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Selective optimization of side activities: the SOSA approach

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Selective optimization of side activities of drug molecules (the SOSA approach) is an intelligent and potentially more efficient strategy than HTS for the generation of new biological activities. Only a limited number of highly diverse drug molecules are screened, for which bioavailability and toxicity studies have already been performed and efficacy in humans has been confirmed. Once the screening has generated a hit it will be used as the starting point for a drug discovery program. Using 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 significantly reduced or abolished. This strategy has a high probability of yielding safe, bioavailable, original and patentable analogues.

'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 Medicine [1].

HTS of large compound libraries is still the mainstay of hit generation at most pharmaceutical companies. However, the approach sometimes gives meager results considering the investment in labor and machinery. Therefore, the current trend is to use smaller and more-efficient libraries, especially libraries with increased drug-likeness. The selective optimization of side activities (SOSA) approach represents a precise alternative to HTS, generating drug-like hits. It is interesting to note that although the terminology drug-like or drug-likeness is recent, the concept is absolutely traditional and has always been intuitively applied by medicinal chemists. In his article 'The benzodiazepine story' published in 1979 [2], Leo Sternbach commented, 'the class of compounds we were seeking had to look as if it could lead to biologically active products'.

Definitions and principle

The SOSA approach [3–7] uses old drugs for new pharmacological targets. The aim is to screen a limited number of drug molecules that are structurally and therapeutically diverse and have known safety and bioavailability in humans. As a result, it is expected that such an approach might reduce the time and the cost compared with a standard hit identification process.

The SOSA approach proceeds in two steps:

(i) Screening a limited set of carefully chosen, structurally diverse drug molecules (a smart-library of ~1000 compounds). For all these drugs, bioavailability and toxicity studies will have been performed already and because they all have demonstrable efficacy in human therapy, all hits developed by this process will be, by definition, drug-like.

(ii) The hits are optimized (by means of traditional, parallel or combinatorial chemistry) to give increased affinity for the new target and decreased affinity for the original target(s). The objective is to prepare analogues of the hit molecule to transform the observed 'side activity' into the main effect and strongly reduce or abolish the initial pharmacological activity.

Rationale of the SOSA approach

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

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*'When we proposed the acronym SOSA we were not aware of the existence of a famous base-ball player, Sammy Sosa, well-known for his home run hitting. Hit the target is our common objective'.

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In other words, if they are able to exert a strong interaction with the main target they can, in addition, interact with other biological targets, albeit less potently. Most of these targets are unrelated to the primary therapeutic activity of the compound. Therefore, the objective is to proceed to a reversal of affinities, such that the identified side effect becomes the principal activity and vice versa. By contrast there is only a limited chemical universe of small molecules that can be safely administered to humans. In this review, I propose that this universe can be adequately covered with currently available drugs.

Historical background

In the early 1970s, we synthesized several central nervous system (CNS)-active pyridazines [8,9] that were studied by Henri Laborit [10], who discovered chlorpromazine. One of these pyridazines, compound **1** (Figure 1), was sufficiently active to be developed by Sanofi and marketed as an atypical antidepressant [11,12] called minaprine (Cantor®).

In the course of SAR investigations, we noticed that discrete functional changes on the minaprine (**1**) scaffold induced important changes in the pharmacological profile. Thus, hydroxylation in the *para* position of the phenyl ring yields the potent dopaminergic compound **2** [13] (this compound is the main first-pass metabolite in humans [14]). By contrast, the replacement of the methyl group by a cyano group yielded bazinaprine **3**, a potent monoamine oxidase-A (MAO-A) inhibitor [15].

In addition to its main effect, reinforcing serotonergic and dopaminergic transmission, minaprine also possesses weak affinity for muscarinic M_1 receptors (K_i = 17 μM). This side effect was confirmed by its cholinergic activity in rats [16] and in patients suffering from Alzheimer's disease and multi-infarct dementia [17]. These observations prompted us to start a SAR program that aimed to increase the cholinergic side effect and to decrease the original main effect on the dopaminergic and serotoninergic transmission (Figure 2).

