L'APPROCHE SOSA : UNE ALTERNATIVE ORIGINALE AU « HIGH THROUGHPUT SCREENING »

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Les risques du métier

- Entre 1992 et 2002 13 molécules ont été arrêtées au cours de la phase I des études cliniques.
- Au cours de la même période 23 molécules ont été arrêtées pendant la phase II.
- Toujours pendant la même période, 26 molécules ont été arrêtées au niveau de la phase III.
- Enfin, toujours pendant la même période, 16 molécules ont été retirées du marché.

Source: D. Schuster et al., Curr. Pharm. Design, 2005, 11, sous presse

Les réponses de l'Industrie Pharmaceutique : Faire du neuf avec du vieux…

"Drug repositioning": nouveaux usages pour de vieux médicaments

"Analogue design": synthèse de d'analogues de médicaments connus et présentant un profil d'action similaire

"SOSA approach": nouvelles touches (hits) au départ de vieux médicaments

“Drug repositioning”: nouveaux usages pour de vieux médicaments

“Analogue design”: synthèse de d’analogues de médicaments connus et présentant un profil d’action similaire

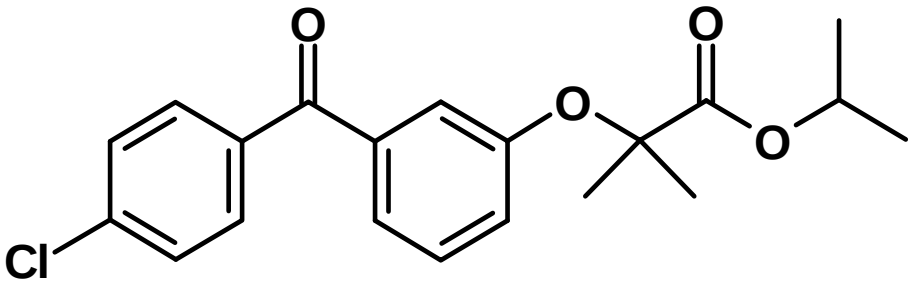
“SOSA approach”: nouvelles touches au départ de vieux médicaments

Première réaction: on revalorise l'acquis

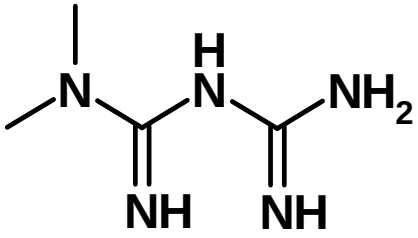
- Lancement d'une nouvelle formulation galénique (effet-retard, prise unique, biodisponibilité améliorée).
- Préparation d'un nouveau sel (rare et utilité difficile à justifier).
- Séparation des énantiomères (permet souvent une prolongation de la protection industrielle).
- Association de deux médicaments (doit correspondre à une habitude de prescription).

La valorisation de l'acquis

Nouvelle formulation



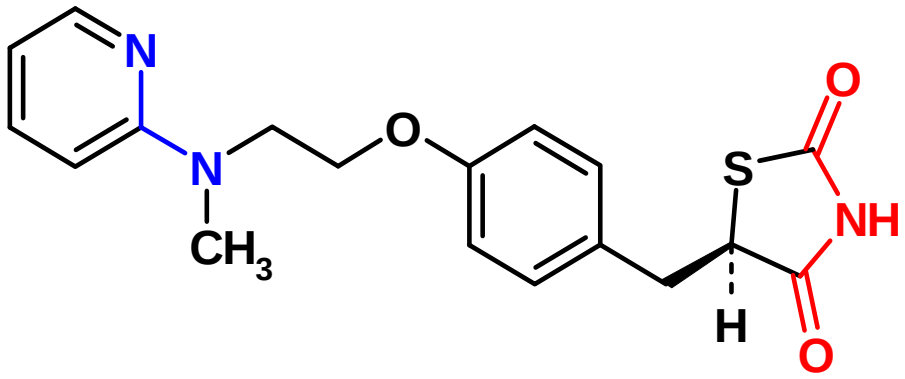
Fénofibrate:
Lipanthyl 300M → Tricor 145
(nanoparticules mieux absorbées)



Métformine:
Glucophage 850 → Glucophage 1000

La valorisation de l'acquis

Nouveau sel



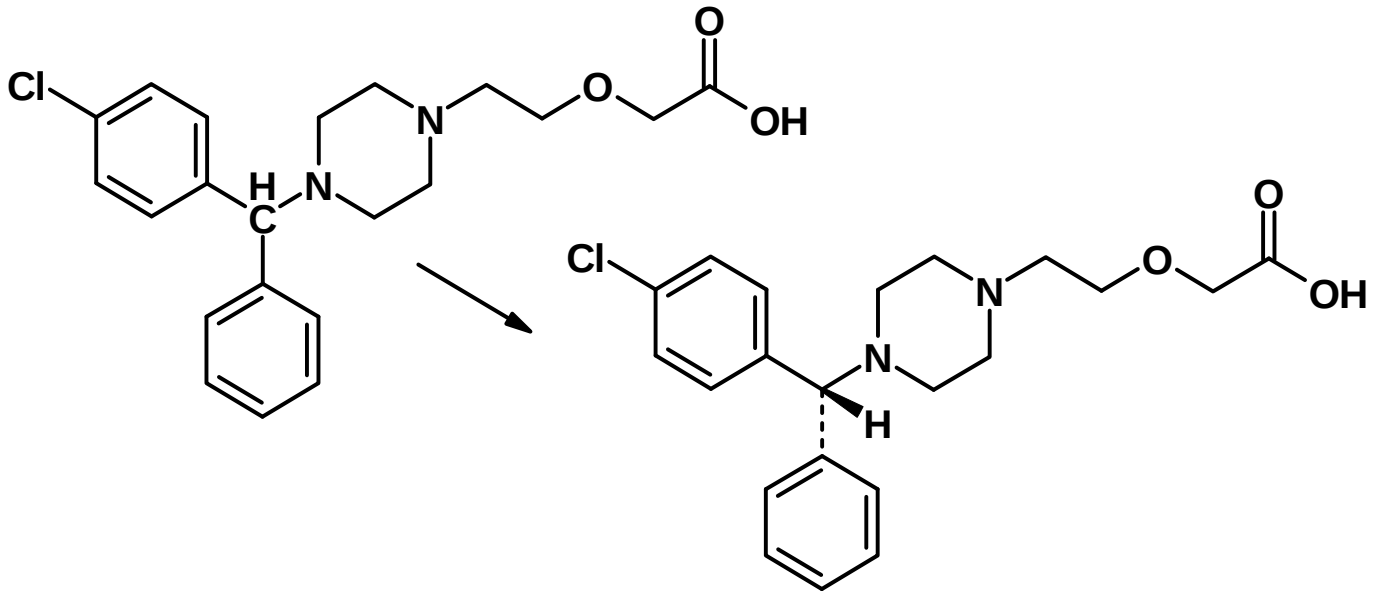
Rosiglitazone (Avandia®):
Zwitterion et sel de Na → maléate

La valorisation de l'acquis

Séparation des énantiomères

Zyrtec® (d,l-cetirizine)
10 mg / comprimé

Xyzall® (l-cetirizine)
5 mg / comprimé



Mais aussi: Lévosimendan, Dexmédétomidine, Lévo-bupivacaine,Esoméprazole, Lévo-vérapamil, Lévo-floxacine…

La valorisation de l'acquis

Associatiation de deux produits «Deux dans Un»

Zyprexa + Prozac =	Symbyax	(Lilly)
Norvasc + Lipitor =	Caduet	(Pfizer)
Zocor + Zetia =	Vytorin	(Merck + Schering Plough)
Glucophage+Micronase=	Glucovance	(BMS)

“Drug repositioning”: nouveaux usages pour de vieux médicaments

“Analogue design”: synthèse d’analogues de médicaments connus et présentant un profil d’action similaire

“SOSA approach”: nouvelles touches au départ de vieux médicaments

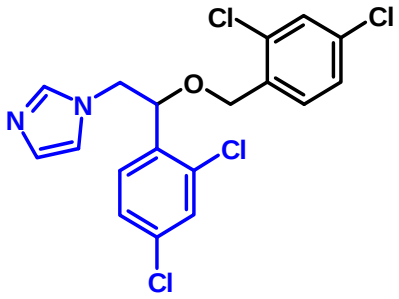
Deuxième réaction: synthétiser des analogues

- Lancement de nouveaux médicaments: un médicament sur deux est un analogue d'un médicament déjà existant.

