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Pyrazolo[1,5-*a*]pyridines: synthetic approaches to a novel class of antiherpetics

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Abstract—Synthesis of a novel class of 7-amino-3-pyrimidinyl-pyrazolo[1,5-*a*]pyridine antiherpetic compounds is described. The synthetic methodology is designed to allow for rapid analog synthesis around the C-3 and C-7 positions of the pyrazolo[1,5-*a*]pyridine. The 7-chloropyrazolo[1,5-*a*]pyridine **D**, produced through an azirine rearrangement, served as a key building block. Two complementary methodologies for construction of the C-3 pyrimidine are described. These methods include the development of a novel cyclization utilizing alkynyl ketones or enones to give highly substituted pyrimidines. The outlined strategies facilitated late stage manipulation of either the C-3 or C-7 positions providing flexibility for rapid analog synthesis.

1. Introduction

The herpesvirus family contains more than 100 different members and can infect most animal species. Within this class of large double stranded DNA viruses there are 8 herpesviruses that infect humans. Herpes simplex viruses 1 and 2 (HSV-1 and -2) are among the best known members of this class. HSV-1 is the causative agent of oral fever blisters (labialis) and it has been estimated that >60% (and as high as 90%) of the US population is infected.[1] Meanwhile, herpes simplex virus 2 (HSV-2), the cause of genital lesions, infects one in five individuals or roughly 50 million people in the US alone.[2] The acyclic nucleoside analog acyclovir was a groundbreaking discovery for the treatment for HSV infections some 25 years ago,[3] however there is still no cure or effective vaccine for HSV infections. While current therapies are efficacious and safe, there is room for improvement in several areas including lesion pain relief, time to healing, viral shedding and reduction in episodes of reactivation. Another area of concern with HSV-2 is transmission rates. Recently it has been shown that the current therapy, valacyclovir, can help reduce rates of transmission by 50%.[4]

Our efforts began through a cell-based high throughput screen to find novel inhibitors of viral replication.[5] The pyrazolo[1,5-*a*]pyridine scaffold GW 3733 (**1**) from a previous in-house research program[6] was observed to have antiviral activity against HSV-1 and -2 similar to acyclovir (ACV) in cell culture. The above scaffold was different from other pyrazolo[1,5-*a*]pyridines that were screened by virtue of the 7-amino-3-pyrimidinyl substitution pattern. These novel antiherpetic compounds led us to believe this scaffold offered a unique opportunity for treatment of HSV-1 and -2[7] (Fig. 1).

Originally, GW 3733 was isolated as a by-product during late stage synthetic manipulations targeting alternative structures.[6] It was our desire to more fully investigate the C-3 and C-7 positions of the pyrazolopyridine ring system. Interestingly, few reports appear in the literature regarding the chemistry of this fused nitrogen heterocycle.[8] The C-3 and C-7 positions that we were interested in appeared to display orthogonal reactivity. We desired to exploit the differing reactivity at these positions and selectively

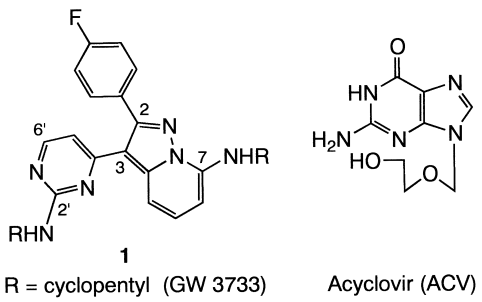

Figure 1.

Keywords: pyrazolo[1,5-*a*]pyridine; alkynyl ketone; pyrimidine synthesis; HSV.

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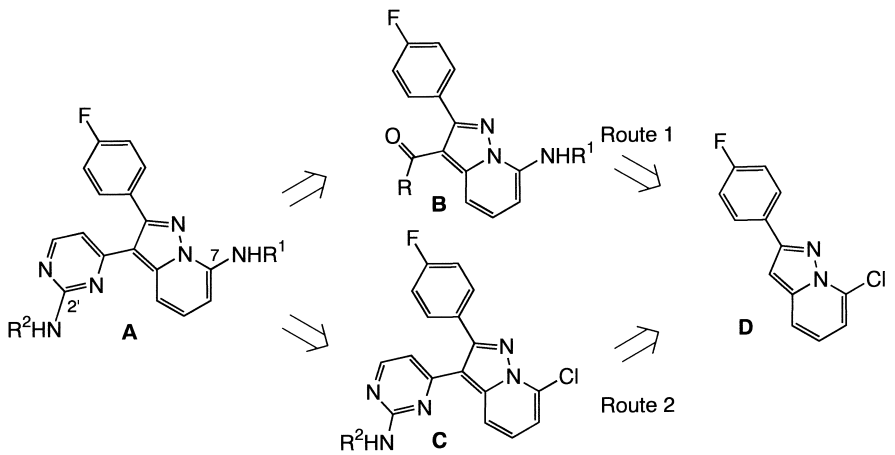


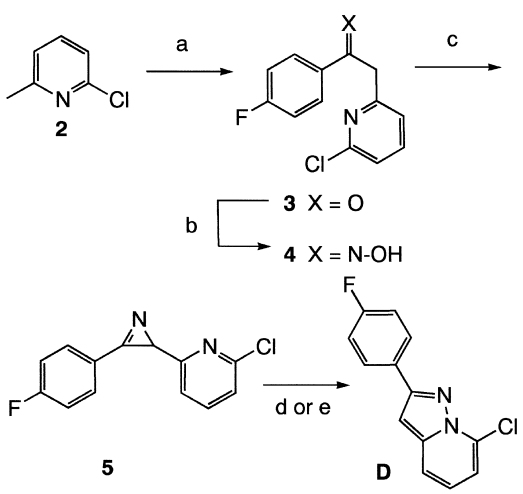
Figure 2. Retrosynthetic strategy.

functionalize these heterocycles to examine the SAR of this class of antivirals.

2. Synthesis

2.1. Construction of intermediate D

Our synthetic approach was designed to have maximum flexibility to examine structure–activity relationships (SAR) around the C-7 and C-3 positions of the pyrazolopyridine ring system. Knowledge gained from the previous in-house synthetic programs directed our attention to the common synthetic intermediate **D**. We envisioned intermediate **D** would serve as a versatile precursor to allow for either manipulation of the C-7 chloro substituent prior to (route 1) or after (route 2) installation of the C-3 pyrimidine. Addressing the C-7 amine substitution first would allow for flexible examination of the C-3 pyrimidine substituent. Alternatively, carrying the C-7 chlorine through to the final step would facilitate easy access to a variety of C-7 substituents (Fig. 2).

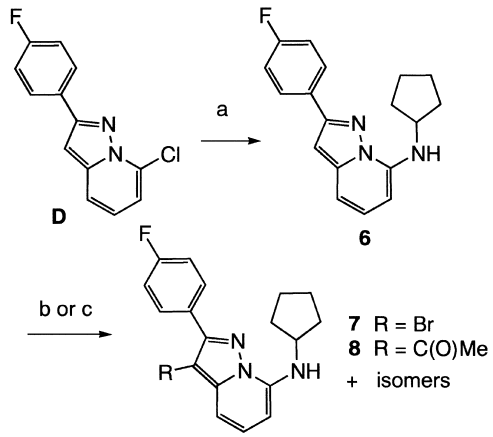


Scheme 1. (a) $LiN(TMS)_2$, 4-F-$C_6H_4CO_2Et$, THF, 45°C, 66%; (b) hydroxylamine HCl, NaOH, MeOH, 86%; (c) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 0°C to rt; (d) 1,2,4-trichlorobenzene, 180°C, 30%; (e) $FeCl_2$, 1,2-dimethoxyethane, 80°C, 68%.

