



Grundlagen der organischen Chemie II

Kombinatorische Chemie 3

Tim Clark

Computer-Chemie-Centrum

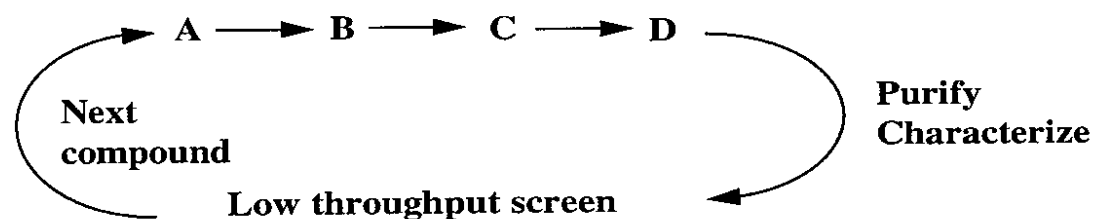
Universität Erlangen-Nürnberg

clark@chemie.uni-erlangen.de



Kombinatorische Chemie in Lösung

- **Orthodox Analogue Synthesis and Screening**



- **Parallel Analogue Synthesis and Screening**

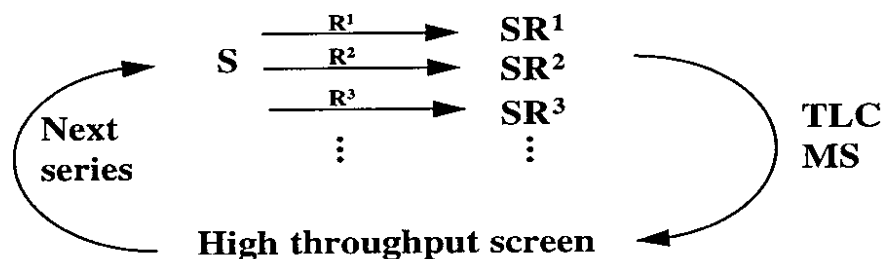
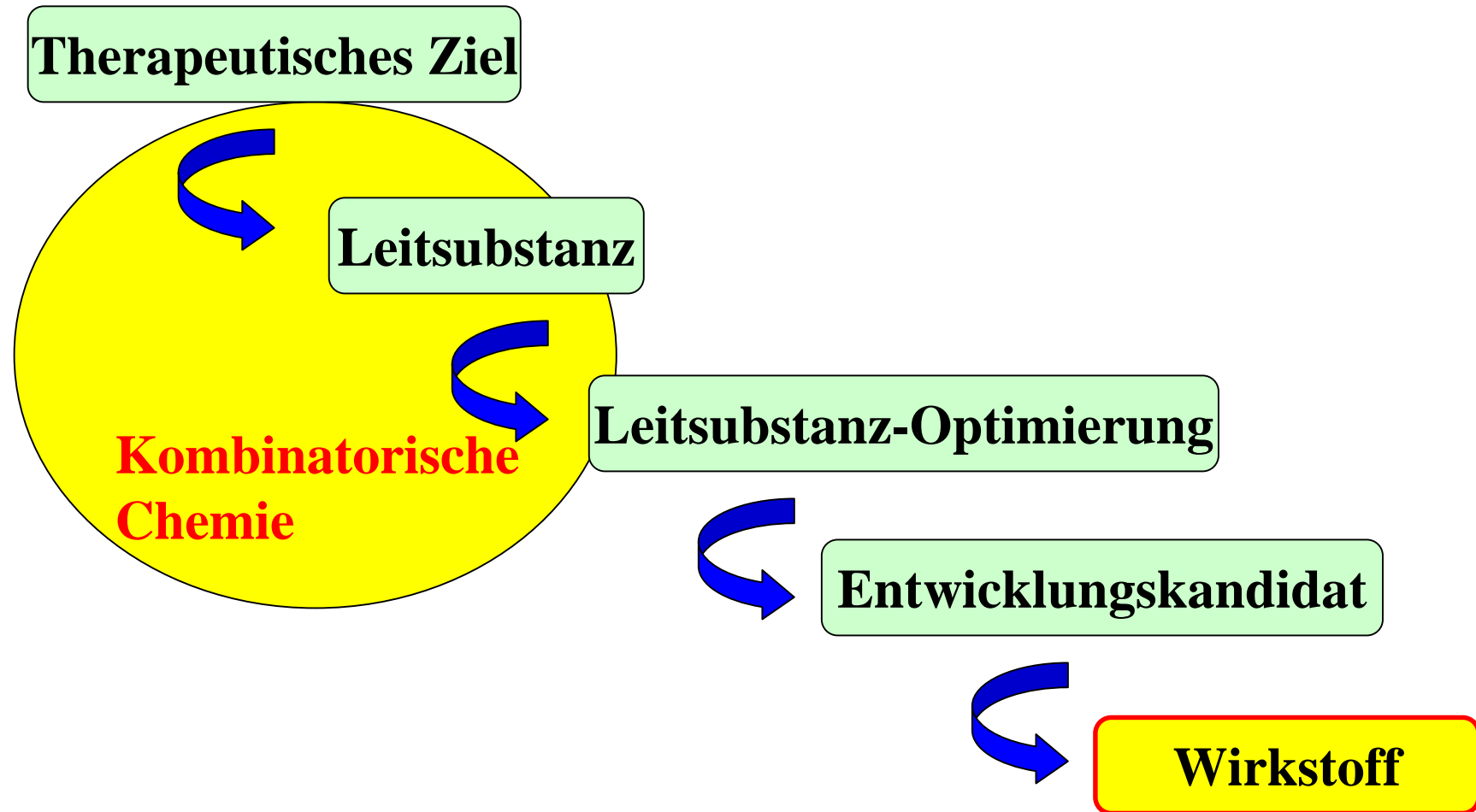


Abb. 4.1 Der Vergleich von herkömmlicher mit paralleler Synthese chemischer Analoga.



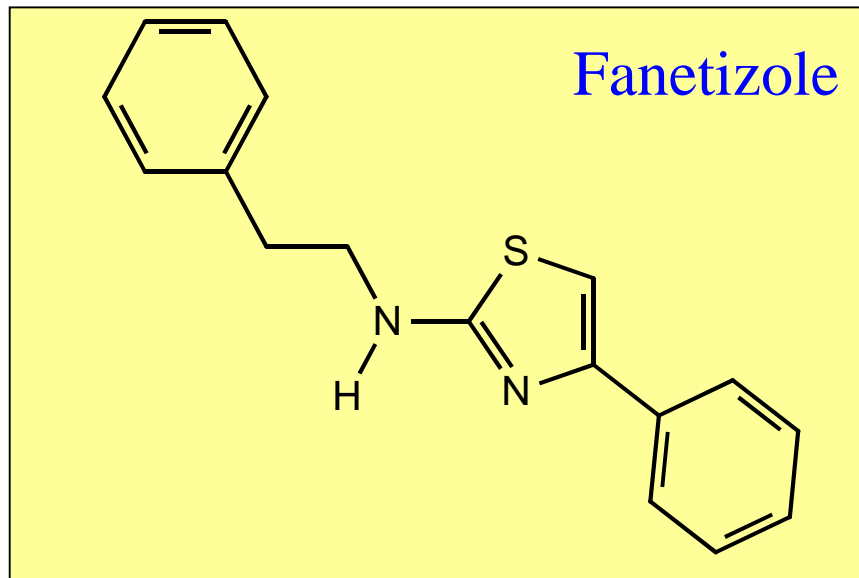
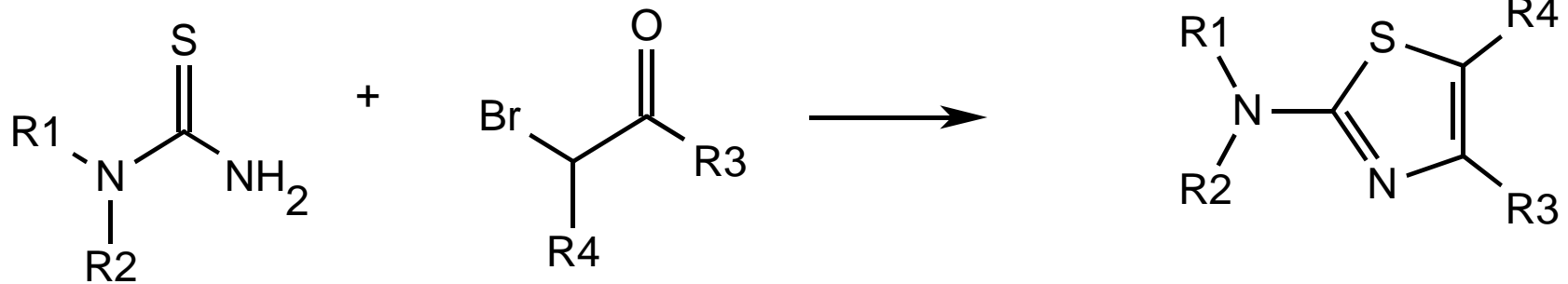
Wirkstofffindung





