Novel Benzo[1,4]diazepin-2-one Derivatives as Endothelin Receptor Antagonists

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Since its discovery in 1988 by Yanagisawa et al., endothelin (ET), a potent vasoconstrictor, has been widely implicated in the pathophysiology of cardiovascular, cerebrovascular, and renal diseases. Many research groups have embarked on the discovery and development of ET receptor antagonists for the treatment of such diseases. While several compounds, e.g., ambrisentan **2,** are in late clinical trials for various indications, one compound (bosentan, Tracleer) is being marketed to treat pulmonary arterial hypertension. Inspired by the structure of ambrisentan **2**, we designed a novel class of ET receptor antagonists based on a 1,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-2-one scaffold. Here, we report on the preparation as well as the in vitro and in vivo structure−activity relationships of these derivatives. Potent dual ET_A/ET_B receptor antagonists with affinities in the low nanomolar range have been identified. In addition, several compounds efficiently reduced arterial blood pressure after oral administration to Dahl salt sensitive rats. In this animal model, the efficacy of the benzo[*e*][1,4]diazepin-2-one derivative rac-**39au** was superior to that of racemic ambrisentan, rac-**2**.

Introduction

The isolation, sequencing, and cloning of the porcine endothelium derived contracting factor, endothelin (ET), by Yanagisawa et al. in 1988[1] triggered a wealth of biological, pharmacological, and pathophysiological research activities. Only 1 year later, the human endothelin family was reported to consist of the three 21 amino acid peptides ET-1, ET-2, and ET-3 each containing two disulfide bridges.[2] The peptide sequences of the three endothelins are highly conserved, if not identical, across various mammalian species such as mouse, rat, pig, and human.[2,3] Each of the human endothelins is expressed as a prepropeptide consisting of about 212 amino acids. This prepropeptide is then processed to a 37−41 amino acid proendothelin, also referred to as big endothelin, which is cleaved to the active peptide by the endothelin converting enzyme (ECE).[4,5] The three highly vasoactive peptides ET-1, ET-2, and ET-3 act by binding to two closely related G-protein-coupled receptors ET_A and ET_B. The two receptors have different affinities for the three endothelins. While the ET_A receptor strongly binds ET-1 and ET-2 but shows considerably lower affinity toward ET-3, the ET_B receptor does not discriminate among the three isopeptides.[6] The ET receptors are not only located in the vasculature of most organs such as heart, lung, kidney, spleen, and liver but are also found in many other tissues such as the myocardium, glomeruli, trachea, testis, and parts of the brain.[6,7] The ET_A receptor subtype is predominantly expressed by smooth muscle cells of the blood vessels and is responsible for a strong, long-lasting vasoconstriction. On the other hand, the ET_B receptor is expressed by endothelial cells and prevails in many nonvascular tissues such as the kidney medulla and the smooth muscle of the airways in the lung. In addition to a strong vasoconstriction, both receptors mediate long-term effects such as cell proliferation and fibrosis. As a consequence, the endothelins may have detrimental effects on angiogenesis, cardiac, and vascular remodeling, inflammation, and fibrosis.[8,9] A pathophysiological role is attributed to the endothelins, in particular to ET-1, in a number of renal, pulmonary,[10,11] cardiac, and vascular diseases[12,13] such as renal failure,[14,15] heart failure,[16,17] hypertension,[18,19] atherosclerosis,[8] acute myocardial infarction, pulmonary arterial hypertension (PAH),[8] and cerebral vasospasm.[20] Accordingly, endothelin receptor antagonists are thought to offer a novel class of drugs to treat or even prevent such disorders.[8,20−24]

Indeed, a first nonpeptidic, orally active endothelin receptor antagonist, bosentan (Tracleer), has recently been approved for the treatment of pulmonary arterial hypertension.[25,26] A number of other nonpeptidic endothelin receptor antagonists are in late clinical trials: atrasentan[27,28] (Abbott) and Y-598 (Yamanouchi) for the treatment of prostate cancer; ambrisentan[29,30] (Abbott, Myogen) and sitaxsentan[31] (Encysive) for PAH and chronic heart failure (CHF); darusentan[32] (Abbott) and enrasentan[33] (GlaxoSmithKline) for CHF; tezosentan (Actelion) for acute heart failure; and S-0139 (Shionogi) and clazosentan (Actelion) for cerebrovascular ischaemia.[7,34,35] While bosentan and tezosentan block both endothelin receptors, the other compounds mentioned above selectively bind to the ET_A receptor. The question whether dual ET_A/ET_B receptor antagonists provide therapeutic advantages over ET_A selective receptor blockers is not yet answered satisfactorily, but there is growing evidence for the superiority of compounds blocking both receptors in chronic pulmonary and cardiac diseases.[34,36−38]

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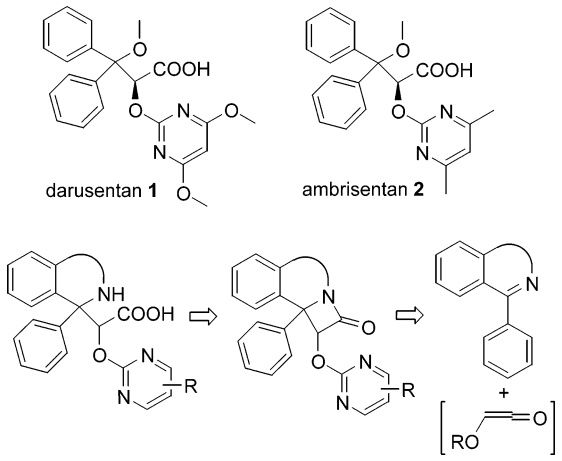


Figure 1. Structure of darusentan **1** and ambrisentan **2**. Retrosynthetic analysis of proposed novel endothelin receptor antagonists based on a benzofused heterocyclic scaffold.

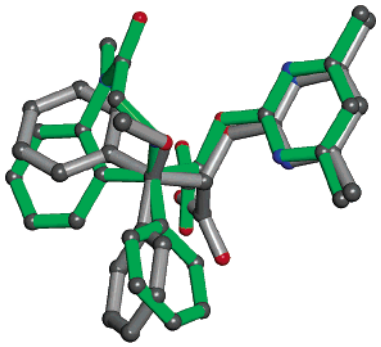


Figure 2. Superposition of ambrisentan (**2**, silver) and (*S*,*S*)-**9b** (Scheme 2) indicating the structural similarity between the two molecules.

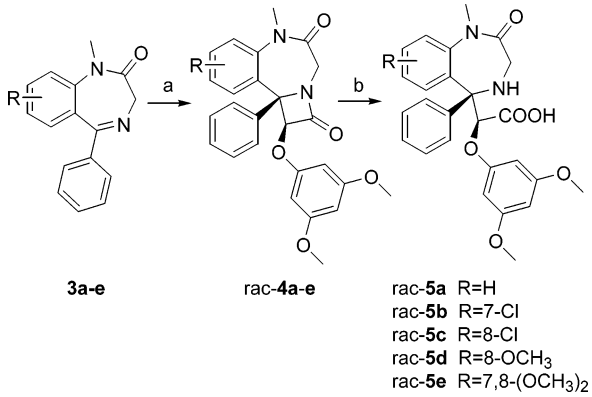
We set ourselves the goal of finding novel ET receptor antagonists. From a careful literature survey of non-peptidic endothelin receptor antagonists,[39,40] darusentan **1** and ambrisentan **2**[29] (Figure 1) emerged as particularly attractive lead structures. Superposition of the three-dimensional structures of **2** and a benzodiazepine derivative formed through the introduction of an additional ring between the methyl group of the carbinol ether and one of the phenyl rings (Figure 2) suggested new target structures such as rac-**9b**. In view of the patent literature[41−43] we speculated that the oxygen atom attached to C_3 of the propionic acid scaffold of **2** could be replaced by a nitrogen without loss of affinity. The fact that the benzo[1,4]diazepine-2,5-dione has been shown to serve as a viable template for endothelin receptor antagonists[44,45] further encouraged our plan to employ a benzofused heterocyclic scaffold. Our synthetic strategy exploited the highly diastereoselective [2 + 2]-cycloaddition of an imine moiety of a benzofused heterocycle to a ketene to generate a β-lactam,[46−48] which upon hydrolysis could create the necessary carboxylic acid functionality (Figure 1).

In this article we describe the discovery of a novel class of 1,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-2-one derivatives that serve as potent, orally active dual ET_A/ET_B endothelin receptor antagonists.

Chemistry

The preparation of the first examples incorporating a benzo[1,4]diazepin-2-one scaffold is outlined in Scheme 1. The synthesis of rac-**4** started with the diastereoselective [2 + 2]-cycloaddition of the 3,5-dimethoxyphenoxy-ketene, generated in situ from 3,5-dimethoxyphenoxyacetic acid in the presence of *N*,*N*-bis[2-oxo-3-oxazolidinyl]phosphordiamidic chloride (BOP-Cl)[49] and triethylamine, to the 1-methyl-5-phenyl-1,3-dihydrobenzo-[*e*][1,4]diazepin-2-ones **3a**−**e**.[50−52] The reaction provided the corresponding racemic β-lactams rac-**4a**−**e** in excellent yields as single diastereoisomers as judged from ^{1}H NMR analysis. In fact, formation of only one diastereoisomer was observed (LC−MS, NMR) for all [2 + 2]-cycloadditions reported in this manuscript. In the literature, the preferred product of the [2 + 2]-addition is reported to be the cis isomer.[48,53] Accordingly, the isolated products rac-**4a**−**e** were supposed to be the racemic cis isomer as shown in Scheme 1. This was confirmed by X-ray analysis of the crystals of three examples (see ORTEP figures of rac-**7**, rac-**92**, and rac-**93** included in the Supporting Information) that were prepared following the pathway given in Schemes 1 and 4. Various conditions have been evaluated for the subsequent β-lactam cleavage, and the use of an approximately 0.2 M LiOH solution in a mixture of THF/methanol/water proved to be most successful for generating the desired amino acids rac-**5** in good yields.

Scheme 1[a]

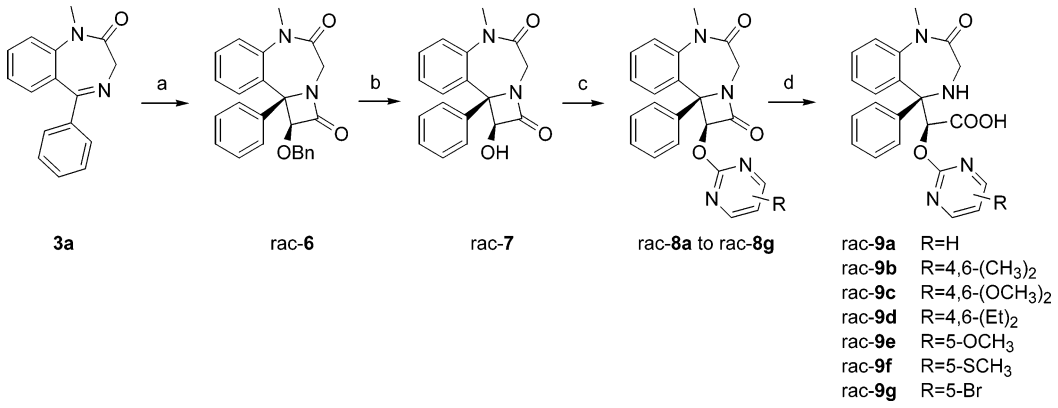


[a] (a) 3,5-Dimethoxyphenoxyacetic acid, Et_3N, BOP-Cl, CH_2Cl_2, 0°C to room temperature, overnight; (b) ca. 0.2 M LiOH in THF/MeOH/H_2O, 45 °C, 1−2 h.

Attempts to react the benzo[1,4]diazepin-2-one **3a** with a (pyrimidin-2-yloxy)acetic acid failed. Thus, to obtain compounds bearing a pyrimidinyloxy substituent at the acetic acid unit, the imine **3a** was first reacted with benzyloxyacetic acid in the presence of BOP-Cl and triethylamine to give the benzyl-protected compound rac-**6** (Scheme 2). As above, the racemic cis diastereoisomer was isolated in good yield as the only [2 + 2]-cycloaddition product. Cleavage of the benzyl ether was achieved by Pd/C catalyzed hydrogenolysis and afforded the alcohol rac-**7**, which was further reacted with a series of either 2-methanesulfonylpyrimidine or 2-chloropyrimidine derivatives in DMF in the presence of K_2CO_3 to provide the derivatives rac-**8a**−**g**. These β-lactams rac-**8a**−**g** were cleaved to the corresponding amino acids rac-**9a**−**g** upon treatment with LiOH.

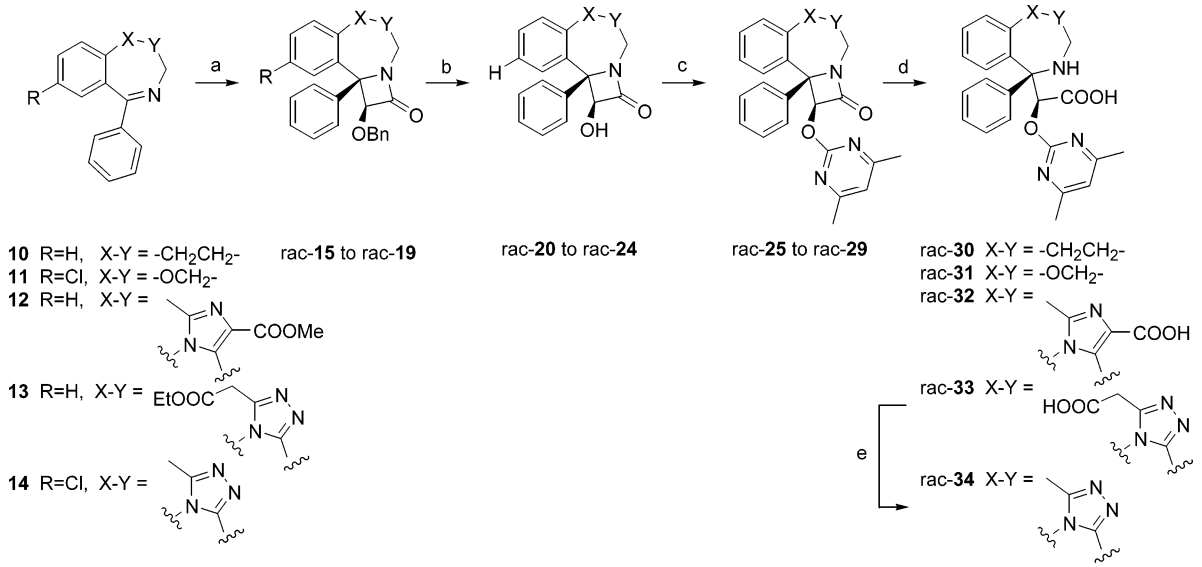
Promising initial results prompted us to apply the above chemistry to the imine scaffolds **10** to **14**[54−59] (Scheme 3), which gave compounds rac-**30** to rac-**34**. Purification of the cycloaddition product was simplified by the use of benzyloxyacetyl chloride rather than

Scheme 2[a]



[a] (a) Benzyloxyacetic acid, BOP-Cl or benzyloxyacetyl chloride, Et_3N, CH_2Cl_2, 0°C to room temperature, overnight; (b) H_2 (7 atm), Pd/C, THF, EtOH, HOAc, 50 °C, 18 h; (c) substituted 2-chloropyrimidine or 2-methanesulfonylpyrimidine, K_2CO_3, DMF, 50 °C, 16 h; (d) approximately 0.2 M LiOH, THF/MeOH/H_2O, 45 °C, 2 h.

Scheme 3[a]



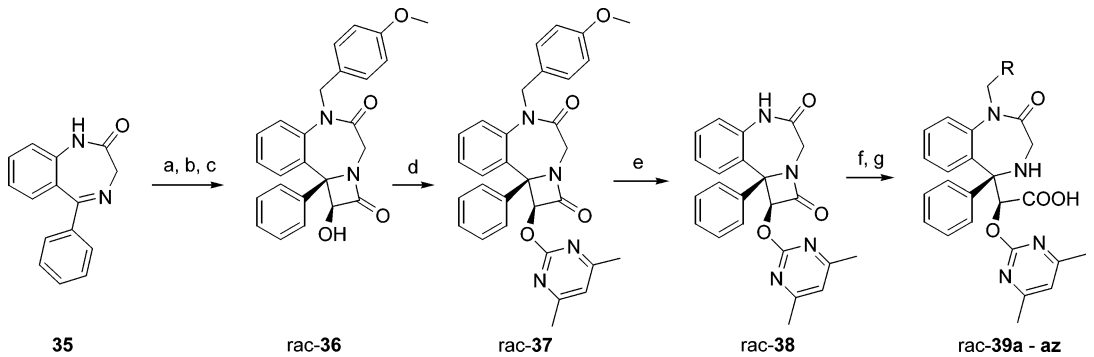
[a] (a) Benzyloxyacetic acid, BOP-Cl or benzyloxyacetyl chloride, Et_3N, CH_2Cl_2, 0 °C to room temperature, overnight; (b) H_2 (7 atm), Pd/C, THF, EtOH, HOAc, 50 °C, 18 h; (c) 2-methanesulfonyl-4,6-dimethylpyrimidine, K_2CO_3, DMF, 50 °C, 16 h; (d) approximately 0.2 M LiOH, THF/MeOH/H_2O, 45 °C, 2 h; (e) DMF, 80 °C, 3 h.

benzyloxyacetic acid because no activating agent had to be added to the reaction mixture.[60] The preparation of compounds based on the benzoxazepine **11** and the triazolo scaffold **14** started with the corresponding 7-chlorobenzodiazepine derivatives. The chlorine was usually lost upon hydrogenolysis of the benzyl ether with palladium on charcoal. However, if the hydrogenolysis was performed in the presence of 1,2-dichlorobenzene, the 7-chloro substituent was not cleaved. The triazolo compound rac-**34** not only was prepared starting from scaffold **14** but could also be obtained by decarboxylating rac-**33** at 80 °C in DMF.

We then drew our attention to the substituent at N_1 of the benzo[1,4]diazepin-2-one scaffold. It was obvious that the synthetic route described above was not useful for a rapid assembly of a larger number of compounds with different substituents at N_1. We therefore envisaged an alternative route where the introduction of the N_1 substituent would occur at a late stage in the synthesis. This was indeed possible by protecting N_1 with a 4-methoxybenzyl group that could be efficiently cleaved from rac-**37** using ammonium cerium(IV) nitrate once the pyrimidine moiety had been attached to the hydroxy group in compound rac-**36** (Scheme 4). The reaction of the deprotected amide rac-**38** with a great variety of alkyl and benzyl halides and the subsequent β-lactam cleavage were carried out in a parallel fashion. Purification of the final products rac-**39a**−**az** was achieved on an automated preparative HPLC-system.

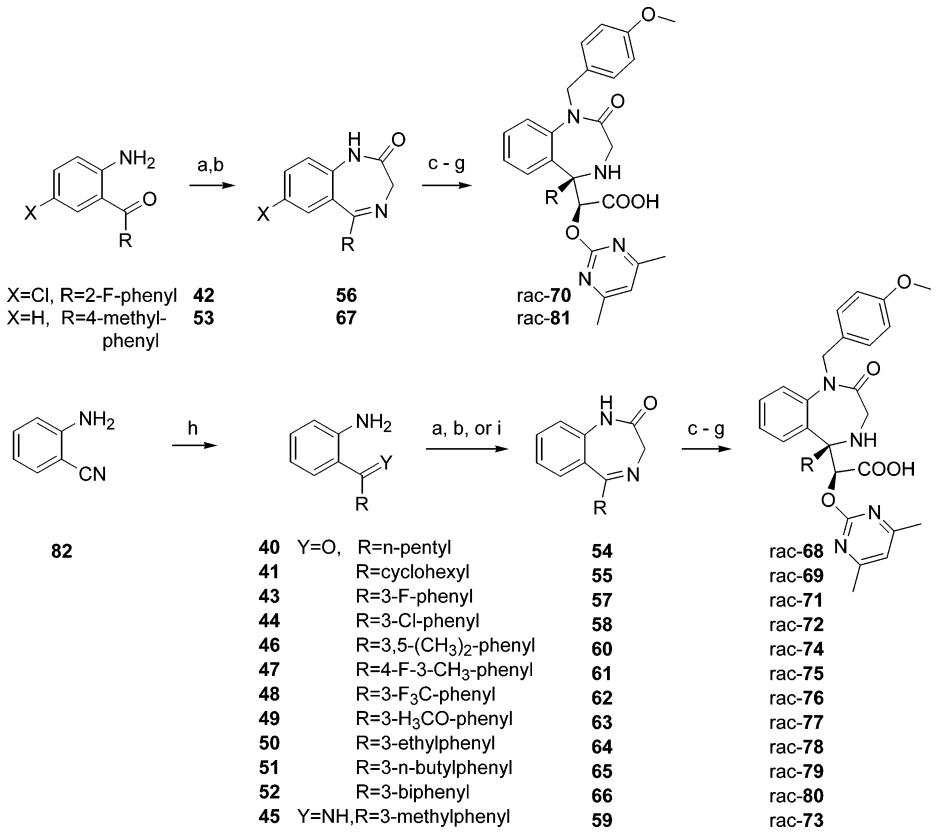
A more detailed SAR study focused on the 5-substituent at the benzo[1,4]-diazepin-2-one scaffold. For this purpose the 5-*n*-pentyl, the 5-cyclohexyl, and a number of substituted 5-phenylbenzo[1,4]diazepin-2-ones have been prepared (Scheme 5). The two benzodiazepinones **56** and **67** were synthesized in analogy to the benzodiazepinone **35**[52] by having them react with the commercially available benzophenones **42** and **53**, respectively, with bromoacetyl bromide followed by ammonia in methanol. In the case of the benzodiazepinones **54**, **55**,[61] and **57**−**66** the corresponding benzophenones **40**, **41**, and **43**−**52** were prepared by reacting 2-aminobenzonitrile **82** with the appropriate alkyl or phenyl Grignard reagents.[62,63] The obtained benzophenones were then either treated with bromoacetyl bromide followed

Scheme 4[a]



[a] (a) 4-Methoxybenzyl chloride, K_2CO_3, DMF, 50 °C, 16 h; (b) benzyloxyacetyl chloride, Et_3N, CH_2Cl_2, 0 °C to room temperature, overnight; (c) H_2 (7 atm), Pd/C, THF/EtOH, HOAc, 50 °C, 18 h; (d) 2-methanesulfonyl-4,6-dimethylpyrimidine, K_2CO_3, DMF, 50 °C, 16 h; (e) ammonium cerium(IV) nitrate, CH_3CN, H_2O, 0 °C to room temperature, 2 h; (f) R−CH_2−Hal, K_2CO_3, DMF, 50 °C, 16 h (for R, see Tables 4 and 5); (g) approximately 0.2 N LiOH in THF/MeOH/H_2O, 45 °C, 2 h.

