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C3′-*cis*-Substituted carboxycyclopropyl glycines as metabotropic glutamate 2/3 receptor agonists: Synthesis and SAR studies

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Abstract—The synthesis of a series of C3′-*cis*-substituted carboxycyclopropyl glycines bearing a wide variety of functional groups is described, and the structure–activity relationship for this series as agonists of group II metabotropic glutamate receptors is reported.

1. Introduction

Most of the excitatory synapses in the central nervous system use the amino acid glutamate (Glu, **1**) as a chemical messenger (Fig. 1).[1] Glutamate mediates its effects via two distinct receptor families, the ionotropic Glu (iGlu) receptors and metabotropic Glu (mGlu) receptors. iGlu receptors are homomeric or heteromeric ligand-gated, cation-specific ion channels, which are classified further into three groups, which are selectively activated by the agonists α-amino-3-hydroxy-5-methylisoazolepropionic acid (AMPA), *N*-methyl-D-aspartate (NMDA), and kainate, from which they take their names.[2] On the other hand, the mGlu receptors are coupled to GTP-binding proteins (G-proteins) to activate systems that generate second messengers within the cell. The mGlu receptor family comprises of eight different receptor subtypes and has been separated into three groups based on their sequence homology, second messenger transduction mechanisms, and pharmacological properties. Group I mGlu receptors (mGlu1, mGlu5) are positively coupled to phospholipase C activation, whereas groups II (mGlu2, mGlu3) and III (mGlu4, mGlu6-8) are negatively coupled to adenylate cyclase.[3] The search for potent and selective ligands as pharmacological tools to understand the functions of the different metabotropic glutamate receptor subtypes has been an area of intense research over the last decade.[4] Recent advances in molecular biology, pharmacology, and medicinal chemistry of the metabotropic glutamate

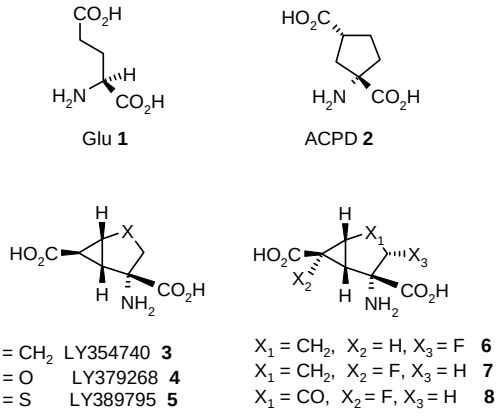

Figure 1. Glutamate and glutamate receptor agonists.

Keywords: Carboxycyclopropyl glycine; CCG; Metabotropic glutamate 2/3 receptor.
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receptors have led to new therapeutic opportunities. In this sense, it has been proposed that agonists for group II and/or group III mGlu receptors might be useful for the treatment of brain disorders and diseases, such as ischemia, anxiety, drug addiction, and schizophrenia.[5]

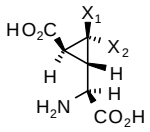
In this context, the first agonist shown to be selective for mGlu receptors compared to iGlu receptors was (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid (ACPD) **2**.[6] Although lacking in subtype selectivity, (1*S*,3*R*)-ACPD has served as a template for the design of new and more selective group II mGlu receptor ligands.[7] On the other hand, (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) **3**, a constrained glutamic acid analog, has been described as a nanomolar potent, highly selective, and orally active group II mGlu receptor agonist with anxiolytic and antipsychotic properties.[8] More recently, some closely related analogs to LY354740 have also been reported as potent and selective group II mGluR agonists. These include heterobicyclic compounds as the 2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid (LY379268) **4** and the 2-thia-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid (LY389795) **5**[9] and the analogs incorporating fluorine atoms at the C3 and C6 positions **6**–**8**[10] (Fig. 1).

Another class of conformationally constrained analogs of glutamate, the 2-(carboxy-cyclopropyl)glycines (CCGs), have also been described as ligands for mGlu receptors. Thus, (2*S*,1′*S*,2′*S*)-2-(2′-carboxycyclopropyl)glycine (L-CCG-I, **9**) is a potent and rather selective agonist for group II mGlu receptors.[11] The C3-difluoro derivative L-F2CCG-I (**10**) is a more potent agonist at mGlu2, although activity at other Glu receptors has not been reported,[12] while the C3′-substituted carboxy derivative DCG-IV **11** displays potent group II mGlu and NMDA receptor agonist activities, as well as group III antagonist effects.[13]

Introduction of a methoxymethyl substituent at the C3 position led to the *cis*-MCG-I and *trans*-MCG-I agonists **12** and **13**.[14] By contrast, the stereoselective introduction of bulky and hydrophobic groups at C3, as in the case of the phenyl substituted PCCG-4 **14**[15] or in the xanthenylmethyl and xanthenylethyl substituted derivatives **15** and **16**, results in group II antagonism.[16] Moreover, it has been described that substitution at the 2 position of L-CCG-I also converts it into group II mGlu antagonists, a prominent example being the nanomolar potency antagonist LY341495 (**17**, Fig. 2).[17]

In our search for more potent and selective group II mGlu agonists, we recently reported that the C3′-*cis*-methyl substituted carboxycyclopropyl glycine **18**, designed as the ring opened version of LY354740, is also a potent and selective group II mGlu receptor agonist with anxiolytic properties.[18] Moreover, we found that introduction of a hydroxymethyl group at the C3′-*cis*-position in analog (+)-**19** results in a potent group II and group III (mGluR6/8) agonist.[19] (Fig. 3). These findings prompted us to explore further the substitution at the C3′-*cis* position of these carboxycyclopropyl glycines, with the aim of finding the structural requirements at this position for Group II metabotropic glutamate receptors selective agonism. Here, we describe the synthesis and structure–activity relationship studies of this family of compounds.

Agonists



X_1	X_2		
H	H	L-CCG-I	**9**
F	F	L-F2CCG-I	**10**
H	CO_2H	DCG-IV	**11**
H	CH_2OMe	cis-MCG-I	**12**
CH_2OMe	H	trans-MCG-I	**12**

Antagonists

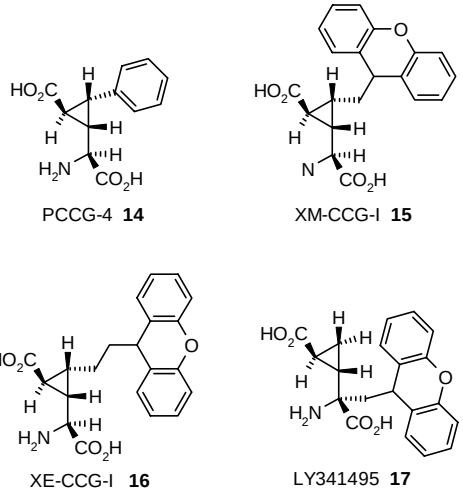


Figure 2.

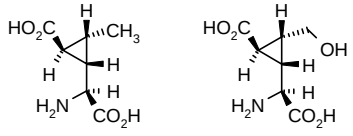


Figure 3.

2. Chemistry

Our goal was to synthesize the C3′-*cis*-substituted CCGs as racemic mixtures for SAR studies. This is supported by the fact that the activity of C3′-*cis*-hydroxymethyl CCG resides only in the enantiomer (+)-**19**, but biological results for the racemic mixture provided a reasonable estimate of its potency (Table 1). In a

Table 1. mGlu receptor affinity, potency, and selectivity C3′-*cis*-substituted CCGs reported in nM values

Compound	C3′-*cis*-Substituent	K_i[a]			EC_{50}[b]	
		mGlu2	mGlu3	mGlu8	mGlu2	mGlu3
18	Me	87.4	162.2	17,087	8.4	38.7
(±)-**19**	CH_2OH	66.1	7.9	4161	5.2	11.5
(+)-**19**	CH_2OH	23	3		4	7
(−)-**19**	CH_2OH	>10,000	>10,000		>1,00,000	>1,00,000
23a	$CH_2OCONHEt$	660	292	34,343	139	3440
23b	$CH_2OCONHPh$	276	71	20,817	70	52
25a	CH_2SH	213	254	4439	47	59[c]
25b	CH_2SPh	602	466	5136	94	1270
26b	CH_2SO_2Ph	4201	2547	7095[d]	1050	2320
28	CH_2N_3	418 [d]	315 [d]	13,280[d]	85	n.t.[e]
32a	$CH_2NHCOMe$	2901	2855	50,680	363	n.t.[e]
32b	$CH_2NHCOPh$	1245[d]	1315 [d]	n.t.[e]	342	2840
33a	$CH_2NHCONHEt$	1236 [d]	678 [d]	11,960 [d]	2800	7200
33b	$CH_2NHCONHPh$	530	115	12,313	121	346
34	CH_2NHSO_2Ph	294 [d]	350 [d]	6808 [d]	2080	6440
35	CH_2NH_2	10,830 [d]	2354 [d]	55,630 [d]	1710	5130
38a	CONHMe	4398 [d]	1687 [d]	27,380 [d]	1310	600
38b	CONHPh	2641	2745 [d]	46,990	2080	6440
40	CN	170	50	26,793	189	64
45	CH_2CH_3	1722	3258	6736[d]	167	3610
52a	CH_2CH_2OH	2649 [d]	4540 [d]	53,190[d]	3060	12,655

[a] Displacement of specific [3H]341495 binding to membranes expressing recombinant human mGlu2, mGlu3, or mGlu8 receptors, as described in Refs. 28a and 30. Unless otherwise noted, reported data are mean values from at least two independent determinations. Typical error limits (±20%).
[b] Functional agonist activity in cells expressing recombinant human mGlu2 or mGlu3 receptor subtypes, as described in Ref. 8b. Reported data are mean values from at least two independent determinations.
[c] Functional antagonist activity (IC_{50}, nM).
[d] $n = 1$.
[e] n.t.: not tested.

retrosynthetic analysis and considering the synthesis of the racemic C3′-*cis*-hydroxymethyl CCG (±)-**19**,[19] its precursor **20** is a versatile intermediate for the preparation of most of our target molecules in this series. Thus, transformation of the hydroxy group into different heteroatom-containing functionalities would allow a rapid expansion of the SAR at this position (Fig. 4). Moreover, the masked aldehyde present in **21**, a precursor to **20**, would allow the preparation of alkyl substituted CCGs at the C3′-*cis*-position through a Wittig olefination, reduction sequence.

