Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 2735–2739
Bioorganic & Medicinal Chemistry Letters

Imidazo[1,2-*a*]pyridines with potent activity against herpesviruses

Kristjan S. Gudmundsson* and Brian A. Johns

Department of Medicinal Chemistry, Infectious Diseases Center of Excellence for Drug Discovery, GlaxoSmithKline Research & Development, Five Moore Drive, Research Triangle Park, NC 27709-3398, USA

Received 24 January 2007; revised 28 February 2007; accepted 28 February 2007
Available online 3 March 2007

Abstract—Synthesis of a series of 2-aryl-3-pyrimidyl-imidazo[1,2-*a*]pyridines with potent activity against herpes simplex viruses is described. Synthetic approaches allowing for variation of the 2-aryl, 3-heteroaryl as well as other imidazopyridine substituents are outlined and resulting effects on antiviral activity are highlighted. Several compounds with in vitro antiviral activity similar or better than acyclovir are described.

The herpesvirus family (Herpesviridae) is highly disseminated in nature and most animal species host at least one member. This family contains eight known human viruses, amongst them herpes simplex virus 1 (HSV-1) and herpes simplex virus 2 (HSV-2).[1] HSV-1 and HSV-2 cause mucocutaneous infections, resulting in cold sores (HSV-1) and genital lesions (HSV-2), respectively. A key feature of these viruses is their ability to cause latent and chronic infection of neurons, which upon reactivation leads to recurrent lesions at the mucocutaneous area of initial infection.[2] Much research has been focused on HSV-1 and HSV-2 as these viruses have a high incidence rate (~1.6 million new cases of HSV-2 predicted per year in the US) and a high prevalence of 50–95% (HSV-1) and 6–50% (HSV-2).[3]

Previous drug discovery efforts targeting herpes simplex viruses has primarily focused on the development of nucleoside analogs that target the viral polymerase.[4] The discovery of acyclovir (Zovirax),[5] was a milestone in the development of antiviral drugs and was followed by a number of other nucleoside analogs (valacyclovir,[6] famciclovir[7] and penciclovir).

Though numerous strategies and considerable effort have been spent in the search for the next generation antiherpetic therapy, it has proved difficult to outperform acyclovir.[8] Immunomodulators (imiquimod and resiquimod),[9] nonnucleoside viral polymerase inhibitors (4-hydroxyquinoline-3-carboxamides)[10] and viral helicase inhibitors (thiazolylphenyl and thiazolylamide)[11] have recently received considerable attention.

We have recently disclosed a series of pyrazolo[1,5-*a*]pyridines, such as **1**, which show potent and selective inhibition of HSV-1 and -2 (Fig. 1).[12] We became interested in the corresponding imidazo[1,2-*a*]pyridines as they can be substituted in the same fashion as the pyrazolopyridines, furthermore imidazopyridines have been widely used in medicinal chemistry. We have disclosed the synthesis of the imidazopyridine **2**.[13] Herein we expand on the synthetic approaches and describe several novel imidazopyridines and their anti-HSV activity.

Initially we chose to prepare several methoxyphenyl analogs as we have previously shown those to be very potent for the related pyrazolopyridine series.[12b] Condensation of 2-amino-3-chloropyridine **3** with commercially available α-bromo ketone **4** was used to prepare

