Antihypertensive β-Adrenergic Blocking Agents: *N*-Aralkyl Analogues of 2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3-cyanopyridine[1]

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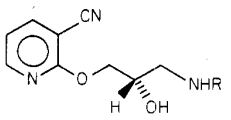
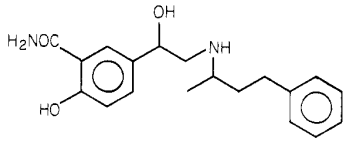
An interest in dual-acting antihypertensive agents, specifically those related to (*S*)-2-[3-(*tert*-butylamino)-2-hydroxypropoxy]-3-cyanopyridine (1), led us to probe the contribution of the side-chain amino substituent in this series. The ability of 1 and its various analogues to displace radiolabeled α_1 (WB-4101 and prazosin) and β (dihydroalprenolol) adrenergic receptor ligands was assessed by receptor-binding techniques. Most of the compounds exhibited high β-adrenoceptor binding affinities, but only the *N*-aralkylamino-substituted compounds showed high α_1-adrenoceptor affinities. Therefore, the vasodilation shown by 1 was not due to an interaction with the α_1 adrenoceptor. The aralkylamino analogues of 1 in spontaneously hypertensive rats and anesthetized dogs exhibited antihypertensive activity and α_1-adrenoceptor blocking properties. Unlike the preference shown by β-adrenoceptors for *S* enantiomers in this oxymethylene class of β blockers, the chirality at the secondary hydroxy center made only a minor contribution to the affinity for the α_1-adrenoceptor and even less of a contribution to the observed antihypertensive effects. This lack of chiral influence at the hydroxy center confirmed what had been previously observed in more limited studies with the isomers of both labetalol and medroxalol.

Adrenergic receptors have been classified as α or β depending upon their relative responses to various adrenergic agonists.[2] This classification was further refined to define α_1, α_2 and β_1, β_2 receptor subtypes.[2] Side effects associated with antihypertensive agents operating via α-adrenergic blockade are reflex tachycardia and postural hypotension.[3] In principle, the reflex tachycardia should be eliminated by concomitant β_1-adrenergic blockade. Problems associated with nonselective β-adrenergic receptor blockade are bronchoconstriction and Raynaud's syndrome;[3,4] these, in principle, should be alleviated by the presence of α_1-adrenergic blocking activity. Thus, the complementary pharmacological profiles suggest that a properly balanced α,β-adrenoceptor antagonist would be free of many of the side effects associated with the use of either type of agent alone.

The application of a strategy considering this complementarity was investigated as part of our program directed toward the development of antihypertensive β-adrenergic receptor antagonists.[5] As a first step, it was necessary to assess the contribution of α_1-adrenergic receptor blockade to the increased peripheral blood flow observed with (*S*)-2-[3-(*tert*-butylamino)-2-hydroxypropoxy]-3-cyanopyridine (1).[5] This analysis was followed by the replacement of the *tert*-butylamino group in 1 with various aralkylamino substituents to determine if such moieties might introduce, or enhance, α-adrenergic blockade. Recently, other dual-acting compounds have been reported. These include labetalol (2),[6,7] medroxalol (3),[8] and sulfinalol



1, R = *tert*-butyl



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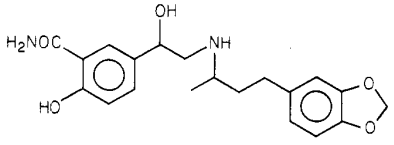

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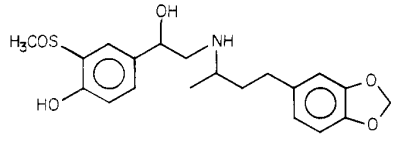

