Synthesis of 1,2,5-Thiadiazolidin-3-one 1,1-Dioxide Derivatives and Evaluation of Their Affinity for MHC Class-II Proteins

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1,2,5-Thiadiazolidin-3-one 1,1-dioxide derivatives (±)-**1a**–**d** and (±)-**2** were designed by molecular modeling as MHC (major histocompatibility complex) class-II inhibitors. They were prepared from the unsymmetrically *N,N′*-disubstituted acyclic sulfamides (±)-**4a**–**d** (*Scheme 1*) and (±)-**11** (*Scheme 2*). These *N*-alkyl-*N′*-arylsulfamide precursors were synthesized by nucleophilic substitution of either a sulfamoyl-chloride or a *N*-sulfamoyloxazolidinone. Extension of base-induced cyclization methods from aliphatic to aromatic sulfamides gave access to the desired target molecules. The *N*-alkyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide derivatives (±)-**3a**–**c** were also prepared by the oxazolidinone route (*Scheme 4*) for coupling to a tetrapeptide fragment. The X-ray crystal structure of 1,2,5-thiadiazolidin-3-one 1,1-dioxide (±)-**21a** was solved, and the directionality of the H-bond donor (N–H) and acceptor (SO_2) groups of the cyclic scaffold determined (*Figs. 1* and *2*). The pK_a value of the N–H group in (±)-**21a** was determined by ^{1}H-NMR titration as 11.9 (*Fig. 3*). Compounds (±)-**1a**–**d** were shown to inhibit competition peptide binding to HLA-DR4 molecules in the single-digit millimolar concentration range.

1. Introduction. – Peptides are often the natural substrates of pharmaceutical targets. However, their poor oral bioavailability and low metabolic stability severely limit their therapeutic application. Replacement of the peptide structure by a small, rigid molecule, commonly a cyclic scaffold bearing the side-chains important for binding, is a strategy to overcome this problem [1–4]. In cases where not only the peptidic side-chains but also the backbone is involved in key bonding interactions, some functional groups should be incorporated within the peptidomimetic scaffold in order to maintain them. Heterocycles, with their restricted conformational mobility and heteroatoms as intrinsic H-bond donor and acceptor sites best serve this purpose and have attracted considerable interest in medicinal chemistry (*e.g.*, see [5] [6]).

In this report, we describe the synthesis of 1,2,5-thiadiazolidin-3-one 1,1-dioxide derivatives as rigid, densely functionalized scaffolds, containing a sulfamide functionality, as a bidentate H-bond donor-acceptor unit. These sulfonylurea heterocycles were designed for the selective blockade of HLA-DR1 and HLA-DR4 proteins [7], two major histocompatibility complex (MHC) class-II alleles linked to rheumatoid arthritis [8]. Studies of peptide-MHC interactions [9–11] and attainment of high-resolution X-ray crystal structures [12] have provided a general understanding of the structural requirements for HLA-DR complexation. In peptide ligands, the NH and CO of the

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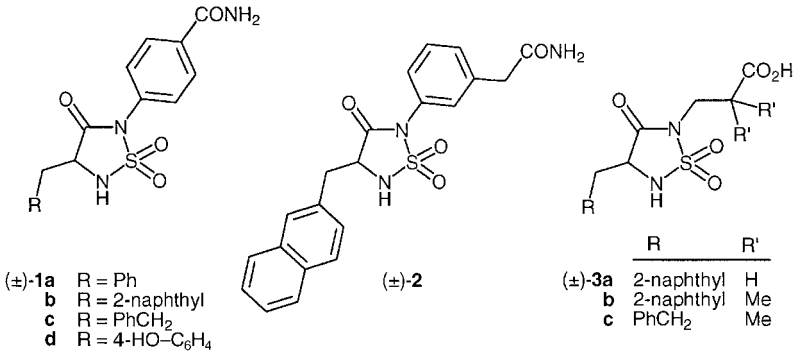
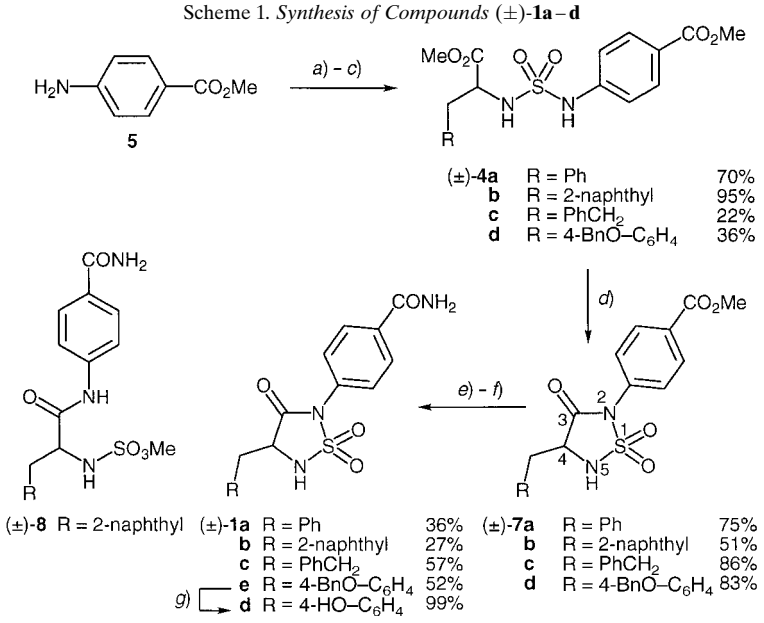
position-2 amino acid form complementary H-bonds to Asn β82 in the HLA-DR molecule. Similar contacts of the position-4 residue are made with Gln α9 and Asn α62. Conformationally restricted peptidic ligands, as well as peptidomimetic-peptide hybrids, have also been obtained [13]. A non-peptidic framework to replace the anchoring amino acids at positions 1 and 2 in peptidic substrates was, however, highly desirable. According to molecular modeling, the 1,2,5-thiadiazolidin-3-one 1,1-dioxide scaffold can serve as surrogate for these positions, the two contiguous H-bonding donor-acceptor sites $-NH-SO_2-$ being complementary to the amide side chain of Asn β82 (position 2). The side chain at C(4) of the rigid scaffold nicely points into a large aromatic pocket that binds aromatic and cycloaliphatic peptide side chains and is essential for high-affinity binding (position 1). Compounds (±)-**1a**–**d** and (±)-**2** were designed as non-peptidic HLA-DR inhibitors bearing an *N*-aryl side chain as vector towards Gln α9 and Asn α62 (position 4). The heterocyclic ring was also used as a peptidomimetic scaffold suitable for appending peptidic fragments (compounds (±)-**3a**–**c**) that were chosen from high-affinity hexapeptide analogs (*e.g.*, Ac-(Cha)-RAMASL-NH_2 [13c]).



2. Results and Discussion. – 2.1. *Synthesis.* Although many sulfamide-containing heterocycles have been reported (for a review, see [14]), 1,2,5-thiadiazolidin-3-one 1,1-dioxides are rarely found. Except for the low-yielding cyclization of an α-amino amide with sulfuryl chloride [15], the general route towards this heterocyclic ring involves cyclization of open-chain sulfamides under basic conditions [16–21]. Recently, serine protease inhibitors incorporating this sulfonylurea scaffold have been prepared by *N*-alkylation of the *N*,*N*′-unsubstituted heterocycles [22]. Although none of these examples involved an *N*-arylsulfamide as required for the synthesis of target compounds (±)-**1a**–**d**, we have planned our synthesis on this base-mediated cyclization strategy. The synthesis of the unsymmetrically disubstituted *N*-alkyl-*N*′-arylsulfamide precursors (±)-**4a**–**d** started with the sequential treatment of methyl 4-aminobenzoate (**5**) with $ClSO_3H$ and PCl_5 to generate *in situ* the corresponding sulfamoyl chloride [23] (*Scheme 1*). Nucleophilic substitution of the (±)-α-amino acid methyl ester hydrochlorides (±)-**6a**–**d** with the sulfamoyl chloride [24] yielded the *N*-alkyl-*N*′-arylsulfamides (±)-**4a**–**d**. The subsequent cyclization proved more difficult than in the case of aliphatic sulfamides [16–21]. Syringe pump addition of (±)-**4a**–**d** to a dilute solution of *t*-BuLi in THF gave the best results and afforded thiadiazolidinone dioxides (±)-**7a**–**d**

in 51 to 86% yield. A low sulfamide concentration was necessary to avoid polymerization. NaH in refluxing THF was later found to also afford the cyclized products in good yields. Methyl-ester hydrolysis, followed by treatment of the resulting carboxylic acids with *N′*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxy-1*H*-benzotriazole (HOBt) formed the corresponding activated esters, which reacted with NH_4OH [25] to give amides (±)-**1a**–**c** and (±)-**1e**. The moderate yields (27–57%) are the result of attack by MeO^-/HO^- ions at the electrophilic S-atom and cleavage of the S(1)–N(2) bond in (±)-**7a**–**d** during basic ester hydrolysis. This was established in the case of (±)-**7b** by the isolation of the corresponding methyl sulfamate (±)-**8** as side-product (13%). The corresponding sulfamic acid was presumably also formed but removed during aqueous workup. Deprotection of (±)-**1e** with CF_3CO_2H in the presence of pentamethylbenzene (PMB) [26] yielded target compound (±)-**1d**. PMB has been reported to not only improve the yield of deprotection but also, by trapping the benzyl cation, to avoid an intramolecular *O*- to *C*-rearrangement of *O*-benzyltyrosine to 3-benzyltyrosine [26] [27].

Scheme 1. *Synthesis of Compounds* (±)-**1a**–**d**

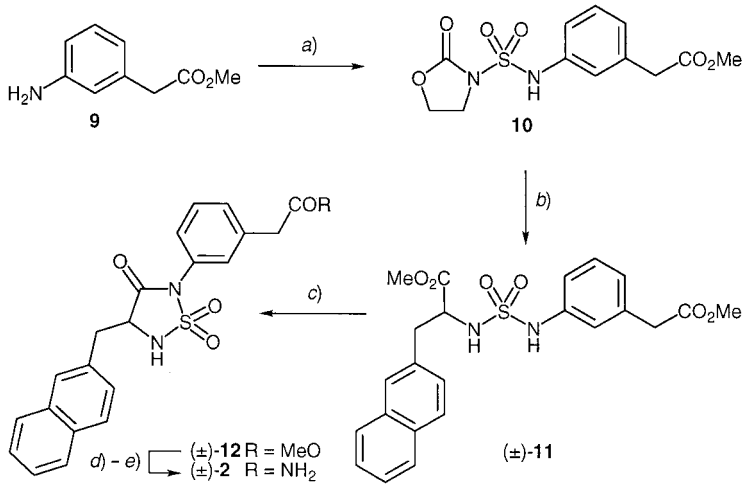


a) $ClSO_3H$, CH_2Cl_2, 0° → r.t., 1 h. *b*) PCl_5, reflux, 3.5 h. *c*) (±)-$MeO_2CCH(CH_2R)NH_2 \cdot HCl$ (R = Ph ((±)-**6a**); R = 2-naphthyl ((±)-**6b**); R = $PhCH_2$ ((±)-**6c**); R = 4-HO–C_6H_4 ((±)-**6d**)], Et_3N, CH_2Cl_2, r.t., 2.5 h. *d*) *t*-BuLi, THF, r.t., 16 h. *e*) KOH, MeOH, H_2O, r.t., 12 h. *f*) EDC, HOBt, NH_4OH, THF, r.t., 5 h. *g*) CF_3CO_2H, PMB, r.t., 1 h.

