Supporting Information

Macrocyclic drugs and clinical candidates – what can medicinal chemists learn from their properties

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METHODS

Macrocyclic drugs were identified using the GVK BIO Online Structure Activity Relationship Database (GOSTAR), a database integrating metadata from several different sources.[1] Chemical structures were recovered from GOSTAR, or from the literature, and molecular entities comprising a ring containing ≥12 atoms were selected for further analysis. Information on their preclinical and clinical development status was retrieved from GOSTAR; compounds not yet marketed and discontinued drugs were excluded. Drugs were then classified based on their therapeutic indication and those for veterinary use only were removed. Contrast agents were also filtered out from the dataset. Finally, biologicals and protein-based therapeutics, here defined using the size limit for polypeptides (number of amino acids ≥30) were excluded from the analysis.

The members of the final dataset of macrocyclic drugs were classified based on the nature of their chemical structure (e.g. being an alkaloid, cyclic peptide, etc), and the two largest classes (i.e. cyclic peptides and macrolides) were further subclassified according to distinguishing structural features (e.g. glycopeptides, erythronolides, etc). Common molecular descriptors were then calculated using AstraZeneca's in silico engine c-lab,[2] for the final set of macrocyclic drugs. Descriptors were not calculated for those drugs consisting of a mixture of different chemical entities, i.e. capreomycin sulphate, ivermectin, polymyxin B sulphate, porfimer sodium and teicoplanin.

Information on the preferred route of administration was also collated from GOSTAR, and confirmed from the literature. For the purpose of this analysis, drugs that are dosed orally but exert their pharmacological action in the gastrointestinal tract, without the need for systemic absorption, were not included in the "oral" class. Instead they were classified as parenteral and included in the overall class of parenteral drugs. If multiple routes of administration were reported for a given drug, e.g. for use in different patient segments or therapeutic indications, the drug was classified as being oral if one route of administration was oral, and further analysis followed accordingly.

Data on the human doses for members of the final set of macrocyclic drugs was retrieved from GOSTAR, and confirmed from the literature, then converted to an average daily dose expressed in milligrams (mg), to adequately normalise across different dosing ranges and regimens (e.g. once daily, twice daily), and dose notations [e.g. milligram/kilogram (mg/kg), gram/body surface (g/m^2)]. Where possible, information on the human pharmacokinetic profile, specifically oral bioavailability (F), was obtained from the literature. To facilitate analysis, human F data were also binned to three categories (Low: F<30%; Medium: 30% < F < 60% and High: F>60%).

A dataset of macrocycles in clinical development was obtained in an analogous manner by mining of Adis R&D Insight,[3] and then complemented by a few additional macrocycles reported in the literature Compounds for which structures were not available were excluded from this

dataset and curation was performed as described above for the set of marketed drugs. Annotation was also carried out as for the marketed macrocyclic drugs. However, the human dose was not included as this either had not been set, or was not publically available, for most of the clinical candidates.

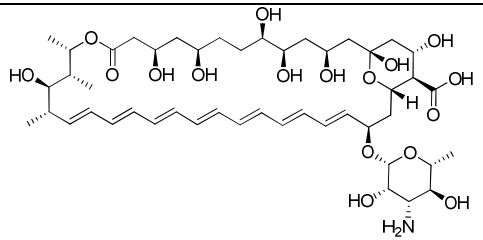
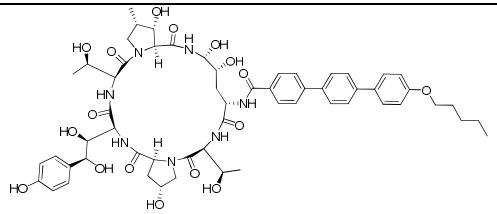
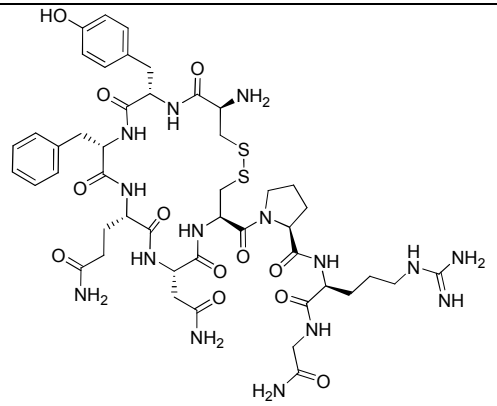
REFERENCES

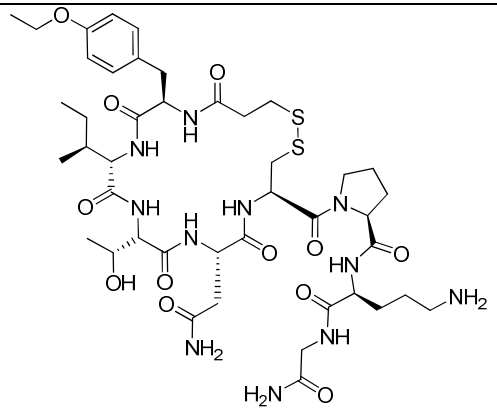
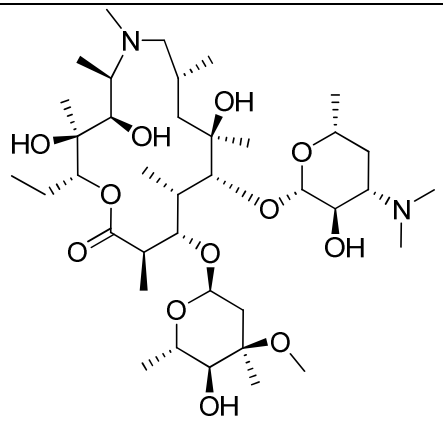
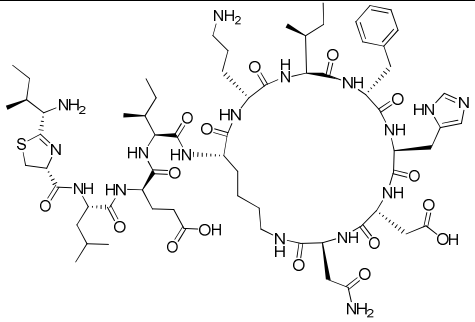
(1) GOSTAR: http://gostardb.com/gostar/doc/HyperlinkDownloadPDF.pdf (accessed in April, 2013).

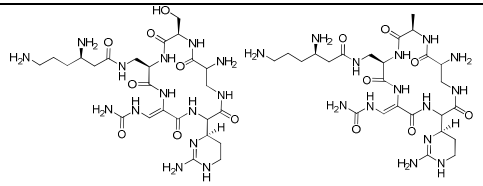
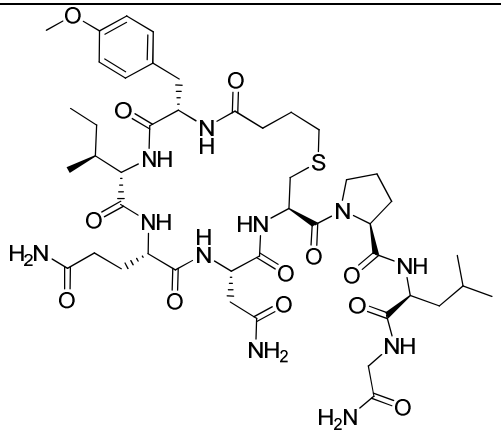
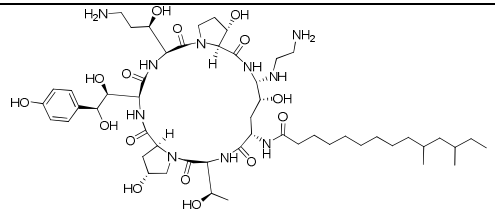
(2) Cumming, J. G.; Winter, J.; Poirrette, A. *Drug Discov. Today* **2012**, *17*, 923-927.

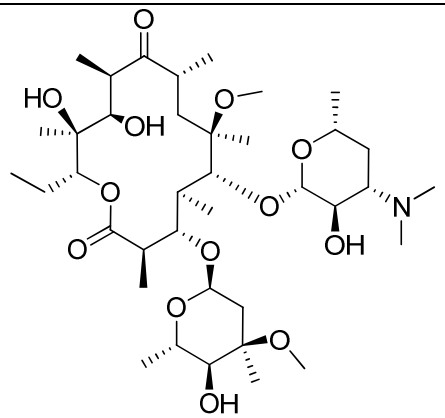
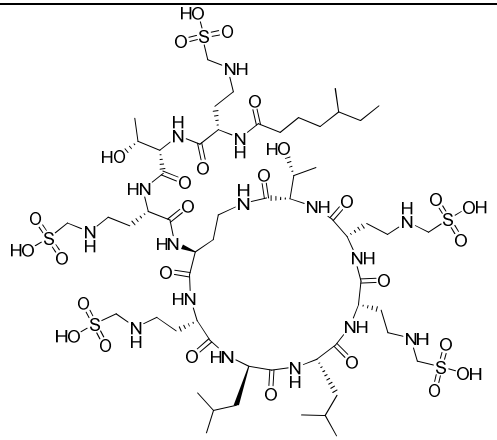
(3) Adis R&D Insight: http://www.springer.com/adis/databases?SGWID=0-1749113-0-0-0

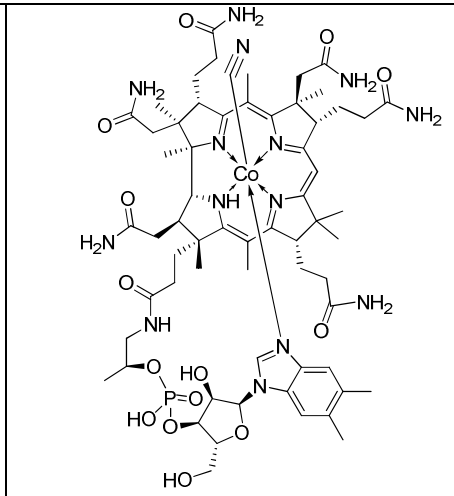
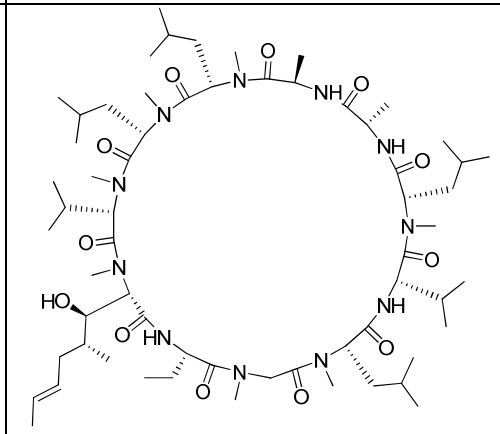
TABLES

