Bioorganic & Medicinal Chemistry Letters 20 (2010) 1994–2000

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

The design and development of 2-aryl-2-hydroxy ethylamine substituted 1*H*,7*H*-pyrido[1,2,3-*de*]quinoxaline-6-carboxamides as inhibitors of human cytomegalovirus polymerase

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ARTICLE INFO

Article history:
Received 7 December 2009
Revised 15 January 2010
Accepted 19 January 2010
Available online 25 January 2010

Keywords:
Inhibitors
HCMV
VZV
DNA polymerase
Pyrido-quinoxalines
Amino ethanol
Antiviral activity

ABSTRACT

Discovery efforts were focused on identifying a non-nucleoside antiviral for treating infections caused by human cytomegalovirus (HCMV) with equal or better potency and diminished toxicity compared to current therapeutics. This Letter describes the HCMV DNA polymerase inhibition and in vitro antiviral activity of various 2-aryl-2-hydroxy ethylamine substituted 1*H*,7*H*-pyrido[1,2,3-*de*]quinoxaline-6-carboxamides.

The *Herpesviridae* family of viruses are ubiquitous worldwide and these viruses are frequent causative agents of viral infections. The members of the Herpes family of viruses which infect humans are the herpes simplex viruses (HSV-1 and HSV-2), varicella zoster virus (VZV), human cytomegalovirus (HCMV), Epstein-Barr virus (EBV), and human herpes viruses (HHV-6, HHV-7 and HHV-8).[1,2] While many in the immunocompetent population might be infected with members of this viral family, these infections generally remain latent in the host but can be reactivated by immunosuppression or stress. Evidence of infection by human cytomegalovirus (HCMV) can be found in ca. 90% of the population, however in immunocompetent individuals this infection is asymptomatic. HCMV infection in the immunocompromised (e.g., AIDS, post-transplant, cancer) is often associated with clinical symptoms such as pneumonia and graft rejection. HCMV infection in neonates can be associated with congenital birth defects.[3] Current treatments for HCMV infections such as ganciclovir, valganciclovir, foscarnet, and cidofovir suffer from shortcomings which include toxicity (hematologic, renal, CNS) and/or poor oral bioavailability.[4] When coupled with emerging drug resistance, especially in the immunocompromised population, these limitations provide a strong impetus for the discovery of new classes of antiviral agents which are safer and more effective.

The project team had previously reported the utility of 4-oxo-dihydroquinolines such as **1** (Fig. 1) as inhibitors of HCMV polymerase (HCMV pol IC_{50}) with broad spectrum antiviral activity (e.g., HCMV plaque reduction assay = HCMV pra IC_{50}, VZV pra IC_{50}) and good selectivity versus human α-DNA polymerase.[5,6] The team found that select structural changes were well tolerated leading to broad spectrum antiviral agents such as the 4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine **2**.[6] Further modification of the thienyl side chain led to a breakthrough in polymerase enzymatic inhibitory activity and antiviral activity as exemplified by the 4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine **3** bearing a chiral amino ethanol at the thienyl-α-position.[7a] Additional structural modifications led to 4-oxo-4,7-dihydrofuro[2,3-b]pyridine-5-carboxamides **4** with a small loss of enzymatic and antiviral activity, and a significant improvement in aqueous solubility relative to **3**.[7b] During the course of the studies leading to compounds **1**–**4** investigations into substitution at the pyridone nitrogen suggested a neutral to

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doi:10.1016/j.bmcl.2010.01.094

