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Improved synthesis and in vitro/in vivo activities of natural product-inspired, artificial glutamate analogs

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ABSTRACT

Here, we report our second-generation synthesis of 12 artificial glutamate analogs, starting from heterotricycle intermediates **3a**–**3d**, readily prepared in three steps including tandem Ugi/Diels-Alder reactions. The new synthesis employs imidate intermediates for the deoxygenation of pyrrolidones (**10a**–**10d** to **6a**–**6d**), and each advanced intermediate **6a**–**6d** was diversified into three glutamate analogs (**1a**–**1d**, **5a**–**5d**, **7a**–**7d**) in 1–2 steps.

In vitro electrophysiological assays revealed that the new piperidine-type analog **7c** alters neuronal function with lower potency than **1a**. Conversely, intracranial injection of **7c** into mice produced a greater degree of hypoactivity than **1a**. Our recent investigation has revealed that this series of compounds antagonizes AMPA-type glutamate receptor-mediated currents in a subtype selective manner. The more efficient syntheses of this novel set of neuroactive molecules will facilitate their pharmacological characterization.

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1. Introduction

Glutamate receptors (GluRs) play a central role in rapid synaptic neurotransmission, and are involved in higher brain functions such as memory and learning.[1] GluRs are also thought to be fully or partly involved in nociception, as well as in a number of brain disorders such as epilepsy, ischemia-induced excitotoxicity, Alzheimer's, Huntington's, and Parkinson's diseases, and schizophrenia.[2] Thus, selective GluR ligands, or even biologically functional glutamate analogs, are of significant biomedical interest in neurobiology.

A variety of glutamate analogs have been isolated from natural resources and characterized pharmacologically,[3] and a number of their analogs have been chemically synthesized. In the latter synthetic studies, three general approaches were used to establish structure–activity relationships; (1) structural modification of natural specimens by newly incorporating a substituent or a functional group, (2) de novo total synthesis of natural product and analogs, and (3) construction of combinatorial library of artificial compounds by diversity-oriented synthesis (DOS).[4]

Within the context of the second approach, de novo synthesis, we have been studying the chemical synthesis and biological function of dysiherbaine[5] and neodysiherbaine A,[6] which are natural glutamate analogs isolated from Micronesian sponge, *L. chondrodes* (Fig. 1).[7,8] Dysiherbaines are now known to be subtype-selective agonists for kainate (KA) receptors and exhibit potent agonistic actions for two of those proteins, GluK1 (GluR5) and GluK2 (GluR6), with the highest affinity of all known ligands.[9,10] By extending the natural product synthesis to analog synthesis, we discovered that MSVIII-19 (8,9-dideoxyneodysiherbaine A), which lacks functional groups at C8 and C9 positions, acts as a functional antagonist.[9]

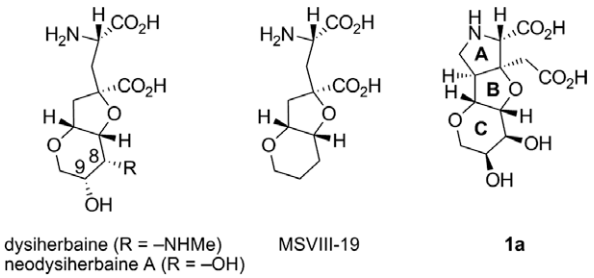

Figure 1. Dysiherbaine congeners,[5,6] antagonistic analog MSVIII-19,[9] and hypoactive artificial glutamate analog **1a**.[11]

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More recently, we began to pursue the third approach, DOS, and consequently discovered the artificial glutamate analog **1a**, which elicits hypoactivity, rather than convulsions, in mice behavioral assays.[11] Interestingly, **1a** also markedly reduced both action potential firing frequency and spontaneous excitatory synaptic currents in current- and voltage-clamp electrophysiological analyses from cultured hippocampal neurons, although **1a** did not displace radioactive ligands for the (*S*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA), kainate (KA), or *N*-methyl-D-aspartate (NMDA) receptors that are constituent members of the ionotropic GluR superfamily. The mechanistic basis for these activities of **1a** is under active investigation.

In these DOS studies, however, only four glutamate analogs were synthesized and biologically evaluated. Here, we report an improved synthetic route to a total of 12 artificial glutamate analogs. In vitro and in vivo biological evaluation of a subset of the compounds identified a new analog **7c** as a ligand that potently altered neuronal excitation and synaptic activity.[12]

2. Results and discussions

2.1. Synthesis of 12 artificial glutamate analogs

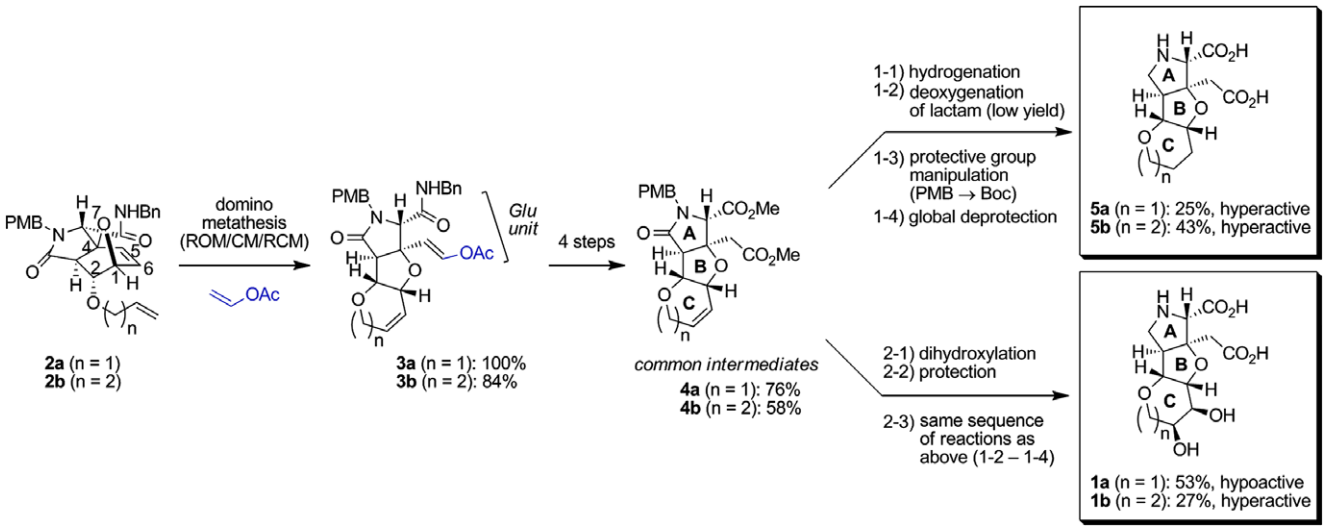
Our first-generation synthesis[11] of artificial glutamate analogs **1a**, **1b**, **5a**, and **5b** is shown in Scheme 1. The 7-oxanorbornenes **2a** and **2b**, readily available in 50% and 33% yields for two steps, respectively, were subjected to the challenging domino metathesis reaction using Hoveyda–Grubbs second-generation catalyst[13] in the presence of electron-rich vinyl acetate as an unprecedented cross metathesis substrate, giving rise to heterotricycles **3a** and **3b** exclusively in 100% and 84% yields, respectively. Four-step transformation led **3a** and **3b** into diesters **4a** and **4b** in 76% and 58% yields. From the common intermediates **4a** and **4b**, two glutamate analogs bearing a saturated ring, **5a** and **5b**, were obtained in 25% and 43% yields for four steps, whereas two dihydroxylated analogs **1a** and **1b** were also furnished in 53% and 27% yields over five steps. However, the first-generation synthetic pathway (Scheme 1) included several problems to be solved. First, deoxygenation of the A ring pyrrolidone lactam with $BH_3{\cdot}Me_2S$ proceeded in only 40–62% yield. Second, since the borane reagent is highly reactive to olefins, the first-generation approach was not capable of synthesizing glutamate analogs with olefin functionality at the C ring. Third, the pathway was not applicable to a synthesis of glutamate analogs with an amino group at the C ring. This was because of steric interference caused by *N*-protecting groups to the reagents used in a series of reactions shown in Scheme 1. Forth, as a branching point,[14] common intermediates **4a** and **4b** were at too early stages in the synthetic pathway (three steps before **5a** and **5b**, and five steps before **1a** and **1b**). This was apparently inconvenient in terms of efficiency in diversity-oriented synthesis.

To solve these problems, we investigated a new efficient route in the present study that resulted in a synthesis of total 12 glutamate analogs, including those bearing an amino group at the C ring, with good overall yield over a shorter series of reactions. The plan is shown in Scheme 2. Here, the advanced intermediates **6a**–**6d** were placed two steps after the common intermediates **4a**–**4d**, and diversified into three glutamate groups in 1–2 steps; a dihydroxylated group (**1a**–**1d**), a saturated group (**5a**–**5d**), and an unsaturated group (**7a**–**7d**).[12]

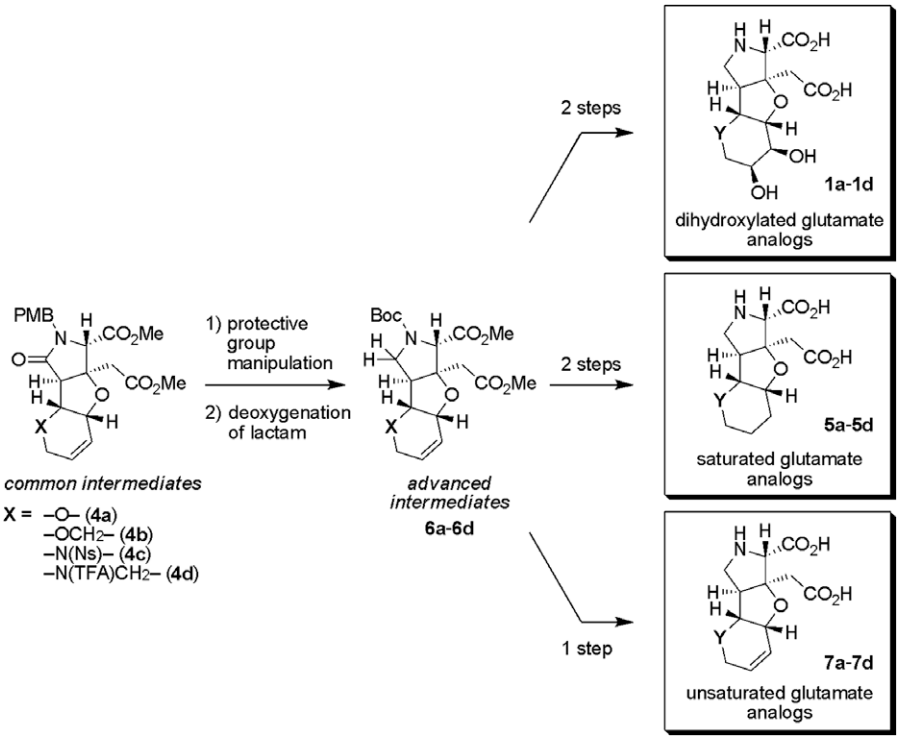
Scheme 3 depicts synthesis of the common intermediates **4c** and **4d**, bearing amino groups at the C rings, from known **3c** and **3d**,[11] respectively, by four-step functional group transformations, which had been developed for the synthesis of **4a** and **4b** (see Scheme 1).[11] First, *N*-Boc imides **8c** and **8d** were prepared by treatment with Boc_2O, triethylamine (TEA), and 4-(dimethylamino)pyridine (DMAP) in 90% and 83% yields, respectively. Alkaline hydrolysis (K_2CO_3, MeOH) was carefully performed on **8c** and **8d**, giving rise to ester aldehydes **9c** and **9d** in good yields (81% and 91%) without affecting β-alkoxyaldehyde moiety. The ester aldehydes in turn were oxidized by $NaClO_2$ followed by esterification ($TMSCHN_2$) to provide **4c** and **4d** in 93% and 85% yields, respectively.

