Bioisosteres

Deutsche Ausgabe: DOI: 10.1002/ange.201510675
Internationale Ausgabe: DOI: 10.1002/anie.201510675

Validating Eaton's Hypothesis: Cubane as a Benzene Bioisostere

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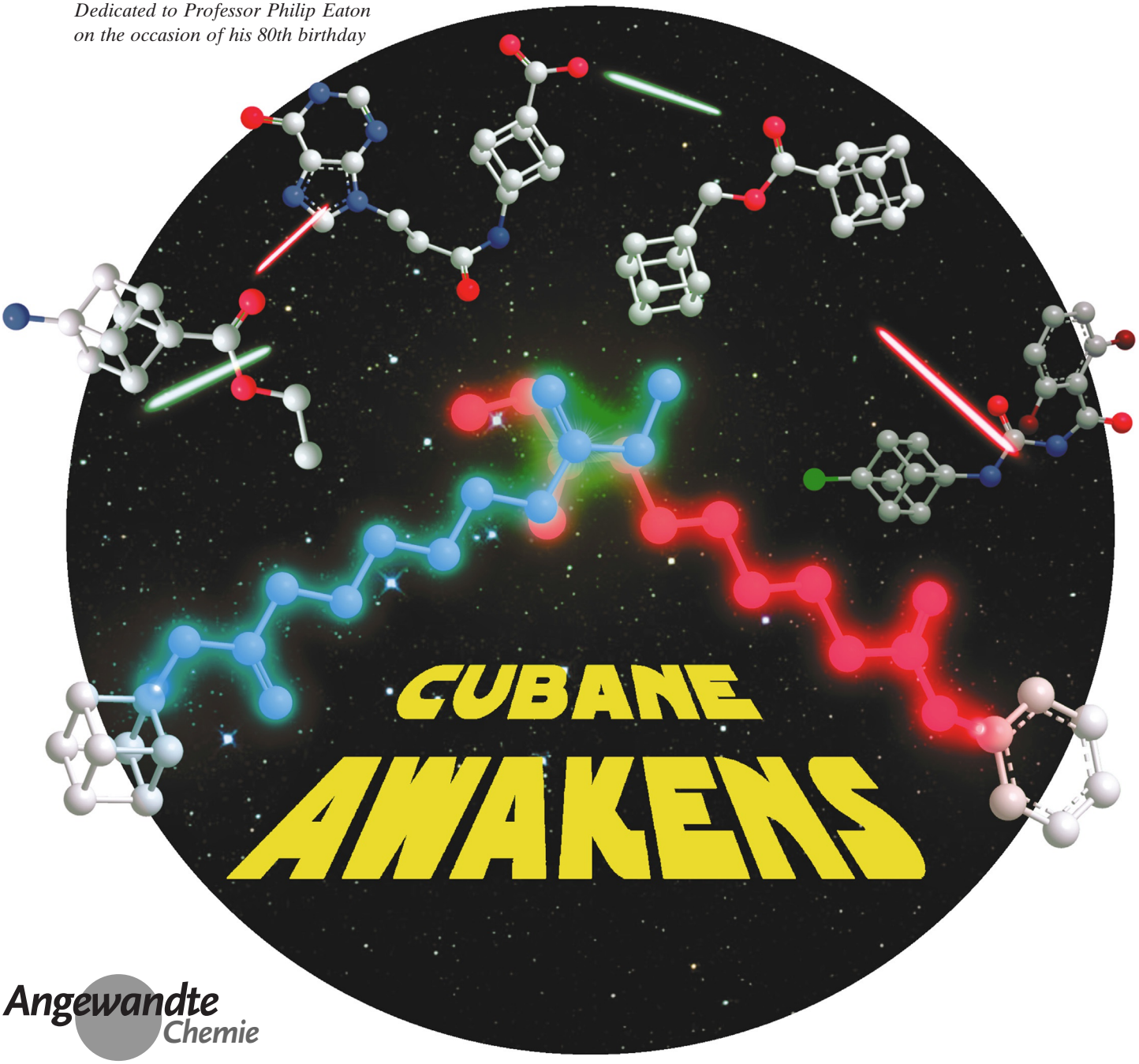
Dedicated to Professor Philip Eaton on the occasion of his 80th birthday



