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One-step reaction leading to new pyrazolo[1,5-*a*]pyrimidines by condensation of 2-pyrone with 5(3)-amino-3(5)-arylpyrazoles

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ABSTRACT

Condensation of 5(3)-amino-3(5)-arylpyrazoles with 4-hydroxy-6-methylpyran-2-one leads to 5,7-dimethyl-2-arylpyrazolo[1,5-*a*]pyrimidines, 5-alkoxycarbonylmethyl-7-methyl-2-arylpyrazolo[1,5-*a*]pyrimidines and their isomeric 7-alkoxycarbonylmethyl-5-methyl-2-arylpyrazolo[1,5-*a*]pyrimidines. These compounds result from competitive reactions and from different cyclization pathways. Structure and mechanism of formation of these new products are reported.

1. Introduction

Pyrazolo[1,5-*a*]pyrimidines have attracted considerable interest because of their biological activity. For instance, this heterocyclic system is found as purine analogues and has useful properties as antimetabolites in purine biochemical reactions.[1] Several compounds of this class display interesting antitrypanosomal[2] and antischistosomal activities.[3] They are used as HMG-CoA reductase inhibitors,[4] COX-2 selective inhibitors,[5] 3′,5′-cyclic-AMP phosphodiesterase inhibitors,[6] CRF_1 antagonists,[7a–d] selective peripheral benzodiazepine receptor ligands,[8a–c] potassium channel[9]and histamine-3 receptor ligands[10] and antianxiety agents.[11] This led to the development of new efficient general procedures for the synthesis of pyrazolo[1,5-*a*]pyrimidines derivatives. As part of our interest in the use of 2-pyrone, as versatile synthon for obtaining new pyrazolo[1,5-*a*]pyrimidine derivatives, we investigated the condensation of 4-hydroxy-6-methylpyran-2-one with 5(3)-amino-3(5)-arylpyrazole in various refluxing alcohols and under microwave irradiation. Pyrone derivatives are versatile synthons often used in organic synthesis, in particular to gain access in new types of heterocyclic compounds. Pyrones are reported to be electrophilic and highly reactive towards binucleophiles.[12–20] Thus condensation of 4-hydroxy-6-methylpyran-2-one with 3-amino-5-hydroxypyrazole is reported to give a single 7-alkoxycarbonylmethyl-5-methyl-2-hydroxy-pyrazolo[1,5-*a*]pyrimidine,[19] whereas, in our investigation, we established that, the use of 5(3)-amino-3(5)-arylpyrazole in place of 5-amino-3-hydroxypyrazole gave a mixture of two isomeric pyrazolo[1,5-*a*]pyrimidines (i) 7-alkoxycarbonylmethyl-5-methyl-2-arylpyrazolo[1,5-*a*]pyrimidines and (ii) 5-alkoxycarbonylmethyl-7-methyl-2-arylpyrazolo-[1,5-*a*]pyrimidines. Hence, we found this condensation was a simple method for preparing new pyrazolo[1,5-*a*]pyrimidines with potential pharmacological activity.

2. Results and discussion

We first tested the reaction conditions already described in the literature.[19] Equimolar amounts of 4-hydroxy-6-methylpyran-2-one **1** and 3-amino-5-phenylpyrazole **2** were reacted in refluxing methanol for 48 h to give compounds **3a** and **4a** in modest 3% and 12% yields, respectively, with a significant amount of starting material **2** being recovered (Table 1, entry 1). The reaction conditions were modified to improve 5-methoxycarbonylmethyl-7-methyl-2-phenylpyrazolo[1,5-*a*] pyrimidine **3a** and 7-methoxycarbonylmethyl-5-methyl-2-phenylpyrazolo[1,5-*a*] pyrimidine **4a** yields.

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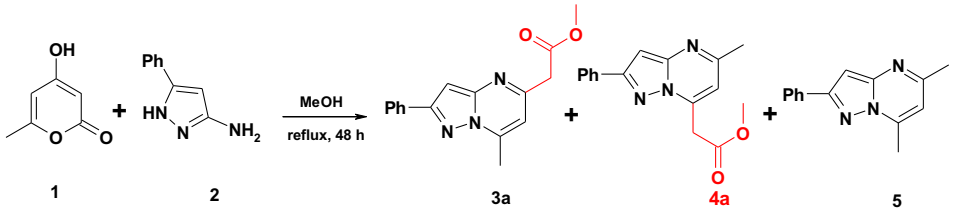
Table 1
Condensation of 2-pyrone **1** with 3-amino-5-phenylpyrazole **2** in refluxing methanol



1 2 3a 4a 5

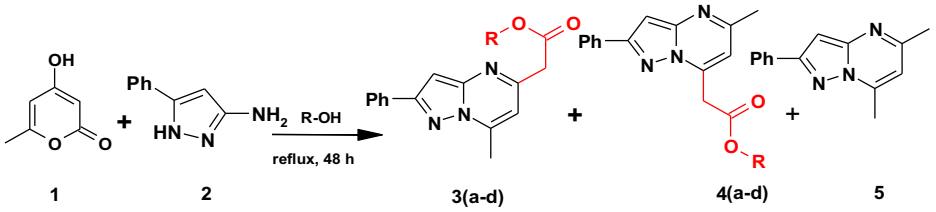
Entry	1[a]	2[a]	3a[b]	4a[b]	5[b]	Global yield[b]
1	1	1	3	12	—	15
2	2	1	19	34	4	57
3	3	1	20	36	4	60

[a] equivalent.
[b] Yields in isolated products.

Compounds **3a**, **4a** and **5** were isolated in 19%, 34% and 4% yield, respectively (Table 1, entry 2), but an excess of **1** was recovered. Moreover, formation of **5** as a new compound was observed when 2 equiv of **1** were used. No significant effect on the yields was observed by using 3 equiv of compound **1** (Table 1, entry 3).

The scope of this reaction under the optimized condition (Table 1, entry 2) was next investigated starting with several alcohols. The results (Table 2) showed that 5,7-dimethyl-2-phenylpyrazolo[1,5-*a*] pyrimidines **5**, 5-alkoxycarbonylmethyl-7-methyl-2-phenylpyrazolo [1,5-*a*]pyrimidines **3**(**a**–**d**) and their isomeric 7-alkoxycarbonylmethyl-5-methyl-2-phenylpyrazolo [1,5-*a*]pyrimidines **4**(**a**–**d**) resulting from two competitive cyclizations were identified in moderate yields in all the conducted experiments (Table 2, entries 1–4).

Table 2
Condensation of 2-pyrone **1** with 3-amino-5-phenylpyrazole **2** in various refluxing alcohols



1 2 3(a-d) 4(a-d) 5

a : R= CH_3 ; **b**: R= C_2H_5
c : R= C_3H_7 ; **d**: R= C_4H_9

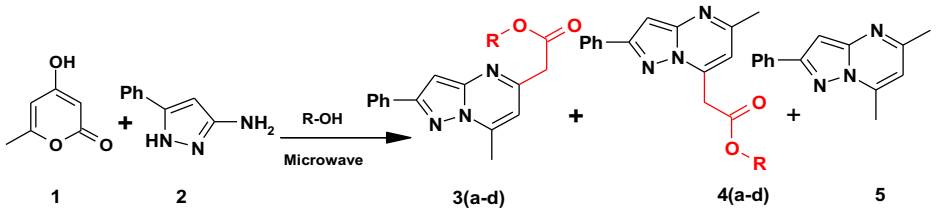
Entry	R–OH	Product yield [%]		Global yield (%)
		3:**5**	**4**	
1	CH_3–OH	19[a]:3[a]	34[a]	56
2	C_2H_5–OH	17[b]:6[b]	32[a]	55
3	C_3H_7–OH	16[b]:6[b]	41[a]	63
4	C_4H_9–OH	17[a]:7[a]	21[a]	45

[a] Yields in isolated products.
[b] The ratio was determined by ^{1}H NMR spectroscopy.

To improve the yields, we decided to optimize the reaction conditions under microwave irradiation. We first irradiated the reaction conditions already used in refluxing methanol under microwave at 100 °C for 30 min. Compounds **3a**, **4a** and **5** were isolated in 17%, 27% and 4% yield, respectively, with a significant amount of starting material **2** being recovered (Table 3, entry 1). On the other hand, the reaction between starting material **2** and compound **1** at 100 °C for 1 h leads to incomplete conversion and **3a**, **4a** and **5** were obtained in only 22%, 36% and 8% yield, respectively, (Table 3, entry 2). However, complete conversion could be achieved in only 1 h when the reaction mixture was heated at 120 °C. Hence, compounds **3a**, **4a** and **5** were obtained in 28%, 68% and 2% yield, respectively, indicating a 98% global yield (Table 3, entry 3). By applying these reaction conditions, i.e. [4-hydroxy-6-methylpyran-2-one **1** (2 equiv), 3-amino-5-phenylpyrazole **2** (1 equiv) in methanol at 120 °C for 1 h under irradiation microwave], we evaluated the scope and limitation of the method by using other alcohols (Table 3, entries 4–8). Thus, under irradiation microwave the condensation of **1** with starting material **2** in ethanol for 1 h at 120 °C gave the desired products in 84% global yield after total conversion (Table 3, entry 4). Increasing the temperature of reaction to 125 °C afforded the desired compounds in similar yield (Table 3, entry 5). Replacement of ethanol with 1-propanol at 130 °C under same reaction conditions led to **3c**, **4c** and **5** in goods yields (Table 3, entry 7).

