Structure−Activity Studies of 6-Substituted Decahydroisoquinoline-3-carboxylic Acid AMPA Receptor Antagonists. 2. Effects of Distal Acid Bioisosteric Substitution, Absolute Stereochemical Preferences, and in Vivo Activity

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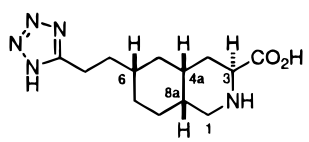
We have explored the excitatory amino acid antagonist activity in a series of decahydroisoquinoline-3-carboxyic acids, and within this series found the potent and selective AMPA antagonist (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-(1*H*-tetrazol-5-yl)ethyl)decahydroisoquinoline-3-carboxylic acid (**1**). In this and the preceding paper, we looked at the structure−activity relationships for AMPA antagonist activity in this series of compounds. We have already shown that **1** had the optimal stereochemical array and that AMPA antagonist activity was maximized for a two-carbon spacer separating a tetrazole from the bicyclic nucleus. In this paper, we explored the effects of varying the distal acid and the absolute stereochemical preferences of many of these analogs. We looked at a variety of different acid bioisosteres, including 5-membered hetereocyclic acids such as tetrazole, 1,2,4-triazole, and 3-isoxazolone; carboxylic, phosphonic, and sulfonic acid; and acyl sulfonamides. Compounds were evaluated in rat cortical tissue for their ability to inhibit the binding of radioligands selective for AMPA ([^{3}H]AMPA), NMDA ([^{3}H]CGS 19755), and kainic acid ([^{3}H]kainic acid) receptors and for their ability to inhibit depolarizations induced by AMPA (40 μM), NMDA (40 μM), and kainic acid (10 μM). A number of compounds from this and the preceding paper were also evaluated in mice for their ability to block maximal electroshock-induced convulsions and ATPA-induced rigidity in mice.

Introduction

Our medicinal chemistry research efforts are targeted toward the identification of compounds which are potent and selective antagonists of excitatory amino acid (EAA) receptors,[1] with the goal of developing these compounds as novel therapeutic agents for the treatment of a variety of central nervous system disorders.[2] Within a series of decahydroisoquinoline-3-carboxylic acids, we found that the 6-tetrazolylethyl-substituted compound **1** is a selective antagonist of neurotransmission mediated through the 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)propanoic acid (AMPA) subclass of excitatory amino acid (EAA) receptors.[3,4] Structure−activity studies (SAR) on this class of EAA antagonists have revealed features which enhance potency and affinity of these compounds for either NMDA[5,6] or AMPA receptors. In the preceding paper,[7] we reported data on the effect of varying stereochemistry in the decahydroisoquinoline ring nucleus, varying the length of the tether connecting a tetrazole to the decahydroisoquinoline and substitution with a nitrogen or oxygen atom on this tether in the postion adjacent to the bicyclic ring, and the effect of substitution with a methyl or phenyl group on the tether. What we found was that activity was optimized for the stereoisomer corresponding to **1** and that a two-atom all-carbon chain was optimal for AMPA antagonist activity. Substitution on the connecting chain (e.g., with a methyl or a phenyl group) was tolerated, but did not enhance affinity. In this paper, we report on the effects of varying the distal acid bioisostere from tetrazole to other 5-membered heterocyclic ring acids and phosphonic, sulfonic, and carboxylic acid. We also look at the absolute stereochemical requirements for AMPA antagonist activity in this series. A number of the more potent compounds from this SAR (from both papers) were evaluated in some behavioral assays in mice.

Chemistry

In the previous study, we established that the stereochemical array for the decahydroisoquinoline nucleus corresponding to **1** was optimal for activity; it was also best to have the distal acid bioisostere (e.g., tetrazole) attached to the bicyclic nucleus through a two-atom spacer. Holding these values constant, we focused in this study on compounds with a variety of different acid isosteres in the distal acid position and on the resolution of a number of analogs to identify the optimal absolute stereochemistry for AMPA antagonist activity. Even though the C-6 stereochemistry of tetrazole-substituted compounds was optimal as in **1**, a number of these compounds with different bioisosteric substitutions were prepared in both C-6 epimeric forms. We thus allowed



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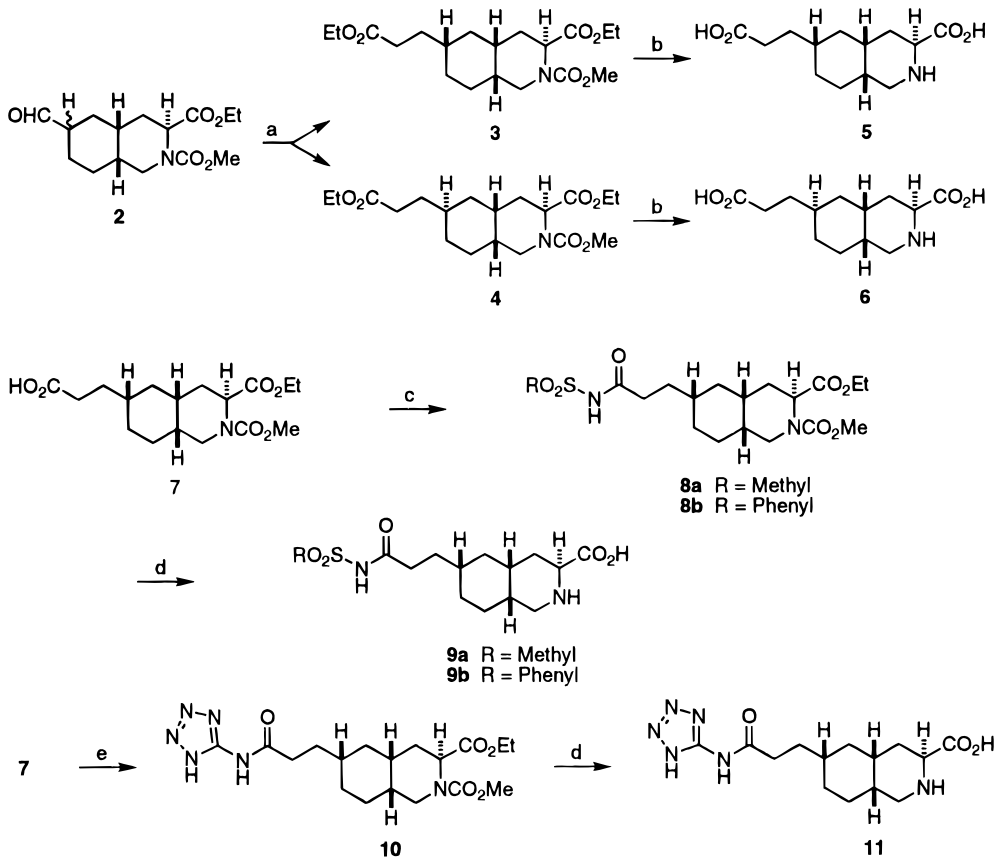
Scheme 1[a]



[a] (a) $Et_2O_3PCH_2CO_2Et$, NaH, THF, 0 °C; H_2, 5% Pd/C, EtOH, 60 psi, room temperature; (b) 6N HCl, reflux; Dowex 50-X8, 10% pyridine/water; (c) $CH_3SO_2NH_2$ (for **8a**) or $C_6H_5SO_2NH_2$ (for **8b**), DCC, DBU, THF, reflux; (d) 1 N NaOH, EtOH, room temperature; Me_3SiI, $CHCl_3$, reflux; Dowex 50-X8, 10% pyridine/water; (e) $(CHN_4)NH_2$, DCC, THF, reflux.

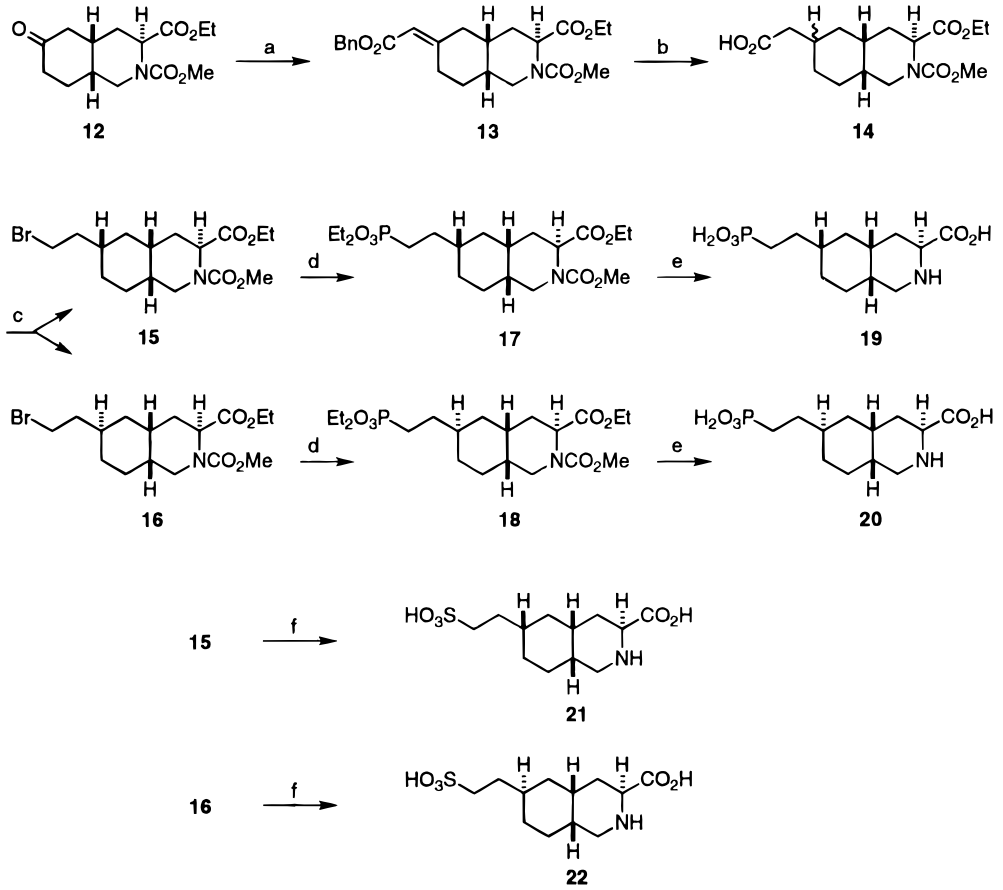
for any unexpected changes in recognition of these ligands by the receptor protein that might occur from a change in the distal acid.