Scheme 5[a]



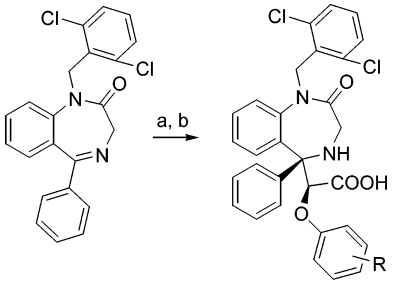
[a] (a) Bromoacetyl bromide, CH_2Cl_2, H_2O, room temp, 2 h; (b) 7 N NH_3/MeOH, 50 °C, 16 h; (c) 4-methoxybenzyl chloride, K_2CO_3, DMF, 50 °C, 16 h; (d) benzyloxyacetyl chloride, Et_3N, CH_2Cl_2, 0 °C to room temperature, 16 h; (e) H_2 (7 atm), Pd/C, THF/EtOH, HOAc, 50 °C, 2−16 h; (f) 2-methanesulfonyl-4,6-dimethylpyrimidine, K_2CO_3, DMF, 50 °C, 16 h; (g) approximately 0.2 M LiOH, THF/MeOH/H_2O, 45 °C, 2 h; (h) R−MgBr, Et_2O, reflux, 2−5 h; (i) ethyl glycinate hydrochloride, pyridine, 100 °C, 16 h.

by ammonia in methanol as above or treated with ethyl glycinate hydrochloride in pyridine[50,64,65] to effect cyclization. In general, the two-step protocol using bromoacetyl bromide gave considerably better yields (64−90%) of the desired benzodiazepinone when compared to the one-step procedure with ethyl glycinate (20−40%). In the case of the Grignard reaction with 3-bromotoluene, mild workup conditions furnished the imine **45** rather than the corresponding benzophenone. However, the use of this imine offered no advantage in the following cyclization step with ethyl glycinate to the benzodiazepinone **59**.

Alkylation of the benzodiazepinones **54**−**67** with 4-methoxybenzyl chloride was effectively carried out in DMF in the presence of an excess of potassium carbonate. The desired amino acids rac-**68** to rac-**81** were obtained following the usual reaction sequence: [2 + 2]-cycloaddition with benzyloxyacetyl chloride, Pd/C catalyzed hydrogenolysis of the benzyl ether, introduction of the 4,6-dimethylpyrimidine moiety, and *β*-lactam cleavage with lithium hydroxide. In the case of the benzodiazepinone **56**, the 7-chloro substituent was cleaved during the hydrogenolysis step.

Compounds based on a potent scaffold were prepared to reevaluate the substitution pattern at the phenyl ring coupled to the hydroxyacetic acid moiety. Hence, the 1-(2,6-dichlorobenzyl)-5-phenyl-1,3-dihydrobenzo[*e*][1,4]-diazepin-2-one **83** was reacted with a number of ap-

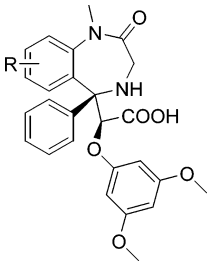
Scheme 6[a]



83 rac-**84a-m**

[a] (a) Substituted phenyloxyacetic acid, Et_3N, BOP-Cl, CH_2Cl_2, 0 °C to room temperature, overnight; (b) approximately 0.2 M LiOH, THF/MeOH/H_2O, 45 °C, 2 h. For R, see Table 7.

Table 1



		$IC_{50} \pm$ SEM (nM)[a]	
compd	R	ET_A	ET_B
rac-**5a**	H	605 ± 86	6270 ± 710
rac-**5b**	7-Cl	262 ± 92	1810 ± 170
rac-**5c**	8-Cl	3840 ± 290	5600 ± 370
rac-**5d**	8-OCH_3	3950 ± 610	7780 ± 430
rac-**5e**	7,8-$(OCH_3)_2$	443 ± 49	8030 ± 1080

[a] Mean value of at least three measurements (in duplicate).

propriately substituted phenyloxyacetic acids and the thus obtained β-lactams were cleaved under basic conditions to furnish the desired compounds rac-**84a**−**m** (Scheme 6).

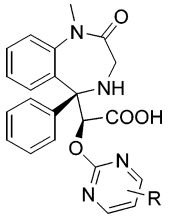
Finally, the compounds rac-**85** to rac-**91** were prepared starting from the benzo[1,4]diazepin-2-one scaffold **3a**, **65**, or **66** using the synthetic strategy described in Schemes 1 and 4.

Structure−Activitiy Relationship. In Vitro Results

The receptor affinities of all compounds (IC_{50} values) were determined in radioligand competition binding studies on membranes of Chinese hamster ovary (CHO) cells expressing the human recombinant ET_A or ET_B receptor using ^{125}I-labeled ET-1.[66] Compounds of particular interest were assessed for functional inhibitory potency at native ET_A and ET_B receptors (pA_2 values) by inhibiting ET-1 contractions of rat aortic rings or sarafotoxin Sf6 contractions of rat tracheal rings.[67]

The 1,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-2-on-5-yl substituted 3,5-dimethoxyphenoxyacetic acid derivative rac-**5a** represents the first example of a benzo-fused heterocyclic derivative we proposed as potential novel endothelin receptor antagonists. As shown in Table 1, this compound indeed exhibited a moderate affinity for the ET_A receptor. The compounds rac-**5b**−**e** illustrate the SAR of positions 7 and 8 of the benzodiazepine scaffold. The 7-chlorobenzo[1,4]diazepin-2-one

Table 2



		$IC_{50} \pm$ SEM (nM)[a]	
compd	R	ET_A	ET_B
rac-**9a**	H	1570 ± 200	>10000
rac-**9b**	4,6-$(CH_3)_2$	12.3 ± 1.1	184 ± 15
rac-**9c**	4,6-$(OCH_3)_2$	23.4 ± 2.2	473 ± 48
rac-**9d**	4,6-$(CH_2CH_3)_2$	20.5 ± 2.9	654 ± 96
rac-**9e**	5-OCH_3	384 ± 45	9250 ± 610
rac-**9f**	5-SCH_3	6600 ± 820	>10000
rac-**9g**	5-Br	927 ± 139	9480 ± 320

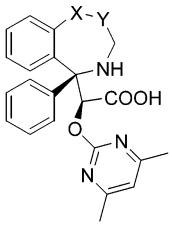
[a] Mean value of at least three measurements (in duplicate).

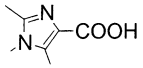
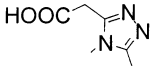
derivative rac-**5b** gave similar IC_{50} values as the unsubstituted compound rac-**5a**. Conversely, neither a chlorine (rac-**5c**) nor a methoxy (rac-**5d**) group was tolerated in position 8 of the benzodiazepinone scaffold. Interestingly, for rac-**5e** where both the 7 and the 8 positions are substituted with a methoxy group, the ET_A receptor affinity was restored. The compounds rac-**5a**−**e** had poor affinity for the ET_B receptor.

The affinity for both receptors was significantly improved when the phenyl substituent at the hydroxy acetic acid unit was replaced by a pyrimidine derivative (Table 2). However, the substitution pattern at the pyrimidine appears to be crucial. While the unsubstituted pyrimidine derivate rac-**9a** showed poor affinity for the ET_A receptor, the 4,6-disubstituted derivatives rac-**9b**−**d** gave potent antagonists. The 4,6-dimethylpyrimidine rac-**9b** showed the best IC_{50} values for both receptors. The compounds bearing a methoxy group (rac-**9e**) and a bromo substituent (rac-**9g**) in the 5-position of the pyrimidine were more potent on the ET_A receptor than rac-**9a**. The methylthio derivative rac-**9f** was clearly inferior to rac-**9a**. The analogous SAR for compounds based on scaffolds other than the above 1-methyl-5-phenyl-1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-one was very similar (data not shown). For subsequent studies the 4,6-dimethylpyrimidine was therefore chosen as the standard substituent at the hydroxyacetic acid moiety.

We varied the nature of the seven-membered heterocycle while leaving the benzo ring as well as the 5-phenyl substituent unsubstituted. The conformationally more flexible benzazepine and benzoxazepine derivatives rac-**30** and rac-**31** were both inferior when compared to the benzodiazepinone rac-**9b** (Table 3). The loss in activity was substantial on the ET_B receptor. This study was then extended by three compounds featuring a five-membered aromatic ring bridging positions 1 and 2 of the benzodiazepine scaffold. The imidazole-4-carboxylic acid derivative rac-**32** was only moderately active on the two ET receptors. The triazole derivative rac-**34** lacking a carboxylic acid function turned out to be significantly more potent on both receptors when compared to rac-**32**. A similar affinity for the ET receptors was observed with the triazole derivative rac-**33** where a carboxylic acid was attached to the exocyclic

Table 3



Compd	-X-Y-	IC_{50} ± SEM (nM)[a]	
		ET_A	ET_B
rac-**9b**	$-NCH_3-CO-$	12.3±1.1	184±15
rac-**30**	$-CH_2-CH_2-$	91.7±5.3	7840±440
rac-**31**	$-O-CH_2-$	69.8±3.2	3640±880
rac-**32**		604±31	711±33
rac-**33**		58.8±9.3	261±29
rac-**34**		55.9±3.4	250±10

[a] Mean value of at least three measurements (in duplicate).

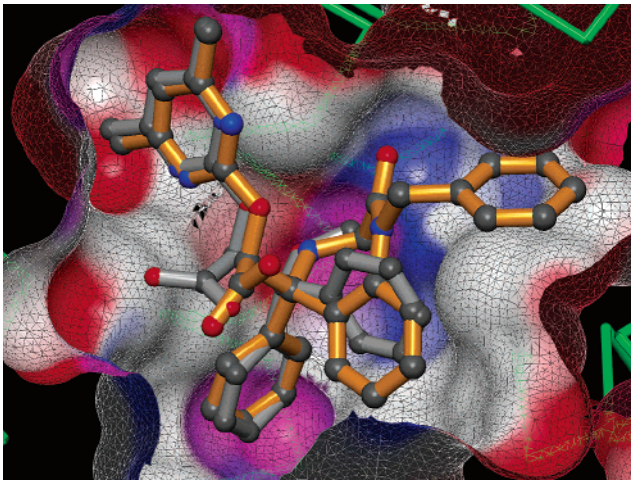
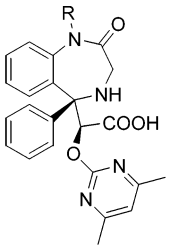


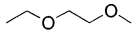
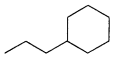
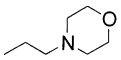
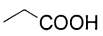
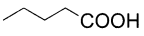
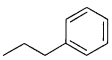
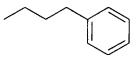
Figure 3. Ambrisentan **2** (silver) and **39l** (orange, Table 5) docked into the active site of a 3D model of endothelin A receptor (C-α representation, green). Pocket in the upper right half of the picture shows the pocket only filled by the benzyl moiety of **39l**.

methyl group. This observation clearly illustrates that the exact positioning of an additional carboxylate function is crucial. The triazole derivative rac-**33** was about as potent on both receptors as the benzodiazepinone rac-**9b**. Studies of ambrisentan **2** docked into the active site of a 3D-model of the ET_A receptor suggested that **2** leaves a pocket in the receptor completely unfilled (Figure 3). We tested this idea by synthesizing benzo[1,4]diazepin-2-one derivatives bearing methylene-bridged cyclic and noncyclic moieties attached to N_1. As discussed in the Chemistry section, protection of this nitrogen allowed rapid access to a large number of compounds in a parallel fashion. The various substituents that have been introduced to this position are summarized in Tables 4 and 5.

The N_1-methyl compound rac-**9b** showed IC_{50} values of 12.3 and 184 nM on the ET_A and ET_B receptor, respectively. With a pA_2 value of 6.87, this compound

Table 4

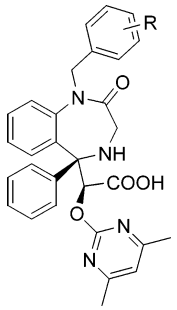


Compd	R	IC_{50} ± SEM (nM)[a]		pA_2[b]
		ET_A	ET_B	aorta
rac-**9b**	$-CH_3$	12.3±1.1	184±15	6.87
rac-**39a**	$-C_6H_{13}$	23.7±3.1	39.9±4.4	6.71
rac-**39b**		7.5±1.7	47.8±6.8	
rac-**39c**		7.3±1.2	87.8±7.4	
rac-**39d**		83.4±19.1	82.0±16.4	
rac-**39e**		146±24	153±17	
rac-**39f**		126±38	743±112	
rac-**39g**		387±36	1780±110	
rac-**39h**		6.9±0.6	108±9	6.79
rac-**39i**		13.0±0.7	558±32	7.35
rac-**39j**		6.6±0.6	65.6±3.1	6.99
rac-**39k**		45.9±4.5	253±22	
rac-**39l**		6.4±1.6	47.4±11.4	7.32
rac-**39m**		3.9±0.5	21.5±2.0	7.46
rac-**39n**		17.1±3.0	18.3±1.2	

[a] Mean value of at least three measurements (in duplicate). [b] Mean of at least three experiments, SEM ≤ ±0.3.

was moderately active in the functional assay on rat aortic rings. The *n*-hexyl substituted compound rac-**39a** had a similar affinity for ET_A but was about 6 times more potent on ET_B compared to rac-**9b**. The functional activity of rac-**39a** on aortic rings was comparable to the one of rac-**9b**. Replacing the *n*-hexyl chain by a 2-methoxyethoxyethyl or a cyclopropylmethyl group had only minimal effect on the compounds' potency on the two receptors. While the affinity for the ET_A receptor dropped slightly with the cyclohexylmethyl substituent in rac-**39d**, the affinity for the ET_B receptor was maintained, yielding a compound of exactly dual receptor antagonism. Less potent dual ET_A/ET_B antagonism was also found for the cyclohexylethyl derivative rac-**39e**. As shown by the morpholinoethyl derivative rac-**39f** and the dimethylaminoethyl substituted compound rac-**39g**, the ET_B receptor does not tolerate a positive charge tethered to N_1. The loss in activity is less pronounced in the case of the ET_A receptor. Conversely, the alcohol functionality in rac-**39h** appears to be tolerated by both receptors. This compound had a

Table 5



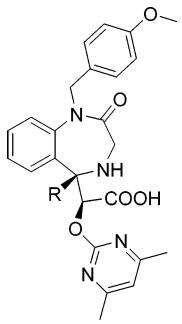
		$IC_{50} \pm SEM$ (nM)[a]					$IC_{50} \pm SEM$ (nM)[a]		
compd	R	ET_A	ET_B	pA_2 [b] aorta	compd	R	ET_A	ET_B	pA_2 [b] aorta
rac-**39l**	H	6.4 ± 1.6	47.4 ± 11.4	7.32	rac-**39ag**	4-$COOCH_3$	7.4 ± 2.0	70.3 ± 11.8	6.98
rac-**39o**	2-F	3.5 ± 0.5	33.1 ± 1.7	7.22	rac-**39ah**	4-COOH	123 ± 19	3530 ± 180	
rac-**39p**	2-Cl	10.2 ± 2.0	48.1 ± 8.8		rac-**39ai**	4-*n*-butyl	3.5 ± 0.8	11.1 ± 1.6	7.84
rac-**39q**	2-CH_3	8.9 ± 1.6	55.0 ± 6.2		rac-**39aj**	4-*tert*-butyl	17.1 ± 3.2	24.1 ± 3.5	
rac-**39r**	2-CF_3	104 ± 18	22.5 ± 2.1		rac-**39ak**	4-phenyl	102 ± 4	534 ± 31	
rac-**39s**	2-OCF_3	98.6 ± 10.3	74.9 ± 8.4		rac-**39al**	2,3-F_2	3.7 ± 0.7	18.5 ± 1.8	
rac-**39t**	3-F	6.7 ± 1.1	26.8 ± 1.9		rac-**39am**	2,4-F_2	6.0 ± 1.7	109 ± 22	
rac-**39u**	3-Cl	5.8 ± 0.2	21.4 ± 2.0		rac-**39an**	2,5-F_2	6.7 ± 2.3	32.9 ± 6.6	
rac-**39v**	3-Br	6.4 ± 1.1	25.5 ± 0.5		rac-**39ao**	2,6-F_2	1.1 ± 0.2	17.7 ± 2.6	7.83
rac-**39w**	3-CH_3	5.0 ± 0.6	16.7 ± 2.4		rac-**39ap**	3,5-F_2	7.9 ± 2.8	13.1 ± 3.2	
rac-**39x**	3-CF_3	9.1 ± 0.4	15.6 ± 1.1		rac-**39aq**	3,4-F_2	6.5 ± 1.2	32.8 ± 5.1	
rac-**39y**	3-OCF_3	11.0 ± 2.3	30.8 ± 1.5		rac-**39ar**	2,3,4-F_3	6.5 ± 1.5	49.7 ± 8.2	7.93
rac-**39z**	4-F	5.9 ± 0.3	49.7 ± 3.5	7.46	rac-**39as**	2,3,6-F_3	2.4 ± 0.4	13.2 ± 1.1	8.38
rac-**39aa**	4-Cl	17.3 ± 2.6	122 ± 9		rac-**39at**	2,4,5-F_3	7.2 ± 2.9	72.7 ± 10.2	
rac-**39ab**	4-Br	25.8 ± 1.5	119 ± 4		rac-**39au**	2,4,6-F_3	2.5 ± 0.4	83.6 ± 8.8	8.18
rac-**39ac**	4-CH_3	30.5 ± 7.9	68.8 ± 5.6		rac-**39av**	3,4,5-F_3	11.8 ± 2.2	25.3 ± 6.3	
rac-**39ad**	4-CF_3	17.0 ± 0.8	47.1 ± 3.6		rac-**39aw**	2-Cl, 6-F	1.4 ± 0.2	10.9 ± 2.4	7.80
rac-**39ae**	4-OCF_3	2.5 ± 0.3	32.2 ± 2.5	7.59	rac-**39ax**	2,6-Cl_2	1.8 ± 0.4	6.6 ± 1.23	8.55
rac-**39af**	4-OCH_3	4.6 ± 0.8	22.4 ± 2.9	7.08	rac-**39ay**	2,3,4,5,6-F_5	6.8 ± 2.4	28.8 ± 6.2	7.87
					rac-**39az**	2,4,6-$(CH_3)_3$	6.7 ± 2.3	15.5 ± 2.9	8.10

[a] Mean value of at least three measurements (all in duplicate). [b] Mean of at least three experiments, SEM ≤ ±0.3.

similar functional potency as rac-**9b**. As anticipated from our earlier findings with rac-**33**, an acidic functionality is tolerated as well. Both rac-**39i** and rac-**39j** furnished in vitro data comparable to those of rac-**9b**. Interestingly, the affinity for the ET_B receptor was improved by the longer linker between N_1 and the carboxylic acid in rac-**39k** whereas the affinity for the ET_A dropped slightly. Furthermore, highly potent compounds with almost equal affinities for the two ET receptors resulted when a phenyl ring was attached via a methylene, an ethylene, or a propylene linker to N_1. Improved potency of the benzyl derivative rac-**39l** and of the phenethyl compound rac-**39m** was also reflected in higher pA_2 values. In the following, a large number of substituted N_1-benzylated derivatives have been studied. Interestingly, ortho, meta, or para substitution with a fluorine, chlorine, or bromine atom, or with a methyl, a trifluoromethyl, or a trifluoromethoxy group had only little effect on the compounds' IC_{50} values. All these examples were highly potent dual ET receptor antagonists. The only exceptions were compounds rac-**39r** and rac-**39s** featuring an *o*-trifluoromethyl and an *o*-trifluoromethoxy group, respectively. While the ester rac-**39ag** showed IC_{50} values comparable to those of other compounds with a 4-substituted benzyl moiety, the corresponding carboxylic acid rac-**39ah** had a significantly lower affinity for the two ET receptors. This clearly demonstrates that a negative charge at this position is not tolerated by the receptors. On the other hand, the *n*-butyl chain in rac-**39ai** and even the bulky *tert*-butyl substituent in rac-**39aj** allowed strong binding to both receptors. Surprisingly, however, the 4-biphenyl substituent in rac-**39ak** significantly hampered the compound's affinity toward the two ET receptors. With the above structure−activity relationship in mind, it came as no surprise that the di- and trihalogenated derivatives rac-**39al** to rac-**39ax**, the pentafluorobenzyl compound rac-**39ay**, and the 2,4,6-trimethylbenzyl derivative rac-**39az** all showed IC_{50} values in the low nanomolar range, in particular on the ET_A receptor. Clearly less anticipated was the observation that many of these substituted benzyl derivatives had a significantly higher functional potency compared to the unsubstituted benzyl compound rac-**39l**. In fact, as we found later in our in vivo studies, only compounds with a pA_2 value greater than 7.80 on aortic rings showed a significant effect on arterial blood pressure after oral administration in hypertensive rats.

