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Cyclocondensation reactions of 5-aminopyrazoles, pyruvic acids and aldehydes. Multicomponent approaches to pyrazolopyridines and related products

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Abstract—The reactions of 3-substituted 5-aminopyrazoles with arylidenepyruvic acids and their synthetic precursors, pyruvic acid and aromatic aldehydes, were studied. Several different reaction pathways for these cyclocondensation reactions were established depending on the reaction conditions and building block selection. The formation of pyrazolo[3,4-*b*]pyridine-6-carboxylic acids as major products and related compounds was discussed from the mechanistic point of view.

1. Introduction

Cyclocondensations of aminoazoles and aminoazines with α,β-unsaturated ketones or their synthetic precursors—aldehydes and ketones containing at least two active hydrogen atoms—are the most widespread and investigated pathways to fused dihydroazaheterocycles.[1] In most cases, both types of reaction pathways, i.e., a sequential protocol involving the initial synthesis of the α,β-unsaturated compounds and the three-component reaction, yield the same products.[2] However, in rare cases the direct multicomponent procedure may lead to the formation of different products,[3] connected to the complex reaction mechanisms of these transformations.[3b,c]

Reactions of pyruvic acid derivatives with dinucleophiles have been applied for the synthesis of various types of heterocycles since the beginning of the last century. Among those, reactions involving acetyl-[4] and arylidenepyruvic[2b,5] acids have been studied intensively. On the other hand, multicomponent reactions of pyruvic acid leading to heterocycles have rarely been investigated. Among those are publications devoted to the treatment of pyruvic acid with aromatic amines and aldehydes yielding either quinolinecarboxylic acids[6] or pyrrolidines.[7] Multicomponent reactions of pyruvic acid with aminoazoles have so far not been described.

Previously we reported[2b,c] two alternative synthetic pathways to fused pyrimidinecarboxylic acids: by treatment of 3-amino-1,2,4-triazole, 5-aminotetrazole and 2-aminobenzimidazole with either arylidenepyruvic acids[2b] or with pyruvic acid and aldehydes[2c] (Scheme 1). At that time we noted that these three-component reactions carried out in refluxing DMF were not regioselective and yielded two isomers.

Our interest in pyridine and pyrimidine heterocycles containing fused pyrazole rings is mainly caused by the known biological activity of these systems reported in the literature.[8] On the other hand, reactions of the 5-aminopyrazole nucleus, having at least three nucleophilic centres, with pyruvic acid derivatives, which also possess several reactive centres, can lead in several directions and are therefore of interest from the point of view of their chemo- and regioselectivity.

Keywords: Heterocycles; Cyclocondensation; Multicomponent reactions; Microwave-assisted organic synthesis; Pyruvic acid derivatives; 5-Aminopyrazoles.
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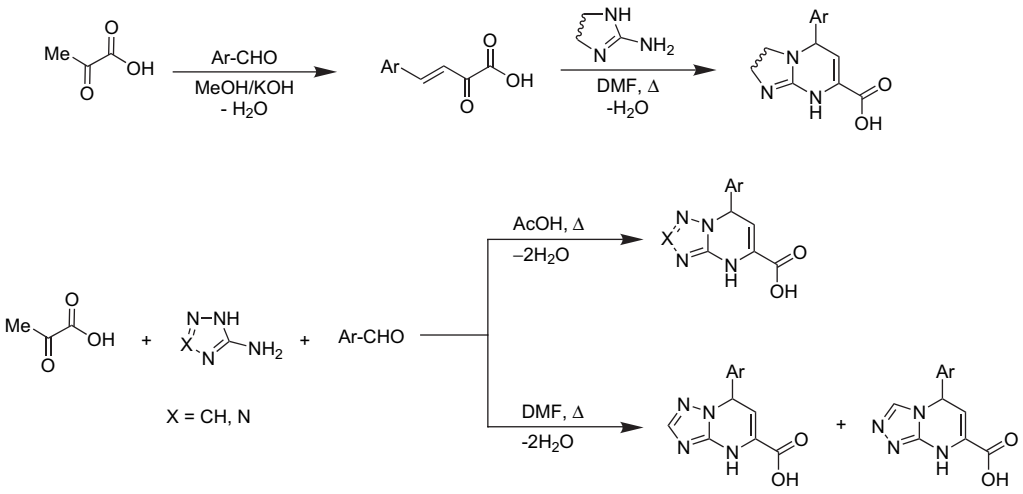


Scheme 1.

2. Results and discussion

In this article, we disclose our results on the condensation reactions of 1-, 3- or 4-substituted 5-aminopyrazoles with both (i) arylidenepyruvic acids and (ii) with their synthetic precursors—pyruvic acids and aromatic aldehydes—leading to fused pyridine or pyrimidine carboxylic acids using conventional thermal or microwave heating conditions.

The starting α,β-unsaturated acids **4a**–**c** were synthesized according to the known literature procedures by reaction of aromatic aldehydes and pyruvic acid in an aqueous methanolic solution of potassium hydroxide,[9] and were subsequently used directly without additional purification. 3-Substituted 5-aminopyrazoles **1**, **2**, **3a**,**b** and 5-amino-*N*-phenylpyrazole-4-carboxamides **10a**,**b** were either commercially available (amine **1**) or synthesized using published procedures.[10a,b] Azomethine **22** was obtained as reported in the literature.[10c]

2.1. Reactions involving arylidenepyruvic acids

In the course of our investigations we found that refluxing on an oil bath of equimolar mixtures of 5-amino-3-methylpyrazole **1** with unsaturated acids **4a**,**c** in DMF or acetic acid led to the formation of a pyridine ring. Addition of EtOH to the reaction mixture allowed to isolate 4-aryl-3-methylpyrazolo[3,4-*b*]pyridine-6-carboxylic acids **5a**,**b** in satisfactory yields (Table 1). It should be noted that heterocyclic products in these reactions were not isolable as dihydroderivatives, which indicate the high propensity of the expected 4-aryl-3-methyl-4,7-dihydropyrazolo[3,4-*b*]pyridine intermediates to oxidation.

Table 1. Reactions of 5-aminopyrazoles with arylidenepyruvic acids (Scheme 2)

Building blocks					Product	
Aminopyrazole			Acid			
Compound	R	R^1	Compound	R^2	Compound	Yield (%)
1	CH_3	H	**4a**	C_6H_5	**5a**	38[a]
1	CH_3	H	**4c**	4-CH_3O–C_6H_4	**5b**	42[a]
2	CH_3	C_6H_5	**4a**	C_6H_5	**6a**	39[b]
2	CH_3	C_6H_5	**4c**	4-CH_3O–C_6H_4	**6b**	48[b]
2	CH_3	C_6H_5	**4a**	C_6H_5	**7a**	68[a]
2	CH_3	C_6H_5	**4c**	4-CH_3O–C_6H_4	**7b**	72[a]
3a	C_6H_5	H	**4a**	C_6H_5	**8a**	75[a]
3a	C_6H_5	H	**4b**	4-Cl–C_6H_4	**8b**	78[c]
3a	C_6H_5	H	**4c**	4-CH_3O–C_6H_4	**8c+9c**	52[a] and 26[a]
3a	C_6H_5	H	**4b**	4-Cl–C_6H_4	**10b**	31[a]
3b	4-Br–C_6H_4	H	**4a**	C_6H_5	**8d**	65[a]
3b	4-Br–C_6H_4	H	**4b**	4-Cl–C_6H_4	**8e**	76[a]
3b	4-Br–C_6H_4	H	**4c**	4-CH_3O–C_6H_4	**8f+10f**	48[a] and 22[a]
3b	4-Br–C_6H_4	H	**4c**	4-CH_3O–C_6H_4	**9f**	56[c]
11a	C_6H_5	—	**4c**	4-CH_3O–C_6H_4	**12a**	68[a]
11b	4-C_2H_5O–C_6H_4	—	**4a**	C_6H_5	**12b**	68[a]
11b	4-C_2H_5O–C_6H_4	—	**4b**	4-Cl–C_6H_4	**12c**	72[a]
11b	4-C_2H_5O–C_6H_4	—	**4c**	4-CH_3O–C_6H_4	**12d**	65[a]
11b	4-C_2H_5O–C_6H_4	—	**4d**	4-CH_3–C_6H_4	**12e**	68[a]

[a] Refluxing in HOAc.
[b] Refluxing in DMF.
[c] Refluxing in HOAc under nitrogen atmosphere.

Refluxing of 5-amino-3-methyl-1-phenylpyrazole **2** with arylidenepyruvic acids **4a**,**c** in DMF also yielded heteroaromatized 4-aryl-3-methyl-1-phenylpyrazolo[3,4-*b*]pyridine-6-carboxylic acids **6a**,**b**, however, treatment in boiling acetic acid allowed us to isolate the corresponding dihydro analogs **7a**,**b** accompanied by only small amounts of the aromatized heterocycles **6a**,**b**. Upon exposure to atmospheric conditions dihydropyridines **7a**,**b** very easily oxidized to pyridines **6a**,**b**.

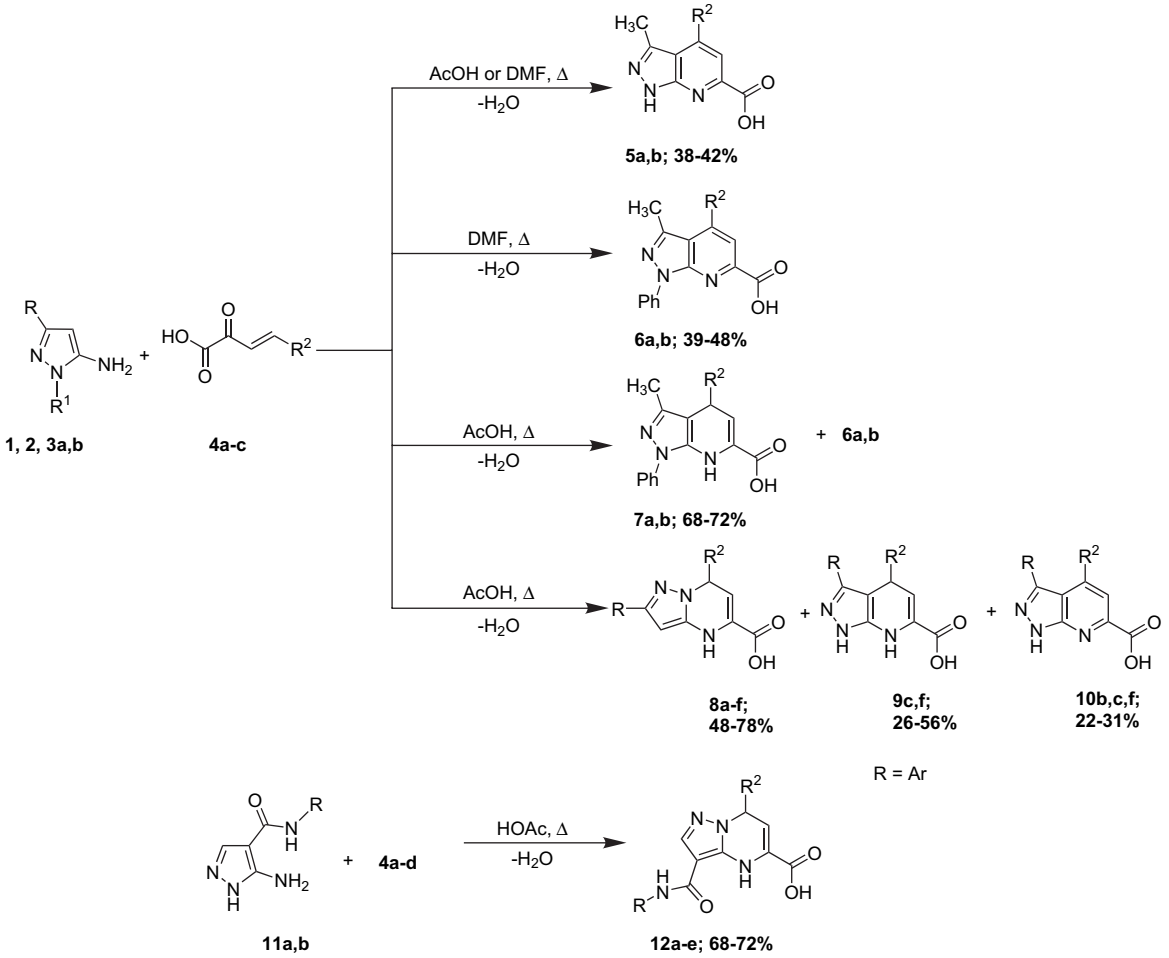
Treatment of arylidenepyruvic acids **4a–c** with 5-amino-3-arylpyrazoles **3a**,**b** in most cases was not regioselective and yielded mixtures of several regioisomers and products of their heteroaromatization (Scheme 2). Thus, in reactions of unsaturated acid **4a** with amines **3a**,**b**, and of acid **4b** with amine **3b**, carboxylic acids **8a**,**d**,**e** were obtained as pure single isomers whereas reaction of acid **4b** with amine **3a** yielded pyrazolopyridine **10b**. It is interesting that under nitrogen atmosphere the reaction of acid **4b** and amine **3a** provided dihydropyrimidine **8b**. On the other hand, treatment of pyrazoles **3a**,**b** with unsaturated acid **4c** containing a methoxyaryl group was less selective and led to the formation of several products: in reaction of amine **3a** with acid **4c** a mixture of 2-phenyl-7-(4-methoxyphenyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acids **8c** (major isomer) and 3-phenyl-4-(4-methoxyphenyl)-4,7-dihydropyrazolo[3,4-*b*]pyridine-6-carboxylic acids **9c** (minor isomer) with small traces of pyridine derivative **10c** was isolated (compound **10c** was not separated from mixture). At that time, treatment of **3b** with unsaturated acid **4c** led to a mixture of **8f** (major isomer) and **10f** (minor isomer), whereas dihydropyridine derivative **9f** was obtained as the single product in the same reaction under nitrogen atmosphere (Table 1).

