

## **Index of compounds with data indicating they either cross or do not cross the bbb (or are found in CSF).**

As described in the preceding review, there are several important issues when considering a chemotherapeutic agent to treat primary brain tumor or metastatic brain tumor. Obviously the most important is that the drug be efficacious against the cancer in question, but it is also extremely important that the drug or its active metabolites be able to reach the brain tumor. Though this seems to be a controversial issue and one that is not totally understood, there seems to be two primary issues in this regard. One is whether the chemotherapeutic agent or the biological agent can be absorbed into the tumor itself. There is some evidence that many chemotherapeutic agents are able to actually concentrate in metastatic brain tumors. The reasoning for this is speculated about in the prior review. It is believed that the metastatic brain tumor reaches a critical mass, it coops the vasculature of the brain, breaching the brain barrier. After this, a battle goes on between the apoptosis and angiogenesis. When angiogenesis wins out the vasculature of the tumor becomes linked with the vasculature of the brain also breaching the brain barrier. It is also thought that the p-glycoprotein and like proteins are low concentration in the vasculature of a brain tumor aiding in the concentration of chemotherapeutic agents including some of the natural toxins in the brain tumor – chemotherapeutic agents which would normally be pumped out or unable to cross the brain barrier by passive diffusion. This is probably the reason there is evidence of efficacy in metastatic brain tumor by compounds that one would normally not believe would cross the brain barrier, such as avastin, cisplatin, etoposide.

On the other hand there is the issue that is seldom addressed and this is the protection of the brain that is susceptible to brain tumor. So often in the literature of recent years there was this discussion of breast tumor taking sanctuary in the brain. Why are the brains of people who have metastatic disease that might easily spread to their brains, such as myeloma, breast cancer and nsclg and sclc – why are these patients not given drugs that simply cross the brain barrier and destroy the microdeposits of brain tumor that do not show up on MRI (limitation of MRI is).

Primary brain tumor is more complex as the vasculature is different. Primary brain tumor is apparently not the best model for developing drugs for metastatic brain tumor.

I propose that is one is choosing a drug for a metastatic brain tumor that one consider primarily its efficacy (obviously its toxicity), its ability to penetrate the brain barrier as well as its ability to penetrate the tumor and its specific efficacy against the metastatic brain tumor.

To this end a search was carried out and is continued to be carried out for information about what is known about the pharmacokinetics of compounds used in cancer treatment, specifically their distribution across the brain barrier and into the cerebral spinal fluid. This search was begun with the BC Cancer Agency Manual which is available on line in which there were 233 entries for cancer agents, some were repetitive in that they were synonyms. The search was continued with AHFS Drug Information Manuals from 2005, 2007 and 2010. This reference was used because the 2007 manual is one of the primary manuals used to support the BC Cancer Agency Manual. Several versions of this were consulted and it was found that they did not all contain the same information or even all the same drugs. Additionally, but less useful, the tenth edition of the Physicians Desk Reference was studied for pharmacology data on cancer agents. The well known text on cancer treatment and diagnosis, by DiVita, DeRosen and was consulted for drugs that are efficacious against primary brain tumor and metastatic brain tumor. Also, a very useful review that appeared in The Oncologist was consulted to include and consider drugs that have been used to treat metastatic brain tumor and are being considered for this purpose. Additional information from the literature is given. Not all cancer agents are included. Only compounds where information was found about the distribution into the brain, compounds that have been stated in the literature to go into the brain, compounds that have been shown to be efficacious against primary brain tumor or metastatic brain tumor or compounds that I felt were analogous by structure and should go into the brain.

To gain quick access to the structures of the compounds and some basic information about molecular weight and formula, Wikipedia was used because it was just extremely easy. I did not download their structures, but redrew them using chemdraw. This exercise was not tedious, but rather really made me deeply think about the structures of the compounds and made patterns amongst them seem more obvious to me.

This is not complete and it is a work in progress. Please note that though this info is meant to be useful to physicians and patients dealing with brain tumor, it is definitely my take on the the compounds based on structure. At the end of the index are compounds that bind the p-glycoprotein which are relevant to this questions. Compounds that bind the p-glycoprotein, such as tamoxifen can be used in principle to increase the permeability of the brain to potentially efficacious drugs.

A few things that seem apparent from our perusal of the information.

1. Compounds that are nucleosides seem to cross the brain barriers, though the somewhat odd pentostatin only slightly crosses – it has structural features in common, but the larger ring in the nitrogen base is a seven membered ring with less unsaturation and a hydroxyl group. This is why it seems rational that gemcitabine might cross since it falls into this groups of antimetabolites, from a structural perspective. Recently, I read

(in reviews that says gliomas are different from mbt), that gemcitabine does cross the brain barrier. It is fair to say that metabolites including the fluoropyrimidines, but excluding any derivative containing sulfur) do cross the brain barrier and do concentrate in mbt (why do they not in gliomas again).

2. It seems that very large molecules that are large proteins - monoclonal antibodies probably do not cross the brain barrier and any efficacy probably comes from the drug passing the vasculature associated with the tumor. This is probably how the drug avastin acts against primary brain tumor. It is a common statement that molecules over a certain size do not cross - talk about banks paper, but this is apparently not true as blah crosses
3. It seems that for the most part that the protein binding of a compound has a high correlation with the ability of a compound to cross the brain barrier. The compounds that cross the brain barrier are not significantly bound to proteins. Less than fifty percent in most cases. This may have been obvious, but I think it is a good predictor.
4. Compounds that are nitrogen mustards and of course, nitrosoureas, tend to cross the brain barrier.
5. Many compounds that cross seems to be smaller and have an elongated structure. Many have a high proportion of nitrogen.
6. Some are larger, but the larger compounds are peptides. They are not in the league of a full protein, but have a number of linked amino acids.
7. Some of the compounds that bind the p-glycoprotein pump are cyclic polypeptides. These kind of compounds could be used perhaps as attenuators to shut the pump down.
8. Supposedly, tamoxifen has some sort of attenuation function, binding the p-glycoprotein pump and may have some antineoplastic activity against primary brain tumors.
9. Lessons I have learned - not all tissues absorb chemotherapy to the same extent, this is really obvious from reading the pharmacokinetics. In some tissues the tumor absorbs more chemo and in some tissues the tissue absorbs more chemo.
10. More lessons I have learned, I believe from several examples in my readings that it is very important to administer chemo slower. The distribution into tissues has kinetics and the kinetics into the brain are slow. I think it is probably safe to say if one is trying to get chemo into the brain, the administration should be slower. See topotecan
11. Anthracyclines do not appear to cross the brain barrier for the most part.

12. Big molecules with lots of oxygens do not seem to cross like etoposide, taxol, taxotere, vincristine, vinblastine. What is surprising is drugs like the epithilones A and particularly B which is patapilone are touted as the next big brain metastasis drugs. They are somewhat different and very interesting. They do not look like the typical drugs that cross.

**Aldesleukin (proleukin):** There is no information on this drug penetrating the central nervous system even in reference 5. This is probably interleukin 2 (spread sheet) but in one reference (reference 5) it said that it may affect central nervous system function. It says, "On set of neurologic effects, including changes in mental status, speech difficulties, corical blindness, limb or gait atazia, hallucinations, agitation, obtundation, and coma, has been reported following aldesleukin therapy in patients without cns metastases."

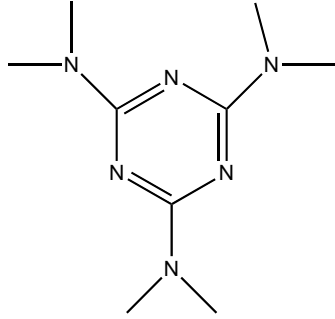
Given the very large size of this molecule and the fact that it is a large protein structure, it would not be expected to readily cross the brain barrier.

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**Altretamine (hexalen):** All this came from reference 3. Precise mechanism of how it exerts its effect not know. But, there are some ideas..... Structurally the compound resembles the alkylating agent triethylenemelamine, yet in vitro test for alkylating activity for hexalen tablets and its metabolites have been negative. Hexalen and its metabolites have been shown to be active in certain ovarian tumors that are resistant to traditional alkylating agents. Some related compounds and their metabolites can form covalent links with macromolecules in different tissues including DNA in vivo

Following intraperitoneal administration of C14 ring labelled drug to mice – rapid radioactivity in all organs reaching max within thirty minutes. Highest concentrations in excretory organs and relatively low concentration in the brain. Ref 3 Needs rewriting. Same into in reference 5

In reference 5: altretamine and its metabolites bind to plasma proteins. The free fractions of altretamine and its metabolites, pentamethylmelamine and tetramethylmelamine are 6, 25 and fifty percent respectively.

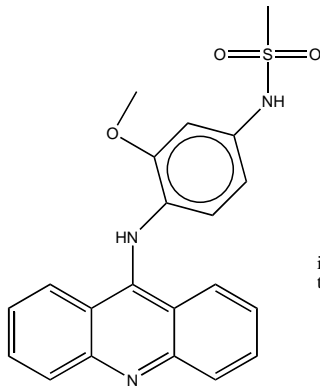


hexalan, altretamine

MW 212.28 formula  $C_9H_{18}N_6$

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**Amsacrine** : minimal from reference 1



intercalator  
topomerase inhibitor

Amsacrine

$C_{21}H_{19}N_3SO_3$  MW= 361

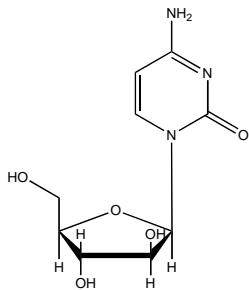
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**Ara-c cytarabine: Cytarabine (ara-C):** from reference 5 Conventional (unencapsulated) cytarabine is rapidly and widely distributed into tissues and fluids..... Following rapid IV injection of conventional cytarabine ....13 percent of the drug was bound to plasma proteins. .... Cytarabine crosses the blood-brain barrier to a limited extent. During a continuous IV or subcutaneous infusion, cytarabine concentrations in the CSF are higher than those attained after rapid IV injection and are about 40-60 percent of plasma concentrations.

Most of an intrathecal dose of conventional cytarabine diffuses into the systemic circulation, but it rapidly metabolized and usually only low plasma concentrations of unchanged drug occur.

Following intrathecal administration of 50 or 75 mg of liposomal cytarabine, systemic exposure to cytarabine is negligible.

Ara-c has cerebellar toxicity.



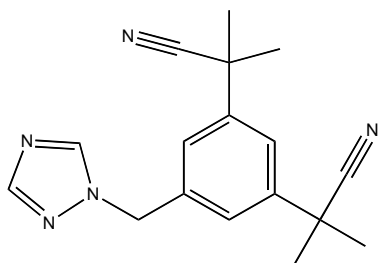
cytarabine

C<sub>8</sub>H<sub>11</sub>N<sub>3</sub>O<sub>4</sub> 193 g/mol N:C ratio 3:8

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**Anastrozole:** no info in reference 5, but 40 percent bound to plasma proteins.

