Synthesis of oxazolo-annulated 3-benzazepines designed by merging two negative allosteric NMDA receptor modulators

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Abstract
To improve the metabolic stability and receptor selectivity of ifenprodil (1), the benzoxazolone moiety of besoprodil (2) and the 3-benzazepone moiety of WMS-1410 (3) were merged to obtain oxazolobenzazepines of type 4. The 5-(hydroxyethyl)benzoxazolone 7 representing the first key intermediate was prepared in four steps starting with the 4-(2-hydroxyethyl)phenol (8). Mitsunobu reaction of primary alcohol 7 with N-sulfonylated glycine esters established the necessary side chain. The intramolecular Friedel–Crafts acylation of acid 12a containing the N-tosyl protective group led upon decarbonylation exclusively to the tricyclic tetrahydroisoquinoline 14. Protection of the amino moiety by the stronger electron-withdrawing triflyl group resulted in the desired 3-benzazepine 15 without the formation of analogous isoquinoline. The triflyl protective group was cleaved off by K2CO3-induced elimination of trifluoromethanesulfinate. In a one-pot three-step procedure, various oxazolobenzazepinediones 15 were obtained, which were reduced to afford the desired secondary alcohols 18.

KEYWORDS benzoxazolone bioisosteres, elimination of trifluoromethylsulfinate, GluN2B subunit, intramolecular Friedel–Crafts acylation, NMDA receptor, trifluoromethylsulfonyl protective group

1 | INTRODUCTION

N-Methyl-D-aspartate (NMDA) represents the prototypical agonist for the NMDA receptor, one of three ionotropic glutamate receptors. Usually, the heterotetrameric NMDA receptor consists of two GluN1 and two GluN2 subunits. As four different GluN2 subunits (GluN2A-D) are encoded by four different genes, the nature of the GluN2 subunit determines the electrophysiological properties of NMDA receptor subtypes.[1,2] We are particularly interested in NMDA receptors containing the GluN2B subunit, as negative allosteric modulators at GluN2B-NMDA receptors could be beneficial for the treatment of acute and chronic neurological disorders (e.g., stroke, Parkinson’s disease).[3,4] The lead compound of this project is the negative allosteric NMDA receptor modulator ifenprodil (1, Figure 1)[5,6] which occupies a binding pocket located at the interface of the GluN1 and GluN2B subunit.[7,8] This ifenprodil binding pocket within the N-terminal domains of both subunits is quite distant from the binding sites of the orthosteric ligands (S)-glutamate and glycine as well as the ion channel. However, binding at the ifenprodil binding site leads to inhibition of the movement of Phe176, which holds the NMDA receptor in its closed inactive state. Negative allosteric modulators like ifenprodil work like a “foot in the door” at the GluN2B-NMDA receptor.[9]

Racemic, unlike configured, ifenprodil is used in Japan to improve cerebral blood circulation. The potential of ifenprodil for the treatment of drug addiction, idiopathic pulmonary fibrosis, and Covid-19 infections...
is investigated in clinical trials\cite{10-12} and, furthermore, its positive effects in animal models of Alzheimer’s disease and neuropathic pain have been reported.\cite{13-15}

However, poor receptor selectivity and low bioavailability represent two major problems associated with ifenprodil. In addition to its interactions with the ifenprodil binding site of the NMDA receptor, ifenprodil interacts on its relative and absolute configuration with related $\sigma_1$, $\sigma_2$, $\alpha_1$, 5-HT$_{1A}$, and 5-HT$_2$ receptors.\cite{16-19} In in vitro and in vivo experiments, fast bio-transformation, in particular, fast conjugation, of the phenol of ifenprodil (1) with glucuronic acid was detected.\cite{20}

In Figure 1, negative allosteric modulators of GluN2B subunit-containing NMDA receptors derived from ifenprodil are displayed. In besonprodil (2, $IC_{50} = 30 \text{ nM}$),\cite{21} the phenol of ifenprodil is replaced by the benzoxazolone system, which cannot be conjugated with glucuronic acid anymore. In WMS-1410 (3) the flexible $\beta$-aminoalcohol moiety of ifenprodil is integrated into a 3-benzazepine ring,\cite{22} which resulted in increased receptor selectivity and metabolic stability.\cite{23,24}

Thus, the metabolically more stable benzoxazolone system of besonprodil (2) and the conformationally restricted 3-benzazepine system of WMS-1410 (3), leading to higher receptor selectivity, should be combined in one compound 4. In this study, we focus on the synthesis of novel oxazolo-annulated 3-benzazepines 4 designed as more selective and metabolically more stable analogs of ifenprodil.

2 | SYNTHESIS

The arylethanol derivative 7 represents the first key intermediate in the synthesis of oxazolo-annulated 3-benzazepines of type 4. At first, commercially available halogenated benzoxazolones 5 were used as starting material. After the introduction of the $p$-methoxybenzyl (PMB) protective group at the benzoxazolone N-atom, the ethanol substructure should be established by halogen–lithium exchange and subsequent trapping of the aryllithium intermediate with ethylene sulfate.\cite{25} Unfortunately, all variations of this experiment led to several compounds. A clear reaction product could not be identified, although the halogen–lithium exchange appeared to be successful. Even the reaction with the test electrophile benzaldehyde did not result in an isolable product (Scheme 1).

