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Discovery of ((*S*)-5-(Methoxymethyl)-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone As a Potent and Selective I_{Kur} Inhibitor

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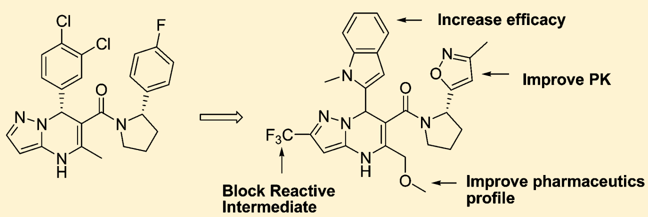
Ⓢ *Supporting Information*

ABSTRACT: Previously disclosed dihydropyrazolopyrimidines are potent and selective blockers of I_{Kur} current. A potential liability with this chemotype is the formation of a reactive metabolite which demonstrated covalent binding to protein in vitro. When substituted at the 2 or 3 position, this template yielded potent I_{Kur} inhibitors, with selectivity over *h*ERG which did not form reactive metabolites. Subsequent optimization for potency and PK properties lead to the discovery of ((*S*)-5-(methoxymethyl)-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)-((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone (**13j**), with an acceptable PK profile in preclinical species and potent efficacy in the preclinical rabbit atrial effective refractory period (AERP) model.



■ INTRODUCTION

Atrial fibrillation (AF) is a condition in which the normal heart rhythm is disrupted by rapid activity in areas of the atria. AF is the most common form of sustained cardiac arrhythmia, and the prevalence is increasing as the population continues to age.[1] AF is projected to affect an estimated 5.6 million patients in the US by 2050.[2] In addition to significantly affecting quality of life, AF is also associated with a 3-fold higher incidence of stroke and a 2-fold increase in mortality.[3] Current therapies for treatment of AF include antithrombotic, rate control, or rhythm control. The termination of AF and restoring of normal sinus rhythm (rhythm control) is typically achieved with antiarrhythmic drugs.[4] Currently available antiarrhythmic drugs target ion channels which are expressed in the human atrium and ventricle, for example, amiodarone/dronedarone,[5] dofetilide,[6] flecainide,[7] and sotalol.[8] Inhibition of ventricular ion channels can lead to prolongation of ventricular effective refractory period and the potentially life threatening arrhythmia torsades de pointe.[9] Initial administration of nonselective rhythm control drugs is, therefore, often limited to a hospital setting where monitoring of ventricular effects are required. Thus, there is currently an unmet medical need for safe and efficacious treatment of AF.

I_{Kur} is a delayed rectifier repolarization potassium current encoded by the $K_v1.5$ gene in humans[10] which is functionally expressed in the human atrium and not in the ventricle. Selective inhibition of I_{Kur} leads to a prolongation in effective refractory period and should terminate AF without being proarrhythmic in the ventricle, leading to a potentially safer treatment for patients with AF.[11]

We have disclosed dihydropyrazolopyrimidines **1**, **2**, and **3** as potent and selective blockers of I_{Kur} (Figure 1).[12−14] Substitution at C7 indicated that a 2,3-dichloro or 3,4-dichloro aryl group was preferred to maintain potency and selectivity for $K_v1.5$. Metabolite identification studies on compounds **1** and **2** established the major routes of hepatic clearance as hydroxylation and aromatization of the dihydropyrazolopyrimidine core. Significantly, in the course of in vitro metabolite identification studies, the formation of covalently bound glutathione (GSH) adducts were observed when these compounds were incubated with liver microsomes in the presence of GSH. The formation of a reactive metabolite was confirmed when the covalently bound protein adduct of radio-labeled compound **2** was subsequently identified.[15] This was of concern as compounds which form reactive intermediates, (for example, those containing unsubstituted thiophenes)[16] and which irreversibly bind to protein in the liver can be hepatotoxic and have the additional liability of potential idiosyncratic toxicity when administered to a diverse patient population.[17] The site of

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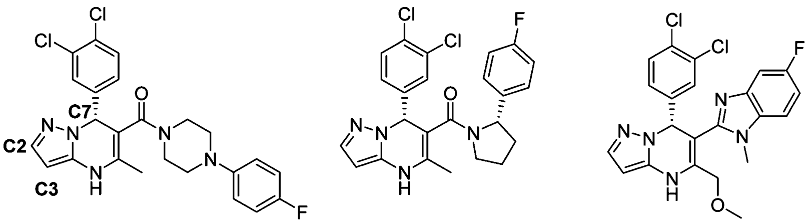
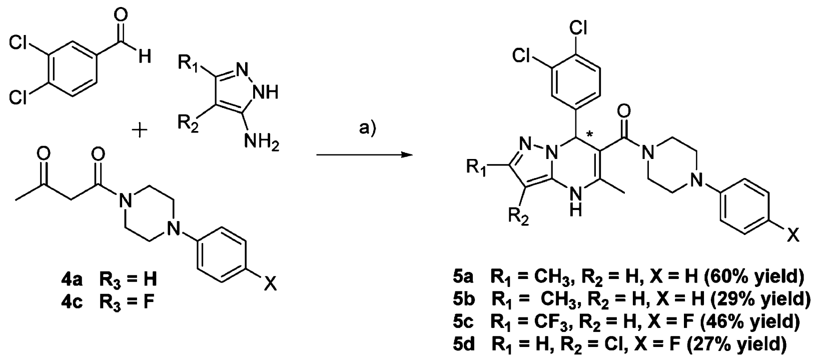


1 K_v 1.5 IC_{50}: 0.07 μM
2 K_v 1.5 IC_{50}: 0.05 μM
3 K_v 1.5 IC_{50}: 0.03 μM

Figure 1. Dihydropyrazolopyrimidines which form reactive intermediates.

Scheme 1[a]



[a]Reagents and conditions: yields (a) DMF, NaOAc, 65 °C, 14 h, yield range 27–60%.

reactive intermediate formation was determined using MS/MS fragmentation analysis, indicating oxidation of the fused pyrazole ring.

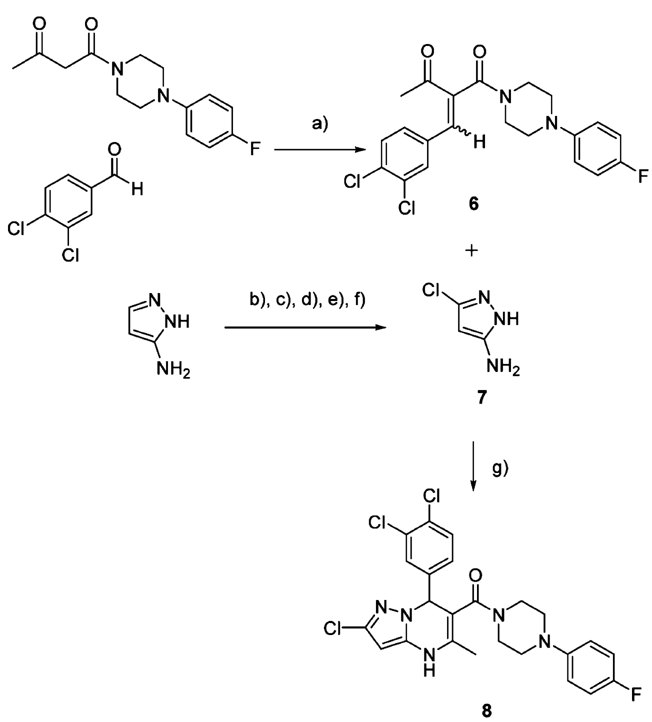
We therefore focused our optimization efforts on blocking the reactive intermediate formation by substitution at the C2 and C3 positions on the fused pyrazole ring.

The first series of C2 substituted analogues containing a C6 phenylpiperazine amide were obtained from the general sequence utilizing the three-component, one-pot Biginelli reaction and commercially available amino-pyrazoles (Scheme 1). Synthesis of additional C2 and C3 substituted dihydropyrazolopyrimidines required initial preparation of noncommercially available amino-pyrazoles. Noncommercially available 3-substituted-1*H*-pyrazol-5-amines were synthesized from the corresponding amino pyrazoles using a multistep sequence, for example, compound **8**, Scheme 2.[18−21] We had previously disclosed SAR in the piperazine amide series, including characterization of the C7 antipodes and determined that K_v1.5 potency was retained in one antipode only.[14] Additional compounds in the piperazine amide series were synthesized and screened as racemates (Table 1) and the SAR utilized in pyrrolo amide series where the diastereomers were separated and characterized (Table 2 and Table 5).

A modified route was also subsequently used to allow installation of the C6 amide functionality at the final step (Scheme 3).

Compounds containing C2 and C3 alkyl and halogen substituents were also prepared wherein the C6 phenylpiperazine amide substituent was replaced with the phenyl pyrrolo amide analogous to that found in compound **2** by the same general methods described in Schemes 1, 2, and 3. Additionally, C2 and C3 substituted compounds wherein the C6 substituent is a heterocyclo-pyrrolo group and the C7 substituent was replaced by a heterocycle were also prepared by essentially the same method utilizing a protection and deprotection sequence to improve the yield in the amide formation step (Scheme 4).

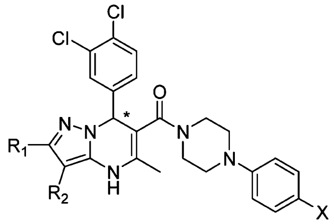
Scheme 2[a]



[a]Reagents and conditions: (a) toluene, 120 °C, 4 h, 84% yield; (b) HCl, dioxane, isoamyl nitrate, −10 °C, 98% yield; (c) Cu(II)Cl_2 Cu(I)Cl, ether, MeOH, −10 °C, 86% yield; (d) AcOH, 90% HNO_3, acetic anhydride, 0 °C, 32% yield; (e) anisole, 130 °C, 24 h, 100% yield; (f) Pd/C, hydrogen, 50 psi, 95% yield; (g) $NaHCO_3$, DMF, 55 °C, 72 h, 24% yield.

In the case wherein the C6 substituent was (*S*)-3-methyl-5-(pyrrolidin-2-yl) isoxazole amide, the noncommercial pyrrolo

Table 1. C2 and C3-Substituted Phenylpiperazine Amides



compd	R_1	R_2	X	$K_v1.5$ IC_{50}, μM^b	% inhibition of *h*ERG current at 10 μM
1[a]	H	H	F	0.070	42 ± 2.7
5a	CH_3	H	F	0.124	60 ± 1.9
5b	CH_3	H	H	0.149	29 ± 10
5c	CF_3	H	F	0.419	NT
5d	H	Cl	F	24%[c]	NT
8	Cl	H	F	0.209	NT

[a]C7 enantiomers separated and active antipode included. [b]Inhibition is measured in duplicate at 3 concentrations and the mean values used to calculate IC_{50} values. [c]% Inhibition of current in L-929 cells at 0.3 μM, 2−4 point determinations.

isoxazole was synthesized as shown in Scheme 4. The pyrrolo isoxazole was then coupled with the BOC protected dihydropyrazolopyrimidine carboxylic acids such as **11**, followed by deprotection of the BOC group, to yield the product as a mixture of diastereomers, which were then separated (Scheme 4).

Utilizing the chemistry described in Schemes 1−4, a series of C6 amide analogues **5a** to **12i** were synthesized. Selected mixtures of enantiomers were separated using chiral preparative chromatography (Chiralcel AD). Diastereomers were separated using normal phase silica gel chromatography. Enantiotopically pure compounds are indicated with an asterisk.

■ RESULTS AND DISCUSSION

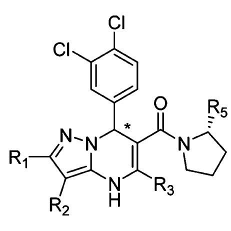
All compounds were assayed for block of I_{Kur} current in patch clamped mammalian L-929 cells which were injected with human $K_v1.5$ mRNA and stably expressed I_{Kur} protein.[22] Inhibition and IC_{50} data for compounds **1−13f** are shown in Tables 1 and 2. Compounds which were potent for $K_v1.5$ were also evaluated for selectivity over the *h*ERG channel,[23] (representative examples are shown in Tables 1, 2, and 5). $K_v1.5$ and *h*ERG channel activity for standard **1** is also included in Table 1 for comparison.

