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(1,4-Benzothiazinyloxy)alkylpiperazine Derivatives as Potential Antihypertensive Agents

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Abstract—A series of compounds having a piperazine moiety variously linked to the benzothiazine nucleus were synthesized and evaluated for their in vitro α-adrenoceptor affinity by radioligand receptor binding assays. Some compounds bearing a oxyalkyl-(2-methoxyphenyl)piperazine side chain were good α_1-adrenoreceptor ligands.

In our research program on antihypertensive agents, we previously described (1,4-benzothiazinyloxy)propanolamine derivatives with a potent β-adrenoceptor blocking activity,[1,2] as well as with combined β-blocking/diuretic properties achieved by a symbiotic approach.[3,4] As an extension of this investigation on benzothiazine derivatives with antihypertensive properties, the 1,4-benzothiazine nucleus has now been variously functionalized with phenylpiperazine (PP) or acylpiperazine (AP) moieties in order to drive the activity towards the α-andrenoceptor (α-AR).

The rationale of this design is due to the high affinity for α-AR, and particularly for α_1-AR, displayed by AP-containing products (e.g. prazosin) or PP-containing products (e.g. urapidil, naftopidil) (Fig. 1). In fact, these moieties furnish an electron-rich aromatic area coupled to a protonable nitrogen atom at a suitable distance which is one of the principal requirements of the ligand for binding to the α_1-AR protein.[5–7]

Thus, looking at naftopidil as a selective α_1-AR blocking template, we decided to insert selected piperazine moieties, instead of a secondary amine, into the oxypropanolamine side chain of the 1,4-benzothiazine derivatives **1**, previously reported to be β-AR antagonists.[1] Accordingly, (1,4-benzothiazinyloxy)propanolpiperazine derivatives **3a–c→6a–c** were synthesized (Fig. 2).

In the radioligand receptor binding assay, some of these synthesized compounds showed notable affinity and selectivity for the α_1-AR, while, as expected, any β-AR affinity was retained. Therefore, to evaluate how the bridge linking the 1,4-benzothiazine nucleus to piperazine moiety affects the α-AR affinity, the oxypropanolpiperazine side chain was modified by eliminating the secondary alcoholic group and then shortening it by one methylene unit to obtain (1,4-benzothiazinyloxy)-propyl- **10a–c** and (1,4-benzothiazinyloxy)ethyl-piperazine derivatives **11a–c**, respectively (Fig. 2). These changes were made by fixing the 1-(2-methoxyphenyl)-piperazine moiety, since it provided compounds with the highest α_1-AR affinity.

Finally, considering that a combined therapy with α- and β-adrenergic blocking agents has synergic effectiveness in hypertension treatment,[8] derivative **13** was synthesized according to a symbiotic approach. It was obtained from the insertion of 3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl side chain, as α-AR activity carrier, at the N-4 position of the 8-[(3-*tert*-butylamino)-2-hydroxypropoxy]-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine derivative (**12**),[1] a potent β-blocker previously synthesized by us (Scheme 3). For a comparison, derivative **15**, devoid of pharmacophoric β-blocking side chain, was also synthesized and tested.

Chemistry

The (1,4-benzothiazinyloxy)propanolpiperazine derivatives **3a–c→6a–c** were synthesized, as illustrated in Scheme 1, by reaction of appropriate epoxide **2a–c**[1] with equimolar amounts of selected piperazine derivative in absolute EtOH.

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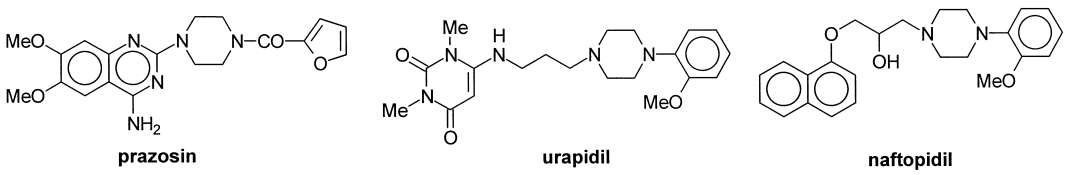


Figure 1.

