Discovery of Orally Efficacious Tetracyclic Metabotropic Glutamate Receptor 1 (mGluR1) Antagonists for the Treatment of Chronic Pain

Wen-Lian Wu,*,† Duane A. Burnett,† Martin Domalski,† William J. Greenlee,† Cheng Li,† Rosalia Bertorelli,‡ Silva Fredduzzi,‡ Gianluca Lozza,‡ Alessio Veltri,‡ and Angelo Reggiani‡

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033, and Schering-Plough Research Institute, San Raffaele Science Park, Via Olgettina, 58, 20132 Milan, Italy

Received May 21, 2007

Abstract: Metabotropic glutamate receptor 1 (mGluR1) plays important roles in the neurotransmission and pathogenesis of several neurological disorders, including chronic pain. Antagonists of mGlur1 are suggested to be useful for the treatment of pain. Herein, we report the discovery of a novel series of tetracyclic mGluR1 antagonists, such as **23c** and **23e**, with oral efficacy of ED_{50} of 8 and 5.1 mg/kg, respectively, in rat spinal nerve ligation neuropathic pain model.

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system. Glutamate synaptic responses in the central nervous system are mediated via activation of two families of receptors: ionotropic glutamate receptors and metabotropic glutamate receptors (mGluRs). The G-protein-coupled mGlu receptors are divided into three different groups, group I (mGluR1 and mGluR5), group II (mGluR2 and mGluR3), and group III (mGluR4, mGluR7 and mGluR8), based on structural homology, pharmacology, and signal transduction mechanisms.[1] Group I receptors (mGluR1 and mGluR5) play a key role in the central sensitization of pain, in addition to a variety of functions with potential implications in neurological and psychiatric disorders.[2] A number of behavioral and electrophysiological studies have demonstrated a specific role for group I mGluRs, and in particular mGluR1 receptors, in nociceptive processing in the CNS, including mechanisms of hyperalgesia and inflammation.[3] The intrinsic activation of spinal mGluR1 in chronic nociception has been demonstrated using antagonists, antibodies, and antisense oligonucleotides. Intrathecal administration of an mGluR1 antagonist produced antinociceptive effects in the second phase of formalin-induced nociceptive behavior.[4] There is mounting evidence to suggest use of mGluR1 antagonists for the treatment of chronic pain.[5] Several groups have reported a variety of structurally diverse mGluR1 antagonists, such as **1** (LY 456066),[6a] **2**,[6b] **3** (JNJ 16259685),[6c] **4** (A-841720),[6d] and other small molecules.[6e,f] Particularly, the publication of tricyclic **4**, derived from a strikingly similar lead series as ours, from Abbott laboratories, prompted us to disclose our novel tetracyclic mGluR1 antagonists.

Our lead compound **5** (Figure 2), which originated from the public domain,[7a] emerged as a potent mGluR1 antagonist in our screening program.[7b] Despite its favorable overall pharmacological properties, it was deemed unsuitable as a clinical candidate. Moreover, it proved to undergo extensive N-demethylation and O-demethylation in a rapid rat pharmacokinetic study (AUC_{0-6h} = 1927 nM·h, AUC_{0-6h} (M-14) = 1337 nM·h), after oral administration at a dosage of 10 mg/kg. In the current investigation, we endeavored to improve the metabolic stability of this compound class and ultimately to achieve novel and potent mGluR1 antagonists. As depicted in Figure 2, our design strategy was based on an observation that bromide **6** (h-mGluR1 IC_{50} = 5.9 nM) was equipotent with lead **5**.[8] Conformational restriction imposed by connecting the two substituents to form a five-membered or six-membered heterocycle fused to the pyridine ring led to novel tetracyclic analogues. In so doing, the metabolically labile dimethylamino group was replaced with a series of heterocycles.

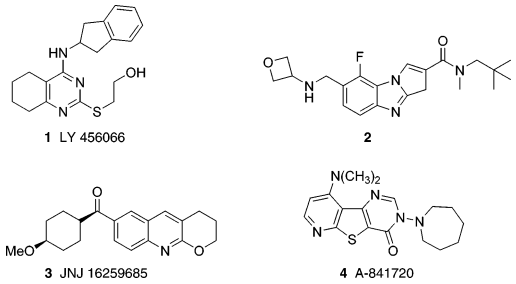


Figure 1. Representative mGluR1 antagonists.