When the nucleophilic position 4 on the pyrazole ring was blocked by an *N*-arylcarboxamide group as in structures **11a**,**b** treatment with acids **4a–d** in boiling acetic acid led to the clean formation of pyrimidine derivatives **12a–e** as the only isolable product (Scheme 2).

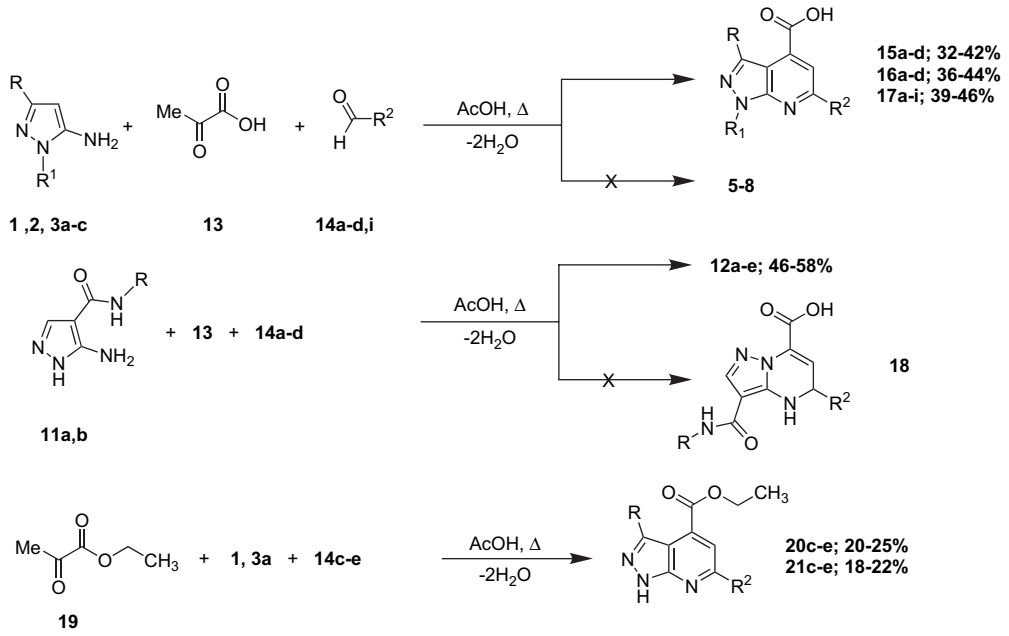
It should be noted that condensation of the unsaturated acids **4a–d** with 5-aminopyrazoles **1**, **2**, **3a**,**b** never yielded isomers with opposite location of the aryl and carboxyl groups at the pyridine or pyrimidine rings, respectively.

2.2. Three-component reactions involving pyruvic acid and aldehydes

As it was pointed out in Section 1, both the sequential and the one-pot multicomponent approach can yield the same or different reaction products. In the case of 3-amino-1,2,4-triazole and 5-aminotetrazol, both types of protocols led to the formation of the same compounds, i.e., 5-aryl-5,8-dihydroazolo[1,5-*a*]pyrimidine-7-carboxylic acids.[2b,c]



Scheme 2.



Scheme 3.

However, we now find that the three-component condensation of amines **1**, **2**, **3a–c** with pyruvic acid **13** and aromatic aldehydes **14a–d**,**i** in refluxing acetic acid leads exclusively to 6-aryl-3-methylpyrazolo[3,4-*b*]pyridine-4-carboxylic acids **15a–d**, 1,6-diaryl-3-methylpyrazolo[3,4-*b*]pyridine-4-carboxylic acids **16a–d** and 3,6-diarylpyrazolo[3,4-*b*]pyridine-4-carboxylic acids **17a–i** as reaction products, instead of the anticipated carboxylic acids **5–9** (Scheme 3, Table 2). The three-component procedures lead exclusively to the formation of heteroaromatized compounds even under a nitrogen atmosphere.

Similarly, multicomponent condensation of amines **11a**,**b** with pyruvic acid and aldehydes led to pyrimidines **12a–e**

Table 2. Three-component reactions of 5-aminoazoles (Scheme 3)

Building blocks						Product[a]	
Aminopyrazole			Pyruvic acid derivative	Aldehyde			
Compound	R	R^1		Compound	R^2	Compound	Yield (%)
1	CH_3	H	**13**	**14a**	C_6H_5	**15a**	42
1	CH_3	H	**13**	**14b**	4-Cl–C_6H_4	**15b**	39
1	CH_3	H	**13**	**14c**	4-CH_3O–C_6H_4	**15c**	42
1	CH_3	H	**13**	**14d**	4-CH_3–C_6H_4	**15d**	32
2	CH_3	C_6H_5	**13**	**14a**	C_6H_5	**16a**	38
2	CH_3	C_6H_5	**13**	**14b**	4-Cl–C_6H_4	**16b**	44
2	CH_3	C_6H_5	**13**	**14c**	4-CH_3O–C_6H_4	**16c**	42
2	CH_3	C_6H_5	**13**	**14d**	4-CH_3–C_6H_4	**16d**	36
3a	C_6H_5	H	**13**	**14a**	C_6H_5	**17a**	42
3a	C_6H_5	H	**13**	**14b**	4-Cl–C_6H_4	**17b**	44
3a	C_6H_5	H	**13**	**14c**	4-CH_3O–C_6H_4	**17c**	42
3a	C_6H_5	H	**13**	**14d**	4-CH_3–C_6H_4	**17d**	39
3b	4-Br–C_6H_4	H	**13**	**14a**	C_6H_5	**17e**	40
3b	4-Br–C_6H_4	H	**13**	**14b**	4-Cl–C_6H_4	**17f**	45
3b	4-Br–C_6H_4	H	**13**	**14c**	4-CH_3O–C_6H_4	**17g**	42
3b	4-Br–C_6H_4	H	**13**	**14d**	4-CH_3–C_6H_4	**17h**	46
3c	4-C_2H_5–C_6H_4	H	**13**	**14i**	2-CH_3O-5-Br–C_6H_4	**17i**	44
11a	C_6H_5	—	**13**	**14c**	4-CH_3O–C_6H_5	**12a**	46
11a	4-C_2H_5O–C_6H_4	—	**13**	**14a**	C_6H_5	**12b**	52
11b	4-C_2H_5O–C_6H_4	—	**13**	**14b**	4-Cl–C_6H_4	**12c**	58
11b	4-C_2H_5O–C_6H_4	—	**13**	**14c**	4-CH_3O–C_6H_4	**12d**	40
11b	4-C_2H_5O–C_6H_4	—	**13**	**14d**	4-CH_3–C_6H_4	**12e**	51
1	CH_3	H	**19**	**14c**	4-CH_3O–C_6H_4	**20c**	25
1	CH_3	H	**19**	**14d**	4-CH_3–C_6H_4	**20d**	20
1	CH_3	H	**19**	**14e**	4-F–C_6H_4	**20e**	23
3a	C_6H_5	H	**19**	**14c**	4-CH_3O–C_6H_4	**21c**	21
3a	C_6H_5	H	**19**	**14d**	4-CH_3–C_6H_4	**21d**	18
3a	C_6H_5	H	**19**	**14e**	4-F–C_6H_4	**21e**	22

[a] Refluxing in HOAc.

(Scheme 3), which were identical to the compounds isolated from the reaction of **11** with arylidenepyruvic acids (Scheme 2).

Surprisingly, treatment of 3-substituted 5-aminopyrazoles **1**, **2**, **3a–c** with arylidenepyruvic acids **4a–c** and the three-component reaction of the same amines with pyruvic acids **13** and aldehydes **14a–d**,**i** led to the formation of a different set of reaction products, which vary in the position of the acid and R_2 substituents.

We have also established the possibility of using ethyl pyruvate **19** instead of pyruvic acid as a building block in the three-component reaction with amines **1**, **3a** and aldehydes. In this case, however, the corresponding pyrazolopyridines **20a–c** and **21a–c** were isolated in comparatively low yields (18–25%).

2.3. Microwave-assisted three-component reactions

As has been amply demonstrated, controlled microwave (MW) irradiation is a powerful tool for both speeding up reaction optimizations and for the efficient preparation of new target structures,[11] with numerous examples of microwave-assisted multicomponent condensations for the construction of heterocycles being reported.[12]

We therefore also studied the possibility to use MW irradiation for the optimization of the three-component reaction of 3-substituted 5-aminopyrazoles with pyruvic acid (ethyl pyruvate) and aromatic aldehydes (Table 3).

It was quickly established that the condensations of aminoazoles **1**, **3a** with pyruvic acid (**13**) and aldehydes **14a–d** could be carried out very efficiently under MW conditions, either in acetic acid or in ethanol in the presence of HCl as catalyst. Yields for both protocols were similar and also comparable to the yields obtained under conventional thermal reflux conditions (35–45%). Optimal reaction conditions involved MW irradiation of an equimolar mixture of starting materials in ethanol/HCl for 10 min at 150 °C. In this case, the final fused heterocyclic products **15a–d** and **17a–d** did not require additional purification.

Gratifyingly, it was also established that the MW-assisted reaction of ethyl pyruvate **19** with pyrazole **1**, **3a** and aldehydes **14c–h** in EtOH with acid catalysis allowed not only to decrease the reaction time from 120 to 10 min and made recrystallization of the crude product unnecessary, but also facilitated the isolation and considerably raised the yields of the target compounds **20c–h** and **21c–h** (from 18–25% to 35–48%).

In summary, the advantages of using the MW-assisted three-component procedure for the synthesis of pyrazolo[3,4-*b*]-pyridine-4-carboxylic acids are following: (i) replacement of acetic acid with ethanol, which allows a simplified work-up protocol; (ii) a 8–12-fold reduction of the reaction time; and (iii) a significantly increased product yield.

