INVESTIGATION OF A BICYCLO [1.1.1]PENTANE AS A PHENYL REPLACEMENT WITHIN AN $LpPLA_2$ INHIBITOR

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Celeste Alverez

Current Literature

April 15, 2017

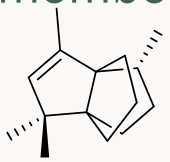
Propellanes

[*m*,*n*,*l*] propellane

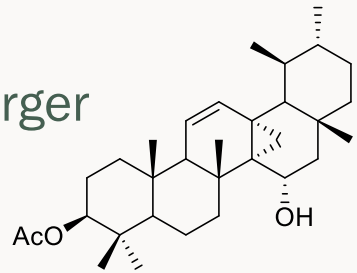
[1.1.1] [2.2.2] [2.2.1] [10.3.3] [10.3.3]

Small-ring propellanes | Large-ring propellanes

- Small-ring propellanes (*m*,*n*,*l* <3): Strained systems that allow for enhanced reactivity
- Large-ring propellanes (*m*,*n*,*l* ≥3): Ring strain minimized, appealing for "beauty of the structures and the elegance of the synthetic approach"
- Common in natural products
  - Typically 2 of the rings are 5-membered or larger



modhephene

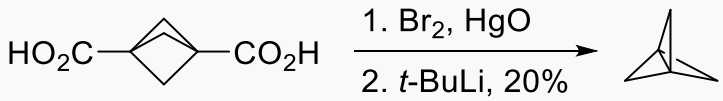


3-acetoxy-15-hydroxy-13,27-cyclours-11-ene
isolated from *Ficus microcarpa*

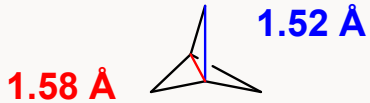
Yang and Cook, *J. Org. Chem*., **1976**, 41, 1903-7.
Dilmaç et. al. *Angew. Chem. Int. Ed.* **2017**, *56*, 2-37.

[1.1.1]Propellane

- Tricyclo[1.1.1.$0^{1,3}$]pentane
- Smallest possible propellane
- Proposed theoretically first in 1972 by Newton and Schulman
- First synthesized in 1982 by Wiberg and Walker:



- Largest strain energy (SE)



- Surprisingly stable: bond dissociation energy to the diradical predicted to be 65 kcal/mol
  - Relatively thermally stable: ring opening to methylenecyclobutene at 114-140 °C

Wiberg and Walker *J. Am. Chem. Soc.* **1982**, *104*, 5239-5240.
Wu et. al. *Angew. Chem. Int. Ed.* **2009**, 48, 1407-1410.
Dilmaç et. al. *Angew. Chem. Int. Ed.* **2017**, *56*, 2-37.

[1.1.1]Propellane

Table 1: Calculated strain energies for different small-ring propellanes.[15]

Entry	Propellane	Calculated strain energy [kcal mol^{-1}]		
		B3LYP/6-31G*[a]	B3LYP/cc-pVTZ[b]	MM/2[c]
1	[1.1.1]	98.2	100.6	113.2
2	[2.1.1]	98.1	100.1	94.4
3	[2.2.1]	96.9	100.7	80.7
4	[2.2.2]	90.2	95.6	78.7
5	[3.1.1]	–	77.1	73.5
6	[3.2.1]	–	67.2	62.7
7	[3.2.2]	–	61.3	61.7
8	[3.3.1]	–	45.1	40.0
9	[3.3.2]	–	32.6	40.5
10	[3.3.3]	–	11.2	21.4

[a] Ref. [15a]. [b] Ref. [15b]. [c] Listed values are only for *syn* conformations. Ref. [15c].

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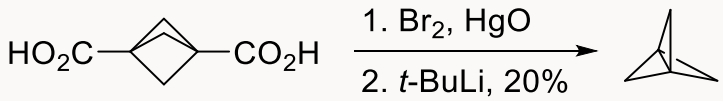

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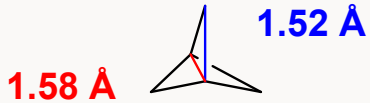

