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SECTION: *GENERAL ORGANIC SYNTHESIS*
SUBMISSION ID: *Sciforum-006353*

Synthesis of azepino[4,5-*b*]indol-4-ones by Ugi-type / free radical cyclization and *in vitro* studies as 5-Ht_6R ligands

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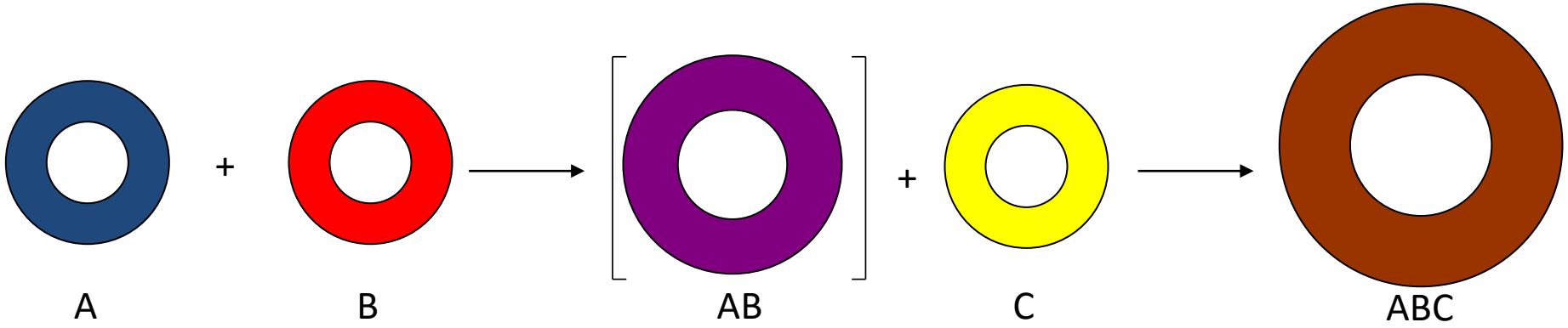
INTRODUCTION

MULTICOMPONENT REACTIONS



Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210.

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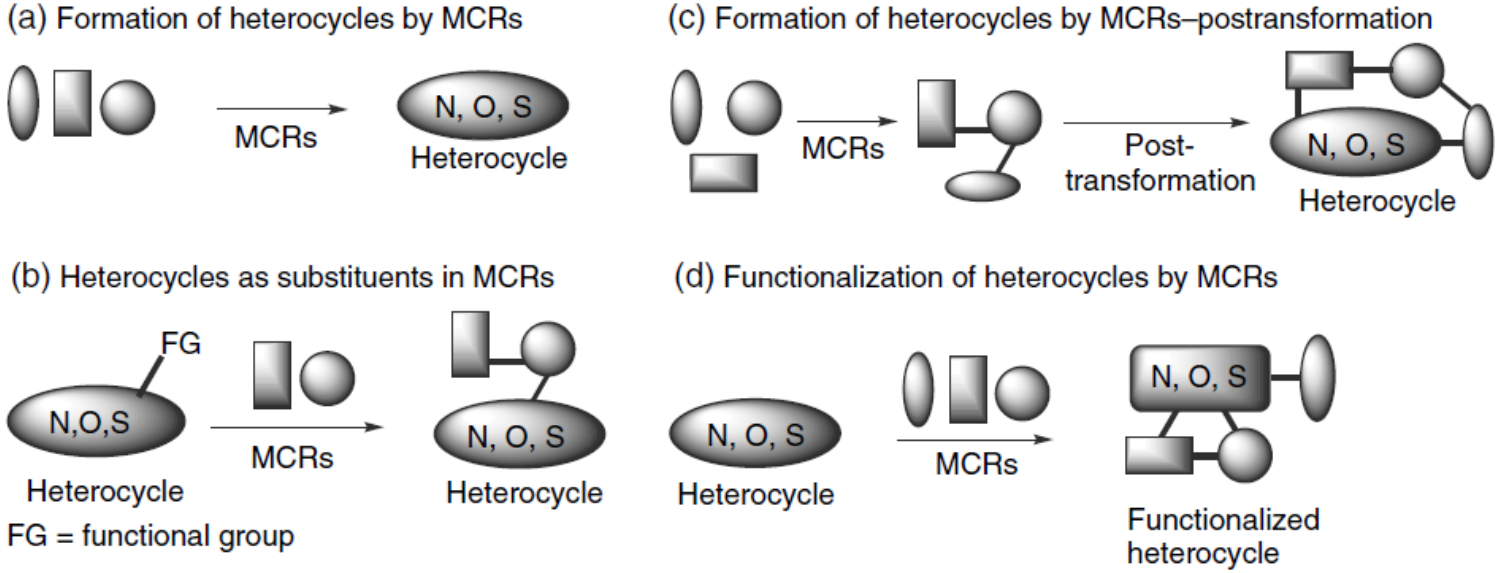
INTRODUCTION

MULTICOMPONENT REACTIONS IN HETEROCYCLIC CHEMISTRY

160 | *6 Functionalization of Heterocycles by MCRs*



Scheme 6.1 Roles of heterocycles in MCRs.

Zhu, J.; Wang, Q.; Wang, M.-X. *Multicomponent Reactions in Organic Synthesis*. Wiley-VCH. Weinheim **2015**. ISBN: 978-3-527-33237-3. Chapter 6.

