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Graphical Abstract

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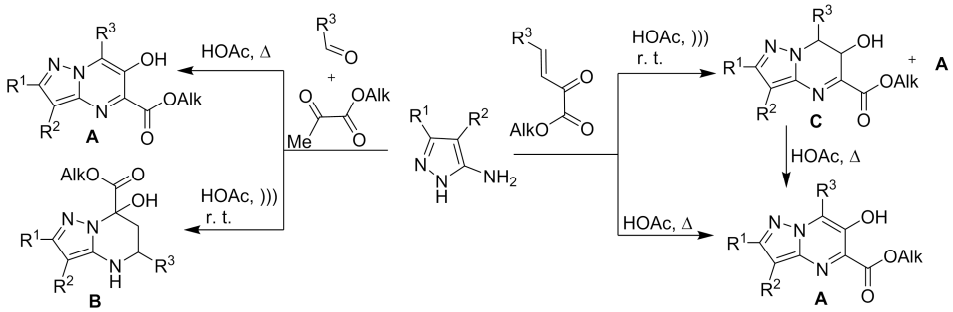

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ABSTRACT

Three-component heterocyclizations of pyruvic acids and their esters with 5-aminopyrazoles and aromatic aldehydes, in addition to the sequential versions of these reactions, under different activating conditions were studied. Under conventional heating, pyrazolopyrimidine derivatives containing a hydroxyl group in the 6-position were formed in both two- and three-component treatments. Whereas the application of an inert atmosphere did not influence the outcome of these reactions, the use of ultrasonic irradiation led to the formation of 7-hydroxy-tetrahydropyrazolopyrimidines in multi-component reactions and 6-hydroxy-dihydropyrazolopyrimidines in the case of a step-by-step approach. The products of the latter treatment were further transformed into heteroaromatized 6-hydroxy-pyrazolopyrimidines by conventional heating.

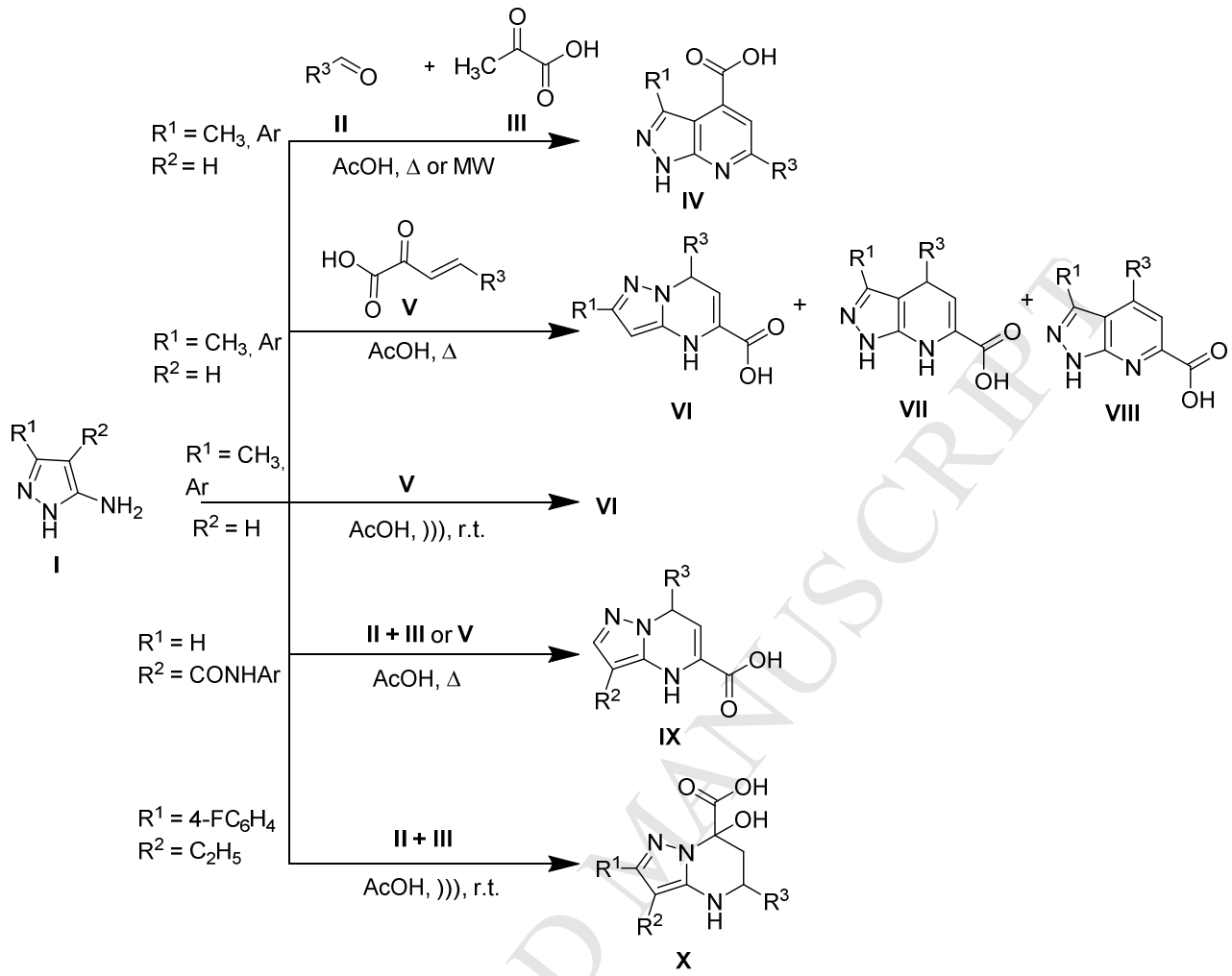
1. Introduction

The reactions of pyruvic acid derivatives have been used for the synthesis of various heterocyclic compounds since the beginning of the twentieth century. Among these processes, the most thoroughly studied were those dealing with benzylidene- and acetylpyruvic acids.[1-18] A series of our previous publications was also devoted to two- and multicomponent reactions (MCRs) involving pyruvic acids and different aminoazoles, such as 5-amino-1,2,4-triazoles,[1,19-23] 5-aminotetrazole,[2,19] 5-amino-3-methylisoxazole,[24] 5-aminopyrazoles[7,8,10,25] and tuning the selectivity of these heterocyclizations.[7,10,20,25]

Interest in the mechanism and outcome of these reactions arose due to the proven biological activity of the final products[21,25,26] and their multi-vector character.[19-25] In particular, in the case of pyruvic acid heterocyclizations with different aminopyrazoles, the approach based on the application of specific catalytic systems and non-classical activation methods (microwave and ultrasonic irradiation), gave the opportunity to develop selective synthetic procedures to afford various classes of heterocyclic compounds.[7,8,10,19-25] For instance, pyrazolopyridine acids **IV** were formed when 3-aryl-5-aminopyrazole was used as a reagent in the MCRs with aromatic aldehydes **II** and pyruvic acid **III** (Scheme 1).[8] However, applying benzylidenepyruvic acid and its substituted derivatives **V** and 3-aryl-5-aminopyrazole in two-component reactions resulted in a mixture of dihydropyrazolopyrimidines **VI** and dihydopyrazolopyridines **VII** and heteroaromatic pyrazolopyridines **VIII** (Scheme 1). Application of ultrasonication in a two-component reaction yielded dihydropyrazolopyrimidines **VI** selectively (Scheme 1).[7] On the other hand, the introduction of a carboxamide substituent in the 4-position of 5-aminopyrazole led to exclusively pyrimidine acids **IX** both in two-component and three-component reactions with pyruvic acid derivatives (Scheme 1). Tetrahydropyrazolopyrimidines **X** were formed when ultrasonic irradiation was applied in a three-component reaction of 5-amino-4-ethyl-3(4'-fluorophenyl)pyrazole, pyruvic acid, and aromatic aldehydes (Scheme 1).[21]

It should be noted that using alkyl pyruvates as starting reagents in the three-component reaction with substituted aminopyrazoles **I** (R^2 = H), and aldehydes led to the formation of a set of reaction products which were similar to the compounds isolated from the MCRs involving pyruvic acid with aminoazoles and aromatic aldehydes.[8,27-29]

The sequential and multicomponent reactions of aromatic anilines with pyruvic acid based β,γ-unsaturated ester or with pyruvates and aromatic aldehydes yielding 2- or 4-substituted quinolines and pyrrol-2-ones have been studied. The formation of different reaction products was described depending on whether the reaction is sequential or a multicomponent, and on specific reaction conditions.[30-32]



Scheme 1. Some sequential and multicomponent reactions involving pyruvic acids and different 5-aminopyrazoles.