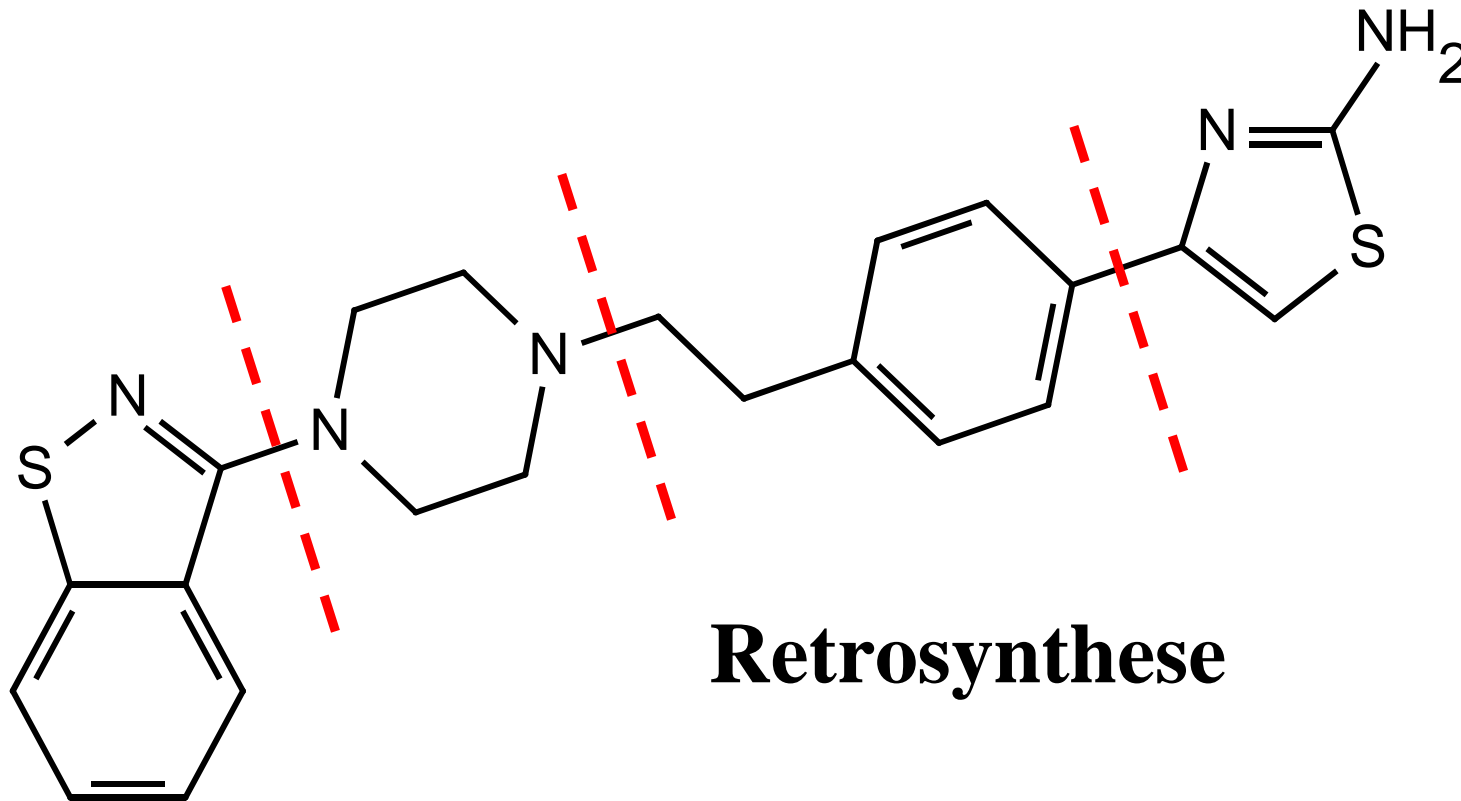
Kombinatorische Hantzsch-Synthese

Glaxo-Wellcome





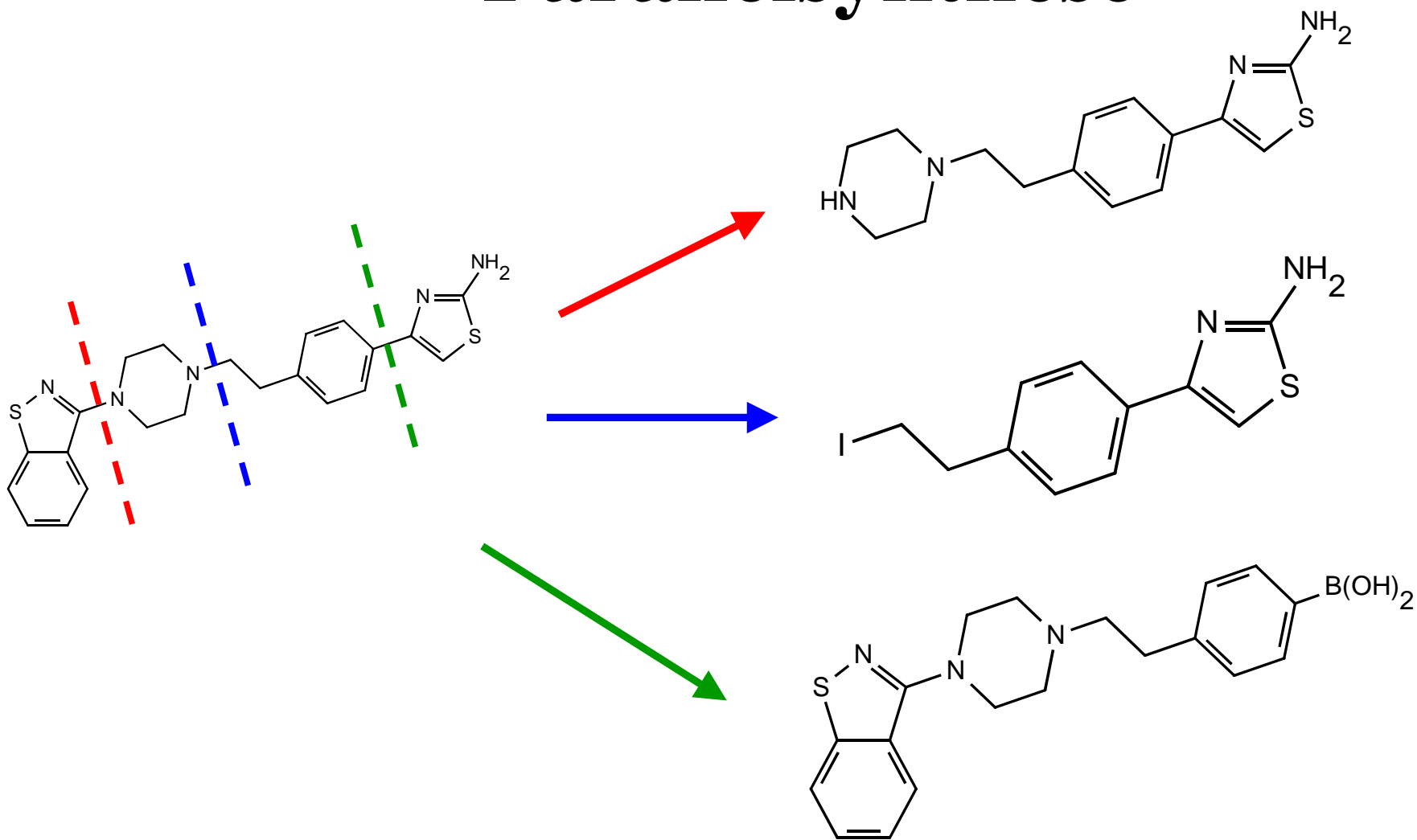
Planung einer Parallelsynthese



Retrosynthese

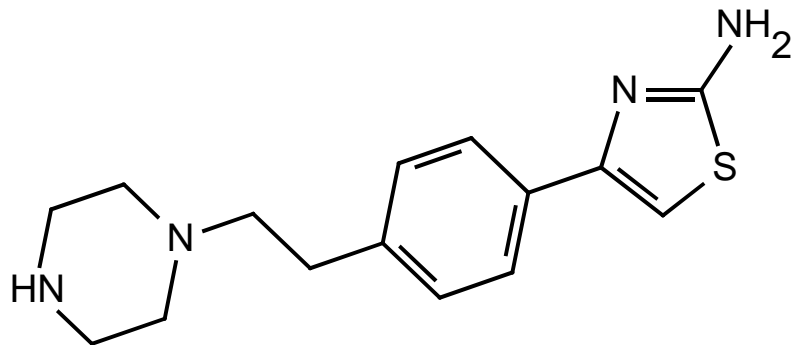


Planung einer Parallelsynthese

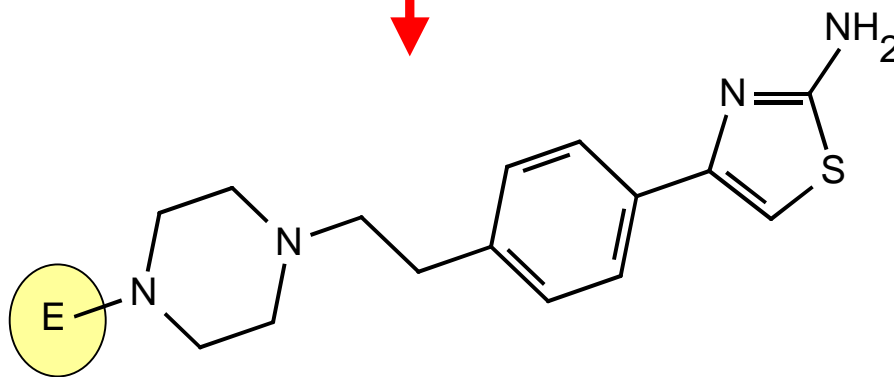




Planung einer Parallelsynthese

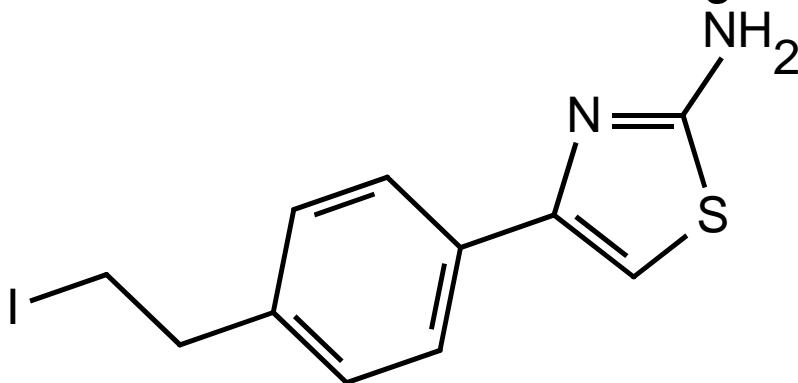


