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# Syntheses, Activity and Modeling Studies of 3- and 4-(Sulfo- and Sulfonamidoalkyl)pyridine and Piperidine-2-carboxylic Acid Derivatives as Analogs of NMDA Receptor Antagonists

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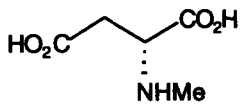
**Abstract**—A series of 3- and 4-(sulfo- and sulfonamidoalkyl)pyridine and piperidine-2-carboxylic acid derivatives as analogs of NMDA receptor antagonists was prepared. Affinity for the NMDA receptor was determined by binding assays using the specific radioligand [$^3$H] (2*SR*,4*RS*)-4-(phosphonomethyl)piperidine-2-carboxylic acid (CGS-19755). The 3-alkylsulfonyl moiety was introduced by selective reduction of a carboxylic acid function followed by bromination, substitution by $Na_2SO_3$ and catalytic reduction. For the 4-alkylsulfonic derivatives the crucial step was the introduction of the 2-cyano function and its further conversion to 2-carboxylic acid. The most potent compound of the series was the pyridine (**11a**) [4-(sulfomethyl)pyridine-2-carboxylic acid] with a modest $IC_{50}$ of 40 μM. A molecular modeling study has been undertaken to understand the pharmacological results. In a first step, a comparative modeling study of the active pyridine and the poorly active piperidine sulfonic acid derivatives **11a** and **10a** [4-(sulfomethyl)piperidine-2-carboxylic acid] and of the phosphonic homologues was performed. We propose that the binding geometry of the sulfonic moiety within the NMDA receptor is different from that of the phosphonic containing antagonists. In order to test this assumption, we have made, in a second step, a complete conformational analysis of the sulfonic acid derivatives, as well as some analogs taken from the literature, either active or inactive as NMDA antagonists. A preferred conformation of the sulfonic acids is proposed.

## Introduction

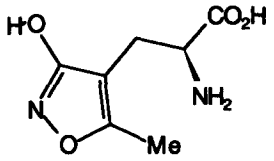
The involvement of excitotoxicity effects occurring in various pathologies of neurons has stimulated interest in excitatory amino acids (EAA) and their receptors.[1,2]

There are at least four well characterized EAA receptor subtypes. The inotropic *N*-methyl-D-aspartic acid (NMDA), 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)-propanoic acid (AMPA) and kainic acid (KA) receptors are all linked to ion channels permeable to sodium and, in the case of NMDA and AMPA receptors, to calcium. The metabotropic (1S,3R)-1-amino cyclopentane-1,3-dicarboxylic acid-sensitive glutamate receptor (1*S*,3*R*-ACPD) is coupled via a G-protein to phosphoinositide hydrolysis.

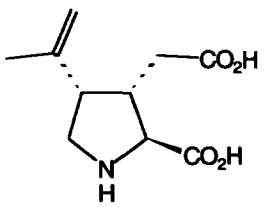
Amino-diacids, in particular glutamic acid, are now recognized as major excitatory neurotransmitters of the central nervous system (CNS) of mammals.[3] Further-



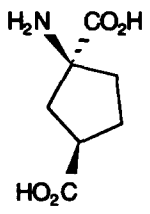
NMDA



AMPA



Kainic Acid



1S,3R-ACPD

more, although glutamic acid may also hypothetically play a role in chronic neurodegenerative disorders such as Huntington's chorea,[4] Parkinson's disease[5] and Alzheimer's disease.[6,7] There is also a wealth of evidence indicating that glutamic acid may be involved in different types of neuronal plasticity, in particular those involved with cognition and learning processes.[8]

Several competitive NMDA antagonists were found active both in the management of epilepsy[9-11] and in the protection against ischemia and hypoglycemia.[10] Thus, there are a large number of therapeutic targets for NMDA receptor antagonists, and the synthesis of novel antagonist structures represent a significant goal for medicinal chemists.

The *N*-methyl-D-aspartic acid subtype of excitatory aminoacid receptors is actually a macromolecular complex (Fig. 1)[12,13] which contains six sites: (1) the transmitter recognition site which binds agonists (NMDA, L-glutamate) and competitive antagonists **1** (CGS-19755);[14-16] (2) a glycine binding site through which glycine allosterically increases the probability of glutamate action [synthetic compound **2** (L-689,560)[17,18] which is a glycine antagonist, acts as a negative modulator of glutamate action]; (3) and (4) a cation binding-site where $Mg^{2+}$ binds and blocks transmembrane ion fluxes and a PCP binding site where PCP and compound **3** (MK-801)[19] bind and block the ion channel in the open state; (5) a zinc binding site which binds antagonist **4** (imipramine);[20] (6) a polyamine binding-site which binds agonists (spermine, spermidine) and antagonist **5** (ifenprodil).[21,22]

Competitive NMDA antagonists exhibit a more favorable side-effect profile than that of their non competitive analogs,[23-25] therefore we focused our efforts on the synthesis of substances belonging to the former class.

Chart 1 shows some representative examples of competitive NMDA antagonists. Potent NMDA antagonist activity has been observed with 3- and 4-substituted piperidine- and piperazine-2-carboxylic acids such as **1**[14-16], **6** (MDL 100,925),[26] **7**[14-16], and CPP **9a**.[27] Modest NMDA antagonist activity was also described for γ-D-glutamyl-aminomethyl sulfonate **8**[1,28] (it is noteworthy that **8** was a more potent antagonist at non-NMDA receptors), CPS **9b**,[27] and CPC **9c**.[27]

Although the few examples of sulfonic acids described[1,29] so far are comparatively less active than their phosphonic and carboxylic acid analogs, it seemed of interest to explore further the sulfonic acid function and that of sulfonamides as novel potential antagonists of the NMDA receptor. One attractive feature of molecules **10** (Chart 2) is the fact that they contain at least two asymmetric centers, thus enabling further probing of the stereochemical requirements for binding to the NMDA receptor.

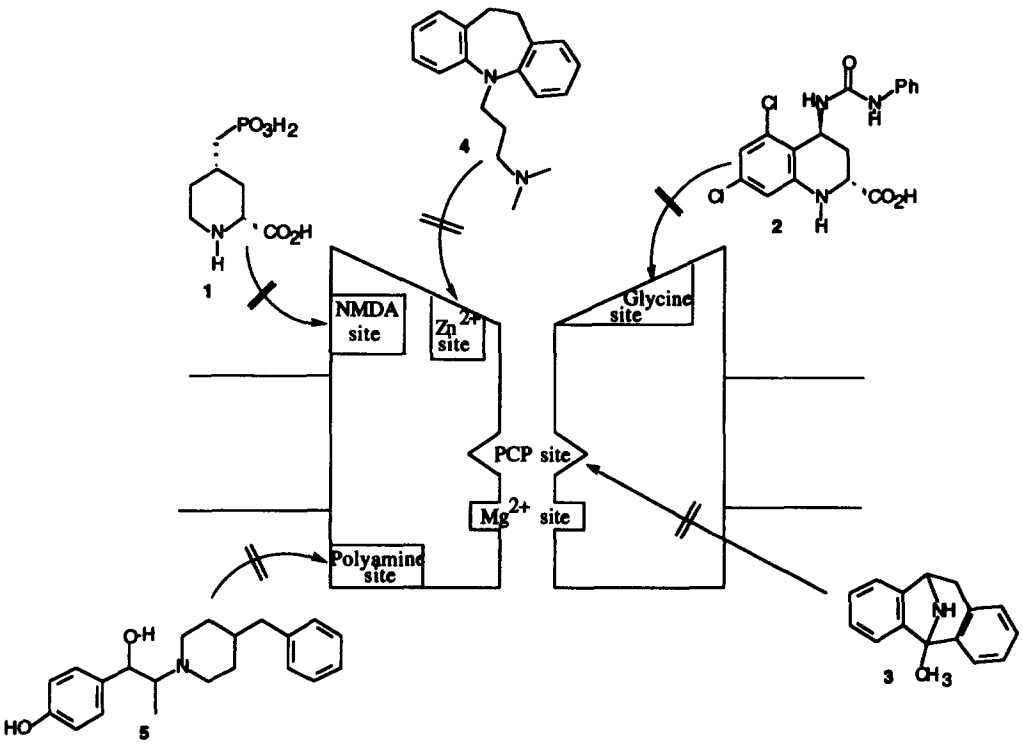



**Figure 1.** A representation of the NMDA receptor complex, showing the ion channel and associated agonist and antagonist binding sites, along with representative examples of antagonists acting at each of these sites.

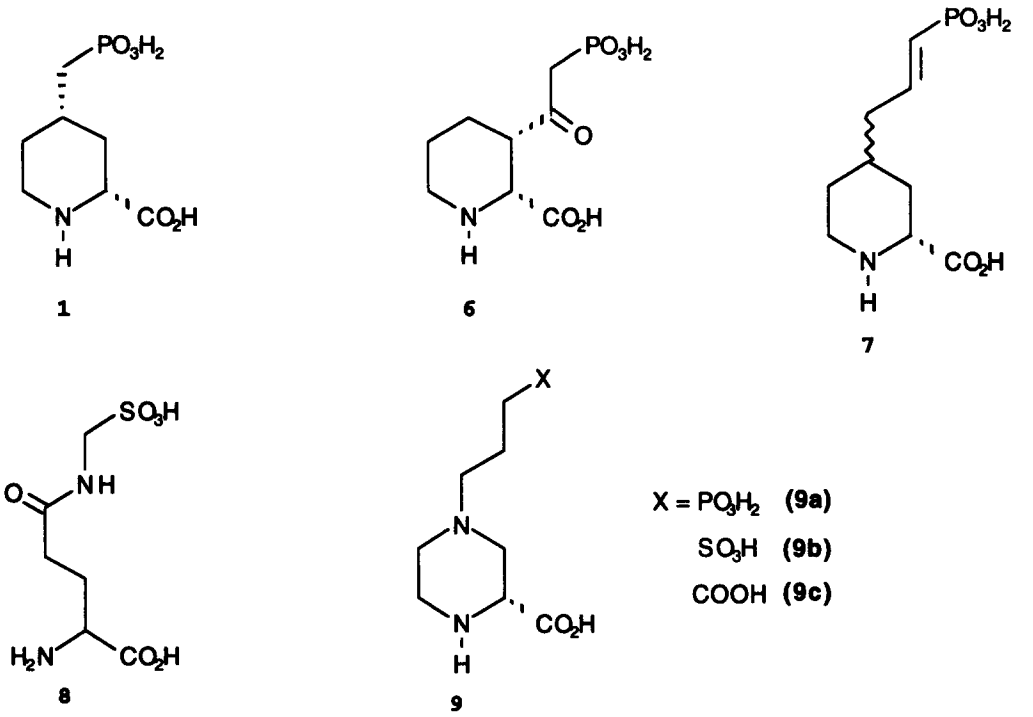



Chart 1.

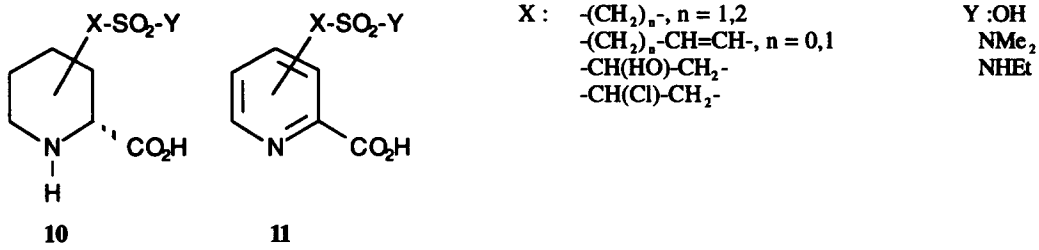



Chart 2.

