Facile and Regioselective Synthesis of Substituted 1*H*-Pyrazolo[3,4-*b*] quinolines from 2-Fluorobenzaldehydes and 1*H*-Pyrazol-5-amines

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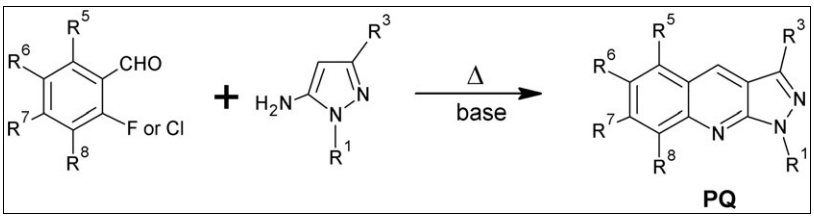


The present article concerns the scope and limitations of the regioselective condensation of 2-fluorobenzaldehydes with 1*H*-pyrazol-5-amines, leading to the synthesis of substituted 1*H*-pyrazolo[3,4-*b*] quinolines (**PQ**), in the presence of a base catalyst (DABCO and 2,4,6-trimethylpyridine). A method to obtain these nitrogen heterocycles with fluorine or trifluoromethyl substituents in different positions in the carbocyclic ring was developed as a part of a systematic research on the influence of fluorine-containing substituents on the parameters of **PQ**. Those compounds, characterized by high-fluorescence intensity, have been tested as emitters for the organic light-emitting diodes since 1997. The functionalization of **PQ** causes changes in various parameters, for example, HOMO and LUMO levels, which are important for the adjustment of fabricated organic light-emitting diodes. One of the easiest methods of **PQ** preparation, namely, the condensation of substituted anilines with 5-chloro-1*H*-pyrazole-4-carbaldehydes, is not regioselective. The method described in this study allows synthesizing of 1*H*-pyrazolo[3,4-*b*]quinolines with good yields and high selectivity – only the expected isomer is obtained. As various different 2-fluorobenzaldehydes are commercially available, and 1*H*-pyrazol-5-amines with different substituents are easy to prepare, the method could be a good alternative to the already known procedures. All possible mechanisms of the reaction were also thoroughly studied.

INTRODUCTION

1*H*-Pyrazolo[3,4-*b*]quinolines (**PQ**, Fig. 1) are tricyclic, heterocyclic compounds known since 1928, when they were obtained for the first time [1]. Various nitrogen heterocycles are commonly used in fabrication of organic light-emitting diodes (OLEDs) [2] – the first one was fabricated on the base of a 8-hydroxyquinoline complex by Tang and Van Slyke in 1987 [3]. In 1997, 4-methyl-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]quinoline luminophor was used for the fabrication of an OLED cell by He *et al.* [4]. Since then, many different **PQ** have been used as emitters in OLED (see examples [5,6]).

As part of the study on the influence of fluorine substitution on the parameters of **PQ**-based emitters [7], we considered the preparation of **PQ** derivatives with the fluorine atom (or trifluoromethyl group) located in all four positions of the carbocyclic ring of **PQ** (Fig. 1, R^5–R^8 = F, CF_3). The most common method of 4-*H*-**PQ** (Fig. 1, R^4 = H) synthesis is the condensation of substituted anilines with different 5-chloro-1*H*-pyrazole-4-carbaldehydes, introduced by Brack in 1965 [8]. Many substituted anilines are available commercially; additionally, the 5-chloro-1*H*-pyrazole-4-carbaldehydes can be easily prepared by the Vilsmeier–Haack formylation of appropriate 1,3-disubstituted-4*H*-pyrazol-5-ones [9]. The method is highly useful for aniline and its 4-substituted derivatives (R^6 as substituent). The yields are good to excellent – 40–96% – almost independently of the substituent (for examples see [6,8,10]). On the other hand, for the 3-subtituted anilines, two isomers are always formed, because the reaction is not regioselective in its origin. These isomers are structurally similar, and their parameters which are important for separation, for example, solubility or time of retention; they are also comparable, and the isomers could be separated in only a few cases [10b]. Therefore, our interest was focused on a search for a regioselective method of the synthesis of **PQ**.

Friedländer condensation of an *o*-aminobenzaldehyde (anthranilic aldehyde) with 1,3-disubstituted-4*H*-pyrazol-5-ones is regioselective (by that method, **PQ** was introduced in chemistry for the first time by Musierowicz *et al.* in 1928 [1]), but only the unsubstituted anthranilic aldehyde is commercially available, and fluorine substituted aldehydes have to be prepared prior to the condensation. Additionally, *o*-aminobenzaldehydes are

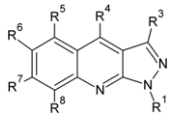


Figure 1. The structure of substituted 1*H*-pyrazolo[3,4-*b*]quinoline, **PQ**.

not very stable compounds and have a limited shelf life [11]. If 2-aminobenzaldehyde is replaced by 2-nitrobenzaldehyde, **PQ** could be obtained in a two-step procedure [12], but in this case, the substrates (substituted 2-nitrobenzaldehydes) also have to be prepared before the condensation. Substituted anthranilic acids could be regioselectively transformed into 4-chloro-1*H*-pyrazolo[3,4-*b*]quinolines, but the procedure is a multistep reaction [13]. The procedure of Neelima *et al.* requires the substituted 2-chloro-3-ketoquinolines to be prepared and reacted with hydrazines to produce the expected **PQ** [14], but 2-chloro-3-ketoquinolines with fluorine atoms or the trifluoromethyl group have not been obtained yet. Finally, we have found a promising paper by Abramov *et al.*, concerning the condensation of pentafluorobenzaldehyde with 1*H*-pyrazol-5-amines in xylene/acetic acid solution [15]. As a result, the 5,6,7,8-tetrafluoro-1*H*-pyrazolo[3,4-*b*]quinolines were synthesized, applying the reaction used earlier for the preparation of substituted acridines [16]. The results of the Abramov *et al.* study on the reaction of pentafluorobenzaldehyde with 1*H*-pyrazol-5-amines seem to be different from those found earlier by Joshi *et al.* [17], who obtained *bis*-pyrazolo[3,4-*b*,4′,3′-*e*]pyridines (**BPP**), rather than **PQ,** in a similar reaction performed in non-solvent conditions at 220–240°C. They only proved the structures of the products by using elemental analysis of nitrogen (with no apparatus details), neither ^{1}H-NMR nor ^{13}C-NMR spectra were present, and the melting point of the suggested product, 1,3,5,7-tetraphenyl-4-(pentafluorophenyl)-*bis*-pyrazolo[3,4-*b*,4′,3′-*e*]pyridine, is similar to that found for the 5,6,7,8-tetrafluoro-1*H*-pyrazolo[3,4-*b*]quinoline by Abramov. It is possible that Joshi obtained not **BPP**, but the same **PQ** as Abramov.

RESULTS AND DISCUSSION

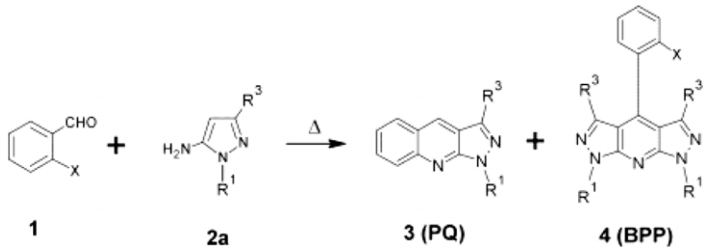
Abramov *et al.* did not perform a systematic research on the scope and limitations of their method, so we decided to continue the research and expand on their findings, and investigate the range of possible applications of that reaction for the synthesis of 1*H*-pyrazolo[3,4-*b*] quinolines, **PQ**.

First, we have condensed benzaldehydes containing a halogen atom in the *ortho* position with 1,3-diphenyl-1*H*-pyrazol-5-amine, **2a** (Table 1).

In the case of 2-chloro, 2-bromo, and 2-iodobenzaldehydes (**1b–d**), the main product was a corresponding 1,3,5,7-tetraphenyl-4-(2′-halophenyl)-*bis*-1*H*,7*H*-pyrazolo[3,4-*b*,4′,3′-*e*]pyridine, **BPP** (**4b–d**, Table 1), as expected, and as observed earlier in similar conditions (for 2-chloro- and 2-bromobenzaldehyde, **1b** and **1c**) by other authors [8,18]. However, for the 2-fluorobenzaldehyde (**1a**), 1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]quinoline, **PQ** (**3a**), was obtained as a major product

Table 1

Synthesis of 1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]quinoline, **PQ** (**3**), and 1,3,5,7-tetraphenyl-4-(2′-halophenyl)-*bis*-pyrazolo[3,4-*b*,4′,3′-*e*]pyridine, **BPP** (**4**) by the reaction of **2a** (R^1,R^3 = Ph) with 2-halobenzaldehydes, **1**.



		Products			
Entry	Aldehyde	**PQ**	Yields (%)	**BPP**	Yields (%)
1	**1a** (X = F)	**3a***	29	**4a**	10
2	**1b** (X = Cl)	**3b***	2.5	**4b**	51
3	**1c** (X = Br)	**3c***	2	**4c**	45
4	**1d** (X = I)	**3d***	1.5	**4d**	37

*__3a–d__ are the same compound, 1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]quinoline.

(proved by the elemental analysis and ^{1}H-NMR/^{13}C-NMR spectra). In all the cases, the products were initially separated by column chromatography, followed by a centrifugally accelerated, radial, thin layer preparative chromatograph (Chromatotron) separation [19]. Our results seem to be different to those found earlier by Quiroga *et al.*, who obtained 5,7-dimethyl-1,3-diphenyl-4-(2′-fluorophenyl)-*bis*-1*H*,7*H*-pyrazolo[3,4-*b*,4′,3′-*e*] pyridine in 80% yield in microwave irradiation reaction conditions [20]. However, the authors used 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, **2b**, in the reaction, instead of a 1,3-diphenyl-1*H*-pyrazol-5-amine, **2a**. The possible reasons for the different results, and the importance of the substituent type in the position 3 of 1*H*-pyrazol-5-amine (R^3 in **2**), will be discussed later.

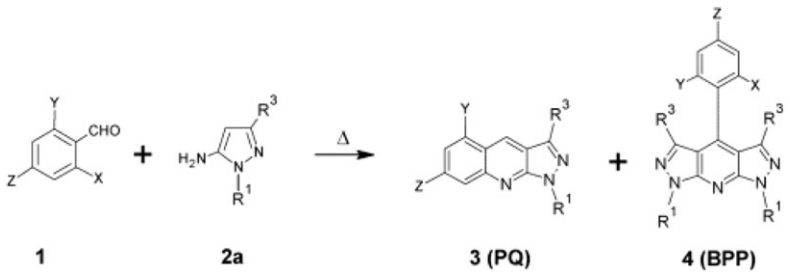
The results we obtained encouraged us to investigate a wider group of reagents. We started with 2,6-dihalogen-substituted and 2,4-dihalogen-substituted benzaldehydes in the same reaction conditions (Table 2).

For comparison, we also performed the reaction with pentafluorobenzaldehyde, **1k** (used by Abramov *et al.* [15]). As can be seen from Table 2, 2-fluoro-6-halogen-benzaldehydes (**1e,f,h**) predominantly form the corresponding 5-halogen-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]quinoline, **PQ** (**3e,f,h**), and in all cases, the fluorine atom is substituted. The highly reactive **1k** forms practically only **PQ**, as expected (84% yield). 2,6-Dichlorbenzaldehyde (**1g**) forms more **BPP** (**4g**) than **PQ** (**3g**), but the amount of **PQ** is still very high, when compared with 2-chlorobenzaldehyde (**3b** and **4b** in Table 1). The use of 2,4-difluorobenzaldehyde (**1i**) results in the **PQ** (**3i**) as the major product, but for the 2,4-dichlorobenzaldehyde (**1j**), the major product appears to be the **BPP**, **4j** (similarly as for 2-chlorbenzaldehyde, **3b** and **4b**, Table 1). It is worth noting here that the yield of 7-fluoro-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]quinoline (**3i**, 49%) and 5-fluoro-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]quinoline (**3e**, 65%), obtained separately from different substrates, is better than the results of the reaction between 3-fluoroaniline and 1,3-diphenyl-5-chloro-1*H*-pyrazole-4-carbaldehyde. In the second case, a mixture of 5-fluoro- and 7-fluoro-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]quinoline was obtained. 7-Fluoro isomer was isolated by fractional crystallization, followed by column chromatography at 39% yield, but the attempts to obtain pure 5-fluoro isomer, free from 7-fluoro, failed.

The interesting effect of using 2,6-dichlorbenzaldehyde (**1g**) was that much more **PQ** (**3g**) was formed, in contrast to the reaction of 2-chlorobenzaldehyde and 2,4-dichlorobenzaldehyde (**1b** and **1j**) – this could be explained by a mechanism proposed earlier by Abramov *et al.* [15]. The tendency of 2-fluorobenzaldehyde (**1a**) to form **PQ** rather than **BPP** possibly means that the first stage of the reaction could be the addition of the amine group of the 1*H*-pyrazol-5-amine to the carbon atom linked with fluorine (Scheme 1) – S_NAr (addition–elimination) mechanism.

