



Selective Optimization of Side Activities (SOSA) as an Efficient Approach for Generation of New Leads from Old Drugs

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The selective optimization of side activities (SOSA) approach appears to be a promising strategy for lead generation. In this approach old drugs are used to generate new hits or leads. The objective of SOSA 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 idea of taking a molecule with a primary activity in humans and then enhancing a secondary effect through structural changes describes the most common implementation of SOSA. An advantage to starting a drug discovery program with molecules that have already been tested in humans is that those molecules have already satisfied many safety criteria. Such molecules also likely have favourable pharmacokinetic profiles. In the present review different successful examples of SOSA switches are summarized. We hope that the present review will be useful for scientists working in the area of drug design and discovery.

Keywords: SOSA; selective optimization of side activities; drug discovery; hit to lead; lead generation.

1. INTRODUCTION

Drug discovery and development may be a very long, expensive and high-risk process, with little or no possibility of a successful outcome. For drugs to be successful, they need to be both efficacious and acceptably safe. These obstacles make drug development increasingly difficult [1]. Since 2003, around 200 drugs per year are reported as discontinued, and ten times this many products are simply dropped from active pipelines. Selective optimization of side activities of drug molecules (SOSA) represents an ingenious and more efficient alternative to high throughput screening (HTS) for the generation of latest biological activities [2,3]. In this strategy, limited number of highly diverse drug molecules for which bioavailability, toxicity and efficacy in humans has been confirmed, are screened. Once a molecule shows the specified sort of activity during a screening, it can be used as the lead for the discovery of new drugs. SOSA approach uses conventional medicinal chemistry techniques along with parallel synthesis to convert the observed initial side activity into the prime effect and to strongly reduce or abolish the initial pharmacological activity. This strategy features a high probability of manufacturing safe, bioavailable, original and patentable analogues [4,5].

Though large and diverse chemical libraries of 'drug-like' compounds are often readily screened to urge chemically novel hits, transforming these chemical scaffolds into drugs may be a difficult task. A more systematic approach involves both phenotypic- and molecular target-based screening of approved and off-patent old drugs which can readily give compounds that may be immediately utilized in clinical trials [6]. Different case studies are there which describe how this SOSA approach has rapidly identified candidate medications suitable for clinical trials in disorders like progressive multifocal leuko encephalopathy and amyotrophic lateral Sclerosis [7,8]. This approach has also led to the invention of the molecular targets responsible for serious drug side effects, thereby allowing efficient 'counter-screening' to avoid these side effects. Unexpected drug side effects may arise because of actions on additional targets or off-targets to those for which they were designed for. Off-target effects are usually unwanted and harmful, but in some cases, they have proved beneficial, leading to new and unexpected indications for drugs.

Furthermore, similar side effects evoked by unrelated drugs have, in some cases, been shown to flow from to their common off-target interactions [9].

No wonder that "repurposing" is generating excitement among pharmaceutical companies and academic researchers. The repurposing approach to drug discovery focuses on the invention of latest uses for known compounds. Because many repurposed drugs are already approved for therapeutic use, the repurposing approach provides a beautiful jumpstart that reduces many of the expenses and risks related to traditional drug discovery [10].

Principle of SOSA approach: The SOSA (selective optimization of side activities) approach constitutes a validated alternative to HTS. It involves testing of old drugs on new pharmacological targets. The aim is to screen a limited number of drug molecules that are structurally and therefore therapeutically very diverse and which have known safety and bioavailability in humans as well. This will reduce the time and the expenses needed for successful identification. The SOSA approach involves two steps. In first step screening is carried out with a finite number (approximately 1000 compounds) of carefully selected, documented drugs. After screening all hits will then be considered "drug like" as bioavailability and toxicity studies for those drugs (belonging to various classes like antibacterials, diuretics, anihypertensives, antidepressants, antivirals, NSAIDs etc.) have already been performed and that they have proven useful in human therapy. In second step hits are optimized so to extend the affinity for the new target and reduce the affinity for the opposite targets. Then analogues of the hit molecule are prepared so as to convert the observed initial side activity into the expected effect and to reduce or nullify the initial pharmacological activity [11].

The SOSA concept is based on the assumption that there's only a limited chemical universe which will be safely administered to humans because of the fact that all drugs act on many receptors. This universe often consists of currently available drugs. As mentioned above, the unusual characteristic of this type of library is that it includes drug molecules that have already been safely given to humans. Thus, there is a high chance that a compound which hits with

sufficient potency on an orphan target, could rapidly be tested in patients for proof of principle. If one or more compounds hit but with less potency, optimized analogues are often synthesized and thus the chances that these analogues will be good candidate drugs for further development increases if the initial lead is toxic or not bioavailable. One among these new types of chemical library referred to as the Prestwick Chemical Library has recently become available [12]. It includes 1120 biologically active compounds with high chemical and pharmacological diverseness along with known bioavailability and safety in humans. Over 90% of the compounds are well-established drugs, and 10% are bioactive alkaloids.