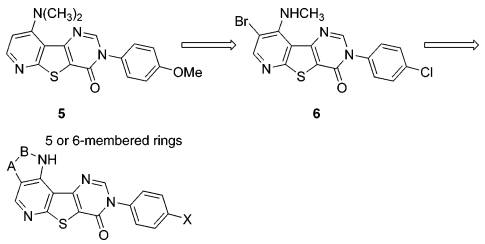


Figure 2. Lead compound and design of the tetracyclic analogues.

The synthesis of the pyrrolo analogues **11a**−**c** is outlined in Scheme 1. Treatment of **7a**[7b] with ammonium acetate gave 4-amino compound **8a**, which was converted to its bromide **9a**.[9] Palladium-mediated cross-coupling reaction of **9a** and ethoxyvinyltributyltin provided **10a**, which was subsequently hydrolyzed to furnish **11a**.[10] The corresponding 4-methoxy analogue **11c** was prepared in a similar way. The synthesis of **11b** was achieved by a modified approach. Cross-coupling reaction of **9b** and allyltributyltin gave **10b**;[11] subsequent oxidative cleavage produced an aldehyde intermediate, which spontaneously formed **11b**.

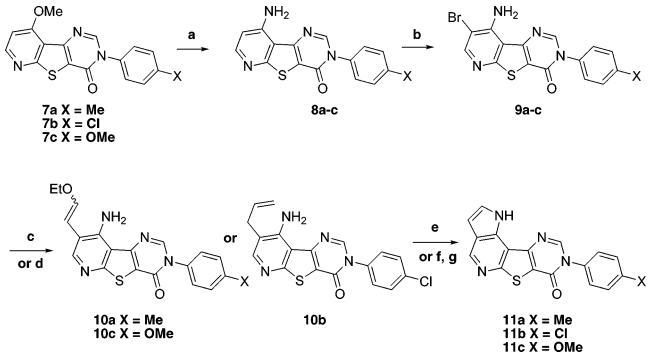
Compounds **14a** and **14b** were prepared via the syntheses depicted in Scheme 2. Nitration of **12**[6d,7b] in refluxing TFA took place selectively on the pyridine ring, yielding **13a** and **13b**. The exact mechanism of the N-demethylation is not clear. Under prolonged heating, the reaction proceeded to completion, yielding **13a** almost exclusively.[12] Subsequent reduction of the nitro groups of **13a** and **13b** followed by ring closure led to **14a** and **14b**, respectively.

The indazole analogues **18a** and **18b** were synthesized utilizing intermediates **7a** and **7b** as scaffolds,[7b] respectively, as illustrated in Scheme 3. Removal of the Me group of **7b** gave 4-hydroxypyridine **15b**; bromination followed by replacement of the hydroxyl group with chloro substituent afforded **16b**.[13] Exchange of the bromo substituent to a vinyl group was achieved by a cross-coupling reaction. Oxidative cleavage of the vinyl group provided an aldehyde intermediate, which was

* To whom correspondence should be addressed. Phone: (908) 740-6525. Fax: (908) 740-7164. E-mail: wen-lian.wu@spcorp.com.
† Schering-Plough Research Institute, NJ.
‡ Schering-Plough Research Institute, Italy.

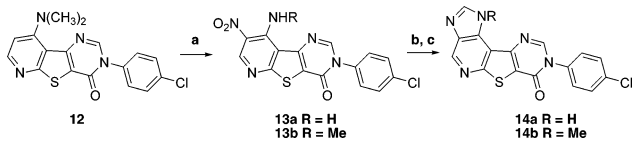
10.1021/jm070590c CCC: $37.00
Published on Web 10/11/2007

Scheme 1[a]



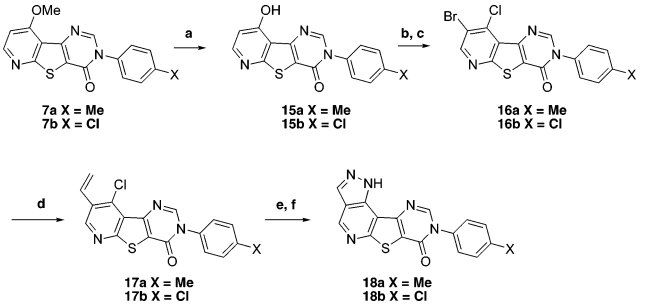
[a] Reagents and conditions: (a) NH_4OAc, 130 °C, neat, ~60% (**8a**); (b) Br_2, AcOH, 87% (**9a**); (c) ethoxyvinyltributyltin, $Pd(PPh_3)_4$, DIEA, 180 °C (microwave), 20 min; (d) allyltributyltin, $Pd(PPh_3)_4$, DIEA, 175 °C (microwave), 30 min, 37% (**10b**); (e) HCl, THF, 51% (**9c**−**11c**); (f) OsO_4 (cat.), NMO, 29%; (g) $NaIO_4$, H_2O, 86%.