→ 400 neue Analoga

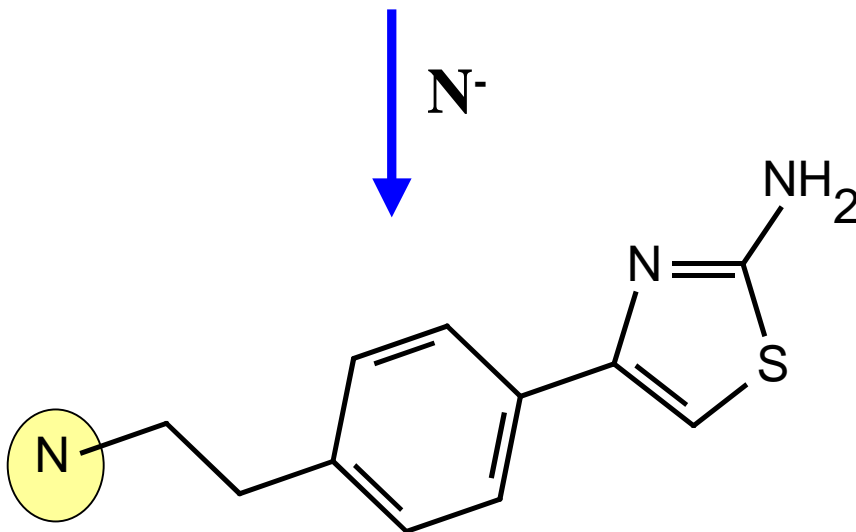




Planung einer Parallelsynthese

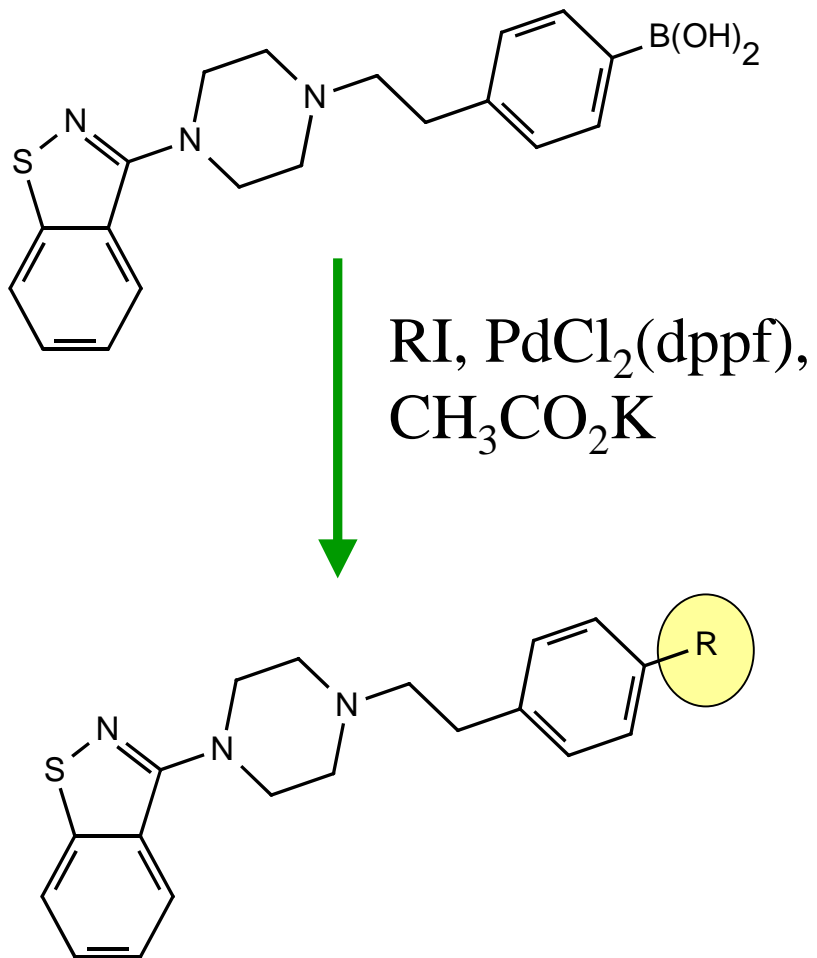


→ 360 neue Analoga

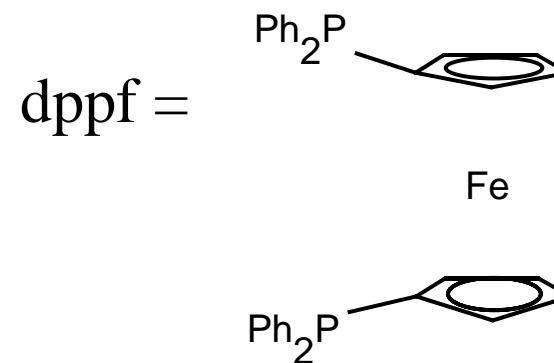




Planung einer Parallelsynthese



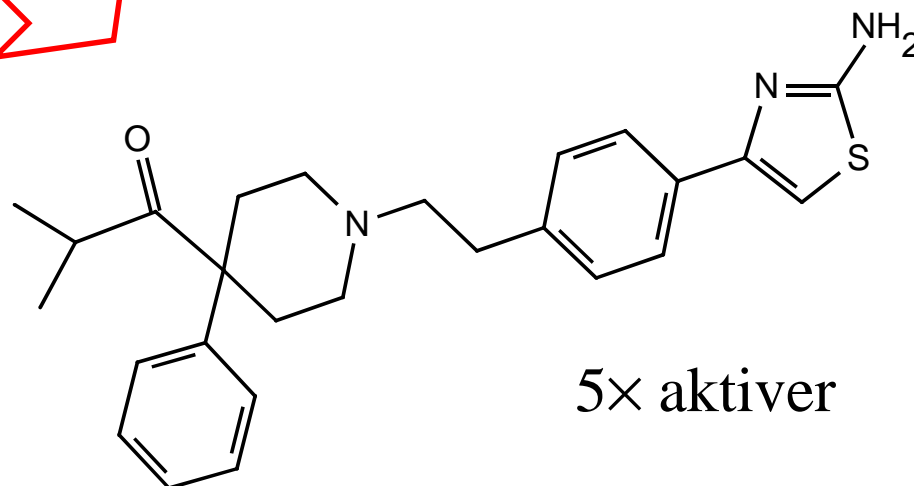
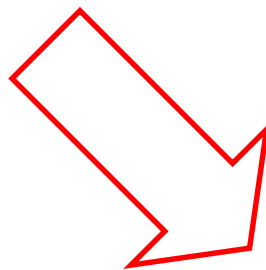
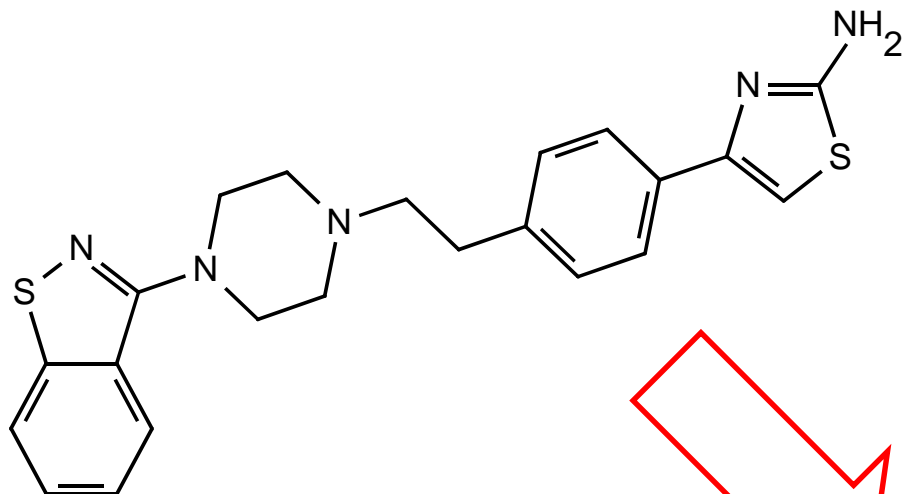
Suzuki-Kopplung,