The common intermediates **4a** and **4b** were also synthesized with a similar scheme as was reported recently in our first-generation synthesis.[11]

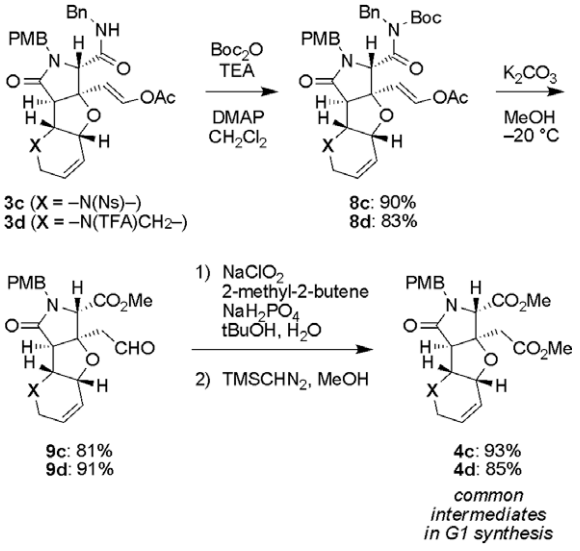
An improved synthesis of the advanced intermediates **6a**–**6d** from **4a**–**4d**, employed also as common intermediates in our first-generation synthesis, is shown in Scheme 4. Here, the key transformation is deoxygenation of pyrrolidone lactam, which was successfully achieved by a two-step reaction including reduction of the imidate. Initially, the PMB group was removed oxidatively by ceric ammonium nitrate (CAN) at −10 °C to give **10a**–**10d** in 71–80% yield. Upon treatment of **10a**–**10d** with Meerwein reagent ($Me_3O{\cdot}BF_4$) and K_2CO_3, corresponding imidates were readily generated.[15] Without purification, the imidates were reduced with $NaBH_3CN$ under acidic conditions (TFA, MeOH) to provide the corresponding pyrrolidines,[16] which were subsequently protected by Boc group (Boc_2O, TEA) to furnish advanced



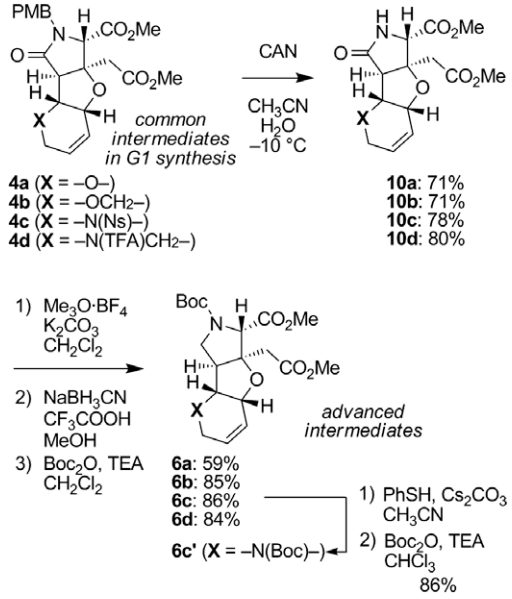
Scheme 1. Our first-generation synthetic pathway toward artificial glutamate analogs.[11]



Scheme 2. The second-generation synthetic plan for artificial glutamate analogs (in the present study).



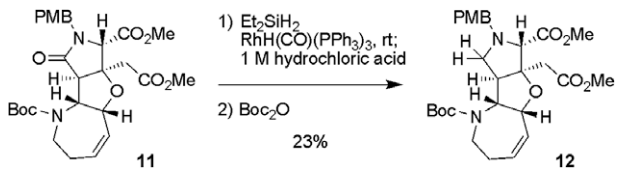
Scheme 3. Synthesis of common intermediates **4c** and **4d**.



Scheme 4. Synthesis of advanced intermediates **6a**–**6d** by an improved deoxygenation.

intermediates **6a**–**6d** in 59–86% yields over three steps. As compared to the first-generation synthesis (see Scheme 1),[11] the yields and reproducibility of the deoxygenation steps were improved satisfactorily. For a convenient, one-step deprotection at the final stage of the synthesis, 2-nitrobenzenesulfonyl (Ns)[17] group in **6c** was replaced with Boc group by two-step transformation (PhSH, Cs_2CO_3; Boc_2O, TEA) to give **6c′** in 86% yield.

It should be noted here that rhodium-catalyzed reduction reported by Kuwano et al.[18] also worked for this transformation. However, the yield was not practical; when pyrrolidone lactam **11** was treated with $RhH(CO)(PPh_3)_3$ and Et_2SiH_2, the desired product **12** was obtained in only 23% yield after acid treatment



Scheme 5. An attempt to deoxygenate pyrrolidone lactam **11** by rhodium-catalyzed hydrosilylation.

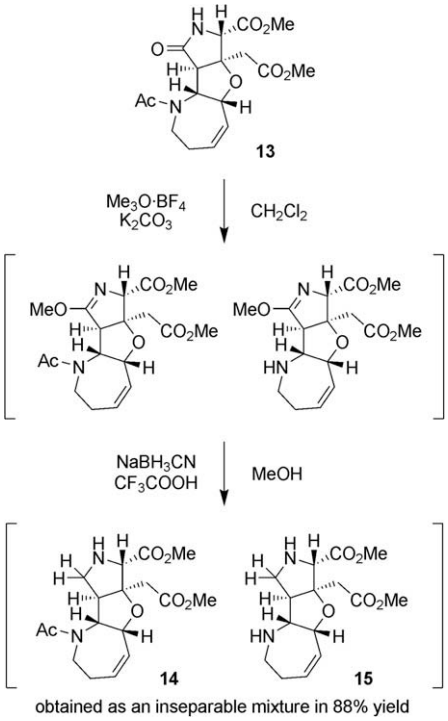
(1 M hydrochloric acid) followed by regeneration of *N*-Boc amine (Boc_2O) (Scheme 5). The method by way of imidate shown in Scheme 4 is, therefore, more practical than borane reduction,[11] or hydrosilylation, for deoxygenation of the pyrrolidone ring leading to advanced intermediates, *N*-Boc-protected pyrrolidine **6a**–**6d**.[19]

During the deoxygenation studies, the *N*-Ac group was found to be unstable under reaction conditions amenable to imidate formation. For example, when **13** was subjected to Meerwein reagent and K_2CO_3, the desired imidate formation cleanly proceeded while deacetylation was partially observed (Scheme 6).[20] Thus, pyrrolidines **14** and **15** were obtained as a mixture in 88% yield. The undesirable side reaction was not observed with *N*-TFA compound **10d** (Scheme 4), however, and we therefore expect that TFA amide could be generally stable under Meerwein conditions.

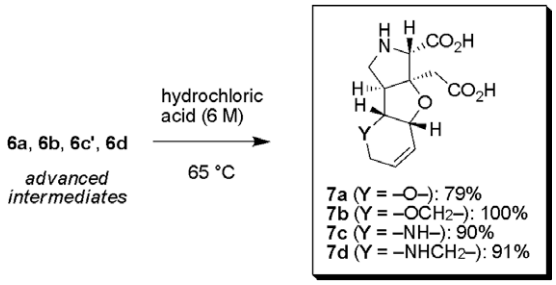
With the advanced intermediates **6a**–**6d**, four glutamate analogs bearing an olefin functionality at the C ring were directly synthesized by global deprotection of all protecting groups under acidic hydrolysis conditions (6 M hydrochloric acid, 65 °C) as shown in Scheme 7.[8] After reversed-phase column chromatography using water as an eluant, the artificial glutamate analogs **7a**–**7d** were obtained cleanly in 79–100% yield without any detectable by-products.

Next, glutamate analogs **5a**–**5d** saturated at the C ring were synthesized as shown in Scheme 8. Four advanced intermediates **6a**–**6d** were hydrogenated (H_2, 10% Pd/C, ca. 3 h) to give **16a**–**16d** in excellent yields (96–100%). Chromatographic and spectroscopic data of **16a** and **16b** were completely identical with those of compounds obtained in the first-generation synthesis.[11] Finally, all protecting groups were simultaneously removed (6 M hydrochloric acid, 65 °C) to furnish **5a**–**5d** in 63–100% yield. Again, **5a** and **5b** were identical in all respects with specimens prepared by our first-generation synthesis.[11]

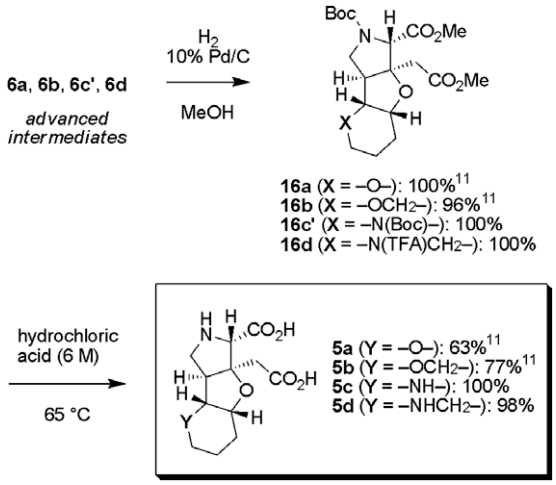
The dihydroxylated glutamate analogs **1a**–**1d** were synthesized as shown in Scheme 9. OsO_4-induced dihydroxylation of advanced intermediates **6a**–**6d** was performed using *N*-methylmorpholine *N*-oxide (NMO) as a co-oxidant to provide **17a**–**17d** quantitatively in all cases. Although the reason is not clear at present, yields for



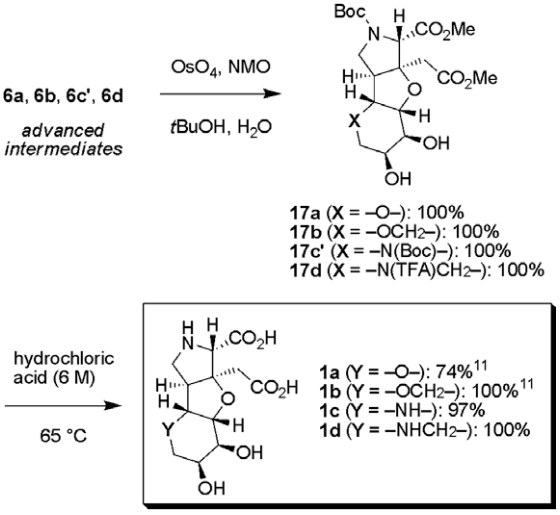
Scheme 6. Undesired decomposition of *N*-Ac group under Meerwein conditions.