Therefore, the alternative synthesis of 7 involved the establishment of the oxazolone ring starting with the phenol 8 already containing the hydroxyethyl moiety. The oxazolone moiety of 10 was prepared in three steps comprising regioselective nitration of phenol 8, reduction of the nitro compound 9a with $\text{H}_2$ and $\text{Pd/C}$, and finally, treatment of the aminophenol 9b with 1,1-dimethoxypropane, which is investigated in clinical trials,\cite{10-12} and, furthermore, its positive effects in animal models of Alzheimer’s disease and neuropathic pain have been reported.\cite{13-15}

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\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Evolution of oxazolo-annulated 3-benzazepines 4 starting with the lead compound ifenprodil (1) via benzoxazolone besonprodil (2) and 3-benzazepine WMS-1410 (3). *Only one enantiomer of the racemic mixture is depicted for clarity.}
\end{figure}
faster than the cyclization of the acylium ion. Thus, the stabilized iminium ion 13 is formed, which reacts intramolecularly in an electrophilic aromatic substitution to provide the tetrahydroisoquinoline 14 (Scheme 2).

To avoid the undesired decarbonylation, the intermediate iminium ion of type 13 was destabilized by the introduction of a stronger electron-withdrawing group at the N-atom. For this purpose, the trifluoromethylsulfonyl (triflyl, SO2CF3, Tf) moiety was selected as a protective group.[29,30] Thus, the Mitsunobu reaction of the primary alcohol 7 with N-triflylglycine methyl ester provided the methyl ester 11b, which was saponified with LiOH to obtain the acid 12b. The reaction of the triflyl-protected acid 12b with P4O10 in CH2Cl2 at reflux temperature led to the seven-membered ketone 15 in 60% yield. The corresponding tetrahydroisoquinoline could not be detected. Obviously, the electron-withdrawing triflyl group inhibited completely the release of CO. It has to be noted that the yield of 60% is the result of several optimization rounds (Scheme 2).

The first oxazolobenzazepin-9-ol 18a was prepared by NaBH4 reduction of the ketone 15 (Scheme 3). However, the pharmacological activity, that is, the interaction of the compounds with the ifenprodil binding site, requires the basicity of the amino moiety within the tricyclic system. Therefore, the CF3SO2 moiety has to be removed. The
removal of the triflyl protective group represents the third key feature of the complete synthetic route. Initial attempts to remove the triflyl protective group hydrolytically with base (1 M NaOH or 10 M NaOH) or reductively (TiCl4/Li0) failed to give the secondary amine. However, it has been reported that the triflyl protective group can be cleaved off by the elimination of sulfinate (CF3SO2−) using strong bases. As an example, n-BuLi was able to remove the triflyl group from N,N-dibenzyl-1,1,1-trifluoromethanesulfonamide, leading to CF3SO2− and an imine, which was trapped by n-BuLi.[31]

In the case of ketone 15, strong bases such as LDA or KOtBu led to decomposition. However, the weak base K2CO3 in refluxing acetone resulted in the elimination of trifluoromethanesulfinate. The intermediate iminoketone 16 was not isolated but directly treated with NaBH(OAc)3.[32] The reducing agent NaBH(OAc)3 was able to reduce the cyclic imine, but not the ketone. Moreover, the solvent acetone formed an iminium ion with the new secondary amine, which was also reduced by NaBH(OAc)3 to afford the isopropylamine 17a (Scheme 3).

To avoid the direct reductive alkylation of the intermediate secondary amine with acetone, the solvent acetone was replaced by acetonitrile during the elimination of CF3SO2−. The subsequent reduction with NaBH(OAc)3 provided the secondary amine, which was alkylated with benzyl bromide or reductively alkylated with benzaldehyde and NaBH(OAc)3 to obtain benzylamine 17b in 28% and 23% yield, respectively. The phenylethylamine 17c was prepared by the addition of phenylacetaldehyde after the reduction of the imine. Phenylacetaldehyde underwent a reductive alkylation of the secondary amine to afford 17c.

Reduction of the ketone 17b with NaBH4 yielded the secondary alcohol 18b. Treatment of ketone 17c with H2 in the presence of the catalyst Pd/C should reduce the ketone and simultaneously hydrogenolytically remove the PMB-protective group. However, even with an H2 pressure of 5 bar and the addition of HCl only the ketone was reduced to give alcohol 18c, the PMB group was not cleaved off. Moreover, all attempts to remove the PMB moiety hydrogenolytically (H2, different catalysts), oxidatively (CAN, (NH4)2Ce(NO3)6), or with acid (TFA, different concentrations) or with α-chloroethyl chloroformate failed to give the free oxazolone system.

3 | CONCLUSION

Replacement of the phenol of ifenprodil (1) by the benzoazolone system (compare 2) led to increased metabolic stability. Incorporation of the flexible β-aminoalcohol of ifenprodil (1) into the 3-benzazepine scaffold of WMS-1410 (3) resulted in increased receptor selectivity. Therefore, ligands were envisaged containing both, the benzoazoline as well as the 3-benzazepine system.

