Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 20, pp. 2687-2690, 1997

PII: S0960-894X(97)10057-9
0960-894X/97 $17.00 + 0.00

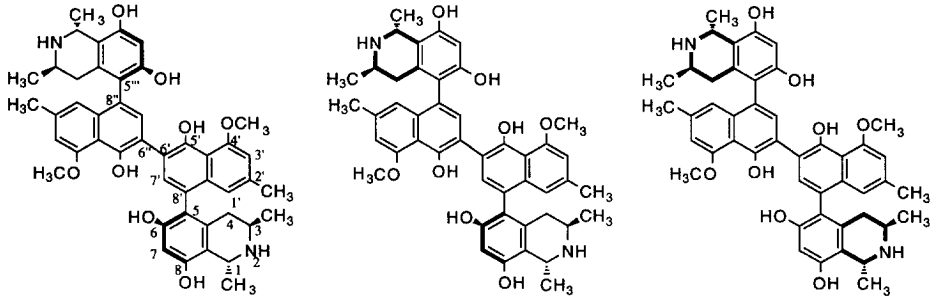
STRUCTURAL ANALOGUES OF THE MICHELLAMINE ANTI-HIV AGENTS. IMPORTANCE OF THE TETRAHYDROISOQUINOLINE RINGS FOR BIOLOGICAL ACTIVITY

Heping Zhang, David E. Zembower,* and Zhidong Chen

MediChem Research, Inc., 12305 South New Avenue, Lemont, Illinois 60439, U.S.A.

Abstract. A series of michellamine structural analogues was prepared in which the tetrahydroisoquinoline rings were substituted with a variety of simple aromatic ring systems. Additionally, the methyl groups on the central bis-naphthalene cores were replaced with hydrogen and methoxy. All the analogues were devoid of anti-HIV activity, suggesting that the heterocyclic portion of the tetrahydroisoquinoline ring is crucial for biological activity.

The michellamines, represented as A, B, and C (Figure), are a series of atropisomeric alkaloids isolated from *Ancistrocladus korupensis.*[1] All three isomers were equally effective against HIV-1 (RF strain) in a CEM-SS cytoprotection assay, while michellamines B and C were more effective than michellamine A against HIV-2 (CBL-20 strain), and michellamine B was more active than A and C against the NIH-DZ strain of HIV-2. Michellamine B was committed to INDA-directed preclinical development by the National Cancer Institute.

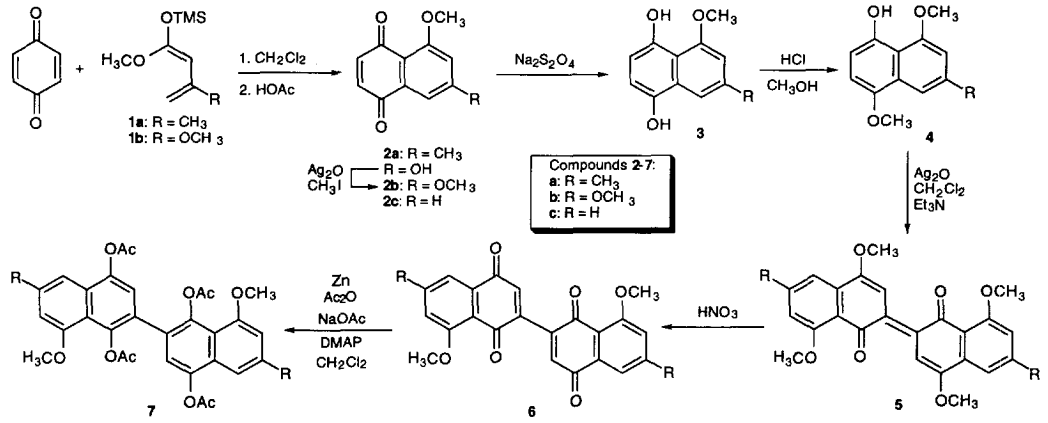


Figure

Michellamine B inhibited reverse transcriptase activity from both HIV-1 and HIV-2. Additionally, michellamine B inhibited formation of syncytium, which is believed to be a primary route of cell-to-cell transmission.[2] Therapeutically significant plasma levels of michellamine were achieved in murine and canine models.[3] Unfortunately, the oral bioavailability was negligible, and the therapeutic threshold was rather narrow in several cell lines. It is possible that a structural analogue could be identified that overcomes the bioavailability and toxicity issues associated with the natural products.