Attempts to synthesize (±)-**2**, containing a modified *N*-aryl side chain, by the route used for (±)-**1a**–**d** were unsuccessful. Reaction of $ClSO_3H$ with methyl (3-aminophenyl)acetate (**9**), followed by treatment with PCl_5, failed to generate the desired sulfamoyl chloride, leading only to decomposition products. Transamination of a monosubstituted sulfamide [28] with **9** to provide the unsymmetrically disubstituted *N*-alkyl-*N′*-arylsulfamide (±)-**11** was also not successful. Alternatively, transsulfamoyl-

ation of *N*-sulfamoyloxazolidinones with primary and secondary aliphatic amines was recently reported by *Montero* and co-workers to give access to various unsymmetrically disubstituted sulfamides [29]. Thus, the sulfamoyl chloride prepared *in situ* from chlorosulfonyl isocyanate and 2-chloroethanol was reacted with ester **9** to afford oxazolidinone **10** (*Scheme 2*). The oxazolidinone moiety of **10** was then substituted by (±)-3-(2-naphthyl)alanine methyl ester hydrochloride ((±)-**6b**), giving access to (±)-**11** in high yield. Attempts at preparing (±)-**11** by the reversed sequence of construction failed due to the insufficient nucleophilicity of the aromatic amine **9** in the last step. This demonstrates that the oxazolidinone strategy by *Montero* and co-workers [29] can be extended to the synthesis of *N*-alkyl-*N*′-arylsulfamides, provided the oxazolidinone is introduced on the aromatic amine allowing displacement by an aliphatic amine. Base-mediated cyclization to thiadiazolidinone dioxide (±)-**12** under the previously applied reaction conditions worked smoothly. Subsequent methyl-ester hydrolysis was achieved with potassium trimethylsilanolate [30] in THF, and the resulting carboxylic acid was transformed into target compound (±)-**2**. This ester-hydrolysis method avoids the use of HO^- and MeO^- ions, which previously caused partial cleavage of the sulfonylurea scaffold.

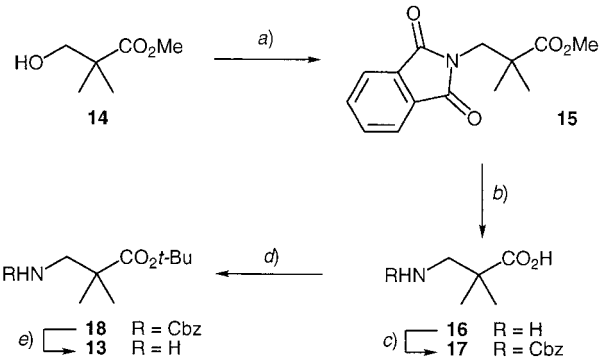
Scheme 2. *Synthesis of Compound* (±)-**2**



a) $OCNSO_2Cl$, $HOCH_2CH_2Cl$, CH_2Cl_2, 0°, 1.5 h, then (±)-**9**, Et_3N, CH_2Cl_2, 0° → r.t., 12 h; 89%. *b*) (±)-**6b**, Et_3N, MeCN, reflux, 12 h, 90%. *c*) *t*-BuLi, THF, r.t.; 16 h; 86%. *d*) Me_3SiOK, THF, r.t., 24 h. *e*) EDC, HOBt, NH_4OH, THF, r.t., 5 h, 38% (from (±)-**12**).

For the preparation of (±)-**3a**–**c**, suitable for anchoring peptidic fragments that extend beyond position 2 into the HLA-DR binding site, we attached propionate side chains to N(2) of the thiadiazolidinone scaffold. Whereas the *tert*-butyl ester of *β*-alanine – required to construct the *N*-alkyl-*N*′-arylsulfamide intermediates – was commercially available, the dimethyl-substituted analog **13** was prepared starting from ester **14** (*Scheme 3*). A *Mitsunobu* reaction provided **15**, and *β*-amino acid **16** was obtained by *Gabriel* synthesis. (Benzyloxy)carbonyl (Cbz) protection to **17** [31] and esterification to **18**, followed by removal of the Cbz group, provided **13**.

Scheme 3. *Synthesis of β-Amino Acid Ester* **13**



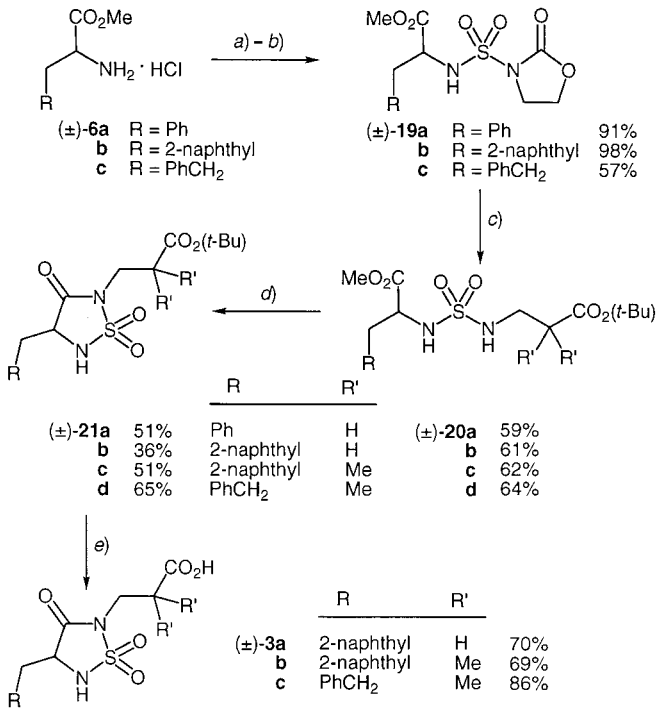
a) Phthalimide, PPh_3, *N,N′*-diethyl azodicarboxylate (DEAD), THF, r.t., 20 h, 77%. *b*) AcOH, HCl, H_2O, reflux, 16 h; 67%. *c*) CbzCl, NaOH, dioxane, H_2O, r.t., 5 h; 68%. *d*) Isobutene, H_2SO_4, CH_2Cl_2, r.t., 65 h; 85%. *e*) H_2, Pd/C, MeOH, 3 h, 89%.

Starting from (±)-**6a**–**c**, the *N*-sulfamoyloxazolidinones (±)-**19a**–**c** were obtained in good yields. Replacing the oxazolidinone moiety by *β*-alanine *tert*-butyl ester or the dimethyl-substituted analog **13** afforded the desired disubstituted sulfamides (±)-**20a**–**d**. In the subsequent cyclization, the presence of two ester groups, as well as two similarly acidic NH groups, could theoretically lead to four different regioisomers. However, strained three- and four-membered ring compounds were anticipated not to be formed, and the *tert*-butyl ester would be sterically too hindered for nucleophilic attack, thereby preventing formation of undesired six-membered ring product. Indeed, cyclization selectively afforded the corresponding desired 1,2,5-thiadiazolidin-3-one 1,1-dioxides (±)-**21a**–**d**. In the preparation of (±)-**21a**–**b**, *β*-elimination occurred as a side reaction as evidenced by the isolation of the corresponding N(2)-unsubstituted 1,2,5-thiadiazolidin-3-ones, 1,1-dioxides. Ester cleavage finally yielded (±)-**3a**–**c** with carboxy side chains for peptide attachment.

2.2. *Properties of 1,2,5-Thiadiazolidin-3-one 1,1-Dioxides.* We were interested in obtaining structural informations on the class of compounds prepared in this study and in estimating their H-bonding potential. Crystals of (±)-**21a** suitable for X-ray analysis were obtained by recrystallization from hexane/AcOEt (for details; see *Exper. Part*; for two other X-ray crystal-structure analyses of 1,2,5-thiadiazolidin-3-one 1,1-dioxides, see [18] and [21]). The extended crystal structure of this molecule is shown in *Fig. 1*. The five-membered ring shows an out-of-plane deformation towards an envelope shape, *i.e.*, the S-Atom deviates by *ca.* 0.37 Å from the remaining four coplanar atoms. The two planes passing through the N–S–N and the O–S–O fragments, respectively, are nearly orthogonal to one another (within *ca.* 2°) [32].

Of particular interest is the orientation of the H-bonding donor (NH) and acceptor (SO_2) groups in the cyclic scaffold. The crystal packing (*Fig. 2*) shows that there is a strong intermolecular N–H···O=C H-bond (N···O distance 2.73 Å) between the NH group of the sulfamide moiety and the ester C=O group. The N–H group is clearly oriented out of the five-membered ring plane and adopts a nearly eclipsed orientation with one of the vicinal S–O bonds (torsion angle H(14)–

Scheme 4. *Synthesis of Compounds* (±)-**3a**–**c**



a) $OCNSO_2Cl$, $HOCH_2CH_2Cl$, CH_2Cl_2, 0°, 1.5 h. *b*) (±)-**6a**, (±)-**6b**, or (±)-**6c**, Et_3N, CH_2Cl_2, 0° → r.t., 12 h. *c*) β-Alanine *tert*-butyl ester or **13**, Et_3N, MeCN, reflux, 12 h. *d*) NaH, THF, reflux, 7 h. *e*) TFA, r.t., 3 h.

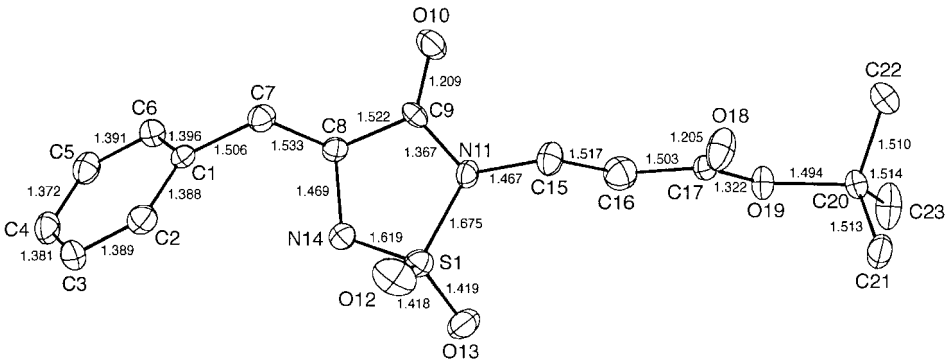


Fig. 1. *X-Ray crystal structure of* (±)-**21a**. Arbitrary numbering. Atomic displacement parameters obtained at 193 K are drawn at the 30% probability level. Selected bond angles [°]: N(14)–S(1)–N(11): 95.28; C(8)–N(14)–S(1): 110.63; N(14)–C(8)–C(9): 107.0; N(11)–C(9)–C(8): 110.4; C(9)–N(11)–S(1): 112.04

N(14)–S(1)–O(13) = –14°), a favorable orientation from the viewpoint of stabilization of local dipoles.