The use of 1-butanol as the solvent, permitting an irradiation microwave at 138 °C for 1 h afforded the desired compounds in 99% global yield. These results enlightened the favourable influence of microwave irradiation for the preparation of compounds **3**(**a**–**d**), **4** (**a**–**d**) and **5**. The reaction was completed and both electron-rich (R_1=OMe) and electron-poor (R_1=F) substituents in the *para*-position of 3(5)-amino-5(3)-phenylpyrazoles **2** reacted to give **4**(**e**–**l**) as major products (Table 4). Structures of **5**–**7** were determined by

Table 3
Microwave assisted condensation of 2-pyrone **1** with 3-amino-5-phenylpyrazole **2** in various alcohols



a : R= CH_3 ; b: R= C_2H_5
c : R= C_3H_7 ; d: R= C_4H_9

Entry	R	*t* (h)	*T* (°C)	Yield[a] (%)			Global yield (%)
				3	**4**	**5**	
1	CH_3	0.5	100	17	27	4	48
2	CH_3	1	100	22	36	8	66
3	CH_3	1	120	28	68	2	98
4	C_2H_5	1	120	15	67	2	84
5	C_2H_5	1	125	17	68	2	87
6	C_3H_7	1	120	15	58	1	74
7	C_3H_7	1	130	23	66	2	91
8	C_4H_9	1	120	23	62	0	85
9	C_4H_9	1	138	27	69	3	99

[a] Yields in isolated products.

comparison of theirs physical and spectral characteristics with the references.[21,22] In compounds **3**(**a**–**l**) ^{1}H NMR spectrum revealed a singlet at 3.9 ppm corresponding to the methylene protons at the α position of the carbonyl ester, while the signal shifts downfield to 4.2 ppm in **4**(**a**–**l**). ^{13}C NMR spectrum of compounds **3**(**a**–**l**) and **4**(**a**–**l**) revealed in particular the signal attributed to the carbonyl, at 170–168 ppm (see Experimental data). The structures of **3b** and **4a** were confirmed using X-ray diffraction (Figs. 1 and 2). The proposed mechanism for explaining the synthesis of **3**(**a**–**l**), **4**(**a**–**l**) and **5**–**7** can be subdivided into two ways[18] (Scheme 1). Initial competitive attack (way a) of the amino group of **2** takes place on carbon C_6 of 4-hydroxy-6-methylpyran-2-one **1**, giving the intermediate [**A**]. Afterwards [**A**] evolves according to decarboxylation and esterification competitive reactions towards the intermediates [**B**] and [**C**]. Intramolecular cyclization of the aforementioned intermediates leads, after the loss of a water molecule to **4**(**a**–**l**) and **5**–**7**. Second competitive attack (way b) of the (–NH) group of the 5(3)-amino-3(5)-arylpyrazole **2** takes place on carbon C_6 of **1** giving the intermediate [**D**]. [**D**] evolves according to decarboxylation and esterification competitive reactions towards the intermediates [**E**] and [**F**]. Intramolecular cyclization of the aforementioned intermediates leads, after the loss of a water molecule, to **3**(**a**–**l**) and **5**–**7** (Scheme 1).

3. Conclusion

We have confirmed the interest of 4-hydroxy-6-methylpyran-2-one in the synthesis of new pyrazolo[1,5-*a*]pyrimidines substituted at position 5 and 7, some of these molecules presented biological interesting properties[23] or can be used as precursors for other heterocyclic systems.

4. Experimental section

4.1. General remarks and methods

All reagents were purchased from Sigma–Aldrich, Acros Organics or Alfa Aesar and were used without further purification. Microwave assisted reactions were carried out in a Biotage Initiator microwave synthesis instrument and temperatures were measured by an IR sensor. Melting points were determined with a Büchi SMP-20 melting point apparatus and were uncorrected. ^{1}H and ^{13}C NMR were recorded on a Bruker Avance DPX400 spectrometer (400.13 MHz ^{1}H, 100.62 MHz ^{13}C) and a Bruker Avance DPX250 spectrometer (250.19 MHz ^{1}H, 62.89 MHz ^{13}C), using TMS as the internal standard, multiplicities were determined by the DEPT 135 sequence. Chemical shifts (δ) are reported in parts per million. Coupling constants are reported in hertz. The following abbreviations are used in splitting patterns as s=singlet, br=broad single, dd=double doublet, d=doublet, t=triplet, dt=double triplet, m=multiplet. HRMS was recorded with a TOF spectrometer (ESI mode) or with a Finnigan MAT 95 XL (CI mode) at the Regional Center of Physical Measurement University Blaise Pascal Clermont-Ferrand. IR spectra (wave numbers in cm^{-1}) were recorded on a NICOLET IS10 FT-IR spectrometer. All commercial solvents were used without further purification. Column chromatography was carried out with silica gel 60 N (spherical, neutral, 40–63 mm, Merck).

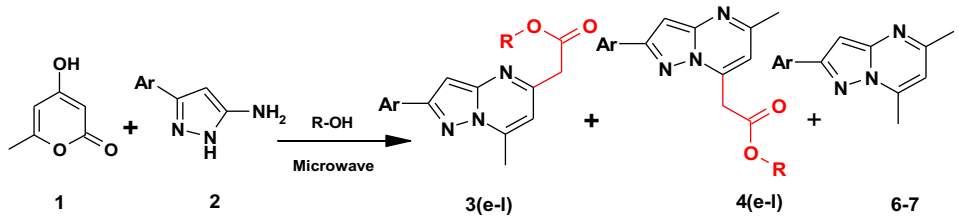
4.2. General procedure for the synthesis of compounds 3 (a–d), 4(a–d) and 5 in various refluxing alcohols (Tables 1 and 2)

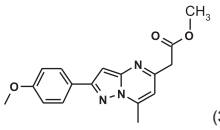
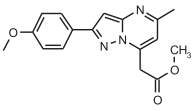
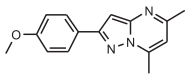
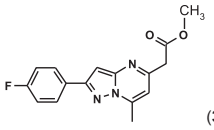
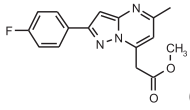
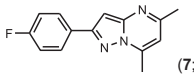
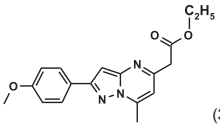
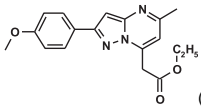
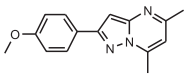
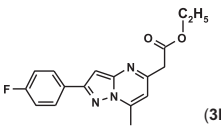
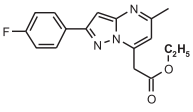
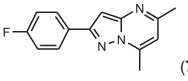
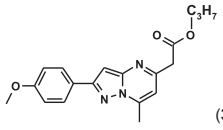
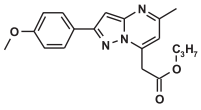
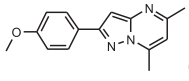
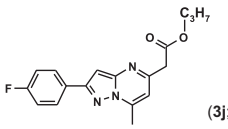
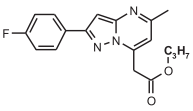
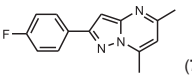
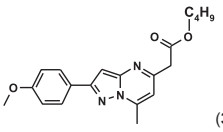
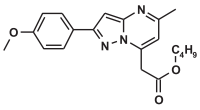
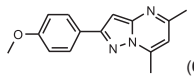
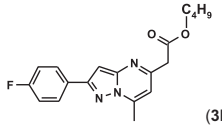
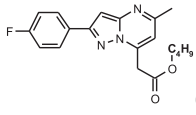
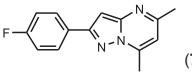
A solution of 4-hydroxy-6-methylpyran-2-one **1** (1.6 g, 12.6 mmol) and 5(3)-amino-3(5)-arylpyrazole **2** (1 g, 6.3 mmol) in 40 mL of alcohol, under an atmosphere of argon, was heated to reflux for 48 h. After evaporation of solvent under reduced pressure, the residue was purified on silica gel by column chromatography using 90:10 (v/v) mixture of petroleum ether and ethyl acetate as eluent to give compounds **3**(**a**–**d**), **4**(**a**–**d**) and **5**.

