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Perspective

α- and β-Adrenoceptors: From the Gene to the Clinic. 2. Structure–Activity Relationships and Therapeutic Applications

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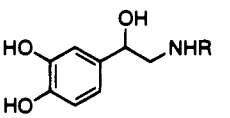
Editor's Note

The present Perspective is the second in a two-part, in-depth overview of the current status of α- and β-adrenoceptor pharmacology and medicinal chemistry. The first part was published in the previous issue. (Hieble, J. P.; Bondinell, W.; Ruffolo, R. R., Jr. α- and β-Adrenoceptors: From the Gene to the Clinic. 1. Molecular Biology and Adrenoceptor Subclassification. *J. Med. Chem.* **1995**, *38*, 3415–3444.)

1. Structural Elements Required for Affinity and Efficacy at α- and β-Adrenoceptors

1.1. Structural Requirements for Agonist and Antagonist Affinity, Efficacy, and Selectivity. 1.1.1. Phenethylamines. The catecholamine neurotransmitters, norepinephrine (**1**) and epinephrine (**2**) are the prototypical agonists for both α- and β-adrenoceptors. These biogenic amines are capable of activating all subtypes of both of the major adrenoceptor classes. Although there is no substantial subtype selectivity among the α-adrenoceptor subtypes, norepinephrine can differentiate the β-adrenoceptors, having higher affinity for the β_1- and β_3-adrenoceptors than for the β_2-adrenoceptor. In contrast, epinephrine has comparable affinity for all three β-adrenoceptor subtypes. Because most β_1-adrenoceptors, but not β_2-adrenoceptors, are directly activated by neuronal released transmitter, the selectivity of norepinephrine for β_1- versus β_2-adrenoceptors is consistent with a neurotransmitter role for this catecholamine, as opposed to epinephrine, which functions primarily as a circulating hormone in most mammalian species. The role of sympathoadrenal activation in the modulation of β_3-adrenoceptor activity in adipose tissue and at other sites has not yet been established.



(1) Norepinephrine (R = H)
(2) Epinephrine (R = CH_3)

On the basis of the stereochemical requirements for agonist activity (see Section 2.1), the catecholamines appear to bind to at least three motifs on the adrenoceptor proteins, presumably through the aliphatic amino nitrogen atom, catechol hydroxyl groups, and the benzylic β-hydroxyl group. As noted above, addition of an *N*-methyl substituent to norepinephrine can influence its subtype selectivity for the β-adrenoceptors. Increasing the steric bulk of the N-substituent to ethyl, isopropyl, or *tert*-butyl can maintain, or even increase, affinity for the β-adrenoceptors, while essentially eliminating α-adrenoceptor agonist activity, resulting in catecholamines that are highly selective for *β-vis-α-vis* α-adrenoceptors.[1] As observed for epinephrine, the N-substituted catecholamines can activate all β-adrenoceptor subtypes. The *N-tert*-butyl analog has moderate selectivity for β_2- versus β_1-adrenoceptors. Even larger arylalkyl substituents on the nitrogen atom of norepinephrine are compatible with quite potent β-adrenoceptor agonist activity[2] (Table 1).

Removal of either of the catechol hydroxyl groups reduces agonist potency at both α- and β-adrenoceptors. However, analogs bearing only a *m*-hydroxyl group can retain significant affinity and full efficacy as α-adrenoceptor agonists. For example, phenylephrine (**3**), the analog of epinephrine lacking the *p*-hydroxyl group, is useful both as a pharmacological tool to characterize

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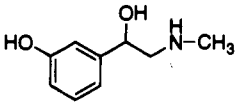
Table 1. Structural Elements Required for Adrenoceptor Agonist Activity in Phenethylamines

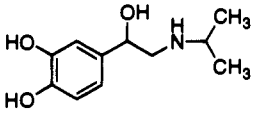
receptor	aromatic ring[a]	side chain[a]	nitrogen
α_1		β-hydroxyl (+)	H, CH_3
α_2	catechol (++)	α-methyl (+)	H, CH_3
		β-hydroxyl (+)	
β_1	catechol (+)	β-hydroxyl (++)	H, CH_3, or larger
β_2		β-hydroxyl (++)	CH_3 or larger
β_3		β-hydroxyl (++)	large substituents tolerated

[a] (++) denotes substituents required for pharmacologically significant agonist activity, (+) denotes substituents which, although not present in all active molecules, generally enhance agonist activity.

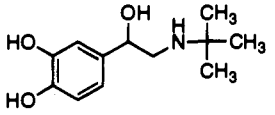
α-adrenoceptors and as a therapeutic agent when selective α-adrenoceptor stimulation is required. The α-adrenoceptor activity of phenylephrine is limited primarily to the α_1-adrenoceptor subtypes. In contrast, an intact catechol moiety appears to be required for efficacy of phenethylamines at the α_2-adrenoceptors. It is likely that the presence of both phenolic hydroxyl groups is also required for agonist activity at the β_1-adrenoceptor, inasmuch as replacement of the *m*-hydroxyl group of isoproterenol (**4**) or *tert*-butylnorepinephrine (**5**) with a substituent bearing an active hydrogen atom (*e.g.*, hydroxymethyl, sulfonamido, ureido) results in agonists that are selective for β_2-adrenoceptors. Several members of this class are used clinically as bronchodilators, and new analogs have recently been developed where duration of action has been enhanced by increasing the size of the nitrogen substituent (*e.g.*, salmeterol (**6**)[3]). Analogs bearing two aromatic ring hydroxyl groups in a 3,5-configuration can also show selectivity for β_2-adrenoceptors, although potency is typically reduced.[4]



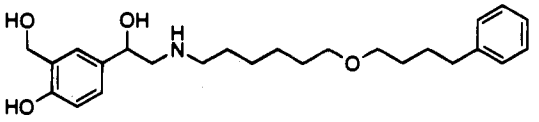
(3) Phenylephrine



(4) Isoproterenol



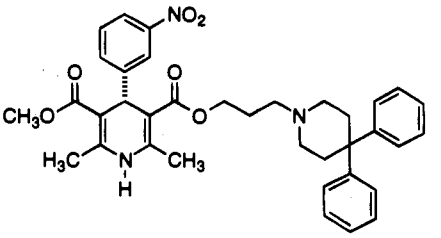
(5) tert-Butylnorepinephrine



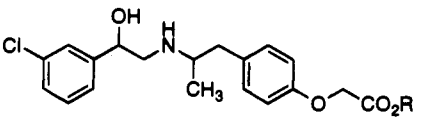
(6) Salmeterol

Methoxamine (**7**), despite having no active hydrogen substituents on the aromatic ring, is a full agonist at the α_1-adrenoceptor in most systems, although the compound is substantially less potent than phenylephrine or norepinephrine. Interestingly, recent evidence suggests that methoxamine can differentiate between α_1-adrenoceptor subtypes, having moderate selectivity for the α_{1A}-adrenoceptor in assays using native tissues,[5] and selectivity for the recombinant α_{1d}- and α_{1a}-adrenoceptors, versus the α_{1b}-adrenoceptor.[6] Methoxamine also appears to have selectivity for the prazosin-resistant α_{1L}-adrenoceptor.[7]

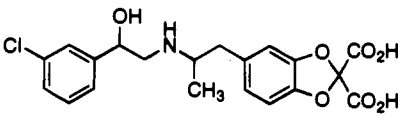
Detailed structure–activity relationships for selective activation of the β_3-adrenoceptor have not been reported



(7) (S)-Niguldipine



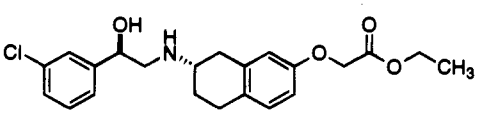
(8) BRL 37344 (R = H)
(9) BRL 35135 (R = CH_3)



(10) CL 316,243

to date. BRL 37344 (**8**), the most extensively studied examples of this class, is a phenylethanolamine with a 3-chloro substituent on the aromatic ring and a complex arylalkyl nitrogen substituent bearing a free carboxyl group. The analog of BRL 37344 in which the carboxyl is esterified, BRL 35135 (**9**), is also a β_3-adrenoceptor agonist and is metabolized *in vivo* to BRL 37344.[8] A structurally related analog, CL 316,243 (**10**), has even greater selectivity the for β_3-adrenoceptor.[9] A carboxyl or carboxamido group appears to be a common structural element found on several other agonists of diverse structure that have been reported to be selective agonists of the β_3-adrenoceptor.[10]

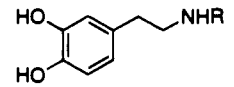
A series of phenethylamines bearing an aminotetralin substituent on the nitrogen atom have been shown to inhibit selectivity motility in the rat colon.[11] A pharmacological analysis of this response suggests that it is mediated by the β_3-adrenoceptor. SR 58611A (**11**), the most potent β-adrenoceptor agonist in the colon, stimulates adenylate cyclase activity in CHO cells expressing the recombinant human β_3-adrenoceptor.[12] Consistent with data derived from other phenylethanolamines, SR 58611A is more than 1000-fold greater in potency than the corresponding diastereomer in which the phenethylamine β-carbon atom is in the *S* absolute configuration.[11] The configuration of the asymmetric carbon atom of the nitrogen substituent does not influence β_3-adrenoceptor agonist potency, but the isomer having this asymmetric center in the *R* configuration is nearly 10-fold greater in potency than SR 56811A at the β_2-adrenoceptor.



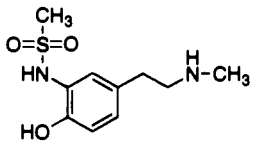
(11) SR 58611A

Although removal of the β-hydroxyl group of phenylethanolamines substantially reduces its affinity at all of the α- and β-adrenoceptor subtypes, dopamine (**12**) and epinine (**13**) retain high efficacy at the α- and β-adrenoceptors. In certain test models, epinine shows

selectivity for α_2-adrenoceptors.[13] Discrete receptors are present for dopamine in many tissues, both in the periphery and central nervous system. These dopamine receptors have structural requirements that are quite distinct from α- and β-adrenoceptors, and dopamine receptors do not recognize most adrenoceptor agonists and antagonists. A phenethylamine analog lacking the β-hydroxyl group and having the *m*-hydroxyl group replaced by a sulfonamido group (SK&F 102652, **14**) is a potent and selective α_1-adrenoceptor agonist.[14]

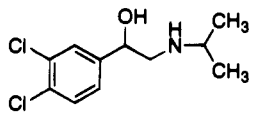


(12) Dopamine (R = H)
(13) Epinine (R = CH_3)

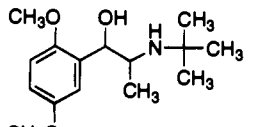


(14) SK&F 102652

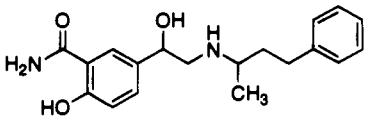
Structural modification of the catecholamines typically reduces only affinity for the α- and β-adrenoceptors, rather than reducing efficacy as a receptor agonist. For example, removal of one or both catechol hydroxyl groups of epinephrine or isoproterenol results in a phenethylamine which, although weak, retains substantial efficacy (intrinsic activity = 0.5−0.8) at the α- and β-adrenoceptors.[2,15] Nevertheless, β-adrenoceptor antagonists (which by definition have no intrinsic activity) have been identified through structural modification of catecholamines and other phenethylamine agonists. The 3,4-dichloro analog of isoproterenol (**15**) was the first compound reported to have β-adrenoceptor antagonist activity, although this and other phenethylamine β-adrenoceptor antagonists typically retain partial agonist activity, the principal exception being sotalol. The *N-tert*-butyl analog of methoxamine, butoxamine (**16**), was the first β-adrenoceptor antagonist reported to have selectivity for the β_2-adrenoceptor subtype.



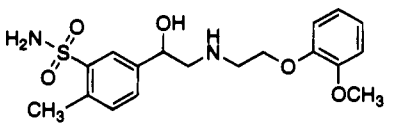
(15) Dichloroisoproterenol



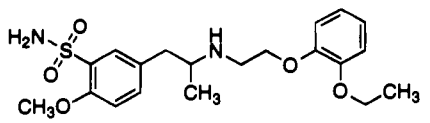
(16) Butoxamine



(17) Labetalol



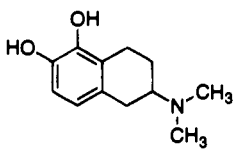
(18) Amosulalol



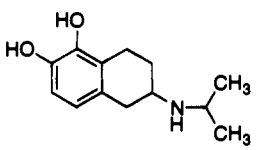
(19) Tamsulosin

Catecholamines bearing a large arylalkyl nitrogen substituent are often β-adrenoceptor agonists while having weak antagonist activity at the α-adrenoceptor. Several related phenethylamines lacking the catechol moiety (*e.g.*, labetalol (**17**) and amosulalol (**18**)) are antagonists of both α- and β-adrenoceptors and are utilized clinically as antihypertensive drugs. Tamsulosin (YM-617, **19**), a structurally related molecule that lacks the β-hydroxyl group, the latter being critical for affinity to the β-adrenoceptors, is one of the most potent α_1-adrenoceptor antagonists identified to date, with modest selectivity for the α_{1A}-adrenoceptor subtype.[5]

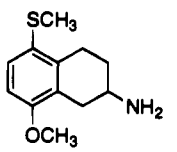
1.1.2. Cyclized Phenethylamines. Incorporation of the side chain of a phenethylamine into a second ring to form an aminotetralin can be compatible with substantial agonist activity at α- and β-adrenoceptors. Depending upon the position of the aromatic ring hydroxyl groups and the nature of the nitrogen substituent, cyclized analogs of dopamine can have agonist activity at both α- and β-adrenoceptors, in addition to the dopamine receptor (see Section 2.3 below). (±)-2-(*N,N*-Dimethylamino)-5,6-dihydroxytetralin (M-7, **20**) is a potent and selective agonist at the α_2-adrenoceptor. The presence of a hydroxyl group at carbon-1 on the aliphatic ring increases the potency of 2-(*N*-isopropylamino)-5,6-dihydroxytetralin (**21**) as a β_1-adrenoceptor agonist by several orders of magnitude.[16] However, this hydroxyl group is not required for agonist activity at α-adrenoceptors, and indeed, in the 5,8-dimethoxy series corresponding to a cyclized methoxamine, both stereoisomers of the hydroxylated derivative have lower affinity for the α_1-adrenoceptor than the corresponding 2-aminotetralin that lacks a substituent at carbon-4.[17] Cyclized derivatives of methoxamine and analogs where one of the methoxy groups is replaced by S-CH_3 (SK&F 89748, **22**) are potent and selective α_1-adrenoceptor agonists.[18,19] An additional ring can be added to 5,8-dimethoxy-2-aminotetralin to form the corresponding 7,10-dimethoxybenzhydro[*f*]quinoline (**23**), without influencing α_1-adrenoceptor agonist activity (Hieble, unpublished data), as long as the ring junction between the two aliphatic rings is *trans*.



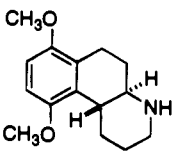
(20) M-7



(21)



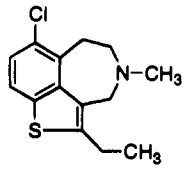
(22) SK&F 89748



(23) 7,10-Dimethoxybenzhydro[f]quinoline

The structural modifications described above were designed to increase the lipophilicity of α_1-adrenoceptor agonists to allow selective activation of central α_1-adrenoceptors. This was not successful, since blood pressure increases were produced at the doses required to stimulate central α_1-adrenoceptors.[20] However, structural modification of SK&F 89748 has lead to a series of lipophilic α_1-adrenoceptor agonists, typified by SDZ NVI 085 (**24**), which can activate central α_1-adrenoceptors without causing an elevation in blood pressure.[21]

Table 2. Affinity of 3-Benzazepines and Their Heterofused Analogs to α-Adrenoceptor Subtypes

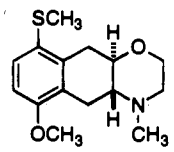


SK&F 106686

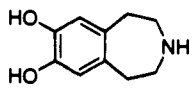
compound	α_{1a}[a]	α_{1b}[b]	α_{1d}[c]	α_{2a}[d]	α_{2b}[e]	α_{2c}[f]	RA[g]	CSV[h]	GPA[i]
SK&F 86466	449	485	126	9.4	16	20	600	42	17
SK&F 104078	33	87	33	114	142	64[j]	150	76	>3000
SK&F 104856	36	23	1.6	24	3.4	21	25	29	>3000
SK&F 105854	3300	783	72	54	14	28	>1000	40	>3000
SK&F 106686	58	15	1.2	31	15	35	56	84	>3000

[a] K_i (nM) for inhibition of [^{3}H]prazosin binding to CHO cells expressing the human α_{1A}-adrenoceptor. [b] K_i (nM) for inhibition of [^{3}H]prazosin binding to CHO cells expressing the human α_{1B}-adrenoceptor. [c] K_i (nM) for inhibition of [^{3}H]prazosin binding to CHO cells expressing the human α_{1D}-adrenoceptor. [d] K_i (nM) for inhibition of [^{3}H]rauwolscine binding to CHO cells expressing the human α_{2A}-adrenoceptor. [e] K_i (nM) for inhibition of [^{3}H]rauwolscine binding to CHO cells expressing the human α_{2B}-adrenoceptor. [f] K_i (nM) for inhibition of [^{3}H]rauwolscine binding to CHO cells expressing the human α_{2C}-adrenoceptor. [g] K_B (nM) for blockade of norepinephrine-induced contraction in rabbit aorta. [h] K_B (nM) for blockade of B-HT 920-induced contraction in canine saphenous vein. [i] K_B (nM) for blockade of B-HT 920-induced inhibition of the inotropic response to field stimulation in superfused guinea pig atrium. [j] Mean values of data obtained in human or rat (RNG, RG10 clones) receptors, as reported by O'Rourke *et al.*,[298] Lanier *et al.*,[299] Uhlen *et al.*,[300] Marjamaki *et al.*,[301] Lomasney *et al.*,[302] Xia *et al.*,[303,304] and Harrison *et al.*[305]

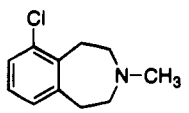
A catechol-containing 3-benzazepine (SK&F 39315, **25**) was found to be a potent agonist at α_1- and α_2-adrenoceptors.[22] Removal of the ring hydroxyl groups resulted in antagonists of the α-adrenoceptor. Such 3-benzazepines can either have moderate selectivity for the α_2-adrenoceptor (*e.g.*, SK&F 86466, **26**) or they can be mixed α_1-/α_2-adrenoceptor antagonists. These compounds have been used to subclassify α_2-adrenoceptor responses in functional *in vitro* assays (*e.g.*, SK&F 104078, **27**).[23] The functional α_2-adrenoceptor subclassification that resulted from the use of agents such as SK&F 104078 has not yet been reconciled with the subclassification of the α_2-adrenoceptors based on radioligand binding affinities or the molecular identification of recombinant receptor proteins, inasmuch as SK&F 104078 has nearly equal affinity for all three of the recombinant α_2-adrenoceptors (Table 2).



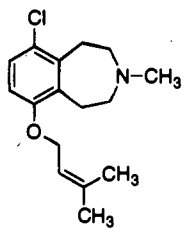
(24) SDZ NVI 085



(25) SK&F 39315

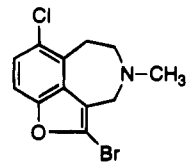


(26) SK&F 86466

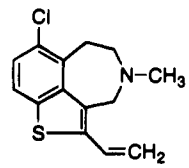


(27) SK&F 104078

Addition of a fused hetero-ring to the 3-benzazepine SK&F 86466 does not influence affinity for vascular α_2-adrenoceptors in canine saphenous vein. However, both furo and thieno substitution of SK&F 86466 result in a functional selectivity pattern that is similar to that observed with SK&F 104078 (Table 2). Interestingly, the thienobenzazepines also have high affinity for α_1-adrenoceptors, with consistently observed selectivity for the α_{1d}-adrenoceptor subtype. The furo analog, SK&F 105854 (**28**), has much lower functional α_1-adrenoceptor antagonist affinity than the thieno analog and lower absolute affinity for the recombinant α_1-adrenoceptors, but equivalent relative selectivity for the α_{1d}-adrenoceptor. SK&F 104856 (**29**) has approximately 10-fold selectivity for the α_{2b}-adrenoceptor, compared to the other recombinant α_2-adrenoceptors; however, this selectivity is diminished in other structural analogs.



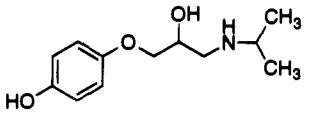
(28) SK&F 105854



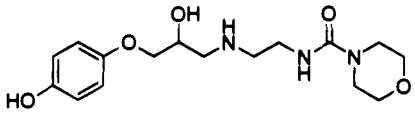
(29) SK&F 104856

1.1.3. Phenoxypropanolamines. Inserting an OCH_2 linkage between the aromatic and ethanolamine portions of isoproterenol or *N-tert*-butylnorepinephrine does not eliminate agonist activity at the β-adrenoceptor. Indeed, in the *tert*-butyl series, the phenoxypropanolamine analogs are more potent than the corresponding phenylethanolamine analogs at both β_1- and β_2-adrenoceptors.[24] Structural modifications of these agonists, through removal of one of the catechol hydroxyl groups and/or modification of the N-substituent, has been exploited in the design of partial agonists that have selectivity for the β_1-adrenoceptor[25] (*e.g.*, prenalterol (**30**) and xamoterol (**31**)).