Table 2

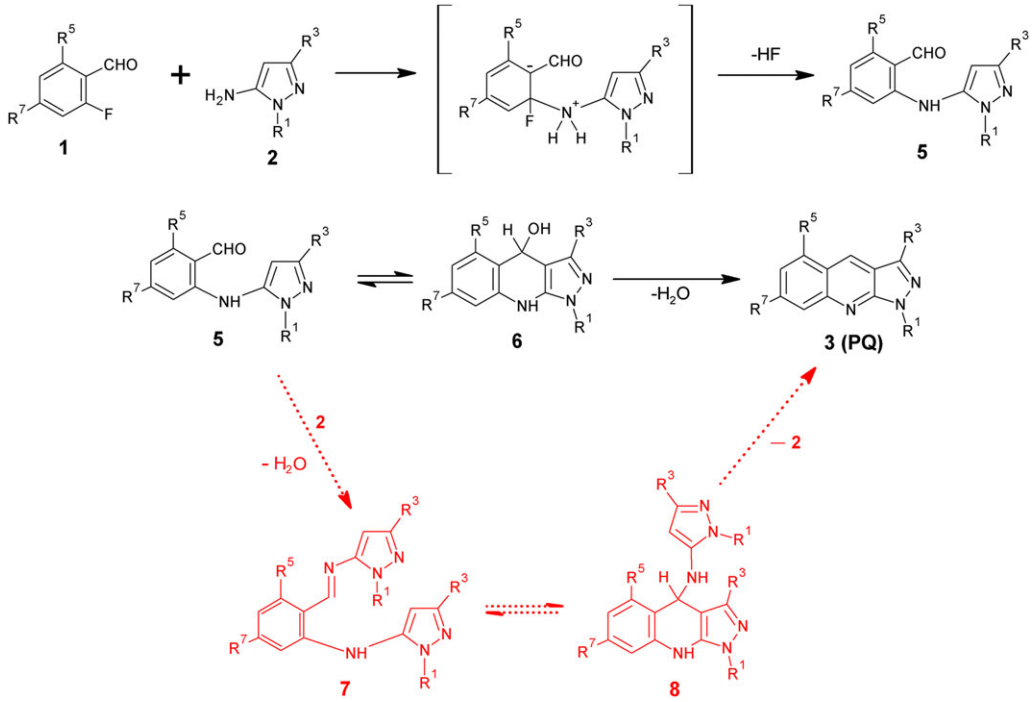
Synthesis of substituted 1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]quinoline, **PQ** (**3**), and 1,3,5,7-tetraphenyl-4-(substituted-phenyl)-*bis*-pyrazolo[3,4-*b*,4′,3′-*e*] pyridine, **BPP** (**4**) by the reaction of **2a** (R^1,R^3 = Ph) with substituted benzaldehydes, **1**.



		Products			
Entry	Aldehyde	**PQ**	Yields (%)	**BPP**	Yields (%)
1	**1e** (X,Y = F, Z = H)	**3e**	65	**4e**	2.5
2	**1f** (X = F, Y = Cl, Z = H)	**3f***	57	**4f**	9
3	**1g** (X,Y = Cl, Z = H)	**3g***	22	**4g**	38
4	**1h** (X = F, Y = I, Z = H)	**3h**	68	**4h**	9
5	**1i** (X,Z = F, Y = H)	**3i**	49	**4i**	7
6	**1j** (X,Z = Cl, Y = H)	**3j**	6	**4j**	49
7	**1k** (pentafluorobenzaldehyde)	**3k**	84	**4k**	traces

*__3f__ and __3g__ are the same compound, 6-chloro-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]quinoline.

Scheme 1. The proposed mechanism of the formation of **PQ** (**3**) in the reaction of 2-fluorobenzaldehydes (**1**) and 1*H*-pyrazol-5-amine **2**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

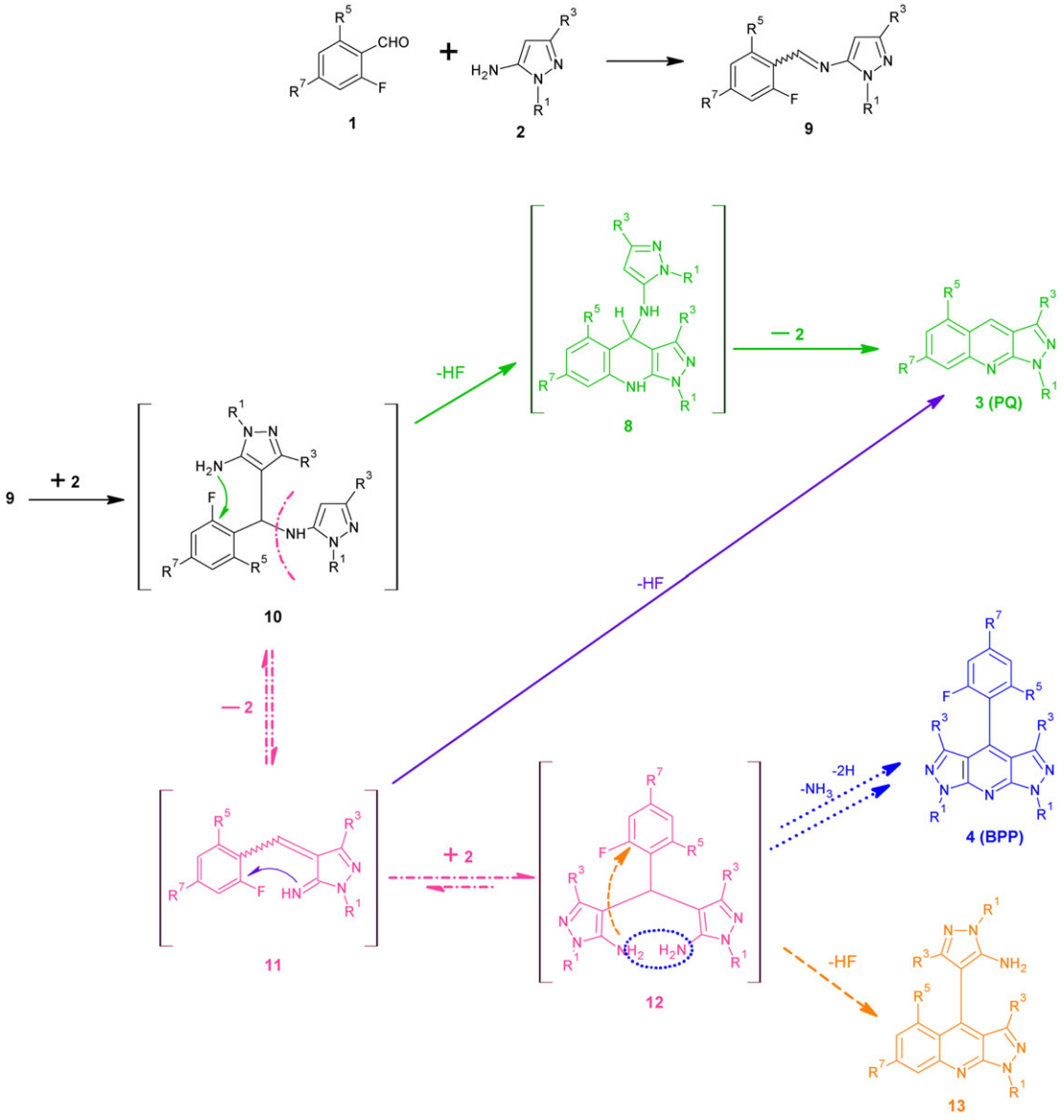


The fluorine atom is the most electronegative of all elements and stabilizes the transition state better than the other halogens [21]. The fluorine is also the smallest one and causes the lowest steric hindrance. The elimination of halogen is the easiest for iodine, but as the elimination stage is not rate-determining, 2-iodobenzaldehyde (**1d**) forms mostly **BPP** (**4d** in Table 1). That elimination step ends with the formation of *o*-[(1,3-disubstituted-1*H*-pyrazol-5-yl)amino]benzaldehyde, **5**, with subsequent intramolecular electrophilic substitution (S_E) and the formation of 4-hydroxy-4,9-dihydro-1,3-disubstituted-1*H*-pyrazolo[3,4-*b*]quinoline, **6** (Scheme 1, solid arrows, black). This compound could easily eliminate a water molecule, forming **PQ** (**3**). At this stage, an alternative reaction route is also possible: **5** reacts with **2** (dotted arrows, red) and, after losing a water molecule, forms Schiff's base of **5** and **2**: *N*-{*o*-[(1,3-disubstituted-1*H*-pyrazol-5-yl)amino]benzylideno}-1,3-disubstituted-1*H*-pyrazol-5-amine, **7**. It could also undergo the intramolecular S_E reaction and form 4-[(1,3-disubstituted-1*H*-pyrazol-5-yl)amino]-4,9-dihydro-1,3-disubstituted-1*H*-pyrazolo[3,4-*b*]quinoline, **8**, with subsequent elimination of **2**. As a result, **PQ** is formed. That second route was proposed by Abramov as an explanation of **PQ** formation in the reactions between **1k** and 1*H*-pyrazol-5-amines, **2** [15]. That mechanism readily explains the tendency of 2-fluorobenzaldehydes to form **PQ**, but does not explain why small amounts of **BPP** are formed as well. Moreover, our attempts to obtain **5** from 2-halogenbenzaldehydes (**1a–d**) and **2a**, using Buchwald catalysts [22], failed to produce expected products. In the examined cases, we have obtained only Schiff's bases of **1** and **2a**.

Considering the previous statement, it is safe to assume that another mechanism is probably more correct – the one proposed earlier by Hennig *et al.* as an explanation for the formation of **BBP** in the reaction of 1*H*-pyrazol-5-amines with benzaldehydes [23]. The authors observed that performing the reaction in boiling ethanol produced a Schiff's base, **9**, as the main product. In higher temperatures, and with the excess of the 1*H*-pyrazol-5-amine, **BPP** is formed (Scheme 2).

The mechanism proposed by Hennig and developed here explains not only the formation of **PQ** and **BPP** but also the formation of another product found by us: the 4-(1,3-disubstituted-1*H*-pyrazolo[3,4-*b*]quinolin-4-yl)-1,3-disubstituted-1*H*-pyrazol-5-amine, **13**. The first stage, described in Scheme 2, after the formation of Schiff's base, **9**, is its reaction with another **2** molecule and the formation of a by-product, 4-{[(1,3-disubstituted-1*H*-pyrazol-5-yl)amino](phenyl)methyl}-1,3-disubstituted-1*H*-pyrazol-5-amine, **10**. That molecule could reversibly lose molecule **2** and again react with **2** forming a 4,4′-(phenylmethanediyl)bis(1,3-disubstituted-1*H*-pyrazol-5-amine), **12** (dashed/dotted arrows, pink). Finally, after losing a NH_3 molecule and being oxidized, the **BPP** (**4**) is formed (dotted arrows, blue). But in some cases, other paths are also possible. When fluorine in the *ortho*

Scheme 2. "Hennig's" mechanism of the formation of **PQ**, **BBP**, and **13** in the reaction of 2-fluorobenzaldehydes **1** and 1*H*-pyrazol-5-amine **2**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



position (in respect to formyl group) is present, its high electronegativity causes the free amine group of **10** to attack the carbon atom linked with fluorine and, after losing a HF molecule, to form **8** (proposed also in Scheme 1). In the next stage, **2** is eliminated from **8**, and **PQ** (**3**) is formed (solid arrows, green on Scheme 2). The formation of **PQ** is also possible at the stage of **11** – nitrogen of imine group could attack the carbon atom linked to fluorine, and after dehydrofluorination, the **PQ** is formed (solid arrow, violet). We have also found another product, **13**: yellow compound exhibiting very weak fluorescence in the solution, with R_f much lower than those of **PQ** (**3**) and **BPP** (**4**). This yellow, nonfluorescent compound was observed on the chromatographic column or the chromatotron plate in most of the studied reactions, but because of its strong affinity to the stationary phase, it remained unisolated, or the amounts were too small to identify the compound (<1 mg). The reaction between **1a** and **2a** was repeated several times, and all collected samples of **13** (**13a** in that case) were mixed together and purified by crystallization, and the structure of **13a** was confirmed. The ^{1}H-NMR/^{13}C-NMR spectra were complex, suggesting a molecule with 29 non-equivalent carbon atoms, 24 aromatic hydrogens, and an amine group. To unambiguously determine the structure of that molecule, single crystal X-ray diffraction experiment was performed. The shape of the molecule with the atom numbering scheme is presented in Figure 2 [24].