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Abstract: *Pharmaceutical and agrochemical 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 validation of Eaton's hypothesis with cubane derivatives of five molecules that are used clinically or as agrochemicals. Two cubane analogues showed increased bioactivity compared to their benzene counterparts whereas two further analogues displayed equal bioactivity, and the fifth one demonstrated only partial efficacy. Ramifications from this study are best realized by reflecting on the number of bioactive molecules that contain a benzene ring. Substitution with the cubane scaffold where possible could revitalize these systems, and thus expedite much needed lead candidate identification.*

The necessity for innovations to bolster pharmaceutical and agrochemical 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 agrochemical discovery and still continue to deliver useful agents in the modern era.[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 to provide fascinating potential for pharmaceutical research.[4] This hypothesis was based on the cubane framework being approximately the same size and shape as a benzene ring (**2**) and thus a suitable bioisostere for benzene replacement. Specifically, 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; Figure 1).[5]

Despite Eaton's postulate in 1992, surprisingly few cubane-containing molecules have been evaluated for pharmaceutical/agrochemical potential[6] given the impact of bioisosteres, for example, in drug discovery.[7] This apparent lack of interest in cubane presumably follows the incorrect assumption that such compounds are esoteric, unstable, or synthetically intractable.

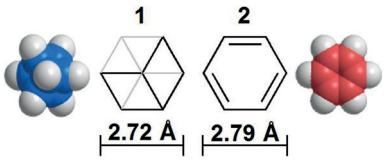

Figure 1. Two- and three-dimensional body diagonal views of cubane (**1**) and benzene (**2**).

Herein, we describe the first broad validation of Eaton's proposal that cubane (**1**) can act as a benzene (**2**) bioisostere. An array of known biologically active molecules (**3**, **5**, **7**, **9**, and **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 hypothesis (**4**, **6**, **8**, **10**, and **12**; Figure 2).

The initial target selected for investigation was the histone deacetylase inhibitor SAHA[8] (**3**, suberanilohydroxamic acid), which gained approval from the FDA for the treatment of cutaneous T-cell lymphoma (CTCL) in 2006.[9] The comparative activities of SAHA (**3**) and its cubane analogue (SUBACUBE **4**) were determined by tumor cell (MM96L and MCF7) and primary (NFF) line inhibition studies. When incubated at various concentrations, both compounds inhibited the growth of both tumor cell lines with similar IC_{50} values of 0.01 to 0.07 $\mu g\,mL^{-1}$ 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 than **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 tumor 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 NODSCIDIL2R$\gamma^{-/-}$ (NSG) mice. Mice treated with **4** showed equivalent tumor growth rates relative to **3** (Fig-

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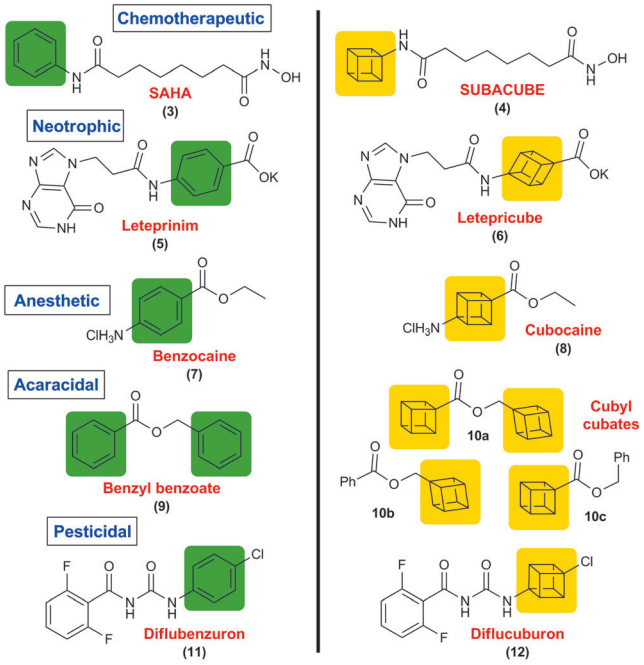

Figure 2. Benzene-ring-containing pharmaceutical and agrochemical compounds and the corresponding cubane analogues with hypothetical trade names.