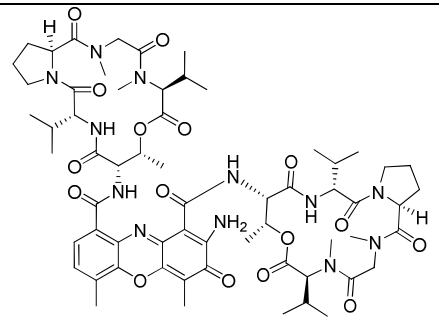
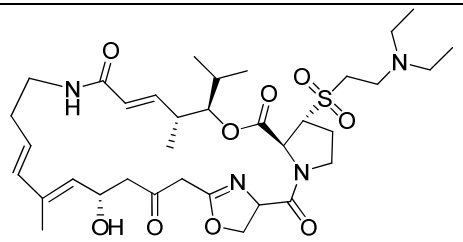
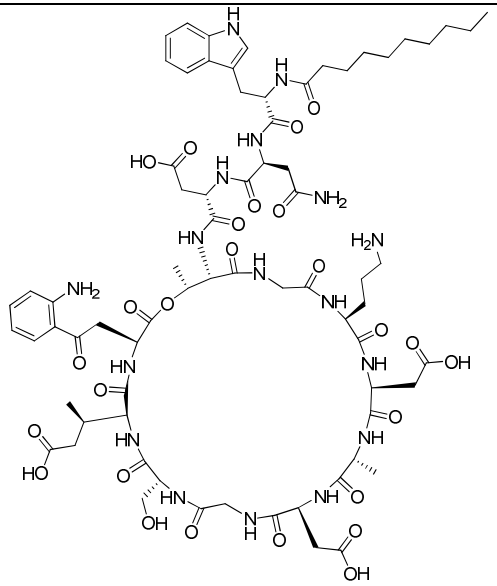
Drug Name		Class	SubClass	Therapeutic Area	Oral	Avg Dose (mg/day)	Human F (%)	Human F Class	HBD	PSA	MW	ClogP
Amphotericin b		Macrolide	Polyene	Infection	No	43,75			13	348	924	-3,7
Anidulafungin		Cyclic peptide	Echinocandin	Infection	No	200			14	416	1140	2,2
Argipressin		Cyclic peptide	Disulfide bridge	Cardiovascular	No				20	505	1084	-3,8

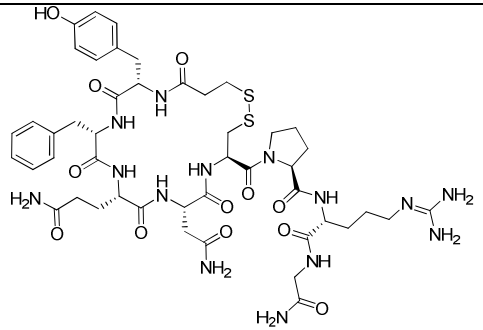
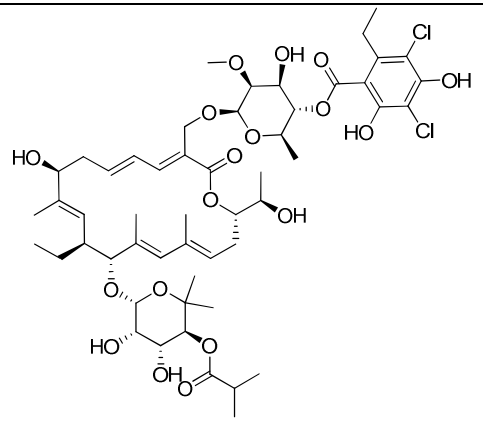
Atosiban		Cyclic peptide	Disulfide bridge	Gynecology	No				14	402	994	-0,1
Azithromycin		Macrolide	Erythronolide	Infection	Yes	500	37	Med	5	186	749	2,64
Bacitracin		Cyclic peptide	Lactam bridge	Infection	No				20	579	1423	-2,1

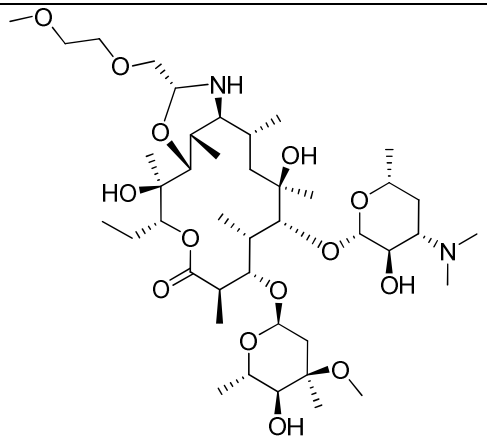
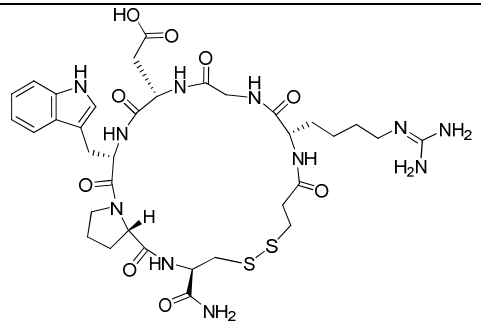
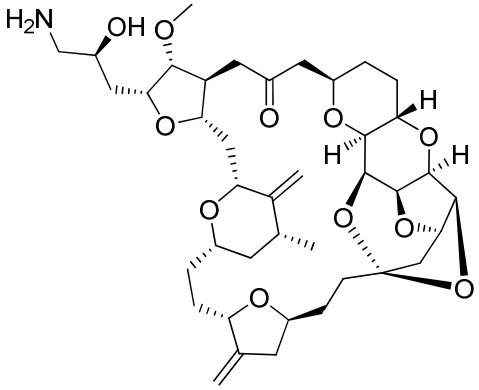
Capreomycin		Cyclic peptide	Sidechain modification	Infection	No	1000						
Carbetocin		Cyclic peptide	Thioether bridge	Gynecology	No	0,1			13	398	988	-0,03
Caspofungin		Cyclic peptide	Echinocandin	Infection	No	120			18	454	1093	-2,9

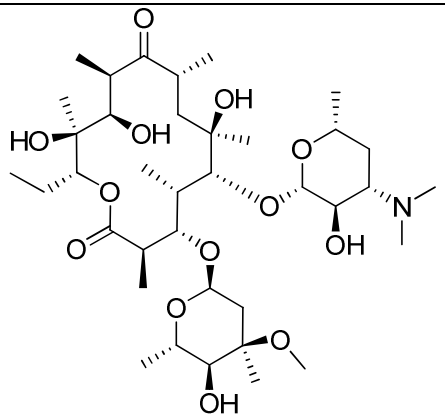
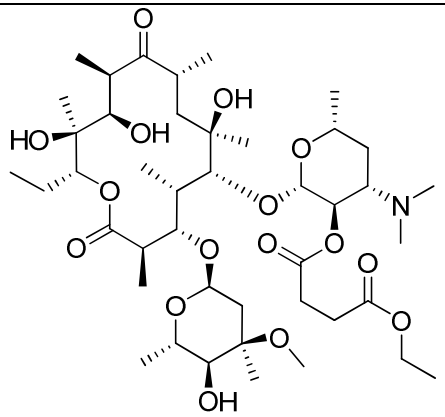
Clarithromycin		Macrolide	Erythronolide	Infection	Yes	1000	55	Med	4	190	748	2,4
Colistimethate		Cyclic peptide	Sidechain modification	Infection	No	787,5			23	778	1640	-24

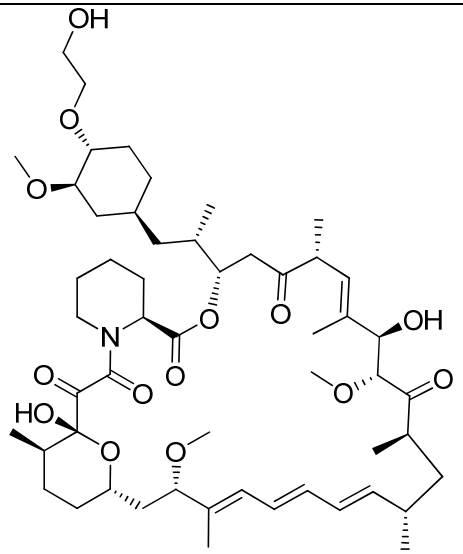
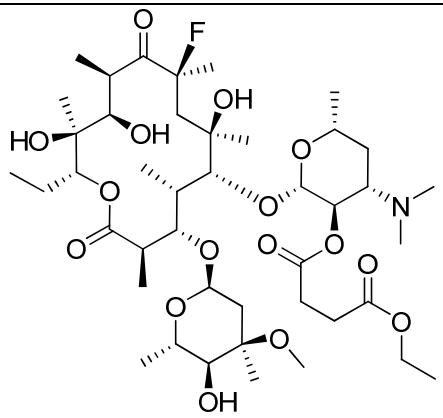
Cyanocobalamin		Porphyrin		Hematology	No	0,625			16	492	1355	-0,5
Cyclosporine		Cyclic peptide	N-methylated	Immunology	Yes	950	30	Med	5	290	1203	14

