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Features of switchable multicomponent heterocyclizations of salicylic aldehydes and 5-aminopyrazoles with pyruvic acids and antimicrobial activity of the reaction products

Maryna V. Murlykina [a], Yana I. Sakhno [a], Sergey M. Desenko [a,b], Iryna S. Konovalova [a], Oleg V. Shishkin [a], Dmytro A. Sysoiev [c], Maryna N. Kornet [d], Valentin A. Chebanov [a,b,*]

[a] Division of Chemistry of Functional Materials, State Scientific Institution "Institute for Single Crystals" of National Academy of Sciences of Ukraine, Lenin Ave. 60, 61001 Kharkiv, Ukraine
[b] Faculty of Chemistry, V.N. Karazin Kharkiv National University, Svobody Sq. 4, 61077 Kharkiv, Ukraine
[c] Fachbereich Chemie, University of Konstanz, Fach M-720, Universitaetsstrasse 10, 78457 Konstanz, Germany
[d] Laboratory of Biotechnology of Physiologically Active Substances, Zaporizhzhya National University, Zhukovsky Str. 66, Zaporizhzhya 69600, Ukraine

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ABSTRACT

Three-component reactions of 5-aminopyrazoles and salicylic aldehydes with pyruvic acids were studied. The method of tuning of the selectivity of the heterocyclizations allowing to change its direction by variation of the reaction parameters was worked out. The treatment involving pyruvic acid can be selectively directed to the formation to either 3-aryl-10,11-dihydro-4,10-methano-pyrazolo[4,3-*c*][1,5]benzoxazocine-4-carboxylic acids or 3,6-diarylpyrazolo[3,4-*b*]pyridine-4-carboxylic acids, while the reaction involving arylpyruvic acid leads only to 7-hydroxy-2,5,6-triaryl-4,5,6,7-tetrahydro-pyrazolo[1,5-*a*]pyrimidine-7-carboxylic acids. Antimicrobial activity of the compounds obtained was also studied: Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) were found sensitive to the substances tested, however, only in the highest concentration.

1. Introduction

The intense interest in multicomponent reactions observed in recent decades has been related to the development of combinatorial and medicinal-orientated chemistry as well as to their high efficiency and convenience in comparison with multistage procedures. Herewith, scientific efforts are focused on multicomponent procedures for generation of heterocyclic compound libraries and, in last years, on Diversity Oriented Synthesis.[1]

Studying the multicomponent cyclizations involving carbonyl compounds and aminoazoles containing several alternative reaction centers is an important task due to the possibility of several different reaction pathways depending on the structure of reagents, type of solvent, and catalyst.[2] Moreover, the introduction of an OH-group in the *ortho*-position of an aromatic ring of the aldehyde additionally allows oxygen-bridged and several other types of final structure.[3,4]

Multicomponent synthesis of oxygen-bridged pyrimidine systems has been described in several publications.[3–6] In most cases it was realized as three-component condensation of a nitrogen-containing binucleophile (urea and its derivatives, aminoazoles), *ortho*-salicylaldehyde, and CH-acid (ketones, 1,3-dicarbonyl compounds, β-ketoacids, and their derivatives etc.). Such heterocyclizations were carried out both under the classical conventional conditions and with the use of microwave irradiation,[3] as well as with application of different catalysts.[5,6] Application of sequential reactions of nitrogen-containing binucleophiles with preliminary obtained α,β-unsaturated ketones was also described for the synthesis of oxygen-bridged pyrimidine systems.[7]

However, multicomponent heterocyclizations based on aminoazoles and *ortho*-salicylaldehydes is sometimes ambiguous.

For instance, in the Biginelli-like heterocyclization of salicylaldehyde **I** and 3-amino-1,2,4-triazole **II** with acetone **III**, Gorobets et al.[3] obtained either benzoxadiazocine **IV** (pathway A, Scheme 1) or tetrahydropyrimidine **V** (pathway B) depending on the reaction conditions. In the same reaction in the presence of a double excess of salicylaldehyde **I**, instead of the expected bridged structure, spiroheterocyclic compound **VII** (Scheme 1) was isolated by Svetlik et al.[8]

* Corresponding author. Tel.: +380 57 341 01 91; fax: +380 57 341 02 73; e-mail address: chebanov@isc.kharkov.com (V.A. Chebanov).

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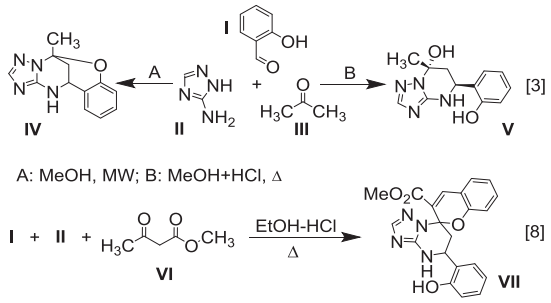
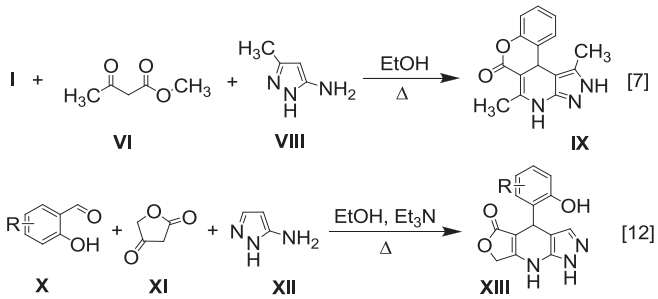


Scheme 1.

Oxygen-bridged pyridines were also obtained in the three-component reaction of ammonium acetate, 4-(2-hydroxyphenyl) but-3-en-2-one, and different CH-acids (methyl acetoacetate,[9] pentane-2,4-dione,[9] dimedone,[9] Meldrum acid[10]), in condensation of urea, salicylaldehyde, and Meldrum acid,[10] as well as by sequential reaction of enaminonitriles with 4-(2-hydroxyphenyl) but-3-en-2-one.[9,11]

Another reaction was described by Svetlik et al.[7]—it was found that the reaction of salicylaldehyde **I**, methylacetoacetate **VI**, and 5-amino-3-methylpyrazole **VIII** led to lactonization and formation of tetracyclic pyrazolopyridine **IX** (Scheme 2).



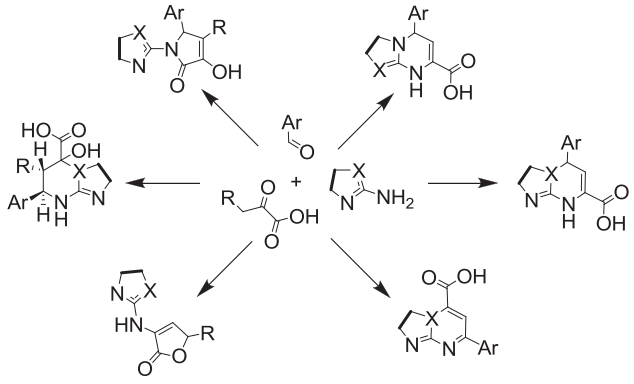
Scheme 2.

Dihydropyridopyrazoles **XIII** were obtained when furan-2,4-dione **XI** was used as CH-acid in the reaction with salicylaldehydes **X** and 5-aminopyrazole **XII** in ethanol with catalytic amounts of Et_3N.[12] In this case the hydroxyl group of the salicylaldehyde was not involved in the reaction (Scheme 2).

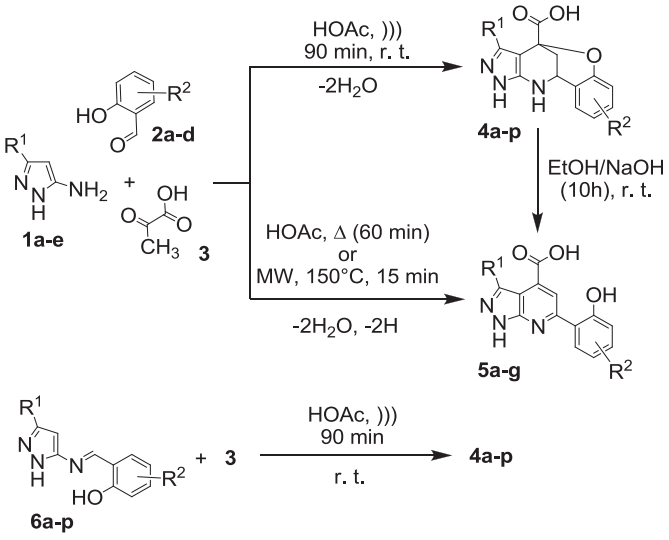
Thus, multicomponent reactions based on the treatment of CH-acids, aminoazoles, and *ortho*-salicylaldehydes can proceed by several alternative pathways and, therefore, are challenging objects for study. In continuation of our recent research[13] devoted to the tuning of the selectivity of heterocyclizations involving aminoazoles, aromatic aldehydes, and pyruvic acids usually resulting in formation of different types of heterocyclic compounds (Scheme 3), we studied similar MCRs with the participation of *ortho*-salicylaldehydes.

2. Results and discussion

It was established that the three-component reaction of an equimolar mixture of 5-amino-3-arylpyrazole **1a**–**e**, salicylaldehyde **2a**–**d**, and pyruvic acid (**3**) under conventional refluxing in acetic acid led to 3-aryl-6-(2-hydroxyphenyl)-pyrazolo[3,4-*b*]pyridine-4-carboxylic acids **5a**–**g** (Scheme 4, Table 1). These substances could also be obtained under microwave irradiation (AcOH, 150 °C,



Scheme 3.



