Pergamon

Bioorganic & Medicinal Chemistry 7 (1999) 921–932

BIOORGANIC & MEDICINAL CHEMISTRY

Synthesis and Benzodiazepine Receptor (ω Receptor) Affinities of 3-Substituted Derivatives of Pyrrolo[2,3-*c*]pyridine-5-carboxylate, a Novel Class of ω_1 Selective Ligands†

Xavier Doisy,[a] Mouloud Dekhane,[a] Mireille Le Hyaric,[a] Jean-François Rousseau,[a] Sunil K. Singh,[a] Suan Tan,[b] Valérie Guilleminot,[b] Hans Schoemaker,[b] Mireille Sevrin,[b] Pascal George,[b] Pierre Potier[a] and Robert H. Dodd[a,*]

[a]*Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique, 91198 Gif-sur-Yvette Cedex, France*
[b]*Synthelabo Research (L.E.R.S.), 31, Avenue Paul Vaillant Couturier, 92220 Bagneux, France*

Received 28 September 1998; accepted 30 December 1998

Abstract—Based on the structure of ZK91296 (**4d**), a high affinity partial agonist of the central benzodiazepine (ω) receptor, a series of pyrrolo[2,3-*c*]pyridine-5-carboxylate derivatives having mainly aralkyl and aralkyloxy substituents at C-3 was synthesized. The in vitro binding affinities of these compounds for three subclasses of the ω receptor (ω_1, ω_2, ω_5) were determined using rat brain tissue. Practically all of these compounds (except the diethyl ester derivative **22c**) showed an approximately twofold selectivity for ω_1 (IC_{50}'s in the 200–500 nM range) compared to ω_2 receptors and practically no affinity for ω_5 receptors. Compound **22c** showed the highest affinity of all the compounds synthesized ($IC_{50} = 70$ nM for ω_1 receptors) as well as a fivefold selectivity for ω_1 versus ω_2 receptors but also displayed significant binding to ω_5 receptors ($IC_{50} = 250$ nM). The absence of appreciable binding of 4-methyl and 4-methoxymethyl derivatives to ω receptors, in contrast to β-carbolines having these similarly located substituents, suggests that the pyrrolo[2,3-*c*]pyridine-5-carboxylates may be considered an entirely novel class of selective ω receptor ligands.

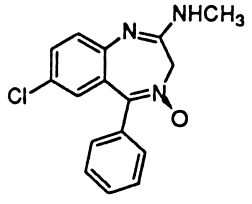
Introduction

It has now been almost 40 years since the introduction of the prototypic 1,4-benzodiazepines, chlordiazepoxide (Librium®, **1**) and diazepam (Valium®, **2**) for clinical use in the treatment of convulsions, anxiety and sleep disorders.[1] This class of compounds, now represented by a myriad of structural analogues, is still today one of the most highly prescribed drugs in the world.[2] Since their initial discovery, the ensuing study of the mechanism of action of 1,4-benzodiazepines has been marked by a number of key discoveries which have fueled further intense interest in the area and, significantly, led to the development of more efficacious and selective drugs. Thus, while an intimate connection between benzodiazepines and the γ-aminobutyric acid (GABA) inhibitory neurotransmitter system was convincingly demonstrated in the early 1970s,[3] it was not until 1977 that a pharmacologically relevant recognition site for benzodiazepines was discovered independently by several groups.[4] It also became clear that this recognition site, now commonly referred to as the benzodiazepine receptor (ω receptor or BZR), in fact resided on the GABAergic receptor complex itself, modulating the activity of the latter via allosteric interactions.[5] The use of radioligand binding techniques (mainly with tritiated diazepam) subsequently led to two major advances. The first was the discovery of the benzodiazepine receptor antagonist Ro 15-1788 (flumazenil, **3**).[6] The second advance was the observation that many classes of compounds structurally unrelated to 1,4-benzodiazepines could also bind with high affinity to the benzodiazepine receptor.[2b] While some of these compounds (e.g. the triazolopyridazine CL 218,872,[7] the pyrazoloquinoline CGS 9896)[8] exhibited to varying degrees the same pharmacological properties as 1,4-benzodiazepines, others, such as the methyl and ethyl esters of β-carboline-3-carboxylates (β-CCM, **4a** and β-CCE, **4b**) actually produced behavioral effects opposite to those of benzodiazepines. Thus, these β-carbolines were shown in rodents to be respectively convulsant and proconvulsant as well as anxiogenic.[9] These types of ligands were termed inverse agonists to distinguish them from the agonist benzodiazepines. At first sight the pharmacological profile of inverse agonists would seem to exclude them from possible therapeutic applications.

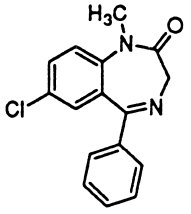
Key words: Pyrrolo[2,3-*c*]pyridine-5-carboxylate; benzodiazepine receptor; selectivity; synthesis; modeling.
*Corresponding author. Tel.: 33-1-69-82-45-94; fax: 01-69-07-72-47; e-mail: robert.dodd@icsn.cnrs-gif.fr
† This article is dedicated to the memory of our friend and colleague, Sir Derek Barton.

0968-0896/99/$ - see front matter
PII: S0968-0896(99)00053-X

However, the demonstration that β-CCM[10] facilitates memorization in animal models of learning, again in contrast to the well documented amnesic effects of benzodiazepines, suggested that inverse agonists of the BZR may in fact have a therapeutic future. The β-carbolines (as well as other compounds such as CL 218,872)[7] were also of paramount importance in showing that the benzodiazepine receptor, and by extension the GABA receptor, exists in multiple forms.[11] Various in vitro and in vivo techniques convincingly showed that β-carbolines bound to at least two different subclasses of benzodiazepine receptor, the BZ1 (or ω_1) and the BZ2 (or ω_2) receptors, having different molecular weights, ligand affinities and brain distributions.[12] The extremely powerful techniques of molecular biology and receptor cloning led, toward the end of the 1980s, to a much more complicated vision of the multiplicity of the GABA/benzodiazepine receptor system.[13] In the presently accepted model, the $GABA_A$ receptor is a supramolecular complex formed by five protein subunits of which at least 15 have so far been identified by cloning techniques. Based on the sequence homology of these proteins, they have been classified as α (6 isoforms), β (3 isoforms), γ (3 isoforms), δ and ρ (2 isoforms) subunits. GABA/benzodiazepine receptor subtypes would then result from the possibility of combining any five of these subunits into a functional entity.[14] In reality, using cloned subunits, it has been shown that the association of α, β, and γ subunits is the minimum requirement to produce benzodiazepine-responsive recombinant receptors.[15] The affinities, efficacies and presumably even the intrinsic activities (agonist or inverse agonist) of BZR ligands would then be controlled by the specific subunit compositions of each $GABA_A$ receptor subtype.[16] For instance, in the case of the BZ1 (ω_1) subtype, the predominant subtype found in mammalian cerebellum, the subunit composition corresponds to $\alpha_1\beta_2\gamma_2$.[14,17] However, little is known for the moment concerning either the regional composition and stoichiometry of different $GABA_A$ receptor subtypes in the brain or their precise physiological roles.



1



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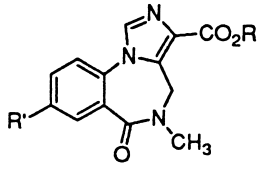
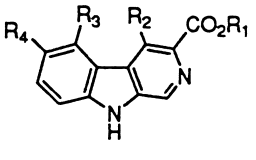
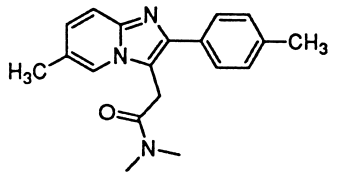


3

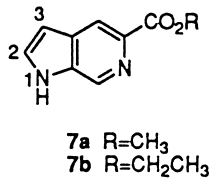
3 R=Et; R'=F
6 R=*t*-Bu; R'=C≡CH



4a $R_1=CH_3$; $R_2=R_3=R_4=H$
4b $R_1=CH_2CH_3$; $R_2=R_3=R_4=H$
4c $R_1=CH_2CH_3$; $R_2=CH_2OCH_3$; $R_3=H$; $R_4=OCH_2Ph$
4d $R_1=CH_2CH_3$; $R_2=CH_2OCH_3$; $R_3=OCH_2Ph$; $R_4=H$



5



7a R=CH_3
7b R=CH_2CH_3

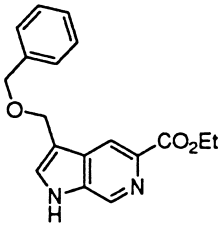
In order to obtain information concerning the contribution of each of the major subtypes of $GABA_A$ receptors to the multiple pharmacological properties of BZR ligands (e.g. anticonvulsant, anxiolytic, sedative–hypnotic, muscle relaxant and cognitive effects) the discovery of subtype-selective ligands remains today a major goal. Such selective ligands could also perhaps alleviate some of the major inconveniences of benzodiazepines such as dependence, ethanol potentiation and over-sedation. Some progress in this area has been made over the years. Thus, zolpidem (**5**) shows good selectivity for the ω_1 subtype of benzodiazepine receptors displaying only intermediate affinity for the ω_2 subtype (thought to be associated with $GABA_A$ receptors containing the α_2 or α_3 subunits) and very low affinity for ω_5 subtype (thought to be associated with the α_5 subunit).[18] Recently, ligands of type **6** selective for α_5-subunit containing receptors, were also described.[19]