With the directionality of the H-bonding centers in the cyclic scaffold established, we were interested in estimating their H-bonding ability. *Ab initio* molecular-orbital

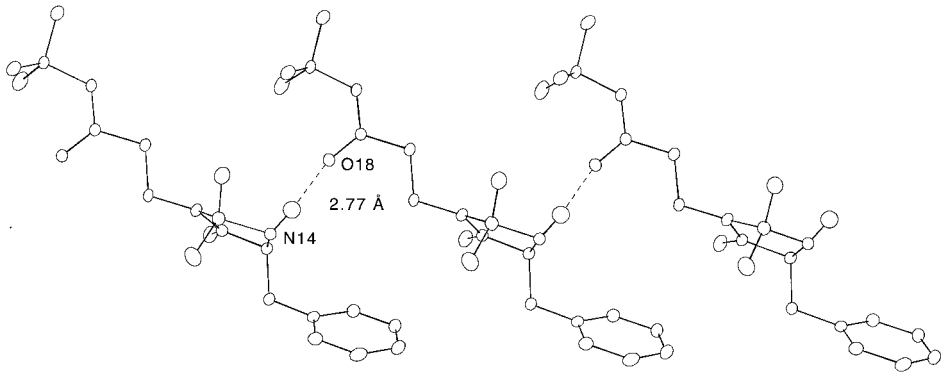


Fig. 2. *Crystal packing of* (±)-**21a**

calculations had indicated that sulfamide S−O bonds are highly polarized with the O-atoms retaining practically three lone pairs [32]. H-Bonding networks of acyclic *N,N′*-disubstituted sulfamides in the solid state have been reported [33], and cyclic sulfamides were essential structural components in the construction of H-bonding capsules built from four self-complementary sub-units [34]. Sulfonamide S−O groups were calculated to be poorer H-bond acceptors than P−O groups of phosphonamides, although better than P−O groups in phosphonamidates [35]. In a separate study in $CHCl_3$, S−O groups in sulfonamides were reported to be weaker H-bond acceptors than C=O groups in amides, carbamates, and even carboxylic esters, although conformational effects and the use of different H-bond donors might have influenced this result [36]. Whereas the H-bond acceptor capacity of S−O groups in sulfamides (and sulfonamides) remains therefore unclear, the H-bond donor ability of the N−H group can be estimated from its pK_a value. The acidity of some sulfamide derivatives had previously been reported [37]. However, none of these compounds is similar to ours. We, therefore, determined the pK_a of (±)-**21a** by ^{1}H-NMR titration [38]. A 0.03M solution of (±)-**21a** in CD_3COCD_3/D_2O 1:1 was prepared and titrated with a 0.1M solution of NaOD in D_2O up to pH 12.0. Thereafter, at higher pH, the titration was performed with a 1M solution of the base so as to minimize the dilution. The deprotonation was monitored by measuring, at different pH, the chemical-shift difference between the signal of a proton which is affected by the deprotonation (H−C(4′), H−C(6′), H−C(3)) and the signal of the *t*-Bu group which remains practically unchanged. Titration curves were obtained by plotting the difference in chemical shift against the pH of the solution (*Fig. 3*). The pH value at the inflection point of the sigmoidal curve was taken as a measure of the pK_a value. With a pK_a value of 11.9, the N−H group in (±)-**21a** is quite acidic and should undergo formation of strong H-bonds. It is even more acidic than that of the N−H group in hydantoin analog (±)-**22** [39], the pK_a value of which was determined as 12.5 by the same method.

Compounds (±)-**1a**–**d**, (±)-**2**, as well as (±)-**3a**–**c**, attached *via* an amide bond to the MASL-NH_2 tetrapeptide [40], were tested in a competitive inhibition assay using the 'scintillation proximity assay' method [13c]. None, however, had detectable binding affinity for HLA-DR4 proteins ($IC_{50} > 100$ μM according to the test sensitivity). The

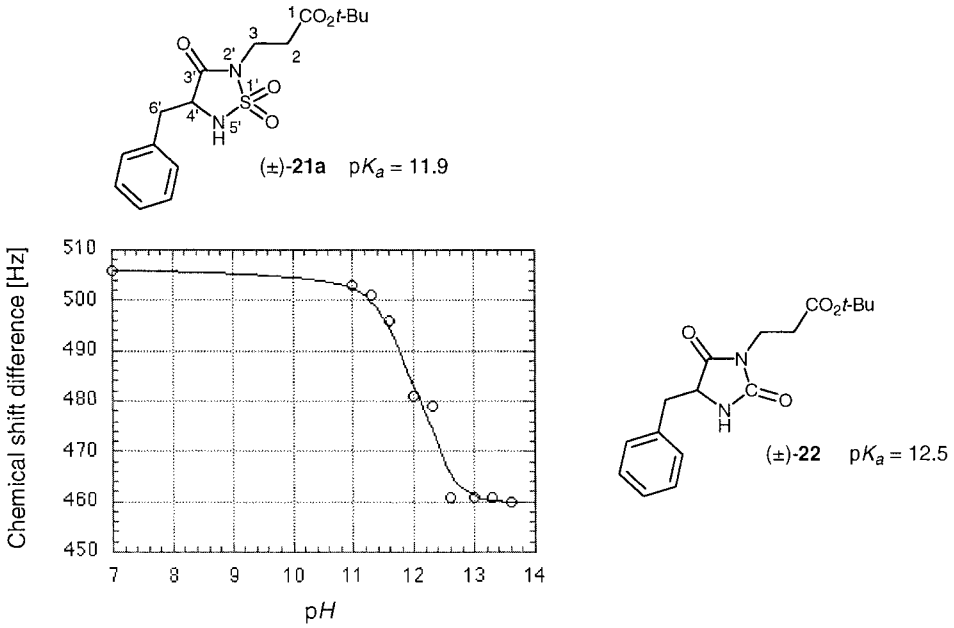


Fig. 3. *^{1}H-NMR Titration to determine the p*K$_a$ *value of* (±)-**21a**. The chemical shift difference between the signal of H–C(6′) and the *t*-Bu group is plotted against pH. Shown is also hydantoin analog (±)-**22**, for which the pK_a value was also determined by ^{1}H-NMR titration (not shown) [39].

higher solubility of benzamides (±)-**1a**–**d** in Me_2SO/H_2O compared to the cyclic scaffold-peptide hybrids allowed tests under more concentrated conditions, thereby increasing the detection limit of the assay. They were found to inhibit HLA-DR4 molecules in the single-digit millimolar concentration range (50% inhibition at 5 mM for compounds (±)-**1a**, (±)-**1b**, and (±)-**1d**, and 35% inhibition for (±)-**1c**). X-Ray crystal-structure data on MHC-peptide co-crystals [12b] [13c] demonstrated that the *N*-Ac group (position 0) is interacting with residues Ser α53 and His β81, and that de-amino compounds have diminished affinity. Consequently, the properties of the cyclic scaffold are not factors responsible for the diminished binding. Introduction of appropriate side chains at C(4) of the cyclic scaffold is planned to test this hypothesis.

3. Conclusion. – Unsymmetrically disubstituted *N*-alkyl-*N*′-arylsulfamides were synthesized from amino-acid building blocks by two different methods. Compounds (±)-**4a**–**d** were obtained by reaction of amino acid methyl esters with a sulfamoyl chloride, whereas (±)-**11** was prepared from a *N*-sulfamoyloxazolidinone. Cyclization of aliphatic sulfamides was then extended to the aromatic sulfamides (±)-**4a**–**d** and (±)-**11** with *t*-BuLi as base and afforded the *N*-aryl-1,2,5-thiadiazolidin-3-one 1,1-dioxide derivatives (±)-**1a**–**d** and (±)-**2**, respectively. Compounds (±)-**3a**–**c** with a propionate side chain at N(2) were also prepared by the oxazolidinone method for attachment to a tetrapeptide fragment. The X-ray crystal structure of 1,2,5-thiadiazolidin-3-one 1,1-dioxide (±)-**21a** was solved, and the directionality of the H-bond donor (N–H) and acceptor (SO_2) groups of the cyclic scaffold was determined. Analysis of the crystal packing showed that the N–H bond is oriented out of the five-membered-

ring plane and adopts a nearly eclipsed orientation with one of the two vicinal S–O bonds. The pK_a value of the N–H group in (±)-**21a** was determined by ^{1}H-NMR titrations as 11.9, making it a strong H-bond donor. Despite low potency so far obtained for HLA-DR4 molecules, the 1,2,5-thiadiazolidin-3-one 1,1-dioxide scaffold offers an interesting opportunity in medicinal chemistry as a rigid, easily accessible heterocycle featuring H-bonding sites in a quite unique array.

Experimental Part

General. Reagent-grade solvents and reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. The (±)-amino acid methyl ester hydrochlorides (±)-**6a** [41], (±)-**6b** [42], (±)-**6c** [43], and (±)-**6d** [44] were prepared according to the literature procedures. THF and Et_2O were freshly distilled from sodium benzophenone ketyl. Evaporation *in vacuo* was conducted at H_2O aspirator pressure. Flash chromatography (FC): silica gel *60* (230–400 mesh, 0.040–0.063 mm) from *Fluka*. M.p.: *Büchi SMP-20*; uncorrected. IR Spectra [cm^{-1}]: *Perkin-Elmer 1600-FT IR*. NMR Spectra: *Bruker AMX 500* and *Varian Gemini 300* or *200* at 296 K, with solvent peak as reference. MS (*m/z* (%)): EI: *VG TRIBRID* spectrometer at 70 eV; FAB: *VG ZAB2-SEQ* spectrometer with 3-nitrobenzyl alcohol (NOBA) as matrix; ESI: *Finnigan TSQ 7000* spectrometer. Elemental analyses were performed by the *Mikrolabor at the Laboratorium für Organische Chemie, ETH Zürich.*

Procedure A. To a soln. of **5** (16.50 mmol) in CH_2Cl_2 (100 ml) cooled to 0° was added dropwise $ClSO_3H$ (18.00 mmol). After stirring at r.t. for 1 h, PCl_5 (18.00 mmol) was added, and the soln. was heated to reflux for 3.5 h. The amino acid methyl ester hydrochloride (15.00 mmol) was added to the soln. of sulfamoyl chloride prepared *in situ*. The soln. was made basic (pH 8–9) by the addition of Et_3N and stirred at r.t. for 2.5 h. The reaction was quenched with sat. aq. NaCl soln. (100 ml), the org. phase was separated and the aq. phase extracted with CH_2Cl_2 (2 × 100 ml). The combined org. extracts were dried ($MgSO_4$), evaporated *in vacuo*, and purified by FC (SiO_2; hexane/AcOEt 6:4).

Procedure B. To *t*-BuLi (1.7M soln. in pentane; 5.00 mmol) in dry THF (100 ml) at r.t. under Ar was added a soln. of sulfamide (2.00 mmol) in THF (20 ml) over 4 h *via* syringe pump, and the mixture was stirred for 12 h. The reaction was quenched with sat. aq. NaCl soln. (100 ml) and 1M aq. HCl soln. (50 ml), the org. phase was separated, and the aq. phase extracted with CH_2Cl_2 (2 × 100 ml). The combined org. extracts were dried ($MgSO_4$), evaporated *in vacuo*, and purified by FC (SiO_2; CH_2Cl_2/MeOH 9:1).

Procedure C. A soln. of methyl (1,1,3-trioxo-1,2,5-thiadiazolidin-2-yl)benzoate (2.00 mmol) in MeOH (50 ml) and 1M aq. KOH soln. (50 ml) was stirred at r.t. for 12 h. The MeOH was evaporated *in vacuo*, the soln. made acidic with 1M aq. HCl soln. (60 ml) and extracted with AcOEt (4 × 100 ml). The combined org. extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was dissolved in THF (20 ml), EDC (2 mmol) and HOBt (2 mmol) were added, and the soln. was stirred at r.t. for 1 h. A 25% aq. NH_4OH soln. (2 mmol) was then added, and stirring was continued for 4 h. The mixture was filtered, the filtrate evaporated *in vacuo* and purified by FC (SiO_2; CH_2Cl_2/MeOH/NH_3 85:14:1).