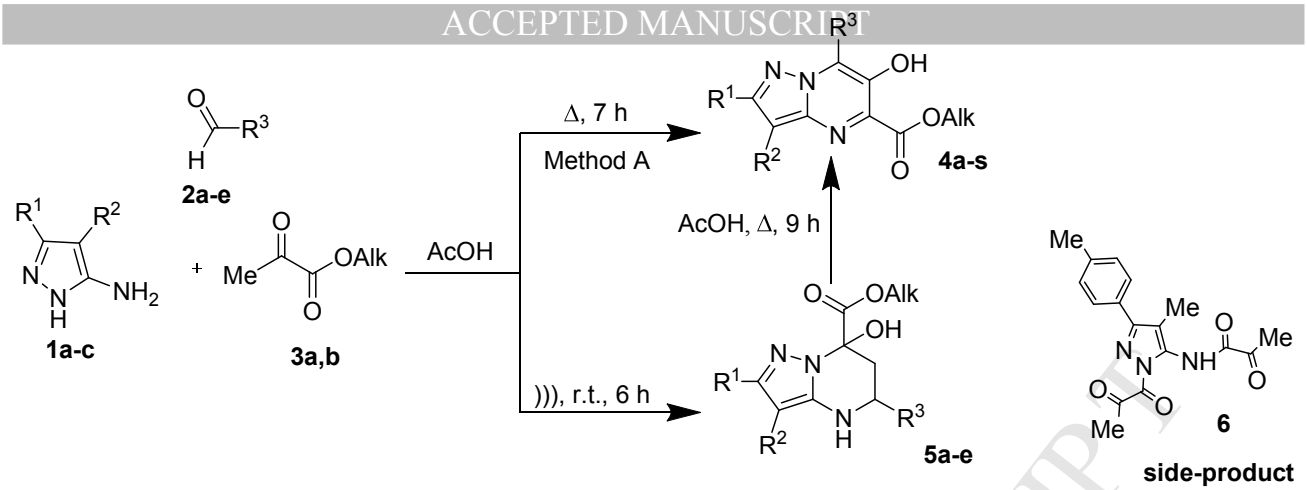
2. Results and discussion

The present paper is devoted to the study of some features of MCRs between 3-aryl-4-alkyl-substituted 5-aminopyrazoles, aromatic aldehydes, and alkyl pyruvates as well as of the sequential version of these treatments under conventional heating and ultrasonication.

In particular, it was established that the three-component reaction of an equimolar mixture of 5-aminopyrazoles **1a-c**, aromatic aldehydes **2a-e**, and pyruvic acid esters **3a,b** under conventional heating at reflux in acetic acid for 7 hours led to the formation of a pyrimidine ring followed by an oxidative heteroaromatization process which finally gave alkyl 6-hydroxy-2,7-diphenylpyrazolo[1,5-*a*]pyrimidine-5-carboxylates **4a-s,** (Scheme 2, Table 1, Method A). It is worth noting that the same treatment under an inert atmosphere also yielded compounds **4a-s** while neither dihydropyrazolopyrimidine nor the compound without a hydroxyl-group were observed. This experimental fact shows that the oxidation occurs irrespective of the presence of oxygen in the reaction mixture and may be connected with more complex processes such as disproportionation.[8,21] Indeed, the yields of pyrimidine derivatives were always lower than 50%, both under atmospheric and inert conditions.

On the other hand, MCR of the same reagents **1a-c**, **2a-e** and **3a,b** under ultrasonication in acetic acid at room temperature for 6 hours redirected the reaction towards the formation of alkyl 7-hydroxy-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-7-carboxylates **5a-e** (Scheme 2, Table 1). Replacement of ultrasonication by mechanical stirring at room temperature allowed us to obtain compounds **5a-e** in a much longer reaction time (20 h) and with lower yields and purity (TLC and NMR control). It is believed, that the cavitation effect and the specific influence of ultrasonication on the mass transfer enhance the reaction and its overall efficiency.[33-37]Compounds **5** were transformed into substances **4** upon boiling in acetic acid for 9 hours. The same transformations for similar compounds had been described in our previous publications.[10,20,25]

In our previous work[8] it was found that three-component reactions of 5-amino-3-methylpyrazole or 5-amino-3-arylpyrazole (R^2 = H) with aromatic aldehydes and ethyl pyruvate under conventional heating at reflux always led to the formation of heteroaromatized pyrazolopyridines with no hydroxy-group in the pyridine ring (e.g. compound **IV**, Scheme 1).



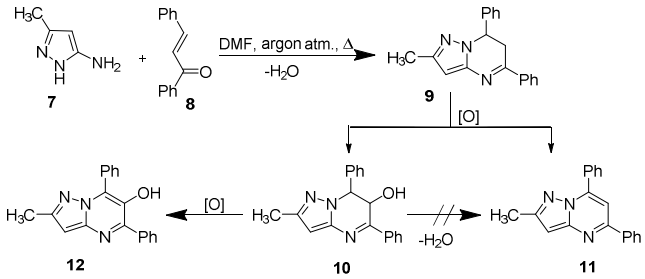
Scheme 2. Multicomponent reactions of 5-aminopyrazoles **1a-c**, aldehydes **2a-e**, and alkyl pyruvates **3a,b.**

Table 1. Three-component reactions of 5-aminopyrazoles **1a-c**, aldehydes **2a-e**, and alkyl pyruvates **3a,b** (See Scheme 2).

Building block							Product	
Aminoazole			Aldehyde		Pyruvic Acid Esters			
N	R^1	R^2	N	R^3	N	Alk	N	Yield (%)
1a	C_6H_5	C_2H_5	**2a**	4-CH_3O-C_6H_4	**3a**	C_2H_5	**4a**	23
1b	4-F-C_6H_4	C_2H_5	**2a**	4-CH_3O-C_6H_4	**3a**	C_2H_5	**4b**	32
1c	4-CH_3-C_6H_4	CH_3	**2a**	4-CH_3O-C_6H_4	**3a**	C_2H_5	**4c**	17
1a	C_6H_5	C_2H_5	**2b**	C_6H_5	**3a**	C_2H_5	**4d**	18
1a	C_6H_5	C_2H_5	**2c**	4-F-C_6H_4	**3a**	C_2H_5	**4e**	27
1a	C_6H_5	C_2H_5	**2d**	4-Cl-C_6H_4	**3a**	C_2H_5	**4f**	24
1a	C_6H_5	C_2H_5	**2e**	4-$COOCH_3$-C_6H_4	**3a**	C_2H_5	**4g**	17
1b	4-F-C_6H_4	C_2H_5	**2b**	C_6H_5	**3a**	C_2H_5	**4h**	23
1b	4-F-C_6H_4	C_2H_5	**2c**	4-F-C_6H_4	**3a**	C_2H_5	**4i**	27
1b	4-F-C_6H_4	C_2H_5	**2d**	4-Cl-C_6H_4	**3a**	C_2H_5	**4j**	29
1b	4-F-C_6H_4	C_2H_5	**2e**	4-$COOCH_3$-C_6H_4	**3a**	C_2H_5	**4k**	18
1b	4-F-C_6H_4	C_2H_5	**2c**	4-F-C_6H_4	**3b**	*i*-C_3H_7	**4l**	19
1b	4-F-C_6H_4	C_2H_5	**2d**	4-Cl-C_6H_4	**3b**	*i*-C_3H_7	**4m**	17
1c	4-CH_3-C_6H_4	CH_3	**2b**	C_6H_5	**3a**	C_2H_5	**4n**	22
1c	4-CH_3-C_6H_4	CH_3	**2c**	4-F-C_6H_4	**3a**	C_2H_5	**4o**	21
1c	4-CH_3-C_6H_4	CH_3	**2d**	4-Cl-C_6H_4	**3a**	C_2H_5	**4p**	25
1c	4-CH_3-C_6H_4	CH_3	**2e**	4-$COOCH_3$-C_6H_4	**3a**	C_2H_5	**4q**	18
1c	4-CH_3-C_6H_4	CH_3	**2a**	4-CH_3O-C_6H_4	**3b**	*i*-C_3H_7	**4r**	18
1c	4-CH_3-C_6H_4	CH_3	**2d**	4-Cl-C_6H_4	**3b**	*i*-C_3H_7	**4s**	19
1a	C_6H_5	C_2H_5	**2a**	4-CH_3O-C_6H_4	**3a**	C_2H_5	**5a**	50
1a	C_6H_5	C_2H_5	**2b**	C_6H_5	**3a**	C_2H_5	**5b**	50
1a	C_6H_5	C_2H_5	**2c**	4-F-C_6H_4	**3a**	C_2H_5	**5c**	52
1a	C_6H_5	C_2H_5	**2d**	4-Cl-C_6H_4	**3a**	C_2H_5	**5d**	50
1a	C_6H_5	C_2H_5	**2e**	4-$COOCH_3$-C_6H_4	**3a**	C_2H_5	**5e**	49

To identify the cause of the low yields of products **4a-s** the corresponding mother liquors were examined by ^{1}H NMR spectroscopy and it was determined that the reaction solution contained unreacted aromatic aldehyde and an additional compound which was identified as a diacylation product **6**. The structure of compound **6** was proven by counter synthesis. To avoid the formation of the unwanted side-product **6,** different reaction conditions were tested with application of several protic and aprotic solvents containing acid and base catalysts as well as microwave irradiation. However, all of these efforts were in vain.

