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REACTIONS OF 2-MONO- AND 2,6-DISUBSTITUTED 4-PYRONES WITH PHENYLHYDRAZINE AS GENERAL METHOD FOR THE SYNTHESIS OF 3-(*N*-PHENYLPYRAZOLYL)INDOLES

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Phenylhydrazine reacted regioselectively with 6-substituted 4-pyrone-2-carboxylic acids (or esters) in protic and aprotic solvents, leading to phenylhydrazones of 3-(3-R-1-phenylpyrazol-5-yl)- or 3-(5-R-1-phenylpyrazol-3-yl)pyruvic acids (or esters), respectively. 6-Di(tri)fluoromethylcomanic acids (or esters) reacted analogously, forming the corresponding phenylhydrazones with R^F group in the side chain. The obtained phenylhydrazones underwent Fischer reaction under acidic conditions, forming the respective 3-(N-phenylpyrazolyl)indoles. In contrast to comanic acid and its ester, the reactions of 2-substituted 4-pyrones occurred non-selectively and gave mixtures of regioisomeric pyrazoles with phenylhydrazone group in the side chain or 3-(N-phenylpyrazolyl)indoles. A mechanism was proposed to explain the effect of solvent on the course of reaction.

Keywords: comanic acid, indoles, phenylhydrazine, pyrazoles, 4-pyrones, Fischer reaction, regio-selectivity.

3-(Pyrazolyl)indoles containing two pharmacophore fragments, indole and pyrazole rings, may possess diverse biological activity and thus attract the attention of researchers [1-7]. Methods for the synthesis of these heterocycles have been based on cross-coupling reactions [1-14] as well as on the interaction of polycarbonyl compounds with hydrazines [15, 16]. 4-Pyrones can be viewed as masked triketones, enabling their application in the synthesis of 3-(pyrazolyl)indoles.

Prior to our work in this area [17-21], the only such examples known were reactions of unsubstituted γ-pyrone with arylhydrazines [22], and 2,6-dimethyl-γ-pyrone with phenylhydrazine [23], leading to arylhydrazones of 2-(*N*-phenylpyrazol-5-yl)acetaldehyde, products of attack by the more nucleophilic primary amino group at the C-2 atom with subsequent recyclization to a pyrazole and addition of a second arylhydrazine molecule. The interaction of 2-mono- and 2,6-disubstituted unsymmetrical γ-pyrones with phenylhydrazine theoretically could produce a mixture of four regioisomeric phenylhydrazones of 2-oxoethyl-*N*-phenylpyrazoles, but our study showed that the reaction proceeded quite selectively in most cases, and its products could be used in Fischer synthesis of 3-(pyrazolyl)indoles [17-21].

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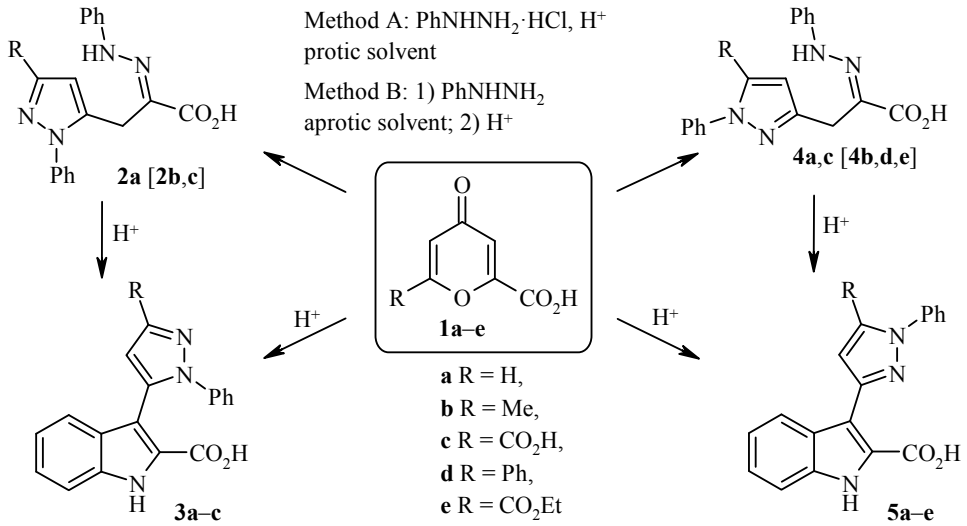
Taking into account the high biological activity of some 3-(pyrazolyl)indoles [1-7] and also in order to develop a general method for their preparation, in the current work we studied the interaction of phenylhydrazine with a wide range of substituted γ-pyrones under various conditions and generalized all available results for this reaction. We should note that our previous investigations in this direction were devoted mainly to trifluoromethylated derivatives of 4-pyrone-2-carboxylic (comanic) acid [18, 19, 21], which did not allow to make any general conclusions about the effect of substituents and solvent on the regiochemistry of products.

The first stage of this study concerned the interaction of phenylhydrazine with comanic (**1a**), 6-methylcomanic (**1b**), chelidonic (**1c**), and 6-phenylcomanic (**1d**) acids, as well as with monoethyl ester of chelidonic acid (**1e**). We established that these reactions, depending on the nature of solvent and pH of the medium, occurred with the formation of regioisomeric pyrazoles **2** or **4**, which could undergo Fischer reaction under acidic conditions, forming the indoles **3** and **5**, respectively. Performing the reaction with phenylhydrazine hydrochloride in protic solvents in the presence of acid (method A) gave mainly phenylhydrazones of 3-(*N*-phenylpyrazol-5-yl)pyruvic acid **2**, but reaction with phenylhydrazine itself in aprotic solvents (method B) produced phenylhydrazones of 3-(*N*-phenylpyrazol-3-yl)pyruvic acid **4** (Scheme 1). In a range of cases (compounds **2b**,**c**, **4b**,**d**,**e**) the reaction did not stop at the stage of intermediate hydrazone **2** or **4**, but gave directly the indoles **3** or **5**.

Scheme 1



We used the example of comanic acid (**1a**) to study the effect of reaction conditions on the regioselectivity of the process in more detail. It was found that performing the reaction under the conditions of method A ($PhNHNH_2 \cdot HCl$, water, 60°C, 0.1 ml of conc. HCl (experiment 1, Table 1)) gave 81% yield of isomeric mixture *E*-**2a**+*Z*-**2a**+*E*-**4a** in 86:5:9 ratio, from which the *E*-hydrazone **2a** was isolated in pure form with 47% yield by recrystallization from a toluene–ethanol mixture. As shown by further study, the majority of the obtained hydrazones had *E*-configuration, which was supported by data of X-ray structural analysis (see below). When using phenylhydrazine as base (H_2O, ~20°C (experiment 2, Table 1)), the *E*-hydrazone **2a** was formed in lower yield (18%) [17]. When refluxing in 70% AcOH with added HCl (method C), this compound underwent Fischer reaction, giving the expected indole **3a**. Refluxing of pyrone **1a** with $PhNHNH_2 \cdot HCl$ in 70% aqueous AcOH formed the indole **3a** directly (method A, yield 50% (experiment 3, Table 1)) [17], while refluxing with $PhNHNH_2$ in dioxane followed by addition of HCl gave the indole **5a** (method B, yield 35% (experiment 5, Table 1)). Performing the reaction in dioxane without addition of HCl gave a 63% yield of hydrazone mixture *E*-**4a**+*Z*-**4a**+*Z*-**2a**+*E*-**2a** (51:18:18:13) (experiment 4, Table 1), which explained the rather low yield of indole **5a** under those conditions.

TABLE 1. Synthesis of Pyrazoles **2**, **4**, **7** and Indoles **3**, **5**, **8** from Pyrones **1** and **6**

Experiment	Pyrone	Conditions* (method)	Pyrazole	Yield, %	Conditions (method)	Indole	Yield, %
1	**1a**	$PhNHNH_2 \cdot HCl$, H_2O, 0.1 ml HCl, 60°C, 8 h (A)	*E*-**2a**+*Z*-**2a**+ + *E*-**4a** (86:5:9)	81	—	—	—
			E-**2a**	47			
2	**1a**	$PhNHNH_2$, H_2O, ~20°C, 18 h (B)	*E*-**2a**	18 [17]	70% AcOH, 0.15 ml HCl, Δ, 1 h (C)	**3a**	67 [17]
3	**1a**	$PhNHNH_2 \cdot HCl$, 70% AcOH, Δ, 4 h (A)	—	—	—	**3a**	50 [17]
4	**1a**	$PhNHNH_2$, dioxane, Δ, 8 h (B)	*E*-**4a**+*Z*-**4a**+ + *Z*-**2a**+*E*-**2a** (51:18:18:13)	63	—	—	—
5	**1a**	$PhNHNH_2$, dioxane, Δ, 6 h, then 0.75 ml HCl, Δ, 2 h (B)	—	—	—	**5a**	35
6	**1b**	$PhNHNH_2 \cdot HCl$, EtOH, Δ, 24 h (A)	—	—	—	**3b**	21
						5b	5
7	**1b**	$PhNHNH_2$, dioxane, Δ, 4 h (B)	*E*-**4b**	32	AcOH–HCl (12:1), Δ, 4 h (C)	**5b**	36
8	**1c**	$PhNHNH_2 \cdot HCl$, 5 ml H_2O–HCl 4:1, Δ, 1 h (A)	—	—	—	**3c**+**5c** (53:47)	48
						5c	18
9	**1d**	$PhNHNH_2$, dioxane, Δ, 2.5 h (B)	*E*-**4d**	20 [20]	AcOH, 0.25 ml HCl, Δ, 4 h (C)	**5d**	68 [20]
10	**1e**	$PhNHNH_2$, dioxane, Δ, 4 h (B)	*E*-**4e**	13	5 ml AcOH, 0.15 ml HCl, Δ, 4 h (C)	**5e**	42
11	**6a**	$PhNHNH_2 \cdot HCl$, EtOH, ~20°C, 24 h, 60°C, 3 h (A)	**7a**	31 (*E*) 8 (*Z*)	4 ml AcOH, 0.15 ml HCl, Δ, 4 h (C)	**8a**	58
12	**6b**	$PhNHNH_2 \cdot HCl$, EtOH, 60°C, 24 h (A)	*E*-**7b**	9	$PhNHNH_2$ HCl, EtOH, Δ, 24 h (A)	**8b**	18 (from **6b**)
13	**6c**	$PhNHNH_2 \cdot HCl$, EtOH, 60°C, 8 h (A)	*E*-**7c**	40	4 ml AcOH, 0.3 ml HCl, Δ, 4 h (C)	**8c**	43

*Standard load of reactants: 1.5 mmol of 4-pyrone **1a-e**, **6a-c** and 3.3 mmol of $PhNHNH_2$ (either salt or base).