Scheme 2[a]



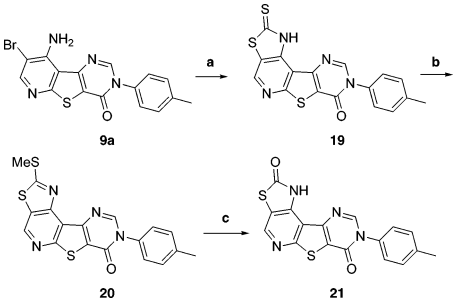
[a] Reagents and conditions: (a) HNO_3, TFA, reflux, 8 h, 75% (**13a**); or 1 h, 31% (**13b**); (b) $SnCl_2$, HCl; (c) HCOOH, *o*-xylene, heat, 9% (**14a**); 70% (**14b**) in two steps.

Scheme 3[a]



[a] Reagents and conditions: (a) BBr_3, DCM, −78 °C, 78% (**15a)**; (b) Br_2, AcOH, room temp; (c) $POCl_3$, reflux, 94% (**16b**, in two-step); (d) vinyltributyltin, $Pd(PPh_3)_4$, DIEA, microwave, 140 °C, 40 min, 37%; (e) OsO_4 (cat.), $NaIO_4$, 68%; (f) NH_2NH_2, *t*-BuOH, 70 °C, 23%.

Scheme 4[a]

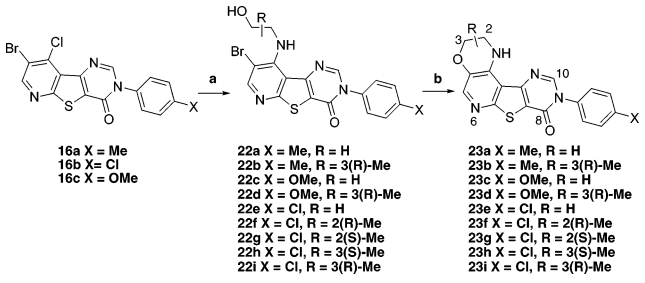


[a] Reagents and conditions: (a) potassium xanthate, DMF, 160 °C, 74%; (b) K_2CO_3, MeI, DMF, room temp, 76%; (c) NaOMe, DMF, room temp, 48%.

treated with hydrazine to furnish **18b**.[14] Compound **18a** was prepared accordingly.

The syntheses of **19**−**21** are shown in Scheme 4. Heating **9a** with potassium xanthate afforded **19**, which in turn was easily methylated to give **20**. Finally, hydrolysis of **20** was effected by treatment with sodium methoxide in DMF to furnish **21**.[15]

Scheme 5[a]



[a] Reagents and conditions: (a) hydroxyethylamine, MeCN, 100 °C, 1 day, 80% (**22e**); (b) $Pd(OAc)_2$, racemic 2-(di-*tert*-butylphosphino)-1,1′-binaphthyl, Cs_2CO_3, toluene, 125 °C, 20 h, 37% (**23e**).

Table 1. In Vitro Biological Data

	IC_{50} (nM)[a,b]		
compd	mGluR1	mGluR5	rat K_i (nM)[a,c]
5	9.5	10000	7.9
11a	0.7	>1000	16.9
11b	0.4	1.7%	2.4
11c	4.9	>10000	28.6
14a	6.0	−1.7%	10.8
14b	9.8	0.15%	103.5
18a	16.8	5%	17.8
18b	37.6	−12%	19.6
19	541	−10%	1000
20	636	−2%	788
21	446	−8%	1000
23a	2.2	702	0.5
23b	5.3	609	0.6
23c	2.5	>1000	1.0
23d	2.4	>1000	0.3
23e	2.9	>1000	0.4
23f	24.4	>1000	9.1
23g	12	>1000	0.5
23h	2.2	>1000	1.5
23i	1.4	>1000	0.2

[a] The IC_{50} and K_i data are an average of at least three measurements, performed on human mGlu1/5 and rat mGlu1 receptors, respectively. The standard error was 10%, and variability was less than 2-fold from assay to assay. [b] Data for inhibition of radioligand binding. % indicates percent inhibition at 1 μM. [c] See ref 19.

