Oxadiazolone-based Pictet-Spengler-type Reaction for the Synthesis of Bioactive and Fluorescent Pyrrole-fused 3-Aminoisoquinolines

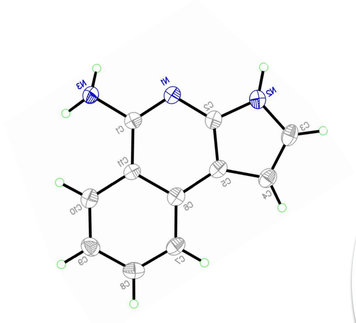
Zhu, W. F.;[a] Franz, H. M.;[a] Krämer, A.;[a,b] Empel, C.;[c] Koenigs, R. M.;[c] Knapp, S.;[a,b] Proschak, E.;[a,d,‖] Hernandez-Olmos, V.[a,d,‖]

[a] Institute of Pharmaceutical Chemistry, Goethe University Frankfurt, Max-von-Laue-Str. 9, 60438 Frankfurt am Main, Germany.
[a] Structural Genomics Consortium (SGC), Buchmann Institute for Molecular Life Sciences (BMLS), 60438 Frankfurt am Main, Germany
[c] RWTH Aachen University, Institute of Organic Chemistry, Landoltweg 1, 52074 Aachen, Germany.
[d] Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Theodor-Stern-Kai 7, 60596 Frankfurt am Main, Germany.

Abstract

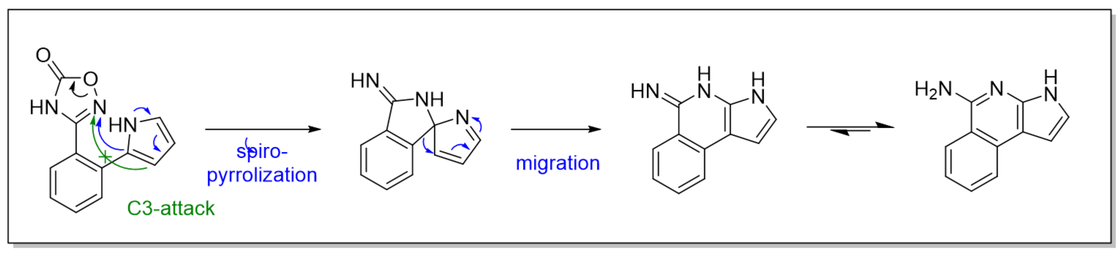
Heterocycles represent the most common structural motif in approved drugs. Synthetic methods that enable the access to novel heterocycles advance the scope of these scaffolds for drug discovery. For this purpose, the Pictet-Spengler reaction is being extensively utilized in the synthesis of alkaloid scaffolds. Typically, a nucleophilic aromatic ring undergoes intramolecular condensation with an iminium ion under acid catalysis. With our ongoing interest in oxadiazolone-based annulations, we investigated in this study the annulation with pyrroles and found that oxadiazolones undergo as the electrophile a base-mediated Pictet-Spengler-type reaction, affording pyrrole-fused 3-aminoisoquinolines. For the mechanistic pathway of the actual Pictet-Spengler reaction both the direct cyclization and the formation of the spiro intermediate are being discussed. In the herein described Pictet-Spengler-type reaction, the structure of the selectively formed isomer indicate that pyrroles selectively undergo the spiropyrrolization pathway with oxadiazolones. Furthermore, these undescribed heterocycles possess bioactive and fluorescent properties, which make them ideal for applications in chemical biology.

Crystal structure



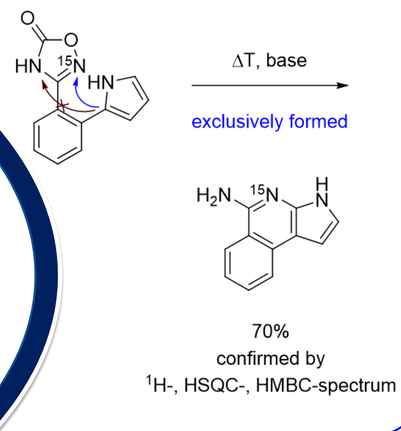
X-ray crystal structure indicate spiropyrrolization

Oxadiazolone-based Pictet-spengler-type rearrangement with pyrroles

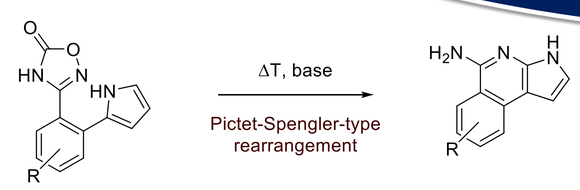


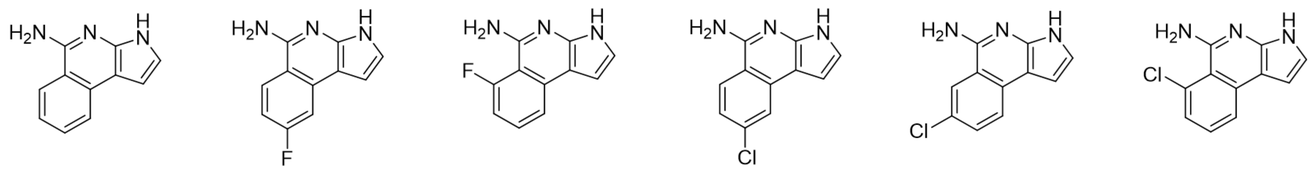
• X-ray crystal structure • ^{15}N-incorporation • Kinase-privileged scaffold • Small-molecule fluorophore