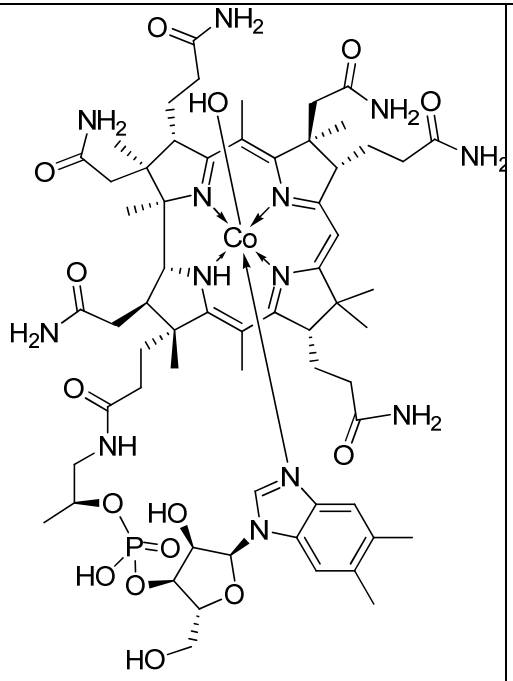
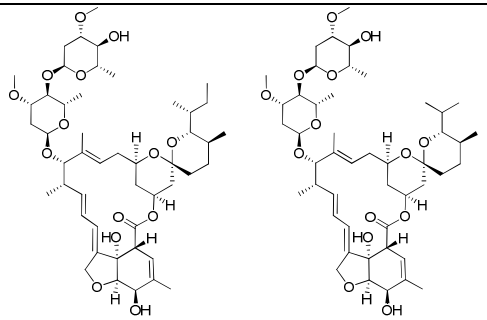
Dactinomycin		Cyclic peptide	N-methylated	Oncology	No	0,5			6	368	1255	8,1
Dalfopristin		Macrolide	Streptogramin	Infection	No	1312,5			2	178	691	1,4
Daptomycin		Cyclic peptide	Lipopeptide	Infection	No	280			25	774	1621	-2,4

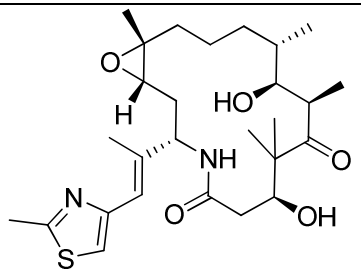
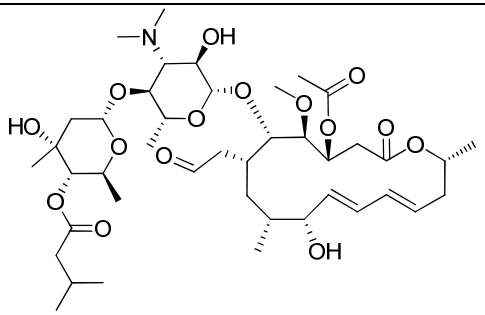
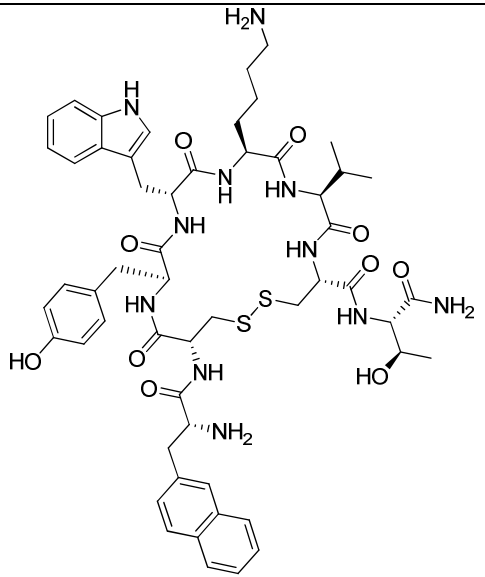
Desmopressin		Cyclic peptide	Disulfide bridge	Cardiovascular	No	0,1			18	477	1069	-3,2
Difimicin		Macrolide	Tiacumicin	Infection	No	400			7	284	1058	7,2

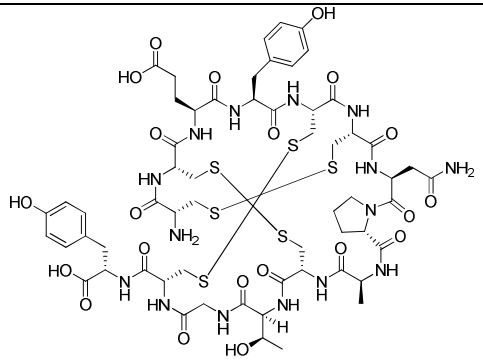
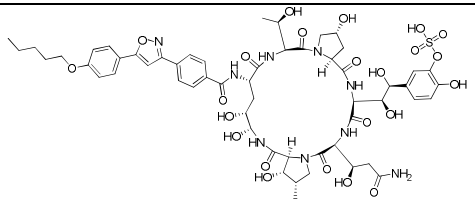
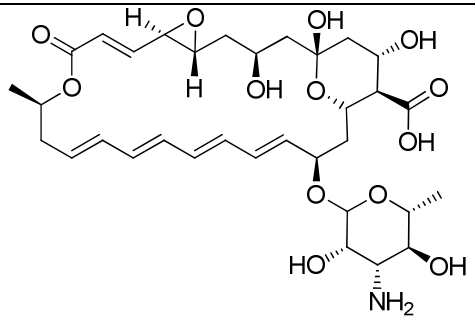
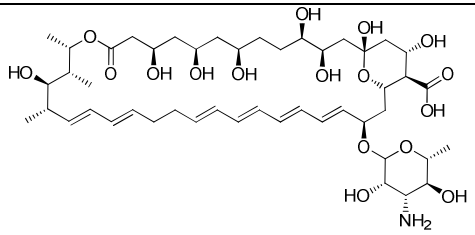
Dirithromycin		Macrolide	Erythronolide	Infection	Yes	500	10	Low	5	204	835	2,8
Eptifibatide		Cyclic peptide	Disulfide bridge	Cardiovascular	No	12,6			13	350	832	-2,9
Eribulin		Macrolide	Halicondrin	Oncology	No	2,268			3	148	730	1,2

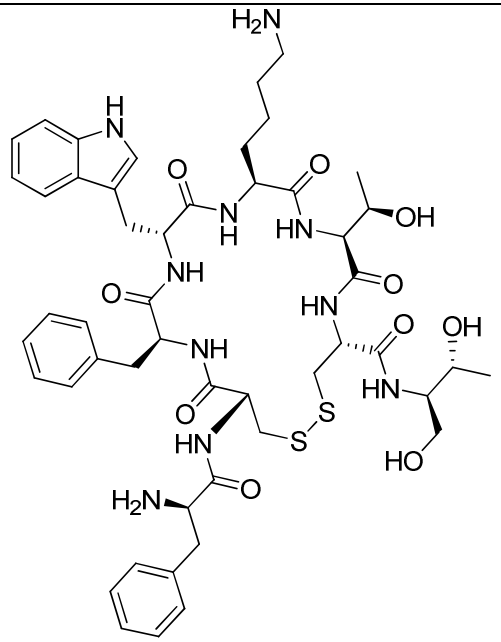
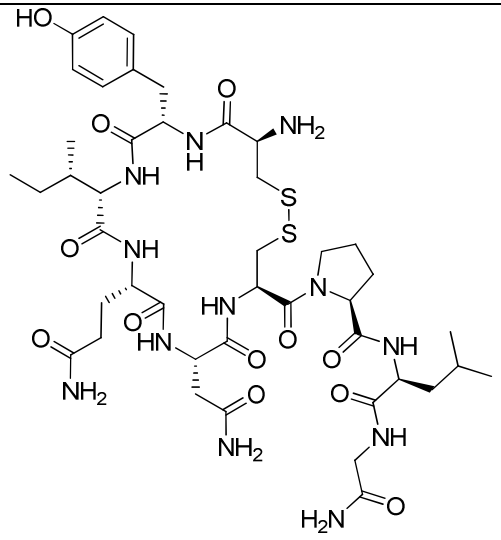
Erythromycin		Macrolide	Erythronolide	Infection	Yes	2500	25	Low	5	203	734	1,6
Erythromycin ethyl succinate		Macrolide	Erythronolide	Infection	Yes	500	55	Med	4	235	862	3,2

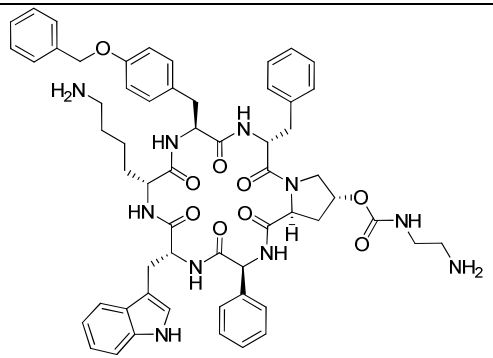
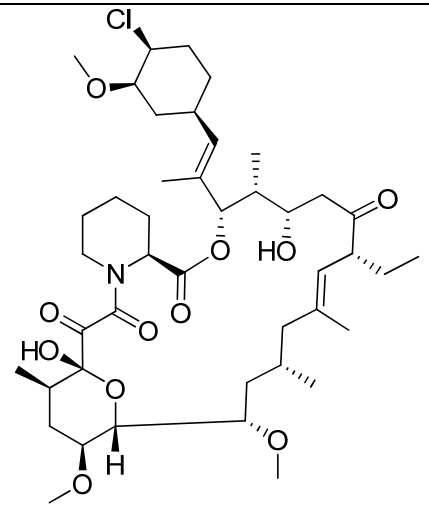
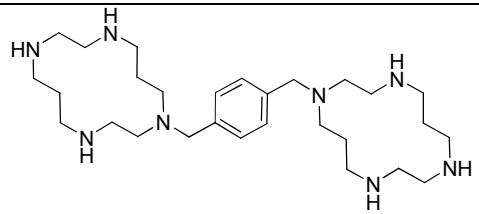
Everolimus		Macrolide	Rapamycin	Immunology	Yes	2,75	16	Low	3	213	958	7,1
Flurithromycin ethylsuccinate		Macrolide	Erythronolide	Infection	Yes	500		Med	4	235	880	3,0

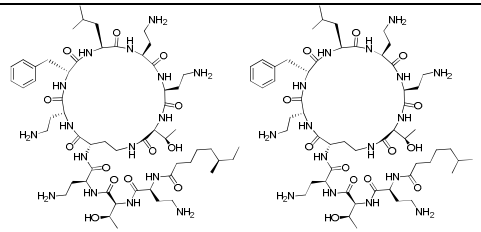
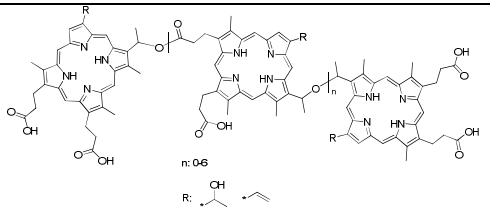
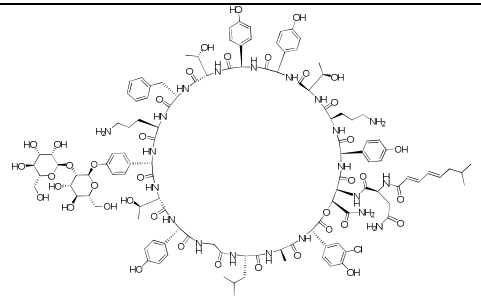
Hydroxocobalamin		Porphyrin		Hematology	No	0,625			17	507	1347	-1,2
Ivermectin		Macrolide	Avermectin	Infection	Yes	9	60	Med				

