Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry 11 (2003) 197–205

BIOORGANIC & MEDICINAL CHEMISTRY

Synthesis and Structure–Activity Relationship Studies of Novel 2-Diarylethyl Substituted (2-Carboxycycloprop-1-yl)glycines as High-Affinity Group II Metabotropic Glutamate Receptor Ligands

Ulrik S. Sørensen, Thomas J. Bleisch, Anne E. Kingston, Rebecca A. Wright, Bryan G. Johnson, Darryle D. Schoepp and Paul L. Ornstein*

Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center, DC 1523 Indianapolis, IN 46285, USA

Received 14 March 2002; accepted 5 August 2002

Abstract—The major excitatory neurotransmitter in the central nervous system, (*S*)-glutamic acid (**1**), activates both ionotropic and metabotropic excitatory amino acid receptors. Its importance in connection to neurological and psychiatric disorders has directed great attention to the development of compounds that modulate the effects of this endogenous ligand. Whereas L-carboxycyclopropylglycine (L-CCG-1, **2**) is a potent agonist at, primarily, group II metabotropic glutamate receptors, alkylation of **2** at the α-carbon notoriously result in group II mGluR antagonists, of which the most potent compound described so far, LY341495 (**12**), displays IC_{50} values of 23 and 10 nM at the group II receptor subtypes mGlu2 and mGlu3, respectively. In this study we synthesized a series of structural analogues of **12** in which the xanthyl moiety is replaced by two substituted-phenyl groups. The pharmacological characterization shows that these novel compounds have very high affinity for group II mGluRs when tested as their racemates. The most potent analogues demonstrate K_i values in the range of 5–12 nM, being thus comparable to LY341495 (**12**).

Introduction

(*S*)-Glutamic acid (**1**) is the major excitatory neurotransmitter in the central nervous system (CNS), and activates both ionotropic and metabotropic excitatory amino acid (EAA) receptors. The three subclasses of ionotropic EAA receptors are *N*-methyl-D-aspartic (NMDA),[1,2] 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)propanoic acid (AMPA),[3–6] and kainic acid (KA) receptors.[3–5,7,8] In contrast to these ligand gated ion channel receptors, the metabotropic glutamate receptors (mGluRs) are G-protein coupled receptors, linked to multiple signal transduction pathways, including phosphatidylinositide and cyclic-AMP production.[9–11]

Based on sequence homology and pharmacological properties, three subclasses of mGluRs have so far been identified; group I (comprising the receptor subtypes mGlu1 and mGlu5), group II (mGlu2 and mGlu3), and group III (mGlu4, mGlu6, mGlu7, and mGlu8). The mGluRs have not yet been as well characterized pharmacologically as the ionotropic glutamate receptors, but it is generally agreed that all classes of EAA receptors play important roles in the CNS, and that ligands affecting ionotropic[12,13] as well as metabotropic[12–17] receptors would serve as useful therapeutic targets in relation to various neurologic disorders.

A large number of mGluR ligands have been developed, of which L-carboxycyclopropylglycine (L-CCG-1, **2**),[18] 2-amino-4-phosphonobutanoic acid (L-AP4, **3**),[19] and (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid (1*S*,3*R*)-ACPD, **4**)[20] were among the first potent agonists identified. Compound **3** is a relatively selective group III agonist whereas **4** shows activity at both group I and group II mGluRs. Also, the potent group II mGluR agonist **2** shows some activity at group I mGluRs. These structures have helped lead the way for further development aimed at understanding the pharmacology of the mGluRs. An example of a potent and selective group II agonist is LY354740 (**5**).[21–25] The recently described heterocyclic derivatives of **5**, LY379268 (**6**) and LY389795 (**7**),[22,26] have displayed EC_{50} values between 3 and 8 nM, and are among the most potent group II mGluR agonists known to date. Also, modification of **3** led to α-methyl-AP4 (MAP-4,

*Corresponding author. Tel.: +1-317-276-3226; fax: +1-317-277-2035; e-mail: ornstein_paul@lilly.com

0968-0896/03/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0968-0896(02)00387-5

8), a selective but relatively nonpotent group III mGluR antagonist.[27]

We previously made a detailed structure activity relationship (SAR) study showing that substitution of **2** in the α-position of the amino acid moiety with an alkyl or especially arylalkyl substituent has a marked effect on both potency and selectivity.[28,29] Thus, systematic substitution with unbranched and branched alkyl chains led to compound **9** with an IC_{50} in glutamate binding of 1.4 μM.[28]

Further elaboration of **9** to the cyclohexylmethyl analogue **10** and the phenylethyl derivative **11** led to a further increase in glutamate binding affinity (IC_{50} 0.23 and 0.32 μM, respectively). The most potent compound synthesized in this series was the 9-xanthylmethyl derivative,[28] of which the *S,S,S*-stereoisomer, LY341495 (**12**),[28,30] displayed IC_{50} values of 23 and 10 nM at mGlu2 and mGlu3 receptors, respectively. LY341495 has now been developed into a useful radioligand.[31–33] Modification of **12** into its 3′-ethyl analogue CECXG (**13**) improves overall group II selectivity but also gives a 5-fold loss of potency.[34]

Compared to compound **11**, the introduction of an additional phenyl group to give compound **14** gives not only improved potency (IC_{50} 0.24 μM) but also a 16-fold increase in selectivity for mGlu3 relative to mGlu2.[28] This finding has prompted us to study whether substituents on the phenyl groups of **14** would further improve selectivity as well as potency. This paper reports the synthesis and pharmacological characterization of a number of analogues of **14** containing a variety of different phenyl ring substituents.

Chemistry

A number of the novel amino acid derivatives **22** presented in this paper were synthesized by our previously published pathway with only minor changes in the procedure (Scheme 1).[28,29] All of the compounds that we prepared contain multiple racemic diastereomers. Through the synthetic methods utilized, we typically obtained a nearly 1:1 or 1:1:1 ratio of diastereomers, and no attempt was made to separate these diastereomers; nor did we do anything to separate the different enantionmeric pairs.

