ONE-POT SYNTHESIS OF 4,5-DISUBSTITUTED 2-AMINO-1*H*-IMIDAZOLES FROM MANNICH PRECURSORS

Zsófia Makra[1], Dr. László G. Puskás[1], Dr. Iván Kanizsai[1]

[1]*AVIDIN Ltd., Alsókikötő sor 11/D, 6726 Szeged, H-6726, Hungary*

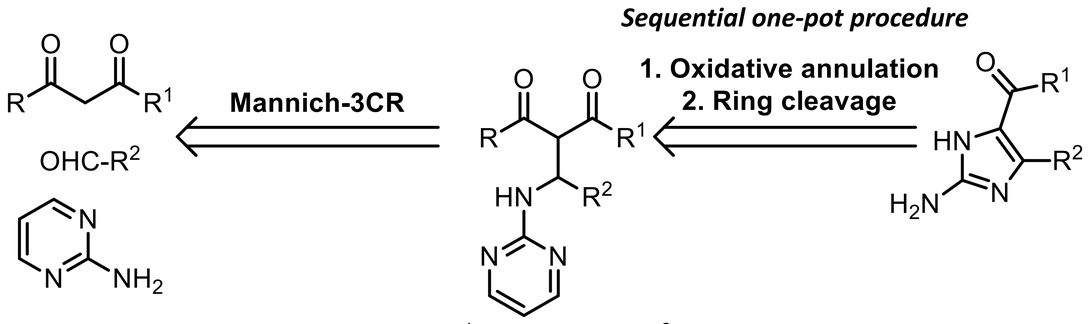
www.avidinbiotech.com

INTRODUCTION

The 2-aminoimidazole (2-AI) core is general motif occurring in marine alkaloids isolating from different species of sponge, in addition, excellent precursor for drug discovery studies.[1] Depending on the substitution pattern, some 2-AI-s possess wide range of biological activities, particularly (C5-carbonyl/carboxylate) 4,5-disubstituted scaffold.[2],[3] Numerous synthetic methodologies are known in the literature in regard to the preparation of the novel 4,5-disubstituted structures focusing on condensations or reductive cleavage protocol of imidazo[1,2-*a*]pyrimidine ring.[4],[5],[6]

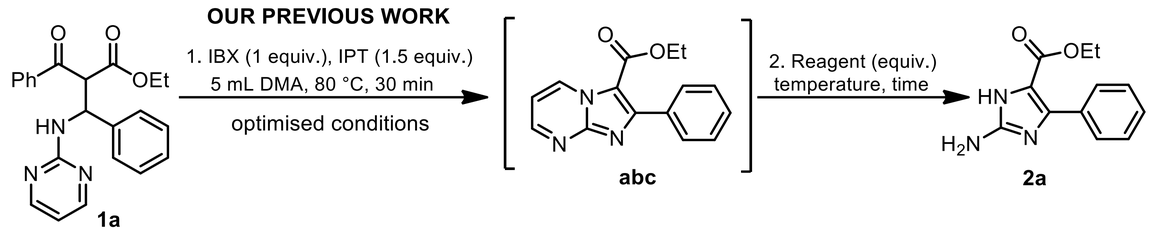
Our synthetic strategy is based on the multisynthetic pathway starting from Mannich-3CR followed by an oxidative intramolecular annulation then reductive cleavage sequence.

Our retrosynthetic strategy [7]



