Synthesis of azepino[4,5-*b*]indol-4-ones by Ugi-type / free radical cyclization and in vitro studies as 5-Ht$_6$R ligands

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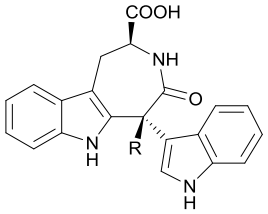
Summary

A series of novel 3-amide-azepino[4,5-*b*]indol-4-ones and 3-tetrazolyl-azepino[4,5-*b*]indol-4-ones were synthesized by Ugi-type / free radical cyclization in moderate to good yields. All products were tested in vitro for their binding properties on the 5-Ht$_6$R protein.

Introduction

Azepino[4,5-*b*]indol-4-one is the core of various naturally occurring products such as the malassezindoles (**1a**-**1b**),[1] Fig. 1.



1a, R = OH
1b, R = H

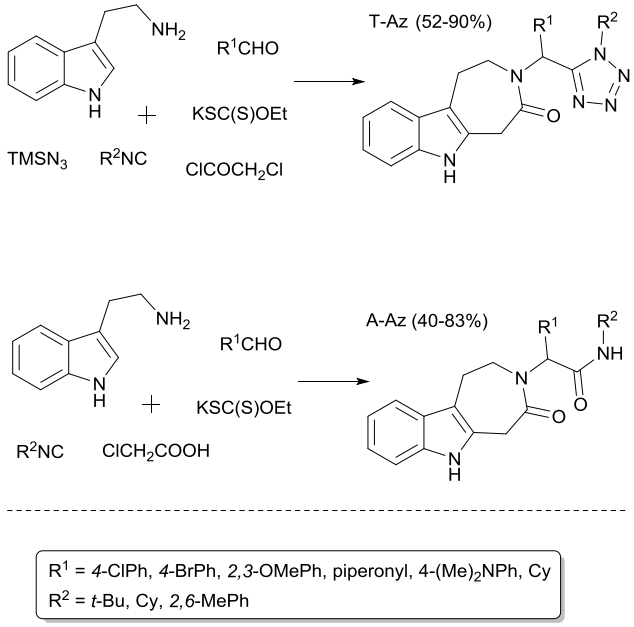
Fig. 1. malassezindoles.

Several stepwise methodologies toward azepino[4,5-*b*]indol-4-ones have been reported in which the last step has been the construction of the seven-membered ring, for example via S_EAr, Pd-catalyzed alkyne arylations, lactamizations, photocyclizations, or free radical cyclizations.

On the other side, tetrazoles are the core of various valued drugs such as the losartan, which exhibits a vasorelaxant activity acting as angiotensin II receptor antagonist. 5-substituted-1*H*-tetrazoles behave as metabolism resistant bioisosters of carboxylic acids as a result of their similar physicochemical properties such as the ability to present similar tautomeric forms. Several reports describe the preparation of compounds having the 1,5-DS-1*H*-T ring, mainly based on either, [2+3] dipolar cycloadditions between azides and cyanides,[2] or via Ugi-azide reaction.[3]

Results and discussion

The two series of azepino[4,5-*b*]indol-4-ones were successfully synthesized in moderate yields (52-90%) and (40-83%), respectively (Scheme 1). It is noteworthy that variations of yields depend little on the stereo-electronic nature of the isocyanide used as starting reagent.



Scheme 1. Synthesis of azepino[4,5-*b*]indol-4-ones

The main hypothesis in this work was that the 3-tetrazolyl-azepino[4,5-b]indol-4-ones ***T-Az*** and the 3-amide-azepino[4,5-*b*]indol-4-ones ***A-Az*** will show binding affinity on the 5-Ht_6R[4] (Table 1).

Table 1. Binding affinity *in vitro* of the 3-tetrazolylmethyl-azepino[4,5-b]indol-4-ones ***T-Az*** and the 3-acetamide-azepino[4,5-b]indol-4-ones ***A-Az*** on the 5-Ht_6R.

R^1	**R^2**	*Binding affinity*[a]	
		T-Az	***A-Az***
4-ClPh	*t-Bu*	*11 ± 3*	*42 ± 3*
4-ClPh	*Cy*	*17 ± 3*	*15 ± 4*
4-ClPh	*2,6-MePh*	*19 ± 2*	*21 ± 2*
4-BrPh	*t-Bu*	*57 ± 2*	*66 ± 4*
2,3-OMePh	*t-Bu*	*16 ± 3*	-
Piperonyl	*t-Bu*	*12 ± 2*	*07 ± 1*
4-(Me)2NPh	*t-Bu*	*01 ± 1*	*16 ± 1*
Cy	*t-Bu*	*02 ± 1*	*10 ± 2*
Cy	*2,6-MePh*	*03 ± 2*	*07 ± 3*
Methiothepin[b]		*~ 100*	

[a] % ± SD of radiolabeled ligand (^{3}H-LSD) displacement at 10 μM of the 5-Ht_6R;
[b] (+ control). n = 2.

All products were fully characterized by spectroscopic techniques such as NMR, HRMS and IR. Compound **T-Az-3** (R^1 = Cl; R^2 = 2,6-MePh) was crystallized and could be analyzed by X-ray (ORTEP)[5] (Fig. 2).

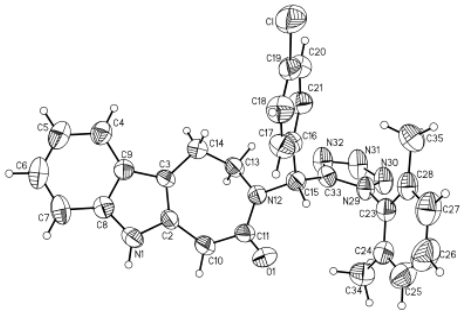


Fig. 2 ORTEP of compound **T-Az-3**

References

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[5] Cambridge Crystallographic Data Code: **948622**