It should be noted that heterocyclization reactions leading to the formation of 6-hydroxy-containing azoloazines were discussed only in a few publications[38-40] and never for MCRs. For instance, Desenko *et al*.[40] described the two-component treatment of 5-amino-3-methylpyrazole (**7**) with *α,β*-unsaturated ketone **8**: the reagents were heated in DMF under an argon atmosphere and a mixture of four products **9**, **10**, **11**, **12** was formed (Scheme 3).

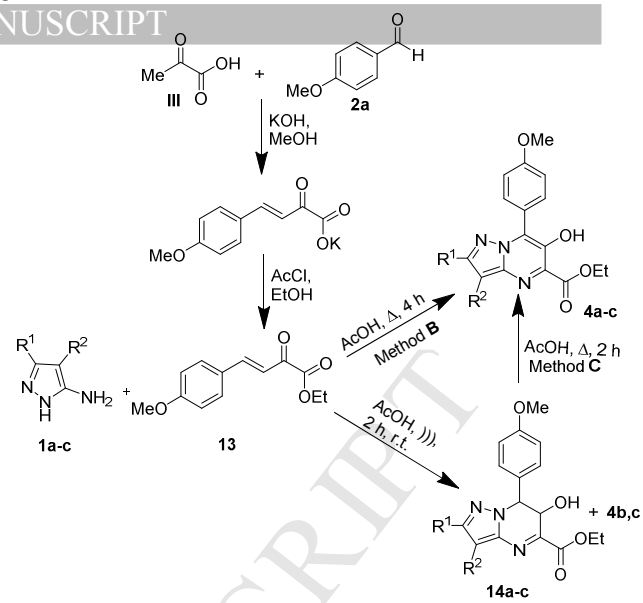


Scheme 3. The two-component reaction of 5-amino-3-methylpyrazole (**7**) with *α,β*-unsaturated ketone **8**.[40]

Compound **9** was obtained under an inert atmosphere and its reaction with oxygen led to formation of substance **10** while further oxidation led to product **12**. Attempts at the dehydration of compound **10** in different solvents (DMF, alcohols with HCl, KOH, $ZnCl_2$ or *p*-TsOH) were unsuccessful.

Therefore, the next step of the study was to apply a sequential reaction instead of the three-component one. The linear pathway included the two-step synthesis of *β,γ*-unsaturated ketoester **13** starting from 4-methoxybenzaldehyde **2a** and pyruvic acid **III**, followed by reaction with ethanol and acetyl chloride.[41-43] Further reactions of 3-aryl-4-alkylsubstituted 5-aminopyrazoles **1a-c** with the ethyl ester of *p*-methoxybenzylidenepyruvic acid **13** under conventional heating gave pyrazolopyrimidine carboxylic acid esters **4a-c** (Scheme 4, Method B), which were identical to the compounds isolated from the MCR of 5-aminopyrazoles **1a-c**, aromatic aldehydes **2a-e**, and pyruvic acid esters **3a,b** (Scheme 2). The yields were rather low (28-37%) as in the case of the MCR (Table 2). Application of an inert atmosphere had no influence on the outcome of the reaction, as was stated above for the MCR.

On the other hand, carrying out the same treatment under ultrasonic irradiation for 2 hours at room temperature instead of compounds **5** (Scheme 2), led to other heterocyclic compounds - ethyl 6-hydroxy-7-(4-methoxyphenyl)-3-alkyl-2-aryl-6,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylates **14a-c** which in cases of aminoazoles **1b,c** were accompanied by small amounts of the heterocycles **4b,c** (Scheme 4, Table 2). All attempts to separate these mixtures by crystallization were unsuccessful and only heteroaromatized pyrimidines **4** were isolated. It should be noted that compound **14a** and a mixture of pyrimidines **14b,c** and **4b,c** were transformed into individual substances **4a-c** upon boiling in acetic acid for 2 hours open to the air (Method C).



Scheme 4. The sequential reaction of 5-aminopyrazoles **1a-c** with ethyl *p*-methoxybenzylidenepyruvate (**13**).

Table 2. The two-component reactions of 5-aminopyrazoles **1a-c** with ethyl *p*-methoxybenzylidenepyruvate (**13**) (See Scheme 4).

Aminoazole			Activation method				
			Heating			Ultrasonication	
N	R^1	R^2	N	Yield (%)		N	Yield (%)
				B	C		
1a	C_6H_5	C_2H_5	**4a**	31	75	**14a**	42
1b	4-FC_6H_4	C_2H_5	**4b**	37	64	**14b** + **4b**	49
1c	4-$CH_3C_6H_4$	CH_3	**4c**	28	72	**14c** + **4c**	41

3. Structure elucidation

Purity and structures of the synthesized compounds were established by elemental analysis, mass-spectrometry, ^{1}H and ^{13}C NMR spectroscopy, and by X-ray diffraction study (see Experimental part).

For instance, the ^{1}H NMR spectra of 6-hydroxy-pyrazolopyrimidines **4a-s** exhibited a broad singlet for the OH-group at 9.8-10.2 ppm, peaks of aromatic protons at 7.2-8.45 ppm and signals corresponding to the alkyl substituent. However, this spectral data is not enough to establish the structure of compounds **4a-s** and to identify one of two possible isomers **XI** and **XII** (Fig. 1).

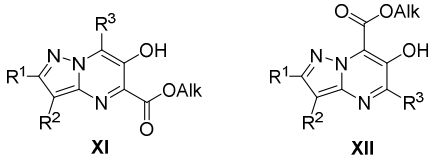


Fig. 1. Alternative structures **XI** and **XII** for 6-hyrdoxypyrazolopyrimidines **4a-s**.

Therefore, the structure of compounds **4a-s** was additionally proven by an X-ray analysis of compound **4o** (Fig. 2).

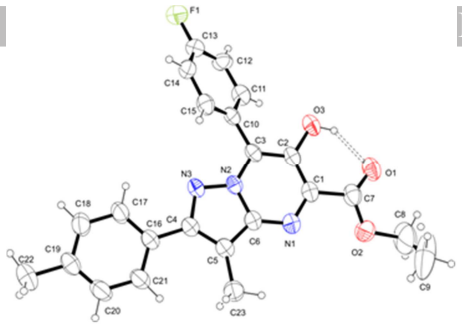


Fig. 2. Molecular structure of ethyl 7-(4-fluorophenyl)-6-hydroxy-3-methyl-2-(*p*-tolyl)-pyrazolo[1,5-*a*]pyrimidine-5-carboxylate (**4o**) according to X-ray diffraction analysis.

The ^{1}H NMR spectra of ethyl carboxylates **5a-e** exhibited a multiplet for the CH_2-group at ca. 1.95-2.38 ppm, a broad signal for the NH-group at 7.21-7.30 ppm, a broad singlet of the OH-group at 6.40-6.60 ppm, a multiplet for the CH-group at position 5 at 4.46-4.76 ppm and a multiplet of aromatic protons at 6.88-8.07. The spectra also contained signals of an ethyl ester group as well as a quartet of the CH_2-group at 4.05-4.26 and a triplet of the methyl group at 1.16-1.17 ppm and signals for the other terminal substituents. The spectral data obtained for the pyrazolopyrimidines **5** may also correspond to two possible isomers **XIII** and **XIV** (Fig. 3). Additional NOE experiments, confirming the spatial closeness of the CH-proton at position 5 with the pyrimidine NH-group, allowed us to exclude structure **XIV**. Also, the structure of compounds **5a-e** was additionally confirmed from the ^{1}H NMR spectra by their comparison with literature data for similar pyrimidines.[21,25]

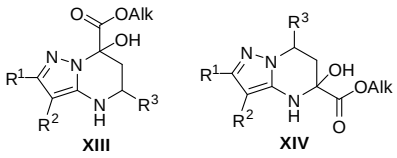


Fig. 3. Alternative structures **XIII** and **XIV** for pyrimidines **5**.

The ^{1}H-NMR spectra of pyrimidines **14a-c** exhibited a doublet for the OH-group at 6.61 ppm (*J* 4.6 Hz), doublet (*J* 1.1 Hz) for the CH group at 5.57, a doublet of doublets (*J* 5.3, 1.1 Hz) for the CH group at 4.79, and peaks for aromatic protons around 6.64-7.75 ppm. For ethyl esters of compounds **14**, the quartet of the CH_2-group was around 4.10-4.41 and triplet of the methyl-group was at 1.26 ppm. Therefore spectral data confirmed the structure of compounds **14** as 6-hydroxy-6,7-dihydropyrazolo[1,5-a]pyrimidines.

4. Conclusion

In summary, the multicomponent and sequential reactions involving 3-aryl-4-alkylsubstituted 5-aminopyrazoles, aromatic aldehydes and *p*-methoxybenzylidenepyruvic esters or pyruvic acid esters were studied. Multicomponent heterocyclization of pyrazoles **1** and aromatic aldehydes **2** with ethyl pyruvate under ultrasonication in contrast to two-component reactions involving *β,γ*-unsaturated ketoester **13** proceeded with the formation of tetrahydropyrimidine ring (compounds **5**) instead of dihydropyrimidines **14**. On the other hand, MCRs under conventional heating at reflux yielded ethyl 6-hydroxy-2,7-diphenylpyrazolo[1,5-*a*]pyrimidine-5-carboxylates **4** containing an OH-group in the 6-position of heterocycle. The same compounds **4** were isolated from the reaction of 5-aminopyrazoles **1** with *p*-methoxybenzylidenepyruvic acid ethyl ester (**13**).