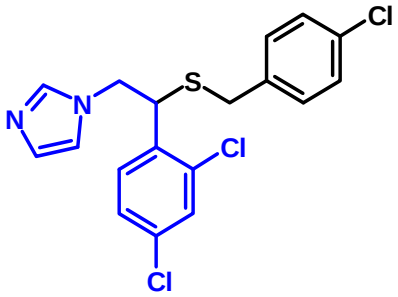
- Le chiffre d'affaires des analogues est égal aux 2/3 du marché total des médicaments *(J. Fischer & C.R. Ganellin, «Analogue-Based Drug Discovery», John Wiley, in press).*

- Sur 29 médicaments mis sur le marché en 2000, 24 sont des copies *(J.R. Proudfoot, BioOrg MedChem Lett. 2002, 12, 1647-1650).*

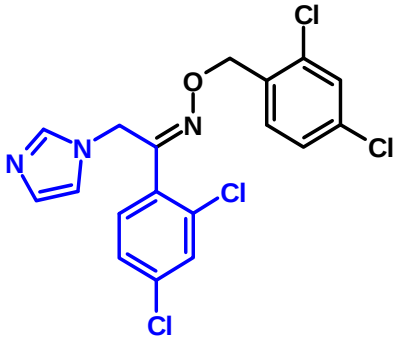
La famille des «conazoles»



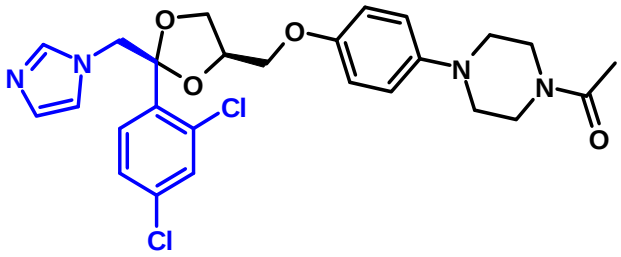
miconazole
Janssen (1968/1971)



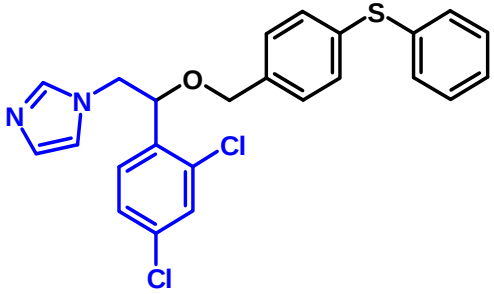
sulconazole
Syntex (1974/1985)



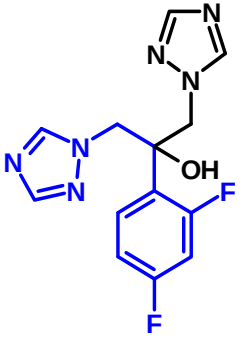
oxiconazole
Siegfried (1975/1983)



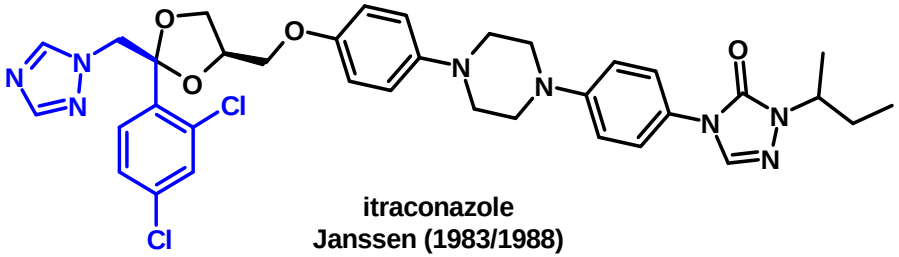
ketoconazole
Janssen (1977/1981)



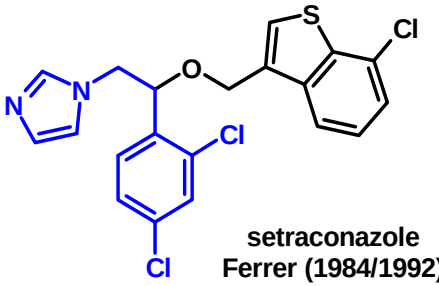
fenticonazole
Recordati (1978/1987)



fluconazole
Pfizer (1981/1988)

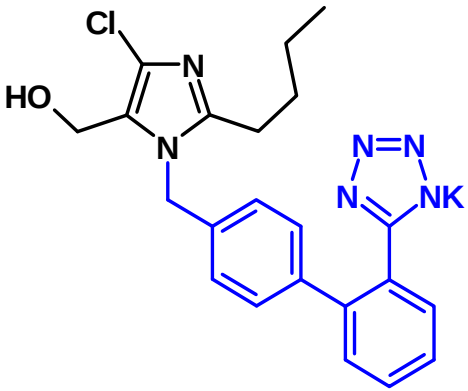


itraconazole
Janssen (1983/1988)

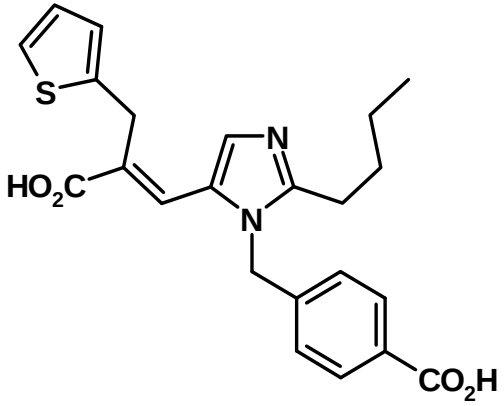


setraconazole
Ferrer (1984/1992)

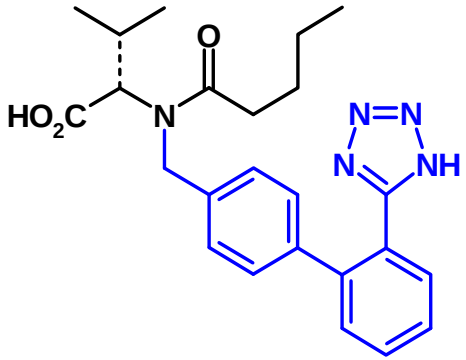
La famille des «sartan»



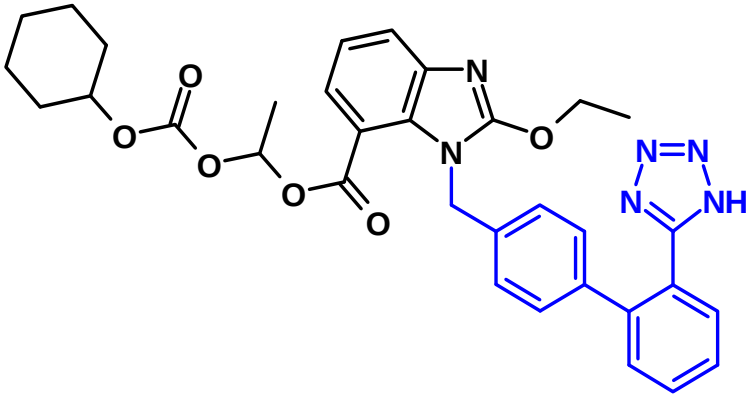
losartan
DuPont (1986/1994)



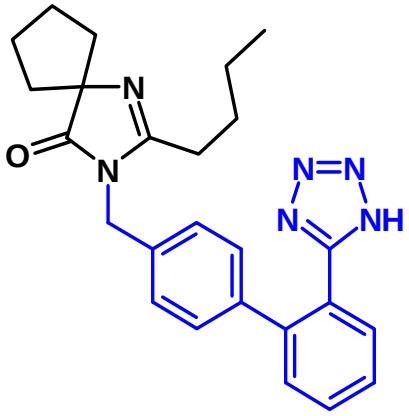
eprosartan
SmithKline Beecham (1989/1997)



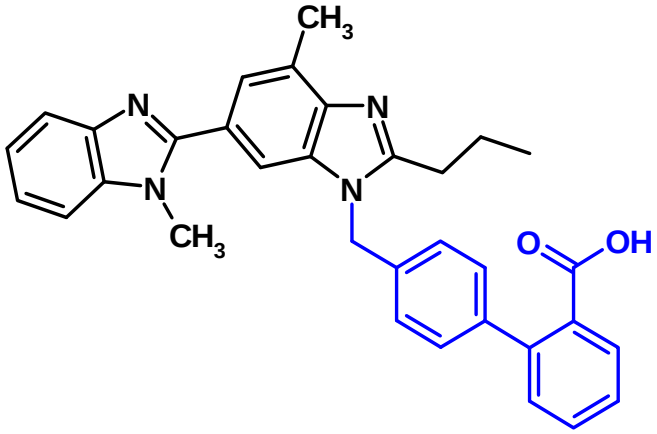
valsartan
Novartis (1990/1996)



candesartan
Takeda (1990/1999)

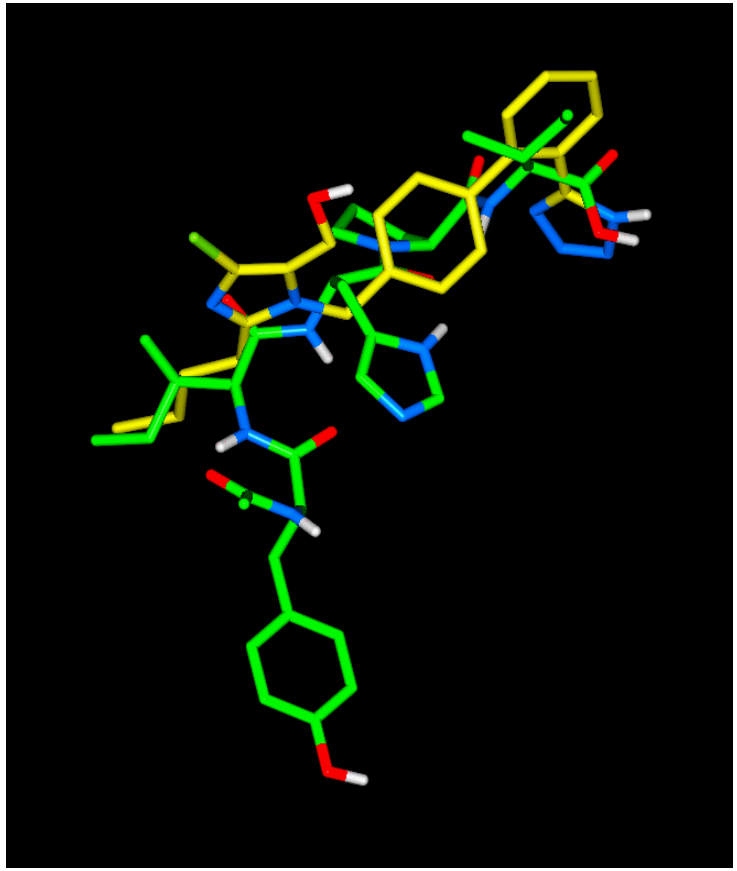


irbesartan
Sanofi (1990/1997)