There is an increasingly large demand for new pharmaceutical agents for the treatment of pain.[12] Thus the analgesic effects of a widely used local anesthetic, the non-selective sodium ion channel blocker benzocaine (**7**),[13] were directly compared with cubocaine (**8**) and vehicle, following single intraplantar bolus injections into one hind paw 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 three 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 cubane analogue **8** had the same local anesthetic efficacy as benzocaine (**7**) in this model (Figure 3c).

The acaracide benzyl benzoate (**9**) is used as a topical human treatment for scabies,[14] 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.[15] All combinations of benzene ring replacement were synthesized, giving three different cubane analogues (**10a**–**10c**, Figure 2). When exposed to a solution of benzyl benzoate (**9**; 25 mM), all scabies mites perished within five 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**–**10c**, ure 3a). Both treatments were efficacious as demonstrated by a significant reduction ($p < 0.005$) in tumor growth rate compared to the vehicle-treated control mice. Thus cubane analogue **4** performed almost identically to SAHA (**3**).

In previous studies, administration of the neotrophic drug leteprinim (**5**) was shown to impart significantly increased neurite outgrowth, a measure of neuronal differentiation, in PC12 neural precursor cells derived from a rat pheochromocytoma.[10] Additional studies revealed neuroprotective properties, which may provide a preventative measure for stroke as well as other neurodegenerative diseases.[11] 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 compounds induced neurite outgrowth when compared to NGF alone. Moreover, in the presence of NGF, the differentiation capacity of cubane analogue **6** was markedly greater than that of 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 the Supporting Information), indicating that they influence only the initial step in the neuronal differentiation pathway.

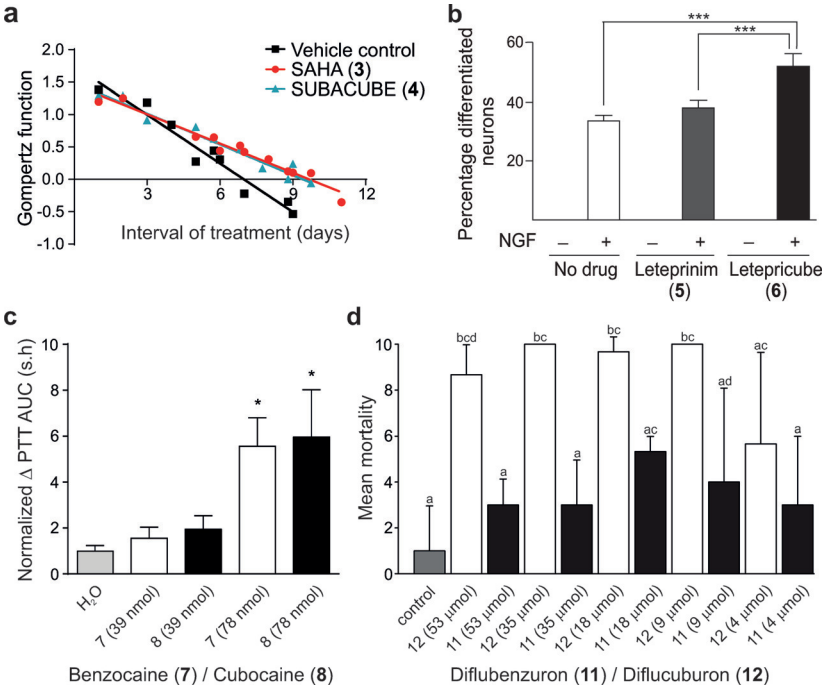

Figure 3. Biological data for cubane analogues and their pharmaceutical and agrochemical progenitors. a) Gompertz plot of tumor growth rates for animals treated with SUBACUBE (**4**) and SAHA (**3**) versus control animals. Each line is a representative animal whose tumor growth rate mirrors the average 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 intraplantar bolus doses of benzocaine (**7**) or cubocaine (**8**). Negative control: water. d) Mean (±SE) mortality of *T. castaneum* caused by different doses of diflucuburon (**12**; white) and diflubenzuron (**11**; black). Different letters above the bars indicate significant differences ($P < 0.05$) across doses of particular test substances and across test substances.