The preceding SAR studies established the 1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-one scaffold as a viable template for potent endothelin receptor antagonists. So far, we discussed how the substitution pattern around the fused benzene ring, the various substituents at N_1, and the pyrimidine moiety affect the compound's affinity for the two receptors. The compounds in Table 6 illustrate the influence of the substituent in position 5 of the 1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-one scaffold. All compounds studied so far invariably featured a phenyl ring at this position. Replacing this phenyl ring in rac-**39af** by an *n*-pentyl chain (rac-**68**) or a cyclohexyl ring (rac-**69**) clearly reduced the compound's affinity for both receptors. On the other hand, as manifested by the corresponding IC_{50} values, a 2-fluoro substituent and a series of substituents at the

Table 6



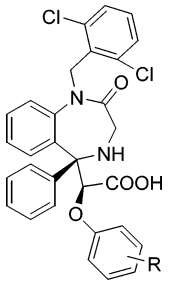
compd	R	$IC_{50} \pm SEM$ (nM)[a] ET_A	$IC_{50} \pm SEM$ (nM)[a] ET_B	pA_2[b] aorta
rac-**68**	*n*-pentyl	355 ± 99	73.6 ± 22.1	
rac-**69**	cyclohexyl	112 ± 2	105 ± 2	
rac-**39af**	phenyl	4.6 ± 0.8	22.4 ± 2.9	7.08
rac-**70**	2-fluorophenyl	30.3 ± 8.4	80.2 ± 14.9	
rac-**71**	3-fluorophenyl	9.1 ± 2.9	49.3 ± 7.0	
rac-**72**	3-chlorophenyl	25.0 ± 10.0	78.2 ± 4.5	
rac-**73**	3-methylphenyl	6.3 ± 1.1	50.7 ± 3.1	6.32
rac-**74**	3,5-dimethylphenyl	278 ± 42	761 ± 52	
rac-**75**	3-methyl-4-fluorophenyl	7.3 ± 1.5	33.2 ± 3.5	6.53
rac-**76**	3-trifluoromethyl-phenyl	24.9 ± 5.2	241 ± 14	
rac-**77**	3-methoxyphenyl	10.2 ± 2.0	94.3 ± 14.4	
rac-**78**	3-ethylphenyl	3.1 ± 0.4	68.0 ± 9.4	7.55
rac-**79**	3-*n*-butylphenyl	7.9 ± 2.2	36.5 ± 4.8	7.69
rac-**80**	3-biphenyl	3.0 ± 0.3	86.8 ± 5.1	7.28
rac-**81**	4-methylphenyl	221 ± 43	181 ± 32	

[a] Mean value of at least three measurements (in duplicate). [b] Mean of at least three experiments, SEM ≤ ±0.3.

3-position of the phenyl ring were tolerated by the receptor. Even a large substituent such as an *n*-butyl chain or an additional phenyl ring had only little effect on the compounds' receptor affinity and selectivity profile. In addition, a fluorine appeared to be tolerated in the para position of the phenyl ring as illustrated by compound rac-**75**. Conversely, the para methyl substituent in rac-**81** led to a considerable loss in affinity, in particular on the ET_A receptor. Interestingly, an even greater loss in affinity was observed with the 3,5-dimethylphenyl substituted compound rac-**74**.

In light of the improved potency of compounds bearing a benzyl substituent at N_1, it appeared worthwile to reevaluate a phenyl rather than a pyrimidine ring at the hydroxyacetic acid moiety with the N_1 benzylated benzo[1,4]diazepin-2-one scaffold. The 2,6-dichlorobenzyl, which has previously been shown to lead to highly potent compounds, was chosen for this study. The results are summarized in Table 7. The 3- and 5-substituted phenyl derivatives were slightly less potent when compared to the corresponding pyrimidine compounds, and structure−activity trends were parallel in the two series. The unsubstituted phenyl derivative rac-**84a** showed moderate activity on the ET_A receptor but lost all its affinity for the ET_B receptor. Whenever an ortho substituent was introduced to the phenyloxy moiety, inactive derivatives resulted (rac-**84b**−**d**,**l**,**m**). On the other hand, a substituent in position 3 improved the compounds' affinity for both receptors considerably. The affinity toward the ET_B receptor was further improved by an additional substituent in position 5 as shown by the 3,5-disubstituted examples rac-**84h** and rac-**84i**. A methyl group at position 4 of the phenyl ring gave a moderately active compound (rac-**84j**), while the more bulky isopropyl group at the same position (rac-**84k**) destroyed the compound's potential to block the ET receptors. Even though some potency is lost in vitro by replacing the 4,6-disubstituted pyrimidine with the corresponding 3,5-disubstituted phenyl derivative, the resulting compounds appeared to be worth testing in the in vivo model (Table 8).

Table 7



compd	R	$IC_{50} \pm SEM$ (nM)[a] ET_A	$IC_{50} \pm SEM$ (nM)[a] ET_B
rac-**84a**	H	211 ± 30	3700 ± 180
rac-**84b**	2-Cl	>10000	>10000
rac-**84c**	2-CH_3	>10000	>10000
rac-**84d**	2-OCH_3	5920 ± 660	>10000
rac-**84e**	3-CH_3	29.9 ± 7.8	745 ± 115
rac-**84f**	3-Cl	101 ± 23	3150 ± 360
rac-**84g**	3-OCH_3	129 ± 28	1470 ± 260
rac-**84h**	3,5-CH_3	20.5 ± 3.7	109 ± 24
rac-**84i**	3,5-OCH_3	46.2 ± 12.9	392 ± 56
rac-**84j**	4-CH_3	156 ± 29	966 ± 111
rac-**84k**	4-isopropyl	>10000	8620 ± 690
rac-**84l**	2,3-$(CH_3)_2$	>10000	>1000
rac-**84m**	2,5-$(CH_3)_2$	>10000	>1000

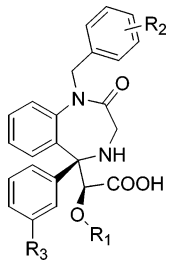
[a] Mean value of at least three measurements (in duplicate).

With the information of the above SAR studies at hand, about 25 compounds combining the most promising residues that had emerged in the individual assessments were prepared. From these 25 compounds (results not shown) and from the compounds listed in the above tables, those with IC_{50} values in the low nanomolar range on ET_A showing a pA_2 value greater than 7.0 were screened for their activity in our in vivo model.

In Vivo Activity Assessment

Oral activity was assessed in Dahl salt sensitive hypertensive rats as previously described,[68−70] using a screening dose of 30 mg/kg. In this model efficient blockade of the ET_A receptors results in a significant reduction of arterial blood pressure as measured by the area between the curves (ABC) from the blood pressure recordings before and after treatment. More than 50 1,3,4,5-tetrahydrobenzo[1,4]diazepin-2-one derivatives were characterized in this manner. The heart rate remained unaffected in all experiments (data not shown). An IC_{50} value on the ET_A receptor in the low nanomolar range and a pA_2 value on aortic rings greater than 7.80 were necessary but not sufficient to achieve oral activity. Eight compounds showed a significant reduction in blood pressure after oral administration (ABC ≥ 200). The in vivo data of these compounds are compiled in Table 8. The best compounds reduced the blood pressure by about 25 mmHg and had a duration of action greater than 32 h. For comparison, one group of animals was treated with 30 mg/kg of the racemic form of ambrisentan, rac-**2**. At this dose rac-**2** reaches an ABC of 409 mmHg·h (Table 8). The racemates rac-**85**, rac-**86**, rac-

Table 8. Summary of the Orally Active Compounds



compd	R_1	R_2	R_3	IC_{50} ± SEM (nM)[a] ET_A	IC_{50} ± SEM (nM)[a] ET_B	pA_2[b] aorta	pA_2[b] trachea	ABC[c] (mmHg·h) (*n*)	max effect[d] (mmHg)	DA[e] (h)
rac-**39au**	4,6-$(H_3C)_2$-2-pyrimidine	2,4,6-F_3	H	2.5 ± 0.4	83.6 ± 8.8	8.18	6.18	674 (10)	−21 ± 4	54
rac-**85**	4,6-$(H_3C)_2$-2-pyrimidine	2,4,6-$(H_3C)_3$	*n*-butyl	18.3 ± 1.1	13.6 ± 3.1	7.83	7.44	285 (12)	−21 ± 4	24
rac-**86**	4,6-$(H_3C)_2$-2-pyrimidine	2,4,6-F_3	*n*-butyl	13.9 ± 4.0	33.2 ± 4.9	8.36	7.72	214 (6)	−13 ± 5	18
rac-**87**	4,6-$(H_3C)_2$-2-pyrimidine	2-Cl, 6-F	*n*-butyl	7.6 ± 1.2	7.1 ± 1.3	8.72	7.88	409 (12)	−23 ± 5	36
rac-**88**	4,6-$(H_3C)_2$-2-pyrimidine	2,6-Cl_2	phenyl	16.9 ± 1.5	25.0 ± 2.3	8.98	7.37	200 (12)	−15 ± 5	18
rac-**89**	4,6-$(H_3C)_2$-2-pyrimidine	2,4,6-F_3	phenyl	7.9 ± 1.6	89.8 ± 16.4	9.03	7.07	250 (15)	−12 ± 4	24
rac-**90**	3,5-$(H_3C)_2$-phenyl	2-Cl, 6-F	H	18.9 ± 5.9	184 ± 39	6.59	6.89	267 (12)	−13 ± 2	30
rac-**91**	3,5-$(H_3C)_2$-phenyl	2,4,6-F_3	H	17.2 ± 2.8	565 ± 52	8.27	7.02	483 (14)	−28 ± 2	32
rac-**2** (rac-ambrisentan)				21.7 ± 1.0	1190 ± 170	7.09	5.63	409 (6)	−17 ± 7	32

[a] Mean value of at least three measurements (in duplicate). [b] Mean value of at least three measurements, SEM ≤ ±0.3. [c] Area between curve (ABC) as calculated from the blood pressure recordings before and after administration of 30 mg/kg of the compound to hypertensive Dahl salt sensitive rats; *n* = number of animals. [d] Reduciton of mean arterial blood pressure. [e] DA = duration of action.

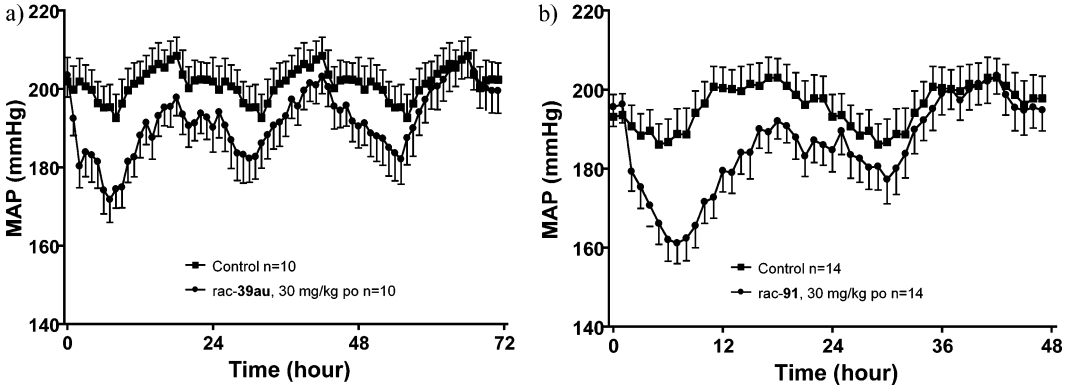


Figure 4. Mean arterial blood pressure recordings before (control) and after administration of 30 mg/kg rac-**39au** (a) and rac-**91** (b) to Dahl salt sensitive rats. The heart rate remained unchanged (data not shown).

88, rac-**89**, and rac-**90** were less efficacious than rac-**2**, while the two compounds rac-**87** and rac-**91** were equally efficacious with an ABC of 409 and 483, respectively. The compound rac-**39au**, however, was superior to rac-**2** in this test (ABC = 674). It is interesting to note that out of the eight orally active benzodiazepinone derivatives, four (i.e., rac-**39au**, rac-**86**, rac-**89**, and rac-**91**) featured the 2,4,6-trifluorobenzyl substituent at N_1. The compounds rac-**87**, rac-**88**, and rac-**90** bearing a 2,6-dihalogenated benzyl substituent at N_1 constitute a second cluster of orally active benzodiazepinone derivatives. Because a large number of compounds with other substituents at N_1 have been subjected to the in vivo testing, the observed clustering is not likely a result of biased selection for in vivo screening. No such privileged pattern emerged for the meta substituent at the 5-phenyl ring. Another interesting observation was the fact that the 4,6-dimethylpyrimidine compound rac-**39au** and its phenyl analogue rac-**91** both showed a similar efficacy in the in vivo model. The blood pressure recordings before and after administration of these two compounds are shown in Figure 4. The efficacy of rac-**91** has been studied in more detail with dose−response experiments (Figure 5). At a dose of 1 mg/kg the reduction of the mean arterial blood pressure was small (approximately −10 mmHg). The maximal effect was close to −30 mmHg and was reached with a dose of 10 mg/kg. There was no significant gain in efficacy when the dose was further increased to 30 mg/kg. In future studies, the compound's efficacy in blocking the ET_B receptor will be assessed by measuring the plasma ET-1 levels after oral admin-

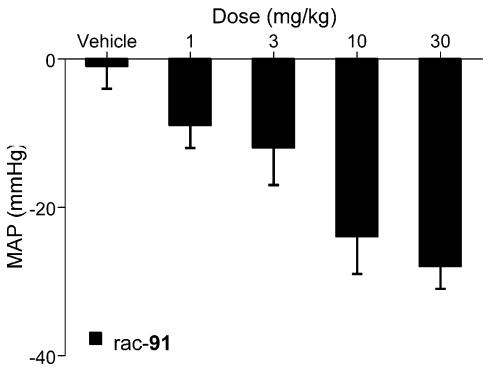


Figure 5. Dose−response results of rac-**91**. The compound was administered orally at the dose indicated to hypertensive Dahl salt sensitive rats (1 mg/kg (*n* = 6), 3 mg/kg (*n* = 6), 10 mg/kg (*n* = 10), 30 mg/kg (*n* = 14)).

Table 9. IC_{50} Values of Cytochrome P450 Inhibition and log $D_{7.4}$ Values

	IC_{50} (μM)			
compd	2C9	2D6	3A4	log $D_{7.4}$
rac-**9b**	>50	>50	>50	−2.0
rac-**39au**	>50	>50	41	0.4
rac-**86**	15	>50	5	2.3
rac-**89**	28	>50	7	1.8
rac-**91**	15	>50	14	2.1

istration of the benzodiazepinone derivatives listed in Table 8 to Wistar rats.[71]

One compound, rac-**88**, has been resolved into its pure enantiomers by means of HPLC on a chiral stationary phase. While (+)-**88** showed IC_{50} values of 10.8 ± 1.4 and 20.4 ± 2.5 nM at the ET_A and ET_B receptor, respectively, the (−)-isomer was almost inactive with IC_{50} values in the micromolar range on both receptors. This suggests that only half of the orally administered dose is responsible for the observed effects.

Pharmacokinetic Analysis

The pharmacokinetic behavior of two prototypical structural representatives, i.e., rac-**39au** and rac-**91**, has been investigated in the Wistar rat with a limited number of animals in order to characterize the absorption, distribution, and elimination properties of this novel class of compounds. Both compounds exhibited systemic plasma clearances in the range 30−70% of liver blood flow. Experiments exploring the metabolic stability in the presence of rat liver microsomes and primary hepatocytes (data not shown) indicated a very low intrinsic metabolic clearance, suggesting excretion of unchanged drug as the major pathway of elimination. Distribution into tissues was limited on the basis of the observed volumes of distribution of 1.0−1.2 L/kg. Terminal half-lives were between 1 and 2 h for both compounds. After oral administration of 10 mg/kg, peak plasma concentrations were ca. 40 and 250 ng/mL for rac-**39au** and rac-**91**, respectively, translating into oral bioavailabilities of 13% and 19%.

A number of compounds have been tested for their potential to inhibit the activity of the major human cytochrome P450 enzymes (CYP). As expected from their hydrophilic nature, the inhibitory potency of most of the compounds was low, with IC_{50} values above 50 μM for the three CYP isoenzymes 2C9, 2D6, and 3A4. However, there was a general trend for the more lipophilic compounds (as judged from their respective log *D* values) to inhibit the CYPs 2C9 and 3A4, as exemplified by the compounds rac-**86**, rac-**89**, and rac-**91** (Table 9).

Conclusion

We have prepared novel benzo[1,4]diazepin-2-one derivatives that serve as potent orally active dual ET_A/ET_B endothelin receptor antagonists. All examples discussed in this report have been prepared and tested as racemic mixtures. In our in vivo model, the efficacy of rac-**39au** was superior to the one of the racemate of ambrisentan, rac-**2**. Future efforts shall aim at an enantioselective synthesis of the benzodiazepinone derivatives discussed above. In addition, more detailed pharmacokinetic analyses may support the design of compounds with an improved bioavailability.

Experimental Section

Chemistry. All reagents and solvents were used as purchased from commercial sources (Sigma-Aldrich Co., Fluka Chemie AG, Lancaster Synthesis GmbH, Acros Organics). Moisture-sensitive reactions were carried out under an argon atmosphere. Progress of the reactions was followed either by thin-layer chromatography (TLC) analysis (Merck, 0.2 mm silica gel 60 F_{254} on glass plates) or by LC−MS (Finnigan Navigator with HP 1100 binary pump and DAD; column Zorbax SB-AQ, 5 μm, 120 Å, 4.6 mm × 50 mm; gradient, 5−95% acetonitrile in water, 0.04% trifluoroacetic acid, in 1.5 min; flow rate, 4.5 mL/min). Flash column chromatography was carried out using silica gel 60 (Fluka). For preparative TLC, glass plates coated with 0.5 mm of silica gel 60 F_{254} (Merck) were used. Melting points were measured in glass capillary tubes on a Büchi B-540 apparatus and are uncorrected. All compounds were characterized by LC−MS and NMR. According to these analyses, the puritiy of the intermediates as well as the final products generally exceeded 95%. In vivo active compounds were further characterized by elemental analysis carried out at Solvias AG, Basel, Switzerland.

NMR Spectrometry. NMR spectra were recorded on a Varian Mercury 300VX spectrometer (^{1}H, 300 MHz; ^{13}C, 75 MHz; ^{19}F, 282 MHz). Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS), and multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). NMR spectra of the final β-amino acid compounds (e.g., rac-**39**) often were of poor resolution at room temperature. To enhance the resolution, most of the spectra of such compounds were acquired at elevated temperatures. Despite this measure, some aromatic carbons still gave broad signals in the ^{13}C NMR. On the other hand, the methyl group as well as carbon C_5 of the 4,6-dimethylpyrimidine moiety often gave rise to a set of two sharp signals around 24 and 115 ppm. While one of the H_3 hydrogens of the benzodiazepinone scaffold gave a sharp doublet ($J \approx 16$ Hz) in the ^{1}H NMR, its coupling partner sometimes appeared as a broad, barely visible signal.