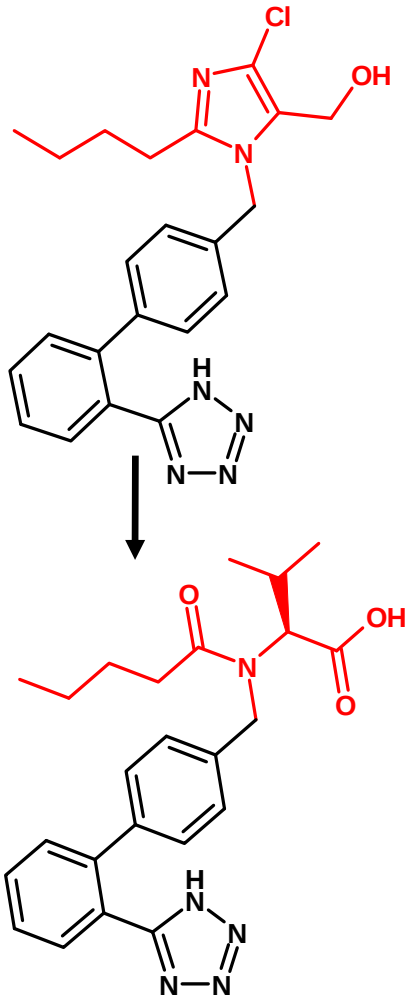


telmisartan
Boehringer Ingelheim (1991/1999)

Synthèse d'analogues



Superposition avec la partie
C-terminale de l'angiotensine II



Losartan

(Du Pont)

A_{II} antagonist

Valsartan

(Novartis)

P. Buehlmayer, P. Furet et al. *Bioorg.Med.Chem.Lett.* **1994**, *4*, 29

Troisième réaction: pratiquer de la recherche fondamentale

- C'est la recherche fondamentale, publique ou privée, qui est à la base des traitements originaux par des médicaments pionniers

- Elle vise des besoins thérapeutiques non encore satisfaits

- Elle met en jeu la chemoinformatique, le criblage à haut flux, la génomique chimique, la stratégie SOSA, le screening virtuel etc.

- Elle est risquée, coûteuse et elle n'aboutit qu'à un tiers des médicaments sur le marché

Mais on ne révolutionne pas la médecine tous les 15 jours!

Tendances

- Prise en compte précoce (au stade des essais *in vitro*) des paramètres ADME et de toxicité

- Toujours des petites molécules, mais rôle grandissant des peptides et des protéines

- Quatre médicaments «moyens» sont plus sûrs qu'un médicament phare («blockbuster»)

- Valorisation des «anges déchus»: médicaments actifs sur une sous-classe de patients

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Le principe de l'approche SOSA

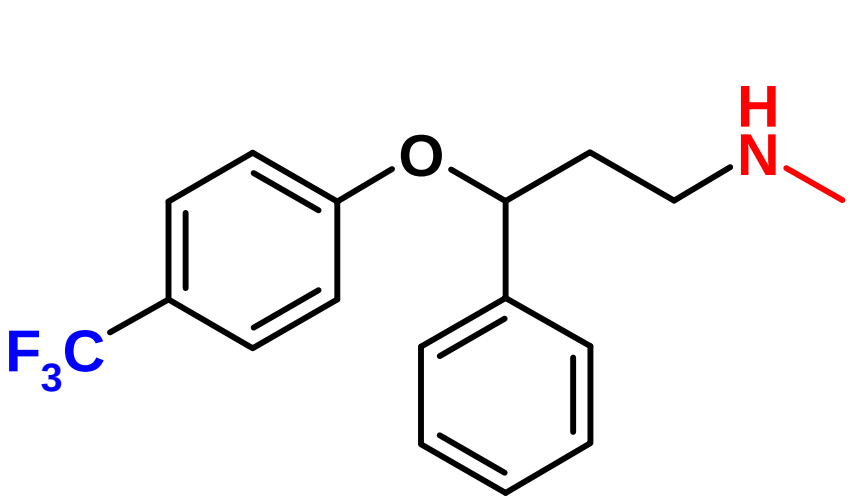
SOSA = Selective Optimization of Side Activities

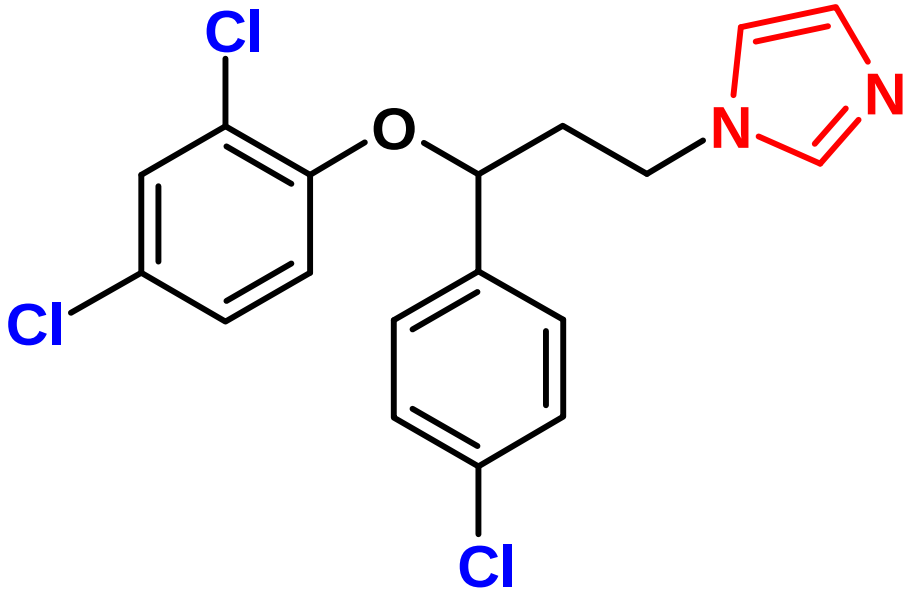
Selective Optimization of a Side Activity = SOSA Approach. How does it work?

1 – The first step is to screen on a new target a smart library (≈1,000 compounds) of carefully chosen, structurally diverse ***drug molecules***. Since bioavailability and toxicity studies have already been performed for those drugs and since they have proven their usefulness in human therapy, all hits will be "drug-like!"

2 – The second step aims to optimize the hits (by means of medicinal chemistry) in order to increase the affinity for the new target and decrease the affinity for the other targets. The objective is to prepare analogues of the hit molecule in which the "side activity" becomes the main activity and, *vice-versa*, for which the original pharmacological activity is strongly reduced or even abolished.

SOSA Approach: a typical example



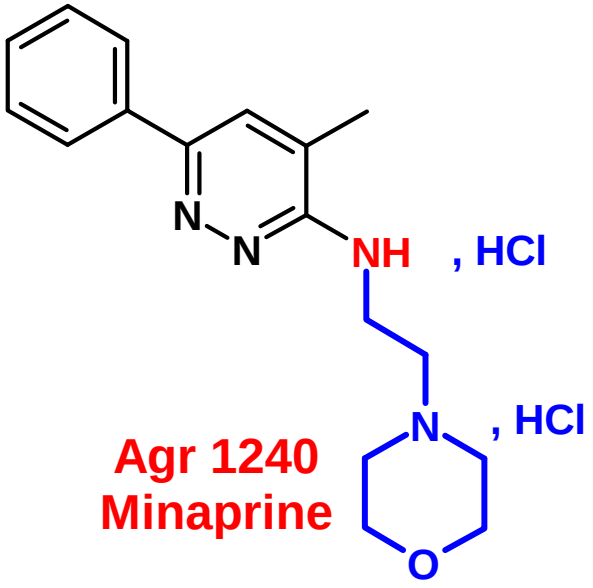


Starting from the serotonin reuptake inhibitor fluoxetine the synthesis of imidazole analogues and some changes of the aromatic substituents yielded anti-*Candida* agents
(R. Silvestri et al. J.Med. Chem. 2004 **47** 3924-3926)

DISCOVERY OF THE SOSA APPROACH

From minaprine to cholinergic agents

In the early eighties we prepared the atypical antidepressant drug minaprine dihydrochloride (Cantor®,Isopulsan®). It was the result of a collaborative research on psychoactive pyridazines undertaken with Dr Henri Laborit and the scientists of the Sanofi Group.