4.3. General procedure for the synthesis of compounds 3 (a–l), 4(a–l) and 5–7 under microwave irradiation (Tables 3 and 4)

4-Hydroxy-6-methylpyran-2-one **1** (0.16 g, 1.26 mmol) was added under argon to a solution of 5(3)-amino-3(5)-arylpyrazole **2** (0.1 g, 0.63 mmol) in 4 mL of alcohol in microwave tube. The

Table 4
Microwave assisted condensation of 2-pyrone **1** with 5(3)-amino-3(5)-arylpyrazole **2** in various alcohols



Entry	Ar	R	*t* (min)	T (°C)	Products; yields (%)[a]			Global yields (%)
1		CH_3	60	120	 (**3e**; 20)	 (**4e**; 48)	 (**6**; 1)	69
2		CH_3	70	120	 (**3f**; 14)	 (**4f**; 25)	 (**7**; 2)	41
3		C_2H_5	60	120	 (**3g**; 15)	 (**4g**; 48)	 (**6**; 1)	64
4		C_2H_5	65	120	 (**3h**; 11)	 (**4h**; 28)	 (**7**; 2)	41
5		C_3H_7	60	130	 (**3i**; 17)	 (**4i**; 40)	 (**6**; 2)	59
6		C_3H_7	60	130	 (**3j**; 13)	 (**4j**; 37)	 (**7**; 2)	52
7		C_4H_9	70	138	 (**3k**; 20)	 (**4k**; 56)	 (**6**; 0)	76
8		C_4H_9	60	138	 (**3l**; 15)	 (**4l**; 46)	 (**7**; 1)	62

[a] Yields in isolated products.

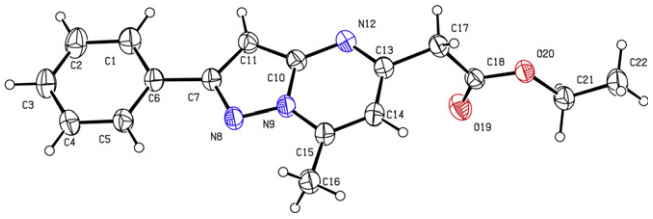


Fig. 1. ORTEP diagram derived from the single-crystal X-ray analysis of compound **3b**.

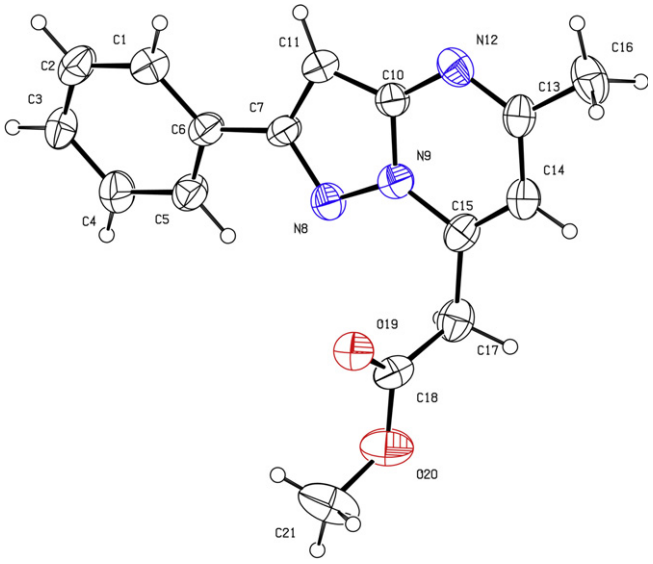
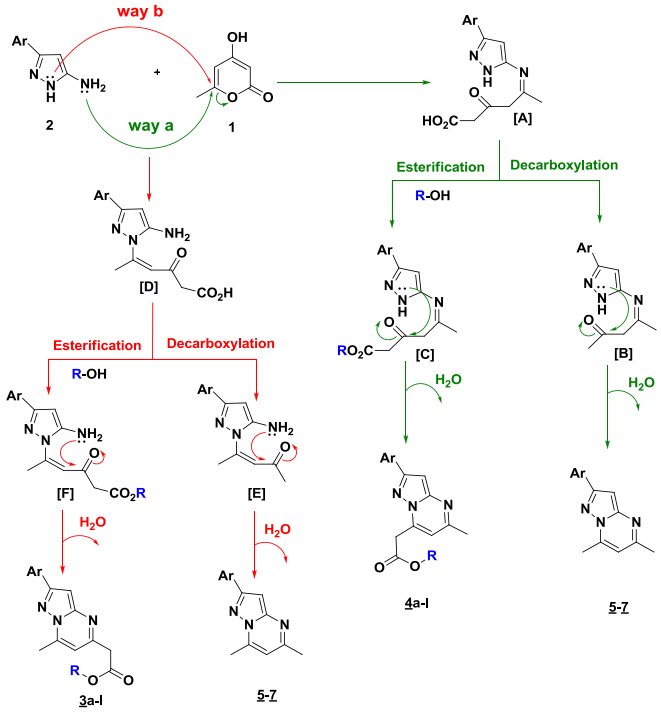


Fig. 2. ORTEP diagram derived from the single-crystal X-ray analysis of compound **4a**.



Scheme 1. Proposed mechanism.

reaction vessel was sealed with a silicon septum and subjected to microwave at *T* (°C) with stirring for (60–70) min. The reaction vessel then was allowed to cool to room temperature. After evaporation of solvent under reduced pressure, the residue was purified on silica gel by column chromatography using mixture of petroleum ether and ethyl acetate as eluent to give compounds **3**(**a**–**l**), **4** (**a**–**l**) and **5**–**7**.[20,21]

4.4. Experimental data

4.4.1. 5,7-Dimethyl-2-phenylpyrazolo[1,5-a]pyrimidine ***5***. Beige sol id, mp 154–155 °C[21]. ^{1}H NMR (400 MHz, $CDCl_3$): 8.01 (2H, *2H*–Ar, d, *J*=8.0 Hz), 7.46 (2H, *2H*–Ar, t, *J*=7.5 Hz), 7.38 (1H, *1H*–Ar, t, *J*=7.3 Hz), 6.85 (1H, ***H*****3**, s), 6.54 (1H, ***H*****6**, s), 2.79 (3H, C***H*****3**–C_7, s), 2.56(3H, C***H*****3**–C_5, s). ^{13}C NMR (100.62 MHz, $CDCl_3$): 158.3 (*C*), 155.6 (*C*), 149.7 (*C*), 145.2 (*C*), 133.2 (*C*), 128.7 (CH), 128.7 (2×CH), 126.5 (2×CH), 108.3 (CH, ***C*****6**), 92.6 (***C*****3**), 24.6(CH_3–C_5), 17.1(CH_3–C_7). IR: ν_{C-N}=1030 cm^{-1}, $\nu_{C=C}$=1549 cm^{-1}. HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{14}H_{14}N_3$: 224.1202; found: 224.1188.4.4.2.

4.4.2. 5,7-Dimethyl-2-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine ***6***. Yellow solid, mp 150–151 °C. ^{1}H NMR (250 MHz, $CDCl_3$): 7.94 (2H, *2H*–Ar, d, *J*=9 Hz), 6.99 (2H, *2H*–Ar, d, *J*=9 Hz), 6.76 (1H, ***H*****3**, s), 6.50 (1H, ***H*****6**, d, *J*=0.7 Hz), 3.86 (3H, C***H*****3** s), 2.76(3H, C***H*****3**–C_7, d, *J*=0.7 Hz), 2.55 (3H, C***H*****3**–C_5, s). ^{13}C NMR (62.89 MHz, $CDCl_3$): 160.2 (*C*), 158.1 (*C*), 155.5 (*C*), 149.7 (*C*), 145.1 (*C*), 127.8 (2×CH), 125.9 (*C*), 114.1 (2×CH), 108.0 (CH, ***C*****6**), 91.9 (CH, ***C*****3**), 55.3(O–CH_3), 24.6 (CH_3–C_5), 17.1 (CH_3–C_7). IR: ν_{C-O}=1025 cm^{-1}, ν_{C-N}=1172 cm^{-1}, $\nu_{C=C}$=1520 cm^{-1}. HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{16}N_3O$: 254.1306; found: 254.1293.

