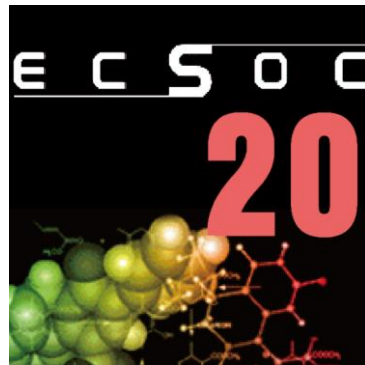


20th Electronic Conference on Synthetic Organic Chemistry 2016

Synthesis of 1-tetrazolyl-1,2,3,4-tetrahydroisoquinoline bound-type *bis*-heterocycles via oxidative-Ugi-azide

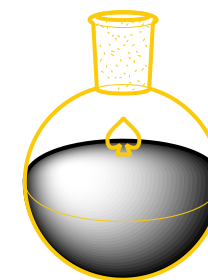
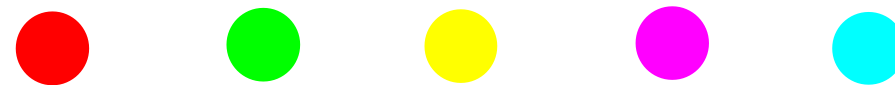
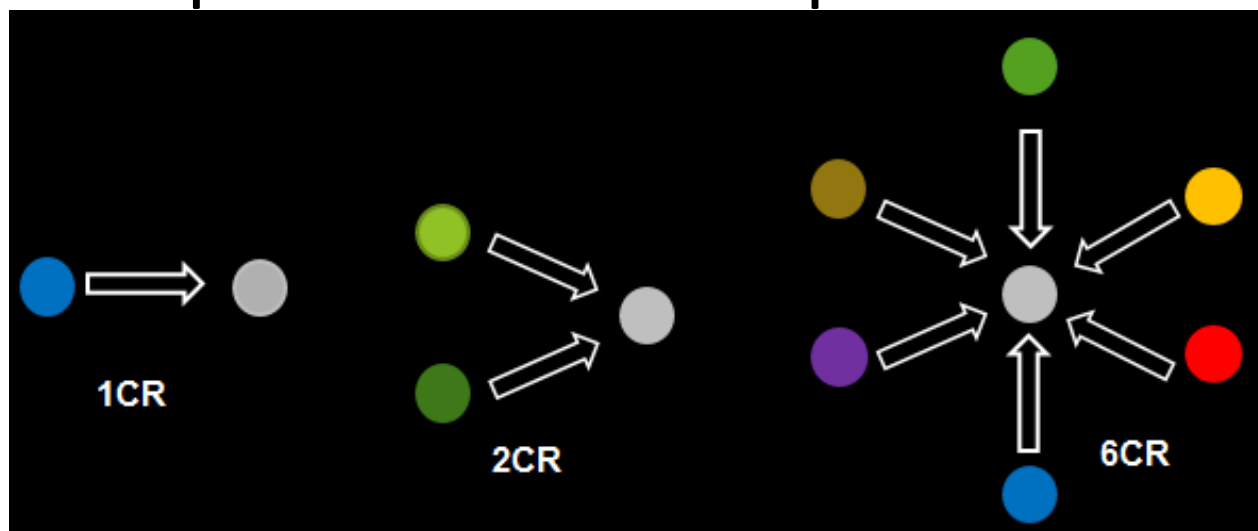
Manuel A. Rentería-Gómez, Alejandro Islas-Jácome,
Rocío Gámez-Montaño*

Departamento de Química, División de Ciencias Naturales y Exactas, Universidad de Guanajuato, Noria Alta S/N, Col. Noria Alta, Guanajuato, C.P. 36050, Gto., México.

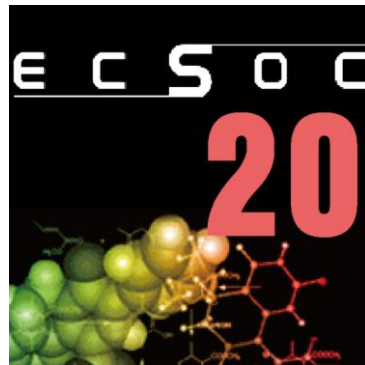


Multicomponent reactions (MCR)

MCR are one-pot processes employing more than two starting materials, where most of the atoms of the reagents are incorporated into final products

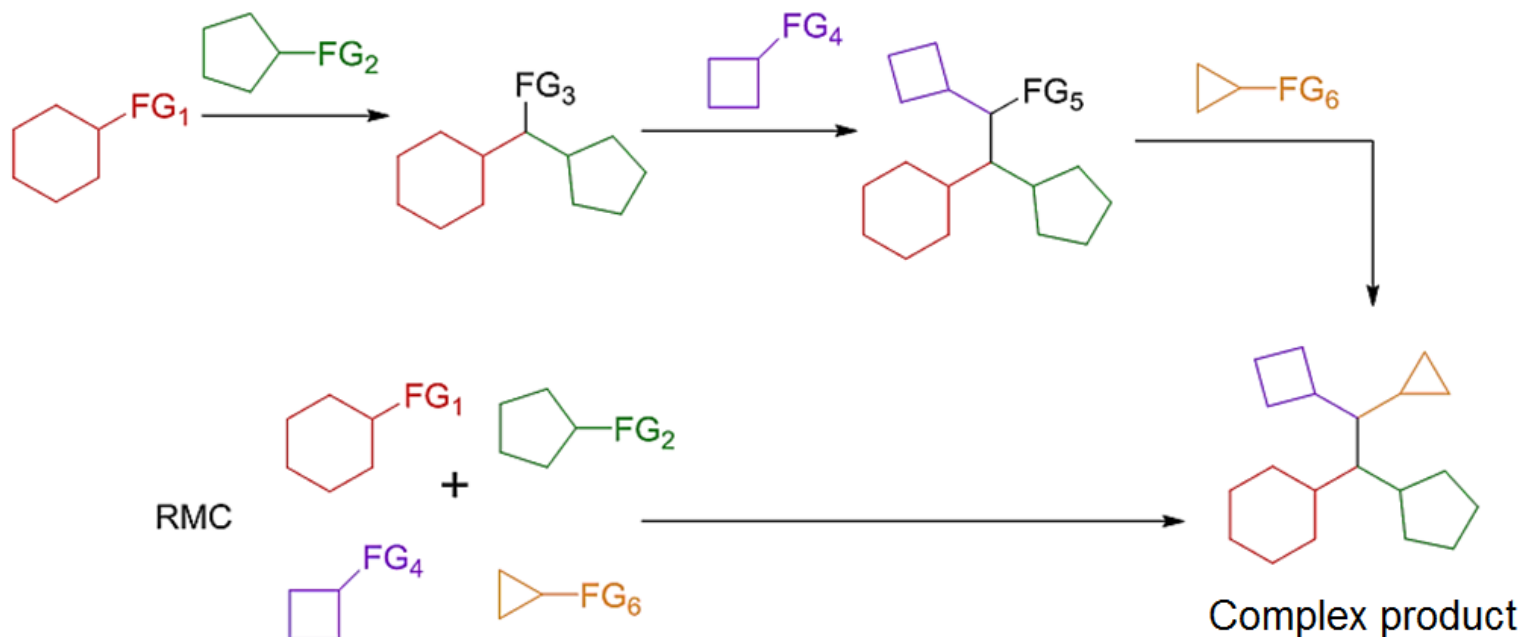


¹ (a) A. Dömling, I. Ugi, *Angew. Chem. Intl. Ed.* **2000**, 39, 3168. (b) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, 112, 3083–3135