Reference 5



Anastrozole (aramidex)

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**Asparaginase:** When asparaginase was injected directly into the CSF in one patient, there was a rapid transfer into the plasma. Reference 2

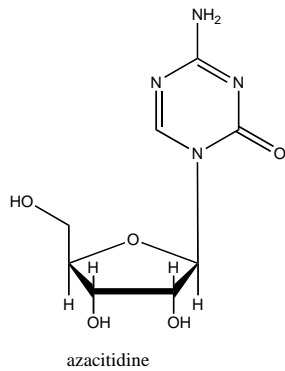
Asparaginase not detectable in csf, but csf asparagine is depleted with systemic administration of any formulation. Reference 1

Large molecule –enzyme formula is huge. We would not expect a big drug like this to cross.

C<sub>1377</sub>H<sub>2208</sub>N<sub>382</sub>O<sub>442</sub>S<sub>17</sub> MW 31731.9 g/mol

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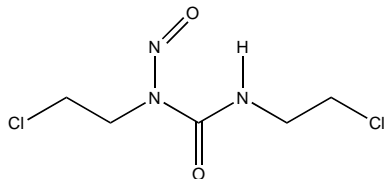
**Azacididine:** Reference 5 no info, but interested in structure.



Structure analogous to cytarabine.

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**Bcnu, carmustine:** passes the bbb readily and is 70 percent of concurrent plasma concentrations, in children it is greater than 90 percent. This is from reference 1. Because of their high lipid solubility carmustine and /or its metabolites readily cross the blood brain barrier. Substantial CSF concentrations occur almost immediately after IV administration of carmustine and CSF concentrations of radioactivity occur from 15-70 percent of the concurrent plasma concentrations. Reference 2



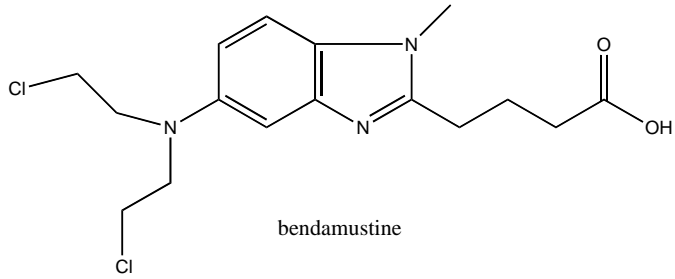
BCNU Carmustine

$C_5H_9N_3O_2Cl_2$  MW = 209

Also administered as Gliadel wafer: profileprosan 20 with carmustine implant designed to be implanted into surgical cavity after a brain tumor has been surgically resected. Really, just direct delivery into tumor, so not so relevant here. This is a method where the physician is going behind the brain barrier. This is from reference 2.

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**Bendamustine**, looks like it should , but no information in reference 5. A lot of nitrogen mustards cross brain barrier. Should be an alkylating agent.



$C_{16}H_{21}Cl_2N_3O_2$

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**Bevacizumab**, large monoclonal antibody. Recent paper in October 1, 2010 jco  
large activity against primary brain tumor with and without irinotecan.

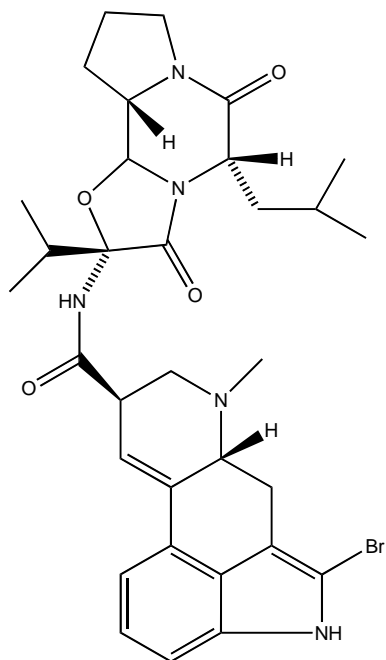
149 kda

$C_{6638}H_{10160}N_{1720}$

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**Bromocriptine**: crosses brain barrier from reference 1.





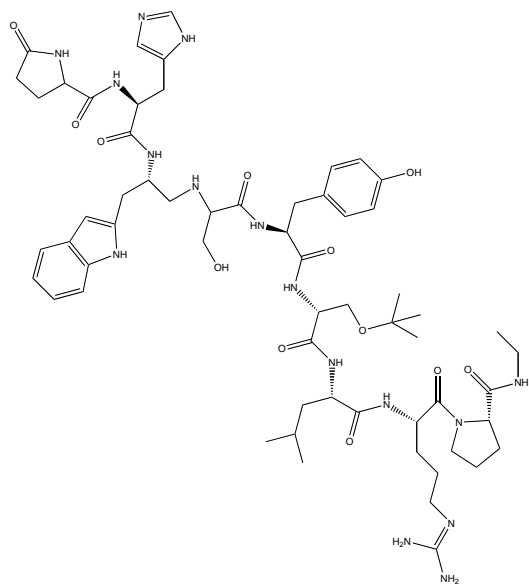
Bromocriptine

$C_{32}H_{44}BrN_5O_5$

MW 654.595? N:C ratio 5:32



**Buserelin:** crosses brain barrier



Very large polypeptide structure

C<sub>62</sub>H<sub>90</sub>N<sub>16</sub>O<sub>15</sub> MW = 1299.48 N:C ratio 16:62 relatively large polypeptides do seem to cross, though proteins do not seem to.

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**Busulfan (Busulfex IV form, myleran):** a small and highly lipophilic molecule easily crosses the blood brain barrier, busulfan concentrations are approximately equal to plasma concentrations.

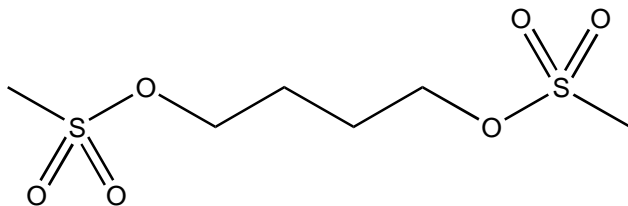
Reference 2

Classed as alkylating agent. Mechanism of action: two labile methanesulfonate groups are attached to opposite ends of a four carbon alkyl chain. In aqueous media, busulfan hydrolyses to release the methane sulfonate groups. This produces reactive carbonium ions that can alkylate DNA. DNA damage is through this to be responsible for much of the cytotoxicity of busulfane reference 3

Distribution studies not done of busulfex, but studies of oral busulfan. Maybe busulfex is iv version of busulfan.

Busulfan achieves concentrations in the cerebrospinal fluid approximately equal to those in plasma. Irreversible binding to plasma elements, primarily albumin has been estimated to be 32.4 +/- 2.2 percent which is consistent with the reactive electrophilic properties of busulfan. Reference 3

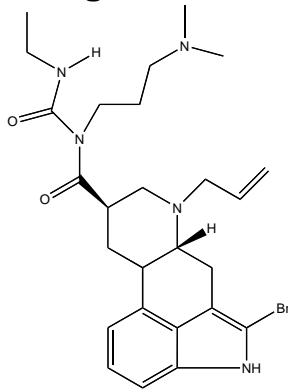
Reference 5 gives the same information.



busulfan

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**Cabergolin** crosses brain barrier reference 1

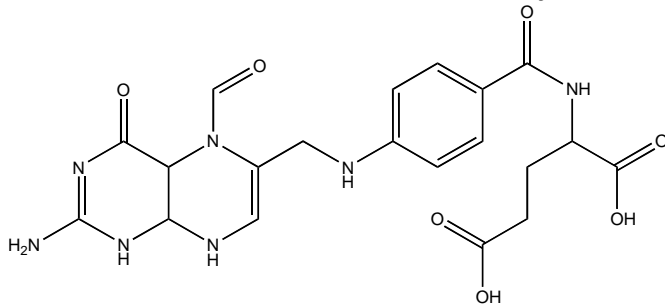


Cabergoline

$C_{25}H_{37}N_4O_2Br$  N:C ratio 4:25

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**Calcium folinate = leucovorin:** readily crosses the brain barrier from reference 1



Folinic Acid , Leucovorin

$C_{20}H_{23}N_7O_7$  N:C ratio 7:20

Given at an appropriate time after methotrexate to save bone marrow.

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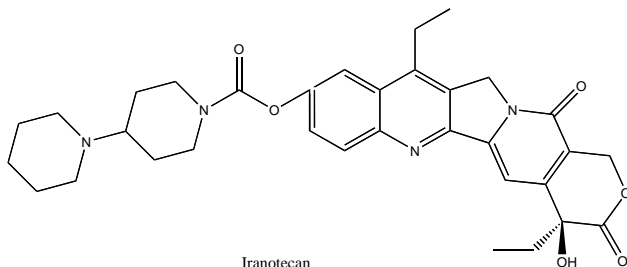
**Camptosar, irinotecan:**no information found reference no. 1

Oct 1 JCO article about irinotecan being used to treat primary brain tumor with and without avastin. (reference 6) I also found an article that said in animal models irinotecan penetrates cns to a significantly lesser extent than topotecan. (need to find reference)

Irinotecan only modestly improves the PFS6 for patients in recent studies with avastin (references 6 and 7). As stated in reference 7, irinotecan makes a questionable contribution.

From reference 8: After intravenous (IV) injection, irinotecan is metabolized in the liver into the active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), which has a low molecular weight and lipophilic properties, enabling it to cross the blood-brain barrier. I can find no verification of this in the paper that was cited in this

(reference 9) statement. The paper cited dealt with pharmokinetics, but as far as I can tell gave no information on the distribution of SN-38.



Irinotecan

$C_{33}H_{38}N_4O_6$  N:C ratio 4:33

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### Capecitabine (xeloda)

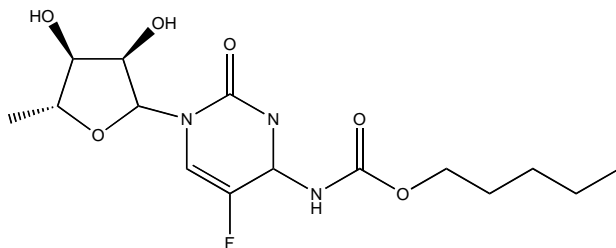
animal studies show that capecitabine and its metabolites do not readily penetrate the blood brain barrier, it is not known whether capecitabine or its metabolites distribute into CSF and brain tissue in humans reference 2  
no information found but produces fluorouracil. Fluorouracil is thought to cross the brain barrier. See below reference 1

From reference 5: plasma protein binding of capecitabine is mainly to albumin and its and its metabolites binding is less than 60 percent to protein.

“Animal studies who that capecitabine and its metabolites do not readily penetrate the blood-brain barrier, it is not known whether capecitabine or its metabolites distribute into csf and brain tissue in humans” reference 5

weird because it says in same reference that 5-fu crosses.

Capecitabine has been used in a number of studies on brain tumor and brain metastasis as shown earlier in this treatise.