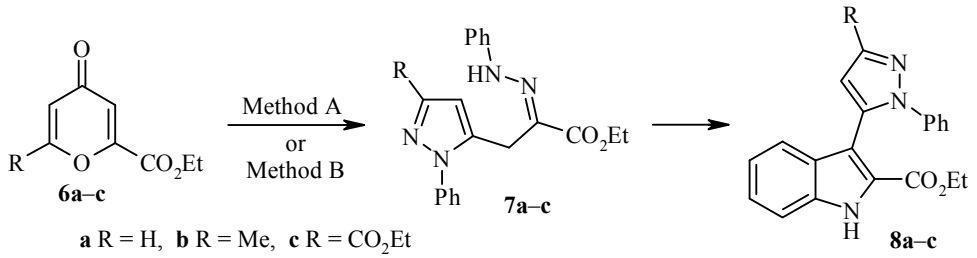
In the case of 6-methylcomanic acid (**1b**) under the conditions of method A ($PhNHNH_2 \cdot HCl$, ethanol, refluxing for 24 h (experiment 6, Table 1)), the major product was indole **3b** (yield 21%), while indole **5b** was also isolated from the reaction mixture as by-product by recrystallization from ethanol (yield 5%). The intermediate hydrazone **2b** was detected in the reaction mixture as *Z*- and *E*-isomers in 64:36 ratio after refluxing for 1 h during this experiment. Performing the reaction in refluxing dioxane gave the hydrazone *E*-**4b** (method B, yield 32% (experiment 7, Table 1)), from which the indole **5b** was obtained in 36% yield.

The reaction of chelidonic acid (**1c**) with phenylhydrazine hydrochloride in water with added HCl (method A) was non-selective and gave 48% yield of a 53:47 mixture of two indoles **3c** and **5c**, which were regioisomers at the pyrazole ring. The indole **5c** was isolated from this mixture in 18% yield, using its different solubility in ethanol (experiment 8, Table 1). The acid **3c** was previously obtained by hydrolysis of 3-(3-ethoxy-

carbonyl-1-phenylpyrazol-5-yl)trifluoroacetone phenylhydrazone in the presence of KOH [18]. The diacid **1c** did not react with phenylhydrazine in aprotic solvents. Reactions of 6-phenylcomanic acid (**1d**) and monoethyl chelidonate (**1e**) with phenylhydrazine hydrochloride also occurred non-selectively and resulted in complex mixtures, from which individual products could not be isolated. At the same time, the interaction of these acids with phenylhydrazine in dioxane (method B), gave phenylhydrazones of 3-(*N*-phenylpyrazol-3-yl)pyruvic acids *E*-**4d**,**e**, albeit in low yields (13-20%). These compounds were converted to 3-(pyrazolyl)indoles **5d**,**e** by refluxing in acetic acid with added HCl (experiments 9 [20], 10, Table 1).

The reactivity of ethyl esters **6a-c** was found to be lower than that of comanic acids **1a-c**, as they practically did not react with phenylhydrazine under the conditions of method B (in dioxane or toluene) or gave complex mixtures of products in ethanol. However, the reactions of esters **6a**,**c** with phenylhydrazine hydrochloride in ethanol (method A) occurred sufficiently regioselectively and produced the expected major products, phenylhydrazones **7a,c** of 3-(*N*-phenylpyrazol-5-yl)pyruvic acid, which in acetic acid with added HCl were converted to 3-(*N*-phenylpyrazol-5-yl)indoles **8a**,**c** in 43-58% yields (Scheme 2; experiments 11, 13, Table 1). The less reactive ethyl ester of 6-methylcomanic acid (**6b**) gave directly the indole **8b** (18% yield) upon refluxing with $PhNHNH_2 \cdot HCl$ in ethanol, and the pyrazole **7b** (isolated in only 9% yield due to incomplete conversion of the starting ester) at 60°C (experiment 12, Table 1).

Scheme 2



It should be noted that we observed a clear relationship during this stage of investigation, where the side chain of phenylhydrazone always contained a carboxyl group, regardless of the reaction conditions. In addition, the use of phenylhydrazine in the form of hydrochloride in protic solvent (method A) gave predominantly the 3-R-1-phenylpyrazole, while the reaction with phenylhydrazine in the base form in aprotic solvent (method B) led to 5-R-1-phenylpyrazole. In order to determine the general applicability of these observations, we extended our study by including 6-[tri(di)fluoromethyl]comanic acids **9a**,**c** and their esters **9b**,**d**, as well as monosubstituted γ-pyrones **14a-c**. At first, we set out to establish the location of tri(di)fluoromethyl group (further in text – R^F group) of phenylhydrazone – either at the side chain or at the pyrazole ring, and the possible solvent effects on the regiochemistry of product, which were observed in the case of comanic acid derivatives. Besides that, the possibility of preparing 3-(*N*-phenylpyrazolyl)indoles containing R^F group also attracted our interest, which would allow to recommend the reaction of γ-pyrones with phenylhydrazine as a general method for the preparation of these potentially biologically active compounds.

We found that, in contrast to comanic acids **1a-e** and their esters **6a-c**, the γ-pyrones **9a-d** containing an R^F group reacted with phenylhydrazine and produced hydrazones with R^F group instead of CO_2R in the side chain (Scheme 3). As expected, under the conditions of method A the major products were 1-Ph-3-CO_2R-pyrazoles **10a-d**, while 1-Ph-5-CO_2R-pyrazoles **12a-d** were produced under the conditions of method B (Table 2). We should note that the reactions were smoother and more selective when $R^F = CF_3$. The second major difference was that the products formed could not be indolized in acetic acid in the presence of HCl. Nevertheless, targeted search for more suitable conditions of Fischer reaction showed that treatment of CF_3-hydrazones **10a**,**b** and **12a**,**b** with a mixture of $MeSO_3H$ and P_2O_5 (method D) gave the desired 3-(*N*-phenylpyrazolyl)-2-trifluoromethylindoles **11a**,**b** and **13a**,**b** in 40-73% yields (experiments 1-4, Table 2) [19], while CHF_2-phenylhydrazones **10c**,**d** and **12c**,**d** only produced intractable resins under these conditions as well. It should be noted that introducing an R^F group into the pyrone

ring increased the reactivity of not only comanic acids, but also their ethyl esters, which, unlike compounds **6a-c**, reacted with phenylhydrazine both in protic and aprotic media, producing 1-Ph-3-CO_2Et-pyrazoles **10b**,**d** and 1-Ph-5-CO_2Et-pyrazoles **12b**,**d**, respectively, as the major products.

Scheme 3

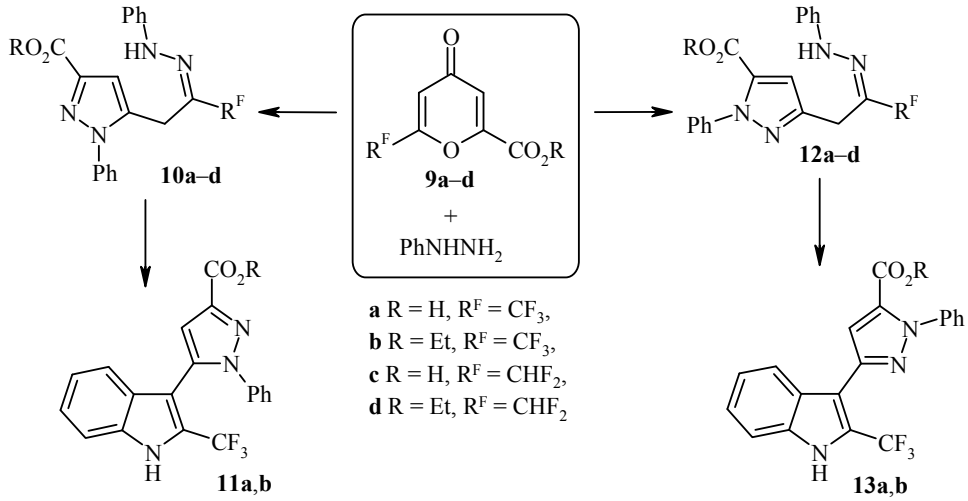


TABLE 2. Synthesis of Pyrazoles ***E*-10a-d**, ***E*-12a-d** and Indoles **11a**,**b**, **13a**,**b** from Pyrones **9a-d**

Experiment	Pyrone	Conditions* (method)	Pyrazole	Yield, %	Conditions (method)	Indole	Yield, %
1	**9a**	$PhNHNH_2$·HCl, 10% HCl, 10 min (A)	**10a**	64 [19]	$MeSO_3H$, P_2O_5, 60°C, 6 h (D)	**11a**	45 [19]
2	**9a**	$PhNHNH_2$, dioxane, Δ, 1.5 h (B)	**12a**	30 [19]	$MeSO_3H$, P_2O_5, 60°C, 6 h (D)	**13a**	73 [19]
3	**9b**	$PhNHNH_2$, EtOH, ~20°C, 2 days (B)	**10b**	58 [19]	$MeSO_3H$, P_2O_5, 60°C, 6 h (D)	**11b**	40 [19]
4	**9b**	$PhNHNH_2$, toluene, Δ, 12 h (B)	**12b**	34 [19]	$MeSO_3H$, P_2O_5, 60°C, 6 h (D)	**13b**	65 [19]
5	**9c**	$PhNHNH_2$, dioxane, 0.1 ml HCl, 60°C, 3 h (B)	**12c**	31	—	—	—
6	**9c**	$PhNHNH_2$·HCl, H_2O, 50°C, 16 h (A)	**10c**+**12c** (1:1)*[2]	68	—	—	—
7	**9d**	$PhNHNH_2$, EtOH, ~20°C, 2 days (B)	**10d**	22	—	—	—
8	**9d**	$PhNHNH_2$, toluene, ~20°C, 4 days (B)	**12d**	12	—	—	—