Scheme 4.

20 min), which allows a four-fold reduction in the time of the process due to the higher reaction temperature.

Treatment of the same starting materials **1**, **2**, and **3** in acetic acid at room temperature under ultrasonic irradiation yielded 3-aryl-10,11-dihydro-4,10-methanopyrazolo[4,3-*c*][1,5]benzoxazocine-4-carboxylic acids **4a**–**p** (Scheme 4). These oxygen-bridged heterocycles were stable upon boiling in a series of solvents (acetic acid, methanol, ethanol, and butanol). However, stirring in ethanol with addition of sodium hydroxide led to cleavage of the bridged fragment, oxidation, and formation of compounds **5** with 90% yield (Scheme 4). After MW irradiating compounds **4** in HOAc (150 °C, 15 min) or heating them in DMSO for 48 h the formation of heteroaromatic carboxylic acids **5** was also observed. On the other hand, refluxing benzoxazocines **4** in DMF for 2 h led to their decomposition with formation of a resinous mixture in which the components were not identified.

Synthesis of the benzoxazocines **4** was also possible without using ultrasonic irradiation just by mechanical stirring. However, in this case the reaction time increased from 90 min to 20 h, and there were impurities of azomethines **6** in the final products. The same impurities as well as some amount of the starting materials were in the precipitate, and in the mother liquor when synthesizing compounds **4** in methanol with catalytic amount of HCl.

It seems that azomethines can be intermediates of both heterocyclizations mentioned above. Indeed, treatment of preliminary

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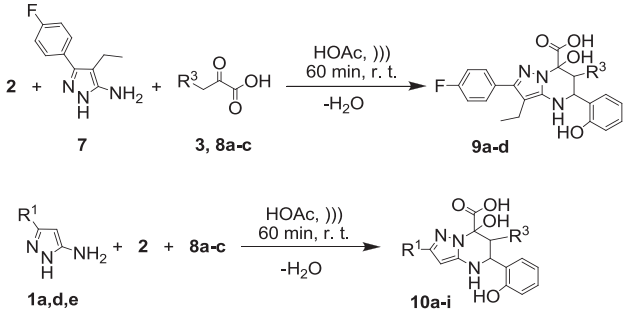
Table 1
Three-component reactions of 5-amino-3-arylpyrazoles, salicylaldehydes, and pyruvic acid via Scheme 4

Building blocks				Product	
Aminopyrazole		Salicylaldehyde			
Compound	R^1	Compound	R^2	Compound	Yield (%)
1a	C_6H_5	**2a**	H	**4a**	72
1b	4-$CH_3OC_6H_4$	**2a**	H	**4b**	88
1c	4-BrC_6H_4	**2a**	H	**4c**	82
1d	4-ClC_6H_4	**2a**	H	**4d**	80
1e	4-$C_2H_5C_6H_4$	**2a**	H	**4e**	74
1a	C_6H_5	**2b**	3-CH_3O	**4f**	75
1b	4-$CH_3OC_6H_4$	**2b**	3-CH_3O	**4g**	76
1c	4-BrC_6H_4	**2b**	3-CH_3O	**4h**	78
1d	4-ClC_6H_4	**2b**	3-CH_3O	**4i**	85
1e	4-$C_2H_5C_6H_4$	**2b**	3-CH_3O	**4j**	80
1a	C_6H_5	**2c**	5-Cl	**4k**	70
1b	4-$CH_3OC_6H_4$	**2c**	5-Cl	**4l**	73
1c	4-BrC_6H_4	**2c**	5-Cl	**4m**	81
1d	4-ClC_6H_4	**2c**	5-Cl	**4n**	72
1e	4-$C_2H_5C_6H_4$	**2c**	5-Cl	**4o**	79
1b	4-$CH_3OC_6H_4$	**2d**	5-NO_2	**4p**	67
1a	C_6H_5	**2a**	H	**5a**	30[a]
1b	4-$CH_3OC_6H_4$	**2a**	H	**5b**	45[a]
1c	4-BrC_6H_4	**2a**	H	**5c**	42[a]
1d	4-ClC_6H_4	**2a**	H	**5d**	40[a]
1e	4-$C_2H_5C_6H_4$	**2a**	H	**5e**	39[a]
1a	C_6H_5	**2c**	5-Cl	**5f**	35[a]
1d	4-ClC_6H_4	**2b**	3-CH_3O	**5g**	28[a]

[a] MW irradiation in HOAc.

obtained imines **6a**–**p** with pyruvic acid **3** in acetic acid under ultrasonication led to the formation of benzoxazocines **4a**–**p** (Scheme 4). The possibility of the transformation of azomethines into pyrazolopyridines like **5** by refluxing with pyruvic acid was described in our earlier publications.[13c,d,14c]

5-Aminopyrazoles containing a substituent in the fourth position in order to promote only one possible reaction pathway sometimes possessed specific properties and exhibited unusual behavior in multicomponent reactions.[14] In our case, heterocyclization of 5-amino-4-ethyl-3-(4-fluorophenyl)-pyrazole **7** with salicylaldehyde **2** and pyruvic acid **3** led to tetrahydropyrimidine carboxylic acid **9a** while the expected formation of an oxygen-bridged compound was not observed (Scheme 5).



Scheme 5.

On the other hand, modifying the pyruvic acid with an aryl substituent considerably influences the reaction behavior, and sometimes can cause the formation of other types of heterocyclic compound in comparison with heterocyclizations involving pyruvic acid.[13c,14c] However, it was found that the three-component reaction of pyrazole **7**, salicylaldehyde **2**, and arylpyruvic acids **8a**–**c** in acetic acid under ultrasonication at room temperature led to the tetrahydro derivatives **9b**–**d** as in the case of pyruvic acid (Scheme 5, Table 2).

Table 2
Reactions of 5-aminopyrazoles, salicylaldehydes, and pyruvic acid derivatives via Scheme 5

Building blocks				Product	
Aminopyrazole		Pyruvic acid derivative			
Compound	R^1	Compound	R^3	Compound	Yield (%)
7	—	**3**	H	**9a**	65
7	—	**8a**	C_6H_5	**9b**	75
7	—	**8b**	4-$CH_3OC_6H_4$	**9c**	52
7	—	**8c**	4-ClC_6H_4	**9d**	70
1a	C_6H_5	**8a**	C_6H_5	**10a**	70
1a	C_6H_5	**8b**	4-$CH_3OC_6H_4$	**10b**	56
1a	C_6H_5	**8c**	4-ClC_6H_4	**10c**	59
1d	4-ClC_6H_4	**8a**	C_6H_5	**10d**	79
1d	4-ClC_6H_4	**8b**	4-$CH_3OC_6H_4$	**10e**	68
1d	4-ClC_6H_4	**8c**	4-ClC_6H_4	**10f**	74
1e	4-$C_2H_5C_6H_4$	**8a**	C_6H_5	**10g**	69
1e	4-$C_2H_5C_6H_4$	**8b**	4-$CH_3OC_6H_4$	**10h**	58
1e	4-$C_2H_5C_6H_4$	**8c**	4-ClC_6H_4	**10i**	64

On the other hand, heterocyclization of pyrazoles **1a**,**d**,**e** and salicylaldehyde **2** with arylpyruvic acids **8a**–**c** under ultrasonic irradiation, in contrast to multicomponent reactions involving pyruvic acid, proceeded with the formation of a pyrimidine ring instead of a pyridine one (carboxylic acids **10a**–**i**, Scheme 5). Compounds **9** and **10** were also obtained in the reaction of the corresponding azomethines **6** with arylpyruvic acids **8**.

It should be noted that tetrahydropyrimidines **9** and **10** are unstable and they decompose gradually in HOAc and rapidly in DMSO to the mixture of starting materials. All our attempts to carry out dehydration in order to obtain dihydropyrimidine or oxygen-bridged azoloazines from compounds **9** and **10** employing different conditions were unsuccessful, as was described in our earlier publications for similar heterocycles.[13c,14c]

Three-component reactions of pyrazoles **1** and **7** with salicylaldehyde **2** and arylpyruvic acids **8** carried out in the different solvents (also by adding of alkali or protic acids) both under the conventional refluxing and microwave irradiation led to the mixtures of starting materials, sometimes with the impurities consisting of azomethines or other difficult to identify compounds.

3. Structure elucidation

The structures of the synthesized heterocyclic compounds were established by means of elemental analysis, mass-spectrometry, NMR spectroscopy, and X-ray diffraction study.

The ^{1}H NMR spectra of benzoxazocines **4** exhibit a broad singlet for the pyrazole NH and COOH groups at 12.00–12.50 ppm, a broad singlet for the pyridine NH near 6.40–6.57 ppm, a multiplet for the CH_2-group at 2.19–2.22 ppm, a multiplet for the CH-group at 4.39–4.42 ppm, peaks for aromatic protons around 6.70–7.70 ppm as well as signals for other terminal substituents. The ^{1}H NMR spectra of carboxylic acids **5** also contain a broad peak for both pyrazole NH and COOH functionalities ca. at 14.00 ppm, a broad singlet for the OH-group at 12.50 ppm, and signals for the aromatic protons including a sharp singlet for the pyridine CH near 7.00–8.00 ppm.

The presence of a resonance signal for the pyrazole NH (for compound **4** and **5**) and the absence of a singlet for the pyrazole CH group confirmed the formation of the pyridine but not pyrimidine ring.