The synthesis of intermediate **D** proceeded smoothly beginning with a benzoylation of 6-chloropicoline (**2**) in the presence of lithium bistrimethylsilyl amide to yield the desired ketone **3**. Subsequent treatment of **3** with hydroxylamine gave the oxime **4** as a stable crystalline solid. Treatment of **4** with trifluoroacetic anhydride and warming to room temperature in the presence of base facilitated formation of the azirine intermediate **5**. Typically the azirine intermediate was not isolated however, the isolation and characterization of this intermediate was possible and **5** proved remarkably stable. Heating the azirine to 180°C in trichlorobenzene led to the formation of the desired pyrazolo[1,5-*a*]pyridine core **D**, albeit in modest yield. At these high temperatures numerous undesired by-products were formed, likely due to the reactive chloro substituent. Fortunately during the course of our studies, it came to our attention that the azirine rearrangement could be catalyzed with an iron(II) salt at a much lower temperature.[9] Heating azirine **5** with a catalytic amount of $FeCl_2$ in DME gave a clean conversion to the desired pyrazolopyridine intermediate **D** in good yield (Scheme 1).

2.2. Route 1: amine first strategy

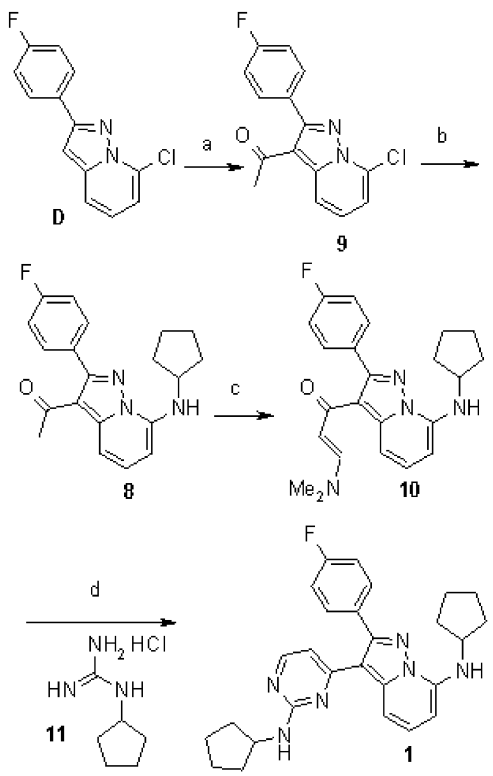
We now turned our attention to methodology designed to complete the construction of GW 3733 (**1**). Our intentions were to introduce the 7-amino functionality early in the sequence and carry this through the construction of the C-3 pyrimidine as the last step in the synthesis. Our initial plans were to build up the pyrimidine via a methyl ketone intermediate which could then be homologated into a vinylogous amide and ultimately condensed with the desired guanidine to produce the pyrimidine moiety. During our studies we discovered the stage at which the C-7 amine was introduced proved crucial to the success of the route. Initial attempts at introducing the amine directly onto intermediate **D** under thermal conditions proved satisfactory for unhindered amines such as *n*-butylamine, but were modest at best for more hindered amines such as cyclopentylamine. The Pd(0) mediated Buchwald–Hartwig type of amination couplings were found to be preferable for these systems.[10] Treatment of intermediate **D** with cyclopentylamine under standard coupling conditions ($Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3, PhMe, 85–100°C) resulted in quantitative conversion to the 7-aminopyrazolopyridine derivative



Scheme 2. (a) $Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3, *c*-$C_5H_9NH_2$, PhMe, 85–100°C, 99%; (b) for **7**, NBS, THF 0°C to rt; (c) for **8**, Ac_2O, $BF_3{\cdot}OEt_2$, PhMe, Δ.

6 (Scheme 2). The 7-aminopyrazolopyridine **6** was subjected to various Friedel–Crafts acetylation conditions as well as bromination conditions in an attempt to functionalize the nucleophilic C-3 position for further elaboration. Unfortunately, these conditions resulted in several regioisomeric products as well as di- and tri-substituted products in the case of the bromination attempts.

It was clear at this point that the 7-aminopyrazolopyridine derivatives such as **6** were too electron rich to allow satisfactory control during C-3 electrophilic aromatic substitutions. This observation led us to examine functionalization of the C-3 position prior to introduction of the C-7 amine. Compound **D** underwent Friedel–Crafts acylation smoothly to give the desired 3-acetyl derivative in good yield (Scheme 3).

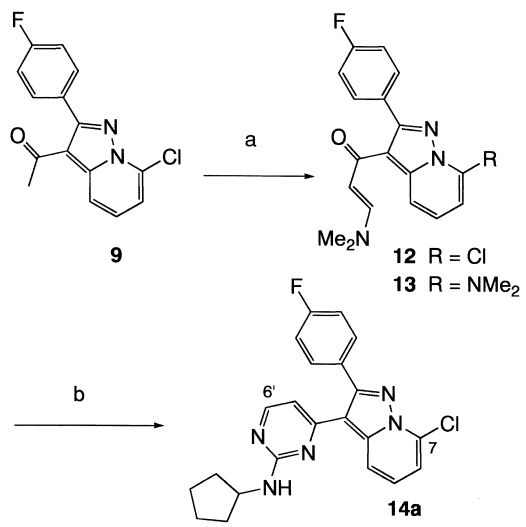


Scheme 3. (a) Ac_2O, $BF_3{\cdot}OEt_2$, PhMe, 100°C, 77%; (b) $Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3, *c*-$C_5H_9NH_2$, PhMe, 85–100°C, 95%; (c) DMF-DMA, reflux, 6d, 99%; (d) *t*-BuOK, THF, Δ, 91%.

We now returned to the introduction of the C-7 amine and again found the Pd(0) mediated amination method to be preferable to thermal conditions to give **8** in near quantitative yield. Refluxing methyl ketone **8** in neat dimethylformamide dimethylacetal (DMF-DMA) over several days resulted in complete conversion to the vinylogous amide **10**. While the yield was excellent for this reaction, the long reaction time was undesirable. By using a stoichiometric amount of DMF di-*tert*-butyl acetal (DMF-DTBA) in DMF instead of the neat dimethyl acetal, a similar conversion was achieved in only a few hours for related analogs. Treatment of the keto-enamine **10** with the cyclopentylamine derived guanidine **11**[11] resulted in clean conversion to the desired GW 3733 (**1**).

2.3. Route 2: amine last strategy

With a reliable and scalable synthesis of **1** in hand we now turned our attention to methodology which would allow access to divergent analog synthesis. The synthesis previously described allows for easy variation of the C-2′ amine via altering the guanidine condensation at the final step in the sequence.[12] However, changes of the C-7 amine substituent in the aforementioned synthesis requires multiple additional steps for each analog. Since our goals were to not only examine the C-2′ SAR but also other positions, introduction of the C-7 substituent as a final step was an option we sought to explore. As we looked at the existing route, an obvious permutation was to alter the order of steps to introduce the amine as a last step and simply carry the C-7 chloro group through the penultimate intermediate. We found that homologation of **9** by treatment with DMF-DMA resulted in production of the desired vinylogous amide **12** (Scheme 4). However, the major product from this reaction was the undesired C-7 dimethylamine derivative **13**. Use of the more reactive DMF-DTBA minimized by-product formation to a large degree, primarily by reducing the reaction time. However, as we considered this synthetic issue, it became clear that it would be desirable to have a method that would allow us to tolerate



Scheme 4. (a) DMF-DMA, Δ; (b) for **12**; **11**, *t*-BuOK, THF, Δ.