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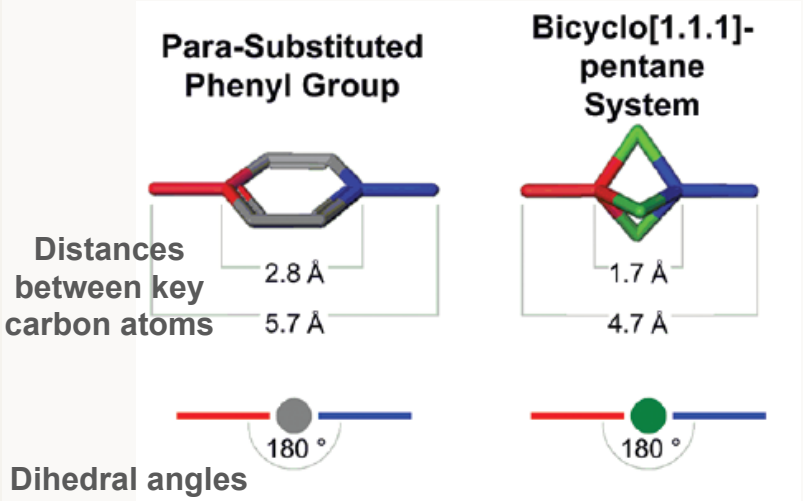
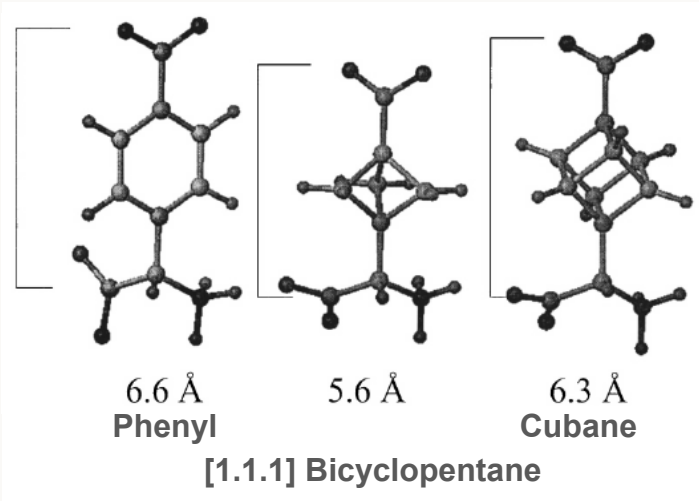
Propellanes as Isosteres

- Bioisostere: replacement of an atom or structural feature that results in similar biological effects as the parent
  - Replacement can maintain physiochemical properties or topology

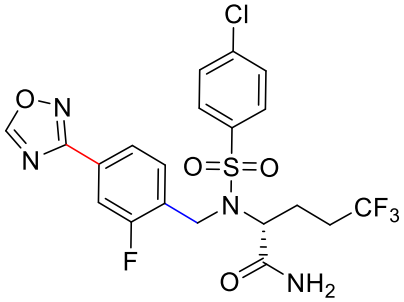




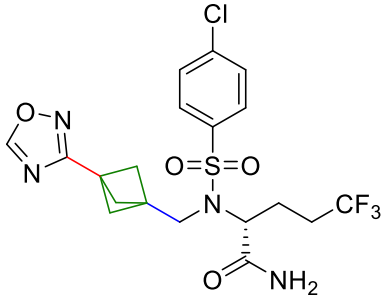
Cambridge MedChem Consulting: Bioisostere
Stepan et al. *J. Med. Chem.* **2012**, *55*, 3414−3424.
Costantion et. al. *Bioorg. Med. Chem.* **2001**, *9*, 221-7.

Propellanes in Drugs

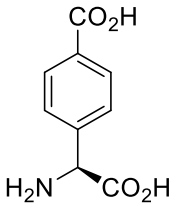
- Good isosteric replacement:



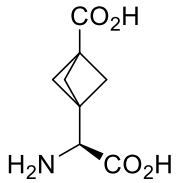
Avagacestat
IC_{50} ($A\beta_{42}$) = 0.225 nM



3
IC_{50} ($A\beta_{42}$) = 0.178 nM

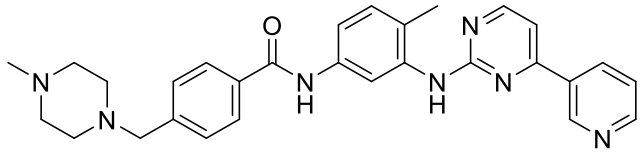


(*S*)-4CPG
IC_{50} (mGluR1) = 40 uM

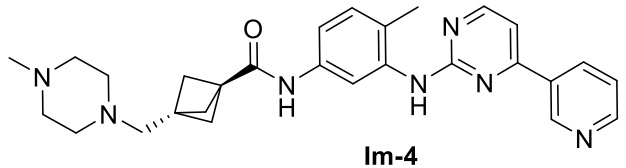


S-(+)-CBPG
IC_{50} (mGluR1) = 25 uM

- Poor isosteric replacement:



Imatinib (**Im-1**)
IC_{50} (ALB1) = 0.371 uM

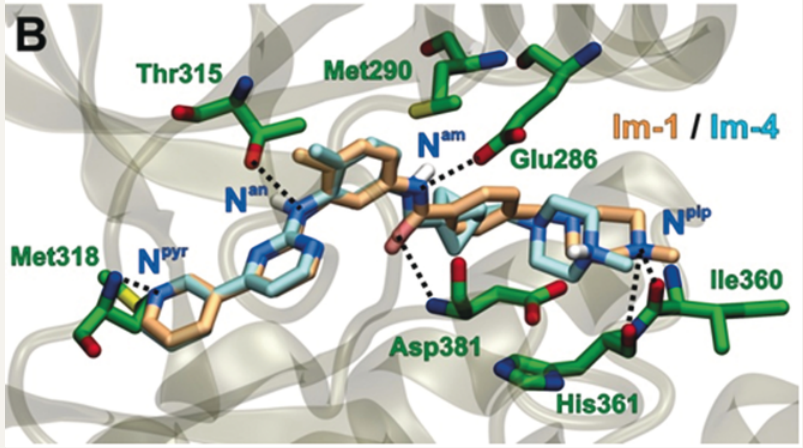


Im-4
IC_{50} (ALB1) = >30 uM

Stepan et. al. *J. Med. Chem*. **2012**, *55*, 3414−3424.
Pellicciari et. al. *J. Med. Chem*., **1996**, *39*, 2874 – 2876.
Nicolaou et. al. *ChemMedChem*, **2016**, *11*, 31-37.