$C_{15}H_{22}FN_3O_6$  N:C 3:15

Interestingly, when asked my former student who is now a oncologist in Singapore and by the way, she is fairly experienced – is over 40 and was trained at Baylor. Very, very smart student when I had her. Her name is Dr. Lavinia Bharwani and she

is at Johns Hopkins in Singapore. She gives her patients capecitabine for their brain mets.

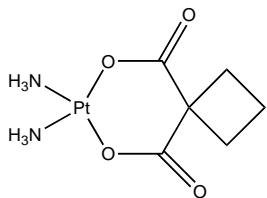
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**Carboplatin (paraplatin):** crosses brain barrier

A small, polar molecule. I actually took this drug for a number of months to control brain metastasis and found that the tumor in my brain shrank as did some tumor in my body. A small study of one, but this drug has been shown to be efficacious in the treatment of brain tumor and brain metastasis. I have read information about this crossing, though these references say there is no information.

Carboplatin (paraplatin) Lower concentrations are found in the fat and brain reference 2

Reference 5: "Following IV administration of carboplatin, platinum is widely distributed into body tissues and fluids with highest concentrations in the kidney, liver, skin, body tissue. Lower concentrations are found in fat and brain." "In vitro studies show carboplatin is not bound to proteins. In vivo, platinum products of carboplatin become increasingly bound to protein. After IV infusion, after 4 hours, 24 percent bound - after 24 hours, 87 percent of platinum is bound to protein.



Carboplatin

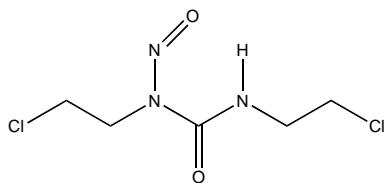
$C_6H_{12}O_4N_2 Pt$  358.1 N:C ratio 2:6

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**Carmustine : Bcnu, carmustine:** passes the bbb readily and is 70 percent of concurrent plasma concentrations, in children it is greater than 90 percent. This is from reference 1.

Because of their high lipid solubility carmustine and /or its metabolites readily cross the blood brain barrier. Substantial CSF concentrations occur almost immediately after IV administration of carmustine and CSF concentrations of radioactivity occur from 15-70 percent of the concurrent plasma concentrations.

Reference 2 exactly the same in reference 5



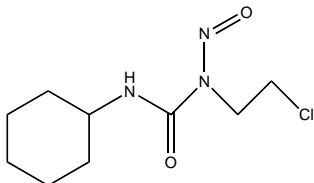
BCNU Carmustine

C<sub>5</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub>Cl<sub>2</sub> MW = 209

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**CCNU, lomustine:** passes readily greater than fifty percent of concurrent plasma concentration

lomustine ccnu

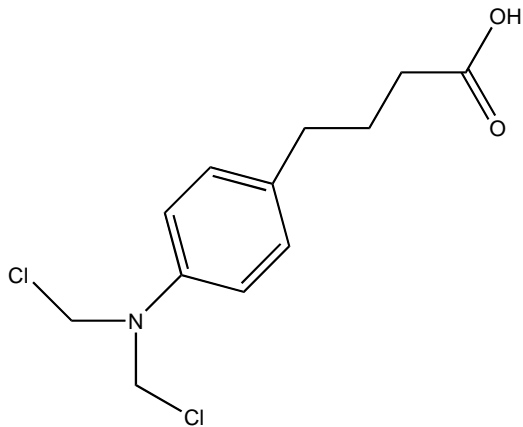


C<sub>9</sub>H<sub>16</sub>N<sub>3</sub>O<sub>2</sub>Cl

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**Chlorambucil (leukeran)** Although adverse CNS effect have been reported it is not known if chlorambucil crosses the blood brain barrier. Reference 2

Is a functional alkylating agent of the nitrogen mustard type that has been found active against selected human neoplastic diseases. Name: 4-(bis(2-chloroethyl)amino)benzenebutanoic acid



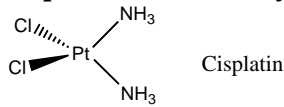
chlorambucil, leukeran

Rapidly undergoes metabolism to phenylacetic acid mustard, the major metabolite, and the combined compound plus metabolite low urinary excretion.

Extensively bound to plasma proteins 99 percent bound chlorambucil and metabolites Cerebrospinal levels of the drug and metabolites have not been determined. Reference 3 also true in reference 5

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**Cisplatin** not readily



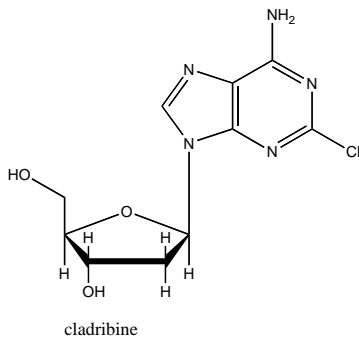
$PtN_2Cl_2H_6$  inorganic

Cis-platin Although there is evidence to the contrary, cisplatin and its platinum containing products do not penetrate the brain barrier the cns. Following IV administration of cis-platin, platinum is distributed into intracerebral tumor tissue and edematous brain tissue adjacent to tumor, however, only low concentrations of platinum have been detected in healthy brain tissue. Reference 2

Reference 5: following IV administration it is widely distributed in tissues, lower concentrations in a bunch of organs including cerebellum and cerebrum. "Although there is some evidence to the contrary, cisplatin and or its platinum containing products apparently do not readily penetrate the CNS. Following IV administration of cis-platin, platinum is distributed into intracerebral tumor tissue and edematous brain tissue adjacent to tumor; however, only low concentrations of platinum have been detected in healthy brain tissue. In one study in patients with brain tumors, platinum was barely or not detectable in csf following IV administration of cisplatin, but in other reports, platinum was detected in the csf of patients with or without brain tumors following IV administration of the drug. When platinum has been detected in csf, peak csf platinum concentrations occurred within 30-60 minutes after IV administration of cisplatin and csf platinum concentrations ranged from less than five percent to up to 100 percent of concurrent plasma concentrations.

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**Cladribine** – crosses brain barrier approximately 25 percent of plasma concentration Also called leustatin  
Clatribine no info, though neurological effects reference 2 Is Clatribine, the same as Cladribine.



C<sub>10</sub>H<sub>10</sub>N<sub>5</sub>O<sub>3</sub>Cl N:C ratio 5:10

More about cladribine from reference 4 (10<sup>th</sup> edition of pdr). Penetrates cerebral spinal fluid achieves a concentration that is 25 percent of plasma proteins. This compound it bound to 20 percent of plasma proteins. Cladribine passively crosses cell membrane, cytotoxic to both actively dividing and quiescent lymphocyte and monocytes, inhibits both DNA synthesis and repair.

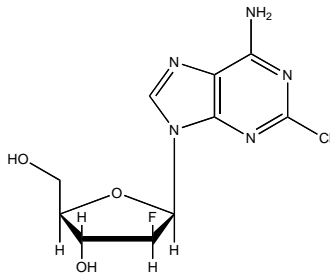
Looks like a compound that would cross brain barrier.

In reference 5 there is no info on pharmacokinetics. Though it says it has been associated with severe, irreversible neurological toxicity in 35% of patients. Paraparesis and quadriparesis. Many adverse events involving headache and fatigue.

Think it crosses.

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### Clofarabine



clofarabine

No pharmacokinetic information reference 5

Purine nucleoside, antimetabolite

According to reference 3: clofarabine which is also called clorar is 47 percent bound to proteins, mainly albumin.

C<sub>10</sub>H<sub>9</sub>N<sub>5</sub>O<sub>3</sub>FCl

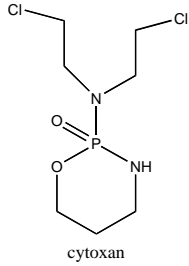
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### Cytarabine (see ara-c above)

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**Cytosin = cyclophosphamide** crosses to a limited extent

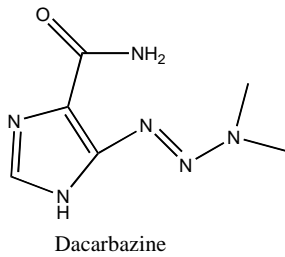




According to reference 5, “cyclophosphamide and its metabolites appear to be distributed throughout the body, including the brain and CSF, but probably not in concentrations sufficient to treat meningeal leukemia.” “Although in vitro binding of cyclophosphamide has not been demonstrated, in vivo binding generally has been reported to range from 0-10 percent and protein binding for some alkylating metabolites has been reported to exceed 60 percent.”

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### Dacarbazine

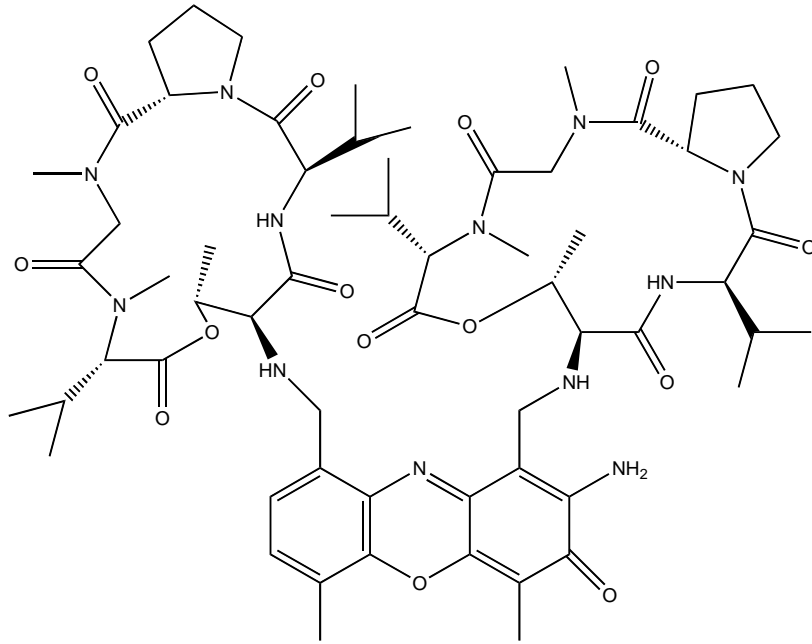


According to the AHFS Drug Manual 2010 (reference 5), “The drug is only slightly bound to plasma proteins.” “The drug crosses the brain barrier to a limited extent:CSF concentrations are reported to be about 14 percent of plasma concentrations.”

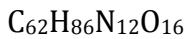
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**Dactinomycin** crosses brain barrier achieves less than ten percent of plasma concentration. According to reference 5, the drug crosses the brain barrier poorly if at all. Nothing about proteins.

In reference 3, it says it does not cross the brain barrier.

