History of SPM 007

Monheim, 17 November 2000

To
L. Hakes PCD
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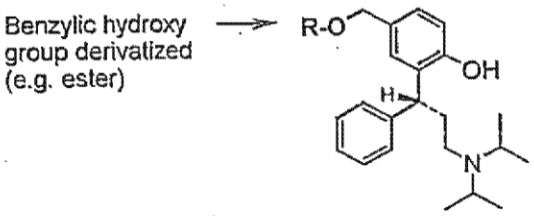
It is known since several years that the major metabolite DD 01 of Tolterodine is equipotent to the parent drug:

PCT WO 94/11337 (26.05.1994); US 5,559,269 (24.9.1996); H. Postlind, A. Lindgren, S. H. G. Anderssen: XIth Symp. In Microsomes and Drug Oxidation, July 21-24, 1996, Los Angeles (USA); P.-G. Gillberg, B. Sparf, L. Nilvebrant: Neurourol. Urodyn., 15 (1996) 308-9; L. Palmer, L. Andersson, T. Andersson, U. Stenberg: J. Pharmac. Biomed. Anal., 16 (1997) 155-165.

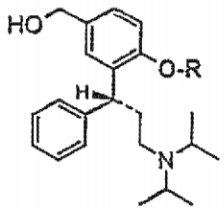
During a meeting, helt at Monheim on August 28th (1997), the options were discussed between Bengt Sparf, Peter Ney, and Claus O. Meese that the scaffold of the active hydroxy metabolite DD 01 could be chemically converted into a different active derivative.
From the knowledge of the patent literature (PCT WO 89/06644, 27.07.1989 and EP 325 571, 07.08.1991) it appeared obvious to Bengt Sparf that the phenolic hydroxy group of the active derivative of DD 01 should be free in order to elicit optimum anti-muscarinic receptor binding:

Proposals of B. Sparf



However, subsequent laboratory work disclosed that this objective cannot be achieved. In contrast, the following discoveries led to SCHWARZ Pharma's proposals for novel (inactive) prodrugs.

Prodrug Proposals of SCHWARZ Pharma



Phenolic hydroxy group derivatized (e.g. ester)

- Benzylic monoesters of DD 01 cannot be prepared chemically. A new enzymatic process was then developed which regioselectively led to benzylic monoesters. Studies on these derivatives showed that these are chemically unstable.

- Both phenolic monoesters and diester derivatives of DD 01 are chemically stable and biologically inactive, but release the active parent hydroxy metabolite under in-vitro or in-vivo conditions (prodrug principle).

- The novel prodrugs exhibit improved oral bioavailability and transdermal penetration rate.

- New synthetic routes were developed that reduce the number of steps and allow for a enantiomer resolution on an early stage.

- Stable, non-hygroscopic, and crystalline salts were developed, among those the fumarate salt SPM 8272, SP's drug candidate of the SPM 007 series.

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SIL

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