5. Experimental section

5.1. General experimental details

The starting *β,γ*-unsaturated ketoester **13**[41-43], 3,4-substituted 5-aminopyrazoles **1a-c**[44] and isopropyl 2-oxopropanoate (**3b**)[45] were synthesized according to the known literature methods. Ethyl 2-oxopropanoate (**3a**) is commercially available.

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 and $CDCl_3$ at 400 MHz with a Varian MR-400 spectrometer, at 400 MHz (100 MHz for ^{13}C) and at 600 MHz (150 MHz for ^{13}C) with a Bruker Avance DRX600. The mass spectra were measured on a GS-MS Varian 1200L (direct input of sample, ionizing voltage 70 eV) instrument. Elemental analysis was performed on a Euro Vector EA-3000.

Ultrasonication was performed using the standard US-bath (SELDI, Ukraine) with a 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. The reaction time reflects irradiation times at the set reaction temperature (fixed hold times).

*5.2. General procedure for the synthesis of alkyl 6-hydroxy-2,7-diphenylpyrazolo[1,5-a]pyrimidine-5-carboxylates **4***

(Method A) A mixture of appropriate 3-aryl-4-alkyl-substituted 5-aminopyrazole **1** (0.54 mmol), aromatic aldehyde **2** (0.54 mmol) and alkyl pyruvate **3** (0.54 mmol) in 2 mL of acetic acid was heated at reflux under argon atmosphere for 7 hours. The mixture was allowed to stand until a precipitate formed. The precipitate was then filtered off and dried in vacuo.

(Method B) A mixture of the appropriate 5-aminopyrazole **1** (0.54 mmol) and the ethyl (*E*)-4-(4-methoxyphenyl)-2-oxobut-3-enoate (**13**) (0.12 g, 0.54 mmol) in 2 mL of acetic acid was heated at reflux for 4 h. After cooling, the precipitate was filtered off and vacuum dried.

(Method C) Compound **14** was heated at reflux for 2 h in 2 mL of acetic acid. After cooling, the precipitate was filtered off and vacuum dried.

*5.2.1. Ethyl 3-ethyl-6-hydroxy-7-(4-methoxyphenyl)-2-phenylpyrazolo[1,5-a]pyrimidine-5-carboxylate (**4a**)*

Yellow solid (0.05 g, 23%), m.p. 149-150 °C; [Found: C, 68.91; H, 5.61; N, 10.18. $C_{24}H_{23}N_3O_4$ requires C, 69.05; H, 5.55; N, 10.07%]; δ_H (400 MHz, $CDCl_3$) 10.32 (s, 1H, OH), 7.02-8.16 (m, 9H, Ar), 4.62 (q, *J* 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 3.92 (s, 3H, OCH_3), 3.14 (q, *J* 7.5 Hz, 2H, $C\underline{H}_2CH_3$), 1.56 (t, *J* 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.37 (t, *J* 7.5 Hz, 3H, $CH_2C\underline{H}_3$); δ_C (150 MHz, $CDCl_3$) 169.0, 160.9, 153.7, 143.6, 141.3, 134.0, 132.4, 131.7, 128.5, 131.0, 128.4, 128.2, 119.3, 113.5, 112.0, 63.1, 55.4, 16.7, 14.9, 14.2; MS (EI, 70 eV), m/z (%): 418 (26.8), 417 (99.9) [M+], 356 (25.9), 314 (25.4).

*5.2.2. Ethyl 3-ethyl-2-(4-fluorophenyl)-6-hydroxy-7-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-5-carboxylate (**4b**)*

Yellow solid (0.08 g, 32%), m.p. 193-194 °C; [Found: C, 65.86; H, 5.15; N, 10.05. $C_{24}H_{22}FN_3O_4$ requires C, 66.2; H, 5.09; N, 9.65%]; δ_H (400 MHz, DMSO-d_6) 10.05 (s, 1H, OH), 7.00-7.90 (m, 8H, Ar), 4.44 (q, *J* 7.2 Hz, 2H, OC$\underline{H}_2$CH$_3$), 3.81 (s, 3H, OCH$_3$), 2.96 (q, *J* 7.5 Hz, 2H, C$\underline{H}_2$CH$_3$), 1.37 (t, *J* 7.0 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.21 (t, *J* 7.5 Hz, 3H, CH$_2$C$\underline{H}_3$); δ_C (150 MHz, $CDCl_3$) 166.7, 162.6 (d, J_{C-F} 245.7 Hz), 160.9, 151.8, 143.3, 141.7, 138.6, 138.5, 133.5, 132.7, 130.4 (d, J_{C-F} 8.4 Hz), 119.6, 116.1 (d, J_{C-F} 21.5 Hz), 114.0, 110.5, 62.7, 55.8, 16.4, 15.3, 14.5; MS (EI, 70 eV), m/z (%): 435 (99.9) [M+], 388 (92.7), 332 (86.2).

*5.2.3. Ethyl 6-hydroxy-7-(4-methoxyphenyl)-3-methyl-2-(p-tolyl)pyrazolo[1,5-a]pyrimidine-5-carboxylate (**4c**)*

Yellow solid (0.04 g, 17%), m.p. 179-180 °C; [Found: C, 68.92; H, 5.68; N, 10.17. $C_{24}H_{23}N_3O_4$ requires C, 69.05; H, 5.55; N, 10.07%]; δ_H (400 MHz, DMSO-d_6) 10.06 (s, 1H, OH), 6.86-8.45 (m, 8H, Ar), 4.45 (q, *J* 7.2 Hz, 2H, OC$\underline{H}_2$CH$_3$), 3.85 (s, 3H, OCH$_3$), 2.47 (s, 3H, CH$_3$), 2.33 (s, 3H, CH3), 1.38 (t, *J* 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$); δ_C (150 MHz, $CDCl_3$) 168.9, 160.9, 154.0, 144.0, 141.2, 138.1, 131.7, 130.9, 128.6, 127.5, 123.7, 121.0, 119.3, 111.1, 105.1, 63.2, 55.4, 21.3, 14.1, 9.04; MS (EI, 70 eV), m/z (%): 417 (99.9) [M+], 370 (86.7).

*5.2.4. Ethyl 3-ethyl-6-hydroxy-2,7-diphenylpyrazolo[1,5-a]pyrimidine-5-carboxylate (**4d**)*

Yellow solid (0.04 g, 18%), m.p. 141-142 °C; [Found: C, 72.21; H, 6.10; N, 11.38. $C_{23}H_{21}N_3O_3$ requires C, 71.3; H, 5.46; N, 10.85%]; δ_H (400 MHz, DMSO-d_6) 9.99 (s, 1H, OH), 7.20-8.0 (m, 10H, Ar), 4.45 (q, *J* 7.0 Hz, 2H, OC$\underline{H}_2$CH$_3$), 2.97 (q, *J* 7.7 Hz, 2H, C$\underline{H}_2$CH$_3$), 1.37 (t, *J* 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.22 (t, *J* 7.4 Hz, 3H, CH$_2$C$\underline{H}_3$); δ_C (150 MHz, $CDCl_3$) 168.9, 153.8, 143.5, 141.4, 140.8, 136.6, 133.7, 131.6, 131.1, 128.4, 126.9, 123.7, 112.4, 112.2, 109.2, 63.1, 16.6, 14.9, 14.1; MS (EI, 70 eV), *m*/z (%): 387 (58.7) [M^+], 372 (56.1), 341 (99.9), 284 (58.8).

*5.2.5. Ethyl 3-ethyl-7-(4-fluorophenyl)-6-hydroxy-2-phenylpyrazolo[1,5-a]pyrimidine-5-carboxylate (**4e**)*

Yellow solid (0.06 g, 27%), m.p. 152-153 °C; [Found: C, 68.08; H, 5.08; N, 10.40. $C_{23}H_{20}FN_3O_3$ requires C, 68.14; H, 4.97; N, 10.36%]; δ_H (400 MHz, DMSO-d_6) 9.83 (s, 1H, OH), 7.17-8.19 (m, 9H, Ar), 4.45 (q, *J* 7.1 Hz, 2H, OC$\underline{H}_2$CH$_3$), 2.97 (q, *J* 7.5 Hz, 2H, C$\underline{H}_2$CH$_3$), 1.37 (t, *J* 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.22 (t, *J* 7.9 Hz, 3H, CH$_2$C$\underline{H}_3$); δ_C (150 MHz, $CDCl_3$) 168.5, 162.7 (d, J_{C-F} 159.2 Hz), 153.5, 147.0, 144.3, 143.1, 141.0, 133.2, 132.6, 132.5, 130.7, 130.2, 128.0 (d, J_{C-F} 34.5 Hz), 114.9 (d, J_{C-F} 21.8 Hz), 112.0, 62.8, 16.3, 14.5, 13.8; MS (EI, 70 eV), m/z (%): 405 (40.2) [M+], 390 (40.8), 359 (99.9), 302 (88.6).