2.4. Structure elucidation

The structures of the heterocyclic compounds synthesized were established by IR spectroscopy, mass spectrometry, NMR spectral data and an X-ray diffraction study (for details, see Section 4).

The ^{1}H NMR spectra of the fused pyridine analogs **5**, **15**, **17**, **20** and **21** exhibit apart from signals for the terminal substituents and aromatic rings sharp singlets for the CH groups of the pyridine ring at ca. 8 ppm and broad peaks due to the NH– and COOH functionalities around 13–14 ppm.

Similarly, the ^{1}H NMR spectra of 2,7-diaryl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acids **8a–f** exhibit

Table 3. Microwave-assisted three-component reactions

Building blocks						Product[a]	
Aminopyrazole			Pyruvic acid derivative	Aldehyde			
Compound	R	R^1		Compound	R^2	Compound	Yield (%)
1	CH_3	H	**13**	**14a**	C_6H_5	**15a**	45
1	CH_3	H	**13**	**14b**	4-Cl–C_6H_4	**15b**	42
1	CH_3	H	**13**	**14c**	4-CH_3O–C_6H_4	**15c**	43
1	CH_3	H	**13**	**14d**	4-CH_3–C_6H_4	**15d**	35
3a	C_6H_5	H	**13**	**14a**	C_6H_5	**17a**	43
3a	C_6H_5	H	**13**	**14b**	4-Cl–C_6H_4	**17b**	44
3a	C_6H_5	H	**13**	**14c**	4-CH_3O–C_6H_4	**17c**	42
3a	C_6H_5	H	**13**	**14d**	4-CH_3–C_6H_4	**17d**	41
1	CH_3	H	**19**	**14c**	4-CH_3O–C_6H_4	**20c**	42
1	CH_3	H	**19**	**14d**	4-CH_3–C_6H_4	**20d**	42
1	CH_3	H	**19**	**14e**	4-F–C_6H_4	**20e**	47
1	CH_3	H	**19**	**14f**	4-Br–C_6H_4	**20f**	45
1	CH_3	H	**19**	**14g**	3-Cl–C_6H_4	**20g**	40
1	CH_3	H	**19**	**14h**	2-Cl–C_6H_4	**20h**	35
3a	C_6H_5	H	**19**	**14c**	4-CH_3O–C_6H_4	**21c**	43
3a	C_6H_5	H	**19**	**14d**	4-CH_3–C_6H_4	**21d**	48
3a	C_6H_5	H	**19**	**14e**	4-F–C_6H_4	**21e**	48
3a	C_6H_5	H	**19**	**14f**	4-Br–C_6H_4	**21f**	45
3a	C_6H_5	H	**19**	**14g**	3-Cl–C_6H_4	**21g**	41
3a	C_6H_5	H	**19**	**14h**	2-Cl–C_6H_4	**21h**	36

[a] Reaction in EtOH/HCl under MW irradiation for 10 min at 150 °C.

doublet of doublets for protons at positions 6 (~5.8 and 6.2 ppm, ^{3}J~4.2 Hz, ^{4}J~1.5 Hz with NH of pyrimidine ring) and a doublet of the CH proton at position 7 (~5.8 ppm, ^{3}J~4.2 Hz). The presence in spectra of a sharp singlet for the pyrazole CH at ~6 ppm shows that treatment did not affect this nucleophilic centre and confirms the formation of the pyrimidine ring. The resonances for the pyrimidine NH and COOH groups are present in the spectra at approximately 9.3 and 12.5 ppm, respectively.

The signals for the C=CH–CH fragment of the pyridine nucleus in dihydroderivatives **7a**,**b** and **9a**–**c**,**e**,**f** are shifted upfield as compared to compounds **8** and **12**, and the ethylene proton (doublet) does not show coupling with the amino group. The presence of a NH resonance signal for the pyrazole nucleus (for compound **9**) and the absence of a singlet for the pyrazole CH group confirmed the formation of the pyridine but not pyrimidine ring.

The structures of compounds **17a**–**i** were finally proven by an X-ray analysis (Fig. 1). Here it was also established that the bicyclic fragment is a planar within 0.02 Å. The bond alternation is observed within the pyridine ring (the C(3)–C(4) 1.419(6) Å and C(5)–C(6) 1.415(6) Å bonds are longer and the C(4)–C(5) 1.366(6) Å bond is shortened as compared to their mean value for a pyridine ring[13] 1.380 Å). The carboxylic group at the C(4) atom and the aromatic ring of the substituent at the C(2) atom are not coplanar with respect to the bicyclic fragment (the C(3)–C(4)–C(14)–O(1) and the C(3)–C(2)–C(15)–C(20) torsion angles are −31.9(7)° and −40.3(8)°, respectively). Such an arrangement of these substituents is caused, probably, by the repulsion between them (the shortened intramolecular contacts C(14)···C(20) 3.34 Å (the sum of the corresponding van der Waals radii[14] is 3.42 Å), O(1)···C(20) 2.94 Å (3.00 Å)).

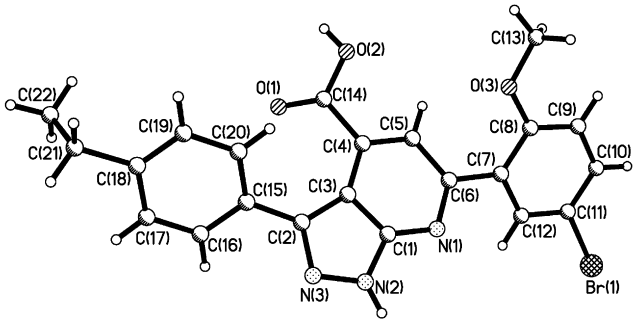


Figure 1. Molecular structure (X-ray diffraction data) of 3-(4-ethylphenyl)-6-(5-bromo-2-methoxyphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic acid (**17i**).

The benzene ring of the substituent at the C(6) atom is turned relatively the mean plane of the bicyclic fragment (the C(5)–C(6)–C(7)–C(8) torsion angle is 34.9(7)°). It can be assumed that such orientation of the substituent is stabilized by the attractive interactions C(5)–H(5)···O(3) 2.28 Å, and the C(12)–H(12)···N(1) 2.57 Å. The methoxy group and the benzene ring are almost coplanar (the C(13)–O(3)–C(8)–C(9) torsion angle is 6.2(7)°) despite of the repulsion between the methyl group and atoms of the aromatic ring (the shortened intramolecular contacts H(9)···C(13) 2.51 Å (2.87 Å), H(9)···H(13) 2.28 Å (2.34 Å), H(13b)···C(9) 2.71 Å (2.87 Å), H(13c)···C(9) 2.79 Å (2.87 Å)).

To establish the relative location of substituents in the other fused pyridine or pyrimidine derivatives, several additional experiments were carried out. Thus, compound **9f** was heteroaromatized in NMR tubes in DMSO-d_6, which confirmed that the products of oxidation have ^{1}H NMR spectra different from structures **17f** and equivalent to **10f**. On this basis, and with regard to the additional spectral data, the structure of 3,4-diaryl-4,7-dihydropyrazolo[3,4-*b*]pyridine-6-carboxylic acids were assigned to **9c**,**f**.

The locations of the substituents in pyrazolopyridines and pyrazolopyrimidines **5**–**9**, **16**, **17** were also derived on the basis of NOE experiments (Fig. 2). Thus, the presence or absence of an NOE between specific protons allowed to establish the structures for these compounds unequivocally.

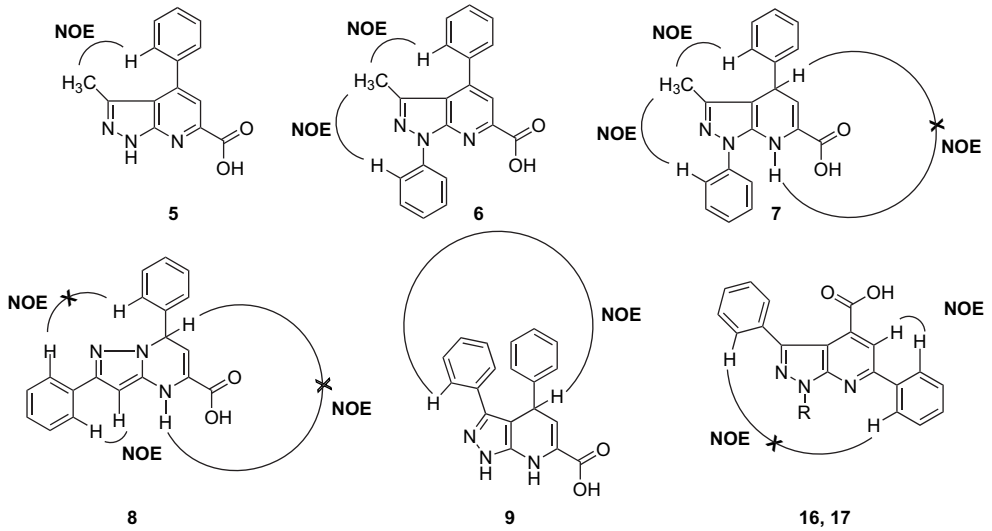
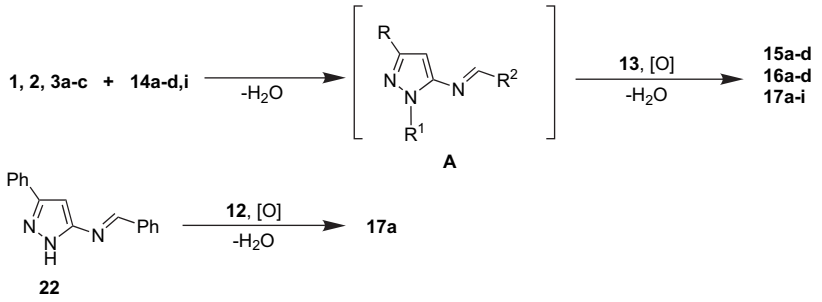


Figure 2. NOE experiments for structure determinations.



Scheme 4.

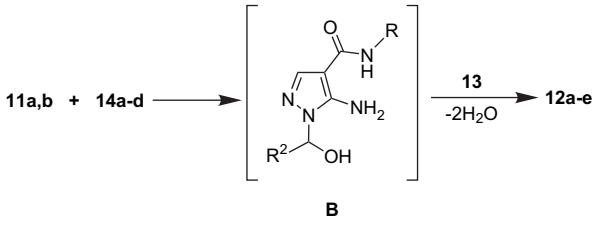
The similarity of the ^{1}H NMR spectra between dihydropyrimidines **12a–d** and compounds **8a–f** allowed to assign them the structure of 7-aryl-3-(arylcarbamoyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acids.

2.5. Mechanistic aspects

The different reaction pathways experienced in the transformation studies in the present investigation can be rationalized from the mechanistic point of view.

It is most likely that the three-component condensation of 3-substituted 5-aminopyrazoles **1**, **2**, **3a**,**b** with pyruvic acid (or ethyl pyruvate) and aromatic aldehydes proceeds through initial formation of the corresponding azomethine (intermediate **A**) with subsequent heterocyclization with pyruvic acid yielding the observed pyridine carboxylic acids **15**–**17** as products (Scheme 4). The condensation of independently synthesized azomethine **22** with pyruvic acid confirmed this assumption.

