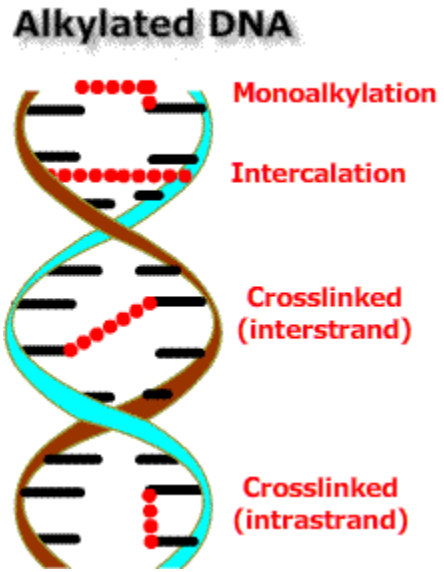
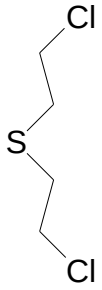
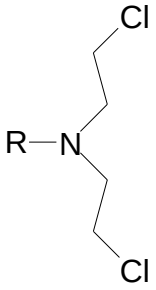
Αλκυλιωτικοί παράγοντες

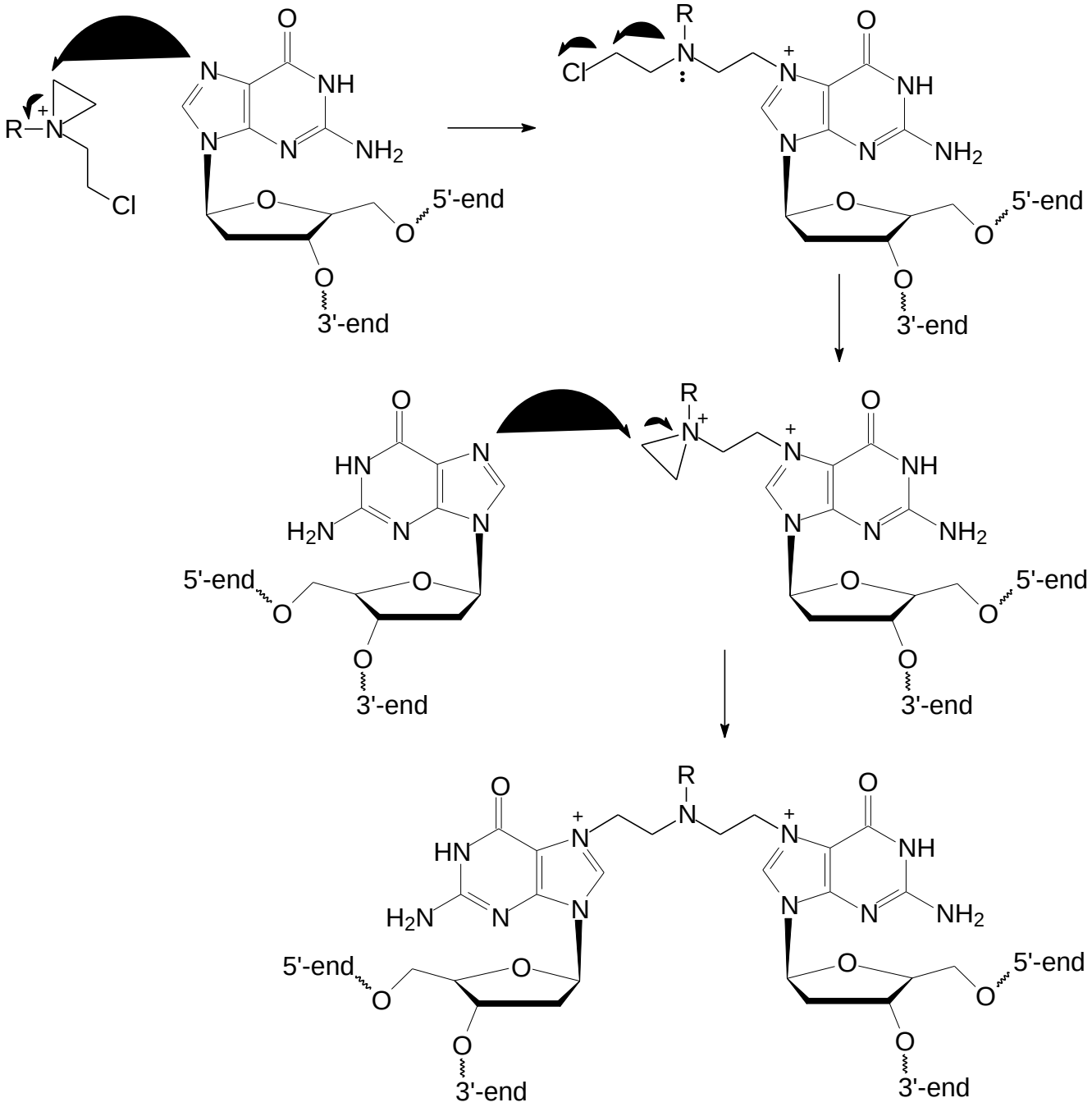


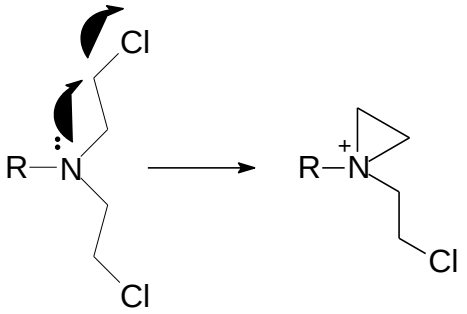
Sulfur mustards

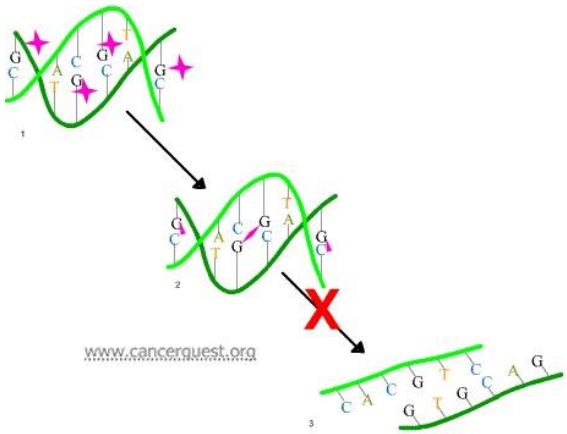


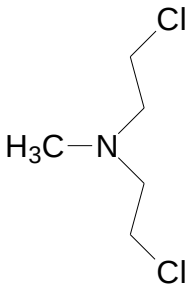
Nitrogen mustards



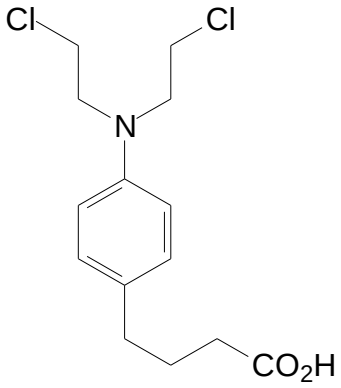

R
N
Cl
O
NH
N
NH2
5'-end
3'-end
HN
H2N


Cl
R
N
Cl

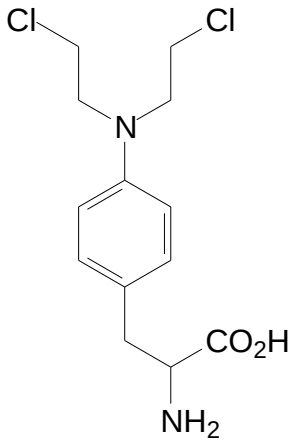