Three simple chemical variations abolished the dopaminergic and serotoninergic activities: shifting the methyl group from the 3- to the 4-position (**1**→**4**); replacing the morpholine by a tropane (**4**→**5**); and introducing an OH in the *ortho* position of the phenyl ring (**5**→**6**). The partial agonist cholinergic activity of compound **6** was also boosted, to the nanomolar level (K_i = 3 nM) [18,19]. Most remarkably, the original activity of minaprine on dopaminergic and serotoninergic receptors was completely absent in the final compound **6**.

Later, starting from the same minaprine lead, we imagined that minaprine might also possess an affinity for acetylcholinesterase, because it was capable of being recognized by acetylcholine receptors. In fact, minaprine only had a very weak affinity for the enzyme (600 μM for cholinesterase from the electric eel). However, relatively simple modifications that yielded the indenopyridazine **8** (creation of a lipophilic cationic head, increasing side chain length and bridging the phenyl and the pyridazinyl rings) allowed us to produce molecules with nanomolar affinity (Figure 3, **7** and **8**) [20,21].

These examples illustrate how, starting from a marketed drug, it is possible to derive a whole panel of new active molecules (i.e. practicing a selective optimization of an existing and generally discrete side effect). We found that the most important advantage with this method is that the molecules derived from SOSA switches

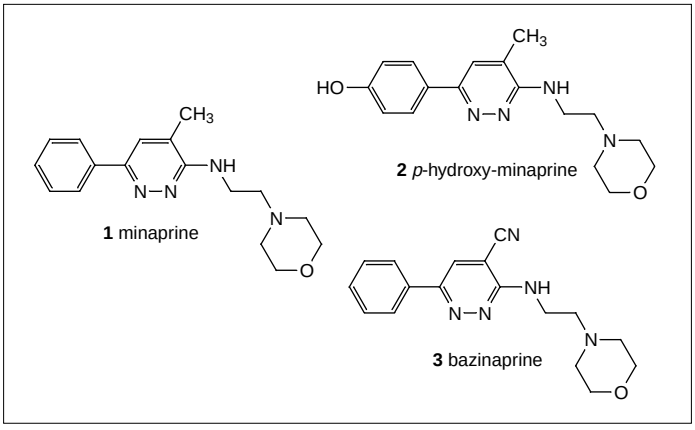


FIGURE 1

Discrete functional changes on the minaprine scaffold. Discrete changes on the minaprine scaffold induce important changes in the pharmacological profile.

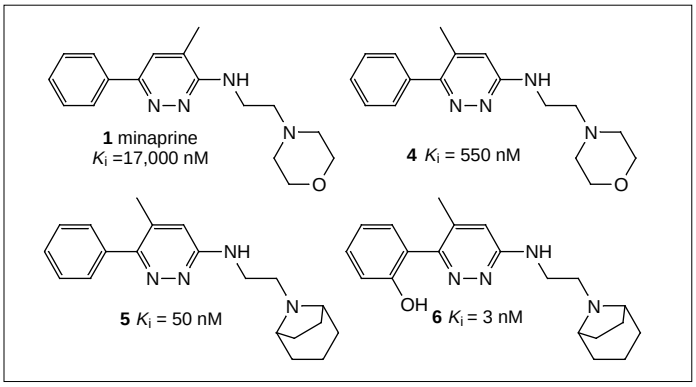


FIGURE 2

SOSA switch. The SOSA switch from the antidepressant, minaprine, to compound **6** – a nM partial agonist for muscarinic M_1 receptors – is shown. The K_i values shown refer to their activity at the M_1 receptor.