4.4.3. 7,5-Dimethyl-2-(4-fluorophenyl)pyrazolo[1,5-a]pyrim-idine ***7***. Yellow solid, mp 186–187 °C.[22] ^{1}H NMR (250 MHz, $CDCl_3$): 7.98 (2H, *2H*–Ar, dd, $J_{H,H}$=8.8 Hz, $^4J_{H,F}$=5.5 Hz), 7.14 (2H, *2H*–Ar, t, J_{HH}=$^3J_{H,F}$=8.8 Hz), 6.79 (1H, ***H*****3**, s), 6.54 (1H, ***H*****6**, s), 2.77 (3H, C***H*****3**–C_7, s), 2.56 (3H, C***H*****3**–C_5, s). ^{13}C NMR (100.62 MHz, $CDCl_3$): 163.2(*C*, d, J_{CF}=248.5 Hz), 158.4 (*C*), 154.6 (*C*), 149.7 (*C*), 145.2 (*C*), 129.5 (*C*, d, *J*=3.02 Hz), 128.3 (2×CH, d, $^3J_{CF}$=8.05 Hz), 115.6 (2×CH, d, $^2J_{CF}$=22.1 Hz), 108.4 (CH, ***C*****6**), 92.3 (CH, ***C*****3**), 24.6 (CH_3–C_5), 17.0 (CH_3–C_7). IR: ν_{C-N}=1159 cm^{-1}, ν_{C-F}=1220 cm^{-1}, $\nu_{C=C}$=1529 cm^{-1}. HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{14}H_{13}N_3F$: 242.1086; found: 242.1094.

4.4.4. 5-Methoxycarbonylmethyl-7-methyl-2-phenylpyrazolo[1,5-a] pyrimidine ***3a***. White solid, mp 96–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.01 (2H, *2H*–Ar, d, *J*=8.0 Hz), 7.47 (2H, *2H*–Ar, t, *J*=7.4 Hz), 7.39 (1H, *1H*–Ar, t, *J*=7.3 Hz), 6.93 (1H, ***H*****3**, s), 6.70 (1H, ***H*****6**, s), 3.86 (2H, C***H*****2**–CO, s), 3.76 (3H, CH_3–O, s), 2. 82 (3H, C***H*****3**–C_7, s). ^{13}C NMR (100.62 MHz, $CDCl_3$): 170.1 (*CO*), 156.0 (*C*), 153.6 (*C*), 149.5 (*C*), 145.9 (*C*), 133.1 (*C*), 128.9 (*CH*), 128.7 (2×CH), 126.6 (2×CH), 108.0 (CH, ***C*****6**), 93.4 (CH, ***C*****3**), 52.4 (CH_3–O), 43.8 (CH_2–CO), 17.3 (CH_3–C_7). IR: ν_{C-N}=1150 cm^{-1}, $\nu_{C=C}$=1552 cm^{-1}, $\nu_{C=O}$=1721 cm^{-1}. HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_{16}H_{15}N_3O_2Na$: 304.1072; found: 304.1062.

4.4.5. 7-Methoxycarbonylmethyl-5-methyl-2-phenylpyrazolo[1,5-a] pyrimidine ***4a***. White solid, mp 118–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.98 (2H, *2H*–Ar, d, *J*=8.0 Hz), 7.45 (2H, *2H*–Ar, t, *J*=7.4 Hz), 7.38 (1H, *1H*–Ar, t, *J*=7.3 Hz), 6.87 (1H, ***H*****3**, s), 6.69 (1H, ***H*****6**, s), 4.20 (2H, C***H*****2**–CO, s), 3.78 (3H, C***H*****3**–O, s), 2, 60 (3H, C***H*****3**–C_5, s). ^{13}C NMR (100.62 MHz, $CDCl_3$): 168.4 (*CO*), 158.4 (*C*), 155.58 (*C*), 149.6 (*C*), 140.7 (*C*), 133.0 (*C*), 128.8 (*CH*), 128.7 (2×CH), 126.5 (2×CH), 109.0 (CH, ***C*****6**), 92.9 (CH, ***C*****3**), 52.6 (CH_3–O), 36.0 (CH_2–CO), 24.8 (CH_3–C_5). IR: ν_{C-N}=1203 cm^{-1}, $\nu_{C=C}$=1556 cm^{-1}, $\nu_{C=O}$=1731 cm^{-1}. HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{16}N_3O_2$: 282.1257; found: 282.1243.

4.4.6. 5-Ethoxycarbonylmethyl-7-methyl-2-phenylpyrazolo[1,5-a] pyrimidine ***3b***. White solid, mp 92–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.01(2H, *2H*–Ar, d, *J*=8.0 Hz), 7.47 (2H, *2H*–Ar, t, *J*=7.4 Hz), 7.39 (1H, *1H*–Ar, t, *J*=7.3 Hz), 6.92 (1H, ***H*****3**, s), 6.72 (1H, ***H*****6**, s), 4.22 (2H, C***H*****2**–O, q, *J*=7.1 Hz), 3.84 (2H, C***H*****2**–CO, s), 2.83 (3H, C***H*****3**–C_7, s)

1.29 (3H, C*H*$_3$, t, *J*=7.1 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$): 169.5 (*C*O), 155.7 (*C*), 153.6 (*C*), 149.3 (*C*), 145.7 (*C*), 132.9 (*C*), 128.7 (*C*H), 128.5 (2×*C*H), 126.4 (2×*C*H), 107.8 (CH, *C*$_6$), 93.2 (CH, *C*$_3$), 61.2 (CH$_2$, C*H*$_2$–O), 43.8 (CH$_2$, C*H*$_2$–CO), 17.1 (C*H*$_3$–C$_7$), 14.0 (3H, C*H*$_3$). IR: ν_{C-N}=1023 cm^{-1}, $\nu_{C=C}$=1551 cm^{-1}, $\nu_{C=O}$=1722 cm^{-1}. HRMS: *m*/*z* [M+Na]$^+$ calcd for $C_{17}H_{17}N_3O_2Na$: 318.1229; found: 318.1218.

4.4.7. 7-Ethoxycarbonylmethyl-5-methyl-2-phenylpyrazolo[1,5-a] pyrimidine ***4b***. White solid, mp 116–117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.98 (2H, *2H*–Ar, d, *J*=6.8 Hz), 7.45 (2H, *2H*–Ar, t, *J*=7.4 Hz), 7.38 (1H, *1H*–Ar, t, *J*=7.3 Hz), 6.87 (1H, *H*$_3$, s), 6.69 (1H, *H*$_6$, s), 4.24 (2H, C*H*$_2$–O, t, *J*=7.1 Hz), 4.18 (2H, C*H*$_2$–CO, s), 2, 60 (3H, C*H*$_3$–C$_5$, s) 1.27 (3H, C*H*$_3$ t, *J*=7.1 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$): 167.9 (*C*O), 158.4 (*C*), 155.5 (*C*), 149.6 (*C*), 140.9 (*C*), 133.0 (*C*), 128.8 (*C*H), 128.7 (2×*C*H), 126.5 (2×*C*H), 109.0(CH, *C*$_6$), 92.8 (CH, *C*$_3$), 61.6(*C*H$_2$–O), 36.2 (*C*H$_2$–CO), 24.8 (*C*H$_3$–C$_5$), 14.1 (*C*H$_3$). IR: ν_{C-N}=1027 cm^{-1}, $\nu_{C=C}$=1555 cm^{-1}, $\nu_{C=O}$=1722 cm^{-1}. HRMS: *m*/*z* [M+Na]$^+$ calcd for $C_{17}H_{17}N_3O_2Na$: 318.1215; found: 318.1218.

4.4.8. 7-Methyl-5-propoxycarbonylmethyl-2-phenylpyrazolo[1,5-a] pyrimidine ***3c***. White solid, mp 79–80 °C. ^{1}H NMR (400 MHz, DMSO): 8.06 (2H, *2H*–Ar, d, *J*=6.8 Hz), 7.45 (2H, *2H*–Ar, t, *J*=7.4 Hz), 7.43 (1H, *1H*–Ar, t, *J*=7.3 Hz), 7.16 (1H, *H*$_3$, s), 6.98 (1H, *H*$_6$, s), 4. 05 (2H, C*H*$_2$–O, t, *J*=6.6 Hz), 3.91 (2H, C*H*$_2$–CO, s), 2.77 (3H, C*H*$_3$–C$_7$, s), 1.64–1.56 (2*H*, CH$_2$–C*H*$_2$–CH$_3$, m), 0.87 (3H, CH$_2$–C*H*$_3$ t, *J*=7.4 Hz). ^{13}C NMR (100.62 MHz, DMSO): 169.5(*C*O), 154.8(*C*), 154.6 (*C*), 148.9 (*C*), 145.6 (*C*), 132.6 (*C*), 128.9 (*C*H), 128.8 (2×*C*H), 126.2 (2×*C*H), 108.79 (CH, *C*$_6$), 92.78(CH, *C*$_3$), 66.02 (*C*H$_2$–O), 43.11 (*C*H$_2$–CO), 21.47 (*C*H$_2$), 16.63 (*C*H$_3$–C$_7$), 10.18 (*C*H$_3$). IR: ν_{C-N}=1149 cm^{-1}, $\nu_{C=C}$=1553 cm^{-1}, $\nu_{C=O}$=1720 cm^{-1}. HRMS: *m*/*z* [M+Na]$^+$ calcd for $C_{18}H_{19}N_3O_2Na$: 332.1388; found: 332.1375.

