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The First CNS-Active Carborane: A Novel $P2X_7$ Receptor Antagonist with Antidepressant Activity

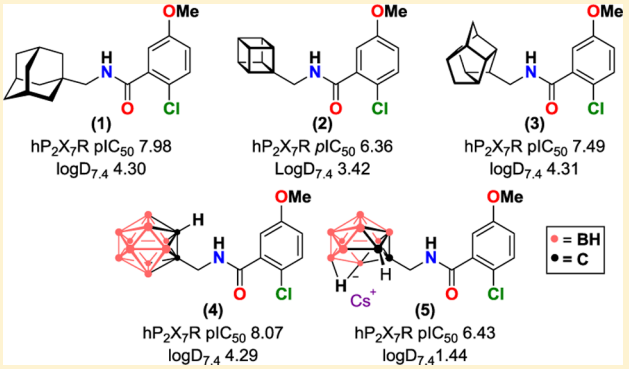
Shane M. Wilkinson,[†] Hendra Gunosewoyo,[†] Melissa L. Barron,[‡,⊥] Aurelie Boucher,[‡,⊥] Michelle McDonnell,[⊥,§] Peter Turner,[†] Daniel E. Morrison,[†] Maxwell R. Bennett,[⊥] Iain S. McGregor,[∥] Louis M. Rendina,*[,†] and Michael Kassiou*[,†,‡,⊥]

[†]School of Chemistry, [‡]Faculty of Health Science, [§]Discipline of Pharmacology, and [∥]School of Psychology, Sydney University, NSW 2006, Australia

[⊥] Brain and Mind Research Institute, 100 Mallett Street, Camperdown, NSW 2050, Australia

Supporting Information

ABSTRACT: Relative to other polycyclic frameworks (**1**–**3**), a carborane cage (**4** and Cs·**5**) exerts a significant biological effect as an inhibitor of the purinergic $P2X_7$ receptor ($P2X_7R$) which allows one to target depression in vivo and thus demonstrate, for the first time, that a carborane has the capacity to modify CNS activity.



KEYWORDS: *Carborane, blood-brain barrier, $P2X_7$, polycycle, antidepressant*

Since the discovery by Davies et al.[1] in 1964 that 1-aminoadamantane (amantadine) displayed antiviral effects, polycyclic hydrocarbon cage compounds, including adamantane, trishomocubane, and cubane, have made unique contributions to medicinal chemistry.[2] Their rigid scaffold provides compounds with improved metabolic stability and allows substituents to be precisely positioned in three dimensions. More importantly, they facilitate transport across the blood-brain barrier (BBB) which is a major challenge in central nervous system (CNS) drug development.

A recently introduced polycycle in medicinal chemistry is the carborane cluster.[3] Carboranes are pseudoaromatic polyhedral clusters consisting of boron, carbon, and hydrogen atoms which have been utilized as a rich source of boron for boron neutron capture therapy (BNCT).[4] Carboranes can also act as useful bioisosteres for phenyl rings and adamantane as their size and lipophilicity are comparable but their unique structures allow new frontiers to be explored in drug development.[3,5] An additional feature of carboranes for application in medicinal chemistry is the ability to convert the neutral, lipophilic *closo* cluster into the anionic, hydrophilic *nido* species in a single synthetic step and still preserve much of the steric features of the *closo* cluster. The incorporation of carboranes as a unique bioisostere in medicinal chemistry is still in its infancy, but there is significant interest in the exploitation of this polycycle in recent years which can, in part, be attributed to an expanding field of synthetic methodology, their remarkable stability toward moisture and biological degradation, and their low toxicity. Only recently has it been conclusively demonstrated that carboranes can cross the BBB,[6] but never before has it been reported that carboranes can elicit a CNS-modifying effect. Herein we report the first example of a carborane-containing compound with the ability to target the purinergic $P2X_7$ receptor ($P2X_7R$) in vivo, resulting in the observation of antidepressant activity in mice.

