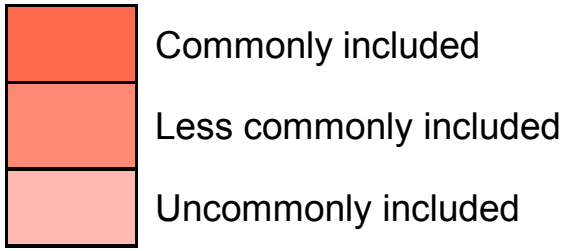
Metalloid and Metal-Based Drugs

- **Metalloid-based drugs**

Metalloids are the elements which possess the qualities of metals as well as non metals, hence they are also known as semimetals.

Metalloids in the periodic table are placed between the metals and the non metals and are located in a step-like structure.

	13	14	15	16	17
2	B	C	N	O	F
3	Al	Si	P	S	Cl
4	Ga	Ge	As	Se	Br
5	In	Sn	Sb	Te	I
6	Tl	Pb	Bi	Po	At



Properties of metalloids

•Metalloids are usually characterized as metallic-looking brittle solids with intermediate to relatively good electrical conductivities, and each has the electronic band structure of a semimetal or semiconductor.

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•Chemically, they behave as non metals when they react with metals and behave as metals when they react with non metals.
They are amphoteric oxides which means they can behave as basic oxides as well as acidic oxides.

Uses of Metalloids

- Metalloids are too brittle to have any structural uses in their pure forms.
- Typical applications have instead encompassed their presence in, or specific uses as, glasses, fire retardants, alloying components, semiconductors, electronics, and optical storage media.

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- They are also used in many biological processes.
- B, Si, As and Se are essential trace elements.
- All metalloid elements have toxic and medicinal properties to greater
- or lesser degrees.

- **Application of metalloids**
- **in medicinal chemistry**

Arsenic (As)

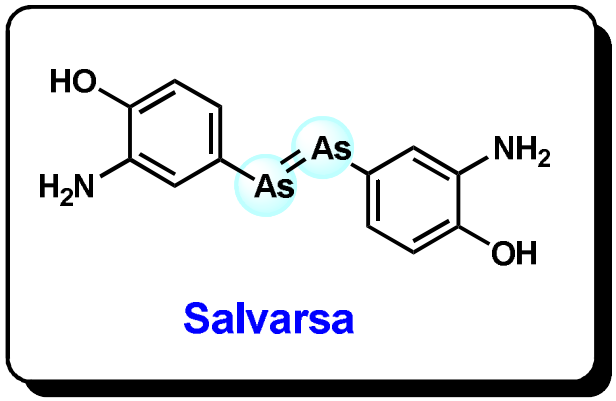
Arsenic compounds resemble in some respects those of phosphorus, which occupies the same group of the periodic table.

Arsenic disrupts ATP production through several mechanisms. By competing with phosphate, arsenate uncouples oxidative phosphorylation.

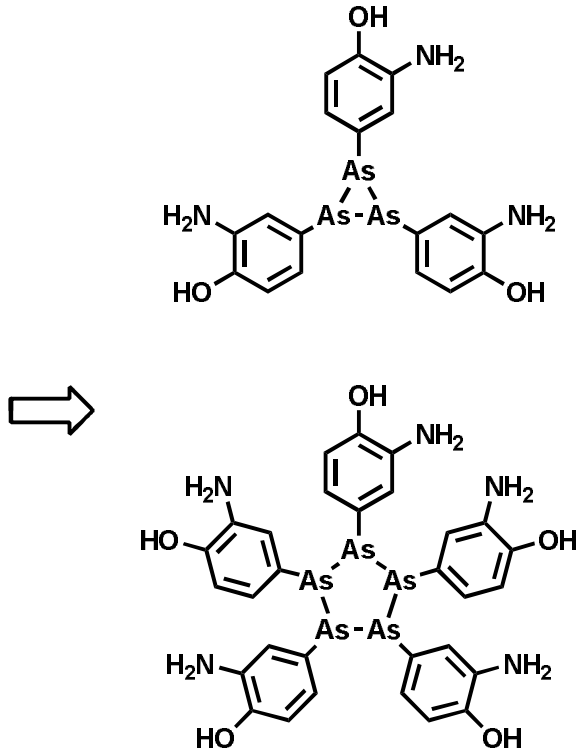
The toxicity of arsenic to insects, bacteria and fungi led to its use as a wood preservative or as a feed additive. Arsenic was also used in various agricultural insecticides, termination and poisons.

Salvarsan

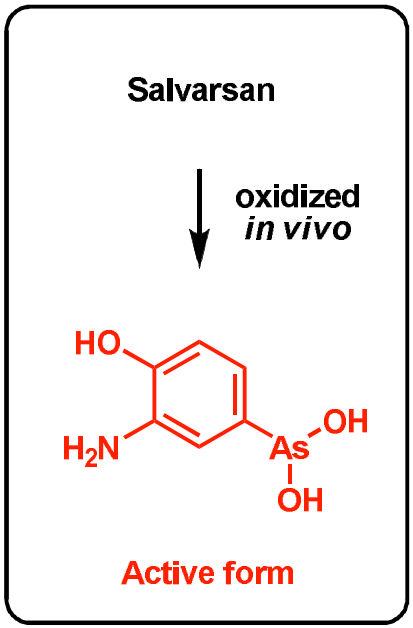
Salvarsan was the first chemotherapeutic compound that was introduced in 1910 as the effective treatment for syphilis. Salvarsan came with considerable risk of side effects, nevertheless demand for this compound remained very strong until 1943 when penicillin became available.



Assigned structure by Ehrlich in 1910

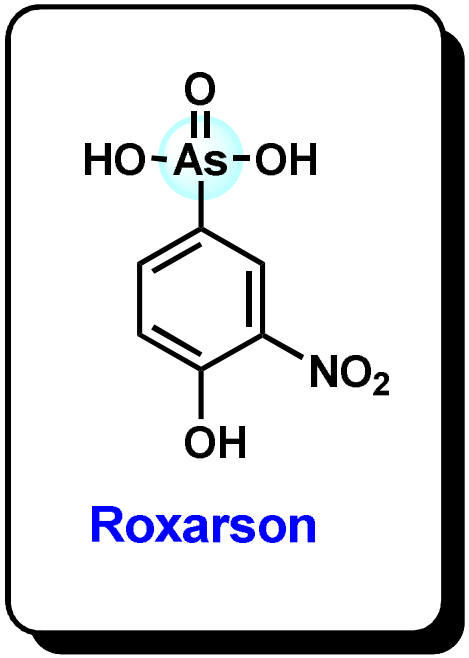


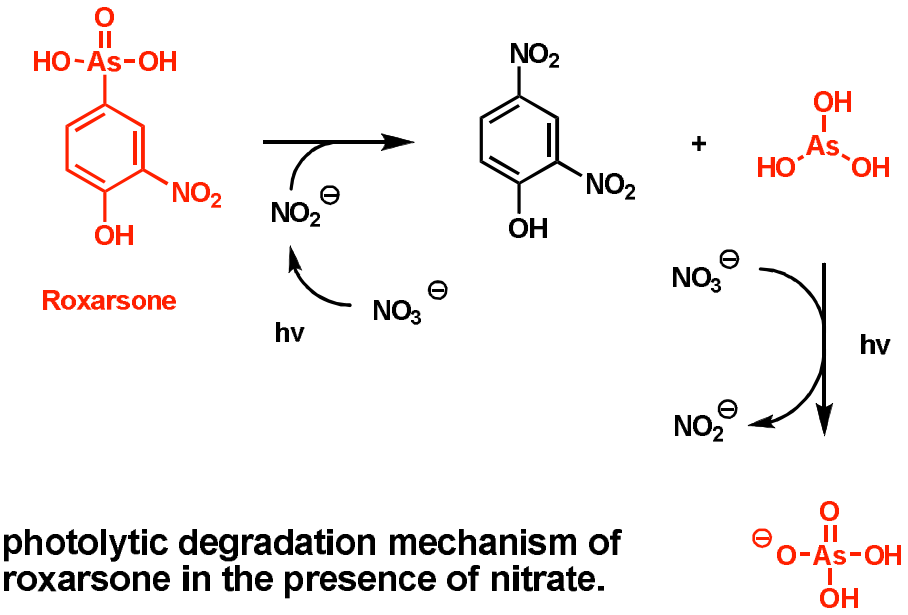
Revised structures by Nicholson in 2005
(trimer and pentamer mixture)



Roxarsone

Roxarsone is widely used agriculturally as a chicken-feed additive to help prevent coccidiosis (a parasitic disease). About 1 million kgs of this compound were produced in 2006 in the US.
In 2011, Pfizer voluntarily discontinued selling this product; the FDA's findings indicated elevated levels of arsenic in the livers of chickens consuming the arsonic acid.