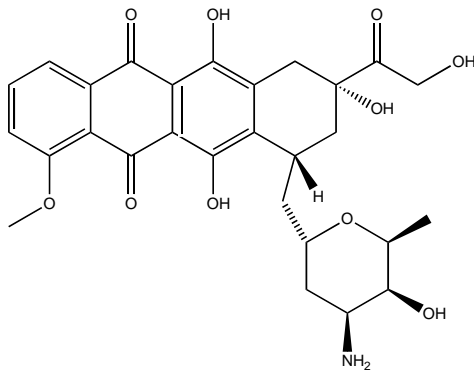


dactinomycin



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**Daunorubicin:**



Doxorubicin, Adriamycin

From reference 5: daunorubicin is approximately 63 percent bound to proteins, principally albumin. Protein binding of the liposomally encapsulated drug is minimal .

Encapsulation of daunorubicin in liposomes substantially slows the rate of distribution of the drug into the extravascular space. As a result, the liposomally encapsulated daunorubicin citrate does not distribute into the plasma and tissues as widely as daunorubicin hydrochloride administered conventionally. Liposomal daunorubicin distributes mainly into intravascular fluid; whereas nonencapsulated daunorubicin distributes widely into extravascular fluids and tissues. Animal

studies indicate that liposomally encapsulated daunorubicin citrate distributes from blood vessels into tumors and once distributed into the tissue compartments, the drug is released. Exact mechanism of how this happens not known. Liposomes may penetrate tumor cells by endocytosis and drug is directly into the cell.

From reference 5 again.... "There is no evidence that daunorubicin administered as a conventional injection crosses the blood brain barrier. Although preclinical data suggest that liposomal daunorubicin crosses the blood-brain barrier in animals, it is not known whether liposomal daunorubicin crosses the blood brain barrier in humans. It appears that daunorubicin crosses the placenta. "

\*\*\*\*\*

### **Decitabine:**

No information

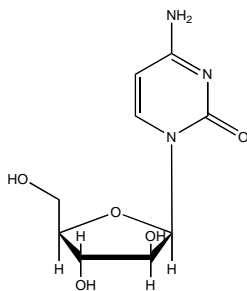
Look up structure

\*\*\*\*\*

**Depocyt** cytarabine liposome injection – discussed above under ara-c

According to reference 5: Following intrathecal administration of 50 or 75 mg of liposomal cytarabine, systemic exposure to cytarabine is negligible.

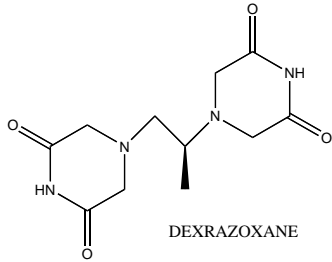
According to reference 3: Only speak about intrathecal administration.



cytarabine

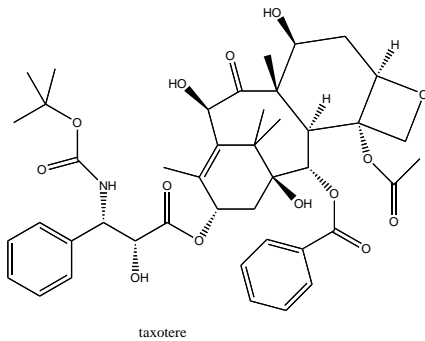
$C_8H_{11}N_3O_4$  193 g/mol N:C ratio 3:8

**Dexrazoxan** does not cross brain barrier



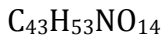
\*\*\*\*\*

**Docetaxel (taxotere):**



Docetaxel= taxotere very low levels were found in brain in animal studies. In single patient with leptomeningeal carcinomatosis docetaxel detected in cfs two hours after infusion cessation. This is doxil and the way it works is similar to encapsulated daunorubicin – it just injects into the tumor though they claimed they don't know the mechanisms.

In reference 5: 94 percent bound to plasma proteins.



\*\*\*\*\*

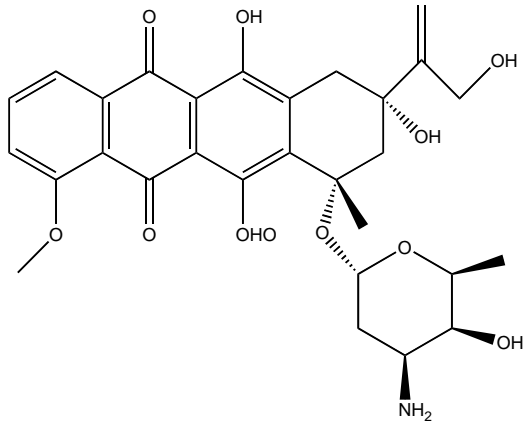
**Doxorubicin hydrochloride = hydroxydaunorubicin : adriamycin “the red devil”**

The structure is exactly the same as daunorubicin, except for an additional hydroxyl group on the acyl group on the D ring.

According to reference 5. Non encapsulated doxorubicin is about 50-85% bound to proteins. The liposomally bound form – it is not known how much is bound.

Encapsulation in pegylated liposomes substantially slows the rate of distribution of the doxorubicin in to the extravascular space. Mostly in intravascular fluid unlike the nonencapsulated form which is absorbed into tissue.

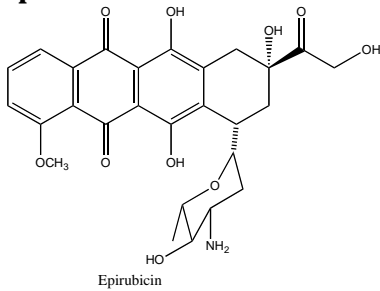
Reference 5. Doxorubicin does not cross the blood brain barrier or achieve a measurable concentration in the csf. Don't know about encapsulated.



doxorubicin, adriamycin  $C_{27}H_{29}NO_{11}$

\*\*\*\*\*

**Epirubicin:** does not cross brain barrier

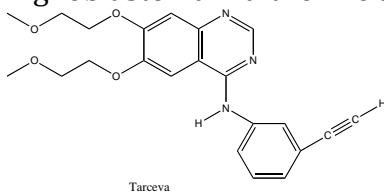


reference 5: no pharmokinetic data

$C_{27}H_{29}NO_{11}$

\*\*\*\*\*

**Erlotinib = tarceva** not fully characterized, but preliminary studies show efficacy in glioblastoma multiforme and malignant glioma

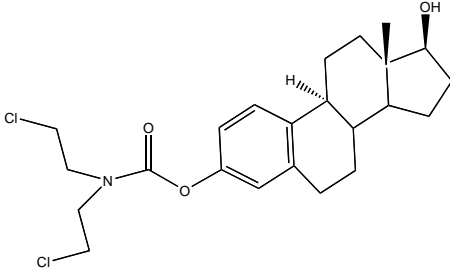


## No info

\*\*\*\*\*

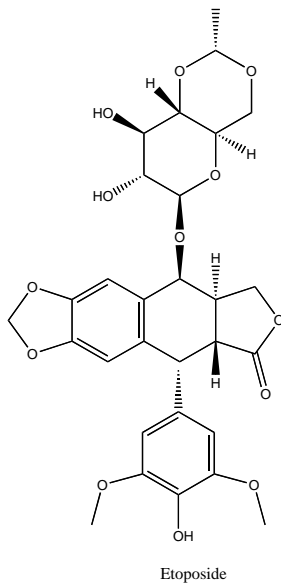
## Estramustine: crosses brain barrier

estramustane



\*\*\*\*\*

**Etoposide** – in low and variable concentrations. It achieves only 5 percent of plasma concentrations in csf and is pumped out of the brain by the p-glycoprotein pump. See references.

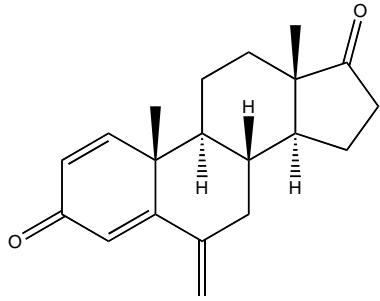


## C<sub>29</sub>H<sub>32</sub>O<sub>9</sub>

From reference 5: Etoposide and its metabolites apparently do not readily penetrate the ccns. While variable, csf etoposide concentrations generally range from undetectable to less than 5 % of concurrent plasma concentrations during the initial 24 hours after iv administration of the drug, even after administration of very high doses. Limited data suggest that etoposide distributes into brain tumor tissue more readily than healthy brain tissues. Concentration of the drug is higher in healthy lung tissues than in lung metastases.

\*\*\*\*\*

**Exemestane, Aromasin:**

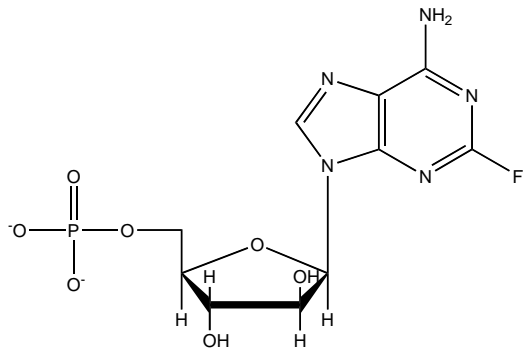


exemestane

no information, though structure indicates it should cross

\*\*\*\*\*

**Fludarabine:**



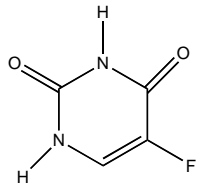
Fludarabine

Reference 5: Although the extent to which fludarabine and or metabolites of the drug distribute into the CNS in humans has not been determined to date, seven neurologic toxicity (e.g., blindness, coma)has been reported in patients receiving the drug, particularly in high dosages.

According to high in vitro data, ,about 19-29 oercent of fludarabine is bound to plasma.

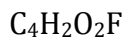
\*\*\*\*\*

**Fluorouracil** : crosses the brain barrier



Fluorouracil

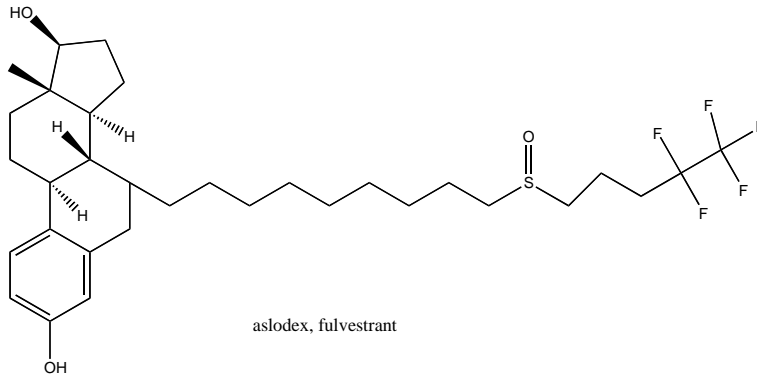
Reference 5: Despite its limited lipid solubility, the drug readily crosses the blood brain barrier and distributes into csf and brain tissue. Distribution studies in humans and animals have usually shown a higher concentration of the drug or its metabolites in the tumor than in surrounding tissue or in corresponding normal tissue. Maybe due to impaired uracil metabolites.



