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α_2-Adrenoceptor agonist properties of *exo*- and *endo*-isomers of 2-amino-6,7,dihydroxybenzonorbornene designed as rigid catecholamines

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A series of *N*-substituted *exo*- and *endo*-isomers of 2-amino-6,7-dihydroxybenzonorbornene, designed as rigid catecholamines, have been studied in the pithed rat in-vivo, as vasoconstrictor agents, and as inhibitors of the twitch response in the transmurally stimulated guinea-pig ileum. The *exo*-isomers examined were vasoconstrictor agonists in the pithed rat and inhibited the twitch response of the ileum. The corresponding *endo*-isomers were inactive in both preparations. The *exo*-isomers were less potent than the α_2-receptor agonist TL99, but were all directly acting vasoconstrictor agents, since they were still effective in reserpine-pretreated animals. Responses induced by members of the *exo*-series were selectively antagonized by the α_2-receptor antagonist rauwolscine, but were not antagonized by the α_1-receptor antagonist, prazosin, or the dopamine-receptor antagonist α-flupenthixol. The results demonstrate important conformational requirements for the interaction of catecholamines at presynaptic or postsynaptic α_2-receptors, and suggest that a fully extended or *anti*-conformation of the noradrenaline molecule is involved in α_2-receptor-agonist interaction.

A considerable body of evidence is now available which suggests that α-adrenoceptors can be classified into α_1- or α_2-categories (Langer 1974; Berthelsen & Pettinger 1977). Futhermore, α-adrenoceptors are located both prejunctionally (for a recent review see Langer 1981) and postjunctionally on vascular smooth muscle, where they can mediate vasoconstriction (for recent reviews see Timmermans & Van Zwieten 1981; McGrath 1982).

A number of studies have been documented which relate to the conformational requirements of agonist molecules at the α-adrenoceptor (Kier 1969; Erhardt et al 1979; De Marinis et al 1981; Ruffolo et al 1982). Although some reports have been purely hypothetical, in other reports, the use of non-selective agonist molecules or the use of biological tissue which contains a heterogeneous population of α-receptors have frequently detracted from the validity of these structure-activity studies. The neurotransmitter noradrenaline (NA) has an affinity for both prejunctional α_2- and postjunctional α_1 and α_2-adrenoceptors, and since NA is a flexible molecule, it can exist in several conformational forms. It is generally believed that the topography of the different adrenoceptors is such that they may bind selectively to different conformational forms of the NA molecule. The understanding of drug-receptor interactions involving α-adrenoceptors has recently been aided by the use of selective agonists at α_1- or α_2-receptors, and 2-aminotetrahydronaphthalene (ATN; 2-aminoTetralin) derivatives such as TL99 (6,7) and M7 (5,6-dihydroxy-2-*NN*-dimethylATN) have particularly potent and selective agonist activities at α_2-receptors (Hicks & Cannon 1979, 1980; Drew 1980; Shepperson & Langer 1981). However, these compounds represent conformationally loose molecular structures, which have limited usefulness in studying α_2-adrenoceptor topography, since they still retain a good degree of structural flexibility.

To further study the conformationl requirements for the interaction of agonist molecules at α_2-receptors, we have synthesized a series of substituted *exo* and *endo* isomers of 2-amino-6,7-dihydroxybenzonorbornenes (Ia–Ic and IIa–IIc respectively, Fig. 1), which are completely rigid molecules. These structures, although lacking the aliphatic β-hydroxyl group present in the NA molecule provide spatial approximations of the catechol and amino groups in the *anti*- (extended) or *gauche*- (folded) forms of the NA molecule (see Fig. 1, Structures III and IV).

