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Pyrazolopyridine antiherpetics: SAR of C2′ and C7 amine substituents

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Abstract—A novel series of potent pyrazolo[1,5-*a*]pyridine inhibitors of herpes simplex virus 1 replication have been identified. Several complimentary synthetic methods were developed to allow facile access to a diverse set of analogs from common late stage intermediates. Detailed examination of the amine substituents at the C2′ position of the pyrimidine and C7 position of the core pyrazolopyridine is described. The antiviral data suggests that non-polar amines are preferred for optimal activity. Additionally, the 2′ position has been shown to require an NH group to retain activity levels similar to that of the gold standard acyclovir.

1. Introduction

Herpesviruses are a large family of double-stranded DNA viruses that infect most animal species.[1] Within the herpesvirus family, there are eight members that infect humans. Of particular concern are herpes simplex viruses 1 and 2 (HSV-1, HSV-2) due to their high prevalence and resulting symptoms of oral fever blisters and genital lesions, respectively. The current gold standard therapy based on acyclovir (**3**) and its prodrug valacyclovir is both safe and efficacious, however there is still significant interest in finding new therapeutic agents with a different mode of action.[2] Our group recently identified pyrazolo[1,5-*a*]pyridine GW3733 (**1**)[3] and its corresponding imidazo[1,2-*a*]pyridine derivative GW4637 (**2**)[4] as potent and selective inhibitors of herpes simplex viruses HSV-1 and HSV-2 (Fig. 1).

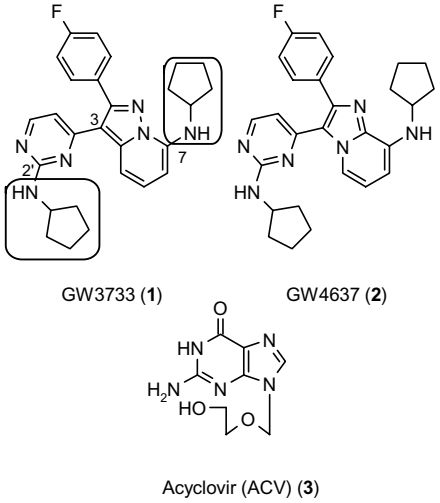

Figure 1.

The 7-amino-3-pyrimidyl substituted pyrazolo[1,5-*a*]-pyridine **1** was initially identified as a hit from a high throughput antiviral screen.[5] Early screening results suggested that a 7 substituent and in particular a 7-amino group gave good activity albeit based on a limited data set around the core heterocyclic scaffold. Pyrazolopyridine **1** was the only analog with the C2′/C7 diamine substitution pattern available for study at the conclusion

Keywords: Pyrazolo[1,5-*a*]pyridine; Antiherpetic; HSV.
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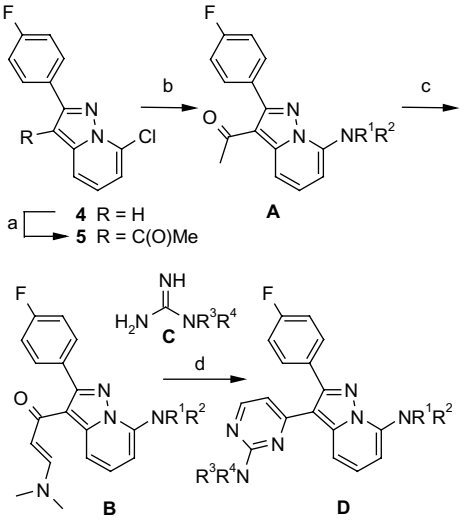
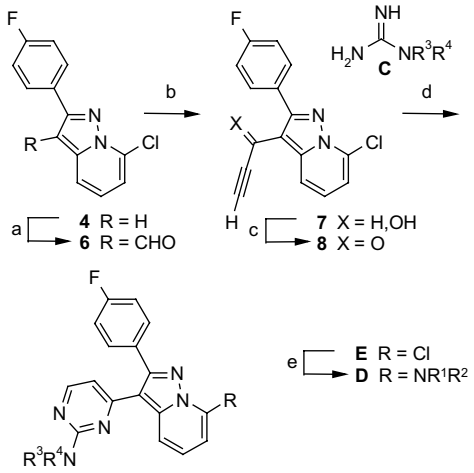
of the screen. The lack of antiviral data in this series and encouraging potency provided impetus to develop a chemistry strategy to explore the overall SAR of the pyrazolopyridine core structure. It was an early goal of our synthetic effort to explore the SAR attributes of the combination of C2′ and C7 amines in particular. The screening hit GW3733 had originally been isolated as an undesired by-product during late stage synthetic manipulations targeting alternative structures for an unrelated program.[6] Because of this, an efficient synthesis of 2′,7-diamino substituted 3-pyrimidyl-pyrazolopyridines had not been established. To this end, several complimentary synthetic strategies were developed to efficiently derivatize the 2′ and 7 position at a late stage in the synthesis to allow for diversification of the analogs from a handful of common advanced intermediates.

2. Chemistry[7]

The previously described pyrazolopyridine intermediate **4**[3] served as a key branching point for a number of C2′ and C7 analogs. The 3- and 7-position of this unique heterocycle lend nicely to orthogonal functionalization due to their nucleophilic and electrophilic character, respectively. The two synthetic routes described in Schemes 1 and 2 allow for either an early or late manipulation of the C3 and C7 positions as desired, to maximize the flexibility of the common intermediate **4**. The first route (Scheme 1) focused on constructing the pyrimidine with the aim of introducing diversity at the C2′ position as the final step in the synthetic sequence. This methodology takes advantage of the nucleophilic nature of the 3 position of pyrazolopyridine intermediate **4** under Friedel–Crafts acylation conditions, thus upon treatment with an acylating agent, methyl ketone **5** was obtained. At this point it was necessary to introduce the C7 amine group prior to final elaboration of



Scheme 1. Reagents and conditions: (a) Ac_2O, $BF_3{\cdot}OEt_2$, PhMe, 100 °C, 77%; (b) $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, HNR^1R^2, PhMe, 85–100 °C; (c) DMF–DMA, Δ; (d) *t*-BuOK, THF, Δ.



Scheme 2. Reagents and conditions: (a) $POCl_3$, DMF, H_2O, 95%; (b) ethynyl-MgBr, THF, −78 to 0 °C, 88%; (c) MnO_2, $CHCl_3$, 77%; (d) K_2CO_3 or NaOEt, NMP or EtOH, Δ; (e) HNR^1R^2, Δ or HNR^1R^2, $Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3, PhMe, 85–100 °C.

the pyrimidine moiety. Direct nucleophilic displacement of the 7-chloro substituent provided results that were highly dependent on the choice of amine under thermal conditions and did not provide the level of reproducibility that was desired. However, a Buchwald–Hartwig palladium catalyzed version of this transformation proved to be quite general resulting in good to excellent yields of **A** employing a wide variety of amines.[8] Methyl ketone **A** was treated with neat dimethylformamide dimethyl acetal under reflux for several days to produce the corresponding vinylogous amide **B**. Subsequent exposure of **B** to a series of guanidines **C** gave the fully elaborated C3 pyrimidine analogs **D**.

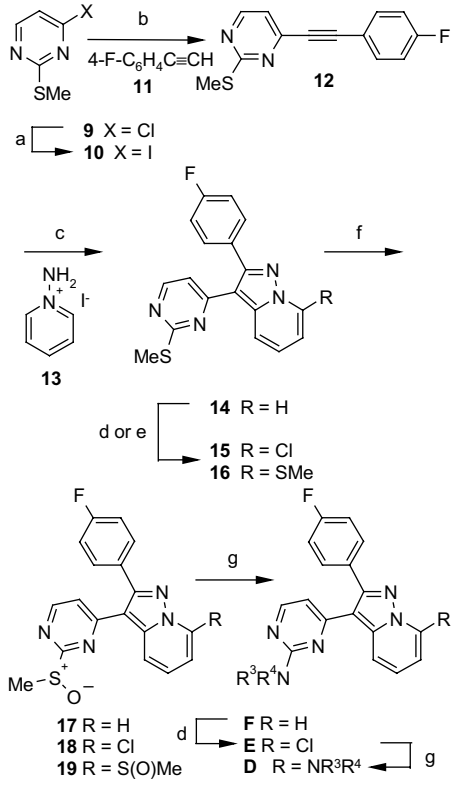
A complementary strategy (Scheme 2) was developed whereby the 7-amine could be installed at the final stage of the synthesis to allow for an efficient diversification of the C7 substituent. This amine-last strategy required modifications beyond simply re-ordering the steps of the synthesis outlined in Scheme 1. This was primarily due to the inability of the 7-chloro substituent to tolerate the harsh conditions of the vinylogous amide formation and its subsequent condensation with various guanidines used to form the C3 pyrimidine. An alternative pyrimidine condensation strategy was developed whereby a more reactive vinylogous amide surrogate was used, which could also be formed under significantly milder conditions to retain the integrity of the 7-chloro group through the synthesis. The alternative strategy made use of a more reactive alkynyl ketone functionality in place of the vinylogous amide resulting in milder condensation conditions. This strategy removed the need for the DMF–DMA condensation and the dimethylamine associated with it at elevated temperatures.[9]

Intermediate **4** was subjected to Vilsmeier–Haack formylation conditions to provide aldehyde **6** in excellent yield. The commercially available ethynyl Grignard reagent added smoothly to aldehyde **6** at low temperature to provide the propargyl alcohol **7**. This material could be oxidized using manganese dioxide to the alkyn-

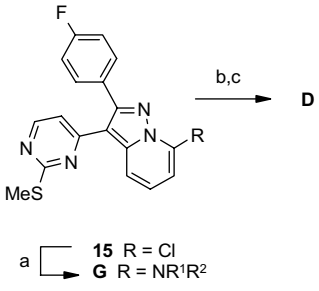
yl ketone **8**. At this point the reactive unsaturated ketone **8** was condensed with a series of guanidines **C** to provide the cyclized pyrimidines **E** containing the C7 chloro substituent. These penultimate intermediates could be subjected to either thermal or Buchwald–Hartwig amination conditions to rapidly modify the C7 amino substituent as a final step in the sequence.

