Author/s:
Chalmers, BA;Xing, H;Houston, S;Clark, C;Ghassabian, S;Kuo, A;Cao, B;Reitsma, A;Murray, CEP;Stok, JE;Boyle, GM;Pierce, CJ;Littler, SW;Winkler, DA;Bernhardt, PV;Pasay, C;De Voss, JJ;McCarthy, J;Parsons, PG;Walter, GH;Smith, MT;Cooper, HM;Nilsson, SK;Tsanaktsidis, J;Savage, GP;Williams, CM

Title:
Validating Eaton's Hypothesis: Cubane as a Benzene Bioisostere

Date:
2016-03-07

Citation:
Chalmers, B. A., Xing, H., Houston, S., Clark, C., Ghassabian, S., Kuo, A., Cao, B., Reitsma, A., Murray, C. E. P., Stok, J. E., Boyle, G. M., Pierce, C. J., Littler, S. W., Winkler, D. A., Bernhardt, P. V., Pasay, C., De Voss, J. J., McCarthy, J., Parsons, P. G. ,... Williams, C. M. (2016). Validating Eaton's Hypothesis: Cubane as a Benzene Bioisostere. Angewandte Chemie International Edition, 55 (11), pp.3580-3585. https://doi.org/10.1002/anie.201510675.

Title: Validation of Eaton's Cubane for Benzene Bioisostere Conjecture

Authors: Craig McKenzie Williams; Benjamin Chalmers; Hui Xing; Sevan Houston; Charlotte Clark; Sussan Ghassabian; Andy Kuo; Benjamin Cao; Andrea Reitsma; Cody-Ellen Murray; Jeanette Stok; Glen Boyle; Carley Pierce; Stuart Littler; David Winkler; Paul Bernhardt; Cielo Pasay; James De Voss; James McCarthy; Peter Parsons; Gimme Walter; Maree Smith; Helen Cooper; Susan Nilsson; John Tsanaktsidis; Paul Savage

To be cited as: 10.1002/anie.201510675

Link to VoR: https://doi.org/10.1002/anie.201510675

Validation of Eaton's Cubane for Benzene Bioisostere Conjecture**

Benjamin A. Chalmers,[a] Hui Xing,[a] Sevan Houston,[a] Charlotte Clark,[b] Sussan Ghassabian,[c] Andy Kuo,[c] Benjamin Cao,[d,e] Andrea Reitsma,[d,e] Cody-Ellen P. Murray,[f] Jeanette E. Stok,[a] Glen M. Boyle,[g] Carly J. Pierce,[g] Stuart W. Littler,[d] David A. Winkler,[d,h] Paul V. Bernhardt,[a] Cielo Pasay,[g] James J. DeVoss,[a] James McCarthy,[g,i] Peter G. Parsons,[g] Gimme H. Walter,[f] Maree T. Smith,[c] Helen M. Cooper,[b] Susan K. Nilsson,[d,e] John Tsanaktsidis,[d,*] G. Paul Savage,[d,*] and Craig M. Williams[a,*]

Dedicated to Professor Philip Eaton on the occasion of his 80th birthday.

Abstract: *Pharmaceutical and agrichemical discovery programs are under considerable pressure to meet increasing global demand, and thus require constant innovation. Classical hydrocarbon scaffolds have long assisted in bringing new molecules to the market place, but an obvious omission is that of the Platonic solid cubane. Eaton, however, suggested that this molecule has the potential to act as a benzene bioisostere. Herein, we report the prosecution of Eaton's conjecture using cubane derivatives of five molecules deployed clinically, or as agrichemicals. All derivatives were observed to manifest, partial, equal or greater activity relative to their benzene ring comparator thereby validating this long-standing conjecture. Ramifications from this study are best realized by reflecting on the number of bioactive molecules that contain a benzene ring. Substitution, where possible with the cubane scaffold, could revitalize these systems, and thus expedite much needed lead candidate identification.*