Procedure D. To a stirred soln. of chlorosulfonyl isocyanate (4.00 mmol) in CH_2Cl_2 (50 ml) cooled to 0° was added 2-chloroethanol (4.00 mmol) at such a rate that the reaction temp. did not exceed 5°. After stirring at 0° for 1.5 h, a soln. of amine (4.00 mmol) and Et_3N (12.00 mmol) in CH_2Cl_2 (50 ml) was slowly added so that the reaction temp. remained under 5°. When the addition was complete, the soln. was allowed to warm to r.t. and stirred for 12 h. The reaction was quenched with 2M aq. HCl soln. sat. with NaCl (100 ml), the org. phase was separated and the aq. phase extracted with CH_2Cl_2 (2 × 100 ml). The combined org. extracts were dried (Na_2SO_4) and filtered. Et_3N (5 ml) was added, and the soln. was stirred at r.t. for 6 h. The reaction was quenched with 1M aq. HCl soln. (200 ml), the org. phase was separated and the aq. phase extracted with CH_2Cl_2 (2 × 100 ml). The combined org. extracts were dried (Na_2SO_4) and evaporated *in vacuo*.

Procedure E. A soln. of oxazolidinone (1.00 mmol), amine (1.00 mmol), and Et_3N (1 ml) in MeCN (25 ml) was heated to reflux for 12 h. MeCN was removed *in vacuo*, 1M aq. HCl soln. (50 ml) was added to the residue, and the product was extracted with CH_2Cl_2 (3 × 50 ml). The combined org. extracts were dried (Na_2SO_4), evaporated *in vacuo*, and purified by FC (SiO_2; hexane/AcOEt 7:3).

Procedure F. A soln. of sulfamide (1.00 mmol) and NaH (2.50 mmol) in THF (50 ml) was heated to reflux for 7 h. The mixture was allowed to cool to r.t., quenched with 1M aq. HCl soln. (50 ml), and extracted with AcOEt (3 × 50 ml). The combined org. extracts were dried ($MgSO_4$), evaporated *in vacuo*, and purified by FC (SiO_2; hexane/AcOEt 8:2 to 7:3).

Procedure G. A soln. of 1,2,5-thiadiazolidin-3-one 1,1-dioxide (1 mmol) in CF_3CO_2H (50 ml) was stirred at r.t. for 3 h. The residue obtained by evaporation *in vacuo* was recrystallized (hexane/Et_2O).

(±)-Methyl 4-[({[1-(Methoxycarbonyl)-2-phenylethyl]amino}sulfonyl)amino]benzene-1-carboxylate ((±)-**4a**). Treatment of (±)-**6a** (5.00 g, 23.18 mmol) according to *Procedure A* gave (±)-**4a** (6.34 g, 70%). Colorless solid. M.p. 153–155° (hexane/AcOEt). IR (KBr): 3223*m*, 1724*s*, 1700*m*, 1610*m*, 1350*m*, 1281*m*, 1154*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.93, 7.04 (*AA′BB′*, J = 8.8, 4 H); 7.22–7.16 (*m*, 3 H); 7.06–7.01 (*m*, 2 H); 5.31 (*d*, J = 9.1, 1 H); 4.33 (*m*, 1 H); 3.90 (*s*, 3 H); 3.61 (*s*, 3 H); 3.00 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.8; 166.5; 141.2; 134.8; 131.1; 129.2; 128.7; 127.5; 125.4; 117.8; 57.4; 52.8; 52.2; 38.8. DEI-MS: 392 (14, M^+), 333 (9), 241 (46), 230 (12), 151 (32), 120 (62), 91 (100). Anal. calc. for $C_{18}H_{20}N_2O_6S$ (392.4): C 55.09, H 5.14, N 7.14, S 8.17; found: C 55.26, H 5.12, N 7.21, S 8.09.

(±)-Methyl 4-[({[1-(Methoxycarbonyl)-2-(naphthalen-2-yl)ethyl]amino}sulfonyl)amino]benzene-1-carboxylate ((±)-**4b**). Treatment of (±)-**6b** (810 mg, 3.05 mmol) according to *Procedure A* gave (±)-**4b** (1.28 g, 95%). Colorless solid. M.p. 180–182° (hexane/AcOEt). IR (KBr): 3278*m*, 3230*m*, 1717*m*, 1697*s*, 1610*m*, 1436*m*, 1339*m*, 1290*s*, 1239*m*, 1154*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.80–7.67 (*m*, 3 H); 7.70 (*d*, J = 8.7, 2 H); 7.56–7.44 (*m*, 3 H); 7.18 (*d*, J = 8.3, 1 H); 6.92 (*d*, J = 8.7, 2 H); 6.83 (*s*, 1 H); 5.26 (*d*, J = 8.7, 1 H); 4.48–4.38 (*m*, 1 H); 3.91 (*s*, 3 H); 3.70 (*s*, 3 H); 3.28, 3.11 (*AB* of *ABX*, J_{AX} = 4.8, J_{BX} = 6.6, J_{AB} = 14.0, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$/CD_3OD, ca. 99:1): 172.7; 167.2; 142.2; 133.3; 133.1; 132.5; 130.6; 128.2; 128.1; 127.6 (2×); 126.8; 126.1; 125.7; 123.8; 116.5; 57.4; 52.4; 51.8; 38.6. DEI-MS: 442 (5, M^+), 241 (8), 212 (14), 168 (7), 151 (14), 141 (100), 120 (19). Anal. calc. for $C_{22}H_{22}N_2O_6S$ (442.5): C 59.72, H 5.01, N 6.33, S 7.25; found: C 59.92, H 5.16, N 6.52, S 7.16.

(±)-Methyl 4-[({[1-(Methoxycarbonyl)-3-phenylpropyl]amino}sulfonyl)amino]benzene-1-carboxylate ((±)-**4c**). Treatment of (±)-**6c** (2.01 g, 8.75 mmol) according to *Procedure A* gave (±)-**4c** (762 mg, 22%). Colorless solid. M.p. 143–145° (hexane/AcOEt). IR (KBr): 3263*m*, 1722*s*, 1610*m*, 1437*m*, 1349*m*, 1292*s*, 1147*s*, 1106*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.01 (*d*, J = 8.3, 2 H); 7.29–7.14 (*m*, 5 H); 7.06–7.02 (*m*, 2 H); 4.09 (*m*, 1 H); 3.91 (*s*, 3 H); 3.58 (*s*, 3 H); 2.60 (*m*, 2 H); 2.17–1.87 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.8; 166.8; 141.7; 140.2; 131.4; 128.8; 128.6; 126.6; 125.8; 118.0; 56.0; 52.9; 52.2; 34.4; 31.2. DEI-MS: 406 (20, M^+), 347 (7), 182 (9), 151 (100), 120 (40), 117 (74), 105 (29), 91 (97). Anal. calc. for $C_{19}H_{22}N_2O_6S$ (406.5): C 56.15, H 5.46, N 6.89, S 7.89; found: C 56.27, H 5.53, N 7.07, S 7.92.

(±)-Methyl 4-[({[1-(Methoxycarbonyl)-2-[4-(phenylmethoxy)phenyl]ethyl]amino}sulfonyl]amino}benzene-1-carboxylate ((±)-**4d**). Treatment of (±)-**6d** (4.50 g, 13.98 mmol) according to *Procedure A* gave (±)-**4d** (2.48 g, 36%). Colorless solid. M.p. 152-154° (hexane/AcOEt). IR (KBr): 3300*m*, 3224*m*, 1722*s*, 1612*m*, 1514*m*, 1351*m*, 1278*m*, 1156*m*, 1117*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.95, 7.05 (*AA′BB′*, J = 8.8, 4 H); 7.45–7.32 (*m*, 5 H); 6.96, 6.81 (*AA′BB′*, J = 8.7, 4 H); 5.24 (*d*, J = 9.1, 1 H); 4.99 (*s*, 2 H); 4.29 (*m*, 1 H); 3.86 (*s*, 3 H); 3.63 (*s*, 3 H); 2.96 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.9; 166.5; 158.1; 141.1; 136.9; 131.0; 130.3; 128.6; 128.0; 127.5; 126.9; 125.4; 117.7; 115.0; 69.9; 57.5; 52.8; 52.1; 38.0. DEI-MS: 498 (3, M^+), 226 (4), 197 (78), 178 (11), 151 (36), 120 (57), 107 (10), 91 (100). Anal. calc. for $C_{25}H_{26}N_2O_7S$ (498.6): C 60.23, H 5.26, N 5.62, S 6.43; found: C 60.16, H 5.30, N 5.78, S 6.43.

(±)-Methyl 4-[4-(Phenylmethyl)-1,1,3-trioxo-1λ⁶,2,5-thiadiazolan-2-yl]benzoate ((±)-**7a**). Treatment of (±)-**4a** (1.50 g, 3.82 mmol) according to *Procedure B* gave (±)-**7a** (1.03 g, 75%). Yellow solid. M.p. 169–171° (hexane/AcOEt). IR (KBr): 3267*m*, 1725*m*, 1605*m*, 1333*m*, 1289*m*, 1153*s*, 1106*m*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 8.38 (*d*, J = 9.4, 1 H); 7.75, 7.05 (*AA′BB′*, J = 8.7, 4 H); 7.16–7.05 (*m*, 5 H); 3.90–3.84 (*m*, 1 H); 3.81 (*s*, 3 H); 2.89 (*AB* of *ABX*, J_{AX} = 6.0, J_{BX} = 8.6, J_{AB} = 13.7, 2 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 172.5; 165.9; 143.1; 136.6; 130.0; 128.9; 127.9; 126.3; 122.4; 116.5; 57.2; 51.7; 37.5. DEI-MS: 360 (1, M^+), 332 (5), 151 (51), 120 (100), 91 (43). HR-DEI-MS: 360.0779 (M^+, $C_{17}H_{16}N_2O_5S$; calc. 360.0780).

(±)-Methyl 4-[4-(Naphthalen-2-ylmethyl)-1,1,3-trioxo-1λ⁶,2,5-thiadiazolan-2-yl]benzoate ((±)-**7b**). Treatment of (±)-**4b** (900 mg, 2.03 mmol) according to *Procedure B* gave (±)-**7b** (425 mg, 51%). Yellow solid. M.p. 172–175° (hexane/AcOEt). IR (KBr): 3251*m*, 1722*m*, 1609*s*, 1434*m*, 1406*m*, 1322*m*, 1280*s*, 1148*s*, 1106*m*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 7.78–7.62 (*m*, 3 H); 7.67 (*d*, J = 8.7, 2 H); 7.50 (*s*, 1 H); 7.40–7.30 (*m*, 3 H); 7.00 (*d*, J = 8.7, 2 H); 3.89–3.83 (*m*, 1 H); 3.77 (*s*, 3 H); 3.19, 2.98 (*AB* of *ABX*, J_{AX} = 4.6, J_{BX} = 7.3, J_{AB} = 14.0, 2 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 173.5; 166.1; 144.0; 136.4; 132.9; 131.8; 130.4; 128.3; 127.8; 127.4 (2×); 127.1; 125.7; 125.2; 122.2; 116.4; 58.9; 51.7; 38.0. DEI-MS: 410 (1, M^+), 169 (2), 151 (55), 141 (9), 120 (100), 92 (19). HR-DEI-MS: 410.0936 (M^+, $C_{21}H_{18}N_2O_5S$; calc. 410.0936).

