Hz, Ph), 7.25–7.29 (2H, m, Ph), 12.18 (1H, s, NNH), 13.46 (1H, s, CO_2H); δ_F (376.5 MHz, DMSO-d_6) 102.3 (c, CF_3).

*4.12. 1-Phenyl-5-[3,3,3-trifluoro-2-(2-phenylhydrazono)propyl]-1H-pyrazole (**13**)*

A mixture of pyrone **12a** (160 mg, 0.98 mmol) and freshly distilled phenylhydrazine (250 mg, 2.3 mmol) was kept at 120 °C within 1 h. After cooling to room temperature the mixture was mixed with ethanol (1 mL), the resulting residue was filtered off, washed with ethanol, dried and recrystallized from toluene (5 mL) to give **13** (50 mg, 16%) as a colourless solid, mp 166–167 °C; ν_{max} (KBr) 1625, 1605, 1537, 1502, 1455 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 4.03 (2H, s, CH_2), 6.11 (1H, d, *J* 1.8 Hz, H-4-pyraz.), 6.92 (1H, tt, *J* 7.3, 1.1 Hz, H-4′), 7.17 (2H, dd, *J* 8.6, 1.1 Hz, H-2′, H-6′), 7.29 (2H, dd, *J* 8.4, 7.4 Hz, H-3′, H-5′), 7.45 (1H, tt, *J* 6.9, 1.8 Hz, H-4″), 7.54–7.60 (4H, m, Ar), 7,61 (1H, d, *J* 1.8 Hz, H-3-pyraz.); 10.02 (c, 1H, NH); δ_F (376.5 MHz, DMSO-d_6) 96.7 (s, CF_3); [Found: C, 62.67; H, 4.29; N, 16.14. $C_{18}H_{15}F_3N_4$ requires C, 62.79; H, 4.39; N, 16.27%]. The reaction of thiopyrone **12b** with phenylhydrazine in ethanol (reflux 4 h) gave pyrazole **13** in 14% yield.

*4.13. 1-Phenyl-3-[3,3,3-trifluoro-2-(2-phenylhydrazono)propyl]-1H-pyrazole (**14**)*

The residue, isolated after evaporation of toluene from the filtrate from **13** was crystallized from ethanol to give **14** (71 mg, 21%) as a colourless solid, mp 67–68 °C; ν_{max} (ATR) 1598, 1552, 1518, 1499, cm^{-1}; δ_H (400 MHz, DMSO-d_6) 4.02 (2H, s, CH_2), 6.38 (1H, d, *J* 2.1 Hz, H-4-pyraz.), 6.90 (1H, t, *J* 7.2 Hz, H-4′), 7.21 (2H, d, *J* 7.8 Hz, H-2′, H-6′), 7.28 (3H, m, H-3′, H-5′, H-4″), 7.48 (2H, t, *J* 7.8 Hz, H-2″, H-6″), 7.79 (2H, d, *J* 7.9 Hz, H-3″, H-5″), 8,45 (1H, d, *J* 2.1 Hz, H-5-pyraz.); 10.28 (c, 1H, NH); δ_F (376.5 MHz, DMSO-d_6) 96.6 (s, CF_3); [Found: C, 62.79; H, 4.39; N, 16.27. $C_{18}H_{15}F_3N_4$ requires C, 62.61; H, 4.33; N, 16.26%].

4.14. Syntheses of 2-CF_3-3-(pyrazolyl)indoles

Method A (*using $MeSO_3H/P_4O_{10}$*): A CF_3-phenylhydrazone (0.48 mmol) was added to a mixture of $MeSO_3H$ (1.0 g) and P_4O_{10} (0.17 g). The reaction mixture was heated at 60 °C for 6 h. The resulting solution was diluted with water (10 mL), the residue was filtered off, and dried. Compounds **4a,b**, **5b** and **15** were solved in hot toluene (5 mL), the hot solution was then passed through a layer of silica gel (0.7 cm^3), and the layer washed with hot toluene (10 mL). After removal of the solvent, the solid residue was recrystallized from a solvent. After crystallization, the majority of the synthesized 3-(pyrazolyl)indoles contained 5–8% of the solvent (toluene or another). Therefore, all crystallized indoles were dried at 130 °C for 6 h.

