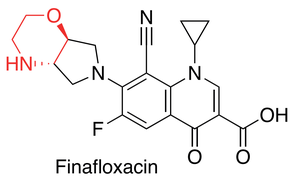
Oxazepines fused with another heterocycles by e or f edge

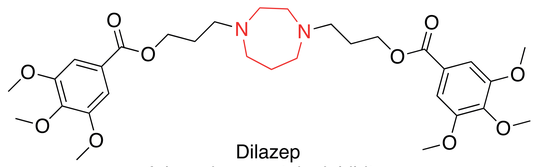
O. Kaliberda, E. Zarudnitskii, D. Volochnyuk, S. Ryabukhin

Background of the project

- 1,4-Oxazepane ring[1-3] can be regarded as a homologue of morpholine and an analog of 1,4-diazepane. Both cores are widespread in medicinal chemistry.



Finafloxacin
Antibiotic

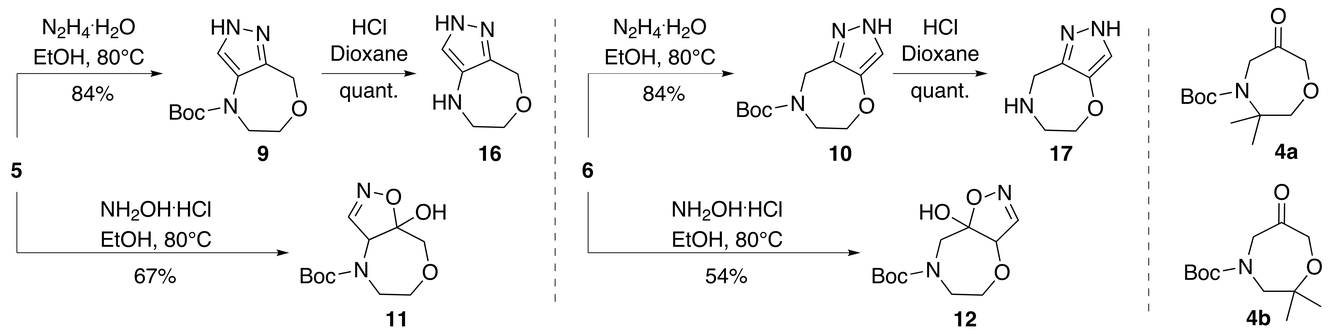


Dilazep
Adenosine reuptake inhibitor

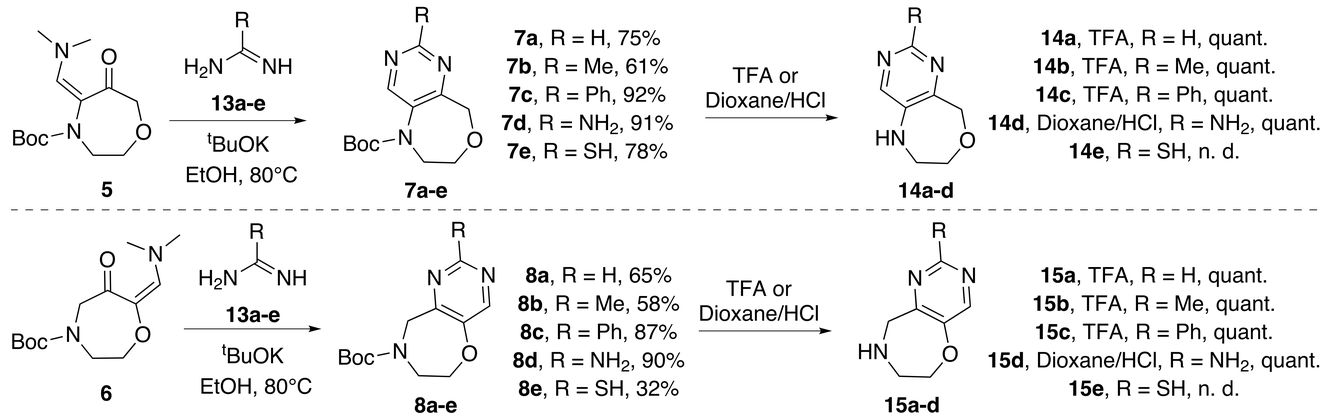
- Alkene **3** was obtained from compounds **1** and **2** *via* [4+3]-cyclization and then oxidized with $NaIO_4/RuCl_3$ system to ketone **4**. Synthesis of the key intermediate **4** was scaled up to 300 g from a single run, the structure was proved by X-rays diffraction.
- After enamination of ketone **4** with DMF-DMA[4-5], enaminones **5** (major) and **6** (minor) were isolated in ca. 60:40 ratio.
- Finally, the products **5** and B were applied as 1,3-CCC-bielectrophilic reagents for production of fused heterocyclic systems **7-12**.

Scope and limitations

- Enaminones **5** and **6** entered [3+3]-annulation with amidines **13a-e** to give fused pyrimidines **7a-e** and **8a-e**, respectively. The reaction proceeded well with phenylamidine **13c** and guanidine hydrochloride **13d**, while yields with formamidine acetate **13a**, methylamidine **13b** and thiourea **13e** were moderate.
- The obtained Boc-protected products **7a-e** and **8a-e** were deprotected with either trifluoroacetic or hydrochloric acid. MedChem relevant building blocks **14a-d** and **15a-d** formed quantitatively. Unfortunately, organosulfur compounds **7e** and **8e** decomposed under acidic conditions.



- [3+2]-Annulation with hydrazine yielded the desired pyrazoles **9** and **10** that were quantitatively deprotected.
- Annulation with hydroxylamine under the same conditions stopped at semi-products **11** and **12**.



7a, R = H, 75%
7b, R = Me, 61%
7c, R = Ph, 92%
7d, R = NH_2, 91%
7e, R = SH, 78%

14a, TFA, R = H, quant.
14b, TFA, R = Me, quant.
14c, TFA, R = Ph, quant.
14d, Dioxane/HCl, R = NH_2, quant.
14e, R = SH, n. d.

8a, R = H, 65%
8b, R = Me, 58%
8c, R = Ph, 87%
8d, R = NH_2, 90%
8e, R = SH, 32%

15a, TFA, R = H, quant.
15b, TFA, R = Me, quant.
15c, TFA, R = Ph, quant.
15d, Dioxane/HCl, R = NH_2, quant.
15e, R = SH, n. d.

- The reaction was performed only with parent hydrazine, therefore interaction with its substituted derivatives are yet to be investigated. Moreover, dimethylated analogs of ketone **4** were obtained in multigram amounts (intermediates **4a** and **4b**). By contrast, syntheses of similar monomethylated analogs were not successful. The outcome can be explained by Thorpe-Ingold effect.

Contact

Sergey V. Ryabukhin, Prof. Dr. Sci.; s.v.ryabukhin@gmail.com,
Dmitriy M. Volochnyuk, Prof. Dr. Sci. d.volochnyuk@gmail.com.
Enamine Ltd, www.enamine.net
78 Winston Churchill St, 02094, Kyiv, Ukraine

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