Evaluation of oxetan-3-ol, thietan-3-ol, and derivatives thereof as bioisosteres of the carboxylic acid functional group

Lassalas, P.; Oukoloff, K.; Makani, V.; James, M.; Tran, V.; Yao, Y.; Huang, L.; Vijayendran, K.; Monti, L.; Trojanowski, J. Q.; Lee, V. M.-Y.; Kozlowski, M. C.; Smith, III, A. B.; Brunden, K. R.; Ballatore, C.

ACS Med. Chem. Lett. **ASAP**

Celeste Alverez
Current Literature
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Isosteres in Medicinal Chemistry

- Recent definition:

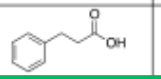
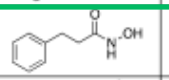
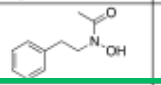
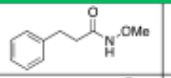
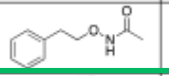
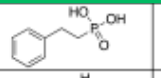
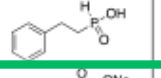
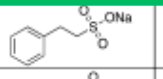
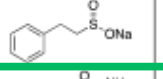
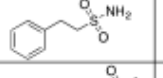
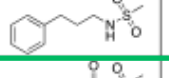
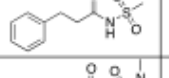
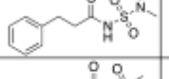
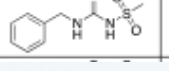
"Similarities must exist between at least some of the properties of the isostere and those of the fragment being replaced, such that the new analogs retain the biological activities of the parent compound."

"At the same time, however, the isosteric replacement must produce changes in the physicochemical properties or susceptibility to metabolism compared to the parent compound in order to lead to improved derivatives."

- Lassalas et al. *J. Med. Chem.* **2016**, *59*, 3183–3203.

Carboxylic acid Isosteres

- Many reported in literature

Class	Cpd #	Structure	Aq. Solub.[a] (μM)	$logD_{7.4}$[b]	$logD_{7.4}$ calc.[c]	PAMPA			pK_a[g]	pK_a calc.[c]	PPB (% fu)[h]
						Pe (cm/s)[d]	% retention[e]	$logP_{app}$[f]			
Carboxylic acid	1*		110.69 ± 3.04	−0.49 ± 0.19	−0.56	1.66E-06 ± 0.35E-06	−7 ± 11	−5.79 ± 0.10	4.64	4.73	9.5 ± 0.4
Hydroxamic acids	2*		≥ 200	0.71	1.23	4.97E-06	0.03	−5.30	8.18	8.90	29 ± 2
	3*		≥ 200	1.52	1.16	4.53E-06	1.1	−5.34	8.83	8.37	37 ± 10
Hydroxamic esters	4		≥ 200	1.16	1.59	7.28E-06	5.3	−5.14	9.47	8.45	68 ± 3
	5*		199.88 ± 0.49	1.18	1.35	4.60E-06	−2.9	−5.34	9.58	8.88	64 ± 3
Phosphonic acid	6*		152.36 ± 1.18	−1.14	−1.54	9.40E-08	−2.7	−7.03	2.34 (8.49)	1.81	31 ± 5
Phosphinic acid	7		127.73 ± 1.96	−1.44	−1.36	1.70E-08	−2.1	−7.77	1.98	2.24	8.86 ± 0.06
Sulfonic acid	8*		≥ 200	−1.45	−1.17	3.84E-08	−6.1	−7.42	<2.0	−0.81	0.31 ± 0.08
Sulfinic acid	9		≥ 200	−1.30	−0.84	ND†	−6.8	ND†	2.1	2.00	5.0 ± 0.7
Sulfonamides	10*		≥ 200	0.96	0.63	2.13E-06	4.2	−5.67	10.04	11.38	60.72 ± 0.04
	11*		≥ 200	1.42	1.15	1.05E-05	8.1	−4.98	>12	12.06	37.27 ± 0.06
Acyl-sulfonamides	12*		199.70 ± 0.30	−1.02	−0.21	3.45E-07	1.4	−6.46	4.94	4.08	12.8 ± 0.2
	13*		199.03 ± 1.24	0.17	−0.22	1.53E-06	2.2	−5.81	5.86	4.12	8.1 ± 0.2
Sulfonylurea	14*		197.76 ± 2.24	−1.23 ± 0.06	−0.87	2.61E-07 ± 1.01E-07	3.0 ± 5.4	−6.61 ± 0.20	5.04	4.14	31 ± 2

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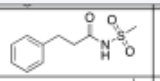
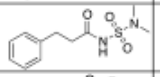
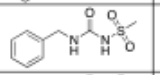
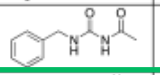
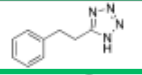
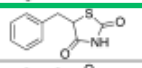
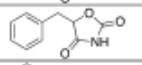
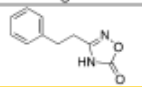
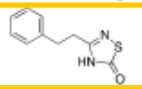
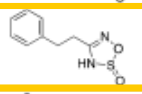
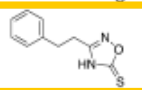
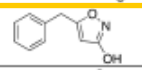
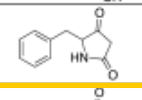
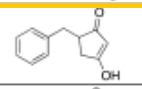
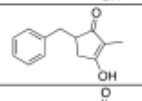
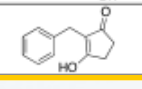
Carboxylic acid Isosteres

Acyl-sulfonamides	12*		199.70 ± 0.30	−1.02	−0.21	3.45E-07	1.4	−6.46	4.94	4.08	12.8 ± 0.2
	13*		199.03 ± 1.24	0.17	−0.22	1.53E-06	2.2	−5.81	5.86	4.12	8.1 ± 0.2
Sulfonylurea	14*		197.76 ± 2.24	−1.23 ± 0.06	−0.87	2.61E-07 ± 1.01E-07	3.0 ± 5.4	−6.61 ± 0.20	5.04	4.14	31 ± 2
Acylurea	15*		≥ 200	1.42	0.57	1.63E-05	−3.3	−4.79	>12	11.77	77 ± 1
Tetrazole	16*		≥ 200	−0.25 ± 0.10	0.10	4.83E-07 ± 1.48E-07	4.7 ± 2.8	−6.33 ± 0.15	5.09	5.08	1.12 ± 0.12
Thiazolidine dione	17*		200.41 ± 0.41	1.07 ± 0.03	1.12	8.77E-06 ± 1.32E-06	5.5 ± 1.7	−5.06 ± 0.06	6.19	6.61	3.40 ± 0.11
Oxazolidine dione	18*		≥ 200	−0.16	0.70	2.46E-06	−0.6	−5.61	5.86	6.63	14 ± 1
Oxadiazol-5(4*H*)-one	19*		≥ 200	0.32	1.26	1.22E-06	−4.0	−5.91	5.73	6.04	1.10 ± 0.12
Thiadiazol-5(4*H*)-one	20*		200.47 ± 0.47	1.66	2.18	1.14E-05	−0.7	−4.94	6.50	7.19	1.17 ± 0.45
Oxathiadiazole-2-oxide	21		7.13 ± 0.74	ND	0.95	1.10E-07‡	−1432	−6.96‡	5.23	6.41	ND
Oxadiazol-5(4*H*)-thione	22*		≥ 200	−0.25	2.84	3.27E-07	−3.4	−6.49	3.58	7.77	0.65 ± 0.16
Isoxazole	23		≥ 200	0.46	1.34	4.65E-06	−11	−5.33	5.36	6.21	0.10 ± 0.10
Tetramic acid	24		≥ 200	−0.35	1.34	2.50E-06	1.3	−5.60	6.08	10.54	ND
Cyclopentane 1,3-diones	25		194.93 ±1.01	−0.70	2.32	2.12E-07	−3.0	−6.67	4.01	8.82	7.96 ± 0.35
	26*		≥ 200	−0.33	2.71	2.60E-07	−5.1	−6.58	4.47	8.72	11.09 ± 0.14
	27		199.04 ± 0.76	−0.60	2.16	1.54E-07	−8.8	−6.81	4.44	8.65	14.3 ± 0.6

