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# CARBOXY-SUBSTITUTED 2-AZETIDINONES AS CHOLESTEROL ABSORPTION INHIBITORS

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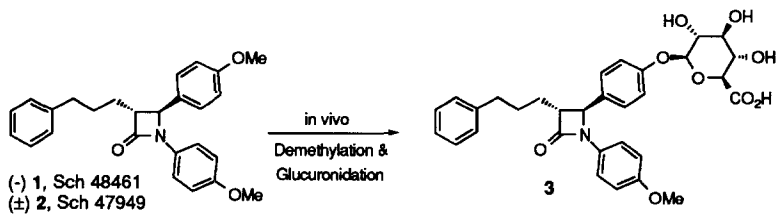
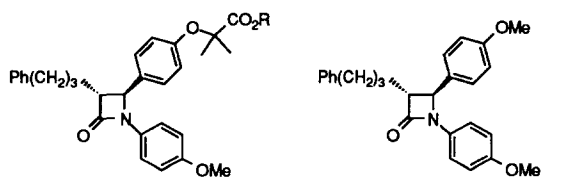
**Abstract:** Metabolism initiated SAR studies led to the discovery of a new class of potent 2-azetidinone cholesterol absorption inhibitors. These studies found that a heteroatom at the *para* position of the C-4 phenyl ring is not a requirement for cholesterol absorption inhibition as was suggested by earlier findings. Substitution of Ph-linker-COOR for PhOMe at the C-4 position enhanced cholesterol absorption inhibition.



We previously disclosed that the 2-azetidinone **1**, Sch 48461, is a potent inhibitor of cholesterol absorption.[1,2] Subsequent metabolism studies found that **1** is rapidly converted in vivo into a number of metabolites.[3] Of these, the glucuronide **3** was identified as the major and most potent metabolite of **1**.




Since the glucuronide **3** is much more polar than **1**, we postulated that increasing the polarity of 2-azetidinones may be beneficial for the inhibition of cholesterol absorption. To test this theory, the racemic fibric acid derivatives[4] (±) **4** and (±) **5** were prepared. Encouragingly, **4** and **5** were equipotent with **2** in reducing cholesterol esters (CE) when given orally in the seven day cholesterol fed hamster assay.[1]




(±) **4** R = H, CE Rdn: -75 % (50 mpk)
(±) **5** R = Me, CE Rdn: -80 % (50 mpk)

(±) **2** CE Rdn: -78 % (50 mpk)

Compounds (±) **6** and (±) **7** were prepared to determine if the C-4 aryl ether moiety is indeed required for cholesterol absorption inhibition. Gratifyingly, both **6** and **7** demonstrated promising reductions in cholesterol esters. Earlier work suggested that a heteroatom located at the *para* position of the C-4 phenyl ring

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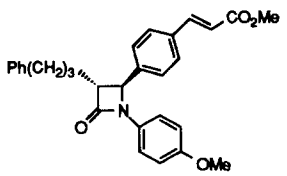
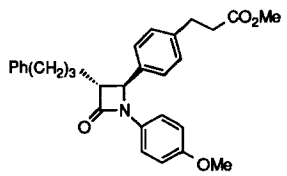
was crucial for cholesterol absorption inhibition.[1,2] The discovery of compounds **6** and **7** proves otherwise and establishes a new class of cholesterol absorption inhibitors, the carboxy-substituted 2-azetidinones. Since it was previously demonstrated that the cholesterol absorption inhibition resides principally in the diastereomer with the 3*R*,4*S* absolute configuration, subsequent SAR studies were carried out with enantiomerically pure 2-azetidinones prepared as described below.