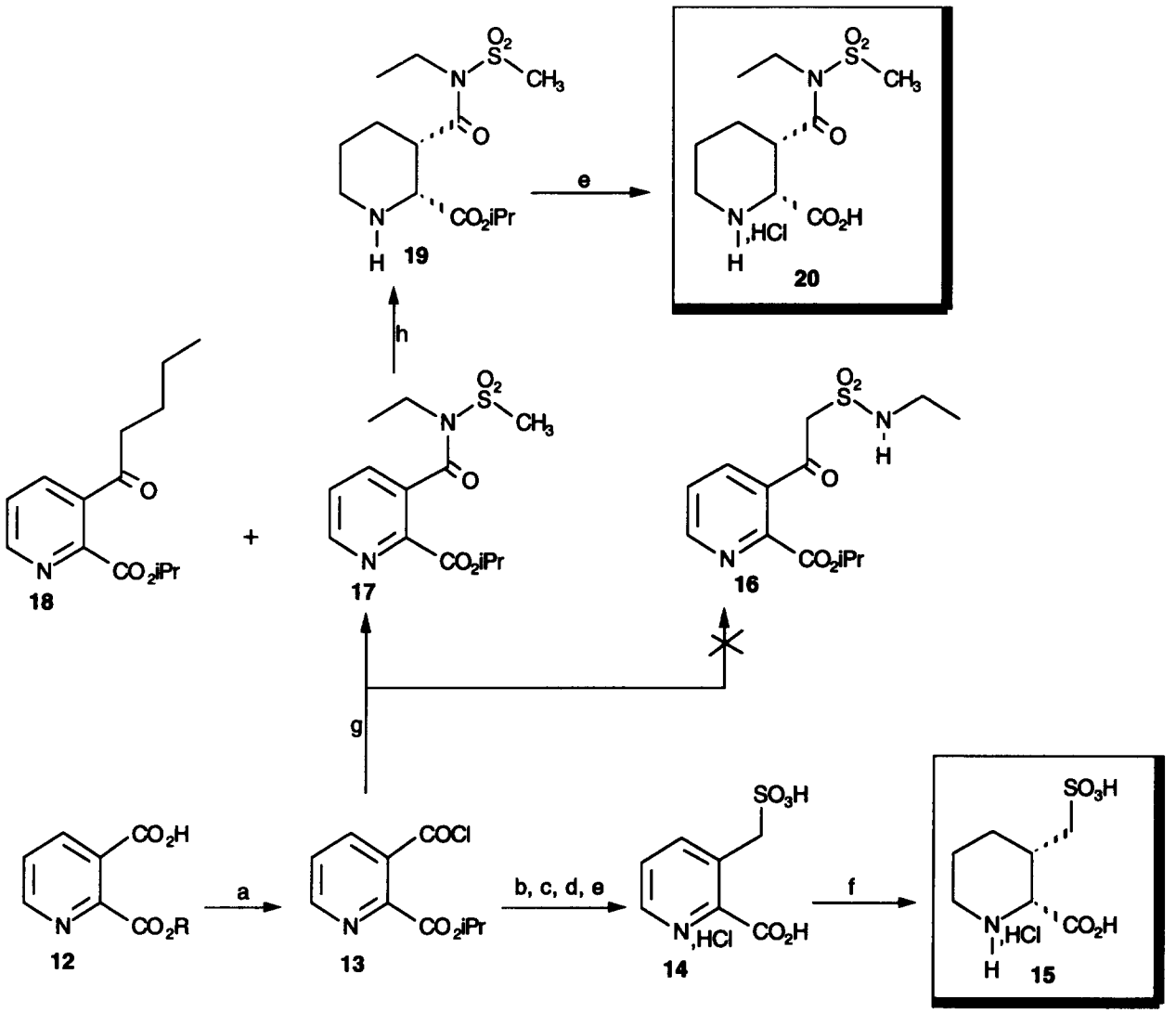
## Chemistry

The key compound in the preparation of *cis*-2,3-disubstituted piperidines **15** and **20** (Scheme 1) was the pyridine derivative **13**.[30] Selective reduction of the acid chloride function of **13** with sodium borohydride followed by bromination and substitution by $Na_2SO_3$ gave **14**, which upon reduction gave the *cis*-disubstituted piperidine **15** as described previously.[31] Treatment of **13** with *N*-ethylmethyl sulfonamide[32] and *n*-BuLi gave **17** (25% yield) accompanied by a substantial amount of ketone **18** (35%). Catalytic hydrogenation of **17**, followed by hydrolysis of the ester yielded the *cis*-piperidine **20**.

The synthesis of the 2,4-disubstituted compounds involved the preparation of the 2-cyano pyridine **26**.[33] The target compound **23** was obtained either by basic hydrolysis of the corresponding sulfonamides or by introducing the sulfonic acid function via the alcohol derivatives as described in Scheme 1. Thus sulfonamide **24** (Scheme 2) was prepared from picolyl chloride and dimethyl lithiomethylsulfonamide. This reaction also gave 22% of tripyridyl cyclopropane **25** previously described.[34] The sulfonamide **24** was converted to the acid **27** via the cyano analog **26**, and catalytically reduced ($PtO_2$) to *cis*-**28**. Further hydrolysis yielded the sulfonic acid **23**.

Pyridine 4-carboxaldehyde **29** was found to be suitable for the preparation of *cis*-sulfonamides bearing an alcoholic or an ethylenic function in the side-chain. Thus treatment of **29** with the dianion of *N*-ethylmethylsulfonamide (Scheme 3) gave 87% of **30**. Nitrile **31** and ester **32** were prepared by a procedure previously described in our laboratory.[31] Unexpectedly the treatment of **32** with 6 N HCl gave the chloro compound **33**. Catalytic reduction of **32** led to **35** in 95% yield, which upon dehydration under basic conditions ($NEt_3$, $MeSO_2Cl$)[32] led to **37**. Hydrolysis of the ester led to the target compound **38**.

Compound **36** was prepared from **35** by basic hydrolysis. Compound **34** was obtained by catalytic reduction of the pyridine derivative **33**.




**Scheme 1.** (a) $SOCl_2$/reflux; (b) $NaBH_4$/THF/0 °C; (c) $Ph_3PBr_2/CH_2Cl_2$/25 °C; (d) $Na_2SO_3/H_2O$–DMF; (e) 6 N HCl/reflux/16 h; (f) $H_2$/15% $PtO_2$/60 psi; (g) $CH_3SO_2NHEt$, *n*-BuLi (2.5 M)/THF/–78 °C; (h) $H_2$, HOAc/$PtO_2$/60 psi.

Catalytic hydrogenation in $PtO_2$/HOAc of **21**[31] (Scheme 4) gave mixtures of *cis* and *trans* isomers as indicated by NMR and NOE experiments.[35] Protection of piperidines **39** and **40** by di-*tert*-butylcarbonate followed by pyridinium chlorochromate oxidation[36] gave excellent yields of **41** and **42**. The first strategy investigated for the synthesis of **45** was to prepare thealcohol **43** as described in Scheme 3 (**29–30**). All our attempts were unsuccessful.

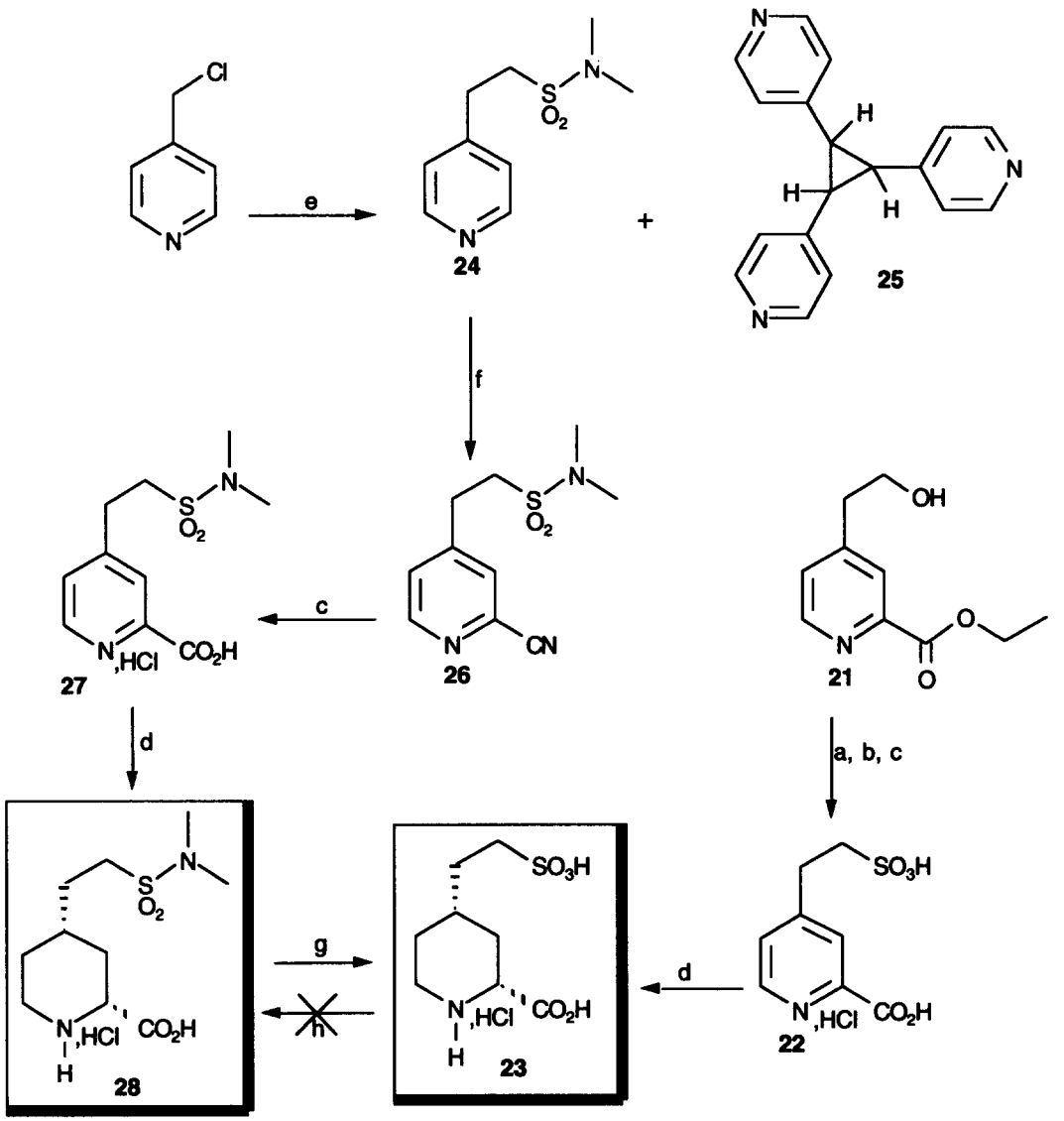
To circumvent this problem, the preparation of a new Wittig–Horner type reagent **44** was developed (Scheme 5). The desired compound **44** could only be prepared by reaction of *N,N*-dimethylmethyl sulfonamide and diethoxyphosphoryl chloride with *n*-BuLi in THF. Addition of the anion of **44** on aldehydes **41** and **42** followed by acidic treatments gave (*E*)-ethylenic sulfonamides **45** and **46** (Scheme 4).

## Pharmacology

All the amino acids were evaluated for their ability to displace [$^3$H]CGS-19755 (10 nM) binding,[37] as a measure of their affinity for the glutamate recognition site on the NMDA receptor complex, and the $IC_{50}$ or % displacement ($10^{-4}$ M) values determined are shown in Table 1.

Although the data are not shown, each of these compounds was also evaluated for its affinity at AMPA ([$^3$H]AMPA binding[38]) and KA ([$^3$H] KA binding[39]) receptors.

As a measure of *in vivo* NMDA antagonist activity, the most active compound, **11a** ($IC_{50}$ = 40 μM),[31] was evaluated for it's ability to protect mice from lethality induced by a 175 mg $kg^{-1}$ intraperitoneal injection of



**Scheme 2.** (a) $Ph_3PBr_2/CH_2Cl_2/25$ °C; (b) $Na_2SO_3/H_2O$–DMF; (c) 6 N HCl/reflux/16 h; (d) $H_2$/15% $PtO_2$/60 psi; (e) $CH_3SO_2NMe_2$, *n*-BuLi (1.6 M)/THF/–78 °C; (f) *m*-CPBA/$CH_2Cl_2$/25 °C, TMSCN, $Me_2NCOCl/CH_2Cl_2$/25 °C; (g) EtONa/EtOH/ reflux/16 h; (h) $SOCl_2$/reflux, $HNR_2/Et_2O$.