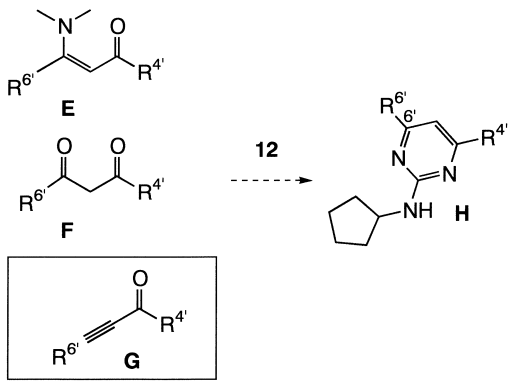


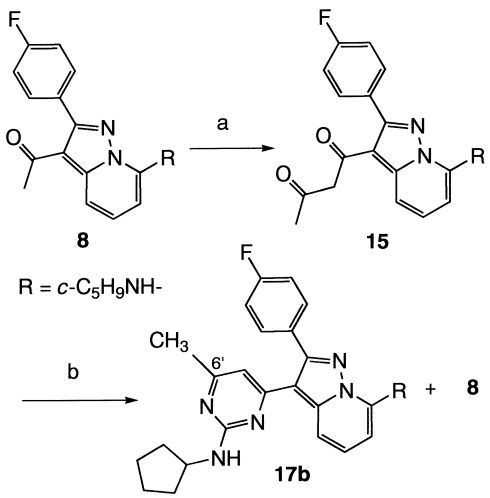
Figure 3. Alternative precursors for pyrimidine synthesis.

sensitive functionality and alter other previously unsubstituted positions of the pyrimidine ring.

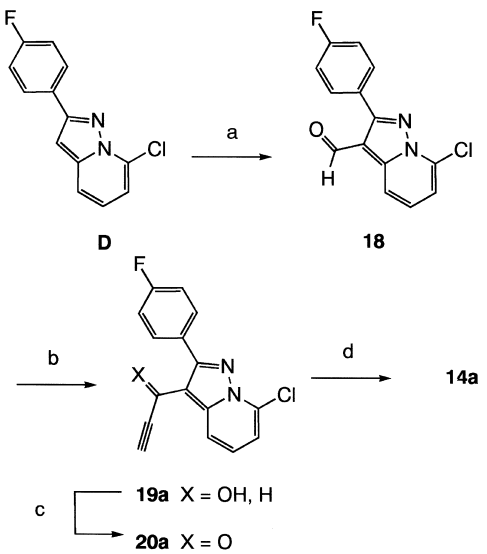
Our attention subsequently focused on modification of the current condensation methodology which utilized an intermediate such as **E** (Fig. 3) produced via the DMF-DMA conditions. In addition to the harsh conditions required for formation of the enamine moiety, introducing substitution at the C-6′ ($R^{6\prime}$) position would require preparation of the appropriately substituted amide acetals or functional variants. Numerous attempts to condense **8** with dimethyl acetamide dimethyl acetal to form an intermediate representative of **E** ($R^{6\prime}$=Me) were unsuccessful.

The β-dicarbonyl **F** was briefly studied. Since we had access to the methyl ketone **8** it was decided to use this material for a model study to examine the ease of introduction of the β-dicarbonyl functionality and its subsequent condensation with guanidines. The enolate of **8** was acylated with Weinreb amide **16** to give the cyclization precursor **15**. Diketone **15** was treated with guanidine **11** under various conditions and only low yields of the desired pyrimidine **17** resulted. The remainder of the material fragmented to produce a significant amount of the starting methyl ketone **8** (Scheme 5).

Reflecting on the oxidation state of the vinylogous amide functionality, it was reasoned that alkynyl ketone **G** would



Scheme 5. (a) $LiN(TMS)_2$, THF, −78°C; $CH_3C(O)NMe(OMe)$ (**16**), 26% (b) **11**, K_2CO_3, DMF, Δ, 19% of **17**, 70% of **8**.

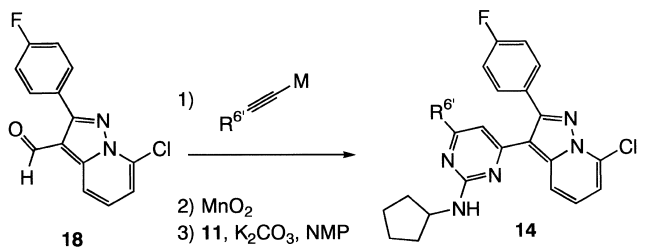


Scheme 6. (a) $POCl_3$, DMF; H_2O, 95%; (b) ethynyl–MgBr, THF, −78 to 0°C, 88%; (c) MnO_2, $CHCl_3$, 77%; (d) **11**, K_2CO_3, NMP, 70°C, 44%.

serve as a suitable surrogate. We expected the alkynyl ketone to be more reactive than either of the previous two cyclization precursors and speculated that the fragmentation pathway observed for compounds such as **15** would be avoided. Considering our intentions for examining numerous analogs, we felt that the plethora of methods to form and modify alkynes would give us ample opportunity to increase the diversity of C-6′ substituents. Most importantly, we anticipated that the mild conditions required to form an intermediate such as **G** would tolerate the C-7 chloro substituent and allow us to accomplish our synthetic goal. Upon examination of the literature, we found a couple of recent reports of a related pyrimidine construction.[13]

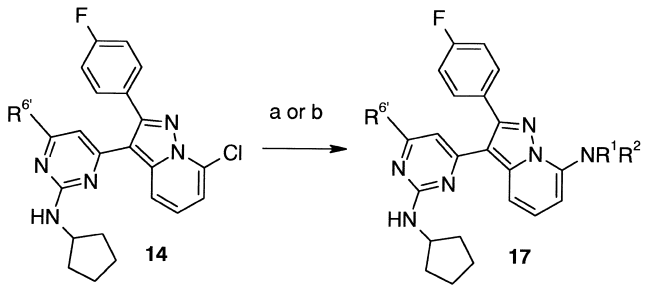
Subjection of intermediate **D** to standard Vilsmeier–Haack formylation conditions led to smooth conversion to aldehyde **18** upon hydrolysis (Scheme 6). Adventitiously, this aldehyde was highly crystalline and could be stored indefinitely without any special precautions. As a first attempt, aldehyde **18** was treated with commercially available ethynyl Grignard at low temperature and allowed to warm to 0°C resulting in clean conversion to the desired propargylic alcohol **19a** in excellent yield. Oxidation of **19a** to the desired alkynyl ketone **20a** occurred without incident

Table 1. Alkynyl ketone cyclizations



Entry	M	$R^{6\prime}$	Cyclization yield (%)	Product **14**
1	–MgBr	–H	44	**14a**
2	–MgBr	–Me	98	**14b**
3	–Li	$-CH_2OTHP$	71	**14c**
4	–Li	–Ph	84	**14d**

Table 2. Amine displacements



Entry	R^1R^2NH	Condition	$R^{6'}$	Yield (%)	Product **17**
1	*c*-C_5H_9-NH_2	a	–Me	64	**17b**
2	*c*-C_5H_9-NH_2	a	–CH_2OTHP	82	**17c**
3	*c*-C_5H_9-NH_2	a	–Ph	97	**17d**
4	NH_2NH_2	b	–Me	46	**17e**
5	*N*-methylpiperazine	b	–Me	70	**17f**
6	*N*-methylpiperazine	b	–Ph	96	**17g**
7	Ethylenediamine	a	–Ph	48	**17h**
8	*p*-anisidine	a	–H	60	**17i**
9	Methyl glycinate HCl	a	–Me	90	**17j**

[a] Condition (a) $Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3, R^1R^2NH, PhMe, 85–100°C.
[b] Conditions (b) R^1R^2NH, heat.

upon exposure to an excess of MnO_2. Other oxidation methods were attempted but gave lower yields or were complicated by undesirable work-up conditions. We found that treatment of alkynyl ketone **20a** with guanidine **11** led to clean formation of the desired pyrimidine **14a** with the requisite C-7 chloro substituent intact. As was alluded to above, our primary goal was establishment of a route that could facilitate installation of the pyrimidine moiety while retaining a C-7 chlorine. However the current route also provides a nice opportunity to introduce a vast array of substituents at the C-6′ position. Table 1 surveys some of the groups that have been exemplified using this method.