[a] Dr. B. A. Chalmers, H. Xing, S. D. Houston, Dr. E. Stok, Prof. P. Bernhardt, Prof. J. D. Voss, A/Prof. C. Williams*
School of Chemistry and Molecular Biosciences, University of Queensland (UQ), Brisbane, 4072, Queensland (QLD), Australia (AU)
c.williams3@uq.edu.au
[b] Dr. C. E. J. Clark, A/Prof. H. Cooper
Queensland Brain Institute, UQ
[c] Dr. S.Ghassabian, Dr. A. Kuo, Prof. M. Smith
Centre for Integrated Preclinical Drug Development, UQ
[d] B. Cao, A. Reitsma, S. Littler, Prof. D. Winkler, A/Prof. S. K. Nilsson, Dr. J. Tsanaksidis*, Dr. P. Savage*
CISRO Manufacturing Flagship, Ian Wark Laboratory, Melbourne, 3168, Vicotoria (VIC), AU
John.Tsanaktsidis@csiro.au; Paul.Savage@csiro.au
[e] Australian Regenerative Medicine Institute, Monash University (MU) Melbourne, 3168, VIC, AU
[f] C-E. P. Murray, Prof. G. Walter
School of Biological Sciences, UQ
[g] Dr. G. M. Boyle, C. J. Pierce, Dr. C. Pasay, Prof. J. McCarthy, Prof. P. G. Parsons
QIMR Berghofer Medical Research Institute, PO Royal Brisbane Hospital
Brisbane, 4029, QLD, AU
[h] Institute of Pharmaceutical Sciences, MU
[i] Australian Centre for International and Tropical Health, UQ
[**] This work was supported by the Australian Research Council, via a Future Fellowship to C.M.W (FT110100851), the University of Queensland, the CSIRO (Melbourne), NCRIS 2013 THD grant funding to the TIA-QLD Node from Therapeutic Innovation Australia (TIA), and infrastructure purchased using investment funds from the Queensland Government Smart State Research Facilities Fund as well as from Therapeutic Innovation Australia. We would sincerely like to thank Mr Michael Falkiner (CSIRO) for the supply of dimethyl cubane-1,4-dicarboxylate. Furthermore, we acknowledge Ms. Dani Cardozo (CSIRO) for assistance with the SAHA related animal work and Prof. Anders Woetmann (University of Copenhagen) for kindly supplying the MyLa2059 cell line. The Australian Government's Australia-India Strategic Research Fund (GCF010006) is also kindly acknowledged.

Supporting information for this article is given via a link at the end of the document.

The necessity for innovations to bolster pharmaceutical and agrichemical discovery pipelines has become ever more important to address current and future challenges in health and food security.[1] Classical caged hydrocarbons, such as norbornene and adamantane have been widely used scaffolds throughout the history of drug and agrichemical discovery, which in the modern era continue to still deliver useful agents.[2] A hydrocarbon system missing from this scene, however, is that of cubane (**1**, pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane),[3] which Eaton predicted should provide fascinating potential for pharmaceutical research.[4] This conjecture was based on the cubane frame being approximately the same size and shape as a benzene ring (**2**) i.e. a novel bioisostere/cubane for benzene replacement. Specifically, when viewed along an axis the C-C bond length of 1.362 Å approaches that of benzene at 1.397 Å. Moreover, the distance across the cube body diagonal (2.72 Å) is almost equivalent to the distance across the benzene ring, 2.79 Å.[5]

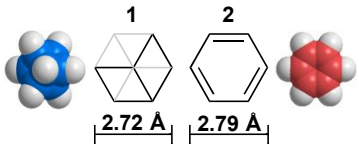


Figure 1. Two and three dimensional body diagonal views of cubane (**1**) as compared to benzene (**2**).

Despite Eaton's 1992 postulate surprisingly few cubane containing molecules have been evaluated for pharmaceutical/agrichemical potential, [9-12] given the impact of bioisosteres, for example, in drug discovery.[13] This apparent lack of interest in cubane presumably follows the incorrect assumption that the structure is esoteric, unstable, or synthetically intractable.

Herein we describe the first broad validation of Eaton's conjecture that cubane (**1**) can act as a benzene (**2**) bioisostere. An array of known biologically active molecules (i.e. **3**, **5**, **7**, **9**, **11**) with target indications ranging from cancer, Alzheimer's disease and pain to human parasites and agricultural pests, were chosen as diverse compounds to evaluate Eaton's benzene bioisostere conjecture (i.e. **4**, **6**, **8**, **10**, **12**) (Figure 2).