Sometimes Side Effects Are Good: Discovery of valuable therapeutic agents as a result of testing a candidate drug for an expected pharmacological effect and finding a quite different effect is one among the aspects of empirical drug discovery. In such case, the test substance is then developed to realize the second effect [13]. Some related examples are as follows:

- Piperazine (hexahydropyrazine) was introduced earlier as a treatment for gout because it forms a readily soluble salt with acid. This treatment was discontinued in the early 20th century because of unsatisfactory response; but a pharmacist in France had noticed that though treated patients might not have lost their pain, they often had lost their intestinal worms. Based on this observation, the Wellcome organization in Britain developed piperazine citrate into one among the foremost widely used anthelmintics of the 20th century [14].
- Sildenafil citrate (Viagra) is the most famous example of drug discovery arising from the use of a side effect. Initially this drug was being given to patients for the treatment of heart condition. But during treatment patients exhibited an unexpected

elevation in erectile function which further led to its development for the treatment of sexual dysfunction [15,16].

- AZT, also referred to as Zidovudine, is another pharmaceutical that has been successfully repurposed. AZT was originally developed as a treatment for cancer, but was shown to lack efficacy against neoplastic cells. The invention by Burroughs Wellcome that AZT was effective as a treatment for patients with HIV/AIDS transformed the failed chemotherapeutic into an anti-retroviral blockbuster [17].

2. SUCCESSFUL EXAMPLES OF SOSA SWITCHES

2.1 From Antibacterial Sulfonamides to Endothelin Receptor Antagonists

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

At the origin a modest affinity for the Endothelin-A (ETA) receptor was observed with the antibacterial sulfonamide, sulfathiazole. Extension to other sulfonamides led to sulfisoxazole which found to be more potent. Optimization of this latter yielded the compound BMS-182874, a potent and selective antagonist (Fig.1). This compound is orally active and produces a long-term hypotensive effect. Further optimization based on pharmacokinetic considerations like potency, bioavailability, efficacy and selectivity, led the BMS scientists to replace the naphthalene ring with a diphenyl system which gave rise to a compound BMS-193884. Among all these prepared compounds BMS-193884 showed promising hemodynamic effects in a phase II clinical trial for congestive heart failure [18,19].

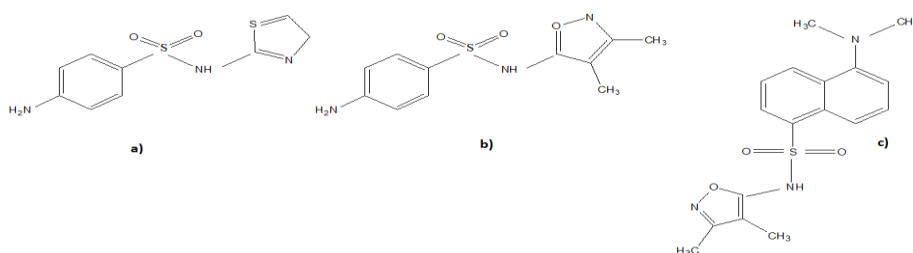


Fig. 1. Structures of a) sulfathiazole b) sulfisoxazole c) BMS-182874

2.2 From diuretic Amiloride to Myocardiac Na(+)/H(+) Exchange (NHE) Inhibitors

Till now five isoforms of Na(+)/H(+) exchanger have been found in the plasma membrane of mammalian cells and a sixth has been found in the mitochondria. NHE-1 is the name of the main isoform found in the heart which belongs to type 1 isoform. Karmazyn in 1988 published a paper suggesting a cardioprotective role of inhibiting NHE. It was shown that a potassium-sparing diuretic, amiloride, having NHE inhibitory activity, produced an enhanced recovery of contractile function in isolated rat hearts which are subjected to global ischemia and reperfusion. Afterwards, a number of scientists used amiloride and its 5-amino substituted pyrazinoyl guanidine derivatives to find out the cardioprotective potential of inhibiting NHE in the ischemic myocardium. But later it was observed that these derivatives of amiloride interacted with other cation transporters and showed cardioprotective activities which was independent of their NHE inhibitory activity. Subsequently, scientists at Hoechst synthesized the benzoyl guanidine derivatives HOE-694 and HOE-642 or cariporide mesylate (Fig. 3), a new class of more selective NHE-1 inhibitors. These compounds showed better potency, efficacy and selectivity over amiloride (IC_{50} 10–20-fold lower than amiloride). In several animal models HOE-694 showed remarkable antiarrhythmic and anti-ischemic activity and low toxicity profile. HOE-642 or cariporide mesylate was synthesized by substituting piperidine by an isopropyl group. This change in the structure increased water solubility, activity in vitro, and better NHE-1 selectivity than HOE-694 [20,21,22].