(±)-Methyl 4-[4-(2-Phenylethyl)-1,1,3-trioxo-1λ⁶,2,5-thiadiazolan-2-yl]benzoate ((±)-**7c**). Treatment of (±)-**4c** (750 mg, 1.85 mmol) according to *Procedure B* gave (±)-**7c** (592 mg, 86%). Yellow solid. M.p. 105–107° (hexane/AcOEt). IR (KBr): 3265*m*, 1718*s*, 1609*s*, 1433*m*, 1322*m*, 1283*s*, 1151*s*, 1106*m*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 7.89, 7.21 (*AA′BB′*, J = 8.7, 4 H); 7.24–7.13 (*m*, 3 H); 6.98–6.94 (*m*, 2 H); 3.83 (*s*, 3 H); 3.63–3.58 (*m*, 1 H); 2.50–2.41 (*m*, 2 H); 1.92–1.80 (*m*, 2 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 173.8; 166.2; 144.3; 142.1;

130.6; 128.3 (2×); 125.7; 122.4; 116.6; 56.9; 51.8; 45.3; 34.1. DEI-MS: 374 (2, M^+), 346 (3), 343 (2), 270 (22), 191 (11), 151 (90), 120 (100). HR-DEI-MS: 374.0939 (M^+, $C_{18}H_{18}N_2O_5S$; calc. 374.0936).

(±)-*Methyl 4-(4-{[4-(Phenylmethoxy)phenyl]methyl}-1,1,3-trioxo-1λ⁶,2,5-thiadiazolan-2-yl)benzoate* ((±)-**7d**). Treatment of (±)-**4d** (1.13 g, 2.27 mmol) according to *Procedure B* gave (±)-**7d** (0.87 g, 83%). Yellow solid. M.p. 113–115° (hexane/AcOEt). IR (KBr): 3262*m*, 1718*m*, 1609*s*, 1513*m*, 1282*s*, 1239*m*, 1152*s*, 1106*m*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 7.81, 7.04 (*AA′BB′*, $J = 8.6$, 4 H); 7.45–7.31 (*m*, 5 H); 7.04, 6.77 (*AA′BB′*, $J = 8.6$, 4 H); 5.00 (*s*, 2 H); 3.77 (*s*, 3 H); 3.90–3.84 (*m*, 1 H); 3.00, 2.77 (*AB* of *ABX*, $J_{AX} = 4.3$, $J_{BX} = 7.8$, $J_{AB} = 13.7$, 2 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 172.8; 165.8; 156.7; 143.3; 137.1; 130.0 (2×); 129.1; 128.3; 127.6; 127.4; 122.2; 116.4; 114.0; 68.8; 57.8; 51.6; 36.6. DEI-MS: 466 (3, M^+), 435 (2), 197 (17), 178 (5), 151 (49), 134 (3), 120 (100), 91 (42). HR-DEI-MS: 466.1226 (M^+, $C_{24}H_{22}N_2O_6S$; calc. 466.1198).

(±)-4-[4-(Phenylmethyl)-1,1,3-trioxo-1λ⁶,2,5-thiadiazolan-2-yl]benzene-1-carboxamide ((±)-**1a**). Treatment of (±)-**7a** (500 mg, 1.39 mmol) according to *Procedure C* gave (±)-**1a** (172 mg, 36%). Colorless solid. M.p. 174–176° (Et_2O/MeOH). IR (KBr): 3456*m*, 3367*m*, 1744*m*, 1654*s*, 1606*m*, 1325*s*, 1183*m*, 1161*m*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 9.08 (*s*, 1 H); 8.11 (*s*, 1 H); 8.03, 7.45 (*AA′BB′*, $J = 8.6$, 4 H); 7.54 (*s*, 1 H); 7.37–7.27 (*m*, 5 H); 4.76, 3.28, 3.04 (*ABX*, $J_{AX} = 3.9$, $J_{BX} = 10.1$, $J_{AB} = 14.3$, 3 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 168.1; 166.8; 136.2; 135.2; 132.7; 129.5; 128.9; 128.2; 126.7 (2×); 61.0; 36.3. DEI-MS: 345 (2, M^+), 317 (11), 146 (19), 136 (13), 118 (28), 91 (100). Anal. calc. for $C_{16}H_{15}N_3O_4S$ (345.4): C 55.64, H 4.38, N 12.17, S 9.28; found: C 55.78, H 4.46, N 12.05, S 9.16.

(±)-*4-[4-(Naphthalen-2-ylmethyl)-1,1,3-trioxo-1λ⁶,2,5-thiadiazolan-2-yl]benzene-1-carboxamide* ((±)-**1b**). Treatment of (±)-**7b** (400 mg, 0.97 mmol) according to *Procedure C* gave (±)-**1b** (104 mg, 27%). Colorless solid. M.p. >175° (dec.). IR (KBr): 1754*m*, 1742*m*, 1729*m*, 1610*m*, 1322*s*, 1186*s*, 1165*s*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 9.13 (br. *s*, 1 H); 8.10 (*s*, 1 H); 8.02 (*d*, $J = 7.8$, 2 H); 7.91–7.85 (*m*, 4 H); 7.52–7.46 (*m*, 6 H); 4.87–4.84 (*m*, 1 H); 3.47–3.41 (*m*, 1 H); 3.26–3.21 (*m*, 1 H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): 168.5; 167.0; 135.0; 134.2; 133.2; 132.9; 132.0; 128.8 (2×); 127.9 (2×); 127.7; 127.4; 126.5; 126.1; 125.6; 61.3; 36.8. FAB-MS: 396 (25, MH^+), 391 (41), 149 (100), 141 (19). HR-FAB-MS: 396.1015 (MH^+, $C_{20}H_{18}N_3O_4S$; calc. 396.1018).

(±)-4-[4-(2-Phenylethyl)-1,1,3-trioxo-1λ⁶,2,5-thiadiazolan-2-yl]benzene-1-carboxamide ((±)-**1c**). Treatment of (±)-**7c** (500 mg, 1.34 mmol) according to *Procedure C* gave (±)-**1c** (270 mg, 57%). Colorless solid. M.p. 168–170° (AcOEt). IR (KBr): 3445*m*, 3378*m*, 1739*m*, 1654*s*, 1606*m*, 1322*m*, 1183*m*, 1161*m*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 7.87, 7.42 (*AA′BB′*, $J = 8.7$, 4 H); 7.25–7.07 (*m*, 5 H); 4.09 (*dd*, $J = 9.5$, 4.6, 1 H); 2.92–2.65 (*m*, 2 H); 2.33–2.05 (*m*, 2 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 169.5; 169.4; 139.9; 134.3; 133.9; 129.1; 128.8; 128.7; 126.9; 126.6; 59.5; 32.9; 31.5. DEI-MS: 360 (5, MH^+), 359 (4, M^+), 331 (5), 255 (54), 191 (38), 147 (33), 134 (63), 117 (45), 105 (29), 91 (100). Anal. calc. for $C_{17}H_{17}N_3O_4S$ (359.4): C 56.81, H 4.77, N 11.69, S 8.92; found: C 56.54, H 4.80, N 11.76, S 8.93.

(±)-4-(4-{[4-(Phenylmethoxy)phenyl]methyl}-1,1,3-trioxo-1λ⁶,2,5-thiadiazolan-2-yl)benzene-1-carboxamide ((±)-**1e**). Treatment of (±)-**7d** (600 mg, 1.29 mmol) according to *Procedure C* gave (±)-**1e** (300 mg, 52%). Colorless solid. M.p. 216–218° (Et_2O/MeOH). IR (KBr): 3222*m*, 1724*m*, 1689*m*, 1672*m*, 1513*m*, 1395*m*, 1317*s*, 1233*m*, 1178*s*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 9.06 (*s*, 1 H); 8.13 (*s*, 1 H); 8.05 (*d*, $J = 8.7$, 2 H); 7.56 (*s*, 1 H); 7.49–7.34 (*m*, 7 H); 7.28, 7.01 (*AA′BB′*, $J = 8.6$, 4 H); 5.12 (*s*, 2 H); 4.72, 3.22, 3.00 (*ABX*, $J_{AX} = 3.9$, $J_{BX} = 9.9$, $J_{AB} = 14.0$, 3 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 168.2; 166.8; 157.2; 137.1; 135.1; 132.8; 130.7; 130.5; 128.8; 128.3; 127.7; 127.5; 126.6; 114.5; 69.0; 61.2; 35.5. DEI-MS: 451 (1, M^+), 197 (3), 146 (3), 134 (2), 120 (4), 107 (6), 91 (65). Anal. calc. for $C_{23}H_{21}N_3O_5S$ (451.5): C 61.19, H 4.69, N 9.31, S 7.10; found: C 61.15, H 4.71, N 9.16, S 7.00.

(±)-*4-{4-[(4-Hydroxyphenyl)methyl]-1,1,3-trioxo-1λ⁶,2,5-thiadiazolan-2-yl}benzene-1-carboxamide* ((±)-**1d**). A soln. of (±)-**1e** (330 mg, 0.73 mmol) and pentamethylbenzene (1.08 g, 7.29 mmol) in CF_3CO_2H (20 ml) was allowed to stand at r.t. for 1 h. The soln. was evaporated *in vacuo*, the residue washed with Et_2O (5 ml) and dried *in vacuo* to give (±)-**1d** (261 mg, 99%). Colorless solid. M.p. >200° (dec.; hexane/AcOEt/MeOH). IR (KBr): 3433*m*, 3189*m*, 1728*m*, 1646*s*, 1611*m*, 1511*m*, 1339*s*, 1189*s*, 1167*s*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 9.22 (*s*, 1 H); 9.03 (*s*, 1 H); 8.12 (*s*, 1 H); 8.05, 7.46 (*AA′BB′*, $J = 8.7$, 4 H); 7.55 (*s*, 1 H); 7.15, 6.75 (*AA′BB′*, $J = 8.7$, 4 H); 4.67, 3.17, 2.95 (*ABX*, $J_{AX} = 3.7$, $J_{BX} = 9.9$, $J_{AB} = 14.1$, 3 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 168.5; 167.2; 156.5; 135.4; 133.0; 130.7; 129.1; 126.9; 126.4; 115.2; 61.5; 35.7. DEI-MS: 361 (4, M^+), 238 (4), 191 (6), 146 (20), 136 (31), 120 (39), 107 (100). HR-DEI-MS: 361.0729 (M^+, $C_{16}H_{15}N_3O_5S$; calc. 361.0732).

(±)-*Methyl N-[2-{[4-(Aminocarbonyl)phenyl]amino}-1-(naphthalen-2-ylmethyl)-2-oxoethyl]sulfamate* ((±)-**8**). The procedure described for (±)-**1b** also afforded (±)-**8** (54 mg, 13%). Colorless solid. M.p. >165° (dec.). IR (KBr): 3489*m*, 3378*m*, 1733*m*, 1659*s*, 1606*m*, 1144*m*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 10.08 (br. *s*, 1 H); 8.62 (br. *s*, 1 H); 7.86–7.62 (*m*, 7 H); 7.51–7.43 (*m*, 2 H); 7.30–7.26 (*m*, 1 H); 7.20 (*s*, 1 H); 7.06 (*d*, $J = 8.7$, 2 H); 4.18–4.04 (*m*, 1 H); 3.40 (*s*, 3 H); 3.09, 2.95 (*AB* of *ABX*, $J_{AX} = 7.3$, $J_{BX} = 8.1$, $J_{AB} = 13.7$, 2 H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): 171.8; 167.6; 141.4; 134.1; 133.0; 132.0; 128.4; 127.9; 127.8; 127.6; 127.5; 127.5; 127.4; 126.1; 125.8;

116.6; 57.2; 51.7; 37.8. DEI-MS: 427 (2, M^+), 409 (3), 229 (10), 212 (7), 141 (100). Anal. calc. for $C_{21}H_{21}N_3O_5S$ (427.5): C 59.00, H 4.95, N 9.83, S 7.50; found: C 58.82, H 5.15, N 9.60, S 7.30.

