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Perspective

Selective Optimization of Side Activities: Another Way for Drug Discovery

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"*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

A retrospective analysis of the ways leading to discovery of new drugs suggests that there are four types of successful strategies leading to new lead compounds.

The first strategy consists of systematic screening of sets of compounds arbitrarily chosen for their diversity, by selected biological assays. This approach was useful in the past for the discovery of new antibiotics such as streptomycin and for the identification of compactin as an HMG-CoA reductase inhibitor. Presently, as high-throughput screening (HTS), it is applied in a very general manner to synthetic as well as to natural compounds. Experience gathered has confirmed that high-throughput screening allows for the rapid identification of numerous hits, and the literature is full of success stories obtained with that approach. Among them, one could mention the discovery of insulin mimetics,[2] of ORL1 receptor agonists,[3] of protein tyrosine phosphatase-1B inhibitors,[4] of selective neuropeptide Y5 receptor antagonists,[5] of selective COX-2 inhibitors,[6] of corticotropin releasing factor (CRF) receptor modulators,[7] and of CXCR2 receptor antagonists.[8] Yet the HTS strategy for drug discovery has several limitations. It suffers from inadequate diversity, has low hit rates, and often leads to compounds with poor bioavailability or toxicity profiles.

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, improved safety, and a formulation that is easier to handle by physicians and nurses or more acceptable to the patient are claimed. A typical illustration of this approach is found in the series of lovastatin analogues (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, etc.). In the pharmaceutical industry, motivations for this kind of research are often driven by competitive and economic factors. Indeed, if the sales of a given medicine are high and if a company is in a monopolistic situation protected by patents and trademarks, other companies will want to produce similar medicines, if possible with some therapeutic improvements. They will therefore use the already commercialized drug as a lead compound and search for ways to modify its structure and some of its physical and chemical properties while retaining or improving its therapeutic properties.

The third approach resides in the retroactive exploitation of various pieces of biological information that sometimes result from new discoveries made in biology and medicine and sometimes are just the fruits of more or less serendipitous observations. Examples are the chance discovery of the vasodilating activity of trinitroglycerol, the antibiotic activity of *Penicillium notatum*, and the clinical observation of the activity of sildenafil on erectile dysfunction. Research programs based on the exploitation of clinical observations of side effects are of great interest in the discovery of new tracks insofar

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Table 1. Affinities of Some Antipsychotics for Various Neuronal Receptors[23]

	affinity, K_i (nM)									
compd	D_1	D_2	D_3	$D_{4.2}$	5-HT_{2A}	5-HT_{2C}	α1	α2	muscarinic receptor	H_1
haloperidol	270	1.4	21	11	25	>5000	19	>5000	4670	730
clozapine	540	150	360	40	3.3	13	23	160	34	2.1
risperidone	620	3.3	13	16	0.16	63	2.3	7.5	>5000	2.6
olanzapine	250	17	54	28	1.9	7.1	60	230	26	3.5
sertindole	210	7.4	8.2	21	0.85	1.3	1.8	1680	>5000	570
quetiapine	4240	310	650	1600	120	3820	58	87	1020	19
ziprasidone	330	9.7	7.5	39	0.3	13	12	390	>5000	5.3
zotepine	84	13	16	39	0.91	2.9	3.4	960	550	3.4

as they are based on information about activities *observed directly in man* and not in animals. They can also detect new therapeutic activities *even when no pharmacological models in animals exist*.

Finally, the fourth route to new active compounds is a rational design based on the knowledge of the molecular cause of the pathological dysfunction. Examples are the design of captopril as a hypotensive drug or of cimetidine as a treatment for peptic ulcers. This approach depends heavily on the progress made in fundamental research, particularly in the identification and structural elucidation of a new receptor or enzyme subclass involved in a specific disease.

It would be imprudent to compare hastily the merits of each of these approaches. Indeed, "poor" research can end with a universally recognized medicine and, conversely, a brilliant rationale can remain sterile. *It is therefore of the highest importance that decision makers in the pharmaceutical industry appeal to all four above-mentioned strategies and that they realize that the strategies are not mutually exclusive.*

The present trend is mass screening of huge libraries containing several thousand molecules. This was made possible by the association of combinatorial chemistry with high-throughput screening (HTS). However, other alternatives leading to interesting hits exist. The objective of the present perspective is to review one of these: the SOSA approach.

II. New Leads from Old Drugs: The Sosa Approach

Definitions and Principle. The SOSA (selective optimization of side activities) approach represents a validated alternative to HTS.[9−12] It consists of testing "old" drugs on new pharmacological targets. The aim is to subject to pharmacological screening a limited number of drug molecules that are structurally and therapeutically very diverse and that have known safety and bioavailability in humans and thereby shorten the time and the cost needed for a hit identification.

The SOSA approach proceeds in two steps.

(1) Start the screening with a limited set of carefully chosen, structurally diverse drug molecules (a smart library of about 1000 compounds). 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 "druglike!"

(2) Optimize hits (by means of traditional, parallel, or combinatorial 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 order to transform the observed "side activity" into the main effect and to strongly reduce or abolish the initial pharmacological activity.

The strength of the SOSA concept[13] is based on the fact that all drugs act on many receptors (known and unknown) and the assumption that there is only a limited chemical universe that can be safely administered to humans. This universe can be adequately covered with currently available drugs.

As mentioned above, a differentiating peculiarity of this type of library is that it is constituted of 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. Alternatively, if one or more compounds hit but with insufficient potency, optimized analogues can be synthesized and the chances that these analogues will be good candidate drugs for further development are much higher than if the initial lead is toxic or not bioavailable. One of these "new types" of chemical library has recently become available.[14] It contains 880 biologically active compounds with high chemical and pharmacological diversity as well as known bioavailability and safety in humans. Over 85% of the compounds are well-established drugs, and 15% are bioactive alkaloids. For scientists interested in druglikeness, such a library certainly fulfills in the most convincing way the quest for "druglike" leads! Other libraries containing various amounts of drug molecules are also available.[15,16]

Rationale of the SOSA Approach. The rationale for using chemical libraries composed of marketed drugs is that most drugs used in humans interact with more than one target/receptor. Binding to one target mediates efficacy, whereas binding to other targets is often the source of side effects. There are many published examples of drugs that interact with several receptors. The anxiolytic diazepam not only binds to the benzodiazepine receptor but also inhibits phosphodiesterases.[17] The GABA-A receptor antagonist gabazine is a potent inhibitor of monoamine-oxidase type A.[18] Compounds as different as benzyl penicillin or D-tubocurarine unexpectedly show micromolar affinity for GABA-A receptors.[19] *N*-α-Nitroarginine, a competitive antagonist of nitric oxide synthase, was also shown to be a muscarinic receptor antagonist.[20] The dopamine receptor antagonist spiperone shows a strong affinity for serotonin 5-HT_{2a} receptors.[21] Other antipsychotics such as clozapine and olanzapine have been shown to bind to at least 14 different receptors such as D_1, D_2, D_3, 5-HT_{2a}, 5-HT_{2c}, 5-HT_3, M_1, M_2, M_3, M_4, M_5, α_1, α_2, and H_1 receptors.[22] This seems to be a rather common feature as shown in Table 1 (results from Schaus' and