With the exception of a few phenylethanolamines (*e.g.*, sotalol (**32**), labetalol, amosulalol), virtually all of the clinically useful β-adrenoceptor antagonists contain a phenoxypropanolamine moiety, typically with isopropyl or *tert*-butyl as an N-substituent, attached to an aromatic or heterocyclic ring system. Data on a vast number of these analogs have been reported, and nearly 100 representatives of this class are in clinical use for hypertension or angina pectoris in various countries. The phenoxypropanolamines include both nonselective

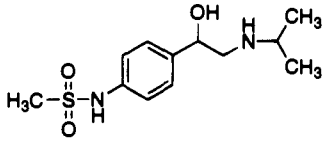


(30) Prenalterol

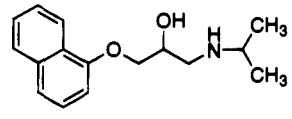


(31) Xamoterol

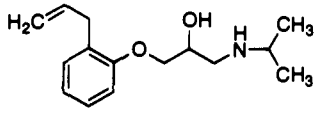
agents (*e.g.*, propranolol (**33**), alprenolol (**34**), pindolol (**35**)) and selective β_1-adrenoceptor antagonists (*e.g.*, atenolol (**36**), bisoprolol (**37**), CGP 20712 (**38**)).



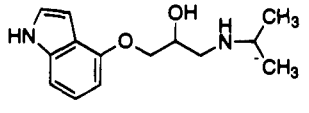
(32) Sotalol



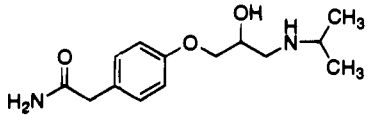
(33) Propranolol



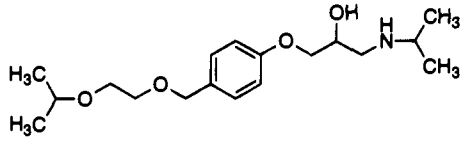
(34) Alprenolol



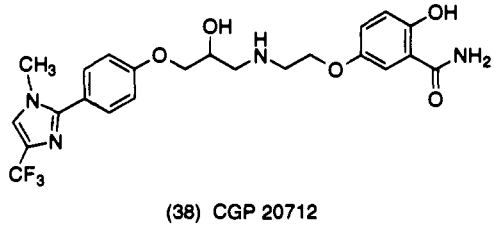
(35) Pindolol



(36) Atenolol

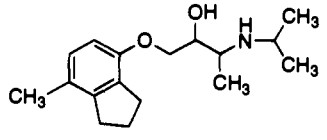


(37) Bisoprolol



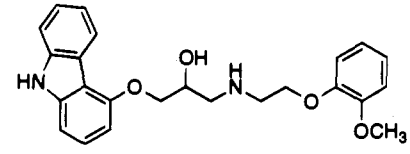
(38) CGP 20712

Less effort has been directed toward the design of selective β_2-adrenoceptor antagonists, since this pharmacological class has fewer, if any, obvious clinical applications. ICI 118,551 (**39**), the prototypical selective β_2-adrenoceptor antagonist, is a phenoxybutanolamine, analogous to other β-adrenoceptor antagonists, but with a methyl group added to the side chain.

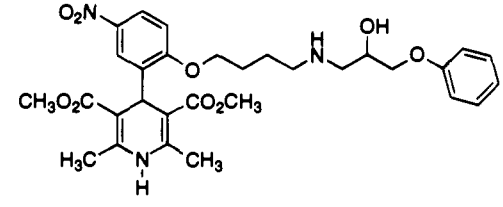


(39) ICI 118,551

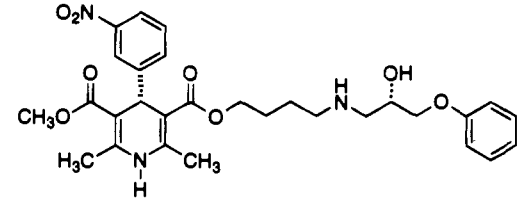
Although the basic (aryloxy)propanolamine nucleus must remain intact for significant β-adrenoceptor antagonist activity, a wide variety of aromatic ring or nitrogen substituents can be tolerated. This has allowed for the design of therapeutic agents that combine β-adrenoceptor antagonist activity with several other useful pharmacological actions, including α-adrenoceptor blockade (*e.g.*, carvedilol (**40**), see below), calcium channel blockade (*e.g.*, YM-16151-4 (**41**),[26] YM-15430-1 (**42**)[27]), direct vasodilation (*e.g.*, prizidilol (**43**)[2]), inhibition of angiotensin converting enzyme (*e.g.*, BW A575C (**44**)[28]), and Class III antiarrhythmic activity (*e.g.*, CK-3579 (**45**)[29]).



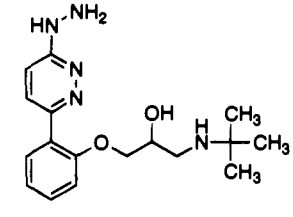
(40) Carvedilol



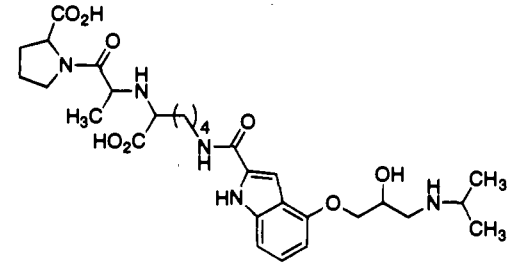
(41) YM-16151-4



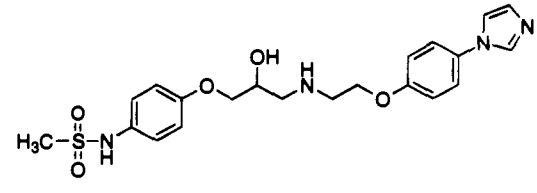
(42) YM-15430-1



(43) Prizidilol

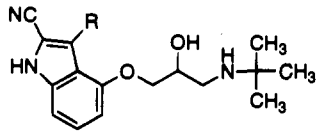


(44) BW A575C

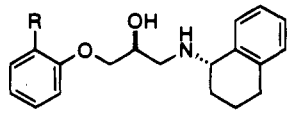


(45) CK-3579

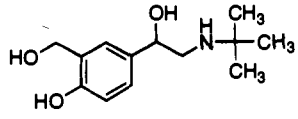
Most of the classical β-adrenoceptor antagonists have low affinity for the β_3-adrenoceptor. Cyanopindolol (**46**) and iodocyanopindolol (**47**) appear to have higher affinity for the β_3-adrenoceptor than other phenoxypropanolamines, although still lower than the affinity for the β_1- or β_2-adrenoceptors. Recently, two phenoxypropanolamines containing a tetralin substituent on the amino nitrogen, SR 58894A (**48**) and SR 59230A (**49**), have been shown to produce a selective blockade of β_3-adrenoceptors, with dissociation constants against SR 56811A in rat proximal colon (which contains β_3-adrenoceptors) that are 10−100-fold lower than those against isoproterenol or salbutamol (**50**) induced activation of β_1-adrenoceptors (guinea pig atrium) or β_2-adrenoceptors (guinea pig trachea), respectively.[30]



(46) Cyanopindolol (R = H)
(47) Iodocyanopindolol (R = I)



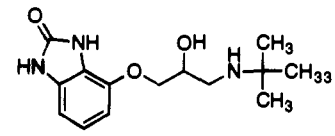
(48) SR 58894A (R = $CH_2CH{=}CH_2$)
(49) SR 59230A (R = CH_2CH_3)



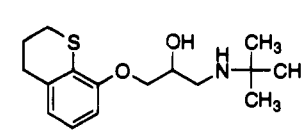
(50) Salbutamol

Interestingly, several phenoxypropanolamines that are potent antagonists of β_1- and β_2-adrenoceptors also have a significant degree of agonist activity at the β_3-adrenoceptor. CGP 12177 (**51**) has been shown to be a partial agonist at the native β_3-adrenoceptor found in mammalian adipocytes from several species.[31] In CHO cells expressing recombinant human β_3-adrenoceptors, other phenoxypropanolamines, such as tertatolol (**52**) and carazolol (**53**), produce a maximum response that is greater than that produced by CGP 12177 and equivalent to that produced by isoproterenol.[12] Other phenoxypropanolamines, such as ICI 198,157 (**54**) and its metabolite, ICI 201,651 (**55**), have been reported to be selective β_3-adrenoceptor agonists.

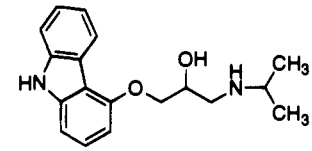
1.1.4. Imidazolines and Imidazolidines. In addition to the phenethylamines, the benzylimidazolines and phenyliminoimidazolidines represent an important class of agents that interact with the α-adrenoceptors. Most representatives of these structural classes are partial agonists, although some are full agonists while others are competitive antagonists. None of the imidazoline analogs have appreciable affinity for any of the β-adrenoceptor subtypes. Although most active agents in this class are either imidazolines or imidazolidines (generically referred to hereafter as imidazolines), examples do exist of potent α-adrenoceptor agonists having their aromatic and imidazoline rings joined by



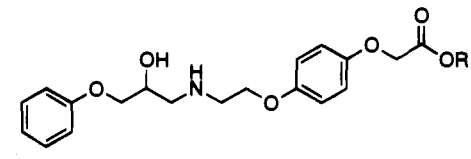
(51) CGP 12177



(52) Tertatolol

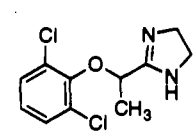


(53) Carazolol

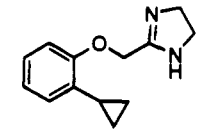


(54) ICI 198,157 (R = CH_3)
(55) ICI 201,651 (R = H)

different linkages (*e.g.*, lofexidine (**56**) and cirazoline (**57**)).



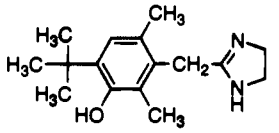
(56) Lofexidine



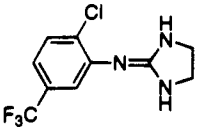
(57) Cirazoline

Comparison of interatomic distances between the aromatic ring and either of the nitrogen atoms in the imidazoline ring suggests that the imidazolines cannot be structural mimics of the endogenous catecholamines or other phenethylamines. Differences in structure−activity relationships between the phenethylamines and imidazolines also show that the two structural classes interact with the α-adrenoceptors in different manners. Hydroxylation of the methylene carbon (analogous to the β-carbon atom of the phenethylamines) of the benzylimidazolines reduces, rather than enhances, affinity for the α-adrenoceptor, in marked contrast to the phenethylamines where this substitution always increases affinity. Although catechol substitution on the phenyl ring of the imidazolines results in highest efficacy at both α_1- and α_2-adrenoceptors, analogs containing no aromatic hydroxyl groups still retain high affinity and moderate efficacy as α-adrenoceptor agonists, including analogs bearing bulky alkyl substituents on the aromatic ring (*e.g.*, oxymetazoline (**58**)), which typically eliminates activity in the phenethylamine series. Although a catechol moiety is required for efficacy at α_2-adrenoceptors in the phenylethanolamines, many imidazolines with no ring hydroxyl groups are potent α_2-adrenoceptor agonists.

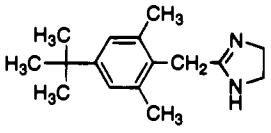
Imidazolines can have selectivity for α_1-adrenoceptors (St 587 (**59**), cirzoline), mixed α_1-/α_2-adrenoceptor agonist activity (oxymetazoline, xylometazoline (**60**)) or selectivity for α_2-adrenoceptors (clonidine (**61**), UK-14,-304 (**62**)). [For a detailed review of the relationship between structure and α-adrenoceptor affinity and efficacy for the imidazolines, refer to Ruffolo and Waddell.[15]] In general, the aminoimidazolidines have greater selectivity for α_2-adrenoceptors than the benzylimidazolines and, when bearing electron-withdrawing sub-



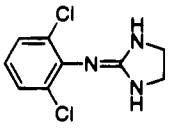
(58) Oxymetazoline



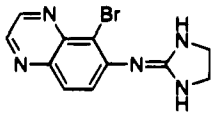
(59) St 587



(60) Xylometazoline



(61) Clonidine

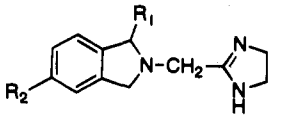


(62) UK-14,304

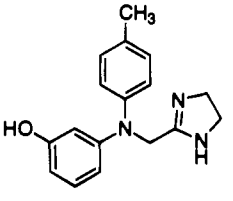
stituents at the 2- and/or 6-positions of the aromatic ring, can readily cross the blood–brain barrier due to incomplete ionization at physiological pH.[32] Clonidine has several important clinical applications, all of which depend on its ability to stimulate central α_2-adrenoceptors.

Oxymetazoline can discriminate between α_2-adrenoceptor subtypes, having highest affinity for the α_{2A}-adrenoceptor. Another imidazoline, BRL 44408 (**63**), as well as its analog, BRL 44409 (**64**), also shows selectivity for the α_{2A}-adrenoceptor.[33,34] Although an antagonist at α_2-adrenoceptors, BRL 44408 retains some partial agonist activity at the α_1-adrenoceptor.

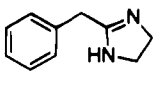
Other imidazolines are potent α-adrenoceptor antagonists. These antagonists may be nonselective (*e.g.*, phentolamine (**65**) and tolazoline (**66**)) as well as selective for the α_2-adrenoceptors (*e.g.*, idazoxan (**67**) and RX 821002 (**68**)). Although most 2-substituted imidazoles, or N-substituted imidazolines, have very low affinity for α-adrenoceptors, a 1,2-disubstituted imidazole, imiloxan (RS 21361 (**69**)), is a moderately potent, but highly selective, α_2-adrenoceptor antagonist. Interestingly, imiloxan is the only reported compound not having potent α_1-adrenoceptor antagonist activity which can selectively antagonize the α_{2B}-adrenoceptor.[35]



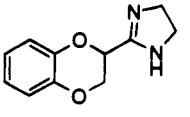
(63) BRL 44408 ($R_1 = CH_3$, $R_2 = H$)
(64) BRL 44409 ($R_1 = H$, $R_2 = Cl$)



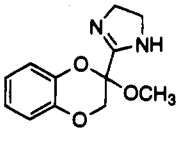
(65) Phentolamine



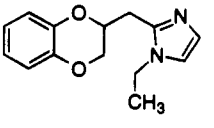
(66) Tolazoline



(67) Idazoxan

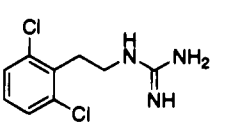


(68) RX 821002

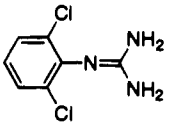


(69) Imiloxan

1.1.5. Substituted Guanidines. Guanabenz and guanfacine are potent and selective agonists at the α_2-adrenoceptor and are utilized clinically as centrally-acting antihypertensive drugs. An analog, SK&F 70699 (**70**), retains α_2-adrenoceptor agonist activity.[36] Although these analogs have affinity for the α_2-adrenoceptor comparable to that of clonidine,[37] the guanidine compound corresponding to an "acyclic" clonidine (**71**) has 50-fold lower affinity for the α_2-adrenoceptor,[38] and SK&F 108767 (**72**), the imidazoline analog of SK&F 70699, is inactive as an α_2-adrenoceptor agonist.[36]



(70) SK&F 70699



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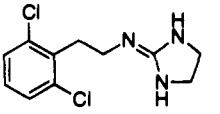
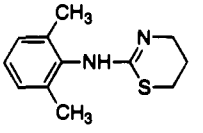
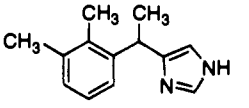


(72) SK&F 108767

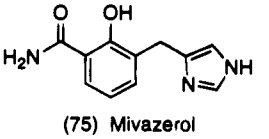
1.1.6. Other Heterocyclic Analogs. (Arylamino)-thiazines (*e.g.*, xylazine (**73**)) are active as α_2-adrenoceptor agonists. Xylazine is primarily utilized as an anesthetic/sedative in veterinary practice. Although aminoimidazoles structurally analogous to the aminoimidazolines and benzylimidazolines have not been found to have affinity for α-adrenoceptors, medetomidine (**74**), a benzylimidazoline linked through carbon-4 of the imidazoline ring, is a highly potent and selective agonist at the α_2-adrenoceptor.[39] Like xylazine, medetomidine is used as a veterinary anesthetic. Mivazerol (**75**), which is structurally analogous to medetomidine, also shows selective agonist activity at the α_2-adrenoceptor[40] and has been evaluated clinically as an antianginal drug.[41] Atipamezole (**76**) is a 4-substituted imidazole that is an α_2-adrenoceptor antagonist which has been used to reverse the sedative actions of α_2-adrenoceptor agonists.



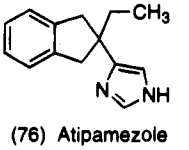
(73) Xylazine



(74) Medetomidine



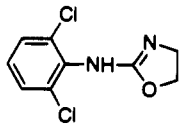
(75) Mivazerol



(76) Atipamezole

The phenylaminooxazoline (**77**), analogous to clonidine, is active as an α_2-adrenoceptor agonist, although the compound is at least 10-fold less potent than clonidine.[38] Other (phenylamino)oxazolines are potent and selective α_2-adrenoceptor agonists. Although struc-

ture–activity relationships have not been carefully compared, these data suggest that the oxazolines and imidazolines may interact slightly differently with the α_2-adrenoceptor. Interestingly, several aminooxazolines bearing a saturated substituent on the amino nitrogen (*e.g.*, Bay_a-6781 (**78**) and rilmenidine (**79**)) are potent and selective α_2-adrenoceptor agonists.



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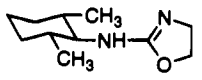
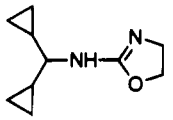
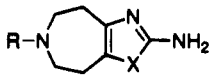


(78) BAY_a-6781



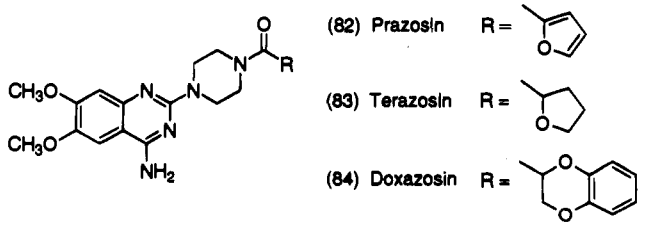
(79) Rilmenidine



(80) B-HT 933 (X = O, R = CH_2CH_3)
(81) B-HT 920 (X = S, R = $CH_2CH{=}CH_2$)

Several heterofused azepine analogs have been found to be selective agonists at the α_2-adrenoceptor. B-HT 933 (azepexole) (**80**) and B-HT 920 (**81**) are widely used pharmacological tools, and B-HT 933 has been shown to have efficacy clinically as an antihypertensive agent.

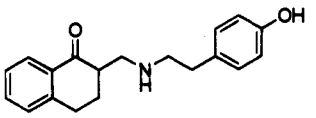
1.1.7. Quinazolines. In contrast to the β-adrenoceptor antagonists, which all can be considered as structural analogs of isoproterenol, most α-adrenoceptor antagonists bear little resemblance to the catecholamine agonists. This includes the quinazolines, which are α_1-adrenoceptor antagonists currently used clinically for the treatment of hypertension and benign prostatic hypertrophy (see Section 3.2). The quinazolines do not discriminate between the α_1-adrenoceptor subtypes, but several, including prazosin (**82**) and terazosin (**83**), have relatively high affinity for the α_{2B}-adrenoceptor. The structural requirements for interaction of α_1- and α_{2B}-adrenoceptors within this series are different, inasmuch as doxazosin (**84**) is of comparable potency to prazosin



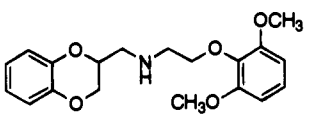
(82) Prazosin R =
(83) Terazosin R =
(84) Doxazosin R =

as an α_1-adrenoceptor antagonist, but has virtually no affinity for the α_{2B}-adrenoceptor.[42] While the *R* and *S* enantiomers of terazosin have equivalent affinity for native α_1-adrenoceptors in rat liver, canine prostate, or human brain,[43,44] the *S* enantiomer has at least 10-fold higher affinity for the mixed α_2-adrenoceptor population in rat cerebral cortex.[43] It is likely that the affinity of terazosin for α_2-adrenoceptors in rat cortex primarily reflects binding to α_{2B}-adrenoceptors. The enantioselectivity of terazosin's interaction with the α_{2B}-adrenoceptor, as well as the inability of doxazosin to interact with this subtype, suggests an important contribution of the substituent on the piperazine ring to antagonist–α_{2B}-adrenoceptor interaction.

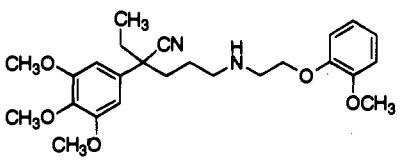
1.1.8. Arylalkylamines. This broad structural class includes α-adrenoceptor antagonists of diverse chemical structure, all of which are lipophilic amines. Tamsulosin can be considered a member of this class, although this compound has been discussed above with the phenethylamines due to its structural analogy to the natural adrenoceptor agonists. Another potent α-adrenoceptor antagonist, BE-2254 (HEAT, **85**) contains a phenethylamine moiety, and several other compounds possess a (phenoxyethyl)amino group, usually substituted on the aromatic ring with a 2-methoxy group (*e.g.*, WB 4101 (**86**), HV-723 (**87**), benoxathian (**88**), carvedilol).