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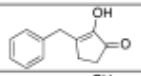
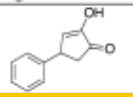
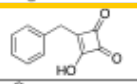
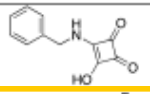
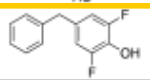
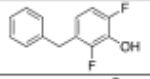
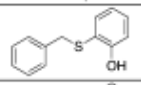
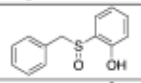
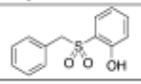
Carboxylic acid Isosteres

Class	Cpd #	Structure	Aq. Solub.[a] (μM)	$logD_{7.4}$[b]	$logD_{7.4}$ calc.[c]	PAMPA			pK_a[g]	pK_a calc.[c]	PPB (% fu)[h]
						Pe (cm/s)[d]	% retention[e]	$logP_{app}$[f]			
Cyclopentane 1,2-diones	28*		195.03 ± 1.75	1.85	2.34	1.14E-05	1.5	–4.94	8.88	9.24	16 ± 4
	29		192.44 ± 4.06	1.71	1.94	1.70E-05	–8.6	–4.77	8.28	9.37	ND
Squaric acid derivatives	30		165.79 ± 0.06	–0.84	1.36	ND†	–13	ND†	<2.0	6.56	8.19 ± 0.18
	31		≥ 200	–1.40	1.18	2.24E-07	–6.6	–6.65	<2.0	7.97	6.45 ± 0.34
Substituted phenols	32*		109.17 ± 1.35	3.34	3.88	7.05E-06	49‡	–5.15	7.19	7.74	0.26 ± 0.08
	33		148.70 ± 3.91	3.56	3.85	4.71E-06	–32	–5.33‡	7.05	7.62	0.52 ± 0.21
	34		ND§	>3.78	3.91	ND	ND	ND	9.06	9.18	ND
	35*		≥ 200	2.16	2.55	1.23E-05	1.1	–4.91	7.70	7.25	12 ± 3
	36*		197.11 ± 0.29	1.76	2.31	1.57E-05	7.2	–4.80	7.12	6.74	1.59 ± 0.03

