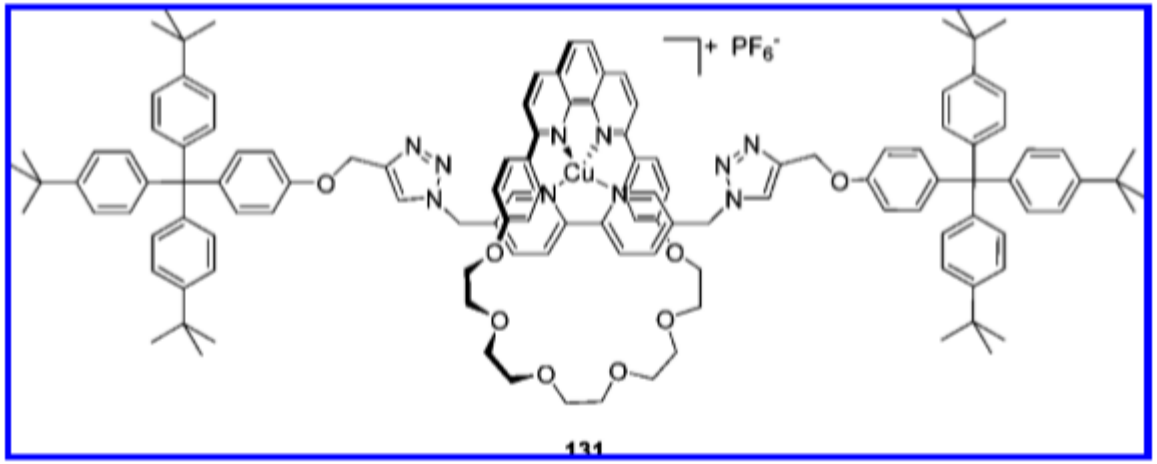
CLICK CHEMISTRY
varianti e applicazioni

Uso in Chimica Supramolecolare

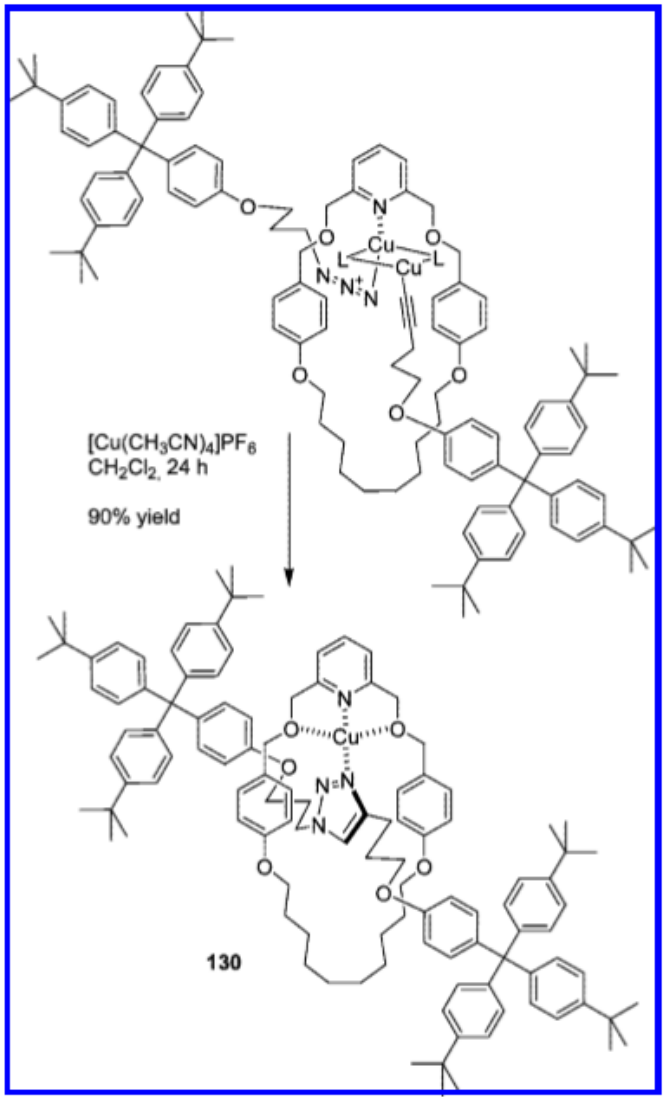
(sintesi di rotaxani)

La coordinazione con il rame è fondamentale nel tenere le molecole in posizione e permettere alte rese di reazione (altrimenti con rese molto basse)

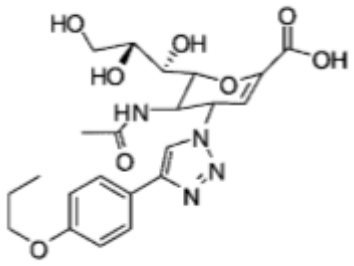


stopper conjugation through CuAAC the bis-azide was held in place by bipyridine coordination,

