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Highly regioselective synthesis of trifluoromethyl derivatives of pyrazolo[1,5-*a*]pyrimidines bearing fused cycloalkane rings using (2-ethoxycycloalkenyl)-2,2,2-trifluoroethanones

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ABSTRACT

8-Trifluoromethyl-6,7-dihydro-5*H*-1,4,8a-triaza-*s*-indacene and 9-trifluoromethyl-5,6,7,8-tetrahydropyrazolo[5,1-*b*]quinazolines were efficiently generated by condensation of 5(3)-aminopyrazoles with (2-ethoxycycloalkenyl)-2,2,2-trifluoroethanones and isolated in excellent yields. The regiochemistry of the prepared compounds was established by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy and X-ray diffraction analysis.

1. Introduction

Pyrazolopyrimidine derivatives, being purine analogs, are of considerable chemical and pharmacological importance. Indeed, representatives of this type heterocycles exhibit a wide range of biological activity [1,2] and some pyrazolopyrimidines serve as efficient sedative-hypnotic and anxiolytic drugs like zaleplon (Sonata, hypnotic) [3], indiplon (hypnotic) [4], and ocinaplon (anxiolytic) [5]. These drugs are related to the class of non-benzodiazepines, and their therapeutic effect is due to allosteric enhancement of the action of the inhibitory neurotransmitter GABA at the $GABA_A$ receptor [3,4].

In view of our ongoing interest in the chemistry of pyrazolopyrimidines [6–8], we have now focused our attention on development of efficient routes to tricyclic compounds with pyrazolopyrimidine core bearing a CF_3-group. Trifluoromethyl-containing compounds are commonly applied in material and pharmacological research as agents with better pharmacokinetic properties like increased membrane permeability, enhanced hydrophobic properties, and comparatively less environmental and mammalian toxicity [4,12]. It is anticipated that the integration of a pyrazolopyrimidine and CF_3-group in one molecule could lead to a modified and enhanced biological activity as compared to the other derivatives of pyrazolo[1,5-*a*]pyrimidines.

The synthetic routes for preparation of pyrazolo[1,5-*a*]pyrimidines involves the cyclocondensation of aminopyrazoles with 1,3-biselectrophiles such as 1,3-dicarbonyl compounds, α-acetylene and unsaturated ketones, alkoxymethylene carbonyl compounds, 1,3-enaminones [2,6–11].

We report here on a convenient and regioselective synthetic protocol to obtain new trifluoromethyl-containing tricyclic compounds: 5,6,7,8-tetrahydropyrazolo[5,1-*b*]quinazolines and 6,7-dihydro-5*H*-1,4,8a-triaza-*s*-indacenes. These compounds are generated *via* the condensation of 5(3)-aminopyrazoles **1** with new synthons, enol ethers of cyclic trifluoromethyl-containing diketones. In recent years β-trihaloacetylated enol ethers started to be intensely applied as useful precursors for preparation of various trihalomethylated heterocycles, *e.g.*, isoxazoles, pyrazoles, pyrimidines, derivatives of pyridopyrazolopyrimidines [12–14], and these processes were highly regioselective. Cyclic analogs of trifluoroacylated enol ethers of ketones as building-blocks for tricyclic fused heterocycles have never been used before in reactions with 5(3)-aminopyrazoles.

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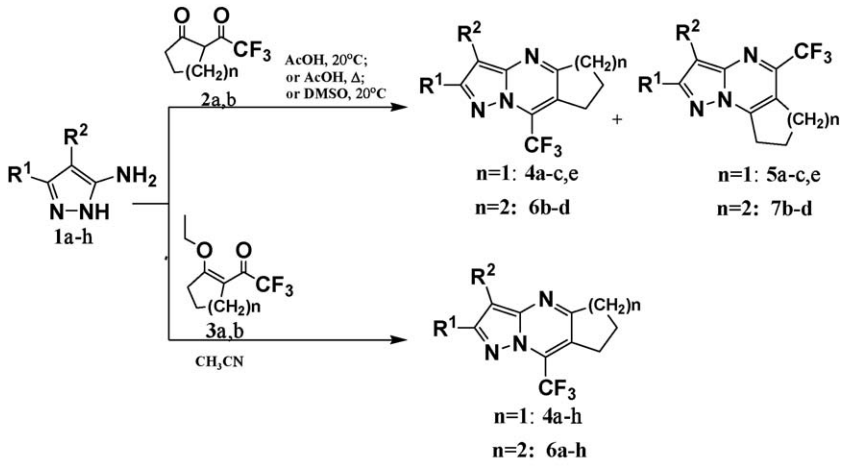


1, a) $R^1 = CH_3$, $R^2 = H$; **b)** $R^1 = 4\text{-}CH_3C_6H_4$, $R^2 = H$; **c)** $R^1 = 4\text{-}ClC_6H_4$, $R^2 = H$; **d)** $R^1 = H$, $R^2 = 4\text{-}ClC_6H_4$; **e)** $R^1 = CH_3$, $R^2 = CN$; **f)** $R^1 = CH_3$, $R^2 = C_6H_5$; **g)** $R^1 = CH_3$, $R^2 = 4\text{-}ClC_6H_4$; **h)** $R^1 = H$, $R^2 = CN$.
2, **a)** n = 1; **b)** n = 2. **3, a)** n = 1; **b)** n = 2.
4, n = 1, **a)** $R^1 = CH_3$, $R^2 = H$; **b)** $R^1 = 4\text{-}CH_3C_6H_4$, $R^2 = H$; **c)** $R^1 = 4\text{-}ClC_6H_4$, $R^2 = H$; **d)** $R^1 = H$, $R^2 = 4\text{-}ClC_6H_4$; **e)** $R^1 = CH_3$, $R^2 = CN$; **f)** $R^1 = CH_3$, $R^2 = C_6H_5$; **g)** $R^1 = CH_3$, $R^2 = 4\text{-}ClC_6H_4$; **h)** $R^1 = H$, $R^2 = CN$.
5, n = 1, **a)** $R^1 = CH_3$, $R^2 = H$; **b)** $R^1 = 4\text{-}CH_3C_6H_4$, $R^2 = H$; **c)** $R^1 = 4\text{-}ClC_6H_4$, $R^2 = H$; **d)** $R^1 = H$, $R^2 = 4\text{-}ClC_6H_4$; **e)** $R^1 = CH_3$, $R^2 = CN$;
6, n = 2, **a)** $R^1 = CH_3$, $R^2 = H$; **b)** $R^1 = 4\text{-}CH_3C_6H_4$, $R^2 = H$; **c)** $R^1 = 4\text{-}ClC_6H_4$, $R^2 = H$; **d)** $R^1 = H$, $R^2 = 4\text{-}ClC_6H_4$; **e)** $R^1 = CH_3$, $R^2 = CN$; **f)** $R^1 = CH_3$, $R^2 = C_6H_5$; **g)** $R^1 = CH_3$, $R^2 = 4\text{-}ClC_6H_4$; **h)** $R^1 = H$, $R^2 = CN$.
7, n = 2, **b)** $R^1 = 4\text{-}CH_3C_6H_4$, $R^2 = H$; **c)** $R^1 = 4\text{-}ClC_6H_4$, $R^2 = H$; **d)** $R^1 = H$, $R^2 = 4\text{-}ClC_6H_4$.

Scheme 1.

2. Results and discussion

A conventional synthetic route to CF_3-containing pyrazolo[1,5-*a*]pyrimidines involves the cyclocondensation of 5(3)-aminopyrazoles with 1,3-biselectrophiles [2,7,10,11]. Following this synthetic strategy the reaction of 5(3)-aminopyrazoles **1a**–**c**,**e** with 2-(2,2,2-trifluoroacetyl)-1-cycloalkanones **2a**,**b** in both acetic acid and dimethyl sulfoxide affords a mixture of regioisomeric compounds, such as dihydrotriazaindacenes (**4a**–**c**,**e** and **5a**–**c**,**e**) formed in the reaction with 2-(2,2,2-trifluoroacetyl)-1-cyclopentanone **2a** and tetrahydropyrazoloquinazolines (**6b**,**c**,**e** and **7b**,**c**,**e**) derived from the reaction with 2-(2,2,2-trifluoroacetyl)-1-cyclohexanone **2b** (Scheme 1, Table 1).

When the cyclocondensation was carried out in acetic acid or in DMSO, the content of the major regioisomer (**4a**–**c**,**e** or **6b**,**d**,**e**) in the reaction mixture was 70–100% depending on temperature (Table 1).

(2-Ethoxycycloalk-1-enyl)-2,2,2-trifluoroethanones **3a**,**b** are synthetic analogs of 1,3-diketones [13,14]. In the reaction of these species with 5(3)-aminopyrazoles **1a**–**h** (Scheme 1) only compounds **4a**–**h** or **6a**–**h** were obtained; the process proceeded under mild conditions and gave nearly quantitative yields of the products. The variation in the structures of aminopyrazoles **1a**–**h** did not lead to the generation of regioisomers **5**,**7** in the reaction mixture.

Table 1
Regioisomeric ratio[a] for products in the reaction between **1a**–**e** with **2a**,**b**.

Compound number	Ratio (%)			
	AcOH, reflux	AcOH, r.t.	DMSO, 100 °C	DMSO, r.t.
4a/**5a**	81/19	89/11		
4b/**5b**	85/15	95/5	70/30	36/64
4c/**5c**	95/5	100/0	80/20	40/60
4e/**5e**	94/6	100/0	59/41	
6b/**7b**	88/12	92/8		
6c/**7c**	67/33	75/25		
6d/**7d**	76/24	80/20		

[a] Regioisomeric ratio was determined by ^1H NMR.

