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Synthesis and Pharmacological Properties of Nebivolol, a new antihypertensive compound

RESUME

La synthèse des α,α' (iminobis(méthylène))-bis-(3,4-dihydro-2H-1benzopyran-2-méthanol) substitués ainsi que la stéréochimie et l'activité biologique de cette nouvelle classe de composés antihypertenseurs sont décrites. Enfin, la sélection et l'activité biologique du composé préféré, le nebivolol et ses énantiomeres, sont discutées.

SUMMARY

The synthesis of α,α' (iminobis(methylene))-bis-(3,4-dihydro-2H-1benzopyran-2-methanol) derivatives and the stereochemistry and pharmacological profile of this new class of antihypertensive compounds are described. Finally, the selection and pharmacological profile of the preferred compound of this series, nebivolol and its enantiomers, is discussed.

All the currently investigated β-blockers are derivatives of ethanolamine. Some of them belong to the hydroxyphenetylamine type, the vast majority however has the phenoxypropanolamine structure (fig. 1).
Already in the early days of β-blockers, cyclic analogs of these phenoxypropanolamines have been synthetized (1). (fig. 2).
The chromanes were shown at that time to be less active than other cyclic analogs and so, for many years, they remained unexplored in this field.
However, when we synthetized a number of analogs with more complex N-substituents, we observed that a number of these compounds showed excellent β-blocking properties. Especially

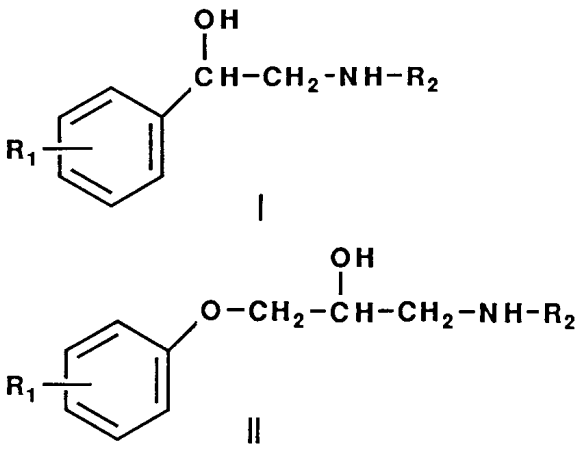
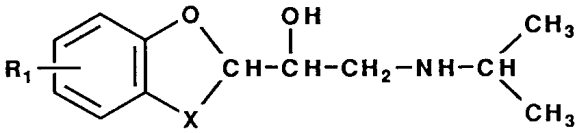


Fig. 1



X : $-CH_2-CH_2$: CHROMANES

Fig. 2

the symmetric double structures (fig. 3) were very interesting.
These compounds not only had a high affinity for the β-adrenergic receptor, but they showed also an immediate antihypertensive effect in spontaneous hypertensive rats, an observation not common to the classical β-blockers. Moreover, in vivo, these compounds showed an attractive

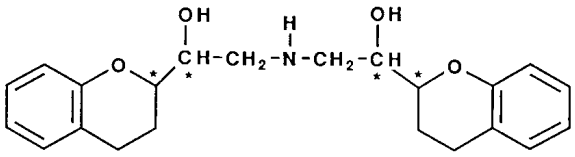
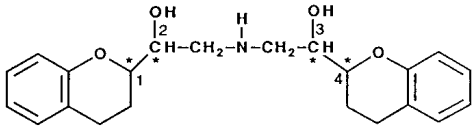


Fig. 3

haemodynamic profile: small doses gave a reduction in peripheral resistance and cardiac function was not impaired. Enough reasons to induce a more systematic study of these molecules.
For the medicinal chemist, these compounds were also challenging: these structures have four asymmetric carbon atoms and so 10 stereoisomers are possible. Asymmetrical substitution even leads to a mixture of 16 stereoisomers.
As separation of these isomers in the endproducts is not very practical, we successfully developed a stereoselective synthesis route, allowing us to synthetize unambiguously each of the isomers (fig. 6).
Starting from the known benzopyrane -2- carboxylic acid, the key epoxide can be prepared via the aldehyde. The two diastereoisomers of the epoxide can be separated by HPLC and combination of these with benzylamine followed by hydrogenolysis gives the final products.
When we start now with enantiomerically pure benzopyrane -2- carboxylic acid instead of with the racemic mixture, it is possible to obtain the 4 isomers of the epoxide. Combination of these leads to the 10 stereoisomers of the final product.
Starting from substituted benzopyrane -2- carboxylic acids, substituted analogues can be synthetized essentially via the same scheme.