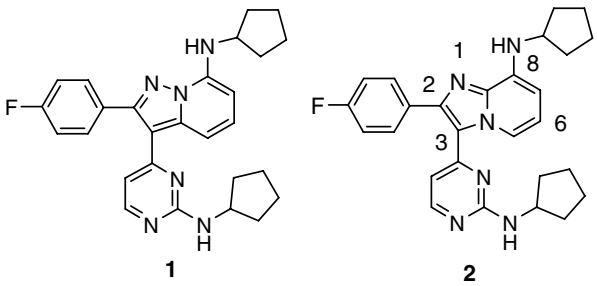


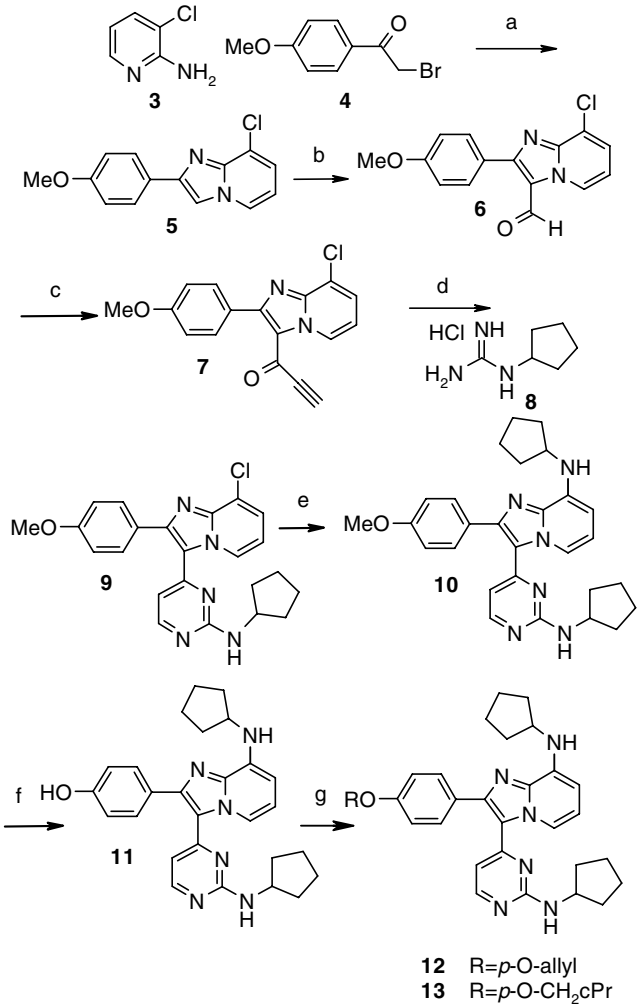
Figure 1. Pyrazolopyridine and imidazopyridine scaffolds.

Keywords: Imidazo[1,2-*a*]pyridine; Antiherpetic; HSV.
* Corresponding author. Tel.: +1 919 483 5862; fax: +1 919 483 6053; e-mail: Kristjan.S.Gudmundsson@gsk.com

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.02.079

imidazopyridine core **5** as outlined in Scheme 1. We have previously shown[13] that an efficient route to construct the C-3 pyrimidine is to build the pyrimidine from alkynyl ketones via a cyclization with guanidines.

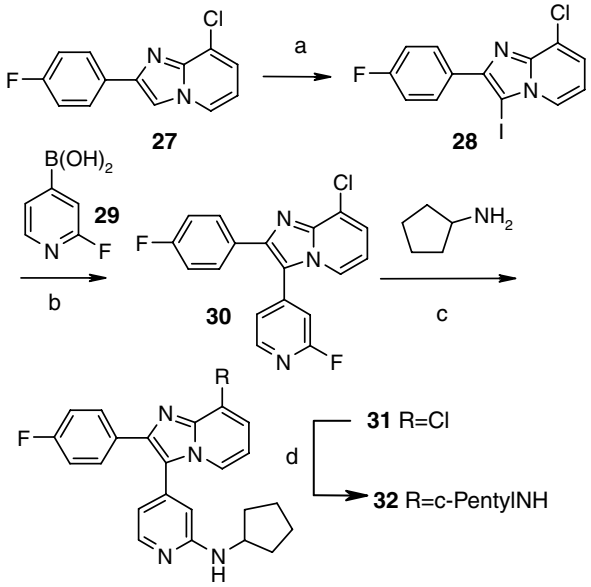
Thus, formylation of **5** under Vilsmeier–Haack conditions gave an excellent yield of the remarkably stable aldehyde **6**. This aldehyde was treated with the commercially available ethynyl Grignard reagent at low temperature to give the propargyl alcohol in excellent yield. This alcohol was easily oxidized to ketone **7** using MnO_2. Other oxidation methods (e.g., Swern and Dess–Martin oxidations) gave lower yields. Treatment of the alkynyl ketone **7** with cyclopentylguanidine **8**, resulted in formation of the 8-chloro intermediate **9**. Initial attempts at thermally displacing the 8-chloro substituent of **9** with cyclopentylamine failed, but the 8-position could be coupled with cyclopentylamine using Buchwald amination conditions ($Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3).[14] Demethylation with BBr_3 in CH_2Cl_2 gave phenol **11**, that could be alkylated with allylbromide or cyclopropylmethylbromide to give, respectively, **12** and **13**.