General Procedure for the Grignard Reaction of Alkyl- and Arylmagnesium Bromides with 2-Aminobenzonitrile. Method A. The alkyl- and arylmagnesium bromides were prepared by slowly adding the alkyl or aryl bromide (3 equiv) dissolved in diethyl ether (0.5−2 mL/mmol) to magnesium turnings (4 equiv) suspended in diethyl ether (0.1−0.6 mL/mmol Mg). After the gray-brownish reaction mixture was refluxed for 1−3 h, it was cooled to room temperature and a solution of 2-aminobenzonitrile (15−150 mmol, 1 equiv) in diethyl ether (1−2 mL/mmol) was added dropwise. The pale-yellow precipitate, which formed immediately upon each addition, slowly dissolved again. Upon completion of the addition, the slightly turbid solution was heated to reflux for 1−16 h, then cooled with an ice bath. The reaction mixture was carefully quenched with water followed by 2 N aqueous HCl. Stirring of the mixture was continued for 3−18 h at room temperature to 45 °C, and the progress of the hydrolysis was monitored by LC−MS. The pH of the mixture was adjusted to 8−9 with aqueous NaOH and saturated aqueous $NaHCO_3$. The layers were separated, the aqueous layer was extracted with diethyl ether (2×), the combined organic extracts were washed with brine and dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was either used as such in the following step or purified by column chromatography on silica gel.

General Procedure for the Preparation of Benzo[1,4]-diazepin-2-ones Starting from 2-Aminobenzophenones. Method B.[52] To a cooled (0 °C) solution of the substituted 2-aminophenone (15−500 mmol) in CH_2Cl_2 (1.5−6 mL/mmol), was added water (0.1−0.4 mL/mmol). The mixture was stirred vigorously while bromoacetyl bromide (1.15 equiv, either neat or as a solution in CH_2Cl_2 (0.4 mL/mmol)) was slowly added. Stirring was continued at room temperature for 2−15 h. The reaction was quenched by carefully adding saturated aqueous $NaHCO_3$. The layers were partitioned, the aqueous layer was

extracted once more with CH_2Cl_2, and the combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvent and drying under high vacuum furnished the crude acylation product in almost quantitative yield. In a few cases the product was further purified by crystallization from diethyl ether/hexane.

The obtained bromoacetylated aminophenone was dissolved in methanol saturated with ammonia (approximately 7 M, 3−10 mL/mmol) and heated to 45 °C for 2−15 h. The solvent was removed in vacuo, the crude product was dissolved in CH_2Cl_2, washed with water and brine, and dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was precipitated from diethyl ether or diethyl ether/hexane, filtered off, washed with additional diethyl ether or diethyl ether/hexane, and dried under high vacuum to furnish the desired benzo[1,4]diazepin-2-one in good yield.

Method C. The 2-aminobenzophenone derivative (10−71 mmol) was dissolved in absolute pyridine (2−7 mL/mmol), glycine ethyl ester hydrochloride (1.6 equiv) was added, and the reaction mixture was heated to reflux for 16−72 h. Upon completion of the reaction, toluene was added and the solvent was removed in vacuo. The reaction mixture was partitioned between water and ethyl acetate, the layers were separated, and the aqueous layer was extracted once again with ethyl acetate. The combined organic extracts were washed with brine and dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was purified over silica (heptane/ethyl acetate or CH_2Cl_2/heptane) to yield the desired benzo[1,4]-diazepin-2-one in moderate yield.

General Procedure for the Protection of N_1 of 1,3-Dihydrobenzo[*e*][1,4]diazepin-2-ones with 4-Methoxybenzyl Chloride. Method D. To a solution of the N_1-unprotected benzo[1,4]diazepin-2-one (4−42 mmol) in dry DMF (2−7 mL/mmol), was added K_2CO_3 (3 equiv) followed by 4-methoxybenzyl chloride (1.05−1.15 equiv). The mixture was stirred at constant temperature between room temperature and 45 °C over 16−42 h, diluted with ethyl acetate, and washed with water. The aqueous phase was extracted with ethyl acetate (2×), the combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was removed in vacuo. The crude residue was precipitated by adding diethyl ether to afford the 1-(4-methoxybenzyl)-1,3-dihydrobenzo[*e*]-[1,4]diazepin-2-one derivative in high yield.

General Procedure for the [2 + 2]-Cycloaddition Reaction. Method E. To a cooled solution (0 °C) of the imine (0.4−10 mmol), benzyloxyacetic acid or a substituted phenoxyacetic acid (1.3−1.5 equiv), and triethylamine (5 equiv) in dry CH_2Cl_2 (2.5−25 mL/mmol) was added bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (2 equiv). The suspension was stirred for 3−18 h at room temperature. The reaction mixture was diluted with CH_2Cl_2, washed once with saturated aqueous $NaHCO_3$, and once with saturated aqueous NaCl. The organic extracts were dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by crystallization from methanol or by chromatography on silica gel to give the desired β-lactam in high yield.

Method F. To a cooled solution (0 °C) of the imine (3−40 mmol) and triethylamine (3−5 equiv) in CH_2Cl_2 (5−10 mL/mmol imine) benzyloxyacetyl chloride (1.3−1.5 equiv) was added dropwise. The mixture was stirred at 0 °C for 40 min, then at room temperature for 20 h before it was diluted with ethyl acetate and washed three times with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by crystallization from diethyl ether or, if crystallization failed, by column chromatography on silica gel. The desired β-lactam was obtained in high yield.

General Procedure for the Benzyl Ether Cleavage. Method G. The benzyl ether (1−70 mmol) was dissolved in THF (3−25 mL/mmol), and the resulting solution was diluted with ethanol (3−25 mL/mmol). After the careful addition of the palladium catalyst (80−300 mg/mmol 10% Pd on charcoal, suspended in THF), the mixture was treated with acetic acid (0.5−1 mL) and stirred for 3−18 h at 45−60 °C under 7 atm of H_2. Upon completion of the reaction, the catalyst was removed by filtration over a glass microfiber filter (Whatman GF/B). The filtrate was evaporated under reduced pressure and the obtained solid was suspended in diethyl ether, filtered off, and dried under high vacuum to furnish the desired alcohol in almost quantitative yield.

General Procedure for the Introduction of the Pyrimidine Moiety. Method H. To a solution of the alcohol (0.5−36 mmol) in DMF (3−15 mL/mmol), was added K_2CO_3 (3−5 equiv) followed by the appropriate 2-methanesulfonyl- or 2-chloropyrimidine (1.2−2 equiv). The mixture was stirred at room temperature to 50 °C overnight before it was diluted with ethyl acetate and washed three times with water. The organic layer was dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography on silica gel or by crystallization from diethyl ether/hexane to furnish the pure pyrimidine derivative in good yield.

General Procedure for the Cleavage of the 4-Methoxybenzyl Protecting Group. Method I. To an ice cold solution of the 4-methoxybenzyl protected amide (1−30 mmol) in CH_3CN (12−25 mL/mmol), an approximately 2 M aqueous solution of ammonium cerium(IV) nitrate (CAN, 3 equiv) was slowly added over a period of 30 min. Upon completion of the addition, stirring was continued at room temperature for 1−6 h. The orange reaction mixture was diluted with water and extracted three times with CH_2Cl_2. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The pure deprotected benzodiazepinone was obtained in good yield either by column chromatography of the crude material or by washing the solid residue with CH_3CN, ethyl acetate, or diethyl ether.

General Procedure for the N_5-Alkylation of the 1-(Pyrimidin-2-yloxy)-5,9b-dihydro-1*H*-2a,5-diazabenzo[*a*]cyclobuta[*c*]cycloheptene-2,4-dione Derivatives. Method J. A mixture of the 1-(pyrimidin-2-yloxy)-5,9b-dihydro-1*H*-2a,5-diazabenzo[*a*]cyclobuta[*c*]cycloheptene-2,4-dione (0.4−6 mmol), K_2CO_3 (3 equiv), and the alkyl or benzyl halide (1.2−1.5 equiv) in DMF (6−20 mL/mmol) was stirred at 50−60 °C for 18 h. If required, further alkyl or benzyl halide (1−1.5 equiv) and K_2CO_3 (3 equiv) were added and stirring was continued for an additional 24 h at 50−60 °C. Upon completion of the reaction, the mixture was diluted with water and extracted twice with ethyl acetate. The organic extracts were washed with brine, dried over $MgSO_4$, and evaporated. The crude product was purified by chromatography on preparative TLC plates (heptane/ethyl acetate) to furnish the desired N_5 alkylated or benzylated 5,9b-dihydro-1*H*-2a,5-diazabenzo[*a*]cyclobuta[*c*]-cycloheptene-2,4-dione derivative in good yield.

General Procedure for the β-Lactam Cleavage. Method K. A solution of the β-lactam (0.1−2 mmol) in THF/methanol/water 5:4:1 (10−30 mL/mmol) was treated with a 2 N aqueous solution of LiOH (2−4 mL/mmol). The resulting solution was stirred at 45−60 °C for 2−4 h, diluted with 10% aqueous citric acid solution (50 mL), and extracted three times with CH_2Cl_2 (50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The desired amino acid was purified either by crystallization from methanol or by chromatography on preparative TLC plates using a mixture of CH_2Cl_2/methanol 10:1 as solvent.

General Procedure for the Parallel Synthesis of Compounds rac-39. Method L. A large number of the compounds rac-**39** have been prepared in a parallel fashion as follows: A mixture of rac-**38** (0.1 mmol), K_2CO_3 (0.3 mmol), and the alkyl or benzyl halide (0.15 mmol) in DMF (1 mL) was shaken at 60 °C for 40 h. The solid was filtered off, and the filtrate was evaporated under reduced pressure. The residue was dissolved in acetonitrile/acetic acid/DMF 3:1:1 (1.2 mL) and subjected to preparative HPLC (column, Phenomenex AQUA, 5 μm, 125 Å, 21 mm × 60 mm; gradient, 10−95% acetonitrile in water containing 0.5% formic acid, in 3.5 min; flow rate, 40 mL/min). The purified alkylated β-lactam intermediates were dissolved in THF (2 mL) and methanol (1 mL) and treated with 2 N aqueous LiOH solution (0.4 mL). The reaction mixture was

stirred at 40 °C for 2 h before it was neutralized with acetic acid (0.4 mL). The solvent was removed in vacuo, and the remaining residue was dissolved in water/acetic acid/acetonitrile 2:1:2 (1.2 mL) and purified by automated HPLC (conditions as above). The desired amino acids were obtained as colorless lyophilisates with UV purities exceeding 95% (LC−MS).

(3,5-Dimethoxyphenoxy)acetic Acid. A mixture of 3,5-dimethoxyphenol (10 g, 64.8 mmol), ethyl bromoacetate (7.2 mL, 64.8 mmol), and potassium carbonate (13.4 g, 97.3 mmol) in acetone (100 mL) was refluxed for 5 h. The mixture was filtered and the filtrate was evaporated to give (3,5-dimethoxyphenoxy)acetic acid ethyl ester (16.16 g) as an orange oil. This oil was dissolved in THF (100 mL) and methanol (40 mL) and treated with a solution of lithium hydroxide monohydrate (6.99 g, 166.5 mmol) in water (100 mL) at 5 °C. The resulting solution was stirred at room temperature for 5 h, then poured into 1 M aqueous HCl. The aqueous phase was extracted twice with ethyl acetate. The organic extracts were dried over $MgSO_4$ and evaporated to give (3,5-dimethoxyphenoxy)acetic acid (6.75 g, 98%) as a beige solid. $R_f = 0.44$ (heptane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): δ 6.06−6.08 (m, 3H), 4.51 (s, 2H), 3.71 (s, 6H). MS (ES^+) *m/z*: 241 (M + H).

(3,5-Dimethylphenoxy)acetic Acid. The title compound was prepared in analogy to (3,5-dimethoxyphenoxy)acetic acid using 3,5-dimethylphenol on a 81 mmol scale. Crystallization from diethyl ether/hexane furnished the acid in 90% yield as fine, colorless crystals, mp 112−113 °C. ^{1}H NMR ($CDCl_3$): δ 9.35 (s br, 1H), 6.66 (s, 1H), 6.55 (s, 2H), 4.66 (s, 2H), 2.30 (s, 6H, CH_3).

rac-(*S)-(3,5-Dimethoxyphenoxy)-{(5*S**)-1-methyl-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-5-yl}acetic Acid (rac-5a).** According to method E, 1-methyl-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one **3a**[52] (200 mg, 0.8 mmol) was reacted with 3,5-dimethoxyphenoxyacetic acid to furnish rac-**4a** (258 mg, 73%) after crystallization from methanol as a beige powder, mp 221−223 °C. ^{1}H NMR ($CDCl_3$): δ 7.68−7.64 (m, 1H), 7.54−7.41 (m, 2H), 7.31−7.21 (m, 6H), 6.09 (t, J = 2.3 Hz, 1H), 6.00 (d, J = 2.3 Hz, 2H), 5.79 (s, 1H), 4.42 (d, J = 13.5 Hz, 1H), 3.82 (d, J = 13.5 Hz, 1H), 3.69 (s, 6H), 2.57 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 165.4, 163.9, 161.4, 159.0, 141.7, 137.5, 133.5, 130.3, 128.30, 128.28, 127.7, 126.8, 126.6, 126.4, 95.8, 95.6, 86.3, 71.2, 55.7, 45.7, 36.8. MS (ES^+) *m/z*: 445 (M + H). The β-lactam rac-**4a** (228 mg, 0.51 mmol) was hydrolyzed according to method K to furnish the title compound rac-**5a** (182 mg, 77%) after purification on preparative TLC plates (CH_2Cl_2/methanol 10:1) as an amorphous pale-beige solid. ^{1}H NMR (DMSO-d_6, 65 °C): δ 7.63 (d br, J = 7.0 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.33−7.10 (m, 7H), 6.04 (t, J = 2.3 Hz, 1H), 5.92 (d, J = 2.3 Hz, 2H), 5.07 (s, 1H), 3.63 (s, 6H), 3.39 (d, J = 12.9 Hz, 1H), 3.26 (d, J = 12.9 Hz, 1H), 2.25 (s, 3H). ^{13}C NMR (DMSO-d_6, 65 °C): δ 170.9, 167.9, 161.5, 160.1, 143.5, 143.3, 135.2, 129.8, 128.2, 127.6, 127.4, 127.2, 126.4, 124.9, 95.6, 94.8, 82.7, 67.8, 55.9, 47.9, 33.9. MS (ES^+) *m/z*: 463 (M + H). Anal. ($C_{26}H_{26}N_2O_6 \cdot 0.5H_2O \cdot 0.125 SiO_2$) C, H, N.

rac-(*S)-{(5*S**)-1-Methyl-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-5-yl}(pyrimidin-2-yloxy)-acetic Acid (rac-9a).** 1-Methyl-5-phenyl-1,3-dihydrobenzo-[*e*][1,4]diazepin-2-one **3a**[52] (8.0 g, 32 mmol) was treated with benzyloxyacetyl chloride (method F). The crude solid obtained after the extraction step was washed with methanol to yield rac-**6** (11.7 g, 92%) as a beige solid. ^{1}H NMR (CDC_3): δ 7.51−7.44 (m, 1H), 7.40−7.19 (m, 11H), 6.98−6.93 (m, 2H), 5.27 (s, 1H), 4.44 (s, 2H), 4.37 (d, J = 13.6 Hz, 1H), 3.75 (d, J = 13.6 Hz, 1H), 2.58 (s, 3H). MS (ES^+) *m/z*: 399 (M + H). The benzyl ether in rac-**6** (11.7 g, 29.4 mmol) was cleaved (method G) to yield rac-**7** (6.7 g, 74%) as a colorless solid. ^{1}H NMR ($CDCl_3$): δ 7.64 (dd, J = 1.9, 7.1, 1H), 7.47−7.36 (m, 2H), 7.35−7.22 (m, 4H), 7.18−7.12 (m, 2H), 5.36 (s, 1H), 4.32 (d, J = 13.6 Hz, 1H), 3.69 (d, 13.6 Hz, 1H), 2.66 (s br, 1H), 2.51 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 168.3, 164.3, 141.5, 137.7, 133.7, 130.2, 129.0, 128.6, 127.7, 127.0, 126.4, 126.1, 82.0, 71.8, 45.5, 36.9. MS (ES^+) *m/z*: 309 (M + H). The alcohol rac-**7** (100 mg, 0.324 mmol) was reacted with 2-chloropyrimidine (method H) to furnish rac-(1*S**,9b*S**)-5-methyl-9b-phenyl-1-(pyrimidin-2-yloxy)-5,9b-dihydro-1*H*-2a,5-diaza-benzo[*a*]cyclobuta[*c*]cycloheptene-2,4-dione rac-**8a** (110 mg, 88%) as a colorless foam after purification on preparative TLC plates (heptane/ethyl acetate 1:3). ^{1}H NMR ($CDCl_3$): δ 8.51−8.47 (m, 1H), 8.42 (d, J = 4.7 Hz, 2H), 7.55−7.08 (m, 8H), 6.92 (t, J = 4.6 Hz, 1H), 6.60 (s, 1H), 4.44 (d, J = 13.5 Hz, 1H), 3.87 (d, J = 13.5 Hz, 1H), 2.54 (s, 3H). MS (ES^+) *m/z*: 387 (M + H). Hydrolysis (method K) of the β-lactam rac-**8a** (100 mg, 0.258 mmol) afforded the title compound rac-**9a** (79 mg, 75%) after purification by preparative TLC (CH_2Cl_2/methanol 10:1) as a colorless foam. ^{1}H NMR (DMSO-d_6, 60 °C): δ 8.49 (d, J = 4.7 Hz, 2H), 7.44−6.99 (m, 10H), 5.96 (s, 1H), 3.34 (d, J = 12.9 Hz, 1H), 3.20 (d, 13.5 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (DMSO-d_6, 65 °C): δ 170.1, 167.8, 167.7, 164.3, 159.8, 143.6, 135.7, 129.3, 128.0, 127.5, 127.2, 126.2, 124.4, 116.4, 78.8, 67.2, 55.6, 48.8, 34.0. MS (ES^+) *m/z*: 405 (M + H).

rac-(*S)-(4,6-Dimethylpyrimidin-2-yloxy)-{(1*S**)-1-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-yl}acetic Acid (rac-30).** 1-Phenyl-4,5-dihydro-3*H*-benzo[*c*]azepine **10**[54] (1.16 g, 5.24 mmol) was reacted with benzyloxyacetic acid (method E) to furnish the β-lactam rac-**15** (124 mg, 6%) after column chromatography (CH_2Cl_2/methanol 9:1) as a pale-yellow foam. ^{1}H NMR ($CDCl_3$): δ 7.51−7.09 (m, 11H), 7.04−6.90 (m, 3H), 5.21 (s, 1H), 4.52 (d, J = 10.8 Hz, 1H), 4.36 (d, J = 10.8 Hz, 1H), 4.25−4.12 (m, 1H), 3.26−3.08 (m, 1H), 2.80−2.66 (m, 1H), 2.56−2.44 (m, 1H), 1.92−1.76 (m, 1H), 1.76−1.56 (m, 1H). MS (ES^+) *m/z*: 370 (M + H). The benzyl ether in rac-**15** (124 mg, 0.335 mmol) was cleaved (method G) to furnish the alcohol rac-**20** (92 mg, 98%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.44−6.92 (m, 9H), 5.31 (s, 1H), 4.12−4.00 (m, 1H), 3.57 (s, 1H), 3.15−3.02 (m, 1H), 2.70−2.58 (m, 1H), 2.50−2.36 (m, 1H), 1.83−1.40 (m, 2H). MS (ES^+) *m/z*: 280 (M + H). The alcohol rac-**20** (45 mg, 0.161 mmol) was treated with 2-methanesulfonyl-4,6-dimethylpyrimidine (method H) to yield the pyrimidine derivative rac-**25** (49 mg, 79%) as a pale-yellow foam after chromatography on preparative TLC plates (heptane/ethyl acetate 3:7). ^{1}H NMR ($CDCl_3$): δ 8.74 (dd, J = 1.1, 7.7 Hz, 1H), 7.42−7.08 (m, 6H), 7.03−6.97 (m, 2H), 6.55 (s, 1H), 6.48 (s, 1H), 4.30−4.20 (m, 1H), 3.25 (dt, J_d = 3.8 Hz, J_t = 12.8 Hz, 1H), 2.74−2.63 (m, 1H), 2.52−2.40 (m, 1H), 2.31 (s, 6H), 1.90−1.80 (m, 1H), 1.76−1.60 (m, 1H). MS (ES^+) *m/z*: 386 (M + H). Hydrolysis (method K) of the β-lactam rac-**25** (49 mg, 0.127 mmol) afforded the title compound rac-**30** (30 mg, 59%) after HPLC purification (conditions as for rac-**5c**) as a white lyophilisate. ^{1}H NMR (DMSO-d_6, 65 °C): δ 7.48−7.05 (m, 9H), 6.80 8s, 1H), 6.21 (s, 1H), 3.43−3.31 (m, 2H), 2.62−2.50 (m, 2H), 2.62−2.50 (m, 1H), 2.45−2.32 (m, 1H), 2.29 (s, 6H), 1.80−1.70 (m, 1H), 1.64−1.42 (m, 2H). MS (ES^+) *m/z*: 404 (M + H).

