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THE ANTI-ULCER DRUG RANITIDINE HYDROCHLORIDE AND ITS SYNTHETIC INTERMEDIATES ARE INACTIVATORS OF MONOAMINE OXIDASE-B

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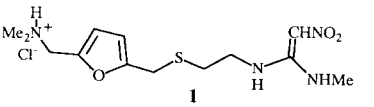
Ranitidine hydrochloride (**1**) and two of its synthetic precursors (**2** and **3**) were found to be time-dependent, irreversible inactivators of monoamine oxidase-B from beef liver.

KEY WORDS: Ranitidine hydrochloride, monoamine oxidase-B, inactivation, 2-(hydroxymethyl)-5-(dimethylaminomethyl)furan, 2-(2-thia-4-aminobutyl)-5-(dimethylaminomethyl)furan.

INTRODUCTION

The binding of histamine to H_2 receptors stimulates gastric acid secretion.[1] Compounds that antagonize this receptor (H_2 blockers) are used for the treatment of duodenal and gastric ulcers. The first H_2 histamine receptor antagonist, cimetidine (Smith, Kline and French),[2] was followed later by ranitidine (**1**, Glaxo), and famotidine (Merck, Sharp and Dohme). Recently, we synthesized ranitidine hydrochloride and it occurred to us that this compound and two of the synthetic intermediates (**2** and **3**) have structures that are related to those of substrates and inhibitors of monoamine oxidase (EC 1.4.3.4; MAO). Here we show that these compounds are time-dependent inactivators of MAO.



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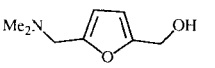

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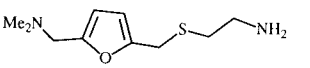


3

* Correspondence.

MATERIALS AND METHODS

Ranitidine hydrochloride (**1**) was synthesized by the procedure of Price *et al.*[3] The synthetic intermediates, 2-(hydroxymethyl)-5-(dimethylaminomethyl)furan (**2**) and 2-(2-thia-4-aminobutyl)-5-(dimethylaminomethyl)furan (**3**), were obtained in the synthesis of **1**.

Bovine monoamine oxidase-B was isolated by the method of Salach.[4] MAO activity was assayed in Tris-HCl buffer (100 mM, pH 9.0) at 25°C with cinnamylamine as the substrate as previously described.[5] Inactivation experiments were carried out as previously described.[5]

RESULTS AND DISCUSSION

Because of the enormous worldwide usage of ranitidine hydrochloride in the treatment of ulcers, we thought that it would be interesting to assess the effect of this drug and of related compounds on MAO. Incubation of MAO-B with compounds **1–3** led to time-dependent inactivation of the enzyme; dialysis for 24 h did not restore enzyme activity. Figure 1 shows the time-dependent loss of MAO activity as a function of the concentration of **3**; Figure 2 is a Kitz and Wilson[6] replot of the data from which the kinetic constants were obtained. The kinetic constants for all of these reactions are given in Table 1. The dimethylaminomethylfuran moiety resembles that of *N*,*N*-dimethylbenzylamine, a substrate for MAO.[7] In the case of **3** the primary amine end of the molecule resembles 4-phenylbutylamine, a good substrate for MAO.[8] We have found that, when an electron-withdrawing group is attached beta to an amino group that is oxidized by MAO, these analogues can be potent inactivators of MAO.[5,9] The sulfur atom in **3** and the furan moiety of **1** and **2** are electron-withdrawing groups which can stabilize a potential adduct with the enzyme. In general, however, primary amines are more potent inactivators of MAO than tertiary ones, which may explain the better inactivation efficiency of **3** than the others. It is apparent from the magnitude of the K_I value for ranitidine hydrochloride that there is little danger of this drug causing CNS or hypertensive effects as a result of MAO inactivation. Nonetheless, all of these structures represent new lead compounds for the design of future monoamine oxidase inhibitors.

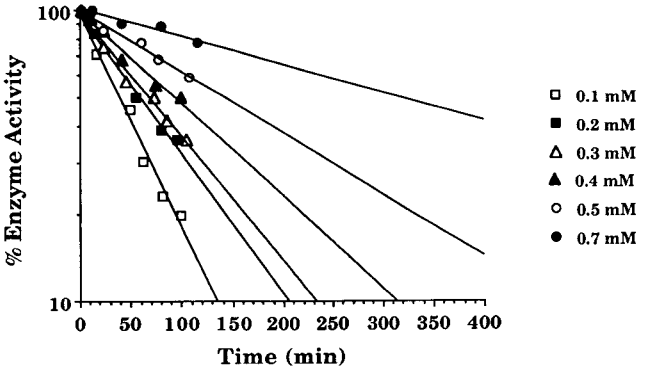


Figure 1 Time-dependent inactivation of MAO by various concentrations of 2-(2-thia-4-aminobutyl)-5-(dimethylaminomethyl)furan (**3**) at 37°C.

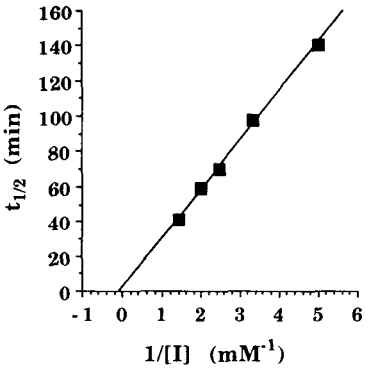
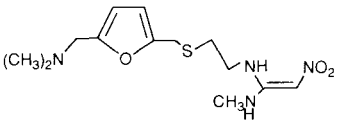
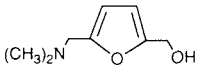
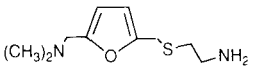


Figure 2 Kitz and Wilson[6] replot of the data in Figure 1.

Table 1 Inactivation of MAO by ranitidine and its synthetic precursors

Compound	t (°C)	K_I (mM)	k_{inact} (min^{-1})	k_{inact}/K_I ($min^{-1}/mM \times 10^{-4}$)
	37	10.0	0.032	32
	37	623	0.104	1.67
	25	2.4	0.094	390
	37	11.8	0.29	246

Acknowledgement

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