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A versatile synthesis of pyrazolo[3,4-*c*]isoquinoline derivatives by reaction of 4-aryl-5-aminopyrazoles with aryl/heteroaryl aldehydes: the effect of the heterocycle on the reaction pathways

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The reaction of 4-(3,4-dimethoxyphenyl)-5-aminopyrazoles **7A–D** with aromatic and heterocyclic aldehydes in strong acidic media (trifluoroacetic or formic acid) has been studied. The initial azomethine derivatives **8** undergo cyclization similar to the Pictet–Spengler condensation to form the intermediate 4,5-dihydroisoquinolines **9** which readily dehydrogenate giving 5-aryl(heteroaryl)-pyrazolo[3,4-*c*]isoquinoline derivatives **10** as the final products. Whereas for benzaldehyde and its derivatives this one-pot synthesis presents a convenient general route to 5-aryl-pyrazolo[3,4-*c*]isoquinolines **10**, in the case of heterocyclic aldehydes the product structure varies markedly with the structure of the aldehyde used: (i) 3-pyridyl-, 3-quinolyl-, 3-thienyl-, and 1,2,3-thiadiazolyl-5-carboxaldehydes give 5-heteroarylpyrazolo[3,4-*c*]isoquinolines; (ii) 1-methylbenzimidazolyl-2-carboxaldehyde gives only intermediate azomethine **8Dh**, which does not cyclize; (iii) 1-R-3-indolylcarboxaldehydes (R = H, CH_3, CH_2Ph) eliminate the heteroaryl fragment resulting in 5-unsubstituted pyrazolo[3,4-*c*]isoquinolines **11**. Thienyl-2-carboxaldehyde reacts by both pathways (i) and (iii) depending on the reaction conditions. The single crystal X-ray structures for **10Dj, 10Cd** and **11D** provide confirmation of the different types of products formed in these reactions. Mechanisms which explain these transformations are presented.

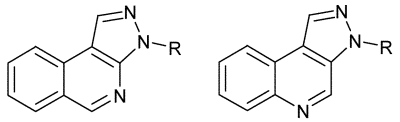
Introduction

Condensed polyazaaromatic ring systems are present in a variety of biologically active compounds (both naturally-occurring and synthetic). Although a large number of methods for their syntheses have been documented in the literature, many of them require multistep procedures using intermediates which are not readily available.[1]

Pyrazolo[3,4-*c*]isoquinolines **1** are benzannelated analogues of pyrazolo[3,4-*b*]pyridines, the chemical properties and biological activity of which have recently been extensively studied.[2] Among compounds which contain the pyrazolo-pyridine core, novel antidepressants,[3] anxyolitics,[4] and platelet aggregation inhibitors[5] have been found. Several routes to pyrazolo[3,4-*c*]-, pyrazolo[4,3-*c*]-quinoline and -isoquinoline derivatives **1**–**4**[6–8] and some other isomers (*e.g.* pyrazolo[3,4-*b*]quinolines[9] and pyrazolo[3,4-*f*]quinolines[10]) have been described in the literature. This interest stems from the wide range of biological activity of these polyazaarenes: *e.g.* as antiinflammatory, antimalarial, antiallergic, and antiviral agents,[11] acetylcholinesterase inhibitors,[12] selective serotonin re-uptake inhibitors,[13] benzodiazepine[14] and interleukin 1[11b] antagonists, as well as agents to displace specific flunitrazepam binding.[15] There are also applications in materials science: pyrazolo[3,4-*b*]quinolines,[16a,b] dipyrazolo[3,4-*b*;4′,3′-*e*]pyridines[16a,c,d] and pyrazolo[3,4-*b*]-quinoxalines[17] are efficient emitting materials for multilayer organic light emitting diodes (OLED) with bright blue electroluminescence. Additionally, some related tetrahydropyrazolo[3,4-*c*]isoquinoline **5**[18] and 4,5-dihydropyrazolo[3,4-*c*]isoquinolin-5(4*H*)-one **6**[19] derivatives are known in the literature.

Whereas the classical Pictet–Spengler reaction and its many variations are convenient routes to tetrahydroisoquinolines, sometimes with high stereoselectivity,[20–22] further dehydration into isoquinolines is not always an easy or high yielding reaction.

Recently, we found that cyclization of 5-aminopyrazoles with formaldehyde under Pictet–Spengler conditions provides exclusively 5-unsubstituted pyrazolo[3,4-*c*]isoquinolines.[23] The aromatic pyrazole ring annelated to the dihydroisoquinoline moiety makes the molecule highly reactive towards oxygen/air (particularly because of the gain in aromatisation energy), and under the reaction conditions yielded exclusively the aromatic pyrazolo[3,4-*c*]isoquinoline core.



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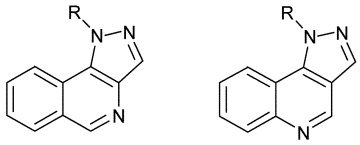

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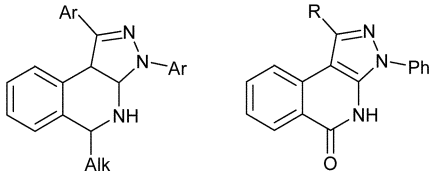

5 **6**

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In the present paper we study in detail the reaction of 4-(3,4-dimethoxyphenyl)-5-aminopyrazoles with various aromatic (benzaldehydes) and heterocyclic aldehydes (pyridine, quinoline, thiophene, indole, benzimidazole and 1,2,3-thiadiazole derivatives) and establish that different products are formed depending upon the structure of the aldehydes used. This is especially the case for heterocyclic aldehydes, for which reaction mechanisms are discussed.

Results and discussion

Synthesis

Starting aminopyrazoles **7A–D** have been prepared by reaction of the corresponding ethyl carboxylates $R^1CH_2CO_2Et$ (R^1 = Ph, Et, CH_2Ph, Me) with 3,4-dimethoxyphenylacetonitrile in the presence of sodium 2-propylate to yield α-propionyl-3,4-dimethoxyphenylacetonitrile, and further reaction of the latter with phenylhydrazine, similar to the procedures described in the literature.[8a,c,d]

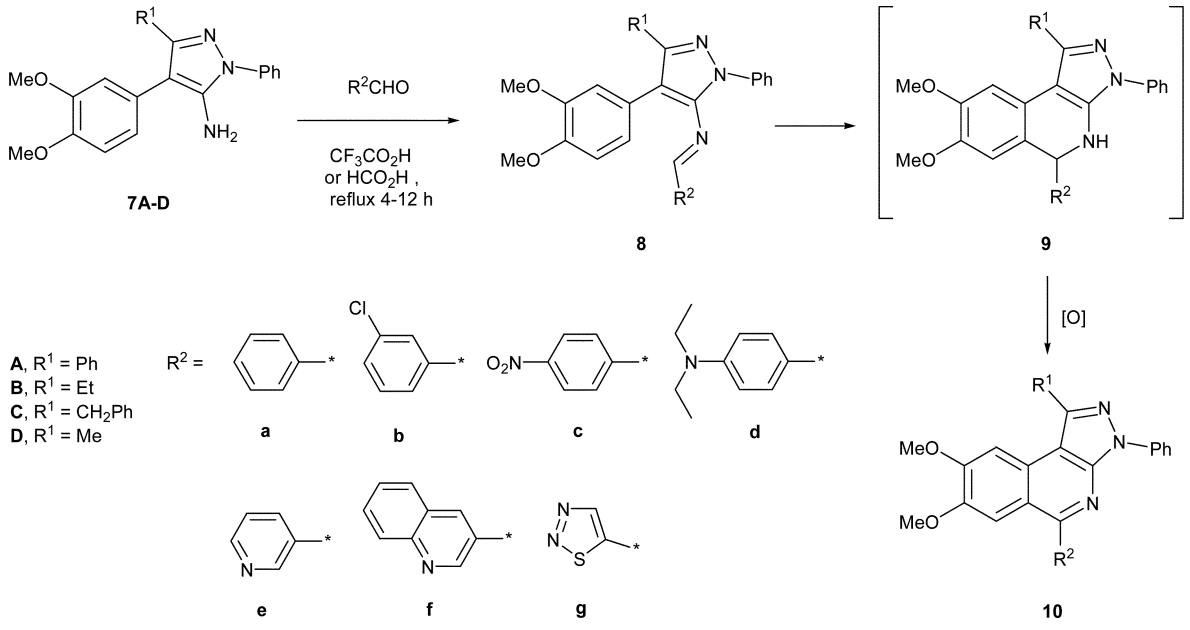
5-Aminopyrazoles **7A,C,D** reacted with aromatic aldehydes (benzaldehyde, 3-chlorobenzaldehyde, 4-nitrobenzaldehyde or 4-diethylaminobenzaldehyde) in trifluoroacetic or formic acids yielding 5-arylpyrazolo[3,4-*c*]isoquinolines **10Aa,10Cb,10Cd, 10Dc**, respectively (Scheme 1),[24] in 46–72% yields, *i.e.* the reaction followed the same course as the reaction of 5-aminopyrazoles with formaldehyde.[23] The reaction with 3-pyridyl- and 3-quinolyl-carboxaldehydes proceeded in a similar manner, yielding analogues **10e,f**, respectively.