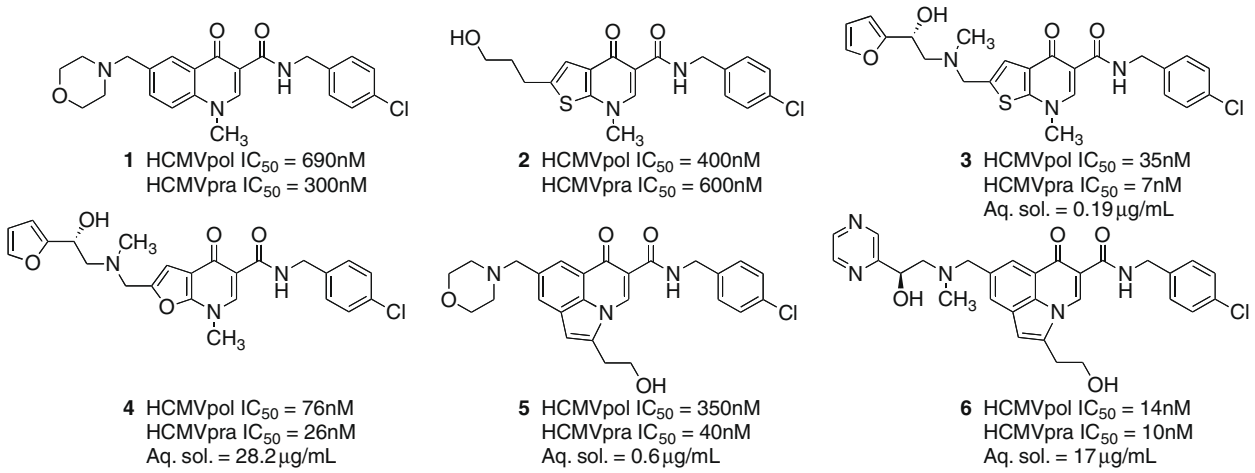


Figure 1. The development of pyridone amides as *Herpes* antiviral agents.

negative impact with the possibility of utilizing this substitution to alter the physical properties of the various series. The team wished to further investigate the vectors emanating from this southern region of the molecule to determine if high levels of enzymatic/antiviral activity might be melded with improved physical properties. This led to the preparation of a series of 6-oxo-6*H*-pyrrolo[3,2,1-i,j]quinoline-5-carboxamides as exemplified by **5**[8] and the amino ethanol substituted **6**.[9] It is clear from a perusal of compounds **1**–**6** that one can realize good antiviral potency and reasonable solubility in a single entity via the choice of side chain (amino ethanol versus morpholinomethyl), alteration of the nucleus (thienyl versus furyl), and modification in the southern region (hydroxyethyl–pyrrolyl). Also, during the study leading to **4** Schnute et al.[7b] have discussed the fit of the *p*-Cl-benzamide moiety into the lipophilic pocket in the crystal structure of HSV-1 DNA polymerase and a study of *p*-Cl-benzamide replacements suggests that this group is preferred.

The data of Figure 1 demonstrates that the nature of the side chain (amino ethanol strongly preferred) is a crucial element in the synthesis of a potent *Herpes* antiviral. The amino ethanol segment improves solubility as does substitution on the pyridone nitrogen.[7] To date, pyridone N-substitution has been limited and we were drawn to compounds such as those shown in Fig. 2. We reasoned that 1,9-disubstituted 1*H*,7*H*-pyrido[1,2,3-*de*]quinoxaline-6-carboxamides such as **7**, with a simple morpholino-side chain or a more complex amino ethanol side chain at the 9-position, would allow us to further alter the characteristics of the molecule by variation of R^1 at the 1-position.

Our initial target in the pyridoquinoxaline series was the 1-methyl-9-morpholinomethyl pyridoquinoxaline **11** (Scheme 1). The choice of the 9-morpholinomethyl entity is based upon precedent with respect to antiviral activity[5–9] as well as the demonstrated ability of the morpholinomethyl to serve as a placeholder for the reactive chloromethyl[7,9] via a chlorinative deamination with a chloroformate.[10] Commercially available 2-fluoro-4-methyl nitrobenzene was brominated (NBS, AIBN, 57%) and the resulting bromide alkylated with morpholine to provide amine **8** (87%). The fluorine was replaced with methyl amine, the nitro was reduced (50 psi H_2, Pd-C), and the crude diamine was bis-acylated ($ClCH_2COCl$) to give **9** (76% from **8**). Treatment with aq. NaOH in THF closed the lactam ring and cleaved the more accessible amide moiety to provide the intermediate lactam.[11] Treatment of the lactam with diethyl ethoxymethylene malonate (DEEM) (toluene 110 °C) gave methylenemalonate **10** (78% over two steps) which was smoothly cyclized upon treatment with Eaton's reagent (**11a**, 90 °C, 89%).[11,12] The sequence was completed by heating **11a** in the presence of 4-Cl-benzyl amine to afford the target pyridoquinoxaline **11b** in an unoptimized 26% yield from the ester. Preliminary evaluation of **11b** suggested that the alteration in the southern region of the molecule was tolerated as **11b** was associated with

