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Symbiotic approach to drug design: *N*-[(4-chloro-3-sulfamoylbenzamido)-ethyl]propanolamine derivatives as β-adrenergic blocking agents with diuretic activity*

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Summary — A series of oxypropanolamines and iminoxypropanolamines, in which the aminic substituent was the 2-(4-chloro-3-sulfamoylbenzamido)-ethyl group, were synthesized as potential β-blocker/diuretic agents. All of these compounds were tested for β_1-adrenoceptor affinity and β-blocking potency. For the most active compounds, diuretic and antihypertensive properties as well as affinity for α_1-adrenoceptors were also investigated. Compounds **4** and **10** were found to display contemporaneously β-blocking, diuretic and antihypertensive activities.

Résumé — Approche symbiotique du drug design: dérivés de la *N*-[(4-chloro-3-sulfamoylbenzamido)-éthyl]propanolamine, agents β-bloquants adrénergiques à activité diurétique. *Une série d'oxypropanolamines et d'iminoxypropanolamines, ayant comme substituant aminé le groupement (4-chloro-3-sulfamoylbenzamido)-2-éthyle, ont été synthétisées comme molécules β-bloquantes/diurétiques potentielles. Tous les composés ont été testés pour leur affinité aux récepteurs β_1 et leur activité β-bloquante. Pour les molécules les plus actives, l'activité diurétique et antihypertensive, a été aussi étudiée ainsi que leur affinité aux récepteurs α_1. Les composés **4** et **10** montrent, à la fois une activité β-bloquante, diurétique et antihypertensive.*

oxypropanolamines / iminoxypropanolamines / β-blocking-diuretic activity / antihypertensive activity

Introduction

In current clinical practice, a β-blocker diuretic combination is one of the most common approaches for hypertension management [1–3]. The β-blocker ameliorates certain adverse effects associated with diuretic monotherapy such as having a potassium-sparing action and blocking the diuretic-induced renin release [4].

An attractive research target, as an alternative to this association therapy, is therefore the synthesis of a single molecule that can combine both of these valuable complementary activities, maximizing the likelihood of a balanced profile during the entire course of the drug's action. Only a few attempts to achieve this goal, by synthesizing hybrid molecules combining the structures of a diuretic and a β-adrenoceptor antagonist, have been described [5–7]. According to this drug design and, as an extention of our investigation on β-blocking agents [8–10], we now report the synthesis of compounds in which the conventional alkyl substituent at the side chain nitrogen atom of β-blockers was replaced with 2-(4-chloro-3-sulfamoylbenzamido)-ethyl. This type of substitution retains the structural requirements for the interaction with β-adrenoceptor, thanks to the presence of a 2-amidoethyl group known to impart high β-blocking potency [11–15] and, at the same time, allows the diuric *o*-chlorobenzenesulfonamidic moiety [16–18] to be incorporated into the molecule. This replacement was made on oxypropanolamine and iminoxypropanolamine derivatives of 1,4-benzothiazine, previously reported by us as β-adrenoceptor antagonists [9, 10], on carteolol, selected for isostery of the carbostyril nucleus with the 1,4-benzothiazine one, and on well-known propranolol (table I).

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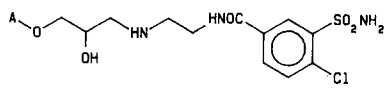
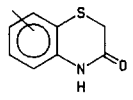
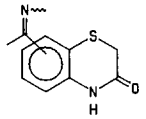
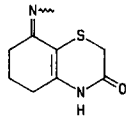
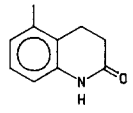
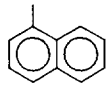
Table I. Physical properties of *N*-[(4-chloro-3-sulfamoylbenzamido)-ethyl]propanolamine derivatives.



compd	A	position[a]	mp, °C[b]	yield, %	formula[c]
2		6	110-115	24	$C_{20}H_{23}ClN_4O_6S_2$
3		7	115-130	26	$C_{20}H_{23}ClN_4O_6S_2$
4		8	123-135	37	$C_{20}H_{23}ClN_4O_6S_2$
5		6	113-123	24	$C_{22}H_{26}ClN_5O_6S_2$
6		7	114-134	28	$C_{22}H_{26}ClN_5O_6S_2$
7		8	116-125	32	$C_{22}H_{26}ClN_5O_6S_2$
8			113-122	26	$C_{20}H_{26}ClN_5O_6S_2$
9			110-123	35	$C_{21}H_{25}ClN_4O_6S$
10			89-100	32	$C_{22}H_{24}ClN_3O_5S$

[a]Substituted position on the aromatic nucleus. [b]Amorphous solids, melting point of these substances is the temperature at which the white solid became a colorless glass with decomposition. [c]C, H, N analyses were within ± 0.4% of the theoretical values.