We observed that direct analogues with a C2 (R_1) methyl group on the dihydropyrazolopyrimidine were within 1−2-fold for $K_v1.5$ potency (for example, **5a** compared to **1**, **13a** compared to **2**, and **13d** compared to **13c**). Substitution on the C2 (R_1) position with chlorine resulted in a 4-fold loss of potency for $K_v1.5$ (example **5d** compared to **1**) and, at the C3 (R_2) position, a significant decrease in potency (example **5c** compared to **1**). Trifluoromethyl substitution at C2 (R_1) reduced $K_v1.5$ inhibition in the piperazine and phenylpyrrolidine amide series significantly as shown for examples **5c** and **13b** compared to the unsubstituted analogues **1** and **2**, respectively. However, we were surprised to observe that the C2-trifluoromethyl compound was equipotent with the 3-methylisoxazol-5-yl pyrrolidine amide analogues (compound **13e** compared to **13c**).

Compound **10b** with a methyl substituent at C3 (R_2) showed reduced $K_v1.5$ inhibition and was not profiled further. Compounds **5a**, **13a**, and **13d** with the methyl substituent at C2, **and** compounds **13b** and **13e** with a trifluoromethyl substituent at C2 and C3 substituted analogues **5d** and **10b** were subsequently assayed to determine if reactive intermediates were formed.[14]

The potential for reactive intermediate formation was compared to the C2 and C3 unsubstituted analogues **2** and **13c**. The formation of reactive intermediates was quantified as fluorescent GSH adducts (Table 3). Dihydropyrazolopyrimidine C6 amides without substitution at positions 2 or 3 on the fused pyrazole showed significant incorporation of labeled GSH (**2** and **13c**). We were gratified to see that corresponding analogues with substituents at either C2 or C3 significantly reduced reactive intermediate formation, confirming that this is the principal site of oxidation on the dihydropyrazolopyrimidine template, (C2 substituted examples **5a**, **13a**, **13d**, and **13e** and C3 substituted analogues **5d** and **10b**). Potent $K_v1.5$ inhibitors with acceptable selectivity versus *h*ERG and <1% of detected GSH adduct were advanced to in vitro liability screening and liver microsomal stability testing. C2 methyl analogues **5a** and **13a** and **13d** had poor liver microsome stability (human

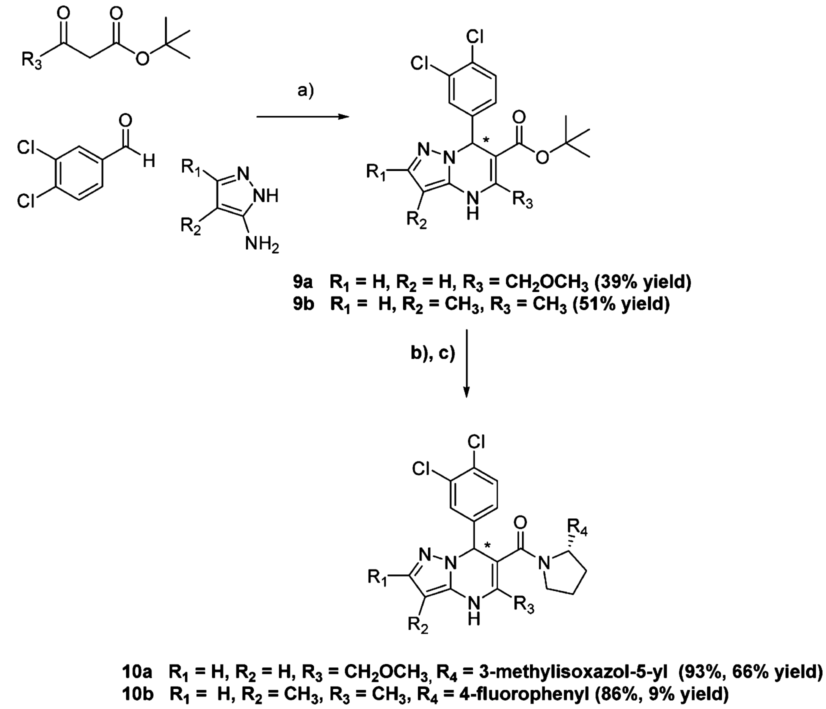
Table 2. C6 Pyrrolo Amides



compd	R_1	R_2	R_3	R_5	$K_v1.5$ IC_{50}, μM^b	% inhibition of *h*ERG current at 10 μM
2[a]	H	H	CH_3	4-fluorophenyl	0.053	30
10a[a]	H	H	CH_2OCH_3	3-methylisoxazol-5-yl	0.070	14 ± 3.3
10b[a]	H	CH_3	CH_3	4-fluorophenyl	45%[c]	NT
13a[a]	CH_3	H	CH_3	4-fluorophenyl	0.100	10 ± 1.2
13b[a]	CF_3	H	CH_3	4-fluorophenyl	37 ± 4.1%[c]	NT
13c[a]	H	H	CH_3	3-methylisoxazol-5-yl	0.083	41 ± 0.1
13d[a]	CH_3	H	CH_3	3-methylisoxazol-5-yl	0.165	13 ± 3.4
13e[a]	CF_3	H	CH_3	3-methylisoxazol-5-yl	0.101	47 ± 4.1
13f	cyclopropyl	H	CH_3	3-methylisoxazol-5-yl	0.227	NT

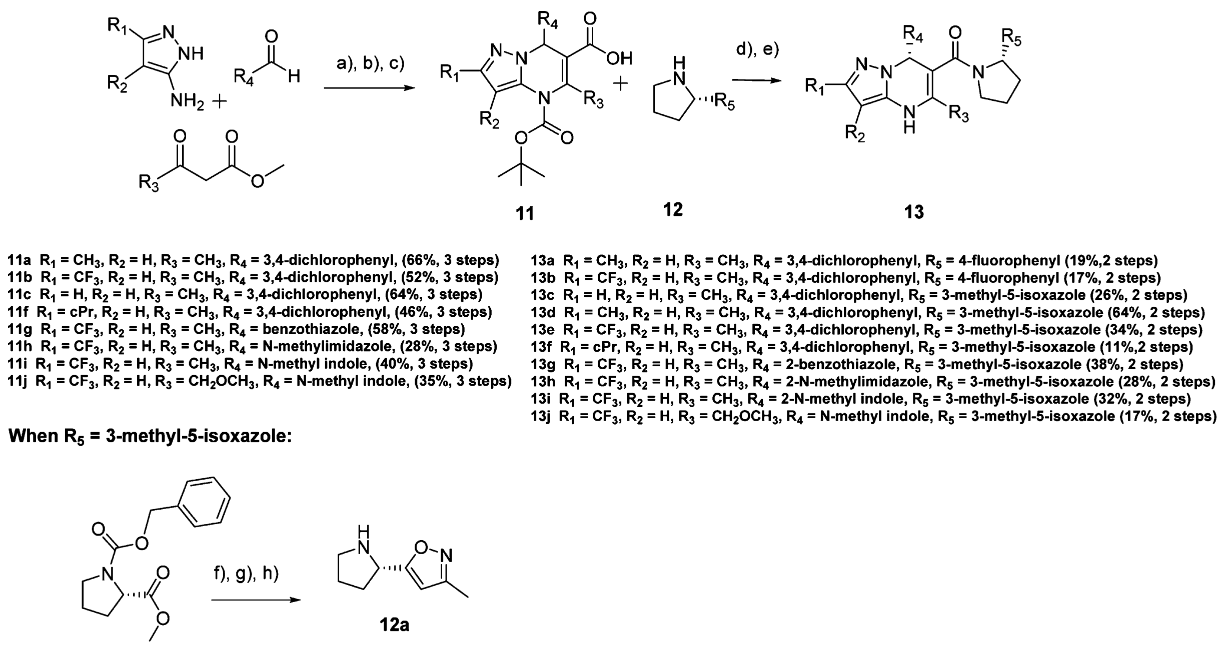
[a]C7 diastereomers separated and active antipode included. [b]Inhibition is measured in duplicate at 3 concentrations and the mean values used to calculate IC_{50} values. [c]Percent inhibition of current in L-929 cells at 0.3 μM, 2−4 point determinations.

Scheme 3[a]



[a]Reagents and conditions: (a) DMF, $NaHCO_3$, 65 °C, 24 h; (b) TMSOTf, DCM, RT; (c) EDCI, DCM, TEA, RT, 14 h.

Scheme 4[a]



[a]Reagents and conditions: (a) heptane, catalytic piperidine, 75 °C, 120 h; (b) di-*tert*-butyl carbonate, THF, DMAP, RT; (c) LiOH, THF; (d) EDCI, DCM; (e) AcOH, microwave 150 °C, 2 min; (f) acetone oxime, nBuLi, THF, −15 °C to RT; (g) H_2SO_4, −15 °C to RT, 51% yield, 2 steps; (h) TfOH, DCM RT, 42% yield.

and rat) compared with C2 CF_3 analogue **13e**. Compound **13e** had the best combination of potency, selectivity, and microsomal stability and was advanced to PK profiling in rat and dog (Table 4). Compound **13e** had an acceptable PK profile in rat and dog with moderate clearance and good bioavailability and was further evaluated for efficacy in the rabbit pharmacodynamic model.[25]

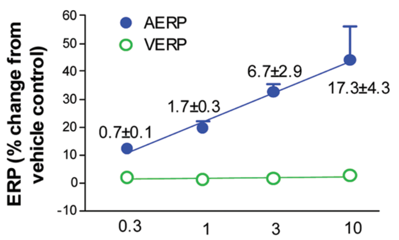
Like humans, rabbits express the I_{Kur} current in atrium but not ventricle and compound **13e** demonstrated a dose dependent increase in atrial effective refractory period (AERP) without increasing ventricular effective refractory period (VERP) (Figure 2).[24] At a dose of 1 mg/kg, compound **13e** achieved a 20% increase in AERP at a plasma concentration of 1.7 μM. This is noteworthy, as an increase of AERP by 10−20% in this

Table 3. Percentage Parent Trapped As Fluorescent GSH Adduct

compd	%fluorescent adducts as % initial parent	compd	%fluorescent adducts as % initial parent
2	33	**10b**	<1
5a	<1	**13c**	21
5d	4	**13d**	<1
13a	5	**13e**	<1

Table 4. PK Summary for Compound 13e in Rat and Dog

	rat	dog
dose (μmol/kg)	12 iv; 26 po	5.6 iv, 5.2 po
V_{ss} (L/kg)	3.0	1.7
Cl (mL/min/kg)	27	11
$t_{1/2}$ (h)	1	1.8
%*F*	68	53



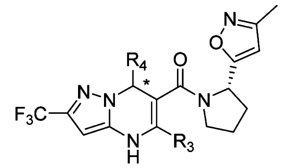
Dose (mg/kg IV) with plasma concentration in μM at each dose (n=3)

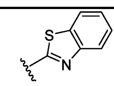
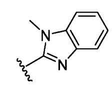
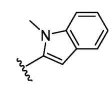
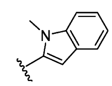
Figure 2. Effect on AERP and VERP in rabbit for compound **13e**. Dose (mg/kg IV) with plasma concentration in μM at each dose (n = 3)

model is considered sufficient to produce a clinically relevant effect.[11] Concomitant with evaluating compound **13e** in vivo, we sought to identify additional compounds which maintain the improved liability profile and further increase the potency in this series.

After optimizing the substitution on the pyrazole ring to address the problem of reactive intermediate formation, we attempted to further optimize these compounds by modification of the substituent at the C7 position on the pyrazolo-dihydropyrimidine core (Table 5). We reasoned that a bicyclic heterocycle may fill the same space as the dichlorophenyl group in the previous compounds. The 2-benzothiazole (**13g**) was 2–3-fold less potent than the corresponding 3,4-dichlorophenyl analogue, and 2-*N*-methyl indole (**13i**) showed similar potency to the dichlorophenyl analogue (**13e**). The *N*-methyl benzimidazole (**13h**) was significantly less potent than the isosteric *N*-methyl indole, possibly due to the greater basicity. Because of superior potency, the *N*-methylindole compound (**13i**) was chosen for further optimization of the 5-substituent. We had discovered that replacing the 5-methyl substituent in **13c** with the 5-methoxymethyl substituent was well tolerated when the 7-substituent was 3,4-dichlorophenyl as illustrated by compound **10a** compared to compound **13c**. Likewise, potency was maintained within 2-fold when the 5-methyl substituent was replaced with the 5-methoxymethyl substituent when the 7-substituent was *N*-methylindole as illustrated by compound **13j** compared to compound **13i**. In addition, we observed that compounds substituted with a methoxymethyl group at C5 had improved solubility in the vehicles used for PK dosing

Table 5. Examples of C7 Substituted Methylisoxazolopyrrolo Amides



Compound	R_3	R_4	K_V 1.5 IC_{50}, μM[a]	% Inhibition of *h*ERG current at 10 μM
13g*	CH_3		**0.281**	**NT**
13h*	CH_3		**36%±3.3[b]**	**NT**
13i*	CH_3		**0.072**	**19±1.9**
13j*	CH_2OCH_3		**0.150**	**14±0.0**

[a]Inhibition is measured in duplicate at three concentrations and the mean values used to calculate IC_{50} values. [b]Percent Inhibition of current in L-929 cells at 0.3 μM, 2–4 point determinations. [c]*C7 diastereomers separated and active antipode included.

