Cubanes in Medicinal Chemistry

Tristan A. Reekie,[1] Craig M. Williams,[2] Louis M. Rendina,[1] Michael Kassiou[1*]

[1] School of Chemistry, The University of Sydney, NSW 2006, Australia

[2] School of Chemistry and Molecular Biosciences, University of Queensland, QLD 4072, Australia

ABSTRACT

Cubane is a highly strained saturated hydrocarbon system that has historically been of interest in theoretical organic chemistry. More recently it has become a molecule of interest for biological applications due to its inherent stability and limited toxicity. Of greater significance is the ability to potentially functionalize cubane at each of its carbon atoms providing complex biologically active molecules with unique spatial arrangements for probing active sites. This has seen an increase use of cubane in pharmaceutically-relevant molecules. In this perspective we describe synthetic methodology for accessing a range of functionalized cubanes and their applications in pharmaceuticals. Lastly we provide some perspectives on challenges and future directions in the advancement of this field.

INTRODUCTION

On first glance, pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane, or simply cubane (**1**), looks to be an unrealistic framework for organic chemistry. However, this view could not be further from the truth, as cubane and its substituted derivatives have found multiple applications in varied chemical fields. Cubane is thermodynamically unstable and highly strained, with the geometry

around the carbon atom being far removed from tetrahedral. Importantly though, no kinetically viable path exists for its thermal rearrangement, meaning that cubane is stable up to 220 °C, and even then decomposition is slow.[1] It is the high energy, but relative stability of cubane, combined with its high density, that saw its initial application in explosives. It has only been in recent years that cubane has made its impact in the field of medicinal chemistry, making it a chemical moiety with significant potential as a robust scaffold.[2] There have been previous reviews of cubane that cover its history and application outside the field of medicinal chemistry,[2-4] whereas this perspective will discuss its relatively recent impact in drug design, including potential opportunities in unexplored areas, and future challenges.

CHARACTERISTICS OF CUBANE

The interest in cubane for pharmaceutical incorporation arises from the idea that it can act as a bioisostere of benzene (**2**), first proposed by Eaton.[2] The distance between the body diagonal of cubane (2.72 Å) matches closely with that of benzene (2.78 Å) (Figure 1),[5] even though the individual C–C bond lengths are slightly longer (1.573 Å *vs* 1.397 Å).[6] Cubane has the benefit over its benzene isostere in that it is biologically stable and there is no inherent toxicity associated with this moiety.[2] Further benefits exist with cubane, in that the eight contact points allow for substitution in defined 3D-spatial arrangements, including what can be considered "above" (A) and "below" (B) the benzene plane, in addition to "within" (C) the benzene plane (Figure 1).[2] Moreover, and as will be discussed later, there are multiple practical synthetic considerations that currently hamper the full exploration of these key spatial arrangements.

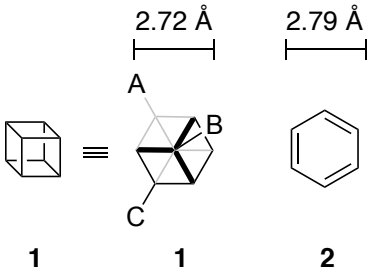


Figure 1. Cubane (**1**) and comparison to benzene (**2**), incliding the "above" (A), "below" (B) and "within" (C) the benzene plain.

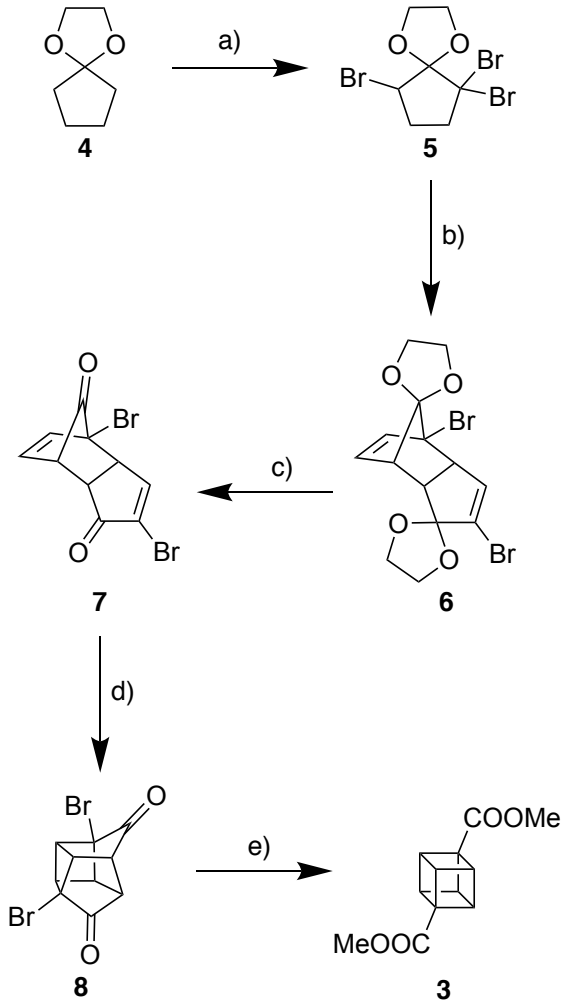
Additional benefits attributed to cubane include its complete stability to light, air, and moisture, and its relatively high melting point of 130–131 °C.[7] These attributes were capitalized upon for the promotion of cubane itself as the ideal internal NMR standard, because in addition both the hydrogen and carbon atoms resonate at uniquely reliable chemical shifts.[8] As will be outlined below, cubane is also stable to most common reagents allowing for synthetic manipulation without disrupting its key core structure.

Due to the highly strained geometry of the cubane system the C–C bonds take on much more *p*-character, which in turn provide the C–H bonds with increased *s*-character. As a result, the C–H bond is much more acidic than what is observed for unstrained hydrocarbons.[9] Neighboring-group participation allows for *ortho* lithiation with LiTMP,[10] though transmetallation is generally required to give a more useful transformation.[10-12] Despite the unfavorable considerations behind the generation of a cubyl cation, such as geometry and high *s*-character of the exocyclic orbitals, experimental evidence has been provided that supports facile formation of a cubyl cation.[13] Its formation is attributed to the *p*-character of the C–C bonds allowing for charge delocalization by donation of electron density to the cationic center.[14] Furthermore, no cationic rearrangement of the cubane skeleton is observed. Finally,

the existence of cubyl radicals has been shown through a combination of practical and computational experiments.[15-21]

SYNTHESIS OF CUBANE AND MONOSUBSTITUTED BUILDING BLOCKS

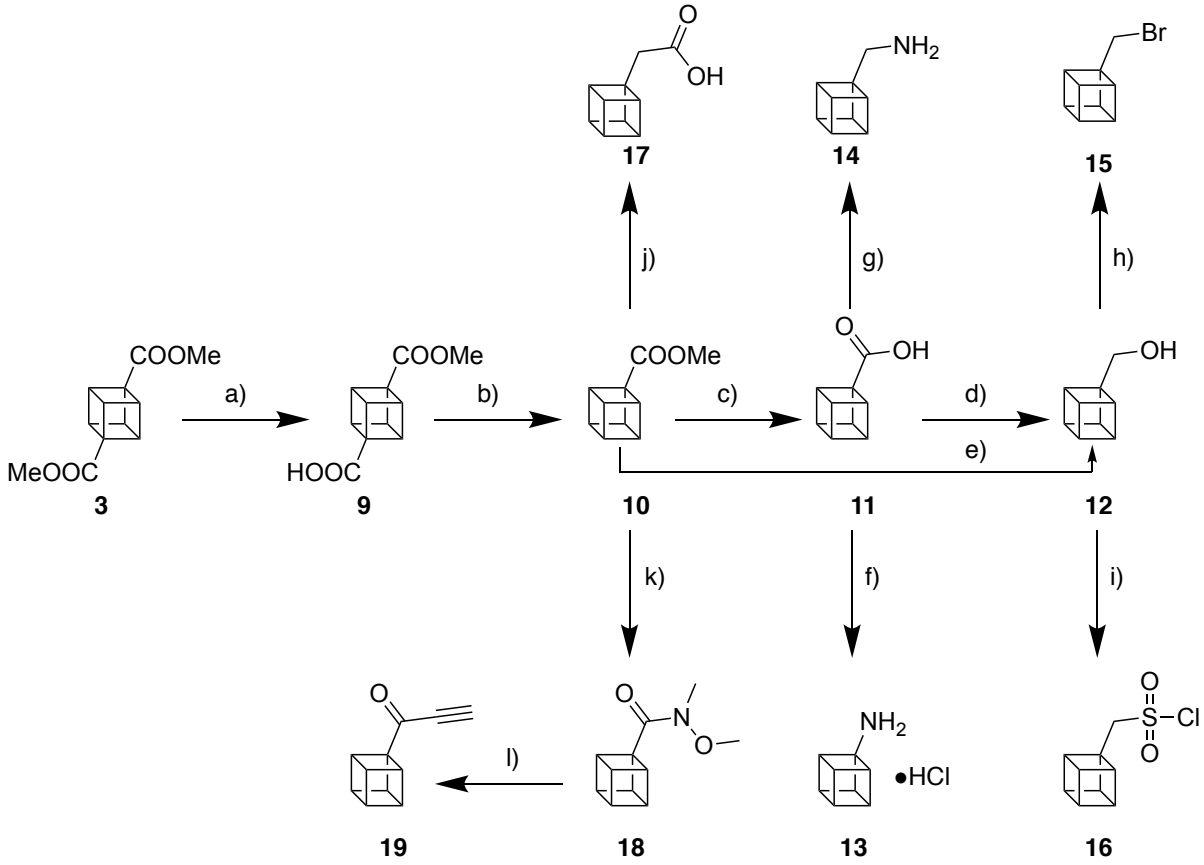
Cubane was first synthesized and reported in 1964[7] following the work of Eaton and Cole who had, earlier in the same year, reported the synthesis of the dimethyl-1,4-cubanedicarboxylate (**3**).[22] Chapman and co-workers reported several modifications to this protocol utilizing cyclopentadienone ethylene ketal (**4**) as the starting material.[23] Tsanaktsidis and co-workers integrated key elements of the Eaton and Chapman approaches to describe an improved protocol for the production of kilogram quantities of **3**, which has become the key building block for cubane-based chemistry (Scheme 1).[24, 25] Tribromination of **4** using three equivalents of bromine affords the intermediate **5** that, following bromide elimination, undergoes Diels-Alder dimerization to afford **6**. Ketal removal affords **7** that engages in a [2π +2π] ene-enone photocyclization, with subsequent hydrolysis of dimethyl ketals that form during the reaction, to afford caged compound **8**. A double Favorskii ring contraction, followed by acidification then methyl ester formation converts **8** into the solid dimethyl 1,4-cubanedicarboxylate (**3**) in 22% overall yield on kilogram scales.