→ 60 neue Analoga



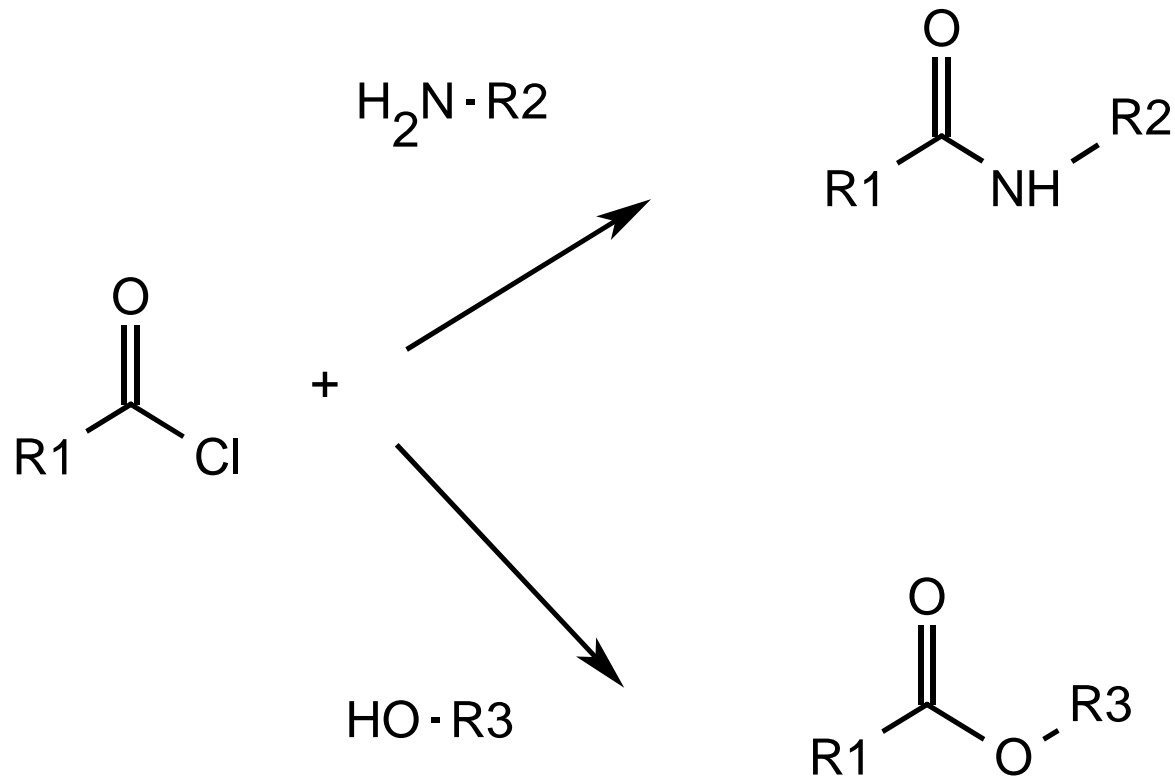
Planung einer Parallelsynthese



5× aktiver



Indizierte Bibliotheken





Indizierte Bibliotheken

Satz 1	Satz 2
$A_1 + N_{1-40}$	$N_1 + A_{1-40}$
$A_2 + N_{1-40}$	$N_2 + A_{1-40}$
$A_3 + N_{1-40}$	$N_3 + A_{1-40}$
$A_4 + N_{1-40}$	$N_4 + A_{1-40}$
$A_5 + N_{1-40}$	$N_5 + A_{1-40}$
.....
$A_{40} + N_{1-40}$	$N_{40} + A_{1-40}$

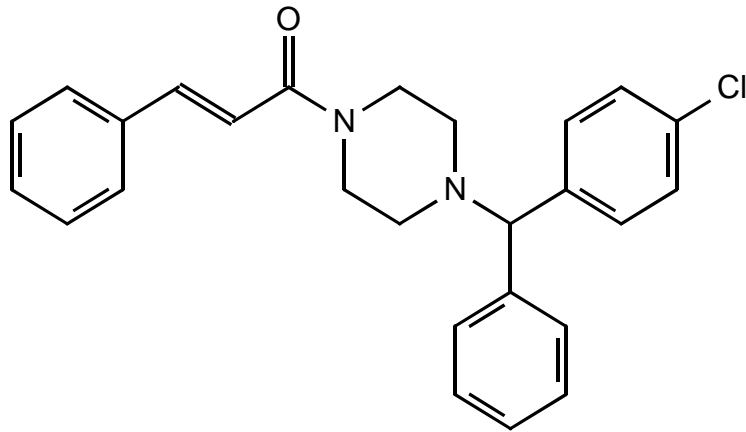


Indizierte Bibliotheken

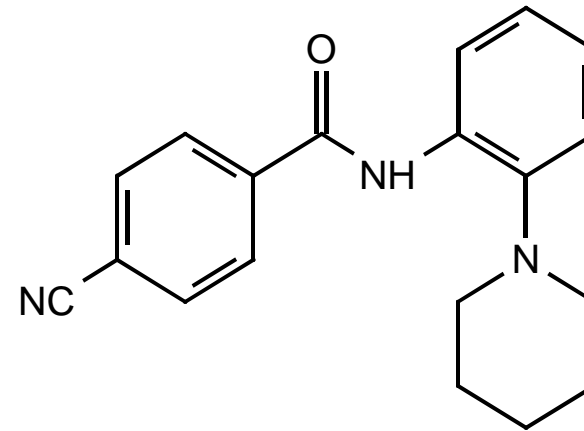
Satz 1	Satz 2
$A_1 + N_{1-40}$	$N_1 + A_{1-40}$
$A_2 + N_{1-40}$	$N_2 + A_{1-40}$
$A_3 + N_{1-40}$	$N_3 + A_{1-40}$
$A_4 + N_{1-40}$	$N_4 + A_{1-40}$
$A_5 + N_{1-40}$	$N_5 + A_{1-40}$
.....
$A_{40} + N_{1-40}$	$N_{40} + A_{1-40}$



Neue Verbindungen



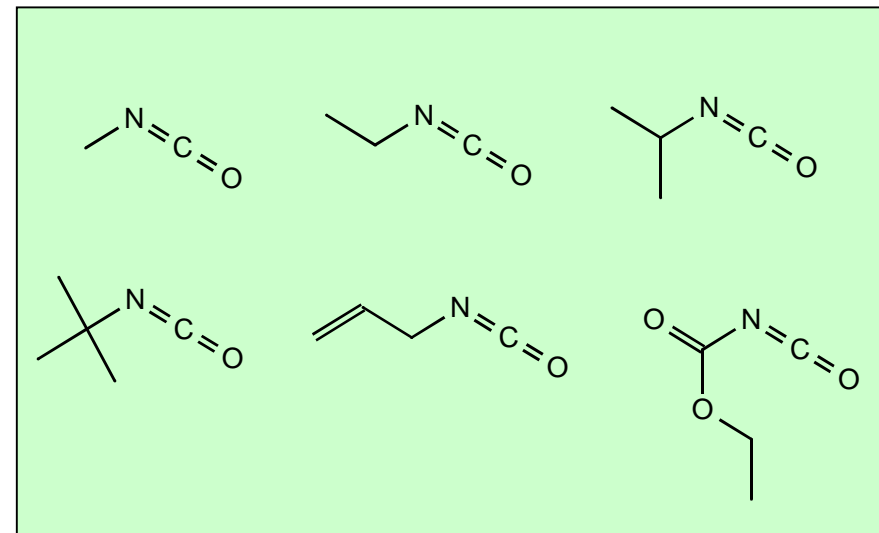
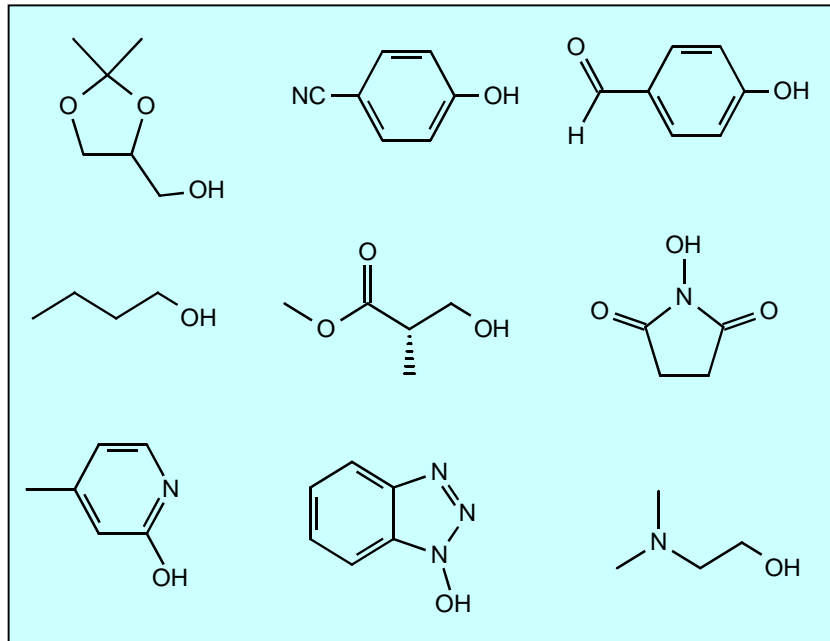
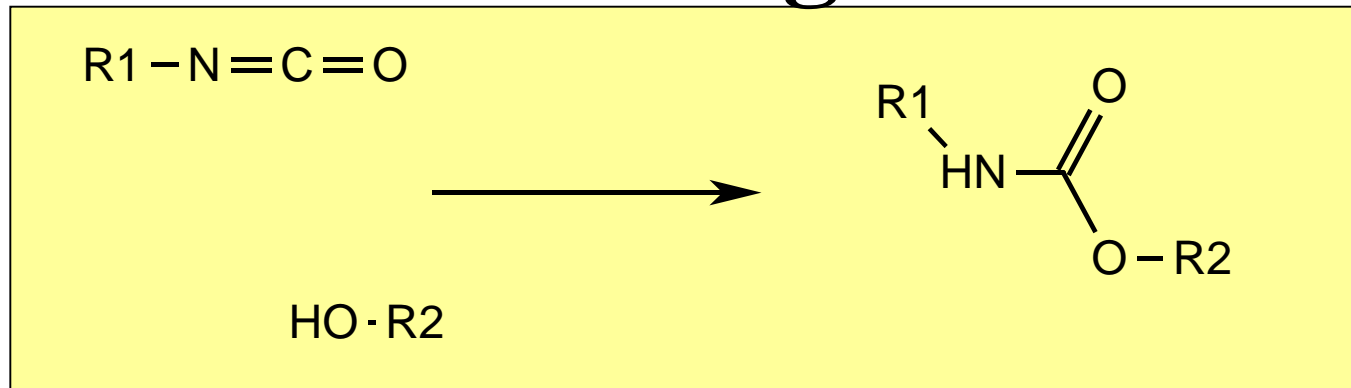
Neurokinin-3-Rezeptor-
Antagonist (60 μM)