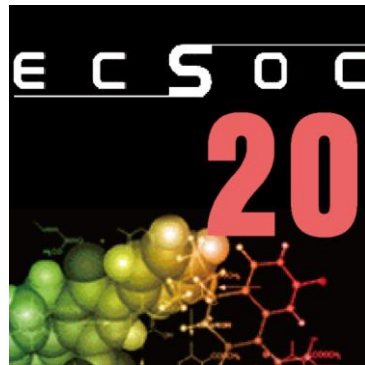
Multistep reaction vs MCR's

Multistep reaction

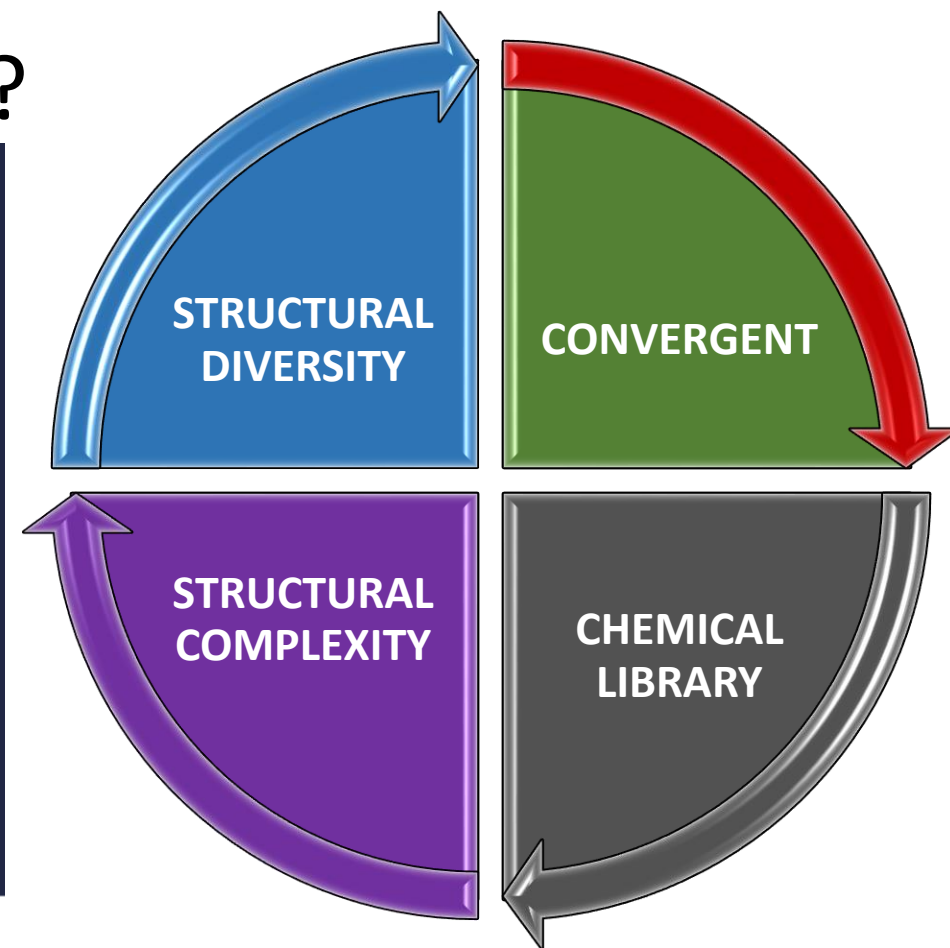
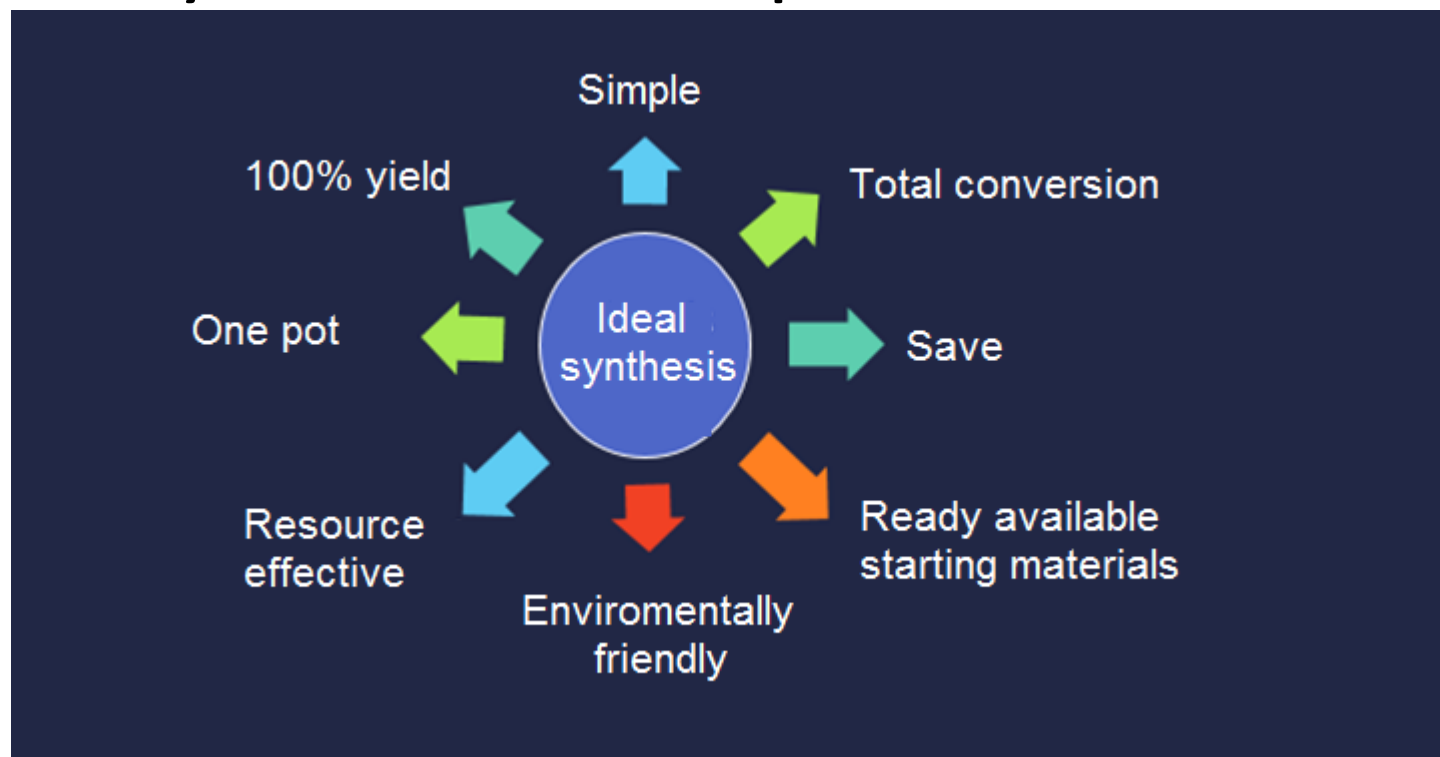


Scheme 1. Traditional multistep synthesis (3 steps) vs. multicomponent assembly (1 step).

Slobbe, P.; Ruijter, E.; Orru, R. V. A. *Med. Chem. Commun.* **2012**, 3, 1189-1218.

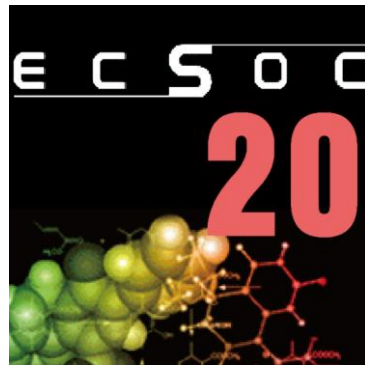


Why use multicomponent reactions?

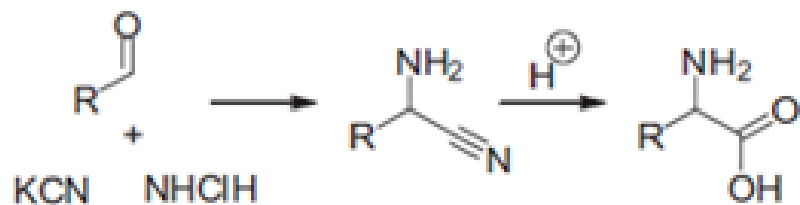


3.(a) Dömling, A.; Ugi, I. *Angew. Chem. Int.* **2000**, 39, 3168-3210.