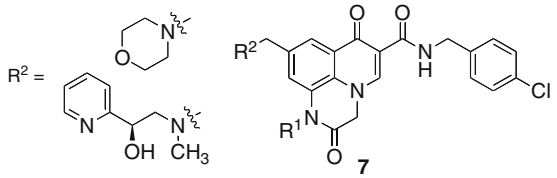
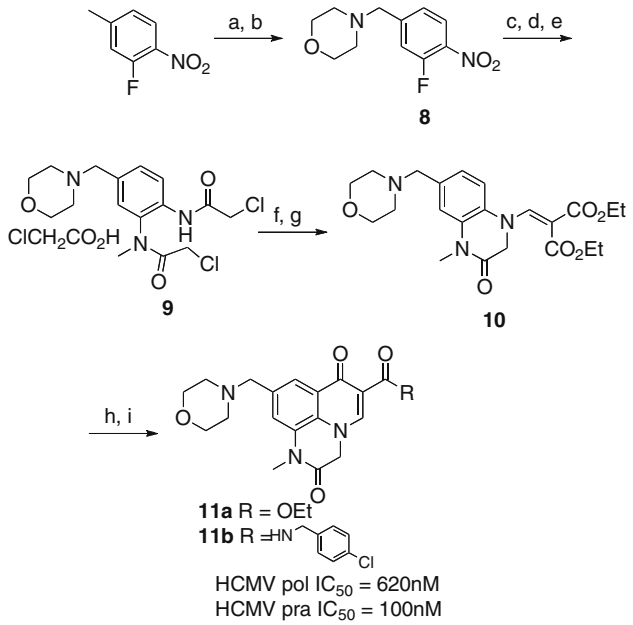


Figure 2. Proposed 1*H*,7*H*-pyrido[1,2,3-de]quinoxaline-6-carboxamide *Herpes* antivirals.



Scheme 1. Synthesis of 1*H*,7*H*-pyrido[1,2,3-*de*]quinoxaline-6-carboxamides **11a**, **11b**. Reagents and conditions: (a) NBS, DCE, AIBN, Δ, 57%; (b) morpholine, MeOH, 87%; (c) aq $MeNH_2$, DMSO, Δ, 97%; (d) H_2 (50 psi), 5% Pd-C, THF; (e) chloroacetic anhydride, THF 79%; (f) aq 1 N NaOH, THF; (g) diethyl ethoxymethylene malonate, toluene, 110 °C, 78%; (h) Eaton's reagent, 89%; (i) 4-$ClPhCH_2NH_2$, ethylene glycol, 120 °C, 26%.

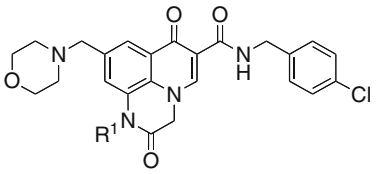
modest enzymatic activity (HCMV pol IC_{50} = 620 nM) and quite reasonable antiviral activity (HCMV pra IC_{50} = 100 nM).

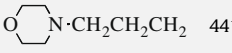
Despite the reasonable enzymatic and antiviral activity associated with the first member of the pyridoquinoxaline series, we were concerned with the synthetic sequence. A nine step sequence which provided **11b** in ca. 6.9% overall yield and calls for the introduction of the amide substituent R^1 (see: **7** Fig. 2) in the third step is of concern for an analog program. Also of note will be the additional two steps required to convert compounds **7** (R^2 = morpholine) to target amnioethanols (vide supra, Fig. 2).[7,9] As a result of these concerns we elected to examine a new synthetic sequence which was initiated as the chemistry of Scheme 1 was being completed. It was our desire to develop a route which would allow the introduction of groups R^1 (Fig. 2) at a later stage of the sequence, enabling greater flexibility in analog design while potentially providing higher overall yields.

Two major variations were considered for this modified route, the first an *abnormal* intramolecular S_NAr reaction[13] to construct the tricycle from a hydroxyquinoline, while the second major change was the introduction of the morpholinomethyl moiety. In this route we planned to construct the hydroxyquinoline nucleus via a standard Gould–Jacob[11,12] cyclization, affording an 8-fluoro-4-hydroxy quinoline which should serve as a substrate for the *abnormal* intramolecular S_NAr reaction, while an iodide in the 6-position was viewed as a precursor to the desired morpholinomethyl via a Pd-mediated carbonylation. These efforts are presented in Scheme 2.