R= Ph or Me; R^1= OEt, Me, Ph; R^2= Alkyl, Aryl

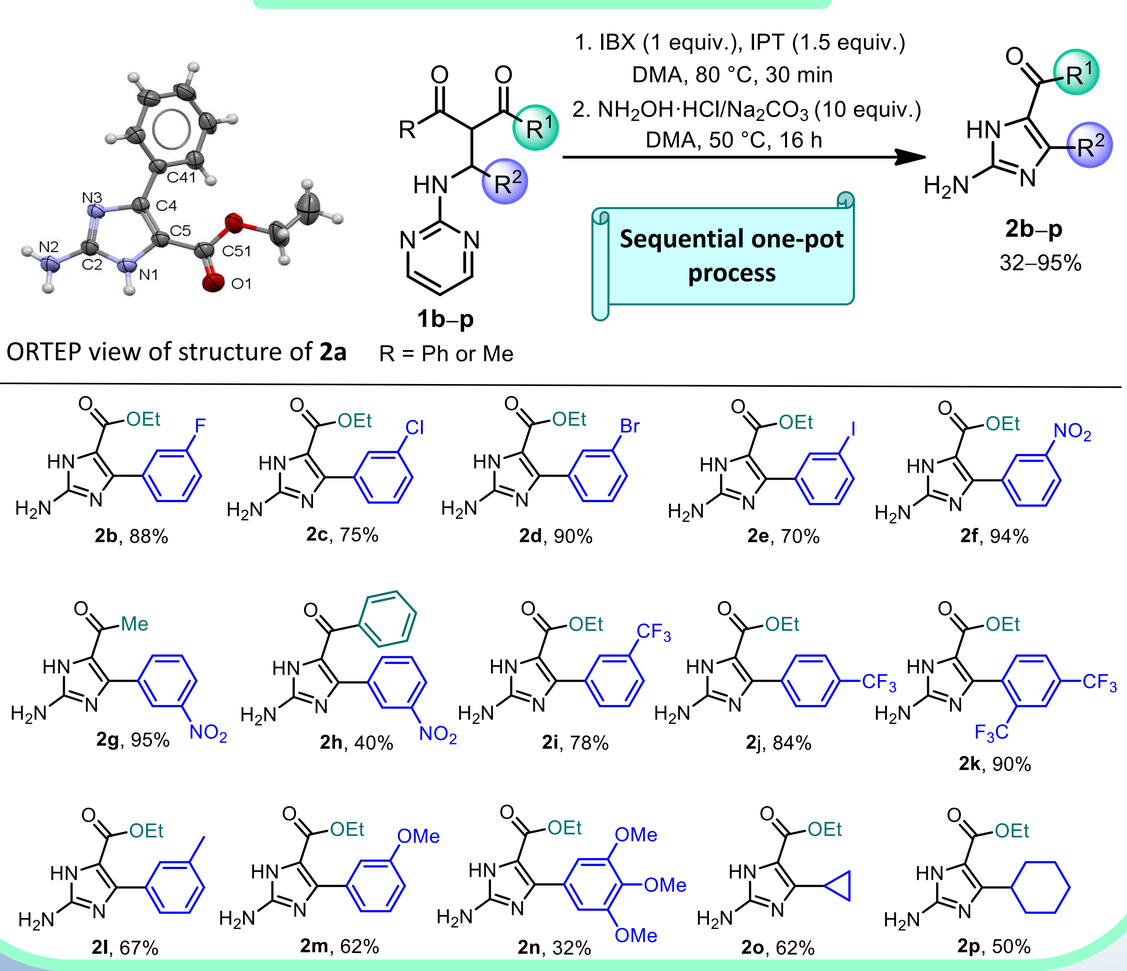
OPTIMIZATION OF THE ONE-POT PROTOCOL



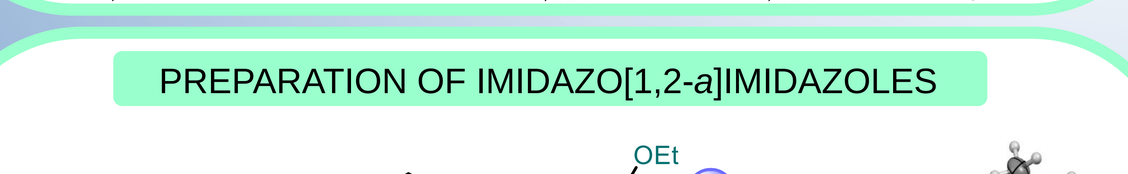
Entry	Reagent(s) (equiv.)	Temperature [°C]	Time [h]	Yield [%][a]
1	$NH_2NH_2.H_2O$ (4)	80	48	58[b]
2	$NH_2NH_2.H_2O$ (6)	80	16	74
3	$NH_2NH_2.H_2O$ (8)	80	1	78
4	$NH_2OH.HCl$/TEA (8/8)	80	16	67
5	$NH_2OH.HCl$/TEA (8/8)	50	16	80
6	$NH_2OH.HCl$/DIPEA (8/8)	50	16	50
7	$NH_2OH.HCl$/DBU (8/8)	500	16	65
8	$NH_2OH.HCl/Na_2CO_3$ (8/8)	50	16	82
9	$NH_2OH.HCl/Na_2CO_3$ (8/8)	50	16	78[c]
10	$NH_2OH.HCl/Na_2CO_3$ (8/8)	50	16	72[d]
11	***$NH_2OH.HCl/Na_2CO_3$ (10/10)***	***50***	***16***	***92***
12	$NH_2OH.HCl/Na_2CO_3$ (10/10)	rt	24	40[e]
13	$NH_2OH.HCl/Na_2CO_3$ (10/10)	50	16	60[f]

a) Isolated yields after column chromatography, full conversion (TLC); b) 75% conversion; c) Addition of sodium dithionite/TEA (3/3 equiv.); d) Addition of sodium thiosulfate pentahydrate/TEA (3/3 equiv.); e) 60% conversion; f) Reaction carried out in 10 ml DMA.