Several total syntheses of the michellamines have been reported.[4–8] Two structural analogues were prepared in which the central bis-naphthalene core was modified, resulting in decreased biological activity.[9] However, no systematic study of the importance of the tetrahydroisoquinoline rings has been reported. In an effort to probe the importance of the tetrahydroisoquinoline rings, we prepared a series of structural analogues in which the tetrahydroisoquinoline rings were replaced with simpler, non-chiral aryl and heteroaryl functional groups, using a modification of the procedure described by Kelly and co-workers.[6]

Kelly's synthesis involved palladium/copper-catalyzed dimerization of a 3-bromonaphthoquinone derivative. However, in our hands, the syntheses of the brominated naphthoquinones, as well as the metal catalyzed dimerization, resulted in poor yields and tedious purifications. We thus utilized the method of Laatsch[10] for preparation of the crucial bis-naphthalene intermediates, which involved dimerization of appropriately substituted dihydronaphthoquinone monomethyl ethers, as illustrated in Scheme 1.

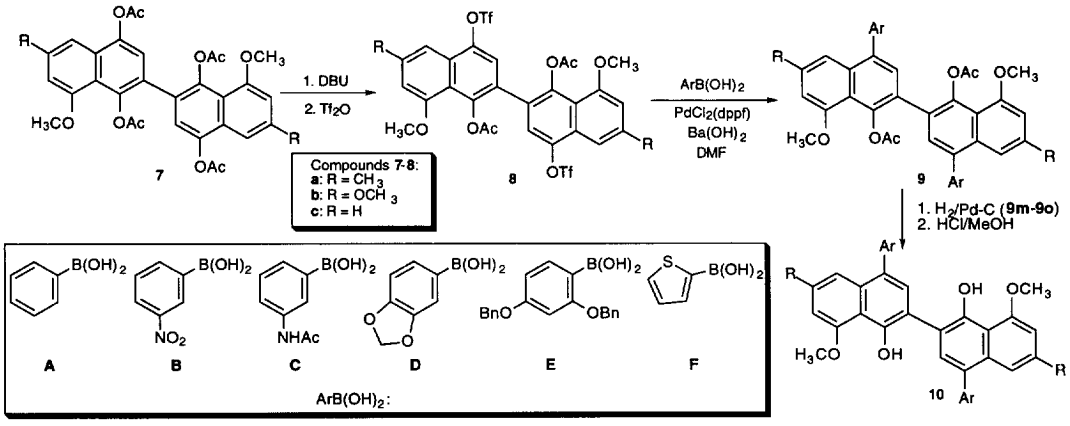


Scheme 1

Three different naphthoquinones (**2a**, **2b**, and **2c**) were utilized to prepare three bis-naphthalene cores, in which the 2′- and 2″-positions (R in Scheme 1, michellamine numbering system), occupied by methyl groups in the natural product, were also substituted with hydrogen and methoxy. These three different cores were intended to provide SAR information regarding steric and electronic factors at the 2′- and 2″-positions. Cyclization of 1,4-benzoquinone with dienes **1a**[11] and **1b**[12] followed by treatment with acetic acid[13] and, in the case of **2b**, methylation of the 7-hydroxyl intermediate, provided naphthoquinones **2a** and **2b** in very good yields. Quinone **2c** was prepared via methylation of 5-hydroxy-1,4-benzoquinone with Ag_2O/methyl iodide in 94% yield.