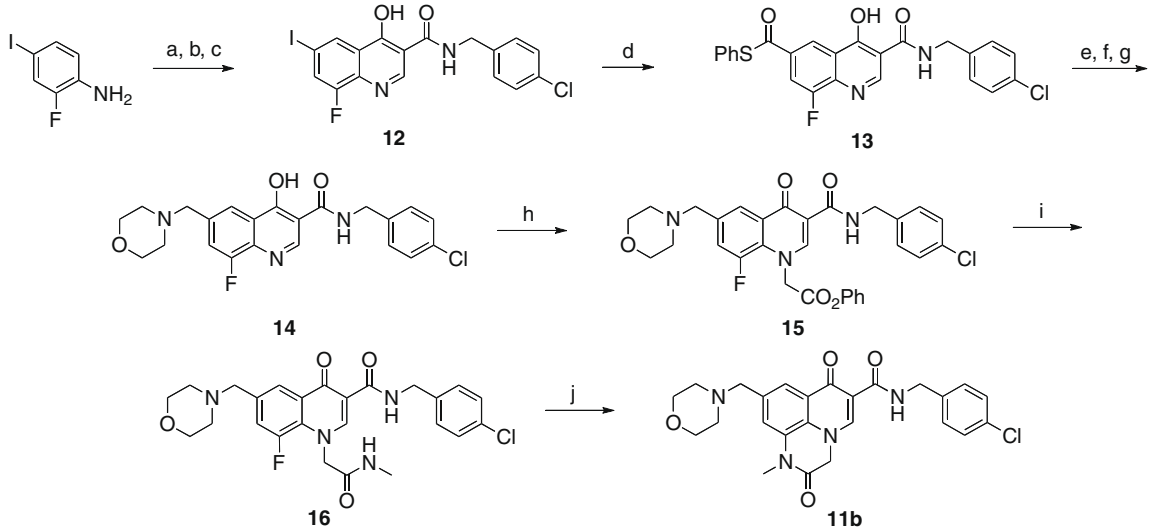
Commercially available 2-fluoro-4-iodoaniline was heated with DEEM to afford the related methylene malonate (83%) which was smoothly cyclized in Gould–Jacob fashion upon heating in diphenyl ether (250 °C, sparge with nitrogen, 91%). The resulting ester was then converted to amide **12** upon treatment with 4-Cl-benzyl amine (NaOMe, MeOH, DMSO, 120 °C, 90%) setting the stage for the Pd-mediated carbonylation. In our initial plan, we wished to convert **12** to a carbonylated product which would be readily transformed into an alcohol, ester, amide, or aldehyde in a single step from said intermediate. These desires led us to consider developing a simple Pd-mediated thioester formation as this entity is ideally suited for conversion into an alcohol under mild conditions ($LiBH_4$),[14] and has been converted directly to aldehydes (Pd-C, Et_3SiH),[15] esters (ROH, base, mild heat),[16] and amides (amine, mild heat).[17] We initiated our search for a general and mild Pd-mediated thioester formation unaware of the work of Alper[18] which has led to the formation of phenylthioesters from aryl iodides utilizing an ionic liquid (trihexyl(tetradecyl)phosphonium hexafluorophosphate), $Pd(OAc)_2$, Ph_3P, and CO at 200 psi and 100 °C. We examined $Pd(OAc)_2$ (5 mol %)/Ph_3P and $Pd(PPh_3)_4$ as palladium sources, THF and DMF as solvents, CO at 1 atm and at pressures up to 400 psi, and PhSH and NaSPh as thiol sources for this conversion. We discovered[19] that **12** can be smoothly converted to **13** in 91% yield upon treatment with $Pd(PPh_3)_4$, PhSH (1.1 equiv), *i*-Pr_2NEt, and CO (1 atm via gas dispersion tube), in DMF at 90 °C on a 100 mmol scale. Reduction ($LiBH_4$, THF, EtOH, 82%), conversion to the related chloride (MsCl, LiCl, *s*-collidine, 89%)[20] and treatment with morpholine (*i*-Pr_2NEt, DMF, 80%) then provided amine **14**. Alkylation of **14** with phenyl bromoacetate (Cs_2CO_3, DMF, 60 °C) gave the relatively reactive quinolone phenyl ester **15** which was easily converted to the abnormal S_NAr substrate **16** (93% from **14**) after exposure to methylamine in THF at room temperature. A number of conditions were examined for their ability to effect the desired abnormal S_NAr ring closure with KO-*t*-Bu in THF providing **11b** (50%) from **22**. Surprisingly, alternate bases and