With the objective of designing novel ligands of the benzodiazepine receptor possessing, ideally, good affinities, subtype selectivities and partial agonist properties, we have concentrated our efforts over the past years on the study of compounds having the β-carboline nucleus as a common motif.[20] This seemed reasonable in that it has been shown by others that in the form of the 6- and 5-benzyloxy 4-methoxymethyl derivatives ZK93423 and ZK91296 (**4c** and **4d**, respectively), all these qualities are united.[21] High benzodiazepine receptor affinities for β-carbolines in general are assured by (1) a completely aromatic nucleus, (2) a free indolic NH function, (3) a pyridinyl nitrogen at the 2 position and (4) a carbonyl group at C-3. Agonist, as opposed to inverse agonist activity, is conferred by a combination of substituents at C-4 (methoxymethyl) and C-5 or C-6 (benzyloxy).[22] Interestingly, while the analogue of **4c** devoid of the C-4 methoxymethyl chain maintains a good affinity for the benzodiazepine receptor, the resulting compound no longer displays agonist activity in vivo.[21b] On the other hand, nothing is known about the contribution of the A-ring of the β-carboline nucleus to receptor affinity and selectivity. In this paper, then, we describe the synthesis of compounds having the 6-azaindole-5-carboxylate nucleus (i.e., **7**) as a common structural unit. While this nucleus represents the β-carboline skeleton devoid of the A-ring, it still maintains the minimal structural characteristics enumerated above which allow binding of β-carbolines to the benzodiazepine receptor. In order to provide further anchoring points for the 6-azaindole derivatives on the binding site, substituents were incorporated at C-3 mimicking the benzyloxy moiety of ZK91296 (**4d**). Molecular modeling studies defining the target molecules, synthesis

of the latter and the determination of their binding affinities for three different subclasses of the benzodiazepine receptor (ω_1, ω_2, ω_5) are described below.

Molecular modeling studies

By analogy with the active β-carboline ZK91296 (**4d**), our intention was to prepare 6-azaindole-5-carboxylate derivatives incorporating a phenyl group tethered to the C-3 position. While the exocyclic phenyl group of the rigid ZK91296 is relatively restricted in its movements, a phenyl group attached to the azaindole nucleus by a chain of three atoms would have considerably more flexibility. We thus decided to resort to simple computer assisted molecular modeling to ensure that any proposed structures had a reasonable chance, energetically-speaking, of adopting a conformation close to that of ZK91296, at least as far as the proposed phenyl group was concerned. Figure 1 shows minimized structures for ZK91296 obtained using Macromodel® software as well as for two candidate 3-substituted azaindole structures, one having a benzyloxymethyl group at C-3 (**8**), the other having a phenylpropene moiety at this position (**9**). Superposition of either **8** or **9** with ZK91296 showed surprisingly high positional concordance of the phenyl groups of both azaindoles with that of the β-carboline, especially for **9** (Fig. 2). Moreover, the tether functions of each azaindole also adopt a spatial geometry which mimics that of the C_5-O-CH_2 component of ZK91296.



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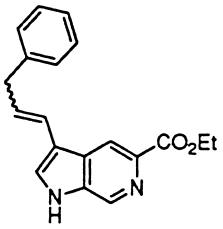


9

Each of the proposed azaindole structures presents certain characteristics which could be potentially advantageous to benzodiazepine receptor binding. Thus, azaindole **8** maintains the entire benzyloxy motif and although it has never been demonstrated in ZK91296 that the ether oxygen atom of the benzyloxy group actually takes part in receptor interactions, it is quite obvious that it by no means interferes with binding. On the other hand, azaindole **9**, unlike **8**, has a π-electron system which, as originally planned, was meant to partially recreate the π environment of the A-ring of the β-carbolines, no doubt an integral part of the receptor interactions of this class of high affinity compound. As it happens, though, our modeling studies show that the exocyclic double bond of azaindole **9** adopts a position which precludes superposition with the A ring of ZK91296. However, since it was felt that

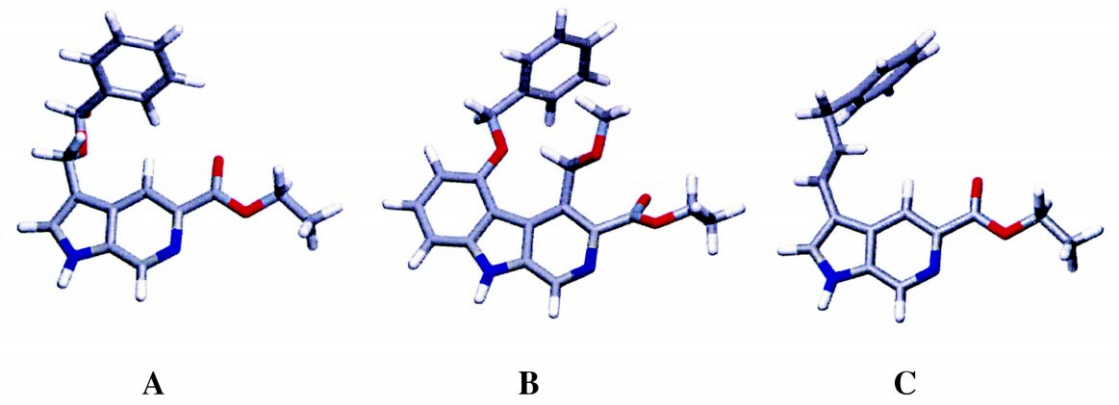


Figure 1. Minimized structures of (**A**) azaindole **8**, (**B**) ZK91296 (**4d**) and (**C**) azaindole **9**.

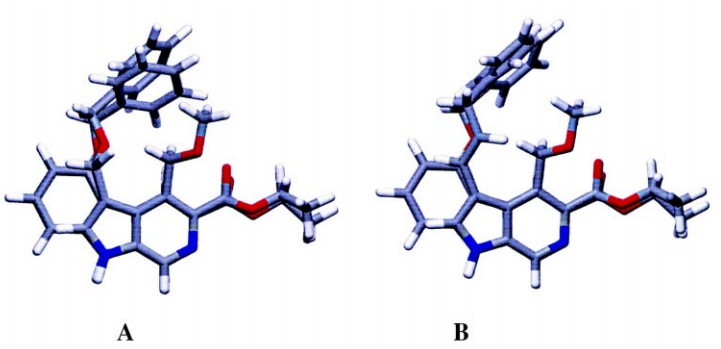


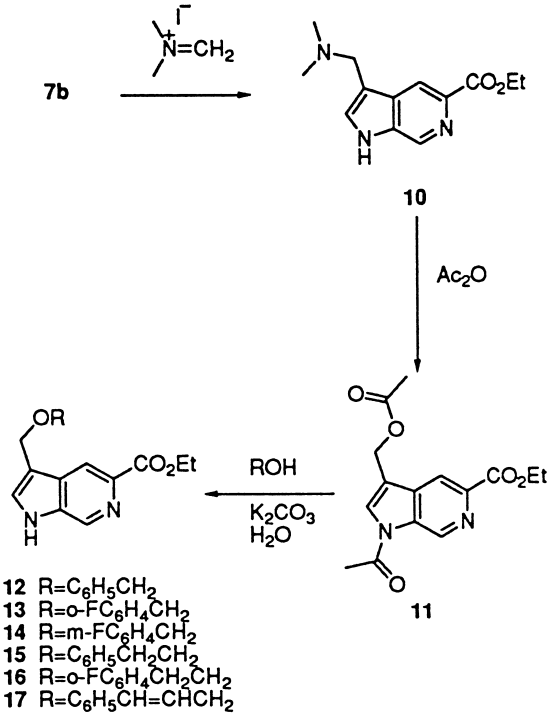
Figure 2. (**A**) Superposition of ZK91296 (**4d**) and azaindole **8**. (**B**) Superposition of ZK91296 (**4d**) and azaindole **9**.

both a π-electron system at C-3 and an ether oxygen atom could be beneficial to receptor binding, both types of azaindole **8** and **9** were synthesized and tested for benzodiazepine receptor affinity.

Chemistry

Two general routes were used to introduce substituents at C-3 of the starting ethyl 6-azaindole-3-carboxylate (**7b**).[23] In the first, azaindole **7b** was efficiently transformed into the azagramine derivative **10** by treatment with *N*,*N*-dimethylmethyleneammonium iodide (Eschenmoser's salt) in refluxing acetonitrile (Scheme 1). Compound **10** was then quantitatively converted into the *N*,*O*-diacetyl derivative **11** by the action of sodium acetate in acetic anhydride.[24] Compound **11** subsequently served as the reactive intermediate for the introduction at C-3 of phenyl ring-containing side-chains of varying lengths. Thus, **11** was dissolved in the given aralkyl alcohol (benzyl, phenethyl alcohols and fluorinated derivatives thereof as well as cinnamyl alcohol) and allowed to stir for 2–18 h in the presence of excess solid potassium carbonate and a trace of water, forming ethers **12**–**17**. *N*-Deacylation occurred concomitantly. The major side-products in these reactions arose from transesterification of the ethyl ester of **7b** by the aralkyl alcohol.

