

Anti-hypertensives: 1-alkyl-2-arylpiperazinoethyl-1H-naphth[1,2-d]imidazoles

Emilio TOJA¹, Giuseppe DI FRANCESCO², Domenico BARONE, Emiliana BALDOLI,
Nerina CORSICO and Giorgio TARZIA*

Lepetit Research Laboratories, Via Durando 38, Milan 20158, Italy

(Received October 20 1986, accepted January 5 1987)

Summary — L 15848 (8b citrate) is a new anti-hypertensive agent belonging to the class of 1-alkyl-2-aminoethylnaphth[1,2-d]imidazoles. It lowers blood pressure in spontaneously hypertensive rats (50 mg/kg, *p.o.*) and in conscious normotensive and renal hypertensive dogs (5—20 mg/kg, *p.o.*). The decrease in systolic blood pressure is dose related and long lasting, and is evident for periods of up to 7 h. A slight and transient decrease in heart rate was observed in the renal hypertensive dogs. CNS depressant effects were not apparent after L 15848 administration in doses up to 100 mg/kg, *p.o.* (rat, mouse and dog). The criteria for the selection of L 15848 are discussed and two alternative synthetic pathways are presented.

Résumé — **Anti-hypertenseurs: alkyl-1 arylpiperazinoéthyl-2[1H] naphth[1,2-d]imidazoles.** L 15848 (8b citrate) est un nouvel agent anti-hypertenseur appartenant à la classe des alkyl-1-aminoéthyl-2 naphth[1,2-d]imidazoles. Il montre une activité hypotensive chez les rats spontanément hypertendus à la dose de 50 mg/kg, *p.o.* et chez les chiens normotendus et hypertendus traités par la voie orale avec des doses de 5—20 mg/kg. La diminution de la pression artérielle est dose corrélée et de longue durée. Chez les chiens hypertendus, une faible et fugace diminution de la fréquence cardiaque est observée. L 15848 ne cause aucune dépression du SNC jusque à 100 mg/kg, *p.o.* (chez les rats, les souris et les chiens). Les critères de sélection du L 15848 sont discutés et deux schémas alternatifs de synthèse sont présentés.

naphth[1,2-d]imidazoles / N¹-alkyl-1,2-naphthalendiamines / anti-hypertensives / L15848

Introduction

The hypotensive and anti-hypertensive activity of the post-synaptic α -adrenergic blocking agent indoramin has been reported [1—4]. It was also demonstrated that compounds in which the indole ring of indoramin had been replaced with a variety of aromatic or heteroaromatic ring systems [5, 6] retained their anti-hypertensive and/or hypotensive activity and that in the case of the 1,4-bis(indoleglyoxyloyl)-piperazines, it was possible to dissociate the hypotensive, anti-hypertensive and CNS depressant activities by structural modifications of the parent molecule [7]. This lead was apparently not pursued and because of its sedative side effects [8] indoramin itself has only recently been considered clinically useful [9]. It has been suggested [4] that a selective post-synaptic α -adrenoceptor antagonist like indoramin

with negligible affinity for presynaptic α -adrenoceptors might be valuable in the treatment of hypertension. It was therefore decided to explore classes of compounds structurally related to indoramin in hope of achieving, by chemical manipulation, the desired degree of selectivity. The class of 1- and 3-alkylnaphth[1,2-d]imidazoles bearing an aminoethyl chain in the 2-position (Table I) seemed worth considering. These compounds are clearly related to indoramin and to the anti-hypertensive α -adrenolytic phenylpiperazines [10—12]. Information was available in the patent literature concerning the adrenolytic and sedative properties of the 2-[2-(4-phenyl-1-piperazinyl)ethyl]benzimidazoles [13, 14] to which class the 1- and 3-alkylnaphth[1,2-d]imidazoles can also be related. Our compounds showed sedative [15] and anti-hypertensive activity. This paper reports the selection of an essentially anti-hypertensive agent.

¹Present address: Roussel Maestretti, Via Gran Sasso 18, 20131 Milan, Italy.

²Present address: Merrell Dow Research Center, 16, rue d'Ankara, 67084 Strasbourg Cedex, France.

* To whom correspondence should be addressed.

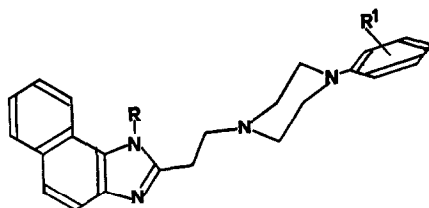
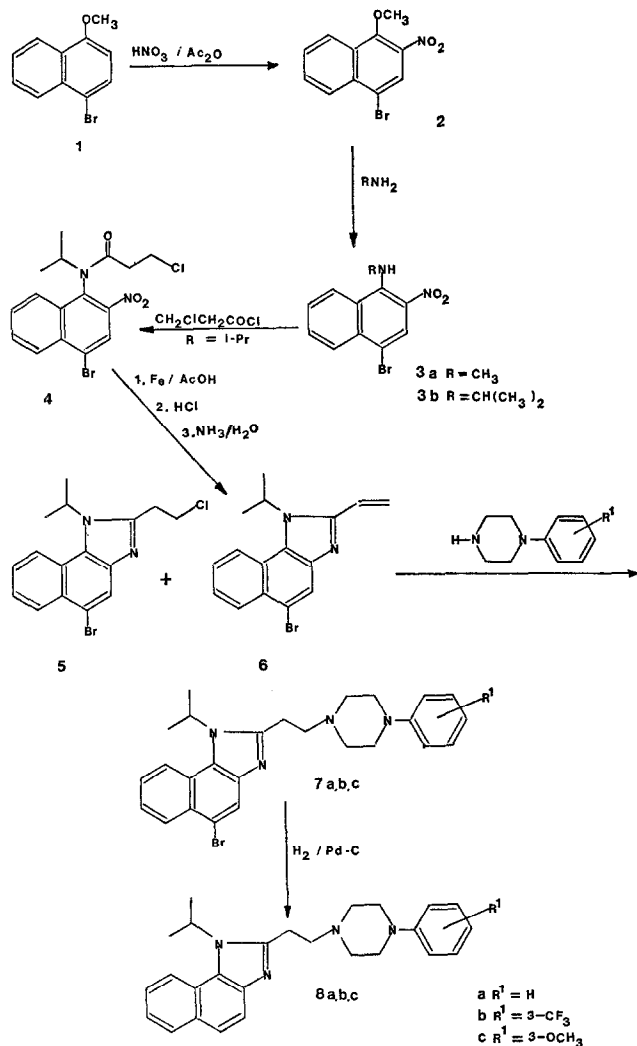


Table I. 1-Alkyl-2-(2-(4-aryl)-1-piperazinyl)ethyl-1H-naphth[1,2-d]imidazoles.