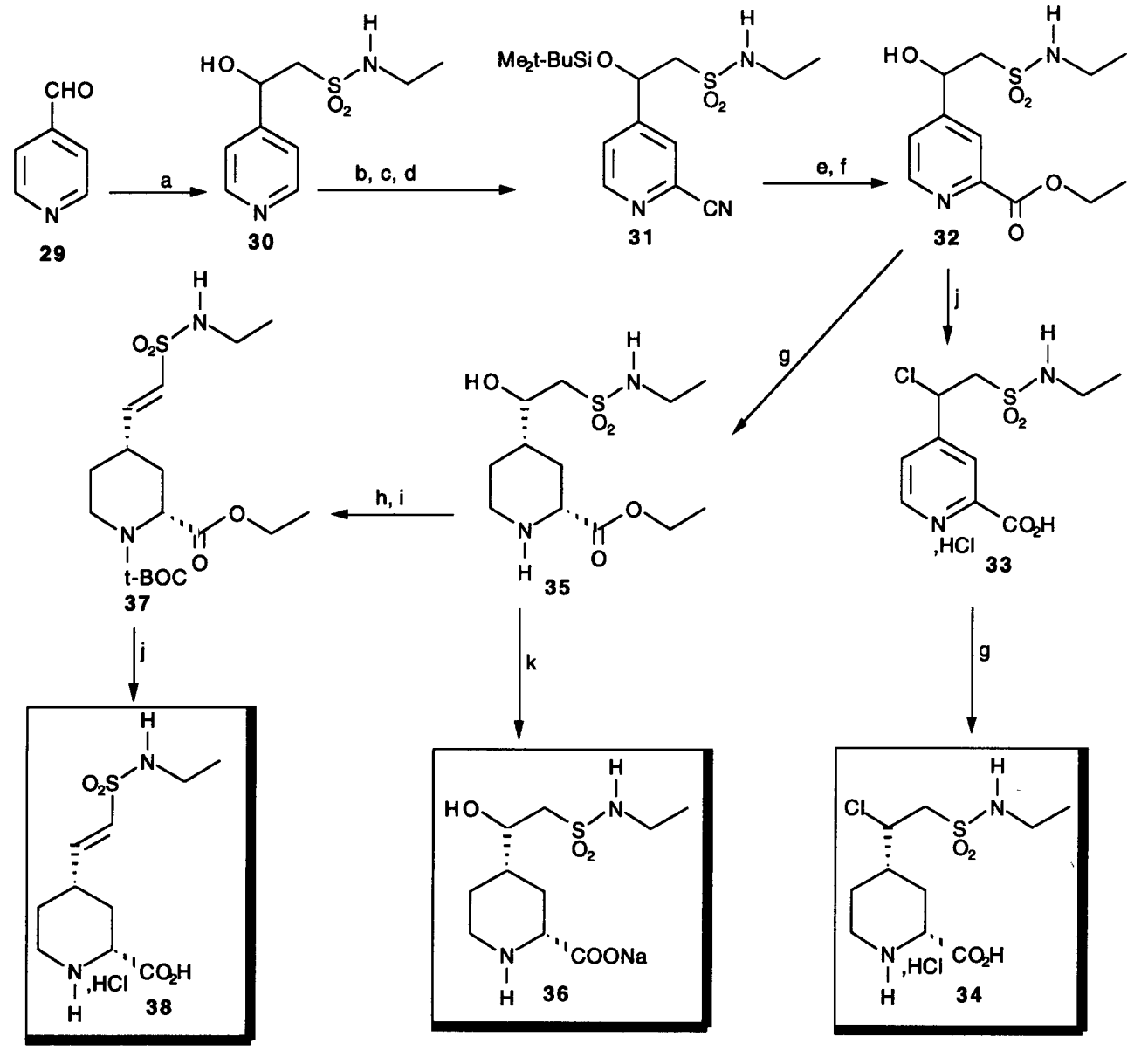
NMDA.[40] One hundred milligrams of **11a** was unable to protect the five animals tested from death.

## Discussion and Molecular Modeling

From this pharmacological study on some sulfonic derivatives as competitive NMDA antagonists, only one compound has been found to exhibit an activity, namely the pyridine compound **11a**, whereas the piperidine compound **10a** is poorly active. Both of these key results should be interestingly compared with the NMDA antagonist potency observed on the phosphonic analogs: the 4-(phosphonomethyl)pyridine-2-carboxylic acid **47** has been described as inactive,[30] whereas the sulfonic analog **11a** is active (40 μM). The opposite results have been obtained for the piperidine compounds: the sulfonic piperidine **10a** is poorly active, in contrast to the phosphonic derivative **1**, which is a well known NMDA antagonist (CGS-19755).

The assumption that a secondary sulfonamide function could mimic a phosphonic acid cannot be ruled out at the present time owing to there only being a few prepared compounds. Therefore, they will not be considered in computer modeling studies.

This discrepancy in the pharmacological activity between the sulfonic and phosphonic derivatives deserves special interest as it may reveal differences in the interaction of the potent antagonist with the NMDA receptor site. To go further into the interpretation of our results, compared to those already available in the literature, we have thus performed a thorough molecular modeling study. As a matter of fact, an extensive work has already been published on phosphonic derivatives,[41-43] in order to gain information on the conformational features of a potent agonist or antagonist, as well as on the binding sites of the NMDA receptor. In that context, we have carried out, in a first step, a comparative conformational study of the four com-




**Scheme 3.** (a) $CH_3SO_2NHEt$, *n*-BuLi (2.5 M)/–78 °C to –35 °C; (b) TDMSCl, imidazole/DMF/60 °C; (c) *m*-CPBA/$CH_2Cl_2$/20 h; (d) TMSCN, $Me_2NCOCl$/25 °C; (e) EtONa/EtOH/25 °C; (f) 6 N HCl/ 0 °C/24 h; (g) $H_2$, HOAc/15% $PtO_2$/60 psi; (h) $(t\text{-BOC})_2O/CH_2Cl_2$/24 h; (i) MsCl, $Net_3$; (j) 6 N HCl/reflux; (k) 1 N NaOH/25 °C/72 h.

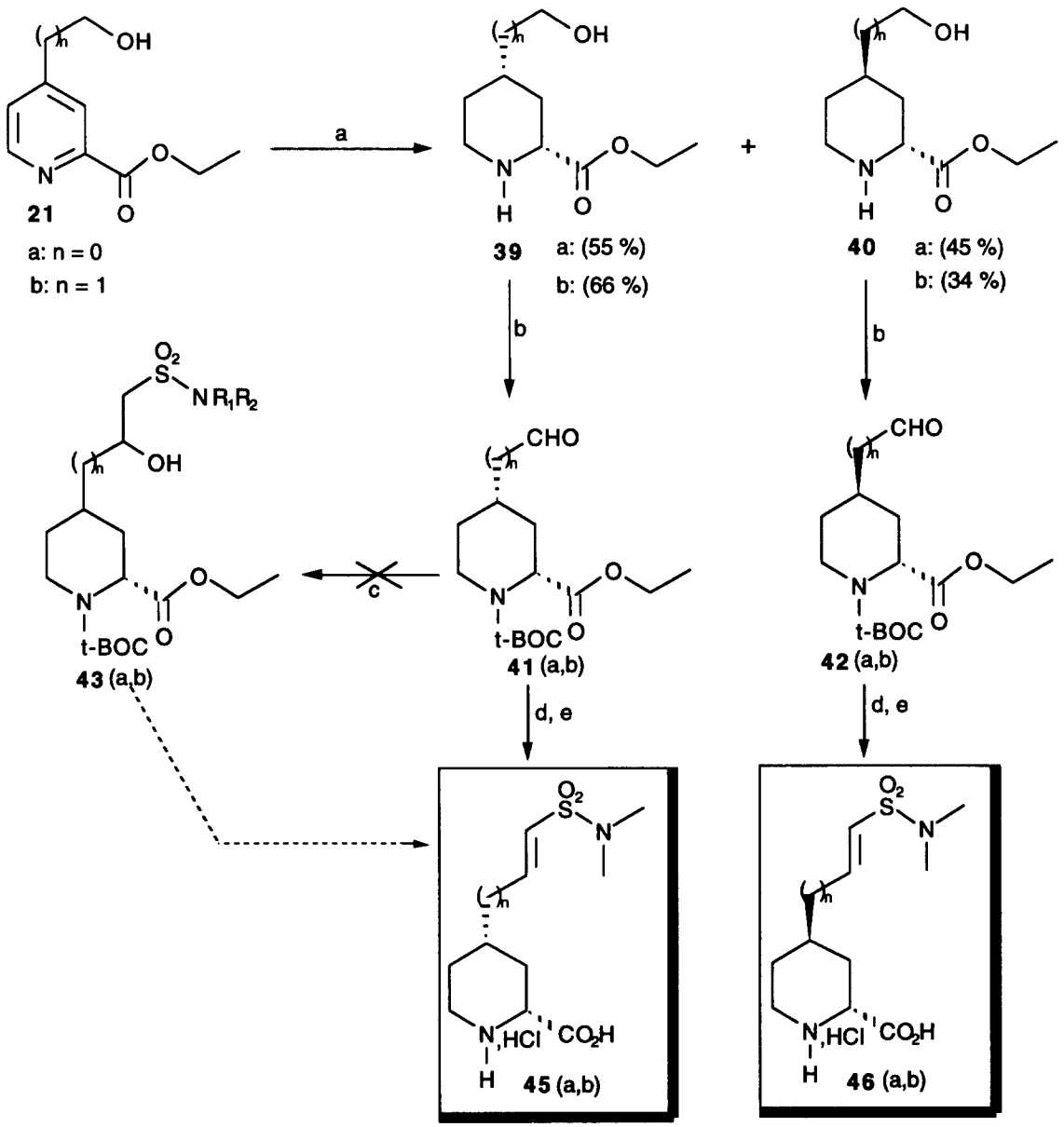
pounds **1**, **47**, **10a** and **11a**, in order to better understand the differences between sulfonic and phosphonic antagonists. In a second step, we have also performed comparative studies on the whole sulfonic series described in the first part of this paper, as well as on some sulfonic derivatives taken from the literature.[27,29]

*General features of the molecular modeling studies*

All the molecules described below have been built in fully extended conformations, then subjected to a full minimization. The *cis*-disubstituted piperidine derivatives, which contain two chiral centers, have been built with both absolute configurations, i.e. the α-carbon between the basic nitrogen and the carboxylic group in *R* and *S* configurations.

For 2,4-*cis*-disubstituted piperidine derivatives (**10a** and **23**), the starting point for conformational analyses was the minimized geometry with all equatorial substituents, as has been shown to be the case by NMR experiments (see Experimental). In the case of the 2,3-*cis*-disubstituted piperidine (compound **15**), two starting structures have been examined: one with the carboxylic group in axial and the methylsulfonic group in equatorial positions, and conversely the carboxylic in equatorial and the methylsulfonic group in axial positions. This was made for both absolute configurations, i.e. a total of four isomers was studied.

We have checked the influence of atomic charges on minimization and conformational analysis calculations for all the compounds described below. Charges were calculated by a semi-empirical method (see details in



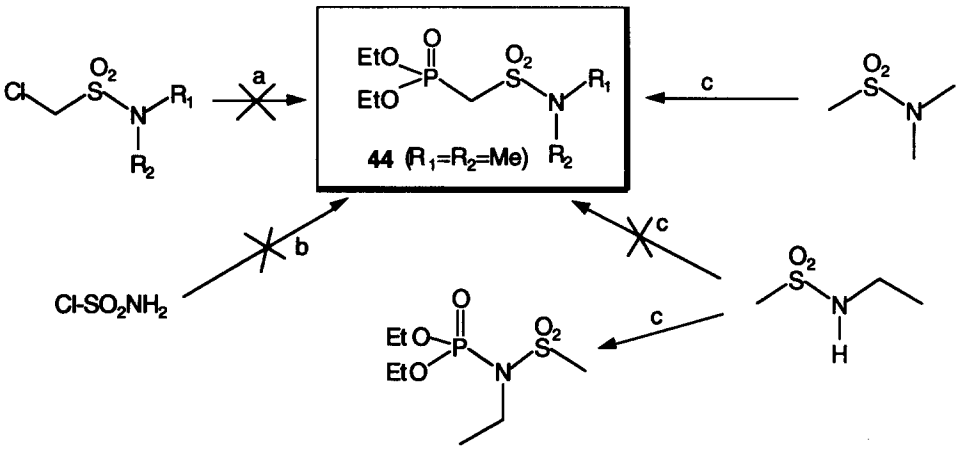

**Scheme 4.** (a) $H_2$, HOAc/15% $PtO_2$/60 psi; (b) $(t\text{-BOC})_2O/CH_2Cl_2$, PCC/$CH_2Cl_2$/3 h; (c) $CH_3SO_2NR_1R_2$, *n*-BuLi/THF/–78 °C to 25 °C; (d) $(EtO)_2POCH_2SO_2NMe_2$, *n*-BuLi/THF/–78 °C to reflux/16 h; (e) 6 N HCl/reflux/12 h.

the Experimental), with the generally accepted assumption[41–43] that all basic and acidic functions were completely ionized at physiological pH (7.4). The structures minimized, either with or without the electrostatic term derived from a Coulomb's law, were found to be identical. Thus all the results presented thereafter were obtained without considering the electrostatic term. We feel that at a first level, the interaction of a potent NMDA antagonist with the receptor site is mainly due to crucial conformational properties, even if this interaction is based on the presence of charges on specific interacting atoms. As a matter of fact, to exhibit an activity, the first requirement is that the molecule is able to adopt a particular conformation in order to bind to specific points within the receptor site. The influence of atomic charges could be invoked in a further step, to explain slight potency differences between NMDA antagonists already exhibiting a satisfactory binding conformation.