BETA ANTAGONISTS
R 59902 AND STEREO-ISOMERS

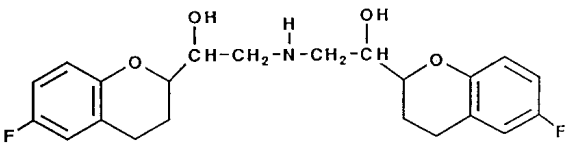


Rnr	CONFIGURATION 1*	2*	3*	4*	ED_{50} ATRIUM** β_1	ED_{50} TRACHEA** β_2
R 59534	S	R	S	S	0.00125	2.5
R 59536	S	R	R	R	0.00063	0.63
R 59537	R	S	S	S	>0.0025	>2.5
R 59538	R	S	R	R	0.00125	>2.5
R 59902	S	R	R	S	0.00051	3
R 59904	S	R	S	R	>0.0025	>10
R 61045	R	S	S	R	>0.0025	>10
R 61048	R	R	S	S	>0.0025	>10
R 61050	R	R	R	R	>0.0025	8.95
R 61630	S	S	S	S	>0.0025	>10

** ED_{50} : inhibition of isoprenaline after 60 minutes mg/l

Fig. 4

The screening results of the β-blockade for the unsubstituted isomers are show in fig. 4.
As could be expected, some of the isomers are highly active β-blockers whereas others are almost inactive.



SRRR + RSSS

NEBIVOLOL

SRRR	RSSS
d-NEBIVOLOL	l-NEBIVOLOL
R 67138	R 67145

Fig. 5

The most potent compound at that time «R59902» was studied in more detail. Some surprises came out of this research.

