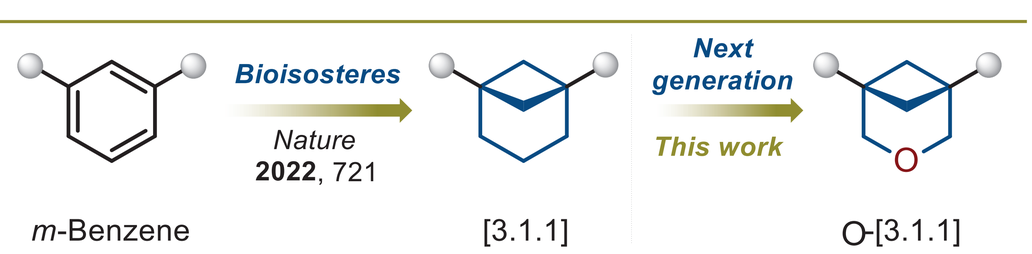
3-Oxabicyclo[3.1.1]heptanes as SP³-Rich Meta-Benzene Isosteres for Drug Design

D. Dibchak, O. Kolodiazhna, P. Mykhailiuk

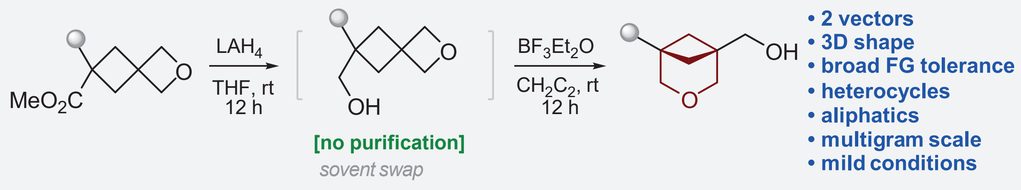
Enamine Ltd., Winston Churchill Street 78, 02094, Kyiv, Ukraine

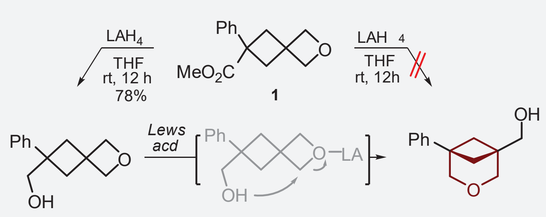
Introduction and Aim

Benzene is still the most common ring in drugs and natural products.[1] Since the “Escape from Flatland” concept (2009)[2], sp³-rich frameworks have gained popularity for improving solubility and metabolic stability. In this work, we present 3-oxabicyclo[3.1.1]heptanes as novel saturated bioisosteres of meta-substituted benzenes.[3] They were synthesized via a Lewis acid-catalyzed ring opening of spirocyclic oxetanes. A key analogue of Sonidegib retained nanomolar potency while showing >500% improved solubility and lower lipophilicity. These results highlight the potential of this new scaffold in drug design.



