Suramin: Clinical Uses and Structure-Activity Relationships

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Abstract: Suramin is a polysulfonated polyaromatic symmetrical urea. It is currently used to treat African river blindness and African sleeping sickness. Suramin has also been extensively trialed recently to treat a number of other diseases, including many cancers. Here, we examine its modes of action and discuss its structure-activity relationships.

Key Words: Suramin, trypanosomiasis, onchocerciasis, FGF.

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INTRODUCTION

Suramin (**1**) (also known as Germanin and Bayer-205) is a symmetrical polysulfonated polyaromatic urea. The hexasodium salt ($C_{51}H_{34}N_6Na_6O_{23}S_6$, molecular weight 1429.2) is a highly water-soluble, hygroscopic pale pink powder. Its discovery in 1916 developed out of earlier observations that trypan red (**2**), and other dyes such as trypan blue (**3**) and afridol violet (**4**) [1], cured trypanosomiasis in mice [2]. The composition of suramin was kept secret by Bayer, until Fourneau and coworkers elucidated the chemical structure and published it in 1924 [3].

Suramin has been used as an early stage treatment of trypanosome-caused onchocerciasis (African river blindness) and African trypanosomiasis (African sleeping sickness) since 1920 [4]. It is currently under clinical evaluation for its potential to regress a number of cancer cell lines, including non-small cell lung cancer, advanced breast cancer, hormone refractory prostate cancer, metastatic renal cell cancer, colorectal cancer and high-grade gliomas [5-7]. Suramin's *in vitro* activity against HIV led to it being trialed in AIDS patients [8, 9]. Suramin binds to a large number of peptidic growth factors [10]. The extremely diverse range of biologically important molecules and cell lines that suramin has been reported to inhibit is, perhaps, due to its non-specific mode of binding [11]. As a result, however, its clinical applications are significantly limited because non-specific binding leads to side effects and high toxicity. Additionally, its great metabolic stability, long plasma half-life (41-78 days) and a relatively low therapeutic index are significant hurdles to overcome if members of this family of compound are to be more broadly developed as drugs [12-14].

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DISEASES TREATABLE WITH SURAMIN

Malignant Neoplasms

In 1989 suramin was trialed on 15 patients against a number of metastatic cancers, with some encouraging results [15]. Its efficacy as a treatment for metastatic adrenocortical carcinoma was examined, with the authors concluding that suramin possessed antineoplastic efficacy in the treatment of this disease, but that its toxic side effects and narrow therapeutic window required strict monitoring of serum suramin levels in patients and made it unsuitable as a first-line treatment for this carcinoma [16]. Although suramin caused significant dose-dependent growth inhibition of human breast cancer cells *in vitro* [17-19], pilot studies which examined suramin's efficacy in treating breast cancer revealed no tumor responses [20, 21]. More recent work, however, has shown a marked enhancement of the anti-cancer effects of paclitaxel when co-administered with low-dose suramin to human MCF7 breast xenograft tumors in mice, leading to the initiation of phase I/II trials of paclitaxel and low-dose suramin combination in advanced metastatic breast cancer patients [22].

Suramin has shown promise as a treatment option for hormone-refractory prostate cancer [23-30]. In 2000, a randomized phase III trial comparing suramin plus hydrocortisone to placebo plus hydrocortisone showed that moderate palliative benefit was achieved with suramin, and that time to disease progression was longer in patients who received suramin [5]. However, a later study by Rosen and coworkers was unable to confirm the previously reported high rate of activity and durability of remission achieved using suramin [31]. Kaur and coworkers [14], and Autorino and coworkers [32] have critically reviewed the phase II and phase III clinical trial outcomes of suramin in the treatment of prostate cancer. A 1992 study of the effectiveness of suramin in treating advanced platinum-resistant ovarian cancer showed that some patients experienced disease stabilization and clinical