Carrying out the reaction at reflux did not allow the isolation or detection of any intermediates in the reaction. However, ^{1}H NMR monitoring of the reaction of aminopyrazole **7D** with quinolyl-3-carboxaldehyde at 15–20 °C indicated that in the first step the azomethine derivative **8** is formed, which can be isolated in high to near-quantitative yields. Subsequent cyclization of **8** in trifluoroacetic or formic acid and oxidation of the derived 4,5-dihydropyrazolo[3,4-*c*]isoquinoline **9** results in compound **10Df**. We suggest that the limiting step in the transformation of **8** into **10** is the cyclization of azomethine **8**, because 4,5-dihydropyrazolo[3,4-*c*]isoquinolines **9** were not detected among the products nor in the reaction mixture during the reaction. Obviously, oxygen from the air is responsible for the transformation of **9** into **10** (or at least it is the main oxidant), as no other oxidants/dehydrogenating agents are present in the reaction mixture. To prove this we performed the reaction under nitrogen (starting from both aminopyrazoles **7** and azomethines **8**). Whereas under nitrogen azomethines **8** can be obtained from **7** in similar very high yields, prolonged reflux of **7** or **8** in trifluoroacetic or formic acid resulted in tars containing only trace amounts of compounds **10** (TLC evidence), and no intermediates **9** were isolated.

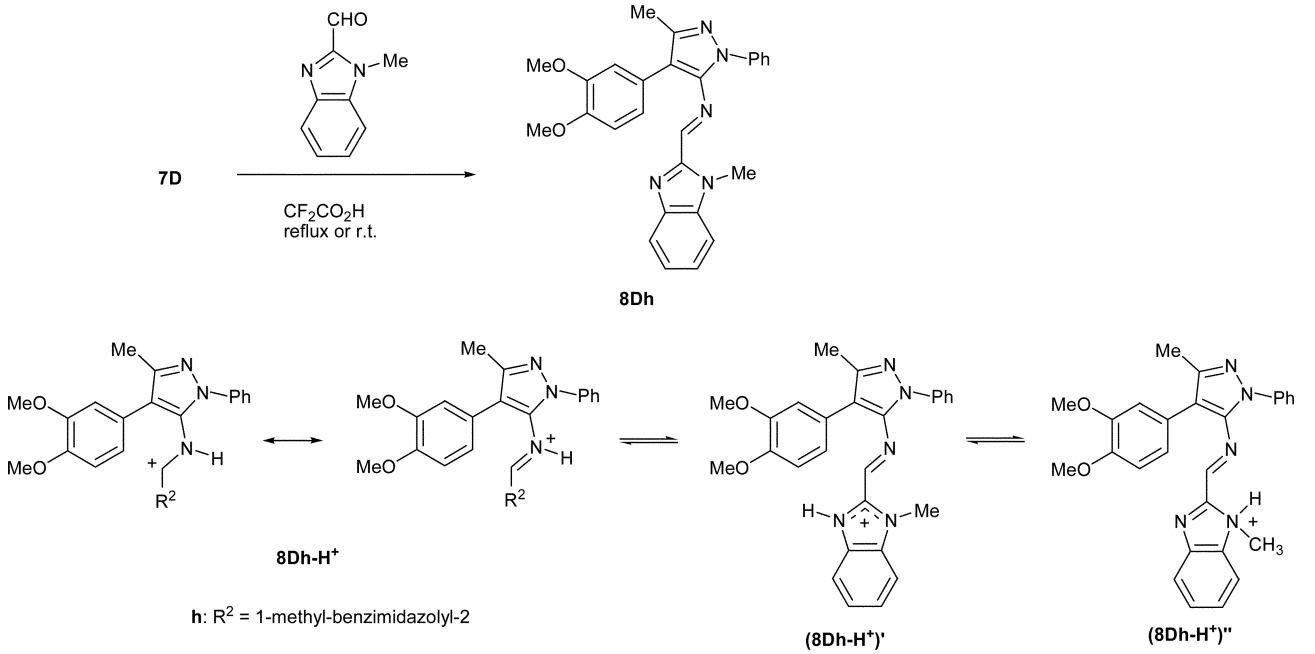
The course of the reaction of aminopyrazoles **7** with five-membered heterocyclic aldehydes depends markedly on the nature of the heterocycle. Thus, whereas reaction of **7B** with 1,2,3-thiadiazolyl-5-carboxaldehyde gave the pyrazolo[3,4-*c*]isoquinoline derivative (**10Bg**) (Scheme 1), in contrast, 1-methylbenzimidazolyl-2-carboxaldehyde resulted in azomethine **8Dh** only, which was stable under the reaction conditions (Scheme 2). A possible reason for the failure of azomethine **8Dh** to cyclize could be that protonation occurs preferentially on the imidazole ring thereby delocalizing the positive charge on the benzimidazolium fragment [(**8Dh-H**$^+$)′ and (**8Dh-H**$^+$)″] and hence decreasing the reactivity of **8Dh-H**$^+$.

The most interesting and unexpected results were obtained from the reactions of formyl derivatives of thiophene and indole. Thus, reaction of thienyl-3-carboxaldehyde with aminopyrazole **7B** resulted in pyrazolo[3,4-*c*]isoquinoline **10Bi** (76% yield) (Scheme 3). In contrast, heating aminopyrazoles **7A** or **7D** for 0.5–1 h with equimolar amounts of thienyl-2-carboxaldehyde resulted in a more complex transformation to give **11A** and **11D** in low yields. Their analytical data (^{1}H and ^{13}C NMR spectra, combined with mixed melting point data) were identical to the products obtained from aminopyrazoles **7** and paraformaldehyde,[23] *i.e.* 5-unsubstituted pyrazolo[3,4-*c*]isoquinolines **11** (Scheme 3). Incontrovertible proof of the structure of compound **11D**, synthesized according to Scheme 3, was obtained by single-crystal X-ray analysis (see below).

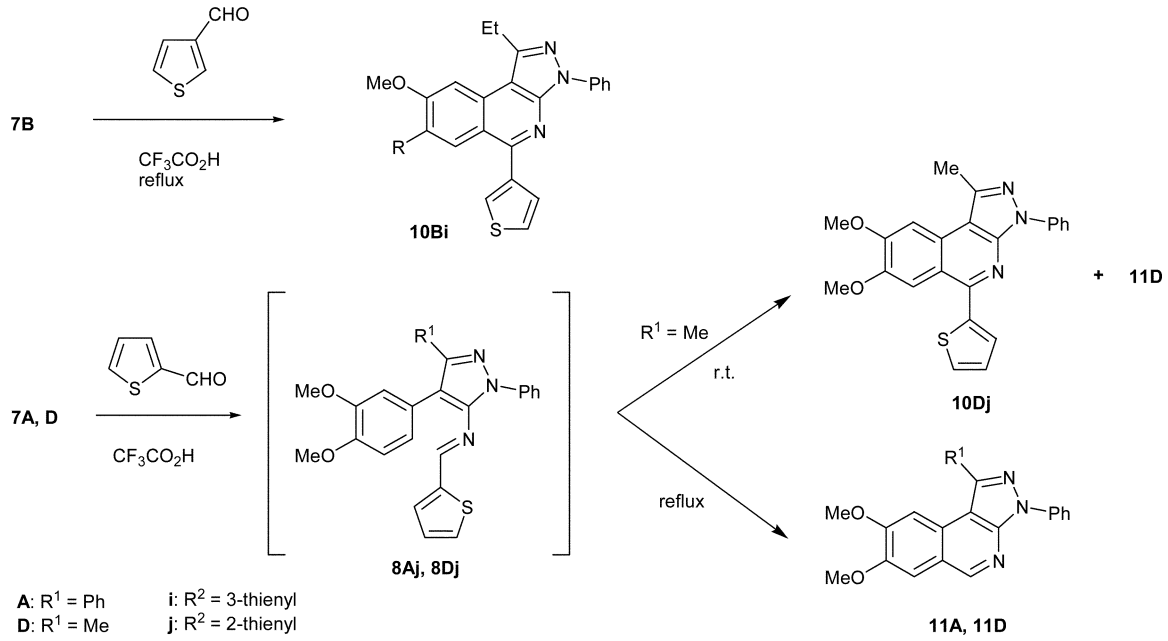
The same products **11** were isolated when 1-R-indolyl-3-carboxaldehydes (R = H, CH_3, CH_2Ph) were used in the reaction. To clarify this unusual behavior we monitored, by TLC and ^{1}H NMR, the reaction of aminopyrazole **7D** with thienyl-2-carboxaldehyde and 1-R-indolyl-3-carboxaldehydes in trifluoroacetic acid at 15–20 °C. The reactions were complete after 60–80 days. For thienyl-2-carboxaldehyde, two main products were isolated (total yield 35%), *viz.* pyrazolo[3,4-*c*]isoquinoline **11D** and 5-(2-thienyl)pyrazolo[3,4-*c*]isoquinoline **10Dj** (Scheme 3).