($PEG/EtOH/H_2O$) and subsequently the vehicle used for the slow infusion PD studies (DMF).

Compound **13j** also showed good selectivity over other cardiac ion channels (Table 6) and was evaluated for reactive intermediate formation in the same assay using fluorescently labeled glutathione. Like compound **13e**, compound **13j** showed less than 1% GSH adduct formation quantified by the detection of fluorescently labeled material.

Table 6. Cardiac Ion Channel Inhibition for Compound 13j

channel/current	IC_{50} (μM)
K_v1.5	0.15
*h*ERG	>10 (14% inhibition at 10 μM)
I_{CaL}	>10 (37% inhibition at 10 μM)
I_{Na}	>10 (10% inhibition at 10 μM)
K_v4.3	5.8

Compound **13j** was evaluated for pharmacokinetic properties in rats and dogs (Table 7) and showed acceptable half-life and

Table 7. PK Summary for Compound 13j in Rat, Dog, and Rabbit

	rat	dog	rabbit
dose (μmol/kg)	12 iv; 25.5 po	5.6 iv, 5.2 po	5.6 iv
V_{ss} (L/kg)	1.9	3.7	5.0
Cl (mL/min/kg)	12	29	47
$t_{1/2}$ (h)	2.5	1.8	2.0
%*F*	61	31	ND

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bioavailability with moderate clearance. The pharmacodynamic effect of **13j** was tested in the rabbit PD model, which measured the effective refractory period (ERP) in both atrium and ventricle.[25] The compound was dosed at 0.3, 1.0, 3.0, and 10 mg/kg, and at a dose of 1 mg/kg, compound **13j** achieved a 20% increase in AERP at a plasma concentration of 0.7 μM. There was no effect on VERP for either **13e** or **13j** reflecting the selectivity for $K_v1.5$ over ventricular ion channels (Figures 1 and 3).

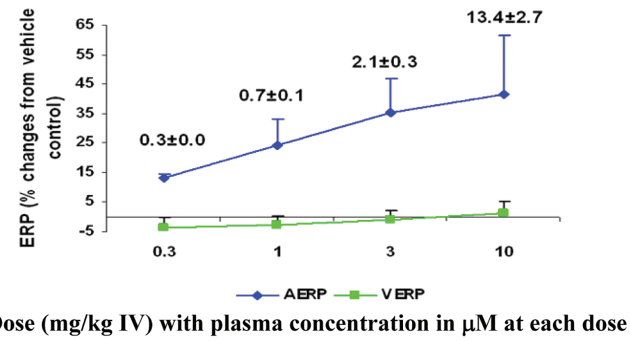

Figure 3. Effect on AERP and VERP in rabbit for compound **13j**.

Because of the superior effect in the pharmacodynamic assay and the acceptable projected human dose derived from allometric scaling of the rat and dog PK properties, compound **13j** was chosen for additional characterization in preclinical toxicology studies.

■ CONCLUSIONS

In conclusion, we identified and blocked the site(s) of reactive intermediate formation in the described dihydropyrazolopyrimidine $K_v1.5$ inhibitors. In general, although 1−2-fold less potent, the 2-methyl and 2-trifluoromethyl substituted analogues offered a profile worthy of follow up. Compound **13e** was identified with less than 1% GSH adduct formation with an improved PK profile and equivalent PD efficacy to lead compound **2**. Subsequent concomitant optimization at the C7 and C5 positions resulted in discovery of compound **13j**, a potent $K_v1.5$ inhibitor which showed less than 1% GSH adduct formation and had an improved PK profile and increased PD efficacy compared to compounds **1** and **13e**. Compound **13j** was advanced to preclinical single dose toxicology studies in rats and dog, and there were no clinical observations related to liver toxicity observed.

■ EXPERIMENTAL SECTION

All reactions were carried out under a static atmosphere of argon or nitrogen and stirred magnetically unless otherwise stated. All reagents used were of commercial quality and were obtained from Aldrich Chemical Co., Sigma Chemical Co., Lancaster Chemical Co., Oakwood Chemical Co., and Matrix Chemical Co. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a JEOL GSX400 spectrometer using tetramethylsilane as an internal standard unless otherwise stated. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a JEOL JNM-ECP500 spectrometer. Chemical shifts are given in parts per million (ppm) downfield from internal reference tetramethylsilane in δ units, and coupling constants (J values) are given in hertz (Hz). Selected data are reported in the following manner: chemical shift, multiplicity, coupling constants. All reactions were carried out using commercially available anhydrous solvents from Aldrich Chemical Co. or EM Science Chemical Co. unless otherwise stated. All flash chromatographic separations were performed using E. Merck silica gel (particle size 0.040−0.063 mm). Reactions were monitored by TLC using 0.25 mm E. Merck silica gel plates (60 F_{254}) and were visualized with UV light, with 5% phosphomolybdic acid in 95% EtOH, or by sequential treatment with 1N HCl/MeOH followed by ninhydrin staining. LC MS data were recorded on a Shimadzu LC-10AT equipped with a SIL-10A injector, a SPD-10AV detector, normally operating at 220 nm, and interfaced with a Micromass ZMD mass spectrometer. LC MS or HPLC retention times, unless otherwise noted, are reported using a Phenomenex Luna C-18 4.6 mm × 50 mm column eluted with a 4 min gradient from 0 to 100% B, where A = 10% MeOH−90% H_2O−0.1% TFA and B = 90% MeOH−10% H_2O−0.1% TFA. All solvents were removed by rotary evaporation under vacuum using a standard rotovap equipped with a dry ice condenser. All filtrations were performed with a vacuum unless otherwise stated. Purity of all intermediates and final compounds was determined to be >95% by HPLC (Phenomenex Luna C-18 4.6 mm × 50 mm column eluted with a 4 min gradient from 0 to 100% B, where A = 10% MeOH−90% H_2O−0.1% TFA and B = 90% MeOH−10% H_2O−0.1% TFA and detection at 220 nm (method A), Xbridge C18 3.5 μm, 4.6 mm × 150 mm, 1.0 mL/min gradient 10−100% 95:5 AcCN in H_2O (0.05% TFA) in 5:95 AcCN in H_2O (0.05% TFA) (method B) and Xbridge Phenyl 3.5 μm, 4.6 mm × 150 mm, 1.0 mL/min gradient 10−100% 95:5 AcCN in H_2O (0.05% TFA) in 5:95 AcCN in H_2O (0.05% TFA) (method C)) and/or elemental analyses.

(7-(3,4-Dichlorophenyl)-2,5-dimethyl-4,7-dihydropyrazolo-[1,5-*a*]pyrimidin-6-yl)(4-phenylpiperazin-1-yl)methanone (5a). 1-(4-Phenylpiperazin-1-yl)butane-1,3-dione (**4a**) (0.40 g, 1.5 mmol) and 3,4-dichlorobenzaldehyde (0.32 g, 1.8 mmol) was dissolved in DMF (10 mL). NaOAc (0.37 g, 4.0 mmol) and 3-methyl-1*H*-pyrazol-5-amine (0.26 g, 1.9 mmol) were added and the solution heated to 55 °C for 24 h. The cooled solution was diluted with EtOAc and the organic portion washed with water and satd NaCl, dried over Na_2SO_4, decanted, and concentrated. The residue was purified by silica gel chromatography elution with 1:1 hexane:acetone to yield **5a** as a pale-yellow solid (450 mg, 60% yield). ^{1}H NMR (400 MHz, MeOD) δ 7.47 (d, J = 8.3 Hz, 1H), 7.22 (d, J = 2.0 Hz, 1H), 6.95 (m, 4H), 6.84 (m, 2H), 6.13 (s, 1H), 5.49 (s, 1H), 4.23 (br s, 2H), 3.31 (br s, 4H), 2.87 (br s, 2H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 169.66, 163.15, 160.50, 158.09, 155.36, 151.27, 149.22, 143.53, 141.83, 133.83, 133.01, 132.18, 129.87, 127.72, 120.37, 120.29, 116.55, 116.33, 100.60, 87.71, 61.27, 16.32, 13.19. LCMS: [M + 1] 500.1. HPLC: purity 94%, retention time 7.11 min, method B; purity 94%, retention time 7.18 min, method C.

(7-(3,4-Dichlorophenyl)-2,5-dimethyl-4,7-dihydropyrazolo-[1,5-*a*]pyrimidin-6-yl)(4-phenylpiperazin-1-yl)methanone (5b). (7-(3,4-Dichlorophenyl)-2,5-dimethyl-4,7-dihydropyrazolo[1,5-*a*]-pyrimidin-6-yl)(4-phenylpiperazin-1-yl)methanone was prepared from **4a** and 3-methyl-1*H*-pyrazol-5-amine as described for example **5a** in 29% yield, R_f 0.29 5% MeOH in EtOAc. ^{1}H NMR (400 MHz, MeOD) δ 7.49 (d, J = 8.3 Hz, 1H), 7.21−7.29 (m, 3H), 7.00 (dd, J = 8.3, 2.1 Hz, 1H), 6.92−6.82 (m, 3H), 6.16 (s, 1H), 5.51 (s, 1H), 4.29 (s, 2H), 3.38 (s, 4H), 2.97 (s, 2H),2.14 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 169.66, 152.54, 151.27, 143.50, 141.83, 133.87, 133.00, 132.16, 130.14, 129.84, 127.70, 122.03, 118.43, 100.62, 87.70, 61.69, 16.71, 13.66. HPLC: purity 96%, retention time 7.52 min, method B; purity 96%, retention time 7.58 min, method C. LCMS: [M + 1] 482.1, [M + 3] 484.1.

(7-(3,4-Dichlorophenyl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)(4-(4-fluorophenyl)-piperazin-1-yl)methanone (5c). (7-(3,4-Dichlorophenyl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)(4-(4-fluorophenyl)piperazin-1-yl)methanone was prepared from 1-(4-(4-fluorophenyl)piperazin-1-yl)butane-1,3-dione (**4b**) and 3,3-(trifluoromethyl)-1*H*-pyrazol-5-amine as described for example **5a** in 46% yield, R_f 0.38 10% MeOH in DCM. ^{1}H NMR (400 MHz, MeOD) δ 8.00 (s, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.29 (dd, J = 12.4, 2.1 Hz, 1H), 7.09−6.93 (m, 3H), 6.89−6.79 (m, 2H), 6.28 (s, 1H), 5.95 (s, 1H), 4.24 (s, 1H), 3.87−3.68 (m, 1H), 3.58−3.16 (m, 4H), 1.96 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 169.04, 164.90, 160.53, 158.07, 149.22, 144.35, 143.88, 142.52, 142.20, 133.98, 133.46, 132.35, 130.05, 127.83, 120.37, 120.30, 116.56, 116.34, 101.09, 86.13, 62.52, 49.33,

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49.55, 16.72. HPLC: purity 96%, retention time 10.32 min, method B; purity 95%, retention time 9.37 min, method C. LCMS: [M + 1] 554.1.