Chemistry

The title compounds **2–10** were synthesized (scheme 1) by reaction of the appropriate known epoxide with 2-(4-chloro-3-sulfamoylbenzamido)-ethylamine (**1**) which was obtained, in turn, by treatment of methyl 4-chloro-3-sulfamoylbenzoate with an excess of ethylenediamine.

Pharmacology

All target compounds **2–10** were screened at the receptor level to determine their ability to displace the binding of [^{3}H]dihydroalprenolol from turkey erythrocyte membranes (β_1-adrenoceptors) and *in vivo* to evaluate their β-blocking potency by the inhibition of isoprenaline-induced tachycardia in rats (table II). Subsequently, the most active compounds **4**, **9** and **10** proved to have an interesting β-blocking activity even after oral dosing. Their diuretic (table III) and antihypertensive (table IV) properties were therefore investigated in rats and in spontaneously hypertensive rats (SHR) respectively, as well as their affinity for α_1-adrenoceptors by binding techniques using [^{3}H]-prazosin on rat brain membranes.

Results and Discussion

β_1-Adrenergic receptor affinity

When compared with propranolol, carteolol and *tert*-butyl-1,4-benzothiazine derivative **11** (table II), compound **4** was found to possess the highest affinity for β_1-adrenoceptors with a K_i value of 7.4 10^{-9} M. The insertion of an iminoxy bridge between the aromatic ring and propanolamine side chain proved to be detrimental for binding at β_1-adrenoceptors (compare **4** *vs* **7**). This is in agreement with our previous findings obtained on 1,4-benzothiazine derivatives [10]. Regarding all the other compounds, only iminoxy derivative **6** and carbostyril derivative **9** showed a K_i value of 3.0 10^{-7}.

β-Blocking activity

In the isoprenaline induced tachycardia test, after intravenous dosing, compound **4** displayed total inhibition at 4 and 2 mg/kg. The same total blockade occurred with doses of carbostyril derivative **9** from **4** to 0.4 mg/kg. Iminoxy derivative 6 (affinity $K_i \approx 10^{-7}$ M) displayed no *in vivo* β-blocking activity, while naphthyl derivative **10**, despite a lower affinity value (K_i = 8.2 10^{-7} M), blocked 61% at 2 mg/kg. However, for this compound, such inhibition decreased to 28% when the dose was increased to 4 mg/kg. This leads one to hypothesize that there may be a partial agonistic activity at a higher dose. The same effect was previously observed by us for reference compound **11** [10].

β-Blocking potency, evaluated for compounds **4**, **9** and **10** after oral dosing, was found to be best for carbostyril derivative **9**, with a total inhibition at 30 mg/kg in comparison to propranolol which blocked 62.7% at the same dose, while reference carbostyril analogue, carteolol, showed a total inhibition at 16 mg/kg. Naphthyl derivative **10**, which is less potent than compound **9** and **4** after intravenous dosing displayed, on the contrary, an activity similar to that of reference propranolol and superior to that of benzothiazine derivative **4** after oral administration. The decrease of activity for compound **4** suggests a lower bioavailability after oral administration.

Diuretic activity

After oral administration urinary output, produced by benzothiazine derivative **4** at 50 mg/kg and naphthyl

derivative **10** at doses of 8 and 15 mg/kg, was approximately 2-fold above the control and a little less than that produced by hydrochlorothiazide at 15 mg/kg *po*. On the contrary, carbostyril derivative **9**, which displayed the best *in vivo* β-blocking potency, was not active in the diuretic assay. The Na^+/K^+ ratio of the best compounds was less than those of hydrochlorothiazide, with the exception of compound **10** at 15 mg/kg which had a saluretic effect similar to hydrochlorothiazide at the same dose.

Antihypertensive activity

No antihypertensive activity was observed in SHR after oral administration of compounds **4**, **9** and **10** at 30 mg/kg, while at 60 mg/kg a reduction in blood pressure was observed particularly for compounds **4** and **10** between 90–240 and 180-240 min respectively. It must be pointed out that the experimental model employed measures the non-β-blocking component of activity; indeed, in this test, propranolol was found to be inactive. Therefore, the observed antihypertensive effect could depend on vasodilatation due to the diuretic activity of these molecules and, only for compound **4**, on its α_1-adrenoceptor affinity.