4.4.9. 5-Methyl-7-propoxycarbonylmethyl-2-phenylpyrazolo[1,5-a] pyrimidine ***4c***. White solid, mp 102–104 °C. ^{1}H NMR (400 MHz, DMSO): 7.99 (2H, *2H*–Ar, d, *J*=7.2 Hz), 7.48 (2H, *2H*–Ar, t, *J*=7.4 Hz), 7.41 (1H, *1H*–Ar, t, *J*=7.3 Hz), 7.09 (1H, *H*$_3$, s), 6.98 (1H, *H*$_6$, s), 4.27 (2H, C*H*$_2$–CO, s), 4.05 (2H, C*H*$_2$–O, t, *J*=6.6 Hz), 2.54 (3H, C*H*$_3$–C$_5$, s), 1.59–1.50 (2H, CH$_2$–C*H*$_2$–CH$_3$, m), 0.75 (3H, CH$_2$–C*H*$_3$, t, *J*=7.4 Hz). ^{13}C NMR (100.62 MHz, DMSO): 167.9 (*C*O), 158.7 (*C*), 154.2 (*C*), 149.1 (*C*), 141.2 (*C*), 132.6 (*C*), 128.9(*C*H), 128.8 (2×*C*H), 126.0 (2×*C*H), 109.9 (CH, *C*$_6$), 92.3 (CH, *C*$_3$), 66.2 (*C*H$_2$–O), 36.0 (*C*H$_2$–CO), 24.3 (*C*H$_3$–C$_5$), 21.4 (*C*H$_2$), 10.0 (*C*H$_3$). IR: ν_{C-N}=1181 cm^{-1}, $\nu_{C=C}$=1555 cm^{-1}, $\nu_{C=O}$=1729 cm^{-1}. HRMS: *m*/*z* [M+H]$^+$ calcd for $C_{18}H_{20}N_3O_2$: 310.1561; found: 310.1556.

4.4.10. 5-Butoxycarbonylmethyl-7-methyl-2-phenylpyrazolo[1,5-a]pyrimidine ***3d***. White solid, mp 75–76 °C. ^{1}H NMR (400 MHz, DMSO): 8.06 (2H, *2H*–Ar, d, *J*=7.2 Hz), 7.50 (2H, *2H*–Ar, t, *J*=7.4 Hz), 7.42 (1H, *1H*–Ar, t, *J*=7.3 Hz), 7.15 (1H, *H*$_3$, s), 6.97 (1H, *H*$_6$, d, *J*=0.8 Hz), 4.09 (2H, C*H*$_2$–O, t, *J*=6.6 Hz), 3.90 (2H, C*H*$_2$–CO, s), 2.77 (3H, C*H*$_3$–C$_7$, s) 1.60–1.53 (2H, C*H*$_2$, m), 1.34–1.27 (2H, C*H*$_2$, m), 0.87 (3H, CH$_2$–C*H*$_3$, t, *J*=7.4 Hz). ^{13}C NMR (100.62 MHz, DMSO): 169.5 (*C*O), 154.7 (*C*), 154.6 (*C*), 148.9 (*C*), 145.6 (*C*), 132.6 (*C*), 128.9 (*C*H), 128.8 (2×*C*H), 126.2 (2×*C*H), 108.8 (CH, *C*$_6$), 92.8 (CH, *C*$_3$), 64.3 (*C*H$_2$–O), 40.1 (*C*H$_2$–CO), 30.1 (*C*H$_2$), 18.5 (*C*H$_2$), 16.6 (*C*H$_3$–C$_7$), 13.5 (*C*H$_3$). IR: ν_{C-N}=1209 cm^{-1}, $\nu_{C=C}$=1555 cm^{-1}, $\nu_{C=O}$=1717 cm^{-1}. HRMS: *m*/*z* [M+H]$^+$ calcd for $C_{19}H_{22}N_3O_2$: 324.1713; found: 324.1712.

4.4.11. 7-Butoxycarbonylmethyl-5-methyl-2-phenylpyrazolo[1,5-a] pyrimidine ***4d***. White solid, mp 98–99 °C. ^{1}H NMR (400 MHz, DMSO): 8.00 (2H, *2H*–Ar, d, *J*=7.2 Hz), 7.48 (2H, *2H*–Ar, t, *J*=7.3 Hz), 7.41 (1H, *1H*–Ar, t, *J*=7.3 Hz), 7.09 (1H, *H*$_3$, s), 6.98 (1H, *H*$_6$, s), 4.26 (2H, C*H*$_2$–CO, s), 4.09 (2H, C*H*$_2$–O, t, *J*=6.4 Hz), 2.54 (3H, C*H*$_3$–C$_5$, s), 1.53–1.46 (2H, C*H*$_2$, m), 1.22–1.13 (2H, C*H*$_2$, m), 0.74 (3H, CH$_2$–C*H*$_3$, t, *J*=7.4 Hz). ^{13}C NMR (100.62 MHz, DMSO): 167.9 (*C*O), 158.7 (*C*), 154.2 (*C*), 149.1 (*C*), 141.2 (*C*), 132.6 (*C*), 128.9 (*C*H), 128.7 (2×*C*H), 126.0 (2×*C*H), 109.9(CH, *C*$_6$), 92.2 (CH, *C*$_3$), 64.4 (*C*H$_2$–O), 36.1 (*C*H$_2$–CO), 30.1 (*C*H$_2$), 24.3 (*C*H$_3$–C$_5$), 18.4 (*C*H$_2$), 13.4 (*C*H$_3$). IR: ν_{C-N}=1197 cm^{-1}, $\nu_{C=C}$=1556 cm^{-1}, $\nu_{C=O}$=1722 cm^{-1}. HRMS: *m*/*z* [M+H]$^+$ calcd for $C_{19}H_{22}N_3O_2$: 324.1713; found: 324.1712.

4.4.12. 5-Methoxycarbonylmethyl-2-(4-methoxyphenyl)-7-methylpyrazolo[1,5-a]pyrimidine ***3e***. White solid, mp 86–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.94 (2H, *2H*–Ar, d, *J*=8.4 Hz), 6.99 (2H, *2H*–Ar, d, *J*=8.4 Hz), 6.84 (1H, *H*$_3$, s), 6.67 (1H, *H*$_6$, s), 3.87 (3H, OC*H*$_3$), 3.84(2H, C*H*$_2$–CO, s), 3.75 (3H, C*H*$_3$–O, s), 2. 81(3H, C*H*$_3$–C$_7$, s). ^{13}C NMR (100.62 MHz, $CDCl_3$): 170.2 (*C*O), 160.3 (*C*), 155.9 (*C*), 153.5 (*C*), 149.5 (*C*), 145.8 (*C*), 127.9 (2×*C*H), 125.8 (*C*), 114.1 (2×*C*H), 107.7 (CH, *C*$_6$), 92.7 (CH, *C*$_3$), 55.3(*C*H$_3$–O), 52.4 (*C*H$_3$–O), 43.8 (*C*H$_2$–CO),17.3 (*C*H$_3$–C$_7$). IR: ν_{C-O}=1031 cm^{-1}, ν_{C-N}=1155 cm^{-1}, $\nu_{C=C}$=1532 cm^{-1}, $\nu_{C=O}$=1729 cm^{-1}. HRMS: *m*/*z* [M+H]$^+$ calcd for $C_{17}H_{18}N_3O_3$: 312.1362; found: 312.1348.

4.4.13. 7-Methoxycarbonylmethyl-2-(4-methoxyphenyl)-5-methylpyrazolo[1,5-a]pyrimidine ***4e***. White solid, mp 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.91 (2H, *2H*–Ar, d, *J*=8.8 Hz), 6.97 (2H, *2H*–Ar, d, *J*=8.8 Hz), 6.78 (1H, *H*$_3$, s), 6.65 (1H, *H*$_6$, s), 4.18 (2H, C*H*$_2$–CO, s), 3.86 (3H, C*H*$_3$–O, s), 3.77 (3H, C*H*$_3$–O, s), 2.59 (3H, C*H*$_3$–C$_5$, s). ^{13}C NMR (100.62 MHz, $CDCl_3$): 168.4 (*C*O), 160.2 (*C*), 158.3 (*C*), 155.5 (*C*), 149.6 (*C*), 140.6 (*C*), 127.8 (2×*C*H), 125.7 (*C*), 114.1 (2×*C*H), 108.7 (CH, *C*$_6$), 92.2 (CH, *C*$_3$), 55.3 (*C*H$_3$–O), 52.6 (*C*H$_3$–O), 36.0 (*C*H$_2$–CO), 24.7 (*C*H$_3$–C$_5$). IR: ν_{C-O}=1029 cm^{-1}, ν_{C-N}=1179 cm^{-1}, $\nu_{C=C}$=1533 cm^{-1}, $\nu_{C=O}$=1731 cm^{-1}. HRMS: *m*/*z* [M+H]$^+$ calcd for $C_{17}H_{18}N_3O_3$: 312.1364; found: 312.1348.