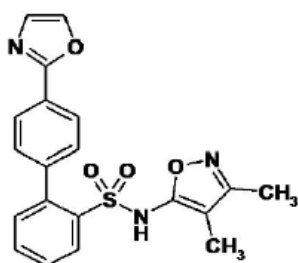


Fig. 2. Structure of BMS-193884

2.3 Calcium Channel Blocker Niguldipine as a Source of α 1A-Adrenergic Antagonists

The common symptoms of prostatism are obstructive (weak stream of urine, dribbling, large

residual urine volume) and irritative (pain during urination, increased urinary frequency, nocturia) in nature and may significantly compromise the standard of lifetime of patients. While surgical procedures or the use of 5 α -reductase inhibitors such as finasteride are used to reduce the prostatic mass, α 1A-adrenergic receptor antagonists such as tetrazosin, doxazosin, and tamsulosin relax the smooth muscles in the prostate and in the lower urinary tract and facilitate the urine flow. However, nonselective α 1A-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 [23]. A screening program identified the calcium channel blocker niguldipine as a potent ligand (K_i 0.16 nM) of the recombinant human α 1A-adrenoceptor. Moreover, niguldipine presents considerable α 1A-selectivity (>300-fold over α 1B- and α 1D-receptors) [24]. 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 trans membrane domain 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 phenyl ethylamine type of agonists. Progressive optimization of niguldipine yielded compounds such as SNAP-5089 (-), SNAP-5399 and SNAP-6383 (Fig.4). These compounds display nanomolar affinities for the α 1A -receptor subtype, which correlates well with the potency to inhibit the phenylephrine- induced contraction of dog prostate. Compound SNAP-6383 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. 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 [25].

2.4 Conversion of Antidepressant Minaprine to a Muscarinic M1 Partial Agonists

Various SOSA switches could be derived in the field of pyridazine chemistry, starting from the

antidepressant minaprine. Minaprine itself possesses weak affinity for muscarinic M1 receptors (K_i 17 μ M), in addition to serotonergic and dopaminergic activity. Three simple changes in the structure of minaprine (Fig. 5) like shifting of the methyl group from the 3- to the 4-position (Compound 1), substitution of the morpholine by a tropane (Compound 2), and introduction of an

hydroxyl group in the ortho position of the phenyl ring (Compound 3) eliminated the dopaminergic and serotonergic activities and improved the partial agonistic cholinergic activity of compound 3 [26-28]. The noteworthy result was the total abolition of initial activity of minaprine on the dopaminergic and serotonergic transmission in the final compound 3.

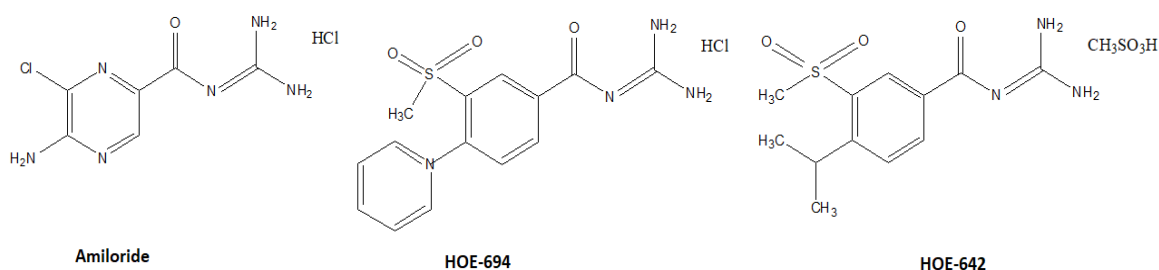


Fig. 3. Structures of amiloride and cardioprotective Na (+)/H(+) exchange (NHE) inhibitors