Propellanes in Drugs

	N^{pyr} Met318	N^{an} Thr315	N^{am} Glu286	C=O Asp381	N^{pip} His361	N^{pip} Ile360
Im-1	2.94	3.01	3.09	2.98	3.12	2.72
Im-4	2.84	3.03	3.84	2.75	3.46	4.39



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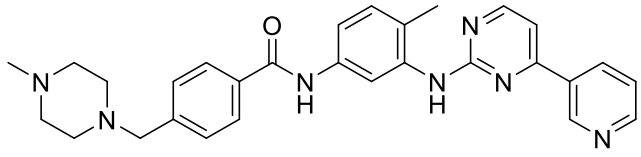

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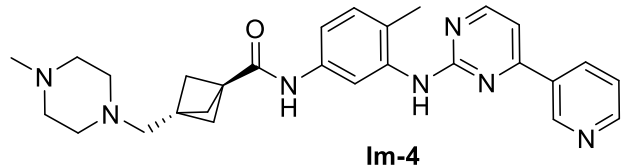

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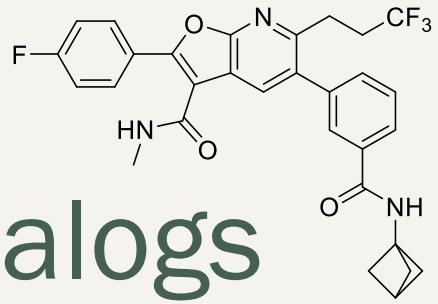


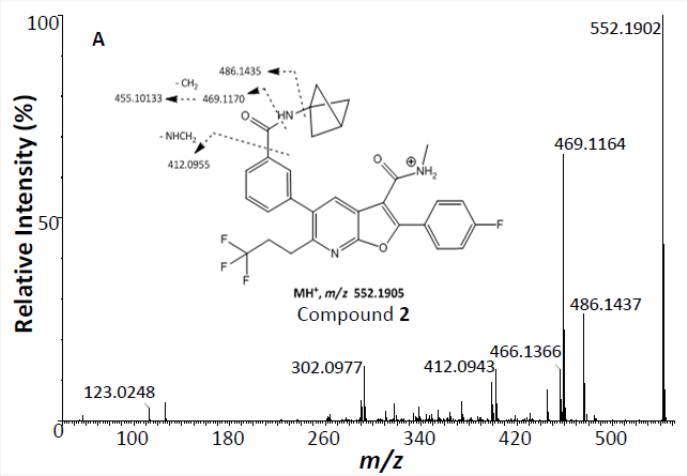
Stability of Propellane Analogs

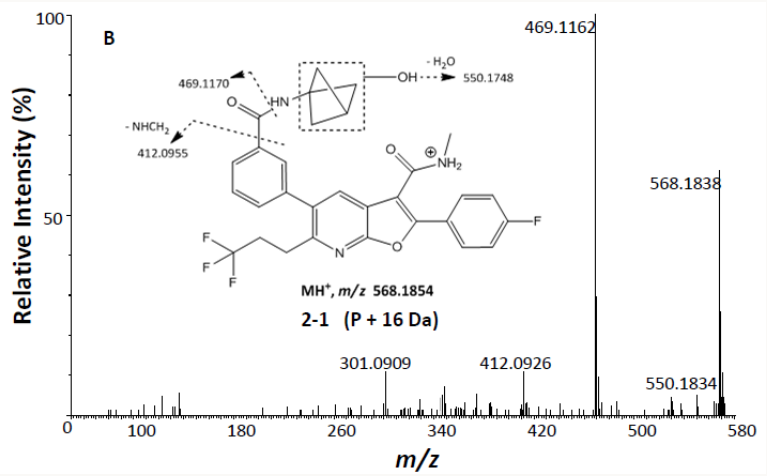
	Metabolism on the bicycle[1.1.1]pentane moiety					Metabolism on other moieties
	Parent	Mono-Ox	P + 181 Da	Bis-Ox	Mono-/Bis-Ox + dehydrogenation	Mono-Ox, ect.
Aroclor-induced rat liver S9 (30 min)	95	5	ND	ND	ND	ND
Human liver s9 (30 min)	99	<1	ND	ND	ND	ND
Rat hepatocytes (2 h)	99	<1	ND	ND	ND	ND
Human hepatocytes (2 h)	99	<1	ND	ND	ND	ND
Rat bile ducts (0-24 h)	4	55 (**2-1**), 6	6 (**2-3**)	4 (1 pdt)	18 (4 pdts)	13
Rat plasma (0.5, 1, 3, 6, 24 h)	100	ND	ND	ND	ND	ND