Scheme 1 Synthesis of pyrazolo[3,4-*c*]isoquinolines **10**.



Scheme 2 Synthesis of azomethine **8Dh** and explanation of its stabilization toward further cyclization into pyrazolo[3,4-*c*]isoquinoline.



Scheme 3 Reaction pathways of aminopyrazoles **7** with thiophene-3- and thiophene-2-aldehydes.

(The X-ray crystal structure of **10Dj** is given below). Heating compound **10Dj** in trifluoroacetic acid at reflux temperature did not give **11D**, which establishes that in the transformations **7**→**11** (and **8**→**11**) elimination of the 2-thienyl fragment occurs before the formation of the pyrazolo[3,4-*c*]isoquinoline core. The reaction conditions and yields for all the above described transformations are given in Table 1.

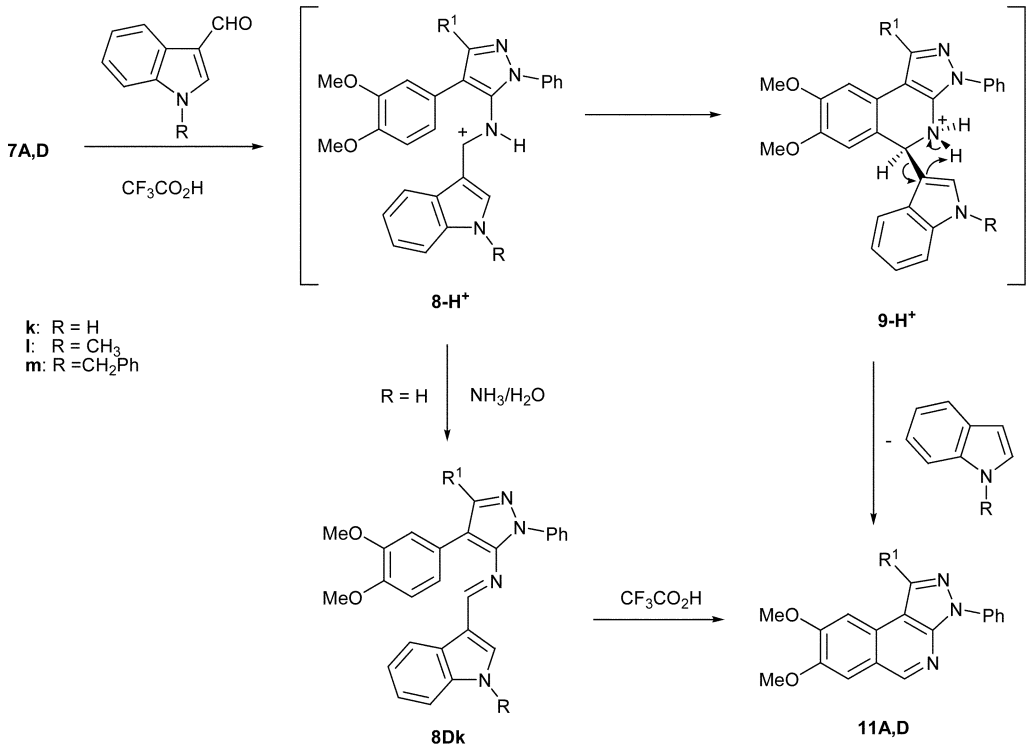
The reaction of aminopyrazole **7D** with 1-methyl- or 1-benzyl-indolyl-3-carboxaldehyde only gave product **11D** whether the reaction was carried out at reflux for 10–12 h or at room temperature for 60–90 days. In the case of indolyl-3-carboxaldehyde, intermediate azomethine **8Dk** was isolated when the reaction was carried out at room temperature for several hours. Further heating of compound **8Dk** in trifluoroacetic acid gave **11D** as the only product (Scheme 4). Moreover, the same product **11D** was also obtained in similar yields when aminopyrazole **7D** or azomethine **8Dg** were heated in trifluoroacetic acid under nitrogen.

From these observations we conclude that the formation of compounds **11** accompanied by cleavage of the heterocycle moiety is different from the reaction of 5-aminopyrazoles **7** with other aromatic and heterocyclic carboxaldehydes (**a–g,i**), which proceed *via* an "azomethine formation–cyclization–oxidative aromatization" route. The difference between thienyl-2- or indolyl-3-carboxaldehydes on the one hand, and carboxaldehydes (**a–g,i**) on the other hand, is that in the former two compounds the formyl group is in the position of maximal electron density of these electron rich heterocycles, which is easily protonated.[25] It is also known that electron withdrawing substituents on C-2 of thiophene and C-3 of indole are relatively easily eliminated by the action of strong acids,[26] and that 3-alkyl(aryl)-indoles are easily isomerized.[27] As a result, protonated azomethine **8-H**$^+$ could cyclize into protonated dihydroisoquinoline derivative **9-H**$^+$, from which elimination of indole (or thiophene) would give **11** (Scheme 4).

Table 1 Reaction conditions, products and their yields in the reaction of aminopyrazoles **7** with aryl/heteroaryl aldehydes

R^1	R^2	Starting compound	Product	Yield	Conditions
Ph	Ph	**7A**	**10Aa**	67%	CF_3CO_2H, reflux, 3–5 h (or HCO_2H, reflux, 10–12 h)
$PhCH_2$	3-ClPh	**7C**	**10Cb**	74%	CF_3CO_2H, reflux, 3–5 h (or HCO_2H, reflux, 10–12 h)
$PhCH_2$	4-Et_2NPh	**7C**	**10Cd**	46%	CF_3CO_2H, reflux, 3–5 h (or HCO_2H, reflux, 10–12 h)
Me	4-NO_2Ph	**7D**	**10Dc**	72%	CF_3CO_2H, reflux, 3–5 h (or HCO_2H, reflux, 10–12 h)
Ph	3-Pyridyl	**7A**	**10Ae**	71%	CF_3CO_2H, reflux, 3–5 h
Et	3-Pyridyl	**7B**	**10Be**	66%	CF_3CO_2H, reflux, 3–5 h
$PhCH_2$	3-Pyridyl	**7C**	**10Ce**	69%	CF_3CO_2H, reflux, 3–5 h
Me	3-Quinolyl	**7D**	**10Df**	70%	CF_3CO_2H, reflux, 3–5 h
Me	3-Quinolyl	**7D**	**8Df**	88%	r.t., 1.5–2 h.
Me	1-Methyl-benzimidazolyl-2-	**7D**	**8Dh**	75%	CF_3CO_2H, reflux, 3–5 h
Et	1,2,3-Thiadiazolyl-5-	**7B**	**10Bg**	69%	CF_3CO_2H, reflux, 3–5 h
Et	3-Thienyl	**7B**	**10Bi**	76%	CF_3CO_2H, reflux, 3–5 h
Ph	H	**7A**	**11A**	15–26%	CF_3CO_2H, reflux, 3–5 h[a]
Me	H	**7D**	**11D**	15–22%	CF_3CO_2H, reflux, 3–5 h[a]
Me	2-Thienyl	**7D**	**10Dj**	21%	CF_3CO_2H, 15–20 °C, 80–90 d; thienyl-2-carboxaldehyde
	H		**11D**	14%	
Me	3-Indolyl	**7D**	**8Dk**	17%	CF_3CO_2H, 15–20 °C, 60 d; indolyl-3-carboxaldehyde
	H		**11D**	15%	

[a] Reaction with either thienyl-2-, indolyl-3-, 1-methylindolyl-3-, or 1-benzylindolyl-3-carboxaldehyde.



Scheme 4 Abstraction of indole moiety in condensation of aminopyrazoles **7A,D** with indole-3-aldehyde resulting in 5-unsubstituted pyrazolo[3,4-*c*]isoquinolines **11A,D**.

