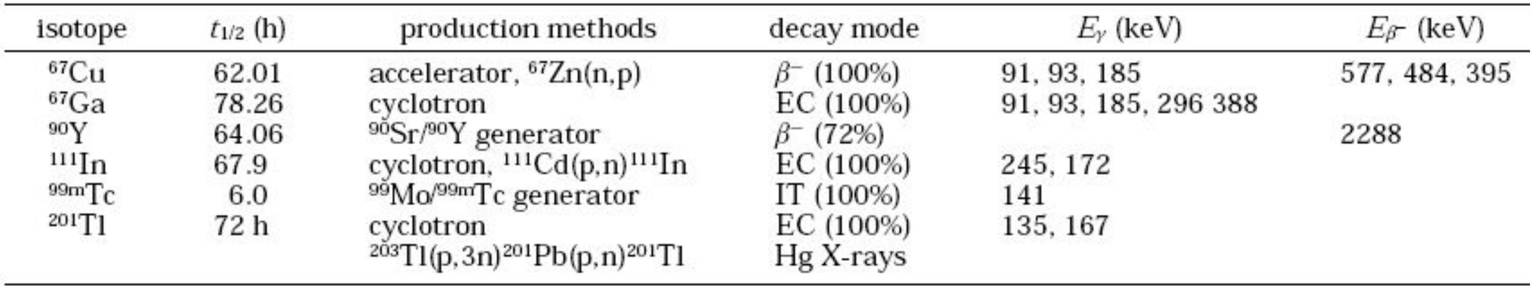
Неорганические вещества в медицине

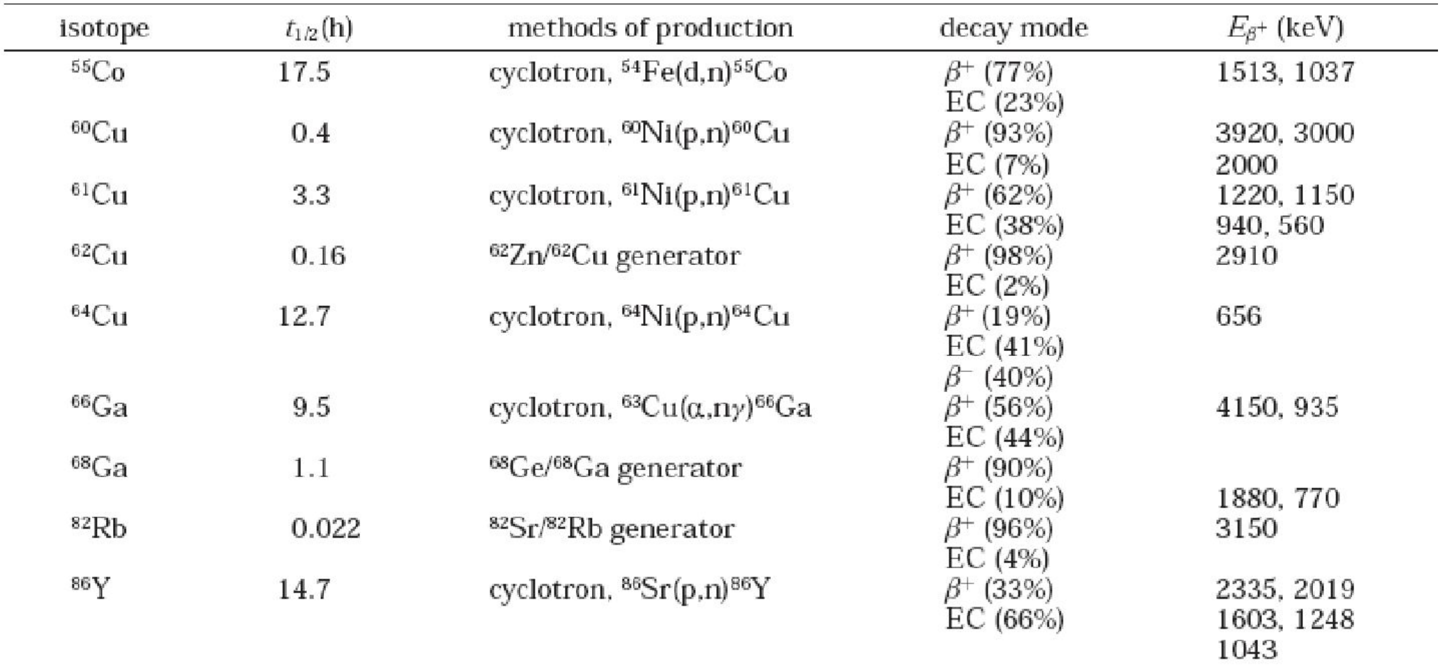
I. Радиоактивные изотопы для целей диагностики и терапии

Важнейшие изотопы - γ-излучатели, используемые в целях радиодиагностики



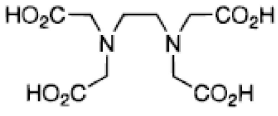
isotope	$t_{1/2}$ (h)	production methods	decay mode	E_γ (keV)	E_{β^-} (keV)
^{67}Cu	62.01	accelerator, ^{67}Zn(n,p)	β^- (100%)	91, 93, 185	577, 484, 395
^{67}Ga	78.26	cyclotron	EC (100%)	91, 93, 185, 296 388	
^{90}Y	64.06	^{90}Sr/^{90}Y generator	β^- (72%)		2288
^{111}In	67.9	cyclotron, ^{111}Cd(p,n)^{111}In	EC (100%)	245, 172	
^{99m}Tc	6.0	^{99}Mo/^{99m}Tc generator	IT (100%)	141	
^{201}Tl	72 h	cyclotron ^{203}Tl(p,3n)^{201}Pb(p,n)^{201}Tl	EC (100%) Hg X-rays	135, 167	

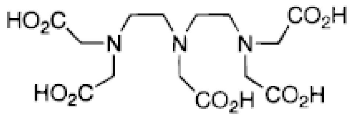
Важнейшие позитрон-излучающие изотопы, используемые в целях радиодиагностики

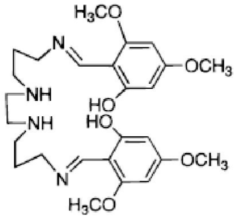


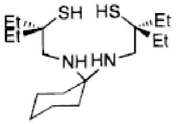
isotope	$t_{1/2}$(h)	methods of production	decay mode	E_{β^+} (keV)
^{55}Co	17.5	cyclotron, ^{54}Fe(d,n)^{55}Co	β^+ (77%) EC (23%)	1513, 1037
^{60}Cu	0.4	cyclotron, ^{60}Ni(p,n)^{60}Cu	β^+ (93%) EC (7%)	3920, 3000 2000
^{61}Cu	3.3	cyclotron, ^{61}Ni(p,n)^{61}Cu	β^+ (62%) EC (38%)	1220, 1150 940, 560
^{62}Cu	0.16	^{62}Zn/^{62}Cu generator	β^+ (98%) EC (2%)	2910
^{64}Cu	12.7	cyclotron, ^{64}Ni(p,n)^{64}Cu	β^+ (19%) EC (41%) β^- (40%)	656
^{66}Ga	9.5	cyclotron, ^{63}Cu(α,nγ)^{66}Ga	β^+ (56%) EC (44%)	4150, 935
^{68}Ga	1.1	^{68}Ge/^{68}Ga generator	β^+ (90%) EC (10%)	 1880, 770
^{82}Rb	0.022	^{82}Sr/^{82}Rb generator	β^+ (96%) EC (4%)	3150
^{86}Y	14.7	cyclotron, ^{86}Sr(p,n)^{86}Y	β^+ (33%) EC (66%)	2335, 2019 1603, 1248 1043

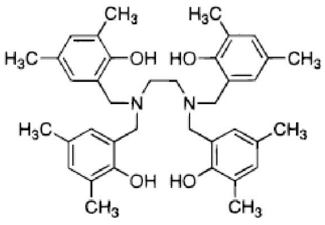
Хелатообразующие лиганды, используемые для связывания ионов галлия и индия

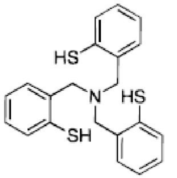

EDTA


DTPA

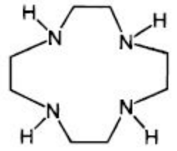

[(4,6-MeO$_2$sal)$_2$BAPEN]

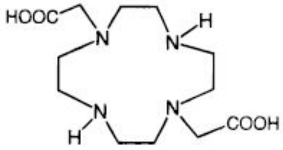

BAT-TECH

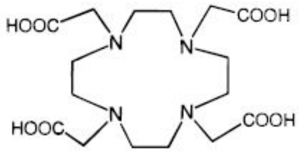

THM$_2$BED

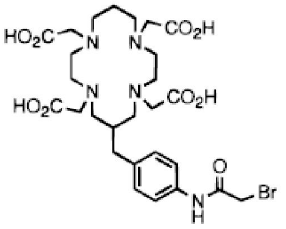

tris(2-mercaptobenzyl)amine (S$_3$N)

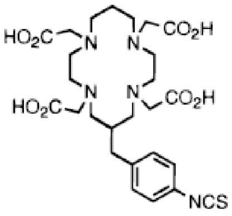
Макроциклические лиганды, используемые для связывания ионов меди

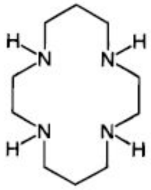

cyclen

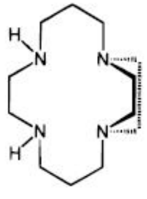

DO2A

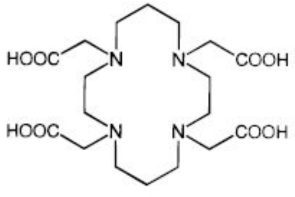

DOTA

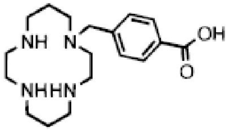

BAT

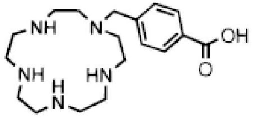

SCN-TETA


cyclam


et-cyclam


TETA


CPTA


PCBA

Некоторые применяемые в клинической практике препараты технеция

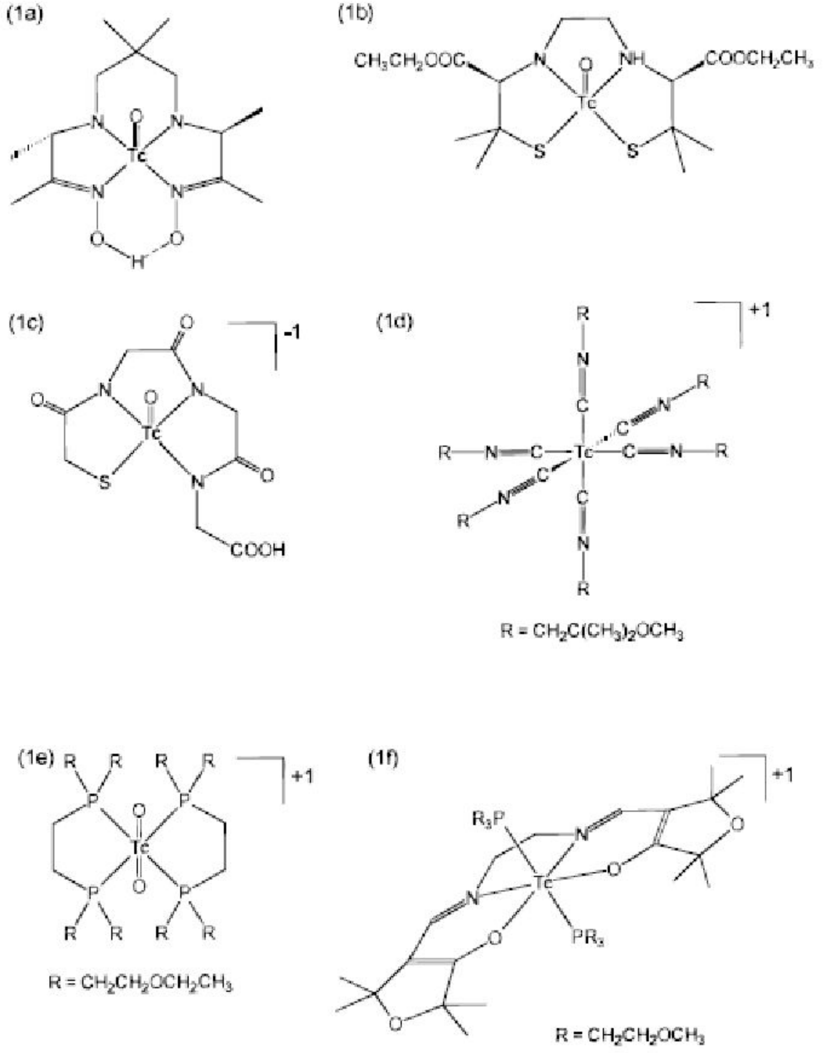

(1a)
Tc
O
N
O
H
(1b)
CH$_3$CH$_2$OOC
COOCH$_2$CH$_3$
N
NH
O
Tc
S
(1c)
-1
O
N
Tc
S
COOH
(1d)
+1
R
N
C
Tc
R = CH$_2$C(CH$_3$)$_2$OCH$_3$
(1e)
+1
R
P
O
Tc
R = CH$_2$CH$_2$OCH$_2$CH$_3$
(1f)
+1
R$_3$P
N
Tc
O
PR$_3$
R = CH$_2$CH$_2$OCH$_3$

Figure 1. Some currently approved ^{99m}Tc radiopharmaceuticals: (a) ^{99m}Tc−D,L-HM-PAO (Ceretec); (b) ^{99m}Tc−LL-ECD (Neurolite); (c) ^{99m}Tc−MAG$_3$ (Technescan); (d) ^{99m}Tc−sestamibi (Cardiolite); (e) ^{99m}Tc−tetrofosmin (Myoview); (f) ^{99m}Tc−furifosmin (TechneScan Q12).

Радиоактивные метки для допаминовых рецепторов

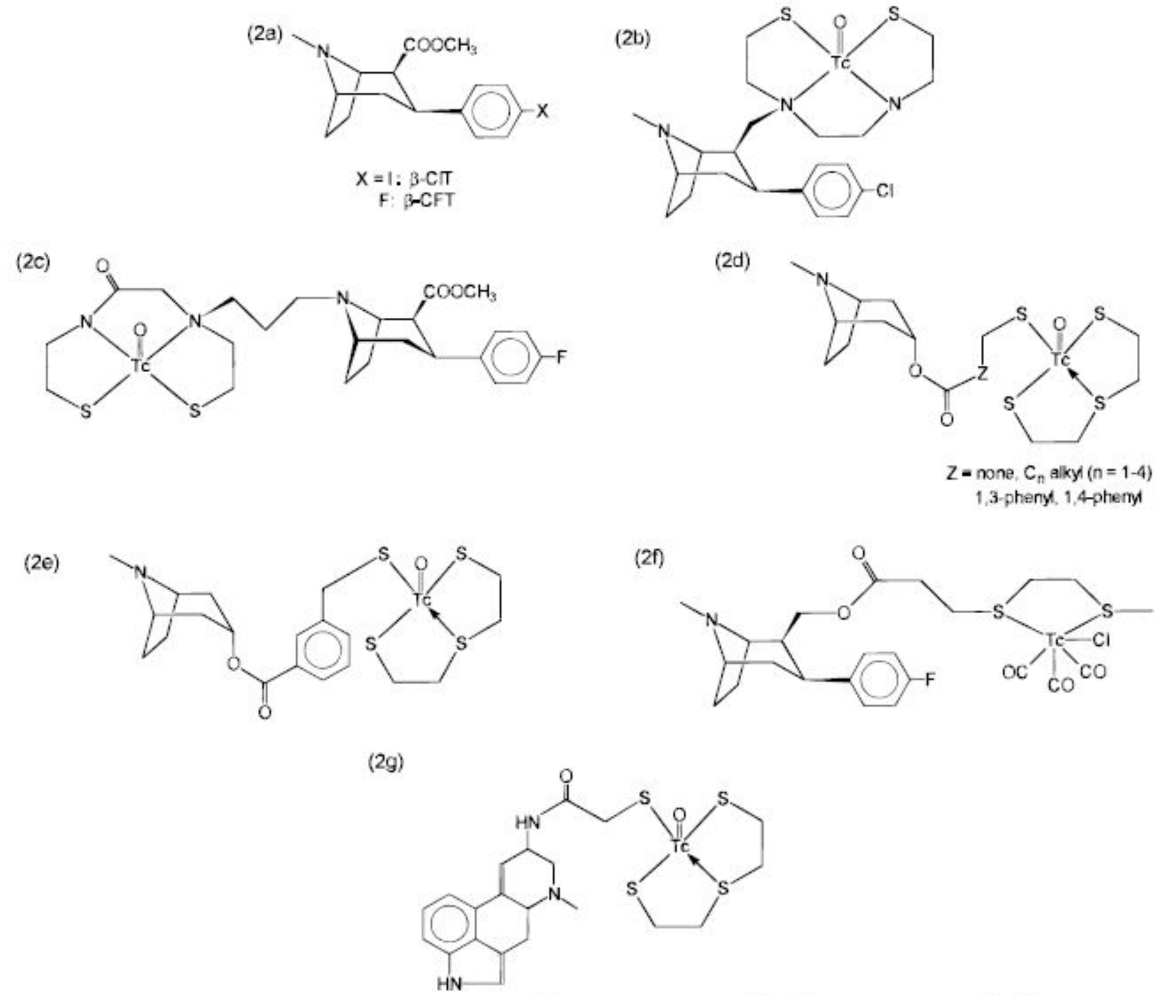
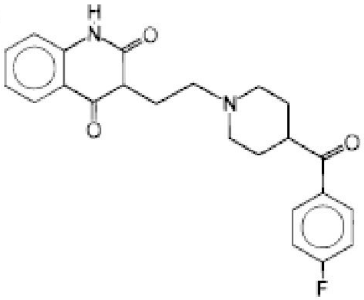

(2a)
COOCH₃
N
X
X = I: β-CIT
F: β-CFT
(2b)
S
O
S
Tc
N
N
N
Cl
(2c)
O
N
O
N
Tc
S
S
N
COOCH₃
F
(2d)
N
S
O
S
O
Z
Tc
S
S
O
Z = none, Cn alkyl (n = 1-4)
1,3-phenyl, 1,4-phenyl
(2e)
N
S
O
S
Tc
S
S
O
O
(2f)
O
N
O
S
S
Tc
Cl
OC
CO
CO
F
(2g)
O
HN
S
O
S
Tc
S
S
N
HN

Figure 2. Dopamine transporter-selective molecules: (a) β-CIT or β-CFT; (b) [^{99m}Tc]TRODAT-1; (c) [^{99m}Tc]Technepine; (d) [^{99m}Tc]-3 + 1-α-tropanol; (e) [^{99m}Tc]-3 + 1-α-tropanol, Z = 1,3-phenyl; (f) [^{99m}Tc]TROTEC-1; (g) [^{99m}Tc]-3 + 1-ergoline.

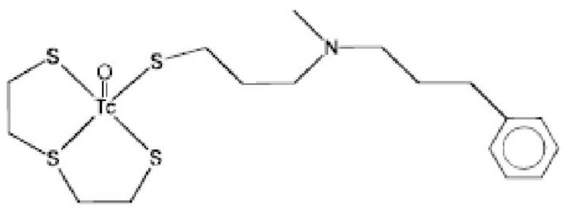
Метки на рецепторы серотонина

Метки для амилоидных бляшек

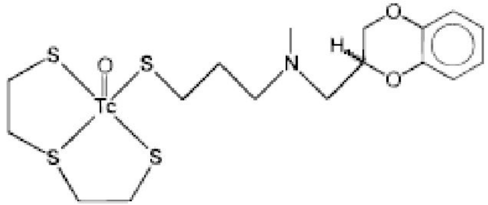
(3a)

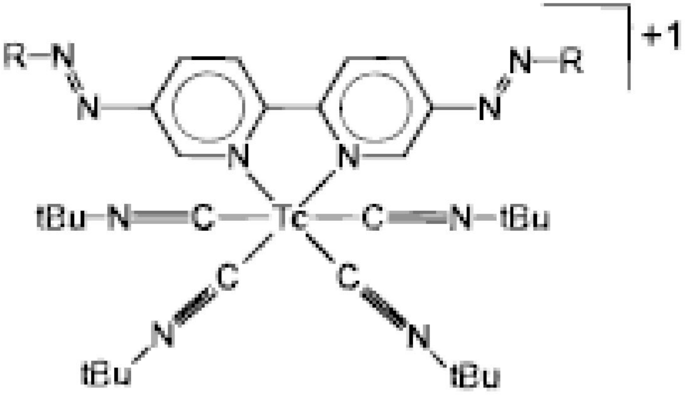


(3b)

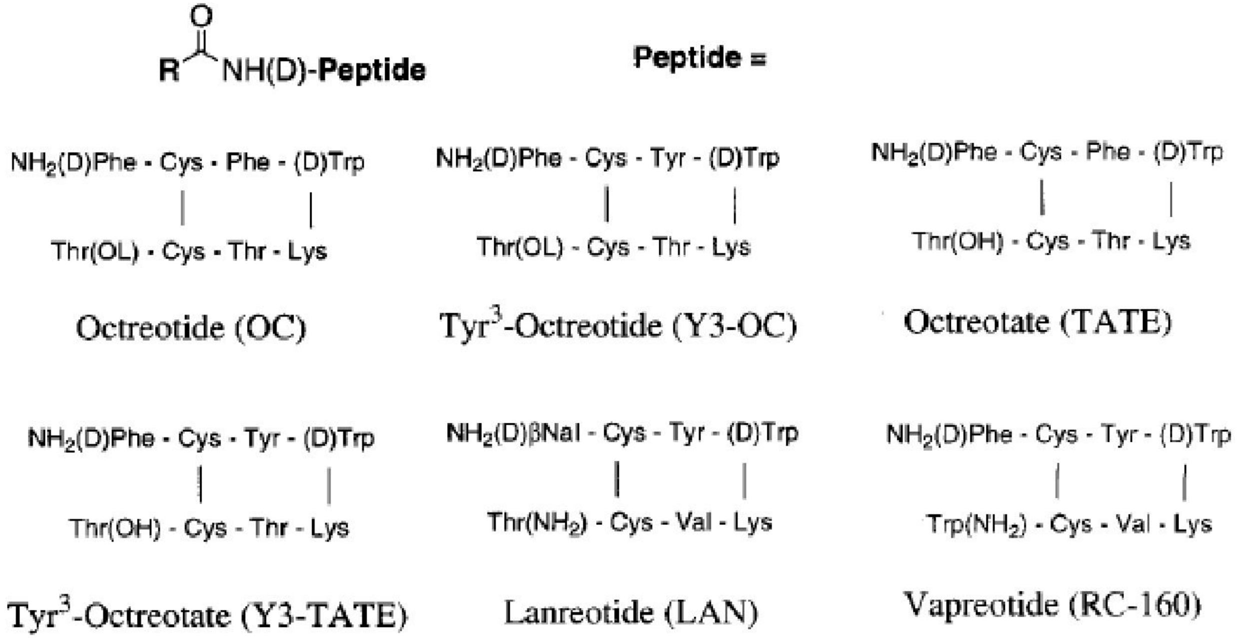


(3c)


S
O
Tc
S
N
H
O
O
S
S


R—N
N
N—R
+1
N
N
N
N
tBu—N≡C—Tc—C≡N—tBu
C
C
N
N
tBu
tBu

Пептиды, селективно связываемые рецепторами соматостатина


R
O
NH(D)-Peptide
Peptide =
NH2(D)Phe - Cys - Phe - (D)Trp
Thr(OL) - Cys - Thr - Lys
NH2(D)Phe - Cys - Tyr - (D)Trp
Thr(OL) - Cys - Thr - Lys
NH2(D)Phe - Cys - Phe - (D)Trp
Thr(OH) - Cys - Thr - Lys
NH2(D)Phe - Cys - Tyr - (D)Trp
Thr(OH) - Cys - Thr - Lys
NH2(D)βNal - Cys - Tyr - (D)Trp
Thr(NH2) - Cys - Val - Lys
NH2(D)Phe - Cys - Tyr - (D)Trp
Trp(NH2) - Cys - Val - Lys