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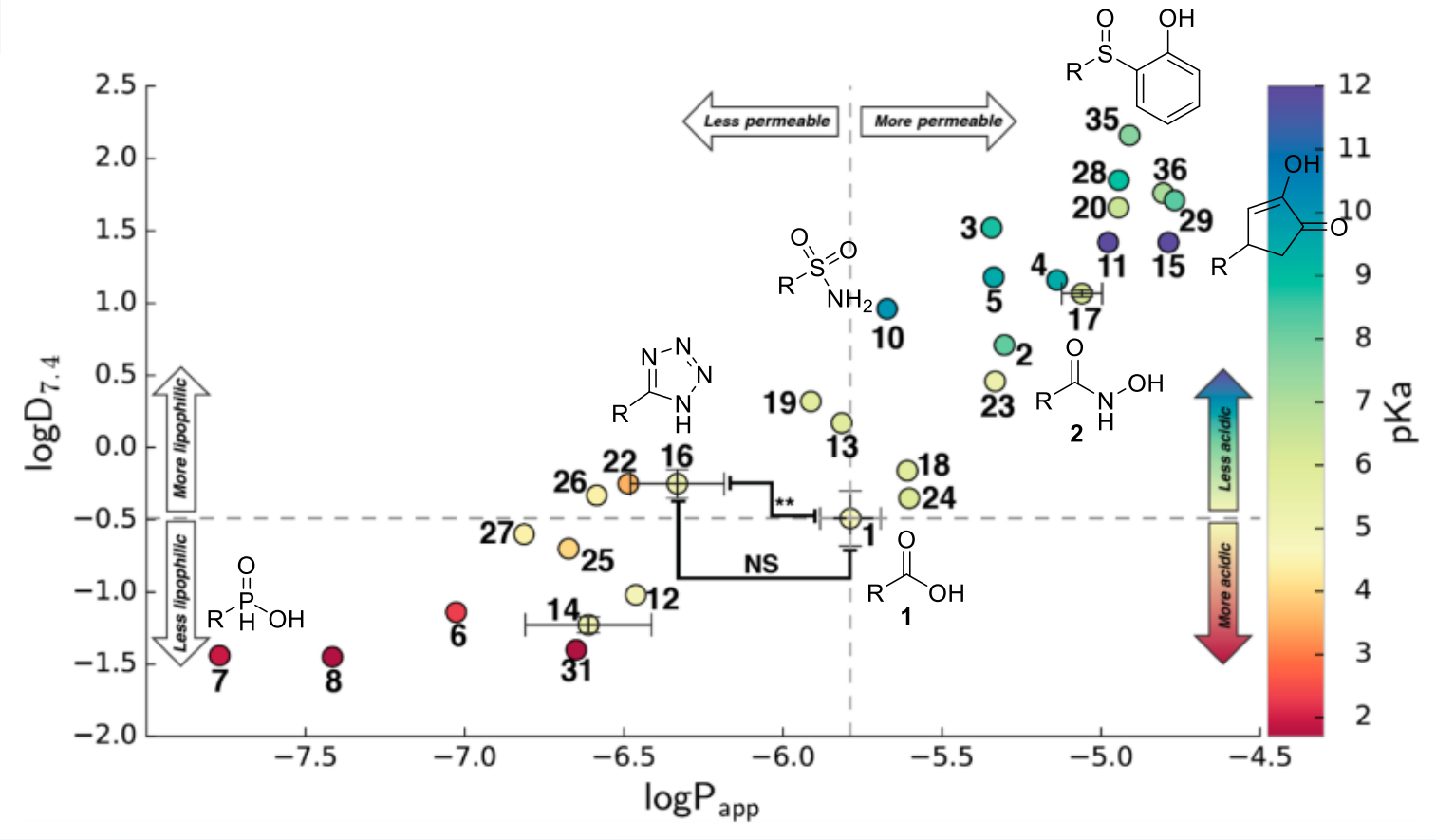
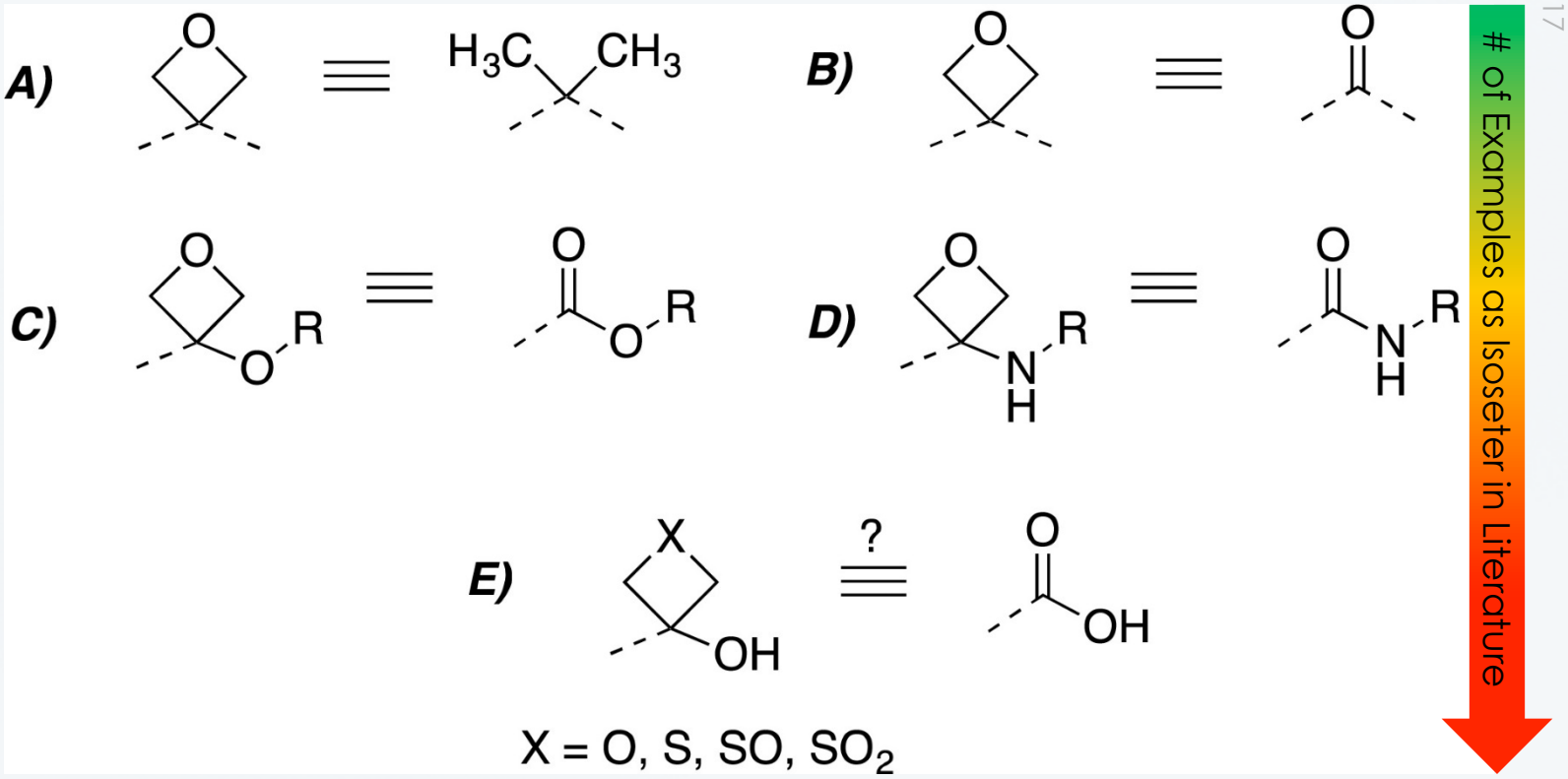
Carboxylic acid Isosteres



Lassalas et al. *J. Med. Chem.* **2016**, *59*, 3183–3203.

Oxetanes as Isosteres

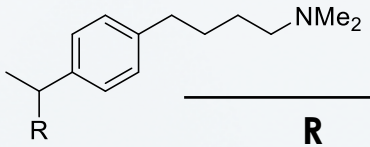


Lassalas et al. *ACS Med. Chem. Lett.* **ASAP**

Oxetanes in Medicinal Chemistry

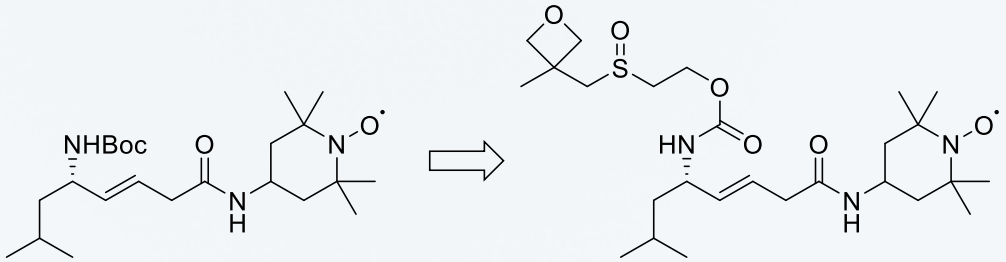
- Modulate lipophilicity
- Improve solubility, stability

Carreira et al. *J. Med. Chem.*, **2010**, *53*, 3227.



R	logD	Solubility (μM)	Cl_{int} (h/m)	pK_a
CH_2	1.8	250	37/520	9.9
gem Me_2	2.5	<4	16/420	9.9
oxetane	0.8	18,000	0/43	9.9

Wipf et al. *ACS Med. Chem. Lett*. **2014**, *5*, 900.

