Synthesis of a New Series of Pyrazolo[1,5-*a*]pyrimidines Structurally Related to Zaleplon

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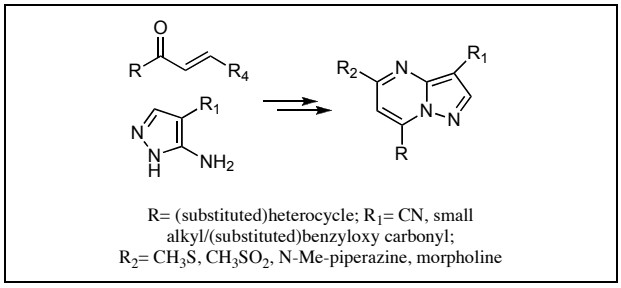

The reaction between 3-(dimethylamino)/3,3-bis(methylthio)-1-(substituted)prop-2-en-1-ones and 4-substituted-5-amino-1*H*-pyrazoles afforded new pyrazole[1,5-*a*]pyrimidines structurally related to Zaleplon. The chemical modifications introduced at the 3-, 5-, and 7-positions of the bicyclic structure revealed new promising candidates for the treatment of sleep disorders.

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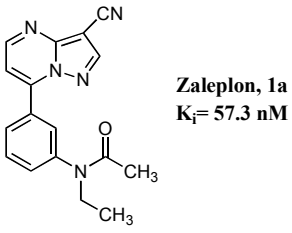
INTRODUCTION

In the last decade, the treatment of insomnia has been supplemented by the introduction of a number of non-benzodiazepine hypnotics including zolpidem, zopiclone and, most recently, zaleplon [1-4].

Zaleplon (*N*-[3-(cyanopyrazolo[1,5-*a*]pyrimidin-7-yl)-phenyl]-*N*-ethylacetamide, **1a**, Figure 1) is a new pyrazolopyrimidine hypnotic that selectively binds to the α1-$GABA_A$ receptor subunit, enhancing the function of GABA as a result of an allosteric interaction with the $GABA_A$-receptor chloride anion channel complex [5,6]. Zaleplon was approved in August 1999 by the Food and Drug Administration and its preparation has been reported only in an American Cyanamid patent [7].



Zaleplon, 1a
K_i= 57.3 nM

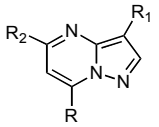
Figure 1. Zaleplon, a pyrazolopyrimidine hypnotic that selectively binds to $GABA_A$ receptor.

There are only few examples in the literature concerning the chemical modifications introduced to Zaleplon structure. These inventions described the replacement of the 3-cyano group with oxadiazole nucleus and/or the substitution of the pyrazole moiety with other hereocycles (triazole or imidazole) [8,9].

Here we report the synthesis of a new series of zaleplon analogs in which the phenyl N-ethylacetamido moiety was replaced by (substituted)heterocycles and the 3- and 5-positions of the pyrazolo[1,5-*a*]pyrimidine nucleus were differently functionalised (Table 1).

The phenyl N-ethylacetamido molecular fragment was replaced by different examples of substituted heterocycles like pyridine, thiophene, pyrrole and furane whereas the cyano group at the 3-position was replaced by substituted carboxylates such as linear or branched alkyl ester functions (ethyl, methyl, *tert*-butyl, isopropyl, *n*-propyl, 2-phenyl ethyl), simple benzyl esters or benzyl esters 4-substitued with electron withdrawing radicals (chloro, fluoro, nitro) or electron donor groups (methoxy). The 5-position, unmodified in the parent compound **1a**, was also analyzed by the introduction of short thioalkyl radical like SCH_3, alkyloxy group and basic centres such as 1-methyl-piperazine and morpholine.