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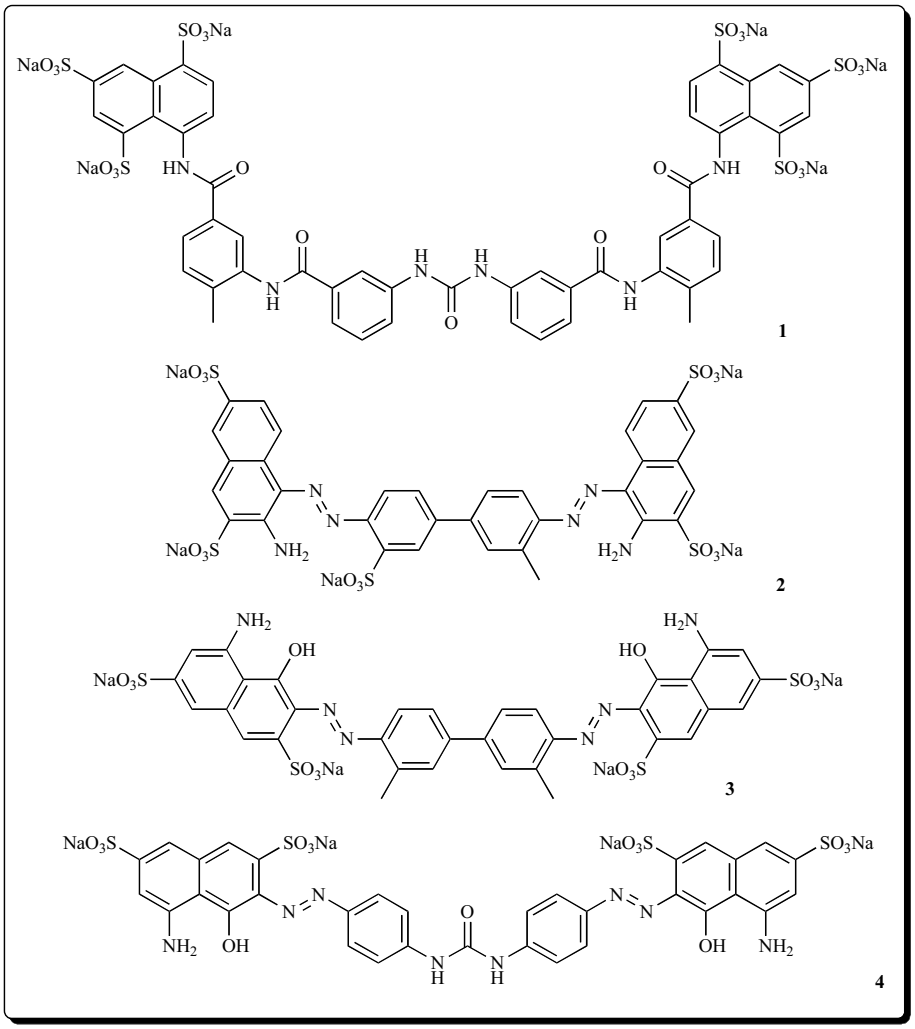


improvements [33]. Suramin caused significant dose-dependent growth inhibition of rat pancreatic tumors *in vivo* [17].

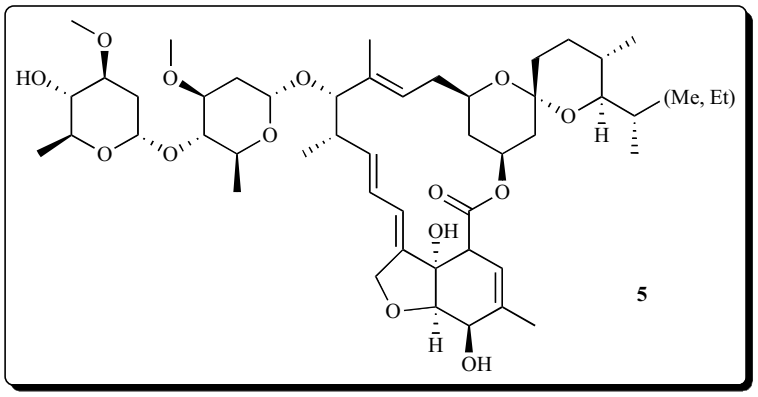
The effect of suramin on the human esophageal squamous cell carcinoma cell line KEsC-II was studied. Cell proliferation was stimulated at low concentrations of suramin, and inhibited at high concentrations, with the effects suggested to arise *via* phosphorylation of epidermal growth factor (EGF) receptors [34]. Suramin inhibits the growth of human rhabdomyosarcoma [35]. The mechanism of action in this case was determined to be the interference of the binding of insulin-like growth factor II (IGF-II) to the type I IGF receptor, thereby interrupting the IGF-II autocrine growth in these cells [35]. Similarly, suramin inhibits the growth of non-small cell lung cancer cells that express EGF receptors, and suramin was shown to inhibit, in a concentration-dependent manner, the binding of EGF to its receptors in these cells [36]. A 2000 study evaluated the activity of suramin and a number of its analogues against a panel of human tumor cell lines and in primary cultures of tumor cells from patients, in an attempt to identify the suramin pharmacophore so as to develop suramin analogs with improved therapeutic ratios. These studies suggested that the pharmacophore for cytotoxicity was different for tumor cells from patients and for cell lines. It was also shown that suramin and its analogs were insensitive to a number of drug resistance mechanisms [37].

