Chimie durable
et Chimie Médicinale

Marc Lemaire ; Antananarivo 09

1°Les 12 principes de la « green chemistry »

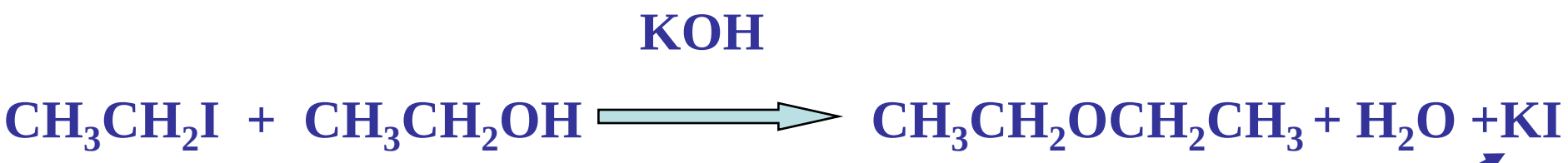
1° Prevention
2°Atom economy
3°Less Hazardous chemical synthesis
4°Designing Safer chemicals
5°Safer solvents and auxiliaries
6°Design energy efficiency
7°Use of renewable feedstocks
8°Reduce derivatives
9°Catalysis
10°Design for degradation
11°Real time analysis for pollution prevention
12° Inherent Safer Chemistry for accident prevention

Advancing Sustainility through Green ; R.L. Lankey & P.T. Anastas / Chemistry and Engineering ACS Symposium Series 823 2002
Green Chemistry ; P.T. Anastas & T.C. Williamson Oxford University Press 1998

1.1 formation de fonction éther

2°Atom economy

Synthèse des éthers de Williamson (1851)

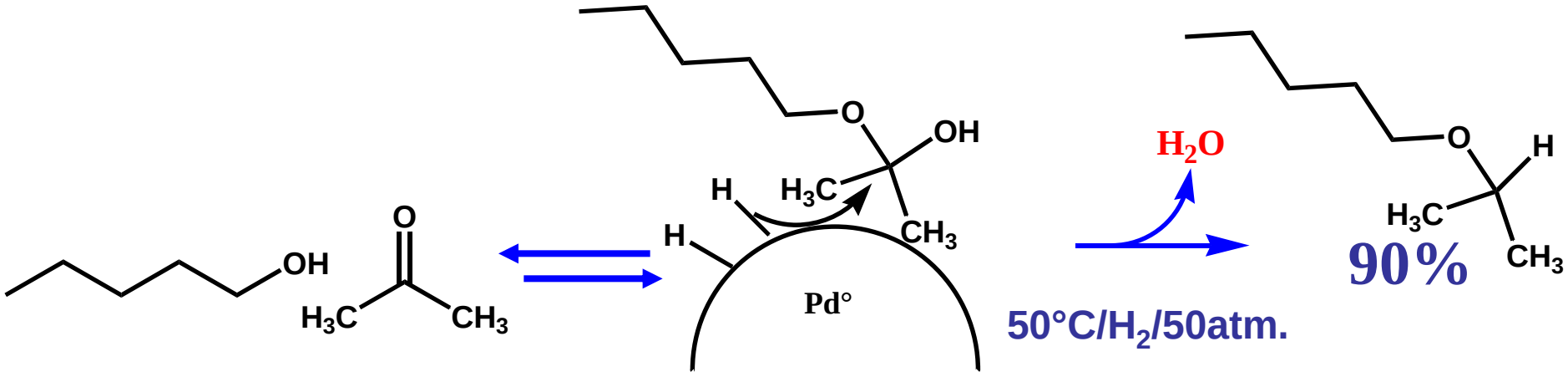


Réaction efficace et toujours utilisée
Mais production de sels

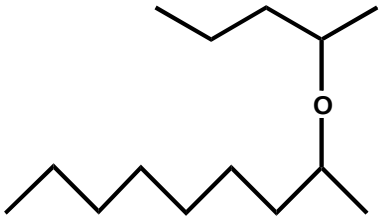
Williamson W. Liebigs Ann. Chem. 1851 , 77 , 37-49

économie d'atome

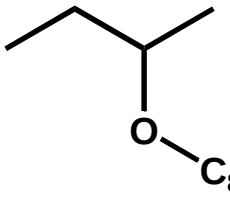
Synthèse d'éther par alkylation réductrice



90%

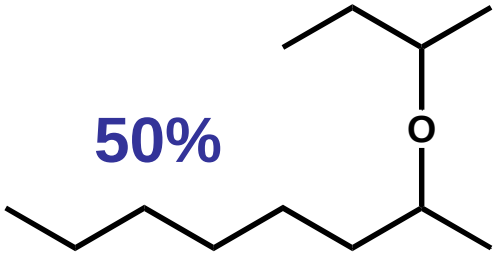


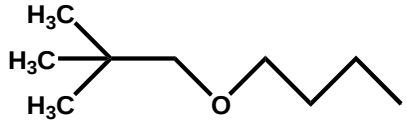
65%



80%

50%





95%

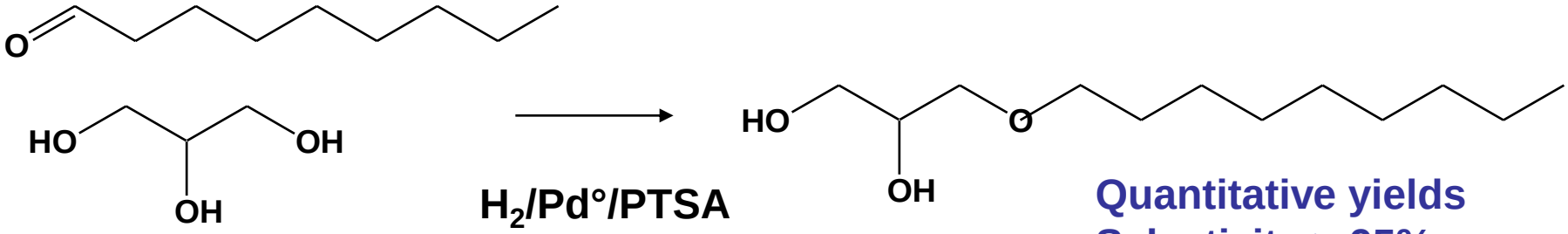
2°Atom economy
7°Use of renewable feedstocks

Shi Yan

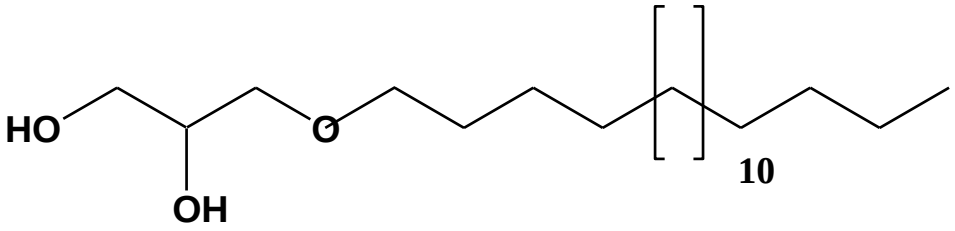
Utilisation de la catalyse et valorisation des ressources renouvelables

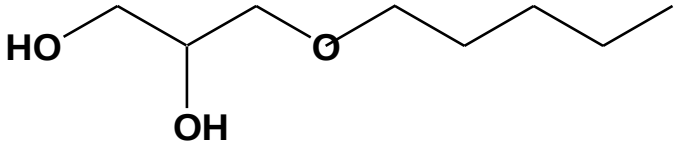
ethers du glycerol

Développement : Rhodia & Sofiproteol



Quantitative yields
Selectivity > 95%





1.2 Nouvelles méthodes catalytiques de formation de liaison Aryl-aryl

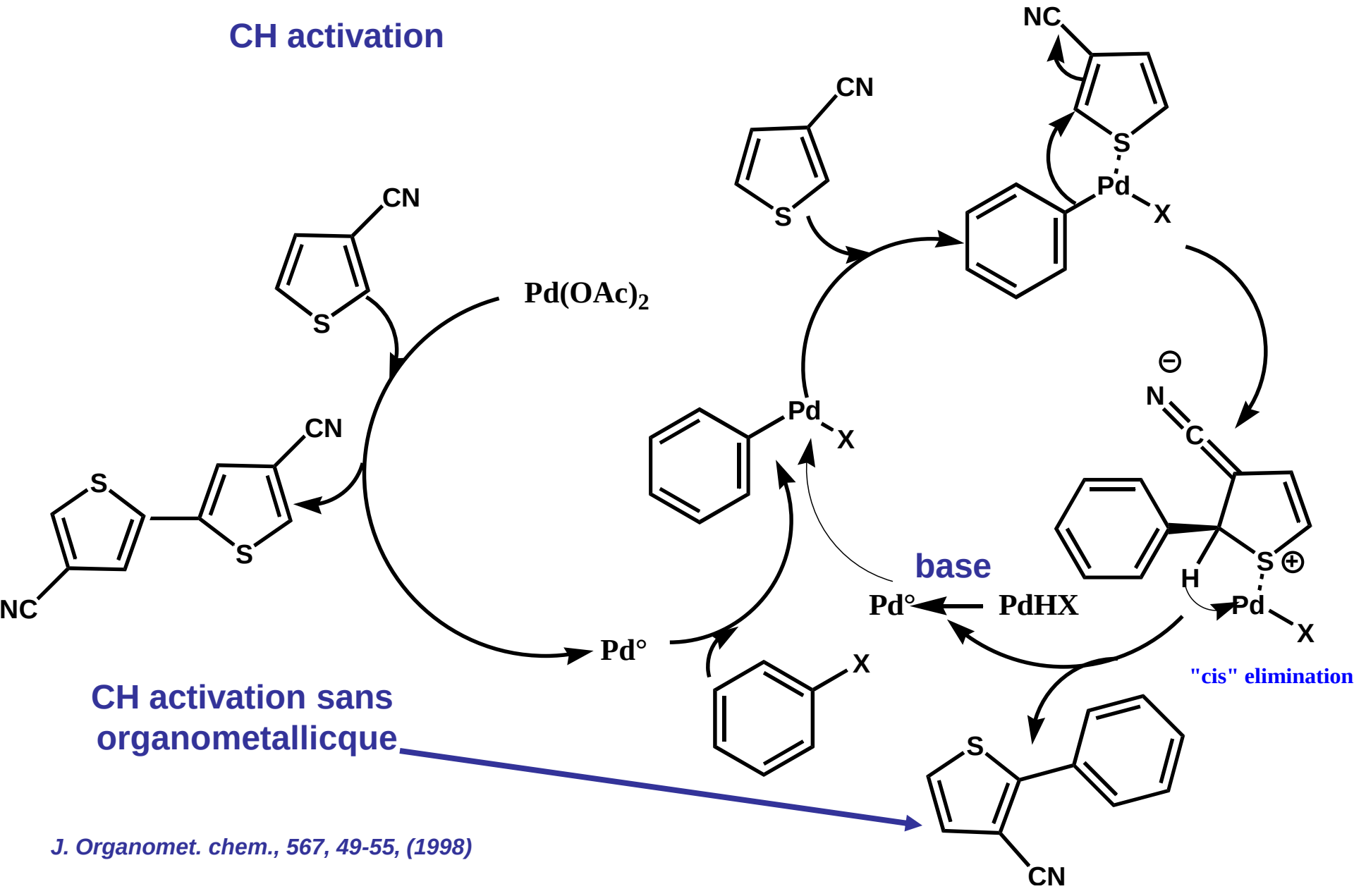
2°Atom economy 8°Reduce derivatives 9°Catalysis

1902 Réaction de Ullmann (cuivre stoechiométrique)
1972 Réaction de Kumada-Corriu (nickel/magnésien)
1976 Réaction de Negishi (palladium/zincique)
1978 Réaction de Stille (palladium/stannique)
1979 Réaction de Suzuki-Miyaura (palladium/boronique)

1970 Réaction de Heck-Mizoroki (palladium)

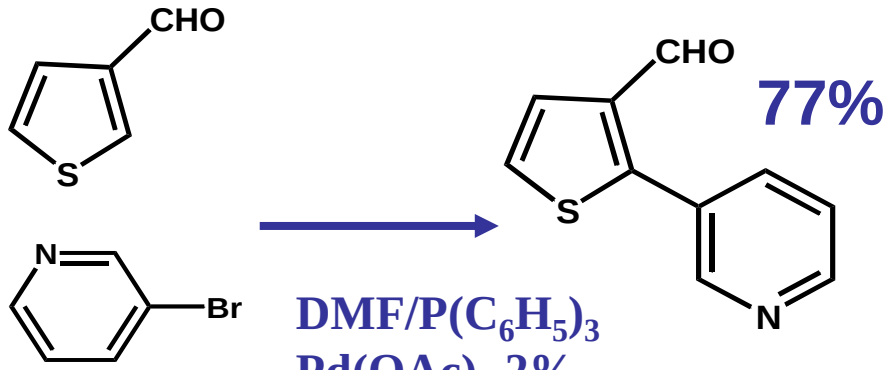
Chemical Review, 102, 1359-1469, 2002

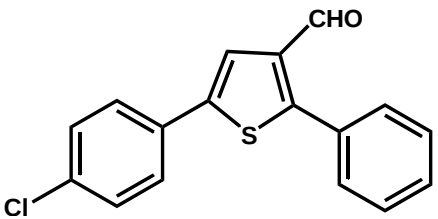
Arylation directe du thiophène

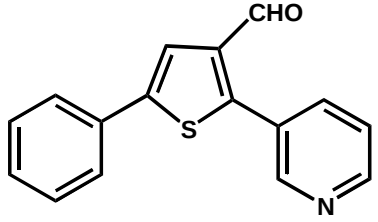


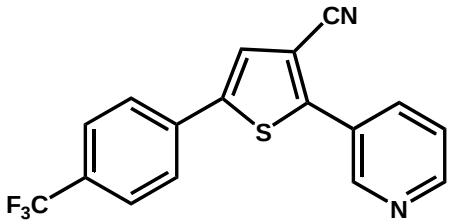
J. Organomet. chem., 567, 49-55, (1998)