A third method was developed utilizing a [3 + 2] cycloaddition strategy[10] (Scheme 3). With this method an electrophilic a diaryl alkyne is treated with an *N*-aminopyridinium salt to form upon treatment with base in one pot a diaryl substituted pyrazolopyridine. In preparation for the cyclization event, alkyne **12** was readily prepared via a Sonogashira coupling of 4-iodopyrimidine **10**[11] and terminal alkyne **11**. Treatment of alkyne **12** with the commercially available *N*-aminopyridinium iodide **13** in the presence of DBU provided pyrazolopyridine core **14**. The C2′ methylthio functionalized pyrazolopyridine **14** proved to be a useful intermediate allowing for either introduction of the C7 or the C2′ amine first followed by functionalization of the remaining position based on the conditions employed. This also allowed the 2′ amine to be introduced via nucleophilic substitution rather than as part of a preformed guanidine as in the previous routes. While the 2′ thioether was resistant to amine displacement using thermal conditions the corresponding sulfoxide was easily displaced and provided a facile method to selectively activate the 2′ position at various points in the synthesis. Oxidation of the C2′ *S*-methyl group to the corresponding sulfoxide was readily accomplished by treatment with 1 equiv of *m*-CPBA in dichloromethane. The sulfoxides were routinely isolated and could be stored for extended periods. Treatment of the sulfoxide **17** with a wide variety of amines at ambient or slightly elevated temperatures resulted in clean displacement of the sulfoxide to give the C7 unsubstituted pyrazolopyridine **F**. Alternatively C7 protio derivative **14** could be treated with a strong base to selectively deprotonate the 7 position.[12] This could be further functionalized by trapping the resulting anion with an electrophile such as CCl_4 (R = Cl, **15**), or dimethyl disulfide (R = SMe, **16**). The 2′-methylthio pyrimidine derivatives (**14**, **15**, **16**) could be further functionalized in an analogous fashion by oxidation to their corresponding sulfoxides (**17**, **18**, **19**) followed by amine displacement. In the case of bis-*S*-methyl derivative **16** the oxidation was not regioselective but by treatment with 2 equiv of *m*-CPBA the bis-sulfoxide product could be obtained cleanly. Double displacement of the two sulfoxides was achieved to yield a version of the target pyrazolopyridine **D** where identical amines were substituted at the 2′ and 7 positions. In the case of the 7-chloro derivative **15**, the oxidation/displacement protocol left the 7-Cl group untouched due to the relatively low temperatures required to displace the 2′ sulfoxide **18** and gave the desired 7-halo derivative **E**, the penultimate intermediate in Scheme 2 outlined above. At higher temperatures, the 7-chloro could be displaced to yield the diamine **D** in an analogous fashion to that of the bis-sulfoxide **19**. Alternatively, the 7-chloro derivative **E** could be isolated and re-subjected to conditions employing a different amine at elevated temperatures or under palladium mediated conditions as described above to yield the versions of **D** containing differing amino groups at the 2′ and 7 positions.

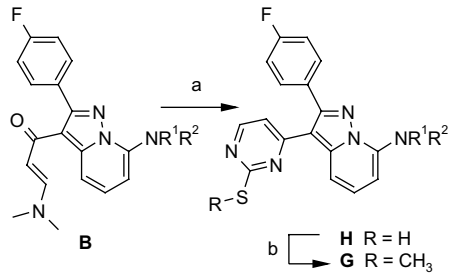
A minor permutation of the above methods outlined in Scheme 3 involved taking advantage of the unique reactivity of the C7 chloro substituent. Subjecting the 7-chloro-2′-methylthio derivative **15** to palladium mediated amination prior to oxidation of the sulfur resulted in a mild and selective conversion to the 7-amino-2′methylthio derivative **G** with complete regioselectivity. Oxidation and displacement of the 2′ *S*-methyl group proceeded as before to give the fully elaborated pyrazolopyridine **D** (Scheme 4). This strategy effectively



Scheme 3. Reagents and conditions: (a) aqueous HI, 99%; (b) $PdCl_2(PPh_3)_2$, CuI, THF, 73%; (c) DBU, MeCN, 0 °C to rt, 79%; (d) *n*-BuLi, CCl_4, THF; (e) *n*-BuLi, MeSSMe, THF; (f) *m*-CPBA, CH_2Cl_2, 0 °C, 99%; (g) HNR^3R^4; (h) HNR^1R^2, Δ or HNR^1R^2, $Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3, PhMe, 85–100 °C.



Scheme 4. Reagents and conditions: (a) HNR^1R^2, $Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3, PhMe, 85–100 °C; (b) *m*-CPBA, CH_2Cl_2, 0 °C; (c) HNR^3R^4, Δ.



Scheme 5. Reagents: (a) thiourea, KOH, EtOH; (b) NaOH, H_2O, MeI.

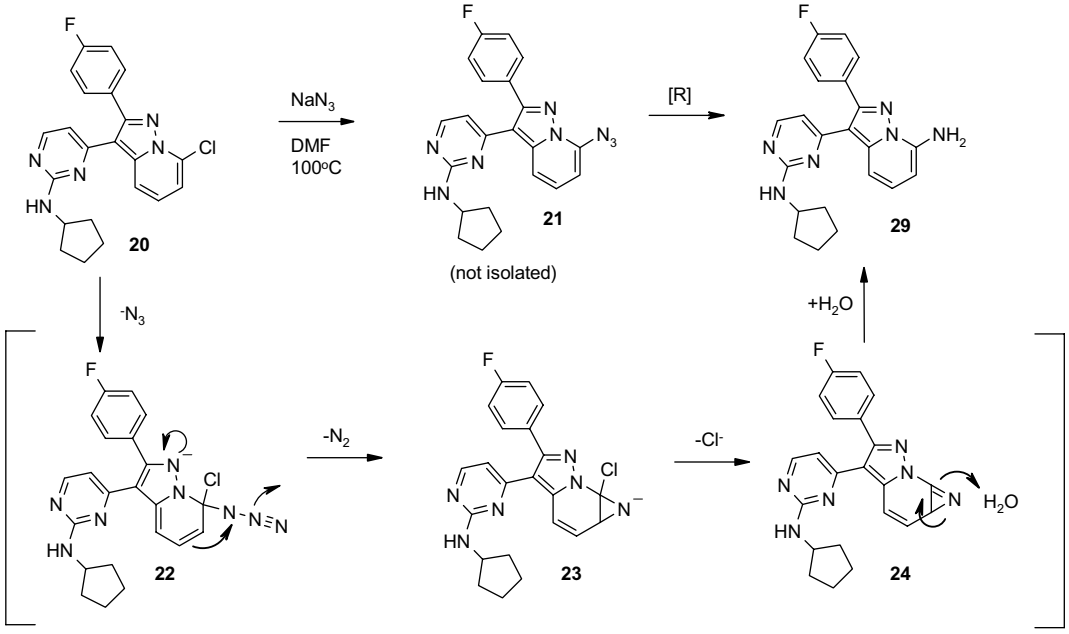
reversed the substitution order described above simply based on the orthogonal reactivity of the 2′ and 7 position functionality present in intermediate **15**.

The methylthio-pyrimidine **G** has also been accessed using a variation on the chemistry described in Scheme 1 to offer an alternative route into this useful penultimate intermediate. In this case, vinylogous amide **B** can be treated with thiourea to produce the corresponding thiol substituted pyrimidine **H**. Methylation of this material with methyl iodide using Schotten–Bauman conditions produced the *S*-methyl pyrimidine **G** (Scheme 5).

During our 7-amino SAR investigations we desired to access the parent unsubstituted 7-NH_2 compound **29**. We were of course interested in the activity of this derivative but also thought it might offer an opportunity for additional SAR modifications via reductive amination methodology. Our first attempt to access the 7-NH_2 analog was designed to take advantage of the electrophilic nature of the 7-chloro derivative **20** via treatment with sodium azide to produce the 7-azido derivative **21**. The azide strategy was chosen primarily to avoid the relatively weak nucleophile ammonia or aqueous ammonium hydroxide, which we thought would require much harsher conditions. The resultant azide would then be reduced to its corresponding amine and thereby gain access to the parent unsubstituted derivative **29**. Interestingly, we observed only the 7-amino derivative **29** upon treating **20** with sodium azide in DMF at 100 °C overnight followed by an aqueous work-up. It was not immediately clear how this occurred however we propose a possible mechanism in Scheme 6. The addition of azide is suspected to proceed as planned but rather than an addition elimination reaction we propose an aziridine ring formation across the C6–C7 double bond of the pyrazolopyridine ring system as depicted by structure **23** resulting in the loss of N_2. The chloroaziridine could then eliminate chloride to form the azirine **24**, which could rearrange the presence of water to reduce the increasing ring strain while forming the 7-amino-pyrazolopyridine derivative **29** (Scheme 6). At this time we have not examined this process in detail, but it does appear to be reproducible and give the 7-amino derivative **29** as the sole product.

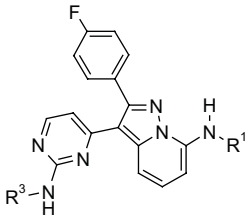
3. Results and discussion

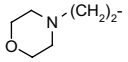
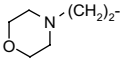
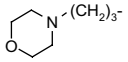
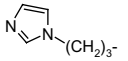
The initial screening hit GW3733 (**1**) established an initial lead with similar potency to the 'gold standard' acyclovir (Table 1, entries 1 and 2) in Vero cell culture. Also noteworthy is that the pyrazolopyridines described herein are not DNA synthesis inhibitors and thus have a different mechanism of action from the currently marketed nucleoside analogs. We were very excited about our prospects and decided to look at several close analogs that might enhance the activity or increase the drug-like properties of the molecule.[13] One of the primary drawbacks with GW3733 (**1**) is its inherent lipophilicity and limited solubility in a biologically relevant medium. As



Scheme 6.