Agr 1240
Minaprine

Minaprine proved to be active on animal models of depression and its mechanism of action was attributed to an enhancement of the dopaminergic transmission and, to a lesser extend, of the serotoninergic transmission.

ARZNEIMITTEL-FORSCHUNG
DRUG RESEARCH

Arzneim.-Forsch. / Drug Res. 32 (II), 8, 824–831 (1982)

Editio Cantor · D-7960 Aulendorf

From the Centre de Recherches Clin-Midy, Groupe Sanofi, Department of Neurobiology, Montpellier (France)

Pharmacological Evaluation of Minaprine Dihydrochloride, a New Psychotropic Drug

By K. Bizière, J. P. Kan, J. Souilhac, J. P. Muyard, and R. Roncucci

Summary: *Minaprine (3-[2-morpholino-ethylamino]-4-methyl-6-phenyl-pyridazine dihydrochloride; 30038CM; trade name in France: Cantor®) is a new psychotropic drug. The therapeutic profile of minaprine differs from that of other known psychotropic agents; in man the drug antagonizes the "inhibitory syndrome" characterized by decreased spontaneous activity, reduction in basic drives, slowed thoughts, feelings of tiredness and social withdrawal. Preliminary clinical trials have indicated that minaprine may also be effective in certain depressive states. This finding prompted us to study the effects of minaprine in animal models for depression. Like most antidepressants minaprine antagonizes behavioral despair, but the effect exhibits a slow onset and maximal activity is reached 24 h after administration. Minaprine also antagonizes reserpine-induced ptosis, this effect has a rapid onset, and is long-lasting. In contrast, minaprine poorly antagonizes reserpine-induced hypothermia. Unlike most antidepressants minaprine does not potentiate yohimbine-induced lethality. Minaprine potently antagonizes prochlorperazine-induced catalepsy in rats and potentiates amphetamine-induced stereotyped behavior, suggesting that the drug may enhance dopaminergic transmission. Finally, minaprine does not antagonize either oxotremorine-induced tremors or physiostigmine-induced lethality. Taken together the results of the present study indicate that minaprine is active on certain, but not all, animal models for depression and suggest the drug may have a potential clinical utility in the treatment of human depressions.*

Minaprine exhibits cholinergic properties

Rapidly it was observed that, beside its dopaminergic and serotoninergic profile, minaprine exhibits also some cholinergic activity:

1984: Garattini, S.; Forloni, G.L.; Tirelli, S.; Ladinsky, S. & Consolo, S. Neurochemical effects of minaprine, a novel psychotropic drug, on the central cholinergic system of the rat.
Psychopharmacology, 1984, ***82***, 210-214

1989: Worms, P.; Kan, J.P.; Steinberg, R.; Terranova, J.P.; Pério, A. & Bizière, K. Cholinomimetic activities of minaprine.
Naunyn Schmiedebergs Arch. Pharmacol. 1989, ***340***, 411-418

Can minaprine be a possible lead for Alzheimer's disease?

Cholinergic hypothesis

According to the cholinergic hypothesis, memory impairments in patients with senile dementia of the Alzheimers type (SDAT) result from a deficit of cholinergic functions in the brain.

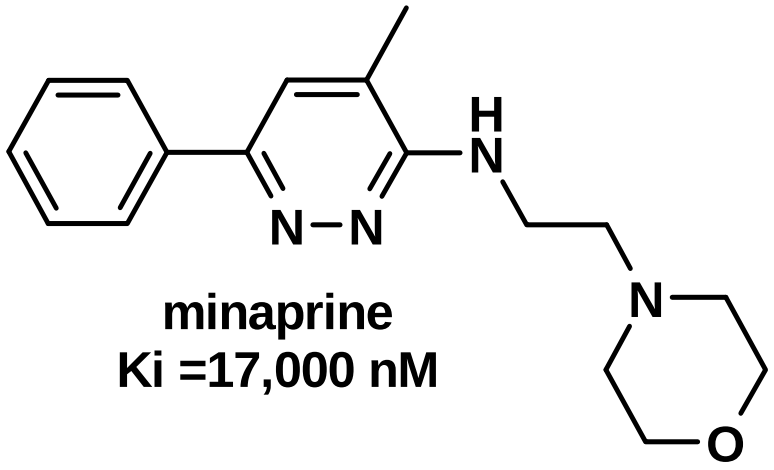
Bartus, R.T.; Dean, L.D. III; Beer, B.; Lippa, A.S.

The Cholinergic Hypothesis of Geriatric Memory Dysfunction.

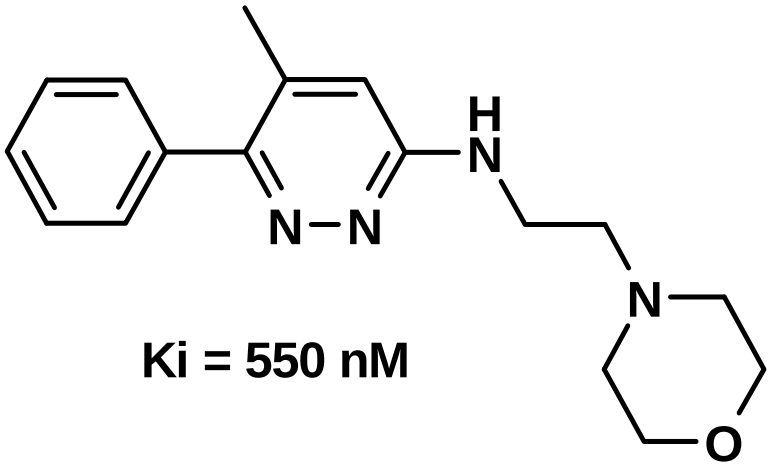
Science 1982, 217, 408-417.

SAR for cholinergic activity

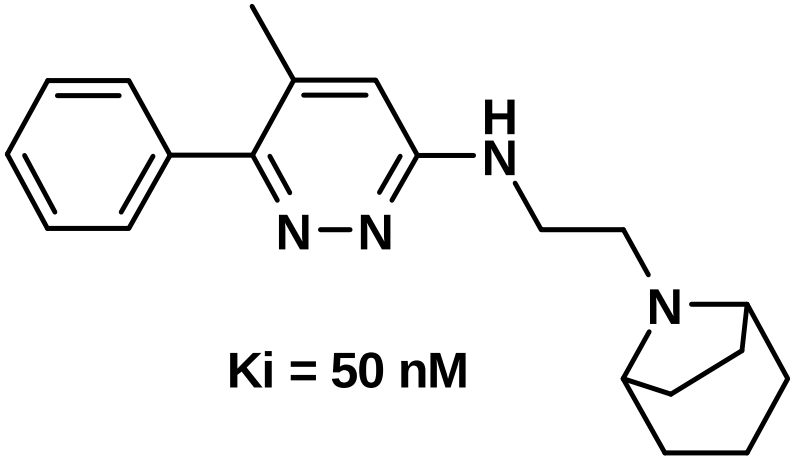
(Affinity for muscarinic M1 receptors)



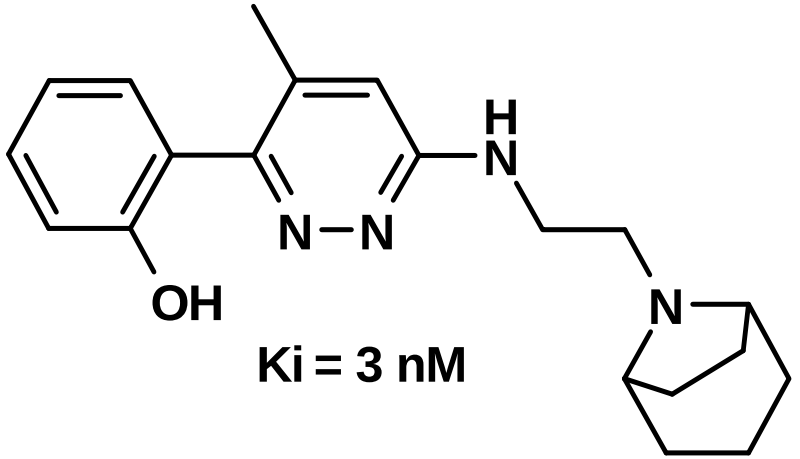
minaprine
Ki =17,000 nM



Ki = 550 nM



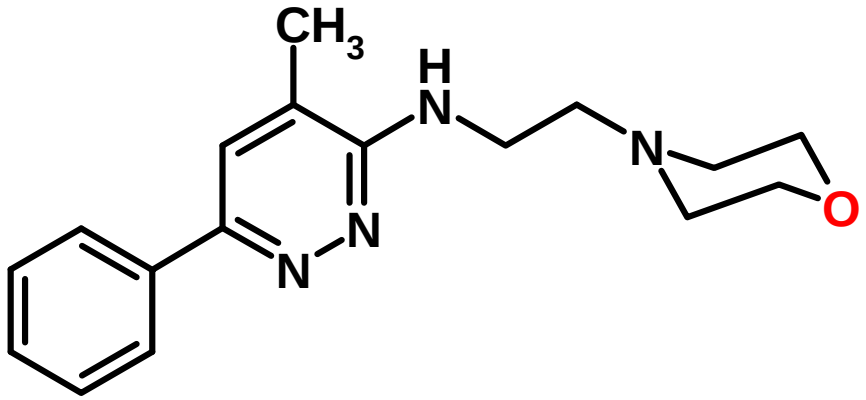
Ki = 50 nM



Ki = 3 nM

Wermuth, C. G. *Il Farmaco* **1993**, *48*, 253-274.

