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Biphenyl-indanones: Allosteric potentiators of the metabotropic glutamate subtype 2 receptor

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Abstract—We have identified and synthesized a series of biphenyl-carboxylic acid indanones as allosteric potentiators of the metabotropic glutamate receptor 2. Structure–activity relationship studies directed toward improving the potency and the brain to plasma ratio of the initial lead led to the discovery of **5** and **23** (EC_{50} = 111 and 5 nM, respectively).

Glutamate, one of the most abundant neurotransmitters in the brain, plays a dual role in a wide variety of central nervous system functions. It activates both ionotropic glutamate receptors (iGluRs), which are glutamate-gated ion channels, and the metabotropic glutamate receptors (mGluRs) which belong to the family of G-protein coupled receptors.[1,2] Currently, mGluRs are divided into eight subtypes and three main groups (I–III). Group II (mGluR2 and 3) mGluRs are mainly localized presynaptically and generally inhibit neurotransmission. Therefore, agents targeting group II mGluRs may have utility in a variety of clinical conditions,[3–5] including epilepsy, anxiety, and schizophrenia.[6]

Recently, nonselective mGluR2/3 agonists[7–9] have shown activity in numerous animal models as well as clinical trials.[10,11] However, compounds selective for mGluR2 over mGluR3 have not been discovered using this approach, probably due to the high degree of sequence homology between group II mGluRs, especially at the glutamate binding site. Therefore, another strategy for selectivity involves the discovery of allosteric modulators (potentiators) that do not bind at the glutamate binding site.[12–14] Furthermore, a recent study demonstrated that potentiators may overcome the desensitization of GPCR observed after repeated dosing of agonists.[15] Previously published work on potentiators from our laboratories[16–19] and from Eli Lilly[20–23] has yielded moderately potent compounds. Herein, we report the discovery of a new series of indanone potentiators with improved potency, potentiation, and selectivity which also, at times, gave significant brain penetration.

Compound **1** was identified as a racemate from an internal screen[24,25] as a weak mGluR2 potentiator with poor rat pharmacokinetic properties characterized by high plasma clearance (Cl_p = 502 mL/min/kg) and a short half life ($t_{1/2}$ = 0.3 h). Indanone **1** displayed no activity in the absence of glutamate, as well as no activity at mGluR3[24] in the presence or absence of glutamate, confirming it was a selective mGluR2 modulator. Compounds **2** and **3** were subsequently identified as potent alternatives via structure–activity relationship (SAR) studies on a second lead containing an acetophenone moiety.[26] Unfortunately, these two compounds were plagued with either poor brain/plasma ratio (B/P = 0.1% for **2**) or reduced potentiation (44% for

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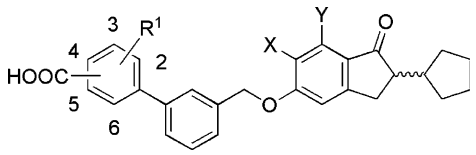
Table 1. Binding affinities for compounds **4**–**23**

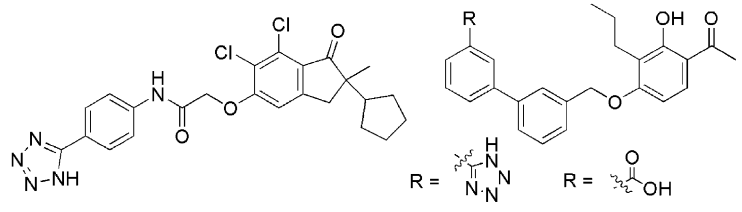


Entry	–COOH (C3 or C4)	R^1	X	Y	hmGluR2 GTP-γS EC_{50} (nM)	% potentiation
4	C3	H	CH_3	CH_3	69	118
5	C4	H	CH_3	CH_3	111	114
6	C3	2-CH_3	CH_3	CH_3	252	94
7	C3	4-Cl	CH_3	CH_3	24	109
8	C3	4-OCH_3	CH_3	CH_3	202	81
9	C3	4-OH	CH_3	CH_3	62	113
10	C3	5-F	CH_3	CH_3	91	124
11	C3	6-CH_3	CH_3	CH_3	140	100
12	C3	6-F	CH_3	CH_3	176	97
13	C3	6-OMe	CH_3	CH_3	36	114
14	C4	2-CH_3	CH_3	CH_3	353	103
15	C4	2-F	CH_3	CH_3	416	119
16	C4	3-CH_3	CH_3	CH_3	158	98
17	C4	3-Cl	CH_3	CH_3	119	97
18	C3	H	CH_3	Cl	64	122
19	C4	H	CH_3	Cl	49	110
20	C3	4-Cl	CH_3	Cl	67	121
21	C3	5-F	CH_3	Cl	41	161
22	C4	H	Cl	Cl	240	98
23	C3	4-Cl	Cl	Cl	5	117