Onchocerciasis

Onchocerciasis (African river blindness) is caused by *Onchocerca volvulus*, a parasitic worm that is transmitted by blackflies of *Simulium* species, and is very long-lived in the human body. It is endemic in many countries in Africa and Latin America. The disease results in a number of morbidities, including blindness, skin rashes, lesions, intense itching and skin depigmentation [38]. Suramin has been used since the 1920s as an anthelmintic to treat onchocerciasis [4, 39]; however, it has now been largely superseded by ivermectin (**5**) [40]. Nevertheless, suramin remains the only drug in clinical use for the treatment of onchocerciasis that is effective against adult worms.

Trypanosomiasis

Trypanosomiasis (African sleeping sickness) is a disease of humans and cattle endemic in regions of sub-Saharan Africa. It is caused by a trypanosome (a parasitic protozoon of *Trypanosoma* species) and is transmitted by the tsetse fly. Left untreated, it is invariably fatal [41, 42]; the World Health Organization estimates that there are 40,000 mortalities per year [41]. Suramin and pentamidine (**6**) have been used as an early stage treatment of trypanosomiasis (before the parasites invade the central nervous system (CNS)) since 1920 [4, 43]. Eflornithine (**7**) and the arsenic-containing



drug, melarsoprol (**8**), are used for later stages of the disease when the parasites are established in the CNS.

Suramin accumulates only slowly in trypanosomes, and it has been suggested that uptake of this drug occurs *via* endocytosis bound to low-density lipoprotein [44]. Its mode of action against trypanosomes is unknown.

Toxicity

The toxic effects of suramin are well documented [14]. Clinical trials of suramin in cancer patients have uncovered frequent toxic side effects, including proteinuria, reversible liver toxicity, cornea damage such as vortex keratopathy, adrenal insufficiency, coagulopathy, and reversible acute demyelinating polyneuropathy [15]. A trial of suramin's efficacy in treating metastatic adrenocortical carcinoma, in which the drug was administered for periods of up to 15 months, reported serious side effects in patients, including coagulopathy, thrombocytopenia, polyneuropathy and allergic skin reactions. The deaths of two patients in that trial were suggested by the authors to be possibly related to suramin therapy [16]. In a clinical trial of hormone-refractory prostate cancer, the most commonly encountered side effect was fatigue but, again, a fatality due to idiosyncratic myelosuppression (grade V) was observed in one patient [31]. Another trial of suramin's efficacy against metastatic prostate cancer reported frequent ocular symptoms such as corneal deposits and lacrymation [45]. Skin reactions to suramin are common, most usually pruritus or urticaria, but fatal toxic epidermal necrolysis has been reported [46, 47]. The most common dose-limiting toxic effects are malaise and lethargy [48], and neurotoxicity [49]. Suramin has been shown to prevent and terminate pregnancy in mice [50].

Suramin is notable for its very high (99.7%) serum protein binding, its very long half-life (41-78 days [6]), and high metabolic stability [51]. Suramin's volume of distribution is 31-46 litres and 80% of the drug is excreted renally [52].

MODES OF ACTION

Interaction of Suramin with Proteins

The anti-tumor activity of suramin [34, 53] has been proposed to stem from either its binding to essential growth factors (antagonizing the ability of these factors to stimulate the growth of tumor cells *in vitro* [15]), inhibition of protein tyrosine phosphatases, inhibition of angiogenesis, or a combination of these three processes [35, 36, 53-57]. In fact, two of these mechanisms are probably interconnected, as several reports have noted that the known angiostatic activity of suramin is at least in part related to fibroblast growth factor (FGF) binding and inhibition [58-64]. Table **1** summarizes the growth factors and enzymes that have been shown to be inhibited by, or bind to, suramin.

