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Pyrazolo-[1,5-*a*]-1,3,5-triazine Corticotropin-Releasing Factor (CRF) Receptor Ligands

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Abstract—The syntheses and rat CRF receptor binding affinities of 'retro-pyrazolotriazine' corticotropin-releasing factor (CRF) ligands **4** are reported. Some have high affinity for rat CRF receptors ($K_i \leq 10$ nM). The data provide additional support for the hypothesis that it is possible to interchange isosteric cores with similar electronic properties in the design of high-affinity CRF receptor ligands, provided the peripheral pharmacophore elements are maintained in the same three-dimensional array.

Corticotropin-releasing factor (CRF) receptors have become targets for the design of potential antidepressant and anxiolytic drugs because of the central role CRF plays in the regulation of the endocrine, neural and immune responses to stress.[1,2] CRF is the prime regulator of the hypothalamus–pituitary–adrenal (HPA) axis, which is the physiological entity mediating the body's responses to stress. CRF mediates its effects through two receptor subtypes, CRF_1 and CRF_2. In rodent studies, the CRF_1 receptor subtype appears to play a greater role in stress-related responses than the CRF_2 subtype. However, additional studies with subtype-selective ligands are needed to definitively assign the physiological roles of the two subtypes in rodents as well as higher species.

Preclinical studies have established a potential role for CRF in anxiety and depression.[3,4] Intracerebroventricular (icv) injection of CRF in rodents and primates induces a broad spectrum of electrophysiological, immune and behavioral changes similar to those evoked by natural stressors.[5] Chronic stress in rats and non-human primates has been shown to alter the plasticity of the HPA axis and to cause long-term hypersensitivity to natural stressors.[6,7] The selective non-peptide antagonist CP154526-1 has shown efficacy in rodent models for anxiety and depression.[8–10]

In clinical studies, hypersecretion of CRF has been linked to depression and affective disorders.[11–14] Elevation of plasma cortisol concentrations has been documented in many, but not all, depressed patients. Cortisol exerts negative feedback control on the secretion of CRF in the hypothalamus in normal patients; this feedback is believed to be defective in many depressed patients. Hypersecretion of CRF in the cerebrospinal fluid (CSF) parallels the hypersecretion of cortisol. Chronic antidepressant or electroconvulsive shock therapy ameliorates the clinical signs of depression with concomitant reductions in plasma levels of cortisol and CSF levels of CRF. Finally, the selective non-peptide CRF_1 antagonist R121919 has shown some efficacy in an open label clinical trial with a small group of depressed patients, with improvements in anxiety-related parameters being noted as well. Unfortunately,

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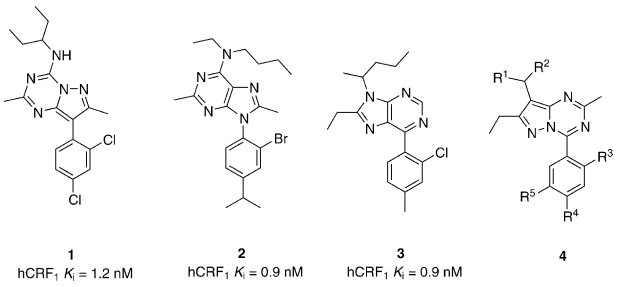
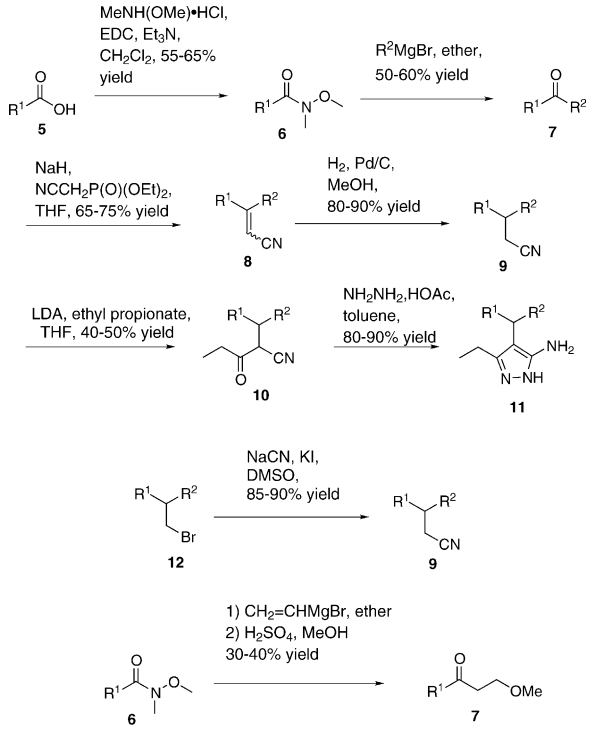


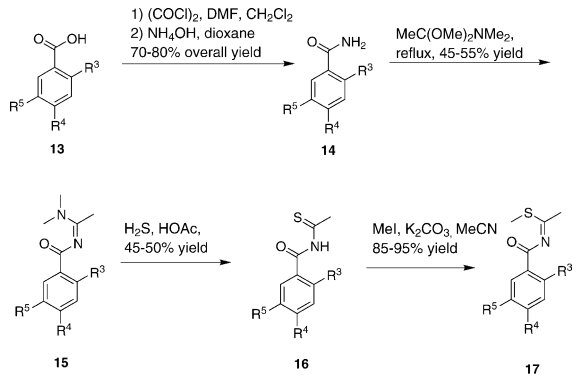
Scheme 1.



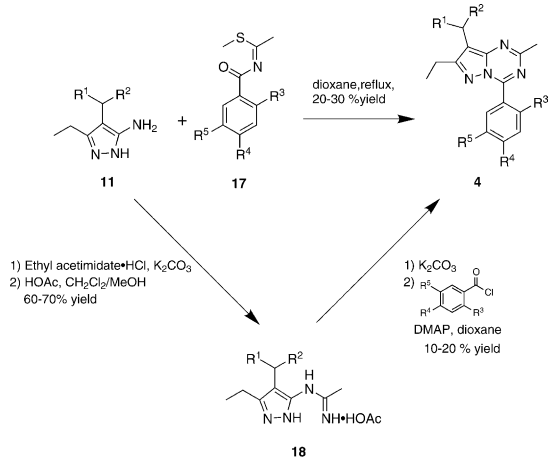
Scheme 2.

liver toxicity precluded further evaluation of this compound.[15] Controlled double-blind clinical trials with a selective CRF antagonist are still needed to provide proof of principle. Nonetheless, the case for CRF antagonists as potential neuropsychiatric drugs is still compelling and has inspired new efforts to discover structurally diverse CRF antagonists.

This report describes the syntheses and in vitro pharmacological properties of a novel series of CRF ligands. Previous reports have documented the excellent receptor binding affinity of bicyclic CRF ligands, wherein a six-membered ring is fused to a five-membered ring (examples **1**, **2** and **3**, Scheme 1).[1,2,16,17] In the purine series, the interchangeability of the five- and six-membered rings has also been examined (examples 2 and 3).[18,19] We undertook the syntheses and pharmacological evaluation of a series of 'retro-pyrazolotriazines' **4** (Scheme 1) to test whether the interchangeability of the five- and six-membered rings was applicable to other bicyclic cores.



Scheme 3.



Scheme 4.

Results and Discussion

Retro-pyrazolotriazines **4** were prepared in a convergent fashion by the couplings of pyrazoles **11** with aroyl thioimidates **17**. The requisite pyrazoles were synthesized by the general methods depicted in Scheme 2. Carboxylic acids **5** were converted to the corresponding amides **6**. Conversion of amides **6** to ketones **7** occurred after treatment with various Grignard reagents. The ketones **7** underwent a condensation with diethyl phosphonoacetonitrile to generate acrylonitriles **8** as a mixture of *E*- and *Z*-isomers. Hydrogenation afforded nitriles **9**. Generation of the carbanion with lithium bis(trimethylsilyl)amide and condensation with propionyl chloride provided ketonitriles **10**. Subsequent condensation with hydrazine gave the aminopyrazole intermediates **11**. The nitriles **9** could also be prepared by nucleophilic displacement of bromides **12** with sodium cyanide. Compounds **7** where $R^2 = CH_2CH_2OMe$ were prepared by the reaction of amides **6** with vinyl magnesium bromide, followed by treatment with H_2SO_4 and methanol.

