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One Hundred Years of Suramin

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Abstract

Suramin is a hundred years old and still being used to treat the first stage of acute human sleeping sickness, caused by *Trypanosoma brucei rhodesiense*. Suramin is a multifunctional molecule with a wide array of potential applications, from parasitic and viral diseases to cancer, snakebite and autism. Suramin is also an enigmatic molecule: What are its targets? And how does it get into cells in the first place? Here we provide an overview on the many different candidate targets of suramin, discuss modes of action, and routes of cellular uptake. We reason that once the polypharmacology of suramin is understood at the molecular level, new, more specific, and less toxic molecules can be identified for the numerous potential applications of suramin.

Suramin, the fruit of early medicinal chemistry

When suramin was introduced for the treatment of African sleeping sickness in 1922, it was one of the first anti-infective agents that had been developed in a medicinal chemistry program. Starting from the antitrypanosomal activity of the dye trypan blue, synthesized in 1904 by Paul Ehrlich, Bayer made a series of colorless and more potent derivatives. Molecule 205 was suramin (Figure 1), synthesized by Oskar Dressel, Richard Kothe and Bernhard Heymann in 1916. Sleeping sickness (also known as human African trypanosomiasis, HAT) was at the forefront of research at that time, not a neglected disease as it is today, and the development of suramin was a breakthrough for the emerging field of chemotherapy. While the history of suramin has been reviewed elsewhere (1), we focus here on the many potential applications of suramin and its enigmatic mode of action.

Suramin as an antiparasitic drug

Suramin is still being used for the treatment of *Trypanosoma brucei rhodesiense* infections (2). However, it does not cross the blood-brain barrier and therefore is administered only for the first, hemolymphatic stage of sleeping sickness, when the trypanosomes have not yet invaded the patient's CNS. The standard treatment regimen for suramin is an initial test dose of 4-5 mg/kg followed by five weekly doses of 20 mg/kg (but not more than 1 g) injected i.v. (3). Suramin is also used for Surra (mal de caderas), caused by *T. evansi*, in particular for the treatment of camels (4). The treatment regimen is a single injection i.v. of 10 mg/kg suramin, i.e. about 6-10 g (4). *In vitro*, suramin also has some activity against *T. cruzi* (5). However, it is not used for Chagas' disease, and studies in mice even suggested that suramin would exacerbate the disease (6). *In vitro* activity of suramin against *Leishmania major* and *L. donovani* has recently been described (7). Furthermore, suramin blocks host cell invasion by the malaria parasite *Plasmodium falciparum*. This was observed for both the invasion of erythrocytes by *P. falciparum* merozoites (8) and the invasion of HepG2 hepatoma cells by *P. falciparum* sporozoites (9).

Suramin had been in use for river blindness, caused by the filarial parasite *Onchocerca volvulus* (10). It acts on both microfilariae and, to a larger extent, on adult worms (11, 12). However, suramin was subsequently replaced by the less toxic, and orally bioavailable, ivermectin (13, 14). The adverse effects of suramin are indeed manifold, including nephrotoxicity, hypersensitivity reactions, dermatitis, anemia, peripheral neuropathy and bone marrow toxicity (3, 15). But despite its potential toxicity, the lack of bioavailability, and absence of lead-like properties (Figure 1), suramin has found a surprising variety of repurposing applications. Table 1 provides an overview on the biological activities of suramin and Table 2 lists clinical trials performed with suramin.

Suramin as an antiviral agent

The antiviral and antibacteriophage activities of suramin are known since the mid-20th century (19, 20). Soon after the discovery of retroviruses, suramin was found to inhibit retroviral reverse transcriptase (21), which served as a rationale to test suramin against human immunodeficiency virus (HIV). Suramin protected T-cells from HIV infection *in vitro* (22), and in AIDS patients it reduced the viral burden in some of the study subjects; however, no improvement of the immunological features and clinical symptoms was achieved (17, 23, 24). Later-on suramin was found to inhibit host cell attachment through binding to the HIV-1 envelope glycoprotein gp120, indicating that the *in vitro* protection against HIV infection is mediated through inhibition of viral entry (25).