α_1-Adrenergic receptor affinity

Only compound **4** was found to possess high affinity for α_1-adrenoceptors, with a K_i value of $1.3\ 10^{-8}$ M, while compounds **9** and **10** exhibited no affinity.
These results indicate that the replacement of the conventional alkyl nitrogen substituent in β-blockers with 2-(4-chloro-3-sulfamoylbenzamido)ethyl group allows the desired diuretic activity even if it decreases β-blocking potency.

Among the test compounds, benzathiazine derivative **4** and naphtyl derivative **10** showed contemporaneously β-blocking, diuretic and antihypertensive activity. It is interesting to note that compound **4** also possesses high α_1-adrenoceptor affinity and displays β-blocking and diuretic activities in the rat at the same dosage after oral administration.

Compounds **4** and **10** have been selected for further pharmacological investigation.

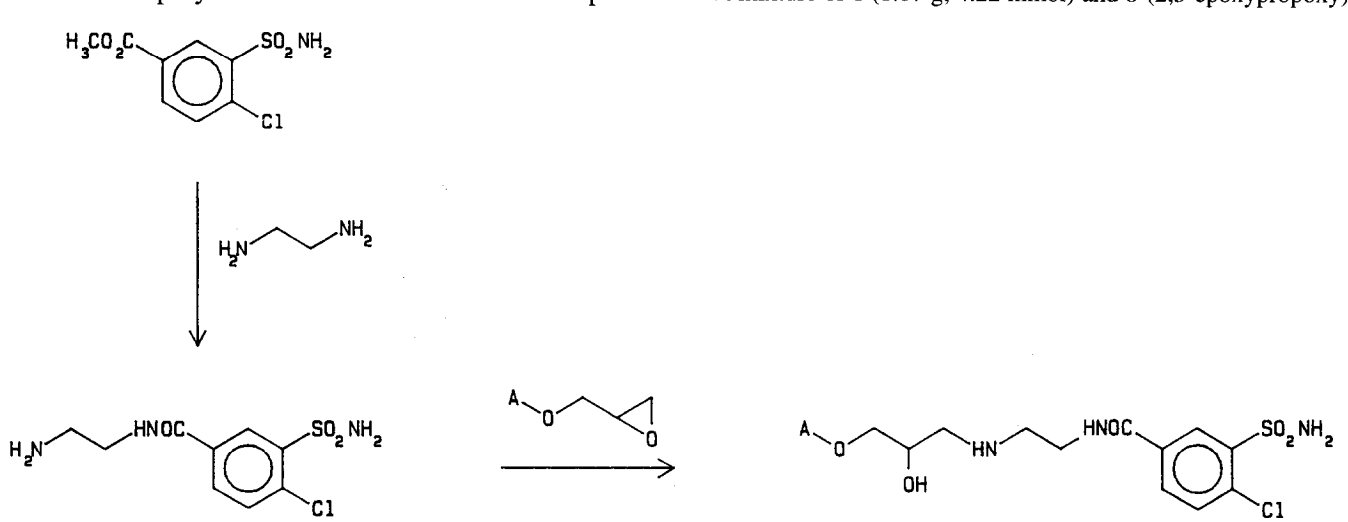
Experimental protocols

Chemistry

Melting points were determined in capillary tubes (Gallenkamp melting point apparatus) and are uncorrected. ^{1}H-NMR spectra were recorded on a 90 MHz Varian EM 390 spectrometer with tetramethylsilane as an internal standard and dimethylsulfoxide-d_6 as solvent. Chemical shifts are given in ppm (δ) and the spectral data are consistent with the assigned structures. Elemental analyses were performed on a Carlo Erba elemental analyzer, Model 1106, and the data for C, H, N are within ± 0.4% of the theoretical values. Column chromatographic separations were carried out on Merck silica gel 40 (mesh 70–230). Final products 2–10 were purified by column chromatography eluting with $CHCl_3$/MeOH 8:2 and were not recrystallized. Yields are of purified products and were not optimized. The characteristics of the synthesized compounds are summarized in table I.