4.Wender, P. A.; Handy, S; Wright, D. L; Towards the ideal synthesis. *Chem. Ind.* **1997**, 765.

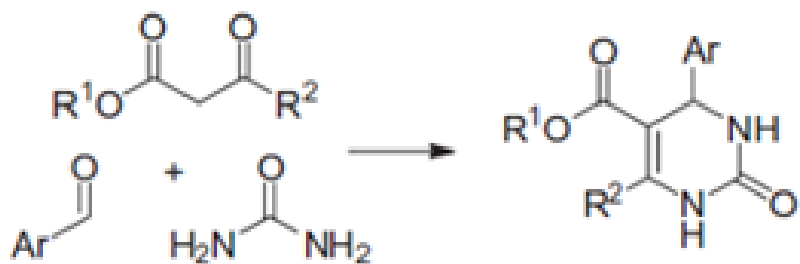


History of MCR's: Non-Isocyanide based MCRs



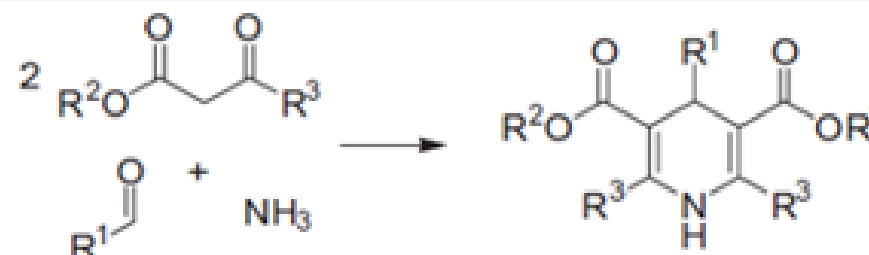
Strecker reaction (1850)

Strecker, A. *Ann. Chem. Pharm.* **1854**, *91*, 349.



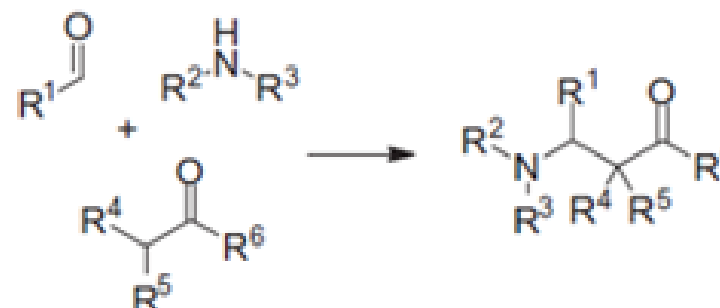
Biginelli reaction (1891)

Han (a) Biginelli, P. *Chem. Ber.* **1891**, *24*, 1317; (b) Biginelli, P. *Chem. Ber.* **1891**, *24*, 2962; (c) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.



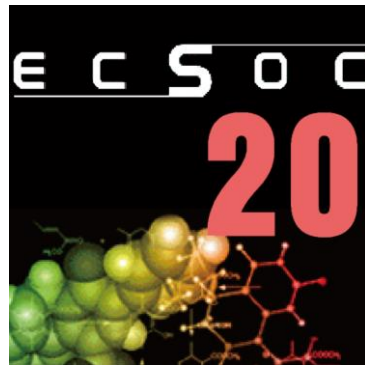
Hantzsch reaction (1882)

Hantzsch, A. *Chem. Ber.* **1881**, *14*, 1637.

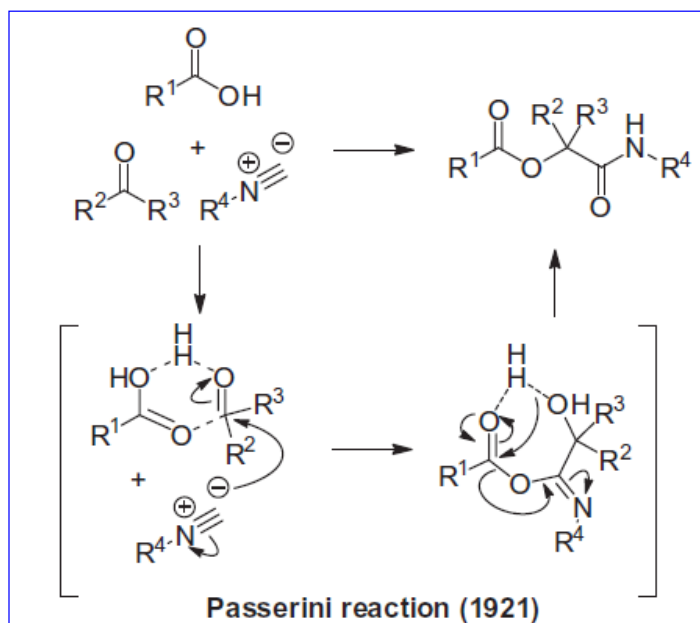


Mannich reaction (1912)

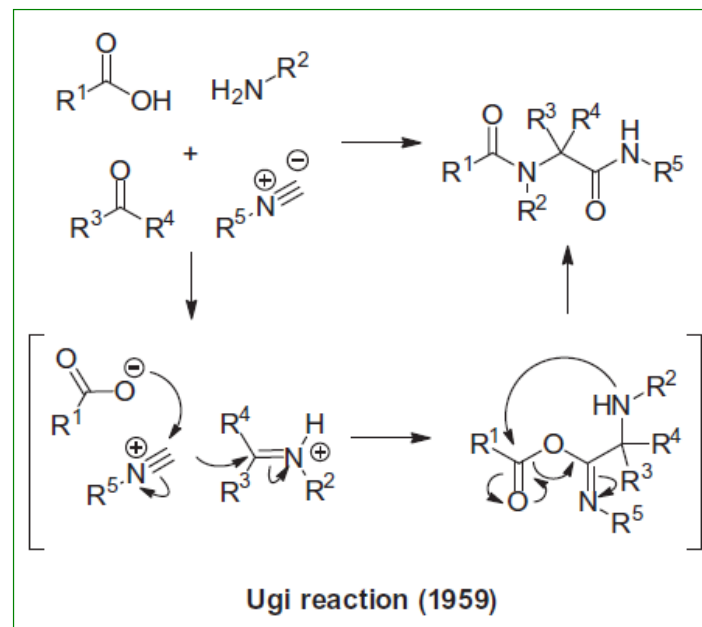
Mannich, C.; Krosche, W. *Arch. Pharm.* **1912**, *250*, 647.



Isocyanide based MCR's (I-MCR's)



Passerini, M. *Gazz. Chim. Ital.* **1921**, 51, 126.

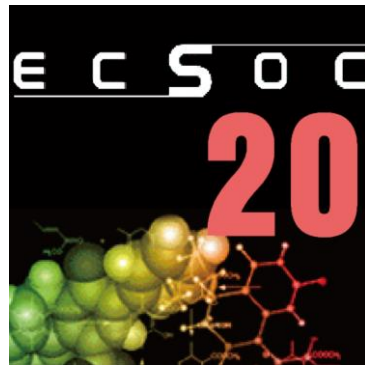


Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, 71, 386.

Other I-MCR's:

Groebke-Blackburn-Bianayme-3CR, Orru-3CR, Van Leusen-3CR.

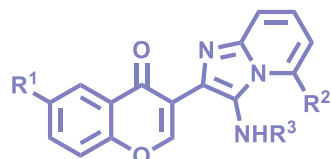




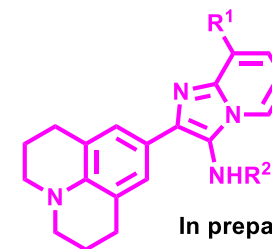
Our group work

Synthesis of bound-type *bis*-heterocycles

Imidazopiridin-chromonas

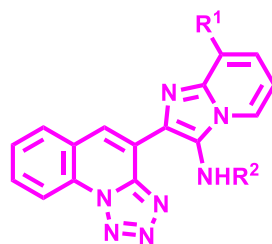


Tetrahedron Lett. **2016**, *56*, 155-158.



