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Triprotic acid–base microequilibria and pharmacokinetic sequelae of cetirizine

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ABSTRACT

^{1}H NMR-pH titrations of cetirizine, the widely used antihistamine and four related compounds were carried out and the related 11 macroscopic protonation constants were determined. The interactivity parameter between the two piperazine amine groups was obtained from two symmetric piperazine derivatives. Combining these two types of datasets, all the 12 microconstants and derived tautomeric constants of cetirizine were calculated. Upon this basis, the conflicting literature data of cetirizine microspeciation were clarified, and the pharmacokinetic absorption–distribution properties could be interpreted. The pH-dependent distribution of the microspecies is provided.

1. Introduction

Cetirizine (Fig. 1), the widely used antihistamine is a drug of rapid absorption (Slater et al., 1999; Curran et al., 2004), long lasting action (Spencer et al., 1993), low cerebral uptake (Pagliara et al., 1998; Curran et al., 2004), strong serum protein binding (Pagliara et al., 1998; Slater et al., 1999), little affinity to the lean and myocardial tissues (Pagliara et al., 1998), and low potential for drug interactions (Spencer et al., 1993; Walsh et al., 2001; Curran et al., 2004). The biochemical processes governing the therapeutic properties are highly influenced by the site-specific charges of the molecule. The acid–base properties of cetirizine and related molecules have therefore been the subject of extensive studies (Hanocq et al., 1989; Pagliara et al., 1998; Tam and Quéré, 2001) in the hope of understanding the low CNS penetration and other pharmacokinetic properties at the molecular level.

Pagliara et al. used hydroxyzine as model compound, and determined 4 of the 12 microconstants and one of the 6 tautomeric constants, with certainly reliable results. Tam and Quéré have reported 12 + 5 constants, using an earlier unused computer program in the evaluation. Their primary results may not appear to be problematic, the derived values, especially the principally non-changing interactivity parameters (see later) show, however several orders of magnitude (!) differences in their own set of data, which makes the reported values and the evaluation method highly dubious.

Cetirizine ((±)-[2-[4-[(4-chlorophenyl)phenylmethyl]-piperazin-1-yl]ethoxy]acetic acid) has three basic centers, the two nonequivalent piperazine amines and the carboxylate. Being a triprotic molecule, the total number of microspecies and microconstants are 8 and 12, respectively (Szakács and Noszál, 1999) (Fig. 2). Among the 8 microspecies, 3 monoprotonated and also 3 diprotonated protonation isomers (tautomers) exist, which differ only in the site of protonation (Noszál, 1986).

The difficulties in cetirizine microspeciation lie in the facts:

(A) Some of the microspecies occur in very low concentration, providing only negligible contribution to any analytical signal. Such minor microspecies must therefore be modeled by auxiliary compound(s) because of their significance: Minor microspecies can be the acting, most important ones in highly specific biochemical processes (Noszál et al., 1982). Chemical evidences on cetirizine indicate that microspecies of protonated carboxylate and non-protonated amino sites, is a certainly minor one to a large extent.
(B) Proximity of the basic sites and the compact electronic system of the molecule preclude analytical signals of site-specificity: any UV, NMR, etc., changes upon protonation are composite ones. Each of them at any wavelength, any NMR nucleus, etc.,

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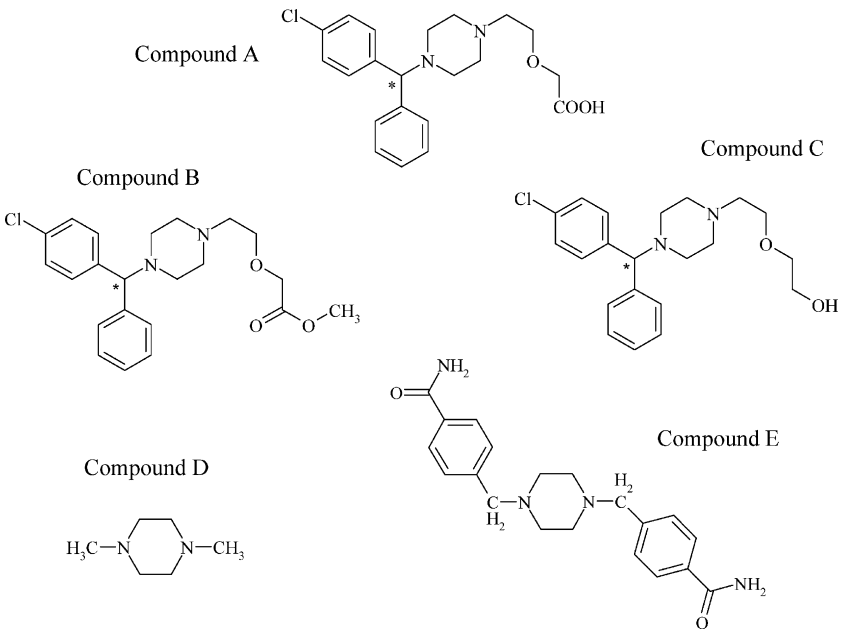

