Bioorganic & Medicinal Chemistry Letters, Vol.2, No.6, pp. 589-592, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

PREPARATION OF THE ENANTIOMERS OF THE NOVEL CA-SENSITIZER EMD 53 998

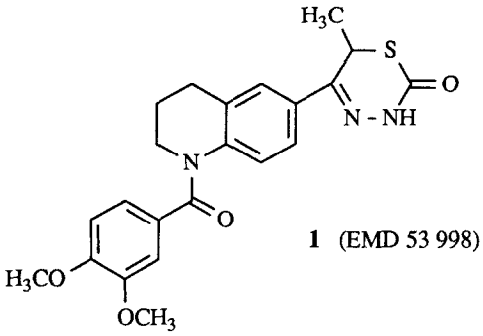
R. Jonas*, M. Klockow, and I. Lues
Pharmaceutical Research Department, E. Merck, Darmstadt, F. R. G.

(*Received* 9 *March* 1992)

Abstract:
Both enantiomers of EMD 53 998 (**1**), a novel cardiotonic with Ca-sensitizing activity, were readily prepared by kinetic resolution of the N-acylthiadiazinone **2**. The Ca-sensitizing effect is highly stereospecific and resides in the (+)-enantiomer. The (-)-entantiomer is a pure PDE inhibitor devoid of any Ca-sensitizing activity.

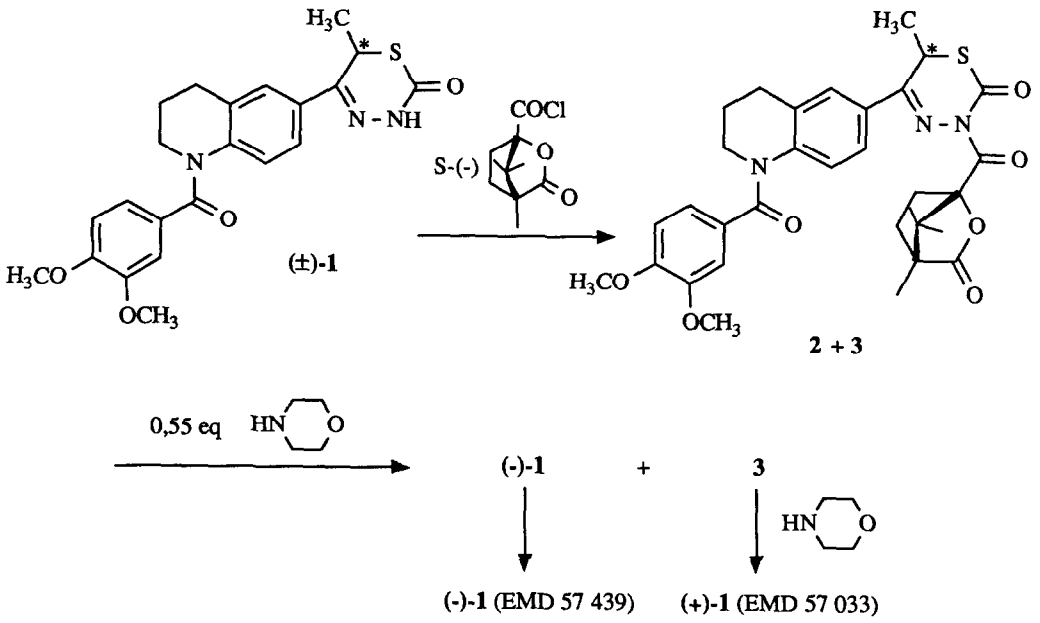
The sensitization of contractile proteins to calcium constitutes an attractive new approach to the treatment of heart failure[1]. Ca-sensitizers are devoid of the disadvantageous calcium overload caused by other inotropic interventions which may lead to serious arrhythmias[2]. It has been claimed that some newer inotropic compounds, e. g. Sulmazole[3], Isomazole[4], Pimobendane[5] and MCI-154[6] have calcium sensitizing activity. However, they mainly act through their strong PDE-inhibiting activity.

During our search for more specific Ca-sensitizers, we discovered a new class of cardiotonic agents, the 5-(1-acyl-tetrahydroquinolyl)-thiadiazinones. The synthetic procedures have been disclosed in a patent application[7]. Among various analogs 3,6-Dihydro-5-[1,2,3,4-tetrahydro-1-(3,4-dimethoxybenzoyl)-6-quinolyl]-6-methyl-2H-1,3,4-thiadiazin-2-one (**1**), EMD 53 998, exhibited promising activity. In vitro studies revealed a dual mechanism of action: it potently increases the calcium responsiveness of cardiac contractile proteins; and, it selectively inhibits PDE III[8]. In order to evaluate the stereoselectivity of these two modes of action, the pure enantiomers were needed. Here we describe the synthesis and preliminary in vitro results of the enantiomers of EMD 53 998.