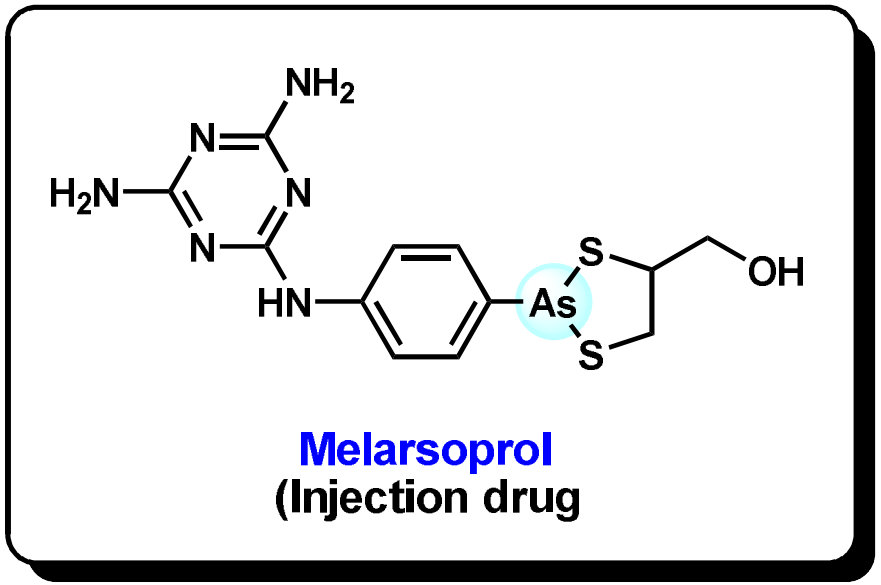


photolytic degradation mechanism of roxarsone in the presence of nitrate.

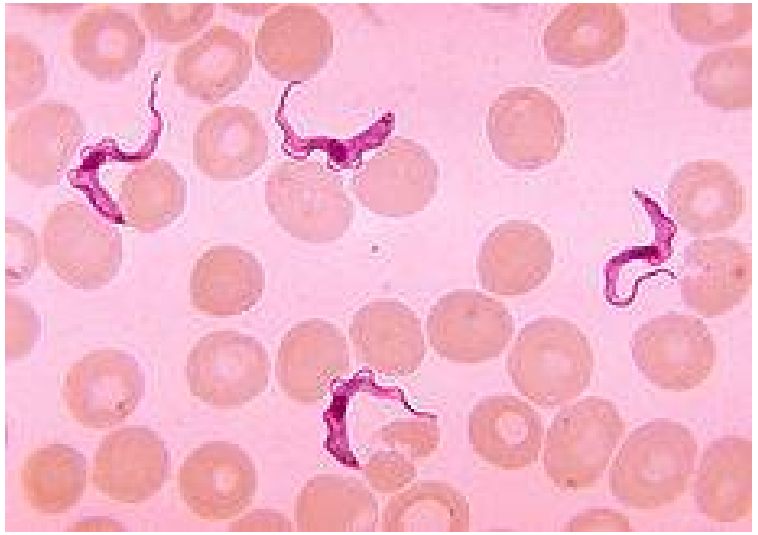
Roxarsone can degrade in poultry litter leachates to produce more toxic inorganic forms of arsenic, such as arsenite and arsenate.

Melarsoprol

Melarsoprol is now widely used in the treatment of late-stage human African trypanosomiasis (sleeping sickness). Melarsoprol is extremely toxic to humans, causing life-threatening brain disease in about 5–10 percent of patients. The mechanism of action has never been entirely understood.



Trypanosoma



Sleeping sickness is a parasitic disease caused by *Trypanosoma brucei* transmitted by the tsetse fly.
About 48,000 people died of it in 2008.

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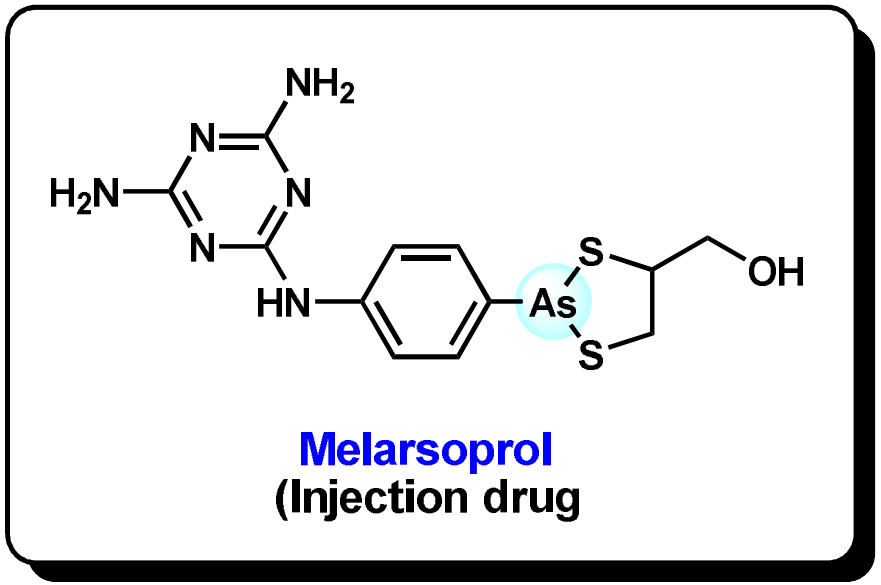
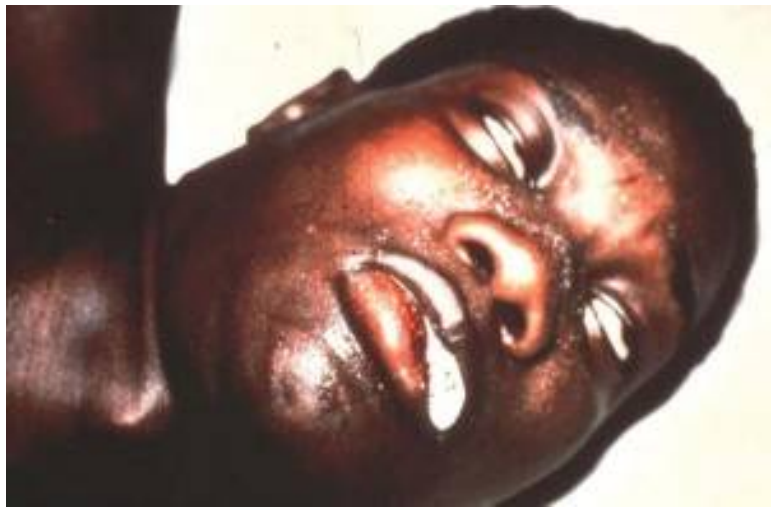


Sleeping sickness image



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Boron (B)

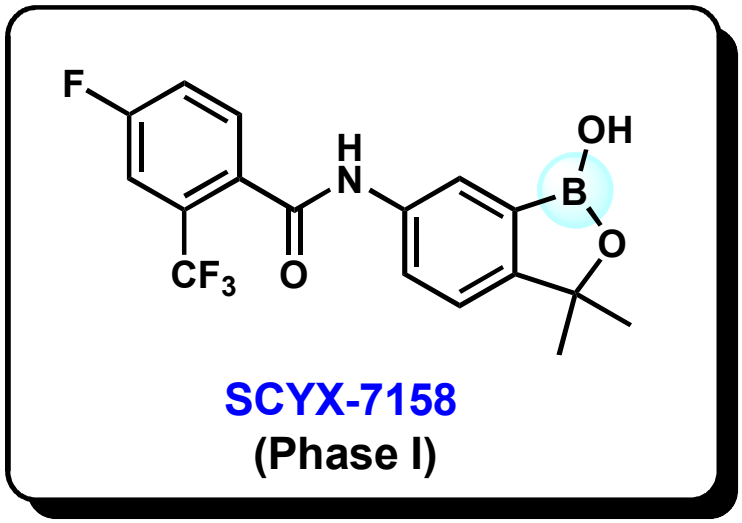
Boron atom has a vacant orbital which generates a new stable interaction between a boron atom and a donor molecule through a covalent bond.

In biology, borates have low toxicity in mammals (similar to table salt), but are more toxic to arthropods and are used as insecticides.

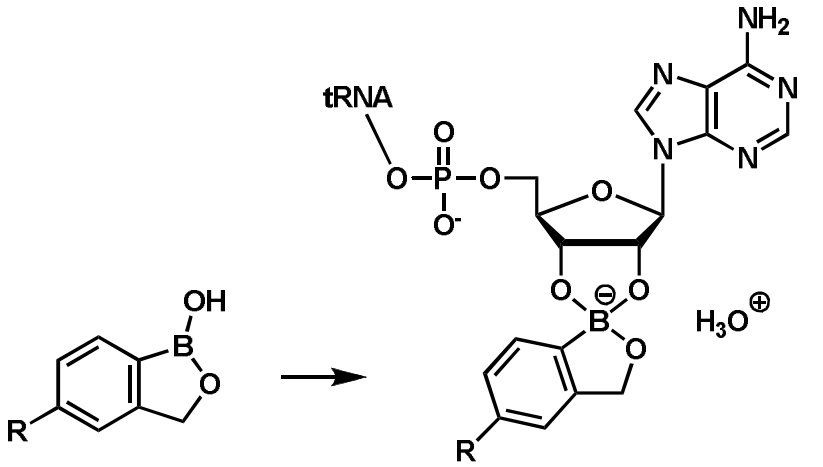
Boric acid has antiseptic, antifungal and antiviral properties and for this reasons is applied as a water clarifier in swimming pool water treatment and eye antiseptics.

Benzoxaboroles

Benzoxaboroles were developed by Anacor as oral treatment for human African trypanosomiasis (sleeping sickness). **SCYX-7158** was shown to be safe and exhibited excellent *in vivo* PK and *in vivo* efficacy.