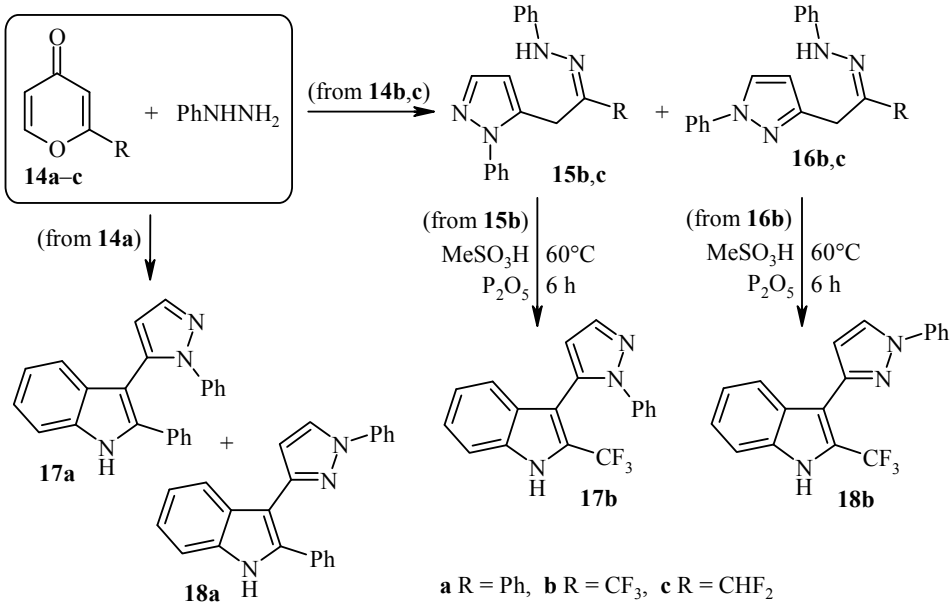
*Standard load of reagents: 1.5 mmol of 4-pyrone **9a-d** and 3.3 mmol of $PhNHNH_2$ (as salt or base).

*[2]Besides compounds **10c** and **12c**, the mixture contained ~20% of the regioisomer with CHF_2 group in the pyrazole ring.

Monosubstituted 4-pyrones **14a-c**, obtained by decarboxylation of the respective comanic acids [24, 25], reacted with phenylhydrazine showing little regioselectivity. Thus, reaction of 2-phenyl-4-pyrone (**14a**) with $PhNHNH_2$·HCl in refluxing ethanol for 24 h (method A) allowed to isolate 25% yield of the indole **17a**,

which contained 16% of the regioisomeric indole **18a** according to ^{1}H NMR spectrum (Scheme 4, Table 3, experiment 1); this reaction could not be stopped at the stage of phenylhydrazone intermediate. In the case of 2-trifluoromethyl- and 2-difluoromethyl-4-pyrones **14b**,**c** the optimum reaction conditions were heating for 1 h in phenylhydrazine at 120°C (method B, experiments 2, 3, Table 3). In both cases this led to a mixture of two regioisomeric pyrazoles *E*-**15b**+*E*-**16b** and *E*-**15c**+*E*-**16c**, which were separated by recrystallization from ethanol. The Fischer indolization could be accomplished only for CF_3-substituted hydrazones **15b** and **16b** in the presence of $MeSO_3H$ and P_2O_5 (method D), and resulted in the synthesis of 2-CF_3-indoles **17b**, **18b** (experiment 2, Table 3).

Scheme 4



The structures of all obtained compounds were confirmed by elemental analysis, IR spectra, as well as ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy. Besides that, the regio- and stereochemistry of phenylhydrazones **4b** (Fig. 1) and **12b** [19] was reliably established by X-ray structural analysis. The ^{1}H NMR spectra of pyrazoles **2**, **4**, **7**,

TABLE 3. Synthesis of Pyrazoles **15b**,**c**, **16b**,**c** and Indoles **17**, **18a**,**b** from Pyrones **14a-c**

Experiment	Pyrone	Conditions* (method)	Pyrazole	Yield, %	Conditions	Indole	Yield, %
1	**14a**	$PhNHNH_2$·HCl, EtOH, Δ, 24 h (A)	—	—	—	**17a**+**18a** (84:16)	25
2	**14b**	$PhNHNH_2$, 120°C, 1 h (B)	**15b**+**16b**	16 (**15b**) [19] 21 (**16b**) [19]	$MeSO_3H$, P_2O_5, 60°C, 6 h (D)	**17b** **18b**	65 [19] 60 [19]
3	**14c**	$PhNHNH_2$, 120°C, 1 h (B)	**15c**+**16c**	18 (**15c**) 13 (**16c**)	—	—	—

*Standard load of reagents: 1.5 mmol of 4-pyrone **14a-c** and 3.3 mmol of $PhNHNH_2$ (as salt or base).

10, **12**, **15**, **16** (in DMSO-d_6) contained a downfield signal of NH proton in the region of 9.91-10.43 ppm, which indicated *E*-configuration of the phenylhydrazone fragment, confirmed by X-ray structural analysis. The *Z*-phenylhydrazones were observed in crude products **2a**,**b** and **4a**, while only the hydrazone *Z*-**7a** was isolated in pure form with 8% yield. This hydrazone featured an NH proton involved in the formation of intramolecular

hydrogen bond with ester group and gave a more downfield ^{1}H NMR signal at 11.88 ppm (Fig. 2), which was in a good agreement with the literature data for *Z*-phenylhydrazone of 3-(pyrazolyl)pyruvic acid [18].

The ^{1}H NMR spectral analysis of the synthesized compounds allowed to identify a range of trends useful for establishing the regiochemistry of 3-(1-phenylpyrazolyl)indoles (Table 4).

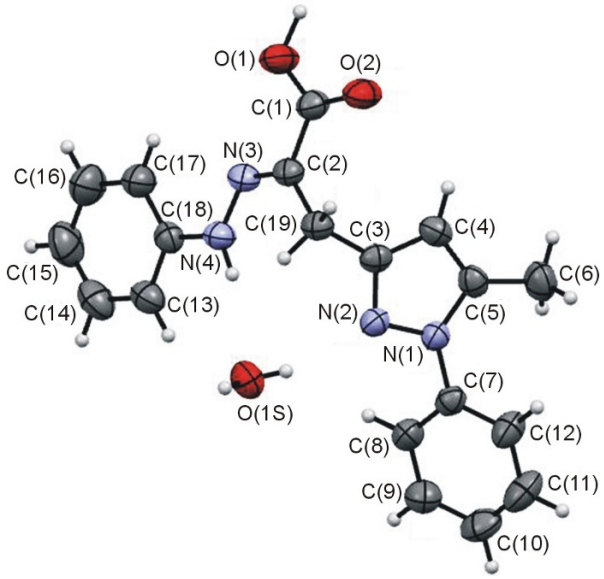


Fig. 1. The molecular structure of phenylhydrazone *E*-**4b** with atoms represented by thermal vibration ellipsoids of 50% probability.

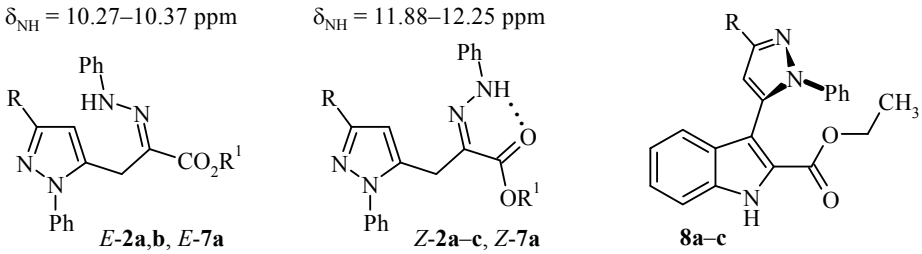


Fig. 2. Geometric isomers of phenylhydrazones **2a-c** and **7a**, and the non-planar structure of 3-(*N*-phenyl-pyrazol-5-yl)indoles **8a-c**.

1) The most characteristic ^{1}H NMR signal for regioisomeric *N*-phenylpyrazoles with *E*-phenylhydrazone fragment was that of the H-4 proton in the pyrazole ring (H-4 Pz). This signal was shifted downfield by 0.24-0.38 ppm when going from compounds **2a**,**b**, **10a-d**, and **15b**,**c** to compounds **4a**,**b**, **12a-d**, and **16b**,**c**. At the same time, the chemical shift of methylene group practically did not change and depended only on the nature of substituent in the side chain, for example, δ_{CH_2} was 4.02-4.05 ppm for CF_3-hydrazones, and 3.88-3.93 ppm for CHF_2-hydrazones.

2) In the *N*-phenylpyrazoles **2a**,**b**, **7a** with *Z*-phenylhydrazone fragment, compared to the corresponding *E*-isomers, the H-4 Pz proton signals were shifted downfield by 0.25-0.29 ppm, while the signals of methylene protons – upfield by 0.13-0.18 ppm.