In the second approach, the 3-formyl-6-azaindole derivative **18** was first prepared from **7b** by reaction with 1,1-dichloromethyl methyl ether in the presence of aluminum chloride[25] (Scheme 2). Use of the more traditional Vilsmeier conditions for formylating indoles ($POCl_3$, DMF) failed to give any trace of **18** when applied to azaindole **7b**. Protection of the nitrogen function of compound **18** with a benzenesulfonyl group then gave **19**. Wittig condensations of **19** with benzyl-, phenethyl- and (carbethoxymethylene)triphenyl-phosphoranes provided the vinylic derivatives **21a**–**c**. While the diester **21c** was obtained exclusively in the *E* form, **21a** and **21b** were isolated as inseparable mixtures of the *E* and *Z* geometrical isomers, with the former predominating. Removal of the benzenesulfonyl protecting group of **21a**–**c** by treatment with sodium ethoxide in ethanol afforded azaindoles **22a**–**c**. Both **22a** and **22b** showed a tendency to isomerize to the *E* form when left in solution (e.g. in $CDCl_3$). Catalytic hydrogenation (palladium on carbon) of the exocyclic double bond of compounds **22a**–**c** provided the corresponding saturated derivatives **23a**–**c** in good yield.



Scheme 1.

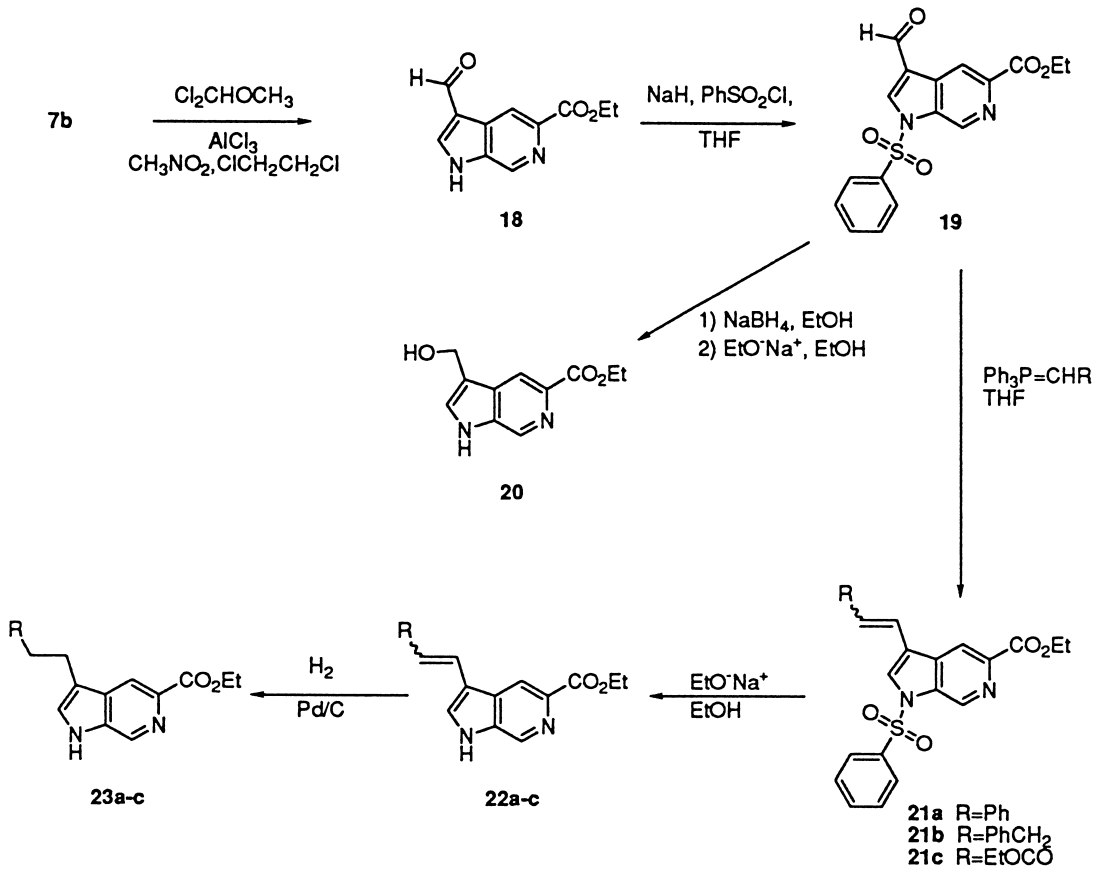
Reduction of the 3-formyl functionality of compound **19** using sodium borohydride in ethanol followed by *N*-deprotection of the product (EtONa/EtOH) afforded the 3-hydroxymethyl azaindole **20** in 33% overall yield. The synthesis of 4-methyl 6-azaindole-5-carboxylate **28** was accomplished using a methodology previously developed by us in the β-carboline area.[26] Thus, *N*-benzenesulfonylpyrrole-2-carboxaldehyde (**24**) reacted with methyl 2-amino-3,3-diethoxybutyrate in dichloromethane in the presence of triethylamine and molecular sieves to give an imine which was directly reduced to amine **26** with sodium cyanoborohydride (Scheme 3). Compound **26** was then cyclized using titanium(IV) chloride in refluxing benzene, affording the 4-methyl azaindole derivative **27** in 65% overall yield (from **24**). *N*-Deprotection of **27** was effected by the action of sodium methoxide in methanol, giving compound **28**. Treatment of the 4-methyl derivative **27** with *N*-bromosuccinimide and AIBN in CCl_4 produced the 4-bromomethyl compound **29** as the major product (61%). Treatment of **29** with sodium methoxide in methanol then resulted in simultaneous nucleophilic displacement of the bromide and *N*-deprotection, forming the 4-methoxymethyl azaindole derivative **30**.

In vitro binding assays

The concentrations of test compounds inhibiting 50% of tritiated flumazenil binding (IC_{50}) to selected rat brain tissues were determined in vitro using previously described techniques.[18c] Tissues were taken from the cerebellum, containing mainly the BZ_1 or ω_1-subtype of benzodiazepine receptor (i.e., α_1-subunit combining receptors), from the spinal cord, containing BZ_2 or ω_2 receptor subtypes (and which is actually a mixture of α_2-, α_3- and α_5-subunit combining receptors) and, finally, from the hippocampus, a source of mainly α_5-subunit containing receptors.[17a,c,27] Results of the binding assays are given in Table 1.

Results and Discussion

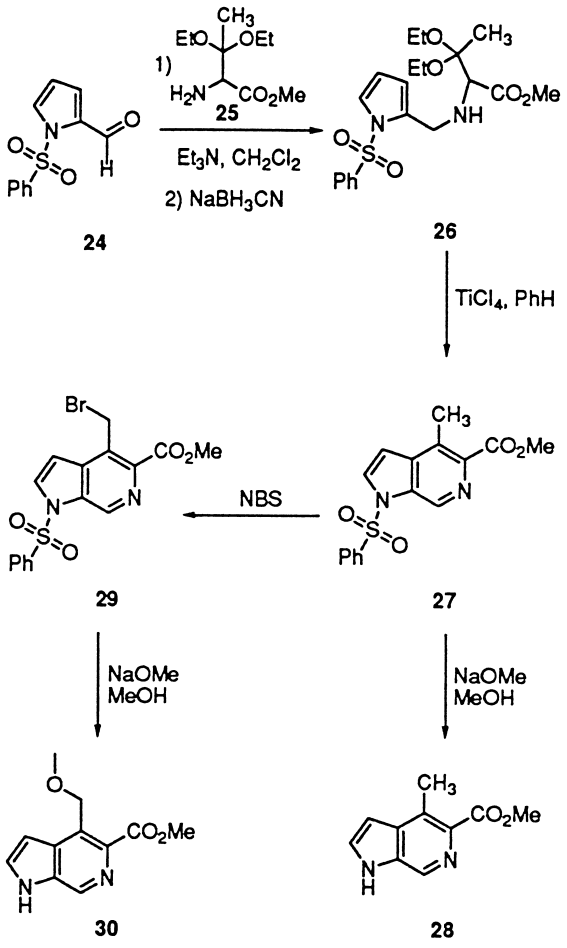
As shown in Table 1, ethyl 6-azaindole-5-carboxylate (**7b**) itself has very mediocre affinity for the BZR, showing IC_{50}s greater than 1 μM for all three subtypes of receptor (ω_1, ω_2, ω_5). A simple substitution at C-3, in the form of the formyl group, provides a compound (**18**) displaying significant binding to ω_1 and ω_2 receptors, with a twofold selectivity for the former (0.17 versus



Scheme 2.