SCYX-7158
(Phase I)

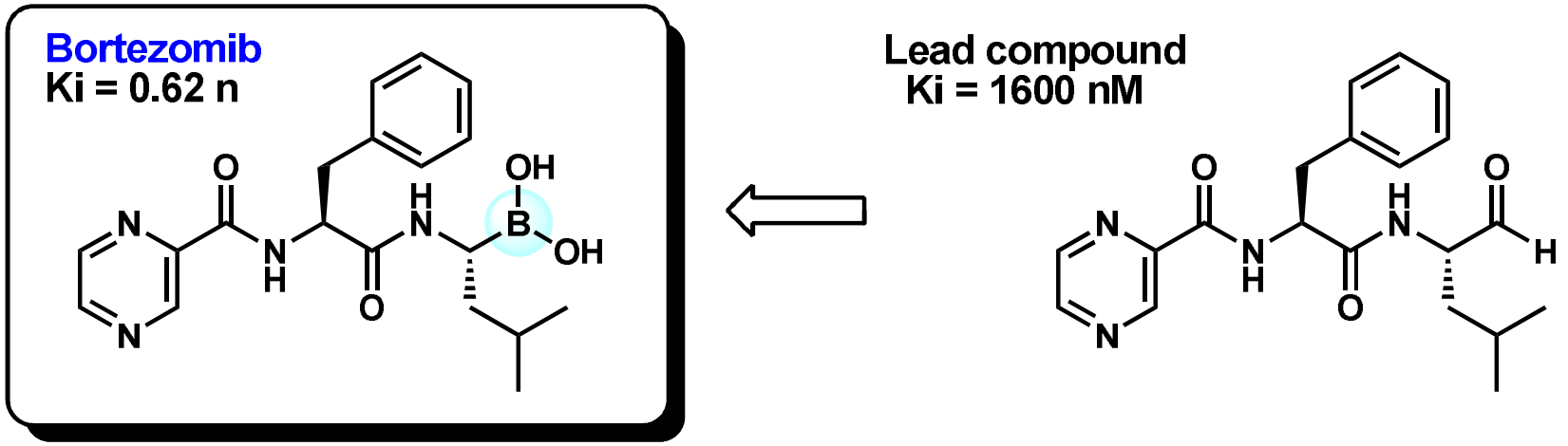


$tRNA^{Leu}$ - benzoxaborole adduct

The mechanism by which SCYX-7158 is trypanocidal is currently unknown.
Other antifungal benzoxaboroles developed by Anacor inhibit Leucyl tRNA Synthetase by trapping tRNA on the fungal enzyme.

Bortezomib (VELCADE®)

Bortezomib is the first-in-class proteasome inhibitor for the treatment of multiple myeloma (a plasma cell cancer) approved in the US in 2003. Multiple myeloma was an incurable malignancy that was diagnosed in about 15,000 people in the US each year.



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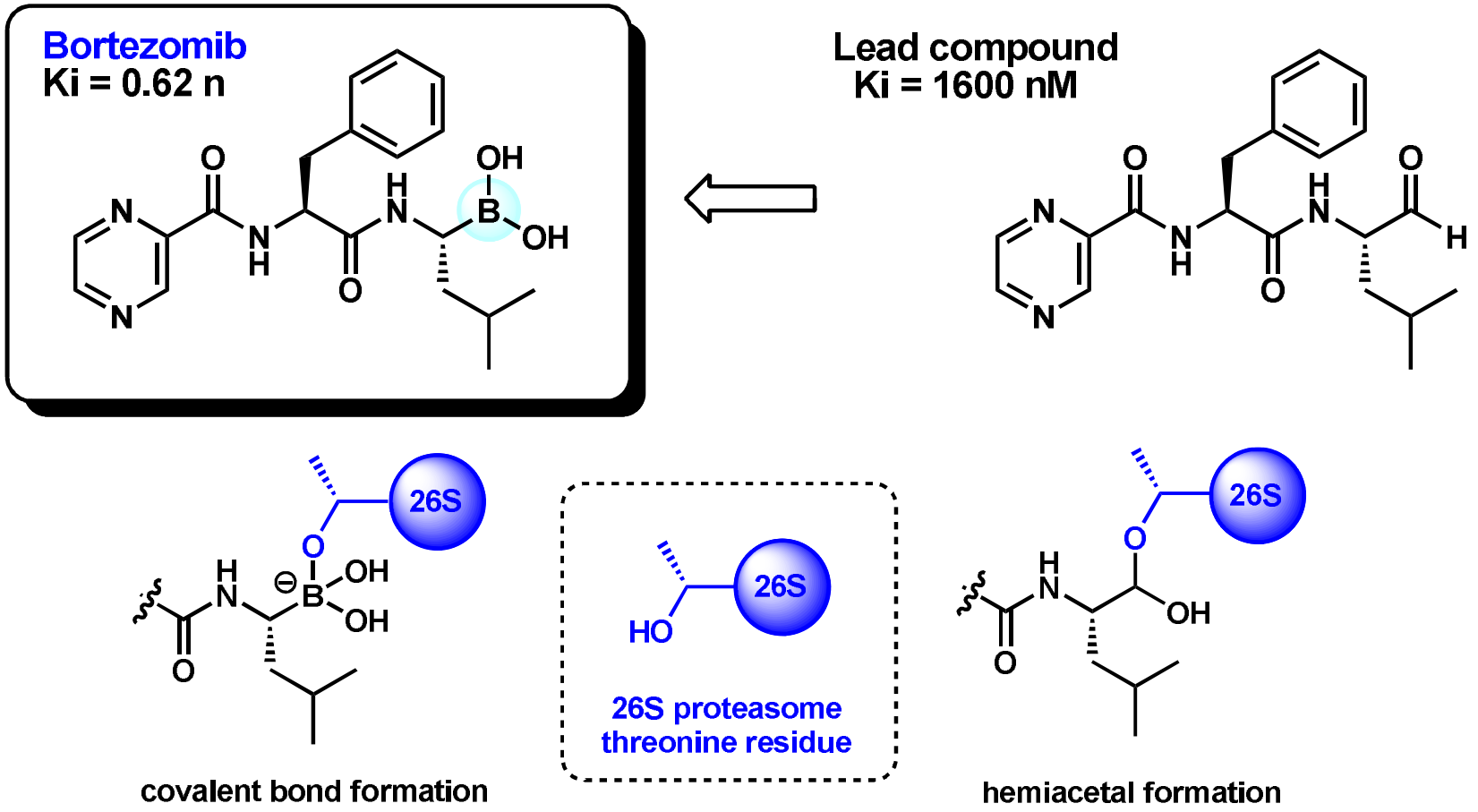
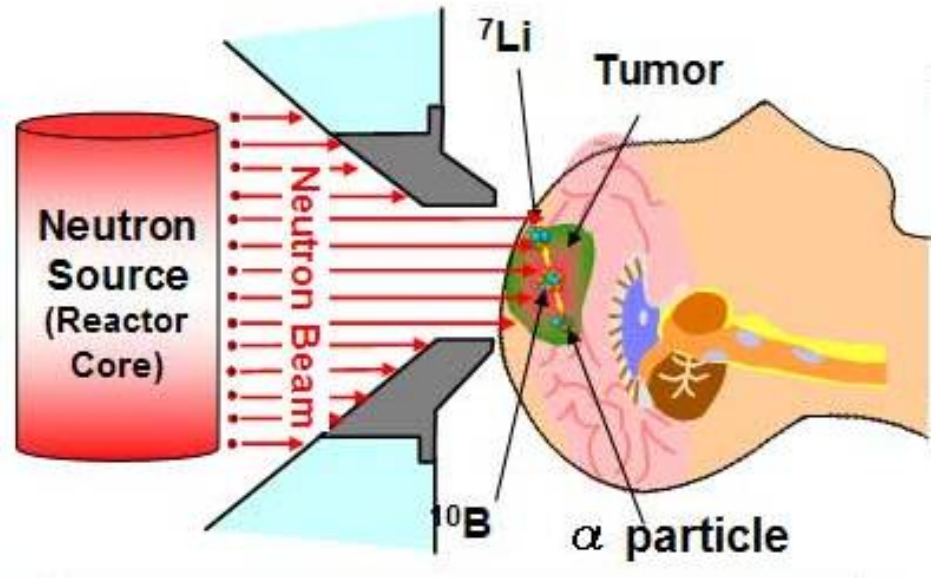
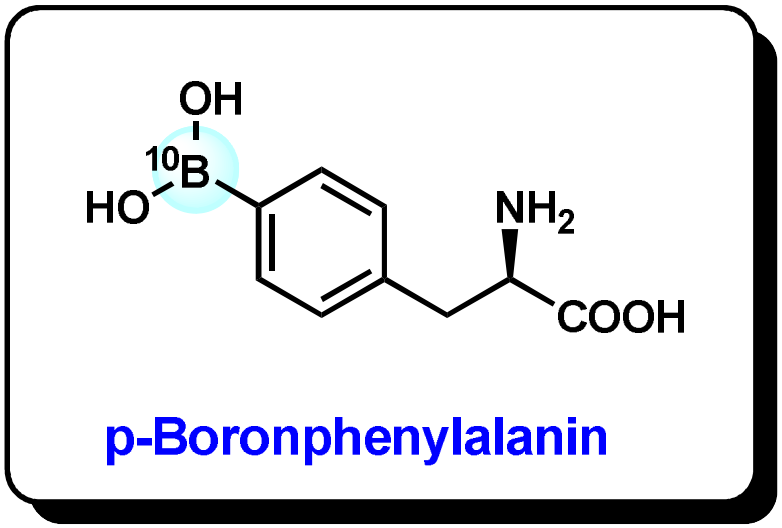


Boron neutron capture therapy (BNCT)

BNCT is a combination of treatment with boron and low energy neutrons. Radiotherapy using neutrons can get rid of glioblastoma cells. The boron molecules give off radiation within the brain tumor cells when the external neutron radiation hits them.