Reduction of the quinones with aqueous sodium dithionite[10] (biphasic mixture with EtOAc) afforded the dihydroquinones **3** quantitatively, which were converted to their 1-monomethyl ethers (**4**) via treatment with anhydrous HCl in methanol, in 60–90% yields. Oxidative dimerization with Ag_2O in dichloromethane/Et_3N provided the enol ether intermediates **5**, which were immediately hydrolyzed with concentrated HNO_3 (2 min) to provide the bis-naphthoquinones **6**, with an average yield of 90% for the two step conversion of **4** to **6**. Reductive acetylation of **6** with zinc in the presence of excess acetic anhydride/sodium acetate and 2 equiv 4-dimethylaminopyridine (DMAP) in dichloromethane[6] provided the tetraacetates **7** in 85–90% yields.

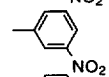
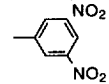
Selective deacetylation of **7** followed by treatment with triflic anhydride afforded the ditriflates **8** (Scheme 2)[6] in 60–80% yields for the two steps. The ditriflates were cross-coupled[14,15] with a variety of aryl boronic acids[16] to afford intermediates **9**, which were readily deacetylated to provide the michellamine congeners **10**. For analogues **9n–9p**, deacetylation was preceded by hydrogenolysis of the benzyl protective groups. For intermediates **9** which were obtained relatively cleanly from the cross-coupling reaction, deprotection was conducted with the crude products, while the other intermediates were purified via silica gel column chromatography. The final products **10** were obtained in 40 to 70% yields from intermediates **8**.

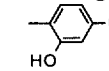
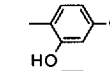
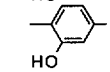


Scheme 2

The michellamine analogues **10a–10r** were evaluated for anti-HIV-1 activity in a CEM-SS cytoprotection assay, as previously described.[17] As shown in the Table, all of the analogues were devoid of anti-HIV activity up to a concentration of 100 μM. Interestingly, all of the compounds except for **10m**, **10n**, and **10o** were also devoid of toxicity in the CEM-SS cell line up to a concentration of 100 μM.

Table. Anti-HIV-1 Activity (EC_{50}) and Cytotoxicity (IC_{50}) of Michellamine Analogues

Compound	R	Ar	EC_{50}(μM)[a]	IC_{50}(μM)
10a	H		NA	>100
10b	CH_3		NA	>100
10c	OCH_3		NA	>100
10d	H		NA	>100
10e	CH_3		NA	>100
10f	OCH_3		NA	>100
10g	H		NA	>100
10h	CH_3		NA	>100
10i	OCH_3		NA	>100

Compound	R	Ar	EC_{50}(μM)[a]	IC_{50}(μM)
10j	H		NA	>100
10k	CH_3		NA	>100
10l	OCH_3		NA	>100
10m	H		NA	2.2
10n	CH_3		NA	2.6
10o	OCH_3		NA	3.9
10p	H		NA	>100
10q	CH_3		NA	>100
10r	OCH_3		NA	>100

[a]NA = No Activity

It is noteworthy that analogues **10m**, **10n**, and **10o**, which bear the same dihydroxyphenyl substitution pattern as the tetrahydroisoquinoline rings of the natural michellamines, are the only analogues that elicited toxicity in the CEM-SS cells. The same relative levels of toxicity were evident regardless of whether the 2′- and 2″-positions (michellamine numbering system) were substituted with hydrogen, methyl or methoxy. These data suggest that the 2,4-dihydroxy substitution pattern in the benzenoid ring may play a significant role in the cellular toxicities previously reported for the natural products, but that the pathway leading to toxicity is not significantly affected by substitutions at the 2′- and 2″-positions. Two analogues reported by others[9] also indicated that the central bis-naphthalene core does not play as important a role as the tetrahydroisoquinoline rings in mediating anti-HIV activity.

The lack of anti-HIV activity for the analogues illustrated in the Table suggests that the heterocyclic portion of the tetrahydroisoquinoline ring is a significant determining factor for desirable biological activity. Future analogue design will focus on the relationships between: (a) toxicity and the benzenoid ring, and (b) antiviral activity and the heterocyclic ring, and the possibility of "fine tuning" these two factors to identify a michellamine analogue possessing potent anti-HIV activity with decreased toxicity levels.

