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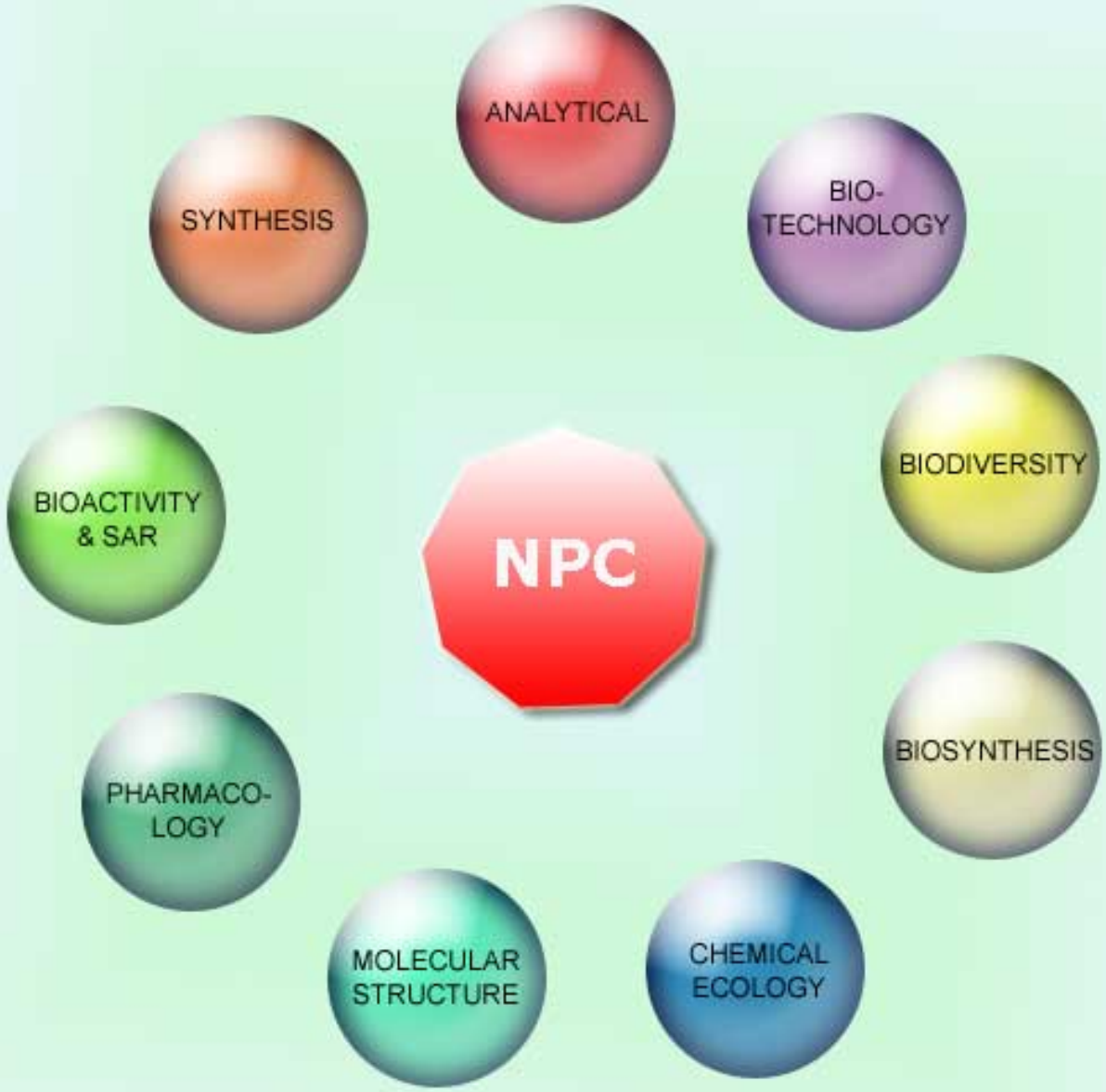

This Issue is Dedicated to
Professor Pedro Joseph-Nathan
on the Occasion of his 65th Birthday

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Monoaminergic, Ion Channel and Enzyme Inhibitory Activities of Natural Aporphines, their Analogues and Derivatives

Bruce K. Cassels* **and Marcelo Asencio**

[a]*Department of Chemistry*, *Faculty of Sciences*, *and Millennium Institute for Cell Dynamics and Biotechnology*, *University of Chile*, *Casilla 653*, *Santiago*, *Chile*

bcassels@uchile.cl

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This paper is dedicated to Professor P. Joseph-Nathan for his 65th birthday

The aporphine alkaloids constitute the second-largest group of isoquinoline alkaloids. Nevertheless, only a relatively small number of natural aporphines and their derivatives have been studied from a pharmacological viewpoint. Here we review the pharmacological data available for these compounds as related to their dopaminergic, noradrenergic and serotonergic activities, and also some results pertaining to their effects on ion channels and enzymes.