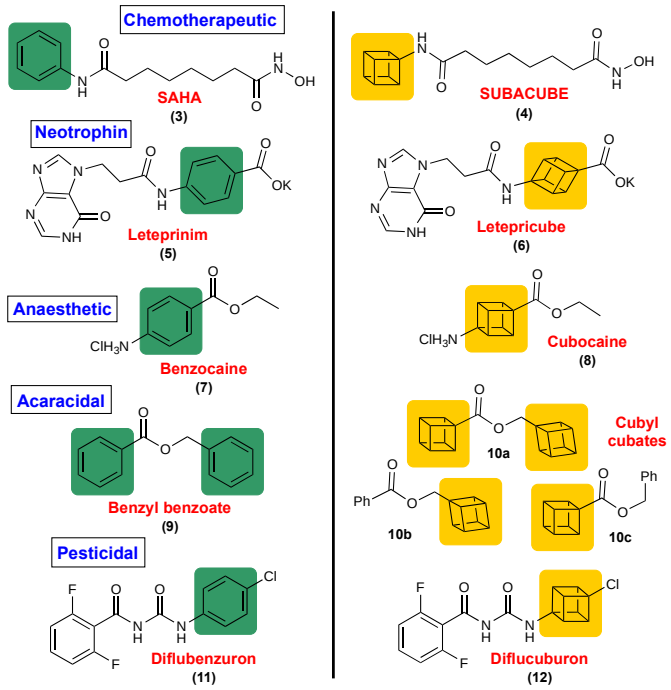


Figure 2. Benzene ring containing pharmaceutical and agrichemical compounds, and the corresponding cubane analogues with hypothetical trade names.

SAHA: The initial target selected for investigation was the histone deacetylase inhibitor SAHA[6] (**3**, suberanilohydroxamic acid), which gained approval from the FDA for the treatment of cutaneous T-cell lymphoma (CTCL) in 2006.[7] The comparative activities of the cubane analogue (SUBACUBE **4**) and SAHA (**3**) were determined via tumour cell (MM96L and MCF7) and primary (NFF) line inhibition studies. Both compounds, when incubated at varying concentrations, inhibited the growth of both tumour cell lines with similar IC_{50} values of between 0.01 to 0.07 µg/mL when allowed to grow to confluence (5-6 days). Both compounds were significantly less toxic to NFF primary cells. Interestingly SAHA (**3**) exhibited a slightly greater toxicity towards NFF cells compared to **4**. *In vitro* analysis using the MyLa2059 cell line demonstrated that both compounds were very efficient at killing the cell line and significantly better than the vehicle ($p<0.001$). The *in vivo* tumour suppression activity of SUBACUBE (**4**) and SAHA (**3**) was assessed in a T-cell lymphoma xenograft model, which was generated by transplantation of MyLa2059 cells into NODSCIDIL2Rγ$^{-/-}$ (NSG) mice. Mice treated with **4** showed equivalent tumour growth rates relative to **3** (Figure 3a). Both treatments were efficacious as demonstrated by a significant reduction ($p<0.005$) in tumour growth rate compared to the vehicle treated control mice. Thus, the cubane analogue **4** performed almost identically to SAHA (**3**).

Leteprinim: Evaluation of the neotrophic drug leteprinim (**5**) was explored, based on previous studies, which demonstrated that **5** imparts significantly greater neurite outgrowth, a measure of neuronal differentiation, in PC12 neural precursor cells derived from a rat pheochromocytoma.[8] Additional studies revealed neuroprotective properties, which may, as a result, provide a preventative measure for stroke as well as other neurodegenerative diseases.[9] Treatment of PC12 cells with either leteprinim (**5**) or letepricube (**6**) alone failed to induce neuronal differentiation (Figure 3b). However, in combination with nerve growth factor (NGF), both induced neurite outgrowth when compared to NGF alone. Moreover, in the presence of NGF the differentiation capacity of the cubane analogue **6** was markedly greater than leteprinim (**5**). Despite their ability to induce more vigorous neuronal differentiation than NGF, **5** and **6** did not enhance the length of neurites above that induced by NGF alone (see Supporting Information), indicating that they influence only the initial step in the neuronal differentiation pathway.