The thio-imidates **17** were prepared by a modification of a published procedure (Scheme 3).[20] Acids **13** were converted to primary amides **14** by conversion to acid chlorides and subsequent treatment with ammonium hydroxide in dioxane. Intermediates **14** were then condensed with dimethylformamide dimethyl acetal to generate compounds **15**. Reaction of **15** with H_2S in

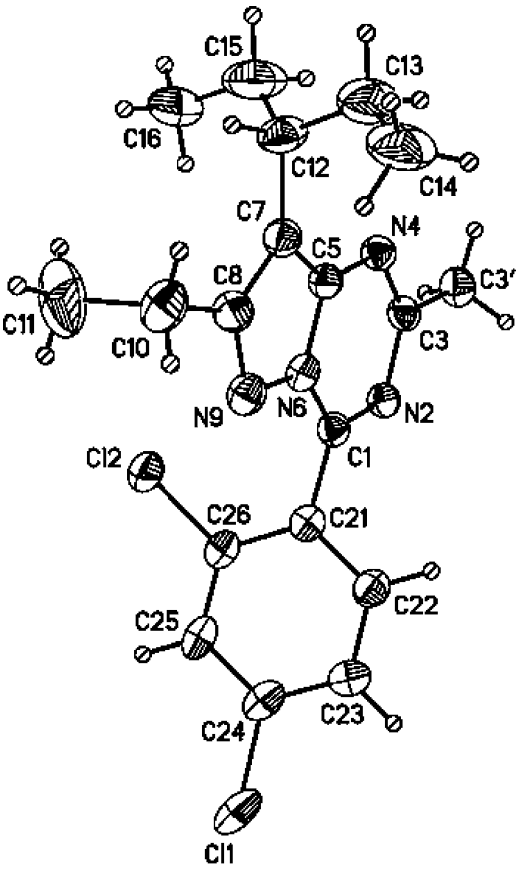


Figure 1.

acetic acid provided thioimides **16**. Methylation provided the thio-imidates **17**, with no evidence of *N*-methylation.

Condensation of pyrazoles **11** with thio-imidates **17** in dioxane at reflux temperature provided retro-pyrazolotriazines **4** (Scheme 4). Only the desired regio-isomers were formed. In the case of analogue **4e**, the structure was confirmed by X-ray crystallography (Fig. 1).[21]

An alternate synthesis of compounds **4** was devised to expedite SAR exploration on the phenyl substituent (Scheme 4). Conversion of aminopyrazoles **11** to the corresponding amidines **18** was accomplished by reaction with ethyl acetamidate. Treatment of intermediates **18** with aroyl chlorides afforded targets **4** in modest yields.

Compounds **4** were tested for their binding affinity to rat CRF receptors using cortical homogenates and [^{125}I]-Tyr^0-ovine CRF as the radioligand.[22] The data are summarized in Table 1. Previous work has established that 2,4-dichlorophenyl and 2-chloro-4,5-dimethoxyphenyl groups enhance receptor binding affinity in this series.[23,24] Sidechain modifications were investigated initially with these two cores (Table 1). Branched alkyl groups at the 8-position of the pyrazolotriazine core enhance binding affinity for rat CRF receptors. Preferred chain lengths for R^1 and R^2 are three to four atoms. Propyl, methoxymethyl and methoxyethyl chains have comparable effects on affinity (cf. **4a**, **4b**, **4k**, **4l**). Reductions in chain length decrease binding affinity (cf. **4e**, **4f**, **4m**, **4o**). A cyclobutyl group may replace the propyl moiety with little effect on affinity while a 3-tetrahydrofuranyl group can not. Replacement of the branched alkyl sidechain CHR^1R^2 with cyclopentyl or tetrahydropyranyl moieties significantly reduces binding affinity. These findings can be extended to the 2-chloro-4-methylphenyl, 2-chloro-5-fluoro-4-methoxyphenyl and 2,4-dimethoxyphenyl cores (entries **4t**–**4z**). Comparison of the data for the compounds in this paper with those for the literature compounds **1**, **2**, **3** and their analogues[16–18] provides additional support for the hypothesis that it is possible to interchange isosteric cores with similar electronic properties in the design of high affinity CRF receptor ligands, provided the peripheral pharmacophore elements are maintained in the same three-dimensional array. The impact of changing the cores on CRF receptor subtype binding selectivity, functional antagonism and in vivo parameters (e.g., rat behavioral efficacy and pharmacokinetics) is under investigation.

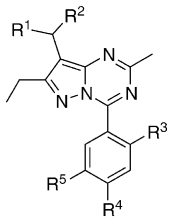
Experimental

Analytical data were generated using the following procedures. Proton NMR spectra were recorded on an Varian FT-NMR (300 MHz); chemical shifts were recorded in ppm (δ) from an internal tetramethysilane standard in deuterochloroform or deuterodimethylsulfoxide as specified below. Mass spectra (MS) or high resolution mass spectra (HRMS) were recorded on a Finnegan MAT 8230 spectrometer (using chemi-ionization (CI) with NH_3 as the carrier gas or gas chromatography (GC) as specified below) or a Hewlett Packard 5988A model spectrometer. Melting points were recorded on a Buchi Model 510 melting point apparatus and are uncorrected. Boiling points are uncorrected. All pH determinations during workup were made with indicator paper. Combustion analyses were performed by Quantitative Technologies, Whitehouse, NJ, USA.

Reagents were purchased from commercial sources and, where necessary, purified prior to use.[25] Chromatography [thin-layer (TLC) or preparative] was performed on silica gel using the solvent systems indicated below. For mixed solvent systems, the volume ratios are given. Otherwise, parts and percentages are by weight.

4-(2,4-Dichlorophenyl)-7-ethyl-2-methyl-8-(3-pentyl)-pyrazolo[1,5-a]-1,3,5-triazine (4e) (Method A). A mixture of NaCN (4.1 g, 82.7 mmol) and KI (154 mg, 0.9 mmol) in anhydrous dimethylsulfoxide (40 mL) was heated to 40 °C with stirring. 3-Ethyl-1-bromobutane (12.4 g, 75.2 mmol) was added dropwise over 10 min. The reaction mixture was first stirred and heated at 80 °C for 1 h, then at 120 °C for 5 h. The reaction mixture was cooled to ambient temperature and a precipitate formed. Dilution with water (150 mL), extraction with ether (3×100 mL), washing the combined organic layers with a saturated NaCl solution, drying over $MgSO_4$ and filtration

Table 1. Rat CRF receptor binding affinity data



Example	CHR^1R^2	R^3	R^4	R^5	K_i (nM)(n)[a]
4a	$CHPr_2$	Cl	Cl	H	1.0±0.2 (4)
4b	$CHPr(CH_2OMe)$	Cl	Cl	H	1.4±0.1 (3)
4c	CH(cyclobutyl)–(CH_2CH_2OMe)	Cl	Cl	H	2.1±0.9 (3)
4d	CHMePr	Cl	Cl	H	8.0±4.7 (5)
4e	$CHEt_2$	Cl	Cl	H	19.4±10.7 (3)
4f[b]	$CH(CH_2CH_2OMe)$-(3-tetrahydrofuranyl)	Cl	Cl	H	8.5±1.3 (3)
4g[b]	$CH(CH_2CH_2OMe)$-(3-tetrahydrofuranyl)	Cl	Cl	H	20.8±10.6 (3)
4h	4-Tetrahydropyranyl[c]	Cl	Cl	H	57.2±25.3 (3)
4i	Cyclopentyl[c]	Cl	Cl	H	74.1±46.1 (3)
4j	$CHPr_2$	Cl	MeO	MeO	0.7±0.2 (3)
4k	$CHPr(CH_2OMe)$	Cl	MeO	MeO	2.0±0.1 (3)
4l	CHMePr	Cl	MeO	MeO	2.6±1.0 (4)
4m	$CH(cyclobutyl)(CH_2CH_2OMe)$	Cl	MeO	MeO	3.7±1.1 (3)
4n	$CHEt_2$	Cl	MeO	MeO	5.0±1.1 (3)
4o	cyclopentyl	Cl	MeO	MeO	18.2±3.3 (3)
4p	$CH(CH_2CH_2OMe)$–(3-tetrahydrofuranyl)	Cl	MeO	MeO	69.0±42.0 (4)
4q	Cyclobutyl	Cl	MeO	MeO	78.4±13.0 (3)
4r	4-Tetrahydropyranyl[c]	Cl	MeO	MeO	204.0±23.4 (3)
4s	$CHPr_2$	Cl	MeO	H	1.2±0.4 (3)
4t	$CHPr(CH_2OMe)$	Cl	MeO	H	1.4±0.3 (3)
4u	$CHPr_2$	Cl	EtO	H	11.9±2.7 (3)
4v	$CHPr(CH_2OMe)$	Cl	MeO	F	1.3±0.3 (3)
4w	CH(cyclobutyl)–(CH_2CH_2OMe)	Cl	MeO	F	2.7±0.8 (3)
4x	$CH(CH_2CH_2OMe)$-(3-tetrahydrofuranyl)	Cl	MeO	F	25.9±5.2 (3)
4y	$CHPr_2$	MeO	MeO	H	4.1±1.1 (3)
α-Helical CRF_{9-41}					7.6±0.8 (3)