1. ^{10}B compound which accumulates in the cancer cell is injected in a patient
2. The neutron beam is irradiated to the lesion
3. The cancer cells are selectively destroyed using α-particles which are generated by the ^{10}B

Silicon (Si)

Silicon and carbon have similar properties because of their adjacent positions in group 14 of the periodic table.

There is no known intrinsic “element-specific” toxicity associated with organosilicon small molecules.

Silicones (silicon containing polymers) are used in the applications requiring high biocompatibility such as bandages, breast implants and contact lenses.

Chemical properties of silicon

The medicinal applications of organosilicon molecule are particularly interesting because of differences in the chemical properties of organosilicon molecules compared to carbon-based functional groups.

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Chemical properties of organosilicon

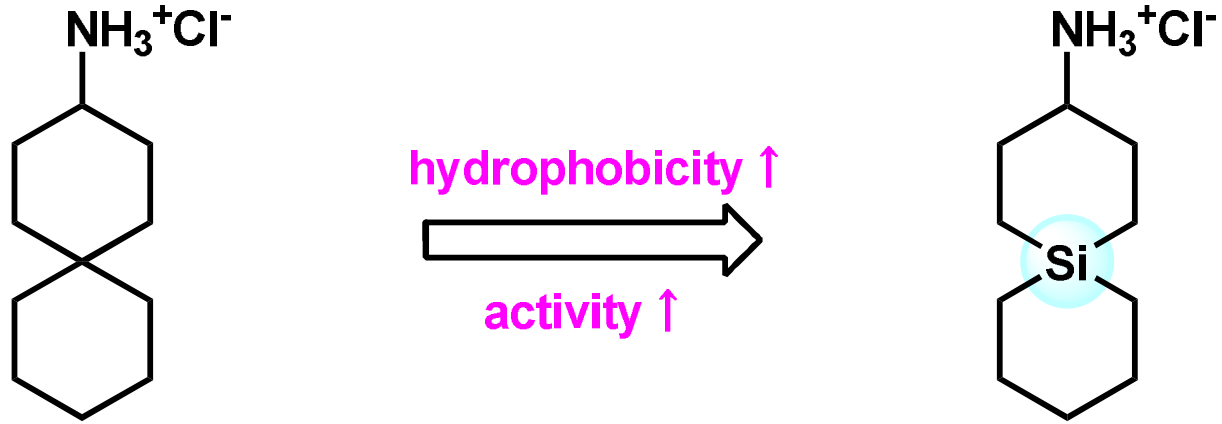
1) The larger covalent radius of silicon contributes to about 20% longer bond lengths and different bond angles

2) The increased lipophilicity of organosilicon often enhances cell penetration and alters the potency and selectivity

3) The electropositive nature of silicon contributes to an electron deficient center in a molecule and reversed bond polarization

Replacement of quaternary C with Si

In the influenza A virus M2 proton channel inhibitor, hydrophobicity is known to play a critical role in improving the antiviral potency. The larger size and increased lipophilicity of silicon can provide a better hydrophobic contact between the inhibitor and the channel.



Spirane amine

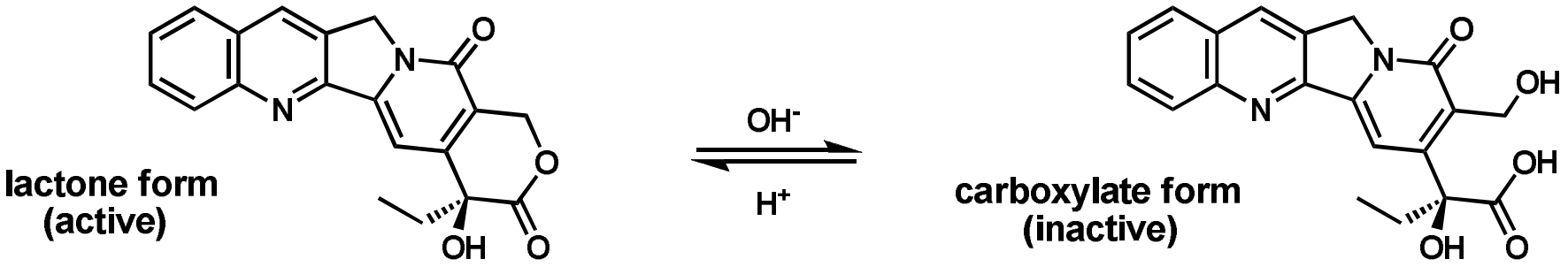
IC_{50} = 84.9 μM

Silaspirane amine

IC_{50} = 31.3 μM

Trialkylsilyl derivatives of drugs

Camptothecin (CPT) is a natural quinoline alkaloid which inhibit DNA topoisomerase I for the treatment of solid tumors. CPT contains an α-hydroxy γ-lactone, which reacts with H_2O to form inactive ring-opened structure. The trialkylsilyl analogs have been designed to increase the stability of γ-lactone.



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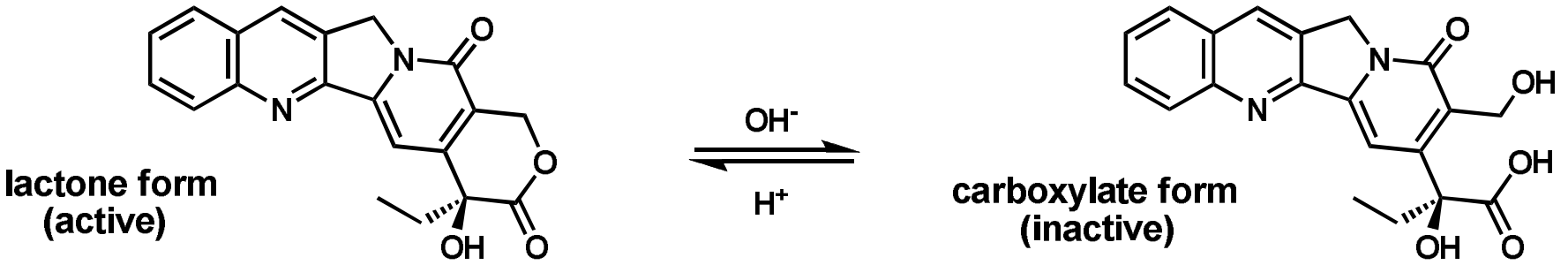
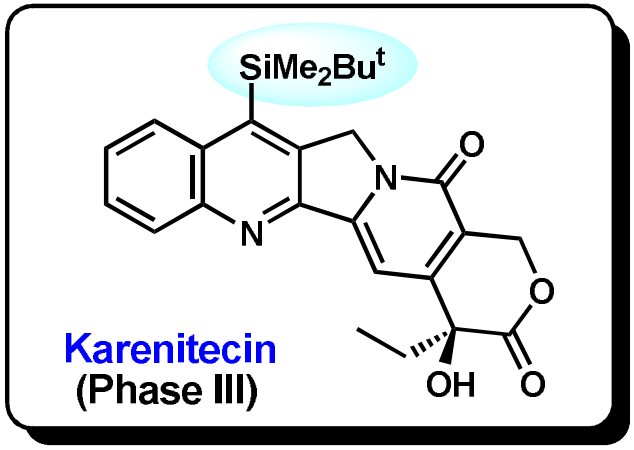
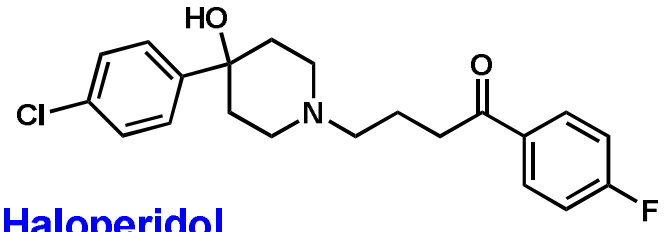


lipophilicity ↑
stability ↑



Silanol as an isostere of alcohol

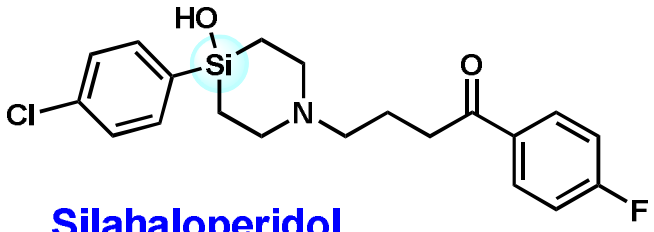
A clinically useful antipsychotic drug, **haloperidol** is associated with a problematic metabolic pathway. The sila-analogs show a higher potency and selectivity than haloperidol and avoid the formation of a toxic metabolite.