3) When comparing indoles to phenylhydrazones, the signal of H-4 Pz was always shifted downfield in the case of indoles due to the deshielding effect of adjacent indole fragment. Thus, Δδ was 0.62-0.69 ppm for 3-(*N*-phenylpyrazol-5-yl)indole-2-carbonic acids **3** and their esters **8**, obtained from compounds *E*-**2** and *E*-**7**,

respectively, while Δδ was 0.93-1.04 ppm for the regioisomeric products **5**, obtained from phenylhydrazones *E*-**4**, which was explained by the more planar conformation of heterocyclic rings in the latter compounds. In the case of 3-(*N*-phenylpyrazol-5-yl)-2-trifluoromethylindoles **11a**,**b**, **17b**, this value was close to Δδ of indoles **3**, **8** and was equal to 0.50-0.62 ppm. At the same time, Δδ = 0.36-0.41 ppm for regioisomeric indoles **13a**,**b**, **18b**, despite their planar structure, apparently due to the effect of substituent at the indole ring position 2.

4) The chemical shift of H-4 Pz strongly depended on the substituent at the indole ring position 2 in the regioisomeric pairs of 3-(*N*-phenylpyrazol-5-yl)- and 3-(*N*-phenylpyrazol-3-yl)indoles. This difference was 0.68-0.73 ppm in the case of indole-2-carboxylic acids **3a-c** and **5a-c**, while for 2-CF_3-indoles **11a**,**b** and **13a**,**b**, **17b** and **18b** Δδ was 0.12-0.18 ppm, and for 2-phenylindoles **17a** and **18a** Δδ was -0.20 ppm.

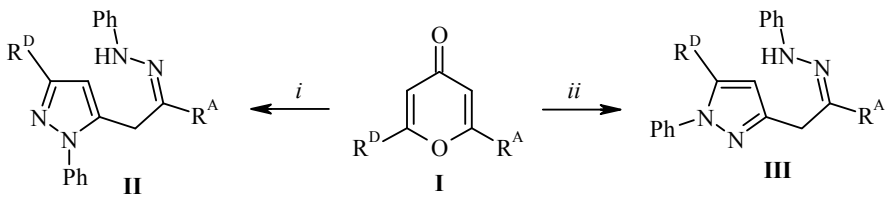
5) Another important signal in 3-(*N*-phenylpyrazol-3-yl)indoles **5**, **13** and **18** was the downfield doublet of indole proton H-4 Ind at 8.10-8.31 ppm (J = 7.9-8.3 Hz), which was linked to the deshielding effect of the planar pyrazole ring. This signal allowed to easily distinguish regioisomeric indoles, because the pyrazole fragment deviated from the molecular plane due to steric hindrance in 3-(*N*-phenylpyrazol-5-yl)indoles **3**, **8**, **11**, **17** and thus shielded the H-4 Ind proton, shifting its signal upfield by ~0.9 ppm to the region of 7.20-7.40 ppm. In this case, the most downfield signal was that of indole H-7 proton, which was observed as doublet at 7.44-7.51 ppm (J = 8.1-8.3 Hz).

6) The non-planar conformation and hindered rotation of heterocyclic rings in 3-(*N*-phenylpyrazol-5-yl)indoles resulted in non-equivalent methylene protons of ethoxycarbonyl group in ethyl esters **8a-c**, observed as unresolved ABX_3 system at 3.85-4.20 ppm (Fig. 2). The chemical shifts of these protons pointed to the presence of ester group in indole, instead of pyrazole ring, because the methylene protons gave quartets with J = 7.1 Hz at 4.36 and 4.23-4.24 ppm in the cases of 5-(indol-3-yl)-*N*-phenylpyrazole-3-carboxylic acid and 3-(indol-3-yl)-*N*-phenylpyrazole-5-carboxylic acids **11b**, **5e**, **13b**, respectively.

7) The spin-spin coupling constant between the pyrazole ring protons was larger ($J_{H\text{-}4,H\text{-}5}$ = 2.1-2.6 Hz) in 3-monosubstituted *N*-phenylpyrazoles **4a**, **5a**, **16b**,**c**, and **18a**,**b**, compared to 5-monosubstituted *N*-phenylpyrazoles **2a**, **3a**, **7a**, **8a**, **15b**,**c**, and **17a**,**b** ($J_{H\text{-}3,H\text{-}4}$ = 1.1-1.8 Hz), making it a convenient indicator for establishing the regiochemistry of these compounds.

The obtained results allowed to reach some general conclusions. First of all, reactions of 2-mono- and 2,6-disubstituted 4-pyrones with phenylhydrazine produced phenylhydrazones of (2-oxoethyl)-*N*-phenylpyrazoles, containing a relatively electron-donating substituent (R^D) in the pyrazole ring and a relatively electron-withdrawing substituent (R^A) in the hydrazone fragment of the starting γ-pyrone **I**. Thus, 6-substituted comanic acids and their esters, where CO_2R is the most electron-withdrawing group, formed ethoxycarbonylhydrazones, while fluorine-containing derivatives with stronger electron-withdrawing R^F group than CO_2R [26] gave R^F-hydrazones. Secondly, reaction in protic solvents in the presence of acid gave mainly 1-phenyl-3-R^D-pyrazoles **II**, while 1-phenyl-5-R^D-pyrazoles **III** were formed in aprotic solvents. Based on the obtained experimental data and taking into account that the primary amino group of phenylhydrazine is the more nucleophilic center, the general scheme of the process could be presented in the following way (Scheme 5).

Scheme 5

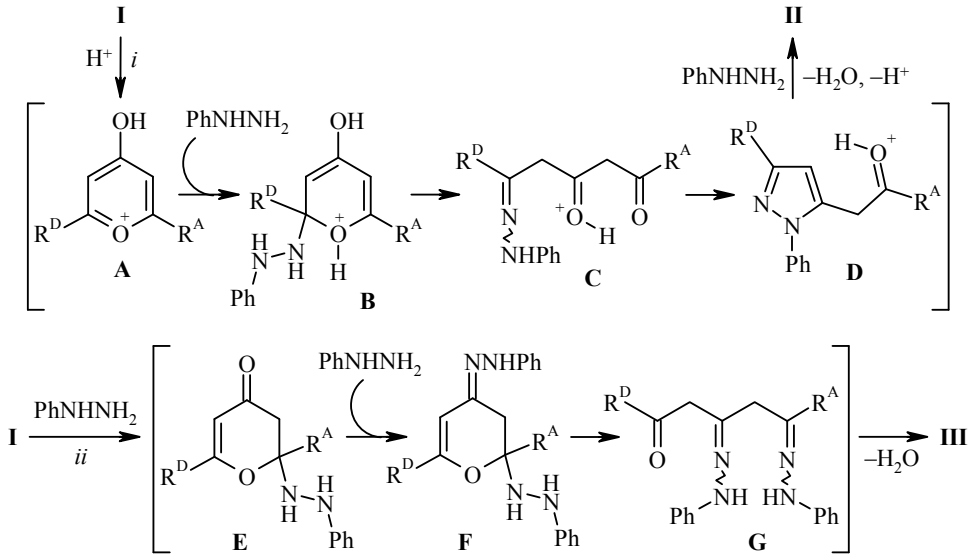


R^D – more electron-donating substituent, R^A – more electron-accepting substituent; *i* – protic solvent, *ii* – aprotic solvent

TABLE 4. The Characteristic ^{1}H NMR Signals of Regioisomeric Pyrazoles and Indoles

Pyrazole	H-4 Pz	CH_2	Indole	H-4 Pz	H-4 Ind
E-**2a**	5.94 (d, *J* = 1.6)	4.02	**3a**	6.56 (d, *J* = 1.6)	7.32 (d, *J* = 8.2)
Z-**2a**	6.19 (d, *J* = 1.1)	3.84			
E-**2b**	5.74	3.96	**3b**	6.36	7.33 (d, *J* = 8.1)
Z-**2b**	6.01	3.81			
Z-**2c**	6.66	3.88	**3c**	6.97	7.36 (d, *J* = 8.4)
E-**4a**	6.27 (d, *J* = 2.3)	4.03	**5a**	7.24 (d, *J* = 2.5)	8.30 (d, *J* = 8.2)
Z-**4a**	6.30 (d, *J* = 2.3)	3.81			
E-**4b**	6.05	3.97	**5b**	7.09	8.20 (d, *J* = 8.3)
Z-**4b**	—	—			
4c	—	—	**5c**	7.66	8.18 (d, *J* = 8.2)
E-**4d**	6.42	4.07	**5d**	overlapped	8.31 (d, *J* = 8.3)
E-**4e**	6.78	4.05	**5e**	7.71	8.19 (d, *J* = 8.2)
E-**7a**	5.96 (d, *J* = 1.6)	4.04	**8a**	6.59 (d, *J* = 1.1)	7.39 (d, *J* = 8.1)
Z-**7a**	6.25	3.91			
E-**7b**	5.74	3.98	**8b**	6.38	7.40 (d, *J* = 8.2)
E-**7c**	6.36	4.05	**8c**	7.05	7.40 (d, *J* = 8.1)
E-**10a**	6.46	4.05	**11a**	7.08	7.26–7.36
E-**10b**	6.51	4.05	**11b**	7.11	7.27–7.35
E-**10c**	6.44	3.91	—	—	—
E-**10d**	6.47	3.93	—	—	—
E-**12a**	6.84	4.02	**13a**	7.20	8.10 (d, *J* = 8.1)
E-**12b**	6.88	4.03	**13b**	7.24	8.09 (d, *J* = 8.1)
E-**12c**	6.78	3.91	—	—	—
E-**12d**	6.82	3.92	—	—	—
15a	—	—	**17a**	6.44 (d, *J* = 1.8)	7.20-7.30 (m)
E-**15b**	6.11 (d, *J* = 1.8)	4.03	**17b**	6.61 (unresolved d)	7.20-7.36 (m)
E-**15c**	6.06 (d, *J* = 1.7)	3.91	**17c**	—	—
16a	—	—	**18a**	6.24 (d, *J* = 2.6)	8.11 (d, *J* = 7.9)
E-**16b**	6.38 (d, *J* = 2.1)	4.02	**18b**	6.79 (d, *J* = 2.5)	8.19 (d, *J* = 8.1)
E-**16c**	6.30 (d, *J* = 2.4)	3.88	**18c**	—	—

Scheme 6



Quantum-chemical calculations have been used to demonstrate [27] that the course of 4-pyrone and 2-methyl-4-pyrone reaction with ammonia depends on the polarity of medium, where the reaction in polar solvent proceeds through unstable charged intermediates **A**-**D**, while in non-polar solvent – through the stable cyclic enones **E**. The possible mechanism of reaction between 4-pyrones and phenylhydrazine, which accounts for the calculated data and explains our obtained results, is presented in Scheme 6.

