Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 24, pp. 2947-2952, 1995

0960-894X/95 $9.50+0.00

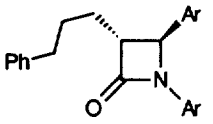
0960-894X(95)00516-1

GAMMA-LACTAMS AND RELATED COMPOUNDS AS CHOLESTEROL ABSORPTION INHIBITORS: HOMOLOGS OF THE *BETA*-LACTAM CHOLESTEROL ABSORPTION INHIBITOR SCH 48461[1]

Sundeep Dugar,* Michael P. Kirkup, John W. Clader, Sue-Ing Lin, Razia Rizvi, Mark E. Snow, Harry R. Davis Jr. and Stuart W. McCombie
Schering Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033

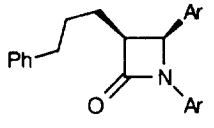
Abstract: Our search for potent cholesterol absorption inhibitors led to the discovery of the β-lactam SCH 48461. Structure activity relationship studies prompted us to this study of γ-lactams, ring homologs of β-lactam SCH 48461, to determine their potential as cholesterol absorption inhibitors. The results indicate that the γ-lactams have moderate cholesterol absorption inhibitory properties.

High serum cholesterol levels have been unequivocally implicated as a cause of coronary artery disease (CAD). A diet high in saturated fat and cholesterol has been singled out as a major risk factor for CAD and hence drug therapy to inhibit intestinal cholesterol absorption has been important for control of hyperlipidemia.[2] Though numerous agents that affect cholesterol absorption inhibition (CAI) have been reported, the search for safe and effective inhibitors of cholesterol absorption has continued unabated.[3] Our



(±)SCH 47949
L/CE: -78% @ 50mpk

(-)[3R,4S]SCH 48461
L/CE: -93% @ 10mpk



(±)SCH 48375
L/CE: -95% @ 50 mpk

(-)[3S,4S]SCH 48678
L/CE: -69% @ 10 mpk

Ar = 4-MeO-C_6H_4

research efforts to develop novel hypolipidemic agents led to the identification of SCH 48461 as a very potent CAI *in vivo*, as determined in the cholesterol fed hamster model.[1,4] The compounds in this series appear to inhibit cholesterol absorption by a new and as yet undefined mechanism.[4] Further studies indicated that SCH 48461 was also very effective in lowering plasma lipoprotein levels in cholesterol fed rhesus monkeys,[5] and demonstrated a synergistic effect with HMG-CoA reductase inhibitor, lovastatin, even in chow fed dogs and rhesus monkeys.[6] As a part of our structure activity studies we decided to investigate whether the rigid β-lactam ring is acting merely as a template to optimally orient the various substituents or is an integral part of the pharmacophore in itself. To evaluate this we decided to investigate the potential of conformationally flexible γ-lactams as cholesterol absorption inhibitors, Figure 1.

Homologation of the β-lactam ring to a γ-lactam results in the three γ-lactam regioisomers **A**, **B**, and **C**, Figure 1. This required the evaluation of all three diastereomers that were direct homologs of SCH