Scheme 1. Synthesis of dimethyl 1,4-cubanedicarboxylate (**3**). Reagents and conditions a) Br_2, 1,4-dioxane, 10 °C to RT, 1 day; b) NaOH, MeOH, 5 °C to reflux, 20 h; c) H_2SO_4, 25 °C, 30 h; d) 1) $h\nu$ (Hg, Pyrex), aq. MeOH, H_2SO_4, 40–45 °C, 173 h; 2) H_2O, reflux, 3 h; e) 1) NaOH (30% aq.), reflux, 3 h; 2) HCl (32%), <5 °C, 18 h; 3) Dowex 50WX8–100, MeOH, reflux, 18 h.

Given the ready accessibility of **3**, various methods have been used to convert this starting material into synthetic building blocks (Scheme 2). Mono-ester hydrolysis of **3** affords **9** that can then undergo a Barton decarboxylation to afford the mono-substituted ester **10**.[26, 27] Hydrolysis affords the acid **11**, which could be reduced to the alcohol **12**, though direct reduction from the methyl ester **10** gives higher yields.[18, 28] Alternatively, the carboxylic acid

can be converted to the primary amine hydrochloride **13** or the methylamine **14**.[29] The alcohol **12** can be further converted to the bromo derivative **14**[30] or the sulfonyl chloride **16** *via* the corresponding thioacetate.[28] The mono-methyl ester **10** can be homologated to the cubanyl acetic acid **17**[28, 30] or to the Weinreb amide **18**, allowing for further functionalization, as exemplified by the formation of alkyne **19**.[28]



Scheme 2. Synthesis of cubane-based building blocks. Reagents and conditions: a) NaOH, THF/MeOH, RT, 18 h, 88%; b) $(COCl)_2$, DMF, CH_2Cl_2, 1 h then mercaptopyridine *N*-oxide sodium salt, 2,6-lutidine, *h*ν (500 W tungsten), $CHCl_3$, reflux, 1 h, 78%; c) NaOH, MeOH, RT, 2 h, 85% d) BH_3•SMe_2, THF, 0 °C to RT, 4 h, 95%; e) $LiBH_4$, THF, 0 °C to RT, 12 h, 96%; f) 1) DPPA, Et_3N, ^{t}BuOH, reflux, 5 h, 77% 2) HCl (gas), MeOH, –60 °C to RT, 20 h, 96%; g) 1) CDI, THF, RT, 2 h, then NH_3, H_2O, 0 °C to RT, 5 h, 87%; 2) $LiAlH_4$, THF, 0 °C to reflux, 16 h, 70%; h) PPh_3, CBr_4, CH_2Cl_2, RT, 5 h, 71%; i) 1) PPh_3, DIAD, AcSH, 0 °C to RT, 2 h, 94%; 2) NCS, HCl (2.0 M), MeCN, 10 °C to 20 °C, 25 min, 55%; j) 1) CH_2Br_2, LiTMP, THF, –78

°C, 20 min, 88%; 2) LHMDS, ^{n}BuLi, THF, –78 °C to 0 °C, 70 min, 60%; k) MeNHOMe•HCl, ^{i}PrMgCl, THF, –40 °C to –30 °C, 2 h, 88%; l) lithium (trimethylsilyl)acetylide, THF, –30 °C to RT, 2 h, 98%.

Compounds **9**–**19** provide multiple varied handles for incorporating cubane into larger molecules, though other building blocks have been generated, as shown in Figure 2. Substituted cubanes with a simple functionality, such as an aldehyde,[31] thiol,[32] alcohol,[33] nitrile,[34] alkyne and azide[35] moiety have all been generated (compounds **20**–**25**, respectively). Although, the aldehyde is best utilized *in situ* as it can readily decompose in pure form, whereas Eaton postulated that hydroxyl cubanes can readily undergo rearrangement *via* a ketene intermediate.[2, 32] Hydroxyacid **26**, accessible from ester **10**, can also be used to generate amino acid substituted cubanes **27**–**29**.[36] In the case of **27**, the Boc and methyl ester protected compound can undergo chiral (enantioselective) HPLC separation that affords, following deprotection, (+)- and (–)-**27**.[36] The cyanoformamide **30** has been prepared as an electrophilic carbonyl source to incorporate the cubyl amide directly.[37] The nitrile **31** has also been prepared and used to generate isoxazole cubane **32** with a primary amine for further functionalization.[28] Alternatively, the imidazole heterocycle **33** can be generated, also with a nucleophilic nitrogen atom.[28]

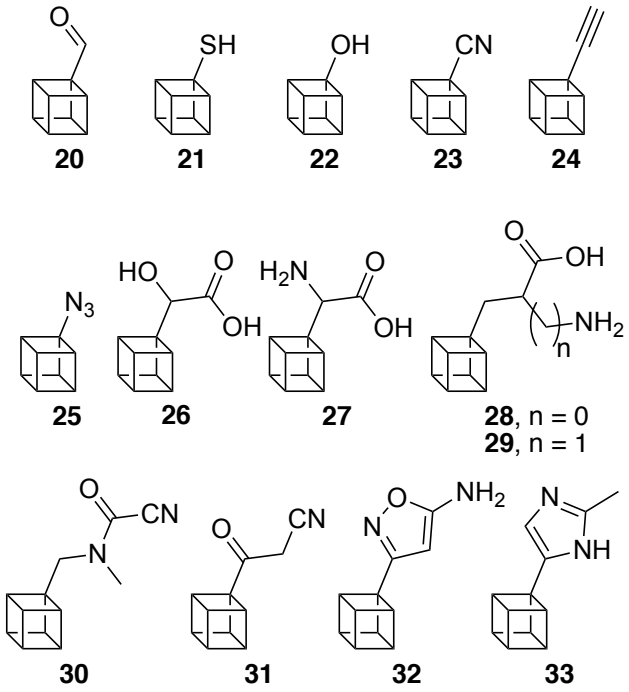


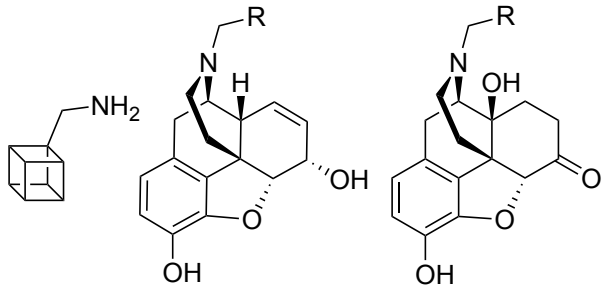
Figure 2. Cubane-based building blocks.

MONOSUBSTITUTED CUBANES IN PHARMACEUTICALS

With the accessibility of key monosubstituted cubane building blocks, the cubane motif has begun to appear in pharmaceutically-relevant molecules. One of the first examples of using a cubane compound for biological applications was (aminomethyl)cubane (**14**) to inhibit monoamine oxidase-B (Figure 3).[38] Rather than looking to develop a pharmaceutical, **14** was used to probe the mechanism by which the enzyme is able to oxidize amine containing neurotransmitters.

The strategic replacement of key moieties with cubane in pharmaceutical leads was demonstrated with the development of morphine analogues **34c** and **35c** (Figure 3).[39] Morphine (**34a**, K_i = 38 nM and 1870 nM at μ and κ opioid receptor, respectively) and oxymorphone (**35a**, K_i = 15 nM and 725 nM at μ and κ opioid receptor, respectively) are potent opioid ligands

while *N*-allyl derivatives (**34b** and **34b** respectively) are at least 8-fold more potent, as is the *N*-cyclopropylmethyl (not shown). The comparable electronic character between cubylmethyl and the *N*-allyl and *N*-cyclopropylmethyl moieties make for an interesting comparison. At both the μ and κ opioid receptor, binding was improved when comparing the *N*-methylated compounds **34a** and **35a** with the cubane substituted compounds **34c** (K_i = 17.3 nM and 107 nM at μ and κ opioid receptor, respectively) and **35c** (K_i = 13.6 nM and 19.5 nM at μ and κ opioid receptor, respectively). However, the most potent binding was still observed with derivatives **34b** (K_i = 4.5 nM and 131 nM at μ and κ opioid receptor, respectively) and **34b** (K_i = 1.1 nM and 12 nM at μ and κ opioid receptor, respectively). This improvement was rationalized because while the cubane maintained the favorable electronics of **34b** and **35b**, the larger size of cubylmethyl compared to allyl and cyclopropylmethyl groups introduced unfavorable steric interactions.



14

34a, R = H
34b, R = vinyl
34c, R = cubane

35a, R = H
35b, R = vinyl
35c, R = cubane

Figure 3. Early mono-substituted cubane containing molecules for biological applications.

Structure-activity relationships (SAR) that incorporate the cubane moiety have normally involved it as an isostere for a phenyl group or as a substitute for cyclic or polycyclic functionality. Validation of Eaton's hypothesis stating cubane is a benzene isostere has only recently been reported.[40] In doing so, the authors investigated known pharmaceuticals and agrochemicals that contain phenyl rings and generated their cubane analogues. Two of the

mono-substituted cubane derivatives are shown in Figure 4. Compound **36a** (SAHA) is a histone deacetylase inhibitor approved for treatment of cutaneous T-cell lymphoma.[41, 42] The cubane analogue **36b**, in a side-by-side assessment with **36a**, obtained comparative IC_{50} values against tumor cells and were significantly less toxic against NFF primary cells. Further comparisons were conducted *in vivo* with both compounds demonstrating significant reduction in tumor growth compared to vehicle. Furthermore, both compounds performed almost identically in these studies.

Benzyl benzoate (**37a**) can be used to kill mites that are responsible for causing the scabies skin disease.[43] Three cubane analogues **37b-d** were synthesized substituting either one or both phenyl groups. While **37a** exerts complete acaricide after 5 minutes, the most potent cubane derivative **37d** took 24 hours to elicit 55% mortality. These results show that a phenyl to cubane swap of a drug lead will not always retain or enhance biological function.

Kassiou and co-workers examined substitution of D_3-trishomocubane for the development of σ receptor ligands.[44] As part of that study they synthesized analogues **38** that examined the difference in phenyl (**38a**), cyclohexyl (**38b**), cubane (**38c**) and a number of other substituted phenyl derivatives (not shown). The phenyl derivative **38a** showed a K_i of 78 and 19 nM at the σ_1 and σ_2 receptors, respectively. Cyclohexyl substitution brought binding down to 4.0 and 1.9 nM while the cubyl derivative showed a K_i of 3.0 nM at the σ_1 receptor and 2.0 nM at the σ_2 receptor. Improved affinity was argued through the increased 3D steric bulk associated with the cyclohexyl and cubyl moieties. Interestingly, some selectively was also lost with affinity for the DA transporter observed with **38c** (126 nM) whereas the phenyl derivative **38a** had a K_i of 3480 nM, and the cyclohexyl derivative lacked affinity.

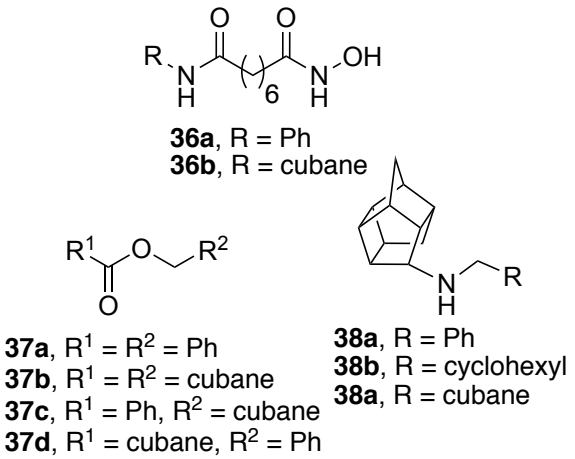


Figure 4. Examining cubane as a substitute for a phenyl group.