[a]Arithmetic means and standard deviations are reported for the K_i values; n is the number of determinations.
[b]Individual diastereomers.
[c]R^1 and R^2 taken together with the methine carbon form the cyclic substituents denoted in the table.

afforded a solution. Removal of solvent in vacuo provided 3-ethylpentanenitrile (7.4 g, 89% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.33 (d, 2H, J=6 Hz), 1.45–1.40 (m, 5H), 0.92 (t, 6H, J=7 Hz). MS (H_2O–GC/MS) m/e 112 (100).

A solution of di-isopropylamine (14.8 g, 20.5 mL, 147 mmol) in anhydrous THF (40 mL) was cooled to −78 °C with stirring under a nitrogen atmosphere. A solution of *n*-butyl lithium in hexanes (1.6 M, 87.5 mL, 140 mmol) was added dropwise over 15 min. The resulting solution was stirred for an additional 30 min. A solution of 3-ethylpentanenitrile (7.4 g, 67 mmol) in THF (30 mL) was added dropwise over 15 min and then the reaction mixture was stirred for 30 min. A solution of ethyl propionate (6.8 g, 7.6 mL, 67 mmol) in THF (20 mL) was added dropwise; then the reaction mixture was warmed with stirring to ambient temperature over 3 h. The mixture was poured onto water (200 mL) and the pH was adjusted to ∼4 by the slow addition of a concentrated HCl solution. Three extractions with ether (100 mL), drying the combined organic layers over $MgSO_4$, filtration and removal of solvent in vacuo provided 4-cyano-5-ethyl-3-heptanone **9**, an oil (9.53 g). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.50 (d, 1H, J=4 Hz), 2.74 (q, 2H, J=7 Hz), 1.85–1.75 (m, 1H), 1.45–1.35 (m, 4H), 1.12 (t, 3H, J=7 Hz), 1.0–0.8 (m, 6H). MS (H_2O–GC/MS) m/e 167 (100).

A mixture of the above intermediate (7.0 g), hydrazine hydrate (2.30 g, 2.23 mL, 46 mmol) and glacial acetic acid (1 mL) in toluene was heated to reflux temperature in a Dean–Stark apparatus and stirred for 16 h. The reaction mixture was cooled to ambient temperature and solvent was removed in vacuo. EtOAc (100 mL) was added to the residue and the resulting solution was washed three times with a saturated $NaHCO_3$ solution (25 mL). The organic solution was dried over $MgSO_4$, filtered and concentrated in vacuo to provide 3-amino-5-ethyl-4-(3-pentyl)pyrazole, an oil (6.7 g, 88% overall yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.53 (q, 2H, J=7 Hz), 1.70–1.50 (m, 5H), 1.20 (t, 3H, J=7 Hz), 0.83 (t, 6H, J=7 Hz). MS (NH_3–CI) m/e 183 (12), 182 (100).

A mixture of 2,4-dichlorobenzamide (1.9 g, 10 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (3.5 g, 3.8 mL, 26 mmol) was heated at 120 °C and stirred under a nitrogen atmosphere for 2 h. After being cooled to room temperature, the reaction mixture was concentrated in vacuo to afford an oil. Medium pressure chromatography on silica gel (EtOAc–hexanes: 1:3 to 1:1), followed by removal of solvent in vacuo afforded

N - (1 - (dimethylamino)ethylidene) - 2,4 - dichlorobenzamide, a solid (2.03 g, 78% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.73 (d, 1H, J=8 Hz), 7.39 (d, 1H, J=2 Hz), 7.24 (dd, 1H, J=8,2 Hz), 3.16 (s, 3H), 3.13 (s, 3H), 2.39 (s, 3H).

Hydrogen sulfide was bubbled through glacial acetic acid (20 mL) for approximately 5 min. *N*-(1-(Dimethylamino)ethylidene)-2,4-dichlorobenzamide was added portionwise over 5 min. Additional hydrogen sulfide was bubbled through the reaction mixture for approximately 10 min. Nitrogen was then bubbled through the reaction mixture to purge the excess H_2S. Dilution with water (25 mL) caused a precipitate to form. The solid was collected by filtration, washed with copious amounts of water and dried in vacuo. *N*-(Thioacetyl)-2,4-dichlorobenzamide, a solid (1.75 g, 90% yield), was used without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.9 (br s, 1H), 7.68 (d, 1H, J=8 Hz), 7.51 (d, 1H, J=2 Hz), 7.40 (dd, 1H, J=8 Hz, 2), 3.10 (s, 3H).

A mixture of *N*-(thioacetyl)-2,4-dichlorobenzamide (200 mg, 0.81 mmol) and 3-amino-5-ethyl-4-(3-pentyl)pyrazole (146 mg, 0.81 mmol) in dioxane (1 mL) was stirred at reflux temperature for 16 h. After being cooled to room temperature, the reaction mixture was concentrated in vacuo. Preparative TLC (EtOAc–hexanes: 1:1) provided the title product (77.3 mg, 24% yield) mp 91–93 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.64 (d, 1H, J=8 Hz), 7.57 (d, 1H, J=2 Hz), 7.44 (dd, 1H, J=8.2), 2.77 (q, 2H, J=8), 2.69 (s, 3H), 2.80–2.60 (m, 1H), 2.00–1.80 (m, 4H), 1.25 (t, 3H, J=8), 0.82 (t, 6H, J=7 Hz). CI-HRMS *m*/*z* calcd: 377.1294, found: 377.1303.

4-(2,4-Dichlorophenyl)-7-ethyl-2-methyl-8-(3-pentyl)-pyrazolo[1,5-*a*]-1,3,5-triazine (4e) (Method B). A mixture of *N*-(thioacetyl)-2,4-dichlorobenzamide (400 mg, 1.6 mmol) and K_2CO_3 (445 mg, 3.22 mmol) in anhydrous acetonitrile (20 mL) was stirred at ambient temperature. Iodomethane (458 mg, 0.2 mL, 3.22 mmol) was added and the reaction mixture was then stirred for 2.5 h. Solvent was removed in vacuo and the residue was partitioned between ether and water. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to give *N*-(1-(methylthio)ethylidene)-2,4-dichlorobenzamide, an oil (406 mg). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86 (d, 1H, J=8 Hz), 7.47 (d, 1H, J=2 Hz), 7.32 (dd, 1H, J=8, 2 Hz), 2.40 (s, 3H), 2.29 (s, 3H).

A mixture of *N*-(1-(methylthio)ethylidene)-2,4-dichlorobenzamide (100 mg, 0.38 mmol) and 3-amino-5-ethyl-4-(3-pentyl)pyrazole (69 mg, 0.38 mmol) in dioxane (1 mL) was stirred at reflux temperature for 2 h. After being cooled to room temperature, the reaction mixture was concentrated in vacuo. Preparative TLC (EtOAc–hexanes: 1:1) provided the title product (68 mg, 47% yield), which was identical to the product obtained by Method A.