Scheme 7. Synthesis of glutamate analogs **7a**–**7d** with unsaturation at the C ring.



Scheme 8. Synthesis of glutamate analogs **5a**–**5d** with saturation at the C ring.



Scheme 9. Synthesis of dihydroxylated glutamate analogs **1a**–**1d**.

the dihydroxylation were substantively improved from the first-generation synthesis,[11] in which the transformation of pyrrolidones **4a** and **4b** to corresponding diols proceeded with 88% and 83% yields, respectively (see Scheme 1). Stereochemistry of **17a** and **17b** was determined after converting into known glutamate analogs **1a** and **1b**,[11] which showed dihydroxylation had took place from a convex β-side of the molecular skeleton. By analogy with **17a** and **17b**, diol group of **17c′** and **17d** was determined also as β-oriented.[21] Global deprotection of all protecting groups was

performed by acidic hydrolysis (6 M hydrochloric acid, 65 °C), giving rise to dihydroxylated artificial glutamate analogs **1a**–**1d** in 74–94% yield after reversed-phase column chromatography. Analogs **1a** and **1b** were identical in all respects with those synthesized using the first-generation synthesis.[11]

2.2. Biological evaluation of the artificial glutamate analogs

On some structurally diverse glutamate analogs thus synthesized in racemic form, biological evaluation was performed in vitro (radioligand binding assays and electrophysiological analyses with GluRs) and in vivo (mice behavioral assays) as follows. In our radioligand binding assays using rat brain synaptic membranes, we did not find evidence for binding of selected analogs (**1a**, **1b**, **5a**, **5b**) to any subtype of ionotropic glutamate receptors (iGluR)—AMPA, KA, or NMDA—at a concentration of 1×10^{-5} M. On the other hand, current- and voltage-clump electrophysiological analysis from cultured hippocampal neurons revealed that one of the new compounds (**7c**) markedly reduced both action potential firing frequency, by 52 ± 9% ($n = 3$, $p < 0.05$) and charge transfer during spontaneous excitatory synaptic currents, by 31 ± 9% ($n = 3$), which was somewhat less than was observed with glutamate analog **1a**.[11,12] Pharmacological characterization of related compound, being named IKM-159, suggests that these activities arise through specific inhibition of AMPA receptors, although the precise mechanism of action remains to be delineated.[22]

The effect of the several compounds was examined in mouse behavioral assays following intracranial injection of each compound (20 μg/mouse).[23] Compounds **1b**, **5a**, **5b**, and **7b** were hyperactive while other analogs were hypoactive.[24] It was somewhat surprising to discover glutamate analogs with hypoactivity in this artificial compound library, since naturally derived glutamates such as dysiherbaine,[5] neodysiherbaine,[6] and kainic acid,[25] are potent convulsants. Among those exhibiting hypoactivity, the piperidine-containing analogs were potent in the assay (**1c** ≈ **5c** > **7c** order of potency); upon intracranial injection (20 μg/mouse), mice developed head tremors accompanied by scratching behavior, and then went into state of immobility lasting for about 50 min. It should be noted that even the new unsaturated analog **7c**, while producing a weaker form of hypoactivity than the other two piperidine-containing analogs, was clearly more potent than **1a**, for which we recently reported similar biological activity.[11,12] The behavioral hypoactivity of **7c** also correlates with the reduced neuronal excitability observed in the in vitro assays, demonstrating that the pharmacological activity of these molecules differs substantively from their progenitor convulsant molecules, kainate and neodysiherbaine A.

3. Conclusions

In conclusion, we have developed an improved, second-generation route amenable to syntheses of 12 artificial glutamate analogs (**1a**–**1d**, **5a**–**5d**, **7a**–**7d**) starting from **3a**–**3d**, readily prepared in three steps. The synthesis features four advanced intermediates **6a**–**6d** at 1–2 steps before the final products in the synthetic scheme, so that the glutamate analogs can be prepared diversely and efficiently. Twelve analogs were thus furnished in 7.2–25.8% overall yields, which were clearly improved from the first-generation route for the synthesis of **1a**, **1b**, **5a**, and **5b** (4.3–16.3% yields, see Scheme 1). Although the total steps are longer in the present study (13–15 steps) than those in the first-generation route (11–12 steps), the new route is capable of synthesizing new analogs bearing amino group and/or olefin functionality at the C ring.

Biological evaluation of a subset of the glutamate analogs showed diverse activities in vitro and in vivo. In particular, the three new piperidine-containing analogs (**1c**, **5c**, **7c**) were discovered to be more hypoactive than the previously reported **1a**. In the case of **7c**, this in vivo hypoactivity was matched by inhibitory actions on neuronal excitability and synaptic transmission in vitro. Further biological studies are under progress to establish the structure–activity relationships and to improve the biological potency, and the results will be reported in due course.

4. Experimental

4.1. General

The experimental techniques and the characterizing apparatuses used are summarized in our previous paper.[8] Electrophysiological experiments were performed according to our published procedure.[11] For procedures and data for intermediates **16a** and **16b**, and glutamate analogs **1a**, **1b**, **5a**, and **5b**, see our first-generation synthesis paper.[11]

4.1.1. (1*E*)-2-((3*S**,3a*S**,4a*R**,8a*R**,8b*R**)-8-Aza-3-((*N*-benzyl-*N*-*tert*-butoxycarbonyl)carbamoyl)-2-(4-methoxybenzyl)-8-(2-nitrobenzenesulfonyl)-2,3,3a,4a,7,8,8a,8b-octahydro-1-oxo-1*H*-benzofuro[2,3-*c*]pyrrol-3a-yl)vinyl acetate (8c)

To a stirred solution of the *N*-Bn amide **3c** (1.00 g, 1.42 mmol) in DCM (15 mL) at 0 °C were added Boc_2O (1.66 mL, 7.10 mmol), TEA (984 μL, 7.10 mmol) and DMAP (86.7 mg, 0.71 mmol). After 2.5 h, the mixture was diluted with EtOAc (50 mL), washed with saturated aqueous NH_4Cl (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20 g, hexane/EtOAc = 7:3) to give the *N*-Boc imide **8c** (1.00 g, 90%) as a pale yellow solid: IR (film) 2930, 1696, 1544, 1370, 1147 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, $J = 8.0$ Hz, 1H), 7.78 (t, $J = 8.0$ Hz, 1H), 7.71 (t, $J = 8.0$ Hz, 1H), 7.65 (d, $J = 8.0$ Hz, 1H), 7.25–7.13 (m, 6H), 6.94 (d, $J = 9.0$ Hz, 2H), 6.77 (d, $J = 9.0$ Hz, 2H), 5.86 (dd, $J = 10.5$ Hz, 1H), 5.78 (d, $J = 10.5$ Hz, 1H), 5.30 (d, $J = 12.5$ Hz, 1H), 5.25 (s, 1H), 5.02 (dd, $J = 7.5$, 2.5 Hz, 1H), 4.82 (d, $J = 14.5$ Hz, 1H), 4.76 (d, $J = 7.5$ Hz, 1H), 4.70 (d, $J = 14.0$ Hz, 1H), 4.48 (d, $J = 14.5$ Hz, 1H), 4.26 (dd, $J = 18.0$, 5.5 Hz, 1H), 3.75 (s, 3H), 3.75 (d, $J = 14.0$ Hz, 1H), 3.46 (d, $J = 18,0$ Hz, 1H), 3.12 (s, 1H), 2.02 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 171.8, 167.2, 159.2, 151.8, 148.0, 138.2, 137.1, 133.8, 132.7, 132.5, 132.1, 130.1 (×2), 128.2 (×2), 128.1 (×2), 127.9, 127.4, 126.4, 126.1, 123.9, 114.1 (×2), 113.0, 84.7, 84.4, 72.3, 68.9, 58.4, 55.8, 55.2, 47.6, 45.8, 40.2, 27.6 (×3), 20.5; HRMS (ESI, positive) calcd for $C_{40}H_{43}N_4O_{12}S$ [$(M+H)^+$] 803.2593, found 803.2591.

4.1.2. (1*E*)-2-((*Z*,1*S**,3a*R**,3b*S**,8a*S**,9a*S**)-4-Aza-1-((*N*-benzyl-*N*-*tert*-butoxycarbonyl)carbamoyl)-2-(4-methoxybenzyl)-9-oxa-4-trifluoroacetyl-2,3,3a,3b,4,5,6,8a,9,9a-decahydro-3-oxo-1*H*-azuleno[2,1-*c*]pyrrol-9a-yl)vinyl acetate (8d)

With the same procedure for the synthesis of **8c**, **8d** (351.3 mg, 83%) was obtained as a pale yellow solid starting from **3d** (363.6 mg, 0.58 mmol), Boc_2O (407.9 mg, 1.74 mmol), DMAP (35.4 mg, 0.29 mmol), and TEA (241.1 μL, 1.74 mmol).