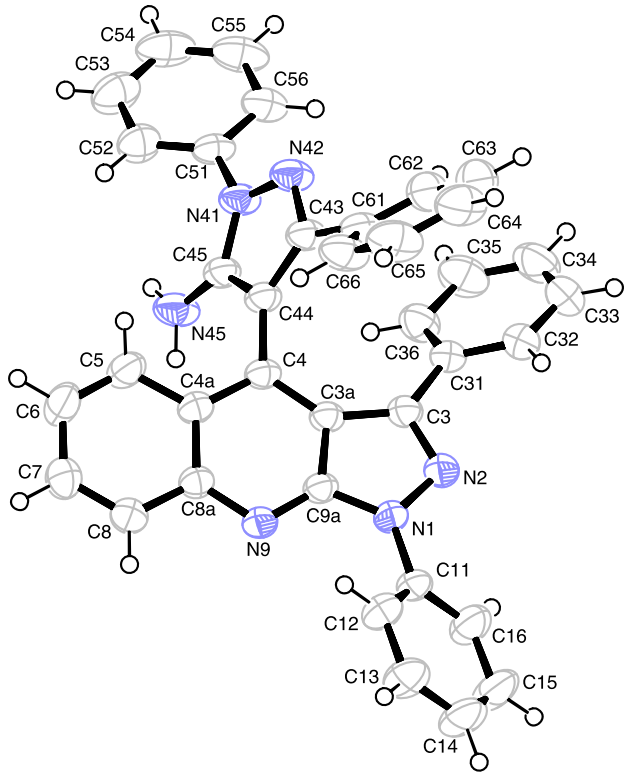


Figure 2. The conformation of **13a** in the crystal structure (ORTEP representation). Atom numbering scheme is shown. The atomic displacement ellipsoids are given at 50% probability level. Significant dihedral angles are the following: Pyrazole_4-Core = 55.47(6), Phenyl_1-Core = 38.47(7), Phenyl_3-Core = 41.03(5), Phenyl_5-Pyrazole_4 = 45.15(9), and Phenyl_6-Pyrazole_4 = 46.87(9)°, where Core is 1*H*-pyrazolo[3,4-*b*]quinoline moiety. The conformation is stabilized by strong intermolecular hydrogen bond N(45)–H(45B)…N(9), intramolecular and intermolecular interactions of C–H…π types. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The formation of **13** is possible at the stage of **12**, when the attack of one of the amine groups on the carbon linked to fluorine is faster than the elimination of ammonia (Scheme 2, dashed arrows, orange). The obtainment of **13** corroborates the existence of a by-product **12**, and as a consequence, it confirms the so-called Hennig's mechanism.

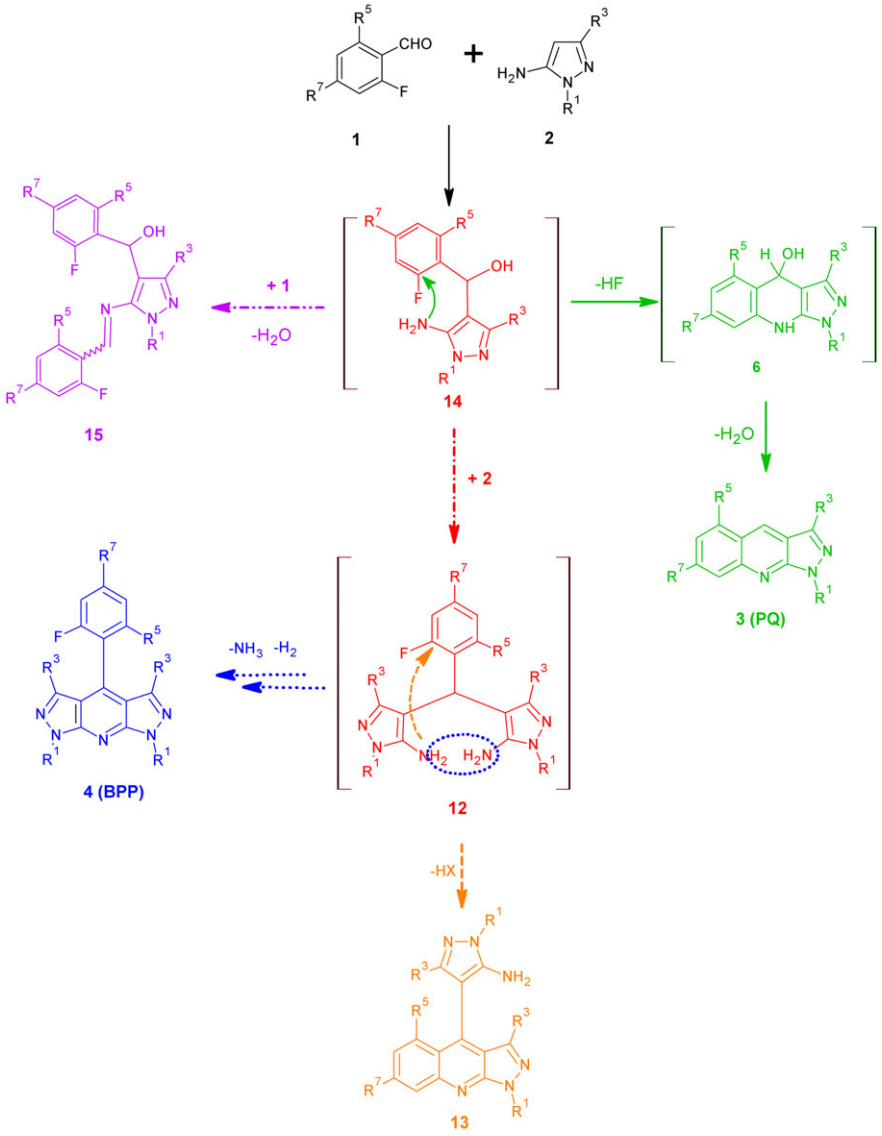
There is also another, slightly different explanation for the formation of the **BPP** (**4**) molecule, proposed by Esteves-Souza *et al* [25]. That proposition could explain the formation of **PQ** (**3**), as well as **13** (in their case, they used 1,3-dimethyl-1*H*-pyrazol-5-amine, **2d**, instead of **2a**, and different benzaldehydes). The authors suggest that the reaction leading to **BPP** (**4**) does not go through the Schiff's base **9** (Scheme 2), but through (5-amino-1,3-disubstituted-1*H*-pyrazol-4-yl)(phenyl)methanol, **14** (Scheme 3)**.**

The compound **14** was not isolated by the authors, but another product, [5-(benzylideneamino)-1,3-dimethyl-1*H*-pyrazol-4-yl](phenyl)methanol, **15a** (R^1,R^2 = Me; X,R^5,R^7 = H), was. The authors emphasized that only the presented route could explain the formation of that compound. **14** could also react with another **2** molecule and form a 4,4′-(phenylmethanediyl)bis(1,3-disubstituted-1*H*-pyrazol-5-amine), **12**. The proposition of Esteves-Souza *et al.* explains the formation of **13** and **BPP** (**4**), as does the mechanism proposed by Hennig [23] – the same intermediate (**12** on Schemes 2 and 3) is observed in both cases. The course of the reaction proposed on Scheme 3 could also prove the formation of **PQ** (**3**) in the case of 2-halogensubstituted benzaldehydes: if the carbinol **14** contains the fluorine substituent in *ortho* position, the amine group could intramolecularly attack the carbon atom linked to fluorine (green on Scheme 3) and form 4,9-dihydro-1,3-disubstituted-1*H*-pyrazolo[3,4-*b*] quinoline, **6** (compare with Scheme 1), which can easily lose a water molecule and aromatize to **PQ** (**3**). In our study, we did not obtain any product of type **15**, but as we had used aldehydes containing the halogen atom in *ortho* position to the carbonyl group, the main products were different.

It is difficult to unambiguously determine which of the presented mechanisms is correct, as we, and other authors, [15,23,25] have found evidence for all of them. Nevertheless, the analysis of the reaction products obtained by us and other authors suggests that the mechanisms depicted in Schemes 2 and 3 are the most probable, as they explain the formation of all the observed compounds. It is also possible that both of them are correct, and the molecules undergo both reactions, with specific conditions and reagents determining which of the routes is preferred.

The behavior of 2,4- and 2,6-dichlorobenzaldehydes (**1j** and **1g** on Table 2) seems to confirm both the mechanisms (Schemes 2 and 3). 2,6-Dichlorobenzaldehyde (**1g**) forms **BPP** (**4g**) as a major product, but the amount of **PQ** (**3g**) is also significant (even though the 2-chlorobenzaldehyde, **1b**, gives almost only **BPP**, **4b**). Two chlorine atoms near the aldehyde group increase the probability of the attack of the amine group on the carbon atom of the aromatic ring, and therefore the yield of **PQ** is increased. These two chlorine atoms could also cause steric hindrance around the carbonyl group and slow down the reversible reaction leading to **12** (Scheme 2, dashed/dotted arrows, pink). As the elimination of HF and the formation of **8** are irreversible, more **PQ** is formed (Scheme 2, solid arrows, green). In the case of 2,4-dichlorobenzaldehyde (**1j**), where the steric hindrance around carbonyl group and the probability of the attack of the amine group on the carbon atom (Scheme 2) are comparable with that found for the 2-chlorbenzaldehyde (**1b**), the reaction leads to an expected **BPP** derivative (**4j**). The behavior of 2-chloro-6-fluoro- and 2-fluoro-6-iodobenzaldehydes (**1f** and **1h**)

Scheme 3. "Esteves-Souza's" mechanism of the formation of **PQ** (**3**), **BPP** (**4**), **13**, and **15** in the reaction of 2-fluorobenzaldehydes **1** and 1*H*-pyrazol-5-amine **2**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



also confirms that conclusion: the most electronegative fluorine atom is substituted, rather than chlorine or iodine, respectively, and in both of those cases, the main product is **PQ** (**3f** and **3h**).

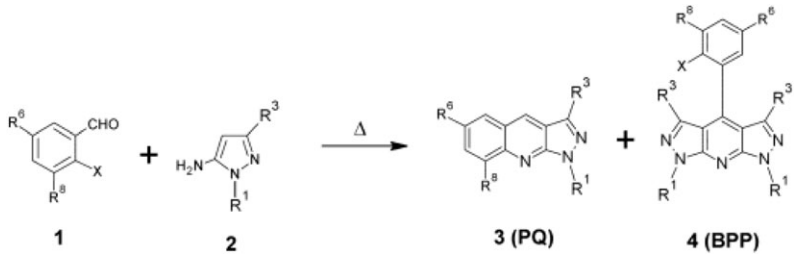
Irrespectively of the actual mechanism leading to the formation of **BPP** and **PQ** in the condensation of 2-halobenzaldehydes and 1*H*-pyrazol-5-amines, we are additionally interested in the limitations of the regioselective formation of the **PQ** molecules. In the next part of the manuscript, we analyze mostly the limitations and conditions of the reaction.

The presented mechanisms suggest that the presence of strong electron-withdrawing groups in the *ortho* or *para* positions, in respect to the halogen atom, should also lead favorably to the formation of **PQ** [21a]. To confirm that thesis, further experiments were conducted as described next (Table 3).

In the following group of reactions, we used 2-halobenzaldehydes with electron-withdrawing groups. As the products of the reaction of **2a** and 2-halo-5-nitrobenzaldehydes (**1l–n**) are weakly soluble, the separation and purification of the products were difficult. Because of that, **2b** was used in place of **2a** in those reactions. From Table 3, one can see that the presence of the nitro group in 2-fluoro-5-nitrobenzaldehyde (**1l**) increases the amount of **PQ**, when compared with the reaction with 2-fluorobenzaldehyde (**1a**) (Table 1). In the case of 2-chloro- and 2-bromo-5-nitrobenzaldehydes (**1m** and **1n**), more **BPP** is formed, than **PQ**, but the ratio is changed in comparison with the reactions with these

Table 3

Synthesis of 1,3-disubstituted-1*H*-pyrazolo[3,4-*b*]quinoline, **PQ** (**3**), and derivatives of 1,3,5,7-tetrasubstituted-4-(2′-halophenyl)-*bis*-pyrazolo[3,4-*b*,4′,3′-*e*]pyridine, **BPP** (**4**) by the reaction of 1*H*-pyrazol-5-amines **2** with substituted benzaldehydes, **1**.



			Products			
Entry	Amine	Aldehyde	**PQ**	Yields (%)	**BPP**	Yields (%)
1	**2b** (R^1 = Ph, R^2 = Me)	**1l** (X = F, R^6 = NO_2, R^8 = H)	**3l***	56	**4l**	traces
2	**2b** (R^1 = Ph, R^2 = Me)	**1m** (X = Cl, R^6 = NO_2, R^8 = H)	**3m***	6	**4m**	30
3	**2b** (R^1 = Ph, R^2 = Me)	**1n** (X = Br, R^6 = NO_2, R^8 = H)	**3n***	7	**4g**	27
4	**2a** (R^1, R^3 = Ph)	**1o** (X = F, R^6 = H, R^8 = CF_3)	**3o****	52	**4h**	traces
5	**2a** (R^1, R^3 = Ph)	**1p** (X = Cl, R^6 = H, R^8 = CF_3)	**3p****	6	**4i**	62
6	**2a** (R^1, R^3 = Ph)	**1q** (X = Cl, R^6 = CF_3, R^8 = H)	**3q**	2.5	**4j**	40

*__3l–n__ are the same compound, 6-nitro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline.
**__3o__ and __3p__ are the same compound, 8-(trifluoromethyl)-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]quinoline.

aldehydes without the nitro group. The presence of the trifluoromethyl group does not significantly affect the **PQ/BPP** ratio, when the halogen is chlorine; only in the case of the reaction with 2-chloro-3-(trifluoromethyl) benzaldehyde (**1p**), the yield of **PQ** (**3p**) is slightly higher. When the halogen is fluorine, the trifluoromethyl group located in the *ortho* position to it increases the halogen's reactivity (when compared with 2-fluorobenzaldehyde **1a**, Table 1). It is worth noting that in this particular reaction, the yield (52%) is much higher than in the Brack's reaction [8] between 2-(trifluoromethyl)aniline and 5-chloro-1,3-diphenyl-1*H*-pyrazol-4-carbaldehyde (<3%) [6g]. All the results summarized in Table 3 are in agreement with the proposed mechanisms.