However, the spectral data obtained for benzoxazocines **4** may correspond to at least two possible isomers **A** and **B** (Fig. 1).

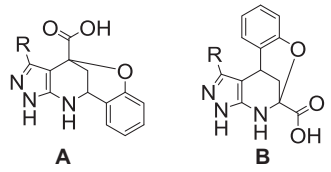


Fig. 1. Alternative structures **A** and **B** for benzoxazocines **4**.

COSY and NOESY experiments showed correlations between the protons of NH and CH groups in the pyridine ring, and no interaction between the aryl and R-substituent was observed, which should be expected in a structure like **B**. All the data obtained from HMBC spectra also corresponded to structure **A** but not to **B**.

Ultimately, the structure of compounds **4a**–**p** was proven by an X-ray analysis of compound **4e** (Fig. 2).

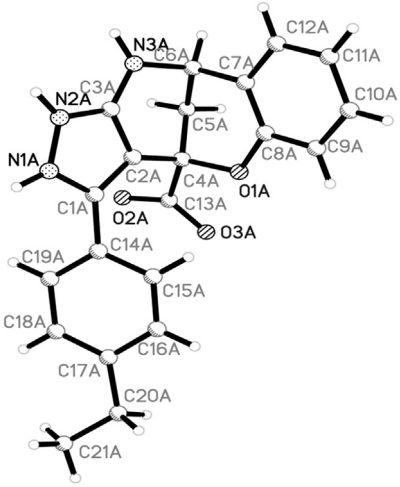


Fig. 2. Molecular structure of 10,11-dihydro-3-(4-ethylphenyl)-4,10-methanopyrazolo[4,3-*c*][1,5]benzoxazocine-4-carboxylic acid **4e** according to X-ray diffraction data.

The structure of compounds **5a**–**g** was established with the help of NMR spectra by their comparison with literature data for similar compounds.[13d]

The ^{1}H NMR spectra of carboxylic acids **9b**–**d** exhibit doublets for the CH-protons at positions 10 and 11 near 5.38–5.43 and 3.92–3.99 ppm, correspondingly, with ^2J ~11.2–11.8 Hz. In the case of compound **9a**, a multiplet for the CH-proton at position 11 at ca. 4.9 ppm and a multiplet for the CH_2-group at ca. 2.2 ppm are observed. The spectra also contain broad singlets for the COOH-group at 12.95–13.06 ppm, pyrimidine NH-group at 6.26–6.33 ppm, and phenol OH-group at 9.39–9.45 ppm as well as a multiplet of aromatic protons including broad singlet of OH-group at 6.58–7.59 ppm.

Similar spectra were observed for compounds **10a**–**i**, which however, may correspond to four possible isomers **A**–**D** (Fig. 3).

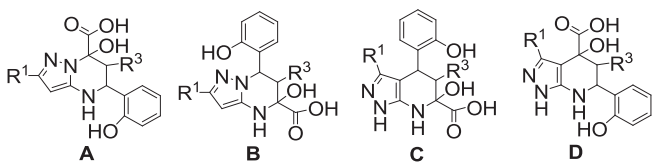


Fig. 3. Alternative structures **A**–**D** for compounds **10**.

Final assignment of the structure **A** for these heterocycles was made with help of 2D NMR experiments (Fig. 4).

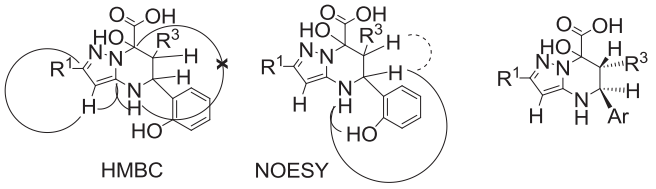


Fig. 4. Selected data of HMBC and NOESY experiments and relative stereochemistry of stereogenic centers at positions 10 and 11.

Relative stereochemistry of stereogenic centers at positions 10 and 11 for compounds **9** and **10** was established by analysis of 1D and 2D NMR spectra. Thus, the spin–spin interaction constants (^3J) for these protons are about 11–12 Hz, which corresponds to their *trans*-orientation, which earlier was found for similar compounds by NMR and X-ray analysis.[13c] The *trans*-orientation of the substituents in the pyrimidine moiety is also understandable from the general steric reasoning.

4. Antimicrobial activity

Antimicrobial activity of compounds **4b**,**g**,**h**, **5f**,**g** and **9a** was studied (see Experimental part for details) against reference strains of following test cultures: *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* (strain 1257) and *Pseudomonas aeroginosa*. It was found that Gram-negative bacteria (*E. coli* and *P. aeroginosa*) had showed resistance to all the compounds tested in the concentration range 250.000–15.625 μg/ml. Strains of Gram-positive bacteria (*B. subtilis* and *S. aureus*) were found more sensitive, however, bacteriostatic activity was fixed only in the highest concentration 250 μg/ml during the first day of the experiment. Thus, the compounds tested inferior in action to nitroxoline being reference substance.

It should be additionally noted that for compounds **4b**,**g**,**h** and **5g** after 48 h sufficient increase in biomass of culture *E. coli* compared with control was found. For compound **4b** the same situation was also observed in the case of *P. aeroginosa*. After detailed study this effect may be used, for instance, to stimulate the growth of producers of biologically active compounds.

5. Conclusions

In summary, the direction of the multicomponent reactions between 5-aminopyrazoles, salicylic aldehydes, and pyruvic acids depends on the temperature regime and structure of the starting materials, which allows controlling chemoselectivity. Thus, three-component treatment of 5-amino-3-arylpyrazole, pyruvic acid, and salicylic aldehyde can proceed under kinetic control (ultrasonication at room temperature) yielding 10,11-dihydro-4,10-methanopyrazolo[4,3-*c*][1,5]benzoxazocine-4-carboxylic acids. On the other hand, under thermodynamic control (refluxing or MW heating), reaction of the same starting materials gives pyrazolo[3,4-*b*]pyridines containing free carboxylic and hydroxyl-groups, which are potentially able to form complexes with different metals. In the case of arylpyruvic acids the multicomponent reaction studied changes direction yielding 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-7-carboxylic acids instead of expected fused pyridine derivatives. The same heterocyclic system was obtained when pyruvic acids and salicylic aldehydes react with 5-amino-4-ethylpyrazole. Most likely all the treatments studied pass via

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formation of azomethines between aminopyrazole and salicylic aldehyde on the first stage of the multicomponent reaction.

6. Experimental section

6.1. General

The starting arylpyruvic acids **8a**–**c** were synthesized according to the known literature procedure[15] and were subsequently used directly without additional purification. 3-Substituted 5-aminopyrazoles **1a**–**e** and 5-amino-4-ethyl-3-(4-fluorophenil)-pyrazole **7** were commercially available. Azomethine **6** was obtained as reported.[16]

Melting points of all the compounds synthesized were determined with a Kofler melting point apparatus and are uncorrected. The NMR spectra were recorded in DMSO-d_6 at 200 MHz with a Varian Mercury VX-200 spectrometer, at 400 MHz (100 MHz for ^{13}C) with a Jeol ECP-Eclipse 400 and at 600 MHz (150 MHz for ^{13}C) with a Bruker Avance DRX600. The MS spectra were measured on a GS-MS Varian 1200L (ionizing voltage 70 eV), on Finnigan MAT 8200 with the use of FAB-method and on LC/MS Agilent 1100. Elemental analysis was realized on Euro Vector EA-3000. IR-spectra were recorded on a Perkin–Elmer 100 Series FT-IR spectrometer and on a Perkin–Elmer Spectrum One FTIR spectrometer.

US-experiments were performed using the standard US-bath (SELDI, Ukraine) with working frequency of 44.2 kHz. Microwave experiments were carried out using the Emrys™ Creator EXP synthesizer from Biotage AB (Uppsala, Sweden) possessing a single-mode microwave cavity producing controlled irradiation at 2.45 MHz. 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).

6.2. General procedure for the synthesis of 3-aryl-10,11-dihydro-4,10-methanopyrazolo[4,3-*c*][1,5]benzoxazocine-4-carboxylic acids 4a–e

The appropriate 5-aminopyrazole **1** (0.9 mmol) was dissolved in HOAc (2.5 ml) then the salicylaldehyde **2a** (0.9 mmol) and pyruvic acid **3** (0.9 mmol) were added. The mixture was put into the US-bath for 1.5 h. The precipitate was filtered and dried under vacuum.

6.3. Characterization data for compounds 4a–e

*6.3.1. 3-Phenyl-10,11-dihydro-4,10-methanopyrazolo[4,3-c][1,5]benzoxazocine-4-carboxylic acid (**4a**).* Colorless solid, mp 191–192 °C. [Found: C, 68.51; H, 4.60; N, 12.58. $C_{19}H_{15}N_3O_3$ requires C, 68.46; H, 4.54; N, 12.61%]; ν_{max} (KBr) 3306, 2927, 1727, 1634, 1588, 1482, 1456, 1121, 900, 757, 697 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.47 (s, 2H, OH+NH), 6.78–7.70 (m, 9H, Ar), 6.45 (s, 1H, NH), 4.35–4.44 (m, 1H, CH), 2.13–2.26 (m, 2H, CH_2); δ_C (100 MHz, DMSO-d_6) 34.24, 46.41, 72.91, 99.65, 117.18, 120.98, 125.75, 127.68, 128.44, 128.88, 129.30, 130.77, 131.42, 142.85, 152.82, 153.28, 172.35; MS (EI, 70 eV): *m*/*z* (%)=333 (64.5, M$^+$), 246 (8.5), 210 (8.0), 127 (19.4), 88 (21.0), 65 (49.5), 63 (99.9).