4.1.2.1. Data for 8d. IR (film) 2894, 1702, 1513, 1210, 1146, 848 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ca. 1:1 mixture of rotamers) δ 7.32 (d, $J = 13.0$ Hz, 0.5H), 7.29–7.19 (m, 5.5H), 6.97–6.94 (m, 2H), 6.79–6.78 (d, $J = 8.0$ Hz, 2H), 5.94–5.86 (m, 0.5H), 5.70–5.62 (m, 0.5H), 5.47 (d, $J = 13.0$ Hz, 0.5H), 5.45 (d, $J = 13.0$ Hz, 0.5H), 5.36 (s, 0.5H), 5.35 (s, 0.5H), 5.18 (m, 0.5H), 4.90–4.83 (m, 3.5H), 4.58 (d, $J = 14.5$ Hz, 0.5H), 4.54 (d, $J = 14.5$ Hz, 0.5H), 4.40–4.28 (m, 1H), 3.95–3.87 (m, 1H), 3.76 (s, 3H), 3.73–3.62 (m, 2H), 3.22 (d, $J = 3.5$ Hz, 1H), 2.67 (m, 0.5H), 2.47–2.22 (m, 1.5H), 2.05 (s,

3H), 1.34–1.28 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 171.6, 171.1, 167.2, 159.3, 159.3, 156.8, 151.7, 139.1, 137.3, 137.0, 130.3 (×2), 128.0 (×2), 127.4 (×2), 121.7, 120.9, 117.4, 114.1 (×2), 84.7, 83.4, 76.1, 70.1, 64.2, 60.9, 55.1, 47.7, 45.5, 41.6, 41.5, 32.6, 27.5 (×3), 20.5; HRMS (ESI, positive) calcd for $C_{37}H_{41}N_3O_9F_3$ [(M+H)$^+$] 728.2789, found 728.2787.

4.1.3. Methyl (3*S**,3a*S**,4a*R**,8a*R**,8b*R**) 8-aza-2-(4-methoxybenzyl)-3a-formylmethyl-8-(2-nitrobenzenesulfonyl)-2,3,3a,4a,7,8,8a,8b-octahydro-1-oxo-1*H*-benzofuro[2,3-*c*]pyrrole-3-carboxylate (9c)

To a stirred solution of the imide **8c** (1.03 g, 1.28 mmol) in methanol (45 mL) at −20 °C was added K_2CO_3 (88.3 mg, 0.64 mmol). After 5 h, the mixture was poured into saturated aqueous NH_4Cl (60 mL), and the mixture was extracted with EtOAc (100 mL). The extract was washed with brine (60 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (6 g, hexane/EtOAc = 7:3) to give the ester aldehyde **9c** (604.4 mg, 81%) as a pale yellow solid: IR (film) 3002, 1748, 1698, 1541, 1508, 1362, 1248, 1172, 1030, 582 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 9.44 (s, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 7.02–6.97 (m, 3H), 6.72–6.99 (m, 3H), 6.56 (t, *J* = 7.5 Hz, 1H), 5.18 (ddd, *J* = 10.8, 2.0, 2.0 Hz, 1H), 5.10 (ddd, *J* = 10.8, 3.5, 3.5 Hz, 1H), 4.93 (d, *J* = 14.5 Hz, 1H), 4.76 (dd, *J* = 6.8, 3.5 Hz, 1H), 4.28 (s, 1H), 4.21 (br s, 1H), 3.92 (d, *J* = 14.5 Hz, 1H), 3.92 (d, *J* = 18.0 Hz, 1H), 3.51 (d, *J* = 4.0 Hz, 1H), 3.48 (d, *J* = 14.5 Hz, 1H), 3.24 (m, 1H), 3.23 (s, 3H), 3.11 (s, 3H), 2.71 (dd, *J* = 17.5, 1.0 Hz, 1H), 2.31 (dd, *J* = 17.5, 1.0 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 197.7, 171.8, 169.5, 159.9, 148.8, 133.8, 132.5, 131.6, 131.2, 130.1 (×2), 127.4, 127.3, 125.5, 123.8, 114.6 (×2), 84.6, 73.7, 68.9, 59.5, 54.7, 54.4, 51.8, 48.7, 45.5, 41.5; HRMS (ESI, positive) calcd for $C_{27}H_{29}N_3O_{10}S$ [(M+H)$^+$] 586.1489, found 586.1490.

4.1.4. Methyl (*Z*,1*S**,3a*R**,3b*S**,8a*S**,9a*S**) 4-aza-2-(4-methoxybenzyl)-9a-formylethyl-9-oxa-4-trifluoroacetyl-2,3,3a,3b,4,5,6,8a,9,9a-decahydro-3-oxo-1*H*-azuleno[2,1-*c*]pyrrole-1-carboxylate (9d)

With the same procedure for the synthesis of **9c**, **9d** (219.4 mg, 91%) was obtained as a pale yellow solid starting from **8d** (345.0 mg, 0.48 mmol) and K_2CO_3 (32.8 mg, 0.24 mmol).

4.1.4.1. Data for 9d. IR (film) 2933, 1748, 1698, 1541, 1508, 1145, 669 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6, ca. 1:1 mixture of rotamers) δ 9.58 (br s, 0.5H), 9.55 (br s, 0.5H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 1H), 5.31–5.25 (m, 1H), 5.16–5.02 (m, 1H), 4.89 (d, *J* = 5.5 Hz, 0.5H), 4.21 (s, 0.5H), 4.08 (s, 0.5H), 4.06 (dd, *J* = 7.3, 5.0 Hz, 0.5H), 3.93 (dd, *J* = 7.3, 5.0 Hz, 0.5H), 3.82–3.74 (m, 1.5H), 3.41 (t, *J* = 13.5 Hz, 0.5H), 3.31–3.22 (m, 6H), 3.15 (s, 1.5H), 3.10 (t, *J* = 12.0 Hz, 0.5H), 2.90 (s. 0.5H), 2.64 (br s, 0.5H), 2.45–2.38 (m, 1.5H), 2.35–2.32 (m, 1H), 1.78 (br t, *J* = 18.0 Hz, 0.5H), 1.66 (br d, *J* = 20.0 Hz, 0.5H), 1.50 (br d, *J* = 20.0 Hz, 0.5H), 0.91 (m, 0.5H); ^{13}C NMR (125 MHz, C_6D_6, selected) δ 197.6, 170.4, 169.8, 161.1, 137.1, 130.6, 128.8 (×2), 127.5, 122.0, 118.3, 114.8 (×2), 82.9, 76.8, 69.5, 65.9, 65.0, 54.9, 52.1, 45.7, 42.1, 32.8, 29.9; HRMS (ESI, positive) calcd for $C_{24}H_{25}F_3N_2O_7Na$ [(M+Na)$^+$] 533.1506, found 533.1493.

4.1.5. Methyl (3*S**,3a*S**,4a*R**,8a*R**,8b*R**) 8-aza-3a-((methoxycarbonyl)methyl)-2-(4-methoxybenzyl)-8-(2-nitrobenzenesulfonyl)-2,3,3a,4a,7,8,8a,8b-octahydro-1-oxo-1*H*-benzofuro[2,3-*c*]pyrrole-3-carboxylate (4c)

To a stirred solution of the aldehyde **9c** (604.4 g, 1.03 mmol) in *tert*-butanol (36 mL) and water (12 mL) at rt were added 2-methyl-2-butene (547.0 μL, 5.16 mmol), $NaH_2PO_4{\cdot}2H_2O$ (177.0 mg, 1.13 mmol), and $NaClO_2$ (278 mg, 3.09 mmol). After 5 h, the mixture was diluted with DCM (100 mL), and the mixture was washed with hydrochloric acid (1 M, 50 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in methanol (36 mL) and cooled to 0 °C. $TMSCHN_2$ (2 M in Et_2O, 1.03 mL, 2.06 mmol) was added, and the mixture was allowed to warm to rt. After stirring for 30 min, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (15 g, hexane/EtOAc = 4:6) to give the diester **4c** (589.6 mg, 93%) as a white solid: IR (film) 2953, 1745, 1699, 1544, 1513, 1248, 1172, 1031, 682 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.82–7.68 (m, 3H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.00 (dt, *J* = 11.0, 4.0 Hz, 1H), 5.80 (dd, *J* = 11.0, 3.0 Hz, 1H), 4.94 (d, *J* = 14.5 Hz, 1H), 4.70 (t, *J* = 7.5 Hz, 1H), 4.63 (br s, 1H), 4.19 (s, 1H), 4.10 (dt, *J* = 16.0, 2.0 Hz, 1H), 3.94 (d, *J* = 14.5 Hz, 1H), 3.91 (d, *J* = 16.0 Hz, 1H), 3.82 (s, 3H), 3.70 (d, *J* = 5.0 Hz, 1H), 3.67 (s, 3H), 3.64 (s, 3H), 2.97 (d, *J* = 16.5 Hz, 1H), 2.82 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 169.3 (×2), 159.3, 148.2, 134.1, 132.2, 132.0, 131.4, 129.8 (×2), 126.8, 126.7, 125.9, 124.2, 114.2 (×2), 84.7, 73.1, 63.4, 58.7, 55.2, 52.8, 52.5, 51.9, 45.2, 40.9, 39.7; HRMS (ESI, positive) calcd for $C_{28}H_{29}N_3O_{11}SNa$ [(M+Na)$^+$] 638.1415, found 638.1392.

4.1.6. Methyl (*Z*,1*S**,3a*R**,3b*S**,8a*S**,9a*S**) 4-aza-9a-((methoxycarbonyl)methyl)-2-(4-methoxybenzyl)-9-oxa-4-trifluoroacetyl-2,3,3a,3b,4,5,6,8a,9,9a-decahydro-3-oxo-1*H*-azuleno[2,1-*c*]pyrrole-1-carboxylate (4d)

With the same procedure for the synthesis of **4c**, **4d** (183.7 mg, 85%) was obtained as a pale yellow oil starting from **9d** (210.4 mg, 0.41 mmol), 2-methyl-2-butene (218.0 μL, 2.06 mmol), $NaH_2PO_4{\cdot}2H_2O$ (70.7 mg, 0.46 mmol), $NaClO_2$ (111.3 mg, 1.24 mmol), and $TMSCHN_2$ (2 M in Et_2O, 0.41 mL, 0.81 mmol).

4.1.6.1. Data for 4d. IR (film) 2954, 1745, 1702, 1513, 1438, 1205, 1167, 1035 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, ca. 6:4 mixture of rotamers) δ 7.12–7.01 (m, 2H), 6.85–6.82 (m, 2H), 5.98–5.90 (m, 1H), 5.60–5.54 (m, 1H), 5.07 (d, *J* = 14.5, 0.4H), 5.00 (d, *J* = 14.5 Hz, 0.6H), 4.99 (d, *J* = 5.5 Hz, 0.6H), 4.72 (d, *J* = 5.5 Hz, 0.4H), 4.15 (s, 0.6H), 4.11–4.03 (m, 1.4H), 3.90–3.85 (m, 2H), 3.79–3.78 (m, 3H), 3.70 (s, 1.2H), 3.66–3.64 (m, 4.8H), 3.56–3.51 (m, 0.6H), 3.43 (s, 0.4H), 3.37 (s, 0.6H), 2.98–2.94 (m, 1.4H), 2.82–2.69 (m, 1H), 2.50–2.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, major rotamer) δ 170.3, 169.4, 168.9, 159.3, 137.0, 130.0 (×2), 126.9, 121.6, 120.5, 114.1 (×2), 82.8, 75.7, 68.4, 64.6, 58.6, 55.2, 52.4, 52.0, 45.1, 41.6, 39.9, 32.7, 29.6; HRMS (ESI, positive) calcd for $C_{25}H_{27}N_2O_8F_3Na$ [(M+Na)$^+$] 563.1612, found 563.1609.