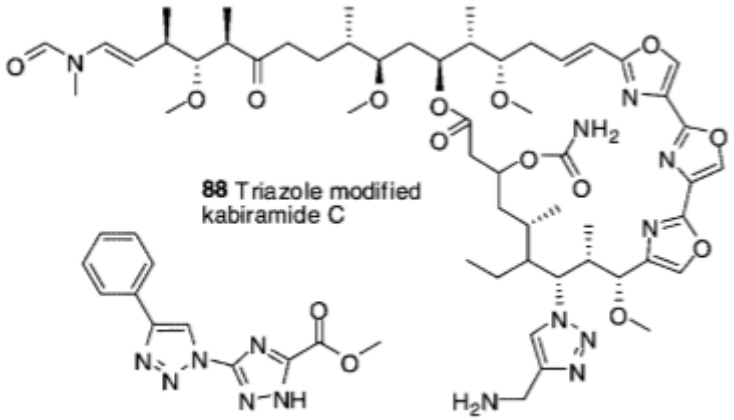
Scheme 23. The Synthesis of Rotaxanes Has Been Facilitated Greatly through CuAAC That Helps Coordinate the Two Reaction Partners in the Arch of the Macrocycle by Auxiliary Coordination of the Catalytic Cu(1)



Uso in Med. Chem.