Keywords: aporphine alkaloids, semi-synthetic derivatives, dopamine, norepinephrine, serotonin, ion channels, enzymes.

The aporphines are alkaloids and related compounds that share the otherwise unusual 5,6,6a,7-tetrahydro-4*H*-dibenzo[*de,g*]quinoline skeleton (Figure 1).

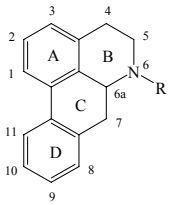


Figure 1: structure and numbering of the aporphine skeleton.

Their natural representatives usually bear a methyl group on N-6, but the corresponding secondary amines or noraporphines, and the *N,N*-dimethylated quaternary salts are also well known. They constitute one of the largest groups of isoquinoline alkaloids and together with biosynthetically related structures such as proaporphines, oxoaporphines, etc., are widespread in the more 'primitive' groups of angiosperms that include the Magnoliaceae, Annonaceae, Monimiaceae, Menispermaceae, Lauraceae, Ranunculaceae, Berberidaceae, Papaveraceae and related families. Although they seldom accumulate in high concentrations, some plant tissues (*e.g.* the bark of *Peumus boldus* Molina, Monimiaceae) can contain more than 10% dry weight of these substances. Both absolute configurations at C-6a occur naturally. As a consequence of their different biosynthetic origins, the ring D-unsubstituted aporphines and those bearing a single oxygen substituent on this ring generally belong to the (6a*R*), levorotatory series, while those with a second substituent on this ring are (6a*S*) and dextrorotatory. It should be pointed out that the semi-rigid conformation of these compounds forces the biphenyl moiety to adopt a twisted conformation with a sign that depends on the configuration at C-6a.

Shamma conjectured that the difference in the absolute values of the optical rotations of 1,2,9,10- and 1,2,10,11-tetraoxygenated aporphines could be explained by a greater torsion angle in the com-pounds with greater steric compression between the C-1 and C-11 substituents [1]. The solid phase torsion angles were discussed thirty years ago for the three aporphine crystal structures known at that time [2], and much more extensively with additional data that indicated that when only one of these key

positions, *i.e.* C-1 or C-11, is substituted with a hydroxyl or a methoxyl group, the torsion angle is less than 30º (sometimes, although not usually, much less), and when these two positions bear oxygen substituents, the torsion angle exceeds 30º, but not by much. It therefore seems possible that crystal packing forces tend to even out the differences between the torsion angles dictated by the twist in the partially saturated ring C and the mutual repulsion of the atoms or substituents at C-1 and C-11 [3]. Unpublished calculations indicate that the aporphine skeleton is far from rigid and some degree of distortion can easily be accommodated by receptor interactions. The same idea is implicit in the suggestion that some aporphines can adopt nearly planar conformations and behave as 'adaptive' DNA intercalators [4]. Thus, a final answer to this problem, of interest for the interactions of aporphines with biological targets, will depend on a systematic study in solution, combining theoretical and experimental approaches.

Dopaminergic activity

The name 'aporphine' stems from that of their first known (unnatural) representative, (-)-apomorphine or (6a*R*)(-)-10,11-dihydroxyaporphine, produced by acid-catalyzed rearrangement of morphine [5]. This substance, a non-selective dopamine receptor agonist, is easily the aporphine that has undergone most pharmacological studies. A very recent review on the development of dopamine receptor subtype-selective agents includes a couple of sections on aporphines, largely apomorphine analogues [6], and was closely followed by another written by the same team, more specifically dedicated to semi-synthetic and natural dopaminergic aporphinoids [7].

The dopaminergic agonist activity of apomorphine itself, long known as a centrally-acting emetic, seems to have been documented for the first time in 1966 [8]. A practical synthesis of enantiomerically pure apomorphines [9] and the subsequent testing of a broad range of synthetic analogues led to the generally accepted proposal that in the aporphine series dopaminergic agonism is associated with the (6a*R*) configuration and enhanced by the presence of a hydroxyl group at C-11 [10]. As the dopaminergic activities of apomorphine and its analogues have been extensively and recently reviewed [7], we will not address them here.