All details concerning the molecular modeling studies are reported in the Experimental.

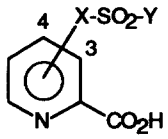
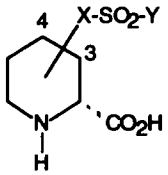
### *Comparative studies of 1, 47, 10a and 11a*

A systematic conformational search has been carried out on compounds **1**, **47**, **10a** and **11a**. The total energies thus found lie generally between 0–3 and 12–13 kcal $mol^{-1}$. Vector maps were then generated in order to visualize the region of space swept by a S–O or P–O bond. These maps are represented on Figure 2. An initial observation leads to the conclusion that the conformational states do not depend on the nature of the distal acidic group. Both pyridine derivatives (as




**Scheme 5.** (a) $(EtO)_3P$/reflux or $(EtO)_2POH$, NaH/THF; (b) $(MeO)_2POCH_3$, *n*-BuLi/THF/–78 °C to 25 °C then reflux; (c) *n*-BuLi (2.5 M)/THF/ –78 °C, $(EtO)_2POCl$.

**Table 1.** *In vitro* data for amino diacids

| formula | compd* | X | Y | $IC_{50}$ (μM) or % displacement ($10^{-4}$ M) versus [$^3$H]CGS-19755 |
|---|---|---|---|---|
|  | **11a** | 4-($CH_2$) | OH | 99% ($IC_{50}$ = 40 μM) |
| | **14** | 3-($CH_2$) | OH | 3% |
| | **27** | 4-($CH_2$)$_2$ | $N(CH_3)_2$ | 20% |
| | **33** | 4-(CHCl-$CH_2$) | NH-$C_2H_5$ | 0% |
|  | **10a** | 4-($CH_2$) | OH | 42% |
| | **15** | 3-($CH_2$) | OH | 15% |
| | **20** | 3-(CO-N-$C_2H_5$) | $CH_3$ | 19% |
| | **23** | 4-($CH_2$)$_2$ | OH | 19% |
| | **28** | 4-($CH_2$)$_2$ | $N(CH_3)_2$ | 17% |
| | **34** | 4-(CHCl-$CH_2$) | NH-$C_2H_5$ | 34% |
| | **36** | 4-(CHOH-$CH_2$) | NH-$C_2H_5$ | 18% |
| | **38** | 4-(CH=CH) | NH-$C_2H_5$ | 42% |
| | **45b** | 4-($CH_2$CH=CH) | $N(CH_3)_2$ | 40% |
| | **46b** | 4-($CH_2$CH=CH) | $N(CH_3)_2$ | 38% |
| CGS-19755 | 1 | | | $IC_{50}$ = 0.054 μM |

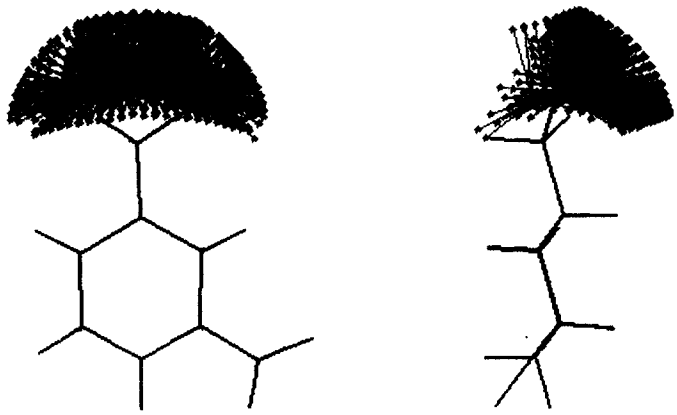
*All disubstituted piperidines are racemics.

well as both piperidine compounds) have the same conformations which can be perfectly superposed.

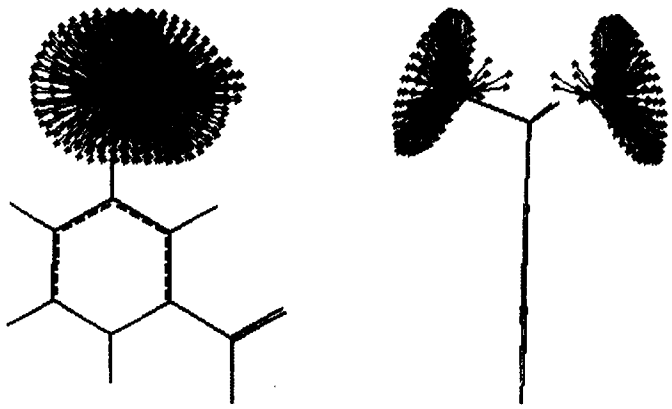
As mentioned above, an extensive modeling work has been published on phosphonic NMDA antagonists, and some conclusions were drawn[41–43] on the conformational state required for the potent antagonist to be able to bind to specific interaction points of the receptor site. Apart from the interaction points with the basic amine and the proximal carboxylate group, two other regions have been located, binded to two oxygen atoms of the phosphonate group. One of these receptor points was found to bind simultaneously to one oxygen of the phosphonate and to one oxygen of the carboxylate, and a secondary interaction point was found for the second oxygen atom of the phosphonate moiety. The resulting required geometry for the antagonist is, therefore, a 'folded' conformation where the phosphonate and carboxylate groups are located on the same side of the molecule (see Fig. 17 in Ref. 41).

The inactivity of the phosphono-pyridine **47** can be explained by examining its vector map (Fig. 2b). Two regions of space are available to the hydroxyl groups, on each side of the pyridine ring, but the region just 'above' the carboxylate group, in the plane of the aromatic ring, is inaccessible, and therefore the folded conformation necessary to bind to the specific points in the NMDA receptor is forbidden.

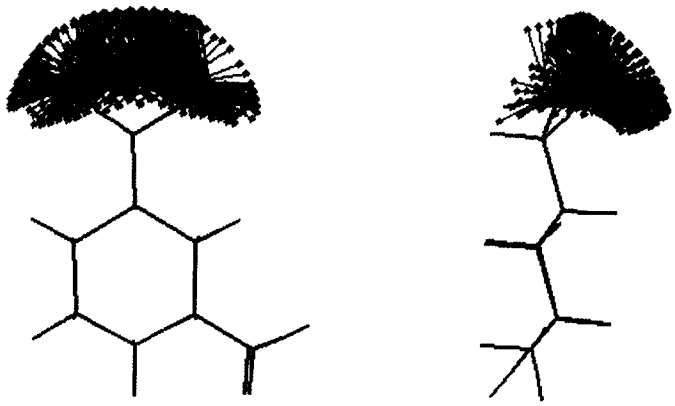
The poor activity of the sulfo-piperidine **10a** (Fig. 2c) which can exhibit this 'folded' conformation, could tentatively be explained by the lack of a second hydroxyl group, which forbids the binding to the secondary interaction point in the NMDA receptor site. But then, how to explain the higher activity of **11a** (Fig.



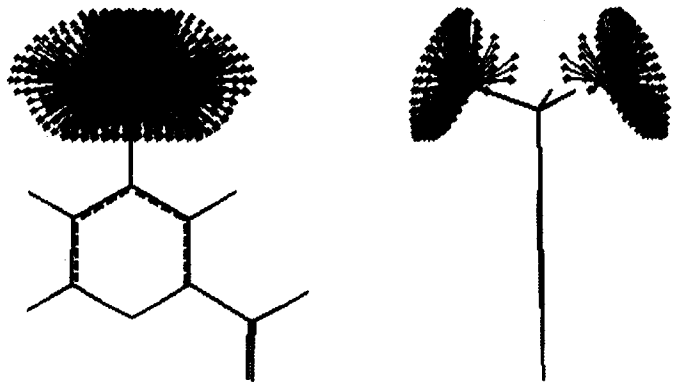
2a



2b



2c



2d

**Figure 2.** Orthographic views of the vector maps generated by a S–O bond for compounds **1**, **47**, **10a** and **11a** (respectively Fig. 2a–d).

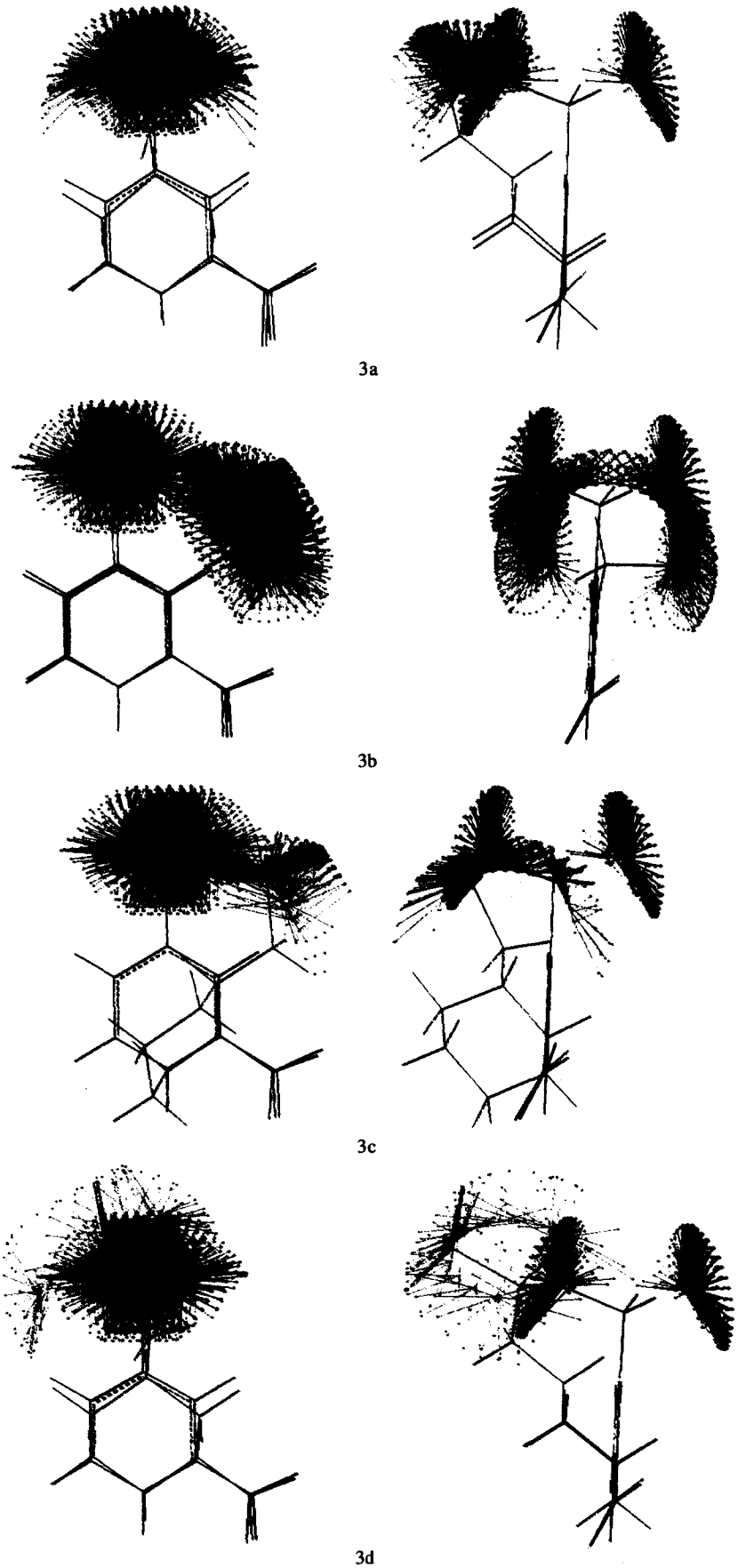



**Figure 3.** Superposition of vector maps of the active sulfonic compound **11a** with that of compounds **10a**, **14**, **15** and **23** (respectively Fig. 3a–d) displayed as orthographic views. Molecules are superposed as described in the text. In blue: vector maps of inactive compounds **10a**, **14**, **15** and **23**; in red: vector map of the potent antagonist **11a**.

2d), which cannot exhibit that so-called 'folded' conformation, claimed to be necessary to have a potent antagonist?

In order to take into account these new results, we feel necessary at this step to add a new assumption concerning the interaction of the sulfonate moiety with the NMDA receptor: the binding geometry of the sulfonate group must be different from that of the phosphonate moiety. In order to test this hypothesis, we have performed a comparative conformational study of all the sulfonate derivatives.