Method B (*using $AcOH/MeSO_3H$*): A CF_3-phenylhydrazone (0.62 mmol) was added to a mixture of AcOH (4 mL) and $MeSO_3H$ (0.12 g, 1.24 mmol). The reaction mixture was refluxed, and then diluted with water (10 mL), the residue was filtered off, and dried. Compounds **5b** and **15** were solved in hot toluene (5 mL), the hot solution was then passed through a layer of silica gel (0.7 cm^3), and the layer washed with hot toluene (10 mL). After removal of the solvent, the solid residue was recrystallized from a solvent. After crystallization, the majority of the synthesized 3-(pyrazolyl)indoles contained 5–8% of the solvent (toluene or another). Therefore, all crystallized indoles were dried at 130 °C for 6 h.

*4.14.1. 5-[2-(Trifluoromethyl)-1H-indol-3-yl]-1-phenyl-1H-pyrazole-3-carboxylic acid (**4a**)*

Yield 45% (A), colourless solid (toluene), mp 242–243 °C; ν_{max} (ATR) 3284, 1689, 1599, 1534, 1485 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.01 (1H, s, pyraz.), 7.08 (1H, t, *J* 7.2 Hz, H-5), 7.21–7.35 (7H, m, H-6, H-4, Ph), 7.50 (1H, d, *J* 8.1 Hz, H-7), 12.70 (1H, s, NH), 13.0–13.1 (1H, br s, CO_2H); δ_F (376.5 MHz, DMSO-d_6) 105.3 (s, CF_3); [Found: C, 61.67; H, 3.52; N, 11.07. $C_{19}H_{12}F_3N_3O_2$ requires C, 61.46; H, 3.26; N, 11.32%].

*4.14.2. Ethyl 5-[2-(trifluoromethyl)-1H-indol-3-yl]-1-phenyl-1H-pyrazole-3-carboxylate (**4b**)*

Yield 40% (A), colourless solid (toluene–petroleum ether), mp 205–206 °C; ν_{max} (ATR) 3280, 1719, 1610 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.07 (3H, t, *J* 7.1 Hz, CH_3), 4.07 (2H, buried m, CH_2), 7.11 (1H, s, pyraz.), 7.12 (1H, td, *J* 7.6, 0.9 Hz, H-5), 7.19–7.22 (2H, m, H-6, Ph), 7.27–7.36 (4H, m, Ph), 7.42 (1H, d, *J* 8.1 Hz, H-4), 7.50 (1H, d, *J* 8.4 Hz, H-7); 12.30 (1H, br s, NH); δ_F (376.5 MHz, DMSO-d_6) 105.3 (s, CF_3); δ_C (100 MHz, DMSO-d_6) 14.2, 60.6, 105.0 (q, *J* 2.8 Hz), 112.1, 112.7, 119.8, 121.0 (q, *J* 269.7 Hz), 121.5, 123.0 (q, *J* 36.7 Hz), 124.0, 125.0, 126.1, 128.3, 129.0, 135.2, 135.3, 139.0, 143.6, 161.5; [Found: C, 63.01; H, 4.10; N, 10.25. $C_{21}H_{16}F_3N_3O_2$ requires C, 63.16; H, 4.04; N, 10.52%].