FGF Binding

Suramin's ability to block the binding of fibroblast growth factor (FGF) to its receptor (FGFR) is of particular interest, because this event is fundamental in the process of angiogenesis. The FGFs comprise a family of proteins which are required for a variety of biological processes including cell growth and movement, differentiation, and protection from cell death [101-103]. They function by interacting with their cognate receptor (FGFR), which is a transmembrane protein possessing an extracellular FGF/heparin ligand binding region and an intracellular tyrosine kinase domain [104]. Activation of the receptor and subsequent signal transduction occurs when two FGF:FGFR complexes dimerize [105].

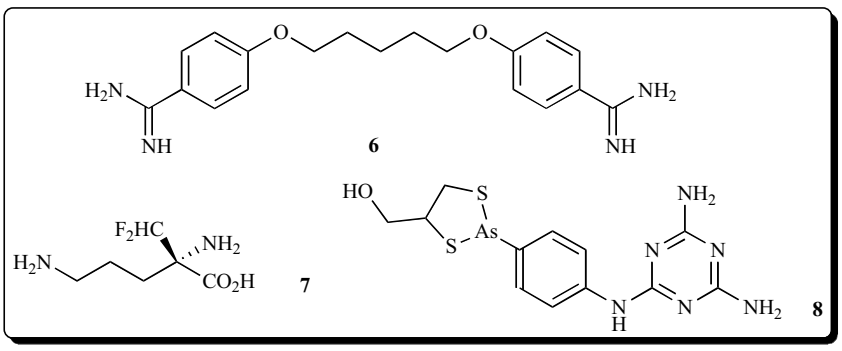


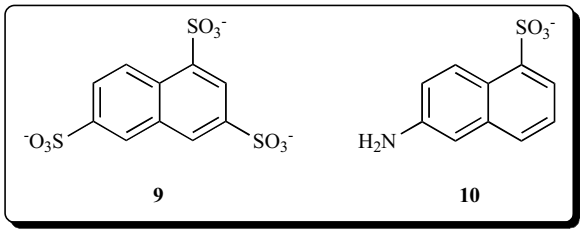
Table 1. Enzymes and Growth Factors Inhibited by Suramin

Enzyme/Growth Factor	References
DNA polymerase	[65]
Reverse transcriptase	[9, 66-68]
Topoisomerase-I and Topoisomerase-II	[69-71]
ATPase	[72, 73]
Heparanase	[74]
Protein tyrosine phosphatases (PTP)	[55, 75]
Protein kinase C	[76, 77]
Phosphoglycerate kinase	[78]
Diacylglycerol kinase	[79]
NAD^+-dependent histone deacetylases (surtuins)	[80]
Phosphatidylinositol kinase	[79]
G-Protein coupled receptor kinases	[81]
Ionotropic adenine and uracil 5′-nucleotide (P2X/P2Y) receptors	[82-84]
Bothrops asper venom phospholipase A2 (PLA2)	[85]
Fibroblast growth factors (FGFs)	[63, 86, 87]
Platelet-derived growth factor (PDGF)	[88, 86]
Epidermal growth factor (EGF)	[15, 36, 86]
Transforming growth factor-beta (TGF-β)	[15, 86]
Insulin-like growth factor II (IGF-II)	[35]
Androgen-induced growth factor (AIGF)	[89, 90]
Nerve growth factor (NGF)	[91]
Heparin-binding growth factor type-2 (HBGF-2)	[86]
Follicle-stimulating hormone (FSH)	[92]
Interleukin-2 (IL-2)	[93]
Interleukin-6 (IL-6)	[94]
Tumor necrosis factor-alpha (TNFα)	[95, 96]
Vaccinia virus complement control protein (VCP)	[97]
Plasmodium falciparum merozoite surface protein-1	[98]
Triosephosphate isomerise (TIM) reactivation	[99, 100]

Heparin is required for dimerization to occur because it is able to bind to both FGF and FGFR, thereby strengthening the ternary complex formed on the cell surface [103]. Two crystal structures of the FGF:FGFR:heparin ternary complex exist, but they differ significantly, and there is uncertainty regarding which of these structures (if either) best represent the biologically relevant structure of the complex [103].

It is clear that the inhibition of FGF activity by suramin results from the formation of a complex with FGF, not from a direct interaction with FGFR [106]. It is also highly likely that suramin binds at or near to the heparin binding site, since heparin physically disrupts suramin-FGF complexes and counteract the angiostatic effects of suramin [59, 61, 63, 107-110]. Marchetti's group has also reported that suramin inhibits heparanase, a glucuronidase whose activity correlates with the metastatic propensity of tumor cells [74].