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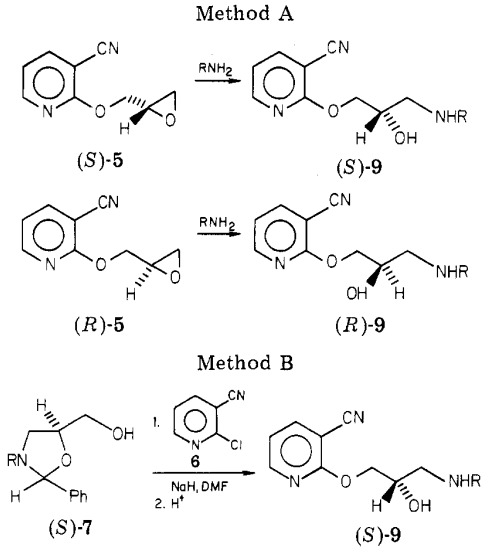
Scheme I



(1) This paper has been presented in part; see "Abstracts of Papers", 181st National Meeting of the American Chemical Society, Atlanta, GA, Mar 29–April 3, 1981; American Chemical Society: Washington, DC, 1981; Abstr MEDI 55.

(2) Lefkowitz, R. J. *Annu. Rep. Med. Chem.* **1980**, *15*, 217. β_1 and β_2: Evans, D. B.; Fox, R.; Hauck, F. P. *Ibid.* **1979**, *14*, 81. Leclerc, G.; Rouot, B.; Velly, J.; Schwartz, J. *Curr. Rev. Biomed.*, **1981**, *1*, 78. Smith, L. H. *J. Appl. Chem. Biotechnol.* **1978**, *28*, 201. O'Donnell, S. R.; Wanstall, J. C. *Life Sci.* **1980**, *27*, 671. α_1 and α_2: Hoffman, B. B.; Lefkowitz, R. J.; *N. Engl. J. Med.* **1980**, *302*, 1390. McGrath, J. C. *Biochem. Pharmacol.* **1982**, *31*, 467.

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(5) Baldwin, J. J.; Lumma, W. C., Jr.; Lundell, G. F.; Ponticello, G. S.; Raab, A. W.; Engelhardt, E. L.; Hirschmann, R. *J. Med. Chem.* **1979**, *22*, 1284.

(6) Bragden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. *Drugs* **1978**, *15*, 251.

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‡ Merck Institute for Therapeutic Research.

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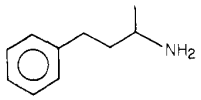
(4),[9] all of which bear aralkylamino groups but belong to the ethanolamine class. In this article, we describe the effect of such aralkylamino substitution in the oxymethylene class of β-adrenergic blocking agents. In addition, the influences of chirality on the relative affinities for the [^{3}H]dihydroalprenolol (DHA, β), the [^{3}H]clonidine (α_2), and the [^{3}H]WB-4101 (α_1) or [^{3}H]prazosin (α_1) binding sites were determined.

Chemistry. The compounds summarized in Table I were synthesized by one of two general methods. The first involved the reaction of various amines with (*RS*)-, (*R*)-, or (*S*)-cyanopyridyloxymethyloxiranes (**5**) (Scheme I; method A). These intermediate epoxides were obtained from the respective glycidols and 2-chloro-3-cyanopyridine (**6**).[10] The second approach (method B) involved the reaction of 2-chloro-3-cyanopyridine (**6**) with the N-substituted (*RS*)-, (*R*)-, or (*S*)-substituted-glycolamines protected as their benzaldehyde oxazolidines.[5,11] Although the schemes show the synthesis of enantiomers only, the sequences were also applicable to the preparation of the corresponding racemates.

In addition, the presence of the 1-methyl-3-phenylpropylamino and related chiral groups in **2**–**4** resulted in diastereomeric mixtures, which presented complications with regard to the interpretation of biological results. Two approaches were considered to resolve this problem in the study of the analogues of **1**; the first involved the preparation of the four individual isomers, while the second focused on the elimination of the chiral center associated with the amino component through the utilization of 1,1-dimethyl-3-phenylpropylamino and related achiral substituents. In order to evaluate the structure–activity relationships in the example bearing the 1-methyl-3-phenylpropylamino substituent (**28**), the individual isomers were prepared. The ready availability of both (*R*)- and (*S*)-**5** and the utilization of the resolved 1-methyl-3-phenylpropylamine (**8**)[12] allowed for the direct synthesis of the individual isomers.