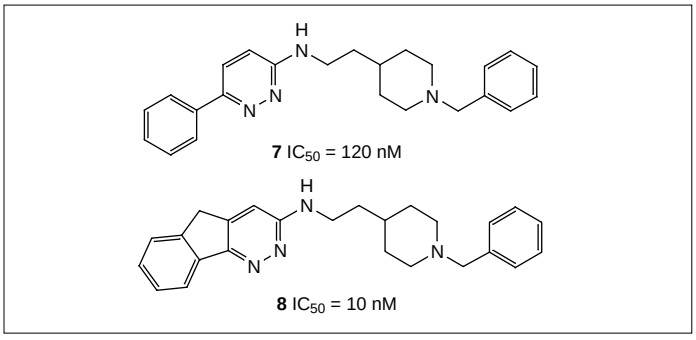


FIGURE 3

Acetylcholinesterase inhibitors derived from minaprine.

already possess drug-like properties and, therefore, show good absorption, distribution, metabolism and excretion (ADME) profiles. In addition, molecules emerging from a SOSA approach frequently present far fewer toxicity problems than would be expected from other approaches.

The SOSA approach – examples from the literature

From sulfathiazole to endotheline ET_A receptor antagonists

A typical illustration of the SOSA approach is given by the

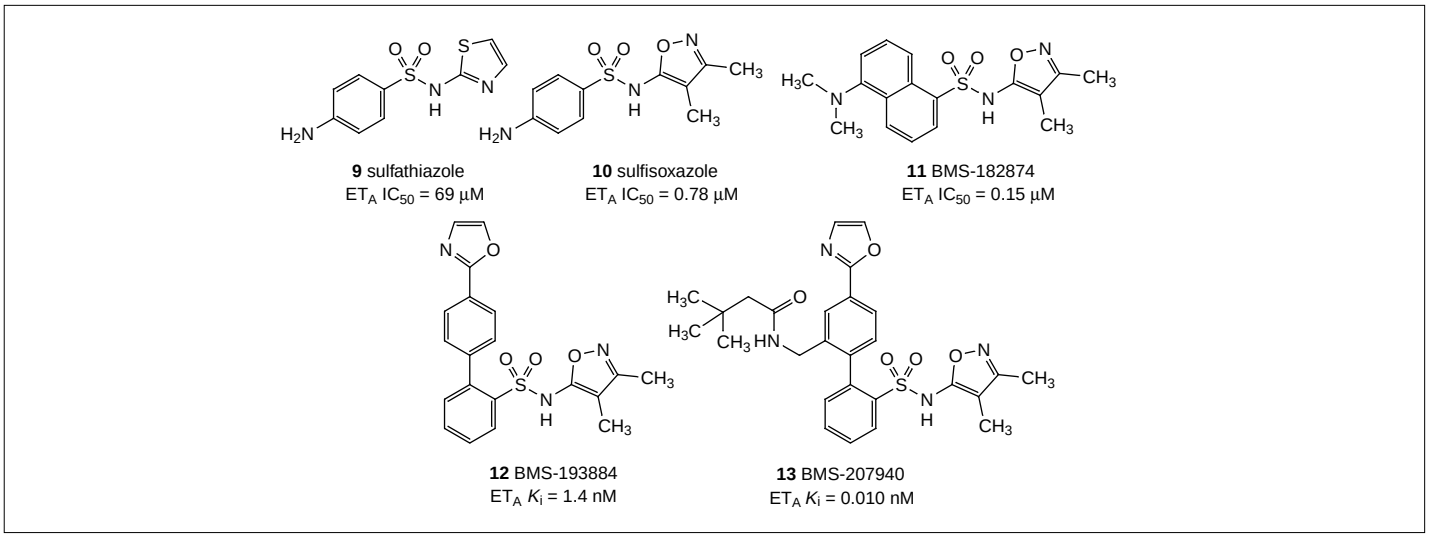


FIGURE 4

A successful SOSA approach. This allowed the identification of the antibacterial sulfonamide sulfathiazole as a ligand of the endothelin ET$_A$ receptor, as well as its optimization to the selective and potent compounds BMS-182874, BMS-193884 and BMS-207940.