The preparation of intermediate **20** has already been described by our group.[19] Treatment of **20** with ethyl or phenylisocyanate in pyridine led to the corresponding protected C3′-carbamoyloxymethyl derivatives **22**. Basic hydrolysis, followed by the N-Boc deprotection using 1 N HCl in ethyl acetate, led, after ion-exchange chromatography, to compounds **23** (Scheme 1). Alternatively, the reaction of **20** with thioacetic acid under Mitsunobu conditions,[20] or the treatment with diphenyldisulfide and tributylphosphine in THF[21] afforded the protected thiomethyl derivatives **24**, which led to compounds **25** after hydrolysis under acidic conditions. Oxidation of the protected thio derivative **24b** with

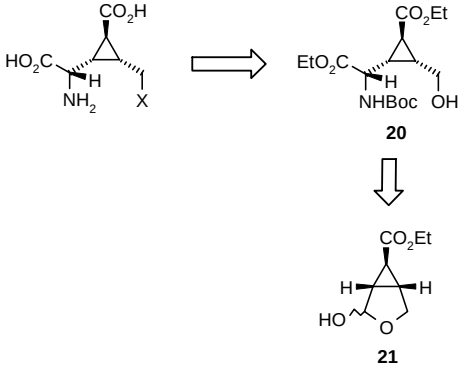
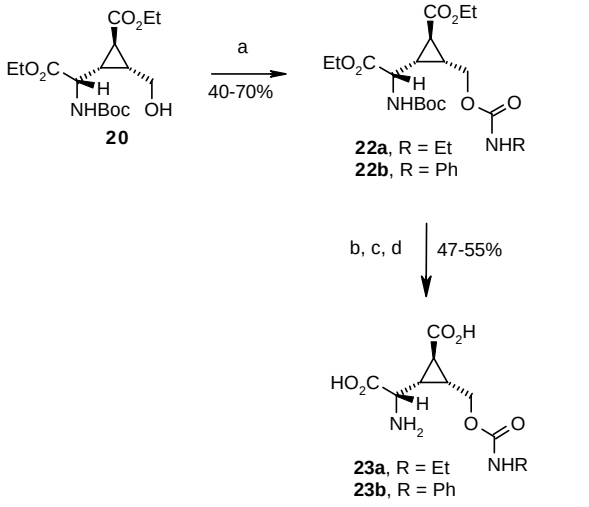
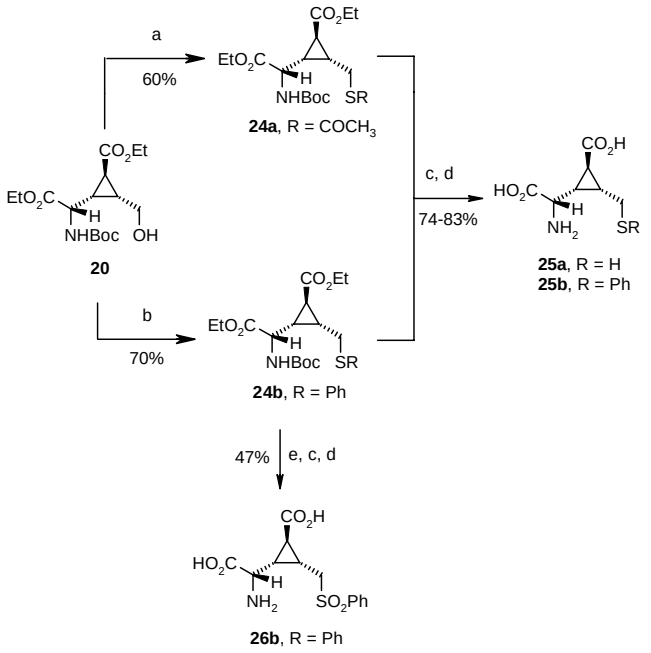


Figure 4. Retrosynthesis of C3′-*cis*-substituted CCGs.



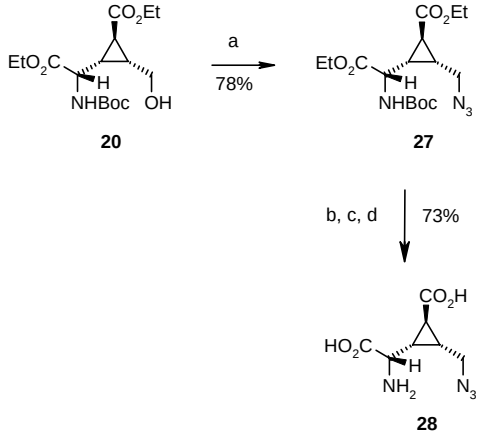
Scheme 1. Reagents and condition: (a) RNCO, Py, rt; (b) 1 N LiOH, THF; (c) 1 N HCl/EtOAc; (d) Dowex 50 × 8 − 100.



Scheme 2. Reagents and condition: (a) CH_3COSH, Ph_3P, DEAD, THF; (b) Ph_2S_2, Bu_3P, THF, rt; (c) 6 N HCl, reflux; (d) Dowex $50 \times 8 - 100$; (e) MCPBA, CH_2Cl_2, 0 °C.

m-CPBA gave rise, after hydrolysis, to the sulfone derivative **26b** (Scheme 2).

To prepare a series of nitrogen-containing analogs, the azidomethyl substituted intermediate **27** was synthesized in good yield from alcohol **20** by the Mitsunobu reaction using diphenylphosphorylazide as a source of azide.[22] The azidomethyl CCG **28** was obtained by deprotection of **27** under the standard hydrolysis conditions (Scheme 3). Intermediate **27** has proven to be pivotal for the preparation of other CCGs bearing different nitrogen-linked functionalities. Thus, catalytic hydrogenation of **27** in the presence of acid anhydrides gave rise to the corresponding protected amides **29** (Scheme 4). In an analogous manner, hydrogenation in the presence of other electrophiles, such as isocyanates and sulfonyl



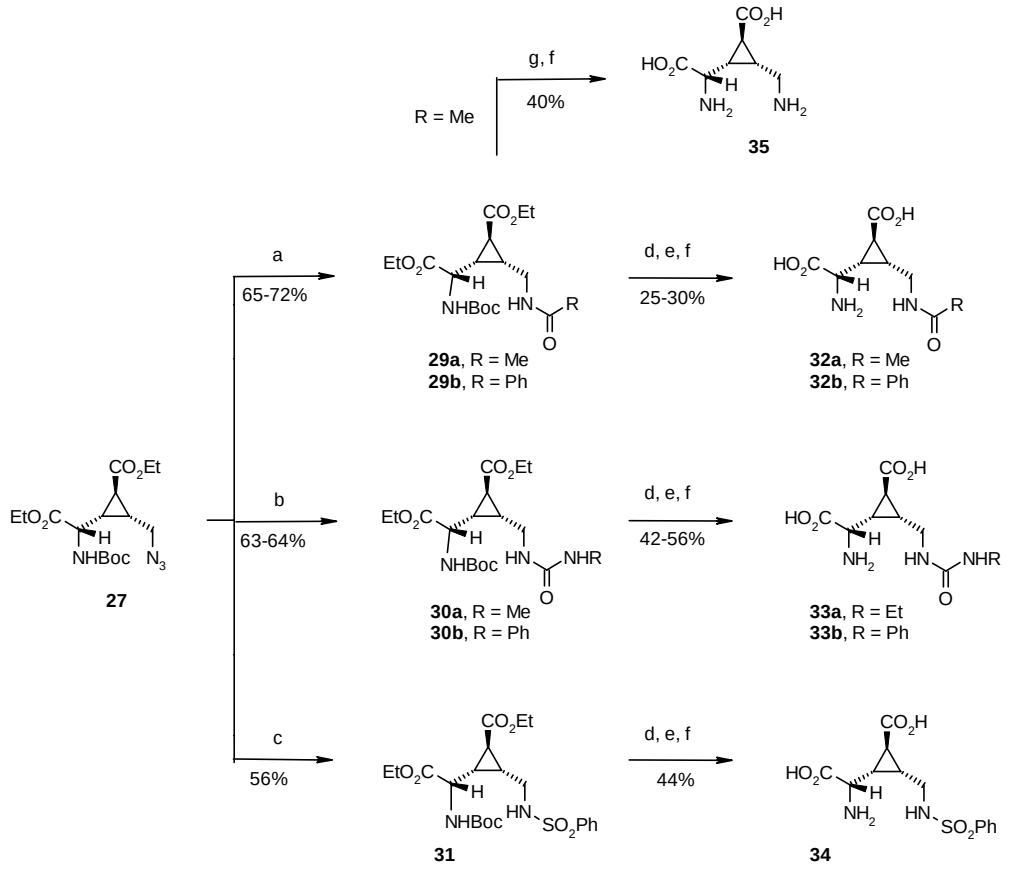
Scheme 3. Reagents: (a) DPPA, Ph_3P, DEAD, THF; (b) 1 N LiOH, THF; (c) 1 N HCl/EtOAc; (d) Dowex.

chlorides, afforded the protected CCGs **30** and **31**, respectively. In these cases, it was necessary to modify the reaction conditions and the reduction was carried out using platinum oxide (IV) as catalyst in ethyl acetate. Application of standard hydrolysis conditions to **29**, **30**, and **31** gave rise to the azamethyl CCG derivatives **32**, **33**, and **34**, respectively. Hydrolysis under acidic conditions of **29a** afforded the C3′-*cis*-aminomethyl CCG **35** (Scheme 4).

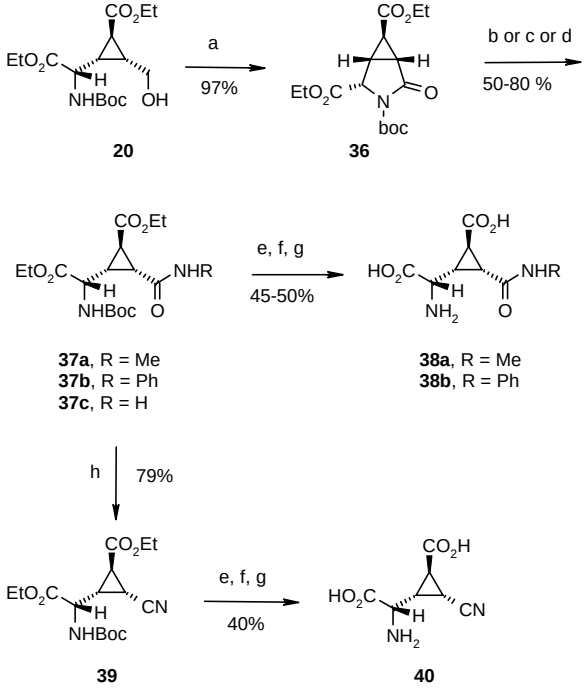
Hydroxymethyl intermediate **20** has also been used as a precursor to a series of CCGs having a carboxamide functionality at the C3′ position. The synthesis of these compounds was achieved through a synthetic sequence involving Jones oxidation of **20** to the corresponding pyroglutamate analog **36**[23] and its subsequent reaction with different amines. The reaction conditions for the second step depend on the nature of the amine. In the case of aliphatic primary amines, the reaction takes place in THF in the presence of catalytic potassium cyanide to give protected carboxamides **37**.[24] However, addition of aromatic amines to **36** required the presence of aluminum trichloride to effect this conversion.[25] Treatment of the protected carboxamides **37** under the standard hydrolysis conditions afforded the corresponding CCGs **38**. The analog **37c** was treated further with trifluoroacetic anhydride to produce cyano derivative **40** after hydrolysis of the corresponding protected analog **39** (Scheme 5).

As mentioned above, the preparation of the ethyl substituted compound **45** was carried out starting from lactol **21**, which was converted into aldehyde **43** in three steps by the Wittig reaction with methyltriphenylphosphonium bromide, followed by catalytic hydrogenation of the carbon–carbon double bond and further oxidation of alcohol **42** under Swern[26] conditions in good overall yield. The Strecker reaction on aldehyde **43** led to a mixture of diastereomeric aminonitriles **44** after acetylation. From this mixture of diasteromeric aminonitriles, the isomer **44b** was crystallized from diethyl ether. Its relative configuration at the amine-bearing carbon was shown by X-ray diffraction to be *R*, as indicated in Figure 5. Therefore, the soluble *S* diastereoisomer, **44a**, was subjected to acid hydrolysis to give the desired aminoacid **45** (Scheme 6).

With the aim of getting information on the optimal distance for the hydroxy group and other functionalities, relative to the cyclopropyl ring, a synthetic route for the synthesis of the hydroxyethyl analog **52a** was developed. The key step is the cyclopropanation of the 2-cyclopenten-1-one **46** with the Payne ylide,[27] which led to the bicyclic intermediate **47** in good yield and with the desired stereochemistry. Treatment of **47** under Baeyer–Villiger conditions gave rise to the lactone **48**, which was reduced with DIBAL-H to afford lactol **49** and subjected further to the Strecker reaction giving rise to a 1:1 mixture of diastereomeric aminonitriles **50**, which were separated by chromatography (Scheme 7). After conversion of both isomers into the corresponding hydroxyethyl-protected compounds, **51a** and **51b**, configuration of the aminoacid center was determined through their



Scheme 4. Reagents and condition: (a) H_2, 10% Pd/C, EtOH, $(RCO)_2O$; (b) H_2, PtO_2, EtOAc, RNCO; (c) H_2, PtO_2, EtOAc, $PhSO_2Cl$; (d) 1 N LiOH, THF; (e) 1 N HCl/EtOAc; (f) Dowex 50 × 8 – 100 or propylene oxide, MeOH; (g) 2 N HCl, 60 °C.



Scheme 5. Reagents and condition: (a) Jones reagent, acetone; (b) $MeNH_2$, KCN, ultrasound, THF; (c) $PhNH_2$, $AlCl_3$, CH_2Cl_2; (d) NH_3, $AlMe_3$, CH_2Cl_2; (e) 1 N LiOH, THF; (f) 1 N HCl/EtOAc; (g) Dowex 50 × 8–100; (h) TFAA, Py.