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The resolution of **8** has been reported,[12] but some confusion exists as to the assignment of the absolute configurations[12] due to the change of sign between chirally pure free bases [(*R*)-**8**, $[\alpha]_D$ −18° (*c* = 1, cyclohexane)][12b] and the corresponding hydrochloride salts [(*R*)-**8**·HCl, $[\alpha]_D$ + 13° (*c* = 1, H_2O)].[12b] Following the reported procedure[12a] for the resolution of **8** via the mandelic acid salt, (+)-**8** [$[\alpha]^{25}_D$ +15.8° (*c* = 1.23, cyclohexane)] and (−)-**8** [$[\alpha]^{25}_D$ −14.9° (*c* = 0.996, cyclohexane)] were obtained. Reaction of chiral **8** with (*R*)- or (*S*)-**5** resulted in the formation of each of the individual isomers (**40**–**43**, Table II).

In order to unambiguously determine the absolute configurations of **40**–**43**, the amides derived from 1-methyl-3-phenylpropylamine (**8**) and (*S*)-*O*-methylmandelic acid were separated by HPLC and one of these, the *S*,*S* isomer, was subjected to single-crystal X-ray analysis.[13] This determination also confirmed the assignment of the absolute configuration as (*R*)-(−)-**8**, as assigned in ref 12b,d,e.

The diastereomeric purity of **28** and **40**–**43** was established by NMR techniques. The methyl region in the ^{1}H NMR exhibited two doublets of about equal intensity in **28**, and several of the ^{13}C peaks also showed doubling in **28** indicative of an approximately 1:1 diastereomeric composition. On the other hand, none of the pure isomers (**40**–**43**) indicated the presence of any of these doublings by ^{1}H NMR and/or ^{13}C NMR. Thus, the maximum diastereomeric contamination in any of these samples was ≤5%. The evaluation of pure isomers rather than mixtures, as was done with medroxalol,[8] avoided potential problems in interpretation of results. These NMR techniques were also used to ascertain that the diastereomeric mixtures shown in Table I were approximately 1:1 mixtures of the expected diastereomers (**29**, **33**–**39**).

The enantiomeric purity of the compounds in Table I was taken to be ≥98%. This conclusion stemmed from the analysis of the NMR spectra of the precursor epoxides, (*R*)- or (*S*)-**5**,[10] and several of the compounds in Table I (**25**, **27**, **31**, **32**) in the presence of a chiral shift reagent, Eu(hfbc)$_3$.[10] In all cases examined, none of the opposite enantiomer was detected, indicating a chiral purity of ≥98%.

Pharmacology. Since the blockade at both α- and β-adrenergic receptors could be important in the pharmacology of **1**, the various N-substituted derivatives were assessed by receptor-binding techniques in isolated membrane preparations by using [^{3}H]WB-4101 (α_1) and [^{3}H]-dihydroalprenolol (DHA, β) as radioligands (Table III). The acute antihypertensive effect was also evaluated in the spontaneously hypertensive rat (SH rat, Table IV). Additional in vivo studies in anesthesized dogs were also performed on selected compounds to determine α- and β-adrenoceptor blockade in a whole animal model (Table VI).

