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Phosphodiesterase Inhibitory Properties of Losartan. Design and Synthesis of New Lead Compounds

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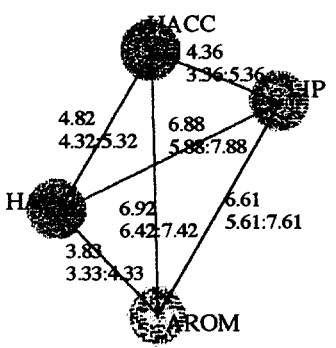
Abstract- A 4-centre PDE 4 pharmacophore search has been carried out in several 3D-databases containing compounds belonging to different therapeutic areas. Losartan, an angiotensin-II antagonist, has been identified as a new lead compound for developping PDE 4 inhibitors. New families of compounds derived from losartan has been synthesized and their PDE inhibition has been measured. © 1998 Elsevier Science Ltd. All rights reserved.

In recent years there has been a renewed interest in the potential utility of isoenzyme-selective phosphodiesterase (PDE) inhibitors.[1,2] There are at present seven PDE isoenzymes (PDE 1-7) which share the property of hydrolysing cyclic nucleotides to their corresponding 5-monophosphates counterparts. At the present time, most of the interest on the potential use of selective PDE inhibitors is focused on drugs capable of inhibiting the cAMP-specific PDE 4 as a possible treatment for allergic diseases such as asthma.[3,4] Although PDE 4 inhibitors can be divided into three structural classes,[5] those related to rolipram, and to xantine and quinazolinedione nuclei, the pharmacological profile of nitraquazone focused our research in discovering new leads related to this compound.[6]



Centre	Centre	Value	Tolerance
HACC	HACC	4.8253	0.5
HACC	AROM	3.8337	0.5
HACC	LIP	6.8813	1.0
HACC	AROM	6.9204	0.5
HACC	LIP	4.3624	1.0
AROM	LIP	6.6183	1.0

Figure 1.- 4-centre PDE 4 pharmacophore

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Initially, an interaction approach based on GRID maps, has been applied to describe a pharmacophoric model[7] that includes different types of phosphodiesterase inhibitors related to the nitraquazone structure.[8,9] A simplified model is shown in figure 1 and consists of two hydrogen bond acceptors, one aromatic ring and a hydrophobic center.

Three-dimensional pharmacophore searching of large databases has proven to be a valuable tool in the drug discovery process.[10-12] From our 4-center simplified model, a 3D-pharmacophore search has been carried out in several 3D-databases containing corporate compounds and standards belonging to different therapeutic areas. 3D-databases were built from the 2D structures using the program Chem-X.[13,14] During the search, conformation flexibility was taken into account applying the flexifit algorithm implemented in Chem-X. A tolerance of 0.5 Å was allowed, except when a hydrofobic center was present, in which a tolerance of 0.1 Å was allowed.

From the hits found in the 3D-search, losartan, an angiotensin-II antagonist, was identified as one of the most relevant. Figure 2 shows the molecular fitting between losartan and PDE 4 pharmacophore used in the search. The inhibition of PDE 4 by losartan has not been described previously, although the compound is known to weakly interact with the calcium and calmodulin dependent PDE (PDE 1).[15,16]

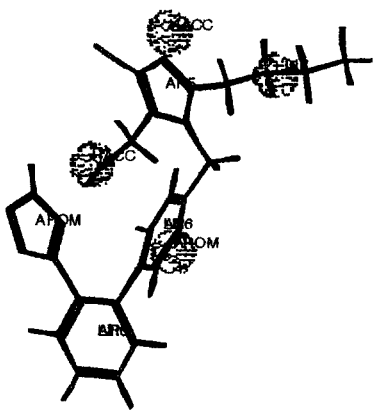


Figure 2.- Losartan fitted into PDE 4 pharmacophore

Losartan was tested against the cAMP-specific PDEs as previously described, [17] and found to have IC_{50} values for PDE 3 and PDE 4 of 13 ± 3 μM and 26 ± 0.5 μM, respectively. These results suggest that losartan can be considered as a new cAMP-specific PDE inhibitor lead compound.

In order to increase both inhibitory potency and selectivity, new compound families derived from losartan were designed. In all cases we attempted to design new compounds with structural and electronical profiles compatible with the proposed pharmacophoric model (Figure 3). Two strategies were followed. In the first one, a fused aromatic ring was added to the heterocyclic moiety, and in the second, tertiary amines with appropiate substituents were synthesized with the aim of alleviating conformational restrictions.