*5.2.6. Ethyl 7-(4-chlorophenyl)-3-ethyl-6-hydroxy-2-phenylpyrazolo[1,5-a]pyrimidine-5-carboxylate (**4f**)*

Yellow solid (0.06 g, 24%), m.p. 157-158 °C; [Found: C, 65.39; H, 4.86; N, 10.04. $C_{23}H_{20}ClN_3O_3$ requires C, 65.48; H, 4.78; N, 9.96%]; δ_H (400 MHz, DMSO-d_6) 10.35 (s, 1H, OH), 7.25-8.11 (m, 9H, Ar), 4.45 (q, *J* 7.0 Hz, 2H, OC$\underline{H}_2$CH$_3$), 2.97 (q, *J* 7.4 Hz, 2H, C$\underline{H}_2$CH$_3$), 1.37 (t, *J* 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.22 (t, *J* 7.5 Hz, 3H, CH$_2$C$\underline{H}_3$); δ_C (150 MHz, $CDCl_3$) 168.8, 153.8, 143.5, 141.4, 136.1, 133.6, 132.7, 131.5, 131.1, 130.3, 128.8, 127.8, 125.5, 125.3, 112.4, 63.1, 16.6, 14.8, 14.1; MS (EI, 70 eV), m/z (%): 423 (47.2), 422 (34), 421 (99.9) [M+], 360 (38.7), 332 (31.0).

*5.2.7. Ethyl 3-ethyl-6-hydroxy-7-(4-(methoxycarbonyl)phenyl)-2-phenylpyrazolo[1,5-a]pyrimidine-5-carboxylate (**4g**)*

Yellow solid (0.04 g, 17%), m.p. 168-169 °C; [Found: C, 67.31; H, 5.34; N, 9.53. $C_{25}H_{23}N_3O_5$ requires C, 67.41; H, 5.2; N, 9.43%]; δ_H (400 MHz, DMSO-d_6) 9.96 (s, 1H, OH), 6.69-8.48 (m, 9H, Ar), 4.46 (q, *J* 7.2 Hz, 2H, OC$\underline{H}_2$CH$_3$), 3.89 (s, 3H, OCH$_3$), 2.98 (q, *J* 7.4 Hz, 2H, C$\underline{H}_2$CH$_3$), 1.37 (t, *J* 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.22 (t, *J* 7.4 Hz, 3H, CH$_2$C$\underline{H}_3$); δ_C (150 MHz, $CDCl_3$) 166.0, 165.9, 152.3, 142.7, 138.8, 138.7, 133.3, 132.2, 131.6, 131.1, 130.7, 128.8, 128.4, 127.9, 110.6, 62.4, 52.4, 16.0, 14.9, 14.1; MS (EI, 70 eV), m/z (%): 445 (88.2) [M+], 430 (39.5), 399 (45.6), 342 (99.9).

*5.2.8. Ethyl 3-ethyl-2-(4-fluorophenyl)-6-hydroxy-7-phenylpyrazolo[1,5-a]pyrimidine-5-carboxylate (**4h**)*

Yellow solid (0.05 g, 23%), m.p. 168-169 °C; [Found: C, 68.03; H, 5.17; N, 10.47. $C_{23}H_{20}FN_3O_3$ requires C, 68.14; H, 4.97; N, 10.36%]; δ_H (400 MHz, DMSO-d_6) 9.99 (s, 1H, OH), 7.22-7.89 (m, 9H, Ar), 4.44 (q, *J* 7.2 Hz, 2H, OC$\underline{H}_2$CH$_3$), 2.95 (q, *J* 7.4 Hz, 2H, C$\underline{H}_2$CH$_3$), 1.36 (t, *J* 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.21 (t, *J* 7.3 Hz, 3H, CH$_2$C$\underline{H}_3$); δ_C (150 MHz, $CDCl_3$) 168.9, 162.9 (d, J_{C-F} 247.8 Hz), 152.9, 143.5, 141.5, 131.7, 131.3, 130.6, 130.3, 130.0 (d, J_{C-F} 8.2 Hz), 129.9, 128.1, 127.1, 115.5 (d, J_{C-F} 21.5 Hz), 111.9, 63.2, 16.6, 14.8, 14.2; MS (EI, 70 eV), m/z (%): 406 (30.3), 405 (99.9) [M+], 344 (26.5).

*5.2.9. Ethyl 3-ethyl-2,7-bis(4-fluorophenyl)-6-hydroxypyrazolo[1,5-a]pyrimidine-5-carboxylate (**4i**)*

Yellow solid (0.06 g, 27%), m.p. 187-188 °C; [Found: C, 65.09; H, 4.67; N, 10.07. $C_{23}H_{19}F_2N_3O_3$ requires C, 65.24; H, 4.52; N, 9.92%]; δ_H (400 MHz, DMSO-d_6) 10.03 (s, 1H, OH), 7.21-7.99 (m, 8H, Ar), 4.45 (q, *J* 7.2 Hz, 2H, OC$\underline{H}_2$CH$_3$), 2.95 (q, *J* 7.3 Hz, 2H, C$\underline{H}_2$CH$_3$), 1.36 (t, *J* 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.20 (t, *J* 7.4 Hz, 3H, CH$_2$C$\underline{H}_3$); δ_C (150 MHz, $CDCl_3$) 168.8, 163.5 (d, J_{C-F} 251.7 Hz), 162.8 (d, J_{C-F} 247.7 Hz), 152.9, 143.5, 141.5, 132.9 (d, J_{C-F} 8.5 Hz), 131.3, 130.6, 130.0 (d, J_{C-F} 8.2 Hz), 129.8, 123.1, 115.6 (d, J_{C-F} 21.6 Hz), 115.3 (d, J_{C-F} 21.8 Hz), 112.1, 63.2, 16.6, 14.8, 14.1; MS (EI, 70 eV), m/z (%): 424 (27.7), 423 (99.9) [M+], 362 (20.2).

*5.2.10. Ethyl 7-(4-chlorophenyl)-3-ethyl-2-(4-fluorophenyl)-6-hydroxypyrazolo[1,5-a]pyrimidine-5-carboxylate (**4j**)*

Yellow solid (0.07 g, 29%), m.p. 239-240 °C; [Found: C, 62.62; H, 4.47; N, 9.69. $C_{23}H_{19}ClFN_3O_3$ requires C, 62.8; H, 4.35; N, 9.55%]; δ_H (400 MHz, DMSO-d_6) 9.95 (s, 1H, OH), 7.16-7.96 (m, 8H, Ar), 4.44 (q, *J* 7.0 Hz, 2H, OC$\underline{H}_2$CH$_3$), 2.95 (q, *J* 7.2 Hz, 2H, C$\underline{H}_2$CH$_3$), 1.36 (t, *J* 7.2 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.20 (t, *J* 7.2 Hz, 3H, CH$_2$C$\underline{H}_3$); δ_C (150 MHz, $CDCl_3$) 168.8, 162.9 (d, J_{C-F} 248.2 Hz), 152.9, 143.5, 141.5, 136.2, 132.1, 131.3, 130.4, 130.0 (d, J_{C-F} 8.1 Hz), 129.8, 128.4, 125.5, 115.6 (d, J_{C-F} 21.5 Hz), 112.2, 63.3, 16.6, 14.8, 14.2; MS (EI, 70 eV), m/z (%): 441 (24.9), 439 (76.4) [M+], 424 (45.5), 395 (25.5), 393 (99.9), 336 (62.0).

*5.2.11. Ethyl 3-ethyl-2-(4-fluorophenyl)-6-hydroxy-7-(4-(methoxycarbonyl)phenyl)pyrazolo[1,5-a]pyrimidine-5-carboxylate (**4k**)*

Yellow solid (0.05 g, 18%), m.p. 222-223 °C; [Found: C, 64.52; H, 4.98; N, 9.56. $C_{25}H_{22}FN_3O_5$ requires C, 64.79; H, 4.78; N, 9.27%]; δ_H (400 MHz, DMSO-d_6) 9.99 (s, 1H, OH), 7.15-8.18 (m, 8H, Ar), 4.45 (q, *J* 7.2 Hz, 2H, OC$\underline{H}_2$CH$_3$), 3.89 (s, 3H, OCH$_3$), 2.96 (q, *J* 7.3 Hz, 2H, C$\underline{H}_2$CH$_3$), 1.37 (t, *J* 7.1 Hz, 3H, CH$_2$C$\underline{H}_3$), 1.21 (t, *J* 7.3 Hz, 3H, CH$_2$C$\underline{H}_3$); δ_C (150 MHz, DMSO-d_6) 166.4, 166.3 , 162.8 (d, J_{C-F} 246.0 Hz), 152.3, 143.4, 139.1, 132.6, 132.2, 131.6, 131.4, 130.4 (d, J_{C-F} 8.3 Hz), 130.2, 129.6, 129.1, 115. 9 (d, J_{C-F} 21.5 Hz), 111.3, 62.7, 52.5, 16.4, 14.9, 14.3; MS (EI, 70 eV), m/z (%): 464 (31.9), 463 (99.9) [M+], 360 (29.2).