Matrix-Metalloproteinase-1-
Antagonist (55 μM)

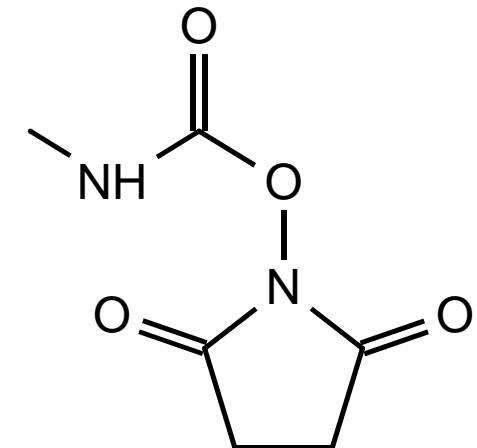
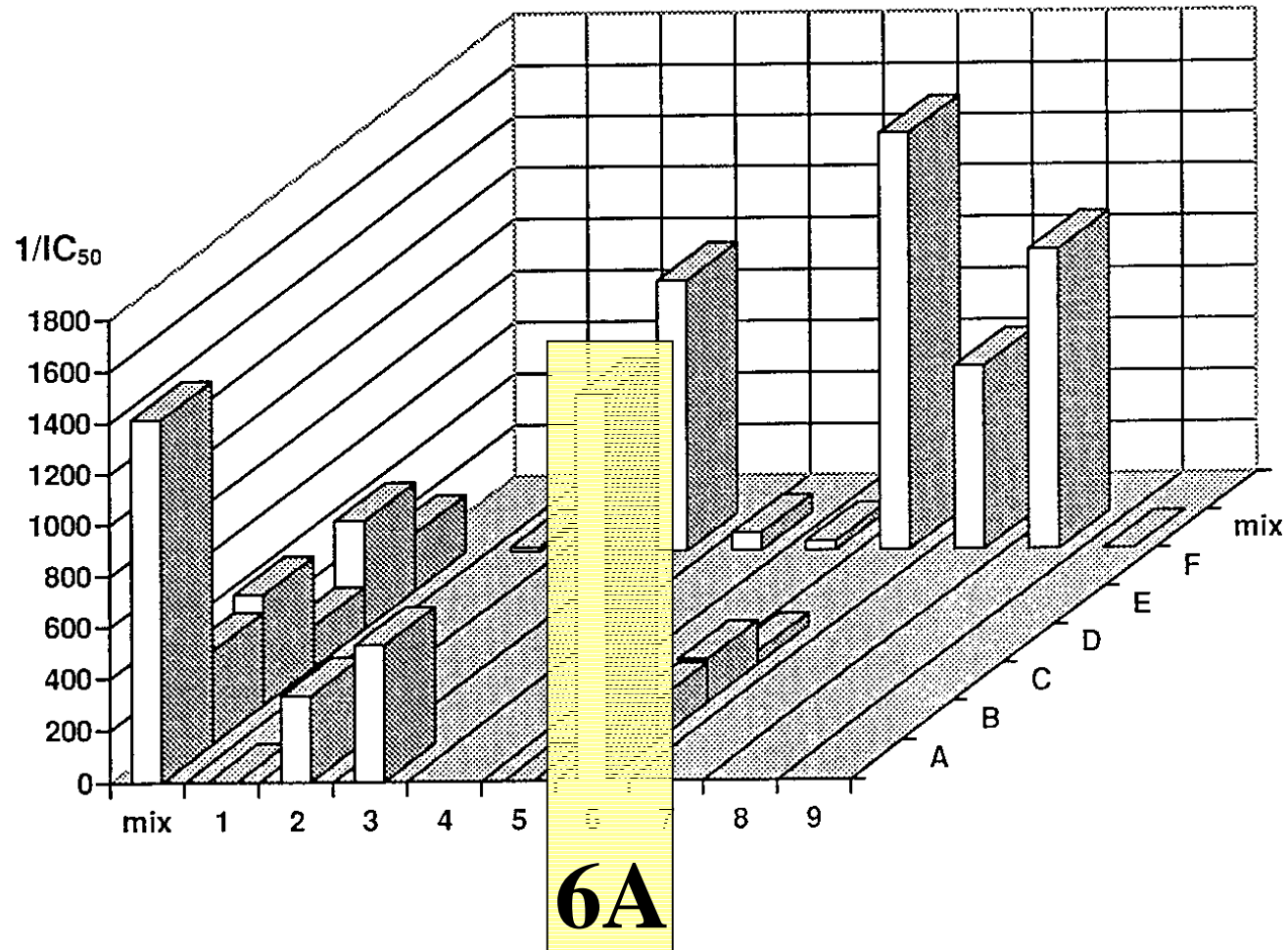