The catatonia that naturally occurring (6a*S*)(+)-bulbocapnine (Figure 2) causes in animals

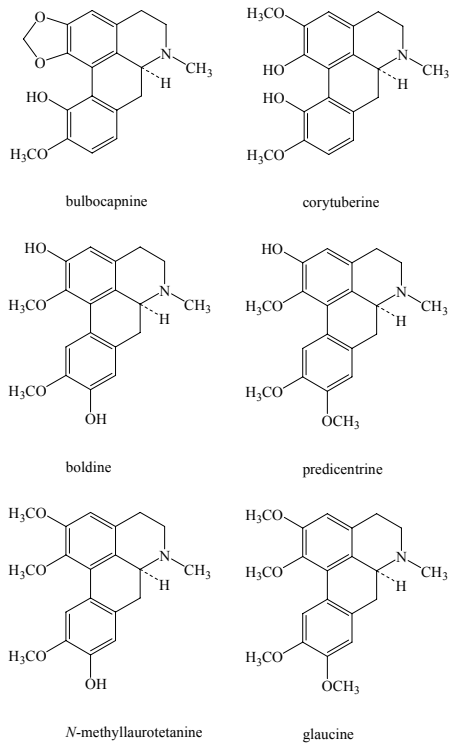
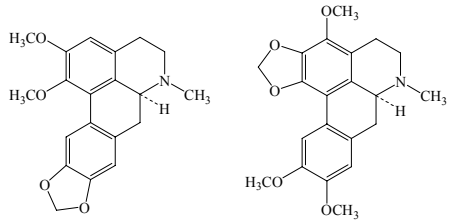
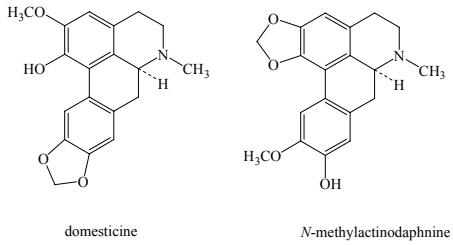


Figure 2: structures of some representative (6a*S*)(+)-aporphine alkaloids.

[11], an early model of schizophrenia, was only ascribed in 1971 to dopaminergic antagonism [12]. Many years later bulbocapnine and its (6a*S*)(+) congeners corytuberine, boldine and glaucine (Figure 2) were shown to exert neuroleptic-like effects [13], suggestive of dopaminergic antagonism as a common feature of this group of natural products. This was confirmed for boldine and glaucine [14] and extended to some halogenated derivatives of these alkaloids and of the closely related predicentrine (9-*O*-methyl-boldine) [15-17]. At about the same time, the expected, nonselective dopaminergic agonist activity of the (6a*R*) and 11-hydroxylated pukateine (Figure 4) was confirmed [18].

Shortly after the identification of bulbocapnine as a dopamine antagonist, a couple of papers confirmed this activity in different models. Thus, it was shown to antagonize adrenergic inhibition in ganglia of the urinary bladder [19] and in right cardioaccelerator postganglionic nerves [20]. In addition to its behavioral effects reminiscent of neuroleptics [13], it was more recently found to inhibit tyrosine hydroxylase, the rate-limiting enzyme of dopamine bio-synthesis, thereby reducing the dopamine content of cultured PC12 cells [21, 22], and providing an additional mechanism to decrease dopaminergic neurotransmission.





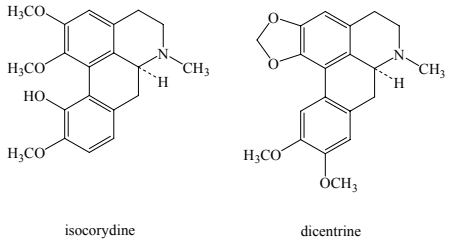


Figure 3: structures of miscellaneous (6a*S*)(+)- aporphine alkaloids.

Once thought to block D1-like dopamine receptors selectively, this was convincingly disproved in 1986 [23]. A similar lack of selectivity, at least as far as dopamine receptor binding is concerned, was observed for boldine and glaucine. Unexpectedly, although the affinities of boldine for D1- and D2-like dopamine receptors *in vitro* are an order of magnitude better than those of glaucine, the latter is more potent in behavioral assays, suggesting that the less lipophilic boldine might have less favorable pharmacokinetics [14]. This hypothesis was later supported by a study showing that the plasma half-life of boldine in rats is of only a few minutes, that the alkaloid is rapidly and extensively glucuronidated in the liver, and that most of the injected boldine is excreted in the urine as a glucuronide. On the other hand, Phase I oxidative demethylation pathways do not seem to be important [24, 25].