*Comparative modeling of sulfonic derivatives*

The active compound **11a** as well as the poorly active **10a** and the inactive derivatives **10a**, **14**, **15** and **23** were submitted to a systematic conformational analysis, with a systematic rotation of all C–C and the C–S bonds between the ring and the sulfonate group, and rotation of the bond between the ring and the carboxylate moiety (details of the procedure are given in the Experimental).

In the case of the piperidine derivative **15**, two conformational analyses were run: one with the carboxylate group in the equatorial position, the methylsulfonate substituent being thus in the axial position, and a second one with the carboxylate group in the axial position and the methylsulfonate substituent equatorial. In the first case, the structures were very hindered owing to the bulky methylsulfonate group in the axial position. The calculation gave only five low energy conformations (below 1000 kcal $mol^{-1}$). A combined procedure was tried, where each conformation found was further minimized: this gave more conformations, but with high energy values (100–300 kcal $mol^{-1}$). In the second case, the methylsulfonate group was in the equatorial position, and even with the carboxylate function in the axial position, the analysis gave numerous low energy conformations. This second more stable conformation has, therefore, been used for further modeling studies with both absolute configurations.

In order to point out, if possible, a difference between the conformational properties of **11a** and the conformational states of all other poorly active or inactive compounds, we generated the vector maps of one S–O bond, represented in Figure 3.

All the molecules have been represented with superposed basic nitrogen and $CO_2$ atoms, the vector maps of inactive compounds being in blue, whereas those of **11a** are in red. From the comparison of these vector maps, one region of space appears to be accessible only to the sulfonate group of compound **11a**, but is unattainable to all inactive compounds. This specific region is located on 'top' of the aromatic ring (as oriented on Fig. 3), and outside the pyridine plane. At this step, we can then suggest that an active sulfonic compound must be able to adopt a geometry which brings one of its S–O bonds in the specific region of the space thus defined. To test this hypothesis, we have modeled other potent sulfonic compounds taken from the literature.

*Conformational analysis of active sulfonic compounds*

Two active derivatives were found. The piperazine compound **9b**[27] and the homocysteic acid **48**,[29] which were built and minimized in fully extended conformations.

Compounds **11a**, **9b** and **48** were subjected to a common minimization procedure (namely a MULTIFIT: see Experimental for details) constrained by the superpositions of the nitrogen atom, the three atoms of the $CO_2$ moiety, the S and one of the O atoms of the $SO_3$ moiety. The homocysteic acid **48** was taken in both *R* and *S* configurations. Both substituents on the piperazine ring of compound **9b** were attached in an equatorial position.

The MULTIFIT procedure was able to converge to moderately low energy conformations where the key atoms described above are well superposed. We report in Table 2 the energy of the resulting conformation for each compound, together with the global minimum energy. In order to measure the quality of the superposition of the key atoms, we have also calculated the deviations of these atoms, in each multifitted conformation, to the average positions of the corresponding atoms, as determined from the four resulting conformations, as well as the root mean square deviation (RMS). We report in Table 2 the values found for the RMS and for the deviations of S and O atoms of the sulfonate group, for each multifitted compound. Both these atoms are important for the interaction with the receptor site, especially because we have assumed that they interact following a different geometry from that of the phosphonate group, and their exact positions must be clarified.

**Table 2.** Results of the MULTIFIT procedure of the four active compounds **11a**, **9b**, *S*-**48** and *R*-**48**: multifit energies (kcal $mol^{-1}$) global minimum energies (see text), deviations of the S and O atoms (Å), RMS deviation.

| Compound | MULTIFIT energy | Global minimum energy | Deviation of S position | Deviation of O position | RMS |
|---|---|---|---|---|---|
| **11a** | 4.0 | –0.6 | 0.05 | 0.07 | 0.06 |
| **9b** | 8.6 | 3.1 | 0.05 | 0.04 | 0.05 |
| *S*-**48** | 3.8 | 0.8 | 0.05 | 0.03 | 0.05 |
| *R*-**48** | 8.4 | 1.0 | 0.09 | 0.15 | 0.11 |

As can be seen, rather low values of RMS were obtained, which indicates that they all exhibit a good fit to this 'active geometry', maybe less pronounced in the case of the **R-48** derivative.

A stereoview of the four conformations is shown in Figure 4 which allows the visualization in three dimensions of the positions of the key atoms interacting with the receptor site. We can observe that the N, α-C and the $CO_2$ moiety are nearly coplanar and that the S–O group points forward toward the sheet.

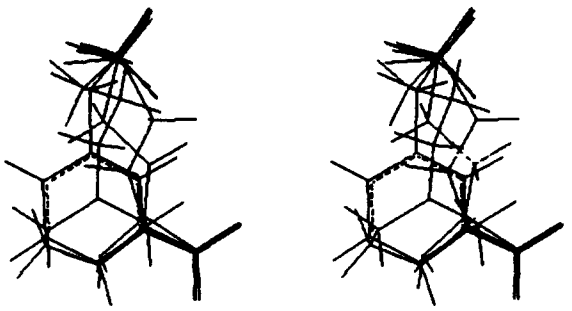


**Figure 4.** Stereo view of multifitted conformations of the active compounds **11a**, **9b**, *R*-**48** and *S*-**48**.

These four multifitted conformations, which correspond in our hypothesis to an 'active geometry', were then compared to the vector maps generated for inactive compounds **10a**, **14**, **15** and **23**. The basic amine, and the $CO_2$ atoms of the 'active geometry' were superposed to the corresponding atoms of each inactive compound. By generating the corresponding vector map, we observed that the S–O bond of the 'active conformations' were located out of the space accessible to the S–O bonds of all inactive compounds. This can be seen in Figure 5a–d, where the multifitted conformation of **10a**, and the vector map of each inactive compound in only one of its absolute configurations have been superposed.

Nevertheless, the generation of these vector maps was obtained by a simple conformational analysis, by systematically rotating the C–C bonds (or C–S bond) of the substituents of the pyridine or piperidine derivatives, and maintaining the ring itself fixed. In order to 'relax' this constraint, we have thus tried to find a minimized structure for each inactive compound described above, where the key atoms (N, $CO_2$, S and one oxygen of the $SO_3$ group) were approaching the positions of the 'active geometry' as closely as possible. To achieve this, each inactive compound was multifitted to this geometry, namely that of compound **11a**, while maintaining that structure rigid (see Experimental for details).

We report in Table 3 the resulting final energies for each of compound **10a**, **14**, **15** and **23**, and the global minimum energy, together with the deviations of the S and O atoms and the RMS, calculated from the 'active geometry' of **11a**. It can be clearly seen that the superposition of these inactive derivatives to the common geometry reached by all the active compounds is poor (RMS between 0.14 and 0.53).

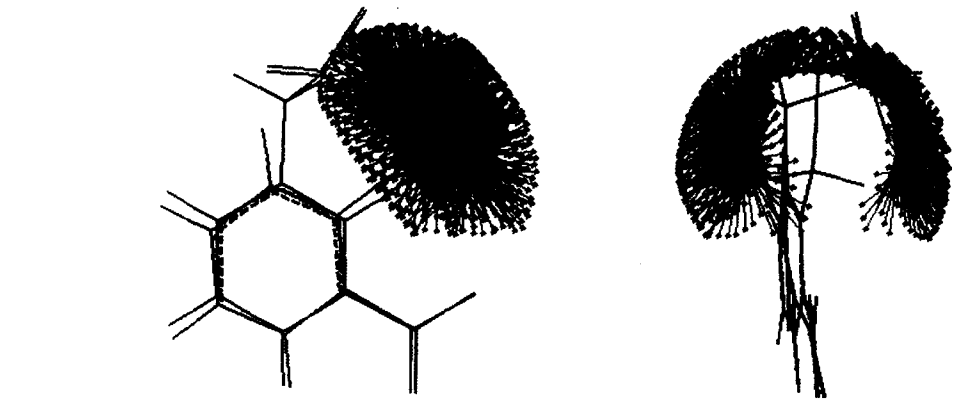
To further our comparative studies of active and inactive compounds, we have also tested four inactive sulfonic acid compounds taken from the literature:[29] the 2-amino-5-sulfopentanoic acid (**AS5**), the 2-amino-5-

**Table 3.** Results of the MULTIFIT procedure of the four inactive compounds **10a**, **14**, **15** and **23**: multifit energies (kcal $mol^{-1}$) global minimum energies, deviations of the S and O atoms (Å), RMS deviation

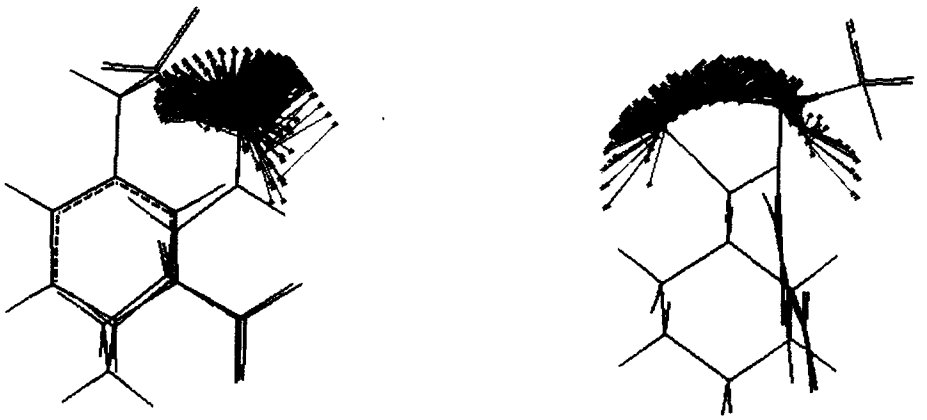
| Compound | MULTIFIT energy | Global minimum energy | Deviation of S position | Deviation of O position | RMS |
|---|---|---|---|---|---|
| **10a** (2*R*, 4*S*) | 5.3 | 1.6 | 0.25 | 0.17 | 0.18 |
| **10a** (2*S*, 4*R*) | 4.2 | 2.2 | 0.72 | 0.54 | 0.38 |
| **14** | 5.6 | 2.7 | 0.22 | 0.20 | 0.18 |
| **15** (2*R*, 3*S*) | 7.2 | 3.3 | 0.34 | 0.20 | 0.53 |
| **15** (2*S*, 3*R*) | 4.4 | 2.2 | 0.06 | 0.18 | 0.14 |
| **23** (2*R*, 4*S*) | 8.7 | 2.6 | 0.50 | 0.31 | 0.36 |
| **23** (2*S*, 4*R*) | 7.5 | 2.6 | 0.33 | 0.23 | 0.28 |

**Table 4.** Results of the MULTIFIT procedure of the four inactive compounds **AS5**, **AS6**, **AS7** and **AS8**: multifit energies (kcal $mol^{-1}$) global minimum energies, deviations of the S and O atoms (Å), RMS deviation

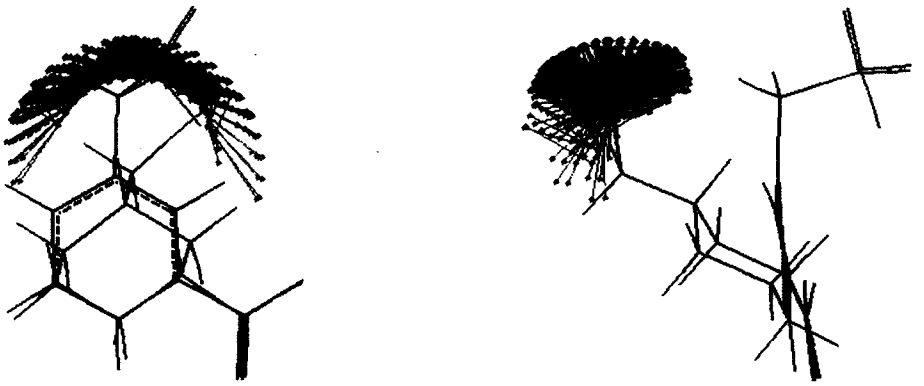
| Compound | MULTIFIT energy | Global minimum energy | Deviation of S position | Deviation of O position | RMS |
|---|---|---|---|---|---|
| *R*-**AS5** | 6.6 | 1.0 | 0.30 | 0.23 | 0.16 |
| *S*-**AS5** | 4.1 | 1.0 | 0.15 | 0.15 | 0.17 |
| *R*-**AS6** | 10.7 | 1.4 | 0.96 | 0.56 | 0.51 |
| *S*-**AS6** | 7.3 | 1.0 | 0.35 | 0.21 | 0.26 |
| *R*-**AS7** | 10.9 | 1.6 | 0.21 | 0.24 | 0.49 |
| *S*-**AS7** | 9.0 | 1.2 | 0.19 | 0.33 | 0.36 |
| *R*-**AS8** | 16 | 2.9 | 0.22 | 0.24 | 0.36 |
| *S*-**AS8** | 10.4 | 2.0 | 1.19 | 1.99 | 0.97 |



5a



5b



5c

5d

**Figure 5.** Orthographic views of the superposition of one of the 'active conformations' (namely that of derivative **11a**) with vector maps generated by each of the inactive compounds **10a**, **14**, **15** and **23** (respectively Fig. 5a–d).

sulfohexanoic acid (**AS6**), the 2-amino-5-sulfoheptanoic acid (**AS7**) and the 2-amino-5-sulfooctanoic acid (**AS8**). They were all subjected, in both *R* and *S* configurations to a MULTIFIT procedure with the 'active geometry' of compound **11a** maintained frozen. The following results are summarized in Table 4: energy of the multifit and of the global minimum energy, deviations of S and O atoms, as well as the RMS.