Table 1. Pyrazolo[1,5-a]pyrimidines synthesized

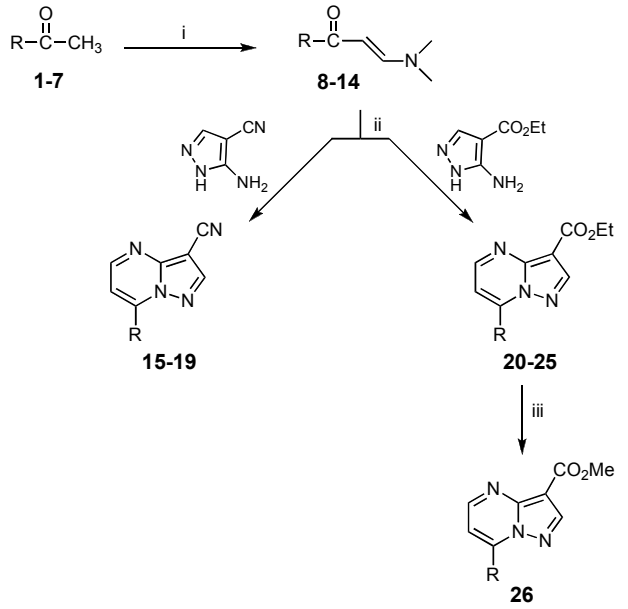


Compound	R	R_1	R_2
15	Pyridin-2-yl	CN	H
16	*N*-methyl-pyrrol-2-yl	CN	H
17	Furan-2-yl	CN	H
18	Pyridin-3-yl	CN	H
19	Thiophen-2-yl	CN	H
20	Pyridin-2-yl	CO_2Et	H
21	Furan-2-yl	CO_2Et	H
22	Pyridin-3-yl	CO_2Et	H
23	Thiophen-2-yl	CO_2Et	H
24	2,5-dimethyl-thiophen-3-yl	CO_2Et	H
25	5-bromo-thiophen-2-yl	CO_2Et	H
26	5-bromo-thiophen-2-yl	CO_2Me	H
28	Thiophen-2-yl	Benzyloxy carbonyl	H
29	Thiophen-2-yl	4-methoxy benzyloxy carbonyl	H
30	Thiophen-2-yl	4-chloro benzyloxy carbonyl	H
31	Thiophen-2-yl	4-fluoro benzyloxy carbonyl	H
32	Thiophen-2-yl	4-nitro benzyloxy carbonyl	H
33	Thiophen-2-yl	*tert*-butyloxycarbonyl	H
34	Thiophen-2-yl	Isopropyloxy carbonyl	H
35	Thiophen-2-yl	*n*-propyloxy carbonyl	H
36	Thiophen-2-yl	2-phenylethyloxy carbonyl	H
38	Thiophen-2-yl	CO_2Et	CH_3S
39	Thiophen-2-yl	CO_2Et	CH_3SO_2
40	Thiophen-2-yl	CO_2Et	Morpholine
41	Thiophen-2-yl	CO_2Et	*N*-CH_3-piperazine
42	Thiophen-2-yl	CO_2Et	*N*-CH_3-piperazine x 2HCl
43	Thiophen-2-yl	CO_2Et	EtO

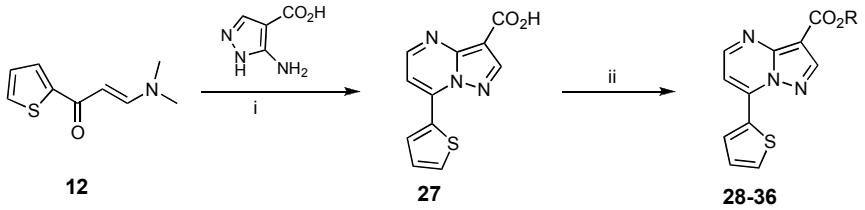
RESULTS AND DISCUSSION

The synthetic pathways employed for the synthesis of compounds **15-43** is depicted in the Schemes 1-3. The starting materials 3-(dimethylamino)-1-(substituted)prop-2-en-1-ones **8-14** were prepared by reacting the corresponding commercially available acetyl heterocycles **1-7** with *N*,*N*-dimethylformamide dimethyl acetal at 100°C for 18 hours. The enaminones obtained were then reacted with 4-cyano-5-amino-1*H*-pyrazole [10] or 5-amino-1*H*-pyrazole-4-carboxylate [11] to furnish the corresponding 3-cyano or 3-carboxylic acid ethyl ester derivatives **15-19** and **20-25** respectively in a quite good yield (Scheme 1).

The introduction of (substituted)benzyl esters or alkyl esters at the 3-position of the pyrazolo[1,5-*a*]pyrimidine nucleus is shown in the synthetic Scheme 2. The 3-(dimethylamino)-1-(thiophen-2-yl)prop-2-en-1-one **12** was reacted with 5-amino-1*H*-pyrazole-4-carboxylic acid [11] in a mixture of acetic acid and water to afford the 7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid **27**. The carboxylic group of **27** was converted into ester (compounds **28-36**) by reaction with several commercially available alkylating agents, using DMF as solvent and K_2CO_3 as a base.



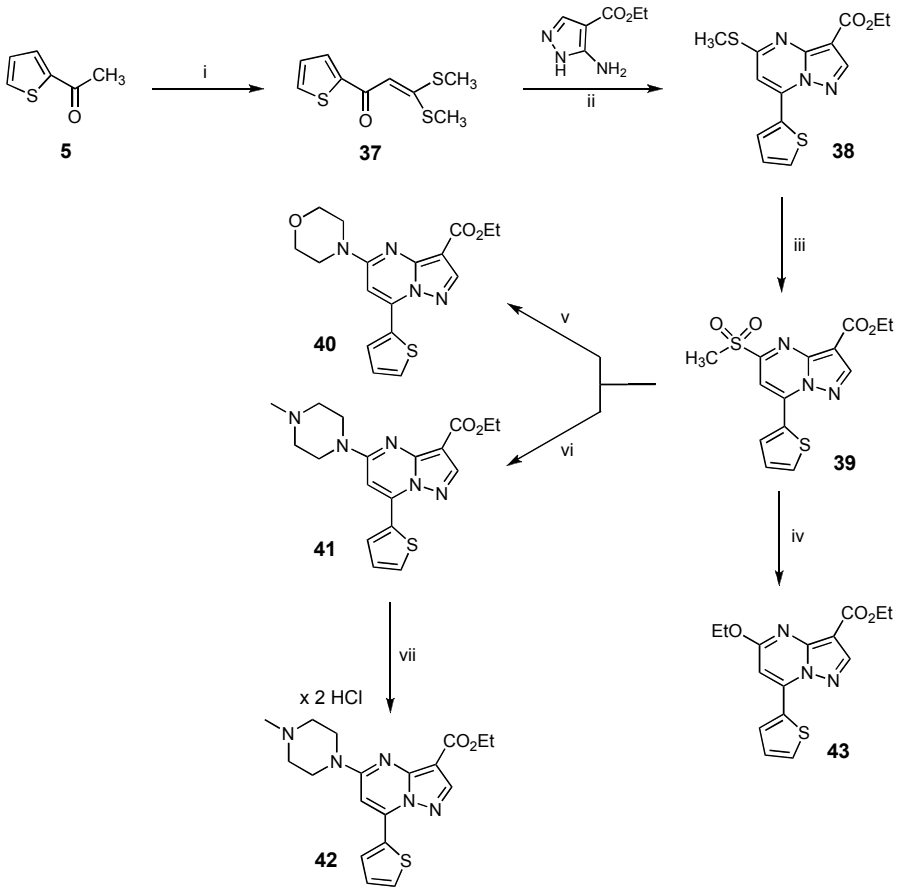
Scheme 1. Reagents and conditions: (i) N,N-Dimethylformamide dimethyl acetal, 100°C, 18 h; (ii) Acetic acid/water 2:1, 110°C; (iii) CH_3ONa, 65°C, 6 h. R= Pyridin-2-yl (1, 8, 15, 20); N-methyl-pyrrol-2-yl (2, 9, 16); furan-2-yl (3, 10, 17, 21); pyridin-3-yl (4, 11, 18, 22); thiophen-2-yl (5, 12, 19, 23); 2,5-dimethyl-thiophen-3-yl (6, 13, 24); 5-bromo-thiophen-2-yl (7, 14, 25, 26).