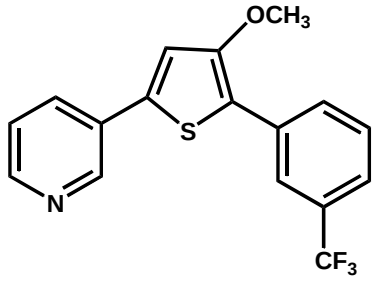
Activation CH du thiophène

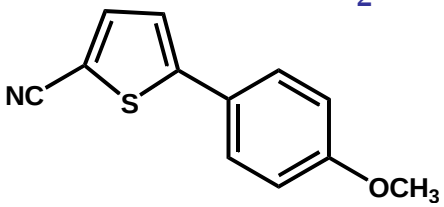


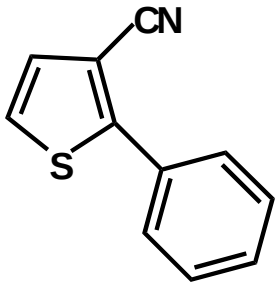


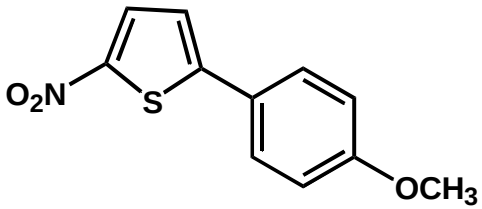


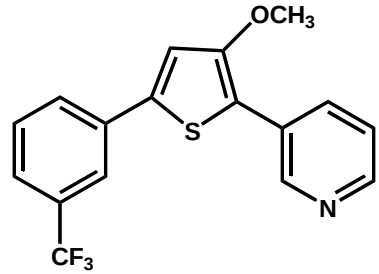


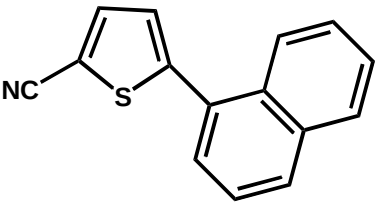


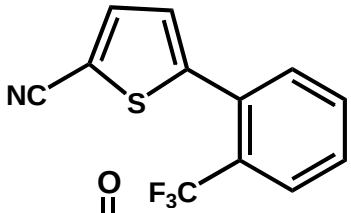


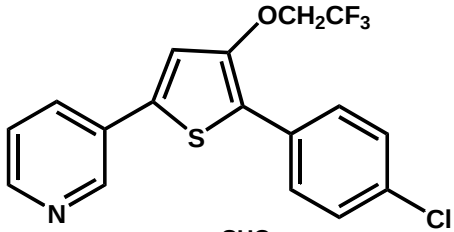


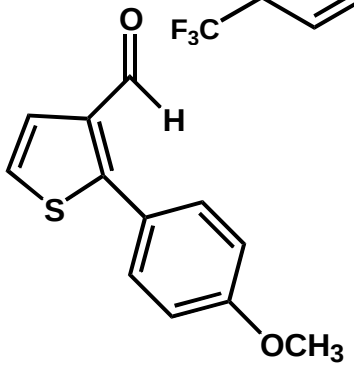


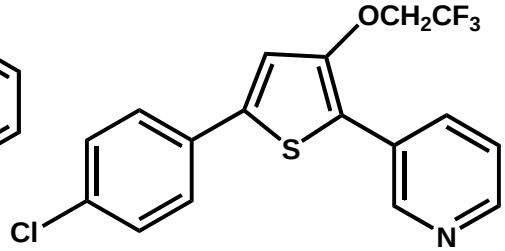


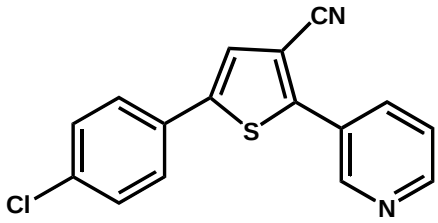


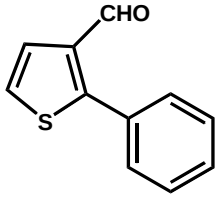


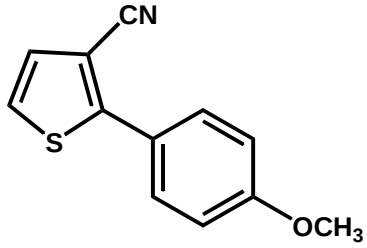


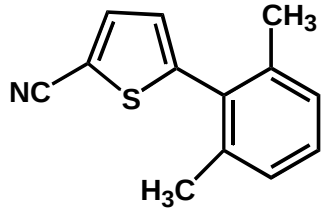


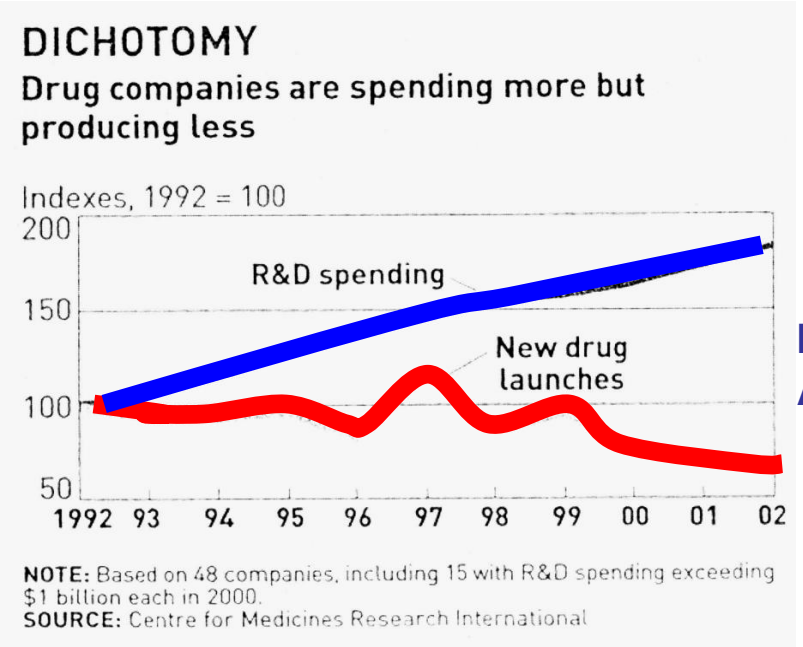












2°Catalyse et chimie médicinale

R & D Pharmacie

Durcissements des conditions de mise sur le marché
Augmentation de la complexité des molécules actives

Diminution rapide du nombre de nouvelles molécules commercialisées

Restructurations

Séparation des industries chimiques et pharmaceutiques
Séparation des industrie agrochimiques et pharmaceutiques
Fusions
Rationalisation; spécialisation
Abandon des domaines les moins « rentables »

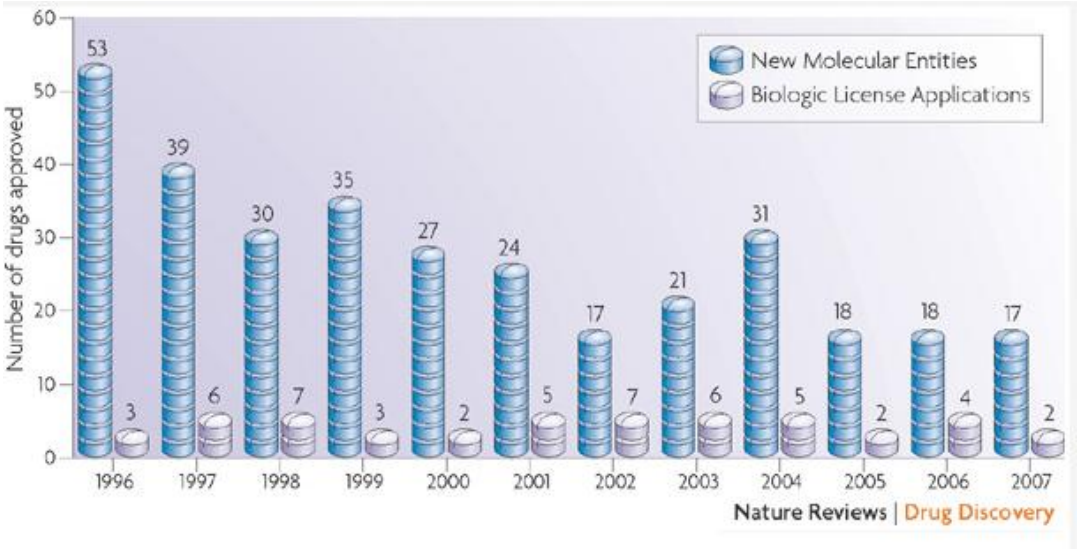
Nouvelles approches :

Synthèses et tests à hauts débits
Chimie combinatoire
Automatisation
Externalisation
Protéomique..
Modélisation, Criblage virtuel…..

Augmentation rapide des dépenses de R&D dans l'industrie pharmaceutique

Commercialisation de nouveaux médicaments 1997-2007

Baisse de la « productivité » en recherche pharmaceutique



-Les matières premières utilisées sont généralement communes:

Matières premières d'origine fossile (pétrole…)

Fournisseurs communs

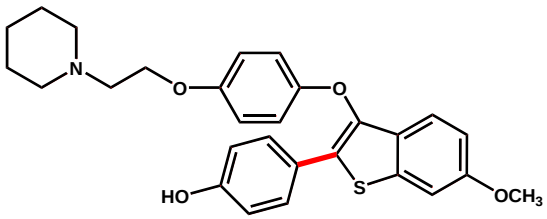
-Les réactions chimiques utilisées en « drug discovery » sont communes à la plupart des équipes académiques ou industrielles.

-Utilisation de relativement faible de catalyse:

mise au point généralement plus longues

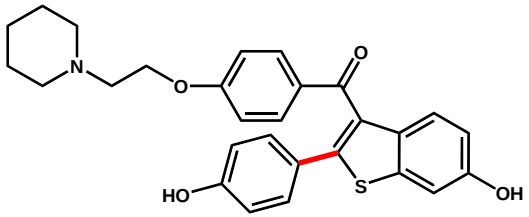
coût plus élevé (pas de recyclage en « discovery)

Propriétés biologiques des benzothiophènes

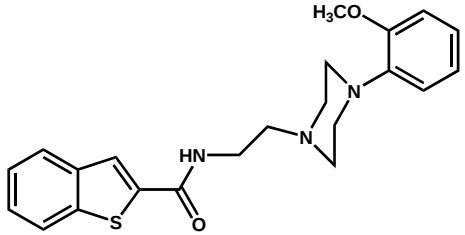


Selective estrogen receptor modulator

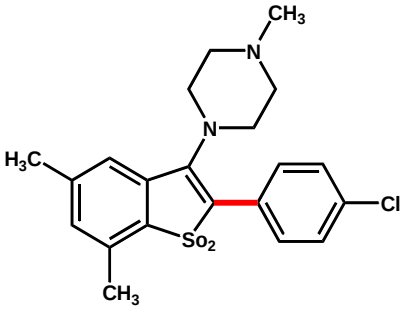
raloxifene



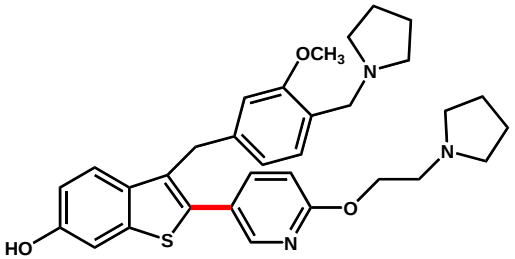
arzoxifene



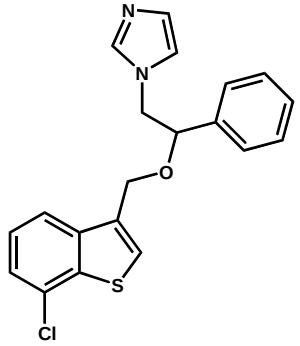
Schizophrenia treatment



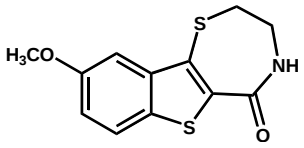
analgesic



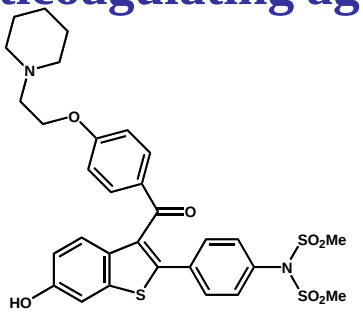
Anticoagulating agent



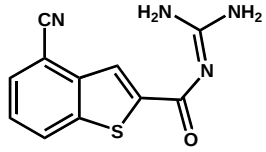
Antifongic (Monaezol^{R})