*6.3.2. 3-(4-Methoxyphenyl)-10,11-dihydro-4,10-methano-pyrazolo [4,3-c][1,5]benzoxazocine-4-carboxylic acid (**4b**).* Colorless solid, mp 197–198 °C. [Found: C, 66.16; H, 4.81; N, 11.53. $C_{20}H_{17}N_3O_4$ requires C, 66.11; H, 4.72; N, 11.56%]; ν_{max} (KBr) 3376, 2925, 2853, 1728, 1614, 1483, 1456, 1253, 840, 761 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.33 (s, 2H, OH+NH), 6.80–7.60 (m, 8H, Ar), 6.40 (s, 1H, 1NH), 4.35–4.42 (m, 1H, CH), 3.77 (s, 3H, CH_3O), 2.15–2.23 (m, 2H, CH_2); δ_C (100 MHz, DMSO-d_6) 34.58, 46.79, 55.93, 73.35, 99.62, 114.55, 117.32, 121.07, 124.34, 126.07, 129.37, 130.84, 142.84, 152.92, 153.58, 159.96, 172.37. MS (EI, 70 eV): *m*/*z* (%)=363 (64.5, M$^+$), 318 (99.9), 270 (14.4), 246 (4.5), 226 (11.2), 189 (15.5), 170 (5.8), 131 (19.7), 102 (5.0), 77 (13.1), 51 (2.9).

*6.3.3. 3-(4-Bromophenyl)-10,11-dihydro-4,10-methanopyrazolo[4,3-c][1,5]benzoxazocine-4-carboxylic acid (**4c**).* Colorless solid, mp 180–181 °C. [Found: C, 55.41; H, 3.38; N, 10.15. $C_{19}H_{14}BrN_3O_3$ requires C, 55.36; H, 3.42; N, 10.19%]; ν_{max} (KBr) 3292, 2930, 1721, 1609, 1482, 1457, 1240, 1012, 830, 759 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.21 (s, 2H, OH+NH), 6.84–7.67 (m, 8H, Ar), 6.56 (s, 1H, NH), 4.37–4.46 (m, 1H, CH), 2.15–2.23 (m, 2H, CH_2); δ_C (100 MHz, DMSO-d_6) 34.00, 46.38, 72.82, 99.50, 117.19, 121.05, 121.73, 125.58, 127.52, 129.36, 129.70, 130.79, 131.83, 142.67, 152.09, 153.21, 172.31. LS/MS: 411 (M$^+$).

*6.3.4. 3-(4-Chlorophenyl)-10,11-dihydro-4,10-methanopyrazolo[4,3-c][1,5]benzoxazocine-4-carboxylic acid (**4d**).* Colorless solid, mp 203–204 °C. [Found: C, 62.11; H, 3.89; N, 11.40. $C_{19}H_{14}ClN_3O_3$ requires C, 62.05; H, 3.84; N, 11.43%]; ν_{max} (KBr) 3388, 2924, 2853, 1734, 1607, 1482, 1457, 1239, 760 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.55 (s, 2H, OH+NH), 6.84–7.64 (m, 8H, Ar), 6.57 (s, 1H, NH), 4.38–4.46 (m, 1H, CH), 2.15–2.24 (m, 2H, CH_2); δ_C (100 MHz, DMSO-d_6) 34.33, 46.72, 73.20, 99.78, 117.36, 121.19, 125.80, 128.96, 129.48, 129.68, 130.87, 131.26, 133.25, 143.09, 152.09, 153.49, 172.32. MS (Mass-FAB): 368 (MH$^+$).

*6.3.5. 3-(4-Ethylphenyl)-10,11-dihydro-4,10-methanopyrazolo[4,3-c][1,5]benzoxazocine-4-carboxylic acid (**4e**).* Colorless solid, mp 206–207 °C. [Found: C, 69.82; H, 5.37; N, 11.60. $C_{21}H_{19}N_3O_3$ requires C, 69.79; H, 5.30; N, 11.63%]; ν_{max} (KBr) 3377, 2931, 2874, 1727, 1647, 1541, 1481, 1240, 1122, 758 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.42 (s, 2H, OH+NH), 6.83–7.56 (m, 8H, Ar), 6.43 (s, 1H, NH), 4.34–4.43 (m, 1H, CH), 2.61 (q, 2H, *J* 7.5 Hz, CH_2CH$_3$), 2.15–2.23 (m, 2H, CH_2), 1.19 (t, 3H, *J* 7.5 Hz, CH$_2$CH_3); δ_C (100 MHz, DMSO-d_6) 15.84, 21.52, 34.28, 46.43, 72.93, 99.59, 117.17, 120.97, 125.80, 127.68, 128.27, 128.65, 129.29, 130.75, 142.52, 144.11, 153.05, 153.29, 172.40. LS/MS: 362 (MH$^+$).

6.4. General procedure for the synthesis of 3-aryl-10,11-dihydro-4,10-methanopyrazolo[4,3-*c*][1,5]benzoxazocine-4-carboxylic acids 4f–p

The appropriate 5-aminopyrazole **1** (0.9 mmol) was dissolved in HOAc (2.5 ml), then the appropriate salicylaldehyde **2** (0.9 mmol) and 1.5 excess of pyruvic acid **3** (1.35 mmol) were added. The mixture was put into the US-bath for 1.5 h. The precipitate was filtered and dried under vacuum.

6.5. Characterization data for compounds 4f–p

*6.5.1. 5-Methoxy-3-phenyl-10,11-dihydro-4,10-methanopyrazolo [4,3-c][1,5]benzoxazocine-4-carboxylic acid (**4f**).* Colorless solid, mp >300 °C. [Found: C, 66.22; H, 4.82; N, 11.52. $C_{20}H_{17}N_3O_4$ requires C, 66.11; H, 4.72; N, 11.56%]; ν_{max} (KBr) 3377, 3314, 1716, 1576, 1534, 1476, 1264, 1229, 1082, 1025, 754 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.33 (s, 2H, OH+NH), 6.68–7.80 (m, 8H, Ar), 6.43 (s, 1H, NH), 4.33–4.43 (m, 1H, CH), 3.73 (s, 3H, CH_3O), 2.16–2.24 (m, 2H, CH_2); δ_C (100 MHz, DMSO-d_6) 34.20, 46.57, 56.26, 72.89, 99.79, 111.97, 120.58, 122.26, 126.29, 127.79, 128.41, 128.84, 131.44, 142.77, 142.97, 148.94, 152.99, 172.37. LS/MS: 364 (MH$^+$).

*6.5.2. 5-Methoxy-3-(4-methoxyphenyl)-10,11-dihydro-4,10-methano pyrazolo[4,3-c][1,5]benzoxazocine-4-carboxylic acid (**4g**).* Colorless solid, mp 225–226 °C. [Found: C, 64.18; H, 4.91; N, 10.62. $C_{21}H_{19}N_3O_5$ requires C, 64.12; H, 4.87; N, 10.68, %]; ν_{max} (KBr) 3338, 2931, 1733, 1615, 1585, 1483, 1260, 1180, 1027, 839 cm^{-1}; δ_H

(200 MHz, DMSO-d_6) 12.16 (s, 2H, OH+NH), 6.70–7.64 (m, 7H, Ar), 6.34 (s, 1H, NH), 4.32–4.40 (m, 1H, CH), 3.73 (s, 3H, CH_3O), 3.77 (s, 3H, CH_3O), 2.13–2.21 (m, 2H, CH_2) ppm; δ_C (100 MHz, DMSO-d_6) 34.20, 46.59, 55.64, 56.21, 72.93, 99.53, 111.89, 114.29, 120.59, 122.22, 123.70, 126.36, 129.22, 142.28, 142.95, 148.94, 153.20, 159.69, 172.44. LS/MS: 394 (MH^+).

*6.5.3. 3-(4-Bromophenyl)-5-methoxy-10,11-dihydro-4,10-methano pyrazolo[4,3-c][1,5]benzoxazocine-4-carboxylic acid (**4h**).* Colorless solid, mp >300 °C. [Found: C, 54.35; H, 3.70; N, 9.48. $C_{20}H_{16}BrN_3O_4$ requires C, 54.31; H, 3.65; N, 9.50%]; ν_{max} (KBr) 3336, 2932, 2852, 1716, 1639, 1585, 1482, 1460, 1263, 1025, 838 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.46 (s, 2H, OH+NH), 6.73–7.72 (m, 7H, Ar), 6.52 (s, 1H, NH), 4.36–4.43 (m, 1H, CH), 3.73 (s, 3H, CH_3O), 2.15–2.22 (m, 2H, CH_2); δ_C (100 MHz, DMSO-d_6) 33.98, 46.55, 56.25, 72.79, 99.67, 111.98, 120.68, 121.71, 122.23, 126.12, 129.79, 131.22, 131.77, 142.69, 142.90, 148.94, 152.24, 172.33. MS (Mass-FAB): 442 (MH^+).