4.4.14. 5-Ethoxycarbonylmethyl-2-(4-methoxyphenyl)-7-methylpyrazolo[1,5-a]pyrimidine ***3g***. White solid, mp 101–102 °C. ^{1}H NMR (250 MHz, $CDCl_3$): 7.94 (2H, *2H*–Ar, d, *J*=8.9 Hz), 6.99 (2H, *2H*–Ar, d, *J*=8.9 Hz), 6.84 (1H, *H*$_3$, s), 6.68 (1H, *H*$_6$, d, *J*=0.8 Hz), 4.22 (2H, C*H*$_2$–O, q, *J*=7.0 Hz), 3.87 (3H, C*H*$_3$–O, s), 3.83(2H, C*H*$_2$–CO, s), 2.81 (3H, C*H*$_3$–C$_7$, d, *J*=0.6 Hz), 1.28 (3H, CH$_2$–C*H*$_3$, t, *J*=7.0 Hz). ^{13}C NMR (62.89 MHz, $CDCl_3$): 169.8 (*C*O), 160.3 (*C*), 153.7 (*C*), 149.5 (*C*), 145.7 (*C*), 127.9 (2×*C*H), 125.8 (*C*), 114.1 (2×*C*H), 107.7 (CH, *C*$_6$), 92.7 (CH, *C*$_3$), 61.3 (*C*H$_2$–O), 55.3 (*C*H$_3$–O), 44.0 (*C*H$_2$–CO), 17.3 (*C*H$_3$–C$_7$), 14.2 (*C*H$_3$). IR: ν_{C-O}=1022 cm^{-1}, ν_{C-N}=1174 cm^{-1}, $\nu_{C=C}$=1526 cm^{-1}, $\nu_{C=O}$=1726 cm^{-1}. HRMS: *m*/*z* [M+H]$^+$ calcd for $C_{18}H_{20}N_3O_3$: 326.1515; found: 326.1505.

4.4.15. 7-Ethoxycarbonylmethyl-2-(4-methoxyphenyl)-5-methylpyrazolo[1,5-a]pyrimidine ***4g***. White solid, mp 109–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.91 (2H, *2H*–Ar, d, *J*=8.4 Hz), 6.97 (2H, *2H*–Ar, d, *J*=8.4 Hz), 6.78 (1H, *H*$_3$, s), 6.65 (1H, *H*$_6$, s), 4.24 (2H, C*H*$_2$–O, q, *J*=7. 2 Hz), 4.16 (2H, C*H*$_2$–CO, s), 3.85(3H, OC*H*$_3$, s), 2.58 (3H, C*H*$_3$–C$_5$, s), 1.26 (3H, C*H*$_3$, t, *J*=7.2 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$): 167.9 (*C*O), 160. 2 (*C*), 158.2 (*C*), 155.3 (*C*), 149.6 (*C*), 140.8 (*C*), 127.7 (2×*C*H), 125.7 (*C*), 114.0 (2×*C*H), 108.6 (CH, *C*$_6$), 92.1 (CH, *C*$_3$), 61.6 (*C*H$_2$–O), 55.3 (*C*H$_3$–O), 36.2 (*C*H$_2$–CO), 24.7 (*C*H$_3$–C$_5$), 14.1 (*C*H$_3$). IR: ν_{C-O}=1028 cm^{-1}, ν_{C-N}=1174 cm^{-1}, $\nu_{C=C}$=1531 cm^{-1}, $\nu_{C=O}$=1730 cm^{-1}, HRMS: *m*/*z* [M+H]$^+$ calcd for $C_{18}H_{20}N_3O_3$: 326.1504; found: 326.1505.

4.4.16. 2-(4-Methoxyphenyl)-7-methyl-5-propoxycarbonylmethylpyrazolo[1,5-a]pyrimidine ***3i***. White solid, mp 68–69 °C. ^{1}H NMR (400 MHz, DMSO): 7.98 (2H, *2H*–Ar, d, *J*=8.8 Hz), 7.06 (1H, *H*$_3$, s), 7.05 (2H, *2H*–Ar, d, *J*=8.8 Hz), 6.93 (1H, *H*$_6$, d, *J*=0.8 Hz), 4.05 (2H, C*H*$_2$–O, t, *J*=6.6 Hz), 3.89 (2H, C*H*$_2$–CO, s), 3.82(3H, OC*H*$_3$), 2.76 (3H, C*H*$_3$–C$_7$, d, *J*=0.4 Hz), 1.64–1.55 (2H, C*H*$_2$, m), 0.87 (3H, C*H*$_3$, t, *J*=7.4 Hz). ^{13}C NMR (100.62 MHz, DMSO): 169.6 (*C*O), 159.9 (*C*), 154.5 (*C*), 149.0 (*C*), 145.4 (*C*), 127.6 (2×*C*H), 125.1 (*C*), 114.2 (2×*C*H), 108.4 (CH, *C*$_6$), 92.0 (CH, *C*$_3$), 66.0 (*C*H$_2$–O), 55.2 (*C*H$_3$–O), 40.1 (*C*H$_2$–CO), 21.5 (*C*H$_2$), 16.6 (*C*H$_3$–C$_7$), 10.2 (*C*H$_3$). IR: ν_{C-O}=1031 cm^{-1}, ν_{C-N}=1174 cm^{-1},

$\nu_{C=C}$=1533 cm^{-1}, $\nu_{C=O}$=1729 cm^{-1}. HRMS: *m/z* [M+H]$^+$ calcd for $C_{19}H_{22}N_3O_3$: 340.1660; found: 340.1661.

4.4.17. 2-(4-Methoxyphenyl)-5-methyl-7-propoxycarbonylmethylpyrazolo[1,5-a]pyrimidine ***4i***. White solid, mp 98–99 °C. ^{1}H NMR (400 MHz, DMSO): 7.92 (2H, *2H*–Ar, d, *J*=8.8 Hz), 7.03 (2H, *2H*–Ar, d, *J*=8.8 Hz), 6.99 (1H, H_3, s), 6.93 (1H, H_6, s), 4.25 (2H, CH_2–CO, s), 4.04 (2H, CH_2–O, t, *J*=6.4 Hz), 3.82(3H, OCH_3), 2.53 (3H, CH_3–C_5, s), 1.59–1.50 (2H, CH_2, m), 0.76 (3H, CH_3, t, *J*=7.4 Hz). ^{13}C NMR (100.62 MHz, DMSO): 167.9 (*C*O), 159.9 (*C*), 158.4 (*C*), 154.2 (*C*), 149.1 (*C*), 141.1 (*C*), 127.4 (2×*C*H), 125.1 (*C*), 114.2 (2×*C*H), 109.5 (CH, C_6), 91.5 (CH, C_3), 66.2 (*C*H$_2$–O), 55.2 (*C*H$_3$–O), 36.0 (*C*H$_2$–CO), 24.3 (*C*H$_3$–C_5), 21.4 (*C*H$_2$), 10.06 (*C*H$_3$). IR: ν_{C-O}=1036 cm^{-1}, ν_{C-N}=1185 cm^{-1}, $\nu_{C=C}$=1531 cm^{-1}, $\nu_{C=O}$=1730 cm^{-1}. HRMS: *m/z* [M+H]$^+$ calcd for $C_{19}H_{22}N_3O_3$: 340.1677; found: 340.1661.

4.4.18. 5-Butoxycarbonylmethyl-2-(4-methoxyphenyl)-7-methylpyrazolo[1,5-a]pyrimidine ***3k***. White solid, mp 77–78 °C. ^{1}H NMR (400 MHz, DMSO): 7.98 (2H, *2H*–Ar, d, *J*=8.8 Hz), 7.05 (1H, H_3, s), 7.06 (2H, *2H*–Ar, d, *J*=8.8 Hz), 6.93 (1H, H_6, d, *J*=0.8 Hz), 4.09 (2H, CH_2–O, t, *J*=6.6 Hz), 3.88 (2H, CH_2–CO, s), 3.82 (3H, OCH_3), 2.75(3H, CH_3–C_7, d, *J*=0.8 Hz), 1.60–1.53 (2H, CH_2, m), 1.31 (2H, CH_2, dq, *J*=14.6, 7.4 Hz), 0.87 (3H, CH_3, t, *J*=7.4 Hz). ^{13}C NMR (100.62 MHz, DMSO): 169.5 (*C*O), 159.9 (*C*), 154.5 (*C*), 149.0 (*C*), 145.4 (*C*), 127.6 (2×*C*H), 125.1 (*C*), 114.2 (2×*C*H), 108.4 (CH, C_6), 92.0 (CH, C_3), 64.2 (*C*H$_2$–O), 55.2 (*C*H$_3$–O), 39.7 (*C*H$_2$–CO), 30.1 (*C*H$_2$), 18.5 (*C*H$_2$), 16.6 (*C*H$_3$–C_7), 13.5 (*C*H$_3$). IR: ν_{C-O}=1030 cm^{-1}, ν_{C-N}=1163 cm^{-1}, $\nu_{C=C}$=1534 cm^{-1}, ν_{CO}=1735 cm^{-1}. HRMS: *m/z* [M+H]$^+$ calcd for $C_{20}H_{24}N_3O_3$: 354.1833; found: 354.1818.