The $P2X_7R$ is a nonsensitizing, cation-selective ion channel which is directly gated by ATP. However, upon repetitive or prolonged agonist exposure, the $P2X_7R$ forms a nonselective pore which is permeable by cations up to 900 Da.[7] Formation of this pore results in apoptosis and the production and release of the cytokine interleukin 1β (IL-1β). High levels of IL-1β in the brain have been implicated in depression,[8] hyperalgesia[9] and neurodegeneration.[10] The development of a $P2X_7R$ antagonist is thus presumed to have antidepressant, analgesic and/or neuroprotective properties.

In recent years, we and others have comprehensively explored the chemical space around AstraZeneca's adamantanyl benzamide series.[11] Removing or flattening the adamantane polycycle to a simpler cycloalkane was detrimental to $P2X_7R$ antagonism, thereby suggesting that occupancy of a globular hydrophobic pocket was found to be central to potent $P2X_7R$ antagonism.[12] To examine this concept further, we explored the

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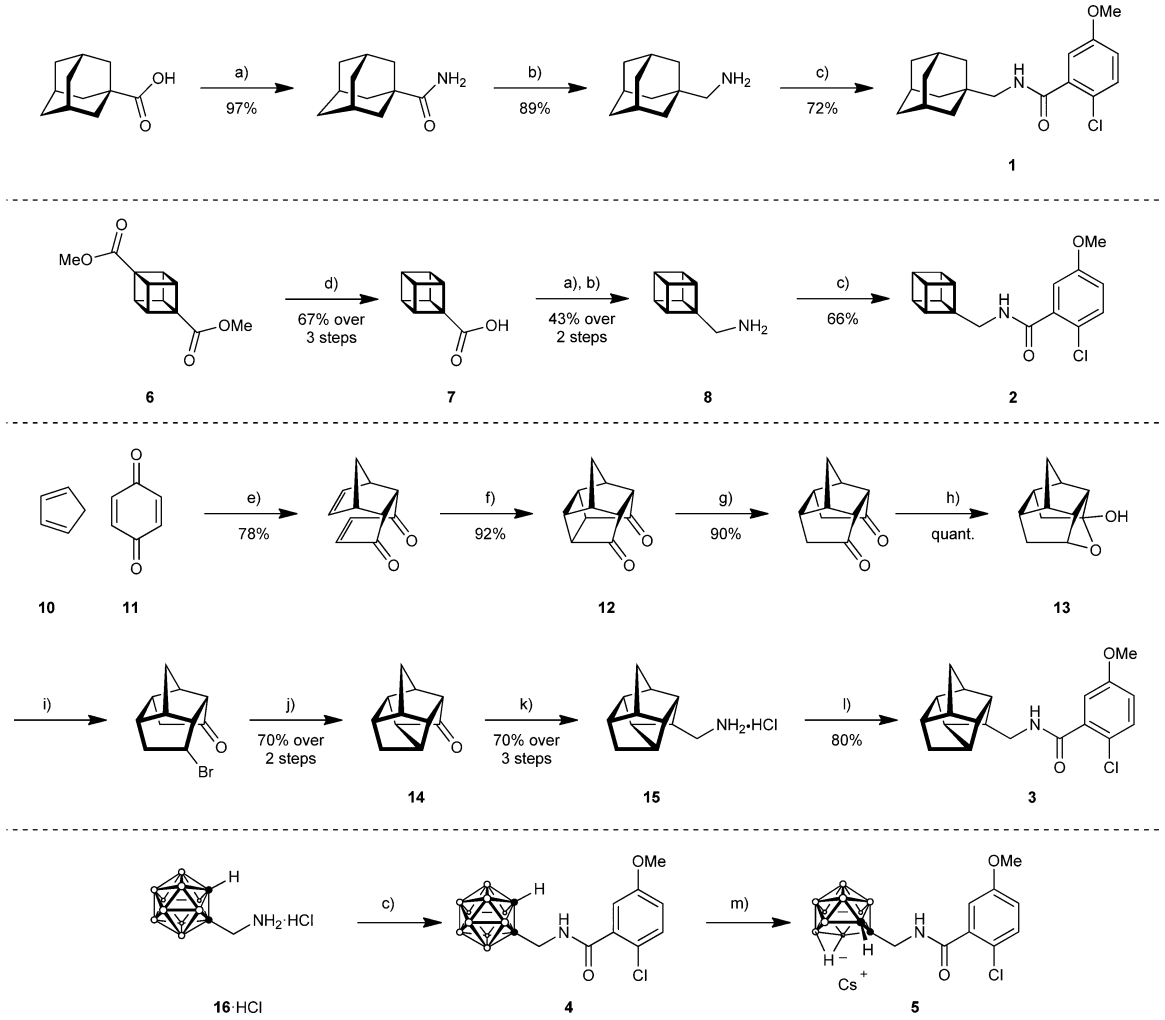
Scheme 1. Synthesis of Adamantane Benzamide 1 and Its Polycyclic Analogues 2−5[a]