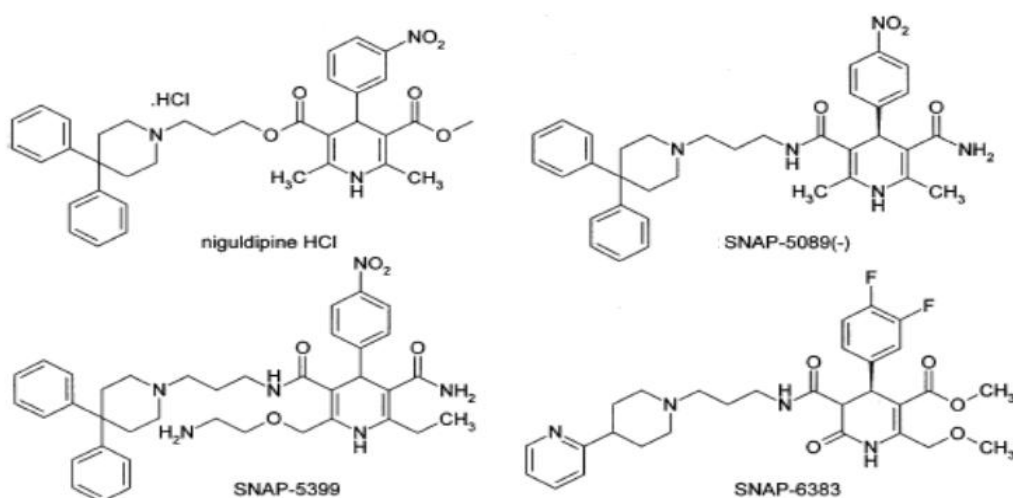


Fig. 4. From the calcium channel antagonist niguldipine to the potent and selective α 1A-adrenergic antagonist 4 (SNAP-6383)

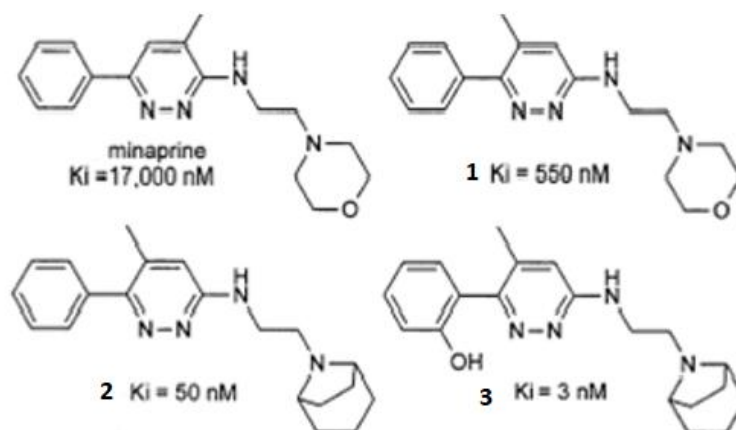


Fig. 5. Structures of minaprine and muscarinic M1 receptor partial agonists

2.5 Thalidomide: A Potent Inhibitor of Tumour Necrosis Factor (TNF)

Thalidomide was first synthesized as an antihistaminic in 1954. Further it was found to have sedative effects but because of catastrophic teratogenicity the drug was withdrawn. Later on, in the early 1960s thalidomide was found to be effective as a sedative in patients suffering from lepromatous leprosy. A rapid and noticeable improvement of the painful neuritis experienced by these patients was observed and published in 1965. Particularly it appeared to be efficacious for the treatment of erythema nodosum leprosum, a possible complication of the chemotherapy of leprosy [29]. This activity was attributed to a blockade of the TNF- α production, and under restricted conditions (no administration during pregnancy or to any woman of childbearing age), thalidomide found a new use as immune modulator. Different derivatives of thalidomide have been prepared such that the desired actions of the drug are maintained without its side effects. One attempt was made to separate the effects of the (*R*)-isomer from the effects of the (*S*)-isomer. But this approach was not found effective as in vivo racemization of thalidomide is very fast. Stable non racemizable analogues of thalidomide were then prepared among which *R*-methyl thalidomide (Fig. 6) was found to be a potent inhibitor of TNF production in some cell lines [30].

2.6 From the Nonsteroidal Anti-inflammatory Drug Diclofenac to an Inhibitor of the Fibrin Transthyretine Amyloid Formation

Transthyretine (TTR) is a tetrameric protein composed of four similar 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. In acidic conditions, such as in the lysosomes, transthyretine undergoes dissociation 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 non-steroidal anti-inflammatory drug diclofenac (Fig.7) as a potent inhibitor of TTR amyloid formation. With the aim of preparing compounds with high inhibition capacities but also with selective binding to transthyretine, optimization of diclofenac produced 3,5-disubstituted positional isomer and the substituted anthranilic acid [31,32] (Fig. 7).