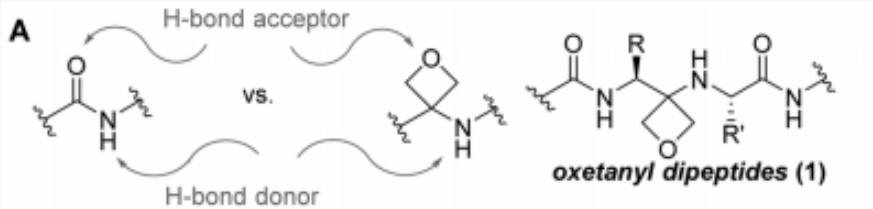


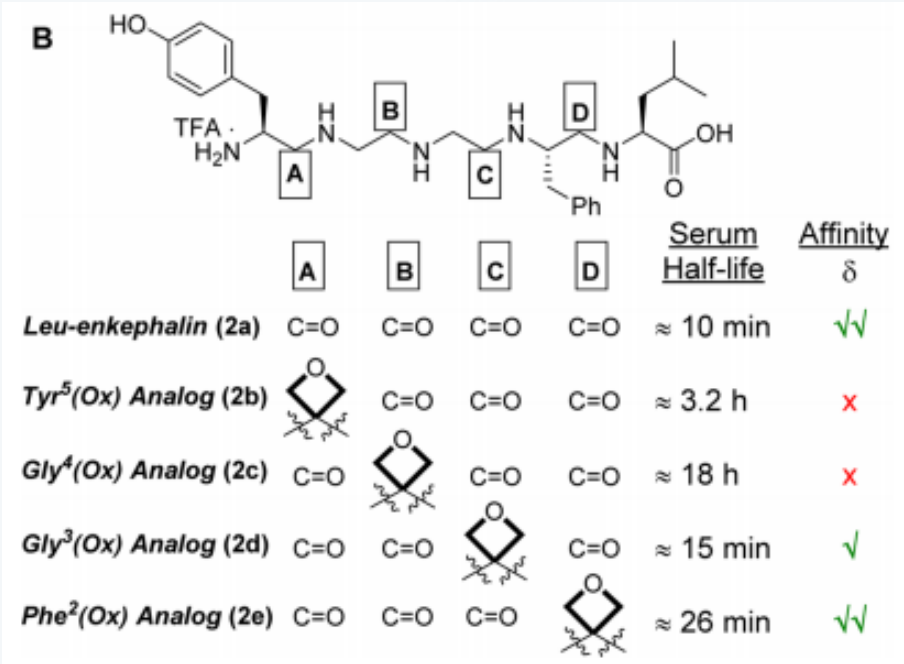
aq. solubility = 580 μM

aq. solubility = 44,000 μM

Recent Uses of Oxetanes as non-classical Isosteres

- Recently Carreria and Shipman groups have utilized oxetanes to mimic amides and esters

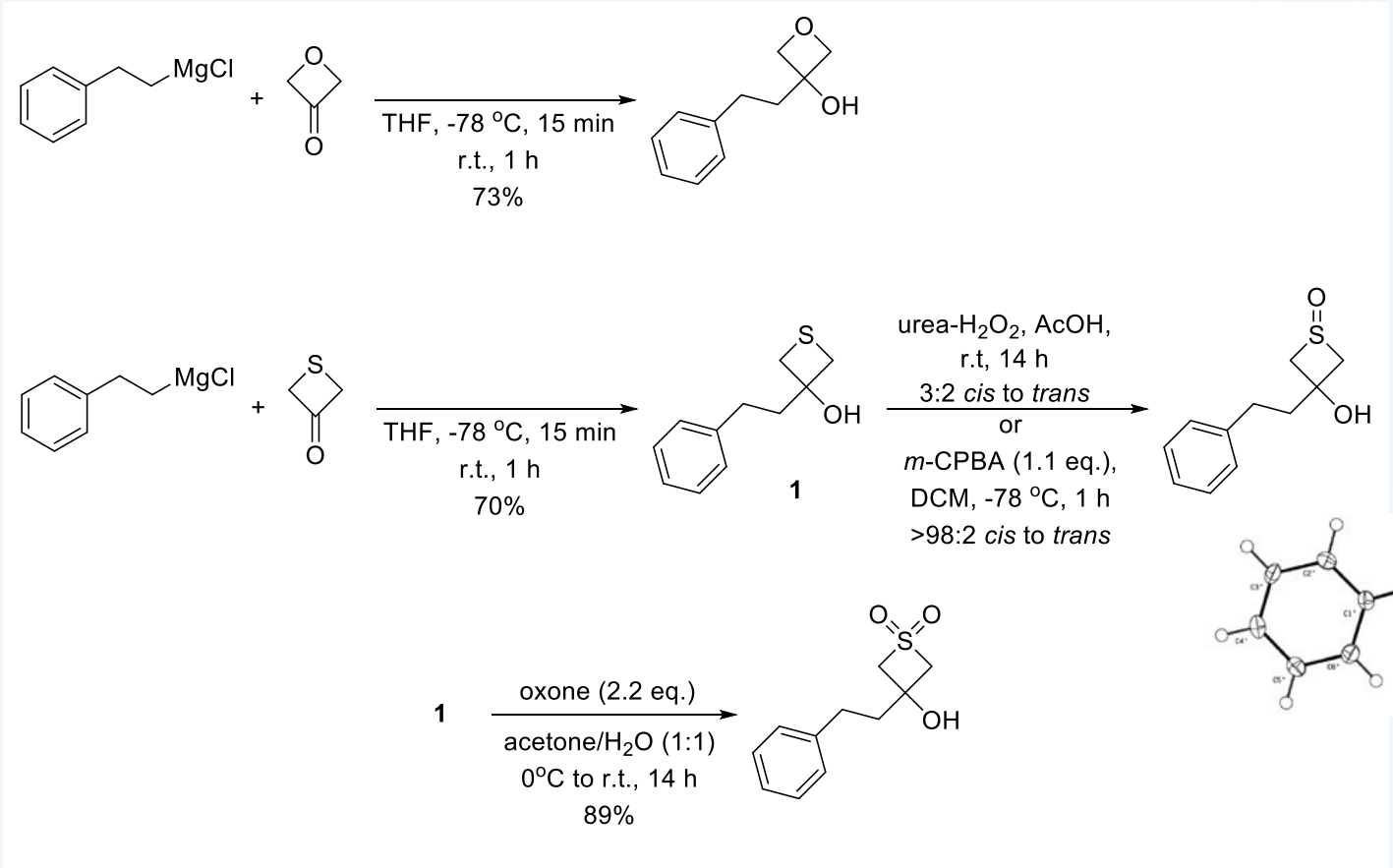


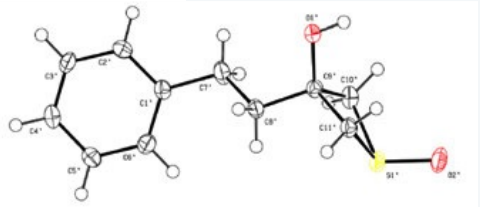


	A	B	C	D	Serum Half-life	Affinity δ
Leu-enkephalin (2a)	C=O	C=O	C=O	C=O	≈ 10 min	√√
Tyr^5(Ox) Analog (2b)		C=O	C=O	C=O	≈ 3.2 h	x
Gly^4(Ox) Analog (2c)	C=O		C=O	C=O	≈ 18 h	x
Gly^3(Ox) Analog (2d)	C=O	C=O		C=O	≈ 15 min	√
Phe^2(Ox) Analog (2e)	C=O	C=O	C=O		≈ 26 min	√√

Möller et al. *Org. Lett*. **2017**, *19*, 2510–2513.