[a]Conditions: (a) CDI, THF, rt, 1 h, then 28% $NH_{3(aq)}$, rt, 4 h; (b) $LiAlH_4$, THF, reflux, 20 h; (c) 2-chloro-5-methoxybenzoic acid **9**, $(COCl)_2$, THF, rt, 1 h, then amine, THF, Et_3N, rt, 16 h; (d) (i) NaOH (1 equiv), MeOH, THF, rt, 16 h, then $HCl_{(aq)}$, (ii) $(COCl)_2$, CH_2Cl_2, rt, 1 h, then 2-mercaptopyridine *N*-oxide sodium salt, *hν*, DMAP, $CHCl_3$, reflux, 1 h, (iii) NaOH, MeOH, reflux, 1 h; (e) PhMe, −10 °C to rt, 3 h, 78%; (f) *hν*, Me_2CO/hexanes, 8 h, 92%; (g) Zn, AcOH, rt, 5 h, 90%; (h) $NaBH_4$, EtOH/H_2O, rt, 3 h, quant.; (i) 33% HBr in CH_3CO_2H, sealed tube, 100 °C, 16 h; (j) *t*-BuOK, Et_2O, rt, 16 h, 70% over 2 steps; (k) (i) TosMIC, *t*-BuOK, $(MeOCH_2)_2$, EtOH, 5-35 °C, (ii) $LiAlH_4$, Et_2O, reflux, 16 h, (iii) anhyd. HCl, Et_2O; (l) 2-chloro-5-methoxybenzoic acid **9**, EDC·HCl, HOBt, NMM, CH_2Cl_2, 0 °C to rt, 16 h; (m) CsF (3 equiv), EtOH, reflux, 24 h.

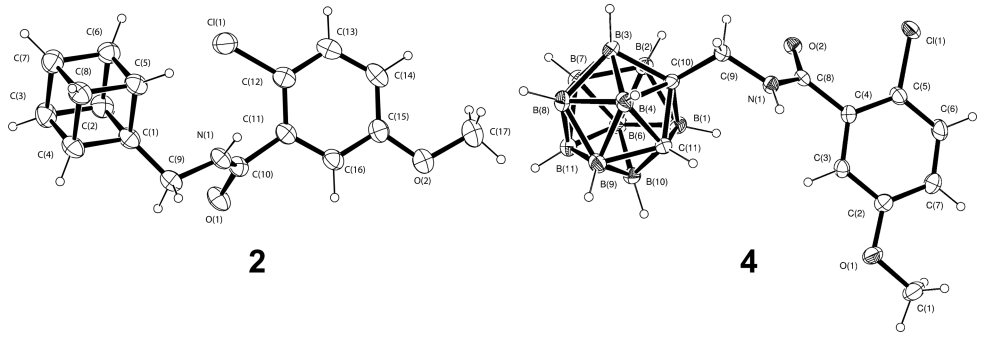


Figure 1. ORTEP depictions of **2** and **4** shown with 50% displacement ellipsoids.

effect of substituting the adamantane of lead benzamide **1** with a variety of polycyclic cages (Scheme 1). This series comprised a cubanyl **2**, trishomocubanyl **3** and the first use of carboranes within this class, namely, *closo*-1,2-carboranyl **4** and *nido*-1,2-carboranyl benzamide **5**.

RESULTS AND DISCUSSION

The smallest polycycle of the series is the cubanyl benzamide **2** prepared from the commercially available methyl cubane-1,4-diester **6** via a decarboxylation to yield cubane carboxylic acid **7** which was converted to cubanylmethylamine **8**, through its

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carboxamide, and subsequently coupled to 2-chloro-5-methoxybenzoic acid **9**. Its X-ray crystal structure (Figure 1) illustrates the highly strained 90° bond angles associated with this polycycle.