antiviral

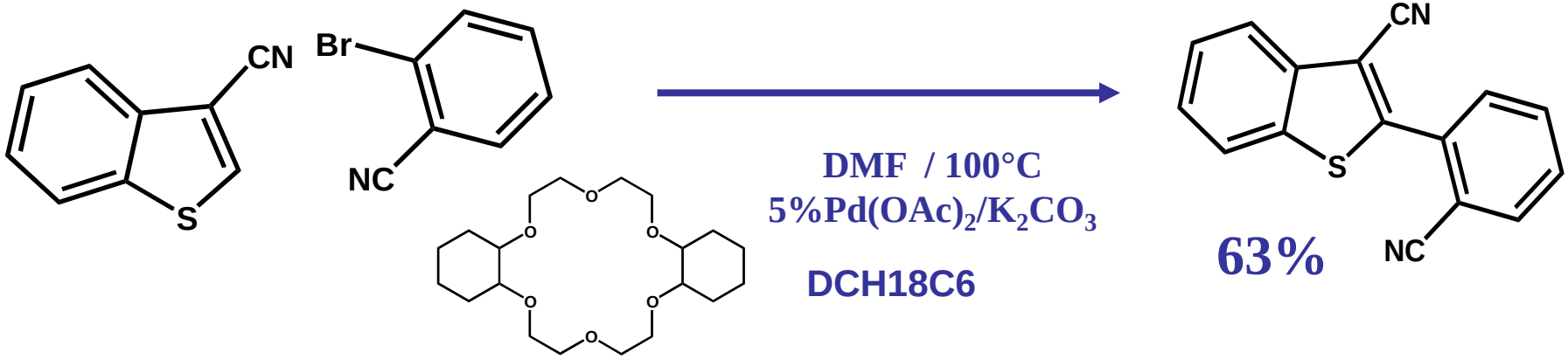


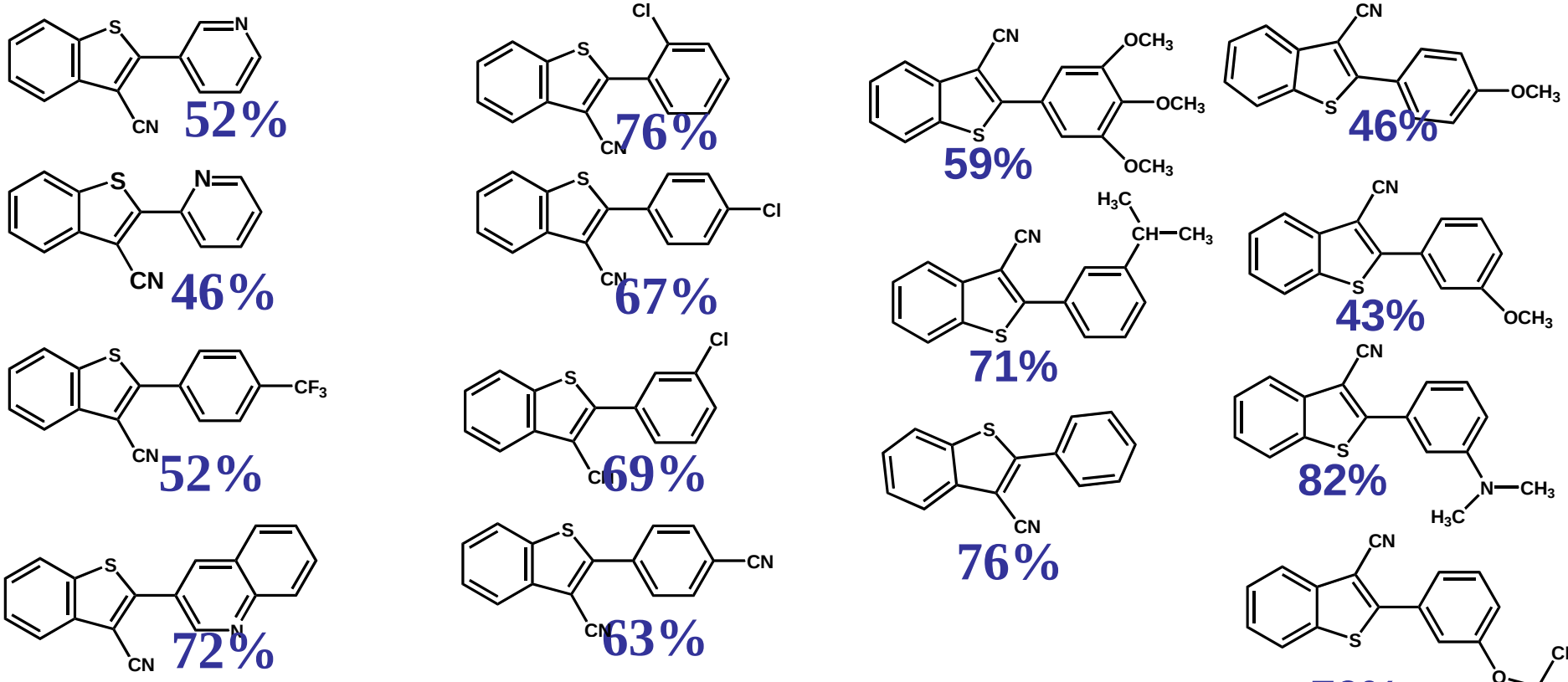
Inhibitor efflux pump



cardioprotector

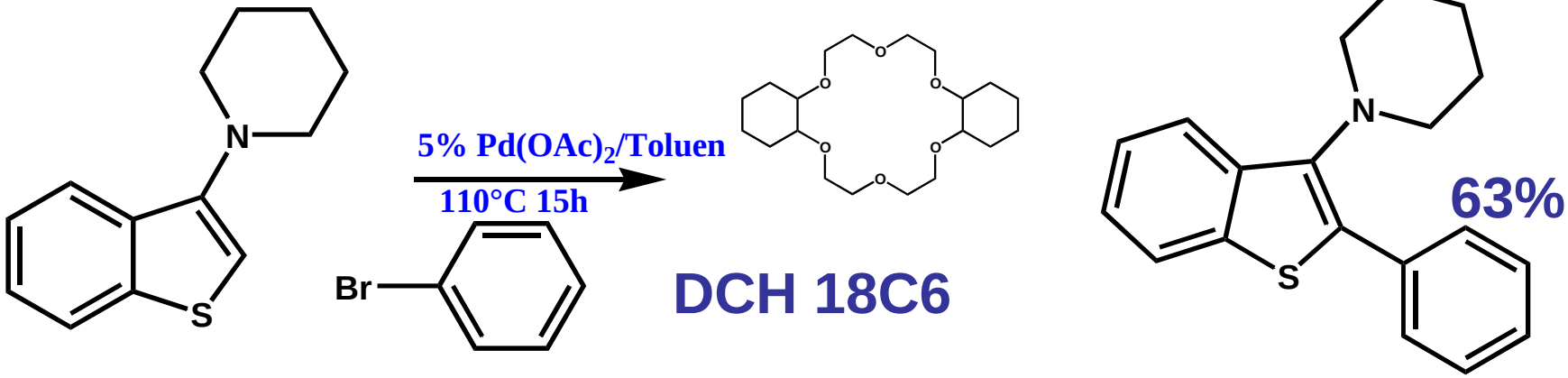
Arylation de benzothiophènes avec des groupements attracteurs

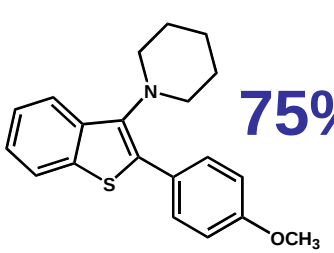


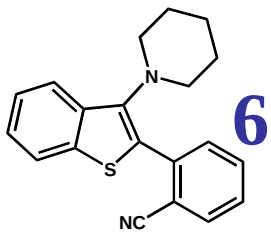


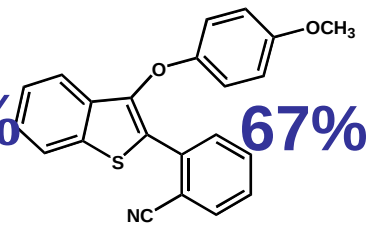
Tetrahedron Letters, 43, 1829-1833, 2002

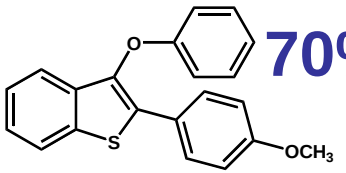
Arylation de benzothiophènes avec des groupements donneurs

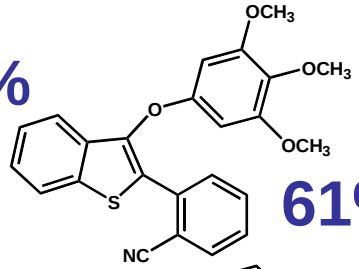


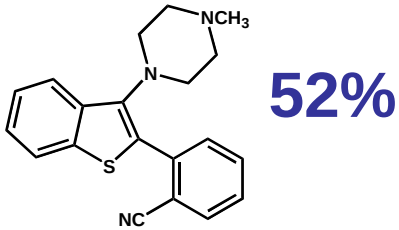


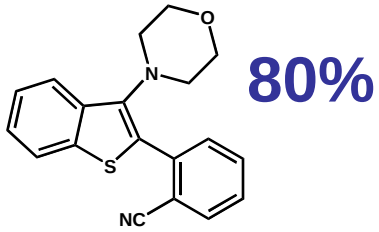


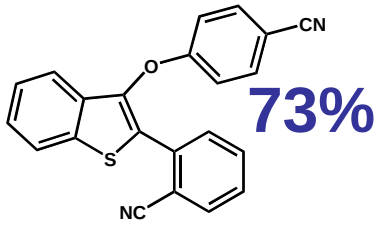


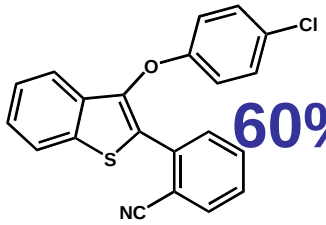


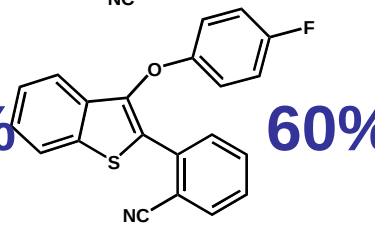


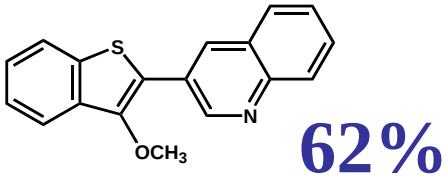


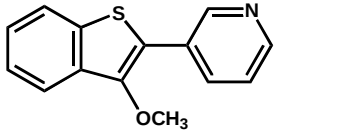


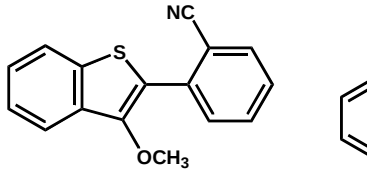


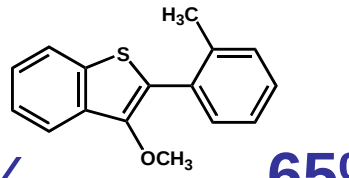


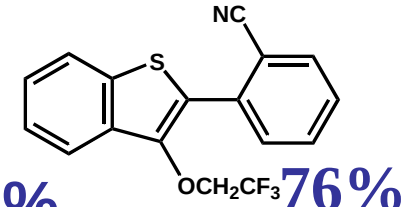












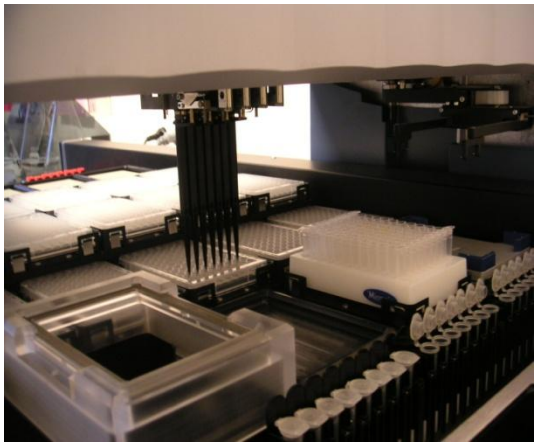
Tetrahedron 63 , (2007) 8999-9006

Chimiothèque de Lyon

Powder compounds

Weighing

operation



Dilution

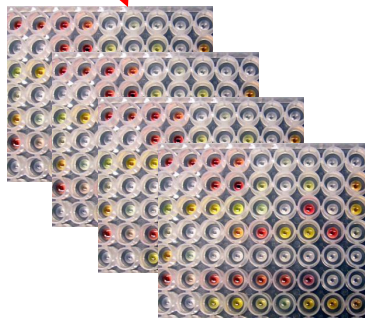
DMSO

96 well master plate
(25 mM)

Stocking of master boxes
and microplates in -28°C freezer

Daughter plates
1mM

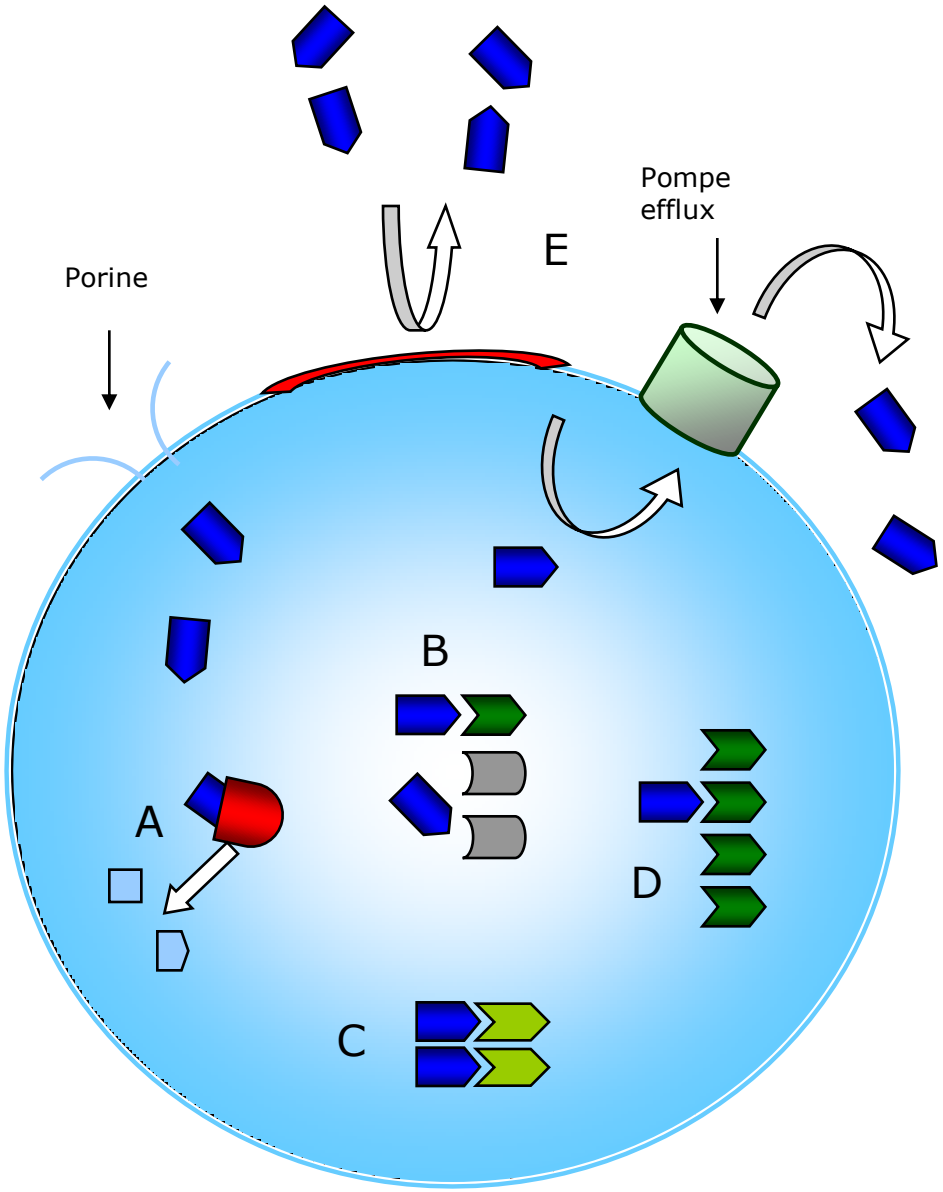
Daughter
plates
10 mM



Daughter plates
25 mM

Biological screening assays

2.1 Bactéries résistantes aux antibiotiques



Mécanismes de résistance :

A : inactivation de l'antibiotique

B : modification de la cible

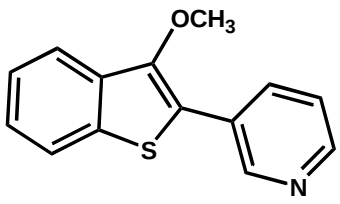
C : substitution de la cible

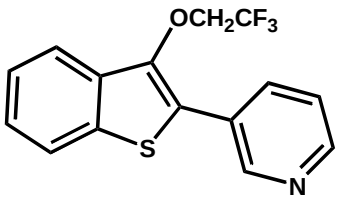
D : surexpression de la cible

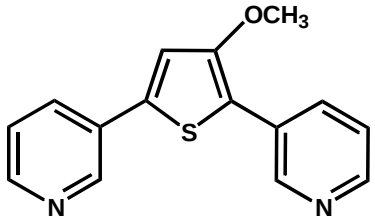
E : diminution de la concentration en antibiotique création de pompes d »efflux

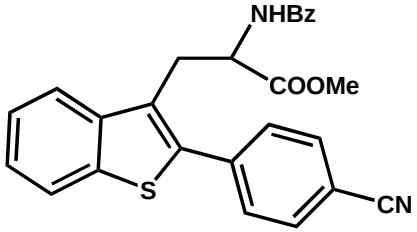
Évaluation des propriétés biologiques (plus de 400 molécules testées!!!)