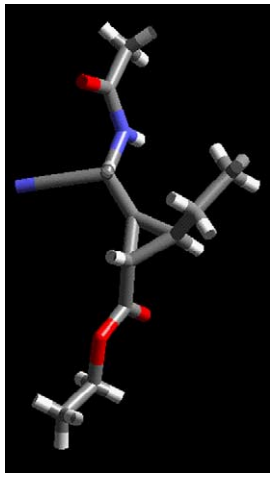
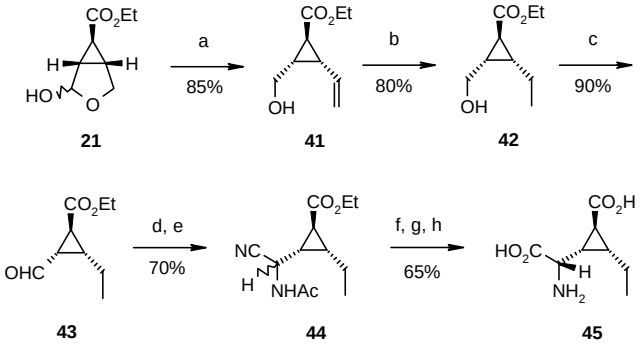
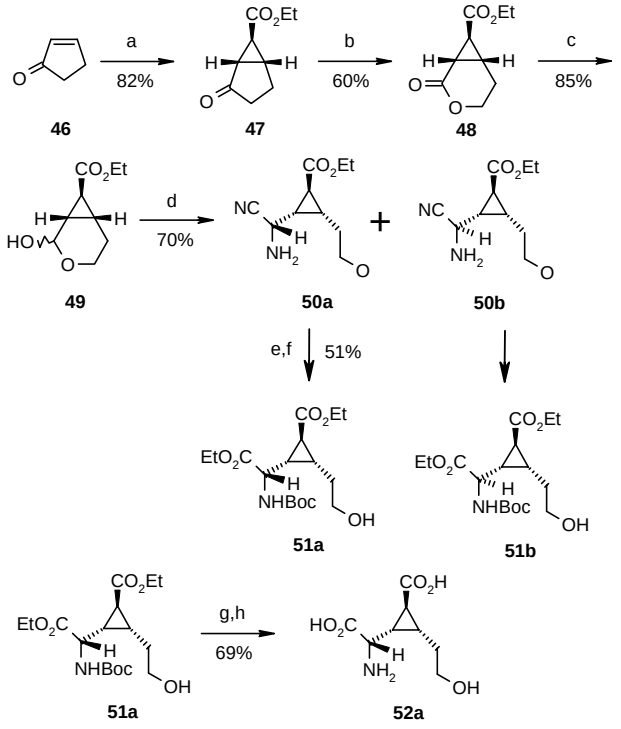


Figure 5. X-ray structure of **44b**.

oxidation with PDC to afford the lactams **53a** and **53b**. NOE experiments were performed with both diastereomers by irradiation of H2, indicating that the lactam **53a** presents a NOE effect between this H2 and the H1, and no effect with H7. However, in the lactam **53b** the NOE effect between H2 and H7 is much higher than in **53a**, indicating that in the lactam **53b** the H2 and H7 are in the same side of the ring system (Fig. 6). Hydro-



Scheme 6. Reagents and condition: (a) CH_3PPh_3Br, KHMDS, THF; (b) H_2, Pd/C; (c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; (d) NH_4Cl, KCN; (e) AcCl, $^iPr_2EtN$, CH_2Cl_2; (f) recrystallization; (g) 1 N HCl, reflux; (h) propylene oxide, MeOH.



Scheme 7. Reagents and condition: (a) $EtO_2CCH_2SMe_2Br$, DBU, $CHCl_3$; (b) MCPBA, CH_2Cl_2; (c) DIBAL-H, THF, −78 °C (d) NH_4Cl, KCN, MeCN, ultrasound; (e) satd HCl/EtOH, H_2O; (f) Boc_2O, $NaHCO_3$, dioxane; (g) 1 N HCl, reflux; (h) propylene oxide, MeOH.

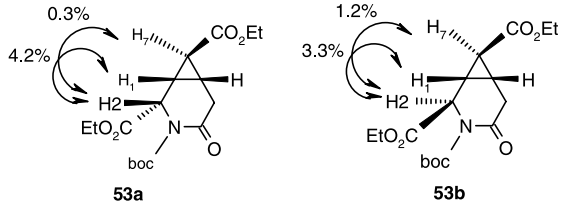


Figure 6.

lysis of the intermediate with the desired relative stereochemistry **51a** with 1 N HCl was carried out, leading to the C3′-hydroxyethyl CCG **52a** after the treatment with propylene oxide (Scheme 7).

3. Biochemical methods

Test compounds were evaluated for their ability to displace ^{3}H-LY341495 from membranes expressing individual recombinant human mGlu2, mGlu3, or mGlu8 receptor subtypes.[28a,29,30] The K_i values were calculated from the IC_{50} values employing the Cheng–Prusoff equation.[31] Test compounds were also evaluated for their ability to influence the production of second messengers in AV12-664 cells co-expressing both GLAST (a recombinant glutamate transporter to minimize constituent glutamate activity) and recombinant human mGlu2 or mGlu3 receptor.[8b]

4. Results and discussion

In our previous studies on the C3′-*cis*-substituted carboxycyclopropyl glycines, we described the C3′-*cis*-methyl substituted CCG **18** as a potent and selective group II mGlu receptor agonist, and its hydroxymethyl substituted analog (+)-**19**, which turned out to be an equally potent group II and group III (mGluR6/8) agonist.[19] Considering these results, we decided to explore the effect of a variety of substituents at this position on their affinity (displacement of [3H]LY341495)[28] and functional activity (influence on cAMP formation in cells expressing recombinant human mGlu2 or mGlu3 receptors at group II mGlu receptors).[29] Since (+)-**19** also shows affinity for the mGlu8 receptor, compounds were also tested in a binding assay using membranes from RGT cells expressing human mGluR8.[30] All new compounds were prepared and tested as racemic mixtures. The results are given in Table 1.

C3′-*cis*-substituted CCGs **23**, **25**, **26**, **28**, **32**–**35**, **38**, **40**, **45**, and **52** all displaced [3H]341495 binding to both mGlu2 and mGlu3 receptors, though with generally lower affinity than those observed for **18** and (+)-**19**, though several of them maintain sub-micromolar affinity for these targets. Affinity for mGlu8 was also observed, albeit generally weak, with K_i values in the micromolar potency range.

Replacement of the methyl group of analog **18** (mGlu2 K_i = 87.4 nM, mGlu3 K_i = 162.2 nM) with a sterically comparable but electron-withdrawing cyano group results in full agonist activity at both receptors and a slight loss of binding affinity at mGlu2 (K_i = 170 nM) and a modest increase in affinity at mGlu3 (K_i = 50 nM) for analog **40**. On the other hand, extending the methyl group of **18** to ethyl (compound **45**) or the hydroxymethyl group of (+)-**19** to hydroxyethyl (compound **52a**) results in a substantial decrease in binding affinity and agonist potency for each of these analogs at both mGlu2 and mGlu3, suggesting that the beneficial effect of hydroxyl group substitution in compound (+)-**19** may be due to a specific polar interaction with a receptor site residue adjacent to the C3′ position of bound CCGs. Replacement of the hydroxyl functionality of (+)-**19** with sulfhydryl results in some loss affinity and agonist potency at mGlu2 for **25a** (mGlu2 K_i = 213 nM, EC_{50} = 47 nM). However, while this analog maintains

mGlu3 affinity (K_i = 254 nM) it produces a full antagonist response against this target (IC_{50} = 59 nM). Replacement of the hydroxyl functionality of (+)-**19** by a polar uncharged azido group (compound **28**) results in full agonist activity at both mGlu2 and mGlu3 receptors with some loss potency, while introduction of a basic (CH_2NH_2) group results in a significant loss of both affinity and agonist potency for **35** (mGlu2 K_i = 10,830 nM, mGlu2 EC_{50} = 1710 nM).

Given these results and the known conversion of agonist to antagonist pharmacology by incorporating large lipophilic substituents onto monocyclic[15–17] carboxycyclopropyl glycine derivatives, we were interested in exploring limits of agonist activity within this series. Replacement of the sulfhydryl in **25a** with thiophenyl (**25b**) results in loss of affinity at both mGlu2 and mGlu3, but also in maintenance of full agonist activity at each of these targets. In this case, the antagonist effect observed for **25a** at mGlu3 is reversed by the addition of a large lipophilic phenyl substituent. This profile is maintained, though with additional loss in potency, in the phenylsulfonyl analog **26b**. Similarly, carbamate analogs of (+)-**19** (**23a** and **23b**), while less potent than (+)-**19**, maintain submicromolar binding affinity and agonist potency at both mGlu2 and mGlu3, with the sterically larger phenyl carbamate analog **23b** demonstrating potency superior to that of ethyl carbamate variant **23a**. A parallel trend is also observed for ethyl and phenyl ureas **33a** and **33b**. Amide pair **32a/32b**, while maintaining full agonist activity in both mGlu2 and mGlu3-expressing cells, does not clearly differentiate from one another as in the aforementioned ethyl and phenyl urea/carbamate pairs. In all cases, acylation or sulfonylation of the primary amino group of **35** provides compounds with generally superior affinity and agonist potency at mGlu2 and mGlu3 receptors. We were interested in whether amide variants of DCG-IV (**11**)[13] might also retain mGlu 2/3 receptor agonist activity. Indeed, both the *N*-methyl and *N*-phenyl amide analogs of **11** (**38a** and **38b**, respectively) retain full agonist activity in cells expressing each of these receptors, though with substantial loss in potency.

Finally, some of the analogs in this account display modest subtype selectivity between mGlu2 and mGlu3. Thus, compounds **23b** and **33b** demonstrate 4-fold selectivity for mGlu3 over mGlu2 based on receptor affinity, but this difference is not maintained in the whole cell functional assay. In contrast, **40** demonstrates 3-fold selectivity for mGlu3 in both the binding and functional assays, and **25a**, while possessing equivalent affinity for both mGlu2 and mGlu3, produces agonist responses in cells expressing the mGlu2 and reverses agonist responses (i.e., is an antagonist) in cells expressing mGlu3.

In conclusion, we have described a series of C3′-*cis*-substituted CCGs bearing a wide variety of functional groups as potent group II mGlu receptor agonists. Most of the compounds in this series have been synthesized from a common and versatile synthetic intermediate **20**. The binding affinity for the group II mGlu receptors depends on the nature of the C3′-substituent, with some of the described analogs displaying mGlu3 subtype selectivity and one, **25a**, possessing a unique mGlu2 agonist/mGlu3 antagonist profile. In contrast to the observed conversion of CCG-based agonists to antagonists upon addition of large aryl or alkylaryl substituents at the C3′ position,[15,16] agonist activity for mGlu2/3 receptors is maintained for nearly all of the C3′-substituted analogs evaluated, regardless of the size of this substituent. It is possible that the presence of certain heteroatom combinations within the C3′-substituent chain (amides, carbamates, and ureas) is responsible for maintaining the agonist response in these analogs, though the molecular basis for this effect remains unclear.

5. Experimental

5.1. General

All solvents and reagents were purchased from commercial sources and used as received, unless otherwise indicated. ^1H NMR and ^{13}C NMR data were recorded on a Bruker AC-200P (200 MHz) or Brucker AM-300 (300 MHz) spectrometer. Chemical shifts are reported as ppm (δ), relative to TMS as internal standard. Analytical TLC was performed on Merck TLC glass plates precoated with F_{254}silica gel 60 (UV, 254 nm and phosphomolybdic acid). Chromatographic separations were performed by using 230–400 mesh silica gel (Merck). Mass spectra were obtained on an Agilent 1100 series instrument. High resolution mass spectra (HRMS) were acquired on a Thermo Electron LTQ-FT Fourier Transform Ion Cyclotron Resonance mass spectrometer with an instrument resolution of 2,00,000 for *m*/*z* 500, using external calibration. Sample ionization was achieved using electrospray and measurement of pseudo-molecular ion clusters $[M+H]^+$ or $[M+Na]^+$ was carried out. Infrared spectra (IR) were recorded on a Perkin-Elmer 1310 spectrophotometer. Melting points were measured with a capillary melting point apparatus and are uncorrected.