X-Ray molecular structures of compounds 10Dj,11D and 10Cd†

The structures of **10Dj,11D**·MeCN and **10Cd** were confirmed by X-ray crystallography (Figs 1–3). These are the first structurally characterized pyrazolo[3,4-*c*]isoquinolines, similar in bond distances to pyrazolo[3,4-*b*]pyridine derivatives.[28] The fused tricyclic system is planar within experimental error in **11D** and slightly puckered in **10Dj** and **10Cd**: the average atomic r.m.s. deviations average 0.005 (**11D**), 0.028 (**10Dj**) and 0.029 Å (**10Cd**), the maximum ones being 0.014, 0.057 and 0.077 Å, respectively. In **10Dj** the puckering can be described as planar pyrazolopyridine and benzene moieties forming an angle of 3.1°; in **10Cd** it is more irregular. In each case, both methoxy groups adopt in-plane conformations, the twists around the C1–O1 and

† CCDC reference numbers 232595–232597. See http://www.rsc.org/suppdata/ob/b4/b417002d/ for crystallographic data in .cif or other electronic format.

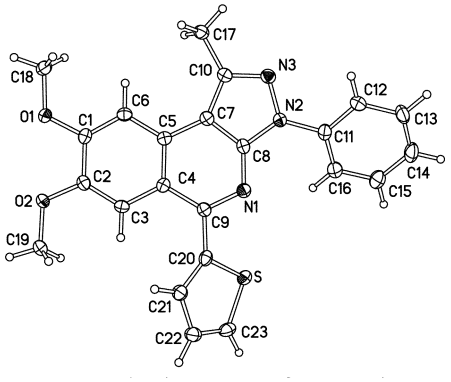


Fig. 1 Molecular structure of compound **10Dj**.

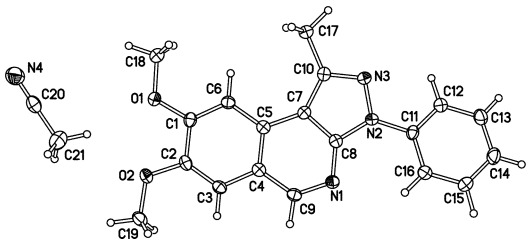


Fig. 2 Molecular structure of **11D**·CH_3CN.

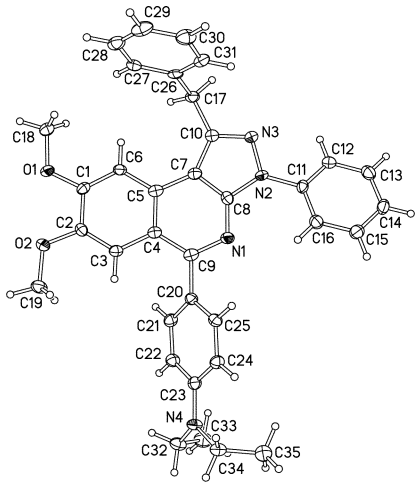


Fig. 3 Molecular structure of compound **10Cd**.

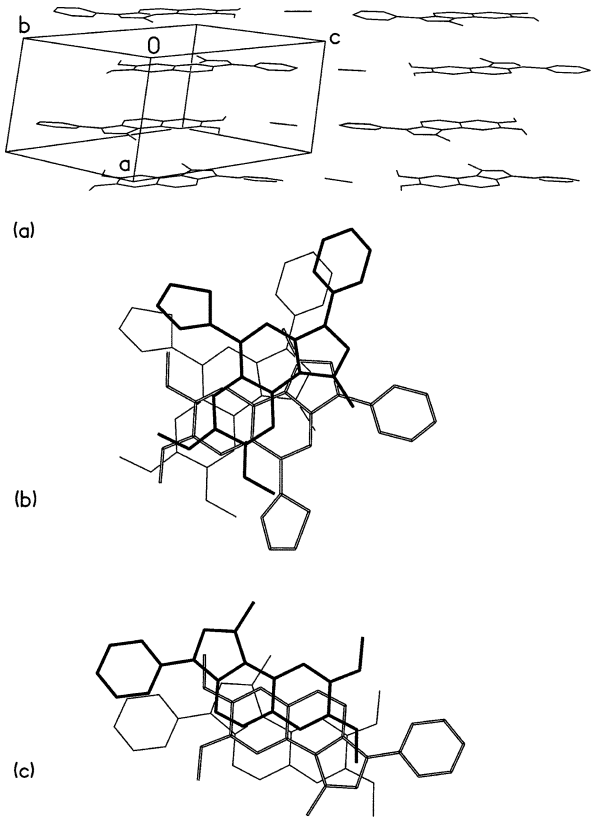


Fig. 4 Crystal packing of **11D** (a), and molecule overlap in single crystals of **11Dj** (b) and **11D** (c).

C2–O2 bonds ranging from 0.5 to 5.9°. The aryl substituents are not coplanar with the fused system: the twist around the N2–C11 bond equals 33.9° (**10Dj**), 19.9° (**11D**) and 20.5° (**10Cd**), that around the C9–C20 bond 39.3° (**10Dj**) and 48.7° (**10Cd**). The N4 atom in **10Cd** has substantial sp^2 character (the sum of the bond angles = 359.0°) and is conjugated with the phenylene group (the twist around the C23–N4 bond is 6.2°).

Applications of organic materials in molecular electronics, for example LEDs based on structurally related pyrazolo-quinolines, pyrazolo-pyridines and pyrazolo-quinoxalines,[16,17] often require consideration of π–π interactions in the system and their crystal arrangements. For the molecules considered, the crystal packing of **10Dj** and **11D** is dominated by stacks of dimethoxy-pyrazoloisoquinoline moieties (Fig. 4). In **11D** the adjacent moieties are related *via* inversion centers and thus strictly parallel; the interplanar separations (alternating between 3.31 and 3.35 Å) indicate a close packing mode, phenyl substituents and the acetonitrile of crystallization fill the interstack gaps. In **10Dj** the adjacent moieties are related by a *c* glide plane and are slightly (by 0.8°) non-parallel; the mean interplanar separation (3.47 Å) is larger than in **11D**. No continuous stacks exist in the structure of **10Cd**.

Conclusions

In conclusion, we have established a general one-pot synthesis of a wide range of pyrazolo[3,4-*c*]isoquinoline derivatives by reaction of readily available 4-aryl-5-aminopyrazoles **7** with benzaldehydes and heterocyclic aldehydes under acidic conditions. The key azomethine intermediates **8** can undergo the following transformations:

(A) protonation of the azomethine C=N bond and its cyclization (Pictet–Spengler type) to afford unstable dihydropyrazolo[3,4-*c*]isoquinolines **9**, which are oxidized to 5-aryl-(heteroaryl)-pyrazolo[3,4-*c*]isoquinolines **10**. This is the pathway for pyridyl-, quinolyl-, thienyl-3- and 1,2,3-thiadiazolyl-5-carboxaldehydes, as well as for benzaldehydes;

(B) the dihydropyrazolo[3,4-*c*]isoquinolines eliminate the heterocycle with no oxidation step.

The products formed in the reaction of aminopyrazole **7D** and thienyl-2-carboxaldehyde at ambient temperature exemplify both transformations of intermediate **8Dj** (Scheme 3), *i.e.* pathways (A) and (B) are concurrent processes with comparable reaction rates. On the other hand, the absence of the products of type **10** in the reaction of aminopyrazoles with indolyl-3-carboxaldehydes indicates that pathway (B) is dominant (Scheme 4) as 3-indolyl is a better leaving group than 2-thienyl. The more π-electron rich indole is more readily protonated at its C-3 position in intermediate **9-H**$^+$ (as compared to protonation at C-2 in the analogous thienyl derivative) and subsequent elimination of indole affords 5-unsubstituted derivatives **11**. If protonation is favoured at a site other than the imine bond [as in **8Dh-H**$^+$ (Scheme 2)] then cyclization is inhibited and the azomethine derivative is the only isolated product.

We are currently extending the scope of this synthetic route by replacing the donor dimethoxybenzene group in structure **7** with electron rich heterocycles. Initial results establish that 4-(3-indolyl)-4-aminopyrazole derivatives undergo the cyclization reaction, thus offering a convenient route to novel heterocyclic systems with an annelated indole moiety, potentially interesting for selective dopamine receptor binding.[29]

Experimental

General

^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury and Varian Unity 300 instruments, operating at 200 and 300 MHz (for ^{1}H), respectively. Chemical shifts were measured in ppm, relative to tetramethylsilane (TMS) as internal reference. Electron impact (EI) mass spectra were recorded on a Micromass AutoSpec spectrometer operating at 70 eV.

The aminopyrazoles **7A**[8c,d] and **7C**[8a] were prepared as described previously.