Manipulation of the C-7 chloro group at the last stage in the synthesis allowed for rapid construction of amine analogs. It was determined that simply heating 7-chloropyrazolopyridine derivatives such as **14** in the neat amine at 130–150°C led to clean conversion to the 7-amino products **17**. Alternatively, the Buchwald–Hartwig methodology was also employed to convert aryl chloride **14** to amino derivatives **17** (Table 2).

2.4. Oxidative enone cyclization method

The C-5′ position remained the last pyrimidine position for analog derivatization. As we again thought about the existing strategy of pyrimidine ring synthesis it seemed reasonable that replacement of the alkynyl ketone **G** with an enone such as **I** could, upon oxidation, lead to the desired pyrimidines in a similar manner (Fig. 4). Of course, the added feature of substitution at either or both the C-5′ and C-6′ positions present in the enone greatly extends the versatility of the method. To that end, aldehyde **18** was treated with commercially available isopropenyl Grignard reagent at low temperature to produce alcohol **21** in excellent yield (Scheme 7). Oxidation as before with activated manganese dioxide led to smooth formation of the desired enone **22** which was subsequently subjected to guanidinium salt **11** in ethanol under free basing conditions.

The dihydropyrimidine intermediate proved resistant to air oxidation, but did undergo dehydrogenation upon the addition of palladium on carbon catalyst to afford the desired pyrimidine **23**. The C-7 amine substituent was then introduced by heating **23** in neat cyclopentylamine to provide the desired C-5′ substituted target **24**. Interestingly,

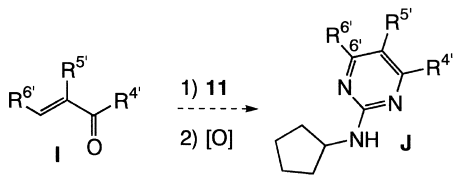
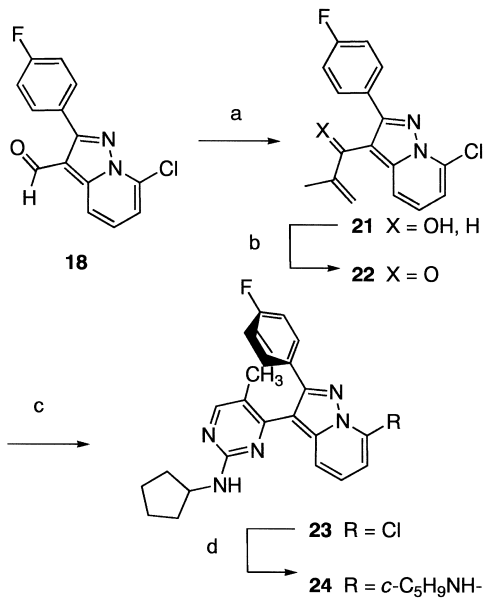


Figure 4. Oxidative enone cyclization.



Scheme 7. (a) Isopropenyl–MgBr, THF, −78 to 0°C, 90%; (b) MnO_2, $CHCl_3$, 74%; (c) **11**, NaOEt, EtOH, rt; Pd/C, 44%. (d) *c*-C_5H_9-NH_2, 130°C, 90%.

introduction of the C-5′ methyl substituent manifested a significant effect on the interaction of the pyrimidine with the 2-aryl substituent. Introduction of the C-5′ methyl appears to flip the 2-(*p*-fluorophenyl) substituent out of plane as is suggested by the upfield ^{1}H (1.64 ppm) and ^{13}C NMR (15.16 ppm) chemical shift of the C-5′ methyl group. The significant upfield shift in both the proton and carbon spectra imply that the methyl group is experiencing the shielding cone of the fluorophenyl ring. We found this to be of significance because previous crystallographic data for related C-5′ protio analogs had shown that the 2-phenyl and 3-pyrimidyl rings existed in a near flat conformation with the pyrazolopyridine core. This presumably allows for maximal overlap of the highly conjugated system. However, crystallographic data has not been obtained to verify this conformational analysis. In addition, C-5′ protio analogs such as **1** showed ^{1}H and ^{13}C NMR chemical shifts for the pyrimidine portion of the scaffold which were consistent with what would be predicted by the crystal structure.

3. Conclusions

We have described synthetic approaches to 7-amino-3-pyrimidinyl-pyrazolo[1,5-*a*]pyridine analogs. A key intermediate 7-chloropyrazolo[1,5-*a*]pyridine was prepared via a mild azirine rearrangement and provided a versatile building block for analog synthesis. During the course of our work, we developed novel methodologies to construct highly substituted pyrimidines based on the condensation of an alkynyl ketone or enone with a guanidine. Our strategy provides facile access to numerous analogs by last step introduction of the C-3 or C-7 substitutent. Detailed SAR of the pyrazolopyridine scaffold along with antiviral data will be the subject of future publications.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were obtained on Varian Unity Plus NMR spectrometers at 300 or 400 MHz, and 75 or 100 MHz, respectively. ^{19}F NMR spectra were recorded at 282 MHz. Mass spectra were obtained on Micromass Platform, or ZMD mass spectrometers from Micromass Ltd. Altrincham, UK, using either Atmospheric Chemical Ionization (APCI) or Electrospray Ionization (ESI). Solvents were purchased as anhydrous grade and used without further purification. Unless otherwise stated, column chromatography for the purification of some compounds, used Merck Silica gel 60 (230–400 mesh), and the stated solvent system under pressure. All compounds were characterized as their free-base form unless otherwise stated. On occasion the corresponding hydrochloride salts were formed to generate solids where noted. Combustion analyses were performed by Atlantic Microlabs, Inc. Norcross, Ga.

4.2. Synthesis of intermediate D

4.2.1. 2-Chloro-2-pyridinyl)-1-(4-fluorophenyl)ethanone (3). To a cold (0°C) solution of 6-chloro-2-picoline (21.4 mL, 196.0 mmol) and ethyl 4-fluorobenzoate (57.5 mL, 391.2 mmol) in THF (311 mL) was added lithium bis(trimethylsilyl)amide (391 mL, 1.0 M in THF, 391.0 mmol) dropwise via a pressure equalizing funnel over 1 h. Upon complete addition, the cold bath was removed and the resultant solution was heated at 45°C for 15 h. The mixture was cooled to room temperature and quenched by the addition of water. Ether was added and the organic layer was washed with brine. The aqueous layer was extracted with ether and the combined organics were dried over magnesium sulfate. Filtration and concentration gave a solid residue which was purified by recrystallization from EtOAc–hexanes to provide ketone **3** (32.2 g, 66%) as a tinted off-white solid existing as a keto–enol tautomeric mixture. ^{1}H NMR ($CDCl_3$): for the keto tautomer δ 8.11 (m, 2H), 7.66 (t, 1H), 7.30–7.25 (m 2H), 7.17 (t, 2H), 4.48 (s 2H); ^{19}F NMR ($CDCl_3$) δ −104.72 (keto), −111.64 (enol); MS *m/z* 250 (M+1).

4.2.2. 2-(6-Chloro-2-pyridinyl)-1-(4-fluorophenyl)ethanone oxime (4). To a solution of ketone **3** (74.9 g, 299.8 mmol) in MeOH (900 mL) was added hydroxylamine hydrochloride (104 g, 1.49 mol) followed by NaOH (600 mL, 10% aqueous, 1.5 mol). The resultant suspension was heated to reflux for 2 h and then cooled to rt. The mixture was concentrated in vacuo and the residue taken up in ether and water. The organic layer was washed with brine. The aqueous layer was extracted with ether and the combined organics were dried over magnesium sulfate. Filtration and concentration gave a solid residue which was purified by recrystallization from EtOAc–hexanes to provide **4** (67.9 g, 86%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.69 (s, 1H), 7.71 (dd, 2H), 7.53 (t, 1H), 7.18–7.16 (m, 2H), 7.03 (t, 2H), 4.37 (s, 2H); ^{19}F NMR ($CDCl_3$) δ −111.77; MS *m/z* 265 (M+1).