Inversion of the activity profile of minaprine: *A new lead results from the Selective Optimization of a Side Activity*

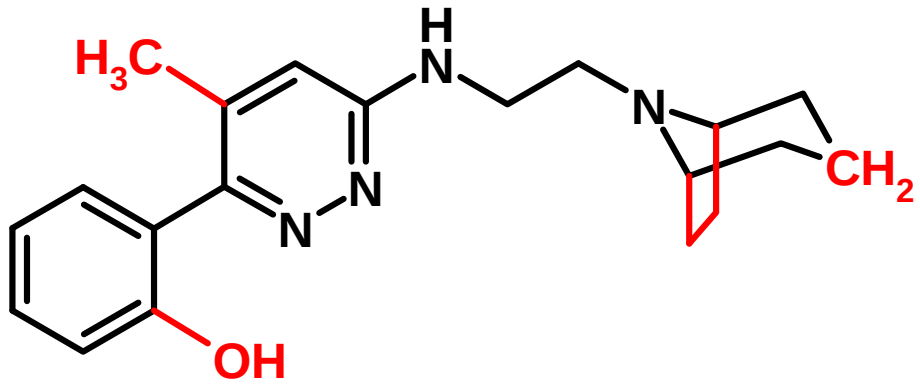


Minaprine (Cantor®)

Dopaminergic: +++

Serotoninergic: ++

Cholinergic: 1/2+



Modified Analogue

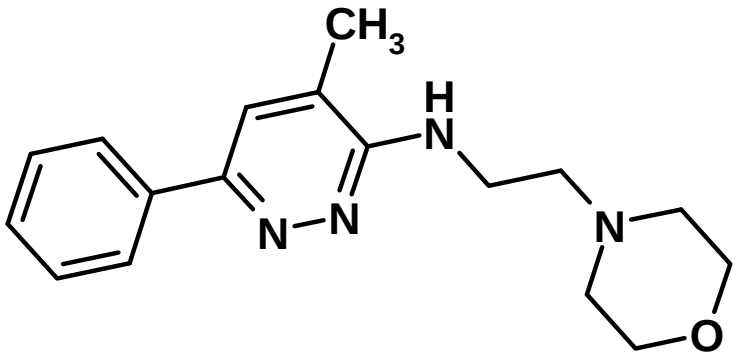
Dopaminergic: 0

Serotoninergic: 0

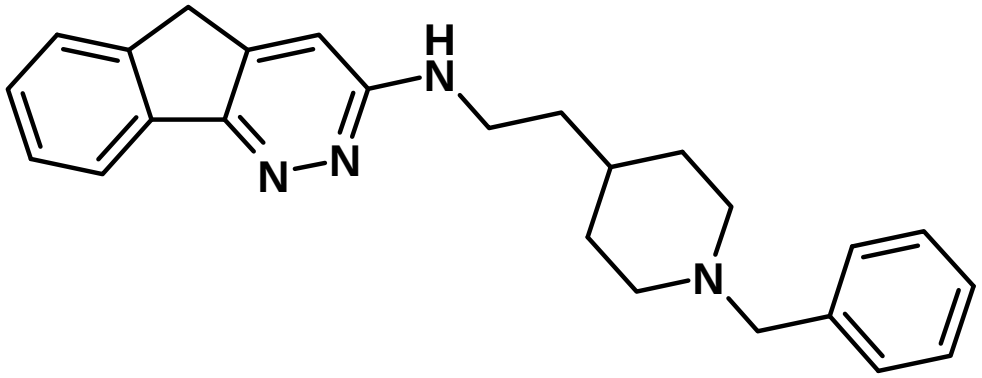
Cholinergic: ++++

Wermuth, C. G. *Il Farmaco* **1993**, *48*, 253-274.

From minaprine to acetylcholinesterase inhibitors



Acetylcholinesterase inhibition (Electric eel): IC_{50} = 85 µM

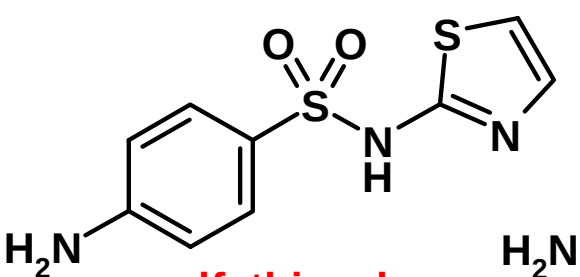


Acetylcholinesterase inhibition (electric eel IC_{50}) = 0.010 µM

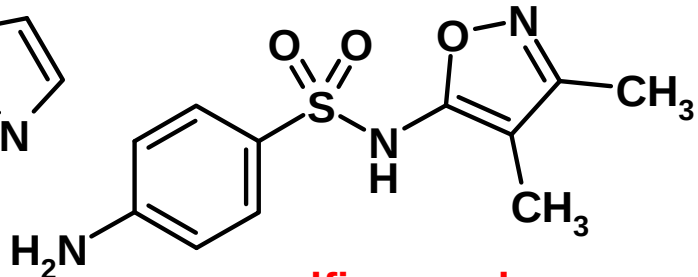
[= approx 8,500 x minaprine]

OTHER EXAMPLES OF THE SOSA APPROACH

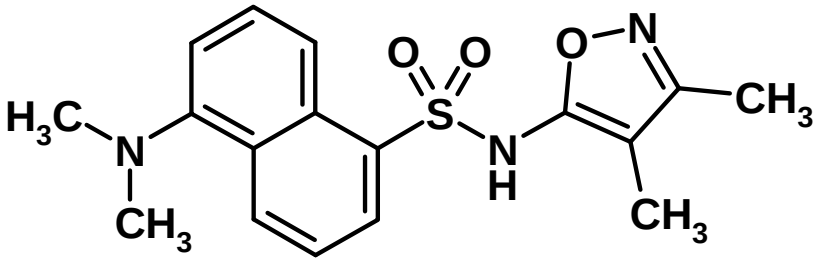
From antibacterial sulfonamides to endothelin receptor antagonists (1/3)



sulfathiazole
IC_{50} = 69 µM



sulfisoxazole
IC_{50} = 0.78 µM



BMS-182874
IC_{50} = 0.15 µM

(IC_{50} values for the endothelin ET_A receptor)

At the origin a modest affinity for the l'endothelin ET_A receptor was observed with the antibacterial sulfonamide sulfathiazole. Extension to other sulfonamides led to sulfisoxazole, by far more potent. Optimisation of this latter ce yielded the compound BMS-182874, a potent and selective antagonist.

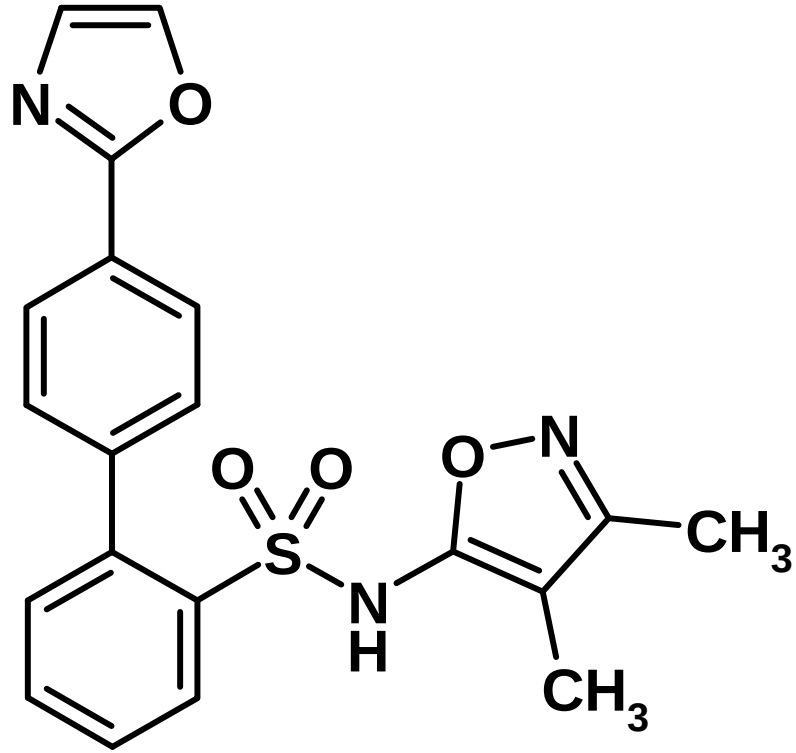
In vivo, this compound is orally active and produces a long-lasting hypotensive effect.

Stein, P. D.et al. *J.Med. Chem.* 1994, *37*, 329-331.

From antibacterial sulfonamides to endothelin receptor antagonists (2/3)

Further optimization guided by pharmacokinetic considerations led the BMS scientists to replace the naphtalene ring with a diphenyl system.

Among the prepared compounds, **4** (BMS-193884, ET_A Ki = 1.4 nM; ET_B Ki = 18,700 nM) showed promising hemodynamic effects in a phase II clinical trial for congestive heart failure.