1-Phenyl-3-ethyl-4-(3,4-dimethoxyphenyl)-5-aminopyrazole (7B)

To a warm solution of sodium 2-propylate [prepared from sodium (3.9 g, 0.17 g-atom)] and 2-propanol (120 cm^3), a solution of 3,4-dimethoxyphenylacetonitrile (20.0 g, 0.113 mol) and ethyl propionate (26 cm^3, 0.24 mol) in 2-propanol (55 cm^3) was slowly added (**WARNING**: the mixture foams). The mixture was heated with a steam bath for 4 h (crystallization of α-propionyl-3,4-dimethoxyphenylacetonitrile sodium salt was observed after 2.5 h) and left at room temperature overnight. The precipitate was filtered off, washed with cool 2-propanol (3 × 30 cm^3), ether and dried *in vacuo* at 30 °C. The resulting α-propionyl-3,4-dimethoxyphenylacetonitrile sodium salt was dissolved in water (250 cm^3) and acidified with 10% aqueous HCl to pH 2. After 2 h, the aqueous solution was decanted from the oil; the oil was dissolved in toluene (150 cm^3), and the aqueous solution was extracted with toluene (2 × 50 cm^3). The combined toluene solutions were washed with water (until pH 7), dried with Na_2SO_4 and the solvent was removed *in vacuo* resulting in α-propionyl-3,4-dimethoxyphenylacetonitrile (21.0 g, 80%) as an oil, which was used in the next step without purification.

A solution of α-propionyl-3,4-dimethoxyphenylacetonitrile (21.0 g, 0.09 mol), phenylhydrazine (14.6 g, 0.135 mol) and glacial acetic acid (1.0 cm^3) in 2-propanol (200 cm^3) was refluxed for 6–8 h and the solvent was removed *in vacuo*. The residue was stirred with water for 1 h, filtered off and recrystallized from a minimal amount of 2-propanol affording compound **7B** (19.4 g, 67% based on 3,4-dimethoxyphenylacetonitrile), mp 87–88 °C (decomp.). The purity of the sample was suitable for further syntheses. Additional crystallization from methanol gave analytically pure **7B** (16.5 g, 51%), mp 88.0–88.3 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.18 (3H, t, J = 8 Hz, CH_3), 2.67 (2H, q, J = 8 Hz, CH_2), 3.77 (2H, br.s., NH_2), 3.89 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.86–6.96 (3H, m), 7.30 (1H, t, ^3J = 7.24 Hz), 7.50 (2H, t, ^3J = 7.24 Hz), 7.62 (2H, d, ^3J = 7.24 Hz). ^{13}C NMR (50 MHz, DMSO-d_6): δ 12.79 (CH_3), 20.03 (CH_2), 55.35 (OCH_3), 55.54 (OCH_3), 103.54, 112.55, 112.94, 120.80 (2C), 122.74, 125.77, 125.83, 128.80 (2C), 139.19, 142,89, 147.03, 148.86, 150.98. MS (EI): m/z 323 (M^+, 100%). IR (ν/cm^{-1}): 3350, 1610, 1600, 1585, 1510, 1500, 1465, 1385, 1330, 1280, 1235, 1170. Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99. Found: C, 70.50; H, 6.48; N, 13.10%.

1-Phenyl-3-benzyl-4-(3,4-dimethoxyphenyl)-5-aminopyrazole (7C)

This compound was obtained from 3,4-dimethoxyphenylacetonitrile, ethyl phenylacetate and phenylhydrazine as described for **7B**. Yield 83%, mp 127–128 °C (decomp.) (from 2-propanol). Intermediate α-phenacetyl-3,4-dimethoxyphenylacetonitrile sodium salt and α-phenacetyl-3,4-dimethoxyphenylacetonitrile were isolated and used in subsequent reactions with phenylhydrazine without purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.62 (3H, s, OCH_3), 3.83 (2H, br.s., NH_2), 3.87 (3H, s, OCH_3), 3.98 (2H, s, CH_2), 6.60 (1H, d, J = 1.8 Hz), 6.78 (1H, dd, J = 1.8 Hz, J = 8.24 Hz), 6.86 (1H, d, J = 8.24 Hz), 7.15 (1H, t J = 4.6 Hz), 7.19–7.27 (4H, m), 7.32 (1H, t, J = 8.0 Hz), 7.48 (2H, t, J = 8.0 Hz), 7.65 (2H, d, J = 8.0 Hz). ^{13}C NMR (50 MHz, DMSO-d_6): δ 32.63 (CH_2), 55.11 (OCH_3), 55.49 (OCH_3), 104.38, 112.39, 112.98, 120.84 (2C), 122.88, 125.51, 125.60, 125.99, 126.01, 127.88 (2C), 128.13 (2C), 128.85 (2C), 139.14, 139.80, 142.23, 148.25, 148.75. MS (EI): m/z 385 (M^+, 100%). IR (ν/cm^{-1}): 3320, 1615, 1600, 1570, 1505, 1495, 1475, 1370, 1320, 1270, 1230, 1170. Anal. Calcd for $C_{24}H_{23}N_3O_2$: C, 74.78; H, 6.01; N, 10.90. Found: C, 74.67; H, 5.95; N, 11.00%.

General procedure for the 5-aryl-7,8-dimethoxypyrazolo[3,4-*c*]-isoquinolines 10Aa,10Cb,10Cd,10Dc

A solution of aminopyrazole **7** (5 mmol) and the corresponding arylaldehyde (5.5 mmol) in trifluoroacetic or formic acid (20 cm^3) was refluxed (3–5 h for trifluoroacetic acid and 10–12 h for formic acid). The solvent was evaporated and the product was precipitated with 5% ammonia, filtered off, washed with water and recrystallized from isopropanol and then from acetonitrile affording colorless (**10Aa** and **10Cb**) or light yellow (**10Cd** and **10Dc**) solids.

10Aa: yield 67%, mp 199–200 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.66 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 7.35 (1H, t, J_{p-m} = 7.4 Hz, N–Ph-*p*), 7.41 (1H, s, C-6), 7.53 (1H, s, C-9), 7.70–7.55 (8H, m, *m*,*p*-Ph, N–Ph-*m*), 7.77 (2H, dd, J_{o-m} = 8.1 Hz, J_{o-p} = 1.8 Hz, *o*-Ph), 7.88 (2H, dd, J_{o-m} = 8.1 Hz, J_{o-p} = 1.8 Hz, *o*-Ph), 8.35 (2H, d, J_{o-m} = 7.9 Hz, N–Ph-*o*). ^{13}C NMR (50 MHz, DMSO-d_6): δ 55.18 (OCH_3), 55.22 (OCH_3), 102.20, 107.13, 108.15, 118.11, 121.22 (2C), 126.02, 127.37, 128.44 (2C), 128.65 (2C), 128.94 (2C), 129.05 (2C), 129.36 (2C), 129.70 (2C), 133.67, 139.12, 139.29, 145.21, 146.57, 147.79, 152.92, 159.03. MS (EI): m/z 457 (M^+, 100%). IR (ν/cm^{-1}): 1625, 1600. Anal. Calcd for $C_{30}H_{23}N_3O_2$ (M.W. 457.19): C, 78.75; H, 5.07; N, 9.18. Found: C, 78.71; H, 5.00; N, 9.25%.

10Cb: yield 74%, mp 193.5–195 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.70 (3H, s, CH_3O), 3.77 (3H, s, CH_3O), 4.72 (2H, s, CH_2), 7.22 (1H, t, J = 6.7 Hz), 7.27–7.38 (7H, m), 7.52–7.66 (4H, m), 7.30 (1H, m), 7.82 (1H, s), 8.33 (2H, d, J = 7.8 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 34.51 (CH_2), 55.17 (OCH_3), 55.79 (OCH_3), 103.06, 107.52, 107.94, 117.60, 120.91 (2C), 125.69, 126.44, 127.31, 128.19 (2C), 128.40, 128.65 (2C), 128.79, 129.04 (2C), 129.31, 130.19, 133.25, 138.17, 139.16, 141.38, 144.09, 146.75, 147.61, 153.23, 157.12. MS (EI): m/z 505 (M^+, 81%). Anal. Calcd for $C_{31}H_{24}ClN_3O_2$ (M.W. 505.99): C, 73.58; H, 4.78; N, 8.30. Found: C, 73.67; H, 4.84; N, 8.22%.