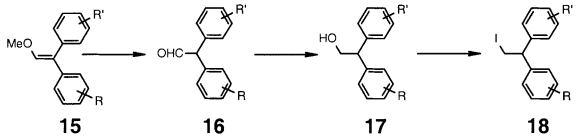
Thus, ketones of the general structure **20** were prepared in five steps from commercially available substituted benzophenones (Scheme 1). In the first step, methyl diarylenol ethers **15** are synthesized from these benzophenones by Wittig methylenation[35] using (methoxymethyl)triphenylphosphonium chloride and sodium bis(trimethylsilyl)amide as base. This transformation is very efficient, typically affording enol ethers **15** in quantitative yields (Table 1).

Enol ethers **15** were hydrolyzed with 70% aqueous perchloric acid in diethyl ether to give the corresponding aldehydes **16**. These reaction conditions were found to be the best; less than favorable results were obtained when we used aqueous hydrochloric acid in either tetrahydrofuran or acetonitrile. The resulting diaryl acetaldehydes **16** were subsequently reduced with $NaBH_4$ to give the primary alcohols **17**. Iodination of **17** with triphenylphosphine diiodide gave iodides **18** that were used in the palladium-mediated acid chloride/organozincate coupling. The iodides were generally quite stable, and could all be purified by flash chromatography on silica gel. Compounds **18** were treated with Zn(Cu) couple and the formed organozincate species were subsequently reacted in situ with $Pd(PPh_3)_4$ and racemic *trans*-carboxylic acid chloride **19** to afford ketones **20** containing the diarylethyl as well as the cyclopropyl moieties.[36] After hydrolysis of the ester group, conversion into hydantoins **21** was accomplished by reaction with potassium cyanide and ammonium carbonate. All synthesized hydantoins were subsequently hydrolyzed using 1 M NaOH at 200 °C to yield amino acids **22**, as a mixture of two or three racemic diastereomers.

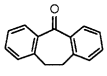
The two step conversion from ketone **20** to amino acid **22** had previously been optimized.[28] However, for the compounds described here, the steric demands of the two phenyl groups required the use of excessive amounts of KCN and $(NH_4)_2CO_3$ and longer reaction times. The subsequent hydantoin hydrolyses were carried out in 1 M aqueous NaOH at 200 °C by heating the reaction mixture in a sealed stainless steel high-pressure vessel as previously reported.[28] In contrast to our prior experience with these type of compounds, these hydantoin and amino acid analogues containing two aromatic rings generally precipitated readily and were therefore quite easily purified. Thus, most hydantoins **21** were recrystallized from $MeOH/H_2O$, and all amino acids, except **22a** and **22o**, were isolated by precipitation without the use of ion exchange chromatography. By these methods, no signficant change in the diastereomeric ratio was observed. The above described route to the desired amino acid analogues resulted in successful preparation of amino acids **22b**, **22d**, **22i**, **22k**, **22l**, and **22s** (Table 2), as mixtures of racemic diastereoemers.

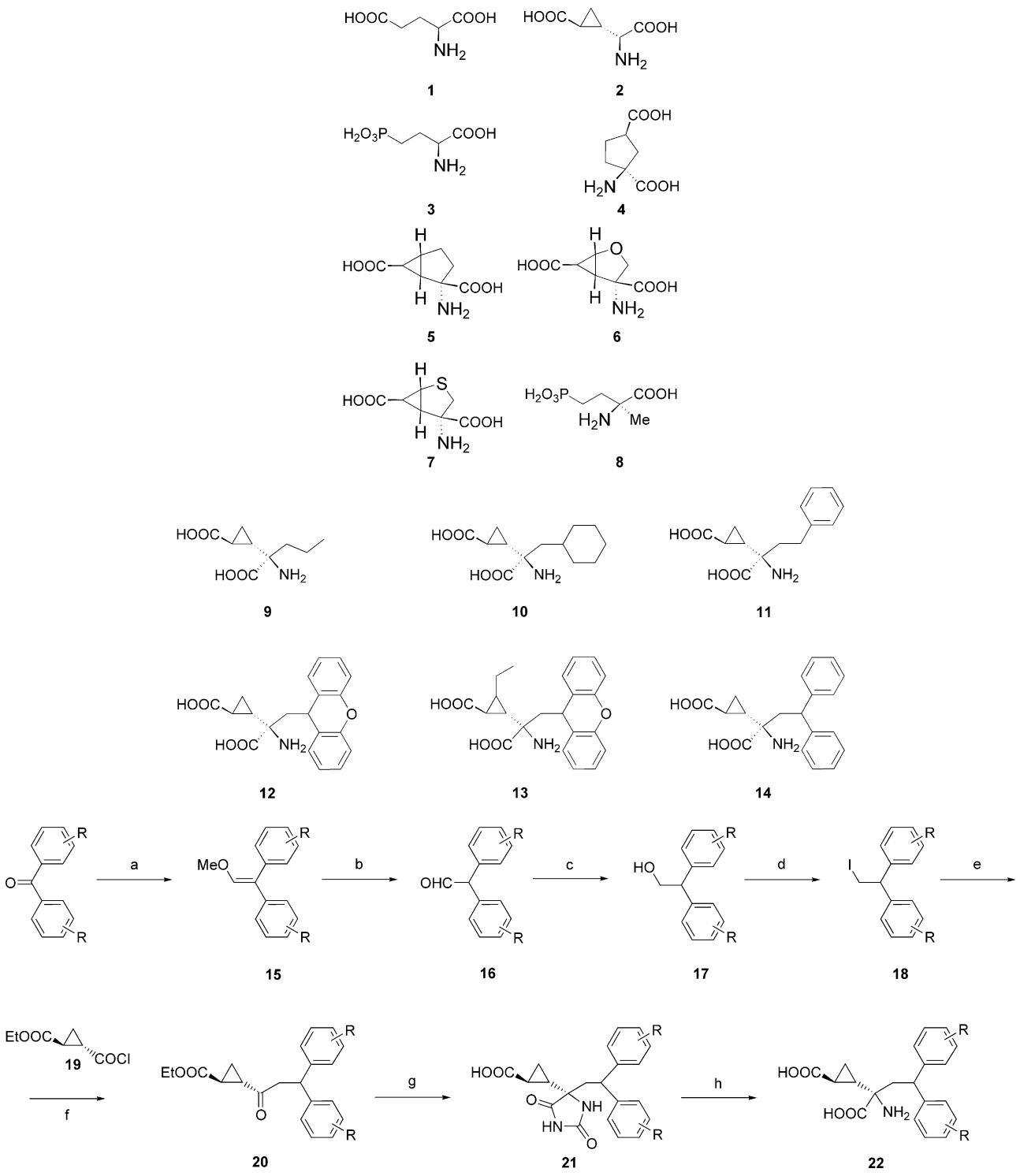
A major limitation of this route was the availability of substituted benzophenones. To further broaden and