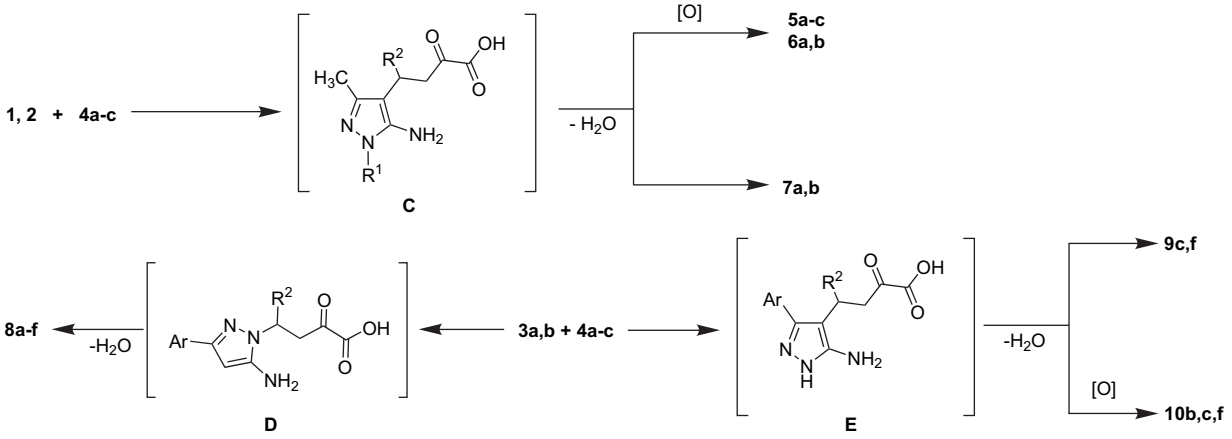
As it was pointed out above, three-component condensations involving aminopyrazoles **11a**,**b** leading to the formation of dihydropyrimidine derivatives **12a**–**e** do not proceed through azomethine formation. This is most likely the result of the influence of the carboxamide fragment on the nucleophilicity of the amino group via π-electron withdrawing effect and the formation of an intramolecular hydrogen bond (shown by the ^{1}H NMR spectrum of amines **11a**,**b**, having non-equivalent NH_2 protons). Here, the reaction is likely to proceed via a different pathway, for example, through initial nucleophilic attack of the endocyclic NH of the aldehyde carbonyl group (intermediate **B**, Scheme 5).



Scheme 5.

For the condensation of 3-methyl-5-aminopyrazoles **1**, **2** with arylidenepyruvic acids **4a–c** the initial reaction step possibly involves a nucleophilic attack of the CH group of the aminopyrazole to the C=C double bond of the unsaturated acid with the formation of Michael adduct **C** and its subsequent cyclization to pyridines **5**–**7** (Scheme 6). On the other hand, in the case of 3-aryl-5-aminopyrazoles **3a**–**c** the C=C double bond of the unsaturated acid may be attacked by both the endocyclic nitrogen atom (intermediate **D**) and (less likely) by the sterically hindered CH group (intermediate **E**), leading to the formation of pyrazolopyrimidines or mixtures with pyrimidine derivatives (structures **8** and **9**, respectively).

As it was pointed out above, the yields of pyridine derivatives **15**–**17**, **20**, **21** were always lower than 50%, both under atmospheric and inert conditions. Participation of one of the intermediates in the mechanistic pathway of the oxidation



Scheme 6.

process may be a reason for this fact. Unfortunately, our attempts to establish the composition of the mother liquor after isolation of the target compounds by preparative HPLC were unsuccessful.

3. Conclusions

The sequential and multicomponent reactions of 1-, 3- or 4-substituted 5-aminopyrazoles with arylidenepyruvic acids or their synthetic precursors were studied. Several different reaction pathways for these cyclocondensation reactions including the formation of pyrazolo[3,4-*b*]pyridine-6-carboxylic acids, pyrazolo[1,5-*a*]pyrimidine-5-carboxylic acids and pyrazolo[3,4-*b*]pyridine-4-carboxylic acids were established depending on the specific reaction conditions and building block selection. Facile and rapid microwave-assisted procedures for the synthesis of pyrazolo[3,4-*b*]pyridine-4-carboxylic acids were elaborated, which allowed a simple work-up protocol, reduction of the reaction time and a significant increase in yields. The formation of different reaction products was discussed from the mechanistic point of view.

4. Experimental

4.1. General

Melting points of all compounds synthesized were determined with a Kofler or Gallenkamp melting point apparatus. The NMR spectra were recorded in DMSO-d_6 at 360 MHz (90.5 MHz for ^{13}C) with a Bruker AMX-360 and at 200 MHz (50 MHz for ^{13}C) with a Varian Mercury VX-200 spectrometer. The MS spectra were measured on a GC–MS Varian 1200L (ionizing voltage 70 eV) instrument. IR spectra were recorded in KBr pellets with a Perkin–Elmer Spectrum One FTIR spectrometer. Elemental analysis was realized on EuroVector EA-3000.

All microwave experiments were performed using the Emrys™ Creator EXP and Emrys™ Initiator 8 synthesizers from Biotage AB (Uppsala, Sweden) possessing a single-mode microwave cavity producing controlled irradiation at 2.45 GHz. Experiments were carried out in sealed microwave process vials utilizing the high absorbance level. Reaction time reflects irradiation times at the set reaction temperature (fixed hold times).

4.1.1. General procedure for the synthesis of 4-aryl-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxylic acids 5a,b. A mixture of 5-amino-3-methylpyrazole **1** (1.1 mmol) and the appropriate arylidenepyruvic acid **4** (1.1 mmol) in 1 mL of acetic acid was refluxed for 1 h. After cooling, 5 mL of EtOH was added and the mixture was allowed to stand overnight. The precipitate formed was isolated by filtration, crystallized from EtOH and air dried.

4.1.1.1. 3-Methyl-4-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxylic acid (5a). Yield: 105 mg (38%) of yellow crystals, mp>300 °C. ^{1}H NMR (DMSO-d_6) δ 2.19 (s, 3H, CH_3), 7.1–7.6 (m, 5H, ArH), 7.65 (s, 1H, 5-H), 12.0 (br s, 1H, COOH), 13.68 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 12.4, 110.3, 119.0, 124.6, 125.8, 128.3, 140.1, 143.3, 144.0, 146.5, 148.2, 166.3. Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.51; H, 4.25; N, 16.61.

4.1.1.2. 4-(4-Methoxyphenyl)-3-methyl-1*H*-pyrazolo-[3,4-*b*]pyridine-6-carboxylic acid (5b). Yield: 130 mg (42%) of yellow crystals, mp>300 °C. ^{1}H NMR (DMSO-d_6) δ 2.24 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3) 7.0–7.5 (m, 4H, ArH), 7.62 (s, 1H, 5-H), 13.60 (s, 1H, NH). Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.71; H, 4.50; N, 14.87.

4.1.2. General procedure for the synthesis of 1,4-diaryl-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxylic acids 6a,b. A mixture of 5-amino-3-methyl-1-phenylpyrazole **2** (1.1 mmol) and the appropriate arylidenepyruvic acid **4** (1.1 mmol) in 0.7 mL of DMF was refluxed for 30 min. After cooling, 5 mL of EtOH was added and the mixture was allowed to stand overnight. The precipitate formed was isolated by filtration, crystallized from EtOH and air dried.

4.1.2.1. 3-Methyl-1,4-diphenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-6-carboxylic acid (6a). Yield: 140 mg (39%) of yellow crystals, mp 268–270 °C. ^{1}H NMR (DMSO-d_6) δ 2.21 (s, 3H, CH_3), 7.2–8.4 (m, 10H, ArH), 7.75 (s, 1H, 5-H), 13.5 (br s, 1H, COOH). ^{13}C NMR (DMSO-d_6) δ 14.2, 107.7, 118.3, 121.1, 123.2, 126.3, 126.6, 127.1, 127.7, 134.6, 142.8, 143.1, 144.1, 147.1, 151.0, 166.0. MS (El, 70 eV): *m*/*z* (%)=329 (100%) [M$^+$], 285 (40.3). Anal. Calcd for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 73.02; H, 4.47; N, 12.80.

4.1.2.2. 4-(4-Methoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxylic acid (6b). Yield: 190 mg (48%) of yellow crystals, mp 262–264 °C. ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3) 7.10–8.33 (m, 10H, ArH), 7.75 (s, 1H, 5-H), 13.5 (br s, 1H, COOH). Anal. Calcd for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.99. Found: C, 70.21; H, 4.68; N, 12.02.

4.1.3. General procedure for the synthesis of 1,4-diaryl-3-methyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxylic acids 7a,b. A mixture of 5-amino-3-methyl-1-phenylpyrazole **2** (1.1 mmol) and the appropriate arylidenepyruvic acid **4** (1.1 mmol) in 3 mL of acetic acid was refluxed for 30 min. The mixture was allowed to stand overnight and the precipitate formed was isolated by filtration. The by-products **6** were removed by crystallization from EtOH.

4.1.3.1. 3-Methyl-1,4-diphenyl-4,7-dihydro-1*H*-pyrazolo [3,4-*b*]pyridine-6-carboxylic acid (7a). Yield: 250 mg (68%) of yellow crystals, mp 222–224 °C. IR (KBr): 3264, 1708, 1596, 1252. ^{1}H NMR (DMSO-d_6) δ 1.75 (s, 3H, CH_3), 4.91 (d, *J*=4 Hz, 1H, 4-H), 5.73 (d, *J*=4 Hz, 1H, 5-H), 7.1–7.7 (m, 10H, ArH), 13.5 (br s, 2H, NH+COOH). ^{13}C NMR (DMSO-d_6) δ 15.1, 44.2, 99.1, 115.6, 123.7, 124.0, 125.1, 128.1, 129.2, 129.1, 131.4, 138.6, 141.8, 145.15, 145.7, 169.3. Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.52; H, 5.06; N, 12.71.

4.1.3.2. 4-(4-Methoxyphenyl)-3-methyl-1-phenyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxylic acid (7b). Yield: 290 mg (72%) of yellow crystals, mp 238–240 °C.

^{1}H NMR (DMSO-d_6) δ 1.75 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 4.85 (d, J=4.3 Hz, 1H, 4-H), 5.70 (d, J=4.3 Hz, 1H, 5-H), 6.8–7.6 (m, 9H, ArH), 13.2 (br s, 2H, NH+COOH). Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.84; H, 5.20; N, 11.64.

4.1.4. General procedure for the synthesis of 2,7-diaryl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acids 8a–c,d–f, 3,4-diaryl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxylic acids 9c,f and 10b,f. A mixture of the appropriate 5-amino-3-arylpyrazole **3** (1.1 mmol) and of the corresponding arylidenepyruvic acid **4** (1.1 mmol) in 3 mL of acetic acid was refluxed for 30 min. After cooling, the precipitate formed was filtered and if needed recrystallized from EtOH. The acids **8c**,**f** were isolated from **9c** and **10f** by crystallization from EtOH. Compounds **8b** and **9f** were obtained using the same procedure under a nitrogen atmosphere.

4.1.4.1. 2,7-Diphenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acid (8a). Yield: 260 mg (75%) of yellowish crystals, mp 215–217 °C. IR (KBr): 3350, 1710, 1597. ^{1}H NMR (DMSO-d_6) δ 5.69 (dd, ^3J=4.5, 1.7 Hz, 1H, 6-H), 6.01 (s, 1H, 3-H), 6.20 (d, J=4.5 Hz, 1H, 7-H), 7.1–7.7 (m, 10H, ArH), 9.28 (d, J=1.7 Hz, NH), 12.53 (br s, 1H, COOH). ^{13}C NMR (DMSO-d_6) δ 61.1, 83.0, 117.1, 125.4, 127.7, 128.5, 130.9, 132.1, 133.8, 134.7, 138.3, 139.1, 141.1, 147.9, 166.3. Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 72.02; H, 4.65; N, 13.27.

4.1.4.2. 7-(4-Chlorophenyl)-2-phenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acid (8b). Yield: 300 mg (78%) of yellowish crystals, mp 216–218 °C. ^{1}H NMR (DMSO-d_6) δ 5.67 (dd, J=4.1, 1.3 Hz, 1H, 6-H), 6.01 (s, 1H, 3-H), 6.23 (d, J=4.1 Hz, 1H, 7-H), 7.15–7.7 (m, 9H, ArH), 9.32 (d, J=1.7 Hz, NH), 12.5 (br s, 1H, COOH). Anal. Calcd for $C_{19}H_{14}ClN_3O_2$: C, 64.87; H, 4.01; N, 11.94. Found: C, 64.83; H, 3.90; N, 11.97.