Table 1. HSV-1 antiviral activity and cytotoxicity of C2′/C7 analogs containing 1° and 2° amine substituents



Entry	Compd	R^3–	R^1–	EC_{50} (μM)	CC_{50} (μM)
1	ACV	—	—	0.39	>100
2	**1**	–*c*-C_5H_9	–*c*-C_5H_9	0.26	>160
3	**25**	–*n*-C_4H_9	–Allyl	0.48	>40
4	**26**	–*n*-C_4H_9	–*n*-C_4H_9	0.33	>160
5	**27**	–*c*-C_5H_9	–*n*-C_4H_9	0.41	>40
6	**28**	–*n*-C_4H_9	–*c*-C_3H_5	0.46	>40
7	**29**	–H	–*c*-C_5H_9	0.46	>40
8	**30**	–*c*-C_3H_5	–*n*-C_4H_9	1.07	126
9	**31**	–*c*-C_5H_9	H	0.83	18
10	**32**	–*n*-C_4H_9	–CH_3	1.46	>40
11	**33**	–*c*-C_5H_9	–Pyrrolidine	0.6	>40
12	**34**	–*c*-C_5H_9	–Morpholine	1.23	>40
13	**35**	–$(CH_2)_3OH$	–*n*-C_4H_9	4.44	19
14	**36**	–*n*-C_4H_9	–$(CH_2)_2OCH_3$	0.25	33
15	**37**		–*n*-C_4H_9	4.19	>5
16	**38**	–*n*-C_4H_9		0.41	12
17	**39**		–*c*-C_5H_9	6.07	15
18	**40**		–*n*-C_4H_9	4.33	ND
19	**41**	2-Py–CH_2–	–*n*-C_4H_9	3.67	ND
20	**42**	–*c*-C_5H_9	4-$MeOC_6H_4$–	1.74	>40
21	**43**	–Ph	–*c*-C_5H_9	0.46	>40
22	**44**	4-$MeOC_6H_4$–	–*c*-C_5H_9	1.22	>40
23	**45**	4-FC_6H_4–	–*c*-C_5H_9	0.57	>40
24	**46**	4-FC_6H_4–	4-FC_6H_4–	>40	>40
25	**47**	–*c*-C_5H_9	4-FC_6H_4–	3.25	>40

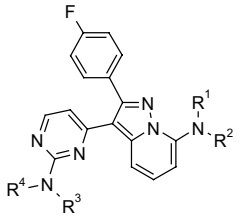
Vero cells, SC-16 strain. EC_{50} is the concentration at which 50% efficacy in the antiviral assay is observed. CC_{50} is the concentration at which 50% cytotoxicity is observed.

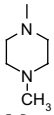
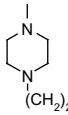
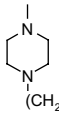
can be seen in Table 1, several analogs with similar lipophilicity to that of the cyclopentylamine substituent were constructed and there was minimal dependence of activity on the steric bulk of these greasy amines (entries 2–10). At most an approximate five-fold loss in activity was observed by altering the hydrocarbon character of the cyclopentyl group. In most cases this resulted from a decrease in the hydrocarbon character rather than an added functionality. However, when more polar functionality was introduced, the activity did decrease in general with basic amines tethered to the C2′ position being the weakest inhibitors (entries 15 and 17–19). Neutral or electron deficient aryl groups at the 2′ position were tolerated nearly as well as aliphatic amines (entries 21 and 23) while electron rich substituents were not as active (entry 22). Similarly anilino groups at the 7 position resulted in an order of magnitude decrease in potency compared to GW3733 (entries 24 and 25).

Additional structural variations were examined consisting of analogs containing tertiary nitrogens at the 2′ and/or 7 positions. A clear trend noted from these data was the requirement that the 2′ position contain an NH moiety to retain interesting levels of activity (Table 2, entries 1, 4–5, 9–11). The 7 position was less sensitive to changing to the fully substituted nitrogen with several analogs delivering compounds with sub-micromolar activity (entries 3, 7–8). The piperidine containing analog **50** had activity similar to the NH containing derivative GW3733 (**1**).

Several analogs were also assayed against HSV-2 in order to assure ourselves that the activity we observed for the inhibition of HSV-1 in the above Tables 1 and 2 was not diverging from the ultimate target virus. As can be seen in Table 3, the activity levels and rank ordering of compounds is very similar for both HSV-1 and HSV-2. Again, the C2′ NH substituted analogs were

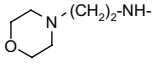
Table 2. HSV-1 antiviral activity and cytotoxicity of C2′/C7 analogs containing tertiary amine substituents



Entry	Compd	R^3R^4N–	R^1R^2N–	EC_{50} (μM)	CC_{50} (μM)
1	**48**	Pyrrolidine	–NH-*n*-C_4H_9	4.9	>160
2	**49**	–NH-*c*-C_5H_9	Pyrrolidine	1.21	>40
3	**50**	–NH-*c*-C_5H_9	Piperidine	0.34	>40
4	**51**	–NMe_2	Pyrrolidine	5.47	ND
5	**52**	–NMe_2	–NH-*c*-C_5H_9	1.45	>40
6	**53**	–NH-*n*-C_4H_9	–NMe_2	1.30	>40
7	**54**	–NH-*n*-C_4H_9		0.77	5.5
8	**55**	–NH-*n*-C_4H_9	Morpholine	0.95	>40
9	**56**	Morpholine	–NH-*n*-C_4H_9	14.7	ND
10	**57**		–NH-*n*-C_4H_9	6.74	ND
11	**58**		–NH-*n*-C_4H_9	11.1	58

Vero cells, SC-16 strain. EC_{50} is the concentration at which 50% efficacy in the antiviral assay is observed. CC_{50} is the concentration at which 50% cytotoxicity is observed.

Table 3. HSV-2 antiviral activity

Entry	Compd	R^3R^4N–	R^1R^2N–	EC_{50} (M)
1	ACV	—	—	0.16
2	**1**	–NH-*c*-C_5H_9	–NH-*c*-C_5H_9	0.16
3	**25**	–NH-*n*-C_4H_9	–NH–allyl	0.74
4	**26**	–NH-*n*-C_4H_9	–NH-*n*-C_4H_9	<0.16
5	**27**	–NH-*c*-C_5H_9	–NH-*n*-C_4H_9	0.27
6	**28**	–NH-*n*-C_4H_9	–NH-*c*-C_3H_5	0.32
7	**29**	–NH_2	–NH-*c*-C_5H_9	4.1
8	**30**	–NH-*c*-C_3H_5	–NH-*n*-C_4H_9	0.99
9	**31**	–NH-*c*-C_5H_9	–NH_2	0.79
10	**32**	–NH-*n*-C_4H_9	–NH–CH_3	2.78
11	**33**	–NH-*c*-C_5H_9	–Pyrrolidine	0.54
12	**36**	–NH-*n*-C_4H_9	–$NH(CH_2)_2OCH_3$	0.60
13	**37**		–*n*-C_4H_9	5.0
14	**42**	–NH-*c*-C_5H_9	4-$MeOC_6H_4NH$–	5.5
15	**52**	–NMe_2	–NH-*c*-C_5H_9	4.0
16	**53**	–NH-*n*-C_4H_9	–NMe_2	2.36

EC_{50} is the concentration at which 50% efficacy in the antiviral assay is observed.

superior to the unsubstituted and tertiary substituted analogs. Also worth noting was the sub-micromolar activity observed for several of these analogs, which is comparable or better than that of the gold standard acyclovir. The above compounds have not been widely screened against other herpesviruses. Several representative examples have been inactive against other viruses such as hepatitis B and HIV-1.

4. Conclusions

In summary, a series of novel antiviral compounds have been identified, which show similar activity against herpes simplex virus to that of the gold standard acyclovir. This new series of inhibitors are not DNA synthesis inhibitors like the currently marketed nucleoside analogs. The 2′,7-diamino substitution pattern about the 3-pyrimidylpyrazolo[1,5-*a*]pyridine core scaffold has been shown to affect the antiviral activity based on numerous examples of combinations of amine groups. The most potent analogs have been shown to require a 2′ NH moiety while the 7 position is slightly more tolerant of a number of amino substituents including primary, secondary, and tertiary nitrogens. This new class of inhibitor shows potent antiviral activity separated from cytotoxicity that suggest its potential use as a therapeutic intervention in HSV-infected patients.

5. Experimental

5.1. 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. In liu of elemental analysis, compound purity was assessed by high field ^{1}H NMR and HPLC. Biological results were obtained with compounds of >98% purity as determined by the above methods.

5.2. Synthesis of GW3733 (1)

5.2.1. 1-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (5). To a solution of **4**[3] (10.0 g, 40.5 mmol) in toluene (225 mL) at rt was added Ac_2O (4.6 mL, 48.6 mmol). $BF_3{\cdot}OEt_2$ (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 aq $NaHCO_3$. 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 $MgSO_4$, filtered, and concentrated. The residue was purified by recrystallization from EtOAc–hexanes to give methyl ketone **5** (9.0 g, 77%) as reddish 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).

5.2.2. 1-[7-(Cyclopentylamino)-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]ethanone (59). To a solution of ketone **5** (2.7 g, 9.5 mmol) in toluene (50 mL) was added successively racemic-BINAP (378 mg, 0.6 mmol), Cs_2CO_3 (4.7 g, 14.3 mmol), cyclopentylamine (4.7 mL, 47.5 mmol), and $Pd(OAc)_2$ (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 $MgSO_4$. Filtration and concentration followed by flash chromatography (4:1 hexanes–EtOAc) provided 7-amino derivative **59** (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).

5.2.3. (2*E*)-1-[7-(Cyclopentylamino)-2-(4-fluorophenyl)-pyrazolo[1,5-*a*]pyridin-3-yl]-3-(dimethylamino)-2-propen-1-one (60). A solution of **59** (3.1 g, 9.2 mmol) in DMF–dimethyl acetal (25 mL) was heated at 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 $MgSO_4$. Filtration and concentration followed by flash chromatography (EtOAc) provided enamine **60** (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 (br, 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).

5.2.4. *N*-Cyclopentylguanidine hydrochloride (61).[14] 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 h 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 (**61**) (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).

5.2.5. *N*-Cyclopentyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-amine (1). To a solution of **60** (3.5 g, 8.9 mmol) in THF (36 mL, 0.25 M) was added *N*-cyclopentylguanidine hydrochloride (**61**) (1.9 g, 11.6 mmol), followed by solid *t*-BuOK (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 $MgSO_4$, 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.

5.3. *N*-Allyl-3-[2-(butylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)-pyrazolo[1,5-*a*]pyridin-7-amine (25)

5.3.1. 7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridine-3-carbaldehyde (6). 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 pyrazolopyridine **4** (10.0 g, 40.5 mmol) and the resultant solution was stirred overnight. Water was added, followed by CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was recrystallized from ether and hexanes to give aldehyde **6** (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.).

5.3.2. 1-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-ol (7). To a cold (0 °C) solution of aldehyde **6** (5.5 g, 20.0 mmol) in THF (130 mL) was added ethynylmagnesium bromide (100 mL, 0.5 M in THF, 50.0 mmol) dropwise. The resultant mixture was stirred at that temperature until the reaction judged complete by TLC (1 h). The resultant solution was quenched with water and extracted with ether. The organic layer was washed with water and brine and the combined organics were dried over Na_2SO_4. Filtration and concentration followed by recrystallization from CH_2Cl_2 provided alcohol **7** (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).