www.cancerquest.org



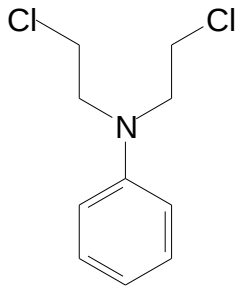
mechlorethamine

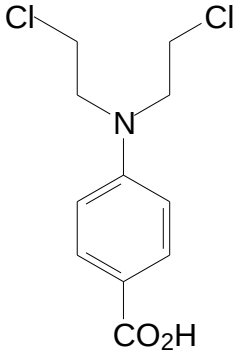


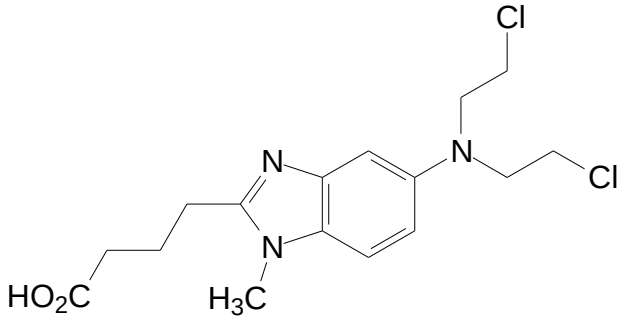
chlorambucil



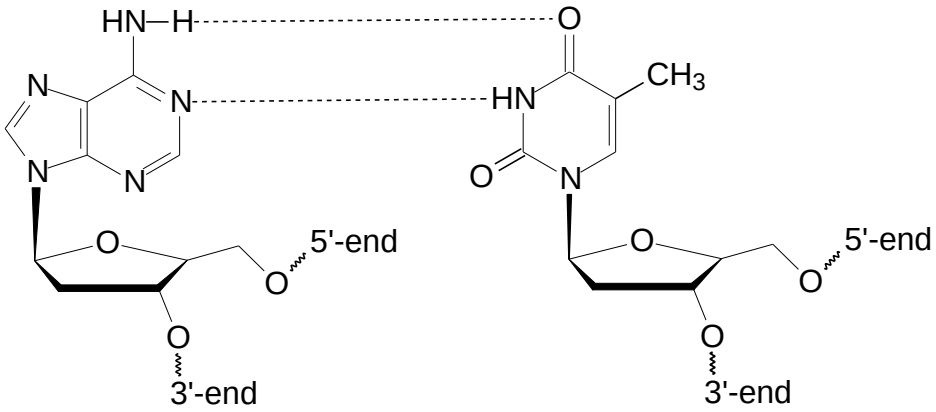
melphalan

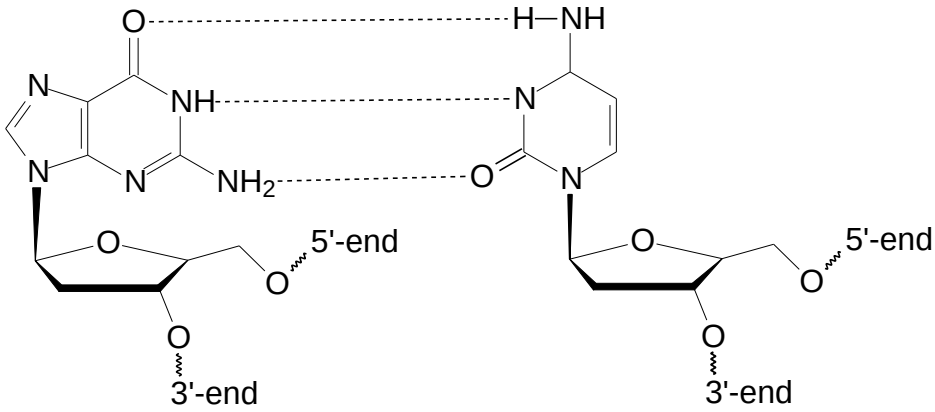


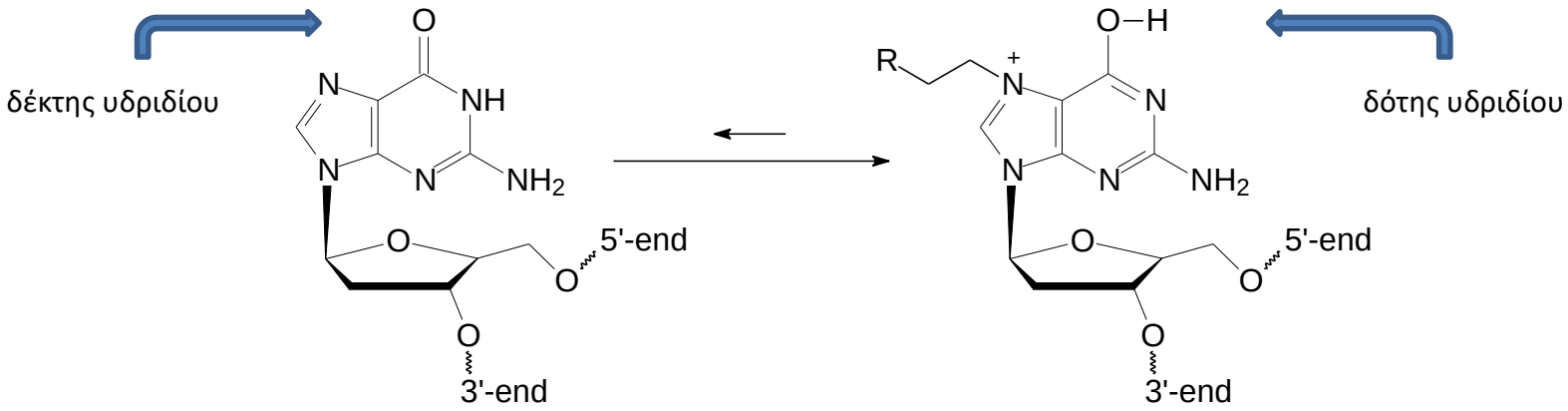


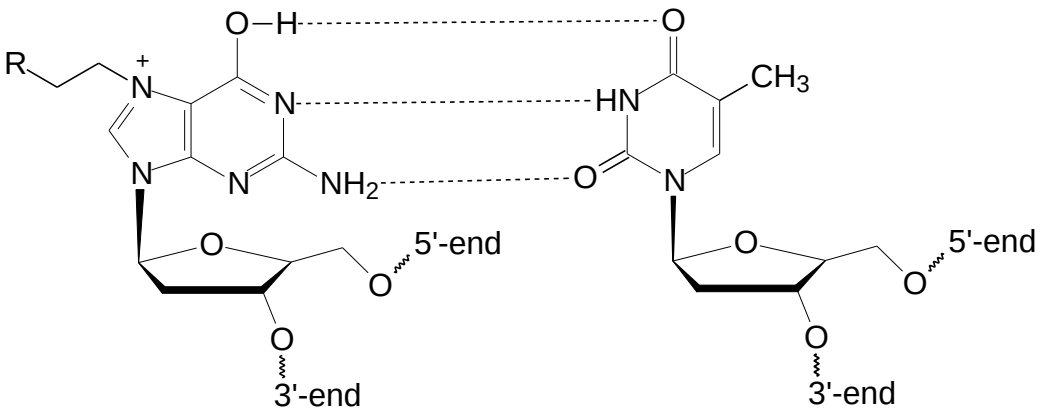


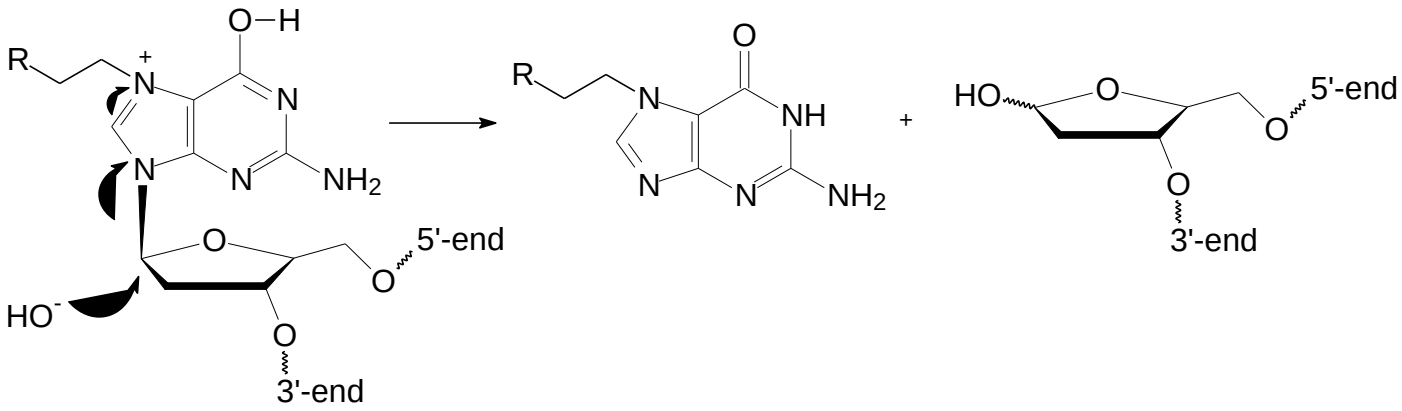
bendamustine


HN—H
N
N
N
N
O
HN
CH3
O
N
O
O