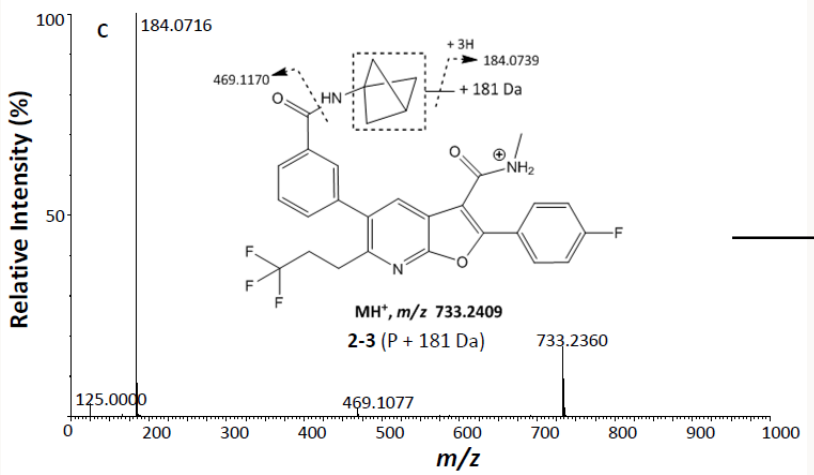
ND = Not Determined
P + 181 = Phosphocholine conjugation @ methine

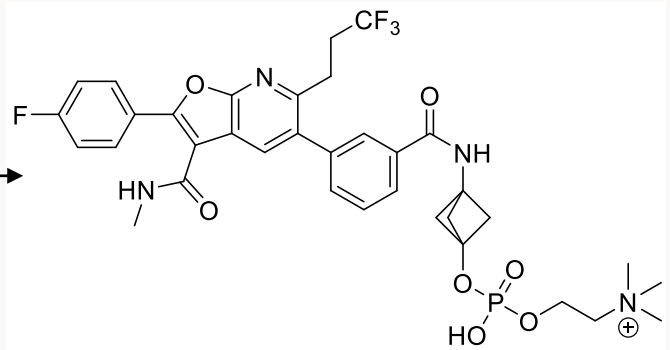
 Zhou et. al. *Drug Metab. Dispos.* ***2016****, 44*, 1332–1340.

Stability of Propellane Analogs





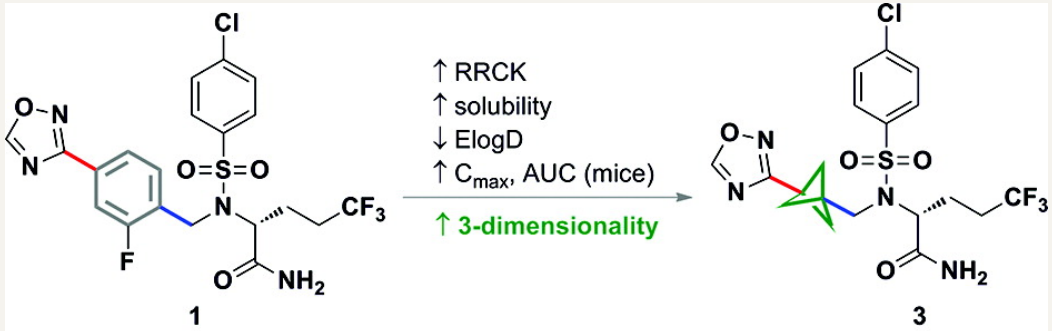




Zhou et. al. *Drug Metab. Dispos.* ***2016****, 44*, 1332–1340.

Stepan et. al. *J. Med. Chem*. **2012**, *55*, 3414−3424.