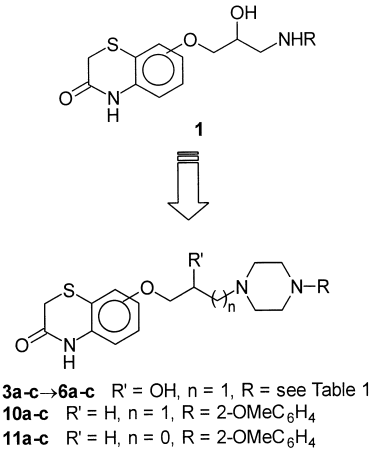


Figure 2.

The reaction of the sodium salt of a suitable hydroxybenzothiazine **7a**–**c**[1] with chloroalkylpiperazine derivative **8**[9] and **9**[9] gave (1,4-benzothiazinyloxy)propyl-**10a**–**c** and (1,4-benzothiazinyloxy)ethyl-piperazine derivatives **11a**–**c**, respectively, as reported in Scheme 2. The chloropropylpiperazine derivative **8** was also reacted, as illustrated in Scheme 3, with β-blocker **12** as well as with benzothiazine **14** in the presence of K_2CO_3 affording compounds **13** and **15**, respectively.

Chemical and physical data of newly synthesized compounds are reported in Tables 1–3. ^{1}H NMR data were consistent with the proposed structures.

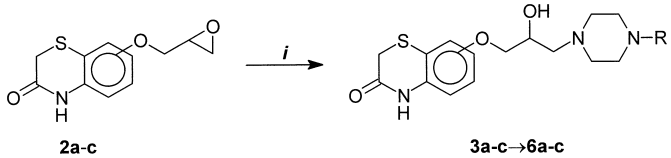
Biological Evaluation

The compounds described in this study were evaluated for their α_1-AR, α_2-AR, β_1-AR, and β_2-AR binding affinities assessed by measuring the displacement of [^{3}H]prazosin binding in rat brain,[10] [^{3}H]clonidin binding in rat cerebral cortex,[11] [^{3}H]dihydroalprenolol ([^{3}H]-DHA) binding in rat heart,[12] and in rat lung,[12] respectively. For (1,4-benzothiazinyloxy)propyl- **10a**–**c** and (1,4-benzothiazinyloxy)ethyl-piperazine derivatives **11a**–**c**, as well as for compound **15**, the β_1-AR and β_2-AR affinities were not evaluated because these compounds lack the structural requirements for interacting with this receptor.

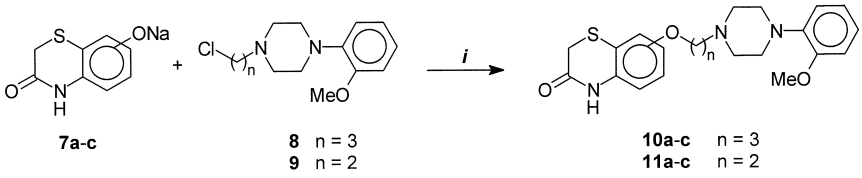
The affinity values of the tested compounds and naftopidil, used for comparison, are reported in Tables 1–3. Affinities are expressed as K_i in nM and standard errors are ±10% of the mean reported values of three to six separate experiments.