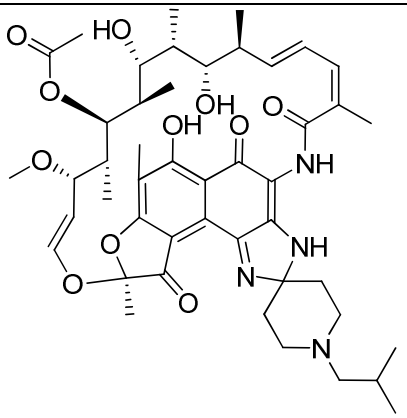
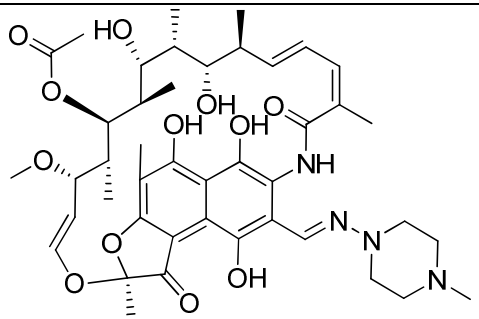
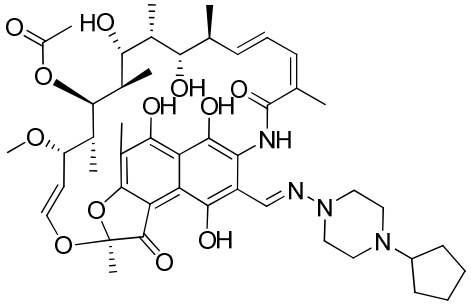
Ixabepilone		Epothilone	Epothilone	Oncology	No	64,8			3	115	507	3,1
Josamycin		Macrolide	Leucomycin	Infection	Yes	1000	95	Hi	3	212	828	3,7
Lanreotide		Cyclic peptide	Disulfide bridge	Endocrinology	No				16	392	1096	3,4

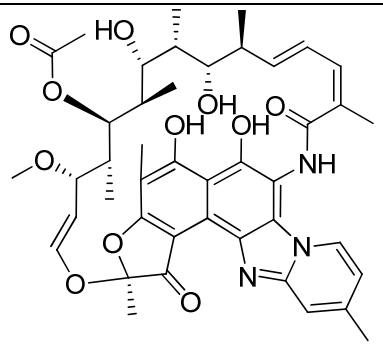
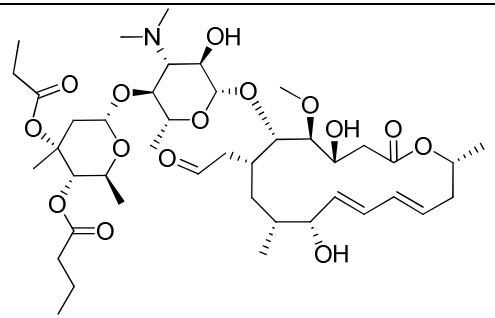
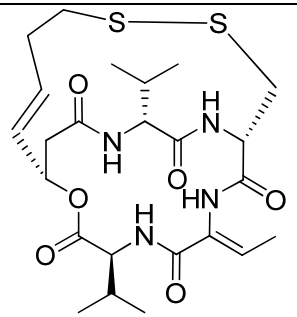
Linaclotide		Cyclic peptide	Disulfide bridge	Gatro-intestinal	No				19	637	1526	-3,1
Micafungin		Cyclic peptide	Echinocandin	Infection	No	50			19	571	1272	-2,6
Natamycin		Macrolide	Polyene	Infection	No	7,5			8	244	666	-4,8
Nystatin		Macrolide	Polyene	Infection	No	100			12	325	924	-2,9

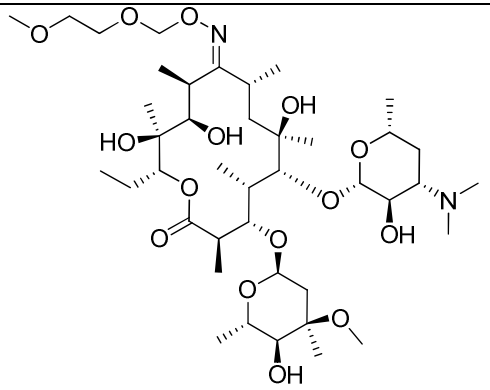
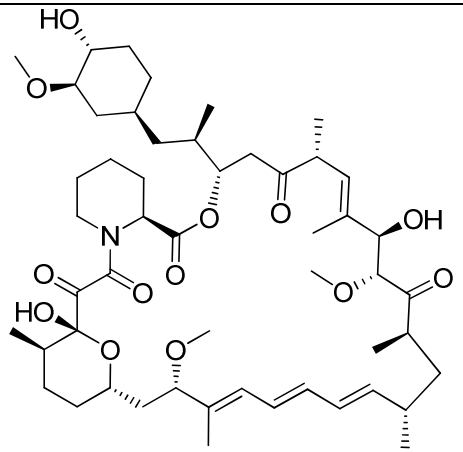
Octreotide		Cyclic peptide	Disulfide bridge	Oncology	No	0,6			15	368	1019	2,5
Oxytocin		Cyclic peptide	Disulfide bridge	Gynecology	No				16	439	1007	-0,7

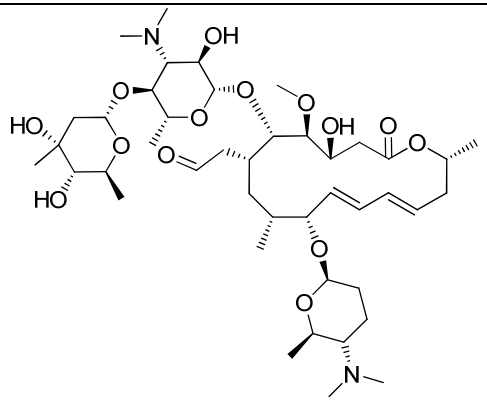
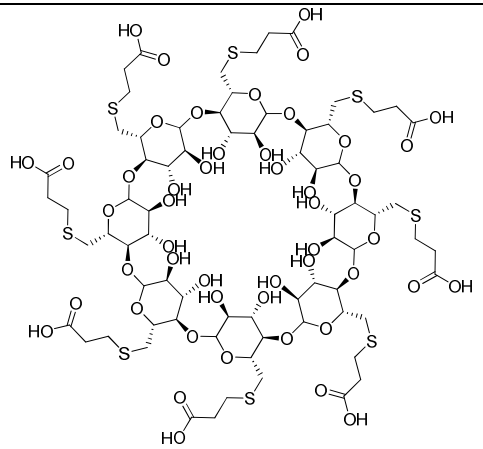
Pasireotide		Cyclic peptide	Sidechain modification	Endocrinology	No	1,2			11	304	1047	6,7
Pimecrolimus		Macrolide	Ascomycin	Dermatology	No				2	158	811	6,0
Plerixafor		Bicyclam	Bicyclam	Oncology	No	16,8			6	90	503	-0,3

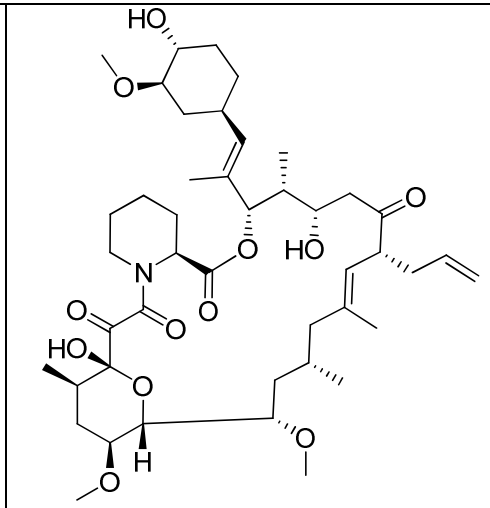
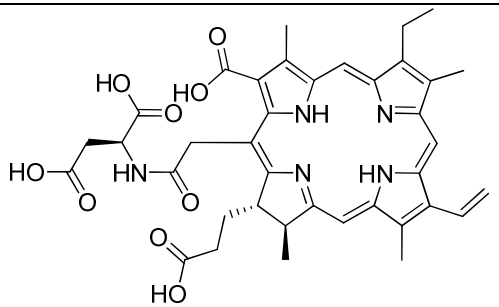
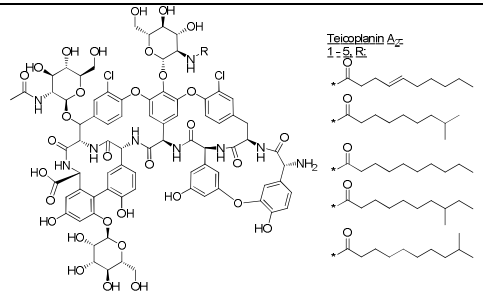
Polymyxin b		Cyclic peptide	Lipopeptide	Infection	No							
Porfimer		Porphyrin		Oncology	No							
Ramoplanin		Cyclic peptide	Depsipeptide	Infection	No				32	891	2144	0