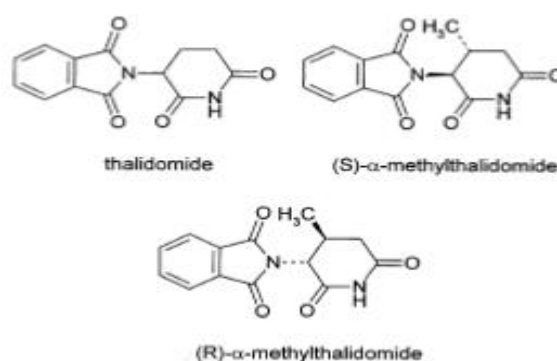


Fig. 6. Structures of Thalidomide and (*S*)- and (*R*)- α -methyl thalidomide

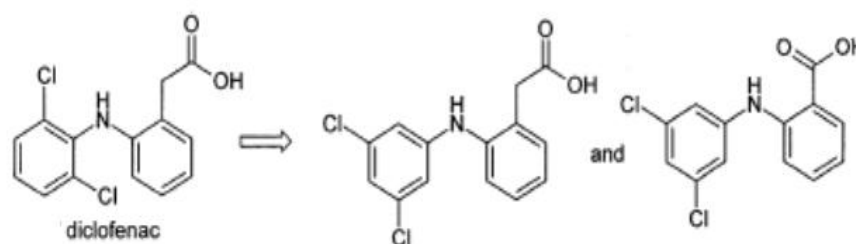


Fig. 7. Structures of diclofenac and its positional isomers

2.7 Orally Active Nonpeptidic Endothelin-a Receptor Antagonists from Herbicides

The two lead structures 1 (Lu 110896) and 2 (Lu110897) (Fig.8) were initially designed as herbicides. By screening the chemical library of BASF these compounds were found to have strong affinity to the recombinant human Endothelin-A (ETA) receptor (K_i 250 and 160 nM) while binding to the ETB receptor was much weaker (K_i 3000 and 4700nM). With few modifications in the structures of Lu 110896 and Lu110897, compound 3 was prepared in order to enhance the potency. Compound 3 exhibited high potency and selectivity (K_i (ETA) 6 nM; K_i (ETB) 1000 nM). It was orally active in vivo and showed a long duration of action [33,34].

2.8 From Laundry Brightener to Antiviral Compounds

The major cause of respiratory tract infections in premature babies and infants upto 6 months of

age is a Human respiratory syncytial virus (RSV). Each year widespread outbreaks occur in the winter months in the northern hemisphere and frequently reach epidemic proportions [35]. During a high-throughput screening of a 20,000-compound library, a whole virus cell-based assay was carried out in which stilbene was found as a potent RSV fusion inhibitor. This compound was synthesized at American Cyanamid's Organic Chemicals Division some 40 years ago as a laundry brightener. But as later it showed antiviral activity (IC_{50} 0.15 μ M) optimisation of stilbene yielded the biphenyl analogue (Fig.9) named RFI-641, with enhanced potency (IC_{50} 0.05 μ M) [36].

2.9 Metformin as a Targeted Therapy for Lung Cancer

Metformin is the most commonly used oral hypoglycemic drug for type II diabetic patients. The use of this drug has unexpectedly been linked to lower incidences of cancer [37,38]. It has been suggested that this finding may be related to metformin's activation of the