A determination of α-receptor agonist activities of the 6,7-dihydroxy-2-amino-benzonorbornenes is of

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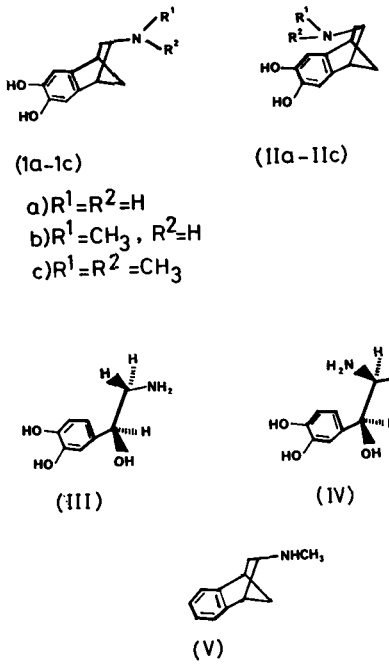

FIG. 1. The structures of the *exo*-(Ia–Ic) and *endo*-(IIa–IIc)-isomers of 2-amino-6,7-dihydroxybenzonorbornene and their *N*-methyl and *NN*-dimethyl derivatives, the *anti*-(III) and *gauche*-(IV) conformations of noradrenaline (NA), and *exo*-2-methylaminobenzonorbornene (V).

particular interest, since these compounds also represent rigid analogues of the very potent α_2-receptor agonist TL99 (Hicks & Cannon 1980), albeit in one of its extreme conformational forms. This communication further extends the evaluation of the non-hydroxylated *exo*- and *endo*-2-aminobenzonorbornenes previously described as sympathomimetics (Burn et al 1980). Preliminary results have been presented to the British Pharmaceutical Conference (Burn et al 1981).

MATERIALS AND METHODS

Preparation of 2-aminobenzonorbornene derivatives

exo-2-Methylaminobenzonorbornene (V) was prepared by treatment of *exo*-2-aminobenzonorbornene (Burn et al 1976) with formic acid, followed by lithium aluminium hydride reduction of the resulting *N*-formyl product, and was used as the fumarate salt. The *exo*-amines Ia-Ic and the *endo*-amines IIa–IIc were prepared as described previously (Burn et al 1982) and were used as hydrobromide salts. The stereochemical identity of the above compounds was established by nuclear magnetic resonance spectroscopic analysis (Burn et al 1978, 1982).

Pithed rat preparation

Male normotensive Wistar rats (250–380 g) were anaesthetized with pentobarbitone (60 mg kg^{-1}; i.p.), pithed through the orbit and respired with room air. A carotid artery and jugular vein were cannulated for measurement of blood pressure and injection of drugs, respectively. All animals were treated with atropine (0·5 mg kg^{-1}; i.v.) and allowed to stabilize for 30 min before injection of test compounds.

Where indicated, propranolol (1 mg kg^{-1}; i.v.) was administered to antagonize β-receptor responses. Some experiments were performed in reserpinized rats (5 mg kg^{-1}; i.p. 24 h) in order to assess the direct sympathomimetic activity of the test compounds. In reserpinized animals electrical stimulation of the whole spinal cord failed to increase blood pressure. Postsynaptic α-adrenoceptor activity was assessed by constructing vasoconstrictor dose-response curves for diastolic blood pressure (DBP) for all agonists (i.v.). No more than three test compounds were used in each animal and these were administered using a randomized block design. In some experiments, administration of approximately ED50 doses of agonist (dose to cause 50 mm Hg DBP) were carried out after treatment for 15 min, with increasing doses of prazosin or rauwolscine, in order to demonstrate selectivity for α_1- or α_2-adrenoceptors.

Guinea-pig ileum

Prejunctional α_2-receptor activity was assessed in the guinea-pig isolated ileum preparation. Male (Duncan Hartley) guinea-pigs (400–450 g) were killed by cervical dislocation. Terminal ileum was set up for transmural field stimulation in Krebs solution at 37 °C, according to Drew (1978). Constant twitch responses were obtained to electrical stimulation (60 v; 1 ms; 0·1 Hz) and inhibition of the twitch response was induced by cumulative addition of agonist into the bath. TL99 (1·0–60 μM) was routinely used as the standard α_2-receptor agonist (Hicks 1981; Maixner et al 1981a), and only one benzonorbornene derivative was administered in each preparation.

In some studies, cumulative inhibitory responses were induced by *exo*-2(*N*-methyl)-amino-6,7,-dihydroxybenzonorbornene (*exo*-Ib) or TL99 before and after incubation (1 h) with increasing concentrations of rauwolscine (10^{-8}, 5×10^{-8} and 10^{-7} M), prazosin (10^{-5} M), α-flupenthixol (10^{-7} M) or propranolol (10^{-7} M), where applicable antagonist

potency was determined as pA_2 (Arunlakshana & Schild 1959).