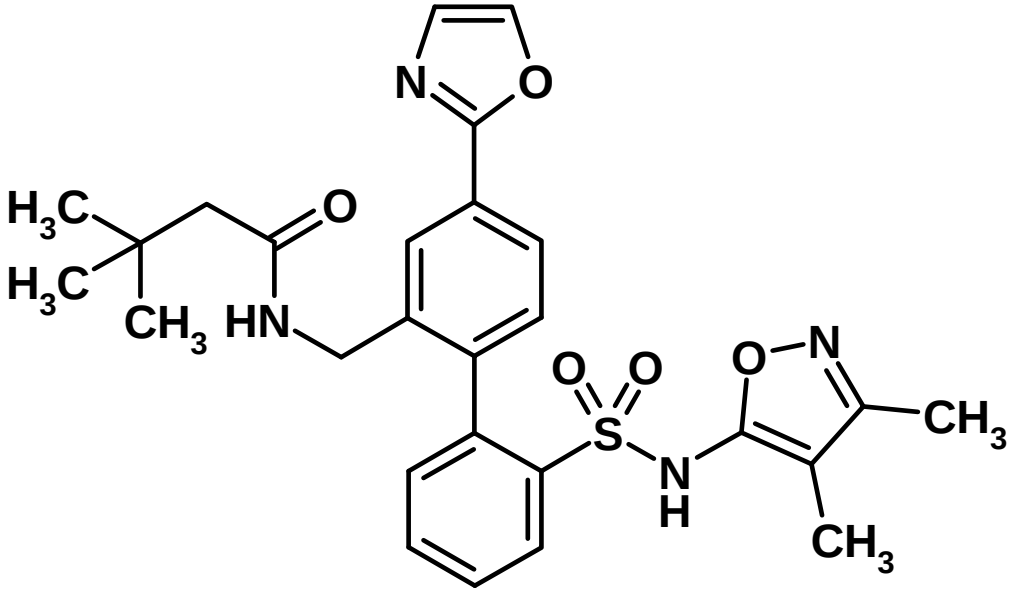


BMS-193884
ET_A Ki = 1.4 nM

From antibacterial sulfonamides to endothelin receptor antagonists (3/3)

Later studies led to the extremely potent antagonist edonentan (BMS-207940; ET_A Ki = 10 pM) this compound presents an 80,000-fold selectivity for ET_A vs ET_B.

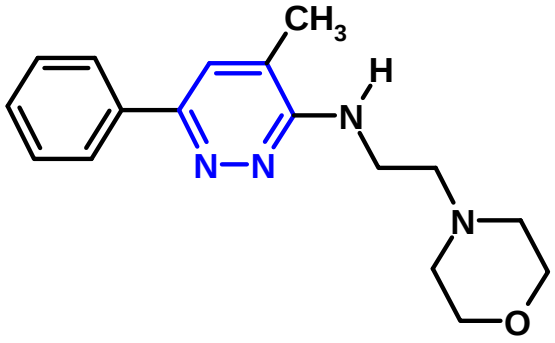
Its bioavailability is 100% in rats and it exhibits oral activity at a dosage of only 3 µM/kg.



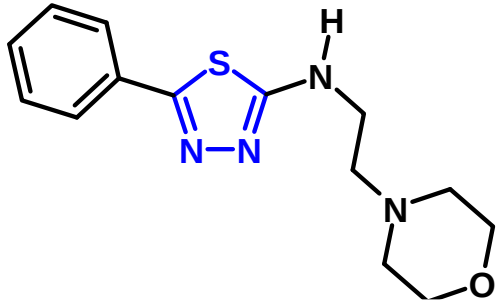
BMS-207940
ET_A Ki = 0.010 nM

N. Murugesan et al.
J.Med. Chem. 2003, *46*, 125-137.

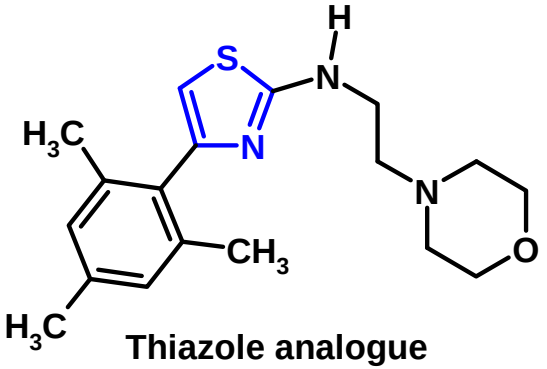
From minaprine to CRF antagonists: obstinate research pays!



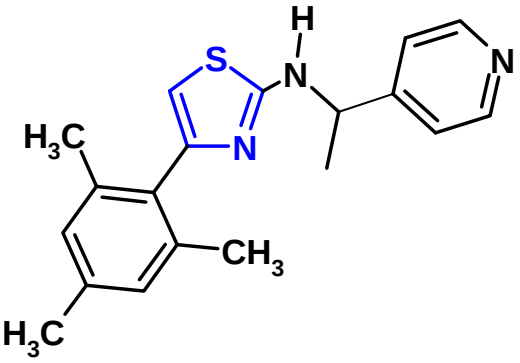
Minaprine



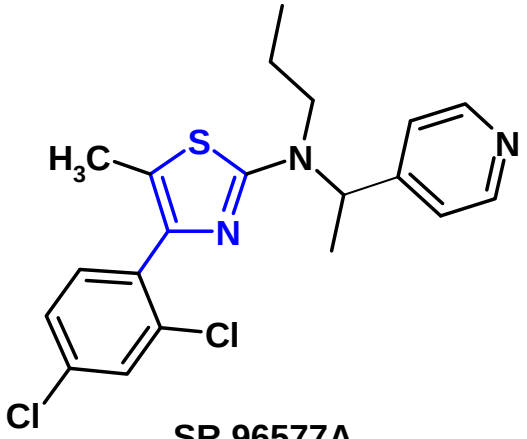
Thiadiazole bioisostere of minaprine



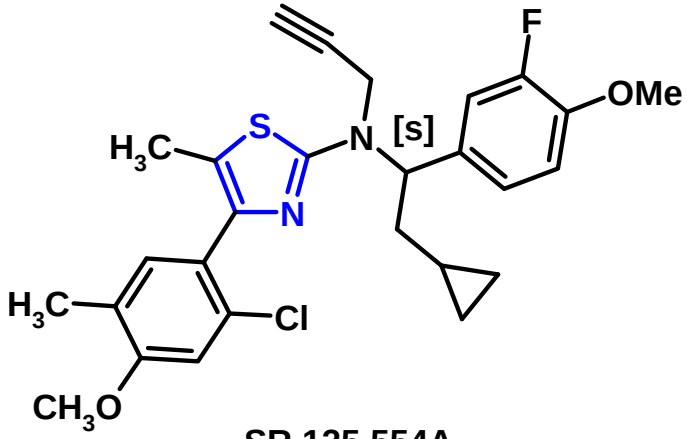
Thiazole analogue of minaprine



SR 27712
IC_{50} = approx. 100 000 nM



SR 96577A
IC_{50} = 200 nM



SR 125 554A
IC_{50} = 0.6 nM

From minaprine to CRF antagonists: Ten years of preclinical development

INITIAL SCREENING. Inhibition of the ACTH secretion induced by CRF. 15000 molecules tested gave 3 hits at a concentration of 10^{-4} M.

SYNTHESIS: 2000 molecules prepared and tested yield 500 compounds acting at nanomolar concentration.

ADME AND TOXICOLOGICAL PARAMETERS: Eliminated about 495 compounds out of 500.

LITERATURE:

D. Gully et al. 4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine hydrochloride (SSR125543A): a potent and selective corticotrophin-releasing factor(1) receptor antagonist. I. Biochemical and pharmacological characterization. *J Pharmacol Exp Ther. 2002 Apr;301(1):322-32*

G. Griebel et al. 4-(2-Chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4 methyl-phenyl)ethyl]5-methyl-N-(2-propynyl)-1, 3-thiazol-2-amine hydrochloride (SSR125543A), a potent and selective corticotrophin-releasing factor(1) receptor antagonist. II. Characterization in rodent models of stress-related disorders. J Pharmacol Exp Ther. 2002 Apr;301(1):333-45.