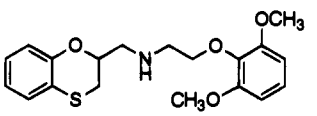
(85) BE-2254 (HEAT)



(86) WB 4101



(87) HV-723

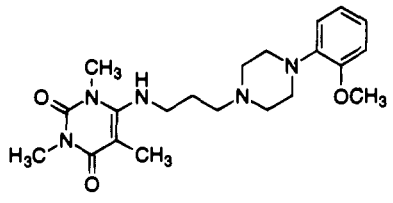


(88) Benoxathian

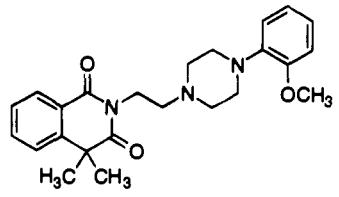
Carvedilol, a mixed α-/β-adrenoceptor antagonist, derives its β-adrenoceptor antagonist activity from the (aryloxy)propanolamine moiety, and the α-adrenoceptor antagonist activity results from the [2-(methoxyphenoxy)ethyl]amino group sharing the amine nitrogen.

The (2-methoxyphenyl)piperazine moiety is present in several other α_1-adrenoceptor antagonists, including 5-methylurapidil (**89**), ARC-239 (**90**), naftopidil (**91**), SL 89.0591 (**92**), and Rec 15/2739 (SB 216469, **93**). The last three compounds listed are being developed for use in benign prostatic hypertrophy (see Section 1.2). Compounds containing a (2-methoxyphenyl)piperazine linked to another aromatic residue can be highly potent α_1-adrenoceptor antagonists, and moderate α_1-adrenoceptor antagonist potency may be present in molecules without the additional aromatic nucleus. α_1-Adrenoceptor subtype selectivity has not been studied systematically in this series, but WB 4101, benoxathian, and 5-methylurapidil are all selective for α_{1A}- versus α_{1B}-adrenoceptors, with 5-methylurapidil being one of the most selective antagonists in this class. ARC-239, in addition to its α_1-adrenoceptor antagonist activity, has high affinity for the α_{2B}-adrenoceptor.

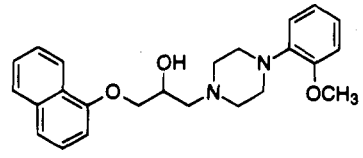
Indoramin (**94**), which contains linked piperidine and indene ring systems, is utilized clinically as an α_1-adrenoceptor antagonist for the treatment of benign prostatic hypertrophy. This compound has been found



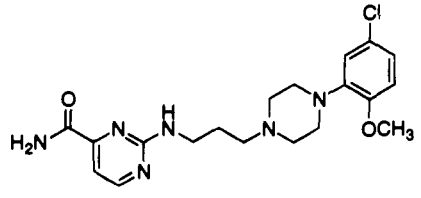
(89) 5-Methylurapidil



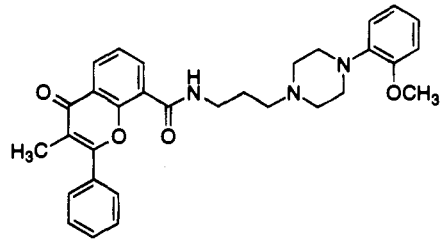
(90) ARC-239



(91) Naftopidil

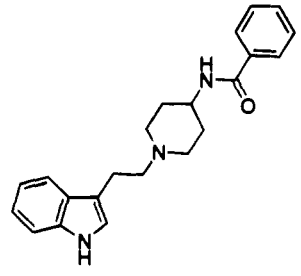


(92) SL 89.0591



(93) Rec 15/2739 (SB 216469)

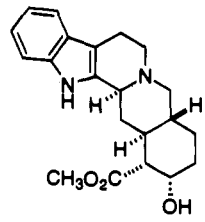
to have selectivity for α_{1A}- versus α_{1B}- and α_{1D}-adrenoceptors.[45]



(94) Indoramin

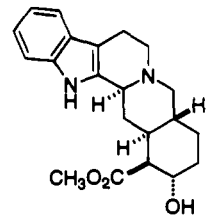
1.1.9. Yohimbine Alkaloids and Structural Analogs. The yohimbine alkaloids, some of which have been used for centuries in herbal medicines, include antagonists having selectivity for both α_2-adrenoceptors (*e.g.*, yohimbine (**95**) and rauwolscine (**96**)) and α_1-adrenoceptors (*e.g.*, corynanthine, **97**). The selectivity profiles of these compounds depend upon the stereochemical configuration of the five asymmetric centers present in the molecules (see Section 2.4).

Several potent and selective α_2-adrenoceptor antagonists contain structural elements that are found in yohimbine. These include the berbanes (CH-38083 (**98**)[46]), benzoquinazolines (WY 26703 (**99**), WY 27127 (**100**)[47,48]), benz[*b*]furoquinazolines (MK 467 (**101**), MK 912 (**102**)[49,50]), and isoquinonaphthyridines (RS 15385-197 (**103**)[51]).

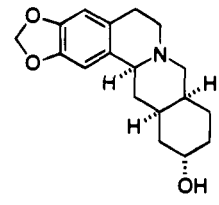


(95) Yohimbine

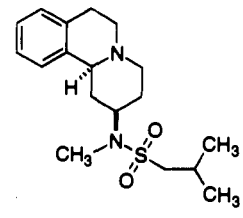
(96) Rauwolscine



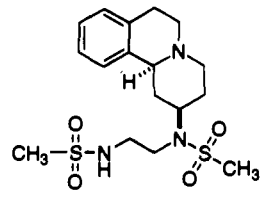
(97) Corynanthine



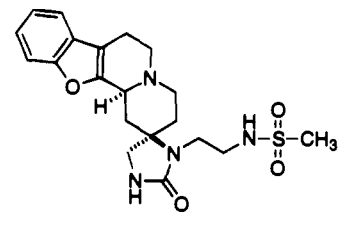
(98) CH-38083



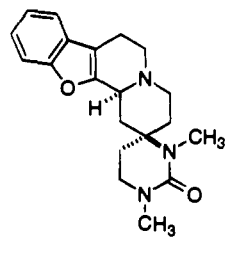
(99) WY 26703



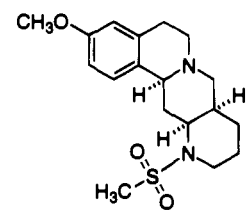
(100) WY 27127



(101) MK 467



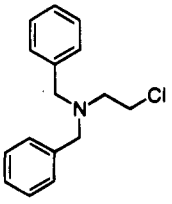
(102) MK 912



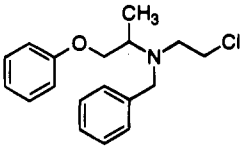
(103) RS 15385-197

1.1.10. Irreversible Adrenoceptor Antagonists. The β-haloalkylamines (*e.g.*, dibenamine (**104**) and phenoxybenzamine (**105**)), which form a covalent bond with the active site of the α-adrenoceptors, have been studied for decades. These agents are useful pharmacologic tools for receptor characterization, in spite of the fact that they are relatively nonselective, being capable of alkylating a variety of neurotransmitter receptors, including muscarinic acetylcholine receptors and histamine receptors. Phenoxybenzamine does have selectivity among the α-adrenoceptors, inasmuch as treatment of a tissue or receptor preparation using conditions that are sufficient to inactivate essentially the entire α_1-adrenoceptor population can leave the population of α_2-adrenoceptors relatively intact. Hence, a tissue containing a mixed population of α_1- and α_2-adrenoceptors can be converted to a predominantly α_2-adrenoceptor-responsive preparation by treatment with phenoxybenzamine. In addition to its utility as a pharmacological tool, phenoxybenzamine was the first α-adreno-

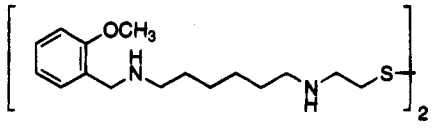
ceptor antagonist to be evaluated in humans. Although generally ineffective as an antihypertensive drug, this agent was shown to be effective in the treatment of benign prostatic hypertrophy. The efficacy of phenoxybenzamine in this condition provided the impetus for the development of newer α-adrenoceptor antagonists for the treatment of benign prostatic hypertrophy (see Section 3.2).



(104) Dibenamine



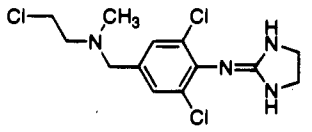
(105) Phenoxybenzamine



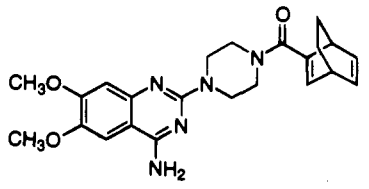
(106) Benextramine

Another class of irreversible α-adrenoceptor antagonists are the tetraamine disulfides (*e.g.*, benextramine) (**106**). Benextramine is somewhat more selective for α-adrenoceptors than are the haloalkylamines, inasmuch as histamine and 5-hydroxytryptamine receptors are unaffected at concentrations that are sufficient to alkylate α-adrenoceptors. Although, benextramine, like phenoxybenzamine, preferentially inactivates the α_1-adrenoceptor, α_2-adrenoceptor blockade may also occur under some conditions.

An α_1-adrenoceptor subtype selective alkylating agent, chloroethylclonidine (**107**), has been useful in the subclassification of α_1-adrenoceptors. The subdivision of α_1-adrenoceptors into the α_{1A}- and α_{1B}-adrenoceptor subclasses was based, in part, on the ability of chloroethylclonidine to produce inactivation of some α_1-adrenoceptor-mediated responses, while leaving others virtually unaffected. Another compound, SZL-49 (**108**),



(107) Chloroethylclonidine

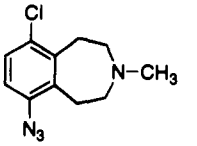


(108) SZL-49

a derivative of prazosin, has been reported to alkylate selectively the α_{1A}-adrenoceptor.[52] However, other studies show this agent to interact with both α_{1A}- and α_{1B}-adrenoceptor subtypes,[53,54] and in contrast to phenoxybenzamine and benextramine, SZL-49 does not produce a time-dependent reduction in the maximum functional response to an α-adrenoceptor agonist.[52]

Although agents purported to alkylate selectively the β-adrenoceptors have been designed by the addition of alkylating moieties to competitive β-adrenoceptor antagonists, these agents have not been proven to be useful pharmacological tools for receptor characterization. Although β-adrenoceptor density can be reduced by these agents in radioligand binding assays,[55,56] functional studies in isolated tissues have failed to show a depression of the maximum response at concentrations which do not produce generalized depressant effects.[57]

Photoaffinity reagents, generally prepared by the attachment of an azido group to an adrenoceptor agonist or antagonist, have been useful for the labeling of adrenoceptors in a tissue prior to receptor solubilization and purification. For example, SK&F 102229 (**109**), the 9-azido analog of SK&F 86466, produces photodependent irreversible alkylation of human platelet α_2-adrenoceptor and was useful in the initial purification of platelet α_2-adrenoceptors.[58]



(109) SK&F 102229

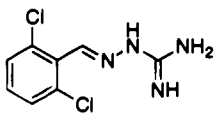
1.2. Newly Reported α- and β-Adrenoceptor Agonists and Antagonists. 1.2.1. α_1-Adrenoceptor Agonists. SDZ NVI 085. It has long been thought that activation of α_1-adrenoceptors in the central nervous system may be associated with an alerting or antidepressant action. However, until recently, it has not proven possible to stimulate central α_1-adrenoceptors with a systematically administered drug without producing a concomitant increase in blood pressure resulting from activation of vascular α_1-adrenoceptors. The naphth[2,3-*b*]oxazine, SDZ NVI 085, a derivative of the aminotetralin, SK&F 89748, penetrates the blood–brain barrier and appears to be able to produce significant alerting effects in normal rats and monkeys and prevents the behavioral/learning deficits induced by either central inhibition of dopamine-β-hydroxylase or noradrenergic neurotoxins.[21] Behavioral effects are produced in the monkey at oral doses which do not increase blood pressure, and phase I studies in normal human volunteers show no increases in blood pressure upon oral administration. Nevertheless, this compound is a full agonist at α_1-adrenoceptors in the rabbit ear artery[21] and hence retains the ability to stimulate vascular α_1-adrenoceptors. This activity is reflected in studies in narcoleptic dogs, where the threshold doses for reversal of food-elicited cataplexy and for increasing blood pressure were similar upon intravenous administration.[59]

The ability of SDZ NVI 085 to produce central α_1-adrenoceptor stimulation without increasing blood pressure may be in part a consequence of its lipophilicity. However, other lipophilic α_1-adrenoceptor agonists, such as SK&F 89748, increase blood pressure in mice and rats at doses that were active centrally,[20] even upon oral adminstration (Hieble, unpublished data). It has been suggested that SDZ NVI 085 is selective for the α_{1A}-adrenoceptor subtype,[60] and examination of its affinity for expressed α_1-adrenoceptor clones shows a rank order of $\alpha_{1a} > \alpha_{1d} > \alpha_{1b}$, with an approximate 10-

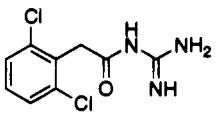
fold affinity difference between each subtype.[61] Whether this *in vitro* selectivity profile can account for the *in vivo* pharmacological effects of SDZ NVI 085 has not been established.

1.2.2. α_2-Adrenoceptor Agonists. Rilmenidine. Since the identification and clinical development of clonidine as a centrally acting antihypertensive drug two decades ago, a separation has been sought between the centrally mediated antihypertensive action and the sedative action, which is also centrally mediated, produced by this class of drug. This goal has proven difficult, and although several drugs have entered clinical trials with the promise of producing less sedation than clonidine, clinical practice has shown no significant difference to exist in therapeutic ratio.

The novel oxazoline derivative, rilmenidine, has been introduced as an antihypertensive agent in several European markets. Rilmenidine has selectivity for α_2- versus α_1-adrenoceptors, but in addition, rilmenidine has affinity for the nonadrenergic imidazoline receptor (see Section 3.2). It has been postulated that the antihypertensive action of rilmenidine (and clonidine) results from an action at I_1 imidazoline receptors in the brainstem, while the sedative action results from activation of α_2-adrenoceptors located in higher central nervous system (CNS) centers. Hence the reduced sedative liability observed with rilmenidine *vis-a-vis* clonidine may related to the greater selectivity of rilmenidine for the I_1 imidazoline receptor. However, there are several arguments against this hypothesis: (i) it is unlikely that the relatively small difference in affinity for I_1 imidazoline receptors versus α_2-adrenoceptors between rilmenidine and clonidine would be translated into a clear difference *in vivo* in therapeutic ratio, (ii) *in vivo* experiments with systemic administration of α_2-adrenoceptor agonists having markedly differing I_1/α_2-adrenoceptor affinity ratios do not demonstrate a difference in mechanism of antihypertensive action,[37,62,63] and (iii) non-imidazoline α_2-adrenoceptor agonists having very low affinity for the I_1 imidazoline receptor (*e.g.*, guanabenz (**110**) and guanfacine (**111**))



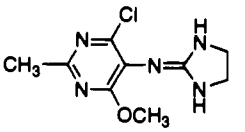
(110) Guanabenz



(111) Guanfacine

are effective antihypertensive agents in humans. It is likely that the antihypertensive and sedative actions of clonidine and its analogs are mediated by activation of α_2-adrenoceptors located in different central nuclei. It has been postulated that the sympatholytic action of centrally acting α_2-adrenoceptor agonists results from a postsynaptic action in the brain, whereas the centrally mediated sedation produced by these compounds likely results from a presynaptic action. Hence, the possibility exists that the α_2-adrenoceptor subtype mediating the sympatholytic and sedative actions of these compounds are different, and that the differences that exist in therapeutic ratio between clonidine and rilmenidine are dependent upon differences in selectivity between different α_2-adrenoceptor subtypes.

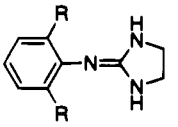
Moxonidine. Like rilmenidine, moxonidine (**112**) is a centrally active α_2-adrenoceptor agonist being marketed in Europe as an antihypertensive drug with purported advantages over clonidine with respect to sedative liability. Moxonidine has higher affinity than



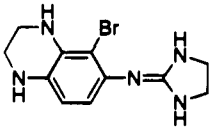
(112) Moxonidine

rilmenidine for the α_2-adrenoceptor and perhaps even greater selectivity for I_1 imidazoline receptors versus α_2-adrenoceptors.[64] Most of the arguments presented above against the role of I_1 imidazoline receptors in the antihypertensive action of rilmenidine also apply to moxonidine. There are also differences in the clinical hemodynamic profile of moxonidine and clonidine, such that bradycardia and reductions in cardiac output are observed less frequently with moxonidine. Interestingly, however, moxonidine appears to have a similar hemodynamic profile to clonidine in animal experiments. In addition to the selective agonist activity of moxonidine at I_1 imidazoline receptors, a different selectivity profile at the α_1-adrenoceptor subtypes has been postulated to explain the differences in the clinical profiles between clonidine and moxonidine.

AGN 190851. Although many centrally active α_2-adrenoceptor agonists have been identified, and several have been developed as antihypertensive drugs, examples of selective α_2-adrenoceptor agonists that act only in the periphery are less common. Structural analogs of clonidine, such as St-91 (**113**) and SK&F 35886 (**114**), although potent α_2-adrenoceptor agonists *in vitro*, do not produce clonidine-like stimulation of central α_2-adrenoceptor in the intact animal. AGN 190851 (**115**) is an analog of UK 14,304 in which the



(113) St-91 (R = CH_2CH_3)
(114) SK&F 35886 (R = CH_3)

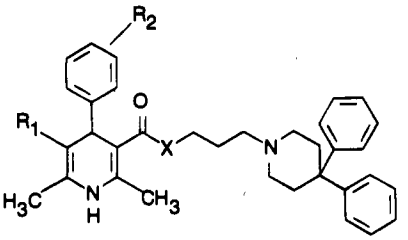


(115) AGN 190851

heterocyclic ring is saturated.[65,66] This modification dramatically changes the partition coefficient between octanol and neutral phosphate buffer,[66] presumably as a consequence of increasing the basicity of the molecule. AGN 190851 is a potent α_2-adrenoceptor agonist in several *in vitro* assays, such as inhibition of adrenergic neurotransmission in the guinea pig atrium or contraction of canine saphenous vein. In these assays, AGN 190851 and UK 14,304 are nearly equipotent, and both drugs are highly selective for α_2- versus α_1-adrenoceptors. However, AGN 190851 is several orders of magnitude weaker than UK 14,304 in its ability to potentiate hexobarbital sleep time in the rat, an index of central α_2-adrenoceptor activation.[67]

An interesting application for a peripherally acting α_2-adrenoceptor agonist is as an antidiarrheal drug. α_2-Adrenoceptors are known to be present in the intestinal mucosa, with an anatomical distribution that is consistent with their control of secretion.[68] AGN 190851 inhibits short-circuit current in an isolated segment of gastrointestinal mucosa, blocks PGE_2 induced enteropooling in conscious rats, and blunts diarrhea in the rat by

Table 3. Effect of Structural Changes on the Relative Affinities[a] of Niguldipine Analogs for α-Adrenoceptor Subtypes and Calcium Channels



X	R_1	R_2	α_{1a}	α_{1b}	α_{1d}	α_{2a}	α_{2b}	α_{2c}	Ca^{2+}
O	$COOCH_3$	3-NO_2 (niguldipine)	1.8[b]	85	191	645	>5000	370	9
NH	$COOCH_3$	3-NO_2	0.4	234	426	1550	1230	560	30
O	$COOCH_3$	4-NO_2	3.3	85	302	1023	758	1700	135
NH	$COOCH_3$	4-NO_2 (SNAP 5089)	1.3	269	1047	3300	1170	1320	741
NH	$CONH_2$	4-NO_2	1.3[b]	407	346	148	275	165	$>10^6$
NH	$CONHCH_3$	4-NO_2	3.1	416	616	398	912	323	>5000

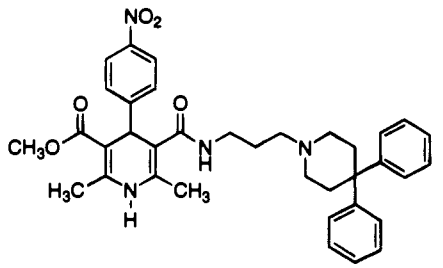
[a] Affinity for adrenoceptors expressed as K_i (nM) for inhibition of the binding of [^{3}H]prazosin (α_1-adrenoceptors) or [^{3}H]rauwolscine (α_2-adrenoceptors) to recombinant human receptors. Affinity for calcium channels expressed as K_i (nM) for inhibition of [^{3}H]nitrendipine binding to membrane homogenates of rat cardiac muscle. Data from Glucowski et al.[73] [b] Tested as active enantiomer.

a variety of agents, including PGE_2, cholera toxin, and reserpine. Antidiarrheal effects of AGN 190851 are produced at doses that have no effects resulting from stimulation of α_2-adrenoceptors in the brain. In addition to antisecretory effects, AGN 190851 is also a potent inhibitor of gastrointestinal transit (Hieble and Kolpak, unpublished data).