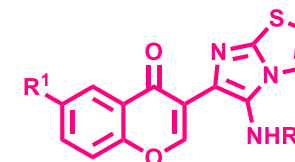
In preparation

Tetrazolo-imidazoquinolinas



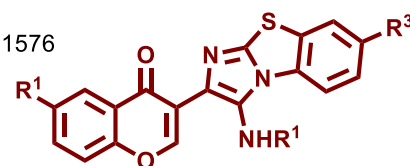
J. Org. Chem. **2016**, Doi:10.1021/acs.joc.6b01576

Imidazotiazol-chromonas



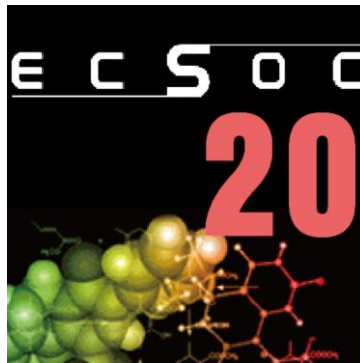
Tetrahedron Lett. **2016**, *57*, 3556-3560.

benzoimidazoltiazol-chromonas

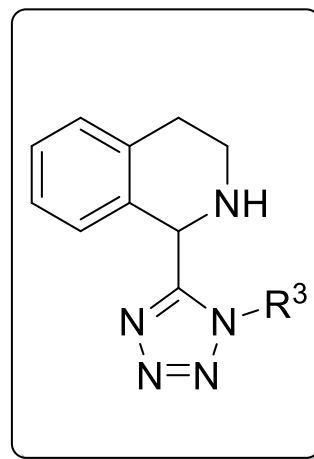


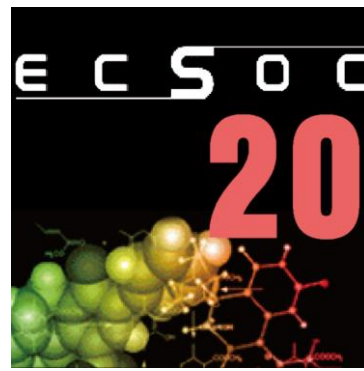
Tetrahedron Lett. **2016**, *57*, 3556-3560.



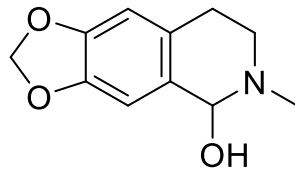


Synthesis of 1-tetrazolyl-1,2,3,4-tetrahydroisoquinoline bound-type *bis*-heterocycles via oxidative-Ugi-azide.

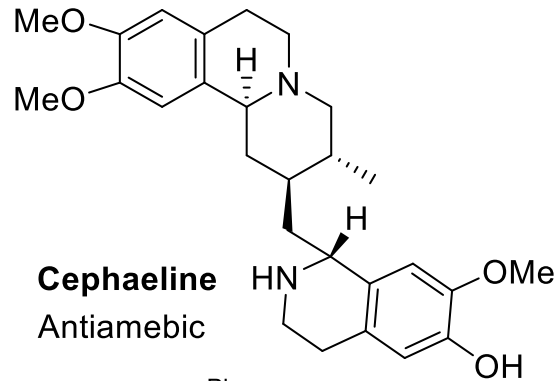




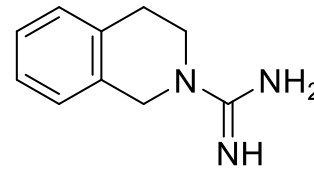
Medicinal applications of 1,2,3,4-Tetrahydroisoquinoline and Tetrazoles



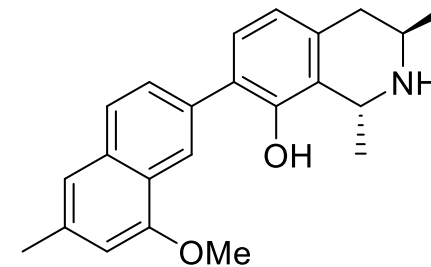
Hydrastine
Hemostatic



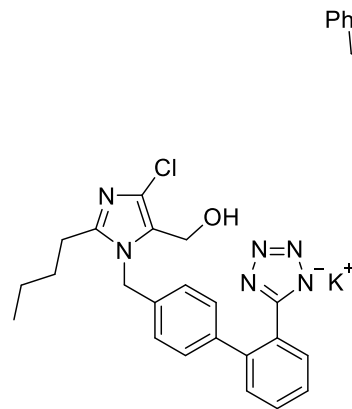
Cephaeline
Antiamebic



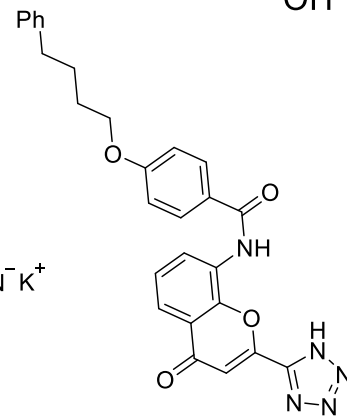
Debrisoquin
Antihypertensive



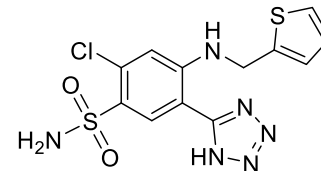
Dionocophylline B
Activity against *P. falciparum*,
Leishmania and *Trypanosoma*



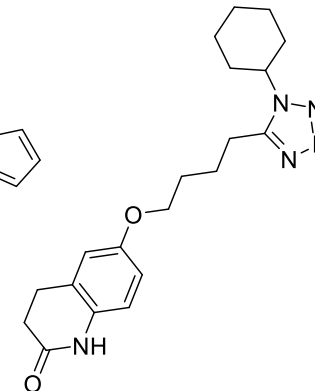
Losartan
Vasorelaxant and angiotensin II
receptor antagonist



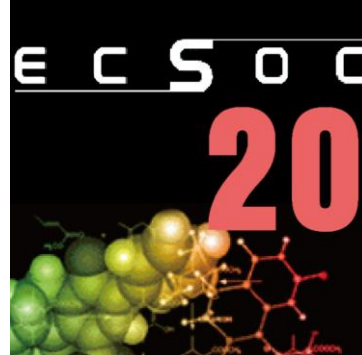
Pranlukast
Antiallergic



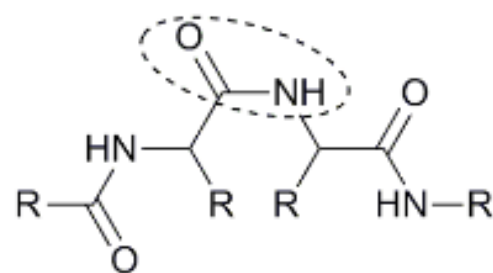
Azosemide
Diuretic agent



Cilostazol
Thrombogenesis inhibitors

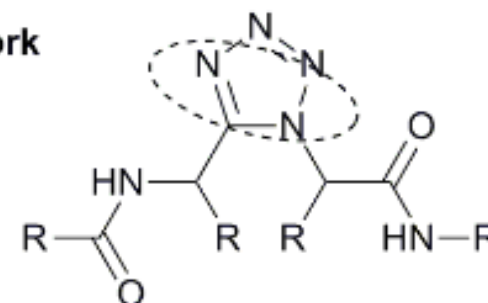


Tetrazole rings are usually attributed to the possibility of this moiety to mimic a carboxyl group or a *cis* amide bond.