0.39 μM, respectively). Interestingly, compound **18** showed practically no affinity for ω_5 receptors (i.e., $IC_{50} > 1$ μM). Reduction of the formyl group of **18** to the primary alcohol **20** abolished binding to ω_1 and ω_2 receptors, suggesting that a π-electron system at C-3 of azaindoles may be favorable to receptor binding. Both compounds **18** and **20** have oxygen atoms at C-3 though in the formyl derivative **18**, it is more likely to act as a hydrogen-bond acceptor in any eventual interactions with the receptor, in the same way as the equidistant ether oxygen of ZK91296 (**4d**). The primary alcohol of **20** would, however, most probably behave as a hydrogen bond donor, an apparently receptor-disfavored situation. This assumes, of course that the azaindole occupies the same receptor pocket as a β-carboline such as ZK91296 and that, moreover, the structural features common to both types of compounds are oriented in the same fashion with respect to the receptor. This assumption can, however, be disputed based on results to be discussed later. The binding profiles of the aralkyl ether series of compounds **12**–**15** were somewhat similar to that of the 3-formyl derivative, showing an approximately twofold selectivity for the ω_1 versus the ω_2 receptor subclass and negligible binding to ω_5 receptors. Thus, the simplest member of this group, the benzyloxymethyl derivative **12**, displayed ω_1 and ω_2 binding affinities of 0.31 and 0.76 μM, respectively. Incorporation of an *o*-fluoro substituent on the phenyl ring (compound **13**) produced a slight increase in affinity for the ω_1 receptor ($IC_{50} = 0.24$ μM) but a twofold increase for ω_2 ($IC_{50} = 0.32$ μM) with the overall effect of a decreased selectivity for the two receptor subclasses. On the other hand, substitution of the phenyl ring with a fluorine atom at the *meta* position (compound **14**) had only a mild effect on affinity for ω_1 and ω_2 receptors compared to the unsubstituted analogue **12**. Lengthening of the chain separating the phenyl group from the azaindole nucleus led to substantial loss of binding affinity, as demonstrated by results with the phenethyl derivative **15** ($IC_{50} = 0.56$ μM for ω_1) and the cinnamyl derivative **17** ($IC_{50} = 2.23$ μM for ω_1). Surprisingly, an attempt to improve the affinity of the phenethyl compound **15** by adding an *o*-fluoro substituent (analogous to the effect obtained by *o*-fluorination of **12**) led to quite the opposite effect, the product, compound **16**, being almost completely inactive. The combined steric effects of the extra carbon atom (relative to **12**) and the fluorine atom apparently override any positive electronic effects which the latter can offer.

Comparison of the latter binding results with those in which the ether linkage is absent (i.e., compounds **22a**,**b**, **23a**,**b**) shows that for the same tether length between the aromatic and heteroaromatic rings, equivalent or even superior affinities are obtained in the absence of the ether oxygen function, while the rank order of selectivities ($\omega_1 > \omega_2 \gg \omega_5$) is maintained. This effect is particularly flagrant in compound **22b**, in which the oxygen atom of the ether derivative **12** is replaced by an sp_2 carbon atom. Not only is the affinity of compound **22b**

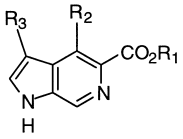


Scheme 3.

for ω_1 receptors improved compared to compound **12** (0.21 μM versus 0.31 μM), but its selectivity for this receptor subclass is also enhanced. Reduction of the double bond of **22b** (to give **23b**) maintains the same relative selectivity but produces some loss in ω_1 receptor affinity ($IC_{50} = 0.35\,\mu M$). Although this result would appear to lend credence to our working hypothesis that π-electron systems in this part of the molecule may tend to enhance receptor binding, a paradoxically different effect is observed in the case of the one-carbon shorter analogues **22a** and **23a**. In this case, saturation of the double bond leads to a minor gain in ω_1 receptor affinity, but an equally small loss in ω_2 receptor affinity. The effects of fluoro substituents on the aromatic rings of compounds **22a**,**b** and **23a**,**b** have not yet been investigated.

Two results were obtained, however, which have caused us to question our original premise that the 6-azaindole-5-carboxylate nucleus is recognized by the BZR in the same manner as β-carboline-3-carboxylates. Firstly, the most active of the 3-substituted azaindoles prepared in this study was actually the diethyl ester derivative **22c** ($IC_{50} = 70\,nM$ for ω_1), which is devoid of any phenyl group on the C-3 side-chain and is thus structurally very different from ZK91296 (**4d**), the molecular template serving as the starting point in our study. While it can be argued that the π-electron system of the ester function at C-3 of compound **22c** can mimic that of the C-5 benzyloxy group of ZK91296, interactions of these two functions with the receptor would probably be of a very different nature. Interestingly, while compound **22c** also shows the highest ω_1 to ω_2 selectivity of all the compounds synthesized (greater than fivefold), it is also the only azaindole derivative displaying any significant

Table 1. In vitro ω receptor binding affinities of the synthesized 3-substituted 6-azaindole-5-carboxylate derivatives



Compound	R^1	R^2	R^3	IC_{50} (μM)[a]		
				ω_1	ω_2	ω_5
7b	Et	H	H	> 1	> 1	> 1
12	Et	H	$PhCH_2OCH_2$	0.31	0.76	> 10
13	Et	H	*o*-$FPhCH_2OCH_2$	0.24	0.32	~10
14	Et	H	*m*-$FPhCH_2OCH_2$	0.39	0.60	> 10
15	Et	H	$PhCH_2CH_2OCH_2$	0.56	1.08	~10
16	Et	H	*o*-$FPhCH_2CH_2OCH_2$	> 1	> 1	> 1
17	Et	H	$PhCH=CHCH_2OCH_2$[b]	2.23	5.28	> 10
18	Et	H	CHO	0.17	0.39	> 1
20	Et	H	$HOCH_2$	> 1	> 1	> 1
22a	Et	H	PhCH=CH[b]	0.37	0.55	> 1
22b	Et	H	$PhCH_2CH=CH$[b]	0.21	> 1	> 1
22c	Et	H	(*E*)-EtOCOCH=CH	0.07	0.37	0.25
23a	Et	H	$PhCH_2CH_2$	0.32	0.62	> 1
23b	Et	H	$PhCH_2CH_2CH_2$	0.35	> 1	> 1
23c	Et	H	$EtOCOCH_2CH_2$	0.13	0.46	> 1
28	Me	CH_3	H	> 1	> 1	> 1
30	Me	CH_2OCH_3	H	> 10	> 10	> 10
Zolpidem	(**5**)			0.014	0.130	> 10
β-CCE	(**4b**)			0.0007	0.0061	0.13

[a]Determined by the method of refs 18c and 29, see Experimental.
[b]Predominantly the *E* geometrical isomer.

binding to ω_5 receptors. Saturation of the double bond of **22c**, to give **23c**, abolishes affinity for ω_5 receptors while affinity for ω_1 receptors is diminished only twofold.

Finally, very unexpected results were obtained with the 4-methyl and 4-methoxymethyl azaindoles **28** and **30**, respectively. Neither of these compounds demonstrated any significant binding to any of the three BZR subclasses studied. This is a major difference with the well-documented structure–activity relationships of β-carboline-3-carboxylates in which such groups are known not to interfere with binding to the BZR and in fact can actually enhance binding.[20c,21b,28]

Conclusion

The 3-substituted 6-azaindole-5-carboxylate derivatives described in this study represent a new class of benzodiazepine (ω) receptor ligands showing selectivity for the ω_1 subclass of receptors. While none of these compounds simultaneously shows as high an affinity and an ω_1 receptor selectivity as zolpidem (**5**), certain derivatives do demonstrate separately one or the other of these properties. Thus, the diethyl ester derivative **22c** possesses a good affinity for ω_1 receptors ($IC_{50} = 70$ nM, compared to 14 nM for zolpidem) as well as a fivefold selectivity for this receptor subclass with respect to ω_2 receptors (compared to a ninefold selectivity for zolpidem), but also shows appreciable binding to ω_5 receptors. On the other hand, both the 3-phenylpropenyl and 3-phenylpropyl derivatives (**22b** and **23b**, respectively) exhibit only modest affinities for ω_1 receptors ($IC_{50} = 210$ and 350 nM, respectively) but very good selectivity for this receptor subclass. Further structure–activity studies in this series should help pinpoint the structural characteristics which influence both of these properties. In this regard, while the high affinity β-carboline partial agonist ZK91296 (**4d**) originally served as our model in choosing the aralkyl substituents introduced at C-3 of the azaindole nucleus, it is now apparent, in view of some of the results obtained in this study (i.e., in particular, the unexpected lack of receptor binding by the 4-substituted azaindoles **28** and **30**) that the structural elements common to both the azaindoles and the β-carbolines are recognized by the ω receptor in a different manner. This implies that, in future work, any proposed structural modifications of these azaindoles, aimed at improving their affinities and selectivities, will not necessarily be guided by the well-documented structure–activity relationships in the β-carboline family of ω receptor ligands.

Experimental

Chemistry

General procedures. Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra of samples were obtained either as KBr pellets or as films with a Nicolet 205 FT-IR spectrometer. ^{1}H NMR and ^{13}C-NMR were determined on a Bruker 200, 250, or 300 MHz instrument. Chemical shifts are given as δ values with reference to Me_4Si as internal standard. Electron impact and chemical ionization mass spectra were recorded on an AEI MS-50 and AEI MS-9 spectrometer, respectively. High-resolution mass spectra were obtained using a Kratos MS-80 spectrometer. Thin-layer chromatography was performed on Merck silica gel plates with fluorescent indicator. The plates were visualized with UV light (254 nm) or with a 3.5% solution of phosphomolybdic acid in ethanol. All column chromatography was conducted on Merck 60 silica gel (230–400 mesh) at medium pressure (200 mbar). All reagents were purchased from the Aldrich Chemical Co. and were used without further purification. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette.