1.2.3. α_1-Adrenoceptor Antagonists. SB 216469 (Rec 15/2739). Like several other potent α_1-adrenoceptor antagonists, SB 216469 contains a 1-(2-methoxyphenyl)piperazine moiety. Determination of affinity for recombinant human α-adrenoceptors shows SB 216469 to be moderately selective for the α_{1a}-adrenoceptor (K_i = 0.7 nM) compared to the α_{1b} (K_i = 19 nM) and α_{1d} (K_i = 6.3 nM) subtypes.[69] Functional experiments using isolated rabbit tissues show SB 216469 to produce selective blockade of norepinephrine-induced contraction in prostate versus ear artery. This prostate versus vascular selectivity of SB 216469 has been confirmed *in vivo* in the anesthetized dog by comparing the doses of SB 216469 required to block norepinephrine or nerve stimulation-induced urethral contractions with those doses of the compound required to reduce blood pressure.[70]

SL 89.0951. Little information has been reported on SL 89.0951, other than its *in vivo* selectivity for urethral versus blood pressure responses in the anesthetized cat.[71] This antagonist contains the (2-methoxyphenyl)-piperidine moiety present in several other α_1-adrenoceptor blockers. SL 89.0951 is in phase II clinical trials for the treatment of benign prostatic hypertrophy and has been reported to be well-tolerated upon single dose administration to normal human volunteers.

SNAP-5089. An examination of the affinity of several structural series of α-adrenoceptor antagonists for affinity to cell lines expressing the six known α-adrenoceptor clones showed (*S*)-niguldipine to have more than 10-fold selectivity for the α_{1a}-adrenoceptor subtype, compared to either the α_{1b}- or α_{1d}-subtypes.[72] Replacement of the ester linkage between the dihydropyridine and arylpiperidine moieties of niguldipine by an amide does not markedly influence affinity for the calcium channel but increases selectivity for the α_{1A}-adrenoceptor. This amide analog of niguldipine shows almost 1000-fold selectivity for the human recombinant α_{1a}-adrenoceptor versus the five other human recombinant α-adrenoceptors.[73] Moving the NO_2 group of niguldipine to the para position reduced calcium channel blocking activity, with this analog being 15-fold weaker than (*S*)-niguldipine, without markedly influencing the α_{1A}-adrenoceptor selectivity.[74] The amide-linked analog with a *p*-nitrophenyl substituent (SNAP-5089, **116**) combines high selectivity for the α_{1A} adrenoceptor with low affinity for the calcium channel.[74] Replacement of the methyl ester group of SNAP 5089 by an amide totally abolishes affinity for the calcium channel (Table 3).



(116) SNAP-5089

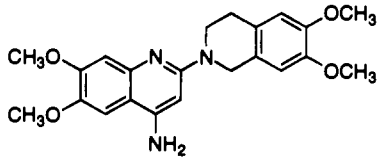
Data on a series of over 200 dihydropyridines structurally analogous to SNAP 5089 have recently been reported.[73] Almost all compounds in this structural series have selectivity for the α_{1a}-adrenoceptor, with a few having 1000-fold selectivity versus the other five α-adrenoceptor subtypes. Except for analogs with a 3-nitrophenyl substituent, these dihydropyridines do not have pharmacologically relevant affinity for the calcium channel (Table 3). Structural modification has the greatest affect on α_{1a}-adrenoceptor affinity, with the weak affinity for the other α_1-adrenoceptor subtypes, and for α_2-adrenoceptors, being relatively insensitive to structural modification.

Naftopidil. Although naftopidil has been known for many years, it has only recently been evaluated for efficacy in the treatment of benign prostatic hypertrophy. Furthermore, naftopidil may show selectivity in functional assays for α_2-adrenoceptors. Naftopidil combines the (methoxyphenyl)piperazine moiety present in

many α-adrenoceptor antagonists with the (aryloxy)-propanolamine structure common to β-adrenoceptor antagonists. The tertiary substitution on the propanolamine nitrogen eliminates β-adrenoceptor antagonist activity. Naftopidil is a potent antagonist of α_1-adrenoceptors; however, as indicated above, its α_2-adrenoceptor affinity depends on the model examined. In the human platelet and human prostate, naftopidil inhibits α_2-adrenoceptor antagonist binding with an affinity that is comparable to its affinity for α_1-adrenoceptors,[75] whereas the α_2-adrenoceptor agonist-induced contraction is antagonized with only moderate potency.[76] However, in several prejunctional α_2-adrenoceptor test systems, such as the rat vas deferens and guinea pig atrium, naftopidil has no activity at concentrations up to 3 μM. Hence, naftopidil appears to have a functional selectivity profile at α_2-adrenoceptors that is similar to that observed with the structurally dissimilar compounds, SK&F 104078 and SK&F 104856.[77]

Naftopidil has demonstrated clinical efficacy in the treatment of benign prostatic hypertrophy[78] and is currently being developed for this indication.

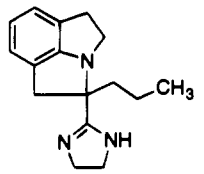
Abanoquil. Abanoquil (UK 52,046, **117**) is a novel α_1-adrenoceptor antagonist that contains some of the structural elements found in prazosin. Abanoquil has



(117) Abanoquil

been shown to be efficacious as an antiarrhythmic agent, and it has been proposed that abanoquil possesses selectivity for the cardiac α_1-adrenoceptor.[79] Using radioligand binding assays in cells expressing rat (α_{1d}), hamster (α_{1b}), and bovine (α_{1a}) adrenoceptors, Marshall *et al.*[80] have reported abanoquil to have high affinity for all three α_1-adrenoceptor subtypes, with 100-fold selectivity for the α_{1d}-adrenoceptor.[80] However, although other investigators, using identical recombinant α_1-adrenoceptors, can confirm the high affinity, they fail to demonstrate substantial subtype selectivity.[69] Data using recombinant human α_1-adrenoceptors also shows high affinity with little or no subtype selectivity.[45] Functional data with abanoquil shows qualitative differences to exist between tissues. For example, in the rat vas deferens, a marked reduction in the maximum response to α_1-adrenoceptor stimulation was produced by abanoquil, indicating noncompetitive antagonism,[81] while competitive blockade of α_1-adrenoceptor-mediated responses was observed in rat atria and aorta,[82] with no effect seen against norepinephrine induced contraction in human prostate even at high concentrations.[80] The noncompetitive action of abanoquil in the vas deferens would suggest that the compound has another pharmacological action in addition to α_1-adrenoceptor blockade.

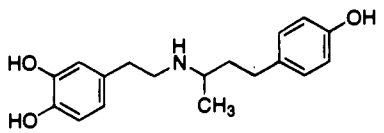
1.2.4. α_2-Adrenoceptor Antagonists. SL 84.0418. SL 84.0418 (**118**), a potent and selective α_2-adrenoceptor antagonist of the imidazoline class, was evaluated clinically for the treatment of non-insulin-dependent diabetes. The compound is able to inhibit epinephrine-



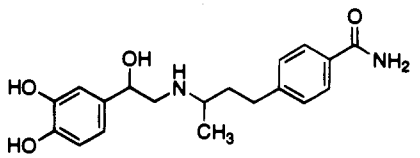
(118) SL 84.0418

induced inhibition of insulin secretion both *in vivo* and *in vitro*[83–85] and shows efficacy as a hypoglycemic agent in several animal models.[84,86] Radioligand binding assays to cells expressing the α_2-adrenoceptor clones shows SL 84.0418 to have high affinity (2–3 nM) for both α_{2a}- and α_{2b}-adrenoceptors.[87]

1.2.5. β-Adrenoceptor Agonists. GP-2-128. Dobutamine (**119**) (see Section 2.5.1) is a mixed α-/β-adrenoceptor agonist. GP-2-128 (**120**), a derivative of dobutamine in which a *p*-carbamoyl group has been introduced on the phenyl ring of the arylalkyl nitrogen substituent, is several orders of magnitude more potent than dobutamine as an agonist at both β_1- and β_2-adrenoceptors.[88] Although GP-2-128 is a partial agonist



(119) Dobutamine



(120) GP-2-128

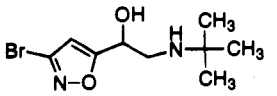
of the α_1-adrenoceptor, the concentrations required to produce this effect are much higher than those required to stimulate β-adrenoceptors, and as such, the compound can be considered to be a selective β-adrenoceptor agonist. Like isoproterenol, GP-2-128 can also stimulate β_3-adrenoceptors, as evidenced by stimulation of lipolysis in rat white adipocytes and hamster brown adipocytes. GP-2-128 appears to be a full agonist in the β-adrenoceptor models in which it has been examined, with a potency that is 100-fold greater than isoproterenol.

1.2.6. β_2-Adrenoceptor Agonists. Broxaterol. The catechol ring of isoproterenol can be replaced by a 3-substituted isoxazole, with retention of β-adrenoceptor agonist activity.[89] In contrast to the phenylethanolamines, a hydroxyl substituent on the ring is not required for agonist activity, and indeed the 3-hydroxy, *N*-isopropyl, or *N*-*tert*-butyl derivatives in the isoxazole series are inactive as β-adrenoceptor agonists. Broxaterol (**121**), the 3-bromo, *N*-*tert*-butyl analog in this series, is a potent and selective β_2-adrenoceptor antagonist, which has undergone clinical evaluation as a bronchodilator.

Table 4. Stereoselectivity of Catecholamines in Functional Assays for Adrenoceptor Agonist Activity

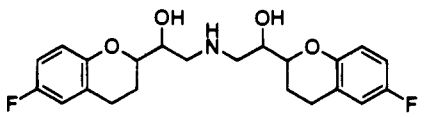
compound	EC_{50} (nM)[a] α_1	α_2	β_1	β_2	β_3	ref
(−)-norepinephrine	15800[b]					103
			30[c]	213[d]		97
					1580[e]	306
	1.2[f]					97
	6.6[g]					97
	112[h]	30[i]				95
(+)-norepinephrine	83200[b]					103
			10000[c]	30000[d]		97
					>100000[e]	306
	200[f]					97
	2000[g]					97
	12000[h]	14500[i]				95
(−)-epinephrine			15[c]	15[d]		97
	4073[b]					103
(+)-epinephrine			436[c]	436[d]		97
	>100000[b]					103
(1*R*,2*S*)-(−)-*erythro*-α-methylnorepinephrine	776[h]	19[i]				95
(1*S*,2*R*)-(+)-*erythro*-α-methylnorepinephrine	46800[h]	10000[i]				95
(−)-isoproterenol			2.2[c]	3.0[d]		97
					200[e]	306
(+)-isoproterenol			2200[c]	1700[d]		97
					63000[e]	306

[a] Intrinsic activity ranged from 0.7 to 1.0 in the various isolated tissue preparations. [b] Contraction of reserpine-pretreated rat vas deferens. [c] Stimulation of contractile rate of isolated guinea pig atrium. [d] Relaxation of guinea pig trachea. [e] Stimulation of lipolysis in rat adipocytes. [f] Contraction of rat aorta. [g] Contraction of rabbit aorta. [h] Contraction of reserpine-pretreated guinea pig aorta. [i] Inhibition of neurotransmission in field-stimulated, reserpine-pretreated guinea pig ileum.



(121) Broxaterol

1.2.7. β_1-Adrenoceptor Antagonists. Nebivolol. Nebivolol (**122**) is a complex molecule, which contains two cyclized phenoxypropanolamine moieties joined at the amino nitrogen. Ten stereoisomers are possible



(122) Nebivolol

(four enantiomeric pairs and two mesoforms). Nebivolol, the racemic mixture of the *R,S,S,S* and *S,R,R,R* enantiomers, is a selective β_1-adrenoceptor antagonist, currently being developed for the treatment of hypertension.[90] Although the β-adrenoceptor antagonist activity of nebivolol is derived primarily from the *S,R,R,R* enantiomer, there is evidence to suggest that the *R,S,S,S* enantiomer may also contribute to the antihypertensive effect of the racemate by potentiation of the "active" enantiomer. This hypothesis is supported by the ability of the *R,S,S,S* enantiomer to potentiate the action of several antihypertensive agents that act by several distinct mechanisms.[91] However, recent clinical evaluation shows the active (*S,R,R,R*) enantiomer and racemic nebivolol produce equal reductions in blood pressure in hypertensive patients.[92] It has been shown that both enantiomers of nebivolol can block of the prejunctional β-adrenoceptor, which mediates a positive feedback on neurotransmitter release from adrenergic nerve terminals and thereby decreases norepinephrine release at the vascular neuroeffector junction.[93,94]

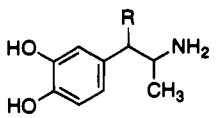
2. Chirality in α- and β-Adrenoceptor Agonists and Antagonists

2.1. Configurational Requirements for Directly and Indirectly Acting Adrenoceptor Agonists of the Phenethylamine Class. 2.1.1. Catecholamines. The endogenous adrenergic neurotransmitter, norepinephrine, and the adrenal neurohormone and central neurotransmitter, epinephrine, have an asymmetric β-carbon atom, and the naturally occurring molecules are of the *R* (−) absolute configuration. When the affinities of two enantiomers of norepinephrine or epinephrine are determined in functional assays for activity at any of the adrenoceptors, the *R* enantiomer is generally found to be approximately 100-fold more potent than the *S* enantiomer. This stereoselectivity occurs at all adrenoceptor subtypes, although the magnitude of the enantiomeric activity ratio appears to be greater at the α_2-adrenoceptors. Functional selectivity ratios for the enantiomers of norepinephrine were determined to be 107, 479, 60, 70, and 100 at the α_1-, α_2-, β_1-, β_2-, and β_3-adrenoceptors, respectively.[95–97] For the β-adrenoceptor subtypes, isoproterenol shows even greater enantioselectivity, with the *R* enantiomer being more than 1000-fold greater in potency than the *S* enantiomer at the β_1-adrenoceptor, 600–800-fold more potent at the β_2-adrenoceptor,[96,97] and 300-fold more potent at the β_3-adrenoceptor[97] (Table 4).

The Easson–Stedman hypothesis[98,99] explains the stereoselectivity of phenylethanolamines by a three point attachment between agonist and receptor, through (i) the catechol hydroxyl groups, (ii) the aliphatic β-hydroxyl group, and (iii) the amine nitrogen. The active enantiomer appears to bind through all three of these sites, whereas the inactive enantiomer would have at least one structural element (*i.e.*, the β-hydroxyl group) in an orientation incompatible with receptor binding. This model would predict that removal of the β-hydroxyl group of (*R*)-(−)-norepinephrine, which would eliminate one point of attachment with the receptor, would reduce

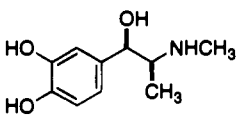
agonist affinity to the same extent as observed for the less active *S* (+)-enantiomer. This is indeed the case for the adrenoceptors, where the rank order of potency is found to be (*R*)-(−)-norepinephrine > (*S*)-(+)-norepinephrine = dopamine (*i.e.*, desoxynorepinephrine), in accordance with the Easson−Stedman hypothesis.

Asymmetry at the α-carbon has a selective influence on the affinity of a catecholamine for the α_2-adrenoceptor. While the *S* and *R* enantiomers of α-methyldopamine have essentially equal affinity for the α_1-adrenoceptor, the *S* (+)-enantiomer is 9-fold more potent than the *R* (−)-enantiomer at the α_2-adrenoceptor.[100] It is possible that the α_2-adrenoceptor has a specific binding pocket that can interact with or accommodate an α-methyl group, since both α-methyldopamine (**123**) and α-methylnorepinephrine (**124**) (see below) have substantial selectivities for α_2- versus α_1-adrenoceptors. Although stereochemistry has not been examined, α-methyl substitution also appears to increase the affinity of catecholamines for the β_2-adrenoceptor, but not for the β_1-adrenoceptor.[101]



(123) α-Methyldopamine (R = H)
(124) α-Methylnorepinephrine (R = OH)

In the case of α-methyl-substituted phenylethanolamines, which possess asymmetric centers at both the α- and β-carbon atoms, the influence of stereochemistry on receptor affinity can vary between adrenoceptor classes. Only the 1*R*,2*S* (−)-*erythro* form of α-methylnorepinephrine has pharmacologically significant affinity for α_1- and α_2-adrenoceptors. Interestingly, although of relatively low potency, the *threo* isomers of α-methylnorepinephrine are only slightly weaker than the *erythro* isomers as β_2-adrenoceptor agonists, and in the case of α-methylepinephrine, the *threo* isomer is the most potent β_2-adrenoceptor agonist.[97] (1*R*,2*S*)-(−)-*erythro*-α-Methylepinephrine (**125**) has been shown to

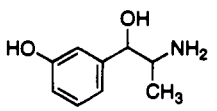


(125) (1R,2S)-(-)-*erythro*-α-Methylepinephrine

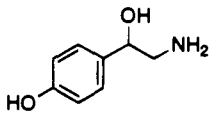
be a potent and selective β_2-adrenoceptor agonist *in vivo*.[101] As observed for norepinephrine, the enantiomers of *erythro*-α-methylnorepinephrine show greater stereoselectivity at the α_2-adrenoceptor compared to the α_1-adrenoceptor, with the 1*R*,2*S* (−)-*erythro* enantiomer being 60- and 550-fold more potent than the 1*S*,2*R* (+)-*erythro* enantiomer at α_1- and α_2-adrenoceptors, respectively.[95] Even greater enantioselectivity is observed at β_1- and β_2-adrenoceptors, with enantiomeric potency ratios of over 2000 being observed at either subtype.[96]

The α_2-adrenoceptor selectivity conferred by α-methyl substitution of norepinephrine has suggested that (1*R*,2*S*)-(−)-*erythro*-α-methylnorepinephrine may bind to the α_1- and α_2-adrenoceptor through three and four points of attachment, respectively.[101,102] This is consistent with the observation that (1*R*)-(−)-norepinephrine is equipotent to (1*R*,2*S*)-(−)-*erythro*-α-methylnorepinephrine at the α_1-adrenoceptor, whereas (1*R*,2*S*)-(−)-*erythro*-α-methylnorepinephrine is significantly more potent than (1*R*)-(−)-norepinephrine at the α_2-adrenoceptor.[101] On the basis of the similar enhancement of β_2-adrenoceptor potency by α-methyl substitution of norepinephrine and epinephrine, it is possible that this receptor subtype may also possess a fourth binding site which accommodates the α-methyl group.

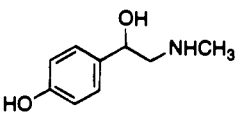
2.1.2. Other Directly Acting Phenethylamines. Phenethanolamines bearing only one ring hydroxyl group, in either the meta (phenylephrine, metaraminol (**126**)) or para (octopamine (**127**), synephrine (**128**)) positions also show substantial enantioselectivity as α_1-adrenoceptor agonists. In each case, the (−)-enantiomer



(126) Metaraminol



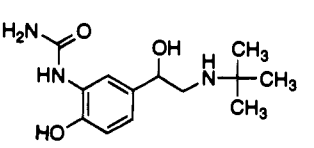
(127) Octopamine



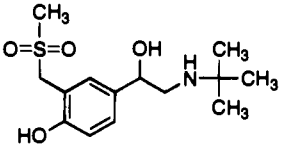
(128) Synephrine

is more potent than the (+)-enantiomer.[103] Enantiomeric selectivity ratios cannot be determined for most of these compounds, because the maximum responses produced by the (+)-enantiomers are typically not sufficient for determination of an ED_{50}. Furthermore, it is important to perform these studies under conditions where an indirect effect resulting from the displacement of neuronal norepinephrine stores cannot contribute, (*i.e.*, in a reserpine-pretreated preparations) since the (+)-enantiomers are still capable of indirect activity (see below).[102]

Analogs of *N*-*tert*-butylnorepinephrine in which the *m*-hydroxyl group has been replaced by a ureido (carbuterol, **129**) or sulfonylalkyl (sulfonterol, **130**) group have enantiomeric selectivity ratios of over 100-fold at the β_2-adrenoceptor, with the (−)-enantiomer being the more potent.[104,105] Although these agents show substantial selectivity for β_2- versus β_1-adrenoceptors, a similar degree of stereoselectivity is observed for the activation of the β_1-adrenoceptor.