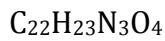
N:C ratio 2:4

\*\*\*\*\*

**Fulvestrant** : the bc cancer agency manual says there is no info, but an article I read said it does not cross I have to get reference.



aslodex, fulvestrant

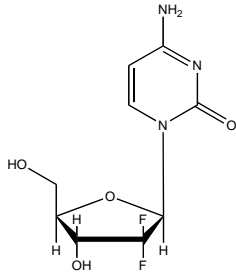


\*\*\*\*\*



**Gemcitabine, gemzar:** no info, but I have read elsewhere that it does not.

Think it does based on structure analysis



Gemzar

compound is actually a hydrochloride, so I have to fix this. Gemcitabine exhibits cell phase specificity primarily killing cells undergoing S phase DNA synthesis and also blocking the progression of the G1/phase S phase boundary. The compound is metabolized to the active diphosphate and triphosphate nucleosides which leads to inhibition of DNA synthesis. Complex mechanism described in reference 3.

Demonstrated dose dependent synergistic activity with cis-platin. Reference 3

It does not give info on distribution reference 3

Very interesting points from reference 3.... Gemcitabine half life for short infusions ranged from 42 to 94 minutes and for long infusions ranged from 245-638 minutes. Depending on age and gender. Longer infusion greater dose, female or older slower clearance greater dose.

Very important. Volume distribution of gemcitabine was 50 L/m<sup>2</sup> following infusions lasting less than 70 minutes, indicating that gemcitabine after shorter infusions isn't extensively distributed into tissues. For long infusions, the volume of distribution rose to 370 L/m<sup>2</sup> reflecting slow equilibration of gemcitabine within the tissue compartment. This is important. How is it administered. More and more I feel this is an issue with every infusion. Reference 3

Gemcitabine

According to reference 3: it has negligible plasma protein binding.

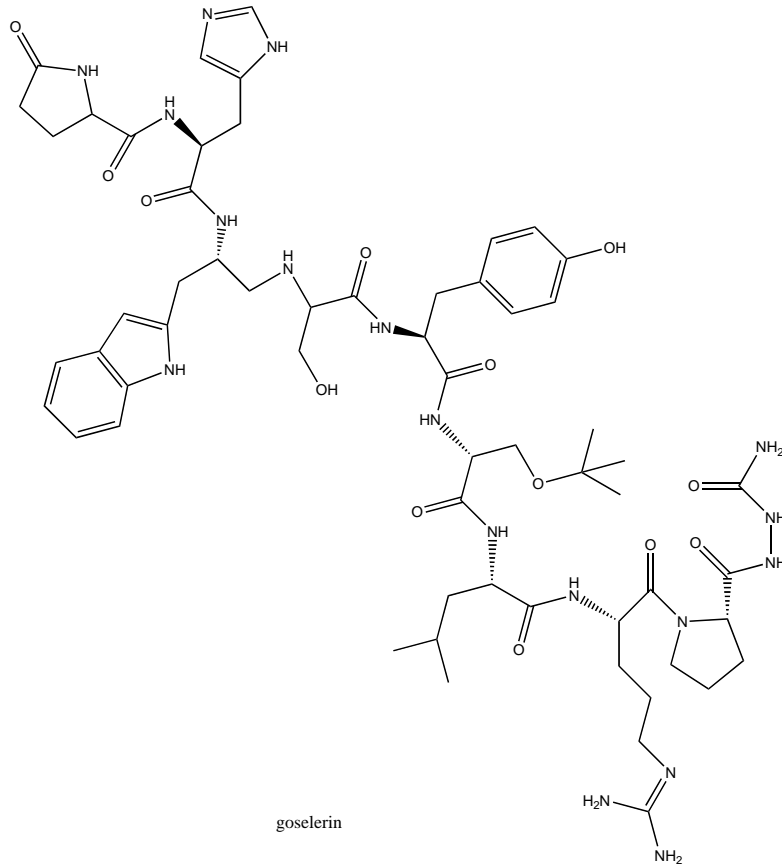
But now I think it does cross the brain barrier

Reference 5: no info.

\*\*\*\*\*

**Goserelin, zoladex** crosses brain barrier

Large polypeptide  $C_{59}H_{84}N_{18}O_{14}$



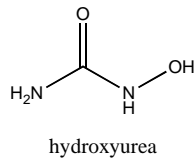
**Herceptin** no info, but I have read that it does not

Very large protein structure  $C_{6470}H_{10012}N_{1726}O_{2013}S_{42}$

\*\*\*\*\*

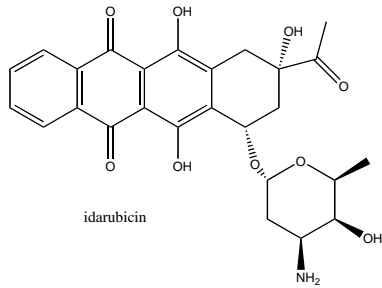
**Hydroxyurea:**

**Reference 5:** Hydroxyurea: crosses the brain barrier. Peak csf concentrations are attained within three hours of oral administration.



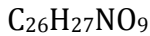
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**Idarubicin:**



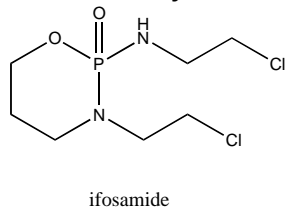
The principle metabolite of idarubicin is idarubicinol. For idarubicin and idarubicinol, the extent of protein binding is 97 percent and 95 percent, respectively.

The distribution of idarubicin and idarubicinol into csf has been studied in pediatric patients with leukemia receiving idarubicin on a schedule of once weekly for three weeks or once daily for three days every three weeks. Idarubicin was detected in csf of 2 of 21 samples and idarubicinol was detected in 20 of 21 percent of samples. The clinical importance of these findings is unclear.



\*\*\*\*\*

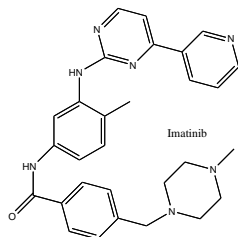
**Ifosfamide** yes in subtherapeutic amounts.



Reference 5: Ifosfamide and its metabolites appear to be distributed everywhere in the body, including the brain and csf.

\*\*\*\*\*

**Imatinib** animal studies showed poor penetration of the brain barrier.



C<sub>29</sub>H<sub>31</sub>N<sub>7</sub>O

Reference 5: there is no information

\*\*\*\*\*

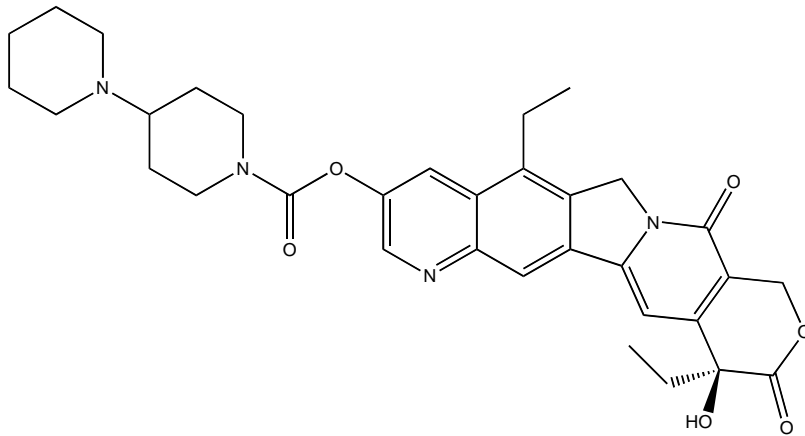
**Interferon** very large protein, with many alpha helices.

[http://upload.wikimedia.org/wikipedia/commons/9/97/1RH2\\_Recombinant\\_Human\\_Interferon-Alpha\\_2b-01.png](http://upload.wikimedia.org/wikipedia/commons/9/97/1RH2_Recombinant_Human_Interferon-Alpha_2b-01.png)

Reference 5: Interferon alfa does not readily distribute into csf following systemic administration fo mixtures of naturally occurring human or recombinant interferons in animals or humans, although low concentrations have been detected in csf following administration of large systemic doses. Following IM injection of a mixture of naturally occurring human leukocyte interferon, no interferon activity was detectable

\*\*\*\*\*

**Irinotecan (camptosar):**



Irinotecan: In reference 5 there is no information on the distribution of this compound. There is a very important paper that was published in the Journal of Clinical Oncology on October 1, 2009. I will get exact reference. In this paper, there was data on a study of irinotecan with and without avastin for primary brain tumor. The irinotecan increased the numbers by about 6 percent. Not a huge effects and in studies where it is used as a single agent, it is not particularly efficacious. There is a reference that is related to this paper that claims the drugs intermediate does cross the brain barrier – it is a pharmacokinetic study done in 1997, in the same journal. I have read this paper and see no evidence of this claim, but I am still working on it.

The compound, of course, is a close structural analogue of topotecan which is thought to cross the brain barrier.

I believe the great efficacy of avastin lies in its breaching the brain barrier due to the vasculature developed by the primary brain tumor as it is a very large molecule.

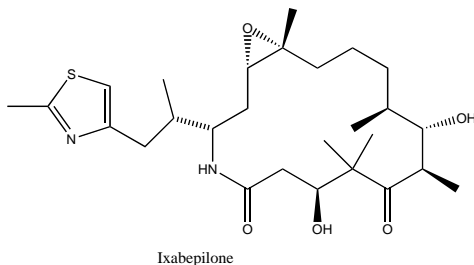
Have to find reference

After intravenous (IV) injection, irinotecan is metabolized in the liver into the active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), which has a low molecular weight and lipophilic properties, enabling it to cross the blood-brain barrier.<sup>9</sup>

$C_{33}H_{38}N_4O_6$

\*\*\*\*\*

**Ixempra = Ixabepilone:** no info - I think this one does and it is new drug  
This drug's structure does not look like a bbb crosser, but it is a close relative of patupilone which I believe is epithilone B and is touted as being a drug that crosses the brain barrier. Will be discussed later. There is no pharmacokinetic data in reference 5.



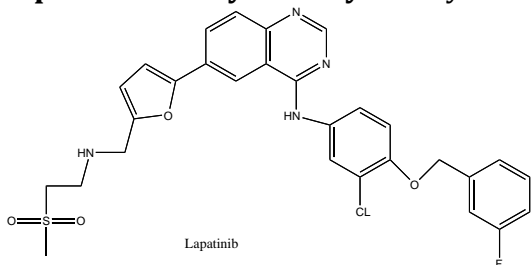
$C_{27}H_{42}N_2O_5S$

\*\*\*\*\*

**Lanvis thioguanine** negligible  
 $C_{23}H_{27}N$  cant find the structure

\*\*\*\*\*

**Lapatinib ditosylate = tykerb** yes though I have read it does not



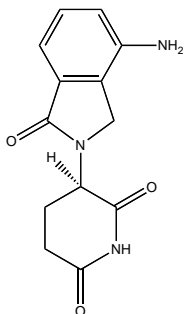
no info in reference 5, but has always been touted as the drug to take in place or with herceptin since it is a small molecule and should cross the brain barrier. In the paper by Loeffner and Eichler and many other references, it is stated that it has

given very disappointing results for people with breast cancer brain metastasis. Get reference. I have read in a few references, that it is not known whether this drug crosses the brain barrier.