Scheme 1. Reagents and conditions: (a) $NaHCO_3$ (1 equiv), EtOH, reflux, 6 h, (73%); (b) $POCl_3$ (2 equiv), DMF, rt, 12 h (86%); (c) Ethynyl magnesium bromide (2 equiv), THF, −78–0 °C, 2 h. Then MnO_2 (10-fold excess), CH_2Cl_2, 1 h (51%, two steps); (d) cyclopentyl guanidine HCl (1.5 equiv), K_2CO_3 (1.5 equiv), EtOH, 80 °C, 12 h (50%); (e) $Pd(OAc)_2$ (0.2 equiv), BINAP (0.3 equiv), Cs_2CO_3 (2 equiv), cyclopentylamine (neat), 100 °C, 18 h (53%); (f) BBr_3 (1.1 equiv), CH_2Cl_2 −78 °C to rt, 15 h (70%); (g) allyl bromide or cyclopropylmethylbromide (1.5 equiv), Cs_2CO_3 (2 equiv), DMF, 80 °C, 3 h (34% for **12**; 47% for **13**).

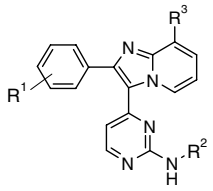
By chosing differently substituted commercially available α-bromoacetophenones, the substitution pattern of the 2-phenyl moiety was further altered. Substituents were chosen based on our previous experience from the analogous pyrazolopyridine series, where small substituents generally appeared to be preferred over large groups (halogen, alkyl, alkoxy and cyano substituents gave best antiviral activity).[12b] Thus *m*-substituted alkoxy derivatives (**14**–**17**) as well as nitriles (**18** and **19**) and a methyl derivative (**20**) were prepared in a similar fashion as outlined in Scheme 1 starting from commercially available α-bromoacetophenones. The nature of the substituent or location (*meta* vs *para*) on the 2-phenyl moiety did not significantly alter anti-HSV activity as shown by the fact that strongly electron withdrawing groups (fluoro) showed similar potency as the strongly electron donating groups (methoxy) and both of these showed comparable activity to nitrile substituents. For further studies we chose to focus on *p*-fluorophenyl derivatives (such as **2**) as these showed excellent anti-HSV activity while containing a non-reactive substituent with low molecular weight.

The synthetic method outlined in Scheme 1 was thus used to make a small set of 8-amino-2-(*p*-fluorophenyl)-derivatives **21**–**24** via a Buchwald coupling methodology. These indicate that secondary alkylamines are favored at the C8 position.



Scheme 2. Reagents and conditions: (a) NIS (1.5 equiv), CH_2Cl_2, rt 12 h, (80%); (b) $PdCl_2(PPh_3)_2$ (0.2 equiv), aq Na_2CO_3 (2 equiv), DMF, 100 °C, 12 h, (81%); (c) cyclopentylamine (neat), 150 °C, 3 days, (76%); (d) $Pd(OAc)_2$ (0.2 equiv), BINAP (0.3 equiv), Cs_2CO_3 (2 equiv), cyclopentylamine (neat), 100 °C, 18 h (27%).

Table 1. HSV-1 antiviral activity and cytotoxicity of C8-substituted imidazopyridine analogs