Octreotide (OC)

Tyr^3-Octreotide (Y3-OC)

Octreotate (TATE)

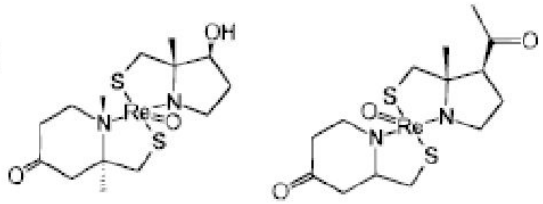
Tyr^3-Octreotate (Y3-TATE)

Lanreotide (LAN)

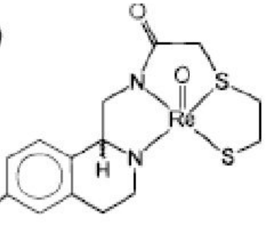
Vapreotide (RC-160)

Метки гормональных рецепторов

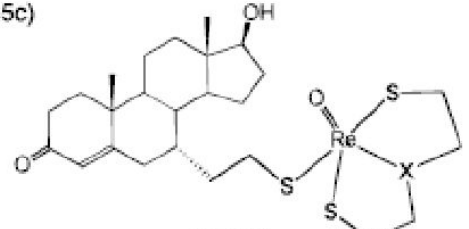
(5a)



(5b)

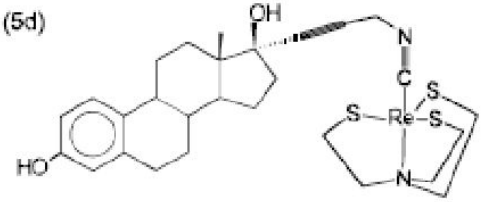


(5c)

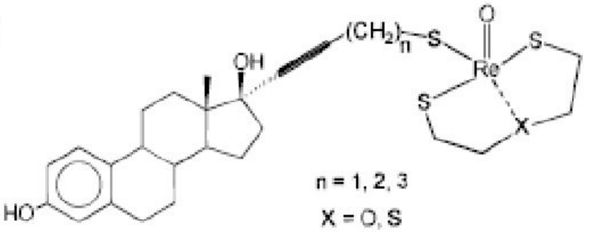


X = S,O

(5d)



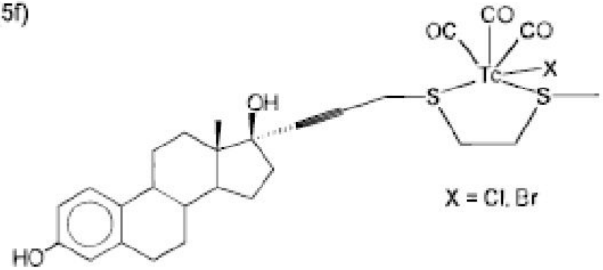
(5e)



n = 1, 2, 3

X = O, S

(5f)

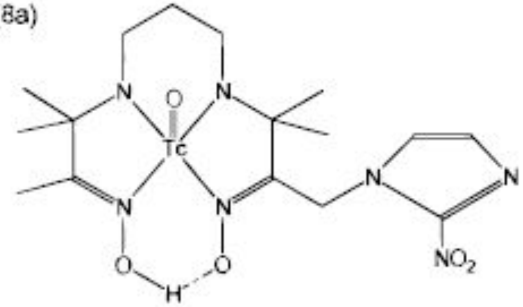


X = Cl, Br

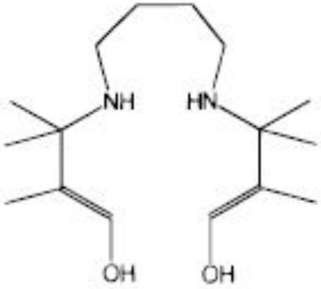
(a) прогестрон и андроген; (b) эстроген; (c) прогестрон; (d) -(f) эстроген

Метки для идентификации гипоксии

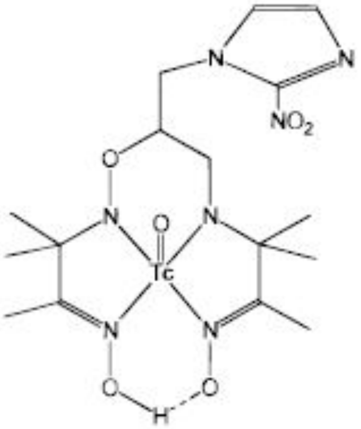
(8a)


N
O
N
Tc
N
N
N
N
O
H
O
NO2

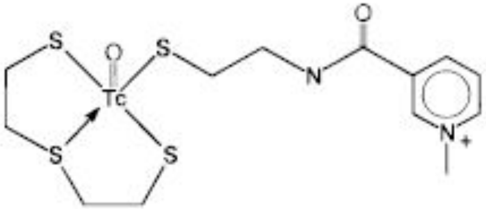
(8b)



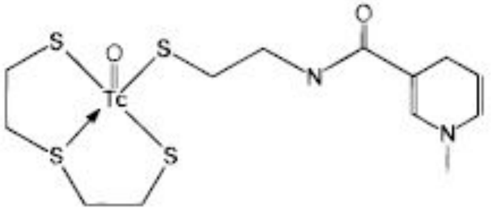
(8c)


N
N
NO2
O
N
O
N
Tc
N
N
O
H
O

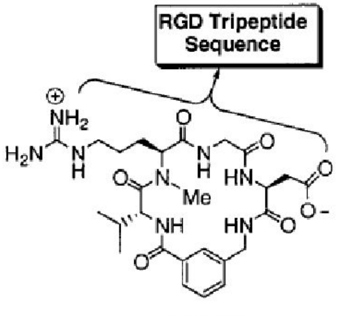
(8d)


O
S
O
S
Tc
N
S
S
N+

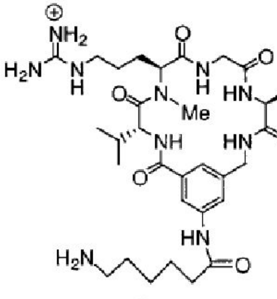
(8e)


O
S
O
S
Tc
N
S
S
N

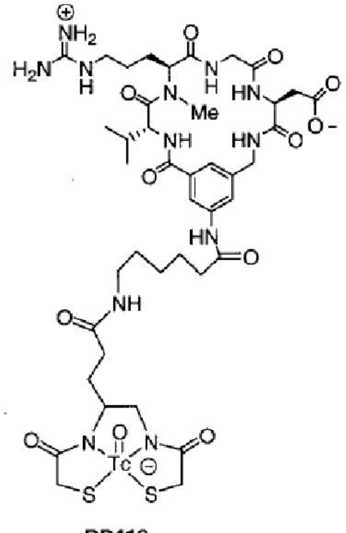
Некоторые клинически значимые белковые радиофармпрепараты, содержащие технеций


RGD Tripeptide Sequence

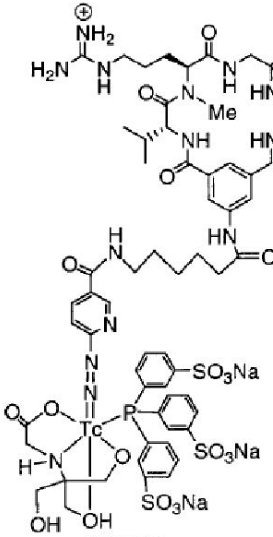
DMP757



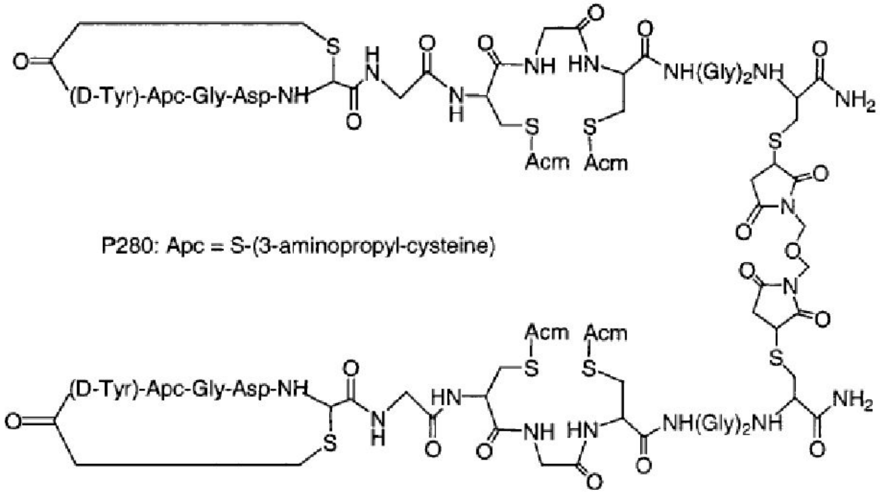
XVO60



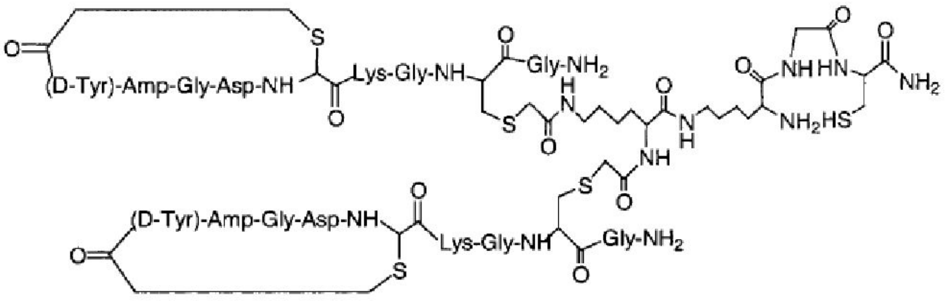
RP419



DMP444

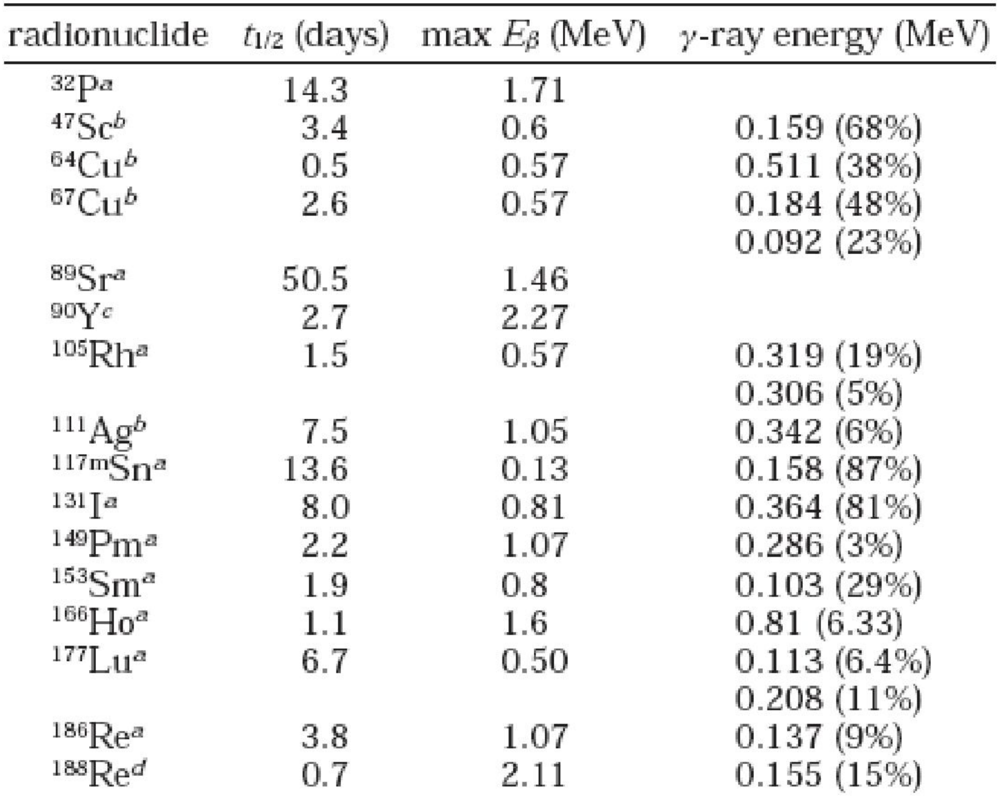

(D-Tyr)-Apc-Gly-Asp-NH
NH(Gly)$_2$NH
Acm

P280: Apc = S-(3-aminopropyl-cysteine)


(D-Tyr)-Amp-Gly-Asp-NH
Lys-Gly-NH
Gly-NH$_2$

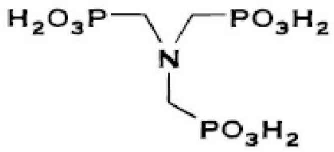
P748: (Amp = 4-amidino-phenylalanine)

Основные β-излучатели для лучевой терапии

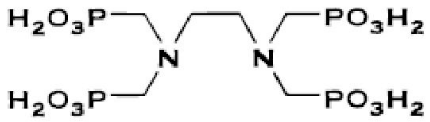


radionuclide	$t_{1/2}$ (days)	max E_β (MeV)	γ-ray energy (MeV)
^{32}P^{a}	14.3	1.71	
^{47}Sc^{b}	3.4	0.6	0.159 (68%)
^{64}Cu^{b}	0.5	0.57	0.511 (38%)
^{67}Cu^{b}	2.6	0.57	0.184 (48%) 0.092 (23%)
^{89}Sr^{a}	50.5	1.46	
^{90}Y^{c}	2.7	2.27	
^{105}Rh^{a}	1.5	0.57	0.319 (19%) 0.306 (5%)
^{111}Ag^{b}	7.5	1.05	0.342 (6%)
^{117m}Sn^{a}	13.6	0.13	0.158 (87%)
^{131}I^{a}	8.0	0.81	0.364 (81%)
^{149}Pm^{a}	2.2	1.07	0.286 (3%)
^{153}Sm^{a}	1.9	0.8	0.103 (29%)
^{166}Ho^{a}	1.1	1.6	0.81 (6.33)
^{177}Lu^{a}	6.7	0.50	0.113 (6.4%) 0.208 (11%)
^{186}Re^{a}	3.8	1.07	0.137 (9%)
^{188}Re^{d}	0.7	2.11	0.155 (15%)

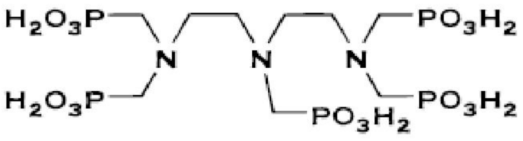
Лиганды, используемые при проведении лучевой терапии


H_2O_3P
PO_3H_2
N
PO_3H_2

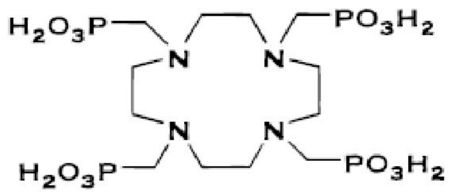
NTMP


H_2O_3P
PO_3H_2
N
N
H_2O_3P
PO_3H_2

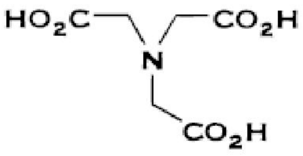
EDTMP


H_2O_3P
PO_3H_2
N
N
N
H_2O_3P
PO_3H_2
PO_3H_2

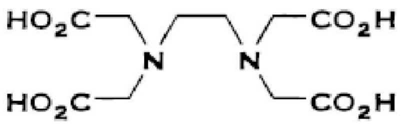
DTPMP


H_2O_3P
PO_3H_2
N
N
N
N
H_2O_3P
PO_3H_2

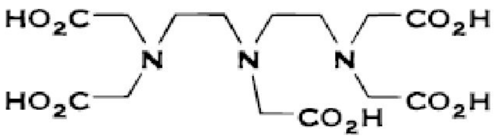
DOTMP


HO_2C
CO_2H
N
CO_2H

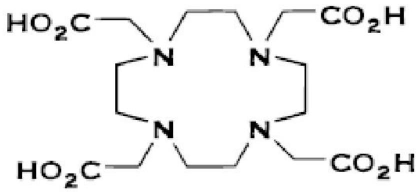
NTA


HO_2C
CO_2H
N
N
HO_2C
CO_2H

EDTA

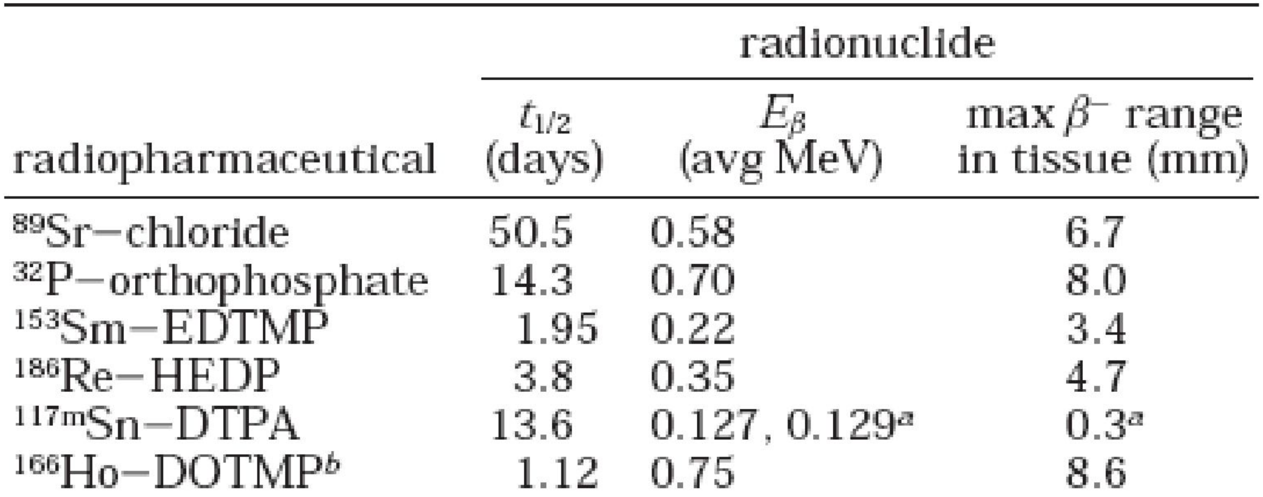

HO_2C
CO_2H
N
N
N
HO_2C
CO_2H
CO_2H

DTPA


HO_2C
CO_2H
N
N
N
N
HO_2C
CO_2H

DOTA

Радиофармпрепараты для лечения опухолей костей

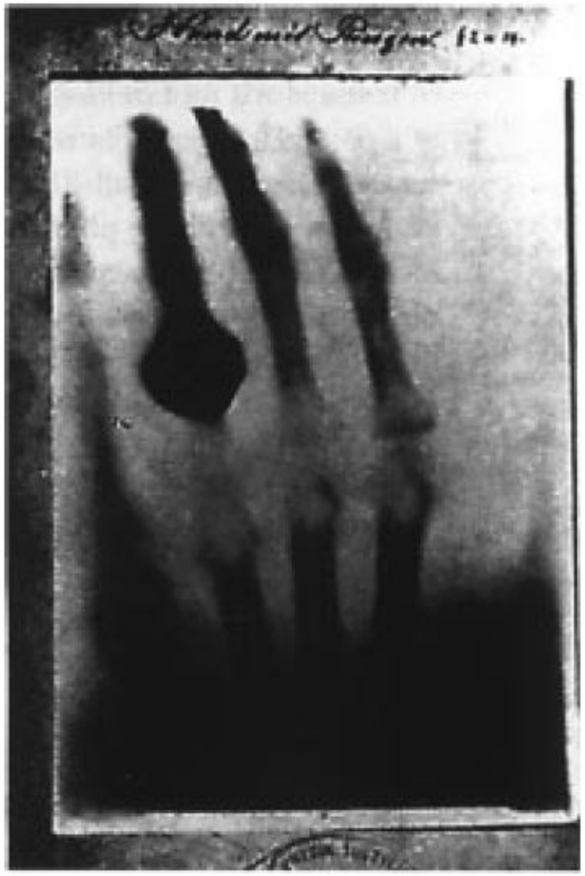


	radionuclide		
radiopharmaceutical	$t_{1/2}$ (days)	E_β (avg MeV)	max β^- range in tissue (mm)
^{89}Sr–chloride	50.5	0.58	6.7
^{32}P–orthophosphate	14.3	0.70	8.0
^{153}Sm–EDTMP	1.95	0.22	3.4
^{186}Re–HEDP	3.8	0.35	4.7
^{117m}Sn–DTPA	13.6	0.127, 0.129[a]	0.3[a]
^{166}Ho–DOTMP[b]	1.12	0.75	8.6

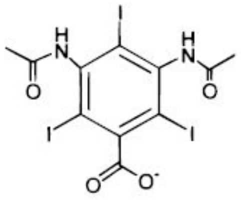
Неорганические вещества в медицине

II. Контрастные вещества

Первый рентгеновский снимок

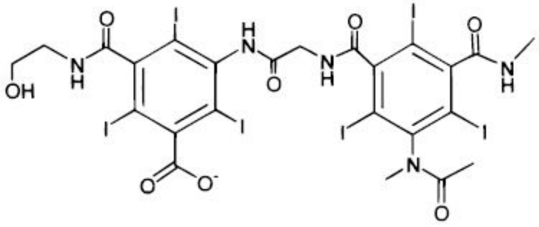

Hand mit Ringen

Иодсодержащие контрастные вещества



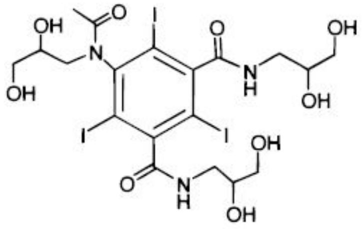
Diatrizoate

Ionic Monomer



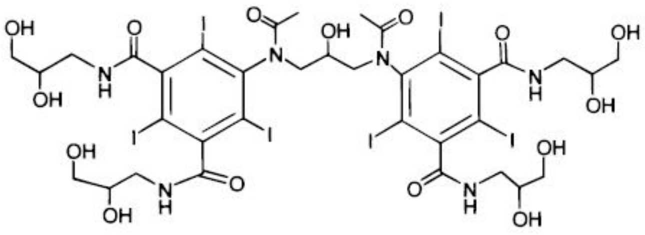
Ioxaglate

Ionic Dimer



Iohexol

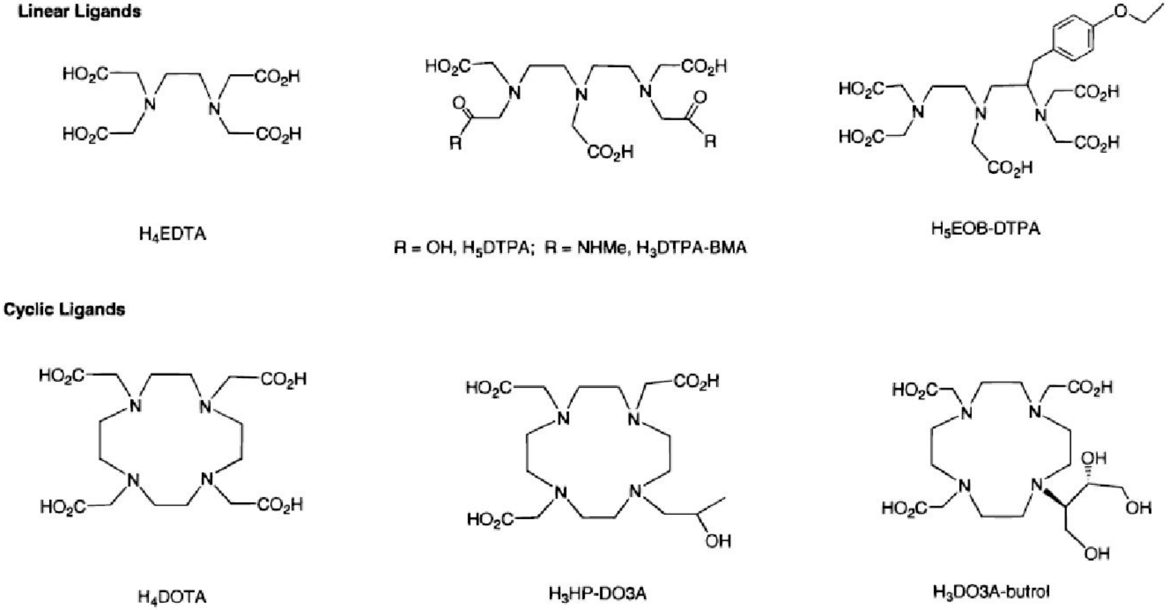
Nonionic Monomer



Iodixanol

Nonionic Dimer

Хелатобразующие лиганды, используемые для введения контрастных препаратов, и некоторые характеристики соответствующих комплексов