Compd	R	R ¹	m.p. °C		Formula base
			base (solvent ^a)	citrate ^b	
8a	(CH ₃) ₂ CH	H	190—92 (A)	169—71	C ₂₆ H ₃₀ N ₄
8b	(CH ₃) ₂ CH	3-CF ₃	140—41 (A)	141—43	C ₂₇ H ₂₈ F ₃ N ₄
8c	(CH ₃) ₂ CH	3-OCH ₃	140—42 (B)	143—44	C ₂₇ H ₃₂ N ₄ O
8d	(CH ₃) ₂ CH	4-Cl	179—80 (C)	183—84	C ₂₆ H ₂₉ ClN ₄
8e	CH ₃	3-CF ₃	138—39 (A)	143—44	C ₂₅ H ₂₅ F ₃ N ₄
8f	CH ₃	4-Cl	213—15 (D)	191—92	C ₂₄ H ₂₅ ClN ₄

^a A = *t*-BuOMe; B = MeOH; C = EtOAc; D = EtMeCO.

^b The citrates melted with decomposition.

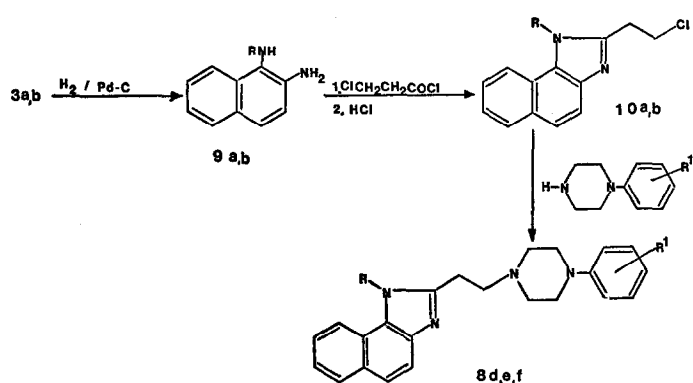


Scheme 1

Chemistry

The synthetic route used for most of the 1-alkylnaphth[1,2-d]imidazoles is exemplified in Scheme 1 for R = isopropyl. Bromination of 1-methoxynaphthalene with *N*-bromosuccinimide in carbon tetrachloride [16] protected the *para* position and directed to the 2-position the subsequent nitration; which was best accomplished using a slight excess of 99% nitric acid in acetic anhydride as a solvent at —30°C in the presence of catalytic amounts of sulfuric acid. The 4-bromo-1-methoxy-2-nitronaphthalene **2** [17] was reacted with a primary amine in dimethylformamide and the resulting 1-amino group was acylated with 3-chloropropionyl chloride in 1,2-dichloroethane without any acid acceptor. Reduction of the nitro group with iron and acetic acid and cyclization of the crude reaction mixture in refluxing amyl alcohol with a double molar excess of hydrochloric acid gave **5** [18] (R. Meldola first reported the synthesis of naphth[1,2-d]imidazoles through acylation of 4-bromo-1-ethylamino-2-nitronaphthalene followed by reduction of the nitro group and cyclization). Isolation of the intermediate 1-alkyl-5-bromo-2-(2-chloroethyl)-1H-naphth[1,2-d]imidazole **5** by means of aqueous ammonia caused partial dehydrohalogenation of the 2-chloroethyl chain to form the vinyl derivative **6**. The amount of **6** in the final mixture was consistently between 30 and 40% as determined by NMR and as an average of several experiments. Compounds **5** and **6** reacted with various amines in refluxing amyl alcohol through mixed SN₂ and addition to the double bond mechanisms. In a comparative experiment in which **5** was completely transformed by base treatment into **6** and then made to react with 1-(trifluoro-*m*-tolyl)piperazine, compound **7b** was obtained in lower yield with respect to the original procedure starting from a mixture of **5** and **6**. This is likely due to the concomitant polymerization of **6**. The protective bromine atom was finally removed by hydrogenolysis with 10% palladium on carbon in methylcellosolve containing equimolar amounts of potassium hydroxide. Attempts to improve water solubility and wetability of the final compounds **8** through formation of pharmacologically acceptable salts was partly successful. The final choice of citrates, among the twenty salts prepared, was based upon their ease of formation and crystallization, non-hygroscopicity and stability upon exposure to air and light.

Compounds bearing on the phenyl ring R¹ substituents such as chlorine (**8d, f**) cannot be prepared according to Scheme 1 due to the experimental conditions of the last step. An alternative pathway was investigated to overcome this difficulty (Scheme 2). Catalytic reduction of **3a, b** gave **9a, b** as brown oils which were made to react with 3-chloropropionyl chloride in methylene chloride in the presence of triethylamine. The resulting acylated intermediates were immediately cyclized by warming with 5% hydrochloric acid to give **10a** or by refluxing with an excess of *p*-toluenesulfonic acid in toluene to give **10b**. Final compounds **8d-f** were obtained by reaction with substituted phenylpiperazines in refluxing amyl alcohol. This synthetic route is of wider applicability than the first one, but the hazards connected with the manipulation of 1,2-naphthalenediamines limit its interest. The first procedure represents,



a: $R = CH_3$; b: $R = CH(CH_3)_2$; d: $R = CH(CH_3)_2$; $R^1 = 4-Cl$;
e: $R = CH_3$; $R^1 = 3-CF_3$; f: $R = CH_3$; $R^1 = 4-Cl$.

Scheme 2

however, a straightforward route to N^1 -alkyl-1,2-naphthalenediamines **9** starting from the inexpensive 1-methoxynaphthalene. The generality of the procedure and the possibility of avoiding the nitration step will be reported in a forthcoming paper. The physicochemical properties of compounds **8a-f** are reported in Table I.