(3-Chloro-7-(3,4-dichlorophenyl)-5-methyl-4,7-dihydropyrazolo-[1,5-*a*]pyrimidin-6-yl)(4-(4-fluorophenyl)piperazin-1-yl)-methanone (5d). 7-(3,4-Dichlorophenyl)-5-methyl-4,7-dihydropyrazolo-[1,5-*a*]pyrimidin-6-yl)(4-(4-fluorophenyl)piperazin-1-yl)methanone was prepared by the method described for **5a** from **4b** and pyrazol-5-amine in 27% yield. HPLC: purity 99%, retention time 8.59 min, method B; purity 99%, retention time 8.24 min, method C. ^{1}H NMR (400 MHz, MeOD) δ 7.59 (s, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.32 (d, J = 2.1 Hz, 1H), 7.08−6.98 (m, 3H), 6.97−6.88 (m, 3H), 6.32 (s, 1H), 4.25 (brs, 1H), 3.44 (brs, 3H), 2.99 (brs, 1H), 2.65 (brs, 1H), 1.99 (s, 3H), 1.60 (brs, 1H). ^{13}C NMR (101 MHz, MeOD) δ 169.08, 161.03, 160.30, 159.90, 158.65, 148.09,142.33, 142.01, 140.61, 134.07, 133.59, 132.41, 130.05, 127.84, 120.82, 120.74, 118.13, 116.81, 116.59, 115.34, 100.82, 61.98, 16.69. LCMS: [M + 1] 485.9, [M + 3] 487.7. 7-(3,4-Dichlorophenyl)-5-methyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)(4-(4-fluorophenyl)piperazin-1-yl)methanone (59 mg, 0.12 mmol) was dissolved in DCM (4 mL) and NCS (18 mg, 0.13 mmol) was added at 0 °C. After 30 min, the crude solution was applied directly to a prep TLC plate (25 cm × 25 cm, 1 mm thickness of silica) and eluted with 1:1 hexane:acetone. Compound **5d** was isolated as a white solid (38 mg, 61% yield). ^{1}H NMR (400 MHz, DMSO) δ 9.52 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.44 (s, 1H), 7.26 (d, J = 1.8 Hz, 1H), 7.00−7.05 (m, 3H), 6.95 (d, J = 8.4 Hz, 1H), 6.83 (m, 2H), 6.08 (s, 1H), 4.00 (s, 2H), 3.20 (s, 4H), 2.90 (s, 2H), 1.90 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 181.55, 168.80, 157.93, 148.72, 142.56, 139.51, 137.46, 134.06, 133.09, 132.29, 130.10, 127.92, 120.39, 120.31, 116.56, 116.34, 101.43, 90.86, 62.53, 49.33, 49.12, 30.63, 16.59. HPLC: purity 94%, retention time 9.67 min, method B; purity 94%, retention time 8.89 min, method C. LCMS: [M + 1] 520.1.

2-(1-(3,4-Dichlorophenyl)ethylidene)-1-(4-phenylpiperazin-1-yl)butane-1,3-dione (6). To a solution of *tert*-butyl 3-oxobutanoate (1.2 g, 7.7 mmol) in toluene (10 mL) was added 1-(4-fluorophenyl)piperazine (1.4 g, 7.7 mmol). The reaction mixture was heated to 120 °C for 4 h and then the cooled solution was extracted with HCl (1N aqueous solution, 3 × 20 mL). Satd $NaHCO_3$ was added to the combined aqueous portions until the pH was adjusted to pH 8. A white precipitate formed which was extracted into EtOAc. The combined EtOAc portions were dried over Na_2SO_4, decanted, and concentrated to yield intermediate 1-(4-(4-fluorophenyl)piperazin-1-yl)butane-1,3-dione (**4a**), which was used directly without further purification (1.7 g, 84% yield, 98% purity retention time 2.50 min). 1-(4-(4-Fluorophenyl)piperazin-1-yl)butane-1,3-dione (200 mg, 0.76 mmol) was dissolved in DMF (2 mL). To the reaction mixture was added 3,4-dichlorobenzaldehyde (0.13 g, 0.76 mmol), acetic acid (20 mg), piperidine (30 mg), and powdered 3A molecular sieves (100 mg). The resulting solution was heated to 55 °C for 14 h and then the cooled slurry was diluted with EtOAc (50 mL) and poured into LiCl (10% aqueous solution, 50 mL). The organic portion was separated and washed further with LiCl (10% aqueous solution), dried over Na_2SO_4, decanted, and concentrated. The residual oil was purified by column chromatography elution with 5:1 hexane: acetone to yield 2-(1-(3,4-dichlorophenyl)ethylidene)-1-(4-phenyl-piperazin-1-yl)butane-1,3-dione (0.25 g, 79% yield, 98% purity retention time 4.16 min method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.31 (dd, J = 2.0 and J = 8.4 Hz, 1H), 6.87 (m, 2H), 6.73 (m, 2H), 3.84 (t, J = 5.2 Hz, 2H), 3.30 (broad s, 1H), 3.20 (broad s, 1H), 3.05 (broad s, 1H), 2.95 (broad s, 1H), 2.90 (broad s, 1H), 2.50 (broad s, 1H), 2.37 (s, 3H). LCMS [M + 1] 421.07.

3-Chloro-1*H*-pyrazol-5-amine (7). HCl (4.0 M in dioxane, 6.0 mL, 24 mmol) was added to a stirred solution of 1*H*-pyrazol-5-amine (1.5 g, 18 mmol) in MeOH (15 mL) at RT. After 3 h, the solvents were removed in vacuo and the residue redissolved in MeOH (10 mL). A further 3 mL of HCl (4.0 M in dioxane, 12 mmol) was added and the turbid solution stirred for 2 h and then concentrated, yielding a pale-yellow solid. The residue was redissolved in MeOH (15 mL) at 0 °C, and then isoamylnitrate was added dropwise (2.7 mL, 16 mmol). The resulting slurry was stirred at 0 °C for 90 min, diluted with ether (100 mL), and the solid collected by filtration and washed further with ether, yielding intermediate 5-diazo-1*H*-pyrazole (2.0 g, 98% yield). 5-Diazo-1*H*-pyrazole (1.0 g, 7.3 mmol) was suspended in concentrated HCl (10 mL), ether (10 mL), and MeOH (10 mL) at −10 °C, and then CuCl (0.038 g, 0.38 mmol) and $CuCl_2$ (0.50 g, 3.7 mmol) were added. The reaction mixture was stirred at 0 °C for 48 h and then poured into saturated ammonium hydroxide (37%, 30 mL) and then extracted with EtOAc. The combined organic portions were dried over Na_2SO_4, decanted, and concentrated under reduced pressure to yield 5-chloro-1*H*-pyrazole (0.64 g, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (broad s, 1H), 6.28 (broad s, 1H). 5-Chloro-1*H*-pyrazole (0.65 g, 6.3 mmol) was dissolved directly in acetic acid (0.91 mL) and then HNO_3 (90%, 0.91 mL) was added dropwise at 0 °C followed by acetic anhydride (2.3 mL). The reaction mixture allowed to warm to room temperature and stirred for 14 h and then poured cautiously into water (50 mL). The pH of the solution was adjusted to pH 7−8 by the addition of Na_2CO_3 and the aqueous solution extracted with ether. The combined ether portions were dried over Na_2SO_4, decanted, concentrated, and the residue purified by column chromatography eluting with 4:1 hexane:EtOAc, yielding 3-chloro-1-nitro-1*H*-pyrazole as a white solid (0.30 g, 32% yield, R_f 0.65 in 4:1 hexane:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 4.4 Hz, 1H), 6.47 (d, J = 4.4 Hz, 1H). 3-Chloro-1-nitro-1*H*-pyrazole (0.30 g, 2.0 mmol) was dissolved in anisole (4 mL) and the solution heated at 130 °C for 48 h. The cooled reaction mixture was poured into 1:1 hexane:water (100 mL), the aqueous phase separated and the organic portion extracted with NaOH (10% aqueous solution, 4 × 10 mL). The combined aqueous extracts were acidified to pH 2 by the addition of concentrated HCl and extracted with EtOAc. The combined EtOAc extracts were dried over Na_2SO_4, decanted, and concentrated to yield 3-chloro-5-nitro-1*H*-pyrazole as a white solid (0.30 g, 100% yield, R_f 0.2 in 4:1 hexane:EtOAc) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 1H). HPLC: purity 97%, retention time 6.18 min, Xbridge C18 3.5 μm, 4.6 mm × 150 mm, 1.0 mL/min gradient 10−100% 95:5 AcCN in H_2O (0.05% TFA) in 5:95 AcCN in H_2O (0.05% TFA); purity 97%, retention time 5.38 min, Xbridge Phenyl 3.5 μm, 4.6 mm × 150 mm, 1.0 mL/min gradient 10−100% 95:5 AcCN in H_2O (0.05% TFA) in 5:95 AcCN in H_2O (0.05% TFA). A Parr thick walled reaction vessel was charged with chloro-5-nitro-1*H*-pyrazole (0.66 g, 4.5 mmol), Pd/C (33 mg, 5% by weight), and MeOH (40 mL). The reaction mixture was hydrogenated at 50 psi (3.6 atm) for 2 h 15 min. The reaction mixture was flushed with nitrogen, diluted with MeOH, and filtered through a pad of Celite. The solvents were removed to yield 3-chloro-1*H*-pyrazol-5-amine as brown needles (0.48 g, 95% yield, R_f 0.2 in 2:1 hexane:acetone). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (s, 1H), 4.30 (broad s, 2H). ^{13}C NMR (101 MHz, MeOD) δ 153.75, 142.43, 91.48. HPLC: purity 95%, retention time 3.20 min, method B; purity 95%, retention time 2.95 min, method C.

(2-Chloro-7-(3,4-dichlorophenyl)-5-methyl-4,7-dihydropyrazolo-[1,5-*a*]pyrimidin-6-yl)(4-phenylpiperazin-1-yl)methanone (8). A Teflon screw capped vial was charged with 2-(1-(3,4-dichlorophenyl)-ethylidene)-1-(4-phenylpiperazin-1-yl)butane-1,3-dione (0.13 g, 0.31 mmol), 3-chloro-1*H*-pyrazol-5-amine (0.040 g, 0.34 mmol), $NaHCO_3$ (0.078 g, 0.93 mmol), and DMF (1.5 mL). The sealed reaction vessel was heated at 55 °C for 72 h and the cooled solution poured into LiCl (10% aqueous solution). The solution was extracted with EtOAc, and the combined organic portions were dried over Na_2SO_4, decanted, and concentrated. The residue was purified by prep HPLC (YMC S5 ODS 30 mm × 100 mm, gradient 40−100% B where A = 10% MeOH−90% H_2O−0.1% TFA and B = 90% MeOH−10% H_2O−0.1% TFA and detection at 220 nm, retention time 10.1 min) to yield (2-chloro-7-(3,4-dichlorophenyl)-5-methyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)(4-phenylpiperazin-1-yl)-methanone (38 mg, 24% yield, 95% purity, retention time 4.27 min, method A). ^{1}H NMR (400 MHz, MeOD) δ 7.50 (d, J = 8.3 Hz, 1H), 7.27 (d J = 2.2 Hz, 1H), 7.01 (dd, J = 8.3 Hz and J = 2.2 Hz, 1H), 6.94−6.98 (m, 2H), 6.86 (m, 2H), 6.12 (s, 1H), 5.64 (s, 1H), 4.25 (s, 2H), 3.40 (s, 4H), 2.90 (s, 2H), 1.92 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 169.15, 159.53, 158.62, 142.19, 133.11, 132.31, 130.01, 127.84, 120.63, 118.62, 116.74, 116.52, 101.58, 87.11, 61.87, 49.68, 49.47, 49.26, 49.04, 48.83, 48.61, 48.40, 16.70. LCMS: [M + 1] 520.0, [M + 3] 522.0