Benzocaine: There is an increasingly large demand for new pharmaceutical agents for the treatment of pain.[10] Thus the analgesic effects of the widely used local anaesthetic, the non-selective sodium ion channel blocker benzocaine (**7**)[11] were directly compared with cubocaine (**8**), and vehicle, following single intraplantar bolus injections into one hindpaw of adult male Sprague-Dawley rats. An acute noxious heat stimulus was applied to the ipsilateral (injected) hind paws immediately pre-dose and at pre-defined intervals over a 3 hour post-dosing period to generate paw thermal threshold (PTT) versus time curves. The extent and duration of antinociception evoked by **7**, **8** and vehicle indicated that the cubane analogue **8** had equal local anaesthetic efficacy to that of benzocaine (**7**) in this model (Figure 3c).

Benzyl benzoate: This acaracide (**9**) is used as a topical human treatment for scabies,[12] a very common skin disease in developing countries that causes major morbidity. Although highly effective, its use is limited by transient, intense local skin irritation.[13] All combinations of benzene ring replacement were synthesized giving three different cubane analogues (**10a-c**, Figure 2). When exposed to a solution of benzyl benzoate (**9**) (25 mM) all scabies mites, perished within 5 minutes of exposure. A negative control assay consisting of mites exposed to pure mineral oil, showed no toxicity after 48 hours of exposure. When mites were exposed to **10a-c** significantly lower activity was observed compared to the positive control (**9**, 100% mortality). Cubyl cubate **10c** displayed the highest acaracidal activity at 55% mortality. Furthermore, **10c** required 24 hours to reach 55% mortality compared to 5 minutes for benzyl benzoate.

Diflubenzuron: *Tribolium castaneum* (rust-red flour beetle), is a major pest of stored grain and derivative products worldwide and has been tested with benzoylphenylureas (BPUs), such as diflubenzuron (**11**). This insect growth regulator is considered most effective on the larval stages of arthropods.[14] Late instar larvae of laboratory cultured T. castaneum were exposed to diflubenzuron (**11**) and diflucuburon (**12**). The latter (**12**) consistently and significantly out-performed the former (**11**) in this (Figure 3d), and in additional evaluations (see Supporting Information).

Of the five cases evaluated above, either *in vitro* or *in vivo*, four cubane analogues were observed to manifest equal (SUBACUBE **4**, cubocaine **8**) or increased bioactivity (letepricube and diflucuburon analogues **6** and **12**) as compared to their corresponding benzene counterparts. Whereas, the cubyl cubates (**10a-c**) demonstrated only partial efficacy.