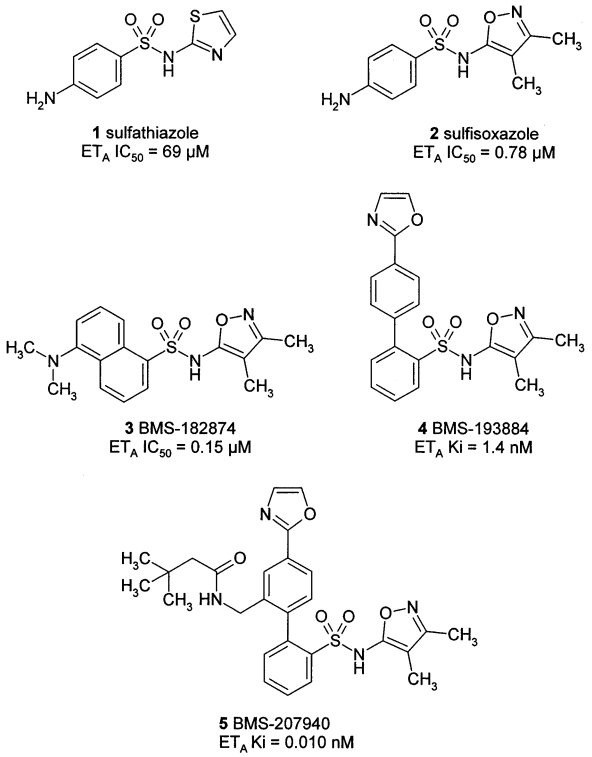


Figure 1. A successful SOSA approach identified the antibacterial sulfonamide sulfathiazole as a ligand of the endothelin ET_A receptor and its optimization to the selective and potent compounds BMS-182874, BMS-193884, and BMS-207940.[24,25]

Bymaster's review[23]), which compares some affinities for a series of eight antipsychotic agents.

The above observations justify the strategy of testing well-known drugs on newly discovered targets. When an "old" drug binds to a new target, the objective is to synthesize analogues with increased affinity for the new target and decreased affinity for the old target. Many examples of such activity profile reversals have been published and are usually the result of traditional, well-established medicinal chemistry approaches.

III. Successful Examples of SOSA Switches

1. Sulfonamides as Lead Compounds. The first two examples of SOSA switches show that extremely potent and selective antagonists of G-protein-coupled receptors and myocardiac sodium/hydrogen exchange (NHE) inhibitors could be derived from traditional drugs such as sulfathiazole and amiloride.

1.1. From Sulfathiazole to Endotheline ET_A Receptor Antagonists. A typical illustration of the SOSA approach is given by the development of a selective antagonist for the endotheline ET_A receptors by scientists from Bristol-Myers-Squibb (BMS).[24] Starting from an in-house library, the antibacterial compound sulfathiazole (**1**, Figure 1) was an initial, but weak, hit (ET_A $IC_{50} = 69\ \mu M$). Testing of related sulfonamides identified the more potent sulfisoxazole (**2**, ET_A $IC_{50} = 0.78\ \mu M$). Controlled variations led finally to the potent and selective ligand (**3**, BMS-182874). In vivo, this compound was orally active and produced a long-lasting hypotensive effect.

Further optimization guided by pharmacokinetic considerations led the BMS scientists to replace the naphthalene ring with a diphenyl system.[25] Among the compounds prepared, **4** (BMS-193884, ET_A $K_i = 1.4$ nM; ET_B $K_i = 18\ 700$ nM) showed promising hemodynamic effects in a phase II clinical trial for congestive heart failure. Later studies led to the extremely potent antagonist **5** (BMS-207940 ET_A $K_i = 10$ pM) presenting an 80000-fold selectivity for ET_A vs ET_B. The bioavailability of **5** is 100% in rats, and it exhibits oral activity at a dosage of only 3 μmol/kg.[25]

1.2. Diuretic Amiloride as a Lead to Myocardiac Sodium/Hydrogen Exchange (NHE) Inhibitors. Currently, five isoforms of sodium/hydrogen exchanger have been found in the plasma membrane of mammalian cells and a sixth has been found in the mitochondria.[26] The predominant isoform in the heart is type 1 (NHE-1). One of the first papers to suggest a cardioprotective role of inhibiting NHE was published by Karmazyn in 1988[27] where it was shown that amiloride **6** (Figure 2), a potassium-sparing diuretic with NHE inhibitory activity, produced an enhanced recovery of contractile function in isolated rat hearts subjected to global ischemia and reperfusion. Subsequently, several investigators used amiloride and its 5-amino substituted pyrazinoyl guanidine derivatives to demonstrate the cardioprotective potential of inhibiting NHE in the ischemic myocardium.[26,28] However, it was found later that these amiloride derivatives interacted with other cation transporters and shared cardiodepressive activities independent of their NHE blocking activity.

Investigators at Hoechst[28] were the first to synthesize a new class of more selective NHE-1 inhibitors, the benzoylguanidine derivatives **7** and **8** (Figure 2). The first compound showing superior efficacy and selectivity over amiloride derivatives was **7** (Hoe-694). This compound showed marked antiarrhythmic and antiischemic activity in several animal models and had a low toxicity profile. To synthesize a compound superior to **7**, investigators from Hoechst made **8** (Hoe-642, or cariporide

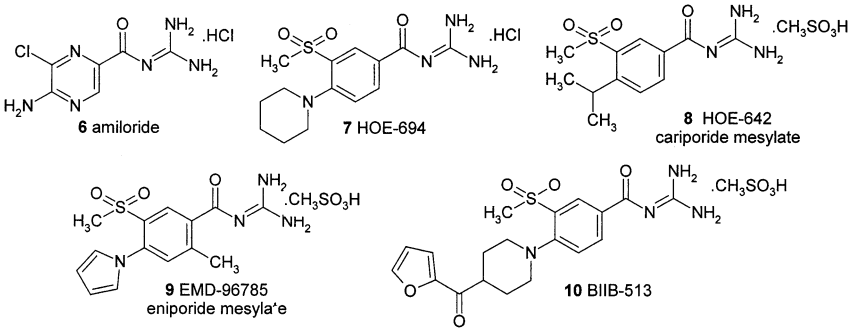


Figure 2. Amiloride-derived cardioprotective sodium/hydrogen exchange (NHE) inhibitors.