Table 1. Isolated yields (%) of compounds **15**–**18b**, **d**, **i**, **k**, **l**, **s**



15 **16** **17** **18**

		15	16	17	18
R = 2,5-diMe, R′ = H	**b**	97	77	84	60
R = R′ = 4-Me	**d**	100	95	82	87
R = R′ = 2-Cl	**i**	100	78	68	86
R = R′ = 4-F	**k**	100	100	74	83
R = R′ = 3-F	**l**	100	67	76	81
From 	**s**	100	81	81	82

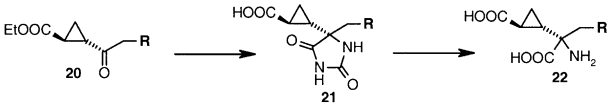


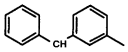
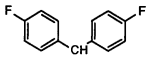
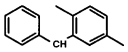
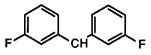
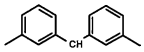
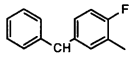
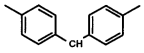
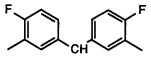
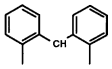
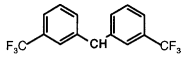
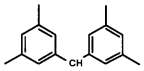
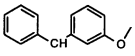
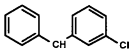
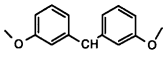
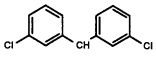
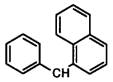
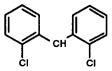
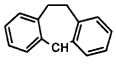
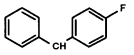
Scheme 1.

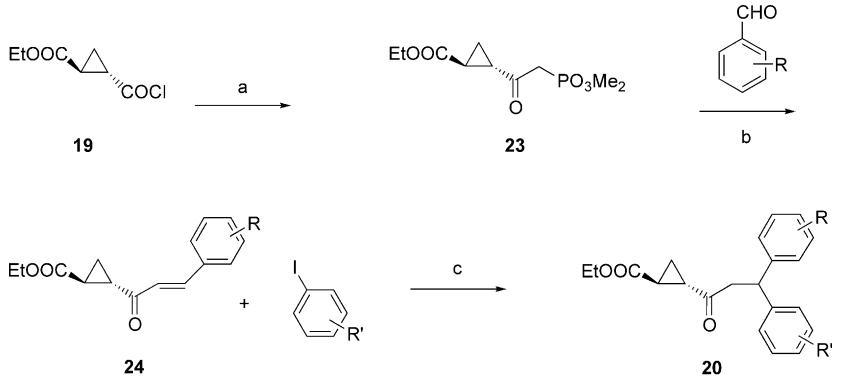
complete the SAR study it was essential to synthesize a wider range of analogues with both *ortho*, *meta*, and *para* substituted benzene rings. We therefore had to find an alternative route to prepare these target amino acids and focused on a strategy that introduces the two phenyl groups one at a time. Our approach was to start by first incorporating a phenyl group through a Wittig–Horner–Emmons methylenation reaction to give an α,β-unsaturated ketone **24** (Scheme 2).

The use of this transformation is already well established through our synthesis of derivatives of the phenyl ethyl compound **11**.[29] Dimethyl phosphonate **23**[29] was deprotonated using sodium bis(trimethylsilyl)amide as

Table 2. Structure and yield of ketones **20a–s**, hydantoins **21a–s** and amino acids **22a–s**



	**a**	63	70	43		**k**	68	89	58
	**b**	62	71	31		**l**	17	56	32
	**c**	65	73	51		**m**	65	83	26
	**d**	54	83	45		**n**	72	58	32
	**e**	86	61	38		**o**	54	93	30
	**f**	97	84	48		**p**	95	87	34
	**g**	61	95	18		**q**	80	81	15
	**h**	37	81	26		**r**	85	69	29
	**i**	52	99	67		**s**	50	80	35
	**j**	64	74	32					



24a	R = H (67%)	**24g**	R = 3,5-di-Me (60%)
24b	R = 2-Me (81%)	**24h**	R = 3-Me, 4-F (56%)
24c	R = 3-Me (68%)	**24i**	R = 3-CF3 (56%)
24d	R = 3-Cl (74%)	**24j**	R = 3,5-bis-CF3 (49%)
24e	R = 2-F (48%)	**24k**	Aromatic Ring = 1-Naphthyl (51%)
24f	R = 3-MeO (56%)		

Scheme 2.

base and subsequently condensed with a benzaldehyde to give **24a–k** in moderate to good yields.