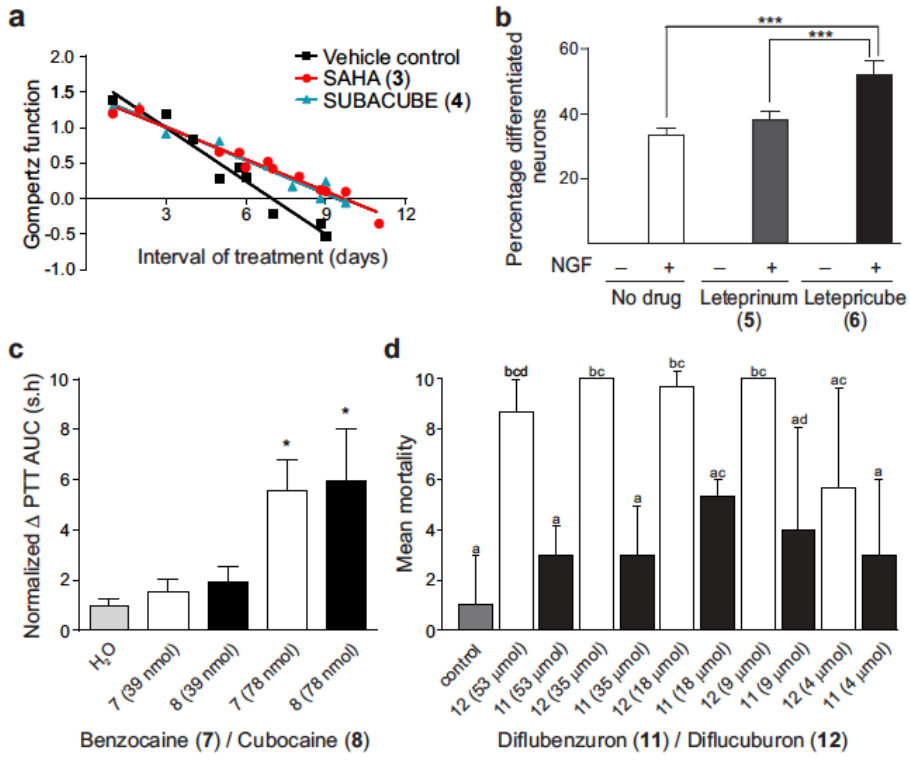
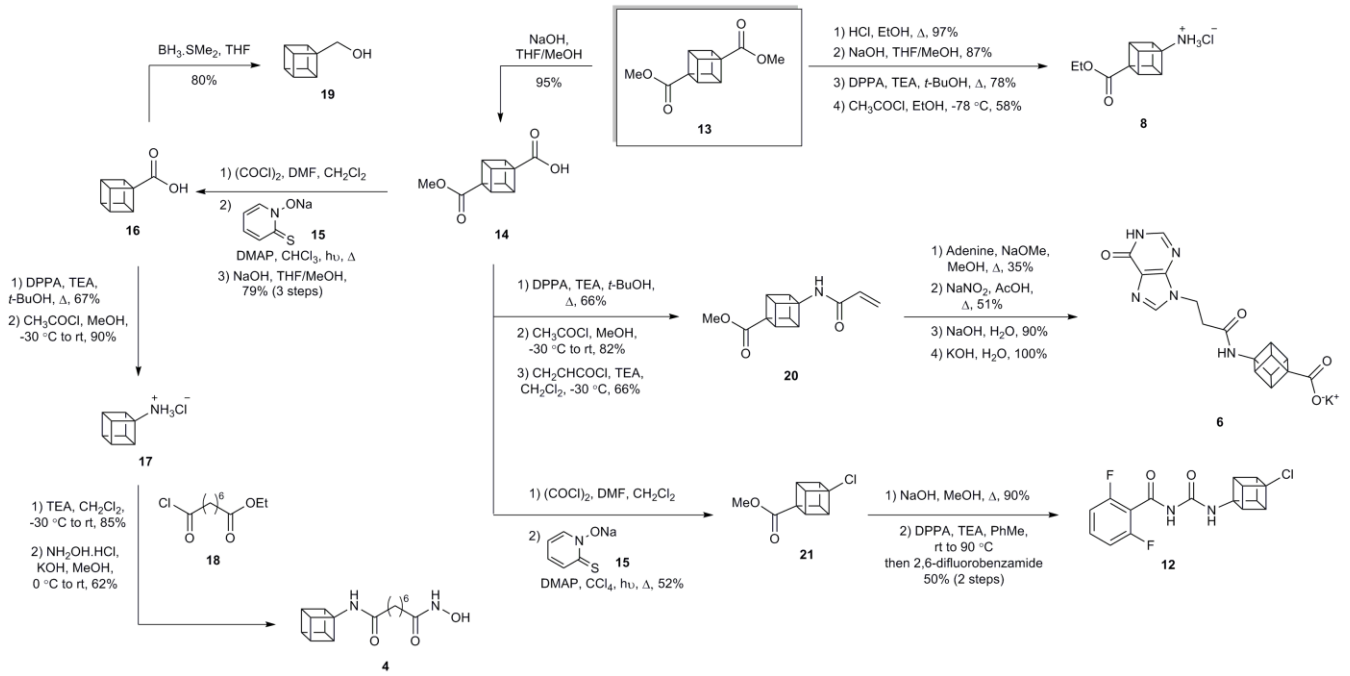


Figure 3. Biological data for cubane analogues and their pharmaceutical and agrochemical progenitors. a) Gompertz plot of tumour growth rates for SUBACUBE (**4**) and SAHA (**3**) treated versus control animals. Each line is a representative animal whose tumour growth rate mirrors the average of mice in the relevant treatment group; b) NGF-dependent PC12 cell differentiation was enhanced by letepricube (**6**); c) Extent and duration of antinociception (ΔPTT AUC values) evoked by single i.pl. bolus doses of benzocaine (**7**) with cubocaine (**8**). Negative control (water for injection); d) Mean (±SE) mortality of *T. castaneum* caused by different doses of diflucuburon (**12**) (white) and diflubenzuron (**11**) (black), with equivalent micromolar amounts of each compound used at each dose. Different superscripts above bars indicate significant differences (P<0.05) across doses of particular test substances and across test substances.