*5.2.12. Isopropyl 3-ethyl-2,7-bis(4-fluorophenyl)-6-hydroxypyrazolo[1,5-a]pyrimidine-5-carboxylate (**4l**)*

Yellow solid (0.05 g, 19%), m.p. 182-183 °C; [Found: C, 65.78; H, 4.92; N, 9.66. $C_{24}H_{21}F_2N_3O_3$ requires C, 65.90; H, 4.84;

N, 9.61%]; δ_H (400 MHz, DMSO-d_6) 10.04 (s, 1H, OH), 6.85-8.39 (m, 8H, Ar), 5.23 (gept, *J* 6.3 Hz, 1H, C<u>H</u>$(CH_3)_2$), 2.96 (q, *J* 7.3 Hz, 2H, C<u>H</u>$_2$CH$_3$), 1.37 (d, *J* 6.2 Hz, 6H, CH(C<u>H</u>$_3$)$_2$), 1.21 (t, *J* 7.9 Hz, 3H, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz, DMSO-d_6) 168.4, 163.5 (d, J_{C-F} 251.0 Hz), 162.9 (d, J_{C-F} 247.7 Hz), 152.7, 143.5, 141.4, 132.9 (d, J_{C-F} 8.8 Hz), 131.6, 130.6, 129.9 (d, J_{C-F} 8.4 Hz), 129.8, 123.0, 115.5 (d, J_{C-F} 21.8 Hz), 115.2 (d, J_{C-F} 22.2 Hz), 112.0, 71.4, 21.7, 16.6, 14.7; MS (EI, 70 eV), m/z (%): 437 (86.8) [M+], 377 (99.9), 320 (40.8).

*5.2.13. Isopropyl 7-(4-chlorophenyl)-3-ethyl-2-(4-fluorophenyl)-6-hydroxypyrazolo[1,5-a]pyrimidine-5-carboxylate (**4m**)*

Yellow solid (0.04 g, 17%), m.p. 181-182 °C; [Found: C, 63.42; H, 4.72; N, 9.35. $C_{24}H_{21}ClFN_3O_3$ requires C, 63.51; H, 4.66; N, 9.26%]; δ_H (400 MHz, DMSO-d_6) 9.87 (s, 1H, OH), 6.98-8.41 (m, 8H, Ar), 5.27 (gept, *J* 6.4 Hz, 1H, C<u>H</u>$(CH_3)_2$), 2.96 (q, *J* 7.6 Hz, 2H, C<u>H</u>$_2$CH$_3$), 1.38 (d, *J* 6.3 Hz, 6H, CH(C<u>H</u>$_3$)$_2$), 1.21 (t, *J* 7.5 Hz, 3H, CH$_2$C<u>H</u>$_3$); δ_C (150 MHz, $CDCl_3$) 168.0, 162.4 (d, J_{C-F} 240.8 Hz), 152.4, 143.1, 141.1, 135.7, 131.7, 131.2, 129.8 (d, J_{C-F} 8.5 Hz), 129.8, 129.4, 128.1, 125.1, 115.2 (d, J_{C-F} 21.7 Hz), 111.8, 71.2, 21.3, 16.2, 14.4; MS (EI, 70 eV), m/z (%): 455 (5.5), 453 (17.4) [M+], 413 (52.1), 411(99.9), 336 (41.5).

*5.2.14. Ethyl 6-hydroxy-3-methyl-7-phenyl-2-(p-tolyl)pyrazolo[1,5-a]pyrimidine-5-carboxylate (**4n**)*

Orange solid (0.05 g, 22%), m.p. 203-204 °C; [Found: C, 71.22; H, 5.52; N, 10.97. $C_{23}H_{21}N_3O_3$ requires C, 71.3; H, 5.46; N, 10.85%]; δ_H (400 MHz, $CDCl_3$) 10.27 (s, 1H, OH), 6.89-8.23 (m, 9H, Ar), 4.61 (q, *J* 4.9 Hz, 2H, OC<u>H</u>$_2$CH$_3$), 2.65 (s, 3H, CH$_3$), 2.40 (s, 3H, CH$_3$), 1.56 (t, *J* 5.0 Hz, 3H, CH$_2$C<u>H</u>$_3$); δ_C (150 MHz, $CDCl_3$) 168.5, 153.7, 143.6, 140.9, 137.8, 131.3, 130.6, 130.4, 130.3, 129.9, 128.8, 127.7, 127.6, 126.7, 104.9, 62.9, 21.0, 13.8, 8.7; MS (EI, 70 eV), m/z (%): 387 (99.9) [M+], 341 (33.3), 284 (40.5), 270 (47.0).

*5.2.15. Ethyl 7-(4-fluorophenyl)-6-hydroxy-3-methyl-2-(p-tolyl)pyrazolo[1,5-a]pyrimidine-5-carboxylate (**4o**)*

Orange solid (0.05 g, 21%), m.p. 195-196 °C; [Found: C, 68.09; H, 5.06; N, 10.48. $C_{23}H_{20}FN_3O_3$ requires C, 68.14; H, 4.97; N, 10.36%]; δ_H (400 MHz, DMSO-d_6) 10.21 (s, 1H, OH), 6.97-8.19 (m, 8H, Ar), 4.46 (q, *J* 7.0 Hz, 2H, OC<u>H</u>$_2$CH$_3$), 2.47 (s, 3H, CH$_3$), 2.35 (s, 3H, CH$_3$), 1.39 (t, *J* 7.0 Hz, 3H, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 168.8, 163.0 (d, J_{C-F} 249.1 Hz), 154.0, 143.8, 141.2, 138.2, 132.7, 130.9, 130.7, 130.5 (d, J_{C-F} 8.2 Hz), 129.2, 128.9, 123.0, 115.1 (d, J_{C-F} 23.2 Hz), 105.4, 63.3, 28.7, 23.4, 8.0; MS (EI, 70 eV), m/z (%): 405 (33.6) [M+], 359 (23.3), 289 (22.3), 288 (99.9).

*5.2.16. Ethyl 7-(4-chlorophenyl)-6-hydroxy-3-methyl-2-(p-tolyl)pyrazolo[1,5-a]pyrimidine-5-carboxylate (**4p**)*

Yellow solid (0.06 g, 25%), m.p. 194-195 °C; [Found: C, 65.39; H, 4.84; N, 10.01. $C_{23}H_{20}ClN_3O_3$ requires C, 65.48; H, 4.78; N, 9.96%]; δ_H (400 MHz, DMSO-d_6) 10.21 (s, 1H, OH), 6.97-8.19 (m, 8H, Ar), 4.46 (q, *J* 7.0 Hz, 2H, OC<u>H</u>$_2$CH$_3$), 2.47 (s, 3H, CH$_3$), 2.35 (s, 3H, CH$_3$), 1.39 (t, *J* 7.0 Hz, 3H, CH$_2$C<u>H</u>$_3$); δ_C (150 MHz, $CDCl_3$) 168.8, 154.1, 143.9, 141.3, 138.3, 136.1, 132.2, 131.0, 130.6, 130.4, 129.8, 128.4, 128.0, 125.6, 105.6, 63.3, 21.3, 14.1, 9.1; MS (EI, 70 eV), m/z (%): 423 (32.8), 421 (84.3) [M+], 320 (48.7), 319 (32.9), 318(99.9).

*5.2.17. Ethyl 6-hydroxy-7-(4-(methoxycarbonyl)phenyl)-3-methyl-2-(p-tolyl)pyrazolo[1,5-a]pyrimidine-5-carboxylate (**4q**)*

Yellow solid (0.04 g, 18%), m.p. 225-226 °C; [Found C, 67.37; H, 5.26; N, 9.37. $C_{25}H_{23}N_3O_5$ requires C, 67.41; H, 5.20; N, 9.43%]; δ_H (400 MHz, DMSO-d_6) 10.36 (s, 1H, OH), 6.62-8.99 (m, 8H, Ar), 4.63 (q, *J* 8.0 Hz, 2H, OC<u>H</u>$_2$CH$_3$), 3.98 (s, 3H, CH$_3$), 2.66 (s, 3H, CH$_3$), 2.40 (s, 3H, CH$_3$), 1.55 (t, *J* 7.9 Hz, 3H, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz, DMSO-d_6) 169.8, 166.2, 160.6, 155.6, 153.5, 144.1, 134.1, 132.6, 131.7, 130.0, 127.4, 127.1, 126.9, 126.1, 122.8, 112.8, 106.2, 61.9, 52.7, 21.3, 8.7; MS (EI, 70 eV), m/z (%): 445 (49.7) [M+], 399 (29.8), 371 (22.5), 343 (27.4).