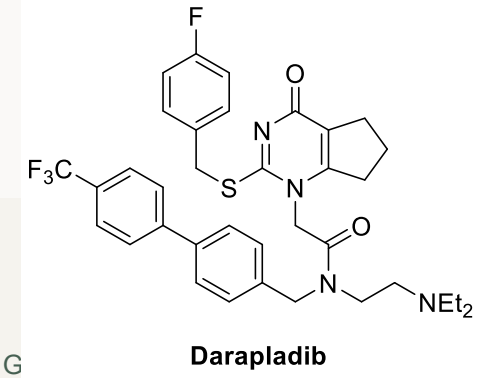
PK Properties of Propellanes



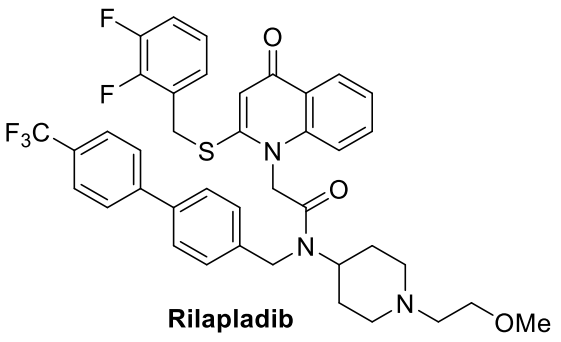
	1	3
IC_{50}(Aβ$_{42}$, nM)[a,b]	0.225 (52)	0.178 (4)
Notch selectivity[b]	350 (14)	178 (4)
human hepatocytes $CL_{int,app}$ (μL/min/million cells)[c]	15.0	<3.80
HLM $CL_{int,app}$(mL/min/kg)[b,d]	<16.2 (4)	<8.17 (2)
RRCK P_{app}(A to B)(10^{-6} cm/s)[e]	5.52	19.3
ElogD[f]	4.70	3.80
kinetic solubility (pH = 6.5, μM)	0.60	216
thermodynamic solubility (pH = 6.5, μM)	1.70	19.7
thermodynamic solubility (pH = 7.4, μM)	0.90	29.4
MDR1/MDCKBA/AB ratio[g]	1.72	1.66

$LpPLA_2$

- Lipoprotein-associated phospholipase A_2
  - or Platelet-activating factor acetylhyrolase (PAF-AH)
- Plays a role in atherosclerosis and diseases associated with vascular inflammation (ie. Alzheimer's disease)
- Elevated levels linked to increased risk for:
  - Myocardial infarction
  - Ischemic stroke
  - Cardiac death in patients with cardiovascular disease
- 2 GSK compounds:



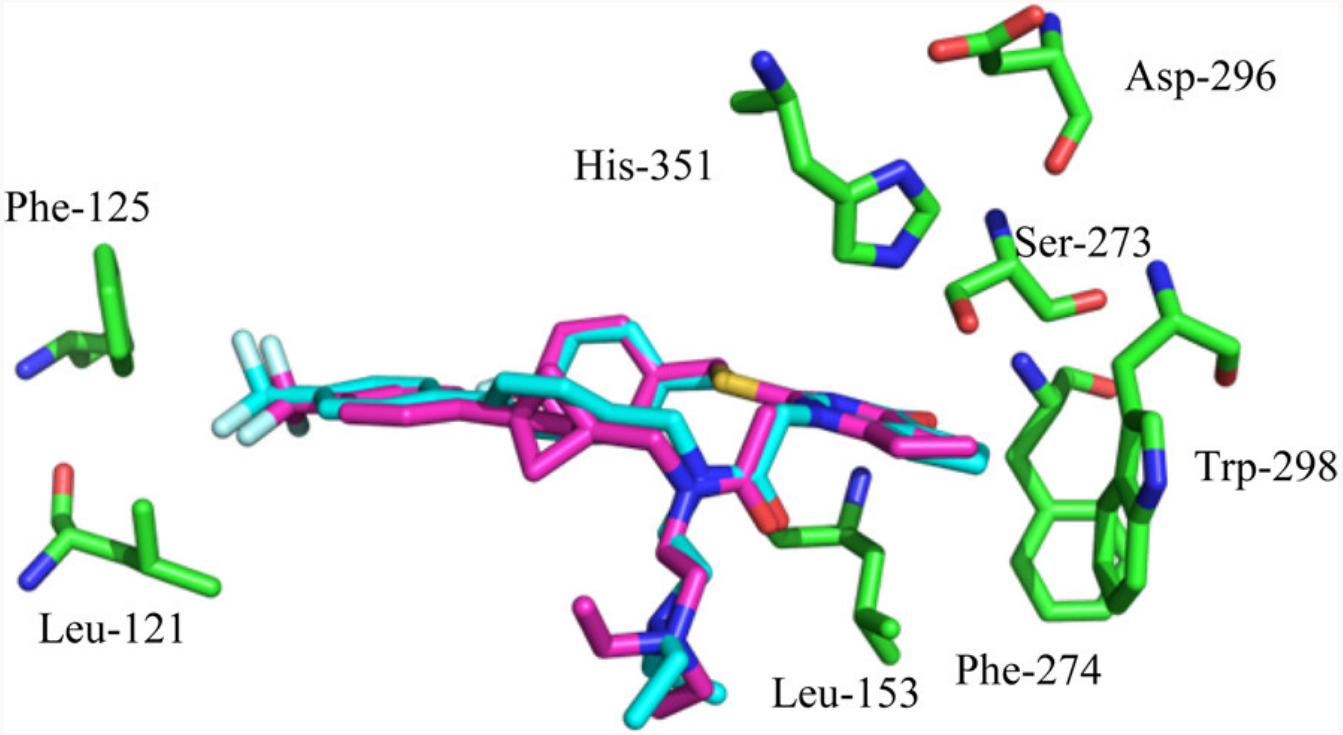
Darapladib



Rilapladib

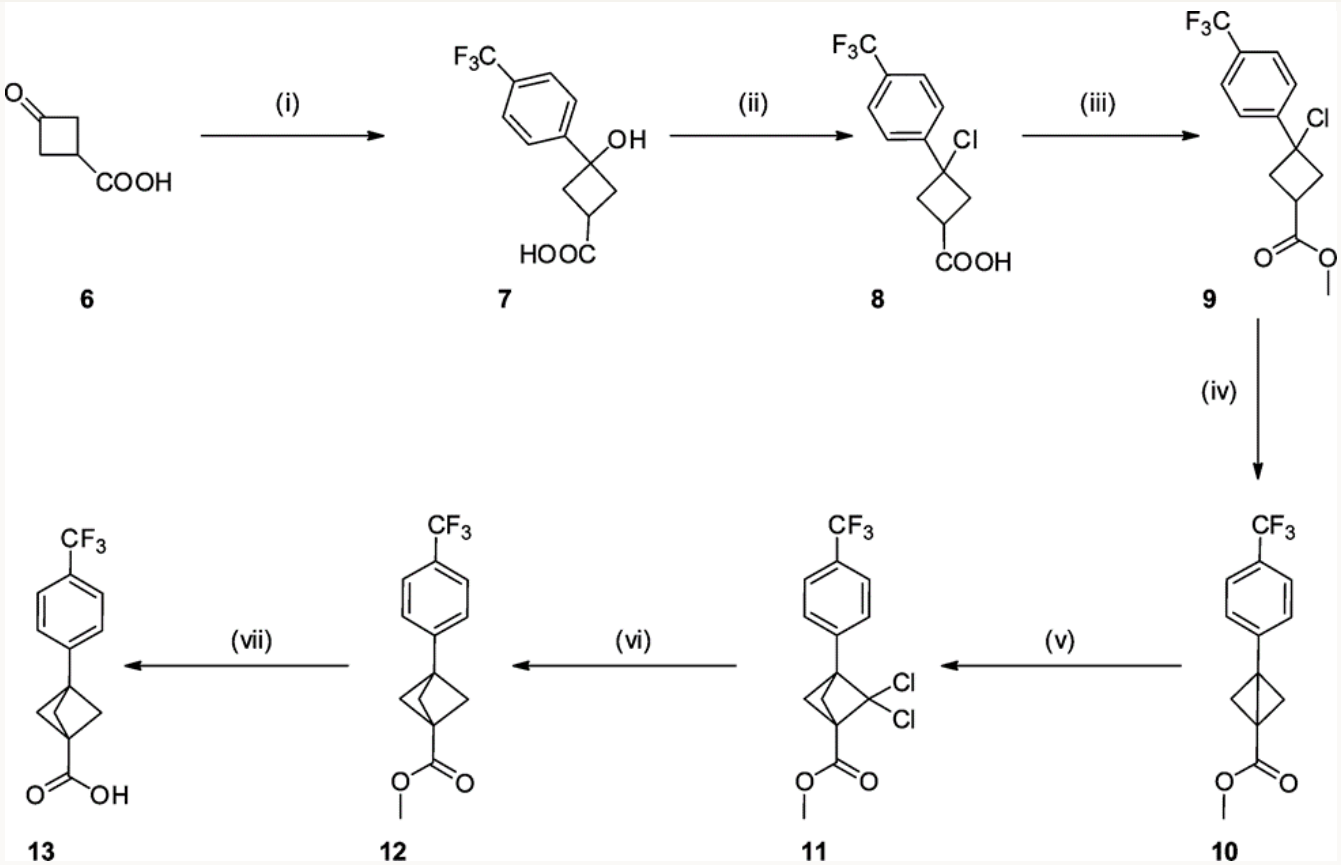
ACS Med. Chem. Lett. **2017**, *8*, 43−48

Binding vs. Phenyl (Docking)



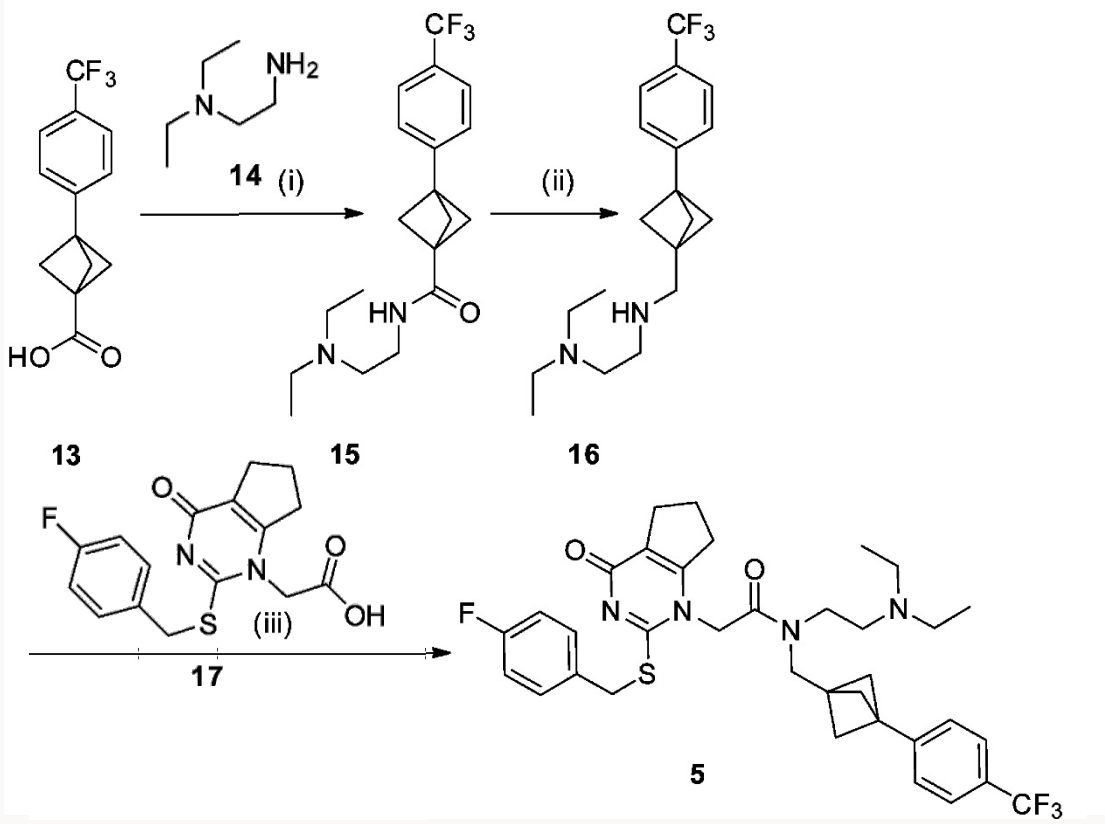
X-ray crystal structure of darapladib (blue) in LpPLA2 overlaid with modeled bioisosteric replacement (magenta)