4.2.3. 7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridine (intermediate D). To a solution of **4** (109.2 g, 414 mmol) in 1,2-dimethoxyethane (500 mL) at 0°C was added trifluoroacetic anhydride (59 mL, 414 mmol), keeping the temperature below 10°C. After the addition was complete, the reaction was warmed to 15°C. The solution was then cooled to 4°C and a solution of triethylamine (116 mL, 828 mmol) in 1,2-dimethoxyethane (60 mL) was added over 0.5 h. After warming to rt, the mixture was stirred for 1.5 h. To this was added iron(II) chloride (0.52 g, 4.1 mmol) and the reaction was heated to reflux for 3 h. The reaction was concentrated and the resulting solid was recrystallized from ethyl acetate–hexanes to give intermediate **D** (69.7 g, 68%) as off-white needles. ^{1}H NMR ($CDCl_3$): δ 8.03 (m, 2H), 7.54 (d, 1H), 7.16 (m, 3H), 6.93 (d, 1H), 6.91 (s, 1H); MS *m/z* 247 (M+1); mp 156–157°C.

4.3. Synthesis of 1—Route 1

4.3.1. 1-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (9). To a solution of intermediate **D** (10.0 g, 40.5 mmol) in toluene (225 mL) at rt was added acetic anhydride (4.6 mL, 48.6 mmol). Boron trifluoride diethyletherate (5.6 mL, 44.6 mmol) was then added dropwise and the resultant solution was heated to reflux for 3.5 h. The reaction mixture was cooled to rt and quenched by the

dropwise addition of aqueous sodium bicarbonate. Ether was added and the organic layer was washed with brine. The aqueous layer was extracted with ether and the combined organics were dried over magnesium sulfate, filtered and concentrated. The residue was purified by recrystallization from EtOAc–hexanes to give methyl ketone **9** (9.0 g, 77%) as redish needles. ^{1}H NMR ($CDCl_3$): δ 8.41 (d, 1H), 7.59 (m, 2H), 7.45 (dd, 1H), 7.26–7.13 (m 3H), 2.15 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −112.06; MS *m*/*z* 289 (M+1).

4.3.2. 1-[7-(Cyclopentylamino)-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (8). To a solution of ketone **9** (2.7 g, 9.5 mmol) in toluene (50 mL) was added successively *racemic*-BINAP (378 mg, 0.6 mmol), cesium carbonate (4.7 g, 14.3 mmol), cyclopentylamine (4.7 mL, 47.5 mmol), and palladium(II) acetate (86 mg, 0.4 mmol). The resultant mixture was heated to 95°C for 2.5 h at which time the reaction was judged complete by thin layer chromatography. The solution was cooled to rt and ether was added. The organic layer was washed with water and brine. The aqueous layer was extracted with ether and the combined organics dried over magnesium sulfate. Filtration and concentration followed by flash chromatography (4:1 hexanes–EtOAc) provided 7-amino derivative **8** (3.1 g, 95%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 7.62 (d, 1H), 7.55 (dd, 2H), 7.40 (t, 1H), 7.15 (t, 2H), 6.10 (d, 1H), 5.99 (d, 1H), 3.94 (m, 1H), 2.09 (s, 3H), 2.12–2.04 (m, 2H), 1.78–1.58 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 192.63, 163.28 (d, J_{CF}=247.3 Hz), 154.89, 142.65, 142.38, 131.66 (d, J_{CF}=8.3 Hz), 131.09, 130.03 (d, J_{CF}=3.8 Hz), 115.33 (d, J_{CF}=22.0 Hz), 111.32, 105.41, 91.97, 53.81, 33.21, 30.10, 23.96; ^{19}F NMR ($CDCl_3$) δ −112.70; MS *m*/*z* 338 (M+1).

4.3.3. (2*E*)-1-[7-(Cyclopentylamino)-2-(4-fluorophenyl)-pyrazolo[1,5-*a*]pyridin-3-yl]-3-(dimethylamino)-2-propen-1-one (10). A solution of **8** (3.1 g, 9.2 mmol) in *N*,*N*-dimethylformamide dimethyl acetal (25 mL) was heated to reflux for 6 days. The mixture was cooled to room temperature, EtOAc was added followed by water. The organic layer was washed with brine. The aqueous layer was extracted with EtOAc and the combined organics were dried over magnesium sulfate. Filtration and concentration followed by flash chromatography (EtOAc) provided enamine **10** (3.6 g, 99%) as a tinted oil. ^{1}H NMR ($CDCl_3$): δ 7.73–7.61 (m, 4H), 7.32 (t, 1H), 7.14 (t, 2H), 6.03 (d, 1H), 5.96 (d, 1H), 5.05 (d, 1H), 3.99 (m, 1H), 5.15–2.42 (broad, 6H), 2.19–2.08 (m, 2H), 1.86–1.62 (m, 6H); ^{19}F NMR ($CDCl_3$) δ −113.75; MS *m*/*z* 393 (M+1).

4.3.4. *N*-Cyclopentylguanidine hydrochloride (11). To a solution of 2-methyl-2-thiopseudourea sulfate (13.9 g, 50.0 mmol) in water (40 mL) was added cyclopentylamine (14.8 mL, 150 mmol). The resultant mixture was heated to 55°C for 20 min and then to reflux for 2.5 h. The mixture was cooled to room temperature and concentrated in vacuo and azeotroped with MeOH. Water was added (~100 mL) and Amberlite IRA 400 (Cl^-) resin was added. The mixture was stirred for 1 hour and then the resin was removed by filtration. The solution was concentrated in vacuo and azeotroped with MeOH. The residue was recrystallized from MeOH–acetone to yield *N*-cyclopentylguanidine hydrochloride (7.0 g, 86%) as a fine white solid. ^{1}H NMR (D_2O): δ 3.62 (m, 1H), 1.75 (m, 2H), 1.52–1.32 (m, 6H); ^{13}C NMR (D_2O) δ 156.23, 53.11, 32.15, 23.13; MS *m*/*z* 128 (M+1).

4.3.5. *N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-amine (1). To a solution of **10** (3.5 g, 8.9 mmol) in THF (36 mL, 0.25 M) was added *N*-cyclopentylguanidine hydrochloride (**11**) (1.89 g, 11.6 mmol), followed by solid potassium tert-butoxide (2.6 g, 23.2 mmol) in two portions. The resultant solution was heated to reflux for 23 h. Upon cooling to rt, ether was added followed by water. The organics were washed with brine, and the aqueous layer was extracted with ether. The combined organics were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica to give **1** (3.7 g, 91%) as an off white solid. ^{1}H NMR ($CDCl_3$): δ 7.97 (d, 1H), 7.68 (d, 1H), 7.59 (dd, 2H), 7.27 (t, 1H), 7.10 (t, 2H), 6.24 (d, 1H), 5.99 (d, 1H), 5.96 (d, 1H), 5.01 (d, 1H), 4.28 (m, 1H), 3.97 (m, 1H), 2.12–1.99 (m, 4H), 1.79–1.44 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 163.12 (d, J_{CF}=246.6 Hz), 162.09, 161.53, 156.67, 152.15, 142.66, 141.09, 131.46 (d, J_{CF}=8.0 Hz), 129.92 (d, J_{CF}=3.1 Hz), 128.39, 115.45 (d, J_{CF}=21.3 Hz),108.68, 107.13, 105.15, 90.13, 53.84, 52.87, 33.50, 33.30, 24.05, 23.70; ^{19}F NMR ($CDCl_3$) δ −113.49; MS *m*/*z* 457 (M+1); Anal. Calcd for $C_{27}H_{29}FN_6$: C, 71.03; H, 6.40; N, 18.41. Found: C, 71.20; H, 6.37; N, 18.52.