*4.14.3. 3-[2-(Trifluoromethyl)-1H-indol-3-yl]-1-phenyl-1H-pyrazole-5-carboxylic acid (**5a**)*

Yield 73% (A), 46% (B, reflux for 8 h), colourless solid (toluene), mp 240–241 °C; ν_{max} (ATR) 1700, 1597, 1577, 1527, 1501 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.20 (1H, s, pyraz.), 7.21 (1H, t, *J* 7.5 Hz, H-5), 7.36 (1H, t, *J* 7.7 Hz, H-6), 7.46–7.56 (4H, m, H-7, Ph), 7.60 (2H, d, *J* 7.4 Hz, Ph), 8.10 (1H, d, *J* 8.1 Hz, H-4); 12.50 (1H, s, NH), 13.33–13.66 (1H, br s, CO_2H); δ_F (376.5 MHz, DMSO-d_6) 106.2 (s, CF_3); [Found: C, 61.60; H, 3.48; N, 11.09. $C_{19}H_{12}F_3N_3O_2$ requires C, 61.46; H, 3.26; N, 11.32%].

*4.14.4. Ethyl 3-[2-(trifluoromethyl)-1H-indol-3-yl]-1-phenyl-1H-pyrazole-5-carboxylate (**5b**)*

Yield 65% (A), 71% (B, reflux for 4 h), yellow solid (toluene–petroleum ether), mp 155–156 °C; ν_{max} (ATR) 3359, 1718, 1592, 1575, 1501 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.20 (3H, t, *J* 7.1 Hz, CH_3), 4.24 (2H, q, *J* 7.1 Hz, CH_2), 7.22 (1H, t, *J* 7.5 Hz, H-5), 7.24 (1H, s, pyraz.), 7.37 (1H, t, *J* 7.5 Hz, H-6), 7.50–7.58 (4H, m, Ph), 7.59–7.64 (2H, m, Ph, H-7), 8.09 (1H, d, *J* 8.1 Hz, H-4), 12.53 (1H, br s, NH); δ_F (376.5 MHz, DMSO-d_6) 106.2 (s, CF_3); δ_C (100 MHz, DMSO-d_6) 13.8, 61.1, 108.6 (q, *J* 2.9 Hz), 111.4 (q, *J* 3.0 Hz), 112.5, 121.2, 121.3 (q, *J* 37.3 Hz), 121.8 (q, *J* 269.1 Hz), 121.9, 124.8, 125.5, 125.7, 128.5, 128.6, 133.9, 135.4, 139.9, 144.1, 158.4; [Found: C, 63.65; H, 3.85; N, 10.12. $C_{21}H_{16}F_3N_3O_2$ requires C, 63.16; H, 4.04; N, 10.52%].

*4.14.5. 3-[2-(Trifluoromethyl)-1H-indol-3-yl]-1-phenyl-1H-pyrazole-5-carboxamide (**5c**)*

Yield 60% (A) 60% (B, reflux for 4 h), colourless solid (toluene), mp 207–208 °C; ν_{max} (ATR) 3332, 3181 1664, 1626, 1601 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.16 (1H, s, pyraz.), 7.17–7.27 (2H, m, Ph, H-5), 7.36 (1H, t, *J* 7.2 Hz, H-6), 7.43 (1H, m, H-7), 7.47–7.67 (4H, m, Ph), 7.66 (1H, c, NHH), 8.10 (1H, d, *J* 8.1 Hz, H-4), 8.24 (1H, c, NHH), 12.45 (1H, s, NH); δ_F (376.5 MHz, DMSO-d_6) 106.2 (s, CF_3); [Found: C, 61.82; H, 3.77; N, 14.97. $C_{19}H_{13}F_3N_4O$ requires C, 61.62; H, 3.54; N, 15.13%].