Propellane Synthesis



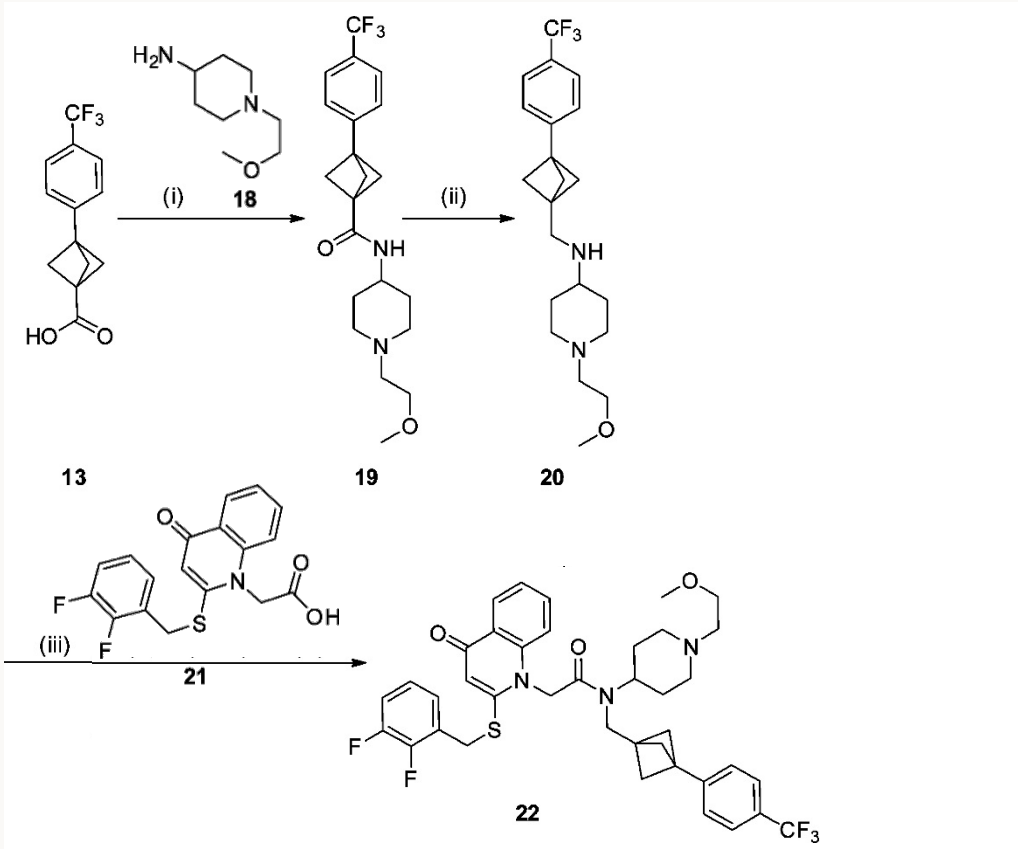
Reagents and conditions: (i) 4-bromotrifluorotoluene, *n*BuLi, THF, −78 °C to rt, **77%**; (ii) conc. HCl, PhMe, rt, sonication, **75%**; (iii) HCl, MeOH, 1,4-dioxane, rt, **quant**.; (iv) NaH, THF, rt, **98%**; (v) sodium trichloroacetate, tetrachloroethylene, diglyme, 120-140 °C, **38%**; (vi) TTMSS, 1,1′-azobis (cyclohexanecarbonitrile), PhMe, 110 °C, **74%**; (vii) LiOH, 1,4-dioxane, rt, **95%**.