Satisfactory microanalyses (C, H) corresponded to compounds **4a**–**h**, **5b**,**d**, and **6a**–**h**, and they were characterized by ^1H, ^{13}C and ^{19}F NMR spectroscopy. The structures of minor isomers **5a**,**c**,**e** and **7b**–**d** were elucidated based on ^1H and ^{13}C NMR monitoring of the reaction mixtures and MS(ESI) data as obtained mixtures were difficult to separate. In the ^1H NMR spectra of **4a**–**h** the methylene protons signals appear as a quintet ($J_{HH} \sim 7.5$ Hz), a triplet ($J_{HH} \sim 7.5$ Hz), and a triplet of quartets ($J_{HH} \sim 7.5$ Hz and $^5J_{HF} \sim 3$ Hz), whereas the signals due to the methylene protons of isomeric compounds **5a**–**c**,**e** give rise to two triplets and a quintet ($J_{HH} \sim 7.5$ Hz). It is reported that for pyridine and pyrimidine derivatives [7,8,15] the scalar interaction is more effectively transmitted via double bonds than through a chain of single bonds. The coupling constant $^5J_{HF} \sim 3$ Hz, observed in the ^1H NMR spectra of **4a**–**h**, apparently corresponds to the coupling of the hydrogen of the group H_2C-7 with the F atoms of the trifluoromethyl group suggesting that **4a**–**h** contain the fragment C(7a) = C(8)–CF_3, and, consequently, compounds **5a**–**c**,**e** have the C(5a)–C(5)–CF_3 moiety.

The comparison of the chemical shifts of the carbon atoms resonances in the **C**CF_3 moiety in the ^{13}C NMR spectra of **4a**–**h**, **5a**–**d**, **6a**–**h** with the previously reported characteristic chemical shifts of carbon atoms of the pyrimidine ring [CF_3–C = N– ($\delta \sim 146.0$ ppm) and –C=**C**–CF_3 ($\delta \sim 134$ ppm)] [7,8,15] allows the unambiguous determination of structures of the regioisomeric compounds: in **4a**–**h** trifluoromethyl group is linked to C-8 atoms, in **6a**–**h**, to C-9 atoms, and in **5a**–**d**, to C-5 atoms.

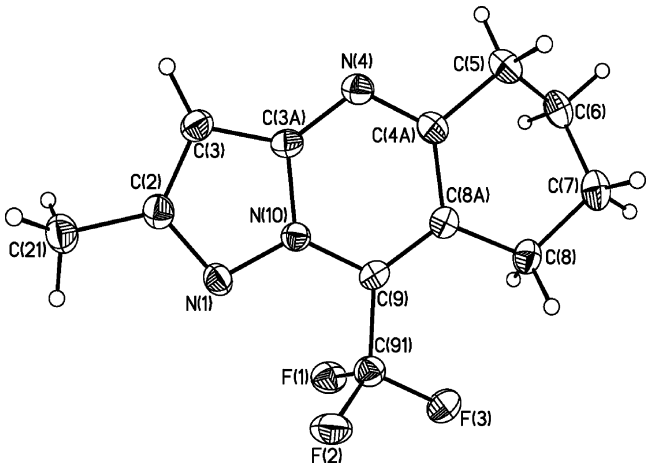


Fig. 1. General view of compound **6a** in representation of atoms *via* thermal ellipsoids at 50% probability level.

In the spectra of **4a**–**h**, carbon signals from C-7 atom appear as quartets with the coupling constant $^4J_{CF} \sim 3$ Hz, and the signals from C-6 atom of **5a**–**d** are observed as quartets with the coupling constant $^4J_{CF} \sim 1$ Hz. Large values of these coupling constants in case of **4a**–**h** can be rationalized by the involvement of a C=C-double bond in the transfer of the spin–spin C–F interaction, and it is consistent with the assumed regioisomeric structure.

^{19}F NMR spectrum of compounds **4**, **6** contains a triplet signal at ~ -60.7 ppm for **4a**,**c**–**g** and ~ -57.1 ppm for **6a**,**d**,**f**,**g**, but a singlet signal for compound **5a**,**c**–**e** (~ -64.4 ppm) and **7c**,**d** (~ -62.9 ppm).

The solid state structure of **6a** was studied by X-ray diffraction analysis (Fig. 1). The heteroatomic bicyclic (N-1, C-2, C-3, C-3a, N-4, C-4a, C-8a, C-9, N-10) system is close to planar; the maximum deviation from the least-square plane is 0.035 Å (for the N-10 atom). The conformation of the cyclohexane ring can be described as *sofa* with the maximum deviation (0.866 Å) of C-6 atom from the plane; carbon atoms C-5, C-7, C-8 are located above the plane at the distance of 0.117, 0.145, and 0.147 Å, respectively. All formally single bonds C–C, C–N, and N–N of the pyrazolopyrimidine system (Table 2) are greatly shortened compared to the typical bond distances (1.54, 1.47 and 1.45 Å, respectively [16]) indicating a considerable degree of π- and n-electron delocalization.

As to the crystal packing of **6a**, the molecules are assembled into centrosymmetric dimers by means of relatively weak N···H–C bonds with the N···N distance of 3.529(2) Å and the corresponding N–HC angle of 169(1)°. These supramolecular associates are held together through a number of H···π contacts. It is worth mentioning that in the crystal structure of **6a**, the CF_3 group of each molecule is located above the C-**4a**–C-**8a** bond of the neighboring molecule forming F···π contacts (F···C distances are 3.084(2) and 3.156(2) Å). The trifluoromethyl group of compound **6a** is located at the C-9 atom (Fig. 1) confirming the assignment of the regioisomeric structure of **4**–**7** based on the NMR data (*vide supra*).

The reaction mechanism of nitrogen-containing binucleophiles and 1,3-dicarbonyl compounds is discussed in detail in the literature [17,18]. According to the plausible mechanism of the cyclocondensation two routes are possible: (*i*) the nitrogen functionality of an aminopyrazole (**1a**–**h**) adds to the carbonyl group of a diketone (**2a**,**b**) followed by dehydration to furnish the enaminoketone as the intermediate that further undergoes cyclization and dehydration into final compounds **4**–**7**; (*ii*) the nitrogen functionality of an aminopyrazole (**1a**–**h**) adds to the carbonyl group of a diketone (**2a**,**b**) followed by intramolecular cyclization that leads to the cyclic diols whose subsequent dehydration also results in the formation of **4**–**7**.

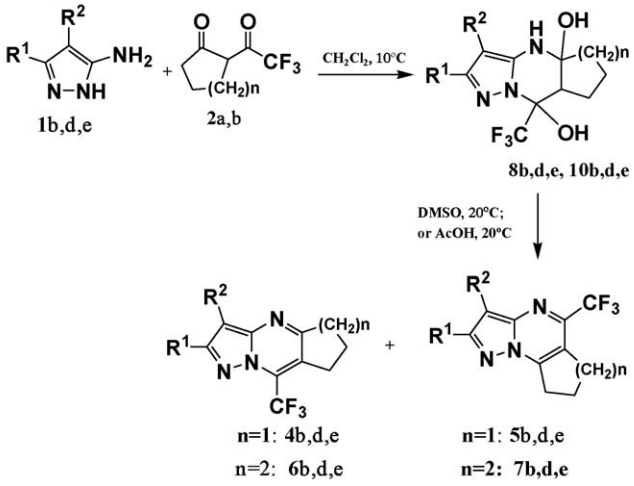
We monitored the reaction progress by ^{1}H NMR, in order to determine the actual routes of the interaction between cyclic trifluoromethyl-containing diketones **2** and 5(3)-aminopyrazoles **1**. It turned out that in the course of the reaction a large number of signals were observed in the spectra which could be assigned to different intermediates. Part of them were interconvertable hampering their exact identification and suggesting several path to the final products formation (i and ii) [8,17–19].

We succeeded in isolation of diols **8b**,**d**,**e** and **10b**,**d**,**e** in the reactions of substituted 5(3)-aminopyrazoles **1b**,**d**,**e** with cyclic diketones **2a**,**b** performed in CH_2Cl_2 at 5–10 °C (Scheme 2).

These diols are presumably possible intermediates of the investigated reaction both in acetic acid and DMSO. The structure of these compounds and their transformations were studied in DMSO-d_6 by ^{1}H and ^{13}C NMR at ambient temperature. In the ^{1}H NMR spectrum of diol **8b** measured just after its dissolution in DMSO-d_6 a single set of signals is observed and these peaks originate from the protons of two hydroxy groups and the H-3 and NH protons. The signal at 5.72 ppm may be assigned to the proton linked to the C-3 carbon for it is flanked with ^{13}C-satellites. We identified signal of the NH proton in the NOESY experiment, where a cross-peak was observed between the signal of the H-3 proton and the signal at 7.73 ppm. It is noteworthy that the two hydroxy protons (6.39 and 7.08 ppm) are involved in an exchange process with traces of water in DMSO-d_6 solution. After 10–15 min, a second set of peaks appeared in the ^{1}H NMR spectrum and we assigned the new resonances to isomeric diol **9b** recognized by the position of the trifluoromethyl group (C(5)–CF_3, C(8)–CF_3) and of the cycloalkane ring. The assignment of the proton signals of the second diol was performed analogously to the procedure described above for diol **8b**. The cyclic structure of diols **8b**, **9b** was also confirmed by ^{13}C{^{1}H} NMR spectroscopy; the spectra display two characteristic signals of quaternary carbon atoms linked to hydroxy group at 81–85 ppm, *i.e.* a singlet from C(OH) and a quartet due to C(CF_3)OH ($^2J_{CF} \sim 30$ Hz). The obtained spectral

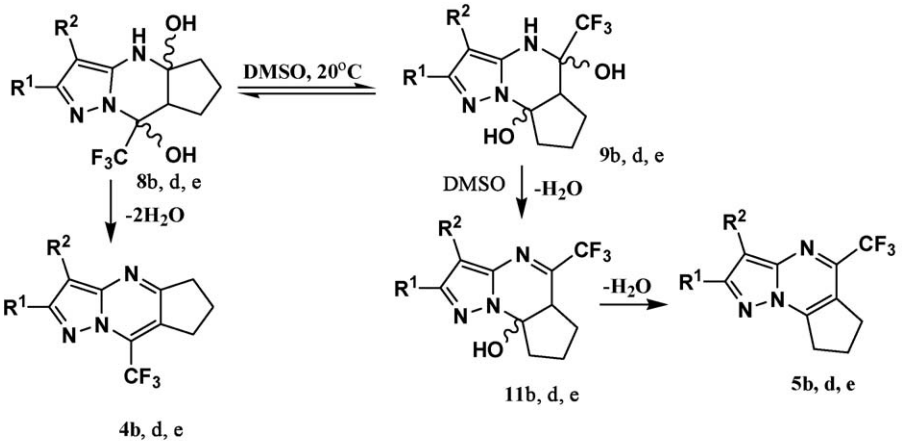
Table 2
Selected bond length and bond angles for compound **6a**.