*6.5.4. 3-(4-Chlorophenyl)-5-methoxy-10,11-dihydro-4,10-methano pyrazolo[4,3-c][1,5]benzoxazocine-4-carboxylic acid (**4i**).* Colorless solid, mp >300 °C. [Found: C, 60.41; H, 4.09; N, 10.54. $C_{20}H_{16}ClN_3O_4$ requires C, 60.38; H, 4.05; N, 10.56%]; ν_{max} (KBr) 3362, 2931, 2852, 1710, 1646, 1585, 1480, 1265, 1090, 842, 735 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.38 (s, 2H, OH+NH), 6.70–7.76 (m, 7H, Ar), 6.50 (s, 1H, NH), 4.35–4.44 (m, 1H, CH), 3.73 (s, 3H, CH_3O), 2.14–2.23 (m, 2H, CH_2); δ_C (100 MHz, DMSO-d_6) 34.00, 46.56, 56.27, 72.80, 99.67, 112.00, 120.67, 122.24, 126.14, 128.85, 129.50, 130.89, 133.07, 142.57, 142.92, 148.95, 152.25, 172.32. LS/MS: 398.1 (MH^+).

*6.5.5. 3-(4-Ethylphenyl)-5-methoxy-10,11-dihydro-4,10-methano pyrazolo[4,3-c][1,5]benzoxazocine-4-carboxylic acid (**4j**).* Colorless solid, mp 177–178 °C. [Found: C, 67.56; H, 5.49; N, 10.71. $C_{22}H_{21}N_3O_4$ requires C, 67.51; H, 5.41; N, 10.74%]; ν_{max} (KBr) 3369, 2930, 1733, 1645, 1586, 1483, 1263, 1023, 765 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.34 (s, 2H, OH+NH), 6.70–7.67 (m, 7H, Ar), 6.37 (s, 1H, NH), 4.32–4.42 (m, 1H, CH), 3.73 (s, 3H, CH_3O), 2.60 (q, 2H, *J* 7.5 Hz, CH_2CH$_3$), 2.09–2.25 (m, 2H, CH_2), 1.19 (t, 3H, *J* 7.5 Hz, CH$_2$CH_3); δ_C (100 MHz, DMSO-d_6) 15.76, 28.54, 34.58, 46.97, 56.97, 73.33, 99.94, 113.12, 120.71, 122.67, 126.73, 128.12, 128.21, 129.26, 143.17, 143.67, 144.13, 149.32, 153.02, 172.35. LS/MS: 392.0 (MH^+).

*6.5.6. 7-Chloro-3-phenyl-10,11-dihydro-4,10-methanopyrazolo[4,3-c][1,5]benzoxazocine-4-carboxylic acid (**4k**).* Colorless solid, mp 205–206 °C. [Found: C, 62.10; H, 3.91; N, 11.47. $C_{19}H_{14}ClN_3O_3$ requires C, 62.05; H, 3.84; N, 11.43%]; ν_{max} (KBr) 3336, 2931, 1718, 1635, 1458, 1026, 837 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.17 (s, 2H, OH+NH), 6.84–7.70 (m, 8H, Ar), 6.51 (s, 1H, NH), 4.37–4.46 (m, 1H, CH), 2.13–2.27 (m, 2H, CH_2); δ_C (100 MHz, DMSO-d_6) 33.83, 46.22, 73.26, 99.33, 119.09, 124.50, 127.69, 127.85, 128.52, 128.90, 129.05, 130.19, 131.23, 142.38, 152.23, 152.71, 171.98. MS (Mass-FAB): 368 (MH^+).

*6.5.7. 7-Chloro-3-(4-methoxyphenyl)-10,11-dihydro-4,10-methano pyrazolo[4,3-c][1,5]benzoxazocine-4-carboxylic acid (**4l**).* Colorless solid, mp 193–194 °C. [Found: C, 60.43; H, 4.11; N, 10.51. $C_{20}H_{16}ClN_3O_4$ requires C, 60.38; H, 4.05; N, 10.56%]; ν_{max} (KBr) 3334, 2933, 1705, 1614, 1476, 1252, 1173, 1029, 837 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.13 (s, 2H, OH+NH), 6.80–7.65 (m, 7H, Ar), 6.44 (s, 1H, NH), 4.36–4.45 (m, 1H, CH), 3.76 (s, 3H, CH_3O), 2.15–2.22 (m, 2H, CH_2); δ_C (100 MHz, DMSO-d_6) 33.86, 46.26, 55.67, 73.33, 99.06, 114.36, 119.06, 123.53, 124.48, 127.96, 129.02, 129.09, 130.18, 142.25, 152.24, 152.95, 159.73, 172.02. LS/MS: 398 (MH^+).

*6.5.8. 3-(4-Bromophenyl)-7-chloro-10,11-dihydro-4,10-methano pyrazolo[4,3-c][1,5]benzoxazocine-4-carboxylic acid (**4m**).* Colorless solid, mp 203–204 °C. [Found: C, 51.16; H, 2.99; N, 9.37. $C_{19}H_{13}BrN_3O_3$ requires C, 51.09; H, 2.93; N, 9.41%]; ν_{max} (KBr) 3306, 2925, 1716, 1641, 1476, 1243, 1174, 1013, 823 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.44 (s, 2H, OH+NH), 6.86–7.71 (m, 7H, Ar), 6.60 (s, 1H, NH), 4.40–4.49 (m, 1H, CH), 2.15–2.23 (m, 2H, CH_2); δ_C (100 MHz, DMSO-d_6) δ 33.59, 46.18, 73.16, 99.22, 119.11, 121.83, 124.57, 127.67, 129.13, 129.72, 130.21, 130.97, 131.85, 142.69, 152.08, 152.15, 171.96. MS (Mass-FAB): 446 (MH^+).

*6.5.9. 7-Chloro-3-(4-chlorophenyl)-10,11-dihydro-4,10-methano pyrazolo[4,3-c][1,5]benzoxazocine-4-carboxylic acid (**4n**).* Colorless solid, mp 204–205 °C. [Found: C, 56.77; H, 3.33; N, 10.42. $C_{19}H_{13}Cl_2N_3O_3$ requires C, 56.73; H, 3.26; N, 10.45%]; ν_{max} (KBr) 3338, 2925, 1724, 1607, 1532, 1476, 1173, 1093, 835 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.55 (s, 2H, OH+NH), 6.83–7.71 (m, 7H, Ar), 6.58 (s, 1H, NH), 4.40–4.49 (m, 1H, CH), 2.14–2.26 (m, 2H, CH_2); δ_C (100 MHz, DMSO-d_6) 33.60, 46.18, 73.16, 99.24, 119.11, 124.57, 127.68, 128.94, 129.12, 129.43, 130.21, 130.62, 133.19, 142.63, 152.02, 152.15, 171.96. LS/MS: 402.0 (MH^+).

*6.5.10. 7-Chloro-3-(4-ethylphenyl)-10,11-dihydro-4,10-methano pyrazolo[4,3-c][1,5]benzoxazocine-4-carboxylic acid (**4o**).* Colorless solid, mp 198–199 °C. [Found: C, 63.79; H, 4.65; N, 10.61. $C_{21}H_{18}ClN_3O_3$ requires C, 63.72; H, 4.58; N, 10.62%]; ν_{max} (KBr) 3311, 2964, 2873, 1733, 1635, 1593, 1476, 1244, 1173, 819 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.25 (s, 2H, OH+NH), 6.78–7.60 (m, 7H, Ar), 6.49 (s, 1H, NH), 4.37–4.46 (m, 1H, CH), 2.60 (q, 2H, *J* 7.5 Hz, CH_2CH$_3$), 2.14–2.25 (m, 2H, CH_2), 1.18 (t, 3H, *J* 7.5 Hz, CH$_2$CH_3); δ_C (100 MHz, DMSO-d_6) 15.83, 28.39, 33.89, 46.25, 73.29, 99.26, 119.07, 124.49, 127.68, 127.92, 128.28, 128.49, 129.03, 130.18, 142.47, 144.16, 152.25, 152.94, 172.00. LS/MS: 396 (MH^+).

*6.5.11. 3-(4-Methoxyphenyl)-7-nitro-10,11-dihydro-4,10-methano pyrazolo[4,3-c][1,5]benzoxazocine-4-carboxylic acid (**4p**).* Colorless solid, mp 203–204 °C. [Found: C, 58.89; H, 3.99; N, 13.75. $C_{20}H_{16}N_4O_6$ requires C, 58.82; H, 3.95; N, 13.72%]; ν_{max} (KBr) 3334, 2928, 1760, 1706, 1650, 1520, 1477, 1340, 1255, 1027, 836 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.08 (s, 2H, OH+NH), 6.82–8.46 (m, 7H, Ar), 6.64 (s, 1H, NH), 4.54–4.62 (m, 1H, CH), 3.77 (s, 3H, CH_3O), 2.24–2.31 (m, 2H, CH_2); δ_C (50 MHz, DMSO-d_6) 33.90, 46.46, 55.90, 74.81, 98.99, 114.61, 118.48, 123.83, 125.21, 127.23, 127.28, 129.43, 141.70, 143.07, 152.61, 159.47, 160.13, 171.47. MS (Mass-FAB): 409 (MH^+).

6.6. General procedure for the synthesis of 3-aryl-6-(2-hydroxyphenyl)-pyrazolo[3,4-*b*]pyridine-4-carboxylic acids 5a–g

The appropriate 5-aminopyrazole **1** (0.9 mmol) was dissolved in HOAc (2.5 ml), then the appropriate salicylaldehyde **2** (0.9 mmol) and pyruvic acid **3** (0.9 mmol) were added. The mixture was refluxed for 1 h or MW irradiated (15 min, 150 °C). The precipitate was filtered and dried under vacuum.