Synthesis

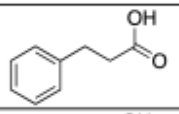
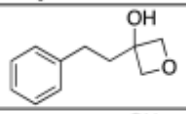
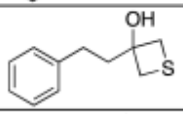
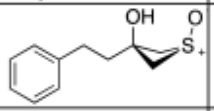
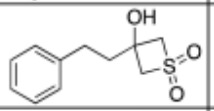
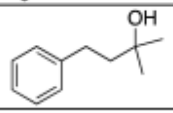




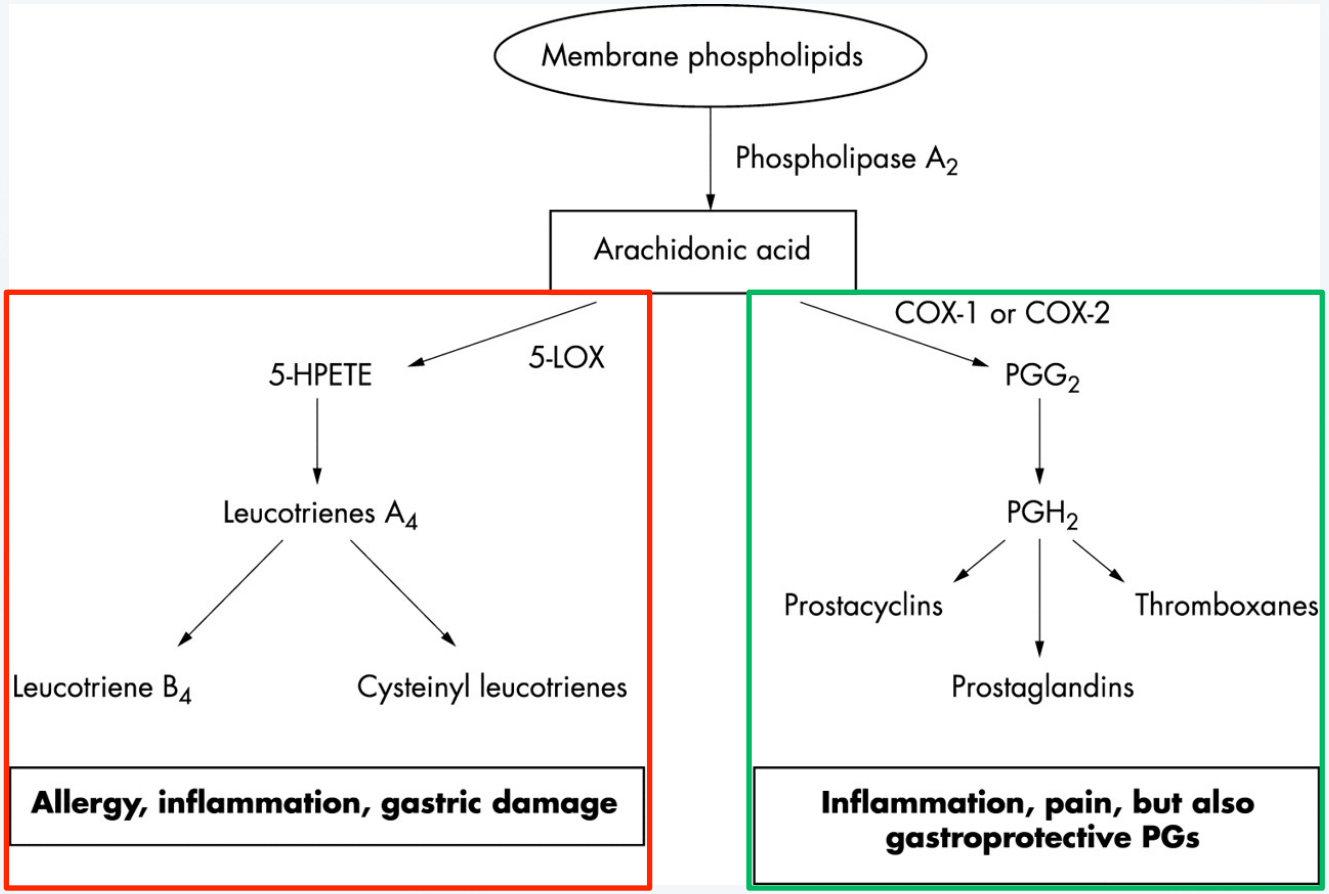
Lassalas et al. *ACS Med. Chem. Lett.* **ASAP**

Properties of 4-membered Heterocycle Isosteres

Table 1. Calculated and Experimental Properties of Test Compounds

Cpd #	Structure	$logD_{7.4}$[a]	$logD_{7.4}$ calc.[b]	PAMPA			pK_a[f]	pK_a calc.[b]	H bonding $ln(K_{eq})$[g]
				Pe (cm/s)[c]	% retention[d]	$logP_{app}$[e]			
1		−0.49 ± 0.19*	−0.56*	1.66E−06 ± 3.48E−7*	−6.8 ± 11*	−5.79 ± 0.10*	4.64*	4.7*	4.31*
3		2.07	1.7	8.27E−06	−11.9	−5.08	>12	13.5	2.53
4		2.99	2.28	1.32E−05	11.4	−4.88	>12	14.3	2.40
5		1.22	0.48	6.23E−06	10.0	−5.21	>12	14.2	3.46
6		1.24	0.58	1.22E−05	10.7	−4.91	9.31	13.6	3.76
16		ND	2.64	ND	ND	ND	ND	15.4	1.62