10Cd: yield 46%, mp 200–200.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.16 (6H, t, J = 6.9 Hz, CH_3CH_2), 3.44 (4H, q, J = 6.9 Hz, CH_3CH_2), 3.75 (6H, s, OCH_3), 4.71 (2H, s, CH_2Ph), 6.84 (2H, d, J = 7.8 Hz), 7.22 (1H, t, J = 6.8 Hz), 7.28 (1H, s), 7.29–7.38 (5H, m), 7.57 (2H, t, J = 7.8 Hz), 7.62 (1H, s), 7.66 (2H, d, J = 8.4 Hz), 8.42 (2H, d, J = 8.1 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.41 ($2CH_3$), 34.54 (CH_2Ph), 43.58 ($2CH_2CH_3$), 55.19 (OCH_3), 55.65 (OCH_3), 103.09, 106.94, 108.55, 110.70 (2C), 117.61, 120.56 (2C), 125.32, 125.54, 126.37, 127.28, 128.17 (2C), 128.61 (2C), 128.97 (2C), 131.20 (2C), 138.30, 139.47, 144.01, 147.19, 147.34, 147.84, 152.74, 159.16. MS (EI): m/z 542 (M^+, 100%), 527 ($M^+ - CH_3$, 34%). Anal. Calcd for $C_{35}H_{34}N_4O_2$ (M.W. 542.67): C, 77.46; H, 6.32; N, 10.32. Found: C, 77.36; H, 6.28; N, 10.40%.

10Dc: yield 72%, mp 260–262 °C (decomp.). ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.91 (3H, s, CH_3), 3.77 (3H, s, OCH_3), 4.09 (3H, s, OCH_3), 7.29 (1H, t, J_{p-m} = 7.0 Hz, N–Ph-*p*), 7.34 (1H, s, C-6), 7.52 (2H, dd, J_{m-p} = 7.0 Hz, J_{m-o} = 7.7 Hz, N–Ph-*m*), 7.69 (1H, s, C-9), 8.05 (2H, d, J = 8.7 Hz, –PhNO_2), 8.27 (2H, d, J_{o-m} = 7.7 Hz, N–Ph-*o*), 8.41 (2H, d, J = 8.7 Hz, –PhNO_2). MS (EI): m/z 440 (M^+, 100%). IR (ν/cm^{-1}): 1630, 1605, 1555. Anal. Calcd for $C_{25}H_{20}N_4O_4$ (M.W. 440.45): C, 68.17; H, 4.58; N, 12.72. Found: C, 68.10; H, 4.47; N, 12.87%.

1,3-Diphenyl-5-(3-pyridyl)-7,8-dimethoxypyrazolo[3,4-*c*]-isoquinoline (10Ae)

A solution of aminopyrazole **7A** (1.85 g, 5.0 mmol) and pyridyl-3-carboxaldehyde (0.59 g, 5.5 mmol) in trifluoroacetic acid (20 cm^3) was refluxed for 3–5 h and the solvent was removed *in vacuo*. The product was precipitated with 5% ammonia, filtered off, washed with water and recrystallized from acetonitrile affording compound **10Ae** (1.62 g, 71%), mp 202.5–204 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.66 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 7.32 (1H, s), 7.36 (1H, t, J = 7 Hz), 7.5–7.7 (7H, m), 7.80–7.95 (2H, m), 8.21 (1H, dt, J = 4.6 Hz, J = 1.5 Hz), 8.30

(2H, d, $J = 8$ Hz), 8.79 (1H, dd, $J = 4.6$ Hz, $J = 1.5$ Hz), 8.99 (1H, d, $J = 1.5$ Hz). ^{13}C NMR (50 MHz, DMSO-d_6): δ 55.24 (OCH_3), 55.27 (OCH_3), 102.21, 107.38, 107.53, 118.20, 121.29 (2C), 123.45, 126.13, 127.39, 128.67 (2C), 128.99, 129.08 (2C), 129.35 (2C), 133.53, 135.04, 137.23, 138.99, 145.21, 146.46, 148.06, 149.83, 149.99, 153.11, 156.03. MS (EI): m/z 458 (M^+, 37%), 443 ($M^+ - CH_3$, 10%), 427 ($M^+ - OCH_3$, 4%). IR (ν/cm^{-1}): 1630, 1610, 1595, 1500, 1475, 1420, 1375, 1270, 1180. Anal. Calcd for $C_{29}H_{22}N_4O_2$: C, 75.97; H, 4.84; N, 12.22. Found: C, 75.90; H, 4.77; N, 12.35%.

1-Ethyl-3-phenyl-5-(3-pyridyl)-7,8-dimethoxypyrazolo[3,4-*c*]-isoquinoline (10Be)

This compound was obtained similarly to compound **10Ae** from aminopyrazole **7B** and pyridyl-3-carboxaldehyde. Yield 66%, mp 212.5–213.5 °C (from acetonitrile). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.48 (3H, t, $J = 8$ Hz, CH_3), 3.30 (2H, q, $J = 8$ Hz, CH_2), 3.77 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 7.29 (1H, t, $J = 7.4$ Hz), 7.36 (1H, s), 7.53 (2H, t, $J = 7.4$ Hz), 7.55–7.66 (2H, m), 8.10–8.32 (3H, m), 8.76 (1H, dd, $J = 4.8$ Hz, $J = 1.5$ Hz), 8.98 (1H, d, $J = 1.5$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6, 90 °C): δ 11.68 (CH_3), 21.84 (CH_2), 55.28 (OCH_3), 55.52 (OCH_3), 102.49, 107.32, 108.04, 117.68, 120.35 (2C), 122.86, 124.96, 127.73, 128.42 (2C), 134.91, 136.57, 139.10, 146.44, 146.77, 147.72, 149.21, 149.50, 153.68, 155.23. MS (EI): m/z 410 (M^+, 88%), 395 ($M^+ - CH_3$, 25%). IR (ν/cm^{-1}): 1620, 1610, 1600, 1510, 1470, 1425, 1370, 1270, 1175. Anal. Calcd for $C_{25}H_{22}N_4O_2$: C, 73.15; H, 5.40; N, 13.65. Found: C, 73.04; H, 5.33; N, 13.75%.

1-Benzyl-3-phenyl-5-(3-pyridyl)-7,8-dimethoxypyrazolo[3,4-*c*]-isoquinoline (10Ce)

This compound was obtained similarly to compound **10Ae** from aminopyrazole **7C** and pyridyl-3-carboxaldehyde. Yield 69%, mp 202.5–203 °C (from acetonitrile). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.73 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.76 (2H, s, CH_2), 7.15–7.40 (8H, m), 7.50–7.70 (3H, m), 8.24 (1H, dt, $J = 8.0$ Hz, $J = 1.5$ Hz), 8.35 (2H, d, $J = 8.4$ Hz), 8.77 (1H, dt, $J = 5.0$ Hz, $J = 1.5$ Hz), 9.01 (1H, m.). ^{13}C NMR (50 MHz, DMSO-d_6): δ 34.49 (CH_2), 55.23 (OCH_3), 55.83 (OCH_3), 103.16, 107.36, 107.99, 117.86, 120.92 (2C), 123.42, 125.72, 126.44, 127.33, 128.19 (2C), 128.65 (2C), 129.07 (2C), 135.14, 137.21, 138.18, 139.16, 144.18, 146.90, 147.78, 149.75, 149.99, 153.32, 155.89. MS (EI): m/z 472 (M^+, 100%), 457 ($M^+ - CH_3$, 18%), 441 ($M^+ - OCH_3$, 8%). IR (ν/cm^{-1}): 1625, 1610, 1590, 1500, 1470, 1430, 1360, 1265, 1165. Anal. Calcd for $C_{30}H_{24}N_4O_2$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.15; H, 5.07; N, 12.00%.

1-Methyl-3-phenyl-5-(3-quinolyl)-7,8-dimethoxypyrazolo[3,4-*c*]-isoquinoline (10Df)

This compound was obtained similarly to compound **10Ae** from aminopyrazole **7D** and quinolyl-3-carboxaldehyde. Yield 70%, mp 243–244 °C (from acetonitrile). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.0 (3H, s, CH_3), 3.48 (3H, s, OCH_3), 4.12 (3H, s, OCH_3), 6.88 (1H, s), 7.25 (1H, t, $J = 7.3$ Hz), 7.40–7.55 (4H, m), 7.70–7.90 (3H, m), 8.15–8.30 (3H, m), 8.12 (1H, d, $J = 4.4$ Hz). ^{13}C NMR (50 MHz, DMSO-d_6): δ 15.21 (CH_3), 55.20 (OCH_3), 55.85 (OCH_3), 102.26, 107.22, 108.85, 118.57, 120.49 (2C), 122.11, 125.47, 125.62, 126.22, 127.15, 128.01, 129.00 (2C), 129.50, 129.71, 139.16, 142.32, 144.64, 146.35, 147.86, 147.99, 150.19, 153.95, 155.27. MS (EI): m/z 446 (M^+, 100%), 431 ($M^+ - CH_3$, 17%), 415 ($M^+ - OCH_3$, 29%). IR (ν/cm^{-1}): 1635, 1600, 1580, 1505, 1470, 1430, 1380, 1270, 1180. Anal. Calcd for $C_{28}H_{22}N_4O_2$: C, 75.32; H, 4.97; N, 12.55. Found: C, 75.24; H, 4.93; N, 12.68%.