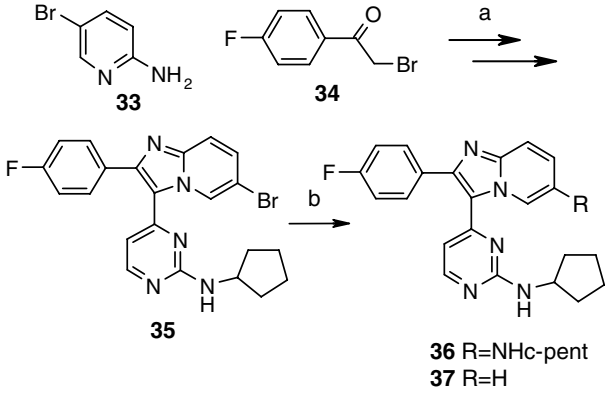
Compound	Subst. R^1	Subst. R^2	Subst. R^3	IC_{50}[a] (μM)	CC_{50}[b] (μM)
2	*p*-F	c-Pent	c-PentNH	0.59	>40
9	*p*-OCH_3	c-Pent	Cl	1.43	30.1
10	*p*-OCH_3	c-Pent	c-PentNH	0.48	>10
11	*p*-OH	c-Pent	c-PentNH	3.40	>40
12	*p*-$OCH_2CH{=}CH_2$	c-Pent	c-PentNH	0.57	>40
13	*p*-OCH_2c-Propyl	c-Pent	c-PentNH	0.27	>40
14	*m*-OCH_3	c-Pent	Cl	1.73	>40
15	*m*-OCH_3	c-Pent	c-PentNH	0.71	>40
16	*m*-OH	c-Pent	c-PentNH	3.13	>40
17	*m*-$OCH_2CH{=}CH_2$	c-Pent	c-PentNH	0.30	>40
18	*p*-CN	c-Pent	c-PentNH	0.32	>40
19	*m*-CN	c-Pent	c-PentNH	0.36	>40
20	*p*-CH_3	c-Pent	c-PentNH	1.61	>40
21	*p*-F	c-Pent	c-PropylNH	0.51	33
22	*p*-F	c-Pent	n-ButylNH	0.80	32
23	*p*-F	c-Pent	1-pyrrolidinyl	1.88	>40
24	*p*-F	c-Pent	2-methoxyethylNH	0.26	>40
25	*p*-F	Me	Cl	9.3	>40
26	*p*-F	Me	c-PentNH	>5	>40
32[c]	*p*-F	c-Pent	c-PentNH	0.6	>40
1	—	—	—	0.26	>160
ACV	Acyclovir	—	—	0.39	>200

[a] Vero cells, HSV-1, SC-16 strain. IC_{50} is the concentration at which 50% efficacy in the antiviral assay is observed using a capture hybrid method.[12b]
[b] CC_{50} is the concentration at which 50% cytotoxicity is observed.
[c] Analog contains a C3-pyridine rather than C3-pyrimidine.

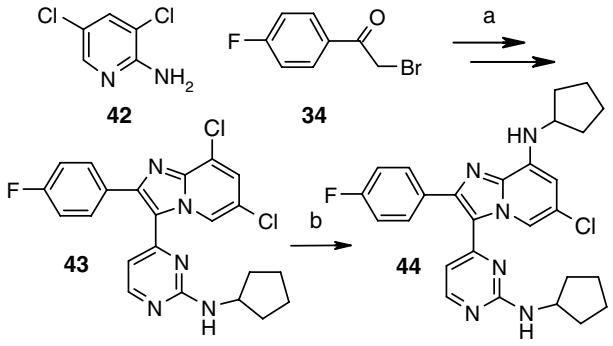
For the pyrazolopyridine series we had observed that lipophilic alkylamines (cyclopentylamine being optimal) were the preferred 2-pyrimidinyl substituents.[12d] This also appears to be the case for the imidazopyridines. Derivatives prepared with methylguanidine, **25** and **26**, showed reduced anti-HSV activity.

We were also interested in seeing how a C3 2-aminopyridine substituent compared with the 2-aminopyrimidine substituent. Thus 3-iodoimidazopyridine **28** was synthesized (Scheme 2) from **27** by treatment with *N*-iodosuccinimide.

Subsequent Suzuki coupling of **28** and boronic acid **29** gave the 2-fluoropyridine **30**. Displacement of the 2-fluorine with cyclopentylamine under thermal conditions gave the 2-aminopyridine **31** in good yield.

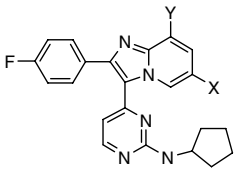


Scheme 3. Reagents and condition: (a) for conditions see Scheme 1; (b) $Pd(OAc)_2$ (0.2 equiv), BINAP (0.3 equiv), Cs_2CO_3 (2 equiv), cyclopentylamine (neat), 100 °C, 18 h (43% of **36** and 12% of **37**).