*2-(4-Chloro-3-sulfamoylbenzamido)etnylamine (**1**)*
A mixture of methyl 4-chloro-3-sulfamoylbenzoate [17] (5 g, 0.02 mol) and an excess of ethylendiamine (5 ml) was heated at 30–40°C for 3 h. The reaction mixture was cooled and then diluted with EtOH (20 ml). The resulting solid was filtered off and crystallized from EtOH to give 4.6 g (83%) of 1; mp 184–6°C dec. Anal ($C_9H_{12}ClN_3O_3S$) C, H, N. ^{1}H-NMR 2.57–2.80 (2H, m, CH_2NH_2), 3.15–3.45 (2H, m, CH_2NHCO), 4.60 (4H, bs, CH_2NH_2 and SO_2NH_2), 7.65 (1H, d, J = 9 Hz, H-5), 7.98 (1H, dd, J = 2.5 and 9 Hz, H-6), 8.38 (1H, d, J = 2.5 Hz, H-2), 8.67 (1H, bs, CONH).

*3-{[2-(4-Chloro-3-sulfamoylbenzamido)ethyl]amino}-1-[(3,4-dihydro-3-oxo-2H-1,4-benzothiazin-8-yl)oxy]propan-2-ol (**4**)*
A mixture of 1 (1.17 g, 4.22 mmol) and 8-(2,3-epoxypropoxy)-



Scheme 1. 1 2-10

Table II. Inhibition of [^{3}H]DHA binding in turkey erythrocytes and anti-isoprenaline activity in normal rats.

compd	inhibition of [^{3}H]DHA binding	anti-isoprenaline activity			
	K_i (M)	dosage (mg/kg, iv)	inhibition of tachycardia[a, b] (%)	dosage (mg/kg, po)	inhibition of tachycardia[b, c] (%)
2	$>10^{-5}$	4	NA[d]		
3	$1.2 \cdot 10^{-6}$	4	NA		
4	$7.4 \cdot 10^{-9}$	4	100 ± 0	4	NA
		2	100 ± 0	8	NA
		1	79.1 ± 6.38	16	NA
		0.4	14.7 ± 2.90	30	49.0 ± 1.96
				60	70.6 ± 5.89
5	$>10^{-5}$	4	NA		
6	$3.0 \cdot 10^{-7}$	4	NA		
		2	12.0 ± 7.22		
7	$3.7 \cdot 10^{-6}$	4	NA		
8	$1.1 \cdot 10^{-6}$	4	5.5 ± 5.53		
		2	3.0 ± 4.06		
9	$3.0 \cdot 10^{-7}$	4	100 ± 0	4	NA
		2	85.3 ± 14.66	8	19.6 ± 1.96
		1	100 ± 0	16	33.3 ± 10.93
		0.4	100 ± 0	30	100 ± 0
		0.04	9.5 ± 5.64		
10	$8.2 \cdot 10^{-7}$	4	28.0 ± 10.85	4	NA
		2	61.0 ± 7.26	8	NA
		1	4.1 ± 4.75	16	25.5 ± 7.08
		0.4	NA	30	68.6 ± 3.92
Prop[e]	$1.2 \cdot 10^{-8}$	2	100 ± 0	4	NA
				8	NA
				16	35.3 ± 5.88
				30	62.7 ± 1.96
Cart[f]	$9.3 \cdot 10^{-9}$	2	100 ± 0	4	49.0 ± 1.96
				8	76.5 ± 5.89
				16	100 ± 0
11[g]	$2.6 \cdot 10^{-8}$	4	66.3 ± 8.87		
		0.4	100 ± 0		[g]
		0.04	100 ± 0		

[a]Two minutes after INA (0.12 μg/kg) administration. [b]Mean ± SE for 3 separate observations per dosage. [c]1 h after INA (0.12 μg/kg) administration. [d]NA = no active β-blocking compound. [e]Prop: propanolol. [f]Cart: carteolol. [g]Compound **11** = 8-(3-*tert*-butylamino-2-hydroxypropoxy)-3,4-dihydro-3-oxo-2H-1,4-benzothiazine; see [9].

3,4-dihydro-3-oxo-2H-1,4-benzothiazine [9] (1 g, 4.22 mmol) in 300 ml of absolute EtOH was heated under reflux for 16 h. The solution was then evaporated to dryness and the residue purified by silica gel column chromatography eluting with $CHCl_3$/MeOH 8:2 to give 0.8 g (37%) of 4 as amorphous white solid; mp 123–135°C dec. Anal ($C_{20}H_{23}ClN_4O_6S_2$) C, H, N. ^{1}H-NMR: 2.69–2.90 (4H, m, CH_2NHCH_2), 3.25–3.50 (4H, m, SCH_2 and CH_2NHCO), 3.78–4.05 [3H, m, $OCH_2CH(OH)$],