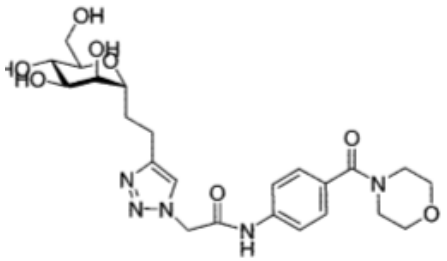


86 Anti-AIV agent

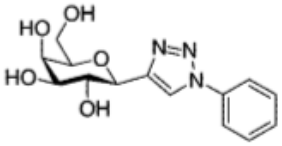


88 Triazole modified kabiramide C

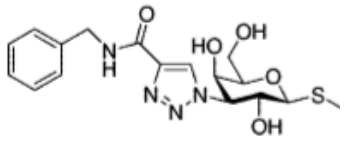
89 Antiviral bis-triazole



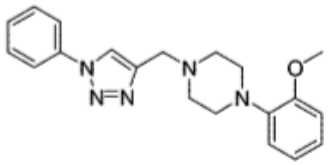
70 *Leishmania* Man-T substrate



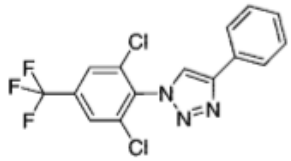
68 Galactosidase inhibitor



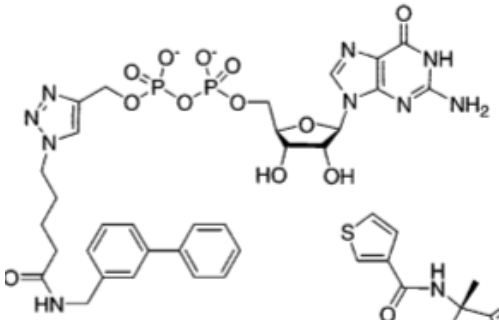
69 Galectin-3 inhibitor



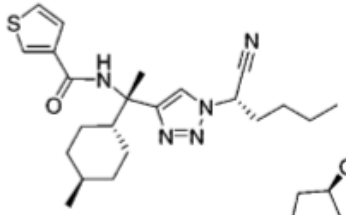
71 D4-R partial agonist



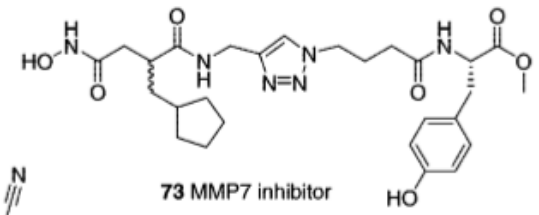
72 GABA-R antagonist



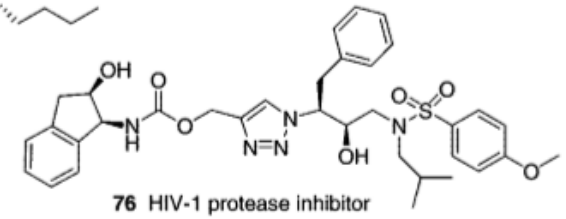
74 α-1,3-Fuc-T inhibitor