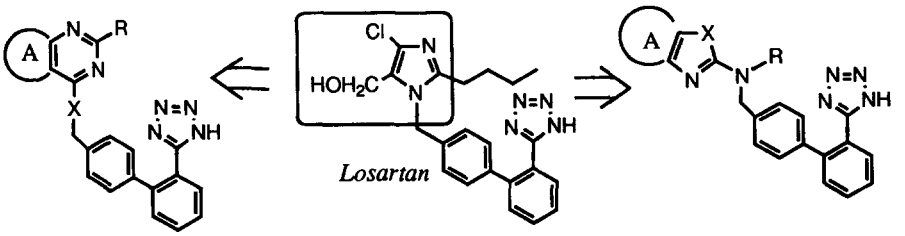
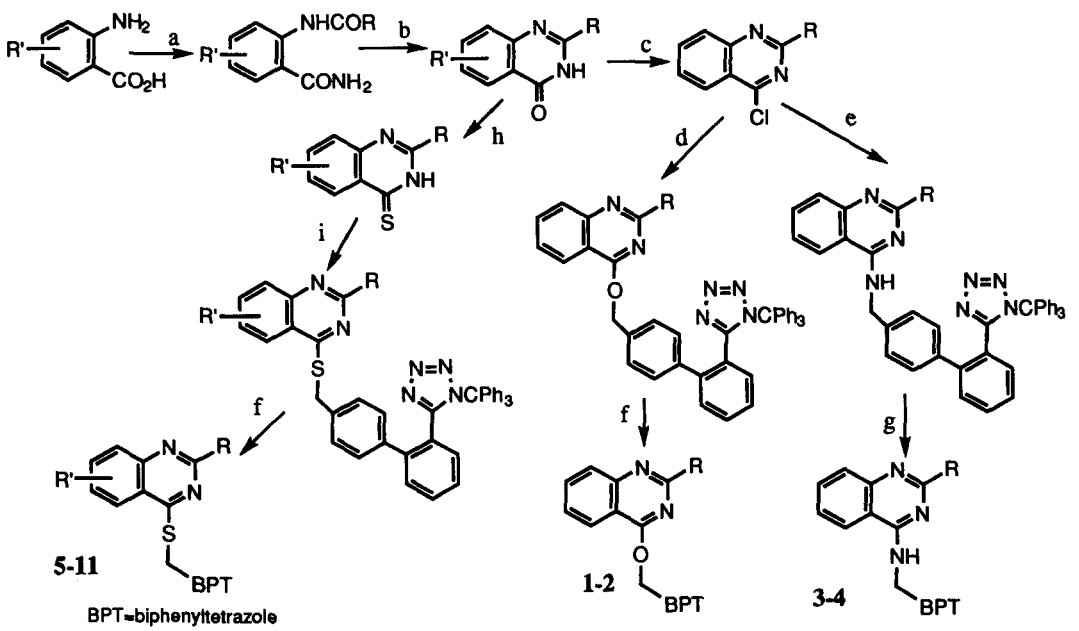


Figure 3

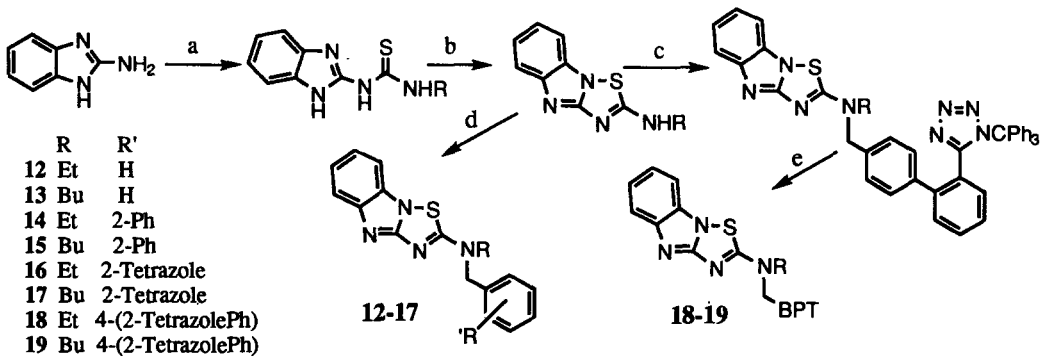
Synthesis: The quinazolines were prepared as shown in Scheme 1, according to synthetic routes described in the literature.[18-20]



a) 140°C, $(RCO)_2O$, then NH_3 30% r.t.; b) NaOH 2N/Δ; c) $POCl_3$, diisopropylamine, $PhCH_3$/Δ; d) $CPh_3BPT\text{-}CH_2OH$,[21] HNa, DMSO, r.t.; e) $CPh_3BPT\text{-}CH_2NH_2$,[22] diisopropylamine, THF/Δ; f) MeOH/Δ; g) HCl(g), THF; h) Lawesson'reagent, $PhCH_3$/Δ; i) $CPh_3BPT\text{-}CH_2Br$,[23] K_2CO_3, DMF.