The ω-carboxy analogues (Scheme 1) were prepared from the aldehyde **2**, obtained as a 2:1 mixture of diastereomers from acidic hydrolysis of the corresponding enol ether.[6] Horner−Emmons condensation with the sodium salt of triethyl phosphonoacetate followed by catalytic hydrogenation of the resulting enoate afforded a seperable mixture of diesters **3** and **4**, epimeric at C-6. Exhaustive hydrolysis of **3** then afforded amino acid **5**, while hydrolysis of **4** afforded **6**, respectively. The ω-acyl sulfonamide analogs were prepared by a similar route; however, the sodium salt of benzyl (diethylphosphono)acetate was used in the Horner−Emmons condensation; selective deprotection of the ω-acid could then be achieved during catalytic hydrogenation of the olefin. The acid **7**[7] was reacted with methane- or benzenesulfonamide in the presence of DCC to afford the desired acyl sulfonamides **8a** (R = methyl) or **8b** (R = phenyl). Basic hydrolysis of the ester followed by treatment with excess iodotrimethylsilane cleaved the carbamate under conditions that precluded hydrolysis of the acyl sulfonamide, leading to **9a** (R = methyl) and **9b** (R = phenyl). The acid **7** was also condensed with 5-aminotetrazole to afford amide **10** which was deprotected as for the acyl sulfonamides to afford **11**.

The phosphono and sulfono amino acids were prepared through reaction of a bromoethyl intermediate such as **15** (Scheme 2). Ketone **12**[8] was converted as for **3** and **4** to the unsaturated benzyl ester **13**, which upon hydrogenation gave the acid **14** as a 2:1 mixture of diastereomers (ratio by ^{1}H NMR integration of the C-3 proton). Selective reduction of the acid with borane methyl sulfide afforded a mixture of alcohols that were subsequently reacted with triphenylphosphine dibromide to give bromides **15** and **16** (chromatographically separable; **16**, the higher R_f C-6 epimer is the minor product; **15**, the lower R_f C-6 epimer is the major product). Arbuzov reaction of **15** with triethyl phosphite afforded phosphonate **17**, which upon exhaustive hydrolysis afforded **18**. The same sequence of reactions applied to bromide **16** afforded **19** and ultimately **20**. Reaction of either bromide **15** or **16** with sodium sulfite in aqueous ethanol followed by exhaustive hydrolysis afforded the ω-sulfonic acid derivatives **21** or **22**, respectively.

We also prepared a series of thiotetrazoles, where the thio group was incorporated either as a constituent atom in the two-atom connecting chain or as a substituent on the tetrazole ring (Scheme 3). Reaction of bromides **23**[9] and **24**[9] with 5-thiotetrazole and triethylamine in acetonitrile affored tetrazoles **25** and **26**, respectively. Only *S*-alkylation was seen in this reaction. Exhaustive hydrolysis of **25** and **26** afforded the desired amino acids **27** and **28**, respectively. Alternatively, bromide **23** was reacted with 5-(*S*-phenacylthio)tetrazole (**29**) to give a separable mixture of the N-1 and N-2 alkylated products **30** and **31**, respectively. After photolytic removal of the phenacyl group, either **30** or **31** was exhaustively

Scheme 2[a]



[a] (a) $Bn_2O_3PCH_2CO_2Et$, NaH, THF, room temperature; (b) H_2, 5% Pd/C, EtOAc, 60 psi, room temperature; (c) $BH_3{\cdot}SMe_2$, THF, 0 °C to room temperature; Ph_3P, Br_2, pyridine, CH_2Cl_2, 0 °C; (d) $(EtO)_3P$, 150 °C; (e) 6 N HCl, reflux; propylene oxide, EtOH; (f) Na_2SO_3, EtOH, H_2O, reflux; 6 N HCl, reflux; Bio-Rad AG1-X8, 3 N HOAc.

hydrolyzed to afford the desired ω-tetrazolethiols **32** or **33**, respectively.

As for the above tetrazoles, we prepared thiotriazole-substituted amino acids where the sulfur atom was incorporated as a constituent of the two-atom connecting chain (Scheme 4). Reaction of bromide **23** with 3-thio-1,2,4-triazole afforded **34**, which was then exhaustively hydrolyzed to the sulfide **35**. Alternatively, **34** was first oxidized to the sulfone with *m*-CPBA and then exhaustively hydrolyzed to afford amino acid **36**. All attempts to oxidize the sulfide of **25** to the corresponding sulfone were unsuccessful. Either no reaction occurred, or when starting material was consumed, no product was obtained that could be characterized as the sulfone. Scheme 4 also shows the preparation of an amino-tetrzole compound, whereas for the thiotetrazoles and triazoles, the amine is part of the two-atom connecting chain. Alkylation of **23** with 5-aminotetrzole afforded **37**, which after exhaustive hydrolysis yielded amino acid **38**.

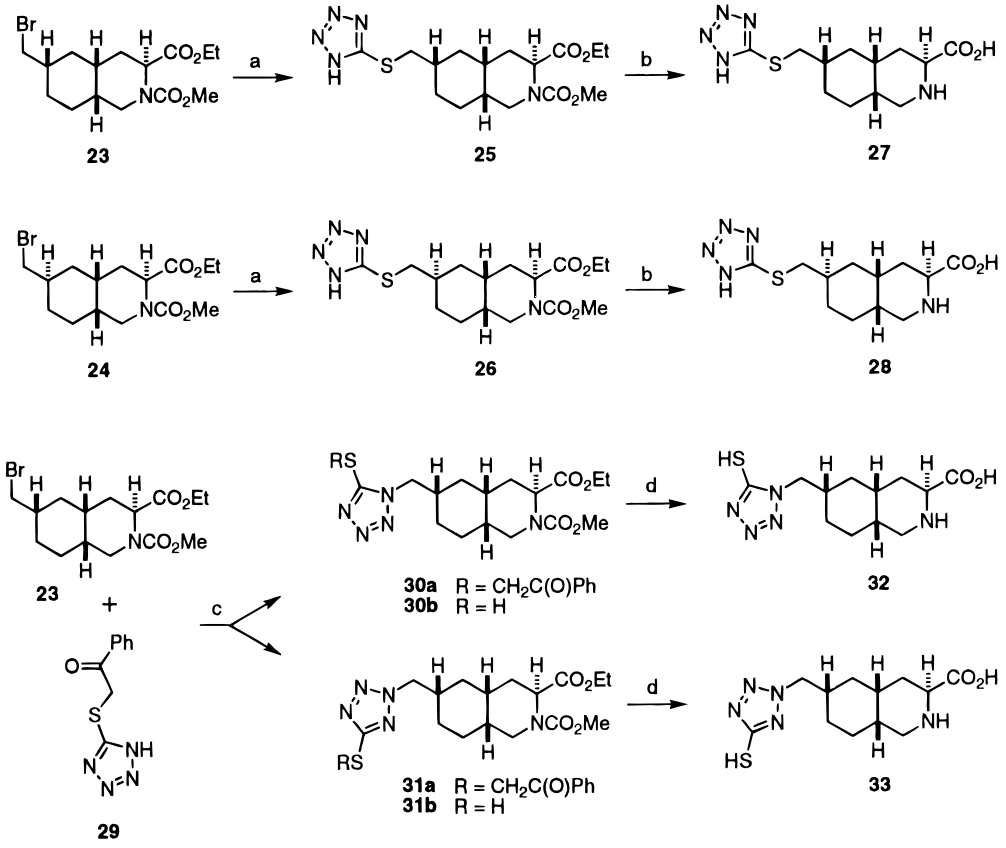
In order to prepare amino acids substituted with an isoxazole, as is found in AMPA, we required the novel isoxazole substituted Horner−Emmons reagent **44** (Scheme 5). Conversion of 3-bromo-5-(hydroxymethyl)-isoxazole[10] (**39**, which was contaminated with about 10% of 3-bromo-4-(hydroxymethyl)isoxazole; this was removed upon purification of **42**) to the corresponding 3-methoxy compound **42** was achieved only when the alcohol was first oxidzed to the corresponding acid **40**.[11] Without oxidation to the acid, displacement of the bromide in **39** with methoxide did not occur. Sodium borohydride reduction of the mixed anhydride formed from **41** and isobutyl chloroformate gave the desired **42**. Bromination of **42** gave **43**, which upon displacement with triethyl phosphite afforded **44**. Condensation of the sodium salt of **44** with the above-mentioned 2:1 mixture of aldehydes **2** followed by catalytic hydrogenation of the olefin gave a separable mixture of C-6 epimers **45** and **46**. Exhaustive hydrolysis of **45** then afforded amino acid **47**, while hydrolysis of epimer **46** afforded amino acid **48**.

For the preparation of the above compounds in nonracemic form, the chemistry thus described was carried out using the 3*S*,4a*R*,8a*R*- or 3*R*,4a*S*,8a*S*-isomers of ketone **12**.[8] Table 1 shows analytical data and melting points for the novel intermediates and products from this SAR. Also given in Table 1 is the optical rotations ($[\alpha]_D$) for nonracemic amino acids.