A solution structure of FGF-1 complexed with l,3,6-naphthalenetrisulfonate (NTS) (**9**) showed that NTS weakly and heterogeneously bound to the heparin binding site of this growth factor [111]. NTS has been shown to have angiostatic activity and, according to Lozano *et al*. [111], it can be considered a minimal model for suramin action. In another study by the same group, the crystal structure of FGF-1 in complex with 5-amino-2-naphthalenesulfonate (ANS) (**10**) was solved. The solved structure revealed a 1:1 stoichiometric ratio of FGF-1 to ANS, with ANS bound to the positively-charged heparin binding site of FGF-1 [112].



9 **10**

Two recent studies have published evidence not in concord with previous models on suramin's interactions with FGF. Ganesh *et al*. reported the crystal structure and intermolecular interactions of a 1:1 complex of suramin with the heparin-binding site in vaccinia virus complement control protein (VCP), which is geometrically similar to many heparin-binding proteins, including FGF [97]. The authors were able to compare this crystal structure with the crystal structure of the heparin-VCP complex, and so determine that suramin interacts with a single heparin-binding site in VCP [97]. This study showed significant differences in the orientations of the naphthalene rings (end groups of suramin) relative to the configuration of binding of NTS and ANS to FGF as described in previous studies [111, 112]. Ganesh and coworkers also noted that superimposition of each of the naphthalene rings in suramin, from the crystal structure [97], on the naphthalene rings in ANS and NTS complexes [111, 112] resulted in suramin either having severe steric clashes with the FGF or no interaction beyond the naphthalene ring. They concluded therefore that the structural information gained from the ANS and NTS complexes was of limited use in elucidating the mode of binding of suramin to FGF.

Using isothermal titration calorimetry, Kathir *et al*. [113] suggested that human FGF-1 (hFGF-1) binds to two molecules of suramin with nanomolar affinity. This ternary complex subsequently oligomerizes to form a stable inactive tetramer which is incapable of binding to the receptor (Fig. (**1**)). The binding of the suramin molecules to hFGF-1 was shown to occur simultaneously at specific sites on the protein, inducing a conformational change and revealing solvent-exposed hydrophobic residues at the surface. Formation of the inactive tetramer then occurs due to the hydrophobic

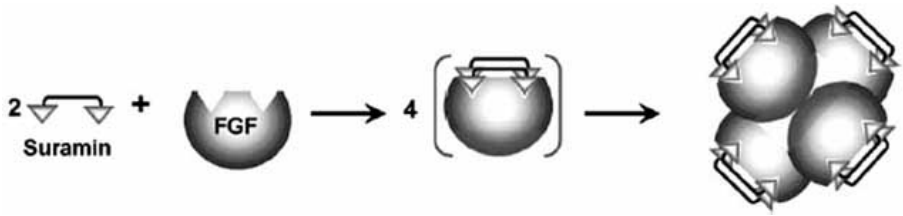


Fig. (1). Cartoon representing the primary mechanism by which suramin inhibits FGF-1. Reprinted with permission from Kathir, K. M. *et al*., *Biochem*., **2006**, *45*, 899-906. Copyright 2006 American Chemical Society [113].

attraction between the transiently exposed non-polar surfaces. Further NMR experiments revealed that suramin binds to residues of FGF that are involved in binding to heparin, as well as residues involved in binding to the FGFR. These two binding sites are separated by a distance of ~32 Å which suggested that a single molecule of suramin with a length of ~24 Å could not bind simultaneously to both sites [113].

Structure-Activity Relationships of FGF Binding

There have been a number of studies in which suramin analogs were prepared to determine structure-activity relationships (SARs) for suramin-FGF binding. These studies focused on a number of aspects of the structure of suramin, including the length and rigidity of the molecule, the nature of its end groups, its symmetry, the central urea group, and its methyl substituents [12, 37, 58, 62, 106, 112, 114-119]. The results of these SAR studies often differ from those directed at HIV (reverse transcriptase inhibition) [120], trypanosomiasis [121], the P2 receptor [84], or class III histone deacetylases (surtuins) [80].

The major deficiency in most of these studies is that they focused on the potential angiostatic or anti-cancer activities of suramin analogs, which are consequences of complex processes rather than the effect resulting from the direct binding of suramin to FGF or its receptor [58, 62, 106, 115-119]. Therefore, structure-activity relationships derived from these investigations do not necessarily mean that activity against proliferation and differentiation was through the inhibition of FGF by suramin. Furthermore, the SAR study summarised by Fig. (**2**) were obtained from different studies, many employing different cell lines (Table **2**), so biological activity observed for a particular functional group in one particular cell line may not necessarily confer activity in a different biological context.