The results of Abramov *et al*, [15] slightly different to ours in the case of 2-chloro-5-nitrobenzaldehyde (**1m**), could be explained by the use of acidic conditions (CH_3COOH) of the reaction and a lower temperature. The amino group of the 1,3-disubstituted-1*H*-pyrazol-5-amine, **2**, could be protonated in those conditions, leading the reaction mostly to a **BPP** derivative.

To understand the influence of the acids and bases on the studied reactions, the condensation of 2-fluorobenzaldehyde (**1a**) with **2a** was repeated with the addition of a relatively strong H-acid (*p*-toluenesulfonic acid, *p*-TSA), weak H-acid (*p*-toluic acid, *p*-TA), Lewis acid (zinc chloride, $ZnCl_2$), and a strong, non-nucleophilic amine (1,4-diazabicyclo[2.2.2]octane, DABCO). The results are summarized in Table 4.

As can be seen in Table 4, small amounts of catalyst (1 mol%) have relatively low influence on the yields of both products, **PQ** and **BPP**: irrespectively of the character of the additive, the yield is slightly increased. When the concentration of the strong acid is increased,

Table 4

Products of the reactions between 1,3-diphenyl-1*H*-pyrazol-5-amine (**2a**) and 2-fluorobenzaldehyde (**1a**) with different catalyst.

		Products yields (%)	
Entry	Catalyst*	**PQ**	**BPP**
1	*p*-TSA 1	35	14
2	*p*-TSA 10	34	33
3	*p*-TSA 100	4	23
4	*p*-TA 1	32	12
5	*p*-TA 10	29	14
6	*p*-TA 100	29	23
7	$ZnCl_2$ 1	36	16
8	$ZnCl_2$ 10	32	23
9	$ZnCl_2$ 100	8	14
10	DABCO 1	36	14
11	DABCO 10	55	12
12	DABCO 100	59	4

*Amount of catalyst in mol%.
PQ, 1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]quinoline **3a**; **BPP**, 1,3,5,7-tetraphenyl-4-(2′-fluorophenyl)-*bis*-pyrazolo[3,4-*b*,4′,3′-*e*]pyridine **4a**.

the yield of **PQ** at first does not change, but in the case of **BPP**, its yield increases. With the high concentration of *p*-TSA (100 mol%), the yield of both products is decreased, but the amount of **BBP** is around six times higher than that of **PQ**. Weak acid (*p*-TA) does not have significant influence on the **PQ** yield, while the yield of **BPP** increases with an increasing concentration of acid. Those observations are in agreement with the proposed mechanisms: while the concentration of H-acid is increased, the amine **2** is deactivated by protonation of the amine group; meanwhile, the aldehyde is activated by the protonation of the oxygen atom of the formyl group: the overall yield of the products is increased, because more **9** on Scheme 2 (or **14** on Scheme 3) is formed. High concentration of the strong acid deactivates **2** so strongly, that the yield of both products is decreased. The weak acid has less protonation ability than the strong acid, so the deactivation of the amine is weaker. H-acid also deactivates the amine group of **10**, but the protonation of only one of the amine groups of **12** (more probable that the protonation of both groups) facilitates the elimination of ammonia and the formation of **BPP**. It was also observed that in acidic conditions, the yellow by-product (presumably **13**) was not formed: one protonated amine substituent in **12** is a good leaving group, leading the reaction at this stage mostly to **BPP**. Lewis acid with moderate concentration (10 mol%) increases the yield of **BPP**, while not significantly changing the yield of **PQ**. A high concentration of $ZnCl_2$ decreases the yields of both products, most probably because of an inactivation of the amine group (as it was observed in the case of *p*-TSA). An addition of amine (DABCO) should not have any influence on the rate of the reaction leading to **BPP** and **13** (dashed/dotted arrows, pink on Scheme 2 and red on Scheme 3), as none of the stages require a base to go forward. However, the irreversible elimination of HF (solid arrows, green on Schemes 2 and 3) would go faster, and therefore the yield of **PQ** is increased. Protonated DABCO could also act as a weak H-acid and assist in the elimination of **2** from **8**.

As the addition of an amine proved to be the best method to obtain **PQ** with the highest yield and selectivity, other non-nucleophilic, high-boiling amines were also examined: 1,9-diazabicyclo[5.4.0]undec-7-ene (DBU), triethanolamine, quinoline, isoquinoline, and 2,4,6-trimethylpyridine, all 90 mol% to **1a** and **2a**. The results are summarized in Table 5. A total of 90 mol% of amine was used instead of 100 mol% to prevent the presence of free amines in the products.

From Tables 4 and 5, one can notice that the best yield of **PQ** is achieved with DABCO and quinoline, but in both cases, **BPP** is also formed. In the case of 2,4,6-trimethylpyridine, the yield of **PQ** is 5 percentage points lower, but **PQ** is practically the only product. When comparing the toxicity of these three amines, DABCO and 2,4,6-trimethylpyridine seem to be the best choices: they are non-toxic and not dangerous to the environment. Quinoline is much cheaper, but it is classified as a carcinogen and an environmental pollutant, toxic for aquatic life. These factors are highly important, especially when considering the use of such method in a large-scale production.

Table 5

Products of the reactions between 1,3-diphenyl-1*H*-pyrazol-5-amine (**2a**) and 2-fluorobenzaldehyde (**1a**) in the presence of different amines.

		Products yields (%)	
Entry	Amine	**PQ**	**BPP**
1	DBU	6.5	traces
2	triethanolamine	31.5	traces
3	quinoline	60	10
4	isoquinoline	56	5
5	2,4,6-trimethylpyridine	55	traces

PQ, 1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]quinoline, **3a**; **BPP**, 1,3,5,7-tetraphenyl-4-(2′-fluorophenyl)-*bis*-pyrazolo[3,4-*b*,4′,3′-*e*]pyridine, **4a**.

The reactions of **2a** with 2,6-dichlorobenzaldehyde (**1g**) and **2b** with 2-chloro-5-nitro-benzaldehyde (**1m**) were also repeated, in the presence of 2,4,6-trimethylpyridine, to test whether the change in conditions for these compounds will change the **PQ/BPP** ratio to **PQ**'s advantage (Table 6).

The results confirmed the presented mechanisms – in both cases, the amount of **PQ** increased, and the amount of **BBP** decreased or remained unchanged. In the case of 2,6-dichlorobenzaldehyde (**1g**), the yields were even inverted (when compared with the reaction with no additives, Table 2).

We have also checked if the change in the ratio between 2-fluorobenzaldehyde (**1a**) and 1,3-diphenyl-1*H*-pyrazol-5-amine (**2a**) has any influence on the **PQ/BPP** output proportion and **PQ** yield (the reaction was performed in the presence of 2,4,6-trimethylpyridine, compare with Table 5). In the case of **2a/1a** = 2/1 ratio (commonly used for the synthesis of **BPP**) [23], the

Table 6

Products of the reactions between 1*H*-pyrazol-5-amines **2** and selected aldehydes **1** in the presence of 2,4,6-trimethylpyridine.

	Products			
Aldehyde and amine	**PQ**	Yields (%)	**BPP**	Yields (%)
1g + 2a	**3g**	43	**4g**	11
1m + 2b	**3m**	15	**4m**	35

PQ, 1*H*-pyrazolo[3,4-*b*]quinoline derivatives; **BPP**, bis-pyrazolo[3,4-*b*,4′,3′-*e*] pyridine derivatives.

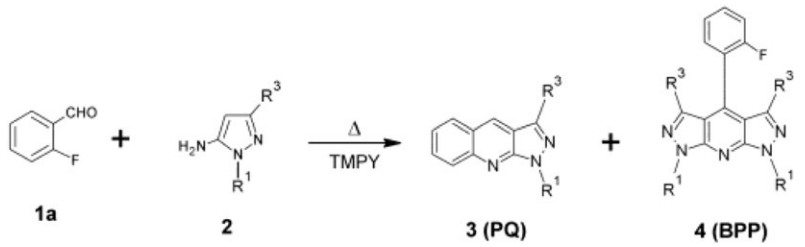
yield of **PQ** (**3a**) was 52%, and **BPP** (**4a**) was also observed, with a 2.5% yield. Changing the ratio towards 2-fluorobenzaldehyde's advantage (2:1 and even 5:1) lowered the yield of **PQ** to about 30–40%, probably because of a more complicated purifying procedure (excess of benzaldehyde was present in the reaction mixture). **BPP** was no longer observed. These results indicate that the yields are optimal when 1:1 ratio is used. Another important condition to be tested is the temperature of the reaction. For all investigated examples, the temperature of 170–180°C was used, common in the **BPP** synthesis [23]. To check whether such high temperature is required in the studied reactions, we examined three most representative examples: weakly reactive 2-fluorobenzaldeyde (**1a**), reactive 2,6-difluorobenzaldehyde (**1e**), and highly reactive pentafluorobenzaldehyde (**1k**) in the reaction with 1,3-diphenyl-1*H*-pyrazol-5-amine (**2a**). The very reactive **1k** starts to form a product at 100°C; at 120°C, the rate increases; and at 140°C, the reaction is finished in 5–10 min. **1e**, less reactive than **1k**, starts to form a product at 120°C, and at 160°C, the reaction becomes rapid enough to be finished in 10–15 min. For the not activated **1a**, the first traces of products are observed above 130°C after 20 min, but below 160°C, the reaction is too slow to be profitable. At 170–180°C, the reaction is effectively finished after 45–60 min. Time of the reaction should not be extended over 60–90 min, as significant amounts of temperature-degradation products are formed (black tars adsorbed on the Al_2O_3 column) and the overall yield is diminished.

Finally, the last group of reactions was carried out in order to check the reactivity of different 1*H*-pyrazol-5-amines (**2**) with the 2-fluorobenzaldehyde (**1a**) in the best conditions: 90 mol% of 2,4,6-trimethylpyridine, temperature 170–180°C. The results are summarized in Table 7.

From Table 7, one can observe that the change of the substituent R^1 of 1*H*-pyrazol-5-amine does not significantly affect the **PQ/BPP** ratio. The situation is different when phenyl in position 3 is changed to methyl (**3s** and **4s**, **3t** and **4t**): in these cases, more **BPP** is formed. That cannot be explained by the mechanism proposed in Scheme 1, also the "Hennig" mechanism (Scheme 2, [23]) does not explain the change readily, because the smaller methyl should not influence the reaction at the stage of **10**. Most probably, the difference lies in the **12** formation stage, as the compound with two methyl substituents in position 3 of 1*H*-pyrazol-5-amine moiety should be more stable than that with phenyl substituents. The third proposition (Scheme 3, [25]) could also explain the changed preference in **PQ/BPP** ratio, as the first intermediate, **14**, could be attacked by another **2** molecule (dashed/dotted downward arrow, red), most likely when the smaller methyl substituent in the position 3 of 1*H*-pyrazol-5-amine moiety is present. When the phenyl in position 3 is changed to a bulky *tert*-butyl, **PQ** is even more favored, than in the case of a phenyl substituent, and **BPP** (**4u**) is not formed at all (compare **3u** in Table 7 with **3a** and **4a** in the presence of 2,4,6-trimethylpyridine, Table 5). Because of the steric hindrance in the case of **3u**, a higher temperature must be used.

Table 7

Synthesis of 1,3-disubstituted-1*H*-pyrazolo[3,4-*b*]quinoline, **PQ** (**3**), and 1,3,5,7-tetrasubstituted-4-(2′-fluorophenyl)-*bis*-pyrazolo[3,4-*b*,4′,3′-*e*]pyridines, **BPP** (**4**) by the reaction of 1*H*-pyrazol-5-amines, **2**, with 2-fluorobenzaldehyde, **1a**, in the presence of 2,4,6-trimethylpyridine.



		Products			
Entry	Amine	**PQ**	Yields (%)	**BPP**	Yields (%)
1	**2b** (R^1 = Ph, R^2 = Me)	**3r**	43	**4r**	18
2	**2c** (R^1 = Me, R^2 = Ph)	**3s**	38	**4s**	5
3	**2d** (R^1, R^2 = Me)	**3t**	19	**4t**	22
4*	**2e** (R^1 = Ph, R^2 = *t*-Bu)	**3u**	52	**4u**	0

*Because of lower reactivity of **2e**, the reaction temperature was increased to 200°C.