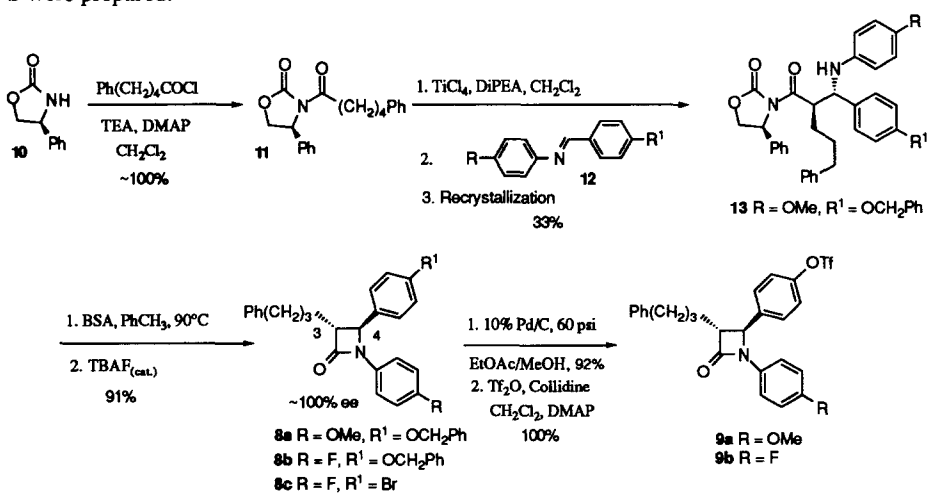

(±) **6** CE Rdn: -90 % (50 mpk)




(±) **7** CE Rdn: -93 % (50 mpk)

## Chemistry

The enantiomerically pure bromide **8c** and triflates **9a** and **9b** were targeted as key synthetic intermediates, since they afford ready access to a variety of analogs for SAR studies. The preparation of **9a** is presented in detail. 5(*S*)-phenyloxazolidinone **10** was acylated with 5-phenylvaleryl chloride to provide **11**. Treatment of **11** with titanium tetrachloride generated the corresponding titanium enolate, subsequent addition of imine **12** provided a mixture of β-amino amides as a 4:1 ratio of diastereomers. A single recrystallization of the mixture from ethyl acetate/hexanes gave **13** in enantiomerically pure form (33% yield, unoptimized). Silylation of **13** with bis(trimethylsilyl)acetamide followed by fluoride catalyzed cyclization gave the 2-azetidinone **8a** in a one pot operation. HPLC analysis indicated that **8a** was optically pure when compared with racemic **8a**.[5] The absolute stereochemistry of **8a** was assigned as 3*R*,4*S* by analogy to **1**.[6] Hydrogenolysis of **8a** and subsequent treatment with triflic anhydride provided triflate **9a**. Using a similar protocol compounds **8c** and **9b** were prepared.




A variety of palladium mediated coupling protocols were employed to prepare carboxy-substituted 2-azetidinones derived from **8c**, **9a**, and **9b**. Representative methods for the introduction of ester functionality

directly attached[7] or attached by 1[8] or 2[9] carbon linkers to the C-4 phenyl ring is shown below. Some of the esters were subsequently converted to the corresponding acids and amides. Carboxy-substituted 2-azetidinones **14 - 25** prepared by the described methods are reported in Table 1.

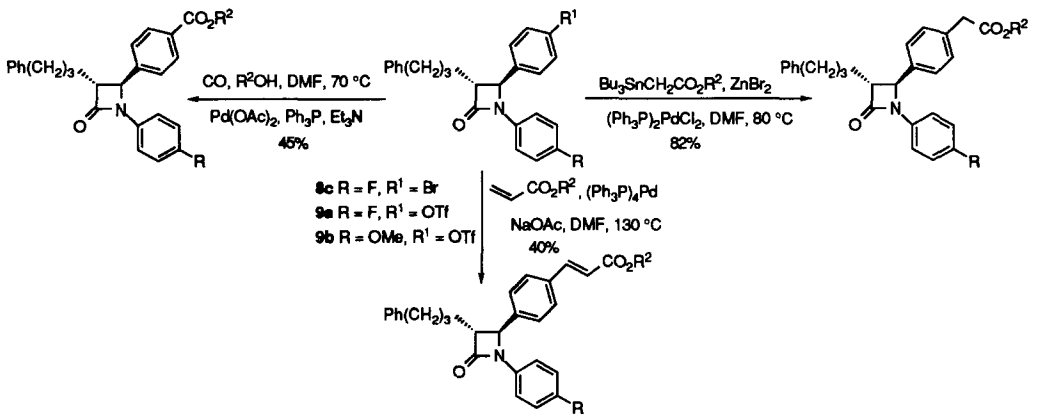
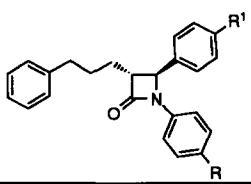