The protonation of carbonyl oxygen atom in polar solvent in the presence of acid leads to pyrilium intermediate **A**, which is attacked by the primary amino group of phenylhydrazine at the C-6 atom, where the electron-donating substituent R^D is located, and gives the addition product **B**, stabilized by conjugation of its diene fragment with the electron-withdrawing group R^A. Subsequent opening of the pyrone ring to the intermediate **C** is accompanied by the formation of pyrazole **D**, which reacts with the second phenylhydrazine molecule and gives the final 3-R^D-1-phenylpyrazole **II**. In aprotic medium, the phenylhydrazine NH_2 group attacked the more electrophilic C-2 atom bearing the electron-withdrawing group R^A, leading to the cyclic enone **E**, which reacted at keto group with a second phenylhydrazine molecule, giving the intermediate **F**. The latter opened to dihydrazone **G**, which then cyclized to the regioisomeric 5-R^D-1-phenylpyrazole **III** (Scheme 6). We explained the higher reactivity of comanic acids **1**, compared to their esters **6**, with the specific properties of CO_2H group, which was apparently coordinated through intermolecular hydrogen bond with the phenylhydrazine molecule, and directed its attack towards the C-2 atom bearing the carboxyl group.

Thus, we have demonstrated a regioselective reaction of comanic acid derivatives with phenylhydrazine, giving pyrazoles that, regardless of the conditions, were always substituted in the phenylhydrazone side chain with the most electron-withdrawing group of the starting 4-pyrone. The regiochemistry of pyrazole ring was determined by reaction conditions, mainly by the nature of solvent. The use of protic solvent gave mainly phenylhydrazones of 5-(2-oxoethyl)-1-phenyl-3-R-pyrazoles, while phenylhydrazones of 3-(2-oxoethyl)-1-phenyl-5-R-pyrazoles were obtained in aprotic solvents. These compounds could be converted by Fischer reaction under acidic conditions to 3-(3-R-1-phenylpyrazol-5-yl)indoles and 3-(5-R-1-phenylpyrazol-3-yl)indoles, respectively, providing a general method for the preparation of these important heterocyclic compounds.

EXPERIMENTAL

IR spectra were recorded on IKS-29 (KBr pellets, compounds *E*-**12c**, *E*-**12d**), Perkin-Elmer Spectrum BX-II, and Nicolet 6700 with ATR accessory instruments (the rest of compounds). ^1H and ^{13}C NMR spectra were acquired on a Bruker Avance II spectrometer (400 and 100 MHz, respectively) in DMSO-d_6, with TMS as internal standard. The following abbreviations were used in reporting ^1H NMR spectra of phenylhydrazones **2**, **4**, **7**, **10**, **12**, **15** and **16**: Ph – phenyl ring at the hydrazone fragment, Ph' – phenyl ring at the pyrazole fragment. The pyrazole ring protons were denoted as H Pz, the indole ring protons – as H Ind. Elemental analysis was performed on a PE 2400 automated analyzer. Melting points were determined on a Stuart SMP30 apparatus.

Reaction of 4-Pyrones with Phenylhydrazine.

Method A. A mixture of 4-pyrone (1.5 mmol) and $PhNHNH_2 \cdot HCl$ (3.3 mmol) in protic solvent (H_2O, EtOH, AcOH) was heated for several hours.

Method B. A mixture of 4-pyrone (1.5 mmol) and $PhNHNH_2$ (3.3 mmol) in aprotic solvent (dioxane, toluene) was heated for several hours.

Cyclization of Phenylhydrazones to Indoles by the Action of Acids.

Method C. A solution of phenylhydrazone (0.50 mmol) in AcOH was refluxed with added HCl, the reaction mixture was then diluted with water, the precipitate that formed was filtered off, and recrystallized from a suitable solvent.

Method D. A reaction mixture, containing trifluoromethyl-substituted phenylhydrazone (0.48 mmol), $MeSO_3H$ (1.0 g, 10.40 mmol), and P_2O_5 (0.17 g, 1.20 mmol) was heated for 6 h at 60°C, followed by addition of H_2O (10 ml), the precipitate was filtered off, dried, and recrystallized from a suitable solvent.

(*E*)-2-(Phenylhydrazono)-3-(1-phenyl-1*H*-pyrazol-5-yl)propionic acid (*E*-2a) was obtained according to method A from pyrone **1a** in H_2O (4 ml) with the addition of conc. HCl (0.1 ml) by heating for 8 h at 60°C. The precipitate that formed (0.389 g, 81%) was a 86:5:9 mixture of three isomers *E*-**2a**+*Z*-**2a**+*E*-**4a** and gave the acid *E*-**2a** in 0.226 g (47%) yield after recrystallization from a toluene–EtOH mixture. White powder. Mp 214-215°C (mp 215°C [17]). Spectral characteristics (IR and ^{1}H NMR spectra) matched the literature data [17].

3-(3-Methyl-1-phenyl-1*H*-pyrazol-5-yl)-2-(phenylhydrazono)propionic acid (2b) was not isolated in pure form. A mixture of *E*-**2b** and *Z*-**2b** isomers was found in the product obtained according to method A by refluxing pyrone **1b** in 25% EtOH (9 ml) for 1 h. After the reaction was complete, the mixture was diluted with water, the precipitate was filtered off, and recrystallized from aqueous EtOH. This product had the mass of 0.155 g and consisted of indole **3b** (41%) as well as *E*- and *Z*-phenylhydrazones **2b** (59%) in 36:64 ratio. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *E*-**2b** isomer: 2.14 (3H, s, CH_3); 3.96 (2H, s, CH_2); 5.74 (1H, s, H-4 Pz); 6.87-7.63 (10H, m, H Ph); 10.28 (1H, s, NH); the CO_2H signal was not observed; *Z*-**2b** isomer: 2.18 (3H, s, CH_3); 3.81 (2H, s, CH_2); 6.01 (1H, s, H-4 Pz); 6.91 (1H, t, *J* = 7.2, H-4 Ph); 7.11 (2H, d, *J* = 7.2, H-2,6 Ph); 7.22-7.63 (7H, m, H Ph, H Ph'); 12.11 (1H, s, NH); the CO_2H signal was not observed.

3-(3-Methyl-1-phenyl-1*H*-pyrazol-5-yl)-1*H*-indole-2-carboxylic acid (3b) was obtained according to method A by refluxing pyrone **1b** in EtOH (6.5 ml) for 24 h. After cooling of the reaction mixture, the precipitate that formed was filtered off, yielding 0.024 g (5%) of compound **5b** as by-product. The filtrate was diluted with water, the precipitate was recrystallized from toluene, giving the acid **3b**. Yield 0.100 g (21%). Gray powder. Mp 254-255°C. IR spectrum, ν, cm^{-1}: 3425, 3268, 1686, 1664, 1499. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, CH_3); 6.36 (1H, s, H-4 Pz); 7.06 (1H, t, *J* = 7.6, H-4 Ph); 7.08-7.16 (3H, m, H-5 Ind, H-2,6 Ph); 7.21 (2H, t, *J* = 7.5, H-3,5 Ph); 7.28 (1H, t, *J* = 7.6, H-6 Ind); 7.33 (1H, d, *J* = 8.1, H-4 Ind); 7.46 (1H, d, *J* = 8.3, H-7 Ind); 11.98 (1H, s, NH); 12.60-13.20 (1H, br. s, CO_2H). Found, %: C 69.11; H 5.08; N 12.32. $C_{19}H_{15}N_3O_2 \cdot 0.75H_2O$. Calculated, %: C 68.97; H 5.03; N 12.70.

Mixture of (*E*)- and (*Z*)-2-(phenylhydrazono)-3-(1-phenyl-1*H*-pyrazol-3-yl)propionic acids (*E*-4a) and (*Z*-4a) and (*Z*)- and (*E*)-2-(phenylhydrazono)-3-(1-phenyl-1*H*-pyrazol-5-yl)propionic acids (*Z*-2a) and (*E*-2a) was obtained according to method B by refluxing pyrone **1a** in dioxane (6 ml) for 8 h. After evaporation of dioxane, the residue was treated with 10% aqueous HCl (6 ml), the aqueous phase was decanted, the resinous residue was washed with water, dissolved in EtOH, treated with water, and the product that crystallized was filtered off. Yield 0.303 g (63%). Gray powder. Mp 110-120°C. The product was a 51:18:18:13 mixture of isomers *E*-**4a**+*Z*-**4a**+*Z*-**2a**+*E*-**2a**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *E*-**4a** isomer: 4.03 (2H, s, CH_2); 6.27 (1H, d, *J* = 2.3, H-4 Pz); 6.85 (1H, t, *J* = 6.9, H-4 Ph); 7.15-7.60 (7H, m, H-3,5 Ph, H Ph'); 7.75 (1H, d, *J* = 7.6, H-2,6 Ph'); 8.25 (1H, d, *J* = 2.3, H-5 Pz); 10.10 (1H, s, NH); 11.50-13.50 (1H, br. s, CO_2H); *Z*-**4a** isomer: 3.81 (2H, s, CH_2); 6.30 (1H, d, *J* = 2.3, H-4 Pz); 6.60-7.90 (10H, m, H Ph, H Ph'); 8.21 (1H, d, *J* = 2.3, H-5 Pz); 11.50-13.50 (2H, br. s, NH, CO_2H); *Z*-**2a** isomer: 3.84 (2H, s, CH_2); 6.19 (1H, d, *J* = 1.1, H-4 Pz); 6.60-7.90 (11H, m, H-5 Pz, H Ph, H Ph'); 12.25 (1H, s, NH); 11.50-13.50 (1H, br. s, CO_2H). The spectrum of *E*-**2a** isomer was identical to that described above.