Length and Symmetry of Suramin

Several SAR studies have noted that a minimum molecular length of suramin analogs was required for activity, so that compounds without at least one aromatic "spacer" positioned symmetrically either side of the central urea group had little or no biological effect compared to suramin itself [12, 58, 62, 106, 114, 117]. The spacing between the anionic binding sites in FGF is ~32 Å and thus these pockets require inhibitors in which the two anionic end-groups are similarly separated.

Molecular symmetry does not appear to be a requirement for inhibitory activity in suramin analogs, since some asymmetric compounds were found to have similar activity to suramin [106]. However, these compounds still satisfied the minimum length requirement for an inhibitor. Most analogs tested have been symmetrical due to ease of synthesis. Interestingly, some studies showed that smaller, asymmetric compounds containing a naphthalenesulfonate moiety had antiproliferative or angiostatic activity against FGF-promoted cell lines [83, 111, 112, 115, 118].

Table 2. Assays Used for Suramin and its Analogs

Type of Assay	Specific Assay	References
Cell proliferation/tumor growth inhibition	Inhibition of cell growth (various cell lines including carcinomas)	[37, 58, 112, 115-118]
	Observation of tumor colon cancer cell differentiation	[119]
	Mouse *in vivo* tumor growth inhibition	[118]
Angiogenesis inhibition	Neovascularization of the chorioallantoic membrane (CAM assay)	[12, 62, 106, 114-116, 118]
	Mouse angiogenesis assay – sponges implanted in backs of mice and evaluated for angiogenesis	[12, 58, 106, 112, 114]
	Microcarrier angiogenesis assay	[117]
FGF binding inhibition	Inhibition of FGF-2-stimulated bovine adrenalcapillary endothelial cell [^{3}H]methyl-thymidine uptake	[58]
	Inhibition of specific ^{125}I-FGF-2 binding to FGFR	[12, 58, 106, 114]

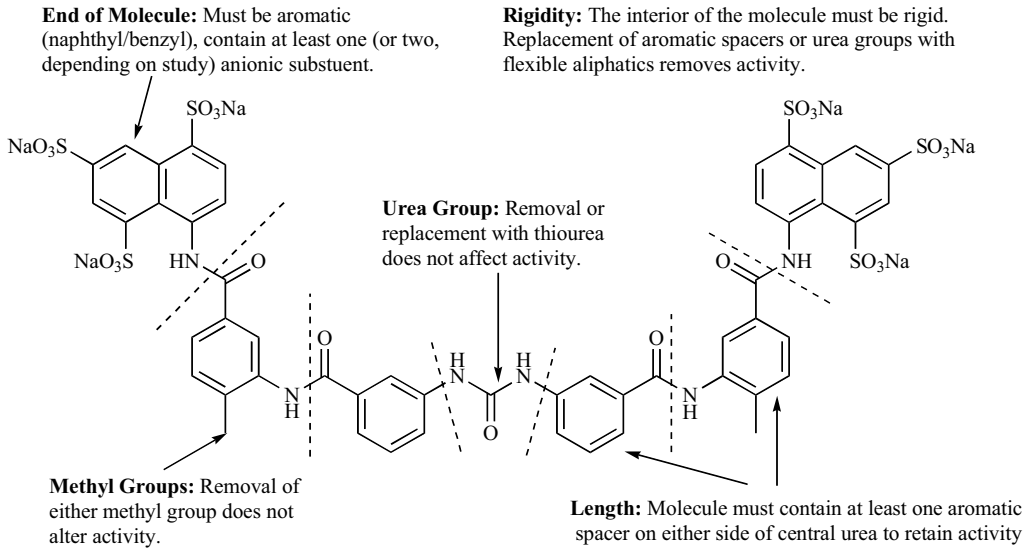


Fig. (2). Summary of the structure-activity relationships of suramin.