Methyl 2-(3-{[(2-Oxo-1,3-oxazolan-3-yl)sulfonyl]amino}phenyl)ethanoate (**10**). Treatment of **9** (1.00 g, 4.96 mmol) [45] according to *Procedure D* gave **10** (1.39 g, 89%). Colorless solid. M.p. 72–74° (hexane/AcOEt). IR ($CHCl_3$): 1773*s*, 1737*s*, 1418*m*, 1388*m*, 1182*s*, 1156*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.39–7.18 (*m*, 4 H); 4.33–4.25 (*m*, 2 H); 3.88–3.80 (*m*, 2 H); 3.70 (*s*, 3 H); 3.63 (*s*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 172.1; 153.4; 136.0; 135.6; 130.1; 128.1; 124.0; 122.0; 63.0; 52.0; 46.5; 40.7. DEI-MS: 314 (100, M^+), 255 (24), 165 (63), 163 (54), 106 (69). Anal. calc. for $C_{12}H_{14}N_2O_6S$ (314.3): C 45.86, H 4.49, N 8.91, S 10.20; found: C 45.93, H 4.52, N 8.76, S 10.47.

(±)-Methyl 2-{[({3-[(Methoxycarbonyl)methyl]phenyl}amino)sulfonyl]amino}-3-(naphthalen-2-yl)propanoate ((±)-**11**). Treatment of **10** (2.06 g, 6.55 mmol) and (±)-**6b** (2.06 g, 6.55 mmol) according to *Procedure E* gave (±)-**11** (2.69 g, 90%). Colorless solid. M.p. 128–130° (hexane/AcOEt). IR (KBr): 3278*m*, 3222*m*, 1739*m*, 1721*s*, 1350*m*, 1289*m*, 1149*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.81–7.69 (*m*, 3 H); 7.51–7.44 (*m*, 3 H); 7.20–7.14 (*m*, 1 H); 7.08 (*d*, J = 7.9, 1 H); 6.97–6.88 (*m*, 3 H); 6.54 (*s*, 1 H); 5.19 (*d*, J = 9.1, 1 H); 4.49–4.38 (*m*, 1 H); 3.66 (*s*, 3 H); 3.64 (*s*, 3 H); 3.50 (*s*, 2 H); 3.28–3.10 (*m*, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 171.8; 171.6; 137.0; 135.2; 133.3; 132.5; 132.5; 129.3; 128.3; 128.3; 127.6; 127.6; 127.0; 126.2; 125.9; 125.4; 120.7; 118.5; 57.3; 52.6; 52.0; 40.8; 39.0. DEI-MS: 456 (11, M^+), 255 (36), 212 (24), 165 (29), 141 (100). Anal. calc. for $C_{23}H_{24}N_2O_6S$ (456.5): C 60.51, H 5.30, N 6.14, S 7.02; found: C 60.65, H 5.52, N 6.02, S 7.09.

(±)-Methyl 2-(3-{4-[(Naphthalen-2-yl)methyl]-1,1,3-trioxo-1λ^6,2,5-thiadiazolan-2-yl}phenyl)ethanoate ((±)-**12**). Treatment of (±)-**11** (1.32 g, 2.89 mmol) according to *Procedure B* gave (±)-**12** (1.05 g, 86%). Yellow solid. M.p. 135–137°. IR (KBr): 3256*m*, 1733*m*, 1594*m*, 1561*m*, 1416*m*, 1144*s*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 7.81–7.76 (*m*, 1 H); 7.69–7.65 (*m*, 2 H); 7.51 (*s*, 1 H); 7.45–7.29 (*m*, 3 H); 7.15–7.03 (*m*, 1 H); 6.96–6.93 (*m*, 2 H); 6.81 (*d*, J = 7.5, 2 H); 3.90–3.82 (*m*, 1 H); 3.55 (*s*, 3 H); 3.53 (*s*, 2 H); 3.16, 2.77 (*AB* of *ABX*, J_{AX} = 5.4, J_{BX} = 6.2, J_{AB} = 14.1, 2 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 173.5; 171.6; 139.5; 136.6; 135.1; 133.0; 131.8; 129.0; 128.7; 127.9; 127.5 (2×); 127.0; 125.7; 125.2; 123.1; 119.0; 116.6; 58.7; 51.6; 45.3; 37.9. DEI-MS: 424 (8, M^+), 165 (82), 141 (53), 106 (100). HR-DEI-MS: 424.1116 (M^+, $C_{22}H_{20}N_2O_5S$; calc. 424.1093).

(±)-2-(3-{4-[(Naphthalen-2-yl)methyl]-1,1,3-trioxo-1λ^6,2,5-thiadiazolan-2-yl}phenyl)acetamide ((±)-**2**). A soln. of (±)-**12** (500 mg, 1.18 mmol) and potassium trimethylsilanolate (454 mg, 3.54 mmol) in THF (25 ml) was stirred at r.t. for 24 h. The reaction was quenched with 1M aq. HCl soln. (50 ml) and the mixture extracted with AcOEt (3 × 50 ml). The combined org. extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was dissolved in THF (25 ml), EDC (226 mg, 1.18 mmol) and HOBt (159 mg, 1.18 mmol) were added, and the soln. was stirred at r.t. for 1 h. A 25% aq. NH_4OH soln. (0.09 ml, 1.18 mmol) was added, and stirring was continued for 4 h. The mixture was filtered, evaporated *in vacuo*, and purified by FC (SiO_2; CH_2Cl_2/MeOH/NH_4OH 85 : 14 : 1) to give (±)-**2** (180 mg, 38%). Colorless solid. M.p. 160–163° (Et_2O/CH_2Cl_2). IR (KBr): 3378*m*, 1739*m*, 1656*s*, 1339*m*, 1322*m*, 1178*m*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 7.95–7.88 (*m*, 4 H); 7.59–7.42 (*m*, 6 H); 7.30–7.22 (*m*, 2 H); 6.99 (*s*, 1 H); 4.87 (*dd*, J = 9.9, 3.7, 1 H); 3.50–3.42 (*m*, 1 H); 3.48 (*s*, 2 H); 3.23 (*dd*, J = 14.3, 9.9, 1 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 171.8; 168.6; 138.6; 134.3; 133.1; 132.2; 130.7; 130.4; 129.7; 128.1; 128.0 (2×); 127.9; 127.7 (2×); 126.3; 125.9; 125.6; 61.0; 41.2; 36.7. DEI-MS: 409 (9, M^+), 169 (18), 141 (100). Anal. calc. for $C_{21}H_{19}N_3O_4S$ (409.5): C 61.60, H 4.68, N 10.26, S 7.83; found: C 61.39, H 5.08, N 9.83, S 7.66.

*Methyl 2,2-Dimethyl-3-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)propanoate* (**15**). To a soln. of phthalimide (2.52 g, 17.16 mmol), PPh_3 (4.50 g, 17.16 mmol), and **14** (1.99 ml, 15.60 mmol) in dry THF (180 ml) was added DEAD (2.91 ml, 18.72 mmol), and the soln. was stirred at r.t. for 20 h. The reaction was quenched with a sat. aq. NaCl soln. (100 ml) and the mixture extracted with AcOEt (3 × 100 ml). The combined org. phases were dried ($MgSO_4$), evaporated *in vacuo*, and purified by FC (SiO_2; hexane/AcOEt 6 : 4) to give **15** (3.60 g, 77%). Colorless solid. M.p. 92–94°. IR (KBr): 1767*m*, 1719*s*, 1428*m*, 1388*m*, 1344*m*, 1267*m*, 1156*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.88–7.82 (*m*, 2 H); 7.77–7.70 (*m*, 2 H); 3.85 (*s*, 2 H); 3.73 (*s*, 3 H); 1.26 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 176.5; 168.8; 134.3; 132.1; 123.6; 52.4; 46.2; 43.7; 23.4. DEI-MS: 261 (3, M^+), 202 (7), 160 (100). Anal. calc. for $C_{14}H_{15}NO_4$ (261.3): C 64.36, H 5.79, N 5.36; found C 64.41, H 5.84, N 5.31.

3-Amino-2,2-dimethylpropionic Acid (**16**). A soln. of **15** (800 mg, 3.06 mmol) in AcOH (10 ml), conc. aq. HCl soln. (10 ml), and H_2O (10 ml) was heated to reflux for 16 h. The soln. was evaporated *in vacuo*, the residue diluted with H_2O (50 ml), washed with Et_2O (2 × 50 ml), and purified by ion-exchange chromatography (*Dowex W X 8*) to afford **16** (243 mg, 67%). Colorless solid. M.p. >200° ([46]: 239°). ^{1}H-NMR (200 MHz, D_2O): 3.04 (*s*, 2 H); 1.22 (*s*, 6 H).

3-{[(Benzyloxy)carbonyl]amino}-2,2-dimethylpropionic Acid (**17**). To **16** (573 mg, 4.89 mmol) in 1M aq. NaOH soln. (20 ml) at 0° was added dropwise a soln. of benzyl chloroformate (0.90 ml, 6.36 mmol) in dioxane (3 ml) during 30 min, and the soln. was stirred at r.t. for 5 h. The dioxane was removed *in vacuo*, the soln. made

acidic with 1M aq. HCl soln. (50 ml) and extracted with AcOEt (3 × 50 ml). The combined org. extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give **17** (830 mg, 68%). Colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.39–7.30 (*m*, 5 H); 5.35–5.25 (*m*, 1 H); 5.16 (*s*, 2 H); 3.33 (*d*, *J* = 6.6, 2 H); 1.25 (*s*, 6 H).

tert-*Butyl 3-{[(Benzyloxy)carbonyl]amino}-2,2-dimethylpropanoate* (**18**). To a suspension of **17** (2.02 g, 8.04 mmol) in CH_2Cl_2 (16 ml) in a sealed tube was added conc. H_2SO_4 (0.08 ml). Isobutene (16 ml) was then added at −78°, and the soln. was shaken at r.t. for 65 h. The mixture was poured into 1M aq. NaOH soln. (50 ml) and extracted with CH_2Cl_2 (3 × 50 ml). The combined org. extracts were dried (Na_2SO_4), evaporated *in vacuo*, and purified by FC (SiO_2; hexane/AcOEt 9:1) to give **18** (2.10 g, 85%). Colorless oil. IR ($CHCl_3$): 2981*m*, 1719*s*, 1514*s*, 1369*m*, 1314*m*, 1144*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.38–7.36 (*m*, 5 H); 5.32–5.30 (br. *s*, 1 H); 5.11 (*s*, 2 H); 3.27 (*d*, *J* = 6.2, 2 H); 1.44 (*s*, 9 H); 1.15 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 176.7; 157.0; 136.9; 128.7; 128.3 (2×); 80.9; 66.8; 48.9; 44.0; 28.0; 23.1. FAB-MS: 308 (39, MH$^+$), 252 (100), 234 (26), 208 (26), 91 (52). Anal. calc. for $C_{17}H_{25}NO_4$ (307.4): C 66.43, H 8.20, N 4.56, O 20.82; found C 66.62, H 8.11, N 4.74, O 20.96.

tert-*Butyl 3-Amino-2,2-dimethylpropanoate* (**13**). A soln. of **18** (600 mg, 1.95 mmol) in MeOH (50 ml) was treated with 10% Pd/C (60 mg) under H_2 (1 bar) for 3 h. The mixture was filtered and evaporated *in vacuo* to give **13** (300 mg, 89%). Colorless oil. IR ($CHCl_3$): 2979*m*, 1714*s*, 1474*m*, 1392*m*, 1380*m*, 1295*m*, 1151*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.68 (*s*, 2 H); 1.44 (*s*, 9 H); 1.11 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 176.9; 80.3; 51.6; 45.0; 28.1; 22.9. EI-MS: 173 (2, M^+), 144 (28), 100 (21), 88 (100).