(*E*)-3-(5-Methyl-1-phenyl-1*H*-pyrazol-3-yl)-2-(phenylhydrazono)propionic acid (*E*-4b) was obtained according to method B from pyrone **1b** by refluxing in dioxane (4 ml) for 4 h. The reaction mixture was diluted with H_2O (6 ml) with the addition of conc. HCl (0.3 ml), the precipitate was filtered off and recrystallized from aqueous EtOH. Yield 0.204 g (32%). Light-brown crystals. Mp 114-115°C. IR spectrum, ν, cm^{-1}: 3247, 2924, 1665, 1583, 1498. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.28 (3H, s, CH_3); 3.97 (2H, s, CH_2); 6.05 (1H, s, H-4 Pz); 6.89 (1H, unresolved t, H-4 Ph); 7.10-7.57 (9H, m, H Ph, H Ph'); 10.22 (1H, s, NH); 12.06 (1H, s, CO_2H). Found, %: C 66.13; H 5.43; N 16.08. $C_{19}H_{18}N_4O_2 \cdot 0.5H_2O$. Calculated, %: C 66.46; H 5.58; N 16.32.

(*E*)-3-[5-(Ethoxycarbonyl)-1-phenyl-1*H*-pyrazol-3-yl]-2-(phenylhydrazono)propionic acid (*E*-4e) was obtained according to method B from pyrone **1e** by refluxing in dioxane (3 ml) for 3 h. The reaction mixture was diluted with water with the addition of conc. HCl (0.3 ml), the aqueous layer was decanted, toluene was added to the residue, the precipitate was filtered off, and recrystallized from toluene. Yield 0.077 g (13%).

Yellowish crystals. Mp 203-204°C. IR spectrum, ν, cm^{-1}: 3270, 2874, 1732, 1666, 1568. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.13 (3H, t, *J* = 6.6, $OCH_2C\underline{H}_3$); 4.05 (2H, s, CH_2); 4.15 (2H, q, *J* = 6.6, $OC\underline{H}_2CH_3$); 6.78 (1H, s, H-4 Pz); 6.89 (1H, t, *J* = 6.2, H-4 Ph); 7.20-7.60 (9H, m, H Ph, H Ph'); 10.23 (1H, s, NH); 12.11 (1H, br. s, CO_2H). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.3 (qt, *J* = 127.1, *J* = 2.6, $OCH_2\underline{C}H_3$); 23.7 (t, *J* = 129.3, CH_2); 61.0 (m, $O\underline{C}H_2CH_3$); 111.9 (dt, *J* = 179.9, *J* = 3.0, C-4); 114.4 (dm, *J* = 162.3, C-2,6 Ph); 121.3 (dt, *J* = 160.6, *J* = 7.1, C-4 Ph); 126.0 (dt, *J* = 162.8, *J* = 6.0, C-2,6 Ph'); 128.4 (dt, *J* = 162.3, *J* = 8.7, C-4 Ph'); 128.6 (dd, *J* = 162.1, *J* = 8.0, C-3,5 Ph); 129.1 (dd, *J* = 159.3, *J* = 8.0, C-3,5 Ph'); 131.9 (m, C=N); 134.0 (d, *J* = 7.8, C-5); 140.3 (t, *J* = 8.0, C-1 Ph); 144.5 (m, C-1 Ph'); 148.3 (td, *J* = 7.8, *J* = 4.2, C-3); 158.6 (t, *J* = 3.1, C=O); 166.3 (t, *J* = 3.5, C=O). Found, %: C 64.40; H 5.20; N 14.44. $C_{21}H_{20}N_4O_4$. Calculated, %: C 64.28; H 5.14; N 14.28.

3-(1-Phenyl-1*H*-pyrazol-3-yl)-1*H*-indole-2-carboxylic acid (5a) was obtained from pyrone **1a** in dioxane (9 ml) according to method B. The reaction mixture was refluxed for 6 h, then treated with H_2O (1.5 ml) and conc. HCl (0.75 ml), and refluxed for another 2 h. The obtained solution was cooled, diluted with H_2O (20 ml), the residue was filtered off and recrystallized from EtOH. Yield 0.159 g (35%). Gray powder. Mp 269-270°C (mp 270°C [17]). Spectral characteristics (IR and ^1H NMR spectra) corresponded to the literature data [17].

3-(5-Methyl-1-phenyl-1*H*-pyrazol-3-yl)-1*H*-indole-2-carboxylic acid (5b) was obtained according to method C from phenylhydrazone *E*-**4b** by refluxing in AcOH (6 ml) with the addition of conc. HCl (0.5 ml) over 4 h. After the reaction was complete, the mixture was treated by addition of H_2O (10 ml), the precipitate was filtered off and dried. Yield 0.058 g (36%). Yellow crystals. Mp 279-280°C. IR spectrum, ν, cm^{-1}: 3268, 1664, 1559, 1492. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.46 (3H, d, *J* = 0.6, CH_3); 7.09 (1H, q, *J* = 0.6, H-4 Pz); 7.17 (1H, td, *J* = 7.6, *J* = 0.9, H-5 Ind); 7.32 (1H, td, *J* = 7.7, *J* = 1.0, H-6 Ind); 7.49 (1H, tt, *J* = 7.3, *J* = 1.5, H-4 Ph); 7.52 (1H, d, *J* = 8.2, H-7 Ind); 7.61 (2H, t, *J* = 7.8, H-3,5 Ph); 7.68 (2H, dd, *J* = 8.5, *J* = 1.2, H-2,6 Ph); 8.20 (1H, d, *J* = 8.3, H-4 Ind); 11.96 (1H, s, NH); 14.20-15.20 (1H, br. s, CO_2H). Found, %: C 70.69; H 4.49; N 13.03. $C_{19}H_{15}N_3O_2 \cdot 0.33H_2O$. Calculated, %: C 70.58; H 4.88; N 13.00.

3-(5-Carboxy-1-phenyl-1*H*-pyrazol-3-yl)-1*H*-indole-2-carboxylic acid (5c) was obtained according to method A from pyrone **1c** by refluxing in H_2O (6 ml) with adding conc. HCl (1.5 ml), over 1 h. The white precipitate that formed was a mixture of two regioisomeric indoles **3c** (53%) and **5c** (47%). The combined yield was 0.25 g (48%). The obtained mixture was stirred for 5 min at room temperature in EtOH (5 ml). The precipitate of pure compound **5c** was filtered off. Yield 0.094 g (18%). White powder. Mp 305-306°C. IR spectrum, ν, cm^{-1}: 3261, 1719, 1671, 1561. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.08 (1H, td, *J* = 7.6, *J* = 0.5, H-5 Ind); 7.25 (1H, td, *J* = 7.6, *J* = 0.9, H-6 Ind); 7.44-7.49 (2H, m, H-7 Ind, H-4 Ph); 7.52 (2H, t, *J* = 7.5, H-3,5 Ph); 7.57 (2H, d, *J* = 7.6, H-2,6 Ph); 7.65 (1H, s, H-4 Pz); 8.18 (1H, d, *J* = 8.2, H-4 Ind); 11.82 (1H, s, NH); 12.00-15.00 (2H, br. s, $2CO_2H$). Found, %: C 63.63; H 3.46; N 11.63. $C_{19}H_{13}N_3O_4 \cdot 0.5H_2O$. Calculated, %: C 64.04; H 3.96; N 11.79.

3-[5-Ethoxycarbonyl-1-phenyl-1*H*-pyrazol-3-yl]-1*H*-indole-2-carboxylic acid (5e) was obtained according to method C from phenylhydrazone *E*-**4e** by refluxing in AcOH (5 ml) with adding conc. HCl (0.15 ml) over 4 h. After the reaction was complete, the mixture was stored for 24 h, the crystals that formed were filtered off and washed with water. Yield 0.080 g (42%). Yellowish crystals. Mp 264-265°C. IR spectrum, ν, cm^{-1}: 3293, 2984, 1733, 1665, 1556. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.19 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 4.23 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 7.12 (1H, t, *J* = 7.5, H-5 Ind); 7.30 (1H, td, *J* = 7.2, *J* = 0.7, H-6 Ind); 7.46-7.55 (2H, m, H-7 Ind, H-4 Ph); 7.55 (2H, t, *J* = 7.3, H-3,5 Ph); 7.61 (2H, d, *J* = 7.1, H-2,6 Ph); 7.71 (1H, s, H-4 Pz); 8.19 (1H, d, *J* = 8.2, H-4 Ind); 11.96 (1H, s, NH); 13.30-13.50 (1H, br. s, CO_2H). Found, %: C 67.25; H 4.49; N 11.35. $C_{21}H_{17}N_3O_4$. Calculated, %: C 67.19; H 4.56; N 11.19.

Ethyl (*E*)-2-(phenylhydrazono)-3-(1-phenyl-1*H*-pyrazol-5-yl)propionate (*E*-7a) was obtained according to method A from pyrone **6a** by stirring in EtOH (5 ml) at room temperature for 24 h and then for additional 3 h at 60°C temperature. The reaction mixture was diluted with water, the precipitate was filtered off and recrystallized from toluene. Yield 0.162 g (31%). Colorless crystals. Mp 153-154°C. IR spectrum, ν, cm^{-1}: 3216, 3006, 1697, 1597. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.20 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 4.04 (2H, s, CH_2);

4.12 (2H, q, J = 7.1, OC<u>H</u>$_2$CH$_3$); 5.96 (1H, d, J = 1.7, H-4 Pz); 6.93 (1H, t, J = 7.0, J = 1.6, H-4 Ph); 7.24-7.34 (4H, m, H Ph); 7.44-7.51 (1H, m, H-4 Ph'); 7.56 (1H, d, J = 1.7, H-3 Pz); 7.57-7.62 (4H, m, H Ph'); 10.37 (1H, s, NH). Found, %: C 68.80; H 5.77; N 15.98. $C_{20}H_{20}N_4O_2$. Calculated, %: C 68.95; H 5.79; N 16.08.