Anticholinergic activity of *exo*-Ib was evaluated in the non-stimulated ileum against the contractile effects of acetylcholine.

Drugs used

Acetylcholine (Sigma), Atropine sulphte (BDH), α-flupenthixol hydrochloride (Janssen), (−)-phenylephrine hydrochloride (Koch-Light), prazosin hydrochloride (Pfizer), propranolol hydrochloride (ICI), rauwolscine hydrochloride (Karl-Roth), reserpine (Koch-Light), TL99 hydrobromide (Research Biochemicals Incorporated).

RESULTS

Pithed rats

Vasoconstrictor dose response curves were constructed for *exo* 2-amino-6,7,dihydroxybenzonorbornene and its *N*-methyl and *NN*-dimethyl derivatives (see Fig. 1, Ia–Ic). Typical vasoconstrictor dose-response curves for *exo*-Ib and *endo*-IIb are shown in Fig. 2.

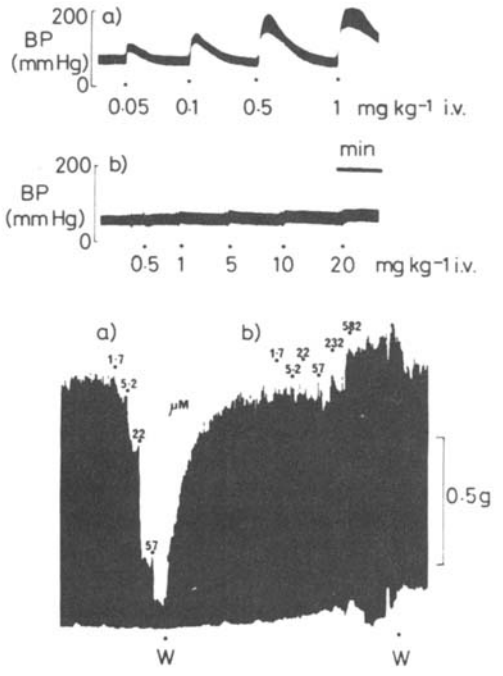

FIG. 2. Vasoconstrictor (DBP) dose-response curves in a propranolol (1 mg kg^{-1} i.v.) treated pithed rat (upper) and inhibition of the twitch response in the transmurally stimulated guinea-pig ileum (lower) in response to (a) *exo*-2-*N*-methylamino-6,7-dihydroxybenzonorbornene (*exo*-Ib) or (b) *endo*-2-*N*-methylamino-6,7-dihydroxybenzonorbornene (*endo*-Ib).

All *endo*-isomers (IIa–IIc) were inactive as vasoconstrictor agonists in doses of 20 mg kg^{-1} i.v. The non-hydroxylated compound, *exo*-2-methylaminobenzonorbornene (V) also failed to cause vasoconstriction at 10 mg kg^{-1} i.v. (Table 1).

Table 1. Vasoconstrictor agonist potencies of *N*-substituted 2-aminobenzonorbornenes in pithed rats.

Agonist	Control	Vasoconstrictor effect ED50 (μg kg^{-1}) Reserpine[a]	Propranolol[b]
TL99	2·6 (1·9–3·2)	0·5 (0·2–0·8)*	1·68 (1·37–1·99)
Exo-Ia	315 (225–437)	229 (107–488)	272 (209–354)
Exo-Ib	587 (425–813)	323 (164–638)	175 (117–263)*
Exo-Ic	4570 (3483–5997)†	6025 (3019–11 748)†	2722 (2187–3388)*†
Exo-V	>10 000	NT	>10 000
Endo-IIa–a	inactive 20 000	inactive 20 000	inactive 20 000

ED50 = dose (+95% confidence limits) to cause 50 mm Hg rise in DBP.
* Significantly different from control.
† Partial agonist.
(a) reserpine (5 mg kg^{-1} i.p. 24 h), (b) propranolol (1 mg kg^{-1} i.p.), n = 6–8.
NT Not tested.