Linear Ligands

H_4EDTA

R = OH, H_5DTPA; R = NHMe, H_3DTPA-BMA

H_5EOB-DTPA

Cyclic Ligands

H_4DOTA

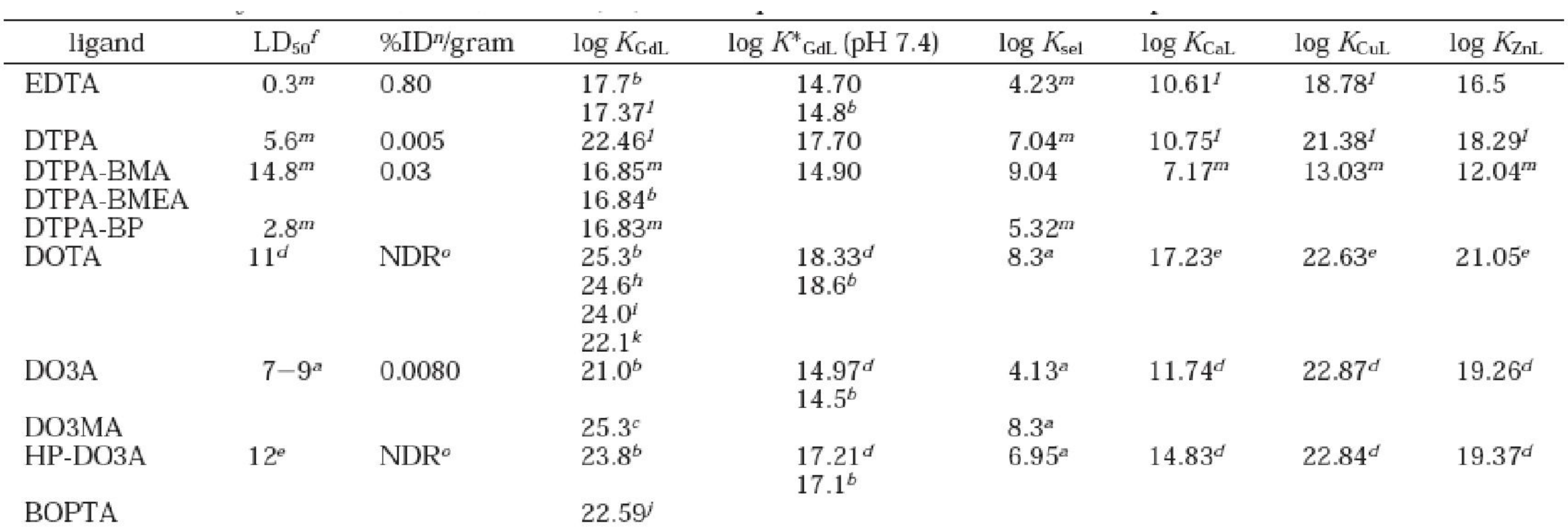
H_3HP-DO3A

H_3DO3A-butrol

complexes	log K	LD_{50}
$(NMG)_2GdDTPA$	22.4	6−10
$Na_2YbDTPA$	22.6	10 (rat)
GdDTPA-BMA	16.9	14.8
(NMG)GdDOTA	25.8	11
GdHP-DO3A	21.8	12
GdDO3A-butrol	23.8	~30
$(NMG)_2GdEOB$-DTPA		7.5
(NMG)GdEDTA	17.3	0.3
$Na_2PbEDTA$	18.1	~1.5 (rabbit)
$Na_2BiDTPA$	27.8	<1.4 (dog)

	molecular solubility (M)	tungsten atom solubility (M)	LD_{50} (mmol/kg)
$Na_2[W_2O_4(EDTA)]$	0.5	1.0	10
$Na_2[W_2O_2S_2(EDTA)]$	0.075	0.15	~2.5 (MLD)
$(NMG)_2[W_2O_2S_2(EDTA)]$	0.3	0.6	~5 (MLD)
$Na_2[W_3S_4O(TTHA)]$	0.17	0.51	6.5
$(NMG)_2[W_3S_4O(TTHA)]$	0.49	1.47	7.2
$Na_4[(W_3S_4)_2(EGTA)_3]$	0.04	0.24	
$(NMG)_4[(W_3S_4)_2(EDTA)_3]$	0.072	0.43	4 (MLD)
$Na_2P_2W_{18}O_{64}$			≪1 (MLD)

Некоторые характеристики комплексов гадолиния



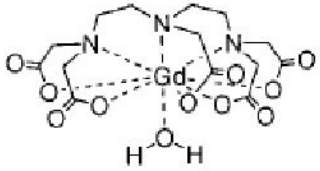
ligand	LD$_{50}$^{f}	%ID^{n}/gram	log K_{GdL}	log K^{*}_{GdL} (pH 7.4)	log K_{sel}	log K_{CaL}	log K_{CuL}	log K_{ZnL}
EDTA	0.3^{m}	0.80	17.7^{b}	14.70	4.23^{m}	10.61^{l}	18.78^{l}	16.5
			17.37^{l}	14.8^{b}				
DTPA	5.6^{m}	0.005	22.46^{l}	17.70	7.04^{m}	10.75^{l}	21.38^{l}	18.29^{l}
DTPA-BMA	14.8^{m}	0.03	16.85^{m}	14.90	9.04	7.17^{m}	13.03^{m}	12.04^{m}
DTPA-BMEA			16.84^{b}					
DTPA-BP	2.8^{m}		16.83^{m}		5.32^{m}			
DOTA	11^{d}	NDR^{o}	25.3^{b}	18.33^{d}	8.3^{a}	17.23^{e}	22.63^{e}	21.05^{e}
			24.6^{h}	18.6^{b}				
			24.0^{i}					
			22.1^{k}					
DO3A	$7-9^{a}$	0.0080	21.0^{b}	14.97^{d}	4.13^{a}	11.74^{d}	22.87^{d}	19.26^{d}
				14.5^{b}				
DO3MA			25.3^{c}		8.3^{a}			
HP-DO3A	12^{e}	NDR^{o}	23.8^{b}	17.21^{d}	6.95^{a}	14.83^{d}	22.84^{d}	19.37^{d}
				17.1^{b}				
BOPTA			22.59^{j}					

LD – летальная доза

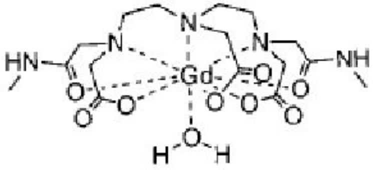
ID - присутствие в бедренной кости через 14 дней после введения

NDR – определить не удалось

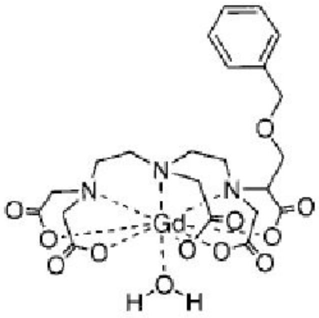
Важнейшие соединения, используемые при проведении МРТ



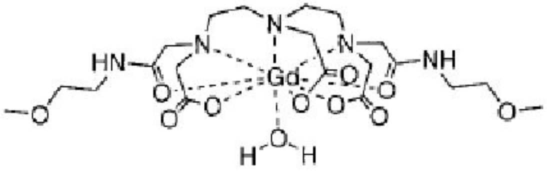
[Gd(DTPA)(H_2O)]$^{2-}$ (Magnevist™)



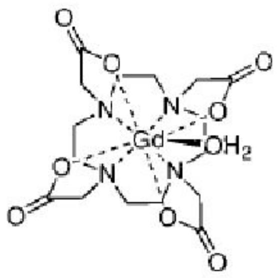
[Gd(DTPA-BMA)(H_2O)] (Omniscan™)



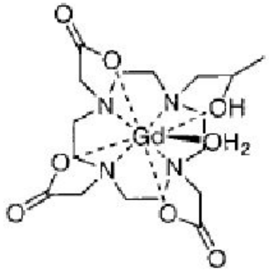
[Gd(BOPTA)(H_2O)]$^{2-}$ (MultiHance™)



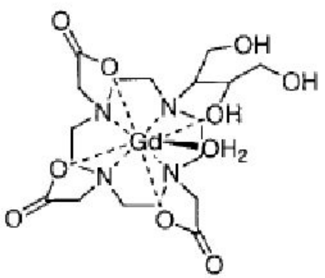
[Gd(DTPA-BMEA)(H_2O)] (OptiMARK™)



[Gd(DOTA)(H_2O)]$^{-}$ (Dotarem™)

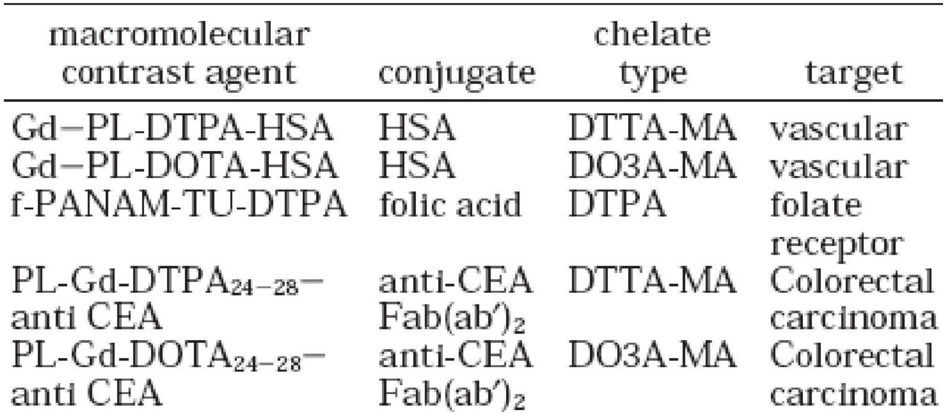


[Gd(HP-DO3A)(H_2O)] (ProHance™)

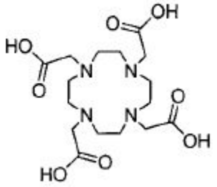


[Gd(DO3A-butrol)(H_2O)] (Gadovist™)

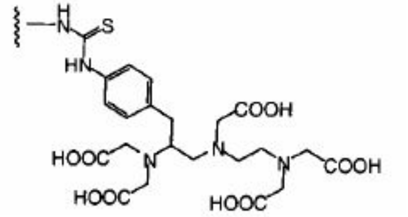
Таргетные контрастные агенты на основе комплексов гадолиния



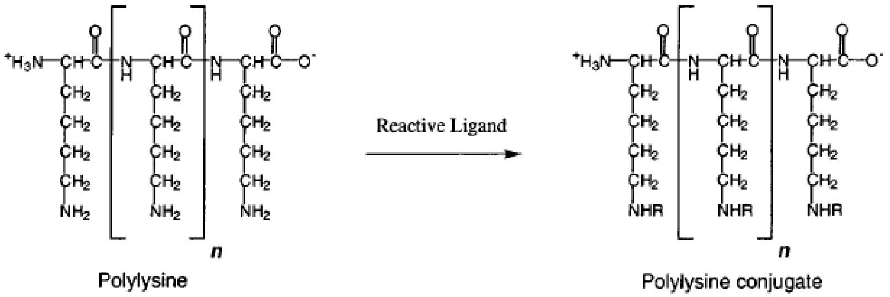
macromolecular contrast agent	conjugate	chelate type	target
Gd–PL-DTPA-HSA	HSA	DTTA-MA	vascular
Gd–PL-DOTA-HSA	HSA	DO3A-MA	vascular
f-PANAM-TU-DTPA	folic acid	DTPA	folate receptor
PL-Gd-DTPA$_{24-28}$–anti CEA	anti-CEA Fab(ab′)$_2$	DTTA-MA	Colorectal carcinoma
PL-Gd-DOTA$_{24-28}$–anti CEA	anti-CEA Fab(ab′)$_2$	DO3A-MA	Colorectal carcinoma

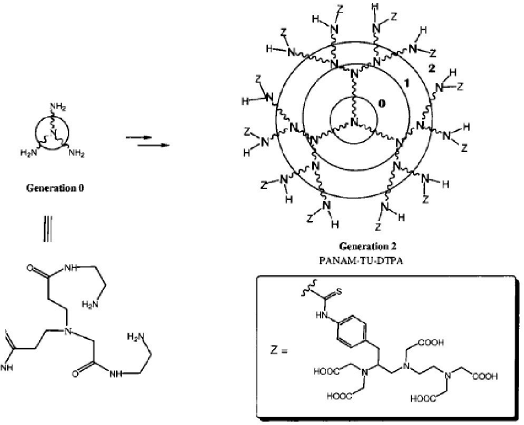

HO
OH
O
N
HO
OH

DOTA


H
N
S
HN
COOH
HOOC
N
N
N
COOH
HOOC
HOOC

DTPA


Reactive Ligand
n
Polylysine
Polylysine conjugate
NH2
NHR

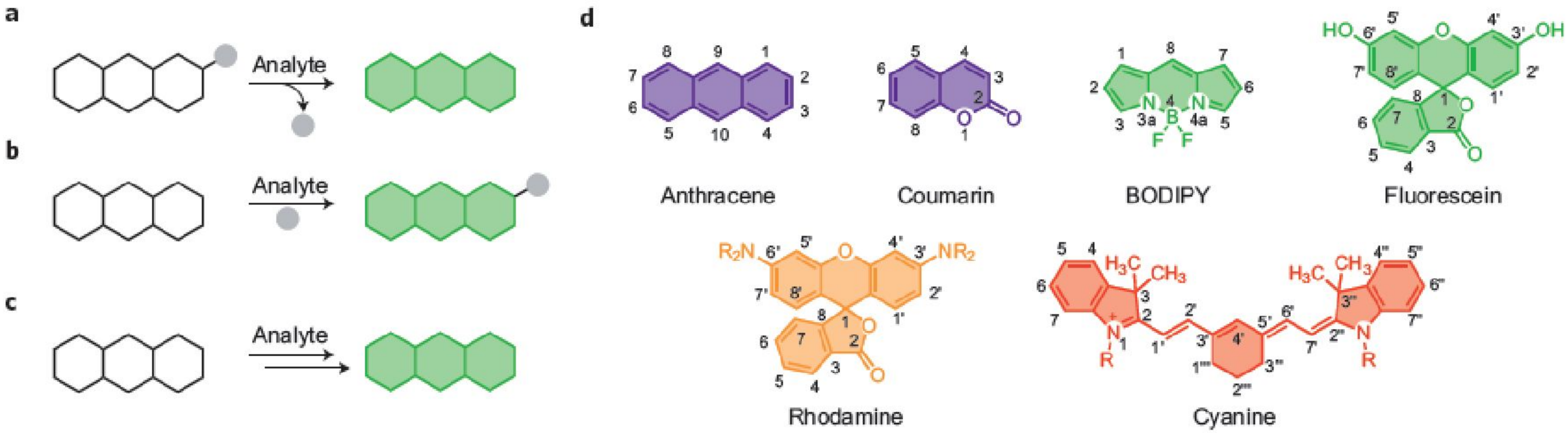

Generation 0
Generation 2
PANAM-TU-DTPA
Z =
COOH
HOOC
0
1
2

PANAM-TU-DTPA dendrimer

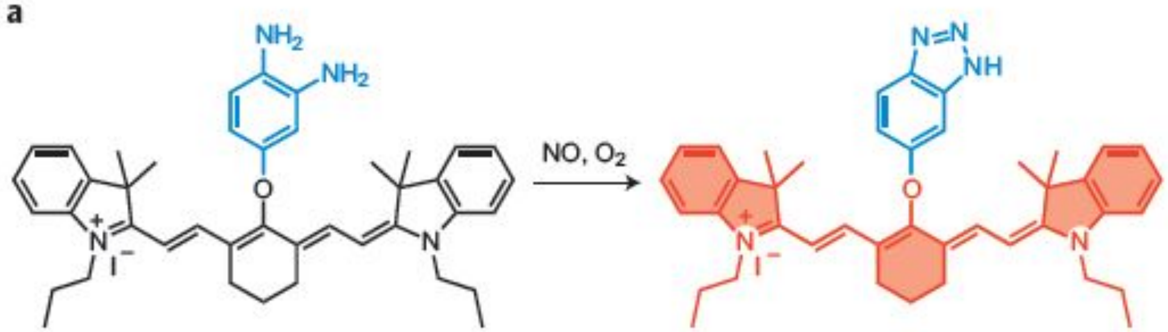
Неорганические вещества в медицине

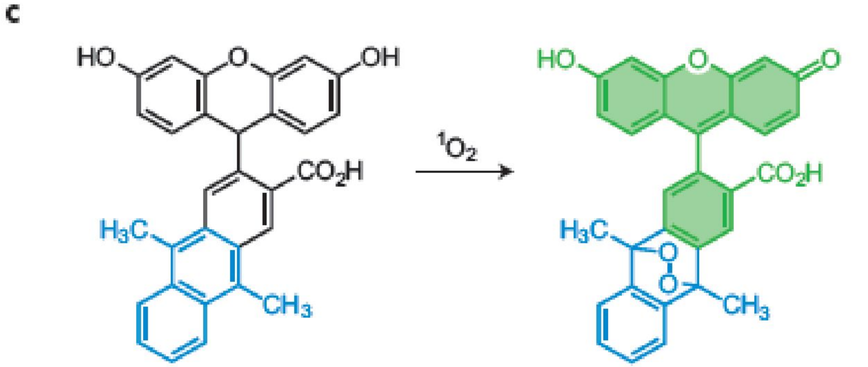
IV. Биовизуализация

Стратегия биовизуализации

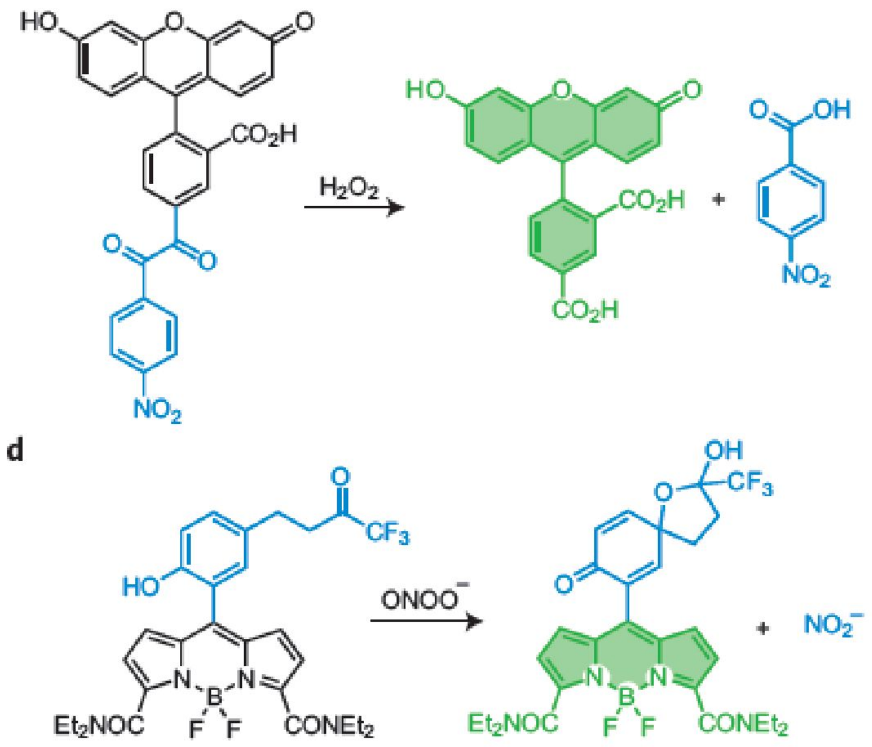

a
Analyte
b
Analyte
c
Analyte
d
Anthracene
Coumarin
BODIPY
Fluorescein
Rhodamine
Cyanine
HO
OH
O
N
B
F
F
R_2N
NR_2
H_3C
CH_3
R
R

