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# Substituted 1,6-Naphthyridines as Human Cytomegalovirus Inhibitors: Conformational Requirements

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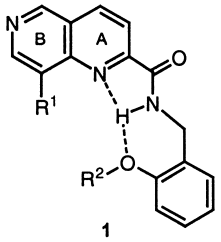
**Abstract**—Substituted 1,6-naphthyridine derivatives, a new class of human cytomegalovirus inhibitors, were prepared to demonstrate the role of intramolecular hydrogen bonds to maintain the compounds in their active conformation. 

Very recently, we have reported the discovery of a novel class of human cytomegalovirus (HCMV) inhibitors.[1] In this communication, the structure–activity relationship (SAR) has clearly shown that the 1,6-naphthyridine 2-carboxylic acid 2-alkoxy benzylamide **1** series possesses the most potent anti-HCMV activity among all naphthyridine derivatives that we have prepared. The fact that the antiviral activity is optimal when an alkoxy group is present at the *ortho* position of the benzyl amide, led us to believe that an intramolecular hydrogen bond (IHB) is present between the NH and the oxygen limiting the free rotation through the $CH_2$-N bond. Moreover, the need to have a nitrogen in the naphthyridine A ring for potent anti-HCMV activity, suggests the presence of another IHB between the NH and this nitrogen. Similar rationale has been previously used by Morin et al.[2] to explain the SAR of their antiviral phenethylthiazolethiourea class of compounds. In order to probe this hypothesis, we have prepared a number of derivatives[3] (Scheme 1) according to previously described methodology.[1,4]




**1**

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The anti-HCMV activity of these new derivatives is displayed in Table 1. The possibility of having intramolecular hydrogen bonds with the NH bond is highly variable from compounds **1** to **6**. The most potent derivative that has been identified, compound **1a**, has two hydrophobic groups $R^1$ and $R^2$ that may prevent water from disrupting the IHBs, thus preserving the compound more tightly in its active conformation. Replacement of the methyl group on naphthyridine B ring by a hydrogen (**1b**) reduces the anti-HCMV activity by about 10-fold. When the isopropyl group is replaced by an ethyl group (**1c**), another 20-fold reduction in the antiviral activity is observed. For compound **1d**, the anti-HCMV activity drops to 0.3 μg/mL; in this case, the IHB is well exposed to water and can be easily disrupted. The introduction of a trifluoromethyl group in compound **2** leads to a less basic oxygen, and the possibility of establishing an IHB with the NH group is greatly diminished. Consequently, **2** is less potent than the methoxy derivative and is equipotent to compound **3** for which no IHB is possible. The free rotation through the $CH_2$–N bond still gives access to the active conformation, but without any preference over the other rotamers.

This concept was further verified by the preparation of conformationally restricted derivatives **4** and **5**, which, while retaining all desirable features, allow IHB only to a limited extent. In these derivatives, the possibility of forming an IHB between the NH and the oxygen of the newly formed ring varies with ring size. The flexibility of the seven-membered ring allows the formation of an IHB (Fig. 1), and thus helps to maintain the active conformation. In this case, compound **4** retains reasonable antiviral activity with an $IC_{50}$ of 0.5 μg/mL. However,

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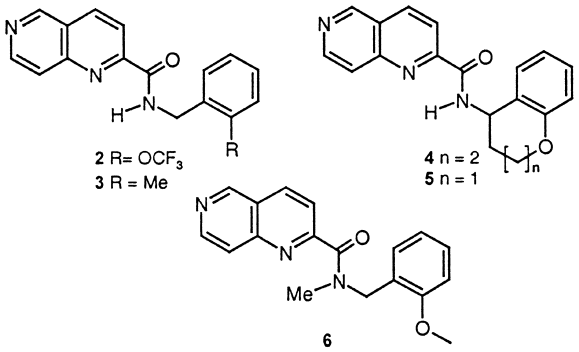