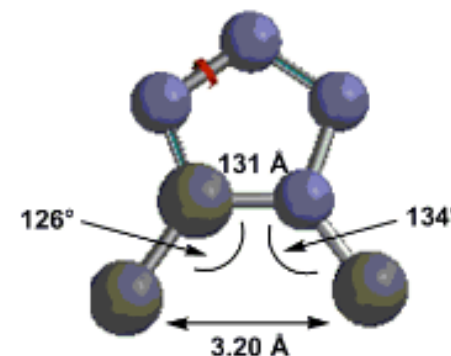
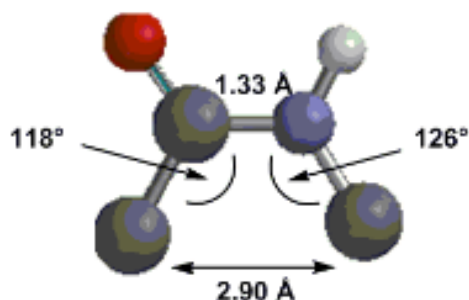


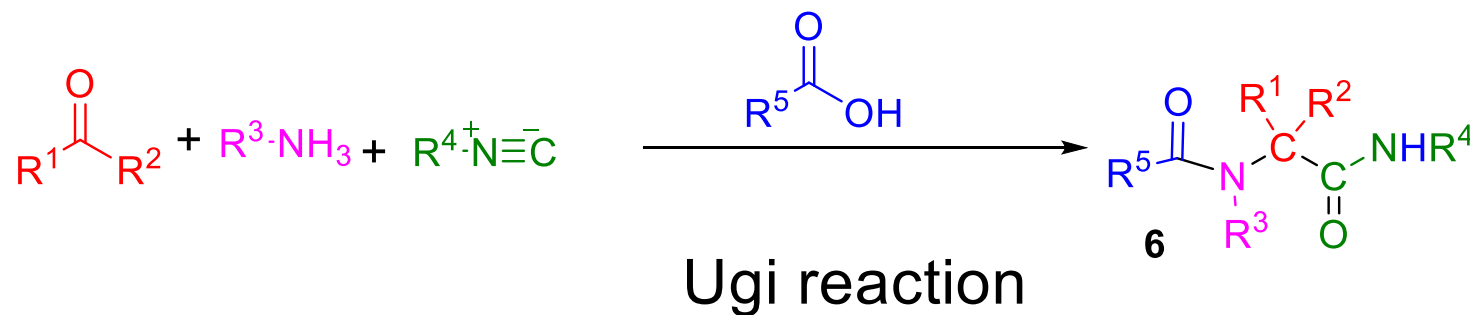
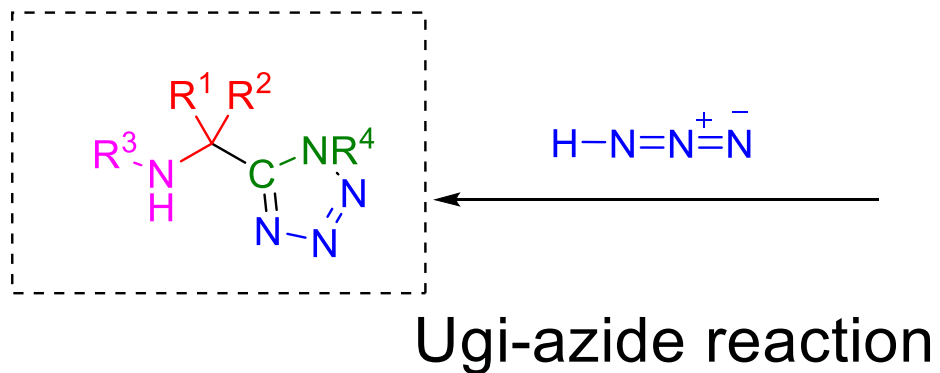
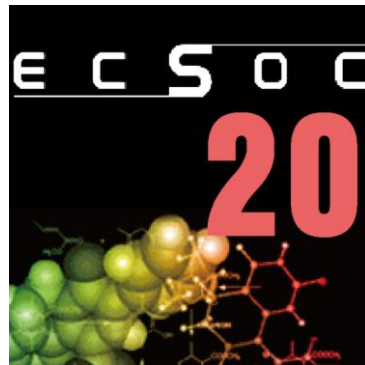
cis amide bond
of peptides

Marshall's work

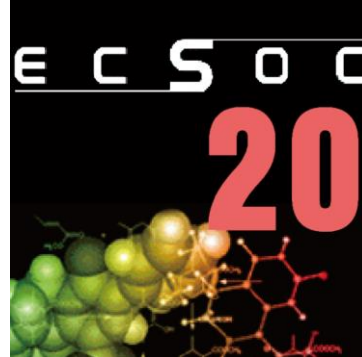


bioisosters of
cis amides



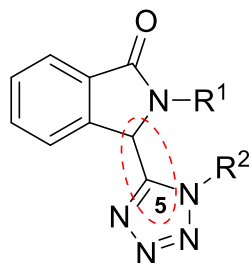


- (a) Cárdenas-Galindo, L. E.; Islas-Jácome, A.; Alvarez-Rodríguez, N. V.; El Kaïm, L.; Gámez-Montaño, R. *Synthesis* **2014**, 46, 49;
(b) Gordillo-Cruz, R. E.; Rentería-Gómez, A.; Islas-Jácome, A.; Cortes-García, C. J.; Díaz-Cervantes, E.; Robles, J.; Gámez-Montaño, R. *Org. Biomol. Chem.* **2013**, 11, 6470.

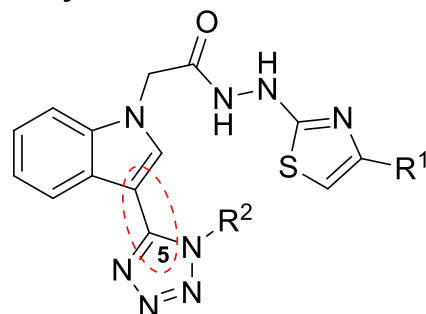
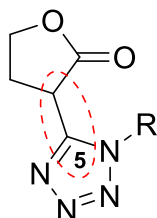


Bound-type *bis*-heterocycles

1,5-DS-T bound in C-5 with a heterocycle

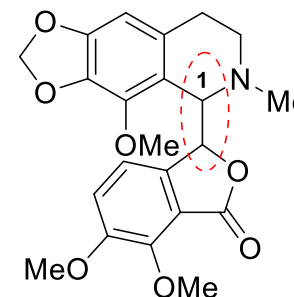


Activity as LuxR-dependent QS modulators

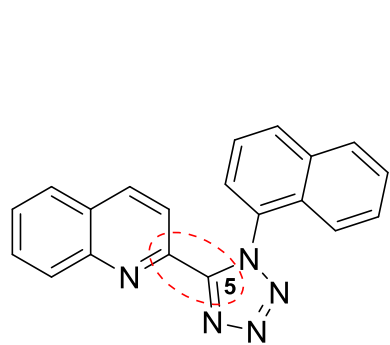
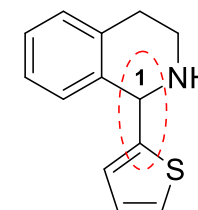
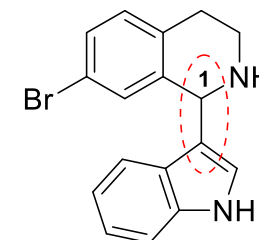


In vitro antitumor activity

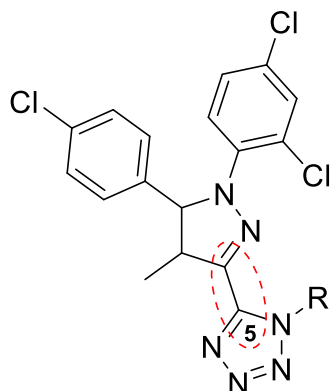
1,2,3,4-tetrahydroisoquinolines bound in C-1 with a heterocycle