3), with potentiation being defined as the response obtained using the test compound up to 10 μM plus an EC_{10} of glutamate normalized to the maximal response obtained with glutamate alone. Additionally, compounds **2** and **3** were not selective for mGluR2 over mGluR3. In the present communication, SAR of a new class of compounds based on a combination of **1**, **2**, and **3** will be discussed.

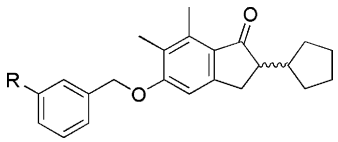
The compounds described in Tables 1 and 2 (**4**–**27**) were synthesized following the synthetic route outlined in Scheme 1.[27] The synthesis began with the initial formation of boronic esters **30** by alkylation of a hydroxylindanone[28] (**29**, racemic mixture) with 2-[3-(bromo methyl)phenyl]-5,5-dimethyl-1,3,2-dioxaborinane **28**. Suzuki coupling with the desired bromo-aryl derivatives (**31**) afforded compounds **32**. In the case where R was an ester, the final products **4**–**24** were accessed via hydrolysis with aqueous lithium hydroxide in warm ethanol. When R was a cyano group, compounds **25** and **26** were obtained via a tin catalyzed tetrazole formation using trimethylsilyl azide in refluxing toluene in generally good yield. The acyl sulfonamide **27** was obtained by reacting the acyl chloride of **4** with the sodium salt of methanesulfonamide.

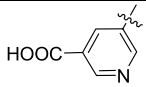
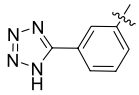
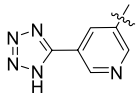
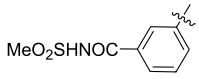
The indanone class of compounds incorporating the biphenyl carboxylic acid of **3** revealed that, unlike the acetophenones, they are inactive against mGluR3.[25] Importantly, as shown with previous work, the presence of an acidic proton is crucial for maintaining for good levels of potency and potentiation.[17] SAR results around this new class of compounds are shown in Tables 1 and 2. All compounds synthesized showed good levels of potentiation (81–165%), so binding affinities were used to drive the SAR.



	1	2	3
GTP-γS EC_{50} (nM) =	600	73	398
% Potentiation =	86	113	44

Table 2. Binding affinities for compounds **24**–**27**



Entry	R	hmGluR2 GTP-γS EC_{50} (nM)	% potentiation
24		38	111
25		87	107
26		73	103
27		369	43

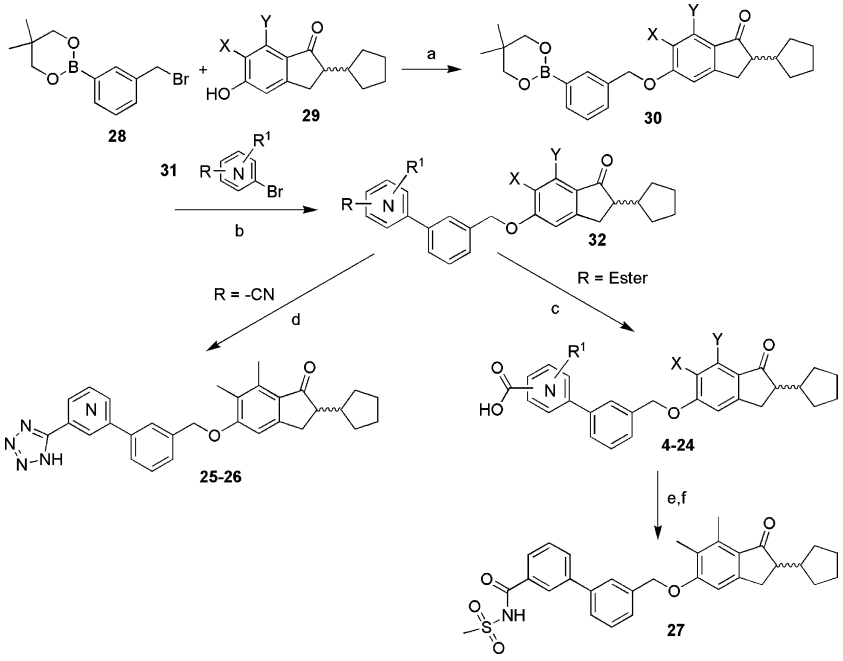
Previous SAR on the indanone moiety and the middle ring revealed that (1) X and Y cannot both be hydrogens,[29] (2) cyclopentyl/hydrogen is one of the best combinations for the α position of the ketone,[19] (3) unsubstituted phenyl is the best option for the middle ring,[30] and (4) the benzyl linker does not tolerate substituents.[30]