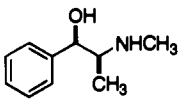
(129) Carbuterol



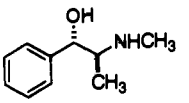
(130) Sulfonterol

Methoxamine, which has two asymmetric centers, is one of the few phenylethanolamines to lack ring hydroxyl groups and still retain direct agonist activity at α_1-adrenoceptors. As observed for α-methylnorepinephrine, the *erythro* form rather than the *threo* form is the configuration that is most active.[106] Although little data on the pharmacological activity of the methoxamine stereoisomers has been reported, (1*S*,2*R*)-(+)-*erythro*-methoxamine was found to be 30-fold less potent than the racemate as an α_1-adrenoceptor agonist in the isolated rabbit aorta (Hieble, unpublished data). (1*R*,2*S*)-

(−)-*erythro*-Ephedrine (**131**) has weak partial agonist activity at α_1- and β_2-adrenoceptors.[97] The 1*S*,2*R* (+)-*erythro* enantiomer is over 10-fold weaker as a β_2-adrenoceptor agonist and has substantially reduced potency and efficacy at the α_1-adrenoceptor. Neither enantiomer of the *threo* configuration (pseudoephedrine, e.g., (1*S*,2*S*)-(+)-*threo*-ephedrine, **132**) has measurable activity as a directly acting α_1-adrenoceptor agonist; however, as observed for α-methylnorepinephrine, both enantiomers of pseudoephedrine can activate the β_2-adrenoceptor. There is no significant difference in potency between the 1*R*,2*R* and 1*S*,2*S* isomers, but the 1*R*,2*R* enantiomer has greater intrinsic activity.[97]



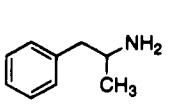
(131) (1R,2S)-(-)-*erythro*-Ephedrine



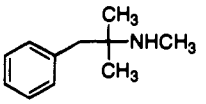
(132) (1S,2S)-(+)-*threo*-Ephedrine

2.1.3. Indirectly Acting Phenethylamines. As noted above, many phenethylamines have the ability to displace norepinephrine from its vesicular storage sites in adrenergic varicosities. This can result in an indirect stimulation of either α- or β-adrenoceptors. It is difficult to establish structure−activity relationships for this indirect effect, since the magnitude of the indirect stimulation of the adrenoceptors is dependent upon other factors besides the ability of an amine to displace vesicular norepinephrine, including its ability to be transported across the neuronal membrane and its ability to block neuronal reuptake of norepinephrine. Furthermore, there may be different mechanisms for indirect sympathomimetic activity, dependent on both the structure of the indirect agonist and the tissue studied. Also, many phenethylamines can produce both direct and indirect adrenoceptor activation, making quantitation of each individual component difficult.

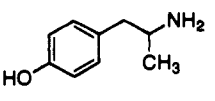
Most phenethylamines lacking the β-hydroxyl group have a significant indirect component to their adrenoceptor agonist activity. The indirect agonist activity of a deshydroxy analog is nearly always greater than that of the "inactive" enantiomer of the hydroxylated amine, perhaps as a consequence of more efficient neuronal uptake of the deshydroxy analog.[96] Phenethylamines with neither ring nor side-chain hydroxyl groups, such as amphetamine (**133**) and mephentermine (**134**), produce adrenoceptor activation exclusively through an indirect action. While some stereoselectivity is observed in the ability of the enantiomers of amphetamine to displace norepinephrine,[107] with the *S* (+)-enantiomer being more potent, the magnitude of the enantiomeric ratio is less than that observed for the directly acting phenylethanolamines. The (+)- and (−)-enantiomers of *p*-hydroxyamphetamine (**135**) were equipotent in producing indirect activation of α_1-adrenoceptors in the rat vas deferens.[103] The pressor activity of a series of nonphenolic amines, expected to act primarily *via* indirect stimulation of the α-adrenoceptor, showed enantiomeric ratios of less than 4 in almost all cases.[96] Because the (+)-enantiomers of most phenolic phenylethanolamines show little direct α_1-adrenoceptor agonist activity, the actions of these agents in intact rat vas deferens, which often have potencies and intrinsic activities that are comparable to that of the (−)-enantiomer, suggests that the (+)-analogs are effective indirect sympathomimetics.[103]



(133) Amphetamine



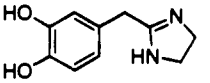
(134) Mephentermine



(135) p-Hydroxyamphetamine

2.2. Comparison of the Configurational Requirements of Phenethylamines and Imidazolines as α-Adrenoceptor Agonists. The two most widely studied structural classes of α-adrenoceptor agonists are the phenethylamines and the imidazolines. This latter class can be further subdivided into the benzylimidazolines and (phenylamino)imidazolines (tautomeric with phenyliminoimidazolidines). Although it is clear that phenethylamines and imidazolines both can interact with α_1- and α_2-adrenoceptors, it also appears clear that their mode of interaction with the α-adrenoceptors differs. The 3- or 4-point attachment of phenethylamines with the adrenoceptors, which is consistent with the Easson−Stedman hypothesis and data from recombinant adrenoceptors, does not apply to the imidazolines.

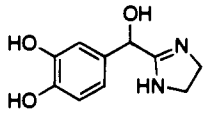
Although the presence of a β-hydroxyl group in the proper configuration (*R*) markedly enhances the affinity of a phenethylamine for the α-adrenoceptor, the presence of a hydroxyl group on the corresponding benzylic carbon in a benzylimidazoline does not increase, but rather decreases, affinity for the receptor.[15,108−110] In these hydroxylated imidazolines, the absolute configuration of the asymmetric center has only a minor influence on receptor affinity,[109] in contrast to the 100-fold stereoselectivity commonly observed for the phenethylamines. Interestingly, although benzylic hydroxylation of 3,4-dihydroxytolazoline (**136**) decreases its affinity for the α_2-adrenoceptor, its efficacy at this receptor is substantially increased.[109] This increase in efficacy is observed with both *R* and *S* enantiomers of the hydroxylated analog, with the *R* enantiomer showing a 5.6-fold greater affinity than the *S* enantiomer. Hence, it is possible that benzylic hydroxylation enhances the ability of an imidazoline to activate the α_2-adrenoceptor. As noted above, molecular biology studies have detected important differences in the site of interaction of agonists and antagonists with adrenoceptor proteins, and it is possible that hydroxylation of the imidazoline molecule in the benzylic position could selectively enhance its ability to interact with sites responsible for G-protein activation.



(136) 3,4-Dihydroxytolazoline

Although most imidazolines are highly selective for α- versus β-adrenoceptors, the *R* enantiomer of α,3,4-trihydroxytolazoline (**137**) (an imidazoline analog of

norepinephrine) had significant *in vivo* activity at both β_1- and β_2-adrenoceptors.[109] The *S* enantiomer and the



(137) α,3,4-Trihydroxytolazoline

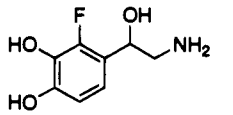
corresponding analog lacking the benzylic hydroxyl were 10–30-fold weaker than the *R* enantiomer, and the enantiomeric potency ratio was at least 30 at either the β_1- or β_2-adrenoceptor. Hence, in contrast to the results obtained in α-adrenoceptor models, the imidazolines hydroxylated in the benzylic position appear to conform to the Easson–Stedman hypothesis when β-adrenoceptor-mediated responses are evaluated.

In some phenethylamines with complex arylalkyl substituents on the nitrogen atom, the configuration of an asymmetric center in the N-substituent can influence agonist activity at both α_1- and β-adrenoceptors (*e.g.*, dobutamine, see Section 2.5.1. below). Alkyl substitution on carbon-3 of the imidazoline ring produces at least a 100-fold reduction in the affinity of benzylimidazolines for the α_1-adrenoceptor.[111] In contrast to the phenethylamines, the configuration of this asymmetric center generated by this substitution does not influence affinity or efficacy for the α_1-adrenoceptor.

2.3. Conformational Requirements of the Adrenoceptors. Norepinephrine, epinephrine, and other phenethylamine agonists of the α- and β-adrenoceptors are flexible molecules capable of adopting many conformations. Because the lowest energy conformation of a molecule is not necessarily the one which will interact optimally with the receptor, studies on the conformations of these molecules have been used to relate structure to adrenoceptor agonist activity. To minimize steric interactions between nonbonding atoms, these molecules would be expected to adopt an antiperiplanar conformation. Physical studies with (*R*)-(−)-norepinephrine have shown that both in solution and in the crystalline state, this conformation is favored.

Most molecular modeling of adrenoceptor agonists assumes that the catecholamine ligand interacts with the receptor in a conformation approximating the antiperiplanar fully extended *trans* conformation. Many catecholamine analogs have been prepared in which the conformation of the side chain is fixed by incorporation into an aliphatic ring. While most of these compounds are less potent than the nonrigid catecholamines themselves, most likely due to the additional steric bulk of the aliphatic ring, all such data are consistent with the requirement for an antiperiplanar conformation for receptor interaction. Perhaps the most potent of these rigid analogs are the 2-amino-1,2,3,4-tetrahydronaphthalene derivatives (see Section 1.1 above).

The antiperiplanar conformation of phenethylamines can exist in two rotameric states, which have been designated as α and β.[112] The particular rotamer required for receptor interaction appears to differ for the α- and β-adrenoceptors. The adrenoceptor selectivity of the 2- and 6-fluoro analogs of norepinephrine differ dramatically. 2-Fluoronorepinephrine (**138**) is equipotent with norepinephrine at β-adrenoceptors but is 10–30-fold weaker at the α-adrenoceptor. In contrast, 6-fluoronorepinephrine (**139**) is equipotent with norepinephrine at the α-adrenoceptor, but is 10–100-fold weaker at the β-adrenoceptor.[113] Because 2- or 6-fluoro substitution of dopamine, or 5-fluoro substitution of norepinephrine, had little effect on activity at either α- or β-adrenoceptors,[113] fluoro substitution of norepinephrine must be influencing adrenoceptor selectivity through stabilization of a particular rotameric conformation, possibly through an interaction between the halogen and β-hydroxyl group. The results of ring chlorination on the β-adrenoceptor agonist activity of isoproterenol and other N-substituted phenylethanolamines are consistent with the observations described above. 2-Chloroisoproterenol (**140**) is equipotent with isoproterenol as an agonist at β-adrenoceptors, whereas the 6-chloro analog (**141**) is approximately 30-fold less potent.[114] In contrast, ring methylation in the 2-position decreases the affinity of norepinephrine for α_1-, α_2-, and β_1-adrenoceptors by 100–200-fold (Hieble, unpublished data). These results suggest that the effects of halogen substitution on subtype selectivity of the catecholamines are due to electronic rather than steric effects.



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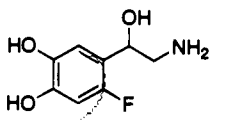

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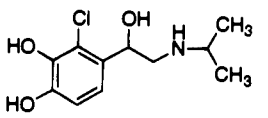

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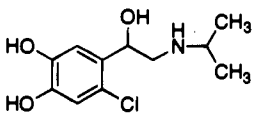


(141)

A difference in rotameric preference between α- and β-adrenoceptors is also observed with the hydroxylated 2-aminotetrahydronaphthalenes. Although the nature of the amino substituent will influence the absolute potency at both the α- and β-adrenoceptors, 6,7-dihydroxy substitution is consistently preferred for activity at the α-adrenoceptor,[112] whereas 5,6-dihydroxysubstitution favors agonist activity at β-adrenoceptors.[115]

As noted in Section 1.1, cyclized derivatives of methoxamine, such as SK&F 89748, are potent and selective agonists of the α_1-adrenoceptor. The enantiomers of SK&F 89748 have been resolved and examined for α_1-adrenoceptor agonist activity in the isolated rabbit ear artery. An enantiomeric potency ratio of approximately 7 was observed, with the *S* enantiomer being more potent.[19] While this degree of stereoselectivity is less than that observed with phenethylamines having an asymmetric β-carbon atom, it is greater than that observed at the α_1-adrenoceptor for α-methyldopamine, which has asymmetry at a position corresponding to that in SK&F 89748, and is comparable to the value obtained for this catecholamine at the α_2-adrenoceptor, where the *S* enantiomer is 9-fold more potent than the *R* enantiomer.[100]

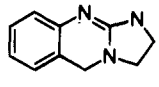
Conformational requirements for the interaction of imidazolines with the adrenoceptors are less clearly understood. The most energetically stable conformation of the imidazoline agonists appears to be one in which the planes of the imidazoline and aromatic rings are perpendicular to one another.[116] This conformation of an imidazoline would place one nitrogen atom of the imidazoline ring and the aromatic ring in a relative

Table 5. α-Adrenoceptor Selectivity of Yohimbine and Related Alkaloids

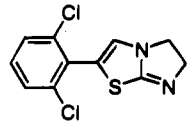
compound	structural series	adrenoceptor selectivity
yohimbine	normal	$\alpha_2 \gg \alpha_1$
apoyohimbine	normal	$\alpha_2 > \alpha_1$
corynanthine	normal	$\alpha_1 \gg \alpha_2$
β-yohimbine	normal	$\alpha_2 > \alpha_1$
yohimbol	normal	$\alpha_2 > \alpha_1$
raubasine	normal	$\alpha_1 > \alpha_2$
rauwolscine	allo	$\alpha_2 \gg \alpha_1$
tetrahydroalstonine	allo	$\alpha_2 \gg \alpha_1$
pseudoyohimbine	pseudo	*a*
epi-3α-yohimbine	epiallo	*a*
akuammigine	epiallo	*a*

[a] No pharmacologically significant functional activity at either α_1- or α_2-adrenoceptors (Weitzell *et al.*, 1979[124]).

orientation similar to that of the phenethylamines in the antiperiplanar conformation, although other structural elements would still differ between the two classes. The preference for perpendicular aromatic and imidazoline rings is consistent with the ability of *ortho* substituents to enhance the affinity of imidazolines for the α-adrenoceptor. Because similar enhancement is observed with halogen or alkyl substituents in these positions,[117] the effect is likely to be steric, rather than electronic. Although unsubstituted (phenylamino)- and benzylimidazolines may preferentially assume a solution conformation where the phenyl and imidazoline rings are mutually perpendicular,[118,119] the presence of *ortho* substituents could force the molecule into this conformation. An imidazoline analog in which the phenyl and imidazoline rings are fused into a planar orientation (**142**) lacks activity at central α_2-adrenoceptors, whereas a clonidine analog, Sandoz 44-549 (**143**), containing the 2,6-dichlorophenyl ring linked to a fused imidazo[2,1-*b*]thiazole, is extremely potent as a central α_2-adrenoceptor agonist.[120] However, the affinity of these fused imidazoline analogs for α-adrenoceptors has apparently not been directly determined, and other molecular alterations to favor or force a particular conformation have not been studied in detail for the imidazolines.

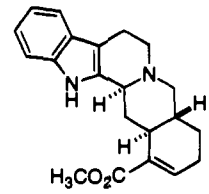


(142)

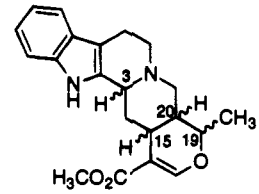


(143) SDZ 44-549

2.4. Relationship between Configuration and Subtype Selectivity of Yohimbine Alkaloids and Congeners as α-Adrenoceptor Antagonists. Although several alkaloid families have α-adrenoceptor antagonist activity, such as the ergots, berbanes,[46] and aporphines,[121] the only family studied extensively to date has been the yohimbanes. These alkaloids are complex polycyclic structures with five asymmetric centers. Three diastereoisomers, yohimbine, rauwolscine, and corynanthine, have been characterized extensively as α-adrenoceptor antagonists; limited data are available on a few of the remaining possible stereoisomers and on a dehydrated analog, apoyohimbine (**144**). Several related alkaloids (heteroyohimbines) (**145**–**147**) have been isolated from the same sources as yohimbine and also have α-adrenoceptor antagonist activity.



(144) Apoyohimbine



(145) Raubasine (Stereochemistry: 3α, 15α, 19α, 20β)[a]
(146) Akuammigine (Stereochemistry: 3β, 15α, 19α, 20α)
(147) Tetrahydroalstonine (Stereochemistry: 3α, 15α, 19α, 20α)

[a] For stereochemical conventions see Lambert et al., (123)

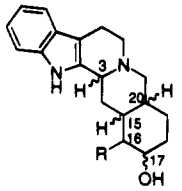
On the basis of the stereochemistry of the ring junctions, the known yohimbine alkaloids can be divided into four classes, designated as normal, pseudo, allo and epiallo.[122,123] Examples of each series has been tested for α_1- and α_2-adrenoceptor antagonist affinity (Tables 5 and 6). Examples of the normal series include yohimbine, corynanthine, β-yohimbine (**148**), and raubasine. The position of the carbomethoxy substituent at position 16 appears to be an important factor in the determination of affinity for the α_2-adrenoceptor. Corynanthine, the 16-epimer of yohimbine, had essentially no functional activity as a prejunctional α_2-adrenoceptor antagonist, while epimerization of the 17-hydroxyl group (β yohimbine) did not substantially reduce α_2-adrenoceptor antagonist activity. Removal of the 16-substituent (yohimbol) (**149**) reduces, but does not eliminate, antagonist activity at the prejunctional α_2-adrenoceptor.[124] These structural alterations had little effect on α_1-adrenoceptor antagonist activity, with only a 4-fold difference in affinity being observed between the most potent (corynanthine) and least potent (yohimbol) antagonist. The selectivity of yohimbine and corynanthine for α_2-adrenoceptors and respectively α_1-adrenoceptors has been confirmed in a variety of *in vitro* and *in vivo* functional assays. Apoyohimbine, in which the carbomethoxy group is attached to a sp^2-hybridized carbon atom, and hence is close to the molecular plane, was found to be more potent than yohimbine as a functional antagonist at both α_1- and α_2-adrenoceptors, but with somewhat less α_2-adrenoceptor selectivity.[125] Raubasine, a heteroyohimbine analog with similar stereochemistry to apoyohimbine with respect to both the carbomethoxy substituent and molecular backbone, has been found to be a moderately potent antagonist *in vitro* at both α_1- and α_2-adrenoceptors in the rat vas deferens, with 3-fold selectivity for the α_1-adrenoceptor;[126] however, *in vivo* testing of this analog in the pithed rat showed marked selectivity for the α_1-adrenoceptor.[127]

The alkaloids noted above all have a near planar orientation of the molecular backbone. Changing the stereochemistry of the ring junction at C_3 results in molecules in which the molecular plane markedly deviates from planarity. Compounds with a β orientation of the hydrogen at this ring junction (pseudo and epiallo series) (**150**, **151**) have very low affinity for both α_1- and

Table 6. Affinity[a] of Yohimbine Alkaloids for Cloned α-Adrenoceptor Subtypes

compound	α_{1a}	α_{1b}	α_{1d}	α_{2a}	α_{2b}	α_{2c}	α_{2d}
yohimbine	1057 (1)	966 ± 289 (3)	289 (1)	7.5 ± 3.6 (5)	4.6 ± 1.2 (7)	2.3 ± 0.4 (8)	45 ± 7 (4)
rauwolscine	4400 (2)	2270 (2)	1320 (2)	4.6 ± 1.5 (5)	4.7 ± 1.4 (8)	1.0 ± 0.2 (8)	40 ± 10 (3)
corynanthine	142 (1)	517 (1)	253 (1)	1218 (2)	455 ± 172 (4)	161 ± 31 (5)	1250 (1)
raubasine	ND	ND	ND	8.2 (2)	14.5 (1)	5.0 (1)	289 (1)
akuammigine	ND	ND	ND	106 (2)	116 (1)	28 (1)	1210 (1)

[a] K_i values (nM) for inhibition of [^{3}H]prazosin or [^{3}H]rauwolscine binding to recombinant α_1- and α_2-adrenoceptors, respectively. Affinity for α_{1D}-adrenoceptors determined using rat (corynanthine, Lomasney *et al.*, 1991;[307] Saussy *et al.*, 1994[146]) or human (Hieble, unpublished data) receptors. Affinity for α_{1B}-adrenoceptors determined using rat (rauwolscine, corynanthine, Lomasney *et al.*, 1991[307]), hamster (yohimbine, Ramarao *et al.*, 1992;[308] rauwolscine, Saussy *et al.*, 1994[146]), or human (yohimbine, Ramarao *et al.*, 1992;[308] Hieble, unpublished data) receptors. Affinity for α_{1A}-adrenoceptors determined using bovine (corynanthine, rauwolscine, Lomasney *et al.*, 1991;[309] Saussy *et al.*, 1994[146]) or human (yohimbine, Hieble, unpublished data) receptors. Affinity for α_{2A}-, α_{2B}-, and α_{2C}-adrenoceptors using rat, mouse, or human receptors (data from Devedjian *et al.*, 1994;[310] Bylund *et al.*, 1992;[311] Uhlen *et al.*, 1992;[300] Link *et al.*, 1992;[312] Xia *et al.*, 1993;[304] Voigt *et al.*, 1991;[304] Harrison *et al.*, 1991;[304] Chruscinski *et al.*, 1992;[314] Lanier *et al.*, 1991;[299] Weinshank *et al.*, 1990;[316] Marjamaki *et al.*, 1993;[301] Flordellis *et al.*, 1991;[317] Blaxall *et al.*, 1994;[313] and Lomasney *et al.*, 1991[309]). Affinity for α_{2D}-adrenoceptors determined using rat (Lanier *et al.*, 1991;[299] Harrison *et al.*, 1991;[305] Blaxall *et al.*, 1994[313]) or mouse (Link *et al.*, 1992;[312] Blaxall *et al.*, 1994[313]) receptors. The number of reported values used in calculation of each mean K_i values is denoted in parentheses.



(148) β-Yohimbine (R = CO_2CH_3; Stereochemistry: 3α, 15α, 16α, 17β, 20β)[a]
(149) Yohimbol (R = H; Stereochemistry: 3α, 15α, 17α, 20β)
(150) Pseudoyohimbine (R = CO_2CH_3; Stereochemistry: 3β, 15α, 16α, 17α, 20β)
(151) Epi-3α-Yohimbine (R = CO_2CH_3; Stereochemistry: 3β, 15α, 16β, 17α, 20α)
[a] For stereochemical conventions see Lambert et al., (123)

α_2-adrenoceptors.[124,126] Introduction of bulky substituents at C_{14} of yohimbine, which would be expected to disrupt the planarity of the molecule, abolishes affinity for both α-adrenoceptor subtypes.[128] Interestingly, introduction of a hydroxyl group at this position reduces the affinity of yohimbine for the α_2-adrenoceptor (by 275-fold) to a much greater degree than for the α_1-adrenoceptor (6-fold reduction), resulting in an antagonist having essentially equal affinity for the two α-adrenoceptor subtypes.