Ethyl (*Z*)-2-(Phenylhydrazono)-3-(1-phenyl-1*H*-pyrazol-5-yl)propionate (*Z*-7a). The toluene filtrate after isolation of isomer *E*-**7a** was passed through a thin layer of silica gel (approximately 1 cm^3), the solvent was removed by evaporation, the residue was recrystallized from aqueous EtOH. Yield 0.043 g (8%). Colorless powder. Mp 110-111°C. IR spectrum, ν, cm^{-1}: 3212, 3049, 1676, 1599. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.13 (3H, t, J = 6.9, OCH$_2$C<u>H</u>$_3$); 3.91 (2H, s, CH$_2$); 4.14 (2H, q, J = 6.9, OC<u>H</u>$_2$CH$_3$); 6.25 (1H, s, H-4 Pz); 6.94 (1H, t, J = 7.1, H-4 Ph); 7.12 (2H, d, J = 7.4, H-2,6 Ph); 7.27 (2H, t, J = 7.1, H-3,5 Ph); 7.38-7.58 (5H, m, H Ph'); 7.60 (1H, s, H-3 Pz); 11.88 (1H, s, NH). Found, %: C 68.09; H 6.00; N 15.38. $C_{20}H_{20}N_4O_2 \cdot 0.33H_2O$. Calculated, %: C 67.78; H 5.88; N 15.81.

Ethyl (*E*)-3-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-2-(phenylhydrazono)propionate (*E*-7b) was obtained according to method A from pyrone **6b** by stirring in EtOH (6 ml) at 60°C for 24 h. After cooling, the reaction mixture was diluted with water, decanted, the resinous residue was treated with 1:1 mixture of hexane–toluene (6 ml), the precipitate that formed was filtered off and washed with hexane. Yield 0.049 g (9%). Gray powder. Mp 172-173°C. IR spectrum, ν, cm^{-1}: 3171, 2970, 1698, 1585, 1500. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.23 (3H, t, J = 7.1, OCH$_2$C<u>H</u>$_3$); 2.15 (3H, s, CH$_3$); 3.98 (2H, s, CH$_2$); 4.13 (2H, q, J = 7.1, OC<u>H</u>$_2$CH$_3$); 5.74 (1H, s, H-4 Pz); 6.91 (1H, tt, J = 5.6, J = 2.3, H-4 Ph); 7.22-7.32 (4H, m, H Ph); 7.41 (1H, tt, J = 7.0, J = 1.4, H-4 Ph'); 7.53 (2H, t, J = 8.2, H-2,6 Ph'); 7.57 (2H, d, J = 7.5, H-3,5 Ph'); 10.29 (1H, s, NH).

Ethyl (*E*)-3-(3-ethoxycarbonyl-1-phenyl-1*H*-pyrazol-5-yl)-2-(phenylhydrazono)propionate (*E*-7c) was obtained according to method A from pyrone **6c** by stirring for 8 h in EtOH (3 ml) at 60°C. The precipitate that formed was filtered off, washed with H$_2$O, EtOH, and recrystallized from toluene. Yield 0.252 g (40%). Colorless powder. Mp 205-207°C. IR spectrum, ν, cm^{-1}: 3221, 3037, 2975, 2928, 1716, 1669. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.20 (3H, t, J = 7.1, OCH$_2$C<u>H</u>$_3$); 1.25 (3H, t, J = 7.1, OCH$_2$C<u>H</u>$_3$); 4.05 (2H, s, CH$_2$); 4.12 (2H, q, J = 7.1, OC<u>H</u>$_2$CH$_3$); 4.25 (2H, q, J = 7.1, OC<u>H</u>$_2$CH$_3$); 6.36 (1H, s, H-4 Pz); 6.92-6.98 (1H, m, H-4 Ph); 7.24-7.35 (4H, m, H Ph); 7.53-7.58 (1H, m, H-4 Ph'); 7.60-7.66 (4H, m, H Ph'); 10.43 (1H, s, NH). Found, %: C 65.70; H 5.77; N 13.09. $C_{23}H_{24}N_4O_4$. Calculated, %: C 65.70; H 5.75; N 13.32.

Ethyl 3-(1-phenyl-1*H*-pyrazol-5-yl)-1*H*-indole-2-carboxylate (8a) was obtained according to method C from phenylhydrazone *E*-**7a** by refluxing in AcOH (4 ml) with adding conc. HCl (0.15 ml) over 4 h. After cooling, the reaction mixture was diluted with water, the precipitate was filtered off and recrystallized from aqueous AcOH. Yield 0.097 g (58%). Colorless powder. Mp 185-186°C. IR spectrum, ν, cm^{-1}: 3136, 2983, 1716, 1500. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.04 (3H, t, J = 7.1, OCH$_2$C<u>H</u>$_3$); 3.85-4.15 (2H, unresolved ABX$_3$, OC<u>H</u>$_2$CH$_3$); 6.59 (1H, d, J = 1.1, H-4 Pz); 7.11 (1H, t, J = 7.5, H-4 Ph); 7.14 (2H, d, J = 7.1, H-2,6 Ph); 7.18 (1H, t, J = 6.8, H-5 Ind); 7.25 (2H, t, J = 7.7, H-3,5 Ph); 7.32 (1H, t, J = 7.7, H-6 Ind); 7.39 (1H, d, J = 8.1, H-4 Ind); 7.50 (1H, d, J = 8.2, H-7 Ind); 7.83 (1H, d, J = 1.1, H-3 Pz); 12.15 (1H, s, NH). Found, %: C 71.51; H 5.08; N 12.31. $C_{20}H_{17}N_3O_2 \cdot 0.25H_2O$. Calculated, %: C 71.52; H 5.25; N 12.51.

Ethyl 3-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-1*H*-indole-2-carboxylate (8b) was obtained according to method A from pyrone **6b** by refluxing in EtOH (8 ml) for 24 h. After cooling, the reaction mixture was diluted with water, the precipitate was filtered off, dissolved in refluxing toluene, and passed through a silica gel layer. The filtrate was evaporated to small volume, the residue was diluted with petroleum ether, the precipitated crystals were filtered off. Yield 0.093 g (18%). Yellow powder. Mp 158-159°C. IR spectrum, ν, cm^{-1}: 3315, 2982, 1684, 1510. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.05 (3H, t, J = 7.0, OCH$_2$C<u>H</u>$_3$); 2.33 (3H, s, CH$_3$); 3.85-4.16 (2H, unresolved ABX$_3$, OC<u>H</u>$_2$CH$_3$); 6.38 (1H, s, H-4 Pz); 7.06-7.17 (4H, m, H-5 Ind, H Ph); 7.21 (2H, t, J = 7.5, H-3,5 Ph); 7.31 (1H, t, J = 7.7, H-6 Ind); 7.40 (1H, d, J = 8.2, H-4 Ind); 7.49 (1H, d, J = 8.2, H-7 Ind); 12.15 (1H, br. s, NH). Found, %: C 73.23; H 5.38; N 12.31. $C_{21}H_{19}N_3O_2$. Calculated, %: C 73.03; H 5.54; N 12.17.

Ethyl 3-[3-(ethoxycarbonyl)-1-phenyl-1*H*-pyrazol-5-yl]-1*H*-indole-2-carboxylate (8c) was obtained according to method C from phenylhydrazone *E*-**7c** by refluxing in AcOH (4 ml) with adding conc. HCl

(0.3 ml) over 4 h. After cooling, the reaction mixture was diluted with water, the precipitate was filtered off and recrystallized from aqueous AcOH. Yield 0.087 g (43%). Colorless powder. Mp 167-168°C. IR spectrum, ν, cm^{-1}: 3337, 2983, 1708, 1509. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.07 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 1.34 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 3.91-4.20 (2H, unresolved ABX_3, $OC\underline{H}_2CH_3$); 4.36 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 7.05 (1H, s, H-4 Pz); 7.12 (1H, tt, *J* = 7.6, *J* = 0.7, H-4 Ph); 7.19 (2H, dd, *J* = 7.5, *J* = 1.0, H-2,6 Ph); 7.24-7.31 (3H, m, H-5 Ind, H-3,5 Ph); 7.33 (1H, td, *J* = 8.1, *J* = 1.0, H-6 Ind); 7.40 (1H, d, *J* = 8.1, H-4 Ind); 7.50 (1H, d, *J* = 8.3, H-7 Ind); 12.24 (1H, s, NH). Found, %: C 68.62; H 5.08; N 10.31. $C_{23}H_{21}N_3O_4$. Calculated, %: C 68.47; H 5.25; N 10.42.

5-[3,3-Difluoro-2-(phenylhydrazono)propyl]-1-phenyl-1*H*-pyrazole-3-carboxylic acid (*E*-10c) was obtained as a mixture with acid *E*-**12c** according to method A from pyrone **9c** by maintaining for 16 h in a mixture of H_2O (4 ml) and 20% HCl (2 ml) at 50°C. The precipitated mixture contained isomers *E*-**10c** and *E*-**12c** in approximately equal amounts. It was filtered off and recrystallized from toluene (20 ml). Yield 0.378 g (68%). Yellow powder. Mp 180-185°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): isomer *E*-**10c**: 3.91 (2H, s, CH_2); 6.44 (1H, s, H-4 Pz); 6.48 (1H, t, *J* = 54.5, CHF_2); 6.88 (1H, tt, *J* = 7.3, *J* = 1.1, H-4 Ph); 7.16 (2H, dd, *J* = 7.5, *J* = 1.2, H-2,6 Ph); 7.20-7.66 (7H, m, H-3,5 Ph, H Ph'); 10.04 (1H, s, NH); 12.60-13.90 (1H, br. s, CO_2H).