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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.

Tribolium castaneum (rust-red flour beetle), is a major pest of stored grain and derivative products worldwide and has been tested with benzoyl phenyl ureas (BPUs), such as diflubenzuron (**11**). This insect growth regulator is considered most effective on the larval stages of the arthropods.[16] Late instar larvae of laboratory-cultured *T. castaneum* were exposed to diflubenzuron (**11**) and diflucuburon (**12**). The latter (**12**) consistently and significantly outperformed the former (**11**) in this (Figure 3d) and additional evaluations (see the 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 **6** and diflucuburon **12**) compared to their corresponding benzene counterparts. The cubyl cubates (**10a**–**10c**), on the other hand, demonstrated only partial efficacy.

What are the main implications for using the cubane motif as a benzene bioisostere in future bioactive molecule discovery in terms of solubility, metabolism, stability, and tractability?

Solubility[17] and permeability are key parameters for biomolecule design and discovery. SUBACUBE (**4**) had only a slightly higher $\log P$ value (1.52) than SAHA (0.99). For cancer cell line investigations, this had little impact, whereas for the 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 because of solubility issues, as was the case for the benzocaine analogue (**8**, $\Delta(\log P) = 0.07$). 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 fibers.[18] Diflucuburon (**12**) showed a $\log P$ 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**–**10c**) highlight the intrinsic differences in polarity and subsequent effects on activity in some cases, when considering substitution of a benzene ring moiety for the cubane framework. In this extreme case, the delivery vehicle (mineral oil) required heating to solubilize analogues **10a** ($\log P = 5.43$) and **10b** ($\log P = 5.10$), but not for **10c** ($\log P = 4.22$; benzyl benzoate: $\log P = 3.86$). Among 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, except in such cases where cubane has limited substitution to significantly alter the overall solubility (i.e., cubyl cubates **10a**–**10c**).

Phase I drug metabolism[19] 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.[20] 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^{-1}), but hindered tertiary C–H bonds because of the increased s character,[21] it is expected that metabolism by hydroxylation of the cubane core would be decreased. P450-catalyzed oxidation of a phenyl ring proceeds by addition to the electron-rich π-moiety and does not occur by simple C–H abstraction.[22] 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 core.[23] With this in mind, we evaluated the oxidation of *tert*-butylcubane (see the Supporting Information) with a model bacterial P450 enzyme (P450cam), which afforded only one detectable product, apparently from hydroxylation at one of the methyl groups. Interestingly, P450cam-catalyzed oxidation of analogous *tert*-butylbenzene proceeded to give approximately equal amounts of the products 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;[24] presumably, at least the latter pathway is significantly diminished by cubane incorporation. Finally, to determine whether cubane-for-benzene replacement would promote alternative drug metabolism pathways, a phase I and II metabolic analysis of both leteprinim (**5**) and its cubane analogue (**6**) was undertaken. Utilizing in vitro human liver microsomes, glucuronide metabolites were not observed for either compound, indicating that neither of these compounds was metabolized, and thus cleared, by this pathway.

Although cubane (**1**) itself is thermodynamically unstable ($\Delta H_f = 144$ kcal mol^{-1}) and highly strained (SE = 161.5 kcal mol^{-1}), 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.[25]

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.[26] All analogues (**4**, **6**, **8**, **10a**–**10c**,[27] **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 core has proven to be robust and is tolerant to a wide range of conditions [e.g., acid-catalyzed transesterification (**8**) and deprotection (**17**), base-mediated hydrolysis (**14**), Curtius rearrangement (**8**, **17**, **20**), Barton decarboxylation (**16**) and chlorination (**21**) via the *N*-hydroxy-2-thiopyridone (**15**), diazotization (**12**), and borane reduction (**19**)], and for the most part, these transformations