4.1.4.3. 7-(4-Methoxyphenyl)-2-phenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acid (8c). Yield: 200 mg (52%) of yellowish crystals, mp 214–216 °C. ^{1}H NMR (DMSO-d_6) δ 3.69 (s, 3H, OCH_3), δ 5.67 (dd, J=4.2, 1.8 Hz, 1H, 6-H), 5.98 (s, 1H, 3-H), 6.13 (d, J=4.2 Hz, 1H, 7-H), 6.82–7.68 (m, 9H, ArH), 9.22 (d, J=1.8 Hz, NH), 12.56 (br s, 1H, COOH). Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.16; H, 4.85; N, 12.13.

4.1.4.4. 2-(4-Bromophenyl)-7-phenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acid (8d). Yield: 280 mg (65%) of yellowish crystals, mp 222–225 °C. ^{1}H NMR (DMSO-d_6) δ 5.69 (dd, ^3J=4.2 Hz, ^4J=1.8 Hz, 1H, 6-H), 6.02 (s, 1H, 3-H), 6.19 (d, J=4.2 Hz, 1H, 7-H), 7.1–7.6 (m, 9H, ArH), 9.32 (s, 1H, NH), 12.58 (br s, 1H, COOH). Anal. Calcd for $C_{19}H_{14}BrN_3O_2$: C, 57.59; H, 3.56; N, 10.60. Found: C, 57.62; H, 3.42; N, 10.62.

4.1.4.5. 2-(4-Bromophenyl)-7-(4-chlorophenyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acid (8e). Yield: 360 mg (76%) of yellowish crystals, mp 220–222 °C. IR (KBr): 3413, 1710, 1595. ^{1}H NMR (DMSO-d_6) δ 5.68 (dd, J=4.3, 1.7 Hz, 1H, 6-H), 6.03 (s, 1H, 3-H), 6.22 (d, J=4.3 Hz, 1H, 7-H), 7.14–7.65 (m, 8H, ArH), 9.38 (s, NH), 12.70 (br s, 1H, COOH). Anal. Calcd for $C_{19}H_{13}BrClN_3O_2$: C, 52.99; H, 3.04; N, 9.76. Found: C, 53.01; H, 2.98; N, 9.80.

4.1.4.6. 2-(4-Bromophenyl)-7-(4-methoxyphenyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acid (8f). Yield: 220 mg (48%) of yellowish crystals, mp 214–216 °C. ^{1}H NMR (DMSO-d_6) δ 3.7 (s, 3H, OCH_3), δ 5.66 (dd, J=4.3, 1.9 Hz, 1H, 6-H), 6.0 (s, 1H, 3-H), 6.13 (d, J=4.3 Hz, 1H, 7-H), 6.8–7.6 (m, 8H, ArH), 9.27 (d, J=1.9 Hz, NH). Anal. Calcd for $C_{20}H_{16}BrN_3O_3$: C, 56.35; H, 3.78; N, 9.86. Found: C, 56.38; H, 3.65; N, 9.82.

4.1.4.7. 4-(4-Methoxyphenyl)-3-phenyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxylic acid (9c). Yield: 100 mg (26%) of yellow crystals, mp 265–267 °C. ^{1}H NMR (DMSO-d_6) δ 3.63 (s, 3H, OCH_3), 5.11 (d, J=4.9 Hz, 1H, 4-H), 5.54 (d, J=4.9 Hz, 1H, 5-H), 6.68–7.47 (m, 9H, ArH), 7.78 (s, NH), 14.22 (br s, NH), 12.78 (br s, 1H, COOH). Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.18; H, 4.82; N, 12.12.

4.1.4.8. 3-(4-Bromophenyl)-4-(4-methoxyphenyl)-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxylic acid (9f). Yield: 260 mg (56%) of yellow crystals, mp 276–278 °C. IR (KBr): 3480, 1711, 1666, 1605, 1509. ^{1}H NMR (DMSO-d_6) δ 3.64 (s, 3H, OCH_3), 5.12 (d, J=4.7 Hz, 1H, 4-H), 5.53 (d, J=4.7 Hz, 1H, 5-H), 6.7–7.5 (m, 8H, ArH), 7.86 (s, NH), 14.3 (br s, NH), 12.85 (br s, 1H, COOH). Anal. Calcd for $C_{20}H_{16}BrN_3O_3$: C, 56.35; H, 3.78; N, 9.86. Found: C, 56.39; H, 3.65; N, 9.75.

4.1.4.9. 4-(4-Chlorophenyl)-3-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-6-carboxylic acid (10b). Yield: 120 mg (31%) of yellowish crystals, mp>300 °C. ^{1}H NMR (DMSO-d_6) δ 7.80 (s, 1H, 5-H), 7.0–7.4 (m, 9H, ArH), 14.3 (br s, 1H, NH), 13.9 (br s, 1H, COOH). Anal. Calcd for $C_{19}H_{12}ClN_3O_2$: C, 65.24; H, 3.46; N, 12.01. Found: C, 65.31; H, 3.36; N, 12.05.

4.1.4.10. 3-(4-Bromophenyl)-4-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxylic acid (10f). Yield: 100 mg (22%) of yellow crystals, mp>300 °C. ^{1}H NMR (DMSO-d_6) δ 3.75 (s, 3H, OCH_3), 7.78 (s, 1H, 5-H), 6.7–7.4 (m, 8H, ArH), 14.31 (br s, 1H, NH), 13.95 (br s, 1H, COOH). Anal. Calcd for $C_{20}H_{14}BrN_3O_3$: C, 56.62; H, 3.33; N, 9.90. Found: C, 56.69; H, 3.22; N, 9.87.

4.1.5. General procedures for the synthesis of 7-aryl-3-(arylcarbamoyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acid 12a–e. *Method A*: A mixture of the appropriate 5-amino-*N*-aryl-1*H*-pyrazole-4-carboxamide **11** (1 mmol) and the corresponding arylidenepyruvic acid **4** (1 mmol) was refluxed in 5 mL of acetic acid for 10–20 min until a solid started to precipitate. After cooling, the crystals formed were removed by filtration, washed with EtOH and air dried. If required, products were crystallized from EtOH.

Method B: A mixture of the appropriate 5-amino-*N*-aryl-1*H*-pyrazole-4-carboxamide **11** (1 mmol), pyruvic acid **13**

(1 mmol) and the corresponding aldehyde **14** (1 mmol) was refluxed in 3 mL of acetic acid for 2 h. After cooling, the crystals precipitated were removed by filtration, washed with EtOH and air dried. If required, products were crystallized from EtOH.

4.1.5.1. 7-(4-Methoxyphenyl)-3-(phenylcarbamoyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acid (12a). Yields: 265 mg (68%, method A) and 180 mg (46%, method B) of yellowish crystals, mp 254–256 °C. ^{1}H NMR (DMSO-d_6) δ 3.71 (s, 3H, OCH_3), 5.81 (dd, J=4.1, 1.8 Hz, 1H, 6-H), 6.17 (d, J=4.1 Hz, 1H, 7-H), 6.8–7.7 (m, 9H, ArH), 8.06 (br s, 1H, 2-H), 8.39 (d, J=1.8 Hz, 1H, NH), 9.76 (s, 1H, CONH). Anal. Calcd for $C_{21}H_{18}N_4O_4$: C, 64.61; H, 4.65; N, 14.35. Found: C, 64.63; H, 4.57; N, 14.37.

4.1.5.2. 3-[(4-Ethoxyphenyl)carbamoyl]-7-phenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acid (12b). Yields: 275 mg (68%, method A) and 210 mg (52%, method B) of yellowish crystals, mp 266–268 °C. IR (KBr): 3400, 1746, 1722, 1600, 1509. ^{1}H NMR (DMSO-d_6) δ 1.3 (t, 3H, OCH_2CH_3), 3.98 (q, 2H, OCH_2CH_3), 5.83 (dd, J=4.1, 1.8 Hz, 1H, 6-H), 6.23 (d, J=4.1 Hz, 1H, 7-H), 6.8–7.6 (m, 9H, ArH), 8.04 (s, 2-H), 8.42 (d, J=1.8 Hz, 1H, NH), 9.68 (s, 1H, CONH). Anal. Calcd for $C_{22}H_{20}N_4O_4$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.38; H, 4.87; N, 13.86.

4.1.5.3. 5-(4-Chlorophenyl)-3-[(4-ethoxyphenyl)carbamoyl]-4,5-dihydropyrazolo[1,5-*a*]pyrimidine-7-carboxylic acid (12c). Yields: 310 mg (72%, method A) and 250 mg (58%, method B) of yellowish crystals, mp 267–269 °C. IR (KBr): 3393, 3361, 1755, 1721, 1603, 1510. ^{1}H NMR (DMSO-d_6) δ 1.3 (t, 3H, OCH_2CH_3), 3.98 (q, 2H, OCH_2CH_3), 5.82 (d, J=4.2 Hz, 1H, 6-H), 6.27 (dd, J=4.1, 1.7 Hz, 1H, 7-H), 6.8–7.6 (m, 8H, ArH), 8.05 (s, 1H, 2-H), 8.43 (d, J=1.7 Hz, 1H, NH), 9.68 (s, 1H, CONH). Anal. Calcd for $C_{22}H_{19}ClN_4O_4$: C, 60.21; H, 4.36; N, 12.77. Found: C, 60.25; H, 4.24; N, 12.80.

4.1.5.4. 3-[(4-Ethoxyphenyl)carbamoyl]-7-(4-methoxyphenyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acid (12d). Yields: 290 mg (68%, method A) and 170 mg (40%, method B) of yellowish crystals, mp 267–269 °C. IR (KBr): 3388, 1720, 1599, 1509. ^{1}H NMR (DMSO-d_6) δ 1.3 (t, 3H, OCH_2CH_3), 3.98 (q, 2H, OCH_2CH_3), 3.72 (s, 3H, OCH_3), 5.81 (dd, J=4.1, 1.8 Hz, 1H, 6-H), 6.17 (d, J=4.1 Hz, 1H, 7-H), 6.8–7.6 (m, 8H, ArH), 8.02 (s, 1H, 2-H), 8.4 (d, J=1.8 Hz, 1H, NH), 9.66 (s, 1H, CONH). Anal. Calcd for $C_{23}H_{22}N_4O_5$: C, 63.59; H, 5.10; N, 12.90. Found: C, 63.61; H, 5.00; N, 12.92.

4.1.5.5. 3-[(4-Ethoxyphenyl)carbamoyl)-5-*p*-tolyl-4,5-dihydropyrazolo[1,5-*a*]pyrimidine-7-carboxylic acid (12e). Yields: 270 mg (65%, method A) and 210 mg (51%, method B) of yellowish crystals, mp 265–267 °C. IR (KBr): 3416, 1717, 1602, 1510. ^{1}H NMR (DMSO-d_6) δ 1.3 (t, 3H, OCH_2CH_3), 3.98 (q, 2H, OCH_2CH_3), 2.26 (s, 3H, CH_3), 5.80 (dd, J=4.1, 1.7 Hz, 1H, 6-H), 6.18 (d, J=4.1 Hz, 1H, 7-H), 6.8–7.6 (m, 8H, ArH), 8.02 (s, 1H, 2-H), 8.39 (d, J=1.7 Hz, 1H, NH), 9.67 (s, 1H, CONH). Anal. Calcd for $C_{23}H_{22}N_4O_4$: C, 66.02; H, 5.30; N, 13.39. Found: C, 66.07; H, 5.19; N, 13.42.