5'-end
O
O
3'-end
O
O
5'-end
O
O
3'-end

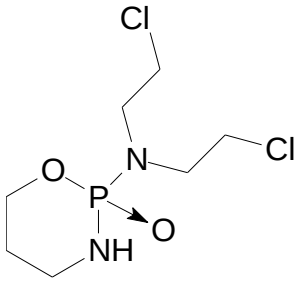

O
H—NH
N
NH
N
N
NH2
O
N
O
O
5'-end
O
O
3'-end
O
O
5'-end
O
O
3'-end


δέκτης υδριδίου
O
N
NH
N
N
NH2
O
O
5'-end
O
O
3'-end
O—H
R
+
N
N
N
NH2
O
O
5'-end
O
O
3'-end
δότης υδριδίου

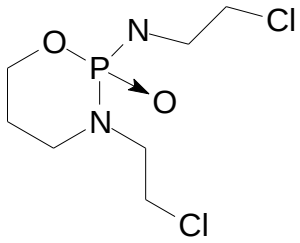

O—H
O
R
+
N
N
N
N
NH2
HN
CH3
O
N
O
O
5'-end
O
O
3'-end
O
O
5'-end
O
O
3'-end


R
O–H
+
N
N
N
N
NH2
O
5'-end
O
HO-
O
3'-end
R
O
N
NH
N
N
NH2
+
HO
O
5'-end
O
O
3'-end