1°activité antibiotique vis-à-vis de souches non résistantes de S. Aureus (ATCC 25923)

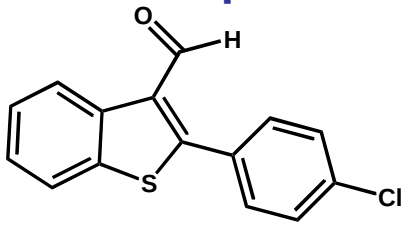


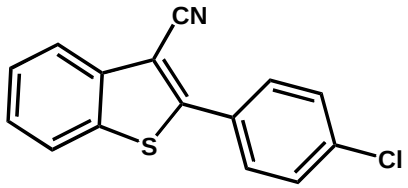


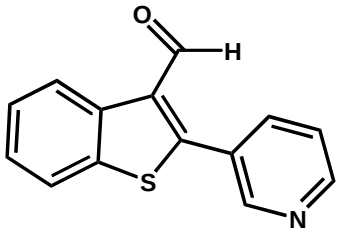


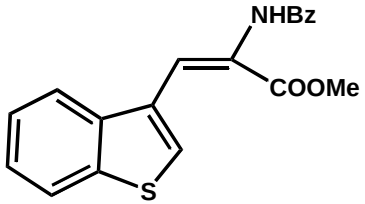


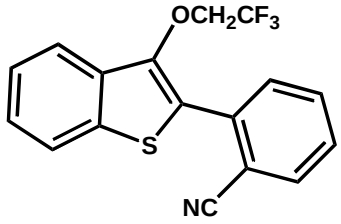
2° inhibiteur de résistance aux antibiotiques non spécifiques : fluoroquinolone (surexpression de pompes NORA) & macrolides 14 et 15 membres surproduction de plasmide pUL 5054



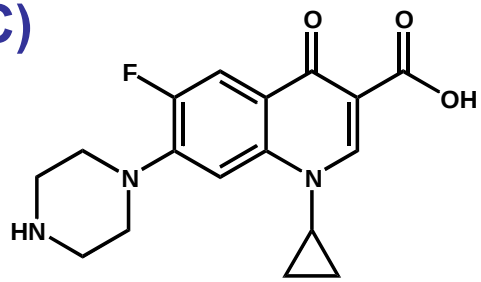








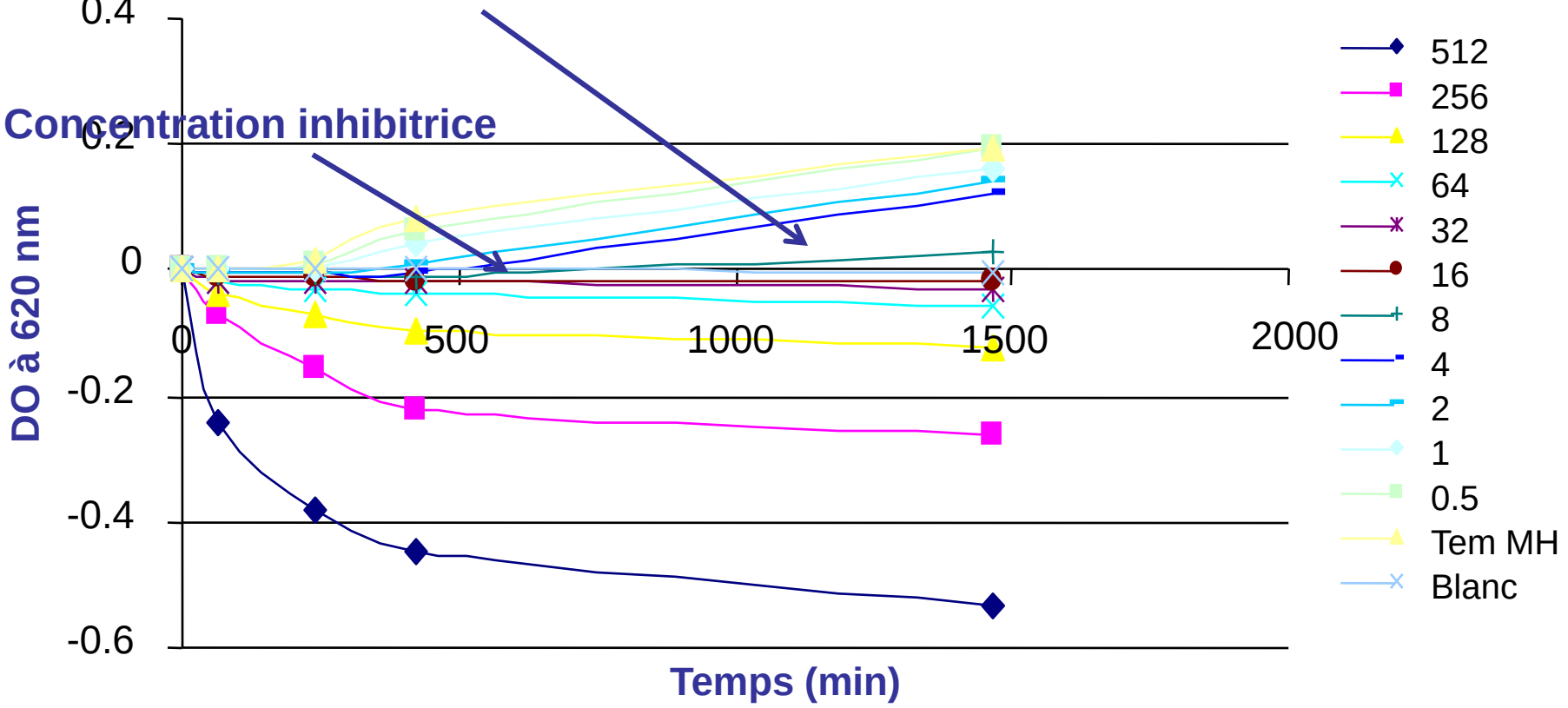
Inhibition spécifique de résistance à la ciprofloxacine (4 µg/ml)
Concentration minimum d'inhibition (MIC)



Souche résistante S. Aureus ATCC25923

Croissance bactérienne

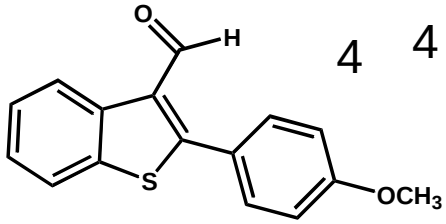
Concentration inhibitrice



CMI molécule 07010501H05 (GM1153)

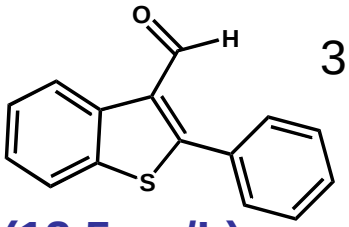
Inhibition spécifique de résistance à la ciprofloxacine (4 µg/ml)
Concentration minimum d'inhibition (MIC)

1° Benzothiophènes avec aldéhyde en position 3



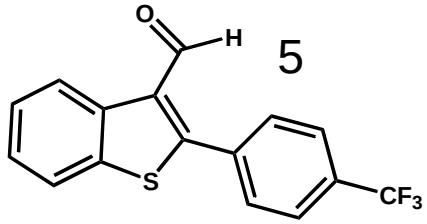
4 4

(12.5mg/L)



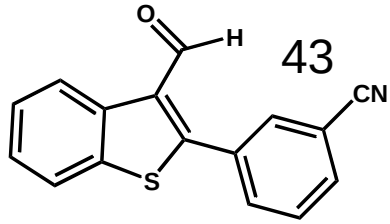
3

(12.5mg/L)



5

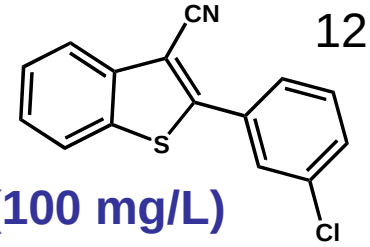
(25 mg/L)



43

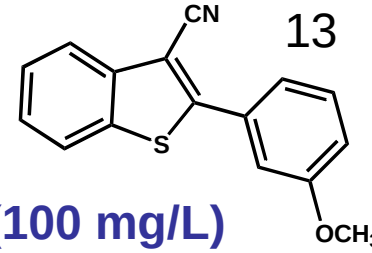
(100 mg/L)

2° Benzothiophènes avec groupe cyano



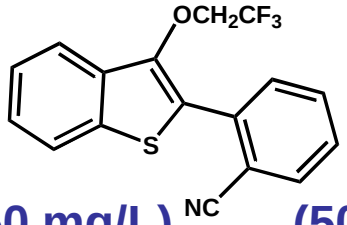
12

(100 mg/L)



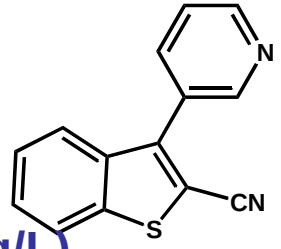
13

(100 mg/L)



18

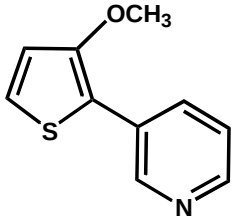
(50 mg/L)



19

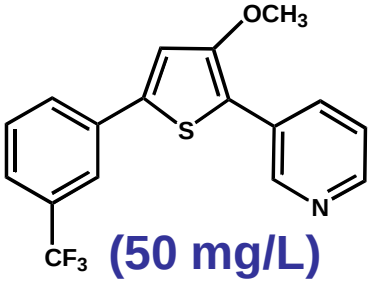
(50 mg/L)

3° thiophènes



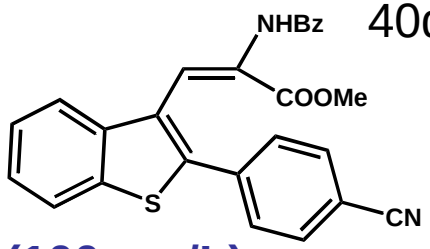
24

(100 mg/L)



33

(50 mg/L)

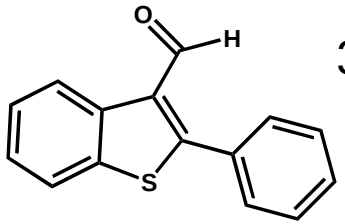


40d

(100 mg/L)

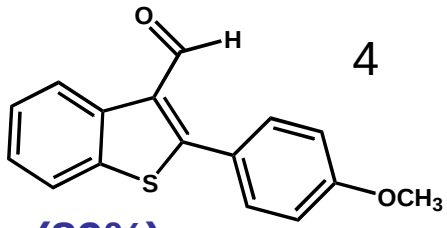
Citotoxicité vis-à-vis de KB cells at 10 µM
Référence taxotère à 0.25µM: 87 % inhibition de croissance

1° Benzothiophènes avec aldéhyde en position 3



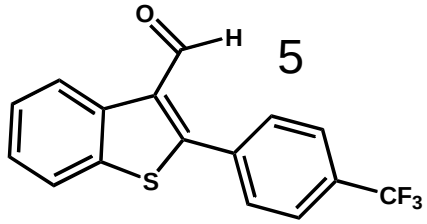
3

(42%)



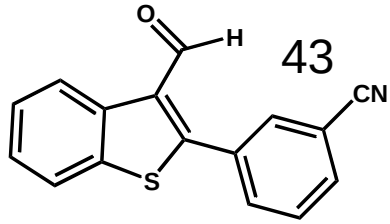
4

(89%)



5

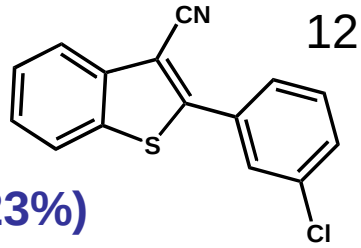
(88%)



43

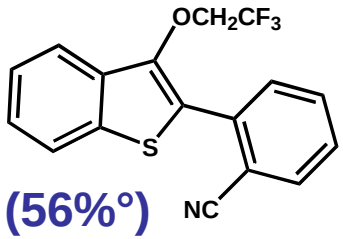
(51%)

2° Benzothiophènes avec groupe cyano



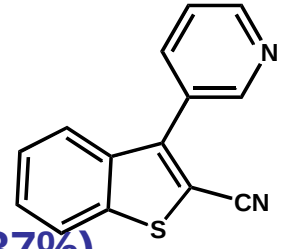
12

23%)



18

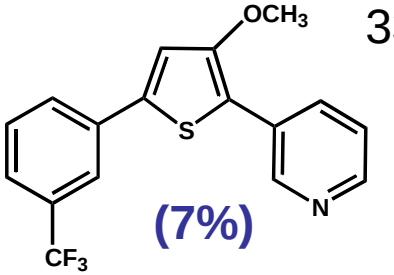
(56%°)



19

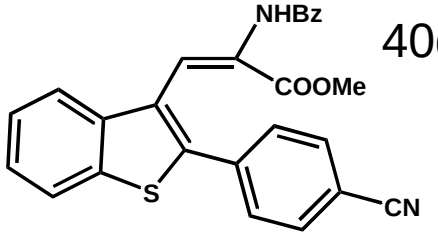
(37%)

3° thiophènes



33

(7%)

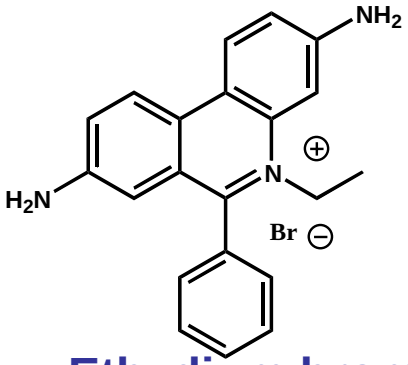


40d

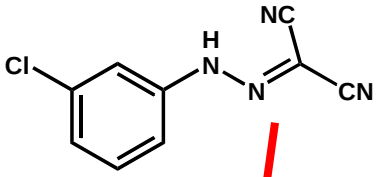
(24%)

Inhibition pompes NORA de souches résistantes S. aureus

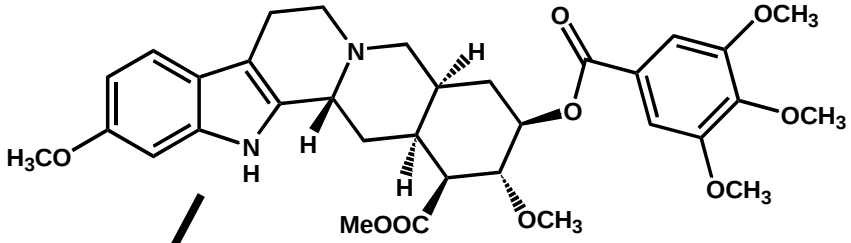
Mesure de l'efflux du bromure d'éthydium : comparaison avec des inhibiteurs connus