New SAR around the indanone and the terminal phenyl can be summarized as follows. When X = Y = CH_3, the acid at the C3 position appears to be preferred (**4** vs **5**, **6** and **11** vs **14**, and **12** vs **15**). When X = CH_3 and Y = Cl (**18** vs **19**), the position of the acid group does not matter as both compounds may have similar potencies.

The potency could further be improved by adding a substituent on the terminal phenyl ring. Extensive SAR with the acid at C3 and X = Y = CH_3 revealed that electron-withdrawing groups at the C4 position or electron-donating groups at C6 position were favored (**7** and **13**, respectively). Substitutions at C2 and C5 positions (**6** and **10**) were tolerated but resulted in a moderate loss of potency compared to **4**. Preliminary SAR with the C4 acid led to moderate losses in potency with most substitution patterns investigated (**14**–**17**). The potencies were not affected by substitution when X = CH_3, Y = Cl (**20** and **21**). Combining the potency enhancing 4-Cl substituent in the dichloro indanone series resulted in an unexpected large boost in potency. To date, compound **23** (as a racemic mixture) is the most potent mGluR2 potentiator synthesized. The racemic mixture could be separated into enantiomers using chiral chromatography (Chiralcel OD column) at the ester stage, but racemization was observed during the LiOH hydrolysis step.[31]

A number of acid bioisosteres were also investigated (Table 2). The *m*-tetrazole (**25**) was essentially equipotent to acid **4**, while the acyl sulfonamide (**27**) lost significant potency. Additionally, compounds containing a terminal pyridine with a tetrazole or a carboxylic acid (**24** and **26**, respectively) (Table 2) were made to alter the physical properties of the molecules. These, too, were potent with good levels of potentiation.

As previously suspected,[19] the tetrazole is partially responsible for the low *B*/*P* (**2**, **25**, and **26**). Substitution



Scheme 1. Reagents and conditions: (a) K_2CO_3, acetone, 50 °C, 18 h, 75–92%; (b) $PdCl_2(PPh_3)_2$, K_2CO_3, toluene/MeOH (10:1), 80 °C, 18 h, 59–76%; (c) LiOH (1 M in H_2O), THF, 50 °C, 48 h, 82–89%; (d) $TMSN_3$, *n*-Bu_2SnO, toluene, 110 °C, 18 h, 62–83%; (e) $(COCl)_2$, THF, DMF, rt, 5 h, 85%; (f) $MeSO_2NH_2$, NaH, THF, 65 °C, 18 h, 71%.

Table 3. Rat brain and plasma levels and *B*/*P* ratio for compounds **2**–**5**, **18**, and **24**–**27**

Entry	Brain level (μM)[a]	Plasma level (μM)[a]	*B*/*P*
2	0.06	6	0.01
3	0.89	5.5	0.16
4	12	36	0.33
5	12	16	0.75
18	3	4.5	0.67
24	0.06	1.5	0.04
25	0.01	9	0.001
26	2	264	0.008
27	<LOQ[b]	2	0

[a] Dosed 20 mpk ip, levels at 2 h.
[b] LOQ = limit of quantification.

of the tetrazole with a carboxylic acid (i.e., **2** → **3**, **25** → **4**, and **26** → **24**) did improve the *B*/*P* (0.01–0.16, 0.001–0.33, and 0.008–0.04, respectively), while substitution with an acyl sulfonamide (**27**) did not (no compound could be detected in the brain) (Table 3). Replacement of the terminal phenyl with a pyridine (**24** and **26**), while leading to potent compounds, did not improve the *B*/*P* (0.0076 and 0.04, respectively) as hoped. Replacement of one of the methyl groups by a chlorine atom on the indanone ring (**18**) led to excellent *B*/*P* (0.67), however, lower plasma levels resulted in lower brain level.