A crucial step is the incorporation of the second phenyl moiety by a 1,4 conjugate addition of a substituted phenyl iodide to the α,β-unsaturated ketone **24**. Reacting **24b** with 2-iodotoluene in a Heck-type[37] coupling reaction using palladium acetate as catalyst and formic acid as a proton donor afforded the desired addition product **20e** in 86% yield with no detectable amounts of

the unreduced product. It is thus possible to achieve, in one step, ketone **20**, thereby avoiding a reduction of the C–C double bond in a later step. Regarding the mechanism, it has been suggested that migratory insertion of the reactive palladium species to the C–C double bond is followed by release of palladium, generating an anionic intermediate which reacts with the formic acid present.[38] Another mechanism suggested, involves enones in a palladotropic shift to give a palladium enolate which after reduction gives the Michael addition product.[37]

The reductive Heck type coupling was carried out on several enones **24** using differently substituted iodobenzenes (Table 2). In most cases, good yields were obtained, except for enones **24e** and **24j**, containing the electron withdrawing substituents fluorine and 3,5-bis(trifluoromethyl), for which only trace amounts of product was formed (according to ^{1}H NMR). However, 3-methyl-4-fluoro enone **24h** successfully couples with both iodobenzene and 2-fluoro-5-iodotoluene to give ketones **20m** and **20n**, respectively. With the phenyl substituent being 3-chloro or 3-trifluoromethyl, products **20h** and **20o** were isolated, albeit in moderate yields. Whereas all of these observations concern the nature of the enone **24**, no limitations in the reactivity was experienced regarding the choice of aryl iodides, and substrates containing either electron withdrawing or donating substituents give the desired coupling products **20** in good yield.

In summary, the route including a reductive Heck type coupling (Scheme 2) has numerous advantages compared to the pathway first applied (Scheme 1). First of all, only two steps are needed from methyl phosphonate **23** to ketone **20**, compared to the five steps required when starting from a benzophenone. Second, the abundance of inexpensive commercially available benzaldehydes as well as their corresponding phenyl iodides makes it possible to synthesize a much greater variety of ketones **20**. Thus, we were able to synthesize amino acids **22** with symmetrically as well as unsymmetrically substituted aromatic rings (Table 2), and thereby reach the target compounds required to complete the SAR study.

Pharmacology

We found that all of the α-alkylated analogues of L-CCG-1 (**2**) described in our earlier studies were potent antagonists at group II mGlu receptors.[28,29] Therefore, we only tested compounds synthesized in this study for their binding affinity to the two cloned human mGluR group II subtypes, mGlu2 and mGlu3. These assays were performed in competition with radiolabelled LY341495 (**12**).[32,33,39] Furthermore, to show whether group I activity is also present, all compounds were tested on mGlu1 and mGlu5 expressing RGT cells for their ability to antagonize a response induced by the agonist quisqualic acid.[23,30] To represent group III mGlu receptors, membranes from RGT cells expressing human mGlu8 receptors were used in a binding assay similar to the one used for mGlu2 and mGlu3 receptors. As previously mentioned, all of the compounds prepared in this study were obtained as mixtures of racemic diastereomers, and no effort was made to separate these isomers.

Concerning the symmetrically substituted analogues, substitution at the *ortho* position results in a substantial decrease in potency, as seen for **22b**, **22e**, and **22i** which were all several orders of magnitude less potent when compared to analogues substituted in the *meta* and *para* positions (Table 3).

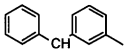
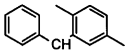
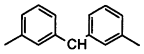
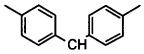
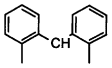
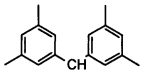
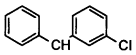
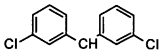
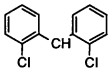
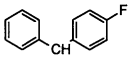
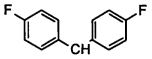
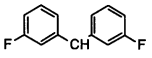
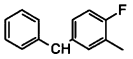
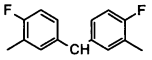
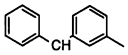
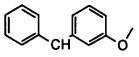
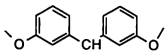
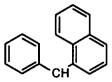
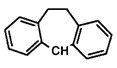
The introduction of more than one substituent on each aromatic ring does not lead to further increased binding. Thus, **22f**, having a methyl group at all four *meta* positions, is three-fold less potent than **22c**, having two symmetric *meta*-Me substituents. Although less significant, the same can be concluded from **22n** (*para*-fluoro, *meta*-Me) being slightly less active than **22k** (*para*-fluoro). An explanation to this finding can be the larger steric bulk of the substituents leading to weaker binding between receptor and ligand. The importance of steric factors is also demonstrated by compounds substituted at only one of the phenyl rings, which, in most cases, show slightly higher binding affinity than the symmetrically disubstituted analogues. The differences are nevertheless small, but the tendency is found when pairwise comparing **22a**/**22c**, **22m**/**22n** and **22p**/**22q**. Exceptions to this are the mono- and di-halogen substituted analogues, demonstrated by **22h**, displaying approximately five-fold higher binding than **22g**, and **22k** being slightly more potent than **22j**.

Whereas racemic **14** was previously reported to show 16-fold selectivity for mGlu3 over mGlu2,[28] none of the synthesized amino acids with the general structure **22** displayed significant subtype selectivity between mGlu2 and mGlu3. The compounds are, however, still far more potent at group II than at group I and III. The most potent analogues, displaying low nanomolar affinities at mGlu2 and mGlu3, are also the compounds being most active at groups I and III (although with K_i and IC_{50} values in the μM range).

It should be noticed that the compounds presented here are synthesized and tested as racemic mixtures. For already resolved racemates, like **14** and the xanthylmethyl analogue LY341495 (**12**), the*S,S,S*-stereoisomer is the most active component. Racemic **12** displays between two and eight times weaker binding at mGlu2 and mGlu3 as compared to the resolved *S,S,S*-isomer,[28,29] and the most active racemates synthesized in the present study are thus comparable to the racemic form of this very potent ligand **12**.