Vasoconstrictor potencies (ED50) of benzonorbornene derivatives are shown in Table 1, in control, reserpinized (5 mg kg^{-1} i.p.; 24 h) and in propranolol (1 mg kg^{-1} i.v.) treated rats. *Exo*-Ia and *exo*-Ib were full vasoconstrictor agonists of similar potency, but were less potent than TL99 (maximum vasoconstriction = 90–100 mm Hg DBP). *Exo*-Ic was a partial agonist in the pithed rat and was 10–20 times less potent than the other *exo*-isomers (Table 1).

Pretreatment with propranolol significantly ($P < 0.05$) increased the potency of the *exo*-compound Ib (Table 1). The vasoconstrictor effects of these compounds were not significantly changed in reserpinized rats, while the potency of TL99 was significantly ($P < 0.05$) increased in these reserpine-pretreated animals (Table 1). Rauwolscine (1 mg kg^{-1} i.v.; 15 min) caused a rightward parallel displacement of the vasoconstrictor curves induced by TL99 (dose ratio 11 ± 1·7) or *exo*-Ib (dose ratio 9·4 ± 2·6). The effects of prazosin (0·0005–2·0 mg kg^{-1} i.v.) or rauwolscine (0·5–4·0 mg kg^{-1} i.v.) were further examined against repeated equieffective, submaximal vasoconstrictor doses of either phenylephrine (PE) (5 μg kg^{-1} i.v.), TL99 (5 μg kg^{-1} i.v.) *exo*-Ia–Ib (500 μg kg^{-1} i.v.), or *exo*-Ic (5 mg kg^{-1} i.v.). Antagonist potencies are shown in Table 2, and were assessed as ID50 (dose of antagonist to cause 50% inhibition of pressor effects). Rauwolscine was equipotent against TL99 or *exo* Ia–Ic, but was also of similar potency against PE (Table 2). Prazosin was an extremely potent antagonist of PE-induced vasoconstriction (Table 2)

Table 2. Antagonist potencies of rauwolscine or prazosin in propranolol treated pithed rats.

Agonist	n	ID50 (mg kg^{-1}) Rauwolscine	Prazosin
TL99	8	0·3 (0·14–0·64)	>2·0
Exo-Ia	6	0·34 (0·21–0·54)	>1·0
Exo-Ib	6	0·61 (0·39–0·98)	>1·0
Exo-Ic	5	0·5 (0·29–0·85)	>1·0†
Phenylephrine	8	0·71 (0·49–1·18)	0·00066 (0·00054–0·00081)

ID50 = dose of antagonist causing 50% reduction in diastolic pressor response (95% confidence limits).
† 30% reduction at 1 mg kg^{-1}.

but failed to antagonize the vasoconstriction induced by *exo*-Ia or *exo*-Ib at 1 mg kg^{-1} i.v. Prazosin reduced *exo*-Ic-induced pressor responses by 30% (Table 2).

Guinea-pig ileum

In the transmurally stimulated guinea-pig ileum, TL99 was a very potent inhibitor of the twitch response (Table). *Exo*-Ib and *exo*-Ic were full agonists in this preparation and were of similar potency, but were 466–700 times less potent than TL99 as inhibitors of the twitch response. Neither TL99 nor *exo*-Ib antagonized the contractile effects of acetylcholine at concentrations which completely inhibited the stimulated twitch response of the ileum. The primary amine *exo*-Ia did not cause inhibition of the twitch response at concentrations less than 52 μM (Table 3); a higher concentrations, *exo*-Ia contracted the ileum. The *endo*-isomers IIa–IIc failed to inhibit the twitch response over the concentration range 228–261 μM (Table 3, Fig. 2).

Table 3. Agonist potencies of *N*-substituted 2-aminobenzonorbornenes in the transmurally stimulated guinea-pig ileum.

Agonist	Twitch response IC50 (μM)
TL99	0·03 (0·02–0·04)
Exo-Ia	>51[a]
Exo-Ib	14 (9–21)
Exo-Ic	21 (12–37)
Endo-II a–c	inactive 227–261

IC50 = 50% inhibition of twitch response (+95% confidence limits).
(a) >52 μM caused contractile effects.
n = 6–8.

Rauwolscine was a competitive antagonist of the inhibitory effects of *exo*-Ib (Table 4). The pA_2 values for rauwolscine against *exo*-Ib or TL99 were not significantly different. However, the slope of the Schild plot for rauwolscine against TL99 was significantly less than unity (Table 4). Prazosin (10^{-5} M), propranolol (10^{-7} M), or α-flupenthixol (10^{-6} M) failed to antagonize the inhibitory effects of these agonists in the ileum (Table 4).