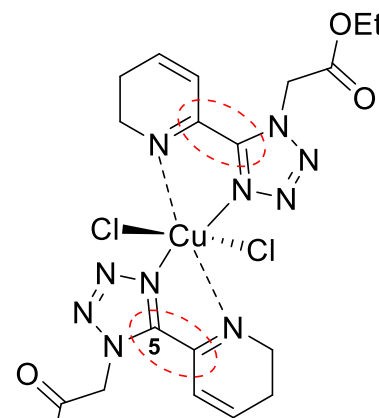
Antitussive



Chemosensor

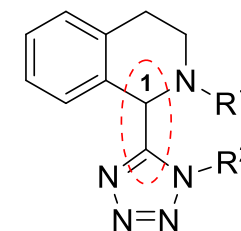


Cannabinoid Inhibitor

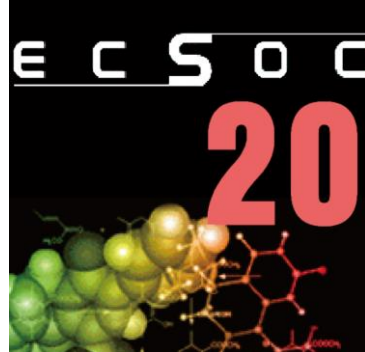


MOF precursor

1,2,3,4-tetrahydroisoquinolines bound in C-1 with the C-5 of the 1,5-DS-T



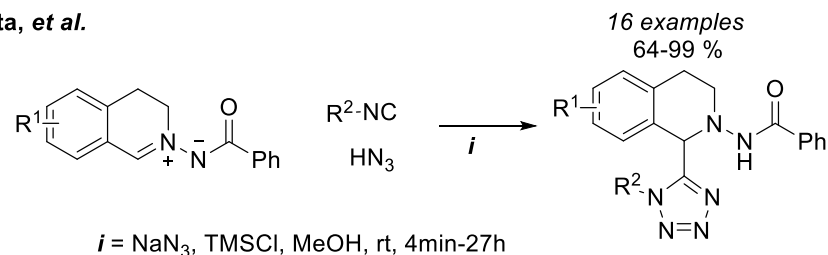
R's = alkyl or aryl



Synthetic background

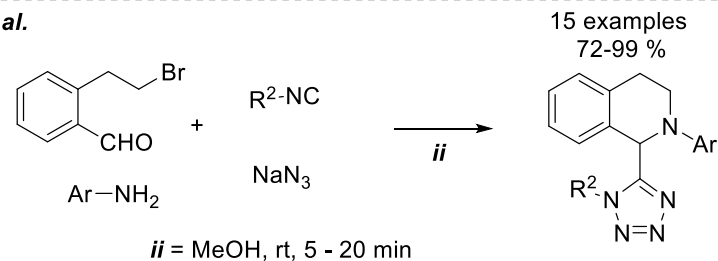
Synthesis of bound-type THIQ-T *bis*-heterocycles

Soeta, *et al.*



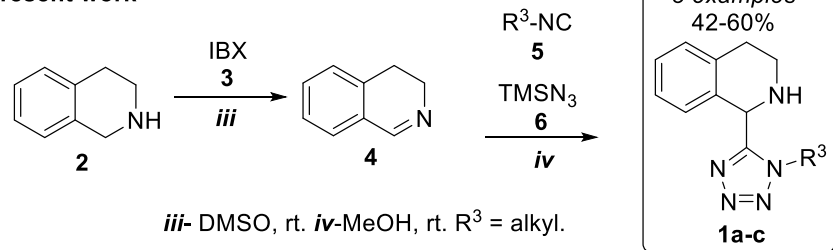
Soeta, T.; Tamura, K.; Fujinami, S.; Ukaji, Y. *Org. Biomol. Chem.*, **2013**, 11, 2168.

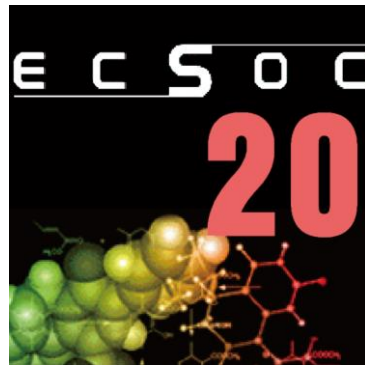
Shinde, *et al.*



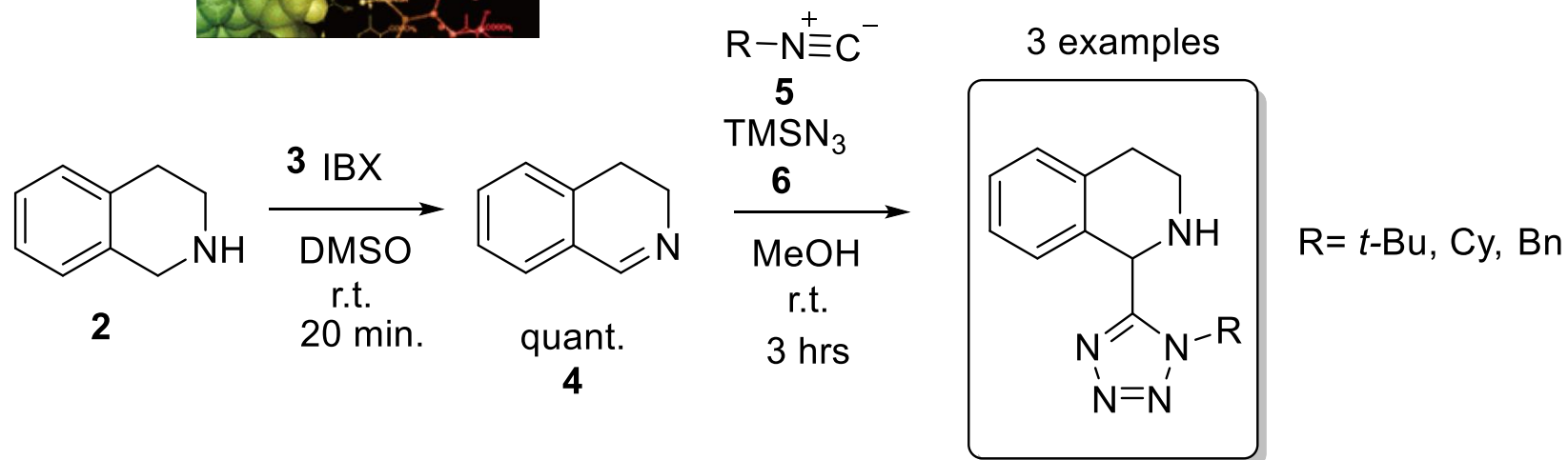
Shinde, A. H.; Archith, N.; Srilaxmi, M.; Sharada, D. S. *Tetrahedron Letters* **2014**, 55, 6821.