Scheme 2. Reagents and conditions: (i) Acetic acid/water 2:1, 110°C; (ii) alkyl halides, K_2CO_3.
R= Benzyl (28); 4-methoxy benzyl (29); 4-chloro benzyl (30); 4-fluoro benzyl (31); 4-nitro benzyl (32); *tert*-butyl (33); isopropyl (34); n-propyl (35); 2-phenylethyl (36).

The 5-position of the pyrazolo[1,5-*a*]pyrimidine core was functionalised by the introduction of basic groups or short alkyloxy radical like ethoxy. The synthetic pathway used is depicted in the Scheme 3. The 2-acetyl thiophene **5** was transformed into the corresponding 3,3-bis(methylthio)-prop-2-en-1-one **37** by reaction with carbon disulfide and methyl iodide in the presence of 60% NaH. This intermediate was cyclized into **38** by reaction with 5-amino-1*H*-pyrazole-4-carboxylate and a catalytic amount of piperidine [12]. In order to increase the reactivity and the exchangeability of the thiomethyl radical of compound **38**, it was oxidized into the methylsulfonyl derivative **39** in a quantitative yield by treatment with 70% *m*-chloroperbenzoic acid [13] in dichloromethane as solvent. This intermediate was reacted in neat with an excess of morpholine, N-methyl piperazine or just refluxed in ethanol to afford the 5-substituted compounds **40-43**. The piperazino radical of compound **41** was converted into the hydrochloric salt **42** by treatment with a saturated solution of hydrochloric acid in methanol.

To determine the relative affinities of compounds **15-43** to the α1-$GABA_A$ receptor in rat cerebral cortex, membranes were labelled with the benzodiazepine site



Scheme 3. Reagents and conditions: (i) CS_2, CH_3I, NaH; (ii) acetic acid/water 3:1, piperidine; (iii) *m*-chloroperbenzoic acid, CH_2Cl_2; (iv) abs. EtOH, reflux; (v) morpholine, 60°C, 30'; (vi) N-methyl piperazine, 70°C, 30'; (vii) HCl g/MeOH, 0°C.

antagonist [^{3}H]Ro 15-1788 (Flumazenil). The majority of compounds synthesized exhibited improved or comparable affinity with respect to zaleplon (K_i= 57.3 nM) [14] and were able to compete for the binding of [^{3}H]Ro 15-1788. The replacement of the phenyl N-ethylacetamido moiety of **1a** with heterocycles, preferably with thiophene, along with oxycarbonyl radicals at the 3-position, preferably (4-methoxy)benzyloxy carbonyl radicals, revealed new chemical candidates with an enhanced receptor affinity with respect to that of zaleplon (compounds **23**, **28** and **29**, K_i= 18 nM, 14 nM and 7.6 nM respectively).

EXPERIMENTAL

Reaction courses and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel (precoated F254 Merck plates) and visualized with aqueous potassium permanganate or ethanolic ninhydrin solutions. Infrared spectra (ir) were measured on a Perkin-Elmer 257 instrument using KBr Wafer technique. ^{1}H nmr were determined in $CDCl_3$, or DMSO-d_6 solutions with a Varian VXR 200 spectrometer. Peak positions are given in parts per million (δ) downfield from tetramethylsilane as internal standard, and J values are given in Hz. Light petroleum refers to the fractions boiling at 40-60°C. Melting points were determined on a Buchi-Tottoli instrument and are uncorrected. Mass spectra (ms) were obtained with a Shimadzu QP5050 DI 50 spectrometer. Chromatography was performed with Merck 60-200 mesh silica gel. All products reported showed ^{1}H nmr spectra in agreement with the assigned structures. Organic solutions were dried over anhydrous sodium sulphate. Elemental analyses were performed by the micro analytical laboratory of Dipartimento di Chimica, University of Ferrara, and were within ± 0.4% of the theoretical values for C, H and N

General Procedure for the Preparation of 3-(Dimethylamino)-1-(substituted)prop-2-en-1-ones (8-14). To the acetyl compounds **1-7** (1 mL) was added *N,N*-dimethylformamide dimethyl acetal (1.03 mol eq) and the mixture was heated at 100°C for 18 h. The solvent was removed at reduced pressure and the residue was recrystallized from EtOAc to furnish derivatives **8-14** as solids.

3-(Dimethylamino)-1-(pyridin-2-yl)prop-2-en-1-one (8). Yield 70%; yellow crystals; mp 110°C; ^{1}H nmr ($CDCl_3$) δ 2.98 (s, 3H), 3.17 (s, 3H), 6.5 (d, 1H, J=14), 7.32 (m, 1H), 7.91 (m, 1H), 7.99 (d, 1H, J=13.8), 8.19 (d, 1H, J=7.9), 8.65 (dd, 1H, J=2); ir (KBr) 1693 cm^{-1}; ms: m/z 176 (M^+). *Anal.* Calcd. for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.24; H, 6.73; N, 15.77.

3-(Dimethylamino)-1-(1-methyl-1*H*-pyrrol-2-yl)prop-2-en-1-one (9). Yield 11%; yellow crystals; mp 115°C; ^{1}H nmr ($CDCl_3$) δ 2.98 (s, 3H), 3.98 (bs, 6H), 5.63 (d, 1H, J=12), 6.09 (m, 1H), 6.71 (m, 1H), 6.80 (m, 1H), 7.63 (d, 1H, J=12.2); ir (KBr) 1699 cm^{-1}; ms: m/z 178 (M^+). *Anal.* Calcd. for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.01; H, 7.88; N, 15.64.