What seems to be more common in SAR studies is the comparison of cubane with other polycyclics, most commonly adamantane (Figure 5). Cubane differs from adamantane in terms of its reduced size and lipophilicity whilst also showing increased metabolic stability.[45] Polycyclic differences have been examined with GluN2B-containing NMDA receptors.[40, 46] While no direct comparison with the phenyl derivative was reported, the 3-fluorophenyl-containing compound **39a** showed one of the best affinities , a K_i of 2.86 nM. Converting to the adamantyl compound **39b** saw a significant reduction in affinity (K_i = 4810 nM) which was mostly regained through the incorporation of cubane (K_i = 150 nM). These results provide a key example of how the steric bulk of the adamantane can be detrimental and that by using cubane, this issue can be avoided. Given the different affinities obtained by changing phenyl substitution, it exemplifies the need to examine different cubane substitution.

Given the considerable lipophilicity associated with polycyclics, such entities have made a number of appearances in drugs designed for the central nervous system.[47] One such example is the cation-selective ion channel $P2X_7R$.[27, 48] It has been shown that the cyanoguanidine **40** gave the best results when flanked by a hydrogen-bond accepting aromatic and an adamantane linked by a methylene unit.[49] Additional studies were then reported examining the role of the

polycyclic.[48] An IC_{50} of 57 nM for **40a** was significantly reduced to 3467 nM for the cubane containing **40b**. In this instance, the importance of steric bulk was clearly exemplified.

Also with the $P2X_7R$, a range of polycycles linked *via* an amide bond to an aromatic (**41**) have also been reported.[27, 29] A change from the adamantane **41a** to cubane **41b** saw a reduction in IC_{50} from 10 nM to 436 nM, while the D_3-trishomocubane **41c** saw a smaller drop to 32 nM. Interestingly the *closo*-1,2-carborane derivative **41d** saw a small improvement in IC_{50} with 8 nM. With these examples, there is a clear correlation between the size of the polycyclic cage and inhibition of the $P2X_7R$ observed, with bigger polycyclics being more effective in the inhibition of this receptor. These reports also evaluated the lipophilicity of the various polycycles.[27, 29] As expected, cubane is less lipophilic than the adamantane and *closo*-carborane cage, though calculated values from various computational methods can be quite removed from those determined experimentally. For example, the HPLC-determined $logD_{7.4}$ for **41b** was 3.42 while the cLog*P* was calculated as 1.46,[27] though different experimental results gave a $logD_{7.4}$ of 2.90 and clog*P* and log*P* of 2.67 and 1.94, respectively.[29] The discrepancy between these results has yet to be rationalized.

The adenosine A_1 receptor agonists **42** were synthesized as a comparison between the cubane and trishomocubane (**45**) substituent.[50] In this example, the cubane derivative **42b** showed vastly superior results over the D_3-trishomocubane **42a**, in both binding (K_i = 363 nM *vs* 3838 nM) and activity (EC_{50} = 14 nM *vs* 3438 nM). In this example, the smaller cubane group was better accommodated in the N^6-binding pocket of the receptor.

Utilizing the scaffolds **43**[51] and **44**,[52] Emmitte and co-workers have explored substitution of many cyclic and polycyclic moieties for metabotropic glutamate receptor (mGluR) negative

allosteric modulation. When testing against mGluR 1, the adamantyl compound **43a** gave an IC_{50} of 85 nM[51] whereas the cubane compound **43b** had an IC_{50} greater than 10,000 nM. In this instance, the cyclohexyl **43c** and *tert*-butyl **43d** compounds also lost all activity. This was replicated with compound **44a** with the IC_{50} of 161 nM going above 10,000 nM for compounds **44b**–**d**.[52] Given the loss of activity for all aliphatic substitutions (others not shown), these results suggest more the success of the adamantyl group rather than any obvious trend of cubane substitution.

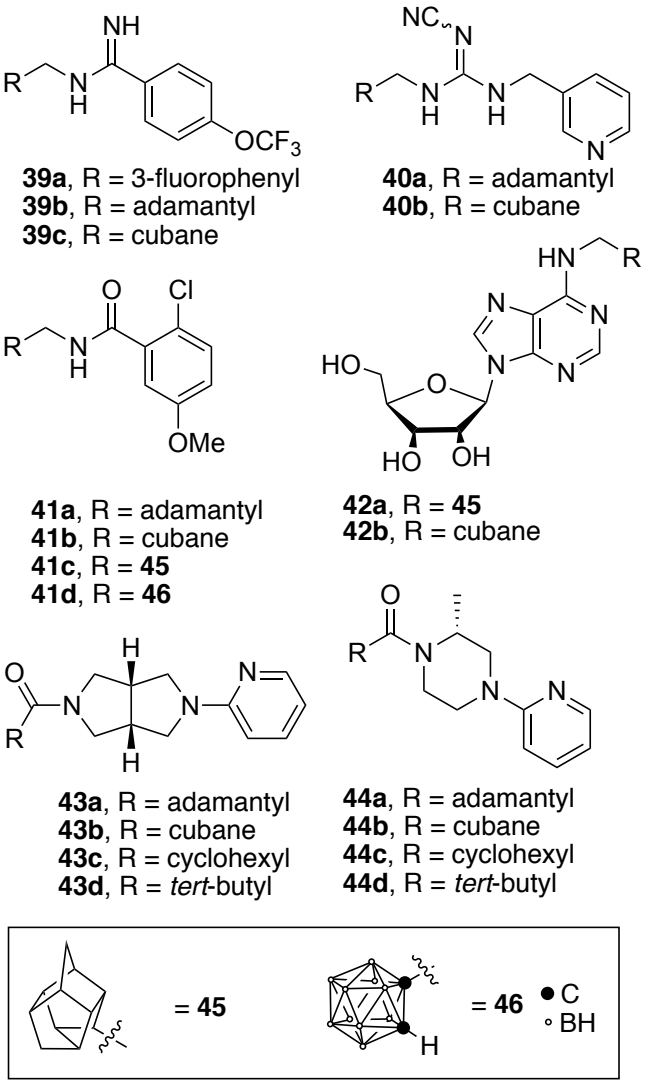


Figure 5. Examining cubane as a substitute for cyclics and polycyclics.

Mono-substituted cubanes have also made multiple appearances in the patent literature (Figure 6). However, detailed biological data have not been included, meaning that the role cubane plays in activity is difficult to quantify. Compound **47** was shown to be an inhibitor of receptor interacting protein kinase 1 at less than 1 μM but so were many other substitutions, both cyclic and acyclic, meaning that little benefit was attributed to the cubane.[53] Compound **48** (with various aryl substitution) also showed potent activity (0.01-10 nM) as casein kinase 1 inhibitors for subtypes ε and δ.[54] Again, the cubane was one of many cyclic and acyclic analoges, all of which showed good activity. **49** showed a K_i of between 10 nM and 100 nM against Muscarinic 4 receptor,[55] while **50** (and other cubane analogues) were patented as metalloprotease inhibitors.[56]

The number of publications and patent filings, most of which have occurred since the turn of the century, illustrate the increasing consideration that mono-substituted cubanes are getting for incorporation into pharmaceuticals. Multiply-substituted cubanes have also made an impact and will be examined in the following sections.

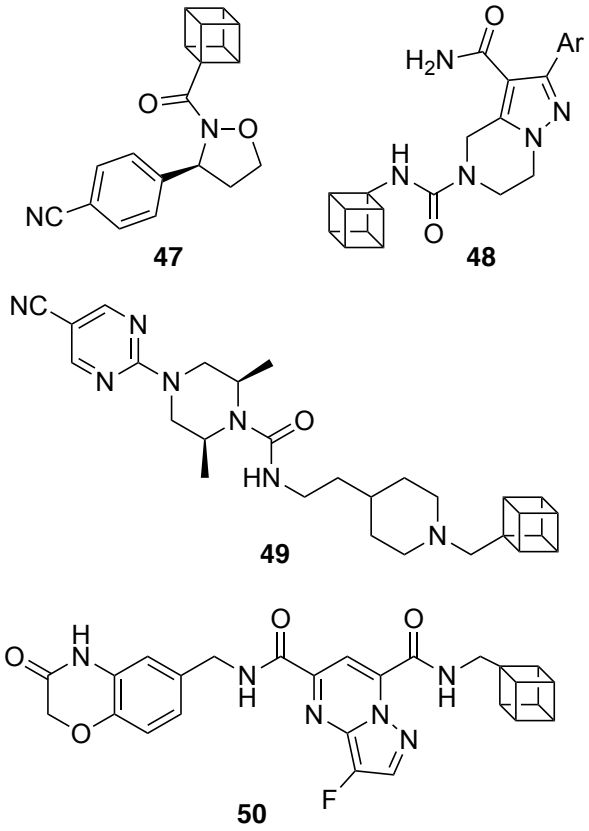
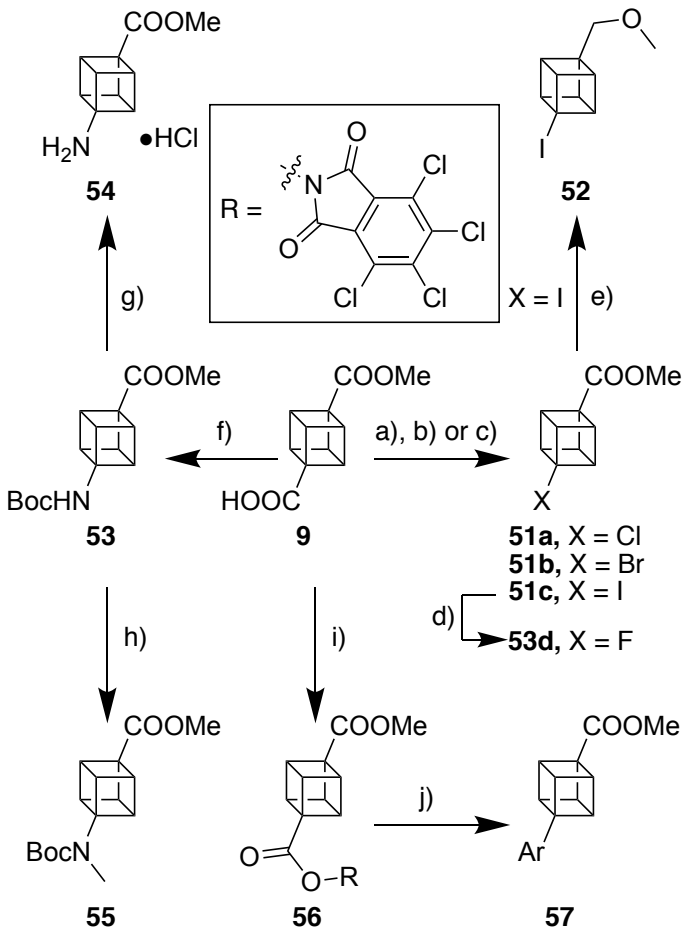


Figure 6. Cubane-containing molecules from the patent literature.

