

# Chemical Development Plan

## Incontinence Project

Aim: Synthesis of prodrugs

Update (5) Feb. 10 - Feb. 20, 1998

- Pure hydroxy metabolite is now available (> 10g), another lot of ca. 60g is expected CW 9, first 4 scaleup steps (kg-scale) are outsourced
- Chemical and enzymatic synthesis of totally 22 potential prodrugs
- The in-vitro assay with human liver homogenate (hepatic S9 supernatant) shows the following results (X/Y for X-CH<sub>2</sub>-[para-Phenyl]-Y):

Efficient liberation of hydroxy metabolite:

AcO/OAc, i-ButO/Oi-But, HO/Oi-But

Moderate liberation of hydroxy metabolite:

PivO/OPiv, MeO/OH

Marginal liberation of hydroxy metabolite:

HO/OBn, AcO/OBn, i-BuO/OBn, BzO/OBn, HO/OTBDMS, TBDMSO/OH

Non-enzymatic hydrolysis:

AcO/OH, n-BuO/OH, i-BuO/OH, PivO/OH, BzO/OH

No hydroxy metabolite formation:

HO/O-Et-carbam, TBDMSO/OTBDMS, Et-carbamO/OTBDMS, Et-carbamO/OH, Et-carbamO/O-Et-carbam, Et-carbonO/O-carbon-Et

Next challenge:

- Preparation of further prodrugs of the hydroxy metabolite (s. patent draft)
- Assessment of the chemical stability, enzymatic lability and salt formation
- Scaleup of drug candidate
- Patent application

Pat. - Konzept:  
 - Hyd. metab. ist besser  
 - BA insufficient (10%)  
 - Prodrug: besser als ↑

Feb 20, 1998  
 Schwarz Pharma  
 C. O. Meese

cc: Team

<upd5.txt>

- human plasma: spätes, Probleme mit Protein
- log P, Protein binding
- andere pharmakologische Eigenschaften / Aktivitäten



22 Prüfung - Kandidaten : Kaste Eth, Ester, Carbamat, Carbonat  
noch nicht alle getestet

59 - Inkub : F-Zucker, chromatogr., F-Zershad (Metabolit-Entstehung)  
=> zeitl. Verlauf verfolgen!

Stabilität : Prüfung F-Milch  
von Prüfung

1-Bakterie : 3 Vertreter im Vergleich phenol./benzyl./Diester  
zeitabhängigkeit

Beweis : Prüfung -> Hydroxymetabol. (HS) Büchsch. Hammes

Bilz-Bildung / Löslichkeit

● Coco-2 : 10 Substanzen ca 5-10 mg jeweils

Am, DMF, MeOH, EtOH, DMSO, 1,2-PrOH | Konz: 4-5 mg/ml

läuft derzeit : OH/OH und dring  
8 Substanzen auswählen!

marginal (+) uncertain (?)  
Amulation

18. Vermessen!

setzen Hydroxymetabolit frei :

HO/O-TB-DMS

TB-DMSO/OH

OH/O-Bn

AcO/O-Bn

i-ButO/O-Bn

BE-O/O-Bn

1. viel ~ AcO/AcO

2. MeO/OH

wenig?

3. PivO/PivO -> Stab. (RT)  
pH 3: OK  
pH 7.4: t1/2 9h

4. i-ButO/i-ButO

5. HO/i-ButO

Baufan bes. Fehl (Leewert) !  
sich ohne Enzym

PivO/OH

i-ButO/OH

BE/OH ?

n-ButO/OH

AcO/OH

due to  
non-enzymatic  
hydrolysis

excellent (++) to moderate (++)  
liberation of hydro. met. from  
präparat

Rein Hydroxymet.

HO/O-Et-Carb

TB-DMSO/TB-DMSO

Et-CarbO/O-TB-DMSO

Et-CarbO/OH



Abl. → Klausur - Projekt 2  
Biol. Daten, S. 9 - 1/16 -

ent. 20.4.98  
Info: Labor

**vertraulich**

Monheim, 23 March 1998

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Method Report BA 263-02

Incubations of prodrugs of SPM 7500 with human liver S9-fraction to investigate the in-vitro metabolism with regard to the effect of different protective moieties.

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