The affinity of **AS6**, **AS7** and **AS8** for the 'active geometry' is rather poor, an observation which is in good agreement with their complete inactivity ($IC_{50}$ > 500 μM).[29] It is somewhat better for the **AS5** derivative (RMS = 0.16 for the *R* configuration and 0.17 for the *S* configuration), which is a weakly active NMDA antagonist ($IC_{50}$ = 140 μM).[29]

Thus we have been able to find by modeling studies a spatial organization of the key atoms in the interaction with the NMDA receptor, which can be accomodated, at low energy cost, by all potent sulfonic derivatives. The inactive compounds do not present any low energy conformation able to reach this 'active geometry', whereas a weakly active compound has a low affinity, as it is reflected by the RMS.

In addition, we have reported in Figure 6 some interesting interatomic distances between the atoms of the $SO_3$ group and the basic nitrogen as well as the oxygen atoms of the $CO_2$ moiety, measured on the multifitted conformation of **11a**. It is clear that the $SO_3$ group is further from the $CO_2$ than the $PO_3$ group in phosphonic antagonists.[41]

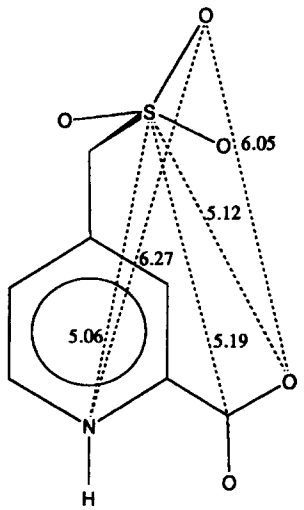



**Figure 6.** Interatomic distances shown on the 'active geometry' of compound **11a**.

Our results support the hypothesis that we had made on the specific geometry of interaction of potent sulfonic NMDA antagonists being different from that proposed for the active phosphonic compounds. Could this be due to the difference of electronegativity between S and P atoms or to the change of a dianion $PO_3^{2-}$ into a monoanion $SO_3^-$?

Of course, we cannot confirm that the 'active geometry' described here is the actual conformation of the active sulfonic derivatives, but it allows us to corroborate all the pharmacological results obtained on a series of such derivatives. In order to fully confirm this assumption, it would be interesting to elaborate new potent sulfonic antagonists and to compare their modeling properties with the results presented here. As a complementary work, it would also be interesting to systematically study crystallographic structures of sulfonic substrates bound to a receptor site, in order to extract general binding geometrical features of the $SO_3$ moiety, as has been made for $PO_3$ containing substrates.[41]

## Experimental

All experiments were run under a positive pressure of dry nitrogen. Tetrahydrofuran (THF) was distilled from sodium prior to use. All other solvents and reagents were used as obtained. All melting points were determined on a Kofler bench and are uncorrected. $^1H$ NMR spectra were obtained on a JNM-PM x 60 SI at 60 MHz and a Bruker AC 200 FT at 200 MHz. $^{13}C$ NMR, COSY and NOE were obtained on a Bruker AC 200 FT with tetramethylsilane as an internal standard.

*3-(Sulfomethyl)pyridine-2-carboxylic acid (14).* A mixture of 15.7 g (75 mmol) of the monoester **12** in 80 mL of thionyl chloride was heated to reflux until the reaction was homogeneous and then concentrated *in vacuo*. Residual thionyl chloride was removed by dissolving the residue in THF and evaporating. This process was repeated twice. The resulting acid chloride was dissolved in 80 mL of THF and cooled to 0 °C. Sodium borohydride (2.86 g, 75 mmol) in 20 mL of THF was added and the resulting solution was stirred at 0 °C for 1 h. The reaction was carefully poured into ice and extracted with $CH_2Cl_2$. The extract was dried ($Na_2SO_4$) and concentrated *in vacuo* to give the crude alcohol which was purified by chromatography on a silica gel column with $CH_2Cl_2$:MeOH (95:5) as the eluent to give a yellow solid (8.5 g, 58%): mp 69 °C. This alcohol was converted to the sulfonic acid with 60% overall yield as described:[31] mp > 260 °C; $^1H$ NMR ($D_2O$, 200 MHz): δ 4.71 (2H, *s*), 7.91 (1H, *dd*, *J* = 4.65, 7.62 Hz), 8.48 (1H, *dd*, *J* = 1.63, 7.62 Hz), 8.52 (1H, *dd*, *J* = 1.63, 4.65 Hz); $^{13}C$ NMR ($D_2O$): δ 51.22, 127.49, 132.0, 140.13, 144.27, 149.93, 163.07 ($CO_2H$).

*Isopropyl 3-[(N-ethyl,N-methylsulfonyl)carbamoyl]pyridine-2-carboxylate (17).* To a stirred solution of 3.1 g (25 mmol) of *N*-ethylmethylsulfonamide in 50 mL of dry THF was added 20 mL (50 mmol) of 2.5 M *n*-butyllithium in hexane in a dropwise manner at –78 °C, and the mixture was stirred for 2 h at –35 °C. To this solution cooled again at –78 °C was added a solution of 3.46 g (24 mmol) of acid chloride **13** in 30 mL of dry THF. After 30 min at room temperature, the reaction mixture was diluted with $H_2O$, and extracted with $CH_2Cl_2$. After drying over $MgSO_4$, the solvents were removed and the residue was purified by chroma-

tography on a silica gel column with EtOAc as the eluent to afford 1.9 g (25%) of **17** as a colorless oil. $^1$H NMR ($CDCl_3$, 200 MHz): δ 1.25 (3H, *t*, *J* = 7 Hz), 1.42 (6H, *d*, *J* = 6.2 Hz), 3.34 (*s*, 3H), 3.70 (2H, *q*, *J* = 6.95 Hz), 5.29 (1H, heptuplet, *J* = 6.1 Hz), 7.55 (1H, *dd*, *J* = 4.8, 7.81 Hz), 7.78 (1H, *dd*, *J* = 1.64, 7.81 Hz), 8.82 (1H, *dd*, *J* = 1.64, 4.76 Hz).

cis-*Isopropyl 3-[(*N-*ethyl,*N-*methylsulfonyl)carbamoyl]-piperidine-2-carboxylate (19).* A mixture of 1 g (3.12 mmol) of **17**, 0.13 g (0.6 mmol) of $PtO_2$, and 15 mL of HOAc was hydrogenated (60 psi) for 10 h at room temperature. After filtration through Celite and removal of the solvent the residue was dissolved in 20 mL of $CH_2Cl_2$ and stirred with excess $K_2CO_3$ for 1 h. After filtration and removal of the solvent the residue was purified by chromatography on silica gel with $CH_2Cl_2$:MeOH (20:1) as the eluent to afford 72% of the corresponding *cis*-piperidine derivative **19** as a colorless oil. $^1$H NMR ($CDCl_3$, 200 MHz): δ 1.25 (3H, *d*, *J* = 6.3 Hz), 1.27 (3H, *d*, *J* = 6.3 Hz), 1.30 (3H, *t*, *J* = 7.2 Hz), 1.50 (2H, *m*), 1.90 (1H, *m*), 2.28 (2H, *m*), 2.66 (1H, *m*), 3.26 (1H, *m*), 3.31 (3H, *s*), 3.51 (1H, *m*), 3.62 (1H, *d*, *J* = 3.9 Hz), 3.74 (1H, *sextet*, *J* = 7.1, 14.2 Hz), 3.90 (1H, *sextet*, *J* = 7.1, 14.1 Hz), 5.06 (2H, *quintet*, *J* = 6.3 Hz).

*4-(Sulfoethyl)pyridine-2-carboxylic acid (22).* The sulfonic acid **22** was synthesized from the alcohol ester **21** with 65% overall yield as described;[31] $^1$H NMR ($D_2O$, 200 MHz): δ 3.07 (*t*, 2H, *J* = 6.0 Hz), 3.73 (*t*, 2H, *J* = 6.0 Hz), 7.88 (*dd*, 1H, *J* = 1.25, 6.0 Hz), 8.15 (*d*, 1H, *J* = 1.25 Hz), 8.46 (*d*, 1H, *J* = 6.0 Hz).

*General procedure for the hydrolysis of esters and nitriles to carboxylic acids (the following example is representative)*

Isopropylester **19** was dissolved in 6 N aqueous HCl and heated to reflux overnight. The mixture was cooled and concentrated *in vacuo*. Ethanol was added, and the resulting solid was filtered, washed with EtOH and $Et_2O$, recrystallized from $H_2O$:$Me_2CO$ (2:8) and filtered as above to afford the desired amino acid **20**.

cis-*3-[(*N-*Ethyl,*N-*methylsulfonyl)carbamoyl]piperidine-2-carboxylic acid (20).* 79% yield; $^1$H NMR ($D_2O$, 200 MHz): δ 1.09 (3H, *t*, *J* = 7.1 Hz), 1.70 (4H, *m*), 2.82 (1H, *dt*, *J* = 3.13, 13.0 Hz), 3.21 (3H, *s*), 3.31 (1H, *dd*, *J* = 2.3, 13.0 Hz), 3.56 (1H, *sextet*, *J* = 7.1, 14.2 Hz), 3.77 (1H, *sextet*, *J* = 7.01, 14.2 Hz), 3.80 (1H, *m*), 3.91 (1H, *d*, *J* = 4.2 Hz); $^{13}$C NMR ($D_2O$): δ 13.95, 16.79, 23.09, 38.08, 41.38, 41.95, 43.19, 56.43, 169.94 (N-CO), 175.87 ($CO_2H$).

*4-(*N,N-*Dimethyl sulfonamidoethyl)pyridine-2-carboxylic acid (27).* 76% yield; $^1$H NMR ($D_2O$, 200 MHz): δ 2.64 (*s*, 6H), 3.27 (*t*, 2H, *J* = 7.0 Hz), 3.45 (*t*, 2H, *J* = 7.0 Hz), 7.85 (*dd*, 1H, *J* = 1.3, 6.0 Hz), 8.15 (*d*, 1H, *J* = 1.3 Hz), 8.46 (*d*, 1H, *J* = 6.0 Hz); $^{13}$C NMR ($D_2O$): δ 28.49, 36.26, 45.50, 126.15, 128.11, 140.11, 144.19, 160.56, 162.52 ($CO_2H$).

*4-(*N-*Ethyl-2-chloroethylsulfamoyl)pyridine-2-carboxylic acid (33).* 82% yield; mp 156–157 °C; $^1$H NMR ($D_2O$, 200 MHz): δ 0.94 (*t*, 3H, *J* = 7.2 Hz), 2.92 (*q*, 2H, *J* = 7.2 Hz), 3.47 (*d*, 2H, *J* = 5.9 Hz), 5.37 (*t*, 1H, *J* = 5.9 Hz), 7.99 (*dd*, 1H, *J* = 1.7, 6.0 Hz), 8.26 (*d*, 1H, *J* = 1.7 Hz), 8.54 (*d*, 1H, *J* = 6.0 Hz); $^{13}$C NMR ($D_2O$): δ 14.12, 37.47, 56.10, 66.96, 123.32, 125.30, 140.91, 144.58, 162.33, 162.59 ($CO_2H$). Anal. ($C_{10}H_{14}N_2O_4SCl_2$, $H_2O$) C, H, N, S.

cis-*4-[(*E)N-*ethylsulfonamidoethenyl]piperidine-2-carboxylic acid (38).* 68% yield; $^1$H NMR ($D_2O$, 200 MHz): δ 0.98 (*t*, 3H, *J* = 7.2 Hz), 1.44 (*m*, 2H), 1.87 (*m*, 1H), 2.24 (*dt*, 1H, *J* = 2.0, 13.0 Hz), 2.35 (*m*, 1H), 2.95 (*q*, 2H, *J* = 7.2 Hz), 3.39 (*dd*, 1H, *J* = 3.0, 12.6 Hz), 3.50 (*m*, 1H), 3.76 (*dd*, 1H, *J* = 3.0, 12.6 Hz), 6.29 (*d*, 1H, *J* = 15.4 Hz), 6.57 (*dd*, 1H, *J* = 6.1, 15.4 Hz).