Bond length (Å)		Bond angle (°)		Bond angle (°)	
N(1)–C(2)	1.350(2)	C(2)–N(1)–N(10)	103.4(1)	N(10)–C(3a)–C(3)	105.8(1)
N(1)–N(10)	1.364(2)	C(3a)–N(4)–C(4a)	118.4(1)	N(4)–C(4a)–C(5)	116.3(1)
C(2)–C(3)	1.394(2)	N(1)–N(10)–C(3a)	112.4(1)	N(4)–C(4a)–C(8a)	123.7(1)
C(3)–C(3a)	1.386(2)	N(1)–N(10)–C(9)	126.4(1)	C(5)–C(4a)–C(8a)	120.0(1)
C(3a)–N(4)	1.351(2)	C(3a)–N(10)–C(9)	121.2(1)	C(4a)–C(8a)–C(8)	120.1(1)
C(3a)–N(10)	1.393(2)	N(1)–C(2)–C(3)	113.3(2)	C(4a)–C(8a)–C(9)	116.8(1)
N(4)–C(4a)	1.314(2)	C(2)–C(3)–C(3a)	105.1(1)	C(8)–C(8a)–C(9)	123.0(1)
C(4a)–C(8a)	1.450(2)	N(4)–C(3a)–N(10)	121.0(1)	N(10)–C(9)–C(8a)	119.0(1)
C(8a)–C(9)	1.369(2)	N(4)–C(3a)–C(3)	133.2(1)		
C(9)–N(10)	1.375(2)				



4, 5, 8 (n = 1), **6, 7, 10** (n = 2) **1, 4-8, 10** R^1 = 4-$CH_3C_6H_4$, R^2=H (b); R^1 = H, R^2 = 4-ClC_6H_4 (d); R^1 = CH_3, R^2 = CN (e)

Scheme 2. 4, **5**, **8** (*n* = 1), **6**, **7**, **10** (*n* = 2) **1**, **4**–**8**, **10**, R^1 = 4-$CH_3C_6H_4$, R^2 = H (b); R^1 = H, R^2 = 4-ClC_6H_4 (d); R^1 = CH_3, R^2 = CN (e).



4, 5, 8, 9, 11 R^1 = 4-$CH_3C_6H_4$, R^2=H (b); R^1 = H, R^2 = 4-ClC_6H_4 (d); R^1 = CH_3, R^2 = CN (e)

Scheme 3. 4, **5**, **8**, **9**, **11** R^1 = 4-$CH_3C_6H_4$, R^2 = H (b); R^1 = H, R^2 = 4-ClC_6H_4 (d); R^1 = CH_3, R^2 = CN (e).

data do not allow the unambiguous assignment of the regiostructure of diols **8b**,**d**,**e** and **9b**,**d**,**e** (Scheme 3).

It should be emphasized that we do not give complete possible mechanism of interconversion of diols on Scheme 2, because has been described in detail by Katritzky et al. [17] and Selivanov et al. [18] by the example of interaction of 1,3-dicarbonyl compounds with such binucleophiles as hydrazines, urea, hydroxylamine.

In the course of further monitoring of transformations that proceed in DMSO-d_6 solution of diols **8b**–**9b**, signals from a number of intermediates were registered in the ^{1}H NMR spectra, but only one of them (whose amount gradually grew in the course of the reaction) were inexplicitly identified and the structure of this intermediate was established by both ^{1}H and ^{13}C NMR spectroscopy (Fig. 2). In the ^{1}H NMR spectra, a single broad peak from the hydroxy group was observed at *ca.* 7.2 ppm and a triplet from the H-5a proton emerged at 3.29 ppm; the signal from the NH proton was not observed. These findings allowed the conclusion that the intermediate had structure **11b** that contained the hydroxy group at the C-8a atom. In the ^{13}C NMR spectrum of intermediate **11b** registered without proton decoupling a quartet

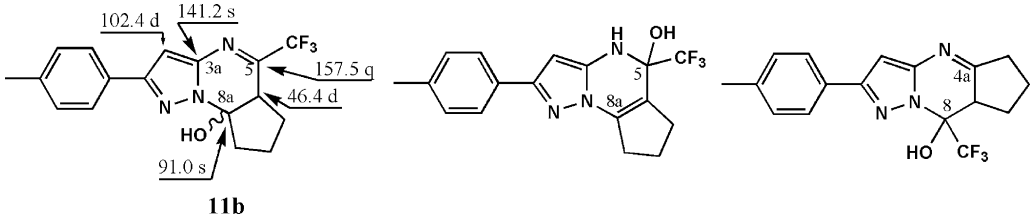


Fig. 2. The structure of intermediate **11b** and two other possible intermediates.

Table 3
Regioisomeric ratio[a] for **4**/**5** and **6**/**7** upon the dehydration of diols **8b**,**d**,**e** and **10b**,**d**,**e**.

Compound number	Regioisomeric ratio (%)				
	AcOH, reflux	AcOH, r.t.	DMSO, 100 °C	DMSO, r.t.[b]	100 °C
4b/**5b**	80/20	97/3	45/55	0/100	35/65
4d/**5d**	92/8	96/4	80/20	0/100	50/50
4e/**5e**	95/5	100/0	40/60	33/67	40/60
6b/**7b**	79/21	83/17			63/37
6d/**7d**		100/0			62/38
6e/**7e**		89/11			67/33

[a] Regioisomeric ratio was determined by ^{1}H NMR.
[b] Stable intermediate **11** was formed after 30 d at r.t., whereupon the cyclocondensation was completed at 140 °C for 10 min.

from the carbon atom N=C-5–CF_3 (157.54 ppm) was observed, one singlet from the quaternary carbon C-8a bearing the hydroxy group (δ 91.84 ppm), and four signals from the carbons of the cyclopentane ring (δ 21.95 tm, 30.29 tm, 37.45 tm, 46.40 dm) confirming the structure of **11b** and ruling out two other plausible structures (Fig. 2). Compound **11b** is stable in solution in DMSO and was converted to final product 4b only on heating at 100 °C. Thus, studying one of the routes of aminopyrazoles **1** and 1,3-diketones **2** interaction proceeding through diol formation has shown that in the solution the fast dehydration of diol **8** does not occur but its transformation goes on followed by dehydratation of the intermediates formed, which results in a regioisomeric products mixture.

In the spectra of diols **10b**,**d**,**e** in DMSO-d_6 recorded just after dissolution, a single set of signals was observed and these peaks were assigned analogously to those of diol **8b**.

In the dehydration of diols **8b**,**d**,**e** in DMSO the regioisomeric ratio strongly depends on the reaction temperature. Thus, at 100 °C the reaction is relatively fast and brings about a mixture of isomers (Table 3). At room temperature the cyclocondensation proceeds very slowly (*ca*. 1 month), giving the regioisomer with a trifluoromethyl group at C-5 atom as the major product **5b**,**d**,**e**. Compounds **5b**,**d** were isolated and characterized. Compounds **5e** and **7b**–**d** were isolated as mixtures with the corresponding regioisomers **4e** and **6b**–**d**. It is important to note, that the region of cycloalkane rings protons signals in the ^{1}H NMR spectrum of these compounds is fairly characteristic and allows to determine the presence and estimate the ratio of regioisomers in the reaction mixture.

The dehydration of diols **8b**,**d**,**e** and **10b**,**d**,**e** in acetic acid at room temperature occurs rather rapidly (24–48 h) yielding compounds with the trifluoromethyl group at the atoms C-8 (**4b**,**d**,**e**) and C-9 (compounds **6b**,**d**,**e**), respectively, as the major products.

In acetic acid, the cyclocondensation proceeds faster than in dimethyl sulfoxide probably due to acid catalysis of the dehydration step. Taking into account that in acetic acid the main product is regioisomer **4** we believe that just the regioisomeric diol **8** is subject to dehydration. Furthermore, regioisomer **5**, formed as a result of **8** to **9** conversion followed by dehydration of the latter, is the minor product (r.t., 3–17%, Table 3, Scheme 3).

The plausible reaction scheme indicates that diol **8** bears the trifluoromethyl group in the position 8; diols **10** have a similar structure. It is anticipated that diols **8**, **10** are among possible intermediates of the reaction between 5(3)-aminopyrazoles and trifluoroacetylcycloalkanones **2a**,**b**.

Our data on the reaction between aminopyrazoles **1** with diketones **2a**,**b** indicate that dioles are stable intermediates of the reaction and their interconversion and subsequent dehydration might control the formation of two regioisomeric products **4**,**5** or **6**,**7**. In the first step, the interaction between diketone ethers **3a**,**b** and aminopyrazoles **1** follows the mechanism of the vinyl substitution [8,20], which involves fast elimination of the alcohol thus providing the formation of a sole regioisomer, *i.e.* **4** or **6**.

3. Conclusion

In summary, employing the reaction between the 2-ethoxycycloalkenyl)-2,2,2-trifluoroethanones and 5(3)-aminopyrazoles we succeeded in the development of a highly efficient method for preparation of trifluoromethyl-containing derivatives of pyrazolo[1,5-*a*]pyrimidines bearing fused cycloalkane rings. This process proceeds regioselectively under mild conditions and affords products in high yield. The reaction between 2-(2,2,2-trifluoroacetyl)-1-cycloalkanones and 5(3)-aminopyrazoles leads to the generation of two regioisomers, whose structures has been determined by X-ray diffraction analysis and NMR (^{1}H, ^{19}F and ^{13}C) experiments. Stable diols were isolated as probable intermediates of the reaction. Their interconversion and subsequent dehydration might control the formation of two regioisomeric products. The reaction between diketone ethers and aminopyrazoles follows the mechanism of the vinyl substitution, which involves fast elimination of the alcohol thus providing the formation of a sole regioisomer.