4-(2-Chloro-4-methoxyphenyl)-7-ethyl-8-(4-heptyl)-2-methyl - pyrazolo[1,5-*a*]-1,3,5-triazine (4s) (Method C). Ethyl acetimidate hydrochloride (3.20 g, 25.9 mmol) was added to a solution of K_2CO_3 (3.58 g, 25.9 mmol) in H_2O (20 mL) in a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (4×6 mL). The combined organic layers were dried with Na_2SO_4, and filtered through a plug of cotton. The CH_2Cl_2 extract containing the free base was transferred directly into a round bottom flask containing of 3-amino-5-ethyl-4-(4-heptyl)pyrazole **11** (1.77 g, 8.63 mmol). Acetonitrile (5 mL, anhydrous) was added followed by HOAc (0.54 mL, 9.49 mmol) and the mixture was stirred overnight at room temperature. The solid was collected by filtration to give 2.07 g (78% yield) of 3-acetamidino-5-ethyl-4-(4-heptyl)pyrazole acetic acid salt **18** as a white solid, mp 154–156 °C. ^{1}H NMR 300 MHz (D_2O) δ 2.70–2.61 (m, 3H), 2.40 and 2.17 (s, 3H, amidine rotomers), 1.87 (s, 3H), 1.64–1.48 (m, 4H), 1.26–1.14 (m, 7H), 0.86 (t, J=7.3 Hz, 6H). CI-HRMS *m*/*e* 251.2225 [$(M+H)^+$, free base]; calcd for $C_{14}H_{27}N_4$: 251.2236].

To a solution of K_2CO_3 (250 mg, 0.35 mmol) in H_2O (3 mL) in a separatory funnel was added 3-acetamidino-5-ethyl-4-(4-heptyl)pyrazole acetic acid salt **18** (175 mg, 0.565 mmol). The aqueous layer was extracted with CH_2Cl_2 (4×15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the free base (105 mg, 0.419 mmol). This intermediate (105 mg, 0.419 mmol) was dissolved in dioxane (3 mL) and a solution of 2-chloro-4-methoxybenzoyl chloride (112 mg, 0.545 mmol) in dioxane (1 mL) was added via cannula followed by the addition of a catalytic amount of 4-dimethylaminopyridine (5 mg). The mixture was stirred at room temperature for 15 min (turned cloudy then clear) and was subsequently heated at reflux temperature for 15 h. The mixture was cooled to room temperature and concentrated. The residue was purified via preparative TLC (EtOAC–hexanes, 1:3) to give 45 mg (27% yield) of the title compound **4s** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J=8.4 Hz, 1H), 7.07 (d, J=2.5 Hz, 1H), 6.96 (dd, J=8.5, 2.2 Hz, 1H), 3.88 (s, 3H), 2.88–2.81 (m, 1H), 2.77 (q, J=7.7 Hz, 2H), 2.69 (s, 3H), 1.95–1.83 (m, 2H), 1.77–1.66 (m, 2H), 1.31–1.13 (m, 4H), 1.23 (t, J=7.4 Hz, 3H), 0.88 (t, J=7.3 Hz, 6H). Cl-HRMS *m*/*e* 401.2101 [$(M+H)^+$; calcd for $C_{22}H_{30}N_4OCl$: 401.2108].

4-(2,4-Dichlorophenyl)-7-ethyl-8-(4-heptyl)-2-methyl-pyrazolo[1,5-*a*]-1,3,5-triazine (4a). The title compound was prepared according to Method C to give a yellow solid, mp 76–77 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J=8.5 Hz, 1H), 7.57 (d, J=1.8 Hz, 1H), 7.43 (dd, J=8.4, 2.2 Hz, 1H), 2.88–2.78 (m, 1H), 2.77 (q, J=7.4 Hz, 2H), 2.69 (s, 3H), 1.95–1.82 (m, 2H), 1.77–1.66 (m, 2H), 1.31–1.13 (m, 4H), 1.25 (t, J=7.7 Hz, 3H), 0.88 (t, J=7.3 Hz, 6H). Cl-HRMS *m*/*e* 405.1614 [$(M+H)^+$; calcd for $C_{21}H_{27}N_4Cl_2$: 405.1613]. Anal. calcd for $C_{21}H_{26}N_4Cl_2$: C, 62.22; H, 6.48; N, 13.82. Found: C, 62.27; H, 6.36; N, 13.49.

4-(2,4-Dichlorophenyl)-7-ethyl-8-(1-methoxymethylbutyl)-2-methyl-pyrazolo[1,5-*a*]-1,3,5-triazine (4b). The title compound was prepared according to Method C to give a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J=8.1 Hz, 1H), 7.57 (d, J=1.9 Hz, 1H), 7.43 (dd,

$J = 8.4$, 1.9 Hz, 1H), 3.75 (ABq, $J_{AB} = 9.2$ Hz, $\Delta\upsilon = 15.1$ Hz, 2H), 3.35 (s, 3H), 3.19–3.10 (m, 1H), 2.79 (q, $J = 7.4$ Hz, 2H), 2.69 (s, 3H), 1.97–1.77 (m, 2H), 1.28-1.17 (m, 2H), 1.25 (t, $J = 7.3$ Hz, 3H), 0.90 (t, $J = 7.3$ Hz, 3H). Cl-HRMS *m/e* 407.1424 [$(M+H)^+$; calcd for $C_{20}H_{25}N_4OCl_2$: 407.1405]. Anal. calcd for $C_{20}H_{24}N_4OCl_2$: C, 58.97; H, 5.95; N, 13.75. Found: C, 59.11; H, 5.90;N, 13.61.

8-(1-Cyclobutyl-3-methoxypropyl)-4-(2,4-dichlorophenyl)-7-ethyl-2-methyl-pyrazolo[1,5-*a*]-1,3,5-triazine (4c). The title compound was prepared according to Method B to give a yellow amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, $J = 8.1$ Hz, 1H), 7.58 (d, $J = 2.2$ Hz, 1H), 7.4 (dd, $J = 8.4$, 1.8 Hz, 1H), 3.29–3.23 (m, 1H), 3.24 (s, 3H), 3.15–3.07 (m, 1H), 2.98–2.88 (m, 2H), 2.80 (q, $J = 7.7$ Hz, 2H), 2.69 (s, 3H), 2.21–2.14 (m, 1H), 2.13–1.93 (m, 2H), 1.86–1.71 (m, 4H), 1.59–1.45 (m, 1H), 1.27 (t, $J = 7.7$ Hz, 3H). CI-HRMS *m/e* 433.1583 [$(M+H)^+$; calcd for $C_{22}H_{27}N_4OCl_2$: 433.1562]. Anal. calcd for $C_{22}H_{26}N_4OCl_2$: C, 60.97; H, 6.06; N, 12.93. Found: C, 60.84; H, 5.84; N, 12.66.

8-(2-Pentyl)-4-(2,4-dichlorophenyl)-7-ethyl-2-methyl-pyrazolo[1,5-*a*]-1,3,5-triazine (4d). The title compound was prepared according to Method B to give a yellow amorphous solid, mp 80–82 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, $J = 8.4$ Hz, 1H), 7.57 (d, $J = 1.9$ Hz, 1H), 7.43 (dd, $J = 8.4$, 1.9 Hz, 1H), 3.08–2.88 (m, 1H), 2.78 (q, $J = 7.7$ Hz, 2H), 2.70 (s, 3H), 1.95–1.85 (m, 1H), 1.76–1.71 (m, 1H), 1.40 (d, $J = 7.0$ Hz, 3H), 1.25 (t, $J = 7.7$ Hz, 3H), 1.30–1.20 (m, 2H), 0.90 (t, $J = 7.3$ Hz, 3H). CI-HRMS *m/e* 377.1326 [M^+; calcd for $C_{19}H_{23}N_4Cl_2$: 377.1300].