4.1.7. Methyl (3*S**,3a*S**,4a*R**,8a*R**,8b*R**) 3a-((methoxycarbonyl)methyl)-8-oxa-2,3,3a,4a,7,8,8a,8b-octahydro-1-oxo-1*H*-benzofuro[2,3-*c*]pyrrole-3-carboxylate (10a)

To a stirred solution of the *N*-PMB amide **4a** (187.3 mg, 0.43 mmol) in CH_3CN (10.0 mL) and water (2.4 mL) at −10 °C was added a solution of CAN (1.19 mg, 2.17 mmol) in water (6.6 mL) portionwise. After 5 h, the mixture was poured into saturated aqueous $Na_2S_2O_3$ (20 mL) and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (5 g, hexane/EtOAc = 4:6) to give the lactam **10a** (95.2 mg, 71%) as a white solid: IR (film) 2953, 1747, 1698, 1508, 1436, 1250, 1211, 1087, 848, 688 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.16 (s, 1H), 6.05 (dd, *J* = 10.0, 4.0 Hz, 1H), 5.98 (ddd, *J* = 10.0, 4.0, 2.0 Hz, 1H), 4.44 (s, 1H), 4.29 (d, *J* = 2.0 Hz, 1H), 4.15 (s, 1H), 4.13 (dd, *J* = 16.5, 4.0 Hz, 1H), 4.00 (d, *J* = 16.5 Hz, 1H), 3.67 (s, 3H), 3.60 (s, 3H), 3.28 (s, 1H), 3.14 (d, *J* = 17.5 Hz, 1H), 2.85 (d, *J* = 17.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 170.4, 170.3, 130.9, 122.0, 87.3, 78.1,

73.2, 64.7, 64.1, 56.7, 52.5, 51.6, 40.3; HRMS (ESI, positive) calcd for $C_{14}H_{17}NO_7Na$ [(M+Na)$^+$] 334.0897, found 334.0899.

4.1.8. Methyl (*Z*,1*S**,3a*R**,3b*S**,8a*S**,9a*S**) 9a-((methoxycarbonyl) methyl)-2,3,3a,3b,4,5,6,8a,9,9a-decahydro-4,9-dioxa-3-oxo-1*H*-azuleno[2,1-*c*]pyrrole-1-carboxylate (10b)

With the same procedure for the synthesis of **10a**, **10b** (67.4 mg, 71%) was obtained as a white solid starting from **4b** (130 mg, 0.29 mmol) and CAN (801 mg, 1.46 mmol).

4.1.8.1. Data for 10b. IR (film) 2953, 1743, 1715, 1436, 1362, 1211, 1046, 669 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (br s, 1H), 5.81 (ddd, *J* = 11.5, 5.0, 5.0 Hz, 1H), 5.64 (dd, *J* = 11.5, 2.5 Hz, 1H), 4.54 (br s, 1H), 4.40 (s, 1H), 4.37 (br s, 1H), 3.96 (ddd, *J* = 11.5, 5.5, 4.5 Hz, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 3.62 (ddd, *J* = 11.5, 5.5, 4.5 Hz, 1H), 3.29 (s, 1H), 3.22 (d, *J* = 17.5 Hz, 1H), 2.92 (d, *J* = 17.5 Hz, 1H), 2.35 (dd, *J* = 5.5, 5.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 170.4, 170.3, 129.7, 126.1, 85.8, 82.5, 82.0, 68.9, 64.6, 58.0, 52.5, 51.6, 39.6, 30.3; HRMS (ESI, positive) calcd for $C_{15}H_{19}NO_7Na$ [(M+Na)$^+$] 348.1054, found 348.1060.

4.1.9. Methyl (3*S**,3a*S**,4a*R**,8a*R**,8b*R**) 8-aza-3a-((methoxycarbonyl)methyl)-8-(2-nitrobenzenesulfonyl)-2,3,3a,4a,7,8,8a,8b-octahydro-1-oxo-1*H*-benzofuro[2,3-*c*]pyrrole-3-carboxylate (10c)

With the same procedure for the synthesis of **10a**, **10c** (178.4 mg, 78%) was obtained as a white solid starting from **4c** (278.4 mg, 0.45 mmol) and CAN (1.24 g, 2.26 mmol).

4.1.9.1. Data for 10c. IR (film) 2922, 1715, 1541, 1362, 1253, 1166, 683, 584 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 5.5, 4.5 Hz, 1H), 7.72–7.64 (m, 3H), 6.02 (br s, 1H), 5.91 (dd, *J* = 10.0, 1.0 Hz, 1H), 5.74 (d, *J* = 10.0 Hz, 1H), 4.91 (t, *J* = 7.5 Hz, 1H), 4.80 (br s, 1H), 4.41 (s, 1H), 4.13 (d, *J* = 19.0 Hz, 1H), 3.87 (d, *J* = 19.0 Hz, 1H), 3.75 (s, 3H), 3.59 (s, 3H), 3.37 (d, *J* = 7.5 Hz, 1H), 3.05 (d, *J* = 16.5 Hz, 1H), 2.81 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 169.3, 169.2, 148.0, 134.0, 132.4, 132.1, 131.9, 126.4, 126.3, 124.5, 87.5, 73.7, 65.6, 58.0, 52.8, 52.0, 50.8, 40.8, 40.1; HRMS (ESI, positive) calcd for $C_{20}H_{22}N_3O_{10}S$ [(M+H)$^+$] 496.1020, found 496.1020.

4.1.10. Methyl (*Z*,1*S**,3a*R**,3b*S**,8a*S**,9a*S**) 4-aza-9a-((methoxycarbonyl)methyl)-9-oxa-4-trifluoroacetyl-2,3,3a,3b,4,5,6,8a,9,9a-decahydro-3-oxo-1*H*-azuleno[2,1-*c*]pyrrole-1-carboxylate (10d)

With the same procedure for the synthesis of **10a**, **10d** (109.4 mg, 80%) was obtained as a pale yellow solid starting from **4d** (175.5 mg, 0.33 mmol) and CAN (891 mg, 1.63 mmol).

4.1.10.1. Data for 10d. IR (film) 2930, 1716, 1436, 1209, 1146, 1046, 730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, ca. 1:1 mixture of rotamers) δ 6.15 (br s, 0.5H), 6.09 (br s, 0.5H), 6.03–5.97 (m, 1H), 5.78–5.72 (m, 1H), 5.04 (d, *J* = 6.0 Hz, 0.5H), 4.75 (d, *J* = 6.0 Hz, 0.5H), 4.49–4.45 (m, 1H), 4.29 (s, 0.5H), 4.24 (s, 0.5H), 4.06 (dd, *J* = 13.5, 4.5 Hz, 0.5H), 3.85 (d, *J* = 8.0 Hz, 1H), 3.77 (s, 1.5H), 3.76 (s, 1.5H), 3.64 (s, 1.5H), 3.63 (s, 1.5H), 3.45 (ddd, *J* = 12.5, 10.5, 3.5 Hz, 0.5H), 3.40 (d, *J* = 17.0 Hz, 0.5H), 3.25–3.24 (m, 1H), 3.24 (d, *J* = 17.0 Hz, 0.5H), 2.96 (d, *J* = 17.0 Hz, 0.5H), 2.94 (d, *J* = 17.0 Hz, 0.5H), 2.82 (m, 0.5H), 2.57–2.36 (m, 1.5H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 173.4, 172.9, 169.6, 169.3, 137.7, 120.3, 85.3, 75.3, 64.8, 63.6, 59.2, 52.7, 52.0, 41.2, 39.8, 32.3, 29.1; HRMS (ESI, positive) calcd for $C_{17}H_{19}N_2O_7Na$ [(M+Na)$^+$] 443.1037, found 443.1038.

4.1.11. Methyl (3*S**,3a*S**,4a*R**,8a*R**,8b*R**) 2-(*tert*-butoxycarbonyl)-3a-((methoxycarbonyl)methyl)-8-oxa-2,3,3a,4a,7,8,8a,8b-octahydro-1*H*-benzofuro[2,3-*c*]pyrrole-3-carboxylate (6a)

To a stirred solution of the pyrrolidinone **10a** (65.8 mg, 0.212 mmol) in DCM (2.0 mL) at 0 °C were added $Me_3O{\cdot}BF_4$ (94.1 mg, 0.636 mmol) and K_2CO_3 (117.2 mg, 0.848 mmol). After stirring at rt for 4 h, the mixture was diluted with DCM (20 mL), washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude imidate thus obtained was used in the next reaction without purification.

To a stirred solution of the above imidate in methanol (2.0 mL) at 0 °C were added $NaCNBH_3$ (40 mg, 0.636 mmol) and TFA (31.5 μL, 0.424 mmol). After stirring at rt for 4 h, the mixture was diluted with DCM (20 mL), washed with saturated aqueous $NaHCO_3$ (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure to a final volume of ca. 2 mL. Boc_2O (149 μL, 0.636 mmol) and TEA (88 μL, 0.636 mmol) were added, and the mixture was stirred at rt for 2 h. The mixture was then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (3 g, hexane/EtOAc = 8:2) to give the pyrrolidine **6a** (49.4 mg, 59%, three steps) as a white solid: IR (film) 1742, 1701, 1395, 1366, 1174, 1013, 689 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, ca. 7:3 mixture of rotamers) δ 6.01 (m, 2H), 4.74 (s, 1H), 4.29 (br s, 0.7H), 4.26 (br s, 0.3H), 4.15 (d, *J* = 16.5 Hz, 1H), 3.98 (d, *J* = 16.5 Hz, 1H), 3.94–3.90 (m, 2H), 3.66 (s, 4.2H), 3.65 (s, 1.8H), 3.37 (dd, *J* = 10.0, 4.5 Hz, 0.7H), 3.32 (m, 0.3H), 3.17 (d, *J* = 17.0 Hz, 0.7H), 3.14 (d, *J* = 17.0 Hz, 0.3H), 3.07 (br d, *J* = 6.0 Hz, 0.3H), 3.00 (dd, *J* = 10.0, 4.5 Hz, 0.7H), 2.68 (d, *J* = 17.0 Hz, 0.3H), 2.62 (d, *J* = 17.0 Hz, 0.7H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 171.0, 170.3, 154.0, 130.5, 122.7, 92.0, 81.1, 80.4, 73.0, 69.0, 64.0, 52.0, 51.6, 51.5, 48.7, 40.4, 28.2 (×3); HRMS (ESI, positive) calcd for $C_{19}H_{27}N_1O_8Na$ [(M+Na)$^+$] 420.1629, found 420.1622.