3-(Dimethylamino)-1-(furan-2-yl)prop-2-en-1-one (10). Yield 74%; pale orange solid; mp 121°C; ^{1}H nmr ($CDCl_3$) δ 2.91 (s, 3H), 3.12 (s, 3H), 5.68 (d, 1H, J= 12), 6.47 (m, 1H), 7.05 (d, 1H, J=2), 7.48 (s, 1H), 7.82 (d, 1H, J=12.3); ir (KBr) 1701 cm^{-1}; ms: m/z 165 (M^+). *Anal.* Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.28; H, 6.59; N, 8.26.

3-(Dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one (11). Yield 55%; red scarlet crystals; mp 113°C; 1H nmr ($CDCl_3$) δ 2.95 (s, 3H), 3.17 (s, 3H), 5.70 (d, 1H, J=12), 7.35 (m, 1H), 7.87 (d, 1H, J=11.9), 8.17 (m, 1H), 8.67 (dd, 1H), 9.08 (d, 1H, J=2); ir (KBr) 1688 cm^{-1}; ms: m/z 176 (M^+). *Anal.* Calcd. for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.09; H, 6.78; N, 15.96.

3-(Dimethylamino)-1-(thiophen-2-yl)prop-2-en-1-one (12). Yield 73%; yellow crystals; mp 128°C; ^{1}H nmr ($CDCl_3$) δ 2.93 (bs, 3H), 3.11 (bs, 3H), 5.65 (d, 1H, J=12.1), 7.07 (m, 1H), 7.46 (d, 1H, J=6), 7.62 (d, 1H, J=4), 7.81 (d, 1H, J=13); ir (KBr) 1691 cm^{-1}; ms: m/z 181 (M^+).

Anal. Calcd. for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.73. Found: C, 59.39; H, 6.02; N, 7.59.

3-(Dimethylamino)-1-(2,5-dimethyl-thiophen-3-yl)prop-2-en-1-one (13). Yield 56%; orange crystals; mp 114°C; ^{1}H nmr ($CDCl_3$) δ 2.39 (s, 3H), 2.67 (s, 3H), 2.98 (bs, 6H), 5.44 (d, 1H, J=12), 7.28 (s, 1H), 7.68 (d, 1H, J=12.1); ir (KBr) 1710 cm^{-1}; ms: m/z 209 (M^+). *Anal.* Calcd. for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 62.98; H, 7.11; N, 6.54.

3-(Dimethylamino)-1-(5-bromo-thiophen-2-yl)prop-2-en-1-one (14). Yield 64%; yellow crystals; mp 120-3°C; ^{1}H nmr ($CDCl_3$) δ 2.42 (s, 3H), 2.71 (s, 3H), 5.61 (d, 1H, J=12.6), 6.89 (d, 1H, J=4), 7.11 (d, 1H, J=3.8), 7.70 (d, 1H, J=12.1); ir (KBr) 1699 cm^{-1}; ms: m/z 258 (M^+). *Anal.* Calcd. for $C_9H_{10}BrNOS$: C, 41.55; H, 3.87; N, 5.38. Found: C, 41.29; H, 3.79; N, 5.28.

General Procedure for the preparation of 7-(substituted)-pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles (15-19). To a solution of compounds **8-14** (2.8 mmol) in a mixture of acetic acid/water (2:1, 10 mL) was added 4-cyano-5-amino-1*H*-pyrazole (1 mol eq) and the reaction was heated at reflux for 1-2 h. Then was added cold water until the complete precipitation of compound was observed*. The solid formed was collected by filtration and recrystallized from hot methanol to furnish **15-19** as solids.

*For compound **16**: the aqueous phase was extracted with CH_2Cl_2 (3X20 mL), the recombined organic layers were washed two time with NaOH 5% (15 mL), anhydrified over Na_2SO_4 and evaporated under reduced pressure. The residue obtained was recrystallized from a mixture of CH_2Cl_2 /Et_2O.

7-(Pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (15). Yield 83%; yellow solid; mp 192-4°C. ^{1}H nmr ($CDCl_3$) δ 7.56 (m, 1H), 7.98 (m, 2H), 8.50 (s, 1H), 8.87 (m, 2H), 8.97 (d, 1H, J=7.9); ir (KBr) 2229 cm^{-1}; ms: m/z 221 (M^+). *Anal.* Calcd. for $C_{12}H_{17}N_5$: C, 65.15; H, 3.19; N, 31.66. Found: C, 65.10; H, 3.15; N, 31.58.

7-(*N*-Methyl-pyrrol-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (16). Yield 45%; pale yellow solid; mp 180-2°C. ^{1}H nmr ($CDCl_3$) δ 3.79 (s, 3H), 6.39 (m, 1H), 7.11 (m, 2H), 7.13 (m, 1H), 8.42 (s, 1H), 8.71 (d, 1H, J=6); ir (KBr) 2231 cm^{-1}; ms: m/z 223 (M^+). *Anal.* Calcd. for $C_{12}H_9N_5$: C, 64.56; H, 4.06; N, 31.37. Found: C, 64.49; H, 4.01; N, 31.29.

7-(Furan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (17). Yield 89%; pale yellow crystals; mp 204-5°C. ^{1}H nmr ($CDCl_3$) δ 6.77 (m, 1H), 7.56 (d, 1H, J=4.1), 7.79 (s, 1H), 8.24 (d, 1H, J=4), 8.48 (s, 1H), 8.77 (d, 1H, J=5.9); ir (KBr) 2228 cm^{-1}; ms: m/z 210 (M^+). *Anal.* Calcd. for $C_{11}H_6N_4O$: C, 62.86; H, 2.88; N, 26.66. Found: C, 62.87; H, 2.75; N, 26.58.