CONCLUSIONS

In the present study, we proposed a regioselective method for the synthesis of 1*H*-pyrazolo[3,4-*b*]quinoline (**PQ**) derivatives, from 2-halogenbenzaldehydes and 1*H*-pyrazol-5-amines. The method produced the best results with 2-fluorobenzaldehydes in the presence of bases: 1,3,5-trimethylpyridine, 1,4-diazabicyclo[2.2.2]octane (DABCO), and quinoline. The highly reactive pentafluoro- and 2-fluoro-5-nitrobenzaldehyde form solely **PQ**, without the presence of any catalyst. The use of 2-chlorobenzaldehydes gives satisfactory results only for 2,6-dichloro- and 2-chloro-5-nitrobenzaldehyde. From the possible 1*H*-pyrazol-5-amine derivatives, the best results are obtained with phenyl and *tert*-butyl substituents in position 3, while 3-methyl substituted substrates give worse results, as significant amounts of *bis*-pyrazolo[3,4-*b*,4′,3′-*e*]pyridine, **BPP**, are also formed. As a wide variety of 2-fluorobenzaldehydes is commercially available or easy to synthesize, this could be the method of choice in those procedures when other accessible methods result in a mixture of isomers that are difficult to separate (condensation of 3-substituted anilines with 5-chloro-1*H*-pyrazole-4-carbaldehydes) or the yields are very low (condensation of 2-electron-withdrawing group substituted anilines with 5-chloro-1*H*-pyrazole-4-carbaldehydes). It could also be an excellent choice, when the other possible regioselective methods require multistep preparation procedures, and unstable or expensive reagents.

EXPERIMENTAL

All the solvents used for purification were purchased from Chempur (Polish supplier), and all were of analytical grade. For Chromatotron purification, the Harrison Research model 7924T was used [26]. Silica gel with gypsum (for Chromatotron purification), silica gel 60, and aluminum oxide 90 (for column chromatography) were purchased from Merck. Substituted benzaldehydes were purchased from Alfa Aesar or Aldrich or prepared as stated. 1*H*-Pyrazol-5-amines were prepared as stated. $CDCl_3$ with TMS was purchased from Aldrich. Melting points were determined on a MEL-TEMP II apparatus, and they are uncorrected. ^{1}H-NMR and ^{13}C-NMR were recorded at 600 MHz and 150 MHz, respectively, with a Bruker Avance III 600 spectrometer using $CDCl_3$ as a solvent. Chemical shifts were given in ppm (δ) from TMS as an internal standard. Elemental analyses were conducted at Elementar Vario MICRO cube. Diffraction data for structural analysis were collected at ambient temperature for single crystal with an Agilent Technologies SuperNova diffractometer, equipped with Atlas CCD detector, using graphite-monochromated Mo Kα radiation (50 kV, 0.8 mA).

General procedure for the reaction of benzaldehydes with 1,3-diphenyl-1*H*-pyrazol-5-amine (2a). **2a** was prepared from phenylhydrazine and benzoylacetonitrile by the known procedure [27]. To the equimolecular mixture (1–10 mmol) of corresponding benz aldehyde (**1**) and **2a**, a few drops of ethanol were added to form a suspension. The mixture was slowly heated on Wood's alloy bath until the temperature reached 170–180°C and then maintained for 10–60 min (monitored by TLC). After that, the mixture was cooled to room temperature. Brown glassy solid (or oil) was dissolved in chloroform and flashed through aluminum oxide 90. In most cases, Chromatotron was used for separation and purification of products, using silica gel + gypsum plates (1- or 2-mm thickness). Elution was started with petroleum ether, followed by the mixture of that solvent with toluene. The speed of solvent's flow and the composition of the solvent mixture were not constant; those parameters were based on the still observation of plate during the purification. If additional or different separation and/or purification technique was used, it was stated in each case.

Reaction of 2-fluorobenzaldehyde (1a) with 1,3-diphenyl-1*H*-pyrazol-5-amine 2a. Reaction was performed according to the general procedure with 1 mmol of **1a** and **2a** (60 min):

1,3-Diphenyl-1H-pyrazolo[3,4-b]quinoline (3a). Yellow needles, 29% yield (94 mg); m.p. 163–164°C (Lit. 167°C [28]); ^{1}H-NMR ($CDCl_3$): $\delta = 7.29–7.35$ (m, 1H), 7.48–7.63 (m, 6H), 7.80 (ddd, $J = 8.7$, 6.7, 1.5 Hz, 1H), 8.03 (br d, $J = 8.1$ Hz, 1H), 8.16–8.22 (m, 3H), 8.61–8.64 (m, 2H), 8.94 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 116.6, 120.7, 124.4, 124.8, 125.4, 127.5, 128.96, 129.03, 129.05, 129.08, 129.2, 130.8, 130.9, 132.6, 140.0, 144.6, 148.2, 150.9. *Anal.* Calcd for $C_{22}H_{15}N_3$: C 82.22, H 4.70, N 13.08. Found: C 82.20, H 4.77, N 13.03.

1,3,5,7-Tetraphenyl-4-(2-fluorophenyl)-bis-pyrazolo[3,4-b,4',3'-e]pyridine (4a). A light-yellow crystalline powder, 10% yield (29 mg); m.p. 263–264°C; ^{1}H-NMR ($CDCl_3$): $\delta = 6.55$ (ddd, $J = 9.4$, 8.4, 1.1 Hz, 1H), 6.64 (td, $J = 7.5$, 1.1 Hz, 1H), 6.83 (td, $J = 7.4$, 1.8 Hz, 1H), 7.03–7.10 (m, 5H), 7.15–7.18 (m, 6H), 7.32–7.38 (m, 2H), 7.55–7.62 (m, 4H), 8.52–8.56 (m, 4H); ^{13}C-NMR ($CDCl_3$): $\delta = 112.9$, 114.9 (d, $J_{C–F} = 21.4$ Hz), 120.9, 121.7 (d, $J_{C–F} = 15.9$ Hz), 123.2 (d, $J_{C–F} = 3.2$ Hz), 125.7, 127.4, 127.8, 129.0, 129.1, 130.7 (d, $J_{C–F} = 8.0$ Hz), 131.3 (d, $J_{C–F} = 1.9$ Hz), 132.3, 135.1, 139.6, 147.7, 150.5, 159.1 (d, $J_{C–F} = 247.2$ Hz). *Anal.* Calcd for $C_{37}H_{24}FN_5$: C 79.70, H 4.34, N 12.56. Found: C 80.02, H 4.41, N 12.44.

4-(1,3-Diphenyl-1H-pyrazolo[3,4-b]quinolin-4-yl)-1,3-diphenyl-1H-pyrazol-5-amine (13a). The product was isolated from all studied reactions between **1a** and **2a** and purified by

crystallization from DMF/methanol; deep-yellow crystals, 315 mg (estimated average yield 3%); m.p. 274°C; ^{1}H-NMR ($CDCl_3$): $\delta = 3.42$ (s, 2H), 7.03–7.06 (m, 2H), 7.10–7.13 (m, 1H), 7.22–7.23 (m, 2H), 7.26–7.29 (m, 3H), 7.32–7.42 (m, 7H), 7.48–7.51 (m, 2H), 7.58–7.61 (m, 4H), 7.76 (ddd, J = 8.7, 6.6, 1.5 Hz, 1H), 8.07 (ddd, J = 8.6, 1.5, 0.6 Hz, 1H), 8.24 (ddd, J = 8.7, 1.2, 0.6 Hz, 1H), 8.62–8.63 (m, 1H); ^{13}C-NMR ($CDCl_3$): $\delta = 97.5$, 115.6, 120.8, 124.2 (two overlapped signals), 124.5, 125.5, 126.8, 127.1, 127.5, 127.7, 127.8, 128.2, 128.3, 129.1, 129.2 (two overlapped signals), 129.5, 130.8, 132.5, 132.6, 135.8, 138.1, 139.8, 143.8, 146.8, 148.9, 149.7, 150.6 ppm. *Anal.* Calcd for $C_{37}H_{26}N_6$: C 80.12, H 4.73, N 15.15. Found: C 79.90, H 4.76, N 15.10.

Reaction of 2-chlorobenzaldehyde (1b) with 1,3-diphenyl-1*H*-pyrazol-5-amine 2a. Reaction was performed according to the general procedure with 1 mmol of **1b** and **2a** (60 min):

1,3-Diphenyl-1H-pyrazolo[3,4-b]quinoline (3b, identical with 3a). Yellow crystals, 2.5% yield (8 mg). ^{1}H-NMR was identical with corresponding spectra of **3a**.

1,3,5,7-Tetraphenyl-4-(2-chlorophenyl)-bis-pyrazolo[3,4-b,4',3'-e]pyridine (4b). A light-yellow powder, 52% yield (147 mg); m.p. 253–254°C (Lit. 251–253°C [18b]); ^{1}H-NMR ($CDCl_3$): $\delta = 6.78$–6.83 (m, 1H), 6.89–6.95 (m, 2H), 7.00–7.06 (m, 5H), 7.13–7.18 (m, 6H), 7.33–7.38 (m, 2H), 7.57–7.62 (m, 4H); ^{13}C-NMR ($CDCl_3$): $\delta = 112.7$, 120.8, 125.7, 125.8, 127.4, 127.8, 128.8, 129.0, 129.1, 129.9, 131.2, 132.3, 133.1, 133.3, 138.3, 139.6, 147.8, 150.6. *Anal.* Calcd for $C_{37}H_{24}ClN_5$: C 77.41, H 4.21, N 12.20. Found: C 77.30, H 4.25, N 12.15.

Reaction of 2-bromobenzaldehyde (1c) with 1,3-diphenyl-1*H*-pyrazol-5-amine 2a. Reaction was performed according to the general procedure with 1 mmol of **1c** and **2a** (60 min):

1,3-Diphenyl-1H-pyrazolo[3,4-b]quinoline (3c, identical with 3a). Yellow crystals, 2% yield (6 mg). ^{1}H-NMR was identical with corresponding spectra of **3a**.

1,3,5,7-Tetraphenyl-4-(2-bromophenyl)-bis-pyrazolo[3,4-b,4',3'-e]pyridine (4c). A light-yellow powder, 45% yield (140 mg); m.p. 246–247°C (Lit. 242–243°C [18b]); ^{1}H-NMR ($CDCl_3$): $\delta = 6.83$–6.97 (m, 3H), 7.01–7.06 (m, 4H), 7.12–7.19 (m, 7H), 7.32–7.38 (m, 2H), 7.56–7.62 (m, 4H), 8.54–8.57 (m, 4H); ^{13}C-NMR ($CDCl_3$): $\delta = 112.6$, 120.8, 123.4, 125.7, 126.3, 127.3, 127.8, 129.0, 129.2, 129.9, 131.3, 132.0, 132.3, 135.0, 139.6, 139.8, 147.8, 150.6. *Anal.* Calcd for $C_{37}H_{24}BrN_5$: C 71.85, H 3.91, N 11.32. Found: C 71.49, H 3.93, N 11.20.

Reaction of 2-iodobenzaldehyde (1d) with 1,3-diphenyl-1*H*-pyrazol-5-amine 2a. Reaction was performed according to the general procedure with 1 mmol of **1d** and **2a** (60 min). The products were separated and purified by column chromatography (silica gel, toluene/petroleum ether):

1,3-Diphenyl-1H-pyrazolo[3,4-b]quinoline (3d, identical with 3a). Yellow crystals, 1.5% yield (5 mg). ^{1}H-NMR was identical with corresponding spectra of **3a**.

1,3,5,7-Tetraphenyl-4-(2-iodophenyl)-bis-pyrazolo[3,4-b,4',3'-e]pyridine (4d). The fraction obtained from column was crystallized from toluene; a light-yellow crystalline powder, 37% yield (124 mg); m.p. 237–239°C; ^{1}H-NMR ($CDCl_3$): $\delta = 6.77$ (ddd, $J = 8.0$, 6.7, 2.3 Hz, 1H), 6.90–6.94 (m, 2H), 7.02–7.05 (m, 4H), 7.15 (br t, $J = 7.5$ Hz, 2H), 7.17–7.20 (m, 4H), 7.15 (br t, $J = 7.4$ Hz, 2H), 7.42 (ddd, $J = 8.1$, 1.0, 0.5 Hz, 1H), 7.58–7.61 (m, 4H), 8.56–8.58 (m, 4H); ^{13}C-NMR ($CDCl_3$): $\delta = 99.2$, 112.4, 120.8, 125.7, 127.1, 127.3, 127.8, 129.0, 129.4, 129.6, 130.7, 132.3, 138.5, 138.8, 139.6, 142.6, 147.8, 150.7. *Anal.* Calcd for $C_{37}H_{24}IN_5$: C 66.77, H 3.63, N 10.52. Found: C 66.80, H 3.70, N 10.11.

Reaction of 2,6-difluorobenzaldehyde (1e) with 1,3-diphenyl-1*H*-pyrazol-5-amine 2a. Reaction was performed according to the general procedure with 10 mmol of **1e** and **2a** (20 min):

5-Fluoro-1,3-diphenyl-1H-pyrazolo[3,4-b]quinoline (3e). The product was isolated and purified by column chromatography (silica gel, toluene/petroleum ether) followed by crystallization from toluene; yellow fluorescent needles, 65% yield (2206 mg); m.p. 210–211°C; ^{1}H-NMR ($CDCl_3$): $\delta = 7.14$ (ddd, $J = 10.1$, 7.6, 1.0 Hz, 1H), 7.30–7.36 (m, 1H), 7.49–7.63 (m, 5H), 7.69 (ddd, $J = 8.8$, 7.6, 6.2 Hz, 1H), 7.97 (d, $J = 9.7$ Hz, 1H), 8.14–8.17 (m, 2H), 8.56–8.59 (m, 2H), 9.17 (d, $J = 0.8$ Hz, 1H); ^{13}C-NMR ($CDCl_3$): $\delta = 107.3$ (d, $J_{C-F} = 19.4$ Hz), 116.1 (d, $J_{C-F} = 17.2$ Hz), 116.3 (d, $J_{C-F} = 1.8$ Hz), 120.8, 124.7 (d, $J_{C-F} = 13.2$ Hz), 124.7 (d, $J_{C-F} = 3.7$ Hz), 125.6, 127.5, 129.0, 129.1, 129.2, 130.2 (d, $J_{C-F} = 9.5$ Hz), 132.2, 139.7, 144.9, 148.7 (d, $J_{C-F} = 2.8$ Hz), 150.9, 159.0 (d, $J_{C-F} = 251.3$ Hz). *Anal.* Calcd for $C_{22}H_{14}FN_3$: C 77.86, H 4.16, N 12.38. Found: C 78.14, H 4.00, N 12.32.