Table 1
HCMV polymerase inhibition for compounds **17b**, **23**–**26**



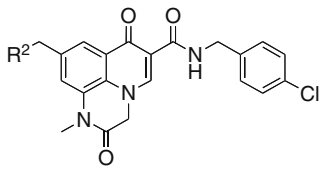
	R^1	HCMV pol IC_{50}[a] (nM)	HCMV pra IC_{50}[a] (nM)
11b	CH_3	620	100
17	CH_3CH_2	1280	ND
18	$HOCH_2CH_2$	830	700
19	$HOCH_2CH_2CH_2$	1840	ND
20		4410	ND

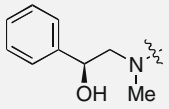
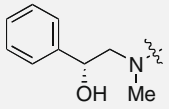
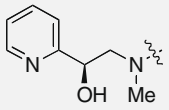
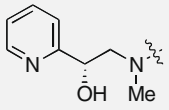
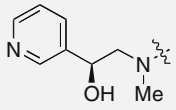
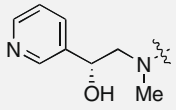
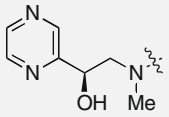
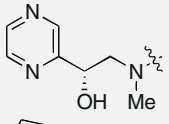
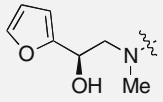
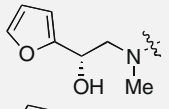
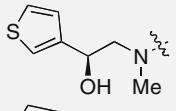
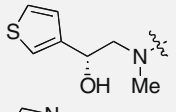
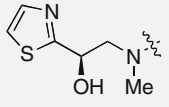
[a] Ref. 6.



Scheme 2. Synthesis of 1*H*,7*H*-pyrido[1,2,3-*de*]quinoxaline-6-carboxamide **11b**. Reagents and conditions: (a) diethyl ethoxymethylene malonate, 120 °C, 83%; (b) Ph_2O, 250 °C, 91%; (c) 4-$ClPhCH_2NH_2$, NaOMe–MeOH, DMSO, 120°, 90%; (d) $Pd(PPh_3)_4$, CO, PhSH, *i*-Pr_2NEt, 90 °C, 91%; (e) $LiBH_4$, THF, EtOH, 82%; (f) MsCl, LiCl, s-collidine, DMAP, THF, DMF, 89%; (g) morpholine, *i*-Pr_2NEt, DMF, 80%; (h) $BrCH_2CO_2Ph$, Cs_2CO_3, DMF, 60 °C; (i) RNH_2, THF, (R = CH_3, 93%); (j) KO-*t*-Bu, THF, rt, 50%.

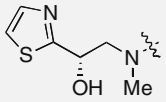
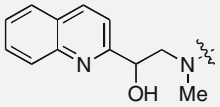
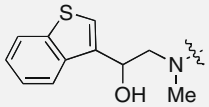
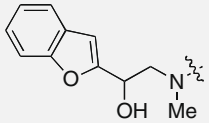
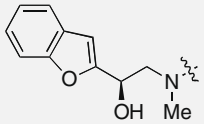
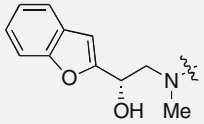
Table 2
HCMV pol/pra IC_{50} and *c*Log *P*/*c*Log *D* for compounds **11b**, **22**–**35**



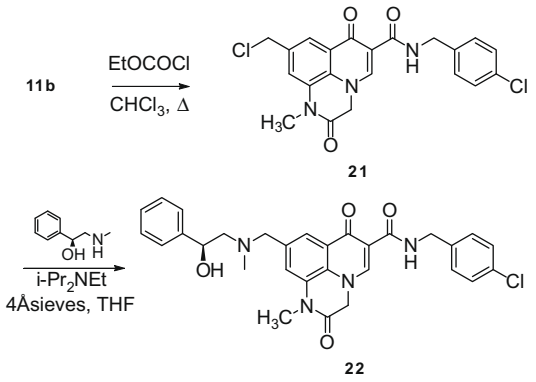
	R^2	HCMV pol IC_{50}[a] (nM)	HCMV pra IC_{50}[a] (nM)	*c*Log *P*[b] (*c*Log *D*[b])	LipE[d]
11b		620	100	0.80 (0.78)	6.20
22[c]		130	100	3.10 (2.74)	3.10
23		9160	ND		
24[c]		300	20	1.61 (1.40)	6.08
25		5250	ND		
26[c]		150	10	1.61 (1.38)	6.39
27		4550	ND		
28		260	200	0.61 (0.43)	6.08
29		7700	ND		
30[c]		110	10	2.26 (2.04)	5.74
31		4930	ND		
32[c]		190	100	2.78 (2.48)	4.22
33		5720	ND		
34		490	100	3.14 (3.04)	3.86