4.1.12. Methyl (*Z*,1*S**,3a*R**,3b*S**,8a*S**,9a*S**) 2-(*tert*-butoxycarbonyl)-9a-((methoxycarbonyl)methyl)-4,9-dioxa-2,3,3a,3b,4,5,6,8a,9,9a-decahydro-1*H*-azuleno[2,1-*c*]pyrrole-1-carboxylate (6b)

With the same procedure for the synthesis of **6a**, **6b** (10.4 mg, 85%) was obtained as a white solid starting from **10b** (9.7 mg, 0.030 mmol), $Me_3O{\cdot}BF_4$ (13.2 mg, 0.090 mmol), and $NaCNBH_3$ (5.62 mg, 0.089 mmol).

4.1.12.1. Data for 6b. IR (film) 1745, 1701, 1396, 1171, 669 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, ca. 7:3 mixture of rotamers) δ 5.76 (dt, *J* = 12.0, 4.5 Hz, 1H), 5.67 (dd, *J* = 12.0, 4.5 Hz, 1H), 4.68–4.64 (br s, 2H), 3.95–3.88 (m, 3H), 3.71–3.61 (m, 6H), 3.52–3.48 (m, 1H), 3.32 (m, 1H), 3.16 (d, *J* = 17.0 Hz, 0.7H), 3.12 (d, *J* = 17.0 Hz, 0.3H), 3.05 (dd, *J* = 10.0, 5.0 Hz, 0.3H), 2.97 (dd, *J* = 10.0, 5.0 Hz, 0.7H), 2.67 (d, *J* = 17.0 Hz, 0.3H), 2.60 (d, *J* = 17.0 Hz, 0.7H), 2.36–2.26 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 171.0, 170.3, 154.0, 129.5, 126.8, 90.5, 85.5, 82.1, 80.4, 68.9, 68.8, 52.9, 52.0, 51.5, 49.5, 39.7, 30.6, 28.2 (×3); HRMS (ESI, positive) calcd for $C_{20}H_{29}NO_8Na$ [(M+Na)$^+$] 434.1785, found 434.1788.

4.1.13. Methyl (3*S**,3a*S**,4a*R**,8a*R**,8b*R**) 8-aza-2-(*tert*-butoxycarbonyl)-3a-((methoxycarbonyl)methyl)-8-(2-nitrobenzenesulfonyl)-2,3,3a,4a,7,8,8a,8b-octahydro-1*H*-benzofuro[2,3-*c*]pyrrole-3-carboxylate (6c)

With the same procedure for the synthesis of **6a**, **6c** (162.1 mg, 86%) was obtained as a pale yellow solid starting from **10c** (160.1 mg, 0.323 mmol), $Me_3O{\cdot}BF_4$ (143.3 mg, 0.969 mmol), and $NaCNBH_3$ (101.5 mg, 1.615 mmol).

4.1.13.1. Data for 6c. IR (film) 2977, 1747, 1698, 1542, 1364, 1168, 682 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, ca. 1:1 mixture of rotamers) δ 8.08 (d, *J* = 8.0 Hz, 0.5H), 8.02 (d, *J* = 8.0 Hz, 0.5H), 7.74–7.67 (m, 3H), 5.81 (dd, *J* = 10.8, 3.5 Hz, 0.5H), 5.75 (dd, *J* = 10.8, 3.5, Hz, 0.5H), 5.65–5.62 (m, 1H), 4.63 (d, *J* = 7.0 Hz, 0.5H), 4.56 (d, *J* = 7.0 Hz, 0.5H), 4.52 (s, 0.5H), 4.51–4.45 (m, 1H), 4.37 (s, 0.5H), 4.15 (br d, *J* = 18.0 Hz, 0.5H), 4.01 (d, *J* = 11.5 Hz, 0.5H), 3.96 (br d, *J* = 18.0 Hz, 0.5H), 3.81–3.77 (m, 1H), 3.69 (s, 1.5H), 3.67 (s, 1.5H),

3.62 (dd, J = 11.8, 5.5 Hz, 0.5H), 3.59 (s, 3H), 3.58 (d, J = 11.5 Hz, 0.5H), 3.51 (dd, J = 11.8, 5.5 Hz, 0.5H), 3.06 (m, 1H), 2.83 (d, J = 15.5 Hz, 0.5H), 2.77 (d, J = 15.5 Hz, 0.5H), 2.72 (d, J = 15.5 Hz, 0.5H), 2.67 (d, J = 15.5 Hz, 0.5H), 1.46 (s, 4.5H), 1.39 (s, 4.5H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 170.3, 169.8, 154.6, 147.8, 134.0, 132.4, 132.0, 131.0, 126.9, 124.7, 124.2, 90.7, 80.8, 71.6, 69.8, 58.8, 52.2, 51.8, 48.5, 46.7, 40.5, 39.7, 28.2 (×3); HRMS (ESI, positive) calcd for $C_{25}H_{31}N_3O_{11}Na$ [(M+Na)$^+$] 604.1571, found 604.1566.

4.1.14. Methyl (*Z*,1*S**,3a*R**,3b*S**,8a*S**,9a*S**) 4-aza-2-(*tert*-butoxycarbonyl)-9a-((methoxycarbonyl)methyl)-2-(4-methoxybenzyl)-9-oxa-4-trifluoroacetyl-2,3,3a,3b,4,5,6,8a,9,9a-decahydro-1*H*-azuleno[2,1-*c*]pyrrole-1-carboxylate (6d)

With the same procedure for the synthesis of **6a**, **6d** (110.1 mg, 84%) was obtained as a pale yellow solid starting from **10d** (109.0 mg, 0.259 mmol), $Me_3O{\cdot}BF_4$ (114.9 mg, 0.777 mmol), and $NaCNBH_3$ (48.8 mg, 0.777 mmol).

4.1.14.1. Data for 6d. IR (film) 1746, 1688, 1394, 1211, 1143, 731 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, ca. 6:4 mixture of rotamers) δ 5.98–5.89 (m, 1H), 5.75–5.68 (m, 1H), 4.70 (s, 0.4H), 4.54–4.50 (m, 1H), 4.44–4.37 (m, 0.6H), 4.01–3.98 (m, 1H), 3.92–3.78 (m, 3H), 3.71 (s, 3H), 3.65 (s, 3H), 3.45 (m, 0.6H), 3.14 (m, 0.4H), 3.00–2.97 (m, 1H), 2.90–2.81 (m, 1.6H), 2.73 (t, J = 16.0 Hz, 0.4H), 2.49 (br s, 0.6H), 2.42–2.30 (m, 1.4H), 1.45 (br s, 3.6H), 1.39 (s. 5.4H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 170.5, 169.6, 157.3, 153.3, 136.6, 121.7, 117.5, 90.8, 81.0, 75.9, 68.6, 68.6, 54.7, 51.9, 51.0, 42.2, 39.0, 32.7, 29.6, 28.1 (× 3); HRMS (ESI, positive) calcd for $C_{22}H_{29}N_2O_8Na$ [(M+Na)$^+$] 529.1768, found 529.1753.

4.1.15. Methyl (3*S**,3a*S**,4a*R**,8a*R**,8b*R**) 8-aza-2,8-bis(*tert*-butoxycarbonyl)-3a-((methoxycarbonyl)methyl)-2,3,3a,4a,7,8,8a,8b-octahydro-1*H*-benzofuro[2,3-*c*]pyrrole-3-carboxylate (6c′)

To a stirred solution of **6c** (141.2 mg, 0.243 mmol) in CH_3CN (3.0 mL) at 0 °C were added thiophenol (49.8 μL, 0.485 mmol) and Cs_2CO_3 (119.0 mg, 0.365 mmol). After stirring at rt for 1.5 h, the mixture was diluted with chloroform (50 mL), washed with saturated aqueous $NaHCO_3$ (25 mL), dried over Na_2SO_4, and concentrated under reduced pressure to a final volume of ca. 3 mL. Boc_2O (170.9 μL, 0.729 mmol) and pyridine (59 μL, 79.1 mmol) were added, and the mixture was stirred at rt for 2 h. The mixture was then diluted with DCM (50 mL), washed with saturated aqueous NH_4Cl (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (2 g, hexane/EtOAc = 8:2) to give the *N*-Boc pyrrolidine **6c′** (103.3 mg, 86%) as a colorless solid: IR (film) 2976, 1746, 1702, 1395, 1367, 1171, 681 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, ca. 1:1 mixture of rotamers) δ 5.78 (d, J = 9.0 Hz, 1H), 5.62 (dd, J = 9.0, 2.0 Hz, 1H), 4.87 (br s, 1H), 4.58 (br s, 1H), 4.48 (s, 0.4H), 4.40 (s, 0.6H), 4.20 (br d, J = 19.0 Hz, 1H), 3.93 (d, J = 11.0 Hz, 0.6H), 3.84–3.82 (m, 0.4H), 3.69 (s, 3H), 3.67–3.58 (m, 1H), 3.60 (s, 3H), 3.55 (br d, J = 19.0 Hz, 1H), 2.96–2.91 (m, 1H), 2.83–2.65 (m, 2H), 1.5–1.38 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 170.6, 169.7, 154.3, 153.6, 125.6, 125.3, 91.2, 80.4, 72.5, 70.5, 56.8, 52.1, 52.0, 51.8, 49.3, 47.6, 46.3, 40.5, 28.2 (×3), 28.1 (×3); HRMS (ESI, positive) calcd for $C_{24}H_{36}N_2O_9Na$ [(M+Na)$^+$] 519.2313, found 519.2294.

4.1.16. General procedures for the synthesis of the glutamate analogs 7a–7d (as well as 1a–1d and 5a–5d)

A suspension of fully protected glutamate analogs **6a**–**6d** in hydrochloric acid (6 M, 0.5 mL) was heated at 65 °C for 10 h. The reaction mixture was then cooled to rt and concentrated under reduced pressure. The residue was purified by column chromatography on reversed-phase silica gel (500 mg, water). The active fractions were lyophilized to afford the glutamate analogs **7a**–**7d**.