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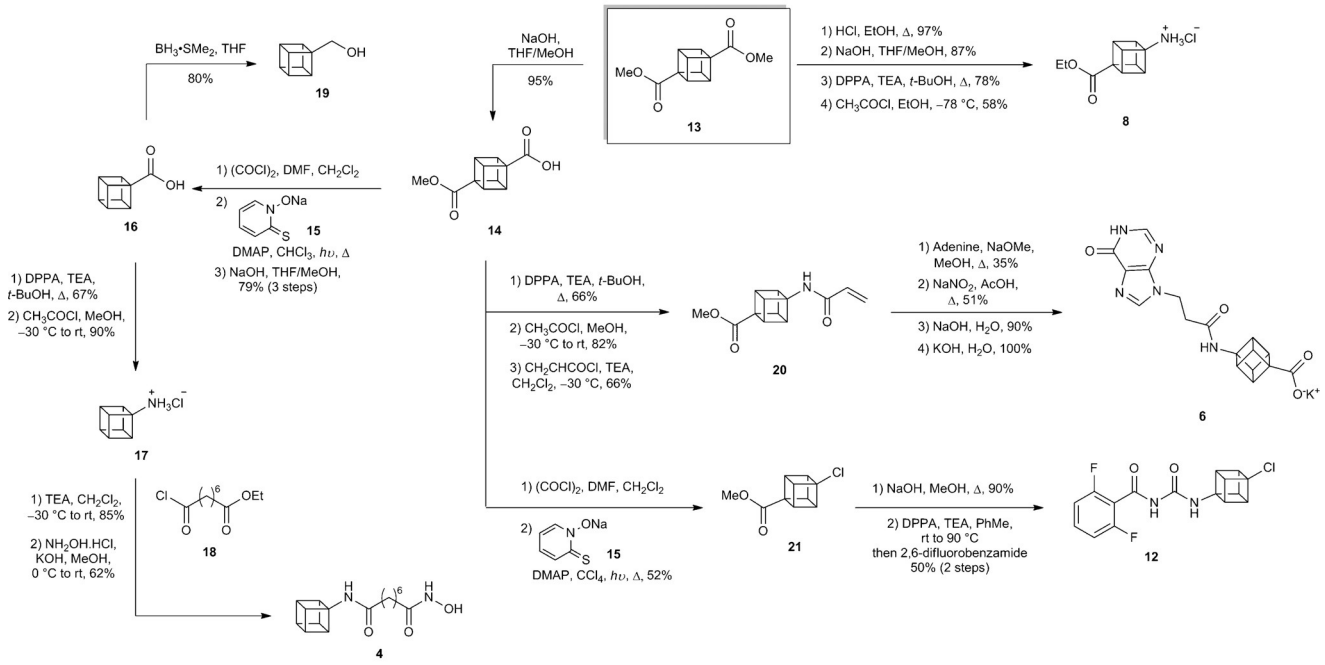

Scheme 1. Synthesis of the cubane analogues **4**, **6**, **8**, and **12**. DMAP = *N*,*N*-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, DPPA = diphenylphosphoryl azide, TEA = triethylamine.

gave similarly good yields to those obtained for the benzene analogues (see Scheme 1 and the 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.[28]

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

Acknowledgements

This work was supported by the Australian Research Council (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 sincerely thank Michael Falkiner (CSIRO) for the supply of dimethyl cubane-1,4-dicarboxylate. Furthermore, we acknowledge 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. Dr. Greg Daglish (Department of Agriculture and Fisheries) kindly provided the *Tribolium castaneum* material for use in tests. The Australian Regenerative Medicine Institute is supported by grants from the State Government of Victoria and the Australian Government.

Keywords: agrochemicals · bioisosteres · cubane · pharmaceuticals · structure–activity relationships

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 3580–3585
Angew. Chem. **2016**, *128*, 3644–3649

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Received: November 17, 2015
Revised: January 3, 2016
Published online: February 5, 2016

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