4.1.6. General procedure for the synthesis of 6-aryl-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic acids 15a–d and 3,6-diaryl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic acids 17a–i. *Conventional method C*: A mixture of the appropriate 5-aminopyrazole **1** or **3a** (2 mmol), pyruvic acid **13** (2 mmol) and the corresponding aromatic aldehyde **14** (2 mmol) in 3 mL of acetic acid was refluxed for 10–40 min until a solid started to precipitate. After cooling, the crystals formed were removed by filtration, crystallized from EtOH and air dried.

Microwave-assisted method D: A mixture of the appropriate 5-aminopyrazole **1** or **3a** (1.3 mmol), pyruvic acid **13** (1.3 mmol) and the corresponding aromatic aldehyde **14** (1.3 mmol) in 1 mL of EtOH with two drops of HCl was irradiated under sealed vessel microwave conditions at 150 °C for 10 min in a 5 mL microwave process vial. After cooling, the crystals formed were removed by filtration, washed with EtOH and air dried.

4.1.6.1. 3-Methyl-6-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic acid (15a). Yields: 210 mg (42%, method C) and 150 mg (45%, method D) of yellow crystals, mp>300 °C. IR (KBr): 3244, 1708, 1592. ^{1}H NMR (DMSO-d_6) δ 2.60 (s, 3H, CH_3), 7.4–8.2 (m, 5H, ArH), 8.02 (s, 1H, 5-H), 13.55 (br s, 2H, NH+COOH). ^{13}C NMR (DMSO-d_6) δ 14.5, 115.1, 119.7, 128.6, 129.0, 131.5, 134.8, 135.2, 142.5, 148.3, 155.7, 167.7. Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.57; H, 4.25; N, 16.54.

4.1.6.2. 6-(4-Chlorophenyl)-3-methyl-1*H*-pyrazolo-[3,4-*b*]pyridine-4-carboxylic acid (15b). Yields: 220 mg (39%, method C) and 160 mg (42%, method D) of yellow crystals, mp>300 °C. IR (KBr): 3172, 1716, 1592. ^{1}H NMR (DMSO-d_6) δ 2.59 (s, 3H, CH_3), 7.53–8.25 (m, 4H, ArH), 7.98 (s, 1H, 5-H), 13.58 (br s, 2H, NH+COOH). Anal. Calcd for $C_{14}H_{10}ClN_3O_2$: C, 58.42; H, 3.50; N, 14.61. Found: C, 58.36; H, 3.35; N, 14.58.

4.1.6.3. 6-(4-Methoxyphenyl)-3-methyl-1*H*-pyrazolo-[3,4-*b*]pyridine-4-carboxylic acid (15c). Yields: 240 mg (42%, method C) and 160 mg (43%, method D) of yellow crystals, mp>300 °C. IR (KBr): 3248, 1712, 1596. ^{1}H NMR (DMSO-d_6) δ 2.58 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 7.0–8.2 (m, 4H, ArH), 7.95 (s, 1H, 5-H), 13.56 (br s, 2H, NH+COOH). Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.57; H, 4.50; N, 14.87.

4.1.6.4. 3-Methyl-6-*p*-tolyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic acid (15d). Yields: 170 mg (32%, method C) and 120 mg (35%, method D) of yellow crystals, mp>300 °C. IR (KBr): 3248, 1712, 1592. ^{1}H NMR (DMSO-d_6) δ 2.59 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 7.3–8.1 (m, 4H, ArH), 7.97 (s, 1H, 5-H), 13.56 (br s, 2H, NH+COOH). Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.90; N, 15.72. Found: C, 67.44; H, 4.79; N, 15.68.

4.1.6.5. 3,6-Diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic acid (17a). Yields: 265 mg (42%, method C) and 180 mg (43%, method D) of yellow crystals, mp>300 °C. IR (KBr): 3268, 1708, 1592. ^{1}H NMR (DMSO-d_6) δ 7.4–8.3 (m, 10H, ArH), 7.97 (s, 1H, 5-H),

13.50 (br s, 1H, COOH), 14.13 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 114.92, 118.3, 128.7, 128.9, 129.3, 130.1, 130.3, 131.0, 134.1, 135.7, 142.1, 143.6, 147.3, 156.1, 167.5. Anal. Calcd for $C_{19}H_{13}N_3O_2$: C, 72.37; H, 4.16; N, 13.33. Found: C, 72.25; H, 4.22; N, 13.36.

4.1.6.6. 6-(4-Chlorophenyl)-3-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-4-carboxylic acid (17b). Yields: 310 mg (44%, method C) and 200 mg (44%, method D) of yellow crystals, mp>300 °C. IR (KBr): 3264, 1712, 1596. ^{1}H NMR (DMSO-d_6) δ 7.37–8.33 (m, 9H, ArH), 8.00 (s, 1H, 5-H), 13.49 (br s, 1H, COOH), 14.16 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 107.8, 113.7, 128.6, 128.61, 129.1, 129.2, 129.66, 129.69, 134.51, 135.44, 137.45, 137.62, 154.37, 155.19, 168.04. Anal. Calcd for $C_{19}H_{12}ClN_3O_2$: C, 65.24; H, 3.46; N, 12.01. Found: C, 65.18; H, 3.58; N, 12.05.

4.1.6.7. 6-(4-Methoxyphenyl)-3-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-4-carboxylic acid (17c). Yields: 290 mg (42%, method C) and 190 mg (42%, method D) of yellow crystals, mp>300 °C. IR (KBr): 3260, 1708, 1596. ^{1}H NMR (DMSO-d_6) δ 7.0–8.30 (m, 9H, ArH), 7.91 (s, 1H, 5-H), 13.58 (br s, 1H, COOH), 14.02 (br s, 1H, NH), 3.83 (s, 3H, OCH_3). Anal. Calcd for $C_{20}H_{15}N_3O_3$: C, 69.56; H, 4.38; N, 12.76. Found: C, 69.51; H, 4.25; N, 12.68.

4.1.6.8. 3-Phenyl-6-*p*-tolyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic acid (17d). Yields: 260 mg (39%, method C) and 180 mg (42%, method D) of yellow crystals, mp>300 °C. ^{1}H NMR (DMSO-d_6) δ 7.3–8.2 (m, 9H, ArH), 7.94 (s, 1H, 5-H), 13.65 (br s, 1H, COOH), 14.08 (br s, 1H, NH), 2.38 (s, 3H, CH_3). Anal. Calcd for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 72.90; H, 4.67; N, 12.79.

4.1.6.9. 3-(4-Bromophenyl)-6-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-4-carboxylic acid (17e). Yield: 310 mg (40%, method C) of yellow crystals, mp>300 °C. ^{1}H NMR (DMSO-d_6) δ 7.5–8.2 (m, 9H, ArH), 8.00 (s, 1H, 5-H), 14.20 (br s, 1H, NH). Anal. Calcd for $C_{19}H_{12}BrN_3O_2$: C, 57.89; H, 3.07; N, 10.66. Found: C, 57.84; H, 3.15; N, 10.61.

4.1.6.10. 3-(4-Bromophenyl)-6-(4-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic acid (17f). Yield: 380 mg (45%, method C) of yellow crystals, mp>300 °C. ^{1}H NMR (DMSO-d_6) δ 7.5–8.3 (m, 8H, ArH), 8.02 (s, 1H, 5-H), 13.4 (br s, 1H, COOH), 14.24 (br s, 1H, NH). Anal. Calcd for $C_{19}H_{11}BrClN_3O_2$: C, 53.24; H, 2.59; N, 9.80. Found: C, 53.20; H, 2.50; N, 9.84.

4.1.6.11. 3-(4-Bromophenyl)-6-(4-methoxyphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic acid (17g). Yield: 350 mg (42%, method C) of yellow crystals, mp>300 °C. ^{1}H NMR (DMSO-d_6) δ 7.0–8.30 (m, 8H, ArH), 7.95 (s, 1H, 5-H), 14.12 (br s, 1H, NH), 3.83 (s, 3H, OCH_3). Anal. Calcd for $C_{20}H_{14}BrN_3O_3$: C, 56.62; H, 3.33; N, 9.90. Found: C, 56.58; H, 3.23; N, 9.94.

4.1.6.12. 3-(4-Bromophenyl)-6-*p*-tolyl-1*H*-pyrazolo-[3,4-*b*]pyridine-4-carboxylic acid (17h). Yield: 370 mg (46%, method C) of yellow crystals, mp>300 °C. ^{1}H NMR (DMSO-d_6) δ 7.3–8.2 (m, 8H, ArH), 7.96 (s, 1H, 5-H), 13.6 (br s, 1H, COOH), 14.12 (br s, 1H, NH), 2.38 (s, 3H, CH_3). Anal. Calcd for $C_{20}H_{14}BrN_3O_2$: C, 58.84; H, 3.46; N, 10.29. Found: C, 58.87; H, 3.33; N, 10.34.

4.1.6.13. 6-(5-Bromo-2-methoxyphenyl)-3-(4-ethylphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic acid (17i). Yield: 395 mg (44%, method C) of yellow crystals, mp>300 °C. ^{1}H NMR (DMSO-d_6) δ 1.22 (t, 3H, CH_2CH_3), 2.66 (q, 2H, CH_2CH_3), 3.86 (s, 3H, OCH_3), 7.3–8.2 (m, 8H, ArH), 7.86 (s, 1H, 5-H), 13.5 (br s, 1H, COOH), 14.09 (br s, 1H, NH). Anal. Calcd for $C_{22}H_{18}BrN_3O_3$: C, 58.42; H, 4.01; N, 9.29. Found: C, 58.46; H, 4.11; N, 9.26.

4.1.7. General procedure for the synthesis of 1,6-diaryl-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic acids 16a–d. A mixture of 5-amino-3-methyl-1-phenylpyrazole **2** (1.1 mmol), pyruvic acid **13** (1.1 mmol) and the appropriate aromatic aldehyde **14** (1.1 mmol) in 0.5 mL of DMF was refluxed for 20–25 min. Then 5 mL of MeOH was added and the reaction mixture was allowed to stand overnight. The solid precipitated was removed by filtration, washed with MeOH and air dried. If required, the crude compounds were recrystallized from EtOH.

4.1.7.1. 3-Methyl-1,6-diphenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-4-carboxylic acid (16a). Yield: 140 mg (38%) of yellow crystals, mp 285–287 °C. ^{1}H NMR (DMSO-d_6) δ 2.70 (s, 3H, CH_3), 7.3–8.4 (m, 10H, ArH), 8.15 (s, 1H, 5-H), 13.70 (br s, 1H, COOH). ^{13}C NMR (DMSO-d_6) δ 13.5, 114.3, 118.3, 121.1, 126.6, 127.1, 129.0, 129.1, 130.3, 133.3, 134.7, 138.5, 142.7, 150.7, 155.4, 170.1. Anal. Calcd for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 73.03; H, 4.41; N, 12.79.

4.1.7.2. 6-(4-Chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic acid (16b). Yield: 180 mg (44%) of yellow crystals, mp 280–282 °C. ^{1}H NMR (DMSO-d_6) δ 2.68 (s, 3H, CH_3), 7.3–8.4 (m, 9H, ArH), 8.14 (s, 1H, 5-H). Anal. Calcd for $C_{20}H_{14}ClN_3O_2$: C, 66.03; H, 3.88; N, 11.55. Found: C, 66.07; H, 3.72; N, 11.57.

4.1.7.3. 6-(4-Methoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic acid (16c). Yield: 170 mg (42%) of yellow crystals, mp 278–280 °C. ^{1}H NMR (DMSO-d_6) δ 2.68 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 7.1–8.35 (m, 9H, ArH), 8.09 (s, 1H, 5-H), 14.1 (br s, 1H, COOH). Anal. Calcd for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.69. Found: C, 70.22; H, 4.58; N, 11.72.

4.1.7.4. 3-Methyl-1-phenyl-6-*p*-tolyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic acid (16d). Yield: 140 mg (36%) of yellow crystals, mp 275–277 °C. ^{1}H NMR (DMSO-d_6) δ 2.68 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 7.25–8.25 (m, 9H, ArH), 8.11 (s, 1H, 5-H). Anal. Calcd for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.48; H, 4.82; N, 12.21.