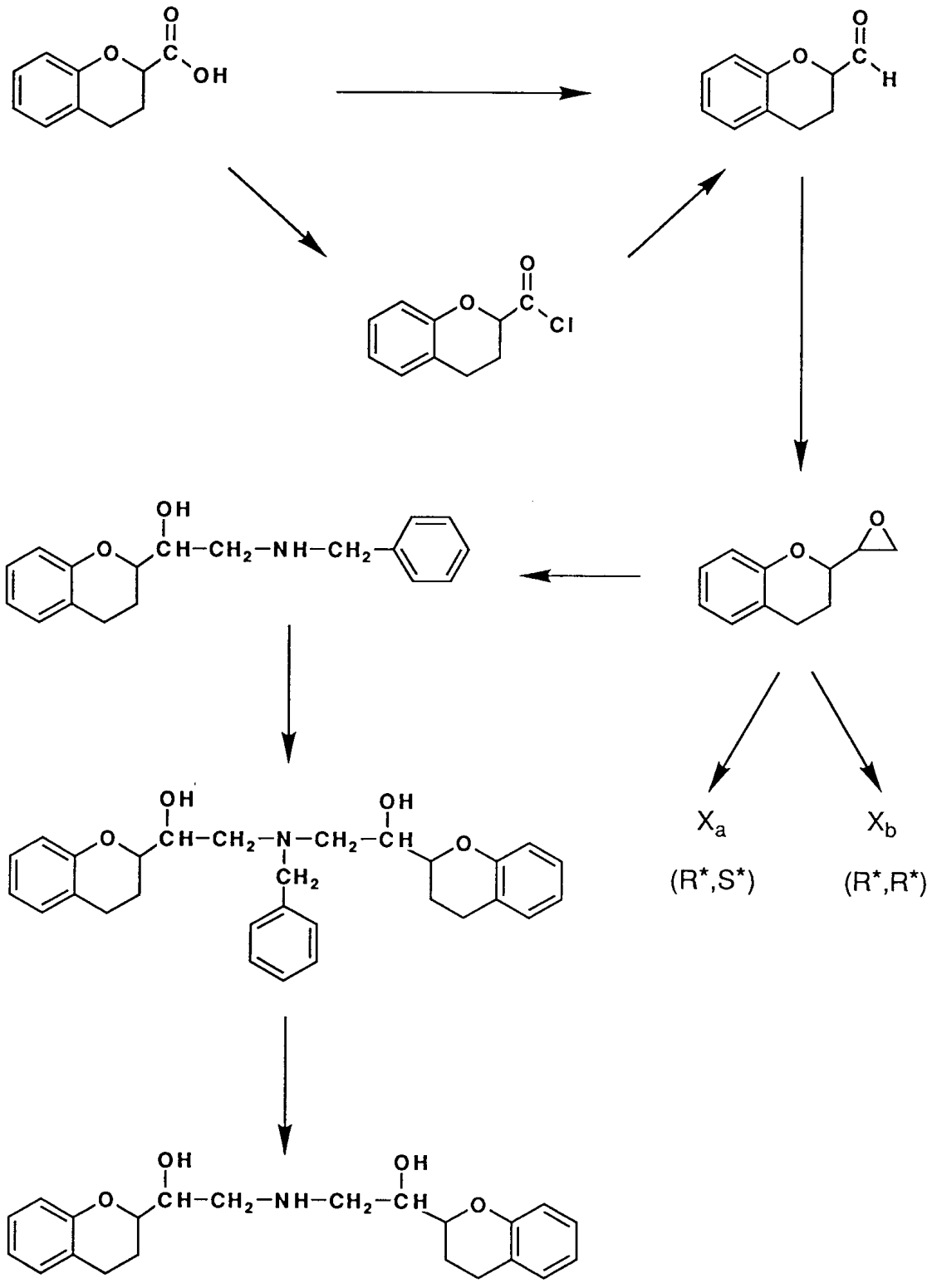


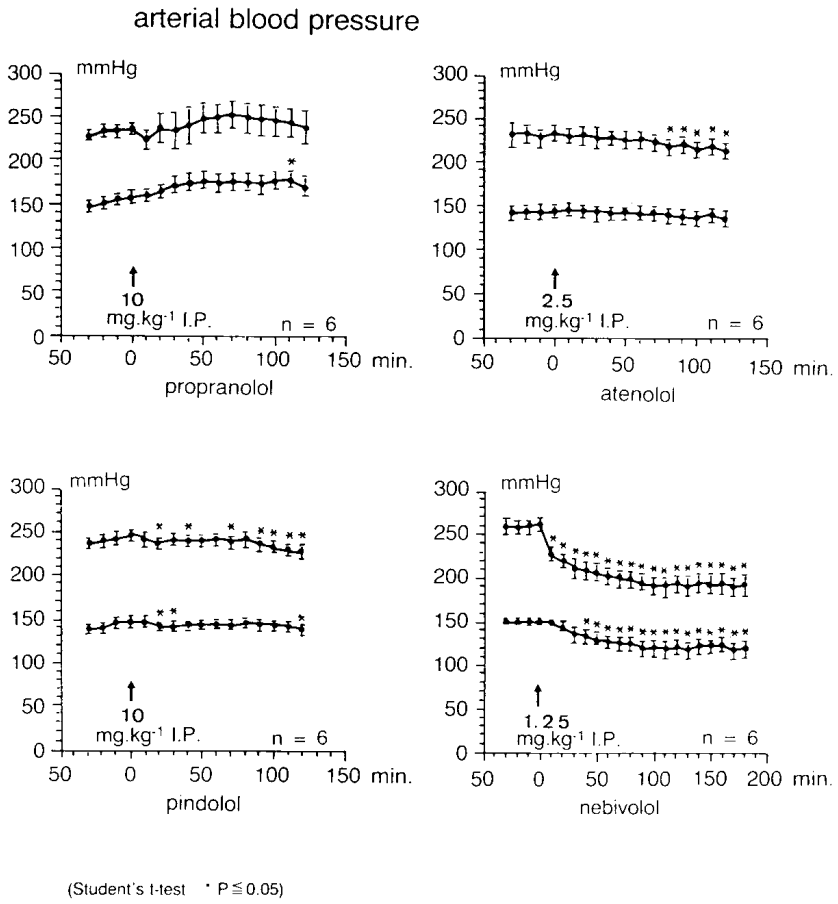
Fig. 6

β-blocking properties of the isomers of nebivolol.

	rat cortex	Receptor binding		*in vitro* isoprenaline inhibition guinea pig atrium
		rabbit lung	rat lung	
		-log IC_{50}		ED_{50} after 60'
	β^a	β_1	β_2	mg/l
Nebivolol	3	8.72	6.57	0.00040
d-nebivolol	3	8.95	6.96	0.00037
l-nebivolol	1	6.53	5.66	>0.0025

activity score 3 : -log IC_{50} >8, score 2 : 8 > -log IC_{50} > 6, score 1 : 6 > -log IC_{50}.

Fig. 7



(Student's t-test * $P \leq 0.05$)

Fig. 8

Firstly the crystallographic structure of the compound was determinded by X-ray diffraction analysis in the laboratory of Prof. C. De Ranter (2). This analysis gave us the absolute configuration SRRS for R59902. This finding is contradictory to the generally accepted rule which states that the active isomer of a β-blocker must have the S-configuration on the hydroxyl-bearing carbon atoms.