7-(Pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (18). Yield 86%; pale yellow solid; mp 268-9°C. ^{1}H nmr

(DMSO-d_6) δ 7.48 (d, 1H, J=4), 7.57 (m, 1H), 8.50 (m, 1H), 8.59 (s, 1H), 8.63 (m, 1H), 8.87 (d, 1H, J=4.2), 9.23 (m, 1H); ir (KBr) 2236 cm^{-1}; ms: m/z 221 (M^+). *Anal.* Calcd. for $C_{12}H_7N_5$: C, 65.15; H, 3.19; N, 31.66. Found: C, 65.09; H, 3.17; N, 31.58.

7-(Thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (19). Yield 88%; yellow solid; mp 272-3°C. ^{1}H nmr (DMSO-d_6) δ 7.35 (m, 1H), 7.80 (d, 1H, J=6), 7.99 (d, 1H, J=4.3), 8.50 (d, 1H, J=2.3), 8.68 (s, 1H), 8.76 (d, 1H, J=6); ir (KBr) 2239 cm^{-1}; ms: m/z 226 (M^+). *Anal.* Calcd. for $C_{11}H_6N_4S$: C, 58.39; H, 2.67; N, 24.76. Found: 58.29; H, 2.59; N, 24.68.

General Procedure for the preparation of ethyl 7-(substituted)pyrazolo[1,5-*a*]pyrimidine-3-carboxylates (20-25). To a solution of compounds **8-14** (2.8 mmol) in a mixture of acetic acid/water (2:1, 10 mL) was added ethyl 5-amino-1*H*-pyrazole-4-carboxylate (1 mol eq) and the reaction was heated at reflux for 1-2 h. After cooling, water was added (30 mL)* and the aqueous phase was extracted with CH_2Cl_2 (3X25 mL). The recombined organic layer was washed with NaOH 5% (2 X 5 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was recrystallized from a mixture of CH_2Cl_2/Et_2O to afford compounds **20-25** as solids.

*For compounds **21** and **23**: after addition of water the formation of a fine precipitate was observed. The solid formed was filtered off and recrystallized from hot CH_3OH (**21**) or EtOAc (**23**).

Ethyl 7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (20). Yield 48%; pale green needles; mp 145°C. ^{1}H nmr ($CDCl_3$) δ 1.45 (t, 3H, J=8), 4.51 (q, 2H, J=8), 7.52 (m, 1H), 7.88 (d, 1H, J=4), 7.96 (m, 1H), 8.67 (s, 1H), 8.86 (m, 1H), 8.93 (d, 1H, J=4), 8.97 (d, 1H, J=6); ms: m/z 267 (M^+). *Anal.* Calcd. for $C_{14}H_{12}N_4O_2$: C, 62.08; H, 4.51; N, 20.88. Found: C, 62.66; H, 4.49; N, 20.65.

Ethyl 7-(furan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (21). Yield 70%; pale yellow solid; mp 140°C. ^{1}H nmr ($CDCl_3$) δ 1.44 (t, 3H, J=6.2), 4.49 (q, 2H, J=6), 6.75 (m, 1H), 7.51 (d, 1H, J=4), 7.76 (m, 1H), 8.27 (d, 1H, J=4.1), 8.67 (s, 1H), 8.82 (d, 1H, J=4.1); ms: m/z 257 (M^+). *Anal.* Calcd. for $C_{13}H_{11}N_3O_3$: C, 60.70; H, 4.31; N, 16.33. Found: C, 60.66; H, 4.24; N, 16.29.

Ethyl 7-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (22). Yield 78%; pale pink solid; mp 177-8°C. ^{1}H nmr ($CDCl_3$) δ 1.45 (t, 3H, J=6.2), 4.49 (q, 2H, J=6.1), 7.15 (d, 1H, J=4), 7.56 (m, 1H), 8.49 (m, 1H), 8.62 (s, 1H), 8.84 (m, 2H), 9.15 (d, 1H, J=3.8); ms: m/z 268 (M^+). *Anal.* Calcd. for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.72; H, 4.55; N, 20.81.

Ethyl 7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (23). Yield 60%; yellow solid; mp 145°C. ^{1}H nmr ($CDCl_3$) δ 1.47 (t, 3H, J=6), 4.49 (q, 2H, J=6.1), 7.33 (m, 1H), 7.42 (d, 1H, J=3.9), 7.81 (d, 1H, J=4), 8.38 (d, 1H, J=4.1), 8.70 (s, 1H), 8.78 (d, 1H, J=4); ms: m/z 273 (M^+). *Anal.* Calcd. for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 4.06; N, 15.37. Found: C, 57.10; H, 3.99; N, 15.29.

Ethyl 7-(2,5-dimethyl-thiophen-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (24). Yield 75%; yellow solid; mp 90-2°C. ^{1}H nmr ($CDCl_3$) δ 1.42 (t, 3H, J=6.2), 2.41 (s, 3H), 2.51 (s, 3H), 4.45 (q, 2H, J=6.1), 6.92 (d, 1H, J=3.8), 7.05 (s, 1H), 8.60 (s, 1H), 8.81 (d, 1H, J=4); ms: m/z 301 (M^+). *Anal.* Calcd. for $C_{15}H_{15}N_3O_2S$: C, 58.79; H, 5.02; N, 13.94. Found: C, 58.70; H, 4.99; N, 13.91.