Results and Discussion

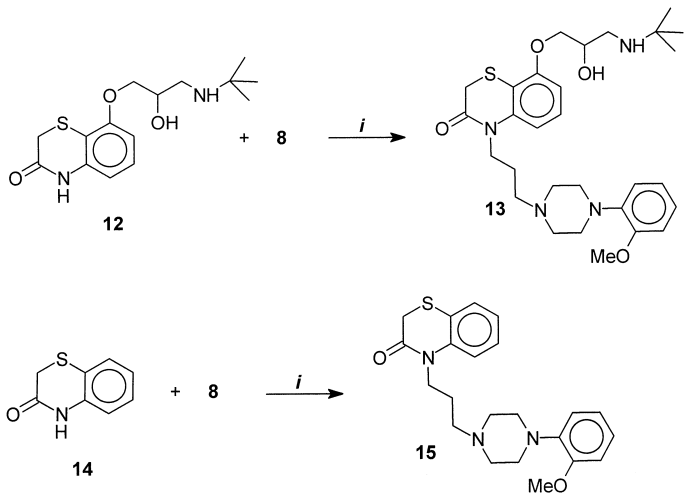
In the oxypropanolpiperazine series (Table 1), both types of PP-derivatives, **3a**–**c** and **4a**–**c**, showed good and selective α_1-AR affinity, which was higher for the (2-methoxyphenyl)piperazine derivatives **3a**–**c**. Among these, compound **3b** showed the highest affinity and selectivity, greater than those of naftopidil. Even if the (4-fluorophenyl)piperazine derivatives **4a**–**c** were from 2 to 6 times less potent than the (2-methoxyphenyl)piperazine counterparts **3a**–**c**, it must be pointed out that, in this case, the presence of *para*-substituent on the phenyl ring of the PP moiety did not drastically reduce the α_1-AR, as previously observed by other authors.[5] The different insertion of the side chain at various positions of the benzothiazine nucleus had little effect on α-AR binding even if the C-7 connection seems more fruitful (compare **3b** versus **3a** and **3c**, as well as **4b** versus **4a** and **4c**). On the contrary, no α-AR affinity was observed



Scheme 1. (i) *N*-substituted piperazine, EtOH, reflux.

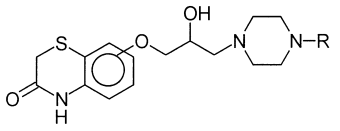


Scheme 2. (i) DMF, reflux.



Scheme 3. (i) K_2CO_3, dry acetone, reflux.

Table 1. Chemical–physical data and binding affinities of (1,4-benzothiazinyloxy)propanolpiperazine derivatives **3**–**6**



Compound	Position[a]	R	Yield (%)	mp (°C)	Formula	K_i (nM)			
						α_1-AR	α_2-AR	β_1-AR	β_2-AR
3a	6	2-$MeOC_6H_4$	69	89–91	$C_{22}H_{27}N_3O_4S$	16	3300	NA[c]	4000
3b	7	2-$MeOC_6H_4$	59	118–120	$C_{22}H_{27}N_3O_4S$	8.3	3000	NA	NA
3c	8	2-$MeOC_6H_4$	69	169–177	$C_{22}H_{27}N_3O_4S$	27	NA	330	88
4a	6	4-FC_6H_4	57	181–183	$C_{21}H_{24}FN_3O_3S$	90	NA	NA	5300
4b	7	4-FC_6H_4	61	189–191	$C_{21}H_{24}FN_3O_3S$	20	4600	NA	4800
4c	8	4-FC_6H_4	68	190–192	$C_{21}H_{24}FN_3O_3S$	60	1500	6700	NA
5a	6	CO(4-FC_6H_4)	57	170–172	$C_{22}H_{24}FN_3O_4S$	NA	100	NA	NA
5b	7	CO(4-FC_6H_4)	71	198–200	$C_{22}H_{24}FN_3O_4S$	NA	NA	NA	NA
5c	8	CO(4-FC_6H_4)	62	79–81	$C_{22}H_{24}FN_3O_4S$	NA	NA	NA	NA
6a	6	CO(C_4H_3O)[b]	40	171–173	$C_{20}H_{23}N_3O_5S$	NA	NA	NA	NA
6b	7	CO(C_4H_3O)[b]	34	64–66	$C_{20}H_{23}N_3O_5S$	NA	NA	NA	NA
6c	8	CO(C_4H_3O)[b]	38	143–145	$C_{20}H_{23}N_3O_5S$	2400	NA	NA	NA
Naftopidil						39	1600	NA	1000

[a]Position of side chain on the benzothiazine nucleus.
[b]2-Furoyl.
[c]NA, not active compound, K_i >10,000 nM.