1 (EMD 53 998)

Enantiomerically pure thiadiazinones have not been previously reported. Our approach was based on the kinetic resolution of the diastereomeric N-acylthiadiazinones **2** and **3**. Cleavage of 3-acetylthiadiazinones by mild methanolysis has been reported[9]. Acylation of **1** with chiral acid chlorides afforded a 1 : 1 mixture of diastereoisomers. Cleavage of the diastereomeric acylthiadiazinones was found to be highly stereoselective. The most favourable results were obtained by aminolysis using secondary amines. Thus, reaction of racemic **1** with S-(-)-camphanoylchloride ($N(Et)_3$, CH_2Cl_2, rt) provided a 1 : 1 mixture of diastereoisomers **2** and **3** in 95 % yield. Subsequent treatment with 0.55 eq. of morpholine (CH_2Cl_2; 5°C, 24 h) afforded (-)-**1** of 75 % ee[10] together with the unreacted diastereoisomer **3** of 99 % de. (-)-**1** was separated from unreacted **3** by chromatography and further purified by crystallization, whereby the racemate selectively crystallizes and leaves behind the (-)-enantiomer (EMD 57 439) of 99,4 % ee (mp 160°C, $[\alpha]_D^{20}$ -515,0° (c = 1; CH_2Cl_2). The diastereoisomer **3** was treated as before to give enantiomerically pure (+)-**1** (EMD 57 033) (mp 160°C, $[\alpha]_D^{20}$ +521,7°C (c = 1; CH_2Cl_2) in 90 % yield. For multigram scale preparation of (-)-**1**, it was more convenient to use the other antipode of camphanic acid for the acylation of **1**, followed by kinetic resolution and cleavage of the unreacted diastereoisomer.



Preliminary results of these compounds on Ca-induced force development in skinned cardiac fibers[4] (as a measure for Ca-sensitization) and on the activity of isolated PDE III isoenzyme[11] from guinea pig hearts are sumarized in table 1.

Table 1

	EC_{50} [μM]		IC_{50} [μM]
EMD 53 998	4.8	(2.5 - 9.0)	0.06 ± 0.01
EMD 57 033	1.7	(1.0 - 3.5)	1.94 ± 0.11
EMD 57 439	>100		0.05 ± 0.01

EC_{50}: Drug concentration which increased force in skinned fibers at constant buffered Ca-concentration by 50 % (X 95 % confidence limits).

IC_{50}: Drug concentration which inhibited the activity of purified PDE III isoenzyme by 50 %. (X ± SEM).

The results show clearly that only the (+)-enantiomer EMD 57 033 exhibits strong Ca-sensitizing activity, indicating a high stereospecifity of this mode of action. The (-)-enantiomer EMD 57 439 is a potent PDE III-inhibitor with no effect on Ca-sensitization. A detailed report on the biological effects of the enantiomers will be published elsewhere[12].

References and Notes

1. Lee, J. A.; Allen, D. G. Br. Med. J. **1990**, 300, 551
2. Kass, R. S.; Lederer, W. J.; Trier, R. W.; Weingart, R. J. Physiol. (London) **1978**, 281, 187
3. Henig, J. W.; Feike, K.; Rüegg, J. C. Arzneimittelforschung **1981**, 31, 188
4. Lues, I.; Siegel, R. Harting, J. Europ. J. Pharmacol. **1988**, 146, 145
5. Meel van, J. Arzneimittelforschung/Drug Res. **1987**, 37, 679
6. Kitada, Y.; Morita, M.; Narimatsu, A. Japan J. Pharmacol. **1988**, 50, 4117
7. Europ. Pat. 0294647 (25.5.1988)
8. Beier, N.; Harting, J.; Jonas, R.; Klockow, M.; Lues, I., and Häusler, G. J. Cardiovasc. Pharmacol. **1991**, 18, 17
9. Ege, G.; Arnold, P., Joors, P. Noronka, R. Liebigs Ann. Chem. **1977**, 94, 791
10. The optical purity of the enantiomers was determined by HPLC analysis using a Chiraspher column.
11. Honerjäger, P.; Klockow, M.; Schönsteiner, G.; Jonas, R.; J. Cardiovasc. Pharmacol. **1989**, 13, 673
12. Lues, I.; Beier, N.; Jonas, R.; Klockow, M.; Häusler, G. (submitted for publication).