1,4-SUBSTITUTED CUBANES

Given the key cubane building block is 1,4-disubstituted ester **3**, disubstituted cubanes in medicinal chemistry tend to have a 1,4-substitution pattern. Exceptions to this will be discussed in the next section. Multiple cubane building blocks with 1,4-disubstitution have been prepared using **3**, or its monohydrolyzed derivative **9**, and performing chemistry similar to that outlined in Scheme 1, but without the preceding decarboxylation step. For example, monoacid **9** can be converted to the chlorinated derivative **51a**,[40] brominated derivative **51b**[57] and iodinated derivative **51c**[44] through radical chemistry (Scheme 3). The iodo group can be further converted to the fluoride **51d** using XeF_2.[58] Functional group manipulations of the ester from **51c** lead to compound **52**.[18, 59]

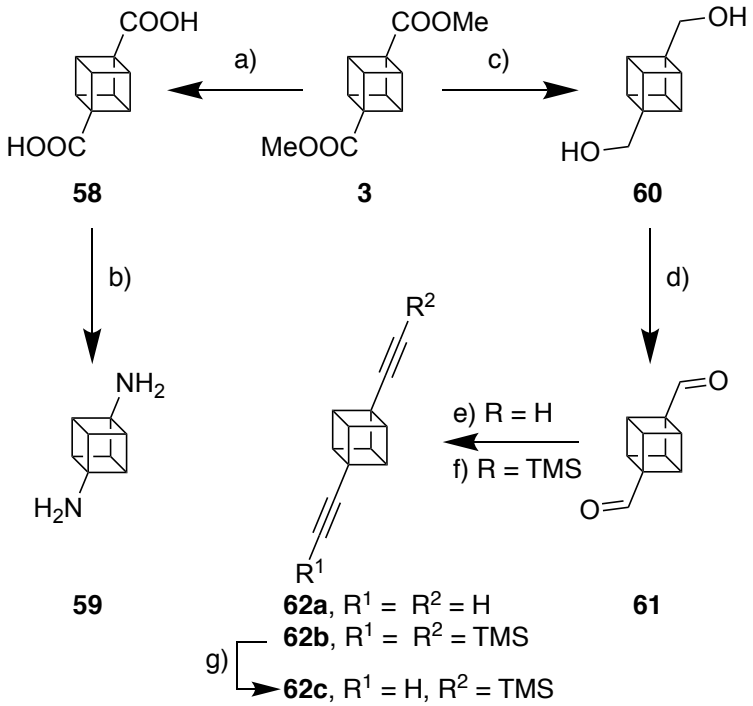
The Boc-protected amine **53** can be derived through a Curtius rearrangement and trapping with *tert*-butanol.[40] Deprotection to the hydrochloride salt **54**[40] or methylation to **55**[60] have both been reported. Given the halogen handles available in **51**, multiple attempts have been made at cross coupling,[31, 61-63] including through first generating metal and metalloid derivatives for transmetallation in the cross-coupling step.[59] However, these attempts have been unsuccessful largely due to the instability of cubane in the presence of palladium. The incorporation of phenyl groups has been successful by using $Pb(OAc)_4$ and the carboxylic acid **9**,[64] PhLi and substituting an iodo group[65] and using $ZnPh_2$ and a redox-active ester.[66] Lithiation of **52** and addition of electrophiles has also allowed for additional substitution, including with silicon, sulfur, phosphorus and metal electrophiles.[59] However, it is only with a recent report that a cross coupling-like reaction with cubanes has been reported.[67] Building upon the redox-active ester approach,[66] compound **56** was first synthesized, before a nickel catalyzed reaction with an arylzinc afforded aryl-substituted analogues **57**. In this approach, rather than an oxidative addition step, a single-electron-transfer was utilized to generate the active species for coupling. A general reaction scope was reported with electron-donating and -withdrawing groups tolerated. Naphthyl and porphyrin substituents were also coupled using this procedure. This work illustrates the growing interest in cubane, and the novel approaches that must be utilized to obtain higher functionalization. As more work is reported, this is likely to have a flow-on effect to medicinal applications of cubane.



Scheme 3. Synthesis of 1,4-disubstitued building blocks. Reagents and conditions a) 1) $(COCl)_2$, CH_2Cl_2, RT, 1 h; 2) mercaptopyridine *N*-oxide sodium salt, DMAP, CCl_4, *h*ν (500 W tungsten), heat, 2 h, 52% over 2 steps; b) HgO, Br_2, CH_2Br_2, 80 °C, 2 h, 85%; c) $PhI(OAc)_2$, I_2, toluene, 80 °C, 8 h, 70%; d) XeF_2, CH_2Cl_2, reflux, 6.5 h, 58%; e) NaOH, MeOH, RT, 18 h, >92%; 2) BH_3•SMe_2, THF, 0 °C, 4.5 h, 95%; 3) NaH, MeI, RT, no time reported, 97%; f) DPPA, Et_3N, ^{t}BuOH, reflux, 2 days, 66%; g) AcCl, MeOH, –15 °C to RT, 1.25 h, 82%; h) NaHMDS, MeI, THF –78 °C to 25 °C, 18 h, 73%; i) tetrachlorohydroxyisoindoline1,3-dione, DIC, DMAP, CH_2Cl_2, RT, 16 h, 73%; j) ArZnCl•LiCl, $NiCl_2$-glyme, dtbbpy, DMF, RT, 2 h, 10-58%.

Functionalization to produce symmetrical 1,4-disubstitution has also been reported, generally as a method of using cubane as a linking moiety (Scheme 4). Saponification of **3** with a larger

equivalent of base affords the diacid **58**[28] which can be converted to the diamine **59** *via* the Boc-protected amine and dihydrochloride salt.[68] Reduction of **3** to give the diol **60**[30] allows for oxidation to the di-aldehyde **61**.[31] The aldehydes can be converted to the terminal dialkyne **62a** or TMS-protected dialkyne **62b**.[31] Selective removal of a single TMS group affords the unsymmetrical dialkyne **62c**. Sonogashira coupling with the terminal alkynes was successfully employed, confirming that palladium insertion directly to the cubane is the problem associated with cubane in cross coupling reactions.[31]



Scheme 4. Synthesis of symmetrical 1,4-disubstitued building blocks. Regents and conditions a) NaOH, MeOH, RT, 18 h, 96%; b) 1) DPPA, Et_3N, ^{t}BuOH, reflux, 12 h, 75%; 2) HCl, MeOH, –61 °C to RT, no time given, 81%; 3) NaOH, H_2O, RT, 10 min 58%; c) $LiAlH_4$, THF, RT to reflux to RT, 10 h, 91%; d) DMSO, $(COCl)_2$, CH_2Cl_2/THF, –78 °C to RT, 30 min, 65%; e) 1) PPh_3, CBr_4, CH_2Cl_2, RT, 10 min, 84%; 2) *n*-BuLi, THF, –78 °C, 1 h, 95%; f) e) 1) PPh_3, CBr_4, CH_2Cl_2, RT, 10 min, 84%; 2) *n*-BuLi, THF, –78 °C, 1 h, then TMSCl, –10 °C, 10 min, 92%; g) MeLi•LiBr, THF, 5 °C, 25 min, 33%.

The use of cubane as part of a SAR study was first reported by Hasegawa and co-workers for the development of anti-ulcer agents (Figure 7).[69] The majority of these efforts were directed to altering the amide of the cubane **63** to examine the effect. A single homocubane analog was also reported, although comparison to other functionality was not made. The disubstituted cubane with the amide was shown to be necessary to retain potency. Though interestingly, 1,2- and 1,3-substitution lost activity. When the piperidinyl amide was used, good oral anti-ulcer activity was observed, although in the gastric fistula rat model, no activity was observed.[69] Radiolabeled compound **64** (^{123}I) was developed as a probe for *in vivo* Staudinger ligation to azide tagged antibodies.[70] In comparison to desferrioxamine type probes with ^{89}Zr or $^{67/68}$Ga radiolabeling (not shown), compound **64** showed poor pharmacokinetics and thus was not explored further in this study. As a way to improve upon compound **12a** for inhibition of monoamine oxidase B, the **12b-c** series of compounds were synthesized.[71] These results showed that disubstitution was advantageous, most likely due to stabilization of the C4 radical intermediate.

Polymers for the release of morphine have been developed from compound **65** through amide linkages (Figure 7).[72] Compound **66** has also been developed as a polymerization precursor. Subjecting **66** to free radical copolymerization with various drugs leads to novel and targeted delivery systems.[73-81]. Nitroxyalkyl groups substituted onto cubane with various linkers have been developed and explored for their anti-ischemic activity (compounds **67**).[82] Compound **67a** showed an improved ratio between the necrotic and ischemic zones (36.1%) over the lead compound nicorandil (**68**, 42.0%), where a mononitroxyalkyl is substituted on a pyridine. Importantly, the cubane derivative also showed reduced toxicity of the lead (commercially sold) pharmaceutical (LD_{50} = 800 mg kg^{-1} for **67a** and 475 mg kg^{-1} for **68**).

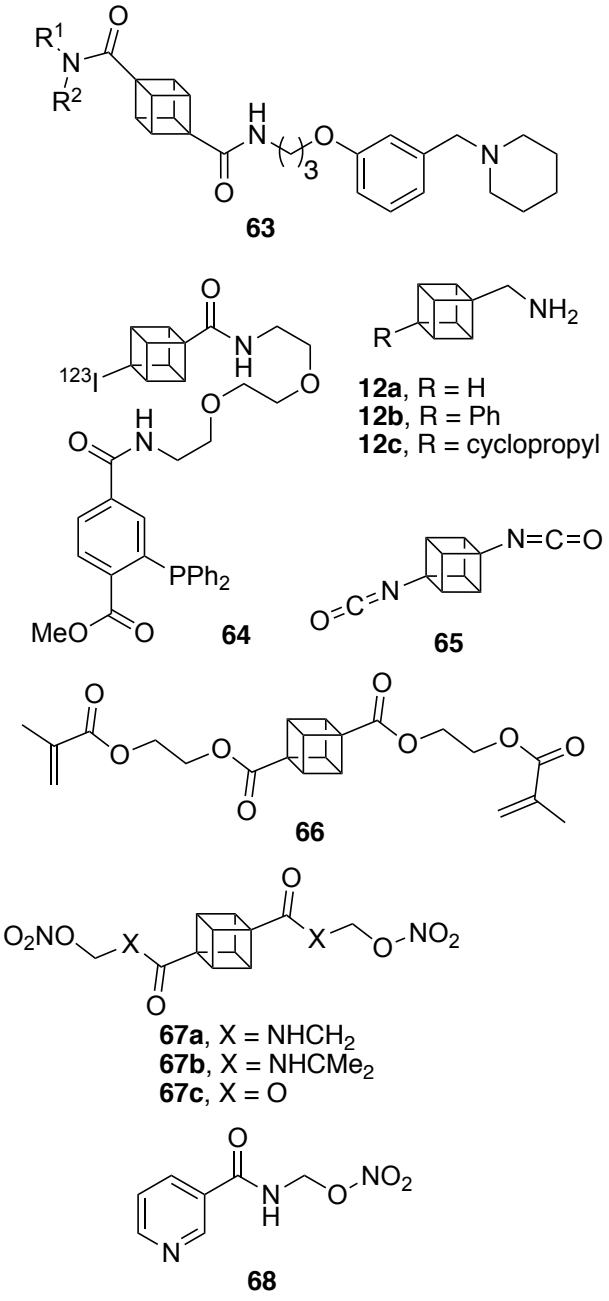


Figure 7. Novel 1,4-disubsituted cubane-containing molecules.