Table 1: Cholesterol Absorption Inhibition Activity of Carboxy-Substituted 2-Azetidinones in Orally Dosed Seven Day Cholesterol Fed Hamsters.[10]



| Compound | $R^1$ | R | Serum Cholesterol (% reduction) | Liver Cholesterol Esters (% reduction) | Dose (mg/Kg/day) | $ED_{50}$ (mg/Kg/day) |
|---|---|---|---|---|---|---|
| **1** | OMe | MeO | -43 | -93 | 10 | 2.0 |
| **14** | $CO_2Me$ | F | 0 | -16 | 3 | |
| **15** | $CO_2H$ | F | 0 | -37 | 3 | |
| **16** | $CH_2CO_2Me$ | F | -16 | -61 | 3 | |
| **17** | $CH_2CO_2Me$ | MeO | -26 | -89 | 3 | 0.95 |
| **18** | $CH_2CO_2H$ | F | -44 | -97 | 10 | 1.1 |
| **19** | $CH_2CONEt_2$ | F | 0 | -19 | 10 | |
| **20** | $(CH_2)_2CO_2Me$ | MeO | -20 | -76 | 3 | 0.85 |
| **21** | $(CH_2)_2CO_2Me$ | F | -26 | -72 | 10 | |
| **22** | $(CH_2)_2CO_2H$ | F | -32 | -63 | 10 | |
| **23** | $(CH_2)_2CONEt_2$ | F | 0 | -19 | 10 | |
| **24** |  trans | MeO | -13 | -72 | 3 | 1.1 |
| **25** |  trans | F | -21 | -48 | 10 | |

**Biological Results**

The cholesterol absorption inhibition of carboxy-substituted 2-azetidinones is presented in Table 1. The most potent analogs **17**, **18**, **20**, and **24** ($ED_{50}$: ~ 1 mg/Kg/day) are approximately twice as potent as our original lead **1** ($ED_{50}$: 2 mg/Kg/day). In regards to linker length (Ph-linker-$CO_2R$), zero, one, and two carbon linkers are allowed. In the two carbon linker series, both alkyl **20** and alkenyl **24** linkers are tolerated. Carboxylic esters and acids are more potent than the corresponding diethylamides in both the two carbon (compare **21**, **22**, and **23**) and one carbon (compare **16**, **18**, and **19**) linked series. In regards to nitrogen substitution, both 4-fluorophenyl and 4-methoxyphenyl substituted compounds are tolerated.

**Conclusions**

Metabolism initiated SAR studies led to the discovery of a new class of potent 2-azetidinone cholesterol absorption inhibitors, the carboxy-substituted 2-azetidinones. The most potent compounds (**17**, **18**, **20**, and **24**) are approximately twice as potent as the original lead **1**. However, since we are presently restricted to an in vivo assay, interpretation of the cholesterol absorption activity of the compounds in Table 1 may not be straightforward. The observed cholesterol absorption inhibition may be a reflection of a compound's bioavailability and/or ease of conversion to active metabolites and not its intrinsic cholesterol absorption activity. Of particular note, these studies found that a heteroatom at the *para* position of the C-4 phenyl ring is not a requirement for cholesterol absorption inhibition as was suggested by earlier findings.

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5. HPLC analysis of **8a**: Analytical Chiracel OD column (3% isopropanol/hexanes, 1.0 mL/min), Rt=17.53 min.(racemic **8a**, enantiomer A, Rt = 17.58 min, enantiomer B, Rt = 22.05 min).
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10. Compounds were evaluated in the cholesterol fed hamster model at the indicated dose (n = 6/group). All compounds were statistically different from the cholesterol fed control group (n = 6/group). The compounds were evaluated in separate studies hence, direct statistical comparisons among the compounds was not performed. For a discussion of the seven day cholesterol fed hamster model see reference.[1]