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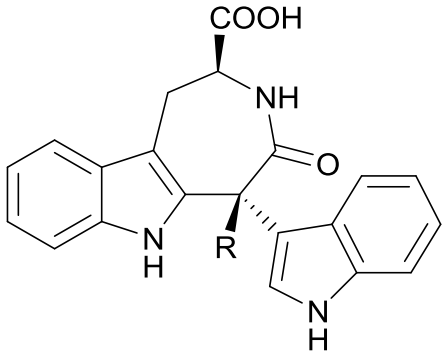
BACKGROUND

Malassezindoles: Natural products containing the azepino[4,5-*b*]indol-4-one core



1a, R = OH

1b, R = H

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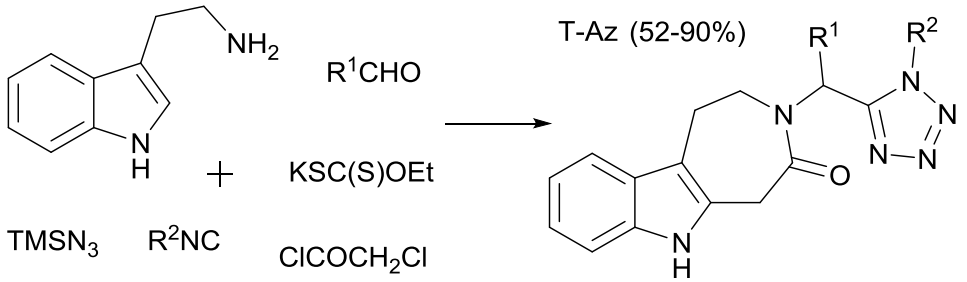
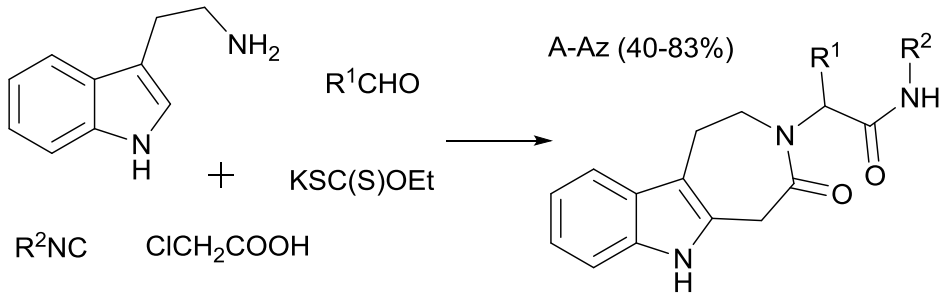
RESULTS

Synthesis of azepino[4,5-*b*]indol-4-ones via MCR / free radical cyclization





R^1 = *4*-ClPh, *4*-BrPh, *2,3*-OMePh, piperonyl, 4-$(Me)_2$NPh, Cy
R^2 = *t*-Bu, Cy, *2,6*-MePh

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RESULTS

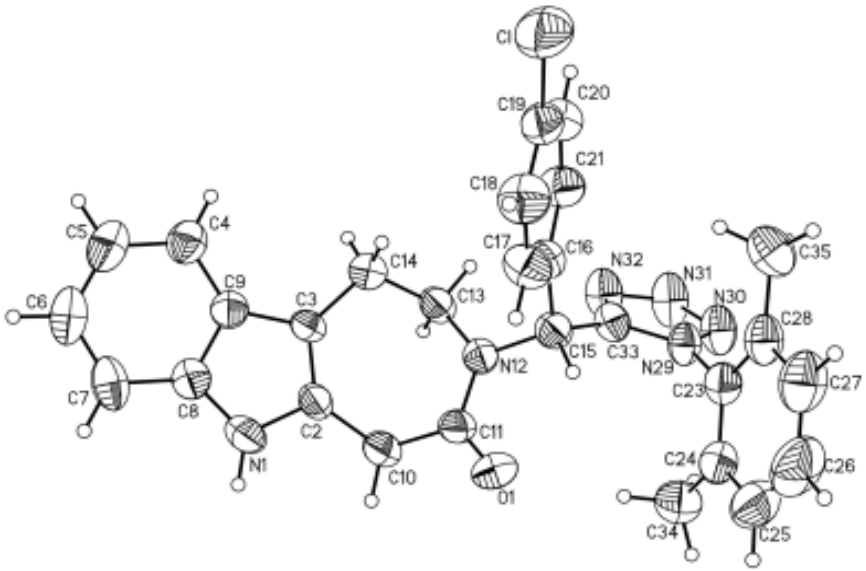
In vitro assays as 5-Ht$_6$R ligands

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$_6$R; [b] (+ control). n = 2.

RESULTS

ORTEP (*x-ray*) of the **T-Az-3** (R^1 = Cl; R^2 = 2,6-MePh)



Cambridge Crystallographic Data Code: **948622**

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CONCLUSION

• Eighteen novel compounds based on the azepino[4,5-*b*]indol-4-one moiety have been prepared in moderate to good overall yields

• The products exhibited moderate binding affinity on the 5-Ht_6R

• All products were characterized using spectroscopic methods such as NMR, IR and HRMS. In the same context, adequate crystals for one product were obtained in order to confirm its structure.