Suramin also inhibits the binding of Dengue virus to host cells through a direct effect on the viral envelope protein (26). Inhibition of host cell attachment was also found for Herpes simplex (27) and Hepatitis C viruses (28), which explained the previously reported protective effects of suramin against *in vitro* herpes simplex infections (29) and *in vivo* infections of ducks with Duck Hepatitis B Virus (30). Similar to the experience with HIV, suramin had initially been

tested against Hepatitis viruses due to its inhibitory effect on the viral DNA polymerase (31, 32). But in a small clinical trial suramin was found to be ineffective and toxic in chronic active Hepatitis B patients (18). Suramin neutralized enterovirus 71 (EV71) in cell culture and in a mouse model by binding to capsid proteins (33–35).

Suramin also bears potential against emerging viruses. It was shown to inhibit both RNA synthesis and replication in Chikungunya virus (36). *In vitro* suramin conferred protection if present at the time of infection, and this was attributed to a reduction of viral host cell binding and uptake (37). In the murine model suramin led to a reduction of pathognomonic lesions if injected prior to Chikungunya infection (38). Suramin also inhibited host cell invasion by Ebola virus (39) and Zika virus, even when added after viral exposure of the cell cultures (40).

Suramin against cancer

The first studies on the effects of suramin on neoplasms in animals were carried out in the 1940's; mice engrafted with lymphosarcoma developed significantly smaller tumors when simultaneously treated with suramin (41). In the 1970's it was shown that suramin can enhance the action of cyclophosphamide and adriamycin in mice engrafted with Ehrlich carcinoma (42). A first clinical trial with suramin was carried out in the 1980's in advanced-stage adrenal and renal cancer patients (16). Around half of the patients showed either partial or minimal responses, none showed complete remission. Nevertheless, a number of subsequent clinical trials with suramin were carried out (Table 2). In particular, suramin was tested against prostate cancer (43–51), non-small cell lung cancer (52), breast cancer (52), bladder cancer (53, 54) and brain tumors (55, 56). Most of these studies were based on the potential of suramin to act as an antagonist of growth factors (57–59), which are often overexpressed by tumors. In addition, suramin directly exhibits cytostatic activity on cultured tumor cells (60–62). However, the initial clinical tests did not warrant the further development of suramin as an anticancer monotherapy.

Subsequent tests focused on suramin as a chemosensitizer, based on the findings that at sub-cytotoxic levels (<50 µM), it enhanced the efficacy of anticancer drugs such as mitomycin C, taxol or doxorubicin in *ex vivo* cultures and in animal models (63–65). Suramin combined with taxol inhibited invasiveness and prevented metastasis in a xenograft mouse model (66). Different explanations are conceivable for the chemosensitizing effects of suramin on tumor cells, including inhibition of telomerase (67) or inhibition of fibroblast growth factors and angiogenesis (68). A phase II clinical study was performed in patients with advanced, drug-resistant, non-small cell lung cancer treated with taxol or carboplatin; supplementation with nontoxic doses of suramin did not overcome drug resistance (69). Randomized controlled studies to validate the use of suramin as a chemosensitizer in chemotherapy-naive lung cancer patients remain to be performed. A combination of estramustine, docetaxel and suramin gave promising results in hormone-refractory prostate cancer patients (51).