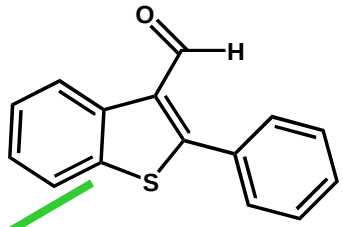
Ethydium bromine



CCCP

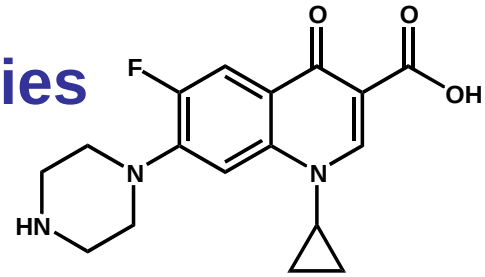


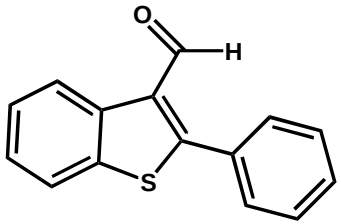
Reserpine



Sans inhibiteur

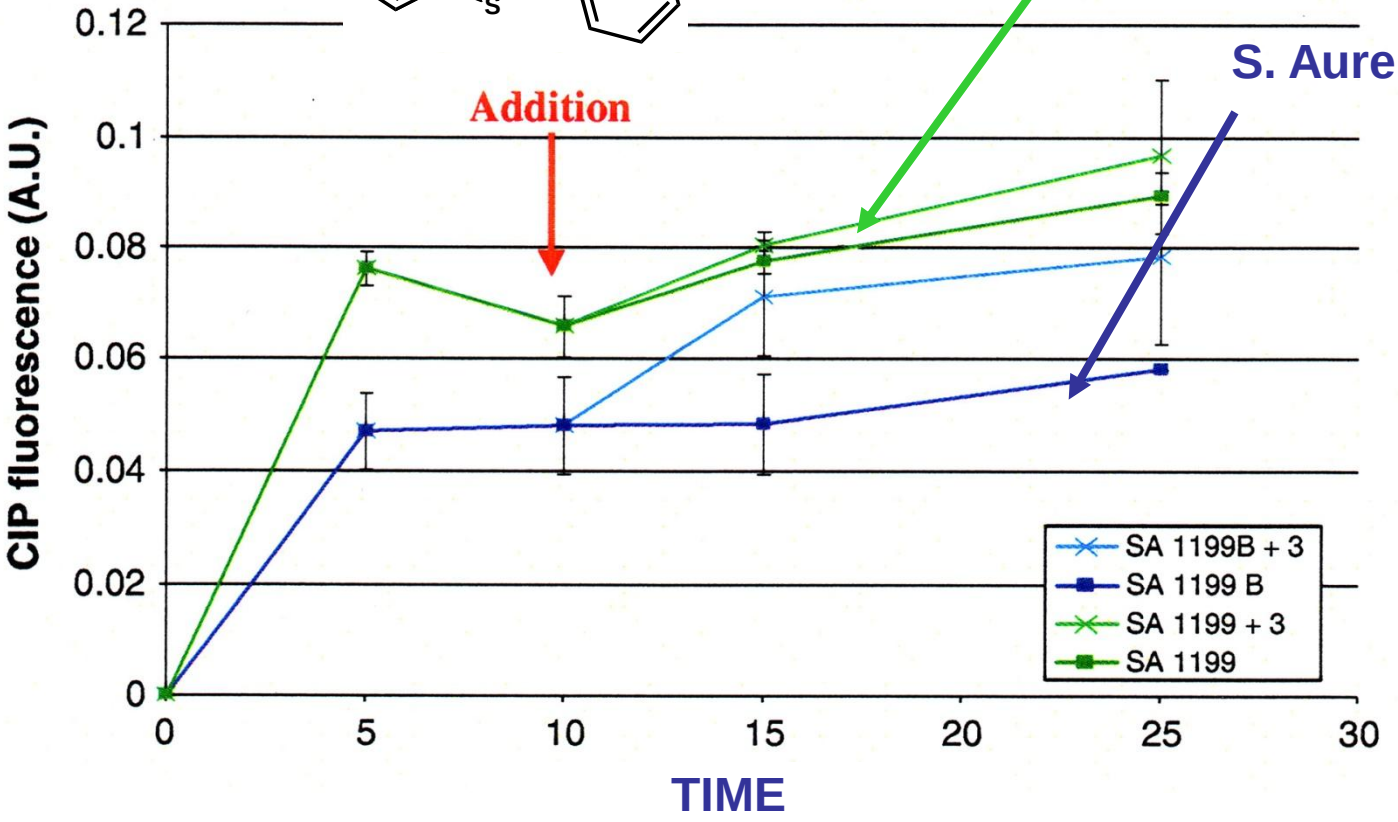
Expulsion de la ciprofloxacine par des bactéries S. Aureus sensibles and résistantes





S. Aureus sensible

S. Aureus résistant



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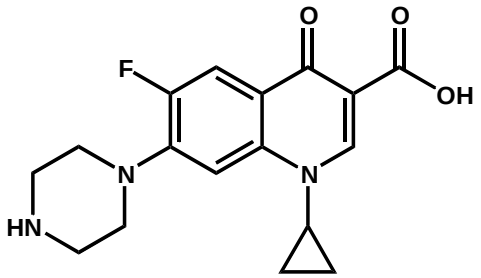
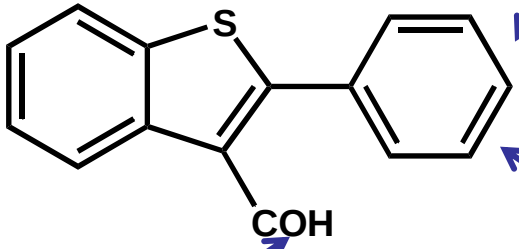
Première génération d'inhibiteur

Plus de 400 molécules originales : 1 restaure l'activité de la ciprofloxacine à une concentration de 12.5 mg/L pour une concentration de 4 mg/L en ciprofloxacine



Pas d'étude de l'effet de substituant sur la partie benzène

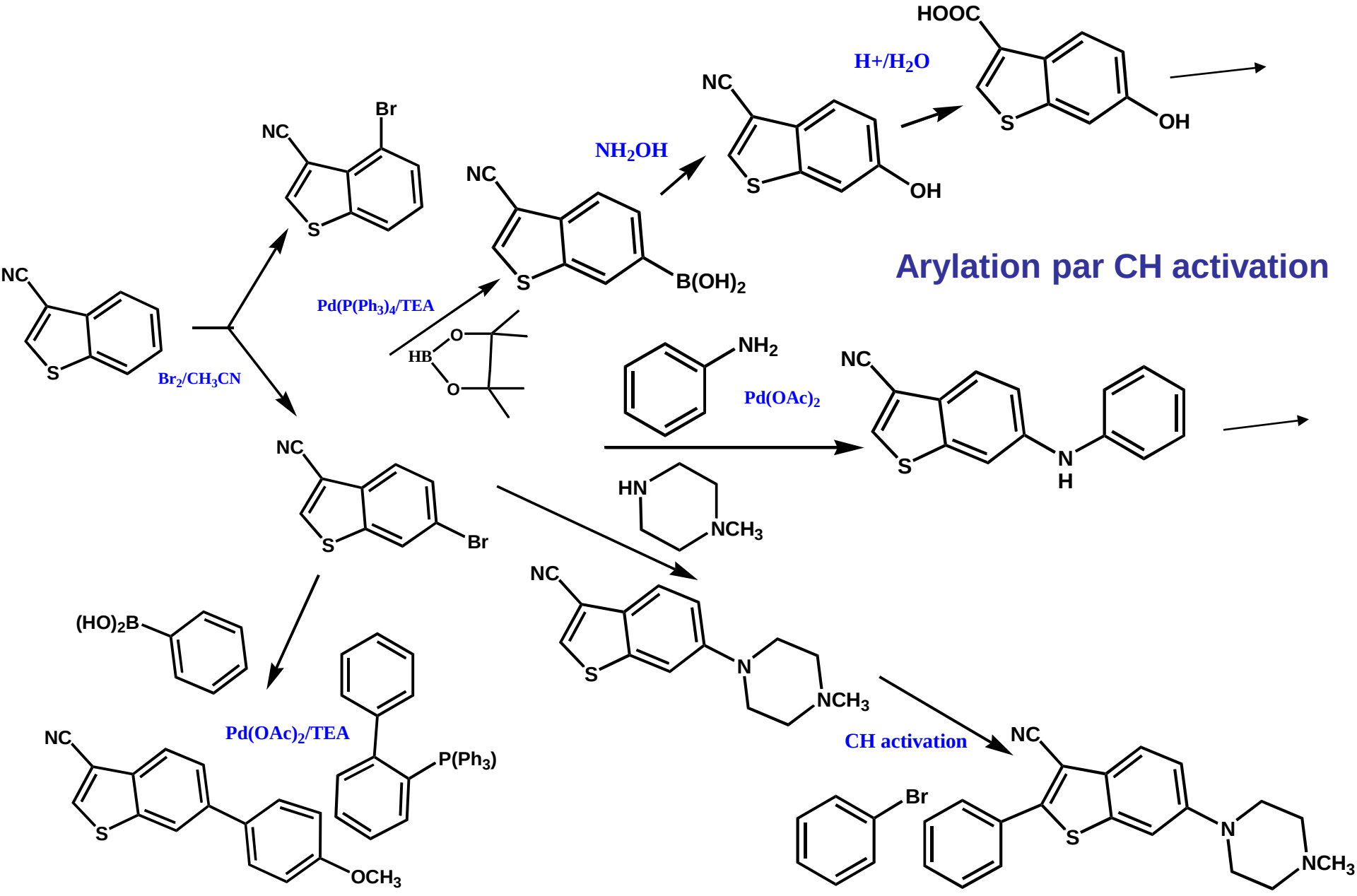
Substituant sans effet



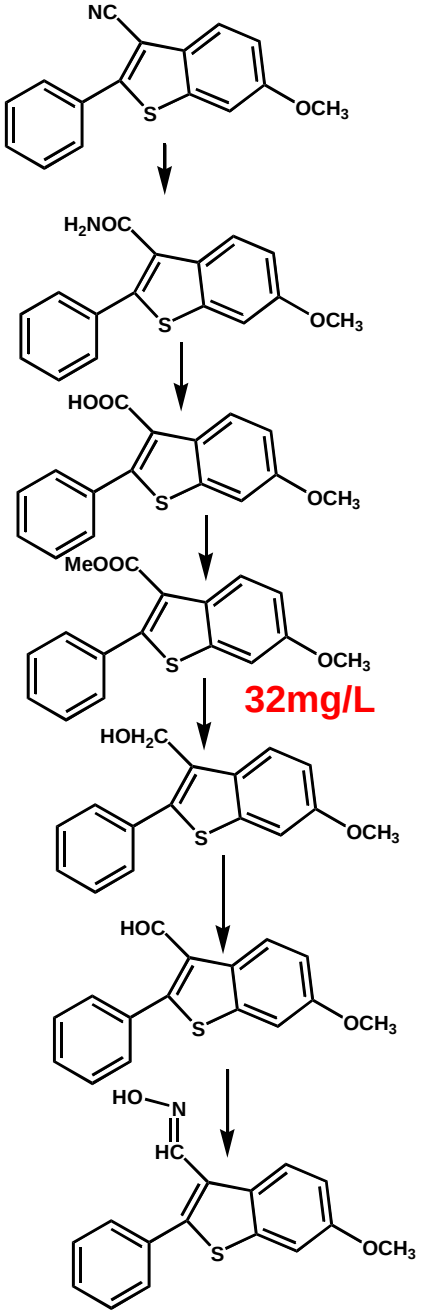
Aromatique nécessaire

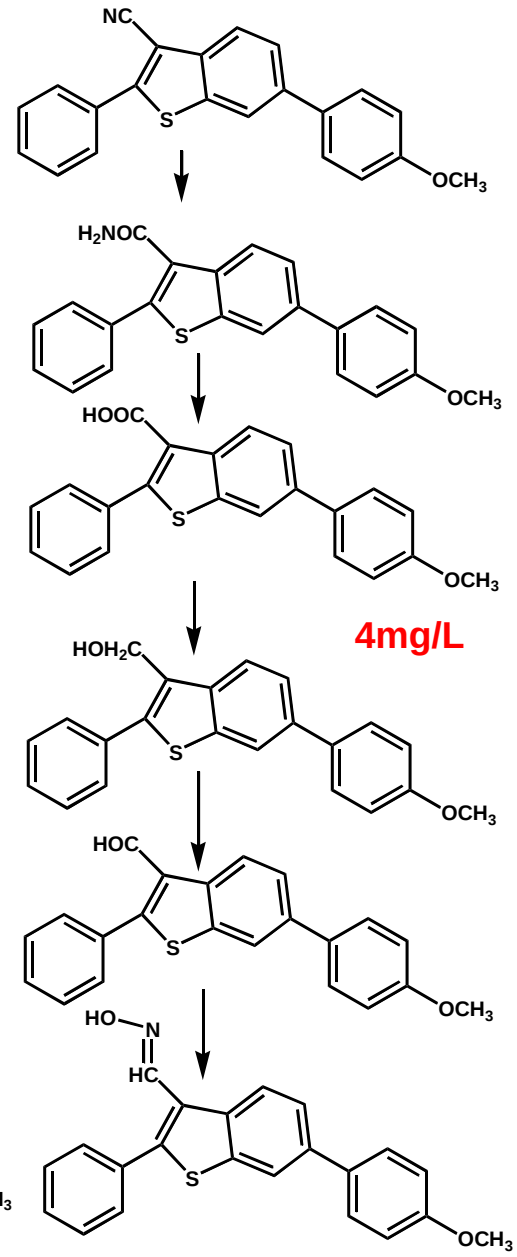
Groupement attracteur nécessaire mais l'aldéhyde augmente la toxicité

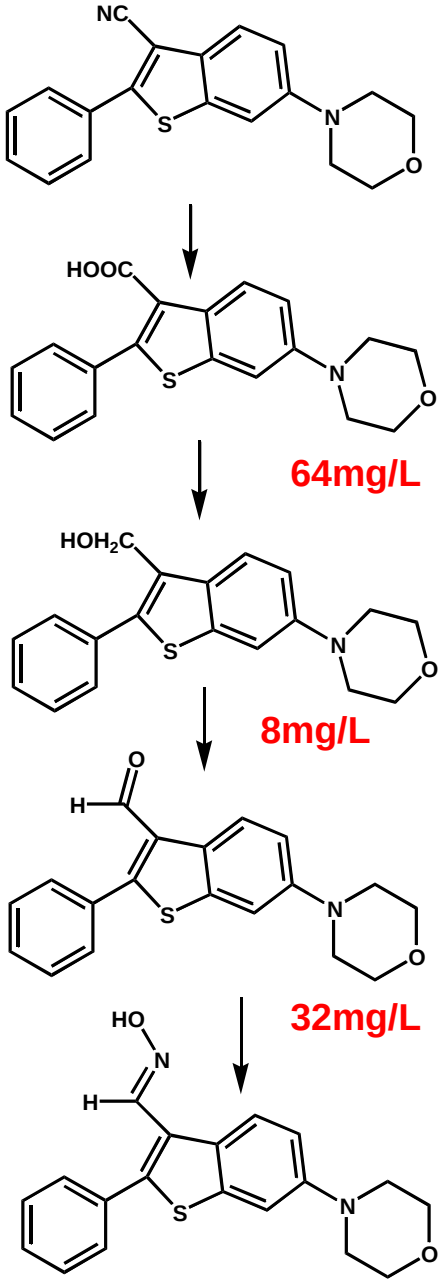
Synthèse d'inhibiteurs fonctionnalisés sur le noyau benzènique

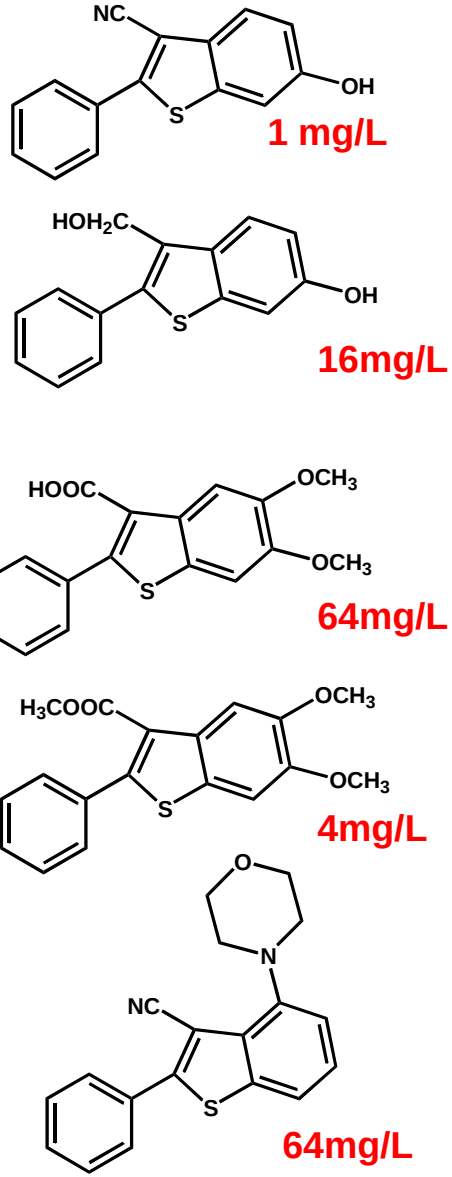


Inhibiteurs fonctionnalisés sur le noyau benzothiophénique (CMI SA 1199B)