(*continued on next page*)

Table 2 (*continued*)

	R^2	HCMV pol IC_{50}[a] (nM)	HCMV pra IC_{50}[a] (nM)	*c*Log *P*[b] (*c*Log *D*[b])	LipE[d]
35		6200	ND		
36[c]		42	ND	2.97 (2.75)	
37[c]		97	100	5.27 (5.06)	1.73
38[c]		8	ND	3.56 (3.33)	
39[c]		4	1	3.56 (3.33)	5.44
40[c]		180	90	3.56 (3.33)	3.48

[a] Ref. 6.
[b] Calculated utilizing ACD Labs 12.0 software.
[c] CC_{50} > 15 μM (Ref. 6).
[d] Ref. 21.



Scheme 3. Synthesis of side chain modified 1*H*,7*H*-pyrido[1,2,3-*de*]quinoxaline-6-carboxamide **22**.

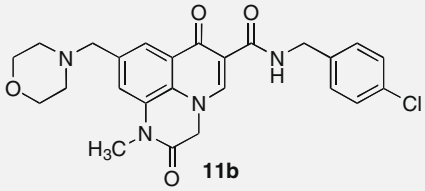
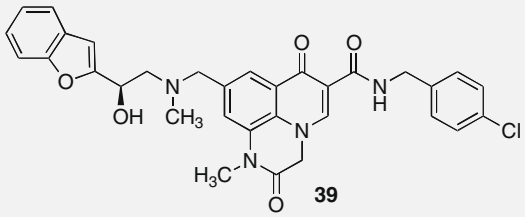
solvents proved ineffective in this cyclization during our initial trials. The alternate route to **11b** afforded the target material in 10 steps and 17% overall yield. As a result of the higher overall yield and the late introduction of the pyridoquinoxaline N-substituent (**15**–**16**), we were well positioned for our planned studies of the impact both the R^1 and R^2 substituents.

Utilizing the chemistry of Scheme 2, but altering the amine used in the conversion of ester **15** to the cyclization substrate **16**, we prepared the compounds of Table 1. Despite our initial desire to alter the physical characteristics of the pyridoquinoxaline series by varying the R^1 group of compound **7** (Fig. 2), it is clear from an inspection of Table 2 that the modification of the R^1 group to larger than a methyl, with or without added polarity, is neutral to detrimental, with only the hydroxyethyl containing compound **18** preserving the bulk of the activity of the parent **11b**. Moving forward, we will examine changes at R^2 while keeping R^1 (**7**, Fig. 2) as a methyl group.

Variation of the R^2 substituent of **7** (Fig. 2) calls for us to employ the chiral amino ethanols[7c] as side chains. These entities have afforded high levels of enzymatic and antiviral activity while altering the properties of the final molecules.[6–9] Toward that end, amine **11b** will serve as the starting material, affording the desired chloromethyl intermediate **21** (92%, Scheme 3) after treatment with ethyl chloroformate.[6,7,9,10] Alkylation of **21** with (*S*)-2-(methylamino)-1-phenylethanol[21] (THF, *i*-Pr_2NEt, activated 4 Å molecular sieves) then afforded the target analog **22** in 85% yield. Utilizing the chemistry of Scheme 3, the compounds of Table 2 were prepared.

An examination of Table 2 indicates that the impact of the amino ethanol side chain is apparent in the pyridoquinoxaline series and that the preferred asymmetry of the amino ethanol remains the same as previous studies.[7,9] Potent HCMV pol activity (IC_{50} < 500 nM) and excellent antiviral activity (HCMV pra IC_{50} < 200 nM) are associated with each of the favored monocyclic-aminomethanol enantiomers (compounds **22**, **24**, **26**, **28**, **30**, **32**, and **34**). The most potent compounds of this series furan **30** (HCMV pol IC_{50} = 110 nM; HCMV pra IC_{50} = 10 nM) and pyridine **26** (HCMV pol IC_{50} = 150 nM; HCMV pra IC_{50} = 10 nM) present a hydrogen bond acceptor α- or β-to the point of attachment. An extension of this series to a small set of bicyclic-aminoethanols[7a] was next examined. These had proven useful in the dihydrothieno[2,3-b]pyridine series but had not provided optimal physical characteristics in that series. Three bicyclic aryl-aminoethanols were selected, each with a heteroatom α- or β- to the point of attachment to the carbinol carbon: 2-quinolinyl-, benzothienyl-, and benzofuranyl. As shown in Table 2 all of the racemic bicyclic