*5.2.18. Isopropyl 6-hydroxy-7-(4-methoxyphenyl)-3-methyl-2-(p-tolyl)pyrazolo[1,5-a]pyrimidine-5-carboxylate (**4r**)*

Yellow solid (0.04 g, 18%), m.p. 199-200 °C; [Found: C, 69.51; H, 5.92; N, 9.77. $C_{25}H_{25}N_3O_4$ requires C, 69.59; H, 5.84; N, 9.74%]; δ_H (400 MHz, DMSO-d_6) 10.02 (s, 1H, OH), 7.04-7.99 (m, 8H, Ar), 5.30 (gept, *J* 6.1 Hz, 1H, C<u>H</u>$(CH_3)_2$), 3.85 (s, 3H, OCH$_3$), 2.46 (s, 3H, CH$_3$), 2.34 (s, 3H, CH$_3$), 1.39 (d, *J* 6.3 Hz, 6H, CH(C<u>H</u>$_3$)$_2$); δ_C (100 MHz, DMSO-d_6) 171.8, 166.4, 160.8, 142.1, 140.8, 135.1, 133.4, 132.6, 129.6, 128.0, 126.9, 126.1, 122.3, 114.1, 113.9, 106.2, 70.8, 55.8, 21.9, 21.3, 9.0; MS (EI, 70 eV), m/z (%): 431 (93.9) [M+], 371 (41.1), 300 (27.8).

*5.2.19. Isopropyl 7-(4-chlorophenyl)-6-hydroxy-3-methyl-2-(p-tolyl)pyrazolo[1,5-a]pyrimidine-5-carboxylate (**4s**)*

Yellow solid (0.05 g, 19%), m.p. 215-216 °C; [Found: C, 66.05; H, 5.15; N, 9.72. $C_{24}H_{22}ClN_3O_3$ requires C, 66.13; H, 5.09; N, 9.64%]; δ_H (400 MHz, $CDCl_3$) 10.43 (s, 1H, OH), 6.84-8.39 (m, 8H, Ar), 5.40 (gept, *J* 6.1 Hz, 1H, C<u>H</u>$(CH_3)_2$), 2.64 (s, 3H, CH$_3$), 2.41 (s, 3H, CH$_3$), 1.54 (d, *J* 5.9 Hz, 6H, CH(C<u>H</u>$_3$)$_2$); δ_C (100 MHz, DMSO-d_6) 168.1, 153.5, 144.6, 141.0, 137.8, 136.56, 135.6, 131.8, 131.0, 130.3, 129.8, 128.9, 128.0, 127.6, 125.2, 105.2, 71.3, 21.3, 21.0, 8.7; MS (EI, 70 eV), m/z (%): 437 (20.1), 435 (47.7) [M+], 377 (41.5), 351 (22.8), 350 (29.0), 348 (33.2), 347 (38.6), 320 (42.7), 319 (42.7), 319 (34.5), 318 (99.9), 304 (41.3).

*5.3. General procedure for the synthesis of ethyl 3-ethyl-7-hydroxy-2-phenyl-5-aryl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylates **5***

A mixture of 3-phenyl-4-ethyl 5-aminopyrazole **1a** (0.1 g, 0.54 mmol), aromatic aldehyde **2** (0.54 mmol) and ethyl pyruvate **3a** (0.06 g, 0.54 mmol) in 2 mL of acetic acid was ultrasonicated at room temperature for 6 h. The mixture was allowed to stand overnight. The solid precipitated was collected by filtration and vacuum dried.

*5.3.1. Ethyl 3-ethyl-7-hydroxy-5-(4-methoxyphenyl)-2-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylate (**5a**)*

White solid (0.11 g, 50%), m.p. 139-140 °C; [Found: C, 68.27; H, 6.52; N, 10.10. $C_{24}H_{27}N_3O_4$ requires C, 68.39; H, 6.46; N, 9.97%]; δ_H (400 MHz, DMSO-d_6) 6.88-7.61 (m, 9H, Ar), 7.27 (d, *J* 6.9 Hz, 1H, NH), 6.43 (s, 1H, OH), 4.46-4.69 (m, 1H, CH), 4.18 (q, *J* 6.9 Hz, 2H, OC<u>H</u>$_2$CH$_3$), 3.74 (s, 3H, OCH$_3$), 2.42 (q, *J* 7.2 Hz, 2H, C<u>H</u>$_2$CH$_3$), 1.95-2.35 (m, 2H, CH$_2$), 1.17 (t, *J* 7.0 Hz, 3H, OCH$_2$C<u>H</u>$_3$), 1.00 (t, *J* 7.2 Hz, 3H, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz, DMSO-d_6) 169.6, 158.9, 148.7, 144.3, 134.9, 134.0, 128.2, 128.1, 127.1, 113.9, 98.2, 82.0, 61.5, 55.2, 50.2, 42.1, 15.2, 14.9, 14.0; MS (EI, 70 eV), m/z (%): 421 (89.1) [MH+], 348 (48.3), 306 (49.0), 187 (61.3), 172 (90.1), 161 (99.9).

*5.3.2. Ethyl 3-ethyl-7-hydroxy-2,5-diphenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylate (**5b**)*

Pale yellow solid (0.12 g, 50%), m.p. 136-137 °C; [Found: C, 70.49; H, 6.37; N, 10.65. $C_{23}H_{25}N_3O_3$ requires C, 70.57; H, 6.44; N, 10.73%]; δ_H (400 MHz, DMSO-d_6) 7.20-7.61 (m, 10H, Ar), 7.30 (d, *J* 7.1 Hz, 1H, NH), 6.51 (s, 1H, OH), 4.49-4.74 (m, 1H, CH), 4.18 (q, *J* 7.2 Hz, 2H, OC<u>H</u>$_2$CH$_3$), 2.43 (q, *J* 7.3 Hz, 2H, C<u>H</u>$_2$CH$_3$), 2.05-2.36 (m, 2H, CH$_2$), 1.17 (t, *J* 7.1 Hz, 3H, OCH$_2$C<u>H</u>$_3$), 1.01 (t, *J* 7.2 Hz, 3H, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz, DMSO-d_6) 169.6, 148.7, 148.4, 144.3, 134.9, 128.5, 128.3, 127.7, 127.1, 126.9, 104.8, 98.3, 82.0, 61.5, 50.8, 42.1, 15.3, 14.9, 14.0; MS (EI, 70 eV), m/z (%): 392 (99.9) [MH+], 344 (90.5), 276 (10).

*5.3.3. Ethyl 3-ethyl-5-(4-fluorophenyl)-7-hydroxy-2-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylate (**5c**)*

Pale yellow (0.12 g, 52%), m.p. 128-129 °C; [Found: C, 67.41; H, 5.83; N, 10.28. $C_{23}H_{24}FN_3O_3$ requires C, 67.47; H, 5.91; N, 10.26%]; δ_H (400 MHz, DMSO-d_6) 7.23-7.59 (m, 9H, Ar), 7.20 (d, *J* 8.2 Hz, 1H, NH), 6.49 (s, 1H, OH), 4.53-4.75 (m, 1H, CH), 4.18 (q, *J* 7.3 Hz, 2H, OC$\underline{H}_2$CH$_3$), 2.50 (q, *J* 7.4 Hz, 2H, C$\underline{H}_2$CH$_3$), 2.0-2.35 (m, 2H, CH$_2$), 1.17 (t, *J* 7.3 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.01 (t, *J* 7.3 Hz, 3H, CH$_2$C$\underline{H}_3$); δ_C (100 MHz, DMSO-d_6) 169.9, 162.0 (d, J_{C-F} 250.0 Hz), 160.8, 149.2, 144.6, 138.7, 135.2, 129.3 (d, J_{C-F} 8.4 Hz), 128.7, 127.5, 115.6 (d, J_{C-F} 21.4 Hz), 98.8, 82.4, 62.0, 50.5, 42.4, 15.7, 15.4, 14.4; MS (EI, 70 eV), m/z (%): 410 (99.9) [MH+], 362 (90.1), 294 (12.5).

*5.3.4. Ethyl 5-(4-chlorophenyl)-3-ethyl-7-hydroxy-2-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylate (**5d**)*

Pale yellow solid (0.12 g, 50%), m.p. 126-127 °C; [Found: C, 64.72; H, 5.78; N, 9.82. $C_{23}H_{24}ClN_3O_3$ requires C, 64.86; H, 5.68; N, 9.87%]; δ_H (400 MHz, DMSO-d_6) 7.23-7.59 (m, 9H, Ar), 7.30 (d, *J* 6.1 Hz, 1H, NH), 6.52 (s, 1H, OH), 4.46-4.76 (m, 1H, CH), 4.18 (q, *J* 7.1 Hz, 2H, OC$\underline{H}_2$CH$_3$), 2.43 (q, *J* 7.3 Hz, 2H, C$\underline{H}_2$CH$_3$), 2.05-2.34 (m, 2H, CH$_2$), 1.17 (t, *J* 7.2 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.01 (t, *J* 7.3 Hz, 3H, CH$_2$C$\underline{H}_3$); δ_C (100 MHz, DMSO-d_6) 169.9, 149.2, 148.4, 144.5, 141.6, 136.5, 129.3, 128.9, 128.7, 127.6, 127.5, 98.8, 82.3, 62.0, 50.6, 42.3, 15.7, 15.4, 14.5; MS (EI, 70 eV), m/z (%): 426 (100) [MH+].