1,3,5,7-Tetraphenyl-4-(2,6-difluorophenyl)-bis-pyrazolo[3,4-b,4',3'-e]pyridine (4e). The product was isolated from the residues of **3e** purification, separated from **3e** and purified by Chromatotron (silica gel, toluene/petroleum ether), using a special technique that will be published at a later date, a light-yellow solid, 2.5% yield (43 mg); m.p. 250–252°C; ^{1}H-NMR ($CDCl_3$): $\delta = 6.38$–6.41 (m, 2H), 7.00–7.05 (m, 1H), 7.08–7.10 (m, 4H), 7.17–7.20 (m, 2H), 7.23–7.25 (m, 4H), 7.34–7.36 (m, 2H), 7.54–7.60 (m, 4H), 8.53–8.54 (m, 4H); ^{13}C-NMR ($CDCl_3$): $\delta = 110.6$ (dd, $J_{C-F} = 21.1$, 4.2 Hz), 111.6 (t, $J_{C-F} = 20.3$ Hz), 113.2, 120.9, 125.8, 127.5, 128.1, 128.9, 129.0, 131.2 (t, $J_{C-F} = 10.0$ Hz), 131.9, 139.5, 147.6, 150.5, 159.2 (dd, $J_{C-F} = 249.4$, 6.4 Hz). *Anal.* Calcd for $C_{37}H_{23}F_2N_5$: C 77.20, H 4.03, N 12.17. Found: C 76.80, H 4.22, N 11.82.

Reaction of 2-chloro-6-fluorobenzaldehyde (1f) with 1,3-diphenyl-1*H*-pyrazol-5-amine 2a. Reaction was performed according to the general procedure with 2.2 mmol of **1f** and **2a** (40 min):

5-Chloro-1,3-diphenyl-1H-pyrazolo[3,4-b]quinoline (3f). The Chromatotron purification was followed by crystallization from toluene; yellow, fluorescent needles, 57% yield (423 mg); m.p. 221–222°C; ^{1}H-NMR ($CDCl_3$): $\delta = 7.33$ (tt, $J = 7.4$, 1.2 Hz, 1H), 7.51–7.54 (m, 1H), 7.57–7.63 (m, 5H), 7.67 (dd, $J = 8.7$, 7.3 Hz, 1H), 8.11 (dt, $J = 8.7$, 1.0 Hz, 1H), 8.16–8.18 (m, 2H), 8.57–8.60 (m, 2H), 9.33 (d, $J = 0.9$ Hz, 1H); ^{13}C-NMR ($CDCl_3$): $\delta = 117.0$, 120.7, 122.9, 124.4, 125.6, 127.6, 128.2, 128.3, 129.1, 129.16, 129.22, 130.2, 132.3, 132.5, 139.7, 144.9, 148.7, 150.8. *Anal.* Calcd for $C_{22}H_{14}ClN_3$: C 74.26, H 3.97, N 11.81. Found C 74.08, H 4.04, N 11.59.

1,3,5,7-Tetraphenyl-4-(2-chloro-6-fluorophenyl)-bis-pyrazolo[3,4-b,4',3'-e]pyridine (4f). Light-yellow needles, 9% yield (67 mg); m.p. 252°C; ^{1}H-NMR ($CDCl_3$): $\delta = 6.53$ (td, $J = 8.5$, 1.0 Hz, 1H), 6.76 (dt, $J = 8.2$, 1.0 Hz, 1H), 6.80 (td, $J = 8.3$, 6.0 Hz, 1H), 7.06–7.09 (m, 4H), 7.16–7.18 (m, 2H), 7.22–7.25 (m, 4H), 7.36 (tt, $J = 7.4$, 1.1 Hz, 2H), 7.58–7.61 (m, 4H), 8.54–8.56 (m, 4H); ^{13}C-NMR ($CDCl_3$): $\delta = 113.0$, 113.2 (d, $J_{C-F} = 22.0$ Hz), 120.8, 121.9 (d, $J_{C-F} = 19.4$ Hz), 124.6 (d, $J_{C-F} = 3.1$ Hz), 125.7, 127.4, 128.1, 128.9, 129.0, 130.9 (d, $J_{C-F} = 9.4$ Hz), 131.3, 131.9, 134.2 (d, $J_{C-F} = 4.1$ Hz), 139.6, 147.7, 150.6, 159.5 (d, $J_{C-F} = 249.1$ Hz). *Anal.* Calcd for $C_{37}H_{23}ClFN_5$: C 75.06, H 3.92, N 11.83. Found C 74.68, H 3.95, N 11.71.

Reaction of 2,6-dichlorobenzaldehyde (1g) with 1,3-diphenyl-1*H*-pyrazol-5-amine (2a). Reaction was performed according to the general procedure with 2 mmol of **1g** and **2a** (60 min):

5-Chloro-1,3-diphenyl-1H-pyrazolo[3,4-b]quinoline (3g, identical with 3f). Yellow needles, 22% yield (155 mg); m.p. 220–221°C; ^{1}H-NMR and ^{13}C-NMR were identical with corresponding spectra of **1f**.

1,3,5,7-Tetraphenyl-4-(2,6-dichlorophenyl)-bis-pyrazolo[3,4-b,4',3'-e]pyridine (4g). A light-yellow powder, 38% yield (230 mg); m.p. 252–255°C; ^{1}H-NMR ($CDCl_3$): $\delta = 6.88$ (d, $J = 9.4$ Hz, 1H), 6.88 (d, $J = 6.4$ Hz, 1H), 6.92 (dd, $J = 6.4$, 9.4 Hz, 1H), 7.06–7.08 (m, 4H), 7.16 (tt, $J = 7.5$, 1.3 Hz, 2H), 7.24–7.25 (m, 4H), 7.35 (tt, $J = 7.4$, 1.2 Hz, 2H), 7.58–7.61 (m, 4H), 8.55–8.57 (m, 4H); ^{13}C-NMR ($CDCl_3$): $\delta = 112.5$, 120.8, 125.7, 127.2, 127.3, 128.0, 128.9, 129.0, 130.3, 131.9, 132.1, 134.5, 135.0, 139.6, 147.7, 150.7 ppm. *Anal.* Calcd for $C_{37}H_{23}Cl_2N_5$: C 73.03, H 3.81, N 11.51. Found: C 73.20, H 3.72, N 11.31.

Reaction of 2-fluoro-6-iodobenzaldehyde (1h) with 1,3-diphenyl-1*H*-pyrazol-5-amine 2a. Reaction was performed according to the general procedure with 1 mmol of **1h** and **2a** (30 min):

5-Iodo-1,3-diphenyl-1H-pyrazolo[3,4-b]quinoline (3h). The Chromatotron purification was followed by crystallization from toluene; deep-yellow needles, 68% yield (231 mg); m.p. 200–202°C; ^{1}H-NMR ($CDCl_3$): $\delta = 7.33$ (tt, $J = 7.4$, 1.2 Hz, 1H), 7.45 (dd, $J = 8.6$, 7.1 Hz, 1H), 7.52–7.55 (m, 1H), 7.56–7.59 (m, 2H), 7.62–7.64 (m, 2H), 7.35 (dd, $J = 7.1$, 1.1 Hz, 1H), 8.16–8.19 (m, 3H), 8.58–8.60 (m, 2H), 8.54 (d, $J = 0.8$ Hz, 1H); ^{13}C-NMR ($CDCl_3$): $\delta = 99.9$, 117.7, 120.6, 125.6, 126.4, 127.6, 129.1, 129.20, 129.22, 130.1, 131.4, 132.3, 135.9, 136.0, 139.7, 144.8, 148.4, 151.1. *Anal.* Calcd for $C_{22}H_{14}IN_3$: C 59.08, H 3.15, N 9.39. Found C 59.06, H 3.21, N 9.39.

1,3,5,7-Tetraphenyl-4-(2-fluoro-6-iodophenyl)-bis-pyrazolo[3,4-b,4',3'-e]pyridine (4h). A light-yellow powder, 9% yield (30 mg); m.p. 245–246°C; ^{1}H-NMR ($CDCl_3$): $\delta = 6.62$ (td, $J = 8.6$, 1.0 Hz, 1H), 6.75 (td, $J = 8.2$, 5.7 Hz, 1H), 7.06–7.09 (m, 4H), 7.15–7.18 (m, 2H), 7.22 (d, $J = 7.9$ Hz, 1H), 7.24–7.26 (m, 4H), 7.36 (tt, $J = 7.4$, 1.2 Hz, 2H), 7.58–7.61 (m, 4H), 8.56–8.57 (m, 4H); ^{13}C-NMR ($CDCl_3$): $\delta = 99.6$, 112.6, 114.5 (d, $J_{C-F} = 22.1$ Hz), 120.8, 125.7, 127.2 (d, $J_{C-F} = 18.1$ Hz), 127.4, 128.0, 129.0, 129.2, 131.5 (d, $J_{C-F} = 8.6$ Hz), 131.9, 134.2 (d, $J_{C-F} = 3.3$ Hz), 136.1, 139.6, 147.6, 150.6, 158.7 (d, $J_{C-F} = 250.5$ Hz). *Anal.* Calcd for $C_{37}H_{23}FIN_5$: C 65.02, H 3.39, N 10.25. Found: C 64.95, H 3.53, N 10.08.

Reaction of 2,4-difluorobenzaldehyde (1i) with 1,3-diphenyl-1*H*-pyrazol-5-amine (2a). Reaction was performed according to the general procedure with 1 mmol of **1i** and **2a** (60 min):

7-Fluoro-1,3-diphenyl-1H-pyrazolo[3,4-b]quinoline (3i). A yellow solid, 49% yield (165 mg); m.p. 197–198°C; ^{1}H-NMR ($CDCl_3$): $\delta = 7.29$ (ddd, $J = 9.1$, 7.9, 2.5 Hz, 1H), 7.32 (tt, $J = 7.4$, 1.2 Hz, 1H), 7.49–7.52 (m, 1H), 7.56–7.60 (m, 4H), 7.78 (dd, $J = 10.6$, 1.3 Hz, 1H), 7.98 (dd, $J = 9.1$, 6.2 Hz, 1H), 8.11–8.13 (m, 2H), 8.56–8.57 (m, 2H), 9.17 (d, $J = 0.6$ Hz, 2H); ^{13}C-NMR ($CDCl_3$): $\delta = 112.0$ (d, $J = 20.8$ Hz), 115.8 (d, $J_{C-F} = 26.6$ Hz), 116.2 (d, $J_{C-F} = 2.3$ Hz), 120.7, 121.0, 125.6, 127.5, 129.0, 129.1, 129.2, 131.1, 131.3 (d, $J_{C-F} = 10.6$ Hz), 132.5, 139.8, 144.7, 149.2 (d, $J_{C-F} = 13.6$ Hz), 151.3, 164.2 (d, $J_{C-F} = 252.3$ Hz). *Anal.* Calcd for $C_{22}H_{14}FN_3$: C 77.86, H 4.16, N 12.38. Found: C 77.90, H 4.25, N 12.30.

1,3,5,7-Tetraphenyl-4-(2,4-difluorophenyl)-bis-pyrazolo[3,4-b,4',3'-e]pyridine (4i). Light-yellow crystals, 7% yield (20.5 mg); m.p. 236–238°C; ^{1}H-NMR ($CDCl_3$): $\delta = 6.30$ (td, $J = 9.2$, 2.4 Hz, 1H), 6.37 (td, $J = 8.2$, 2.3 Hz, 1H), 6.77 (td, $J = 8.2$, 6.4 Hz, 1H), 7.10–7.12 (m, 4H), 7.16–7.18 (m, 4H), 7.21–7.24 (m, 2H), 7.35 (tt, $J = 7.4$, 1.2 Hz, 2H), 7.57–7.60 (m, 4H), 8.52–8.53 (m, 4H) ppm; ^{13}C-NMR ($CDCl_3$): $\delta = 103.3$ (t, $J_{C-F} = 25.5$ Hz), 110.5 (dd, $J_{C-F} = 21.6$, 3.5 Hz), 113.0, 117.9 (dd, $J_{C-F} = 16.2$, 3.9 Hz), 120.8, 125.8, 127.5, 128.1, 129.0, 129.1, 132.0 (dd, $J_{C-F} = 9.9$, 4.0 Hz), 132.2, 133.8, 139.5, 147.5, 150.5, 159.2 (dd, $J_{C-F} = 250.1$, 12.4 Hz), 163.5 (dd, $J_{C-F} = 251.6$, 11.6 Hz). *Anal.* Calcd for $C_{37}H_{23}F_2N_5$: C 77.20, H 4.03, N 12.17. Found: C 77.38, H 4.13, N 12.10.