Ethyl 3-*N*,*N*-dimethylaminomethyl-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (10). A solution of compound **7b** (410 mg, 2.15 mmol) and *N*,*N*-dimethylmethyleneammonium iodide (439 mg, 2.37 mmol) in acetonitrile (25 mL) was refluxed for 12 h under argon. The reaction mixture was cooled, concentrated to near dryness under reduced pressure and the residue was taken up in CH_2Cl_2 and EtOH (25 mL of a 9/1 mixture). Saturated aqueous $NaHCO_3$ (10 mL) was added, the organic layer was separated and the aqueous layer was extracted with 9/1 CH_2Cl_2/EtOH (3×10 mL). The organic extracts were combined, dried (Na_2SO_4) and evaporated under reduced pressure, leaving a white solid (430 mg, 81%) which crystallized in $CHCl_3$: mp 128–130 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.46 (t, $J = 7.2$, 3H), 2.34 (s, 6H), 4.03 (s, 2H), 4.49 (q, $J = 7.2$, 2H), 7.67 (s, 1H), 8.57 (s, 1H), 9.12 (s, 1H), 12.81 (s, 1H, exchangeable with D_2O); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 17.0, 47.5, 54.0, 69.4, 113.1, 133.8, 135.2, 136.7, 137.8, 139.0, 166.7; IR (film) 1714 cm^{-1}. HREIMS calcd for $C_{13}H_{17}N_3O_2$ m/z 247.1319, found 247.1320.

Ethyl 3-acetoxymethyl-1-acetylpyrrolo[2,3-*c*]pyridine-5-carboxylate (11). A solution of the azagramine **10** (100 mg, 0.4 mmol) in anhydrous acetic anhydride (1.5 mL) containing dry sodium acetate (76.5 mg, 0.93 mmol) was refluxed for 4 h under argon. The reaction mixture was cooled, saturated aqueous $NaHCO_3$ (5 mL) was added and the solution was extracted with ethyl acetate (3×5 mL). The organic extracts were combined, dried (Na_2SO_4) and evaporated under reduced pressure. Traces of acetic anhydride were removed by repeated co-evaporation of the residue with toluene. The residual white solid (101 mg, 82%) could be used in the following steps without further purification: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.48 (t, $J = 7.2$, 3H), 2.09 (s, 3H), 2.70 (s, 3H), 4.51 (q, $J = 7.2$, 2H), 5.28 (s, 2H), 7.73 (s, 1H), 8.44 (s, 1H), 9.75 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.5, 20.9, 23.6, 56.9, 62.0, 116.6, 117.3, 129.0, 134.0, 135.3, 138.4, 142.1, 165.6, 167.9, 170.8; IR (film) 1735, 1725, 1709 cm^{-1}; EIMS m/z 304 $(M)^+$. Anal. ($C_{15}H_{16}N_2O_5$) C, H, N.

Ethyl 3-(benzyloxymethyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (12). A mixture of compound **11** (100 mg, 0.32 mmol), benzyl alcohol (1.5 mL), solid potassium carbonate (45 mg) and water (0.5 mL) was stirred for 10 h at rt. The reaction mixture was diluted with

dichloromethane (25 mL) and the solution was washed with water (2×5 mL). The organic layer was dried (Na_2SO_4), the solvents were removed under reduced pressure and the residue was purified by column chromatography on silica gel (CH_2Cl_2/EtOH, 95/5) affording compound **12** as a white solid (50 mg, 50%): mp 187–189 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48 (t, J=7.2, 3H), 4.52 (q, J=7.2, 2H), 4.60 (s, 2H), 4.84 (s, 2H), 7.37 (m, 5H), 7.78 (s, 1H), 8.61 (s, 1H), 9.23 (s, 1H), 12.12 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.7, 61.5, 63.7, 72.0, 114.2, 118.0, 127.8, 128.1, 128.6, 131.1, 132.4, 134.0, 135.6, 137.1, 179.3; IR (film) 2870, 1719 cm^{-1}; EIMS m/z 310 $(M)^+$. Anal. ($C_{18}H_{18}N_2O_3$.1/6 H_2O) C, H, N.

Ethyl 3-(*o*-fluorobenzyloxymethyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (13). A mixture of compound **11** (250 mg, 0.82 mmol), *o*-fluorobenzyl alcohol (1 mL), K_2CO_3 (80 mg) and water (100 μL) was stirred at rt for 4 h. The reaction mixture was then applied directly to a column of silica gel which was first developed with heptane until complete elution of the excess *o*-fluorobenzyl alcohol. Further elution of the column with CH_2Cl_2/EtOH (95/5) afforded compound **13** as a white solid (91 mg, 34%) which was crystallized in EtOH: mp 195–197 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.49 (t, J=7.2, 3H), 4.53 (q, J=7.2, 2H), 4.68 (s, 2H), 4.87 (s, 2H), 7.09 (t, J=9.5, 1H), 7.14 (t, J=7.4, 1H), 7.28 (m, 1H, partially hidden by $CHCl_3$), 7.45 (dt, J=1.5 and 7.4, 1H), 7.74 (d, J=1.5, 1H), 8.62 (s, 1H), 9.16 (s, 1H), 11.71 (br s, 1H, exchangeable with D_2O); IR (KBr) 1720 cm^{-1}; EIMS m/z 328 $(M)^+$. Anal ($C_{18}H_{17}N_2O_3F$.1/3 H_2O) C, H, N.

Ethyl 3-(*m*-fluorobenzyloxymethyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (14). A mixture of compound **11** (250 mg, 0.82 mmol), *m*-fluorobenzyl alcohol (1 mL), K_2CO_3 (80 mg) and water (100 μL) was stirred at rt for 18 h. The reaction mixture was then passed through a column of silica gel, which was developed first with hexane until complete elution of the excess *m*-fluorobenzyl alcohol and afterwards with CH_2Cl_2/EtOH (95/5), affording compound **14** (134 mg, 50%). The latter was obtained as white crystals from ethanol: mp 194–195 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.49 (t, J=7.2, 3H), 4.53 (q, J=7.2, 2H), 4.58 (s, 2H), 4.86 (s, 2H), 6.98–7.14 (m, 4H), 7.80 (s, 1H), 8.61 (s, 1H), 9.24 (s, 1H), 12.36 (br s, 1H, exchangeable with D_2O); IR (KBr) 1711 cm^{-1}; EIMS m/z 328 $(M)^+$. Anal. ($C_{18}H_{17}N_2O_3F$.1/3 H_2O) C, H, N.

Ethyl 3-[2-(phenyl)ethyloxymethyl]-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (15). A mixture of compound **11** (151 mg, 0.5 mmol), phenethyl alcohol (2.5 mL), K_2CO_3 (41 mg) and water (50 μL) was stirred for 7 h at rt. Water (10 mL) was added to the reaction mixture and the latter was extracted with CH_2Cl_2/EtOH (3×5 mL of a 95/5 mixture). The organic extracts were combined, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using heptane as developer until complete elution of the excess phenethyl alcohol. Further elution of the column with CH_2Cl_2/EtOH (9/1) afforded compound **15** as a white solid (65 mg, 40%): mp 162–164 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.50 (t, J=7.2, 3H), 2.94 (t, J=7.5, 2H), 3.74 (t, J=7.5, 2H), 4.55 (q, J=7.2, 2H), 4.81 (s, 2H), 7.23 (m, 5H), 7.77 (s, 1H), 8.59 (s, 1H), 9.24 (s, 1H), 12.73 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.6, 36.3, 61.4, 64.4, 70.7, 113.9, 117.8, 126.1, 128.3, 128.9, 131.5, 132.2, 133.7, 135.5, 136.4, 138.9, 166.5; IR (KBr) 3217, 1721 cm^{-1}; EIMS m/z 324 $(M)^+$. Anal. ($C_{19}H_{20}N_2O_3$.H_2O) C, H, N.

Ethyl 3-[2-(*o*-fluorophenyl)ethyloxymethyl]-1*H*-pyrrolo-[2,3-*c*]pyridine-5-carboxylate (16). A mixture of compound **11** (186 mg, 0.61 mmol), *o*-fluorophenethyl alcohol (1.5 mL), K_2CO_3 (50 mg) and water (50 μL) was stirred overnight at rt. The reaction mixture was diluted with ethyl acetate (10 mL) and the solution was washed with water (3×5 mL). The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using CH_2Cl_2 as developer until complete elution of the excess *o*-fluorophenethyl alcohol. Further elution of the column with CH_2Cl_2/EtOH (95/5) afforded compound **16** as a white solid (65 mg, 31%) which was crystallized from CH_2Cl_2/pentane: mp 170–171 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.48 (t, J=7.2, 3H), 2.97 (t, J=6.9, 2H), 3.75 (t, J=6.9, 2H), 4.54 (q, J=7.2, 2H), 4.78 (s, 2H), 7.01–7.25 (m, 4H), 7.75 (s, 1H), 8.57 (s, 1H), 9.21 (s, 1H), 12.56 (br s, 1H, exchangeable with D_2O); IR (KBr) 3061, 1717 cm^{-1}; CIMS m/z 343 $(MH)^+$. Anal. ($C_{19}H_{19}N_2O_3F$) C, H, N, F.