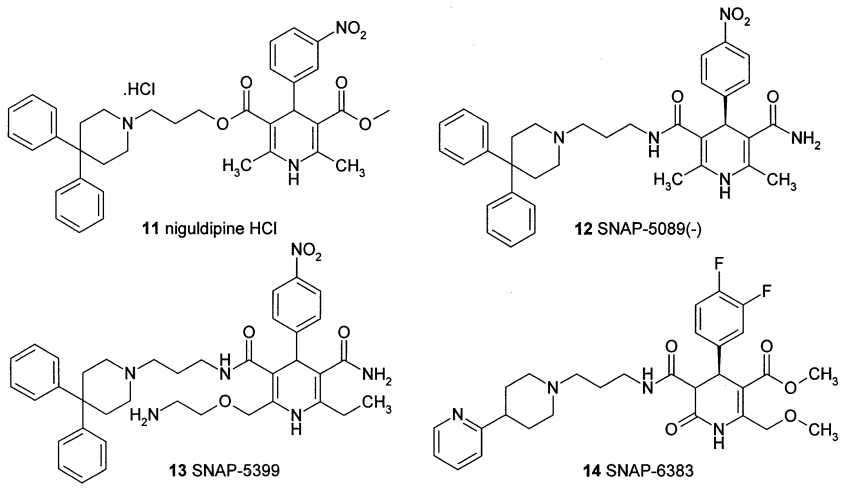


Figure 3. Passage from the calcium channel antagonist niguldipine to the potent and selective α_{1A}-adrenergic antagonist **14** (SNAP-6383).[34]

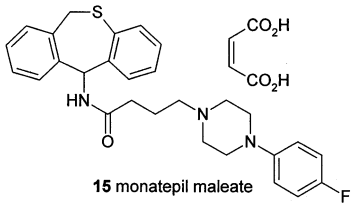


Figure 4. Monatepil maleate (**15**) combines calcium channel blocking activity, α_1-adrenoceptor antagonism, and inhibition of lipid hydroperoxidation.[37,39]

mesilate) by substituting an isopropyl for a piperidine group. This change enhanced water solubility, activity in vitro, and NHE-1 selectivity over **7**. Subsequently, other companies, for example, Merck KGaA and Boehringer, also synthesized benzoylguanidine derivatives such as **9** (EMD-96785, or eniporide mesilate) and **10** (BIIB-513).[29] All these compounds have been shown to be cardioprotective in a number of ischemic animal and human models.

2. Dihydropyridines as Leads. Retrospective analyses of various drug structures led the medicinal chemists to identify some molecular motifs that are associated with high biological activity more frequently than other structures. Such molecular motifs were called "privileged structures" by Evans et al.[30] to mean substructures that confer activity on two or more different receptors. The implication was that the privileged structure provides the scaffold and that the substitutions on it provide the specificity to a particular receptor. Two monographs deal with the privileged structure concept.[31,32]

The Ca^{2+} channel blockers containing the dihydropyridine motif certainly belong to the class of privileged stuctures.[33] We will discuss how they served as a starting point for the synthesis of α_{1A}-adrenergic antagonists and of multidrug-resistance modulators.

2.1. Calcium Channel Blocker Niguldipine as a Source of α_{1A}-Adrenergic Antagonists.[34] The typical symptoms of prostatism are obstructive (poor urine stream, dribbling, large residual urine volume) and irritative (hesitancy, increased frequency of urination, nocturia) in nature and can significantly compromise the quality of life of patients. While surgical procedures or the use of 5α-reductase inhibitors such as finasteride are used to reduce the prostatic mass, α_1-adrenergic receptor antagonists such as terazozin, doxazocin, and tamsulosin relax the smooth muscles in the prostate and in the lower urinary tract and facilitate the urine flow. However, nonselective α_1-adrenergic receptor antagonists present cardiovascular side effects (tachycardia and orthostatic hypotension). Selective blockers of the α_{1A}-subtype of adrenergic receptors are assumed to alleviate the symptoms associated with benign prostatic hyperplasia (BPH) with minimal cardiovascular side effects.

A screening program identified the calcium channel blocker niguldipine **11** (K_i = 4.6 nM for rat L-type calcium channel) as a potent ligand (K_i = 0.16 nM) of the recombinant human α_{1A}-adrenoceptor (Figure 3). Moreover, niguldipine presents considerable α_{1A}-selectivity (>300-fold over α_{1B}- and α_{1D}-receptors. Niguldipine was developed as a racemate; however, the α_1-adrenergic receptor antagonist properties are mainly concentrated in the (*S*)-(+)-enantiomer. During mutation studies of a series of α_{1A}-adrenergic ligands, it appeared that mutation of either Phe-308 or Phe-312 in the transmembrane domain 7 of the α_{1A}-receptor results in significant losses of affinity (4- to 1200-fold) for the antagonists prazosin, WB4101, BMY7378, (*S*)-(+)-niguldipine, and 5-methyluradipil. No affinity changes were observed for the phenylethylamine type of agonists.[35]

Progressive optimization of niguldipine yielded compounds such as **12** (SNAP-5089 (−)), **13** (SNAP-5399), and **14** (SNAP-6383).[34] These compounds display nanomolar affinities for the α_{A1}-receptor subtype, which correlates well with the potency to inhibit the phenylephrine-induced contraction of dog prostate. Compound **14** binds to the human recombinant α_{1A} adrenergic receptor with a K_i of 0.36 nM and exhibited a 1000-fold selectivity improvement over other subtypes.[36] It proved to be efficacious in clinical trials but was finally discarded for its cytochrome P450 3A4 isozyme-mediated metabolism and the corresponding risk of drug−drug interaction.[34]

A similar finding associating calcium channel blocking activity with α_1-adrenoceptor antagonism is found in the drug monatepil maleate (**15**, Figure 4).[37−39]

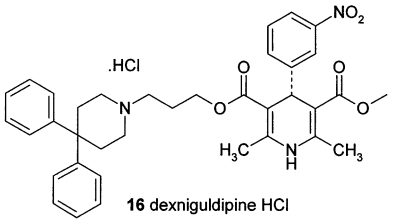


Figure 5. Dexniguldipine **16**, the (*R*)-(−)-enantiomer of niguldipine, is less active as a calcium channel blocker but potent as a reverser of multidrug resistance.