Suramin as an antidote

Three of the many biological activities of suramin support a potential use as a protective agent: the inhibition of thrombin, the inhibition of phospholipase A2, and the inhibition of purinergic signaling. Several vipers possess toxins that mimic thrombin (70), perfidiously triggering the coagulation cascade in the mammalian blood. Suramin not only inhibits thrombin itself (71) but also the thrombin-like proteases of snake venom (72), and was therefore proposed as an antidote for snakebite. Other common constituents of metazoan venoms are phospholipases A2 that convert phospholipids into lysophospholipids. Again, suramin inhibits mammalian phospholipase A2 (73) as well as the orthologs from snake venom (74–76) and bee venom (77), suggesting that it can act as an antidote. A certain degree of protection from venoms by suramin was confirmed in mouse models (77–79). The potential use of suramin as an antidote is attractive given the high global burden of snakebites (80) and the current shortage of antivenom (81).

Suramin's ability to block P2 purinergic, G protein-coupled receptors (82) may counteract the action of neurotoxins that trigger arachidonic acid signaling, e.g. via phospholipase A2 activity (83). A possible explanation is that suramin prevents the activation of ATP receptors at the motor nerve ending, which otherwise would depress Ca^{2+} currents and reduce acetylcholine release at the presynaptic membrane (84). Suramin was also proposed to serve as a neuroprotective agent (85, 86), as an antidote for kidney toxicity during cancer chemotherapy (87) and, based on its antiapoptotic effect, to protect from liver failure (88). Suramin also inhibits connexin channels of the tight junction, thereby suppressing ATP release and protecting cells from pore-forming bacterial toxins such as hemolysin (89). The suramin analogs NF340 and NF546 were cardioprotective in a mouse model for heart graft rejection, presumably via inhibition of the purinergic G protein-coupled receptor P2Y11 (90).

Further potential uses of suramin

Suramin was found to have beneficial effects in a rat arthritis model (91) and to suppress fear responses in the rat (92). It also promoted the expansion of T cells during immunization of mice and was therefore considered as a small molecule adjuvant for vaccination (93). Based on the cell danger hypothesis, suramin has recently been tested for the treatment of autism spectrum disorders (ASD). The cell danger hypothesis suggests that a systemic stress response, which involves mitochondria and purinergic signaling, contributes to the development of psychopathologies like autism. Suramin had been shown to act as an inhibitor of purinergic signaling (94) and mitochondrial function (95), and was therefore proposed as a potential therapy for ASD (96). First tests in mouse models showed correction of symptoms in juveniles (96) as well as in adults (97). A first small human trial was carried out and, even though difficult to quantify, showed improvement of ASD symptoms (98).

(Too) many targets

Suramin is a large molecule that carries six negative charges at physiological pH (Figure 1). It is likely to bind to, and thereby inhibit, various proteins (99). Thus the many and diverse potential applications of suramin reflect the polypharmacology of suramin. Indeed, a large number of enzymes have been shown to be inhibited by suramin (Table 3). Suramin inhibits many glycolytic enzymes (100, 101), enzymes involved in galactose catabolism (PubChem BioAssay: 493189) and enzymes of the Krebs cycle (102). Suramin further decreases the activity of a large number of enzymes involved in DNA and RNA synthesis and modification: DNA polymerases (103, 104), RNA polymerases (103, 105, 106), reverse transcriptase (21, 103), telomerase (67), and enzymes involved in winding/unwinding of DNA (107, 108) are inhibited by suramin, as well as histone- and chromatin modifying enzymes like chromobox proteins (109), methyltransferases (110) and sirtuin histone deacetylases (111). Suramin is also an inhibitor of other sirtuins (112) and protein kinases (113, 114), glutaminase (PubChem BioAssay: 624170), phospholipase A2 (115, 116), protein tyrosine phosphatases (117), lysozyme (118) and different serine- and cysteine-proteases (119–121). For caspases, cysteine proteases involved in apoptosis, suramin was described to act as either inhibitor or activator (122, 123). Suramin further inhibits the Na^+,K^+-ATPase and other ATPases (124–126), certain classes of GABA receptors (127, 128), and several G protein-coupled receptors (129) including P2 purinoceptors and follicle-stimulating hormone receptor (130, 131). Suramin also showed inhibitory effects against components of the coagulation cascade (71, 132) and the complement system (133–135), and against deubiquitinating enzymes (PubChem BioAssay: 504865; 463106). It also interacts with prion protein, inhibiting the conversion into the pathogenic form PrP^{Sc} (136). Beside the many inhibitory activities, suramin also activates certain nuclear receptors that act as transcription factors (137), and intracellular calcium channels (138).