In conclusion, a new class of biphenyl-indanone mGluR2 potentiators has been described. Optimization of the original lead led to compounds such as **23** which are, to date, the most potent mGluR2 selective (over mGluR3) potentiators from our laboratories. Additionally, potent compounds such as **4** and **5** were identified with good to excellent plasma exposure (16–36 μM) and brain exposure (12 μM) upon ip dosing in rats at 20 mpk. Finally, preliminary in vivo data[32] suggest that these allosteric modulators may have therapeutic potential for the treatment of schizophrenia and will be described in a future communication.

References and notes

1. (a) Pin, J.-P.; Acher, F. *Curr. Drug Targets: CNS Neurol. Disord.* **2002**, *1*, 297; (b) Conn, P. J.; Pin, J. P. *Annu. Rev. Pharmacol. Toxicol.* **1997**, *37*, 205.
2. Schoepp, D. D.; Jane, D. E.; Monn, J. A. *Neuropharmacology* **1999**, *38*, 1431.
3. Lam, A. G.; Soriano, M. A.; Monn, J. A.; Schoepp, D. D.; Lodge, D.; McCulloch, J. *Neurosci. Lett.* **1998**, *254*, 121.
4. Kingston, A. E.; O'Neill, M. J.; Lam, A.; Bales, K. R.; Monn, J. A.; Schoepp, D. D. *Eur. J. Pharmacol.* **1999**, *377*, 155.
5. Helton, D. R.; Tizzano, J. P.; Monn, J. A.; Schoepp, D. D.; Kallman, M. J. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 651.
6. Chavez-Noriega, L. E.; Schaffhauser, H.; Campbell, U. C. *Curr. Drug Targets: CNS Neurol. Disord.* **2002**, *1*, 261.
7. 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.
8. 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.
9. 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.
10. Levine, L.; Gaydos, B.; Sheehan, D.; Goddarg, A. W.; Feighner, J.; Potter, W. Z.; Schoepp, D. D. *Neuropharmacology* **2002**, *43*, 294.
11. (a) Grillon, C.; Cordova, J.; Levine, L. R.; Morgan, C. A., III *Psychopharmacology* **2003**, *168*, 446; (b) Schoepp, D. D.; Wright, R. A.; Levine, L. R.; Gaydos, B.; Potter, W. Z. *Stress* **2003**, *6*, 189.
12. Knoflach, F.; Mutel, V.; Jolidon, S.; Kew, J. N. C.; Malherbe, P.; Viera, E.; Wichmann, J.; Kemp, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 13402.
13. (a) Johnson, M. P.; Baez, M.; Jagdmann, G. E., Jr.; Britton, T. C.; Large, T. H.; Callagaro, D. O.; Tizzano, J. P.; Monn, J. A.; Schoepp, D. D. *J. Med. Chem.* **2003**, *46*, 3189; (b) Barda, D. A.; Wang, Z.; Britton, T. C.; Henry, S. S.; Jagdmann, G. E.; Coleman, D. S.; Johnson, M. P.; Andis, S. L.; Schoepp, D. D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3099.
14. Schaffhauser, H.; Rowe, B. A.; Morales, S.; Chavez-Noriega, L. E.; Yin, R.; Jachec, C.; Rao, S. P.; Bain, G.; Pinkerton, A. B.; Vernier, J.-M.; Linda, J.; Bristow, L. J.; Varney, M. A.; Daggett, L. P. *Pharmacology* **2003**, *64*, 798.
15. Pin, J. P.; Parmentier, M. L.; Prezeau, L. *Mol. Pharmacol.* **2001**, *60*, 881.
16. (a) Pinkerton, A. B.; Vernier, J.-M.; Shaffhauser, H.; Rowe, B. A.; Campbell, U. C.; Rodriguez, D. E.; Lorrain, D. S.; Baccei, C. S.; Daggett, L. P.; Bristow, L. J. *J. Med. Chem.* **2004**, *47*, 4595; (b) Hu, E.; Chua, P. C.; Tehrani, L.; Nagasawa, J. Y.; Pinkerton, A. B.; Rowe, B. A.; Vernier, J.-M.; Hutchinson, J. H.; Cosford, N. D. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5071.
17. Pinkerton, A. B.; Cube, R. V.; Hutchinson, J. H.; Rowe, B. A.; Schaffhauser, H.; Zhao, X.; Daggett, L. P.; Vernier, J.-M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5329.
18. Pinkerton, A. B.; Cube, R. V.; Hutchinson, J. H.; James, J. K.; Gardner, M. F.; Schaffhauser, H.; Rowe, B. A.; Daggett, L. P.; Vernier, J.-M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5867.
19. Pinkerton, A. B.; Cube, R. V.; Hutchinson, J. H.; James, J. K.; Gardner, M. F.; Rowe, B. A.; Schaffhauser, H.; Rodriguez, D. E.; Campbell, U. C.; Daggett, L. P.; Vernier, J.-M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1565.
20. Barda, D. A.; Wang, Z.-Q.; Britton, T. C.; Henry, S. S.; Jagdmann, G. E.; Coleman, D. S.; Johnson, M. P.; Andis, S. L.; Schoepp, D. D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3099.
21. Johnson, M. P.; Baez, M.; Jagdmann, G. E.; Britton, T. C.; Large, T. H.; Callagaro, D. O.; Tizzano, J. P.; Monn, J. A.; Schoepp, D. D. *J. Med. Chem.* **2003**, *46*, 3189.
22. Johnson, M. P.; Barda, D. A.; Britton, T. C.; Emkey, R.; Hornback, W. J.; Jagdmann, G. E.; McKinzie, D. L.; Nisenbaum, E. S.; Tizzano, J. P.; Schoepp, D. D. *Psychopharmacology* **2005**, *179*, 271.
23. Johnson, M. P.; Nisenbaum, E. S.; Large, T. H.; Emkey, R.; Baez, M.; Kingston, A. E. *Biochem. Soc. Trans.* **2004**, *32*, 881.
24. Screening of compounds was carried out using a Ca^{2+} flux functional (FLIPR384) assay using a stable cell line co-