Oxazaphosphorines

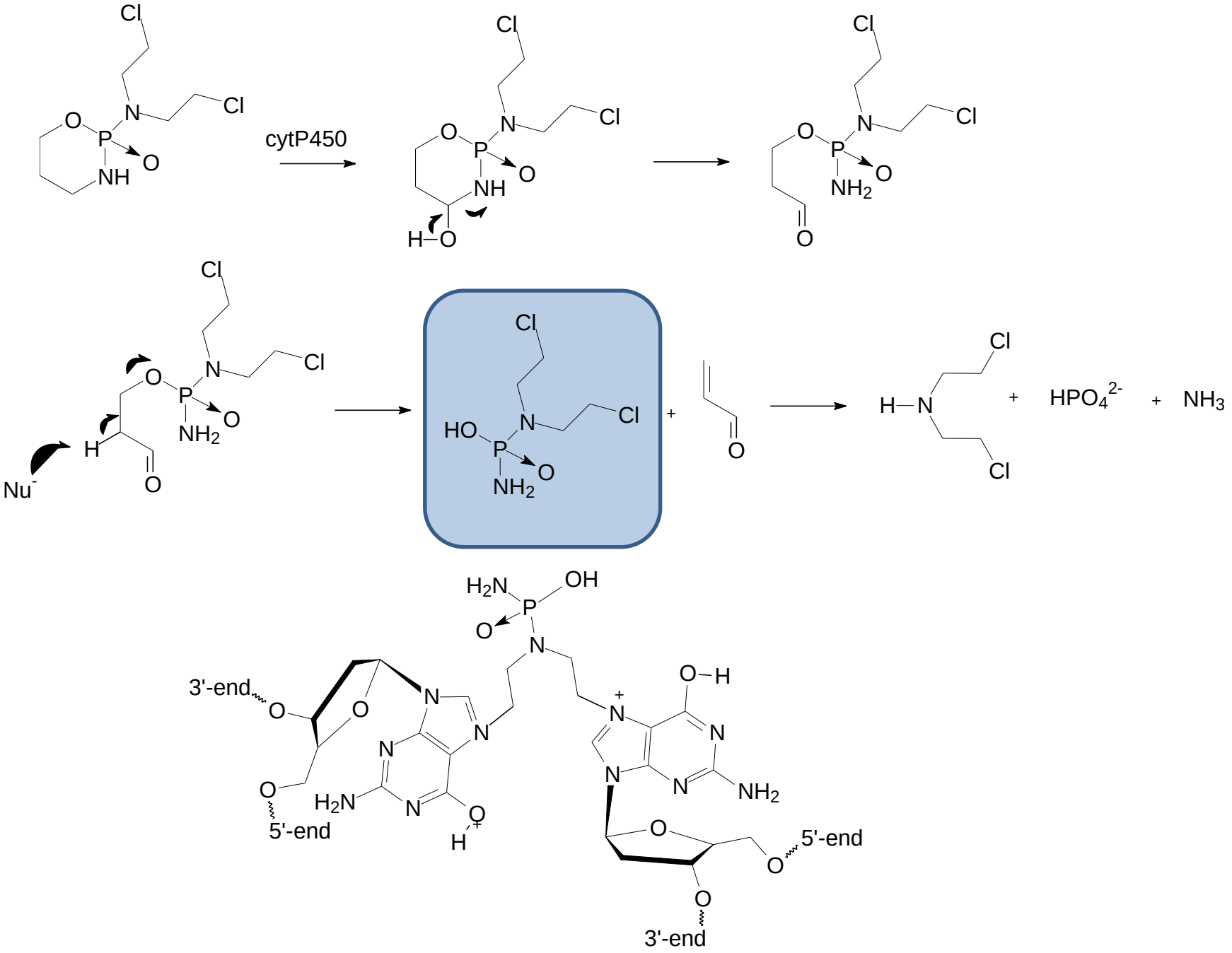


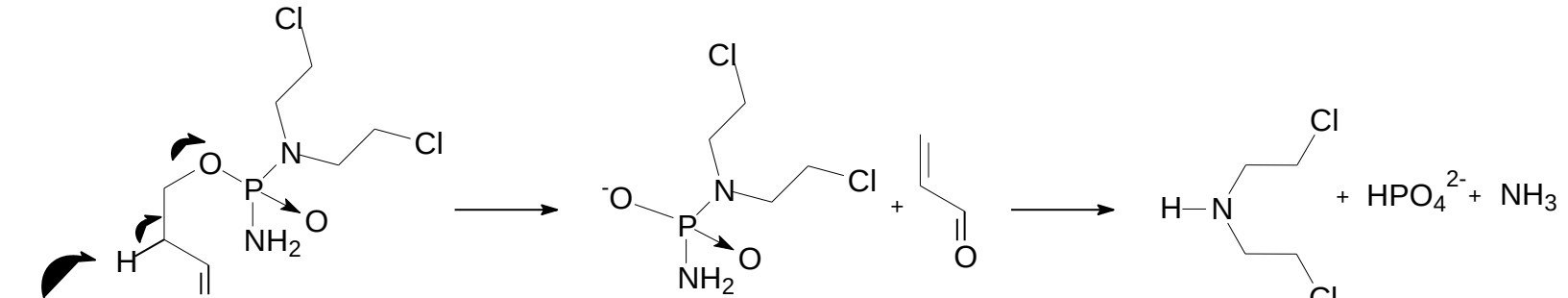
cyclophosphamide



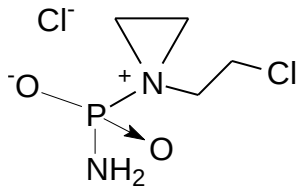
ifosfamide

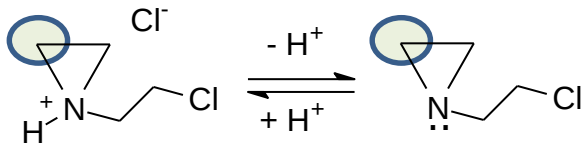
Στα καρκινικά κύτταρα, σε αντίθεση με τα φυσιολογικά, υπερεκφράζονται οι φωσφοραμιδάσες.