Enigmatic mechanisms of action against African trypanosomes

Somewhat ironically, much less appears to be known about the targets of suramin in African trypanosomes, where it has been in use for a century, than in tumor cells or viruses. Suramin was shown to inhibit glycolytic enzymes of *T. brucei* with selectivity over their mammalian orthologues, in particular hexokinase, aldolase, phosphoglycerate kinase and glycerol-3-phosphate dehydrogenase (100). Intriguingly, the trypanosomal enzymes have higher isoelectric points (>9), which is due to extra arginines and lysines that are absent in the mammalian orthologues (165). These residues form positively charged, surface exposed 'hot spots' that were proposed to be bound by the negatively charged suramin (100). Inhibition of trypanosomal glycolysis by suramin is in agreement with the dose-dependent inhibition of oxygen consumption and ATP production observed in trypanosomes isolated from suramin-treated rats (166). However, the glycolytic enzymes of *T. brucei* are localized inside glycosomes (167), and it is unclear how suramin could penetrate the glycosomal membrane, or if suramin could bind to glycolytic enzymes in the cytosol, before they are imported into the glycosomes (168). Alternative targets proposed for the trypanocidal effect of suramin are glycerophosphate oxidase (139, 169), a serine oligopeptidase termed OP-Tb (170), and REL1 (171), the RNA-editing ligase of the trypanosome's kinetoplast. It is unclear how suramin would pass the inner mitochondrial membrane, but suramin inhibited oxidative phosphorylation in mitochondrial preparations of the trypanosomatid *Crithidia fasciculate* (172). Suramin also appeared to inhibit cytokinesis in *T. brucei*, as indicated by the finding that suramin treatment resulted in an increased number of trypanosomes with two nuclei (173).

Uptake routes of suramin into cells

The negative charges of suramin (Figure 1) not only promote binding to various proteins, they also prevent diffusion across biological membranes. However, the majority of targets (Table 3) are

intracellular, and radiolabeled suramin was shown to be taken up by human endothelial and carcinoma cells (174, 175) and by *T. brucei* bloodstream forms (166, 176). Suramin is not a substrate of P-glycoprotein (177), nor of any other known transporter. Thus suramin must be imported by endocytosis. Mammalian cells can take up suramin in complex with serum albumin by receptor-mediated endocytosis (178). This had originally also been thought to happen in *T. brucei* (166). However, the trypanosomes do not take up albumin by receptor-mediated endocytosis (179), and LDL (low density lipoprotein) was proposed to act as the vehicle instead (176). Suramin bound to LDL and inhibited the binding and uptake of LDL, while LDL enhanced the uptake of suramin in bloodstream-form *T. brucei* (176). In contrast, overexpression in procyclic *T. b. brucei* of Rab4, a small GTPase involved in the recycling of endosomes, decreased suramin binding and uptake without affecting LDL binding or uptake (180). In the same study, overexpression of a mutant Rab5, which was locked in the active, GTP-bound form, increased LDL uptake without affecting suramin uptake (180). These findings indicated that, at least in the procyclic trypanosomes of the tsetse fly midgut, LDL and suramin are imported independently of each other.