The comparison between 1,4-substituted cubanes and 1,4-substituted phenyl groups has also been reported (Figure 8).[40] Compound **69a** (leteprinim) has been shown to increase neurite outgrowth with potential neuroprotective properties.[83, 84] A head-to-head comparison between **69a** and the cubane analog **69b** showed that both compounds enhanced the ability for nerve growth factor to enhance neurite growth. In this instance, the cubane analog **69b** actually

showed a greater effect than the phenyl lead **69a** (approximately 48% *vs* 38% differentiated neurons, respectively). The common pain medication benzocaine (**70a**) was also compared to the cubane analog **70b** in a noxious heat stimulus test with results showing the same local anesthetic efficacy between the compounds.[40] The role of cubane in pesticides was also investigated through comparison of diflubenxuron (**71a**) and the cubane analog **71b**. Investigating these compounds' ability to illicit mortality of larval *Tribolium castaneum* showed an approximate 2-fold improvement by the cubane derivative **71b** over **71a**. These results indicate that while cubane offers a viable alternative to the phenyl group, no clear prediction of the expected pharmacology can be made.

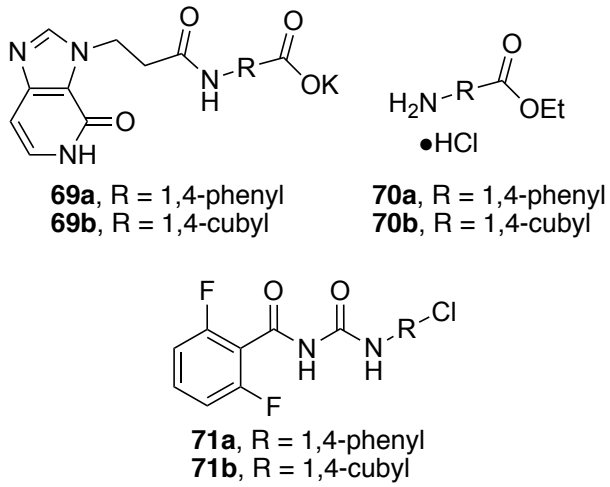


Figure 8. Examining 1,4-disubsituted cubanes as phenyl isosteres.

1,4-Disubstituted cubanes have made a bigger impact in SAR studies as a linker comparison between cyclics such as cyclobutane or cyclohexane, and polycyclics such as bicyclo[1.1.1]pentane (**72**), bicyclo[2.2.2]octane (**73**), adamantane (**74**) and bicyclo[2.2.1]heptane (**75**). Compounds **76** were analyzed for non-specific binding and results showed that **72** linked compound **76c** had a much lower propensity for non-specific binding compared to **76a**, **76b** and **76d**.[85]

Compounds **77** with various polycyclic rings and iodo substitution were synthesized as potential ligands for single photon emission computerized tomography (SPECT) imaging of the 5-HT_{1A} receptor.[86] Compounds **77a**, **77c**, **77d**, all gave IC_{50} values less than 2.6 nM and K_i of around 1 nM. The adamantyl **77b** showed slightly reduced inhibition with an IC_{50} of 5.04 nM and K_i of 2.15 nM. The cubane compound **77a** also showed selectivity over other receptor subtypes. This investigation was instigated due to the lead compound (not shown) which contained a cyclohexyl group rather than a polycycle (and no iodination), undergoing metabolism through amide hydrolysis. This reaction was not observed with the cubane polycycle, nor was C–I bond cleavage, which allowed for ^{123}I labelling for SPECT imaging by means of a copper-mediated transhalogenation of the 'cold' bromo compound. Unfortunately, despite the positive properties of this molecule, it ultimately failed as a SPECT imaging agent due to its poor brain uptake, and poor *in vivo* specificity.

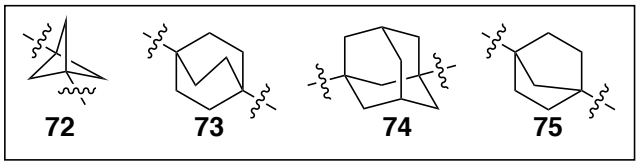
Given the initial success of the **77** compounds, further modifications were made in an attempt to image 5-HT_{1A} using PET. For this goal, compounds **78** were synthesized, including the ^{18}F tracers for imaging.[87] In rats, all three compounds showed a higher uptake in the hippocampus and cortex, regions where the 5-HT_{1A} receptor would be expected. Compound **78a** showed slightly higher uptake in the liver than **78b**, which was explained by the enhanced hepatic activity for the cubyl moiety.[88, 89] The brain uptake of **78c** was higher than **78a** and **78b** which were almost identical, and selectivity for 5-HT_{1A} was shown by means of competitive binging studies. Unfortunately, during these studies the rat bone uptake as observed resulting from defluorination, again with **78a** and **78b** showing faster bone uptake than **78c**. While ultimately unsuccessful for imaging applications, this work does nicely illustrate the role cubane can have as a linking functionality in medicinal chemistry.

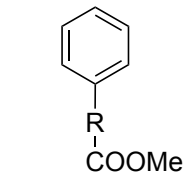
The ABL1 kinase inhibitor imatinib (**79a**) was subjected to an SAR study incorporating cyclic linking groups.[90] Compounds **79b** and **79c** showed higher thermodynamic solubility than other analogs, including the parent **79a**, but lost inhibitory activity against the ALB1 kinase with IC_{50} values of >1 μM and >30 μM respectively. When examined in cell cytotoxicity assays, cubane-containing compound **79b** still performed the best of the new analogs against KU-812 and MEG-01 cells, with an estimated EC_{50} value of 1.4 μM and 1.8 μM, respectively. Though lead compound **79a** showed sub-micromolar potency this could be attributed to its potency against ABL1. Given the lack of ALB1 activity for **79b**, it was suggested that off-target effects were causing the cytotoxicity, though which targets these are is not currently known.

Various polycyclic linkers were also explored as inhibitors of Bruton's Tyrosine Kinase, namely compounds **80**.[91] In all cases IC_{50} values between 0.1 and 0.4 nM were found, indicating great tolerance for this alteration. Potencies were replicated in human peripheral blood mononuclear cell and human whole blood activity studies. Compounds **80a** and **80b** showed a greater reduction in potency in those studies compared to the bridged cyclohexyls **80c** and **80d**. It should be noted that the cubane compound **80a** differed slightly in that it had a remote aromatic F-substitution (X = F) while the others lacked this substitution (X = H). Despite these encouraging results, compounds **80a**–**d** were hampered by increased adenosine uptake inhibition which has potential negative effects on the cardiovascular system.

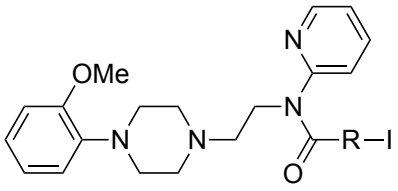
A comparison between phenyl, **72** and cubane linkers was made with compounds **81** as they antagonize the mGluR1. These results showed that the phenyl ring in **81a** is not necessary for activity at the receptor provided that a suitable spacer, such as that observed with **81c** is able to keep the amino acidic moiety and distal carboxylate in a co-linear arrangement.[92] When investigating the cubane-linked **81b**, despite maintaining the co-linear arrangement, it showed

a nine-fold decrease in potency, which was ascribed to the increase in volume of the spacer.[93] Despite the low potency at mGluR1, it showed greater selectivity than either **81a** or **81c**, as it was devoid of any effect at mGluR5, suggesting a more sterically demanding receptor. With these results, it was derivatives of **81c** that were investigated further, rather than the cubane-containing molecule.[94]

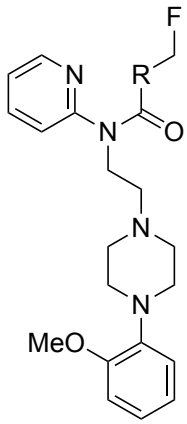




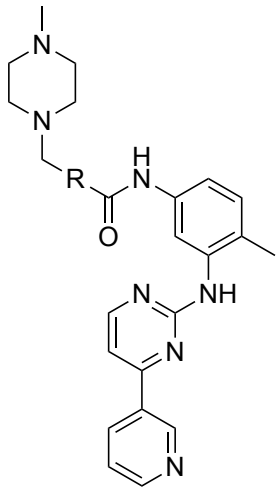
76a, R = 1,4-phenyl
76b, R = 1,4-cubyl
76c, R = **72**
76d, R = **73**



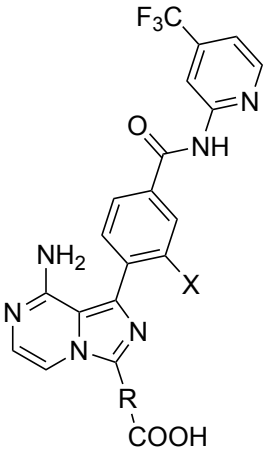
77a, R = 1,4-cubyl
77b, R = **74**
77c, R = **72**
77d, R = **73**



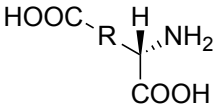
78a, R = 1,4-cubyl
78b, R = **75**
78c, R = **72**



79a, R = Ph
79b, R = 1,4-cubyl
79c, R = **72**



80a, R = 1,4-cubyl, X = F
80b, R = **72**, X = H
80c, R = **73**, X = H
80d, R = **75**, X = H



81a. R = 1,4-phenyl
81b, R = 1,4-cubyl
81c, R = **72**

Figure 9. Comparing 1,4-disubsituted cubanes with cyclics and polycyclics.

Cubane has also been featured as a linker in peptides, specifically as analogs to the cytotoxic natural products tubulysins (Figure 10).[60, 95] These result immediately showed that substitution to give analogs **82** was tolerated, and this included other alkyl and aryl linkages (not shown). While analogs **82** accepted some modifications, particularly aromatic linkers, the inclusion of 3-D linkers such as cubane or **72** was not tolerated. However, **81** analogs showed that 3-D linkers could be incorporated at the carboxyl end. Both **81** compounds showed toxicity against cancer cell lines MESSA and HEK 293T. The cubyl compound **81a** showed reduced activity for both cell lines (IC_{50} = 840 nM and 260 nM at MES SA and HEK 293 T, respectively) compared to the **72** linked compound **81b** (IC_{50} = 350 nM and 110 nM at MES SA and HEK 293 T, respectively).

