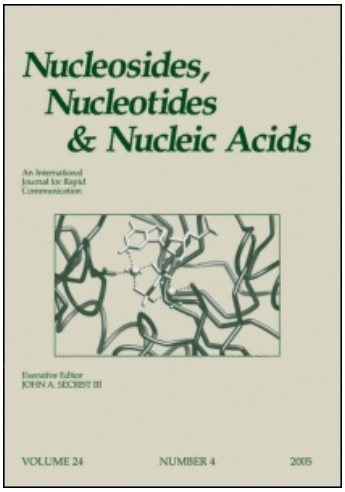

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Analogues of Azepinomycin: Inhibitors of Guanase

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ANALOGUES OF AZEPINOMYCIN: INHIBITORS OF GUANASE

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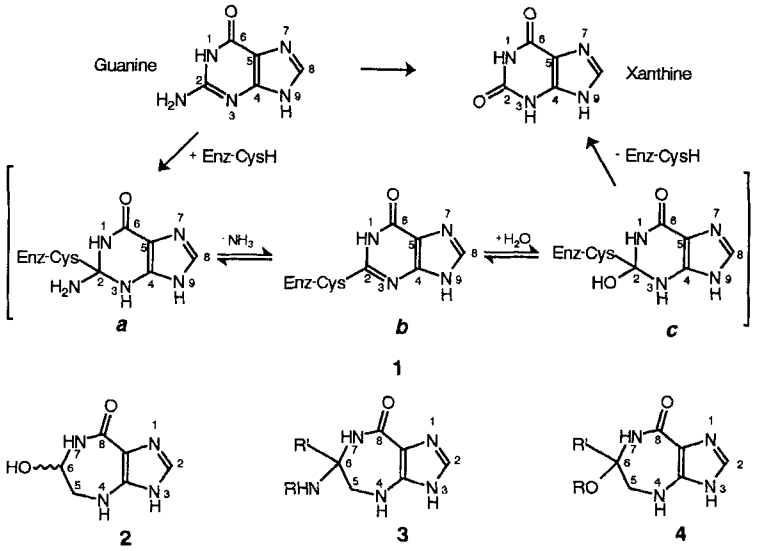
ABSTRACT

Synthesis and guanase inhibitory activity of two novel 5:7-fused heterocyles, ***15*** *and* ***16****, containing the imidazo[4,5-e][1,4]diazepine ring system, have been reported.*

INTRODUCTION

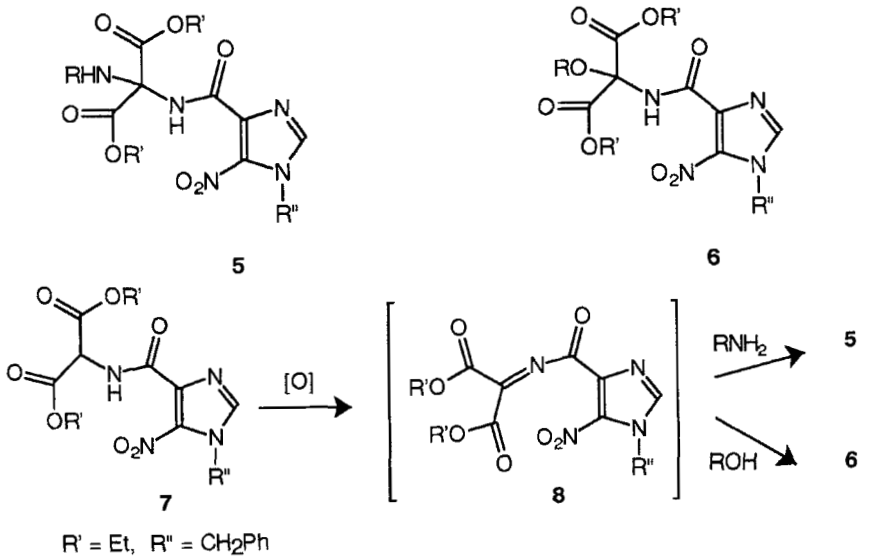
Guanase catalyzes the hydrolysis of guanine to xanthine (**Scheme I**) via the putative sequence of intermediates, collectively depicted as **1**.[1] Azepinomycin (**2**) is a