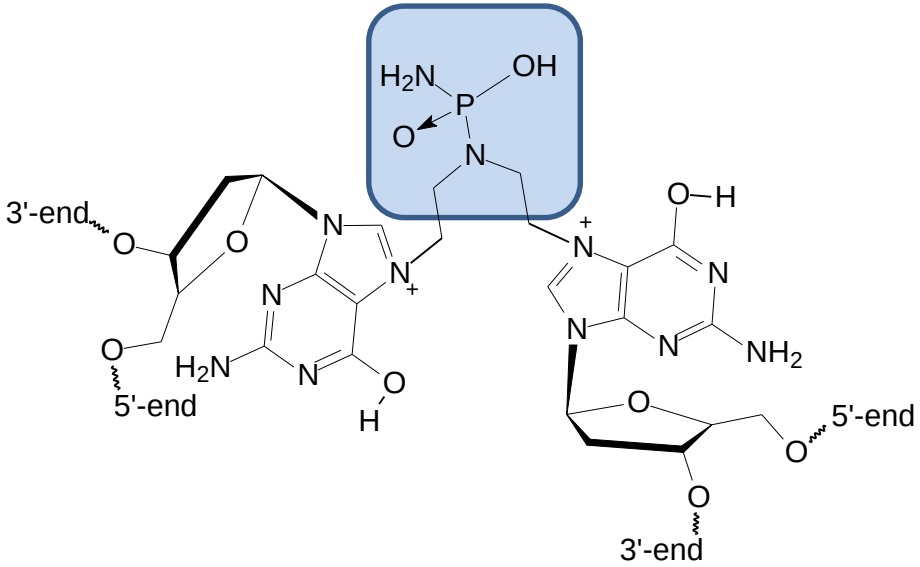

Cl
N
Cl
O
P
O
NH
cytP450
H–O
NH2
Nu-
HO
+
HPO4 2-
NH3
H2N
OH
3'-end
5'-end
O–H

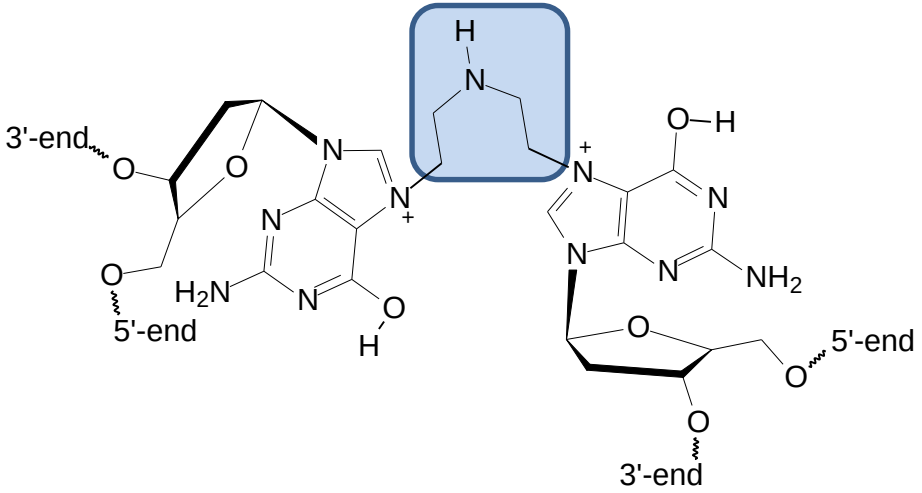


Φωσφοραμιδο-μουστάρδα
pKa= 4.75, συσσώρευση εντός κυττάρων



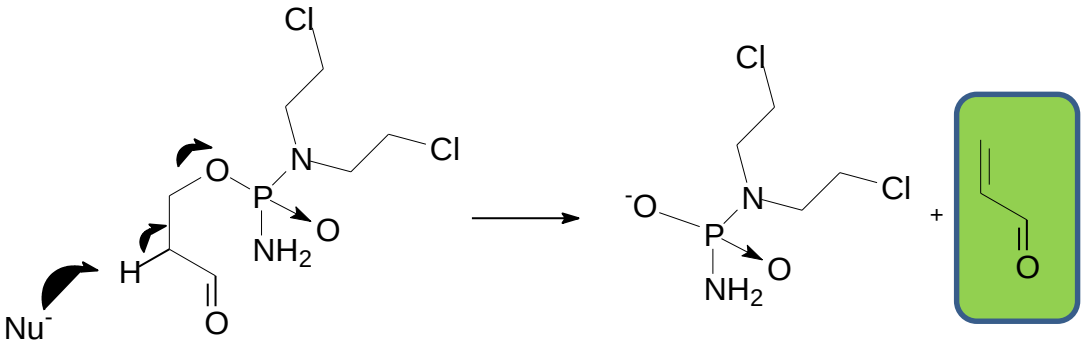




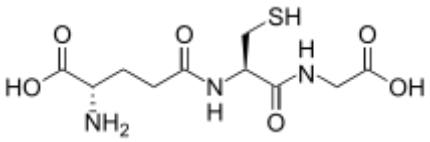


Πρωτεύων μηχανισμός (λόγω αζιριδινικού κατιόντος)

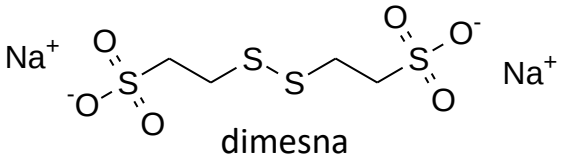
Δευτερεύων μηχανισμός, λόγω μειωμένου ηλεκτρονιόφιλου χαρακτήρα του αζιριδινικού C



Η ηπατική μεταβολική ενεργοποίηση, συνεπάγεται χαμηλότερη τοξικότητα στο γαστρεντερικό και σχετικά πιο εκλεκτική κυτταροτοξικότητα.
Παρόλα αυτά το φάρμακο δεν είναι απαλλαγμένο παρενεργειών…