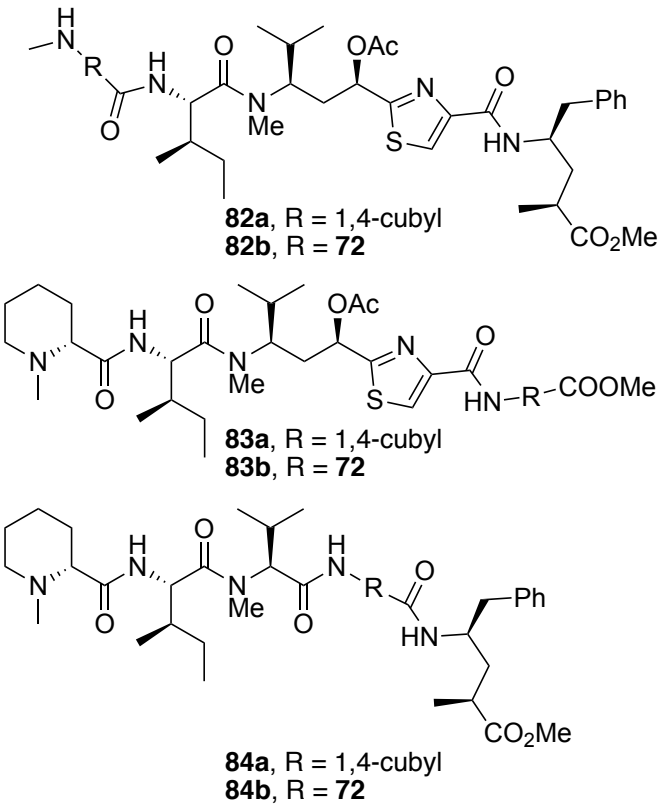


Figure 10. Peptides containing 1,4-disubsituted cubanes.

1,4-Disubstituted cubanes have also featured prominently in the patent literature (Figure 11). Compounds **85** were developed as prostaglandin D synthase inhibitors.[96] In addition to cubane,

many cycloalkyl, aryl, heterocyclic and polycyclic linkers were used. Though direct comparison with IC_{50} values is not possible, compounds **85** were reported with values between 10 and 79 nM. Compounds **86** were included in a screen as Type II sodium dependent phosphate transporter 2A inhibitors with IC_{50} values of 7 and 9 nM for **86a** and **86b**, respectively.[96] While obviously showing reasonable results, a direct analog with another linker was not included to allow for an indication of the exact role of cubane.

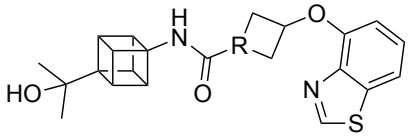
Compound **87** was tested against Janus kinases 1-3 and Tyk2 and displayed EC_{50} values of less than 100 nM, but so did a significant number of other non-cubyl analogs.[97] Compound **88** was developed to target the human histamine H1 and H4 receptor with a K_i value, along with many other analogs, of less than 100 nM.[98] This was very similar for compound **89** and many non-cubyl analogues showing an IC_{50} of less than 100 nM for phosphoinositide 3-kinases-gamma.[99] Compounds **90a**[100] and **90b** [101] were developed as antagonists for mGluR, though specific biological results were not provided, the only analogs reported included the cubane moiety. Compound **91** was developed as a linker between two cytotoxic agents to generate bifunctional molecules.[102] While the linker was reported, along with other polycyclic linkers, examples of where they were conjugated to the cytotoxic agents was not reported, with only a propyl chain example being provided. Compound **90**[103] was one of many analogs patented for targeting the HDM2 oncogene that regulates p53, though no biological data was included for this specific compound. Compounds **93** showed 100% inhibition of human 11-β-hydroxysteroid dehydrogenase type 1 enzyme at 100 nM but no unique role of the cubane was identified as other cyclics and polycyclics also elicited the same result.[104]

Compounds **94** were synthesized and tested against the human and mouse retinoid-related orphan receptor γ.[105] Similar results were obtained for both species, but for the human receptor

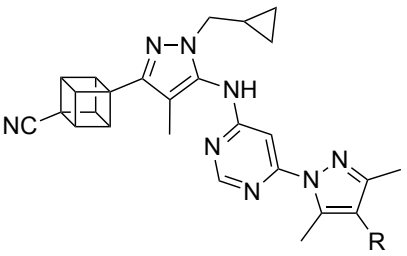
94a showed and EC_{50} of 32 nM, while **94b** and **94c** gave values of 38 nM and 21 nM, respectively. Compound **95** showed an IC_{50} between 0.1 and 1 μM for the Janus kinase 3, but again, so did many other non-cubane analogs.[106] More information could be obtained from the IC_{50} values for retinoid-related orphan receptor γ for compounds **96**. Of related compounds **96a** showed the best value with an IC_{50} 106 nM, while the analogs **96b** and **96c** had values of 1344 nM and 392 nM, respectively.[107] This is one of the clearest examples from the patent literature describing the benefit of a 1,4-disubstituted cubane analog. Compound **97** showed good activity against SET and MYND Domain Containing protein 3 (IC_{50} = 142 nM), which was also carried through to cellular analysis (IC_{50} = 1308 nM). Though no clear advantage was suggested for the cubane over other linkers.[108]

Compound **98** was reported as an adenosine receptor antagonist but no specific biological results were reported,[109] while compound **99** gave an EC_{50} value of between 10 and 50 nM against ATF4 luciferase.[110]

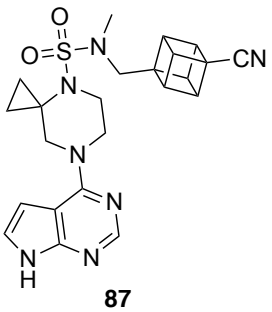
Compounds **100** were tested against matrix metalloproteinase 13 with results showing tolerance for both hydroxylmethyl and carboxylic acid substitution.[111] However, a clear advantage for the cubane linkage was shown with both substituents showing improved binding compared to the **73** linkage (**100a** K_i = 0.57 nM, **100b** K_i = 0.13 nM, **100c** K_i = 10.6 nM, **100d** K_i = 2.63 nM). Derivatives of compounds **49**[54] and **50**[56] with a simple second 1,4-disubstitution of the cubane moiety were also reported, but no quantification of biological data was provided.



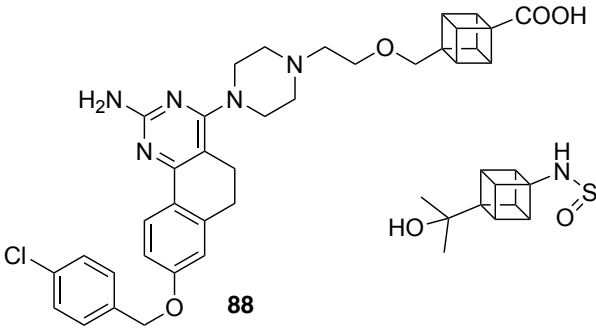
85a, R = N
85b, R = *trans*-CH



86a, R = OMe
86b, R = Cl



87



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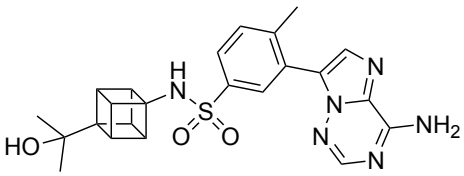

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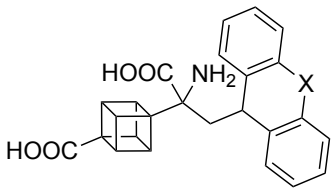
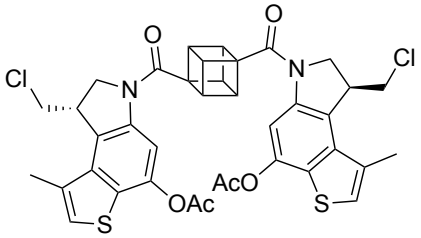


90a, X = S
90b, X = O



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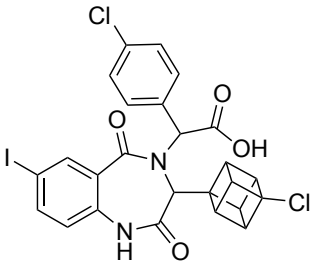

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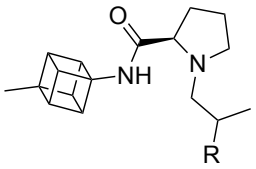
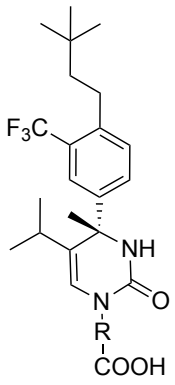
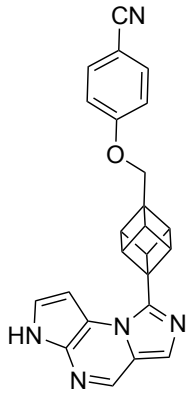


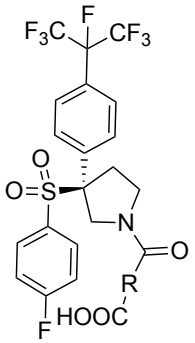
93a, R = H
93b, R = Me



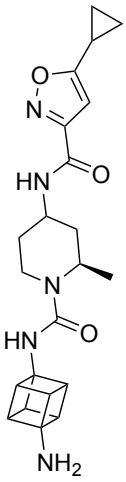


94a, R = 1,4-cubyl
94b, R = **75**
94c, R = **72**

95



96a, R = 1,4-cubyl
96b, R = **75**
96c, R = **73**



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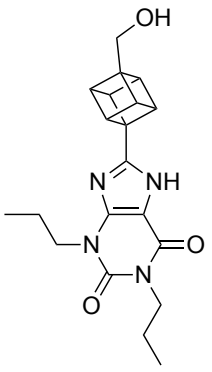

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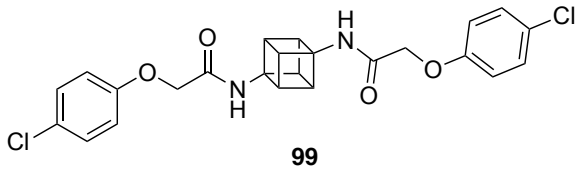

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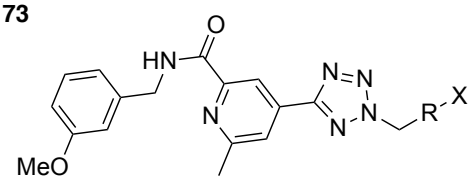