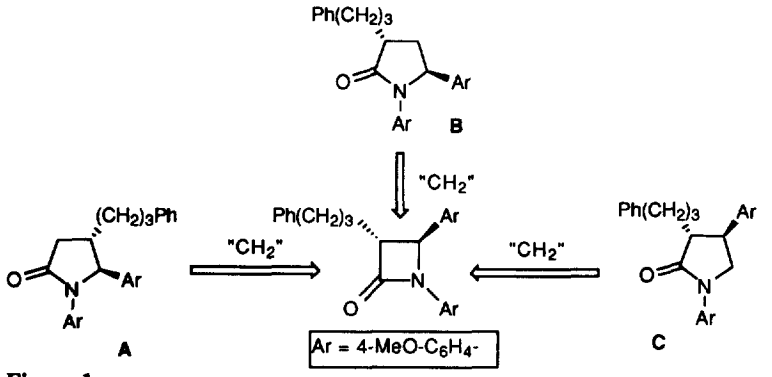
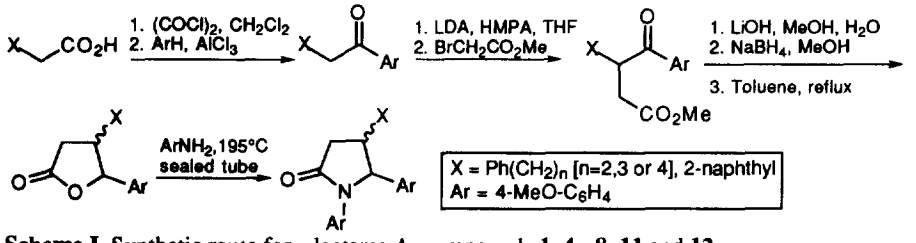
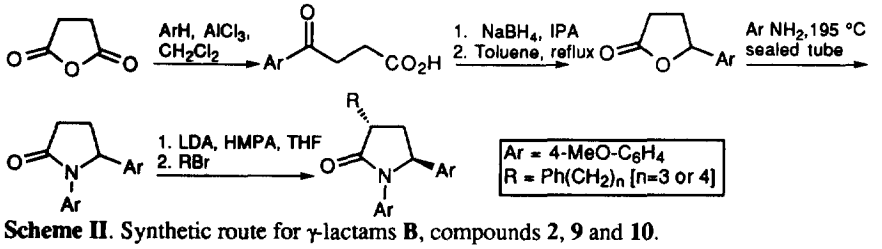


Figure 1

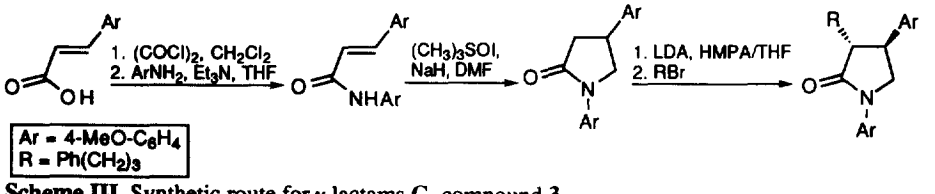
47949 to identify the diastereomer, if any, that was a potential cholesterol absorption inhibitor and then further investigate the structure activity relationships in this series. The compounds for this study were synthesized by the routes outlined in Schemes I, II, III, IV, V and VI.



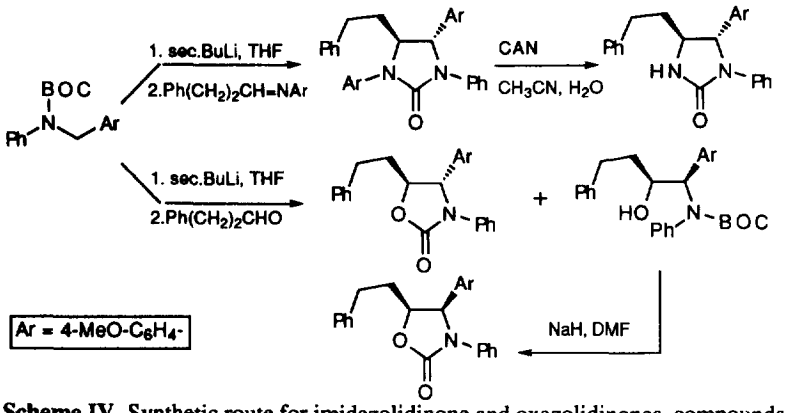
Scheme I. Synthetic route for γ-lactams **A**, compounds **1**, **4** - **8**, **11** and **12**.