The development of genome-wide RNAi screens in bloodstream-form *T. brucei* combined with next-generation sequencing offered new opportunities to address the genetics of drug resistance. This approach identified genes, silencing of which reduced the sensitivity to suramin (181). These included a number of genes encoding for endosomal and lysosomal proteins, in agreement with uptake of suramin through endocytosis. The invariant surface glycoprotein ISG75 was identified as a likely receptor of suramin since knock-down of ISG75 in bloodstream-form *T. brucei* decreased suramin binding and suramin susceptibility (181). ISG75 is a surface protein of unknown function whose abundance is controlled by ubiquitination (182). Thus, there appear to be (at least) two pathways for receptor-mediated endocytosis of suramin in *T. brucei*

bloodstream forms: either directly with ISG75 as the receptor or, after binding of suramin to LDL, together with the LDL receptor.

Conclusion

Suramin remains controversial. Is its polypharmacology a liability or an asset? Is it toxic or protective? Dated or timeless? Whatever the verdict on suramin, there is hardly a molecule with as many biological activities. The list of potential targets is indeed impressive, and the publication stream on suramin is not stagnating. The large majority of papers is not about trypanosomes or trypanosomiasis (Figure 2). The list of potential targets has to be taken with a grain of salt, though, since the negative charges of suramin, and its promiscuity in protein binding, can cause all kinds of artefacts. Suramin can dissolve matrigel (183), resulting in a false positive signal in cell-based screening campaigns that use matrigel for support, e.g. for inhibitors of angiogenesis (183). On the other hand, suramin's high affinity to albumin (184) may give false negative results in cell-based tests that contain mammalian serum. But in spite of the various confounders, a number of different drug-target interactions for suramin have been experimentally validated, and are directly supported by crystal structures (Table 4).

Several routes of investigation on the bioactivities of suramin have culminated in clinical trials with healthy volunteers (i.e. phase I) or patients (i.e. phases II and III; Table 2). Yet, to our knowledge, none of these trials was a striking success, and it is unclear whether suramin will ever find medical applications outside the field of parasitology. However, molecules that act in a similar way than suramin may be identified via target-based screening once the mode of action is understood – new molecules that are more specific, less toxic, and possess better pharmacological properties than suramin. Thus it will be important to dissect the polypharmacology of suramin at the molecular level. We hope that the compiled list of targets (Table 3) will serve this purpose.

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833 TABLES

834

835 **Table 1.** Diseases and pathogens susceptible to suramin.

836

Disease, pathogen	Activity in cell culture	Activity in animal model	Activity in patient
Parasitic infections			
T. b. rhodesiense HAT	x	x	x
T. b. gambiense HAT	x	x	x
Surra, *T. evansi*	x	x	n.a.
River blindness, *O. volvulus*	x	x	x
Trypanosoma cruzi	x		
Leishmania spp.	x		
Plasmodium falciparum	x		
Viral infections			
Hepatitis	x	x	x
AIDS, HIV	x		x
Herpes simplex	x	x	
Chikungunya	x	x	
Enterovirus 71	x	x	
Dengue	x		
Zika	x		
Ebola	x		
Neoplastic diseases			
Non-small cell lung cancer	x	x	
Breast cancer	x	x	
Bladder cancer	x	x	
Brain tumors	x	x	
Prostate cancer	x	x	x
Other uses			
Snake bite	x	x	
Arthritis	x	x	
Autism	n.a.	x	x

837

838

839 **Table 2.** Clinical trials with suramin. Trials with a registered NCT number are from
840 ClinicalTrials.gov; others are from the literature.
841

