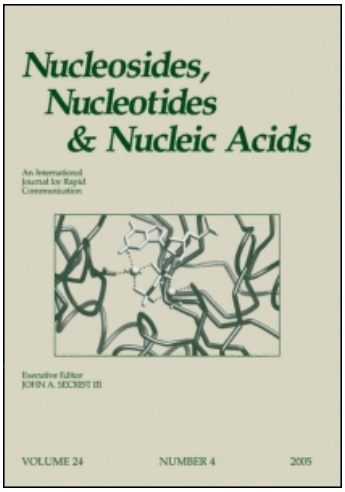


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Investigations into Biochemical Mode of Inhibition of Guanase by Azepinomycin: Synthesis and Biochemical Screening of Several Analogues of Azepinomycin

Vasanthakumar P. Rajappan[a]; Ramachandra S. Hosmane[a]
[a] Laboratory for Drug Design and Synthesis, Department of Chemistry & Biochemistry, University of Maryland, Baltimore, Maryland, USA

To cite this Article Rajappan, Vasanthakumar P. and Hosmane, Ramachandra S.(1999) 'Investigations into Biochemical Mode of Inhibition of Guanase by Azepinomycin: Synthesis and Biochemical Screening of Several Analogues of Azepinomycin', Nucleosides, Nucleotides and Nucleic Acids, 18: 4, 835 — 836
To link to this Article: DOI: 10.1080/15257779908041573
URL: http://dx.doi.org/10.1080/15257779908041573

NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 835–836 (1999)

INVESTIGATIONS INTO BIOCHEMICAL MODE OF INHIBITION OF GUANASE BY AZEPINOMYCIN: SYNTHESIS AND BIOCHEMICAL SCREENING OF SEVERAL ANALOGUES OF AZEPINOMYCIN

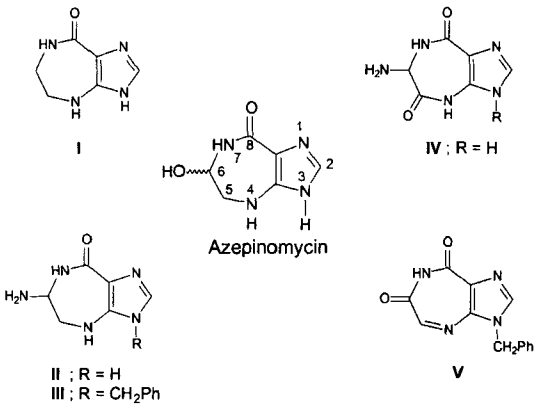
Vasanthakumar P. Rajappan and Ramachandra S. Hosmane*

Laboratory for Drug Design and Synthesis, Department of Chemistry & Biochemistry
University of Maryland, Baltimore County (UMBC), 1000 Hilltop Circle
Baltimore, Maryland 21250, USA

Abstract: *In an effort to explore the biochemical mode of guanase inhibition as well as the structure-activity relationships of azepinomycin, five analogues (I-V) of azepinomycin were synthesized and screened against guanase from rabbit liver. Our results suggest that while the 6-hydroxy group of azepinomycin is crucial for activity, its putative transition state mode of inhibition of guanase is questionable. The additional H-bonding sites at position 5, and hydrophobic groups in and around position 3 of azepinomycin appear to be tolerated, and may in fact enhance the potency of inhibition.*

Azepinomycin, a natural product containing a 5:7-fused heterocyclic ring system, is known to inhibit guanase,[1] an important enzyme in the salvage pathway of purine metabolism. Inhibition of guanase has implications in viral and cancer chemotherapy.[2,3] Guanase catalyzes the hydrolysis of guanine to xanthine.[4] Because of its structural and functional similarity to coformycin, another natural product that strongly inhibits adenosine deaminase (ADA),[5] and is known to be a transition state analogue inhibitor of ADA,[6] azepinomycin is widely regarded as a transition state analogue inhibitor of guanase. However, azepinomycin has only a moderate K_i against guanase ($K_i \approx 10^{-5}$ *M*)[1] in comparison with coformycin which has a K_i of $\approx 10^{-11}$ M.[5,6] The observed significantly lower inhibition of azepinomycin as compared with coformycin raises serious doubts about the mechanistic similarity of inhibition of azepinomycin to that of coformycin, despite the fact both contain the crucial tetrahedral junction with a hydroxy group attached to an sp^3 carbon in their 7-membered rings to qualify them as transition state analogue inhibitors. In order to enable rational design of potent inhibitors of guanase, it is necessary to explore the biochemical mode of inhibition as well as structure-activity relationships of azepinomycin. A few analogues of azepinomycin were synthesized and biochemically screened in order to specifically address the following five questions: (a) Is the hydroxy group at position-6 absolutely necessary for inhibition? (b) could this hydroxy