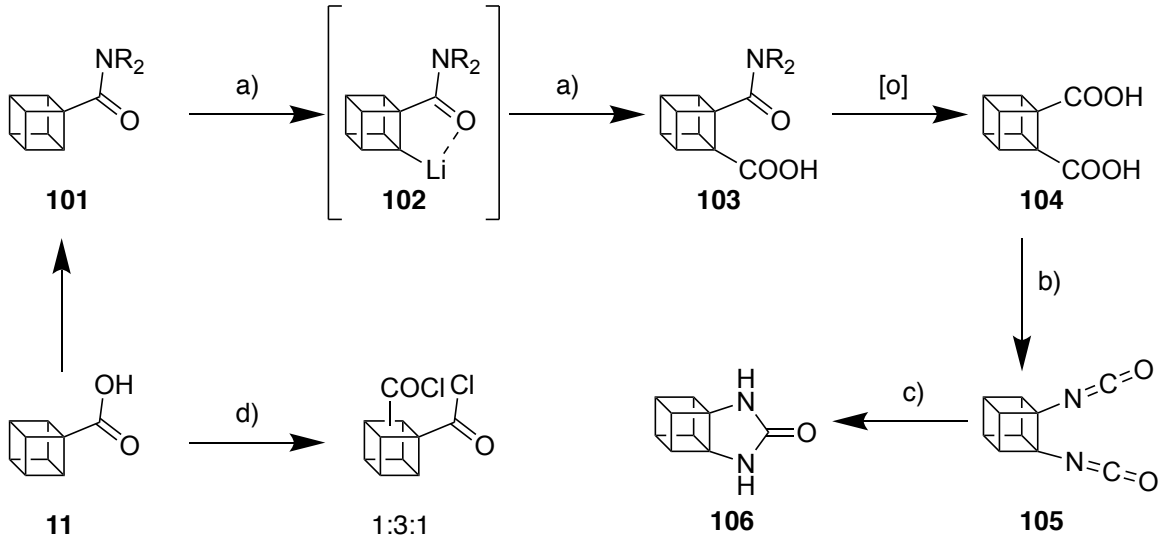
100a, R = 1,4-cubyl, X = COOH
100b, R = 1,4-cubyl, X = CH_2OH
100c, R = **73**, X = COOH
100d, R = **73**, X = CH_2OH

Figure 10. 1,4-Disubsituted cubanes reported in the patent literature for medicinal applications.

1,2- AND 1,3-DISUBSTITUTED CUBANES

Access to 1,2-disubstituted cubanes occurs through neighboring group participation, namely using the *ortho*-lithiation approach (Scheme 5). Taking an amide **101**, simply derived from acid **11** and a variety of amines, lithiation with LiTMP affords lithiated intermediate **102** that can be treated with an electrophile, e.g. CO_2, to afford the 2-substituted acid **103**.[112] Originally the diisopropyl amide (R = ^{i}Pr) was used, which requires aggressive conditions to further manipulate (e.g. $LiAlH_4$ followed by DMDO for conversion to a carboxylic acid),[2] but other amide examples also exist.[69] Transmetallation of the lithiated species[10-12] can also be used to broaden the scope of the transformation, as is the case here with magnesium. Unfortunately, no procedures for the synthesis of 1,2-dicarboxylic acid **104** have been reported, but oxidation of the amide to acid has been shown with the iodo, rather than COOH, analog,[113] and other suggested methods have also been reported.[114] Furthermore, the diacid **104** was used in a subsequent transformation, to afford **105** and then **106**,[115] so it must be accessible. Direct irradiation of **11** in oxalyl chloride affords the diacid chloride but in 1:3:1 ratio between 1,2-, 1,3- and 1,4-disubstition, making it a less than practical approach.[116]

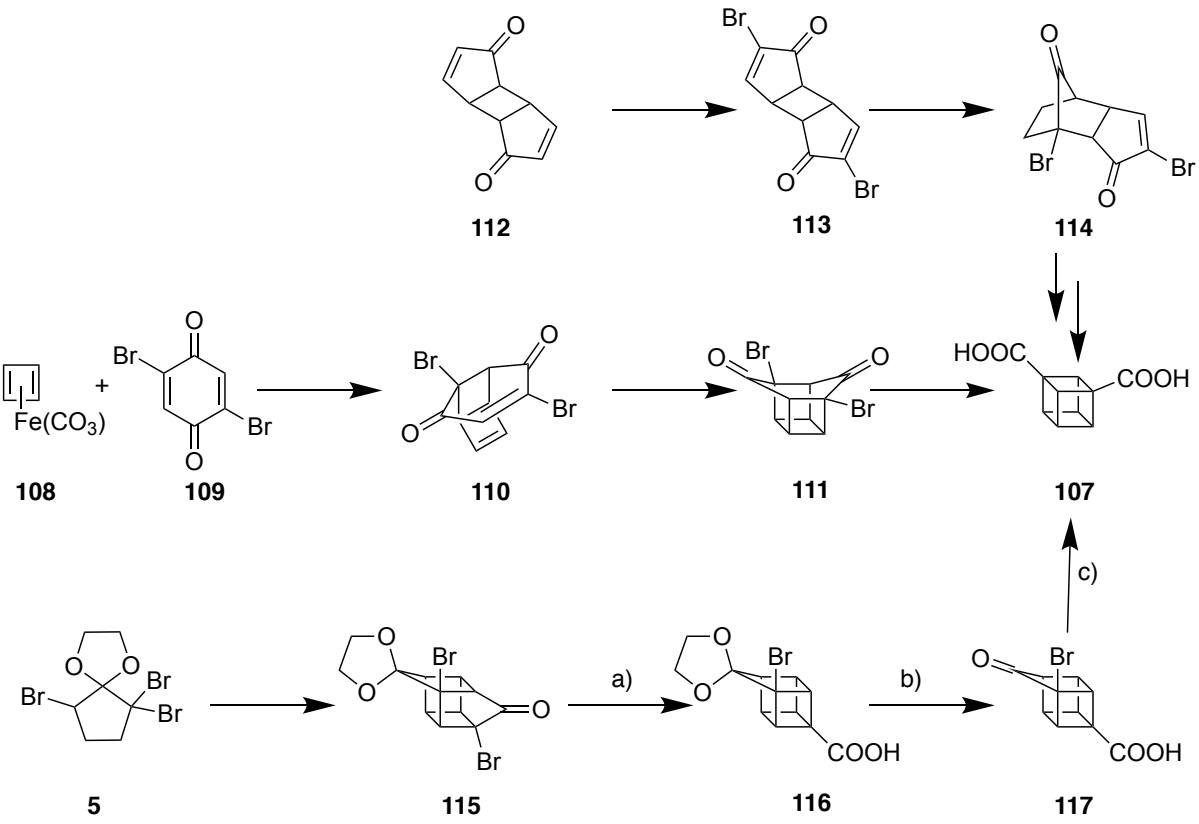
The application of 1,2 substituted cubanes to medicinal is limited. The 1,2-substituted analog of **63** required a dosage 3-times that of **63** to elicit the same response,[69] and to date it remains the only example.



Scheme 5. Synthesis of 1,2-disubstituted cubane. Reagents and conditions a) LiTMP, $MgBr_2 \bullet OEt_2$, THF, –78 °C to 0 °C, 5 h, then CO_2, –40 °C, 1 h, then HCl in H_2O, 12% (R = piperidinyl amide); b) $(COCl)_2$, reflux, 4 h, then $TMSN_3$, benzene, RT, 2 h, then benzene, reflux, no time given, 92%; c) H_2O, acetone, RT, 12 h, 51%; d) $(COCl)_2$, $h\nu$ (sun lamp, pyrex), 10 to 20 °C, 5 h, no yield given.

The synthesis of 1,3-disubstituted cubane **107** was first reported in 1966 from **108** and **109** to give **110** (Scheme 6).[117] Photocyclization of **110** in benzene, to give **111** then allows for a double ring-contraction to give **107**. Though reported, experimental details for these transformations are not provided. A second method was provided in 1970 from **112**, through a dibromination to give **113** followed by photochemical rearrangement to **114**.[118] The authors then converted **114** into **107** following their procedures for the 1,4-disubstitution,[22] though again no details were provided. Utilizing **115**, which is obtained as a minor byproduct (4.5%) from the debromination and dimerization of **5**,[112] conditions for the formation of **107** were provided. A ring contraction to **116**, followed by deprotection to **117**, then allows for a second ring contraction to give **107**. Given the challenges with accessing **107**, it becomes clear why

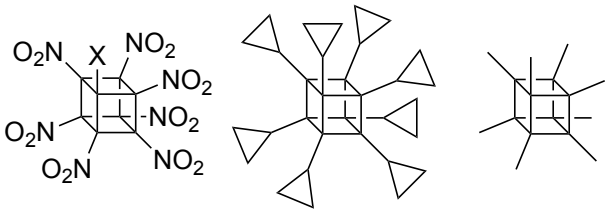
1,3-disubstition is not commonly observed with cubane derivatives. In the case of 1,3-substituted analog of **63**, it required a dosage 3-times that of **63** to elicit the same response.[69]



Scheme 6. Synthesis of 1,3-disubstituted cubane. Reagents and conditions a) KOH (10%), H_2O, reflux, 2.5 h, 92%; b) H_2SO_4 (75% in H_2O), RT, 24 h, 92%; c) KOH (25%), H_2O, reflux, 3.5 h, 25% (following conversion to the dimethyl ester with diazomethane).

POLYSUBSTITUTED CUBANES

Cubane substitution has been reported all the way to octasubstitution (Figure 11). However, in these instances, substitution tends to involve the same functional group, as seen in the examples of **118b**[119], **119**[120] and **120**.[121] In the case of **119** and **120**, new cubane syntheses were devised. For the nitro derivative **118b**, it was synthesized from the heptanitrocubane (**118a**), itself derived from the tetranitrocubane.[119, 122]