4. Experimental

4.1. Instruments and materials

^{1}H (300.13 MHz) and ^{13}C (75.47 MHz) NMR spectra were recorded on a Bruker DPX-300 spectrometer and ^{19}F (470 MHz) NMR spectra were recorded on a Bruker AM-500 spectrometer at ambient temperature. Chemical shifts δ_H were measured from the residual proton signals of the deuterated solvents $CDCl_3$ (7.28 ppm) and DMSO-d_6 (2.50 ppm), δ_C from signals of $CDCl_3$ (76.90 ppm) and DMSO-d_6 (39.50 ppm), and δ_F from signals of $CFCl_3$ (0.00). High-resolution mass spectra were recorded on a Bruker Daltonics microTOF mass spectrometer in positive electro spray ionization (ESI). Microanalyses were carried out on a CHN-analyzer HP-185B. Mp's were determined on a Boëtius block.

5(3)-Aminopyrazoles (**1a**–**h**) were synthesized as described in Refs. [21,22], 2-trifluoroacetylcycloalkanones (**2a**,**b**) were prepared by the procedure reported in Ref. [23], 8-(trifluoromethyl)-6,7,7a,8-tetrahydro-4*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidine-4a,8(5*H*)-diols (**8b**,**c**,**e**), and 9-(trifluoromethyl)-5,6,7,8,8a,9-hexahydropyrazolo[5,1-*b*]quinazoline-4a,9(4*H*)-diols (**10b**,**d**,**e**) were obtained by treatment of 2-trifluoroacetylcycloalkanones (**2a**,**b**) with 5(3)-aminopyrazoles (**1b**–**e**) in CH_2Cl_2 according to Ref. [7].

4.1.1. General procedure for preparation of enol ethers of 2-trifluoroacetylcycloalkanones (3a,b)

Compounds were synthesized according to Ref. [24].

To a stirred mixture of cycloalkanone diethyl acetal (20.6 mmol) (prepared from cyclohexanone or cyclopentanone and triethylorthoformate), pyridine (3.6 g, 42.2 mmol), and chloroform (5 ml) cooled with ice is added dropwise a solution of trifluoroacetic anhydride (8.44 g, 41,2 mmol) in chloroform (5 ml), and the obtained mixture is stirred for 3 h at room temperature. Then, ice water (20 ml) is added and the mixture is extracted with dichloromethane (50 ml). The dichloromethane extract is washed with 2N hydrochloric acid (20 ml), aqueous 10% sodium carbonate (30 ml), and water (2× 30 ml), and is dried with sodium sulfate. The pure product (**3a** or **3b**) is obtained by distillation of the

resultant residue after removal of the solvent under reduced pressure.

*4.1.2. 1-(2-Ethoxycyclopent-1-enyl)-2,2,2-trifluoroethanone (**3a**)*

Yield 92%; bp 137 °C (8 Torr). ^{1}H NMR ($CDCl_3$): δ 1.35 (3H, t, J_{HH} = 7 Hz, CH_3), 2.27 (2H, qui, J_{HH} = 7.5 Hz, CH_2), 3.08 (2H, t, J_{HH} = 7.5 Hz, CH_2), 3.24 (2H, tq, CH_2), 4.27 (2H, q, J_{HH} = 7 Hz, OCH_2). ^{13}C NMR ($CDCl_3$): δ 14.90 (CH_3), 23.90 (C-3), 29.10 (q, $^4J_{CF}$ = 2.9 Hz, C-4), 34.24 (C-5), 67.82 (OCH_2), 117.50 (q, $^1J_{CF}$ = 275.5, CF_3), 95.67 (C-1), 172.41 (C-3), 176.63 (C=O). Anal. Calcd. for $C_9H_{11}F_3O_2$: C, 51.93; H, 5.33. Found: C, 51.75; H, 5.45.

*4.1.3. 1-(2-Ethoxycyclohex-1-enyl)-2,2,2-trifluoroethanone (**3b**)*

Yield 85%; bp 145 °C (10 Torr). ^{1}H NMR ($CDCl_3$): δ 1.37 (3H, t, J_{HH} = 7 Hz, CH_3), 1.92, 3.10 (8H, m, $4CH_2$), 4.27 (2H, q, J_{HH} = 7 Hz, CH_2). ^{13}C NMR ($CDCl_3$), δ, ppm: 14.64 (CH_3), 21.99, 22.72 (C-4, C-5), 24.99 (q, $^4J_{CF}$ = 3.8 Hz, C-3), 24.78 (C-6), 67.82 (OCH_2), 117.45 (q, $^1J_{CF}$ = 275.5 Hz, CF_3), 92.67 (C-1), 174.41 (C-3), 179.63 (C=O). Anal. Calcd for $C_{10}H_{13}F_3O_2$: C, 54.05; H, 5.90. Found: C, 53.90; H, 6.00.

*4.1.4. General procedure for preparation of 8-trifluoromethyl-6,7-dihydro-5H-1,4,8a-triaza-s-indacene (**4a–h**) and 9-(trifluoromethyl)-5,6,7,8-tetrahydropyrazolo[5,1-b]quinazolines (**6a–h**)*

The mixture of 5(3)-aminopyrazole **1a–h** and 1-(2-ethoxycycloalk-1-enyl)-2,2,2-trifluoroethanone (**2a**,**b**) (5.5 mmol) in acetonitrile (10 ml) or chloroform (10 ml) was stirred at room temperature for 1 h, whereupon refluxed for 1 h. After removal of the solvent under reduced pressure, the resultant solid was recrystallized from boiling ethanol.

*4.1.5. 2-Methyl-8-trifluoromethyl-6,7-dihydro-5H-1,4,8a-triaza-s-indacene (**4a**)*

Yield 93%; pale yellow solid, mp 89 °C. ^{1}H NMR ($CDCl_3$): δ 2.24 (2H, qui, J_{HH} = 7.6 Hz, H-6), 2.53 (3H, s, CH_3), 3.03 (2H, t, J_{HH} = 7.6 Hz, H-5), 3.20 (2H, tq, J_{HH} = 7.6 Hz, $^5J_{FH}$ = 2.7 Hz, H-7), 6.43 (^{1}H, s, H-3). ^{13}C NMR ($CDCl_3$): δ 14.64 (CH_3), 23.32 (C-6), 28.48 (q, $^4J_{CF}$ 2.7, C-7), 33.63 (C-5), 95.83 (C-3), 120.50 (q, $^1J_{CF}$ 274.7, 8-CF_3), 121.37 (C-7a), 128.15 (q, $^2J_{CF}$ 36.8, C-8), 149.90 (C-3a), 154.90 (C-2), 168.32 (C-4a). ^{19}F NMR ($CDCl_3$): δ −60.95 (t, $^5J_{FH}$ = 2.7 Hz, CF_3-8). Anal. Calcd for $C_{11}H_{10}F_3N_3$: C, 54.77; H, 4.18. Found: C, 54.60; H, 4.32.

*4.1.6. 2-(4-Methylphenyl)-8-trifluoromethyl-6,7-dihydro-5H-1,4,8a-triaza-s-indacene (**4b**)*

Yield 88%; greenish-yellow solid; mp 199 °C. ^{1}H NMR ($CDCl_3$:DMSO-d_6 = 1:1, v/v): δ 2.28 (2H, qui, J_{HH} = 7.7 Hz, H-6), 2.42 (3H, s, CH_3), 3.08 (2H, t, J_{HH} = 7.7 Hz, H-5), 3.20 (2H, tq, J_{HH} = 7.7 Hz, $^5J_{FH}$ 2.8, H-7), 6.92 (1H, s, H-3), 7.26–7.92 (4H, m, Ar). ^{13}C NMR ($CDCl_3$): δ 21.23 (CH_3), 23.28 (C-6), 28.55 (q, $^4J_{CF}$ = 2.7 Hz, C-7), 33.65 (C-5), 92.72 (C-3), 120.48 (q, $^1J_{CF}$ = 275.3 Hz, 8-CF_3), 122.07 (C-7a), 128.47 (q, $^2J_{CF}$ = 37.6 Hz, C-8), 150.27 (C-3a), 155.99 (C-2), 168.51 (C-4a), 126.34, 129.29, 129.67, 138.87 (Ar). Anal. Calcd. for $C_{17}H_{14}F_3N_3$: C, 64.35; H, 4.45. Found: C, 64.15; H, 4.55.

*4.1.7. 2-(4-Chlorophenyl)-8-trifluoromethyl-6,7-dihydro-5H-1,4,8a-triaza-s-indacene (**4c**)*

Yield 90%; yellow solid; mp 205 °C. ^{1}H NMR ($CDCl_3$): δ 2.28 (2H, qui, J_{HH} = 7.5 Hz, H-6), 3.08 (2H, t, J_{HH} = 7.5 Hz, H-5), 3.24 (2H, tq, J_{HH} = 7.5, $^5J_{FH}$ = 2.7 Hz, H-7), 6.91 (1H, s, H-3), 7.42–7.90 (4H, m, Ar). ^{13}C NMR ($CDCl_3$): δ 23.32 (q, $^4J_{CF}$ = 1.1 Hz, C-6), 28.62 (q, $^4J_{CF}$ = 2.9 Hz, C-7), 33.73 (C-5), 93.05 (C-3), 120.42 (q, $^1J_{CF}$ = 276.1 Hz, 8-CF_3), 122.60 (q, $^3J_{CF}$ 2.2 Hz, C-7a), 128.61 (q, $^2J_{CF}$ = 37.5 Hz, C-8), 150.35 (C-3a), 154.72 (C-2), 168.95 (C-4a), 127.72, 128.78, 131.02, 134.78 (Ar). ^{19}F NMR ($CDCl_3$): δ −60.85 (t, $^5J_{FH}$ = 2.7 Hz, CF_3-8). Anal. Calcd. for $C_{16}H_{11}ClF_3N_3$: C, 56.90; H, 3.28. Found: C, 56.65; H, 3.36.