Present work





Results

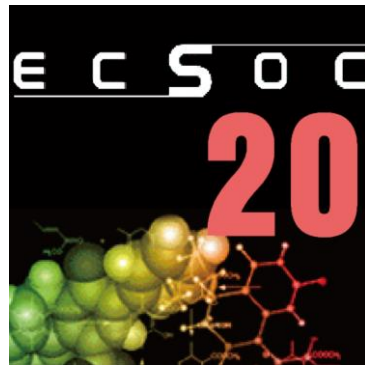


Entry ^a	R	Yield (%) ^{b,c}
1	<i>t</i> -Bu	56
2	Cy	60
3	Bn	42

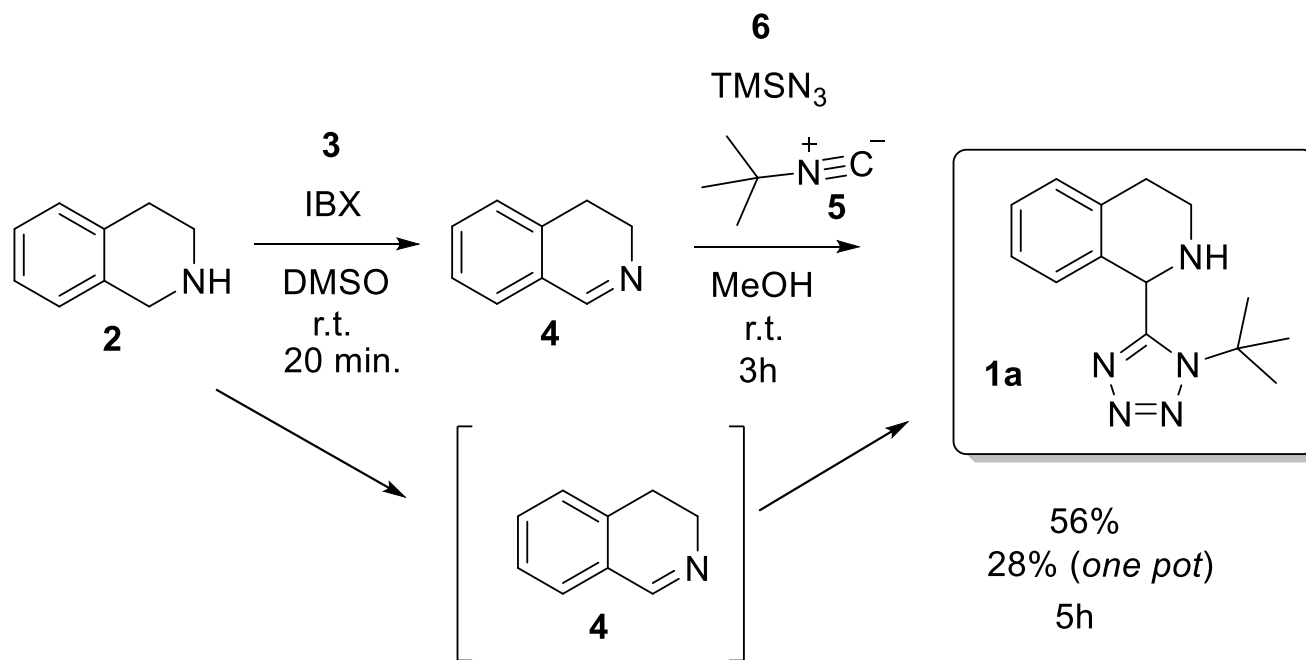
^a Reaction conditions: Imine **4** (1 equiv.), isocyanide **5** (1 equiv.), TMSN₃ **6** (1 equiv.). MeOH [1.0 M]. 3 hrs.

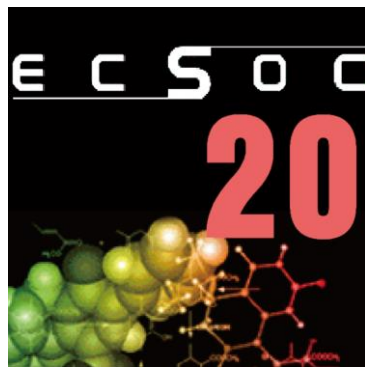
^b Product characterized by ¹H NMR and ¹³C NMR.

^c Isolated yields after column chromatography.