4.1.17. (3*S**,3a*S**,4a*R**,8a*R**,8b*R**)-3a-Carboxymethyl-8-oxa-2,3,3a,4a,7,8,8a,8b-octahydro-1*H*-benzofuro[2,3-*c*]pyrrole-3-carboxylic acid (7a)

With the general procedure above, **6a** (13.6 mg, 0.034 mmol) was deprotected to give the glutamate analog **7a** (8.2 mg, 79%) as a white solid: IR (film) 1713, 1634, 1402, 1029 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 6.11 (dd, J = 10.0, 3.5 Hz, 1H), 5.91 (ddd, J = 10.0, 3.5, 2.0 Hz, 1H), 4.49 (s, 1H), 4.43 (t, J = 1.5 Hz, 1H), 4.11 (dd, J = 17.3, 3.5 Hz, 1H), 4.05 (d, J = 2.5 Hz, 1H), 4.02 (d, J = 17.3 Hz, 1H), 3.93 (dd, J = 12.5, 10.0 Hz, 1H), 3.20 (d, J = 17.0 Hz, 1H), 3.15 (dd, J = 12.5, 8.5 Hz, 1H), 3.10 (t, J = 8.5 Hz, 1H), 2.88 (t, J = 17.0 Hz, 1H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 174.0, 168.6, 132.4, 120.4, 90.6, 79.1, 72.8, 67.3, 64.3, 52.2, 45.7, 40.5; HRMS (ESI, positive) calcd for $C_{12}H_{16}NO_6$ [(M+H)$^+$] 270,0978, found 270.0976.

4.1.18. (*Z*,1*S**,3a*R**,3b*S**,8a*S**,9a*S**)-9a-Carboxymethyl-4,9-dioxa-2,3,3a,3b,4,5,6,8a,9,9a-decahydro-1*H*-azuleno[2,1-*c*]pyrrole-1-carboxylic acid (7b)

With the general procedure above, **6b** (9.4 mg, 0.023 mmol) was deprotected to give the glutamate analog **7b** (7.4 mg, 100%) as a white solid: IR (film) 1715, 1621, 1405, 1361, 1075 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 5.88 (ddd, J = 11.5, 5.5, 5.5 Hz, 1H), 5.60 (dd, J = 4.0, 1.5 Hz, 1H), 4.75 (s, 1H), 4.16 (s, 1H), 4.14 (d, J = 3.0 Hz, 1H), 3.85 (dd, J = 17.5 Hz, 1H), 3.84 (m, 1H), 3.57 (m, 1H), 3.15 (d, J = 17.5 Hz, 1H), 3.12–3.02 (m, 2H), 2.81 (d, J = 17.5 Hz, 1H), 2.37–2.21 (m, 2H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 174.6, 170.0, 132.0, 124.8, 88.8, 83.7, 81.0, 69.1, 67.6, 53.6, 46.2, 40.7, 29.7; HRMS (ESI, positive) calcd for $C_{13}H_{18}NO_6$ [(M+H)$^+$] 284.1129, found 284.1128.

4.1.19. (3*S**,3a*S**,4a*R**,8a*R**,8b*S**)-8-Aza-3a-carboxymethyl-2,3,3a,4a,7,8,8a,8b-octahydro-1*H*-benzofuro[2,3-*c*]pyrrole-3-carboxylic acid (7c)

With the general procedure above, **6c′** (23.7 mg, 0.048 mmol) was deprotected to give the glutamate analog **7c** (14.7 mg, 90%) as a white solid: IR (film) 1713, 1624, 1417, 1257, 1085, 967 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 6.11 (dd, J = 10.3, 4.5 Hz, 1H), 6.07 (br d, 10.3 Hz, 1H), 4.75 (br s, 1H), 4.34 (s, 1H), 3.99 (dd, J = 12.5, 9.0 Hz, 1H), 3.86 (d, J = 4.0 Hz, 1H), 3.78 (dd, J = 17.3, 4.0 Hz, 1H), 3.65 (d, J = 17.3 Hz, 1H), 3.48 (t, J = 9.0 Hz, 1H), 3.32 (dd, J = 12.5, 9.0 Hz, 1H), 3.08 (br s, 2H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 174.2, 168.4, 126.7, 121.7, 89.3, 70.2, 65.5, 60.3, 49.1, 46.2, 42.3, 38.3; HRMS (ESI, positive) calcd for $C_{12}H_{17}N_2O_5$ [(M+H)$^+$] 269.1131, found 269.1130.

4.1.20. (*Z*,1*S**,3a*R**,3b*S**,8a*S**,9a*S**)-4-Aza-9a-carboxymethyl-2,3,3a,3b,4,5,6,8a,9,9a-decahydro-9-oxa-1*H*-azuleno[2,1-*c*] pyrrole-1-carboxylic acid (7d)

With the general procedure above, **6d** (31.4 mg, 0.062 mmol) was deprotected to give the glutamate analog **7d** (20.1 mg, 91%) as a white solid: IR (film) 1730, 1624, 1405, 1243, 1087, 991 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 5.92 (m, 1H), 5.69 (d, J = 11.0Hz, 1H), 5.13 (br s, 1H), 4.15 (s, 1H), 4.11 (d, J = 4.5 Hz, 1H), 3.97 (dd, J = 13.0, 10.5 Hz, 1H), 3.51 (t, J = 8.5 Hz, 1H), 3.31–3.25 (m, 3H), 3.09 (d, J = 18.0 Hz, 1H), 2.92 (d, J = 18.0 Hz, 1H), 2.55 (m, 1H), 2.27 (m, 1H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 173.3, 167.9, 127.7, 125.8, 87.9, 78.1, 65.2, 61.9, 51.1, 46.8, 45.4, 38.6, 21.4; HRMS (ESI, positive) calcd for $C_{13}H_{19}N_2O_5$ [(M+H)$^+$] 283.1288, found 283.1296.

4.1.21. Methyl (3*S**,3a*S**,4a*R**,8a*R**,8b*S**) 8-aza-2,8-bis(*tert*-butoxycarbonyl)-3a-((methoxycarbonyl)methyl)-decahydro-2-methyl-1*H*-benzofuro[2,3-*c*]pyrrole-3-carboxylate (16c′)

To a stirred solution of **6c′** (32.8 mg, 0.066 mmol) in methanol (6.0 mL) at rt was added palladium (10 wt % on carbon, 3.3 mg). The mixture was stirred vigorously under hydrogen atmosphere (1 atm) for 1 h. The catalyst was then removed by filtration and the filtrate was then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.5 g, hexane/EtOAc = 8:2) to give **16c′** (32.8 mg, 100%) as a white solid: IR (film) 1747, 1696, 1393, 1367, 1254, 1165, 1063, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 4.49–4.45 (m, 1H), 4.28–4.21 (m, 2H), 3.83–3.75 (m, 1H), 3.73–3.69 (m, 4H), 3.67–3.62 (m, 3H), 3.55–3.50 (m, 1H), 3.29–3.11 (m, 2H), 2.76–2.64 (m, 2H), 1.68–1.37 (m, 22H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 171.2, 170.2, 156.0, 153.9, 90.9, 80.8, 74.9, 70.3, 61.0, 60.3, 52.2, 52.1, 50.3, 49.3, 41.0, 39.8, 28.6 (× 3), 28.4 (× 3), 26.1, 19.4; HRMS (ESI, positive) calcd for $C_{24}H_{38}N_2O_9Na$ [$(M+Na)^+$] 521.2469, found 521.2466.

4.1.22. Methyl (1*S**,3a*R**,3b*S**,8a*S**,9a*S**) 4-aza-2-(*tert*-butoxycarbonyl)-9a-((methoxycarbonyl)methyl)-dodecahydro-9-oxa-4-trifluoroacetyl-1*H*-azuleno[2,1-*c*]pyrrole-1-carboxylate (16d)

With the same procedure for the synthesis of **16c′**, **16d** (34.8 mg, 100%) was obtained as a white solid starting from **6d** (34.7 mg, 0.069 mmol) and palladium (10 wt % on carbon, 3.5 mg).

4.1.22.1. Data for 16d. IR (film) 1747, 1692, 1393, 1209, 1016, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ca. 6:4 mixture of rotamers) δ 5.05 (m, 0.4H), 4.45–4.40 (m, 1.6H), 4.33–4.32 (m, 1H), 4.07 (br d, 0.6H), 3.98 (m, 0.4H), 3.89 (m, 0.6H), 3.81–3.74 (m, 3.4H), 3.67–3.62 (m, 4H), 3.19–3.01 (m, 1.4H), 2.88–2.73 (m, 2.6H), 2.22 (m, 1H), 1.85–1.38 (m, 14H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 170.4, 170.0, 153.9, 153.4, 117.7, 90.5, 81.1, 78.3, 67.7, 66.5, 53.3, 52.1, 52.0, 44.7, 37.6, 30.8, 28.2 (× 3), 28.1, 27.4, 20.9; HRMS (ESI, positive) calcd for $C_{22}H_{31}N_2O_8F_3Na$ [$(M+Na)^+$] 531.1925, found 531.1936.

4.1.23. (3*S**,3a*S**,4a*R**,8a*R**,8b*S**)-8-Aza-3a-carboxymethyl-decahydro-1*H*-benzofuro[2,3-*c*]pyrrole-3-carboxylic acid (5c)

With the general procedure shown above, **16c′** (18.1 mg, 0.036 mmol) was deprotected to give the glutamate analog **5c** (12.3 mg, 100%) as a white solid: IR (film) 1715, 1625, 1404, 1255, 1031, 975 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.47 (br s, 1H), 4.25 (s, 1H), 3.90 (t, J = 11.5 Hz, 1H), 3.71 (s, 1H), 3.37 (d, J = 12.5 Hz, 1H), 3.32 (t, J = 9.0 Hz, 1H), 3.22 (s, 1H), 3.15 (d, J = 18.0 Hz, 1H), 3.02 (d, J = 18.0 Hz, 1H), 2.87 (t, J = 12.5 Hz, 1H), 2.11 (d, J = 15.5 Hz, 1H), 1.87 (t, J = 13.0 Hz, 1H), 1.71–1.63 (m, 2H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 174.7, 168.4, 88.7, 72.4, 65.5, 59.7, 49.4, 45.6, 43.4, 37.2, 22.7, 16.5; HRMS (ESI, positive) calcd for $C_{12}H_{19}N_2O_5$ [$(M+H)^+$] 271.1288, found 271.1291.