Results and Discussion

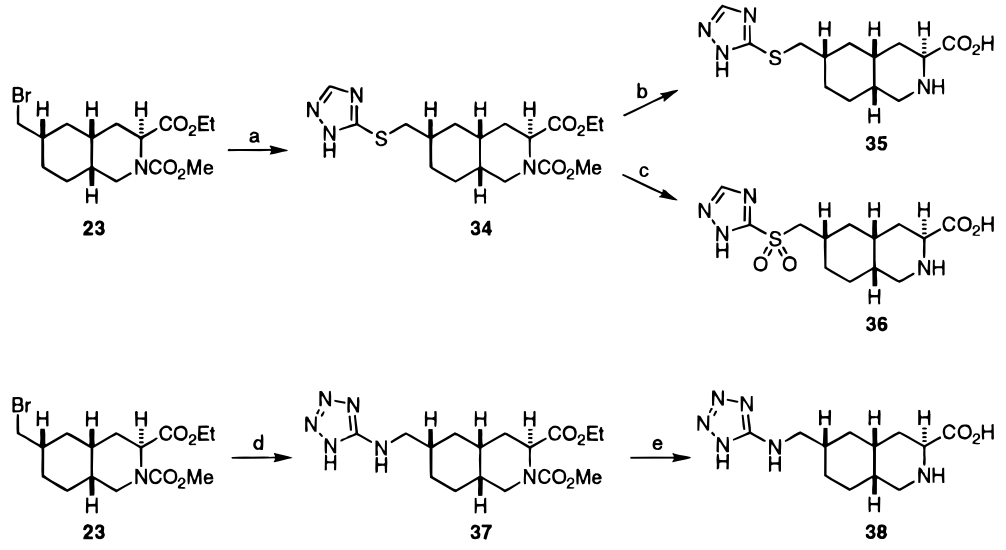
All of the compounds that we prepared were evaluated in selective radioligand binding assays for affinity at NMDA, AMPA, and kainic acid receptors using [^{3}H]-CGS 19755,[12] [^{3}H]AMPA,[13] and [^{3}H]kainic acid,[14] respectively; and for functional activity at NMDA, AMPA, and kainic acid receptors using a cortical slice preparation (cortical wedge) by measuring their ability to inhibit depolarizations induced by 40 μM NMDA, 40 μM AMPA (or in a few cases, 40 μM quisqualic acid (QUIS)), and 10 μM kainic acid, respectively.[15] While the data is not

Scheme 3[a]



[a] (a) $(CHN_4)SH$, Et_3N, CH_3CN; (b) 6N HCl, reflux; Dowex 50-X8, 10% pyridine/water (for **28** only); (c) K_2CO_3, DMF, 90 °C; EtOH, *hν*, ambient temperature; (d) 6 N HCl, reflux.

Scheme 4[a]

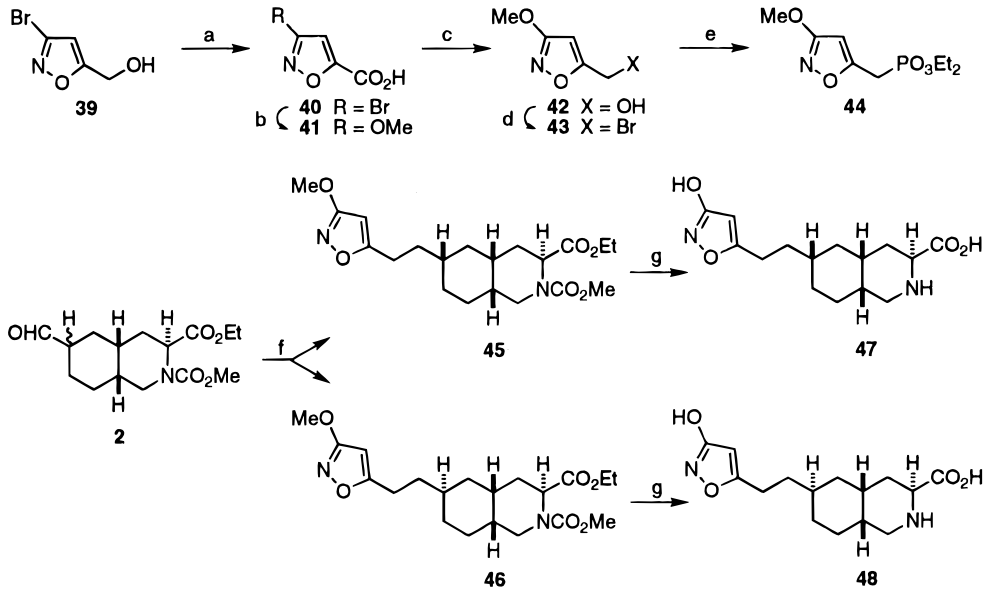


[a] (a) $(C_2H_2N_3)SH$, DMF, 100 °C; (b) 6 N HCl, reflux; Dowex 50-X8, 10% pyridine/water; (c) *m*-CPBA, CH_2Cl_2, room temperature; 6 N HCl, reflux; Dowex 50-X8, 10% pyridine/water; (d) K_2CO_3, $(CHN_4)NH_2$, CH_3CN, reflux; 6 N HCl, reflux; Dowex 50-X8, 10% pyridine/water.

shown, none of the compounds showed significant agonist activity when tested alone in the cortical slice preparation. The data for these novel compounds are shown in Tables 2 and 3, with data for the AMPA antagonist **1**[3,4] and its corresponding C-6 epimer **49**[3] included for comparison. Selected compounds were evaluated in mice (Table 4) for NMDA and AMPA antagonist activity by examining their ability to protect mice from lethality induced by a 200 mg/kg (ip) dose of NMDA (data not shown in Table 4);[16] to block maximal electroshock-induced convulsions in mice;[17] to block the characteristic rigidity induced in mice by a 30 mg/kg (iv) dose of the systemically active AMPA agonist 2-amino-3-(3-hydroxy-5-*tert*-butylisoxazol-4-yl)propanoic acid (ATPA);[18] and to produce neurological impairment in a horizontal screen assay.[17] Compounds were administered intraperitoneally (ip) in mice.

Having previously established the optimal stereochemistry and length of tether that joins the requisite distal acidic moiety to the bicyclic ring nucleus, we next

Scheme 5[a]



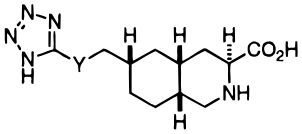
[a] CrO_3, H_2SO_4, H_2O; (b) KOH, MeOH, H_2O, reflux; (c) $ClCO_2$-*i*-Bu, Et_3N, THF, 0 °C; $NaBH_4$, H_2O, room temperature; (d) Ph_3P, Br_2, pyridine, CH_2Cl_2, 0 °C; (e) $(EtO)_3P$, toluene, 120 °C; (f) **44**, $NaN(SiMe_3)_2$, THF, −17 °C, then **2**, room temperature; H_2, 5% Pd/C, EtOAc, 60 psi, room temperature; (g) 48% aqueous HBr, reflux; Dowex 50-X8, 10% pyridine/water.

Table 1. Analytical Data, Melting Points, and Optical Rotations for Novel Compounds

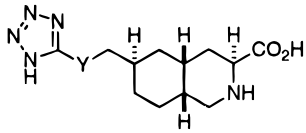
compd	formula	analysis	mp (°C)	$[\alpha]_D$[a]
4	$C_{19}H_{31}NO_6$	C,H,N	oil	
5	$C_{13}H_{21}NO_4.H_2O$	C,H,N	190−191	
6	$C_{13}H_{21}NO_4$	C,H,N	270−271	
8a	$C_{18}H_{30}N_2O_7S$	C,H,N	oil	
9a	$C_{14}H_{24}N_2O_5S$	C,H,N	208−215	
8b	$C_{23}H_{32}N_2O_7S$	C,H,N	oil	
9b	$C_{19}H_{26}N_2O_5S\cdot H_2O$	C,H,N	215−218	
10	$C_{18}H_{28}N_6O_5$	C,H,N	oil	
11	$C_{14}H_{22}N_6O_3\cdot 2.5H_2O$	C,H,N	223−225	
13	$C_{23}H_{29}NO_6\cdot 0.05CHCl_3$	C,H,N	oil	
15	$C_{16}H_{26}BrNO_4$	C,H,N	oil	
16	$C_{16}H_{26}BrNO_4$	C,H,N	oil	
18	$C_{12}H_{22}NO_5P\cdot 0.75H_2O$	C,H,N	oil	
19	$C_{20}H_{36}NO_7P$	C,H,N	oil	
20	$C_{12}H_{22}NO_5P\cdot 1.25H_2O$	C,H,N	157−160	
21	$C_{12}H_{21}NO_5S\cdot 0.25H_2O$	C,H,N	>265	
22	$C_{12}H_{21}NO_5S\cdot 0.75H_2O$	C,H,N	>265	
25	$C_{16}H_{25}N_5O_4S\cdot 0.25C_2H_4O_2$	C,H,N	oil	
27	$C_{12}H_{19}N_5O_2S\cdot HCl$	C,H,N	285	
(−)-**27**	$C_{12}H_{19}N_5O_2S$	C,H,N	199−207	-53.2
(+)-**27**	$C_{12}H_{19}N_5O_2S\cdot 0.5H_2O\cdot 0.1C_5H_5N$	C,H,N	165−172	+49.3
26	$C_{16}H_{25}N_5O_4S\cdot 0.1C_2H_4O_2\cdot 0.1CH_2N_4S$	C,H,N	oil	
28	$C_{12}H_{19}N_5O_2S$	C,H,N	257	
(+)-**28**	$C_{12}H_{19}N_5O_2S\cdot 0.25H_2O$	C,H,N	246	+34.6
(−)-**28**	$C_{12}H_{19}N_5O_2S\cdot 0.25H_2O$	C,H,N	275−276	-35.6
30	$C_{16}H_{25}N_5O_4S\cdot 0.5H_2O$	C,H; N[b]	oil	
31	$C_{16}H_{25}N_5O_4S$	C,H; N[c]	oil	
32	$C_{12}H_{19}N_5O_2S\cdot HCl$	C,H,N	279−280	
33	$C_{12}H_{19}N_5O_2S\cdot HCl$	C,H,N	250−251	
35	$C_{13}H_20N_4O_2S\cdot 2.0H_2O$	C,H,N	156−160	
36	$C_{13}H_20N_4O_4S\cdot H_2O$	C,H,N	215−221	
(−)-**36**	$C_{13}H_20N_4O_4S\cdot 0.6H_2O$	C,H,N	286−287	−39.4
(+)-**36**	$C_{13}H_20N_4O_4S\cdot 0.75H_2O$	C,H,N	267−270	+33.8
37	$C_{16}H_{26}N_6O_4\cdot 0.1C_4H_8O\cdot 0.2C_6H_{14}$	C,H,N	oil	
38	$C_{12}H_20N_6O_2\cdot 1.5H_2O$	C,H,N	197	
43	$C_5H_6NO_2Br$	C,H,N	oil	
44	$C_9H_{16}NO_5P\cdot 0.5H_2O$	C,H,N	oil	
45	$C_{20}H_{36}N_2O_6\cdot 0.25H_2O$	C,H,N	oil	
46	$C_{20}H_{36}N_2O_6$	C,H,N	oil	
47	$C_{15}H_{22}N_2O_4\cdot 1.0H_2O$	C,H,N	256	
48	$C_{15}H_{22}N_2O_4\cdot 2.0H_2O$	C,H,N	244	
(+)-**49**	$C_{13}H_{21}N_5O_2\cdot 0.75H_2O$	C,H,N	201−209	+20.4
(−)-**49**	$C_{13}H_{21}N_5O_2\cdot 0.5H_2O$	C,H,N	250−252	−22.0

[a] All optical rotations were determined in 1 N HCl at a concentration, $c = 1$. [b] Anal. C, H. N; calcd, 17.84; found, 17.07. [c] Anal. C, H. N: calcd, 18.26; found, 19.07.