Registry ID	Disease	Phase	Year
NCT02508259	Autism spectrum disorders	I, II	2015
NCT01671332	Non-small cell lung cancer	II	2012
NCT01038752	Non-small cell lung cancer	II	2010
NCT00083109	Recurrent renal cell carcinoma	I, II	2004
NCT00066768	Recurrent non-small cell lung cancer	I	2003
NCT00054028	Recurrent breast cancer	I, II	2002
NCT00006929	Recurrent non-small cell lung cancer	II	2000
NCT00006476	Bladder cancer	I	2000
NCT00004073	Brain and central nervous system tumors	II	1999
NCT00002921	Adrenocortical carcinoma	II	1997
NCT00003038	Advanced solid tumors	I	1997
NCT00002723	Prostate cancer	III	1996
NCT00002881	Prostate cancer	III	1996
NCT00002652	Multiple myeloma and plasma cell neoplasm	II	1995
NCT00002639	Brain and central nervous system tumors	II	1995
NCT00001381	Bladder neoplasms, transitional cell carcinoma	I	1994
NCT00001266	Prostatic neoplasm	II	1990
NCT00001230	Filariasis	observ.	1988
(16)	Solid tumors	observ.	1987
(17)	AIDS	observ.	1987
(18)	Hepatitis B	observ.	1987

842
843

844 **Table 3.** Putative target proteins of suramin, biological processes and mechanisms. Suramin acts as
845 an inhibitor or antagonist in all cases except for the pregnane X receptor and the ryanodine receptor.
846 The mode of action against caspase is controversial.
847

Putative target	Reference
Metabolism	
6-Phosphofructokinase	(100)
Fructose-l,6-bisphosphate aldolase	(100)
Glucose-6-phosphate isomerase	(100)
Glyceraldehyde-3-phosphate dehydrogenase	(100)
Glycerol-3-phosphate dehydrogenase	(100, 139)
Glycerol kinase	(100)
Hexokinase	(100)
Phosphoglycerate kinase	(100)
Pyruvate kinase	(101)
Triose-phosphate isomerase	(100)
Succinic dehydrogenase	(102)
Galactokinase	493189*
Glutaminase	624170*
Glycerophosphate oxidase	(139)
Nucleoside triphosphate diphosphohydrolase 1 & 2	(125, 126, 140–143)
Nucleotide pyrophosphatase/phosphodiesterase 1 & 3	(144)
Nucleic acids	
DNA polymerase alpha	(103, 104)
DNA polymerase beta	(103, 104)
DNA polymerase gamma	(103)
DNA polymerase delta	(104)
DNA polymerase I	(103, 104)
Terminal deoxynucleotidyltransferase	(103)
DNA primase	(103)
DNA dependent RNA polymerase	(103, 106)
RNA dependent RNA polymerase	(105)
Reverse transcriptase	(21, 103)
Telomerase	(67)
RNAse H	(145)
Flavivirus RNA helicase	(40, 107, 146)
DNA Topoisomerase II	(108)
Tyrosyl-DNA phosphodiesterase 1	(147)
Human antigen R	(148)
DNA-binding protein MCM10	(149)
Epigenetics	
Chromobox protein homologue 1 beta	488953*
Chromobox protein homologue 7	(109)
Histone methyltransferases	(110, 150)
Precorrin-4 C(11)-methyltransferase	(151)
Sirtuin 1, 2, 5	(111, 112, 152)

Protease	
Kallikrein	(121)
Alpha Thrombin	(71)
Human neutrohphil cathepsing G	(120)
Human neutrophil elastase	(120)
Human neutrophil proteinase 3	(120)
Rhodesain	(119)
Caspases 1, 2, 8, 9, 10	(122, 123, 153, 154)
Falcipain-2	(155)
Extracellular matrix	
Hyaluronidase	(156, 157)
Iduronate sulfatase	(157)
β-glucuronidase	(157)
Membrane channels and signaling	
Non-junctional connexin 43 hemichannels	(89)
Na^+,K^+-ATPase	(124)
Cystic fibrosis transmembrane regulator	(158)
Ryanodine receptor 1	(138)
$GABA_A$ receptors	(127, 128)
P2X Purinergic receptors	(94)
P2Y Purinergic receptors	(94)
N-methyl-D-aspartate receptor	(159)
DNA-dependent protein kinase	(113)
Protein kinase C	(114)
Protein tyrosine phosphatases	(117)
VIP receptor	(129)
Follicle-stimulating hormone receptor	(131)
Pregnane X receptor	(137)
Diadenosine tetraphosphate hydrolase	(160)
Other	
Prion (Prp^C)	(136)
Complement factors	(121, 133–135)
Phospholipase A_2	(116, 161)
Lysozyme	(118)
Antimicrobial Peptide CM15	(162)
Ubiquitin carboxyl-terminal hydrolases 1 & 2	504865; 463106*
HSP 60 chaperonin system	(163, 164)
GroEL chaperonin system	(163, 164)