Herein, we present the synthesis of the envisaged oxazolobenzazepinols 4. The benzoazoxylethanol 7 and 10 represent the first key intermediates of the synthesis. They were accessible by the stepwise establishment of the annulated oxazolone ring. The second key intermediate is the oxazolobenzazepine 15, which can only be prepared with the N-triflyl protective group, as during the intramolecular Friedel–Crafts acylation of the corresponding tosyl derivative 12a, exclusive formation of the tetrahydroisoquinoline 14 was observed. Finally, the triflyl protective group could be cleaved off by the base-induced elimination of trifluoromethanesulfinate. In a one-pot three-step procedure, various N-substituted oxazolobenzazepine-9-ol 18a-c were available.

As the substitution pattern of the final products 18a-c differs considerably from the lead compounds, the affinity toward GluN2B subunit-containing NMDA receptors was not yet evaluated. However, the synthetic route to get access to this novel type of negative
allosteric modulators at GluN2B-NMDA receptors has been established and will be exploited by the introduction of appropriate substituents at both the N-atom of the oxazolone system and the benzazepine ring.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

Unless otherwise noted, moisture-sensitive reactions were conducted under dry nitrogen. Thin-layer chromatography: Silica gel 60 F254 plates (Merck). Flash chromatography: Silica gel 60, 40–64 μm (Merck); parentheses include: diameter of the column (d), fraction size (v), eluent, Rf value. Melting point: Melting point apparatus S SMP3 (Stuart Scientific), uncorrected. Mass spectrometry (MS): MAT GCQ (Thermo Finnigan); electron ionization (EI): MAT LCQ (Thermo Finnigan): Electrospray ionization (ESI). 1H NMR (nuclear magnetic resonance) (400 MHz), 13C NMR (100 MHz): Mercury Plus AS 400 NMR spectrometer (Varian); δ in ppm related to tetramethylsilane; coupling constants are given with 0.5 Hz resolution; the assignments of 13C and 1H NMR signals were supported by two-dimensional NMR techniques. Infrared (IR): IR spectrophotometer 480Plus FT-ATR-IR (Jasco) or FT/IR Prestige 21 (Shimadzu). Elemental analysis: CHNOS Elementar Analysator Vario EL III (Elementar).

The InChI codes of the investigated compounds are provided as Supporting Information. The Supporting Information also contains 1H NMR spectra and HPLC chromatograms of prepared compounds.

4.1.2 | High-performance liquid chromatography (HPLC) method to determine the purity

HPLC: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; column: LiChrospher® 60 RP-select B (5 μm); LiChroCART® 250–4 mm cartridge; flow rate: 1.0 ml/min; injection volume: 5.0 μl; detection at λ = 210 nm; solvents: A: water with 0.05% (v/v) trifluoroacetic acid; B: acetonitrile with 0.05% (v/v) trifluoroacetic acid: gradient elution: (A%B): 0–4 min: 90%, 4–29 min: 90% → 0%, 29–31 min: 0%, 31–31.5 min: 0% → 90%, 31.5–40 min: 90%. Unless otherwise noted, the purity of all test compounds is >95% according to this HPLC method.

4.1.3 | Synthetic procedures

5-Chloro-3-(4-methoxybenzyl)benzoxazol-2(3H)-one (6a)

Under N2 atmosphere, 5a (158 mg, 0.93 mmol) and 4-methoxybenzyl bromide (364 mg, 1.81 mmol) were dissolved in acetonitrile (5 ml) and K2CO3 (740 mg, 5.35 mmol) was added. The suspension was stirred at 80°C for 5 h. Then K2CO3 was filtered off and the solvent was removed from the filtrate under reduced pressure giving a yellowish solid, which was purified by recrystallization in ethanol. Colorless crystals, yield 222 mg (82%), C17H14ClNO3 (M+ = 289.7). MS (ESI): m/z (%) = 601 (2M+Na, 100), 312 (M+Na, 13), and 290 (M+H, 4). 1H NMR (CDCl3): δ [ppm] = 3.80 (s, 3H, Ar–OCH3), 4.91 (s, 2H, N–CH2–Ar), 6.84 (d, J = 2.0 Hz, 1H, 4-H), 6.89 (d, J = 9.0 Hz, 2H, 3-H/5-H4-methoxybenzyl), 7.05 (dd, J = 8.6/2.0 Hz, 1H, 1-H), 7.11 (d, J = 8.6 Hz, 1H, 7-H), 7.29 (d, J = 9.0 Hz, 2H, 2-H/6-H4-methoxybenzyl). IR (neat): ν [cm⁻¹] = 2960 (w), 2916 (w)/2845 (w, v C-H aliph.), 1766 (s, v C=O), 1611 (s)/1583 (w)/1509 (s, v C=C arom.), 1015 (s, v C–C aliph.), and 815 (s, Y1,4-disubst. arom.).

5-Bromo-3-(4-methoxybenzyl)benzoxazol-2(3H)-one (6b)

Under N2 atmosphere, 5b (215 mg, 1.00 mmol) and 4-methoxybenzyl bromide (305 mg, 1.52 mmol) were dissolved in acetonitrile (5 ml) and K2CO3 (694 mg, 5.02 mmol) was added. The suspension was stirred at 80°C for 3 h. Then K2CO3 was filtered off and the solvent was removed from the filtrate under reduced pressure giving a yellowish solid, which was purified by recrystallization in ethanol. Colorless crystals, yield 243 mg (72%), C15H12BrNO3 (M+ = 334.2). 1H NMR (CDCl3): δ [ppm] = 3.80 (s, 3H, Ar–OCH3), 4.90 (s, 2H, N–CH2–Ar), 6.89 (d, J = 9.0 Hz, 2H, 3-H/5-H4-methoxybenzyl), 6.99 (d, J = 2.0 Hz, 1H, 4-H), 7.06 (d, J = 8.6 Hz, 1H, 1-H), 7.21 (d, J = 8.6/2.0 Hz, 1H, 4-H), and 7.28 (d, J = 9.8 Hz, 2H, 2-H/6-H4-methoxybenzyl). IR (neat): ν [cm⁻¹] = 2913 (w)/2844 (w, v C-H aliph.), 1765 (s, v C=O), 1605 (s)/1582 (w)/1509 (s, v C=C arom.), 1016 (s, v C–C aliph.), and 812 (s, Y1,4-disubst. arom.).