5.3.3. 1-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-propyn-1-one (8). To a solution of alcohol **7** (5.3 g, 17.6 mmol) in CH_2Cl_2 (600 mL) was added MnO_2 (61.3 g, 705 mmol). The reaction mixture was stirred at room temperature for 20 min. The suspension was filtered through a pad of Celite and the filtrate was concentrated in vacuo to give ketone **8** (4.0 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).

5.3.4. *N*-Butyl-4-[7-chloro-2-(4-fluorophenyl)pyrazolo-[1,5-*a*]pyridin-3-yl]-2-pyrimidinamine (61). To a solution of ketone **8** (0.5 g, 1.7 mmol) in EtOH (10 mL) was added *N*-butylguanidine sulfate[15] (0.5 g, 2.2 mmol) and NaOEt (0.8 mL, 21 wt % in EtOH, 2.2 mmol) at rt. After 2 h, water was added and the resultant mixture was extracted with EtOAc. The combined organics were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica to give pyrimidine **61** (0.4 g, 59%) as a fluffy pale yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.40 (d, 1H), 8.07 (d, 1H), 7.65 (m, 2H), 7.29 (m, 1H), 7.15 (t, 2H), 7.06 (d, 1H), 6.32 (d, 1H), 5.16 (br s, 1H), 3.49 (q, 2H), 1.71–1.41 (m, 4H), 0.99 (t, 3H); ^{19}F NMR ($CDCl_3$): δ −112.77; MS *m*/*z* 396 (M+1).

5.3.5. *N*-Allyl-3-[2-(butylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)-pyrazolo[1,5-*a*]pyridin-7-amine (25). A solution of **61** (150 mg, 0.4 mmol) in allylamine (5 mL, 67 mmol) was heated at 85 °C in a sealed tube for 88 h. After cooling and concentrating the reaction mixture, flash chromatography (4:1 hexanes–EtOAc) afforded **25** (140 mg, 88%) as a pale yellow foam. ^{1}H NMR ($CDCl_3$): δ 7.89 (br s, 1H), 7.78 (d, 1H), 7.62 (m, 2H), 7.36 (t, 1H), 7.16 (t, 2H), 6.31–6.26 (m, 2H), 6.09–5.92 (m, 2H), 5.39–5.24 (m, 2H), 4.06 (t, 2H), 3.50 (q, 2H), 1.72–1.41 (m, 4H), 0.98 (t, 3H); ^{19}F NMR ($CDCl_3$): δ −113.16; MS *m*/*z* 417 (M+1). Anal. Calcd for $C_{24}H_{25}FN_6$: C, 69.21; H, 6.05; N, 20.18. Found: C, 69.27; H, 6.07; N, 20.03.

5.4. *N*-Butyl-3-[2-(butylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-amine (26)

Compound **26** was made in a similar manner as described for compound **1** to give a yellow solid. R_f 0.67 (1:1 hexanes–EtOAc); ^{1}H NMR ($CDCl_3$): δ 7.98 (d, 1H), 7.68 (d, 1H), 7.59 (m, 2H), 7.27 (t, 1H), 7.10 (t, 2H), 6.25 (d, 1H), 6.00–5.96 (m, 2H), 5.05 (m, 1H), 3.41 (m, 2H), 3.33 (m, 2H), 1.71 (m, 2H), 1.60 (m, 2H), 1.50–1.36 (m, 4H), 0.97–0.91 (m, 6H); MS *m*/*z* 433 (M+1).

5.5. *N*-Butyl-3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-amine (27)

Compound **27** was made in a similar manner as described for compound **1** to give a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.01 (d, 1H), 7.73 (d, 1H), 7.62 (m, 2H), 7.29 (t, 1H), 7.12 (t, 2H), 6.28 (d, 1H), 6.05 (m, 1H), 5.98 (d, 1H), 5.27 (br, 1H), 4.32 (m, 1H), 3.34 (m, 2H), 2.10–2.00 (m, 2H), 1.77–1.41 (m, 10H), 0.97 (t, 3H); ^{13}C NMR ($CDCl_3$): δ 163.03 (d, J_{CF} = 244.5 Hz), 162.14, 161.41, 156.74, 152.10, 142.99, 141.02, 131.36 (d, J_{CF} = 8.0 Hz) 129.92 (d, J_{CF} = 3.0 Hz), 128.31, 115.36 (d, J_{CF} = 21.0 Hz), 108.58, 107.9, 105.17, 89.21, 52.79, 42.27, 33.40, 31.06,

23.65, 20.13, 13.70; ^{19}F NMR ($CDCl_3$): δ −113.42; MS *m*/*z* 445 (M+1).

5.6. 3-[2-(Butylamino)-4-pyrimidinyl]-*N*-cyclopropyl-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-amine (28)

Compound **28** was made in a similar manner as described for compound **25**, to give a fluffy pale yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.40 (d, 1H), 8.07 (d, 1H), 7.65 (m, 2H), 7.29 (m, 1H), 7.15 (t, 2H), 7.06 (d, 1H), 6.32 (d, 1H), 5.16 (br s, 1H), 3.49 (q, 2H), 1.71–1.41 (m, 4H), 0.99 (t, 3H); ^{19}F NMR ($CDCl_3$): δ −112.77; MS *m*/*z* 396 (M+1).

5.7. 3-(2-Amino-4-pyrimidinyl)-*N*-cyclopentyl-2-(4-fluorophenyl)pyrazolo-[1,5-*a*]pyridin-7-amine (29)

Compound **29** was made in a similar manner as described for compound **1** to give a white solid. ^{1}H NMR ($CDCl_3$): δ 7.98 (d, 1H), 7.66 (d, 1H), 7.59 (m, 2H), 7.28 (t, 1H), 7.10 (t, 2H), 6.31 (d, 1H), 6.00 (d, 1H), 5.96 (d, 1H), 4.97 (br s, 2H), 3.96 (m, 1H), 2.14–2.06 (m, 2H), 1.83–1.63 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 163.39 (d, J_{CF} = 246.6 Hz), 163.20, 162.25, 157.27, 152.33, 142.88, 141.32, 131.64 (d, J_{CF} = 8.4 Hz), 129.91 (d, J_{CF} = 3.8 Hz), 128.84, 115.75 (d, J_{CF} = 22.0 Hz), 110.31, 106.85, 105.31, 90.53, 54.06, 33.53, 24.27; ^{19}F NMR ($CDCl_3$): δ −113.20; MS *m*/*z* 389 (M+1). Anal. Calcd for $C_{22}H_{21}FN_6$: C, 68.03; H, 5.45; N, 21.63. Found: C, 67.96; H, 5.50; N, 21.82.

5.8. *N*-Butyl-3-[2-(cyclopropylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)-pyrazolo[1,5-*a*]pyridin-7-amine (30)

Compound **30** was made in a similar manner as described for compound **1** to give a white solid. R_f 0.55 (1:1 hexanes–EtOAc); ^{1}H NMR ($CDCl_3$): δ 8.09 (d, 1H), 7.92 (d, 1H), 7.67 (dd, 2H), 7.34 (t, 1H), 7.18 (t, 2H), 6.37 (d, 1H), 6.09–6.04 (m, 2H), 5.53 (br, 1H), 3.40 (m, 2H), 2.88 (m, 1H), 1.79 (m, 2H), 1.52 (m, 2H), 1.02 (t, 3H), 0.88 (m, 2H), 0.64 (m, 2H); MS *m*/*z* 417 (M+1).

5.9. 3-[2-(Cyclopentylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-amine (31)

5.9.1. 4-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyrimidinamine (62). In a similar manner as described for compound **61** ketone **8** (210 mg, 0.7 mmol), cyclopentylguanidine hydrochloride (**61**) (291 mg, 2.1 mmol), and K_2CO_3 (345 mg, 2.1 mmol) were heated at 120 °C for 1.5 h in NMP (8 mL) to form 7-chloro derivative **62** (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).

5.9.2. 3-[2-(Cyclopentylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-amine (31). To a solution of 4-[7-chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyrimidinamine (**62**) (53 mg, 0.1 mmol) in DMF (4 mL) was added NaN_3 (85 mg, 1.3 mmol). The resultant mixture was heated to 100 °C for 18 h. The reaction mixture was cooled to room temperature and ether was added. The organic layer was washed with brine. The aqueous layer was extracted with ether and the combined organics dried over $MgSO_4$. Filtration and concentration followed by flash chromatography (2:1–1:1 hexanes–ethyl acetate) provided compound **31** (30 mg, 60%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.97 (d, 1H), 7.77 (d, 1H), 7.60 (m, 2H), 7.22 (m, 1H), 7.10 (t, 2H), 6.26 (d, 1H), 6.14 (d, 1H), 5.26 (s, 2H), 5.09 (d, 1H), 4.29 (m, 1H), 2.06–1.99 (m, 2H), 1.75–1.45 (m, 6H); MS *m*/*z* 389 (M+1). 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.

5.10. 3-[2-(Butylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)-*N*-methylpyrazolo[1,5-*a*]pyridin-7-amine (32)

In a similar manner as described in for compound **25**, 7-chloro derivative **61** was heated with methylamine (40% aqueous soln) in a sealed tube to give 7-*N*-methyl derivative **32** as a pale yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.01 (d, 1H), 7.75 (d, 1H), 7.62 (m, 2H), 7.34 (t, 1H), 7.13 (t, 2H), 6.30 (d, 1H), 6.03–5.99 (m, 2H), 5.11 (br, 1H), 3.46 (q, 2H), 3.10 (d, 3H), 1.69–1.42 (m, 4H), 0.97 (t, 3H); ^{19}F NMR ($CDCl_3$): δ −113.39; MS *m*/*z* 391 (M+1).

5.11. 3-[2-(Cyclopentylamino)pyrimidin-4-yl]-2-(4-fluorophenyl)-*N*-pyrrolidin-1-ylpyrazolo[1,5-*a*]pyridin-7-amine (33)

To a solution 4-[7-chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-cyclopentyl-2-pyrimidinamine (**62**) (120 mg, 0.3 mmol) in anhydrous toluene (5 mL) was added *rac*-BINAP (18 mg, 0.03 mmol), Cs_2CO_3 (380 mg, 1.2 mmol), *N*-aminopyrrolidine hydrochloride (180 mg, 1.5 mmol), and $Pd(OAc)_2$ (4.3 mg, 0.02 mmol) and the mixture was heated to 100 °C under nitrogen atmosphere for 3 h. Excess BINAP (18 mg, 0.03 mmol) and $Pd(OAc)_2$ (4.3 mg, 0.03 mmol) and the mixture was heated to 100 °C for 4 h. The mixture was partitioned between EtOAc and water and the organic layer was dried (Na_2SO_4), concentrated, and purified by chromatography (silica gel, hexanes–EtOAc, 4:1) to provide the title compound as a yellow solid foam (25 mg). ^{1}H NMR ($CDCl_3$): δ 1.6–1.5 (m, 2H), 1.7–1.6 (m, 2H), 1.8–1.7 (m, 2H), 1.9 (br s, 4H), 2.1–2.0 (m, 2H), 3.0 (br s, 4H), 4.33 (sextuplet, 1H), 5.4 (br s, 1H), 6.28 (d, 1H), 6.56 (s, 1H), 6.64 (d, 1H), 7.14 (t, 2H), 7.38 (t, 1H), 7.62 (dd, 2H), 7.79 (d, 1H), 7.96 (br s, 1H); MS *m*/*z* 458 (M+1).