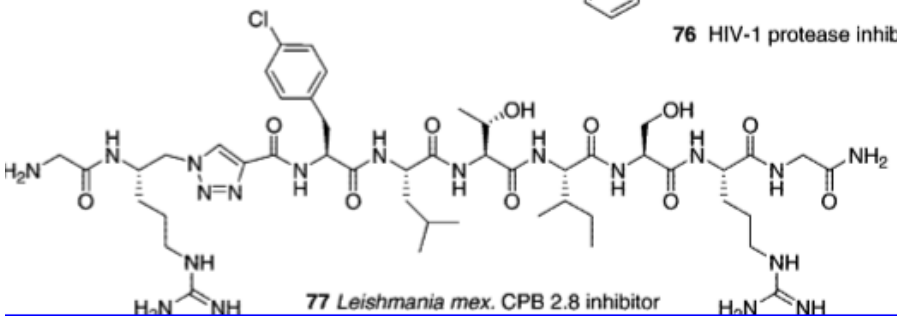
75 Cathepsin S inhibitor



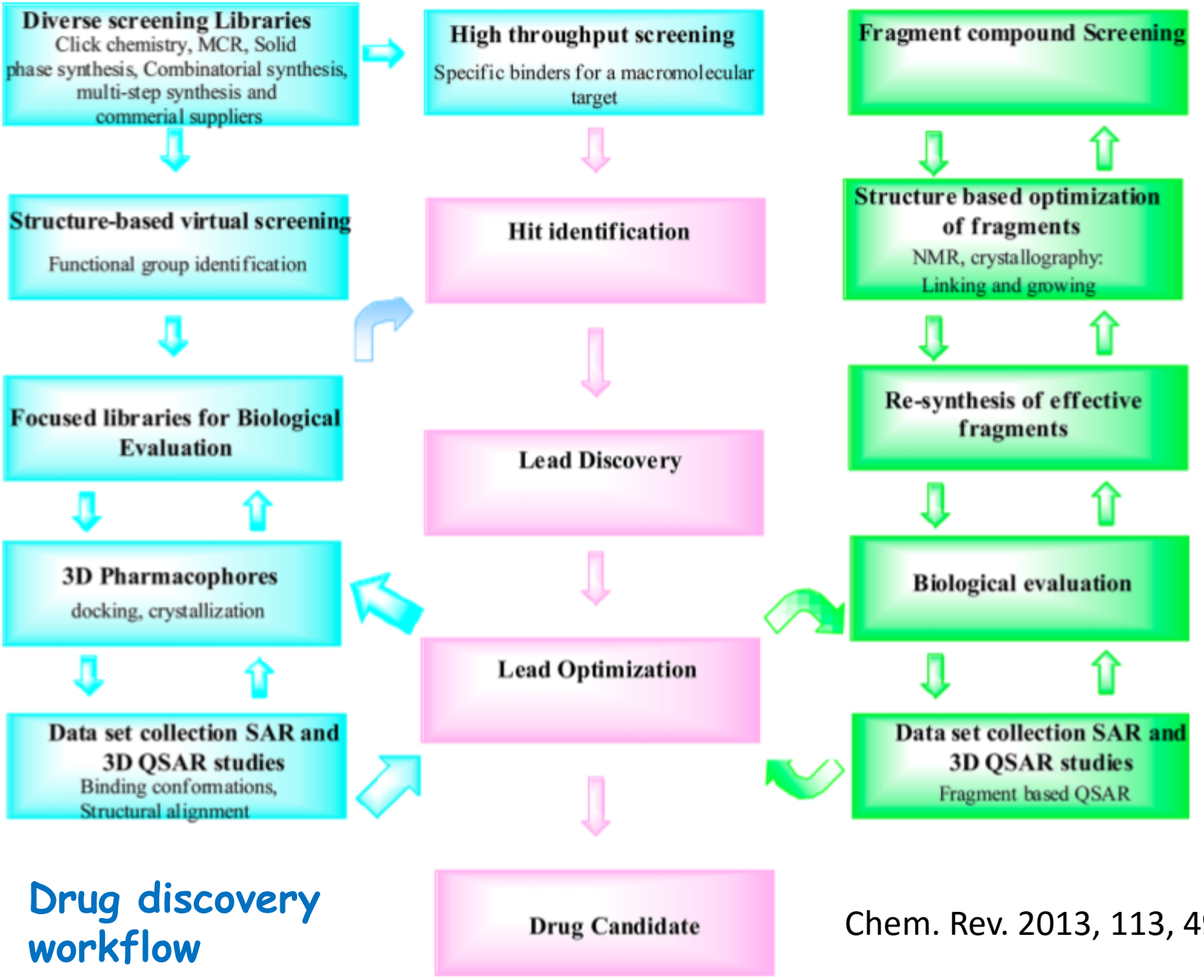
73 MMP7 inhibitor



76 HIV-1 protease inhibitor



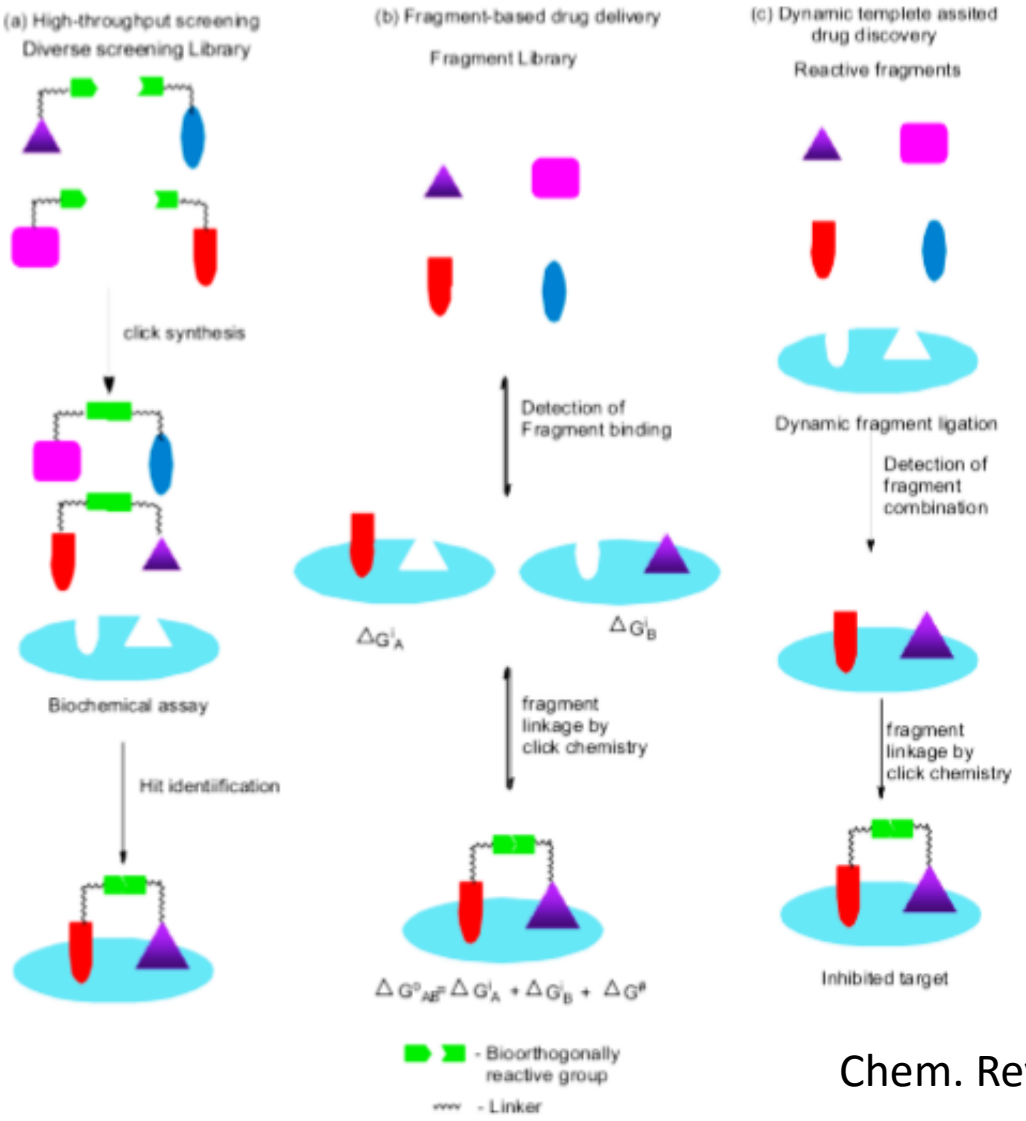
77 *Leishmania mex.* CPB 2.8 inhibitor



Drug discovery workflow

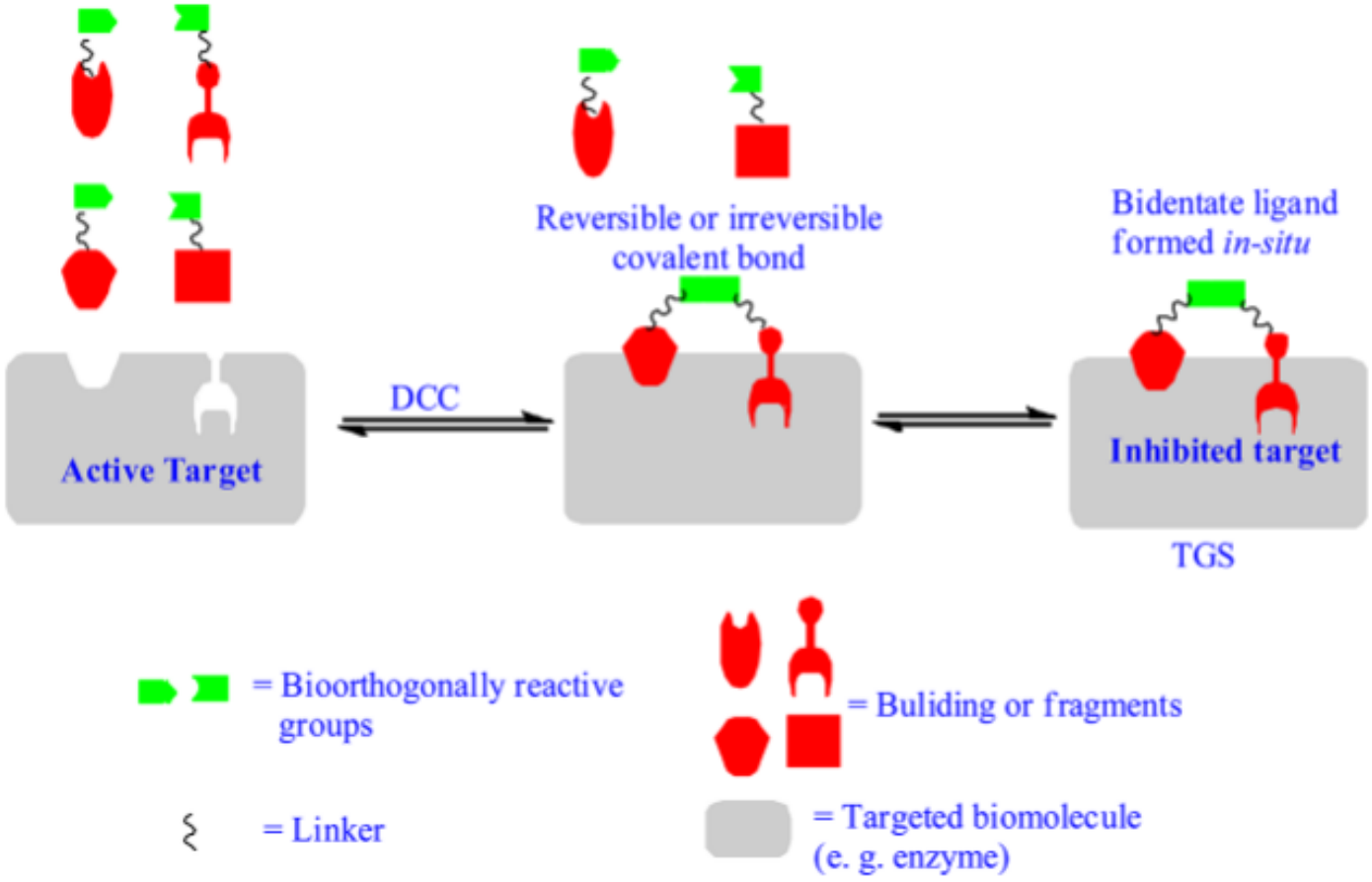
Chem. Rev. 2013, 113, 4905

FBDD, fragment-based drug design; QSAR, quantitative SAR; SAR, structure–activity relationship.



Chem. Rev. 2013, 113, 4905

Figure 2. Concepts in lead discovery. (a) High-throughput screening (HTS). A diverse library of chemical compounds is collected and tested against the drug target. (b) Fragment-based lead discovery. The binding of small molecular fragments to the protein is detected. Low-affinity fragments can be linked to provide high-affinity ligands.The binding constant K_{AB} is an exponential function of the binding energy. (c) Dynamic strategies in fragment-based drug discovery. Reactive fragments are incubated with the protein and form specific combinations of fragments on the protein template, which facilitates fragment detection and linkage to a new ligand.



Schematic representation of in situ click chemistry used for the development of enzyme inhibitors.