Ethyl 7-(5-bromo-thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (25). Yield 71%; yellow solid; mp 164-5°C.^{1}H nmr ($CDCl_3$) δ 1.43 (t, 3H, J=6.1), 4.43 (q, 2H, J=6.2), 7.20 (s, 1H), 7.41 (d, 1H, J=3.8), 8.01 (d, 1H, J=3.9), 8.63 (s, 1H), 8.80 (d, 1H, J=4); ms: m/z 352 (M^+). *Anal.* Calcd. for $C_{13}H_{10}BrN_3O_2S$: C, 44.33; H, 2.86; N, 11.93. Found: C, 44.29; H, 2.81; N, 11.88.

Preparation of methyl 7-(5-bromo-thiophen-2-yl)pyrazolo-[1,5-*a*]pyrimidine-3-carboxylate (26). To a solution of **25** (80 mg, 0.23 mmol) in CH_3OH (10 mL) was added CH_3ONa (12 mg, 1 mol eq) and the mixture was heated at 65°C for 6 h. After cooling the solid formed was collected by filtration and washed with cold CH_3OH (20 mL) and then with Et_2O (15 mL) to furnish **26** as pale yellow solid. Yield 90% (70 mg, 2 mmol); mp 211-3°C.^{1}H nmr ($CDCl_3$) δ 4.01 (s, 3H), 7.23 (s, 1H), 7.38 (d, 1H, J=3.8), 8.11 (d, 1H, J=3.9), 8.56 (s, 1H), 8.82 (d, 1H, J=4); ms: m/z 338 (M^+). *Anal.* Calcd. for $C_{12}H_8BrN_3O_2S$: C, 42.62; H, 2.38; N, 12.43. Found: C, 42.59; H, 2.32; N, 12.40.

Preparation of 7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (27). To a solution of compound **12** (0.2 g, 1.10 mmol) in a mixture of acetic acid/water (2:1, 12 mL) was added 5-amino-1*H*-pyrazole-4-carboxylic acid (0.14 g, 1 mol eq) and the reaction was heated at reflux for 1 h. Water was added until the complete precipitation of compound was observed. The solid formed was collected by filtration and recrystallized from hot CH_3OH to furnish **27** as pale yellow solid. Yield 88% (0.22 g, 0.90 mmol); mp 270-1°C; ^{1}H nmr (DMSO-d_6) δ 7.40 (m, 1H), 7.97 (d, 1H, J=6), 8.17 (m, 1H), 8.55 (m, 1H), 8.74 (s, 1H), 8.81 (d, 1H, J=4.1), 12.45 (bs, 1H); ir (KBr) 1694, 3321 cm^{-1}; ms: m/z 245 (M^+). *Anal.* Calcd. for $C_{11}H_7N_3O_2S$: C, 53.87; H, 2.88; N, 17.13. Found: C, 53.66; H, 2.74; N, 17.02.

General Procedure for the Preparation of (substituted)-7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylates (28-36). To a solution of **27** (0.1 g) in DMF (8 mL) was added K_2CO_3 (2.5 mol eq) and the appropriate alkyl halide (1.2 mol eq), then the reaction was heated at 80-100°C for 3-4 h. After cooling, the solid formed* was collected by filtration under reduced pressure, washed with cold water (15 mL), dried and recrystallized from CH_3OH to afford **28-36** as solids.

*For compounds **32** and **36**: after addition of water the reaction was extracted with EtOAc (3X15 mL) and the recombined organic phases were anhydrified (Na_2SO_4) and evaporated at reduced pressure. The residue obtained was recrystallized from CH_3OH.

Benzyl 7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (28). Yield 68%; pale yellow solid; mp 176°C.^{1}H nmr ($CDCl_3$) δ 5.46 (s, 2H), 7.35 (m, 7H), 7.78 (dd, 1H), 8.39 (d, 1H, J=3.4), 8.70 (s, 1H), 8.79 (d, 1H, J=5.8); ms: m/z 335 (M^+). *Anal.* Calcd. for $C_{18}H_{13}N_3O_2S$: C, 64.40; H, 3.91; N, 12.53. Found: C, 64.46; H, 3.87; N, 12.58.

4-Methoxybenzyl 7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (29). Yield 75%; pale yellow solid; mp 175°C. ^{1}H nmr (DMSO-d_6) δ 3.75 (s, 3H), 5.29 (s, 2H), 6.92 (d, 2H, J=8), 7.42 (d, 2H, 7.8), 7.98 (d, 1H, J=4), 8.18 (d, 1H, J=4.1), 8.57 (d, 1H, J=3.9), 8.80 (s, 1H), 8.84 (d, 2H, J=4); ms: m/z 365 (M^+). *Anal.* Calcd. for $C_{19}H_{15}N_3O_3S$: C, 62.45; H, 4.14; N, 11.50. Found: C, 62.41; H, 4.05; N, 11.40.

4-Chlorobenzyl 7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (30). Yield 34%; pale yellow solid; mp 146-8°C. ^{1}H nmr ($CDCl_3$) δ 5.41 (s, 2H), 7.37 (m, 6H), 7.80 (d, 1H, J=4), 8.38 (d, 1H, J=3.9), 8.69 (s, 1H), 8.77 (d, 1H, J=4.1); ms: m/z 369 (M^+). *Anal.* Calcd. for $C_{18}H_{12}ClN_3O_2S$: C, 58.46; H, 3.27; N, 11.36. Found: C, 58.41; H, 3.26; N, 11.32.

4-Fluorobenzyl 7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (31). Yield 57%; pale yellow solid; mp 149-151°C. [Found: C, 61.09; H, 3.37; N, 11.82. ^{1}H nmr ($CDCl_3$) δ 5.41 (s, 2H), 7.06 (t, 2H, J=8), 7.30 (t, 2H, J=7.8), 7.52 (m, 2H), 7.79 (d, 1H, J=4), 8.38 (d, 1H, J=3.8), 8.69 (s, 1H), 8.78 (d, 1H, J=4.1); ms: m/z 353 (M^+). *Anal.* Calcd. for $C_{18}H_{12}FN_3O_2S$: C, 61.18; H, 3.42; N, 11.89. Found: C, 61.09; H, 3.37; N, 11.82.