((*R*)-7-(3,4-Dichlorophenyl)-5-(methoxymethyl)-4,7-dihydropyrazolo[1,5-a]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone (10a). Intermediate *tert*-butyl 7-(3,4-dichlorophenyl)-5-(methoxymethyl)-4,7-dihydropyrazolo[1,5-*a*]-pyrimidine-6-carboxylate (**9a**). To a solution of 1*H*-pyrazol-5-amine (5.4 g, 63 mmol) in DMF (50 mL) was added 3,4-dichlorobenzaldehyde (9.6 g, 53 mmol) and *tert*-butyl 4-methoxy-3-oxobutanoate (10 g, 53 mmol). $NaHCO_3$ (18 g, 252 mmol) was added, and the solution was heated at 65 °C for 24 h. The cooled reaction mixture was diluted with 10% LiCl solution in water (800 mL) and the precipitate collected, dissolved in DCM, and transferred to a separation funnel. The organic portion was further washed with 10% LiCl solution and the solvents evaporated. The residue was triturated with methanol to yield **9a** as a white powder (8.5 g, 39% yield, purity 91%, retention time 3.82 min). The material was separated into the corresponding enantiomers using a chiral cell AS column elution (5 cm × 50 cm, 20 μm, Chiral Technologies) with 100% IPA (1% TEA) at 60 mL/min. Isomer 1 eluted at a retention time of 56 min, and isomer 2 eluted at a retention time of 98 min. Analytical data for isomer 1: HPLC purity 95%, retention time 11.16 min, method B; purity 95%, retention time 9.67 min, method C. ^{1}H NMR (400 MHz, MeOD) δ 7.43 (d, *J* = 8.3 Hz, 1H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.34 (d, *J* = 2.1 Hz, 1H), 7.11 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.23 (d, *J* = 9.9 Hz, 1H), 5.82 (d, *J* = 2.0 Hz, 1H), 4.76 (s, 2H), 3.50 (s, 3H), 1.35 (d, *J* = 10.0 Hz, 9H). ^{13}C NMR (101 MHz, MeOD) δ 166.39, 147.84, 144.93, 141.56, 138.99, 133.04, 132.54, 131.58, 130.59, 127.92, 96.60, 90.21, 81.89, 70.70, 60.39, 59.49, 28.59, 27.97. LCMS [M + 1] 410.13. *tert*-Butyl 7-(3,4-dichlorophenyl)-5-(methoxymethyl)-4,7-dihydropyrazolo[1,5-*a*]-pyrimidine-6-carboxylate (isomer 1) was treated with TMSOTf to yield 7-(3,4-dichlorophenyl)-5-(methoxymethyl)-4,7-dihydropyrazolo[1,5-*a*]-pyrimidine-6-carboxylic acid in 93% yield, purity 94%, retention time 3.02 min, method A. 7-(3,4-Dichlorophenyl)-5-(methoxymethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid was coupled to (*S*)-3-methyl-5-(pyrrolidin-2-yl)isoxazole (**12**) using the conditions described for example **13a** to yield ((*R*)-7-(3,4-dichlorophenyl)-5-(methoxymethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone as a white solid (66% yield). HPLC: purity 100%, retention time 8.12 min, method B; purity 100%, retention time 7.75 min, method C. ^{1}H NMR (400 MHz, MeOD) δ 7.47 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 1.8 Hz, 1H), 7.21 (s, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 5.80 (brs, 1H), 5.69 (s, 1H), 5.70 (d, *J* = 2.2 Hz, 1H), 5.48 (s, 1H), 5.12 (m, 1H), 4.03 (m, 1H), 3.91 (pentet, *J* = 6.6 Hz, 2H), 3.64 (m, 1H), 3.34 (s, 3H), 3.20 (s, 1H), 2.24 (s, 3H), 1.95 (s, 2H). ^{13}C NMR (101 MHz, MeOD) δ 173.43, 168.41, 161.41, 142.81, 141.56, 141.02, 133.68, 133.07, 131.92, 130.11, 127.95, 103.62, 103.18, 88.53, 69.87, 61.30, 59.04, 11.28. LCMS: [M + 1] 511.41. LCMS [M + 1] 487.9. HRMS calcd 488.126, obsd 488.126. The relative stereochemistry at the C7 postion was inferred from NMR analysis of the diagnostic proton shift for the methylene proton at C7.

((*R*)-7-(3,4-Dichlorophenyl)-3,5-dimethyl-4,7-dihydropyrazolo-[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(4-fluorophenyl)pyrrolidin-1-yl)-methanone (10b). Intermediate *tert*-butyl-7-(3,4-dichlorophenyl)-3,5-dimethyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate (**9b**). To a solution of 4-methyl-1*H*-pyrazol-5-amine (0.36 g, 3.7 mol) in IPA (20 mL) was added 3,4-dichlorobenzaldehyde (0.43 g, 2.4 mol) and methyl 3-oxobutanoate (0.36 g, 2.4 mol). Heptane (4 mL) and piperidine (0.080 mg, 0.93 mmol) was added, and the solution was heated to 95 °C for 48 h. The cooled reaction mixture was concentrated in vacuo and the residue redissolved in THF and purified by silica gel chromatography gradient elution with 4:1 hexane:EtOAc to 2:1 hexane:EtOAc. *tert*-Butyl-7-(3,4-dichlorophenyl)-3,5-dimethyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate was isolated as a pale-yellow powder (0.49 g, 51% yield, 99% purity, retention time 3.95 min, method A). ^{1}H NMR (400 MHz, THF-d_8) δ 8.68 (s, 1H), 7.39 (d, *J* = 1.6 Hz, 1H), 7.36 (d, *J* = 10.0 Hz, 1H), 7.12 (dd, *J* = 1.8 Hz and *J* = 8.4 Hz, 1H), 7.02 (s, 1H), 6.20 (s, 1H), 2.45 (s, 3H), 1.95 (s, 3H), 1.34 (s, 9H). HPLC: purity 95%, retention time 10.52 min, method B; purity 95%, retention time 9.11 min, method C. LCMS [M + 1] 394.46. Compound **11b** (0.20 g, 0.51 mmol) was dissolved in DCM (3 mL), and TMSOTf was added dropwise (0.20 g). The resulting slurry was stirred at room temperature for 1 h, the DCM was removed by pipet, and the residual solid dissolved in THF and treated with $NaHCO_3$ (0.5 g). The organic layer was purified by silica gel chromatography elution with EtOAc (1% AcOH), yielding 7-(3,4-dichlorophenyl)-3,5-dimethyl-4,7-dihydropyrazolo[1,5-*a*]-pyrimidine-6-carboxylic acid as a white powder (0.15 g, 86% yield, 100% purity, retention time 3.89 min). HPLC: purity 99%, retention time 10.47 min, method B; purity 97%, retention time 9.65 min, method C. ^{1}H NMR (400 MHz, THF) δ 9.89 (s, 1H), 7.86 (s, 1H), 7.48 (d, *J* = 2.1 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.31 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.52 (s, 1H), 2.49 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (101 MHz, THF) δ 164.22, 144.05, 139.23, 138.99, 134.74, 131.72, 131.35, 129.86, 128.38, 126.55, 100.96, 97.76, 57.87, 16.47, 5.08. LCMS [M + 1] 338.27, [M + 3] 340.41.

7-(3,4-Dichlorophenyl)-3,5-dimethyl-4,7-dihydropyrazolo[1,5-*a*]-pyrimidine-6-carboxylic acid and (*S*)-2-(4-fluorophenyl)pyrrolidine were coupled under the conditions described for the preparation of example **13a** to yield (7-(3,4-dichlorophenyl)-3,5-dimethyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(4-fluorophenyl)-pyrrolidin-1-yl)methanone as a 1:1 mixture of diastereomers, which was separated by prep TLC plate (25 cm × 25 cm, 1 mm thickness) elution with 1:1 hexane:EtOAc (5% IPA). The R_f values for the diastereomers were 0.55 for ((*S*)-7-(3,4-dichlorophenyl)-3,5-dimethyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(4-fluorophenyl)-pyrrolidin-1-yl)methanone and 0.45 for ((*R*)-7-(3,4-dichlorophenyl)-3,5-dimethyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(4-fluorophenyl)pyrrolidin-1-yl)methanone, which were isolated as white solids in yields of 4% and 5%, respectively. Analytical data for ((*R*)-7-(3,4-dichlorophenyl)-3,5-dimethyl-4,7-dihydropyrazolo[1,5-*a*]-pyrimidin-6-yl)((*S*)-2-(4-fluorophenyl)pyrrolidin-1-yl)methanone. HPLC: purity 95%, retention time 10.50 min, method B; purity 92%, retention time 10.19 min, method C. ^{1}H NMR (400 MHz, THF) δ 7.96 (s, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.29 (s, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 7.02–6.91 (m, 4H), 5.81 (d, *J* = 27.5 Hz, 1H), 4.91 (m, 1H), 3.74 (m, 3H), 3.44 (s, 2H), 2.18 (s, 3H), 1.92 (s, 3H), 1.58 (d, *J* = 13.2 Hz, 1H). LCMS [M + 1] 484.9.

((*R*)-7-(3,4-Dichlorophenyl)-2,5-dimethyl-4,7-dihydropyrazolo-[1,5-*a*]pyrimidin-6-yl) ((*S*)-2-(4-fluorophenyl)pyrrolidin-1-yl)-methanone (13a). Intermediate (*R*)-4-*tert*-butyl-6-methyl-7-(3,4-dichlorophenyl)-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine-4,6(7*H*)-dicarboxylate was prepared as follows. To a solution of 3-methyl-1*H*-pyrazol-5-amine (3.0 g, 0.031 mol) in THF (15 mL) was added 3,4-dichlorobenzaldehyde (6.0 g, 0.034 mol) and methyl 3-oxobutanoate (4.0 g, 0.034 mol). Heptane (4 mL) and piperidine (0.080 mg, 0.93 mmol) were added, and the solution was heated to 69 °C for 12 h. A white precipitate formed and the slurry diluted with hexane (25 mL), filtered, and the filter cake washed further with hexane and dried in vacuo to yield methyl-7-(3,4-dichlorophenyl)-2,5-dimethyl-4,7-dihydro-pyrazolo[1,5-*a*]pyrimidine-6-carboxylate as a white powder (8.3 g, 76% yield, 95% purity, retention time 3.43 min, method A). LCMS: [M + 1] 352.0. To a slurry of methyl 7-(3,4-dichlorophenyl)-2,5-dimethyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate (4.0 g, 0.011 mol) in THF (37 mL) was added BOC anhydride (3.2 g, 0.014 mol) and DMAP (67 mg, 0.55 mol). The solution was stirred at RT for 2 h and then the solvents removed under reduced pressure. The residual oil was dissolved in DCM (100 mL), washed successively with 1 M HCl, satd $NaHCO_3$, and satd NaCl, dried over Na_2SO_4, decanted, and concentrated, yielding racemic 4-*tert*-butyl-6-methyl-7-(3,4-dichlorophenyl)-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine-4,6(7*H*)-dicarboxylate (5.6 g, 100%, purity 95%, retention time 4.21 min). The racemate was separated into the corresponding enantiomers using a Chiral cell AD column (50 mm × 500 mm) elution with 1% anhydrous EtOH in heptane at a flow rate of 40 mL/min with detection at 254 nm. Enantiomer A eluted at a retention time of 70 min and entantiomer B at 582 min. Enantiomer B corresponded to (*R*)-4-*tert*-butyl-6-methyl-7-(3,4-dichlorophenyl)-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine-4,6(7*H*)-dicarboxylate and was isolated in 21% yield from the corresponding racemate in >98% ee purity, retention time 7.50 min, Chiral cell OD column (4.6 mm × 250 mm) elution with 2% IPA in heptane. HPLC: purity 98%, retention time 12.17 min, method B; purity 98%, retention time 10.30 min, method C. LCMS: [M + 1] 452.0, [M + 3] 454.0. ^{1}H NMR (400 MHz, MeOD) δ 7.44 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 2.1 Hz, 1H), 7.13 (dd, J = 8.4, 2.2 Hz, 1H), 6.30 (s, 1H), 6.11 (s, 1H), 3.80 (s, 3H), 2.58 (s, 3H), 2.21 (s, 3H), 1.58 (s,9H). ^{13}C NMR (101 MHz, MeOD) δ 166.47, 151.20, 150.95, 149.09, 141.20, 138.56, 133.85, 133.44, 132.15, 129.35, 127.57, 116.52, 97.42, 86.46, 59.36, 52.80, 28.28, 21.42, 13.92.