The morpholine analogues **23a**−**i** were prepared according to Scheme 5. Compound **16b** was treated with hydroxylamine to give intermediate **22b** (R = H) in high yield. Subsequent intramolecular C−O bond formation under Buchwald conditions led to analogue **23e** (X = Cl, R = H).[16] Related morpholino analogues **23** were obtained using analogous chemistry.

The above-mentioned tetracyclic analogues were assayed on human and mGlu1 receptor in a FLIPR assay and in a rat receptor binding assay,[17] and the data are summarized in Table 1.

The three pyrrolo analogues (**11a**−**c**) are all very potent and selective mGluR1 antagonists. Encouraged by this initial success, we next examined other isosteric five-membered heterocycles. As revealed in Table 1, imidazole analogue **14a** exhibited potency comparable to lead **5**, though 15-fold less than the corresponding pyrrolo compound **11b**. Interestingly, its N−Me derivative **14b** retained similar human mGluR1 potency but much less rat mGluR1 activity. The two indazole analogues (**18a** and **18b**) displayed reduced mGluR1 activity by severalfold, suggesting the 2-position had limited tolerance. Indeed, large substituents as in **19**−**21** resulted in dramatic loss of mGluR1 potency.

It was increasingly apparent that all the flat fused tetracyclic analogues mentioned above have poor water solubility, presumably driven by intermolecular π-stacking of the flat aromatic

Table 2. PK Profile and in Vivo Activity of Selected Compounds

compd	AUC_{0-6h} (nM·h)[a]	T_{max} (h)[a]	C_{max} (nM)[a]	rat SNL PWT (g)[b]	rat SNL MPE (%)[b]
5	1927	0.5	564	13.2 ± 1.3	87 ± 9
11a	35	0.5	71		
11b	18	0.5	37		
11c	1325	2	394	6.6 ± 2.3	39 ± 16
23a	77	1	70		
23c	1563	2	467	8.5 ± 1.6	50 ± 12
23e	366	1	198	11.8 ± 1.6	73 ± 13
23h	8434	2	2046	7.7 ± 1.5	44 ± 12
23i	5187	0.5	1425	10.9 ± 1.6	68 ± 12

[a] Data are from pooled samples from two rats ($n = 2$, dosed at 10 mg/kg, po) in cassette-accelerated rapid rat protocol as described in ref 18. [b] Data are the mean ± SE from 8 to 10 rats dosed at 10 mg/kg, po, and they are expressed as paw withdrawal threshold (PWT, g). MPE (maximal percentage of effect) was also reported. For all experimental details see ref 19.

tetracycles. Therefore, we switched our attention to nonaromatic six-membered ring systems as exemplified by **23a**−**i**. Initially, morpholine analogue **23a** was found to be a very potent mGluR1 antagonist ($IC_{50} = 2.2$ nM). Further isosteric replacement of 4-Me of the right-hand phenyl ring with 4-Cl and 4-MeO generated **23c** and **23e**, with approximately equal potency against mGlu1 receptors. Anticipating that substituents on the morpholine ring would attenuate potential metabolism of the methylene sites and also reduce the π-stacking, we next prepared four methyl-substituted analogues **23f**−**i** from commercially available enantiomerically pure amino alcohols. As shown in Table 1, 3-Me substituted analogues **23h** and **23i** were more potent than their 2-Me countparts **23f** and **22g**, respectively; for 2-Me and 3-Me substituted series, the α-isomers (**23g**, **23i**) were 2-fold more potent than their corresponding β-isomers (**23f**, **23h**). We also examined two 3(*R*)-Me substituted analogues **23b** and **23d**, both of which showed single-digit nanomolar human mGluR1 potency. It is noteworthy that most of the morpholine analogues exhibited subnanomolar K_i values against rat mGlu1 receptors. As shown in Table 1, all the tetracycles demonstrated high selectivity against human mGlu5 receptors.