*4.14.6. 5-[2-(Trifluoromethyl)-1H-indol-3-yl]-1H-pyrazole-3-carboxylic acid (**11**)*

Yield 39% (A, the reaction mixture was kept at ambient temperature for 48 h), white solid (AcOH–H_2O), mp 222–224 °C; ν_{max} (KBr) 3289, 1708, 1604, 1533, 1500 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 6.90 (1H, s, pyraz.), 7.21 (1H, t, *J* 7.6 Hz, H-5), 7.36 (1H, t, *J* 7.4 Hz, H-6), 7.54 (1H, d, *J* 8.6 Hz, H-7), 7.89 (1H, br s, H-4), 12.45 (1H, s, NH-Ind), 12.18–14.52 (2H, br s, NH-pyraz., CO_2H); δ_F (376.5 MHz, DMSO-d_6) 106.2 (s, CF_3); δ_C (100 MHz, DMSO-d_6) 108.0, 112.5, 118.5, 120.8, 121.1, 121.4, 121.6, 121.8 (q, *J* 269.1 Hz), 124.8, 125.0, 125.8, 135.4, 161.4; [Found: C, 52.70; H, 2.97; N, 14.01. $C_{13}H_8F_3N_3O_2$ requires C, 52.89; H, 2.73; N, 14.23%].

4.14.7. 2-(Trifluoromethyl)-3-(1-phenyl-1H-pyrazol-5-yl)-1H-indole (15)

Yield 60% (A), 65% (B, reflux for 4 h), white solid (toluene–petroleum ether), mp 192–193 °C; ν_{max} (ATR) 3108, 1597, 1522, 1500, 1458 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 6.61 (1H, buried d, H-4′), 7.06 (1H, t, *J* 7.5 Hz, H-5), 7.14–7.23 (4H, m, Ph), 7.24–7.35 (3H, m, Ph, Ind), 7.50 (1H, d, *J* 8.3 Hz, H-7), 7.86 (1H, buried d, H-3′), 12.61 (1H, s, NH); δ_F (376.5 MHz, DMSO-d_6) 105.3 (s, CF_3); δ_C (100 MHz, DMSO-d_6) 106.4 (q, *J* 2.8 Hz), 110.4, 112.7, 120.0, 121.2 (q, *J* 269.5 Hz), 121.3, 122.6 (q, *J* 36.6 Hz), 123.4, 124.9, 126.2, 127.2, 128.9, 133.1, 135.4, 139.8, 140.3; [Found: C, 66.17; H, 3.79; N, 12.56. $C_{18}H_{12}F_3N_3$ requires C, 66.05; H, 3.70; N, 12.84%].

4.14.8. 2-(Trifluoromethyl)-3-(1-phenyl-1H-pyrazol-3-yl)-1H-indole (16)

Yield 60% (A), 58% (B, reflux for 4 h), white solid (toluene), mp 214–215 °C; ν_{max} (ATR) 3164, 1597, 1588, 1573, 1510 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 6.79 (1H, buried d, H-4-pyraz.), 7.25 (1H, t, *J* 7.5 Hz, H-5), 7.32–7.40 (2H, m, Ar), 7.56 (3H, m, H-7, Ph), 7.95 (2H, d, *J* 7.9 Hz, H-2″, H-6″), 8.19 (1H, d, *J* 8.1 Hz, H-4), 8.65 (1H, d, *J* 2.5 Hz, H-5-pyraz.), 12.41 (1H, s, NH); δ_F (376.5 MHz, DMSO-d_6) 106.2 (s, CF_3); [Found: C, 66.56; H, 3.47; N, 12.86. $C_{18}H_{12}F_3N_3$ requires C, 66.05; H, 3.70; N, 12.84%].

4.15. 3-[3-(Trifluoromethyl)-1H-pyrazol-5-yl]-1H-indole-2-carboxylic acid (10)