Acetylcholinesterase- Antagonisten



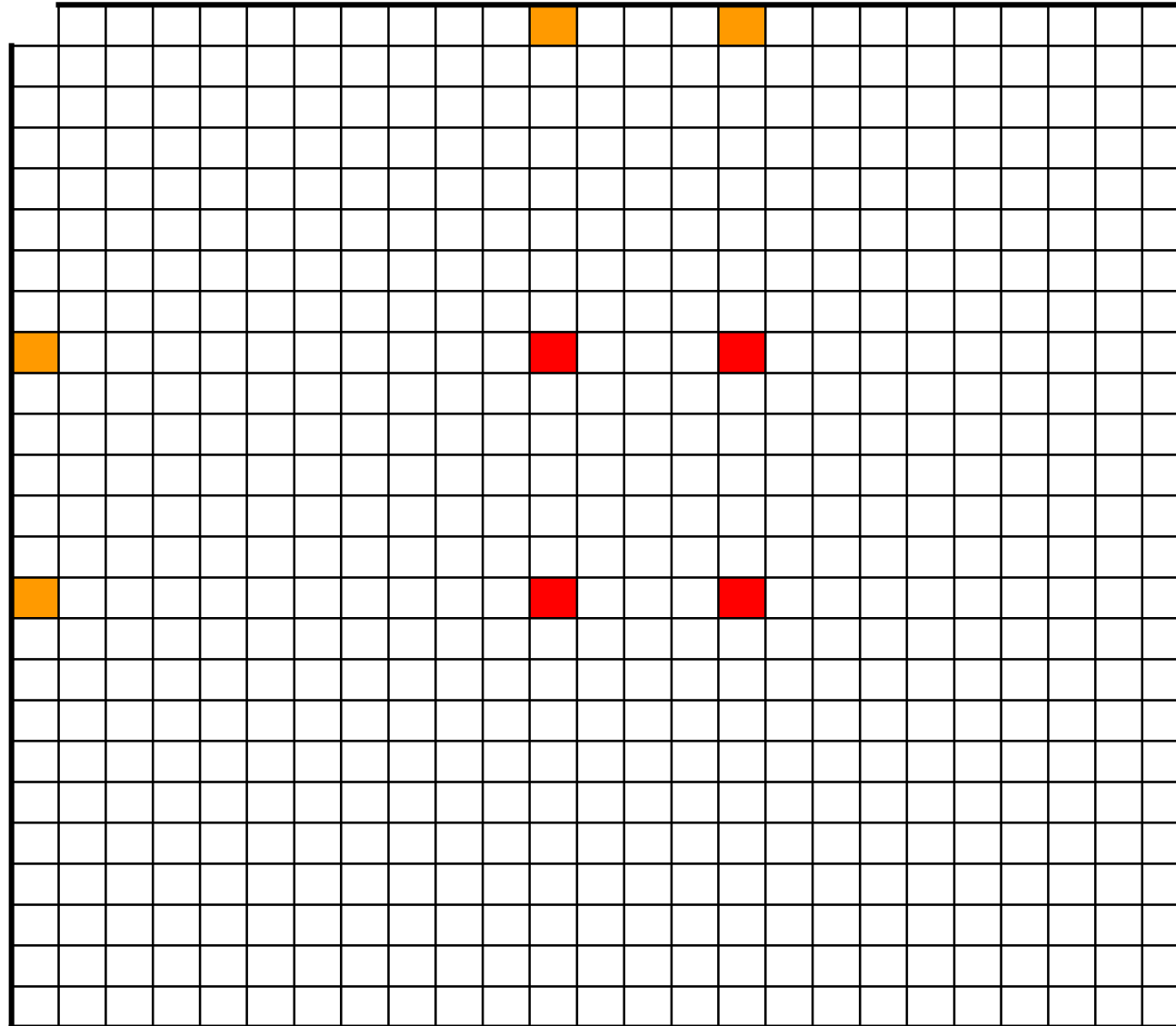


Acetylcholinesterase- Antagonisten



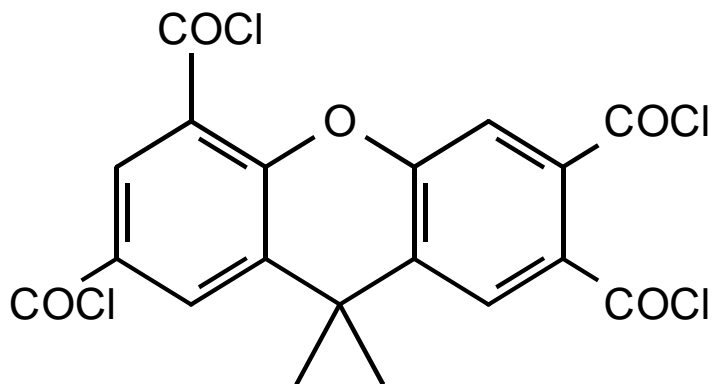


Indizierte Bibliotheken

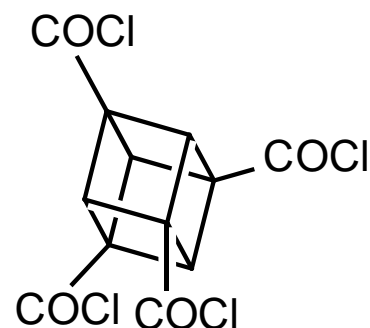




Templat-Synthesen



Xanthen-Bibliothek
21 Amine → 97.461
Verbindungen



Cuban-Bibliothek
21 Amine → 916.611
Verbindungen

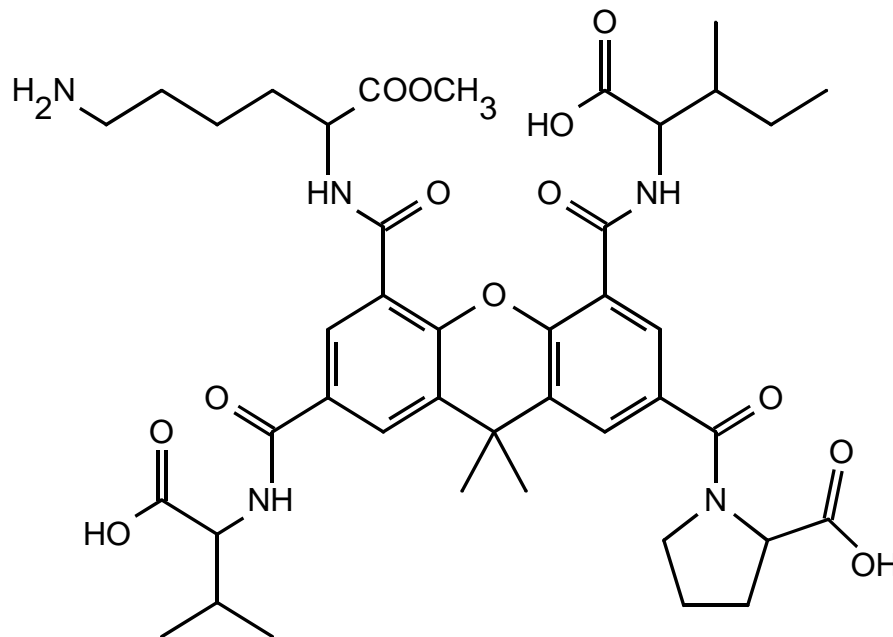
Reaktion mit einer Mischung aus Aminen gibt sowohl Reagenz.Kombinationen als auch Positionsisomerie.



Templat-Synthese

Lys, Ile, Pro und Val am aktivsten → 12 mögliche

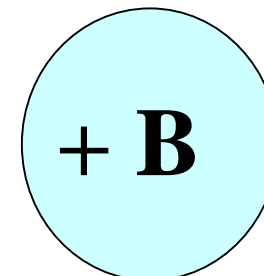
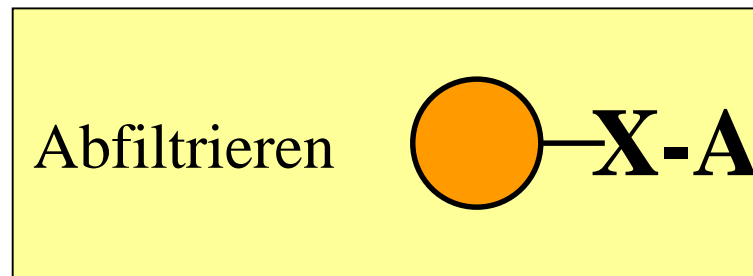
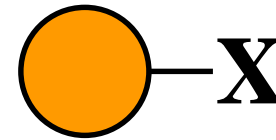
Xanthen-Lys,Ile,Pro,Val-Isomere



9 μ M Tripsin-Inhibitor

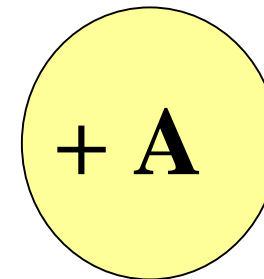
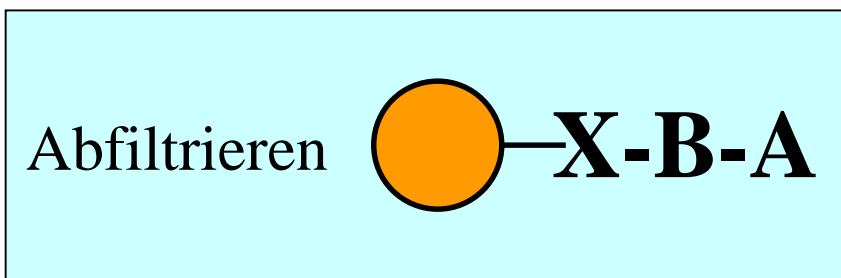
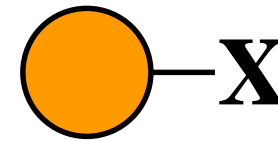


Festphasenreagenzien



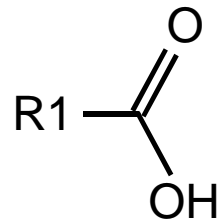


Harzabfangreagenzien

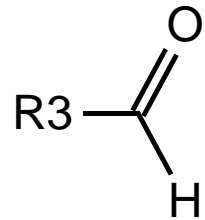




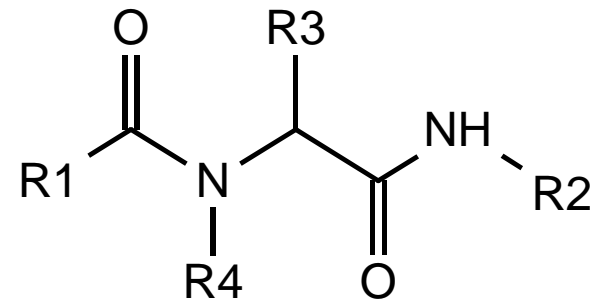
Die Ugi-Reaktion



R2 - NC

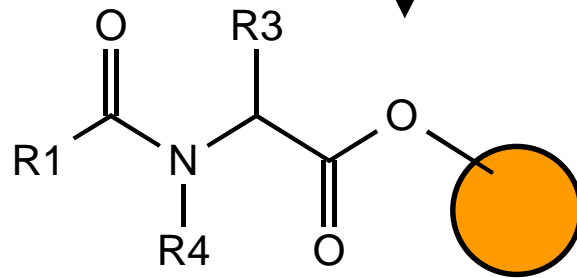
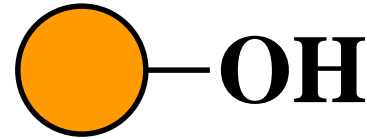
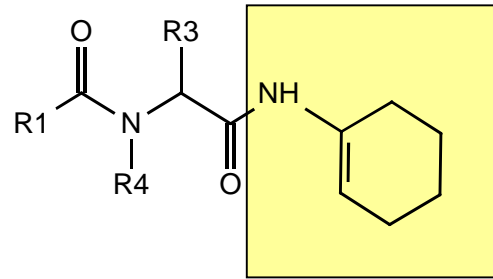
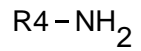
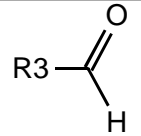
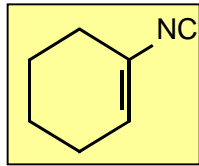
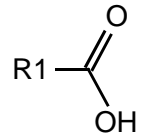