In addition to the above-mentioned properties, monatepil maleate was shown to potently inhibit copper-induced lipid hydroperoxidation of human LDL in vitro.[39]

2.2 Dihydropyridine-Type Calcium Channel Blockers as a Source of Multidrug-Resistance Modulators.[40−42] One type of resistance of neoplastic cells to cytotoxic agents is multidrug resistance, which may occur spontaneously or develop as a response to exposure to several different drugs, including anthracyclines, actinomycin D, epipodophyllotoxins, taxanes, and vinca alkaloids. The transmembrane glycoprotein, 170 kDa P-glycoprotein,[43] actively extrudes susceptible drugs by pumping them out of the cell by an ATP-requiring process. P-glycoprotein is encoded by the multidrug resistance-1 gene (MDR1), which is on the long arm of chromosome 7. Multidrug resistance is due to overexpression of P-glycoprotein and perhaps other factors.

Some compounds, such as the calcium channel blocker verapamil, by binding to P-glycoprotein, increase the intracellular accumulation of the drugs that are actively extruded. The less active (*R*)-(−)-enantiomer of niguldipine, dexniguldipine (Figure 5), is a dihydropyridine derivative, which weakly blocks calcium channels[39] and shows promise as a reverser of multidrug resistance.[39] It only has $^1/_{40}$ the affinity for the L-type calcium channel as its enantiomer, niguldipine.[44] It is also much less active at blocking calcium channels than verapamil and has less cardiovascular effects than verapamil. P-glycoprotein has an intracellular drug acceptor with which dexniguldipine combines. Dexniguldipine binds on receptor site 2 of P-glycoprotein, whereas verapamil, cyclosporin A, etoposide, and vinblastine all bind at receptor site 1.[45] Dexniguldipine inhibits protein kinase C,[46] is a calmodulin antagonist,[47] has antitumor activity,[47,48] and inhibits DNA synthesis in experimental tumors.[49] Dexniguldipine is about 10 times as potent as verapamil at reversing multidrug resistance in many in vitro systems.[50]

3. Cyclic Analogues of *β*-Blockers. Conventional *β*-blockers possess a number of pharmacological properties, e.g., *β*-blocking, quinidine-like, local anesthetic, and hypotensive effects. With the hope of achieving some specificity, Basil et al.[51] considered the possibility of synthesizing ring-closed analogues (closure mode 1; Figure 6). One of the prepared compounds, 3,4-dihydro-3-hydroxy-6-methyl-1,5-benzoxazocine, was a potent *β*-blocker. This activity is unlikely to be due to hydrolysis to the open-chain derivative because the corresponding primary amine, formed by hydrolysis of the benzoxazocine ring, has less than 0.25 the activity of the latter. Yet it is difficult to reconcile the benzoxazocine configuration with the structural requirements associated with the occupation of *β*-receptors.

Attempts to exploit the sedative and anticonvulsant effects observed for propranolol in pharmacological experiments prompted Greenwood et al.[52] to examine the closure mode 2 (Figure 6). Their study led to the norepinephrine reuptake inhibitor viloxazine, which was the first representative of a new class of antidepressant.

Later, Evans et al.[53,54] envisaged the closure mode 3 (Figure 6) for the synthesis of cyclized analogues of the phenylpropanolamine type of *β*-blockers. The authors hoped that by restricting the conformation, *β*-blocking activity would be lost but antihypertensive activity might be retained. This turned out to be true in animal tests and in double-blind clinical studies and justified the development of the potassium channel activator cromakalim.[55] This compound itself was further developed to yield I_{Ks} channel blockers as potential antiarrhytmic agents.

3.1. From *β*-Blockers to the Potassium Channel Blocker Cromakalim. A near-textbook illustration of the SOSA concept is given by the development of the hypotensive drug levocromakalim starting from *β*-blockers such as atenolol.[55] *β*-Blockers were introduced in the early 1970s for the treatment of angina pectoris and hypertension. However, there was some doubt that *β*-blockade was responsible for their antihypertensive activity and it was suggested that analogues with reduced flexibility of the side chain may be devoid of *β*-blocking activity but would retain the antihypertensive activity. This was the initial lead to cyclized analogues (Figure 7).

One of the first compounds prepared was compound **17**, which for chemical reactivity reasons bore a *gem*-dimethyl group at C-2. This compound was indeed found to lower blood pressure in hypertensive rats by a direct peripheral vasodilator mechanism; no *β*-blocking activ-

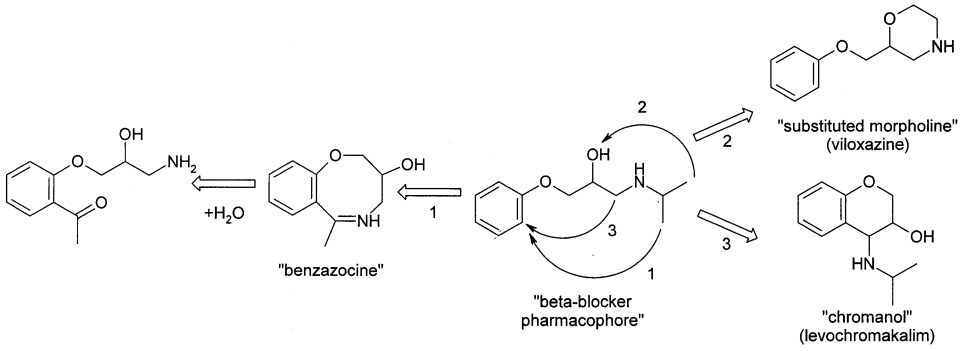


Figure 6. Cyclized analogues of *β*-blocking phenylpropanolamines.[51,52,55]

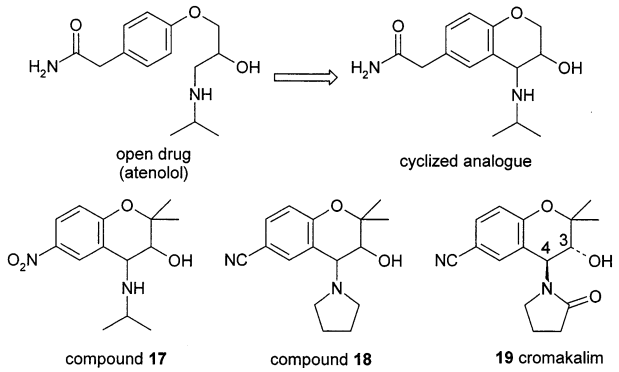


Figure 7. Passage from "open" β-blockers to the corresponding cyclized analogues.[55]

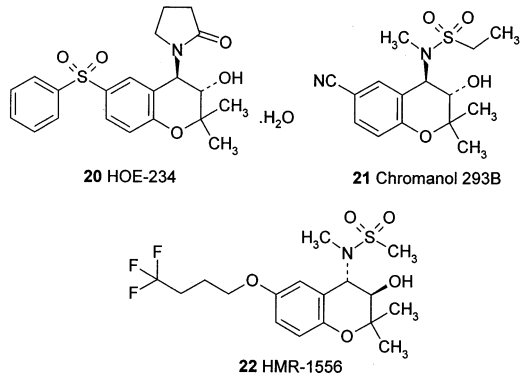


Figure 8. Cromakalim-derived I_{Ks} channel blockers.[56]

ity was observed. Optimization of the activity led to compound **18**, which was more than a 100-fold more potent than the nitro derivative. The replacement of the pyrrolidine by a pyrrolidinone (which is the active metabolite) produced a 3-fold increase in activity. Finally, the optical resolution led to the (−)-(3*S*,4*R*)-enantiomer of cromakalim **19** (levocromakalim, BRL 38227) that concentrates almost exclusively the hypotensive activity and acts exclusively as a potassium channel opener; β-blocking activity is no longer observed.