\*\*\*\*\*

### **Lenalidomide = revlimid no info**

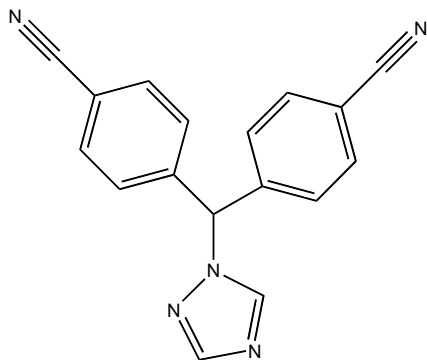
Revlimid Given that thalidomide does cross, this might. They are very similar in structure.



Lenalidamide

\*\*\*\*\*

### **Letrozole = femara**



letrozole



This is an aromatase inhibitor and there is little info in the literature on this compounds pharmokinetics, though there is some info on tamoxifen which is a close structure relative. I have read in DeVito that, tamoxifen binds the p-glycoprotein pump and shuts it down. I have read that tamoxifen in very high levels has some activity against primary brain cancer in the same reference. The mechanism of this activity is thought to be different.

In reference 5 it says that this compound has a large volume of distribution and it is weakly bound to plasma proteins.

\*\*\*\*\*

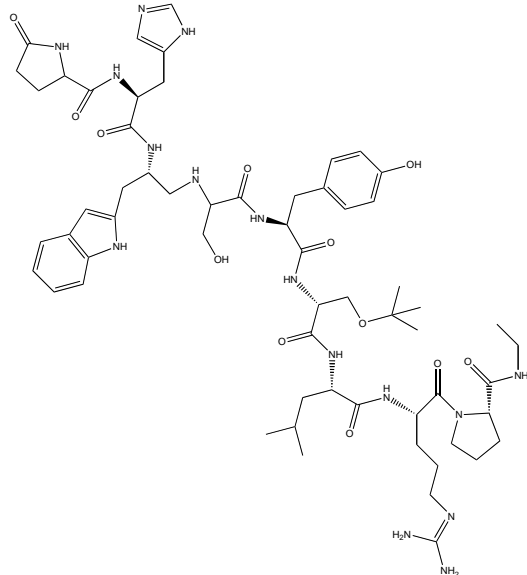
### **Luprone = luprolide - looks the same as buselrin discussed earlier**

From reference 5: Distribution of leuprolide acetate into human body tissues and fluids has not been determined, Since endogenous GnRH is distributed in high concentrations into kidney, liver, pineal and pituitary tissue in animals with lower concentrations in the hypothalamus, cerebral cortex and muscle, it is likely that distribution of leuprolide into these tissues may also occur. In one study, healthy men receiving leuprolide by IV bolus, a mean steady state volume of distribution of 27 liter was reported and in vitro binding to human plasma proteins ranged from 43-49 percent. At therapeutic serum concentrations, leuprolide acetate has been reported to be about 7-15 percent bound to serum proteins – mostly albumin.

crosses the brain barrier

Large polypeptide structure big and bulky  $C_{59}H_{84}N_{16}O_{12}$

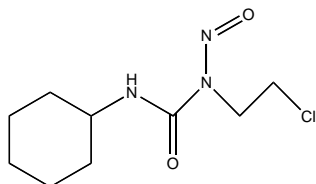
The paper above that speaks of characteristics says that the rule of five says compounds can't be over 600 daltons, but he states there is an example of over 4000 daltons. This seems ok since it is about 1200 or so Daltons.



\*\*\*\*\*

**Lomustine** (alkylating agent ) readily greater than fifty percent of concurrent plasma concentrations

lomustine ccnu

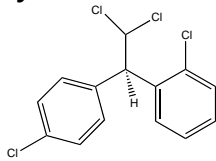


These small nitrosoureas all seem to cross

From reference five, Lomustine is reported to be widely distributed. Lomustine and or its metabolites cross the blood brain barrier and are rapidly transported into cells due to high lipid solubility. Although intact lomustine is not detectable in the csf, active metabolites of the drug appear in substantial concentrations within 30 minutes after oral administration. Csf concentrations of lomustine metabolites have been reported to be 15-50 percent greater than concurrent plasma concentrations.

\*\*\*\*\*

**Lysodren mitotan** small amounts of metabolite detected in csf

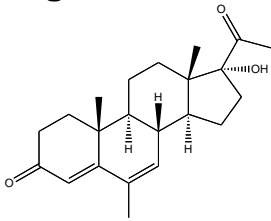


Mitotane, o,p'-ddd used for adrenal carcinoma  
a racemate

No info in reference 5

\*\*\*\*\*

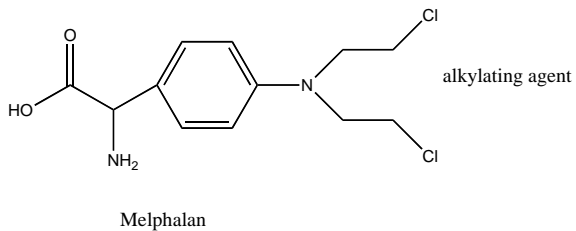
**Megastrol** no info in reference 5, but given its steroid structure, it probably does.



megestrol a progesterone derivative

\*\*\*\*\*

**Melphalan:** low concentration in cerebral spinal fluid plasma:csf ration 10:1 to 100:1



Melphalan

Reference 5: Melphalan distributes into the csf in low concentrations. The drug is reportedly 60-90 percent bound to plasma proteins.

C<sub>12</sub>H<sub>15</sub>N<sub>2</sub>Cl<sub>2</sub>O<sub>2</sub> N:C ratio 2:12 MW 285

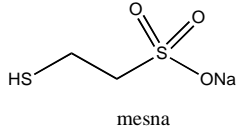


\*\*\*\*\*

## Mensa negligible

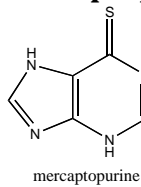
Can't find structure yet.

**Mesna uromitexan** does not cross brain barrier



\*\*\*\*\*

## Mercaptopurine



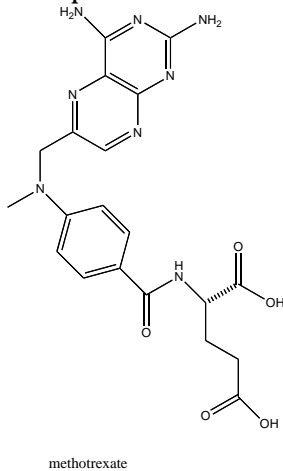
According to reference 5: Although the drug reportedly crosses the blood brain barrier, csf concentrations are not sufficient for the treatment of meningeal leukemia.

Reference 3, when discussing a related compound, says it does not cross.

$C_5H_5N_4S$

\*\*\*\*\*

**Methotrexate** 10-30:1 for cns concentration higher concentration noted in patient with recent cranial irradiation and in patients with primary cns lymphoma disruptions of brain barrier? Check that

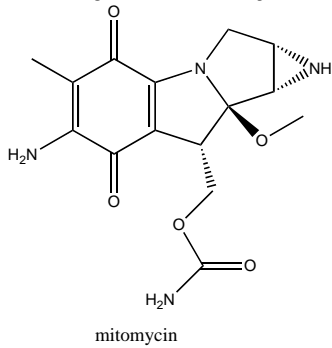


methotrexate has shown some efficacy against brain tumors. Some efficacy no doubt comes from the compound reaching the tumor through the breached brain barrier.

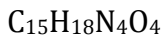
Reference 5: According to the manufacturer, methotrexate does not reach therapeutic concentrations when administered orally or parenterally. High dose systemic methotrexate can result in peak csf concentrations above the therapeutic threshold of 0.001 micromoles /ml and has been used to prevent meningeal leukemia and lymphoma. Concentration in csf is dose related. 500 mg/m<sup>2</sup> 24 hour iv infusion - .0001 micromoles/ml. dose it up to 7500 mg/m<sup>2</sup> csf concentrations of .01 micromoles/ml.

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**Mitomycin unlikely**

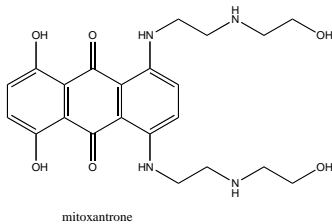


According to reference 5: The drug is not detectable in the liver, spleen or brain which rapidly inactivate mitomycin.



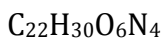
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**Mitoxantrone**



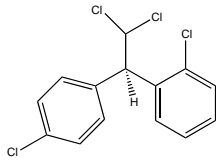
According to reference 5: at plasma concentrations of 26-455 ng/mL, 78 percent of the drug is bound to plasma proteins. Protein binding of this drug is independent of plasma concentration and is unaffected by the presence of aspirin, doxorubicin, heparin, phenytoin, prednisone, prednisolone or methotrexate.

Reference 5: In healthy monkeys, the concentrations of mitoxantrone detected in the brain, spinal cord, eye and csf are low.

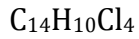


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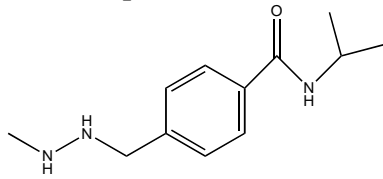
**Mitotane** no small amounts of metabolite detected in csf



Mitotane, o,p'-ddd used for adrenal carcinoma  
a racemate

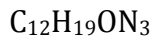


**Natulan procarbazine** crosses the brain barrier

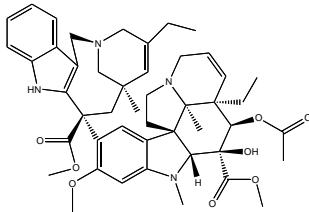


procarbazine

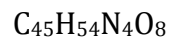
procarbazine:



**Navelbine vinorelbine** brain and plasma levels comparable in animal studies

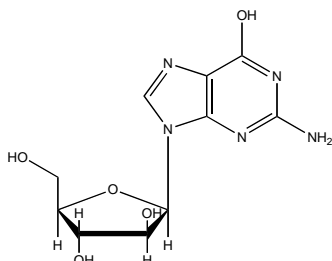


Navelbine, vinorelbine

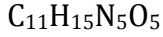


\*\*\*\*\*

**Nelarabine** According to reference 5 there is no pharmokinetic data, however, this compound is a close analogue of compounds that do cross the brain barrier.

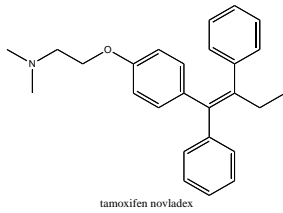


nelarabine

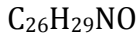


\*\*\*\*\*

**Novladex tamoxifen** no info, but as discussed below I read in Devito that at very high doses it has some activity against primary brain tumor and it deactivates p-glycoprotein.