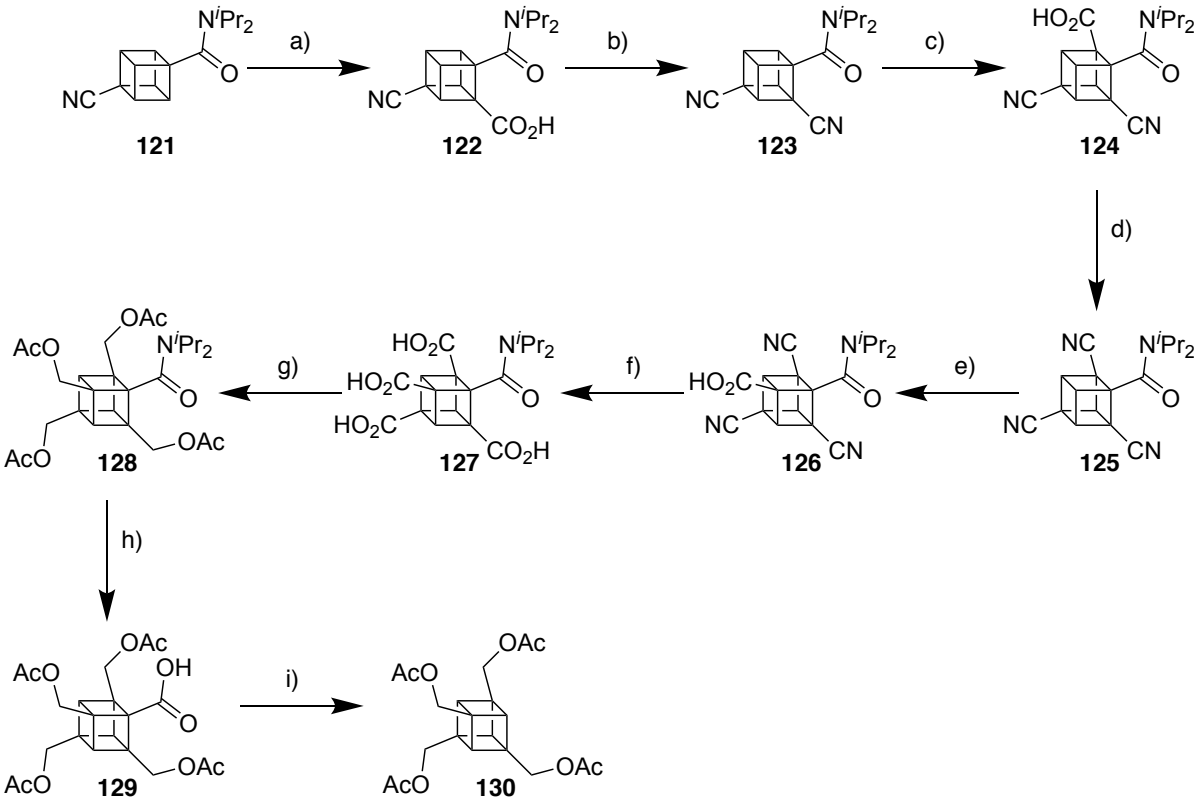
118a, X = H
119b, X = NO_2

120

121

Figure 11. Highly substituted cubanes

Functionality can be introduced through photochemical means, but regulation, both in terms of regiochemistry and level of substitution, can be difficult to control.[116] Also, this method limits the introduction of different functionalities.[123] To introduce variable substitution patterns with some degree of control is best achieved through a halogen handle[65, 124] or a neighboring group directed lithiation approach (Scheme 7),[10, 125-128] Though admittedly this approach is quite step intensive. Beginning with 1,4-disubsituted cubane **121**, selective carboxylation leads to **122** which is then converted to the nitrile **123** to allow for a subsequent carboxylation to **124**. Another nitrile formation gives **125**, which allows for another carboxylation to give **126**. Hydrolysis of the nitriles is selective leaving the amide present in **127**. Carboxylic acid reduction and acetyl protection gives **128** which allows for an oxidative conversion of the amide to acid in **129**. This pentasubstituted cubane **129** can be decarboxylated to the tetrasubstituted cubane **130**.[125]



Scheme 7. Synthesis of 1,3-disubstituted cubane. Reagents and conditions a) $MgTMP_2$, THF, –78 °C to RT, 1h, then –78 °C, CO_2(g), 15 min, 85%; b) $(COCl)_2$, CH_2Cl_2, RT, 45 min, then NH_3(l), THF, –78 °C to RT, 30 min, 99%; c) BrMgTMP, THF, –78 °C to RT, 1h, then –78 °C, CO_2(g), 15 min, 78%; d) $SOCl_2$, CH_2Cl_2, RT, 2 h, then NH_3(l), THF, –78 °C to RT, 30 min, 92%; e) BrMgTMP, THF, –78 °C to –20 °C, 1h, then –78 °C, CO_2(g), 5 min, 77%; f) KOH, EtOH, reflux, 3.5 h, quantitative; g) 1) $LiAlH_4$, THF, reflux, 20 h, 89%; 2) Ac_2O, RT, overnight, 89% over 2 steps; h) dimethyldioxirane (DMDO), acetone, RT, overnight, i) $SOCl_2$, RT, 1 h then mercaptopyridine *N*-oxide sodium salt, DMAP, benzene, RT, 15 min, then, ^{t}BuSH, *h*ν (sunlamp), benzene, reflux, 1.5 h; 72% from **128**.

Radical halogenation is also useful for selective polysubstitution of cubane with different functional groups, but they are then difficult to incorporate into useful molecules.[129, 130]

Regardless of their challenging synthesis, polysubstituted cubanes have still been utilized by medicinal chemists (Figure 12). Cubane **131** showed moderate anti-HIV activity and **132** displayed moderate anti-cancer activity, although no identification of the R groups nor quantification of data or structural comparisons were provided.[131]

The compounds **133** have been patented for their anti-viral and anti-cancer properties though no specific biological data were presented.[132]

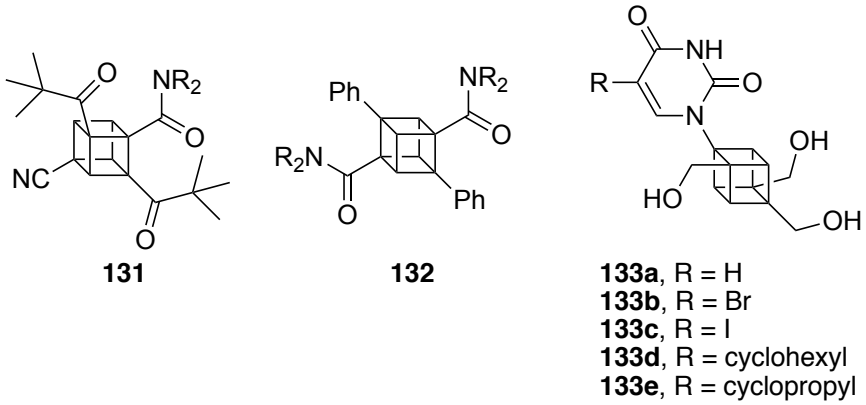


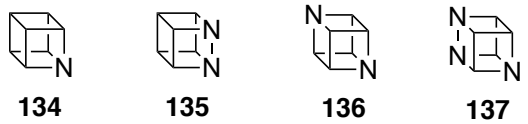
Figure 12. Polysubstituted cubanes in medicinal chemistry.

CONCLUSIONS AND OUTLOOK

From cubane's beginnings as a simple structural motif of somewhat limited interest, to its applicability to high-energy materials, it is clear that cubane is now having a significant impact in medicinal chemistry and the increasing use of the cubane scaffold in this field will undoubtedly open up new vistas in future drug discovery. Indeed, the number of publications and patents that feature cubane in a pharmaceutical context continues to increase each year. The increasing interest in this unique scaffold arises from its benzene isosteric nature, defined 3-D shape, and different properties to other polycyclic caged molecules. As we look to the

future there is no doubt that the number of SARs that feature cubane will continue to increase, allowing further insight into how it can be best utilized.

Current limitations of cubane center around its synthetic accessibility, beyond the readily available commercial dimethyl cubane-1,4-dicarboxylate. Multiple reports for functional group manipulations to generate many mono and 1,4-disubstituted cubanes correspond to the medicinal applications that include these substitution patterns. To fully utilize cubane, its 3D positions need to be fully accessible. Simple and reliable procedures to access 1,2- and 1,3-disubstitution patterns, as well as polysubstitution would greatly aid in the full exploration of its role as a bioisostere. In particular, the exploration of the "above" and "below" benzene plane in 3D arrangements. Given how the interest in high-energy materials resulted in multiple methods for nitrating cubane, the current attention of cubane in medicinal chemistry will likely lead to novel synthetic methodologies involving this moiety. Intriguingly, a common question raised is whether the isostructural aza-cubane **134** can exist (Figure 13). This molecule, and the other polynitrogen containing cubane derivatives (e.g. **135**–**137**, Figure 13), have to date only been the fodder of considerable theoretical thinking.[133-137] That said, should any of these aza-cubanes become synthetically viable, one could easily imagine access to a new class of nitrogen heterocyclic isosteres.



134 **135** **136** **137**

Figure 13. Aza-cubane and selected polynitrogen-containing derivatives.

AUTHOR INFORMATION

Corresponding Author

*E-mail: michael.kassiou@sydney.edu.au Phone: +612 9351 2745

ORCID

Michael Kassiou: 0000-0002-6655-0529

Notes

The authors declare no competing financial interest.

Biographies

Tristan A. Reekie obtained his B.Sc. (Hons.) from the Australian National University, Canberra in 2007, where he also completed his Ph.D. in 2013 in natural product synthesis under the supervision of Prof. Martin Banwell. He worked as a postdoctoral fellow at ETH, Zurich with Prof. François Diederich until 2015 and then took up a postdoctoral position with Prof. Michael Kassiou at the University of Sydney. His current research is in medicinal chemistry, particularly targeting disorders of the central nervous system.

Craig M. Williams received his BSc(Hons) and PhD (1997) in organic chemistry from Flinders University (with Prof. Rolf H. Prager). He worked as an Alexander von Humboldt Postdoctoral Fellow with Prof. Armin de Meijere at the Georg-August-Universität, Göttingen, Germany and then at the Australian National University with Prof. Lewis N. Mander. He has held an academic position at The University of Queensland since 2000 and during this time has won a number of awards including a Thieme Chemistry Journals Award in 2007. His research interests include natural products (isolation, total synthesis, synthetic methodology, med

chem), and bioactive synthetics i.e. developing the area of caged carbocycles (physical organic chemistry) to escape flatland and designing new bioisosteres.

Louis M. Rendina is currently Professor of Chemistry at the University of Sydney, Australia, and an Adjunct Professor at the International Institute of Nano and Molecular Medicine, US. He received his BSc(Hons I) and PhD degrees from the Australian National University. He is the recipient of several research awards and international fellowships, and he is a Fellow of the RACI and a Fellow of the Royal Society of Chemistry, UK. From 2014-16, he was appointed to the ARC College of Experts and, in 2018, he was appointed to the ARC Excellence in Research for Australia Research Evaluation Committee. His current research interests lie in the area of synthesis and inorganic drug discovery, including the use of boron clusters as unique frameworks in medicinal chemistry.

Michael Kassiou is Professor of Medicinal Chemistry and Academic Director of the Drug Discovery Initiative at the University of Sydney. He received his Ph.D. in Chemistry from the University of New South Wales in 1992. He is a Fellow of the Royal Australian Chemical Institute and the Asian Federation of Medicinal Chemistry. He has been a Postdoctoral Fellow at Johns Hopkins University and a Fogarty Fellow at the National Institute of Drug Abuse, National Institutes of Health in the USA. His research interests include medicinal chemistry, heterocyclic chemistry, CNS drug discovery, and structure-activity relationships of bioactive molecules. He serves on several journal editorial boards including ACS Chemical Neuroscience and ChemMedChem.

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ABBREVIATIONS USED

Boc = *tert*-butyloxycarbonyl; CDI = 1,1'-carbonyldiimidazole; DIAD = diisopropyl azodicarboxylate; DIC = *N*,*N*`-diisopropylcarbodiimide; DMAP = 4-dimethylaminopyridine; DMDO = dimethyldioxirane; DPPA = diphenyl phosphorylazide; dtbbpy = 4,4′-di-tert-butyl-2,2′-dipyridyl; HEK 293T = human embryonic kidney cells; LHMDS = lithium *N*,*N*-bis(trimethylsilyl)amide; LiTMP = lithium tetramethylpiperide; MES SA = uterine sarcoma cells; mGluR = metabotropic glutamate receptor; NCS = *N*-chlorosuccinimide; PET = positron emission tomography; SAHA = suberoylanilide hydroxamic acid; SAR = structure-activity relationship; SPECT = single photon emission computerized tomography; TMS = trimethylsilane.

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