What are the main implications for using the cubane for benzene bioisostere in future bioactive molecule discovery i.e. solubility, metabolism, stability and tractability?

Solubility (logP):[15] Solubility and permeability are key parameters for biomolecule design and discovery. SUBACUBE (**4**) had only a slightly higher logP value of 1.52, when compared to that of SAHA (0.99). For cancer cell line investigation this had little impact, although, for mouse studies slight changes to the vehicle delivery method were required to facilitate solubility. Letepricube (**6**) did not require any changes in the testing regime due to solubility, as was the observation for the benzocaine analogue (**8**, ΔlogP 0.07). However, it is surmised that the slight increase in activity observed for **6** may be a reflection of increased lipophilicity matching the known CNS hydrophobic environment associated with myelination of nerve fibres.[16] Diflucuburon (**12**) showed a logP difference of 0.2, which was inconsequential for the *T. castanuem* study, because solid **12** was readily ingested by the target larvae. However, the cubyl cubates (**10a-c**) highlight the intrinsic differences in polarity, and subsequent effect on activity in some cases, when considering substitution of a benzene ring moiety for the cubane nucleus. In this extreme case the delivery vehicle (mineral oil) required heating to solubilise analogues **10a** (logP 5.43) and **10b** (logP 5.10), but not for **10c** (logP 4.22) [benzyl benzoate (logP 3.86)]. Of the cubyl cubates, **10c** had the highest activity, albeit only 55% compared to benzyl benzoate. These observations suggest that it is important for cubane isostere design to aim for solubility matching, and that in most cases utilisation of the cubane nucleus has little effect on solubility except in the cases when cubane has limited counter solubilising substitution.

Metabolism (ADME):[17] Phase I drug metabolism is mainly carried out by members of the Cytochrome P450 superfamily and typically results in insertion of an oxygen atom into a C-H bond to produce an alcohol.[18] The selectivity of this process is determined by a combination of steric and electronic factors, with C-H bond strength believed to be important in directing oxidation. Thus, as cubane possesses unusually strong (BDE 104 kcal/mol), but hindered tertiary C-H bonds because of the increased *s* character,[19] it is expected that metabolism via hydroxylation of the cubane core would be decreased. Of course P450 catalysed oxidation of a phenyl ring proceeds via addition to the electron rich π cloud and does not occur by simple C-H abstraction.[20] Nevertheless, it has been suggested that hydroxylation of methylcubane occurs on both the methyl moiety and the cubane core, although the latter leads to decomposition of the cubane nucleus.[21] With this in mind we evaluated the oxidation of *t*-butylcubane (see Supporting Information) with a model bacterial P450 (P450cam), which afforded only one detectable product, apparently from hydroxylation at one of the methyl groups. Interestingly, P450cam-catalysed oxidation of the analogous *t*-butylbenzene, which proceeded to give approximately equal amounts of aromatic ring and methyl hydroxylation. These observations help to explain why the diflubenzuron analogue (**12**) demonstrates such remarkable activity. Diflubenzuron (**11**) has two known modes of degradation, which promote resistance in arthropods: 1) acyl imide bond cleavage; and 2) metabolic hydroxylation of the aniline ring followed by conjugation to sugars and excretion; [22] presumably the latter pathway at least is significantly diminished by cubane incorporation. Finally, to determine whether cubane for benzene replacement would promote alternative drug metabolism pathways, a phase I & II metabolic analysis of both leteprinim **5**, and the cubane analogue **6**, was undertaken. Utilising *in vitro* human liver microsomes, glucuronide metabolites were not observed for either compound, indicating that neither of these compounds appear to be metabolised, and thus cleared, via this pathway.



Scheme 1. Synthesis of cubane analogues **4**, **6**, **8**, **10**, **12**. DPPA = diphenylphosphoryl azide, TEA = triethylamine, DMAP = *N*,*N*-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide.