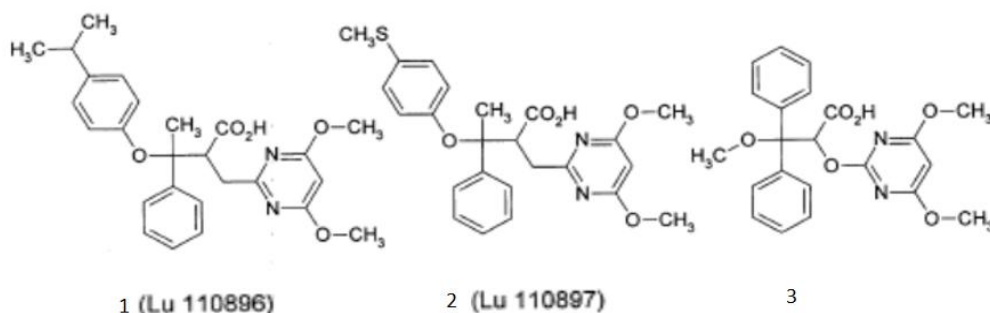


Fig. 8. Structures of two herbicide leads selective ETA antagonist

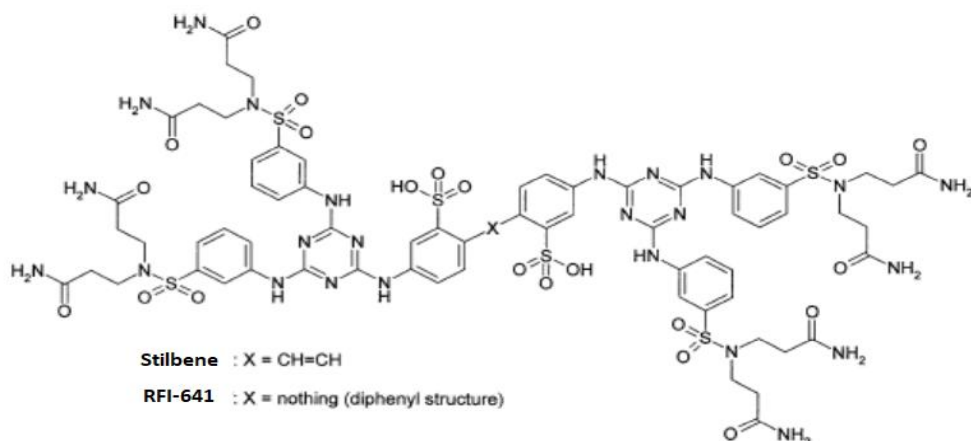


Fig. 9. Laundry brightener as a lead for antiviral compound

Table 1. Some More Examples of SOSA Approach

Initial Drug Lead	Pharmacological profile	SOSA Derived Analogue	Pharmacological profile	Reference
Niguldipine	Ca channel Blocker	SNAP-6383	α_{1A} -adrenergic antagonist	[25]
Amiloride	Diuretic	Cariporiode mesylate	Na/H exchange inhibitor	[42]
Atenolol	B-blocker	Cromakalim	Potassium I _{ks} channel opener	[43,44]
Minaprine	Antidepressant	Various aminothiazoles	CRH-antagonist	[45,46]
Sulpiride	D ₃ /D ₂ non selective dopamine antagonist	Compound Do 897	D ₃ -Selective Partial dopamine agonist	[47]
Tetracyclin	Antibiotic	BMS 1922548	Neuropeptide Y ligand	[48]
Erythromycin A	Antibiotic	Cladinose replacement analogue	Non peptide luteinizing hormone releasing hormone antagonist	[49]
Fluoxetine	Serotonin reuptake inhibitor	Imidazole analogue	Anti candida agent	[50]
Diazepam	Tranquilizer	CI-1044	Selective PDE 4inhibitor	[51]

AMP-activated kinase (AMPK) pathway [39]. This pathway is known to regulate cellular metabolism (hence the drug's efficacy as an antidiabetic agent) as well as inhibits the serine–threonine kinase mammalian target of rapamycin (mTOR), an important molecular target which regulates cellular growth and proliferation. Thus, AMPK has been hypothesized to prevent oncogenesis. Memmott et al, in their recent Cancer Prevention Research paper titled “Metformin prevents tobacco carcinogen-induced lung tumorigenesis” investigated the use of metformin in inhibiting the mTOR pathway [40]. In this research, the authors assessed the utility of metformin in an in vivo model of lung cancer induced by the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). In the experiments described by Memmott et al metformin was found to inhibit NNK-induced tumorigenesis in mice compared to controls in a dose dependent fashion when administered orally, decreasing tumor burden by 50%. Most important observation was the steady-state levels of metformin in the experimental animals fell within the range as achieved by standard oral dosing for diabetic patients. Although this would be particularly convenient for translation to human lung cancer patients, the authors did note an even greater efficacy when metformin was given intra-peritoneally, resulting in greater peak plasma levels of the drug. As this administration decreased tumour burden by more than 70%, it will be worthwhile to explore pharmacologic techniques to deliver metformin or one of its analogues in a way to achieve higher peak plasma concentrations. The exact mechanism responsible for the efficacy of metformin in treating lung cancer is not clear yet. However, there is a potential feasibility of using this drug as an important agent in the future management of lung cancer [41].

3. CONCLUSION

The Selective Optimization of Side Activities (SOSA) approach is based on the screening of drug molecules, and it thus automatically yields drug like hits. It is one of the most effective method of identification and optimization of leads and hence can represent an appealing alternative to costly HTS. In this approach, a side activity of a drug is enhanced by subsequent structural changes. While practicing SOSA approaches, it is observed that starting with a drug molecule as lead substance in synthesis of analogues, the probability of obtaining safe new chemical entities is notably increased. Thus, SOSA is a very

promising strategy for generation of new leads from old drugs having good bioavailability and less toxicity.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Taylor D. The Pharmaceutical Industry and the Future of Drug Development. Pharmaceuticals in the Environment. Issues in Environmental Science and Technology. Royal Society of Chemistry. 2015:1-33.
2. Wermuth CG. The “SOSA” approach: an alternative to high-throughput screening. *Med Chem Res.* 2001;10(7):431-39.
3. Wermuth CG. Possible alternatives to high-throughput screening. Drug discovery and development, Hoboken, NJ: John Wiley & Sons. 2006;1:213-32.
4. Wermuth CG. Selective optimization of side activities: another way for drug discovery. *J Med Chem.* 2004;47(6):1303-14.
5. Wermuth CG. Selective optimization of side activities: The SOSA approach. *Drug Discov Today.* 2006;11(3-4):160-64.
6. Connor KA, Roth BL. Finding New trick for old drug an efficient way public sector drug discovery. *Nat Rev Drug Discov.* 2005;4(12):1005-14.
7. Korálnik IJ. New insights into progressive multifocal leukoencephalopathy. *Curr Opin Neurol.* 2004;17(3):365-70.

