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METABOLISM AND STRUCTURE ACTIVITY DATA BASED DRUG DESIGN: DISCOVERY OF (-) SCH 53079 AN ANALOG OF THE POTENT CHOLESTEROL ABSORPTION INHIBITOR (-) SCH 48461

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ABSTRACT: Based on the metabolism of the potent cholesterol absorption inhibitor (-) SCH48461 and structure activity relationship information, we designed and evaluated (-)SCH 53079. This compound was found to be equipotent to (-)SCH 48461 in both the cholesterol-fed hamster and rhesus monkey assays. Importantly, (-)SCH 53079 was metabolically more stable than (-)SCH 48461 and as desired had very low plasma levels and did not cause hepatic enzyme induction.

(-)SCH 48461 is a potent cholesterol absorption inhibitor in the cholesterol-fed hamster assay.[1] This class of compounds appears to inhibit cholesterol absorption by a new and as yet undefined mechanism. However, there are indications that the site of action for these compounds is at the intestinal wall.[2] Studies have also demonstrated that (-)SCH 48461 is very effective in lowering plasma lipoprotein levels in cholesterol-fed rhesus monkeys[2,3] and has a synergistic effect with the HMG-CoA reductase inhibitors in reducing plasma lipoprotein levels in chow fed dogs and rhesus monkeys.[4]

Metabolism studies indicated that there were four primary sites of metabolism for (-)SCH 48461, (Figure 1), with metabolites resulting from demethylation, hydroxylation and/or oxidation and combinations thereof, resulting in the formation of eleven metabolites.[5] These data along with the structure-activity relationship (SAR) studies were used as a guide in designing a metabolically more stable analog of (-)SCH 48461 without affecting the potency of the compound.

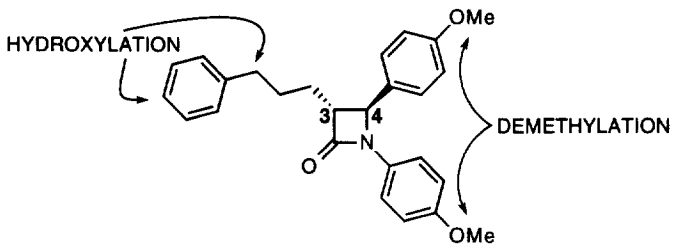


Figure 1: (-) SCH 48461 Sites of Metabolism

Earlier SAR studies had indicated that the methoxy group on the C-4 aryl moiety and the β-lactam ring were critical for activity, the C-3 phenylpropyl group was an essential pharmacophore but tolerated some modification, and the methoxy group on the N-aryl moiety was not required for activity.[6] Hence, of the four primary sites of metabolism, it appeared that benzylic hydroxylation could likely be blocked and the methoxy group of the N-aryl moiety removed without affecting the potency of the compound.

To prevent benzylic oxidation, oxygen was substituted for the C-3' carbon. Unfortunately, this substitution resulted in a substantial decrease in potency of (±) **2**, (Figure 2), when compared to (±) **1**, the racemate of (-)SCH 48461.[7] The reduced potency of (±) **2** may be due to various reasons, including metabolic lability of (±) **2**. It is possible that the hydroxylation of the electron rich phenoxy moiety of (±) **2** is enhanced in comparison to the phenyl moiety of (±) **1** resulting in the formation of less active metabolites, (Figure 3),. If this is a valid rationale, then blocking this site of hydroxylation should restore the activity of (±) **2**. Indeed, (±) **3**, with fluorine blocking the site of metabolism, had activity comparable to (±) **1**.