6.7. Characterization data for compounds 5a–g

*6.7.1. 6-(2-Hydroxyphenyl)-3-phenylpyrazolo[3,4-b]pyridine-4-carboxylic acid (**5a**).* Yellowish solid, mp >300 °C. [Found: C, 68.93; H, 3.99; N, 12.64. $C_{19}H_{13}N_3O_3$ requires C, 68.88; H, 3.95; N, 12.68%]; ν_{max} (KBr) 3236, 2924, 2853, 1712, 1599, 1496, 1456, 1274, 1233, 989, 753 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 14.18 (s, 2H, OH+NH), 12.47 (s, 1H, OH), 8.14 (s, 1H, CH), 6.92–8.12 (m, 9H, Ar); δ_C (100 MHz, DMSO-d_6) 107.37, 114.04, 118.24, 119.94, 120.98, 128.32, 128.45, 128.97, 129.05, 129.38, 132.30, 137.88, 144.92, 151.94, 156.74, 158.71, 167.76. MS (Mass-FAB): 332 (MH^+).

*6.7.2. 6-(2-Hydroxyphenyl)-3-(4-methoxyphenyl)-pyrazolo[3,4-b] pyridine-4-carboxylic acid (**5b**).* Yellowish solid, mp >300 °C. [Found: C, 66.53; H, 4.23; N, 11.60. $C_{20}H_{15}N_3O_4$ requires C, 66.48; H,

4.18; N, 11.63%]; ν_{max} (KBr) 3235, 2924, 2852, 1732, 1602, 1459, 1239, 987, 841, 749, 642 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 14.08 (s, 2H, OH+NH), 12.54 (s, 1H, OH), 8.11 (s, 1H, CH), 6.93–8.11 (m, 8H, Ar), 3.80 (s, 3H); δ_C (100 MHz, DMSO-d_6) 55.69, 107.28, 113.77, 114.00, 118.22, 119.91, 120.96, 126.48, 129.38, 130.25, 132.29, 137.88, 143.66, 151.74, 156.60, 158.70, 159.69, 167.89. LS/MS: 362 (MH^+).

*6.7.3. 3-(4-Bromophenyl)-6-(2-hydroxyphenyl)-pyrazolo[3,4-b]pyridine-4-carboxylic acid (**5c**).* Yellowish solid, mp >300 °C. [Found: C, 55.71; H, 2.98; N, 10.21. $C_{19}H_{12}BrN_3O_3$ requires C, 55.63; H, 2.95; N, 10.24%]; ν_{max} (KBr) 3228, 2924, 2853, 1692, 1600, 1497, 1288, 1238, 987, 841, 753 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 14.23 (s, 2H, OH+NH), 12.35 (s, 1H, OH), 8.16 (s, 1H, CH), 6.84–8.13 (m, 8H, Ar); δ_C (100 MHz, DMSO-d_6) 107.44, 114.71, 118.19, 119.98, 121.14, 121.89, 129.52, 131.19, 131.38, 132.35, 133.54, 137.21, 143.91, 151.94, 156.83, 158.55, 167.54. LS/MS: 410 (MH^+).

*6.7.4. 3-(4-Chlorophenyl)-6-(2-hydroxyphenyl)-pyrazolo[3,4-b]pyridine-4-carboxylic acid (**5d**).* Yellowish solid, mp >300 °C. [Found: C, 62.42; H, 3.37; N, 11.47. $C_{19}H_{12}ClN_3O_3$ requires C, 62.39; H, 3.31; N 11.49%]; ν_{max} (KBr) 3229, 2924, 2853, 1709, 1601, 1497, 1289, 1267, 989, 841, 754 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 14.24 (s, 2H, OH+NH), 12.33 (s, 1H, OH), 8.17 (s, 1H, CH), 6.89–8.15 (m, 8H, Ar); δ_C (100 MHz, DMSO-d_6) 107.47, 114.60, 118.19, 119.98, 121.11, 128.47, 129.49, 130.88, 132.34, 133.17, 133.25, 137.48, 143.90, 151.93, 156.81, 158.57, 167.63. MS (Mass-FAB): 366 (MH^+).

*6.7.5. 3-(4-Ethylphenyl)-6-(2-hydroxyphenyl)-pyrazolo[3,4-b]pyridine-4-carboxylic acid (**5e**).* Yellowish solid, mp >300 °C. [Found: C, 70.25; H, 4.85; N, 11.68. $C_{21}H_{17}N_3O_3$ requires C, 70.18; H, 4.77; N, 11.69%]; ν_{max} (KBr) 3247, 2924, 2854, 1715, 1601, 1460, 1277, 1237, 992, 840, 746 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 14.12 (s, 2H, OH+NH), 12.51 (s, 1H, OH), 8.12 (s, 1H, CH), 6.91–8.11 (m, 8H, Ar), 2.66 (q, 2H, *J* 7.5 Hz, CH_2CH_3), 1.22 (t, 3H, *J* 7.5 Hz, CH_2CH_3); δ_C (100 MHz, DMSO-d_6) 15.94, 28.47, 107.26, 113.84, 118.22, 119.94, 120.94, 127.90, 128.94, 129.40, 131.45, 132.32, 137.90, 144.06, 144.91, 151.81, 156.65, 158.70, 167.88. LS/MS: 360 (MH^+).

*6.7.6. 7-Chloro-3-phenyl-6-(2-hydroxyphenyl)-pyrazolo[3,4-b]pyridine-4-carboxylic acid (**5f**).* Yellowish solid, mp >300 °C. [Found: C, 62.42; H, 3.35; N, 11.51. $C_{19}H_{12}ClN_3O_3$ requires C, 62.39; H, 3.31; N, 11.49%]; ν_{max} (KBr) 3308, 2922, 2853, 1715, 1595, 1475, 1275, 987, 698 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 14.21 (s, 2H, OH+NH), 12.16 (s, 1H, OH), 8.21 (s, 1H, CH), 6.99–8.15 (m, 8H, Ar); δ_C (100 MHz, DMSO-d_6) 107.57, 114.97, 119.85, 123.39, 123.68, 128.49, 128.52, 128.97, 129.02, 131.60, 134.06, 137.56, 144.94, 152.17, 155.03, 156.99, 167.79. MS (Mass-FAB): 366 (MH^+).

*6.7.7. 3-(4-Chlorophenyl)-5-methoxy-6-(2-hydroxyphenyl)-pyrazolo [3,4-b]pyridine-4-carboxylic acid (**5g**).* Yellowish solid, mp >300 °C. [Found: C, 60.71; H, 3.59; N, 10.60. $C_{20}H_{14}N_3ClO_4$ requires C, 60.69; H, 3.57; N, 10.62%]; ν_{max} (KBr) 3302, 2924, 2852, 1706, 1601, 1454, 1245, 1050, 989, 853, 726 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 14.27 (s, 2H, OH+NH), 12.05 (s, 1H, OH), 8.15 (s, 1H, CH), 6.85–7.70 (m, 7H, Ar), 3.83 (s, 3H, CH_3O); δ_C (100 MHz, DMSO-d_6) 55.42, 107.36, 107.46, 114.35, 115.10, 119.32, 120.96, 121.33, 128.46, 130.90, 133.25, 137.04, 143.87, 148.50, 149.19, 158.93, 156.91, 167.54. MS (Mass-FAB): 396 (MH^+).

6.8. General procedure for the synthesis of 3-ethyl-2-(4-fluorophenyl)-7-hydroxy-5-(2-hydroxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-7-carboxylic acid 9a

5-Amino-4-ethyl-3-(4-fluorophenyl)-pyrazole **7** (0.73 mmol) was dissolved in HOAc (2.5 ml), then the salicylaldehyde **2** (0.73 mmol) and pyruvic acid **3** (0.73 mmol) were added. The mixture was put into the US-bath for 60 min. The precipitate was filtered and dried under vacuum. Colorless solid, mp 177–178 °C. [Found: C, 63.53; H, 5.04; N, 10.60. $C_{21}H_{20}FN_3O_4$ requires C, 63.47; H, 5.07; N, 10.57%]; ν_{max} (KBr) 3365, 2960, 2843, 1707, 1576, 1458, 1221, 843 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.96 (s, 1H, OH), 9.59 (s, 1H, OH), 6.82–7.58 (m, 8H, Ar), 6.25 (s, 1H, NH), 4.86–5.06 (m, 1H, CH), 2.40 (q, 2H, *J* 7.5 Hz, CH_2CH_3), 2.02–2.32 (m, 2H, CH_2), 1.01 (t, 3H, *J* 7.5 Hz, CH_2CH_3); δ_C (150 MHz, DMSO-d_6) 15.41, 15.71, 40.42, 44.89, 82.29, 98.68, 115.56, 115.70, 119.62, 127.57, 128.58, 128.61, 129.40, 129.46, 131.88 (d, ^3J 4 Hz), 145.28, 148.00, 155.03, 161.41 (d, ^2J 250 Hz), 171.68. MS (Mass-FAB): 398.4 (MH^+).

6.9. General procedure for the synthesis of 6-aryl-3-ethyl-2-(4-fluorophenyl)-7-hydroxy-5-(2-hydroxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-7-carboxylic acids 9b–d

5-Amino-4-ethyl-3-(4-fluorophenyl)-pyrazole **7** (0.73 mmol) was dissolved in HOAc (2.5 ml), then the salicylaldehyde **2** (0.73 mmol) and appropriate arylpyruvic acid **8** (0.73 mmol) were added. The mixture was put into the US-bath for 60 min. The precipitate was filtered and dried under vacuum.