Table 3
Broad spectrum activity for compounds **11b** and **43** and comparison with established therapies

	HCMV pol IC_{50}[b] (nM)	HCMV pra IC_{50}[b] (nM)	VZV pol IC_{50}[b] (nM)	VZV pra IC_{50}[b] (nM)	Human α-pol IC_{50}[b] (nM)	Solubility[c] (μg/mL)
 **11b**	620	100	180	20	>5000	8.6
 **39**	4	1	29	4	>5000	0.94
Ganciclovir		1300				
Acyclovir		>20,000		8100		
Foscarnet	2500					
Aphidicolin	487		473			
AZT-TP[a]	22,100		5800			

[a] AZT-TP: zidovudine triphosphate.
[b] Ref. 6.
[c] Ref. 22.

aryl-aminoethanols afforded analogs which are as potent (**36**, **37**) or more potent (**38**) in the HCMV pol assay than any of the preceding compounds of Table 2. The HCMV pol IC_{50} = 8 nM associated with *rac*-benzofuranyl containing **38** is noteworthy, suggesting the utility of the chiral congeners. Utilization of (*R*)-1-(benzofuran-2-yl)-2-(methylamino)ethanol[7c] and (*S*)-1-(benzofuran-2-yl)-2-(methylamino)ethanol[7c] led to **39** and **40** respectively. Of special interest is the notable HCMV pol activity (IC_{50} = 4 nM) and HCMV antiviral activity (HCMV pra IC_{50} = 1 nM) associated with the (*R*)-1-(benzofuran-2-yl)-2-(methylamino)ethanol containing compound **39**. The enzymatic and antiviral activity exhibited by the (*S*)-1-(benzofuran-2-yl)-2-(methylamino)ethanol containing **40** (HCMV pol IC_{50} = 180 nM; HCMV pra IC_{50} = 90 nM) is surprising (**23**, **25**, **27**, **29**, **31**, **33**, **35**: HCMV pol $IC_{50} \geqslant 4550$ nM.[7a,b,9]) in light of the data of Table 2 and earlier reports,[7,9] however, given the potency exhibited by **39**, it is possible that this is the result of the ca. 1% contaminant of the antipodal (*R*)-aminoethanol ((*S*)-1-(benzofuran-2-yl)-2-(methylamino)ethanol, 98% ee).

We have examined calculated Log *P* and Log *D* values for the compounds of Table 2 in an attempt to associate the level of observed activity with a particular lipophilicity (Log *P*) and/or Log *D*. The *c*Log *P* and *c*Log *D* values for **39** and **40** (*c*Log *P* = 3.56, *c*Log *D* = 3.33) are higher than the most lipophilic momocyclic-compound of Table 2 (compound **34**; *c*Log *P* = 3.14, *c*Log*D* = 3.04) and lower than that calculated for **37** (*c*Log *P* = 5.27, *c*Log *D* = 5.06) the antiviral data for these compounds does not appear to correlate solely with *c*Log *P*. If we compare **39** to the most potent monocyclic-compound of Table 2, furan containing **30** (*c*Log *P* = 2.26, *c*Log *D* = 2.04) we cannot attribute the difference in activity as being exclusively due to increased lipophilicity (viz. **37**). We have also evaluated the properties of potency and lipophilicity for compounds of Table 2 using the Lipophilic Efficiency paradigm (LipE) recently reported by Ryckmans.[21] If the analysis above *re*: *c*Log *P* and *c*Log *D* is valid, we would expect the most efficient compounds to be clustered near the same LipE line. Should we be gaining potency solely through added lipophilicity, then those compounds should fall off from this line significantly. Utilizing the HCMV pra IC_{50} data of Table 2, LipE values were calculated. The benchmark morpholinomethyl containing **11b** is associated with LipE = 6.20, while 2-pyridyl **24**, 3-pyridyl **26**, 2-furyl **30**, and 2-benzofuranyl **39** are associated with LipE = 6.08, 6.39, 5.74 and 5.44, respectively. Thus, the most interesting compounds of this study are clustered around a similar LipE line = 6 placing them in a *highly optimized* grouping as described by Ryckmans et al.[21]