4-(2-Hydroxyethyl)–2-nitrophenol (9a)

4-(2-Hydroxyethyl)phenol 8 (1.66 g, 12 mmol) was dissolved in glacial acetic acid (12 ml) and cooled down to 0°C. Nitric acid (65%, 970 μl, 13.8 mmol) was added slowly under vigorous stirring and the reaction was continued under these conditions for 30 min before warming up to ambient temperature and stirring for another 30 min. Then, H2O (50 ml) and 10 M NaOH were added until pH 14 and the solution was stirred for 30 min. Then, conc. HCl was added dropwise until pH 5 and the aqueous solution was extracted with ethyl acetate (4×). The combined organic layers were dried (Na2SO4) and the solvent was removed under reduced pressure giving a dark oil. The crude product was purified by distillation under reduced pressure (bpo2,3 = 162°C). The pale yellow oil crystallized while standing at room temperature (rt). Pale yellow solid, mp 57–58°C, yield 1.54 g (70%). Purity (HPLC): tR = 126.6 min, purity 99.8%. C6H4NO2 (M+ = 183.2). MS (ESI): m/z (%) = 183 (M, 7) and 182 (M−H, 100). 1H NMR (CDCl3): δ [ppm] = 2.84 (t, J = 6.3 Hz, 2H, Ph–CH2–CH2OH), 3.86 (t, J = 6.3 Hz, 2H, Ph–CH2–CH2OH), 7.09 (d, J = 8.6 Hz, 1H, 6-H2-nitrophenol), 7.47 (dd, J = 8.6/2.4 Hz, 1H, 5-H2-nitrophenol), 7.96 (d, J = 2.4 Hz, 1H, 3-H2-nitrophenol), and 10.45 (s, 1H, –OH2-nitrophenol). A signal for the aliphatic OH-proton is not seen in the 1H NMR spectrum. IR (neat): ν [cm⁻¹] = 3274 (m, v C-H aliph.), 3085 (w, v C=O aliph.), 2923 (m)/2871 (m, v C-H aliph.), 1630 (m)/1577 (m, v C=C arom.), 1533 (s, v N=O asym.), 1294 (s, v N=O sym.), and 836 (s, Y1,2,4-disubst. arom.).

2-Amino-4-(2-hydroxyethyl)phenol (9b)

Nitrophenol 9a (4.58 g, 25 mmol) was dissolved in absolutemethanol (125 ml) and Pd/C (250 mg) was added. The nitro group was reduced
by shaking the mixture under an H₂ atmosphere (3 bar) for 3 h at rt. The catalyst was filtered off and methanol was removed under reduced pressure giving colorless crystals. The crude product (9b) was used in the next reaction step without further purification. Colorless solid, mp 137–138°C (decomposition). Purity (HPLC): tᵣ = 2.8 min, purity 99.1%. C₆H₅NO₂ (M = 153.2), MS (EI): m/z (%) = 329 (2M + Na, 100), 307 (2M + H, 79), 176 (M + Na, 21), and 154 (M + H, 49). ¹H NMR (CD₃OD): δ [ppm] = 2.64 (t, J = 7.4 Hz, 2H, Ph–CH₂CH₂OH), 3.66 (t, J = 7.4 Hz, 2H, Ph–CH₂CH₂OH), 4.44 (dd, J = 8.2/0.2 Hz, 1H, 5-H₂aminophenol), 6.60 (d, J = 8.2 Hz, 1H, 6-H₂aminophenol), and 6.62 (d, J = 2.0 Hz, 1H, 3-H₂aminophenol). Signals for the OH– and NH– protons are not seen in the ¹H NMR spectrum. IR (neat): ν [cm⁻¹] = 3366 (m)/3268 (m, νN=N), 3122 (m, νO=H), 2931 (w)/2858 (w, νC–H aliph.), 1608 (m)/1518 (m, νC=C arom.), 1040 (s, νC–C), and 809 (s, ¹Y1,2,4-subst. arom.).