^{15}N incorporation



Substrate Scope





FZ296
73%/66%*
*1 g (4.40 mmol) scale

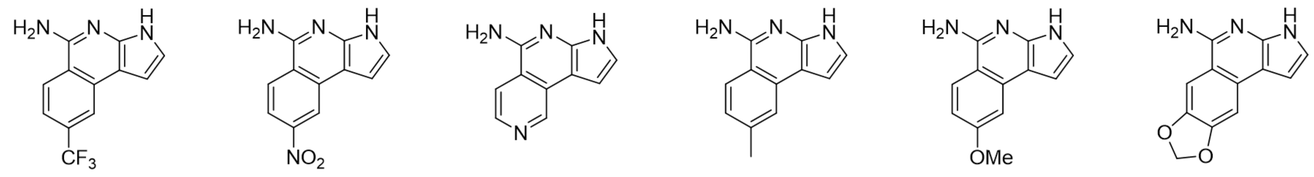
48%
(120 °C)

60 %

53%

53%

0%



43%

0%

33%

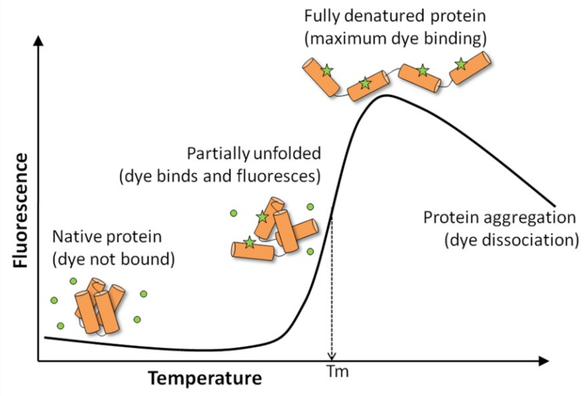
63%

73%

50%

Bioactive properties

DSF screening

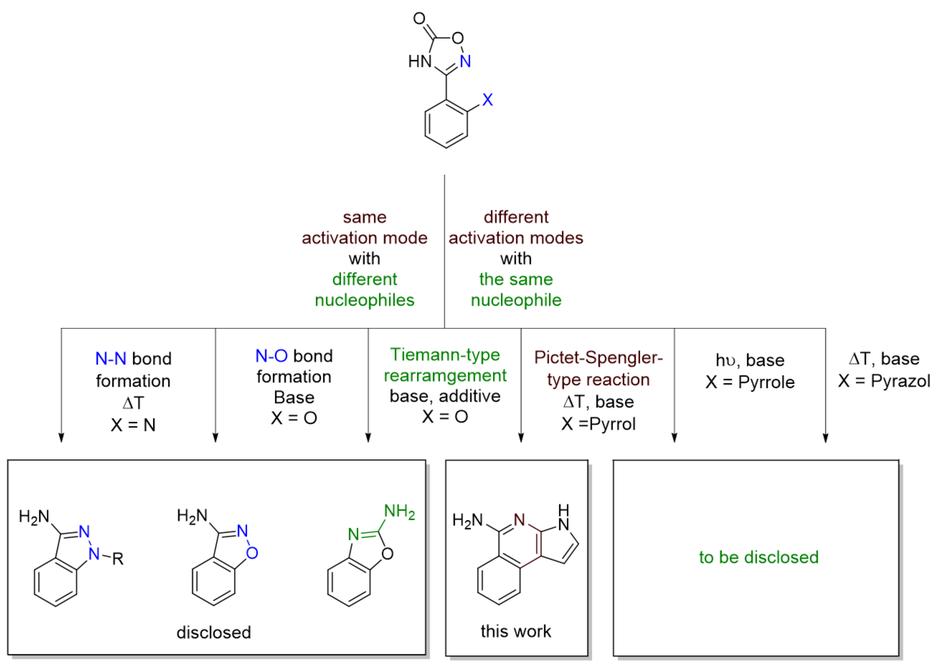


Biotium GloMelt™ kits flyer

	FZ296
BMP2K	11,46
BMPR2	2,95
BRD4	0,99
CAMK1G	5,23
CAMK2D	0,30
CK2A2	3,20
DAPK1	1,90
DMPK	2,90
DYRK2	5,70
EPHA7	3,90
FGFR2	1,80
GSG2	1,70
MAP3K5	9,50
PCTK1	0,40
PHKG2	3,30
PLK4	2,60
STK6	6,00
ULK3	5,60

This assay relies on the correlation between the affinity of a ligand and the thermal stabilization of the protein of interest. **FZ296** exhibits substantial binding towards various kinases.

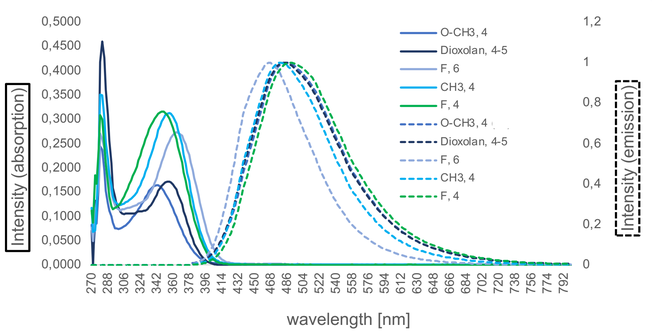
Conclusion



We herein postulate that oxadiazolones are electrophiles undergoing a Pictet-Spengler-type mechanism. The resulting heterocycles demonstrate both biological and fluorescent properties, making them promising candidates for chemical biology.
This represents the third successful application from our group of oxadiazolones as precursors for the synthesis of N-heterocycles.

Fluorescent properties

Of note is the fluorescence given the small molecular weight of the heterocycles and the substantial stokes shift. Electron-withdrawing substituents generally lead to a bathochromic shift.



DPBS buffer (pH = 7), c = 0.1 mM.