rac-(*S)-(4,6-Dimethylpyrimidin-2-yloxy)-{(5*S**)-5-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepin-5-yl}acetic Acid (rac-31).** 7-Chloro-5-phenyl-2,3-dihydrobenzo[*f*][1,4]oxazepine **11**[55] (2.0 g, 7.76 mmol) was reacted with benzyloxyacetic acid (method E) to afford the β-lactam rac-**16** (3.04 g, 97%) as a white solid after column chromatography. ^{1}H NMR ($CDCl_3$): δ 7.40−7.35 (m, 3H), 7.28−7.24 (m, 4H), 7.17−7.13 (m, 2H), 7.04−6.97 (m, 4H), 5.05 (s, 1H), 4.49 (d, J = 11.2 Hz, 1H), 4.37 (d, J = 11.2 Hz, 1H), 4.20 (dt, J_d = 12.3 Hz, J_t = 3.5 Hz, 1H), 4.08 (ddd, J = 2.6, 3.5, 13.7 Hz, 1H), 3.78 (ddd, J = 2.7, 9.5, 12.3 Hz, 1H), 3.38 (ddd, J = 3.3, 9.3, 13.7 Hz, 1H). MS (ES^+) *m/z*: 406 (M + H). The benzyl ether and the 7-chloro substituent in rac-**16** (500 mg, 1.23 mmol) were cleaved (method G) to give the alcohol rac-**21** (290 mg, 84%) as a slightly gray powder. ^{1}H NMR ($CDCl_3$): δ 7.43−7.30 (m, 5H), 7.27−7.21 (m, 1H), 7.13−7.06 (m, 3H), 5.30 (s, 1H), 4.28 (dt, J_d = 12.3 Hz, J_t = 3.5 Hz, 1H), 4.09 (dt, J_d = 14.1 Hz, J_t = 2.9 Hz, 1H), 3.84 (ddd, J = 2.3, 10.0, 12.3 Hz, 1H), 3.48 (ddd, J = 3.5, 9.4, 13.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 167.2, 158.6, 136.8, 132.6, 129.9, 129.4, 128.9, 127.5, 124.0, 123.1, 85.5, 72.6, 71.0, 41.5. MS (ES^+) *m/z*: 282 (M + H). Treatment (method H) of the alcohol rac-**21** (227 mg, 0.807 mmol) with 2-methanesulfonyl-4,6-dimethylpyrimidine furnished the pyrimidine derivative rac-**26** (196 mg, 63%) as colorless fine crystals, mp 202−204 °C

(diethyl ether). ^{1}H NMR ($CDCl_3$): δ 8.73 (dd, J = 1.7, 7.5 Hz, 1H), 7.40−7.26 (m, 2H), 7.20−7.00 (m, 6H), 6.58 (s, 1H), 6.42 (s, 1H), 4.31−4.12 (m, 2H), 3.88−3.78 (m, 1H), 3.56−3.44 (m, 1H), 2.34 (s, 6H). MS (ES^+) m/z: 388 (M + H). Hydrolysis (method K) of the β-lactam rac-**26** (100 mg, 0.258 mmol) furnished the title compound rac-**31** (58 mg, 55%) after HPLC purification (conditions as for rac-**5c**) as a colorless lyophilisate. ^{1}H NMR ($CDCl_3$, 60 °C): δ 7.51−7.46 (m, 1H), 7.41−7.34 (m, 2H), 7.30−6.90 (m, 6H), 6.32 (s, 1H), 6.08 (s, 1H), 4.78−4.68 (m, 1H), 4.32 (ddd, J = 2.3, 4.7, 15.2 Hz, 1H), 4.22−4.10 (m, 1H), 3.94 (ddd, J = 2.3, 4.7, 10.0 Hz, 1H), 2.16 (s br, 6H). ^{13}C NMR ($CDCl_3$, 60 °C): δ 1725., 161.0, 153.0, 141.6, 136.6, 129.7, 127.9, 127.6, 127.5, 127.2, 126.3, 124.8, 123.8, 110.6, 76.0, 75.8, 69.7, 46.4, 23.6. MS (ES^+) m/z: 406 (M + H).

rac-(6*S)-6-[(*S**)-Carboxy-(4,6-dimethylpyrimidin-2-yloxy)methyl]-1-methyl-6-phenyl-5,6-dihydro-4*H*-2,5,10b-triazabenzo[*e*]azulene-3-carboxylic Acid (rac-32).** 1-Methyl-6-phenyl-4*H*-2,5,10b-triazabenzo[*e*]azulene-3-carboxylic acid methyl ester **12**[59] (3.8 g, 10 mmol) was reacted with benzyloxyacetyl chloride (method F) to form the β-lactam rac-**17** (5.0 g, 94%) as colorless fine crystals, mp 215−216 °C (ethyl acetate). ^{1}H NMR (DMSO-d_6): δ 7.99 (d, J = 2.0 Hz, 1H), 7.75 (dd, J = 2.1, 8.6 Hz, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.22−7.09 (m, 6H), 6.94−6.83 (m, 2H), 6.76−6.70 (m, 2H), 5.64 (s, 1H), 5.57 (d, J = 14.6 Hz, 1H), 4.55 (d, J = 10.8 Hz, 1H), 4.32−4.20 (m, 2H), 4.19 (d, J = 10.6 Hz, 1H), 4.16 (d, J = 14.3 Hz, 1H), 1.81 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H). MS (ES^+) m/z: 528 (M + H). Hydrogenolysis (method G) of compound rac-**17** (3.05 g, 5.76 mmol) furnished the alcohol rac-**22** (2.4 g, quantitative) as a white solid. ^{1}H NMR (DMSO-d_6): δ 8.02 (d, J = 7.7, 1H), 7.80−7.60 (m, 3H), 7.18−7.02 (m, 3H), 6.80−6.72 (m 2H), 5.90 (s, 1H), 5.56 (d, J = 14.8 Hz, 1H), 5.54 (s, 1H), 4.40−4.26 (m, 2H), 4.14 (d, J = 14.8 Hz, 1H), 1.86 (s, 3H), 1.38−1.29 (m, 3H). MS (ES^+) m/z: 404 (M + H). Reacting the alcohol rac-**22** (605 mg, 1.5 mmol) with 2-methanesulfonyl-4,6-dimethylpyrimidine (method H) gave the crude pyrimidine derivative rac-**27** (900 mg, >100%) as a yellow resin that was directly subjected to the hydrolysis (method K) to afford the title compound rac-**32** (159 mg, 40% over two steps) as a pale-pink resin after HPLC purification (conditions as for rac-**5c**). ^{1}H NMR (DMSO-d_6, 60 °C): δ 8.00−6.82 (m, 9H), 6.54 (s br, 1H), 5.92 (s br, 1H), 4.82 (d, J = 13.5 Hz, 1H), 3.33 (s, J = 12.9 Hz, 1H), 2.30 (s, 6H), 1.84 (s 3H). MS (ES^+) m/z: 500 (M + H).

rac-(*S)-((6*S**)-1-Carboxymethyl-6-phenyl-5,6-dihydro-4*H*-2,3,5,10b-tetraazabenzo[*e*]azulen-6-yl)-(4,6-dimethylpyrimidin-2-yloxy)acetic Acid (rac-33).** (6-Phenyl-4*H*-2,3,5,10b-tetraazabenzo[*e*]azulen-1-yl)acetic acid ethyl ester **13** (1.18 g, 26%) was prepared in analogy to a literature procedure[56] starting from 5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one (3.0 g, 12.7 mmol) and ethyl 3-hydrazino-3-oxopropionate. The compound was obtained as a pale-yellow foam after column chromatography (CH_2Cl_2/methanol). ^{1}H NMR ($CDCl_3$): δ 7.70−7.51 (m, 4H), 7.48−7.31 (m, 5H), 5.49 (d, J = 12.8 Hz, 1H), 4.17−4.04 (m, 5H), 1.18 (t, J = 7.1 Hz, 3H). MS (ES^+) m/z: 347 (M + H). Compound **13** (770 mg, 2.22 mmol) was reacted with benzyloxyacetyl chloride (method F) to give the β-lactam rac-**18** (863 mg, 79%) as a beige solid. ^{1}H NMR ($CDCl_3$): δ 7.62−7.48 (m, 5H), 7.28−7.22 (m, 1H), 7.20−7.15 (m, 4H), 6.97−6.90 (m, 5H), 5.33 (d, J = 14.8 Hz, 1H), 5.30 (s, 1H), 4.44 (s, 2H), 4.32 (d, J = 14.6 Hz, 1H), 4.22−4.12 (m, 2H), 3.43 (d, J = 16.8 Hz, 1H), 2.97 (d, J = 17.0 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H). MS (ES^+) m/z: 495 (M + H). The benzyl ether (404 mg, 0.817 mmol) in rac-**18** was cleaved by hydrogenolysis (method G) to yield the alcohol rac-**23** (339 mg, 89%) as a white solid containing 1 equiv of acetic acid. ^{1}H NMR ($CDCl_3$): δ 7.90 (d, J = 7.7 Hz, 1H), 7.70 (t, J = 7.5 Hz, 1H), 7.61 (t, J = 7.7 Hz, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.21−7.14 (m, 3H), 6.90 (s br, 2H), 5.49 (s, 1H), 5.35 (d, J = 14.8 Hz, 1H), 4.33 (d, J = 14.6 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.41 (d, J = 17.0, 1H), 2.97 (d, J = 16.8 Hz, 1H), 2.08 (s, 3H (acetic acid)), 1.24 (t, J = 7.1 Hz, 3H). MS (ES^+) m/z: 405 (M + H). The alcohol rac-**23** (200 mg, 0.495 mmol) was treated (method H) with 2-methanesulfonyl-4,6-dimethylpyrimidine to furnish the pyrimidine derivative rac-**28** (205 mg, 81%) after column chromatography (CH_2Cl_2/methanol) as a colorless foam. ^{1}H NMR ($CDCl_3$): δ 8.91 (dd, J = 0.7, 7.7 Hz, 1H), 7.75 (dt, J_d = 1.1 Hz, J_t = 7.5 Hz, 1H), 7.63 (dt, J_d = 1.3 Hz, J_t = 7.7 Hz, 1H), 7.52 (dd, J = 0.9, 7.9 Hz, 1H), 7.00−6.85 (m, 5H), 6.61 (s, 1H), 6.55 (s, 1H), 5.37 (d, J = 14.5 Hz, 1H), 4.41 (d, J = 14.5 Hz, 1H), 4.22−4.11 (m, 2H), 3.35 (d, J = 16.8 Hz, 1H), 2.92 (d, J = 17.0 Hz, 1H), 2.33 (s, 6H), 1.24 (t, J = 7.0 Hz, 3H). MS (ES^+) m/z: 511 (M + H). The compound rac-**28** (205 mg, 0.400 mmol) was treated with LiOH (method K) to form the title compound rac-**33** (195 mg, 97%), which was isolated as a colorless lyophilisate after the crude product had been desalted over a short column of Rp-C_{18} silica gel. ^{1}H NMR (0.2 N NaOD in D_2O): δ 7.58−7.40 (m, 3H), 7.36−7.29 (m, 1H), 7.04−6.90 (m, 5H), 6.78 (s, 1H), 5.74 (s, 1H), 4.30 (d, J = 15.2 Hz, 1H), 3.50 (d, J = 15.2 Hz, 1H), 3.12 (d, J = 17.6 Hz, 1H), 3.02 (d, J = 17.6 Hz, 1H), 2.27 (s, 6H); the two protons at 3.12 and 3.02 ppm exchange with deuterium upon standing of the NMR sample for a few hours. ^{13}C NMR (0.2 N NaOD in D_2O): δ 175.6, 174.0, 170.3, 163.1, 153.0, 150.3, 140.3, 136.4, 132.7, 129.8, 129.7, 129.4, 127.4, 127.2, 126.6, 125.5, 115.2, 79.4, 65.7, 37.3, 23.0. MS (ES^+) m/z: 501 (M + H).

rac-(*S)-(4,6-Dimethylpyrimidin-2-yloxy)-((6*S**)-1-methyl-6-phenyl-5,6-dihydro-4*H*-2,3,5,10b-tetraazabenzo[*e*]azulen-6-yl)acetic Acid (rac-34).** 8-Chloro-1-methyl-6-phenyl-4*H*-2,3,5,10b-tetraazabenzo[*e*]azulene **14** was prepared in analogy to literature procedures.[56] ^{1}H NMR ($CDCl_3$): δ 7.65 (dd, J = 2.6, 8.6 Hz, 1H), 7.55−7.36 (m, 7H), 5.49 (d, J = 12.8 Hz, 1H), 4.08 (d, J = 12.8 Hz, 1H), 2.64 (s, 3H). MS (ES^+) m/z: 309 (M + H). Treatment (method F) of the imine **14** (500 mg, 1.62 mmol) with benzyloxyacetyl chloride furnished the β-lactam rac-**19** (397 mg, 54%) as a beige solid. ^{1}H NMR ($CDCl_3$): δ 7.57-(dd, J = 2.4, 8.4 Hz, 1H), 7.40−7.18 (m, 9H), 7.05−6.90 (m, 3H), 5.30 (d, J = 14.6 Hz, 1H), 5.22 (s, 1H), 4.47 (s, 2H), 4.28 (d, J = 14.3 Hz, 1H), 1.96 (s, 3H). MS (ES^+) m/z: 457 (M + H). Hydrogenolysis (method G) of rac-**19** (198 mg, 0.43 mmol) gave the dechlorinated alcohol rac-**24** (137 mg, 95%) as a brown solid. ^{1}H NMR (CD_3OD): δ 8.10 (d, J = 7.90 Hz, 1H), 7.81−7.76 (m, 3H), 7.63−7.56 (m, 1H), 7.34−7.28 (m, 3H), 7.10−7.00 (m, 2H), 5.70 (s, 1H), 5.36 (d, J = 14.8 Hz, 1H), 4.53 (d, J = 14.7 Hz, 1H), 2.10 (s, 3H). MS (ES^+) m/z: 333 (M + H). Following method H, the pyrimidine derivative rac-**29** (127 mg, 91%) was obtained as a beige solid starting from the alcohol rac-**24** (117 mg, 0.32 mmol) and 2-methanesulfonyl-4,6-dimethylpyrimidine (162 mg, 0.87 mmol). ^{1}H NMR ($CDCl_3$): δ 8.92 (dd, J = 1.5, 7.7 Hz, 1H), 7.74 dt, J_d = 1.5 Hz, J_t = 7.7 Hz, 1H), 7.65 (dt, J_d = 1.6 Hz, J_t = 7.7 Hz, 1H), 7.28 (dd, J = 1.2, 7.7 Hz, 1H), 7.22−6.90 (m, 5H), 6.61 (s, 1H), 6.56 (s, 1H), 5.33 (d, J = 14.6 Hz, 1H), 4.38 (d, J = 14.8 Hz, 1H), 2.33 (s, 6H), 1.93 (s, 3H). MS (ES^+) m/z: 439 (M + H). The β-lactam rac-**29** (145 mg, 0.33 mmol) was treated with LiOH (method K) to furnish rac-**34** (126 mg, 83%) as a beige solid after desalting over a short column of Rp-C_{18}-silica gel. ^{1}H NMR (DMSO-d_6, 80 °C): δ 7.55−7.20 (m, 6H), 7.10−6.98 (m, 3H), 6.79 (s, 1H), 5.66 (s br, 1H), 4.11 (d br, $J \approx$ 13 Hz, 1H), 3.75 (d br, $J \approx$ 13 Hz, 1H), 2.27 (s, 6H), 1.83 (s, 3H) (poor resolution over the range of 25 to 80 °C). ^{13}C NMR (DMSO-d_6, 80 °C): δ 170.0, 169.2, 164.0, 152.0, 151.7, 149.0, 142.9, 136.8, 134.1, 130.7, 129.6, 128.7, 127.9, 127.2, 125.9, 114.9, 114.8, 78.7, 67.6, 39.1, 24.0, 11.0. MS (ES^+) m/z: 457 (M + H).

The compound rac-**34** could also be obtained by decarboxylation of compound rac-**33**. Thus, a solution of rac-**33** (40 mg, 0.08 mmol) in DMF (3 mL) was heated to 80 °C for 3 h. The solvent was removed in vacuo and the remaining solid was washed with diethyl ether and dried under high vacuum to give rac-**34** (34 mg, 93%) as a white powder.

rac-(*S)-(4,6-Dimethylpyrimidin-2-yloxy)-[(5*S**)-1-(4-methoxybenzyl)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-5-yl]acetic Acid (rac-39af).** To a solution of 5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one **35**[52] (19.08 g, 80.8 mmol) in DMF (200 mL), was added K_2CO_3 (33.48 g, 242.3 mmol) followed by 4-methoxybenzyl chloride (13.28 g, 84.8 mmol), and the reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with water (200 mL) and extracted twice with ethyl acetate (300

mL). The organic extracts were washed twice with water, dried over $MgSO_4$, and evaporated. The crude product was purified by crystallization from diethyl ether to furnish the 4-methoxybenzylated benzodiazepinone derivative (27.3 g, 95%) as almost colorless fine crystals, mp 142−143°C (diethyl ether). ^{1}H NMR (DMSO-d_6): δ 7.69 (d, J = 8.4 Hz, 1H), 7.56 (dt, J_d = 1.6 Hz, J_t = 7.1 Hz, 1H), 7.52−7.46 (m, 1H), 7.41 (t, J = 7.8, 2H), 7.32−7.25 (m, 2H), 7.20 (dt, J_d = 0.7 Hz, J_t = 7.8 Hz, 1H), 7.11 (dd, J = 1.5, 7.8 Hz, 1H), 6.88 (d, J = 8.6 Hz, 2H), 6.66 (d, J = 8.6 Hz, 2H), 5.44 (d, J = 15.2 Hz, 1H), 4.83 (d, J = 15.2 Hz, 1H), 4.62 (d, J = 10.3 Hz, 1H), 3.81 (d, J = 10.4 Hz, 1H), 3.64 (s, 3H). MS (ES$^+$) *m/z*: 357 (M + H). Treating the above material (27.31 g, 76.6 mmol) with benzyloxyacetyl chloride according to method F furnished the corresponding α-benzyloxy-*β*-lactam (38.4 g, 99%) in racemic form as fine, colorless crystals, mp 177−178 °C (diethyl ether). ^{1}H NMR (DMSO-d_6): δ 7.84−7.80 (m, 1H), 7.54−7.34 (m, 6H), 7.25−7.05 (m, 5H), 6.91 (d, J = 8.6 Hz, 2H), 6.84−6.79 (m, 2H), 6.76 (d, J = 8.6 Hz, 2H), 5.57 (s, 1H), 4.56 (d, 11.0 Hz, 1H), 4.33 (d, J = 10.8 Hz, 1H), 4.32 (J = 15.6 Hz, 1H), 4.20 (d, J = 13.6 Hz, 1H), 4.03 (d, J = 13.4 Hz, 1H), 3.71 (s, 3H), 3.52 (d, J = 15.6 Hz, 1H). MS (ES$^+$) *m/z*: 505 (M + H). Hydrogenolysis (method G) of the obtained α-benzyloxy-*β*-lactam (12.5 g, 24.8 mmol) afforded the α-hydroxy-*β*-lactam rac-**36** (9.44 g, 92%) as colorless crystals, mp 193−195 °C (diethyl ether). ^{1}H NMR ($CDCl_3$): δ 7.70−7.64 (m, 1H), 7.46−7.28 (m, 7H), 7.04−7.00 (m, 1H), 6.95−6.88 (m, 2H), 6.75−6.68 (m, 2H), 5.40 (s, 1H), 4.53 (d, J = 14.6 Hz, 1H), 4.50 (d, J = 13.5 Hz, 1H), 3.86 (d, J = 13.5 Hz, 1H), 3.78 (s, 3H), 3.30 8d, J = 15.2 Hz, 1H), 2.10 (s br, 1H). MS (ES$^+$) *m/z*: 415 (M + H). Reacting (method H) compound rac-**36** (15.0 g, 36.2 mmol) with 2-methanesulfonyl-4,6-dimethylpyrimidine gave the pyrimidine derivative rac-**37** (16.11 g, 86%) as colorless crystals, mp 212−213 °C (ethyl acetate/diethyl ether). ^{1}H NMR (DMSO-d_6): δ 8.77 (dd, J = 0.7, 7.9 Hz, 1H), 7.60 (dt, J_d = 0.7 Hz, J_t = 7.5 Hz, 1H), 7.45 (dt, J_d = 1.2 Hz, J_t = 8.1 Hz, 1H), 7.25−7.09 (m, 4H), 7.04 (dd, J = 0.7, 7.9 Hz, 1H), 6.92 (s, 1H), 6.90−6.85 (m, 2H), 6.77−6.72 (m, 2H), 6.57 (s, 1H), 4.28 (d, J = 13.6 Hz, 1H), 4.25 (d, J = 15.4 Hz, 1H), 4.11 (d, J = 13.4 Hz, 1H), 3.70 (s, 3H), 3.41 (d, J = 15.4 Hz, 1H), 2.33 (s, 6H). MS (ES$^+$) *m/z*: 521 (M + H). Hydrolysis (method K) of the *β*-lactam rac-**37** (260 mg, 0.5 mmol) gave the title compound rac-**39af** (76 mg, 28%) as a white powder after purification on preparative TLC plates (CH_2Cl_2/methanol 8:1). ^{1}H NMR (DMSO-d_6, 65 °C): δ 7.45−7.33 (m, 3H), 7.30−7.15 (m, 5H), 7.04−6.98 (m, 2H), 6.90−6.80 (m, 4H), 6.00 (s, 1H), 3.81 (d, J = 15.8 Hz, 1H), 3.72 (s, 3H), 3.46 (d, J = 12.9 Hz, 1H), 3.33 (d, J = 12.9 Hz, 1H), 2.31 (s, 6H), one broad signal coverd by H_2O signal. ^{13}C NMR (DMSO-d_6, 65 °C): δ 170.2, 169.4, 169.2, 163.9, 158.9, 143.9, 143.1, 135.0, 130.9, 129.4, 128.9, 128.7, 127.9, 127.6, 127.5, 126.7, 123.7, 115.2, 115.1, 114.6, 78.5, 67.2, 55.9, 51.3, 49.0, 24.0. MS (ES$^+$) *m/z*: 539 (M + H).