**Scheme 1.**

**Table 1.** In vitro anti-HCMV activity of compounds **1**–**7**

| Compound | $IC_{50}$ (μg/mL) |
|---|---|
| **1a** ($R^1$ = Me, $R^2$ = *iso*-Pr) | 0.0004 |
| **1b** ($R^1$ = H, $R^2$ = *iso*-Pr) | 0.005 |
| **1c** ($R^1$ = H, $R^2$ = Et) | 0.1 |
| **1d** ($R^1$ = H, $R^2$ = Me) | 0.3 |
| **2** | 1 |
| **3** | 1 |
| **4** | 0.5 |
| **5** | 20 |
| **6** | >25 |

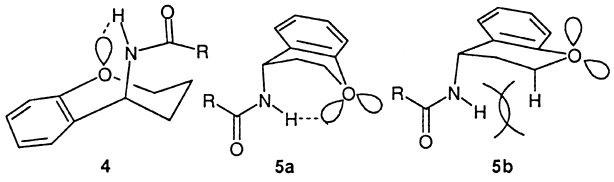


**Figure 1.**

when ring size is reduced to six (compound **5**), the possibility of forming an IHB between the NH and the oxygen of the ring is virtually abolished since only the high energy boat-like conformation (**5a**, Fig. 1) allows the formation of IHB.

The most probable conformation for the six-membered ring in compound **5** is the chair-like conformation (**5b**) in which no IHB is possible. Moreover, 1–3 diaxial interaction between NH and the axial CH bond further inhibits the access to the active conformation; as a result, **5** is essentially inactive.

When the hydrogen of the NH bond is replaced by a methyl group, the corresponding compound **6** does not show any anti-HCMV activity. In this case, no IHBs are possible and the active conformation is highly disfavored because of steric repulsion generated by the methyl group.

Semi-empirical calculations[5] were performed on **1** and **4**–**5** and the results support the presence of intramolecular hydrogen bonds for potent anti-HCMV compounds.

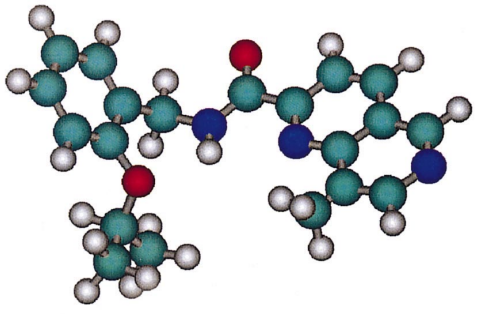

**Figure 2.** X-ray structure of **1a**.

Moreover, the X-ray structure has been obtained for the most potent compound (**1a**) (Fig. 2)[6] and corresponds to the proposed active conformation. The distance between the proton of the NH bond and the oxygen of the ether or the nitrogen of the naphthyridine A ring allows the formation of both IHBs. All the atoms involved in IHBs are also surrounded by hydrophobic groups, which may help exclude water molecules from disrupting the IHB, thus preserving the compound more tightly in the desired conformation.

In conclusion, all compounds described in this communication can in principle adopt the active conformation. However, when IHBs are present to maintain this conformation, the anti-HCMV activity is enhanced. Antiviral activity is lost when IHB is disrupted or not possible. Based on these results, development of new and more potent anti-HCMV compounds is underway in our laboratory.

## Acknowledgements

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## References and Notes

1. Chan, L.; Jin, H.; Stefanac, T.; Lavallée, J.-F.; Falardeau, G.; Wang, W.; Bédard, J.; May, S.; Yuen, L. *J. Med. Chem.* **1999**, *42*, 3023.
2. Bell, F. W.; Cantrell, A. S.; Hoegberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordan, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M., Jr.; Noréen, R.; Öberg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, P.; Sahlberg, C.; Ternansky, R. J.; Vasileff, R. T.; Vrang, L.; West, S. J.; Zhang, H.; Zhou, X.-X. *J. Med. Chem.* **1995**, *38*, 4929.
3. All spectra ($^1H$, $^{13}C$, and/or HRMS and IR) are in perfect agreement with the assigned structures.
4. The bicyclic amines needed for the synthesis of **4** and **5** were prepared from the corresponding alcohol. For the alcohol to make **5** see: Nioche, J. Y.; Decerprit, J.; Festal D. *Eur. J. Med. Chem.* **1995**, *30*, 377.
5. AM1, HyperChem Pro 5.1.
6. Details on X-ray structures will be published elsewhere.