Reaction of 2,4-dichlorobenzaldehyde (1j) with 1,3-diphenyl-1*H*-pyrazol-5-amine (2a). Reaction was performed according to the general procedure with 2 mmol of **1j** and **2a** (60 min):

7-Chloro-1,3-diphenyl-1H-pyrazolo[3,4-b]quinoline (3j). A yellow crystalline powder, 6% yield (40 mg); m.p. 201–202°C; ^{1}H-NMR ($CDCl_3$): $\delta = 7.33$ (tt, $J = 7.4$, 1.1 Hz, 1H), 7.44 (dd, $J = 8.8$, 2.1 Hz, 1H), 7.50–7.52 (m, 1H), 7.56–7.61 (m, 4H), 7.93 (d, $J = 8.8$ Hz, 1H), 8.12–8.13 (m, 2H), 8.20 (d, $J = 1.9$ Hz, 1H), 8.56–8.58 (m, 2H), 8.87 (s, 1H); ^{13}C-NMR ($CDCl_3$): $\delta = 116.6$, 120.7, 123.0, 125.6, 125.7, 127.5, 127.7, 129.0, 129.1, 129.2, 130.3, 130.9, 132.3, 136.9, 139.7, 144.7, 148.3, 151.1. *Anal.* Calcd for $C_{22}H_{14}ClN_3$: C 74.26, H 3.97, N 11.81. Found: C 73.89, H 4.30, N 11.41.

1,3,5,7-Tetraphenyl-4-(2,4-dichlorophenyl)-bis-pyrazolo[3,4-b,4',3'-e]pyridine (4j). Light-yellow crystals, 49% yield (300 mg); m.p. 215°C; ^{1}H-NMR ($CDCl_3$): $\delta = 6.77$ (dd, $J = 8.1$, 1.9 Hz, 1H), 6.80 (d, $J = 8.1$ Hz, 1H), 6.94 (d, $J = 1.8$ Hz, 1H), 7.08–7.11 (m, 4H), 7.15–7.17 (m, 4H), 7.21–7.24 (m, 2H), 7.35 (tt, $J = 7.4$, 1.1 Hz, 2H), 7.57–7.60 (m, 4H), 8.53–8.54 (m, 4H); ^{13}C-NMR ($CDCl_3$): $\delta = 112.8$, 120.9, 125.8, 126.1, 127.5, 128.1, 128.7, 129.1, 129.2, 131.7, 131.9, 132.2, 134.1, 135.4, 136.9, 139.6, 147.6, 150.6 ppm. *Anal.* Calcd for $C_{37}H_{23}Cl_2N_5$: C 73.03, H 3.81, N 11.51. Found: C 72.75, H 3.89, N 11.44.

Reaction of 2,3,4,5,6-pentafluorobenzaldehyde (1k) with 1,3-diphenyl-1*H*-pyrazol-5-amine (2a). Reaction was performed according to the general procedure with 0.5 mmol of **1k** and **2a** (10 min):

5,6,7,8-Tetrafluoro-1,3-diphenyl-1H-pyrazolo[3,4-b]quinoline (3k). The product was purified by crystallization from toluene, yellow crystals with greenish fluorescence, 84% yield (165 mg); m.p. 210–210.5°C (Lit. 207–208°C [15]); ^{1}H-NMR ($CDCl_3$): $\delta = 7.30$ (br t, $J = 7.4$, 1H), 7.52–7.61 (m, 5H), 8.06–8.07 (m, 2H), 8.51–8.53 (m, 2H), 9.04 (s, 1H). ^{13}C-NMR ($CDCl_3$): $\delta = 112.2$ (d, $J_{C-F} = 14.4$ Hz), 116.8 (br s), 120.2, 124.5–124.6 (m), 125.9, 127.4, 129.1, 129.2, 129.6, 131.5, ~134.3 (br d, $J_{C-F} = 10.9$ Hz), 136.1 (dt, $J_{C-F} = 252.2$, ~15.5 Hz), 139.2, ~141.7 (d × m, $J_{C-F} = \sim 250$ Hz, 3 × CF), 144.6, 150.2. *Anal.* Calcd for $C_{22}H_{11}F_4N_3$: C 66.84, H 3.31, N 10.63. Found: C 66.95, H 3.25, N 10.85.

Reaction of 2-fluoro-5-nitrobenzaldehyde (1l) with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (2b). Reaction was performed according to the general procedure with 5 mmol of **1l** and **2b** (20 min). **1l** was prepared by nitration of 2-fluorobenzaldehyde using the method described for 2-bromobenzaldehyde [29]; 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, **2b**, was prepared from 3-aminocrotononitrile and phenylhydrazine by the known procedure [27]. Most of the product was isolated by treating the solid obtained from the reaction mixture with chloroform (**3l** is weakly soluble), and the solid was filtered off. The remaining solution, still containing part of **3l** and impurities, was flashed through Al_2O_3, and then the product was separated by column chromatography (Al_2O_3, toluene). All collected portions of **3l** were combined and crystallized from DMF.

6-Nitro-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]quinoline (3l). Deep-yellow crystals, 56% yield (850 mg); m.p. 259–260°C (Lit. 260–263°C [10b]); ^{1}H-NMR ($CDCl_3$): $\delta = 2.81$ (s, 3H), 7.33 (tt, $J = 7.4$, 1.2 Hz, 1H), 7.56–7.59 (m, 2H), 8.25 (dt, $J = 9.4$, 0.7 Hz, 1H), 8.44–8.45 (m, 2H), 8.51 (dd, $J = 9.4$, 2.6 Hz, 1H), 8.76 (br s, 1H), 9.00 (d, $J = 2.5$ Hz, 1H); ^{13}C-NMR ($CDCl_3$): $\delta = 12.8$, 119.8, 120.5, 122.1, 123.8, 125.8, 126.6, 129.2, 130.4, 132.3, 139.3, 143.6, 144.0, 150.0, 151.5. *Anal.* Calcd for $C_{17}H_{12}N_4O_2$: C 67.10, H 3.97, N 18.41. Found: C 66.80, H 3.98, N 18.11.

Reaction of 2-chloro-5-nitrobenzaldehyde (1m) with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (2a). Reaction was performed according to the general procedure with 4 mmol of **1m** and **2b** (60 min). **1m** was prepared by nitration of 2-chlorobenzaldehyde [30]. The mixture obtained after flash chromatography was dissolved in THF, mixed with Al_2O_3, and dried. Then, the products (**3m** and **4m**) adsorbed on Al_2O_3 were put on the long column filled with Al_2O_3 and eluted with toluene.

6-Nitro-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]quinoline (3m, identical with 3l). First collected fraction was identified as **3m**; a yellow crystalline powder, 6% yield (72 mg); m.p. 257–259°C. ^{1}H-NMR and ^{13}C-NMR were identical with corresponding spectra of **1l**.

3,5-Dimethyl-1,7-diphenyl-4-(2-chloro-5-nitrophenyl)-bis-pyrazolo[3,4-b,4',3'-e]pyridine (2m). The product was eluted as a second fraction from **3m** + **4m** mixture (described earlier), followed by crystallization from toluene; yellow crystals, 30% yield (295 mg); m.p. 240–241°C; ^{1}H-NMR ($CDCl_3$): $\delta = 2.11$ (s, 3H) 7.31 (br t, $J = 7.4$ Hz, 2H), 7.53–7.56 (m, 4H), 7.84 (d, $J = 8.8$ Hz, 1H), 8.38–8.41 (m, 5H), 8.43 (dd, $J = 8.8$, 2.7 Hz, 1H); ^{13}C-NMR ($CDCl_3$): $\delta = 14.2$, 112.8, 120.4, 125.4, 125.5 (two signals shifted by 0.04 ppm), 129.0, 130.8, 134.2, 135.2, 139.4, 140.3, 143.2, 146.2, 150.5. *Anal.* Calcd for $C_{27}H_{19}ClN_6O_2$: C 65.52, H 3.87, N 16.98. Found: C 65.56, H 4.03, N 16.84.

Reaction of 2-bromo-5-nitrobenzaldehyde (1n) with 3-methyl-1-phenyl-1H-pyrazol-5-amine (2b). Reaction was performed according to the general procedure with 4 mmol of **1n** and **2b** (60 min). **1n** was prepared by nitration of 2-bromobenzaldehyde [29]. The products were separated and purified by the method described for **3m** and **4m** (above):

6-Nitro-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]quinoline (3n, identical with 3l). A yellow crystalline powder, 7% yield (84 mg); m.p. 258–259°C. ^{1}H-NMR and ^{13}C-NMR were identical with corresponding spectra of **1l**.

3,5-Dimethyl-1,7-diphenyl-4-(2-bromo-5-nitrophenyl)-bis-pyrazolo[3,4-b,4',3'-e]pyridine (4n). Yellow crystals, 27% yield (291 mg); m.p. 251–252°C; ^{1}H-NMR ($CDCl_3$): $\delta = 2.10$ (s, 6H), 7.31 (tt, $J = 7.4$, 1.1 Hz, 1H), 7.53–7.56

(m, 4H), 8.03 (d, J = 8.8 Hz, 1H), 8.33 (dd, J = 8.8, 2.7 Hz, 1H), 8.38 (d, J = 2.7 Hz, 1H), 8.39–8.41 (m, 4H); ^{13}C-NMR ($CDCl_3$): δ = 14.3, 112.6, 120.3, 125.1, 125.3, 125.4, 129.0, 130.4, 134.0, 136.0, 137.4, 139.4, 143.2, 146.8, 150.5. *Anal.* Calcd for $C_{27}H_{19}BrN_6O_2$: C 60.12, H 3.55, N 15.58. Found: C 60.18, H 3.63, N 15.55.

Reaction of 2-fluoro-3-(trifluoromethyl)benzaldehyde (1o) with 1,3-diphenyl-1*H*-pyrazol-5-amine (2a). Reaction was performed according to the general procedure with 5 mmol of **1o** and **2a** (15 min):

8-(Trifluoromethyl)-1,3-diphenyl-1H-pyrazolo[3,4-b]quinoline (3o). Yellow fluorescent crystals, 52% yield (1030 mg); m.p. 183–184°C (Lit. 179–181°C [7g]); ^{1}H-NMR ($CDCl_3$): δ = 7.31 (tt, J = 7.3, 1.1 Hz, 1H), 7.49–7.52 (m, 2H), 7.56–7.60 (m, 4H), 8.12–8.17 (m, 4H), 8.74–8.75 (m, 2H), 8.92 (br s, 1H); ^{13}C-NMR ($CDCl_3$): δ = 116.9, 119.9, 122.7, 124.2 (q, J_{C-F} = 273.3 Hz, CF_3), 124.7, 125.4, 127.2 (q, J_{C-F} = 29.5 Hz), 127.5, 129.0, 129.1, 129.3, 129.6 (q, J_{C-F} = 5.4 Hz), 131.3, 132.2, 133.7, 139.8, 144.0, 144.4, 150.0. *Anal.* Calcd for $C_{23}H_{14}F_3N$: C 70.95, H 3.62, N 10.79. Found: C 70.59, H 3.64, N 10.73.

Reaction of 2-chloro-3-(trifluoromethyl)benzaldehyde (1p) with 1,3-diphenyl-1*H*-pyrazol-5-amine (2a). Reaction was performed according to the general procedure with 1 mmol of **1p** and **2b** (60 min).

8-(Trifluoromethyl)-1,3-diphenyl-1H-pyrazolo[3,4-b]quinoline (3p, identical with 3o). Yellow fluorescent crystals, 6% yield (22 mg); m.p. 182–183°C. ^{1}H-NMR and ^{13}C-NMR were identical with corresponding spectra of **3o**.

1,3,5,7-Tetraphenyl-4-[2-chloro-3-(trifluoromethyl)phenyl]-bis-pyrazolo[3,4-b,4',3'-e]pyridine (4p). A light-yellow powder, 62% yield (200 mg); m.p. 234–236°C; ^{1}H-NMR ($CDCl_3$): δ = 6.91 (t, J = 7.7 Hz, 1H), 7.02–7.06 (m, 5H), 7.13–7.17 (m, 6H), 7.36 (tt, J = 7.4, 1.1 Hz, 2H), 7.40 (dd, J = 7.9, 1.6 Hz, 1H), 7.58–7.60 (m, 4H), 8.53–8.55 (m, 4H); ^{13}C-NMR ($CDCl_3$): δ = 112.6, 120.8, 122.3 (q, J_{C-F} = 273.6 Hz), 125.7, 125.8, 127.4 (q, J_{C-F} = 5.4 Hz), 127.5, 128.1, 128.7 (q, J_{C-F} = 31.4 Hz), 129.0, 129.1, 131.4 (broad signal), 131.9, 134.1, 135.6, 136.7, 139.5, 147.5, 150.5. *Anal.* Calcd for $C_{38}H_{23}ClF_3N_5$: C 71.08, H 3.61, N 10.91. Found C 71.01, H 3.81, N 10.77.