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Perspective

Selective Optimization of Side Activities: Another Way for Drug Discovery

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Received September 24, 2003

> *"The most fruitful basis for the discovery of a new drug is to start with an old drug."*
> Sir James Black, Winner of the 1988 Nobel prize in Physiology and Medicine[1]

I. Introduction: Strategies in the Search for New Lead Compounds

The second strategy is based on the modification and improvement of existing active molecules. The objective is to start with known active principles and, by various chemical transformations, prepare new molecules (sometimes referred to as "me-too compounds") for which an increase in potency, a better specific activity profile,

Initial drug lead	*Pharmacological profile*	*SOSA-derived analogue*	*Pharmacological profile*	*Reference*
amiloride	**diuretic**	**cariporide mesylate (Hoe 642)**	**Na/H exchange inhibitor**	**27**
niguldipine	**calcium channel blocker**	**SNAP-6383**	**α_{1A}adrenergic antagonist**	**28**
atenolol	**β-blocker**	**cromakalim**	**potassium I_{Ks} channel blocker**	**29**
minaprine	**antidepressant**	**various aminothiazoles**	**CRH antagonists**	**30-32**
sulpiride	**D_3/D_2 non-selective dopamine antagonist**	**compound Do 897**	**D_3-selective partial dopamine agonist**	**33, 34**
Lu 110896 and Lu 110897	**herbicides**	**diphenyl analogue**	**potent and selective ET_A antagonist**	**35**
tetracycline	**antibiotic**	**BMS 1922548**	**neuropeptide Y ligand**	**36**
erythromycin A	**antibiotic**	**cladinose replacement analogue**	**nonpeptide luteinizing hormone-releasing hormone antagonists**	**37**
fluoxetine	**serotonine reuptake inhibitor**	**imidazole analogue**	**anti-Candida agent**	**38**
diazepam	**tranquillizer**	**CI-1044**	**selective PDE 4 inhibitor**	**39**

C.G. Wermuth, Drug Discov. Today, 2006, 11, 160-164

THE SOSA APPROACH: DISCUSSION

«The most fruitful basis for the discovery of a new drug is to start with an old drug»

Sir James Black,
Nobel Laureate 1988 in Physiology and Medecine
Cited by T.N.K. Raju
The Lancet, Vol. 355, N° 9208, 18 march 2000

The rationale of the «SOSA» approach

The rationale behind the SOSA approach lies in the fact that, in addition to their main activity, almost all drugs used in human therapy show one or several side effects.

In other words, if they are able to exert a strong interaction with the main target, they exert also less strong interactions with some other biological targets. Most of these targets are unrelated to the primary therapeutic activity of the compound.

The objective of is then to proceed to a reversal of the affinities (a pharmacological “Umpolung”), the identified side effect becoming the main effect and *vice-versa*.

Multi-affinity Drugs

1. The D_2 antagonist spiperone shows also strong affinities for serotonin 5-HT_{2a} receptors.

2. The GABA-A antagonist gabazine is a potent inhibitor of the enzyme monoamine-oxidase-A.

3. The anxiolytic diazepam also inhibits phosphodiesterase.

4. N^G-Nitro-arginine, the competitive antagonist of nitric synthase possesses also antagonistic activities towards muscarinic receptors.

5. Antipsychotics such as clozapine and olanzapine exhibit affinities for at least fourteen different neurotransmitter receptors such as D_1, D_2, D_3, 5-HT_{2a}, 5-HT_{2c}, 5-HT_3, m1, m2, m3, m4 m5, α_1, α_2, and H_1.

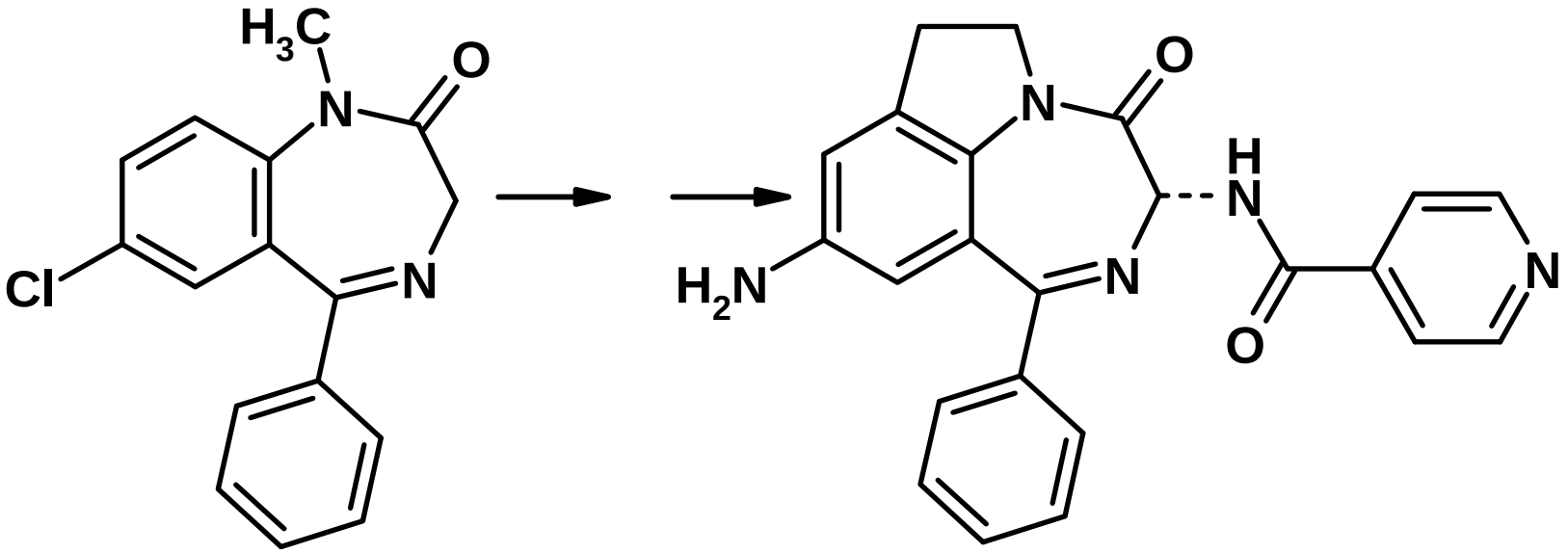
Patentability – Risk of interference

- The risk with the SOSA approach is to prepare a molecule already synthesized by the initial inventors and their early competitors.

- In fact, in optimizing another therapeutic profile than that of the initial one, the medicinal chemist will rapidly prepare analogues with chemical structures very different from that of the original hit.

- As an example, a medicinal chemist interested in phospho-diesterases and using diazepam as lead, will rapidly prepare compounds which are out of scope of the original patents, precisely because they exhibit dominantly PDE inhibiting properties and almost no more affinity for the benzodiazepine receptor.

Analogues of the tranquilizer diazepam are potent and selective PDE4 inhibitors



diazepam **CI-1044**

C. Burnouf et al. J.Med. Chem. 2000 ***43*** 4850-4867

Safety – Bioavailability

- During years of practicing SOSA approaches, we observed that starting with a drug molecule as lead substance in performing analogue synthesis, increased notably the probability of obtaining safe new chemical entities.
- In addition most of them satisfy Lipinski's[1], Veber's[2], Bergström's[3], and Wenlock's[4] recommendations in terms of solubility, oral bioavailability and drug-likeness.

Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney; P.J. Experimental and computational approches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug. Delivery. Rev.* **2001**, *46*, 3-26.

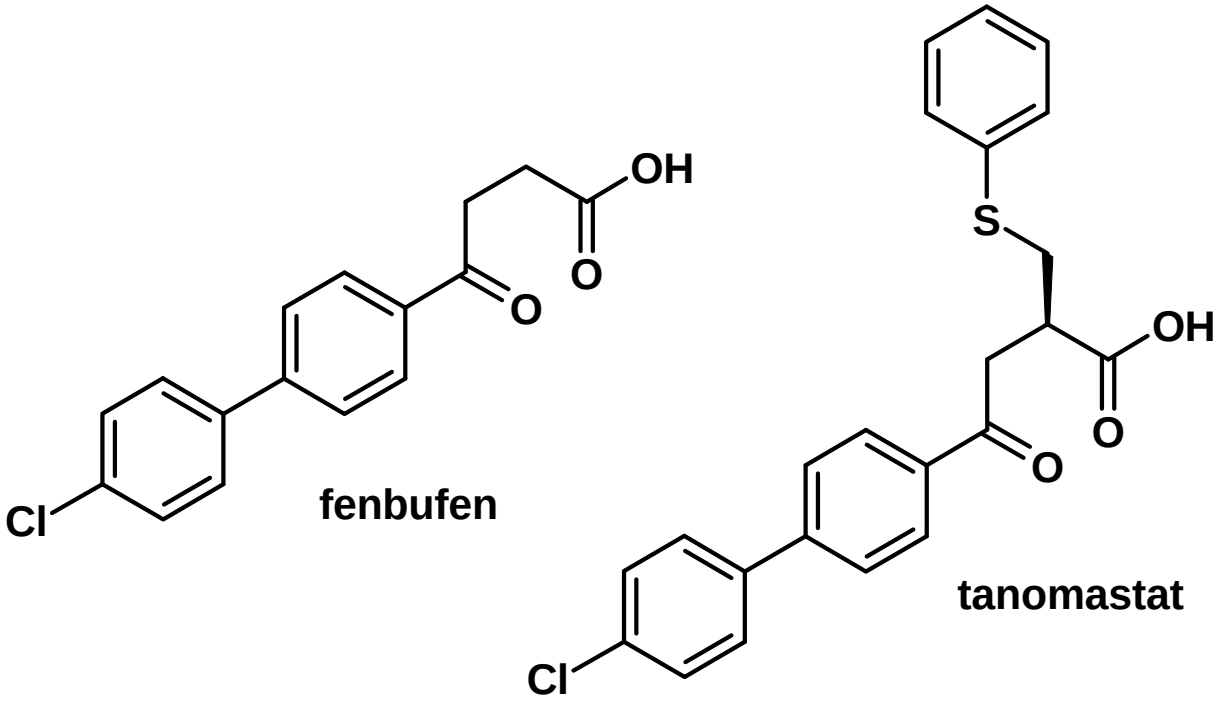
Veber, D. F.; Johnson, S. R.; Cheng, H. Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. Molecular properties that influence the oral bioavailability of drug candidates. *J. Med. Chem.* **2002**, *45*, 2615-2623.