8. Schreiner B, Kieseier BC, Hartung HP, Hohlfeld R, Wiendl H. Blocking adhesion molecules with natalizumab in multiple sclerosis. *Der Nervenarzt*. 2005;76(8):999-1005.
9. Crunkhorn S. New targets for old drugs. *Nat Rev Drug Discov*. 2008;7:729.
10. Aubé J. Drug Repurposing and the Medicinal Chemist. *ACS Med Chem Lett*. 2012;3(6):442-44.
11. Wermuth CG, Villoutreix B, Grisoni S, Olivier A, Rocher J. Strategies in the Search for New Lead Compounds or Original Working Hypotheses. In *The Practice of Medicinal Chemistry*. Elsevier Ltd. 2015:82-83.
12. Prestwick Chemical Library. Prestwick Chemical, Inc., Illkirch and Washington DC, Available: www.prestwickchemical.com.
13. Campbell WC. Serendipity and New Drugs for Infectious Disease. *ILAR J*. 2005;46(4):352-56.
14. Goodwin LG. New drugs for old diseases. *Trans R Soc Trop Med Hyg*. 1980;74: 1-7.
15. Terret NK, Bell AS, Brown D, Ellis P. Sildenafil (Viagra), a potent and selective inhibitor of type 5 cGMP phosphodiesterase with utility for the treatment of male erectile dysfunction. *Bioorg Med Chem Lett*. 1996;6:1819-24.
16. Boolell M, Allen MJ, Ballard SA, Gepi-Attee S, Muirhead GJ, Naylor AM, et al. Sildenafil: An orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int J Urol Res*. 1996;8(2):47-52.
17. Broder S. The development of antiretroviral therapy and its impact on the HIV-1/AIDS pandemic. *Antivir Res*. 2010;85(1):1.
18. Stein PD, Hunt JT, Floyd DM, Moreland S, Dickinson KEJ, Mitchell C, et al. The discovery of sulfonamide endothelin antagonists and the development of the orally active ETA antagonist 5-(dimethylamino)-N-(3,4-dimethyl-5-isoxazolyl)-l-naphthalenesulfonamide. *J Med Chem*. 1994;37(3):329-31.
19. Murugesan N, Gu Z, Spergel S, Young M, Chen P, Mathur A, et al. Biphenylsulfonamide endothelin receptor antagonists. 4. Discovery of N-[(4,5-dimethyl-3-isoxazolyl) amino] sulfonyl]-4-(2-oxazolyl)[1,10 -biphenyl]-2-yl]methyl]-N,3,3-trimethylbutanamide (BMS-207940), a highly potent and orally active ETA selective antagonist. *J Med Chem*. 2003; 46:125-37.
20. Horacio E. Cingolani, Irene L. Ennis. Sodium-Hydrogen Exchanger, Cardiac Overload, and Myocardial Hypertrophy. *Circulation*. 2007;115(9):1090-1100.
21. Masereel B, Pochet L, Laeckmann D. An overview of inhibitors of Na⁺/H⁺ exchanger. *Eur J Med Chem*. 2003;38(6):547-54.
22. Gross GJ, Gumina RJ. Cardioprotective effects of Na⁺/H⁺ exchange inhibitors. *Drugs of the Future*. 2001;26(3):253-60.
23. Lagu B. Identification of 1A-adrenoceptor selective antagonists for the treatment of benign prostatic hyperplasia. *Drug Future*. 2001;26(8):757.
24. Schwinn DA, Price DT, Narayan P. α 1 - Adrenoceptor Subtype Selectivity and Lower Urinary Tract Symptoms. *Mayo Clin Proc*. 2004;79(11):1423-34.
25. Chang RS, et al. In vitro studies on L-771,688 (SNAP 6383), a new potent and selective α (1A)-adrenoceptor antagonist. *Eur J Pharmacol*. 2000;409(3):301-312.
26. Wermuth CG, Schlewer G, Bourguignon J-J, Maghioros G, Bouchet M-J, Moire C et al. 3-Aminopyridazine derivatives with atypical antidepressant, serotonergic and dopaminergic activities. *J Med Chem*. 1989;32(3):528-37.
27. Wermuth CG. Aminopyridazines: an alternative route to potent muscarinic agonists with no cholinergic syndrome. *Farmaco*. 1993;48(2):253-74.
28. Wermuth CG, Bourguignon JJ, Hoffmann R, Boigegrain R, Brodin R, Kan JP, et al. SR 46559A and related aminopyridazines are potent muscarinic agonist with no cholinergic syndrome. *Bioorg Med Chem Lett*. 1992;2(8):833-38.
29. Iyer CGS, Languillon J, Ramanujam K. WHO coordinated short-term double-blind trial with thalidomide in the treatment of acute lepra reactions in male lepromatous patients. *Bull World Health Organ*. 1971; 45(6):719-32.
30. Huang Y, Hsu CW, Chiu TH. Thalidomide and Its Analogs as Anticancer Agents. *Tzu Chi Med J*. 2008;20(3):188-95.
31. Baures PW, et al. Discovering transthyretin amyloid fibril inhibitors by limited screening. *Bioorg Med Chem*. 1998;6(8):1389-1401.
32. Oza VB, et al. Synthesis, structure and activity of diclofenac analogues as transthyretin amyloid fibril formation inhibitors. *J Med Chem*. 2002;45(2):321-32.