The polycyclopentyl framework of D_3-trishomocubanyl benzamide **3** was prepared in 10 steps initiated by the Diels–Alder cycloaddition reaction between cyclopentadiene **10** and benzoquinone **11**. A 2 + 2 photocyclization furnishes Cookson's diketone **12** which is reduced over two steps to open the cyclobutane ring and generate the lactol **13**. Bromination followed by base-catalyzed cyclization affords the D_3-trishomocubanone **14**. This ketone **14** was subjected to a Van Leusen reaction using TosMIC with the corresponding nitrile reduced with $LiAlH_4$ to the precursory D_3-trishomocubanylmethylamine **15**. The amine **15** was then coupled to benzoic acid **9** to afford the trishomocubanyl benzamide **3**.

The *closo*-1,2-carboranyl **4** was synthesized in 64% yield from the amide coupling reaction between *closo*-1,2-carboranylmethylamine hydrochloride[13] **16**·HCl and 2-chloro-5-methoxybenzoic acid **9**. A single crystal X-ray structure of **4** was successfully obtained (Figure 1) which confirms the presence of the *closo*-1,2-carborane cage. The *closo*-1,2-carboranyl benzamide **4** was subsequently converted to the *nido*-7,8-carborane analogue Cs·**5** by means of a mild deboronation reaction (Scheme 1) with CsF/EtOH in a single, high-yielding step (95%).

Compounds **1**–**4** and Cs·**5** were assessed in vitro for their ability to inhibit human $P2X_7R$ ($hP2X_7R$) pore formation by using a functional dye uptake assay in THP-1 cells (Figure 2).[14] The $P2X_7R$ pore formation was determined by means of an agonist-induced uptake of YO-PRO-1, a large, cationic dye molecule (629 Da). 3′-Benzoylbenzoyl adenosine-5′-triphosphate (BzATP), a synthetic and more potent analogue of ATP at $P2X_7R$, was used (100 μM) to induce $P2X_7R$ pore formation. Each compound was assessed over a concentration range of 1 nM to 10 μM with the pIC_{50} values (Table 1) determined by spectrofluorimetry to quantify the amount of YO-PRO-1 uptake into the cells following pore formation.

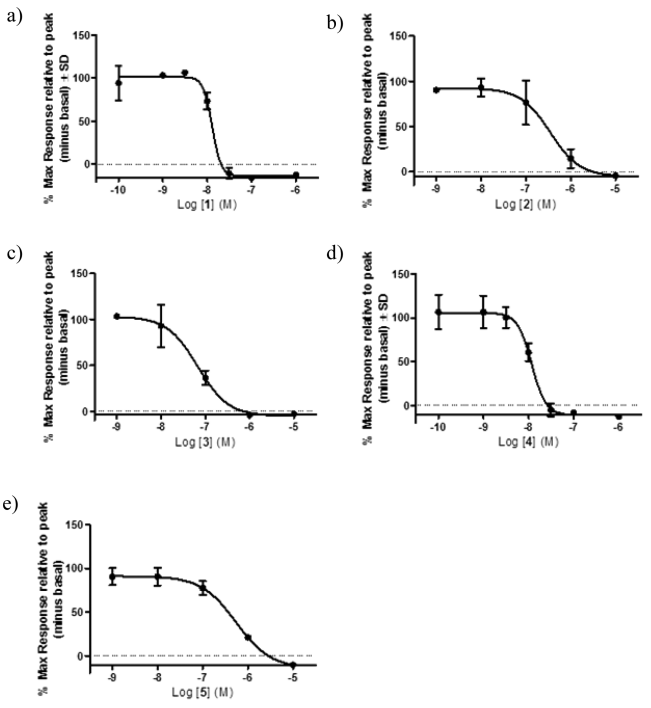

Figure 2. Inhibition of human $P2X_7R$ pore formation by (a) adamantanyl **1**, (b) cubanyl **2**, (c) trishomocubanyl **3**, (d) *closo*-1,2-carboranyl **4**, and (e) *nido*-7,8-carboranyl Cs·**5** benzamides using a functional dye uptake assay in THP-1 cells. Pore formation was assessed by a BzATP-induced uptake of YO-PRO-1.