5-(2-Hydroxyethyl)benzoxazol-2(3H)-one (10)

The crude aminophenol 9b (3.83 g, 25 mmol) was dissolved in abs. THF (105 ml) and 2.1 eq. CDI (8.51 g, 52.5 mmol) were added under N₂ atmosphere. The solution was stirred overnight at rt. Then H₂O (80 ml) followed by 10 M NaOH were added until pH 14 and stirring was continued for 20 min. The pH value was adjusted to pH 2 by conc. HCl and the solution was extracted with ethyl acetate (10x). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a brown solid. The crude product was purified by recrystallization in ethyl acetate. Colorless crystals, mp 153–154°C, yield 4.03 g (90%). Purity (HPLC): tᵣ = 9.7 min, purity 97.6%. C₁₂H₁₀N₂O₃ (M = 226), MS (EI): m/z (%) = 357 (2M–H, 41), 178 (M–H, 100). ¹H NMR (CD₃OD): δ [ppm] = 2.82 (t, J = 7.0 Hz, 2H, Ph–CH₂CH₂OH), 3.74 (t, J = 6.9 Hz, 2H, Ph–CH₂CH₂OH), 6.95–7.00 (m, 2H, 6-H, 4-H), and 7.15 (d, J = 8.6 Hz, 1H, 7-H). Signals for the OH– and NH– protons are not seen in the ¹H NMR spectrum. IR (neat): ν [cm⁻¹] = 3341 (s, νO=H), 3045 (w, νAvy-H), 2945 (m)/2914 (w)/2886 (m, νC–H aliph.), 1741 (s, νC=O), 1625 (w)/1497 (m, νC=C arom.), 1051 (s, νC–O), and 803 (s, ¹Y1,2,4-subst. arom.).

5-(2-Hydroxyethyl)-3-(4-methoxybenzyl)benzoxazol-2(3H)-one (7)

Benzoxazole 10 (1.44 g, 8.02 mmol) and 4-methoxybenzyl bromide (1.61 g, 8.02 mmol) were dissolved in acetonitrile (32 ml) and K₂CO₃ (3.32 g, 24.0 mmol) was added. The suspension was stirred overnight giving a yellow oil as crude product, which was purified by flash column chromatography (Ø 5 cm, 20 cm, ethyl acetate/n-hexane 2:3, fraction size 30 ml, Rₑ = 0.30). Colorless oil, yield 1.545 g (80%). Purity (HPLC): tᵣ = 21.9 min, purity 95.6%. C₂₁H₂₁F₃N₂O₇S (M = 524.6), MS (EI): m/z (%) = 524 (M, 6), 155 (tolylox-S, 11), 121 (4-methoxybenzyl, 100), and 91 (benzyl, 26). ¹H NMR (CDCl₃): δ [ppm] = 2.41 (s, 3H, Ar–CH₃), 2.85 (t, J = 7.5 Hz, 2H, Ar–CH₂CH₂N), 3.40 (t, J = 7.5 Hz, 2H, Ar–CH₂CH₃N), 3.60 (s, 3H, CO₂CH₃), 3.97 (s, 3H, Ar–OCH₃), 3.92 (s, 2H, –N=CH₂–CO₂CH₃), 4.13 (s, 2H, –NH–CH₂–Ar), 6.72 (d, J = 1.6 Hz, 1H, 4-H), 6.83 (dd, J = 8.2/1.6 Hz, 1H, 6-H, 4-H), 6.89 (d, J = 8.6 Hz, 2H, 3-H/5-H₃sulfonamide) and 7.06 (d, J = 8.2 Hz, 1H, 7-H), 7.24 (d, J = 8.0 Hz, 2H, 3-H/5-H₃sulfonamide), 7.32 (d, J = 8.6 Hz, 2H, 2-H/6-H₃sulfonamide), and 7.63 (d, J = 8.2 Hz, 2H, 2-H/6-H₃sulfonamide). IR (neat): ν [cm⁻¹] = 2980 (w)/2954 (w)/2839 (w, νC=H aliph.), 1758 (s, νC=O ester), 1613 (m)/1587 (w)/1513 (s, νC=C arom.), 1338 (s)/1154 (s, νSestansamine), and 812 (s, ¹Y1,2,4-subst. arom.).
Methyl ester 11a (50.3 mg, 0.096 mmol) was dissolved in a mixture of THF/H2O (7:3) (2 ml) and cooled down to 0°C. LiOH·H2O (25.2 mg, 0.6 mmol) was added to the vigorously stirred solution and stirring was continued for 1.5 h at 0°C. Then H2O (20 ml) was added and pH was adjusted to pH 2 with conc. HCl. The reaction mixture was extracted with ethyl acetate (4×), the combined organic layers were dried (Na2SO4) and the solvent was removed under reduced pressure giving a pale yellow oil as crude product, which was purified by flash column chromatography (Ø 2 cm, 19 cm, ethyl acetate/n-hexane 2:3 ± 0.5% HCO2H, fraction size 10 ml, Rf = 0.18). Colorless crystals, mp 57–58°C, yield 31.5 mg (64%). Purity (HPLC): tR = 20.3 min, purity 96.4%. C27H36N2O7S (M = 510.6). MS (EI): m/z (%) = 510 (M, 5), 269 (M-CH2N(Ts)CH2CO2H, 25), 121 (4-methoxybenzyl), 100, and 91 (benzyl, 19). 1H NMR (CDCl3): δ [ppm] = 2.40 (s, 3H, Ar-CH3), 2.84 (t, J = 7.4 Hz, 2H, Ar-CH2CH2N), 3.39 (t, J = 7.4 Hz, 2H, Ar-CH2CH2N), 3.78 (s, 3H, Ar-OCH3), 3.91 (2H, N-CH2CO2H), 4.91 (2H, N-CH2-Ar), 6.68 (d, J = 1.4 Hz, 1H, 4-H), 6.88 (d, J = 8.8 Hz, 2H, 3-H/5-H-methoxybenzyl), 7.06 (d, J = 8.0 Hz, 1H, 7-H), 7.24 (d, J = 8.4 Hz, 2H, 3-H/5-H-tolyl), 7.31 (d, J = 8.8 Hz, 2H, 2-H/6-H-methoxybenzyl), and 7.62 (d, J = 8.4 Hz, 2H, 2-H/6-H-tolyl). A signal for the CO2H-proton is not seen in the 1H NMR-spectrum. IR (neat): ν [cm–1] = 2930 (m, C-H aliph.), 1773 (s, C=O ketone), 1611 (s), 1412 (s, N-H), 1380 (s)/1587 (w)/1514 (s, C=C arom.), 1345 (s)/1152 (s, νsulfonamide), and 806 (s, νt, 4-disub. arom.).