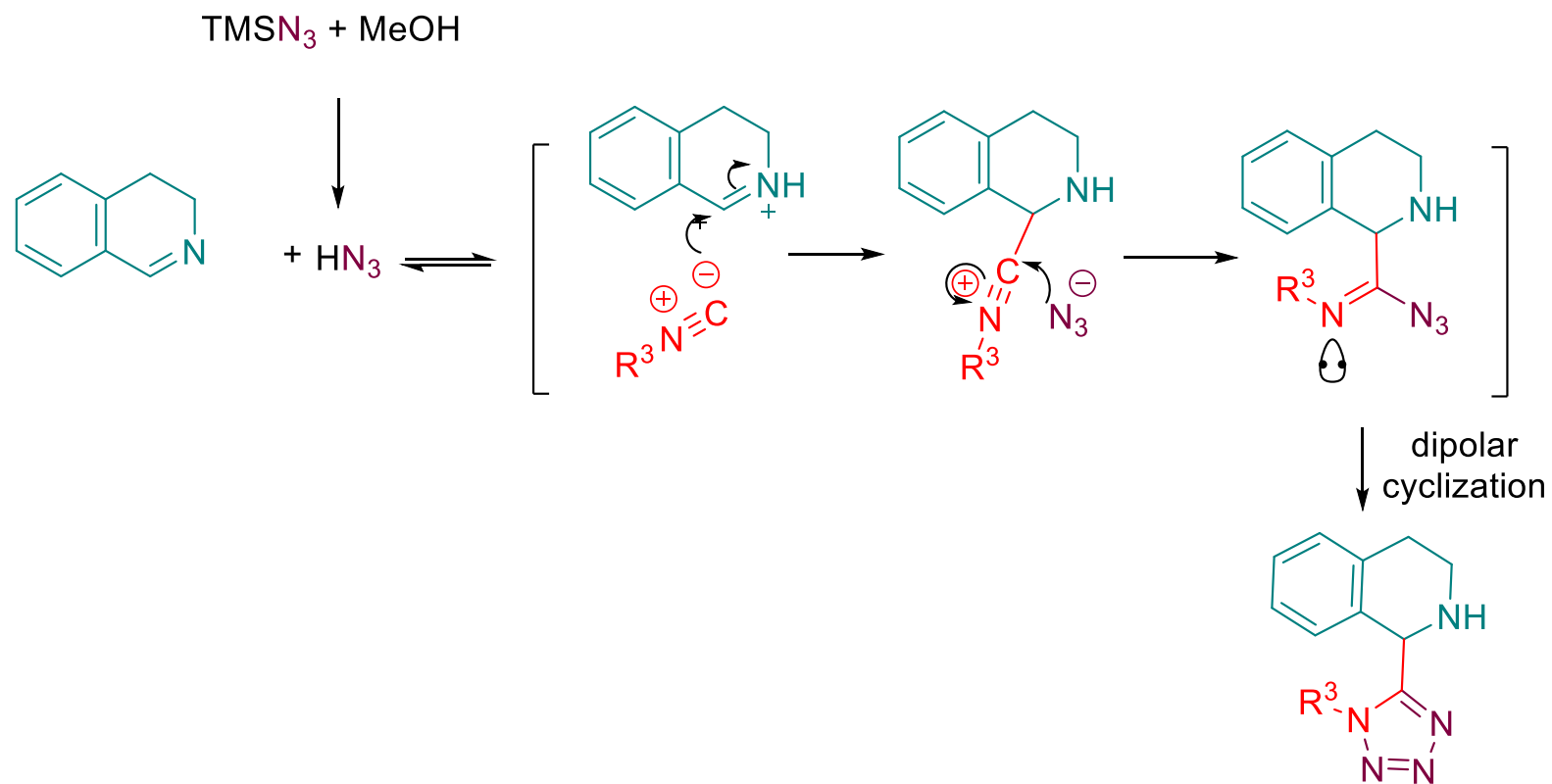


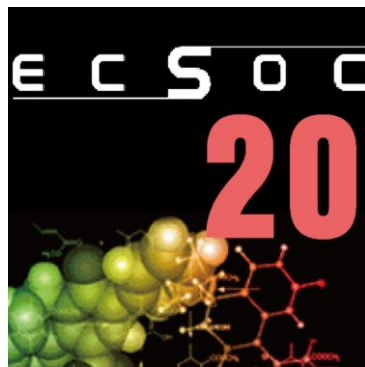
One pot synthesis of **1a**



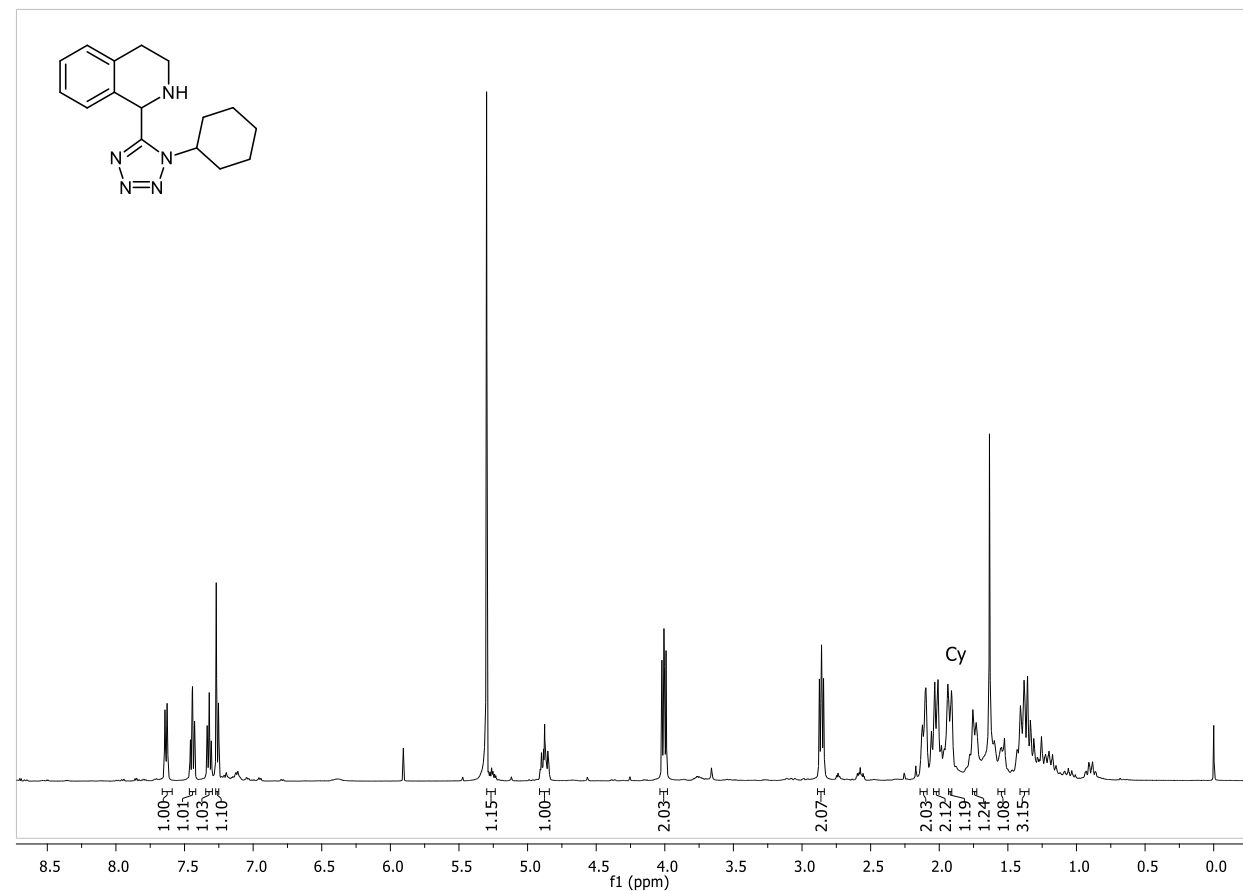
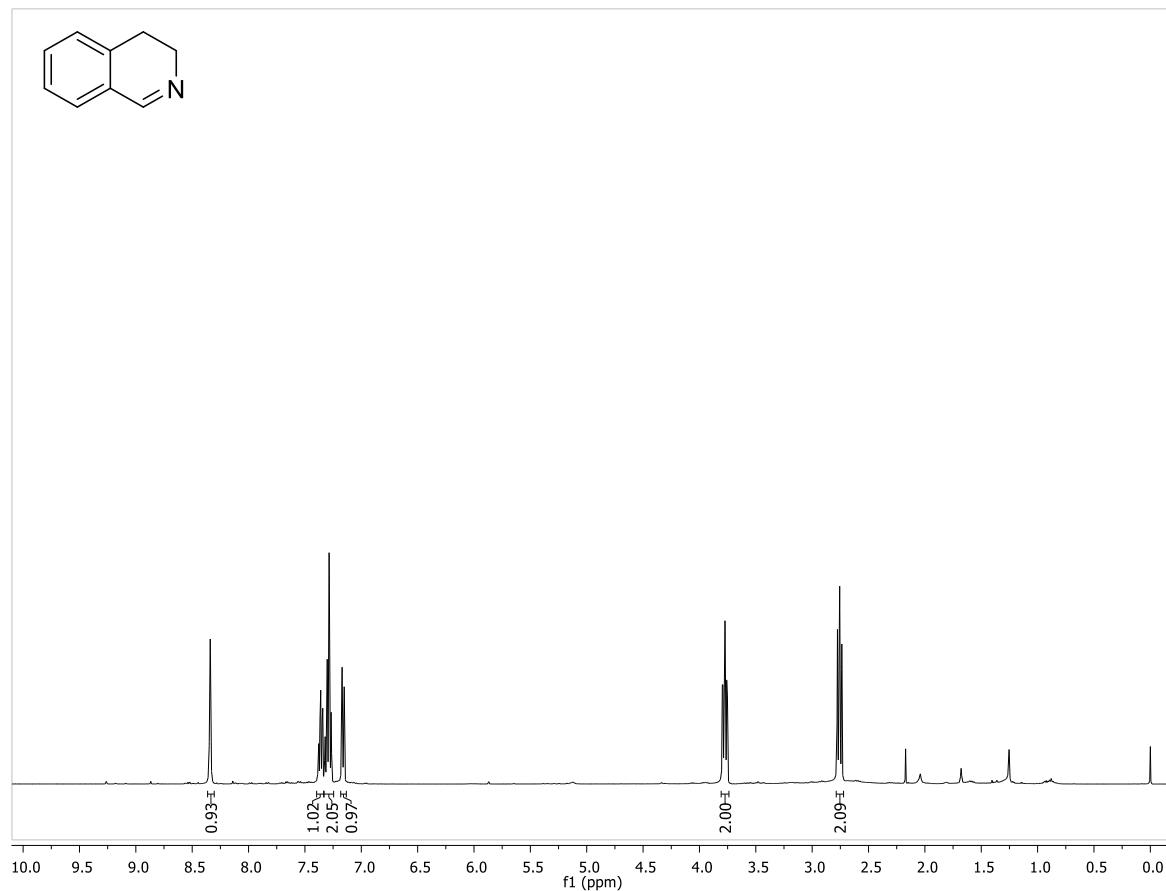


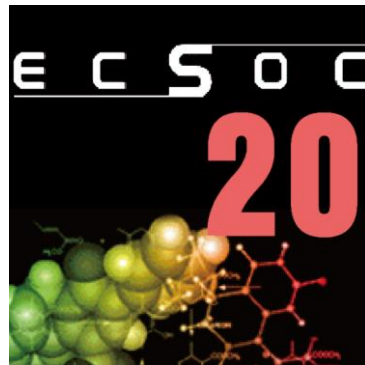
Plausible Mechanism reaction





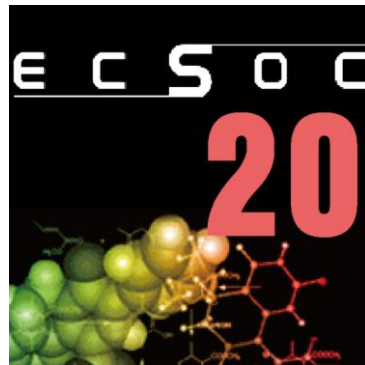
NMR spectra of precursor and one representative final product





Conclusion

- The oxidation of secondary amines toward imines gave higher yields, which could be considered to avoid the inherent difficulties for synthesizing Schiff bases from inactivated aldehydes and anilines. Oxidative Ugi-azide reaction gave good global yields in two steps. The one pot version was performed in lower yield (28%). An extension of this work is being carried out using alternative heat sources (like MW and ultrasound), even to increase substrate scope. It is noteworthy that *bis*-heterocycles herein described may find application in medicinal chemistry because they are formed by two heterocyclic (THIQ and Tetrazol) moieties present in a wide range of bioactive compounds and drugs.



Acknowledgements



R.G.-M. is grateful for financial support from CIO-UG (009/2015), DAIP (859/2016) and CONACYT (CB-2011-166747-Q) projects. A.I.-J (ID: I00247) thanks UG for his temporary position as assistant professor in the R.G.-M. research's group. All authors kindly acknowledge to National Laboratory for the instrumentation time provided (UG-UAA-CONACYT: 123732).