5.2. General hydrolysis procedure A

A 2.5 M solution of $LiOH{\cdot}H_2O$ (40 equiv) in H_2O was added to a 0.1 M solution of the corresponding protected aminoacid in THF and the mixture was stirred at room temperature overnight. EtOAc was added, the organic layer was separated, and the aqueous layer was washed with EtOAc (3×). The aqueous layer was acidified to pH 1 with 1 N HCl and extracted in EtOAc (5×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was dissolved in a 1 N solution of HCl in EtOAc and the solution (0.12 N) was stirred overnight at room temperature. It was then concentrated under vacuum and the resulting solid was washed with Et_2O. The product amino acids were isolated as zwitterions by ion-exchange chromatography.

5.3. General hydrolysis procedure B

A 2.5 M solution of $LiOH{\cdot}H_2O$ (40 eq) in H_2O was added to a 0.1 M solution of the corresponding pro-

tected aminoacid in THF and the mixture was stirred at room temperature overnight. EtOAc was added, the organic layer was separated, and the aqueous layer was washed with EtOAc (3×). The aqueous layer was acidified to pH 1 with 1 N HCl and extracted in EtOAc (5×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was dissolved in a 1 N solution of HCl in EtOAc and the solution (0.12 N) was stirred overnight at room temperature. It was then concentrated under vacuum and the resulting solid was washed with Et_2O. The resulting hydrochloride salt of the title compound was dissolved in methanol (0.2 M) and propylene oxide (25 mL/mmol) was added. The mixture was stirred overnight and the precipitate was filtered and washed with diethyl ether to give the product amino acid as zwitterion.

5.4. General hydrolysis procedure C

A 0.1 M solution of the corresponding protected aminoacid in 6 N HCl was heated under reflux for 16 h. The solvent was then removed under vacuum and the resulting solid was washed with diethyl ether to give the corresponding hydrochloride salt. After purification by ion-exchange chromatography, the final aminoacids were isolated as zwitterions.

5.5. General procedure for the preparation of 22

Two equivalents (2.8 mmol) of the corresponding isocyanate were added to a 0.1 M solution of **20** (500 mg, 1.4 mmol) in pyridine at room temperature and the mixture was stirred for two days. EtOAc and H_2O were added, the organic layer was separated, and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with H_2O (5×), dried over $MgSO_4$, filtered, and concentrated under vacuum. The corresponding glycinates **22** were purified by column chromatography using a 2:1 hexane/EtOAc mixture as eluent.

5.5.1. Ethyl (2*SR*,1′*SR*,2′*RS*,3′*RS*)-*N*-(*tert*-butoxy-carbonyl)-2-[2′-(ethoxycarbonyl)-3′-ethylcarbamoyl-oxy-methylcyclopropyl] glycinate 22a. Yield: 40%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 5.5 (d, J = 8 Hz, 1H), 5.2 (br s, 1H), 4.4 (dd, J = 11, 4 Hz, 1H), 4.2–4.0 (m, 6H), 3.1 (m, 2H), 2.0–1.7 (m, 3H), 1.4 (s, 9H), 1.3–1.1 (m, 6H), 1.0 (t, J = 7 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 172.4, 170.7, 155.7, 155.0, 79.8, 61.5, 60.6, 51.8, 35.5, 28.8, 27.9, 25.5, 22.9, 14.9, 13.8 ppm.

5.5.2. Ethyl (2*SR*,1′*SR*,2′*RS*,3′*RS*)-*N*-(*tert*-butoxy-carbonyl)-2-[3′-phenylcarbamoyloxymethyl-cyclopropyl] glycinate 22b. Yield: 70%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.6 (s, 1H), 7.4 (d, J = 8 Hz, 2H), 7.3 (dd, J = 8, 7 Hz, 2H), 7.0 (t, J = 7 Hz, 1H), 5.5 (d, J = 8 Hz, 1H), 4.6 (dd, J = 12, 5 Hz, 1H), 4.4–4.1 (m, 6H), 2.1–1.7 (m, 3H), 1.5 (s, 9H), 1.3–1.2 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 172.6, 171.1, 155.4, 153.0, 138.0, 128.9, 123.1, 118.4, 80.2, 61.8, 60.9, 60.3, 51.7, 29.2, 28.1, 25.5, 22.6, 14.0 ppm.

5.6. (2*SR*,1′*SR*,2′*RS*,3′*RS*)-2-(3′-ethylcarbamoyloxy-methyl-2′-carboxycyclopropyl)glycine 23a

Prepared from **22a** following the general hydrolysis procedure A. Yield: 47%. ^{1}H NMR (D_2O/Py-d_5, 200 MHz) δ: 4.0 (dd, J = 12, 5 Hz, 1H), 3.7 (dd, J = 12, 7 Hz, 1H), 3.2 (d, J = 10 Hz, 1H), 2.6 (q, J = 8 Hz, 2H), 1.6–1.4 (m, 3H), 0.6 (t, J = 8 Hz, 3H) ppm. ^{13}C NMR (D_2O/MeOH-d_4, 50 MHz) δ: 179.7, 173.2, 158.0, 63.4, 54.6, 35.5, 26.9, 25.9, 24.6, 14.2 ppm.

5.7. (2*SR*,1′*SR*,2′*RS*,3′*RS*)-2-(3′-phenylcarbamoyloxy-methyl-2′-carboxycyclopropyl)glycine 23b

Prepared from **22b** following the general hydrolysis procedure A. Yield: 55%. ^{1}H NMR (D_2O/Py-d_5, 200 MHz) δ: 7.0 (d, J = 8 Hz, 2H), 6.9 (dd, J = 8, 7 Hz, 2H), 6.6 (t, J = 7 Hz, 1H), 4.3 (dd, J = 12, 5 Hz, 1H), 3.9 (dd, J = 12, 7 Hz, 1H), 3.4 (d, J = 10 Hz, 1H), 1.8–1.6 (3H, m) ppm.^{13}C NMR (D_2O/Py-d_5, 50 MHz) δ: 179.6, 172.7, 154.8, 137.3, 129.0, 123.2, 119.3, 63.4, 54.3, 26.7, 24.8, 23.8 ppm. HRMS (M+1): calcd for $C_{14}H_{17}O_6N_2$ 309.10811. Found: 309.10810.

5.8. Ethyl (2*SR*,1′*RS*,2′*RS*,3′*RS*)-*N*-(*tert*-butoxycarbonyl)-2-[2′-(ethoxycarbonyl)-3′-(acetylthiomethyl)cyclo-propyl]-glycinate 24a

Diethyl azodicarboxylate (0.091 mL, 0.58 mmol) was added dropwise to a solution of triphenylphosphine (152 mg, 0.58 mmol) in anhydrous THF (1.8 mL) at 0 °C under argon. The mixture was stirred for 20 min and then a solution of thioacetic acid (0.042 mL, 0.58 mmol) and **20** (100 mg, 0.29 mmol) in anhydrous THF (0.9 mL) was added via cannula and the mixture was stirred overnight at rt. Silica gel was added to the mixture. The solvent was removed under vacuum and the residue was purified by flash chromatography using hexane/ethyl acetate (4:1) as eluent to give 70 mg of **24a** (60% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.02 (br s, 1H), 4.21–3.98 (dc, 6H), 3.20 (m, 1H), 3.00 (m, 1H), 2.27 (s, 3H), 1.74 (m, 1H), 1.38 (s, 9H), 1.19 (dt, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 195.0, 172.2, 170.8, 155.1, 80.1, 61.8, 60.8, 51.9, 30.8, 30.4, 27.9, 27.0, 25.2, 24.9, 14.0 ppm.

5.9. Ethyl (2*SR*,1′*RS*,2′*RS*,3′*RS*) *N*-(*tert*-butoxycarbonyl)-2-[2′-(ethoxycarbonyl)-3′-(phenylthiomethyl)-cyclopropyl] glycinate 24b

A mixture of tributylphosphine (0.26 mL, 1.04 mmol), diphenyl disulfide (170 mg, 0.78 mmol), and **20** (90 mg, 0.26 mmol) in anhydrous THF (2 mL) was stirred at room temperature under argon for 20 h. Then, silica gel was added to the mixture and the solvent was removed under vacuum. The resulting residue was purified by flash chromatography using hexane and ethyl acetate 4:1 as eluent to afford 80 mg (70% yield) of **24b**. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.25 (m, 5H), 5.20 (br d, 1H), 4.10 (m, 5H), 3.30 (dd, 1H), 2.85 (m, 1H), 1.75 (m, 3H), 1.40 (s, 9H), 1.25 (m, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.3, 170.9, 155.2, 135.2, 130.5, 128.9, 126.6, 80.2, 61.7, 60.7, 52.1, 33.3, 30.2, 28.1, 26.9, 25.7, 14.0 ppm.

5.10. (2*SR*,1′*RS*,2′*RS*,3′ *RS*)-2-[3′-Mercaptomethyl-2′-carboxycyclopropyl]glycine 25a

Prepared from **24a** following the general hydrolysis procedure C. Yield: 80% ^{13}C NMR (50 MHz, D_2O/Py-d_5) δ: 178.1, 171.5, 52.7, 28.4, 27.2, 26.6, 21.7 ppm. IR (film): 3437; 1631; 1385; 1234 and 889 cm^{-1}. MS (ES+) = 228 (M^++23). HRMS (M+1): calcd for $C_7H_{12}O_4N_1{}^{32}S_1$ 206.04816. Found: 206.04823. Melting point: 200–202 °C

5.11. (2*SR*,1′*RS*,2′*RS*,3′ *RS*)-2-[3′-(phenylthiomethyl)-2′-carboxycyclopropyl]glycine 25b

Prepared from **24b** following the general hydrolysis procedure C. Yield: 83%. ^{1}H NMR (200 MHz, D_2O/Py-d_5) δ: 6.99–6.47 (m, 5H), 3.11–3.01 (m, 2H), 2.32–2.21 (m, 1H), 1.57–1.41 (m, 2H), 1.24–1.19 (t, 1H) ppm.^{13}C NMR (50 MHz, D_2O/Py-d_5) δ: 179.3, 173.0, 135.4, 129.6, 129.4, 126.3, 54.9, 32.9, 29.4, 27.7, 25.8 ppm. IR (film): 3059, 1716, 1678, 1585, 1514, 1385, 1184, 1014 and 897cm^{-1}. MS (ES+) = 282 (M^++1). HRMS (M+1): calcd for $C_{13}H_{16}O_4N_1{}^{32}S_1$ 282.07946. Found: 282.07947.

5.12. (2*SR*,1′*RS*,2′*RS*,3′ *RS*)-2-[3′-(phenylsulfonylmethyl)-2′-carboxycyclopropyl]glycine 26b

m-Chloroperoxybenzoic acid (54.3 mg, 0.22 mmol) was added to a solution of **24b** (50 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (1 mL) at 0 °C under N_2 and the mixture was stirred for 3 h at this temperature. Then, the residue was diluted with CH_2Cl_2 and washed with a 15% aqueous solution of sodium bisulfite and with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over magnesium sulfate and the solvent was removed under vacuum. The residue was purified by flash chromatography using hexane and ethyl acetate 2:1 as eluent to afford 42 mg of the protected aminoacid. Hydrolysis, following the general hydrolysis procedure B, afforded **26b** as a white solid (overall yield: 47%). ^{1}H NMR (200 MHz, D_2O/Py-d_5) δ: 7.40 (d, 2H), 7.15 (m, 3H), 3.65 (d, 1H), 3.45 (m, 1H), 2.90 (m, 1H), 1.40 (m, 3H) ppm. ^{13}C NMR (50 MHz, D_2O/Py-d_5) δ: 178.1, 172.7, 136.6, 134.7, 129.8, 128.1, 55.3, 54.7, 28.6, 25.0, 19.3 ppm. MS (ES+) = 314 (M^++1). HRMS (M+1): calcd for $C_{13}H_{16}O_6N_1{}^{32}S_1$ 314.06929. Found: 314.06926.