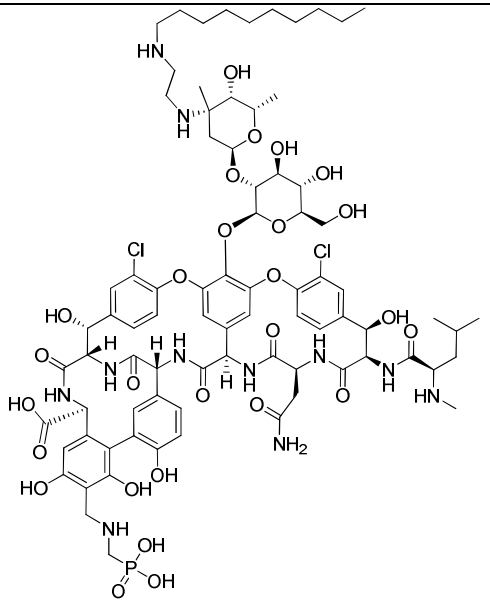
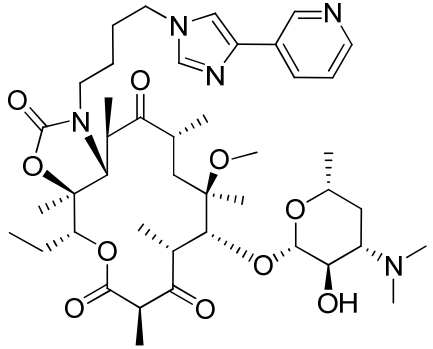
Rifabutin		Ansamycin	Naphtoquinone	Infection	Yes	300	53	Med	5	217	847	4,7
Rifampicin		Ansamycin	Naphtoquinone	Infection	Yes	600	50	Med	6	234	823	3,7
Rifapentine		Ansamycin	Naphtoquinone	Infection	Yes	750	70	Hi	5	211	847	5,1

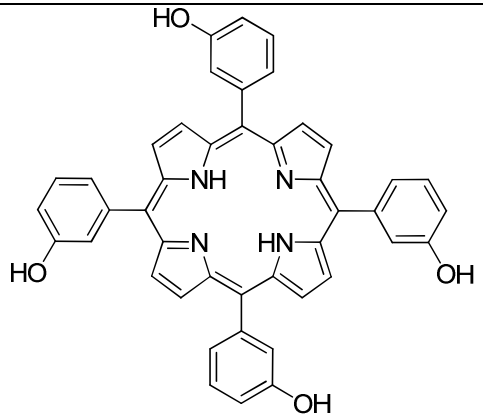
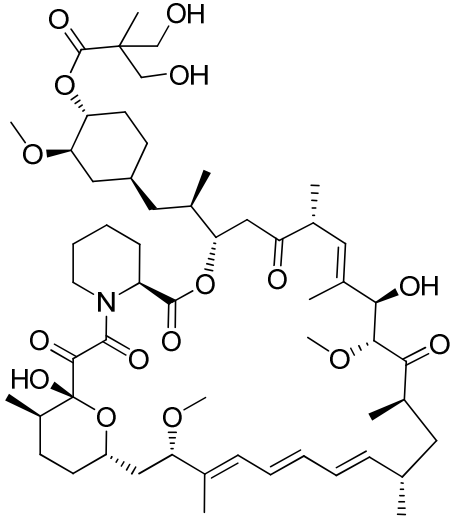
Rifaximin		Ansamycin	Naphtoquinone	Infection	No	600			5	206	786	7,2
Rokitamycin		Macrolide	Leucomycin	Infection	Yes	300			3	212	828	3,8
Romidepsin		Cyclic peptide	Depsipeptide	Oncology	No	22,68			4	158	541	3,4

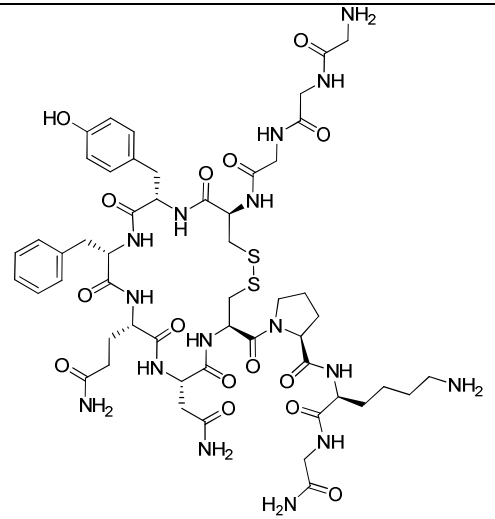
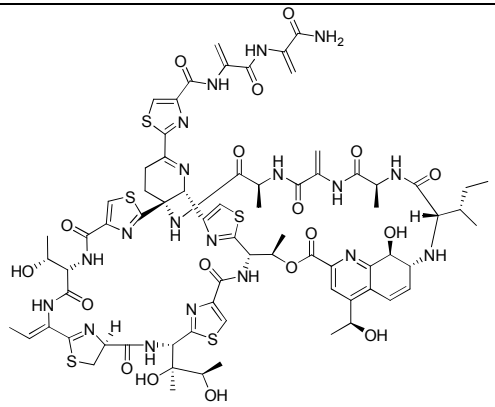
Roxithromycin		Macrolide	Erythronolide	Infection	Yes	300	78	Hi	5	224	837	2,3
Sirolimus		Macrolide	Rapamycin	Immunology	Yes	2	15	Low	3	204	914	7,0

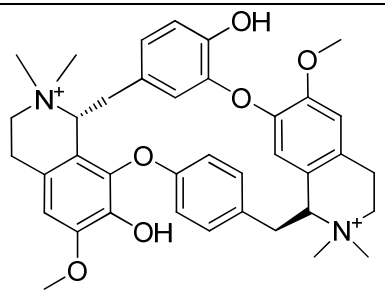
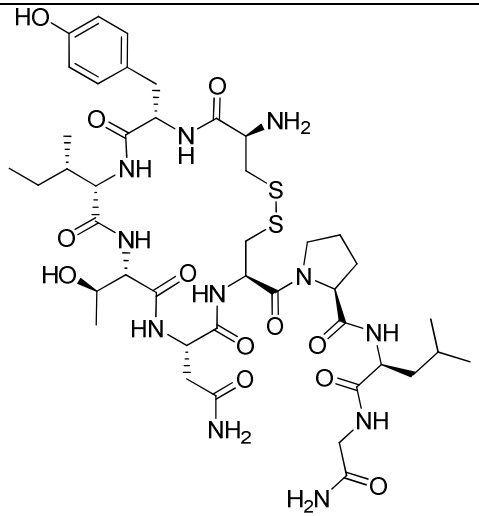
Spiramycin		Macrolide	Leucomycin	Infection	Yes	1500	35	Med	4	200	843	2,0
Sugammadex		Cyclodextrin	Cyclodextrin	Anesthesiology	No				24	828	2002	-12

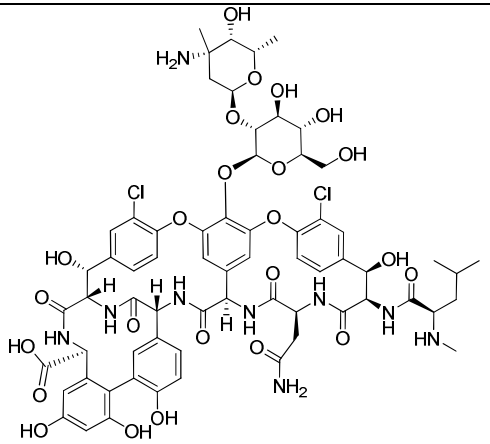
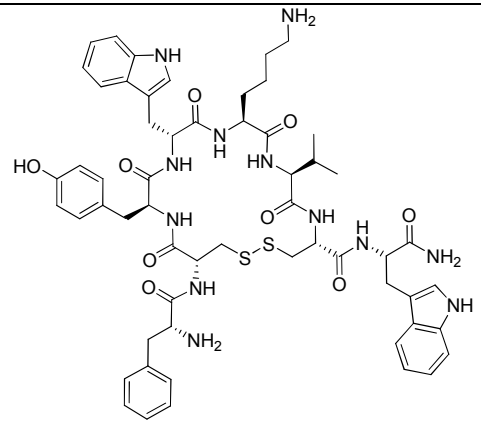
Tacrolimus		Macrolide	Ascomycin	Immunology	Yes	21	15	Low	3	186	804	5,8
Talaporfin		Porphyrin		Oncology	No	70			7	245	712	7,3
Teicoplanin		Cyclic peptide	Glycopeptide	Infection	No							

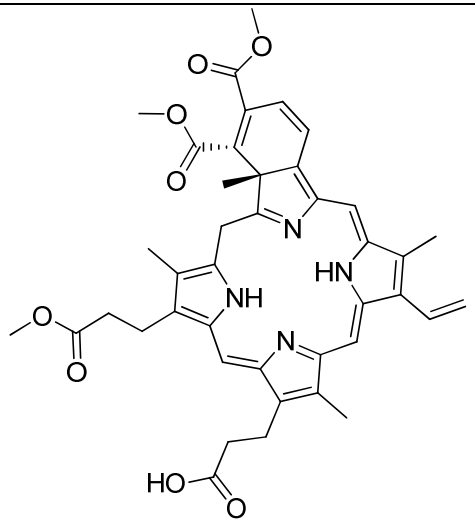
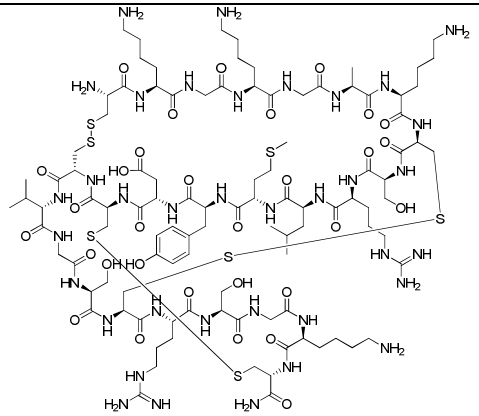
Telavancin		Cyclic peptide	Glycopeptide	Infection	No	700			24	665	1756	1,9
Telithromycin		Macrolide	Erythronolide	Infection	Yes	800	57	Med	1	163	812	3,8

Temoporfin		Porphyrin		Oncology	No				6	140	681	12
Temsirolimus		Macrolide	Rapamycin	Oncology	No	25			4	254	1030	7,5

Terlipressin		Cyclic peptide	Disulfide bridge	Cardiovascular	No	9,5			22	583	1242	-4,1
Thiostrepton		Cyclic peptide		Infection	No				18	600	1665	-0,6

Tubocurarine		Alkaloid		Anesthesiology	No	17,5			2	84	610	3,6
Urofollitropin		Cyclic peptide	Disulfide bridge	Gynecology	No	0,83			15	415	980	0,4

Vancomycin		Cyclic peptide	Glycopeptide	Infection	No	2000			21	585	1449	-1,1
Vapreotide		Cyclic peptide	Disulfide bridge	Cardiovascular	No	1,2			16	383	1131	4,3