Having achieved potent and selective mGluR1 anatagonists, we chose several compounds for pharmacokinetic (PK) investigations in rats.[18] The PK profiles are exhibited in Table 2.

To improve the overall pharmacokinetic properties, we aimed to eliminate the metabolically unstable dimethylamino substituent. As shown in Table 2, the area under curves (AUCs) of pyrrolo compounds **11a** and **11b**, free of the dimethylamino groups, were very low, likely results of their poor absorption. Compound **11c**, bearing a polar *p*-MeO phenyl group, had moderate plasma AUC. The AUC of morpholine **23a** did not improve, consistent with observation of the PK of other analogues bearing a *p*-tolyl substituent (data not shown here). However, **23c** and **23e** displayed improved AUCs compared to **23a**.

As expected, introduction of methyl substituents on the morpholine ring, such as **23h** and **23i**, conferred an advantage over their parent **23e**. The significantly improved AUCs may be attributed, at least partially, to less metabolism and/or better absorption. In contrast to the flat five-membered counterparts, these morpholine rings are not aromatic and cannot be metabolized to aromatics. As a result, the morpholine analogues have less π-stacking and thereby greater water solubility.

Compounds **11c** and **23c**,**e**,**h**,**i**) have been chosen for further study in the rat spinal nerve ligation neuropathic pain model (SNL model).[19] While **11c** exhibited modest in vivo potency in SNL (39% reversal at 10 mg/kg), **23c** and **23e** demonstrated strong activity, with ED_{50} of 8 (95% confidence interval of 2.6−24) and 5.1 (95% confidence interval of 0.9−28.2) mg/kg. Compounds **23h** and **23i** also showed significant activity at dose of 10 mg/kg (the ED_{50} values were not determined).

In summary, using heterocycles as surrogates for the metabolically labile dimethylamino group of the lead **5**, we have succeeded in the identification of three distinctive types of tetracyclic mGluR1 antagonists, namely, indoles **11a**−**c**, imidazole **14a**, and morpholine analogues **23a**−**i**. Among them, especially remarkable are the mopholine analogues with improved pharmacokinetic profiles (**23h** and **23i**) and excellent in vivo activity in rat SNL model (**23c** and **23**e). The high potency and subtype selectivities, combined with pronounced oral efficacy, rendered these mGluR1 antagonists valuable tools for in vivo proof of principle animal studies in neuropathic pain. Further investigation will be reported in due course.

Acknowledgment. The authors thank Dr. Deen Tulshian and Dr. John Hunter for their support and helpful discussions. We gratefully acknowledge Lisa Broske's group for animal dosing and Sam Wainhaus' group for the PK sample analysis. We thank Dr. Birendra Pramanik's group and Dr. Tse-Ming Chan's group for analytical support, and Dr. Jesse Wong, Dr. Xian Liang, and Yan Jin for scale-up of some key intermediates. We also thank Robert Budich for the nomenclature of all the compounds.

Note Added after ASAP Publication. This manuscript was released ASAP on October 11, 2007 with errors in Table 1. The correct version was posted on October 16, 2007.

Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Nakanishi, S.; Masu, M. Molecular diversity and functions of glutamate receptors. *Annu. Rev. Biophys. Biomol. Struct.* **1994**, *23*, 319−348. (b) Hermans, E.; Challiss, R. A. J. structural, signaling and regulatory properties of the group I metabotropic glutamate receptors: protypic family C G-protein-coupled receptors. *Biochem. J.* **2001**, *359*, 465−484.

(2) (a) Schoepp, D. D.; Jane, D. E.; Monn, J. A. Pharmacological agents acting at subtypes of metabotropic glutamate receptors. *Neuropharmacology* **1999**, *38*, 1431−1476. (b) Han, J. S.; Neugebauer, V. mGluR1 and mGluR5 antagonists in the amygdale inhibit different components of audible and ultrasonic vocalizations in a model of arthritic pain. *Pain* **2005**, *113*, 211−222.