Cubane chemistry: While cubane (**1**) itself is thermodynamically unstable (ΔH_f = 144 kcal/mol), and highly strained (SE = 161.5 kcal/mol), it and many of its known derivatives are indefinitely stable at ambient temperatures. This anomaly arises because cubane has no kinetically viable pathways for thermal rearrangement: carbon-carbon bond homolysis leads to a high-energy biradical that is still very strained, and two-bond ring-opening reactions are thermally disallowed by orbital symmetry considerations.[23] Perhaps the primary concern regarding the use of cubane in both academic and industrial settings is the availability of suitable cubane precursors on significant scale. This has largely been addressed with our finding that dimethyl cubane-1,4-dicarboxylate (**13**) can be produced in kilogram quantities.[24] All analogs (**4**, **6**, **8**, **10a-c,**[25] **12**) were synthesized from this precursor using standard transformations. A secondary concern, however, is functional group placement and manipulation. When compared to synthetic chemistry associated with the benzene ring cubane chemistry is not as well established. Nevertheless, the cubane nucleus has proven to be robust and is tolerant to a wide range of conditions [e.g. acid catalyzed transesterification (i.e. **8**) and deprotection (i.e. **17**), base mediated hydrolysis (i.e. **14**), Curtius rearrangement (i.e. **8**, **17**, **20**), Barton decarboxylation (i.e. **16**) and chlorination (i.e. **21**) via the *N*-hydroxy-2-thiopyridone (**15**), diazotization (i.e. **12**), and borane reduction (i.e. **19**)] and for the most part in similarly good yields to that obtained for the benzene analogues (see Scheme 1, and Supporting Information). In both a synthetic and medicinal chemistry sense, recent work has further demonstrated the synthetic potential of cubane towards potentially biologically active pharmacophores.[26]

In summary, cubane can act as a suitable isostere for benzene in biological applications, as Eaton postulated, with the caveat that biological uptake of the compound must be feasible. This finding facilitates two significant bioactive discovery innovations: 1) it provides a tangential chemical bioisostere approach in drug and agrichemical discovery thinking, and 2) will revitalise new and old commercial compounds that have already been refined based on various drug discovery principles, and thus expedite lead candidate identification for rapid pipeline bolstering.

Experimental Section

Experimental details, characterization data, copies of NMR spectra, and author contributions are provided in the supporting information document.

Keywords: Cubane • Eaton • Pharmaceutical • Agrichemical • Eaton's conjecture

How to cite: *Angew. Chem. Int. Ed….*

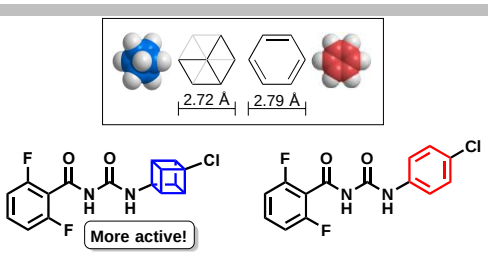
[1] a) M. Hay, D. W. Thomas, J. L. Craighead, C. Economides, J. Rosenthal, *Nat. Biotech.* **2014**, *32*, 40-51; b) C. Lamberth, S. Jeanmart, T. Luksch, A. Plant, *Science* **2013**, *341*, 742-746.

[2] a) W. Krämer, *Modern crop protection compounds, Vol. 2nd, rev. and enl.*, Wiley-VCH, Chichester, **2012**; b) L. Wanka, K. Iqbal, P. R. Schreiner, *Chem. Rev.* **2013**, *113*,