*General procedure for the hydrogenation of pyridine derivatives*

The 3- and 4-(sulfo and sulfonamidoalkyl)pyridine-2-carboxylic acids were hydrogenated (60 psi) overnight with 10–20% by weight of $PtO_2$ in $H_2O$ at room temperature. The reaction mixture was filtered through Celite and concentrated *in vacuo* to afford a solid. $Me_2CO$ or MeCN was added, the precipitate was filtered and washed with MeCN and $Et_2O$.

cis-*3-(sulfomethyl)piperidine-2-carboxylic acid (15).* 81% yield; mp > 260 °C; $^1$H NMR ($D_2O$, 200 MHz): δ 1.62 (3H, *m*), 1.97 (1H, *m*), 2.69 (2H, *m*), 2.90 (2H, *d*, *J* = 7,0 Hz), 3.21 (1H, *m*), 3.97 (1H, *d*, *J* = 3.85 Hz); $^{13}$C NMR ($D_2O$): δ 17.19, 23.90, 31.05, 42.64, 48.39, 59.61, 172.00 ($CO_2H$). Anal. ($C_7H_{14}O_5ClN_5$, $H_2O$) C, H, N, S.

cis-*4-(Sulfoethyl)piperidine-2-carboxylic acid (23).* 84% yield; $^1$H NMR ($D_2O$, 200 MHz): δ 1.15 (*m*, 2H), 1.55 (*m*, 2H), 1.72 (*m*, 2H), 2.11 (*dd*, 1H, *J* = 2.6, 14.0 Hz), 2.79 (*m*, 3H), 3.25 (*dd*, 1H, *J* = 2.0, 14.0 Hz), 3.37 (*dd*, 1H, *J* = 2.6, 13.0 Hz); $^{13}$C NMR ($D_2O$): δ 26.88, 29.62, 31.91, 32.47, 42.79, 47.67, 58.61, 173.84 ($CO_2H$).

cis-*4-(*N,N-*dimethylsulfonamidoethyl)piperidine-2-carboxylic acid (28).* 96% yield; $^1$H NMR ($D_2O$, 200 MHz): δ 1.18 (*m*, 2H), 1.60 (*m*, 2H), 1.80 (*m*, 2H), 2.14 (*d*, 1H, *J* = 2.68, 14.2 Hz), 2.66 (*s*, 6H), 2.80 (*dt*, 1H, *J* = 2.68, 12.66, 14.0 Hz), 3.04 (*t*, 2H, *J* = 7.0 Hz), 3.27 (*dd*, 1H, *J* = 2.13, 14.0 Hz), 3.50 (*dd*, 1H, *J* = 2.68, 12.66 Hz); $^{13}$C NMR ($D_2O$): δ 26.70, 27.59, 31.31, 32.28, 36.41, 42.71, 43.87, 57.80, 172.68 ($CO_2H$). Anal. ($C_{10}H_{21}N_2O_4SCl$, $H_2O$) C, H, N, S.

cis-*4-(*N-*Ethyl-2-chloroethylsulfamoyl)piperidine-2-carboxylic acid (34).* 79% yield; $^1$H NMR ($D_2O$, 200 MHz): δ 0.90 (*t*, 3H, *J* = 7.1 Hz), 1.32 (*m*, 3H), 1.71 (*m*, 2H), 2.15 (*dt*, 1H, *J* = 2.2, 13.0 Hz), 2.70 (*m*, 1H), 2.86 (*q*, 2H, *J* = 7.1 Hz), 3.12 (*d*, 2H, *J* = 4.8 Hz), 3.32 (*m*, 1H), 3.74 (*m*, 1H); $^{13}$C NMR ($D_2O$): δ 14.15, 21.54 (23.48, 25.93, 27.58), 26.69 (29.45, 30.79, 31.97), 37.42, 38.56, 42.60 (42.70, 43.00, 47.55), 54.11, 55.92 (55.98, 56.02, 56.27), 68.20, 170.62 ($CO_2H$).

N,N-*Dimethyl-4-pyridylethylsulfonamide (24) and* N-*ethyl-2-hydroxy-2-(4-pyridyl)ethylsulfonamide (30).* To a stirred solution of 4.92 g (40 mmol) of methyl sulfonamide in 30 mL of dry THF was added 1 eq. (or 2 eq. in the case of secondary sulfonamide) of 2.5 M *n*-butyllithium in hexane in a dropwise manner at –78 °C. The mixture was then stirred for 2 h at –40 °C.To this solution cooled at –78 °C was added a solution of 40 mmol of 4-picolyl chloride (or pyridyl carboxaldehyde) in 30 mL of dry THF. After 30 min at room temperature the reaction mixture was diluted with water, and the aqueous phase extracted with $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$, the solvents were removed *in vacuo* and the residue was purified by chromatography on a silica gel column with ethyl acetate as the eluent.

**(24)**. 40% yield; mp 90–91 °C; $^1$H NMR ($CDCl_3$, 200 MHz): δ 2.88 (6H, *s*), 3.15 (4H, *s*), 7.16 (2H, *dd*, *J* = 1.34, 4.62 Hz), 8.55 (2H, *dd*, *J* = 1.34, 4.62 Hz).

**(30)**. 87% yield; mp 132–133 °C; $^1$H NMR ($CD_3OD$, 200 MHz): δ 1.17 (3H, *t*, *J* = 7.2 Hz), 3.11 (2H, *dq*, *J* = 1.37, 7.2 Hz), 3.32 (1H, *dd*, *J* = 4.2, 14.5 Hz), 3.42 (1H, *dd*, *J* = 8.0, 14.5 Hz), 5.18 (1H, *dd*, *J* = 4.2, 8.0 Hz), 7.50 (1H, *ddd*, *J* = 0.5, 1.64, 4.54 Hz), 8.51 (1H, *dd*, *J* = 1.64, 4.54 Hz). Anal. ($C_9H_{14}N_2O_3S$) C, H, N, S.

*Preparation of* N-*ethyl-2-[(*tert-*butyldimethylsilyl)oxy]-2-[4-(2-cyanopyridyl)] ethylsulfonamide (31) (includes general procedure for 2-cyanation of pyridines)*

A mixture of 5 g (21.7 mmol) of **30**, 4 g (24.5 mmol) of TBDMSCl, 2 g (27 mmol) of imidazole in 50 mL of dry DMF was heated at 60 °C for 5 h. The solvent was evaporated *in vacuo*, the residue was diluted with water and extracted with $CH_2Cl_2$. The organic layer was dried over $MgSO_4$ and the solvent evaporated *in vacuo* to give 7.38 g (99%) of the *O*-silyl intermediate as a yellow oil. To a solution of the above 4-(sulfonamidoalkyl)pyridine in 80 mL of $CH_2Cl_2$ was added *m*-CPBA (5.6 g, 32 mmol) over 15 min at room temperature. After stirring for 20 h more, the reaction mixture was washed with 1 N NaOH and extracted with $CH_2Cl_2$. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford the corresponding pyridine *N*-oxide. To this material dissolved in 60 mL of dry $CH_2Cl_2$ was added 2.76 g (28 mmol) of TMSCN and 2.56 g (28 mmol) of *N,N*-dimethylcarbamoyl chloride in 20 mL of dry $CH_2Cl_2$. After stirring for 24 h at room temperature, the reaction was carefully quenched with 40 mL of 10% aqueous $K_2CO_3$ and stirred for 15 min at room temperature. The organic layer was separated and the aqueous solution was extracted with $CH_2Cl_2$ (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on a silica gel column with EtOAc:cyclohexane (3:1) to afford 6 g (75%) of **31** as a white solid: mp 66–67 °C, $^1$H NMR ($CDCl_3$, 200 MHz): δ –0.12 (*s*, 3H), 0.15 (*s*, 3H), 0.90 (*s*, 9H), 1.19 (*t*, 3H, *J* = 7.2 Hz), 3.13 (*q*, 2H, *J* = 7.2 Hz), 3.18 (*dd*, 1H, *J* = 5.1, 14.5 Hz), 3.39 (*dd*, 1H, *J* = 7.66, 14.5 Hz), 5.26 (*dd*, 1H, *J* = 5.1, 7.66 Hz), 7.55 (*ddd*, 1H, *J* = 0.4, 1.63, 5.0 Hz), 7.75 (*dd*, 1H, *J* = 0.73, 1.63 Hz), 8.70 (*d*, 1H, *J* = 5.0 Hz). Anal. ($C_{16}H_{27}N_3O_3SSi$) C, H, N, S.

N,N-*Dimethyl-4-(2-cyanopyridyl)ethylsulfonamide (26).* 90% yield; mp 97–98 °C; $^1$H NMR ($CDCl_3$, 200 MHz): δ 2.90 (*s*, 6H), 3.19 (*s*, 4H), 7.42 (*d*, 1H, *J* = 5.0 Hz), 7.59 (*s*, 1H), 8.66 (*d*, 1H, *J* = 5.0 Hz).

*Ethyl 4-(*N-*ethyl-2-hydroxyethylsulfamoyl)pyridine-2-carboxylate (32).* A solution of sodium ethoxide was prepared from 0.144 g (63.3 g-atoms) of Na and 30 mL of dry EtOH, 14.2 g (38.4 mmol) of **31** in 80 mL of dry EtOH was added to this solution. After stirring for 20 h at room temperature, the reaction mixture was cooled at 0 °C and a solution of 6 N HCl (15.6 mL) was added. After stirring for 20 h at room temperature, a solution of 6 N NaOH (15.6 mL) was added (pH 6.5). The solvents of the reaction mixture were evaporated, the residue was diluted with $H_2O$ and 10% aqueous $NaHCO_3$, and the product was extracted with $CH_2Cl_2$. After drying over $Na_2SO_4$, the solvent was removed *in vacuo* and the residue was purified by chromatography on a silica gel column with EtOAc to give 11.6 g (75%) of **32** as a colorless oil. $^1$H NMR ($CDCl_3$, 200 MHz): δ 1.27 (*t*, 3H, *J* = 7.0 Hz), 1.45 (*t*, 3H, *J* = 7.2 Hz), 3.23 (*q*, 2H, *J* = 7.0 Hz), 3.28 (*dd*, 1H, *J* = 7.8, 18.0 Hz), 3.36 (*dd*, 1H, *J* = 3.9, 18.0 Hz), 4.49 (*q*, 2H, *J* = 7.2 Hz), 4.64 (*t*, NH, *J* = 5.0 Hz), 5.38 (*dd*, 1H, *J* = 3.9, 7.8 Hz), 7.56 (*dd*, 1H, *J* = 1.2, 5.0 Hz), 8.14 (*d*, 1H, *J* = 1.2 Hz), 8.75 (*d*, 1H, *J* = 5.0 Hz).

cis-*Ethyl 4-(*N-*ethyl-2-hydroxyethylsulfamoyl)piperidine-2-carboxylate (35).* Compound **32** was hydrogenated (60 psi) with $PtO_2$ in HOAc in the same manner as described for **19**, 95% yield; $^1$H NMR ($CDCl_3$, 200 MHz): δ 1.23 (*t*, 3H, *J* = 7.2 Hz), 1.28 (*t*, 3H, *J* = 7.1 Hz), 1.678 (*m*, 2H), 2.19 (*m*, 3H), 2.65 (*dt*, 1H, *J* = 2.4, 12.0 Hz), 3.24 (*m*, 6H), 4.01 (*m*, 1H), 4.19 (*q*, 2H, *J* = 7.1 Hz), 4.74 (*br*, OH).

cis-*4-(N-ethyl-2-hydroxyethylsulfamoyl)piperidine-2-carboxylic acid, sodium salt (36).* A mixture of 0.4 g (1.3 mmol) of **35**, 10 mL of EtOH and 2 mL (2 mmol) of 1 N NaOH was stirred at room temperature for 72 h. After lyophilization, the residue was washed with MeCN and $Et_2O$ to give 0.3 g (77%) of **36** as a white hygroscopic solid. $^1$H NMR ($D_2O$, 200 MHz): δ 0.88 (*m*, 2H), 0.91 (*t*, 3H, *J* = 7.2 Hz), 1.44 (*m*, 2H), 1.79 (*m*, 2H), 2.32 (*dt*, 1H, *J* = 3.0, 12.6 Hz), 2.83 (*q*, 2H, *J* = 7.2 Hz), 2.88 (*m*, 3H), 3.07 (*dd*, 1H, *J* = 12.6 Hz), 3.70 (*m*, 1H); $^{13}$C NMR ($D_2O$): δ 14.72, 25.58 (26.93), 30.46 (31.42), 37.84, 41.00, 43.55, 53.57, 59.81, 69.78 (69.90), 180.36 ($CO_2Na$).