In conclusion, a number of high affinity ligands for group II mGlu receptors have been synthesized and characterized pharmacologically. With varying patterns of aromatic substitution, subtype selectivity between mGlu2 and mGlu3 was not achieved. The most potent of these compounds, **22h**, **22k**, and **22m**, that all contained chloro- or fluoro-substituents in the *meta* or *para*

Table 3. Pharmacological data of synthesized amino acids **22a–s**

HOOC, R, HOOC, NH_2		MGlu2		mGlu3		mGlu1	mGlu5	mGlu8
		K_i (μM)	Relative potency[a]	K_i (μM)	Relative potency[a]	IC_{50} (μM)		K_i (μM)
	**22a**	0.049	21	0.062	47	72	54	2.8
	**22b**	1.8[b]	800	3.6[b]	2700	> 100	> 100	35
	**22c**	0.086	38	0.21	160	> 100	> 100	1.9
	**22d**	0.17	75	0.73[b]	560	> 100	> 100	1.1[b]
	**22e**	14	6000	15	12,000	> 100	> 100	> 100
	**22f**	0.26	113	0.69	530	> 100	> 100	9.3
	**22g**	0.040	17	0.045	34	36	6	0.80
	**22h**	0.007	3	0.010	8	43	49	1.8
	**22i**	0.73[b]	320	1.2[b]	903	> 100	> 100	64[b]
	**22j**	0.29	12	0.009	7	3	62	0.85
	**22k**	0.012	5	0.005	4	3[c]	14	0.34
	**22l**	0.019	8	—	—	38	61	0.25[c]
	**22m**	0.012	5	0.009	7	29	23	0.86
	**22n**	0.019	8	0.024	18	9	44	0.68
	**22o**	0.045	20	0.16	125	28	38	0.90
	**22p**	0.034	15	0.049	38	92	> 100	0.50
	**22q**	0.067	29	0.10	79	> 100	> 100	5.6
	**22r**	0.25[b]	108	0.29	220	83	38	2.2[b]
	**22s**	0.031	13	0.014	11	5	27	0.83[b]

[a]Potency of LY341495 relative to tested compound based on a K_i for Ly341495 of 0.0023 μM and 0.0013 μM at mGlu2 and mGlu3 respectively. Each compound is tested once except in the following cases (average used). [b] $n = 2$. [c] $n = 3$.

positions of the benzene rings, demonstrated K_i values in the range of 5–12 nM. Thus, the best compounds from this SAR study were comparable to one of the most potent group II antagonists known, LY341495 (12). Also, the compounds are far more potent at group II than at mGlu1, mGlu5 and mGlu8 and can thus serve as useful tools for the differentiation between group II and group I/III mGluRs.

Supporting information available

For the synthesized structures, experimental data obtained from NMR spectroscopy, elemental analyses, and mass spectroscopy are included, together with the assigned compound names. Supporting information is available as a Microsoft Word file upon request to the corresponding author.

Experimental

General methods. Pharmacology. Receptor binding assays on cloned cells expressing metabotropic glutamate receptors were performed as previously described:[32,33,39] Membranes, from cells expressing recombinant human mGlu receptors, were prepared by scraping attached cells from T-150 flasks, centrifuging, and freezing resultant pellets. Frozen cell pellets were thawed on the day of assay, suspended in ice-cold assay buffer (10 mM potassium phosphate pH 7.6 + 100 mM potassium bromide), homogenized and washed 3 times by centrifugation at 50,000*g* for 10 min. To start the reaction, washed tissue (0.05–0.20 mg protein) was added to deep-well polypropylene microtiter plates containing [^{3}H]-LY341495 (1 nM for mGlu2 and mGlu3, and 10 nM for mGlu6, mGlu7, and mGlu8) and appropriate concentrations of test compounds in assay buffer. Final assay volume was 0.5 mL. Nonspecific binding was defined with 1 mM L-serine-*O*-phosphate (for mGlu7) or 1 mM L-glutamate (all other receptors). Assay plates were incubated on ice for 45 min and the reaction was terminated by rapid filtration.

Chemistry. Solvents and reagents were purchased from commercial sources and used without further purification unless otherwise stated. Elemental and MS analyses were performed by the Physical Chemistry Department of Lilly Research Laboratories. Column chromatography (CC) was carried out using silica gel 60 (230–400 mesh) from Merck. Compounds were visualized on TLC plates (5 × 10 cm, 0.25 mm thickness, silica gel 60 F_{254}, Merck) using UV light followed by either a ceric ammonium molybdate[28] or ninhydrin solution. Anion exchange chromatography was performed on a Bio-Rad AG1-X8 resin by the procedure previously described.[28]

General procedure for the preparation of methyl diarylenol ethers. Synthesis of 1,1-bis(4-tolyl)-2-methoxyethene (15d). (Methoxymethyl)triphenylphosphonium chloride (57.0 g, 167 mmol) was suspended in dry dioxane (250 mL). A 1 M solution of sodium bis(trimethylsilyl)amide (166 mL) in THF was added dropwise and the reaction mixture stirred 30 min at room temperature. 4,4′-Dimethylbenzophenone (25.0 g, 119 mmol) was added and stirring continued 2 h at reflux temperature. After cooling to room temperature, H_2O (500 mL) was added and the mixture extracted with EtOAc. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. CC (5% EtOAc/hexane) of the residue afforded **15d** as a colorless oil (28.5 g, 100%). ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 6H), 3.74 (s, 3H), 6.41 (s, 1H), 7.10–7.35 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.2, 60.4, 120.4, 128.1, 128.7, 128.9, 129.7, 134.9, 136.0, 136.1, 137.7, 145.6. MS(ES) *m*/*z* 239 ($[M+1]^+$, 32%). Anal. ($C_{17}H_{18}O$) C, H.