5.13. Ethyl (2*SR*,1′*SR*,2′*SR*,3′*RS*)-*N*-(*tert*-butoxycarbonyl)-2-[2′-(ethoxycarbonyl)-3′-(azidomethyl)cyclopropyl] glycinate 27

Diethyl azodicarboxylate (1.08 mmol, 0.17 mL) was added dropwise to a solution of triphenylphosphine (1.08 mmol, 0.285 g) in anhydrous THF (20 mL) at −20 °C under N_2 and the reaction mixture was stirred at the same temperature for 10 min. A solution of **20** (0.87 mmol, 300 mg) in anhydrous THF (5 mL) was then added and the resulting mixture was stirred for 10 min at −20 °C. After that time, diphenylphosphoryl azide (1.13 mmol, 0.25 mL) was added to the reaction mixture at the same temperature and then allowed to react at rt for 3 days. The reaction mixture was quenched with water and the organic layer was extracted with EtOAc (2× 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The product was purified by column chromatography using hexane and ethyl acetate 4:1 as eluent to give 250 mg (78% yield) of **27** as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 5.2 (d, J = 8 Hz, 1H), 4.3–3.9 (m, 5H), 3.6 (dd, J = 13, 5 Hz, 1H), 3.3 (dd, J = 13, 7 Hz, 1H), 1.9–1.7 (m, 3H), 1.4 (s, 9H), 1.3–1.2 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 172.1, 170.7, 155.2, 80.2, 61.8, 61.0, 52.0, 49.4, 29.0, 28.1, 25.4, 24.0, 14.0 ppm.

5.14. (2*SR*,1′*SR*,2′*SR*,3′ *RS*)-2-(3′-azidomethyl-2′-carboxycyclopropyl)glycine 28

Prepared from **27** following the general hydrolysis procedure B as a white solid. Yield: 73%. ^{1}H NMR (D_2O, 200 MHz) δ: 3.6 (dd, J = 13, 5 Hz, 1H), 3.3 (d, J = 10 Hz, 1H), 3.2 (dd, J = 13, 8 Hz, 1H), 1.9–1.7 (m, 3H) ppm. ^{13}C NMR (D_2O/MeOH-d_4, 50 MHz) δ: 177.4, 173.2, 54.7, 50.1, 27.4, 26.9, 25.7 ppm. MS (FAB+): 215 (M^++1). Anal. Calcd for $C_7H_{10}N_4O_4$: C, 39.25; H, 4.71; N, 26.16. Found: C, 39.36; H, 4.79; N, 26.26.

5.15. Ethyl (2*SR*,1′*SR*,2′*SR*,3′*RS*)-*N*-(*tert*-butoxycarbonyl)-2-[2′-(ethoxycarbonyl)-3′-(acetylaminomethyl)-cyclopropyl] glycinate 29a

Acetic anhydride (0.3 mL, 2.7 mmol) and 10% palladium on activated carbon (90 mg) were added to a solution of **27** (500 mg, 1.35 mmol) in ethanol (15 mL) and the resulting mixture was stirred at rt under H_2 for 2 h. Then, it was filtered through Celite and concentrated under vacuum. The resulting residue was purified by column chromatography using hexane and ethyl acetate 1:1 as eluent to afford 375 mg (72% yield) of **29a**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.6 (broad s, 1H), 5.3 (d, J = 8 Hz, 1H,), 4.3–3.9 (m, 6H), 2.9–2.8 (m, 1H), 1.9 (s, 3H), 1.9–1.7 (m, 3H), 1.4 (s, 9H), 1.3–1.1 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 172.1, 171.6, 169.9, 155.5, 80.4, 62.1, 60.9, 52.4, 37.7, 28.9, 28.1, 26.6, 23.2, 14.0 ppm.

5.16. Ethyl (2*SR*,1′*SR*,2′*SR*,3′*RS*)-*N*-(*tert*-butoxycarbonyl)-2-[2′-(ethoxycarbonyl)-3′-(benzoylaminomethyl)-cyclopropyl]glycinate 29b

Benzoic anhydride (0.23 mL, 2.0 mmol) and platinum (IV) oxide (61 mg, 0.27 mmol) were added to a solution of **27** (500 mg, 1.35 mmol) in EtOAc (15 mL) and the resulting mixture was stirred at rt under H_2 for 2 h. Then, the mixture was filtered through Celite and concentrated under vacuum. The residue was purified by column chromatography using hexane and ethyl acetate 1:1 as eluent to afford 363 mg (65% yield) of **29b**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.9 (m, 2H), 7.6–7.4 (m, 3H), 5.3 (d, J = 8 Hz, 1H), 4.5 (m, 1H), 4.4–4.1 (m, 5H), 3.1–3.0 (m, 1H), 2.0–1.8 (m, 3H), 1.5 (s, 9H), 1.3–1.2 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 172.1, 171.7, 167.0, 155.4, 134.2, 131.3, 128.4, 127.0,

80.5, 62.4, 61.0, 52.5, 38.0, 28.9, 28.2, 26.6, 23.0, 14.0 ppm.

5.17. (2*SR*,1′*SR*,2′*SR*,3′ *RS*)-2-(3′-acetylaminomethyl-2′-carboxycyclopropyl)glycine 32a

Prepared from **29a** following the general hydrolysis procedure B as a white solid. Yield: 30%. ^{1}H NMR (D_2O/MeOH-d_4, 200 MHz) δ: 3.7 (dd, J = 14, 6 Hz, 1H), 3.2 (d, J = 10 Hz, 1H), 3.0 (dd, J = 14, 7 Hz, 1H), 1.9 (s, 3H), 1.8–1.6 (m, 3H) ppm. ^{13}C NMR (D_2O/MeOH-d_4, 50 MHz) δ: 175.4, 172.3, 171.4, 52.8, 36.9, 26.0, 25.2, 23.5, 21.0 ppm.

5.18. (2*SR*,1′*SR*,2′*SR*,3′*RS*)-2-(3′-benzoylaminomethyl-2′-carboxycyclopropyl)glycine 32b

Prepared from **29b** following the general hydrolysis procedure A as a white solid. Yield: 25%. ^{1}H NMR (D_2O/Py-d_5, 200 MHz) δ: 7.6–7.1 (m, 5H), 3.8 (dd, J = 14, 5 Hz, 1H), 3.3 (d, J = 10 Hz, 1H), 2.7 (dd, J = 14, 8 Hz, 1H), 1.7–1.5 (m, 3H) ppm. ^{13}C NMR (D_2O/Py-d_5, 50 MHz) δ: 179.7, 173.3, 169.1, 133.2, 132.2, 128.8, 127.3, 54.6, 38.8, 27.1, 26.4, 25.0 ppm. HRMS (M+1): calcd for $C_{14}H_{17}O_5N_2$ 293.11320. Found: 293.11319.

5.19. General procedure for the preparation of 30

Two equivalents of the corresponding isocyanate (2.7 mmol) and 0.2 equivalents of PtO_2 (0.27 mmol, 60 mg) were added to a solution of **27** (1.35 mmol, 500 mg) in EtOAc (15 mL), and the mixture was stirred at rt under H_2 for 4 h. The mixture was filtered through Celite and concentrated under vacuum. The residue was chromatographed using a 2:1 hexane/EtOAc mixture as eluent giving rise to **30**.

5.19.1. Ethyl (2*SR*,1′*SR*,2′*SR*,3′*RS*)-*N*-(*tert*-butoxycarbonyl)-2-[2′-(ethoxycarbonyl)-3′-ethylureidomethyl-cyclopropyl]glycinate 30a. Yield: 64%. ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 172.3, 171.5, 158.2, 155.3, 79.7, 61.6, 60.5, 52.4, 38.5, 34.8, 28.7, 28.0, 27.3, 23.3, 15.2, 13.8 ppm.

5.19.2. Ethyl (2*SR*,1′*SR*,2′*SR*,3′*RS*)-*N*-(*tert*-butoxy-carbonyl)-2-[2′-(ethoxycarbonyl)-3′-phenylureido-methylcyclopropyl]glycinate 30b. Yield: 63%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.5–7.2 (m, 5H), 7.1–7.0 (m, 1H), 5.9 (t, J = 6 Hz, 1H), 5.4 (d, J = 8 Hz, 1H), 4.2–4.0 (m, 5H), 3.8–3.7 (m, 1H), 3.3–3.1 (m, 1H), 2.0–1.7 (m, 3H), 1.5 (s, 9H), 1.3–1.2 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 172.4, 171.5, 155.7, 155.4, 138.9, 129.7, 128.9, 123.0, 120.4, 80.4, 62.0, 60.9, 52.4, 38.5, 28.9, 28.1, 27.2, 23.3, 14.0 ppm.

5.20. (2*SR*,1′*SR*,2′*SR*,3′*RS*)-2-(3′-ethylureidomethyl-2′-carboxycyclopropyl)glycine 33a

Prepared from **30a** following the general hydrolysis procedure A. Yield: 42%. ^{13}C NMR (D_2O, 50 MHz) δ: 177.6, 172.8, 53.7, 38.4, 34.9, 26.7, 26.7, 24.6, 14.2 ppm. MS (ES+) = 260 (M^++1). HRMS (M+1): calcd for $C_{10}H_{18}O_5N_3$ 260.12410. Found: 260.12405.

5.21. (2*SR*,1′*SR*,2′*SR*,3′*RS*)-2-(3′-phenylureidomethyl-2′-carboxycyclopropyl)glycine 33b

Prepared from **30b** following the general hydrolysis procedure A. Yield 56%. ^{1}H NMR (D_2O, 200 MHz) δ: 7.6–7.0 (m, 7H), 4.3 (dd, J = 10, 5 Hz, 1H), 3.9 (m, 1H), 3.3 (d, J = 10 Hz, 1H), 1.8–1.5 (m, 3H) ppm. ^{13}C NMR (D_2O/Py-d_5, 50 MHz) δ: 180.1, 173.4, 157.7, 138.2, 129.1, 123.7, 120.9, 54.3, 38.7, 26.8, 26.1, 25.8 ppm.

5.22. Ethyl (2*SR*,1′*SR*,2′*SR*,3′*RS*)-*N*-(*tert*-butoxycarbonyl)-2-[2′-(ethoxycarbonyl)-3′-benzene-sulfonylaminomethyl-cyclopropyl]glycinate 31

PtO_2 (0.27 mmol, 60 mg) was added to a solution of **27** (1.35 mmol, 500 mg) in EtOAc (15 mL) and the reaction mixture was stirred at rt under H_2 for 4 h. Then, benzenesulfonyl chloride (2.7 mmol) was added and the mixture was stirred under N_2 overnight. The mixture was filtered through Celite and concentrated under vacuum. The residue was chromatographed using a 2:1 hexane/EtOAc mixture as eluent giving rise to **31**. Yield: 56%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.8 (m, 2H), 7.5 (m, 3H), 5.8 (dd, J = 9, 3 Hz, 1H), 5.2 (d, J = 8 Hz, 1H), 4.3–4.0 (m, 4H), 3.8 (m, 1H), 3.5 (m, 1H), 2.8 (m, 1H), 1.9–1.6 (m, 3H), 1.4 (s, 9H), 1.3–1.1 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 171.7, 171.1, 155.1, 140.0, 132.3, 128.9, 126.6, 80.0, 62.1, 60.7, 52.0, 41.9, 28.8, 27.9, 26.1, 23.2, 13.8, 13.7 ppm.

5.23. (2*SR*,1′*SR*,2′*SR*,3′*RS*)-2-(3′-benzenesulfonylaminomethyl-2′-carboxycyclopropyl)glycine 34

Prepared from **31** following the general hydrolysis procedure A. Yield: 44%. ^{13}C NMR (D_2O/MeOH-d_4, 50 MHz) δ: 179.5, 173.8, 139.3, 134.6, 130.7, 127.8, 55.0, 43.3, 27.6, 27.1, 25.7 ppm. HRMS (M+1): calcd for $C_{13}H_{17}O_6N_2{}^{32}S_1$ 329.08018. Found: 329.08017.