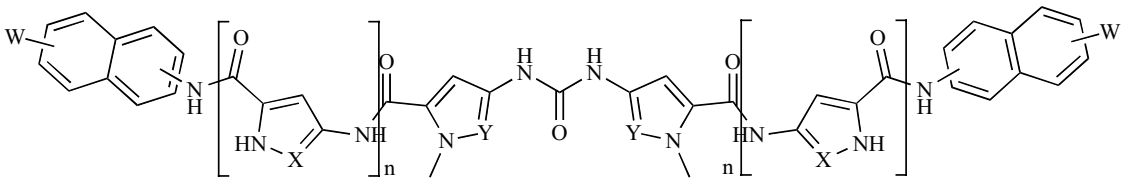
Rigidity

Suramin displays a high degree of rigidity due to the conjugated nature of the molecule. Modelling studies of suramin and structurally related molecules belonging to the suradista family (Fig. (**3**)) showed that in solution the compounds preferentially adopt a symmetrical, extended, quasi-planar arc shape with a distance between the two naphthalenesulfonate units of either 16-20 or 24-30 Å [12, 78, 114, 122]. Several reports have shown that the molecular rigidity of suramin is essential for inhibitory activity. Replacement of the central urea group or the aromatic spacers with more flexible aliphatic groups translated into a sharp decrease in activity [12, 62, 117]. Interestingly, Ganesh *et al*. have suggested that suramin experiences much greater conformational flexibility in solution than is generally believed, and they noted that suramin adopts a helical (non-planar) conformation in the crystal structure of the suramin-VCP complex [97].

Nature of the Aromatic Anionic Region

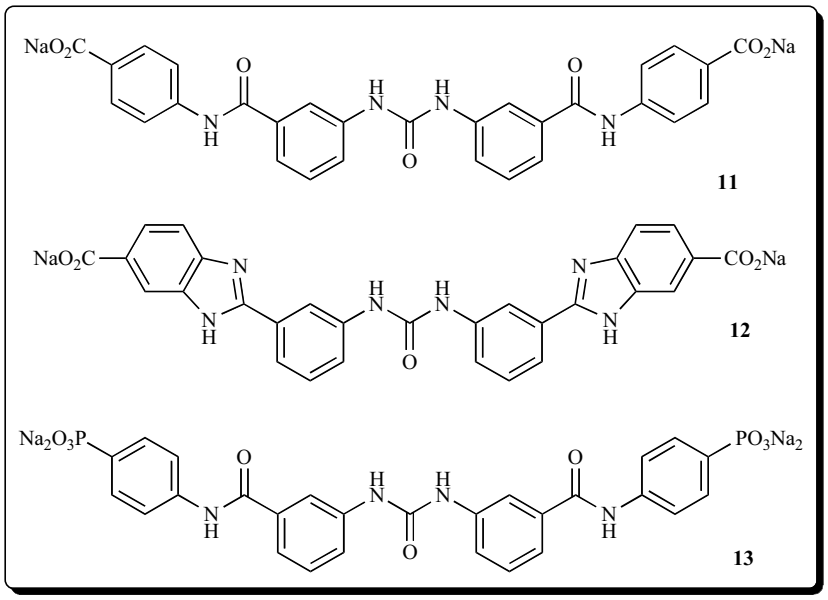
All SAR studies of suramin analogs agree on the necessity for anionic aromatic regions at each end of the compound [12, 37, 58, 62, 114-117]. While sulfonates have been the default choice of anionic group, a few studies at least have suggested that the aromatic portion can contain anionic groups other than sulfonates. Analogs where the sulfonates were replaced with carboxylates (e.g. **11** and **12**) were found to display activity [115], as were analogs, such as **13**, incorporating phosphonate groups [37].

The aromatic end group need not necessarily be a naphthalene derivative because several studies have found that analogs such as **11-13**, or those containing benzene monosulfonic acid groups were also active. For these compounds Gagliardi *et al*. demonstrated a reduced efficacy in the CAM assay (Table **2**, 7-26% inhibition compared to 64% inhibition for suramin) [62]. However, in studies by Firsching *et al*. [116, 117] and Kreimeyer *et al*. [115], analogs containing benzene monosulfonic acids had comparable activities to suramin in the majority of assays. Several studies altered the number of sulfonate groups (suramin contains six, three at each end) with varying results [12, 58, 62, 106, 112, 114, 116, 117]. While several benzene monosulfonic acid derivatives were found to display reasonable activity (see above), many studies argued that analogs required at least four sulfonate groups for good activity, with six required for activity comparable to that of suramin [12, 62, 106, 114, 116]. The majority of reports agreed that the actual positions of the sulfonate groups on the aromatic rings did not significantly affect activity [58, 62, 115-117].