General procedure for the preparation of diaryl acetaldehydes. Synthesis of 2,2-bis(4-tolyl)acetaldehyde (16d). Compound **15d** (27.0 g, 113 mmol) was dissolved in Et_2O (400 mL) and to this solution was slowly added a 70% aqueous solution of $HClO_4$ (115 mL). After stirring overnight at room temperature the mixture was added slowly to saturated $NaHCO_3$ (aq) (1.2 L). The organic phase was isolated and the aqueous phase extracted with Et_2O. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. CC of the residue (10% EtOAc/hexane) afforded 24.1 g (95%) of **16d** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 6H), 4.81 (s, 1H), 7.01–7.20 (m, 8H), 9.90 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 63.4, 129.0, 129.7, 133.5, 137.3, 198.8. MS(FD^+) *m*/*z* 224 (M^+, 100%). Anal. ($C_{16}H_{16}O$) C, H.

General procedure for the preparation of diaryl ethanols. Synthesis of 2,2-bis(4-tolyl)ethanol (17d). Compound **16d** (23.0 g, 103 mmol) was dissolved in EtOH (300 mL) and added $NaBH_4$ (3.88 g, 103 mmol). The mixture was stirred at room temperature for 4 h and then concentrated in vacuo. H_2O (300 mL) was added and the solution extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. CC (10–20% EtOAc/hexane) afforded **17d** as a white solid (19.2 g, 82%). ^{1}H NMR ($CDCl_3$) δ 1.48 (s br, 1H), 2.31 (s, 6H), 4.12–4.13 (m, 3H), 7.14–7.17 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 21.0, 52.9, 66.3, 128.2, 129.4, 136.3, 138.6. MS(FD^+) *m*/*z* 226 (M^+, 100%). Anal. ($C_{16}H_{18}O$) C, H.

General procedure for the preparation of Iodo diarylethanes. Synthesis of 1,1-bis(4-tolyl)-2-iodoethane (18d). Triphenylphosphine (30.1 g, 115 mmol) dissolved in dry CH_2Cl_2 (250 mL) was added iodine (29.1 g, 115 mmol) and stirred 5 min at room temperature. Imidazole (13.0 g, 191 mmol) was added and the mixture stirred 15 min followed by addition of alcohol **17d** (17.3 g, 76.4 mmol) dissolved in dry CH_2Cl_2 (35 mL). After stirring overnight at room temperature the reaction mixture was quenched by addition of 10% aqueous $NaHSO_4$ (200 mL). The solution was extracted with CH_2Cl_2 and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. After CC (10% EtOAc/hexane) compound **18d** was isolated as a colorless oil in 87% yield (22.3 g). ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 6H), 3.71 (d, J = 8.0 Hz, 2H), 4.27 (t, J = 8.0 Hz, 1H), 7.11–7.12 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 10.0, 21.0, 53.6, 127.5, 129.3, 136.5, 139.8. MS(FD^+) *m*/*z* 336

(M^+, 100%). Anal. ($C_{16}H_{17}I$) H; C: calcd 57.16; found, 58.03.

Method A. General procedure for the preparation of ketones by Zn(Cu) couple mediated coupling of iodo diarylethanes and carboxylic acid chloride 19. Synthesis of 2,2-bis(4-tolyl)ethyl (1*RS*,2*RS*)-2-carbethoxycycloprop-1-yl ketone (20d). A solution of **18d** (22.0 g, 65.4 mmol) and Zn(Cu) couple (10.2 g, 157 mmol) in dry toluene (250 mL) and *N,N*-dimethylacetamide (35 mL) was heated to 60 °C for 3 h. The heating bath was removed and tetrakis(triphenylphosphine)palladium(0) (3.0 g, 2.6 mmol) added. After 5 min acyl chloride **19** (11.6 g, 65.7 mmol) was added and the reaction mixture stirred at room temperature overnight. The solution was then filtered through Celite and the filtrate washed with 10% aqueous $NaHSO_4$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. CC of the residue (10–15% EtOAc/hexane) afforded **20d** as a colorless oil (12.4 g, 54%). ^{1}H NMR ($CDCl_3$) δ 1.25–1.34 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H), 1.99–2.05 (m, 1H), 2.28 (s, 6H), 2.39–2.45 (m, 1H), 3.31 (d, J = 7.7 Hz, 2H), 4.12 (q, J = 7.0 Hz, 2H), 4.52 (t, J = 7.7 Hz, 1H), 7.05–7.11 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 14.2, 17.1, 20.9, 24.1, 29.5, 45.5, 50.2, 61.0, 127.5, 129.2, 135.9, 140.8, 172.0, 205.8. MS(ES) m/z 350 (M^+, 17%). Anal. ($C_{23}H_{26}O_3$) C, H.

Method B. General procedure for the preparation of ketones by a Heck type 1,4 conjugate addition. Synthesis of of 2,2-bis(2-tolyl)ethyl (1*RS*,2*RS*)-2-carbethoxycycloprop-1-yl ketone (20e). Enone **24b** (4.89 g, 18.9 mmol) in triethylamine (6.51 g, 64.4 mmol) was added 2-iodotoluene (9.91 g, 45.4 mmol), palladium(II)acetate (21.2 mg, 0.095 mmol), dry CH_3CN (11 mL) and formic acid (1.97 g, 49.2 mmol). After stirring overnight at 80 C the reaction mixture was added additional palladium(II)acetate (21.2 mg, 0.095 mmol) and stirred for another 16 h at 80 C. After cooling to room temperature the mixture was added H_2O (50 mL) and extracted with EtOAc. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography (10% EtOAc/hexane) of the residue afforded **20e** as a colorless oil (5.72 g, 86%). ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H), 1.30–1.37 (m, 2H), 1.99–2.05 (m, 1H), 2.26 (s, 3H), 2.30 (s, 3H), 2.39–2.45 (m, 1H), 3.20 (d, J = 7.6 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 4.90 (t, J = 7.6 Hz, 1H), 7.02–7.23 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 14.2, 17.0, 19.4, 24.2, 29.4, 38.8, 49.1, 61.0, 126.0, 126.1, 126.4, 126.4, 126.7, 126.9, 130.7, 130.7, 135.9, 136.00, 140.9, 141.0, 171.9, 205.8. MS(ES) m/z 351 ($[M+1]^+$, 22%). Anal. ($C_{23}H_{26}O_3$) C, H.