Table 1. $hP2X_7R$ Inhibition Functional Assay and Lipophilic Evaluation of the Benzamide Series 1–4 and Cs·5

benzamide	pIC_{50}[a]	cLogP[b]	log $D_{7.4}$[c]	LLE[d]
adamantanyl **1**	7.98 ± 0.15	4.12	4.30	3.68
cubanyl **2**	6.36 ± 0.12	1.46	3.42	2.94
trishomocubanyl **3**	7.49 ± 0.19	2.98	4.31	3.18
closo-carboranyl **4**	8.07 ± 0.19	–[e]	4.29	3.78
nido-carboranyl Cs·**5**	6.43 ± 0.10	–[e]	1.44	4.99

[a]pIC_{50} values were derived from concentration–response curves (n > 4) ± SD. [b]Predicted using Spartan 10 (V1.1.0) using H–F calculations with a 6-31G* basis set. [c]Experimentally determined by HPLC method. [d]Ligand–lipophilicity efficiency (LLE) = pIC_{50} − log D. [e]Could not be predicted with software.

A trend was observed between the potency of $hP2X_7R$ inhibition and the size of the polycyclic cage with those molecules possessing larger polycycles, that is, **1**, **3**, and **4**, causing greater inhibition of $hP2X_7R$ pore formation. Indeed, the lead adamantanyl benzamide **1** demonstrated potent $hP2X_7R$ antagonism (pIC_{50} = 7.98 ± 0.15). Contracting the size of the adamantane cage in **1** by the use of a D_3-trishomocubane group (**3**) reduced potency by approximately one-third, while reducing the polycycle volume even further to a cubane (**2**) resulted in a decrease of over one-order of magnitude in $hP2X_7R$ inhibition. The *closo*-1,2-carborane cage is equivalent in size to adamantane but is more lipophilic due to the presence of low-polarity B–H bonds.[15] Interestingly, the *closo*-1,2-carboranyl benzamide **4** displayed a slight improvement in $hP2X_7R$ antagonism over **1**. The *nido*-7,8-carboranyl benzamide Cs·**5** was prepared with the aim of retaining potency through its polycyclic cage, while simultaneously reducing the lipophilic properties due to its anionic charge. Indeed, the anionic charge of Cs·**5** resulted in a dramatic diminution in $hP2X_7R$ pore inhibition when compared to **4**. It is worthy to note that the Hill slope calculated for the adamantanyl **1** and *closo*-1,2-carboranyl benzamide **4** is −4.3 and −2.7, respectively (whereas the remaining benzamides equate to −1). We speculate this is due to cooperativity, which is known to occur for related adamantane antagonists of the $P2X_7R$.[16] Future work involving radioligand binding is intended to elucidate the mechanistic aspects of these ligands.

Animal behavioral tests were performed in order to assess the in vivo efficacy of benzamides **1**–**4** and Cs·**5**, evaluate their BBB penetration, and also validate their CNS activity. The antidepressant potential of the benzamides **1**–**4** and Cs·**5** were evaluated by means of a forced-swim test (FST) which induces depressive behavior (Figure 2).[17] The FST paradigm utilizes the observation that rodents initially engage in escape-directed behavior when placed in an inescapable scenario, but will eventually develop a passive immobile posture which can be measured as a model of depression.[18] It has also been recently shown that $P2X_7R$ knockout (KO) mice show resilience in the FST (i.e., increased mobility compared to WT mice), an observation which both validates the use of such a behavioral

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model for this target and also provides a maximal response benchmark for $P2X_7R$ antagonism.[19]