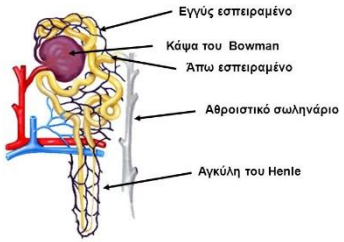
GSH

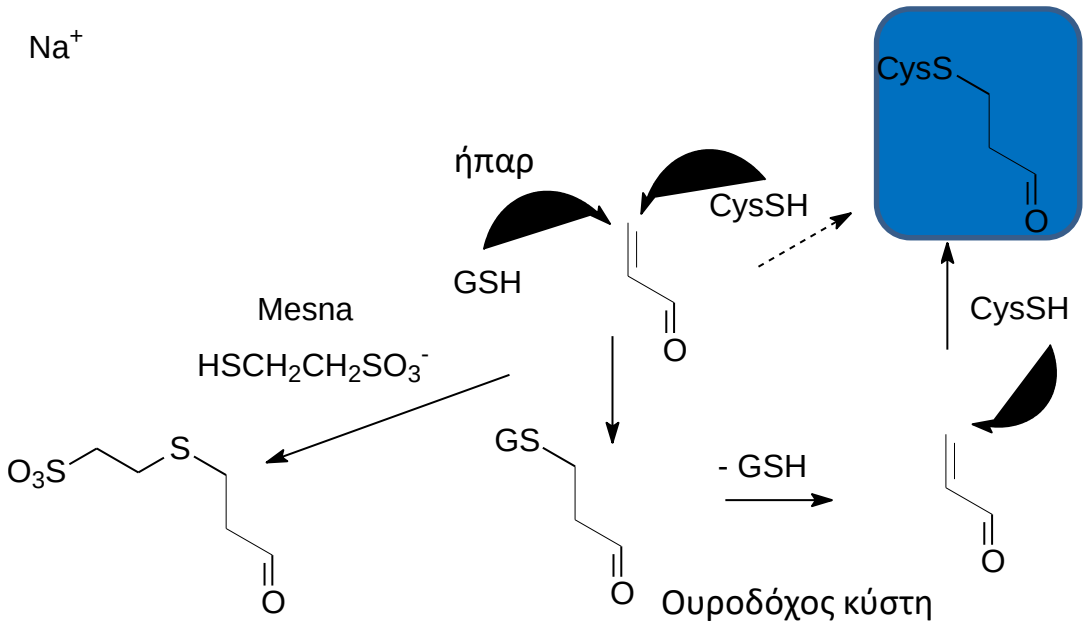


dimesna

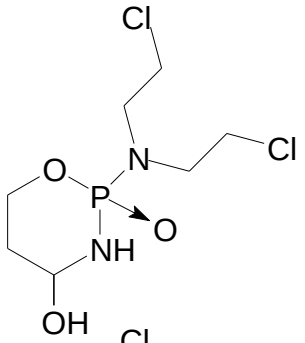
Εκλεκτική αναγωγή στα εγγύς σωληνάρια

ΝΕΦΡΙΚΑ ΣΩΛΗΝΑΡΙΑ

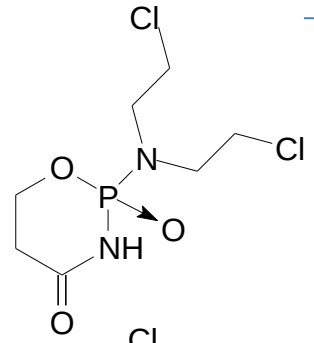


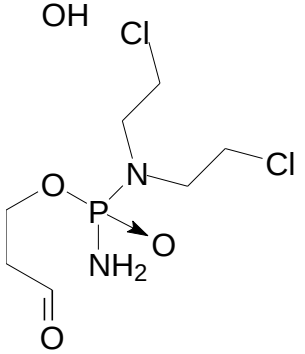


Οι σημαντικότερες συγκεντρώσεις mesna είναι στην ουροδόχο κύστη

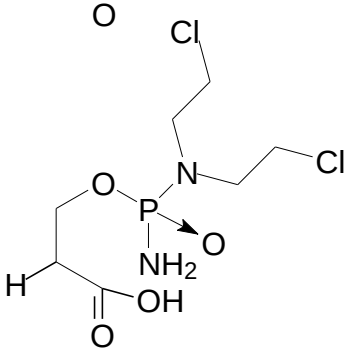


alcohol dehydrogenase



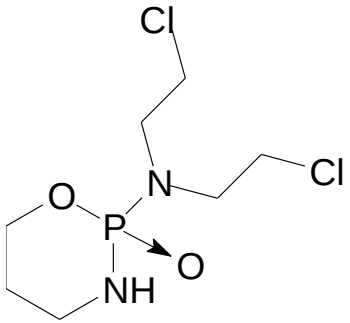


aldehyde dehydrogenase

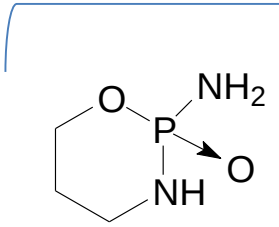


Αδρανή

Αδρανή



cytP450



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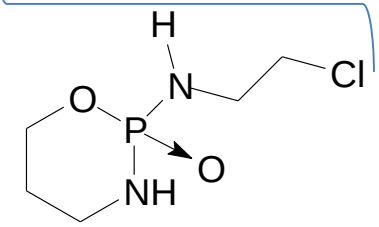

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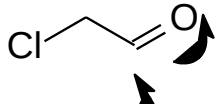
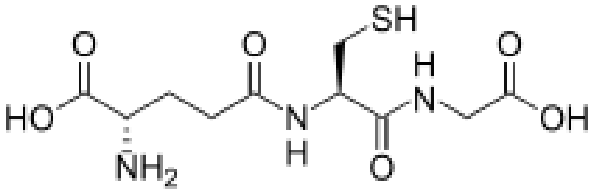
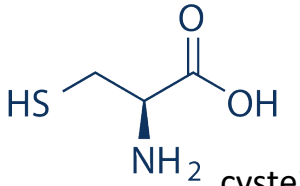