(±)-Methyl 2-{[(2-Oxo-1,3-oxazolan-3-yl)sulfonyl]amino}-3-phenylpropanoate ((±)-**19a**). Treatment of (±)-**6a** (5.00 g, 23.18 mmol) according to *Procedure D* gave (±)-**19a** (6.88 g, 91%). Colorless solid. M.p. 132–133° (hexane/AcOEt). IR ($CHCl_3$): 3196*m*, 1754*s*, 1380*m*, 1223*m*, 1175*m*, 1149*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.38–7.17 (*m*, 5 H); 4.66–4.60 (*m*, 1 H); 4.30 (*t*, *J* = 7.7, 2 H); 3.86 (*t*, *J* = 7.7, 2 H); 3.77 (*s*, 3 H); 3.18, 3.08 (*AB* of *ABX*, J_{AX} = 6.0, J_{BX} = 7.1, J_{AB} = 14.2, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.6; 153.3; 135.3; 129.7; 129.1; 127.7; 62.6; 58.2; 53.1; 45.2; 38.9. DEI-MS: 329 (5, MH$^+$), 269 (7), 237 (17), 182 (12), 177 (10), 162 (100), 150 (24), 118 (26), 91 (67). Anal. calc. for $C_{13}H_{16}N_2O_6S$ (328.3): C 47.55, H 4.91, N 8.53, S 9.77; found: C 47.48, H 4.84, N 8.51, S 9.67.

(±)-Methyl 3-(Naphthalen-2-yl)-2-{[(2-oxo-1,3-oxazolan-3-yl)sulfonyl]amino}propanoate ((±)-**19b**). Treatment of (±)-**6b** (2.50 g, 9.41 mmol) according to *Procedure D* gave (±)-**19b** (3.48 g, 98%). Colorless solid. M.p. 115–117° (hexane/AcOEt). IR (KBr): 3216*m*, 1751*s*, 1380*m*, 1205*m*, 1181*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.83–7.78 (*m*, 3 H); 7.64 (*s*, 1 H); 7.50–7.42 (*m*, 2 H); 7.33–7.27 (*m*, 1 H); 5.71 (br. *s*, 1 H); 4.78–4.63 (*m*, 1 H); 4.17–3.97 (*m*, 2 H); 3.82–3.66 (*m*, 2 H); 3.77 (*s*, 3 H); 3.33, 3.20 (*AB* of *ABX*, J_{AX} = 5.4, J_{BX} = 7.2, J_{AB} = 14.2, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 171.4; 153.0; 133.4; 132.7; 132.6; 128.6 (2×); 127.8; 127.6; 127.3; 126.5; 126.1; 62.4; 58.2; 53.0; 45.0; 39.1. ESI-MS: 442 (100, [M + Na + MeCN]$^+$), 401 (49, [M + Na]$^+$), 379 (3, MH$^+$). Anal. calc. for $C_{17}H_{18}N_2O_6S$ (378.4): C 53.96, H 4.79, N 7.40, S 8.47; found: C 54.17, H 4.82, N 7.34, S 8.22.

(±)-Methyl 2-{[(2-Oxo-1,3-oxazolan-3-yl)sulfonyl]amino}-4-phenylbutanoate ((±)-**19c**). Treatment of (±)-**6c** (637 mg, 2.77 mmol) according to *Procedure D* gave (±)-**19c** (540 mg, 57%). Colorless solid. M.p. 87–89° (hexane/AcOEt). IR (KBr): 3208*m*, 1746*s*, 1385*m*, 1178*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.35–7.21 (*m*, 5 H); 5.94 (*s*, 1 H); 4.46–4.38 (*m*, 2 H); 4.38–4.31 (*m*, 1 H); 4.12–3.92 (*m*, 2 H); 3.77 (*s*, 3 H); 2.82–2.74 (*m*, 2 H); 2.32–1.98 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.2; 153.5; 140.3; 128.8; 128.7; 126.6; 62.8; 56.9; 53.1; 45.5; 34.5; 31.3. DEI-MS: 343 (5, MH$^+$), 342 (4, M^+), 283 (2), 132 (52), 117 (100), 91 (82). Anal. calc. for $C_{14}H_{18}N_2O_6S$ (342.4): C 49.11, H 5.30, N 8.18, S 9.37; found C 49.23, H 5.35, N 8.01, S 9.35.

*(±)-Methyl 2-[({[2-(*tert*-Butoxycarbonyl)ethyl]amino}sulfonyl)amino]-3-phenylpropanoate* ((±)-**20a**). Treatment of (±)-**19a** (3.77 g, 11.48 mmol) and β-alanine *tert*-butyl ester (2.09 g, 11.48 mmol) according to *Procedure E* gave (±)-**20a** (2.61 g, 59%). Light-yellow oil. IR ($CHCl_3$): 1739*m*, 1721*m*, 1153*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.38–7.13 (*m*, 5 H); 4.94–4.87 (*m*, 1 H); 4.86 (*d*, *J* = 9.6, 1 H); 4.36–4.21 (*m*, 1 H); 3.78 (*s*, 3 H); 3.15 (*dd*, *J* = 13.5, 5.6, 1 H); 3.07–2.97 (*m*, 1 H); 3.09–2.89 (*m*, 2 H); 2.38 (*t*, *J* = 5.8, 2 H); 1.46 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.6; 171.8; 135.8; 129.7; 128.9; 127.6; 81.6; 57.1; 52.7; 39.1; 38.8; 34.8; 28.1. DEI-MS: 387 (1, MH$^+$), 331 (12), 313 (9), 295 (12), 281 (11), 271 (40), 253 (28), 239 (100), 162 (9), 91 (5). HR-DEI-MS: 387.1595 (MH$^+$, $C_{17}H_{27}N_2O_6S$; calc. 387.1590).

*(±)-Methyl 2-[({[2-(*tert*-Butoxycarbonyl)ethyl]amino}sulfonyl)amino]-3-(naphthalen-2-yl)propanoate* ((±)-**20b**). Treatment of (±)-**19b** (500 mg, 1.32 mmol) and β-alanine *tert*-butyl ester (241 mg, 1.32 mmol) according to *Procedure E* gave (±)-**20b** (350 mg, 61%). Colorless oil. IR ($CHCl_3$): 1740*m*, 1722*m*, 1150*s*, 1136*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.85–7.78 (*m*, 3 H); 7.66 (*s*, 1 H); 7.53–7.43 (*m*, 2 H); 7.33–7.28 (*m*, 1 H); 4.92–4.88 (*m*, 2 H); 4.41–4.30 (*m*, 1 H); 3.76 (*s*, 3 H); 3.30, 3.19 (*AB* of *ABX*, J_{AX} = 5.8, J_{BX} = 6.9, J_{AB} = 13.8, 2 H); 3.11–2.82 (*m*, 2 H); 2.28 (*t*, *J* = 5.8, 2 H); 1.43 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.6; 171.8; 133.6; 133.2; 132.8; 128.6 (2×); 127.9 (2×); 127.5; 126.5; 126.2; 81.6; 57.1; 52.7; 39.3; 38.8; 34.6; 28.1. DEI-MS: 436 (1, M^+),

239 (16), 212 (70), 168 (16), 141 (100). Anal. calc. for $C_{21}H_{28}N_2O_6S$ (436.5): C 57.78, H 6.46, N 6.42, S 7.35; found: C 57.70, H 6.28, N 6.16, S 7.41.

*(±)-Methyl 2-[({[2-(*tert*-Butoxycarbonyl)-2,2-dimethylethyl]amino}sulfonyl)amino]-3-(naphthalen-2-yl)-propanoate* ((±)-**20c**). Treatment of (±)-**19b** (574 mg, 1.52 mmol) and **13** (239 mg, 1.38 mmol) according to *Procedure E* gave (±)-**20c** (400 mg, 62%). Colorless solid. M.p. 121–122° (hexane/AcOEt). IR (KBr): 3263*m*, 1740*s*, 1705*s*, 1162*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.82–7.78 (*m*, 3 H); 7.66 (*s*, 1 H); 7.51–7.44 (*m*, 2 H); 7.34–7.29 (*m*, 1 H); 4.93–4.79 (*m*, 2 H); 4.37–4.26 (*m*, 1 H); 3.76 (*s*, 3 H); 3.31, 3.16 (*AB* of *ABX*, J_{AX} = 5.4, J_{BX} = 7.1, J_{AB} = 13.7, 2 H); 2.71 (*dd*, *J* = 12.5, 7.1, 1 H); 2.51 (*dd*, *J* = 12.5, 6.6, 1 H); 1.41 (*s*, 9 H); 1.01 (*s*, 3 H); 0.91 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 176.3; 172.8; 133.7; 133.5; 132.8; 128.7; 128.6; 127.9; 127.9; 127.7; 126.5; 126.1; 81.2; 57.4; 52.7; 50.7; 42.8; 39.3; 27.9; 23.1. DEI-MS : 464 (1, M^+), 267 (15), 249 (8), 232 (6), 212 (97), 187 (23), 168 (15), 141 (100). Anal. calc. for $C_{23}H_{32}N_2O_6S$ (464.6): C 59.46, H 6.94, N 6.03, S 6.90; found C 59.69, H 6.86, N 6.03, S 7.10.

*(±)-Methyl 2-[({[2-(*tert*-Butoxycarbonyl)-2,2-dimethylethyl]amino}sulfonyl)amino]-4-phenylbutanoate* ((±)-**20d**). Treatment of (±)-**19c** (747 mg, 2.18 mmol) and **13** (340 mg, 1.96 mmol) according to *Procedure E* gave (±)-**20d** (540 mg, 64%). Colorless solid. M.p. 79–81° (hexane/AcOEt). IR ($CHCl_3$): 1739*s*, 1711*m*, 1369*m*, 1348*m*, 1309*m*, 1145v*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.34–7.12 (*m*, 5 H); 5.02–4.97 (*m*, 2 H); 4.15–3.99 (*m*, 1 H); 3.75 (*s*, 3 H); 3.02 (*d*, *J* = 6.6, 2 H); 2.78–2.70 (*m*, 2 H); 2.24–1.93 (*m*, 2 H); 1.44 (*s*, 9 H); 1.19 (*s*, 3 H); 1.17 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 176.5; 173.4; 140.6; 128.8; 128.7; 126.5; 81.4; 55.7; 52.8; 51.1; 43.1; 34.8; 31.4; 28.0; 23.4. DEI-MS: 429 (1, MH^+), 372 (26), 313 (46), 285 (68), 256 (14), 196 (32), 117 (100), 91 (43). Anal. calc. for $C_{20}H_{32}N_2O_6S$ (428.6): C 56.05, H 7.53, N 6.54, S 7.48; found C 56.27, H 7.78, N 6.49, S 7.47.