R4 - NH₂



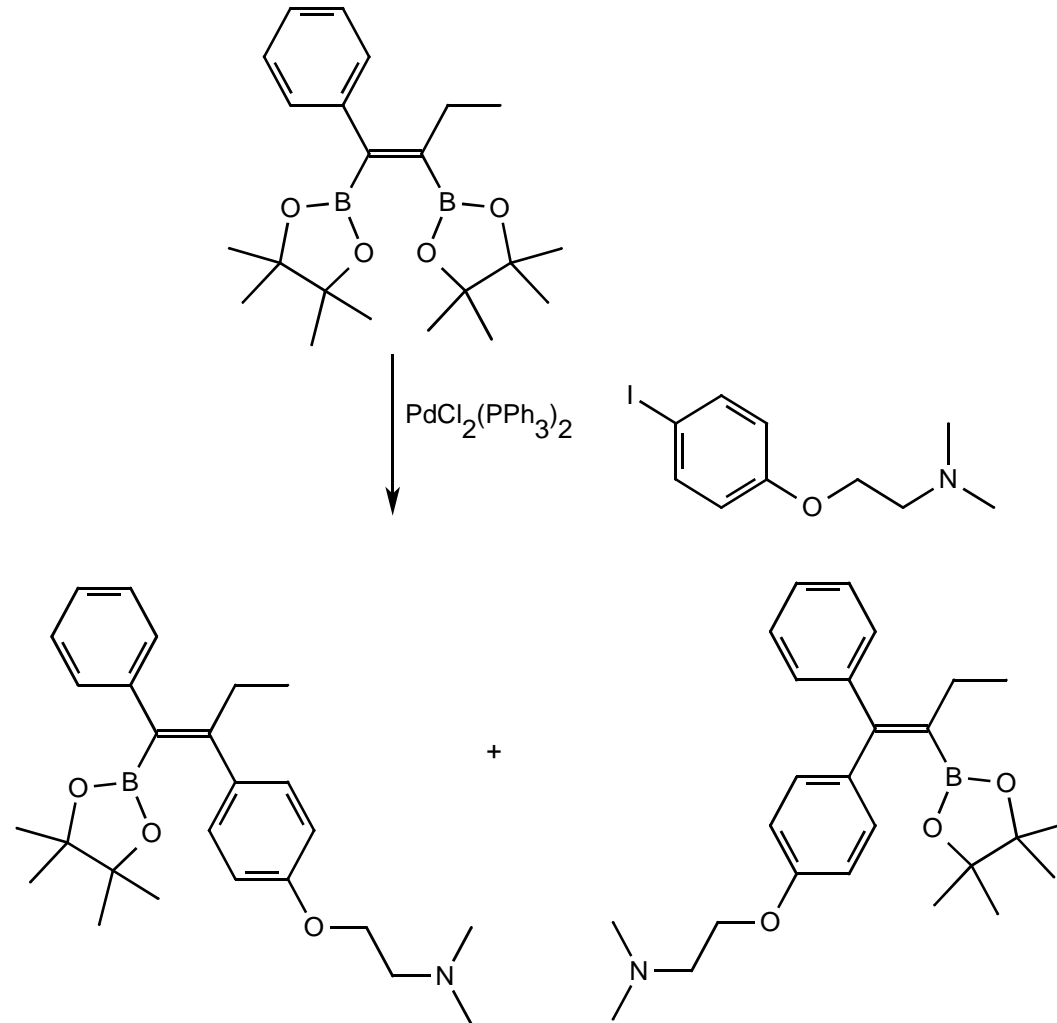
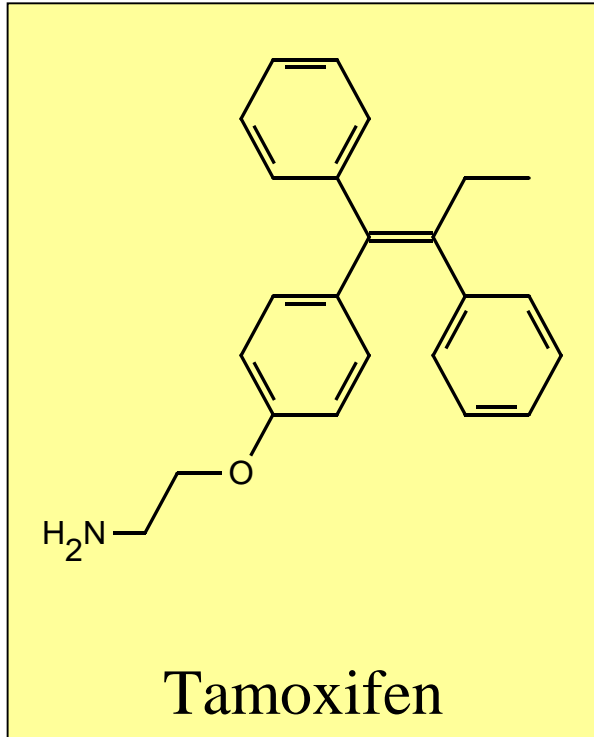


