Design and synthesis of new sp2-sp3 hybrid fragments using the Debus-Radziszewski imidazole reaction

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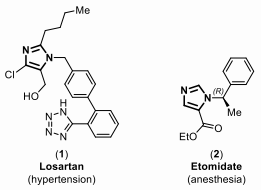
Introduction

Fragment-Based Drug Design (FBDD) has evolved into an established methodology for the identification of small molecules and the development of new drug candidates. At SpiroChem, we use our knowledge and expertise to continuously design and synthesize readily available sp^3-enriched fragment libraries to support Life Sciences companies in exploring new chemical spaces and generating IP-protected starting points for drug discovery programs.

The initial synthesis of these fragments should be straightforward and modulable to generate diversity for the screening studies and facilitate further optimization *via* a synthetically useful platform. The use of multicomponent reactions (MCRs) is a highly versatile strategy to access three-dimensional scaffolds. In addition, small aliphatic rings and bicyclo[x.y.z]alkanes are nowadays extensively used in medicinal chemistry as a useful tool to « **escape from flatland** ».[1]

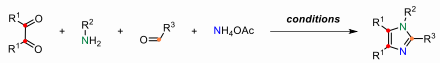
Imidazole derivatives are biologically active and pharmacologically important heterocycles that are core scaffolds of FDA-approved drugs, *e.g.* Losartan (**1**), Etomidate (**2**). In this context, we used the *Debus-Radziszewski* reaction to access bis- and tetra-substituted imidazole derivatives which will be evaluated as sp^2-sp^3 hybrid fragments.[2]



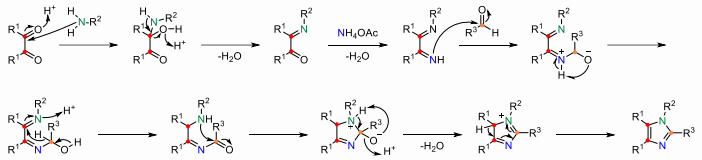
(**1**) **Losartan** (hypertension)

(**2**) **Etomidate** (anesthesia)

General Scheme and Mechanism

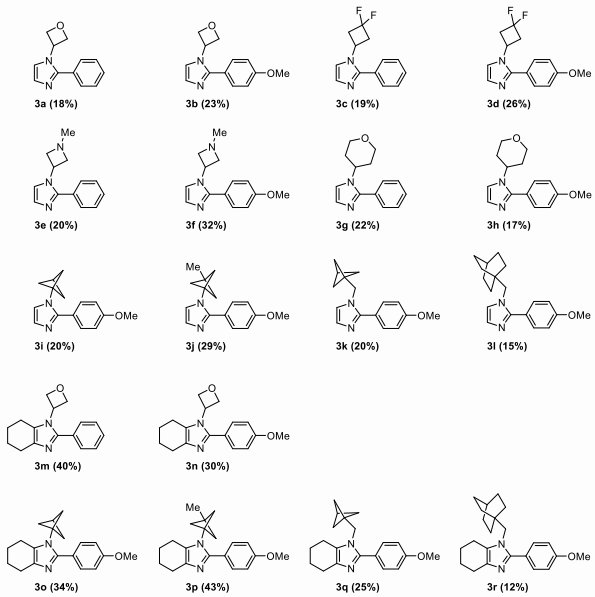


Reaction conditions:
1,2-diketone (2.0 equiv.), amine (1.0 equiv.), aldehyde (2.0 equiv.), ammonium acetate (2.0-3.0 equiv.), MeOH [0.30M], 80°C (sealed tube), 16 hrs.



Scope and Limitations

We first investigated the scope of the reaction using aqueous 40% glyoxal, benzaldehyde derivatives, and amines on 4-membered rings (such as oxetane (**3a**, **3b**) fluorinated cyclobutane (**3c**, **3d**), and *N*-methyl azetidine (**3e**, **3f**)) and on a 6-membered ring (such as tetrahydropyran (**3g**, **3h**)). The pure disubstituted imidazole derivatives were generally isolated in modest yields (from **17%** to **32%**). Moreover, we also investigated bulky bicyclo[1.1.1]pentane and bicyclo[2.2.2]octane amino derivatives (**3i** to **3l**): the yields were low (from **15%** to **29%**). We next used 1,2-cyclohexanedione to access tetrasubstituted imidazole derivatives: fragments containing an oxetane moiety (**3m**, **3n**) were isolated in acceptable yields (**40%** and **30%** respectively). In addition, we were able to incorporate bicyclo[1.1.1]pentane (**3o** to **3q**) and bicyclo[2.2.2]octane (**3r**) moieties (from **15%** to **29%**) on this imidazole core.