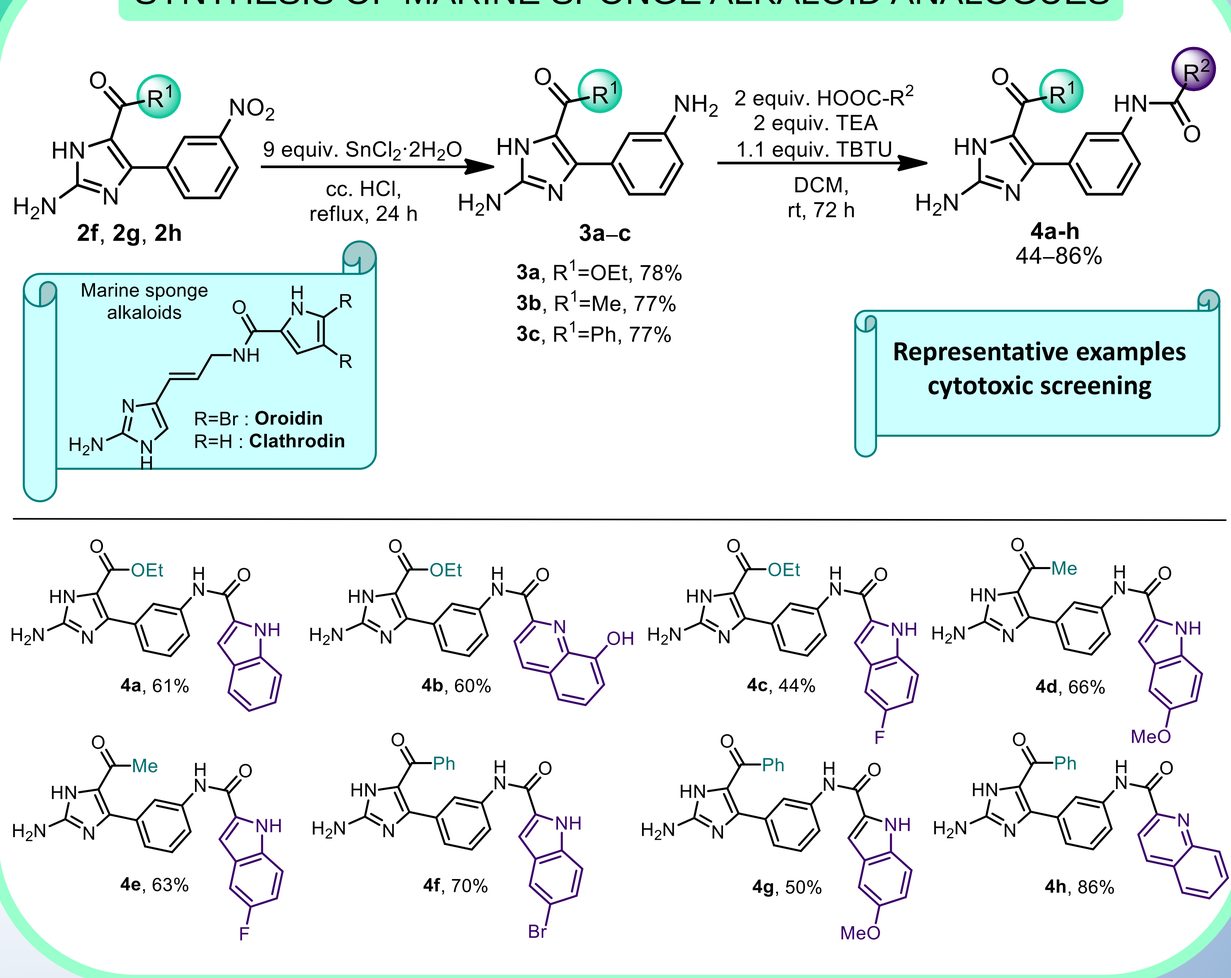
2-AI FRAGMENT LIBRARY

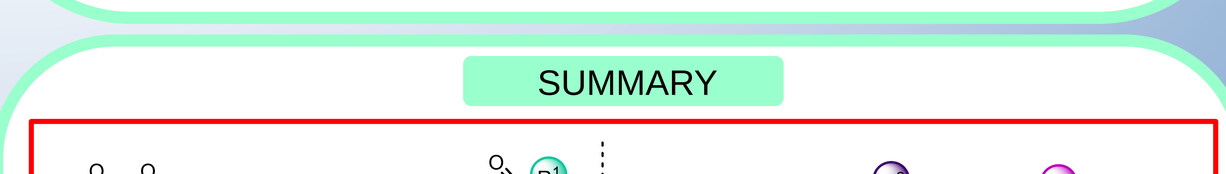


ORTEP view of structure of **2a** R = Ph or Me

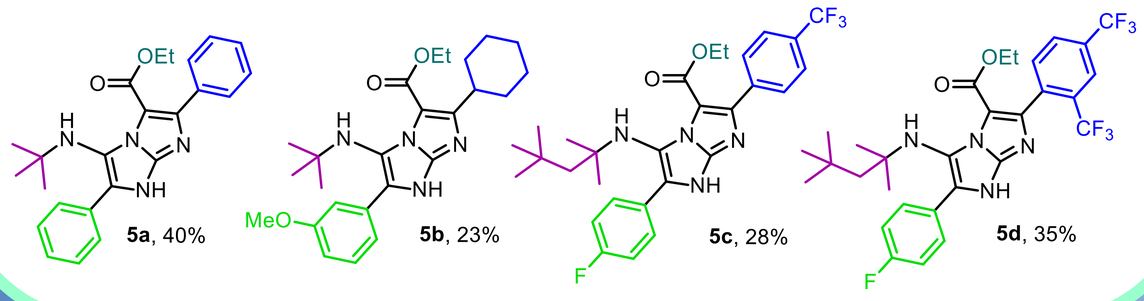


SYNTHESIS OF MARINE SPONGE ALKALOID ANALOGUES

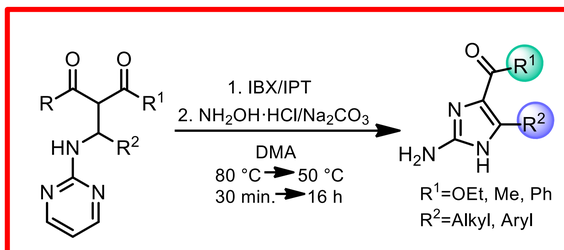




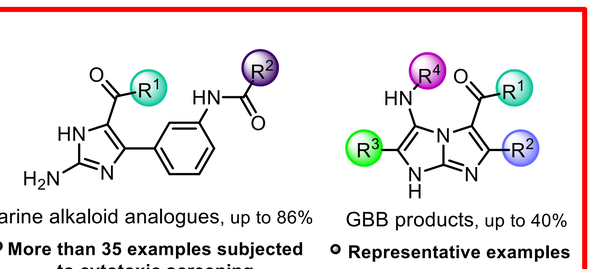
PREPARATION OF IMIDAZO[1,2-*a*]IMIDAZOLES



SUMMARY



- **Sequential one-pot reaction**
- **Mild reaction conditions**
- **Up to 95% isolated yields**



Marine alkaloid analogues, up to 86%

- **More than 35 examples subjected to cytotoxic screening**

R^1 = OEt, Me, Ph;
R^2 = indolyl, pyridyl, quinolyl

GBB products, up to 40%

- **Representative examples**

R^1 = OEt; R^2 = Ar, cycloalkyl;
R^3 = Ar; R^4 = alkyl

REFERENCES

[1] R. G. S. Berlinck, M. H. Kossuga, *Nat. Prod. Rep.* **2005**, *22*, 516–550.
[2] V. Chaudhary, J. B. Venghateri, H. P. S. Dhaked, A. S. Bhoyar, S. K. Guchhait, D. Panda, *J. Med. Chem.* **2016**, *59*, 3439–3451.
[3] A. S. Hogendorf, A. Hogendorf, R. Kurczab, J. Kalinowska-Tłuścik, P. Popik, A. Nikiforuk, M. Krawczyk, G. Satała, T. Lenda, J. Knutelska, et al., *Eur. J. Med. Chem.* **2019**, *179*, 1–15.
[4] A. Žula, D. Kikelj, J. Ilaš, *J. Heterocycl. Chem.* **2016**, *53*, 345–355.
[5] E. V. Babaev, *Stud. Nat. Prod. Chem.* **2017**, *52*, 69–113.
[6] D. S. Ermolat, E. P. Svidritsky, E. V Babaev, E. Van Der Eycken, *Tetrahedron Lett.* **2009**, *50*, 5218–5220.
[7] Zs. Makra, A. Bényei, L. G. Puskás, I. Kanizsai, *Eur. J. Org. Chem.* **2020**, *2020*, 7184–7196.