1-Phenyl-3-methyl-4-(3,4-dimethoxyphenyl)-5-(quinolyl-3-ylideneimino)-pyrazole (8Df)

This compound was obtained by stirring equimolar amounts of aminopyrazole **7D** and quinolyl-3-carboxaldehyde in formic acid at room temperature for 1.5–2 h. Yield 88%, mp 134.5–135.5 °C (from ethanol). ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.26 (3H, s, CH_3), 3.65 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 6.95–7.10 (3H, m), 7.39 (1H, t, $J = 7.2$ Hz), 7.48–7.60 (3H, m), 7.68–7.85 (4H, m), 8.13 (2H, dd, $J = 8.8$ Hz, $J = 10$ Hz), 9.02 (1H, d, $J = 4.4$ Hz), 9.18 (1H, s). ^{13}C NMR (50 MHz, DMSO-d_6): δ 12.63 (CH_3), 55.46 (OCH_3), 55.52 (OCH_3), 101.31, 110.99, 112.37, 113.34, 120.49, 121.96, 123.30, 123.74 (2C), 124.29, 124.72, 126.77, 127.66, 128.84 (2C), 129.80, 137.52, 138.97, 145.10, 147.42, 148.03, 148.29, 149.06, 150.52, 161.09. MS (EI): m/z 448 (M^+, 100%), 433 ($M^+ - CH_3$, 10%). IR (ν/cm^{-1}): 1635, 1600, 1665, 1510, 1505, 1460, 1410, 1370, 1330, 1270, 1265, 1170, 1150. Anal. Calcd for $C_{28}H_{24}N_4O_2$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.92; H, 5.30; N, 12.63%.

1-Phenyl-3-methyl-4-(3,4-dimethoxyphenyl)-5-(1-methyl-benzimidazolyl-2-ylideneimino)-pyrazole (8Dh)

This compound was obtained similarly to compound **10Ae** from aminopyrazole **7D** and 1-methylbenzimidazolyl-2-carboxaldehyde. Yield 75%, mp 187.5–189 °C (from acetonitrile). ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.21 (3H, s, CH_3), 3.70 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 6.90–7.10 (3H, m), 7.27 (1H, t, $J = 7.3$ Hz), 7.32–7.76 (8H, m), 8.57 (1H, s). ^{13}C NMR (50 MHz, DMSO-d_6): δ 12.47 (CH_3), 31.90 (NCH_3), 55.34 (OCH_3), 55.50 (OCH_3), 110.76, 110.87, 112.20, 113.12, 120.17, 121.80, 122.89, 124.07, 124.38 (2C), 124.95, 127.00, 128.68 (2C), 136.94, 138.84, 142.39, 143.79, 146.70, 147.64, 148.03, 149.01, 153.64. MS (EI): m/z 451 (M^+, 61%), 436 ($M^+ - CH_3$, 11%), 420 ($M^+ - OCH_3$, 9%), 319 ($M^+ - N$-methylbenzimidazole, 100%), 304 ([$M^+ - N$-methylbenzimidazole] $- CH_3$, 13%). IR (ν/cm^{-1}): 1630, 1610, 1550, 1505, 1470, 1400, 1380, 1325, 1260, 1140. Anal. Calcd for $C_{27}H_{25}N_5O_2$: C, 71.82; H, 5.58; N, 15.51. Found: C, 71.80; H, 5.53; N, 15.50%.

1-Ethyl-3-phenyl-5-(1,2,3-thiadiazolyl-5)-7,8-dimethoxypyrazolo[3,4-*c*]isoquinoline (10Bg)

This compound was obtained similarly to compound **10Ae** from aminopyrazole **7B** and 1,2,3-thiadiazolyl-5-carboxaldehyde. Yield 69%, mp 243.5–244.5 °C (from acetonitrile). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.52 (3H, t, CH_3, $J = 7.5$ Hz), 3.37 (2H, q, CH_2, $J = 7.5$ Hz), 3.87 (3H, s, OCH_3), 4.10 (3H, s, OCH_3), 7.34 (1H, t, $J = 7.2$ Hz), 7.57 (2H, dd, $J = 7.2$ Hz, $J = 8.4$ Hz), 7.67 (1H, s), 8.32 (2H, d, $J = 8.4$ Hz), 8.40 (1H, s), 9.92 (1H, s). ^{13}C NMR (50 MHz, DMSO-d_6): δ 12.73 (CH_3), 22.04 (CH_2), 55.47 (OCH_3), 55.70 (OCH_3), 102.47, 107.27, 108.09, 118.34, 120.35 (2C), 125.46, 128.61 (2C), 132.12, 140.53, 151.32, 151.88, 157.24, 164.33, 165.53, 166.12, 168.17. MS (EI): m/z 417 (M^+, 100%). IR (ν/cm^{-1}): 1625, 1600, 1580, 1530, 1500, 1420, 1370, 1300, 1280, 1265, 1205, 1170. Anal. Calcd for $C_{22}H_{19}N_5O_2S$ (M.W. 417.48): C, 63.29; H, 4.59; N, 16.78; S, 7.68. Found: C, 63.21; H, 4.55; N, 16.85; S, 7.57%.

1-Ethyl-3-phenyl-5-(3-thienyl)-7,8-dimethoxypyrazolo[3,4-*c*]-isoquinoline (10Bi)

This compound was obtained similarly to compound **10Ae** from aminopyrazole **7B** and thienyl-3-carboxaldehyde. Yield 76%, mp 267–269 °C (decomp.) (from acetonitrile). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.51 (3H, t, CH_3, $J = 7.45$ Hz), 3.37 (2H, q, CH_2, $J = 7.4$ Hz), 3.85 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 7.28 (1H, t, $J = 6.7$ Hz), 7.53 (2H, t, $J = 6.7$ Hz), 7.63 (1H, s), 7.66 (1H, s), 7.73 (1H, s), 7.77 (1H, d, $J = 1.3$ Hz), 8.10 (1H, d, $J = 1.3$ Hz), 8.33 (2H, d, $J = 6.7$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.08 (CH_3), 22.12 (CH_2), 55.49 (OCH_3), 55.85

(OCH_3), 102.30, 107.17, 108.00, 116.64, 119.78 (2C), 125.11, 128.05, 128.30, 129.00 (2C), 129.35, 139.27, 140.57, 142.07, 143.15, 146.17, 148.24, 150.26, 153.33. MS (EI): *m/z* 401 (M^+, 100%). IR (ν/cm^{-1}): 1635, 1600, 1590, 1530, 1500, 1465, 1420, 1390, 1265, 1230, 1160. Anal. Calcd for $C_{24}H_{21}N_3O_2S$: C, 69.38; H, 5.09; N, 10.11; S, 7.72. Found: C, 69.30; H, 5.05; N, 10.27; S, 7.60%.

1,3-Diphenyl-7,8-dimethoxypyrazolo[3,4-*c*]isoquinoline (11A)

This compound was obtained similarly to compound **10Ae** from aminopyrazole **7A** and heterocyclic aldehyde (thienyl-2-aldehyde, indolyl-3-aldehyde, 1-methylindolyl-3-aldehyde or 1-benzylindolyl-3-aldehyde). Yields 15–26% depending on the aldehyde, mp 155.5–156.5 °C (from acetonitrile). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.64 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 7.31 (1H, t, J = 8 Hz), 7.35 (1H, s), 7.53 (2H, dd, J = 8 Hz, J = 8 Hz), 7.54 (1H, s), 7.4–7.6 (3H, m), 7.7–7.82 (2H, m), 8.34 (2H, d, J = 8 Hz), 8.91 (1H, s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.11 (OCH_3), 55.42 (OCH_3), 102.08, 108.43, 109.20, 120.64 (2C), 121.21, 125.72, 125.89, 127.97, 128.40, 128.45 (2C), 128.84, 129.13 (2C), 129.36 (2C), 131.64, 147.35, 152.13, 160.65, 164.73. MS (EI): *m/z* 381 (M^+, 100%). IR (ν/cm^{-1}): 1625, 1605, 1600, 1530, 1510, 1470, 1425, 1265, 1170. Anal. Calcd for $C_{24}H_{19}N_3O_2$ (M.W. 381.43): C, 75.57; H, 5.02; N, 11.02. Found: C, 75.50; H, 4.91; N, 11.20%.