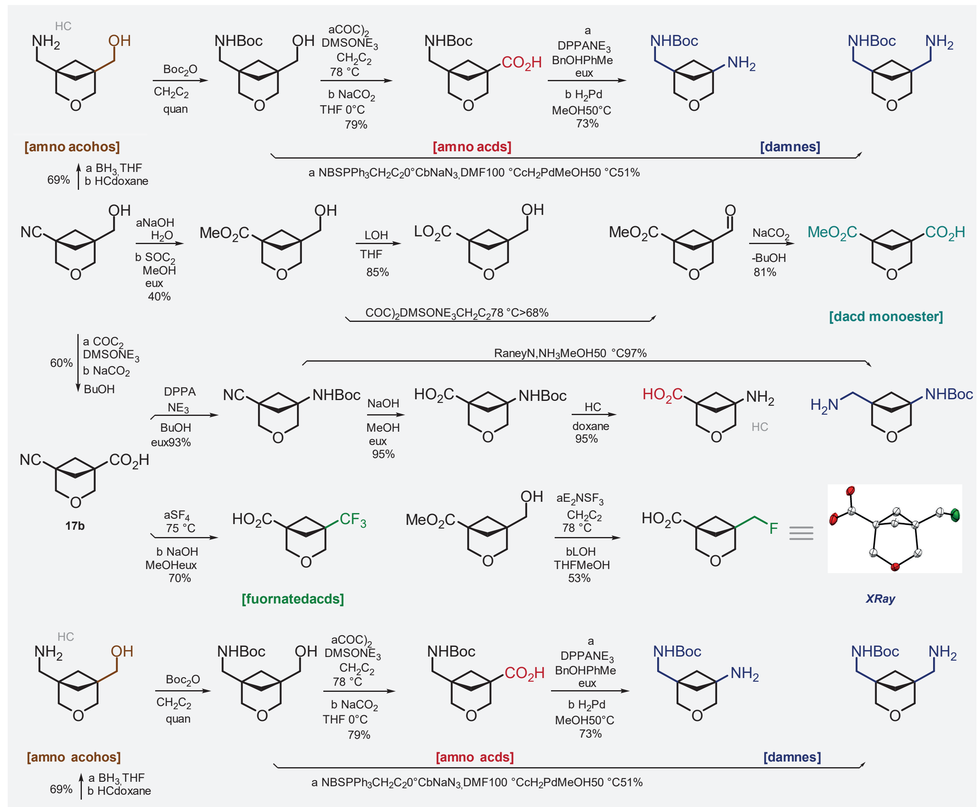
Synthesis



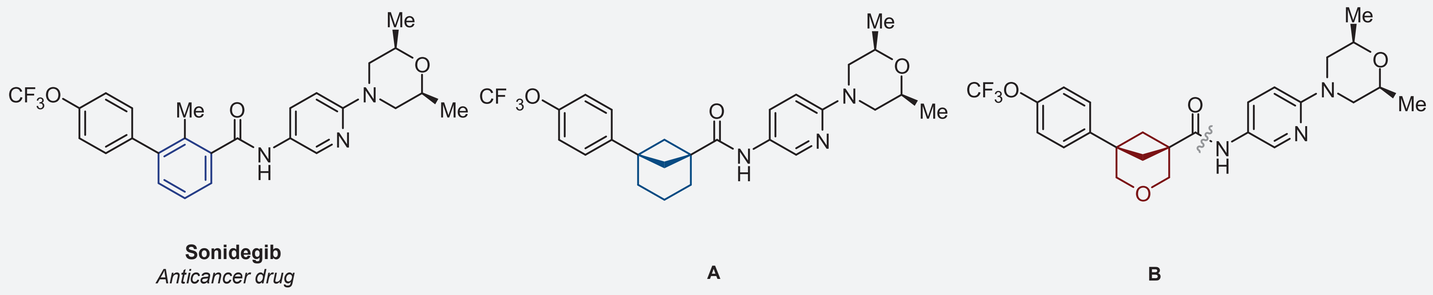


entry	conditions (*Lewis acid*)	conversion.[a]
1	THF, rt, 24 h	0% (SM)
2	THF, reflux, 1 h	0% (SM)
3	$BF_3{\cdot}Et_2O$ (10% mol.), CH_2Cl_2, rt, 2 h	100% (97%) [b]
4	10N HCl (5 eq.), rt, 2 h	95%
5	10N HCl (5 eq.), rt, 8 h	100%
6	H_3PO_4 (20% mol.), dioxane, rt, 2 h	95%
7	H_3PO_4 (20% mol.), dioxane, rt, 8 h	100%

