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Omeprazole and talampanel as two examples of retrometabolic drug design

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The goal of retrometabolic drug design is: "to design safe, locally active compounds with an improved therapeutic index". Here we describe two cases from our own practice, talampanel and omeprazole.

1. Introduction

In 1968 we synthesized 2-pyridyl-thioacetamide (2-PTA) which showed strong gastric acid secretion inhibiting effect in animals and men. But in the 2-year carcinogenicity test it caused some hepatic injury in rats, for this reason its development was stopped. The story was described formerly in this journal (Andrási 2001), so only some additional information will be presented here.

2. Investigations and results

During the metabolism of thioamides one highly reactive sulphene intermediate is formed, which by establishing a covalent bond with enzymes can produce various effects. 2-PTA predominantly accumulated in the stomach wall (Elekes et al. 1971), and therefore inhibited preferentially the proton pump. But when it was applied life-long in high doses, other proteins were affected too generating side-effects (Scheme).

From structure-activity studies (Farkas et al. 1973, Andrási et al. 1973) we know that the pyridin-ring and the thioacetamide part are equally important for the biological effect, consequently we tried to eliminate its toxicity by forming masked thioamides (Fig. 1).

We synthesized about 200 congeners of 2-PTA but could not find a satisfactory compound, and therefore dropped the project.

At the same time another Hungarian group synthesized 2-pyridyl-alkyl-2′-thio-benzimidazoles for purposes of obtaining chemotherapeutic agents (Hideg et al. 1969). But their effect on gastric acid secretion was not investigated.

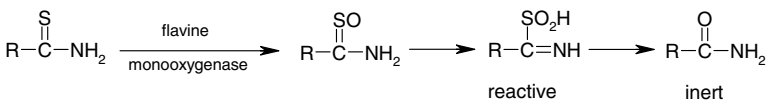
On the other hand Hässle AB (a subsidiary of Astra in Gothenburg) took our lead molecule and produced about 500 derivatives of 2-PTA, and at last found omeprazole. This drug generated $ 6.3 billion sales in 2000.

Omeprazole is activated only at pH = 1, for this reason absolute tissue-selectivity is attained: only the stomach H^+, K^+, ATPase will be blocked after an intramolecular rearrangement of the drug. Consequently, practically no side-effects were observed. This is a good example of "molecular packaging".

2.2. Talampanel

In the course of our work on 2,3-benzodiazepines the first *in vivo* active, selective, non-competitive AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor antagonist GYKI-52466 was synthesized at IDRI in May