4.1.8. General procedures for the synthesis of ethyl 6-aryl-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylates 20c–h and ethyl 3,6-diaryl-1*H*-pyrazolo[3,4-*b*]-pyridine-4-carboxylates 21c–h. *Conventional method E*: A mixture of corresponding 5-aminopyrazol **1** or **3a** (1.3 mmol), ethyl pyruvate **19** (1.3 mmol) and the appropriate aromatic aldehyde **14** (1.3 mmol) in 5 mL of acetic acid

was refluxed for 100–120 min (TLC control). Then 10 mL of EtOH/H_2O (1:1) was added to the reaction mixture, the crystals formed were removed by filtration, washed with EtOH/H_2O (1:1) and air dried. The crude products were recrystallized from EtOH.

MW-assisted method F: A mixture of the corresponding 5-aminopyrazole **1** or **3a** (1.3 mmol), ethyl pyruvate **19** (1.3 mmol) and the appropriate aromatic aldehyde **14** (1.3 mmol) in 1 mL of EtOH containing one drop of concd HCl was irradiated under sealed vessel microwave conditions at 150 °C for 10 min in a 5 mL microwave process vial. Then 4 mL of EtOH/H_2O (1:1) was added to the reaction mixture, the crystals formed were removed by filtration, washed with EtOH/H_2O (1:1) and air dried.

4.1.8.1. Ethyl 6-(4-methoxyphenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (20c). Yields: 100 mg (25%, method E) and 170 mg (42%, method F) of yellowish crystals, mp 177–180 °C. ^{1}H NMR (DMSO-d_6) δ 1.41 (t, J=7.0 Hz, 3H, CH_3CH_2), 2.58 (s, 3H, CH_3), 3.83 (s, 3H, CH_3O), 4.45 (q, J=7.0 Hz, 2H, CH_3CH_2), 7.07 (d, J=9 Hz, 2H, ArH), 7.97 (s, 1H, 5-H), 8.12 (d, J=9 Hz, 2H, ArH), 13.54 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 14.5, 16.2, 55.8, 62.2, 108.8, 113.5, 114.8, 129.0, 130.8, 134.0, 141.0, 154.4, 155.6, 161.2, 165.9. MS (El, 70 eV): m/z (%)=312 (100%) [M$^+$]. Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.40; H, 5.59; N, 13.48.

4.1.8.2. Ethyl 3-methyl-6-*p*-tolyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (20d). Yields: 80 mg (20%, method E) and 140 mg (42%, method F) of yellowish crystals, mp 188–191 °C. ^{1}H NMR (DMSO-d_6) δ 1.38 (t, J=7.0 Hz, 3H, CH_3CH_2), 2.34 (s, 3H, CH_3), 2.57 (s, 3H, CH_3O), 4.43 (q, J=7.0 Hz, 2H, CH_3CH_2), 7.30 (d, J=8.3 Hz, 2H, ArH), 7.96 (s, 1H, 5-H), 8.02 (d, J=8.3 Hz, 2H, ArH), 13.58 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 14.5, 21.2, 62.21, 109.1, 113.8, 127.4, 130.0, 134.0, 135.6, 140.0, 141.0, 154.4, 155.8, 165.8. MS (El, 70 eV): m/z (%)=296 (100%) [M$^+$]. Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.25; H, 5.71; N, 14.26.

4.1.8.3. Ethyl 6-(4-fluorophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (20e). Yields: 90 mg (23%, method E) and 180 mg (47%, method F) of yellowish crystals, mp 160–163 °C. ^{1}H NMR (DMSO-d_6) δ 1.39 (t, J=7.0 Hz, 3H, CH_3CH_2), 2.57 (s, 3H, CH_3), 4.43 (q, J=7.0 Hz, 2H, CH_3CH_2), 7.33 (m, 2H, ArH), 7.97 (s, 1H, 5-H), 8.17 (m, 2H, ArH), 13.61 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 14.5, 16.2, 62.3, 109.2, 113.9, 116.1, 116.4, 129.7, 129.9, 134.2, 134.8, 141.0, 145.3, 154.7, 162.3, 165.1, 165.7. Anal. Calcd for $C_{16}H_{14}FN_3O_2$: C, 64.21; H, 4.71; N, 14.04. Found: C, 64.14; H, 4.87; N, 14.02.

4.1.8.4. Ethyl 6-(4-bromophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (20f). Yield: 210 mg (45%, method F) of yellowish crystals, mp 131–135 °C. ^{1}H NMR (DMSO-d_6) δ 1.39 (t, J=7.0 Hz, 3H, CH_3CH_2), 2.58 (s, 3H, CH_3), 4.44 (q, J=7.0 Hz, 2H, CH_3CH_2), 7.70 (d, J=8.8 Hz, 2H, ArH), 7.99 (s, 1H, 5-H), 8.08 (d, J=8.8 Hz, 2H, ArH), 13.66 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 14.5, 16.2, 62.3, 109.5, 113.9, 123.9, 129.6, 132.4, 134.3, 137.5, 141.0, 154.3, 154.5, 166.0. MS (El, 70 eV): m/z (%)=362 (100%) [M$^+$]. Anal. Calcd for $C_{16}H_{14}BrN_3O_2$: C, 53.35; H, 3.92; N, 11.67. Found: C, 53.21; H, 4.06; N, 11.63.

4.1.8.5. Ethyl 6-(3-chlorophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (20g). Yield: 160 mg (40%, method F) of yellowish crystals, mp 112–114 °C. ^{1}H NMR (DMSO-d_6) δ 1.39 (t, J=7.0 Hz, 3H, CH_3CH_2), 2.57 (s, 3H, CH_3), 4.44 (q, J=7.0 Hz, 2H, CH_3CH_2), 7.53 (d, J=4.6 Hz, 2H, ArH), 8.00 (s, 1H, 5-H), 8.07 (dd, J=4.6, 1.5 Hz, 1H, ArH), 8.15 (d, J=1.5 Hz, 1H, ArH), 13.66 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 14.5, 16.1, 62.4, 109.7, 114.1, 126.2, 127.2, 130.0, 131.3, 134.3, 134.4, 140.4, 154.1, 165.7. MS (El, 70 eV): m/z (%)=316 (100%) [M$^+$]. Anal. Calcd for $C_{16}H_{14}ClN_3O_2$: C, 60.86; H, 4.47; N, 13.31. Found: C, 60.71; H, 4.54; N, 13.28.

4.1.8.6. Ethyl 6-(2-chlorophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (20h). Yield: 140 mg (35%, method F) of yellowish crystals, mp 170 °C (dec). ^{1}H NMR (DMSO-d_6) δ 1.37 (t, J=7.0 Hz, 3H, CH_3CH_2), 2.64 (s, 3H, CH_3), 4.44 (q, J=7.0 Hz, 2H, CH_3CH_2), 7.4–7.7 (m, 4H, ArH), 7.73 (s, 1H, 5-H), 13.75 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 14.5, 16.3, 62.4, 109.2, 118.0, 128.0, 130.5, 131.1, 131.7, 132.2, 133.2, 138.6, 141.2, 154.0, 155.8, 165.5. MS (El, 70 eV): m/z (%)=316 (100%) [M$^+$]. Anal. Calcd for $C_{16}H_{14}ClN_3O_2$: C, 60.86; H, 4.47; N, 13.31. Found: C, 60.99; H, 4.57; N, 13.28.

4.1.8.7. Ethyl 6-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (21c). Yields: 100 mg (21%, method E) and 210 mg (43%, method F) of yellowish crystals, mp 128–130 °C. ^{1}H NMR (DMSO-d_6) δ 0.75 (t, J=7.0 Hz, 3H, CH_3CH_2), 3.84 (s, 3H, CH_3O), 3.93 (q, J=7.0 Hz, 2H, CH_3CH_2), 7.1–8.2 (m, 9H, ArH), 7.97 (s, 1H, 5-H), 14.18 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 13.5, 55.8, 62.0, 107.1, 113.6, 114.8, 128.5, 128.6, 128.7, 129.2, 130.6, 134.7, 135.3, 144.6, 154.2, 156.1, 161.4, 166.7. MS (El, 70 eV): m/z (%)=374 (100%) [M$^+$]. Anal. Calcd for $C_{22}H_{19}N_3O_3$: C, 70.76; H, 5.13; N, 11.25. Found: C, 70.60; H, 5.25; N, 11.27.

4.1.8.8. Ethyl 3-phenyl-6-*p*-tolyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (21d). Yields: 85 mg (18%, method E) and 220 mg (48%, method F) of yellowish crystals, mp 188–191 °C. ^{1}H NMR (DMSO-d_6) δ 0.75 (t, J=7.0 Hz, 3H, CH_3CH_2), 2.37 (s, 3H, CH_3), 3.91 (q, J=7.0 Hz, 2H, CH_3CH_2), 7.3–8.2 (m, 9H, ArH), 7.99 (s, 1H, 5-H), 14.20 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 13.5, 21.3, 62.1, 107.4, 113.2, 127.6, 128.5, 128.6, 128.8, 130.1, 134.7, 135.4, 135.5, 140.2, 144.6, 154.2, 156.4, 166.6. MS (El, 70 eV): m/z (%)=358 (100%) [M$^+$]. Anal. Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 74.09; H, 5.22; N, 11.79.

4.1.8.9. Ethyl 6-(4-fluorophenyl)-3-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (21e). Yields: 100 mg (22%, method E) and 225 mg (48%, method F) of yellowish crystals, mp 160–163 °C. ^{1}H NMR (DMSO-d_6) δ 0.75 (t, J=7.0 Hz, 3H, CH_3CH_2), 3.93 (q, J=7.0 Hz, 2H, CH_3CH_2), 7.3–8.3 (m, 9H, ArH), 8.03 (s, 1H, 5-H), 14.22 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 13.5, 62.1, 107.6, 114.0, 116.3, 116.5, 128.5, 128.7, 128.8, 130.0, 130.1, 134.8, 135.6, 154.1, 150.2, 155.3, 166.5. MS (El, 70 eV):

m/*z* (%)=362 (100%) [M$^+$]. Anal. Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 74.09; H, 5.22; N, 11.79.

4.1.8.10. Ethyl 6-(4-bromophenyl)-3-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (21f). Yield: 240 mg (45%, method F) of yellowish crystals, mp 131–135 °C. ^{1}H NMR (DMSO-d_6) δ 0.75 (t, J=7.0 Hz, 3H, CH_3CH_2), 3.94 (q, J=7.0 Hz, 2H, CH_3CH_2), 7.4–8.3 (m, 9H, ArH), 8.04 (s, 1H, 5-H), 14.20 (s, 1H, NH). MS (El, 70 eV): *m*/*z* (%)=422 (100%) [M$^+$]. Anal. Calcd for $C_{21}H_{16}BrN_3O_2$: C, 59.73; H, 3.82; N, 9.95. Found: C, 59.60; H, 3.99; N, 10.00.

4.1.8.11. Ethyl 6-(3-chlorophenyl)-3-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (21g). Yield: 200 mg (41%, method F) of yellowish crystals, mp 173–175 °C. ^{1}H NMR (DMSO-d_6) δ 0.75 (t, J=7.0 Hz, 3H, CH_3CH_2), 3.94 (q, J=7.0 Hz, 2H, CH_3CH_2), 7.4–8.4 (m, 9H, ArH), 8.09 (s, 1H, 5-H), 14.18 (s, 1H, NH). MS (El, 70 eV): *m*/*z* (%)=378 (100%) [M$^+$]. Anal. Calcd for $C_{21}H_{16}ClN_3O_2$: C, 66.76; H, 4.27; N, 11.12. Found: C, 66.89; H, 4.15; N, 11.14.