Yield 35% (A, stirring at ambient temperature for 1 h and at 70 °C for 30 min), white powder (aqueous ethanol), mp 256–257 °C; ν_{max} (ATR) 3593, 3466, 3132, 1693, 1589 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 6.99 (1H, s, pyraz.), 7.17 (1H, t, *J* 7.5 Hz, H-5), 7.34 (1H, t, *J* 7.5 Hz, H-6), 7.52 (1H, d, *J* 8.1 Hz, H-7), 7.18 (1H, d, *J* 8.1 Hz, H-4), 12.17 (1H, s, NH-pyraz.), 13.45 (1H, br s, CO_2H), 13.71 (1H, s, NH-Ind); δ_F (376.5 MHz, DMSO-d_6) 102.6 (s, CF_3); δ_C (100 MHz, DMSO-d_6) 103.6, 108.0, 112.8, 120.5, 121.0, 122.0 (q, *J* 268.0 Hz), 125.2, 125.4, 126.2, 135.8, 136.8, 140.9 (q, *J* 34.3 Hz), 162.5; [Found: C, 51.03; H, 3.03; N, 13.70. $C_{13}H_8F_3N_3O_2 \cdot 0.5H_2O$ requires C, 52.32; H, 2.89; N, 13.81%].

Acknowledgment

This work was financially supported by the Ministry of Education and Science (Contract No. П1370).