In general, the compounds rac-**39** have been prepared either in a parallel (method L) or in a classical, nonautomated fashion (method J, K) starting from intermediate rac-**38**. The intermediate rac-**38** (12.23 g, 98%) was obtained as fine, beige crystals after treatment of the 4-methoxybenzyl protected compound rac-**37** (16.10 g, 30.9 mmol) with ammonium cerium(IV) nitrate following method I, mp 257°C (dec, CH_3CN). ^{1}H NMR (DMSO-d_6): δ 9.77 (s, 1H), 8.82−8.77 (m, 1H), 7.47−7.41 (m, 2H), 7.17−7.11 (m, 3H), 7.07−7.03 (m, 1H), 6.99−6.95 (m, 2H), 6.90 (s, 1H), 6.50 (s, 1H), 4.45 (d, J = 15.6 Hz, 1H), 4.23 (d, J = 15.6 Hz, 1H), 2.33 (s, 6H). ^{13}C NMR (DMSO-d_6): δ 169.6, 165.6, 163.5, 162.6, 137.2, 136.5, 132.2, 130.1, 129.5, 128.39, 128.36, 127.4, 125.1, 124.0, 115.8, 84.8, 71.5, 46.5, 23.8. MS (ES$^+$) *m/z*: 401 (M + H).

rac-(*S)-(4,6-Dimethylpyrimidin-2-yloxy)-[(5*S**)-2-oxo-5-phenyl-1-(2,4,6-trifluorobenzyl)-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-5-yl]acetic Acid (rac-39au).** This compound was prepared following methods J and K and purified by crystallization from methanol, mp 164−165 °C (dec). ^{1}H NMR (DMSO-d_6, 60 °C): δ 7.42−7.14 (m, 8H), 7.06−6.94 (m, 3H), 6.86 (s, 1H), 5.96 (s, 1H), 3.84 (d, J = 15.8 Hz, 1H), 3.66 (s br, 1H), 3.36 (d, J = 12.3 Hz, 1H), 3.20 (d, J = 12.3 Hz, 1H), 2.31 (s, 6H). ^{13}C NMR (DMSO-d_6, 60 °C): δ 170.1, 169.4, 169.0, 163.8, 161.9 (dt, J_d = 246 Hz, J_t = 16.3 Hz), 161.2 (ddd, J = 248, 15.3, 10.9 Hz), 142.8, 142.7, 135.7, 129.5, 128.9, 128.0, 127.6, 127.0, 124.7, 115.3, 115.2, 110.7 (dt, J_d = 4.2 Hz, J_t = 21.7 Hz), 101.3 (m), 78.5, 67.2, 48.7, 24.0. ^{19}F NMR (DMSO-d_6, 60 °C): δ −110.1, −111.9. Anal. ($C_{30}H_{25}F_3N_4O_4$·0.33CH_3OH) C, H, N, O, F.

rac-(*S)-[(5*S**)-5-(3-*n*-Butylphenyl)-1-(4-methoxybenzyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-5-yl]-(4,6-dimethylpyrimidin-2-yloxy)acetic acid (rac-79).** A solution of 1-bromopropane (29.53 g, 240 mmol) in THF (100 mL) was slowly added to a suspension of fine magnesium turnings (5.35 g, 220 mmol) in THF (60 mL). Heating of the mixture and addition of the bromopropane were controlled such that the mixture was kept at a gentle reflux. Upon completion of the addition, the mixture was refluxed for 1 h before it was transferred into a dropping funnel. The thus obtained Grignard reagent was then added dropwise to a stirred suspension of 3-bromobenzyl bromide (50.0 g, 200 mmol) in THF (100 mL) cooled to −70 °C. Upon completion of the addition the reaction mixture was stirred at −70 to −60 °C for 30 min before a Li_2CuCl_4 solution (10 mL, 0.1 M in THF) was slowly added. The cooling was removed, and the yellow to green suspension slowly became warm. At 40 °C the mixture was cooled again to 10 °C. After 2 h, the dark-brown suspension was carefully treated with saturated aqueous NH_4Cl solution (100 mL) and diluted with diethyl ether (300 mL) and water (100 mL). The layers were separated, the dark-blue aqueous layer was extracted once more with diethyl ether, and the combined organic extracts were washed with water and brine, dried over $MgSO_4$, and evaporated. The resulting oil was purified by column chromatography (hexane) to furnish 1-bromo-3-butylbenzene (16.42 g, 39%) as a volatile, colorless liquid. ^{1}H NMR ($CDCl_3$): δ 7.35−7.27 (m, 2H), 7.16−7.07 (m, 2H), 2.59 (t, J = 7.6 Hz, 2H), 1.65−1.54 (m, 2H), 1.35 (h, J = 7.6 Hz, 2H), 0.94 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 145.4, 131.6, 129.9, 128.9, 127.3, 122.5, 35.7, 33.7, 22.6, 14.3. Grignard reaction (method A) of the above 1-bromo-3-*n*-butylbenzene (19.5 g, 91.5 mmol) with 2-aminobenzonitrile (3.60 g, 30.5 mmol) gave the aminobenzophenone **51** (7.22 g, 93%) as a yellow oil after column chromatography (heptane/ethyl acetate 2:1). ^{1}H NMR ($CDCl_3$): δ 7.48−7.41 (m, 3H), 7.35−7.25 (m, 3H), 6.74 (d, J = 8.2 Hz, 1H), 6.63−6.57 (m, 1H), 5.95 (s br, 2H), 2.68 (t, J = 7.6 Hz, 2H), 1.69−1.58 (m, 2H), 1.45−1.30 (m, 2H), 0.95 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 199.4, 150.9, 143.0, 140.2, 134.8, 134.3, 131.4, 129.2, 128.1, 126.7, 118.6, 117.2, 115.7, 35.9, 33.9, 22.7, 14.3. MS (ES$^+$) *m/z*: 254 (M + H). The aminobenzophenone **51** (7.20 g, 28.4 mmol) was then treated with bromoacetyl bromide followed by ammonia (method B) to give the benzodiazepinone **65** (5.25 g, 64%) as fine colorless crystals, mp 179−181 °C (diethyl ether/hexane). ^{1}H NMR ($CDCl_3$): δ 9.19 (s br, 1H), 7.54−7.47 (m, 1H), 7.41 (s, 1H), 7.34−7.25 (m, 4H), 7.20−7.11 (m, 2H), 4.33 (s, 2H), 2.63 (t, J = 7.6 Hz, 1H), 1.66−1.55 (m, 2H), 1.42−1.29 (m, 2H), 0.92 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 172.0, 171.8, 143.2, 139.14, 139.06, 132.1, 131.8, 130.9, 129.9, 128.2, 127.6, 127.3, 123.5, 121.4, 56.6, 35.8, 33.9, 22.7, 14.3. MS (ES$^+$) *m/z*: 293 (M + H). The benzodiazepinone **63** (5.15 g, 17.6 mmol) was reacted with 4-methoxybenzyl chloride (method D) to furnish the N_1 benzylated benzodiazepinone derivative (7.12 g, 98%) as an almost colorless resin after column chromatography (heptane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): δ 7.47−7.37 (m, 2H), 7.29−7.15 (m, 4H), 7.13−7.06 (m, 2H), 6.99−6.94 (m, 2H), 6.67−6.61 (m, 2H), 5.58 (d, J = 15.2 Hz, 1H), 4.86 (d, J = 10.0 Hz, 1H), 4.69 (d, J = 15.2 Hz, 1H), 3.86 (d, J = 10.0 Hz, 1H), 3.70 (s, 3H), 2.65−2.55 (m, 2H), 1.65−1.55 (m, 2H), 1.43−1.30 (m, 2H), 0.94 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 171.3, 169.3, 158.9, 143.2, 142.3, 138.3, 131.5, 131.0, 130.71, 130.67, 129.7, 129.0, 128.9, 128.1, 127.5, 124.6, 122.7, 114.1, 56.8, 55.4, 49.6, 35.8, 33.9, 22.8, 14.3. MS (ES$^+$) *m/z*: 413 (M + H). The [2 + 2]-cycloaddition reaction (method F) was carried out with the above material (7.10 g, 17.2 mmol) to furnish the α-benzyloxy-*β*-lactam intermediate (9.79 g, quantitative) as a colorless precipitate from diethyl ether. ^{1}H

NMR ($CDCl_3$): δ 7.42−7.22 (m, 9H), 7.17−7.12 (m, 1H), 7.01−6.93 (m, 5H), 6.79−6.72 (m, 2H), 5.27 (s, 1H), 4.56−4.41 (m, 4H), 3.83 (d, J = 12.9 Hz, 1H), 3.77 (s, 3H), 3.17 (d, J = 15.2 Hz, 1H), 2.66−2.56 (m, 2H), 1.62−1.52 (m, 2H), 1.38−1.25 (m, 2H), 0.90 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 166.5, 164.6, 158.9, 143.3, 141.4, 137.9, 136.5, 133.0, 129.76, 129.72, 129.3, 128.8, 128.52, 128.51, 128.28, 128.24, 127.8, 126.9, 126.8, 126.1, 124.2, 114.1, 87.3, 72.6, 71.5, 55.5, 53.1, 45.9, 36.1, 34.2, 22.7, 14.3. MS (ES^+) m/z: 561 (M + H). Hydrogenolysis (method G) of the above α-benzyloxy-β-lactam (5.00 g, 8.92 mmol) afforded the α-hydroxy-β-lactam (4.09 g, 97) as a colorless foam. ^{1}H NMR ($CDCl_3$): δ 7.69 (dd, J = 1.2, 7.6 Hz, 1H), 7.43 (dt, J_d = 1.2 Hz, J_t = 7.6 Hz, 1H), 7.30 (J_d = 1.2 Hz, J_t = 7.6 Hz, 1H), 7.29−7.21 (m, 2H), 7.15−7.11 (m, 1H), 7.00−6.90 (m, 4H), 6.75−6.70 (m, 2H), 5.41 (s, 1H), 4.53 (d, J = 15.2 Hz, 1H), 4.48 (d, J = 13.5 Hz, 1H), 3.84 (d, J = 13.5 Hz, 1H), 3.77 (s, 3H), 3.23 (d, J = 15.2 Hz, 1H), 2.63−2.56 (m, 2H), 1.63−1.51 (m, 2H), 1.38−1.26 (m, 2H), 0.91 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 168.3, 164.8, 158.9, 144.0, 141.0, 137.3, 133.5, 129.8, 129.5, 129.4, 129.0, 128.9, 128.0, 127.1, 126.5, 126.0, 124.0, 114.1, 82.3, 72.0, 55.5, 53.0, 45.9, 36.0, 34.0, 22.7, 14.3. MS (ES^+) m/z: 471 (M + H). Reaction of the above α-hydroxy-β-lactam (4.08 g, 8.67 mmol) with 2-methanesulfonyl-4,6-dimethylpyrimidine (method H) furnished the α-pyrimidinyloxy-β-lactam (4.24 g, 85%) as a colorless foam after column chromatography (heptane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): δ 8.71 (dd, J = 1.2, 8.2 Hz, 1H), 7.58−7.40 (m, 2H), 7.32 (dt, J_d = 1.2 Hz, J_t = 7.6 Hz, 1H), 6.99−6.70 (m, 2H), two aromatic H appear as broad signals in the range 7.4−7.1 ppm, 6.64 (s, 1H), 6.52 (s, 1H), 4.52 (d, J = 13.5 Hz, 1H), 4.47 (d, J = 15.2 Hz, 1H), 3.92 (d, J = 13.5 Hz, 1H), 3.76 (s, 3H), 3.10 (d, J = 15.2 Hz, 1H), 2.38 (s, 6H), the butyl chain appears as two broad multiplets at 1.4−1.0 and 0.9−0.8 ppm. ^{13}C NMR ($CDCl_3$): δ 169.2, 164.5, 164.4, 162.7, 158.9, 141.2, 136.6, 134.0, 129.7, 129.6, 129.4, 128.3, 128.0, 127.7, 126.7, 125.9, 124.1, 115.5, 114.1, 83.2, 71.3, 55.5, 52.8, 46.1, 35.9, 34.0, 23.9, 22.5, 14.3. MS (ES^+) m/z: 577 (M + H). Hydrolysis of this β-lactam (150 mg, 0.259 mmol) with LiOH (method K) gave the title compound rac-**79** (145 mg, 94%) as a colorless foam after chromatography on preparative TLC plates (CH_2Cl_2/methanol 10:1). ^{1}H NMR (DMSO-d_6, 65 °C): δ 7.47 (s br, 1H), 7.32−7.20 (m, 3H), 7.14−7.06 (m, 2H), 7.02−6.93 (m, 3H), 6.87−6.79 (m, 4H), 6.01 (s, 1H), 3.82 (d, J = 15.8 Hz, 1H), 3.72 (s, 3H), 3.48−3.28 (m, 3H), 2.28 (s, 6H), 2.25−2.08 (m, 1H), 1.98−1.84 (m, 1H), 1.56−1.42 (m, 2H), 1.34−1.22 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H). ^{13}C NMR (DMSO-d_6, 65 °C): δ 170.3, 169.2, 169.1, 164.0, 158.8, 143.9, 143.3, 141.4, 135.4, 130.9, 129.2, 128.6, 128.0, 127.3, 126.7, 125.4, 123.7, 114.8, 114.6, 78.7, 67.3, 55.9, 51.3, 48.9, 36.0, 33.9, 24.0, 22.5, 14.6. MS (ES^+) m/z: 595 (M + H). Anal. ($C_{35}H_{38}N_4O_5 \cdot 0.4H_2O \cdot 0.1SiO_2$) C, H, N.

rac-(*S)-[(5*S**)-5-Biphenyl-3-yl-1-(4-methoxybenzyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-5-yl]-(4,6-dimethylpyrimidin-2-yloxy)acetic Acid (rac-80).** 2-Aminobenzonitrile (980 mg, 8.29 mmol) was reacted with 3-bromobiphenyl (5.80 g, 24.9 mmol) under Grignard conditions (method A) to give the benzophenone **52** (2.00 g, 88%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 7.85 (t, J = 1.8 Hz, 1H), 7.75 (dt, J_d = 7.6 Hz, J_t = 1.8 Hz, 1H), 7.63−7.58 (m, 3H), 7.55−7.28 (m, 8H), 6.82 (d, J = 8.2 Hz, 1H), 6.68−6.62 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 199.0, 150.1, 141.3, 140.7, 140.5, 134.7, 134.5, 130.0, 129.1, 128.8, 128.2, 128.0, 127.9, 127.4, 118.9, 117.7, 116.5. MS (ES^+) m/z: 274 (M + H). The benzophenone **52** (4.80 g, 17.6 mmol) was treated with bromoacetyl bromide followed by ammonia in methanol (method B) to afford the benzodiazepinone **66** (4.28 g, 82%) as an almost colorless crystalline powder, mp 189−190°C (diethyl ether). ^{1}H NMR ($CDCl_3$): δ 9.46 (s br, 1H), 7.80 (s, 1H), 7.71−7.66 (m, 1H), 7.61−7.56 (m, 2H), 7.54−7.30 (m, 6H), 7.26−7.12 (m, 3H), 4.36 (s, 2H). MS (ES^+) m/z: 313 (M + H). The benzodiazepinone **66** (3.68 g, 11.8 mmol) was reacted with 4-methoxybenzyl chloride (method D) to furnish the N_1 4-methoxybenzylated benzodiazepinone (4.46 g, 88%) as a colorless crystalline powder, mp 147−148 °C (diethyl ether). ^{1}H NMR ($CDCl_3$): δ 7.69−7.65 (m, 1H), 7.57−7.30 (m, 6H), 7.23−7.20 (m, 1H), 7.15−7.09 (m, 1H), 7.00−6.95 (m, 2H), 6.65−6.60 (m, 2H), 5.65 (d, J = 15.2 Hz, 1H), 4.90 (d, J = 10.0 Hz, 1H), 4.68 (d, J = 15.2 Hz, 1H), 3.88 (d, J = 10.0 Hz, 1H), 3.58 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 171.1, 169.1, 158.9, 142.3, 141.3, 140.4, 138.9, 131.7, 130.6, 130.5, 129.6, 129.1, 129.0, 128.9, 128.8, 128.6, 127.8, 127.3, 124.8, 122.9, 114.1, 56.8, 55.4, 49.5. MS (ES^+) m/z: 433 (M + H). [2 + 2]-Cycloaddition reaction (method F) with the above benzodiazepinone (4.40 g, 10.2 mmol) furnished the α-benzyloxy-β-lactam intermediate (5.84 g, 98%) as a colorless crystalline powder, mp 170−171 °C (diethyl ether). ^{1}H NMR ($CDCl_3$): δ 7.57−7.21 (m, 15H), 7.04−6.91 (m, 5H), 6.73−6.68 (m, 2H), 5.31 (s, 1H), 4.60−4.46 (m, 4H), 3.87 (d, J = 13.5 Hz, 1H), 3.72 (s, 3H), 3.32 (d, J = 15.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 166.6, 164.8, 158.9, 141.7, 141.3, 140.9, 138.7, 136.4, 133.6, 129.9, 129.42, 129.40, 129.0, 128.6, 128.4, 128.3, 127.9, 127.7, 127.5, 127.2, 126.9, 126.1, 125.71, 125.69, 114.1, 87.4, 72.7, 71.6, 55.5, 53.0, 46.0. MS (ES^+) m/z: 581 (M + H). The α-benzyloxy-β-lactam (5.80 g, 9.99 mmol) was subjected to hydrogenolysis (method G) to furnish the α-hydroxy-β-lactam derivative (4.78 g, 98%) as a colorless foam. ^{1}H NMR ($CDCl_3$): δ 7.70 (d, J = 7.6 Hz, 1H), 7.60−7.28 (m, 11H), 7.02 (d, J = 8.2 Hz, 1H), 6.92−6.84 (m, 2H), 6.70−6.62 (m, 2H), 5.44 (s, 1H), 4.56 (d, J = 15.2 Hz, 1H), 4.50 (d, J = 14.1 Hz, 1H), 3.85 (d, J = 12.9 Hz, 1H), 3.70 (s, 3H), 3.44 (d, J = 15.2 Hz, 1H), 3.16 (s br, 1H). ^{13}C NMR ($CDCl_3$): δ 168.3, 164.9, 158.9, 142.0, 140.9, 140.5, 138.0, 133.4, 129.9, 129.5, 129.4, 129.1, 128.1, 127.9, 127.6, 127.5, 127.2, 126.0, 114.1, 82.5, 72.1, 55.5, 52.9, 46.0. MS (ES^+) m/z: 491 (M + H). The above α-hydroxy-β-lactam (2.50 g, 5.10 mmol) was reacted with 2-methanesulfonyl-4,6-dimethylpyrimidine (method H) to afford the α-pyrimidinyloxy-β-lactam (2.60 g, 86%) as a colorless crystalline powder, mp 211−213 °C (diethyl ether). ^{1}H NMR ($CDCl_3$): δ 8.74 (d, J = 7.6 Hz, 1H), 7.58−7.26 (m, 8H), 7.02−6.84 (m, 5H), 6.72−6.56 (m, 5H), 4.57 (d, J = 12.9 Hz, 1H), 4.51 (d, J = 15.2 Hz, 1H), 3.95 (d, J = 12.9 Hz, 1H), 3.68 (s, 3H), 3.26 (s br, 1H), 2.37 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 169.4, 164.7, 164.4, 162.9, 158.9, 141.0, 140.9, 137.4, 133.8, 129.8, 129.5, 129.4, 128.8, 128.0, 127.8, 127.5, 127.0, 126.0, 125.7, 125.6, 115.2, 114.1, 83.4, 71.5, 55.4, 52.8, 46.2, 23.9. MS (ES^+) m/z: 597 (M + H). Hydrolysis of this β-lactam (120 mg, 0.201 mmol) with LiOH (method K) gave the title compound rac-**80** (91 mg, 74%) as a colorless foam after chromatography on preparative TLC plates (CH_2Cl_2/methanol 10:1). ^{1}H NMR (DMSO-d_6, 65 °C): δ 7.79 (s br, 1H), 7.63−7.58 (m, 2H), 7.54−7.48 (m, 1H), 7.46−7.39 (m, 3H), 7.34−7.13 (m, 5H), 7.00−6.95 (m, 2H), 6.91−6.85 (m, 1 H), 6.83−6.77 (m, 3H), 6.05 (s, 1H), 3.88 (d, J = 15.8 Hz, 1H), 3.70 (s, 3H), 3.52 (d, J = 12.9 Hz, 1H), 3.36 (d, J = 12.9 Hz, 1H), 2.27 (s, 6H), one proton as broad signal in the range 3.6−3.3. ^{13}C NMR (DMSO-d_6, 65 °C): δ 170.3, 169.4, 169.2, 164.0, 158.9, 143.94, 143.85, 141.7, 139.7, 135.4, 130.8, 129.3, 128.7, 128.1, 127.8, 127.6, 127.3, 126.9, 125.9, 123.8, 115.0, 114.7, 78.6, 67.3, 55.9, 51.3, 49.0, 24.1. MS (ES^+) m/z: 615 (M + H).