4-Nitrobenzyl 7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (32). Yield 75%; pale yellow solid; mp 188-9°C. ^{1}H nmr ($CDCl_3$) δ 5.55 (s, 2H), 7.32 (t, 1H, J=4.1), 7.68 (d, 1H, J=4), 7.81 (d, 2H, J=8), 7.84 (d, 1H, J=5.8), 8.26 (d, 2H, J=8.1), 8.39 (m, 1H), 8.74 (s, 1H), 8.81 (d, 1H, J=4); ms: m/z 380 (M^+). *Anal.* Calcd. for $C_{18}H_{12}N_4O_4S$: C, 56.84; H, 3.18; N, 14.73. Found: C, 58.79; H, 3.19; N, 14.69.

***tert*-Butyl 7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (33).** Yield 81%; pale orange solid; mp 248°C. ^{1}H nmr (DMSO-d_6) δ 2.6 (s, 9H), 7.41 (t, 1H), 7.96 (d, 1H, J=4), 8.18 (d, 1H, J=3.8), 8.58 (d, 1H, J=3.9), 8.75 (s, 1H), 8.82 (d, 1H, J=4.1); ms: m/z 301 (M^+). *Anal.* Calcd. for $C_{15}H_{15}N_3O_2S$: C, 59.78; H, 5.02; N, 13.94. Found: C, 59.72; H, 4.98; N, 13.89.

Isopropyl 7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (34). Yield 69%; pale yellow solid; mp 124°C. ^{1}H nmr ($CDCl_3$) δ 1.39 (s, 3H), 1.42 (s, 3H), 5.33 (m, 1H), 7.30 (t, 1H, J=4), 7.38 (d, 1H, J=6), 7.80 (d, 1H, J=4), 8.37 (m, 1H), 8.65 (s, 1H), 8.76 (d, 1H, J=4.1); ms: m/z 287 (M^+). *Anal.* Calcd. for $C_{14}H_{13}N_3O_2S$: C, 58.52; H, 4.56; N, 14.62. Found: C, 58.58; H, 4.51; N, 14.55.

***n*-Propyl 7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (35).** Yield 35%; yellow solid; mp 128°C. ^{1}H nmr ($CDCl_3$) δ 1.05 (t, 3H, J=6.1), 1.86 (q, 2H, J=6), 4.36 (t, 2H, J=6.2), 7.28 (t, 1H, J=4), 7.40 (d, 1H, J=4), 7.81 (d, 1H, J=3.9), 8.38 (d, 1H, J=3.8), 8.69 (s, 1H), 8.78 (d, 1H, J=5.8); ms: m/z 287 (M^+). *Anal.* Calcd. for $C_{14}H_{13}N_3O_2S$: C, 58.52; H, 4.56; N, 14.62. Found: C, 58.39; H, 4.55; N, 14.63.

2-Phenylethyl 7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (36). Yield 68%; pale yellow solid; mp 99-100°C. ^{1}H nmr ($CDCl_3$) δ 3.13 (t, 2H, J=8), 4.60 (t, 2H, J=7.8), 7.32 (m, 6H), 7.44 (d, 1H, J=6), 7.82 (d, 1H, J=4), 8.38 (d, 1H, J=3.9), 8.66 (s, 1H), 8.78 (d, 1H, J=3.9); ms: m/z 349 (M^+). *Anal.* Calcd. for $C_{19}H_{15}N_3O_2S$: C, 65.33; H, 4.33; N, 12.03. Found: C, 65.27; H, 4.28; N, 12.00.

Preparation of 3,3-bis(methylthio)-1-(thiophen-2-yl)prop-2-en-1-one (37). An ice chilled solution of **5** (3 mL, 28 mmol) in dry toluene (50 mL) was treated with 60% NaH (2.3 g, 2 mol eq) and the mixture was stirred at 0°C for 10 min. Carbon disulfide (2.52 mL, 1.5 mol eq) and methyl iodide (5.23 mL, 3 mol eq) were added to the cold solution over a period of 20 min. Dimethylacetamide (1.8 mL) was added dropwise while the mixture was kept below 45°C. After the mixture was stirred for 24 h at room temperature, a small amount of crash ice was added to consume the unreacted NaH. The toluene was removed at reduced pressure and the residue was portioned between water and chloroform. The organic layer was dried (Na_2SO_4) and evaporated at reduced pressure. The residue was recrystallized from abs. EtOH to furnish **37** as yellow needles. Yield 67% (4.3 g, 18.7 mmol); mp 94-5°C; ^{1}H nmr ($CDCl_3$) δ 2.53 (s, 3H), 2.56 (s, 3H), 6.62 (s, 1H), 7.10 (t, 1H, J=4), 7.56 (d, 1H, J=3.9), 7.66 (d, 1H, J=4.1); ms: m/z 229 (M^+).

Preparation of ethyl 5-(methylthio)-7-(thiophen-2-yl)-pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (38). To a solution of **37** (0.3 g, 1.3 mmol) in a mixture of acetic acid/water (3:1, 16 mL) was added ethyl 5-amino-1*H*-pyrazole-4-carboxylate (0.20 g, 1 mol eq) and a catalytic amount of piperidine (2 drops). The resulting solution was heated at reflux for 20 h then, after cooling, water was added (35 mL). The solid formed was collected by filtration and recrystallized from a mixture of $CHCl_3$/*n*-hexane to furnish **38** as yellow solid. Yield 32% (0.1 g, 0.31 mmol); mp 195-6°C. ^{1}H nmr ($CDCl_3$) δ 1.43 (t, 3H, J=7.3), 2.76 (s, 3H), 4.40 (q, 2H, J=8), 7.18 (s, 1H), 7.27 (m, 1H), 7.72 (d, 1H), 8.27 (d, 1H, J=3.9), 8.54 (s, 1H); ms: m/z 319 (M^+). *Anal.* Calcd. for $C_{14}H_{13}N_3O_2S_2$: C, 52.64; H, 4.10; N, 13.16. Found: C, 52.58; H, 3.98; N, 13.05.