(3) (a) Bhave, G.; Karim, F.; Carlton, S. M.; Gereau, R. W., IV. Peripheral group I metabotropic glutamate receptors modulate nociception in mice. *Nat. Neurosci.* **2001**, *4*, 417−423. (b) Dolan, S.; Nolan, A. M. *Neuropharmacology* **2002**, *43*, 319−326. (c) Dolan, S.; Kelly, J. G.; Monteiro, A. M.; Nolan, A. M. *Pain* **2003**, *106*, 501−512. (d) Young, M. R.; Fleetwood-Walker, S. M.; Mitchell, R.; Munro, F. E. Evidence for a role of metabotropic glutamate receptors in sustained nociceptive inputs to rat dorsal horn neurons. *Neuropharmacology* **1994**, *33*, 141−144. (e) Young, M. R.; Fleetwood-Walker, S. M.; Dickinson, T.; Blackburn-Munro, G.; Sparrow, H.; Birch, P. J.; Bountra, C. Behavoiral and electrophysiological evidence supporting a role for group I metabotropic glutamate receptors in the mediation of nociceptive inputs to the rat spinal cord. *Brain Res.* **1997**, *777*, 161−169.

(4) Neugebauer, V. Peripheral metabotropic glutamate receptors: fight the pain where it hurts. *Trends Neurosci.* **2001**, *24*, 550−552.

(5) (a) Neugebauer, V.; Carlton, S. M. Peripheral metabotropic glutamate receptors as drug targets for pain relief. *Expert Opin. Ther. Targets* **2002**, *6*, 349−361. (b) Swanson, C. J.; Bures, M.; Johnson, M. P.; Linden, A.-M.; Monn, J. A.; Schoepp, D. D. Metobotropic glutamate receptors as novel targets for anxiety and stress disorders. *Nat. Rev. Drug Discovery* **2005**, *4*, 131−144.

(6) (a) Ambler, S. J.; Baker, S. R.; Clark, B. P.; Coleman, D. S.; Foglesong, R. J.; Goldsworthy, J. Jagdmann, G. K., Jr.; Johnson, K. W.; Kingston, A. E.; Owton, W. M.; Schoepp, D. D.; Hong, J. E.; Schkeryantz, J. M.; Vannieuwenhze, M. S.; Zia-ebrahimi, M. S. Preparation of heterocycles containing a 4-substituted pyrimidine subunit for pharmaceutical use as mGluR1 antagonists. WO 2001032632, 2001. (b) Itahana, H.; Fujisayu, J.; Watanabe, T.; Okada,

M.; Toya, T. Preparation of aminomethyl-substituted fluorothiazolobenzimidazole derivatives with affinity for mGluR1 receptors. WO 2004106348, 2004. (c) Mabire, D.; Coupa, S.; Adeline, C.; Poncelet, A.; Simonnet, Y.; Venet, M.; Wouters, R.; Lesage, A. S. J.; Beijsterveldt, L. V.; Bischoff, F. Synthesis, structure−activity relationship, and receptor pharmacology of a new series of quinoline derivatives acting as selective, noncompetitive mGluR1 antagonists. *J. Med. Chem.* **2005**, *48*, 2134−2153. (d) Zheng, G. Z.; Bhatia, P.; Daanen, J.; Kolasa, T.; Patel, M.; Latshaw, S.; Kouhen, O. F. E.; Chang, R.; Uchic, M. E.; Miller, L.; Nakane, M.; Lehto, S. G.; Honore, M. P.; Moreland, R. B.; Brioni, J. D.;Stewart, A. O. Structure−activity relationship of triazafluorenone derivatives as potent and selective mGluR1 antagonists. *J. Med. Chem.* **2005**, *48*, 7374−7388. (e) Owen, D. R.; Dodd, P. G.; Gayton, S.; Greener, B. S.; Harbottle, G. W.; Mantell, S. J.; Maw, G. N.; Osborne, S. A.; Rees, H.; Ringer, T. J.; Rodriguez-Lens, M.; Smith, G. F. Structure−activity relationships of novel non-competitive mGluR1 antagonists: a potent treatment for chronic pain. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 486−490. (f) Fabio, R. D.; Micheli, F.; Alvaro, G.; Cavanni, P.; Donati, D.; Gagliardi, T.; Fontana, G.; Giovannini, R.; Maffeis, M.; Mingardi, A.; Tranquillini, M. E.; Vitulli, G. From pyrroles to 1-oxo-2,3,4,9-tetrahydro-1*H*-β-carbolines: a new class of orally bioavailable mGluR1 antagonists. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2254−2259.