Examples of Reversible Binding

RuAAC
Ru-catalysed azide alkyne cycloaddition

1,5-triazoles

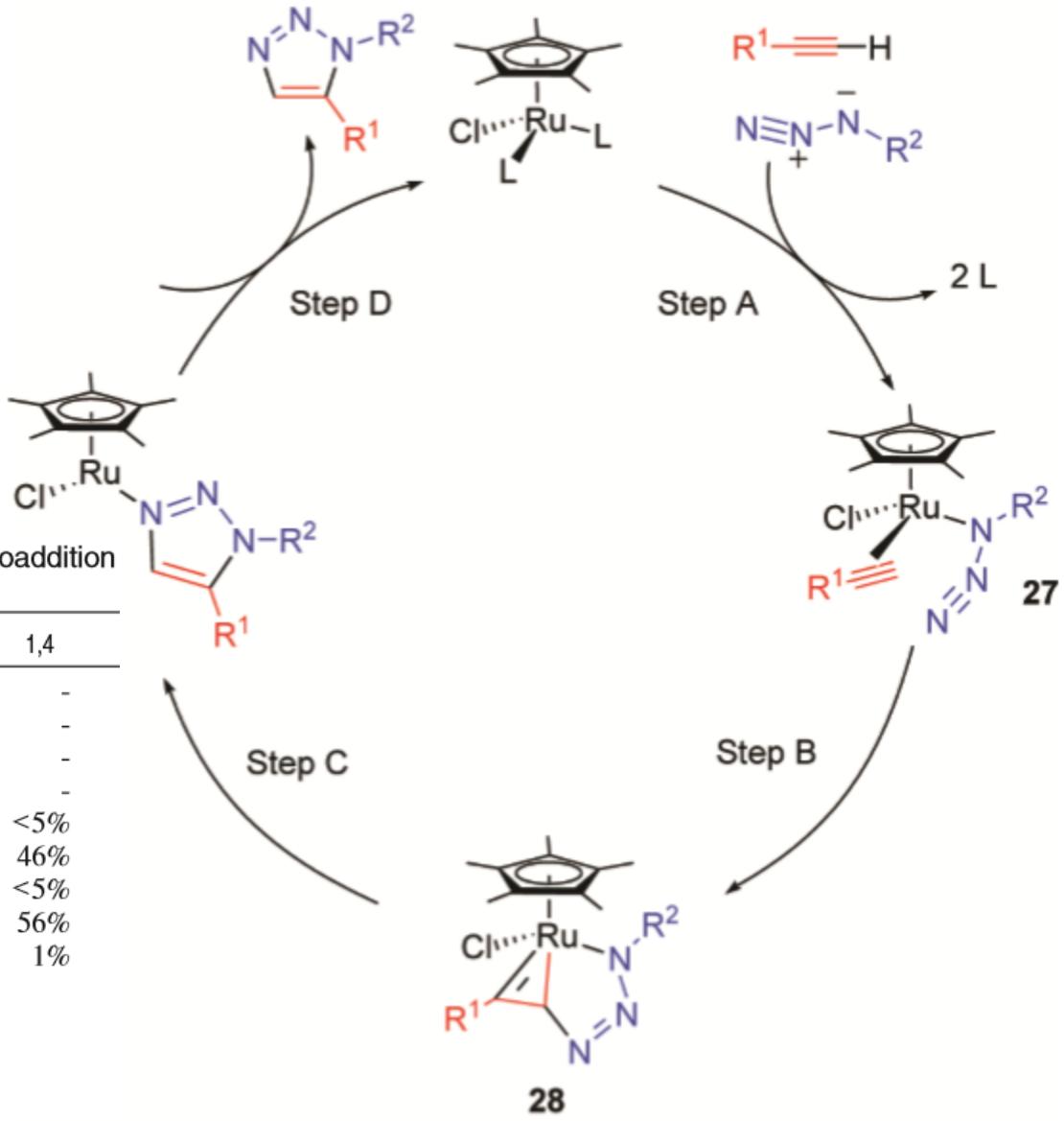


Table 1. Performance of Ruthenium(II) Catalysts in Cycloaddition of Benzyl Azide and Phenyl Acetylene[a]

Ru catalyst	1,5	1,4
$[RuCl_2(COD)]_x$	-	-
$[(p\text{-cym})RuCl_2]_2$	-	-
$[(p\text{-cym})RuCl_2(PPh_3)$	-	-
$[Cp^*Ru(H_2O)(NBD)]BF_4$	-	-
$RuCl_2(PPh_3)_3$	-	<5%
$Ru(OAc)_2(PPh_3)_2$	-	46%
$RuHCl(CO)(PPh_3)_3$	-	<5%
$RuH_2(CO)(PPh_3)_3$	-	56%
$CpRuCl(PPh_3)_2$	13%	1%
$Cp^*RuCl(PPh_3)_2$	100%	
$Cp^*RuCl(COD)$	100%	
$Cp^*RuCl(NBD)$	93%	
$[Cp^*RuCl]_4$	100%	

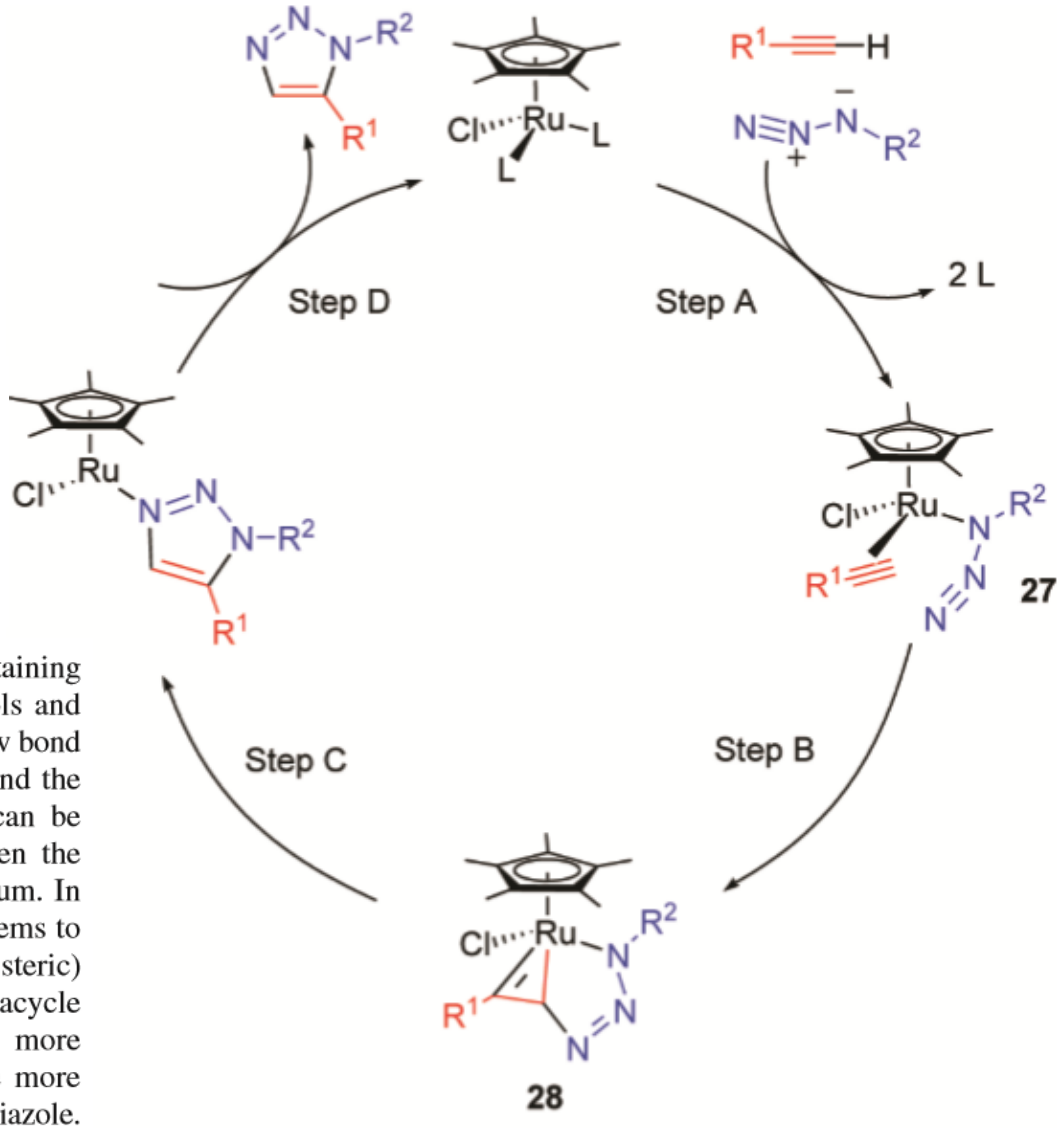
Ru-catalysed azide alkyne cycloaddition (RuAAC)