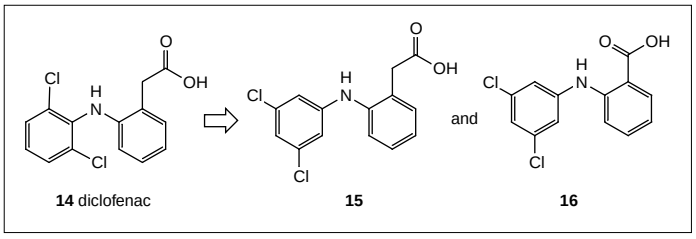


FIGURE 5

Increasing the TTR amyloid inhibitory activity of the NSAID, diclofenac, by synthesizing positional isomers.

development of selective antagonists for the endothelin ET$_A$ receptors by scientists from Bristol-Myers Squibb (BMS) [22]. Starting from an in-house library, the antibacterial compound sulfathiazole **9** (Figure 4) was an initial, but weak, hit (ET$_A$ IC$_{50}$ = 69 μM). Testing of related sulfonamides identified the more potent sulfisoxazole **10** (ET$_A$ IC$_{50}$ = 0.78 μM). Systematic variations finally led to the potent and selective ligand **11** (BMS-182874). This compound was orally active *in vivo* and produced a long-lasting hypotensive effect.

Further optimization guided by pharmacokinetic considerations led the BMS scientists to replace the naphthalene ring by a diphenyl system [23]. Among the prepared compounds, **12** (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. More-recent studies led to the extremely potent antagonist **13** (BMS-207940, ET$_A$ K_i = 10 pM) representing an 80,000-fold selectivity for ET$_A$ over ET$_B$. The oral bioavailability of **13** is 100% in rats and it has been shown to possess activity at a dose of 3 μg/kg by mouth [per os (p.o.)] [23].

From diclofenac to transthyretin amyloid formation inhibitors

A limited screen identified the nonsteroidal anti-inflammatory drug diclofenac **14** as a potent inhibitor of transthyretin (TTR) amyloid formation [24].

Optimization of diclofenac **14** (Figure 5), with the intention of preparing potent inhibitors with greater TTR selectivity over other plasma proteins, yielded the 3,5-disubstituted positional isomer **15** and the substituted anthranilic acid **16** [25]. Other examples, already described in our earlier publication [7], are summarized in Table 1.

Availability

A commercially available library for the SOSA approach contains 1120 biologically active compounds with high chemical and pharmacological diversity, as well as known bioavailability and safety in humans (libchem@prestwickchemical.fr). Over 90% of the constituents are established drug molecules and ~10% are bioactive alkaloids. The compounds are available frozen, in dimethyl sulfoxide (DMSO) solution, or as dry powders. For scientists who are interested in drug-likeness, such a library certainly fulfils the quest for drug-like leads in a convincing way. Other commercial libraries containing significant amounts of drug molecules are also available [Sigma-RBI (Lopac Library of pharmacologically active compounds, ligands@sial.com) and MicroSource (Genesis-Plus Library, compounds@aol.com)].

Discussion

The SOSA approach appears to be an efficient strategy for drug discovery but several questions about its actual application can arise regarding safety (non-toxicity) and bioavailability, as well as originality and patentability of the identified hits.

Safety and bioavailability

During years of carrying out SOSA approaches, we observed that, when performing hit optimization, starting with a drug molecule as a lead substance has notably increased the probability of obtaining new, safe chemical entities. Moreover, because almost all compounds from the SOSA library are drug molecules, optimized analogues still satisfy Lipinski's [26], Veber's [27], Bergström's [28] and Wenlock's [29] observations in terms of solubility, oral bioavailability and drug-likeness.

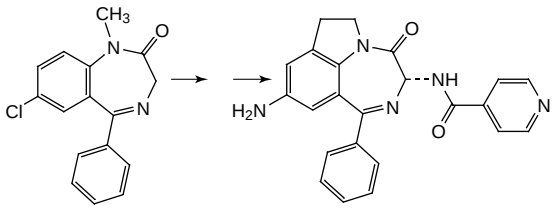
Patentability

When a well-known drug hits a new target there is a risk that several hundreds or thousands of analogues of the original drug molecule

