

CARBOXY-SUBSTITUTED 2-AZETIDINONES AS CHOLESTEROL ABSORPTION INHIBITORS

Wayne D. Vaccaro*, Rosy Sher, and Harry R. Davis, Jr.

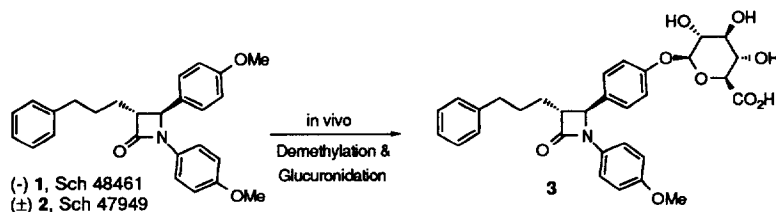
Schering-Plough Research Institute,
2015 Galloping Hill Road, Kenilworth, New Jersey 07033-0539, U. S. A..

Received 19 November 1997; accepted 29 December 1997

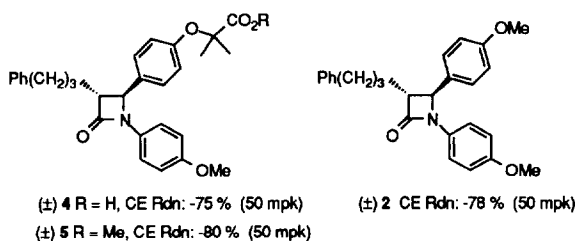
Abstract: Metabolism initiated SAR studies led to the discovery of a new class of potent 2-azetidinone cholesterol absorption inhibitors. These studies found that a heteroatom at the *para* position of the C-4 phenyl ring is not a requirement for cholesterol absorption inhibition as was suggested by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

© 1998 Elsevier Science Ltd. All rights reserved.

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**.

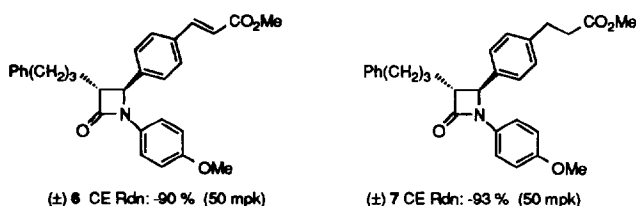


Since the glucuronide **3** is much more polar than **1**, we postulated that increasing the polarity of 2-azetidinones may be beneficial for the inhibition of cholesterol absorption. To test this theory, the racemic fibric acid derivatives⁴ (±) **4** and (±) **5** were prepared. Encouragingly, **4** and **5** were equipotent with **2** in reducing cholesterol esters (CE) when given orally in the seven day cholesterol fed hamster assay.¹



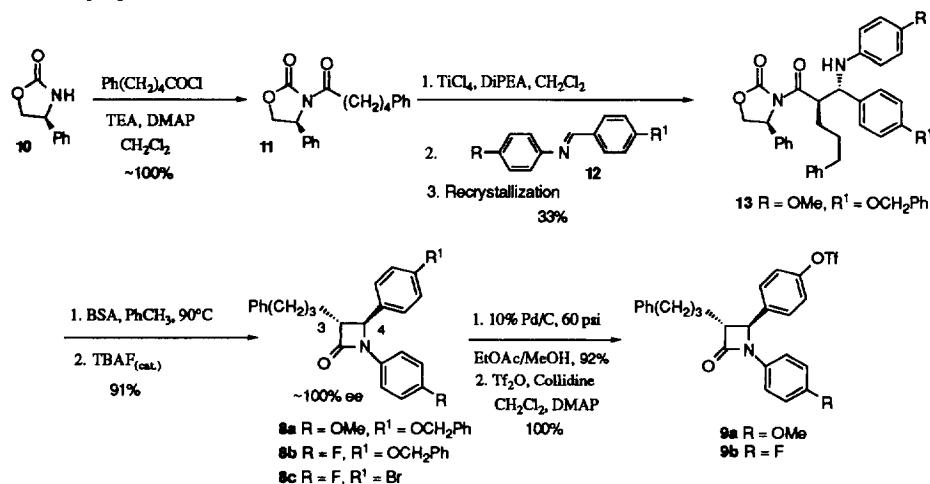
Compounds (±) **6** and (±) **7** were prepared to determine if the C-4 aryl ether moiety is indeed required for cholesterol absorption inhibition. Gratifyingly, both **6** and **7** demonstrated promising reductions in cholesterol esters. Earlier work suggested that a heteroatom located at the *para*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

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.



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 attached⁷ or attached by 1⁸ or 2⁹ 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.