Prior to the FST, a drug tolerability test was performed on the mice with doses up to 20 mg/kg showing no adverse effects to body temperature, locomotor activity, or body weight (see the Supporting Information). The mice were then injected with 20 mg/kg of **1**−**4** and Cs·**5** or vehicle and subjected to a 6 min FST. Compared to wild-type (WT) mice, $P2X_7R$ KO mice remained 32 ± 14% more mobile in the FST, thus demonstrating their antidepressant-like phenotype. Remarkably, the trend observed in the functional cell assay was reversed in the in vivo behavioral assay; that is, compounds **1**, **3**, and **4** exerted no significant antidepressant behavior. In contrast, despite **2** and Cs·**5** having the lowest pIC_{50} values in the series, these compounds were shown to impart significant antidepressant activity (16% and 13% more mobile than WT, respectively). It should be noted that the FST experiments were all performed with mass concentrations of 20 mg/kg and so the relative administered concentration for benzamide Cs·**5** (43 μmol/kg) was lower than that of the other benzamides **1**−**4** (59−66 μmol/kg) assessed in this study due to its significantly higher MW; that is, Cs·**5** inferred significant antidepressant activity of the series despite it being assessed at the lowest dose concentration. Furthermore, despite a very limited collection of studies that demonstrate the capacity of carboranes to cross the BBB,[6b] this is the first study which has demonstrated the ability of a carborane to modify CNS activity.

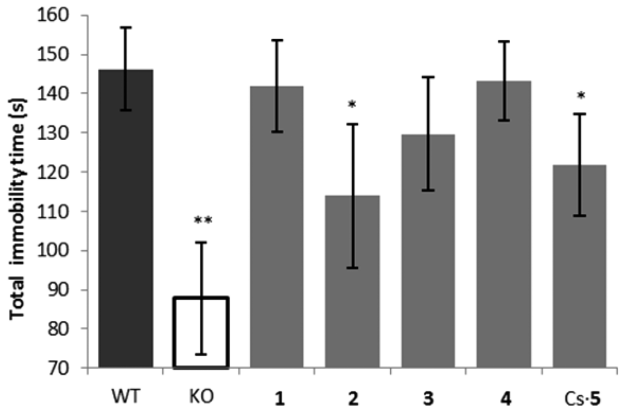

Figure 3. Average immobility time (s) in which mice remained stationary over the final 3 min of a 6 min FST. Wild-type mice were injected (20 mg/kg) with either **1**, **2**, **3**, **4**, Cs·**5**, or vehicle (WT) 20 min prior to a 6 min FST. $P2X_7R$ knockout mice (KO) were injected with vehicle. Error bars denote SEM; $^*P < 0.05$, $^{**}P < 0.01$, Mann−Whitney U-test against WT.

The failure of benzamides **1**, **3**, and **4** to demonstrate antidepressant activity in mice despite their potent $hP2X_7R$ inhibition values suggests a likely inability of these compounds to cross the BBB and/or poor interspecies crossover. Calculated physicochemical properties (Table 1, column 3) of the benzamide series advocate lipophilic penalties may indeed prevent crossing of the BBB.

To validate the BBB penetration with lipophilicity, the log $D_{7.4}$ values of the benzamides were determined experimentally by using a HPLC method (Table 1, column 4).[20] The three benzamides **1**, **3**, and **4**, which showed no antidepressant behavior in the FST, were shown to have log $D_{7.4}$ values much greater than the range reported for successful CNS drugs (cLogP < 3).[21] These values indicate that a high lipophilicity may be inhibiting BBB penetration, which consequently eliminated their efficacy in the FST. Interestingly, substituting adamantane for *closo*-1,2-carborane in the benzamides does not increase the lipophilicity of the drug as previously reported in literature.[15] The log $D_{7.4}$ of **4** is almost equal to that of **1**. However, if **4** is converted to Cs·**5**, a significant drop in lipophilicity by 3 orders of magnitude is observed, and one can thus readily convert a BBB-impenetrable molecule into a CNS-active drug in a single synthetic step.

The ligand−lipophilicity efficiency (LLE)[22] evaluation of the benzamide series (Table 1, column 5) establishes the *nido*-7,8-carborane Cs·**5** as a good lead candidate (LLE ≥ 5). Despite its equivalent in vitro and in vivo results, the higher lipophilicity of cubanyl **2** suggests it will be less bioavailable and may be more susceptible to metabolism. Regardless of its adverse lipophilicity, the high potency of the *closo*-1,2-carboranyl **4** makes it the second best candidate by LLE analysis. However, based on its inactivity in vivo, further structure−activity studies of the aryl moiety would need to be undertaken before this compound could be considered for any further development.