Preparation of ethyl 5-(methylsulfonyl)-7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (39). A solution of MCPBA (70% strength, 0.26 g, 1.5 mmol, 3 mol eq) in CH_2Cl_2 (10 mL) was added to a stirred solution of 38 (0.16 g, 0.5 mmol) in CH_2Cl_2 (10 mL). The resulting solution was strirred at room temperature for 6 h, then the solvent was removed under reduced pressure and abs. EtOH (15 mL) added to the residue. The solid formed was collected by filtration, washed with cold abs. EtOH and dried to give **39** as a yellow solid. Quantitative yield; mp 210-1°C. ^{1}H nmr ($CDCl_3$) δ 1.44 (t, 3H, J=8), 3.48 (s, 3H), 4.46 (q, 2H, J=8.1), 7.36 (t, 1H, J=3.6), 7.94 (d, 1H, J=4), 8.05 (s, 1H), 8.48 (d, 1H, J=3.9), 8.82 (s, 1H); ms: m/z 351 (M^+). *Anal.* Calcd. for $C_{14}H_{13}N_3O_4S_2$: C, 47.85; H, 3.73; N, 11.96. Found: C, 47.77; H, 3.69; N, 11.92.

Preparation of ethyl 5-morpholino-7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (40). The compound **39** (60 mg, 0.17 mmol) was suspended in morpholine (2 mL, exc.) and the mixture was heated at 60°C for 30 min. Then water was added (20 mL) and the solid formed was collected by filtration, dried and recrystallized from EtOAc to furnish **40** as yellow solid. Yield 69% (40 mg, 0.11 mmol); mp 204-6°C. ^{1}H nmr ($CDCl_3$) δ 1.40 (t, 3H, J=8), 3.84 (m, 8H), 4.39 (q, 2H, J=7.8), 6.71 (s, 1H), 7.23 (m, 1H), 7.68 (d, 1H, J=3.9), 8.23 (d, 1H, J=4), 8.40 (s, 1H); ms: m/z 358 (M^+). *Anal.* Calcd. for $C_{17}H_{18}N_4O_3S$: C, 56.97; H, 5.06; N, 15.63. Found: C, 56.91; H, 5.01; N, 15.59.

Preparation of ethyl 5-(4-methylpiperazin-1-yl)-7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (41). The compound **39** (20 mg, 0.057 mmol) was suspended in *N*-methylpiperazine (1.5 mL, exc.) and the mixture was heated at 70°C for 30 min. Then water was added (18 mL) and the aqueous layer was extracted with EtOAc (3X8mL). The recombined organic phases were dried (Na_2SO_4) and evaporated at reduced pressure. The residue was recrystallized from EtOAc to furnish **41** as orange solid. Quantitative yield; mp 138-141°C. ^{1}H nmr ($CDCl_3$) δ 1.41 (t, 3H, J=8), 2.37 (s, 3H), 2.58 (m, 4H), 3.87 (m, 4H), 4.38 (q, 2H, J=7.8), 6.73 (s, 1H), 7.23 (m, 1H), 7.67 (d, 1H, J=5.8), 8.21 (d, 1H, J=4.1), 8.39 (s, 1H); ms: m/z 371 (M^+). *Anal.* Calcd. for $C_{18}H_{21}N_5O_2S$: C, 58.20; H, 5.70; N, 18.85. Found: C, 57.99; H, 5.62; N, 18.83.

Preparation of ethyl 5-(4-methylpiperazin-1-yl)-7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate dihydrochloride (42). A solution of **41** (20 mg, 0.054 mmol) in a methanolic satured solution of HCl (5 mL) was stirred at 0°C for 10 min and then at room temperature for additional 10 min. The solvent was removed at reduced pressure and the residue was recrystallized from MeOH to afford **42** as pale yellow solid. Quantitative yield; mp >240°C. ^{1}H nmr (DMSO-d_6) δ 1.35 (t, 3H, J=8), 2.95 (s, 3H), 3.35 (m, 8H), 4.25 (q, 2H, J=7.9), 4.72 (bs, 2H), 7.29 (m, 1H); 7.43 (s, 1H), 7.95 (d, 1H, J=4), 8.15 (s, 1H), 8.49 (d, 1H, J=3.9). *Anal.* Calcd. for $C_{18}H_{23}Cl_2N_5O_2S$: C, 48.65; H, 5.22; N, 15.96. Found: C, 48.32; H, 5.25; N, 15.09.

Preparation of ethyl 5-ethoxy-7-(thiophen-2-yl)pyrazolo-[1,5-*a*]pyrimidine-3-carboxylate (43). A solution of **39** (60 mg, 0.17 mmol) in abs. EtOH (10 mL) was refluxed for 8 h. The solvent was removed at reduced pressure and the residue was recrystallized from cold abs. EtOH to give **43** as pale orange solid. Yield 74% (40 mg, 0.12 mmol); mp 139-141°C. ^{1}H nmr ($CDCl_3$) δ 1.44 (m, 6H), 4.41 (q, 2H, J=8), 4.65 (q, 2H, J=7.8), 6.83 (s, 1H), 7.25 (m, 1H), 7.72 (m, 1H), 8.25 (m, 1H), 8.49 (s, 1H); ms: m/z 317 (M^+). *Anal.* Calcd. for $C_{17}H_{18}N_4O_3S$: C, 56.77; H, 4.76; N, 13.24. Found: C, 56.74; H, 4.69; N, 13.18.

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