rac-(*S)-[(5*S**)-1-(2,6-Dichlorobenzyl)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-5-yl]phenoxyacetic Acid (rac-84a).** To a solution of the benzodiazepinone **35**[52] (2.36 g, 10 mmol) in DMF (30 mL) was added K_2CO_3 (4.15 g, 30 mmol) and 2,6-dichlorobenzyl chloride (2.40 g, 12 mmol), and the resulting suspension was stirred at room temperature for 20 h before it was diluted with water and extracted three times with ethyl acetate. The organic extracts were washed with brine, dried over $MgSO_4$, and evaporated. The crude product was purified by crystallization from a small amount of ethyl acetate/diethyl ether. The solid material was collected, washed with cold diethyl ether, and dried under high vacuum to furnish the 1-(2,6-dichlorobenzyl)-5-phenyl-1,3-dihydrobenzo[*e*][1,4]diazepin-2-one **83** (2.60 g, 66%) as a pale-yellow crystalline powder, mp 156−158 °C (ethyl acetate/diethyl ether). ^{1}H NMR ($CDCl_3$): δ 7.51 (d, J = 8.2 Hz, 1H), 7.47−7.30 (m, 6H), 7.15−6.99 (m, 5H), 5.84 (d, J = 15.2 Hz, 1H), 5.09 (d, J = 14.7 Hz, 1H), 4.83 (d, J = 10.6 Hz, 1H), 3.83 (d, J = 10.6 Hz, 1H). MS (ES^+) m/z: 395 (M + H). The benzodiazepinone **83** (150 mg, 0.379 mmol) was then reacted with phenoxyacetic acid (method E) to give the corresponding β-lactam intermediate

(192 mg, 96%) as a colorless solid after purification on preparative TLC plates (CH_2Cl_2/methanol 12:1). ^{1}H NMR ($CDCl_3$): δ 7.65 (dd, J = 1.2, 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.40−7.26 (m, 4H), 7.24−7.13 (m, 6H), 7.10 (dt, J_d = 1.2 Hz, J_t = 7.6 Hz, 1H), 7.03−6.95 (m, 1H), 6.83 (d, J = 8.2 Hz, 2H), 6.18 (d, J = 8.2 Hz, 1H), 5.78 (s, 1H), 5.25 (d, J = 14.7 Hz, 1H), 4.47 (d, 12.3 Hz, 1H), 3.80 (d, J = 12.3 Hz, 1H), 2.98 (d, J = 14.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 165.8, 163.7, 157.2, 138.2, 137.6, 136.7, 134.6, 132.5, 130.1, 129.6, 129.3, 128.8, 128.7, 128.6, 128.5, 128.4, 127.2, 126.7, 123.0, 117.0, 86.6, 71.8, 46.1, 45.9. MS (ES$^+$) m/z: 529 (M + H). The β-lactam (188 mg, 0.355 mmol) was hydrolyzed with LiOH (method K) to furnish the title compound rac-**84a** (170 mg, 87%) as a colorless foam after purification on preparative TLC (CH_2Cl_2/methanol 10:1). ^{1}H NMR (DMSO-d_6, 60 °C): δ 7.74 (d, J = 7.0 Hz, 1H), 7.48−7.09 (m, 12H), 6.88 (t, J = 7.3 Hz, 1H), 6.78 (d, J = 7.6 Hz, 2H), 6.20 (dd, J = 1.2, 8.2 Hz, 1H), 5.11 (s, 1H), 4.67 (d, J = 14.7 Hz, 1H), 3.44 (d, J = 12.9 Hz, 1H), 3.24 (d, J = 12.3 Hz, 1H), 2.87 (d br, $J \approx$ 15 Hz, 1H). ^{13}C NMR (DMSO-d_6, 60 °C): δ 170.8, 167.9, 158.2, 142.8, 141.0, 136.3, 133.1, 130.9, 129.8, 129.6, 129.1, 128.3, 127.9, 127.7, 127.6, 127.4, 126.1, 121.5, 116.3, 82.7, 67.5, 48.0, 44.9. MS (ES$^+$) m/z: 547 (M + H).

rac-(*S)-[(5*S**)-5-(3-*n*-Butylphenyl)-2-oxo-1-(2,4,6-trimethylbenzyl)-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-5-yl]-(4,6-dimethylpyrimidin-2-yloxy)acetic Acid (rac-85).** The α-pyrimidinyloxy-β-lactam (4.08 g, 7.07 mmol), which was obtained during the course of the synthesis of rac-**79**, was treated with ammonium cerium(IV) nitrate (method I) to furnish the N_1 deprotected benzodiazepinone derivative (2.34 g, 72%) as a pale-yellow foam after column chromatography (heptane/ethyl acetate 3:7). ^{1}H NMR ($CDCl_3$): δ 8.79 (dd, 2.3, 7.0 Hz, 1H), 7.62 (s br, 1H), 7.46−7.36 (m, 2H), 7.07−6.96 (m, 2H), 6.94−6.88 (m, 2H), 6.74 (s, 1H), 6.61 (s, 1H), 6.46 (s, 1H), 4.42 (d, J = 15.8 Hz, 1H), 4.34 (d, J = 16.4 Hz, 1H), 2.41−2.33 (m, 8H), 1.34−1.24 (m, 2H), 1.20−1.06 (m, 2H), 0.83 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 169.2, 166.3, 163.6, 162.7, 142.7, 135.22, 135.17, 132.2, 129.8, 129.6, 128.5, 128.2, 127.5, 125.3, 124.8, 123.2, 115.2, 85.5, 71.7, 45.3, 35.8, 33.9, 23.8, 22.5, 14.3. MS (ES$^+$) m/z: 457 (M + H). The above N_1 deprotected benzodiazepinone derivative (150 mg, 0.329 mmol) was reacted with 2,4,6-trimethylbenzyl chloride (method J) to furnish the N_1 2,4,6-trimethylbenzylated α-pyrimidinyloxy-β-lactam (193 mg, 99%) as a colorless foam after purification on preparative TLC plates (heptane/ethyl acetate 1:2). ^{1}H NMR ($CDCl_3$): δ 8.75−8.65 (m, 1H), 7.67−7.60 (m, 1H), 7.51−7.43 (m, 1H), 7.40−7.30 (m, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.71−6.66 (m, 3H), 6.55−6.50 (m, 1H), 6.44−6.38 (m, 1H), 6.03−5.99 (m, 1H), 5.06 (d, J = 14.7 Hz, 1H), 4.46 (d, J = 12.9 Hz, 1H), 3.79 (d, J = 12.9 Hz, 1H), 2.68 (d br, $J \approx$ 16 Hz, 1H), 2.41 (s, 6H), 2.35−2.08 (m, 5H), 1.77−1.60 (m, 7H), 1.42−1.26 (m, 1H), 1.06−0.93 (m, 4H), 0.80−0.74 (m, 3H). MS (ES$^+$) m/z: 589. Hydrolysis of this β-lactam (193 mg, 0.328 mmol) with LiOH (method K) gave the title compound rac-**85** (185 mg, 93%) as a colorless foam after chromatography on preparative TLC plates (CH_2Cl_2/methanol 10:1). ^{1}H NMR (DMSO-d_6, 65 °C): δ 7.60−7.34 (m, 2H), 7.29−7.09 (m, 3H), 7.01−6.91 (m, 2H), 6.80 (s, 1H), 6.75 (s, 2H), 6.01−5.99 (m, 2H), 4.50 (s br, 1H), 3.40 (d, J = 12.9 Hz, 1H), 3.18 (d, J = 12.3 Hz, 1H), 2.56−2.49 (m, 2H), 2.29 (s, 6H), 2.20 (s, 3H), 1.82 (s, 6H), 1.60−1.50 (m, 2H), 1.36−1.24 (m, 2H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C NMR (DMSO-d_6, 65 °C): δ 170.2, 169.1, 168.5, 164.0, 142.5, 141.5, 141.1, 138.2, 137.2, 136.8, 131.6, 129.6, 128.4, 128.2, 127.6, 127.4, 127.2, 126.7, 125.9, 114.8, 78.8, 67.1, 48.5, 42.4, 36.0, 33.7, 24.0, 22.6, 21.3, 20.5, 14.6. MS (ES$^+$) m/z: 607 (M + H). Anal. ($C_{37}H_{42}N_4O_4 \cdot 0.2H_2O \cdot 0.2SiO_2$) C, H, N,O.

rac-(*S)-[(5*S**)-5-(3-*n*-Butylphenyl)-2-oxo-1-(2,4,6-trifluorobenzyl)-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-5-yl]-(4,6-dimethylpyrimidin-2-yloxy)acetic Acid (rac-86).** The N_1 deprotected benzodiazepinone intermediate (200 mg, 0.438 mmol), which was obtained during the course of the preparation of rac-**85** (method I), was reacted with 2,4,6-trifluorobenzyl chloride (method J) to furnish the N_1 2,4,6-trifluorobenzylated α-pyrimidinyloxy-β-lactam (225 mg, 86%) as a colorless foam after purification on preparative TLC plates (heptane/ethyl acetate 1:2). ^{1}H NMR ($CDCl_3$): δ 8.77 (dd, J = 1.2, 7.6 Hz, 1H), 7.53 (dt, J_d = 1.2 Hz, J_t = 7.6 Hz, 1H), 7.42 (dt, J_d = 1.2 Hz, J_t = 7.6 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 6.88−6.84 (m, 1H), two aromatic protons appear as a very broad signal in the range 7.2−6.9 ppm, 6.63 (s, 1H), 6.47 (s, 1H), 6.42−6.33 (m, 2H), 6.15 (s br (!), 1H), 4.49 (d, J = 13.5 Hz, 1H), 4.44 (d, J = 15.2 Hz, 1H), 4.00 (d br, $J \approx$ 15 Hz, 1H), 3.88 (d, J = 13.5 Hz, 1H), 2.37 (s, 6H), the *n*-butyl side chain appears as three very broad signals at 2.3−2.0 (2H), 1.3−0.9 (4H), and 0.9−0.7 ppm (3H). ^{19}F NMR ($CDCl_3$): δ −108.4, −109.7. MS (ES$^+$) m/z: 601. Hydrolysis of this β-lactam (225 mg, 0.375 mmol) with LiOH (method K) gave the title compound rac-**86** (187 mg, 81%) as a colorless foam after chromatography on preparative TLC plates (CH_2Cl_2/methanol 10:1). ^{1}H NMR (DMSO-d_6, 60 °C): δ 7.60−7.20 (m, 3H), 7.16−6.90 (m, 7H), 6.80 (s, 1H), 5.99 (s, 1H), 3.88 (d, J = 15.8 Hz, 1H), 3.39 (d, J = 12.9 Hz, 1H), 3.20 (d, J = 12.3 Hz, 1H), 2.50−2.44 (m, 1H), 2.29 (s, 6H), 2.20−2.08 (m, 1H), 1.54−1.40 (m, 2H), 1.32−1.22 (m, 2H), 0.86 (t, J = 7.6 Hz, 3H), one proton covered by H_2O signal. ^{13}C NMR (DMSO-d_6, 60 °C): δ 172.3, 170.3, 169.2, 169.0, 167.3, 164.0, 161.4 (dd, J = 15, 248 Hz), 161.2 (dd, J = 15, 248 Hz), 142.9, 142.8, 141.5, 136.0, 129.4, 128.1, 127.4, 127.0, 125.5, 124.7, 114.9, 110.8 (dt, J_d = 5 Hz, J_t = 18 Hz), 101.3 (t, J = 26 Hz), 78.7, 67.3, 48.6, 36.0, 35.7, 33.8, 24.0, 22.5, 14.6. ^{19}F NMR (DMSO-d_6, 60 °C): δ −110.0, −112.0. MS (ES$^+$) m/z: 619 (M + H). Anal. ($C_{34}H_{33}F_3N_4O_4 \cdot H_2O \cdot 0.1SiO_2$) C, H, N,O, F.

rac-(*S)-[(5*S**)-5-(3-*n*-Butylphenyl)-1-(2-chloro-6-fluorobenzyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-5-yl]-(4,6-dimethylpyrimidin-2-yloxy)acetic Acid (rac-87).** The N_1 deprotected benzodiazepinone intermediate (300 mg, 0.657 mmol), which was obtained during the course of the preparation of rac-**85** (method I), was reacted with 2-chloro-6-fluorobenzyl chloride (method J) to furnish the N_1 2-chloro-6-fluorobenzylated α-pyrimidinyloxy-β-lactam (332 mg, 84%) as a colorless foam after purification on preparative TLC plates (heptane/ethyl acetate 1:2). ^{1}H NMR ($CDCl_3$, 55 °C): δ 8.72 (d, J = 7.6 Hz, 1H), 7.54−7.48 (m, 1H), 7.28−7.00 (m, 5H), 6.94−6.89 (m, 2H), 6.86−6.78 (m, 1H), 6.67 (d, J = 7.6 Hz, 1H), 6.62 (s, 1H), 6.50 (s, 1H), 4.85 (d, J = 15.2 Hz, 1H), 4.47 (d, J = 12.9 Hz, 1H), 3.84 (d, J = 12.9 Hz, 1H), 3.29 (d, J = 15.2 Hz, 1H), 2.44−2.35 (m, 8H), 1.40−1.10 (m, 4H), 0.85 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 55 °C): 169.1, 164.4, 164.0, 163.0, 162.0 (d, J = 251 Hz), 142.5, 139.6, 136.4, 136.0 (d, J = 5 Hz), 135.1, 129.6 (d, J = 10 Hz), 129.3, 128.3, 128.0, 127.0, 125.6, 124.3, 122.9 (d, J = 16 Hz), 114.9, 114.5 (d, J = 23 Hz), 83.4, 71.6, 45.9, 44.0, 35.8, 33.7, 23.8, 22.5, 14.1. ^{19}F NMR ($CDCl_3$, 55 °C): δ −112.8. MS (ES$^+$) m/z: 600. Hydrolysis of this β-lactam (320 mg, 0.534 mmol) with LiOH (method K) gave the title compound rac-**87** (292 mg, 89%) as a colorless solid after chromatography on preparative TLC plates (CH_2Cl_2/methanol 10:1). ^{1}H NMR (DMSO-d_6, 60 °C): δ 7.50−7.20 (m, 5H), 7.16−7.05 (m, 3H), 7.01−6.95 (m, 2H), 6.83 (s, 1H), 6.73−6.67 (m, 1H), 5.95 (s, 1H), 4.09 (d, J = 15.8 Hz, 1H), 3.39 (d, J 0 12.9 Hz, 1H), 3.22 (d, J = 12.9 Hz, 1H), 2.53−2.45 (m, 2H (+DMSO)), 2.30 (s, 6H), 1.58−1.42 (m, 2H), 1.35−1.23 (m, 2H), 0.87 (t, J = 7.6 Hz, 3H), one proton covered by H_2O signal. ^{13}C NMR (DMSO-d_6, 60 °C): δ 170.2, 169.3, 168.8, 163.9, 161.5 (d, J = 249 Hz), 142.6, 142.5, 141.6, 136.0, 134.3 (d, J = 6 Hz), 130.3 (d, J = 10 Hz), 129.3, 128.8, 128.0, 127.4, 127.1, 126.3, 125.6, 124.7, 123.6 (d, J = 14 Hz), 115.8 (d, J = 23 Hz), 115.0, 78.5, 67.2, 48.5, 44.4, 36.0, 33.8, 24.0, 22.6, 14.6. ^{19}F NMR (DMSO-d_6, 60 °C): δ −115.7. MS (ES$^+$) m/z: 617 (M + H). Anal. ($C_{34}H_{34}N_4O_4FCl \cdot 0.1SiO_2$) C, H, N,O, F, Cl.

rac-(*S)-[(5*S**)-5-Biphenyl-3-yl-1-(2,6-dichlorobenzyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-5-yl]-(4,6-dimethylpyrimidin-2-yloxy)acetic acid (rac-88).** The α-pyrimidinyloxy-β-lactam (2.55 g, 4.27 mmol), which was obtained during the course of the synthesis of rac-**80**, was treated with ammonium cerium(IV) nitrate (method I) to furnish the N_1 deprotected benzodiazepinone derivative (1.23 g, 60%) as a pale-beige crystalline powder, mp 260−261 °C

(dec, ethyl acetate/CH_3CN/diethyl ether). ^{1}H NMR ($CDCl_3$): δ 8.82−8.75 (m, 1H), 7.84 (s, 1H), 7.44−7.37 (m, 2H), 7.35−7.19 (m, 7H), 7.14−7.10 (m, 2H), 7.02−6.97 (m, 1H), 6.59 (s, 1H), 6.53 (s, 1H), 4.38 (s, 2H), 2.35 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 169.4, 166.4, 163.6, 162.7, 141.1, 140.8, 136.1, 135.2, 131.9, 130.1, 129.5, 128.81, 128.79, 127.5, 127.3, 127.2, 126.4, 126.3, 125.5, 123.4, 115.3, 85.5, 71.7, 45.4, 23.8. MS (ES^+) *m/z*: 477 (M + H). The above N_1 deprotected benzodiazepinone derivative (600 mg, 1.26 mmol) was reacted with 2,6-dichlorobenzyl chloride (method J) to furnish the N_1 2,6-dichlorobenzylated α-pyrimidinyloxy-*β*-lactam (722 mg, 90%) as a colorless foam after column chromatography (heptane/ethyl acetate 2:3). ^{1}H NMR ($CDCl_3$): δ 8.75 (d, J = 7.0 Hz, 1H), 8.04−7.60 (m, 2H), 7.52 (dt, J_d = 1.2 Hz, J_t = 7.6 Hz, 1H), 7.46−6.80 (m, 11H), 6.62 (s br, 1H), 6.56 (s, 1H), 6.16 (d, J = 8.2 Hz, 1H), 5.29 (d, J = 14.1 Hz, 1H), 4.53 (d, J = 12.3 Hz, 1H), 3.86 (d, J = 12.9 Hz, 1H), 2.97 (d, J = 14.1 Hz, 1H), 2.40 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 169.4, 164.5, 164.0, 162.8, 140.8, 138.1, 137.5, 136.7, 135.1, 132.4, 130.0, 129.1, 128.7, 128.6, 128.5, 128.1, 127.8, 127.5, 127.0, 126.8, 115.3, 83.3, 71.8, 46.07, 46.04, 24.0. MS (ES^+) *m/z*: 635. Hydrolysis of this *β*-lactam (705 mg, 1.11 mmol) with LiOH (method K) gave the title compound rac-**88** (565 mg, 78%) as fine colorless crystals from CH_2Cl_2/methanol, mp 179°C (dec, CH_2Cl_2/methanol). ^{1}H NMR ($CDCl_3$): δ 7.88 (d, J = 7.6 Hz, 1H), 7.52−7.10 (m, 14H), 6.69 (s, 1H), 6.20 (s, 1H), 5.04 (d, J = 14.1 Hz, 1H), 3.71 (d, J = 13.5 Hz, 1H), 3.62 (d, J = 13.5 Hz, 1H), 2.73 (d, J = 14.7 Hz, 1H), 2.15 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 °C): δ 169.6, 169.1, 167.3, 162.9, 141.1, 140.7, 140.5, 139.9, 137.2, 133.7, 132.8, 130.0, 129.8, 128.9, 128.7, 128.5, 128.4, 127.7, 127.5, 127.3, 127.2, 126.6, 125.8, 114.7, 78.5, 67.7, 47.2, 44.8, 23.6. MS (ES^+) *m/z*: 653 (M + H). Anal. ($C_{36}H_{30}N_4O_4Cl_2$·0.16H_2O·0.16CH_2Cl_2·0.16 methanol) C, H, N,O, Cl, H_2O.