Verteporfin		Porphyrin		Ophthalmology	No	9,72			3	170	719	6,5
Ziconotide		Cyclic peptide	Disulfide bridge	Pain	No	0,24			50	1259	2639	0

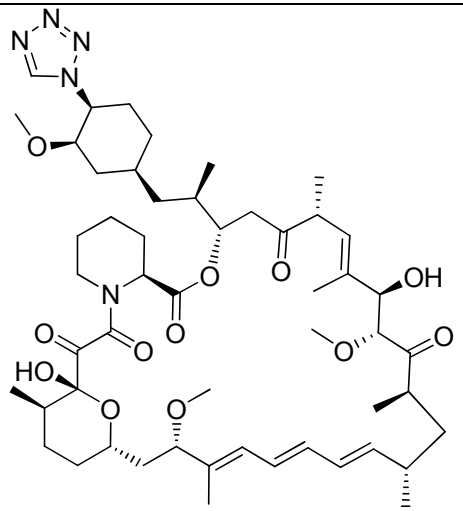
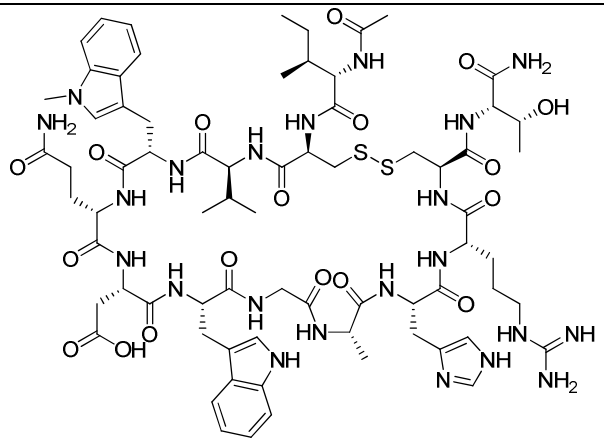
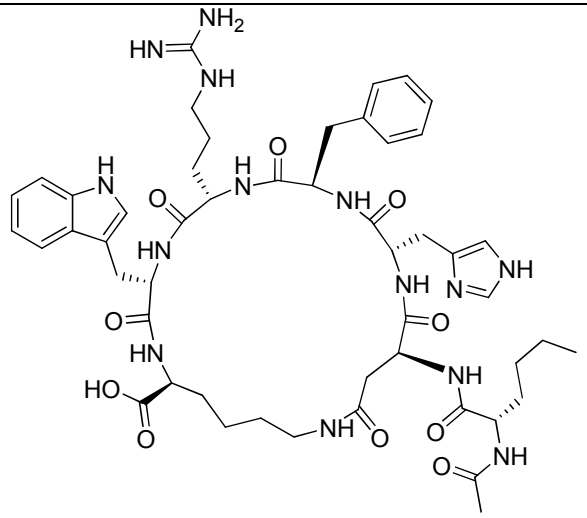
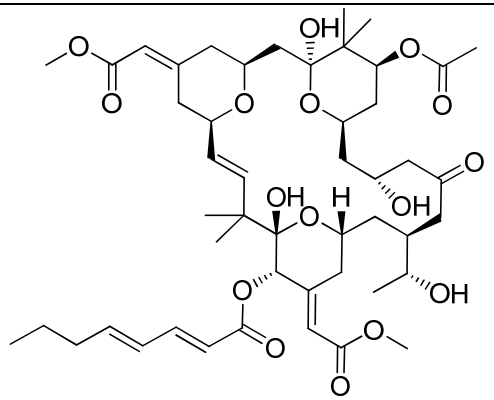
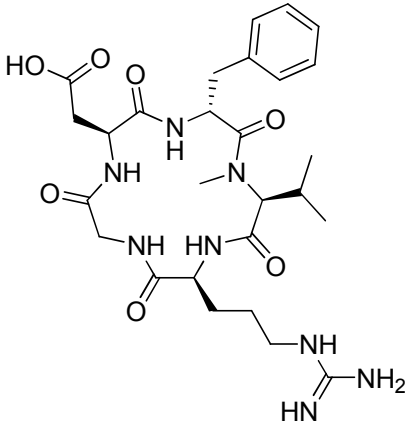
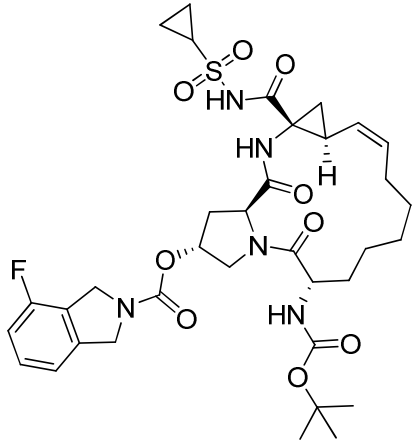
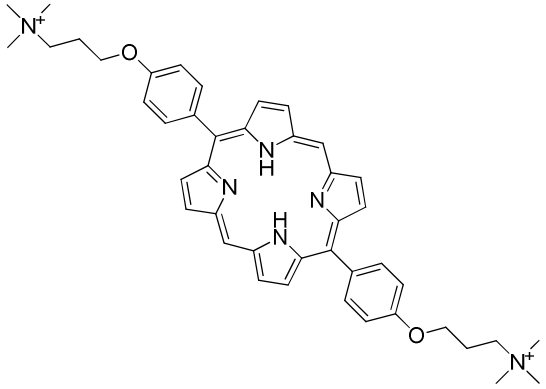
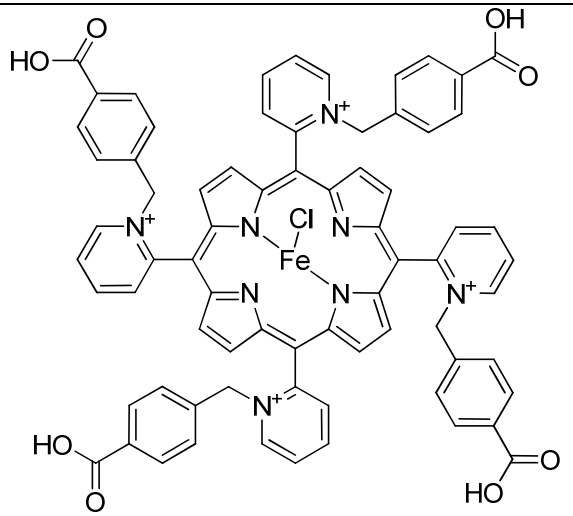
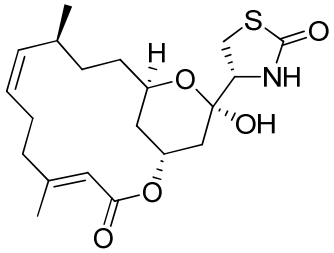
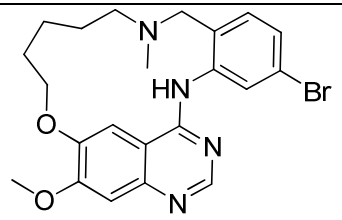
Zotarolimus		Macrolide	Rapamycin	Immunology	No	0,3			2	222	966	7,5

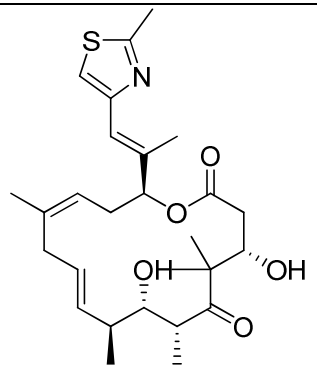
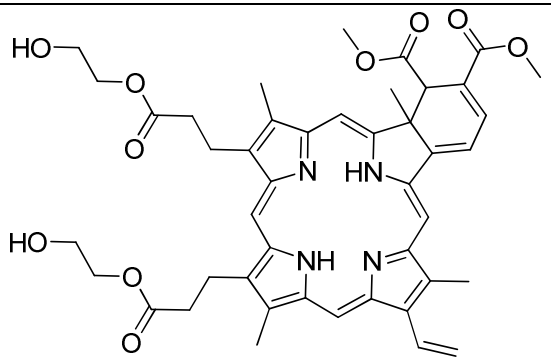
Table S1. Registered macrocyclic-based drugs as of April 2013.

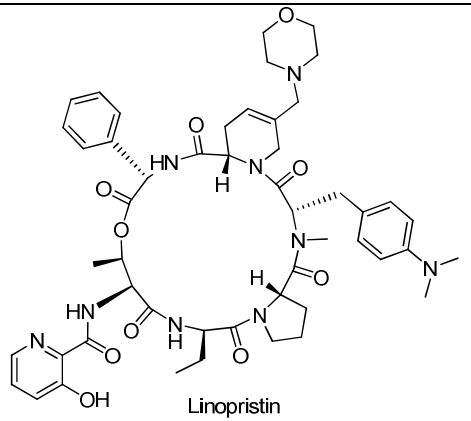
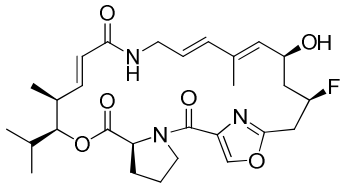
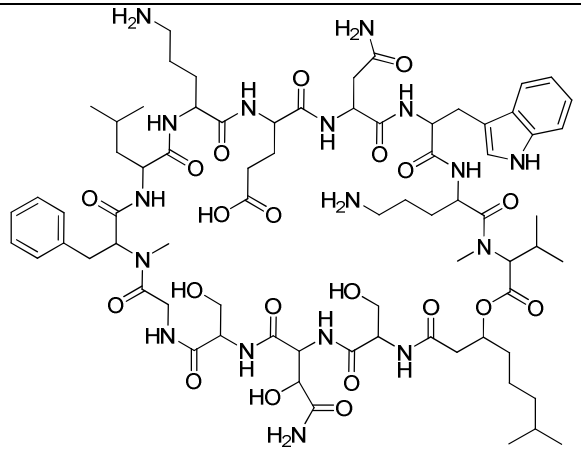
Drug Name	Structure	Class	Subclass	Therapeutic Area	Clinical Phase	Oral	HBD	PSA	Mw	ClogP
AL 78898A		Cyclic peptide	Disulfide bridge	Ophthalmology	II	No	25	687	1628	-3.9
Bremelanotide		Cyclic peptide	Lactam bridge	Endocrinology	II	No	15	407	1025	-1.8