Since alteration of the amino substituent usually produced relatively minor changes in β-receptor affinity, these derivatives of the highly potent β-adrenoceptor antagonist **1** would be expected to exhibit relatively low K_I values vs. [^{3}H]DHA (Table III). All of the compounds were rather potent at displacing [^{3}H]DHA from rat neocortical membrane homogenates, although only a few (**27**, **28**, **31**, **34**) approached the affinity of **1**. When comparisons were made between *S* enantiomers and their corresponding racemates (**24**, **25**; **26**, **27**; **30**–**32**; **33**, **34**), the *S* isomers

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(12) (a) van Dijk, J.; Keizer, V. G.; Mold, H. D. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 189. (b) Cannata, V.; Samori, B.; Tramontini, M. *Tetrahedron* **1971**, *27*, 5247. (c) Cervinka, O.; Kroupova, E.; Belovsky, O. *Collect. Czech. Chem. Commun.* **1968**, *33*, 3551. (d) Potapov, V. M.; Dem'yanovick, V. M.; Teret'ev, A. P. *Zh. Obshch. Khim.* **1965**, *35*, 1538; *Chem. Abstr.* **1965**, *63*, 17854*h*. (e) Yamamoto, Y.; Oda, J.; Inouye, Y. *Bull. Chem. Jpn.* **1975**, *48*, 3744.

(13) The HPLC separation of the amides was accomplished by Y. Girard, M. Larue, J. Rokach, and J. Atkinson at Merck Frosst Canada, Inc., in Montreal. J. Hirshfield in our Rahway laboratories was responsible for the solution of the X-ray crystal structure. We are indebted to these co-workers for their results, the details of which will be reported in the near future.

exhibited affinities higher than, or at least equal to, the respective racemate as would be expected for oxymethylene β-adrenoceptor antagonists.[14]

The potential of these compounds for α_1-adrenergic receptor blockade was evaluated via the radioligand displacement of [^{3}H]WB-4101 from calf neocortical membrane homogenates, and the dissociation constants (K_I's) were calculated (Table III). Even though this ligand showed biphasic displacement curves,[15] it was still selective for the α_1 adrenoceptor, and it provided comparative data for mechanistic consideration. For the isomeric 1-methyl-3-phenylpropylamino analogues (**28**, **40–43**), the more specific α_1 radioligand, [^{3}H]prazosin, was employed.[15]

Both **1** and the alkylamino analogues **10–19** showed a very low affinity, i.e., high K_I values, for the displacement of [^{3}H]WB-4101 from α_1-adrenoceptors. Compound **19** bearing a 4-*tert*-butylcyclohexylamino substituent had the highest affinity for the α_1 adrenoceptor in this series (K_I = 400 nM). The aralkylamino analogues (**20–39**) represented a demarcation in pharmacological profile; most possessed K_I's ranging from 18–380 nM against [^{3}H]WB-4101. The most active compounds in this series (**27**, **28**, **33**, **34**, **36**) and labetalol (**2**) exhibited similar affinities for α_1-adrenergic receptors. Thus, the presence of an *N*-aralkylamino group induced an interaction with the α_1 adrenoceptor, yielding compounds that showed potencies up to 500 times greater than **1** and related alkylamino analogues with the only exception being **19**. The most obvious aralkylamino exception to this rule was the indanyl derivative **22**; reduction of flexibility may be a causative factor in this result.

Comparisons of pure enantiomers and the corresponding racemates (**24**, **25**; **26**, **27**; **30–32**; **33**, **34**) suggested that structural features other than chirality at the secondary hydroxy center were much more important in determining the α_1-adrenergic receptor binding characteristics. In some cases the *R* enantiomer showed a higher affinity (**24**, **25**; **30–32**), while in others the isomer with higher affinity had the *S* configuration (**26**, **27**; **28**, **40–43**). Comparisons of pure enantiomers and the corresponding racemates (**24**, **25**; **26**, **27**; **30–32**; **33**, **34**) indicated that the antihypertensive activity (Table IV) was not highly dependent upon the chirality at the secondary hydroxy center, which was in agreement with the low chiral influence found in the radioligand displacement studies. Although the influence of chirality on α-adrenoceptor affinity in the related ethanolamine class had been previously probed,[7,8] the mixtures of isomers used in the study of the medroxalol isomers[8] complicated the interpretation of these results, while detailed pharmacology was presented on only one of the isomers of labetalol (*R*,*R* isomer, SCH 19927).[7] The aralkylamino derivatives of **1** provided the first documentation within the oxymethylene class for the importance of chirality at the alcohol center on β-adrenoceptor, but not α_1-adrenoceptor, affinity. Patil et al.[14] had earlier suggested that such may be the case for various α- and β-adrenoceptor antagonists.

