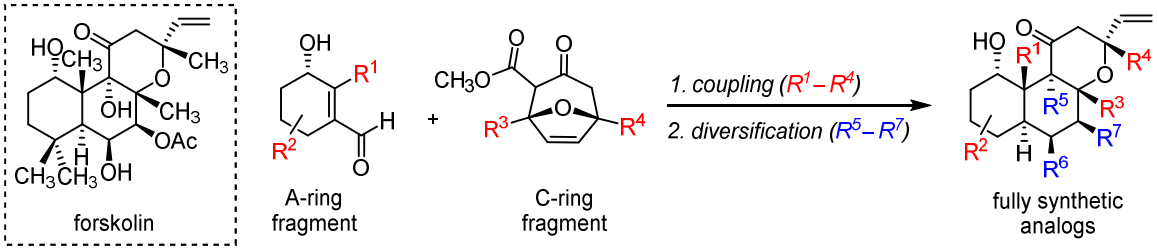
Toward a Flexible Synthesis of Novel Forskolin Analogs

Paweł Marcin Szczepanik,[1,2] Andrey Mikhaylov,[1,2] Jakub Švenda*[,1,2]

[1]*Department of Chemistry, Masaryk University, Kamenice 5, 625 00 Brno*
[2]*International Clinical Research Center, St. Anne's University Hospital, Pekařská 53, 656 91 Brno*
e-mail: szczepanik89@gmail.com, svenda@chemi.muni.cz

Forskolin is a naturally occurring diterpene commonly used as a tool in the biomedical research and also as a precursor to the clinically approved drug colforsin. Forskolin was shown to work by stimulating various isoforms of the enzyme adenylyl cyclase, which catalyze the conversion of ATP (adenosine triphosphate) to cAMP (cyclic adenosine monophosphate).[1] The identification of forskolin analogs with improved selectivity toward a subset of these isoforms has been one of the non-trivial challenges in the research on adenylyl cyclases.

The aim of our work is to develop a flexible synthetic route that would enable the preparation of a series of novel forskolin analogs not accessible by semisynthesis or through the published fully synthetic approaches.[2-7] Following a plan based on a convergence of the A-ring and C-ring fragments ('*coupling*') paired with a late-stage functionalization ('*diversification*'), we have been able to alter the structure of this natural product at multiple positions. The isoform selectivity profile of all newly synthesized forskolin analogs is being examined against a complete panel of membrane-bound adenylyl cyclases.



1 Dessauer, C. W.; Watts, V. J.; Ostrom, R. S.; Conti, M.; Dove, S.; Seifert, R. *Pharmacol. Rev.* **2017**, *69*, 93–139.
2 Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8115–8116.
3 Hashimoto, S.; Sakata, S.; Sonegawa, M.; Ikegami, S. *J. Am. Chem. Soc.* **1988**, *110*, 3670–3672.
4 Corey, E. J.; Jardine, P. da S.; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3672–3673.
5 Delpech, B.; Calvo, D.; Lett, R. *Tetrahedron Lett.* **1996**, *37*, 1015–1018.
6 Hylse, O.; Maier, L.; Kučera, R.; Perečko, T.; Svobodová, A.; Kubala, L.; Paruch, K.; Švenda, J. *Angew. Chem. Int. Ed.* **2017**, *56*, 12586–12589.
7 Thomas, W. P.; Schatz, D. J.; George, D. T.; Pronin, S.V. *J. Am. Chem. Soc.* **2019**, *141*, 12246–12250.