4.4. Amine last strategy—Route 2

4.4.1. 7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridine-3-carbaldehyde (18). DMF (100 mL) was cooled to 0°C and treated with phosphorous oxychloride (5.7 mL, 60.8 mmol). After the addition was complete, the mixture was warmed to room temperature and stirred for 1 h. To this was added 7-chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridine (10.0 g, 40.5 mmol) and the resultant solution was stirred overnight. Water was added, followed by dichloromethane. The aqueous layer was extracted with dichloromethane. The combined organics were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was recrystallized from ether and hexanes to give aldehyde **18** (10.6 g, 95%) as a fluffy white solid. ^{1}H NMR ($CDCl_3$): δ 10.07 (s, 1H), 8.37 (d, 1H), 7.78 (m, 2H), 7.48 (t, 1H), 7.20 (m, 3H); ^{19}F NMR ($CDCl_3$) δ −111.25; MS *m*/*z* 275 (M+1); Anal. Calcd for $C_{14}H_8ClFN_2O$: C, 61.22; H, 2.94; N, 10.20. Found: C, 61.34; H, 2.90; N, 10.15; mp 212–213°C (decomp.).

4.5. General procedure A. Addition of alkynyl/alkenyl Grignard or lithium reagents to aldehyde 18

To a cold (−78°C) solution of aldehyde **18** (1 equiv.) in THF (0.15 M) was added alkynyl magnesium bromide or alkynyl lithium reagent (2.5 equiv.) in THF (0.5–1.0 M) dropwise. The resultant mixture was allowed to warm to 0°C and stirred at that temperature until the reaction judged complete by TLC or LC/MS methods. The resultant solution was poured into water and extracted with ether. The organic layer was washed with water and brine and the combined organics were dried over sodium sulfate. Filtration and

concentration followed by flash chromatography or recrystallization provide the desired alcohol **19**.

4.6. General procedure B. MnO_2 oxidation

To a solution of alcohol **19** (1 equiv.) in CH_2Cl_2 (0.05 M) was added manganese dioxide (40 equiv.). The reaction mixture was stirred at room temperature until judged complete by TLC or LC/MS methods. The suspension was filtered through a pad of Celite and the filtrate was concentrated in vacuo to give ketone **20**. This material is used without further purification.

4.7. General procedure C. Alkynyl ketone/guanidine cyclization

To a dry round bottom flask was added sodium metal (1.3 equiv.). Ethanol (0.15 M) was added and allowed to react with sodium at room temperature until completely dissolved. Guanidinium salt **11** (1.3 equiv.) was added and the mixture was allowed to stir at room temperature for 10 min. To the resultant mixture was added ketone **20** (1 equiv.) and the reaction mixture was stirred at rt or heated to 70°C until judged complete by TLC or LC/MS. The reaction mixture was cooled to room temperature and diluted with water. The mixture was extracted with ethyl acetate, and the combined extracts were washed with water and brine. The organic layer was dried over sodium sulfate. Filtration and concentration followed by flash chromatography or recrystallization provided pyrimidine **14**.

An alternative method involved heating a solution of alkynyl ketone **20** (1 equiv.) guanidine **11** (1.3 equiv.) and K_2CO_3 (1.3 equiv.) in NMP or DMF (0.15 M) at 120°C.

4.7.1. 1-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-ol (19a). Aldehyde **18** was subjected to general procedure A using ethynyl magnesium bromide to give after recrystallization from dichloromethane alcohol **19a** (5.3 g, 88%) as a pale yellow crystalline solid. ^{1}H NMR ($CDCl_3$): δ 8.04 (d, 1H), 7.79 (m, 2H), 7.20 (m, 3H), 7.01 (d, 1H), 5.77 (m, 1H), 2.69 (d, 1H), 2.32 (d, 1H); MS *m*/*z* 301 (M+1).

4.7.2. 1-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-one (20a). Alcohol **19a** was oxidized according to general procedure B to give ketone **20a** (4.04 g, 77%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.45 (d, 1H), 7.67 (m, 2H), 7.50 (t, 1H), 7.19 (d, 1H), 7.12 (t, 2H), 2.93 (s, 1H); MS *m*/*z* 299 (M+1).

4.7.3. 4-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyrimidinamine (14a). Ketone **20a** was treated with guanidine **11** according to general procedure C to provide after flash chromatography pyrimidine **14a** (125 mg, 44%) as a white foam. ^{1}H NMR ($CDCl_3$) δ 8.42 (d, 1H), 8.09 (d, 1H), 7.67 (dd, 2H), 7.30 (m, 1H), 7.17 (t, 2H), 7.06 (d, 1H), 6.33 (d, 1H), 5.30 (d, 1H), 4.35 (m, 1H), 2.18–2.05 (m, 2H), 1.84–1.52 (m, 6H); ^{19}F NMR ($CDCl_3$) δ −112.78; MS *m*/*z* 408 (M+1).

4.7.4. 1-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-butyn-1-ol (19b). Aldehyde **18** was subjected to general procedure A using propynyl magnesium bromide to give after flash chromatography (4:1 hexanes/EtOAc to 1:1 hexanes/EtOAc) alcohol **19b** (1.3 g, 72%) as a white solid. R_f 0.44 (2:1 hexanes/ethyl acetate). ^{1}H NMR ($CDCl_3$) δ 7.99 (d, 1H), 7.78 (m, 2H), 7.14 (m, 3H), 6.95 (d, 1H), 5.70 (m, 1H), 2.21 (d, 1H), 1.85 (d, 3H); MS *m*/*z* 315 (M+1).

4.7.5. 1-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-butyn-1-one (20b). Alcohol **19b** was oxidized according to general procedure B to give ketone **20b** (950 mg, 91%). R_f 0.44 (3:1 hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 8.49 (d, 1H), 7.73 (m, 2H), 7.50 (t, 1H), 7.19 (m, 3H), 1.71 (3H); ^{19}F NMR ($CDCl_3$) δ −112.58; mp 182–183°C.

4.7.6. 4-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-6-methyl-2-pyrimidinamine (14b). Ketone **20a** was treated with guanidine **11** according to general procedure C to provide after flash chromatography pyrimidine **14b** (1.11 g, 98%) as a yellow foam. R_f 0.45 (3:1 hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 8.35 (d, 1H), 7.64 (m, 2H), 7.24 (m, 1H), 7.13 (m, 2H), 7.03 (d, 1H), 6.22 (s, 1H), 5.10 (m, 1H), 4.35 (m, 1H), 2.19 (s, 3H), 2.03 (m, 2H), 1.60 (m, 6H); MS *m*/*z* 422 (M+1).

4.7.7. 1-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-4-(tetrahydro-2*H*-pyran-2-yloxy)-2-butyn-1-ol (19c). To a cold (−78°C) solution of tetrahydro-2-(2-propynyloxy)-2*H*-pyran (0.5 mL, 3.6 mmol) in THF (10 mL) was added n-butyllithium (2.05 mL, 1.6 M in hexanes, 3.3 mmol) dropwise. The reaction mixture was allowed to warm to 0°C, then cooled to −78°C. This reagent was used to treat aldehyde **18** according to general procedure A to give alcohol **19c** (301 mg, 99%) as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$) δ 8.00 (d, 1H), 7.79 (m, 2H), 7.17 (m 3H), 6.99 (m, 1H), 5.79 (s, 1H), 4.81–4.74 (m, 1H), 4.39–4.25 (m, 2H), 3.81 (m, 1H), 3.52 (m, 1H), 3.15 (broad, 1H), 1.90–1.48 (m, 6H); ^{19}F NMR ($CDCl_3$) δ −113.01; MS *m*/*z* 437 (M+Na^+).

4.7.8. 1-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-4-(tetrahydro-2*H*-pyran-2-yloxy)-2-butyn-1-one (20c). Alcohol **19c** was oxidized according to general procedure B to give ketone **20c** (280 mg, 93%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.48 (d, 1H), 7.71 (m, 2H), 7.50 (m, 1H), 7.17 (m, 3H), 4.59 (m, 1H), 4.11 (s, 2H), 3.72 (m, 1H), 3.49 (m, 1H), 1.82–1.50 (m, 6H); ^{19}F NMR ($CDCl_3$) δ −111.89; MS *m*/*z* 435 (M+Na^+).