Pharmacology

Compounds were preliminarily examined in the *in vitro* assays measuring the binding of [3H]spiperone [19], [3H]prazosin [20] and [3H]clonidine [21] to their receptors. The compounds that did not displace [3H]clonidine at the screening concentration of $3 \mu M$ and that showed a lower K_i (nM) for prazosin than for spiperone (K_i spiperone/ K_i prazosin ≥ 25) were checked in the Ames test [22] on the *S. typhimurium* TA-100 strain to discriminate mutagenic products. The compounds that qualified in these two tests were admitted to further pharmacological evaluation.

Anti-hypertensive activity was measured as the percent drop in systolic blood pressure (SBP) in the spontaneously

hypertensive rat model (SHR) of Okamoto and Aoki [23, 24] and in the conscious renal hypertensive dog model (RHD) [25]. Hypotensive activity was measured as the percent drop in the mean blood pressure (MBP) in the conscious normotensive dog model (ND) [26]. During these experiments, the dogs were observed for behavioral alterations with special attention given to ptosis and sedation.

Central nervous system depressant activity was evaluated according to Irwin [27] on the basis of the modifications induced in the normal behavior of mice and of the conditioned avoidance response (CAR) of rats as measured by the pole-climbing avoidance test described by Cook and Weidley [28] and modified by Maffii [29, 30]. In this modification, the anticipatory response (CR_2) is considered to be qualitatively different from the normal conditioned response (CR) and is interpreted as an 'emotional' state or a state of altered reactivity of the rat to environmental stimuli. Inhibition of the CR_2 response is exhibited by minor tranquilizers but also by anti-depressant and α -adrenolytic compounds. The CR is selectively blocked by neuroleptics while a blocked unconditioned response (UR) is an indication of physical inability of the rat to jump onto the pole. The antagonism of the compulsive behavior induced in mice by a single injection of a high dose of morphine (running fit) was measured as an estimate of the adrenolytic and dopaminolytic activity of the compounds [31, 32]. This test was run only on those compounds that were particularly promising or as an internal check on some of the compounds for which high CNS activities were predicted.

Biological Results and Discussion

All the compounds selected for this study were inactive in the *in vitro* [3H]clonidine binding assay at the screening concentration of $3 \mu M$ and all of them showed a wide separation between the K_i (nM) values in the [3H]prazosin and [3H]spiperone binding assays (Table II). Surprisingly,

Table II. *In vitro* binding studies, anti-hypertensive activity in conscious renal hypertensive dogs (RHD) and in normotensive dogs (ND), acute toxicity of **8a-f** citrates.

Compd citrate	K_i (nM) \pm SE		RHD			ND			ID_{50}^e	
	K_{ispip}^a	K_{ipraz}^a	dose ^b	SBP% ^c	HR% ^d	dose ^b	SBP%	HR%	<i>i.p.</i>	<i>p.o.</i>
8a	1800 \pm 104	13 \pm 0.72		NT		5	— 37	+ 50	60	150
8b	940 \pm 33	35 \pm 1.04		see Tables VII—IX					600	1000
8c	2800 \pm 213	16 \pm 0.49	20	— 20	— 11				300	500
			10	— 23	— 26	10	— 34	+ 27		
			5	— 19	— 25					
8d	340 \pm 19	8.3 \pm 0.23	5	— 35	— 13	10	— 25	+ 24	600	1000
			2	— 14	— 8					
8e	1300 \pm 57	37 \pm 1.48	20	— 39	— 17		NT		600	1000
8f	1800 \pm 118	50 \pm 2.1	20	— 31	— 28		NT		600	1000
			10	— 29	— 20					
			5	— 15	— 20					

^a $K_i = IC_{50}/[1 + (C/K_d)]$ where C = concentration of [3H]ligand and K_d = dissociation constant.

^b mg/kg, *p.o.*

^c Variation percent of systolic blood pressure, peak effect.

^d Variation percent of heart rate, peak effect.

^e Values expressed in mg/kg, mice.

NT: not tested.

none of the compounds described in Table II, with the exception of **8b citrate**, produced a significant drop in the systolic blood pressure in the SHR at the screening oral dose (approximately 1/5 of the oral LD_{50} in mice). **8b citrate** was moderately active at the dose of 50 mg/kg, *p.o.* (Table III). This dose is approximately equivalent to

Table III. Effect of L 15848 (50 mg/kg, *p.o.*) on systolic blood pressure SBP (mm Hg) and heart rate HR (beats/min) in SHR treated once a day for 3 days.

day	0	1st	6	0	3rd	6
hr	0	2		0	2	
SBP	232 ± 6	218 ± 7	212 ± 7*	229 ± 8*	201 ± 7**	213 ± 7*
HR	427 ± 13	455 ± 9	422 ± 12	392 ± 20	447 ± 12**	398 ± 20

Results are expressed as mean ± SE for 5 rats and were compared by means of ANOVA.

* $p \leq 0.005$; ** $p \leq 0.001$.

0.1 mg/kg, *p.o.* of prazosin (Table IV). These findings are in contrast with the significantly low K_i (nM) in the [3H]prazosin binding assay and we attributed them to either poor absorption or fast metabolic inactivation of

8a–f; assuming in either case a species dependent phenomenon we tested the compounds in the RHD and/or in the ND model. The results are presented in Table II. All the compounds decreased systolic blood pressure in RHD and mean blood pressure in ND at doses ranging from 2 to 20 mg/kg, *p.o.* Generally a minor and transient decrease in heart rate was observed in the RHD, whereas a slight increase was observed in the ND. All the compounds with the exception of **8b** did not modify CAR (Table V). **8b** modified selectively CR_2 without effecting motor coordination and muscular strength (UR). Behavior of the dogs was examined for signs of CNS depressant activity, and, in particular, sedation, decreased motor activity and ptosis (Table V). Citrates of **8b** and **8e** produced as the only observable side effect, a slight relaxation of the nictitating membrane; this effect is generally interpreted as a sign of adrenergic activity and it was also observed in the RHD treated with prazosin at the dose of 0.1 mg/kg, *p.o.* which produces only a small decrease in blood pressure (Table VI). The remaining citrates showed signs of CNS depressant activity such as ataxia, sedation, motor incoordination, ptosis as well as relaxation of the nictitating membrane. The highest dose shown in Table II elicited all these effects. The close similarity between **8b** and **8e** is reflected by their activities both *in vitro* and *in vivo*, including the acute

Table IV. Effects of prazosin on systolic blood pressure on SHR rats (5 rats).