Окислительное циклоприсоединение

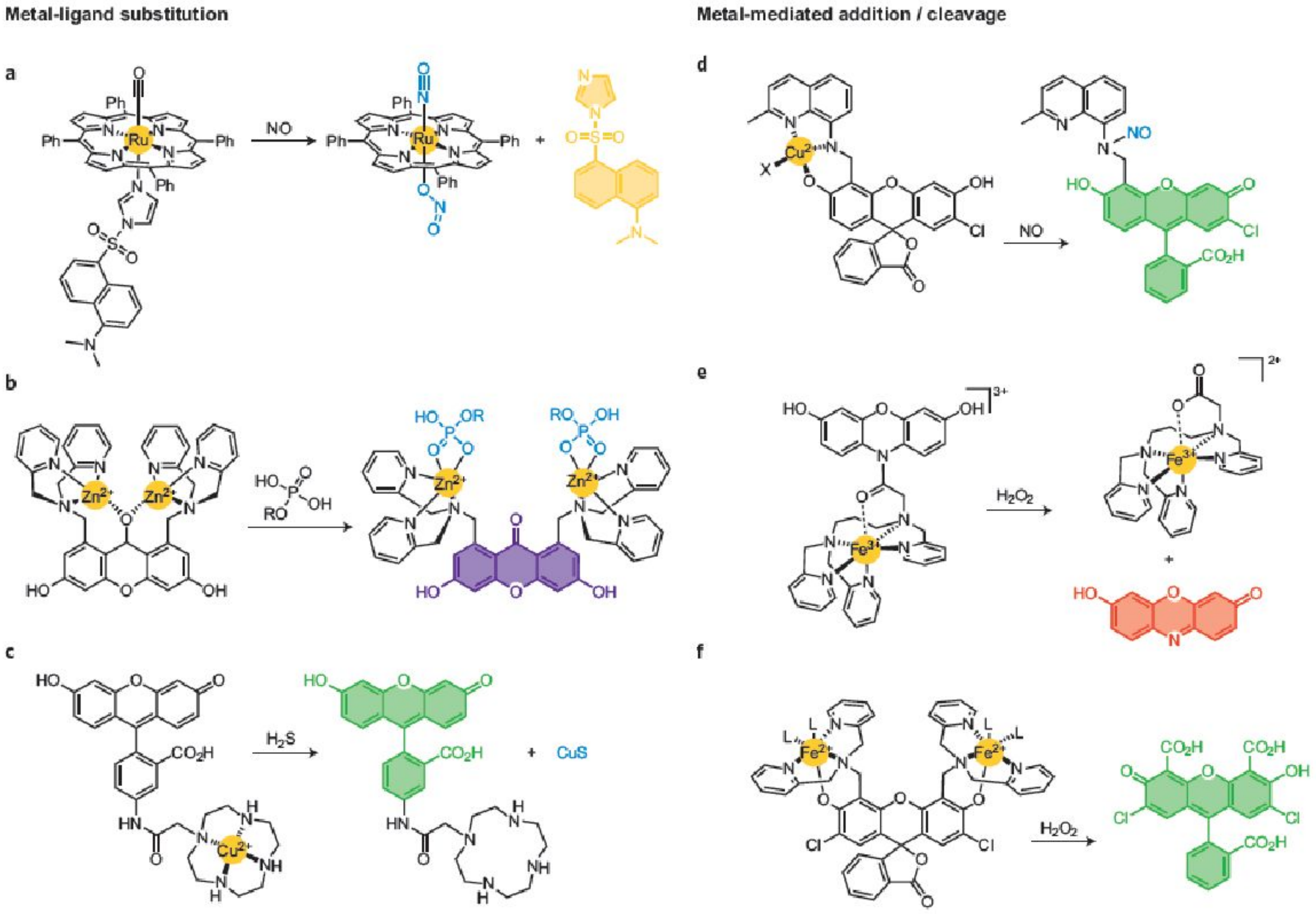

a
NH₂
NH₂
O
N⁺
I⁻
N
NO, O₂
N=N
NH
O
N⁺
I⁻
N


c
HO
O
OH
CO₂H
H₃C
CH₃
¹O₂
HO
O
O
CO₂H
H₃C
O
O
CH₃

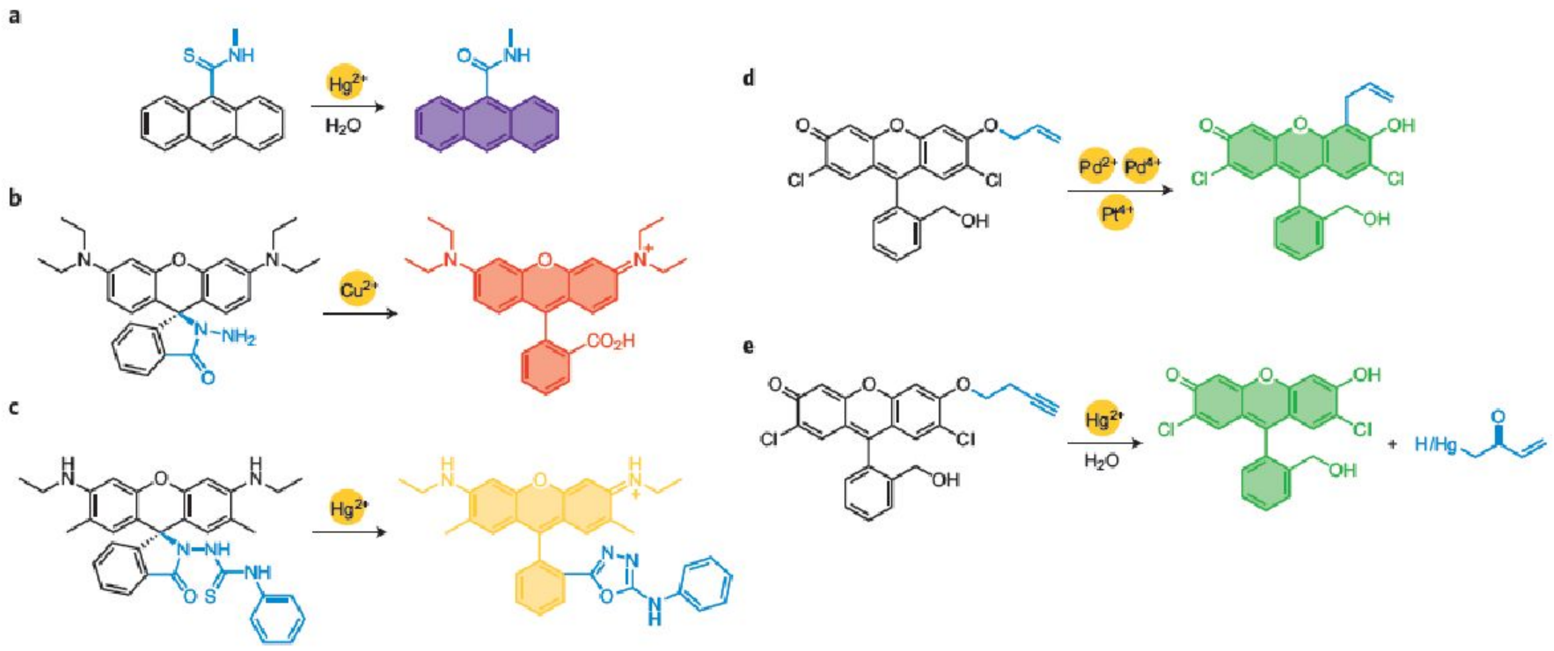
Окислительное расщепление связи


HO
O
O
CO_2H
H_2O_2
HO
O
O
CO_2H
CO_2H
+
O
OH
NO_2
O
O
NO_2
d
O
CF_3
HO
OH
O
CF_3
O
$ONOO^-$
+
NO_2^-
N
B
N
F
F
Et_2NOC
$CONEt_2$
N
B
N
F
F
Et_2NOC
$CONEt_2$

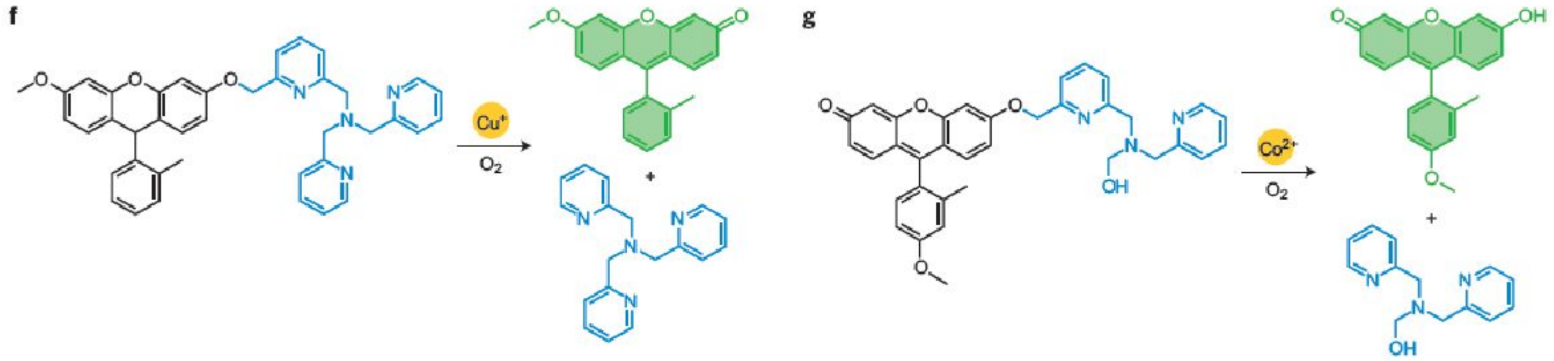
Примеры реакций, используемых для биовизуализации


Metal-ligand substitution
Metal-mediated addition / cleavage
a
NO
Ru
Ph
+
b
Zn²⁺
HO–P(=O)(OH)–OR
c
H₂S
Cu²⁺
CO₂H
+ CuS
d
Cu²⁺
NO
X
OH
Cl
CO₂H
e
Fe³⁺
H₂O₂
3+
2+
f
Fe²⁺
L
H₂O₂
CO₂H
Cl
OH

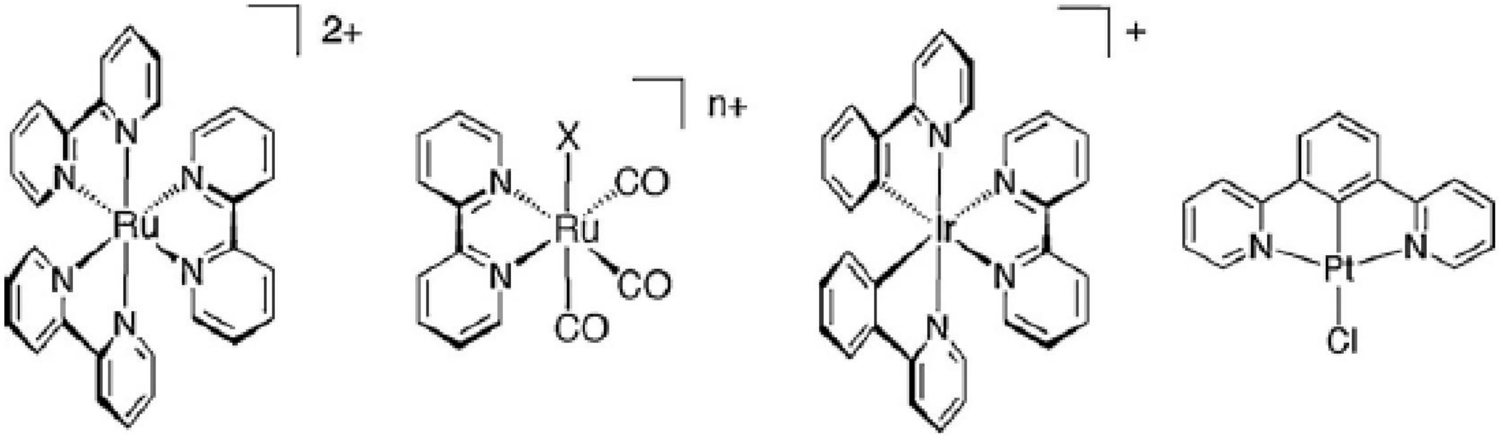
Катализ реакций образования флюорофоров


a
S
NH
Hg^{2+}
H_2O
O
NH
b
N
O
N
N
NH_2
O
Cu^{2+}
N
O
N^+
CO_2H
c
H
N
O
H
N
N
NH
NH
O
S
Hg^{2+}
H
N
O
H
N^+
N
N
O
N
H
d
O
O
O
Cl
Cl
OH
Pd^{2+}
Pd^{4+}
Pt^{4+}
O
O
OH
Cl
Cl
OH
e
O
O
O
Cl
Cl
OH
Hg^{2+}
H_2O
O
O
OH
Cl
Cl
OH
+
H/Hg
O

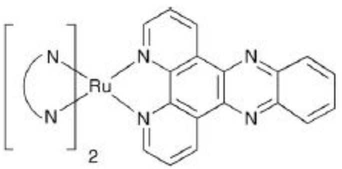
Small-molecule reactivity


f
O
O
O
N
N
N
N
Cu^+
O_2
O
O
O
+
N
N
N
N
g
O
O
O
N
N
N
OH
O
Co^{2+}
O_2
O
O
OH
O
+
N
N
N
OH

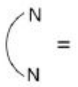
Основные типы комплексных соединений, используемые для биовизуализации

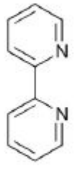

2+
N
Ru
X
CO
n+
+
Ir
Pt
Cl

Примеры комплексов рутения, используемых для биовизуализации

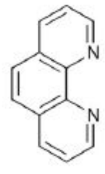


19

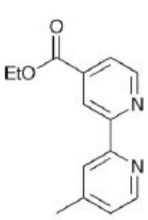




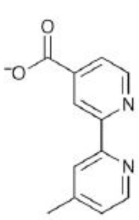
a



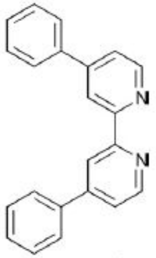
b



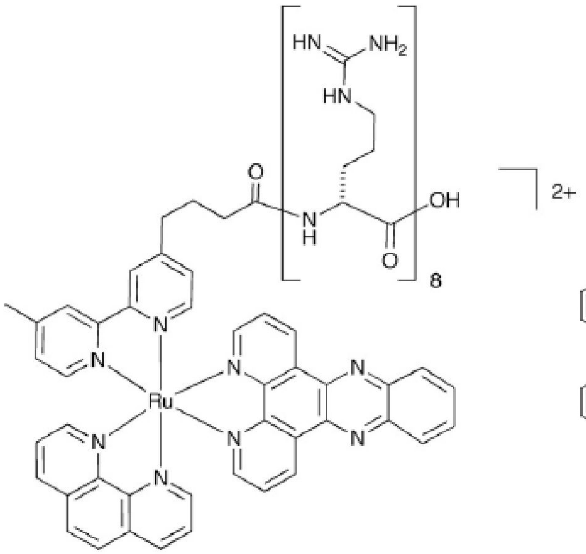
c



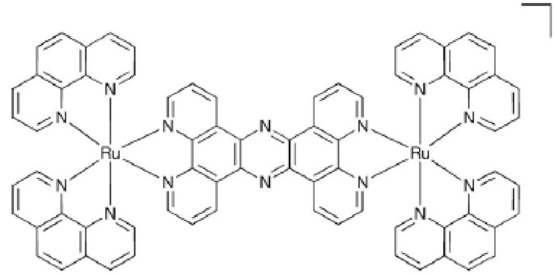
d



e

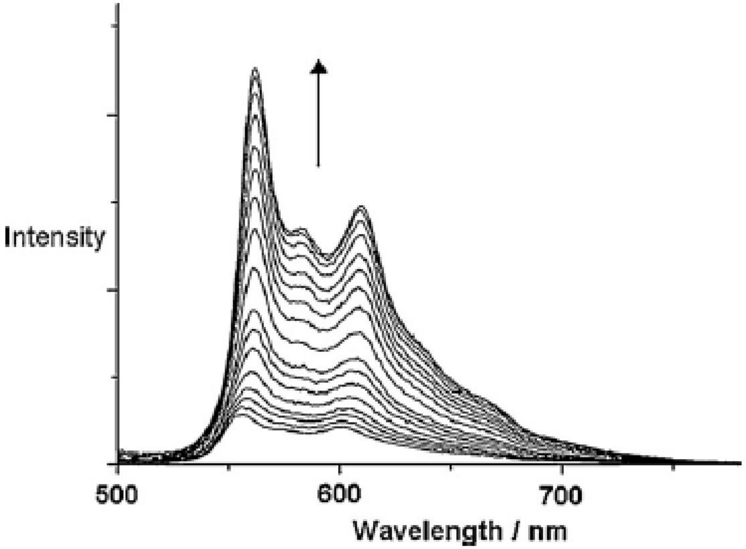

HN
NH2
HN
O
N
H
OH
O
8
2+
Ru

20

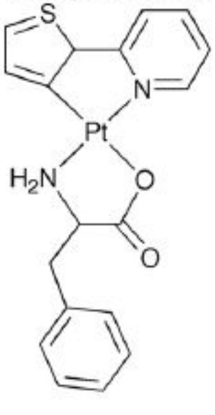


21

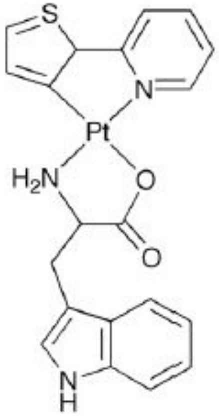
Количественное определение биокомпонентов



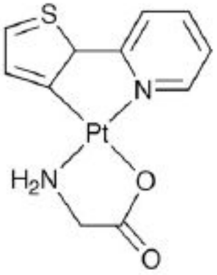
1 > cisplatin > **2** > **3**.



1


S
N
Pt
H_2N
O
O
N
H

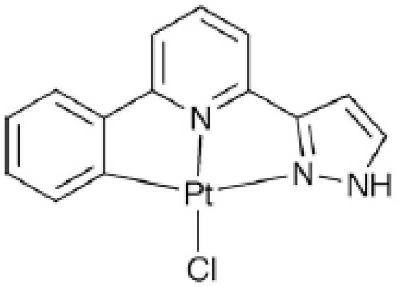
2



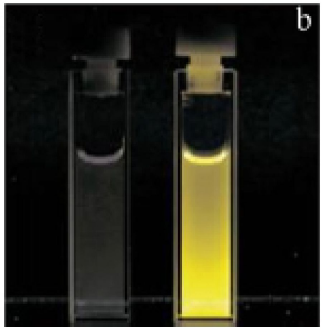
3

Спектр люминесценции комплекса 1 в зависимости от соотношения [HSA]/[1] (HSA – альбумин плазмы крови человека)

Визуализация присутствия биопрепаратов

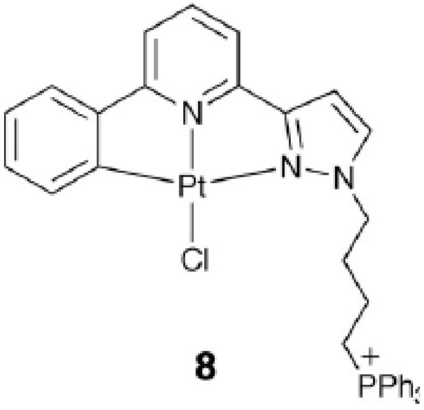


6

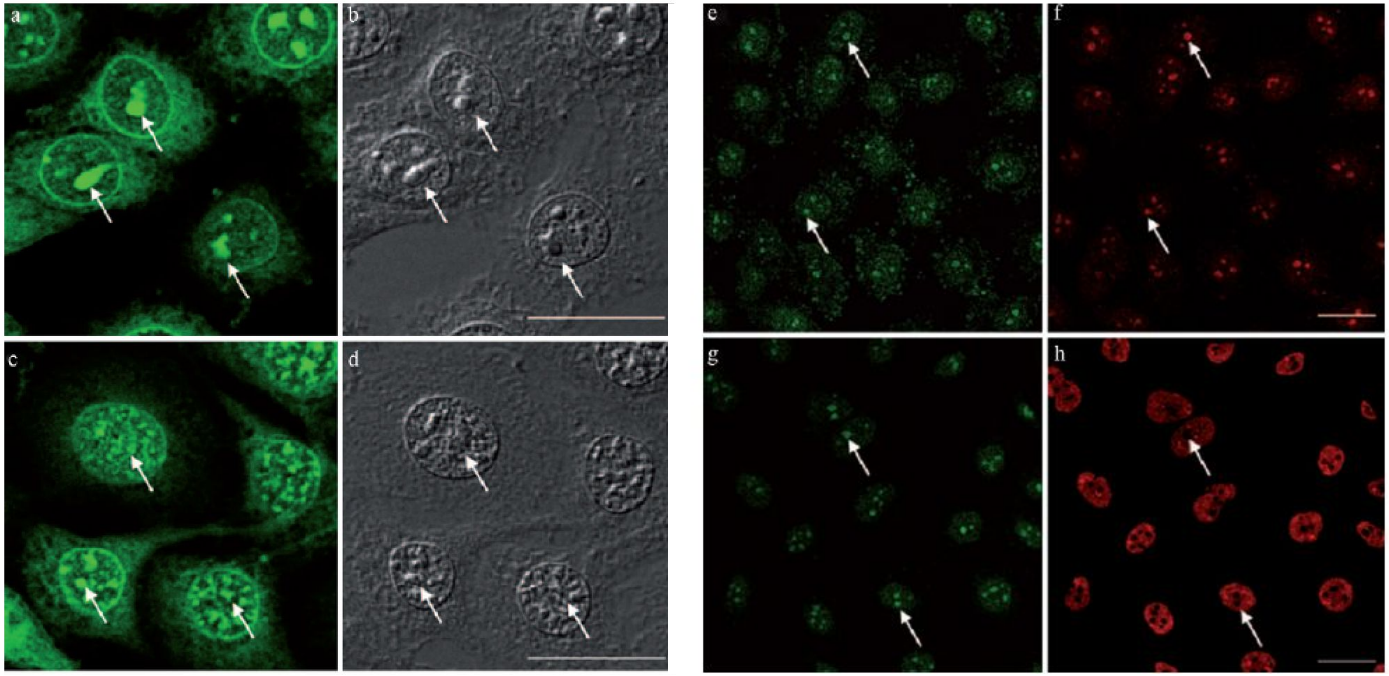


Флуоресценция комплекса в присутствии (справа) и в отсутствие альбумина плазмы крови быка.

Метки на бактериях и специфических белках



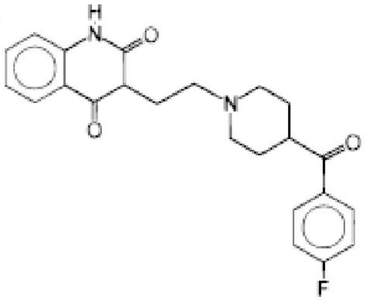
8



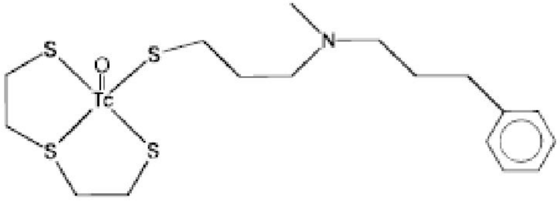
Использование комплекса для создания меток на HeLa бактериях (слева) и на клетках, выделенных из белка, характерного для одного из видов саркомы (справа)

Метки на рецепторы серотонина

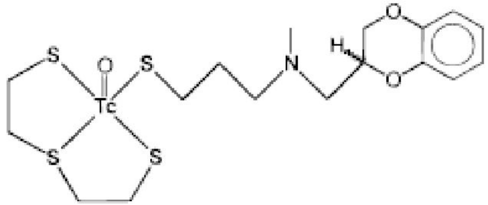
(3a)



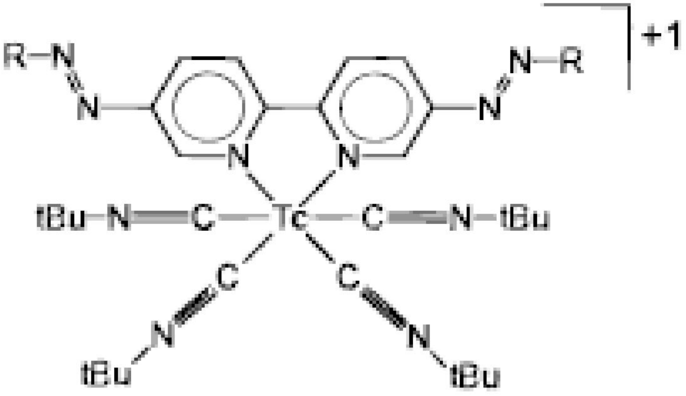
(3b)



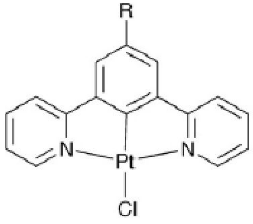
(3c)


S
O
Tc
S
N
H
O
O
S
S

Метки для амилоидных бляшек


+1
R
N
N
N
N
R
N
N
tBu
N
C
Tc
C
N
tBu
C
C
N
N
tBu
tBu

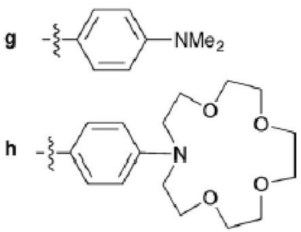
Метки клеток эпидермиса

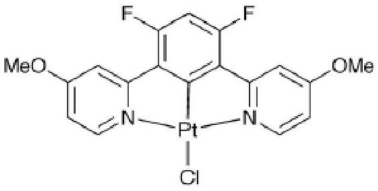


9

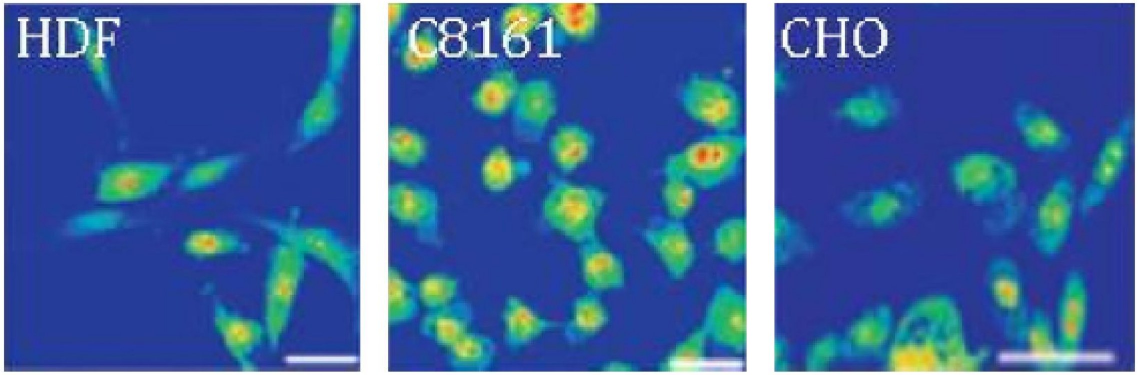
R =

- **a** –H
- **b** –CO_2Me
- **c** –Me
- **d** –*p*-tolyl
- **e** –*p*-biphenylyl
- **f** –2-thienyl


g
NMe_2
h
N
O
O
O
O
O

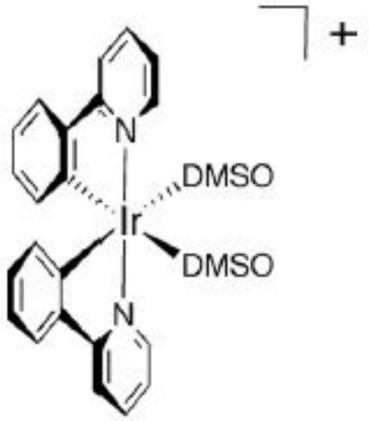

F
F
MeO
OMe
N
Pt
N
Cl

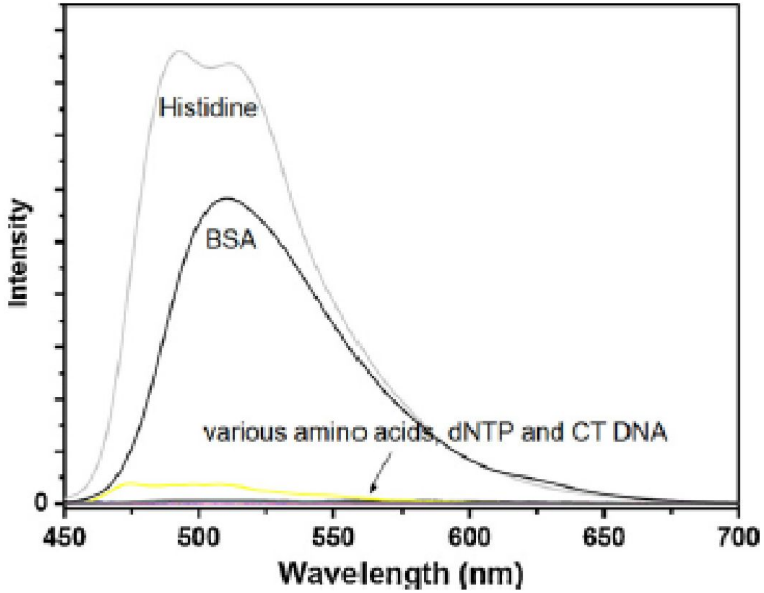
9i


HDF
C8161
CHO

Клетки эпидермиса, инкубированные с комплексом **9a**: нормальные фибропласты человека (HDF), клетки меланомы C8161 и (для сравнения) клетки эпидермиса китайского омара.