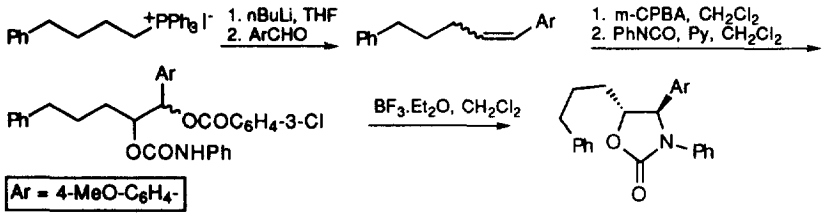
Scheme II. Synthetic route for γ-lactams **B**, compounds **2**, **9** and **10**.



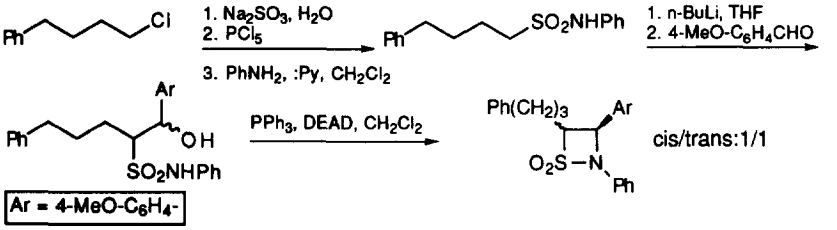
Scheme III. Synthetic route for γ-lactams **C**, compound **3**.



Scheme IV. Synthetic route for imidazolidinone and oxazolidinones, compounds **13**, **14**, and **15**.



Scheme V. Synthetic route for oxazolidinone, compound **16**.

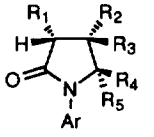


Scheme VI. Synthetic route for β-sultams, compounds **18** and **19**.

In Table 1 compounds **1**, **2**, and **3** represent the three phenylpropyl γ-lactams that are the direct homologs of SCH 48461. Of the three only **1** (Diastereomer Type A) showed any hint of activity.[7] However, the corresponding *cis*- isomer **4**, appeared to have moderate CAI activity. We were encouraged by the activity of **4** to further investigate this class of compounds. The effect of varying the length of the side chain (cf. compounds **5** and **6**) indicated that both the phenylpropyl and the phenylbutyl side chain analogs were moderately active. Interestingly, for the phenylbutyl series both the *trans*-diastereomer **8** and the *cis*-diastereomer **6** appeared to have moderate activity, in contrast to the phenylpropyl side chain analogs

4 and **1**. In fact, the *trans*-phenylbutyl γ-lactam (**8**), was the most active compound in this series, although still not as active as its β-lactam analog SCH 47949. Of the three phenylbutyl γ-lactam diastereomers **8**, **9** and **10** only **8** was found to be active. The two naphthyl analogs **11** and **12**, representing partially restricted analogs of the side chain, appeared less active than the straight chain analogs **8** and **6** respectively.

Table 1: Activity of Various γ-Lactams



#	R_1	R_2	R_3	R_4	R_5	Ar	%L/C*
1	H	$Ph(CH_2)_3$	H	4-MeOPh	H	4-MeOPh	-12
2	$Ph(CH_2)_3$	H	H	4-MeOPh	H	4-MeOPh	NE
3	$Ph(CH_2)_3$	H	4-MeOPh	H	H	4-MeOPh	NE
4	H	H	$Ph(CH_2)_3$	4-MeOPh	H	4-MeOPh	-43
5	H	H	$Ph(CH_2)_2$	4-MeOPh	H	4-MeOPh	-16
6	H	H	$Ph(CH_2)_4$	4-MeOPh	H	4-MeOPh	-30
7	H	$Ph(CH_2)_2$	H	4-MeOPh	H	4-MeOPh	-24
8	H	$Ph(CH_2)_4$	H	4-MeOPh	H	4-MeOPh	-52
9	$Ph(CH_2)_4$	H	H	4-MeOPh	H	Ph	NE
10	$Ph(CH_2)_4$	H	H	H	4-MeOPh	Ph	NE
11	H	2-naphthyl	H	4-MeOPh	H	4-MeOPh	-28
12	H	H	2-naphthyl	4-MeOPh	H	4-MeOPh	-21

*Reduction of Liver Cholesterol Ester (L/CE) levels in the cholesterol fed Hamster model @50mpk.[4,7] NE - no effect. n = 4/group.