General procedure for the carboxylic ester hydrolysis and subsequent hydantoin formation. Synthesis of (5*SR*)- and (5*RS*)-5-(2,2-bis(4-tolyl)ethyl)-5-((1*RS*,2*RS*)-2-carboxycycloprop-1-yl)imidazolidine-2,4-dione (21d). Ketone **20d** (9.60 g, 27.4 mmol) dissolved in EtOH (200 mL) and H_2O (200 mL) was added 1 M NaOH (aq) (41 mL) and stirred at 55 °C for 6 h. KCN (17.8 g, 273 mmol) and $(NH_4)_2CO_3$ (47.4 g, 493 mmol) was added in two portions during the next 5 days while stirring at 55 °C. After cooling to room temperature the reaction mixture was neutralized with 5 M HCl (aq) (Caution: evolution of HCN gas) and extracted with EtOAc. The combined organic extracts were washed with 10% aqueous $NaHSO_4$, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residual solid was recrystallized from MeOH/H_2O, filtered, washed with water, and dried to afford **21d** as a white solid (8.94 g, 83%). ^{1}H NMR (DMSO) δ 0.68–0.74 (m, 1H), 0.83–0.89 (m, 2H), 0.93–0.99 (m, 1H), 1.21–1.27 (m, 1H), 1.50–1.61 (m, 3H), 2.23 (s, 12H), 2.25–2.40 (m, 2H), 2.73–2.94 (m, 2H), 3.94–3.97 (m, 2H), 7.00–7.21 (m, 16H), 7.73 (s, 1H), 7.83 (s, 1H), 10.30 (s, 1H), 10.38 (s, 1H); ^{13}C NMR (DMSO) δ 9.1, 10.2, 14.9, 15.7, 20.5, 20.6, 27.4, 27.9, 41.2, 45.8, 45.9, 63.2, 63.4, 127.0, 127.1, 127.5, 127.6, 128.6, 128.7, 128.9, 128.9, 134.8, 134.8, 135.0, 135.1, 140.3, 140.8, 142.4, 142.6, 156.4, 173.7, 174.0, 176.0, 176.2. MS(ES) m/z 391 ($[M-1]^+$, 100%), 392 (M^+, 31%). Anal. ($C_{23}H_{24}N_2O_4 0.1H_2O$) C, H, N.

General procedure for the hydantoin hydrolysis into amino acid. synthesis of (2*SR*)- and (2*RS*)-2-amino-4,4-bis(4-tolyl)-2-((1*RS*,2*RS*)-2-carboxycycloprop-1-yl)butanoic Acid (22d). Hydantoin **21d** (6.21 g, 15.8 mmol) dissolved in 1 M NaOH (aq) (100 mL) was heated to 200 °C for 24 h in a sealed stainless steel high-pressure vessel. After cooling to room temperature the reaction mixture was filtered and pH adjusted to 4 with 5 M aqueous HCl. The resulting precipitate was filtered off, washed with H_2O, dried, and washed with Et_2O to give amino acid **22d** as an off white solid in 45% yield (2.60 g). ^{1}H NMR (DMSO) δ 0.22–0.35 (m, 1H), 0.55–0.62 (m, 1H), 0.80–0.89 (m, 1H), 1.15–1.25 (m, 2H), 1.40–1.50 (m, 2H), 1.82–1.93 (m, 1H), 2.23 (s, 12H), 4.15–4.23 (m, 2H), 4.35–4.42 2H), 7.02–7.20 (m, 16H). MS(ES) m/z 366 ($[M-1]^+$, 100%), 367 (M^+, 32%). Anal. ($C_{22}H_{25}NO_4 0.3H_2O$) C, H, N.

General procedure for the preparation of aryl enones by Wittig Horner–Emmons methylenation. Synthesis of (1*RS*,2*RS*)-2-carboxycycloprop-1-yl 2-(2-tolyl)ethenyl ketone (24b). Dimethyl phosphonate **23** (6.60 g, 24.5 mmol) dissolved in dry THF (80 mL) was added a 1 M solution of sodium bis(trimethylsilyl)amide (27 mL) in THF dropwise. After stirring 30 min at room temperature 2-tolualdehyde (3.24 g, 27 mmol) was added dropwise. After 1 h the reaction mixture was quenched with H_2O (100 mL) and extracted with Et_2O. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. CC (5–10% EtOAc/hexane) of the residue afforded **24b** as a colorless oil (5.10 g, 81%). ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3H), 1.50–1.59 (m, 2H), 2.28–2.34 (m, 1H), 2.46 (s, 3H), 2.73–2.79 (m, 1H), 4.18 (q, J = 7.2 Hz, 2H), 6.83 (d, J = 15.9 Hz, 1H), 7.21–7.62 (m, 4H), 7.95 (d, J = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 17.6, 19.8, 24.5, 28.4, 61.1, 126.4, 126.5, 127.0, 130.4, 130.9, 133.3, 138.3, 141.0, 172.3, 196.4. MS(ES) m/z 259 ($[M+1]^+$, 66%). Anal. ($C_{16}H_{18}O_3$) C, H.

Acknowledgements

The authors thank the Physical Chemistry Department of Lilly Research Laboratories for ^{13}C NMR spectra as

well as MS and elemental analyses. Also a special thanks to Jack Campbell, Lilly Research Laboratories, for the liberal use of his high-pressure hydrogenation equipment.