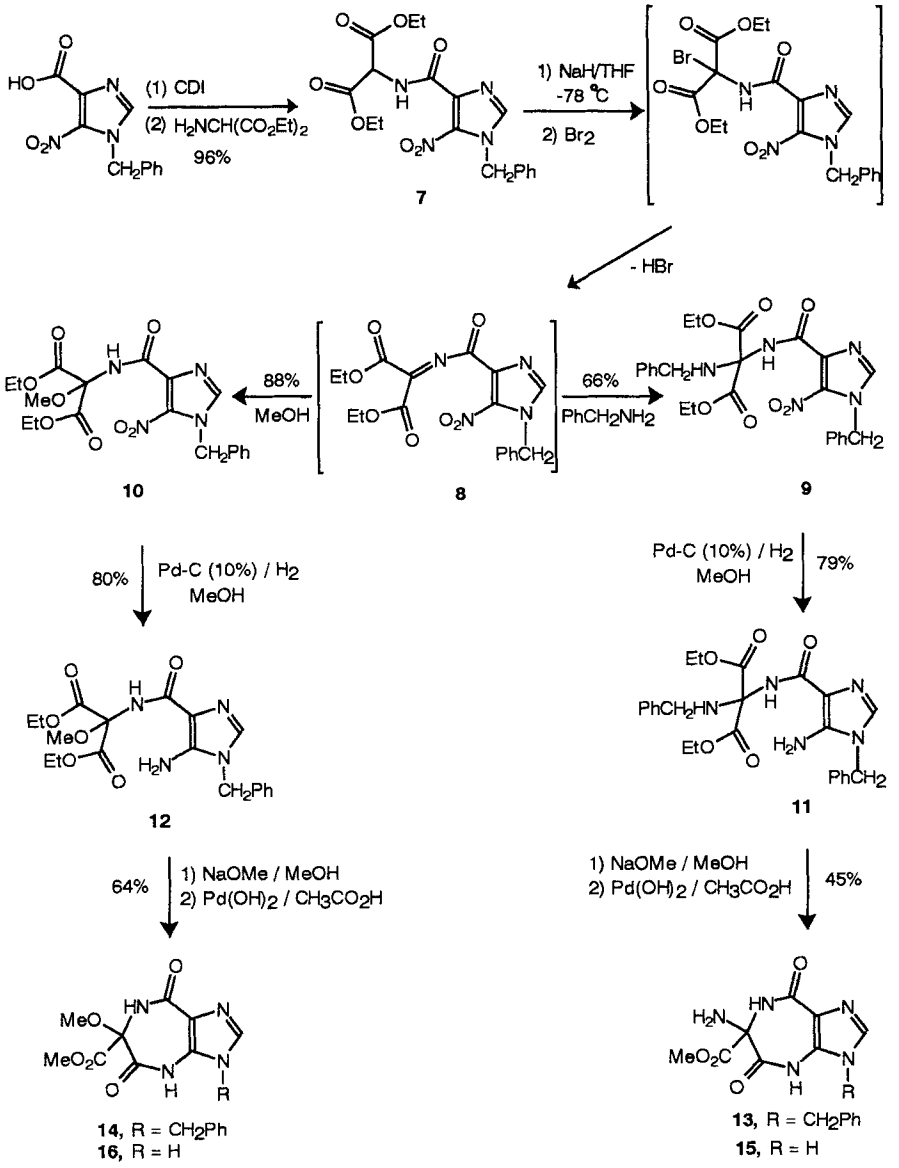


SCHEME I

naturally occurring antitumor antibiotic, and is considered to be the transition state analogue inhibitor of this enzyme.[2] However, an examination of **1** reveals that both **1a** and **1c** contain a quaternary carbon at the 2-position, the site of hydrolysis, with geminal thio/amino or thio/hydroxy functionalities. Therefore, a more appropriate inhibitor to mimic the transition state of the deaminase reaction might be a compound such as **3** or **4** having a quaternary carbon attached to two substituents at the 6-position of the imidazo[4,5-*e*][1,4]diazepine ring, as contrasted with azepinomycin that lacks such a quaternary carbon. We report here the synthesis and biochemical screening of two compounds, **15** and **16**, which incorporate this important structural characteristic of **3** and **4** that is missing in azepinomycin.

A retrosynthetic analysis of **3** and **4** called for a synthon such as **5** and **6** which contain a unique diamino- or alkoxyaminomalonate side chain, and for which there is little literature precedent. A logical precursor to both **5** and **6** is the aminomalonate derivative **7**.[3] Oxidation of **7** to produce the iminomalonate intermediate **8**, followed by conjugate addition by an amine or alkoxy nucleophile would yield the desired diamino- and alkoxyaminomalonate synthons **5** and **6**, respectively. Indeed, bromination of **7** in the presence of sodium hydride, followed by quenching with benzylamine or methanol, afforded the desired **9** (mp 100-101 °C), (**10**; mp 126-127 °C), respectively (**Scheme II**). Reduction of **9** and **10** with Pd-C/H_2 provided the respective **11** (mp 121-123 °C) and **12** (mp 162-163 °C). Treatment of **11** and **12** with sodium methoxide in refluxing methanol resulted in ring-closure with concomitant exchange of the ester ethoxide group





SCHEME II

with a methoxide to produce **13** and **14**, respectively. Debenzylation of **13** and **14** with $Pd(OH)_2/H_2$ in acetic acid provided **15** (mp: sinters at 196 °C and 203 °C (d)) and **16** (mp >280 °C). The structures of both **15** and **16** were confirmed by single-crystal X-ray diffraction analysis.[4]

Finally, both **15** and **16** were screened *in vitro* against rabbit liver guanase in a Tris buffer (pH 7.6) at 21 °C, by spectrophotometrically monitoring the rate of hydrolysis of the substrate guanine at 248 nm. Both were found to be inhibitors of this enzyme with K_i's = 1.9×10^{-4} *M* and 5.4×10^{-4} *M*, respectively.

In view of the recent detection of abnormally high levels of guanase activity in patients with liver diseases[5,6] and those with multiple sclerosis,[7] the search for a suitable guanase inhibitor may be timely for exploration of the biochemical mechanism(s) of these disorders.

ACKNOWLEDGMENTS

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