REGIOSPECIFIC SYNTHESIS OF 2,3-DISUBSTITUTED INDOLES FROM ISATINS

Artur ULIKOWSKI[1]*, Anna JAROMIN[2], Giorgia BRANCOLINI[3], Luca BELLUCCI[4], Bartłomiej FURMAN[1]

[1]*Institute of Organic Chemistry PAS, Kasprzaka 44/52, 01-224, Warsaw*
[2]*Department of Lipids and Liposomes, Faculty of Biotechnology, University of Wroclaw; Joliot-Curie 14A, 50-383 Wroclaw*
[3] *CNR-NANO S3, Institute of Nanoscience, via Campi 213/A, 41125 Modena, Italy*
[4] *UNIMORE – University of Modena and Reggio Emilia, via Campi 183, 41125 Modena, Italy*
* *aulikowski@icho.edu.pl*

Indoles represent a structural element in a myriad of natural products and biologically active molecules.[1-3] Of special importance are 2,3-disubstituted indoles (Fig. 1).[4]

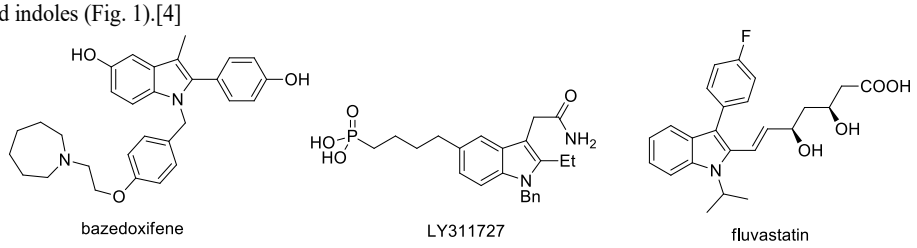
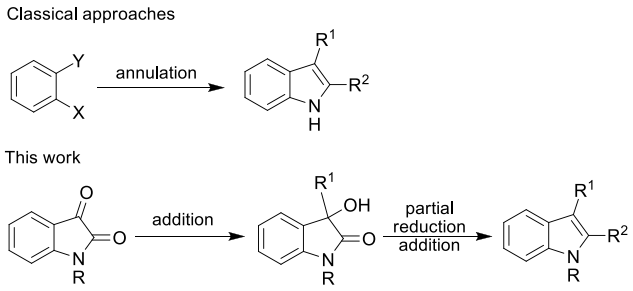


Fig. 1 Selected bioactive compounds containing a 2,3-disubstituted indole moiety

Thus, a number of methods for their synthesis have been described.[5-7] However, these are often hampered by a number of limitations: they often offer poor regioselectivity and suboptimal functional group tolerance. Also, they can normally be adapted to the procurement of a small subclass of indoles only. We have developed an approach to 2,3-disubstituted indoles overcoming these obstacles.[8]



Scheme 1. Different approaches to the synthesis of indoles

By selectively activating the amide carbonyl in isatin-derived oxindoles (Scheme 1), we obtained a number of the title compounds in a regiospecific and functional group-tolerant manner. The methodology is normally characterized by excellent yields. The reaction proceeds by chemoselective partial reduction of the amide moiety to an iminium salt and a subsequent nucleophilic addition followed by dehydration, which furnishes the target indole. A number of nucleophiles, including C- and S-nucleophiles, have been examined.

The obtained compounds were studied towards acetylcholinesterase (AChE) inhibitory activity, as the indole skeleton is often seen in the structure of enzyme inhibitors. Cholinesterase inhibitors are used in the treatment of Alzheimer's disease, increasing available acetylcholine by decreasing the AChE activity. For the tested agents, properties like logP, logBBB (Blood-Brain Barier penetration) and Caco2 permeabilities were also calculated. Based on the predicted values, only two of them are able to penetrate into the CNS (central nervous system).

Molecular docking was performed on the whole set of the syntesized indole derivatives, resulting in a wide range of AChE inhibitory activity. Molecular docking binding interactions reported the lowest energy conformations of the syntesized compounds and the key amino acid residues at the active binding site of AChE. The current synergy between computations and experiments provided the identification of the indole derivatives exhibiting the highest inhibitory activity. The presented results will provide theoretical guidance for further modification and optimization of the indole derivatives.

Acknowledgements

G.B. and L.B. acknowledge Stefano Corni for fruitful discussions. A.U. and B.F. gratefully acknowledge financial support provided by the National Science Centre, grant OPUS 2013/11/B/ST5/01188.

References:

[1] V. Sharma, P. Kumar, D. Pathak, J. Heterocycl. Chem., 47 (2010) 491.
[2] N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma, E. H. Choi, Molecules 18 (2013) 6620.
[3] M. Ishikura, T. Abe, T. Choshi, S. Hibino, Nat. Prod. Rep. 30 (2013) 694.
[4] J. M. Pawlak, V. V. Khau, D. R. Hutchison, M. J. Martinelli, J. Org. Chem. 61 (1996) 9055.
[5] A. Arcadi, S. Cacchi, V. Carnicelli, F. Marinelli, Tetrahedron 50 (1994) 437.

[6] R. C. Larock, E. K. Yum, M. D. Refvik, J. Org. Chem. 63 (1998) 7652.
[7] X. Dou, W. Yao, S. Wen, Y. Lu, Chem. Commun. 50 (2014) 9469.
[8] A. Ulikowski, B. Furman, Org. Lett. 18 (2016) 149.

The form of presentation proposed by the Author:
poster