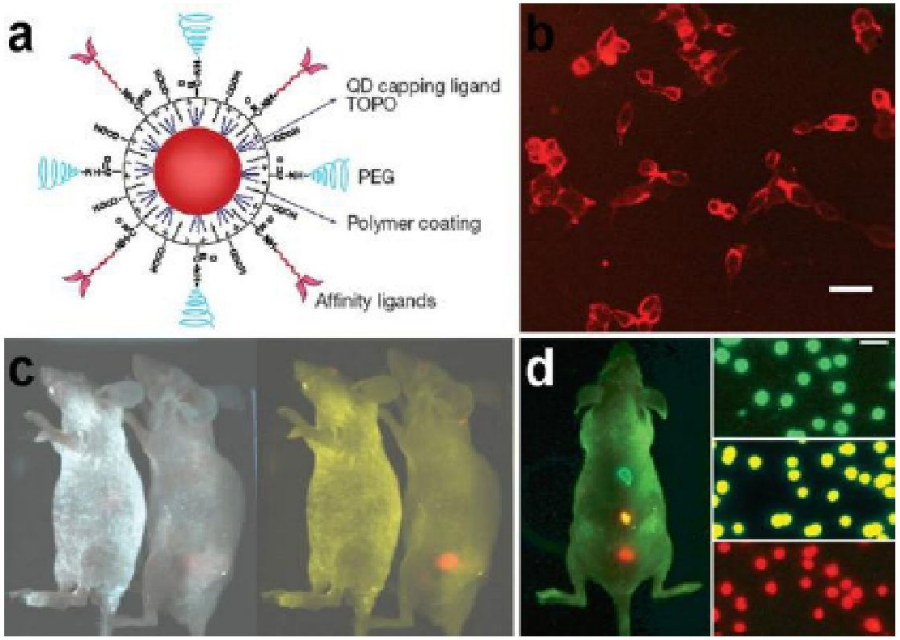
Влияние природы биокомпонента на спектры излучения



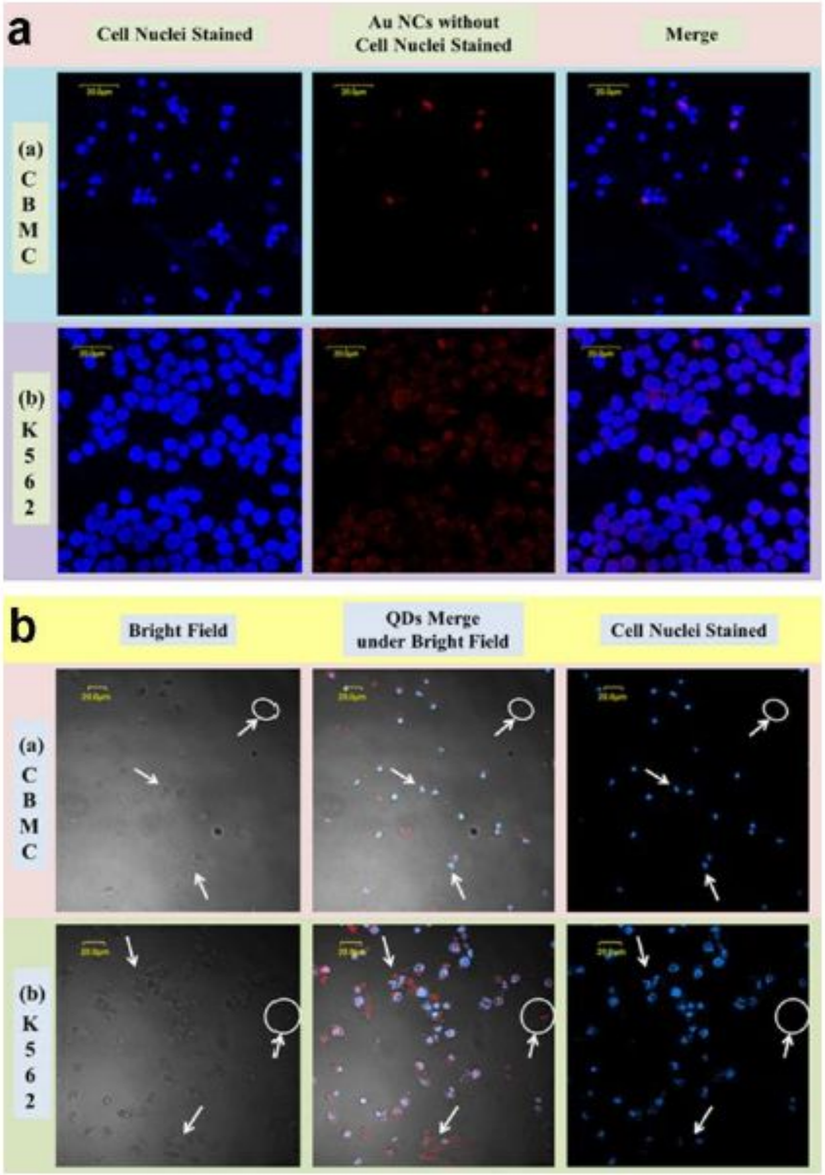


Спектры люминесценции комплекса иридия в присутствии различных биологически активных веществ (BSA – бычий альбумин)

Применение наночастиц CdSe@ZnSe для визуализации ракововой опухоли у мыши


a
QD capping ligand
TOPO
PEG
Polymer coating
Affinity ligands
b
c
d

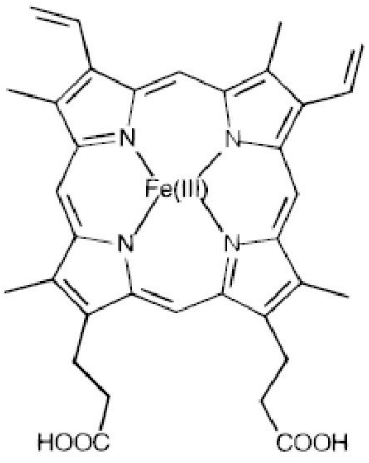
Биовизуализация с использованием квантовых точек (внизу) и нанокластеров металлов (вверху)


a
Cell Nuclei Stained
Au NCs without Cell Nuclei Stained
Merge
(a) C B M C
(b) K 5 6 2
b
Bright Field
QDs Merge under Bright Field
Cell Nuclei Stained
(a) C B M C
(b) K 5 6 2

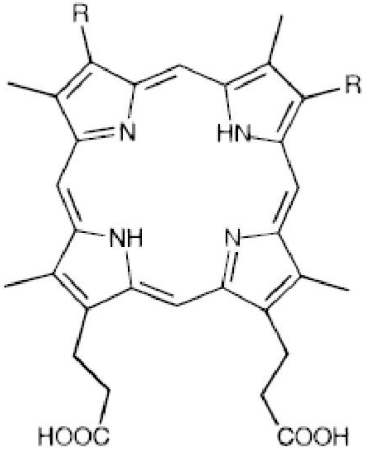
Неорганические вещества в медицине

V. Фото- и радиосенсибилизаторы

Простейшие порфирины

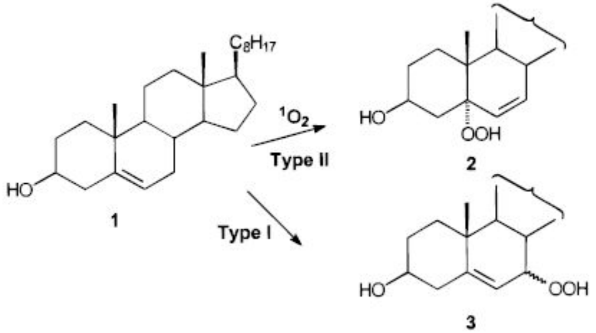

Fe(III)
N
HOOC
COOH

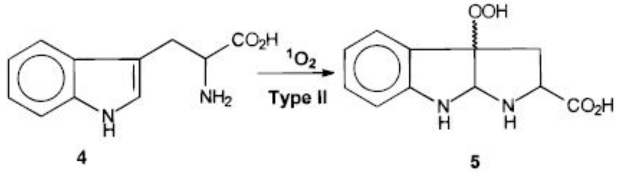
9
Hemin

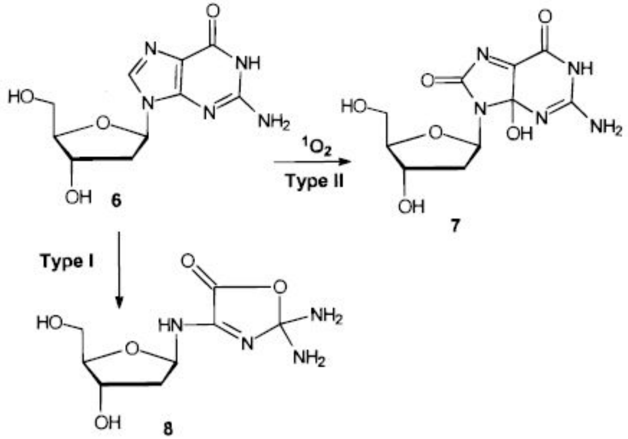

R
R
N
HN
NH
HOOC
COOH

10: Hematoporphyrin (Hp) R = CH(OH)CH$_3$
11: Protoporphyrin IX (Pp IX) R = CHCH$_2$

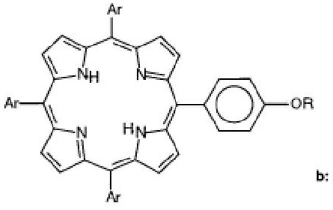
Действие синглетного кислорода


C_8H_{17}
HO
1
$^1O_2$
Type II
Type I
OOH
2
3


CO_2H
NH_2
N H
4
$^1O_2$
Type II
OOH
CO_2H
5

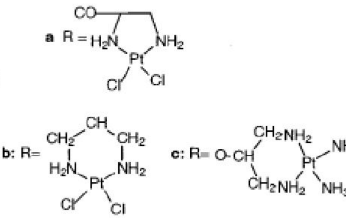

O
NH
N
NH_2
HO
OH
6
$^1O_2$
Type II
7
Type I
HN
NH_2
8

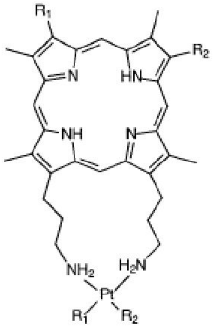
Примеры комплексов на основе порфиринов, обладающих фотодинамической активностью


Ar
NH
N
Ar
OR
N
HN
Ar

12

Ar= *p*-CH_3-C_6H_4

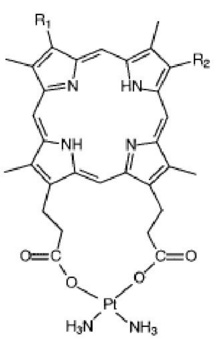

a R =
CO
H₂N
NH₂
Pt
Cl
Cl
b: R=
CH
CH₂
CH₂
H₂N
NH₂
Pt
Cl
Cl
c: R= O-CH
CH₂NH₂
CH₂NH₂
Pt
NH
NH


R₁
R₂
N
HN
NH
N
NH₂
H₂N
Pt
R₁
R₂

13

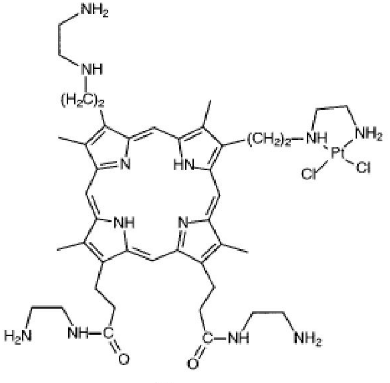
	R_1	R_2
a:	CH(OMe)Me	Cl,Cl
b:	$CH(OCH_2Ph)Me$	Cl,Cl
c:	$CH[(OCH_2CH_2)_2OMe]Me$	Cl,Cl
d:	$CH_2CH(OMe)_2$	Cl,Cl
e:	$(CH_2)_2OH$	Cl,Cl
f:	$(CH_2)_2$Oglucosyl	Cl,Cl
g:	(CH_2)Ogalctosyl	Cl,Cl
h:	$(CH_2)_2OH$	Lactal

R_1=R_2
- **i:** $CHMe(OCH_2)_7CH_3$
- **j:** $CHMeOCH_2C(CH_3)_3$
- **k:** $CHMeO(CH_2CH_2O)_{17}CH_3$
- **l:** SO_3H
- **m:** CH_2NMe_2
- **n:** $CHCHCH_2NMe_2$
- **o:** $CH_2NMe_3{}^+Cl^-$
- **p:** $CHCHCH_2NMe_3{}^+Cl^-$


R₁
R₂
N
HN
NH
N
O
C
O
O
C
O
Pt
H₃N
NH₃

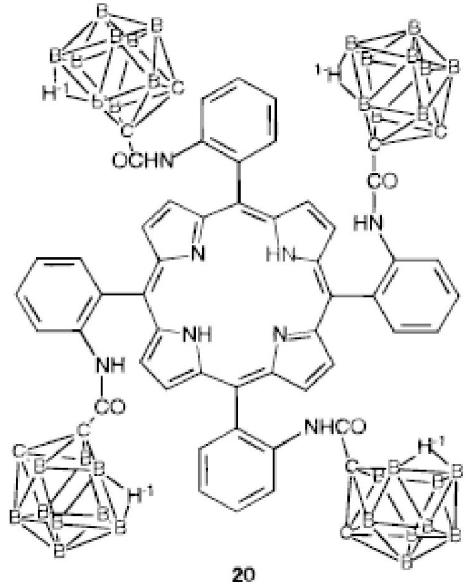
14

	R_1	R_2
a:	CH(OH)Me	CH(OH)Me
b:	CH(OH)Me	$CH[(OHp]_{2-5}]Me$
c:	CH(OH)Me	CH(OHp)MeI
d:	CH(OPh)Me	CH(OPh)Me
e:	CH_2(Ocyclohexyl)Me	CH_2(Ocyclohexyl)Me
f:	$CH(OCH_2CH_2)_2OMe)Me$	$CH(OCH_2CH_2)_2OMe]Me$
g:	$(CH_2)_2$Oglucosyl	$(CH_2)_2$Oglucosyl
h:	$(CH_2)_2$Ogalctosyl	$(CH_2)_2$Ogalctosyl

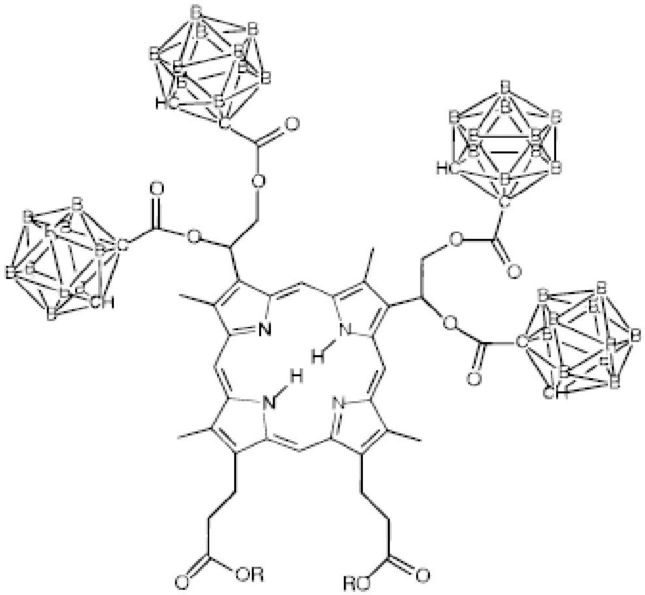

NH₂
NH
(H₂C)₂
N
HN
(CH₂)₂
NH
NH₂
Pt
Cl
Cl
NH
N
H₂N
NH
C
O
C
O
NH
NH₂

15

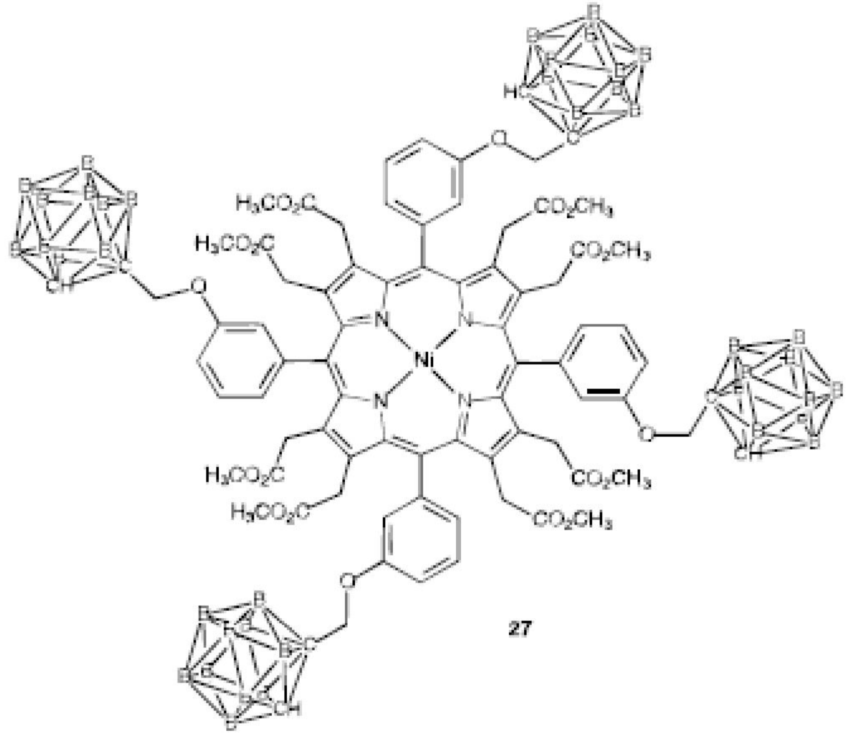
Боронированные порфирины


OCHN
CO
HN
NH
CO
NHCO
N
HN
NH
N

20

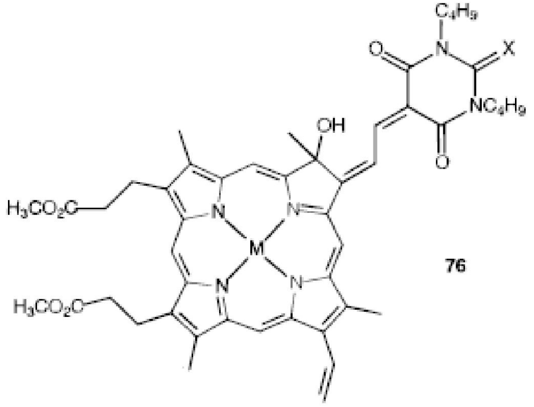


Комплексы переходных металлов с боронированными порфиринами


H₃CO₂C
H₃CO₂C
H₃CO₂C
H₃CO₂C
CO₂CH₃
CO₂CH₃
CO₂CH₃
CO₂CH₃
Ni
N
N
N
N
O
O
O
O
B
CH
HC

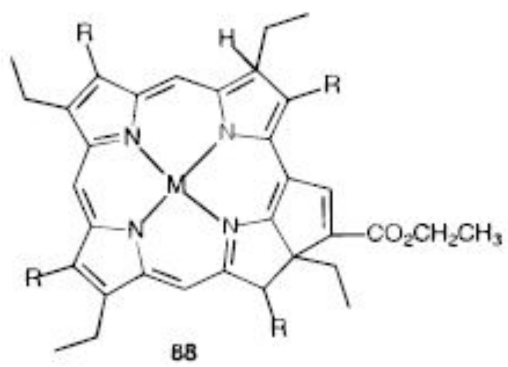
27

Комплексы с представителями других классов макроциклических лигандов


C4H9
O
N
X
NC4H9
OH
O
H3CO2C
N
N
M
N
N
H3CO2C

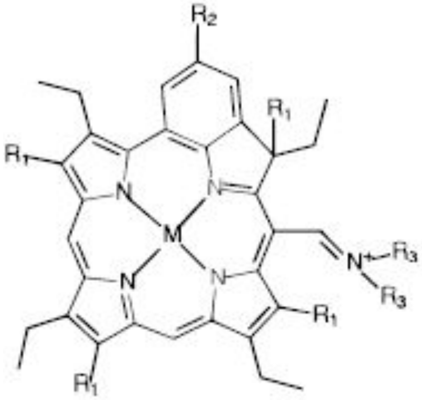
76

Хлорины


R
H
R
N
N
M
N
N
CO2CH2CH3
R
R

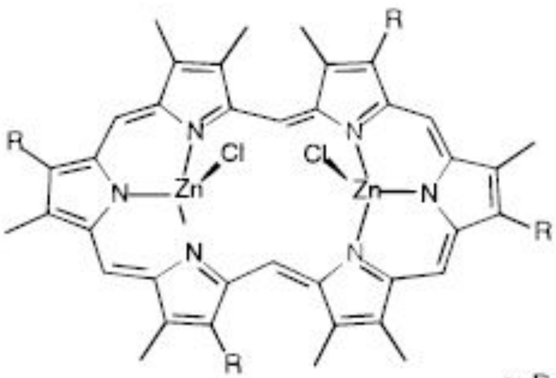
88

Пурпурины

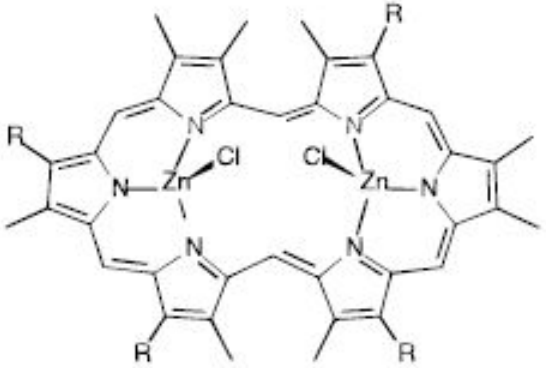

R2
R1
R1
N
N
M
N
N
N+
R3
R3
R1
R1

Порфицены

«Расширенные» порфирины (expanded porphyrins)