In conclusion, the pyridoquinoxaline nucleus has proven to be a useful core for the construction of novel herpes antiviral agents, providing compounds such as **39** which compare favorably to established therapies (Table 3). The *standard* morpholinomethyl side chain affords reasonable levels of enzymatic and antiviral activity exemplified by compound **11b**. The application of the SAR previously described[7,9] for the 2-aryl-2-hydroxyethylamine motif to the pyridoquinoxaline nucleus has provided analogs of good to excellent enzymatic and antiviral activity. Of significance was the impact of the benzofuran moiety in compound **39**, which resulted in extremely potent enzymatic and antiviral activity with a small impact on LipE. Future activities should attempt to maintain the desirable aspects of compounds such as **39** while improving solubility,[22] toward and beyond that exhibited by **11b**, while continuing to improve other biopharmaceutical properties.

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19. *A representative procedure for the conversion of* **12**–**13** *follows:* Iodide **12** (45.66 g, 0.1 mol) was added to a three neck 1 L round-bottomed flask, and it was covered with anhydrous DMF (0.4 L). The flask was equipped with a magnetic stir bar, a 125 mL pressure equalized addition funnel, a medium sized cold finger condenser, and a coarse frit gas dispersion tube. The set up was swept with a flow of argon (addition funnel inlet, cold finger condenser outlet) while *i*-Pr_2NEt (27.14 g, 0.21 mol, 36.6 mL) was added to the reaction flask. The addition funnel was charged with anhydrous DMF (0.1 L) and PhSH (12.12 g, 0.11 mol, 1.1 equiv, 11.3 mL). The argon flow is replaced by a flow of argon through a 20 gauge syringe needle, bubbling through the DMF/PhSH mixture in the addition funnel. The CO flow (vigorous through the gas dispersion tube) into the mixture in the round-bottom flask is initiated and the vessel is lowered into a preheated 90 °C oil bath. Bubbling (CO and Ar) is continued for 10 min while the solution warms and **12** gradually dissolves. During this period the cold finger condenser is charged with a dry ice/*i*-PrOH mixture. At the end of the 10 min period the addition funnel was capped with a serum cap and the argon inlet was switched to a 20 gauge 1.5 inch syringe needle placed into the open outlet of the cold finger condenser. With a vigorous flow of CO bubbling through the DMF solution of **12** and *i*-Pr_2NEt, the center joint of the 3 N RB flask was unstoppered and $Pd(PPh_3)_4$ (0.86 g, 0.75 mmol) was added in one portion. The solution became lemon yellow as the $Pd(PPh_3)_4$ dissolved. After complete dissolution of $Pd(PPh_3)_4$ the PhSH/DMF was added over 75 min. As the addition progressed the reaction mixture turned orange, then red, and finally after ca. 90% of the PhSH had been added, the solution became red–black. HPLC analysis after 75 min indicated that the reaction was complete (17 min gradient, 5:95 $CH_3CN/H_2O[H_3PO_4$–NaH_2PO_4 buffer] to 95:5): **12** t_R = 7.29 min; **13** t_R = 10.87 min). The mixture was cooled to room temperature and the DMF was removed on a cold finger rotary evaporator (vacuum pump pressure) with warming in a 40 °C oil bath to afford a red–black solid. The crude material was triturated with CH_2Cl_2–pentane (0.5 L, 3:1) to furnish a red–black solution and a cream colored solid. The mixture was chilled in an ice-water bath for 30 min, then the solid was isolated by filtration. The solid was rinsed with CH_2Cl_2–pentane (3 × 100 mL, 3:1) to provide 28.92 g of the thioester **13** after drying in a vacuum oven (70 °C). The triturate was concentrated in vacuo to give a sticky red–black solid that was triturated with CH_2Cl_2–pentane (0.25 L, 3:1) to give a red–black solution and a cream colored solid. Isolation of the solid by filtration, washing with CH_2Cl_2–pentane (3 × 75 mL, 3:1) and drying in vacuo (70 °C) gave an additional 9.21 g of thioester **13**. The lots were combined to realize 38.13 g (82%) of **13**. A portion was recrystallized from CH_2Cl_2–MeOH to yield **13** as fine, cream colored needles. Mp 222–223 °C.
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