The activity of electrophilic substitution products of 1,2,9,10-tetraoxygenated aporphines (Figure 4) deserves special mention. Bromination of boldine at C-3 and C-8 with molecular bromine in carbon tetrachloride had been described many years earlier in a paper on the biosynthesis of this alkaloid [26]. Use of *N*-bromosuccinimide and subsequently *N*-chloro- or iodosuccinimide in trifluoroacetic acid a

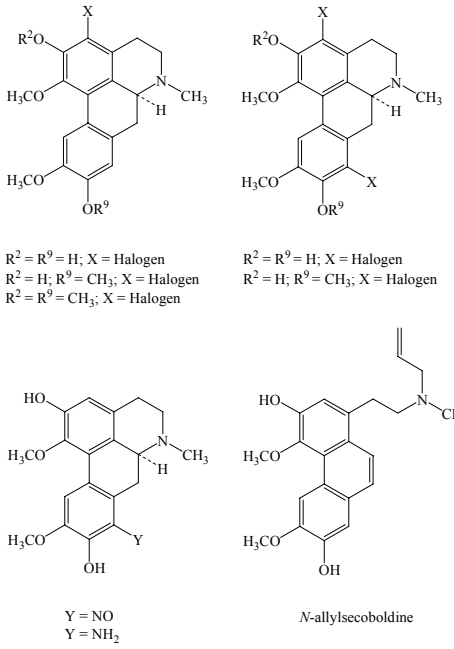


Figure 4: structures of boldine derivatives mentioned in this review.

as the halogen source led to the preparation of the 3-bromo-, 3-chloro-, 3-iodo-, 3,8-dibromo-, and 3,8-dichloro derivatives. Radioligand displacement studies with these products showed that the mono- or dibromo boldines and 3-chloroboldine have slightly decreased affinities for D2-like receptors, but increased D1-like receptor affinities, leading to 9- to 16-fold selectivities. Although 3-iodoboldine binds more strongly than boldine to both major receptor types, it has a very low IC_{50} value at D1-like receptors (2-3 nM), and its selectivity *vs.* D2-like receptors rises to about 32-fold [15].

The *O*-methylation of boldine with diazomethane allows the 9-*O*-methyl derivative predicentrine to be isolated in addition to the di-*O*-methylated glaucine, apparently due to the more rapid reaction of the C-9 hydroxyl group because of its greater acidity and/or its greater exposure due to the preferred coplanarity of the C-10 methoxyl group with aromatic ring D, in contrast to the necessarily perpendicular arrangement of the C-1 methoxyl group as a consequence of its compression between the C-2 hydroxyl and the C-11 hydrogen [27, 28]. The same protocols used before for boldine, glaucine and the haloboldines showed that predicentrine has marginal D1-like dopamine receptor selectivity, but its 3-bromo- and iodo derivatives, though somewhat less potent than 3-iodoboldine, exhibit about 41-fold and 139-fold preferences for the D1-like receptor [17] (Table 1).

Table 1: K_i values for the displacement of [^{3}H]SCH23390 and [^{3}H]raclopride (from rat brain D1-like and D2-like dopamine receptors, respectively) by boldine and derivatives [16, 17].

Aporphine	D1 K_i (nM)	D2 K_i (nM)
Boldine	294	366
3-Chloroboldine	60	507
3-Bromoboldine	49	739
3,8-Dibromoboldine	152	1,345
3-Iodoboldine	2	68
O,O'-Dipivaloylboldine	464	1,898
8-Nitrosoboldine	25	5,116
8-Aminoboldine	962	569
Predicentrine	243	761
3-Bromopredicentrine	15	613
3,8-Dibromopredicentrine	36	866
3-Iodopredicentrine	6	831
Glaucine	2,868	2,831
3-Chloroglaucine	8,566	7,423
3,8-Dichloroglaucine	27,794	7,958
3-Bromoglaucine	522	2,359
3,8-Dibromoglaucine	35,074	10,405
3-Iodoglaucine	2,110	4,514

Boldine undergoes facile nitrosation with sodium nitrite in acetic acid to afford 8-nitrosoboldine and, after catalytic hydrogenation, 8-aminoboldine [29]. Radioligand displacement by these two derivatives showed that the 8-amino compound binds with negligible selectivity to both major dopamine receptor families and with slightly lower affinities than boldine, while 8-nitrosoboldine binds rather strongly to D1-like receptors (IC_{50} = 34 nM) with more than 200-fold selectivity over D2-like receptors [16] (Table 1).

Considering the unfavorable pharmacokinetics of boldine [14, 25], its more lipophilic derivatives might be expected to have stronger *in vivo* activities. For the sake of comparison, the Log *D* values were determined for some of these compounds using the shake-flask method with the 1-octanol / phosphate buffer (pH = 7.4) system and are summarized in Table 2 [30], together with the calculated (ClogP) values for the neutral compounds.

Table 2: Distribution constants (1-octanol / phosphate buffer, pH = 7.4) [30] and ClogP values for boldine and derivatives.