Time / hr	SBP (0.1 mg/kg, <i>p.o.</i>)	SBP (0.3 mg/kg, <i>p.o.</i>)	SBP (2 mg/kg, <i>p.o.</i>)
day 1 0	276 ± 6.7	278 ± 3.7	214 ± 9.3
2	260 ± 10.5	234 ± 12**	197 ± 9.8**
6	240 ± 10	148 ± 8**	166 ± 7.7**
day 3 0	278 ± 5.8	270 ± 5.4	213 ± 6.4
2	266 ± 12.1*	238 ± 5.8	179 ± 6.5**
6	254 ± 6.8	216 ± 9.3	177 ± 7.3**

The results were compared by means of Dunnett *T* test.

* $p \leq 0.05$.

** $p \leq 0.01$.

Table V. Evaluation of the CNS side effects of compounds **8a–f**.

Compd	CR_2^a	CR^a	UR^a	Run. Fit (mg/kg, <i>i.p.</i>)	RHD behavior ^b (mg/kg, <i>p.o.</i>)
citrate	(mg/kg, <i>i.p.</i>)				
8a	3/10 (5)	0/10 (5)	0/10 (5)	— 51%(8)	***S, ***A, **R(5)
8b^c	10/10 (30)	0/10 (30)	0/10 (30)	0%(30-60)	*R(30-10)
8c	(10/10) (15)	3/10 (15)	0/10 (15)	— 28%(8)	**S; **MI; **R; *V(20-5)
8d	NT	NT	NT	NT	***S, ***MI, **R(5)
8e	2/10 (60)	0/10 (60)	0/10 (60)	— 21%(8)	*R(20)
8f	2/10 (60)	0/10 (60)	0/10 (60)	+ 27%(8)	*S; *MI(10); *Pt; *R(20)

^a CR_2 = blockade of anticipatory response; CR = blockade of conditioned response; UR = blockade of unconditioned response.

^b RHD = renal hypertensive dog model; *** marked, ** moderate, * slight. A = ataxia, MI = motor incoordination, Pt = ptosis, R = nictitating membrane relaxation, S = sedation, V = vomiting.

^c **8b citrate** = L 15848.

NT = not tested.

Table VI. Effects of prazosin on systolic blood pressure and heart rate in orally treated renal hypertensive dogs.

Dose	0.1 mg/kg, <i>p.o.</i>		0.3 mg/kg, <i>p.o.</i>		0.5 mg/kg, <i>p.o.</i>	
Hours	SBP	HR	SBP	HR	SBP	HR
0	202 ± 6.0	121 ± 15.8	198 ± 4.4	113 ± 6.6	177 ± 3.7	81 ± 4.7
1	197 ± 7.2	127 ± 7.4	183 ± 9.6	113 ± 1.3**	145 ± 3.9*	97 ± 18.4
3	193 ± 9.3	103 ± 22.5	152 ± 8.3**	104 ± 8.3	130 ± 2.5**	71 ± 7.5
5	180 ± 14.4	99 ± 19.2	158 ± 6.0	100 ± 14.0	136 ± 9.5**	75 ± 14.6
7	187 ± 11.7	101 ± 20.9	163 ± 8.8*	100 ± 4	139 ± 7.8**	68 ± 6.5

The results were compared by means of Dunnett *T* test.

* $p \leq 0.05$.

** $p \leq 0.01$.

toxicity. **8b** citrate (L 15848) was chosen for further study based upon the observation that none of the compounds with a 1-methylethyl group (Table I) had been found to be positive in the Ames test (*S. tiphymurium*, TA-100), whereas some compounds of the 1-methyl series and namely those with R¹ equal respectively to H, 3—OCH₃, 4—OCH₃ and 3—CH₃, had been found to be active in this test (data not reported here). The CNS depressant activity was also higher in the compounds of the 1-methyl series [15] (data not reported here). L 15848 showed a hypotensive activity, without associated tachycardia, lasting up to 7 h in RHD orally treated with 5, 10 and 20 mg/kg (Table VII). This last dose is approximately equivalent to 0.3 mg/kg, *p.o.* of prazosin (Table IV). The hypotensive activity of L 15848 was tested in a conscious normotensive dog at the oral dose of 10 and 20 mg/kg, *p.o.* (Table VIII). Both doses produced similar long lasting decreases in the mean blood

pressure with peak effects at the 5th h accompanied by an increase in the heart rate. In another representative experiment, L 15848 did not induce tachyphylaxis when orally administered to one RHD daily for 7 days at 20 mg/kg, *p.o.* (Table IX). The dog did not reveal any sign of CNS depression during this week. The ratio between the doses inducing the anti-hypertensive (20 mg/kg) and the CNS depressant effects was determined in mongrel and beagle dogs (average weight 14 kg; 4 animals/group) administered *p.o.* with increasing doses of L 15848. Slight sedation and motor incoordination was observed in both species at 100 mg/kg. This effect lasted for about 4 h starting 30–60 min after the treatment.

Dissociation of the anti-hypertensive activity and of the CNS depressant effects seems possible when considering the accompanying data (Table II). The ratio between $K_{\text{isipip}}/K_{\text{ipraz}}$ for compounds **8a–f** ranges between a minimum

Table VII. Effect of L 15848 (**8b**) on systolic blood pressure (SBP) and heart rate (HR) in orally treated renal hypertensive dogs.

Hours	Dose 5 mg/kg, <i>p.o.</i> (2 dogs ± SEM)		Dose 10 mg/kg, <i>p.o.</i> (2 dogs ± SEM)		Dose 20 mg/kg, <i>p.o.</i> (4 dogs ± SEM)	
	SBP mm Hg	HR beats/ min	SBP mm Hg	HR beats/ min	SBP mm Hg	HR beats/ min
Basal	195 ± 21.2	106 ± 2.8	195 ± 14.1	94 ± 2.8	204 ± 10.7	108 ± 7.1
1	193 ± 17.7	98 ± 2.8	185 ± 21.2	88 ± 0	207 ± 9.2	110 ± 7.0
3	178 ± 17.7	92 ± 5.7	165 ± 21.1	96 ± 11.3	180 ± 9.1**	106 ± 4.8
5	178 ± 13.2	106 ± 8.5	165 ± 7.1	99 ± 5.7	166 ± 13.2**	106 ± 17.9
7	180 ± 14.1	106 ± 19.8	180 ± 0	88 ± 5.7	160 ± 18.1**	114 ± 9.3

The results were compared by means of Dunnett *T* test.