Reference 5: no information



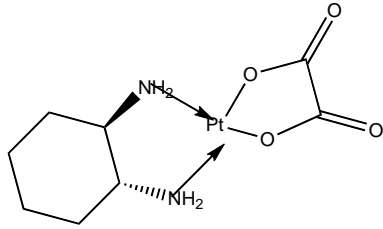
I have read in Devito that it does cross the brain barrier and at very high concentrations has activity against primary brain cancer (different mechanism than its anti-breast cancer activity). It also says in Devito that tamoxifen might bind p-glycoprotein and deactivate it. Got to get reference.

\*\*\*\*\*

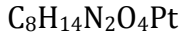
**ostac chodronate**

\*\*\*\*\*

**oxaliplatin** – close relative of paraplalin. No info in reference 5 Might bear some research though.

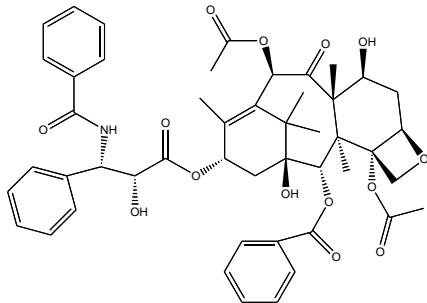


oxaliplatin



\*\*\*\*\*

**Paclitaxel...does not cross the brain barrier**



Taxol, paclitaxel

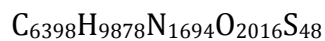
According to reference 5: At plasma concentrations ranging from 0.1-50 mcg/ml 88-98 percent of paclitaxel is bound to plasma proteins.

Same reference.... Conventional Paclitaxel does not appear to readily penetrate the CNS.

Paclitaxel bound to nanoparticles of the serum protein albumin is delivered via endothelial transport mediated by albumin receptors and the resulting concentration of paclitaxel in tumor cells is increased compared with that achieved using an equivalent dose of conventional paclitaxel. Abraxane.

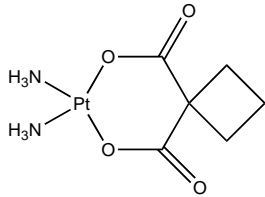
\*\*\*\*\*

**Panitumumab** no information found should not cross  
 Structure can't be drawn. It is a huge monoclonal antibody.  
 Chemical formula



\*\*\*\*\*

**Paraplatin = carboplatin** does cross discussed above

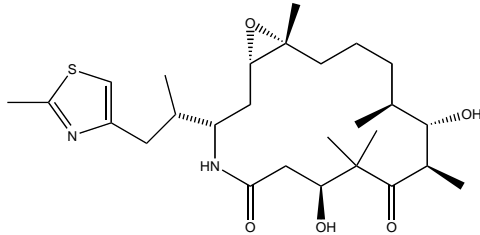


Carboplatin

Have to get more references on carboplatin

\*\*\*\*\*

**Patipilone epithilone B**



Ixabepilone

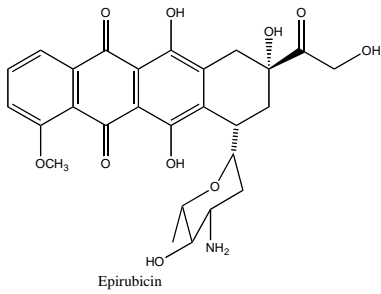
This is currently a big hot drug that people are interested in. One would think because this crosses, that maybe xempra which is also an epithilone might also be effective.

I am not sure but, this is epothilone B which is allegedly patupilone which is definitely a brain barrier drug. Epothilone A has a H at the epoxide rather than the methyl. I am thinking that exempra is epothilone A, but not sure, so I have a little more research to do.

I have no info yet on the pharmokinetics of epithilone B, but I have read in articles, such as the one by Loffner and Eichler that I have referenced below, that this drug is thought to cross the brain barrier and may have efficacy against metastatic breast tumor. There are ongoing studies in this regard.

\*\*\*\*\*

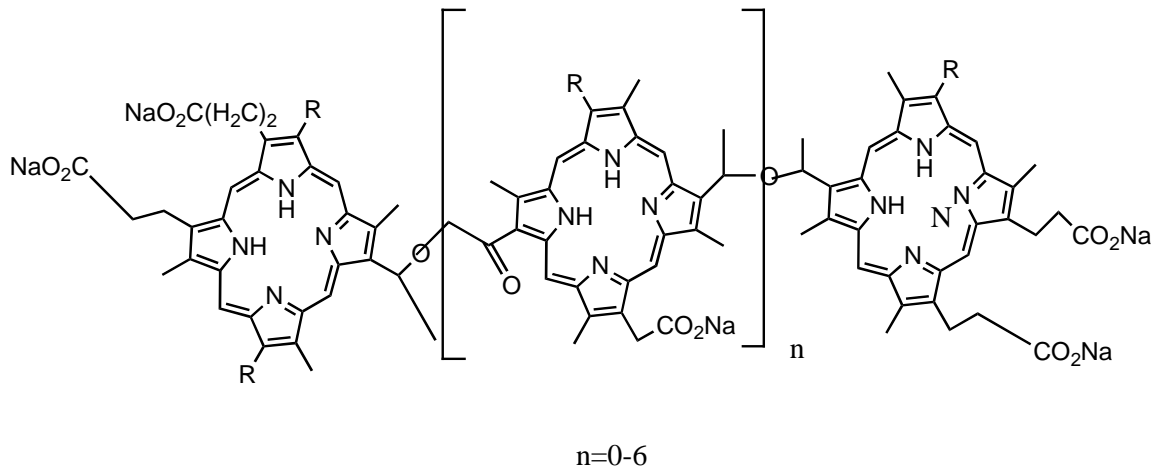
**Pharmorubicin epirubicin** does not cross the brain barrier



\*\*\*\*\*

**Photofrin porfimer** yes it crosses

Very large  $C_{68}H_{74}N_8O_{11}$  large molecule that is a sodium salt has up to eight porphyrin rings linked together. MW about 1100 in range of compounds that cross



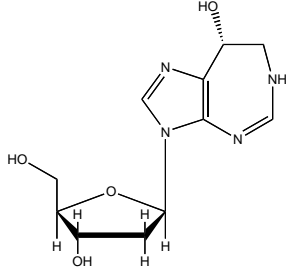
Porfimer sodium

\*\*\*\*\*

**Pentostatin:**

From Reference 5: Limited data in animals and humans indicate that pentostatin distributes relatively poorly into ccsf; with peak csf concentrations averaging approximately 10 percent of concurrent plasma concentrations. In a six year old

leukemia patient receiving pentostatin 0.25 mg/kg daily for 3 successive days by direct IV injection, serum and csf (via lumbar puncture) pentostatin concentrations four hours after the initial dose were approximately 147 and 19 ng/mL respectively.

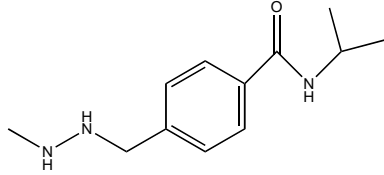


pentostatin

Purine analog, these usually cross brain barrier more significantly.  
 $C_{11}H_{16}N_4O_4$

\*\*\*\*\*

### Procarbazine hydrochloride (natulan):

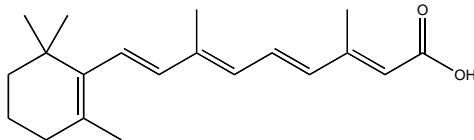


procarbazine

Reference 5: The drug crosses the blood-brain barrier and distributes into CSF. Equilibration of procarbazine between plasma and csf occurs rapidly following oral administration.

\*\*\*\*\*

### Trans-retinoic acid :not detected in the cerebral spinal fluid



trans-retinoic acid

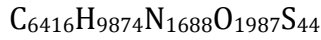
$C_{20}H_{28}O_2$  N:C ration 0:20

\*\*\*\*\*



**Rituxan, rituximab** 1-1.7 percent in csf, however, this is hard to believe. Again, a huge monoclonal antibody.

In reference 5: There is no information.

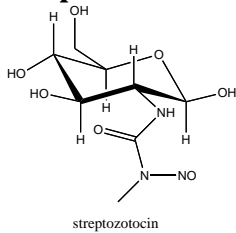


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**Somatuline lanreotide** already looked at I think there is no information, but I will check

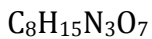
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**Streptozocin** no metabolites, yes



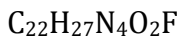
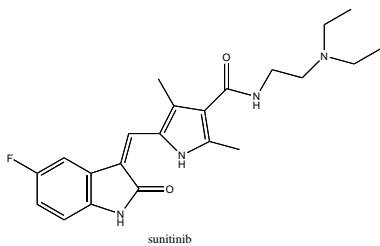
Most nitrosoureas cross the brain barrier

Reference 5: Streptozocin does not appear to cross the blood brain barrier in animals or humans; however, in humans metabolites of streptozocin appear to pass into the csf. In one study in patients receiving 14C and 3H labeled streptozocin, 14C labeled metabolites were found in the csf (the metabolites contained the nitroso moiety). Their concentration was equal to concurrent plasma levels. There was no detection of the tritium label in the csf. It has yet to be determined if these metabolites have any antineoplastic activity against CNS tumor.



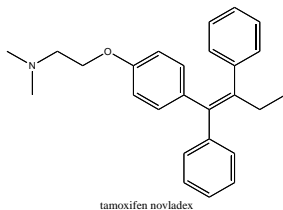
\*\*\*\*\*

**Sunitinib malate, sunit** animal studies suggest that it is able to cross the brain barrier



\*\*\*\*\*

**Tamoxifen Novladox** looked at earlier crosses brain barrier



Reference 5: no information

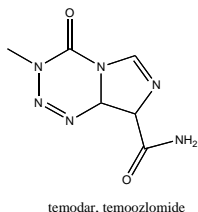
$C_{26}H_{29}NO$

I have read in DeVito that it does cross the brain barrier and at very high concentrations has activity against primary brain cancer (different mechanism than its anti-breast cancer activity). It also says in Devito that tamoxifen might bind p-glycoprotein and deactivate it. Got to get reference.

It could have some utility in breast cancer brain metastasis.

\*\*\*\*\*

**Temodal temozolomide, temodar** crosses the brain barrier 9-29 percent of serum concentration



The molecule is stable at acidic pH less than five and labile at pH greater than 7 hence it can be administered orally (what if patient is using a lot of antacids). The prodrug temosolomide is rapidly hydrolyzed to the active 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide MTIC at neutral and alkaline pH values with hydrolysis even faster at alkaline pH. This compound is abbreviated MTIC which is further hydrolyzed at physiological pH to 5-amino-imidazole-4-caarboxamide AIC which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine which is believed to be the active alkylating species. Reference 3

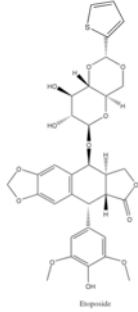
Weakly bound to proteins. Mean radioactivity bound to proteins 15 percent referen ce 3 nothing about brain.

$C_6H_6N_6O_2$

Reference 5: no information.