Table 4. Antagonist potencies against TL99, or *Exo*-Ib in the transmurally stimulated guinea-pig ileum.

Antagonist	TL99 pA_2 (−log M)	TL99 Slope*	*Exo*-Ib pA_2 (−log M)	*Exo*-Ib Slope*
Rauwolscine	8·06 (7·53–8·59)	0·69 (0·58–0·8)	7·52 (7·26–7·78)	0·9 (0·81–1·05)
Prazosin	no blockade at 10^{-5} M			
Propranolol	no blockade at 10^{-7} M			
α-Flupenthixol	no blockade at 10^{-7} M			

* Slope of plot of $\log_{10}$ dose ratio −1 v. $\log_{10}$ dose antagonist.
( ) 95% confidence limits.
n = 6–9.

DISCUSSION

A series of *exo*- and *endo*-2-amino-6,7-dihydroxybenzonorbornenes and their *N*-methyl and *NN*-dimethyl derivatives have been examined for agonist activity at α_2-adrenoceptors in-vivo in the pithed rat and in-vitro in the stimulated guinea-pig ileum. These compounds have been designed as rigid catecholamines which makes them of potential value in determining the conformational requirements for interaction of agonists at α_2-receptors.

Vasoconstriction in the pithed rat can be mediated through both postsynaptic α_1- and α_2-receptors (Timmermans & Van Zwieten 1981; McGrath 1982). These receptor-mediated effects can, however, be differentiated using selective agonists and antagonists at α_1- or α_2-receptors. In the pithed rat, only the *exo*-isomers caused vasoconstriction; the *endo*-isomers were inactive over the dose range studied. In the *exo*-isomeric series (see Fig. 1, Ia–Ic) the ring system is locked into a structure which approximates the fully extended or *anti* conformation of NA. The results from this present study emphasize the importance of this molecular conformation of Na in relation to the in-vivo biological effects observed; furthermore in the guinea-pig ileum, biological activity resided totally in the *exo*-isomers (Fig. 2). These data confirm and extend the findings of Burn et al (1980) who demonstrated that the amphetamine-like activity exhibited by non-hydroxylated 2-aminobenzonorbornene resided only in the *exo*-isomers.

A second important finding of this study relates to the selectivity of action of members of the *exo*-series of compounds examined as agonists at α_2-receptors. The *exo*-isomer Ib was very selective for postsynaptic α_2-receptors in the guinea-pig ileum, since both the vasoconstriction and inhibition of the twitch, in

response to this agonist was selectively antagonized by the α_2-receptor antagonist rauwolscine (Weitzell et al 1979), but not by the selective α_1-receptor antagonist prazosin (Cambridge et al 1977; Roach et al 1978). Interestingly, *exo*-Ia failed to inhibit the twitch response of the ileum but was a full vasoconstrictor agonist in the pithed rat. It remains to be determined whether this difference in agonist potency implies that pre and postsynaptic α_2-receptors have different structure-activity requirements as recently suggested for α_2-receptor antagonists (Hicks & Waldron 1981; Hicks 1981). Higher concentrations of *exo*-Ia caused contraction of the ileum through an undetermined mechanism.

Rauwolscine is a fairly potent α_2-receptor antagonist (Weitzell et al 1979), it is, however, readily apparent that it can also antagonize post-synaptic α_1-receptors in the pithed rat, since vasoconstrictor responses to the α_1-receptor agonist phenylephrine were equally well blocked. Indeed, all the diastereoisomers of yohimbine have been shown to exert significant α_1-receptor antagonism in-vivo (Shepperson et al 1981). This emphasizes the importance of examining the effects of 'selective' α-receptor agonists in the presence of both α_1 and α_2-receptor antagonists. The lack of postjunctional α-adrenoceptors selectivity for rauwolscine, shown in this paper (Table 2), is at variance with the work of Timmermans et al (1980), but is more in agreement with Kobinger & Pichler (1982).