*4.1.8. 3-(4-Chlorophenyl)-8-(trifluoromethyl)-6,7-dihydro-5H-1,4,8a-triaza-s-indacene (**4d**)*

Yield 87%; yellow solid; mp 210–212 °C. ^{1}H NMR ($CDCl_3$): δ 2.29 (2H, qui, J_{HH} = 7.5 Hz, H-6), 3.12 (2H, t, J_{HH} = 7.5 Hz, H-5), 3.24 (2H, tq, J_{HH} = 7.5, $^5J_{FH}$ = 2.6 Hz, H-7), 7.38–7.95 (4H, m, C_6H_4), 8.37 (1H, s, H-2). ^{13}C NMR ($CDCl_3$): δ 23.39 (C-6), 28.59 (q, $^4J_{FH}$ = 2.7 Hz, C-7), 33.86 (C-5), 109.25 (C-3), 120.30 (q, ^1JC_F = 275.5, 8-CF_3), 123.19 (q, ^3JC_F = 1.7 Hz, C-7a), 128.50 (q, ^2JC_F = 36.5 Hz, C-8), 142.13 (C-2), 145.27 (C-3a), 169.41 (C-4a), 127.46, 128.70, 129.84, 131.97 (Ar). ^{19}F NMR ($CDCl_3$): δ −60.96 (t, $^5J_{FH}$ = 2.6 Hz, CF_3-8). Anal. Calcd. for $C_{16}H_{11}ClF_3N_3$: C, 56.90; H, 3.28. Found: C, 56.55; H, 3.40.

*4.1.9. 2-Methyl-8-(trifluoromethyl)-6,7-dihydro-5H-1,4,8a-triaza-s-indacene-3-carbonitrile (**4e**)*

Yield 90%; yellow solid; mp 164 °C. ^{1}H NMR (DMSO-d_6:CCl_4 = 1:2, v/v): δ 2.56 (s, 3H, CH_3), 2.30 (2H, qui, J_{HH} = 7.5 Hz, H-6), 3.11 (2H, t, J_{HH} = 7.5 Hz, H-5), 3.25 (2H, tq, J_{HH} = 7.5, $^5J_{FH}$ = 2.6 Hz, H-7). ^{13}C NMR (DMSO-d_6:CCl_4 = 1:2, v/v): δ 12.99 (CH_3), 22.76 (C-6), 28.13 (q, $^4J_{FH}$ = 2.1 Hz, C-7), 33.43 (C-5), 81.45 (C-3), 112.02 (CN), 119.58 (q, ^1JC_F = 276.4 Hz, 8-CF_3), 127.49 (q, ^2JC_F = 38.9 Hz, C-8), 150.44 (C-3a), 156.45 (C-2), 173.92 (C-4a). ^{19}F NMR ($CDCl_3$): δ −60.44 (t, $^5J_{FH}$ = 2.6 Hz, CF_3-8). Anal. Calcd. for $C_{12}H_9F_3N_4$: C, 54.14; H, 3.41. Found: C, 54.00; H, 3.62.

*4.1.10. 2-Methyl-3-phenyl-8-(trifluoromethyl)-6,7-dihydro-5H-1,4,8a-triaza-s-indacene (**4f**)*

Yield 90%; yellow solid; mp 151–153 °C. ^{1}H NMR ($CDCl_3$): δ 2.26 (2H, qui, J_{HH} = 7.5 Hz, H-6), 3.07 (2H, t, J_{HH} = 7.5 Hz, H-5), 3.24 (2H, tq, J_{HH} = 7.5, $^5J_{FH}$ = 2.8 Hz, H-7), 2.66 (3H, s, CH_3), 7.31–7.70 (5H, m, Ph). ^{13}C NMR ($CDCl_3$): δ 14.13 (CH_3), 23.39 (C-6), 28.48 (q, ^4JC_F 2.7 Hz, C-7), 33.80 (C-5), 109.33 (C-3), 120.53 (q, ^1JC_F = 274.7 Hz, 8-CF_3), 122.57 (C-7a), 128.60 (q, ^2JC_F = 36.5 Hz, C-8), 146.61 (C-3a), 152.40 (C-2), 168.63 (C-4a), 126.46, 128.44, 128.93, 131.65 (Ph). ^{19}F NMR ($CDCl_3$): δ −60.91 (t, $^5J_{FH}$ = 2.7 Hz, CF_3-8). HRMS (ESI): *m*/*z* calcd for $C_{17}H_{15}F_3N_3$ $(M+H)^+$: 318.1218; found 318.1186 (100%). Anal. Calcd. for $C_{17}H_{14}F_3N_3$: C, 64.35; H, 4.45. Found: C, 64.40; H, 4.50.

*4.1.11. 2-Methyl-3-(4-chlorophenyl)-8-(trifluoromethyl)-6,7-dihydro-5H-1,4,8a-triaza-s-indacene (**4g**)*

Yield 88%; yellow solid; mp 210 °C. ^{1}H NMR ($CDCl_3$): δ 2.26 (2H, qui, J_{HH} = 7.5 Hz, H-6), 2.63 (3H, s, CH_3), 3.07 (2H, t, J_{HH} = 7.5 Hz, H-5), 3.24 (2H, tq, J_{HH} = 7.5 Hz, $^5J_{FH}$ = 2.7 Hz, H-7), 7.43–7.63 (4H, m, Ar). ^{13}C NMR ($CDCl_3$): δ 14.68 (CH_3), 23.93 (C-6), 29.03 (q, ^4JC_F = 2.7 Hz, C-7), 34.35 (C-5), 108.67 (C-3), 120.99 (q, ^1JC_F = 275.8 Hz, 8-CF_3), 122.81 (C-7a), 128.64 (q, ^2JC_F = 37.0 Hz, C-8), 147.11 (C-3a), 152.76 (C-2), 169.50 (C-4a), 129.15, 130.61, 130.73, 132.81 (Ar). ^{19}F NMR ($CDCl_3$): δ −60.89 (t, $^5J_{FH}$ = 2.7 Hz, CF_3-8). HRMS (ESI): *m*/*z* calcd for $C_{17}H_{14}ClF_3N_3$ $(M+H)^+$: 352.0828; found 352.0717 (100%). Anal. Calcd. for $C_{17}H_{13}ClF_3N_3$: C, 58.05; H, 3.73. Found: C, 57.80; H, 3.87.

*4.1.12. 8-(Trifluoromethyl)-6,7-dihydro-5H-1,4,8a-triaza-s-indacene-3-carbonitrile (**4h**)*

Yield 89%; yellow solid; mp 176 °C. ^{1}H NMR ($CDCl_3$): δ 2.35 (2H, qui, J_{HH} = 7.5 Hz, H-6), 3.19 (2H, t, J_{HH} = 7.5 Hz, H-5), 3.30 (2H, tq, J_{HH} = 7.5, $^5J_{FH}$ = 2.8 Hz, H-7), 8.34 (s, 1H, H-2). ^{13}C NMR ($CDCl_3$): δ 23.22 (C-6), 28.57 (q, ^4JC_F = 2.7 Hz, C-7), 34.02 (C-5), 83.05 (C-3), 111.97 (CN), 119.78 (q, ^1JC_F = 275.8 Hz, 8-CF_3), 125.92 (C-7a), 129.58 (q, ^2JC_F = 37.0 Hz, C-8), 146.56 (C-3a), 150.51 (C-2), 174.28 (C-4a).

*4.1.13. 2-Methyl-9-(trifluoromethyl)-5,6,7,8-tetrahydropyrazolo[5,1-b]quinazoline (**6a**)*

Yield 87%; yellow solid; mp 87 °C. ^{1}H NMR ($CDCl_3$): δ 1.85, 3.04 (8H, m, $4CH_2$), 2.52 (3H, s, CH_3), 6.40 (1H, s, H-3). ^{13}C NMR ($CDCl_3$): δ 14.59 (CH_3), 21.41, 22.12 (C-6, C-7), 24.38 (q, ^5JC_F = 3.1 Hz, C-8), 33.93 (C-5), 95.13 (C-3), 117.07 (C-8a), 121.12 (q, ^1JC_F = 277.9 Hz,

9-CF_3), 129.89 (q, $^2J_{CF}$ = 37.7 Hz, C-9), 148.22 (C-3a), 155.04 (C-2), 159.03 (C-4a). ^{19}F NMR ($CDCl_3$): δ −57.16 (t, $^5J_{FH}$ = 3.1 Hz, CF_3-9). HRMS (ESI): *m*/*z* calcd for $C_{12}H_{13}F_3N_3$ $(M+H)^+$: 256.1062; found 256.0999 (100%). Anal. Calcd. for $C_{12}H_{12}F_3N_3$: C, 56.47; H, 4.74. Found: C, 56.21; H, 4.89.

4.1.14. 2-(4-Methylphenyl)-9-(trifluoromethyl)-5,6,7,8-tetrahydropyrazolo[5,1-b]quinazoline (6b)

Yield 91%; yellow solid; mp 176–178 °C. ^{1}H NMR ($CDCl_3$): δ 1.90, 3.05 (8H, m, $4CH_2$), 2.39 (3H, s, CH_3), 6.86 (1H, s, H-3), 7.23–7.91 (4H, m, Ar). ^{13}C NMR ($CDCl_3$): δ 21.25 (CH_3), 21.42, 22.10 (C-6, C-7), 24.53 (q, $^4J_{CF}$ = 3.3 Hz, C-8), 34.03 (C-5), 92.03 (C-3), 117.76 (C-8a), 121.13 (q, $^1J_{CF}$ = 278.6 Hz, 9-CF_3), 130.22 (q, $^2J_{CF}$ = 35.4 Hz, C-9), 148.63 (C-3a), 155.94 (C-2), 159.22 (C-4a), 126.39, 129.64, 130.47, 138.89 (Ar). Anal. Calcd. for $C_{18}H_{16}F_3N_3$: C, 65.25; H, 4.87. Found: C, 65.00; H, 4.99.