Modifications

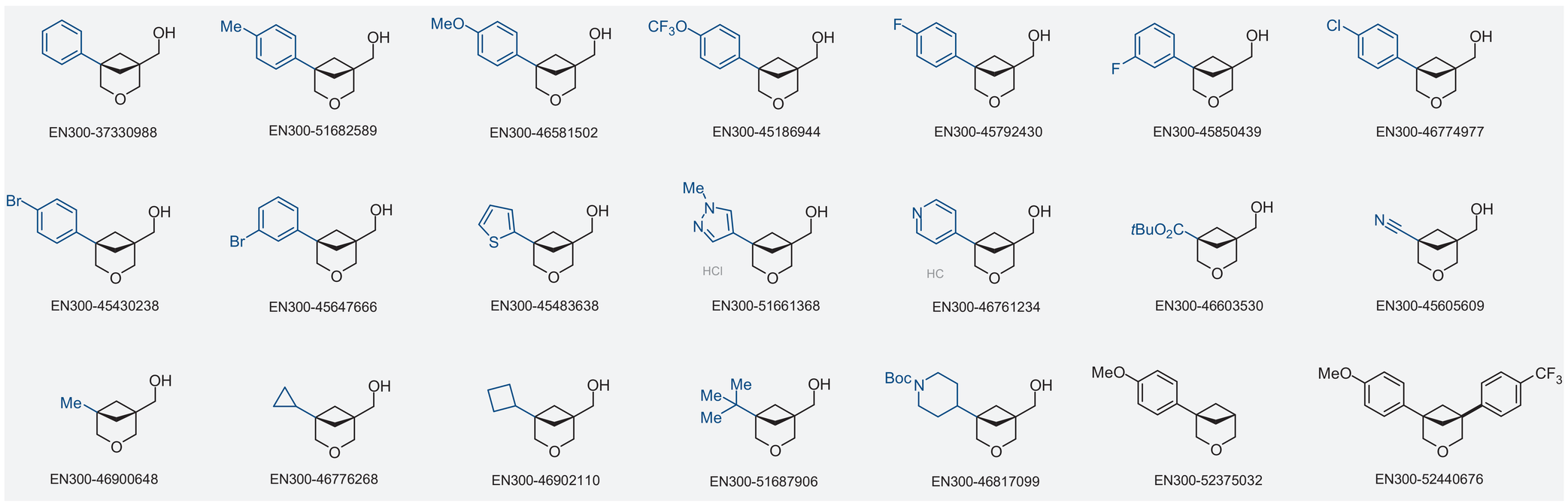


Properties of Sonidegib, and its saturated analogues



Physco-chemca propertes	Sonidegib	A	B
Soubty (μM)	6	4	34
ogD (7.4)	4.0	4.0	4.0
cogD (7.4)	6.8	6.2	4.8
Metaboc stabty			
CL_n (μLmn $^{-1}$ mg^{-1}	16	14	28
t_{12}(mn)	104	120	61
Caco-2			
P_{app} AB/BA [10 $^{-6}$] (cm/s)	2.8/0.9	*n.a.*	5.4/8.0
Effux rato	0.3	*n.a.*	1.5
P_{app} AB/BA wthVerapam [10 $^{-6}$] (cm/s)	1.4/0.9	*n.a.*	9.0/11.8
Effux rato wth Verapam	0.6	*n.a.*	1.3
Recovery AB/BA (%)	36/45	*n.a.*	43/70
Recovery AB/BA wth Verapam (%)	65/61	*n.a.*	51/77
Boogca actvty			
IC_{50} (HH sgnal)(nM)	1	616	96

Results



Contact

Pavel K. Mykhailiuk, Dr. Sci.
pavel.mykhailiuk@gmail.com, mykhailiukchem.org
Enamine Ltd, www.enamine.net
78 Winston Churchill St, 02094, Kyiv, Ukraine

References

1. R. D. Taylor et al., *J. Med. Chem.* **2014**, *57*, 5845-5859
2. F. Lovering et al., *J. Med. Chem.* **2009**, *52*, 6752-6756
3. N. Frank et al., *Nature* **2022**, *611*, 721-726