5.24. (2*SR*,1′*SR*,2′*SR*,3′*RS*)-2-[3′-aminomethyl-2′-carboxycyclopropyl]glycine 35

A solution of **29a** (300 mg, 0.77 mmol) in 2 N HCl (5 mL) was stirred at room temperature for 24 h and then heated at 55 °C for 60 h. The solvent was removed under vacuum to give the corresponding hydrochloride salt of the title compound. After purification by ion-exchange chromatography, 58 mg (40% yield) of **35** was obtained as a white solid. ^{1}H NMR (D_2O/Py-d_5, 200 MHz) δ: 3.3 (m, 1H), 3.3 (d, J = 11 Hz, 1H), 2.7 (dd, J = 13, 10 Hz, 1H), 1.8–1.5 (m, 3H) ppm. ^{13}C NMR (D_2O/Py-d_5, 50 MHz) δ: 178.3, 172.7, 53.8, 38.2, 27.0, 25.6, 21.8 ppm. HRMS (M+1): calcd for $C_7H_{13}O_4N_2$ 189.08698. Found: 189.08698.

5.25. Ethyl (1*SR*,2*SR*,5*RS*,6*RS*)3-*tert*-butoxycarbonyl-4-oxo-3-azabicyclo[3.1.0]-hexane-2,6-dicarboxylate 36

Jones reagent solution (3.8 mL) was added dropwise at 0 °C to a solution of **20** (740 mg, 2.14 mmol) in acetone (17 mL) and the reaction mixture was stirred for 1 h at 0 °C and for 2 h at rt. Then, H_2O (17 mL) and ^{i}PrOH (17 mL) were added and the reaction mixture was

extracted with ethyl acetate (3× 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was chromatographed (EtOAc) to give 710 mg of **36** (97% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.73 (d, J = 5.9 Hz, 1H), 4.26 (dq, J = 7.2, 3.4 Hz, 2H), 2.62 (dt, J = 3.2, 6.6Hz, 1H), 2.52 (dd, J = 2.8, 6.6 Hz, 1H), 2.32 (t, J = 3.0 Hz, 1H), 1.44 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H), (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 168.9, 168.7, 168.1, 148.1, 83.3, 61.7, 61.4, 58.1, 28.6, 27.2, 21.7, 21.5, 13.6 and 13.5 ppm. IR (film): 3380, 2982, 1797, 1732, 1371, 1305, 1194, 1094, 1018, 850 cm^{-1}.

5.26. Ethyl (2*SR*,1′*SR*,2′*RS*,3′*RS*) *N*-(*tert*-butoxycarbonyl)-2-[2′-ethoxycarbonyl-3′- (methylaminocarbonyl)-cyclopropyl]glycinate 37a

Methylamine (2.74 mL, 5.4 mmol) and potassium cyanide (3 mg, 0.05 mmol) were added to a solution of **36** (312 mg, 0.9 mmol) in anhydrous THF (6 mL) under argon. After stirring overnight in an ultrasound bath, the solvent was removed under vacuum. The residue was chromatographed (hexane/ethyl acetate 1:1) to give 272 mg of **37a** (80% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.00 (d, 1H), 5.22 (s, 1H), 4.53 (t, J = 8.6 Hz, 1H), 4.13 (q, 4H), 2.82 (d, 3H), 2.59 (s, 1H), 2.25 (d, J = 4.7 Hz, 1H), 1.91 (s,1H), 1.43 (s, 9H), 1.24 (t, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.3, 171.5, 169.0, 155.0, 80.4, 61.9, 61.6, 51.8, 30.6, 29.5, 28.6, 27.1, 25.7, 14.5 ppm. MS (ES+) = 273 (M^++1−100). HRMS (M+1): calcd for $C_{17}H_{29}O_7N_2$ 373.19693. Found: 373.19704.

5.27. Ethyl (2*SR*,1′*SR*,2′*RS*,3′*RS*) *N*-(*tert*-butoxycarbonyl)-2-[2′-ethoxycarbonyl-3′-(phenylaminocarbonyl)-cyclopropyl]glycinate 37b

A solution of aniline (70 μl, 0.77 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added dropwise to a solution of $AlCl_3$ (53.8 mg, 0.40 mmol) in anhydrous CH_2Cl_2 (1 mL) at 0 °C and the mixture was stirred at rt for 10 min. Then, a solution of **36** (106 mg 0.31 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added and the mixture was stirred at rt for 4 h. A mixture of ice and water was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (X3). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was chromatographed (hexane/ethyl acetate 1:1) to give 67.5 mg **37b** (50% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.50 (d, 2H), 7.25–7.15 (m, 3H), 5.43 (br d, 1H), 4.61 (t, 1H), 4.10 (m, 4H), 2.70 (t, 1H), 2.40 (m, 1H), 2.10 (br s, 1H), 1.45 (s, 9H), 1.20 (t, 3H), 1.10 (t, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.3, 171.2, 166.2, 155.0, 138.0, 129.2, 128.8, 124.1, 119.7, 115.0, 79.9, 61.7, 61.4, 50.5, 30.8, 29.8, 28.1, 25.5, 14.0, 13.8 ppm.

5.28. Ethyl (2*SR*,1′*SR*,2′*RS*,3′*RS*) *N*-(*tert*-butoxycarbonyl)-2-[2′-ethoxycarbonyl-3′-(aminocarbonyl) cyclopropyl]glycinate 37c

NH_3(g) was bubbled for 15 min to a solution of **36** (200 mg, 0.58 mmol) in anhydrous CH_2Cl_2 (3 mL). Then $AlMe_3$ (0.88 mmol) was added and the mixture was stirred for 20 h at rt. The mixture was quenched with HCl (0.1 N) at 0 °C and stirred for 15 min. The white solid formed was filtered, and the filtrate was concentrated under vacuum. The residue was chromatographed (hexane/ethyl acetate 2:1) to give 114 mg of **37c** (54% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.15 (br s, 2H), 5.25 (br s, 1H), 4.53 (dd, 1H), 4.12 (dc, 4H), 2.55 (t, 1H), 2.26 (dd, 1H), 2.04 (m, 1H), 1.43 (s, 9H), 1.24 (dt, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 171.8, 171.1, 170.7, 155.1, 80.0, 61.6, 61.4, 50.3, 30.5, 28.3, 28.1, 25.5, 14.0 ppm. MS (ES+) = 259 (M^++1−100). HRMS (M+Na): calcd for $C_{16}H_{26}O_7N_2{}^{23}Na_1$ 381.16322. Found: 381.16323.

5.29. (2*SR*,1′*SR*,2′*RS*,3′ *RS*)-2-[2′-carboxy-3′-(methylaminocarbonyl) cyclopropyl]glycine 38a

Prepared from **37a** following the general hydrolysis procedure A. Yield: 50%. ^{1}H NMR (200 MHz, D_2O/Py-d_5) δ: 3.65 (d, J = 10.5 Hz, 1H), 2.28 (s, 3H), 1.97–1.62 (m, 1H), 1.75–1.62 (m, 1H) ppm. ^{13}C NMR (50 MHz, D_2O/Py-d_5) δ: 177.5, 172.7, 170.7, 51.7, 27.5, 27.4, 26.9, 25.7 ppm. MS (ES+) = 217 (M^++1). HRMS (M+1): calcd for $C_8H_{13}O_5N_2$ 217.08190. Found: 217.08194.

5.30. (2*SR*,1′*SR*,2′*RS*,3′ *RS*)-2-[2′-carboxy-3′-(phenylaminocarbonyl) cyclopropyl]glycine 38b

Prepared from **37b** following the general hydrolysis procedure A. Yield: 45%. ^{1}H NMR (200 MHz, D_2O/Py-d_5) δ: 7.99 (d, 2H), 7.52 (m, 3H), 4.65 (d, J = 10Hz, 1H), 3.17 (m, 1H), 2.98 (m, 1H), 2.81 (m, 1H) ppm. ^{13}C NMR (50 MHz, D_2O/Py-d_5) δ: 177.9, 173.1, 169.2, 137.3, 129.0, 124.8, 124.2, 120.9, 120.7, 52.3, 28.6, 28.3, 28.1 ppm. MS (ES+) = 279 (M^++1). HRMS (M+1): calcd for $C_{13}H_{15}O_5N_2$ 279.09755. Found; 279.09754.

5.31. Ethyl (2SR,1′SR,2′RS,3′RS) *N*-(*tert*-butoxycarbonyl)-2-[2′-ethoxycarbonyl-3′-cyanocyclopropyl]glycinate 39

Pyridine (0.17 mL, 2.48 mmol) was added to a solution of **37c** (223 mg, 0.62 mmol) in anhydrous THF (4 mL). Then, trifluoroacetic anhydride (0.11 mL, 1.48 mmol) was added dropwise and the mixture was stirred at rt for 19 h. The reaction was quenched with water and extracted with CH_2Cl_2. The residue was chromatographed using AcOEt/hexane (1:1) as eluent to give **39** (79% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.28 (br d, 1H), 4.34–4.11 (dq, 5H), 2.60 (m, 1H), 2.23–2.16 (dd, 1H), 2.06–1.94 (m, 1H), 1.45 (s, 9H), 1.37–1.21 (dt, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.5, 169.4, 116.5, 80.6, 62.4, 61.9, 53.0, 30.8, 28.8, 28.1, 25.4, 13.9 ppm. MS (ES+) = 241 (M^++1−100). HRMS (M+Na): calcd for $C_{16}H_{24}O_6N_2{}^{23}Na_1$ 363.15266. Found: 363.15275.

5.32. (2*SR*,1′*SR*,2′*RS*,3′ *RS*)-2-[2′-carboxy-3-cyanocyclopropyl]glycine 40

Prepared from **39** following the general hydrolysis procedure A. Yield: 40%. ^{1}H NMR (200 MHz, D_2O/

Py-d_5) δ: 3.65 (d, 1H), 2.73 (d, 1H), 2.41–2.22 (m, 2H) ppm. ^{13}C NMR (50 MHz, D_2O/Py-d_5) δ: 174.6, 171.2, 118.5, 54.8, 28.5, 27.2, 25.1 ppm. HRMS (M+1): calcd for $C_7H_9O_4N_2$ 185.05568. Found: 185.05566.

5.33. Ethyl (1*SR*,2*SR*,3*RS*)-2-hydroxymethyl-3-vinyl cyclopropanecarboxylate 41

A 0.5M solution of KHMDS in toluene (24.4 mL, 12.2 mmol) was added to a suspension of methyltriphenylphosphonium bromide (5.2 g, 14.5 mmol) in anhydrous dioxane (75 mL) at rt under nitrogen atmosphere. After 1 h, the mixture was added via cannula to a solution of **21** (1 g, 2.62 mmol) in dioxane (25 mL) under nitrogen atmosphere and the reaction mixture was stirred for 1 h. Then, the mixture was poured onto a mixture of Et_2O and H_2O, and the layers were separated. The aqueous layer was extracted with Et_2O (2× 100 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by column chromatography using AcOEt/hexane (1:2) as eluent to give 840 mg (85% yield) of **41**. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.2 (t, J = 7.1 Hz, 3H), 1.7 (t, J = 4.7 Hz, 1H), 1.8–2.0 (m, 1H), 2.1–2.2 (m, 1H), 3.5–3.6 (m, 1H), 3.7–3.8 (m, 1H), 4.1 (q, J = 7.1 Hz, 2H), 5.1–5.3 (m, 2H), 5.5–5.6 (m, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.7, 133.1, 117.7, 60.7, 60.6, 29.5, 29.4, 25.7, 14.1 ppm. IR (film): 3420, 2980, 1720 cm^{-1}. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.45; H, 8.22.