Ethyl 3-[3-(phenyl)-2,3-propenoxymethyl]-1*H*-pyrrolo-[2,3-*c*]pyridine-5-carboxylate (17). A mixture of compound **11** (170 mg, 0.55 mmol), cinnamyl alcohol (2 mL), potassium carbonate (60 mg) and water (50 μL) was stirred for 2 h at 40 °C. The reaction mixture was cooled to rt and applied to a column of silica gel which was developed with heptane/ethyl acetate (8/2) until complete elution of the excess cinnamyl alcohol. Further elution of the column with dichloromethane/ethanol (95/5) provided compound **17** as an off-white solid (101 mg, 55%): mp 169–171 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.45 (t, J=7.0, 3H), 4.25 (d, J=6.0, 2H), 4.51 (q, J=7.0, 2H), 4.86 (s, 2H), 6.35 (sex, J=6.0 and 15.6, 1H), 6.65 (d, J=15.6, 1H), 7.23–7.41 (m, 5H), 7.78 (s, 1H), 8.64 (s, 1H), 9.21 (s, 1H), 12.13 (br s, 1H, exchangeable with D_2O); IR (film) 3386, 1722 cm^{-1}; EIMS m/z 336 $(M)^+$. Anal. ($C_{20}H_{20}N_2O_3$.0.5 H_2O) C, H, N.

Ethyl 3-formyl-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (18). To a stirring solution of compound **7b** (600 mg, 3.16 mmol) in nitromethane and 1,2-dichloroethane (25 mL of a 1:1 mixture) held at 0 °C under argon was added 1,1-dichloromethyl methyl ether (1.44 mL, 15.8 mmol) and, in small portions, aluminum chloride (1.42 g). The addition of the same quantities of dichloromethyl methyl ether and aluminum chloride was repeated twice at 30 min intervals and the reaction mixture was left to stir for a further 30 min. Water (20 mL) was added followed by saturated aqueous $NaHCO_3$ (100 mL). The mixture was extracted with a solution of

CH_2Cl_2/EtOH (4×100 mL of a 9/1 mixture), the organic extracts were combined, washed with aqueous NaCl (50 mL) and dried over Na_2SO_4. The solvents were removed under reduced pressure and the residue was crystallized in ethanol, affording compound **18** as tan crystals (507 mg, 74%): mp 150 °C. ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.35 (t, J=7.1, 3H), 4.35 (q, J=7.1, 2H), 8.75 (s, 1H), 8.87 (s, 1H), 9.07 (s, 1H), 10.05 (s, 1H), 12.80 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 14.2, 60.7, 117.7, 118.0, 128.9, 134.4, 135.1, 139.6, 141.7, 165.2, 185.7; IR (KBr) 3345, 1714, 1676 cm^{-1}; CIMS m/z 219 $(MH)^+$. Anal. ($C_{11}H_{10}N_2O_3$.0.5 H_2O) C, H, N.

Ethyl 1-benzenesulfonyl-3-formylpyrrolo[2,3-*c*]pyridine-5-carboxylate (19). A solution of compound **18** (300 mg, 1.4 mmol) in anhydrous THF (70 mL) was treated at rt with sodium hydride (70 mg of a 60% dispersion in oil; 1.6 mmol). The mixture was stirred for 1.5 h and a solution of benzenesulfonyl chloride (0.21 mL, 1.6 mmol)) in THF (5 mL) was added dropwise. The reaction mixture was then stirred for 2 h, water (60 mL) was added and the solution was extracted with CH_2Cl_2/EtOH (5×100 mL of a 9/1 mixture). The organic extracts were combined, washed with saturated aqueous NaCl (100 mL) and dried over Na_2SO_4. Removal of the solvents under reduced pressure left a crude product which was purified by column chromatography on silica gel (CH_2Cl_2/EtOH, 98/2), affording compound **19** as a white powder (390 mg, 78%): mp 160 °C (heptane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, J=7.1, 3H), 4.47 (q, J=7.1, 2H), 7.54 (t, J=7.7, 2H), 7.65 (t, J=7.7, 1H), 7.99 (d, J=7.7, 2H), 8.42 (s, 1H), 8.93 (s, 1H), 9.39 (s, 1H), 10.14 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 14.4, 62.2, 119.3, 121.7, 127.5, 130.2, 132.8, 133.1, 135.5, 135.7, 136.5, 138.5, 143.2, 165.2, 184.4; IR (film) 3119, 1713, 1676 cm^{-1}; CIMS m/z 359 $(MH)^+$. Anal. ($C_{17}H_{14}N_2O_5S$.0.3H_2O) C, H, N, S.

Ethyl 3-hydroxymethyl-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (20). A solution of compound **19** (50 mg, 0.14 mmol) in ethanol (10 mL) was treated at 0 °C under argon with sodium borohydride (5.3 mg, 0.14 mmol). The reaction mixture was stirred for 1 h, acetic acid (0.2 mL) and water (10 mL) were added and the solution was extracted with CH_2Cl_2/EtOH (4×10 mL of a 9/1 mixture). The combined organic extracts were dried (Na_2SO_4), the solvents were removed under reduced pressure and the residue was dissolved in anhydrous ethanol (10 mL). The solution was cooled to 0 °C and a 0.4 M solution of sodium in ethanol (1 mL) was added dropwise. The reaction mixture was stirred for 1 h, acetic acid (0.2 mL) and water (20 mL) were added and the solution was extracted with CH_2Cl_2/EtOH (6×50 mL of a 9/1 mixture). The combined organic extracts were dried (Na_2SO_4), the solvents were removed in vacuo and the residue was purified by preparative TLC on silica gel (dichloromethane/ethanol, 9/1) affording compound **20** as a white powder (10 mg, 33%): mp 250 °C (decomp). ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.46 (t, J=7.1, 3H), 4.45 (q, J=7.1, 2H), 4.80 (d, J=5.6, 2H), 7.74 (s, 1H), 8.55 (s, 1H), 8.90 (s, 1H), 11.89 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 14.2, 51.7, 54.7, 117.1, 117.4, 128.4, 134.0, 134.7, 135.9, 148.4, 165.2; IR (KBr) 3365, 1713 cm^{-1}; CIMS m/z 221 $(MH)^+$. Anal. ($C_{11}H_{12}N_2O_3$.0.2H_2O) C, H, N.

(*E*,*Z*)-Ethyl 1-benzenesulfonyl-3-(2-phenylethylene)pyrrolo-[2,3-*c*]pyridine-5-carboxylate (21a). A solution of compound **19** (20 mg, 0.06 mmol), benzyltriphenylphosphonium bromide and sodium amide (42 mg of a commercial packaged mixture; 0.08 mmol) in anhydrous THF (2 mL) was stirred for 2 h at rt. Fresh benzyltriphenylphosphonium bromide/sodium amide mixture (14 mg, 0.03 mmol) was then added and stirring was continued for 2 h. Water (100 mL) was added and the solution was extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried (Na_2SO_4), the solvents were removed under reduced pressure and the residue was purified by preparative TLC on silica gel (heptane/ethyl acetate, 1/1) affording compound **19**, a reddish solid, as an inseparable mixture of *E* and *Z* isomers (3/1) (17 mg, 70%): mp 80 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (t, J=7.1, 0.75H), 1.46 (t, J=7.1, 2.25H), 4.43 (q, J=7.1, 0.5 H), 4.55 (q, J=7.1, 1.5H), 6.56 (d, J=11.8, 0.25H), 6.86 (d, J=11.8, 0.25H), 7.16–7.60 (m, ~10.75 H), 7.90 (d, J=15.1, 0.75 H), 7.98 (s, 0.75H), 8.10 (s, 0.25H), 8.64 (s, 1H), 9.36 (s, 0.25H), 9.43 (s, 0.75H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 14.4, 61.8 (*E*), 62.0 (*Z*), 117.0 (*E*), 117.7 (*Z*), 120.2, 120.9, 126.4, 127.0, 127.9, 128.8, 129.6, 129.7, 131.8, 133.4, 133.9, 134.6, 134.7, 134.9, 135.7, 137.2, 141.0, 141.7, 165.4; IR (KBr) 3205, 1717 cm^{-1}; CIMS m/z 433 $(MH)^+$. Anal. ($C_{24}H_{20}N_2O_4S$.0.5 H_2O) C, H, N.

(*E*,*Z*)-Ethyl 1-benzenesulfonyl-3-(3-phenyl-1,2-propenyl)-pyrrolo[2,3-*c*]pyridine-5-carboxylate (21b). A solution of phenethyltriphenylphosphonium bromide (37.5 mg, 0.08 mmol) in anhydrous THF was treated at −20 °C under argon with a solution of *n*-butyllithium in hexane (52 μL of a 1.6 M solution, 0.08 mmol). The reaction mixture was stirred for 1.5 h and a solution of compound **19** (20 mg, 0.06 mmol) in THF (1 mL) was added dropwise. The reaction mixture was allowed to come to rt and stirring was continued for 3 h. Ethanol (0.5 mL) was added, the solution was evaporated to dryness under reduced pressure and the residue was purified by preparative TLC on silica gel (heptane/ethyl acetate, 3/2). Compound **21b** was isolated as a yellowish solid (20 mg, 82%) in the form of a mixture of *E* and *Z* isomers (4/1): mp 91 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (t, J=7.2, 3H), 3.60 (d, J=5.0, 0.4H), 3.65 (d, J=7.6, 1.6H), 4.51 (q, J=7.1, 2H), 6.14 (m, 1H), 6.55 (m, 1H), 7.20–7.60 (m, 8H), 7.70 (s, 0.2H), 7.73 (s, 0.8H), 7.87 (d, J=7.7, 2H), 8.42 (s, 0.8H), 8.51 (s, 0.2H), 9.40 (s, 0.2H), 9.41 (s, 0.8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5 (*E*), 14.7 (*Z*), 35.7, 62.0, 117.2 (*E*), 117.4 (*E*), 118.8 (*Z*), 119.8 (*Z*), 126.6, 127.0, 127.1, 127.3, 128.2, 128.3, 128.6, 128.7, 128.8, 129.0, 129.2, 129.3, 129.8, 132.0, 133.2, 133.8, 134.3, 134.8, 135.6, 135.7, 136.9, 137.4, 139.2, 165.5; IR (film) 2982, 1716 cm^{-1}; HRCIMS calcd for $C_{25}H_{23}N_2O_4S$ m/z 447.1378, found 447.1365.