However, if the stereochemistry is changed only at C_{20} (allo series), potency and selectivity for the α_2-adrenoceptor is retained. In most models, rauwolscine is even more selective than yohimbine as an α_2-adrenoceptor antagonist, generally as a consequence of reduced α_1-adrenoceptor antagonist activity. Rauwolscine has been widely utilized for characterization of α-adrenoceptor-mediated responses and, when radiolabelled, as a ligand in radioligand binding assays. Although less extensively characterized, the corresponding heteroyohimbine analog in the allo series, tetrahydroalstonine, also appears to be a potent and selective α_2-adrenoceptor antagonist in both *in vitro*[126] and *in vivo*[127] models. It is interesting to note that although the position of the 16-carbomethoxy substituent markedly influences affinity for the α_2-adrenoceptor in the normal series (*e.g.*, yohimbine versus corynanthine), the marked change in orientation predicted by changing the stereochemistry of the ring bearing this substituent does not influence α_2-adrenoceptor affinity (*e.g.*, yohimbine versus rauwolscine). It has been suggested, however, that the spatial positions of the carbomethoxy groups in yohimbine and rauwolscine are similar, despite the different stereochemistry of the ring junction.[129]

In contrast to α_1- versus α_2-adrenoceptor selectivity, relatively little is known of the effects of stereochemistry on the selectivity of yohimbine alkaloids between subtypes of each of the major α_2-adrenoceptor classes. Determination of affinity of these compounds for expressed recombinant α-adrenoceptors, using radioligand binding assays, confirms the selectivity of yohimbine and rauwolscine for α_2- versus α_1-adrenoceptors (Table 6). Interestingly, although corynanthine shows a high degree of functional selectivity for α_1- versus α_2-adrenoceptors, especially *in vivo*,[32] binding affinities for the recombinant receptors show little selectivity for corynanthine between α_1- and α_2-adrenoceptors, although the α_2-adrenoceptor affinity is much lower than that of yohimbine and rauwolscine.

2.5. Relationship between Stereochemistry and Pharmacological Profile in Agents Having Multiple Pharmacologic Actions. 2.5.1. Agents Interacting with Multiple Adrenoceptors. Because the structure–activity relationships for interaction of agonists and antagonists with α- and β-adrenoceptors are well understood (although clearly more is known regarding the β-adrenoceptor), it is possible to design agents capable of interaction with both adrenoceptor subtypes. This is accomplished by combining multiple pharmacophores in a single molecule. If one or more of these pharmacophores contain an asymmetric center, alterations in stereochemistry can result in a qualitative change in the pharmacologic profile of the drug. Several compounds of this type are currently in use as therapeutic agents, including dobutamine, an α-/β-adrenoceptor agonist, and labetalol and carvedilol, α-/β-adrenoceptor antagonists.

2.5.1.1. Dobutamine. Dobutamine, an analog of dopamine bearing a complex arylalkyl substituent on the nitrogen atom, activates both α- and β-adrenoceptors. Compared to dopamine, racemic dobutamine is approximately 100-fold more potent as an α_1-adrenoceptor agonist in rat aorta, 200-fold more potent as a β_1-adrenoceptor agonist in reserpine-pretreated guinea pig atria, and 10-fold more potent as a β_2-adrenoceptor agonist in rat uterus. Dobutamine is approximately 3-fold more potent than dopamine as an α_2-adrenoceptor agonist in the field-stimulated guinea pig ileum, although both compounds are quite weak at this receptor subtype.[130] Dobutamine is a full agonist at the β-adrenoceptor, but a partial agonist, with intrinsic activity ranging from 0.4 to 0.9, in *in vitro* α_1-adrenoceptor models. Dobutamine has equivalent affinity for β_1- and β_2-adrenoceptors.[131]

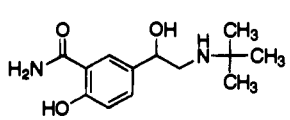
The nitrogen substituent of dobutamine contains one asymmetric center, immediately adjacent to the nitro-

gen atom. When the adrenoceptor activity of the two dobutamine enantiomers was determined, (+)-dobutamine was found to be 10-fold more potent than the (−)-enantiomer as a β-adrenoceptor agonist.[132] It is interesting that the configuration of the nitrogen substituent influences affinity for the β-adrenoceptor, although not to as great a degree as that of the key β-hydroxyl group present in many phenethylamines, which must be in the *R* configuration for any significant receptor affinity. The addition of this N-substituent increases the affinity for β-adrenoceptors by approximately 100-fold, as determined in radioligand binding assays comparing dopamine to racemic dobutamine.[130] Therefore, this substituent, even in the (−)-enantiomer, will have a favorable effect on the interaction with the β-adrenoceptor.

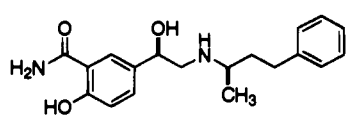
The affinity of the two enantiomers of dobutamine for α_1-adrenoceptors in the rat aorta were equal; however, only the (−)-enantiomer had agonist activity, whereas the (+)-enantiomer acted as a competitive antagonist against phenylephrine-induced contraction. It is not known which portion of the dobutamine molecule interacts with the α_1-adrenoceptor, but the amino nitrogen is clearly a key element, and changing the configuration near this atom must influence its ability to induce the conformational change required for second messenger activation, without affecting affinity for the receptor.

Hence the two dobutamine enantiomers have a markedly different pharmacologic profiles, with (+)-dobutamine being a β-adrenoceptor agonist/α_1-adrenoceptor antagonist, and (−)-dobutamine a partial α_1-adrenoceptor agonist/β-adrenoceptor agonist. α_1-Adrenoceptor stimulation has been shown to contribute to the inotropic activity of (−)-dobutamine.[133] It is likely that the inotropic versus chronotropic selectivity observed with the clinically employed racemic mixture of dobutamine, as well as its ability to produce cardiac stimulation without a marked increase or decrease in blood pressure, results from a summation of the actions of the two enantiomers.[25,133]

2.5.1.2. Labetalol. Labetalol has some structural similarity to dobutamine, with both molecules being phenethylamine analogs having 1-methyl-3-arylpropyl substituents on the nitrogen atom. Their pharmacology differs, however, with labetalol being an antagonist at both α- and β-adrenoceptors. In addition to introducing α-adrenoceptor antagonist activity, this arylalkyl substituent appears to augment affinity for the β-adrenoceptor, since labetalol is substantially more potent as a β-adrenoceptor antagonist than AH 3474 (**152**),[134] the corresponding phenethylamine with a *tert*-butyl substituent on the nitrogen.



(152) AH 3474



(153) Dilevalol

Labetalol has two asymmetric centers, and the form used clinically is an equal mixture of the two diastereomeric pairs. The *R,R* enantiomer (dilevalol) (**153**) is 3−4 times more potent than labetalol as a β-adrenoceptor antagonist *in vivo* and *in vitro*;[135,136] as predicted, the enantiomers with the *S* configuration at the β-carbon atom are at least 67-fold less potent as β-adrenoceptor antagonists.[136] Interestingly, the *R,S* isomer has 20−100-fold lower affinity than the *R,S* isomer for the β-adrenoceptor,[136] showing that, as observed for dobutamine, the configuration of an asymmetric center on the N-substituent can influence affinity for the β-adrenoceptor.

The *S,R* stereoisomer of labetalol is at least 10-fold more potent as an α_1-adrenoceptor antagonist than any of the other three stereoisomers.[136] However, unlike carvedilol (see below), the portions of the labetalol molecule that contribute to α- and β-adrenoceptor antagonist activity cannot be clearly identified, since the configuration at one symmetric center inflences the effect of changes in stereochemistry at the other on the pharmacological profile. However, as observed for dobutamine, the pharmacological profile of labetalol observed clinically is derived from several enantiomers. Interestingly, although lacking potent α_1-adrenoceptor antagonist activity, dilevalol has a vasodilator component in its activity that is not observed with labetalol.[137,138] This vasodilator action may result from subtype selective intrinsic sympathomimetic activity of dilevalol at the β_2-adrenoceptor.[138]

Dilevalol was developed and briefly marketed as a novel antihypertensive drug, but was subsequently withdrawn due to liver toxicity.[139] This toxicity is not observed with labetalol, suggesting that a toxic effect of the pure *R,R* stereoisomer may be counteracted by one of other enantiomers present in labetalol.

2.5.1.3. Carvedilol. Carvedilol, like labetalol, is a mixed α-/β-adrenoceptor antagonist. However, there are several significant differences. Unlike labetalol, the structural elements contributing to the α- and β-adrenoceptor blockade of carvedilol can clearly be differentiated. Carvedilol was derived from carazolol, an extremely potent (K_B < 100 pM) β-adrenoceptor antagonist. In contrast to labetalol, where the arylalkyl substituent contributes to β-adrenoceptor affinity, replacing the *N*-isopropyl substituent of carazolol with the arylalkyl group found in carvedilol reduces the β-adrenoceptor antagonist potency more than 10-fold; even so, carvedilol is still comparable in potency at β_1- and β_2-adrenoceptors to propranolol and most other clinically utilized β-adrenoceptor antagonists. The arylalkyl N-substituent of carvedilol contains the 2-methoxyphenyl element found in many α-adrenoceptor antagonists, and provides affinity for the α-adrenoceptor.

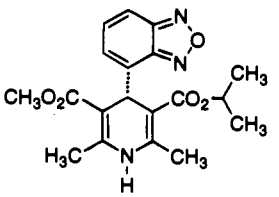
Carvedilol possesses only one asymmetric center, existing on the β-carbon of the (aryloxy)propanolamine element. As observed for all members of this structural class, the *S* enantiomer has 50-fold higher affinity than the *R* enantiomer for the β-adrenoceptor.[140] The two enantiomers of carvedilol are essentially equipotent as α_1-adrenoceptor antagonists, showing that the configuration of the alkylcarbazole substituent does not influence interaction with this receptor. This differs from labetalol, where the configuration of the phenylethanolamine β-carbon atom has a significant effect on α-adrenoceptor antagonist activity,[136] and tamsulosin (YM-617), a highly potent α_1-adrenoceptor antagonist, where there is a 100-fold potency difference between enantiomeric configurations of the carbon atom adjacent to the amino nitrogen.[5] This suggests that the phenylethanolamine or α-methylphenethylamine elements of labetalol and tamsulosin, respectively, play a more sig-

nificant role in binding to the α-adrenoceptor than the alkyl carbazole moiety of carvedilol, which may influence α-adrenoceptor affinity merely as a large lipophilic N-substituent.

Since carvedilol shows stereoselective interaction with β-, but not α-adrenoceptors, the α-/β-potency ratio, and therefore the clinical profile of the drug, will vary substantially between either enantiomer and the racemic mixture. Indeed, (*R*)-carvedilol would act as an α-adrenoceptor antagonist, in contrast to the preferential β-adrenoceptor antagonist activity of the racemic mixture or *S* enantiomer.

2.5.2. Dihydropyridines Having Adrenoceptor Antagonist Activity. 2.5.2.1. Niguldipine. The attachment of an arylalkylamine side chain to the dihydropyridine nucleus results in a compound having high affinity for α_1-adrenoceptors, in addition to potent calcium channel blocking activity. As with other dihydropyridines, such as nifedipine (**154**), the *S* enantiomer of niguldipine is the more potent calcium channel antagonist, as reflected by 45-fold higher affinity for the [^{3}H]-(+)-isradipine (**155**) binding site.[141] The configu-

(154) Nifedipine



(155) (+) Isradipine

ration of this asymmetric center also can influence the α_1-adrenoceptor selectivity of niguldipine, with the *S* enantiomer having much greater α_{1A}- versus α_{1B}-adrenoceptor selectivity.[141] A similar pattern is seen with several niguldipine analogs, where the (−)-enantiomers had 50−100-fold higher affinity for the α_{1A} adrenoceptor than the (+)-enantiomer, while affinity of the enantiomers for the other α_1-adrenoceptor subtypes differed by <10-fold, and affinity for the α_2-adrenoceptors was unaffected by stereochemical configuration.[73] Hence, although most dihydropyridines have no significant affinity for the α_1-adrenoceptors, the dihydropyridine moiety of niguldipine must play an important role in its interaction with the α-adrenoceptor. (*S*)-Niguldipine has become an important pharmacological tool for characterization of α_1-adrenoceptor subtypes, being one of the most selective antagonists for the α_{1A}-adrenoceptor versus either of the other two subtypes, as demonstrated in studies with recombinant α_1-adrenoceptors.[72,142] Niguldipine has also been used as a prototype for even more selective α_{1A}-adrenoceptor antagonists, *e.g.*, SNAP 5089 and its analogs.[73,74]

2.5.2.2. YM-15430. Attachment of the phenoxypropanolamine and dihydropyridine moieties through a methylene linkage results in a compound combining β-adrenoceptor antagonist activity and calcium channel blockade. As expected, the enantiomers with the dihydropyridine asymmetric center in the *S* configuration were substantially more potent as calcium channel blockers, and the *S* configuration of the phenoxypropanolamine center favored β-adrenoceptor antagonist activity.[27] However, it was interesting to note that in the compounds with (*S*)-dihydropyridine centers the configuration of the phenoxypropanolamine center had only a small effect on β-adrenoceptor antagonist activity, with the isomer with this center in the optimal *S* configuration being only 3-fold more potent. In the isomers with an *R* configuration of the dihydropyridine, the *S* configuration of the phenoxypropanolamine resulted in 45-fold greater affinity for the β-adrenoceptor,[27] a potency ratio more consistent with that observed in other (aryloxy)propanolamine β-adrenoceptor antagonists. Hence, as observed with the interaction of niguldipine with the α_1-adrenoceptor, the configuration of the dihydropyridine appears to influence the interaction of the phenoxypropanolamine moiety with the β-adrenoceptor. It is also interesting to note that the *S,S* isomer of YM-15430 (YM-15430-1) has 100-fold selectivity for β_1- versus β_2-adrenoceptors,[27] since it is unusual for phenoxypropanolamines without a ring substituent to show this pattern of subtype selectivity.[2]

3. New Therapeutic Applications

For several decades, there has been intense interest in the development of drugs interacting with α- and β-adrenoceptors as therapeutic agents for a variety of indications. Most of this effort has been concentrated on hypertension, where α_1-adrenoceptor antagonists, centrally acting α_2-adrenoceptor agonists, and β-adrenoceptor antagonists have been found to be effective. Likewise, interest has also focused on bronchospastic diseases, such as asthma, where β-adrenoceptor agonists remain one of the most important modes of therapy. Other diverse therapeutic applications have been established, including β-adrenoceptor antagonists in glaucoma, α-adrenoceptor agonists as nasal decongestants, and centrally active α_2-adrenoceptor agonists for symptomatic relief of opiate withdrawal. These established therapeutic applications will not be discussed here in detail; for reviews on these subjects, see Hieble and Ruffolo[25,143] and Ruffolo *et al.*[102] Despite the duration and extent of research into the therapeutic applications of adrenoceptor agonists and antagonists, there is still active interest in several newer applications, and in the optimization of therapeutic profiles for others, based on the recent refinement of adrenoceptor subclassification.

3.1. Hypertension. Since it has long been known that α-adrenoceptor activation will contract isolated blood vessels and increase blood pressure when administered to an anesthetized or conscious animal, α-adrenoceptor blockade was one of the first pharmacological approaches to the treatment of hypertension. While the nonselective agents such as phentolamine and phenoxybenzamine were not highly efficacious, the development of selective α_1-adrenoceptor antagonists, prazosin being the prototype, has led to widespread use of these agents as antihypertensive drugs. Several α_1-adrenoceptor antagonists, such as terazosin and doxazosin, are currently available for once-daily treatment of hypertension.

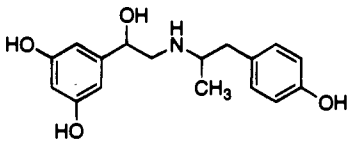
It appears that the α_1-adrenoceptor subtype responsible for vascular contraction depends on both the location of the blood vessel and the species from which it is obtained. While multiple α_1-adrenoceptor subtypes may contribute to the contractile response, there appear to be vascular beds responding primarily to α_{1A}- (rat renal vasculature[144]), α_{1B}- (rabbit aorta[145]), and α_{1D}-

adrenoceptors (rat aorta[146,147]). The contribution of additional α_1-adrenoceptor subtypes, *i.e.*, the prazosin-resistant α_1-adrenoceptors characterized by Muramatsu *et al.*,[145] to vascular contraction appears likely. The magnitude of this contribution can also vary depending on species and vascular bed. Studies in human aorta show the presence of mRNA for both α_{1B}- and α_{1D}-adrenoceptors, with little or no α_{1A}-mRNA.[72,148,149] However, based on mRNA distribution, the α_{1A}-adrenoceptor appears to be the predominant subtype in human vena cava.[148] While the α_1-adrenoceptor subtype(s) responsible for blood pressure regulation in the intact animal is still unclear, it appears that it may be possible to block α_1-adrenoceptors in a specific vascular bed without influencing systemic blood pressure.[150]

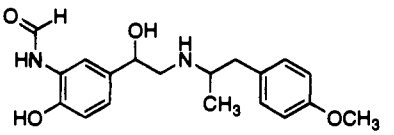
α_2-Adrenoceptors are also present on blood vessels and can mediate vasoconstriction. α_2-Adrenoceptor-mediated vascosontriction appears to play an important functional role in the cutaneous circulation,[151–153] in small arteries, including those isolated from human tissue[154] and in saphenous veins.[23,155,156] Many studies have demonstrated α_2-adrenoceptor-mediated pressor responses in pithed rats.[157,158] mRNA for all three α_2-adrenoceptor subtypes is found in human aorta, with the α_{2C}-adrenoceptor being the predominant subtype.[159] Interestingly, a recent report suggests that α_2-adrenoceptor-mediated contraction of the caudal artery is mediated by the α_{2C}-adrenoceptor subtype.[160] It has been suggested that vascular α_2-adrenoceptors are selectively activated in hypertensive animals,[161,162] but α_2-adrenoceptor blockade has not been evaluated as an approach to antihypertensive therapy.

β-Adrenoceptor antagonists have been utilized clinically as antihypertensive agents for several decades. Both mixed β_1-/β_2-adrenoceptor antagonists and selective β_1-adrenoceptor antagonists are effective. Sparing of pulmonary β_2-adrenoceptors by the selective β_1-adrenoceptor antagonists results in fewer bronchospastic side effects, offering a therapeutic advantage to this class. Activation of vascular β_1- and/or β_2-adrenoceptors will result in vasodilation in vivo or relaxation of spasmogen-induced vascular tone in isolated preparations. Hence, blockade of vascular β-adrenoceptors is unlikely to be involved in the antihypertensive efficacy of β-adrenoceptor antagonists. Despite the extensive use of these drugs, and the basic research directed toward understanding their antihypertensive action, the mechanism for the blood pressure reduction is still unknown. Some proposed mechanisms include the following: reduction in cardiac output; central nervous system effects to decrease sympathetic outflow; reduction in renin secretion; decreases in plasma volume; resetting of baroreceptors; reduction in the vasopressor effects of stress-induced catecholamine release; decreased peripheral neurotransmitter release as a result of blockade of facilitory prejunctional β-adrenoceptors. None of these individual mechanisms will explain the effects of all β-adrenoceptor antagonists on blood pressure. However, it is likely that several of these putative mechanisms contribute to the clinical effects, with the contribution of each varying between the individual compounds.[163]

3.2. Asthma. Inhalant therapy with adrenoceptor agonists has been employed for asthma and other bronchospastic conditions for nearly a century. The agents used have become increasingly selective, from epinephrine (α- and β-adrenoceptor agonist) to isoproterenol (β-adrenoceptor agonist) to the currently preferred agents salbutamol and fenoterol (**156**) which are highly selective β_2-adrenoceptor agonists. While *in vitro* selectivity between the β-adrenoceptor subtypes can readily be achieved, it is likely that both β_1- and β_2-adrenoceptor subtypes make some contribution to the desired therapeutic effect, relaxation of bronchial smooth muscle and the primary side effect, cardiac stimulation.[25] Hence, much of the bronchial selectivity achieved with inhaled β_2-adrenoceptor agonists is likely to be due to selective delivery to the desired site of action.



(156) Fenoterol



(157) Formoterol

Recent research on bronchodilator β_2-adrenoceptor agonists has focused on increased duration of action, allowing for less frequent administration. Two long-acting β_2-adrenoceptor agonists, salmeterol and formoterol (**157**), are currently in clinical use. Formoterol, which contains two asymmetric centers, is marketed as the racemic mixture of *R,R* and *S,S* enantiomers. There has been concern regarding the misuse of these long-acting β_2-adrenoceptor agonists, since downregulation of β_2-adrenoceptors, a problem long associated with β-adrenoceptor agonist therapy of asthma,[164] may be more pronounced with the longer lasting drugs.[165] Long-lasting β_2-adrenoceptor agonists are not appropriate for acute therapy of bronchospasm. Combination of chronic β_2-adrenoceptor agonist therapy with inhaled corticosteroid is often useful, since corticosteroids can prevent or reverse agonist-induced down regulation of the β_2-adrenoceptor.[165]

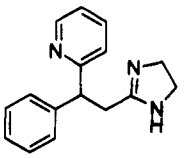
3.3. Non-Insulin-Dependent Diabetes. α_2-Adrenoceptor activation is known to inhibit the secretion of insulin from the β-cell of the pancreatic islet. α_2-Adrenoceptor antagonists, such as rauwolscine, idazoxan, and SK&F 86466, potentiate glucose-induced insulin secretion in the rat and attenuate peak plasma glucose levels attained following an oral glucose challenge.[166] The selective α_1-adrenoceptor antagonist, prazosin, has no effect on this response. Interestingly, the functionally (*i.e.*, prejunctional) selective α_2-adrenoceptor antagonists, SK&F 104078 and SK&F 104856, also fail to attenuate the plasma glucose response.[166]

Studies in normal human subjects show phentolamine to potentiate the acute phase of insulin secretion.[167] α_2-Adrenoceptor antagonists do not influence basal insulin levels.[168] Therefore, blockade of the α_2-adrenoceptor on the pancreatic islet cell may represent an approach to selectively enhancing glucose stimulated insulin secretion in non-insulin dependent diabetes (NIDDM).