Table 2. Effects of Heteroatoms Substitution Adjacent to the Tetrazole in the Two-Atom Linker of 6-Substituted Decahydroisoquinoline-3-carboxylic Acids and Resolution of Selected Compounds



C6 EPIMER A



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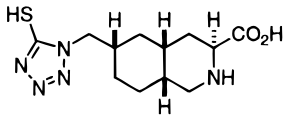

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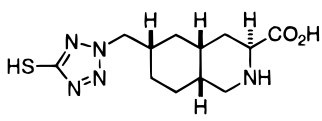

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compound	Y	C-6 epimer	IC$_{50}$ (μM) versus radioligand binding at ionotropic excitatory amino acid receptors[a,b] NMDA	AMPA	kainic acid	IC$_{50}$ (μM) versus agonist-induced depolarizations in a cortical slice preparation[c] NMDA	AMPA	kainic acid
(±)-**1**[d]	CH_2	A	26.4 ± 2.0	4.8 ± 1.2	247 ± 8	61 ± 3	6.0 ± 1.0	31.7 ± 4.4
(−)-3*S*,4a*R*,6*R*,8a*R*-**1**[d]	CH_2	A	12.1 ± 2.0	14. ± 0.1	28.1 ± 1.7	60% at 100 μM[e]	1.8 ± 0.2	60% at 100 μM[e]
(+)-3*R*,4a*S*,6*S*,8a*S*-**1**[d]	CH_2	A	>100	>100	>100	>100	>100	>100
(±)-**49**	CH_2	B	60.6 ± 24.8	59.6 ± 4.3	180 ± 22	>100	<100[f]	>100
(+)-3*S*,4a*R*,6*S*,8a*R*-**49**	CH_2	B	99.2[g]	31.5 ± 7.3	87 ± 5	>100	21.9 ± 3.3	28.9 ± 9.2
(−)-3*S*,4a*R*,6*S*,8a*R*-**49**	CH_2	B	76.9[g]	>100	>100	>100	>100	>100
(±)-**27**	S	A	29.4 ± 6.8	0.9 ± 0.1	30.1 ± 1.6	>100	19.8 ± 2.2	>31.6
(−)-3*S*,4a*R*,6*S*,8a*R*-**27**	S	A	18.1 ± 1.7	0.6 ± 0.03	15.7 ± 2.1	22.9 ± 3.8	1.4 ± 0.4	>31.6
(+)-3*R*,4a*S*,6*R*,8a*S*-**27**	S	A	>10	22.1 ± 1.8	>100	>100	19.8 ± 2.2	>31.6
(±)-**28**	S	B	47.9 ± 3.9	4.9 ± 0.4	37.3 ± 2.3	>100	6.1 ± 1.5	>100
(+)-3*S*,4a*R*,6*R*,8a*R*-**28**	S	B	>100	17.8[g]	27.9[g]	>100	9.0 ± 0.8	29.1 ± 4.3
(−)-3*R*,4a*S*,6*S*,8a*R*-**28**	S	B	29.8 ± 7.1	70.5 ± 8.5	>100	62.2 ± 7.6	>100	>100
(±)-**32**		A	>10	12.9[g]	16.7[g]		agonist	
(±)-**33**		A	>10	57.9 at 100 μM[h]	>100	>100	55% at 100 μM[h]	>100
(±)-**38**	NH	A	>100	>100	>100	>100	>100	>100

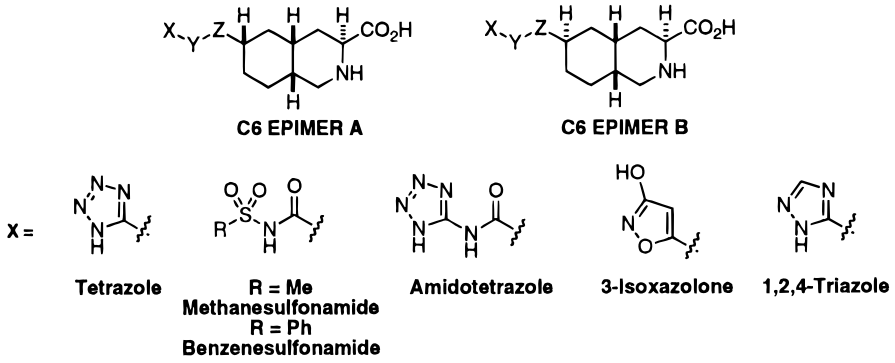
[a] Affinity at NMDA receptors was determined using [^{3}H]CGS 19755; see ref 12. Affinity at AMPA receptors was determined using [^{3}H]AMPA; see ref 13. Affinity at kainic acid receptors was determined using [^{3}H]kainic acid; see ref 14. [b] All assays for affinity were run in triplicate, unless otherwise indicated. [c] See ref 15. [d] Data from refs 3 and 4. [e] Percent inhibition of agonist-induced depolarizations at the concentration shown. [f] Tested versus quisqualic acid instead of AMPA. [g] IC$_{50}$ was the result of a single assay. [h] Percent inhibition of radioligand binding at the concentration shown.

examined effects of bioisosteric replacement of the tetrazole ring and substitution with a heteroatom in the connecting chain adjacent to the acidic moiety. Table 2 shows the effects of substitution of a sulfur or nitrogen atom in the position adjacent to the tetrazole. Compounds **27** and **28** are epimeric with each other at C-6, as in **1** and **49**. Each contains a sulfur atom adjacent to the tetrazole ring in the connecting chain and shows a 5- and 12-fold increase in affinity for AMPA receptors over their all-carbon counterparts, **1** and **49**, respectively. No change in affinity for NMDA receptors is observed so that this sulfur atom imparts slightly higher selectivity for AMPA over NMDA. This increase in affinity for AMPA receptors is also manifest in an increase in AMPA antagonist activity in the cortical slice preparation, with a more robust increase in antagonist activity for the C-6 epimeric thiotetrazole **28**. The corresponding compound, **38**, with a nitrogen atom adjacent to the tetrazole in the two-atom tether, is devoid of affinity or activity at ionotropic EAA receptors. The exact role that sulfur plays in this increase in affinity is not clear. One might envision conformational and electronic effects from this change. If the thiotetrazole moiety is bound to the molecule in a way that maintains the atom count between the acidic site and the bicylic nucleus, as in **32** and **33**, we saw much lower affinity for AMPA receptors, and while **33** was a weak antagonist, **32** actually showed some agonist activity in the cortical slice preparation.

We prepared compounds in which the tetrazole was replaced with either acidic functional groups (e.g., carboxylate, phosphonate, and sulfonate) or an acidic 5-membered ring heterocyclic acid. For most compounds, we prepared both of the C-6 epimers. The carboxylic acid analog (**5**) corresponding to **1** was 5-fold less potent in affinity at AMPA sites and 7-fold less potent as an AMPA antagonist. The C-6 epimer **6** was inactive. Converison of **5** to the corresponding acylmethane- and benzenesulfonamides **9a** and **9b**, respectively, afforded compounds which showed low or no AMPA receptor affinity or antagonist activity. The acylamidotetrazole **11**, while being 12-fold less potent than **1** in terms of affinity at AMPA receptors, nonetheless retained some functional AMPA antagonist activity, with an IC$_{50}$ of 19 μM in the cortical slice preparation. Both C-6 epimers **18** and **20**, which have a phosphonic acid replacing the tetrazole, were inactive. However, the sulfonic acid-substituted compound **21** was only 2-fold less potent in affinity at AMPA sites relative to **1** and 5-fold less potent as an antagonist in the cortical slice. The corresponding C-6 epimeric sulfonic acid **22** was inactive.

Amino acid **47**, in which the tetrazole of **1** was replaced with the 3-isoxazolone moiety found in AMPA, was 2-fold less potent in binding to AMPA recepetors, and 3-fold less potent as an AMPA antagonist in the cortical slice preparation. The corresponding C-6 epimer, **48**, was inactive. We also prepared some triazole-

Table 3. Effects of Bioisosteric Substitution for a Series of 6-Substituted Decahydroisoquinoline-3-carboxylic Acids with a Two-Atom Connecting Chain and Resolution of Selected Compounds



compound	linker Y−Z	C-6 epimer	IC_{50} (μM) versus radioligand binding at ionotropic excitatory amino acid receptors[a,b] NMDA	AMPA	kainic acid	IC_{50} (μM) versus agonist-iinduced depolarizations in a cortical slice preparation[c] NMDA	AMPA	kainic acid
X = CO_2H								
5	CH_2CH_2	A	43.9 ± 4.1	27.8 ± 0.6	>100	57 ± 4.4	42 ± 6.5[d]	>100
6	CH_2CH_2	B	>100	>100	>100	>100	>100	>100
X = methanesulfonamide								
8a	CH_2CH_2	A	>100	>100	>100	>100	>100	>100
X = benzenesulfonamide								
8b	CH_2CH_2	A	>100	>100	>100	>100	>100	>100
X = amidotetrazole								
11	CH_2CH_2	A	>100	72.6 ± 13.6	>100	84 ± 19	19 ± 6	71 ± 28
X = PO_3H_2								
18	CH_2CH_2	A	>10	>100	NT[e]	>100	>100	>100
20	CH_2CH_2	B	>10	>10	NT[e]	>100	>100	>100
X = SO_3H								
21	CH_2CH_2	A	61.8[f]	11.6 ± 1.5	>100	>100	31.4 ± 1.7	100
22	CH_2CH_2	B	>100	>100	>100	>100	>100	>100
X = 3-isoxazolone								
46	CH_2CH_2	A	>100	13.8 ± 1.2	>100	>100	16.5 ± 2.7	>100
47	CH_2CH_2	B	>100	>100	>100			
X = 1,2,4-triazole								
35	SCH[2]	A	>10	>10	>10	>100	68.8 ± 12.3	>100
36	SO_2CH_2	A	>100	1.7 ± 0.1	>100	>100	2.16 ± 0.79	10[g]
(−)-3*S*,4a*R*,6*S*,8a*R*-**36**	SO_2CH_2	A	>100	0.6[f]	>100	NT[e]	NT[e]	NT[e]
(+)-3*R*,4a*S*,6*R*,8a*S*-**36**	SO_2CH_2	A	60.9[f]	23.6[f]	>100	NT[e]	NT[e]	NT[e]

[a] Affinity at NMDA receptors was determined using [^{3}H]CGS 19755; see ref 12. Affinity at AMPA receptors was determined using [^{3}H]AMPA; see ref 13. Affinity at kainic acid receptors was determined using [^{3}H]kainic acid; see ref 14. [b] All assays for affinity were run in triplicate, unless otherwise indicated. [c] See ref 15. [d] Tested versus quisqualic acid instead of AMPA. [e] NT = not tested. [f] IC_{50} was the result of a single assay. [g] Approximately 50% inhibition of kainic acid-induced depolarization at 10 μM.