References

[1] Z. Wang, F. Ge, W. Wan, H. Jiang, J. Hao, J. Fluorine Chem. 128 (2007) 1143–1152.
[2] F. Ge, Z. Wang, W. Wan, J. Hao, Synlett (2007) 447–450.
[3] V.M. Muzalevskiy, A.V. Shastin, E.S. Balenkova, G. Haufe, V.G. Nenajdenko, Russ. Chem. Bull. 57 (2008) 2217–2219.
[4] K. Miyashita, K. Tsuchiya, K. Kondoh, H. Miyabe, T. Imanishi, Heterocycles 42 (1996) 513–516.
[5] K.E. Henegar, D.A. Hunt, Heterocycles 43 (1996) 1471–1476.
[6] Y. Girard, J.G. Atkinson, P.C. Bélanger, J.J. Fuentes, J. Rokach, C.S. Rooney, J. Org. Chem. 48 (1983) 3220–3234.
[7] Q.-Y. Chen, Z.-T. Li, J. Chem. Soc., Perkin Trans. 1 (1993) 645–648.
[8] T. Kino, Y. Nagase, Y. Ohtsuka, K. Yamamoto, D. Uraguchi, K. Tokuhisa, T. Yamakawa, J. Fluorine Chem. 131 (2010) 98–105.
[9] M. Yoshida, T. Yoshida, M. Kobayashi, N. Kamigata, J. Chem. Soc., Perkin Trans. 1 (1989) 909–914.
[10] M.S. Wiehn, V.E. Vinogradova, A. Togni, J. Fluorine Chem. 131 (2010) 951–957.
[11] K. Myiashita, K. Kondoh, K. Tsuchiya, H. Miyabe, T. Imanishi, J. Chem. Soc., Perkin Trans. 1 (1996) 1261–1268.
[12] A. Fürstner, A. Hupperts, J. Am. Ceram. Soc. 117 (1995) 4468–4475.
[13] J. Chae, T. Konno, T. Ishihara, H. Yamanaka, Chem. Lett. 33 (2004) 314–315.
[14] T. Konno, J. Chae, T. Ishihara, H. Yamanaka, J. Org. Chem. 69 (2004) 8258–8265.
[15] J. Fayn, A. Nezis, A. Cambon, J. Fluorine Chem. 36 (1987) 479–482.
[16] Y. Chen, Y. Wang, Z. Sun, D. Ma, Org. Lett. 10 (2008) 625–628.
[17] D.M. Gange, EP Patent 0,697,172 (1996).
[18] V.M. Muzalevskiy, V.G. Nenajdenko, A.V. Shastin, E.S. Balenkova, G. Haufe, Tetrahedron 65 (2009) 7553–7561.
[19] H. Jiang, Y. Wang, W. Wan, J. Hao, Tetrahedron 66 (2010) 2746–2751.
[20] W. Wan, J. Hou, H. Jiang, Y. Wang, S. Zhu, H. Deng, J. Hao, Tetrahedron 65 (2009) 4212–4219.
[21] J.J. Acton, S.D. Debenham, K. Liu, P.T. Meinke, H.B. Wood, R.M. Black, WO Patent 2004/20408 A1 (2004).
[22] B.I. Usachev, D.L. Obydennov, V.Ya. Sosnovskikh, Russ. Chem. Bull. 59 (2010) 300–301.
[23] V.P. Gorbunova, K.F. Turchin, N.N. Suvorov, Chem. Heterocycl. Compd. 6 (1970) 1406–1409.
[24] H. Abdel-Gawad, H.A. Mohamed, K.M. Dawood, F.A.-R. Badria, Chem. Pharm. Bull. 58 (2010) 1529–1531.
[25] S.K. Singh, V. Saibaba, K.S. Rao, P.G. Reddy, P.R. Daga, S.A. Rajjak, P. Misra, Y.K. Rao, Eur. J. Med. Chem. 40 (2005) 977–990.
[26] A. Dandia, V. Sehgal, P. Singh, Indian J. Chem. 32 B (1993) 1288–1291.
[27] J.G. Tikhe, S.E. Webber, Z. Hostomsky, K.A. Maegley, A. Ekkers, J. Li, X.-H. Yu, R.J. Almassy, R.A. Kumpf, T.J. Boritzki, C. Zhang, C.R. Calabrese, N.J. Curtin, S. Kyle, H.D. Tomas, L.-Z. Wang, A.H. Calvert, B.T. Golding, R.J. Griffin, D.R. Newell, J. Med. Chem. 47 (2004) 5467–5481.
[28] S. Servi, Z.R. Akguen, Synth. Commun. 32 (2002) 3399–3406.
[29] E.R.E. Sawy, A.H. Mandour, A.M.E. Metwaly, Egypt. J. Chem. 50 (2007) 667–681.
[30] T.A. Abdallah, J. Heterocycl. Chem. 44 (2007) 961–965.
[31] P. Gmeiner, H. Huebner, K.A.A. Safieh, I.I. Fasfous, M.M. El-Abadelah, S.S. Sabri, W. Voelter, Heterocycles 60 (2003) 1339–1350.
[32] K.A.A. Safieh, M.M. El-Abadelah, S.S. Sabri, M.H.A. Zarga, W. Voelter, C.M. Moessmer, J. Heterocycl. Chem. 38 (2001) 623–628.
[33] K.A. Abu-Safieh, M.M. El-Abadelah, S.S. Sabri, W. Voelter, C.M. Moessmer, M. Stroebele, Z. Naturforsch. B 57 (2002) 1327–1332.
[34] S.N. Haydar, H. Bothmann, C. Ghiron, L. Maccari, I. Micco, A. Nencini, R. Zanaletti, WO Patent 2010/9290 A1 (2010).
[35] W.H. Dekker, H.A. Selling, J.C. Overeem, J. Agric. Food Chem. 23 (1975) 785–791.
[36] C.-S. Chen, H.-C. Chiu, D. Wang, US Patent 20,090,111,799 A1 (2009).
[37] C.-S. Chen, WO Patent WO2005/44130 A1 (2005).
[38] B.I. Usachev, D.L. Obydennov, M.I. Kodess, V.Ya. Sosnovskikh, Tetrahedron Lett. 50 (2009) 4446–4448.
[39] B.I. Usachev, I.A. Bizenkov, V.Ya. Sosnovskikh, Russ. Chem. Bull. (2007) 558–559.
[40] S.L. Leon, J.H. Choi, B.T. Kim, I.H. Leong, J. Fluorine Chem. 128 (2007) 1191–1197.
[41] B.I. Usachev, M.A. Shafeev, V.Ya. Sosnovskikh, Russ. Chem. Bull. 55 (2006) 523–528.
[42] B.I. Usachev, S.A. Usachev, G.-V. Röschenthaler, V.Ya. Sosnovskikh, Russ. Chem. Bull. 59 (2010) 845–847.
[43] G.M. Sheldrick, The SHELX-97 Manual, Univ. of Göttingen, Göttingen (Germany), 1997.