*(±)-*tert*-Butyl 3-[4-(Phenylmethyl)-1,1,3-trioxo-1λ⁶,2,5-thiadiazolan-2-yl]propanoate* ((±)-**21a**). Treatment of (±)-**20a** (150 mg, 0.39 mmol) according to *Procedure F* gave (±)-**21a** (70 mg, 51%). Colorless solid. M.p. 86–88°. IR (KBr): 3222*m*, 1722*s*, 1708*s*, 1350*m*, 1327*m*, 1183*m*, 1144*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.43–7.23 (*m*, 5 H); 4.75 (*d*, *J* = 6.6, 1 H); 4.45–4.35 (*m*, 1 H); 3.88 (*t*, *J* = 7.6, 2 H); 3.31, 3.16 (*AB* of *ABX*, J_{AX} = 4.4, J_{BX} = 8.5, J_{AB} = 14.3, 2 H); 2.67 (*t*, *J* = 7.6, 2 H); 1.47 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.5; 167.8; 134.6; 129.6; 129.5; 128.2; 81.7; 61.7; 36.8; 36.6; 33.5; 28.1. DEI-MS: 355 (1, MH^+), 298 (60), 281 (34), 270 (25), 253 (25), 120 (17), 91 (100). Anal. calc. for $C_{16}H_{22}N_2O_5S$ (354.4): C 54.22, H 6.26, N 7.90, S 9.05; found: C 54.35, H 6.49, N 7.80, S 9.16.

*(±)-*tert*-Butyl 3-[4-(Naphthalen-2-ylmethyl)-1,1,3-trioxo-1λ⁶,2,5-thiadiazolan-2-yl]propanoate* ((±)-**21b**). Treatment of (±)-**20b** (300 mg, 0.69 mmol) according to *Procedure F* gave (±)-**21b** (100 mg, 36%). Yellow, highly viscous oil. IR ($CHCl_3$): 1729*m*, 1333*w*, 1150*s*, 1137*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.88–7.81 (*m*, 3 H); 7.71 (*m*, 1 H); 7.56–7.49 (*m*, 2 H); 7.38–7.32 (*m*, 1 H); 4.67 (*d*, *J* = 6.2, 1 H); 4.52–4.45 (*m*, 1 H); 3.89 (*t*, *J* = 7.6, 2 H); 3.47, 3.31 (*AB* of *ABX*, J_{AX} = 3.9, J_{BX} = 8.5, J_{AB} = 14.3, 2 H); 2.67 (*t*, *J* = 7.6, 2 H); 1.45 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.5; 167.9; 133.7; 132.1; 129.4; 128.7; 128.0; 127.9; 127.0; 126.0; 126.0; 11.3; 81.7; 61.7; 36.9; 36.8; 33.5; 28.1. DEI-MS: 404 (5, M^+), 348 (10), 331 (5), 303 (4), 168 (6), 141 (100). HR-DEI-MS: 404.1398 (M^+, $C_{20}H_{24}N_2O_5S$; calc. 404.1406).

*(±)-*tert*-Butyl 2,2-Dimethyl-3-[4-(naphthalen-2-ylmethyl)-1,1,3-trioxo-1λ⁶,2,5-thiadiazolan-2-yl]propanoate* ((±)-**21c**). Treatment of (±)-**20c** (340 mg, 0.73 mmol) according to *Procedure F* gave (±)-**21c** (160 mg, 51%). Yellow, highly viscous oil. IR ($CHCl_3$): 1726*s*, 1348*m*, 1294*m*, 1183*s*, 1144*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.87–7.79 (*m*, 3 H); 7.70 (*s*, 1 H); 7.55–7.46 (*m*, 2 H); 7.36–7.31 (*d*, *J* = 8.3, 1.7, 1 H); 4.66 (*d*, *J* = 6.7, 1 H); 4.51–4.42 (*m*, 1 H); 3.82 (*s*, 2 H); 3.45, 3.34 (*AB* of *ABX*, J_{AX} = 4.8, J_{BX} = 7.9, J_{AB} = 13.9, 2 H); 1.45 (*s*, 9 H); 1.19 (*s*, 3 H); 1.14 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 174.9; 169.4; 133.7; 133.0; 132.4; 129.2; 128.7; 128.0; 127.9; 127.2; 126.8; 126.5; 81.6; 61.6; 48.9; 43.5; 36.9; 27.8; 23.7; 23.4. DEI-MS: 432 (31, M^+), 376 (15), 359 (17), 331 (15), 279 (17), 168 (20), 141 (100). HR-DEI-MS: 432.1732 (M^+, $C_{22}H_{28}N_2O_5S$; calc. 432.1719).

*(±)-*tert*-Butyl 2,2-Dimethyl-3-[4-(2-phenylethyl)-1,1,3-trioxo-1λ⁶,2,5-thiadiazolan-2-yl]propanoate* ((±)-**21d**). Treatment of (±)-**20d** (450 mg, 1.05 mmol) according to *Procedure F* gave (±)-**21d** (270 mg, 65%). Colorless solid. M.p. 98–99° (hexane/AcOEt). IR (KBr): 3165*m*, 1743*s*, 1702*s*, 1351*m*, 1277*m*, 1180*s*, 1151*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.38–7.17 (*m*, 5 H); 5.05 (*d*, *J* = 7.5, 1 H); 4.20–4.09 (*m*, 1 H); 3.81 (*s*, 2 H); 2.95–2.72 (*m*, 2 H); 2.42–2.03 (*m*, 2 H); 1.48 (*s*, 9 H); 1.22 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 175.0; 170.0; 139.7; 129.0; 128.8; 126.9; 81.6; 60.0; 48.8; 43.5; 33.0; 31.6; 27.9; 23.6. NH_4-DCI-MS: 414 (1, $[M + NH_4]^+$), 397 (1, MH^+), 341 (29), 323 (42), 295 (17), 236 (100). Anal. calc. for $C_{19}H_{28}N_2O_5S$ (396.5): C 57.55, H 7.12, N 7.07, S 8.09; found C 57.54, H 7.32, N 7.08, S 8.07.

(±)-3-[4-(Naphthalen-2-ylmethyl)-1,1,3-trioxo-1λ⁶,2,5-thiadiazolan-2-yl]propanoic Acid ((±)-**3a**). Treatment of (±)-**21b** (100 mg, 0.25 mmol) according to *Procedure G* gave (±)-**3a** (60 mg, 70%). Colorless solid. M.p. 128–131°. IR (KBr): 1717*s*, 1344*m*, 1167*m*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 7.91–7.87 (*m*, 3 H); 7.81 (*s*, 1 H); 7.54–7.46 (*m*, 3 H); 4.68 (*dd*, *J* = 9.8, 3.9, 1 H); 3.75 (*t*, *J* = 7.5, 2 H); 3.10–2.98 (*m*, 2 H); 2.61 (*t*, *J* = 7.5, 2 H). ^{13}C-NMR (125 MHz, $(CD_3)_2SO$): 171.3; 168.4; 134.0; 132.9; 131.9; 127.8; 127.7; 127.6; 127.4 (2×); 126.0; 125.6;

60.9; 36.8; 36.0; 32.1. DEI-MS: 348 (4, M^+), 168 (6), 141 (100). HR-DEI-MS: 348.0775 (M^+, $C_{16}H_{16}N_2O_5S$; calc. 348.0780).

(±)-2,2-Dimethyl-3-[4-(naphthalen-2-ylmethyl)-1,1,3-trioxo-1λ⁶,2,5-thiadiazolan-2-yl]propanoic Acid ((±)-**3b**). Treatment of (±)-**21c** (100 mg, 0.23 mmol) according to *Procedure G* gave (±)-**3b** (60 mg, 69%). Colorless solid. M.p. 188–189°. IR (KBr): 3344*m*, 3189*m*, 1750*s*, 1730*m*, 1333*m*, 1256*m*, 1190*m*, 1154*m*. ^{1}H-NMR (200 MHz, CD_3OD): 7.84–7.76 (*m*, 4 H); 7.47–7.41 (*m*, 3 H); 4.53, 3.40, 3.09 (*ABX*, $J_{AX}=3.9$, $J_{BX}=10.0$, $J_{AB}=14.1$, 3 H); 3.76 (*s*, 1 H); 3.74 (*s*, 1 H); 1.19 (*s*, 3 H); 1.17 (*s*, 3 H). ^{13}C-NMR (75 MHz, CD_3OD): 179.8; 171.9; 135.6; 135.3; 134.3; 129.6; 129.4; 129.0; 128.9 (2×); 127.4; 127.1; 63.0; 44.0; 38.7; 24.1. DEI-MS: 376 (7, M^+), 169 (23), 167 (23), 141 (100). HR-DEI-MS: 376.1098 (M^+, $C_{18}H_{20}N_2O_5S$; calc. 376.1093).

(±)-2,2-Dimethyl-3-[4-(2-phenylethyl)-1,1,3-trioxo-1λ⁶,2,5-thiadiazolan-2-yl]propanoic Acid ((±)-**3c**). Treatment of (±)-**21d** (190 mg, 0.48 mmol) according to *Procedure G* gave (±)-**3c** (140 mg, 86%). Colorless solid. M.p. 105.5–106° (hexane/AcOEt). IR (KBr): 3199*m*, 1735*s*, 1325*m*, 1264*m*, 1180*m*, 1146*m*. ^{1}H-NMR (200 MHz, CD_3OD): 7.33–7.15 (*m*, 5 H); 4.12–4.06 (*m*, 1 H); 3.74 (*s*, 2 H); 2.87–2.67 (*m*, 2 H); 2.26–1.90 (*m*, 2 H); 1.22 (*s*, 6 H). ^{13}C-NMR (75 MHz, CD_3OD): 179.4; 172.7; 142.0; 129.9; 129.9; 127.6; 60.8; 44.0; 34.5; 32.7; 24.1. NH_4-DCI-MS: 341 (9, MH^+), 323 (12), 295 (4), 236 (12), 218 (12), 134 (43), 104 (74), 91 (100). Anal. calc. for $C_{15}H_{20}N_2O_5S$ (340.4): C 52.93, H 5.92, N 8.23, S 9.42; found C 52.99, H 5.78, N 8.09, S 9.33.

X-Ray Crystal Structure of (±)-**21a**. X-Ray crystal data for $C_{16}H_{22}N_2O_5S$ ($M_r=354.4$): monoclinic space group $P2_1/n$, $D_c=1.331$ g·cm^{-3}, $Z=4$, $a=14.491(5)$, $b=7.715(5)$, $c=15.862(5)$ Å, $\beta=93.90(2)°$, $V=1769.2(14)$ Å^3, MoK_α radiation, $\lambda=0.71070$ Å, $1.84\leq\theta\leq24.99°$, 3114 unique reflections, $T=193$ K. The structure was solved by direct methods (SHELXS 86) and refined by full-matrix least-squares analysis (SHELXL-93) using an isotropic extinction correction and an exponentially modified weight factor $r=2.5$ Å^2. All heavy atoms were refined anisotropically, H-atoms isotropically. H-Positions are based on stereochemical considerations, except H–N(14), which was located from an electron-density-difference map. Final $R(F)=0.0340$, w$R(F^2)=0.1416$ for 243 parameters and 2366 reflections with $I>2\sigma(I)$.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-133802. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

This work was supported by *F. Hoffmann-La Roche AG*, Basel, Nutley (USA). We thank Dr. *Carlo Thilgen* (*ETH Zürich*) for assistance with the nomenclature.

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Received September 8, 1999