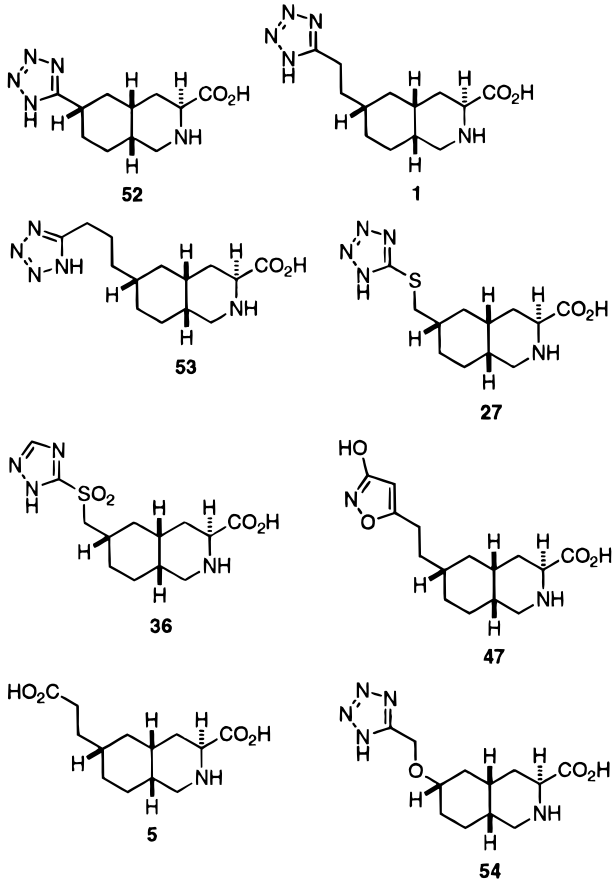
substituted amino acids, which incorporated a sulfide or sulfone in the two-atom connecting chain adjacent to the triazole ring. The sulfide **35** was inactive; however, the sulfonyltriazole **36** was 3-fold more potent in both affinity and antagonist activity when compared to **1**. Both the 3-isoxazolone-substituted amino acid **47** and the sulfonyltriazole **36** were more selectve for AMPA over NMDA and kainic acid receptors than the tetrazole **1**.

The tetrazole-, thiotetrazole-, and sulfonyltriazole-substituted compounds **1**, **49**, **27**, **28**, and **36** were prepared in nonracemic form, and each enantiomer was tested for affinity and antagonist activity at AMPA, NMDA, and kainic acid receptors (Tables 2 and 3). We found that for both C-6 epimers it was the compound having the *S*-absolute stereochemistry at the amino acid carbon (C-3) that had affinity at the AMPA receptor and carried the functional AMPA antagonist activity. This is distinct from what we found in an earlier structure−activity study of hydroisoquinoline amino acids which yielded NMDA antagonists.[6] For example, we found NMDA antagonist activity in the 3*S*-isomer of the tetrazole-substituted compound **50**, but for the corresponding C-6 epimer **51**, NMDA antagonist activity was found in the 3*R*-isomer.[6] Thus, how one might envision an overlap of the two C-6 epimers **1** and **49**, which are AMPA antagonists, or **50** and **51**, which are NMDA antagonists, is distinctly different; we have attempted to show these overlaps in Figure 1. Very different pictures emerge of the pharmacophore for 6-substituted hydroisoquinoline NMDA and AMPA antagonists, and this will be discussed in more detail in a forthcoming paper covering a series of aryl-spaced decahydroisoquinoline amino acids.[19]

SAR Summary

In this and the preceding paper we have detailed the many different aspects that we explored in the structure−activity studies of this class of 6-substituted decahydroisoquinoline-3-carboxylic acids. Optimal activity was observed for the stereoisomer corresponding to **1**. AMPA antagonist activity was optimized when the length of the tether connecting an acidic functionality to the bicyclic nucleus was two atoms. Substitution with a nitrogen or oxygen atom in the tether adjacent to the bicyclic ring led to lower potency, as did substitu-

Table 4. Activity of AMPA Antagonists in Mice versus Maximal Electroshock-Induced Convulsions, ATPA-Induced Rigidity, and Activity on the Horizontal Screen



	ED_{50} [95% CI] (mg/kg, ip)[a] for effects in assays in mice		
compd	30 mg/kg (iv) ATPA-induced rigidity[b]	maximal electroshock-induced convulsions[c]	impairment on the horizontal screen[c]
52[d]	44.5	24.1	NT[e]
1[f]	3.6 [1.8−6.3]	9.0 [6.8−11.8]	19.6 [15.3−25.6]
53	>100	>100	>100
27	8.1 [5.3−13.9]	8.5 [6.2−12.5]	20.1 [14.9−27.4]
36	NT[e]	9.5 [7.0−11.9]	25.2 [20.1−33.8]
47	8.8 [5.0−15.5]	31.1 [17.6−52.9]	>100
5	>100	>100	>100
54	30.6 [19.2−56.0]	24.7 [16.1−40.2]	21.0 [17.8−26.6]

[a] All compounds administered intraperitoneally 30 min prior to testing in mice. [b] See references 18 and 20. [c] See ref 17. [d]See refe ?. [d] Data from ref 20. [e]NT = not tested. [f] Data from refs 3 and 4.

tion with a nitrogen atom adjacent to the tetrazole ring. Substitution with sulfur adjacent to the tetrzole, however, led to an increase in potency and selectivity. Bioisosteric replacement of the tetrazole with a carboxylate, phosphonate, or sulfonate led to a derease in activity, and while the isoxazolone showed only a slight decrease in affinity, a triazole-substituted compound in which a sulfonyl group was incorporated in the tether adjacent to the triazole ring led to a significant increase in potency and selectivity as an AMPA antagonist.

The change in activity observed following small changes in structure is a striking feature of this class of 6-substituted decahydroisoquinoline-3-carboxylic acids. For a series of compounds, **52**,[20] **51**,[6] and **1**[3,4] (Figure 2), where the relative and absolute stereochemistry of the bicyclic ring is the same, and for each the distal acid is a tetrazole, we see a distinct change in activity by changing the length of the all-carbon tether connecting the two groups. Amino acid **52**, where the tetrazole is directly bound to the bicyclic nucleus, is both an AMPA and an NMDA antagonist. Separate the two functionalities by one methylene, and the compound (**51**) is a selective NMDA antagonist; increase the length of the tether to two methylenes, and the compound is a selective AMPA antagonist; compounds with a three- or four-carbon atom tether are only weakly active.

In Vivo Activity

The true utility of an AMPA antagonist can only be realized if the compounds are active in animals following systemic administration. A series of compounds presented in this and the preceding paper[7] were selected for evaluation in a number of assays in mice, and these are shown in Table 4. All of the compounds have the same stereochemistry in the bicyclic ring system and all are racemic. They were all administered by the intraperitoneal route 30 min prior to testing. Two of the compounds, **52** and **53**, are variants of **1** which have

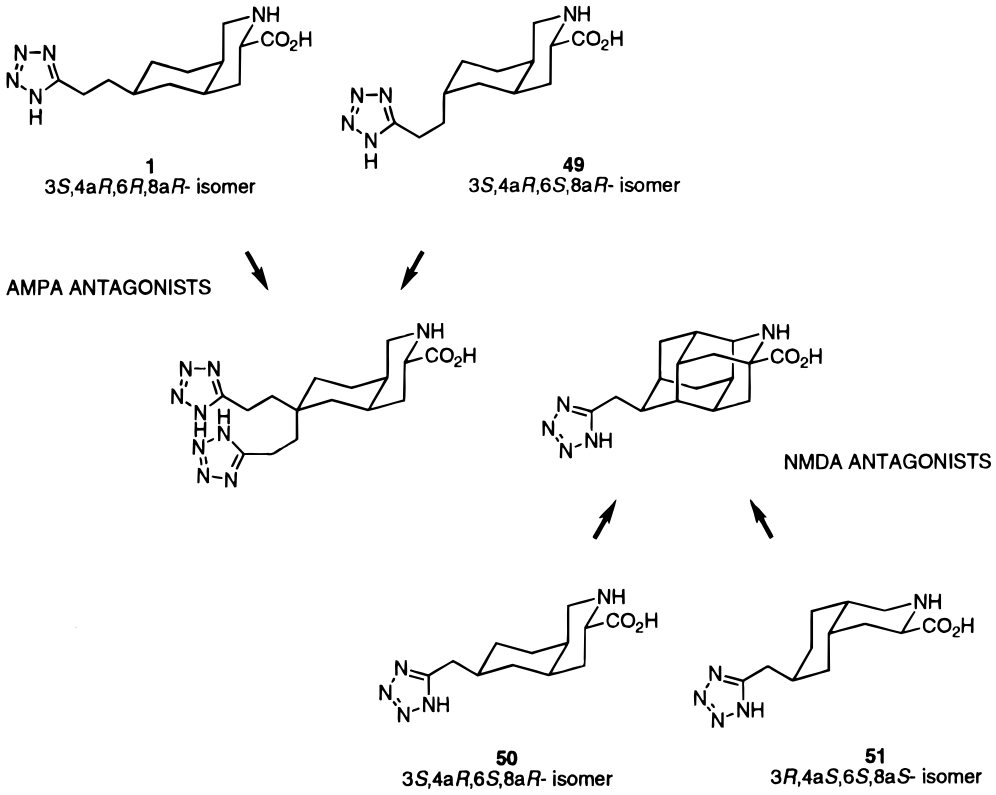


Figure 1. Comparison of AMPA and NMDA receptor pharmacophores as exemplified by compounds from a series of 6-substituted decahydroisoquinoline-3-carboxylic acids. For the AMPA receptor, the two nonracemic amino acids (−)-**1** and (+)-**49** are used; they are epimeric at C-6. For the NMDA receptor, the two nonracemic amino acids (−)-**50** and (+)-**51** are used; they are also epimeric at C-6.