(7) (a) Kadushkin, A. V.; Solovyeva, N. P.; Granik, V. G. DMF diethyl acetal as a one-carbon component in the synthesis of isomeric pyridothienopyrimidines. *Khim.-Farm. Zh.* **1993**, *27*, 40−43. (b) Matasi, J. J.; Tulshian, D.; Burnett, D. A.; Wu, W.-L.; Korakas, P.; Silverman, L. S.; Sasikumar, T. K.; Qiang, L.; Domalski, M. S. Preparation of tricyclic compounds as mGluR1 antagonists. U.S. 2006167029, 2006.

(8) Compound **6** is obtained from treatment of **12** with excess NBS.

(9) Vompe, A. F.; Monitch, N. V.; Turitsyna, N. F.; Ivanova, L. V. New conversions of pyridinium salts and synthesis of γ-amino-substituted pyridines. *Tetrahedron* **1958**, *2*, 90−95.

(10) Sakamoto, T.; Kondo, Y.; Yasuhara, A.; Yamanaka, H. Condensed heteroaromatic ring systems. XVIII. Palladium-catalyzed cross-coupling reaction of aryl bromides with (*Z*)-1-ethoxy-2-tributylstannylethene and its utilization for construction of condensed heteroaromatics. *Tetrahedron* **1991**, *47*, 1877−1886.

(11) Martorell, G.; Garcia-raco, A.; SAA, J. M. Palladium catalyzed cross-coupling of phenol triflates with organostannanes. A versatile approach for the synthesis of substituted resorcinol dimethyl ethers. *Tetrahedron Lett.* **1990**, *31*, 2357−2360.

(12) Ozeryanskii, V. A.; Pozharskii, A. F.; Vistorobskii, N. V. Peri-*n*Naphthylenediamines. 28. Nitration of 1,8-bis(dimethylamino)-naphalene and 5,6-bis(dimethylamino)acenaphthene in neutral and weakly acidic media. The first case of isolation of *o*-nitro and *o*,*o*′-dinitro derivatives of "proton sponges". *Russ. Chem. Bull.* **2000**, *49*, 1212−1217.

(13) Riegel, B.; Lappin, G. R.; Adelson, B. H.; Jackson, R. I.; Albisetti, C. J., Jr.; Dodson, R. M.; Baker, R. H. The synthesis of some 4-quinolinols and 4-chloroquinolinolines by the ethoxymethylene-malonic ester method. *J. Am Chem. Soc.* **1946**, *68*, 1264−1266.

(14) Sekar, M.; Prasad, K. J. R. Synthesis, antimalarial and antibacterial activity of 1-chloro-2-formylcarbazole derivatives and pyrazolo[3,4-*a*]carbazole derivatives. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1998**, *37*, 314−317.

(15) Singh, B.; Pennock, P. O.; Lesher, G. Y.; Bacon, E. P.; Page, D. F. An efficient and novel synthesis of fused thiazol-2(3*H*)-ones. *Heterocycles* **1993**, *36*, 133−144.

(16) Kuwabe, S.-I.; Torraca, K. E.; Buchwald, S. L. Palladium-catalyzed intramolecular C−O bond formation. *J. Am. Chem. Soc.* **2001**, *123*, 12202−12206.

(17) See Supporting Information for details.

(18) Korfmacher, W. A.; Cox, K. A.; Ng, K. J.; Veals, J.; Hsien, Y.; Wainhaus, S.; Broske, L.; Prelusky, D.; Nomeir, A.; White, R. E. Cassette-accelerated rapid rat screen: a systematic procedure for the doing and liquid chromatography/atmospheric pressure ionization tandem mass spectrometric analysis of new chemical entities as part of new drug discovery. *Rapid Commun. Mass. Spectrom.* **2001**, *15*, 335−340.

(19) Varty, G. B.; Grilli, M.; Forlani, A.; Fredduzzi, S.; Grzelak, M. E.; Guthrie, D. H.; Hodgson, R. A.; Sherry, X. L.; Nicolussi, E.; Pond, A. J.; Parker, E. M.; Hunter, J. C.; Higgins, G. A.; Reggiani, A.; Bertorelli, R. The antinociceptive and anxiolytic-like effects of the metabotropic glutamate receptor 5 (mGluR5) antagonists, MPEP and MTEP, and the mGluR1 antagonist, LY456236, in rodents: a comparison of efficacy and side-effect profiles. *Psychopharmacology* **2005**, *179*, 207−217. See also Supporting Information.

JM070590C