3.2. I_{Ks} Channel Blockers as Potential Antiarrhythmic Agents.[56] The I_{Ks} channel blocking ability of compound **21** (293B, Figure 8) was found to be a side activity in another research program dealing precisely with cromakalim-related chromanols such as compound **20** (HOE-234). Initially it was assumed that compound **21** acts indirectly on the Cl^- transport by blocking an associated cAMP-regulated potassium channel.[57]

Subsequent studies on cloned potassium channels from the guinea pig demonstrated that the chromanol **21** specifically blocks I_{Ks} channels expressed in *Xenopus* oocytes with an IC_{50} value of 6.2 μM.[58] The (3*R*,4*S*)-enantiomer was found to be more potent than the (3*S*,4*R*)-enantiomer (IC_{50} = 5 and 39 μM, respectively). Further optimization led to compound **22** (HMR-1556; IC_{50} = 120 nM) characterized by inverted stereocenters and by the replacement of the cyano function by a trifluorobutoxy side chain.[59]

4. Aminopyridazine Minaprine as Lead Substance. Aminopyridazines and, more precisely, 3-amino-6-arylpyridazines represent another group of privileged structures.[9] They present generally favorable ADME and toxicological profiles and allow many chemical variations.

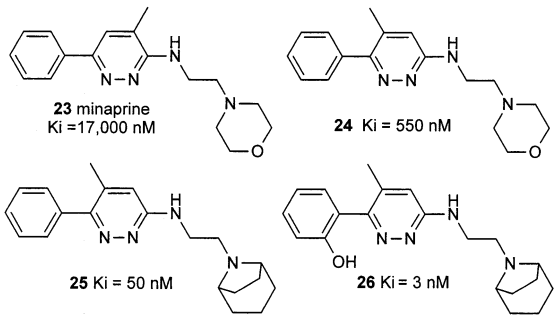


Figure 9. SOSA switch from the antidepressant minaprine to a nanomolar partial agonist for muscarinic M_1 receptors.[60,61]

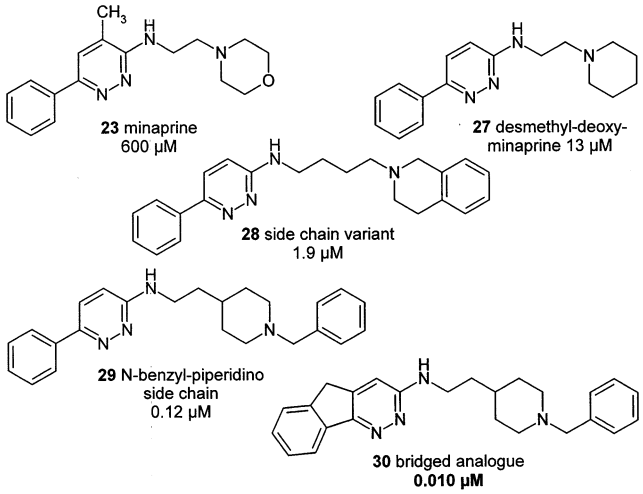


Figure 10. IC_{50} values for acetylcholinesterase inhibition (electric eel enzyme).[62,63]

4.1. Transforming the Antidepressant Minaprine into a Muscarinic M_1 Receptor Ligand. In the field of pyridazine chemistry we could, starting from the antidepressant minaprine **23** (Figure 9), derive various SOSA switches. Minaprine itself, in addition to reinforcing serotonergic and dopaminergic transmission, also possesses weak affinity for muscarinic M_1 receptors (K_i = 17 μM).

Three simple chemical variations (Figure 9) (shift of the methyl group from the 3- to the 4-position (**23** → **24**), replacement of the morpholine by a tropane (**24** → **25**), and introduction of an OH in the ortho position of the phenyl ring (**25** → **26**)) abolished the dopaminergic and serotoninergic activities and boosted the partial agonistic cholinergic activity of compound **26** to nanomolar concentrations.[60,61] The remarkable result was that the initial activity of minaprine on the dopaminergic and serotoninergic transmission was totally abolished in the final compound **26**.

4.2. Minaprine as a Source of Reversible Acetylcholinesterase Inhibitors. Starting from the same minaprine lead, we imagined that this molecule, being recognized by the acetylcholine receptors, should also be recognized by the acetylcholine enzyme. It turned out that minaprine had only a very weak affinity for acetylcholinesterase (600 μM on electric eel enzyme). However, relatively simple modifications (creation of a lipophlic cationic head, increase in side chain length, and bridging of the phenyl and the pyridazinyl rings) allowed us to reach nanomolar affinities (Figure 10).[62,63]

4.3. From Minaprine to CRF Antagonists. Another interesting switch consisted of the progressive

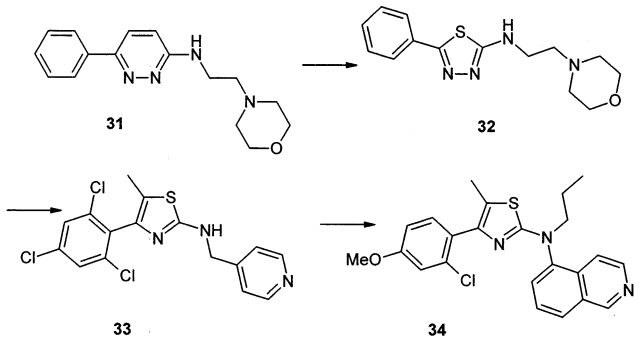


Figure 11. Switch from the antidepressant molecule minaprine to the potent CRF receptor antagonist **34**.[64,65]

passage from desmethylminaprine **31** to the bioisosteric thiadiazole **32** (Figure 11) and then to the bioisosteric thiazoles. Trisubstitution on the phenyl ring and replacement of the aliphatic morpholine by a pyridine led to compound **33**, which exhibited some affinity for the receptor of the 41 amino acid neuropeptide corticotrophin releasing factor (CRF). Further optimization led to nanomolar CRF antagonists such as **34**.[64,65]

5. Neuroleptic Benzamides as Leads. The following two examples illustrate a somewhat more restrictive aspect of the SOSA approach insofar as the starting drug molecules, sulpiride and clebopride, did not actually serve for the design of new and different activities. The objective here was to transform the initial, nonselective dopaminergic antagonists in subtype-selective D_3 and D_4 ligands.