(*E*)-Ethyl 1-benzenesulfonyl-3-[2-(ethoxycarbonyl)ethylene]pyrrolo[2,3-*c*]pyridine-5-carboxylate (21c). A solution

of compound **19** (50 mg, 0.14 mmol) in anhydrous THF (10 mL) was treated at rt under argon with (carbethoxymethylene)triphenylphosphorane (73 mg, 0.21 mmol). The reaction mixture was stirred for 30 min, acetic acid (0.5 mL) was added and the solution was evaporated to dryness under reduced pressure. The residual oil was crystallized in CCl_4, affording compound **21c** as colorless crystals (54 mg, 90%): mp 174 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, J=7.1, 3H), 1.44 (t, J=7.1, 3H), 4.28 (q, J=7.1, 2H), 4.48 (q, J=7.1, 2H), 6.57 (d, J=16.2, 1H), 7.52 (t, J=7.7, 2H), 7.63 (t, J=7.7, 1H), 7.75 (d, J=16.2, 1H), 7.90 (d, J=7.7, 2H), 7.99 (s, 1H), 8.57 (s, 1H), 9.40 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 14.4, 14.5, 35.3, 60.9, 62.2, 117.8, 118.2, 120.6, 127.2, 130.0, 131.2, 133.5, 134.3, 135.1, 135.9, 137.1, 142.5, 165.3, 166.5; IR (KBr) 1712, 1641 cm^{-1}; CIMS m/z 429 $(MH)^+$. Anal. ($C_{21}H_{20}N_2O_6S$) C, H. N.

General procedure for the deprotection of 1-benzenesulfonylpyrrolo[2,3-*c*]pyridine derivatives 21a–c. A solution of **21a**, **21b**, or **21c** (50–60 mg) in absolute ethanol (5 mL) was treated at rt with a solution of sodium ethoxide in ethanol (1 mL of a 0.4 M solution). The reaction mixture was stirred for 2 h, acetic acid (0.5 mL) was added and the solution was evaporated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel using CH_2Cl_2/EtOH (95/5) as eluent. The following compounds were prepared in this manner:

(*E*,*Z*)-Ethyl 3-(2-phenylethylene)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (22a). Compound **22a** was obtained as a tan powder (33 mg, 81%) and as a mixture of *E* and *Z* isomers (3/1) from compound **21a** (60 mg, 0.14 mmol): mp 247 °C (decomp). ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.39 (t, J=7.1, 0.75H), 1.48 (t, J=7.1, 2.25H), 4.35 (q, J=7.1, 0.5 H), 4.50 (q, J=7.1, 1.5H), 6.75 (d, J=12.1, 0.25H), 6.93 (d, J=12.1, 0.25H), 7.35 (d, J=16.6, 0.75H), 7.40 (m, 2H), 7.49 (t, J=7.7, 1H), 7.63 (d, J=16.6, 0.75H), 7.73 (d, J=7.7, 2H), 7.95 (s, 0.25H), 8.18 (s, 0.75H), 8.82 (s, 1H), 8.88 (s, 0.25H), 8.95 (s, 0.75H), 12.10 (br s, 0.25H, exchangeable with D_2O), 12.30 (br s, 0.75H, exchangeable with D_2O); ^{13}C NMR (50 MHz, DMSO-d_6) δ 14.1, 60.3, 116.8, 120.3, 125.7, 125.8, 126.6, 128.4, 129.5, 134.4, 134.8, 137.3, 137.6, 165.0; IR (KBr) 3428, 1721 cm^{-1}; CIMS m/z 293 $(MH)^+$. Anal. ($C_{18}H_{16}N_2O_2.C_2H_5OH$) C, H, N.

(*E*,*Z*)-Ethyl 3-(3-phenyl-1,2-propenyl)-1*H*-pyrrolo[2,3-*c*]-pyridine-5-carboxylate (22b). Compound **22b** was obtained as a white powder (28 mg, 82%) and as a mixture of *E* and *Z* isomers (4/1) from compound **21b** (50 mg, 0.11 mmol): mp 162 °C (decomp). ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.46 (t, J=7.1, 3H), 3.68 (d, J=7.0, 0.4H), 3.80 (d, J=7.0, 1.6H), 4.46 (q, J=7.1, 2H), 5.94 (m, 1H), 6.90 (d, J=11.3, 0.2H), 7.40 (m, 5.8H), 7.90 (s, 1H), 8.55 (s, 0.8H), 8.60 (s, 0.2H), 8.90 (s, 0.2H), 8.96 (s, 0.8H), 12.27 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (50 MHz, DMSO-d_6) δ14.7, 35.9, 61.6, 117.7, 119.7, 126.3, 128.5, 128.8, 130.0, 134.0, 167.9; IR (KBr) 3026, 1724 cm^{-1}; CIMS m/z 307 $(MH)^+$. Anal. ($C_{19}H_{18}N_2O_2.0.6H_2O$) C, H, N.

(*E*)-Ethyl 3-[2-(ethoxycarbonyl)ethylene]-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (22c). Compound **22c** was obtained as white crystals (116 mg, 72%) from compound **21c** (200 mg, 0.56 mmol): mp 290 °C (ethanol) (decomp). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.36 (t, J=7.1, 3H), 1.47 (t, J=7.1, 3H), 4.31 (q, J=7.1, 2H), 4.48 (q, J=7.1, 2H), 6.58 (d, J=16.0, 1H), 8.03 (d, J=16.0, 1H), 8.43 (s, 1H), 8.66 (s, 1H), 9.00 (s, 1H), 12.77 (br s, 1H, exchangeable with D_2O); IR (KBr) 2983, 1716, 1634 cm^{-1}; CIMS m/z 289 $(MH)^+$. Anal. ($C_{15}H_{16}N_2O_4.0.3\ H_2O$) C, H, N.

General procedure for the reduction of the double bonds of compounds 22a–c. A mixture of the unsaturated derivatives **22a**, **22b**, or **22c** (40, 50 and 20 mg, respectively) and an equivalent mass of 10% palladium on carbon in ethanol (5 mL) (**22a**, **22b**) or ethanol (8 mL) and dichloromethane (6 mL) (**22c**) was hydrogenated at atmospheric pressure for 2 h. The reaction mixture was filtered on Celite®, the filtrate was evaporated to dryness under reduced pressure and the residue was purified by preparative TLC on silica gel (CH_2Cl_2/EtOH, 9/1). The following compounds were prepared in this manner:

Ethyl 3-(2-phenylethyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (23a). Compound **23a** was obtained as a white powder (24 mg, 58%) from compound **22a**: mp 179 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.35 (t, J=7.1, 3H), 3.08 (t, J=7.2, 2H), 3.17 (t, J=7.2, 2H), 4.45 (q, J=7.1, 2H), 7.35 (s, 5H), 7.60 (s, 1H), 8.38 (s, 1H), 8.87 (s, 1H), 12.82 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (62.5 MHz, CD_3OD) δ 14.4, 27.8, 38.0, 62.0, 118.1, 127.0, 129.3, 129.6, 129.8, 134.7, 165.5; IR (KBr) 3182, 1708 cm^{-1}; CIMS m/z 295 $(MH)^+$. Anal. ($C_{18}H_{18}N_2O_2.\ 0.3\ H_2O$) C, H, N.

Ethyl 3-(3-phenylpropyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (23b). Compound **23b** was obtained as a light brown powder (30 mg, 42%) from compound **22b**: mp 159 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.45 (t, J=7.1, 3H), 2.07 (t, J=7.1, 2H), 2.75 (t, J=7.1, 2H), 2.84 (t, J=7.1, 2H), 4.42 (q, J=7.1, 2H), 7.36 (m, 5H), 7.65 (s, 1H), 8.39 (s, 1H), 8.88 (s, 1H), 12.02 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 14.2, 23.6, 31.7, 34.8, 60.3, 115.8, 116.2, 125.6, 127.8, 128.2, 130.9, 134.0, 134.5, 135.9, 141.9, 165.9; IR (KBr) 2930, 1716 cm^{-1}; CIMS m/z 309 $(MH)^+$. Anal. ($C_{19}H_{20}N_2O_2.0.5\ H_2O$) C, H, N.