4-(2,4-Dichlorophenyl)-7-ethyl-8-[3-methoxy-1-(tetrahydrofuran-3-yl)-propyl]-2-methyl-pyrazolo[1,5-*a*]-1,3,5-triazine (4f and **4g)**. The title compound was prepared according to Method B to give a mixture of diastereomers which were separated by HPLC (35% ethyl acetate in hexanes, 21 mm silica column, 15 mL/min flow rate).

Data for **4f**: $t_R = 24.4$ min; yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, $J = 8.1$ Hz, 1H), 7.58 (d, $J = 2.2$ Hz, 1H), 7.45 (dd, $J = 8.3$, 2.0 Hz, 1H), 3.98–3.91 (m, 1H), 3.86–3.78 (m, 1H), 3.55 (t, $J = 8.0$ Hz, 1H), 3.29–3.25 (m, 1H), 3.23 (s, 3H), 3.12–3.01 (m, 2H), 2.92–2.84 (m, 1H), 2.78 (q, $J = 7.5$ Hz, 2H), 2.69 (s, 3H), 2.29–2.13 (m, 3H), 1.79–1.69 (m, 2H), 1.26 (t, $J = 7.7$ Hz, 3H). Cl-HRMS *m*/e 449.1523 [$(M+H)^+$; calcd for $C_{22}H_{27}N_4O_2Cl_2$: 449.1511].

Data for **4g**: $t_R = 27.8$ min; yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, $J = 8.1$ Hz, 1H), 7.58 (d, $J = 1.8$ Hz, 1H), 7.45 (dd, $J = 8.5$, 2.2 Hz, 1H), 4.12 (t, $J = 8.0$ Hz, 1H), 3.83–3.78 (m, 1H), 3.70 (q, $J = 6.9$ Hz, 1H), 3.58 (t, $J = 8.0$ Hz, 1H), 3.25–3.20 (m, 1H), 3.22 (s, 3H), 3.08–3.00 (m, 2H), 2.94–2.86 (m, 1H), 2.79 (q, $J = 7.7$ Hz, 2H), 2.70 (s, 3H), 2.33–2.21 (m, 1H), 1.98–1.87 (m, 1H), 1.75–1.65 (m, 1H), 1.50–1.40 (m, 1H), 1.27 (t, $J = 7.7$ Hz, 3H). Cl-HRMS *m/e* 449.1529 [$(M+H)^+$; calcd for $C_{22}H_{27}N_4O_2Cl_2$: 449.1511].

4-(2,4-Dichlorophenyl)-7-ethyl-2-methyl-8-(tetrahydro-4-pyranyl)-pyrazolo[1,5-*a*]-1,3,5-triazine (4h). The title compound was prepared according to Method B to give a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, $J = 8.4$ Hz, 1H), 7.57 (d, $J = 1.8$ Hz, 1H), 7.43 (dd, $J = 8.4$, 1.8 Hz, 1H), 4.15–4.05 (m, 1H), 3.60–3.53 (m, 2H), 3.06–2.98 (m, 2H), 2.82 (q, $J = 7.7$ Hz, 2H), 2.70 (s, 3H), 2.47–2.37 (m, 2H), 1.71–1.61 (m, 2H), 1.26 (d, $J = 7.5$ Hz, 3H). CI-HRMS *m/e* 391.1097 [$(M+H)^+$; calcd for $C_{19}H_{21}N_4OCl_2$: 391.1092].

8-(Cyclopentyl)-4-(2,4-dichlorophenyl)-7-ethyl-2-methyl-pyrazolo[1,5-*a*]-1,3,5-triazine (4i). The title compound was prepared according to Method B to give a yellow amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, $J = 8.0$ Hz, 1H), 7.57 (d, $J = 1.9$ Hz, 1H), 7.43 (dd, $J = 8.4$, 1.8 Hz, 1H), 3.20–2.10 (m, 1H), 2.80 (q, $J = 7.7$ Hz, 2H), 2.69 (s, 3H), 1.95–1.85 (m, 6H), 1.75–1.65 (m, 2H), 1.25 (t, $J = 7.7$ Hz, 3H).

4-(2-Choro-4,5-dimethoxyphenyl)-7-ethyl-8-(4-heptyl)-2-methyl-pyrazolo[1,5-*a*]-1,3,5-triazine (4j). The title compound was prepared according to Method C to give a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.01 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 2.88–2.83 (m, 1H), 2.79 (q, $J = 7.7$ Hz, 2H), 2.70 (s, 3H), 1.96–1.83 (m, 2H), 1.77–1.66 (m, 2H), 1.32–1.13 (m, 4H), 1.27 (t, $J = 7.3$ Hz, 3H), 0.88 (t, $J = 7.3$ Hz, 6H). Cl-HRMS *m/e* 431.2213 [$(M+H)^+$; calcd for $C_{23}H_{32}N_4O_2Cl$: 431.2214].

4-(2-Chloro-4,5-dimethoxyphenyl)-7-ethyl-8-(1-methoxymethylbutyl)-2-methyl-pyrazolo[1,5-*a*]-1,3,5-triazine (4k). The title compound was prepared according to Method C to give a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (s, 1H), 7.01 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.76 (dd, $J = 7.3$, 1.8 Hz, 2H), 3.36 (s, 3H), 3.21–3.10 (m, 1H), 2.81 (q, $J = 7.7$ Hz, 2H), 2.70 (s, 3H), 1.97–1.77 (m, 2H), 1.30–1.18 (m, 2H), 1.28 (t, $J = 7.7$ Hz, 3H), 0.90 (t, $J = 7.3$ Hz, 3H). Cl-HRMS *m/e* 433.2027 [$(M+H)^+$; calcd for $C_{22}H_{30}N_4O_3Cl$: 433.2006]. Anal. calcd for $C_{22}H_{30}N_4O_3Cl$: C, 61.03; H, 6.75; N, 12.94. Found: C, 61.10; H, 6.75; N, 12.98.

4-(2-Chloro-4,5-dimethoxyphenyl)-7-ethyl-2-methyl-8-(1-methylbutyl)-pyrazolo[1,5-*a*]-1,3,5-triazine (4l). The title compound was prepared according to Method C to give an amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.01 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.04–2.96 (m, 1H), 2.80 (q, $J = 7.6$ Hz, 2H), 2.70 (s, 3H), 1.94–1.67 (m, 2H), 1.41 (d, $J = 7.0$ Hz, 3H), 1.41–1.12 (m, 2H), 1.27 (t, $J = 7.5$ Hz, 3H), 0.91 (t, $J = 7.4$ Hz, 3H). Cl-HRMS *m/e* 403.1894 [$(M+H)^+$; calcd for $C_{21}H_{28}N_4O_2Cl$: 403.1901]. Anal. calcd for $C_{21}H_{27}N_4O_2Cl$: C, 62.60; H, 6.75; N, 13.91. Found: C, 62.36; H, 6.89; N, 13.68.

4-(2-Chloro-4,5-dimethoxyphenyl)-8-(1-cyclobutyl-3-methoxypropyl)-7-ethyl-2-methyl-pyrazolo[1,5-*a*]-1,3,5-triazine (4m). The title compound was prepared according to Method B to give a yellow amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.01 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.29–3.23 (m, 1H), 3.25 (s,

3H), 3.16–3.08 (m, 1H), 3.01–2.89 (m, 2H), 2.80 (q, $J=7.7$ Hz, 2H), 2.69 (s, 3H), 2.22–2.15 (m, 1H), 2.13–1.94 (m, 2H), 1.87–1.67 (m, 4H), 1.63–1.48 (m, 1H), 1.29 (t, $J=7.3$ Hz, 3H). Cl-HRMS *m/e* 459.2172 [$(M+H)^+$; calcd for $C_{24}H_{32}N_4O_3Cl$: 459.2163]. Anal. calcd for $C_{24}H_{31}N_4O_3Cl$: C, 62.80; H, 6.82; N, 12.21. Found: C, 62.80; H, 6.73; N, 11.53.