4.1.24. (1*S**,3a*R**,3b*S**,8a*S**,9a*S**)-4-Aza-9a-carboxymethyl-dodecahydro-9-oxa-1*H*-azuleno[2,1-*c*]pyrrole-1-carboxylic acid (5d)

With the general procedure shown above, **16d** (23.5 mg, 0.046 mmol) was deprotected to give the glutamate analog **5d** (16.2 mg, 98%) as a white solid: IR (film) 1731, 1624, 1417, 1258, 1084 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.59 (dt, J = 7.5, 6.0 Hz, 1H), 4.33 (s, 1H), 3.97 (dd, J = 12.8, 10.0 Hz, 1H), 3.86 (d, J = 4.5 Hz, 1H), 3.44 (br s, 1H), 3.43 (t, J = 9.0 Hz, 1H), 3.28 (dd, J = 12.5, 9.0 Hz, 1H), 3.08 (d, J = 18.0 Hz, 1H), 2.99 (d, J = 18.0 Hz, 1H), 2.94 (dd, J = 13.5, 3.5, 3.5 Hz, 1H), 2.26 (m, 1H), 1.88–1.60 (m, 4H), 1.40 (dd, J = 13.5, 12.3 Hz, 1H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 173.5, 168.0, 89.1, 78.4, 67.9, 65.3, 51.1, 49.4, 47.0, 38.6, 28.3, 26.4, 19.8; HRMS (ESI, positive) calcd for $C_{13}H_{21}N_2O_5$ [$(M+H)^+$] 284.1445, found 184.1449.

4.1.25. Methyl (3*S**,3a*S**,4a*S**,5*S**,6*S**,8a*R**,8b*S**) 2-(*tert*-butoxycarbonyl)-3a-((methoxycarbonyl)methyl)-decahydro-5,6-dihydroxy-8-oxa-1*H*-benzofuro[2,3-*c*]pyrrole-3-carboxylate (17a)

To a stirred solution of **6a** (5.40 mg, 0.0136 mmol) in *tert*-butanol (0.2 mL) at rt was added a solution of NMO (100 mg, 0.85 mmol) in water (0.2 mL) and OsO_4 (3.9 mM in *tert*-butanol, 33 μL, 0.0014 mmol). After 3 h, saturated aqueous $Na_2S_2O_4$ (2 mL) was added, and the mixture was extracted with chloroform (3 × 5 mL). The combined extracts were washed with brine (2 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.5 g, methanol/chloroform = 2:98) to give the diol **17a** (5.9 mg, 100%) as a white solid: IR (film) 3400, 1743, 1693, 1401, 1250, 1167, 1090 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 4.71 (m, 1H), 4.16–4.10 (m, 2H), 4.01 (br s, 1H), 3.92 (br s, 1H), 3.81 (m, 1H), 3.70–3.56 (m, 6H), 3.44 (m, 1H), 3.34–3.27 (m, 1H), 3.08 (m, 1H), 2.97–2.80 (m, 2H), 2.64 (m, 1H), 1.42–1.38 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 170.8, 170.3, 154.1, 91.9, 81.6, 80.8, 79.2, 69.3, 66.3, 64.4, 64.0, 52.1, 51.7, 50.9, 48.6, 40.2, 28.2 (× 3); HRMS (ESI, positive) calcd for $C_{19}H_{29}NO_{10}Na$ [$(M+Na)^+$] 454.1684, found 454.1678.

4.1.26. Methyl (1*S**,3a*R**,3b*R**,7*S**,8*R**,8a*R**,9a*S**) 2-(*tert*-butoxycarbonyl)-9a-((methoxycarbonyl)methyl)-dodecahydro-7,8-dihydroxy-4,9-dioxa-4-trifluoroacetyl-1*H*-azuleno[2,1-*c*]pyrrole-1-carboxylate (17b)

With the same procedure for the synthesis of **17a**, **17b** (2.9 mg, 100%) was obtained as a white solid starting from **6b** (2.7 mg, 6.57 μmol).

4.1.26.1. Data for 17b. IR (film) 3406, 1742, 1694, 1394, 1171, 1101, 1074, 904, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 4.62 (br s, 1H), 4.38 (m, 1H), 4.19 (br s, 1H), 4.13–4.09 (m, 1H), 3.91–3.84 (m, 2H), 3.68–3.64 (m, 6H), 3.32–3.24 (m, 1H), 3.08–3.03 (m, 1H), 2.98–2.90 (m, 2H), 2.60–2.51 (m, 2H), 1.92–1.86 (m, 1H), 1.80–1.76 (m, 1H), 1.42–1.38 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 171.1, 170.2, 153.8, 91.2, 85.5, 86.0, 80.6, 77.2, 71.8, 68.6, 67.7, 52.9, 52.1, 51.8, 49.1, 39.3, 34.7, 28.2 (×3); HRMS (ESI, positive) calcd for $C_{20}H_{31}NO_{10}Na$ [$(M+Na)^+$] 468.1840, found 468.1840.

4.1.27. Methyl (3*S**,3a*S**,4a*S**,5*S**,6*S**,8a*R**,8b*S**) 8-aza-2,8-bis(*tert*-butoxycarbonyl)-3a-((methoxycarbonyl)methyl)-decahydro-5,6-dihydroxy-2-methyl-1*H*-benzofuro[2,3-*c*]pyrrole-3-carboxylate (17c′)

With the same procedure for the synthesis of **17a**, **17c′** (34.5 mg, 100%) was obtained as a white solid starting from **6c′** (32.0 mg, 0.065 mmol).

4.1.27.1. Data for 17c'. IR (film) 3412, 1744, 1698, 1396, 1367, 1170, 1133, 1057, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ca. 7:3 mixture of rotamers) δ 4.70–4.62 (m, 1H), 4.48 (br s, 0.3H), 4.39 (br s, 0.7H), 4.24 (m, 1H), 3.96 (br s, 1H), 3.89–3.81 (m, 1H), 3.73 (br s, 3H), 3.67–3.56 (m, 4H), 3.23 (m, 1H), 3.07–2.99 (m, 1H), 2.68–2.65 (m, 2H), 2.55–2.50 (m, 1H), 2.26 (br s, 1H), 1.47–1.44 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 170.8, 170.2, 155.7, 153.5, 90.6, 81.4, 80.7, 79.0, 70.5, 66.4, 57.7, 52.3, 52.1, 48.8, 47.6, 46.8, 43.2, 38.8, 28.2 (×3), 28.1 (×3); HRMS (ESI, positive) calcd for $C_{24}H_{38}N_2O_{11}Na$ [$(M+Na)^+$] 553.2368, found 553.2366.

4.1.28. Methyl (1*S**,3a*R**,3b*R**,7*S**,8*R**,8a*R**,9a*S**) 4-aza-2-(*tert*-butoxycarbonyl)-9a-((methoxycarbonyl)methyl)-dodecahydro-7,8-dihydroxy-9-oxa-4-trifluoroacetyl-1*H*-azuleno[2,1-*c*] pyrrole-1-carboxylate (17d)

With the same procedure for the synthesis of **17a**, **17d** (35.1 mg, 100%) was obtained as a white solid starting from **6d** (33.1 mg, 0.065 mmol).

4.1.28.1. Data for 17d. IR (film) 3413, 1744, 1690, 1395, 1210, 1144, 1049, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ca. 6:4 mixture of rotamers) δ 5.28 (s, 0.6H), 5.07 (m, 0.4H), 4.49–4.31 (m, 3.5H), 4.00–3.89 (m, 2.5H), 3.75–3.61 (m, 7H), 3.29–2.77 (m, 4H), 2.35–1.80 (m, 4H), 1.45 (br s, 5.4H), 1.39 (br s, 3.6H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 170.5, 170.0, 154.2, 153.6, 115.6, 91.3, 81.7, 78.0, 73.4, 69.7, 68.0, 67.0, 52.4, 52.3, 50.3, 39.6, 37.9, 29.3, 28.4, 28.3 (×3); HRMS (ESI, positive) calcd for $C_{22}H_{31}N_2O_{10}F_3Na$ [(M+Na)$^+$] 563.1823, found 563.1827.

4.1.29. (3*S**,3a*S**,4a*S**,5*S**,6*S**,8a*R**,8b*S**)-8-Aza-3a-carboxymethyl-decahydro-5,6-dihydroxy-1*H*-benzofuro[2,3-*c*]pyrrole-3-carboxylic acid (1c)

With the general procedure shown above, **17c′** (20.3 mg, 0.038 mmol) was deprotected to give the glutamate analog **1c** (13.9 mg, 97%) as a white solid: IR (film) 3300, 1714, 1627, 1404, 1256, 1101, 1000 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.44 (br s, 1H), 4.25 (s, 1H), 4.18 (br s, 1H), 3.98 (dd, J = 7.8, 3.5 Hz, 1H), 3.89 (dd, J = 12.8, 10.0 Hz, 1H), 3.85 (d, J = 2.5 Hz, 1H), 3.36 (t, J = 8.5 Hz, 1H), 3.24–3.12 (m, 3H), 3.22 (t, J = 13.5 Hz, 1H), 2.99 (d, J = 17.5 Hz, 1H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 174.7, 168.4, 89.1, 77.8, 65.4, 64.9, 62.8, 57.4, 48.3, 45.6, 41.2, 37.1; HRMS (ESI, positive) calcd for $C_{12}H_{19}N_2O_7$ [(M+H)$^+$] 303.1187, found 303.1190.

4.1.30. (1*S**,3a*R**,3b*R**,7*S**,8*R**,8a*R**,9a*S**)-4-Aza-9a-carboxymethyl-dodecahydro-7,8-dihydroxy-9-oxa-1*H*-azuleno[2,1-*c*] pyrrole-1-carboxylic acid (1d)

With the general procedure above, **17d** (23.3 mg, 0.043 mmol) was deprotected to give the glutamate analog **1d** (16.7 mg, 100%) as a white solid: IR (film) 3350, 1718, 1635, 1405, 1227, 1097, 991 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.37 (t, J = 5.5 Hz, 1H), 4.31 (s, 1H), 4.13 (br s, 1H), 3.98 (dd, J = 13.0, 10.0 Hz, 1H), 3.96 (d, J = 5.5 Hz, 1H), 3.92 (d, J = 5.5 Hz, 1H), 3.46 (t, J = 8.5 Hz, 1H), 3.31 (d, J = 12.5 Hz, 1H), 3.31 (t, J = 13.0 Hz, 1H), 3.16 (m, 1H), 3.11 (d, J = 18.0 Hz, 1H), 3.00 (d, J = 18.0 Hz, 1H), 1.98–1.97 (m, 2H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 173.5, 168.0, 88.8, 81.3, 74.8, 71.3, 65.5, 65.2, 51.1, 47.0, 44.0, 38.7, 29.5; HRMS (ESI, positive) calcd for $C_{13}H_{21}N_2O_7$ [(M+H)$^+$] 317.1343, found 317.1352.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2010.04.044.

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