Aporphine	Log *D*	ClogP
3-Iodoboldine	1.88	3.12
8-Nitrosoboldine	1.56	2.05
3-Bromoboldine	1.23	2.93
3-Chloroboldine	1.19	2.73
O,O'-Dipivaloylboldine	1.18	4.41
Glaucine	0.95	3.08
Predicentrine	0.79	2.60
Boldine	0.78	2.13
8-Aminoboldine	0.36	0.80

The ester derivative 2,9-*O,O'*-dipivaloylboldine showed an unexpectedly low distribution constant, but it nevertheless binds to D1-like receptors with only slightly lower affinity than boldine, and also has modest affinity for D2-like receptors [16]. The latter observation is of interest considering the adrenergic antagonist activity attributed to 2,9-*O,O'*-diacetylboldine (see below).

Adrenergic, calcium channel and phosphodiesterase inhibitory activities

(6a*S*)(+)-Glaucine has been in clinical use in Eastern Europe for many years as a non-narcotic antitussive, and has therefore been the subject of many pharmacological studies. Its hypotensive action, for example, is known at least since 1979 [31]. Experiments with rat vas deferens suggested that glaucine is a non-selective α_1- and α_2-adrenoceptor antagonist, and a weak calcium channel blocker. Interestingly, in spite of its recorded α-adrenoceptor antagonism, glaucine did not modify norepinephrine-induced cardiovascular effects, but markedly reduced those elicited by nicotine [32]. In conscious, normotensive rats, glaucine had no appreciable cardiovascular effects, but in anesthetized animals it significantly reduced mean arterial pressure and heart rate [33].

The first report on the α_1-adrenergic antagonism of the (6a*S*)(+) aporphine alkaloids boldine and glaucine (Figure 2) was apparently published in 1990 [34]. In a subsequent paper, boldine was shown to inhibit contractions evoked by noradrenaline in rat aorta and also behaved as a calcium entry blocker with affinity for the benzothiazepine but not the dihydropyridine binding site on voltage-operated calcium channels [35]. Unlike glaucine [36,37], which binds to α_1-adrenoceptors and the benzothiazepine site on calcium channels, but also inhibits phosphodiesterase IV, boldine has negligible inhibitory effects on all phosphodiesterase forms. Boldine and glaucine were studied further to show that their specific calcium entry blocking activity does not affect the cellular contractile machinery or intracellular calcium levels [38]. α_1-Adrenoceptor blockade by boldine of noradrenaline-elicited contraction of the guinea-pig aorta has the rather low pA_2 value of 5.64 [39]. Comparison of boldine with its 9-*O*-methyl derivative predicentrine and its 2,9-*O,O'*-dimethyl derivative glaucine revealed that, although all three alkaloids bind selectively to α_1-adrenoceptors, the affinity of glaucine is about 10 times lower than that

of the other two, which are also more subtype-selective, suggesting that both affinity and selectivity are favored by the presence of a hydroxyl group at C-2 [40].

The vasodilator effects of boldine are related to both α_1 and α_2-adrenoceptor antagonism [41,42]. A more detailed study of boldine in a number of different models, complemented with radioligand binding studies, revealed that this alkaloid binds to human α_{1A}-adrenoceptors with pK_i = 7.21, but does not discriminate between α_{1B}- and α_{1D}-receptors for which its affinity is barely micromolar. The alkaloid also shows calcium channel blocking properties approximately 50 times weaker than diltiazem [43].

Several of the substituted boldine derivatives (Figure 4) mentioned above as dopamine receptor ligands were assessed at α_1-adrenoceptors in rat brain cerebral cortex membranes. The halogenated compounds bound slightly more strongly than boldine, but its 8-nitroso (reported erroneously as the 3-nitroso) [44] and 8-amino derivatives exhibited very low affinity for the α_{1A} subtype, and 8-aminoboldine is practically devoid of affinity for the α_{1D} subtype (pK_i < 2.5) [45] (Table 3). The boldine derivatives bound poorly to the diltiazem site of potential-operated calcium channels [44].

Table 3: pK_i values for the displacement of [^{3}H]prazosin (from rat brain α_{1A} receptor high affinity sites) by boldine and derivatives [40, 44, 45].

Aporphine	pK_i
Boldine	8.31
3-Chloroboldine	8.65
3-Bromoboldine	8.93
3,8-Dibromoboldine	8.87
8-Nitrosoboldine	6.41
8-Aminoboldine	6.37
Predicentrine	8.13
Glaucine	7.12

2,9-*O,O'*-Diacetylboldine is now sold as a skin-lightening component of cosmetic ingredients such as Lumiskin™ and Lumiwhite™. This activity is ascribed to α-adrenergic antagonism (which seems less surprising given the D1-like dopaminergic activity of the dipivaloyl ester [16]), related to interference with intracellular calcium levels leading to inhibition of the phospholipase C / IP3 / PKC cascade and the subsequent down-regulation of tyrosinase activity [46, 47].