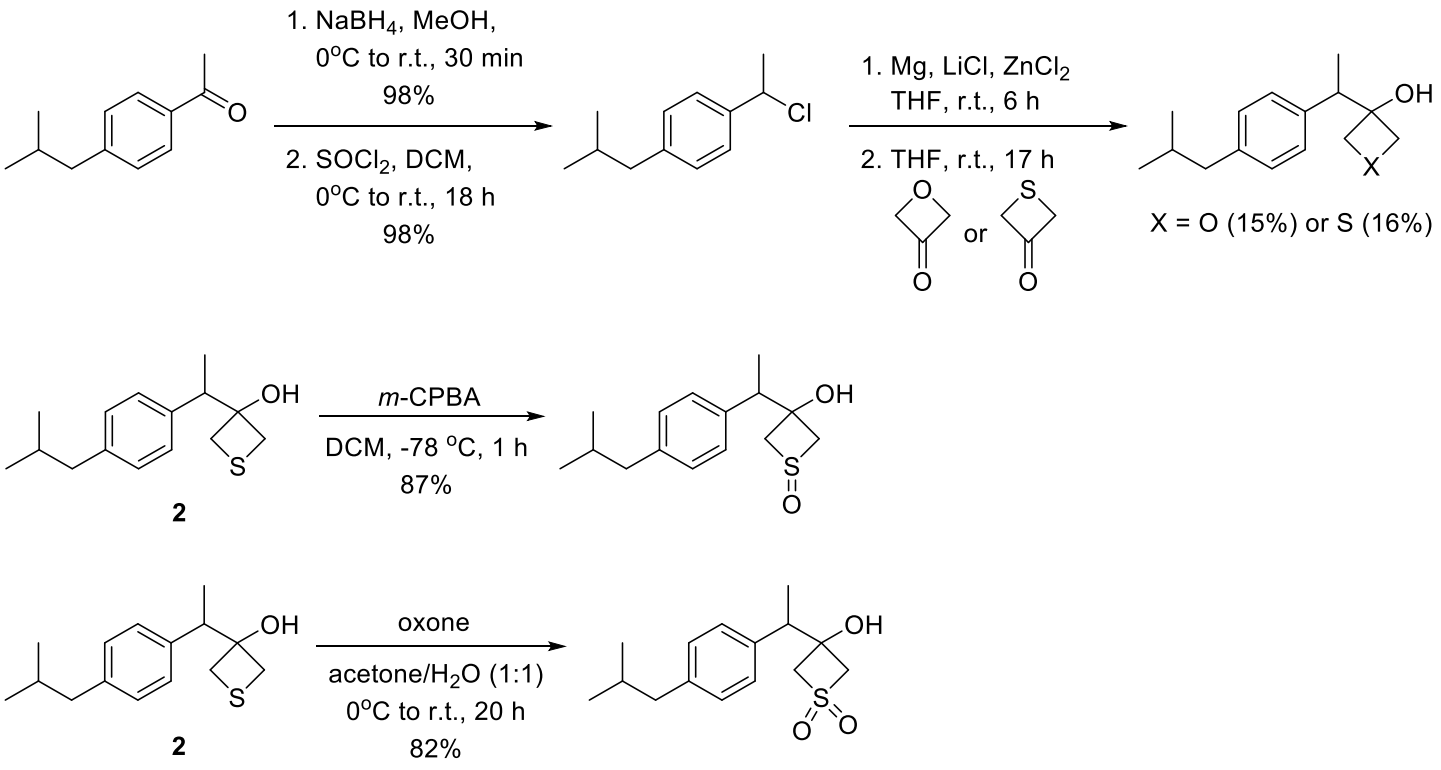
Why modify Ibuprofen?



Martel-Pelletier et al. *Ann. Rheum. Dis.* **2003**, *62*, 501-509.

Synthesis

Celeste Alverez @ Wipf Group
8/5/2017



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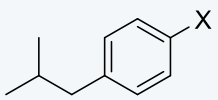
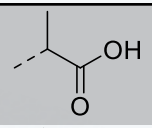
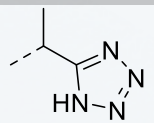
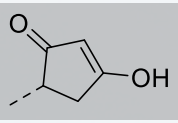
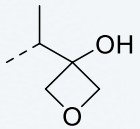
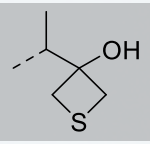
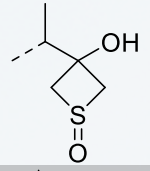
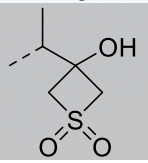
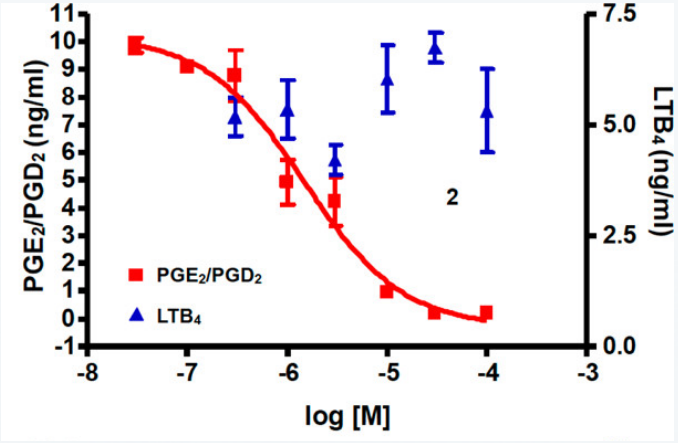
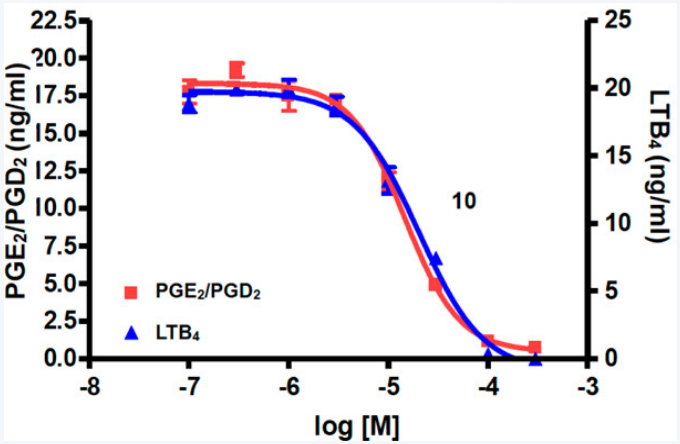
4-Membered Heterocycles in Ibuprofen Analogs

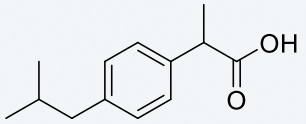
Celeste Alverez @ Wipf Group
8/5/2017

Cmpd		PGE_2/D_2 Assay IC_{50} (μM)	LBT_4 Assay IC_{50} (μM)
2		0.6	>100
17		31.8	>100
18		28.1	>100
7		34.1	8.4
8		>100	7.6
9		17.4	11.7
10		14.6	20.2

4-Membered Heterocycles in Ibuprofen Analogs







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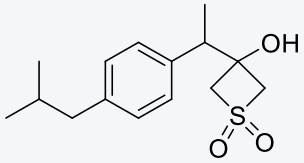
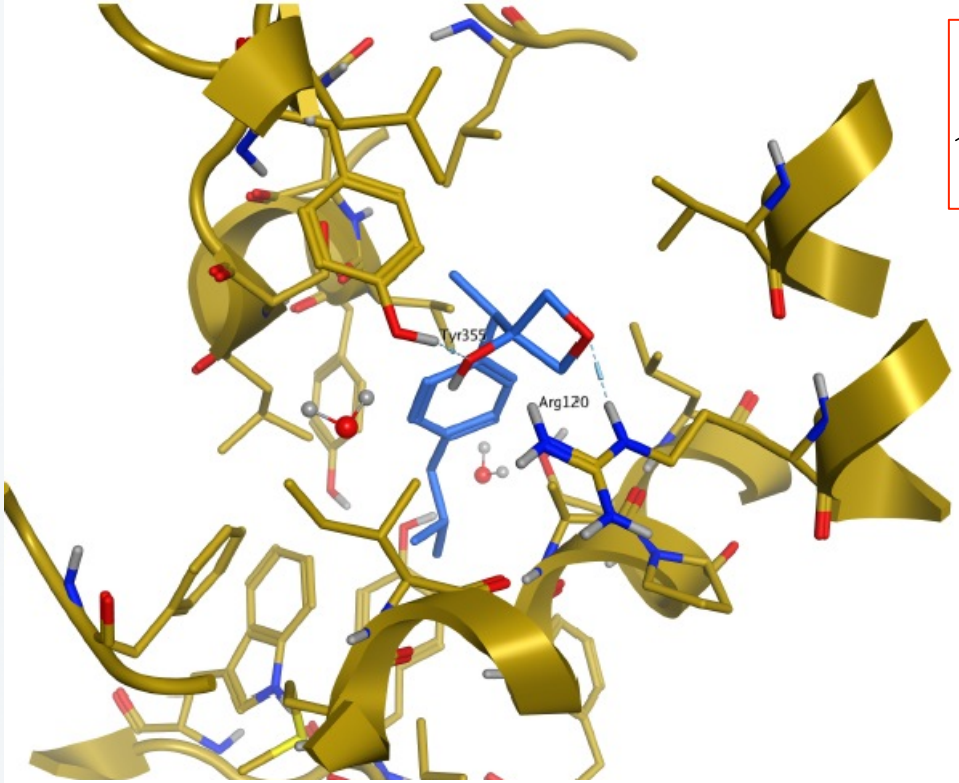