Secondly, despite of R59902 being a very potent β-blocker pharmacologists were much less satisfied with its general haemodynamic profile. Indeed, in vivo, this compound behaves as a classical β-blocking agent including increased systemic vascular resistance and negative influence on cardiac function.

This gave us a first indication that the desired haemodynamic profile observed in the mixtures studied before, could not be obtained within a single isomer.

In the mean time, we synthetized a large number of substituted analogs which were screened, not only for β-blockade but also for their haemodynamic properties. It was clear that the SAR in our series was rather different from the one found in the «open» compounds. For instance, substituents normally improving β1/β2 selectivity didn't improve this factor in our series. It was also clear that β-blockade and immediate antihypertensive effect were not correlated; it was possible to synthetize derivatives with good blood pressure reduction and only moderate β-blocking properties and vice-versa.

Finally, after comparison of the pharmacological data of all these analogs, Nebivolol was selected for further study.

Nebivolol is the racemic mixture of the RSSS and SRRR isomers of the 6,6' bisfluoro compound (fig. 5).

The next figures will give a summary of some important pharmacological properties of this compound.

On figure 7 we can see the in vitro β-blocking properties of Nebivolol and its enantiomers. It is clear that nebivolol is a strong β_1 selective compound and that the β-blocking properties are due to the d-enantiomer (3, 4).

However l-nebivolol plays an important role in the rest of the haemodynamic profile of nebivolol. Figure 8 shows the effect of nebivolol and three classical β-blockers on arterial blood pressure of hypertensive rats. It can be seen that nebivolol lowers very nicely arterial pressure whereas the other β-blockers are inactive in this model.

On figure 9 we can see the effects of the different enantiomers and the racemate on arterial pressure and heart rate. It can be seen that l-nebivolol, being inactive on its own, has a significant synergistic effect on the antihypertensive effect of d-nebivolol.

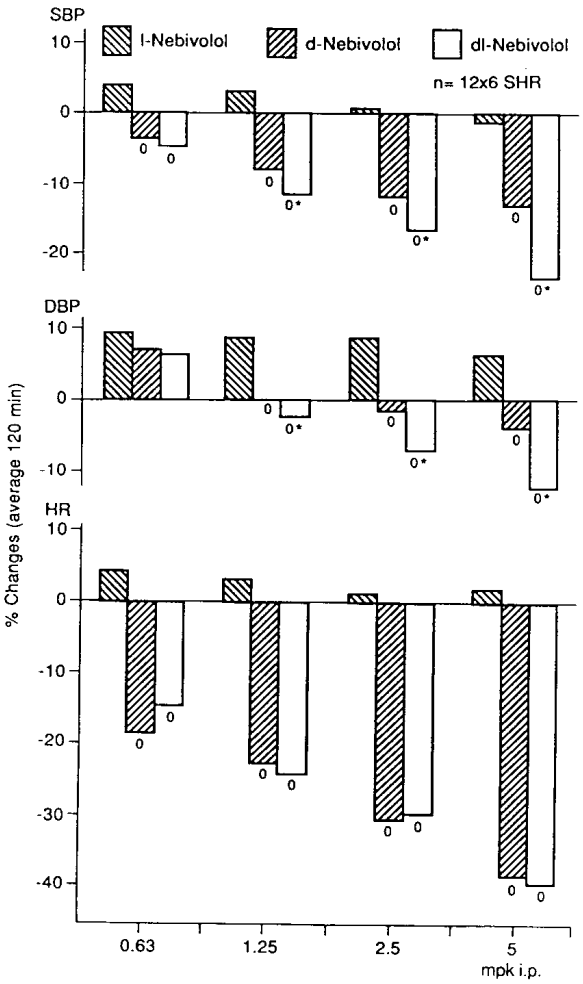


Fig. 9

Further studies indicate that this synergistic effect of l-nebivolol on the antihypertensive properties is not restricted to d-nebivolol, but also other molecules undergo the same effect (propranolol, atenolol, metoprolol). Even the antihypertensive effect of some non-β-blocking drugs is amplified by l-nebivolol (prazosin, hydralazine, phentolamine). On the other hand, other antihypertensives are not influenced (pindolol, celiprolol, clonidine).

At present, the mechanism of this amplification is not fully understood although we believe that the promising pharmacological properties of

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