5.12. 3-[2-(Cyclopentylamino)pyrimidin-4-yl]-2-(4-fluorophenyl)-*N*-morpholin-4-ylpyrazolo[1,5-*a*]pyridin-7-amine (34)

The title compound was prepared in a similar manner as compound **33** to give a yellow foam. ^{1}H NMR ($CDCl_3$): δ 1.6–1.5 (m, 2H), 1.7–1.6 (m, 2H), 1.8–1.7 (m, 2H), 2.1–2.0 (m, 2H), 2.99 (s, 4H), 3.85 (br s, 4H), 4.35 (m, 1H), 5.25 (br s, 1H), 6.28 (d, 1H), 6.66 (d, 1H), 6.72 (s, 1H),

7.14 (t, 2H), 7.37 (t, 1H), 7.63 (dd, 2H), 7.83 (d, 1H), 7.98 (br d, 1H); MS *m*/*z* 474 (M+1).

5.13. 3-({4-[7-(Butylamino)-2-(4-fluorophenyl)pyrazolo-[1,5-*a*]pyridin-3-yl]-2-pyrimidinyl}amino)-1-propanol (35)

5.13.1. 4-[7-(Butylamino)-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-pyrimidinethiolate (64). A solution of (2*E*)-1-[7-(butylamino)-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-3-(dimethylamino)-2-propen-1-one (**63**) (5.92 g, 15.6 mmol), thiourea (2.40 g, 31.1 mmol), and KOH (15.6 mL, 1.0 N in ethanol) in 200 mL of EtOH was heated to reflux until starting material was consumed. The reaction was cooled to room temperature and the resulting precipitate was isolated by filtration. After washing with EtOAc, compound **64** (1.68 g, 44%) was isolated as a tan solid as the potassium salt. ^{1}H NMR (DMSO-d_6): δ 7.68–7.61 (m, 4H), 7.29–7.23 (m, 3H), 6.88 (m, 1H), 6.08 (d, 1H), 6.00 (d, 1H), 3.32–3.22 (m, 2H), 1.59 (m, 2H), 1.34 (m, 2H), 0.87 (t, 3H); MS *m*/*z* 392 (M+1).

5.13.2. *N*-Butyl-2-(4-fluorophenyl)-3-[2-(methylsulfanyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-7-amine (65). A mixture of thiol **64** (2.9 g, 6.9 mmol) in 50 mL water was treated with iodomethane (0.9 mL, 13.8 mmol) and NaOH (4.1 mL, 5 N aqueous solution) and allowed to stir at room temperature for 4 h. The mixture was diluted with additional water and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Flash column chromatography eluting with 9:1 hexanes–EtOAc afforded methylthio ether **65** (1.6 g, 56%) as a yellow foam. ^{1}H NMR ($CDCl_3$): δ 8.15 (d, 1H), 7.73 (d, 1H), 7.56 (m, 2H), 7.33 (t, 1H), 7.13 (t, 2H), 6.62 (d, 1H), 6.02 (m, 2H), 3.35 (q, 2H), 2.55 (s, 3H), 1.76–1.41 (m, 4H), 0.95 (t, 3H); ^{19}F NMR ($CDCl_3$): δ −112.75; MS *m*/*z* 408 (M+1).

5.13.3. 3-({4-[7-(Butylamino)-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-pyrimidinyl}amino)-1-propanol (35). To a cold (0 °C) solution of methylthio ether **65** (1.5 g, 3.7 mmol) in 50 mL chloroform was added *m*-CPBA (0.9 g, 70–75%, 3.7 mmol). The reaction was allowed to warm to rt. After stirring for 5 h, another 0.2 g *m*-CPBA acid was added and the reaction was stirred for 15 min. The reaction was diluted with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was recrystallized from EtOAc and hexanes to afford the corresponding sulfoxide (**66**) (950 mg, 60%) as an orange solid. ^{1}H NMR ($CDCl_3$): δ 8.40 (br, 1H), 7.99 (d, 1H), 7.58 (m, 2H), 7.45 (t, 1H), 7.20 (t, 2H), 6.94 (d, 1H), 6.13 (d, 1H), 6.10 (br, 1H), 3.38 (m, 2H), 2.98 (s, 3H), 1.79–1.42 (m, 4H), 0.97 (t, 3H); MS *m*/*z* 422 (M−1). The sulfoxide **66** (50 mg, 0.12 mmol) and 3-amino-1-propanol (0.45 mL, 5.9 mmol) in 2 mL THF were heated to reflux for 4 h, then the mixture was cooled to rt and concentrated. Flash column chromatography eluting with a gradient of 0–100% EtOAc in hexanes afforded the analog **35** (46.3 mg, 90%) as a yellow foam. ^{1}H NMR ($CDCl_3$): δ 7.97 (d, 1H), 7.67–7.61 (m, 3H), 7.35 (t, 1H), 7.16 (t, 2H), 6.34 (d, 1H), 6.04 (m, 2H), 3.67–3.60 (m, 4H), 3.39 (q, 2H), 1.79–1.45 (m, 6H), 1.00 (t, 3H); ^{19}F NMR ($CDCl_3$): δ −113.10; MS *m*/*z* 435 (M+1).

5.14. 3-[2-(Butylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)-*N*-(2-methoxyethyl)pyrazolo[1,5-*a*]pyridin-7-amine (36)

Compound **36** was made in a similar manner as described for compound **25** to give a yellow foam. ^{1}H NMR ($CDCl_3$): δ 8.02 (d, 1H), 7.76 (d, 1H), 7.65 (m, 2H), 7.32 (t, 1H), 7.15 (t, 2H), 6.29 (m, 2H), 6.05 (d, 1H), 5.10 (br, 1H), 3.72 (t, 2H), 3.57 (q, 2H), 3.47 (q, 2H), 3.43 (s, 3H), 1.69–1.44 (m, 4H), 0.98 (t, 3H); MS *m*/*z* 435 (M+1).

5.15. *N*-Butyl-2-(4-fluorophenyl)-3-(2-{[2-(4-morpholinyl)ethyl]amino}-4-pyrimidinyl)pyrazolo[1,5-*a*]pyridin-7-amine (37)

Compound **37** was made in a similar manner as described for compound **35** to give a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.02 (d, 1H), 7.72 (d, 1H), 7.63 (dd, 2H), 7.33 (t, 1H), 7.14 (t, 2H), 6.31 (d, 1H), 6.03–6.01 (m, 2H), 5.65 (br, 1H), 3.75 (br, 4H), 3.57 (q, 2H), 3.39 (q, 2H), 2.65 (t, 2H), 2.53 (br, 4H), 1.81–1.46 (m, 4H), 0.99 (t, 3H); ^{19}F NMR ($CDCl_3$): δ −113.31; MS *m*/*z* 490 (M+1).

5.16. 3-[2-(Butylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)-*N*-[2-(4-morpholinyl)ethyl]pyrazolo[1,5-*a*]pyridin-7-amine (38)

Compound **38** was made in a similar manner as described for compound **25** to give a yellow solid. ^{1}H NMR ($CDCl_3$): δ 7.97 (br, 1H), 7.76 (d, 1H), 7.65 (m, 2H), 7.34 (t, 1H), 7.16 (t, 2H), 6.54 (t, 1H), 6.32 (d, 1H), 6.04 (d, 1H), 3.76 (t, 4H), 3.48 (m, 4H), 2.78 (t, 2H), 2.55 (br, 4H), 1.68–1.44 (m, 4H), 0.98 (t, 3H); MS *m*/*z* 490 (M+1).

5.17. *N*-Cyclopentyl-2-(4-fluorophenyl)-3-(2-{[3-(4-morpholinyl)propyl]-amino}-4-pyrimidinyl)pyrazolo[1,5-*a*]-pyridin-7-amine (39)

Compound **39** was made in a similar manner as described for compound **1** to give a tan solid. ^{1}H NMR ($CDCl_3$): δ 7.97 (d, 1H), 7.69 (d, 1H), 7.59 (dd, 2H), 7.26 (t, 1H), 7.10 (t, 2H), 6.24 (d, 1H), 6.00 (d, 1H), 5.96 (d, 1H), 5.70 (br, 1H), 3.97 (m, 1H), 3.71 (m, 4H), 3.49 (m, 2H), 2.48–2.45 (m, 6H), 2.10 (m, 2H), 1.83–1.59 (m, 8H); ^{19}F NMR ($CDCl_3$): δ −113.46; MS *m*/*z* 516 (M+1).

5.18. *N*-Butyl-2-(4-fluorophenyl)-3-(2-{[3-(1*H*-imidazol-1-yl)propyl]amino}-4-pyrimidinyl)pyrazolo[1,5-*a*]pyridin-7-amine (40)

Compound **40** was made in a similar manner as described for compound **35** to give a yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.01 (d, 1H), 7.65–7.61 (m, 3H), 7.54 (s, 1H), 7.34 (t, 1H), 7.15 (t, 2H), 7.08 (s, 1H), 6.97 (s, 1H), 6.37 (d, 1H), 6.07–6.03 (m, 2H), 5.32 (br, 1H),

4.08 (t, 2H), 3.48 (q, 2H), 3.39 (q, 2H), 2.14 (m, 2H), 1.77 (m, 2H), 1.51 (m, 2H), 1.00 (t, 3H); MS *m*/*z* 485 (M+1). This material was treated with anhydrous hydrochloride in ether to provide a hydrochloride salt as a gold solid.