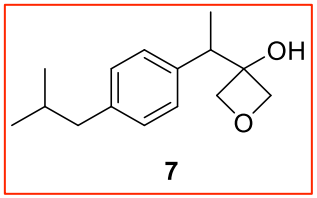
10

Concentration-response of inhibition of 5-LOX derived LTB_4 and COX-derived PGE_2/PGD_2 by **2** (left) and **10** (right)

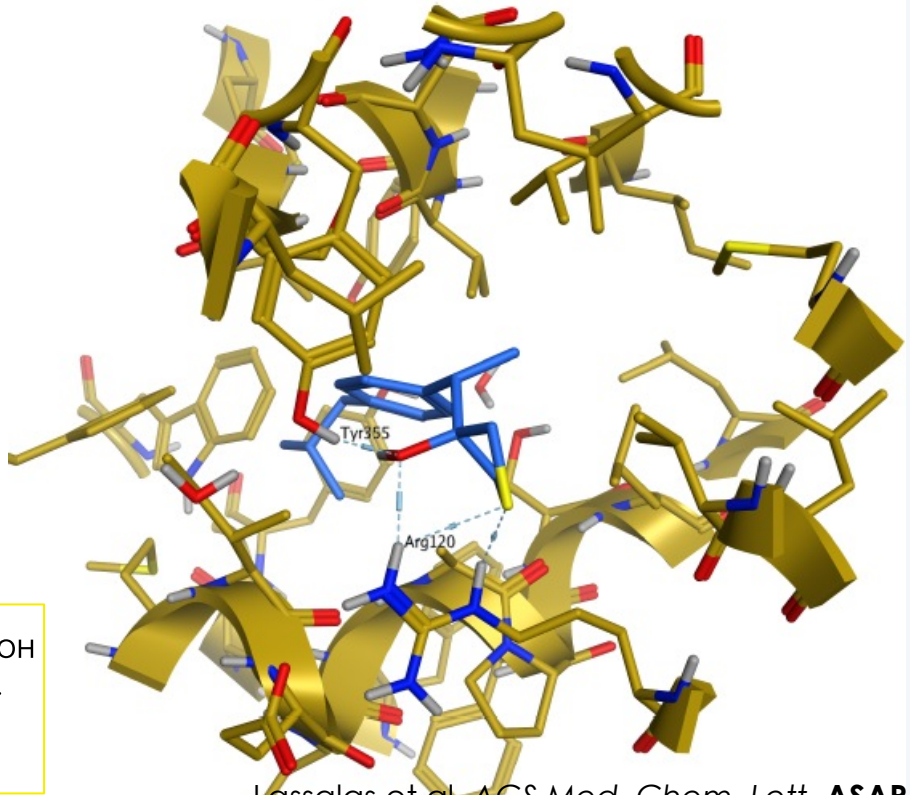
Lassalas et al. *ACS Med. Chem. Lett.* **ASAP**

Proposed binding modes

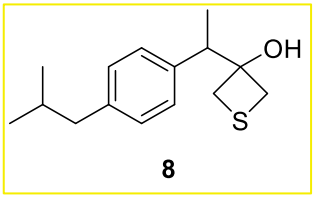




7



COX-1 crystal structure (PDB: 1EQG)



8

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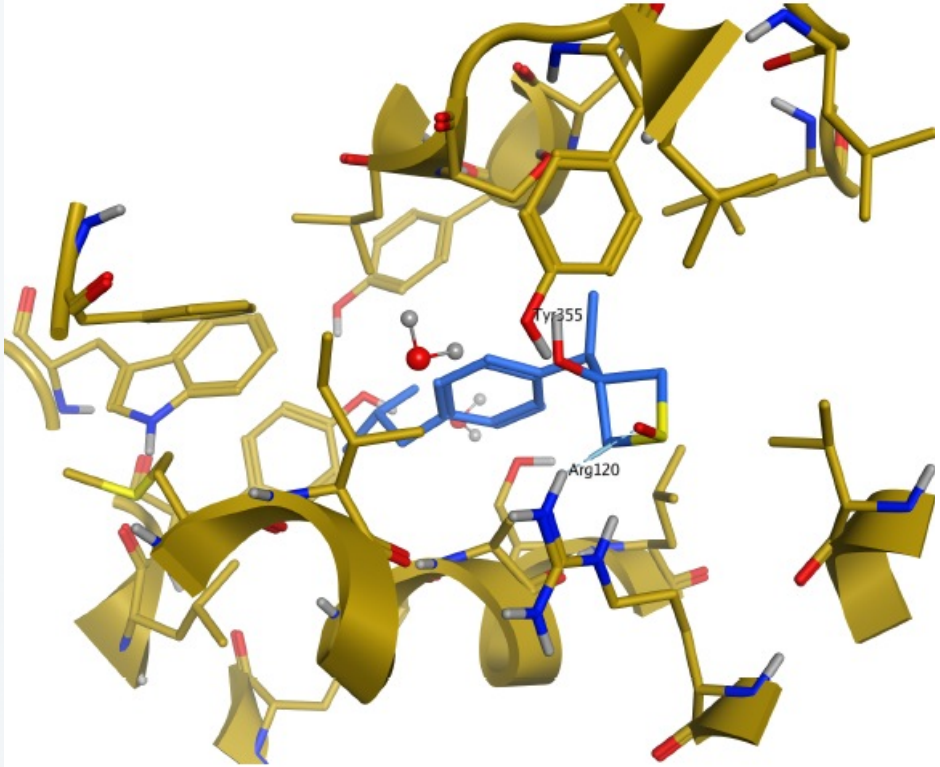
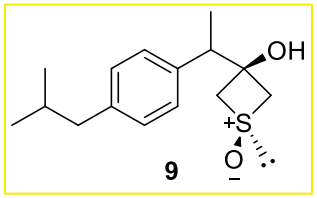
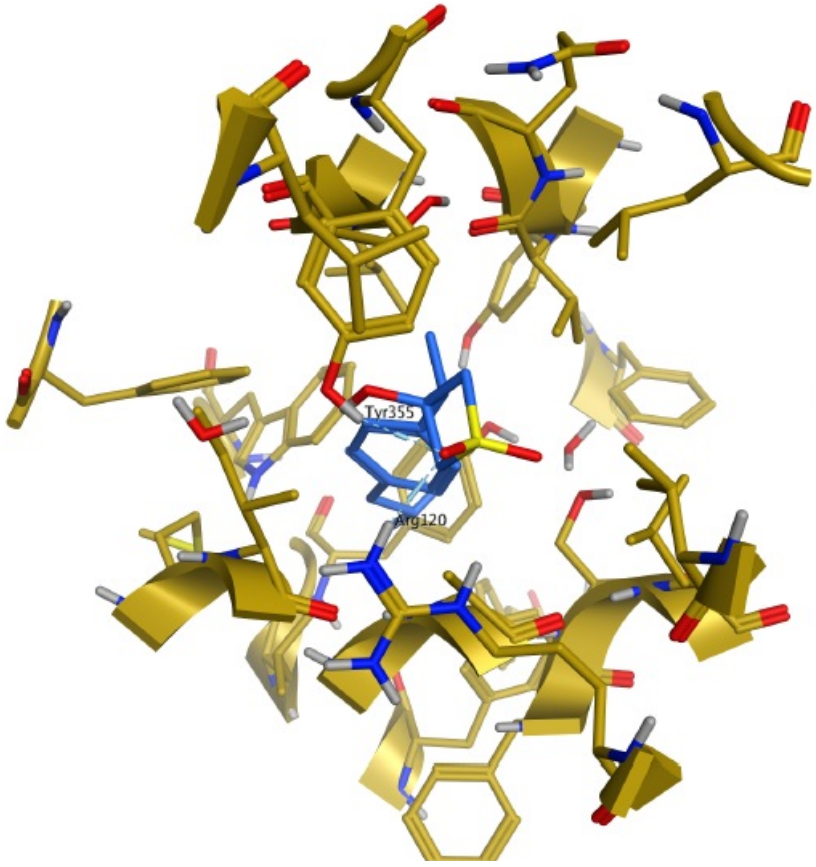
Proposed binding modes