1,5-triazoles

ANCHE per alchini interni

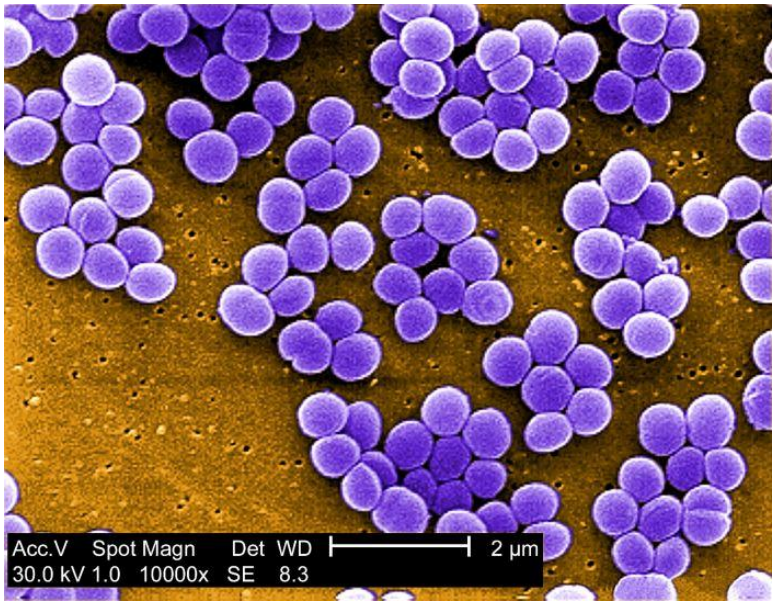
Computational studies indicate that the [Cp*RuCl]-catalyzed reactions of azides with alkynes involve an irreversible oxidative coupling of azide and alkyne to give ruthenacycles, followed by a rate-determining reductive elimination. The regioselectivity is determined by the oxidative coupling step, which can also be viewed as a nucleophilic attack of the activated alkyne at the electrophilic terminal nitrogen of the azide.

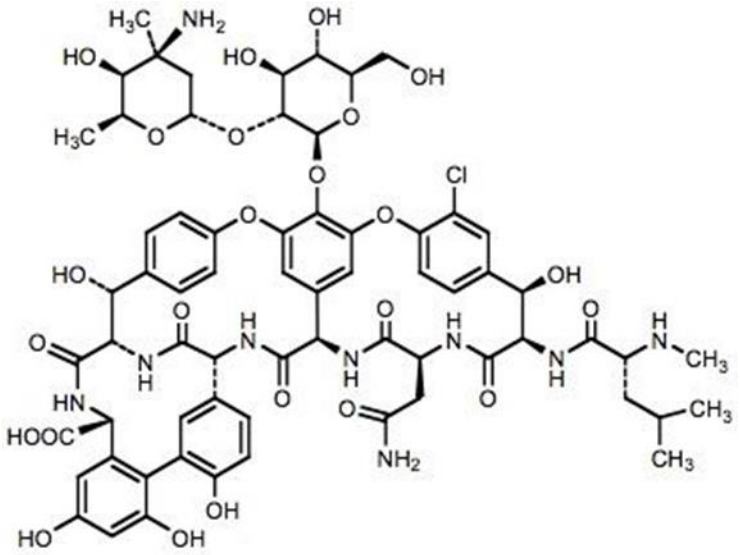
influenced by several factors in these cases. Alkynes containing a hydrogen bond donor group (e.g., propargylic alcohols and amines) exhibit virtually exclusive regioselectivity: the new bond is always formed between the β-carbon of the alkyne and the terminal nitrogen of the azide. This directing effect can be attributed to the formation of a strong H-bond between the alcohol or amine and the chloride ligand on the ruthenium. In the absence of such directing groups, regioselectivity seems to be governed primarily by the electronic (and possibly by steric) properties of the alkyne: the new bond in the metallacycle intermediate **28** (Scheme 3) is formed between the more nucleophilic carbon of the alkyne. In other words, the more electronegative carbon of the alkyne becomes C-4 in the triazole.