Scheme 4. Reagents and condition: (a) for conditions see Scheme 1; (b) $Pd(OAc)_2$ (0.2 equiv), BINAP (0.3 equiv), Cs_2CO_3 (2 equiv), cyclopentylamine (neat), 100 °C, 18 h (50%).

Table 2. HSV-1 antiviral activity and cytotoxicity of C6-, C8-substituted imidazopyridine analogs



Compound	Subst. X	Subst. Y	IC_{50}[a] (μM)	CC_{50}[b] (μM)
35	Br	H	4.08	>40
36	c-PentNH	H	0.33	>40
37	H	H	3.3	>40
38	Br	Me	1.16	>40
39	c-PentNH	Me	0.15	>40
40	H	Me	1.53	>40
41	c-PropylNH	Me	0.12	>40
43	Cl	Cl	1.11	>40
44	Cl	c-PentNH	0.37	>40
45	Br	Br	0.80	>40
46	Br	c-PentNH	0.22	>40
47	Br	n-ButylNH	0.30	>40
1	—	—	0.26	>160
ACV	Acyclovir	—	0.39	>200

[a] Vero cells, HSV-1, SC-16 strain. IC_{50} is the concentration at which 50% efficacy in the antiviral assay is observed using a capture hybrid method.[12b]
[b] CC_{50} is the concentration at which 50% cytotoxicity is observed.

Buchwald coupling of **31** and cyclcopentylamine gave the desired analog **32**. While the C3-pyridine analog **32** was equipotent to the C3-pyrimidine analog (**2**) it did not offer any advantage over **2**. Furthermore, concerns about potential cytochrome inhibition of the 2-aminopyridine moiety prompted us to stick with the C3 pyrimidine moiety for further investigations.

Given the potent anti-HSV activity of several of the C8-substituted imidazopyridines, we were interested in studying how different substitution patterns would affect antiviral activity. We were especially interested in seeing how moving the C8 cyclopentylamino substitutent to the C6 position would affect activity. As can be seen in Table 1, alkylamines at C8 showed better activity than halogens (e.g., **9** vs **10**; **14** vs **15**) and we were curious if the improved potency of the C-8 alkylamines could partially be explained by electron donating effects onto the imidazopyridine N-1. Moving the electron donating alkylamine substituent to C6 would continue to allow resonance electron donation to the N-1 imidazopyridine nitrogen.

The 6-chloro substituent was found to be much less reactive than the corresponding 8-chloro position. Thus C6 alkylamine substituted compounds could not be efficiently prepared by replacement of a 6-chloro group under Buchwald conditions, but required preparation of the more reactive 6-bromo derivatives. The 6-cyclopentylamino derivative **36** was thus prepared from the 6-bromo-imidazopyridine **35** via a Buchwald coupling methodology. A by-product of this coupling was the reduced 6-protio derivative **37**. Low reactivity of the 6-chloro substituent toward Pd catalyzed coupling conditions is in contrast to the relative ease of coupling of 8-position with alkylamines under Buchwald conditions. The 8-methyl analogs **38**–**41** were prepared in a similar fashion as outlined in Scheme 3 from 2-amino-3-methyl-5-bromopyridine. Interestingly the C6 cyclopentylamino analogs **36** and **39** are at least equally potent to their C8 counterpart **2**, thus giving more options for location of the alkylamine substituent during further optimization.

As both C6 as well as C8 alkylamine substituted compounds had shown good potency we became interested in looking at additional 6,8-disubstituted compounds. The 6,8-disubstituted derivatives **43**–**47** were prepared as outlined in Scheme 4. Here Buchwald coupling conditions could be used to cleanly replace the C8 halogen without any noticeable reaction of the C6 halogen.

Several of these 6,8-disubstituted derivatives (**44**, **46** and **47**) showed very promising potency (Table 2).

The above SAR study has begun to delineate the SAR of the imidazopyridine scaffold. Several molecules with potency similar or better than the current gold standard acyclovir were identified, thus establishing the imidazopyridine scaffold as an interesting template for anti-HSV drug discovery.