(6a*S*)(+)-Dicentrine (Figure 3) was shown to be a vascular α_1-adrenoceptor antagonist with higher potency that phentolamine (pA_2 = 8.19 *vs* 7.53) [48]. In anesthetized rats, 0.1, 0.5 and 1.0 mg/kg i.v. elicited a dose-related reduction of mean arterial pressure which reached its maximum after 5-10 minutes and persisted for 2 hours without causing significant changes in heart rate, output or stroke volume. Oral administration (5 or 8 mg/kg) to conscious, spontaneously hypertensive rats caused a hypotensive effect lasting 15 hours. As this effect was abolished by α_1-adrenoceptor blockade, it was concluded that antagonism of these receptors underlies the reduction of arterial blood pressure [49]. The same team showed subsequently that dicentrine blocks sodium and potassium channels, affecting the function of isolated rat heart cells in the same way and to nearly the same extent as quinidine [50]. Further evidence that dicentrine seems to be an α_{1D}-(*vs* α_{1B}) adrenoceptor blocker was provided by a comparative study in rat aortic rings and spleen [51].

(6a*S*)(+)-Nantenine has attracted an unusual degree of attention in the last few years. A preliminary study of its vasorelaxant effects in rat aorta, suggesting α_1-adrenergic and calcium channel antagonism, but neither activation of ATP-sensitive potassium channels nor calcium-activated high-conductance potassium channels, was published in 2001 [52]. A couple of years later similar conclusions were reached in rat vas deferens [53] and, comparing several different rat isolated tissues, the α_1-adrenergic (and serotonergic, see below) blocking activities were judged to be responsible for the pharmacological effects at concentrations below 1 μM, while above this concentration calcium channel blockade, and possibly protein kinase C inhibition and/or α_2-adrenoceptor antagonism were viewed as likely mechanisms [54]. The *in vivo* inhibition of adrenergic pressor responses in both anesthetized and pithed rats and in guinea pig vas deferens also led to the conclusion that this alkaloid antagonizes α_1- and α_2-adrenoceptors and 5-HT_{2A} serotonin receptors [55]. These results were confirmed in part in a later paper, although the participation of α_2-adrenoceptor antagonism and calcium channel blockage was put in doubt [56].

(6a*S*)(+)-*N*-Methylactinodaphnine (Figure 3) is an antagonist of the phenylephrine-elicited contraction of rat thoracic aorta and the clonidine-induced inhibition of the twitch response of rat vas deferens. Additional experiments showed that it is a selective α_1-adrenoceptor antagonist with selectivity for the

α_{1A} subtype and a rather weak blocker of serotonin receptors (see below), but it has extremely low affinity for calcium channels and for a variety of other receptors [57]. Ocoteine and *N*-methylactinodaphnine have very similar pharmacology [58]. Isocorydine (Figure 3) also relaxes noradrenaline or KCl-induced contraction of the rat aorta, suggesting that it is another α_1-adrenoceptor and calcium channel blocker rather like the aporphines mentioned above [59].

The adrenergic effects of a few (6a*R*)(-)-aporphines (Figure 5) have also been examined. Norushinsunine is the only 7-hydroxylated aporphine (strictly, a noraporphine) studied so far, and it seems to differ from the other α_1-adrenoceptor blockers in that its vasorelaxant effect depends more strongly on the blockade of L-type calcium channels [60]. (6a*R*)(-)-Anonaine (the unhydroxylated analog of nor-ushinsunine) and roemerine (*N*-methylanonaine) behave similarly [61]. A more recent comparison of anonaine, roemerine and pukateine determined that they resemble the (6a*S*)(+)-aporphines in that they are more potent as α_1-adrenoceptor inhibitors than as voltage-operated calcium channel blockers (Table 4).

Table 4: pK_i values for the displacement of [^{3}H]prazosin (from cloned α_1 receptor subtpes) by 1,2-methylenedioxy (6aR)-aporphines [62].

Aporphine	α_{1A} pK_i	α_{1B} pK_i	α_{1D} pK_i
Anonaine	6.18	5.13	5.64
Roemerine	6.61	5.53	6.22
Pukateine	5.84	5.00	6.10

Thus, all three block α_{1A}- and α_{1D}-adrenoceptors more than the α_{1B} subtype. Similarly to (6a*R*)(-)-norushinsunine, mentioned above [60], their affinities are rather low and they bind to the diltiazem calcium channel site with the also low pK_i values 4.99, 5.26, and 4.62, respectively [62]. Likewise, none of them inhibit the phosphodiesterases tested (PDE 1-5) to any significant extent [62].