W = SO_3Na; X, Y = CH, N; n = 0-2

Fig. (3). General structure of the suradista family [123].



It should be noted that suramin analogs with fewer anionic groups have been shown in several studies to be significantly less toxic in mice [12, 114-117].

OTHER STRUCTURAL FEATURES

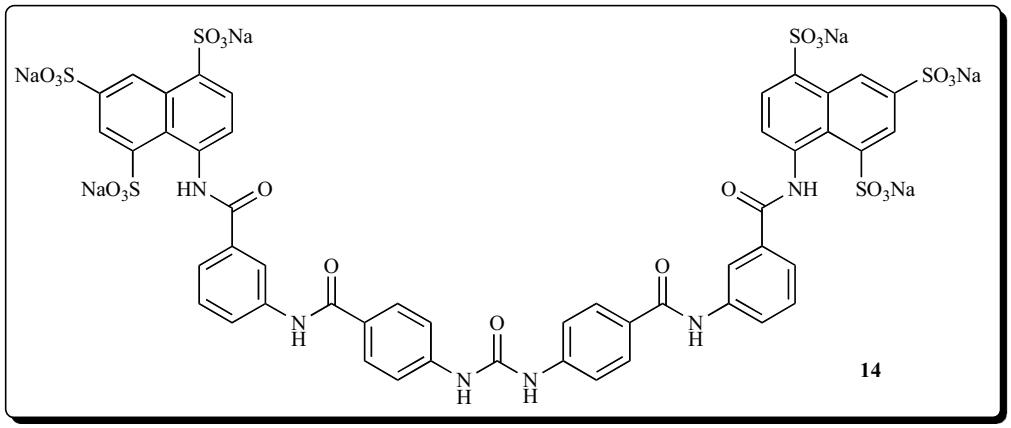
Several studies of anti-proliferative activity or FGF binding, have reported that the removal of the methyl groups of suramin did not affect inhibitory activity [12, 37, 62, 114, 116, 117, 122]. This contrasts the loss of trypanosomiasial activity when the methyl groups are omitted [3]. One study, in which the methyl groups of suramin were replaced with isopropyl groups, reported a increase in activity of the inhibition of cell growth in bovine FGF-stimulated porcine pulmonary artery endothelial cells (IC_{50} of 189 μM compared to suramin's IC_{50} of 521 μM) [4].

Amide Groups

No SAR study has systematically examined the roles of the amide groups of suramin, although one analog, NF279 (**14**), in which the amide groups were repositioned *para*-relative to the central urea group, showed high activity (the methyl groups were also removed) [37, 80, 82]. This deficiency of studies is despite the fact that amides are frequently involved in hydrogen bonding, one of the important means by which drugs can bind to their targets. It is thereby possible that one, or more, of the amide groups or the central urea group could be playing an essential role in the *in vivo* activity of suramin.

SUMMARY AND FUTURE PROSPECTS

Suramin binds to, and inhibits, a large number of enzymes and growth factors. This lack of specificity of binding limits its application as a clinical drug, and results in a broad range of toxicities and side effects. Although suramin remains useful for the treatment of onchocerciasis and trypanosomiasis, new drugs or improved analogs are needed to treat these diseases, as resistance to existing drugs increases. Suramin's promise as an anti-cancer drug has not yet been fulfilled. Suramin's role as an anti-angiogenesis agent appears to be related to its structural similarity to heparin, and its ability to inhibit the formation and dimerization of the FGF:FGF:heparin ternary complex. Structure-activity relationship studies of suramin have revealed much about its pharmacophore, but the development of suramin analogs as drugs will require candidates with much higher selectivities, and much lower toxicities.



ABBREVIATIONS

AIGF	=	Androgen-induced growth factor
ANS	=	5-Amino-2-naphthalenesulfonate
CAM	=	Chorioallantoic membrane
CNS	=	Central nervous system
EGF	=	Epidermal growth factor
FGF	=	Fibroblast growth factor
FGFR	=	FGF Receptor
HBG	=	Heparin-binding growth factor
IGF	=	Insulin-like growth factor
NGF	=	Nerve growth factor
NTS	=	l,3,6-Naphthalenetrisulfonate
PDGF	=	Platelet-derived growth-factor
PTP	=	Protein-tyrosine phosphatase
SAR	=	Structure-activity relationship
TGF	=	Transforming growth factor
VCP	=	Vaccinia virus complement control protein

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