References and notes

1. Roizman, B.; Pellett, P. E. In *Fields Virology*; Knipe, D. M., Howley, P. M., Eds.; Lippincott Williams and Wilkins: Philadelphia, PA, 2001; vol. 2, p 2381.
2. Kleymann, G. *Expert Opin. Investig. Drugs* **2003**, *12*, 165.
3. (a) Corey, L.; Spear, P. *New Engl. J. Med.* **1986**, *314*, 686; (b) Corey, L.; Handsfield, H. H. *J. Am. Med. Assoc.* **2000**, *283*, 791.
4. (a) Moomaw, M. D.; Cornea, P.; Rathbun, R. C.; Wendel, K. A. *Expert Rev. Anti Infect. Ther.* **2003**, *1*, 283; (b) Firestine, S. M. *Expert Opin. Ther. Patents* **2004**, *14*, 1139.

5. Elion, G. B.; Furman, P. A.; Fyfe, J. A.; De Miranda, P.; Beauchamp, L.; Schaeffer, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5716.
6. Perry, C. M.; Faulds, D. *Drugs* **1996**, *52*, 754.
7. Jarvest, R. L.; Sutton, D.; Vere Hodge, R. A. *Pharm. Biotechnol.* **1998**, *11*, 313.
8. (a) Naesens, L.; De Clercq, E. *Herpes* **2001**, *8*, 12; (b) Villerreal, E. C. *Prog. Drug Res.* **2001**, *56*, 77; (c) Snoeck, R.; De Clercq, E. *Curr. Opin. Infect. Dis.* **2002**, *15*, 49.
9. (a) Garland, S. M. *Curr. Opin. Infect. Dis.* **2003**, *16*, 85; (b) Taff, J. *Curr. Opin. Infect. Dis.* **2003**, *4*, 214; (c) Spruance, S. L.; Tyring, S. K.; Smith, M. H.; Meng, T. C. *J. Infect. Dis.* **2001**, *184*, 196.
10. (a) Oien, N. L.; Brideau, R. J.; Hopkins, T. A., et al. *Antimicrob. Agents Chemother.* **2002**, *46*, 724; (b) Wathen, M. W. *Rev. Med. Virol.* **2002**, *12*, 167; (c) Jurk, M.; Heil, R.; Vollmer, J., et al. *Nat. Immunol.* **2002**, *3*, 499.
11. (a) Crute, J. J.; Grygon, C. A.; Hargrave, K. D.; Simoneau, B.; Faucher, A.-M.; Bolger, G.; Kibler, P.; Liuzzi, M.; Cordingley, M. G. *Nat. Med.* **2002**, *8*, 386; (b) Kleymann, G.; Fischer, R.; Betz, U. A. K.; Hendrix, M.; Bender, W.; Schneider, U.; Handke, G.; Eckenberg, P., et al. *Nat. Med.* **2002**, *8*, 392.
12. (a) Johns, B. A.; Gudmundsson, K. S.; Turner, E. M.; Allen, S. H.; Jung, D. K.; Sexton, C. J.; Boyd, F. L., Jr.; Peel, M. R. *Tetrahedron* **2003**, *59*, 9001; (b) Gudmundsson, K. S.; Johns, B. A.; Wang, Z.; Turner, E. M.; Allen, S. H.; Freemen, G. A.; Boyd, F. L., Jr.; Sexton, C. J.; Selleseth, D. W.; Moniri, K. R.; Creech, K. L. *Bioorg. Med. Chem.* **2005**, *13*, 5346; (c) Allen, S. H.; Johns, B. A.; Gudmundson, K. S.; Freeman, G. A.; Boyd, F. L., Jr.; Sexton, C. J.; Selleseth, D. W.; Creech, K. L.; Moniri, K. R. *Bioorg. Med. Chem.* **2006**, *14*, 944; (d) Johns, B. A.; Gudmundsson, K. S.; Turner, E. M.; Allen, S.; Samano, V. A.; Ray, J. A.; Freeman, G. A.; Boyd, F. L., Jr.; Sexton, C. J.; Selleseth, D. W.; Creech, K. L.; Moniri, K. R. *Bioorg. Med. Chem.* **2005**, *13*, 2397.
13. Gudmundsson, K. S.; Johns, B. A. *Org. Lett.* **2003**, *5*, 1369.
14. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144.