5.34. Ethyl (1*SR*,2*SR*,3*RS*)-3-ethyl-2-hydroxymethyl cyclopropanecarboxylate 42

A suspension of a mixture of **41** (500 mg, 2.94 mmol) and 5% Pd/C (70 mg) in MeOH (25 mL) was stirred under hydrogen atmosphere overnight. The catalyst was then filtered through Celite and the solvent was removed under vacuum. The residue was purified by column chromatography using EtOAc/hexane 1:2 as eluent to give 380 mg (80% yield) of **42**. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.1 (t, J = 7.1Hz, 3H), 1.3 (t, J = 7.1Hz, 3H), 1.3 (t, J = 4.4Hz, 1H), 1.4–1.6 (m, 3H), 1.8 (m, 2H), 3.7 (d, J = 7.1Hz, 2H), 4.1 (q, J = 7.1Hz, 2H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.9, 14.2, 20.7, 25.1, 28.8, 29.1, 60.5, 60.9, 173.8 ppm. IR (film): 3430, 2960, 2870, 1720 cm^{-1}. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.84; H, 9.44.

5.35. Ethyl (1*SR*,2*SR*,3*RS*)-2-formyl-3-ethylcyclopropane carboxylate 43

Dimethylsulfoxide (0.36 mL, 5.0 mmol) was added to a solution of oxalyl chloride (0.21 mL, 2.4 mmol) in anhydrous CH_2Cl_2 (30 mL) at −78 °C under N_2 and the reaction mixture was stirred for 30 min. A solution of **42** (350 mg, 2.0 mmol) in anhydrous CH_2Cl_2 (20 mL) was added and the reaction mixture was stirred at the same temperature for 45 min. Then, triethylamine (1.4 mL, 10 mmol) was added and the mixture was allowed to react at rt for 30 min. The reaction was quenched with water (30 mL), the organic layer separated, and the aqueous layer was extracted with CH_2Cl_2 (2× 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. The resulting residue was purified by column chromatography using EtOAc/hexane 1:4 as eluent to afford 310 mg (90% yield) of **43**. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.9 (t, 3H), 1.2 (t, 3H), 1.4–1.5 (m, 1H), 1.6–1.7 (m, 1H), 1.9–2.0 (m, 1H) 2.3 (m, 1H), 2.4–2.5 (m, 1H), 4.1 (q, 2H), 9.5 (d, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.7, 14.0, 19.7, 28.0, 33.4, 35.6, 61.0, 171.2, 197.7 ppm. IR (film): 2960, 2620, 1720, 1700 cm^{-1}. Anal. calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.60; H, 8.34.

5.36. (2*SR*,1′*SR*,2′*RS*,3′*RS*)-*N*-acetyl-2-[2′-(ethoxy-carbonyl)-3′-ethylcyclopropyl]glycinonitrile 44

A suspension of ammonium chloride (5.53 g, 103.5 mmol) and neutral aluminum oxide (10.35 g) in anhydrous acetonitrile (70 mL) was ultrasonicated for 1 h. A solution of **43** (1.76 g, 10.3 mmol) in anhydrous acetonitrile (70 mL) was added and ultrasonicated for 1 h. Potassium cyanide (8.10 g, 124.3 mmol) finely powdered was then added, and the mixture was allowed to react for 2 days. The mixture was filtered through Celite and the solvent was evaporated. The resulting residue (1.92 g) was taken into anhydrous CH_2Cl_2 (100 mL) and the mixture was cooled to 0 °C. Then, *N*,*N*-diisopropylethylamine (2.23 mL, 12.7 mmol) was added to the mixture under N_2, and the reaction mixture was stirred for 15 min. Then, acetylchloride (0.84 mL, 11.8 mmol) was added, and the reaction mixture was stirred at rt for 3 h. The reaction was quenched with water (40 mL), the organic layer separated, and the aqueous layer was extracted with CH_2Cl_2 (2× 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concetrated. The residue was purified by column chromatography using ethyl acetate and hexane (1:1) as eluent to give 1.73 g (70% yield) of a 1:1 mixture of the acetylated aminonitriles **44**. Both isomers were separated by recrystallization. Isomer B was precipitated by recrystallization in diethyl ether, while isomer A remained in the solvent. Isomer A: (**44a**). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.1 (t, 3H), 1.2 (t, 3H), 1.4–1.7 (m, 4H), 1.9–2.0 (m, 1H), 2.1 (s, 3H), 4.1 (m, 2H), 4.6 (dd, 1H), 6.5 (d,1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.8, 14.1, 20.9, 22.8, 25.8, 28.6, 29.0, 38.9, 61.1, 117.7, 169.4, 172.5 ppm. IR (film): 3375, 2980, 2240, 1710, 1685 cm^{-1}. Anal. Calcd for $C_{12}H_{18}N_2O_3$: C 60.49; H 7.61; N 11.76. Found: C, 60.54; H, 7.69; N, 11.79. Isomer B: (**44b**) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.0 (t, 3H), 1.3 (t, 3H), 1.3–1.5 (m,d4H), 1.9 (m,1H), 2.0 (s, 3H), 4.1 (q, 2H), 4.6 (dd, 1H), 6.8 (d,1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.6, 14.0, 20.3, 22.5, 25.1, 28.4, 29.6, 39.0, 61.3, 118.1, 169.3, 172.7 ppm. IR (film): 3400, 2970, 2230, 1700, 1680 cm^{-1}. Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.50; H, 7.63; N, 11.80.

5.37. (2*SR*,1′*SR*,2′*SR*,3′ *RS*)-2-(3′-ethyl-2′-carboxycyclopropyl) glycine 45

Prepared from **44a** following the general hydrolysis procedure C. Yield: 65%. ^{1}H NMR (300 MHz, D_2O) δ: 0.8 (t, 3H), 1.0 (m, 1H), 1.1 (m, 1 H), 1.3 (m, 1H),

1.4 (m, 1H), 1.5 (m, 1H), 3.2 (d,1H) ppm. ^{13}C NMR (75 MHz, D_2O) δ: 15.6, 23.8, 29.9, 30.5, 31.9, 57.3, 176.4, 184.0 ppm. Isomer B: (**44b**) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.0 (t, 3H), 1.3 (t, 3H), 1.3–1.5 (m,d4H), 1.9 (m,1H), 2.0 (s, 3H), 4.1 (q, 2H), 4.6 (dd, 1H), 6.8 (d,1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.6, 14.0, 20.3, 22.5, 25.1, 28.4, 29.6, 39.0, 61.3, 118.1, 169.3, 172.7 ppm. Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C 51.21; H 6.90; N 7.44.

5.38. Ethyl (1*SR*,5*RS*,6*SR*)-2-oxo-bicyclo[3.1.0]hexane-6-carboxylate 47

To a suspension of ethyl (dimethylsulfonium)acetate bromide (13.9 g, 60.9 mmol) in $CHCl_3$ (60 mL), DBU (9.18 mL, 60.9 mmol) was added. The resulting suspension was vigorously stirred at rt for 30 min. Then, cyclopentenone (5.10 mL, 60.9 mmol) was added and the mixture was stirred overnight at rt. The following day additional $CHCl_3$ (60 mL) was added. The organic layer was washed with 40 mL of 0.5 N HCl, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified chromatographed using ethyl acetate:hexane 1:9 as eluent to give 8.4 g (82% yield) of **47** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (t, J = 7.1 Hz, 3H), 1.95–2.24 (m, 6H), 2.44–2.49 (m, 1H), 4.10 (q, J = 7.1 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.0, 22.3, 26.3, 29.1, 31.7, 35.6, 61.1, 170.3, 211.8 ppm. IR (film): 2960, 1735, 1715 cm^{-1}. Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.34; H, 7.23.

5.39. Ethyl (1*SR*,6*SR*,7*SR*)-2-oxo-3-oxa-bicyclo[4.1.0]-heptane-7-carboxylate 48

To a stirred solution of **47** (34.8 g, 207.2 mmol) in (300 mL), 70% *m*-chloroperbenzoic acid (51.1 g, 207.2 mmol) was added and the mixture was refluxed overnight. The following day, additional 70% *m*-chloroperbenzoic acid (51.1 g, 207.2 mmol) was added and the mixture was refluxed for 15 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL), filtered, and washed with 10% Na_2SO_3 (2× 200 mL) and with a saturated aqueous solution of $NaHCO_3$ (2× 200 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified chromatographed using ethyl acetate and hexane 1:2 as eluent to give 22.89 g (60% yield) of **48** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (t, J = 7.1 Hz, 3H), 1.97–2.04 (m, 1H), 2.13–2.28 (m, 3H), 2.38 (dd, J = 8.3, 3.3 Hz, 1H), 2.53 (t, J = 3.9 Hz, 1H), 4.02 (td, J = 8.8, 3.3 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 4.23–4.31 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 19.4, 21.4, 22.2, 24.2, 61.5, 64.3, 167.8, 170.0 ppm. IR (film): 3420, 2980, 1710, 1680 cm^{-1}. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.66; H, 6.50.

5.40. (2*RS*) and (2*SR*) Ethyl (1*SR*,6*RS*,7*SR*)-2-hydroxy-3-oxa-bicyclo[4.1.0]heptane-7-carboxylate 49

A 1.5 M solution of diisobutylaluminum hydride in toluene (82.8 mL, 124.2 mmol) in anhydrous THF (150 mL) at −78 °C under argon was added dropwise via cannula to a solution of **48** (15.2 g, 82.8 mmol) in anhydrous THF (300 mL) at −78 °C under argon. The solution was stirred for 6 h at this temperature and then diluted with EtOAc (200 mL) and quenched with a saturated aqueous solution of sodium tartrate (200 mL). The resulting mixture was stirred at rt overnight. The organic layer was separated, dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was chromatographed using EtOAc and hexane 1:2 as eluent to afford 12.3 g (85% yield) of **49** as a colorless oil, which exists with their corresponding open hydroxyaldehyde forms. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.19–1.24 (m), 1.49–1.52 (m), 1.60–1.94 (m), 2.00–2.08 (m), 2.30–2.34 (m), 2.53–2.58 (m), 3.25–3.30 (m), 3.34–3.50 (m), 3.58–3.63 (m), 3.81–3.90 (m), 4.04–4.09 (m), 5.24 (dd, J = 5.5, 4.4 Hz), 5.29 (d, J = 3.3 Hz), 9.60 (dd, J = 3.3, 1.1 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9, 14.0, 14.1, 18.5, 20.6, 20.9, 21.0, 21.3, 23.7, 25.0, 25.7, 27.3, 28.6, 28.7, 34.8, 54.2, 59.9, 60.5, 60.6, 61.1, 61.6, 89.0, 90.0, 171.3, 173.3, 173.5 ppm. IR (film): 3420, 2985, 2920, 1720, 1700 cm^{-1}.

5.41. (2*SR*) and (2*RS*)-2-(1′*SR*,2′*SR*,3′*RS*)-2′-(ethoxycarbonyl)-3′-(2′′- hydroxyethyl)cyclopropyl] glycinonitrile 50

A suspension of ammonium chloride (29.3 g, 547.3 mmol) and neutral aluminum oxide (54.7 g) in acetonitrile (600 mL) was ultrasonicated for 1 h. A solution of **49** (10.2 g, 54.7 mmol) in acetonitrile (200 mL) was added, and sonication was continued for an additional hour. Then, powdered potassium cyanide (42.8 g, 656.7 mmol) was added and the reaction mixture was ultrasonicated for seven days. After that time, the mixture was filtered through Celite and the inorganics were washed with acetonitrile. The solvent was evaporated under vacuum to give a residue that contained a 1:1 racemic mixture of the two possible diastereomers **50**. Both racemic aminonitriles were purified and separated by column chromatography using acetone/hexane 1:2 as eluent to give 3.89 g of **50a** and 3.67 of **50b**.