R
R
R
R
N
N
N
N
N
N
Zn
Zn
Cl
Cl

+

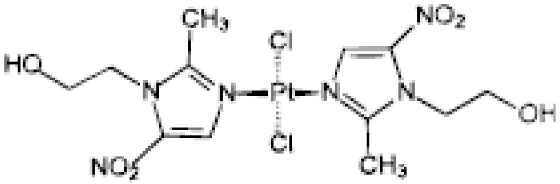

R
R
R
R
N
N
N
N
N
N
Zn
Zn
Cl
Cl

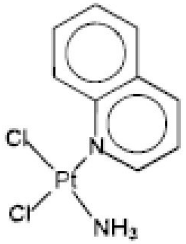
112

a: R = $(CH_2)CO_2Me$
b: R = C_8H_{17}
c: R= $C_{18}H_{17}$
d: R = Me

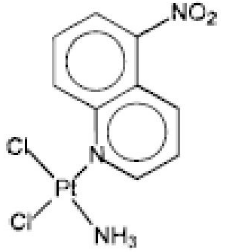
113: R= CO_2Me

Радиосенсибилизаторы (примеры)

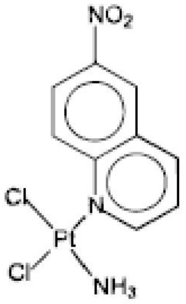




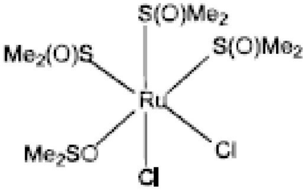
310



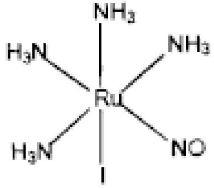
311



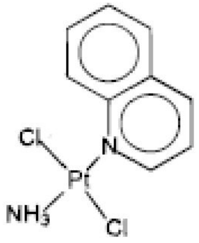
312



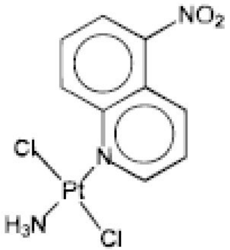
315



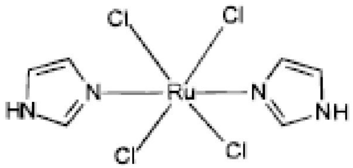
316



313



314



317

$$H_2O \rightarrow \underset{(2.7)}{\bar{e}_{aq}} + \underset{(0.55)}{H^\bullet} + \underset{(0.45)}{H_2} + \underset{(2.7)}{HO^\bullet} + \underset{(2.7)}{H_3O^+} + \underset{(0.7)}{H_2O_2}$$

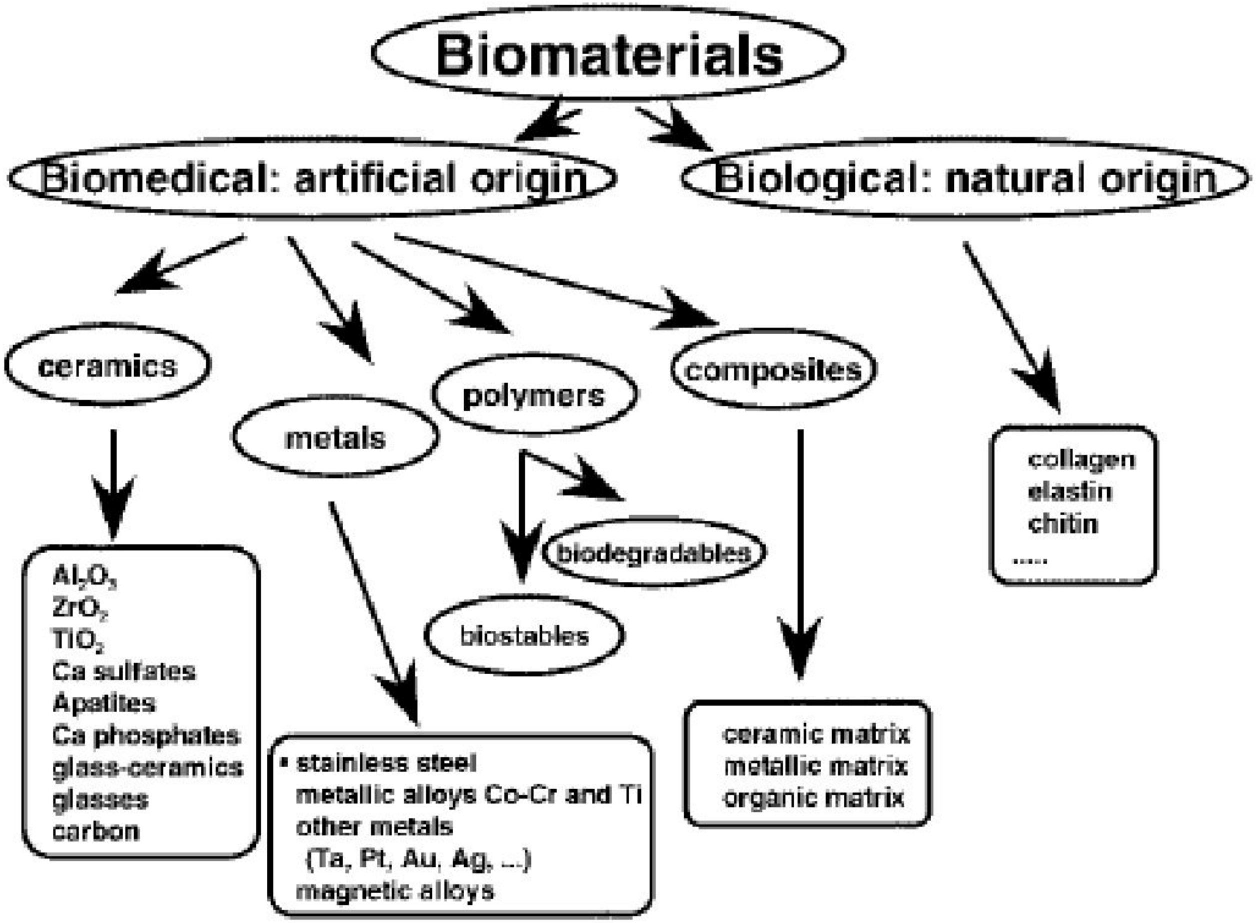
Неорганические вещества в медицине

VI. Медицинская керамика

Неорганические вещества в медицине

VI. Медицинская керамика

Классификация биоматериалов



Biomaterials

Biomedical: artificial origin

Biological: natural origin

ceramics

metals

polymers

composites

biodegradables

biostables

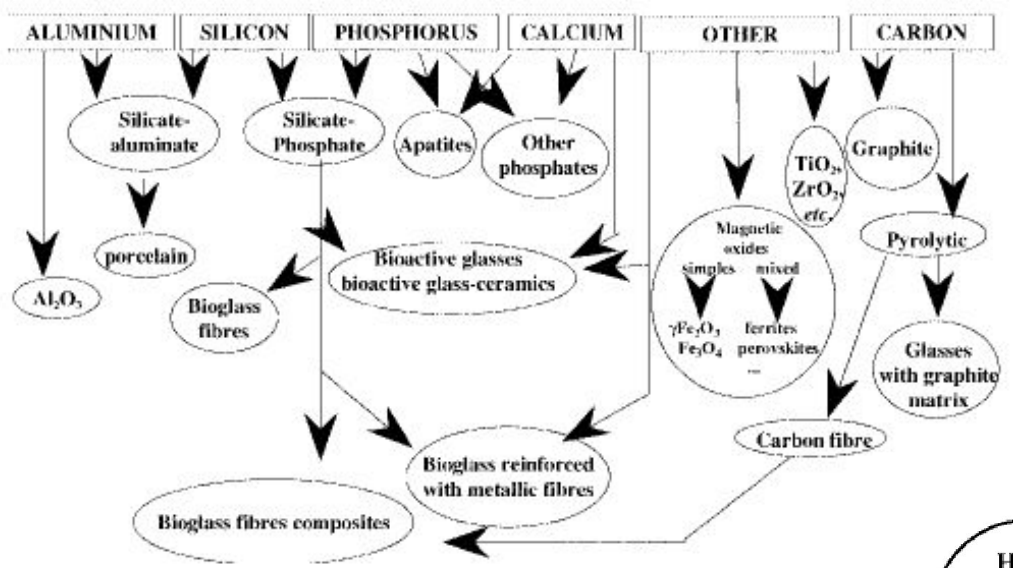
- Al_2O_3
- ZrO_2
- TiO_2
- Ca sulfates
- Apatites
- Ca phosphates
- glass-ceramics
- glasses
- carbon

- stainless steel
- metallic alloys Co-Cr and Ti
- other metals (Ta, Pt, Au, Ag, ...)
- magnetic alloys

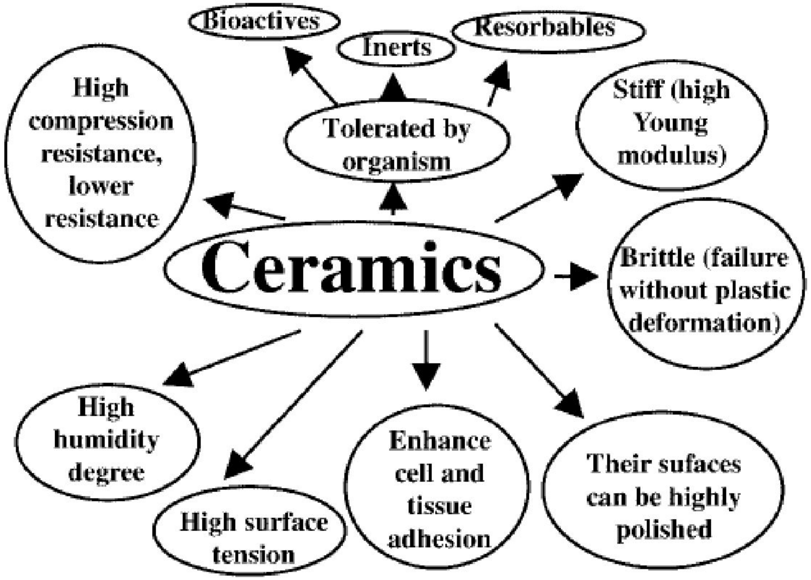
- ceramic matrix
- metallic matrix
- organic matrix

- collagen
- elastin
- chitin
- .....

Классификация биоматериалов

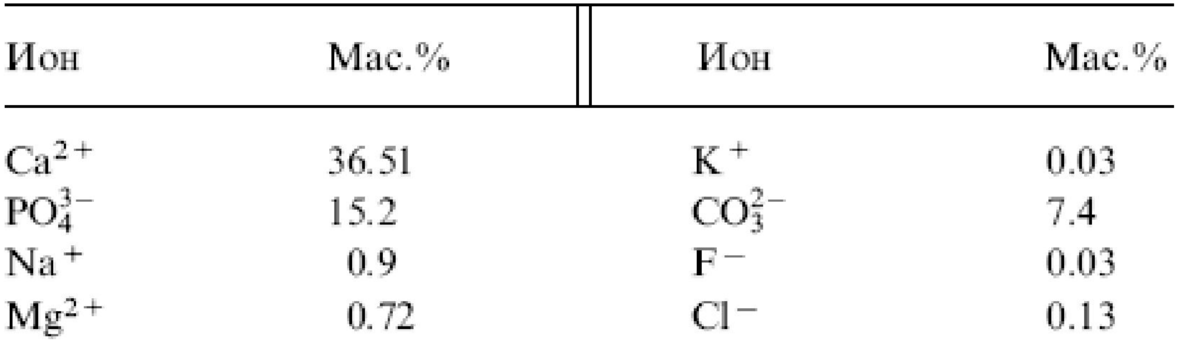


ALUMINIUM
SILICON
PHOSPHORUS
CALCIUM
OTHER
CARBON
Silicate-aluminate
Silicate-Phosphate
Apatites
Other phosphates
TiO$_2$, ZrO$_2$, etc.
Graphite
porcelain
Al_2O_3
Bioactive glasses bioactive glass-ceramics
Bioglass fibres
Magnetic oxides
simples
mixed
γFe_2O_3 Fe_3O_4
ferrites perovskites ...
Pyrolytic
Glasses with graphite matrix
Carbon fibre
Bioglass reinforced with metallic fibres
Bioglass fibres composites

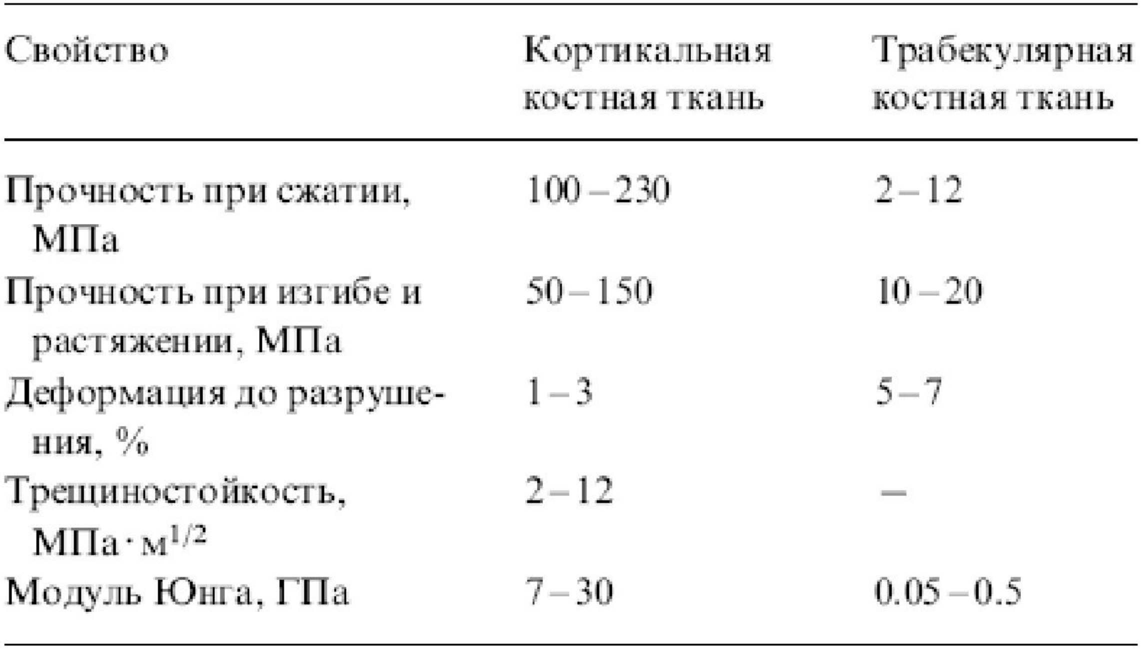


Bioactives
Inerts
Resorbables
Tolerated by organism
High compression resistance, lower resistance
Stiff (high Young modulus)
Ceramics
Brittle (failure without plastic deformation)
High humidity degree
High surface tension
Enhance cell and tissue adhesion
Their sufaces can be highly polished

Состав и свойства костной ткани



Ион	Мас.%	Ион	Мас.%
Ca^{2+}	36.51	K^{+}	0.03
PO_4^{3-}	15.2	CO_3^{2-}	7.4
Na^{+}	0.9	F^{-}	0.03
Mg^{2+}	0.72	Cl^{-}	0.13



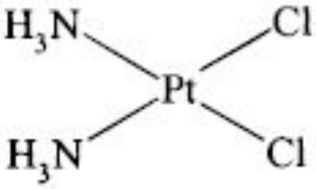
Свойство	Кортикальная костная ткань	Трабекулярная костная ткань
Прочность при сжатии, МПа	100 – 230	2 – 12
Прочность при изгибе и растяжении, МПа	50 – 150	10 – 20
Деформация до разрушения, %	1 – 3	5 – 7
Трещиностойкость, МПа · $м^{1/2}$	2 – 12	–
Модуль Юнга, ГПа	7 – 30	0.05 – 0.5

Неорганические вещества в медицине

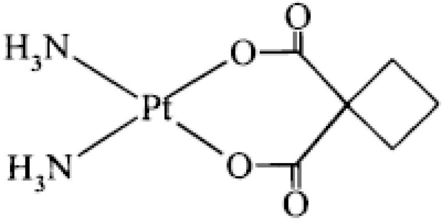
VII. Лекарственные препараты

VIIa. Противоопухолевые агенты

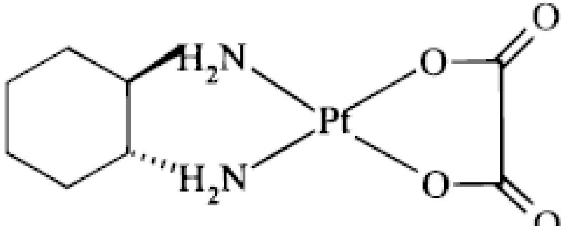
Комплексные соединения в химиотерапии опухолей



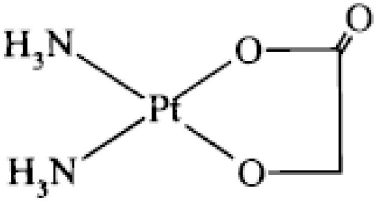
Цис-платин



карбоплатин

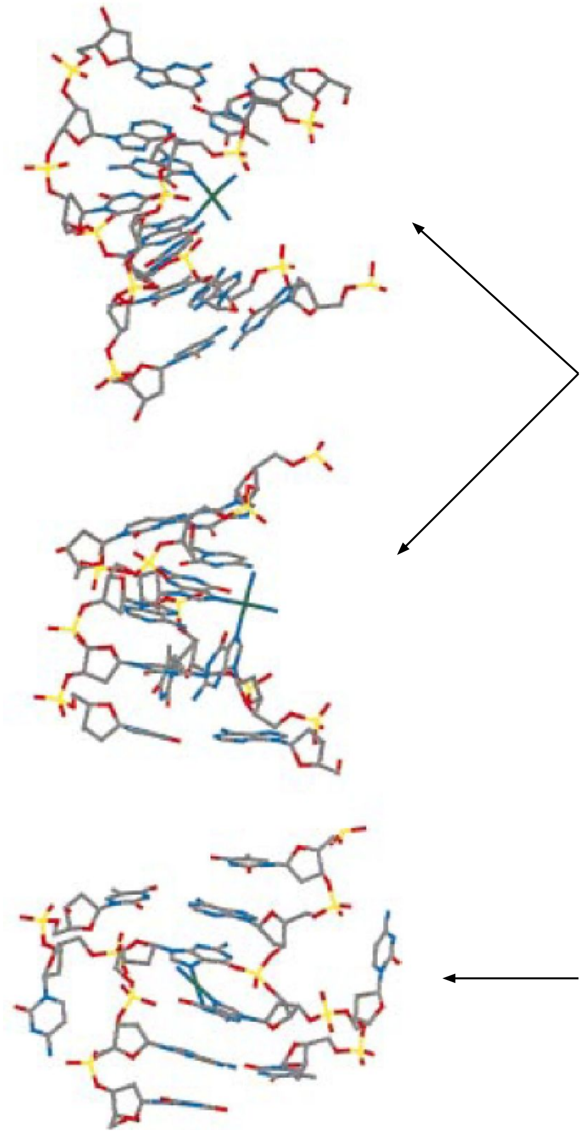


оксалиплатин



недаплатин

Связывание цис-платина с ДНК

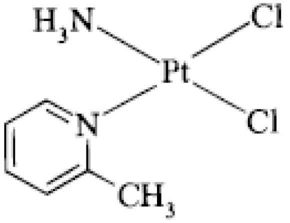


Внутри одной спирали ДНК

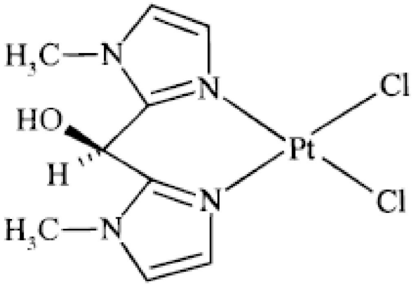
Между двумя спиралями ДНК

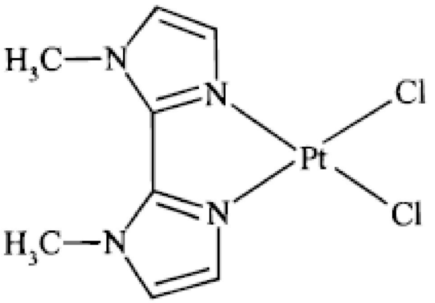
Направления модификации комплексов:

Стерические затруднения

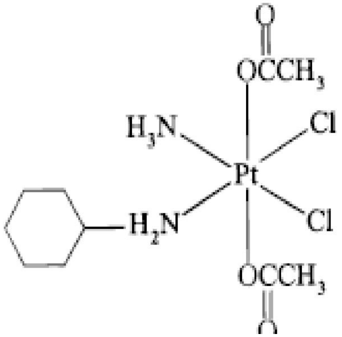


ZDO 473

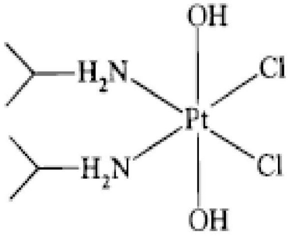


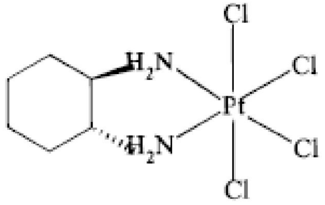


Комплексы платины (IV)

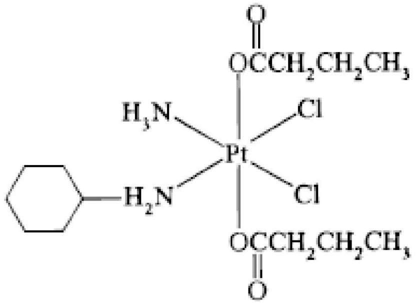


JM-216
(сатраплатин)





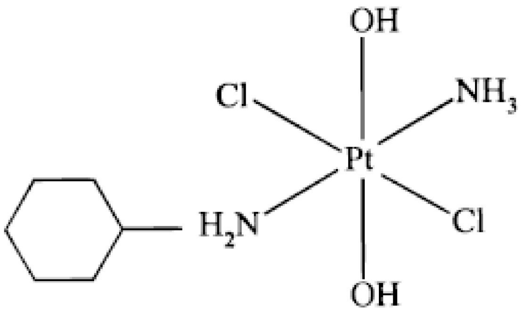
Ормаплатин

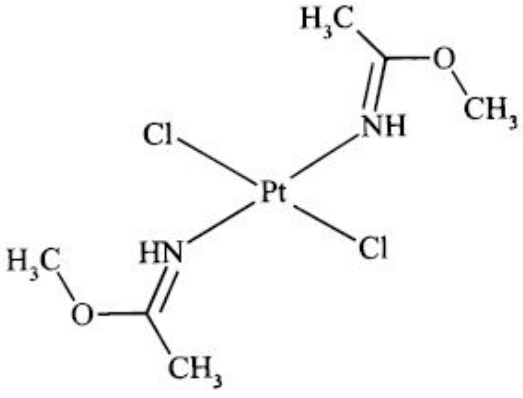


ипроплатин

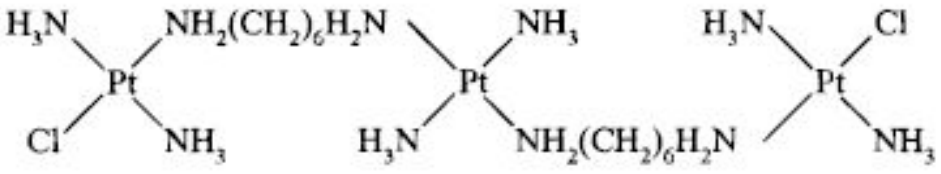
Направления модификации комплексов:

Транс-изомеры


OH
Cl
NH3
Pt
H2N
Cl
OH

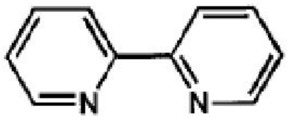

H3C
O
CH3
NH
Cl
Pt
HN
Cl
H3C
O
CH3

Многоядерные комплексы

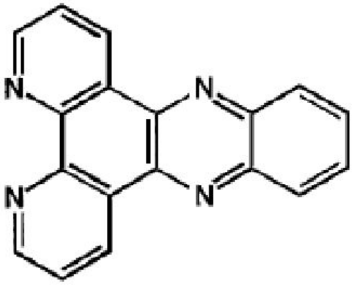

H3N
NH2(CH2)6H2N
NH3
H3N
Cl
Pt
Pt
Pt
Cl
NH3
H3N
NH2(CH2)6H2N
NH3

BBR 3464

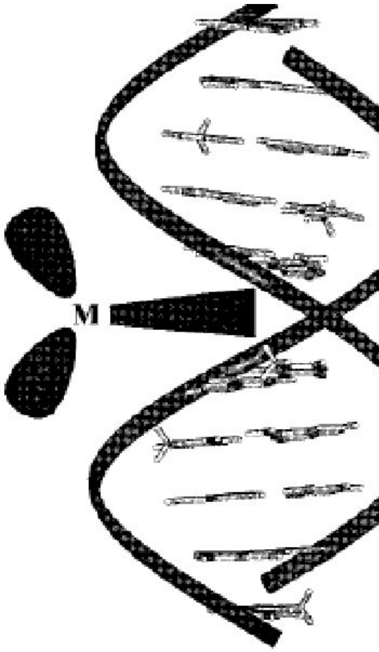
Лиганды-интеркаляторы ДНК

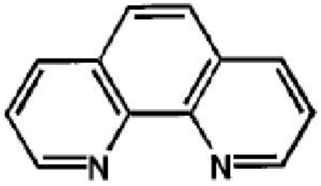


bpy

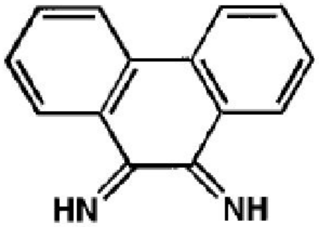


dppz



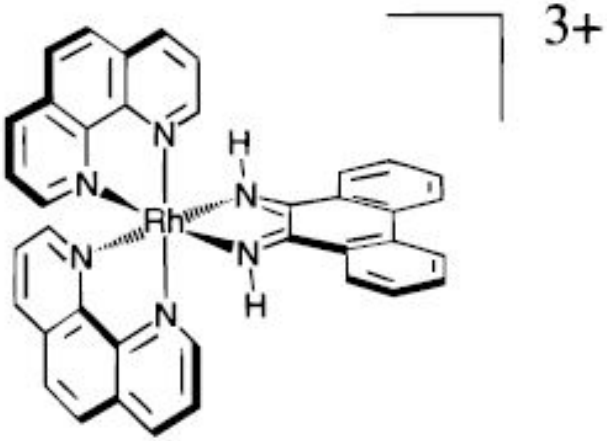


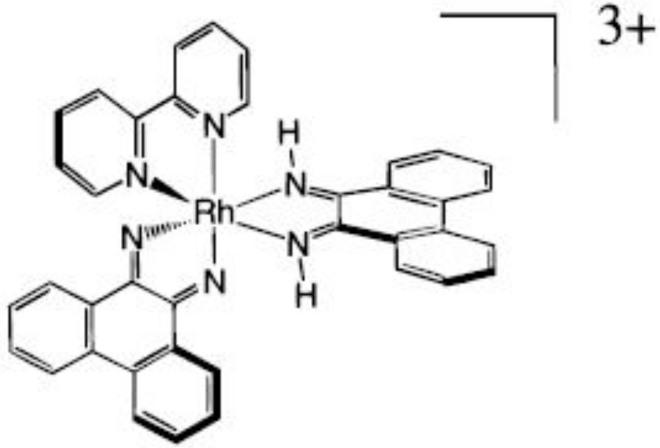
phen

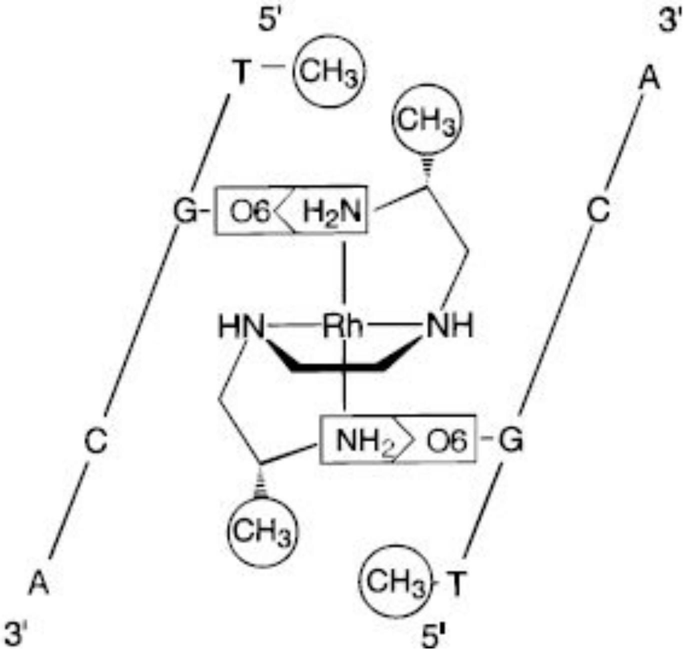


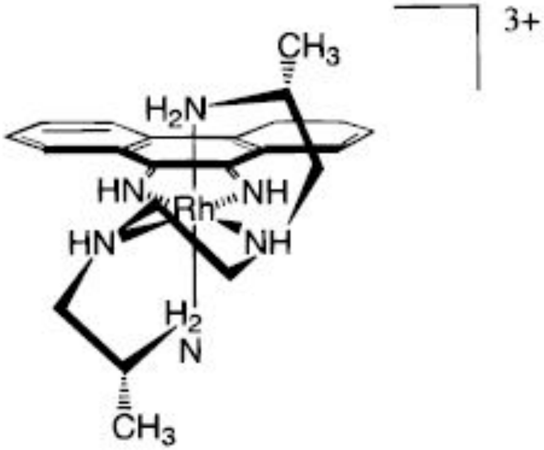
phi

комплексы-интеркаляторы ДНК

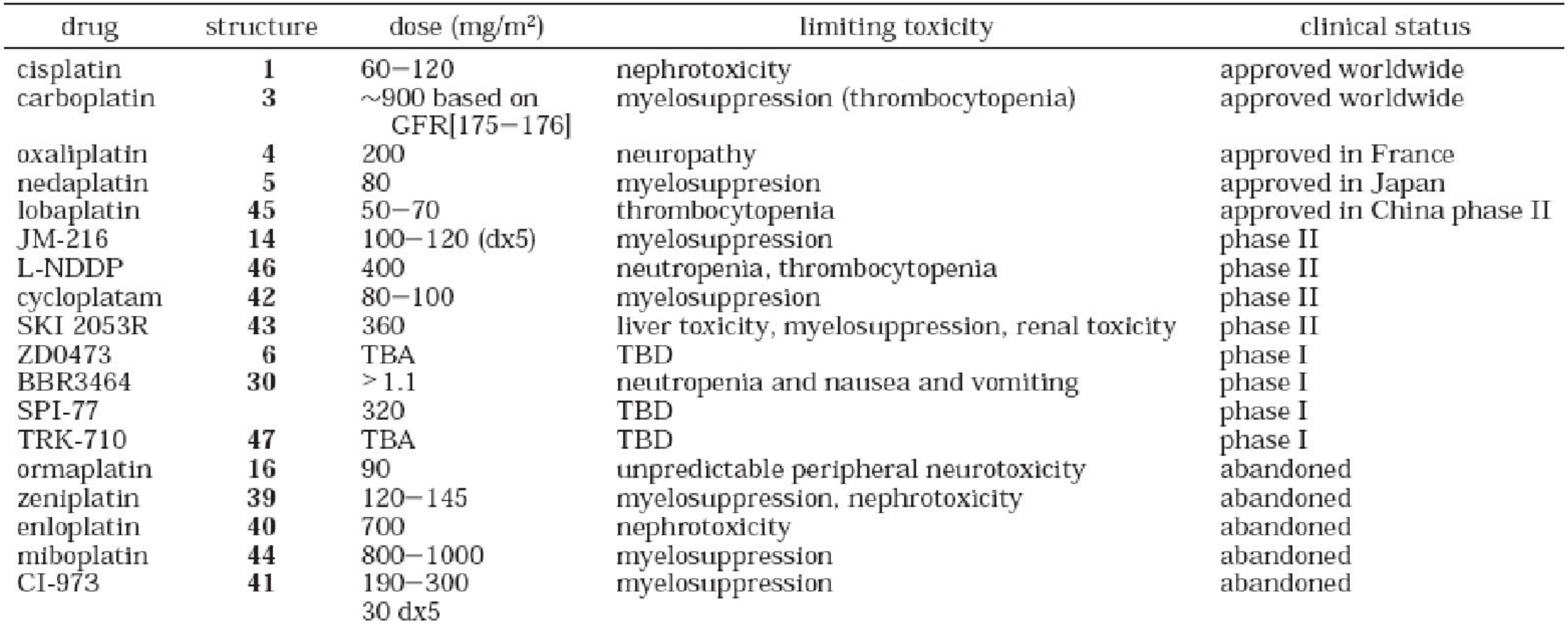

3+
N
N
Rh
H
N
N
H
N
N


3+
N
N
Rh
H
N
N
H
N
N


5'
3'
T
CH3
A
CH3
G
O6
H2N
C
HN
Rh
NH
NH2
O6
G
C
CH3
A
CH3
T
3'
5'

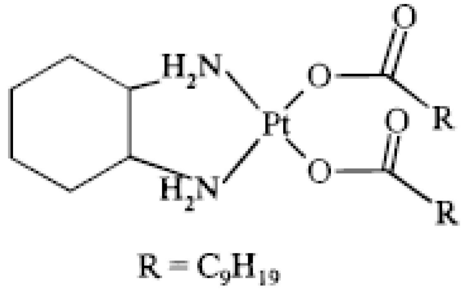

3+
CH3
H2N
HN
Rh
NH
HN
NH
H2
N
CH3

Состояние исследований

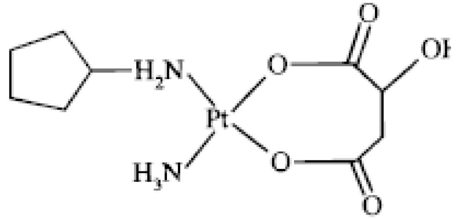


drug	structure	dose (mg/m²)	limiting toxicity	clinical status
cisplatin	1	60–120	nephrotoxicity	approved worldwide
carboplatin	3	~900 based on GFR[175–176]	myelosuppression (thrombocytopenia)	approved worldwide
oxaliplatin	4	200	neuropathy	approved in France
nedaplatin	5	80	myelosuppresion	approved in Japan
lobaplatin	**45**	50–70	thrombocytopenia	approved in China phase II
JM-216	**14**	100–120 (dx5)	myelosuppression	phase II
L-NDDP	**46**	400	neutropenia, thrombocytopenia	phase II
cycloplatam	**42**	80–100	myelosuppresion	phase II
SKI 2053R	**43**	360	liver toxicity, myelosuppression, renal toxicity	phase II
ZD0473	6	TBA	TBD	phase I
BBR3464	**30**	> 1.1	neutropenia and nausea and vomiting	phase I
SPI-77		320	TBD	phase I
TRK-710	**47**	TBA	TBD	phase I
ormaplatin	**16**	90	unpredictable peripheral neurotoxicity	abandoned
zeniplatin	**39**	120–145	myelosuppression, nephrotoxicity	abandoned
enloplatin	**40**	700	nephrotoxicity	abandoned
miboplatin	**44**	800–1000	myelosuppression	abandoned
CI-973	**41**	190–300 30 dx5	myelosuppression	abandoned

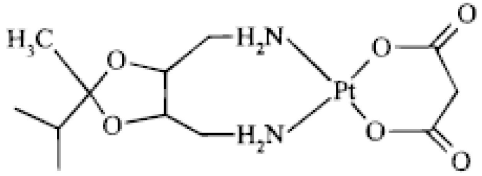
Некоторые платиновые комплексы, проходящие клинические испытания


H2N
Pt
O
R
H2N
R = C9H19

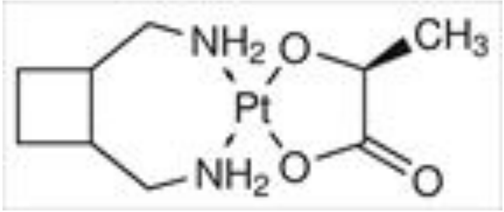
L-NDDP


H2N
Pt
H3N
O
OH

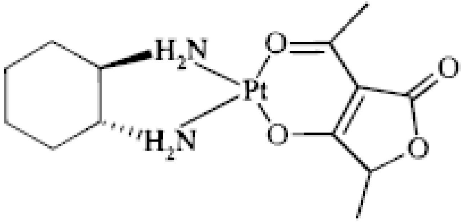
циклоплатам


H3C
O
H2N
Pt
O

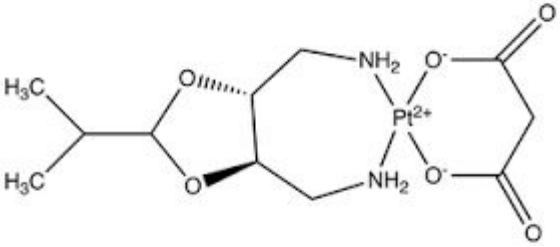
SKI 2053R



лобаплатин

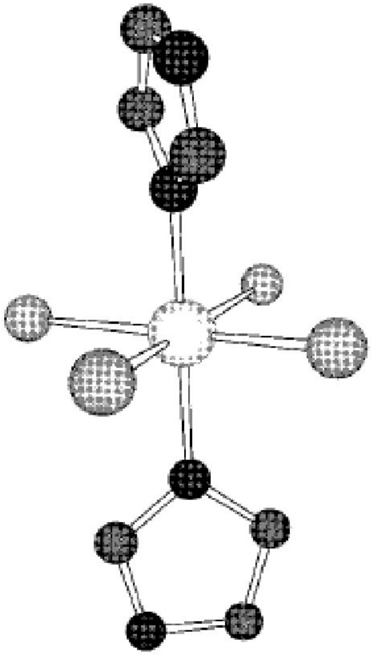


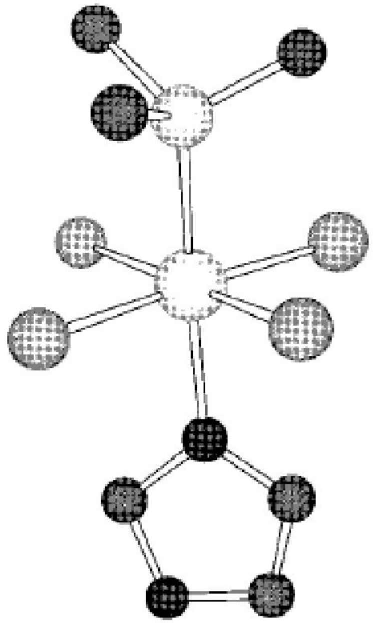
TRK 710

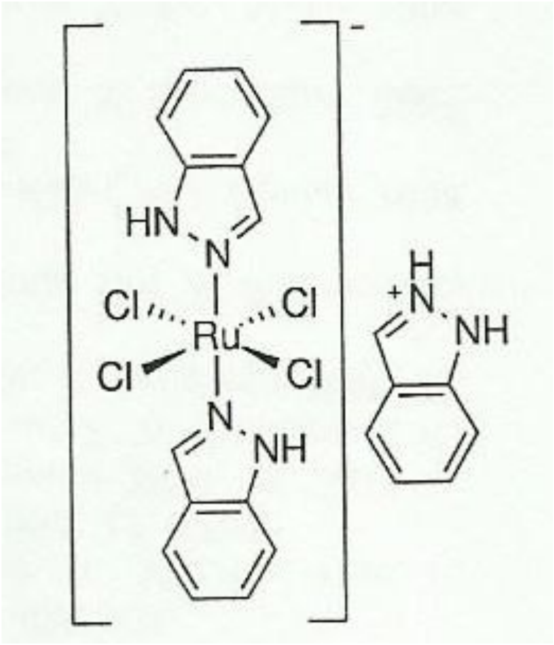

H3C
O
NH2
Pt2+
O-

гептаплатин

Комплексы рутения, обладающие противоопухолевой активностью





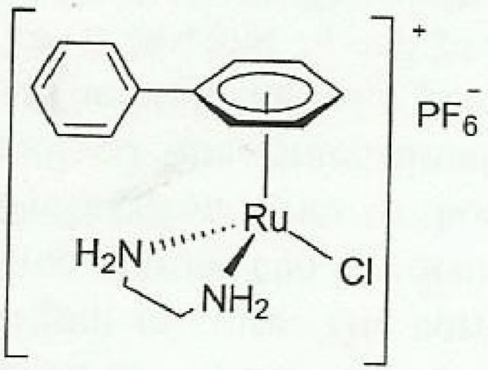

HN
N
Cl
Cl
Ru
Cl
Cl
N
NH
H
+N
NH
-

Транс-$(Im)_2RuCl_4^-$ (NAMI-A)

trans-(*S*-DMSO)(Im)$RuCl_4^-$

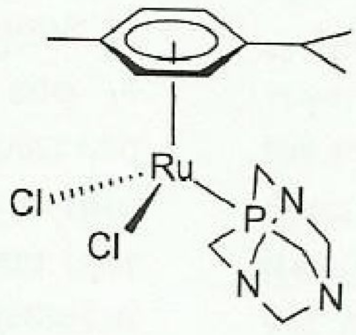
KP-1019

Комплексы рутения, обладающие противоопухолевой активностью



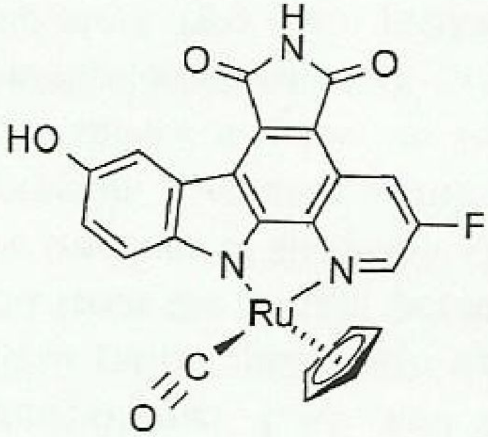
+
PF6−
Ru
H2N
NH2
Cl

RM175



Ru
Cl
Cl
P
N
N
N

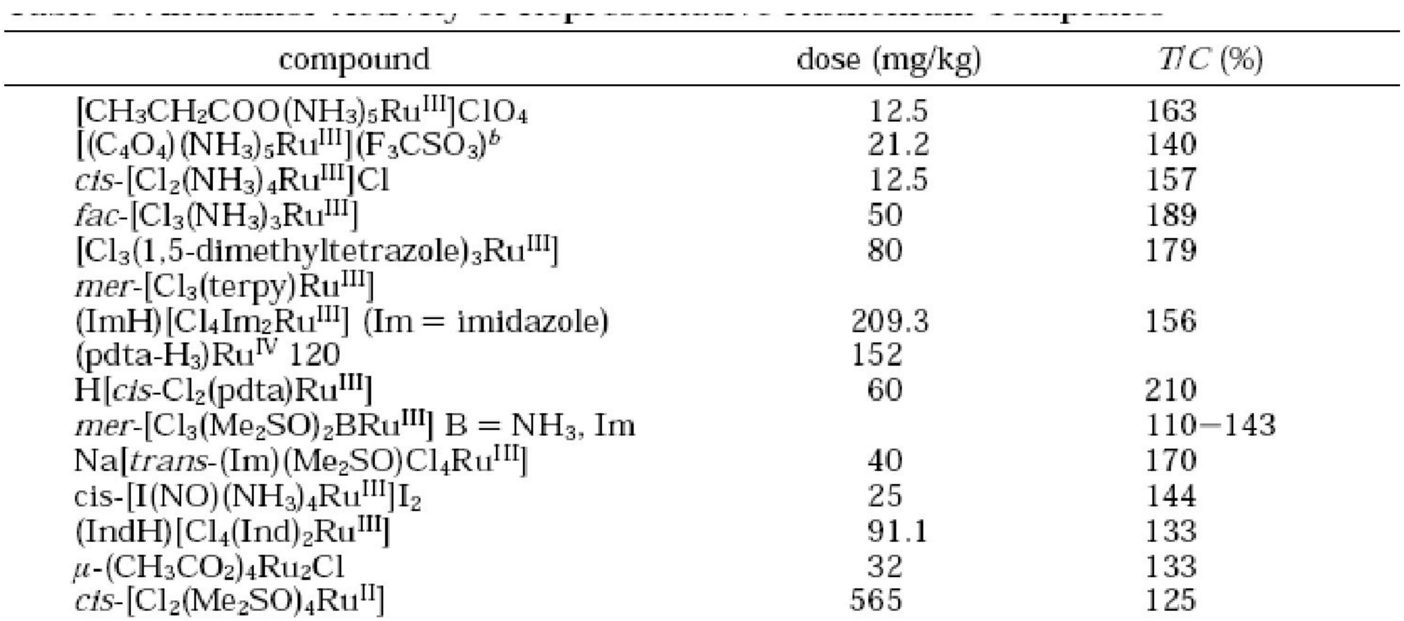
RAPTA-C



H
N
O
O
HO
F
N
N
Ru
C
O

NP309

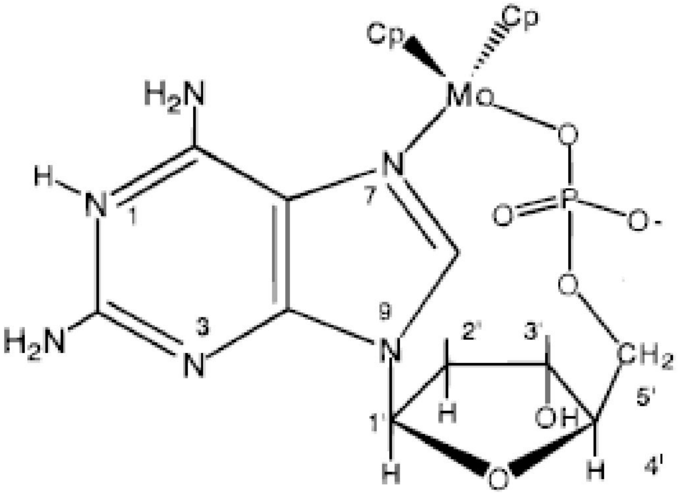
Противоопухолевая активность некоторых комплексов рутения



compound	dose (mg/kg)	*T/C* (%)
$[CH_3CH_2COO(NH_3)_5Ru^{III}]ClO_4$	12.5	163
$[(C_4O_4)(NH_3)_5Ru^{III}](F_3CSO_3)^b$	21.2	140
cis-$[Cl_2(NH_3)_4Ru^{III}]Cl$	12.5	157
fac-$[Cl_3(NH_3)_3Ru^{III}]$	50	189
$[Cl_3$(1,5-dimethyltetrazole)$_3Ru^{III}]$	80	179
mer-$[Cl_3$(terpy)$Ru^{III}]$		
(ImH)$[Cl_4Im_2Ru^{III}]$ (Im = imidazole)	209.3	156
(pdta-H_3)Ru^{IV} 120	152	
H[*cis*-Cl_2(pdta)Ru^{III}]	60	210
mer-$[Cl_3(Me_2SO)_2BRu^{III}]$ B = NH_3, Im		110−143
Na[*trans*-(Im)$(Me_2SO)Cl_4Ru^{III}$]	40	170
cis-$[I(NO)(NH_3)_4Ru^{III}]I_2$	25	144
(IndH)$[Cl_4(Ind)_2Ru^{III}]$	91.1	133
μ-$(CH_3CO_2)_4Ru_2Cl$	32	133
cis-$[Cl_2(Me_2SO)_4Ru^{II}]$	565	125

Т/С – отношение медиан выживаемости животных, получавших препараты рутения, к контрольной популяции * 100%

Взаимодействие металлоценов с нуклеотидами


Cp
Cp
Mo
H_2N
H
N
1
N
7
O
O=P
O-
O
H_2N
3
N
9
N
2'
3'
CH_2
H
OH
5'
1'
H
O
H
4'