5.1. Transforming the D_2/D_3 Nonselective Neuroleptic Sulpiride into a D_3-Selective Partial Agonist. Starting from the D_2/D_3 nonselective neuroleptic sulpiride, we were able to end up with a selective and potent D_3 receptor ligand.[66,67] One of the important findings was that the benzamide present in the sulpiride derivative **35** could be advantageously replaced by a naphthamide and that additional lipophilicity on the pyrrolidine nitrogen increased the potency.

The first interesting compound resulting from these variations was the D_3 antagonist nafadotride **36** in which the cyano group replaced the *N*-methylsulfonamido group.[68] Nafadotride presents an excellent affinity for the D_3 receptor ($K_i = 0.11$ nM) and a D_2/D_3 selectivity of 9.6 (Figure 12). However, nafadotride showed very poor bioavailability in vivo and it could not be retained for clinical development. Further modifications brought us to introduce various piperazine side chains. An example is given by the *o*-methoxyphenylpiperazine **38**, characterized by the deletion of the electron-attracting group in the meta position to the carboxamido function. Surprisingly the additional deletion of the *o*-methoxy group, as in compound **39**, led to a potent dopaminergic ligand ($K_i = 1.2$ nM for D_3) with a 56:1 preferential affinity for the D_3 receptor.[66] This compound, named Do 897 and later BP 897, behaves as a partial dopaminergic agonist and presently undergoes phase II clinical investigations. Potential clinical applications are the selective inhibition of cocaine-seeking behavior by drug addicts and the possible use as neuroleptic and as a means to suppress L-Dopa-induced dyskinesia in the treatment of Parkinson patients.

5.2. Clebopride and Nemonapride as Leads for D4-Selective Dopaminergic Antagonists.[69] In parallel to the search for D_3 subtype ligands, studies aiming to create D_4 subtype-selective agents were undertaken, also starting from benzamide drug molecules. Ohmori and co-workers[70] reported on the results of modification of their potent $D_2/D_3/D_4$ antagonist nemonapride (**41**, YM-09151-2), an analogue of clebopride (**40**), to generate the new benzamide (**42**, YM-43611) (Figure 13). Compound **42** has affinity for both D_4 and D_3 receptors ($K_i = 2.1$ and 21 nM, respectively) but with 110-fold selectivity for D_4 versus D_2. Affinity for α_1-adrenergic, β-adrenergic, serotonergic, muscarinic, or histaminic receptors was weak or negligible. Interestingly this compound shows in vivo activity in the inhibition of apomorphine-induced climbing in mice, with an ED_{50} of 0.32 mg/kg sc.

During further investigations of the benzamide series, Hidaka and co-workers[71] prepared **43** (YM-50001). This compound showed affinity for human D_4 receptors ($K_i = 5.62$ nM) versus hD_2, hD_3, and other receptors.

6. Thalidomide, Diclofenac, and Captopril as Leads. The three following SOSA applications describe examples in which only slight chemical changes were needed to transform the starting drug molecule into an active compound with a different profile.

6.1. Thalidomide: A Potent Inhibitor of TNF.[72] Thalidomide (**44**, Figure 14), first synthesized as an antihistaminic in 1954, was introduced as a sedative/hypnotic drug in 1956 but withdrawn because of its catastrophic teratogenicity.[73]

In the early 1960s, a new use was found for thalidomide as a sedative in patients suffering from lepromatous leprosy (*erythema nodosum leprosum*, ENL). A rapid and noticeable improvement of the painful neuritis experienced by these patients was observed and

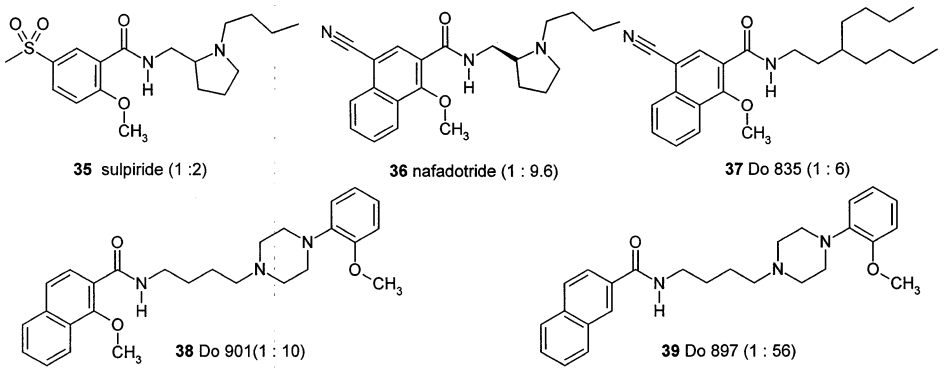


Figure 12. Switch from the D_2/D_3 nonselective dopamine antagonist *N*-methylsulpiride **35** to the D_3-selective partial agonist BP 897 **39**. The numbers in parentheses indicate the D_2/D_3 affinity ratio.

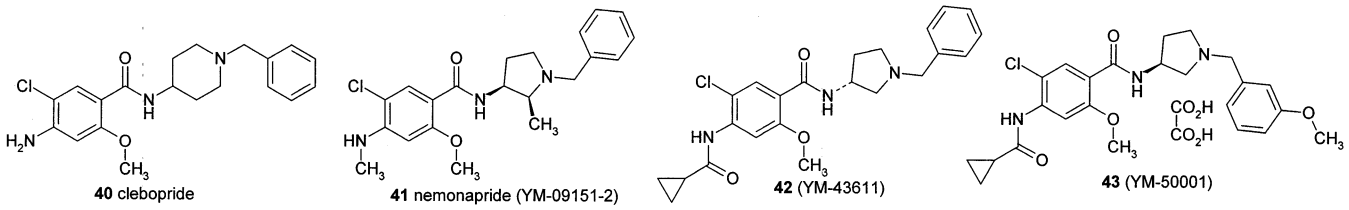


Figure 13. Dopaminergic D4 receptor selective benzamides derived from clebopride and nemonapride.