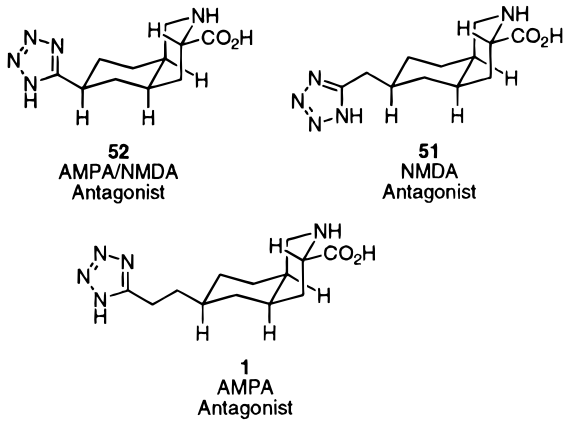


Figure 2. Comparison of structure versus EAA receptor antagonist activity for a series of 6-substituted decahydroisoquinoline-3-carboxylic acids that differ only in the length of an all-carbon tether that connects a tetrazole to the bicyclic ring nucleus. Amino acid **54**, where the tetrazole is directly bound to the ring, is both an AMPA and an NMDA antagonist. Amino acid **51**, with a one-carbon tether, is a selective NMDA antagonist; **1**, with a two-carbon tether, is a selective AMPA antagonist.

different tether lengths; the others are compounds that differ in the distal acid bioisostere (**5**, **36**, and **47**) and/or have a heteroatom as a component of the tether (**27**, **36**, and **51**). While the data are not shown in Table 4, all of these compounds were evaluated for their ability to inhibit lethality induced by a 200 mg/kg (ip) dose of NMDA. Amino acid **52** blocked this lethality with an ED_{50} of 19.4 mg/kg,[20] while the oxa analog **54** blocked this effect at a minimum effective dose of 80 mg/kg.[21] All of the other compounds tested were ineffective at blocking NMDA-induced lethality at a dose of 160 mg/kg.

ATPA, the *tert*-butyl analog of AMPA, is a selective AMPA agonist that shows activity following systemic administration. Intravenous administration of ATPA in mice produces a characteristic muscle rigidity that is blocked selectively by AMPA antagonists.[20] Compounds from this series that potently displaced AMPA binding and were antagonists in the cortical slice preparation dose-dependently prevented ATPA-induced rigidity. Amino acid **1** for example, was effective in this assay with an ED_{50} of 3.6 mg/kg (ip); the lower homolog **52**, which is an AMPA and NMDA antagonist, was much less potent (ED_{50} of 44.5 mg/kg), while the higher homolog **53** was inactive at doses up to 100 mg/kg. Amino acids **27**, **47**, and **54**, which are bioisosteric analogs of **1**, also blocked ATPA-induced rigidity in mice, with ED_{50}s of 8.1, 8.8, and 30.6 mg/kg, respectively; the carboxy analog **5** was inactive at doses up to 100 mg/kg.

These amino acids were also evaluated for their ability to block maximal electroshock (MES)-induced convulsions in mice. While this assay is not specific for AMPA antagonists (NMDA antagonists and conventional anticonvulsant compounds are also active in this assay), it serves as another measure of the in vivo activity of this class of compounds and also serves to demonstrate their potential as anticonvulsant agents. Comparable potency was seen in this assay for amino acids **1**, **27**, and **36** (ED_{50}s of 9.0, 8.5, and 9.5 mg/kg, respectively), with **52**, **47**, and **54** being 3−4-fold less potent (ED_{50}s of 24.1, 31.1, and 24.7 mg/kg, respectively); **53** and **5** were inactive.

Finally, we examined the potential for these com-

pounds to produce neurological impairments in mice using the horizontal screen assay.[22] Before the mice were tested for MES-induced convulsions, they were placed on a horizontal screen. Under control conditions where the mouse is unimpaired, when the screen is turned upside down, the mouse will climb back to the top within 2 min. If the mouse is impaired by the test compound, it will cling to the bottom or fall off. The best amino acids from this SAR impaired performance on the horizontal screen at test doses 2−3-fold higher than their ED_{50}s in the other assays, e.g., **1**, **27**, **36**, and **47** (ED_{50}s of 19.6, 20.1, 25.2, and >100 mg/kg). The two compounds with both NMDA and AMPA antagonist activity, **52** and **54**, impaired performance on the horizontal screen test at doses similar to those that produced protective effects in the other assays.

Conclusions

From a series of 6-substituted decahyroisoquinoline-3-carboxylic acids, we have identified potent excitatory amino acid antagonists. From this SAR we have realized compounds that are selective NMDA antagonists[5,6] and selective AMPA antagonists,[3,4,7] as well as two compounds which possess both NMDA and AMPA antagonist activity within a single entity.[20] We have demonstrated that these compounds are effective in displacing EAA receptor ligand binding and that they antagonize depolarizations due to selective EAA agonists. We have also shown that many of the more potent AMPA antagonists from this SAR are active following systemic administration in mice. Amino acid **1** was evaluated and found to be efficacious in models of ischemia in rats[22] and cats.[23] Thus, these compounds may serve as therapeutic agents in the treatment of acute and chronic neurodegenerative diseases.

Experimental Section

General Experimental. See this section in ref 7. "Anion exchange chromatography" refers to anion exchange with Bio-Rad AG1-X8 anion exchange resin (hydroxide form). The resin (obtained in acetate form) was prepared by washing (in a coarse porosity sintered glass funnel) with water, methanol, water, twice with 1 N sodium hydroxide (converts to the hydroxide form), and then water until pH 7. The resin was packed into a glass column in water, and the compound (at pH ≥ 9) was slowly eluted on with water, and then the column was washed with water, 50% aqueous THF, and then water until the pH was neutral. The compound was eluted off of the column with 3 N aqueous acetic acid, and product-containing fractions (which were detected with ninhydrin stain on a TLC plate) were combined and concentrated in vacuo.

2:1 Mixture of Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)- and (3*SR*,-4a*RS*,6*RS*,8a*RS*)-6-Formyl-2-(methoxycarbonyl)-1,2,3,4,-4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (2). A solution of 3.3 g (10.7 mmol) of ethyl (3*SR*,4a*RS*,8a*RS*)-2-(methoxycarbonyl)-6-(methoxymethylene)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate[9] in 125 mL of THF and 160 mL of 1 N hydrochloric acid was stirred for 4 h at room temperature. Workup (water/3× dichloromethane/saturated sodium bicarbonate) afforded 3.2 g of a 2:1 mixture of **2**, used without purification.

Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-carbethoxyethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (3) and Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(2-carbethoxyethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,-5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (4). To a suspension of 0.6 g (5.0 mmol) of sodium hydride in 20 mL of THF was added 3.4 g (15.0 mmol) of triethyl phosphonoacetate. After 30 min at room temperature, this mixture was treated with 3.2 g (10.7 mmol) of a 2:1 mixture of **2** in 10 mL of THF (5 mL rinse). After an additional half hour at room temperature, workup (water/3× ether) afforded 3.9 g of an oil. This mixture was hydrogenated with 1.0 g of 5% Pd/C in 96 mL of ethanol at room temperature and 60 psi for 3 h and then filtered through diatomaceous earth and concentrated in vacuo. The residue was purified by medium-pressure liquid chromatography on a LOBAR C column, eluting with 25% ethyl acetate/hexane at 12 mL/min, to give 0.6 g (15%) of **4**, 1.5 g (38%) of **3**, and 1.1 g of mixed fractions for a total yield of 3.2 g (80%).

(3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-Carboxyethyl)-1,2,3,4,-4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (5). A 1.4 g (3.8 mmol) portion of **3** was heated to reflux overnight in 50 mL of 6 N hydrochloric acid, cooled, and concentrated in vacuo. Cation exchange chromatography afforded 0.6 g (65%) of **5**.

(3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(2-Carboxyethyl)-1,2,3,4,-4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (6). As for **5**, 0.6 g (1.5 mmol) of **4** gave 0.2 g (46%) of **6**.

Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-(*N*-(methylsulfonyl)-carbamoyl)ethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,-8a-decahydroisoquinoline-3-carboxylate (8a). A solution of 1.9 g (11.7 mmoL) of 1,1′-carbonyldiimidazole and 4.0 g (11.7 mmol) of **7**[7] in 50 mL of THF was heated to reflux for 1 h, then cooled to room temperature, and treated with 1.1 g (11.7 mmol) of methanesulfonamide. After 10 min, this solution was treated with 1.8 g (11.7 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene in 10 mL of THF and then stirred overnight at room temperature. Workup (1 N hydrochloric acid/3× ether/3× saturated sodium bicarbonate) gave 4.4 g (89%) of **8a**.

(3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-(*N*-(Methylsulfonyl)carbamoyl)ethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (9a). A solution of 4.3 g (10.3 mmol) of **8a** and 22.6 mL (22.6 mmol) of 1 N sodium hydroxide in 45 mL of ethanol was stirred overnight at room temperature and then concentrated in vacuo. The residue was dissolved in water and extracted with ethyl acetate, and then the aqueous layer was acidified with 5 N HCl and extracted three times with ethyl acetate. The ethyl acetate extracts were combined, dried over sodium sulfate, filtered, and concentrated in vacuo to give 3.7 g (92%) of the corresponding acid. This was dissolved in 40 mL of chloroform, treated with 11.4 g (57.0 mmol) of iodotrimethylsilane, heated to reflux for 2 h, and then concentrated in vacuo. The residue was dissolved in water, extracted with ether, and concentrated in vacuo. Cation exchange chromatography afforded 2.8 g (87%) of **9a**.

Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-(*N*-(Phenylsulfonyl)-carbamoyl)ethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,-8a-decahydroisoquinoline-3-carboxylate (8b). As for **8a**, 1.9 g (11.7 mmoL) of 1,1′-carbonyldiimidazole, 4.0 g (11.7 mmol) of **7**,[7] 1.1 g (11.7 mmol) of benzenesulfonamide, and 1.8 g (11.7 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene in 60 mL of THF gave 3.8 g (67%) of **8b**.

(3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-(*N*-(Phenylsulfonyl)carbamoyl)ethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (9b). As for **9a**, 3.6 g (7.6 mmol) of **8b** and 16.7 mL (16.7 mmol) of 1 N sodium hydroxide in 30 mL of ethanol gave 3.3 g (96%) of the corresponding acid. This was treated as for **9a** in 30 mL of chloroform with 8.8 g (43.8 mmol) of iodotrimethylsilane to afford 2.2 g (73%) of **9b**.

Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-(*N*-(1*H*-Tetrazol-5-yl)-carbamoyl)ethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,-8a-decahydroisoquinoline-3-carboxylate (10). A solution of 1.9 g (11.7 mmoL) of 1,1′-carbonyldiimidazole and 4.0 g (11.7 mmol) of **7**[7] in 50 mL of THF was heated to reflux for 1 h and then treated with 1.0 g (11.7 mmol) of 5-amino-1*H*-tetrazole, and the solution was refluxed overnight. The cooled solution was treated with 1 N hydrochloric acid and extracted three times with ether. The organic extracts were combined and washed twice with saturated sodium bicarbonate. The aqueous bicarbonate washes were combined, acidified with 5 N hydrochloric acid, and extracted three times with ether. The ether extracts were combined, dried over sodium sulfate, filtered, and concentrated in vacuo to give 4.6 g (96%) of **10**.

(3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-(*N*-(1*H*-Tetrazol-5-yl)carbamoyl)ethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-

carboxylic Acid (11). A solution of 4.4 g (10.8 mmol) of **10** and 23.7 mL (23.7 mmol) of 1 N sodium hydroxide in 45 mL of ethanol was stirred overnight at room temperature and then concentrated in vacuo. Workup (5 N hydrochloric acid/3× ethyl acetate) afforded 3.9 g (95%) of the corresponding acid. This material was treated as for **9a** with 8.7 mL (12.3 g, 61.5 mmol) of iodotrimethylsilane in 45 mL of chloroform to give 3.1 g (84%) of **11**.

Ethyl (*E*)- and (*Z*)-(3*SR*,4a*RS*,8a*RS*)-6-((Benzyloxycarbonyl)methylene)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,-8a-decahydroisoquinoline-3-carboxylate (13). To a suspension of 3.1 g (77.7 mmol) of sodium hydride in 200 mL of THF was added 22.2 g (77.7 mmol) of benzyl (diethylphosphono)acetate in 50 mL of THF. After 30 min, the resulting clear solution was treated with 20.0 g (70.6 mmol) of **12** in 80 mL of THF and then stirred for 5 h at room temperature. Workup (brine/3× ether) and Prep HPLC (hexane to 50% ethyl acetate/hexane) gave 26.3 g of **13**.

Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)- and (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(Carboxymethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,-8a-decahydroisoquinoline-3-carboxylate (14). A solution of 26.2 g (62.9) of **13** in 270 mL of ethyl acetate was hydrogenated with 5.0 g of 5% Pd/C at 60 psi and room temperature for 4 h. Filtration through diatomaceous earth and concentration in vacuo afforded 20.5 g (99%) of **14**, which was used in the next step without further purification.

Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(2-Bromoethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (15) and Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-Bromoethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (16). To a 0 °C solution of 20.5 g (61.1 mmol) of **14** in 200 mL of THF was added 61 mL (122 mmol) of a 2 M solution of borane−methyl sulfide in THF. After 4 h, workup (saturated aqueous sodium bicarbonate/3× ether) gave 19.3 g of a diastereomeric mixture of ethyl 6-(2-hydroxyethyl)-2-(methoxycarbonyl)decahydroisoquinoline-3-carboxylates. A solution of this compound in 225 mL of dichloromethane and 10 mL (9.8 g, 123.4 mmol) of pyridine was added dropwise to a 0 °C suspension of triphenylphosphine dibromide [prepared from 24.3 g (92.6 mmol) of triphenylphosphine and 4.7 mL (14.9 g, 92.6 mmol) of bromine] in 300 mL of dichloromethane. After 15 min at 0 °C, workup (2× 10% aqueous sodium bisulfate/2× ether) afforded a solid, which was suspended in ether and filtered to removed triphenylphosphine oxide. The filtrate was concentrated in vacuo, and this procedure was repeated twice. Preparative HPLC (hexane to 30% ethyl acetate/hexane) gave 3.7 g (16%) of **16** (first eluted) and 5.3 g (23%) of **15** (second eluted).

Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(2-(Diethylphosphono)-ethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (17). A solution of 1.7 g (4.6 mmol) of **15** and 5 mL of triethyl phosphite was heated to 150 °C overnight, at which time an additional 1.6 mL of triethyl phosphite was added. The mixture was heated for 4 h more, then cooled, and concentrated in vacuo. Chromatography (115 g of silica gel; 2.5% ethanol/ethyl acetate) afforded 1.4 g (69%) of **17**.

Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-(Diethylphosphono)-ethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (18). As for **17**, a solution of 1.5 g (4.0 mmol) of **16** and 5 mL of triethyl phosphite gave 1.2 g (67%) of **18**.

(3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(2-Phosphonoethyl)-1,2,3,4,-4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (19). A 1.3 g (3.0 mmol) portion of **17** and 50 mL of 6 N hydrochloric acid were heated to reflux overnight, then cooled, and concentrated in vacuo. The residue was dissolved in 10 mL of ethanol and treated with 1.0 mL of propylene oxide (pH 2−3). The resulting precipitate was filtered, washing with ethanol, acetone, and ether. This solid was suspended in acetone and heated to reflux, then cooled to room temperature, filtered, washed with acetone and ether, and dried in vacuo at 60 °C to afford 0.5 g (61%) of **19**.

(3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-Phosphonoethyl)-1,2,3,4,-4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (20). A 1.1 g (2.5 mmol) portion of **18** and 50 mL of 6 N hydrochloric acid was heated to reflux overnight, then cooled, and concentrated in vacuo. The residue was dissolved in 10 mL of ethanol and treated with 1.0 mL of propylene oxide (pH 2−3). The resulting precipitate was filtered, washing with ethanol, acetone, and ether. The resulting solid was suspended in water, heated to reflux, cooled to room temperature, filtered, washed with acetone and ether, and dried in vacuo at 60 °C to afford 0.2 g (33%) of **20**.

(3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(2-Sulfoethyl)-1,2,3,4,4a,5,6,7,8,-8a-decahydroisoquinoline-3-carboxylic Acid (21). A solution of 1.8 g (4.7 mmol) of **15** and 0.6 g (5.1 mmol) of sodium sulfite in 11 mL of ethanol and 18 mL of water was heated to reflux overnight, and then an additional 0.6 g (5.1 mmol) of sodium sulfite (0.59 g) was added. The mixture was again heated overnight at reflux and then concentrated in vacuo. The residue was partitioned between ether and water, the ether layer was separated and washed again with water, and then the combined aqueous washes were extracted with ether and concentrated in vacuo to afford an oil. This material was heated to reflux overnight in 80 mL of 6 N hydrochloric acid, cooled to room temperature, and concentrated in vacuo. Anion exchange chromatography afforded 0.9 g (65%) of **21**.

(3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-Sulfoethyl)-1,2,3,4,4a,5,6,7,8,-8a-decahydroisoquinoline-3-carboxylic Acid (22). As for **21**, 1.8 g of **16** afforded 0.7 g (50%) of **22**.

Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(2-(1*H*-Tetrazol-5-yl)-2-thiaethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (25). A solution of 8.3 g (23.0 mmol) of **23**,[9] 2.6 g (25.3 mmol) of thiotetrazole (2.58 g), and 6.4 mL (4.7 g, 46.0 mmol) of triethylamine (4.65 g) in 70 mL of acetonitrile was heated to 80 °C for 20 h and then cooled to room temperature. Workup (10% sodium bisulfate/3× ethyl acetate) and chromatography (4/36/60 acetic acid/ethyl acetate/toluene) afforded 8.9 g (99%) of **25**.

Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-(1*H*-Tetrazol-5-yl)-2-thiaethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (26). As for **25**, 1.9 g (5.1 mmol) of **24**,[9] 0.6 g of thiotetrazole, and 1.4 mL (1.0 g, 10.2 mmol) of triethylamine in 20 mL of acetonitrile afforded 1.8 g (91%) of **26**.

(3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(2-(1*H*-Tetrazol-5-yl)-2-thiaethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (27). A solution of 8.9 g (23.2 mmol) of **25** in 100 mL of 6 N hydrochloric acid was heated to 90 °C for 3 h, then cooled to room temperature, and filtered, and the filter cake was washed with water and acetone. The solid was dried in vacuo at room temperature to give 5.4 g (69%) of **27**.

(3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-(1*H*-Tetrazol-5-yl)-2-thiaethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (28). A solution of 1.7 g (4.4 mmol) of **26** in 25 mL of 6 N hydrochloric acid was heated to reflux overnight, then cooled to room temperature, and concentrated in vacuo. Cation exchange chromatography afforded 0.7 g (51%) of **28**.

Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-((5-(Phenacylthio))-1*H*-tetrazol-1-yl)methyl)-2-(methoxycarbonyl)-1,2,3,4,-4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (30a) and Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-((5-(Phenacylthio))-2*H*-tetrazol-2-yl)methyl)-2-(methoxycarbonyl)-1,2,3,4,-4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (31a). A solution of 4.0 g (11.1 mmol) of **23**,[9] 2.7 g (12.2 mmol) of **29**, and 2.7 g (26.7 mmol) of potassium carbonate in 16 mL of dimethylformamide was heated to 90 °C for 5 h and then cooled to room temperature. Workup (water/3× dichloromethane; 1× ether/2× water; 1× brine) and chromatography (350 g of silica gel; linear gradient of 35% to 50% ethyl acetate/hexane) gave 3.1 g (55%) of **31a** and 1.1 g of a mixture of **30a** and **31a**. The latter was rechromatographed using radial chromatography, eluting wtih 50% ethyl acetate/hexane, to afford 0.6 g (11%) of **30a**.

Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-((5-Mercapto-2*H*-tetrazol-2-yl)methyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,-8a-decahydroisoquinoline-3-carboxylate (31b). A degassed solution of 1.8 g (3.5 mmol) of **31a** in 250 mL of ethanol was photolyzed for 3 h using a 450 W medium-pressure mercury lamp and then concentrated in vacuo. The residue

was partitioned between dichloromethane and water, adjusting the pH of the aqueous layer to pH 8−9 using 1 N sodium hydroxide. The organic portion was washed 3× more with water, then the combined aqueous washes were acidified to pH 2−3 with 1 N hydrochloric acid, and the aqueous portion was extracted four times with dichloromethane. The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 1.2 g (87%) of **31b**.

Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-((5-Mercapto-1*H*-tetrazol-1-yl)methyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (30b). As for **31b**, 0.6 g (1.2 mmol) of **30a** in 225 mL of ethanol gave 0.3 g (54%) of **30b**.

(3*SR*,4a*RS*,6*SR*,8a*RS*)-6-((5-Mercapto-2*H*-tetrazol-2-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (33). A solution of 1.8 g (4.7 mmol) of **31b** and 50 mL of 6 N hydrochloric acid was heated to reflux overnight and then cooled to room temperature, whereupon a precipitate formed. The solid was filtered; washed with water, acetone, and ether; and then dried in vacuo at room temperature to afford 1.1 g (72%) of **33**.

(3*SR*,4a*RS*,6*SR*,8a*RS*)-6-((5-Mercapto-1*H*-tetrazol-1-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (32). As for **33**, 0.3 g (0.7 mmol) of **30b** gave 0.2 g (70%) of **32**.

Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(2-(1*H*-1,2,4-Triazol-5-yl)-2-thiaethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (34). A solution of 9.2 g (25.5 mmol) of **23**[9] and 3.1 g (30.5 mmol) of 1*H*-1,2,4-triazole-3-thiol in 92 mL of anhydrous dimethylformamide was heated to 100 °C overnight and then cooled to room temperature. Workup (10% sodium bisulfate/3× 1/1 chloroform/ethyl acetate, 1× ether) and preparative HPLC (linear gradient of 35% ethyl acetate/hexane to ethyl acetate) afforded an oil which by ^{1}H NMR showed the presence of dimethylformamide. The residue was dissolved in ethyl acetate and extracted with 1 N hydrochloric acid and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo to give 9.4 g (96%) of **34**.

(3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(2-(1*H*-1,2,4-Triazol-5-yl)-2-thiaethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (35). A mixture of 1.8 g (5.5 mmol) of **34** in 10 mL of 6 N hydrochloric acid was heated to 100 °C overnight and then concentrated in vacuo. Cation exchange chromatography afforded a solid that was suspended in acetone, heated to reflux for 1 h, filtered, washed with acetone and ether, and then dried in vacuo at 40 °C to give 0.4 g (22%) of **35**.

(3*SR*,4a*RS*,6*SR*,8a*RS*)-6-((1*H*-1,2,4-Triazol-5-ylsulfonyl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (36). A room temperature solution of 9.4 g (24.5 mmol) of **34** in 105 mL of dichloromethane was treated with 13.3 g (61.2 mmol, 80% by weight) of 3-chloroperoxybenzoic acid in three portions over a period of 30 min, then stirred overnight, and concentrated in vacuo. Chromatography (250 g of silica gel; step gradient of 50% ethyl acetate/hexane (500 mL) followed by ethyl acetate (2000 mL)) of the residue gave 9.0 g of a clear oil. This was treated at reflux overnight with 250 mL of 6 N hydrochloric acid, then cooled, and concentrated in vacuo. The residue was dissolved in 100 mL of water and extracted with ether, and then the aqueous phase was concentrated in vacuo. Ion exchange chromatography afforded a solid that was refluxed for 1 h in acetone, filtered, washed with acetone and ether, and dried in vacuo at 60 °C overnight to give 3.4 g (44%) of **36**.

Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS)*-6-(1*H*-Tetrazol-5-ylamino)-methyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (37). A solution of 3.0 g (8.3 mmol) of **23**,[9] 2.9 g (20.7 mmol) of powdered potassium carbonate, and 1.4 g (16.6 mmol) of 5-amino-1*H*-tetrazole in 225 mL of acetonitrile was heated to reflux for 2 days and then concentrated in vacuo. Workup (water/3× ethyl acetate) and chromatography (200 g of silica gel; 25% ethyl acetate/hexane) gave 0.7 g (23%, 60% based on recovered starting material) of **37** and 1.9 g (61%) of starting bromide.

(3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(1*H*-Tetrazol-5-ylamino)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (38). A 0.7 g (1.9 mmol) portion of **37** and 50 mL of 6 N hydrochloric acid were heated to reflux overnight and then concentrated in vacuo. Cation exchange chromatography afforded 0.3 g (58%) of **38**.

3-Bromoisoxazole-5-carboxylic Acid and 3-Bromoisoxazole-4-carboxylic Acid (40). A room temperature solution of 35.2 g (198.0 mmol) of a mixture of 3-bromo-5-(hydroxymethyl)isoxazole and 3-bromo-4-(hydroxymethyl)isoxazole (**39**)[10] in 500 mL of acetone was treated dropwise with 950 mL of Jones reagent, stirred for 6 h at room temperature, and then treated with 1000 mL of 2-propanol. The resulting mixture was filtered through diatomaceous earth, and the filtrate was concentrated in vacuo. Workup (water/3× ether) gave 34.1 g (90%) of **40** (mixture of regioisomers).

3-Methoxyisoxazole-5-carboxylic Acid and 3-Methoxyisoxazole-4-carboxylic Acid (41). A solution of 34.1 g (178.0 mmol) of **40** (mixture of regioisomers) and 169 g (3.0 mol) of potassium hydroxide in 580 mL of methanol and 103 mL of water was heated to reflux for 4 h, then cooled to room temperature, and treated with 450 mL of concentrated hydrochloric acid and 350 mL of water. The resulting solution was extracted six times with ether, and then the ether extracts were combined, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was diluted with toluene and methanol and then concentrated in vacuo to give 20.2 g (79%) of a mixture of **41** (mixture of regioisomers).

3-Methoxy-5-(hydroxymethyl)isoxazole (42) and 3-Methoxy-4-(hydroxymethyl)isoxazole. To a 0 °C solution of 20.2 g (141.0 mmol) of **41** (mixture of regioisomers) and 14.3 g (141.0 mmol) of triethylamine in 210 mL of THF was added a solution of 19.3 g (141.0 mmol) of isobutyl chloroformate in 35 mL of THF. After 1.25 h, the precipitate was removed by filtration and washed with THF. The filtrate was carefully added to a room temperature solution of 13.4 g (353.0 mmol) of sodium borohydride in 140 mL of water (cooled as necessary to avoid a strong exotherm). Workup (1 N hydrochloric acid/3× ether) and preparative HPLC (hexane to 35% ethyl acetate/hexane) gave 1.4 g (7.5%) of 3-methoxy-4-(hydroxymethyl)-isoxazole and 9.1 g (50%) of **42**.

3-Methoxy-5-(bromomethyl)isoxazole (43). A solution of 9.1 g (70.5 mmol) of **42** in 11 mL of dichloromethane and 11.4 mL (11.2 g, 141.0 mmol) of pyridine was added to a 0 °C suspension of triphenylphosphine dibromide [prepared from 27.7 g (105.8 mmol) of triphenylphosphine and 5.4 mL (16.9 g, 105.8 mmol) of bromine] in 425 mL of dichloromethane. Workup (2× 10% sodium bisulfate/2× dichloromethane, 1× ether) and chromatography (450 g of silica gel; step gradient of 10% ethyl acetate/hexane followed by 20% ethyl acetate/hexane) afforded 10.8 g (80%) of **43**.

Diethyl ((3-Methoxyisoxazol-5-yl)methyl)phosphonate (44). A solution of 10.8 g (56.2 mmol) of **43** and 19.3 mL (18.7 g, 112.5 mmol) of triethyl phosphite in 150 mL of toluene was heated to 120 °C overnight and then concentrated in vacuo. Preparative HPLC (ethyl acetate to 5% ethanol/ethyl acetate) of the residue afforded 11.8 g (84%) of **44** (hygroscopic oil).

Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-(3-Methoxyisoxazol-5-yl)ethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (45) and Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(2-(3-Methoxyisoxazol-5-yl)ethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (46). A −17 °C solution of 3.7 g (14.9 mmol) of **44** in 10 mL of THF was treated with 14.9 mL (14.9 mmol) of a 1 M solution of sodium bis(trimethylsilyl)-amide in THF. After 30 min, a solution of 3.2 g (10.6 mmol) of **2**[9] in 10 mL of THF was added, and the susequent mixture was stirred for 1.5 h while warming to room temperature. Workup (water/3× ether) and chromatography (250 g of silica gel; 15% ethyl acetate/toluene) gave 3.0 g (71%) of corresponding unsaturated analogs as a mixture of diastereomers. A solution of 2.3 g (5.9 mmol) of this mixture in 50 mL of ethyl acetate was hydrogenated with 2.3 g of 5% Pd/C for 6 h at 60 psi. The reaction mixture was filtered through diatomaceous earth and then concentrated in vacuo. Chromatography (200 g of silica gel; linear gradient of 5% ethyl acetate/toluene to 15% ethyl acetate/toluene) yielded 0.3 g (14%) of **46** and 1.0 g (43%) of **45**.

(3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-(3-Hydroxyisoxazol-5-yl)-ethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (47). A mixture of 0.9 g (2.3 mmol) of **45** and 10 mL of 48% aqueous hydrobromic acid was heated to reflux for 3 h, then cooled, and concentrated in vacuo. The residue was diluted with water and concentrated in vacuo. This residue was diluted with water, the precipitate was filtered, washing with acetone, and then the filtrate was concentrated in vacuo. Cation exchange chromatography of this residue then afforded 0.1 g (17%) of **47**.

(3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(2-(3-Hydroxyisoxazol-5-yl)-ethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (48). As for **47**, 0.3 g (0.8 mmol) of **46** and 2.5 mL of 48% aqueous hydrobromic acid were heated to reflux for 3 h, then cooled, and concentrated in vacuo. Cation exchange chromatography of this residue afforded 0.1 g (62%) of **48**.

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