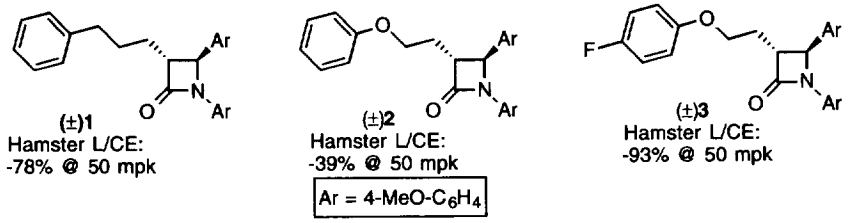


Figure 2

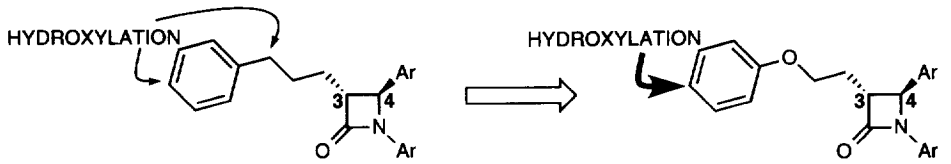
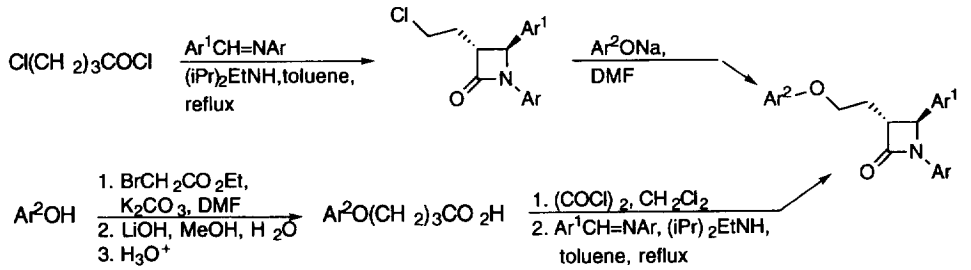


Figure 3

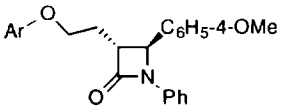
A short SAR study of *para*-substituents (Table 1) indicated that fluorine was optimum for potency. All these compounds were synthesized following one of the two routes outlined in Scheme 1.



Scheme 1. General synthetic route for 3-(2-Aryloxy)ethyl-β-lactams.

Removal of the methoxy group on the N-aryl moiety of (±) **3**, as expected, had no effect on the *in vivo* activity of (±) **4**, (Table 1). Resolution of (±) **4** gave the the active enantiomer **(-) 4** [(-)SCH 53079], (Table 1).[8]

Table 1

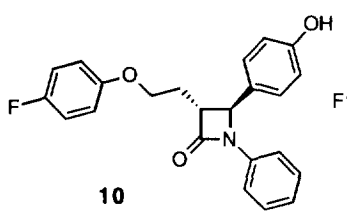


#	Ar	% L/CE *
(±)4	4-F-C_6H_4	-95
(-)4	4-F-C_6H_4	-93
(+)4	4-F-C_6H_4	-28
(±)5	4-NO_2-C_6H_4	-31
(±)6	4-MeO-C_6H_4	-82
(±)7	4-I-C_6H_4	-47
(±)8	2,4-F_2-C_6H_4	-88
(±)9		-46

*Reduction of Liver Cholesterol Ester (L/CE) levels in the cholesterol-fed Hamster model @50mpk. (n = 4/group)

Biliary metabolism studies in bile duct-cannulated laboratory animals indicated that the metabolism of **(-) 4** resulted in the formation of only three metabolites, **10**, **11** and **12**, as glucuronide conjugates.[9] Plasma level determinations in rats[10] indicated that the plasma levels of the parent drug were very low (Table 2) with virtually all of the drug derived materials secreted in the bile. Furthermore **(-) 4** was found not to induce hepatic enzymes. ED_{50} determination in hamsters and rhesus monkeys indicated that **(-) 4** was equipotent to (-)SCH 48461, (Figure 4), in these two *in vivo* models.[2,3]

This study was started with the intent of identifying an equipotent and metabolically more stable analog of (-)SCH 48461. This has resulted in the discovery of **(-) 4** [(-)SCH 53079] which is not only equipotent to (-)SCH 48461, but also metabolically more stable.