CONCLUSION

In conclusion, this study makes a significant contribution to the emerging area of utilizing carboranes as pharmacophores in drug development. The equivalent size and lipophilicity of the *closo*-carborane and the adamantane cages led to identical biological results in this work. However, *closo*-1,2-carborane has a distinct advantage over adamantane due to its robust exogenous scaffold providing excellent metabolic stability and the ability to be converted readily to its corresponding anionic *nido*-carborane cluster. The significant in vivo antidepressant activity of Cs·**5** is consistent with CNS $P2X_7R$ inhibition. This study represents the first account of a carborane molecule possessing CNS-modifying activity, thereby pioneering the application of carboranes in future CNS drug development strategies.

ASSOCIATED CONTENT

Supporting Information

Full experimental details and data for both chemical and biological studies. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

*(M.K.) Telephone: +61 2 9351 0849. Fax: +61 2 9351 9146. E-mail: michael.kassiou@sydney.edu.au.

*(L.M.R.) Telephone: +61 2 9351 4781. Fax: +61 2 9351 3329. E-mail: lou.rendina@sydney.edu.au.

Author Contributions

S.M.W. synthesized benzamides **1**−**5** and prepared drafts of this article. H.G. assisted in the synthesis of **2** and **3**. M.L.B. performed the functional cell assays. A.B. and M.M. carried out the animal behavior testing which was directed by I.S.M. P.T. determined the X-ray crystal structure of **2** and **4**. D.E.M. prepared the carborane precursor **16**·HCl and performed statistical analysis on the biological results. L.M.R. supplied carborane precursors and directed synthetic work involving carboranes. M.K. directed synthetic and in vitro work. M.R.B., M.K., and L.M.R. jointly conceived this project. The manuscript was prepared by M.K. and L.M.R. based on drafts written by S.M.W.

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Notes

The authors declare no competing financial interest.

REFERENCES

(1) Davies, W. L., Grunert, R. R., Haff, R. F., McGahen, J. W., Neumayer, E. M., Paulshock, M., Watts, J. C., Wood, T. R., Hermann, E. C., and Hoffmann, C. E. (1964) Antiviral Activity of 1-Adamantanamine (Amantadine). *Science 144* (3620), 862−863.

(2) Joubert, J., Geldenhuys, W. J., Van der Schyf, C. J., Oliver, D. W., Kruger, H. G., Govender, T., and Malan, S. F. (2012) Polycyclic Cage Structures as Lipophilic Scaffolds for Neuroactive Drugs. *ChemMedChem 7* (3), 375−384.

(3) Issa, F., Kassiou, M., and Rendina, L. M. (2011) Boron in Drug Discovery: Carboranes as Unique Pharmacophores in Biologically Active Compounds. *Chem. Rev. 111* (9), 5701−5722.

(4) Issa, F., Ioppolo, J. A., and Rendina, L. M. (2013) 3.30 - Boron and Gadolinium Neutron Capture Therapy. In *Comprehensive Inorganic Chemistry II* (Reedijk, J., and Poeppelmeier, K., Eds.), 2nd ed., pp 877−900, Elsevier, Amsterdam.

(5) Hawthorne, M. F., and Pushechnikov, A. (2012) Polyhedral borane derivatives: Unique and versatile structural motifs. *Pure Appl. Chem. 84*, 2279−2288.

(6) (a) Crossley, E. L., Issa, F., Scarf, A. M., Kassiou, M., and Rendina, L. M. (2011) Synthesis and cellular uptake of boron-rich pyrazolopyrimidines: exploitation of the translocator protein for the efficient delivery of boron into human glioma cells. *Chem. Commun. 47*, 12179−12181. (b) Hawkins, P. M., Jelliss, P. A., Nonaka, N., Shi, X., and Banks, W. A. (2009) Permeability of the Blood-Brain Barrier to a Rhenacarborane. *J. Pharmacol. Exp. Ther. 329* (2), 608−614.

(7) Surprenant, A., Rassendren, F., Kawashima, E., North, R. A., and Buell, G. (1996) The cytolytic P2Z receptor for extracellular ATP identified as a P2X receptor (P2X7). *Science 272* (5262), 735−738.