4.4.19. 7-Butoxycarbonylmethyl-2-(4-methoxyphenyl)-5-methylpyrazolo[1,5-a]pyrimidine ***4k***. White solid, mp 77–78 °C. ^{1}H NMR (400 MHz, DMSO): 7.92 (2H, *2H*–Ar, d, *J*=8.8), 7.03 (2H, *2H*–Ar, d, *J*=8.8 Hz), 6.99 (1H, H_3, s), 6.93 (1H, H_6, s), 4.24 (2H, CH_2–CO, s), 4.08 (2H, CH_2–O, t, *J*=6.4 Hz), 3.81(3H, OCH_3), 2.53 (3H, CH_3–C_5, s), 1.52–1.46 (2H, CH_2, m), 1.17 (2H, CH_2, dq, *J*=14.6, 7.4 Hz), 0.74 (3H, CH_3, t, *J*=7.4 Hz). ^{13}C NMR (100.62 MHz, DMSO): 167.9 (*C*O), 159.9 (*C*), 158.4 (*C*), 154.2 (*C*), 149.1 (*C*), 141.1 (*C*), 127.4 (2×*C*H), 125.1 (*C*H), 114.1 (2×*C*H), 109.5 (CH, C_6), 91.5 (CH, C_3), 64.3 (*C*H$_2$–O), 55.2 (*C*H$_3$–O), 36.1 (*C*H$_2$–CO), 30.1 (*C*H$_2$), 24.3 (*C*H$_3$–C_5), 18.4 (*C*H$_2$), 13.4 (*C*H$_3$). IR: ν_{C-O}=1025 cm^{-1}, ν_{C-N}=1182 cm^{-1}, $\nu_{C=C}$=1534 cm^{-1}, ν_{CO}=1726 cm^{-1}. HRMS: *m/z* [M+H]$^+$ calcd for $C_{20}H_{24}N_3O_3$: 354.1805; found: 354.1818.

4.4.20. 2-(4-Fluorophenyl)-5-methoxycarbonylmethyl-7-methylpyrazolo[1,5-a]pyrimidine ***3f***. White solid, mp 153–154 °C. ^{1}H NMR (250 MHz, $CDCl_3$): 7.99 (2H, *2H*–Ar, dd, $J_{H,H}$=8.8 Hz, $^4J_{H,F}$=5.4 Hz), 7.15 (2H, *2H*–Ar, t, J_{HH}=$^3J_{H,F}$=8.8 Hz), 6.87 (1H, H_3, s), 6.71 (1H, H_6, d, *J*=0.7 Hz), 3.86 (2H, CH_2–CO, s), 3.76 (3H, CH_3–O, s), 2.82(3H, CH_3–C_7, d, *J*=0.7 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$): 170.1 (*C*O), 163.3 (*C*, d, $^1J_{CF}$=248.5 Hz), 155.0 (*C*), 153.8 (*C*), 149.5 (*C*), 145.9 (*C*), 129.3 (*C*), 128.4 (2×*C*H, d, $^3J_{CF}$=8.05 Hz), 115.7 (2×*C*H, d, $^2J_{CF}$=21.1 Hz), 108.1 (CH, C_6), 93.2 (CH, C_3), 52.4 (*C*H$_3$–O), 43.8 (*C*H$_2$–CO), 17.2 (*C*H$_3$–C_7). IR: ν_{C-N}=1158 cm^{-1}, ν_{C-F}=1205 cm^{-1}, $\nu_{C=C}$=1523 cm^{-1}, $\nu_{C=O}$=1730 cm^{-1}. HRMS: *m/z* [M+H]$^+$ calcd for $C_{16}H_{15}N_3O_2F$: 300.1157; found: 300.1148.

4.4.21. 2-(4-Fluorophenyl)-7-methoxycarbonylmethyl-5-methylpyrazolo[1,5-a]pyrimidine ***4f***. White solid, mp 115–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.95 (2H, *2H*–Ar, dd, $J_{H,H}$=8.8 Hz, $^4J_{H,F}$=5.6 Hz),7.13 (2H, *2H*–Ar, t, J_{HH}=$^3J_{H,F}$=8.8 Hz), 6.81 (1H, H_3, s), 6.69 (1H, H_6, s), 4.18 (2H, CH_2–CO, s), 3.77 (3H, CH_3–O, s), 2.60 (3H, CH_3–C_5, s). ^{13}C NMR (100.62 MHz, $CDCl_3$): 168.3 (*C*O), 163.3 (*C*, d, $^1J_{CF}$=247.5 Hz), 158.6 (*C*), 154.6 (*C*), 149.6 (*C*), 140.7 (*C*), 129.2 (*C*, d, $^4J_{CF}$=4.02 Hz), 128.2 (2×*C*H, d, $^3J_{CF}$=8.05 Hz), 115.6 (2×*C*H, d, $^2J_{CF}$=22.1 Hz), 109.1 (CH, C_6), 92.6 (CH, C_3), 52.6 (*C*H$_3$–O), 35.9 (*C*H$_2$–CO), 24.8 (*C*H$_3$–C_5). IR: ν_{C-N}=1156 cm^{-1}, ν_{C-F}=1201 cm^{-1}, $\nu_{C=C}$=1526 cm^{-1}, $\nu_{C=O}$=1731 cm^{-1}. HRMS: *m/z* [M+H]$^+$ calcd for $C_{16}H_{15}N_3O_2F$: 300.1150; found: 300.1148.

4.4.22. 5-Ethoxycarbonylmethyl-2-(4-fluorophenyl)-7-methylpyrazolo[1,5-a]pyrimidine ***3h***. White solid, mp 107–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.98 (2H, *2H*–Ar, dd, $J_{H,H}$=8.8 Hz, $^4J_{H,F}$=5.2 Hz), 7.15 (2H, *2H*–Ar, t, J_{HH}=$^3J_{H,F}$=8.8 Hz), 6.86 (1H, H_3, s), 6.72 (1H, H_6, d, *J*=0.4 Hz), 4.22 (2H, CH_2–O, q, *J*=7.1 Hz), 3.84 (2H, CH_2–CO, s), 2. 81(3H, CH_3–C_7, s), 1.29 (3H, CH_3 t, *J*=7.1 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$): 169.7 (*C*O), 163.3 (*C*, d, $^1J_{CF}$=248.5 Hz), 155.0(*C*), 154.0 (*C*), 149.5 (*C*), 145.9 (*C*), 129.3 (*C*, d, $^4J_{CF}$=3.02 Hz), 128.4 (2×*C*H, d, $^3J_{CF}$=8.05 Hz), 115.7 (2×*C*H, d, $^2J_{CF}$=22.1 Hz), 108.1(CH, C_6), 93.1 (CH, C_3), 61.4 (*C*H$_2$–O), 44.0 (*C*H$_2$–CO), 17.2 (*C*H$_3$–C_7), 14.2 (*C*H$_3$). IR: ν_{C-N}=1155 cm^{-1}, ν_{C-F}=1201 cm^{-1}, $\nu_{C=C}$=1534 cm^{-1}, $\nu_{C=O}$=1720 cm^{-1}. HRMS: *m/z* [M+H]$^+$ calcd for $C_{17}H_{17}N_3O_2F$: 314.1309; found: 314.1305.