5.19. *N*-Butyl-2-(4-fluorophenyl)-3-{2-[(2-pyridinylmethyl)amino]-4-pyrimidinyl}pyrazolo[1,5-*a*]pyridin-7-amine (41)

Compound **41** was made in a similar manner as described for compound **35** to give a solid. ^{1}H NMR ($CDCl_3$): δ 8.62 (d, 1H), 8.05 (d, 1H), 7.65 (m, 3H), 7.38 (d, 1H), 7.27–7.12 (m, 4H), 6.37 (d, 1H), 6.13 (br, 1H), 6.02–6.00 (m, 2H), 4.83 (d, 2H), 3.38 (q, 2H), 1.75 (m, 2H), 1.49 (m, 2H), 0.99 (t, 3H); ^{19}F NMR ($CDCl_3$): δ −113.22; MS *m*/*z* 468 (M+1). This material was treated with anhydrous hydrochloride in ether to provide a hydrochloride salt as a brown solid.

5.20. 3-[2-(Cyclopentylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)-*N*-(4-methoxyphenyl)pyrazolo[1,5-*a*]pyridin-7-amine (42)

Compound **42** was made in a similar manner as described for compound **25** to give 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 (br, 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).

5.21. 3-(2-Anilino-4-pyrimidinyl)-*N*-cyclopentyl-2-(4-fluorophenyl)-pyrazolo[1,5-*a*]pyridin-7-amine (43)

5.21.1. *N*-Phenylguanidinium nitrate (67). To a room temperature solution of aniline (10.0 g, 107 mmol) in ethanol (100 mL) was added cyanamide (9.6 mL, 50 wt % in water, 123 mmol) followed by the dropwise addition of concentrated HNO_3 (7.6 mL). The mixture was heated at reflux for 3.5 h and allowed to cool to room temperature. The mixture was concentrated in vacuo and the residue was crystallized from MeOH/EtOAc/CH_2Cl_2 to yield guanidinium salt **67** (6.7 g, 32%) as a white crystalline solid. ^{1}H NMR (DMSO-d_6): δ 9.63 (s, 1H), 7.44 (t, 2H), 7.37 (br s, 3H), 7.29 (t, 1H), 7.23 (d, 2H); ^{13}C NMR (DMSO-d_6): δ 156.36, 135.99, 130.40, 127.19, 125.18; MS *m*/*z* 136 (M+1 of free base).

5.21.2. 3-(2-Anilino-4-pyrimidinyl)-*N*-cyclopentyl-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-amine (43). To a solution of vinylogous amide **60** (100 mg, 0.3 mmol) in DMF (5 mL) was added *N*-phenylguanidinium nitrate **67** (252 mg, 1.3 mmol) and K_2CO_3 (175 mg, 1.3 mmol). The suspension was heated at 140 °C (bath temperature) for 21 h. The mixture was cooled to rt, ether was added followed by water. The organic layer was washed with brine. The aqueous layer was extracted with ether and the combined organics were dried over $MgSO_4$. Filtration and concentration followed by flash chromatography (2:1 hexanes–EtOAc) provided pyrimidine **43**, which was recrystallized from ether/hexanes (90 mg, 76%) to give a white crystalline solid. ^{1}H NMR ($CDCl_3$): δ 8.15 (d, 1H), 7.69–7.59 (m, 5H), 7.32–7.27 (m, 3H), 7.18–7.13 (m, 3H), 7.02 (t, 1H), 6.49 (d, 1H), 6.06–6.01 (m, 2H), 4.01 (m, 1H), 2.20–2.10 (m, 2H), 1.86–1.64 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 163.20 (d, J_{CF} = 246.6 Hz), 161.55, 160.11, 156.76, 152.27, 142.72, 141.15, 139.74, 131.47 (d, J_{CF} = 8.3 Hz), 129.72 (d, J_{CF} = 3.4 Hz), 128.82, 128.66, 122.28, 119.52, 115.60 (d, J_{CF} = 21.3 Hz), 110.83, 106.91, 105.15, 90.34, 53.86, 33.32, 24.05; MS *m*/*z* 465 (M+1).

5.22. *N*-Cyclopentyl-2-(4-fluorophenyl)-3-[2-(4-methoxyanilino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-7-amine (44)

5.22.1. *N*-(4-Methoxyphenyl)guanidinium nitrate (68). To a rt solution of 4-methoxyaniline (10.0 g, 81.2 mmol) in ethanol (100 mL) was added cyanamide (7.2 mL, 50 wt % in water, 93.37 mmol) followed by the dropwise addition of concentrated nitric acid (5.7 mL). The mixture was heated at reflux for 3 h and allowed to cool to room temperature. The resulting crystals were isolated on a filter to yield guanidinium salt **68** (7.1 g, 38%) as a violet crystals. ^{1}H NMR (DMSO-d_6): δ 9.39 (s, 1H), 7.22 (s, 3H), 7.17 (d, 2H), 6.99 (d, 2H), 3.76 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 158.17, 156.26, 127.48, 127.27, 114.90, 55.40; MS *m*/*z* 166 (M+1 of free base).

5.22.2. *N*-Cyclopentyl-2-(4-fluorophenyl)-3-[2-(4-methoxyanilino)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-7-amine (44). Compound **44** was made in a similar manner as described for compound **43** to give a white solid. ^{1}H NMR ($CDCl_3$): δ 8.15 (d, 1H), 7.70–7.66 (m, 3H), 7.52–7.49 (d, 2H), 7.33–7.30 (m, 2H), 7.19 (t, 2H), 6.92–6.89 (m, 2H), 6.48 (d, 1H), 6.09–6.04 (m, 2H), 4.03 (m, 1H), 3.85 (s, 3H), 2.17 (m, 2H), 1.90–1.65 (m, 6H); ^{19}F NMR ($CDCl_3$): δ −113.17; MS *m*/*z* 495 (M+1).

5.23. *N*-Cyclopentyl-3-[2-(4-fluoroanilino)-4-pyrimidinyl]-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-amine (45)

5.23.1. *N*-(4-Fluorophenyl)guanidinium nitrate (69). In a similar manner as described for compound **68** from 4-fluoroaniline (10 g, 90 mmol) was obtained *N*-(4-fluorophenyl)guanidine nitrate **69** (7.1 g, 37%) as a powder. ^{1}H NMR (D_2O): δ 7.23–7.08 (m, 4H); ^{19}F NMR (D_2O): δ −114.38; ^{13}C NMR (D_2O): δ 161.99 (d, J_{CF} = 243.5 Hz), 156.83, 130.18 (d, J_{CF} = 3.0 Hz),128.76 (d, J_{CF} = 9.1 Hz), 116.87 (d, J_{CF} = 22.8 Hz); MS *m*/*z* 154 (M+1 of free base).

5.23.2. *N*-Cyclopentyl-3-[2-(4-fluoroanilino)-4-pyrimidinyl]-2-(4-fluorophenyl)pyrazolo-[1,5-*a*]pyridin-7-amine (45). Compound **45** was made in a similar manner as described for compound **43** to give a white solid. ^{1}H NMR ($CDCl_3$): δ 8.13 (d, 1H), 7.65–7.59 (m, 3H), 7.51 (m, 2H), 7.28 (t, 1H), 7.14 (t, 2H), 6.89 (t, 2H), 6.49 (d, 1H), 6.05–6.01 (m, 2H), 4.00 (m, 1H), 2.18–2.10 (m, 2H), 1.86–1.67 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 163.21 (d, J_{CF} = 246.6 Hz), 161.56, 160.16, 158.46 (d, J_{CF} = 239.7 Hz), 156.84, 152.29, 142.75, 141.13, 135.71 (d, J_{CF} = 3.1 Hz), 131.6 (d, J_{CF} = 8.4 Hz), 129.73 (d,

J_{CF} = 3.8 Hz), 128.69, 121.50 (d, J_{CF} = 8.3 Hz), 115.60 (d, J_{CF} = 21.3 Hz), 115.33 (d, J_{CF} = 22.0 Hz), 110.79, 106.84, 104.99, 90.35, 53.88, 33.32, 24.05; ^{19}F NMR ($CDCl_3$): δ −113.09, −121.26; MS *m*/*z* 483 (M+1).

5.24. *N*,2-Bis(4-fluorophenyl)-3-{2-[(4-fluorophenyl)-amino]pyrimidin-4-yl}pyrazolo[1,5-*a*]pyridin-7-amine (8v)

5.24.1. 4-Iodo-2-(methylthio)pyrimidine (10). To a stirring solution of hydriodic acid (100 mL, 4.46 M in water, 0.4 mol) was added 4-chloro-(2-methylthio)pyrimidine (**9**) (18.0 g, 0.12 mol). The reaction mixture was stirred at rt for 6 h, during which a clumpy precipitate formed. The clumps were broken apart and the reaction mixture was stirred an additional 2 h. The solids were collected on a filter, then taken up in water. Saturated aqueous $NaHCO_3$ solution was added until the solution was basic, upon which the aqueous mixture was extracted with $CHCl_3$. The organic layer was washed with 10% aq. $NaHSO_3$ solution and water, then dried over $MgSO_4$. Filtration and concentration provided 4-iodo-2-(methylthio)pyrimidine (**10**) (25.0 g, 99%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, *J* = 5.1 Hz, 1H), 7.39 (d, *J* = 5.1 Hz, 1H), 2.53 (s, 3H); MS *m*/*z* 253 (M+1).

5.24.2. 4-[(4-Fluorophenyl)ethynyl]-2-(methylthio)pyrimidine (12). To a solution of iodide (**10**) (15.0 g, 67.3 mmol) in THF (90 mL) was added triethylamine (12.2 mL, 87.5 mmol). $PdCl_2(PPh_3)_2$ (1.90 g, 2.7 mmol) and CuI (769 mg, 4.0 mmol) were added simultaneously. A solution of 1-ethynyl-4-fluorobenzene (**11**) (8.50 mL, 74.0 mmol) in THF (10 mL) was added dropwise and the reaction mixture was stirred at room temperature for 6 h. Water (20 mL) was added and the resulting solution was concentrated on rotovap to remove the excess THF. The predominantly aqueous mixture was extracted with EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4. Filtration and concentration, followed by flash chromatography (100% CH_2Cl_2) provided diaryl alkyne **12** (12.0 g, 73%) as a pale yellow solid. R_f 0.85 (49:1 CH_2Cl_2–MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (d, *J* = 5.1 Hz, 1H), 7.62 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.13–7.06 (m, 3H), 2.60 (s, 3H); MS *m*/*z* 245 (M+1).