Haloperidol

Ki (hD_2) = 2.84 nM
hD_2 / hD_1 = 37.6

selectivity ↑
activity ↑



Silahaloperidol

Ki (hD_2) = 0.55 nM
hD_2 / hD_1 = 294.5

Silanol as an isostere of alcohol

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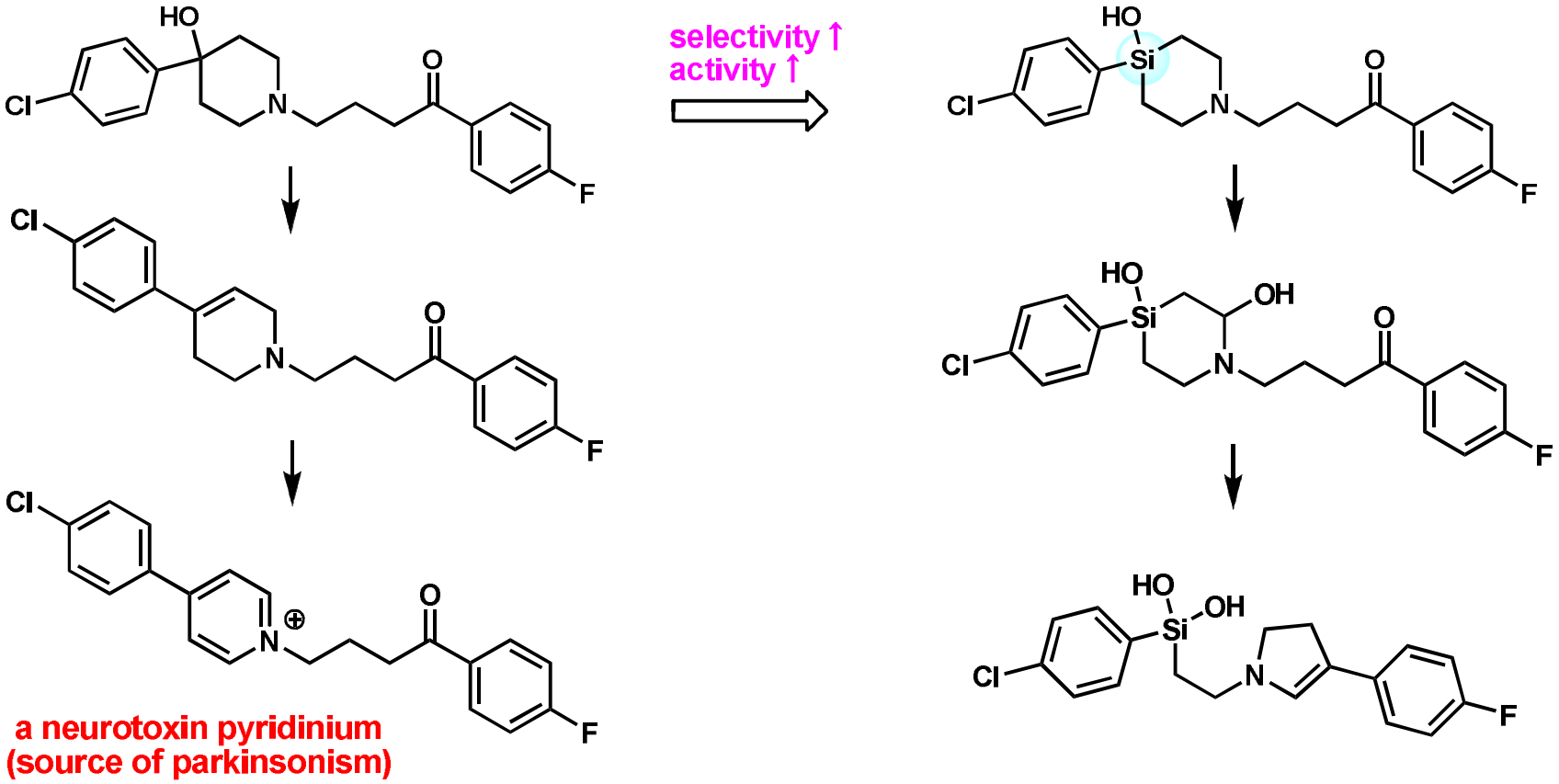
Metabolic pathways



Selenium (Se)

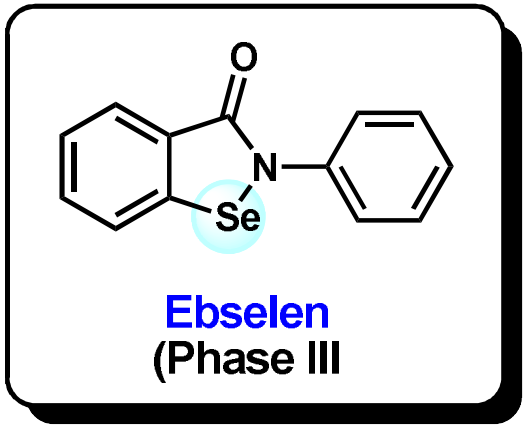
Selenium belongs with oxygen and sulfur in the group of 16, so similarities in chemistry are to be expected.

The beneficial effects of selenium are strongly dependent on its concentration. Selenium salts are toxic in large amounts, but trace amounts are necessary for cellular function in many organisms, including all animals.

Selenium deficiency has been implicated in a number of serious or chronic diseases, such as cancer, diabetes, AIDS and tuberculosis.

Ebselen

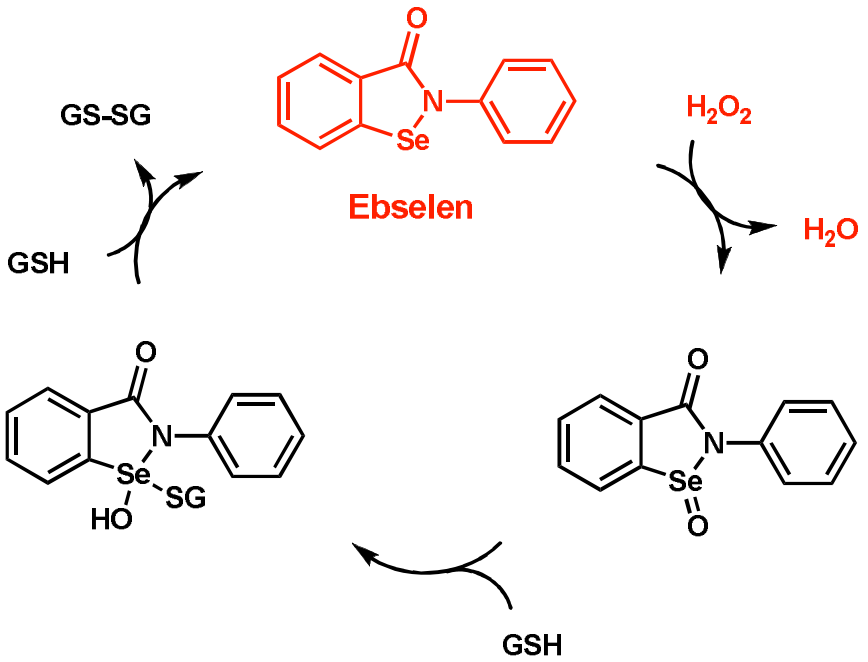
Ebselen is a mimic of the antioxidant enzymes glutathione peroxidase (GPx), which is a potent scavenger of hydrogen peroxide as well as hydroperoxides. It is being investigated as a possible treatment for stroke, tinnitus and manic depression.



Glutathione peroxidase reduce free hydrogen peroxide to water.

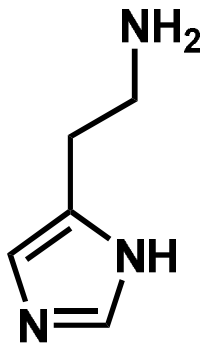
$$2GSH + H_2O_2 \xrightarrow{GPx} GS\text{-}SG + H_2O$$

(GSH : glutathione)



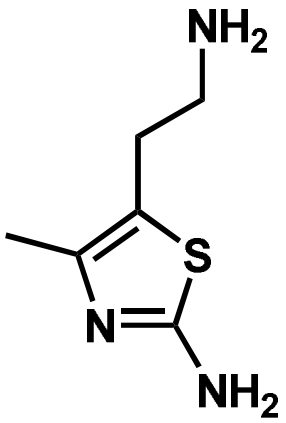
Amselamine

Amselamine, which is the seleno analog of amthamine, behave as a histamine H_2-agonist with a higher potency than histamine and amthamine. Moreover amselamine exerts hardly any activity for histamine H_1 and H_3-receptors, which make it selective for the H_2-receptor.