Although the results with the rigid *exo*-2-aminobenzonorbornene isomers obtained in this present study strongly suggest that the extended conformation of NA is the preferred form for α_2-receptor interaction, it is possible that a small degree of flexibility is required for optimum receptor interaction, since the rigid benzonorbornenes are less potent than the semi-rigid aminotetrahydronaphthalene derivatives, both at pre- and postjunctional α_2-receptor sites. It is further possible that the methylene bridge which imparts conformational rigidity on the benzonorbornene structure, imposes a degree of steric hindrance at the α_2-receptor and does not allow optimum drug-receptor interaction. This may explain why the *exo*-2-amino-6,7-dihydroxybenzonorbornenes are less potent than TL99 as agonists at α_2-receptors. Both TL99 and the *exo*-compounds Ia–Ic lack the aliphatic β-hydroxyl group which is present in the NA molecule. This functional group, therefore, appears to be of only minor importance in α_2-receptor interactions. The importance of catechol groupings for α_2-receptor interaction is, however, less clear. In this study, the non-hydroxylated compound *exo*-2-methylaminobenzonorbornene (V) was inactive at postjunctional α-receptors, while dihydroxylation of this compound in the 6,7-position (*exo*-Ib) imparted considerable α_2-receptor agonist properties on the molecule. In the 2-aminotetrahydronaphthalene series, TL99 (6,7-dihydroxy-2-*NN*-dimethylaminoATN) is a more potent α_2-receptor agonist than the isomeric 5,6-dihydroxylated derivative, M7 (Hicks & Cannon 1979, 1980), furthermore, the non-hydroxylated 2-*NN*-dimethylATN is a very weak vasoconstrictor agent (Hicks, unpublished observations). These data suggest that catechol groups at the 6,7-position are important for agonist activity at α_2-receptors in the benzonorbornene and ATN derivatives. However, catechol groups are not a prerequisite for α_2-receptor agonist activity in other compounds. Various imidazoline derivatives, for example, UK14304 (2-(5-bromoquinoxalin-6-ylamino)-2-imidazoline) (Cambridge 1981) or azepine derivatives, for example, BHT933 (2-amino-6-ethyl-5,6,7,8,-tetrahydro-4H-oxazolo-[4,5-*d*]-azepine; Pichler et al 1980; Timmermans & Van Zwieten 1980) or BHT 920 (2-amino-6-allyl-5,6,7,8,-tetrahydro-4H-thiazolo[5,4,-d]azepine (Kobinger & Pichler 1981) are all selective α_2-receptor agonists which do not contain phenolic hydroxyl groups.

The ATN derivative, TL99, has marked DA-receptor stimulant activity in the peripheral vasculature of the dog (Kitzen et al 1978). However, in the rat and guinea-pig, TL99 does not act at peripheral DA-receptors (Hicks 1981). The benzonorbornenes Ia–Ic also do not possess central DA-receptor activity as determined from stereotyped behavioural studies in the mouse and rat (Burn et al 1982). In the present study, neither pre- nor postjunctional effects of *exo*-Ib were antagonized by the DA-receptor antagonist α-flupenthixol.

The *exo*-isomer Ib does, however, have some β-receptor agonist properties. At higher doses, Ib increased heart rate, and the vasoconstrictor effects of this compound were enhanced after treatment with propranolol. *Exo*-Ib can be compared with other 2-ATNs which also have β-receptor mediated vasodilating properties (Maixner et al 1981b; Beaumont & Waigh 1981).

Finally, neither TL99 nor *exo*-Ib exert their inhibitory effects as a result of muscarinic-receptor antagonism, since neither compound was capable of blocking contractile effects of acetylcholine in the non-stimulated guinea-pig ileum.

In conclusion, a series of *exo*- and *endo*-2-amino-6,7-dihydroxybenzonorbornenes designed as rigid

catecholamines have been examined for selective α_2-adrenoreceptor agonist properties. Biological activity has been shown to reside completely in the fully extended *exo*-series. These results indicate that a fully extended NA conformation (III) is necessary for interaction at the α_2-receptor and are in agreement with Ruffolo et al (1982) but do not support the recent hypothesis of McGrath (1982) who proposes that the 'folded' conformation of NA(IV) is required for α_2-receptor-agonist interaction.

It is envisaged that the use of the completely rigid agonist molecules described in this study and other related compounds presently being synthesized in our laboratory, will be of particular value in understanding the nature of drug interaction at the α-adrenoceptors.

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