Table III. Diuretic and saluretic activity in the rat (0–5 h).

compd	dosage (mg/kg, po)	urinary output [a] (ml)	saluretic activity [b] Na^+ (mequiv/kg)	K^+ (mequiv/kg)	Na^+/K^+ (mequiv/kg)
4	4	1.00 ± 0.27	0.5	0.1	5.0
	8	1.60 ± 0.40	0.9	0.4	2.2
	15	2.00 ± 0.45	1.1	0.4	2.7
	30	2.20 ± 0.58	1.1	0.5	2.2
	50	4.80 ± 0.37	1.7	0.7	2.4
9	4	1.30 ± 0.30	0.6	0.2	3.0
	8	2.40 ± 0.40	1.4	0.6	2.3
	15	2.50 ± 0.28	1.7	0.5	3.4
	30	1.20 ± 0.34	0.9	0.3	3.0
10	4	0.90 ± 0.10	0.4	0.1	4.0
	8	5.00 ± 0.63	2.5	1.0	2.5
	15	4.20 ± 0.49	3.1	0.7	4.4
	30	0.90 ± 0.29	0.6	0.2	3.0
HCT [c]	15	6.27 ± 0.70	3.5	0.8	4.3
saline		2.22 ± 0.33	1.2	0.5	2.4

[a]Mean ± SE for 5 separate observations per dosage. [b]SE for the saluretic data have been calculated and are less then 10% of the mean values. [c]HCT = hydrochlorothiazide.

5.20 (1H, bs, OH), 6.55, 6.65 (each 1H, dd, J = 7.5 and 1.2 Hz, benzothiazinic H-5 and H-7), 7.07 (1H, t, J = 7.5 Hz, benzothiazinic H-6), 7.72 (1H, d, J = 9 Hz, H-5), 8.03 (1H, dd, J = 2.5 and 9 Hz, H-6), 8.48 (1H, d, J = 2.5 Hz, H-2), 8.60–8.80 (1H, m, NHCO).

In the same manner, compounds **2–3**, **5–10** were synthesized starting from appropriate known epoxides which were prepared according to the literature. For 1-(2,3-epoxypropoxy)naphthalene see [19]; for 5-(2,3-epoxypropoxy)-3,4-dihydrocarbostyril see [20]; for 6-, 7-, 8-(2,3-epoxypropoxy)-3,4-dihydro-3-oxo-2H-1,4-benzothiazine see [9]; for 6-, 7-, 8-{1-[(2,3-epoxypropoxy)imino]ethyl}-3,4-dihydro-3-oxo-2H-1,4-benzothiazine and 8-[(2,3-epoxypropy)imino]-3, 4, 5, 6, 7, 8-hexahydro-3-oxo-2H-1,4-benzothiazine see [10].

Pharmacological methods

β-Adrenoceptor binding assay

Pellets containing β_1 type adrenergic receptors were obtained from turkey erythrocyte membranes as described in the literature [21]. [^{3}H]dihydroalprenolol ([^{3}H]DHA) obtained from New England Nuclear (NEN), having a specific activity of 99.9 Ci/mmol and a radiochemical purity > 98.5%, was used as ligand.

β-Adrenergic receptor binding assay was determined as follows: 100 μl of membranes (431 μg/ml of protein diluted 1:8 v/v) were incubated for 15 min at 37°C with 6 nM [^{3}H]DHA and 100 μl of various concentrations of the test compounds (dissolved in DMSO 5%) in 90 mM sodium chloride and 12 mM Tris, pH = 7.5 (total vol 1 ml). The incubations were stopped by adding 3 ml of cold buffer followed by rapid filtration through glass fiber filter disks (Whatman GF/B). The samples were subsequently washed with 4.5 ml of the same buffer and placed into scintillation vials; 10 ml of Filter-count (Packard) liquid scintillation cocktail was then added to each vial and counting was carried out by a scintillation spectrometer (Packard TRI-CARB 300C). Non-specific binding was defined as non-displaceable binding in the presence of 10 μM propranolol, and specific binding as the difference between total and non-specific binding.

α-Adrenoceptor binding assay

Pellets containing α_1 type adrenergic receptors were obtained from rat brain membrane preparations according to the literature [22]. [^{3}H]prazosin (NEN), having a specific activity of 20.2 Ci/mM and a radiochemical purity > 99%, was used as ligand.