5.24.3. 2-(4-Fluorophenyl)-3-[2-(methylthio)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridine (14). To a cold (0 °C) solution of alkyne 12 (4.00 g, 16.4 mmol) and 1-aminopyridinium iodide (**13**) (3.63 g, 16.4 mmol) in acetonitrile (100 mL) was added DBU (2.45 mL, 16.4 mmol). The reaction mixture was warmed to rt and stirred 3 days. The reaction mixture was quenched with water and concentrated in vacuo to remove the excess acetonitrile. The resultant mixture was partitioned between EtOAc and water. The organic layer was washed with water and brine, then dried over Na_2SO_4. Filtration and concentration, followed by flash chromatography (20–25% EtOAc in hexanes) provided pyrazolopyridine **14** (4.34 g, 79%) as a pale yellow solid. R_f 0.20 (4:1 hexanes–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, *J* = 6.8 Hz, 1H), 8.47 (d, *J* = 8.9 Hz, 1H), 8.24 (d, *J* = 5.5 Hz, 1H), 7.59 (dd, *J* = 8.6, 5.3 Hz, 2H), 7.39 (m, 1H), 7.17 (t, *J* = 8.7 Hz, 2H), 6.96 (td, *J* = 6.9, 1.1 Hz, 1H), 6.70 (d, *J* = 5.5 Hz, 1H), 2.61 (s, 3H); MS *m*/*z* 337 (M+1). Anal. Calcd for $C_{18}H_{13}FN_4S$: C, 64.27; H, 3.90; N, 16.66. Found: C, 64.35; H, 3.87; N, 16.70.

5.24.4. 2-(4-Fluorophenyl)-3-[2-(methylsulfinyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridine (17). To a cold (0 °C) solution (**14**) (1.50 g, 4.5 mmol) in CH_2Cl_2 (150 mL) was added *m*-CPBA (1.08 g, 6.2 mmol). The reaction mixture was warmed to rt and stirred overnight. Saturated aq NaS_2O_3 was added and stirred for 1 h. The resulting mixture was partitioned between saturated aq $NaHCO_3$ and CH_2Cl_2. The organic layer was washed with water and brine, then dried over Na_2SO_4. Filtration and concentration provided sulfoxide **17** (1.6 g, 99%) as a beige solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.80 (d, *J* = 8.9 Hz, 1H), 8.56 (d, *J* = 6.9 Hz, 1H), 8.49 (d, *J* = 5.5 Hz, 1H), 7.61 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.51 (m, 1H), 7.23 (t, *J* = 8.6 Hz, 2H), 7.08–7.03 (m, 2H), 3.02 (s, 3H); MS *m*/*z* 353 (M+1).

5.24.5. *N*-(4-Fluorophenyl)-4-[2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-pyrimidinamine (70). To a suspension of sulfoxide **17** (430 mg, 1.2 mmol) in dioxane (500 μL) was added 4-fluoroaniline (232 μL, 2.4 mmol). The reaction mixture was heated at 90 °C in a sealed tube for 2 days. The reaction mixture was cooled, then partitioned between EtOAc and saturated aq $NaHCO_3$. The organic layer was washed with water and brine, then dried over Na_2SO_4. Filtration and concentration, followed by flash chromatography (15–100% EtOAc in hexanes) provided anilinopyrimidine **70** (200 mg, 41%) as a white solid. R_f 0.05 (4:1 hexanes–EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, *J* = 6.9 Hz, 1H), 8.30 (d, *J* = 9.0 Hz, 1H), 8.18 (d, *J* = 5.3 Hz, 1H), 7.63 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.54 (dd, *J* = 9.0, 4.8 Hz, 2H), 7.29 (m, 1H), 7.16 (t, *J* = 8.6 Hz, 2H), 7.09 (s, 1H), 7.02 (t, *J* = 8.6 Hz, 2H), 6.93 (td, *J* = 6.9, 1.2 Hz, 1H), 6.54 (d, *J* = 5.3 Hz, 1H). MS *m*/*z* 400 (M+1).

5.24.6. 4-[7-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*-(4-fluorophenyl)-2-pyrimidinamine (71). To a cold (0 °C) solution of diisopropylamine (164 μL, 1.2 mmol) in THF (2 mL) was added butyllithium (719 μL, 1.6 M in hexanes, 1.1 mmol) dropwise. The reaction mixture was stirred at 0 °C for 10 min then cooled to −78 °C. The reaction mixture was transferred via syringe to a cold (−78 °C) solution of pyrazolopyridine **70** (153 mg, 0.383 mmol) in THF (4 mL). The reaction mixture was stirred at −78 °C for 10 min. CCl_4 (222 μL, 2.30 mmol) was added and stirred at −78 °C for 30 min. The reaction was quenched with water and warmed to room temperature. The resultant mixture was extracted with EtOAc. The organic layer was washed with water and brine, then dried over Na_2SO_4. Filtration and concentration, followed by flash chromatography (5–30% EtOAc in hexanes) provided 7-chloro derivative **71** (109 mg, 66%) as a pale yellow solid. R_f 0.25 (4:1 hexanes–EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.9 Hz, 1H), 8.10 (d, *J* = 5.3 Hz, 1H), 7.55 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.50–7.44 (m, 3H), 7.16 (m, 1H), 7.05 (t, *J* = 8.7 Hz, 2H), 6.98 (d,

J = 7.3 Hz, 1H), 6.89 (t, J = 8.7 Hz, 2H), 6.42 (d, J = 5.3 Hz, 1H); MS m/z 434 (M+1).

5.24.7. *N*,2-Bis(4-fluorophenyl)-3-{2-[(4-fluorophenyl)amino]-4-pyrimidinyl}pyrazolo[1,5-*a*]pyridin-7-amine (46). To a solution of **71** (102 mg, 0.24 mmol) in 4-fluoroaniline (6.00 mL, 63.3 mmol) was added *rac*-BINAP (44 mg, 0.07 mmol), Cs_2CO_3 (115 mg, 0.4 mmol), and $Pd(OAc)_2$ (11 mg, 0.05 mmol), respectively. The reaction mixture was heated at 140 °C for 4 h. The reaction mixture was cooled and quenched with water, then extracted with EtOAc. The organic layer was washed with water and brine then dried over Na_2SO_4. Filtration and concentration provided a crude mass, which was placed under high vacuum to remove the excess 4-fluoroaniline. The resulting material was chromatographed on silica gel (15–40% EtOAc in hexanes) to provide *bis* 4-fluoroaniline derivative **46** (54 mg, 45%) as a beige solid. R_f 0.20 (4:1 hexanes–EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J = 5.3 Hz, 1H), 7.79 (s, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.67 (dd, J = 8.6, 5.4 Hz, 2H), 7.52 (dd, J = 9.0, 4.8 Hz, 2H), 7.34 (dd, J = 8.9, 4.8 Hz, 2H), 7.28–7.23 (m, 2H), 7.20–7.11 (m, 4H), 6.99 (t, J = 8.8 Hz, 2H), 6.54 (d, J = 5.3 Hz, 1H), 6.40 (d, J = 7.6 Hz, 1H); MS m/z 509 $(M+H)^+$.

5.25. 3-[2-(Cyclopentylamino)pyrimidin-4-yl]-*N*,2-bis(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-amine (47)

To a solution of **62** (143 mg, 0.351 mmol) in 4-fluoroaniline (7.00 mL, 73.9 mmol) was added *rac*-BINAP (66 mg, 0.11 mmol), Cs_2CO_3 (172 mg, 0.53 mmol), and $Pd(OAc)_2$ (16 mg, 0.07 mmol), respectively. The reaction mixture was heated at 140 °C for 4 h. The reaction mixture was cooled and quenched with water, then extracted with EtOAc. The organic layer was washed with water and brine then dried over Na_2SO_4. Filtration and concentration provided a crude mass, which was placed under high vacuum to remove the excess 4-fluoroaniline. The resulting material was chromatographed on silica gel (10–40% ethyl acetate in hexanes) to provide 7-anilino derivative **47** (35 mg, 21%) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, J = 5.2 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.81 (s, 1H), 7.68 (dd, J = 8.6, 5.4 Hz, 2H), 7.35 (m, 2H), 7.20–7.10 (m, 3H), 6.86 (t, J = 8.7 Hz, 1H), 6.62 (m, 1H), 6.41 (d, J = 7.8 Hz, 1H), 6.34 (d, J = 5.3 Hz, 1H), 5.14 (d, J = 7.5 Hz, 1H), 4.35 (m, 1H), 2.08 (m, 2H), 1.80–1.50 (m, 6H); MS m/z 483 $(M+H)^+$. Anal. Calcd for $C_{28}H_{24}F_2N_6$: C, 69.70; H, 5.01; N, 17.42. Found: C, 69.91; H, 4.99; N, 17.33.

5.26. *N*-Butyl-2-(4-fluorophenyl)-3-[2-(1-pyrrolidinyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-7-amine (48)

5.26.1. 1-Pyrrolidinecarboximidamide sulfate (72). *O*-Methylisourea hydrogensulfate (10 g, 58.1 mmol) and pyrrolidine (12.1 mL, 145.2 mmol) were heated at reflux in 10 mL of water for 2 h. The solvent was removed in vacuo and the residue was azeotroped with methanol. The resultant material was recrystallized from EtOH to produce the title compound (6.3 g, 51%) as a white crystalline solid. ^{1}H NMR (D_2O): δ 3.17 (m, 4H), 1.78 (m, 4H); ^{13}C NMR (D_2O): δ 154.28, 46.97, 24.92; MS m/z 114 (M+1).

5.26.2. *N*-Butyl-2-(4-fluorophenyl)-3-[2-(1-pyrrolidinyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-7-amine (48). Compound **48** was made in a similar manner as described for compound **1** using guanidine **72**, to give a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.03 (d, 1H), 7.76 (d, 1H), 7.59 (m, 2H), 7.26 (t, 1H), 7.09 (t, 2H), 6.20 (d, 1H), 5.99–5.95 (m, 2H), 3.61 (m, 4H), 3.32 (m, 2H), 1.98 (m, 4H), 1.70 (m, 2H), 1.44 (m, 2H), 0.94 (t, 3H); ^{13}C NMR ($CDCl_3$): δ 163.07 (d, J_{CF} = 246.5 Hz), 161.04, 160.48, 156.56, 152.19, 143.01, 141.13, 131.45 (d, J_{CF} = 8.4 Hz), 130.05 (d, J_{CF} = 3.0 Hz), 128.34, 115.38 (d, J_{CF} = 21.2 Hz), 107.46, 107.22, 105.50, 89.19, 46.59, 42.33, 31.11, 25.55, 20.19, 13.75; MS m/z 431 (M+1).