Boldine and other aporphines, particularly after quaternization of the nitrogen atom, readily undergo Hofmann elimination to afford ring B-opened seco-aporphines. *N*-Allylsecoboldine (Figure 4) has been rather more extensively studied than others, and was early shown to block α_1-adrenergic receptors and potential-gated calcium channels [77]. Its α_{1A}-adrenoceptor blocking activity has been suggested to underlie the inhibitory effect of this derivative (albeit at micromolar concentrations) on neurally mediated contraction of human hyperplastic prostate tissue

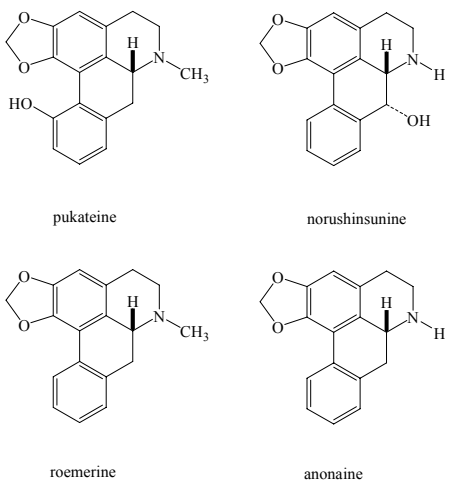


Figure 5: structures of miscellaneous (6a*R*)(-)- aporphine alkaloids.

[78]. *N*-Carbethoxysecoglaucine, on the contrary, was inactive on rat isolated aorta and did not modify arterial pressure or heart rate in rats nor affect the rate and force of contraction of isolated rat atria [33].

Serotonergic activity

Nantenine was first recorded as a vascular serotonergic antagonist in 1984 [63]. This alkaloid inhibits the 5-HT_{2A} receptor-mediated head-twitch, but not the 5-HT_{1A} induced head weaving response in mice at 13.3, 20, and 30 mg/kg i.p. Nantenine showed slightly selective affinity for 5-HT_2 (K_i = 0.4 μM, pK_i = 6.4) over α_1-adrenoceptors and D_2-dopaminergic receptors (K_i = 2.1 and 1.7 μM, pK_i = 5.7 and 5.8, respectively) [64]. It also inhibits several cation-dependent ATP-ases, apparently by interacting with the substrate or by competing with the inorganic cation [65]. The anticonvulsant effect of nantenine at low doses seems to be due to the stimulation of phosphatase activity, while its convulsant effect at high doses might be related to Na^+/K^+-ATPase inhibition [66]. The anticonvulsant and convulsant profiles of nantenine were further studied in the pentylenetetrazole and electroshock-induced seizure models [67]. A recent paper reported that nantenine blocks and reverses hyperthermia, attenuates lethality and reduces hyperlocomotion and head twitches induced in mice by the paradigmatic entactogen MDMA ('ecstasy') [68]. All these effects of nantenine can be attributed at least in part to blockade of serotonin and/or norepinephrine receptor activation.

Quite recently, (+)-*N*-methyllaurotetanine (Figure 2), which only differs from nantenine in that the

9,10-methylenedioxy ring is open, was shown to have high affinity for 5-HT_{1A} receptors (K_i = 85 nM, pK_i = 7.07) [69]. Glaucine is a fairly potent antagonist of serotonin-induced contraction of rat thoracic aorta [70]. Dicentrine (Figure 3) relaxes serotonin-induced rat stomach smooth muscle, suggesting that it can antagonize 5-HT_{2B} receptors [71].

Assays of (±)-nantenine, (±)-nornantenine, (±)-*N*-ethylnornantenine, (±)-domesticine and (±)-nor-domesticine are unusual instances of the testing of synthetic, racemic aporphines [72,73]. (±)-Domesticine was found to be an α_{1D}-adrenoceptor antagonist in rat tissues, with 34-fold and 9-fold selective binding with regard to cloned human α_{1A} and α_{1B} receptors, respectively, and 183-fold selectivity with regard to rat cerebral cortical 5-HT_{1A} receptor binding [74]. In general, affinities and functional potencies were lower for the secondary amines and for the nantenines than for the domesticines [72]. Possible interactions between the enantiomers in these studies could obscure some of their effects. It should be pointed out that these authors refer erroneously to the selective α_{1D}-adrenoceptor blocker (-)-discretamine as an aporphine when it is in fact a berbine or tetrahydroberberine alkaloid.

As mentioned above, *N*-methylactinodaphnine and ocoteine have weak antagonist activity at serotonin receptors [57,58]. (+)-Glaucine relaxes serotonin-elicited rat aortal contraction with similar potency to papaverine, although the specific 5-HT receptor subtype involved was not identified [70].