Homologation of the β-lactam ring clearly results in moderation of CAI activity. To suggest a possible cause for this we performed conformational analyses on the β-lactam and the γ-lactam rings using *ab initio* calculations. This indicated that in homologating the β-lactam ring we have changed the orientation of the substituents and that of the carbonyl moiety, structure C, compared to the β-lactam structure, Figure 2.[8] In order to determine the specific importance of the β-lactam ring we needed to design a template that does not change the orientation of the substituents. Towards this end we investigated the conformations for the imidazolidonone **D** and the oxazolidinone **E**, Figure 2. These *ab initio* calculations indicated that the imidazolidinones **D** and the oxazolidonones **E**, with their flatter ring system, more closely mimic the β-lactam ring with respect to the orientation of the substitutents.

Based on our modeling results we synthesized and tested imidazolidinone **13** and the oxazolidinones **14**, **15**, and **16**, Table 2. All four compounds had moderate activity in the cholesterol fed hamster assay. For compounds **13**, **14**, and **15** their seemed to be no substantial improvement over their corresponding γ-lactam analogs. Compound **16** was decidedly more active than its γ-lactam analog **1** ($p<0.05$), although the potency was still somewhat below that of the β-lactam, SCH 47949. This attenuation of activity upon ring

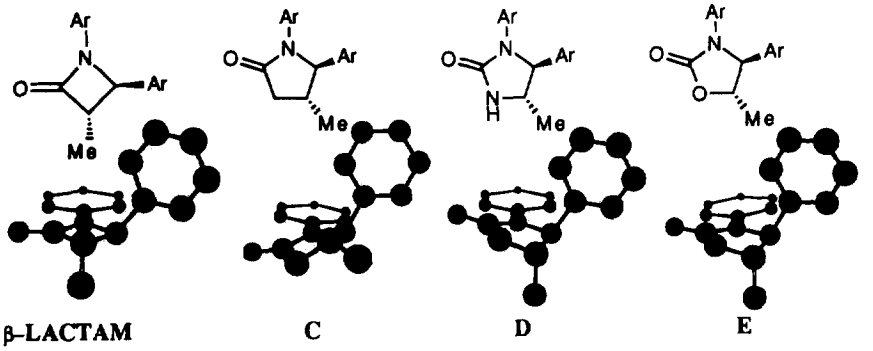
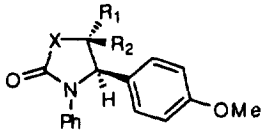


Figure 2. *Ab initio* minimum energy conformations at the 3-21G(*) level for the β-lactam, γ-lactam **C**, imidazolidinone **D** and the oxazolidinone **E**.

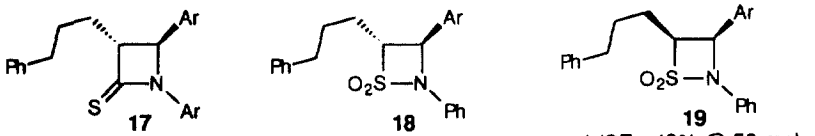
expansion indicated that the carbonyl group of the β–lactam ring is partly responsible for the activity of SCH 47949 and its analogs . The importance of the carbonyl group in the β–lactams was further corroborated by the attenuated activity of the thio-β–lactam **17** [9] and the β–sultams **18** and **19**. All three of these compounds have the rigid framework of a β–lactam but lack the appropriately oriented carbonyl group.

