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Stereoselectivity of the Positive Inotropic Effects of Newer Diazinone-Cardiotonics

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Dedicated to Prof. Dr. H.-J. Langmann on the occasion of his 70th birthday.

Abstract: In 5-methyl-dihydropyridazinones, a stereoselectivity is observed only with respect to the phosphodiesterase III-inhibition. The (-)-enantiomers are very strong inhibitors whereas their (+)-counterparts exibit only a weak activity. In the case of the thiadiazinone EMD 53998 a pronounced stereoselectivity regarding Ca-sensitivity and phosphodiesterase inhibition is apparent. It is concluded that Levosimendan exerts its positive inotropism almost exclusively through its potent phosphodiesterase III-inhibitory effect.

In the current literature a number of diazinones, mainly pyridazinones[1], have been described as cardiotonic agents[2].

Most of these pyridazinones have been identified as powerful inhibitors of phosphodiesterase isotype III (PDE III). Some of these substances possess an additional Ca-sensitising effect.

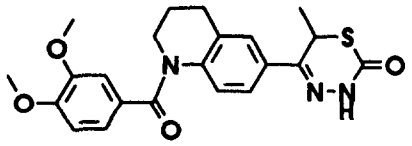
From structure-activity studies with these compounds it became clear that a methyl group in position 5 of the diazinone ring is essential for maximal inotropic potency[3]. This methyl group renders the molecule asymmetric. The (+)- and (-)-enantiomers display different inotropic effects. This has not been investigated in detail.

In the search for more effective Ca-sensitisers we found in the structural class of the quinolyl-thiadiazinones highly potent compounds, e.g. EMD 53998[4].

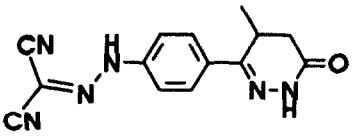
Recently, Ca-sensitisation has been extensively discussed as a new mechanism to improve the contractility of the failing heart. Such a mechanism has been greeted as a possibility to improve the contractility without increasing the oxygen demand. Because the cytosolic free

calcium transient is not increased, Ca-sensitisers should also be devoid of any arrhythmogenic potential.

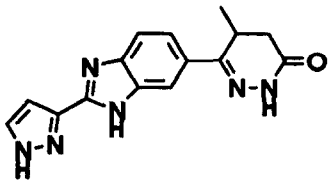
Here we have compiled some newer positive inotropic agents which possess a Ca-sensitising effect according to the literature. The listed compounds all have in common a powerful inhibition of the PDE III, which we think is mainly responsible for their positive inotropic effect combined with a favourable vasodilation[5]. The Ca-sensitising effect is orders of magnitude smaller.



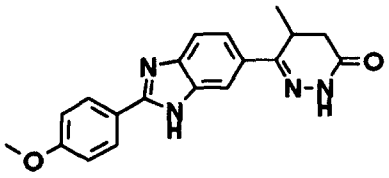
EMD 53998



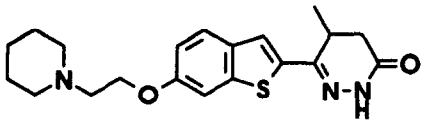
Simendan



Meribendan



Pimobendan



ORG 20494

So far only scarce information is available as to the stereoselectivity of the cardiotonic effect of either mechanism. Therefore we studied the pure enantiomers of the compounds listed in regard to their inhibition of PDE III[6] and Ca-sensitivity[7].

It is apparent that the (-)-enantiomers are the more potent PDE III-inhibitors. Based on the good differentiation of the PDE-inhibitory and Ca-sensitising effect in the class of the thiadiazinones we investigated the stereoselectivity of these effects.

Compound		Ca-sens. [EC_{50}]μM*	PDE III-inhib. [IC_{50}]μM**
EMD 53998 (rac.)			
EMD 57033	(+)	1.7(1.0-3.5)	1.94 ±0.11
EMD 57439	(-)	> 100	0.05 ±0.01
Simendan[8] (rac.)			
	(+)	>> 100	1.5 ±0.4
Levosimendan	(-)	>> 100	0.008 ±0.001
Meribendan[9] (rac.)			
	(+)	470 (380-590)	1.6 ±0.6
	(-)	190 (93-390)	0.04 ±0.01
Pimobendan (rac.)			
	(+)	152 (113-202)	19.0 ±3.5
	(-)	100 (67-149)	0.41 ±0.14
ORG 20494[***10] (rac.)			
	(+)	+	14.8
	(-)	no effect	0.08

*(±95% confidence limits) **±SD ***These data are taken from Lit. 9.

Discussion

From the table it is clear that the PDE III-inhibitory effect resides most prominently in the (-)-enantiomer[11]. This is valid for all diazinones discussed in this work. Because of the structural diversity of the compounds listed we prefer to claim that this holds true for all diazinones.

Regarding the Ca-sensitising effect, the situation is less clear-cut. In the case of the pyridazinones, the differences are not very conclusive, due to the minute effect. A more pronounced Ca-sensitisation is found in the thiadiazinones[12,13]. These display a powerful Ca-sensitising effect while maintaining the same order of PDE III-inhibitory potency as the pyridazinones. Here the Ca-sensitising effect resides in the (+)-enantiomer with the weaker PDE-inhibitory potency. Therefore in this class an unambiguous stereoselectivity of either mechanism responsible for the cardiotonic effect is found.

The results clearly show that only the (+)-enantiomers exhibit strong Ca-sensitising activity, indicating a high stereoselectivity of this mode of action. The (-)-enantiomers are consistently potent PDE-III inhibitors with no significant effect on Ca-sensitisation.

From the data presented in this paper it is quite apparent that even the racemate EMD 53998 is a powerful Ca-sensitiser.

Lately, Levosimendan, the (-)-enantiomer of the racemic Simendan, has been claimed as a Ca-sensitiser[14,15] and was studied in comparison to EMD 53998, which is the racemate of EMD 57033.

In our hands Levosimendan is completely devoid of any Ca-sensitising effect.

We therefore conclude that Levosimendan exerts its activity solely via the inhibition of PDE-III which is in accordance with the data shown.

References and Notes

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