expressing the human mGlu2 receptors coupled to a promiscuous G-protein (Gα 16). Receptor activity was detected by changes in [Ca^{2+}], measured using the fluorescent, Ca^{2+} sensitive dye fura-2. For further information, see: Varney, M. A.; Cosford, N. D.; Jachec, C.; Rao, S. P.; Sacaan, A.; Lin, F. F.; Bleicher, L.; Santori, E. M.; Flor, P. J.; Allgeier, H.; Gasparini, F.; Kuhn, R.; Hess, S. D.; Velicelebi, G.; Johnson, E. C. *J. Pharmacol. Exp. Ther.* **1999**, *290*, 170.

25. The effect of these compounds were confirmed and further characterized in the [^{35}S]-GTPγS binding assay. See Ref. 11 for a detailed description of this assay. First, an EC_{10} (0.5 μM) of glutamate was added to the cell line (expressing hmGluR2 or hmGluR3) followed immediately by the test compound at varying concentrations. The response was then compared to a response using a saturating amount of glutamate (1 mM) to give both an EC_{50} and a percent potentiation (the response normalized to the maximum response of glutamate alone). The same experiment was carried out in the absence of glutamate to test if the compound was truly a positive allosteric modulator. Non-specific binding was determined by addition of 10 μM unlabeled GTPγS.
26. Bonnefous, C.; Vernier, J-.M.; Hutchinson, J. H.; Gardner, M. F.; Rowe, B. A.; Schaffhauser, H.; Campbell, U. C.; Rodriguez, D. E.; James, J. K.; Bristow, L. J.; Daggett, L.; Kamenecka, T. M. Presented at the 229th National Meeting of the American Chemical Society, San Diego, CA, March 2005; poster MEDI-37.
27. All final compounds displayed spectral data (NMR, MS) that was consistent with the assigned structure.
28. DeSolm, J. S.; Woltersdorf, O. W.; Cragoe, E. J.; Watson, L. S.; Fanelli, G. M. *J. Med. Chem.* **1978**, *21*, 437.
29. When X = Y = H, $EC_{50} > 10$ μM.
30. Kamenecka,T. M.; Bonnefous, C.; Hutchison, J. H.; Gardner, M. F.; Cramer, M.; James, J. K.; Rowe, B. A.; Daggett, L. P.; Schaffhauser, H.; Vernier, J.-M., manuscript in preparation.
31. The potency was shown to reside in the (−) isomer. See Ref. 19 for more details.
32. (a) Vernier, J.-M.; Kamenecka, T. M.; Bonnefous, C.; Schaffhauser, H.; Rowe, B. A.; Campbell, U. C.; Rodriguez, D. E.; Gardner, M. F.; James, J.; Bristow, L. J.; Daggett, L. P.; Hutchinson, J. H., manuscript in preparation.; (b) Rodriguez, D.; Bonnefous, C.; Kamenecka, T.; Vernier, J.-M.; Bristow, L.; Campbell, U. Presented at the 34th Annual Meeting of the Society for Neuroscience, San Diego, CA, October 2004; poster 798.8.