** $p \leq 0.01$.

Table VIII. Activity of L 15848 on mean blood pressure (MBP, mm Hg) and heart rate (HR, beats/min) in conscious normotensive dog (ND).

Time/h	MBP (dose, mg/kg, <i>p.o.</i>)		%	MBP		%	HR	%
	(10)	(20)		(10)	(20)			
0	118	108		73	70			
1	123	100	+ 4	70	105	— 4		+ 46
3	101	83	— 14	100	117	+ 37		+ 62
5	86	80	— 27	117	107	+ 60		+ 49
7	100	87	— 15	111	83	+ 52		+ 15

of 35 for **8e** and a maximum of 175 for **8c**. These values compare well with the reversed ratio K_{ipraz}/K_{ispip} obtained for a series of neuroleptic agents *i.e.*, MDL-308, haloperidol and chlorpromazine for which compounds this ratio varies from a minimum of 1.39 for chlorpromazine to a maximum of 27.8 for haloperidol [32]. The wide separation between the K_i (nM) values in the [^3H]prazosin and [^3H]spiperone receptor binding assays can be taken as an indication of a predominant anti-hypertensive effect. This index is in line with the inactivity of the compounds in modifying normal and conditioned behavior of mice and rats, respectively, and with their inactivity in antagonizing the mouse behavioral responses induced by high doses of morphine through stimulation of the dopaminergic system (Table V). The values obtained with our compounds for a minor decrement of the running-fit are particularly striking when compared to the values obtained in the same test for MDL-308, haloperidol and chlorpromazine [32]. The lack of anti-hypertensive activity in the rat detracts however, with the possible exception of L 15848, from the importance of the behavioral data obtained in rodents. The 5-fold difference in induction of CNS depressant and hypotensive effects in dogs has been mentioned earlier. The low acute toxicity (1000 mg/kg), the selectivity for post-synaptic α -adrenoceptors, the long lasting anti-hypertensive effect without reflex tachycardia and the apparent lack of tachyphylaxis and of CNS depressant effects make L 15848 a leading product worthy of further research.

Experimental protocols

Chemistry

Melting points were determined on a Buchi 510 capillary apparatus and are uncorrected. IR spectra were measured in nujol mull with a Perkin—Elmer 157 spectrophotometer. ^1H NMR spectra were recorded on a Bruker WP 60 or WH 270 spectrophotometer using CDCl_3 as the solvent and TMS as the internal reference. Resonance values are expressed in ppm (δ). Analyses indicated by the elemental symbols were within 0.4% of the theoretical values and were performed by Dr. M. Nebuloni and Mr. E. Petressi of the Analytical Department of Gruppo Lepetit.

4-Bromo-1-methoxynaphthalene **1**

A solution of 1-methoxynaphthalene (Fluka) (163 g, 1 mol) and 98% *N*-bromosuccinimide (182 g, 1 mol) in carbon tetrachloride (3 l) was heated at reflux with stirring for 4 h while irradiating with a 500 Watt lamp. The solution was cooled to room temperature, the succinimide removed by filtration and the solvent evaporated under reduced pressure. The residue was distilled and the fraction boiling at 142–146°C, 2 mm Hg, was collected to give 217.8 g (91.5%) of **1** [15].

4-Bromo-1-methoxy-2-nitronaphthalene **2**

A solution of 99% nitric acid (22.5 ml, 0.53 mol) in acetic anhydride (200 ml) was added within 5 min to a solution of **1** (119 g, 0.5 mol) and 96% sulfuric acid (0.5 ml) in acetic anhydride (1 l) while maintaining the temperature at -30°C . The reaction mixture was stirred for an additional 10 min and filtered. The solid was triturated with water, recovered by filtration and dried to give 69.3 g (49%) of **2** mp 99–102°C, lit. [17] 114–115°C. Compound **2** was used in the next step without purification. This material was contaminated by small amounts of 2,4-dibromo-1-methoxynaphthalene which did not interfere with the next steps, in the synthesis.

4-Bromo-*N*-(1-methylethyl)-2-nitro-1-naphthylamine **3b**

A solution of isopropylamine (39.5 ml, 0.46 mol) in *N*-methylformamide (200 ml) was added to a solution of **2** in the same solvent (1 l) and the

reaction mixture was maintained at room temperature under stirring for 1 h. The reaction mixture was poured into a saturated aqueous solution of sodium chloride (15 l), the solid was recovered by filtration (125 g) and used in the next step without purification. An analytical sample was obtained by crystallization from isopropanol.

mp 86–88°C. Anal. ($\text{C}_{13}\text{H}_{15}\text{BrN}_2\text{O}_2$) C, H, N. IR: 3300(NH), 1540(NO_2) cm^{-1} . ^1H NMR: 1.30(d, $J=7$ Hz, 6H, CH_3), 4.10(d, sept, $J=7$ Hz, 1H, CHN), 7.4–8.4(m, 5H, aromatic and NH), 8.37(s, 1H, HC-3).

4-Bromo-*N*-methyl-2-nitro-1-naphthylamine (**3a**) was prepared similarly to **2** with a 35% aqueous solution of methylamine and a 92% crude yield. The analytical sample was obtained by crystallization from ethanol. mp 187–88°C. Anal. ($\text{C}_{11}\text{H}_9\text{BrN}_2\text{O}_2$) C, H, N.

3-Chloro-*N*-(1-methylethyl)-*N*-(4-bromo-2-nitro-1-naphthyl)propionamide **4**

A solution of crude **3b** (125 g, about 0.37 mol) in 1,2-dichloroethane (600 ml) was heated at the boiling point and about 100 ml of the solvent was distilled off to remove traces of water from the reaction mixture. 3-Chloropropionyl chloride (41 ml, 0.42 mol) was added dropwise at 60°C and the solution was heated again in order to distill off 400 ml of the solvent during 5 h. The completion of the reaction was achieved by a second addition of the acid chloride (15 ml, 0.15 mol) and heating at the reflux temperature in an oil bath at 120°C for an additional hour. The mixture was cooled to room temperature, diluted with methylene chloride (500 ml) and made alkaline with 1 N NaOH (300 ml) added under vigorous stirring with cooling. The organic layer was dried (Na_2SO_4), evaporated to dryness and triturated twice with *n*-hexane (250 ml) to yield 102.3 g (64%) of **4** containing trace amounts of by products (TLC silica gel; cyclohexane–ethyl acetate = 9:1). The analytical sample was obtained by crystallization from isopropanol.

mp 125–27°C. Anal. ($\text{C}_{16}\text{H}_{18}\text{BrN}_2\text{O}_3$) C, H, N. IR: 1670(CO), 1540(NO_2) cm^{-1} . ^1H NMR: 0.97–1.08(2d, $J=7$ Hz, 6H, CH_3), 2.18–2.67(2ddd, $J_{\text{gem}}=16.5$ Hz, $J_{\text{vic}}=7$ Hz, CH_2CO), 3.80(m, 2H, CH_2Cl), 4.90(sept, 1H, CHN), 7.7–8.5(m, 4H, aromatic), 8.30(s, 1H, HC-3).