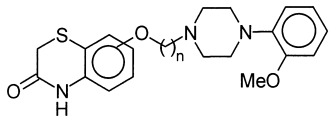
for any type of AP-derivatives **5a**–**c** and **6a**–**c**; only derivative **5a** showed a weak α_2-AR affinity with a K_i value of 100 nM.

Among the modifications made on the bridge linking the benzothiazine nucleus to the piperazine moiety, the elimination of a secondary alcoholic group, as well as the subsequent elimination of a methylene unit gave compounds which maintained the α-AR affinity, even if with reduced α_2/α_1 selectivity ratio (Table 2). Indeed, both (1,4-benzothiazinyloxy)propyl- **10a–c** and (1,4-benzothiazinyloxy)ethyl-piperazine derivatives **11a–c** have K_i values, at α_1-AR level, similar to those of (1,4-benzothiazinyloxy)propanol-PP types **3a**–**c** and **4a**–**c**, but they are less selective having higher α_2-AR affinity values.

High α_1-AR affinity was also obtained by linking 3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl side chain at the N-4 position of the benzothiazine nucleus as in compounds **13** and **15** (Table 3). In particular, compound **13** showed the highest α_1-AR affinity ($K_i = 1.3$ nM) as well as the highest α_1-selectivity ($\alpha_2/\alpha_1 = 407$) coupled with good but not selective β-AR affinities. All these strengthen the validity of symbiotic design which drove the preparation of compound **13**.

In conclusion, it was confirmed that the addition of a (2-methoxyphenyl)piperazine side chain, also onto 1,4-benzothiazine nucleus, provides compounds with α affinity. This effect is only moderately influenced by the length of the alkylic spacer and by the insertion position on the benzothiazine vector. Moreover, it was found that

Table 2. Chemical–physical data and binding affinities of (1,4-benzothiazinyloxy)propyl- and (1,4-benzothiazinyloxy)ethyl-piperazine derivatives **10** and **11**



Compound	Position[a]	*n*	Yield (%)	mp (°C)	Formula	K_i (nM)	
						α_1-AR	α_2-AR
10a	6	3	25	148–150	$C_{22}H_{27}N_3O_3S$	15	370
10b	7	3	27	150–152	$C_{22}H_{27}N_3O_3S$	23	1700
10c	8	3	24	164–166	$C_{22}H_{27}N_3O_3S$	14	950
11a	6	2	30	153–155	$C_{21}H_{25}N_3O_3S$	540	4600
11b	7	2	34	169–171	$C_{21}H_{25}N_3O_3S$	23	320
11c	8	2	28	163–165	$C_{21}H_{25}N_3O_3S$	73	2300
Naftopidil						39	1600

[a]Position of side chain on the benzothiazine nucleus.

Table 3. Chemical–physical data and binding affinities of compounds **12**, **13** and **15**[a]

Compound	Yield (%)	mp (°C)	Formula	K_i (nM)			
				α_1-AR	α_2-AR	β_1-AR	β_2-AR
12[b]				NT[c]	NT	20	23
13	24	64–67	$C_{29}H_{42}N_4O_4S$	1.3	530	5.3	2.7
15	73	113–115	$C_{22}H_{27}N_3O_2S$	38	440	NT	NT

[a]See Scheme 3.
[b]See ref 1.
[c]NT, not tested.

the presence of this α-affinity bearing side chain coupled with an oxypropanolamine β-blocker pharmacophore gave an interesting compound with a high affinity for both α and β-ARs, which could be a new anti-hypertensive drug model.

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