4-(2-Chloro-4,5-dimethoxyphenyl)-7-ethyl-2-methyl-8-(3-pentyl)-pyrazolo[1,5-*a*]-1,3,5-triazine (4n). The title compound was prepared according to Method B to give a solid, mp 103.5–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.01 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 2.79 (q, $J=7.6$ Hz, 2H), 2.70 (s, 3H), 2.71–2.60 (m, 1H), 2.00–1.77 (m, 4H), 1.27 (t, $J=7.7$ Hz, 3H), 0.83 (t, $J=7.4$ Hz, 6H). Cl-HRMS *m/e* 403.1902 [$(M+H)^+$; calcd for $C_{21}H_{28}N_4O_2Cl$: 403.1901].

4-(2-Chloro-4,5-dimethoxyphenyl)-8-(cyclopentyl)-7-ethyl-2-methyl-pyrazolo[1,5-*a*]-1,3,5-triazine (4o). The title compound was prepared according to Method B to give a yellow amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (s, 1H), 7.01 (s, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.17 (m, 1H), 2.81 (q, $J=7.7$ Hz, 2H), 2.70 (s, 3H), 2.05–1.95 (m, 4H), 1.75–1.65 (m, 4H), 1.27 (t, $J=7.5$ Hz, 3H). CI-HRMS *m/e* 401.1746 [$(M+H)^+$; calcd for $C_{21}H_{26}N_4O_2Cl$: 401.1744].

4-(2-Chloro-4,5-dimethoxyphenyl)-7-ethyl-8-[3-methoxy-1-(tetrahydrofuran-3-yl)-propyl]-2-methyl-pyrazolo[1,5-*a*]-1,3,5-triazine (4p). The title compound was prepared according to Method B as a mixture of diastereomers which was isolated by HPLC (50% ethyl acetate in hexanes, 21 mm silica column, 15 mL/min flow rate).

Data for **4p**: $t_R=29.7$ min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (s, 1H), 7.02 (s, 1H), 3.95 (s, 3H), 3.52 (s, 3H), 3.82 (q, $J=6.9$ Hz, 1H), 3.56 (t, $J=8.0$ Hz, 1H), 3.46–3.42 (m, 1H), 3.33–3.24 (m, 1H), 3.24 (s, 3H), 3.10–3.03 (m, 2H), 2.93–2.84 (m, 1H), 2.79 (q, $J=7.7$ Hz, 2H), 2.70 (s, 3H), 2.27–2.10 (m, 4H), 1.73 (dd, $J=12.1$, 8.4 Hz, 1H), 1.28 (t, $J=7.7$ Hz, 3H). $t_R=31.2$ min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (s, 1H), 7.02 (s, 1H), 4.12 (t, $J=8.0$ Hz, 1H), 3.96 (s, 3H), 3.92 (s, 3H), 3.83–3.80 (m, 1H), 3.70 (q, $J=8.1$ Hz, 1H), 3.58–3.55 (m, 1H), 3.22 (s, 3H), 3.09–3.03 (m, 2H), 2.94–2.86 (m, 1H), 2.81 (q, $J=7.7$ Hz, 2H), 2.70 (s, 3H), 2.30–2.22 (m, 1H), 1.96–1.88 (m, 1H), 1.78–1.69 (m, 2H), 1.49–1.42 (m, 1H), 1.30–1.25 (m, 3H). Cl-HRMS *m/e* 475.2093 [$(M+H)^+$; calcd for $C_{24}H_{32}N_4O_4Cl$: 475.2112]. Anal. calcd for $C_{24}H_{31}N_4O_4Cl$: C, 60.69; H, 6.59; N, 11.80. Found: C, 60.50; H, 6.33; N, 11.55.

4-(2-Chloro-4,5-dimethoxyphenyl)-8-(cyclobutyl)-7-ethyl-2-methyl-pyrazolo[1,5-*a*]-1,3,5-triazine (4q). The title compound was prepared according to Method B to give a yellow amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (s, 1H), 7.00 (s, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.71–3.61 (m, 1H), 2.80 (q, $J=7.7$ Hz, 2H), 2.72 (s, 3H), 2.75–2.65 (m, 2H), 2.35–2.25 (m, 2H), 2.05–1.95 (m, 2H), 1.25 (t, $J=7.5$ Hz, 3H). CI-HRMS *m/e* 387.1600 [$(M+H)^+$; calcd for $C_{20}H_{24}N_4O_2Cl$: 387.1588].

4-(2-Chloro-4,5-dimethoxyphenyl)-7-ethyl-2-methyl-8-(tetrahydro-4-pyranyl)-pyrazolo[1,5-*a*]-1,3,5-triazine (4r). The title compound was prepared according to Method B to give a yellow amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (s, 1H), 7.00 (s, 1H), 4.15–4.07 (m, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.61–3.53 (m, 2H), 3.07-2.97 (m, 1H), 2.84 (q, $J=7.7$ Hz, 2H), 2.71 (s, 3H), 2.45–2.41 (m, 2H), 1.75–1.63 (m, 2H), 1.28 (t, $J=7.5$ Hz, 3H). CI-HRMS *m/e* 417.1695 [$(M+H)^+$; calcd for $C_{21}H_{26}N_4O_3Cl$: 417.1693].

4-(2-Chloro-4-methoxyphenyl)-7-ethyl-8-(1-methoxymethylbutyl)-2-methyl-pyrazolo[1,5-*a*]-1,3,5-triazine (4t). The title compound was prepared according to Method C to give a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, $J=8.8$ Hz, 1H), 7.07 (d, $J=2.2$ Hz, 1H), 6.96 (dd, $J=8.8$, 2.2 Hz, 1H), 3.88 (s, 3H), 3.75 (d, $J=7.3$ Hz, 2H), 3.35 (s, 3H), 3.19–3.09 (m, 1H), 2.79 (q, $J=7.3$ Hz, 2H), 2.68 (s, 3H), 1.96–1.77 (m, 2H), 1.29–1.17 (m, 2H), 1.26 (t, $J=7.7$ Hz, 3H), 0.89 (t, $J=6.9$ Hz, 3H). Cl-HRMS *m/e* 402.1818 [M^+; calcd for $C_{21}H_{27}N_4O_2Cl$: 402.1823]. Anal. calcd for $C_{21}H_{26}N_4O_2Cl$: C, 62.60; H, 6.75; N, 13.91. Found: C, 62.43; H, 6.81; N, 13.77.

4-(2-Chloro-4-ethoxyphenyl)-7-ethyl-8-(4-heptyl)-2-methyl-pyrazolo[1,5-*a*]-1,3,5-triazine (4u). The title compound was prepared according to Method C to give a yellow solid, mp 86–87 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, $J=8.8$ Hz, 1H), 7.06 (d, $J=2.5$ Hz, 1H), 6.94 (dd, $J=8.8$, 2.5 Hz, 1H), 4.10 (q, $J=7.0$ Hz, 2H), 2.89–2.81 (m, 1H), 2.77 (q, $J=7.7$ Hz, 2H), 2.69 (s, 3H), 1.95–1.83 (m, 2H), 1.77–1.72 (m, 2H), 1.45 (t, $J=6.9$ Hz, 3H), 1.31–1.12 (m, 4H), 1.26 (t, $J=7.7$ Hz, 3H), 0.88 (t, $J=7.4$ Hz, 6H). Cl-HRMS *m/e* 415.2277 [$(M+H)^+$; calcd for $C_{23}H_{32}N_4OCl$: 415.2256]. Anal. calcd for $C_{23}H_{31}N_4OCl$: C, 66.57; H, 7.54; N, 13.50. Found: C, 66.73; H, 7.66; N, 13.44.

4-(2-Chloro-5-fluoro-4-methoxyphenyl)-7-ethyl-8-(1-methoxymethylbutyl)-2-methyl-pyrazolo[1,5-*a*]-1,3,5-triazine (4v). The title compound was prepared according to Method C to give a yellow solid, mp 122–123 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, $J=11.0$ Hz, 1H), 7.11 (d, $J=7.3$ Hz, 1H), 3.96 (s, 3H), 3.75 (d, $J=7.4$ Hz, 2H), 3.35 (s, 3H), 3.19–3.09 (m, 1H), 2.80 (q, $J=7.7$ Hz, 2H), 2.69 (s, 3H), 1.97–1.77 (m, 2H), 1.30–1.17 (m, 2H), 1.27 (t, $J=7.7$ Hz, 3H), 0.90 (t, $J=7.4$ Hz, 3H). Cl-HRMS *m/e* 421.1798 [$(M+H)^+$; calcd for $C_{21}H_{27}N_4O_2ClF$: 412.1806]. Anal. calcd for $C_{21}H_{26}N_4O_2ClF$: C, 59.92; H, 6.24; N, 13.31. Found: C, 59.84; H, 6.20; N, 13.28.