Acknowledgments. We wish to thank Professor T. Ross Kelly, Department of Chemistry, Boston College, for helpful discussions regarding the synthesis of bis-naphthalene intermediates **8**. Anti-HIV assays were conducted by Ms. Tracy L. Stup in the laboratory of Dr. Robert W. Buckheit, Jr., Southern Research Institute, Frederick, Maryland. This work was supported by a Phase I Small Business Innovation Research grant (R43 AI39339-01) awarded to D.E.Z. by the National Institutes of Health.

References and Notes

1. Boyd, M. R.; Hallock, Y. F.; Cardellina, J. H.; Manfredi, K. P.; Blunt, J. W.; McMahon, J. B.; Buckheit, R. W.; Bringmann, G.; Schaffer, M.; Cragg, G. M.; Thomas, D. W.; Jato, J. G. *J. Med. Chem.* **1994**, *37*, 1740.
2. McMahon, J. B.; Currens, M. J.; Gulakowski, R. J.; Buckheit, R. W.; Lackman-Smith, C.; Hallock, Y. F.; Boyd, M. R. *Antimicrob. Agents Chemother.* **1995**, *39*, 484.
3. Supko, J. G.; Malspeis, L. *Antimicrob. Agents Chemother.* **1995**, *39*, 9.
4. Bringmann, G.; Harmsen, S.; Holenz, J.; Geuder, T.; Gotz, R.; Keller, P. A.; Walter, R.; Hallock, Y. F.; Cardellina, J. H.; Boyd, M. R. *Tetrahedron* **1994**, *50*, 9643.
5. Hoye, T. R.; Chen, M.; Mi, L.; Priest, O. P. *Tetrahedron Lett.* **1994**, *35*, 8747.
6. Kelly, T. R.; Garcia, A.; Lang, F.; Walsh, J. J.; Bhaskar, K. V.; Boyd, M. R.; Gotz, R.; Keller, P. A.; Walter, R.; Bringmann, G. *Tetrahedron Lett.* **1994**, *35*, 7621.
7. Bringmann, G.; Gotz, R.; Harmsen, S.; Holenz, J.; Walter, R. *Liebigs Ann. Chem.* **1996**, 2045.
8. Hobbs, P. D.; Upender, V.; Liu, J.; Pollart, D. J.; Thomas, D. W.; Dawson, M. I. *J. Chem. Soc. Chem. Comm.* **1996**, 923.
9. Upender, V.; Pollart, D. J.; Liu, J.; Hobbs, P. D.; Olsen, C.; Chao, W.; Bowden, B.; Crase, J. L.; Thomas, D. W.; Pandey, A.; Lawson, J. A.; Dawson, M. I. *J. Heterocyclic Chem.* **1996**, *33*, 1371.
10. Laatsch, H. *Liebigs Ann. Chem.* **1980**, 1321.
11. Casey, C. P.; Jones, C. R.; Tukada, H. *J. Org. Chem.* **1981**, *46*, 2089.
12. Chan, T.-H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980**, *102*, 3534.
13. Lang, F. *The Total Synthesis of Dimethyl Sulfomycinamate and Synthesis of the Anti-HIV Agents Michellamine A-C*, Ph.D. Thesis, Boston College, 1996.
14. Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201.
15. For the cross-coupling reaction between triflates **8** and the aryl boronic acids to occur, it was necessary to carefully de-oxygenate the reaction solution by purging with nitrogen for 15 min.
16. Aryl boronic acids **A**, **B**, **C** and **F** were purchased from Aldrich Chemical Company. The *N*-acetate of boronate **C** was hydrolyzed during the deprotection step in the syntheses of **10g–10i**. Boronates **D** and **E** were prepared from the corresponding aryl bromides using standard chemistry.
17. Buckheit, R. W., Jr.; Decker, W. D.; Roberson, J. L.; Pyle, C. A.; White, E. I.; Bowdon, B. J.; McMahon, J. R.; Boyd, M. R.; Bader, J. P.; Nickel, D. G.; Barth, H.; Antonucci, T. K. *Antiviral Res.* **1994**, *25*, 43.

(*Received in USA* 11 *August* 1997; *accepted* 19 *September* 1997)