1-Methyl-3-phenyl-7,8-dimethoxypyrazolo[3,4-*c*]isoquinoline (11D)

This compound was obtained similarly to compound **10Ae** from aminopyrazole **7D** and the heterocyclic aldehyde (thienyl-2-carboxaldehyde, indolyl-3-carboxaldehyde, 1-methylindolyl-3-carboxaldehyde or 1-benzylindolyl-3-carboxaldehyde). Yields 15–22% depending on the aldehyde, mp 166–166.5 °C (from acetonitrile). [Lit.[23] mp 166–166.5 °C]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.78 (3H, s, CH_3), 3.90 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 7.30 (1H, tt, ^3J = 7.4 Hz, ^4J = 1.2 Hz, *p*-Ph), 7.43 (1H, s), 7.54 (2H, t, ^3J = 7.8 Hz, *m*-Ph), 7.61 (1H, s), 8.26 (2H, dd, ^3J = 7.8 Hz, ^4J = 1.2 Hz, *o*-Ph), 8.93 (1H, s, H-5). ^{13}C NMR (75 MHz, DMSO-d_6): δ 15.12, 55.56, 55.68, 101.43, 108.24, 108.64, 120.04, 120.53 (2C), 125.37, 126.58, 129.01 (2C), 139.41, 142.11, 147.17, 147.93, 151.02, 153.71. MS (EI): *m/z* 319 (M^+, 100%), 304 ($M^+ - CH_3$, 25%). IR (ν/cm^{-1}): 1630, 1600, 1595, 1530, 1500, 1450, 1415, 1270, 1170. Anal Calcd for $C_{19}H_{17}N_3O_2$ (M.W. 319.36): C, 71.46; H, 5.37; N, 13.16. Found: C, 71.44; H, 5.24; N, 13.20%.

1-Methyl-3-phenyl-5-(2-thienyl)-7,8-dimethoxypyrazolo[3,4-*c*]-isoquinoline (10Dj) and 1-methyl-3-phenyl-7,8-dimethoxypyrazolo[3,4-*c*]isoquinoline (11D)

A solution of aminopyrazole **7D** (5 mmol) and thienyl-2-carboxaldehyde (5 mmol) in trifluoroacetic acid (20 mL) was stirred at 15–20 °C for 80–90 days (with TLC and ^{1}H NMR monitoring of the reaction). The mixture was treated with 5% ammonia, filtered off, washed with water and dried. The product was twice recrystallized from acetonitrile affording pyrazolo[3,4-*c*]isoquinoline **10Dj**.

The combined mother liquors were evaporated, and the residue was twice recrystallized from 2-propanol and then from acetonitrile affording pyrazolo[3,4-*c*]isoquinoline **11D**.

Compound **10Dj**: yield 21%, mp 209.5–210 °C (from acetonitrile). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.85 (3H, s, CH_3), 3.91 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 7.20–7.40 (2H, m), 7.56 (2H, dd, J = 7.8 Hz, J = 8.0 Hz), 7.60 (1H, s), 7.86 (1H, d, J = 5.0 Hz), 7.91 (1H, d, J = 5.0 Hz), 7.92 (1H, s), 8.35 (2H, d, J = 7.8 Hz). ^{13}C NMR (50 MHz, DMSO-d_6): δ 15.17 (CH_3), 55.33 (OCH_3), 55.73 (OCH_3), 102.35, 107.28, 108.02, 116.76, 119.95 (2C), 125.22, 128.19, 128.36, 128.99 (2C), 129.24 (2C), 139.36, 142.17, 143.00, 146.07, 148.14, 150.76, 153.53. MS (EI): *m/z* 401 (M^+, 100%), 386 ($M^+ - CH_3$, 22%), 371 ($MH^+ - OCH_3$, 22%), 319 (MH^+ − thiophene, 64%). IR (ν/cm^{-1}): 1630, 1600, 1560, 1500, 1420, 1280, 1255. Anal. Calcd for $C_{23}H_{19}N_3O_2S$: C, 68.81; H, 4.77; N, 10.47; S, 7.99. Found: C, 68.70; H, 4.65; N, 10.66; S, 7.95%.

Compound **11D**: yield 14%. ^{1}H and ^{13}C NMR spectra of the sample were identical to those obtained from the reaction in boiling trifluoroacetic acid as described above.

1-Phenyl-3-methyl-4-(3,4-dimethoxyphenyl)-5-(indolyl-3-ylidenimino)-pyrazole (8Dk) and 1-methyl-3-phenyl-7,8-dimethoxypyrazolo[3,4-*c*]isoquinoline (11D)

These compounds were obtained following the above method from aminopyrazole **7D** and indolyl-3-carboxaldehyde at room temperature for 60 days.

Compound **11D**: yield 17%.

Compound **8Dk**: yield 15%, mp 233.5–235 °C (from ethanol). ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.25 (3H, s, CH_3), 3.60 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 6.87 (2H, s + s), 7.0–7.27 (2H, m), 7.22 (1H, t, J = 6 Hz), 7.35 (2H, dd, J = 8 Hz, J = 6 Hz), 7.41 (1H, d, J = 8 Hz), 7.63 (1H, s, N–H), 7.83 (2H, d, J = 8 Hz), 8.23 (1H, d, J = 8 Hz), 8.45 (1H, s), 11.75 (1H, s, N–H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 13.11 (CH_3), 55.19 (OCH_3), 55.32 (OCH_3), 108.84, 112.04, 112.10, 113.08, 114.42, 121.30, 121.39, 121.50, 122.90 (2C), 123.05, 124.43, 125.24, 125.82, 128.48 (2C), 135.00, 137.19, 139.54, 146.77, 147.17, 147.73, 148.59, 159.42. MS (EI): *m/z* 436 (M^+, 100%), 421 ($M^+ - CH_3$, 16%), 320 ($M^+ - C_8H_6N$, 4%). IR (ν/cm^{-1}): 3210, 1630, 1610, 1600, 1655, 1515, 1505, 1470, 1405, 1370, 1325, 1265, 1250, 1185, 1140. Anal Calcd for $C_{27}H_{24}N_4O_2$: C, 74.29; H, 5.54; N, 12.83. Found: C, 74.20; H, 5.45; N, 12.90%.

X-Ray diffraction†

Single crystals of compounds **10Dj** and **11D** were grown from acetonitrile solution, and compound **10Cd** gave single crystals from DMSO-d_6 in an NMR tube.

X-Ray diffraction experiments (see Table 2) for **10Dj** and **11D** were carried out on a 3-circle diffractometer equipped with a SMART 1K CCD area detector and a sealed-tube X-ray source, for **10Cd** on a 3-circle diffractometer equipped with an APEX CCD area detector and a 60 W microfocus Bede Microsource® with glass polycapillary optics. Graphite-monochromated Mo–K_α radiation ($\bar{\lambda}$ = 0.71073 Å) was used in both cases. The crystals were cooled using a Cryostream open-flow N_2 cryostat (Oxford Cryosystems). Full sphere of reciprocal space was covered by five sets of 0.3° ω scans, each set with different φ and/or 2θ angles. The structures were solved by direct methods and refined by full-matrix least squares against

Table 2 Crystal data for compounds **10Dj,11D** and **10Cd**

Compound	**10Dj**	**11D**	**10Cd**
Formula	$C_{23}H_{19}N_3O_2S$	$C_{19}H_{17}N_3O_2{\cdot}C_2H_3N$	$C_{35}H_{34}N_4O_2$
Formula weight	401.47	360.41	542.66
T/K	123	120	120
Symmetry	Orthorhombic	Triclinic	Triclinic
Space group	$Pca2_1$ (# 29)	$P\bar{1}$ (# 2)	$P\bar{1}$ (# 2)
a/Å	22.845(4)	7.086(1)	8.944(4)
b/Å	11.858(2)	10.791(3)	12.945(5)
c/Å	7.188(1)	12.850(2)	13.918(7)
α/°	90	104.16(2)	64.13(2)
β/°	90	105.87(2)	73.04(2)
γ/°	90	95.86(1)	81.00(2)
V/Å^3	1947.2(5)	901.2(3)	1386(1)
Z	4	2	2
Refls collected	13783	10258	10374
Unique refls	4490	4128	5074
Refls $F^2 > 2\sigma(F^2)$	3735	2988	2568
$R[F^2 > 2\,\sigma(F^2)]$	0.039	0.040	0.051
w$R(F^2)$, all data	0.085	0.105	0.093

F^2 of all data, using SHELXTL software.[30] Full crystallographic data, excluding structure factors, are provided in the Electronic Supplementary Information† and have been deposited at the Cambridge Crystallographic Data Centre.

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