Reaction of 2-chloro-5-(trifluoromethyl)benzaldehyde (1q) with 1,3-diphenyl-1*H*-pyrazol-5-amine (2a). Reaction was performed according to the general procedure with 1 mmol of **1q** and **2b** (60 min):

6-(Trifluoromethyl)-1,3-diphenyl-1H-pyrazolo[3,4-b]quinoline (3q). A deep-yellow powder, 3% yield (11 mg); m.p. 176–177°C; ^{1}H-NMR ($CDCl_3$): δ = 7.35 (tt, J = 7.4, 1.1 Hz, 1H), 7.51–7.54 (m, 1H), 7.57–7.62 (m, 4H), 7.92 (dd, J = 9.0, 2.1 Hz, 1H), 8.13–8.14 (m, 2H), 8.27 (d, J = 9.0 Hz, 1H), 8.35 (br s, 1H), 8.56–8.57 (m, 2H), 9.00 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ = 117.3, 120.8, 123.2, 124.1 (q, J_{C-F} = 272.0 Hz), 125.8, 126.2 (q, J_{C-F} = 2.8 Hz), 126.3 (q, J_{C-F} = 32.6 Hz), 127.4 (q, J_{C-F} = 4.6 Hz), 127.5, 129.1, 129.2, 129.4, 130.1, 132.1, 132.2, 139.5, 144.8, 148.8, 151.5. *Anal.* Calcd for $C_{23}H_{14}F_3N_3$: C 70.95, H 3.62, N 10.79. Found: C 70.79, H 3.68, N 10.72.

1,3,5,7-Tetraphenyl-4-[2-chloro-5-(trifluoromethyl)phenyl]-bis-pyrazolo[3,4-b,4',3'-e]pyridine (4q). A light-yellow powder, 40% yield (130 mg); m.p. 260–261°C; ^{1}H-NMR ($CDCl_3$): δ = 7.03–7.06 (m, 5H), 7.12–7.17 (m, 6H), 7.18 (br d, J = 1.9 Hz, 1H), 7.25 (dd, J = 8.4, 1.9 Hz, 1H, partially overlapped with $CHCl_3$ signal), 7.36 (tt, J = 7.4, 1.2 Hz, 2H), 7.58–7.61 (m, 4H), 8.53–8.54 (m, 4H); ^{13}C-NMR ($CDCl_3$): δ = 112.5, 120.3, 123.0 (q, J_{C-F} = 272.5 Hz), 125.8, 126.4 (q, J_{C-F} = 3.6 Hz), 127.5, 128.1, 128.2 (q, J_{C-F} = 3.8 Hz), 128.6 (q, J_{C-F} = 33.4 Hz), 129.0, 129.1, 129.4, 131.8, 133.6, 136.1, 136.9 (br d, J_{C-F} = 1.3 Hz), 139.4, 147.4, 150.5. *Anal.* Calcd for $C_{38}H_{23}ClF_3N_5$: C 71.08, H 3.61, N 10.91, O 5.17. Found: C 70.93, H 3.67, N 10.81.

General procedure for the reaction of 2-fluorobenzaldehyde (1a) with 1*H*-pyrazol-5-amines (2b–e). 1-Methyl-3-phenyl-1*H*-pyrazol-5-amine (**2c**) was prepared from methylhydrazine and benzoylacetonitrile by the known procedure [27]. 1,3-Dimethyl-1*H*-pyrazol-5-amine (**2d**) was prepared from 3-aminocrotononitrile and methylhydrazine by the known procedure [27]. 3-*tert*-Butyl-1-phenyl-1*H*-pyrazol-5-amine (**2e**) was prepared from phenylhydrazine and 4,4-dimethyl-3-oxopentanenitrile, applying the known procedure [27]. The equimolecular mixture (1 mmol) of **1a**, corresponding 1*H*-pyrazol-5-amine (**2**) and 2,4,6-trimethylpyridine (90mol%), was prepared. The mixture was slowly heated on Wood's alloy bath until it reached 180°C and then maintained for 45–70 min (monitored by TLC). After that, the mixture was cooled to room temperature. Brown oil was dissolved in chloroform and flashed through the aluminum oxide 90. Crude product was purified by the methods described in General Procedure for the Reaction of Benzaldehydes with 1,3-diphenyl-1*H*-pyrazol-5-amine (**2a**) section.

Reaction of 2-fluorobenzaldehyde (1a) with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (2b). Reaction was performed according to the general procedure with 1 mmol of **1a** and **2b** (60 min). For Chromatotron separation and purification, toluene/petroleum ether mixture was used as a solvent (elution of **3r**) followed by pure toluene (elution of **4r**).

3-Methyl-1-phenyl-1H-pyrazolo[3,4-b]quinoline (3r). A yellow crystalline powder, 38% yield (98 mg); m.p. 97–98°C (Lit. 88–90°C [12]); ^{1}H-NMR ($CDCl_3$): δ = 2.74 (s, 3H), 7.26 (tt, J = 7.4, 1.2 Hz, 1H), 7.46 (ddd, J = 8.0, 6.6, 1.2 Hz, 1H), 7.53–7.56 (m, 2H), 7.75 (ddd, J = 8.3, 6.7, 1.5 Hz, 1H), 7.95 (br d, J = 8.2 Hz, 1H), 8.15 (d, J = 8.6 Hz, 1H), 8.49–8.51 (m, 3H); ^{13}C-NMR ($CDCl_3$) δ = 12.8, 118.3, 120.0, 124.0, 124.1, 124.8, 128.8, 129.0 (two slightly shifted signals), 129.6, 130.6, 140.0, 143.3,

148.3, 150.4. *Anal.* Calcd for $C_{17}H_{13}N_3$: C 78.74, H 5.05, N 16.21. Found: C 78.57, H 4.99, N 16.37.

3,5-Dimethyl-1,7-diphenyl-4-(2-fluorophenyl)-bis-pyrazolo[3,4-b,4',3'-e]pyridine (4r). A yellowish crystalline powder, 18% yield (38.5 mg); m.p. 253–255°C (Lit. 265–266°C [20]); ^{1}H-NMR ($CDCl_3$): δ = 2.17 (s, 6H), 7.28–7.34 (m, 3H), 7.36 (td, J = 7.5, 1.0 Hz, 1H), 7.44 (td, J = 7.3, 1.8 Hz, 1), 7.53–7.56 (m, 4H), 7.58–7.61 (m, 1H), 8.40–8.42 (m, 4H); ^{13}C-NMR ($CDCl_3$): δ = 14.2, 113.7, 115.9 (d, J_{C-F} = 21.2 Hz), 120.3, 121.9 (d, J_{C-F} = 16.9 Hz), 124.0 (d, J_{C-F} = 3.7 Hz), 125.2, 128.9, 131.2 (d, J_{C-F} = 2.3 Hz), 131.4 (d, J_{C-F} = 7.8 Hz), 134.3, 139.6, 144.1, 150.5, 159.5 (d, J_{C-F} = 247.1 Hz). *Anal.* Calcd for $C_{27}H_{20}FN_5$: C 74.81, H 4.65, N 16.16. Found: C 74.51, H 4.61, N 15.94.

Reaction of 2-fluorobenzaldehyde (1a) with 1-methyl-3-phenyl-1*H*-pyrazol-5-amine (2c). Reaction was performed according to the general procedure with 1 mmol of **1a** and **2c** (60 min). For Chromatotron separation and purification, toluene was used as a solvent (elution of **3s**) followed by toluene/ethyl acetate mixture (elution of **4s**).

1-Methyl-3-phenyl-1H-pyrazolo[3,4-b]quinoline (3s). A yellow, cotton-wool-like solid, 43% yield (110 mg); m.p. 146–147°C (Lit. 149°C [28]); ^{1}H-NMR ($CDCl_3$): δ = 4.29 (s, 3H), 7.43–7.46 (m, 2H), 7.54–7.57 (m, 2H), 7.76 (ddd, J = 8.7, 6.6, 1.5 Hz, 1H), 7.98 (br d, J = 8.2 Hz, 1H), 8.05–8.07 (m, 2H), 8.12 (br d, J = 8.7 Hz, 1H), 8.85 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 34.1, 115.0, 123.7, 124.5, 127.1, 128.3, 128.6, 129.1, 129.4, 130.7, 131.0, 133.1, 142.8, 148.3, 151.4. *Anal.* Calcd for $C_{17}H_{13}N_3$: C 78.74, H 5.05, N 16.21. Found: C 79.02, H 5.02, N 15.86.

1,7-Dimethyl-3,5-diphenyl-4-(2-fluorophenyl)-bis-pyrazolo[3,4-b,4',3'-e]pyridine (4s). A white powder, 5% yield (10 mg); m.p. 228–229°C; ^{1}H-NMR ($CDCl_3$): δ = 4.26 (s, 6H), 6.53 (ddd, J = 9.6, 8.3, 1.0 Hz, 1H), 6.61 (td, J = 7.5, 1.1 Hz, 1H), 6.77 (td, J = 7.3, 1.8 Hz, 1H), 7.00–7.02 (m, 4H), 7.03–7.05 (m, 1H), 7.06–7.08 (m, 4H), 7.10–7.13 (m, 2H); ^{13}C-NMR ($CDCl_3$): δ = 33.9, 110.9, 114.8 (d, J_{C-F} = 21.8 Hz), 122.3 (d, J_{C-F} = 16.0 Hz), 123.1 (d, J_{C-F} = 3.3 Hz), 127.3, 127.4, 128.9, 130.4 (d, J_{C-F} = 8.2 Hz), 131.3 (d, J_{C-F} = 2.1 Hz), 132.8, 134.4, 145.8, 151.8, 159.2 (d, J_{C-F} = 247.4 Hz). *Anal.* Calcd for $C_{27}H_{20}FN_5$: C 74.81, H 4.65, N 16.16. Found: C 74.50, H 4.60, N 16.20.

Reaction of 2-fluorobenzaldehyde (1a) with 1,3-dimethyl-1*H*-pyrazol-5-amine (2d). Reaction was performed according to the general procedure with 1 mmol of **1a** and **2** (45 min). For Chromatotron separation and purification, toluene was used as a solvent (elution of **3t**) followed by toluene/ethyl acetate mixture (elution of **4t**):

1,3-Dimethyl-1H-pyrazolo[3,4-b]quinoline (3t). Light-yellow crystals, 18% yield (35 mg); m.p. 68°C (Lit. 68°C [10a]); ^{1}H-NMR ($CDCl_3$): δ = 2.69 (s, 3H), 4.17 (s, 3H), 7.41–7.44 (m, 1H), 7.73–7.76 (m, 1H), 7.96 (br d, J = 8.2 Hz, 1H), 8.10 (br d, J = 8.7 Hz, 1H), 8.52 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 116.8, 123.3, 123.7, 128.1, 129.3, 129.7, 130.5, 141.0, 148.4, 151.1. *Anal.* Calcd for $C_{12}H_{11}N_3$: C 73.07, H 5.62, N 21.31. Found: C 73.15, H 5.55, N 21.22.

1,3,5,7-Tetramethyl-4-(2-fluorophenyl)-bis-pyrazolo[3,4-b,4',3'-e]pyridine (4t). A white powder, 22% yield (31 mg); m.p. 165–166°C; ^{1}H-NMR ($CDCl_3$): δ = 2.08 (s, 6H), 4.08 (s, 6H), 7.26–7.29 (m, 1H), 7.32 (td, J = 7.4, 0.8 Hz, 1H), 7.36 (td, J = 7.3, 1.8 Hz, 1H), 7.53–7.56 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ = 14.0, 33.4, 111.7, 115.7 (d, J_{C-F} = 21.3 Hz), 122.5 (d, J_{C-F} = 16.9 Hz), 123.8 (d, J_{C-F} = 3.6 Hz), 131.1 (d, J_{C-F} = 7.8 Hz), 131.2 (d, J_{C-F} = 2.6 Hz), 133.8, 141.8, 151.9, 159.5 (d, J_{C-F} = 246.9 Hz). *Anal.* Calcd for $C_{17}H_{16}FN_5$: C 66.01, H 5.21, N 22.64. Found: C 65.70, H 5.25, N 22.53.

Reaction of 2-fluorobenzaldehyde (1a) with 3-tert-butyl-1-phenyl-1H-pyrazol-5-amine (2e). Reaction was performed according to the general procedure with 3 mmol of **1a** and **2e** (70 min). The Chromatotron purification was followed by crystallization from methanol.

3-tert-Butyl-1-phenyl-1H-pyrazolo[3,4-b]quinoline (3u). Light-yellow needles, 52% yield (466 mg); m.p. 114°C; ^{1}H-NMR ($CDCl_3$): δ = 1.66 (s, 9H), 7.25–7.27 (m, 1H), 7.76 (ddd, J = 8.4, 6.6, 1.5 Hz, 1H), 7.53–7.56 (m, 2H), 7.76 (ddd, J = 8.7, 6.6, 1.6 Hz, 1H), 7.98 (dd, J = 8.3, 1.3 Hz, 1H), 8.16 (d, J = 8.6 Hz, 1H), 8.55–8.57 (m, 2H), 8.75 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ = 29.8, 34.7, 116.3, 120.2, 123.8, 124.0, 124.7, 128.7, 129.0, 129.1, 130.5, 131.3, 140.2, 147.8, 151.0, 153.9. *Anal.* Calcd for $C_{20}H_{19}N_3$: C 79.71, H 6.35, N 13.94. Found C 79.36, H 6.07, N 14.01.

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