PhysChem Profiles Relevant to Medicinal Chemistry

The detailed physicochemical properties of the fragments were accessed using our fully automated Pion Sirius T3. The **pKa** value was obtained by pH-metric titration. **LogD** was determined potentiometrically by using the « shake-flask » method, which consists of dissolving part of the solute in question in a volume of *n*-octanol and water, then performing pH-titration. **LogP** was determined as the value of logD at a pH where the molecule was completely not ionized. The **log$D_{7,4}$** value was determined by calculation from the values of the logD obtained previously at pH 7.4, considering the concentration of ionized molecules. The **aqueous solubility** was measured using the « CheqSol » method developed by Pion.

Fragment	MW (g.mol^{-1})	pKa	logP	Log$D_{7.4}$	Aqueous Solubility
3a	200.2	6.15	1.44	1.41	5.0 mM
3b	230.2	6.48	1.40	1.35	2.7 mM
3c	234.2	6.24	2.35	2.32	0.7 mM
3d	264.2	6.65	2.30	2.23	0.5 mM
3e	213.2	5.48	0.24	1.75	1.5 mM
		7.47	3.40		
3f	243.3	5.66	-0.68	1.54	2.0 mM
		7.23	3.18		
3g	228.3	6.67	1.38	1.35	2.0 mM
3h	258.3	6.84	1.00	0.99	1.0 mM
3i	240.3	n.d.	n.d.	n.d.	n.d.
3j	254.3	n.d.	n.d.	n.d.	n.d.
3k	254.3	n.d.	n.d.	n.d.	n.d.
3l	296.4	n.d.	n.d.	n.d.	n.d.
3m	254.3	7.10	2.44	2.36	37 µM
3n	284.3	7.38	2.13	2.02	180 µM
3o	294.4	7.73	4.60	4.23	3.3 mM
3p	308.4	7.57	4.80	4.43	4.3 µM
3q	308.4	8.00	4.15	3.87	633 µM
3r	350.5	n.d.	n.d.	n.d.	n.d.

Our new fragments are mainly following the « rule of three » concept,[3] in which the molecular weight of a fragment is ≤300, the clogP is ≤3, and the number of hydrogen bond donors and acceptors is ≤3.

Conclusion and Outlook

A small **fragment library** focused on new sp^2-sp^3 hybrids containing 4-membered rings (such as cyclobutane, azetidine and oxetane), 6-membered rings (such as tetrahydropyran) as well as bicyclo[1.1.1]pentane moieties was generated using the *Debus-Radziszewski* reaction. Additionally, key relevant physicochemical properties (**pKa**, **logP**, **log$D_{7,4}$** and **aqueous solubility**) were measured to validate that the designed fragments generally followed the widely accepted « rule of three » concept. With these preliminary studies, we identified the scope and limitations of this multi-component reaction for Fragment-Based Drug Design. We are currently applying this methodology to the synthesis of new bicyclic hybrid scaffolds and building blocks ready for DNA-encoded libraries.

References

[1] Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752-6756 ; Lovering, F. *Med. Chem. Commun.* **2013**, 4, 515-519.
[2] Debus, H. *Ann. Chem. Pharm.* **1858**, 107, 199-208 ; Radzisewski, B. *Ber. Dtsch. Chem. Ges.* **1882**, 15, 2706-2708.
[3] Congreve, M.; Carr, R.; Murray, C. W.; Jhoti, H. *Drug Discov. Today* **2003**, 8, 876-877 ; Jhoti, H.; Williams, G.; Rees, D. C.; Murray, C. W. *Nature Rev. Drug Discov.* **2013**, 12, 644-645.