Commentary

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A Note on Purine Analogues with Electronic Absorption in the Visible Region

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Abstract

The absorption spectrum of some 5-substituted derivatives was found to extend to the visible region. These compounds were found to inhibit some enzymes of purine metabolism, like xanthine oxidase or bacterial purine-nucleoside phosphorylase with Ki values in the 10-3 –10-5 M range.

Keywords: Thiazine; Purine analogues; Enzyme inhibitors; Spectroscopic probes.

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Introduction

In particular, the isomeric pyrazolopyrimidines and triazolopyrimidines (8-azapurines) exhibit favourable spectroscopic and biochemical properties and have potential for use in cancer and viral chemotherapy. The starting material 3-methyl-5-methylsulfanyl-1H-pyrazolo[4,3-e] triazine was synthesized from 5-acetyl-3-methylsulfanyl-1,2,4-triazine in a one-pot reaction by condensation with hydrazine hydrochloride, followed by acid-promoted ring closure of the resulting intermediate [1]. According to expectations, compound 1, bearing an NH-fragment, appeared to be unreactive towards nucleophilic displacements and attempts to perform direct nucleophilic substitutions of the methylsulfanyl group with either ammonia or hydrazine failed. Compound 8 was synthesized in four steps from 3-methyl-5-methylsulfanyl-1H-pyrazolo[4,3-e] triazine by methylation with iodomethane, oxidation with potassium manganate (VII),hydrazinolysis with anhydrous hydrazine and treatment of the resulting 5-hydrazino-1,3-dimethyl-1Hpyrazolo[4,3-e] triazine with yellow mercury (II) oxide. Bromination of 8 with N-bromosuccinimide followed by nucleophilic displacement of bromide in the resulting C-bromomethyl derivative by ethylene glycol anion gave aza analogue of acylopurine nucleoside 9. We have examined several purine metabolism enzymes to check if any of these effectively interact with the new compounds [2]. It was found that enzymatic phosphorolysis of m7 Guo , catalyzed by E. coli purine nucleoside phosphorylase (PNP), was inhibited by selected pyrazolotriazines at concentrations of 30-500 µM. The strongest inhibitor was the 5-methylsulfanyl derivative with an IC50 of ~40 µM. Compounds methylated on the N-1 pyrazole ring nitrogen exhibited much weaker inhibitory activity, resembling that reported for the analogous pyrazolopyrimidines.

Description

Calf spleen PNP, examined under identical conditions and was not inhibited by the pyrazolotriazines. This result is not surprising since the bovine enzyme is known to exhibit much higher specificity toward purines and purine moieties of nucleosides than the E. coli enzyme [3]. Since the analogous pyrazolopyrimidines, e.g. allopurinol, have therapeutic applications as known strong inhibitors of the xanthine oxidase (Xox) enzyme, we examined the inhibitory activities of some of pyrazolotriazines toward commercially available Xox from buttermilk. Only weak inhibition was detected in the case of the unsubstituted compound 7, but somewhat surprisingly, moderate inhibitory activity was detected for the 5-thiomethyl derivative 1. The title compound was apparently not a substrate for Xox, at least at the moderate enzyme concentrations employed in this work. Pyrazolotriazines are moderate inhibitors of bacterial (E. coli) PNP, an enzyme employed recently in cancer-oriented gene therapy experiments [4]. There is also a detectable inhibition of xanthine oxidase by the parent 3-methyl-7-azapyrazolo [4, 3-d] pyrimidine, as well as its S-methyl derivative. These compounds are unique among purine analogues as having UV absorption spectra extending into the visible region (ca. 450 nm), some of them being also

weakly fluorescent in aqueous solution and thus are potentially applicable as spectroscopic probes for enzymes of purine metabolism. Nuclear magnetic resonance (1H-NMR) spectra were recorded on a Varian Gemini 200 MHz spectrometer in a suitable deutered solvent using TMS as internal standard. Mass spectra were obtained on AMD 604 [electron impact (EI) and API 350 [electrospray ionization (ESI) spectrometers. IR spectra were measured with a Magna IR-760 spectrophotometer, and UV on a Cary 319. Fluorescence spectra were recorded using a Perkin-Elmer LS-50B spectrofluorometer, equipped with a pulsed xenon light source. Enzymes: xanthine oxidase (Xox) from buttermilk and purine nucleoside phosphorylase. Hypoxanthine and 7-methylguanosine (m7Guo) were from Sigma. All other reagents and chemicals were obtained from Aldrich Chemical Company and were used as received, unless otherwise noted. Enzymatic assays and UV spectra were run using a Cary-319 UV spectrophotometer (Varian), equipped with a thermostatic unit. Unless otherwise indicated, all the reactions were carried out in 50 mM phosphate, pH 7.0, at 25˚C. Inhibitor concentrations were evaluated spectrophotometrically, using data [5]. It was possible to run assays with inhibitor concentrations up to ~300 µM. Activity of PNP was assayed by following phosphorolysis of m7 Guo in 50 mM phosphate, pH 7.0. The reaction mixture was stirred at rt for 1 h. A saturated solution of Na2S2O5 in water was then added to the mixture until the purple colour disappeared. The organic layer was separated and the aqueous phase was extracted with benzene (3x10 mL). The combined organic extracts were dried over anhydrous MgSO4 and concentrated in vacuum. The residue was purified by column chromatography on silica gel (eluent: chloroform) to afford 270 mg (95%) as a yellowish oil.

Acknowledgement

None

Conflict of interest

No conflict of interest

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