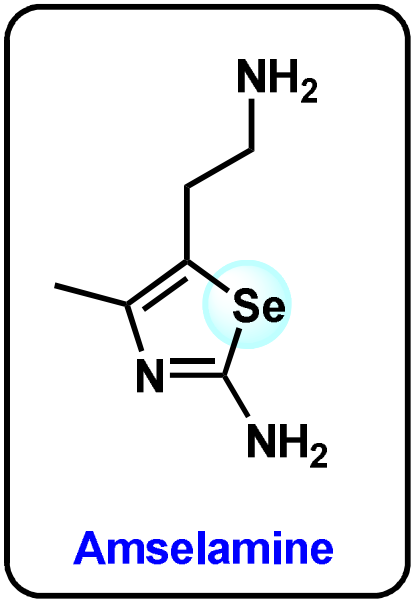
Histamine

pD_2 = 6.14



Amthamine

pD_2 = 6.21



Amselamine

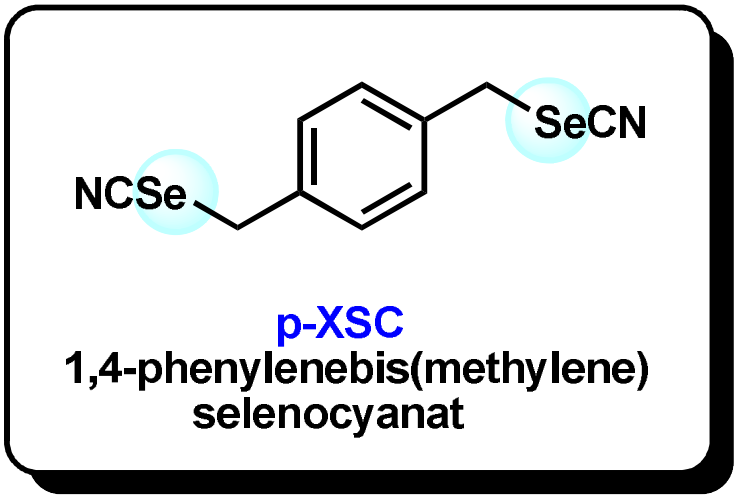
pD_2 = 6.41

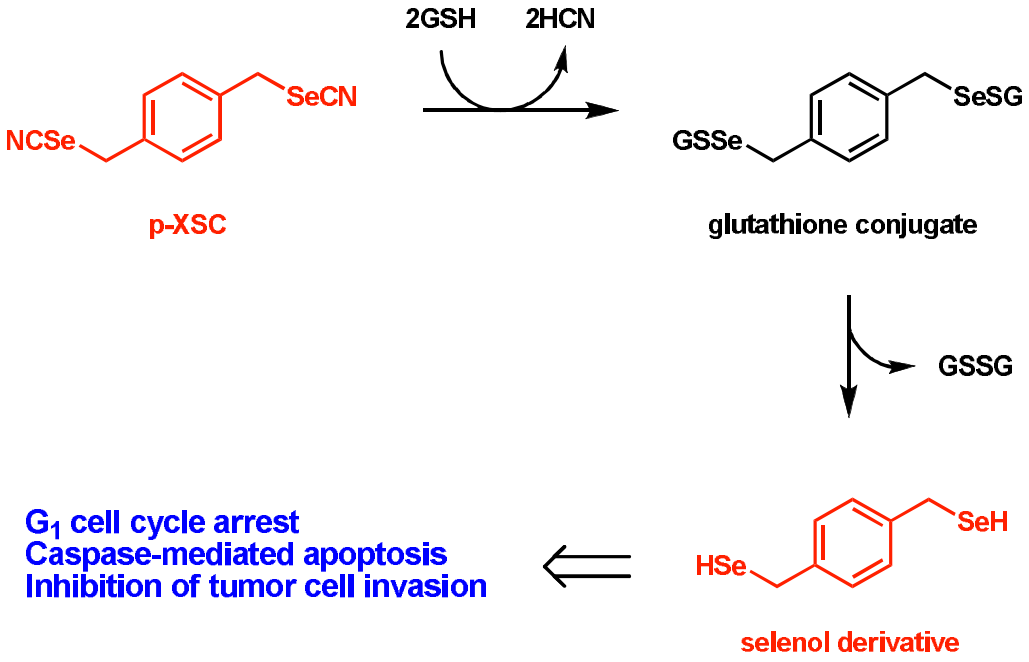
The pD_2 values are derived from the 50% level of the maximum response of the histamine H_2-agonitic dose response curve.

The selenazole ring of amselamine is somewhat more basic than the thiazole ring of amthamine

p-XSC

p-XSC exerts chemopreventive activity for carcinogenesis in colon, lung, liver, intestine and oral tissues. It is has been hypothesized that p-XSC is metabolized to the selenol, which inhibit tumor progression.





The selenol moiety has been hypothesized to be a critical selenium metabolite for anticancer activity in vivo

- **Metal-based drugs**

Biological metals

- Metals are essential for the biological processes of about 30-40% of
- all known proteins including metalloenzymes which require metal cofactors.

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•harmful for the body.

•Examples of specific types of metal deficiency include:

•Fe Iron deficiency results in the loss of functional heme proteins,
• which are responsible for oxygen transport or utilization of oxygen.
•Zn Zinc deficiency due to diet can result in growth retardation.
•Cu Copper deficiency in infants results from infants with a poor diet
• and can cause heart disease.

Metal in medical treatment

•Metals have been used in treatments since ancient times. The Ebers Papyrus from 1500BC is the first written account of the use of metals for treatment and describes the use of Cu to reduce inflammation and the use of Fe to treat anemia.

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•The application of metals to medicine is a rapidly developing field and novel therapeutic and diagnostic metal complexes are now having an impact on medical practice.

Examples of metal-based drugs

Metal	Product name	Active compound	Medical usage
Li	Camcolit	Li_2CO_3	manic depression
Mg	Magnesia	MgO	laxative
Fe	Fenelmin	$Na_4Fe(II)(citrate)$	anemia
Co	Cobaltamin S	Vitamin B_{12}	supplement
Zn	Calamine	ZnO	skin ointment
Ba	Baridol	$BaSO_4$	X-ray contrast medium
Pt	Cisplatin	cis-$[Pt(NH_3)_2Cl_2]$	anticancer
Au	Auranofin	$Au(I)(PEt_3)$ (acetylthioglucose)	rheumatoid arthritis
Bi	De-Nol	$K_3[Bi(III)(citrate)_2]$	antiulcer

- **Application of metals**
- **in medicinal chemistry**

Platinum (Pt)

Platinum-based antineoplastic drugs are chemotherapy-agents to treat cancer.

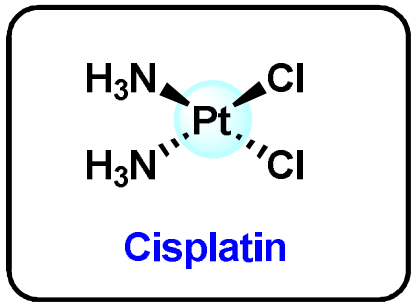
They cause crosslinking of DNA as intrastrand crosslinks or DNA protein crosslinks.

The resultant crosslinking inhibit DNA repair and/or DNA synthesis in cancer cells.

The main dose-limiting side effects of cancer treatment with platinum compounds are nephrotoxicity and peripheral neurotoxicity.

Cisplatin

Cisplatin is the first member of a class of platinum-containing anticancer drugs approved by FDA in 1978. It is used to treat various types of cancers, including sarcomas, some carcinomas, lymphomas, and germ cell tumors.



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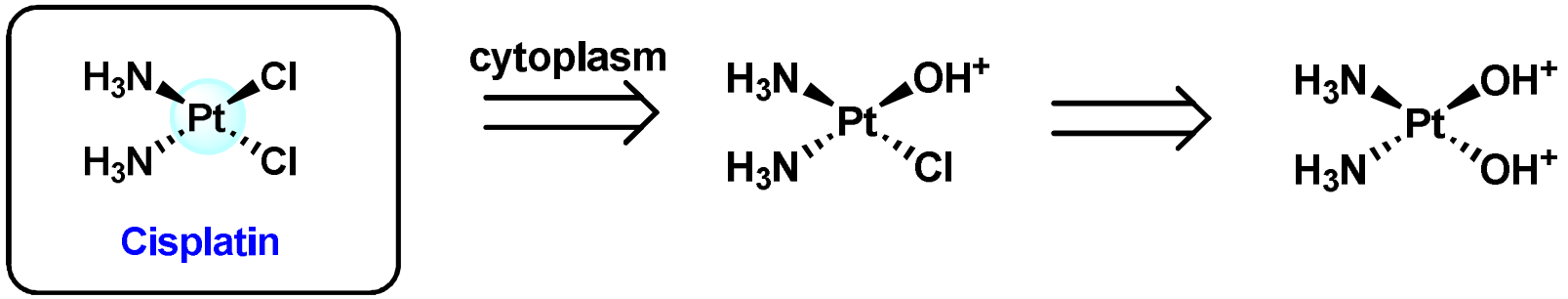

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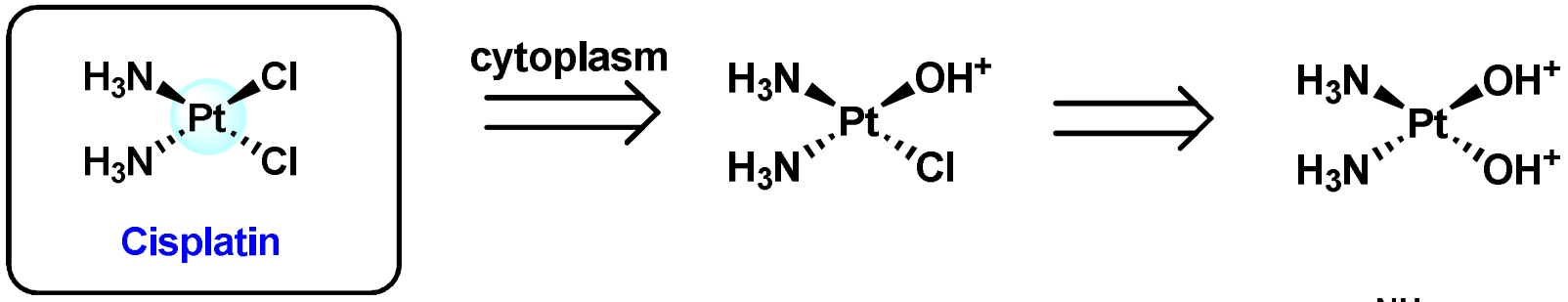
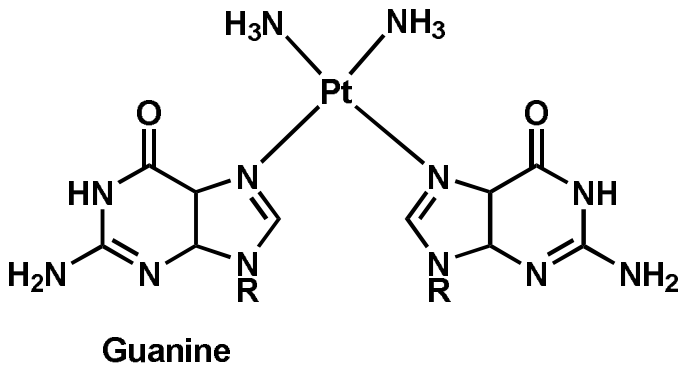
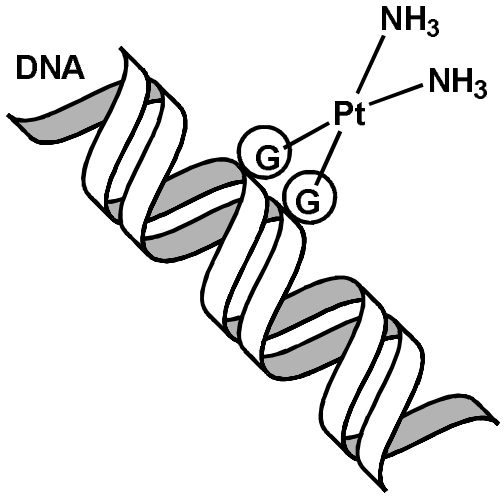
Cisplatin is the first member of a class of platinum-containing anticancer drug approved by FDA in 1978. It is used to treat various types of cancers, including sarcomas, some carcinomas, lymphomas, and germ cell tumors.