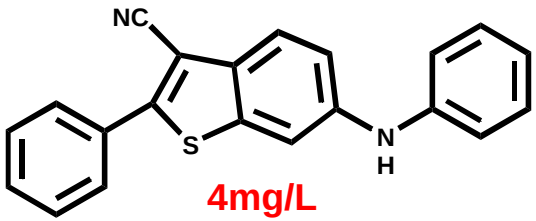




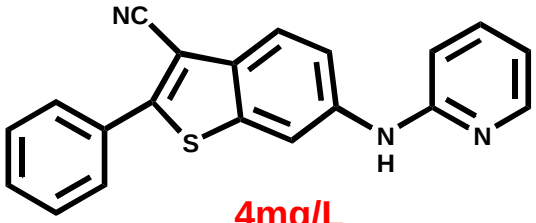


Inhibiteurs fonctionnalisés sur le noyau benzothiophénique

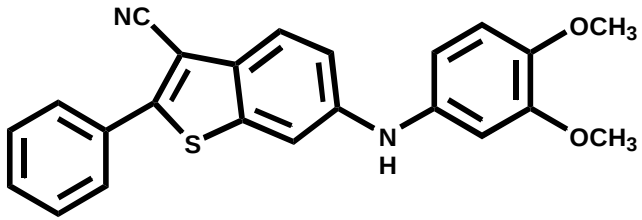
(CMI SA 1199B)

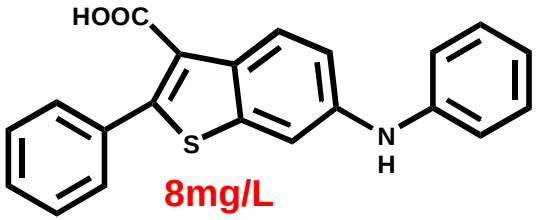


4mg/L

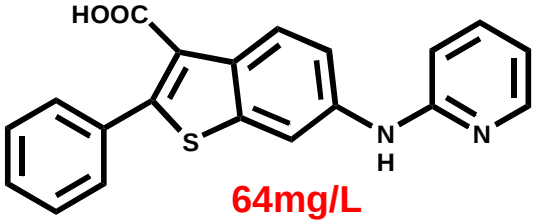


4mg/L

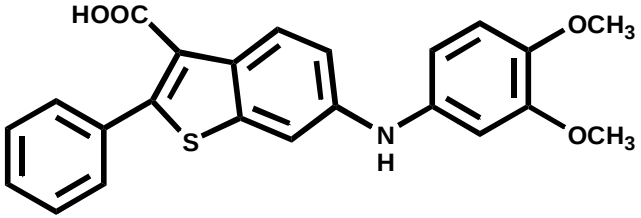


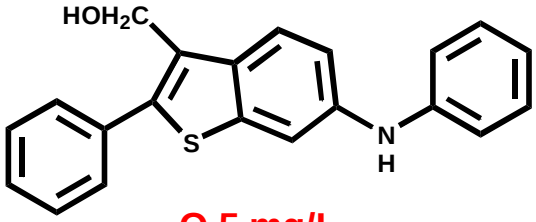


8mg/L

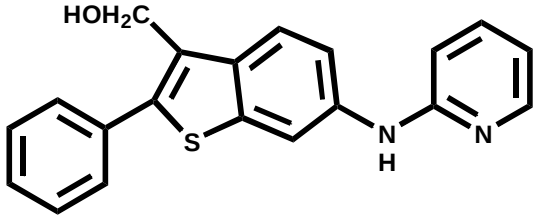


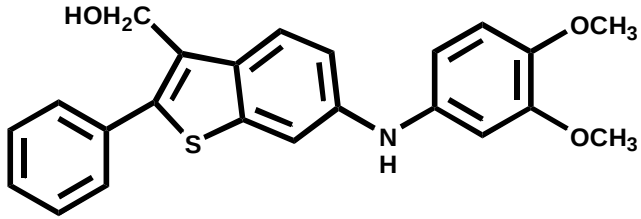
64mg/L





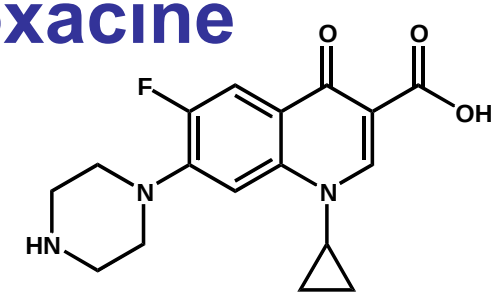
O.5 mg/L





Inhibiteur des pompes NORA, restauration de l'activité de la ciprofloxacine

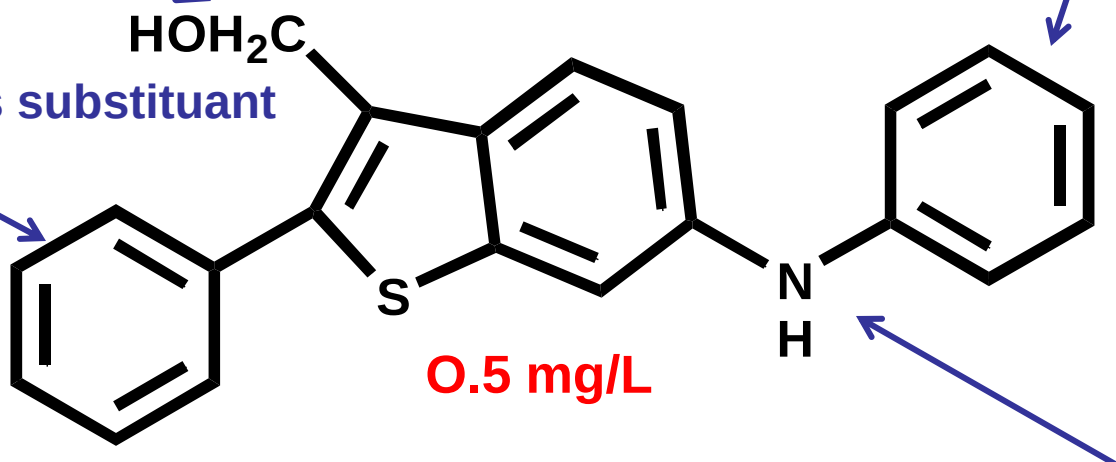
Souche résistante S. Aureus ATCC25923



Groupement attracteur, HBA & HBD

Aromatique (sans substituant ?)

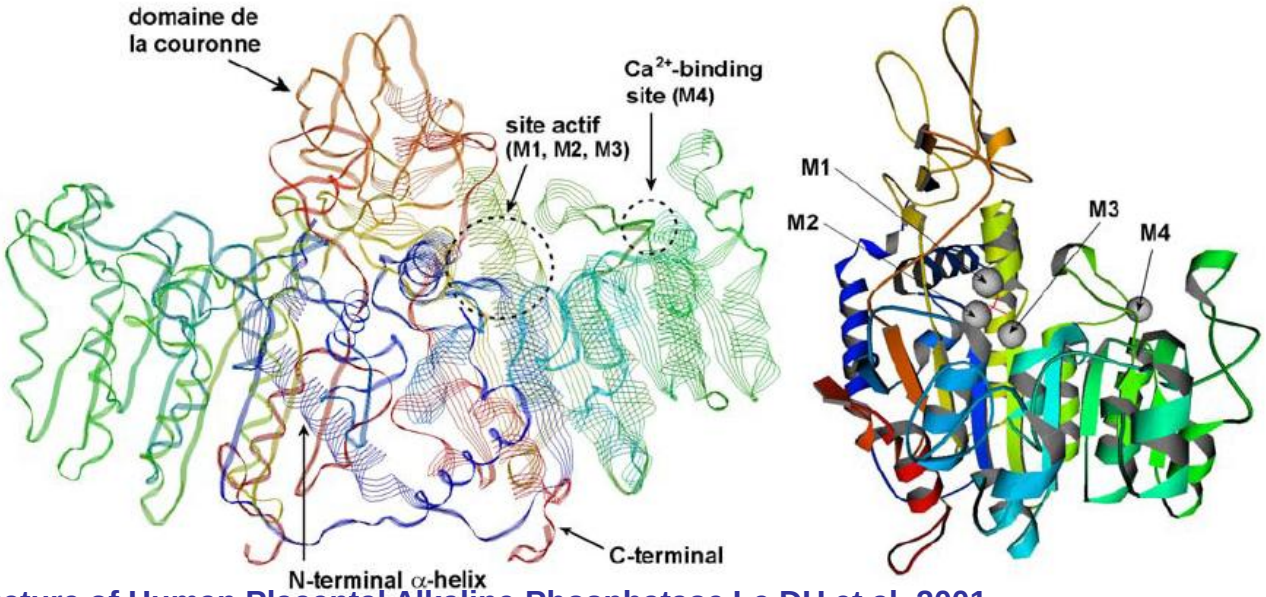
Aromatique sans substituant



O.5 mg/L

Groupe donneur HBA & HBD

2.2 Inhibition de phosphatase alcaline
(TNAP ankylosis osteoarthritis, et calcification artérielle)



Structure of Human Placental Alkaline Phosphatase Le DU et al. 2001

Chez l'homme il existe 4 isozymes

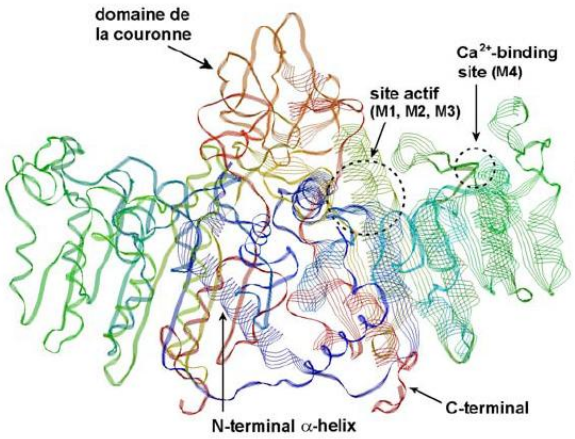
1°)tissue-nonspécifique AP (TNAP), dans les os, le foie et les reins;

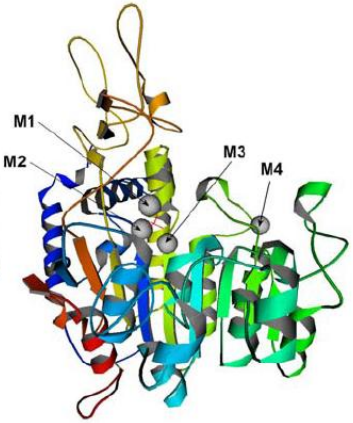
2°)3 tissus spécifiques isozymes — placenta (PLAP), germ cell (GCAP), et dans les intestins Phosphatase Alkaline(IAP).

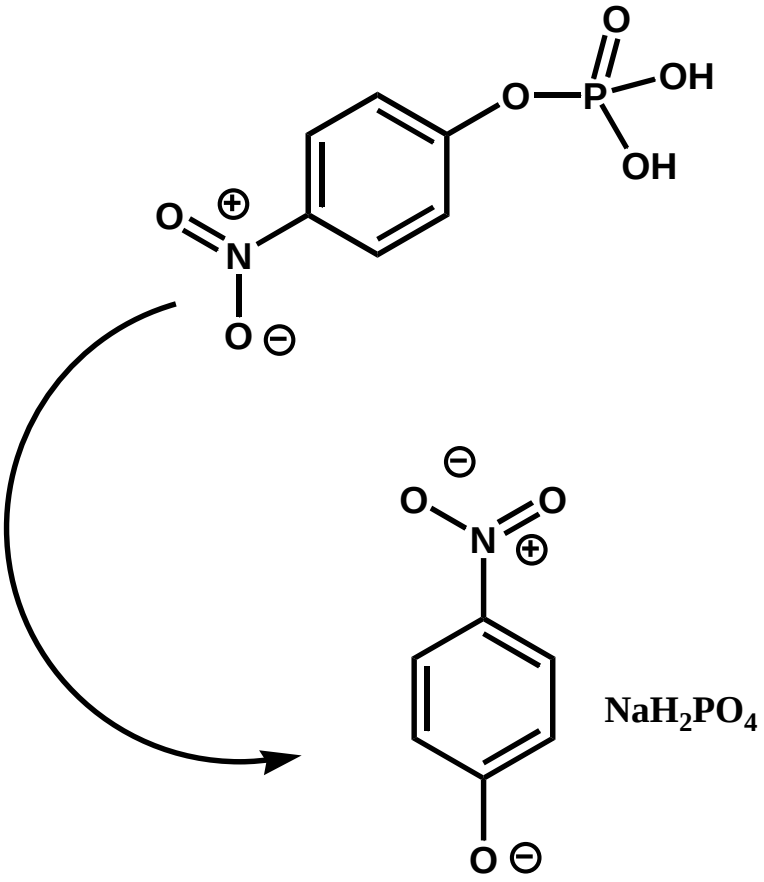
90%–98% homologue, (TNAP est seulement 50% identique avec les trois autres).