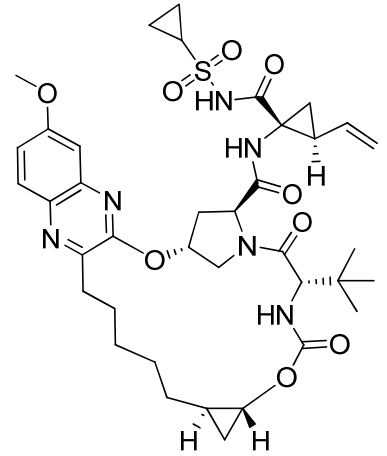
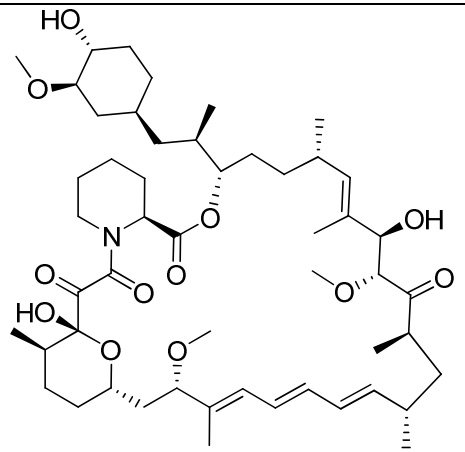
Bryostatin 1		Macrolide	Bryostatin	Oncology	I/II	No	4	243	903	3.0
Cilengitide		Cyclic peptide	N-methylated	Oncology	III	No	9	257	589	-1.7

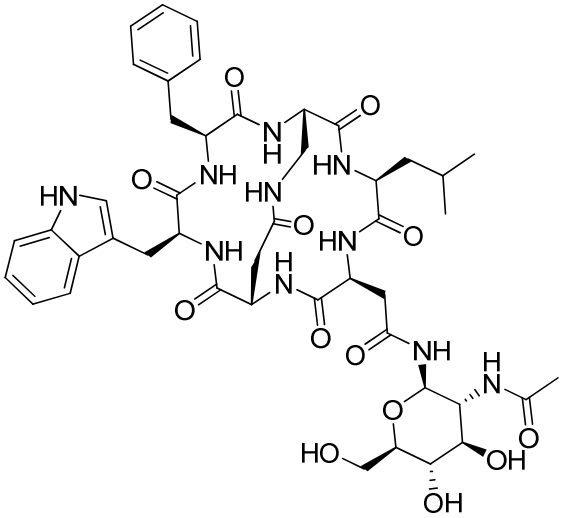
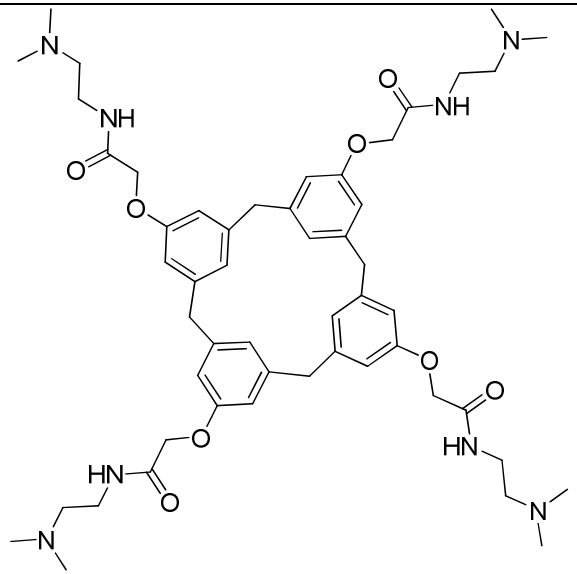
Danoprevir (R7227, ITMN191)		”de novo designed”		Infection	II	Yes	3	193	732	5.6
Exeporfinium (XF-73)		Porphyrin		Infection	I/II	No	2	67	695	2.7

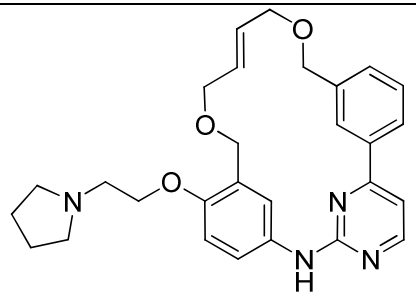
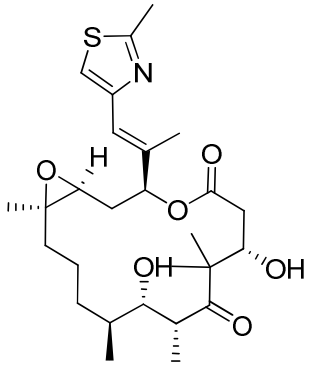
INO 4885		Porphyrin		Urinary	I		4	207	1249	-5.1
Latrunculin B (INS 115644)		Macrolide	Latrunculin	Ophthalmology	I	No	2	91	396	2.6
JNJ 26483327		”de novo designed”		Oncology	I	Yes	1	55	457	6.6

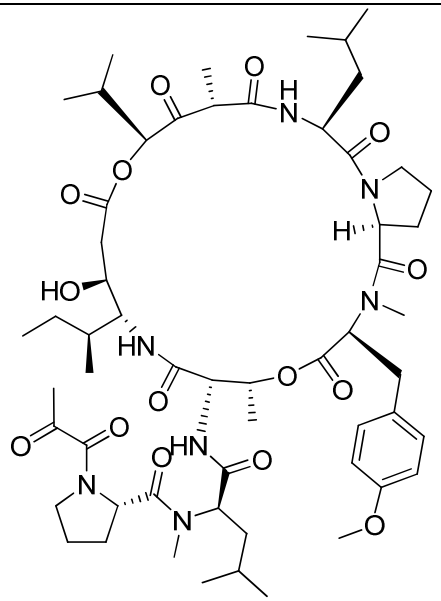
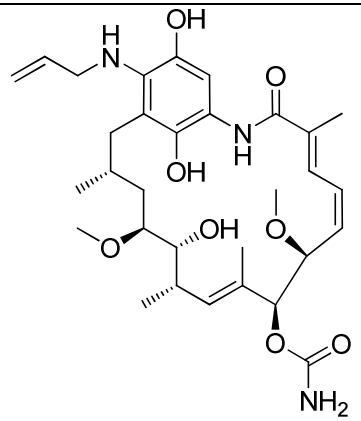
KOS 1584		Epothilone		Oncology	II	No	2	101	490	4.4
Lemuteporfin		Porphyrin		Dermatology	I/II	No	4	202	793	5.4

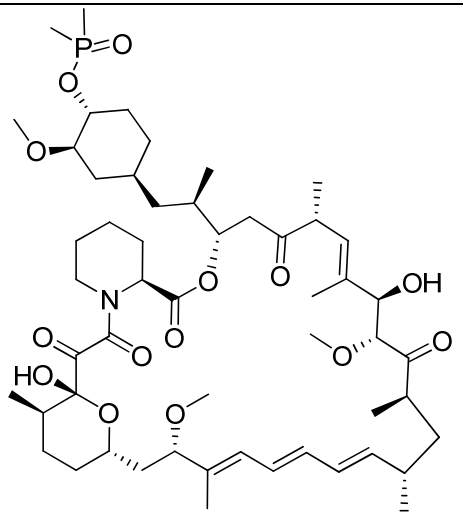
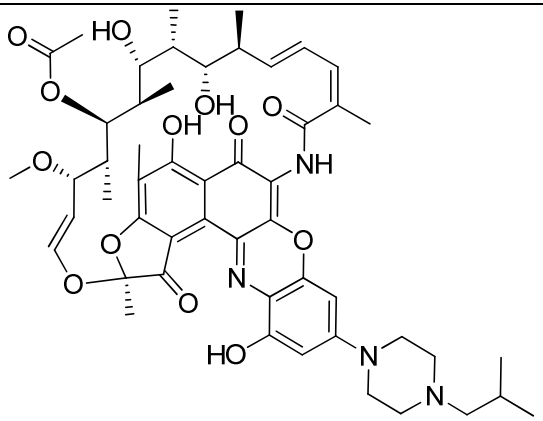
Linopristin/flopristin (NXL-103)	 Linopristin  Flopristin	Cyclic peptide	Depsipeptide	Infection	II	Yes				
Lotilibcin (JA 002, WAP-8294A2)		Cyclic peptide	Depsipeptide	Infection	I	No	23	665	1563	-2.0

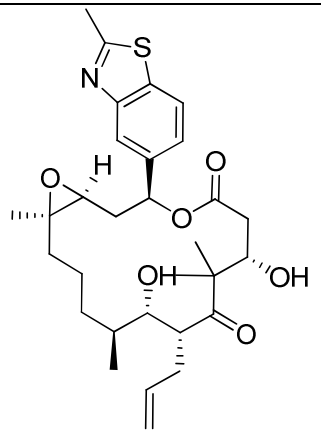
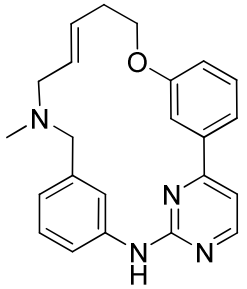
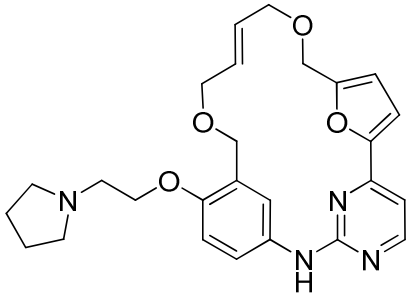
MK 5172		”de novo designed”		Infection	II	Yes	3	203	767	6.3
Myolimus		Macrolide	Rapamycin	Immunology	I	No	3	186	900	8.9