4.1.8.12. Ethyl 6-(2-chlorophenyl)-3-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (21h). Yield: 180 mg (36%, method F) of yellowish crystals, mp 120–123 °C. ^{1}H NMR (DMSO-d_6) δ 0.73 (t, J=7.0 Hz, 3H, CH_3CH_2), 3.91 (q, J=7.0 Hz, 2H, CH_3CH_2), 7.4–7.8 (m, 9H, ArH), 7.69 (s, 1H, 5-H), 14.15 (s, 1H, NH). Anal. Calcd for $C_{21}H_{16}ClN_3O_2$: C, 66.76; H, 4.27; N, 11.12. Found: C, 66.60; H, 4.37; N, 11.09.

4.2. X-ray diffraction data

The crystals of $C_{22}H_{18}N_3O_3Br$ are monoclinic. At 293 K a=7.622(2), b=16.991(6), c=15.354(6) Å, β=95.92(3)°, V=1978(1) Å^3, space group $P2_1/c$, Z=4, d_{calc}=1.519 g/cm^3, μ=2.108 mm^{-1}, F(000)=920. Intensity of 3657 reflections (3392 independent, R_{int}=0.055) was measured on an automatic four circles Siemens P3/PC diffractometer (graphite monochromated Mo K$_\alpha$ radiation, $\Theta/2\Theta$ scanning, $2\Theta_{max}$=50°). The absorption correction was performed analytically (T_{min}=0.365, T_{max}=0.678). The structure was solved by direct method using SHELX97 package.[15] The positions of hydrogen atoms were located from the electron density difference maps and refined by the 'riding' model with $U_{iso}=nU_{eq}$ of non-hydrogen atoms bonded to given hydrogen atoms (n=1.5 for methyl and hydroxyl groups and n=1.2 for other hydrogen atoms). Full-matrix least-squares refinement against F^2 in the anisotropic approximation using 3355 reflections converged to $R1$=0.061 (for 1865 reflections with $F>4\sigma(F)$), $wR2$=0.130, S=0.991. Atomic coordinates and crystallographic parameters have been deposited to the Cambridge Crystallographic Data Centre, deposition number CCDC 617647. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033, e-mail: deposit@ccdc.cam.ac.uk).

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References and notes

1. (a) Chebanov, V. A.; Desenko, S. M. *Curr. Org. Chem.* **2006**, *10*, 297; (b) Desenko, S. M. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1995**, *31*, 125; (c) Desenko, S. M.; Orlov, V. D. *Azaheterocycles Based on Aromatic Unsaturated Ketones*; Folio: Kharkov, 1998; pp 38–101.
2. (a) Lipson, V. V.; Desenko, S. M.; Shirobokova, M. G.; Borodina, V. V. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2003**, *39*, 1213; (b) Chebanov, V. A.; Desenko, S. M.; Sakhno, Y. I.; Panchenko, E. S.; Saraev, V. E.; Musatov, V. I.; Konev, V. F. *Fiziol. Akt. Rechovini* **2002**, *33*, 10; (c) Chebanov, V. A.; Sakhno, Y. I.; Desenko, S. M.; Shishkina, S. V.; Musatov, V. I.; Shishkin, O. V.; Knyazeva, I. V. *Synthesis* **2005**, 2597; (d) Lipson, V. V.; Desenko, S. M.; Borodina, V. V.; Shirobokova, M. G.; Musatov, V. I. *Russ. J. Org. Chem.* **2005**, *41*, 114; (e) Lipson, V. V.; Desenko, S. M.; Shishkina, S. V.; Shirobokova, M. G.; Shishkin, O. V.; Orlov, V. D. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2003**, *39*, 1041; (f) Lipson, V. V.; Borodina, V. V.; Shirobokova, M. G.; Karnozhitskaya, T. M. *Fiziol. Akt. Rechovini* **2002**, *2*, 10.
3. (a) Desenko, S. M.; Orlov, V. D.; Getmanskii, N. V.; Shishkin, O. V.; Lindeman, S. V.; Struchkov, Yu. T. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1993**, *29*, 406; (b) Wermann, K.; Hartman, M. *Synthesis* **1991**, 189; (c) Desenko, S. M.; Orlov, V. D.; Getmanskii, N. V.; Shishkin, O. V.; Lindeman, S. V.; Struchkov, Yu. T. *Dokl. Akad. Nauk* **1992**, *324*, 801; (d) Desenko, S. M.; Orlov, V. D.; Estrada, Kh. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1990**, *26*, 839; (e) Desenko, S. M.; Orlov, V. D.; Estrada, Kh.; Ivkov, S. M. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1991**, *27*, 555.
4. See, for example: (a) Kozminykh, V. O.; Kozminykh, E. M. *Selected Methods for Synthesis and Modification of Heterocycles*; Kartsev, V. G., Ed.; IBS: Moscow, 2002; pp 263–279; (b) Saloutin, V. I.; Burgart, Ya. V.; Chupakhin, O. N. *Usp. Khim.* **1999**, *68*, 227; (c) Perevalov, S. G.; Burgart, Ya. V.; Saloutin, V. I.; Chupakhin, O. N. *Usp. Khim.* **2001**, *70*, 1039; (d) Nosek, E. *Collect. Czech. Chem. Commun.* **1950**, *15*, 335; (e) Mueller, R. *J. Prakt. Chem.* **1959**, 132; (f) Armand, J.; Armand, Y.; Boulares, L.; Bellec, C.; Pinson, J. *J. Heterocycl. Chem.* **1985**, *22*, 1519; (g) Kruglenko, V. P.; Klyuev, N. A.; Povstyanoi, M. V.; Timoshin, A. A. *Chem. Heterocycl. Compd.* **1998**, *34*, 232; (h) Berezina, E. S.; Koz'minykh, V. O.; Igidov, N. M.; Shirinkina, S. S.; Koz'minykh, E. N.; Makhmudov, R. R.; Bukanova, E. V. *Russ. J. Org. Chem.* **2001**, *37*, 539; (i) Kistanova, N. S.; Mashevskaya, I. V.; Bozdyreva, K. S.; Maslivets, A. N. *Chem. Heterocycl. Compd.* **2003**, *39*, 673.
5. (a) Abdel-Haby, S. A. L.; Badawy, M. A.; Kadry, A. M.; Mosselhi, M. A. N. *J. Heterocycl. Chem.* **1987**, *24*, 1587; (b) Abdel-Megid, M. *Pharmazie* **2000**, *55*, 263; (c) El-Maati, T. M. A. *Boll. Chim. Farm* **1999**, *138*, 272.
6. (a) Epling, G. A.; Provatas, A. A. *Chem. Commun.* **2002**, 1036; (b) Garzarolli-Thurnlackh, K. *Monatsh. Chem.* **1899**, *20*, 487; (c) Jablonski, W. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 2925.
7. Borsche, W. *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 3886.
8. See, for example: (a) Alajarin, R.; Avarez-Buila, J.; Vaquero, J. J.; Sunkel, C.; Fau, J.; Statkov, P.; Sanz, J. *Tetrahedron: Asymmetry* **1993**, *4*, 617; (b) Bossert, F.; Vater, W. *Med. Res. Rev.* **1989**, *9*, 291; (c) Trigle, D. J.; Langs, D. A.; Janis, R. A. *Med. Res. Rev.* **1989**, *9*, 123; (d) Tsuda, Y.; Mishina,

T.; Obata, M.; Araki, K.; Inui, J.; Nakamura, T., Patent 8,504,172 PCT Int., 1985; *Chem. Abstr. 104*, 207298; (e) Tsuda, Y.; Mishina, T.; Obata, M.; Araki, K.; Inui, J.; Nakamura, T. Patent 61,227,584 Jpn., 1986; *Chem. Abstr. 109*, 120988; (f) Tsuda, Y.; Mishina, T.; Obata, M.; Araki, K.; Inui, J.; Nakamura, T. 19,870,408 Eur. Pat., 1987; *Chem. Abstr. 106*, 213976; (g) Atwal, K. S.; Vaccaro, W.; Lloyd, J.; Finlay, H.; Yan, L.; Bhandaru, R. S. 20,010,607 PCT Int., 2001; *Chem. Abstr. 135*, 19660; (h) Atwal, K. S.; Moreland, S. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 291.

9. Annan, N.; Paris, R.; Jordan, F. *J. Am. Chem. Soc.* **1999**, *111*, 8895.
10. (a) Hartmann, H.; Liebscher, J. *Synthesis* **1984**, 276; (b) Nenaidenko, V. G.; Golubinskii, I. V.; Lenkova, O. N.; Shastin, A. V.; Balenkova, E. S. *Russ. J. Org. Chem.* **2004**, *40*, 1518; (c) Hennig, L.; Hofmann, J.; Alva-Astudillo, M.; Mann, G. *J. Prakt. Chem.* **1990**, *332*, 351.
11. (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250; (b) Hayes, B. L. *Aldrichimica Acta* **2004**, *37*, 66; (c) Larhed, M.; Hallberg, A. *Drug Discov. Today* **2001**, *6*, 406; Wathey, B.; Tierney, J.; Lidström, P.; Westman, J. *Drug Discov. Today* **2002**, *7*, 373; (d) Al-Obeidi, F.; Austin, R. E.; Okonya, J. F.; Bond, D. R. S. *Mini-Rev. Med. Chem.* **2003**, *3*, 449; (e) Kappe, C. O.; Dallinger, D. *Nat. Rev. Drug Discov.* **2006**, *5*, 51; (f) Shipe, W. D.; Wolkenberg, S. E.; Lindsley, C. W. *Drug Discov. Today Technol.* **2005**, *2*, 155; (g) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, 2005.
12. (a) Xu, Y.; Guo, Q.-X. *Heterocycles* **2004**, *63*, 903; (b) Hamelin, J.; Bazureau, J.-P.; Texier-Boullet, F. *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002; pp 253–294; (c) Besson, T.; Brain, C. T. *Microwave Assisted Organic Synthesis*; Lidsröm, P., Tieney, J. P., Eds.; Blackwell: Oxford, 2005; (d) Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624; (e) Kappe, C. O.; Stadler, A. *Combinatorial Chemistry, Part B*; Bunin, B. B., Morales, G., Eds.; Elsevier Science: 2003; pp 197–223; (f) Öhberg, L.; Westman, J. *Synlett* **2001**, 1296; (g) Bagley, M. C.; Singh, N. *Synlett* **2002**, 1718; (h) Wilson, N. S.; Sarko, C. R.; Roth, G. P. *Tetrahedron Lett.* **2002**, *43*, 581; (i) Devi, I.; Bhuyan, P. J. *Tetrahedron Lett.* **2004**, *45*, 8625; (j) Mont, N.; Teixidó, J.; Borell, J. I.; Kappe, C. O. *Tetrahedron Lett.* **2003**, *44*, 5385; (k) Mont, N.; Teixidó, J.; Borell, J. I.; Kappe, C. O. *Mol. Diversity* **2003**, *7*, 153; (l) Mont, N.; Fernández_Megido, L.; Teixidó, J.; Kappe, C. O.; Borell, J. I. *QSAR Comb. Sci.* **2004**, *23*, 836; (m) Tye, H.; Whittaker, M. *Org. Biomol. Chem.* **2004**, *2*, 813; (n) Molteni, V.; Hamilton, M. M.; Mao, L.; Crane, C. M.; Termin, A. P.; Wilson, D. M. *Synthesis* **2002**, 1669; (o) Ireland, S. M.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2003**, *44*, 4369.
13. Burgi, H.-B.; Dunitz, J. D. *Structure Correlation*; VCH: Weinheim, 1994; Vol. 2, p 741.
14. Zefirov, Yu. V.; Zorky, P. M. *Usp. Khim.* **1989**, *58*, 713.
15. Sheldrick, G. M. SHELXTL PLUS. PC Version. A system of computer programs for the determination of crystal structure from X-ray diffraction data. Rev. 5.1, 1998.