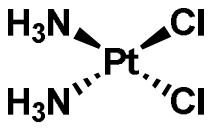




Cisplatin metabolites react with N(7) of guanine in DNA and form intrastrand crosslinks, which ultimately triggers apoptosis.

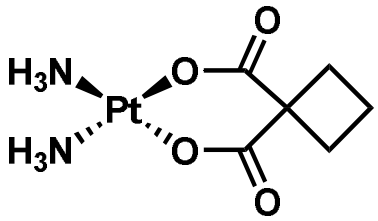
Carboplatin and Oxaliplatin

Carboplatin and **Oxaliplatin** were subsequently introduced and have since gained popularity in clinical treatment due to its vastly reduced side-effects compared to cisplatin.



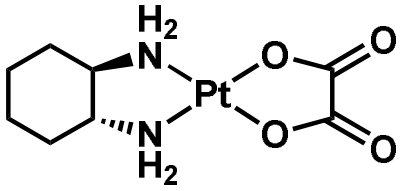
Cisplatin
(1st generation)
1978

Treating various types of cancers
Side Effect : Nephrotoxicity, nausea and vomiting



Carboplatin
(2nd ganeration)
1989

Relative to cisplatin, nephrotoxic effects have been eliminated
Nausea and vomiting are less severe



Oxaliplatin
(3rd generation)
1996

Active against some cisplatin-resistant cancers

Gold (Au)

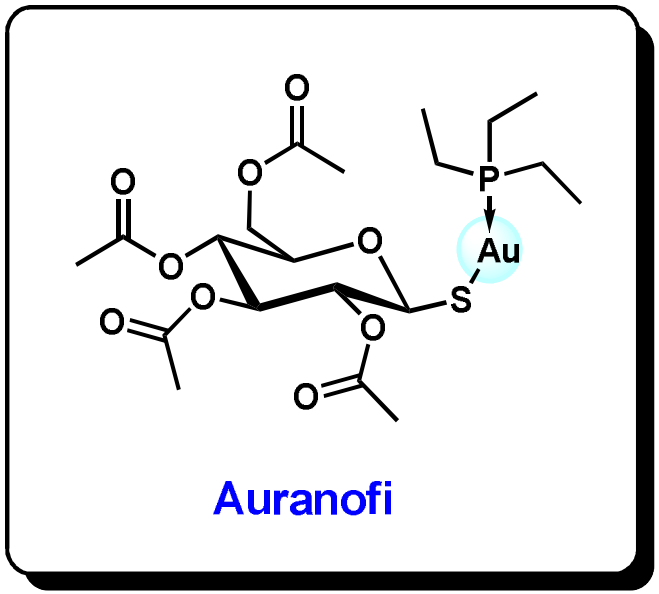
The first reports of gold drugs appeared in 1935, primarily to reduce inflammation and to slow disease progression in patients with rheumatoid arthritis.
The mechanism by which these drugs affect arthritis is still unknown.

One noticeable side-effect of gold-based therapy is the coloring of the skin in shades of mauve to a purplish dark grey when exposed to sunlight.

The application of gold to medicine is called “chrysotherapy”.

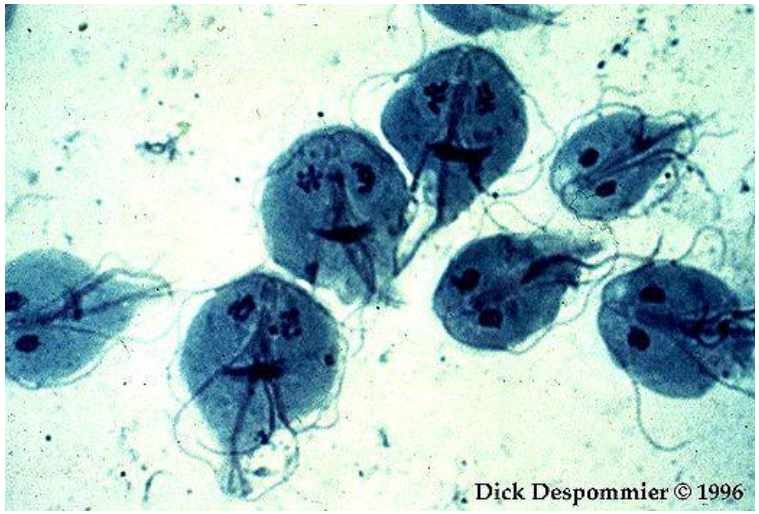
Auranofin (REDAURA®)

Auranofin is an oral drug approved for treating rheumatoid arthritis in 1985.
In 2012, Auranofin was identified as the protozoan agent of human amebiasis.
It targets the thioredoxin reductase, preventing the reduction of thioredoxin to reactive oxygen-mediated killing.



Auranofi

Amebiasis



Amebiasis is the fourth leading cause of death due to protozoan infections worldwide, resulting in 70,000 deaths annually.
FDA has applied for approval to start clinical trials to treat amebiasis.

Bismuth (Bi)

Bismuth is a highly acidic metal ion and may allow it to block Ca^{2+} channels and to disrupt the cell walls of bacteria.

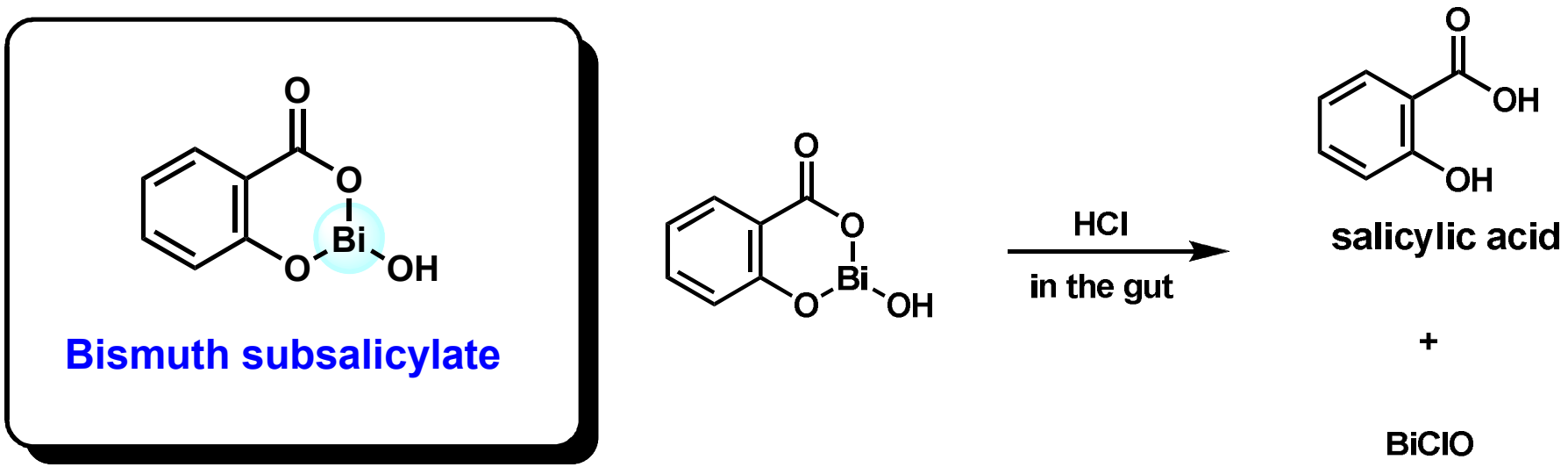
These are also active against the bacterium *Helicobacter pylori* which is associated with the mucus layer of ulcers and cancers

Bismuth drugs are used to treat occasional upset stomach, heartburn, and nausea. It is also used to treat diarrhea.

Overexposure to bismuth can result in the formation of a black deposit on the gingiva, known as a bismuth line.

Bismuth subsalicylate

Bismuth subsalicylate is a drug used to treat temporary discomforts of the stomach and gastrointestinal tract. Commonly known as pink bismuth, it is the active ingredient in popular medications such as Pepto-Bismol.



Salicylic acid produces its anti-inflammatory effects via suppressing the activity of cyclooxygenase (COX).