6.10. Characterization data for compounds 9b–d

*6.10.1. 3-Ethyl-2-(4-fluorophenyl)-7-hydroxy-5-(2-hydroxyphenyl)-6-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**9b**).* Colorless solid, mp 146–147 °C. [Found: C, 68.54; H, 5.15; N, 8.89. $C_{27}H_{24}FN_3O_4$ requires C, 68.49; H, 5.11; N, 8.87%]; ν_{max} (KBr) 3410, 1712, 1635, 1591, 1457, 1352, 1231, 1146, 822, 750 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 13.06 (s, 1H, OH), 9.42 (s, 1H, OH), 6.59–7.54 (m, 13H, Ar), 6.26 (s, 1H, NH), 5.38 (d, *J* 11.8 Hz, 1H, CH), 2.34 (q, 2H, *J* 7.5 Hz, CH_2CH_3), 3.92 (d, *J* 11.8 Hz, 1H, CH), 0.96 (t, 3H, *J* 7.5 Hz, CH_2CH_3); δ_C (150 MHz, DMSO-d_6) 15.48, 15.69, 48.02, 51.81, 85.53, 98.01, 115.53, 115.66, 119.26, 126.97, 127.14, 127.55, 128.46, 129.32, 129.40, 130.76, 131.96 (d, ^3J 3 Hz), 136.89, 144.55, 148.17, 155.84, 161.86 (d, ^2J 240 Hz), 170.49. MS (Mass-FAB): 474.5 (MH^+).

*6.10.2. 3-Ethyl-2-(4-fluorophenyl)-7-hydroxy-5-(2-hydroxyphenyl)-6-(4-methoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**9c**).* Colorless solid, mp 143–144 °C. [Found: C, 66.85; H, 5.29; N, 8.30. $C_{28}H_{26}FN_3O_5$ requires C, 66.79; H, 5.20; N, 8.35%]; ν_{max} (KBr) 3391, 2933, 2717, 1599, 1515, 1460, 1349, 1250, 1034, 845, 753 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.95 (s, 1H, OH), 9.39 (s, 1H, OH), 6.59–7.54 (m, 12H, Ar), 6.26 (s, 1H, NH), 5.38 (d, *J* 11.8 Hz, 1H, CH), 2.34 (q, 2H, *J* 7.0 Hz, CH_2CH_3), 3.92 (d, *J* 11.8 Hz, 1H, CH), 3.60 (s, 3H, CH_3O), 0.96 (t, 3H, *J* 7.0 Hz, CH_2CH_3); δ_C (150 MHz, DMSO-d_6) 15.51, 15.61, 48.19, 51.89, 55.19, 85.53, 98.03, 113.01, 115.54, 115.68, 119.30, 126.98, 128.08, 128.42, 129.34, 129.39, 131.71, 131.99 (d, ^3J 4 Hz), 144.57, 148.16, 155.86, 158.36, 161.88 (d, ^2J 250 Hz), 170.57. MS (Mass-FAB): 504.5 (MH^+).

*6.10.3. 6-(4-Chlorophenyl)-3-ethyl-2-(4-fluorophenyl)-7-hydroxy-5-(2-hydroxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**9d**).* Colorless solid, mp 141–142 °C. [Found: C, 63.89; H, 4.61; N, 8.23. $C_{27}H_{23}FClN_3O_4$ requires C, 63.84; H, 4.56; N, 8.27%]; ν_{max} (KBr) 3393, 2931, 1643, 1598, 1459, 1346, 1238, 1160, 1092, 842, 754 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 13.00 (s, 1H, OH), 9.45 (s, 1H, OH), 6.64–7.53 (m, 12H, Ar), 6.33 (s, 1H, NH), 5.38 (d, *J* 11.2 Hz, 1H, CH), 2.39 (q, 2H, *J* 7.1 Hz, CH_2CH_3), 3.94 (d, *J* 11.2 Hz, 1H, CH), 0.96 (t, 3H, *J* 7.1 Hz, CH_2CH_3); δ_C (150 MHz, DMSO-d_6) 15.50, 15.61, 46.77, 52.64, 85.30, 98.13, 115.57, 115.71, 119.40, 126.57, 127.59, 128.86, 129.36, 129.41, 131.91 (d, ^3J 4 Hz), 131.98, 132.55, 135.24, 144.55, 148.26, 155.78, 161.91 (d, ^2J 245 Hz), 170.38. MS (Mass-FAB): 509 (MH^+).

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6.11. General procedure for the synthesis of 2,6-diaryl-7-hydroxy-5-(2-hydroxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-7-carboxylic acid derivatives 10a–i

5-Amino-3-arylpyrazole **1** (0.6 mmol) was dissolved in HOAc (2.5 ml), then the salicylaldehyde **2** (0.6 mmol) and appropriate arylpyruvic acid **8** (0.73 mmol) were added. The mixture was put into the US-bath for 60 min. The precipitate was filtered and dried under vacuum.

6.12. Characterization data for compounds 10a–i

*6.12.1. 7-Hydroxy-5-(2-hydroxyphenyl)-2,6-diphenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**10a**).* Colorless solid, mp 165–166 °C. [Found: C, 70.29; H, 5.01; N, 9.81. $C_{25}H_{21}N_3O_4$ requires C, 70.25; H, 4.95; N, 9.83%]; ν_{max} (KBr) 3357, 2924, 2704, 1602, 1458, 1339, 1258, 1141, 757, 696 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 13.37 (s, 1H, OH), 9.48 (s, 1H, OH), 6.60–7.66 (m, 14H, Ar), 6.68 (s, 1H, NH), 5.57 (s, 1H, CH), 5.43 (d, *J* 11.2 Hz, 1H, CH), 4.02 (d, *J* 11.2 Hz, 1H, CH); δ_C (150 MHz, DMSO-d_6) 46.72, 52.64, 82.12, 85.63, 115.70, 119.41, 125.55, 126.53, 127.27, 127.71, 127.88, 128.68, 128.93, 129.53, 130.77, 134.45, 136.22, 147.79, 150.45, 155.87, 170.58. MS (Mass-FAB): 428.5 (MH^+).

*6.12.2. 7-Hydroxy-5-(2-hydroxyphenyl)-6-(4-methoxyphenyl)-2-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**10b**).* Colorless solid, mp 155–156 °C. [Found: C, 68.31; H, 5.11; N, 9.14. $C_{26}H_{23}N_3O_5$ requires C, 68.26; H, 5.07; N, 9.19%]; ν_{max} (KBr) 3389, 2932, 1615, 1515, 1457, 1348, 1248, 1178, 1029, 754 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.75 (s, 1H, OH), 9.46 (s, 1H, OH), 6.61–7.81 (m, 13H, Ar), 6.68 (s, 1H, NH), 5.56 (s, 1H, CH), 5.39 (d, *J* 11.0 Hz, 1H, CH), 3.61 (s, 3H, C*H*$_3$O), 3.99 (d, *J* 11.0 Hz, 1H, CH); δ_C (150 MHz, DMSO-d_6) 46.88, 51.84, 55.17, 82.02, 85.61, 113.10, 115.67, 119.37, 125.50, 126.73, 127.80, 128.06, 128.59, 128.88, 131.28, 131.67, 134.46, 147.76, 150.35, 155.84, 158.39, 170.59. MS (Mass-FAB): 458.5 (MH^+).

*6.12.3. 6-(4-Chlorophenyl)-7-hydroxy-5-(2-hydroxyphenyl)-2-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**10c**).* Colorless solid, mp 179–180 °C. [Found: C, 65.10; H, 4.39; N, 9.12. $C_{25}H_{20}ClN_3O_4$ requires C, 65.01; H, 4.36; N, 9.10%]; ν_{max} (KBr) 3372, 2925, 2707, 1607, 1493, 1459, 1345, 1145, 1092, 750 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 13.20 (s, 1H, OH), 9.50 (s, 1H, OH), 6.61–7.65 (m, 13H, Ar), 6.75 (s, 1H, NH), 5.57 (s, 1H, CH), 5.40 (d, *J* 11.9 Hz, 1H, CH), 4.01 (d, *J* 11.9 Hz, 1H, CH); δ_C (150 MHz, DMSO-d_6) 46.49, 52.67, 82.18, 85.39, 115.71, 119.49, 125.54, 126.27, 127.70, 127.88, 128.91, 129.50, 131.33, 132.07, 132.53, 134.39, 135.23, 147.74, 150.48, 155.78, 172.40. MS (Mass-FAB): 463 (MH^+).

*6.12.4. 2-(4-Chlorophenyl)-7-hydroxy-5-(2-hydroxyphenyl)-6-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**10d**).* Colorless solid, mp 137–138 °C. [Found: C, 65.09; H, 4.41; N, 9.06. $C_{25}H_{20}ClN_3O_4$ requires C, 65.01; H, 4.36; N, 9.10%]; ν_{max} (KBr) 3374, 2925, 2718, 1607, 1457, 1339, 1244, 1095, 836, 751, 698 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.99 (s, 1H, OH), 9.49 (s, 1H, OH), 6.64–7.71 (m, 13H, Ar), 6.77 (s, 1H, NH), 5.62 (s, 1H, CH), 5.48 (d, *J* 11.4 Hz, 1H, CH), 4.05 (d, *J* 11.4 Hz, 1H, CH); δ_C (150 MHz, DMSO-d_6) 46.54, 52.51, 82.12, 85.60, 115.64, 119.34, 126.46, 127.18, 127.21, 127.67, 128.64, 128.91, 129.74, 130.71, 132.17, 133.31, 136.12, 147.86, 149.21, 155.81, 170.40. MS (Mass-FAB): 463 (MH^+).