Ethyl 5-[3,3-difluoro-2-(phenylhydrazono)propyl]-1-phenyl-1*H*-pyrazole-3-carboxylate (*E*-10d) was obtained from pyrone **9d** according to method B by maintaining for 48 h in EtOH (10 ml) at 20°C. After the reaction was complete, the mixture was treated with conc. HCl (1.5 ml), the aqueous layer was decanted, and toluene (3 ml) was added to the viscous residue. The precipitate that formed was filtered off and recrystallized from toluene (10 ml). Yield 0.131 g (22%). Beige powder. Mp 186-187°C (mp 186-187°C [28]). Spectral characteristics (IR, ^{1}H and ^{19}F NMR spectra) matched the literature data [28].

3-[3,3-Difluoro-2-(phenylhydrazono)propyl]-1-phenyl-1*H*-pyrazole-5-carboxylic acid (*E*-12c) was obtained according to method B from pyrone **9c** by stirring with dioxane (6 ml) with the addition of conc. HCl (0.1 ml) over 3 h at 60°C. After cooling, the reaction mixture was treated by adding H_2O (10 ml) and 20% HCl (1 ml), the precipitate was filtered off and recrystallized from toluene (40 ml). Yield 0.172 g (31%). Light-yellow powder. Mp 214-215°C. IR spectrum, ν, cm^{-1}: 3448, 3289, 2646, 1703, 1600, 1536. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.91 (2H, s, CH_2); 6.48 (1H, t, *J* = 55.0, CHF_2); 6.78 (1H, s, H-4 Pz); 6.85 (1H, tt, *J* = 7.3, *J* = 1.0, H-4 Ph); 7.16 (2H, dd, *J* = 7.5, *J* = 1.2, H-2,6 Ph); 7.25 (2H, dd, *J* = 8.5, *J* = 7.3, H-3,5 Ph); 7.39-7.49 (5H, m, H Ph'); 10.02 (1H, s, NH); 13.10-13.50 (1H, br. s, CO_2H). Found, %: C 61.55; H 4.27; N 15.30. $C_{19}H_{16}F_2N_4O_2$. Calculated, %: C 61.62; H 4.35; N 15.13.

Ethyl 3-[3,3-difluoro-2-(phenylhydrazono)propyl]-1-phenyl-1*H*-pyrazole-5-carboxylate (*E*-12d) was obtained according to method B from pyrone **9d** by maintaining in toluene (4 ml) for 96 h at room temperature. After removing toluene, the residue was diluted with EtOH (4 ml), the precipitate that formed was filtered off and recrystallized from toluene (2 ml). Yield 0.072 g (12%). Colorless powder. Mp 117-118°C. IR spectrum, ν, cm^{-1}: 3290, 1740, 1603, 1541, 1529, 1504. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.13 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 3.93 (2H, s, CH_2); 4.15 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 6.49 (1H, t, *J* = 54.4, CHF_2); 6.82 (1H, s, H-4 Pz); 6.85 (1H, tt, *J* = 7.3, *J* = 1.0, H-4 Ph); 7.16 (2H, dd, *J* = 8.6, *J* = 1.2, H-2,6 Ph); 7.25 (2H, dd, *J* = 8.6, *J* = 7.3, H-3,5 Ph); 7.40-7.51 (5H, m, H Ph'); 10.01 (1H, s, NH). Found, %: C 63.44; H 5.11; N 14.01. $C_{21}H_{20}F_2N_4O_2$. Calculated, %: C 63.31; H 5.06; N 14.06.

5-[3,3-Difluoro-2-(phenylhydrazono)propyl]-1-phenyl-1*H*-pyrazole (*E*-15c). A mixture of 2-difluoromethyl-4-pyrone **14c** (0.153 g, 1.05 mmol) and freshly distilled phenylhydrazine (0.25 g, 2.31 mmol) was heated for 1 h at 120°C. After cooling, the reaction mixture was treated with EtOH (3 ml), maintained for 1 h at -25°C, the precipitate that formed was filtered off. Yield 0.063 g (18%). White powder. Mp 207-208°C. IR spectrum, ν, cm^{-1}: 3222, 3186, 3122, 1605, 1595, 1496. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.91 (2H, s, CH_2); 6.06 (1H, d, *J* = 1.7, H-4 Pz); 6.46 (1H, t, *J* = 54.9, CHF_2); 6.87 (1H, tt, *J* = 7.2, *J* = 1.1, H-4 Ph); 7.16 (2H, dd, *J* = 8.4, *J* = 1.2, H-2,6 Ph); 7.26 (2H, dd, *J* = 8.6, *J* = 7.3, H-3,5 Ph); 7.46 (1H, tt, *J* = 7.2, *J* = 2.2, H-4 Ph'); 7.54-7.62 (5H, m, H-3 Pz, H Ph'); 10.02 (1H, s, NH). Found, %: C 65.33; H 5.18; N 16.54. $C_{18}H_{16}F_2N_4 \cdot 0.33H_2O$. Calculated, %: C 65.05; H 5.05; N 16.86.

3-[3,3-Difluoro-2-(phenylhydrazono)propyl]-1-phenyl-1*H*-pyrazole (*E*-16c). The filtrate after isolation of phenylhydrazone *E*-**15c** was maintained for 24 h at -25°C, the precipitate that formed was filtered off. Yield 0.045 g (13%). White powder. Mp 75-76°C. IR spectrum, ν, cm^{-1}: 3249, 3043, 1597, 1497. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.88 (2H, s, CH_2); 6.30 (1H, d, *J* = 2.4, H-4 Pz); 6.31 (1H, t, *J* = 55.6, CHF_2); 6.81 (1H, tt, *J* = 7.2, *J* = 1.1, H-4 Ph); 7.13 (2H, d, *J* = 7.8, H-2,6 Ph); 7.19 (2H, t, *J* = 7.1, H-3,5 Ph); 7.25 (1H, tt, *J* = 7.3, *J* = 1.0, H-4 Ph'); 7.44 (2H, t, *J* = 8.2, H-3,5 Ph'); 7.77 (2H, d, *J* = 7.7, H-2,6 Ph'); 8.29 (1H, d, *J* = 2.4, H-5 Pz); 9.91 (1H, s, NH). Found, %: C 66.19; H 5.02; N 16.99. $C_{18}H_{16}F_2N_4$. Calculated, %: C 66.25; H 4.94; N 17.17.

2-Phenyl-3-(1-phenyl-1*H*-pyrazol-5-yl)-1*H*-indole (17a) and 2-Phenyl-3-(1-phenyl-1*H*-pyrazol-3-yl)-1*H*-indole (18a). A mixture of compounds **17a** and **18a** in the ratio of 84:16 was obtained according to method A by refluxing pyrone **14a** in EtOH (7 ml) for 24 h. After cooling, the reaction mixture was diluted with water, the precipitate that formed was filtered off, dissolved in hot toluene, passed through a silica gel layer, the filtrate was evaporated. Yield 0.126 g (25%). Yellow crystals. Mp 175-180°C. IR spectrum, ν, cm^{-1}: 3164, 1597, 1588, 1573, 1510. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): isomer **17a**: 6.58 (1H, d, *J* = 1.8, H-4 Pz); 7.02 (1H, td, *J* = 7.5, *J* = 0.9, H Ph); 7.16 (1H, td, *J* = 7.6, *J* = 1.2, H Ph); 7.26 (2H, d, *J* = 7.4, H Ar); 6.95-7.32 (9H, m, H Ar); 7.44 (1H, dt, *J* = 8.1, *J* = 0.8, H-7 Ind); 7.80 (1H, d, *J* = 1.8, H-3 Pz); 11.72 (1H, s, NH); isomer **18a**: 6.24 (1H, d, *J* = 2.6, H-4 Pz); 6.95-7.30 (9H, m, H Ind, H Ph); 7.65-7.75 (2H, m, H-2,6 Ph); 7.90 (2H, dd, *J* = 1.8, *J* = 8.7, H-2,6 Ph); 8.11 (1H, d, *J* = 7.9, H-4 Ind); 8.45 (1H, d, *J* = 2.6, H-5 Pz); 11.61 (1H, s, NH).

X-Ray Structural Study of Compound *E*-4b. Crystals of compound *E*-**4b** were grown from 1:1 EtOH–H_2O. The X-ray structural study was performed at room temperature on an Xcalibur-3 diffractometer with CCD-detector according to standard procedure (λMoKα radiation, graphite monochromator, ω/2θ-scanning). No correction for absoption was used due to its low value (μ 0.088 mm^{-1}). A fragment of light-brown prismatic crystal of compound *E*-**4b** with dimensions 0.42×0.30×0.18 mm was used for the analysis. The crystal of compound *E*-**4b** ($C_{19}H_{18}N_4O_2 \cdot 0.5H_2O$, *M* 343.38) was monoclinic; *a* 24.0185(19), *b* 7.6114(11), *c* 19.354(3) Å; β 91.633(10)°; *V* 3536.8(8) $Å^3$; *Z* 8; d_{calc} 1.290 g/cm^3; *F*(000) 1448; space group *C*2/*c*. A total of 12968 reflections, including 4297 independent (R_{int} 0.0265), of which 2110 had $I > 2\sigma(I)$, were measured over the range of $2.74 \le \theta \le 28.28°$. The structure was solved and refined with full matrix least squares method by F^2, using the SHELXTL software suite [29]. Non-hydrogen atoms were included in the model in anisotropic approximation. The CH hydrogen atoms were localized by electron density maxima and included in the refinement in isotropic approximation by the "rider" model with dependent thermal parameters. The final refinement parameters: R_1 0.0351, wR_2 0.0750 (by reflections with $I > 2\sigma(I)$), R_1 0.0836, wR_2 0.0801 (by all reflections) with reliability factor *S* 1.005. The maxima and minima of residual electron density were 0.135/-0.144 $\bar{e} \cdot Å^{-3}$. The complete X-ray structural data set for compound *E*-**4b** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1011360).

Supplementary information file, containing synthetic procedures and spectral data for compounds *Z*-**2c**, **3a**,**c**, *E*-**4d**, **5d**, *E*-**10a**,**b**, **11a**,**b**, *E*-**12a**,**b**, **13a**,**b**, *E*-**15b**, *E*-**16b**, **17b**, **18b** is available to authorized users.

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