Methyl ester 11b (2.24 g, 4.46 mmol) was dissolved in a mixture of THF/H2O (7:3) (95 ml) and cooled down to 0°C. LiOH·H2O (1.23 g, 29.3 mmol) was added to this vigorously stirred solution and stirring was continued for 3 h at rt. Then H2O (80 ml) was added and pH was adjusted to pH 2 with conc. HCl. The reaction mixture was extracted with ethyl acetate (4×), the combined organic layers were dried (Na2SO4) and the solvent was removed under reduced pressure giving a pale yellow oil as crude product, which was purified by flash column chromatography (Ø 6 cm, 21 cm, ethyl acetate/n-hexane 3:4 ± 0.5% HCO2H, fraction size 50 ml, Rf = 0.20). Colorless solid, mp 170–171°C, yield 1.86 g (85%). Purity (HPLC): tR = 21.0 min, purity 98.2%. C27H36N2O7S (M = 488.4). MS (EI): m/z (%) = 488 (M, 13), 121 (4-methoxybenzyl), and 91 (benzyl, 8). 1H NMR (CD3OD): δ [ppm] = 2.96 (t, J = 7.6 Hz, 2H, Ph-CH2CH2N), 3.65 (t broad, J = 7.6 Hz, 2H, Ph-CH2CH2N), 3.77 (3H, Ar-OCH3), 4.10 (t broad, 2H, N-CH2CO2H), 4.97 (2H, N-CH2-Ar), 6.90 (d, J = 8.8 Hz, 2H, 3-H/5-H-methoxybenzyl), 6.98 (d, J = 1.2 Hz, 1H, 4-H), 7.00 (d, J = 8.1/1.7 Hz, 1H, 6-H), 7.19 (d, J = 8.0 Hz, 1H, 7-H), and 7.32 (d, J = 8.9 Hz, 2H, 2-H/6-H-methoxybenzyl). A signal for the CO2H-proton is not seen in the 1H NMR-spectrum. IR (neat): ν [cm–1] = 2980 (w, νCH=O aliph.), 1766 (s, νC=O oxazolone), 1711 (s, νC=O carboxylic acid), 1612 (m)/1585 (w)/1514 (s, νC=C arom.), 1388 (s)/1181 (s, νSulfonamide), and 1131 (s, νC-F).

3-(4-Methoxybenzyl)-7-(trifluoromethylsulfonyl)-5,6,7,8-tetrahydrooxazolo[4,5-h]-[3]benzazepine-2,9(3H)-dione (15) Trifluoromethanesulfonamide 12b (97.7 mg, 0.22 mmol) was dissolved in CH2Cl2 (10 ml) under N2 atmosphere and the solution was heated to reflux. P4O10 (284 mg, 2 mmol) was added in small portions to the boiling mixture over 3 h. Then the suspension was cooled down to rt. P2O5 was filtered off and the solvent of the filtrate was removed under reduced pressure giving a brown oil as crude product, which was purified by flash column chromatography (Ø 2 cm, 19 cm, ethyl acetate/n-hexane 1:3, fraction size 10 ml, Rf = 0.18). Colorless solid, mp 162–163°C, yield 34.7 mg (77%). Purity (HPLC): tR = 22.1 min, purity 99.4%. C25H24N2O7S (M = 464.5). MS (ESI): m/z (%) = 1415 (3M+Na, 100), 946 (2M+NH4, 79), and 465 (M+H, 16). 1H NMR (CDCl3): δ [ppm] = 2.44 (s, 3H, Ar-CH3), 2.88 (t, J = 5.8 Hz, 2H, Ar-CH2CH2N), 3.31 (t, J = 5.9 Hz, 2H, Ar-CH2CH2N), 3.78 (s, 3H, Ar-OCH3), 4.21 (2H, 5-H/6-H-tolyl), and 4.88 (2H, 2-H/3-H-nitrobenzyl), 6.52 (s, 1H, 9-H). 6.86 (t, J = 8.6 Hz, 6H, 3-H/5-H-methoxybenzyl). 6.86 (s, 1H, 4-H), 7.25 (d, J = 8.5 Hz, 2H, 3-H/5-H-tolyl), 7.32 (d, J = 8.6 Hz, 2H, 2-H/6-H-methoxybenzyl), and 7.70 (d, J = 8.4 Hz, 2H, 2-H/6-H-tolyl). IR (neat): ν [cm–1] = 2921 (w)/2836 (w, νC=H aliph.), 1776 (s, νC=O oxazolone), 1614 (m)/1587 (w)/1515 (s, νC=C arom.), 1354 (s)/1160 (s, νSulfonamide), and 809 (s, νY, 4-disub. arom.).
the mixture was stirred overnight. Then the suspension was filtered and the solvent was removed under reduced pressure giving a brown oil as crude product, which was purified by flash column chromatography (Ø 2 cm, 19 cm, ethyl acetate/n-hexane 1:2, fraction size 10 ml, Rf = 0.15). Pale yellow crystals, mp 130–131°C, yield 7.8 mg (41%). Purity (HPLC): tR = 16.1 min, purity 99.9%. C20H22F3N2O6S (M₁ = 380.4). MS (ESI): m/z (%) = 1163 (3M+Na, 100), 783 (2M+Na, 71), 761 (2M+H, 65), and 381 (M+H, 18).