Phentolamine enhances the insulin response to glucose challenge in NIDDM patients.[169] Although a

nonadrenergic component to the action of phentolamine on the islet cell, dependent on the presence of an imidazoline ring, has been proposed,[170,171] a highly selective nonimidazoline α_2-adrenoceptor antagonist, MK-912, has been shown to produce a similar clinical effect.[172]

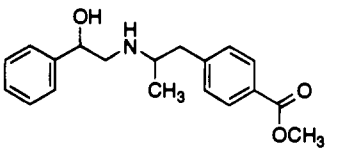
Although a compound (midaglizole) (**158**) purported to act *via* α_2-adrenoceptor blockade has been evaluated clinically in NIDDM,[173,174] this compound has very low affinity for the α_2-adrenoceptor and its clinical profile resembles standard oral hypoglycemic agents, such as the sulfonylureas. Hence, it is likely to be acting primarily through a mechanism that is unrelated to α_2-adrenoceptor blockade.



(158) Midaglizole (DG-5128)

SL 84.0418, a potent and selective α_2-adrenoceptor antagonist,[83] was evaluated as an oral hypoglycemic agent for NIDDM. On the basis of the affinity for recombinant α_2-adrenoceptors, SL 84.0418 does not discriminate between the α_{2A}- and α_{2B}-adrenoceptor subtypes.[87] In rodent models measuring functional blockade of pancreatic α_2-adrenoceptors, SL 84.0418 behaves like other α_2-adrenoceptor antagonists.[83,84] In a primate model in which idazoxan, another imidazoline-containing α_2-adrenoceptor antagonist, is ineffective, SL 84.0418 blunts the hyperglycemic response to oral glucose challenge and stimulates insulin secretion.[86] In contrast to most other α_2-adrenoceptor antagonists, SL 84.0418 can stimulate basal insulin release and produce symptomatic hypoglycemia in normal human volunteers,[175] suggesting another action on the islet cell in addition to α_2-adrenoceptor blockade. A recent study[85] has shown that SL 84.0418, at concentrations higher than those required to block the α_2-adrenoceptor, can block the ATP-sensitive potassium channel. Because potassium channel blockade is known to promote insulin secretion, this mechanism provides a potential explanation for the effects of SL 84.0418.

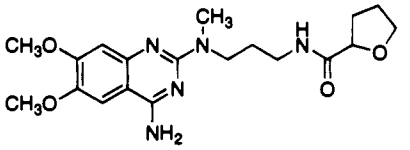
A second adrenoceptor related approach to NIDDM involves the selective stimulation of β_3-adrenoceptors. It is well-known that β_3-adrenoceptor stimulation will induce a thermogenic effect in rodents. BRL 35135, a moderately selective β_3-adrenoceptor agonist, will increase energy expenditure in normal human subjects.[10] Excess weight is believed to be a direct contributor to the insulin resistance observed in patients with NIDDM. Chronic treatment of obese rodents with selective β_3-adrenoceptor agonists produces a marked reduction in both weight. Similar effects have been observed in human subjects.[176] In addition to their ability to reduce body weight, studies in rodents[177,178] and in diabetic patients[10] show that BRL 35135, and an analog, BRL 26830 (**159**), have a direct effect on insulin sensitivity, unrelated to their ability to lower body weight. Hence agents capable of selective stimulation of the β_3-adrenoceptor may prove to be effective therapeutic agents in the treatment of NIDDM, in addition to their potential utility in obesity (see below).



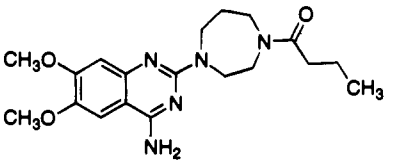
(159) BRL 26830

3.4. Benign Prostatic Hypertrophy (BPH). Currently there is intense interest in the discovery and development of novel α_1-adrenoceptor antagonists for the treatment of benign prostatic hypertrophy. α-Adrenoceptor activation will induce contraction of isolated prostatic strips,[179-180] and α-adrenoceptor-mediated contraction of the prostatic stroma makes a significant contribution to the urethral obstruction produced by the enlarged prostate gland.[181] The α-adrenoceptor antagonist first utilized clinically for the treatment of BPH was phenoxybenzamine, which produces irreversible blockade of both α_1- and α_2-adrenoceptors;[182] although phenoxybenzamine was effective, its use is now limmited due to its toxicities in animals.

Although both α_1- and α_2-adrenoceptors can be detected in human and canine prostate through radioligand binding assays,[183-185] only the α_1-adrenoceptor appears to be localized to the stromal smooth muscle,[184] and the functional response of isolated human prostatic strips to adrenoceptor activation appears to be mediated primarily through the α_1-adrenoceptor.[186] Therefore research into α-adrenoceptor antagonists for BPH has concentrated almost exclusively on selective α_1-adrenoceptor antagonists. Prazosin, terazosin, doxazosin, alfuzosin (**160**), bunazosin (**161**), and tamsulosin are currently marketed for the treatment of BPH in various countries. Other α_1-adrenoceptor antagonists (*e.g.*, naftopidil) are in advanced clinical trials. Of the above mentioned drugs, only naftopidil has pharmacologically relevant affinity for the α_2-adrenoceptor,[75,77] which may contribute to its therapeutic activity.[75]



(160) Alfuzosin



(161) Bunazosin

All α_1-adrenoceptor antagonists currently used in BPH can produce cardiovascular side effects, such as syncope, dizziness, and orthostatic hypotension, all of which are associated with blockade of vascular α_1-adrenoceptors. This phenomenon is to be expected, since most of these antagonists were initially developed as antihypertensive agents. Due to the recent identification of α_1-adrenoceptor subtypes, functional and radioligand binding studies have been performed to characterize the predominant α_1-adrenoceptor subtype in the prostate, with the goal of designing an antagonist capable of differentiating between prostatic and vascular α_1-adrenoceptors.

Recent evidence, involving a correlation of the functional receptor dissociation constants for α_1-adrenoceptor antagonists to block phenylephrine-induced[45,187] or norepinephrine-induced[80] contraction in human prostatic strips with the affinities of these antagonists for expressed α_1-adrenoceptor clones shows the best correlation to exist for the recombinant α_{1A}-adrenoceptor.[187] Messenger RNA for the α_{1a}-adrenoceptor predominates in the human prostate.[188] Autoradiographic analysis using an antagonist that is selective for the recombinant α_{1a}-adrenoceptor suggests that this is the primary subtype present on prostatic stroma, although the α_{1b}-adrenoceptor may be present on epithelial cells.[189] Correlation of binding affinities of α_1-adrenoceptor antagonists for human prostate with those in other native tissues suggests that the α_1-adrenoceptor present in the prostate is the α_{1A}-adrenoceptor.[190]

It has not yet been established that subtype-selective α_1-adrenoceptor antagonists will necessarily result in prostate versus vascular selectivity. Tamsulosin has selectivity for α_{1A}- versus α_{1B}-adrenoceptors in tissue homogenates,[5] and [^{3}H]tamsulosin appears to bind preferentially to α_1-adrenoceptors in human prostate compared to iliac artery.[191] However, studies in the anesthetized dog show tamsulosin to be equipotent against phenylephrine-induced increases in blood pressure and prostatic urethral pressure.[192] On the other hand, another novel α_1-adrenoceptor antagonist, SB 216469, which shows selectivity for native and recombinant α_{1A}-adrenoceptors,[69] was found to have a substantially greater *in vivo* urogenital selectivity in the anesthetized dog than did tamsulosin, prazosin or terazosin, when the doses required to block norepinephrine or stimulation-induced increases in urethral perfusion pressure were compared to those required to reduce diastolic blood pressure.[70] Recent data show that antagonists which are selective for the recombinant α_{1a}-adrenoceptor, while producing potent blockade of prostatic α_1-adrenoceptors,[45,187] are at least 100-fold weaker than prazosin when tested for orthostatic liability in the anesthetized rat.[193] Hence the specific requirements for functional urogenital versus vascular selectivity have not yet been established, although there is promising data suggesting that this selectivity profile is achievable.

There is also evidence for a contribution of prazosin-insensitive α_1-adrenoceptors to prostatic contraction. The dissociation constant for prazosin as an antagonist of norepinephrine-induced contraction in canine prostate is substantially higher (10–20 nM[194–196]) than that found in most blood vessels, and both high and low affinity binding sites for [^{3}H]prazosin can be found in canine,[196] bovine,[197] and human[198] prostate. The presence of prazosin-insensitive α_1-adrenoceptors in the prostate offers another potential approach to the design of agents showing prostate versus vascular selectivity.

There are only a few reports suggesting the possibility that adrenoceptor function may influence the actual growth of the prostate, in addition to the well-established effects to increase stromal smooth muscle tone. As in other tissues, norepinephrine has a direct mitogenic action in cultured stromal cells derived from rat prostate. This effect could be antagonized by propranolol, but not phenoxybenzamine, suggesting a β-adrenoceptor-mediated effect.[199] It is possible that norepinephrine, derived from the sympathetic innervation of the prostate, is required for hormone- and growth factor-induced prostatic growth, as reflected by the content of a specific prostate binding protein.[199] Maximal prostate growth stimulation in intact rats requires combined treatment with androgen and estrogen. α-Adrenoceptor blockade reduces hormally induced increases in prostatic weight, with combined α_1- and α_2-adrenoceptor blockade being more effective than α_1-adrenoceptor blockade alone.[200] Measurement of "stiffness" in prostates removed from these animals also showed a dramatic effect of combined α_1- and α_2-adrenoceptor blockade on hormone-induced stimulation, but not on basal parameters.

3.5. Obesity. Both α- and β-adrenoceptors are present on the adipocyte, exerting a reciprocal modulation of lipolysis.[201] The adipocyte β-adrenoceptor, mediating an increase in lipolysis, has long been known to have atypical characteristics, distinct from the β_1- or β_2-adrenoceptor.[202] Its unique pharmacologic profile led to the proposal for a β_3-adrenoceptor, which was supported by the cloning and expression of a third β-adrenoceptor[203] having pharmacological characteristics consistent with those of the adipocyte receptor. Thermogenesis is a characteristic effect of β_3-adrenoceptor agonists in rodents, mediated through an effect on brown adipose tissue. Isoproterenol produces a thermogenic response in human subjects, which is insensitive to mixed β_1-/β_2-adrenoceptor blockade.[204] One of the consistent characteristics of β_3-adrenoceptor-mediated responses is insensitivity to blockade by most "conventional" β-adrenoceptor antagonists; hence, these data suggest that a β_3-adrenoceptor-mediated metabolic effect can be produced in humans, despite the absence of the discrete brown adipose tissue deposits characteristic of rodents.

As noted above, several selective β_3-adrenoceptor agonists have been evaluated for antiobesity effects in human subjects.[10] While a statistically significant reduction in body weight was observed in most cases, it is likely that greater β-adrenoceptor subtype selectivity will be required, especially for β_3- versus β_2-adrenoceptor-mediated effects, since β_2-adrenoceptor activation is probably responsible for the muscle tremor associated with the drugs evaluated in humans to date.[176,205] However, a clear separation of the pharmacological responses to β_3- and β_2-adrenoceptor activation is not yet possible; for example, β_3-adrenoceptors appear to be present in skeletal muscle,[206] and hence tremor may also have a β_3-adrenoceptor-mediated component. On the other hand, the ability of BRL 35135 to increase plasma glycerol and free fatty acid concentrations in humans appeared to be sensitive to β_2-adrenoceptor blockade.[204] Compounds highly selective for the β_3-adrenoceptor have recently been identified, such as CL 316, 243,[9] but data on their efficacy in human subjects is not yet available.

Another potential problem is the lack of sensitivity of human versus rodent adipose tissue to β_3-adrenoceptor activation. While nonselective β-adrenoceptor agonists, such as isoproterenol, stimulate lipolysis in all adipocytes studied, regardless of species, selective β_3-adrenoceptor agonists, such as BRL 37344, are effective in rat, but not human tissue.[31] This may relate to reduced β_3-adrenoceptor density in human versus rat adipocytes or an inherent difference between the ability

of these agonists to activate the human and rodent β_3-adrenoceptors.[207] Along these lines, several agonists and antagonists show substantial potency differences between recombinant mouse and human β_3-adrenoceptors.[208]

Adipocytes also possess α_2-adrenoceptors, activation of which results in an inhibition of lipolysis. The relative distribution of α- and β-adrenoceptors in various adipose tissue beds suggests that those sites most resistant to the effects of dietary restriction contain the highest relative density of α_2-adrenoceptors.[209,210] This can be explained by an action of catecholamines on both adrenoceptors, with the relative α-/β-adrenoceptor density influencing the extent of lipolysis. In isolated human adipocytes, the mixed α-/β-adrenoceptor agonist, epinephrine, produces less lipolysis than the pure β-adrenoceptor agonist, isoproterenol; in the presence of α_2-adrenoceptor blockade, epinephrine and isoproterenol produce equivalent lipolytic responses.[211] In the conscious or anesthetized rat, an α_2-adrenoceptor antagonist, SK&F 86466, will stimulate epinephrine-induced lipolysis, as assessed through plasma glycerol levels.[212] In normal human volunteers, yohimbine will elevate plasma free fatty acid levels following a calibrated meal;[213] however, this effect appears to be mediated primarily through the indirect activation of β-adrenoceptors, inasmuch as the effect was nearly completely blocked by propranolol pretreatment.

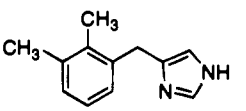
Long-term (2 year) treatment of rats with SK&F 86466 results in a dose-related reduction in body weight, without a significant effect on food consumption.[214] Two limited trials of yohimbine as an adjunct to caloric restriction show either a small but significant effect on body weight[215] or no effect at all;[216] however, the significance of these trials may be compromised by the short duration of action of yohimbine in humans. Hence the clinical utility of α_2-adrenoceptor antagonists in the treatment of obesity has not yet been adequately evaluated.

3.6. Congestive Heart Failure. Activation of myocardial β-adrenoceptor increases the force of cardiac contraction, and the sympathetic nervous system, mediates its regulatory action on cardiac rate and force through the β-adrenoceptor. Therefore, the activation of these receptors with exogenous agonists represents an obvious approach to the treatment on congestive heart failure, since the symptoms associated with this condition result from insufficient cardiac pumping capacity. While β-adrenoceptor stimulation, either with the physiological catecholamines or synthetic analogs, such as dobutamine, is useful in the acute treatment of congestive heart failure, chronic therapy with orally active β-adrenoceptor agonists has been disappointing.[25,217,218] Clinical benefits with xamoterol, a partial agonist at β_1-adrenoceptors,[219] may have resulted from blockade rather than stimulation of cardiac β-adrenoceptors. In this regard, there is increasing evidence that the elevated catecholamine levels associated with congestive heart failure are actually detrimental, rather than necessary, to support cardiac function. Consequently, pure β-adrenoceptor blockade may provide effective therapy in patients with congestive heart failure.[220]

Carvediol, a mixed α-/β-adrenoceptor antagonist (see Section 2.5.3) has been shown to have beneficial effects in congestive heart failure. The additional vasodilatory component resulting from α_1-adrenoceptor blockade may confer an additional therapeutic benefit. However, long-term treatment with the selective α_1-adrenoceptor antagonist, prazosin, has no effect on survival of heart failure patients.[221] Several clinical studies have also shown tolerance to the development of beneficial hemodynamic effects of prazosin in patients with heart failure.[218] It has been postulated that this tolerance results from an increased role of vascular α_2-adrenoceptors in heart failure,[222] consistent with the high levels of plasma catecholamines, and the preferential sensitivity of the vascular α_2-adrenoceptor to activation by circulating catecholamines as opposed to catecholamines released by sympathetic neuronal activation.

3.7. Sedation and Anesthesia. Activation of central α_2-adrenoceptors will result in sedation or even anesthesia in experimental animals. This effect is probably a consequence of activation of presynaptic α_2-adrenoceptors, resulting in decreased release of norepinephrine and other neurotransmitters. Sedation is the principal side effect of α_2-adrenoceptor agonists used in the treatment of hypertension (*e.g.*, clonidine). This sedative action can sometimes be used to therapeutic advantage, as in the treatment of Attention Deficit Hyperactivity Disorder (ADHD). In ADHD, the sedative action of clonidine is a useful adjunct to other benefits provided by clonidine in this disorder,[223] and bedtime administration of clonidine can be used to ameliorate the insomnia induced by other drugs used to treat ADHD.[224]

The sedative effect of clonidine and other α_2-adrenoceptor agonists is also a beneficial characteristic in their use as adjuncts to general anesthesia. Xylazine, a thiazepine α_2-adrenoceptor agonist, has been used for many years as a veterinary anesthetic, either alone or in combination with ketamine.[225] An advantage of α_2-adrenoceptor agonists for this indication is that their effect can be readily reversed by an α_2-adrenoceptor antagonist. More recently, the imidazole derivatives detomidine (**162**) and medetomidine have been intro-



(162) Detomidine

duced as veterinary anesthetics. Although structurally dissimilar to clonidine and other imidazoline α_2-adrenoceptor agonists, these imidazoles are potent and selective agonists of the α_2-adrenoceptor.[39] In both rats[226] and dogs,[227,228] pretreatment with medetomidine will reduce the requirements for gaseous anesthetic by up to 90%. This effect is greater than that observed with clonidine, perhaps being related to the greater selectivity of medetomidine for α_2- versus α_1-adrenoceptors, or its higher intrinsic activity as an α_2-adrenoceptor agonist.

In normal human volunteers, intravenous administration of medetomidine induced sedation in all subjects and often actually induced sleep.[229] The active enantiomer, dexmedetomidine, produced sedative and anxiolytic effects and reduced stress-induced hormonal changes when administered intramuscularly prior to laparoscopy.[230] Intravenous infusion of dexmedetomi-

dine decreased anesthetic requirements and blunted the tachycardia induced by endotracheal intubation.[231] In both of these clinical studies, bradycardia was observed. This is consistent with previous data from experimental animals and probably results both from a centrally mediated action to reduce sympathetic outflow as well as from stimulation of peripheral prejunctional α_2-adrenoceptors to inhibit cardiac neuroeffector transmission.

Lipophilic aminotetralin analogs were designed as selective α_1-adrenoceptor agonists capable of stimulating central α_1-adrenoceptors.[18-20] The most potent example of this structural class is SK&F 89748.[19] Chemical modification of SK&F 89748 leads to SDZ NVI 085, which appears capable of stimulating central α_1-adrenoceptors without markedly increasing systemic blood pressure.[21] SDZ NVI 085 acts as an anticataleptic agent in dogs,[59] providing evidence for the premise that central α_1-adrenoceptor stimulation results in an alerting action. SDZ NVI 085 has been reported to have a selective action at the α_{1A}-adrenoceptor,[60] but a recent report[61] suggests that the compound is a partial agonist at both α_{1A}- and α_{1B}-adrenoceptors.

3.8. Analgesia. Many of the effects of opiate receptor activation can be mimicked by central α_2-adrenoceptor stimulation. This is likely to be a result of the ability of both α_2-adrenoceptor agonists and opiate agonists to inhibit the firing of the locus coeruleus.[232] As noted above, α_2-adrenoceptor agonists, such as clonidine, are useful in the treatment of opiate withdrawal. Therefore it not surprising that α_2-adrenoceptor agonists can be effective analgesics. There have been many clinical trials of clonidine as an analgesic, either alone or in combination with opiates or other analgesics (for a review, see Quan *et al.*[233]). Most of these trials, including several performed according to double blind protocols, show clonidine to be effective, although one double-blind trial failed to demonstrate significant activity.[234] There are cases of clonidine showing efficacy in patients tolerant to opiates.[235] Studies in experimental animals show a different profile between morphine and clonidine, with morphine having greater initial efficacy but losing its effectiveness over a 3-week treatment period, whereas clonidine demonstrated greater activity upon prolonged treatment.[236]

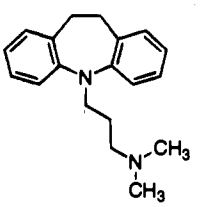
Clonidine produces analgesia when given by oral, intravenous, intramuscular, or epidural administration. As expected, the primary side effects are sedation and hypotension, but the respiratory depression characteristic of the opiates is not observed. In some cases, the utility of clonidines as an analgesic is limited by its short duration of action. Other α_2-adrenoceptor agonists utilized clinically as antihypertensive drugs, such as guanfacine, have a longer duration of action. Studies in experimental animals show intrathecal or epidural administration of guanfacine to have greater potency, and a substantially longer duration of analgesic action, compared to clonidine.[237-239] However, the analgesic effects of guanfacine have yet to be evaluated in human subjects.