Комплексы металлоценов с нуклеотидами

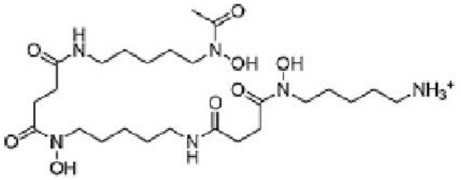
Неорганические вещества в медицине

VII. Лекарственные препараты

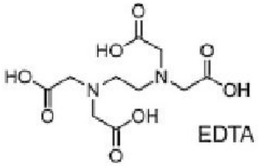
VIIв. Нейродегенеративные заболевания

Нейродегенеративные заболевания

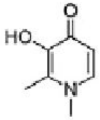
Лиганды для связывания ионов металлов



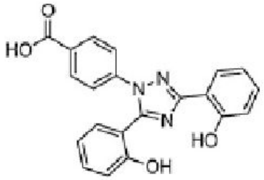
DFO



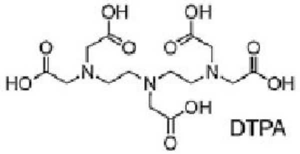
EDTA



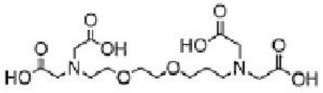
DFP



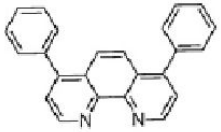
Deferasirox



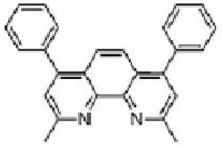
DTPA



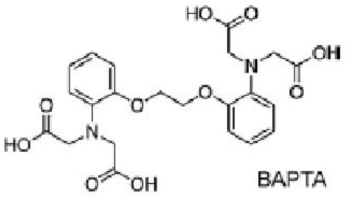
EGTA



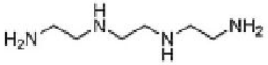
bathophenanthroline



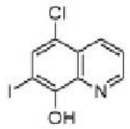
balhocuproine



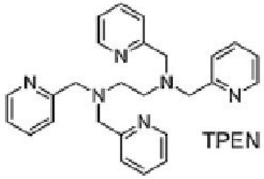
BAPTA



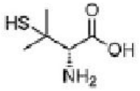
trientine



CQ



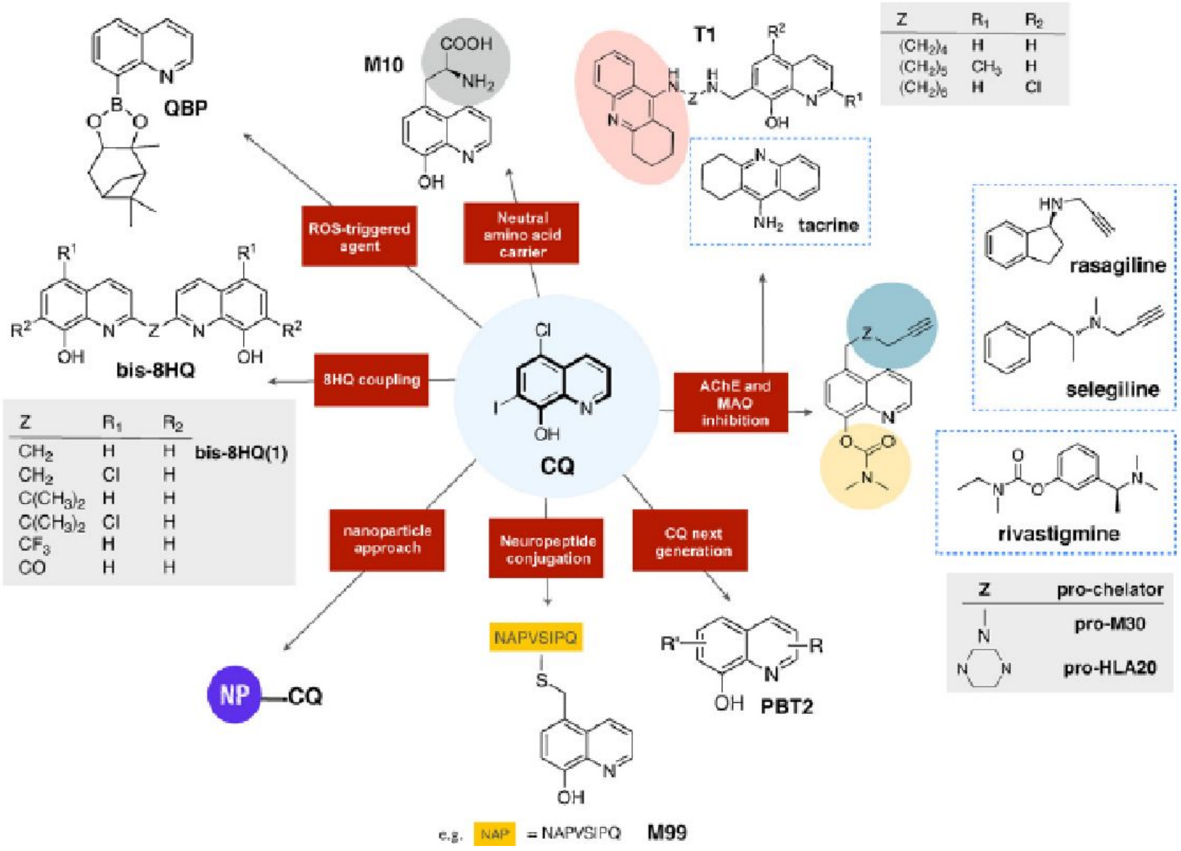
TPEN



D-penicillamine

Нейродегенеративные заболевания

Производные клиохинола



QBP
M10
COOH
NH$_2$
OH
N
T1
tacrine
rasagiline
selegiline
rivastigmine
ROS-triggered agent
Neutral amino acid carrier
8HQ coupling
AChE and MAO inhibition
nanoparticle approach
Neuropeptide conjugation
CQ next generation
Cl
I
CQ
bis-8HQ
R^1
R^2
Z
NP
NP—CQ
NAPVSIPQ
PBT2
R'
R
e.g. NAP = NAPVSIPQ
M99

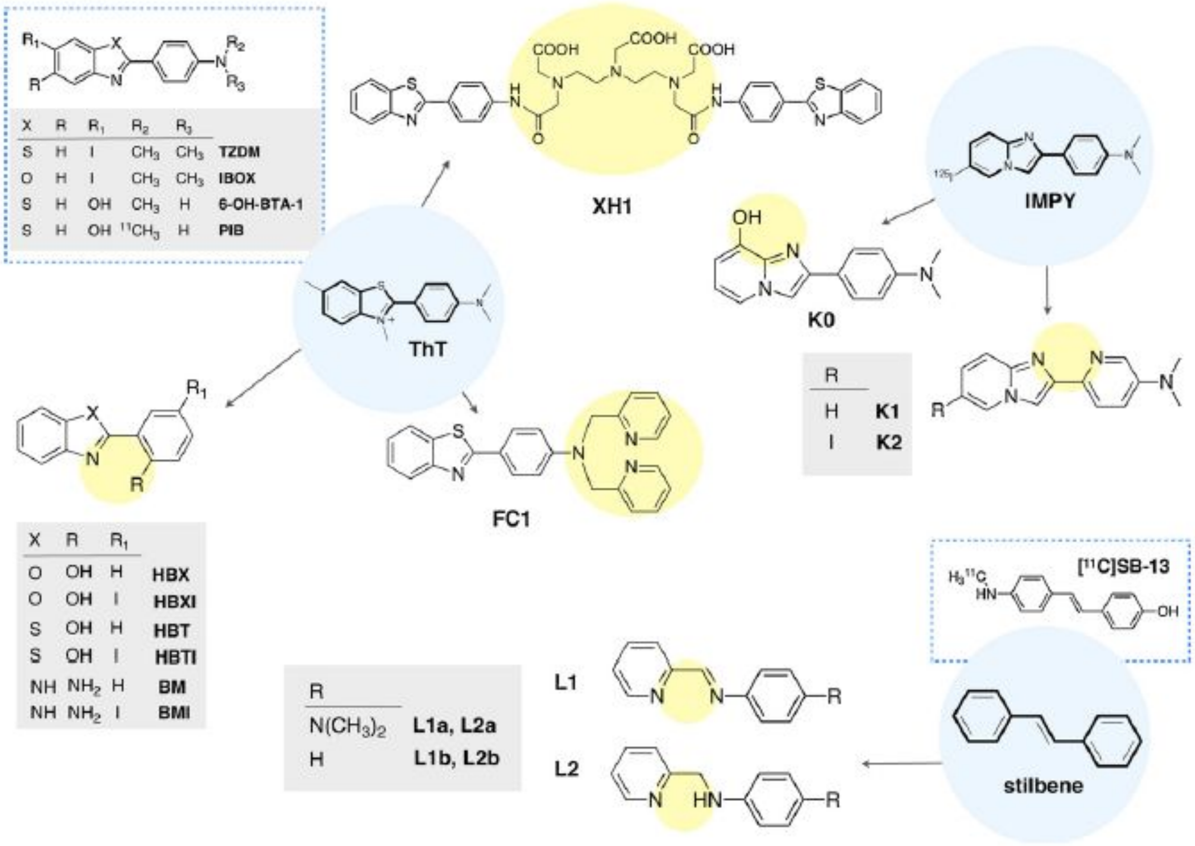
Z	R_1	R_2
$(CH_2)_4$	H	H
$(CH_2)_5$	CH_3	H
$(CH_2)_6$	H	Cl

Z	R_1	R_2	
CH_2	H	H	bis-8HQ(1)
CH_2	Cl	H	
$C(CH_3)_2$	H	H	
$C(CH_3)_2$	Cl	H	
CF_3	H	H	
CO	H	H	

Z	pro-chelator
N	pro-M30
N N	pro-HLA20

Нейродегенеративные заболевания

Производные тиофлавина


ThT
XH1
FC1
IMPY
K0
stilbene
[^{11}C]SB-13
L1
L2
COOH
NH
N
S
X
R
R_1
R_2
R_3
OH
^{125}I
$H_3{}^{11}C$
HN

X	R	R_1	R_2	R_3	
S	H	I	CH_3	CH_3	**TZDM**
O	H	I	CH_3	CH_3	**IBOX**
S	H	OH	CH_3	H	**6-OH-BTA-1**
S	H	OH	$^{11}CH_3$	H	**PIB**

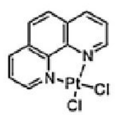
X	R	R_1	
O	OH	H	**HBX**
O	OH	I	**HBXI**
S	OH	H	**HBT**
S	OH	I	**HBTI**
NH	NH_2	H	**BM**
NH	NH_2	I	**BMI**

R	
H	**K1**
I	**K2**

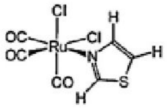
R	
$N(CH_3)_2$	**L1a, L2a**
H	**L1b, L2b**

Нейродегенеративные заболевания

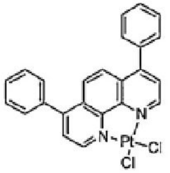
Фенантролиновые комплексы



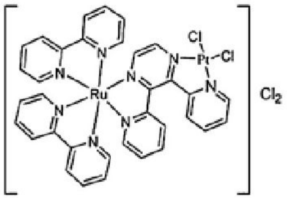
$Pt(1,10\text{-phenanthroline})Cl_2$
Compound 1


Cl
OC
OC
Ru
Cl
N
H
H
S
H
CO

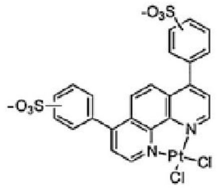
fac-$[Ru(CO)_3Cl_2(N_1\text{-thz})$
Compound 5



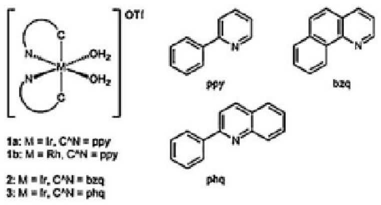
$Pt(4,7\text{-diphenyl-}[1,10]\text{phenanthroline})Cl_2$
Compound 2


N
N
Ru
N
N
N
N
N
Pt
Cl
Cl
N
Cl2

$[(bpy)_2Ru\ (dpp)PtCl_2]Cl_2$
Compound 6


-O3S
-O3S
N
N
Pt
Cl
Cl

$Pt(4,7\text{-diphenyl-}[1,10]\text{phenanthroline disulfonate})Cl_2$
Compound 3


OTf
C
N
M
OH2
OH2
N
C
1a: M = Ir, C^N = ppy
1b: M = Rh, C^N = ppy
2: M = Ir, C^N = bzq
3: M = Ir, C^N = phq
N
ppy
N
bzq
N
phq

$[Ir(C\text{^}N)_2(H_2O)_2]Otf$
Compound 7
$[Rh(ppy)_2(H_2O)_2]OTf$
Compound 8

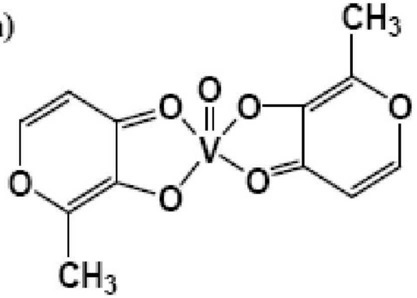
Неорганические вещества в медицине

VII. Лекарственные препараты

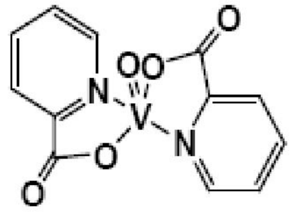
VIIc. Другие заболевания

Лекарства от диабета

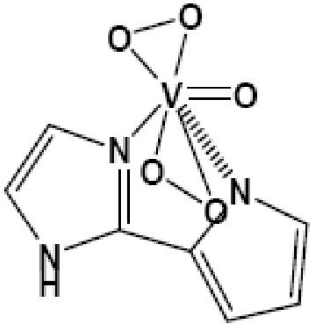
(a)



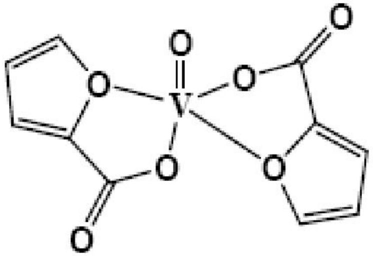
(b)



(c)

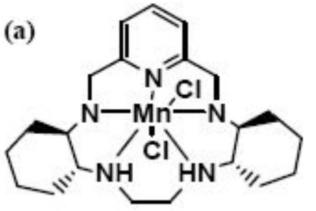


(d)

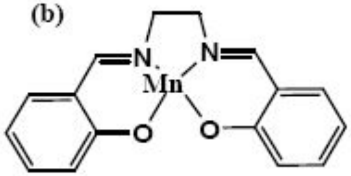


Противовоспалительные агенты

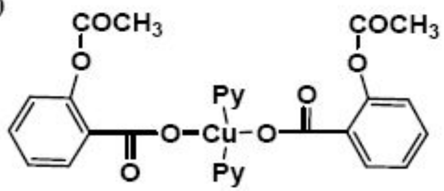
(a)



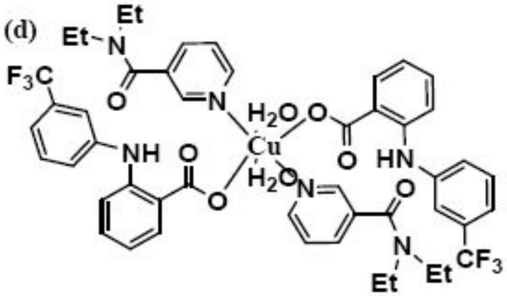
(b)



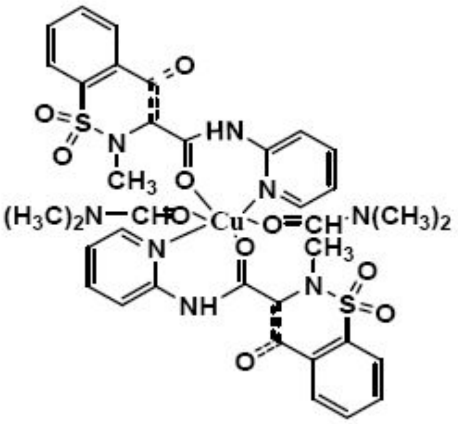
(c)



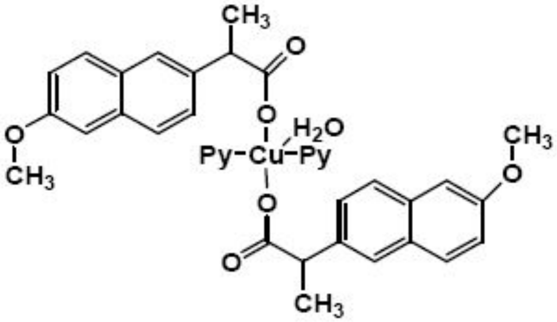
(d)



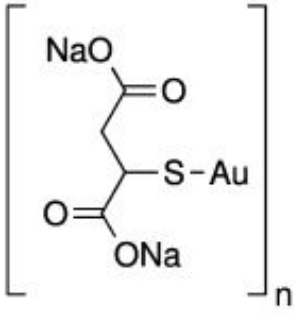
(e)



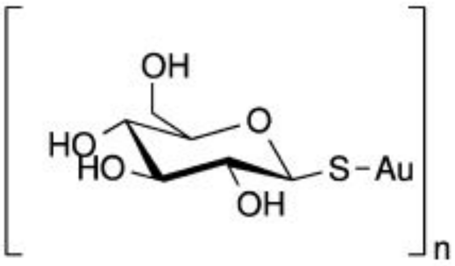
(f)



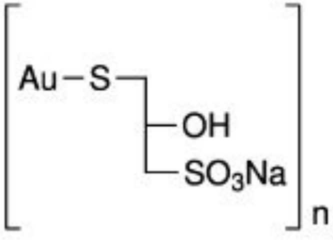
Противоартритные агенты



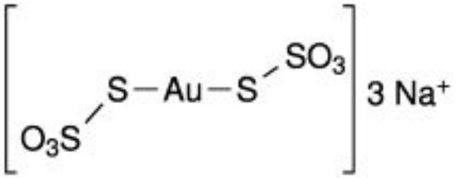
sodium aurothiomalate



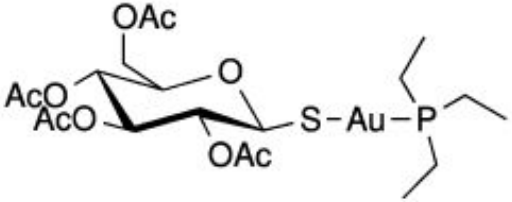
aurothioglucose



sodium aurothiopropanolsulfonate



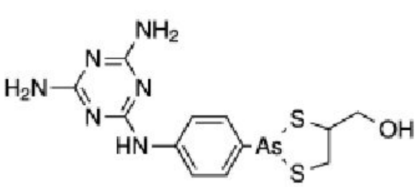
sodium aurothiosulfate



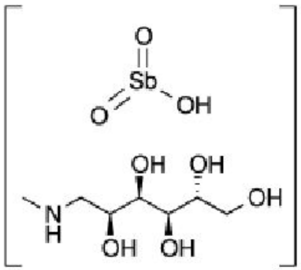
auranofin

Антибактериальные и антипаразитические препараты

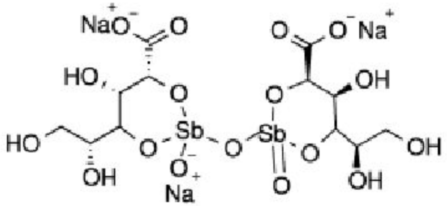
Approved



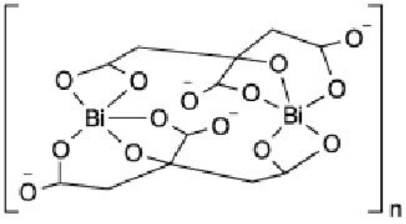
melarsoprol



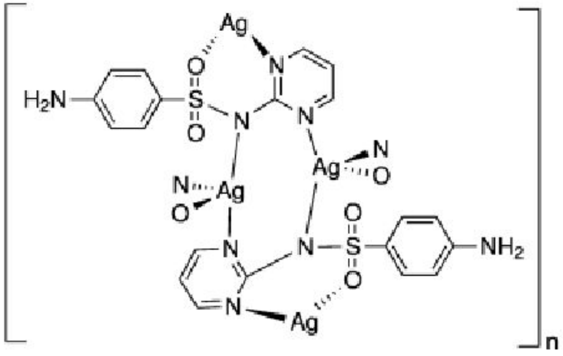
meglumine antimoniate



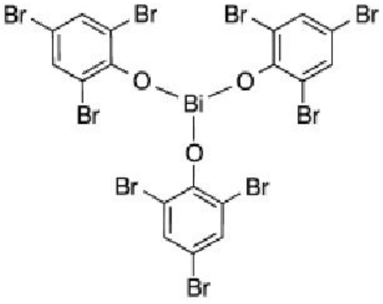
sodium stibugluconate



CBS

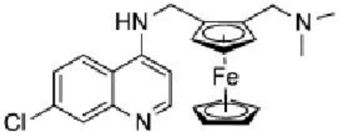


silver sulphadiazine



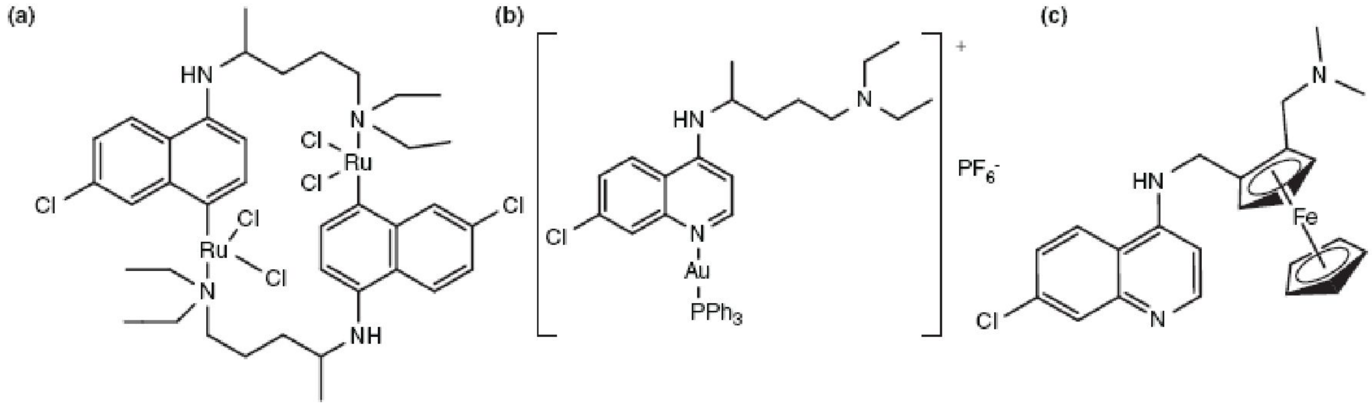
xeroform

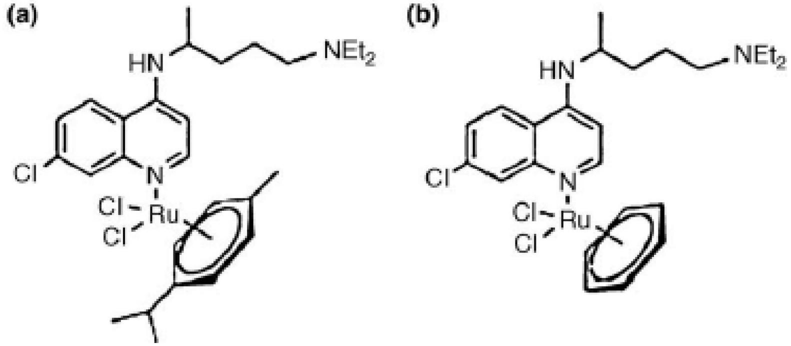
Clinical trials



ferroquine

Противомалярийные препараты


(a)
HN
N
Cl
Ru
Cl
Cl
Cl
Ru
Cl
Cl
Cl
N
NH
(b)
HN
N
Cl
N
Au
PPh3
+
PF6-
(c)
N
HN
Fe
Cl
N


(a)
HN
NEt2
Cl
N
Cl
Ru
Cl
(b)
HN
NEt2
Cl
N
Cl
Ru
Cl