LiOH (10N aqueous solution, 5 mL) was added to a solution of (*R*)-4-*tert*-butyl-6-methyl-7-(3,4-dichlorophenyl)-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine-4,6(7*H*)-dicarboxylate (0.53 g, 1.2 mmol) in THF (5 mL). The reaction mixture was stirred at RT for 15 h and then diluted with HCl (1N aqueous solution, 20 mL) and extracted with DCM. The combined organic portions were dried over Na_2SO_4, decanted, and concentrated to yield (*R*)-4-(*tert*-butoxycarbonyl)-7-(3,4-dichlorophenyl)-2,5-dimethyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (**11a**) as an off-white powder (0.44 g, yield 87%, purity 92%, retention time 4.03 min, method A). LCMS [M + 1] 438.18. To a solution of **11a** (1.2 g, 2.7 mmol) in DCM (40 mL) was added EDCI (0.71 g, 3.7 mmol), HOBt (0.50 g, 3.7 mmol), and (*S*)-2-(4-fluorophenyl)pyrrolidine (0.61 g, 3.7 mmol). The reaction mixture was stirred at room temperature for 14 h and then diluted further with DCM (50 mL) and the solution washed successively with saturated $NaHCO_3$ and satd NaCl. The organic portion was dried over Na_2SO_4, decanted, and concentrated to yield intermediate (*R*)-*tert*-butyl-7-(3,4-dichlorophenyl)-6-((*S*)-2-(4-fluorophenyl)pyrrolidine-1-carbonyl)-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine-4(7*H*)-carboxylate as a tan solid (1.2 g, 75% yield, 95% purity at retention time 4.18 min). LCMS [M + 1] 585.16. To (*R*)-*tert*-butyl-7-(3,4-dichlorophenyl)-6-((*S*)-2-(4-fluorophenyl)pyrrolidine-1-carbonyl)-2,5-dimethylpyrazolo-[1,5-*a*]pyrimidine-4(7*H*)-carboxylate (1.2 g, 2.0 mmol) was added 1:1 DCM:TFA solution (3 mL). The solution was stirred at room temperature for 3 h and then diluted with DCM, and the organic portion was washed with satd $NaHCO_3$, dried over Na_2SO_4, decanted, and concentrated. The residue was purified by silica gel chromatography elution with 1:1:0.1 hexane:EtOAc:IPA to yield compound **13a** as a white powder (0.22 g, 23% yield, 99% purity, retention time 6.83 min, method B); R_f 0.30 10% IPA in 1:1 hexane:EtOAc. ^{13}C NMR (101 MHz, MeOD) δ 164.0, 162.5, 152.0, 145.0, 142.0, 141.0, 133.8, 133.7, 133.6, 132.0, 130.0, 128.3, 116.0, 102.8, 87.58, 62.0, 28.0, 17.0, 13.6. Due to rotomers, the proton spectra for this diastereomer had broad peaks as noted. ^{1}H NMR (400 MHz, MeOD) δ 7.15 (s, 1H), 7.32 (s, 1H), 6.95 (t, J = 8.0 Hz, 2H), 6.73 (s, 1H), 5.95 (s, 1H), 5.41 (s, 2H), 5.05 (s, 1H), 3.69 (s, 2H), 3.47 (m, 1H), 3.30 (s, 1H), 3.19 (s, 1H), 2.30 (s, 1H), 2.06 (s, 3H), 2.00−1.61 (m, 2H). HRMS [M + 1] obsd 485.1309, calcd 485.1311.

4-(*tert*-Butoxycarbonyl)-7-(3,4-dichlorophenyl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylic Acid (11b). Methyl 7-(3,4-dichlorophenyl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate was prepared as described for example **11a** from the condensation of 3-(trifluoromethyl)-1*H*-pyrazol-5-amine, 3,4-dichlorobenzaldehyde, and methyl 3-oxobutanoate to yield intermediate methyl 7-(3,4-dichlorophenyl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]-pyrimidine-6-carboxylate as an orange solid in 52% yield, 96% purity, retention time 2.90 min. ^{1}H NMR (400 MHz,) δ 7.35 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 2.1 Hz, 1H), 7.13 (dd, J = 8.3, 2.1 Hz, 1H), 6.63 (s, 1H), 6.38 (s, 1H), 5.87 (s, 1H), 3.61 (s, 3H), 2.52 (s, 3H). LCMS [M + 1] 405.95, [M + 3] 407.91. Methyl 7-(3,4-dichlorophenyl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate was converted to 4-*tert*-butyl-6-methyl-7-(3,4-dichlorophenyl)-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-4,6(7*H*)-dicarboxylate and subsequently hydrolyzed as described to 4-(*tert*-butoxycarbonyl)-7-(3,4-dichlorophenyl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid using the procedure described in example **13a** in 94% yield. HPLC: purity 96%, retention time 11.85 min, method B; purity 93%, retention time 10.28 min, method C. ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 (d, J = 8.3 Hz, 1H), 7.30 (d, J = 2.1 Hz, 1H), 7.14 (dd, J = 8.3, 2.2 Hz, 1H), 6.51 (s, 1H), 6.47 (s, 1H), 2.66 (s, 3H), 1.59 (s, 9H). ^{13}C NMR (101 MHz, MeOD) δ 167.30, 150.66, 148.79, 141.14, 140.15, 139.06, 136.23, 135.00, 134.15, 133.99, 133.81, 132.34, 129.36, 127.62, 117.59, 113.60, 86.98, 80.66, 60.48, 40.98, 28.17, 22.00, 21.21. LCMS: [M + 1] 491.8.

((*R*)-7-(3,4-Dichlorophenyl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(4-fluorophenyl)pyrrolidin-1-yl)methanone (13b). Compound **11b** and (*S*)-2-(4-fluorophenyl)pyrrolidine were coupled under the conditions described for the preparation of example **13a** to yield intermediate *tert*-butyl 7-(3,4-dichlorophenyl)-6-((*S*)-2-(4-fluorophenyl)-pyrrolidine-1-carbonyl)-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-*a*]-pyrimidine-4(7*H*)-carboxylate (0.53 g, 0.82 mmol) which was dissolved in 1:1 TFA:DCM (20 mL) and the reaction mixture stirred at room temperature for 3 h. The reaction mixture was concentrated and the residue azeotroped with toluene and then purified by silica gel chromatography elution with 1:3:7 IPA:EtOAc:hexane to yield ((*R*)-7-(3,4-dichlorophenyl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(4-fluorophenyl)-pyrrolidin-1-yl)methanone as the less polar diastereomer and ((*S*)-7-(3,4-dichlorophenyl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(4-fluorophenyl)-pyrrolidin-1-yl)methanone as the more polar diastereomer as white solids in yields of 29% and 17%, respectively. HPLC: purity 97%, retention time 3.86 min, method A. ^{1}H NMR (400 MHz,) δ 7.44 (s, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.09 (s, 1H), 7.02 (s, 2H), 6.88 (t, J = 8.5 Hz, 2H), 6.78 (d, J = 10.4 Hz, 2H), 6.23 (s, 1H), 5.56 (s, 1H), 4.86 (t, J = 7.7 Hz, 1H), 4.05−3.82 (m, 1H), 3.32 (s, 1H), 3.13 (s, 1H), 2.19 (m, 2H), 1.74 (s, 3H). ^{19}F NMR (376 MHz) δ −62.53, −114.61. ^{13}C NMR (101 MHz,) δ 167.43, 160.08, 138.57, 132.89, 130.77, 128.30, 127.50, 125.78, 115.45, 115.24, 103.29, 85.29, 77.32, 77.01, 76.69, 64.48, 60.62, 49.31, 34.85, 32.25, 25.32, 16.81, 0.99, −10.63. HRMS [M + 1] obsd 539.1028, calcd 539.1029.

((*R*)-7-(3,4-Dichlorophenyl)-5-methyl-4,7-dihydropyrazolo-[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone (13c). (*R*)-4-(*tert*-Butoxycarbonyl)-7-(3,4-dichlorophenyl)-5-methyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (**11c**) was coupled to (*S*)-3-methyl-5-(pyrrolidin-2-yl)isoxazole (**12**) using the conditions and subsequent deprotection described for example **13a** to yield ((*R*)-7-(3,4-dichlorophenyl)-5-methyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone in 26% yield. HPLC: purity 95%, retention time 7.88 min, method B; purity 96%, retention time 7.59 min, method C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 1.9 Hz, 1H), 7.25 (d, J = 4.4 Hz, 1H), 7.24 (d, J = 1.9 Hz, 1H), 7.01 (dd, J = 8.3, 1.8 Hz, 1H), 6.50 (s, 1H), 6.07 (s, 1H), 5.53 (d, J = 1.9 Hz, 1H), 5.52 (s, 1H), 3.52 (s, 1H), 3.19 (s, 1H), 2.24 (s, 3H), 2.02−1.84 (m, 5H), 2.04 (s, 2H). ^{13}C NMR (101 MHz, MeOD) δ 173.58, 161.88, 151.20, 143.56, 141.76, 133.45, 132.88, 131.93, 130.13, 127.99, 103.10, 102.44, 87.74, 61.17, 16.88, 13.64, 11.32. LCMS: [M + 1] 458.1, [M + 3] 460.1

((*R*)-7-(3,4-Dichlorophenyl)-2,5-dimethyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)-pyrrolidin-1-yl)methanone (13d). Compound **11a** was coupled to (*S*)-3-methyl-5-(pyrrolidin-2-yl)isoxazole (**12**) using the conditions and subsequent deprotection described for example **13a** to yield ((*R*)-7-(3,4-dichlorophenyl)-2,5-dimethyl-4,7-dihydropyrazolo[1,5-*a*]-pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)-methanone in 64% yield. HPLC: purity 94%, retention time 7.22 min, method B; purity 96%, retention time 7.32 min, method C. ^{1}H NMR (400 MHz, MeOD) δ 7.50 (d, J = 8.3 Hz, 1H), 7.22 (d, J = 1.7 Hz, 1H), 7.02 (dd, J = 8.3, 1.9 Hz, 1H), 5.92 (s, 1H), 5.72 (s, 1H), 5.48 (s, 1H), 5.11 (s, 1H), 3.62 (dt, J = 10.8, 7.1 Hz, 1H), 3.21 (s, 1H), 2.26 (s, 3H), 2.12 (s, 3H), 1.98 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 173.58, 161.41, 151.20, 143.56, 141.76, 133.45, 132.88, 131.93, 130.13, 127.99, 103.10, 102.44, 87.74, 61.17, 16.88, 13.64, 11.32. LCMS: [M + 1] 472.1, [M + 3] 474.1

((*R*)-7-(3,4-Dichlorophenyl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone (13e). Compound **11b** was coupled to (*S*)-3-methyl-5-(pyrrolidin-2-yl)isoxazole (**12**) using the conditions and subsequent deprotection described for example **13a** to yield ((*R*)-7-(3,4-dichlorophenyl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)-pyrrolidin-1-yl)methanone in 36% yield. ^{1}H NMR (400 MHz, MeOD) δ 7.52 (d, J = 8.3 Hz, 1H), 7.30 (s, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.14 (s, 1H), 5.92 (s, 1H), 5.69 (s, 1H), 5.13 (s, 1H), 3.65 (dt, J = 10.8, 7.2 Hz, 1H), 2.17 (s, 3H), 2.00 (s, 3H), 1.31 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 173.55, 161.44, 142.27, 141.58, 133.58, 133.34, 132.06, 130.39, 128.80, 128.17, 126.58, 103.04, 102.77, 86.17, 61.90, 49.69, 49.47, 49.26, 49.05, 48.83, 48.62, 48.41, 16.88, 11.29. HPLC: purity 98%, retention time 9.83 min, method B; purity 98%, retention time 8.92 min, method C. LCMS: [M + 1] 526.2

4-(*tert*-Butoxycarbonyl)-2-cyclopropyl-7-(3,4-dichlorophenyl)-5-methyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylic Acid (11f). Intermediate methyl 2-cyclopropyl-7-(3,4-dichlorophenyl)-5-methyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate. To a solution of 3-cyclopropyl-1*H*-pyrazol-5-amine (1.0 g, 8.1 mol) in THF (50 mL) was added 3,4-dichlorobenzaldehyde (1.4 g, 8.1 mol) and methyl 3-oxobutanoate (0.94 g, 8.1 mol). Heptane (10 mL) and piperidine (0.020 mg, 0.24 mmol) were added, and the solution was heated to 75 °C for 18 h. The cooled reaction mixture was concentrated in vacuo and the residue redissolved in THF and purified by silica gel chromatography gradient elution with 2:1 hexane:EtOAc. Methyl 2-cyclopropyl-7-(3,4-dichlorophenyl)-5-methyl-4,7-dihydropyrazolo[1,5-*a*]-pyrimidine-6-carboxylate was isolated as a tan solid (1.7 g, 56% yield, R_f 0.2 in 2:1 hexane:EtOAc). HPLC: purity 99%, retention time 9.42 min, method B; purity 100%, retention time 8.57 min, method C. ^{1}H NMR (400 MHz, MeOD) δ 7.41 (d, J = 8.4, 1H), 7.31 (dd, J = 8.9, 2.2 Hz, 1H), 7.09 (dd, J = 8.4, 2.2 Hz, 1H), 6.18 (s, 1H), 5.38 (s, 1H), 3.66 (s, 3H), 2.44 (s, 3H), 1.91−1.48 (m, 1H), 1.02−0.75 (m, 2H), 0.71−0.46 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 168.19, 158.29, 148.13, 145.17, 139.83, 133.08, 132.39, 131.51, 130.09, 127.74, 115.68, 97.20, 85.25, 59.82, 51.45, 19.43, 10.18, 8.50, 8.30. LCMS [M + 1] 378.19

Methyl 2-cyclopropyl-7-(3,4-dichlorophenyl)-5-methyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate was treated with BOC anhydride and the methyl ester hydrolyzed as described for example **11a** to yield 4-(*tert*-butoxycarbonyl)-2-cyclopropyl-7-(3,4-dichlorophenyl)-5-methyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (**11f**) as an orange foam (0.71 g, 82% yield for 2 steps). HPLC: purity 99%, retention time 11.18 min, method B; purity 99%, retention time 9.80 min, method C. ^{1}H NMR (400 MHz, MeOD) δ 7.48 (d, J = 8.4 Hz, 1H), 7.22 (t, J = 2.1 Hz, 1H), 7.10 (dd, J = 8.0, 2.0 Hz 1H), 6.32 (s, 1H), 6.00 (s, 1H), 2.70 (s, 3H), 1.97−1.76 (m, 1H), 1.58 (m, 9H), 1.02−0.83 (m, 2H), 0.78−0.60 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 157.76, 151.09, 141.72, 138.79, 132.13, 129.20, 127.36, 117.96, 107.21, 94.44, 89.14, 86.22, 75.48, 59.75, 28.22, 21.27, 13.35, 10.24, 8.51. LCMS: [M + 1] 478.15.