Nicotinic cholinergic activity

To the best of our knowledge, boldine and a couple of its brominated derivatives are the only aporphines that have been tested as nicotinic cholinergic ligands. Their affinities for neuronal nicotinic acetylcholine receptors (nAChR), an important family of ligand-gated cation channels, decrease on going from the 3-bromo- to the 3,8-dibromo compound, suggesting that halogenation is not a useful approach to obtain more active nAChR blockers [75] (Table 4).

On the other hand, *N,N*-dimethylaporphinium salts, like many other quaternary nitrogen derivatives, could be expected to block nAChR. A study dating back to 1975 showed that the metho salts of the natural (6a*S*)(+)-corydine, isocorydine, glaucine, and boldine, are slightly more potent than their unnatural enantiomers at the neuromuscular junction [76]. Quite recently it was shown that the methiodides of boldine, predicentrine, glaucine, 3-bromo- and 3,8-dibromo-boldine, and xanthoplanine iodide (the methiodide of *N*-methyllaurotetanine) also block neuronal nicotinic acetylcholine receptors at low micromolar concentrations, with slight (2 to 20-fold) selectivity for the α4β2 over the α7 subtype [75] (Table 5).

Table 5: Binding affinities of some quaternary and tertiary (6a*S*)-aporphines for the major (cloned human) central nervous system nicotinc acetylcholine receptor subtypes [75].

Aporphine	α7 K_i (μM)	α4β2 K_i (μM)
Boldine methiodide	15	2.5
Predicentrine methiodide	21	0.97
Xanthoplanine iodide	10	0.91
Glaucine methiodide	18	10
Boldine	67	3
3-Bromoboldine	83	30
3,8-Dibromoboldine	95	31

Conclusions

Aside from the probably general antioxidative, cytoprotective and related properties of aporphine alkaloids, their derivatives and enantiomers [79], a salient feature of the pharmacological studies reviewed here is the recurrent record of affinities for monoamine receptors. Although most of these studies have dwelt on a single major receptor type (*i.e.* α_1-adrenoceptors, D_1-like or D_2-like dopamine receptors, etc.), it seems likely that many aporphines bind significantly to several of these receptors, with varying degrees of selectivity. In this sense, one might suppose that this class of compounds contains many 'dirty' drugs, meaning that they interact with two or more biological targets. Although the drug discovery efforts of the major companies have concentrated for the last couple of decades on agents acting on single targets, it is becoming increasingly clear that disorders with multifactorial origins tend to respond better to multifunctional drugs [80,81].

This is particularly true of neuropsychiatric illnesses, as shown for the atypical antipsychotics [82]. Many of the older neuroleptic drugs that are characterized mainly by their D_2 dopaminergic receptor antagonism have a tendency to cause serious extra-pyramidal side effects (motion disorders) and are of little use in the management of the so-called negative symptoms of schizophrenia (flattened affect, cognitive impairment). On the other hand, atypical antipsychotics such as clozapine, olanzapine and risperidone have

reduced extra-pyramidal liability and also exert beneficial effects on negative symptomatology. These advantages of the newer drugs have been variously ascribed to the blockade of neuro-transmitter receptors other than the usually implicated dopaminergic D_2 type and the serotonergic 5-HT_2 type. More recently, the activation of 5-HT_{1A} receptors by these drugs has been suggested to result from simultaneous weak D_2 and potent 5-HT_{2A} antagonism [83], which may be responsible for the improved cognitive function observed with some of these compounds. This and related findings have led to a search for novel potential antipsychotics with 5-HT_{1A} agonist activity [84-86] which in addition has been suggested to be useful in the control of parkinsonian tremor [87].

Among the aporphines reviewed here, D1-like and D2-like receptor antagonism (or perhaps partial agonism) and binding to 5-HT_{1A} receptors have been recorded. It does not seem to be an excessive stretch of the imagination to hope that these activities associated with the aporphine scaffold can be modulated until an optimal balance is struck for the treatment of a particular subset of patients. Similarly, our suggestion that the antioxidative, non-selective dopamine agonist pukateine might be a lead for the development of novel antiparkinsonian drugs [18], could be complemented with a search for analogues that additionally inhibit monoamine oxidase-B and/or chelate intracellular iron. Further exploration of the adrenergic antagonist, calcium channel blocking and phosphodiesterase inhibitory actions of aporphines could make valuable contributions to the therapy of a range of cardiovascular diseases. In summary, the relatively scarce pharmacological studies carried out on natural aporphines, considering the enormous structural variety of these alkaloids, have focused excessively on single targets and have made very limited incursions into semi-synthetic modifications. Interest in these compounds in the pharmaceutical industry is understandably limited, but the enormous potential for the discovery of useful drugs based on sometimes quite abundant alkaloids poses a most attractive challenge for natural products chemists with a taste for medicinal chemistry and a friendly relationship with pharmacologists.

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