5-Bromo-2-(2-chloroethyl)-1-(1-methylethyl)-1H-naphth[1,2-d]imidazole **5** and 5-bromo-2-ethenyl-1-(1-methylethyl)-1H-naphth[1,2-d]imidazole **6**

Iron powder (50 g) was added to a stirred solution of **4** (102.3 g, 0.256 mol) in absolute ethanol (800 ml) and acetic acid (100 ml). The mixture was heated at reflux for 20 min under a nitrogen atmosphere, cooled to room temperature, filtered on celite and evaporated to dryness. The residue was taken up with a solution of 37% HCl (50 ml) in amyl alcohol (500 ml) and heated at reflux for 5 h. After standing at room temperature for 24 h, the solid was recovered by filtration and suspended in a mixture of methylene chloride (2 l) and 30% aqueous ammonium hydroxide (200 ml). The organic layer was separated, dried (Na_2SO_4) and evaporated to dryness. NMR spectra showed that the residue (69.44 g) was a mixture of **5** and **6** in the molar ratio 64% and 36%, respectively. The hydrochloride of **5** could be isolated from the mixture of the hydrochlorides of **5** and **6** by trituration with isopropanol and subsequent crystallization of the residue from 95% ethanol.

mp 236°C with decomposition. Anal. ($\text{C}_{16}\text{H}_{16}\text{BrClN}_2\cdot\text{HCl}$) C, H, N. ^1H NMR of **5** as a free base: 1.80(d, $J=7$ Hz, 6H, CH_3), 3.51(t, $J=7$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{Cl}$), 4.16(t, 2H, CH_2Cl), 5.47(br, 1H, CHN), 7.64(m, 2H, HC-7 and HC-8), 8.20(s, 1H, HC-4), 8.38(d, $J=8$ Hz, 1H, HC-6), 8.51(d, $J=8$ Hz, 1H, HC-9). Pure **6** could be isolated by chromatography of the crude reaction mixture on a silica gel column by eluting with 30% ethyl acetate in cyclohexane.

mp 133–35°C after crystallization from cyclohexane. Anal. ($\text{C}_{16}\text{H}_{15}\text{BrN}_2$) C, H, N. ^1H NMR: 1.79(d, $J=7$ Hz, 6H, CH_3), 5.55(sept, 1H, CHN), 5.69(dd, $J_{\text{gem}}=1.5$ Hz, $J_{\text{cis}}=9$ Hz, 1H, $\text{CH}_2=\text{C}=\text{}$), 6.53(dd, $J_{\text{trans}}=16.5$ Hz, 1H, $\text{CH}_2=\text{C}=\text{}$), 7.02(dd, 1H, $-\text{CH}=\text{C}=\text{}$), 7.64(m, 2H, HC-7 and HC-8), 8.24(s, 1H, HC-4), 8.32(d, $J=8$ Hz, 1H, HC-6), 8.53(d, $J=8$ Hz, 1H, HC-9).

5-Bromo-2-[2-(4-aryl)-1-piperazinyl]ethyl-1-(1-methylethyl)-1H-naphth[1,2-d]imidazoles **7a–c**

General procedure. A mixture of **5** and **6** (10.55 g), as obtained in the preceding step, was dissolved in amyl alcohol (200 ml) and a double molar amount of the appropriate 4-arylpiperazine was added. The solution was stirred and heated at reflux for 2 h under a nitrogen atmosphere. The solvent was distilled off at reduced pressure until a viscous residue was obtained. This residue was carefully triturated at

80°C with hot water (250 ml) under vigorous stirring. After cooling, the suspension was filtered to collect the solid which was repeatedly triturated with water and dried to give **7a–c** in a 89–93% yield. **7a**: mp 211–13°C (ethyl acetate). Anal. ($C_{26}H_{29}BrN_4$) C, H, N . **7b**: mp 161–62°C (ethanol). Anal. ($C_{27}H_{28}BrF_3N_4$) C, H, N . **7c**: mp 147–48°C (methyl *tert*-butyl ether). Anal. ($C_{27}H_{31}BrN_4O$) C, H, N .

2-[2-(4-Aryl)-1-piperazinyl]ethyl-1-(1-methylethyl)-1H-naphth[1,2-d]imidazoles 8a–c

General procedure. A solution of **7a–c** (0.035 mol) and potassium hydroxide (2.23 g, 0.035 mol) in methoxyethanol (500 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium on carbon (4 g) until the absorption of hydrogen ceased (3–7 h). The suspension was filtered and the solvent was evaporated under reduced pressure. The residue was triturated with water, collected by filtration, dried and recrystallized to give **8a–c** in over 90% yield. The formulae and melting points of **8a–c** are listed in Table I. As an example we report the 1H NMR spectrum of **8b**: 1.83(d, $J=7$ Hz, 6H, CH_3), 2.77(m, 4H, CH_2 —piperazine), 3.13(m, 2H, CH_2CH_2N), 3.29(m, 6H, CH_2CH_2N and CH_2 piperazine), 5.47(br, 1H, CHN), 7.09(m, 2H, aromatic), 7.15(s, 1H, *H ortho* to CF_3), 7.36(dd, $J=8$ Hz, 1H, HC-6), 7.47(dd, $J=8$ Hz, 1H, HC-9), 7.60(dd, $J=8$ Hz, 1H, *H meta* to CF_3), 7.69(d, $J=8$ Hz, 1H, HC-5), 7.87(d, 1H, HC-4), 8.02(d, 1H, HC-6), 8.38(d, 1H, HC-9).