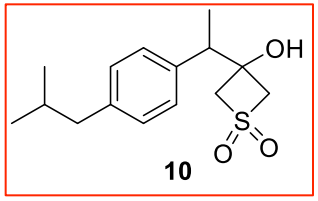




Celeste Alvere
8/5/2017



COX-1 crystal structure (PDB: 1EQG)



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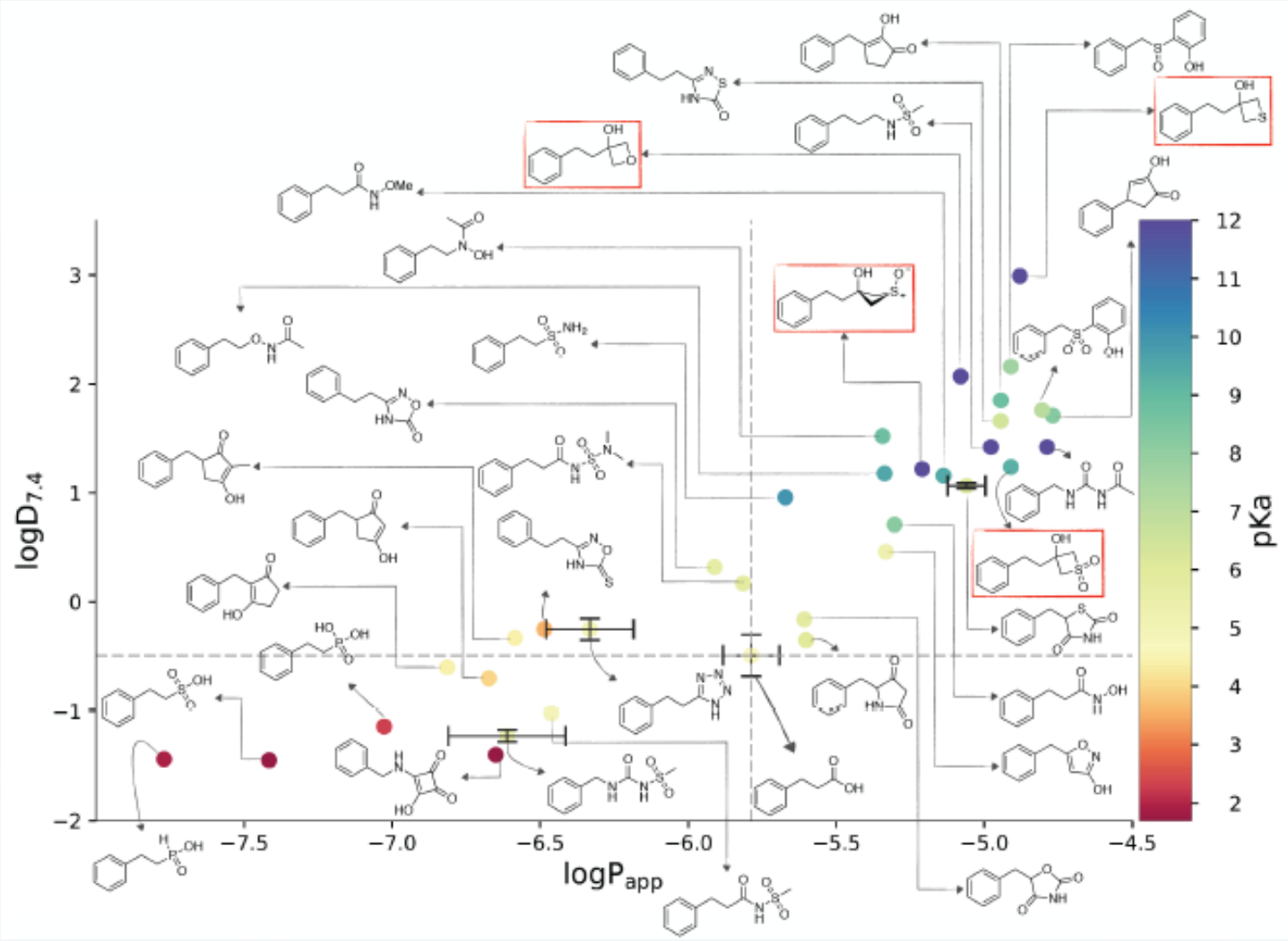
Isosteres of Carboxylic Acids



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Conclusions

- The 4-membered heterocyclic replacements of the carbonyl of carboxylic acids lead to improved lipophilicity and permeability
  - Decreased acidity
- All replacements show weaker H-bonding interactions
- Oxetan-3-ol and thietan-3-ol and related oxidized products can successfully act as bioisosteres of carboxylic acids
  - Potentially especially useful for CNS applications