*5.3.5. Ethyl 3-ethyl-7-hydroxy-5-(4-(methoxycarbonyl)phenyl)-2-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylate (**5e**)*

Pale yellow solid (0.12 g, 49%), m.p. 71-72 °C; [Found: C, 66.69; H, 6.19; N, 9.42. $C_{25}H_{27}N_3O_5$ requires C, 66.80; H, 6.05; N, 9.35%]; δ_H (400 MHz, DMSO-d_6) 7.21-8.07 (m, 9H, Ar), 7.28 (d, *J* 6.4 Hz, 1H, NH), 6.60 (s, 1H, OH), 4.56-4.82 (m, 1H, CH), 4.18 (q, *J* 7.1 Hz, 2H, OC$\underline{H}_2$CH$_3$), 3.85 (s, 3H, OCH$_3$), 2.40 (q, *J* 7.3 Hz, 2H, C$\underline{H}_2$CH$_3$), 2.09-2.36 (m, 2H, CH$_2$), 1.16 (t, *J* 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.02 (t, *J* 7.4 Hz, 3H, CH$_2$C$\underline{H}_3$); δ_C (100 MHz, DMSO-d_6) 169.4, 166.0, 148.8, 147.7, 144.0, 134.8, 129.4, 129.0, 128.3, 127.3, 127.2, 127.1, 125.7, 98.5, 81.9, 61.6, 52.2, 50.6, 41.8, 15.3, 14.9, 14.0; MS (EI, 70 eV), m/z (%): 450 (100) [MH+].

*5.4. Procedure for the synthesis of N-(4-methyl-1-(2-oxopropanoyl)-3-(p-tolyl)-1H-pyrazol-5-yl)-2-oxopropanamide (**6**)*

A mixture of 5-aminopyrazole **1c** (0.1 g, 0.54 mmol) and ethyl pyruvate (**3a**) (0.06 g, 0.54 mmol) in 2 mL of acetic acid was heated at reflux for 6 h. The mixture was concentrated to 1 mL and allowed to stand overnight. The precipitated solid was collected by filtration and vacuum dried. White solid (0.12 g, 41%), m.p. 218-219 °C; [Found: C, 62.21; H, 5.29; N, 12.94. $C_{17}H_{17}N_3O_4$ requires C, 62.38; H, 5.23; N, 12.84%]; δ_H (400 MHz, DMSO-d_6) 9.65 (s, 1H, NH), 7.21-7.48 (m, 4H, Ar), 2.32 (s, 3H, CH$_3$), 2.01 (s, 3H, CH$_3$), 1.93 (s, 3H, CH$_3$), 1.89 (s, 3H, CH$_3$); δ_C (100 MHz, DMSO-d_6) 196.6, 193.6, 169.2, 168.7, 153.9, 153.7, 137.4, 137.1, 129.8, 126.9, 91.5, 23.1, 21.5, 21.2, 9.4; MS (EI, 70 eV), m/z (%): 327 (53.0) [M+], 229 (99.9), 187(75.7).

*5.5. Procedure for the synthesis of ethyl 6-hydroxy-7-(4-methoxyphenyl)-3-alkyl-2-phenyl-6,7-dihydropyrazolo[1,5-a]pyrimidine-5-carboxylates **14***

A mixture of the appropriate 5-aminopyrazole **1** (0.54 mmol) and ethyl (E)-4-(4-methoxyphenyl)-2-oxobut-3-enoate (**13**) (0.12 g, 0.54 mmol) in 2 mL of acetic acid was ultrasonicated at room temperature for 2 h. After cooling, the precipitate formed was filtered off and vacuum dried. Compound **14a** was isolated as individual product. Compounds **14b** and **14c** were obtained as mixtures with **4b** and **4c** respectively.

*5.5.1. Ethyl 3-ethyl-6-hydroxy-7-(4-methoxyphenyl)-2-phenyl-6,7-dihydropyrazolo[1,5-a]pyrimidine-5-carboxylate (**14a**)*

Pale yellow solid (0.1 g, 42%), m.p. 163-164 °C; [Found: C, 68.61; H, 6.18; N, 10.09. $C_{24}H_{25}N_3O_4$ requires C, 68.72; H, 6.01; N, 10.02%]; δ_H (400 MHz, DMSO-d_6) 6.64-7.85 (m, 9H, Ar), 6.61 (d, *J* 5.3 Hz, 1H, OH), 5.57 (d, *J* 1.1 Hz, 1H, CH), 4.79 (dd, *J* 5.3, 1.1 Hz, 1H, CH), 4.25 (q, *J* 7.0 Hz, 2H, OC$\underline{H}_2$CH$_3$), 3.67 (s, 3H, OCH$_3$), 2.86 (q, *J* 7.3 Hz, 2H, C$\underline{H}_2$CH$_3$), 1.26 (t, *J* 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.16 (t, *J* 7.4 Hz, 3H, CH$_2$C$\underline{H}_3$); δ_C (100 MHz, DMSO-d_6) 163.4, 159.1, 153.8, 149.5, 140.7, 133.4, 128.7, 127.9, 126.9, 128.6, 126.7, 119.1, 114.5, 65.7, 64.5, 62.0, 55.1, 16.1, 15.2,14.1; MS (EI, 70 eV), m/z (%): 419 (99.9) [M+], 390 (49.6), 316 (57.1).

*5.5.2. Ethyl 3-ethyl-2-(4-fluorophenyl)-6-hydroxy-7-(4-methoxyphenyl)-6,7-dihydropyrazolo[1,5-a]pyrimidine-5-carboxylate (**14b**)*

δ_H (400 MHz, DMSO-d_6) 6.64-7.85 (m, 8H, Ar), 6.60 (d, *J* 5.1 Hz, 1H, OH), 5.57 (br s, 1H, CH), 4.76-4.83 (m, 1H, CH), 4.25 (q, *J* 7.2 Hz, 2H, OC$\underline{H}_2$CH$_3$), 3.67 (s, 3H, OCH$_3$), 2.86 (q, *J* 7.5 Hz, 2H, C$\underline{H}_2$CH$_3$), 1.21 (t, *J* 7.3 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.13 (t, *J* 7.5 Hz, 3H, CH$_2$C$\underline{H}_3$); δ_C (100 MHz, DMSO-d_6) 163.2, 162.2 (d, J_{C-F} 244.7 Hz), 157.9, 155.2, 147.0, 144.9, 136.5, 130.6 (d, J_{C-F} 8.6 Hz), 128.2, 119.2, 116.2 (d, J_{C-F} 21.0 Hz), 115.7, 114.2, 66.2, 65.8, 62.2, 55.4, 16.2, 15.1,14.3.

*5.5.3. Ethyl 6-hydroxy-7-(4-methoxyphenyl)-3-methyl-2-(p-tolyl)-6,7-dihydropyrazolo[1,5-a]pyrimidine-5-carboxylate (**14c**)*

δ_H (400 MHz, DMSO-d_6) 6.64-7.64 (m, 8H, Ar), 6.59 (d, *J* 5.2 Hz, 1H, OH), 5.56 (br s, 1H, CH), 4.75-4.81 (m, 1H, CH), 4.25 (q, *J* 7.3 Hz, 2H, O*CH*$_2$CH$_3$), 3.67 (s, 3H, OCH$_3$), 2.37 (s, 3H, CH$_3$), 2.32 (s, 3H, CH$_3$), 1.26 (t, *J* 7.3 Hz, 3H, OCH$_2$*CH*$_3$); δ_C (100 MHz, DMSO-d_6) 163.6, 156.9, 147.2, 144.6, 136.4, 131.0, 130.0, 129.6, 128.9, 125.4, 117.1, 114.5, 109.2, 65.5, 64.6, 62.8, 55.6, 21.6, 15.2, 6.7.

5.6. X-ray diffraction study

The colourless crystals of **4o** ($C_{23}H_{20}O_3N_3F$) are monoclinic. At 293 K a = 4.9357(2), b = 19.131(1), c = 21.240(1) Å, β = 91.375(4)°, V = 2005.0(2) Å^3, M_r = 405.42, Z = 4, space group P2$_1$/c, d_{calc} = 1.343 g/cm^3, μ(MoKα) = 0.097 mm^{-1}, F(000) = 848. Intensities of 18554 reflections (3514 independent, R_{int} = 0.042) were measured on the «Xcalibur-3» diffractometer (graphite monochromated MoK$_\alpha$ radiation, CCD detector, ω-scaning, $2\Theta_{max}$ = 50°). The structure was solved by direct method using SHELXTL package[46]. Positions of the hydrogen atoms were located from electron density difference maps and refined using "riding" model with U_{iso} = nU_{eq} of the carrier atom (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 anisotropic approximation for non-hydrogen atoms using 3514 reflections was converged to wR_2 = 0.190 (R_1 = 0.068 for 2227 reflections with F>4σ(F), S = 1.454). The final atomic coordinates, and crystallographic data for molecule **4o** 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 1566003).

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