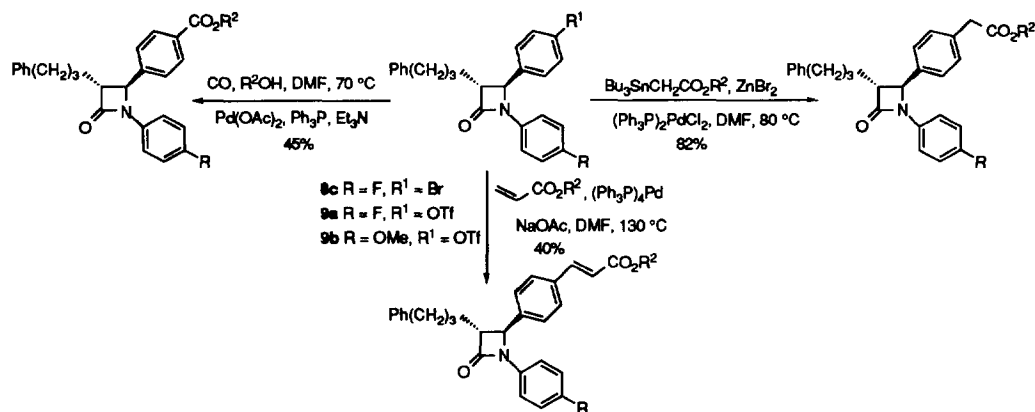
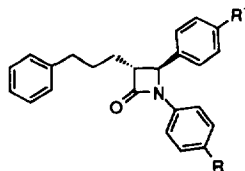


Table 1: Cholesterol Absorption Inhibition Activity of Carboxy-Substituted 2-Azetidinones in Orally Dosed Seven Day Cholesterol Fed Hamsters.¹⁰



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 ₂ Me	F	0	-16	3	
15	CO ₂ H	F	0	-37	3	
16	CH ₂ CO ₂ Me	F	-16	-61	3	
17	CH ₂ CO ₂ Me	MeO	-26	-89	3	0.95
18	CH ₂ CO ₂ H	F	-44	-97	10	1.1
19	CH ₂ CONEt ₂	F	0	-19	10	
20	(CH ₂) ₂ CO ₂ Me	MeO	-20	-76	3	0.85
21	(CH ₂) ₂ CO ₂ Me	F	-26	-72	10	
22	(CH ₂) ₂ CO ₂ H	F	-32	-63	10	
23	(CH ₂) ₂ CONEt ₂	F	0	-19	10	
24	trans CO ₂ Me	MeO	-13	-72	3	1.1
25	trans CO ₂ Me	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** (ED₅₀: ~ 1 mg/Kg/day) are approximately twice as potent as our original lead **1** (ED₅₀: 2 mg/Kg/day). In regards to linker length (Ph-linker-CO₂R), 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.

Acknowledgements. We would like to thank Sundeep Dugar, Duane Burnett, Pradip Das, Peter Bartner, Lizbeth Hoos, and Daniel McGregor for their assistance and helpful discussions.

References:

1. Burnett, D. A.; Caplen, M. A.; Davis, H. R., Jr.; Burrier, R. E.; Clader, J. W. *J. Med. Chem.* **1994**, *37*, 1733.
2. Clader, J. W.; Burnett, D. A.; Caplen, M. A.; Domalski, M. S.; Dugar, S.; Vaccaro, W.; Sher, R.; Browne, M. E.; Zhao, H.; Burrier, E. R.; Salisbury, B.; Davis, H. R., Jr. *J. Med. Chem.* **1996**, *39*, 3684.
3. Van Heek, M.; France, C. F.; Compton, D. S.; Mcleod, R. L.; Yumbie, N. P.; Alton, K. B.; Sybertz, E. J.; Davis, H. R., Jr. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 157.
4. Bencze, W. L.; Kisis, B.; Puckett, R. T.; Finch, N. *Tetrahedron* **1970**, *26*, 5407.
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).
6. Burnett, D. A. *Tetrahedron Lett.* **1994**, *35*, 7339.
7. Peterson, E. M.; Xu, K.; Holland, K. D.; McKeon, A. C.; Rothman, S. M.; Ferrendelli, J. A.; Covey, D. F. *J. Med. Chem.* **1994**, *37*, 275.
8. Kosugi, M.; Negishi, Y.; Kameyama, M.; Migita, T. *Bull. Chem. Soc Jpn.* **1985**, *58*, 3383. Zapata, A.; Acuna A., C. *Syn. Comm.* **1984**, *14*, 27.
9. Spencer, A. *J. Organometal. Chem.* **1983**, *258*, 101.
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