((*R*)-2-Cyclopropyl-7-(3,4-dichlorophenyl)-5-methyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone (13f). Compound **11f** was coupled to (*S*)-3-methyl-5-(pyrrolidin-2-yl)isoxazole (**12**) using the conditions and subsequent deprotection described for example **13a** to yield a 1:1 diasteromeric mixture of (2-cyclopropyl-7-(3,4-dichlorophenyl)-5-methyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone in 51% yield. The diastereomers were separated using prep TLC (25 cm × 25 cm × 1 mm thickness) elution with 1:1 hexane:EtOAc (10% IPA). The R_f values for the diastereomers were 0.60 for ((*R*)-2-cyclopropyl-7-(3,4-dichlorophenyl)-5-methyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)-((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone and 0.35 for ((*S*)-2-cyclopropyl-7-(3,4-dichlorophenyl)-5-methyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)-pyrrolidin-1-yl)methanone, which were isolated as white solids in yields of 31% and 22%, respectively. Analytical data for ((*R*)-2-cyclopropyl-7-(3,4-dichlorophenyl)-5-methyl-4,7-dihydropyrazolo[1,5-*a*]-pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)-methanone. HPLC: purity 99%, retention time 8.96 min, method B; purity 98%, retention time 8.90 min, method C. ^{1}H NMR (400 MHz, MeOD) δ 7.47 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 1.7 Hz, 1H), 6.96 (dt, J = 6.7, 3.4 Hz, 1H), 6.07−5.56 (m, 1H), 5.26 (s, 1H), 5.02 (s, 1H), 3.96−3.84 (m, 1H), 3.59 (dd, J = 10.2, 6.9 Hz, 1H), 2.23 (s, 4H), 1.91 (s, 7H), 1.80−1.66 (m, 1H), 0.92−0.86 (m, 1H), 0.86−0.80 (m, 2H), 0.66−0.53 (m, 2H). ^{13}C NMR (101 MHz, THF) δ 170.49, 168.43, 164.23, 158.03, 151.52, 146.01, 140.87, 139.28, 129.71, 127.87, 126.84, 124.75, 100.27, 99.18, 95.09, 80.49, 65.03, 64.81, 64.59, 64.37, 64.15, 57.39, 51.24, 28.71, 27.10, 22.90, 22.70, 22.50, 22.31, 22.11, 14.07, 8.44, 7.37, 5.27. LCMS: [M + 1] 498.17.

7-(Benzo[*d*]thiazol-2-yl)-4-(*tert*-butoxycarbonyl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylic Acid (11g). Intermediate methyl 7-(benzo[d]thiazol-2-yl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate. Methyl 7-(benzo[*d*]thiazol-2-yl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate was prepared from the condensation of benzo[*d*]thiazole-2-carbaldehyde, 3-(trifluoromethyl)-1*H*-pyrazol-5-amine, and methyl 3-oxobutanoate as described in example **11a**. The solvents from the reaction mixture were removed in vacuo and the residue dissolved in MeOH. The resulting white precipitate was collected and dried to yield methyl 7-(benzo[*d*]thiazol-2-yl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate in 61% yield. HPLC: purity 97%; retention time 2.31 min; method A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.96−7.92 (m, 1H), 7.88−7.84 (m, 1H), 7.51−7.42 (m, 2H), 6.91 (s, 1H), 5.62 (s, 1H), 3.74 (s, 3H), 2.22 (s, 3H). LCMS [M + 1] 395.22.

Methyl 7-(benzo[*d*]thiazol-2-yl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate was treated with BOC anhydride and the methyl ester hydrolyzed as described for example **11a** to yield 7-(benzo[*d*]thiazol-2-yl)-4-(*tert*-butoxycarbonyl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (**11g**) in 95% yield. HPLC: purity 100%, retention time 10.92 min, method B; purity 100%, retention time 9.69 min, method C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.48−7.42 (m, 1H), 7.40−7.34 (m, 1H), 6.97 (s, 1H), 6.59 (s, 1H), 2.67 (s, 3H), 1.59 (s, 9H). LCMS [M + 1] 481.32. ^{13}C NMR (101 MHz, MeOD) δ 168.14, 167.07, 153.94, 150.56, 149.98, 139.79, 136.57, 127.70, 127.08, 124.30, 123.10, 116.02, 96.51, 86.80, 59.48, 44.51, 28.21, 21.19, −1.95. LCMS [M + 1] 480.9.

((*S*)-7-(Benzo[d]thiazol-2-yl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone (13g). Compound **11g** was coupled to (*S*)-3-methyl-5-(pyrrolidin-2-yl)isoxazole (**12**) using the conditions and subsequent deprotection described for example **13a** to yield a 1:1 diasteromeric mixture of 7-(benzo[*d*]thiazol-2-yl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone. The diastereomers were separated using silica gel chromatography gradient elution with 10% EtOAc in hexane to 100% EtOAc over 20 min. The retention times for the diastereomers were 14 min for ((*R*)-7-(benzo[d]thiazol-2-yl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone and 17.5 min for ((*S*)-7-(benzo[*d*]thiazol-2-yl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)-pyrrolidin-1-yl)methanone, which were isolated as white solids in yields of 53% and 50%, respectively. Analytical data for ((*S*)-7-(benzo[*d*]-thiazol-2-yl)-5-methyl-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]-pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)-methanone. HPLC: purity 98%, retention time 10.05 min, method B; purity 99%, retention time 9.35 min, method C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.9 Hz, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.47−7.34 (m, 2H), 6.88 (s, 1H), 6.46 (s, 1H), 6.03 (s, 1H), 5.83 (s, 1H), 5.31 (t, J = 7.7 Hz, 1H), 3.77−3.70 (m, 1H), 3.52−3.40 (m, 1H), 2.21 (m, 3H), 2.08 (m, 3H), 1.93 (m, 2H). ^{13}C NMR (126 MHz, MeOD) δ 168.74, 150.61, 140.60, 133.00, 124.52, 123.77, 121.37, 120.20, 100.08, 97.67, 83.24, 57.62, 51.95, 21.89, 13.41, 8.23, −3.81. LCMS [M + 1] 515.31.

4-(*tert*-Butoxycarbonyl)-5-methyl-7-(1-methyl-1*H*-benzo[d]-imidazol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]-pyrimidine-6-carboxylic Acid (11h). Intermediate methyl 5-methyl-7-(1-methyl-1*H*-benzo[d]imidazol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate. Methyl 5-methyl-7-(1-methyl-1*H*-benzo[d]imidazol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate was prepared from the condensation of 1-methyl-1*H*-benzo[*d*]imidazole-2-carbaldehyde, 3-(trifluoromethyl)-1*H*-pyrazol-5-amine, and methyl 3-oxobutanoate as described in example **11a**. The solvents from the reaction mixture were removed in vacuo and the residue dissolved in MeOH. The resulting white precipitate was collected and dried to yield methyl 5-methyl-7-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate in 56% yield. HPLC: purity 87%, retention time 2.99 min, method A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.61 (brs, 1H), 7.58 (d, J = 8.35 Hz, 1H), 7.50 (d, J = 8.35 Hz, 1H), 7.38 (t, J = 7.69 Hz, 1H), 7.29 (t, J = 7.69 Hz, 1H), 6.78 (s, 1H), 4.21 (s, 3H), 3.66 (s, 3H), 1.56 (s, 3H). LCMS: [M + 1] 392.29.

Methyl 5-methyl-7-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate was treated with BOC anhydride and the methyl ester hydrolyzed as described for example **11a** to yield **11h** in 50% yield. HPLC: purity 94%, retention time 3.13 min, method A. HPLC: purity 96%, retention time 8.91 min, method B; purity 100%, retention time 8.72 min, method C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.35 Hz, 1H), 7.30−7.26 (m, 2H), 7.21−7.16 (m, 1H), 6.80 (s, 1H), 6.47 (s, 1H), 3.99 (s, 3H), 2.71 (s, 3H), 1.57 (s, 9H). LCMS [M + 1] 478.36. ^{13}C NMR (101 MHz, THF) δ 165.45, 150.34, 149.16, 148.68, 142.77, 138.37, 135.99, 122.38, 121.57, 119.66, 114.15, 109.73, 95.21, 84.17, 52.53, 29.42, 27.22, 20.20. LCMS: [M + 1] 477.9.

((*S*)-5-Methyl-7-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone (13h). Compound **11h** was coupled to (*S*)-3-methyl-5-(pyrrolidin-2-yl)isoxazole (**12**) using the conditions and subsequent deprotection described for example **13a** to yield a 1:1 diasteromeric mixture of (5-methyl-7-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)-pyrrolidin-1-yl)methanone. The diastereomers were separated using silica gel chromatography gradient elution with 25% EtOAc in hexane to 100% EtOAc over 20 min. The retention times for the diastereomers were 15 min for ((*R*)-5-methyl-7-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone and 21.5 min for ((*S*)-5-methyl-7-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone, which were isolated as white solids in yields of 30% and 28%, respectively. Analytical data for ((*S*)-5-methyl-7-(1-methyl-1*H*-benzo[d]imidazol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone is as follows. HPLC: purity 96%, retention time 6.87 min, method B; purity 96%, retention time 7.74 min, method C. ^{1}H NMR (400 MHz,) δ 7.63 (d, J = 7.9 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 7.2 Hz, 1H), 7.27 (d, J = 7.1 Hz, 1H), 6.44−6.16 (m, 1H), 5.47 (s, 1H), 5.23 (s, 1H), 3.83 (s, 1H), 3.69 (s, 1H), 2.25 (s, 1H), 2.04 (s, 3H), 2.11−1.94 (m, 6H), 1.58 (s, 3H). ^{13}C NMR (101 MHz, THF) δ 120.60, 119.89, 117.59, 107.95, 51.84, 27.67, 14.27, 7.72. LCMS: [M + 1] 512.36

4-(*tert*-Butoxycarbonyl)-5-methyl-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (11i). Intermediate methyl 5-methyl-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]-pyrimidine-6-carboxylate. Methyl 5-methyl-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate was prepared from the condensation of 1-methyl-1*H*-indole-2-carbaldehyde, 3-(trifluoromethyl)-1*H*-pyrazol-5-amine, and methyl 3-oxobutanoate as described in example **11a**. The solvents from the reaction mixture were removed in vacuo and the residue dissolved in MeOH. The resulting white precipitate was collected and dried to yield methyl 5-methyl-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]-pyrimidine-6-carboxylate in 55% yield. HPLC: purity 99%, retention time 1.94 min, method A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.35 Hz, 1H), 7.24−7.15 (m, 2H), 7.07−7.02 (m, 2H), 6.80 (s, 1H), 6.73 (s, 1H), 5.76 (s, 1H), 3.67 (s, 3H), 3.62 (s, 3H), 2.47 (s, 3H). LCMS: [M + 1] 391.26.

Methyl 5-methyl-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate was treated with BOc anhydride and the methyl ester hydrolyzed as described for example **11a** to yield 4-(*tert*-butoxycarbonyl)-5-methyl-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]-pyrimidine-6-carboxylic acid (**11i**) in 73% yield. HPLC: purity 95%, retention time 3.82 min, method A. HPLC: purity 100%, retention time 10.95 min, method B; purity 100%, retention time 9.76 min, method C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.91 Hz, 1H), 7.33−7.28 (m, 1H), 7.21 (t, J = 7.47 Hz, 1H), 7.04 (t, J = 7.25 Hz, 1H), 6.74 (s, 1H), 6.41 (s, 1H), 6.37 (s, 1H), 4.05 (s, 3H), 2.72 (s, 3H), 1.56 (s, 9H). ^{13}C NMR (101 MHz, THF) δ 163.48, 147.38, 144.32, 135.91, 135.09, 125.52, 124.53, 119.84, 117.66, 117.46, 115.33, 109.52, 107.21, 92.72, 82.43, 52.11, 29.85, 25.21,18.02. LCMS: [M + 1] 477.36.