N^1 -Methyl-1,2-naphthalenediamine 9a

A solution of **3a** (35.3 g, 0.125 mol) and triethylamine (17.6 ml, 0.125 mol) in methanol (600 ml) was hydrogenated at room temperature and 5 atm pressure in the presence of 10% palladium on carbon (1.8 g) until the theoretical amount of hydrogen was absorbed (about 90 min). The catalyst was filtered off under an argon atmosphere and the solvent was distilled under reduced pressure. The residue was taken up with benzene (250 ml) and filtered under argon over clarcel and bleaching earth. The solvent was evaporated to give 19.73 g (91%) of **9a** as an oil which was used in the next step without purification. Contrary to the base, the monohydrochloride of **9a** was stable in air and was recrystallized from ethanol.

mp 250°C with dec. Anal. ($C_{11}H_{12}N_2 \cdot HCl$) C, H, N, Cl . IR: 3400, 3250 and 1640(NH_2) cm^{-1} .

The catalytic reduction of **3b** was run as described for **3a** and gave **9b** as an oil in a 91% yield. The monohydrochloride of **9b** was recrystallized from ethanol.

mp 250–52°C with dec. Anal. ($C_{13}H_{16}N_2 \cdot HCl$) C, H, N . IR: 3350, 3220 and 1660(NH_2) cm^{-1} .

2-(2-Chloroethyl)-1-methyl-1H-naphth[1,2-d]imidazole 10a

To a solution of **9a** (19.73 g, 0.114 mol) and triethylamine (18 ml, 0.128 mol) in methylene chloride (500 ml) was added under an argon atmosphere at 0–5°C a solution of 3-chloropropionyl chloride (14.55 g, 0.114 mol) in the same solvent (140 ml). The reaction mixture was allowed to reach the room temperature, then it was heated at reflux for 30 min, cooled again to room temperature and washed with water. The organic layer was dried ($MgSO_4$) and evaporated. The residue was taken up with 5% HCl (160 ml) and stirred at 60°C for 3 h. The suspension was filtered, the resulting solution was decolorized with charcoal, cooled to 0°C and cautiously basified with 5% aqueous ammonium hydroxide. The product which precipitated was collected by filtration and recrystallized from 95% ethanol to yield 16.1 g (57.7%) of **10a**. mp 251°C with dec. Anal. ($C_{14}H_{13}ClN_2$) C, H, N . 1H NMR: 3.26(t, $J=7$ Hz, 2H, CH_2CH_2Cl), 3.98(t, 2H, CH_2Cl), 4.0(s, 3H, CH_3), 7.26–8.28(m, 6H, aromatic).

Similarly the reaction of **9b** with 3-chloropropionyl chloride gave the intermediate propionamide. The cyclization to **10b** failed after prolonged heating (24 h) with 5% HCl at 60°C or reflux for 7 h in a 14% solution of HCl in ethanol. The cyclization was finally effected by refluxing for 24 h a solution of the intermediate propionamide and a 10 molar amount of *p*-toluenesulfonic acid in toluene with removal of water by means of a Dean–Stark trap, to give **10b** in 10% yield.

mp 98–100°C after recrystallization from methyl *tert*-butyl ether. Anal. ($C_{16}H_{17}ClN_2$) C, H, N . 1H NMR: 1.82(d, $J=7$ Hz, 6H, CH_3), 3.52(t, $J=7$ Hz, 2H, CH_2CH_2Cl), 4.16(t, 2H, CH_2Cl), 5.55(br, 1H, CHN), 7.61 and 7.66(2t, $J=7$ Hz, 2H, HC-7 and HC-8), 7.70 and 7.83(2d, $J=8$ Hz, 2H, HC-4 and HC-5), 7.97(d, $J=8$ Hz, 1H, HC-6), 8.32(d, $J=8$ Hz, 1H, HC-9).

1-Alkyl-2-[2-(4-aryl)-1-piperazinyl]ethyl-1H-naphth[1,2-d]imidazoles 8d–f

The same procedure described for the preparation of **7a–c** was employed to synthesize **8d** (86%), **8e** (96%) and **8f** (72%) from **10a**, **b**. Formulae and melting points are listed in Table I.

General procedure for the preparation of citrates of 8a–f. A solution of citric acid monohydrate (210 mg, 1 mmol) in methanol (1 ml) was added under stirring to a boiling saturated solution of **8a–f** (1 mmol) in the same solvent. Citrates of **8a**, **b**, **c** were collected by filtration at room temperature.

Pharmacology

In vitro binding studies

In vitro [3H]piperone receptor specific binding was measured according to the method of Creese and Snyder [19]. [3H]Prazosin receptor binding was measured according to Greengrass and Bremner [20] and [3H]clonidine receptor binding according to U'Prichard, Greenberg and Snyder [21]. Results are reported in Table II. Full experimental details of our procedure were reported elsewhere [33, 34].

Anti-hypertensive models

Spontaneously hypertensive rat model

5 conscious male rats (Okamoto strain) [23] were used to test the anti-hypertensive activity of L 15848 and prazosin. The compounds were suspended in aqueous 0.5% methocel and administered by stomach tube each morning for three days. Heart rate and systolic blood pressure were measured before and 2 and 6 h after *p.o.* administration by the indirect tail cuff method (W-W BP recorder, Electronic Basel) on the first and third day (Tables III, IV). Details of our procedure were reported elsewhere [24].

Renal hypertensive dog model

Mongrel conscious hypertensive dogs with the two renal arteries constricted as described by Goldblatt [25] were used. The compounds were administered orally as a powder in gelatin capsules. Systolic blood pressure was measured by the tail cuff method and the heart rate was calculated from pressure tracings. Measurements were taken before and 1, 3, 5, 7 h after treatment [24]. Data are reported in Table II and for L 15848 in Tables VII, VIII and IX and for prazosin in Table VI.

Table IX. Activity of L 15848 on systolic blood pressure (SBP, mm Hg) and heart rate (HR, beats/min) in one conscious renal hypertensive dog (RHD) treated once a day for seven days with 20 mg/kg, *p.o.*

Day	1	3	7
SBP, basal value	210	205	200
SBP, peak effect	160	180	175
HR, basal value	92	92	96
HR, peak effect	104	100	100

Normotensive dog model

Mongrel conscious normotensive dogs (1 dog/compound) with an indwelling catheter in the abdominal aorta were used. Mean blood pressure was registered directly using a Bentley (Trantec 800) pressure transducer connected to a Bettaglia Rangoni polygraph. Measurements were taken before and every hour for seven hours after the treatment. Data are reported in Table II and for L 15848 in Table VIII. A detailed description of the technique has previously been reported [26].