5.42. Ethyl (2*SR*,1′*SR*,2′*SR*,3′*RS*)-*N*-(*tert*-butoxycarbonyl)-2-[2′-(ethoxycarbonyl)-3′- (2′′-hydroxyethyl)-cyclopropyl] glycinate 51a

To a solution of **50a** (3.88 g, 18.3 mmol) in EtOH saturated with HCl (200 mL) at 0 °C, distilled H_2O (0.99 mL, 54.9 mmol) was added. The reaction was stirred at rt for four days. Then, the solvent was removed under vacuum and the residue was dissolved in EtOH (100 mL), neutralized with $NaHCO_3$ (solid), and stirred for 30 min. The inorganics were filtered and the solvent was removed under vacuum. The resulting residue was taken into dioxane (150 mL), and a saturated solution of $NaHCO_3$ (50 mL) was added. To this mixture, a solution of di-*tert*-butyldicarbonate (4.80 mg, 22.8 mmol) in dioxane (25 mL) was added and the mixture was stirred overnight at rt. The layers were then separated and the aqueous layer was extracted with EtOAc (2× 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was chromato-

graphed using ethyl acetate/hexane 1:2 as eluent to afford 3.34 g (56% yield) of **51a** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.45 (s, 9H), 1.67–1.69 (m, 2H), 1.97–2.00 (m, 1H), 3.76–3.78 (m, 2H), 4.04 (t, J = 9.3 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 4.23 (q, J = 7.1 Hz, 2H), 5.33 (d, J = 8.2 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.0, 14.1, 24.3, 24.8, 28.2, 29.6, 30.9, 52.1, 60.7, 61.7, 62.0, 80.1, 155.3, 171.4, 173.2 ppm. IR (film): 3480, 3360, 2970, 1720, 1700 cm^{-1}. Anal. Calcd for $C_{17}H_{29}NO_7$: C, 56.81; H, 8.13; N, 3.90. Found: C, 56.74; H, 8.06; N, 3.83. MS (ES−) = 358 (M−1).

5.43. (2*SR*,1′*SR*,2′*SR*,3′ *RS*)-2-[(3′-(2′′-hydroxyethyl)-2′-carboxy)cyclopropyl]glycine 52a

Prepared from **51a** following the general hydrolysis procedure B. Yield: 60%. ^{1}H NMR (200 MHz, D_2O) δ: 1.46–1.84 (m, 4H), 1.92–2.05 (m, 1H), 3.44 (d, J = 10.5 Hz, 1H), 3.71 (br t, J = 6.4 Hz, 2H) ppm. ^{13}C NMR (50 MHz, D_2O) δ: 24.8, 25.7, 26.9, 29.8, 54.0, 60.9, 173.0, 178.0 ppm. Anal. Calcd for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.21; H, 6.36; N, 6.81. MS (ES+) = 204 (M^++1). HRMS (M+1): calcd for $C_8H_{14}O_5N_1$ 204.08665. Found: 204.08664.

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References and notes

1. (a) Johnson, R. L.; Koerner, J. F. *J. Med. Chem.* **1988**, *31*, 2057; (b) Ozawa, S.; Kamiya, H.; Tsuzuki, K. *Prog. Neurobiol.* **1998**, *54*, 581; (c) Michaelis, E. K. *Prog. Neurobiol.* **1998**, *54*, 369.
2. (a) Nakanishi, S. *Science* **1992**, *258*, 597; (b) Bleakman, D.; Lodge, D. *Neuropharmacology* **1998**, *37*, 1187.
3. (a) Schoepp, D. D.; Conn, P. J. *TiPS* **1993**, *14*, 13; (b) Pin, J.-P.; Duvoisin, R. *Neuropharmacology* **1995**, *34*, 1.
4. (a) Pin, J.-P.; De Colle, C.; Bessis, A.-S.; Acher, F. *Eur. J. Pharmacol.* **1999**, *375*, 277; (b) Schoepp, D. D.; Jane, D. E.; Monn, J. A. *Neuropharmacology* **1999**, *38*, 1431; (c) Pellicciari, R.; Costantino, G.; Marinozzi, M.; Macchiarulo, A.; Carnaioni, E.; Natalini, B. *Il Farmaco* **2001**, *56*, 91.
5. (a) Knöpfel, T.; Khun, R.; Allgeier, H. *J. Med. Chem.* **1995**, *38*, 1417; (b) Nicoletti, F.; Bruno, V.; Copani, A.; Casabona, G.; Knöpfel, T. *Trends Neurosci.* **1996**, *19*, 267; (c) Monn, J. A.; Schoepp, D. D. In *Section I. Central Nervous System Diseases*; Robertson, D. W., Ed.; Annu. Rep. Med. Chem., 2000; Vol. 35, p 1; (d) Bräuner-Osborne, H.; Egebjerg, J.; Nielsen, E.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609.
6. (a) Palmer, E.; Monaghan, D. T.; Cotman, C. W. *Eur. J. Pharmacol.* **1989**, *166*, 585; (b) Desai, M. A.; Conn, P. J. *Neurosci. Lett.* **1990**, *109*, 157; (c) Schoepp, D. D.; Johnson, B. G.; Monn, J. A. *J. Neurochem.* **1992**, *58*, 1184; (d) Cartmell, J.; Curtis, A. R.; Kemp, J. A.; Kendall, D. A.; Alexander, S. P. H. *Neurosci. Lett.* **1993**, *153*, 107.
7. (a) Monn, J. A.; Valli, M. J.; Jonson, B. G.; Salhoff, C. R.; Wright, R. A.; Howe, T.; Bond, A.; Lodge, D.; Spangle, L. A.; Paschal, J. W.; Campbell, J. B.; Griffey, K.; Tizzano, J. P.; Schoepp, D. D. *J. Med. Chem.* **1996**, *39*, 2990; (b) Kozikowsky, A. P.; Araldi, G. L.; Tückmantel, W.; Pshenichkin, S.; Surina, E.; Wroblewsky, J. T. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1721; (c) Bräuner-Osborne, H.; Madsen, U.; Mikiciuk-Olasik, E.; Curry, K. *Eur. J. Pharmacol.* **1997**, *332*, 327; (d) Kozikowsky, A. P.; Steensma, D.; Araldi, G. L.; Tückmantel, W.; Wang, S.; Pshenichkin, S.; Surina, E.; Wroblewsky, J. T. *J. Med. Chem.* **1998**, *41*, 1641.
8. (a) Monn, J. A.; Valli, M. J.; Massey, S. M.; Wright, R. A.; Salhoff, C. R.; Johnson, B. G.; Howe, T.; Alt, C. A.; Rhodes, G. A.; Robey, R. L.; Griffey, K. R.; Tizzano, J. P.; Kallman, M. J.; Helton, D. R.; Schoepp, D. D. *J. Med. Chem.* **1997**, *40*, 528; (b) Schoepp, D. D.; Johnson, B. G.; Wright, R. A.; Salhoff, C. R.; Mayne, N. G.; Wu, S.; Cockerham, S. L.; Burnett, J. P.; Belegaje, R.; Bleakman, D.; Monn, J. A. *Neuropharmacology* **1997**, *36*, 1; (c) Schoepp, D. D.; Monn, J. A.; Marek, G. J.; Aghajanian, G.; Moghaddam, B. *CNS Drug Rev.* **1999**, *5*, 1; (d) Moghaddam, B.; Adams, B. W. *Science* **1998**, *281*, 1349.
9. Monn, J. A.; Valli, M. J.; Massey, S. M.; Hansen, M. M.; Kress, T. J.; Wepsiec, J. P.; Harkness, A. R.; Grutsch, J. L.; Wright, R. A.; Johnson, B. G.; Andis, S. L.; Kingston, A.; Tomlinson, R.; Lewis, R.; Griffey, K. R.; Tizzano, J. P.; Schoepp, D. D. *J. Med. Chem.* **1999**, *42*, 1027.
10. Nakazato, A.; Kumagai, T.; Sakagami, K.; Yoshikawa, R.; Suzuki, Y.; Chaki, S.; Ito, H.; Taguchi, T.; Nakanishi, S.; Okuyama, S. *J. Med. Chem.* **2000**, *43*, 4893.
11. Nakagawa, Y.; Saitoh, K.; Ishihara, T.; Ishida, M.; Shinozaki, H. *Eur. J. Pharmacol.* **1990**, *184*, 205.
12. Shibuya, A.; Sato, A.; Taguchi, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1979.
13. Brabet, I.; Parmentier, M. L.; De Colle, C.; Bockaert, J.; Acher, F.; Pin, J. P. *Neuropharmacology* **1998**, *37*, 1043.
14. Shimamoto, K.; Ohfune, Y. *J. Med. Chem.* **1996**, *39*, 407.
15. (a) Pellicciari, R.; Marinozzi, M.; Natalini, B.; Costantino, G.; Luneia, R.; Giorgi, G.; Moroni, F.; Thomsen, C. *J. Med. Chem.* **1996**, *39*, 2259; (b) Marinozzi, M.; Natalini, B.; Costantino, G.; Tijskens, P.; Thomsen, C.; Pellicciari, R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2243.
16. Pellicciari, R.; Costantino, G.; Marinozzi, M.; Macchiarulo, A.; Amori, L.; Flor, P. J.; Gasparini, F.; Kuhn, R.; Urwyler, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3179.
17. (a) Ornstein, P. L.; Bleisch, T. J.; Arnold, M. B.; Wright, R. A.; Johnson, B. G.; Schoepp, D. D. *J. Med. Chem.* **1998**, *41*, 346; (b) Ornstein, P. L.; Bleisch, T. J.; Arnold, M. B.; Kennedy, J. H.; Wright, R. A.; Johnson, B. G.; Tizzano, J. P.; Helton, D. R.; Kallman, M. J.; Schoepp, D. D.; Herin, M. *J. Med. Chem.* **1998**, *41*, 358; (c) Sorensen, U. S.; Bleisch, T. J.; Kingston, A. E.; Wright, R. A.; Johnson, B. G.; Schoepp, D. D.; Ornstein, P. L. *Bioorg. Med. Chem.* **2003**, *11*, 197.
18. Collado, I.; Pedregal, C.; Mazón, A.; Espinosa, J. F.; Blanco-Urgoiti, J.; Schoepp, D. D.; Wright, R. A.; Johnson, B. G.; Kingston, A. E. *J. Med. Chem.* **2002**, *45*, 3619.
19. Collado, I.; Pedregal, C.; Bueno, A. B.; Marcos, A.; González, R.; Blanco-Urgoiti, J.; Pérez-Castells, J.; Schoepp, D. D.; Wright, R. A.; Johnson, B. G.; Kingston, A.; Moher, E. D.; Hoard, D. W. *J. Med. Chem.* **2004**, *47*, 456.
20. Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119.

21. Kotsuki, H.; Matsumoto, K.; Nishizawa, H. *Tetrahedron Lett.* **1991**, *32*, 4155.
22. Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *23*, 1977.
23. Wheeler, W. J.; Clodfelter, D. K.; Kulanthaivel, P.; Pedregal, C.; Stoddard, E. A.; Wright, R. A.; Schoepp, D. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 349.
24. Molina, M. T.; del Valle, C.; Escribano, A. M.; Ezquerra, J.; Pedregal, C. *Tetrahedron* **1993**, *49*, 3801.
25. Bon, E.; Bigg, D. C. H.; Bertrand, G. *Synlett* **1992**, 747.
26. Shibuya, A.; Okada, M.; Nakamura, Y.; Kibashi, M.; Horikawa, H.; Taguchi, T. *Tetrahedron* **1999**, *55*, 10325.
27. Collado, I.; Domínguez, C.; Ezquerra, J.; Pedregal, C.; Monn, J. A. *Tetrahedron Lett.* **1997**, *38*, 2133.
28. (a) Johnson, B. G.; Wright, R. A.; Arnold, M. B.; Wheeler, W. J.; Ornstein, P. L.; Schoepp, D. D. *Neuropharmacology* **1999**, *38*, 1519; (b) Wright, R. A.; Arnold, M. B.; Wheeler, W. J.; Ornstein, P. L.; Schoepp, D. D. *J. Pharmacol. Exp. Ther.* **2001**, *298*, 453.
29. Schoepp, D. D.; Johnson, B. G.; Salhoff, C. R.; Valli, M. J.; Desai, M. A.; Burnett, J. P.; Mayne, N. G.; Monn, J. A. *Neuropharmacology* **1995**, *34*, 843–850.
30. Wright, R. A.; Arnold, M. B.; Wheeler, W. J.; Ornstein, P. L.; Schoepp, D. D. *Naunyn-Schmiedeberg's Arch. Pharm.* **2000**, *362*, 546.
31. Cheng, Y. C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.