Bergström, C. A. S.; Strafford, M.; Lazorova, L.; Avdeef, A.; Luthman, K.; Artursson, P. Absorption classification of oral drugs based on molecular surface properties. *J.Med.Chem.* **2003**, *46*, 558-570.

Wenlock, M. C.; Austin, R. P.; Barton, P.; Davis, A. M.; Leeson, P. D. A comparison of physicochemical property profiles of development and marketed oral drugs. *J.Med.Chem.* **2003**, *46*, 1250-1256.

Safety – Bioavailability

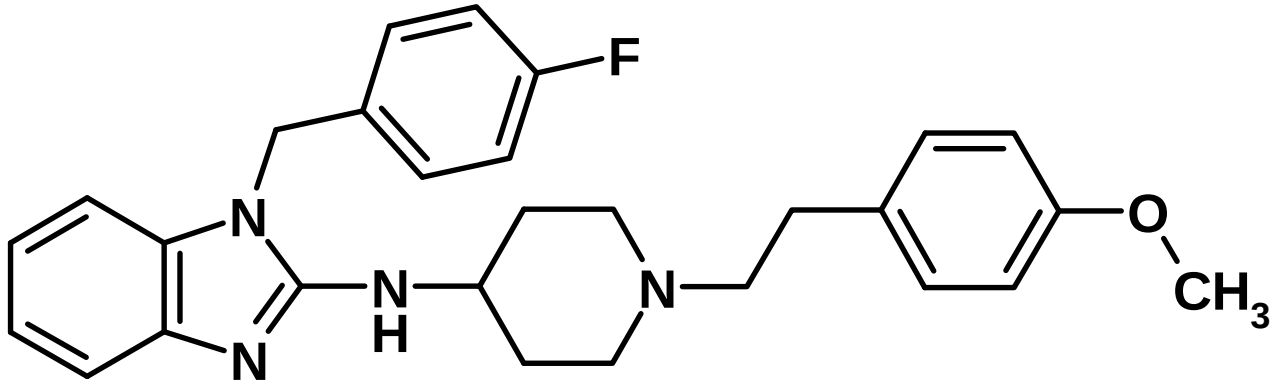
Caveat: An unfavorable attribute of the orignal drug can be carried through to the SOSA procedure and retrieved in the derived drug



For example the Bayer compound tanomastat (Bay 12-9566) derived from the anti-inflammatory drug fenbufen was dropped from development at phase III due to lack of efficacy associated with high protein binding. These unwanted properties are already present in tanomastat.

A clinical drug library screen identified astemizole as antimalarial agent

The H1-histamine antagonist astemizole (Hismanal®) and its principal human metabolite (desmethyl-astemizole) are promising new inhibitors of chloroquine-sensitive and multidrug-resistant *Plasmodium falciparum* parasites. They also show efficacy in two mouse models of malaria [1].

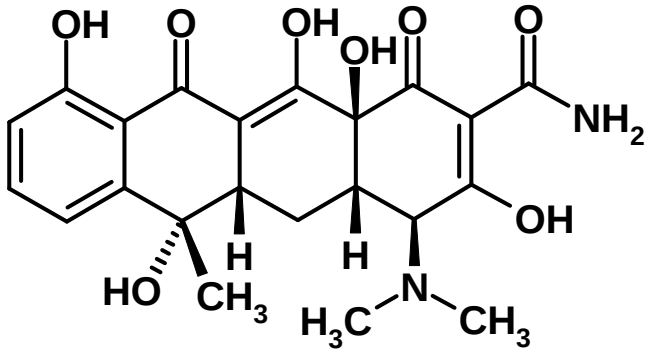


However, the initial optimism about these drugs has to be tempered by the fact that astemizole has a hERG IC_{50} of 0.9 nM [2]!

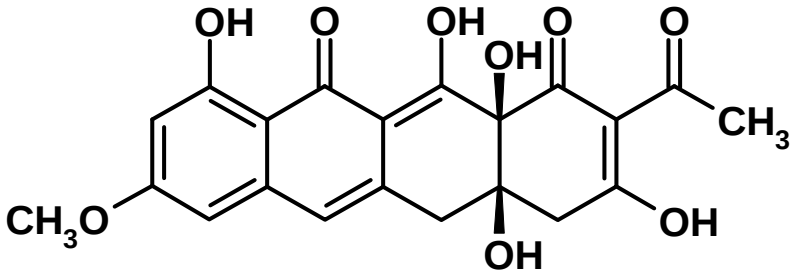
[1] Curtis R. Chong et al. Nature Chemical Biology Published online 02 July 2006
[2] Cavalli et al., J.Med.Chem. 2002, 45, 3844-3853.

Originality

The screening of a library of several hundreds of therapeutically diverse drug molecules sometimes ends up with very surprising results. A nice example of unexpected findings resulting from a systematic screening is found in the tetracyclic compound BMS-192548 extracted from *Aspergillus niger* WB2346



tetracycline



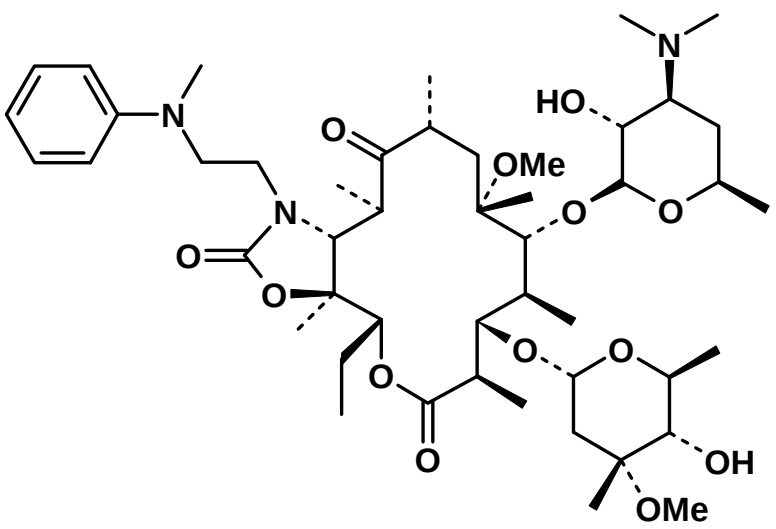
BMS-192548

For any medicinal chemist or pharmacologist the similarity of this compound with the antibiotic tetracycline is striking.
However, none of them would *a priori* forecast that BMS-192548 is a ligand for the neuropeptide Y receptor.

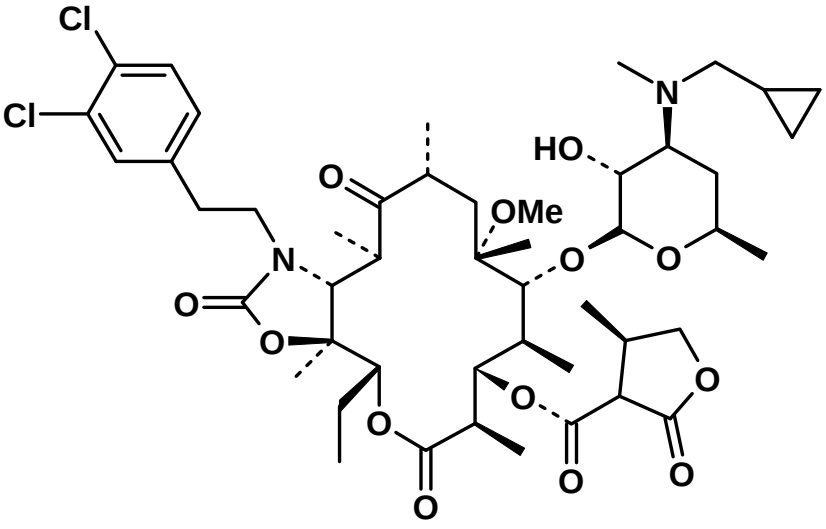
Shu, Y. Z. et al. *J. Antibiot* **1995**, *48*, 1060-1065.

From the antibiotic erythromycin to LHRH antagonists

A screen of the Abbott chemical repository identified erythromycin A derivatives that bound to the rat LHRH receptor with submicromolar affinity and exhibited LHRH antagonistic properties. One of the most potent antagonists was the anilinoethyl cyclic carbamate **1**. Optimisation efforts mainly based on replacement of the cladinose moiety in position 3 led to compound **4** which has 1-2 nM affinity for both rat and human LHRH receptors and is a potent inhibitor of LH release (pA_2 = 8.76) *in vitro*. *In vivo*, compound 4 was found to produce a dose-dependent suppression of LH in male castrate rats via both iv and po dosing.



Compound 1
(pKi = 7.0)



Compound 4
(pKi = 9.17)

Randolph, J. T. et al.*J.Med.Chem.* **2004***, 47*, 1085-1097.

Orphan Diseases

As mentioned earlier, a differentiating peculiarity of the SOSA library is that it is constituted by compounds that have already been safely given to humans.

Thus, if a compound were to “hit” with sufficient potency on an orphan target, there is a high chance that it could rapidly be tested in patients for Proof of Principle.

This possibility represents another advantage of the SOSA approach.

Thank you for your attention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