Die Ugi-Reaktion



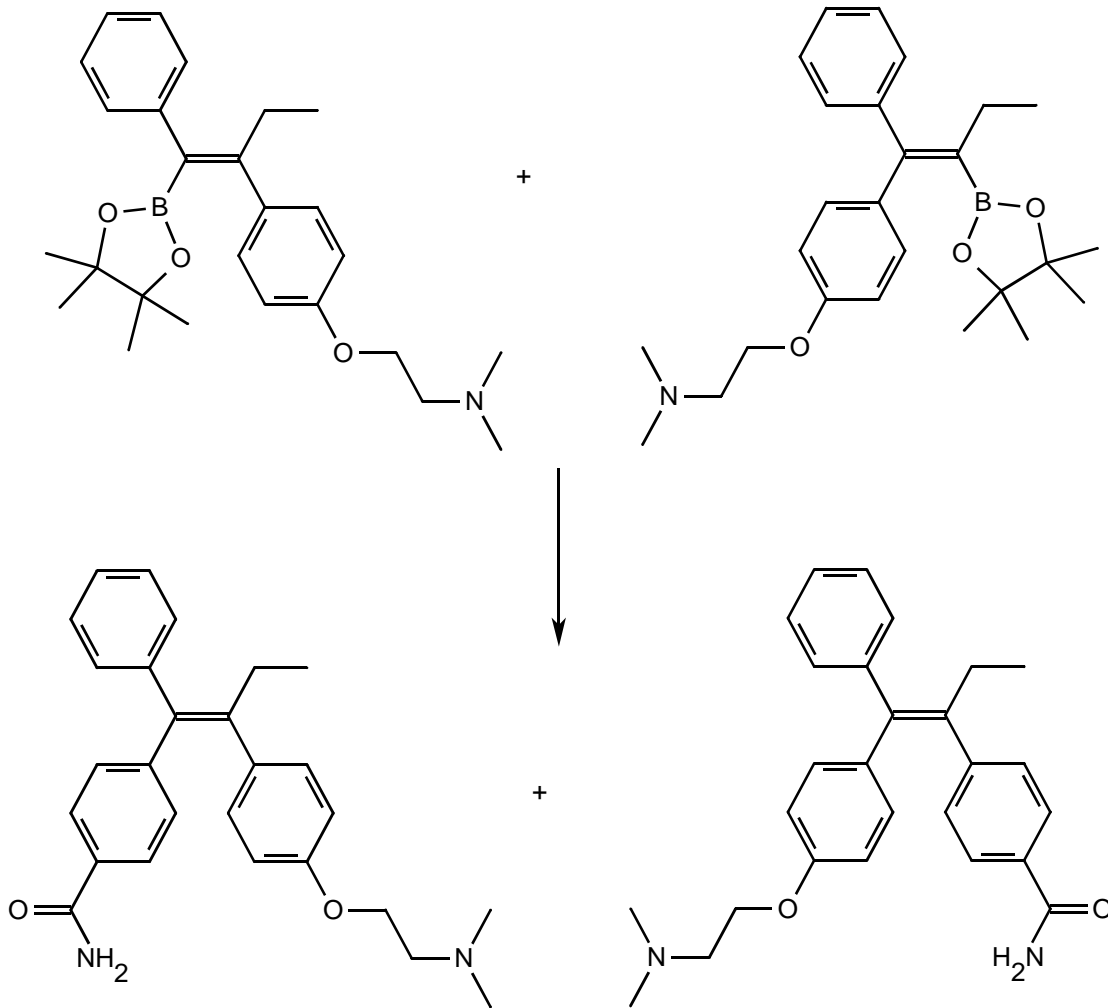


Synthese von Tamoxifen- Analoga





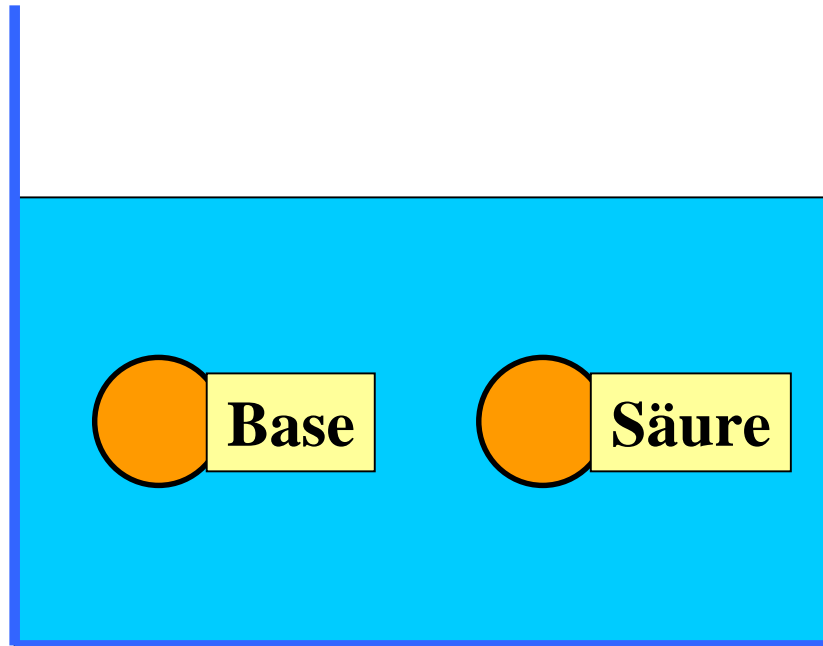
Synthese von Tamoxifen- Analoga



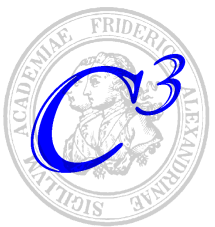
1.
2. CF_3COOH



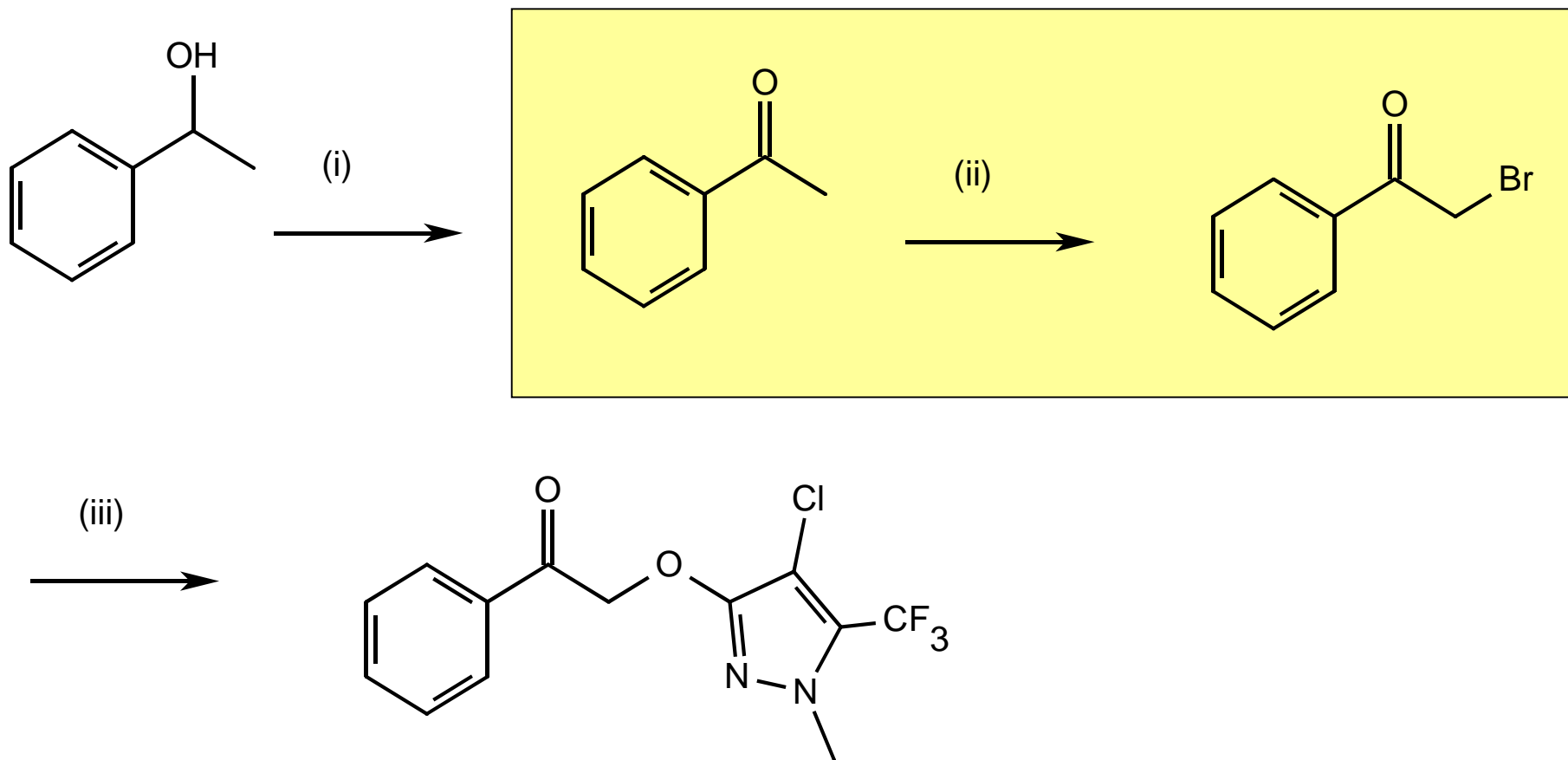
Mehrstufige Synthesen mit Harzreagenzien

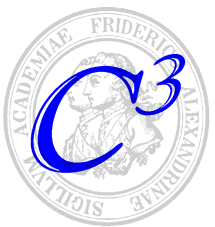


Keine Reaktion!

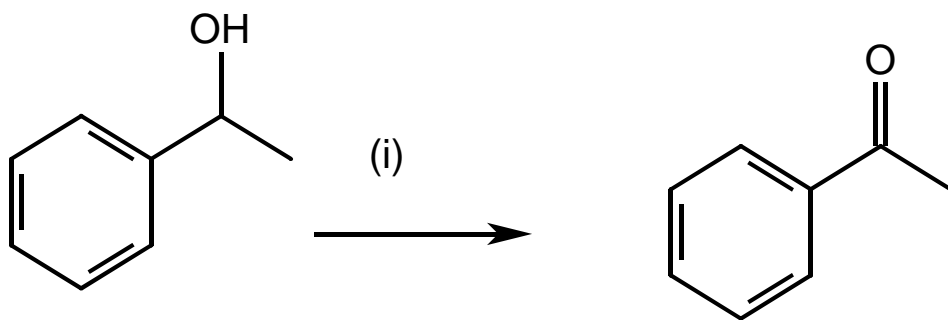


Mehrstufige Synthesen mit Harzreagenzien

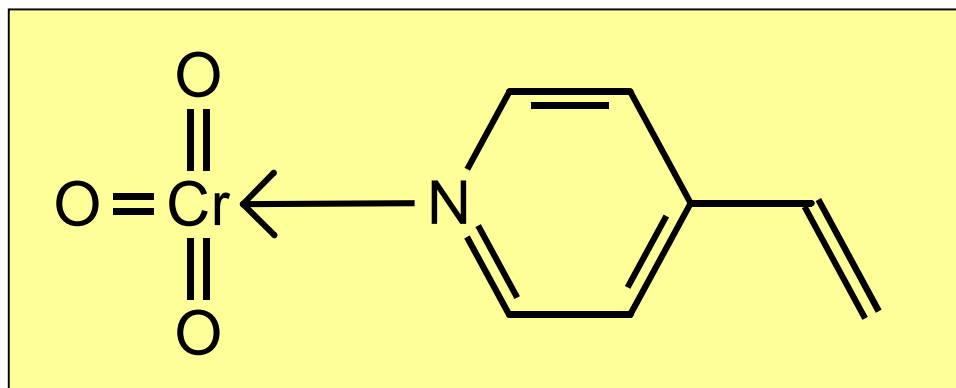


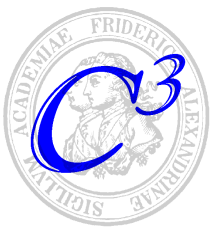


Mehrstufige Synthesen mit Harzreagenzien

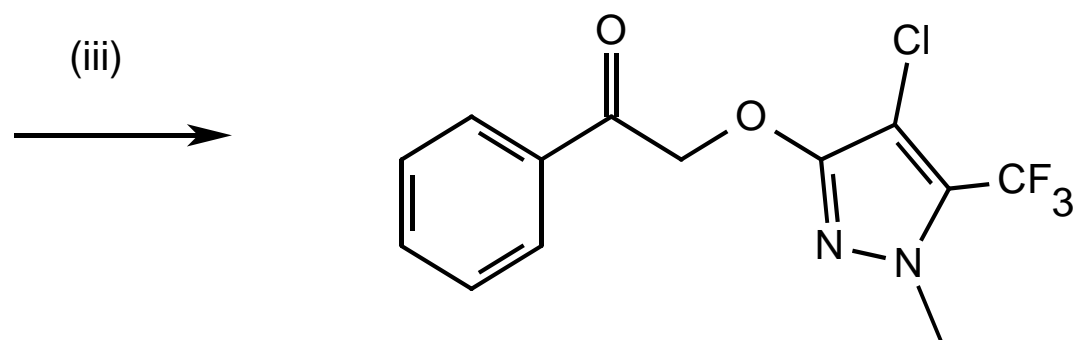
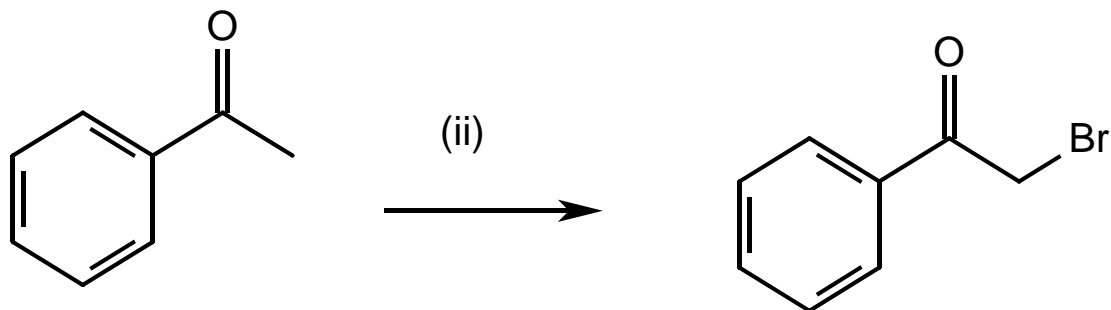


(i) = Poly(4-vinylpyridiniumdichromat)

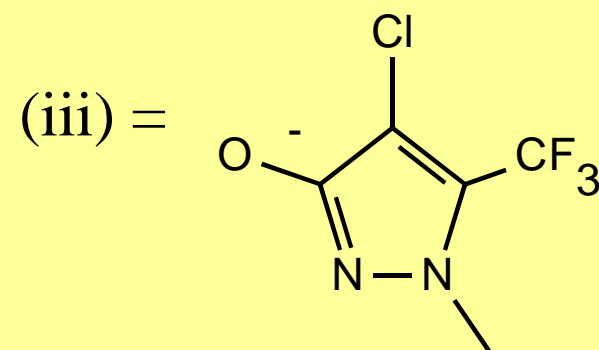




Mehrstufige Synthesen mit Harzreagenzien



(ii) = Perbromid auf
Amberlyst A-26



auf Amberlite IRA 900