4-(2-Chloro-5-fluoro-4-methoxyphenyl)-8-(1-cyclobutyl-3-methoxypropyl)-7-ethyl-2-methyl-pyrazolo[1,5-a]-1,3,5-triazine (4w). The title compound was prepared according to Method B to give a yellow amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, $J=10.6$ Hz, 1H), 7.12 (d, $J=7.3$ Hz, 1H), 3.97 (s, 3H), 3.29–3.23 (m, 1H), 3.25 (s, 3H), 3.15–3.06 (m, 1H), 3.00–2.89 (m, 2H), 2.82 (q, $J=7.7$ Hz, 2H), 2.69 (s, 3H), 2.22–2.15 (m, 1H), 2.14–1.92 (m, 2H), 1.60–1.46 (m, 1H), 1.86-1.65 (m, 4H), 1.29 (t, $J=7.3$ Hz, 3H). Cl-HRMS *m/e* 447.1957 [$(M+H)^+$; calcd for $C_{23}H_{29}N_4O_2ClF$: 447.1963]. Anal.

calcd for $C_{23}H_{28}N_4O_2ClF$: C, 61.81; H, 6.31; N, 12.54. Found: C, 61.55; H, 6.12; N, 11.96.

4-(2-Chloro-5-fluoro-4-methoxyphenyl)-7-ethyl-8-[3-methoxy-1-(tetrahydrofuran-3-yl)-propyl]-2-methyl-pyrazolo[1,5-*a*]-1,3,5-triazine (4x). The title compound was prepared according to Method B to give a mixture of diasteriomers which were separated by HPLC (40% ethyl acetate in hexanes, 21 mm silica column, 15 mL/min flow rate, $t_R = 19.9$ min and 22.2 min).

Data for **4x**: $t_R = 19.9$ min; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, $J = 10.9$ Hz, 1H), 7.12 (d, $J = 7.4$ Hz, 1H), 3.97 (s, 3H), 3.95–3.86 (m, 1H), 3.84–3.78 (m, 1H), 3.56 (t, $J = 7.9$ Hz, 1H), 3.29–3.25 (m, 1H), 3.23 (s, 3H), 3.12–3.01 (m, 2H), 2.92–2.84 (m, 1H), 2.79 (q, $J = 7.5$ Hz, 2H), 2.69 (s, 3H), 2.29–2.11 (m, 3H), 1.79–1.66 (m, 2H), 1.28 (t, $J = 7.6$ Hz, 3H). Cl-HRMS *m/e* 463.1937 [$(M+H)^+$; calcd for $C_{23}H_{29}N_4O_3ClF$: 463.1912].

4-(2,4-dimethoxyphenyl)-7-ethyl-8-(4-heptyl)-2-methyl-pyrazolo[1,5-a]-1,3,5-triazine (4y). The title compound was prepared according to Method C to give a yellow solid, mp = 87–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, $J = 8.4$ Hz, 1H), 6.63 (dd, $J = 8.4$, 2.2 Hz, 1H), 6.60 (d, $J = 2.6$ Hz, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 2.87–2.79 (m, 1H), 2.76 (q, $J = 7.7$ Hz, 2H), 2.67 (s, 3H), 1.95–1.82 (m, 2H), 1.76–1.65 (m, 2H), 1.31–1.13 (m, 4H), 1.25 (t, $J = 7.7$ Hz, 3H), 0.87 (t, $J = 7.3$ Hz, 6H). Cl-HRMS *m/e* 397.2608 [$(M+H)^+$; calcd for $C_{23}H_{33}N_4O_2$: 397.2604]. Anal. calcd for $C_{23}H_{32}N_4O_2$: C, 69.67; H, 8.13; N, 14.13. Found: C, 69.47; H, 8.33; N, 13.96.

5-Ethyl-4-(1-methoxymethylbutyl)-2*H*-pyrazol-3-ylamine (11). A solution of methoxyacetic acid (14.0 g, 155 mmol) in CH_2Cl_2 (400 mL) was treated with triethylamine (40 mL) and *N*,*O*-dimethoxyhydroxylamine (18.20 g, 187 mmol). After stirring 5 min, the solution was cooled to 0 °C. EDC (32.80 g, 171 mmol) was added and the reaction mixture was stirred overnight while allowing the reaction mixture to warm to room temperature. The mixture was diluted with CH_2Cl_2 (400 mL) and was transferred to a separatory funnel. The organic layer was washed with 1 N HCl (2×200 mL), saturated $NaHCO_3$ (2×200 mL), water (1×200 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated to afford 2,*N*-dimethoxy-*N*-methylacetamide **6** (12.85 g, 62% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.23 (s, 2H), 3.70 (s, 3H), 3.47 (s, 3H), 3.20 (s, 3H). MS (NH_3-CI) *m/e* 134.1 [$(M+H)^+$; calcd for $C_5H_{12}NO_3$: 134.1].

Propylmagnesium chloride (36.0 mL, 72.1 mmol, 2 M) was added dropwise to a solution of 2,*N*-dimethoxy-*N*-methylacetamide (8.0 g, 60.08 mmol) in diethyl ether (440 mL) while maintaining the temperature below 8 °C. After the addition was complete, the reaction mixture was stirred at 0 °C for 30 min. The cooling bath was removed and the reaction mixture was stirred for an additional 45 min while allowing it to warm to room temperature. The reaction mixture was then cooled to 0 °C and was quenched by the slow addition of 1 N HCl (200 mL). The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with ether (3×150 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to afford 1-methoxypentan-2-one **7** (6.45 g, 93% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.02 (s, 2H), 3.42 (s, 3H), 2.42 (t, $J = 7.3$ Hz, 2H), 1.63 (sextet, $J = 7.4$ Hz, 2H), 0.94 (t, $J = 7.3$ Hz, 3H). GC/MS *m/e* 116.0 [M^+; calcd for $C_6H_{12}O_2$: 134.1].

NaH (3.37 g, 83.4 mmol, 60% in mineral oil) was added to a three-necked round-bottom flask equipped with an addition funnel. THF was added to the flask and the suspension was cooled to 0 °C. Diethyl cyanomethylphosphonate (15.8 mL, 89 mmol) was added dropwise while maintaining the temperature between 0 and 5 °C. After the addition was complete (reaction mixture turned colorless), the mixture was stirred at 0 °C for 1 h. 1-Methoxypentan-2-one (6.45 g, 55.6 mmol) in THF (100 mL) was added slowly via an addition funnel and the reaction mixture was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and was poured into a separatory funnel containing saturated NH_4Cl (150 mL). The aqueous layer was extracted with EtOAc (3×150 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (10% EtOAc in hexanes) to furnish 3-methoxymethyl-hex-2-enenitrile **8** (7.10 g, 92% yield) as a mixture of E and Z isomers as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.48 (t, $J = 2.0$ Hz, 1H, major), 5.26 (s, 1H, minor), 4.20 (s, 2H, minor), 3.96 (d, $J = 1.8$ Hz, 2H, major), 3.39 (s, 3H, major), 3.37 (s, 3H, minor), 2.35 (t, $J = 7.7$ Hz, 2H, major), 2.25 (t, $J = 7.7$ Hz, 2H, minor), 1.59–1.45 (m, 2H), 0.98 (t, $J = 7.4$ Hz, major), 0.95 (t, $J = 7.4$ Hz, 3H, minor). GC/MS *m/e* 139.0 [M^+; calcd for $C_8H_{13}NO$: 139.1].