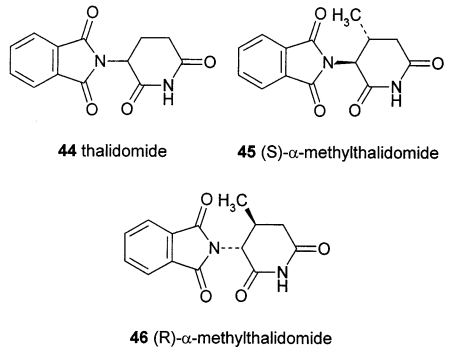


Figure 14. Thalidomide and (*S*)- and (*R*)-α-methylthalidomide.

published in 1965.[74] Particularly it appeared to be efficacious for the treatment of *erythema nodosum leprosum*, a possible complication of the chemotherapy of leprosy.[75] This activity was attributed to a blockade of the TNF production, and under restricted conditions (no administration during pregnancy or to any woman of childbearing age), thalidomide found a new use as immunomodulator (for a detailed monograph, see ref 72).

Efforts have been made to develop derivatives of thalidomide that would specifically maintain the desired actions of the drug without its side effects. One approach was to separate the effects of the (*R*)-isomer from the effects of the (*S*)-isomer. However, this approach was not effective because in vivo racemization of thalidomide is very fast. Stable nonracemizable analogues of thalidomide such as α-methylthalidomide were then prepared. The (*R*)-isomer (Figure 14) was effectively shown to be a potent inhibitor of TNF production in certain cell lines. Further research of selective and potent thalidomide analogues seems promising.[72]

6.2. From the Nonsteroidal Antiinflammatory Drug Diclofenac to an Inhibitor of the Fibrine Transthyretine Amyloid Formation. Transthyretine (TTR) is a tetrameric protein made up of four identical subunits. In human plasma, it is the secondary carrier of thyroxine (thyroid binding globulin being the primary carrier) and the sole transporter of the retinol-binding protein−vitamin A complex. Under acidic conditions, such as found in the lyzosomes, TTR dissociates to an alternatively folded, monomeric intermediate that self-assembles into amyloid fibrils. Deposition of wild-type TTR has been implicated to cause the disease senile systemic amyloidosis (SSA), whereas mutants such as V30M and L55P are connected with familial amyloid cardiomyopathy (FAC) and familial amyloid polyneuropathy (FAP). A limited screening identified the nonsteroidal antiinflammatory drug diclofenac (**47**) as a potent inhibitor of TTR amyloid formation.[76] Optimization of diclofenac (**47**), with the aim of preparing compounds with high inhibition capacities but also with

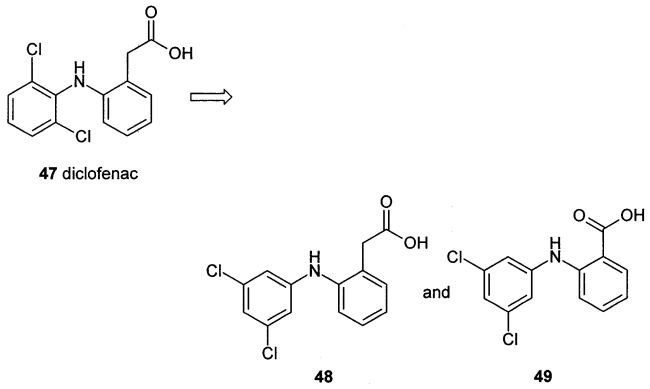


Figure 15. Increasing the TTR amyloid inhibiting activity of the NSAID diclofenac as a result of the synthesis of positional isomers.

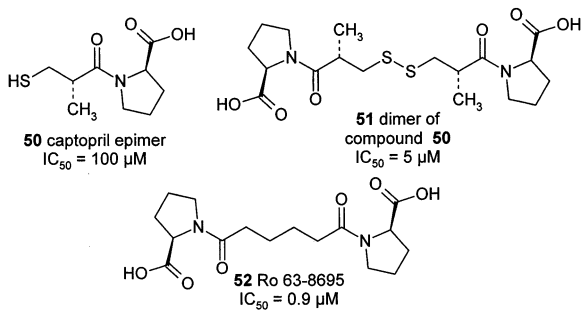


Figure 16. Captopril epimer as lead for the design of serum amyloid component P inhibitors.[78]

preferential binding to TTR with regard to the other plasma proteins, yielded the 3,5-disubstituted positional isomer **48** and the substituted anthranilic acid **49**[77] (Figure 15).

6.3. Captopril Yields Inhibitors of Serum Amyloid Component P ("SAP"). A high-throughput assay for inhibitors of SAP binding to Alzheimer's disease amyloid-β (Aβ) was performed by scientists from Roche on amyloid fibrils immobilized in microtiter plates and was applied to screen the in-house compound library.[78] Two hits were identified. The first one (**50**; $IC_{50} = 100$ μM) was the S-3 epimer of captopril, and the second one (**51**; $IC_{50} = 5$ μM) was the corresponding dimer (Figure 16). Optimization simplified the central spacer group in removing the sensitive disulfide bond as well as the two methyl groups, thus eliminating two chiral centers. The obtained compound **52** (Ro 63-8695) shows a 900 nM affinity for its target.

7. Herbicides and Laundry Brighteners as Lead Substances. The last two examples of this perspective represent "exotic" versions of the SOSA approach. Effectively, they no longer deal with the optimization of side activities of drug molecules but with the optimization of the biological activities of nondrug molecules contained in libraries of various origins. One of the leads

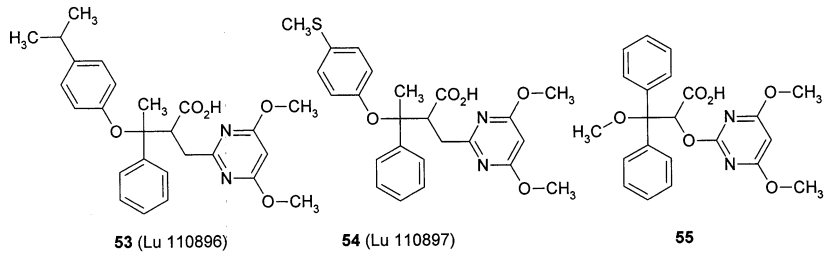


Figure 17. Optimization of the two herbicide leads **53** and **54** to the potent and selective ET_A antagonist **55**.[79]

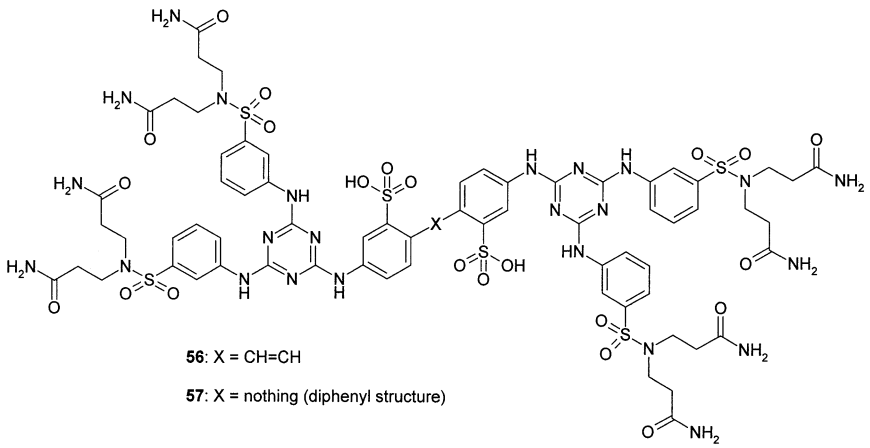


Figure 18. Laundry brightener as starting lead for antiviral compounds.

was an herbicide, and the other one was a laundry brightener.