Acute toxicity and behavioral and physiological observations

Approximate LD_{50} values were determined in CF-1 male mice (Charles River strain) weighing 20–23 g arranged in groups of 6 at each dose level (30, 100, 300 and 1000 mg/kg). Compounds were dissolved in dilute HCl or suspended in 0.5% Dow HG 90 methocel in water. All the compounds were given *i.p.* or *p.o.* in a volume of 10 ml/kg to mice. The same volume of the solvent was given to control animals and the mortality was recorded once a day for 5 days. Data are reported

in Table II. The modifications induced in normal behavioral, neurological and autonomic parameters of mice were investigated according to Irwin [27]. Compounds that caused marked or extreme modifications (score 6–8 of the Irwin's system) of any of these parameters at 1/3 the approximate LD_{50} were discarded.

Inhibition of CR_2 response

Male CF Wistar rats weighing 350 g were used. The compounds were administered i.p. as suspensions in 0.5% Dow HG 90 methocel in water and were given at the screening dose of 1/10 the approximate LD_{50} to groups of 10 animals. The results are expressed as the number of animals with inhibition of the CR_2 response vs the total number of animals used in the experiment [28–30]. Data are reported in Table V.

Antagonism to 'running fit'

The hypermotility associated with the compulsive behavioral 'running fit' [31, 32] was induced in mice (CF-1 male, Charles River, 20–23 g, 10 animals/group) by a single injection of a high dose of morphine (60 mg/kg, i.p.) and measured by means of an Animex (LKB, Sweden) activity counter. Drug-pretreated mice (30 min, 12 animals/group) were placed in individual round plexiglass cages and motility was recorded for 15 min starting 30 min after morphine injection. The results are expressed as % variation relative to the control group. The test compounds were administered i.p. as 0.5% Dow HG 90 methocel in water. Data are reported in Table V.

Acknowledgements

The authors are grateful to Mr. E. Gerli for technical assistance in the synthetic work and to Dr. B. Goldstein for mutagenicity tests.

References

- Archibald J. L., Baum T. & Childress S. J. (1970) *J. Med. Chem.* 13, 138
- Archibald J. L., Alps B. J., Cavalla J. F. & Jackson J. L. (1971) *J. Med. Chem.* 14, 1054
- Variava D. H. & Turner P. (1973) *J. Pharm. Pharmacol.* 23, 629
- Rhodes K. F., Stannard M. & Waterfall J. F. (1983) *Biochem. Pharmacol.* 32, 3875
- Archibald J. L., Fairbrother P. & Jackson J. L. (1974) *J. Med. Chem.* 17, 739
- Archibald J. L. & Benke G. A. (1974) *J. Med. Chem.* 17, 736
- Archibald J. L. & Freed M. E. (1974) *J. Med. Chem.* 17, 745
- Lewis P. J., George C. F. & Dollery C. T. (1973) *Eur. J. Clin. Pharmacol.* 17, 739
- Grube E. & Giesing M. (1986) *J. Cardiovasc. Pharmacol.* 8 (Suppl. 2), 43
- Phillips D. K. (1980) in: *Adrenergic Activators and Inhibitors: Handbook of Experimental Pharmacology* (Srekeres L., ed.), Vol. 54/I, Springer-Verlag, Berlin, p. 43
- Schier O. & Marxer A. (1969) in: *Antihypertensive Agents Progr. Drug Res.* (Jucker E., ed.), Vol. 13, Birkhauser Verlag, Basel, p. 121
- Schier O. & Marxer A. (1981) in: *Antihypertensive Agents Progr. Drug Res.* (Jucker E., ed.), Vol. 25, Birkhauser Verlag, Basel, p. 47
- Archer S. 1-[(Benzimidazolyl)lower alkyl]-4-substd-piperazines, U.S. Pat. 3472854, Appl. 29/05/1967; *Chem. Abstr.* 72, 55505
- Archer S. 1-[(Heterocyclyl)-lower alkyl]-4-substd-piperazines, U.S. Pat. 3362956, Appl. 19/08/1965; *Chem. Abstr.* 69, 10467
- Omodei-Salè A. & Toja E. (1981) *Europ. Pat. Appl.*, 34249; (1982) *Chem. Abstr.* 96, 52306f
- Buu-Hoi (1944) *Liebigs Ann. Chem.* 556, 1
- Meldola R. (1885) *J. Chem. Soc.* 47, 502
- Meldola R. & Lane J. H. (1904) *J. Chem. Soc.* 85, 1592
- Creese I. & Snyder S. H. (1978) *Eur. J. Pharmacol.* 49, 201
- Greengrass P. & Bremner R. (1979) *Eur. J. Pharmacol.* 55, 323
- U'Prichard D. C., Greenberg D. A. & Snyder S. H. (1977) *Mol. Pharmacol.* 13, 454
- Ames B. N., McCann J. & Yamasaki E. (1975) *Mutat. Res.* 31, 347
- Okamoto K. & Aoki K. (1963) *Jap. Circ. J.* 27, 282
- Baldoli E., Bianchi G., Corsico N. & Di Francesco G. F. (1985) *Arzneim.-Forsch/Drug Res.* 35, 818
- Goldblatt H., Lynch J., Hanzall R. F. & Summerville W. W. (1934) *J. Exp. Med.* 59, 347
- Di Francesco G., Baldoli E., Marchetti G. & Glasser A. (1986) *Arzneim.-Forsch/Drug Res.* 36, 84
- Irwin S. (1968) *Psychopharmacologia* 13, 222
- Cook L. & Weidley E. (1957) *Ann. N.Y. Acad. Sci.* 66, 740
- Maffii G. (1959) *Arch. Fisiol.* 59, 85
- Maffii G. (1959) *J. Pharm. Pharmacol.* 11, 129
- Diena A., Restelli A., Pugnetti P. & Glasser A. (1982) *13th CINP. Congress, Jerusalem, June 20–25, Abstr.*, p. 122
- Barone D., Corsico N., Diena A., Restelli A., Rodenghi F. & Glasser A. (1982) *J. Pharm. Pharmacol.* 34, 129
- Winters G., Sala A., Barone D. & Baldoli E. (1985) *J. Med. Chem.* 28, 934
- Barone D., Luzzani F., Assandri A., Galliani G., Mennini T. & Garattini S. (1985) *Eur. J. Pharmacol.* 116, 63