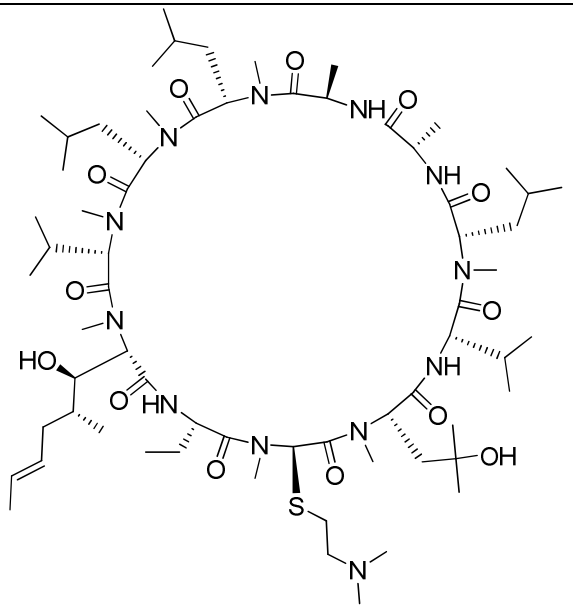
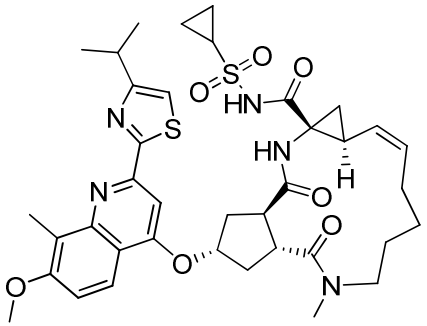
Nepadutant		Cyclic peptide	Lactam bridge	Gastro-Intestinal	II	No	13	386	947	1.1
OTX 008		”de novo designed”		Oncology	I	No	4	173	937	6.1

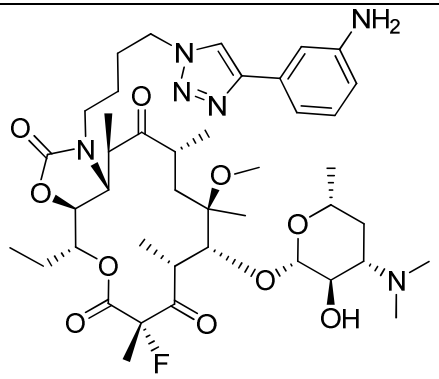
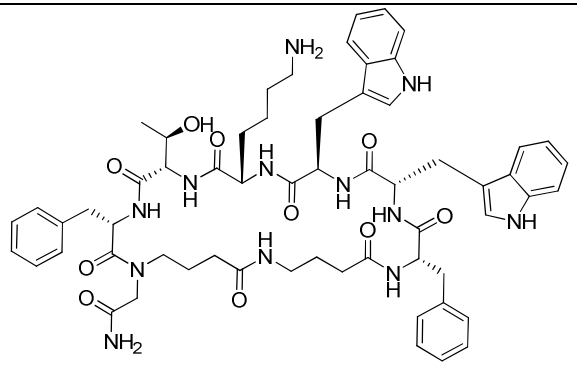
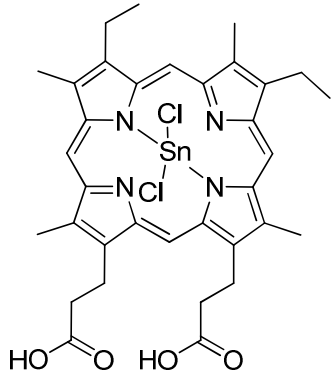
Pacritinib (ONX 0803, SB 1518)		”de novo designed”		Oncology	III	Yes	1	62	473	4.3
Patupilone (Epothilone B, EPO906)		Epothilone		Oncology	II	No	2	110	508	3.2

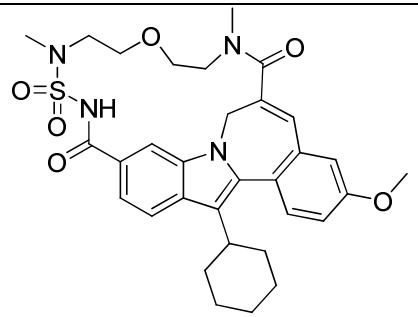
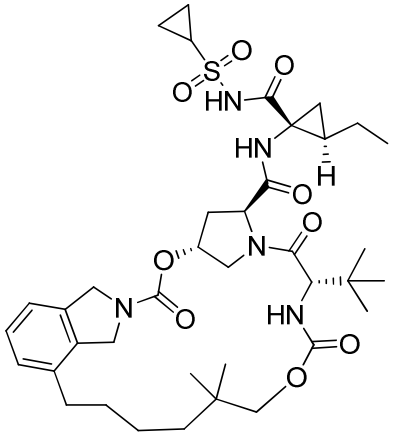
Plitidepsin (Aplidine, Dehydrodidemnin B)		Cyclic peptide	Depsipeptide	Oncology	III	No	4	299	1110	8.0
Retaspimycin (IPI 504, MEDI 561)		Ansamycin	Benzoquinone	Oncology	II	No	7	188	588	3.0

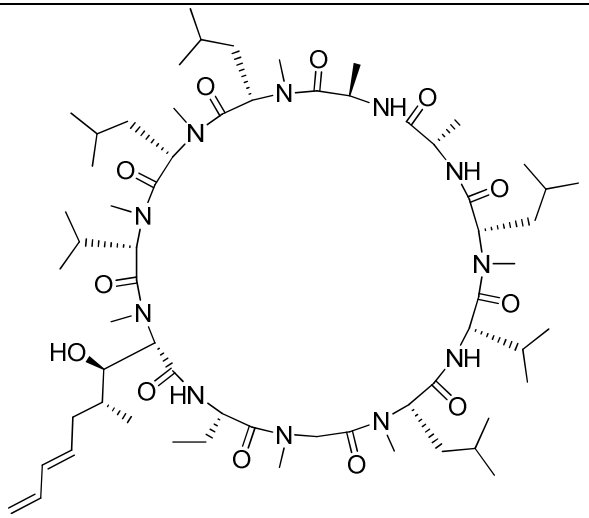
Ridaforolimus (AP23573, Deforolimus, MK 8669)		Macrolide	Rapamycin	Oncology	Preregistration	Yes	2	209	990	7.2
Rifalazil (ABI 1648, KRM 1648, PA 1648)		Ansamycin	Naphtoquinone	Infection	II	Yes	5	235	941	8.2

Sagopilone (BAY86-5302)		Epothilone		Oncology	II	No	2	110	544	4.2
SB1317/TG02		”de novo designed”		Oncology	I	Yes	1	45	373	5.4
SB1578/CT1578		”de novo designed”		Immunology	I	Yes	1	72	462,5	3,7

SCY 635		Cyclic peptide	N-methylated	Infection	II	Yes	6	314	1322	13
Simeprevir (TMC435)		”de novo designed”		Infection	III	Yes	2	161	750	5.3

Solithromycin (CEM 101, OP-1068)		Macrolide	Erithronolide	Infection	III	Yes	3	197	831	3.2
Somatoprim (DG3173, PTR 3173)		Cyclic peptide	Lactam bridge	Endocrinology	II	No	14	374	1123	2.9
Stannsoporfin (Sn mesoporphyrin)		Porphyrin		Gastro-Intestinal	II	No	2	123	754	9.1

TMC647055		”de novo designed”		Infection	II	Yes	1	110	606,7	6,5
Vaniprevir (MK 7009)		”de novo designed”		Infection	III	Yes	3	193	758	7.2

Voclosporin (ISA 247)		Cyclic peptide	N-methylated	Immunology	III	Yes	5	290	1215	14.5

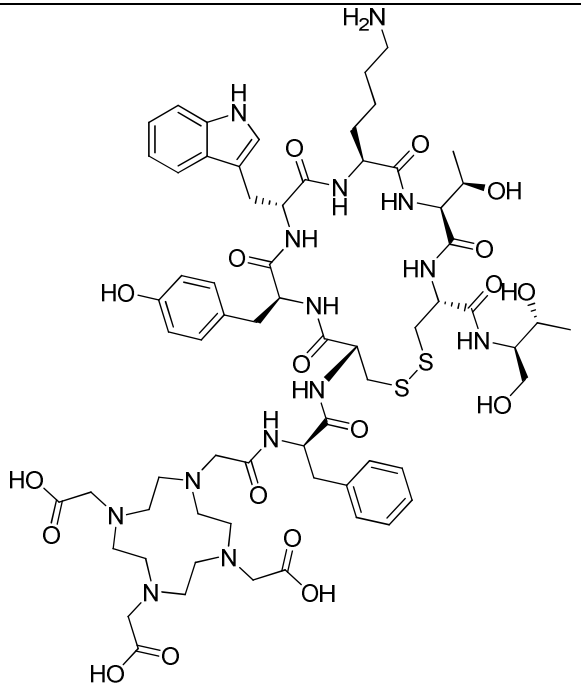
Yttrium 90-labelled edotreotide (90Y-SMT 487)		Cyclic peptide	Disulfide bridge	Oncology	II	No	18	522	1422	-2.8

Table S2. Macrocyclic-based compounds in clinical development as of April 2013.

FIGURES

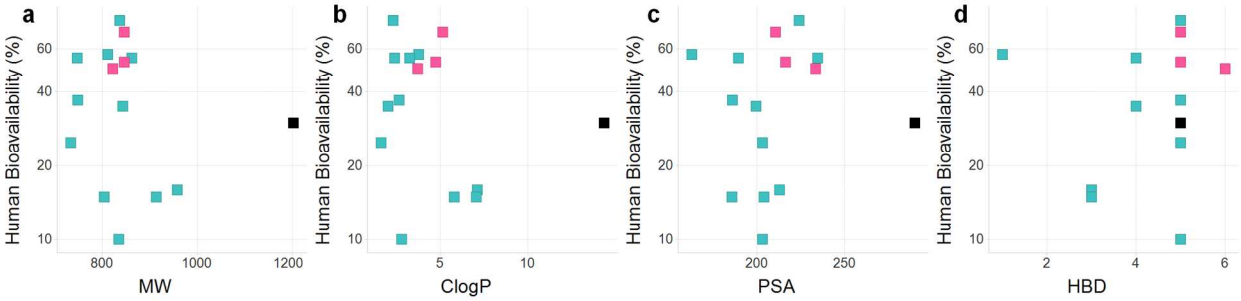


Figure S1. Relationship between Human Oral Bioavailability and (a) molecular weight, (b) ClogP, (c) polar surface area, (d) number of hydrogen bond donors for macrolide (cyan squares), ansamycin (magenta squares) and cyclic peptide (black square) macrocyclic drugs.