Ethyl 3-[2(ethoxycarbonyl)ethyl]-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (23c). Compound **23c** was obtained as a pale-yellow solid (20 mg, 100%) from compound **22c**: mp 190 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25 (t, J=7.1, 3H), 1.50 (t, J=7.1, 3H), 2.82 (t, J=7.2, 2H), 3.20 (t, J=7.2, 2H), 4.15 (q, J=7.1, 2H), 4.48 (q, J=7.1, 2H), 8.03 (s, 1H), 8.67 (s, 1H), 9.04 (s, 1H), 12.77 (br s, 1H, exchangeable with D_2O); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 13.9, 14.1, 19.2, 34.4, 59.8, 61.8, 116.9, 117.2, 130.9, 132.5, 133.0, 134.2, 141.9, 165.9, 172.0; IR (KBr) 2861, 1727, 1716 cm^{-1}; HRCIMS calcd for $C_{15}H_{19}N_2O_4$ m/z 291.1344, found 291.1340.

Methyl 2-[1-(benzenesulfonylpyrrol-2-yl)methyl]amino-3,3-diethoxybutyrate (26). To a solution of aldehyde **24**

(176 mg, 0.75 mmol) in anhydrous CH_2Cl_2 (30 mL) was added freshly activated 4 Å molecular sieves (2 g) and methyl 2-amino-3,3-diethoxybutyrate[26] (384 mg, 1.87 mmol). The reaction mixture was stirred for 36 h at rt and then filtered on Celite®. The filter pad was rinsed with 5% methanolic CH_2Cl_2 (60 mL) and the filtrate was washed with water (3×20 mL), dried (Na_2SO_4) and evaporated leaving the crude imine (210 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (2t, J = 7.0, 6H), 1.51 (s, 3H), 3.41–3.65 (m, 4H), 3.75 (s, 3H), 4.35 (s, 1H), 6.31 (t, J = 3.5, 1H), 7.40–7.56 (m, 6H), 7.81 (d, J = 7.1, 1H), 8.63 (s, 1H); IR (film) 1743, 1675 cm^{-1}; CIMS m/z 423 $(MH)^+$.

This crude material, more than 95% pure and containing no trace of starting material (as evaluated by ^{1}H NMR) was used without further purification in the following step. Thus, a solution of the imine (160 mg, 0.38 mmol) in ethanol (10 mL) was treated with sodium cyanoborohydride (25 mg, 0.40 mmol). The solution was stirred for 50 min at rt, the pH being maintained at 4 by the intermittent addition of alcoholic HCl. The reaction mixture was diluted with water (10 mL), made basic by the addition of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (4×20 mL). The combined organic extracts were washed with water (15 mL), dried (Na_2SO_4) and evaporated under reduced pressure, affording amine **26** as a brown oil (157 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (2t, J = 7.1, 6H), 1.39 (s, 3H), 1.75 (br s, 1H, exchangeable with D_2O), 3.45–3.60 (m, 3H), 3.65 (s, 3H), 3.67–3.80 (m, 3H), 4.65 (s, 1H), 6.42 (m, 1H), 7.15 (m, 1H), 7.45–7.70 (m, 3H), 7.82–8.01 (m, 3H); IR (film) 3156, 1743 cm^{-1}; CIMS m/z 425 $(MH)^+$.

Methyl 1-benzenesulfonyl-4-methylpyrrolo[2,3-*c*]-pyridine-5-carboxylate (27). To a vigorously stirring solution of amine **26** (147 mg, 0.35 mmol) in anhydrous benzene (6 mL) was added at rt under argon titanium (IV) chloride (170 μL, 1.56 mmol). The reaction mixture was refluxed for 2 h, cooled to rt and ethyl acetate (10 mL) followed by saturated aqueous $NaHCO_3$ (10 mL) were added. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3×10 mL). The organic extracts were combined, washed with water (10 mL), dried (Na_2SO_4) and the solvents were removed under reduced pressure. The solid residue was purified by column chromatography on silica gel (heptane/ethyl acetate, 6/4) affording compound **27** as a pale-yellow powder (78 mg, 68%): mp 130 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.74 (s, 3H), 3.98 (s, 3H), 6.84 (d, J = 3.7, 1H), 7.43–7.65 (m, 3H), 7.75 (d, J = 3.7, 1H,), 7.90 (d, J = 7.2, 2H), 9.22 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 15.8, 52.5, 107.5, 126.7, 127.0, 128.1, 129.4, 129.7, 132.8, 134.6, 166.7; IR (film) 1724 cm^{-1}; CIMS m/z 331 $(MH)^+$. Anal. ($C_{16}H_{14}N_2O_4S$) C, H, N.

Methyl 4-methyl-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (28). Using the same general procedure as for the preparation of compounds **22a–c**, compound **27** (46 mg, 0.14 mmol) in methanol (5 mL) was treated with a solution of sodium methoxide in methanol (1.22 mL of a 0.17 M solution; 0.2 mmol). After 2 h, the reaction mixture was treated as before and the crude product was purified by preparative TLC (ethyl acetate/methanol 9/1), affording pure **28** as a white powder (17 mg, 65%): mp 202–203 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.87 (s, 3H), 4.00 (s, 3H), 6.77 (d, J = 3.1, 1H), 7.46 (d, J = 3.1, 1H), 8.79 (s, 1H), 9.22 (br s, 1H, exchangeable with D_2O); IR (KBr) 3416, 1720 cm^{-1}; HRCIMS calcd for $C_{10}H_{11}N_2O_2$ m/z 191.0791, found 191.0828.

Methyl 1-benzenesulfonyl-4-bromomethylpyrrolo[2,3-*c*]-pyridine-5-carboxylate (29). A solution of compound **27** (326 mg, 0.98 mmol) in CCl_4 (15 mL) containing *N*-bromosuccinimide (210 mg, 1.18 mmol) and AIBN (4 mg, 0.02 mmol) was refluxed for 4 h. The reaction mixture was filtered, the filtrate was washed with water (3×10 mL) and the organic phase was dried (Na_2SO_4). Evaporation of the solvent under reduced pressure left a residue which was purified by column chromatography on silica gel (heptane/ethyl acetate, 6/4). Compound **29** was obtained as a white powder (250 mg, 61%): mp 104–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (s, 3H), 5.19 (s, 2H), 6.98 (d, J = 3.2, 1H), 7.54 (t, J = 7.9, 2H), 7.66 (d, J = 7.2, 1H), 7.87 (d, J = 3.2, 1H), 7.97 (d, J = 7.9, 2H), 9.35 (s, 1H); IR (film) 1731 cm^{-1}; CIMS m/z 411 $(MH)^+$ with ^{81}Br, 409 $(MH)^+$ with ^{79}Br. Anal. ($C_{16}H_{13}BrN_2O_4S$) C, H, N.

Methyl 4-methoxymethyl-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (30). Following the same procedure as for the preparation of **28**, a solution of compound **29** (140 mg, 0.34 mmol) in methanol (7 mL) was treated with a solution of sodium methoxide in methanol (5.01 mL of a 0.17 M solution; 0.85 mmol). The reaction mixture was stirred at rt for 2 h and then worked up in the usual manner. The crude product was purified by column chromatography on silica gel (ethyl acetate/methanol, 8/2), affording compound **30** as a white solid (60 mg, 80%): mp 134–135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.46 (s, 3H), 4.01 (s, 3H), 5.22 (s, 2H), 6.95 (d, J = 3.1, 1H), 7.54 (d, J = 3.1, 1H), 8.88 (s, 1H), 9.46 (br s, 1H, exchangeable with D_2O); IR (film) 3412, 1731 cm^{-1}; HRCIMS calcd for $C_{11}H_{13}N_2O_3$ m/z 221.0953, found 221.0918.

Molecular modeling. Molecular modeling was performed using Macromodel (version 5.5) on a Silicon Graphics workstation. For each molecule (**4d**, **8**, and **9**), 5000 conformations were sampled using the Monte Carlo procedure and minimized by use of MM3 force fields. Only the five lowest energy conformers which were generated most frequently and whose ΔE did not exceed 4 kcal/mol were retained. Of these, the ones whose side-chain alignments showed the best superposition are shown in Figure 1.

Receptor binding studies. Inhibition of [^{3}H]flumazenil binding to native benzodiazepine (ω) receptor subtypes in vitro was studied as described by Schoemaker et al.[29] Briefly, the cerebellum, spinal cord or hippocampus of male Sprague-Dawley rats (180–300 g, OFA, Iffa Credo, St. Germain sur l'arbresle, France) were homogenized in 50 mM Tris–HCl buffer (pH 7.4) containing 120 mM NaCl and 5 mM KCl. The binding of [^{3}H]flumazenil

(1 nM; specific activity 70–87 Ci/mmol, NEN Life Science Products) to the ω_1 receptor was studied in membranes from the rat cerebellum, a region enriched in this receptor subtype,[30] using a 45 min incubation at 0–4 °C and 1 μM diazepam to define nonspecific binding. [^{3}H]Flumazenil binding to the ω_2 receptor was studied using membranes from the rat spinal cord, where a majority of the expressed ω receptors appears to be of the ω_2 subtype,[31] under otherwise identical conditions. The native ω_5 receptor was studied using [^{3}H]flumazenil binding to membranes from the rat hippocampus in the presence of 5 μM zolpidem in order to mask the ω_1 and ω_2 receptor subtypes,[17c] under otherwise identical conditions except for the use of 1 μM flunitrazepam to define nonspecific binding. Following incubation, membranes were recovered by vacuum filtration over Whatman GF/B filters, washed and the amount of radioactivity retained on the filter was quantified by liquid scintillation spectrometry. Data are presented in Table 1 as the compound concentration required to inhibit 50% of specific radioligand binding (IC_{50}) and were obtained from a single experiment performed in duplicate.

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