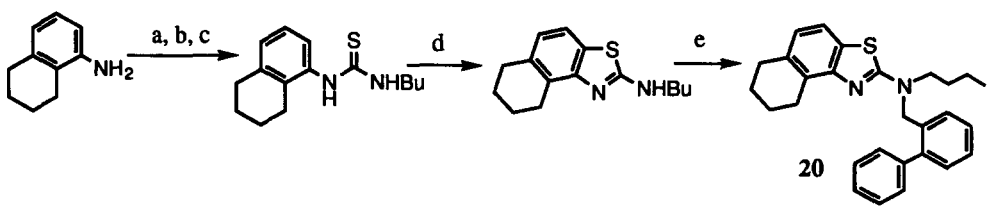
Scheme 1

The synthesis of the tertiary amines was accomplished by a final alkylation of N-alkyl,N'-aryl-amines (Scheme 2 and 3). These compounds were prepared taking profit from the thioureas oxidation properties which open a facile synthetic pathway to many heterocyclic systems.[24,25]



a) R=N=C=S, THF/Δ; b) H_2O_2/NaOH; c) $CPh_3BPT\text{-}CH_2Br$,[23] NaH, DMF/Δ; d) Ar-CH_2Br, NaH, DMF/Δ; e) HCl (10%), THF.

Scheme 2

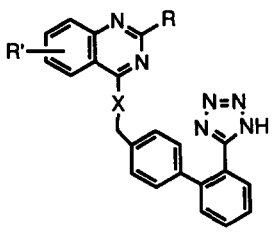


a) CS_2, Et_3N; b) IMe, MeOH; c) Bu-NH_2, THF; d) Cl_2SO_2, $CHCl_3$; e) Ar-CH_2Br, HCO_3Na, H_2O

Scheme 3

Biological evaluation: Compounds **1-20** were assayed as inhibitors of cAMP-specific phosphodiesterase (PDE 4) isolated from guinea pigs ventricular tissue. Selectivity versus cGMP-inhibited phosphodiesterase (PDE 3) isolated from the same tissue, was also determined. Quinazolines **1-11** showed good PDE 4 inhibitory properties but poor PDE 3 selectivity (Table 1). By contrast, compounds **12-20** belonging to the tertiary amines series are less potent PDE 4 inhibitors (IC_{50} around 30 μM for the most active compounds, Table 2) but without activity in the PDE 3 assay (IC_{50} greater than 200 μM in most cases).

Preliminary SAR in the quinazoline series showed that compounds with a sulfur bridge between the fused heterocycle and the biphenyltetrazole are more active than those with an oxygen or amine bridge. The inhibition potency increases in this series with the number of carbon atoms of the alkyl chain attached to the heterocycle, whilst substitution of the benzene fused ring in the position 8 decreases the biological activity.

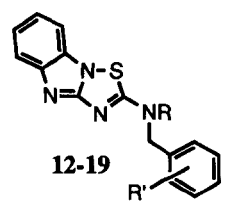


1-11

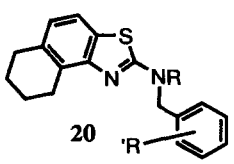
Table 1.- Biological activity of quinazolines
IC_{50} μM (±S.E.M.)

Comp.	X	R	R'	PDE 4	PDE 3
1	O	Et	H	14 ± 0	5.8 ± 0.25
2	O	Bu	H	7.9 ± 0.15	5.4 ± 0.5
3	NH	Et	H	21 ± 3.0	24 ± 2.5
4	NH	Bu	H	7.6 ± 2.3	16 ± 1.5
5	S	Et	H	3.3 ± 0.4	7.0 ± 2.0
6	S	Bu	H	2.9 ± 0.4	8 ± 1.7
7	S	Pr	H	3.8 ± 0.15	6.8 ± 1.3
8	S	^{i}Pr	H	3.8 ± 0.6	2.4 ± 0.2
9	S	Me	H	15 ± 4.0	4.8 ± 2.2
10	S	Pr	6-Me	3.8 ± 0.2	2.4 ± 1.1
11	S	Pr	6,8-diMe	8.6 ± 0.15	11 ± 2.8

In the series of tertiary amines, compounds which contain the tetrazole ring were less potent against PDE 4 and less selective against PDE 3 than the structures without the tetrazole moiety.



12-19



20

Table 2.- Biological activity of tertiary amines .
IC50 μM (± S.E.M.) or % inh. (± S.E.M.) @ dose μM

Comp.	R	R'	PDE 4	PDE 3
12	Et	H	32 ± 10	12% ± 5 @ 200
13	Bu	H	90 ± 38	0% ± 0 @ 200
14	Et	2-Ph	48 ± 2	41% ± 13 @ 200
15	Bu	2-Ph	30 ± 9	31% ± 19 @ 200
16	Et	2-Tetrazole	107 ±50	15% ± 50 @ 200
17	Bu	2-Tetrazole	44% ± 3 @ 200	32% ± 11 @ 200
18	Et	4-(2-TetrazolePh)	74 ± 21	125 ± 8
19	Bu	4-(2-TetrazolePh)	48% ± 2 @ 200	50% ± 7 @ 200
20	Bu	2-Ph	42 ± 4	15% ± 5 @ 200

In conclusion, we have determined a pharmacophore for PDE 4 inhibitors which has led to discovery trough a 3D-database pharmacophoric search, the phosphodiesterase 4 inhibitory properties of losartan. New series of compounds based on losartan, have been designed and synthesized and show promising biochemical profiles.The further optimisation of leads as **6** is underway with the objetive of obtaining a development compound for the treatment of inflamatory diseases such as asthma.

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