848 *PubChem BioAssay, last retrieved 29.04.2019

849

850 **Table 4.** Solved structures of suramin complexed to target proteins.

851

PDB id	Protein	Reference
6CE2	Myotoxin I from *Bothrops moojeni*	(75)
4YV5	Myotoxin II from *Bothrops moojeni*	(74)
1Y4L	Myotoxin II from *Bothrops asper*	(116)
3BJW	Ecarpholin S from *Echis carinatus*	(76)
1RML	Acid fibroblast growth factor	(185)
n.a.	Human epidermal growth factor (hEGF)	(186)
4X3U	CBX7 chromodomain	(109)
3BF6, 2H9T	Human thrombin	(187)
2NYR	Human sirtuin homolog 5	(112)
3PP7	*Leishmania mexicana* pyruvate kinase	(101)
3GAN	*Arabidopsis thaliana* At3g22680	n.a.
3UR0	Murine norovirus RNA-dependent RNA polymerase	(105)
4J4V	Pentameric bunyavirus nucleocapsid protein	(188)
4J4R	Hexameric bunyavirus nucleocapsid protein	(188)

852

853

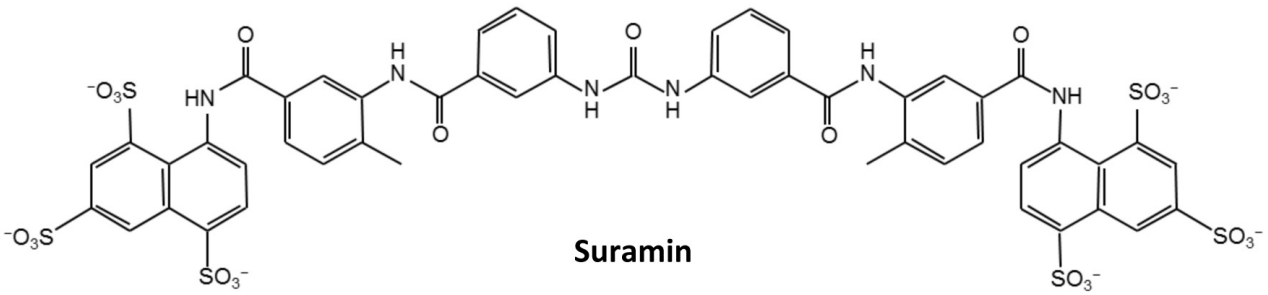
854 FIGURE LEGENDS

855

856 **Figure 1.** Suramin structure and medicinal chemistry parameters. Except for its good solubility in
857 water, suramin lacks lead-like properties as defined e.g. by Lipinsky's rule of 5.

858

859 **Figure 2.** Publications on suramin in PubMed. Cumulative numbers are shown for papers on
860 suramin and trypanosomes or trypanosomiasis (black, search term "trypanosom*"), cancer (red,
861 "cancer OR tumor"), viruses (yellow, "virus OR viral OR hiv OR aids"), and toxins (green, "toxin
862 OR venom"). Other papers on suramin are shown in beige. There is no saturation yet. And it is
863 surprising that only a minority of the publications on suramin actually deal with trypanosomes.



Suramin

Molecular weight	1297 Da
H-bond donors	12
H-bond acceptors	23
logP	0.00023
Protein binding	99.7%
Metabolites	none
Biological half-life	44-54 days
Metabolites	none
Elimination pathway	urinary