RuAAC in Med. Chem.: mimicry della vancomicina

La vancomicina è un glicopeptide ciclico antibiotico che si usa in molte infezioni difficili, come quelli da parte di batteri resistenti agli altri antibiotici (ad es. da parte dello *Stafilococco aureo - foto*).

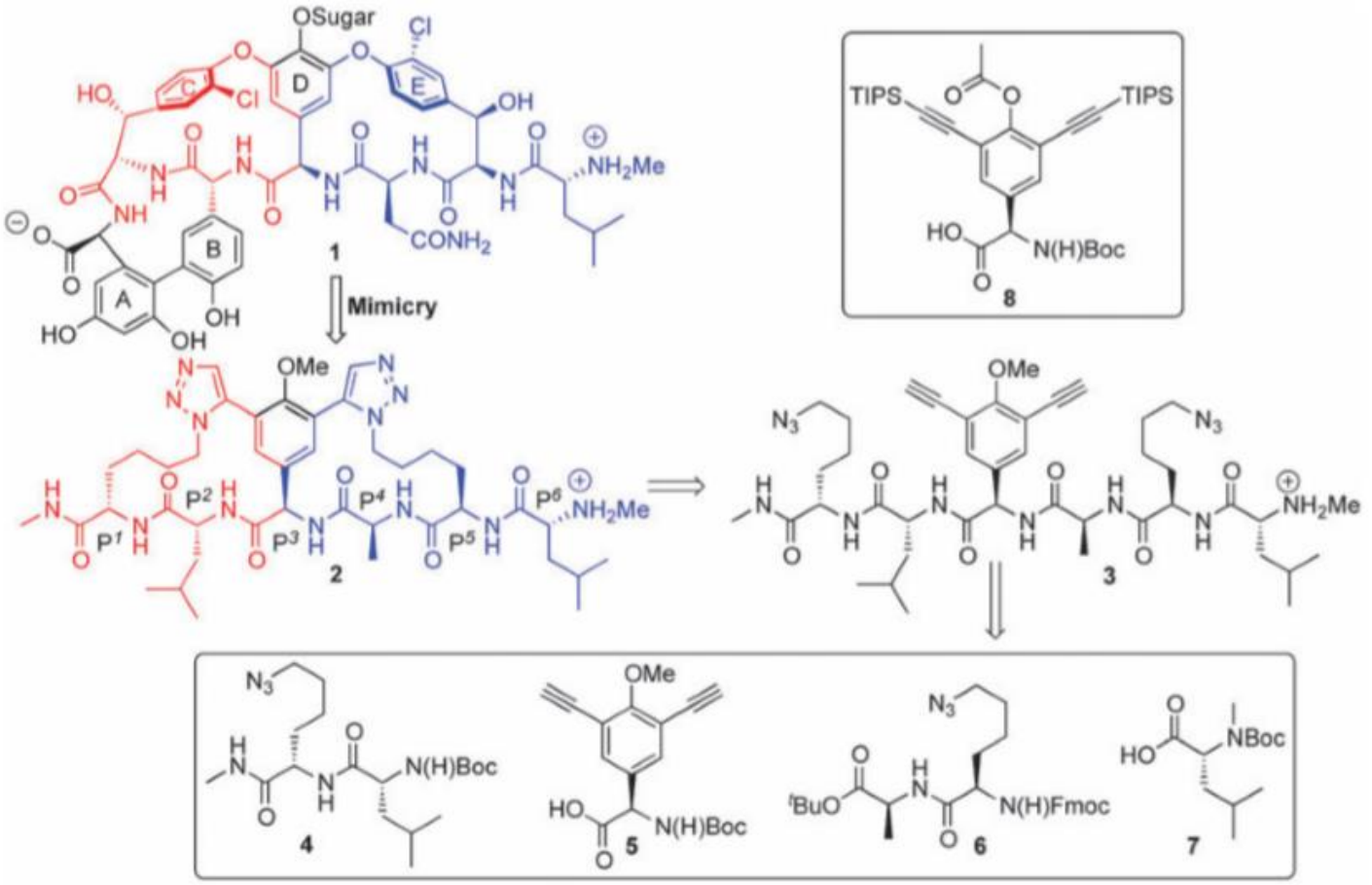




vancomicina

Meccanismo d'azione: inibisce la sintesi del peptidoglicano, componente della parete batterica, per cui la vancomicina ha azione batteriostatica (cioè battericida sui batteri in attiva moltiplicazione).

RuAAC in Med. Chem.: mimicry della vancomicina



Scheme 1 Design and retrosynthesis of the 1,5-triazole-bridged vancomycin CDE-ring mimic **2**.

ChemComm 2013, 49, 4498