TABLE 1

Selected literature examples of SOSA switches

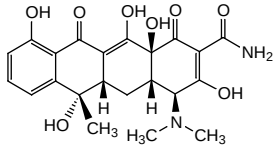
Initial drug lead	Pharmacological profile	SOSA-derived analogue	Pharmacological profile	Refs
Amiloride	Diuretic	Cariporide mesylate (Hoe 642)	Na/H exchange inhibitor	[35]
Niguldipine	Calcium channel blocker	SNAP-6383	α_{1A} adrenergic antagonist	[36]
Atenolol	β-blocker	Cromakalim	Potassium I_{Ks} channel blocker	[37]
Minaprine	Antidepressant	Various aminothiazoles	CRH antagonists	[38–40]
Sulpiride	D_3/D_2 non-selective dopamine antagonist	Compound Do 897	D_3-selective partial dopamine agonist	[41,42]
Lu 110896 and Lu 110897	Herbicides	Diphenyl analogue	Potent and selective ET_A antagonist	[43]
Tetracycline	Antibiotic	BMS 1922548	Neuropeptide Y ligand	[44]
Erythromycin A	Antibiotic	Cladinose replacement analogue	Non-peptide lutenizing hormone-releasing hormone antagonists	[31]
Fluoxetine	Serotonin reuptake inhibitor	Imidazole analogue	Anti-Candida agent	[45]
Diazepam	Tranquillizer	CI-1044	Selective PDE 4 inhibitor	[30]



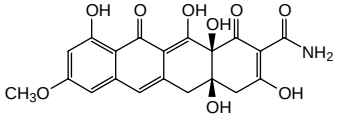
17 diazepam **18** CI-1044

FIGURE 6

Phosphodiesterase inhibitor. The phosphodiesterase inhibitor **18** (CI-1044), derived from the tranquillizer diazepam **17,** is sufficiently chemically different to **17** and does not interfere with earlier patents.



19 tetracycline



20 BMS-192548

FIGURE 7

Tetracycline analogue. Unexpected CNS activity of the tetracycline analogue **20** (BMS-192548).

will already have been synthesized by the original inventors and their competitors. These molecules are usually protected by patents or already belong to the public domain. At a first glance, a high risk of interference appears probable. In fact, optimizing a therapeutic profile other than that of the original inventors, the medicinal chemist will rapidly prepare analogues with chemical structures very different from that of the original hit. For example, a medicinal chemist interested in phosphodiesterases (PDEs) will rapidly prepare compounds, such as **18**, using diazepam **17** as a lead [30]. The new compounds are beyond the scope of the original patents because, in becoming PDE inhibitors, the modified (and thus patentable) structures lack affinity for the benzodiazepine receptor (Figure 6).

Originality

Screening a library containing several hundreds of therapeutically diverse drug molecules occasionally gives rise to some very surprising results. Examples of unexpected findings resulting from systematic screening were found when the antibiotic erythromycin A was changed to luteinizing hormone releasing hormone (LHRH) antagonists [31], and upon the identification of the affinity for the neuropetide Y receptor of the tetracycline **19** analogue **20** (BMS-192548), extracted from *Aspergillus niger* WB2346 (Figure 7).

Orphan diseases

As mentioned above, a differentiating peculiarity of a SOSA-designed drug library is that it is mainly composed of compounds that have already been shown to be safe in humans. Thus, if a compound were to inhibit an orphan target with sufficient potency, there is a good chance that it could rapidly be tested in patients for proof of principle. This possibility represents another (until yet, potential) advantage of the SOSA approach.

Conclusion

The SOSA approach appears to be an efficient strategy for drug discovery, particularly because it is based on screening drug molecules and, thus, automatically yields drug-like hits. Before starting a costly HTS campaign, it can represent an attractive alternative. Once the initial screening has provided a hit, that molecule will be used as the starting point for a drug discovery program. Using 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 has a high probability of yielding safe, bioavailable, original and patentable analogues.

The SOSA approach can be compared with other approaches, such as hit or lead generation from known drug metabolites [32] or the design of drug analogues [33,34], because it makes use of old drugs to generate new hits or leads. As a rule, the activities of metabolites are similar or close to the activity of the corresponding active molecule. Contrary to this, the SOSA approach is based on optimization of side activities that are totally different to the original activity of the molecule.

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