4.1.15. 2-(4-Chlorophenyl)-9-(trifluoromethyl)-5,6,7,8-tetrahydropyrazolo[5,1-b]quinazoline (6c)

Yield 89%; yellow solid; mp 170–172 °C. ^{1}H NMR ($CDCl_3$): δ 1.94, 3.09 (8H, m, $4CH_2$), 6.88 (1H, s, H-3), 7.58–7.90 (4H, m, Ar). ^{13}C NMR ($CDCl_3$): δ 21.38, 22.06 (C-6, C-7), 24.56 (q, $^4J_{CF}$ = 3.3 Hz, C-8), 34.07 (C-5), 92.33 (C-3), 118.30 (C-8a), 121.07 (q, $^1J_{CF}$ = 277.8 Hz, 9-CF_3), 130.38 (q, $^2J_{CF}$ = 37.9 Hz, C-9), 148.66 (C-3a), 154.60 (C-2), 159.60 (C-4a), 127.73, 128.74, 130.97, 134.74 (Ar). Anal. Calcd. for $C_{17}H_{13}ClF_3N_3$: C, 58.05; H, 3.73. Found: C, 57.80; H, 3.82.

4.1.16. 3-(4-Chlorophenyl)-9-(trifluoromethyl)-5,6,7,8-tetrahydropyrazolo[5,1-b]quinazoline (6d)

Yield 89%; yellow solid; mp 176 °C. ^{1}H NMR (DMSO-d_6:CCl_4 = 1:2, v/v): δ 1.91, 3.07 (8H, m, $4CH_2$), 7.34–8.04 (4H, m, Ar), 8.52 (1H, s, H-2). ^{13}C NMR (DMSO-d_6:CCl_4 = 1:2, v/v): δ 20.77, 21.45 (C-6, C-7), 23.87 (q, $^4J_{CF}$ = 3.3 Hz, C-8), 33.86 (C-5), 107.33 (C-3), 118.66 (C-8a), 120.68 (q, $^1J_{CF}$ = 277.2 Hz, 9-CF_3), 129.42 (q, $^2J_{CF}$ = 33.9 Hz, C-9), 141.83 (C-2), 142.88(C-3a), 159.89 (C-4a), 126.89, 128.05, 129.98, 130.55 (Ar). ^{19}F NMR ($CDCl_3$): δ −57.20 (t, $^5J_{FH}$ = 2.9 Hz, CF_3-9). Anal. Calcd. for $C_{17}H_{13}ClF_3N_3$: C, 58.05; H, 3.73. Found: C, 57.93; H, 3.90.

4.1.17. 2-Methyl-9-(trifluoromethyl)-5,6,7,8-tetrahydropyrazolo[5,1-b]quinazoline-3-carbonitrile (6e)

Yield 91%; yellow solid; mp 175 °C. ^{1}H NMR (DMSO-d_6:CCl_4 = 1:2, v/v): δ 1.90 (4H, m, $2CH_2$), 2.56 (3H, s, CH_3), 3.08 (4H, m, $2CH_2$). ^{13}C NMR (DMSO-d_6:CCl_4 = 1:2, v/v): δ 12.09 (CH_3), 20.38, 21.10 (C-6, C-7), 23.98 (q, $^4J_{CF}$ = 4.5 Hz, C-8), 33.68 (C-5), 80.73 (C-3), 112.13 (CN), 120.20 (q, $^1J_{CF}$ = 278.2 Hz, 9-CF_3), 120.92 (C-8a), 130.12 (q, $^2J_{CF}$ = 35.9 Hz, C-9), 156.72 (C-2), 148.68 (C-3a), 164.65 (C-4a). Anal. Calcd. for $C_{13}H_{11}F_3N_4$: C, 55.71; H, 3.96. Found: C, 55.60; H, 4.00.

4.1.18. 2-Methyl-3-phenyl-9-(trifluoromethyl)-5,6,7,8-tetrahydropyrazolo[5,1-b]quinazoline (6f)

Yield 93%; yellow solid; mp 136–138 °C. ^{1}H NMR ($CDCl_3$): δ 1.91, 3.08 (8H, m, $4CH_2$), 2.67 (3H, s, CH_3), 7.31–7.73 (5H, m, Ph). ^{13}C NMR ($CDCl_3$): δ 14.24 (CH_3), 21.44, 22.18 (C-6, C-7), 24.43 (q, $^4J_{CF}$ = 3.5, C-8), 34.24 (C-5), 108.42 (C-3), 117.21 (C-8a), 121.21 (q, $^1J_{CF}$ = 278.1 Hz, 9-CF_3), 126.30, 128.35, 128.85, 131.83 (Ph), 130.27 (q, $^2J_{CF}$ = 34.8 Hz, C-9), 144.98 (C-3a), 152.34 (C-2), 159.43 (C-4a). ^{19}F NMR ($CDCl_3$): δ −57.13 (t, $^5J_{FH}$ = 3.0 Hz, CF_3-9). Anal. Calcd. for $C_{18}H_{16}F_3N_3$: C, 65.25; H, 4.87. Found: C, 65.10; H, 4.95.

4.1.19. 2-Methyl-3-(4-chlorophenyl)-9-(trifluoromethyl)-5,6,7,8-tetrahydropyrazolo[5,1-b]quinazoline (6g)

Yield 92%; yellow solid; mp 181–182 °C. ^{1}H NMR ($CDCl_3$): δ 1.92, 3.07 (8H, m, $4CH_2$), 2.67 (3H, s, CH_3), 7.43–7.67 (4H, m, Ar). ^{13}C NMR ($CDCl_3$): δ 14.24 (CH_3), 21.40, 22.13 (C-6, C-7), 24.45 (q, $^4J_{CF}$ = 3.9, C-8), 34.25 (C-5), 107.24 (C-3), 117.94 (C-8a), 121.13 (q, $^1J_{CF}$ = 278.8 Hz, 9-CF_3), 128.54, 129.94, 130.36, 132.08 (Ar), 129.88 (q, $^2J_{CF}$ = 34.8 Hz, C-9), 144.93 (C-3a), 152.17 (C-2), 159.18 (C-4a). ^{19}F NMR ($CDCl_3$): δ −57.12 (t, $^5J_{FH}$ = 2.9 Hz, CF_3-9). HRMS (ESI): *m*/*z* calcd for $C_{18}H_{16}ClF_3N_3$ $(M+H)^+$: 366.0985; found 366.1006 (100%). Anal. Calcd. for $C_{18}H_{15}ClF_3N_3$: C, 59.10; H, 4.13. Found: C, 58.88; H, 4.29.

4.1.20. 9-(Trifluoromethyl)-5,6,7,8-tetrahydropyrazolo[5,1-b]quinazoline-3-carbonitrile (6h)

Yield 85%; yellow solid; mp 186–188 °C. ^{1}H NMR ($CDCl_3$): δ 1.95, 3.15 (8H, m, $4CH_2$), 8.36 (1H, s, H-3). ^{13}C NMR ($CDCl_3$): δ 20.84, 21.57 (C-6, C-7), 25.10 (q, $^4J_{CF}$ = 3.3 Hz, C-8), 34.32 (C-5), 82.31 (C-3), 112.75 (CN), 120.04 (q, $^1J_{CF}$ = 277.8 Hz, 9-CF_3), 122.29 (C-8a), 131.57 (q, $^2J_{CF}$ = 37.9 Hz, C-9), 146.72 (C-3a), 148.66 (C-2), 165.27 (C-4a). Anal. Calcd. for $C_{12}H_9F_3N_4$: C, 54.14; H, 3.41. Found: C, 54.01; H, 3.63.

4.2. General procedure for preparation of 5a,c and 7b–d

2-(2,2,2-Trifluoroacetyl)-1-cycloalkanone **2a**,**b** (5.5 mmol) in AcOH (5 ml) was added to a solution of 5(3)-aminopyrazole **1a**–**d** (5 mmol) in AcOH (5 ml), the reaction mixture was refluxed for 15 min, whereupon the solvent was removed under reduced pressure and the solid residue was washed with cold water (10 ml). The released solid was separated by filtration and dried in air at room temperature. The crude product was analyzed by ^{1}H NMR and these results are given in Sections 4.2.1–4.2.6.

4.2.1. 2-Methyl-5-trifluoromethyl-7,8-dihydro-6H-1,4,8b-triaza-as-indacene (5a)

Mixture of **4a** and **5a**. **5a**: ^{1}H NMR ($CDCl_3$): δ 2.57 (3H, s, CH_3), 2.39 (2H, qui, J_{HH} = 7.5 Hz, CH_2), 3.20 (2H, t, J_{HH} = 7.5 Hz, CH_2), 3.42 (2H, t, J_{HH} = 7.5 Hz, CH_2), 6.66 (1H, s, H-3). ^{13}C NMR ($CDCl_3$): δ 14.62 (CH_3), 22.24 (C-7), 29.20 (q, $^4J_{CF}$ = 1.0 Hz, C-6), 29.70 (C-8), 97.58 (C-3), 117.94 (C-5a), 121.05 (q, $^1J_{CF}$ = 275.3 Hz, 5-$\underline{C}F_3$), 142.69 (q, $^2J_{CF}$ = 35.8 Hz, C-5), 147.81 (C-3a), 151.67 (C-8a), 156.63 (C-2). ^{19}F NMR ($CDCl_3$): δ −64.37 (CF_3-5). HRMS (ESI) for mixture of compounds **4a** and **5a**: *m*/*z* calcd for $C_{11}H_{11}F_3N_3$ $(M+H)^+$: 242.090; found 242.0935 (100%).

4.2.2. 2-(4-Chlorophenyl)-5-(trifluoromethyl)-7,8-dihydro-6H-1,4,8b-triaza-as-indacene (5c)

Mixture of **4c** and **5c**. **5c**: ^{1}H NMR ($CDCl_3$): δ 2.43 (2H, qui, J_{HH} = 7.6 Hz, H-6), 3.28 (2H, t, J_{HH} = 7.6 Hz, CH_2), 3.50 (2H, t, J_{HH} = 7.6 Hz, CH_2), 7.13 (1H, s, H-3), 7.41–7.97 (4H, m, Ar). ^{13}C NMR ($CDCl_3$): δ 22.01 (C-7), 29.15 (q, $^4J_{CF}$ = 1.1 Hz, C-6), 29.64 (C-8), 94.69 (C-3), 118.97 (C-5a), 120.97 (q, $^1J_{CF}$ = 276.4 Hz, 5-CF_3), 142.92 (q, $^2J_{CF}$ = 35.9 Hz, C-5), 148.05 (C-3a), 152.14 (C-8a), 156.16 (C-2), 127.61, 128.72, 130.71, 134.85 (Ar). ^{19}F NMR ($CDCl_3$): δ −64.42 (CF_3-5). HRMS (ESI) for mixture of compounds **4c** and **5c**: *m*/*z* calcd for $C_{16}H_{12}ClF_3N_3$ $(M+H)^+$: 338.0672; found 338.0590 (100%).