For the binding assay 800 μl of membrane (500 μg/ml of protein diluted 1:50 v/v) were incubated for 30 min at 25°C with 1.2 nM [^{3}H]prazosin and 100 μl of various concentrations of the test compound (dissolved in DMSO 5%) in 50 mM Tris-HCl, pH, 7.7 (total vol 1 ml). Filtration and measurement of radioactivity were performed under the same conditions as those for [^{3}H]DHA binding assays. Non-specific binding was measured in the presence of 10 μM unlabeled prazosin.

Blank experiments were carried out to determine the effect of the solvent (5%) on the binding. The concentration of the test compounds that inhibited [^{3}H]DHA or [^{3}H]prazosin binding by 50% (IC_{50}) were determined by log-probit analysis with 7 concentrations of the displacers, each performed in duplicate. The IC_{50} values obtained were used to calculate apparent inhibition constants (K_i) by the method of Cheng and Prusoff [23], from the following equation: $K_i = IC_{50}/(1 + S/K_D)$ where S represents the concentration of the ligand used and K_D is its receptor dissociation constant (K_D values for [^{3}H]DHA and [^{3}H]prazosin are 3.6 10^{-9} M and 5.7 10^{-10} M respectively). The K_i values for the inhibition of [^{3}H]DHA binding are reported in table II in comparison with propranolol, carteolol and *tert*-butyl-1,4-benzothiazine derivative 11, while the K_i values for the α_1-adrenoceptor binding assay are the following: 1.3 10^{-8} M for compound **4**, > 10^{-5} M for compounds **9** and **10**, in comparison with prazosin K_i = 6.0 10^{-11} M.

Anti-isoprenaline activity

The β-adrenoceptor blocking activity was studied *in vivo* by the inhibition of tachycardia induced by isoprenaline (INA) in rats [24]. For this purpose 0.12 μg/kg of isoprenaline was injected intravenously (jugular vein) into male Wistar rats, weighing 250–300 g, previously anesthetized with sodium nembutal (55 mg/kg, *ip*). The increase in heart rate (HR) was evaluated by electrocardiograph. After several min, when normal heart rate was restored, the test compound was administered intravenously, dissolved in dimethylsulfoxide, or orally, suspended in 1% gum-arabic. Responses to isoprenaline were obtained 2 min after intravenous or 1 h after oral administration. Blank experiments were carried out to determine the effect of the solvent on the test. The comparison was made with two known β-blockers: propranolol and carteolol. Three rats were used per group and the mean percent inhibition was calculated (table II).

Diuretic activity

Groups of 5 male CD rats, weighing 150–170 g, were used. All test compounds and hydrochlorothiazide, as control drug, were

Table IV. Antihypertensive activity in SHR (% reduction in BP). Mean ± SE for 5 separate observations per dosage. NA: no reduction in BP was observed.

compd	dosage (mg/kg, po)	time (min) 30	60	90	120	180	240
4	30	NA [b]	NA	NA	NA	NA	NA
	60	NA	7.37 ± 5.01	17.04±12.93	12.72 ± 5.97	11.27 ± 3.79	10.02 ± 4.37
9	30	NA	NA	NA	NA	8.06 ±5.58	3.57 ± 3.57
	60	NA	NA	7.11±11.09	8.51 ± 9.19	0.69 ±0.69	14.70±11.21
10	30	2.10 ± 1.33	NA	3.00 ± 3.80	1.34 ± 3.29	7.23 ±7.23	7.36 ± 4.69
	60	2.03 ± 1.27	2.78 ± 2.54	3.30 ± 3.86	1.94 ± 1.25	12.17 ±6.36	9.63 ± 5.15

orally administered, dissolved or suspended in 25 ml/kg of saline. Control animals received 25 ml/kg of saline only. The rats were fasted and deprived of water for 18 h prior to dosing and, after administration of the test compounds, were immediately placed singly in metabolic cages. No food and water was supplied during the experimental period. Urine was collected during the 0–5 h interval in volumetric graduate cylinders and was analyzed for sodium and potassium by flame photometry. The results are shown in table III.

Antihypertensive activity

Fasted male spontaneously hypertensive rats (SHR), weighing 300–320 g, were used. The carotid artery was cannulated and connected to a Statham pressure trasducer for blood pressure recording. Test compounds were suspended in CMC and Tween (0.1–1% in H_2O) and orally administered. Blood pressure measurements were taken before and after (30–240 min) drug administration. Activity was determined on groups of 5 animals per dosage and the values of the percent reduction of the studied compounds are reported in table IV. It must be pointed out that propranolol does not act in these SHR rats.

Acknowledgments

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