None of the alkylamino-substituted analogues (**2**, **10–19**) showed an antihypertensive potency comparable to **1** (Table IV) in the SH rat. In contrast, most of the aralkylamino analogues (**20–39**) exhibited acute antihypertensive activity with a potency somewhat less than the standard **1**. Since β-adrenergic antagonists generally exhibited only modest acute antihypertensive effects,[16] it was attractive to postulate that the observed antihypertensive response in compounds other than **1** resulted from α_1-adrenoceptor blockade. Upon analysis, a statistically significant correlation was found between antihypertensive activity in the SH rat and in vitro α_1-binding affinity.[17] Compounds in the group **20–39** for which there was data available (**21–32**, **34**, **37**) were used to construct a plot of in vitro α_1-adrenoceptor affinity (log K_I vs. [^{3}H]WB-4101) vs. antihypertensive activity in the SH rat at an oral dose of 5 mg/kg, giving a correlation coefficient of 0.673.[17] Although statistically significant, this correlation was not a particularly good one, and other mechanisms may contribute to the observed antihypertensive response. Since **1** was a potent antihypertensive agent[5] via a mechanism that did not involve α-adrenoceptor blockade, these aralkylamino analogues may also reduce blood pressure by mechanisms other than α-adrenergic receptor antagonism. This was somewhat similar to the results observed with the isomers of medroxalol[8] and labetalol,[7] i.e., the isomers exhibited similar antihypertensive activity in the SH rat while showing widely different α-adrenoceptor blocking properties in vitro. In these cases a statistically significant correlation was not observed, perhaps due to the much smaller sample size of their studies. Of course, the absorption, distribution, and metabolism of drugs may also complicate the interpretation of any comparisons of in vivo and in vitro responses.

Based on high α_1- and β-adrenoceptor affinities in radioligand displacements, the diastereomeric mixture **28** was a prime candidate for further pharmacological study. It was of interest to prepare and evaluate each of the four isomers to determine the influence of chirality on the pharmacological profile. While the *S* configuration at the alcohol center had been well established as the biologically active isomer in the aminohydroxypropoxy class of β-adrenergic blocking agents,[14] the influence of chirality on α_1-adrenergic receptor blockade has been only recently described in the ethanolamine class with the isomers of labetalol[7,18] and medroxalol.[8] The configuration at the hydroxy carbon in the potent (*S*)-oxymethylene class of β blockers corresponds to the *R* configuration in the ethanolamine class, each of which corresponds to the absolute configuration found in (*R*)-norepinephrine.

The displacements of various radioligands from mammalian cerebral cortex membrane homogenates allowed for the determination of K_I values at α- and β-adrenergic receptors for the four isomers (**40–43**, Table V). In addition to [^{3}H]WB-4101 as the α_1-adrenoceptor ligand, the displacements of [^{3}H]prazosin (an α_1-selective ligand) and [^{3}H]clonidine (an α_2-selective ligand) were also examined in the binding studies. Since [^{3}H]prazosin appeared to be more selective for the α_1-adrenoceptor and to give monophasic displacement curves,[15] the α_1 results presented were derived from its displacement. Each isomer displaced clonidine with K_I's greater than 1 μM, values much greater than those obtained from the [^{3}H]prazosin studies. Thus, these isomerically related compounds were all selective for the α_1-adrenoceptor. Ratios range from ~25 for the least selective compound (**43**) to ~135 for the most selective