BiClO remains in the stomach, and is in intimate contact with the mucus layer, where it stimulates mucus, bicarbonate and prostaglandin secretion.

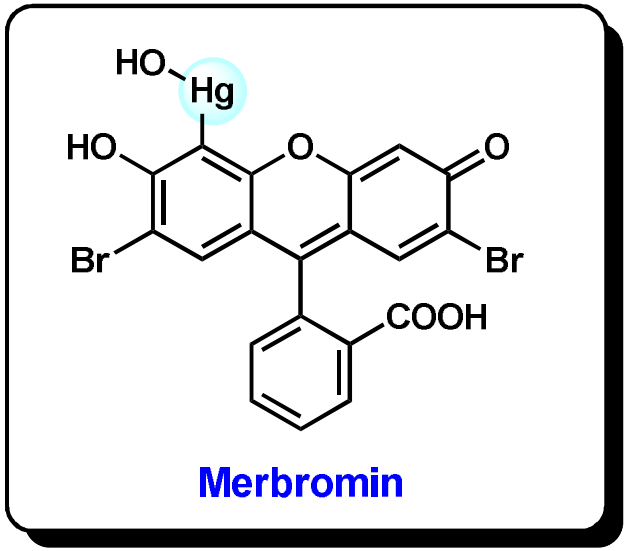
Mercury (Hg)

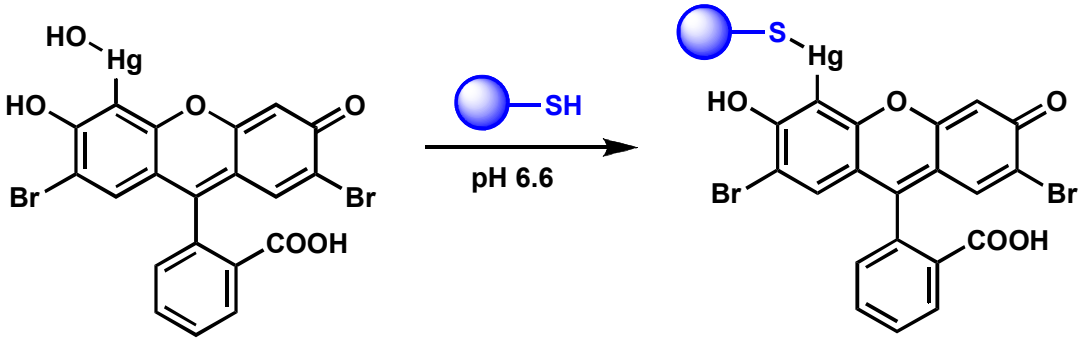
In China, mercury use was thought to prolong life, heal fractures, and maintain generally good health, although it is now known that exposure to mercury leads to serious adverse health effects.

Today, the use of mercury in medicine has greatly declined in all respects, especially in developed countries. Mercury compounds are found in some over-the-counter drugs, including topical antiseptics, stimulant laxatives, diaper-rash ointment, eye drops, and nasal sprays.

Merbromin

Merbromin is a topical antiseptic drug discovered in 1918. This chemical soon became popular among parents and physicians for everyday antiseptic uses. It is readily available in most countries, but because of its mercury content, it is no longer sold in the US, Germany and France.





Merbromin is expected to react with thiol residues of enzyme to form a mercury sulfur bond to inhibit the enzyme activity.

It is still an important antiseptic, particularly in developing nations, due to its “unbelievably low cost”.

Ruthenium (Ru)

As ruthenium is in the same group as iron, ruthenium complexes are able to take advantage of the body's ability to efficiently transport and uptake of iron.

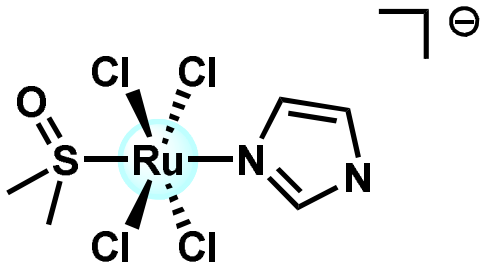
In recent years, ruthenium-based molecules have emerged as promising antitumor and antimetastatic agents.

Ruthenium compounds are usually less toxic and no cross resistant than platinum counterparts, therefore better tolerated *in vivo*.

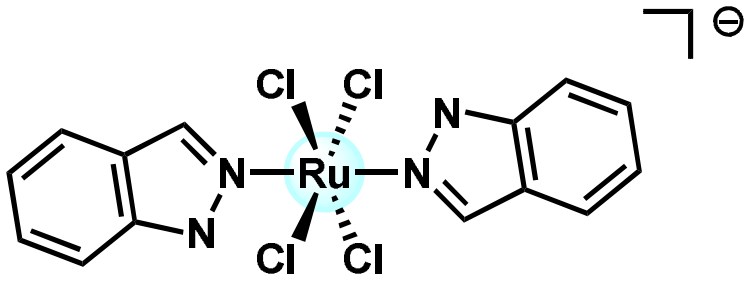
In animal models, ruthenium compounds are effective in the treatment of cancer types which cannot be treated by platinum compounds, most probably due to a different mode of action.

NAMI-A and KP1019

NAMI-A and **KP1019** are two potential ruthenium drugs in phase II clinical trials. Despite their structural and chemical similarities, these two ruthenium complexes show distinct antitumor behaviors.



NAMI-A



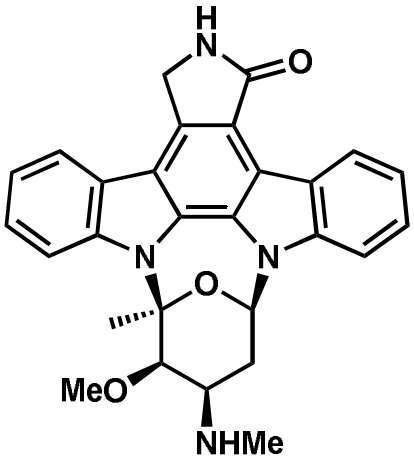
KP1019

NAMI-A induces cell arrest in the premitotic G (2)-M phase, strongly inhibits metastasis without effects on the primary tumor.

KP1019 induces apoptosis in colorectal tumor in which cisplatin is inactive, via intrinsic mitochondria apoptosis pathway.

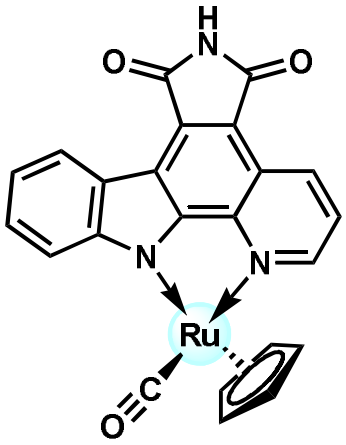
Ru as Protein kinase inhibitors

Staurosporine is known as a nonspecific protein kinase inhibitor. By replacing the globular carbohydrate unit of staurosporine with Ru fragment, a series of selective inhibitors of GSK3 were discovered.



Staurosporin

GSK3α IC_{50} = 50nM



Ru complex

GSK3α IC_{50} = 3nM

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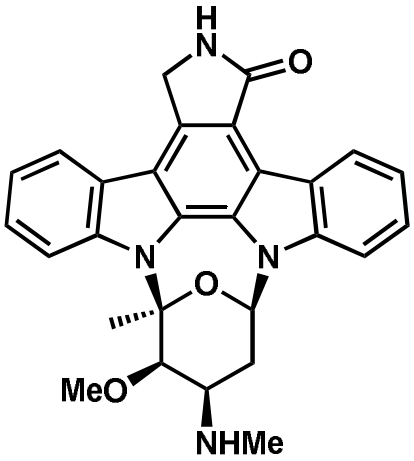

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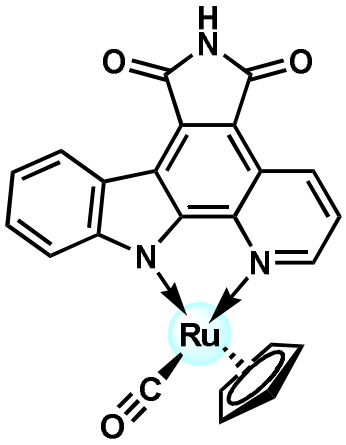

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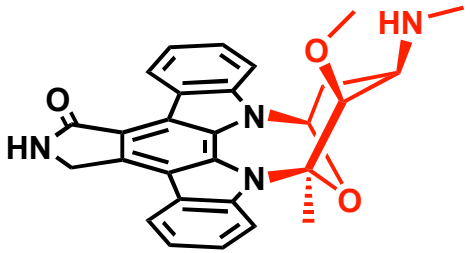
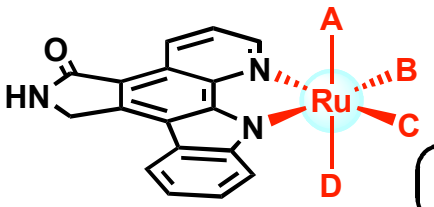


shape mimic



globular unit

Modification is easy (by changing ligands)

Ruthenium tends to form kinetically very inert coordinative bonds.
The ruthenium complexes are stable under air and in water

Summary

Metalloid and metal based drugs are used as chemotherapeutic agents to combat Infectious diseases caused by pathogenic parasites, cancers, inflammation, mental disorders, infection etc.

It is clear that metalloid and metal based compounds offer new properties that cannot be found amongst purely organic agents.

The therapeutic application of metalloids and metals is still an unexplored area of research and continued work in this area is warranted.