4.7.9. 4-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-6-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]-2-pyrimidinamine (14c). Ketone **20a** was treated with guanidine **11** according to general procedure C to provide pyrimidine **14c** (165 mg, 71%) as a clear oil. R_f 0.12 (4:1 hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 8.46 (d, 1H), 7.65 (m, 2H), 7.24 (m, 1H), 7.11 (t, 2H), 7.02 (d, 1H), 6.51 (s, 1H), 5.09 (d, 1H), 4.58 (m, 1H), 4.50 (d, 1H), 4.37 (m, 1H), 4.08 (d, 1H), 3.66 (m, 1H), 3.45 (m, 1H), 2.06 (m, 2H), 1.58 (m, 12H); ^{19}F NMR ($CDCl_3$) δ −113.16; MS *m*/*z* 522 (M+1).

4.7.10. 1-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]-pyridin-3-yl]-3-phenyl-2-propyn-1-ol (19d). Aldehyde **18** was subjected to general procedure A using phenyl

acetylene and *n*-butyllithium to provide alcohol **19d** (250 mg, 96%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.10 (d, 1H), 7.87 (dd, 2H), 7.44–7.41 (m, 2H), 7.37–7.33 (m, 3H), 7.25–7.19 (m, 3H), 7.02 (d, 1H), 6.02 (d, 1H), 2.66 (d, 1H); ^{19}F NMR ($CDCl_3$) δ −113.02; MS *m*/*z* 399 ($M+Na^+$).

4.7.11. 1-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]-pyridin-3-yl]-3-phenyl-2-propyn-1-one (20d). Alcohol **19d** was oxidized according to general procedure B to give ketone **20d** (246 mg, 99%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.47 (d, 1H), 7.76 (dd, 2H), 7.47 (dd, 1H), 7.34 (t, 1H), 7.24 (m, 2H), 7.16 (d, 1H), 7.13–7.05 (m, 4H).

4.7.12. 4-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]-pyridin-3-yl]-*N*-cyclopentyl-6-phenyl-2-pyrimidinamine (14d). Ketone **20a** was treated with guanidine **11** according to general procedure C to provide after flash chromatography (4:1, hexanes/EtOAc) pyrimidine **14d** (265 mg, 84%) as a solid. ^{1}H NMR ($CDCl_3$) δ 8.49 (d, 1H), 7.80–7.75 (m, 4H), 7.44–7.41 (m, 3H), 7.33 (m, 1H), 7.22 (t, 2H), 7.09 (d, 1H), 6.82 (s, 1H), 5.25 (d, 1H), 4.49 (m, 1H), 2.22–2.12 (m, 2H), 1.88–1.61 (m, 6H); ^{19}F NMR ($CDCl_3$) δ −112.89; MS *m*/*z* 484 (M+1).

4.8. General procedure D. Amination of 14

To a solution of aryl chloride 14 (1 equiv.) in toluene (0.2 M) was added successively *racemic*-BINAP (6 mol%), cesium carbonate (1.5 equiv.), cyclopentylamine (5 equiv.), and palladium (II) acetate (4 mol%). The resultant mixture was heated to 95°C until the reaction was judged complete by TLC or LC/MS. The solution was cooled to room temperature and ether was added. The organic layer was washed with water and brine. The aqueous layer was extracted with ether and the combined organics dried over sodium sulfate. Purification by flash chromatography or recrystallization provided 7-amino derivative **17**.

Alternatively, aryl chloride **14** was heated in either neat amine at 130–150°C or a solution of excess amine in ethanol at reflux followed by similar workup to provide derivative **17**.

4.8.1. *N*-Cyclopentyl-3-[2-(cyclopentylamino)-6-methyl-4-pyrimidinyl]-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-amine (17b). Aryl chloride **14b** was reacted according to general procedure D to provide derivative **17b** (41 mg, 64%) as a clear oil. ^{1}H NMR ($CDCl_3$): δ 7.69–7.62 (m, 3H), 7.28 (t, 1H), 7.12 (t, 2H), 6.21 (s, 1H), 6.02–5.99 (m, 2H), 5.05 (d, 1H), 4.33 (m, 1H), 3.99 (m, 1H), 2.15 (s, 3H), 2.15–1.45 (m, 16H); ^{19}F NMR ($CDCl_3$) δ −113.70; MS *m*/*z* 471 (M+1). This material was treated with anhydrous hydrochloric acid in ether to provide a hydrochloride salt as a yellow solid.

4.8.2. *N*-Cyclopentyl-3-{2-(cyclopentylamino)-6-[(tetrahydro-2*H*-pyran-2-yloxy)-methyl]-4-pyrimidinyl}-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-amine (17c). Aryl chloride **14c** was reacted according to general procedure D to provide derivative **17c** (146 mg, 82%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.80 (d, 1H), 7.68 (m, 2H), 7.37–7.13 (m, 3H), 6.53 (s, 1H), 6.06 (m, 2H), 5.04 (d, 1H), 4.63 (broad, 1H), 4.53 (d, 1H), 4.40 (m, 1H), 4.31 (d, 1H), 4.05 (m, 1H), 3.74 (m, 1H), 3.50 (m, 1H), 2.24–1.44 (m, 22H); ^{19}F NMR ($CDCl_3$) δ −113.75; MS *m*/*z* 571 (M+1).

4.8.3. *N*-Cyclopentyl-3-[2-(cyclopentylamino)-6-phenyl-pyrimidin-4-yl]-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-amine (17d). Aryl chloride **14d** was reacted according to general procedure D to provide derivative **17d** (64.1 mg, 97%) as a clear oil. ^{1}H NMR ($CDCl_3$): δ 7.84–7.46 (m, 5H), 7.44–7.33 (m, 4H), 7.22 (t, 2H), 6.81 (s, 1H), 6.10–6.07 (m, 2H), 5.24 (d, 1 h), 4.49 (m, 1H), 4.05 (m, 1H), 2.17 (m, 4H), 1.87–1.59 (m, 12H); ^{19}F NMR ($CDCl_3$): δ −113.49; MS *m*/*z* 533 (M+1). This material was treated with anhydrous hydrogen chloride in ether to give the corresponding HCl salt as a orange solid.

4.8.4. *N*-Cyclopentyl-4-[2-(4-fluorophenyl)-7-hydrazino-pyrazolo[1,5-*a*]pyridin-3-yl]-6-methyl-2-pyrimidinamine (17e). To a solution of **14b** (100 mg, 0.237 mmol) in ethanol (1 mL) was added hydrazine (500 uL, 15.9 mmol). The reaction mixture was heated in a sealed tube at 90°C for 72 h. The mixture was cooled and diluted with EtOAc and washed with saturated aqueous sodium bicarbonate, water and brine. The combined organics were dried over magnesium sulfate. Filtration and concentration followed by flash chromatography (38:2 dichloromethane/MeOH) provided hydrazine **17e** (45 mg, 46%) as a yellow solid. R_f 0.43 (38:2 CH_2Cl_2–MeOH). ^{1}H NMR ($CDCl_3$) δ 7.78 (1H), 7.62 (2H), 7.35 (1H), 7.20 (1H), 7.12 (2H), 6.45 (1H), 6.24 (1H), 5.03 (1H), 4.35 (1H), 3.85 (2H), 2.18 (3H), 2.02 (2H), 1.62 (6H); MS *m*/*z* 418 (M+1).