5.27. *N*-Cyclopentyl-4-[2-(4-fluorophenyl)-7-(1-pyrrolidinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-pyrimidinamine (49)

Compound **49** was made in a similar manner as described for compound **1** to give a yellow solid. ^{1}H NMR ($CDCl_3$): δ 7.95 (d, 1H), 7.82 (d, 1H), 7.61 (m, 2H), 7.22 (t, 1H), 7.08 (t, 2H), 6.28 (d, 1H), 6.07 (d, 1H), 5.25 (br s, 1H), 4.31 (m, 1H), 3.72 (m, 4H), 2.02 (m, 6H), 1.75–1.49 (m, 6H); MS m/z 443 (M+1).

5.28. *N*-Cyclopentyl-4-[2-(4-fluorophenyl)-7-piperidin-1-ylpyrazolo[1,5-*a*]pyridin-3-yl]pyrimidin-2-amine (50)

Compound **50** was made in a similar manner as described for compound **1** to give a yellow solid. Mp 198–199 °C; ^{1}H NMR ($CDCl_3$): δ 1.9–1.5 (m, 12H), 2.1–2.0 (m, 2H), 3.4 (s, 4H), 4.37 (m, 1H), 5.2 (br s, 1H), 6.38–6.30 (m, 2H), 7.1 (t, 2H), 7.28 (t, 1H), 7.68 (dd, 2H), 8.02 (br d, 2H); 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, 70.80; H, 6.40; N, 18.18.

5.29. 4-[2-(4-Fluorophenyl)-7-(1-pyrrolidinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-*N*,*N*-dimethyl-2-pyrimidinamine (51)

Compound **51** was made in a similar manner as described for compound **1** to give a yellow crystalline solid. ^{1}H NMR ($CDCl_3$): δ 8.05 (d, 1H), 7.81 (d, 1H), 7.61 (m, 2H), 7.21 (t, 1H), 7.07 (t, 2H), 6.27 (d, 1H), 6.06 (d, 1H), 3.71 (m, 4H), 3.21 (s, 6H), 2.01 (m, 4H); MS m/z 403 (M+1).

5.30. *N*-Cyclopentyl-3-[2-(dimethylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-7-amine (52)

Compound **52** was made in a similar manner as described for compound **1** to give a white solid. ^{1}H NMR ($CDCl_3$): δ 8.13 (d, 1H), 7.75 (d, 1H), 7.67 (dd, 2H), 7.33 (t, 1H), 7.16 (t, 2H), 6.30 (d, 1H), 6.06–6.04 (m, 2H), 4.02 (m, 1H), 3.26 (s, 6H), 2.16 (m, 2H), 1.84–1.65 (m, 6H); MS m/z 417 (M+1).

5.31. 3-[2-(Butylamino)-4-pyrimidinyl]-2-(4-fluorophenyl)-*N*,*N*-dimethylpyrazolo[1,5-*a*]pyridin-7-amine (53)

Compound **53** was made in a similar manner as described for compound **1** to give a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.00 (m, 2H), 7.62 (m, 2H), 7.28 (t, 1H), 7.08 (t, 2H), 6.29 (m, 2H), 5.24 (br s, 1H), 3.44 (m, 2H), 3.09 (s, 6H), 1.65–1.38 (m, 4H), 0.94 (t, 3H); MS *m*/*z* 405 (M+1).

5.32. *N*-Butyl-4-[2-(4-fluorophenyl)-7-(4-methyl-1-piperazinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-pyrimidinamine (54)

Compound **54** was made in a similar manner as described for compound **1** to give an off-white foam. ^{1}H NMR (DMSO-d_6): δ 7.98 (m, 2H), 7.58 (t, 2H), 7.35 (t, 1H), 7.26 (t, 2H), 7.04 (br s, 1H), 6.46 (d, 1H), 6.14 (br s, 1H), 3.37 (br s, 4H), 3.20 (d, 2H), 2.49 (s, 4H), 2.20 (s, 3H), 1.46 (m, 2H), 1.28 (m, 2H), 0.84 (t, 3H); ^{19}F NMR (DMSO-d_6): δ −113.56; MS *m*/*z* 460 (M+1).

5.33. *N*-Butyl-4-[2-(4-fluorophenyl)-7-(4-morpholinyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-pyrimidinamine (55)

Compound **55** was made in a similar manner as described for compound **1** to give an off-white foam. ^{1}H NMR ($CDCl_3$): δ 8.14 (d, 1H), 8.03 (m, 1H), 7.68 (m, 2H), 7.37 (t, 1H), 7.17 (t, 2H), 6.39 (m, 2H), 5.52 (br s, 1H), 4.04 (m, 4H), 3.66 (m, 6H), 1.70 (m, 2H), 1.52 (m, 2H), 1.02 (t, 3H); MS *m*/*z* 447 (M+1).

5.34. *N*-Butyl-2-(4-fluorophenyl)-3-[2-(4-morpholinyl)-4-pyrimidinyl]pyrazolo[1,5-*a*]pyridin-7-amine (56)

Compound **56** was made in a similar manner as described for compound **35** to give an off-white foam. ^{1}H NMR (DMSO-d_6): δ 8.09 (d, 1H), 7.56 (dd, 2H), 7.44 (d, 1H), 7.35 (t, 1H), 7.26 (t, 2H), 7.06 (t, 1H), 6.30 (d, 1H), 6.14 (d, 1H), 3.59 (m, 8H), 3.28 (m, 2H), 1.59 (m, 2H), 1.33 (m, 2H), 0.87 (t, 3H); ^{19}F NMR (DMSO-d_6): δ −113.70; MS *m*/*z* 447 (M+1).

5.35. 2-(4-{4-[7-(Butylamino)-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridin-3-yl]-2-pyrimidinyl}-1-piperazinyl)ethanol (57)

Compound **57** was made in a similar manner as described for compound **35** to give a pale yellow solid. ^{1}H NMR (DMSO-d_6): δ 8.12 (d, 1H), 7.61 (m, 2H), 7.48 (d, 1H), 7.39 (t, 1H), 7.30 (t, 2H), 7.09 (t, 1H), 6.31 (d, 1H), 6.18 (d, 1H), 4.43 (br, 1H), 3.64 (br, 4H), 3.53 (q, 2H), 3.38–3.27 (m, 4H), 2.44 (br, 4H), 1.63 (m, 2H), 1.37 (m, 2H), 0.91 (t, 3H); ^{19}F NMR ($CDCl_3$): δ −113.30; MS *m*/*z* 490 (M+1).

5.36. *N*-Butyl-2-(4-fluorophenyl)-3-{2-[4-(2-methoxyethyl)-1-piperazinyl]-4-pyrimidinyl}pyrazolo[1,5-*a*]pyridin-7-amine (58)

Compound **58** was made in a similar manner as described for compound **35** to give a pale yellow oil. ^{1}H NMR (DMSO-d_6): δ 8.11 (d, 1H), 7.61 (dd, 2H), 7.48 (d, 1H), 7.40 (t, 1H), 7.30 (t, 2H), 7.09 (t, 1H), 6.31 (d, 1H), 6.18 (d, 1H), 3.64 (br, 4H), 3.46 (t, 2H), 3.38–3.22 (m, 7H), 2.44 (br, 4H), 1.63 (m, 2H), 1.38 (m, 2H), 0.92 (t, 3H); ^{19}F NMR ($CDCl_3$): δ −113.59; MS *m*/*z* 504 (M+1). This material was treated with anhydrous hydrochloride in ether to provide a hydrochloride salt as an orange solid.

5.37. HSV antiviral assay

5.37.1. Cell culture and HSV infection. Vero 76 cells (American Type Culture Collection, Manassas, VA) were grown and passed in MEM with Earle's salts, L-glutamine, penicillin, and streptomycin (Invitrogen Life Technologies, Carlsbad, CA) supplemented with 8% fetal bovine serum (FBS) (Hyclone Laboratories, Logan, UT). The amount of FBS was reduced to 2% for assays.

Vero cells were infected in suspension with either HSV-1 or HSV-2 for 45 min at 37 °C at a multiplicity of infection of 0.001. Infected cells were plated at a density of 50,000 cells/well into 96-well tissue culture plates containing antiviral test compounds and incubated at 37 °C for 40–48 h.

5.37.2. HSV DNA hybridization. The effect of compounds on HSV replication was assessed by conventional DNA hybridization. Cell lysates were prepared for hybridization by removing growth medium from HSV-infected Vero cells 2 days post-infection and adding 150 μL lysis buffer (0.2 N NaOH with 1% NP-40) to each well. The lysates were then incubated at room temperature for 5 days in a humidified chamber to ensure complete DNA hydrolysis. Samples of the lysates were neutralized in a phosphate-buffered guanidine isothiocyanate (GuSCN) solution and combined with a digoxigenin-labeled 710 bp DNA fragment of the HSV UL15 open reading frame. The hybridization solution was heated to 90 °C for 6 min and incubated at 42 °C overnight. Immobilized hybrids were detected by incubation with anti-digoxigenin HRP-conjugated antibody (Boehringer Mannheim, Indianapolis, IN) and subsequent addition of SuperSignal® substrate (Pierce, Rockford, MD). The resulting chemiluminescent signal from compound-treated cells was compared to that of compound-free cells to obtain percent inhibitions, which were used to construct dose response curves to derive 50% inhibitory concentrations (IC_{50}).

5.38. Cytotoxicity assay

Compounds were dissolved in DMSO at a stock concentration of 10 mM and serially diluted twofold in DMSO. Dilutions were carried out in columns 1–9 of a 96-well, v-bottom polypropylene plate. Columns 10, 11, and 12 are control columns that do not contain compound. Plates are then seeded at 10,000 cells/well, columns 1–11, in Minimum Essential medium containing Earle's salt and L-glutamine and supplemented with 10% heat-inactivated fetal bovine serum, 1% penicillin–streptomycin, and 1% L-glutamine (200 mM) resulting in a final 250-fold drug dilution. Thus the maximum compound concentration used in the assay is 40 μM while the final DMSO concentration is 0.4%. Plates are incubated at

37 °C in a humidified, 5% CO_2 atmosphere and growth inhibition is measured after 3 days.

Cytotoxicity is determined in Vero cells using the CellTiter 96® Aqueous Non-Radioactive Cell Proliferation Assay (Promega Corporation, G1111). Metabolically active cells will convert methylthiazol tetrazolium inner salt (MTS), through the actions of cellular dehydrogenases, into a colorized formazan end product. On day 3, MTS solution is added to the assay plates, incubated for 1.5–2 h at 37 °C in a humidified, 5% CO_2 atmosphere, and absorbance is measured at 490 nm using the Wallac Victor2 1420 multilabel counter (Perkin–Elmer, Wellesley, NA). RoboFit 2000 curve-fitting software is then used to obtain a CC_{50} (50% cytotoxicity concentration) value from the curves generated.

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