7.1. Orally Active Nonpeptidic Endothelin-A Receptor Antagonists from Herbicides. The two initial lead structures **53 (**Lu 110896) and **54** (Lu 110897) (Figure 17), initially designed as herbicides, were discovered by screening the chemical library of BASF for compounds that bind to the recombinant human ET_A receptor.[79]

Compounds **53** and **54** bind to the ET_A receptor with K_i values of 250 and 160 nM, respectively. The binding to the ET_B receptor is much weaker (K_i = 3000 and 4700 nM). With the objective of enhancing the potency while simplifying the structure and, particularly, avoiding the presence of one of the two stereocenters, compound **55** was prepared.[79] It demonstrated high potency and selectivity ($K_i(ET_A)$ = 6 nM; $K_i(ET_B)$ = 1000 nM), was orally active in vivo, 30 mg/kg po), and showed a long duration of action.[79]

7.2. Laundry Brightener as Starting Lead for Antiviral Compounds.[80] Human respiratory syncytial virus (RSV) is a major cause of respiratory tract infections in premature babies and infants up to 6 month of age. Widespread outbreaks occur in the winter months in the northern hemisphere each year and frequently reach epidemic proportions. At least 50% of children are infected during their first exposure, and almost all have been infected by 2 years of age. During a high-throughput screen of a 20 000-compound library, a whole virus cell-based assay identified stilbene (**56**, Figure 18) as a potent RSV fusion inhibitor.

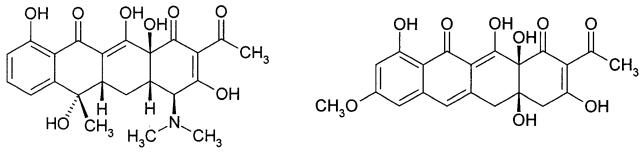
This original lead has an interesting history. The compound was synthesized some 40 years earlier at American Cyanamid's Organic Chemicals Division as part of a program to synthesize new laundry brighteners. Its antiviral activity (IC_{50} = 0.15 μM) led to a synthetic optimizing effort that yielded the biphenyl analogue **57** (IC_{50} = 0.05 μM).[80,81]

IV. Discussion

The SOSA approach appears to be an efficient strategy for drug discovery, particularly because it is based on the screening of drug molecules, and it thus automatically yields druglike hits. Before starting a costly HTS campaign, it can represent an appealing alternative. Once the initial screening has provided a hit, it will be used as the starting point for a drug discovery program. By use of traditional medicinal chemistry as well as parallel synthesis, the initial "side activity" is transformed into the main activity, and conversely, the initial main activity is strongly reduced or abolished. This strategy leads with a high probability to *safe, bioavailable, original, and patentable* analogues.

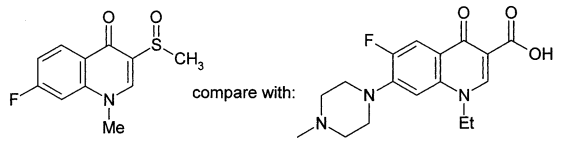
Safety and Bioavailability. During years of practicing SOSA approaches, we observed that starting with a drug molecule as lead substance in performing analogue synthesis increased notably the probability of obtaining safe, new chemical entities. In addition, most of them satisfy Lipinski's,[82] Veber's,[83] Bergström's,[84] and Wenlock's[85] observations in terms of solubility, oral bioavailability, and druglikeness.

Patentability. When a well-known drug hits a new target, there is a risk that several hundred or several thousand analogues of this molecule are already synthesized by the initial inventors and their early competitors. These molecules are usually protected by patents, or they belong already to the public domain. At first glance, a high risk of interference thus appears probable. In fact, in optimizing another therapeutic profile than 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



58: tetracycline **59**: BMS-192548

Figure 19. Unexpected CNS activity of the tetracycline analogue (**59**, BMS-192548).[86]



60: flosequinan **61**: norfloxacin

Figure 20. Striking analogy between the vasodilator drug flosequinan (**60**) and the quinolone antibiotic norfloxacin (**61**).[87]

medicinal chemist interested in phosphodiesterases and using diazepam as lead will rapidly prepare compounds that 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.

Originality. The screening of a library of several hundred 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 (**59**, BMS-192548) extracted from *Aspergillus niger* WB2346 (Figure 19).

For any medicinal chemist or pharmacologist, the similarity of this compound to the antibiotic tetracycline (**58**) is striking. However, none of them would a priori forecast that BMS-192548 exhibits central nervous system (CNS) activities. Actually the compound turns out to be a ligand for the neuropeptide Y receptor preparations.[86]

It seems probable that a similar emergence of a new activity occurred withflosequinan (**60**, Figure 20), which is a sulfoxide bioisostere of the quinolone antibiotics. This compound turned out to be a vasodilator and a cardiotonic drug that totally lost any antibiotic activity.[87]

Orphan Diseases. As mentioned above, a differentiating peculiarity of this type of library is that it is constituted of 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.

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Biography

Camille Georges Wermuth, Professor and Founder of Prestwick Chemical, was Professor of Organic Chemistry and Medicinal Chemistry at the Faculty of Pharmacy, Louis Pasteur University, Strasbourg, France, from 1969 to 2002. Professor Wermuth's main research themes have focused on the chemistry and the pharmacology of pyridazine derivatives. His pharmacological areas of interest have included antidepressant and anticonvulsants; enzyme inhibitors such as monoamine-oxidases, phosphodiesterases, and acetylcholinesterase; and ligands for GABA-A, serotonine 5-HT_3 receptor antagonists, and dopaminergic and muscarinic receptors. Professor Wermuth has coauthored over 360 papers and patents. He was President of the Medicinal Chemistry Section of the International Union of Pure and Applied Chemistry (IUPAC) from 1988 to 1992. From January 1998 to January 2000, he served as President of the IUPAC Division on Chemistry and Human Health.

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