33. Iqbal J, Sanghia R, Das SK. Endothelin receptor antagonists: an overview of their synthesis and structure-activity relationship. *Mini Rev Med Chem*. 2005;5(4):381-408.
34. Riechers H, et al. Discovery and optimization of a novel class of orally active non-peptidic endothelin-A receptor antagonists. *J Med Chem*. 1996;39(11):2123-28.
35. Griffiths C, Drews SJ, Marchant DJ. Respiratory Syncytial Virus: Infection, Detection, and New Options for Prevention and Treatment. *Clin Microbiol Rev*. 2017;30(1):277-319.
36. Razinkov V, Gazumyan A, Nikitenko A, Ellestad G, Krishnamurthy G. RFI-641 inhibits entry of respiratory syncytial virus via interactions with fusion protein. *Chem Biol*. 2001;8(7):645-59.
37. Hung MS, Chuang MC, Tsai YH, Yang YH. Metformin improves survival in lung cancer patients receiving EGFR-TKIs therapy. *Eur Respir J*. 2018;52(62):PA2856.
38. Hung MS, et.al. Metformin Prolongs Survival in Type 2 Diabetes Lung Cancer Patients With EGFR-TKIs. *Integr Cancer Ther*. 2019;18:1-9.
39. Zhou G, et.al. Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest*. 2001;108(8):1167-74.
40. Memmott RM, Mercado JR, Maier CR, Kawabata S, Fox SD, Dennis PA. Metformin prevents tobacco carcinogen--induced lung tumorigenesis. *Cancer Prev Res*. 2010;3(9):1066-76.
41. Antonoff MB, D'Cunha J. Teaching an Old Drug New Tricks: Metformin as a Targeted Therapy for Lung Cancer. *Semin Thorac Cardiovasc Surg*. 2010;22(3):195-96.
42. Harguindey S, et.al. Cariporide and other new and powerful NHE1 inhibitors as potentially selective anticancer drugs – an integral molecular/biochemical/metabolic/clinical approach after one hundred years of cancer research. *J Transl Med*. 2013;11:282.
43. Clapham JC, et.al. Antihypertensive and haemodynamic properties of the potassium channel activating (-) enantiomer of cromakalim in animal models. *Arzneim Forsch*. 1991;41(4):385-91.
44. Gerlach U. IKs channel blockers: potential antiarrhythmic agents. *Drug Future*. 2001;26(5):473-84.
45. Gully D, et al. Biochemical and pharmacological profile of a potent and selective nonpeptide antagonist of the neurotensin receptor. *Proc Natl Acad Sci U. S. A* 1993;90(1):65-69.
46. Gully D, et al. 4-Phenyl-aminothiazole derivatives, method for preparing same and pharmaceutical compositions containing said derivatives. Sanofi: World Patent, WO970086841; 1997.
47. Pilla M. Selective inhibition of cocaine-seeking behaviour by a partial dopamine D3 agonist. *Nature*. 1999;400(6742):371-75.
48. Shu YZ, Cutrone JQ, Klohr SE, Huang S. BMS-192548, a tetracyclic binding inhibitor of neuropeptide Y receptors, from *Aspergillus niger* WB2346. II. Physicochemical properties and structural characterization. *J Antibiot Res (Tokyo)*. 1995;48(10):1060-65.
49. Randolph JT, et al. Nonpeptide luteinizing hormone-releasing hormone antagonists derived from erythromycin A: design, synthesis, and biological activity of cladinose replacement analogues. *J Med Chem*. 2004;47(5):1085-97.
50. Silvestri R, et al. Imidazole analogues of fluoxetine, a novel class of anti-candida agents. *J Med Chem*. 2004;47(16):3924-26.
51. Burnouf C, et al. Synthesis, structure-activity relationships, and pharmacological profile of 9-amino-4-oxo-1-phenyl-3,4,6,7-tetrahydro [1,4] diazepino[6,7,1-hi] indoles: discovery of potent, selective phosphodiesterase type 4 inhibitors. *J Med Chem*. 2000;43(25):4850-67.

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