3516-3604; c) T. P. Stockdale, C. M. Williams, *Chem. Soc. Rev.* **2015**, *44*, 7737-7763.
[3] P. E. Eaton, T. W. Cole, *J. Am. Chem. Soc.* **1964**, *86*, 3157-3158.
[4] P. E. Eaton, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1421-1436.
[5] T. Yildirim, P. M. Gehring, D. A. Neumann, P. E. Eaton, T. Emrick, *Carbon* **1998**, *36*, 809-815.
[6] V. M. Richon, *Br. J. Cancer* **2006**, *95*, S2-S6.
[7] S. Grant, C. Easley, P. Kirkpatrick, *Nat. Rev. Drug. Discov.* **2007**, *6*, 21-22.
[8] P. J. Middlemiss, A. J. Glasky, M. P. Rathbone, E. Werstuik, S. Hindley, J. Gysbers, *Neurosci. Lett.* **1995**, *199*, 131-134.
[9] M. P. Rathbone, P. J. Middlemiss, C. E. Crocker, M. S. Glasky, B. H. J. Juurlink, J. J. Ramirez, R. Ciccarelli, P. Di Iorio, F. Caciagli, *Expert Opin. Investig. Drugs* **1999**, *8*, 1255-1262.
[10] D. Borsook, R. Hargreaves, C. Bountra, F. Porreca, *Sci. Transl. Med.* **2014**, *6*, 249sr243-249sr243.
[11] M. J. O'Neil, C. Royal Society of, *The Merck index: an encyclopedia of chemicals, drugs, and biologicals, Vol. 15th*, Royal Society of Chemistry, Cambridge, UK, **2013**.
[12] B. J. Currie, J. S. McCarthy, *New Engl. J. Med.* **2010**, *362*, 717-725.
[13] R. J. Hay, A. C. Steer, D. Engelman, S. Walton, *Clin. Microbiol. Infec.* **2012**, *18*, 313-323.
[14] H. Merzendorfer, H. S. Kim, S. S. Chaudhari, M. Kumari, C. A. Specht, S. Butcher, S. J. Brown, J. Robert Manak, R. W. Beeman, K. J. Kramer, S. Muthukrishnan, *Insect Biochem. Mol. Biol.* **2012**, *42*, 264-276.
[15] C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Deliv. Rev.* **1997**, *23*, 3-25.
[16] Y. Hu, I. Doudevski, D. Wood, M. Moscarello, C. Husted, C. Genain, J. A. Zasadzinski, J. Israelachvili, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 13466-13471.
[17] J. Hodgson, *Nat. Biotech.* **2001**, *19*, 722-726.
[18] P. R. Ortiz de Montellano, *Chem. Rev.* **2010**, *110*, 932.
[19] W. Adcock, M. J. Brunger, I. E. McCarthy, M. T. Michalewicz, W. von Niessen, F. Wang, E. Weigold, D. A. Winkler, *J. Am. Chem. Soc.* **2000**, *122*, 3892-3900.
[20] O. Sibbesen, Z. Zhang, P. R. Ortiz de Montellano, *Arch. Biochem. Biophys.* **1998**, *353*, 285-296.
[21] M. Newcomb, R. Shen, S.-Y. Choi, P. H. Toy, P. F. Hollenberg, A. D. N. Vaz, M. J. Coon, *J. Am. Chem. Soc.* **2000**, *122*, 2677-2686.
[22] V. Jenkins, R. Perry, A. Ahmed, K. Ives, *Invest. New Drugs* **1986**, *4*, 325-335.
[23] K. F. Biegasiewicz, J. R. Griffiths, G. P. Savage, J. Tsanaktsidis, R. Priefer, *Chem. Rev.* **2015**, *115*, 6719-6745.
[24] M. J. Falkiner, S. W. Littler, K. J. McRae, G. P. Savage, J. Tsanaktsidis, *Org. Process Res. Dev.* **2013**, *17*, 1503-1509.
[25] Cubyl cubates (**10a-c**) were synthesised from a combination of cubanecarboxylic acid (**16**), cubanecarbinol (**19**), benzoic acid and benzyl alcohol. See Supporting Information for details.
[26] a) J. Wlochal, R. D. M. Davies, J. Burton, *Org. Lett.* **2014**, *16*, 4094-4097; b) S. Plunkett, K. J. Flanagan, B. Twamley, M. O. Senge, *Organometallics* **2015**, 34, 1408−1414.

COMMUNICATION

Please consider cubane as a benzene bioisostere! Over 25 years ago Eaton proposed that cubane could act as a benzene bioisostere. Eaton's conjecture has now been validated using cubane derivatives of biologically important molecules. All derivatives were observed to manifest, partial, equal or greater activity relative to the benzene ring counterpart.



B. A. Chalmers, H. Xing, S. Houston, C. Clark, S. Ghassabian, A. Kuo, B. Cao, A. Reitsma, C.-E. P. Murray, J. E. Stok, G. M. Boyle, C. J. Pierce, S. W. Littler, D. A. Winkler, P. V. Bernhardt, C. Pasay, J. J. DeVoss, J. McCarthy, P. G. Parsons, G. H. Walter, M. T. Smith, H. M. Cooper, S. K. Nilsson, J. Tsanaktsidis, G. P. Savage, C. M. Williams

Page No. – Page No.

Validation of Eaton's Cubane for Benzene Bioisostere Conjecture