A solution of 3-methoxymethyl-hex-2-enenitrile (7.0 g, 50.3 mmol) in methanol (310 mL) was treated with 10% Pd/C as a slurry in cold (−78 °C) isopropanol with a stream of nitrogen passing over the reaction mixture. The reaction mixture was evacuated and filled with N_2 (3×) and then H_2 (3×) and was stirred overnight at room temperature. The reaction mixture was placed under a N_2 atmosphere and was filtered through a pad of Celite. The filtrate was concentrated to give 3-methoxymethyl-hexanenitrile **9** (4.85 g, 68% yield) as a colorless oil which was used directly in the next step. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.42 (1/2 ABX, $J_{AB} = 9.6$ Hz, $J_{AX} = 4.4$ Hz, 1H), 3.35 (s, 3H), 3.27 (1/2 ABX $J_{BA} = 9.5$ Hz, $J_{BX} = 7.7$ Hz, 1H), 2.45 (d, $J = 5.9$ Hz, 2H), 2.03–1.93 (m, 1H), 1.43–1.33 (m, 4H), 0.93 (t, $J = 6.9$ Hz, 3H).

To a dried 200 mL round bottom flask containing a solution of THF (36 mL) and *i*-Pr_2NH (10.5 mL, 75.2 mmol) at −78 °C was added dropwise *n*-BuLi (28.7 mL, 71.8 mmol, 2.5 M in hexanes). The mixture was warmed to 0 °C and stirred at 0 °C for 30 min then cooled to −78 °C. 3-Methoxymethylhexanenitrile (4.85 g, 34.2 mmol) in THF (10 mL) was added dropwise via cannula.

The mixture was stirred at −78 °C for 30 min then ethyl propionate (3.92 mL, 34.2 mmol) in THF (3 mL) was added dropwise via cannula. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and was stirred for 4 h. The reaction mixture was transferred to a separatory funnel containing H_2O (100 mL). The layers were separated and the organic layer was extracted with H_2O (4×50 mL). The combined aqueous layers were placed in an ice bath and acidified to pH 4 with concentrated HCl. The aqueous layer was transferred to a separatory funnel and was extracted with ether (4×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to afford 3-methoxymethyl-2-propionylhexanenitrile **10** (5.85 g, 87% yield) as a colorless oil which was used directly in the next step. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.21–4.15 (m, 1H, major), 3.84 (d, J = 4.4 Hz, 1H, minor), 3.52–3.20 (m, 2H), 3.33 (s, 3H, minor), 3.25 (s, 3H, major), 2.88–2.44 (m, 3H), 1.44–1.18 (m, 4H), 1.12 (t, J = 7.3 Hz, 3H, minor), 1.09 (t, J = 7.3 Hz, 3H, major), 0.96–0.88 (m, 3H). GC/MS m/e 197.0 [M^+; calcd for $C_{11}H_{19}NO_2$: 197.1].

Acetic acid (6.52 mL) was added to a solution of 3-methoxymethyl-2-propionylhexanenitrile (5.61 g, 28.7 mmol) and $NH_2NH_2{\cdot}H_2O$ (3.17 mL, 65.3 mmol) in toluene (170 mL) in a flask equipped with a Dean–Stark trap. The solution was heated at reflux overnight. The mixture was cooled to room temperature and concentrated. The residue was dissolved in 1 N HCl (100 mL) and was washed with ether–hexane (1:1, 2×80 mL) then brought to pH 11 with concd NH_4OH (some cooling was required). The solution was extracted with EtOAc (3×80 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to furnish 5-ethyl-4-(1-methoxymethylbutyl)-2*H*-pyrazol-3-ylamine **11** (4.30 g, 72% yield) as a tan oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.56 (1/2 ABX, J_{AB} = 8.8 Hz, J_{AX} = 4.4 Hz, 1H), 3.49 (1/2 ABX, J_{BA} = 8.8 Hz, J_{BX} = 4.4 Hz, 1H), 3.34 (s, 3H), 3.0 (br s, 2H), 2.67–2.58 (m, 1H), 2.53 (q, J = 7.3 Hz, 2H), 1.90 (br s, 1H), 1.75–1.60 (m,2H), 1.31–1.17 (m, 2H), 1.19 (t, J = 7.7 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H). MS (NH_3-CI) m/e 212.2 [$(M+H)^+$; calcd for $C_{11}H_{22}N_3O$: 212.2].

3-Propylhexanenitrile. NaH (3.26 g, 81.5 mmol, 60% in mineral oil) was added to a three-necked round-bottom flask equipped with an addition funnel. THF was added to the flask and the suspension was cooled to 0 °C. Diethyl cyanomethylphosphonate (14.2 mL, 87.3 mmol) was added dropwise while maintaining the temperature between 0 and 5 °C. After the addition was complete (reaction mixture turned colorless), the mixture was stirred at 0 °C for 1 h. 1-Dicyclopropylketone (6.14 g, 54.5 mmol) in THF (120 mL) was added slowly via an addition funnel and the reaction mixture was heated at reflux for 2.5 h. The reaction mixture was cooled to room temperature and was poured into a separatory funnel containing saturated NH_4Cl (150 mL). The aqueous layer was extracted with EtOAc (3×150 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (10% EtOAc in hexanes) to furnish 3,3-dicyclopropylacrylonitrile **8** (6.83 g, 95% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.79 (d, J = 0.70 Hz, 1H), 2.24–2.15 (m, 1H), 1.03–0.94 (m, 5H), 0.85–0.79 (m, 2H), 0.58–0.52 (m, 2H). GC/MS m/e 134.0 [M^+; calcd for $C_9H_{12}N$: 134.0].

A solution of 3,3-dicyclopropylacrylonitrile (4.90 g, 36.8 mmol) in methanol (230 mL) was treated with 10% Pd/C as a slurry in cold (−78 °C) isopropanol with a stream of nitrogen passing over the reaction mixture. The reaction mixture was evacuated and filled with N_2 (3×) and then H_2 (3×) and was stirred overnight at room temperature. The reaction mixture was placed under a N_2 atmosphere and was filtered through a pad of Celite. The filtrate was concentrated to give 3-propylhexanenitrile **9** (4.23 g, 85% yield) as a colorless oil which was used directly in the next step. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.32 (d, J = 5.9 Hz, 2H), 1.74–1.68 (m,1H), 1.44–1.23 (m, 8H), 0.94–0.87 (m, 6H).

1-Cyclobutyl-3-methoxypropan-1-one. To a solution of cyclobutanecarboxylic acid *N*-methoxy-*N*-methyl amide (10.02 g, 70.0 mmol) in THF (200 mL) at −78 °C was added vinylmagnesium bromide (73.5 mL, 73.5 mmol, 1 M in THF) dropwise. The reaction mixture was stirred at −78 °C for 45 min and was subsequently treated with anhydrous methanol (130 mL) followed by concd H_2SO_4 (10.1 mL, 189 mmol). The cooling bath was removed and the reaction mixture was stirred at room temperature overnight. Saturated $NaHCO_3$ (170 mL) was added slowly and the precipitate was removed by filtration through a pad of Celite. The organic solvents were removed under reduced pressure. The aqueous portion was diluted with additional saturated $NaHCO_3$ (200 mL) and was extracted with CH_2Cl_2 (3×200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (20% ether in hexanes) to afford 1-cyclobutyl-3-methoxypropan-1-one **7** (3.22 g, 32% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.64 (t, J = 6.2 Hz, 2H), 3.33 (s, 3H), 3.28 (t, J = 7.7 Hz, 1H), 2.61 (t, J = 6.2 Hz, 2H), 2.28–2.10 (m, 4H), 2.08–1.73 (m, 2H).

Tetrahydrofuran-3-carboxylic acid. A solution of 3-furoic acid (2.0 g, 17.8 mmol) in 3% NaOH solution (25 mL) was treated with Raney–Ni (4.0 g, 50% dispersion in H_2O) and subjected to hydrogenation at room temperature for 78 h at 50 psi. After removal of the catalyst, the solution was acidified with 1 N HCl and was extracted with ether (4×50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to provide tetrahydrofuran-3-carboxylic acid 5 (1.2 g, 58% yield) a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.00 (d, J = 6.9 Hz, 2H), 3.99–3.80 (m, 2H), 3.22–3.09 (m, 1H), 2.31–2.11 (m, 2H).

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