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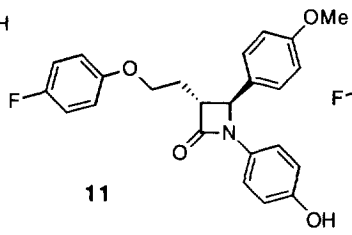

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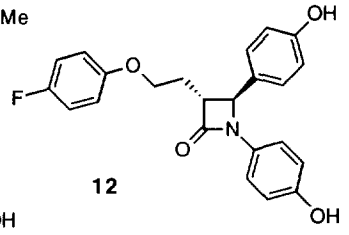

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Table 2

Time (h) Postdose	(-) 4 (ng/mL)* Average± SD
1	< 30
2	41.1± 35.6
4	< 30
8	238.7 ± 191.7
24	< 30

* Female Rats (n = 3/group).

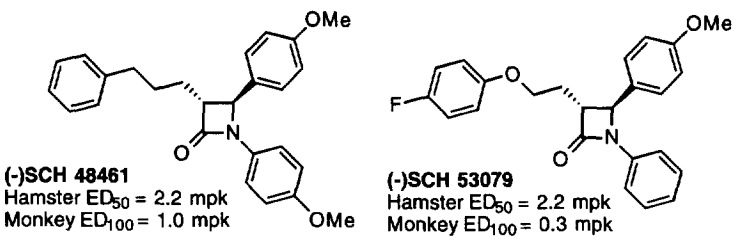

Figure 4

References and Notes

1. Burnett, D.; Caplen, M.; Davis, H. Jr.; Burrier, R.; Clader, J. *J. Med. Chem.* **1994**, *37*, 1733.
2. Salisbury, B.; Davis, H.; Burrier, R., Burnett, D.; Boykow, G.; Caplen, M.; Clemmons, A.; Compton, D.; Hoos, L.; McGregor, D.; Schnitzer-Polokoff, R.; Smith, A.; Weig, B.; Zilli, D.; Clader, J.; Sybertz, E. *Atherosclerosis* **1995**, *115*, 45.
3. Schintzer-Polokoff, R.; Compton, D.; Boykow, G.; Davis, H.; Burrier, R. *Comp. Biochem. Physiol.* **1991**, *197*, 304.
4. Davis, H.; Watkins, R.; Salisbury, B.; Compton, D.; Sybertz, E.; Burrier, R. *Atherosclerosis*, **1994**, *109*, 162.
5. Metabolism studies were carried out in male rats, beagle dogs and cynomolgus monkeys using a single (gavage) oral dose of 50mpk. Bile was collected and part of it was treated with Glusulase®. Both pre- and post-Glusulase® portions were analyzed by HPLC. Individual metabolites were identified by coinjection with authentic samples and confirmed by LC/MS.
6. Clader, J.; Burnett, D.; Caplen, M.; Domalski, M.; Dugar, S.; Vaccaro, W.; Sher, R.; Browne, M.; Zhao, H.; Burrier, R.; Salisbury, B.; Davis, H. Jr. 2-Azetidinone Cholesterol Absorption Inhibitors: Structure-Activity Relationships on the Heterocyclic Nucleus, manuscript in preparation
7. Measured by reduction in liver cholesterol ester levels (L/CE) in the seven-day cholesterol-fed hamster model, see reference 1. All compounds with indicated percent reductions were statistically different from the cholesterol-fed control group. The compounds were evaluated in a series of separate seven- day cholesterol-fed hamster studies hence, direct statistical comparisons among the compounds were not performed.
8. The enantiomers were separated on a Chiralcel OD column (90% hexane/10% 2-propanol).
9. A bile duct-cannulated rat, beagle dog and cynamolgus monkey were each orally administered a single gavage dose of 50 mpk (-) **4** and bile was collected over a 0-24 h period. Bile samples were treated with Glusulase® and both treated and untreated samples were analyzed using a HPLC system with a Hypersil ODS analytical column (4.6 × 250 mm, 5mm) with UV detection at 260 nm. The peaks were isolated using a preparative HPLC system and analyzed by mass spectrometry.
10. Female rats received a single oral (gavage) dose of 487 mg (-)5/kg in corn oil. Plasma levels of parent drug in hamsters or monkeys was not determined.

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