4.8.5. *N*-Cyclopentyl-4-[2-(4-fluorophenyl)-7-(4-methyl-1-piperazinyl)-pyrazolo[1,5-*a*]pyridin-3-yl]-6-methyl-2-pyrimidinamine (17f). Aryl chloride **14b** was reacted according to general procedure D to provide derivative **17f** (80 mg, 70%) as a clear oil. R_f 0.31 (3:2 hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 8.00 (d, 1H), 7.66 (m, 2H), 7.25 (d, 1H), 7.08 (t, 2H), 6.31 (d, 1H), 6.27 (s, 1H), 5.02 (d, 1H), 4.34 (m, 1H), 3.50 (m, 4H), 2.72 (m, 4H), 2.41 (s, 3H), 2.18 (s, 3H), 2.03 (m, 2H), 1.65 (m, 6H); MS *m*/*z* 486 (M+1). This material was taken up in ether and treated with hydrochloric acid in ether to yield an orange precipitate which was isolated by filtration as a hydrochloride salt.

4.8.6. *N*-Cyclopentyl-4-[2-(4-fluorophenyl)-7-(4-methyl-1-piperazinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-6-phenyl-2-pyrimidinamine hydrochloride (17g). Aryl chloride **14d** was reacted according to general procedure D to provide derivative **17g** (70 mg, 99%) as an oil. This material was taken up in ether and treated with hydrochloric acid in ether to yield a yellow precipitate which was isolated by filtration as a hydrochloride salt. ^{1}H NMR (DMSO-d_6) δ 11.18 (broad, 1H), 8.22 (d, 1H), 7.78–7.73 (m, 4H), 7.63–7.36 (m, 6H), 6.77 (s, 1H), 4.29 (broad, 1H), 4.19–4.16 (m, 2H), 3.55 (m, 2H), 3.39–3.29 (m, 4H), 2.83 (d, 3H), 1.95 (m, 2H), 1.73–1.59 (m, 6H); ^{19}F NMR (DMSO-d_6) δ −112.68; MS *m*/*z* 548 (M+1).

4.8.7. *N*^{1}-[3-[2-(Cyclopentylamino)-6-phenyl-4-pyrimidinyl]-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-yl]-1,2-ethanediamine (17h). Aryl chloride **14d** was reacted according to general procedure D to provide derivative **17h**

(30 mg, 48%) as an oil. ^{1}H NMR ($CDCl_3$) δ 7.84–7.72 (m, 6H), 7.42–7.40 (m, 3H), 7.33 (t, 1H), 7.18 (t, 1H), 6.80 (s, 1H), 6.44 (m, 1H), 6.05 (d, 1H), 5.26 (d, 1H), 4.47 (m, 1H), 3.48 (m, 2H), 3.09 (broad, 2H), 2.93 (broad, 2H), 2.13 (m, 2H), 1.83–1.56 (m, 6H); ^{19}F NMR ($CDCl_3$) δ −113.21; MS *m/z* 508 (M+1). This material was taken up in ether and treated with hydrochloric acid in ether to yield an orange precipitate which was isolated by filtration as a hydrochloride salt.

4.8.8. 3-[2-(Cyclopentylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)-*N*-(4-methoxyphenyl)pyrazolo[1,5-*a*]pyridin-7-amine (17i). Aryl chloride **14a** was reacted according to general procedure D to provide derivative **17i** (35 mg, 60%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.99 (d, 1H), 7.84 (d, 1H), 7.70–7.64 (m, 3H), 7.32–7.26 (m, 3H), 7.17 (t, 2H), 9.67 (d, 2H), 6.34–6.31 (m, 2H), 5.43 (broad, 1H), 4.35 (m, 1H), 3.85 (s, 3H), 2.11–2.03 (m, 2H), 1.83–1.55 (m, 6H); ^{19}F NMR ($CDCl_3$) δ −112.97; MS *m/z* 495 (M+1).

4.8.9. Methyl {[3-[2-(cyclopentylamino)-6-methyl-4-pyrimidinyl]-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-yl]amino}acetate (17j). Aryl chloride **14b** was reacted according to general procedure D to provide derivative **17j** (95 mg, 90%) as a yellow foam. ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 1H), 7.67 (dd, 2H), 7.30 (m, 1H), 7.13 (m, 2H), 6.56 (m, 1H), 6.24 (s, 1H), 5.90 (d, 1H), 5.07 (broad, 1H), 4.35 (m, 1H), 4.17 (d, 2H), 3.82 (s, 3H), 2.17 (s, 3H), 2.03 (m, 2H), 1.75–1.50 (m, 6H); ^{19}F NMR ($CDCl_3$) δ −113.61; MS *m/z* 475 (M+1).

4.9. Enone cyclization method

4.9.1. 1-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-methyl-2-propen-1-ol (21). In a similar manner as described in general procedure A from aldehyde **18** (510 mg, 1.9 mmol) and isopropenyl magnesium bromide was obtained alcohol **21** (530 mg, 90%) as an off-white solid. R_f 0.26 (4:1 hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 7.81–7.70 (m, 3H), 7.21–7.08 (m, 3H), 6.95 (d, 1H), 5.41 (s, 1H), 5.30 (s, 1H), 5.08 (s, 1H), 1.62 (s, 3H); MS *m/z* 317 (M+1).

4.9.2. 1-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-methyl-2-propen-1-one (22). In a similar manner as in general procedure B was formed enone **22** (390 mg, 74%) as a white solid. R_f 0.29 (4:1 hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 7.96 (d, 1H), 7.59 (m, 2H), 7.34 (t, 1H), 7.18–7.07 (m, 3H), 5.48 (s, 1H), 5.40 (s, 1H), 1.98 (s, 3H).

4.9.3. 4-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-5-methyl-2-pyrimidinamine (23). To a suspension of guanidinium salt **11** (68 mg, 0.42 mmol) in ethanol (1 mL) was added sodium ethoxide (138 μL, 3 M in ethanol, 0.41 mmol). A solution of enone **22** in ethanol (1 mL) was added and the reaction mixture was allowed to stir at rt for 16 h. An additional aliquot of **11** (68 mg, 0.42 mmol) and sodium ethoxide (138 μL, 3 M in ethanol, 0.41 mmol) in ethanol (1 mL) was added to reaction mixture and allowed to stir an additional 24 h. Palladium on carbon (10%, 30 mg) was added to reaction mixture and allowed to stir at rt for 30 min under an atmosphere of air, at which point additional palladium on carbon (10%, 100 mg) was added. The reaction mixture was allowed to stir at rt 16 h. The suspension was diluted with EtOAc and filtered through Celite. Concentration followed by flash chromatography (4:1 hexanes/ethyl acetate) provided pyrimidine **23** (57 mg, 43%) as a clear oil. R_f 0.24 (4:1 hexanes/ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 1H), 7.64 (m, 2H), 7.57 (d, 1H), 7.17 (m, 1H), 7.08 (t, 2H), 7.00 (d, 1H), 5.09 (d, 1H), 4.26 (m, 1H), 2.03 (m, 2H), 1.82–1.45 (m, 9H); MS *m/z* 422 (M+1). To a solution of the product in ether was added 1 M hydrochloride in ether. The precipitated solid was isolated to give the corresponding hydrochloride salt.

4.9.4. *N*-Cyclopentyl-3-[2-(cyclopentylamino)-5-methyl-4-pyrimidinyl]-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-amine (24). Aryl chloride **23** was reacted according to general procedure D to provide 5′ methyl derivative **24** (47 mg, 90%) as a yellow oil. R_f 0.15 (4:1 hexanes/ethyl acetate). ^{1}H NMR (DMSO-d_6) δ 8.51 (broad, 1H), 8.27 (s, 1H), 7.65 (m, 2H), 7.41 (t, 1H), 7.28 (t, 2H), 6.97 (d, 1H), 6.74 (br, 1H), 6.25 (d, 1H), 4.14 (br, 1H), 4.05 (br, 1H), 2.09 (m, 2H), 1.96–1.42 (m, 14H), 1.64 (s, 3H); MS *m/z* 471 (M+1). To a solution of the product in ether was added 1 M hydrochloride in ether. The precipitated solid was isolated to give the corresponding hydrochloride salt.

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