Collaboration avec le Pr. R. Buchet (Lyon1)

2.2 Inhibition des phosphatases alcalines (TNAP)



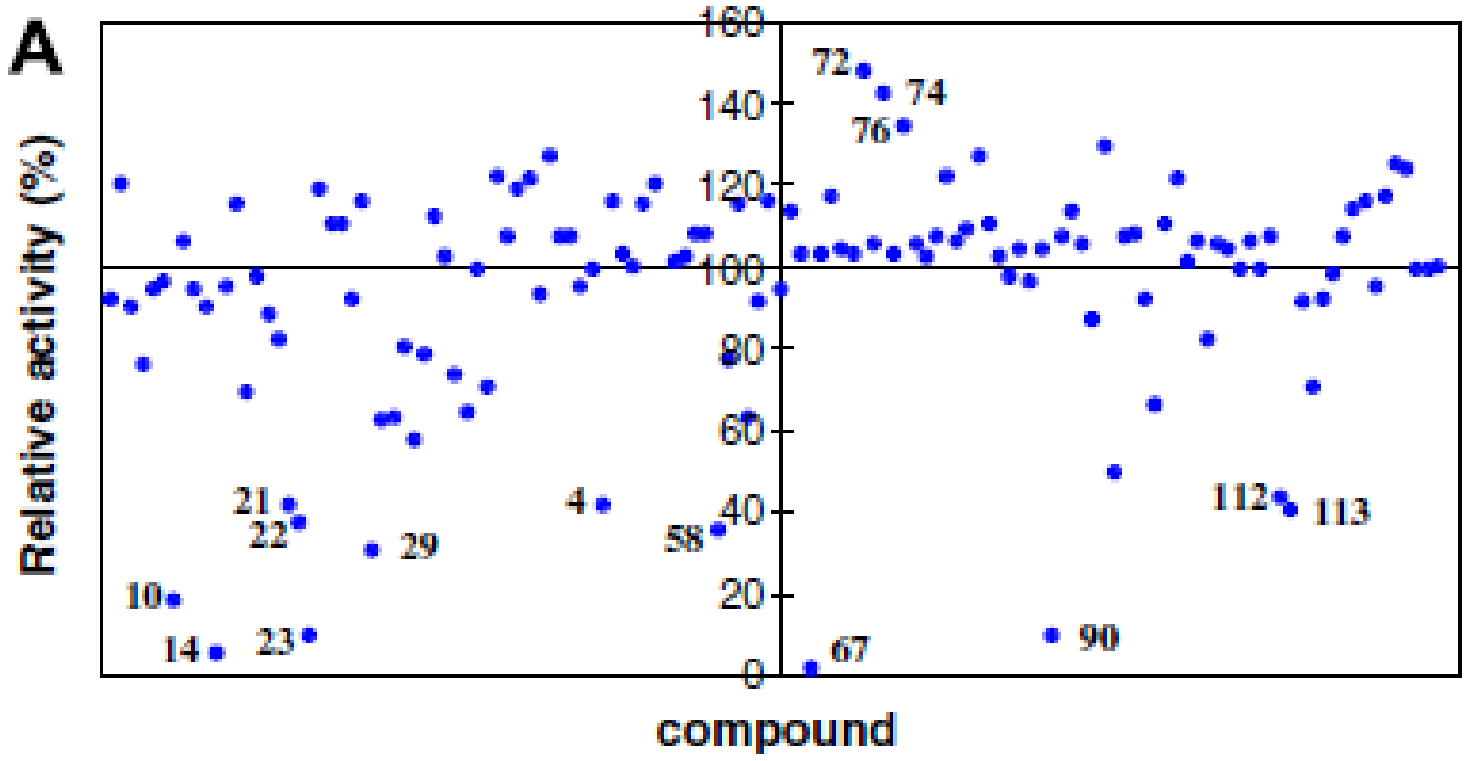




37° C , 25mM piperazine, 25mM glycylglycine, 5 mM MgCl2 et 1µM ZnCl2 :ρ-nitrophenyl phosphate (ρNPP) comme substrat
Paranitrophenolate quantifié par l'absorption à 420 nm

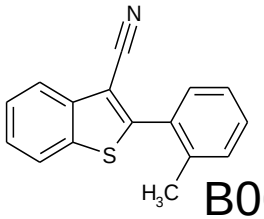
Évaluation des propriétés inhibitrices des composés benzothiophéniques

Inhibition de « bovine intestinal alcaline phosphatase », pH 10.4 à 37°C

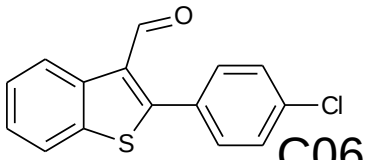


Bioorganic& Medicinal Chemistry 17(2009) 7390-7300

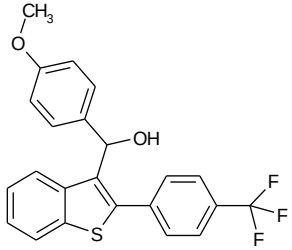
Inhibition de AP par une concentration de 0.1mM d'inhibiteur
Plus de 400 molécules testées



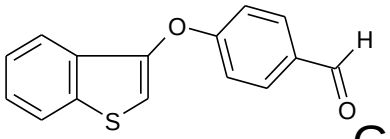
B06



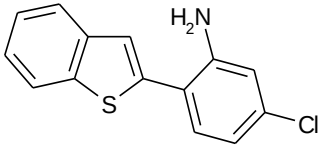
C06



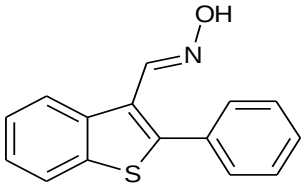
D09



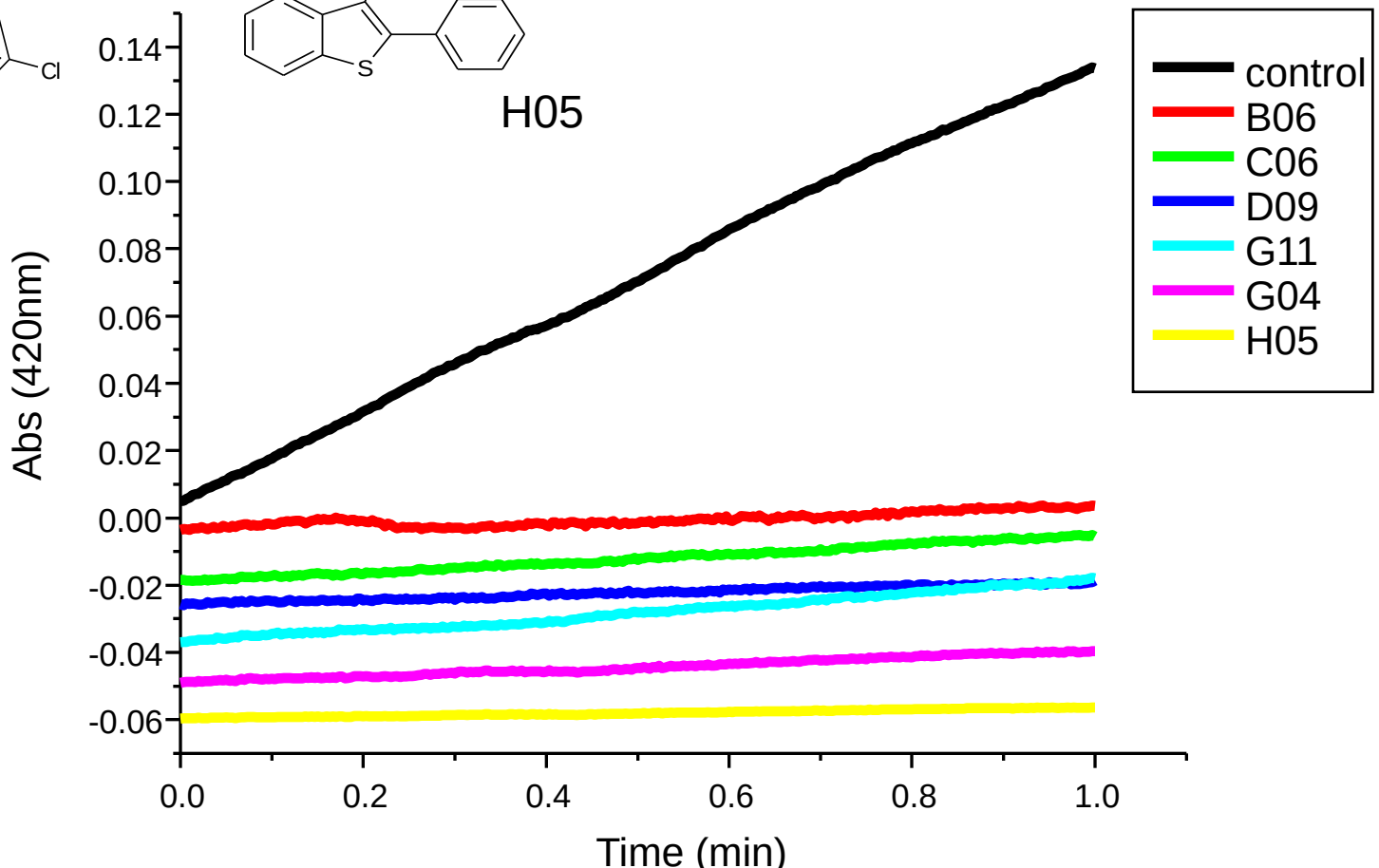
G11



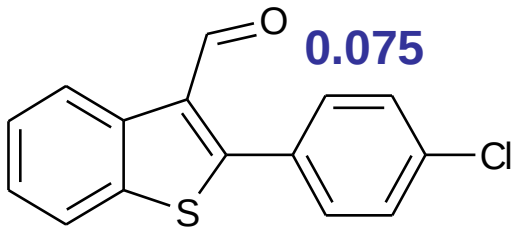
G04



H05

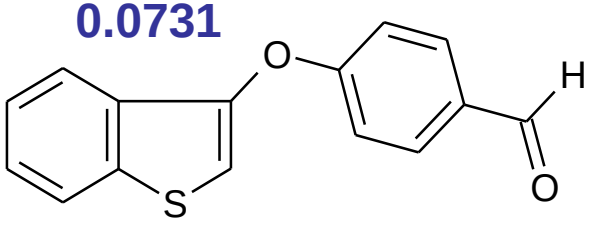


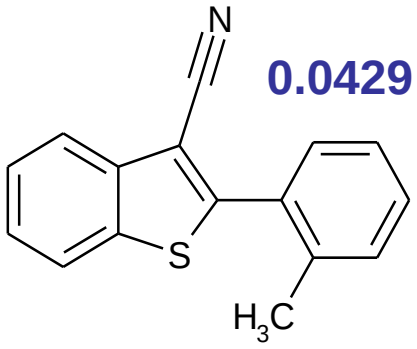
Inhibition AP avec 0.1mM d'inhibiteur (U/ml) ; contrôle 0.08533 U/ml