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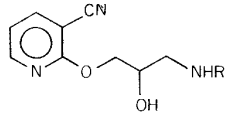
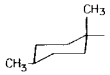
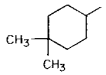
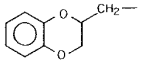
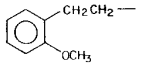
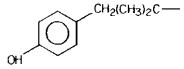
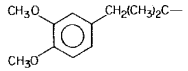
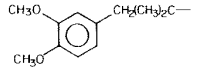
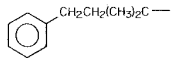
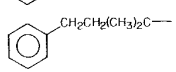
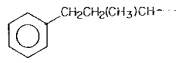
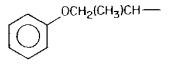
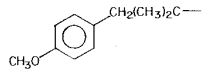
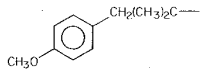
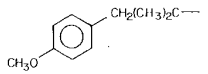
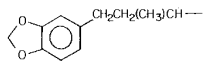
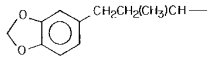
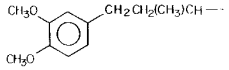
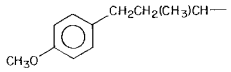
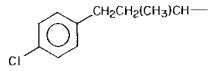
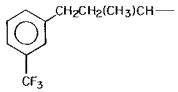
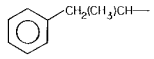
(15) Lyon, T. F.; Randall, W. C. *Life Sci.* **1980**, *26*, 1121.
(16) Watson, L. S.; Ludden, C. T. "New Antihypertensive Drugs"; Scriabine, A.; Sweet, C. S., Eds.; Spectrum Publications: Holliswood, NY, 1976; p 227.
(17) We thank a referee for pointing out that this correlation with 12 degrees of freedom was statistically significant. See George W. Snedecor and William G. Cochran, "Statistical Methods", 7th ed., The Iowa State University Press: Ames, IA, 1980.
(18) Nakagawa, Y.; Shimamoto, N.; Nakazawa, M.; Imai, S. *Jpn. J. Pharmacol.* **1980**, *30*, 743.

Table I. 2-[3-(Substituted-amino)-2-hydroxypropoxy]-3-cyanopyridines 10–39



compd	R	chirality: -CHOH-	method	yield, %	formula	crystn solvent	mp, °C	$[\alpha]^{24}_D$, deg (*c*, solv)	anal.
10	$CH_3CH_2(CH_3)_2C$	*S*	A	18.1	$C_{14}H_{21}N_3O_2 \cdot HCl$	EtOH–Et_2O	141–144		C, H, N, Cl
11	$HC{\equiv}C(CH_3)_2C$	*R,S*	B	9.0	$C_{14}H_{17}N_3O_2 \cdot HCl$	CH_3CN	170–171		C, H, N
12	$HC{\equiv}CCH_2$	*R,S*	B	10.0	$C_{12}H_{13}N_3O_2 \cdot HCl$	*i*-PrOH–Et_2O	155–157		C, H, N
13	$(CH_3)_2CHCH_2CH_2$	*S*	B	47.2	$C_{14}H_{21}N_3O_2 \cdot C_4H_4O_4$	EtOH–Et_2O	95–98	−17.68 (0.92, MeOH)	C, H, N
14		*S*	B	30.7	$C_{15}H_{21}N_3O_2 \cdot C_4H_4O_4$	EtOH–Et_2O	130–134	−17.27 (1.10, MeOH)	C, H, N
15		*S*	B	18.3	$C_{17}H_{25}N_3O_2 \cdot HCl$	EtOH–Et_2O	144–146	−20.08 (0.96, MeOH)	C, H, N, Cl
16		*S*	B	7.0	$C_{19}H_{25}N_3O_2 \cdot HCl \cdot 0.5H_2O$	EtOH–Et_2O	220–221	−17.92 (0.81, MeOH)	C, H, N, Cl
17		*S*	B	15.2	$C_{17}H_{25}N_3O_2 \cdot HCl$	EtOH–Et_2O	165–167	−15.27 (1.02, MeOH)	C, H, N, Cl
18		*S*	B	15.5	$C_{17}H_{25}N_3O_2 \cdot HCl$	EtOH–Et_2O	189–190	−19.24 (1.08, MeOH)	C, H, N, Cl
19		*R,S*	A	12.8	$C_{19}H_{29}N_3O_2 \cdot HCl$	EtOH–Et_2O	161–164		C, H, N, Cl
20		*S*	B	57.2	$C_{15}H_{19}N_3O_4 \cdot C_2H_2O_4 \cdot 0.5H_2O$	EtOH	161–164	−11.67 (1.11, MeOH)	C, H, N
21		*S*	A	18.0	$C_{18}H_{21}N_3O_3$	toluene	97–99	0.00 (0.85, MeOH)	C, H, N
22		*S*	B	15.2	$C_{18}H_{19}N_3O_2 \cdot HCl$	EtOH–Et_2O	130–132	−16.41 (0.59, MeOH)	C, H, N, Cl
23		*R,S*	A	37.0	$C_{19}H_{23}N_3O_3 \cdot HCl$	*i*-PrOH–Et_2O	193–196		C, H, N, Cl
24		*R,S*	A	35.0	$C_{21}H_{27}N_3O_4 \cdot HCl$	EtOH	192–195		C, H, N
25		*S*	A	59.5	$C_{21}H_{27}N_3O_4 \cdot HCl$	EtOH	186–189	−15.79 (1.00, MeOH)	C, H, N, Cl