(8) Basso, A. M., Bratcher, N. A., Harris, R. R., Jarvis, M. F., Decker, M. W., and Rueter, L. E. (2009) Behavioral profile of P2X7 receptor knockout mice in animal models of depression and anxiety: Relevance for neuropsychiatric disorders. *Behav. Brain Res. 198* (1), 83−90.

(9) Samad, T. A., Moore, K. A., Sapirstein, A., Billet, S., Allchorne, A., Poole, S., Bonventre, J. V., and Woolf, C. J. (2001) Interleukin-1[beta]-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. *Nature 410* (6827), 471−475.

(10) Zunszain, P. A., Anacker, C., Cattaneo, A., Choudhury, S., Musaelyan, K., Myint, A. M., Thuret, S., Price, J., and Pariante, C. M. (2012) Interleukin-1[beta]: A New Regulator of the Kynurenine Pathway Affecting Human Hippocampal Neurogenesis. *Neuropsychopharmacology 37* (4), 939−949.

(11) Baxter, A., Bent, J., Bowers, K., Braddock, M., Brough, S., Fagura, M., Lawson, M., McInally, T., Mortimore, M., Robertson, M., Weaver, R., and Webborn, P. (2003) Hit-to-Lead studies: The discovery of potent adamantane amide P2X7 receptor antagonists. *Bioorg. Med. Chem. Lett. 13* (22), 4047−4050.

(12) Dombroski, M. A., and Duplantier, A. J. (2004) Preparation of 3-(3,5-dioxo-4,5-dihydro-3H-(1,2,4)triazin-2-yl)benzamides as P2X7 inhibitors for the treatment of inflammatory diseases. Patent WO2004058270A1.

(13) Wilson, J. G., Anisuzzaman, A. K. M., Alam, F., and Soloway, A. H. (1992) Development of carborane synthons: synthesis and chemistry of (aminoalkyl)carboranes. *Inorg. Chem. 31* (10), 1955−1958.

(14) Donnelly-Roberts, D. L., Namovic, M. T., Han, P., and Jarvis, M. F. (2009) Mammalian P2X7 receptor pharmacology: comparison of recombinant mouse, rat and human P2X7 receptors. *Br. J. Pharmacol. 157* (7), 1203−1214.

(15) Lesnikowski, Z. J. (2007) Boron units as pharmacophores - new applications and opportunities of boron cluster chemistry. *Collect. Czech. Chem. Commun. 72*, 1646−1658.

(16) Michel, A. D., Chambers, L. J., Clay, W. C., Condreay, J. P., Walter, D. S., and Chessell, I. P. (2007) Direct labelling of the human P2X7 receptor and identification of positive and negative cooperativity of binding. *Br. J. Pharmacol. 151* (1), 84−95.

(17) Porsolt, R. D., Brossard, G., Hautbois, C., and Roux, S. (2001) Rodent Models of Depression: Forced Swimming and Tail Suspension Behavioral Despair Tests in Rats and Mice. In *Current Protocols in Neuroscience*, Vol. *14*, pp 1−8, John Wiley & Sons, Inc., New York.

(18) Cryan, J. F., and Holmes, A. (2005) The ascent of mouse: advances in modelling human depression and anxiety. *Nat. Rev. Drug Discovery 4* (9), 775−790.

(19) Boucher, A. A., Arnold, J. C., Hunt, G. E., Spiro, A., Spencer, J., Brown, C., McGregor, I. S., Bennett, M. R., and Kassiou, M. (2011) Resilience and reduced c-Fos expression in P2X7 receptor knockout mice exposed to repeated forced swim test. *Neuroscience 189*, 170−177.

(20) Haky, J. E., and Young, A. M. (1984) Evaluation of a Simple HPLC Correlation Method for the Estimation of the Octanol-Water Partition Coefficients of Organic Compounds. *J. Liq. Chromatogr. 7* (4), 675−689.

(21) Pajouhesh, H., and Lenz, G. (2005) Medicinal chemical properties of successful central nervous system drugs. *Neurotherapeutics 2* (4), 541−553.

(22) Leeson, P. D., and Springthorpe, B. (2007) The influence of drug-like concepts on decision-making in medicinal chemistry. *Nat. Rev. Drug Discovery 6* (11), 881−890.