Table 2. Activity of oxazolidinones and imidazolidinone



#	R_1	R_2	X	% L/CE*
13	$Ph(CH_2)_2$	H	NH	-34
14	$Ph(CH_2)_2$	H	O	-34
15	H	$Ph(CH_2)_2$	O	-21
16	$Ph(CH_2)_3$	H	O	-47

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



Ar = 4-MeO-C_6H_4-

In an effort to understand the SAR around our potent cholesterol absorption inhibitor SCH 48461 we investigated this series of γ-lactams as potential cholesterol absorption inhibitors and found that certain γ-lactams and oxazolidinones related to SCH 47949/48461 moderately inhibited absorption of dietary cholesterol *in vivo* in our hamster model. The poor potency of the γ-lactams compared to that of the β-lactams leads us to conclude that the azetidinone ring is an integral and essential pharmacophore.

Acknowledgement. We wish to thank Dr. D. Burnett, Dr. P. Das, Dr. T. Fevig, Ms. L. Hoos, Mr. D. McGregor, Dr. M. Puar, and Dr. W. Vaccaro for their assistance and helpful discussions.

References and Notes

1. Burnett, D. A.; Caplen, M. A.; Davis, H. R. Jr.; Burrier, R. E.; Clader, L. W. *J. Med. Chem.* **1994**, *37*, 1733.
2. (a) The Nutrition Committee of the American Heart Association. Dietary guidelines for healthy American adults: a statement for physicians and helath professionals *Circulation.* **1988**, 77, 721A. (b) Denke, M. A.; Grundy, S. M. *Arch Intern Med.* **1994**, *154*, 317. (c) The Expert Panel. Summary of the Second Report of the National Cholesterol Eductation Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II) *JAMA* **1993**, *269*, 3015.
3. Lee, H. T.; Picard, J. A. *Exp. Opin. Ther. Patents* **1995**, *5*, 397.
4. Clader, J. W.; Berger, J. G.; Burrier, R. E.; Davis, H. R.; Domalski, M.; Dugar, S.; Kogan, T. P.; Salisbury, B. and Vaccaro, W. *J. Med. Chem.* **1995**, *38*, 1600.
5. (a) Schintzer-Polokoff, R.; Compton, D.; Boykow, G.; Davis, H. R.; Burrier, R. E. *Comp. Biochem. Physiol.* **1991**, *197(1)*, 304. (b) Salisbury, B. G.; Davis, H. R.; Burrier, R. E.; Burnett, D. A.; Boykow, G.; Caplen, M. A.; Clemmons, A. L.; Compton, D. S.; Hoos, L. M.; McGregor, D. G.; Schnitzer-Polokoff, R.; Smith, A. A.; Weig, B. C.; Zilli, D. L.; Clader, J. W.; Sybertz, E. J. *Atherosclerosis*, **1995**, *115*, 45.
6. Davis, H. R.; Watkins, R. W.; Salisbury, B. G.; Compton, D. S.; Sybertz, E. J. and Burrier, R. E. *Atherosclerosis*, **1994**, *109*, 162.
7. All compounds with indicated percent reductions were statistically different from the cholesterol-fed control group. The compounds were evaluated in a series of separate 7 day cholesterol-fed hamster studies hence, direct statistical comparisons among the compounds were not performed.
8. The compounds were first built and optimized using the cff91 forcefield in the INSIGHT/DISCOVER (Biosym Technologies Inc., San Diego, CA 92121) programs, then the cff91 minima were used as starting points for *ab initio* calculations. The *ab initio* geometry optimizations were performed at the RHF/3-21G(*) level using the SPARTAN (Wave Function Inc., 18401 Von Karman Ave., Irvine, CA 92715) program.
9. Clader, J. W.; Burnett, D. A.; Caplen, M. A.; Domalski, M. S.; Dugar, S.; Vaccaro, W.; Sher, R.; Browne, M. E.; Zhao, H.; Burrier, R. E.; Salisbury, B. and Davis, H. R. manuscript in preparation.

(*Received in USA* 27 *July* 1995; *accepted* 6 *November* 1995)