4.4.23. 7-Ethoxycarbonylmethyl-2-(4-fluorophenyl)-5-methylpyrazolo[1,5-a]pyrimidine ***4h***. White solid, mp 130–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.95 (2H, *2H*–Ar, dd, $J_{H,H}$=8.6 Hz, $^4J_{H,F}$=5.4 Hz), 7.13 (2H, *2H*–Ar, t, J_{HH}=$^3J_{H,F}$=8.6 Hz), 6.81 (1H, H_3, s), 6.69 (1H, H_6, s), 4.24 (2H, CH_2–O, q, *J*=7. 1 Hz), 4.17 (2H, CH_2–CO, s), 2.60 (3H, CH_3–C_5, s), 1.27 (3H, CH_3, t, *J*=7.1 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$): 167.9 (*C*O), 163.2(*C*, d, $^1J_{CF}$=248.5 Hz), 158.6 (*C*), 154.5 (*C*), 149.6 (*C*), 140.9 (*C*), 129.2 (*C*), 128.2 (2×*C*H, d, $^3J_{CF}$=8.05 Hz), 115.6 (2×*C*H, d, $^2J_{CF}$=22.1 Hz), 109.1 (CH, C_6), 92.5 (CH, C_3), 61.6 (*C*H$_2$–O), 36.2 (*C*H$_2$–CO), 24.8 (*C*H$_3$–C_5), 14.1 (*C*H$_3$). IR: ν_{C-N}=1156 cm^{-1}, ν_{C-F}=1196 cm^{-1}, $\nu_{C=C}$=1529 cm^{-1}, $\nu_{C=O}$=1724 cm^{-1}. HRMS: *m/z* [M+H]$^+$ calcd for $C_{17}H_{17}N_3O_2F$: 314.1300; found: 314.1305.

4.4.24. 2-(4-Fluorophenyl)-7-methyl-5-propoxycarbonylmethylpyrazolo[1,5-a]pyrimidine ***3j***. Beige solid, mp 98–99 °C. ^{1}H NMR (250 MHz, DMSO): 8.10 (2H, *2H*–Ar, dd, $J_{H,H}$=8.9 Hz, $^4J_{H,F}$=5.6 Hz), 7.33 (2H, *2H*–Ar, t, J_{HH}=$^3J_{H,F}$=8.9 Hz), 7.16 (1H, H_3, s), 6.98 (1H, H_6, s), 4. 05 (2H, CH_2–O, t, *J*=6.6 Hz), 3.91 (2H, CH_2–CO, s), 2.77(3H, CH_3–C_7, s), 1.67–1.53 (2H, CH_2, m), 0.87 (3H, CH_3, t, *J*=7.4 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$): 169.8 (*C*O), 163.3 (*C*, d, $^1J_{CF}$=247.5 Hz), 155.0(*C*), 154.0 (*C*), 149.5 (*C*), 145.8 (*C*), 129.3 (*C*, d, ^4J=3.02 Hz), 128.3 (2×*C*H, d, $^3J_{CF}$=9.05 Hz), 115.7 (2×*C*H, d, $^2J_{CF}$=22.1 Hz), 108.1 (CH, C_6), 93.1 (CH, C_3), 66.9 (*C*H$_2$–O), 44.0 (*C*H$_2$–CO), 21.9 (*C*H$_2$), 17.2 (*C*H$_3$–C_7), 10.3 (*C*H$_3$). IR: ν_{C-N}=1163 cm^{-1}, ν_{C-F}=1204 cm^{-1}, $\nu_{C=C}$=1526 cm^{-1}, $\nu_{C=O}$=1726 cm^{-1}. HRMS: *m/z* [M+H]$^+$ calcd for $C_{18}H_{19}N_3O_2F$: 328.1477; found: 328.1461.

4.4.25. 2-(4-Fluorophenyl)-5-methyl-7-propoxycarbonylmethylpyrazolo[1,5-a]pyrimidine ***4j***. White solid, mp 112–113 °C. ^{1}H NMR (250 MHz, DMSO): 8.03 (2H, *2H*–Ar, dd, $J_{H,H}$=8.7 Hz, $^4J_{H,F}$=5.6 Hz), 7.32 (2H, *2H*–Ar, t, J_{HH}=$^3J_{H,F}$=8.7 Hz), 7.09 (1H, H_3, s), 6.99 (1H, H_6, s), 4.27 (2H, CH_2–CO, s), 4.04 (2H, CH_2–O, t, *J*=6.4 Hz), 2.54 (3H, CH_3–C_5, s), 1.60–1.46 (2H, CH_2, m), 0.74 (3H, CH_3, t, *J*=7.4 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$): 167.9 (*C*O), 163.3 (*C*, d, J_{CF}=247.5 Hz), 158.6 (*C*), 154.6 (*C*), 149.6 (*C*), 140.9 (*C*), 129.2 (*C*), 128.2 (2×*C*H, d, $^3J_{CF}$=8.0 Hz), 115.6 (2×*C*H, d, $^2J_{CF}$=21.1 Hz), 109.1 (CH, C_6), 92.6 (CH, C_3), 67.2 (*C*H$_2$–O), 36.3 (*C*H$_2$–CO), 24.8 (*C*H$_3$–C_5), 21.9 (*C*H$_2$), 10.2 (*C*H$_3$). IR: ν_{C-N}=1155 cm^{-1}, ν_{C-F}=1195 cm^{-1}, $\nu_{C=C}$=1524 cm^{-1}, $\nu_{C=O}$=1725 cm^{-1}. HRMS: *m/z* [M+H]$^+$ calcd for $C_{18}H_{19}N_3O_2F$: 328.1468; found: 328.1461.

4.4.26. 5-Butoxycarbonylmethyl-2-(4-fluorophenyl)-7-methylpyrazolo[1,5-a]pyrimidine ***3l***. White solid, mp 135–136 °C. ^{1}H NMR (250 MHz, DMSO): 8.10 (2H, *2H*–Ar, dd, $J_{H,H}$=8.8 Hz, $^4J_{H,F}$=5.7 Hz), 7.33 (2H, *2H*–Ar, t, J_{HH}=$^3J_{H,F}$=8.8 Hz), 7.16 (1H, H_3, s), 6.98 (1H, H_6, s), 4.09 (2H, CH_2–O, t, *J*=6.5 Hz), 3.90 (2H, CH_2–CO, s), 2.77(3H, CH_3–C_7, s), 1.62–1.47 (2H, CH_2, m), 1.31 (2H, CH_2, dq, *J*=14.5, 7.3 Hz), 0.87 (3H,CH_3, t, *J*=7.3 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$): 169.8 (*C*O), 163.3 (*C*, d, $^1J_{CF}$=248.5 Hz), 155.0 (*C*), 154.0 (*C*), 149.5 (*C*), 145.8 (*C*), 129.3 (*C*),

128.3 (2×*C*H, d, $^{3}J_{CF}$=8.0 Hz), 115.7 (2×*C*H, d, $^{2}J_{CF}$=22.1 Hz), 108.1 (CH, C_6), 93.1 (CH, C_3), 65.3 (CH_2–O), 44.0 (CH_2–CO), 30.5 (CH_2), 19.1 (CH_2), 17.2 (CH_3–C_7), 13.6 (CH_3). IR: ν_{C-N}=1164 cm^{-1}, ν_{C-F}=1206 cm^{-1}, $\nu_{C=C}$=1535 cm^{-1}, $\nu_{C=O}$=1727 cm^{-1}. HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{21}N_3O_2F$: 342.1617; found: 342.1618.

4.4.27. 7-Butoxycarbonylmethyl-2-(4-fluorophenyl) -5-methylpyrazolo[1,5-a]pyrimidine ***4l***. White solid, mp 105–106 °C. ^{1}H NMR (250 MHz, DMSO): 8.03 (2H, *2H*–Ar, dd, $J_{H,H}$=8.8 Hz, $^{4}J_{H,F}$=5.5 Hz), 7.32 (2H, *2H*–Ar, t, J_{HH}=$^{3}J_{H,F}$=8.8 Hz), 7.09 (1H, H_3, s), 6.98 (1H, H_6, s), 4.26 (2H, CH_2–CO, s), 4.08 (2H, CH_2–O, t, *J*=6.4 Hz), 2.54 (3H, CH_3–C_7, s), 1.54–1.42 (2H,CH_2, m), 1.20–1.08 (2H, CH_2, m), 0.73 (3H, CH_3, t, *J*=7.3 Hz). ^{13}C NMR (100.62 MHz, $CDCl_3$): 167.9 (*C*O), 163.3 (*C*, d, $^{1}J_{CF}$=248.5 Hz), 158.6 (*C*), 154.6 (*C*), 149.6 (*C*), 140.9 (*C*), 129.2 (*C*, d, ^{4}J=3.0 Hz), 128.2 (2×*C*H, d, $^{3}J_{CF}$=8.0 Hz), 115.6 (2×*C*H, d, $^{2}J_{CF}$=21.1 Hz), 109.1 (CH, C_6), 92.5 (CH, C_3), 65.5 (CH_2–O), 36.3 (CH_2–CO), 30.5 (CH_2), 24.8 (CH_3–C_5), 19.0 (CH_2), 13.6 (CH_3). IR: ν_{C-N}=1159 cm^{-1}, ν_{C-F}=1210 cm^{-1}, $\nu_{C=C}$=1531 cm^{-1}, $\nu_{C=O}$=1722 cm^{-1}. HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{21}N_3O_2F$: 342.1608; found: 342.1618.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.01.070.

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