Scheme



Metabolic activation of thioamides

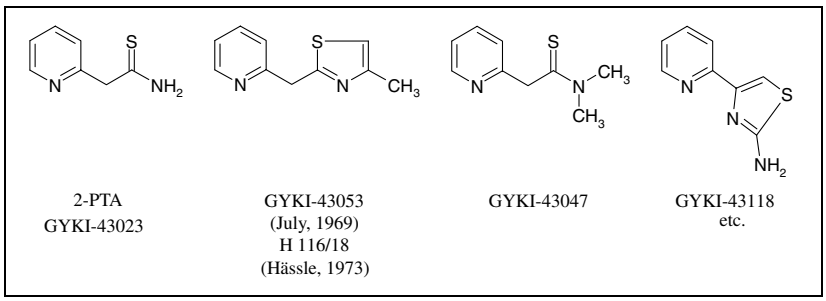


Fig. 1:
Masked derivatives of 2-PTA

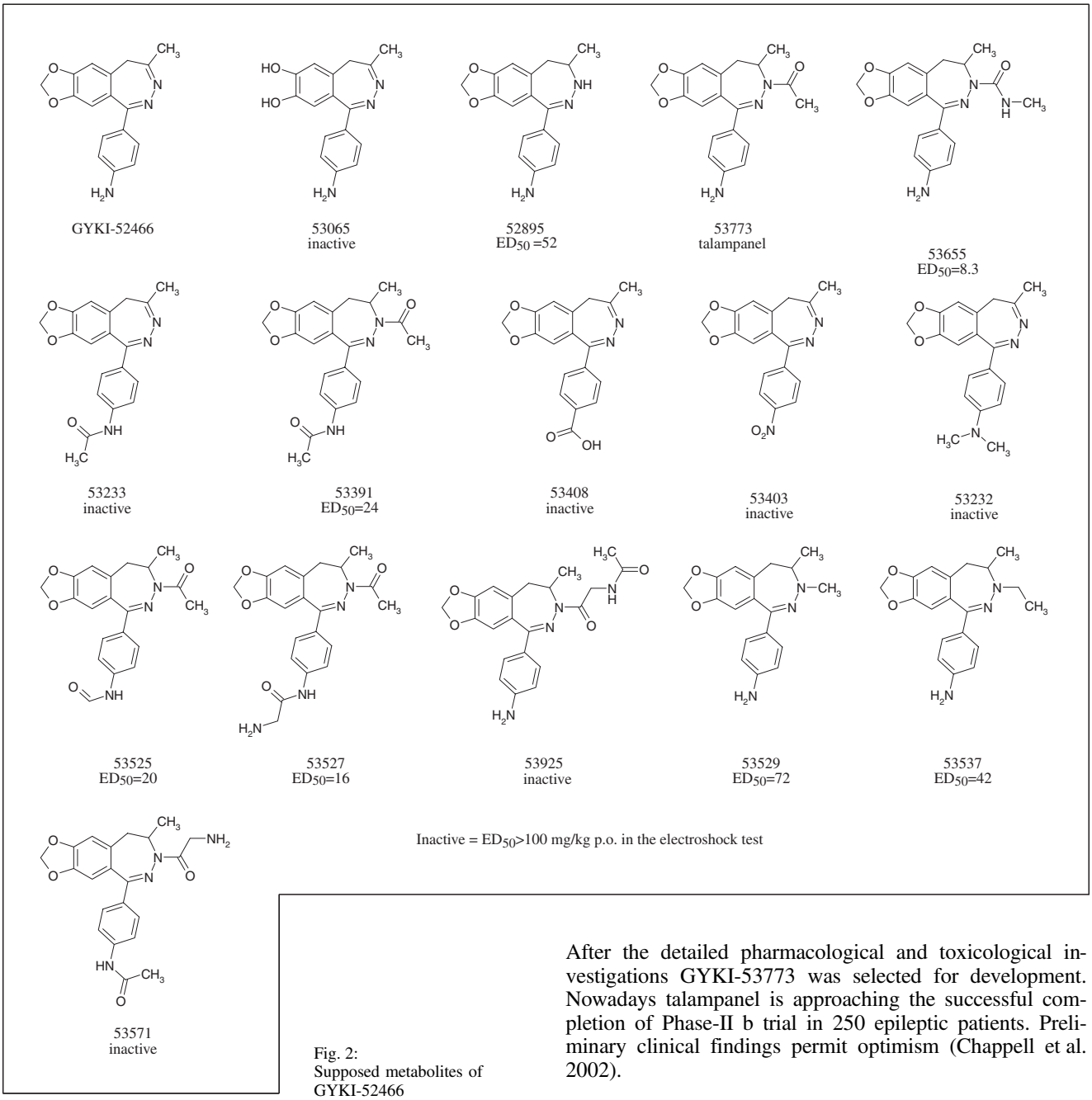


Fig. 2:
Supposed metabolites of GYKI-52466

1984. It showed a broad-spectrum anticonvulsant effect and strong skeletal muscle relaxant activity (Andrási et al. 1988). But its development was suspended due to the positive Ames-test.

To circumvent this problem the potential metabolites were synthesized and tested according to the retrometabolic drug design approach (Bodor and Buchwald 2003) (Fig. 2, Table).

Table: Comparative pharmacology of GYKI-52466 and talampanel

Compound	ED_{50} mg/kg p.o. in mice				
	Electro-shock	Strych-nine	4-NH_2-pyridine	Bicu-culline	Metra-zole
GYKI-52466	37.4	86.7	43.0	35.0	115.0
Talampanel	8.6	17.4	8.4	14.6	16.8

After the detailed pharmacological and toxicological investigations GYKI-53773 was selected for development. Nowadays talampanel is approaching the successful completion of Phase-II b trial in 250 epileptic patients. Preliminary clinical findings permit optimism (Chappell et al. 2002).

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