As noted above, medetomidine is more effective than clonidine as a supplement to general anesthesia; a comparison of clonidine and medetomidine in a rat model of nerve-damage-induced pain[236] suggests medetomidine to be a more effective analgesic.

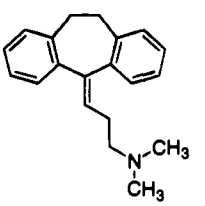
3.9. Cerebral Ischemia. There are several reports of α_2-adrenoceptor stimulation with clonidine or dexmedetomidine attenuating the neuronal damage and neurologic deficits induced by cerebral ischemia in the rat or rabbit.[240-242] The beneficial effects of dexmedetomidine could be reversed by the selective α_2-adrenoceptor antagonist, atipamezole,[241] providing strong evidence that stimulation of α_2-adrenoceptors is responsible for the observed neuroprotection. However, one other study may be at variance with this hypothesis. In a similar rat model, where focal ischemia was induced by occlusion of the middle cerebral artery, infarct size was reduced both by rilmenidine, an α_2-adrenoceptor agonist, and idazoxan, an α_2-adrenoceptor antagonist, but not by another α_2-adrenoceptor antagonist, SK&F 86466.[243] Idazoxan has previously been reported to be neuroprotective in models of global ischemia.[244,245]

It is not clear whether increased activity of central adrenergic neurons is detrimental or protective in cerebral ischemia. Reduction of norepinephrine release has been shown to enhance[246-248] neuronal damage induced by cerebral ischemia. The neuroprotective effect of idazoxan, which should enhance central noradrenergic activity through blockade of prejunctional α_2-adrenoceptors, is inconsistent with the neuroprotective effect observed in similar models with clonidine, rilmenidine, and dexmedetomidine. Since SK&F 86466, another α_2-adrenoceptor antagonist, was not neuroprotective, it seems unlikely that postjunctional α_2-adrenoceptor blockade is responsible. It has been shown that, under some conditions, idazoxan has partial agonist activity at the prejunctional α_2-adrenoceptor, resulting in an inhibition, rather than potentiation, of norepinephrine release.[249] Alternatively, it has been postulated that the beneficial effects of rilmenidine and idazoxan in cerebral ischemia are mediated through an interaction of these compounds with imidazoline receptors (see Section 4.2 below).

3.10. Depression. There is substantial evidence to suggest that depression results from a depletion of norepinephrine and/or serotonin at certain synapses within the central nervous system. The possibility exists that different classes of depression result from selective depletion of norepinephrine or serotonin and that agents selectively elevating synaptic levels of these neurotransmitters may have selective efficacy in alleviating the consequences of this depletion.[250] Classically, depression has been treated with relatively nonselective drugs, such as imipramine (**163**), amitriptyline (**164**), and analogs, which inhibit the reuptake of both



(163) Imipramine



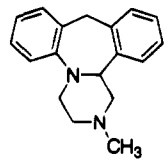
(164) Amitriptyline

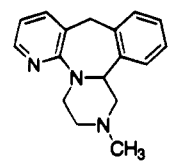
norepinephrine and serotonin, but in addition block multiple neurotransmitter receptors. In recent years, several highly selective blockers of serotonin uptake have become successful antidepressants, with a much better safety profile than the tricyclic agents. Nevertheless, selective norepinephrine uptake inhibitors have

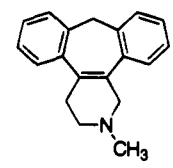
been shown to be effective antidepressants, and several agents blocking both norepinephrine and serotonin uptake, without blocking neurotransmitter receptors, are in late phases of clinical development (see review by Pinder and Wieringa[251]).

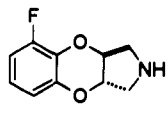
Presynaptic α_2-adrenoceptors are located at many sites within the central nervous system.[252,253] In addition to inhibition of stimulus-evoked release of norepinephrine and epinephrine from catecholaminergic neurons,[252] activation of presynaptic α_2-adrenoceptors can inhibit serotonin release.[254,255] Hence it is possible that blocking these inhibitory receptors with an α_2-adrenoceptor antagonist could result in increased synaptic levels of both norepinephrine and serotonin. Furthermore, α_2-adrenoceptor antagonists can increase the firing rate of the locus coeruleus.[256] Since the locus coreuleus sends projections throughout the brain, activation of this nucleus results in a variety of arousal behaviors.[257]

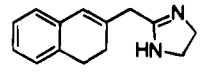
Mianserin (**165**), a marketed antidepressant shown to have efficacy comparable to amitriptyline, is a moderately potent α_2-adrenoceptor antagonist. Although minserin has antagonist activity at serotonin and histamine receptors[258] and is a weak inhibitor of norepinephrine uptake *in vivo*, these activities are probably insufficient to explain its clinical efficacy.[259] Mirtazapine (**166**) (6-azamianserin, ORG 3770) produces stereoselective blockade of the α_2-adrenoceptor and is 100-fold less potent than mianserin as an inhibitor of neuronal uptake, although retaining histamine and serotonin receptor affinity.[258] Mirtazepine has shown efficacy in a 6-week double-blind clinical trial in depressed patients.[260] Another mianserin analog, setiptiline (teciptiline) (**167**), combines clinical antidepressant activity with α_2-adrenoceptor blockade.[251]

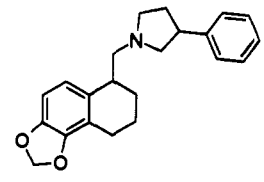

(165) Mianserin


(166) Mirtazapine


(167) Setiptiline

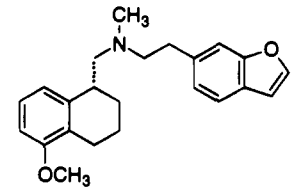

(168) Fluparoxan


(169) Napamezole


(170) ABT-200

Despite this evidence for antidepressant efficacy of compounds having α_2-adrenoceptor antagonist activity, it has been difficult to prove antidepressant activity of selective α_2-adrenoceptor antagonists. Idazoxan has been evaluated for many years, with only a few reports of efficacy in small patient groups.[261] Many highly potent α_2-adrenoceptor antagonists, including MK-912 (L-657,743), CH-38083, imiloxan, and fluparoxan (**168**), were presumably intended as antidepressants, and have entered early clinical trials.[251] Development of all of these agents was terminated, and no evidence for antidepressant efficacy has been published.

Another approach being pursued is the combination of α_2-adrenoceptor antagonist activity with neuronal uptake blockade. Napamezole (**169**) is a moderately potent antagonist at both α_1- and α_2-adrenoceptors, with the ability to inhibit neuronal reuptake of serotonin, norepinephrine and dopamine.[263] *In vivo* studies suggested that napamezole blocks α_2-adrenoceptors and serotonin reuptake at comparable doses.[264] Recently, ABT-200 (**170**) has been shown to be a highly potent α_2-adrenoceptor antagonist, with no pharmacologically relevant antagonist activity at other neurotransmitters and moderate potency as an inhibitor of norepinephrine uptake.[265] Preliminary clinical data suggests potential antidepressant efficacy for ABT-200.[265a] A related compound, A-80426 (**171**), combines blockade of neuronal 5-HT uptake with α_2-adrenoceptor blockade.[265b] Although A-80426 shows high *in vitro* affinity for both synaptosomal 5-HT uptake and for the α_2-adrenoceptor,[265b] A-80426 shows less potent in vivo α_2-adrenoceptor blockade than predicted by its *in vitro* affinity, and results in several animal models suggest that α_2-adrenoceptor blockade does not make a substantial contribution to the antidepressant activity of A-80426, which appears to be acting only via 5-HT uptake blockade.[265c]


(171) A-80426

The subtype of presynaptic α_2-adrenoceptors in human brain has not been established. Presynaptic α_2-adrenoceptors in rat and rabbit cortex have been shown to have α_{2A}- and α_{2D}-adrenoceptor characteristics, respectively,[266] while peripheral prejunctional α_2-adrenoceptors of human kidney have been suggested to be of the α_{2C}-adrenoceptor subtype.[267] The subtype selectivity of most of the α_2-adrenoceptor antagonists tested as antidepressants is not known. ABT-200 has high affinity for α_{2A}-, α_{2B}-, and α_{2C}-adrenoceptors.[265a] Imiloxan has substantial selectivity for α_{2B}- versus α_{2A} adrenoceptors.[35] Perhaps the combination of subtype selective α_2-adrenoceptor blockade with neuronal neurotransmitter uptake may represent a future approach to antidepressant therapy.

4. Future Directions

4.1. Further Adrenoceptor Subclassification as an Approach to Tissue and Organ Selectivity. As adrenoceptors are further subdivided, opportunities have been created for more selective drugs. For example, the recent subdivision of the α_1-adrenoceptor has lead to the development of selective α_{1A}-adrenoceptor antagonists, which may prove to be more effective drugs for the treatment of BPH than the currently available antagonists, which block all three α_1-adrenoceptor subtypes.

On the basis of the current state of α-adrenoceptor subclassification, there are several opportunities which have not yet been exploited for drug discovery. There is marked heterogeneity between blood vessels with respect to prazosin sensitivity, which has lead to the proposal of prazosin-insensitive α_1-adrenoceptors. α-

Table 7. Characterization of Imidazoline Receptors

subtype	location	clonidine affinity (nM)	idazoxan affinity (nM)	selective agonist	selective antagonist
I_1	plasma membrane	<10	100–300	moxonidine, rilmenidine	efaroxan[a]
I_2	mitochondrial outer membrane	>100[b]	<10		RX 801077 (2-BFI)[c]
	outer membrane				RX 821029[c]

[a] Efaroxan differentiates I_1 from I_2 receptors, but retains affinity for the α_2-adrenoceptor. [b] Some I_2 receptors retain moderate affinity for clonidine (K_i < 1000 nM), while others have no pharmacologically relevant affinity (K_i > 10,000 nM). [c] Differentiates I_2 receptors from α_2-adrenoceptors, affinity for I_1 receptors has not yet been reported.

Adrenoceptor antagonists that are selective for one of the two prazosin-insensitive α_1-adrenoceptors (α_{1L}, α_{1N}) may have distinct and potentially useful pharmacological profiles.

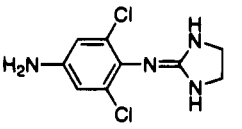
There are no α_2-adrenoceptor antagonists in widespread clinical use, although several agents of this class are currently being developed. Selectivity between α_2-adrenoceptor subtypes has not yet been exploited, perhaps because most of the functional responses produced by α_2-adrenoceptor activation appear to be mediated by the "classical" α_{2A}-adrenoceptor. Nevertheless, there is some evidence for contribution of other α_2-adrenoceptor subtypes to the α_2-adrenoceptor-mediated feedback control of neurotransmitter release from adrenergic nerve varicosities,[266,268] and α_2-adrenoceptor subtype selectivity may offer a mechanism for elimination of some of the undesirable effects associated with α_2-adrenoceptor antagonists resulting from blockade of these prejunctional receptors (*e.g.*, tachycardia).

Functional selectivity, which is not clearly associated with selectivity for known α_2-adrenoceptor subtypes, is observed for several novel antagonists, including SK&F 104078 and SK&F 104856.[23,77,269,270] These antagonists are capable of blocking some, but not all, α_2-adrenoceptor populations. This functional selectivity could have application in the design of drugs to block a specific α-adrenoceptor-mediated response.

The disparities between functional and molecular subclassification of both α_1- and α_2-adrenoceptors suggests the possible existence of additional adrenoceptors which have not yet been cloned and expressed; for example the prazosin-insensitive α_1-adrenoceptors and the SK&F 104078/SK&F 104856 insensitive α_2-adrenoceptors. In addition, because species homologs of an individual receptor subtype have been shown to have substantially different pharmacological characteristics, the cloning of adrenoceptors from additional species is likely to identify further subtle differences. On the other hand, one cannot predict whether new adrenoceptor subtypes will be identified within a single species.

Data in the rabbit show marked differences in yohimbine sensitivity between the adipocyte α_2-adrenoceptor mediating inhibition of lipolysis[271] and the presynaptic α_2-adrenoceptor in the cortex.[266] Although yohimbine-sensitive (α_{2A}) and yohimbine-insensitive (α_{2D}) α_2-adrenoceptors are now assumed to be species variants, these results suggest that four α_2-adrenoceptors may be present in the rabbit. There are other examples of native α-adrenoceptors having characteristics that are distinct from any of the recombinant α-adrenoceptors, suggesting the possibility of additional subtypes.

4.2. Interaction of Adrenoceptor Agonists and Antagonists with Non-Adrenergic Receptors (Imidazoline Receptors). As noted above, imidazole- and imidazoline-containing structures represent an important class of α-adrenoceptor agonists. Over the past decade, it has been established that, in addition to the α-adrenoceptor, many of these agents can interact with discrete "imidazoline" receptors. There appear to be several subtypes of the imidazoline receptor, one (I_1) characterized by [^{3}H]clonidine or [^{3}H]-*p*-aminoclonidine (**172**) binding, and the other (I_2) by [^{3}H]idazoxan binding (Table 7). There may be at least two subtypes of the I_2

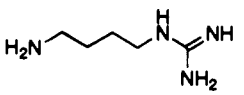


(172) p-Aminoclonidine

receptor, differing in their sensitivity for clonidine and amiloride,[272,273] although there may be interconvertible forms of this receptor,[274] perhaps explaining at least some of the affinity differences observed between tissues. Under some conditions, it now appears that [^{3}H]-clonidine can label I_2-like receptors within the brain stem.[275] A functional response has been attributed to the I_1 receptor and the inhibition of sympathetic outflow, and I_1 receptor-mediated release of arachadonic acid has been demonstrated in isolated pheochromocytoma cells.[276] Although this receptor has been localized to a specific nucleus within the brain stem, the rostral ventrolateral medulla (RVL), little is known about the molecular characteristics of the receptor. The I_2 receptor, which is distributed at various sites within the body, may be located intracellularly, primarily on the mitochondrial membrane.[277,278] It now seems likely that the I_2 receptor is associated with monoamine oxidase and other oxidase systems.[279] A function has not yet been clearly attributed to the I_2 receptor.

It has been proposed that I_1 receptors in the RVL mediate the antihypertensive activity of agents such as clonidine, which were thought to act through stimulation of central α_2-adrenoceptors. This premise is based on the observation that the hypotensive and bradycardic actions of clonidine, when administered locally into the RVL, is blocked by antagonists having affinity for both α_2-adrenoceptors and imidazoline receptors, such as idazoxan, but not by phenethylamine-derived α_2-adrenoceptor antagonists, such as SK&F 86466.[280] Furthermore, the ability of a series of agents to lower blood pressure and heart rate, when administered to the RVL, correlate with their affinity for imidazoline receptors, but not α_2-adrenoceptors.[280]

An endogenous ligand for the I_1 receptor was been postulated to be agmatine (**173**), a guanidine derivative formed by decarboxylation of arginine.[281] Agmatine has affinity for I_1 and I_2 receptors and α_2-adrenoceptors, with the highest affinity being observed for the I_1 receptor.[281,282] However, it is now clear that agmatine has no functional activity as either an agonist or



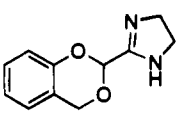
(173) Agmatine

antagonist at α_2-adrenoceptors[283,284] and that central administration of agmatine to intact rats and rabbits does not produce cardiovascular effects resembling those of clonidine.[284,285] Other endogenous substances (clonidine-displacing substances), of unknown structure, which interact with α_2-adrenoceptors and imidazoline receptors, have been isolated from various sources, including rat and bovine brain.[282,286,287] While the chemical and pharmacological properties of these partially purified extracts are distinct from that of agmatine,[282,288] suggesting the presence of a different endogenous ligand for central imidazoline receptors, it is still possible that the pharmacological actions of clonidine-displacing substance could be explained by several different bioactive agents, including agmatine, present in these complex mixtures.[289]

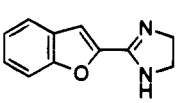
Several new centrally-acting antihypertensive drugs, such as moxonidine and rilmenidine, are proposed to act *via* interaction with the I_1 receptor.[64] They have higher I_1 receptor vs α_2-adrenoceptor selectivity ratios than clonidine. These agents appear to be less sedative than clonidine, and it has been postulated that the sympatholytic and sedative actions of clonidine and related imidazolines result from activation of I_1 receptors and α_2-adrenoceptors, respectively.[290]

However, there are some data that are inconsistent with this premise. The antihypertensive action of intravenous clonidine in the spontaneously hypertensive rat can be blocked by SK&F 86466.[37] Furthermore, the antihypertensive actions of clonidine and guanabenz, an α_2-adrenoceptor agonist having virtually no affinity for the I_1 receptor,[280] have equivalent sensitivities to inhibition by idazoxan and SK&F 86466.[37] In the conscious rabbit, the sympatholytic effect of intravenous rilmenidine, as measured by decreases in heart rate and firing rate of renal sympathetic nerves, was blocked by intravenous yohimbine or SK&F 86466, at doses that are selective for the α_2-adrenoceptor.[62,63] SK&F 86466 is also equipotent against rilmenidine and UK 14,304.[63] Hence, the systemic actions of the imidazolines may be mediated primarily by the α_2-adrenoceptor, in contrast to their selective action at I_1 receptors when administered directly into the RVL.

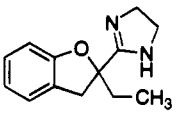
Structure–activity relationships at I_1 and I_2 receptors are still incomplete. The endogenous catecholamines and other phenethylamines have no affinity for either subtype. Idazoxan has high affinity for the I_2 receptor and moderate affinity for the I_1 receptor, where is appears to function as an antagonist (see above). Since no functional response to I_2 receptor activation has been identified, it is difficult to determine whether agents showing affinity for this receptor are agonists or antagonists. However, based on effects of guanine nucleotides on the binding parameters of idazoxan to I_2 receptors, and its ability to induce apparent receptor downregulation, idazoxan may have agonist activity at I_2 receptors.[291] The interaction of idazoxan with the I_2 receptor is stereoselective.[292] The addition of a methoxy group to idazoxan results in an antagonist (RX 821002) having high affinity for α_2-adrenoceptors, but virtually no affinity for the I_2 receptor.[293] Conversely, other idazoxan analogs, such as RX 821029 (**174**) and RX 801077 (**175**), have substantially higher affinity for the I_2 receptor than for the α_2-adrenoceptor.[279] Another idazoxan analog, efaroxan (**176**), has high affinity for the I_1 receptor and α_2-adrenoceptor[294] and functional activity as an I_1 receptor antagonist,[277] but virtually no affinity for the I_2 receptor.[294]



(174) RX 821029



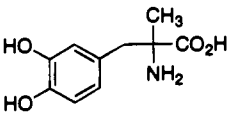
(175) RX 801077



(176) Efaroxan

Imidazoles, such as medetomidine, have affinity for the I_2 receptor; interestingly, the (−)-enantiomer of this agonist is one of the compounds capable of differentiating between the two potential I_2 receptor subtypes.[295] While most guanidines have no affinity for the I_1 receptor, they do interact with the I_2 receptor; this is an interesting observation since the putative endogenous agonist at the I_1 receptor, agmatine, is a guanidine. It was noted above that clonidine can discriminate between two I_2 receptor subtypes. Interestingly, *p*-aminoclonidine may show high selectivity for I_1 versus I_2 receptors, and other potent I_1 agonists, such as moxonidine, may have virtually no affinity for the I_2 receptor.[276]

The I_1 receptor has been postulated to be the target for centrally acting antihypertensive drugs. However, this has not been conclusively established, since all of the drugs examined to date have affinity for both I_1 receptors and α_2-adrenoceptors, and the data with selective antagonists are inconclusive. Furthermore, agents presumably acting through a "pure" α_2-adrenoceptor mechanism, such as α-methyldopa (**177**), produce



(177) α-Methyldopa

a similar clinical profile. More extensive clinical evaluation of these newer antihypertensives will be required to determine whether their sedative actions are significantly less than that of clonidine and other drugs of this class.

I_2 receptors are present in rat pancreatic islets[296] and have been postulated to influence potassium channel opening.[297] This is consistent with the premise that the ability of imidazolines, such as phentolamine, to potentiate insulin secretion is mediated by an I_2 interaction,[170,171] rather than by α_2-adrenoceptor blockade. However, since high concentrations of UK 14,304 and idazoxan, which have high affinity for the I_2 receptor, did not antagonize the inhibitory effect of the potassium channel activator, diazoxide, on insulin secretion, it appears that I_2 receptors are not involved in the control of insulin secretion.[296]

Biographies

Robert R. Ruffolo, Jr., received his B.S. and Ph.D. degrees in pharmacology from The Ohio State University. After postdoctoral training with Marshall Nirenberg at the NIH, Dr. Ruffolo joined Eli Lilly in 1978. He joined SmithKline Bee-

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William E. Bondinell received his Ph.D. in organic chemistry from the University of California, Berkeley, and did his postdoctoral studies at Columbia University. Prior to joining SmithKline Beecham in 1973, he was a Research Associate at the American Health Foundation. He is currently Assistant Director, Medicinal Chemistry, where his current research interests include α-adrenoceptor and integrin receptor antagonists.

J. Paul Hieble received his B.A. and Ph.D. degrees in organic chemistry from North Texas State University. He then obtained a second Ph.D. in pharmacology from the University of Texas Medical Branch. He joined SmithKline Beecham in 1977 where he is currently a Director in the Division of Pharmacological Sciences. His research interests include sympathetic neuroeffector transmission, subclassification of α-adrenoceptors, and the pharmacology of the prostate and bladder.

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