26		*R,S*	A	26.0	$C_{20}H_{25}N_3O_2 \cdot C_4H_4O_4$	*i*-PrOH	134–135		C, H, N
27		*S*	A	24.0	$C_{20}H_{25}N_3O_2 \cdot C_4H_4O_4$	*i*-PrOH	151–153	−14.44 (1.14, MeOH)	C, H, N
			B	22.3	$C_{20}H_{25}N_3O_2 \cdot C_4H_4O_4$		142–145	−13.08	C, H, N
28		*R,S*	A	38.0	$C_{19}H_{23}N_3O_2 \cdot C_4H_4O_4$	*i*-PrOH	117–118		C, H, N
29		*R,S*	A	17.5	$C_{18}H_{21}N_3O_3 \cdot C_4H_4O_4$	*i*-PrOH–Et_2O	86–89		C, H, N
30		*R,S*	A	51.0	$C_{20}H_{25}N_3O_3 \cdot HCl$	EtOH–Et_2O	153–155		C, H, N, Cl
31		*S*	A	31.0	$C_{20}H_{25}N_3O_3 \cdot HCl$	*i*-PrOH–Et_2O	130–133	−14.05 (1.00, MeOH)	C, H, N
32		*R*	A	75.0	$C_{20}H_{25}N_3O_3 \cdot C_4H_4O_4$	*i*-PrOH–Et_2O	128–132	+12.99 (1.22, MeOH)	C, H, N
33		*R,S*	A	34.0	$C_{20}H_{23}N_3O_4 \cdot C_4H_4O_4$	*i*-PrOH–Et_2O	122–127		C, H, N
34		*S*	A	37.9	$C_{20}H_{23}N_3O_4 \cdot C_4H_4O_4$	*i*-PrOH–Et_2O	113–115	−14.09 (1.01, MeOH)	C, H, N
35		*R,S*	A	15.1	$C_{21}H_{27}N_3O_4 \cdot HCl$	*i*-PrOH–EtOH	183–186		C, H, N
36		*R,S*	A	33.6	$C_{20}H_{25}N_3O_3 \cdot HCl$	EtOH–Et_2O	113–116		C, H, N
37		*R,S*	A	32.8	$C_{19}H_{22}ClN_3O_2 \cdot C_4H_4O_4$	*i*-PrOH–Et_2O	112–115		C, H, N
38		*R,S*	A	24.8	$C_{20}H_{22}F_3N_3O_2 \cdot HCl$	EtOH–Et_2O	150–151		C, H, N
39		*R,S*	A	45.3	$C_{18}H_{21}N_3O_2 \cdot C_4H_4O_4$	*i*-PrOH–Et_2O	128–132		C, H, N

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