An analytical sample (50 mg) of rac-**88** was resolved into the two enantiomers (+)-**88** and (−)-**88** by HPLC on a chiral stationary phase (Regis, Pirkle Covalent, (R,R)-Whelk O1, 10 μm, 10 mm × 250 mm; hexane/ethanol with 0.1% TFA 85:15; 4.75 mL/min). According to chiral HPLC analysis, the enantiomeric purity of the two fractions exceeded 99%.

rac-(*S)-[(5*S**)-5-Biphenyl-3-yl-2-oxo-1-(2,4,6-trifluorobenzyl)-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-5-yl]-(4,6-dimethylpyrimidin-2-yloxy)acetic acid (rac-89).** The N_1 deprotected benzodiazepinone intermediate (300 mg, 0.630 mmol), which was obtained during the course of the preparation of rac-**88** (method I), was reacted with 2,4,6-trifluorobenzyl chloride (method J) to furnish the N_1 2,4,6,-trifluorobenzylated α-pyrimidinyloxy-*β*-lactam (367 mg, 94%) as a colorless foam after column chromatography (heptane/ethyl acetate 2:3). ^{1}H NMR ($CDCl_3$): δ 8.79 (dd, J = 1.2, 7.6 Hz, 1H), 7.55 (dt, J_d = 1.2 Hz, J_t = 7.6 Hz, 1H), 7.45 (dt, J_d = 1.2 Hz, J_t = 7.6 Hz, 1H), 7.42−6.75 (m, 9H), 6.65−6.45 (m, 3H), 6.27 (t, J = 8.2 Hz, 2H), 4.56 (d, J = 13.5 Hz, 1H), 4.45 (d, J = 14.7 Hz, 1H), 4.28 (s br, 1H), 3.93 (d, J = 13.5 Hz, 1H), 2.34 (s, 6H). ^{13}C NMR ($CDCl_3$, 55 °C): 169.3, 164.5, 164.3, 162.7, 162.3 (dt, J_d = 250 Hz, J_t = 15 Hz), 161.2 (ddd, J = 10, 15, 251 Hz), 140.6, 139.6, 137.0, 134.3, 129.8, 128.7, 128.4, 127.9, 127.5, 126.8, 126.2, 125.5, 125.3, 115.2, 108.4, 100.4 (t, J = 25 Hz), 83.8, 71.7, 46.2, 40.2, 23.9. ^{19}F NMR ($CDCl_3$): δ −109.4. MS (ES^+) *m/z*: 621. Hydrolysis of this *β*-lactam (350 mg, 0.564 mmol) with LiOH (method K) gave the title compound rac-**89** (307 mg, 85%) as a colorless foam after purification on preparative TLC plates (CH_2Cl_2/methanol 10:1). ^{1}H NMR ($CDCl_3$, 50 °C): δ 7.92 (d, J = 7.0 Hz, 1H), 7.56−7.27 (m, 8H), 7.22−7.08 (m, 3H), 7.05−6.96 (m, 1H), 6.57 (s, 1H), 6.55−6.45 (m, 2H), 6.39 (s, 1H), 4.13 (d, J = 15.2 Hz, 1H), 3.62 (s, 2H), 3.34 (d, J = 15.8 Hz, 1H), 2.13 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 °C): δ 169.7, 169.1, 167.9, 163.0, 162.2 (dt, J_d = 249 Hz, J_t = 15 Hz), 161.7 (ddd, J = 10, 15, 251 Hz), 142.4, 141.3, 140.6, 140.5, 133.3, 130.5, 128.8, 128.3, 127.9, 127.7, 127.3, 126.6, 125.5, 125.3, 114.6, 109.4 (dt, J_d = 5 Hz, J_t = 18 Hz), 100.5 (t, J = 28 Hz), 78.3, 67.5, 47.3, 40.0, 23.6. ^{19}F NMR ($CDCl_3$): δ −108.6, −110.5. MS (ES^+) *m/z*: 639 (M + H). Anal. ($C_{36}H_{29}N_4O_4F_3$·0.25H_2O·0.1CH_2Cl_2) C, H, N, H_2O, F.

rac-(*S)-[(5*S**)-1-(2-Chloro-6-fluorobenzyl)-2-oxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-5-yl]-(3,5-dimethylphenoxy)acetic Acid (rac-90).** Reacting the benzodiazepinone **35** (1.00 g, 4.23 mmol) with 2-chloro-6-fluorobenzyl chloride in analogy to method D gave the N_1 2-chloro-6-fluorobenzylated benzodiazepinone (1.61 g, quantitative) as a colorless foam after column chromatography (heptane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): δ 7.48−7.30 (m, 7H), 7.15−7.04 (m, 3H), 6.99−6.95 (m, 1H), 6.82−6.75 (m, 1H), 5.79 (dd, J = 1.8, 15.2 Hz, 1H), 4.94 (d, J = 14.7 Hz, 1H), 4.84 (d, J = 10.6 Hz, 1H), 3.84 (d, J = 10.6 Hz, 1H). ^{19}F NMR ($CDCl_3$): δ −113.1. MS (ES^+) *m/z*: 379 (M + H). The above benzodiazepinone (500 mg, 1.32 mmol) was subjected to the [2 + 2]-cycloaddition reaction (method E) with 3,5-dimethylphenoxyacetic acid to furnish the α-(3,5-dimethylphenoxy)-*β*-lactam (715 mg, quantitative) as a colorless foam after column chromatography (heptane/ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$): δ 7.61 (dd, J = 1.2, 7.6 Hz, 1H), 7.42 (dt, J_d = 1.2 Hz, J_t = 7.6 Hz, 1H), 7.35−7.05 (m, 8H), 6.88−6.81 (m, 1H), 6.71 (d, J = 8.2 Hz, 1H), 6.62 (s, 1H), 6.43 (s, 2H), 5.74 (s, 1H), 4.85 (dd, J = 1.8, 15.2 Hz, 1H), 4.47 (d, J = 13.5 Hz, 1H), 3.82 (d, J = 12.9 Hz, 1H), 3.37 (d, J = 14.7 Hz, 1H), 2.23 (s, 6H). ^{19}F NMR ($CDCl_3$): δ −113.0. MS (ES^+) *m/z*: 541. The above *β*-lactam (710 mg, 1.31 mmol) was hydrolyzed with LiOH (method K) to furnish the title compound rac-**90** (490 mg, 67%) as a colorless foam after purification on preparative TLC plates (CH_2Cl_2/methanol 10:1). ^{1}H NMR ($CDCl_3$): δ 7.61 (s br, 1H), 7.40−7.04 (m, 10H), 6.71−6.65 (m, 1H), 6.52 (s, 1H), 6.37 (s, 2H), 5.12 (s, 1H), 4.12 (d, J = 15.8 Hz, 1H), 3.42 (d, J = 12.3 Hz, 1H), 3.25 (d, J = 12.3 Hz, 1H), 2.15 (s, 6H), one proton under H_2O signal. ^{13}C NMR ($CDCl_3$): δ 170.9, 168.4, 161.1 (d, J = 249 Hz), 158.2, 143.2, 142.3, 139.0, 136.0, 134.4 (d, J = 6 Hz), 130.4 (d, J = 10 Hz), 129.4, 128.6, 127.8, 127.6, 127.4, 127.1, 126.3, 125.0, 123.8 (d, J = 6 Hz), 123.5 (d, J = 15 Hz), 115.7 (d, J = 22 Hz), 114.0, 82.2, 67.9, 48.1, 44.1, 21.8. ^{19}F NMR ($CDCl_3$): δ −115.2. MS (ES^+) *m/z*: 559 (M + H). Anal. ($C_{32}H_{28}N_2O_4ClF$·0.2SiO_2) C, H, N, O, Cl, F.

rac-(*S)-(3,5-Dimethylphenoxy)-[(5*S**)-2-oxo-5-phenyl-1-(2,4,6-trifluorobenzyl)-2,3,4,5-tetrahydro-1*H*-benzo[*e*]-[1,4]diazepin-5-yl]acetic Acid (rac-91).** Reacting the benzodiazepinone **35** (500 mg, 2.12 mmol) with 2,4,6-trifluorobenzyl chloride in analogy to method D gave the N_1 2,4,6-trifluorobenzylated benzodiazepinone (760 mg, 94%) as a colorless foam after column chromatography (heptane/ethyl acetate 1:2). ^{1}H NMR ($CDCl_3$): δ 7.52−7.40 (m, 3H), 7.39−7.30 (m, 4H), 7.20−7.10 (m, 2H), 6.46−6.38 (m, 2H), 5.73 (d, J = 15.2 Hz, 1H), 4.81 (d, J = 10.6 Hz, 1H), 4.74 (d, J = 15.2 Hz, 1H), 3.81 (d, J = 10.6 Hz, 1H). ^{19}F NMR ($CDCl_3$): δ −108.1 (p, J = 7 Hz), −111.1 (t, J = 7 Hz). MS (ES^+) *m/z*: 381 (M + H). The above benzodiazepinone (500 mg, 1.31 mmol) was subjected to the [2 + 2]-cycloaddition reaction (method E) with 3,5-dimethylphenoxyacetic acid to furnish the α-(3,5-dimethylphenoxy)-*β*-lactam (632 mg, 89%) as fine colorless crystals, mp 198−199 °C (methanol). ^{1}H NMR ($CDCl_3$): δ 7.61−7.55 (m, 1H), 7.46−7.39 (m, 2H), 7.26−7.12 (m, 6H), 6.61 (s, 1H), 6.45−6.36 (m, 4H), 5.72 (s, 1H), 4.50 (d, J = 12.9 Hz, 1H), 4.44 (d, J = 15.2 Hz, 1H), 4.15 (d, J = 15.2 Hz, 1H), 3.87 (d, J = 12.9 Hz, 1H), 2.22 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 166.2, 164.2, 157.3, 162.2 (dt, J_d = 250 Hz, J_t = 16 Hz), 161.5 (ddd, J = 10, 15, 251 Hz), 157.3, 139.7, 139.4, 137.3, 133.9, 129.9, 128.3, 128.0, 127.4, 126.65, 126.61, 124.8, 114.9, 108.5 (dt, J_d = 5 Hz, J_t = 19 Hz), 100.8 (dd, J = 3, 25 Hz), 100.3 (dd, J = 3, 25 Hz), 87.3, 71.7, 46.0, 40.4 (t, J = 3 Hz), 21.7. ^{19}F NMR ($CDCl_3$): δ −108.6 (p, J = 7 Hz), −109.8 (t, J = 7 Hz). MS (ES^+) *m/z*: 543. The above *β*-lactam (610 mg, 1.12 mmol) was hydrolyzed with LiOH (method K) to furnish the title compound rac-**91** (479 mg, 76%) as a colorless crystalline powder, mp 174−175 °C (methanol). ^{1}H NMR ($CDCl_3$): δ 7.83−7.75 (m, 1H), 7.45−7.39 (m, 2H), 7.35−7.10 (m, 5H), 7.08−7.02 (m, 1H), 6.61−6.51 (m, 3H), 6.22 (s, 2H), 4.92 (s br, 1H), 4.07 (d, J = 15.8 Hz, 1H), 3.70 (d, J = 14.0 Hz, 1H), 3.61 (d, J = 14.0 Hz, 1H), 3.17 (d, J = 15.2 Hz, 1H), 2.14 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 170.9, 167.8, 162.2 (dt, J_d = 249 Hz, J_t = 15 Hz), 161.5 (ddd, J = 10, 15, 251 Hz), 157.5, 142.3, 140.6, 139.3, 133.1, 130.6,

128.7, 128.3, 128.1, 127.5, 125.2, 115.1, 109.3 (dt, $J_d = 5$ Hz, $J_t = 18$ Hz), 100.9 (dd, $J = 3$, 25 Hz), 100.5 (dd, $J = 3$, 25 Hz), 84.7, 67.2, 47.2, 40.1, 21.6. ^{19}F NMR ($CDCl_3$): δ −108.5, −110.7. MS (ES^+) *m/z*: 561 (M + H). Anal. ($C_{32}H_{27}N_2O_4F_3$) C, H, N, F.

rac-Ambrisentan (rac-2). The racemic form of ambrisentan was prepared following the procedures given in the literature.[29] The final product was crystallized from diethyl ether, mp 177−179 °C (dec). ^{1}H NMR(DMSO-d_6): 12.49 (s, 1H), 7.17−7.34 (m, 10H), 6.93 (s, 1H), 6.12 (s, 1H), 3.37 (s, 3H), 2.34 (s, 6H). MS (ES^+) *m/z*: 379 (M + H). Anal. ($C_{22}H_{22}N_2O_4$·0.1·dioxane) C, H, N, O.

Endothelin Receptor Inhibition. For competition binding studies, membranes of CHO cells expressing human recombinant ET_A or ET_B receptors were used. Microsomal membranes from recombinant CHO cells were prepared and the binding assay was made as previously described.[66] The assay was performed in 200 μL of 50 mM Tris-HCl buffer, pH 7.4, including 25 mM $MnCl_2$, 1 mM EDTA, and 0.5% (w/v) BSA in polypropylene microtiter plates. Membranes containing 0.5 μg of protein were incubated for 2 h at 20 °C with 8 pM [^{125}I]ET-1 (4000 cpm) and increasing concentrations of unlabeled antagonists. Maximum binding and minimum binding were estimated in samples without and with 100 nM ET-1, respectively. After 2 h, the membranes were filtered on filter plates containing GF/C filters (Unifilterplates from Canberra Packard S.A. Zürich, Switzerland). To each well, 50 μL of scintillation cocktail was added (MicroScint 20, Canberra Packard S.A. Zürich, Switzerland), and the filter plates were counted in a microplate counter (TopCount, Canberra Packard S.A. Zürich, Switzerland). All compounds tested were dissolved, diluted, and added to DMSO. The assay was run in the presence of 2.5% DMSO, which was not found to interfere significantly with the binding. IC_{50} was calculated as the concentration of antagonist inhibiting 50% of the specific binding of ET-1. For reference compounds, the following IC_{50} values were found. ET_A cells: 0.075 nM ($n = 8$) for ET-1 and 118 nM ($n = 8$) for ET-3. ET_B cells: 0.067 nM ($n = 8$) for ET-1 and 0.092 nM ($n = 3$) for ET-3.

Inhibition of Endothelin-Induced Contractions on Isolated Rat Aortic Rings and Rat Tracheal Rings. The functional inhibitory potency of the endothelin antagonists was assessed by their inhibition of the contraction induced by endothelin-1 on rat aortic rings (ET_A receptors) and of the contraction induced by sarafotoxin S6c on rat tracheal rings (ET_B receptors). Adult Wistar rats were anesthetized and exsanguinated. The thoracic aorta or trachea were excised, dissected, and cut into 3−5 mm rings. The endothelium/epithelium was removed by gentle rubbing of the intimal surface. Each ring was suspended in a 10 mL of isolated organ bath filled with Krebs−Henseleit solution (in mM; NaCl 115, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.5, $NaHCO_3$ 25, $CaCl_2$ 2.5, glucose 10) kept at 37 °C and gassed with 95% O_2 and 5% CO_2. The rings were connected to force transducers, and isometric tension was recorded (EMKA Technologies SA, Paris, France). The rings were stretched to a resting tension of 3 g (aorta) or 2 g (trachea). Cumulative doses of ET-1 (aorta) or sarafotoxin S6c (trachea) were added after a 10 min incubation with the test compound or its vehicle. The functional inhibitory potency of the test compound was assessed by calculating the concentration ratio, i.e., the shift to the right of the EC_{50} induced by different concentrations of test compound. EC_{50} is the concentration of endothelin needed to obtain a half-maximal contraction, and pA_2 is the negative logarithm of the antagonist concentration that induces a 2-fold shift in the EC_{50} value.

Telemetric in Vivo Studies. In vivo efficacy of the compounds was assessed by oral administration of 30 mg/kg of the compound suspended in 10% arabic gum to hypertensive Dahl salt sensitive rats equipped with a telemetric system recording the arterial blood pressure and heart rate.[68−70] From the blood pressure recordings the area between the curve (ABC) before and the one after treatment was calculated to assess the compound's efficacy.

Pharmacokinetics in the Rat. Preliminary pharmacokinetic profiles of two prototypical structural representatives, i.e., rac-**39au** and rac-**91**, were determined in the male Wistar rat ($n = 2−3$). For this purpose, compounds were formulated as aqueous solutions containing 10% DMSO for intravenous administration at a dose of 1.0 mg/kg and as microsuspensions in 7.5% gelatin for oral dosing at 10 mg/kg. Blood samples were taken at regular time intervals over a period of 24 h from a preimplanted catheter, and plasma was generated by centrifugation at 4000 rpm at 4 °C. Plasma concentrations were determined using a specific and sensitive LC−MS/MS method with a limit of quantification of 1.5 ng/mL.

Inhibition of Cytochrome P450 Enzymes. The potential of the compounds for inhibition of the main human CYP isoforms, i.e., 2C9, 2D6, and 3A4, was evaluated using human liver microsomes and specific marker reactions for each enzyme. Diclofenac 4′-hydroxylation was used for CYP 2C9,[72] dextromethorphan N-demethylation was used for CYP 2D6,[73] and midazolam-1′-hydroxylation was used for CYP 3A4.[74] Experiments were performed around the respective K_m values of the marker substrates, and metabolite formation was monitored by LC−MS/MS. Inhibitor concentrations up to 50 μM were added, and the performance of the assay was controlled by the use of specific inhibitors for each CYP isoform.

Molecular Modeling. Model building was performed on structures of bovine rhodopsin (PDB codes: 1f88, 1hzx). A sequence alignment of human endothelin-A receptor (SWISSPROT, P25101) and bovine rhodopsin (sequence from PDB file) yielded a sequence identity of 21% with seven transmembrane (TM) domains clearly identifiable. Modeling calculations were done on a SGI Octane with dual R12000 processors using Moloc.[75] An initial C-α model of human ET_A receptor was built by fitting the aligned sequence of human ET_A receptor on the bovine rhodopsin template C-α structure followed by optimization of newly introduced loops that were selected from a database of high-resolution structures on the basis of minimal steric clash with the rest of the model. Subsequently a full atom model was generated and newly inserted loops were optimized with the rest of the protein kept stationary. Refinement of the full model with manual removal of repulsive van der Waals (vdW) interactions was divided into three parts. First, only side chains were allowed to move. In the next step all atoms except α carbons were optimized, and finally no atoms were kept stationary anymore but positional constraints were put on α carbons. Quality checks were made with Moloc internal programs and with a program by Luethy et al.[76]

Determination of log *D* Values. The log *D* values were determinded by the shake flask method following the procedure given in OECD Guideline No. 107.[77] The aqueous phase was buffered to pH 7.4 with 67 mM KH_2PO_4 and 67 mM Na_2HPO_4; the organic phase was *n*-octanol. In all experiments the volume ratio *n*-octanol/aqueous phase was 1:9. The compound concentrations of the two phases were determined by HPLC analysis (column: Phenomenex Synergi, Polar-Rp, 4 μm, 80 Å, 2 mm × 50 mm; gradient, 20−100% acetonitrile in water containing 0.05% formic acid, in 11 min; flow rate, 0.6 mL/min; Waters 2695 separations module; UV detection at 278 nm).

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Supporting Information Available: Synthesis and analytical data of rac-**5b**−**e**, rac-**9b**−**g**, rac-**39a**−**ae**,**ag**−**at**,**av**−**az**, rac-**68**−**78**, rac-**81**, rac-**84b**−**m**, rac-**92**, and rac-**93** and crystal structure analysis data including ORTEP plots and atom coordinates of rac-**7**, rac-**92**, and rac-**93**. This material is available free of charge via the Internet at http://pubs.acs.org.

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