References and Notes

1. McBain, C. J.; Mayer, M. L. *Physiol. Rev.* **1994**, *74*, 723.
2. Kyle, D. J.; Patch, R. J.; Karbon, E. W.; Ferkany, J. W. In *Excitatory Amino Acid Receptors: Design of Agonists and Antagonists,* Krogsgaard-Larsen, P.; Hansen, J. J., Eds.; Ellis Horwood: Chichester, 1992; pp 121–161.
3. Lees, G. J. *Drugs* **2000**, *59*, 33.
4. Bleakman, D.; Lodge, D. *Neuropharmacology* **1998**, *37*, 1187.
5. Fletcher, E. J.; Lodge, D. *Pharmacol. Ther.* **1996**, *70*, 65.
6. Borges, K.; Dingledine, R. *Progr. Brain Res.* **1998**, *116*, 153.
7. Chittajallu, R.; Braithwaite, S. P.; Clarke, V. R. J.; Henley, J. M. *Trends Pharmacol. Sci.* **1999**, *20*, 26.
8. Shinozaki, H. In *Excitatory Amino Acid Receptors: Design of Agonists and Antagonists*; Krogsgaard-Larsen, P., Hansen, J. J., Eds.; Ellis Horwood: Chichester, 1992; pp 261–291.
9. Schoepp, D. D. *J. Pharmacol. Exp. Ther.* **2001**, *299*, 12.
10. Ozawa, S.; Kamiya, H.; Tsuzuki, K. *Progr. Neurobiol.* **1998**, *54*, 581.
11. Schoepp, D. D.; Conn, P. J. *Trends Pharmacol. Sci.* **1993**, *14*, 13.
12. Bräuner-Osborne, H.; Egebjerg, J.; Nielsen, E. Ø.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609.
13. Parsons, C. G.; Danysz, W.; Quack, G. *Drug News Perspect.* **1998**, *11*, 523.
14. Bruno, V.; Battaglia, G.; Copani, A.; D'Onofrio, M.; Iorio, P. D.; Blasi, A. D.; Melchiorri, D.; Flor, P. J.; Nicoletti, F. *J. Cereb. Blood Flow Metab.* **2001**, *21*, 1013.
15. Monn, J. A.; Schoepp, D. D. *Annu. Rep. Med. Chem.* **2000**, *35*, 1.
16. Schoepp, D. D.; Jane, D. E.; Monn, J. A. *Neuropharmacology* **1999**, *38*, 1431.
17. Pin, J.-P.; De Colle, C.; Bessis, A.-S.; Acher, F. *Eur. J. Pharmacol.* **1999**, *375*, 277.
18. Hayashi, Y.; Tanabe, Y.; Aramori, I.; Masu, M.; Shimamoto, K.; Ohfune, Y.; Nakanishi, S. *Br. J. Pharmacol.* **1992**, *107*, 539.
19. Tanabe, Y.; Nomura, A.; Masu, M.; Shigemoto, R.; Mizuno, N.; Nakanishi, S. *J. Neurosci.* **1993**, *13*, 1372.
20. Palmer, E.; Monaghan, D. T.; Cotman, C. W. *Eur. J. Pharmacol.* **1989**, *166*, 585.
21. Schoepp, D. D.; Monn, J. A.; Marek, G. J.; Aghajanian, G.; Moghaddam, B. *CNS Drug Rev.* **1999**, *5*, 1.
22. Kingston, A. E.; O'Neill, M. J.; Lam, A.; Bales, K. R.; Monn, J. A.; Schoepp, D. D. *Eur. J. Pharmacol.* **1999**, *377*, 155.
23. 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.
24. 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.
25. Battaglia, G.; Monn, J. A.; Schoepp, D. D. *Neurosci. Lett.* **1997**, *229*, 161.
26. Monn, J. A.; Valli, M. J.; Massey, S. M.; Hansen, M. M.; Kress, T. J.; Wepsiec, J. P.; Harkness, A. R.; Grutsch, J. L., Jr.; 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.
27. Jane, D. E.; Jones, P. L.; St, J.; Pook, P. C.-K.; Tse, H-W.; Watkins, J. C. *Br. J. Pharmacol.* **1994**, *112*, 809.
28. Ornstein, P. L.; Bleisch, T. J.; Arnold, M. B.; Wright, R. A.; Johnson, B. G.; Schoepp, D. D. *J. Med. Chem.* **1998**, *41*, 346.
29. 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. *J. Med. Chem.* **1998**, *41*, 358.
30. Kingston, A. E.; Ornstein, P. L.; Wright, R. A.; Johnson, B. G.; Mayne, N. G.; Burnett, J. P.; Belagaje, R.; Wu, S.; Schoepp, D. D. *Neuropharmacology* **1998**, *37*, 1.
31. Ornstein, P. L.; Arnold, M. B.; Bleisch, T. J.; Wright, R. A.; Wheeler, W. J.; Schoepp, D. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1919.
32. Johnson, B. G.; Wright, R. A.; Arnold, M. B.; Wheeler, W. J.; Ornstein, P. L.; Schoepp, D. D. *Neuropharmacology* **1999**, *38*, 1519.
33. Wright, R. A.; Arnold, M. B.; Wheeler, W. J.; Ornstein, P. L.; Schoepp, D. D. *J. Pharmacol. Exp. Ther.* **2001**, *298*, 453.
34. Collado, I.; Ezquerra, J.; Mazón, A.; Pedregal, C.; Yruretagoyena, B.; Kingston, A. E.; Tomlinson, R.; Wright, R. A.; Johnson, B. G.; Schoepp, D. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2849.
35. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
36. Tamaru, Y.; Ochiai, H.; Sanda, F.; Yoshida, Z.-i. *Tetrahedron Lett.* **1985**, *26*, 5529.
37. Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.
38. Cacchi, S.; Arcadi, A. *J. Org. Chem.* **1983**, *48*, 4236.
39. Wright, R. A.; Arnold, M. B.; Wheeler, W. J.; Ornstein, P. L.; Schoepp, D. D. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2000**, *362*, 546.