((*S*)-5-Methyl-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone (13i). Compound **11i** was coupled to (*S*)-3-methyl-5-(pyrrolidin-2-yl)isoxazole (**12**) using the conditions and subsequent deprotection described for example **11** to yield a 1:1 diasteromeric mixture of 5-methyl-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)-((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone. The diastereomers were separated using silica gel chromatography gradient elution with 10% EtOAc in hexane to 50% EtOAc over 20 min. The retention times for the diastereomers were 13 min for ((*R*)-5-methyl-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)-((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone and 16 min for ((*S*)-5-methyl-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone, which were isolated as yellow solids in yields of 36% and 32%, respectively. Analytical data for ((*S*)-5-methyl-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone. HPLC: purity 95%, retention time 9.39 min, method B; purity 94%, retention time 8.67 min, method C. ^{1}H NMR (400 MHz, CD_3CN) δ 7.65 (m, 1H), 7.53 (t, J = 10.7 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 7.20 (ddd, J = 24.1, 12.6, 9.1 Hz, 1H), 7.07 (dt, J = 16.1, 4.5 Hz, 1H), 6.44 (s, 1H), 5.92 (s, 1H), 5.01 (s, 1H), 3.95 (m, 1H), 3.60 (s, 2H), 3.54 (s, 3H), 3.28 (s, 1H), 2.03 (s, 3H), 1.98 (s, 2H). ^{13}C NMR (101 MHz, CD_3CN) δ 185.44, 182.95, 173.53, 166.86, 162.84, 141.31, 140.33, 138.39, 132.08, 127.62, 123.07, 121.60, 120.75, 118.30, 110.61, 103.61, 102.18, 98.30, 86.00, 54.67, 47.31, 38.51, 30.31, 17.15, 11.41. LCMS: [M + 1] 511.41.

4-(*tert*-Butoxycarbonyl)-5-(methoxymethyl)-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]-pyrimidine-6-carboxylic Acid (11j). To a solution of 3-(trifluoromethyl)-1*H*-pyrazol-5-amine (2.4 g, 16 mmol) in THF (8 mL) was added 1-methyl-1*H*-indole-2-carbaldehyde (2.5 g, 16 mmol) and methyl 3-oxobutanoate (2.0 g mL, 16 mmol). Heptane (2 mL) and piperidine (78 uL, 0.79 mmol) was added, and the solution was heated to 75 °C for 120 h. The cooled reaction mixture was purified directly using silica gel chromatography gradient elution with 20−80% EtOAc in hexane over 40 min to yield methyl 5-(methoxymethyl)-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]-pyrimidine-6-carboxylate as a white powder (2.3 g, 35% yield, 95% purity, retention time 3.43 min, method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.06 (s, 1H), 6.69 (s, 1H), 6.30 (s, 1H), 5.90 (s, 1H), 4.90 (s, 2H), 4.06 (s, 3H), 3.59 (s, 3H), 3.60 (s, 3H). To a slurry of methyl 5-(methoxymethyl)-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate (2.3 g, 5.5 mmol) in THF (10 mL) was added BOC anhydride (1.4 g, 6.6 mmol) and DMAP (33 mg, 0.27 mmol). The solution was stirred at room temperature for 2 h and then water (10 mL) and LiOH (0.23 g, 5.5 mmol) added. After 14 h, additional LiOH was added (0.46 g, 11 mmol) and the solution stirred for an additional 14 h. The reaction mixture was neutralized by the addition of 1 M HCl and the aqueous portion extracted with EtOAc. The combined organic portions were dried over Na_2SO_4, decanted, and concentrated to yield 4-(*tert*-butoxycarbonyl)-5-(methoxymethyl)-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid as a brown solid (2.5 g, 100% yield). ^{1}H NMR (400 MHz, MeOD) δ 7.46 (d, *J* = 7.9 Hz, 1H), 7.38 (s, 1H), 7.23−7.14 (m, 1H), 7.06−6.95 (m, 1H), 6.86 (s, 1H), 6.54 (s, 1H), 6.37 (s, 1H), 5.24 (d, *J* = 15.1 Hz, 1H), 4.92 (d, *J* = 15.1 Hz, 1H), 4.05 (s, 3H), 3.30 (s, 3H), 1.61 (s, 9H). ^{13}C NMR (101 MHz, MeOD) δ 167.27, 150.90, 148.29, 139.77, 138.78, 136.29, 128.24, 123.64, 121.71, 120.96, 117.60, 110.77, 101.89, 95.29, 86.40, 69.88, 58.83, 54.24, 30.66, 28.12. HPLC: purity 90%, retention time 11.38 min, method B; purity 91%, retention time 9.96 min, method C. LCMS: [M + 1] 507.0.

(*S*)-3-Methyl-5-(pyrrolidin-2-yl)isoxazole (12). Propan-2-one oxime (0.42 g, 5.7 mmol) was dissolved in THF (10 mL), and nBuLi (4.6 mL, 2.5 M solution in hexane, 11 mmol) was added dropwise. The reaction mixture was stirred for 30 min, cooled to 0 °C, and (*S*)-1-benzyl 2-methyl pyrrolidine-1,2-dicarboxylate (1.0 g, 3.8 mmol) was added and the solution stirred for 1.5 h. Concentrated H_2SO_4 was added dropwise (3.5 mL), and the reaction mixture was stirred for an additional 1.5 h and poured cautiously into a 1:1 mixture of ice and NH_4OH. The aqueous portion was extracted with ether and the combined organic portions dried over Na_2SO_4, decanted, and concentrated to yield intermediate (*S*)-benzyl 2-(3-methylisoxazol-5-yl)pyrrolidine-1-carboxylate, which was purified by silica gel chromatography elution with hexane:acetone (3:1) as a yellow oil (0.55 g, 51% yield, 93% purity retention time 1.99 min). (*S*)-Benzyl 2-(3-methylisoxazol-5-yl)pyrrolidine-1-carboxylate (0.39 g, 1.4 mmol) was dissolved in DCM (8 mL), and triflic acid (1.0 g, 6.8 mmol) was added dropwise and the solution stirred for 15 min. Water was added, followed by NaOH (1M), until the pH was adjusted to pH 8. The organic layer was separated and the aqueous portion extracted further with DCM. The combined organic portions were dried over Na_2SO_4, decanted, and concentrated and the residue purified by silica gel chromatography elution with DCM:MeOH (10:1) yielding (*S*)-3-methyl-5-(pyrrolidin-2-yl)isoxazole as a colorless oil (0.87 g, 42% yield). To prevent decomposition, (*S*)-3-methyl-5-(pyrrolidin-2-yl)isoxazole was stored as the NBS monosalt. ^{1}H NMR (400 MHz, MeOD) δ 7.72 (d, *J* = 6.4 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 1H), 6.52 (s, 1H), 4.91 (t, *J* = 7.7 Hz, 1H), 3.47 (dd, *J* = 10.3, 4.2 Hz, 1H), 2.60−2.44 (m, 1H), 2.39 (s, 3H), 2.31 (s, 3H), 2.32−2.26 (m, 2H), 2.29−2.09 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 167.03, 162.03, 143.53, 141.84, 129.92, 126.99, 106.35, 55.55, 47.02, 30.12, 24.66, 21.37, 11.23. HPLC: purity 99%, retention time 4.17 min, method B; purity 95%, retention time 2.12 min, method C. LCMS: [M + 1] 152.9.

((*S*)-5-(Methoxymethyl)-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone (13j). To compound **11j** (0.44 g, 0.87 mmol) in DCM (5 mL) was added EDCI (0.18 g, 0.95 mmol) and (*S*)-3-methyl-5-(pyrrolidin-2-yl)isoxazole (0.13 g, 8.7 mmol). The reaction mixture was stirred at room temperature for 2 h and then purified directly by silica gel chromatography gradient elution with 0−100% EtOAc in hexane over 18 min to yield a diastereomeric mixture of *tert*-butyl 5-(methoxymethyl)-7-(1-methyl-1*H*-indol-2-yl)-6-((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidine-1-carbonyl)-2-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-4(7*H*)-carboxylate as a yellow powder (0.38 g, 69% yield, 95% purity at retention time 2.41 min, method A). ^{1}H NMR (400 MHz,) δ 7.51 (t, *J* = 10.2 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.13−6.99 (m, 1H), 6.59 (d, *J* = 11.7 Hz, 1H), 6.53 (s, 1H), 6.43 (dt, *J* = 24.3, 12.8 Hz, 2H), 5.97 (d, *J* = 22.8 Hz, 1H), 5.65 (d, *J* = 17.0 Hz, 1H), 5.34−5.11 (m, 1H), 4.82 (dd, *J* = 12.0, 7.3 Hz, 1H), 4.74 (dd, *J* = 13.1, 7.5 Hz, 1H), 4.37−4.19 (m, 1H), 4.16−3.93 (m, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.82−3.43 (m, 3H), 3.34 (d, *J* = 16.3 Hz, 2H), 3.22 (d, *J* = 24.1 Hz, 2H), 2.29−2.17 (m, 4H), 2.19−1.97 (m, 4H), 1.57 (s, 9H), 1.58 (s, 9H). *tert*-Butyl 5-(methoxymethyl)-7-(1-methyl-1*H*-indol-2-yl)-6-((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidine-1-carbonyl)-2-(trifluoromethyl)pyrazolo[1,5-*a*]-pyrimidine-4(7*H*)-carboxylate (0.38 g, 0.59 mmol) was dissolved in AcOH (5 mL) and heated to 150 °C in a microwave reactor for 2 min. The solution was neutralized by the addition of satd $NaHCO_3$ and the aqueous solution extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, decanted, and concentrated to yield (5-(methoxymethyl)-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)pyrrolidin-1-yl)methanone as a 1:1 mixture of diastereomers. The diastereomers were separated by silica gel chromatography gradient elution with 40−100% EtOAc in hexane over 20 min. ((*S*)-5-(Methoxymethyl)-7-(1-methyl-1*H*-indol-2-yl)-2-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl)((*S*)-2-(3-methylisoxazol-5-yl)-pyrrolidin-1-yl)methanone (**13j**) was isolated as the more polar isomer as a tan powder (0.074 g, 24% yield). ^{1}H NMR (400 MHz, 55 °C, $CDCl_3$) δ 7.51 (d, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.19 (t, *J* = 7.2 Hz 1H), 7.06 (t, *J* = 7.2 Hz 1H), 6.81 (s, 1H), 6.49 (s, 1H), 6.48 (s, 1H), 5.84 (s, 1H), 5.50 (s, 1H), 5.00 (s, 1H), 4.11 (m, 2H), 3.66 (s, 3H), 3.61 (m, 1H), 3.41 (s, 3H), 3.40 (m, 1H), 2.16 (s, 3H), 1.91 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.36, 165.50, 159.72, 138.72, 138.20, 136.00, 126.88, 122.34, 121.03, 119.84, 109.46, 103.14, 102.33, 101.93, 85.90, 68.29, 58.90, 53.92, 47.02, 31.55, 31.15, 29.91, 22.64, 14.08, 11.30. HPLC: purity 98%, retention time 7.16 min, Zorbax SB C18, 4.6 mm × 75 mm, 2.5 mL/min gradient 10−100% 95:5 MeOH in H_2O (0.1% H_3PO_4) in 5:95 MeOH in H_2O (0.1% H_3PO_4). HRMS: [M + 1] obsd 541.21847 calcd 541.21695. Elemental analysis: C, H, N, F theoretical % 59.99, 5.03, 15.54, 10.54; obsd % 60.00, 4.95, 15.50, 10.16. The absolute stereochemistry at the C7 position was confirmed by the X-ray structure included in the Supporting Information.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Absolute stereochemistry at the C7 position confirmed by the X-ray structure. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.
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■ ABBREVIATIONS USED

AERP, atrial effective refractory period; VERP, ventricular effective refractory period; AF, atrial fibrillation; GSH, glutathione

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■ NOTE ADDED AFTER ASAP PUBLICATION

After this paper was published online March 21, 2012, a correction was made to the TOC graphic and abstract graphic. The corrected version was reposted March 23, 2012.