Fig. 1. Structure of the investigated compounds. (A) Cetirizine, (B) cetirizine-methyl ester, (C) hydroxyzine, (D and E) symmetric piperazine derivatives: 1,4-dimethylpiperazine and 4,4′-[piperazine-1,4-diylbis(methylene)]dibenzamide, respectively (the last one named "Compound E" hereinafter).

originate to nonzero, unknown extent from protonation of all the basic sites.

In our work ^{1}H NMR-pH titration method was chosen to monitor the protonation processes. This technique, unlike the traditional, widespread pH-potentiometry is free of the falsifying effect of the CO_2 in the atmosphere, because the consumption of the titrant does not have to be measured. This method can also characterise molecules without chromophores and it can follow independently the chemical shift changes of all the NMR nuclei. In general, high field NMR can distinguish between peaks of the parent compound and its possible impurities. Several some molecules have selective peak(s) which follow exclusively the protonation of one basic center (Szakács et al., 2005). In cetirizine, all NMR nuclei are multiply influenced: they show the effect of protonation of at least two basic centers. Direct determination of the microconstants from NMR-pH titrations of cetirizine only is therefore impossible. Model compounds were also needed.

To mimic those microspecies in which the carboxylate is protonated, cetirizine-methyl ester ((±)–methyl-[2-[4-[(4-chlorophenyl)-phenylmethyl]-piperazin-1-yl]ethoxy]acetate) and hydroxyzine ((±)–2-[2-[4-[(4-chlorophenyl)-phenylmethyl]-piperazin-1-yl]ethoxy]ethanol) were used as models. Furthermore, to elucidate all the microconstants, the interactivity parameter between the two piperazine amine groups had to be determined in independent experiments on related compounds.

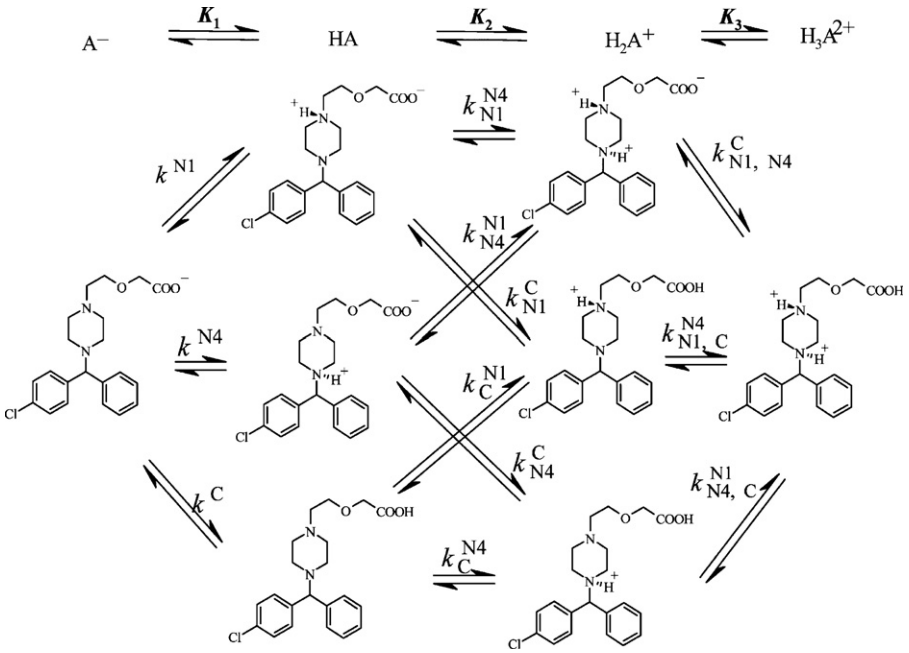

Fig. 2. The protonation scheme of cetirizine and its macro- and microconstants.