cis-*Ethyl 1-(*tert-*butyloxycarbonyl)-4-[(*E*)*N*-ethylsulfonamidoethenyl]piperidine-2-carboxylate (37).* To a solution of 0.2 g (0.65 mmol) of **35** in 20 mL of dry $CH_2Cl_2$ was added 0.142 g (0.65 mmol) of di-*tert*-butyl carbonate. After stirring at room temperature for 24 h, all volatiles were removed *in vacuo* and the residue was

dissolved in 20 mL of $CH_2Cl_2$. To this solution was added 0.10 g (1 mmol) of $Et_3N$ and 0.052 mL (0.8 mmol) of mesyl chloride. After 16 h at room temperature, the solvents were evaporated, the residue was dissolved in 15 mL of $CH_2Cl_2$ and washed with $H_2O$ (2 × 5 mL). The organic layer was dried over $MgSO_4$, the solvent was evaporated and the residue was purified by chromatography on a silica gel column with EtOAc as eluent to afford 0.14 g (56%) of **37** as a colorless oil. $^1H$ NMR ($CDCl_3$, 200 MHz): δ 1.21 (*t*, 3H, *J* = 7.2 Hz), 1.23 (*m*, 2H), 1.26 (*t*, 3H, *J* = 6.4 Hz), 1.40 (*s*, 9H), 1.86 (*m*, 2H), 3.10 (*m*, 4H), 3.36 (*dd*, 1H, *J* = 2.0, 13.0 Hz), 4.02 (*m*, 1H), 4.17 (*q*, 2H, *J* = 7.2 Hz), 6.19 (*dd*, 1H, *J* = 4.4, 15.3 Hz), 6.67 (*dd*, 1H, *J* = 6.4, 15.3 Hz).

*Catalytic hydrogenation of 21*

A mixture of 24 mmol of **21**, 0.45 g (1.98 mmol) of $PtO_2$, and 90 mL of HOAc was hydrogenated (60 psi) for 12 h at room temperature. After filtration through Celite and removal of the solvent the residue was dissolved in $CH_2Cl_2$ and stirred with excess $K_2CO_3$. After filtration and removal of solvent the residue was subjected to flash chromatography on a silica gel column with $CH_2Cl_2$:MeOH (20:1 and 20:5) as the eluent to afford 80% of the *cis* and the *trans* isomers.

cis-*Ethyl 4-(β-hydroxyethyl)piperidine-2-carboxylate (39b).* 58% yield; colorless oil; $^1H$ NMR ($CDCl_3$, 200 MHz): δ 1.07 (*m*, 2H), 1.25 (*t*, 3H, *J* = 7.0 Hz), 1.50 (*q*, 2H, *J* = 6.4 Hz), 1.65 (*m*, 2H), 2.08 (*m*, 1H), 2.61 (*dt*, 1H, *J* = 2.4, 12.4 Hz), 3.14 (*ddd*, 1H, *J* = 1.9, 4.1, 12.4 Hz), 3.29 (*dd*, 1H, *J* = 2.8, 11.6 Hz), 3.67 (*t*, 2H, *J* = 6.4 Hz), 4.15 (*q*, 2H, *J* = 7.0 Hz).

trans-*Ethyl 4-(β-hydroxyethyl)piperidine-2-carboxylate (40b).* 29% yield; colorless oil; $^1H$ NMR ($CDCl_3$, 200 MHz): δ 1.13 (*m*, 2H), 1.27 (*t*, 3H, *J* = 7.1 Hz), 1.54 (*q*, 2H, *J* = 6.4 Hz), 1.69 (*m*, 2H), 2.09 (*m*, 1H), 2.66 (*dt*, 1H, *J* = 3.0, 12.3 Hz), 3.19 (*ddd*, 1H, *J* = 2.28, 4.1, 12.3 Hz), 3.33 (*dd*, 1H, *J* = 2.4, 11.6 Hz), 3.72 (*t*, 2H, *J* = 6.4 Hz), 4.18 (*q*, 2H, *J* = 7.1 Hz).

trans-*Ethyl 1-(*tert*-butyloxycarbonyl)-4-(methylformyl) piperidine-2-carboxylate (42b).* To a solution of 2.31 g (11.5 mmol) of **40b** in 30 mL of $CH_2Cl_2$ was added 2.51 g (11.5 mmol) of di-*tert*-butyl carbonate. After 20 h at room temperature all volatiles were removed *in vacuo* and the residue was dissolved in 40 mL of $CH_2Cl_2$ and treated with 4.3 g (20 mmol) of PCC. After stirring at room temperature for 3 h, the reaction mixture was filtered through a silica gel column with EtOAc:hexane (1:3) as the eluent to afford 2.78 g (81%) of **42b** as a colorless oil. $^1H$ NMR ($CDCl_3$, 200 MHz): δ 1.28 (*t*, 3H, *J* = 7.1 Hz), 1.44 (*s*, 9H), 1.59 (*m*, 3H), 1.96 (*m*, 3H), 2.42 (*m*, 2H), 3.33 (*dt*, 1H, *J* = 2.0, 13.0 Hz), 3.69 (*m*, 1H), 4.19 (*q*, 2H, *J* = 7.1 Hz), 9.74 (*t*, 1H, *J* = 1.33 Hz).

*N,N-Dimethyl(diethoxyphosphoryl)methylsulfonamide (44).* To a stirred solution of 2.5 g (20 mmol) of *N,N*-dimethyl methylsulfonamide in 15 mL of dry THF was added 8.8 mL (22 mmol) of 2.5 M *n*-butyllithium in hexane in the dropwise manner at –78 °C. The mixture was then stirred for 2 h at –40 °C. To this solution cooled at –78 °C was added a solution of 3.45 g (20 mmol) of diethoxyphosphoryl chloride in 20 mL of dry THF. After 1 h at room temperature the reaction mixture was diluted with $H_2O$, and the aqueous phase extracted with $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$, the solvents were removed *in vacuo* and the residue was purified by chromatography on a silica gel column with EtOAc:hexane (3:1) as the eluent to afford 4.4 g (85%) of **44** as a yellow oil. $^1H$ NMR ($CDCl_3$, 200 MHz): δ 1.37 (*t*, 6H, *J* = 7.0 Hz), 2.91 (*s*, 6H), 3.50 (*d*, 2H, *J* = 18.0 Hz), 4.20 (*q*, 2H, *J* = 7.0 Hz), 4.29 (*q*, 2H, *J* = 7.0 Hz).

trans-*4-[(1E)-(*N,N*-Dimethyl-3-sulfonamidoprop-2-enyl)]-piperidine-2-carboxylic acid (46b).* To a stirred solution of 0.88 g (3.4 mmol) of *N,N*-dimethyl(diethoxyphosphoryl)methylsulfonamide in 20 mL of dry THF was added 1.4 mL (3.4 mmol) of 2.5 M *n*-butyllithium in hexane in a dropwise manner at –78 °C. The mixture was then stirred for 1 h at –50 °C.To this solution cooled at –78 °C was added a solution of 0.93 g (3.1 mmol) **42b** in 10 mL of dry THF. After 30 min at room temperature the reaction mixture was refluxed for 18 h. After cooling, the reaction was concentrated *in vacuo*, diluted with $H_2O$ and the aqueous phase extracted with $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$, the solvents were removed *in vacuo* and the residue purified by chromatography on a silicia gel column with EtOAc:hexane (1:3) as the eluent to afford 0.95 g of the corresponding a,b-unsaturated sulfonamide. This material was refluxed for 16 h with 15 mL of 6 N HCl. The solvent was removed and the residue washed with MeCN and $Et_2O$ to give 0.73 g (76%) of **46b** as a white solid, mp 156 °C; $^1H$ NMR ($D_2O$, 200 MHz): δ 1.20 (*m*, 2H), 1.76 (*m*, 3H), 2.17 (*t*, 2H, *J* = 7.2 Hz), 2.53 (*s*, 6H), 2.83 (*dt*, 1H, *J* = 2.0, 13.0 Hz), 3.30 (*dd*, 1H, *J* = 3.0, 12.0 Hz), 3.71 (*dd*, 1H, *J* = 3.0, 12.0 Hz), 6.26 (*d*, 1H, *J* = 15.2 Hz), 6.60 (*dt*, 1H, *J* = 7.2, 15.2 Hz).

The amino acids **45a, b** and **46a** were synthesized in the same manner as described for **46b**.

## Molecular Modeling Studies

All modeling studies described here were performed with the program Sybyl 6.03,[44] running on a Silicon Graphics Iris 4D-20 workstation.

All molecules were constructed with Sybyl tools in fully extended conformations, then minimized with MAXIMIN2, with the standard parameters of minimization of the Tripos force field (powell minimizer).[45] As specified in the text, we have performed calculations either with or without charges. In the former case, the charges were calculated by a semi-empirical method (MNDO, in the MOPAC package included in Sybyl).

*Conformational analysis of compounds 1, 47, 10a and 11a*

We have used the systematic SEARCH module of Sybyl. Three rotatable bonds were defined: the bond between the ring and the $CO_2$ group, and the bonds attaching the distal acidic group ($SO_3$ or $PO_3$) to the ring, with angle increment of 10°. The starting conformation was, in each case, the minimized structure after building.

*Conformational analysis of compounds 10a, 14, 15 and 23*

The same conditions as described above were used for compounds **14** and **15**. For **23**, for which four rotatable bonds were defined, the increment for the bond connected to the $CO_2$ was 30°, and 20° for all other bonds.

*Modeling study of active sulfonic derivatives*

The MULTIFIT procedure of Sybyl was performed on the active sulfonic derivative **11a**, **9b**, *R*-**48** and *S*-**48**. A simultaneous minimization of the four molecules was achieved, by the MAXIMIN2 module (with standard parameters), with constraints of position on several key atoms: the basic nitrogen, the three atoms of the $CO_2$ group, the S and one of the O atoms of the $SO_3$ function. These six atoms were all constrained to superpose through the four molecules, with a spring constant of 20 kcal $mol^{-1}$ $Å^{-2}$.

The deviations of these atoms and the root mean square deviation (RMS) were calculated from the average positions of the six fitting atoms determined from the four resulting conformations. These calculations were made from the mol2 files which contain the cartesian coordinates of the molecules.

*Modeling study of inactive compounds*

The inactive compounds **AS5**, **AS6**, **AS7** and **AS8** were built then minimized with MAXIMIN2 in their fully extended conformation, in both *R* and *S* configurations. The resulting conformations were then used as starting points for the MULTIFIT procedure.

The entire conformation obtained by the precedent MULTIFIT on compound **11a** was defined as an aggregate, and each inactive derivative was multifitted to this geometry, by superposition of the six following atoms: the nitrogen of the basic amine, the three atoms of the $CO_2$ group, the S and O atoms of the $SO_3$ group, with spring constants of 20 kcal $mol^{-1}$ $Å^{-2}$.

The deviations of these atoms and the root mean square deviation (RMS) were calculated as described above.

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35. Examination of $^1$H NMR and COSY spectra of **39a** and **40a** permits the assignment of the stereochemistry of $C_2$ and $C_4$ substituents. However, for **39b** and **40b** only the $C_2$ stereochemistry could be determined from coupling constants measured on the $H_2$ signal (*dd* at $\delta = 3.29$, $J = 13$ and 2.3 Hz) allowing the assignment of an axial position to the proton $\alpha$ to the carboxylic acid. Due to the overlapping of the $H_4$ signal with protons of the adjacent $C_3$ and $C_5$ methylene groups, NOE was necessary to establish the stereochemistry of protons at $C_4$. Selective irradiation at $\delta$ 1.5 of the methylene signal $\beta$ to the OH group, indicates a mutual dependence of $H_{3a}$, $H_{5a}$ and $H_{3e}$ for **39b** (5% NOE for $H_{3a}$, $H_{5a}$ and 5.3% for $H_{3e}$) in agreement with a (±)*cis*-stereochemistry. For **40b** there was no NOE for $H_{3a}$, $H_{5a}$ and $H_{5e}$ and only a weak effect for $H_{2a}$ and $H_{6a}$ indicating a (±)*trans*-stereochemistry.

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