1H NMR (CDCl₃): δ [ppm] = 0.98 (d, J = 6.6 Hz, 6H, NCH₂(Charte₂)), 2.84–2.93 (m, 5H, 5-H/6-H, NCH₂(Charte₂)), 3.43 (s, 2H, 8-H), 3.80 (s, 3H, OCH₃), 4.94 (s, 2H, -CO-N-CH₂-Ar), 6.66 (s, 1H, 4-H), 6.89 (d, J = 8.7 Hz, 2H, 3-H/5-Hₐ, methoxybenzyl), 7.30 (d, J = 8.7 Hz, 2H, 2-H/6-Hₐ, methoxybenzyl), and 7.56 (s, 1H, 10-H). IR (neat): ν [cm⁻¹] = 2966 (m)/2934 (w)/2838 (w)/2803 (w, νCH₃ aliph.), 1765 (s, νC=O oxazolone), 1678 (s, νC=O ester), and 753 (m)/702 (s, νC=O ketone), and 1610 (s)/1588 (w) (νυC=O aron).

7-Benzyl-3-(4-methoxybenzyl)-5,6,7,8-tetrahydrooxazolo[4,5-h]-[3]benzazepine-2,9(3H)-dione (17B)

Method 1: Synthesis by alkylation with benzyl bromide: Triflyl derivative 15 (23.4 mg, 0.05 mmol) was dissolved in dry CH₃CN (1.5 ml) under N₂ atmosphere and K₂CO₃ (27.6 mg, 0.2 mmol) was added. The stirred suspension was heated to reflux for 2 h. After cooling down to rt NaBH₄(OAc)₂ (19 mg, 0.09 mmol) was added and the mixture was stirred for 30 min. Then the suspension was filtered and K₂CO₃ (21 mg, 0.15 mmol) followed by benzyl bromide (25.7 mg, 0.15 mmol) was added. The mixture was heated to reflux for 2 h. After cooling down to rt, K₂CO₃ was filtered off and the solvent was removed under reduced pressure. The resulting brown oil was purified by flash column chromatography (Ø 2 cm, 20 cm, ethyl acetate/n-hexane 2:5, fraction size 10 ml, Rf = 0.17). Colorless solid, mp 173–174°C (decomposition), yield 6 mg (28%).

Method 2: Synthesis by reductive alkylation with benzaldehyde and NaBH₄(OAc)₂: Triflyl derivative 15 (235.2 mg, 0.5 mmol) was dissolved in dry CH₃CN (6 ml) under N₂ atmosphere and K₂CO₃ (207 mg, 1.5 mmol) was added. The stirred suspension was heated to reflux for 2 h. After cooling down to rt, K₂CO₃ was filtered off and benzaldehyde (106 mg, 1 mmol) immediately followed by NaBH₄(OAc)₂ (424 mg, 2 mmol) were added. The mixture was stirred overnight at rt. Then, the suspension was filtered and the solvent was removed under reduced pressure giving a brown oil as crude product, which was purified by flash column chromatography (Ø 2 cm, 20 cm, ethyl acetate/n-hexane 2:5, fraction size 25 ml, Rf = 0.17). Colorless solid, mp 173–174°C (decomposition), yield 48.2 mg (23%).

Purity (HPLC): tR = 18.5 min, purity 95.3%. C₂₁H₂₃N₂O₆S (M₁ = 428.5). MS (ESI): m/z (%) = 1307 (3M+Na, 100), 879 (2M+Na, 75), 857 (2M+H, 37), and 429 (M+H, 14). 1H NMR (CDCl₃): δ [ppm] = 2.86 (t, J = 5.6 Hz, 2H, 6-H), 2.93 (t, J = 5.7 Hz, 2H, 5-H), 3.50 (s, 2H, 8-H), 3.73 (s, 2H, N-CH₂-C₆H₅), 3.80 (s, 3H, -OCH₃), 4.96 (s, 2H, -CO-N-CH₂-Ar), 6.65 (s, 1H, 4-H), 6.89 (d, J = 8.8 Hz, 2H, 3-H/5-Hₐ, methoxybenzyl), 7.10–7.28 (m, 5H, N-CH₂-C₆H₅), 7.31 (d, J = 8.8 Hz, 2H, 2-H/6-Hₐ, methoxybenzyl), and 7.56 (s, 1H, 10-H). IR (neat): ν [cm⁻¹] = 2936 (m)/2823 (w, νC=H aliph.), 1752 (s, νC=O oxazolone), 1678 (s, νC=O ketone), 1608 (s)/1586 (w)/1515 (s, νυC=O aron.), and 753 (m)/702 (s, νυC=O aron.).