4.2.3. 2-Methyl-5-(trifluoromethyl)-7,8-dihydro-6H-1,4,8b-triaza-as-indacene-3-carbonitrile (5e)

Mixture of **4e** and **5e**. **5e**: ^{1}H NMR ($CDCl_3$): δ 2.69 (3H, s, CH_3), 2.48 (2H, qui, J_{HH} = 7.5 Hz, H-6), 3.28 (2H, t, CH_2), 3.49 (2H, t, J_{HH} = 7.5 Hz, CH_2). ^{19}F NMR ($CDCl_3$): δ −64.47 (CF_3-5). HRMS (ESI) for mixture of compounds **4e** and **5e**: *m*/*z* calcd for $C_{12}H_{10}F_3N_4$ $(M+H)^+$: 267.0858; found 267.0868 (100%).

4.2.4. 2-(4-Methylphenyl)-5-(trifluoromethyl)-6,7,8,9-tetrahydropyrazolo[1,5-a]quinazoline (7b)

Mixture of **6b** and **7b**. **7b**: ^{1}H NMR ($CDCl_3$): δ 2.41 (3H, s, CH_3), 1.91, 2.04, 2.94, 3.30 (8H, m, $4CH_2$), 7.09 (1H, s, CH), 7.25–7.93 (4H,

m, Ar). HRMS (ESI) for mixture of compounds **6b** and **7b**: *m*/*z* calcd for $C_{18}H_{16}F_3N_3$ $(M+H)^+$: 332.1374; found 332.1401 (100%).

4.2.5. 2-(4-Chlorophenyl)-5-(trifluoromethyl)-6,7,8,9-tetrahydropyrazolo[1,5-a]quinazoline (7c)

Mixture of **6c** and **7c**. **7c**: ^{1}H NMR ($CDCl_3$): δ 1.93, 2.06, 2.97, 3.26 (4× 2H, m, $4CH_2$), 7.10 (1H, s, CH), 7.45–7.97 (4H, m, Ar). ^{19}F NMR ($CDCl_3$): δ −62.94 (CF_3-5). HRMS (ESI) for mixture of compounds **6c** and **7c**: *m*/*z* calcd for $C_{17}H_{14}ClF_3N_3$ $(M+H)^+$: 352.0828; found 352.0826 (100%).

4.2.6. 3-(4-Chlorophenyl)-5-(trifluoromethyl)-6,7,8,9-tetrahydropyrazolo[1,5-a]quinazoline (7d)

Mixture of **6d** and **7d**. **7d**: ^{1}H NMR ($CDCl_3$): δ 1.94, 2.06, 2.99, 3.28 (8H, m, $4CH_2$), 7.33–7.81 (5H, m, Ph), 8.52 (1H, s, CH). ^{19}F NMR ($CDCl_3$): δ −62.99 (CF_3-5). HRMS (ESI) for mixture of compounds **6d** and **7d**: *m*/*z* calcd for $C_{17}H_{14}ClF_3N_3$ $(M+H)^+$: 352.0828; found 352.0826 (100%).

4.3. General procedure for preparation of 5b,d

A solution of diol **8b** (or **8d**) (5 mmol) in dimethyl sulfoxide (5 ml) was kept for 30 d at room temperature, whereupon refluxed for 1 h. The solvent was removed under reduced pressure, and the resultant solid was recrystallized from boiling ethanol and dried in air at room temperature.

4.3.1. 2-(4-Methylphenyl)-5-(trifluoromethyl)-7,8-dihydro-6H1,4,8b-triaza-as-indacene (5b)

Yield 67%; pale yellow solid; mp 152 °C. ^{1}H NMR ($CDCl_3$): δ 2.42 (2H, qui, J_{HH} = 7.6 Hz, CH_2), 2.43 (3H, s, CH_3), 3.26 (2H, t, J_{HH} = 7.6 Hz, CH_2), 3.49 (2H, t, J_{HH} = 7.6 Hz, CH_2), 7.12 (1H, s, H-3), 7.28–7.93 (4H, m, Ar). ^{13}C NMR ($CDCl_3$): δ 21.25 (CH_3), 22.25 (C-7), 29.30 (q, $^4J_{CF}$ = 1.1 Hz, C-6), 29.82 (C-8), 94.62 (C-3), 118.62 (C-5a), 121.12 (q, $^1J_{CF}$ = 275.3 Hz, 5-CF_3), 142.82 (q, $^2J_{CF}$ = 35.9 Hz, C-5), 148.22 (C-3a), 152.11 (C-8a), 157.74 (C-2), 126.42, 129.41, 129.53, 139.21 (Ar). Anal. Calcd. for $C_{17}H_{14}F_3N_3$: C, 64.35; H, 4.45. Found: C, 64.15; H, 4.55. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{15}F_3N_3$ $(M+H)^+$: 318.1218; found 318.1182 (100%).

4.3.2. 3-(4-Chlorophenyl)-5-(trifluoromethyl)-7,8-dihydro-6H-1,4,8b-triaza-as-indacene (5d)

Yield 72%; yellow solid; mp 201 °C. ^{1}H NMR ($CDCl_3$): δ 2.44 (2H, qui, J_{HH} = 8.0 Hz, H-6), 3.27 (2H, t, J_{HH} = 8.0 Hz, H-7), 3.48 (2H, t, J_{HH} = 8.0 Hz, H-8), 7.44-8.13 (4H, m, Ar), 8.82 (1H, s, H-2). ^{13}C NMR ($CDCl_3$): δ 22.03 (C-7) 29.28 (q, $^4J_{CF}$ = 1.1 Hz, C-6), 29.76 (C-8), 111.05 (C-3), 119.33 (C-5a), 121.00 (q, $^1J_{CF}$ = 264.9 Hz, 5-CF_3), 142.18 (C-2), 143.20 (q, $^2J_{CF}$ = 12.3 Hz, C-5), 143.29 (C-3a), 152.65 (C-8a), 127.83, 128.79, 129.65, 132.03 (Ar). ^{19}F NMR ($CDCl_3$): δ −64.41 (CF_3-5). Anal. Calcd. for $C_{16}H_{11}ClF_3N_3$: C, 56.90; H, 3.28. Found: C, 56.80; H, 3.55.

4.4. General procedure for preparation of the diols (8b,d,e,9b,10b,d,e) [18]

To a solution of 1 mmol of aminopyrazole **1b**,**d**,**e**, in 3 ml of dichloromethane at cooling to −15 °C was added dropwise an equivalent amount (1 mmol) of 2-(2,2,2-trifluoroacetyl)-1-cycloalkanone **2a**,**b** in 3 ml of dichloromethane. The mixture was left standing at the same temperature for 3–24 h, the precipitate formatted was filtered off and washed with cold dichloromethane.

4.4.1. 2-(4-Methylphenyl)-8-(trifluoromethyl)-6,7,7a,8-tetrahydro-4H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine-4a,8(5H)-diol (8b)

Colorless solid, which is subject to dehydration on heating above 50 °C. A mixture of regioisomeric compounds **4b**, **5b** forms immediately when the compound is heated above 150 °C. The NMR spectra were recorded immediately after dissolution of **8b**. ^{1}H NMR (DMSO-d_6): δ 1.83 (4H, m), 2.14 (1H, m, H-7a), 2.43 (2H, m), 2.31 (3H, s, CH_3), 5.74 (1H, s, H-3), 6.39 (1H, s, OH), 7.08 (1H, s, OH), 7.17–7.64 (4H, m, Ar), 7.73 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 20.28 (C-6), 21.60 (C-7), 39.04 (C-5), 46.00 (C-7a), 82.22 (q, $^2J_{CF}$ = 30.3 Hz, C-8), 84.33 (C-3), 88.16 (C-4a), 123.48 (q, $^1J_{CF}$ = 285.2 Hz, 8-CF_3), 143.69 (C-3a), 150.81 (C-2), 20.81, 124.99, 129.03, 131.05, 136.60 (4-$CH_3C_6H_4$).

4.4.2. 2-(4-Methylphenyl)-5-(trifluoromethyl)-4,5,5a,6,7,8-hexahydro-8aH-cyclopenta[e]pyrazolo[1,5-a]pyrimidine-5,8a-diol (9b)

^{1}H and ^{13}C NMR spectra of compound **9b** were extracted from a spectrum of mixture of diols **8b** and **9b** (ratio 3:2) 30 min after diol **8b** dissolved. **9b**: ^{1}H NMR (DMSO-d_6): δ 1.57–2.20, 2.30–2.50 (6H, m, $3CH_2$), 2.60 (1H, t, H-5a), 2.31 (3H, s, CH_3), 5.76 (1H, s, H-3), 6.78 (1H, s, OH), 7.22 (1H, s, OH), 7.17–7.64 (4H, m, Ar), 7.73 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 21.73, 21.87 (C-6, C-7), 34.23 (C-8), 48.55 (C-5a), 81.52 (q, $^2J_{CF}$ = 30.9 Hz, C-5), 84.84 (C-3), 89.75 (C-8a), 124.38 (q, $^1J_{CF}$ = 298.6 Hz, 5-CF_3), 142.85 (C-3a), 149.84 (C-2), 20.81, 124.99, 129.03, 131.05, 136.60 (4-$CH_3C_6H_4$). Anal. Calcd. for $C_{17}H_{18}F_3N_3O_2$: C, 57.79; H, 5.13. Found: C, 57.61; H, 5.23.