Darapladib Analog Synthesis



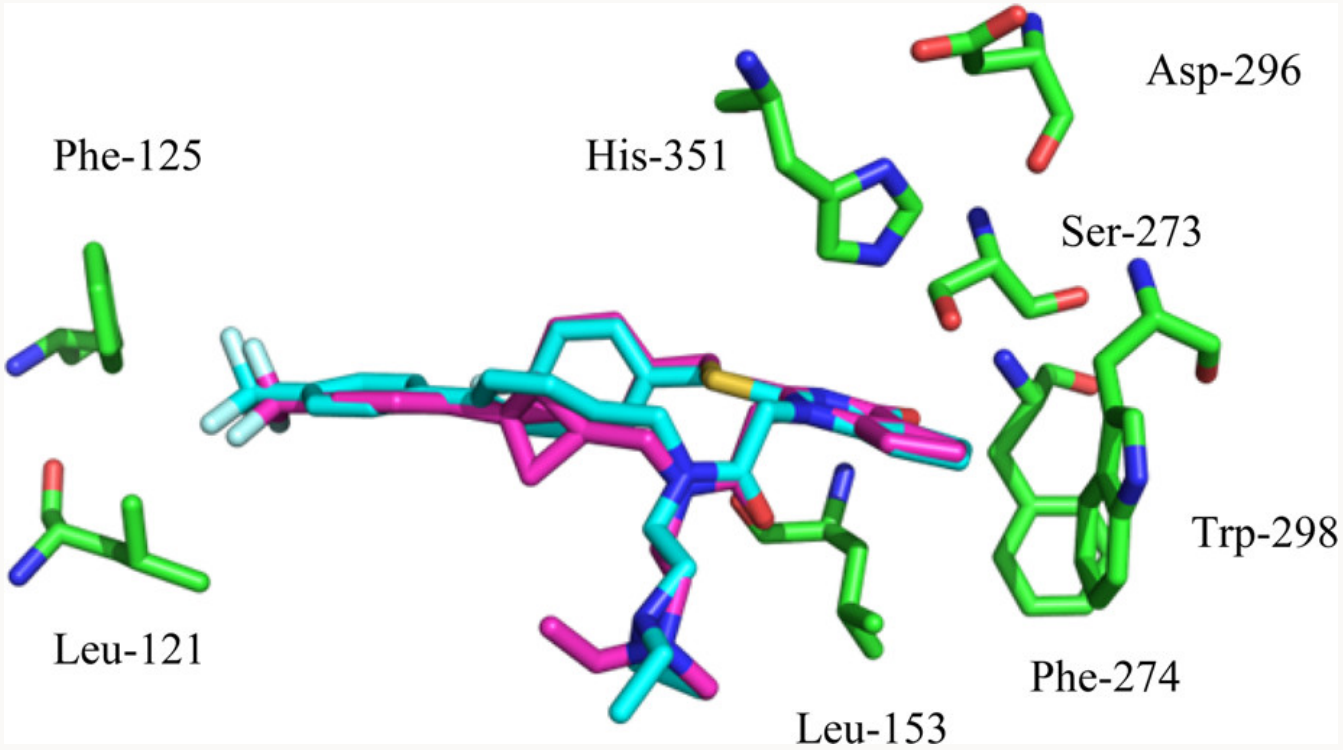
Reagents and conditions: (i) **14**, T3P, Et_3N, EtOAc, rt, **99%**; (ii) $LiAlH_4$, THF, rt, **56%**; (iii) **17**, T3P, Et_3N, rt, CH_2Cl_2, **60%**

Rilapladib Analog Synthesis



Reagents and conditions: (i) **18**, T3P, Et_3N, CH_2Cl_2, rt, **74%**; (ii) $[Ir(COE)_2Cl]_2$, Et_2SiH_2, CH_2Cl_2, rt, **59%**; (iii) **21**, T3P, Et_3N, CH_2Cl_2, rt, **53%**.

Binding vs. Phenyl (X-Ray)



X-ray crystal structure overlays of bound darapladib (blue) and analogue 5 (magenta) in LpPLA2

Physiochemical/PK Properties

	Darapladib	5	Rilapladib	22
pIC_{50}	10.2	9.4	9.6	NT
Kinetic Solubility (uM)	8	74	<1	32
Thermodynamic Solubility (simulated intestinal sol.) [ug/mL]	399	>1000	203	635
Permeability (nm/s)	230	705	NT	NT
Lipophilicity ($ChromLogD_{7.4}$)	6.3	7.0	6.74	7.06
PFI (Property Forcast Index)	10.3	10.0	11.74	11.06
CL (HLM) [mL/min/g]	--	1.22	--	0.76

NT = Not tested

Summary

- The bioisosteric replacement of a phenyl ring with bicyclo [1.1.1]pentane within Darapladib and Rilpladib was successful carried out and resulted in improved physiochemical properties
- In Darapladib the bicyclo[1.1.1]pentane maintained high potency
- The bicyclo[1.1.1]pentane did not disrupt the binding mode of the parent compound, but did shorten the side chain with respect to the biaryl
- Bicyclo[1.1.1]pentane is useful in $LpPLA_2$ inhibition