3-(4-Methoxybenzyl)-7-(2-phenylethyl)-5,6,7,8-tetrahydrooxazolo[4,5-h]-[3]benzazepine-2,9(3H)-dione (17C)

Triflyl derivative 15 (470.4 mg, 1 mmol) was dissolved in dry CH₃CN (15 ml) under N₂-atmosphere and K₂CO₃ (414.6 mg, 3 mmol) was added. The suspension was stirred at 60°C for 5 h. Then K₂CO₃ was filtered off and NaBH₄(OAc)₂ (212.0 mg, 1.0 mmol) was added to the filtrate. The mixture was stirred for 30 min at rt before phenylethylaldehyde (600 mg, 5 mmol) and again NaBH₄(OAc)₂ (212.0 mg, 1.0 mmol) were added. The suspension was stirred at rt overnight. Then the mixture was filtered and the solvent was removed under reduced pressure giving a brown oil as crude product, which was purified by flash column chromatography (Ø 2 cm, 23 cm, ethyl acetate/n-hexane 3:5, fraction size 10 ml, Rf = 0.20). Colorless solid, mp 166–167°C (decomposition), yield 116.6 mg (26%). Purity (HPLC): tR = 18.9 min, purity 96.1%. C₂₃H₂₅N₂O₆S (M₁ = 442.5). MS (EI): m/z (%) = 442 (M, 2), 323 (M-4-methoxybenzyl, 100), and 121 (4-methoxybenzyl, 82). 1H NMR (CDCl₃): δ [ppm] = 2.66–2.73 (m, 2H, -N-CH₂-CH₂-Ph), 2.78–2.84 (m, 2H, 5-H/6-H, NCH₂(Charte₂)₃), 3.56 (s, 2H, 8-H), 3.80 (s, 3H, -OCH₃), 4.95 (s, 2H, -CO-N-CH₂-Ar), 6.66 (s, 1H, 4-H), 6.89 (d, J = 8.7 Hz, 2H, 3-H/5-Hₐ, methoxybenzyl), 7.05–7.22 (m, 5H, N-CH₂-C₆H₅), 7.30 (d, J = 8.7 Hz, 2H, 2-H/6-Hₐ, methoxybenzyl), and 7.57 (s, 1H, 10-H). IR (neat): ν [cm⁻¹] = 2943 (w)/2839 (w, νC=H aliph.), 1753 (s, νC=O oxazolone), 1679 (s, νC=O oxazolone), 1610 (m)/1586 (w)/1492 (s, νυC=O aron.), and 745 (s)/698 (s, νυC=O aron.).
extracted with CH₂Cl₂ (3×). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under reduced pressure giving a pale yellow oil as crude product, which was purified by flash column chromatography (Ø 2 cm, 21 cm, ethyl acetate/hexane 1:1, fraction size 10 ml, Rₙ = 0.12). Colorless solid, m.p. 136–137°C, yield 35.5 mg (83%). Purity (HPLC): tᵣ = 17.8 min, purity 95.4%. C₂₉H₂₇N₂O₄ (Mᵣ = 430.5). MS (ESI): m/z (%) = 1313 (3M+Na, 20), 883 (2M+Na, 15), and 431 (M+H, 100). ¹H NMR (CDCl₃): δ [ppm] = 2.35 (t, J = 11.7 Hz, 1H, 6-H), 2.52 (dd, J = 12.1 Hz, 1H, 8-H), 2.63 (dd, J = 15.3/6.2 Hz, 1H, 5-H), 2.96 (dd, J = 12.1/6.3 Hz, 1H, 4-H), 3.17 (dd, J = 11.6/7.2 Hz, 1H, 8-H), 3.20–3.30 (3H, 1H, 5–H), 3.70 (2H, N–CH₂–C₆H₅), 3.78 (3H, OCH₃), 4.61 (d, J = 6.9 Hz, 1H, 9-H), 4.89 (2H, –CO–N–CH₂–Ar), 6.55 (1H, 4-H), 6.86 (dd, J = 8.7 Hz, 2H, 3-H/5-H4-methoxybenzyl), 7.07 (1H, 10-H), and 7.24–7.37 (7H, 3-H, N–CH₂–C₆H₅, 2-H/6-H4-methoxybenzyl). A signal for the OH proton is not seen in the ¹H NMR-spectrum. IR (neat): ν [cm⁻¹] = 3437 (m, ν(OH)), 2933 (m)/2835 (w, ν(CH₂)), 3.79 (s, 3H, OCH₃), 4.61 (d, J = 6.9 Hz, 1H, 9-H), 4.89 (2H, –CO–N–CH₂–Ar), 6.55 (1H, 4-H), 6.86 (dd, J = 8.7 Hz, 2H, 3-H/5-H4-methoxybenzyl), 7.07 (1H, 10-H), 7.16–7.23 (3H, 2-H/4-H/6-H phenyl), 7.29 (d, J = 8.5 Hz, 2H, 2-H/6-H4-methoxybenzyl), and 7.25–7.33 (2H, 3-H/5-H phenyl). For the OH-proton signal is not seen in the ¹H NMR-spectrum. IR (neat): ν [cm⁻¹] = 3448 (w, ν(OH)), 2932 (m, ν(C–H aliph.), 1766 (s, ν(C=O oxazolone)), 1613 (m)/1586 (w), 1492 (s, ν(C=C arom.), and 745 (s) [δ(ν, Ymonosubstit. arom.)].

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CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

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