4.4.3. 3-(4-Chlorophenyl)-8-(trifluoromethyl)-6,7,7a,8-tetrahydro-4H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine-4a,8(5H)-diol (8d)

Colorless solid, which is subject to dehydration on heating above 50 °C. A mixture of regioisomeric compounds **4d**, **5d** forms immediately when the compound is heated above 150 °C. **8d**: ^{1}H NMR (DMSO-d_6): δ: 1.57–2.08, 2.28–2.30 (6H, m, $3CH_2$), 2.66 (1H, t, H-7a), 6.11 (1H, s, OH), 6.86 (1H, s, OH), 7.49–7.50 (4H, m, Ar), 7.44 (1H, s, NH), 7.68 (1H, s, H-2). ^{13}C NMR (DMSO-d_6): δ 21.58 (C-6), 24.70 (C-7), 40.59 (C-5), 47.69 (C-7a), 82.12 (q, $^2J_{CF}$ = 29.4 Hz, C-8), 89.88 (C-4a), 102.50 (C-3), 124.43 (q, $^1J_{CF}$ = 289.2 Hz, 8-CF_3), 137.48 (C-3a), 138.09 (C-2), 127.17, 128.71, 130.19, 131.91 (Ar). Anal. Calcd. for $C_{16}H_{15}Cl\,F_3N_3O_2$: C, 51.42; H,4.05. Found: C, 51.21; H, 4.35.

4.4.4. 4a,8-Dihydroxy-2-methyl-8-(trifluoromethyl)-4a,5,6,7,7a,8-hexahydro-4H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine-3-carbonitrile (8e)

Colorless solid, which is subject to dehydration on heating above 50 °C. A mixture of regioisomeric compounds **4e**, **5e** forms immediately when the compound is heated above 150 °C. ^{1}H NMR (DMSO-d_6): δ 1.44-1.65, 1.76–2.04, 2.30–2.50 (6H, m, $3CH_2$), 2.60 (1H, t, H-7a), 2.15 (3H, s, CH_3), 6.50 (1H, s, OH), 7.07 (1H, s, OH), 8.53 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 12.66 (CH_3), 20.83, 24.89(C-6, C-7), 39.26 C-5), 47.91 (C-7a), 72.46 (C-3), 81.10 (q, $^2J_{CF}$ = 30.4 Hz, C-8), 88.78 (C-4a), 114.59 (CN), 122.96 (q, $^1J_{CF}$ = 289.1 Hz, 8-CF_3), 145.93 (C-3a), 150.24 (C-2). Anal. Calcd. for $C_{12}H_{13}F_3N_4O_2$: C, 47.68; H, 4.34. Found: C, 47.50; H, 4.58.

4.4.5. 2-(4-Methylphenyl)-9-(trifluoromethyl)-5,6,7,8,8a,9-hexahydropyrazolo[5,1-b]quinazoline-4a,9(4H)-diol (10b)

Colorless solid, which is subject to dehydration on heating above 50 °C. A mixture of regioisomeric compounds **6b**, **7b** forms immediately when the compound is heated above 150 °C.

^{1}H NMR (DMSO-d_6): δ 1.39, 1.64–1.83, 2.67–2.70, 2.81 (9H, m, $3CH_2$, CH), 2.30 (3H, s, CH_3), 5.75 (1H, s, H-3), 6.64 (1H, s, OH), 6.88 (1H, s, OH), 7.58 (1H, s, NH), 7.17–7.63 (4H, m, Ar). ^{13}C NMR (DMSO-d_6): δ 20.73, 21.32, 24.01, 34.55, 43.27 (C-5, C-6, C-7, C-8, C-8a), 81.91 (q, $^2J_{CF}$ = 29.3 Hz, C-9), 81.94 (COH), 84.49 (C-3), 123.64 (q, $^1J_{CF}$ = 286.9 Hz, 9-CF_3), 142.16 (C-3a), 149.52 (C-2), 20.73 (CH_3), 124.95, 129.00, 131.14, 136.54 (4-$CH_3C_6H_4$). Anal. Calcd. for $C_{18}H_{20}F_3N_3O_2$: C, 58.85; H, 5.49. Found: C, 58.70.10; H 5.73.

4.4.6. 3-(4-Chlorophenyl)-9-(trifluoromethyl)-5,6,7,8,8a,9-hexahydropyrazolo[5,1-b]quinazoline-4a,9(4H)-diol (10d)

Colorless solid, which is subject to dehydration on heating above 50 °C. A mixture of regioisomeric compounds **6d**, **7d** forms immediately when the compound is heated above 150 °C.

^{1}H NMR (DMSO-d_6): δ 1.40, 1.64–1.83, 2.52, 2.72 (9H, m, 3CH$_2$, CH), 6.61 (1H, s, OH), 6.94 (1H, s, OH), 7.65 (1H, s, NH), 7.38–7.48 (4H, m, Ar), 8.53 (1H, s, H-2). ^{13}C NMR (DMSO-d_6): δ 20.73, 21.21, 23.90, 34.57, 42.83, (C-5, C-6, C-7, C-8, C-8a), 82.36 (q, $^2J_{CF}$ = 39.6 Hz, C-9), 81.89 (C–OH), 102.60 (C-3), 123.57 (q, $^1J_{CF}$ = 287.2 Hz, 9-CF$_3$), 136.85 (C-3a), 137.61 (C-2), 127.01, 128.54, 129.20, 131.82 (Ar). Anal. Calcd. for $C_{17}H_{17}ClF_3N_3O_2$: C, 52.65; H, 4.42. Found: C, 52.41; H, 4.70.

4.4.7. 4a,9-Dihydroxy-2-methyl-9-(trifluoromethyl)-4,4a,5,6,7,8,8a,9-octahydropyrazolo[5,1-b]quinazoline-3-carbonitrile (10e)

Colorless solid, which is subject to dehydration on heating above 50 °C. A mixture of regioisomeric compounds **6e**, **7e** forms immediately when the compound is heated above 150 °C.

^{1}H NMR (DMSO-d_6): δ 1.34, 1.64–1.80, 2.23, 2.61 (9H, m, 3CH$_2$, CH), 2.15 (3H, s, CH$_3$), 6.56 (1H, s, OH), 7.05 (1H, s, OH), 8.74 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 12.62 (CH$_3$), 20.60, 21.12, 23.81, 34.22, 42.92, (C-5, C-6, C-7, C-8, C-8a), 73.50 (C-3), 81.70 (q, $^2J_{CF}$ = 30.2 Hz, CCF$_3$), 81.87 (COH), 114.44 (CN), 123.35 (q, $^1J_{CF}$ = 287.7 Hz, 9-CF$_3$), 145.35 (C-3a), 149.71 (C-2). Anal. Calcd. for $C_{13}H_{15}F_3N_4O_2$: C, 49.37; H, 4.78. Found: C, 49.15; H, 4.95.

4.4.8. 2-(4-Methylphenyl)-5-(trifluoromethyl)-5a,6,7,8-tetrahydro-8aH-cyclopenta[e]pyrazolo[1,5-a]pyrimidin-8a-ol (11b)

11b is the sole compound that was detected by NMR method after keeping diol **8b** in DMSO-d_6 for 30 d. ^{1}H NMR (DMSO-d_6): δ 1.49 (2H, m, H-6), 1.87 (1H, m, H-8), 2.27 (2H, m, H-7), 2.99 (1H, m, H′-8), 2.31 (3H, s, CH$_3$), 3.29 (1H, t, H-5a), 7.15 (1H, s, H-3), 7.21 (1H, s, br, 8a-OH), 7.22–7.78 (4H, m, Ar). ^{13}C NMR (registered without decoupling from protons) (DMSO-d_6): δ 20.85 (qt, $^1J_{CH}$ = 126.0, $^2J_{CH}$ = 4.5 Hz, CH$_3$), 21.95 (tm, $^1J_{HH}$ = 133.0, $^2J_{CH}$ = 4 Hz, C-7), 30.29 (tm, $^1J_{CH}$ = 128.5, $^2J_{C-H}$ = 4 Hz, C-8), 37.45 (tm, $^1J_{CH}$ = 136.5, $^2J_{CH}$ = 21.1 Hz, C-6), 46.40 (dm, $^1J_{CH}$ = 136.5 Hz, C-5a), 91.01 (C-8a), 102.44 (d, $^1J_{CH}$ = 179.7 Hz, C-3), 120.20 (q, ^1JC_F = 277.0 Hz, 5-CF$_3$), 141.99 (C-3a), 151.12 (C-2), 157.54 (q, ^2JC_F = 34.8 Hz, C-5), 125.13, 129.31, 129.83, 137.55 (Ar).

4.5. X-ray structure determination

Crystals of **6a** suitable for X-ray diffraction were obtained from **6a**. Crystals of **6a** ($C_{12}H_{12}F_3N_3$, M = 255.25) are monoclinic, space group $P21/c$, at 120 K: a = 9.6859(7), b = 7.7505(3), c = 15.2817(11) Å, V = 1135.17(14) Å^3, Z = 4 (Z' = 1), d_{calc} = 1.494 g cm^{-3}, μ(MoKα) = 1.26 cm^{-1}, F(0 0 0) = 528. Intensities of 12091 reflections were measured with a Bruker SMART 1000 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, $2\theta < 58°$] and 3010 independent reflections [R_{int} = 0.0357] were used in further refinement. The structure was solved by the direct method and refined by the full-matrix least-squares technique against F2 in the anisotropic–isotropic approximation. The hydrogen atom positions were calculated. All hydrogen atoms were refined in isotropic approximation in the rider model with the Uiso(H) parameters equal to 1.2 Ueq(Ci), for methyl groups equal to 1.5 Ueq(Cii), where U(Ci) and U(Cii) are respectively the equivalent thermal parameters of the carbon atoms to which the corresponding H atoms are bonded. For **6a** the refinement converged to $wR2$ = 0.1243 and GOF = 1.005 for all independent reflections ($R1$ = 0.0498 was calculated against F for 2008 observed reflections with $I > 2\sigma(I)$). All calculations were performed using SHELXTL PLUS 5.0. The crystallographic data have been deposited to the Cambridge Crystallographic Data Center, CCDC 701934. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2009.06.014.

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