*6.12.5. 2-(4-Chlorophenyl)-7-hydroxy-5-(2-hydroxyphenyl)-6-(4-methoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**10e**).* Colorless solid, mp 142–143 °C. [Found: C, 63.55; H, 4.59; N, 8.51. $C_{26}H_{22}ClN_3O_5$ requires C, 63.48; H, 4.51; N, 8.54%]; ν_{max} (KBr) 3368, 2929, 2853, 1609, 1514, 1458, 1247, 1180, 1094, 752 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 13.06 (s, 1H, OH), 9.46 (s, 1H, OH), 6.60–7.69 (m, 12H, Ar), 6.72 (s, 1H, NH), 5.57 (s, 1H, CH), 5.38 (d, *J* 11.1 Hz, 1H, CH), 3.60 (s, 3H, C*H*$_3$O), 3.94 (d, *J* 11.1 Hz, 1H, CH); δ_C (150 MHz, DMSO-d_6) 46.55, 51.82, 55.19, 82.19, 85.71, 113.14, 115.74, 119.44, 126.68, 127.21, 128.00, 128.66, 128.95, 129.52, 131.71, 132.26, 133.35, 147.93, 149.31, 155.87, 158.45, 170.57. MS (Mass-FAB): 493 (MH^+).

*6.12.6. 2,6-Bis(4-chlorophenyl)-7-hydroxy-5-(2-hydroxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**10f**).* Colorless solid, mp 154–155 °C. [Found: C, 60.53; H, 3.88; N, 8.45. $C_{25}H_{19}Cl_2N_3O_4$ requires C, 60.50; H, 3.86; N, 8.47%]; ν_{max} (KBr) 3373, 2924, 1608, 1459, 1340, 1093, 750 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 13.34 (s, 1H, OH), 9.52 (s, 1H, OH), 6.60–7.69 (m, 12H, Ar), 6.78 (s, 1H, NH), 5.59 (s, 1H, CH), 5.39 (d, *J* 11.0 Hz, 1H, CH), 3.97 (d, *J* 11.0 Hz, 1H, CH); δ_C (150 MHz, DMSO-d_6) 46.20, 52.39, 82.20, 85.38, 115.64, 119.45, 126.22, 127.19, 127.67, 128.83, 128.92, 132.03, 132.20, 132.49, 133.26, 135.13, 147.83, 149.27, 155.72, 170.25. MS (Mass-FAB): 497 (MH^+).

*6.12.7. 2-(4-Ethylphenyl)-7-hydroxy-5-(2-hydroxyphenyl)-6-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**10g**).* Colorless solid, mp 150–151 °C. [Found: C, 71.25; H, 5.50; N, 9.25. $C_{27}H_{25}N_3O_4$ requires C, 71.19; H, 5.53; N, 9.22%]; ν_{max} (KBr) 3371, 2926, 1624, 1491, 1458, 1325, 1237, 1140, 742, 698 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 13.37 (s, 1H, OH), 9.50 (s, 1H, OH), 6.62–7.59 (m, 13H, Ar), 6.68 (s, 1H, NH), 5.54 (s, 1H, CH), 5.45 (d, *J* 11.4 Hz, 1H, CH), 4.02 (d, *J* 11.4 Hz, 1H, CH), 2.59 (q, 2H, *J* 7.5 Hz, C*H*$_2$CH$_3$), 1.17 (t, 3H, *J* 7.5 Hz, CH$_2$C*H*$_3$); δ_C (150 MHz, DMSO-d_6) 16.03, 28.44, 46.53, 52.59, 81.92, 85.53, 115.65, 119.34, 125.54, 126.57, 127.19, 127.66, 128.24, 128.61, 128.82, 130.74, 131.97, 136.23, 143.29, 147.67, 150.43, 155.83, 170.55. MS (Mass-FAB): 456.5 (MH^+).

*6.12.8. 2-(4-Ethylphenyl)-7-hydroxy-5-(2-hydroxyphenyl)-6-(4-methoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**10h**).* Colorless solid, mp 138–139 °C. [Found: C, 69.30; H, 5.66; N, 8.68. $C_{28}H_{27}N_3O_5$ requires C, 69.26; H, 5.61; N, 8.65%]; ν_{max} (KBr) 3377, 2928, 1615, 1514, 1458, 1248, 1036, 843, 749 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.82 (s, 1H, OH), 9.44 (s, 1H, OH), 6.60–7.57 (m, 12H, Ar), 6.64 (s, 1H, NH), 5.51 (s, 1H, CH), 5.38 (d, *J* 11.4 Hz, 1H, CH), 3.60 (s, 3H, C*H*$_3$O), 3.94 (d, *J* 11.4 Hz, 1H, CH), 2.59 (q, 2H, *J* 7.6 Hz, C*H*$_2$CH$_3$), 1.16 (t, 3H, *J* 7.6 Hz, CH$_2$C*H*$_3$); δ_C (150 MHz, DMSO-d_6) 16.03, 28.42, 46.75, 51.93, 55.19, 81.87, 85.57, 113.08, 115.64, 119.35, 125.51, 125.56, 126.77, 128.08, 128.23, 128.55, 131.66, 131.99, 143.26, 147.67, 150.38, 155.83, 158.37, 170.61. MS (Mass-FAB): 486.5 (MH^+).

*6.12.9. 6-(4-Chlorophenyl)-2-(4-ethylphenyl)-7-hydroxy-5-(2-hydroxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**10i**).* Colorless solid, mp 162–163 °C. [Found: C, 66.23; H, 4.99; N, 8.57. $C_{27}H_{24}ClN_3O_4$ requires C, 66.19; H, 4.94; N, 8.58%]; ν_{max} (KBr) 3372, 2926, 1623, 159, 1239, 745 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 12.94 (s, 1H, OH), 9.49 (s, 1H, OH), 6.60–7.58 (m, 12H, Ar), 6.72 (s, 1H, NH), 5.53 (s, 1H, CH), 5.39 (d, *J* 10.6 Hz, 1H, CH), 4.00 (d, *J* 10.6 Hz, 1H, CH), 2.48 (q, 2H, *J* 7.5 Hz, C*H*$_2$CH$_3$), 0.97 (t, 3H, *J* 7.5 Hz, CH$_2$C*H*$_3$); δ_C (150 MHz, DMSO-d_6) 16.03, 28.42, 46.24, 52.44, 81.99, 85.32, 115.66, 119.44, 125.53, 126.31, 127.67, 128.24, 128.79, 131.32, 131.90, 132.02, 132.51, 135.24, 143.32, 147.63, 150.48, 155.74, 170.39. MS (Mass-FAB): 491 (MH^+).

6.13. Methodology of antimicrobial study

Study of antimicrobial activity of the compounds was performed in vitro by the method of two-fold serial dilutions in a liquid culture medium (Hottinger Broth, at pH 7.2–7.4).[17] For this purpose the initial solution of the compound being studied with concentration

of 250 μg/ml of the culture medium was prepared. By means of a serial two-fold dilution the compound concentrations of 125, 62.5, 31.25 etc. μg/ml of the culture medium were obtained. Collectable reference strains of bacteria were used as test cultures: *B. subtilis*, *S. aureus* (Gram-positive cultures), *E. coli* (strain 1257) and *P. aeroginosa* (Gram-negative cultures). Microbial load was prepared according to optical turbidity standard and was 500,000 microbial cells in 1 ml of the daily culture of bacteria (0.5 according to McFarland standard). Each experiment was performed in triplicate. The tubes with a mixture were placed in a thermostat at 37 °C for 24 h, the tube with the 'negative control' containing no substance was placed in a refrigerator at 4 °C. Accounting was performed twice (in 24 h and in 48 h); the presence or absence of growth was assessed visually. The minimum bacteriostatic concentration was defined as the lowest concentration of the compound (μg/ml) able to inhibit any visible bacterial growth on the culture plates. The minimum bactericidal concentration was determined by sowing out the contents of those tubes with the absence of any signs of growth on meat-extract agar in Petri plates.

Nitroxoline, the quinoline based drug, was used as a comparison standard.

6.14. X-ray diffraction data

The colorless crystals of **4e** $C_{21}H_{19}N_3O_3 \cdot 0.5C_2H_3N \cdot 0.5H_2O$ are orthorhombic. At 100 K a=13.840(1), b=19.652(2), c=28.254(4) Å, V=7685(2) Å^3, M_r=390.93, Z=8, space group *Pbca*, d_{calcd}=1.352 g/cm^3, $\mu(MoK_\alpha)$=0.093 mm^{-1}, $F(000)$=3296. Intensities of 26,588 reflections (6761 independent, R_{int}=0.1) were measured on the 'Xcalibur-3' diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω-scanning, $2\Theta_{max}$=50°). The structure was solved by direct method using SHELXTL package.[18] Positions of the hydrogen atoms were located from electron density difference maps and refined by 'riding' model with $U_{iso}=nU_{eq}$ (n=1.5 for methyl and hydroxyl groups and n=1.2 for other hydrogen atoms) of the carrier atom. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 6709 reflections was converged to wR_2=0.054 (R_1=0.043 for 3258 reflections with $F>4\sigma(F)$, S=0.726). The final atomic coordinates and crystallographic data for molecule **4e** have been deposited to the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 930676.

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