group be effectively substituted by an amino group? (c) would additional hydrogen bonding sites on the skeletal structure enhance the activity? (d) would guanase tolerate hydrophobic functional groups at or near positions 3 and 6 of azepinomycin skeletal structure? and (e) how valid is the putative transition state analogue mode of inhibition of azepinomycin?



The following five compounds (**I-V**) were synthesized and screened to address the above five questions. Our results suggest that (a) the 6-hydroxy group of azepinomycin is necessary for inhibition, (b) the amino group is not a good replacement for the 6-hydroxyl, (c) the additional H-bonding sites at position-5 lead to enhancement of activity, (d) the attachment of hydrophobic groups in and around positions 3 and 6 of azepinomycin are tolerated, and may in fact potentiate the inhibition, and (e) the putative transition state analogue mode of inhibition of azepinomycin is questionable, and that more research is needed to verify the validity of this generally believed mode of inhibition of guanase by azepinomycin.

Acknowledgment. This research was supported by a grant (#RO1 CA 71079) from the National Institutes of Health.

REFERENCES

(1) (a) Isshiki, K.; Takahashi, Y.; Linuma, H.; Naganawa, H.; Umezawa, Y.; Takeuchi, T.; Umezawa, H.; Nishimura, S.; Okada, N.; Tatsuta, K. *J. Antibiot.* **1987**, *40*, 1461. (b) Fujii, T.; Saito, T.; Fujisawa, T. *Heterocycles* **1988**, *27*, 1163.

(2) (a) Durak, I.; Cetin, R.; Canbolat, O.; Cetin, D.; Yurtarslani, Z.; Unal, A. *Cancer Lett.* **1994**, *84*, 199. (b) Greengard, O.; Head, J. F.; Goldberg, S. L. *Cancer Res.* **1980**, *40*, 2295.

(3) (a) Nishikawa, Y.; Fukumoto, K.; Watanabe, F.; Yoshihara, H. *J. Clin. Pathol. (Rinsho Byori)* **1989**, 1392. (b) Shiota. G.; Fukuda, J.; Ito, T.; Tsukizawa, M.; Sato, M. *Jpn. J. Med.* **1989**, *28*, 22. (c) Ito, S.; Tsuji, Y.; Kitagawa, N.; Akihiko, I.; Syundo, J.; Tamura, Y.; Kishi, S.; Mori, H. *Hepatology* **1988**, *8*, 383.

(4) Lewis, A. S.; Glantz, M. D. *J. Biol. Chem.* **1974**, *249*, 3862.

(5) (a) Nakamura, H; Koyama, G.; Iitaka, Y.; Ohno, M.; Yagisawa, N.; Kondo, S.; Maeda, K.; Umezawa, H. *J. Am. Chem. Soc.* **1974**, *96*, 4327. (b) Ohno, M.; Yagisawa, N.; Shibahara, S.; Kondo, S.; Maeda, K.; Umezawa, H. *J. Am. Chem. Soc.* **1974**, *96*, 4326.

(6) (a) Wolfenden, R.; Wentworth, D. F.; Mitchell, G. N. *Biochemistry* **1977**, *16*, 5071-5077. (b) Frick, L.; Wolfenden, R.; Amal, D.; Baker, D. C. *Biochemistry* **1986**, *25*, 1616-1621. (c) Kati, W. M.; Wolfenden, R. *Biochemistry* **1989**, *28*, 7919-7927.