0.075

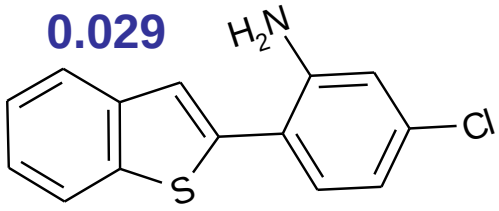
0.0731

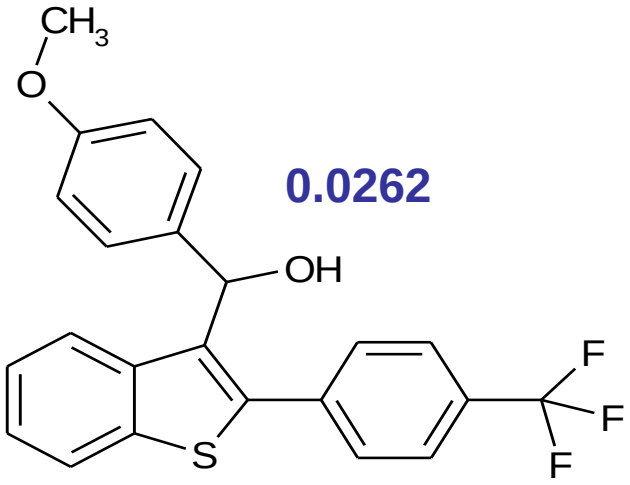




0.0429

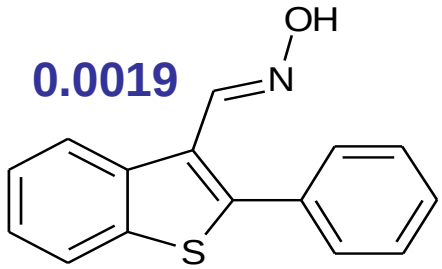
0.029



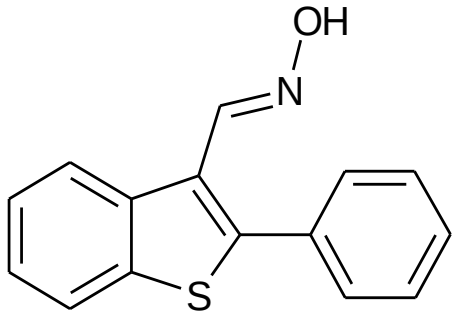


0.0262

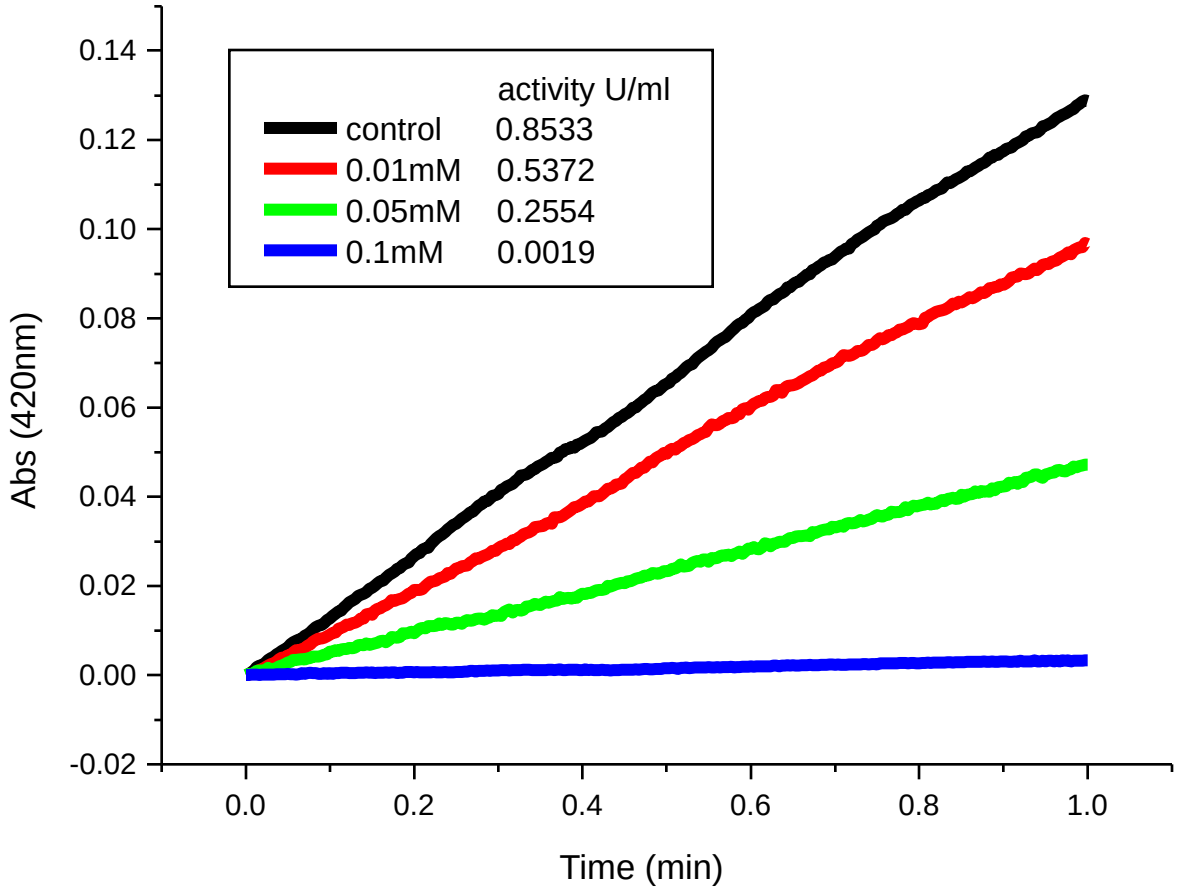
0.0019



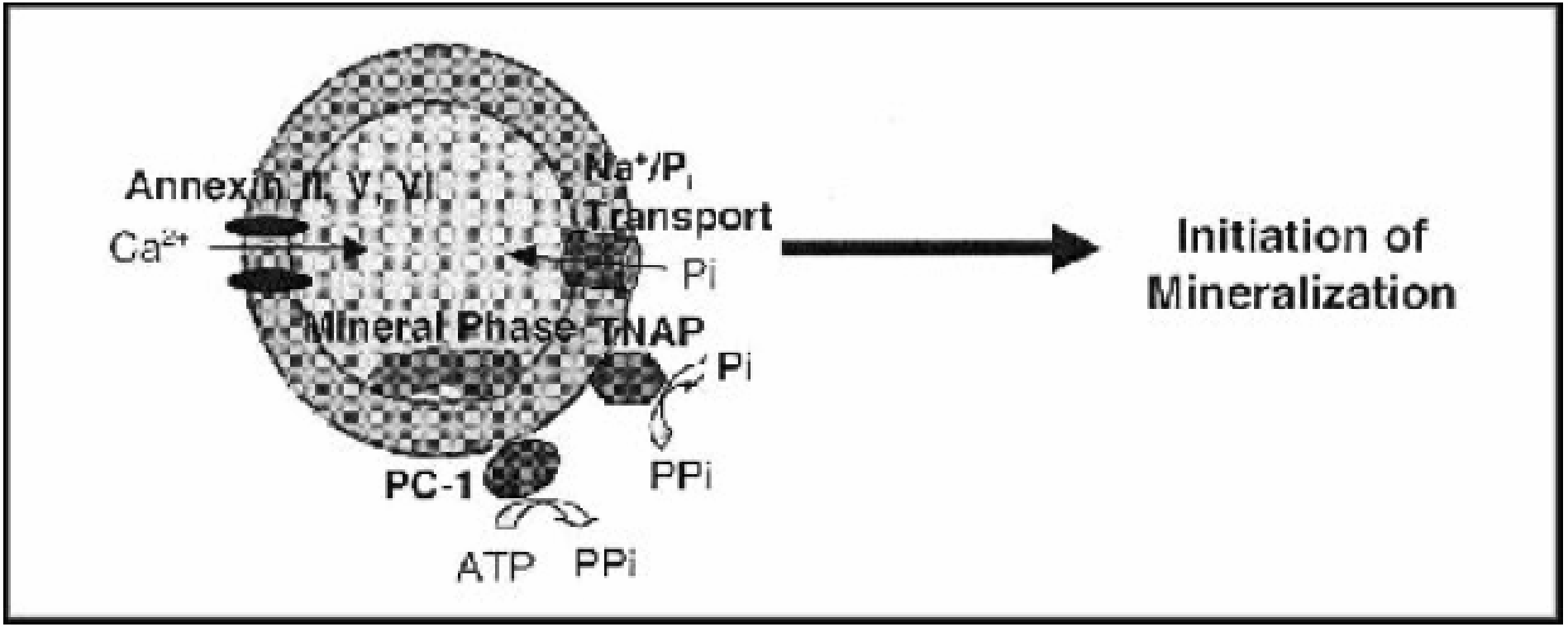
Influence de la concentration de l'inhibiteur



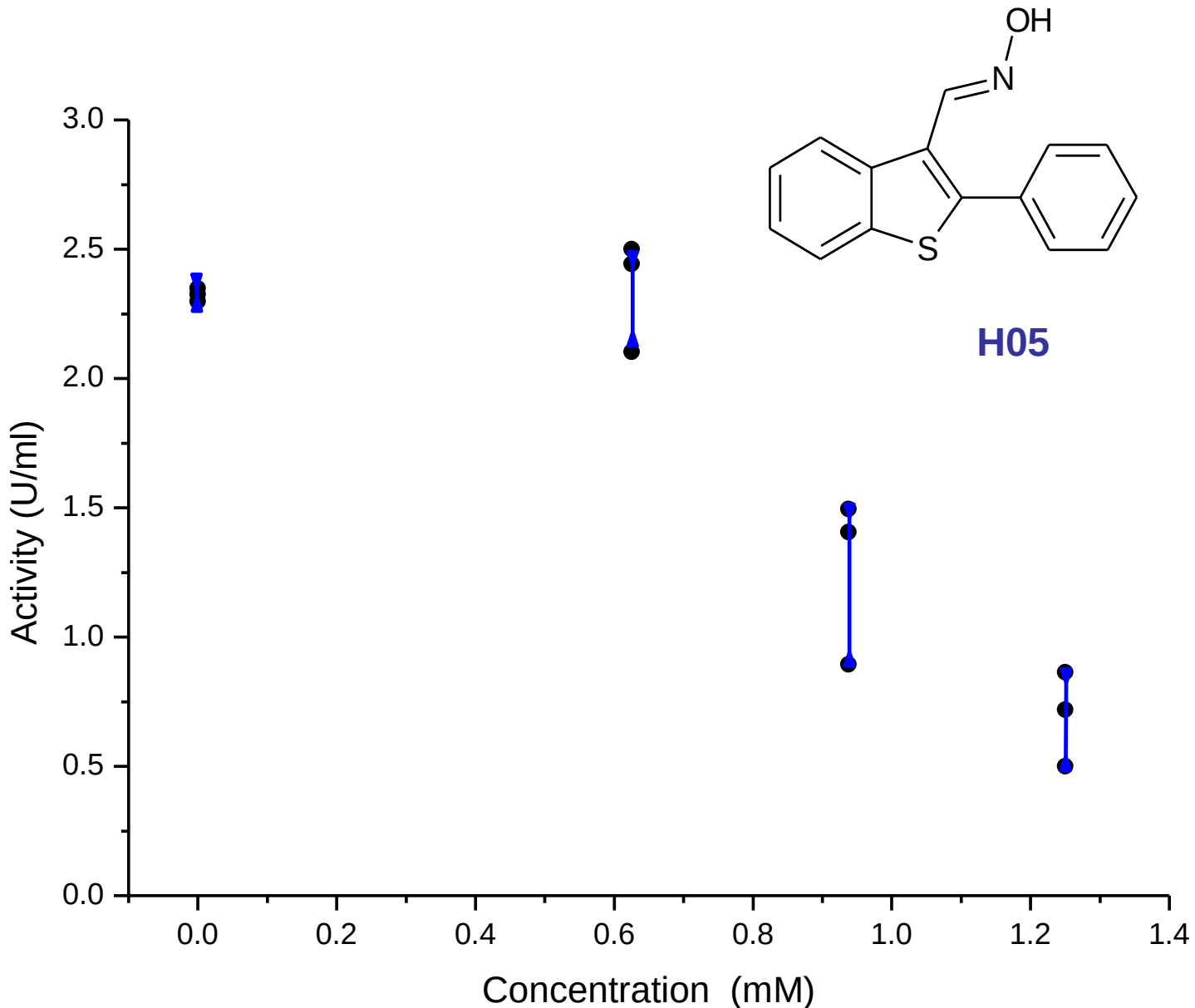
H05



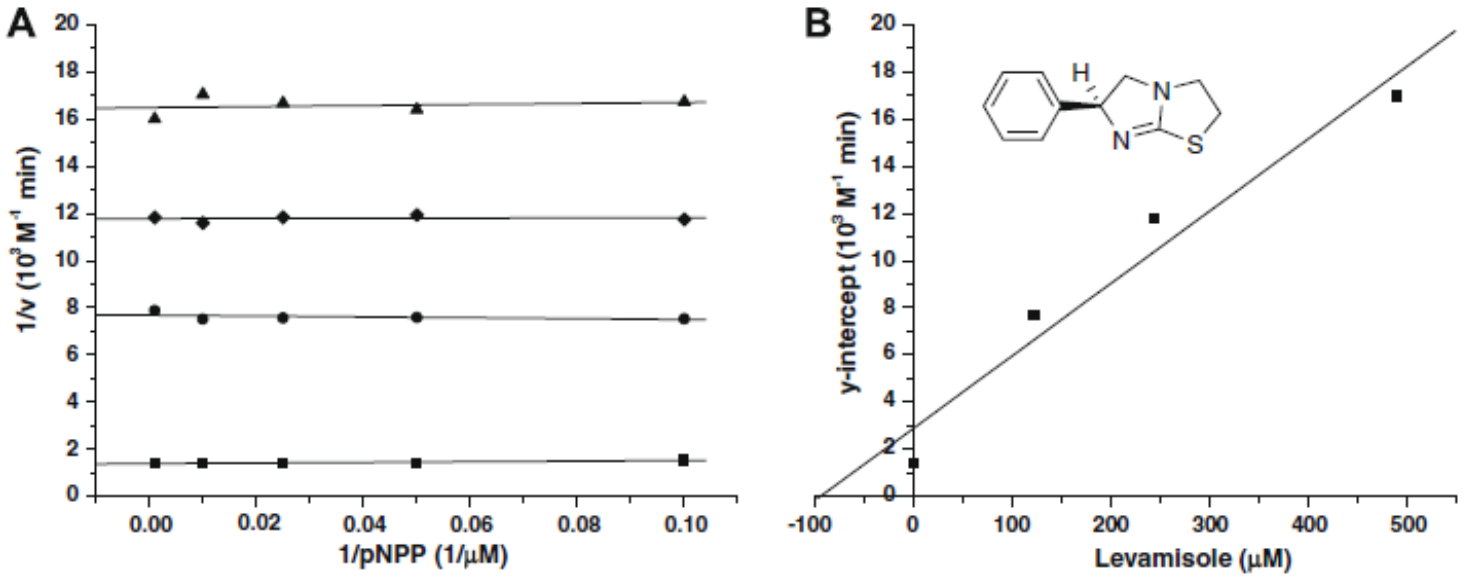
Utilisation d'inhibiteur sur la vésicule, (plusieurs enzymes présentes)



Utilisation d'inhibiteur sur la vésicule, (plusieurs enzymes présentes)
Influence de la concentration en inhibiteur



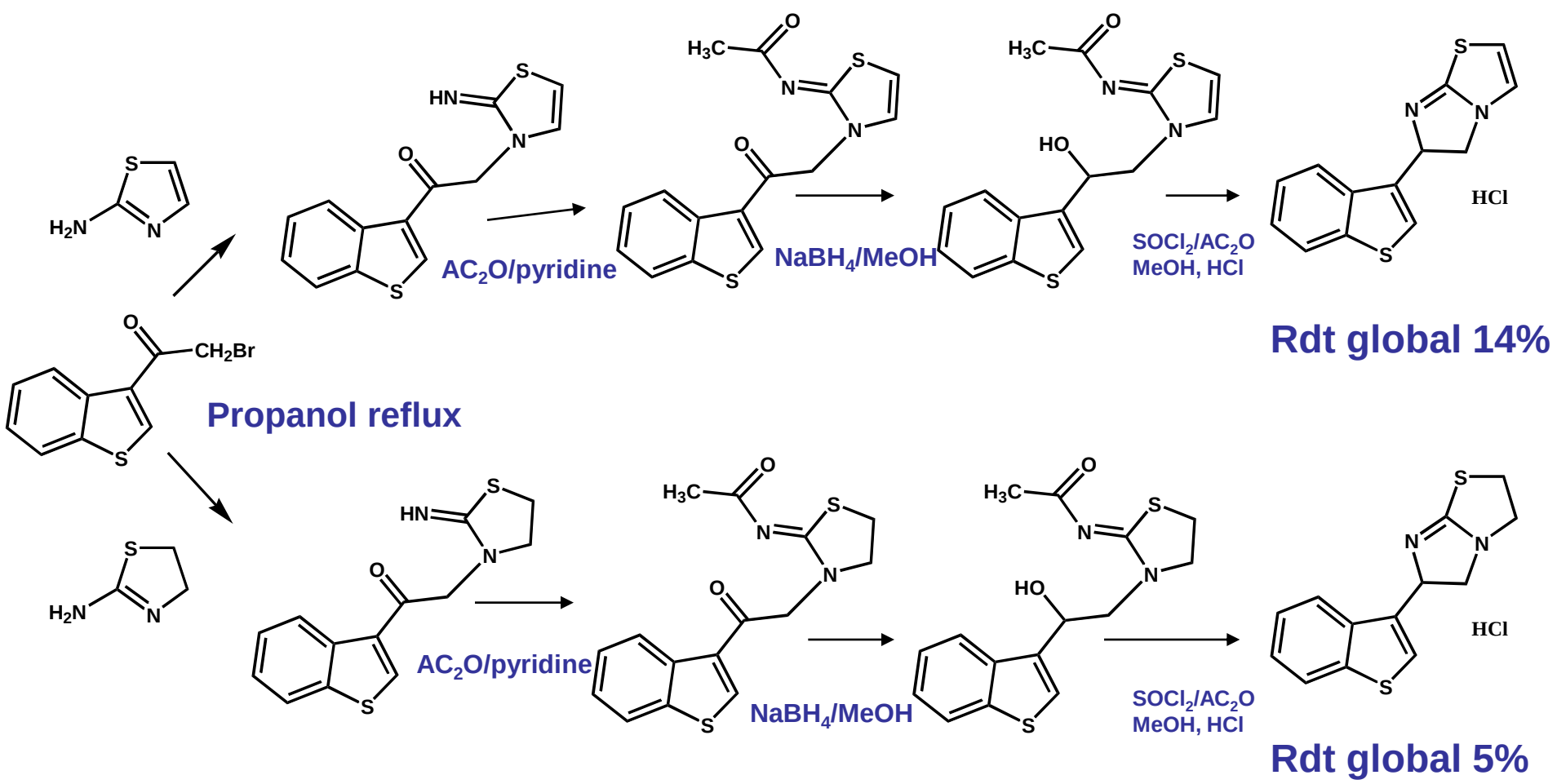
Levamisol , agent efficace inhibiteur de TNAP



TNAP (rein de porc) Ph 7.8 ,37°C , Linewaever-Burk

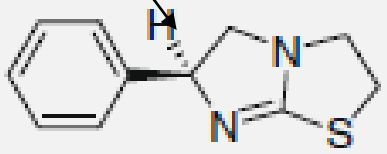
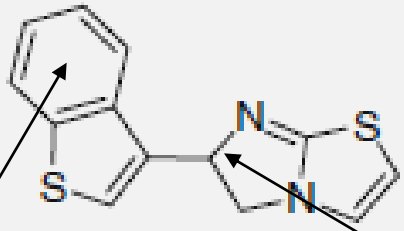
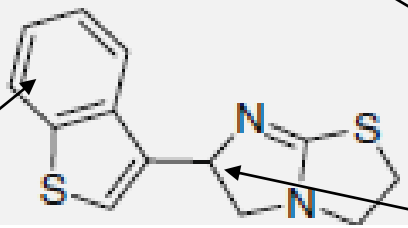
Effets secondaires importants ⇒ **Synthèse « d'hybrides »**

Synthèses d'hybrides



Comparaison des propriétés inhibitrices du levamisol et des dérivés benzothiophèniques

Un énantiomère

	Vis-à-vis de la BIAP	Vis-à-vis de la TNPA
 Levamisole·HCl	99	10
 129·HCl	99	11
 133·HCl	100	19

fonctionnalisation

racémiques

Les outils pour la chimie durable (sustainable chemistry) ou chimie verte (green chemistry)

Développement de l'industrie chimique , pharmaceutique et parachimique

Nouvelles contraintes de production
Réglementations REACH …

Augmentation des coûts
Matières premières et énergie

Gestion des déchets
Production et recyclage

Nouvelles matières premières
Nouveaux scaffolds
« biorafinerie »

Nouveaux concepts
Economie d'atome
Les douze principes de la chimie verte
Les douze principes du
« green chemical ingeneering »

Nouvelles technologies
Nouvelles réactions catalytiques
Nouvelles méthodes d'activation
Nouveaux solvants
Nouveaux réactifs