\*\*\*\*\*

**Teniposide** crosses the brain barrier csf :plasma ration 1-3 percent

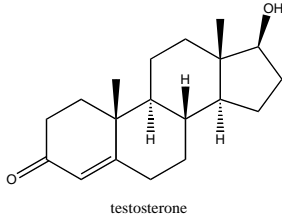


basically this is etoposide with a thiophene ring in place of the methyl group. Very interesting and makes me worried about etoposide. Have to redraw.

$C_{32}H_{32}O_{13}S$

\*\*\*\*\*

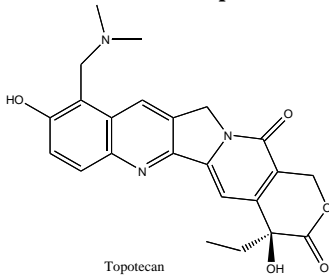
**Testosterone** weird data sheet but I bet it does steroids usually do



Reference 5: no information

\*\*\*\*\*

**Topotecan**: crosses brain barrier csf to plasma ratio is 29 percent after a 24 hour infusion and 42 percent after a 72 infusion. Slower infusion better. Please note.

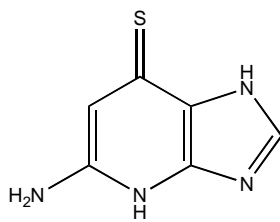


$C_{23}H_{23}N_3O_5$

Reference 5: Following IV administration about 35% of the drug is bound to plasma proteins.

.....

**Thioguanine:** According to reference 3, no measurements of thioguanine have been made in the csf of humans, but observations of tissue distribution in animals along with the lack of cns penetration of the closely related compound, mercaptopurine, suggests that thioguanine does not penetrate the brain barrier.



thioguanine



\*\*\*\*\*

**Traztuzumab: see Herceptin** above.

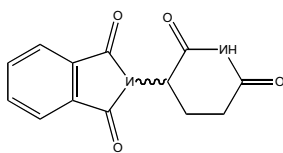
Monoclonal antibody. Large protein

From reference 5: It is not known whether the drug crosses the brain barrier into csf.

\*\*\*\*\*

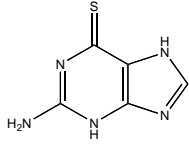
**Thalidomide** crosses the brain barrier

thalidomide



The famous teratogenic compound, it probably crosses the brain barrier as **revlimid** is a structural analogue and is perported to cross and thalidomide I know was used at one time to treat primary brain cancer, maybe metastasis too.

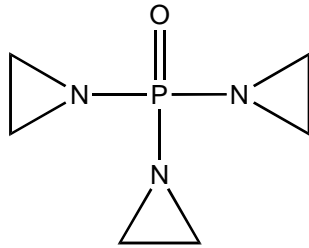
**Thioguanine** negligible



Thioguanine, tioguanine

\*\*\*\*\*

**Thiotepa** crosses brain barrier and triethylenephosphoramidate metabolite crosses as well



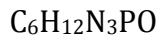
thiotepa

\*\*\*\*\*

**Tretinoin** not detected in csf

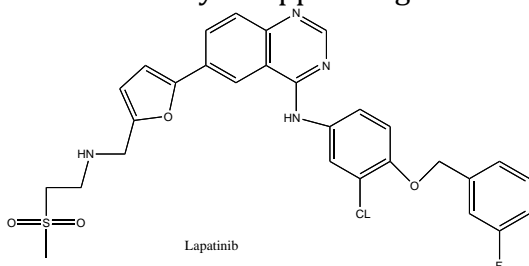
From reference 5: Tretinoin does not appear to be distributed into the csf and probably in not effective for treating leukemia in the CNS.

Plasma protein binding of tretinoin exceeds 95%.



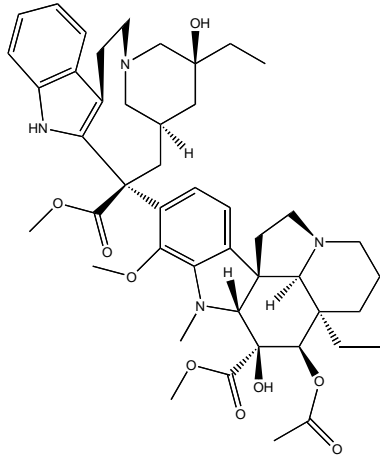
\*\*\*\*\*

**Tykerb** already discussed lapatinib, supposedly does cross, but I have read otherwise Very disappointing in treatment of brain metastasis.



\*\*\*\*\*

**Velbe vinblastine** poorly not in therapeutic concentrations

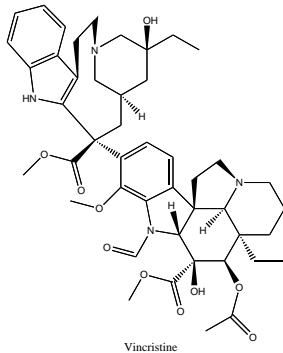


vinblastine

Reference 5: Vinblastine does not appear to distribute into the csf in therapeutic amounts.

\*\*\*\*\*

**Vincristine** no significant amount

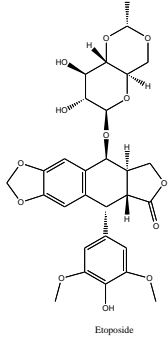


Vincristine

Vincristine and its metabolites appear to poorly cross the blood brain barrier after rapid IV administration and generally do not appear in the csf in cytotoxic concentrations.

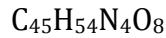
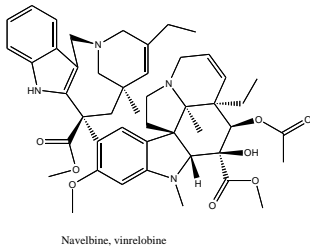
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**Vepesid etoposide** in low and variable concentrations



\*\*\*\*\*

**Vinorelbine** already discussed navelbine brain and plasma levels comparable in animal studies

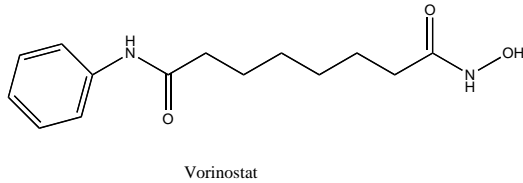


Reference 5: nothing about csf or brain barrier, but binding of drug to plasma proteins in patients with cancer ranges from 79.6 – 91.3 percent.

I doubt very much that this crosses the brain barrier.

\*\*\*\*\*

**Vorinostat** crosses brain barrier



Reference 5: no info, but this compound has been touted in recent articles to be a potential drug for cns tumors and that it will cross the brain barrier.

\*\*\*\*\*

## References

1. BC Cancer Drug Manual
2. [AHFS Drug Information 2005](#)
3. [PDF ninth edition](#)
4. [PDF tenth edition](#)
5. [AHFS Drug Information 2010](#)

6. DeVita, V.T. Hellman, S. Rosenberg, S. A. Cancer Principles and Practice of Oncology, ninth edition
7. Friedman et al. J. Clin. Oncol. 2009, 27, 4733-4740
8. Keiset, J et al. J. Clin. Oncol 2009, 27, 740-745
9. Gupta et al. J. Clin. Oncol. 1997 15, 1502-1510
10. Loeffner, J.S. and Eichler, A.F. 2007, 12, 7, 884-898

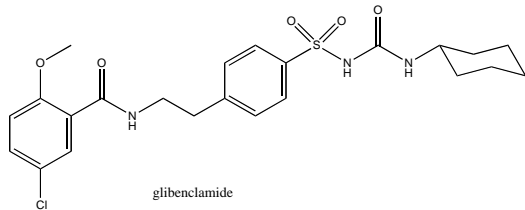
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### Molecules that bind p-glycoprotein pump

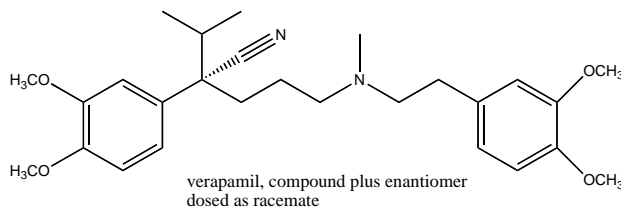
Extensive protein binding greater than 99 percent bound to plasma proteins.

Formula C<sub>23</sub>H<sub>28</sub>ClN<sub>3</sub>O<sub>5</sub>S

Molecular weight 494



### verapamil



C<sub>27</sub>H<sub>38</sub>N<sub>2</sub>O<sub>4</sub>

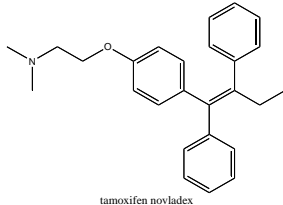
MW= 454.6

According to the drug manual, reference five, Approximately 90 percent of perapamil is bound to proteins. Verapamil and norverapamil distribute into the cns. Following oral administration of 120 mg of the drug 4 times daily to schizophrenic paitents, mean csf concentrations of verapamil and norverapamil were 6 and 4 percent of mean plasma concentrations.

Tamoxifen

**Novladox** looked at earlier crosses brain barrier





tamoxifen novladex

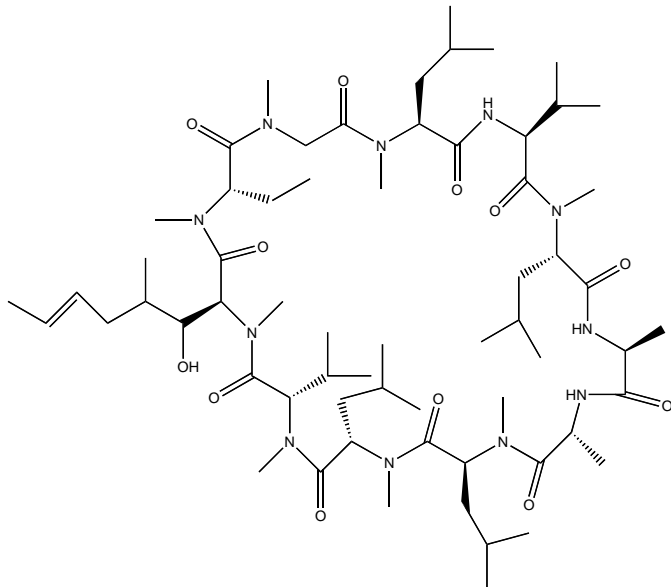
Reference 5: no information

$C_{26}H_{29}NO$

I have read in DeVito that it does cross the brain barrier and at very high concentrations has activity against primary brain cancer (different mechanism than its anti-breast cancer activity). It also says in DeVito that tamoxifen might bind p-glycoprotein and deactivate it. Got to get reference. I can't find this in the papers we copied have to go back maybe tomorrow.

It could have some utility in breast cancer brain metastasis.

cyclosporine A



cyclosporin

dihydropyridines maybe amiodipine

adverse effects such as valsopodar (PSC833)

and biricodor (VX-710).[43-45](#)