10% του συνολικού μεταβολισμού του cyclophosphamide



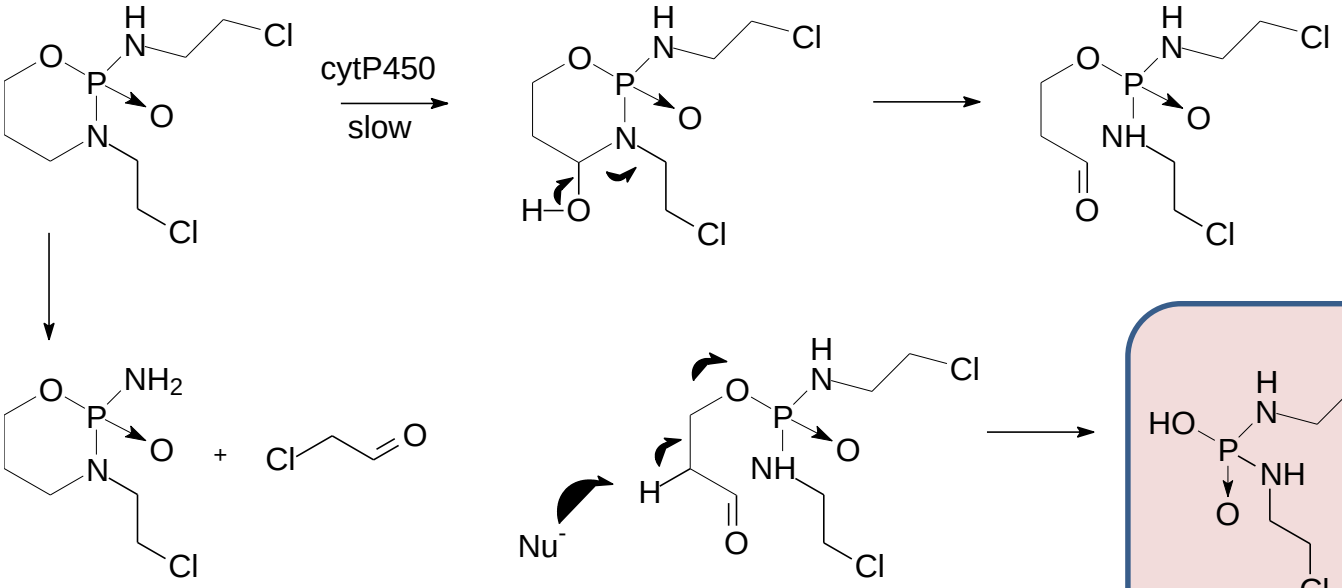
glutathione



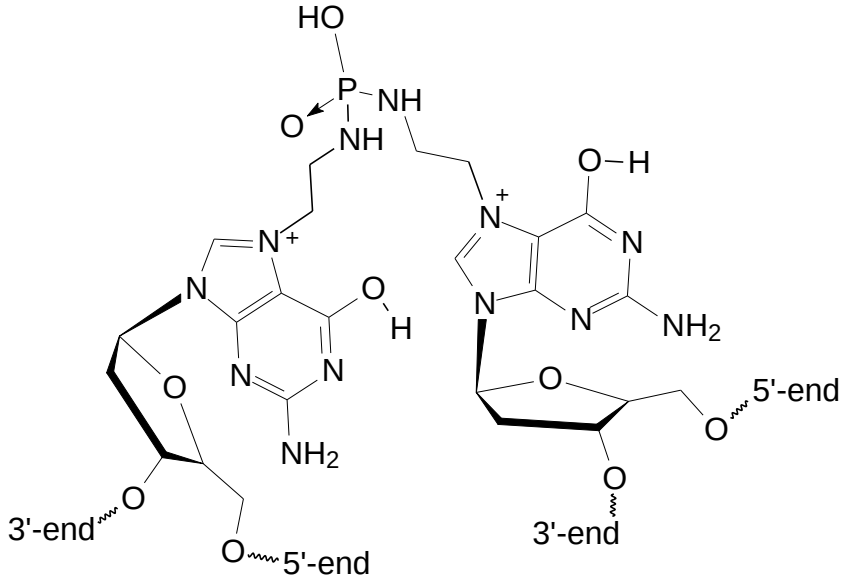
cysteine

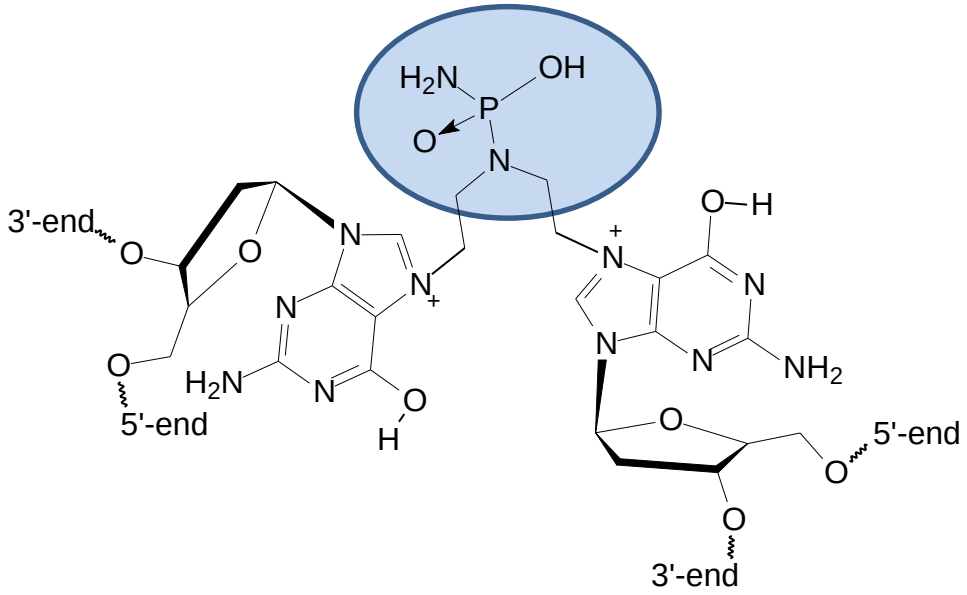
RSH

Νεφροτοξικότητα και νευροτοξικότητα, το mesna δεν είναι αποτελεσματικό

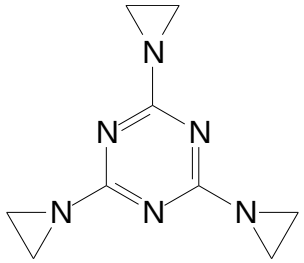


Σε αντίθεση με το cyclophosphamide, η οδός αυτή είναι σημαντική (νεφροτοξικότητα)

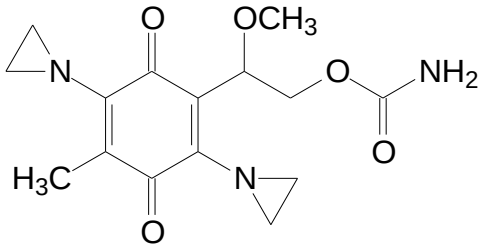




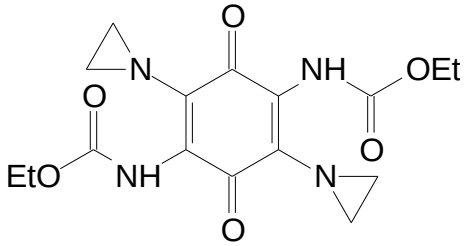
ethylenimines



triethylenemelamine

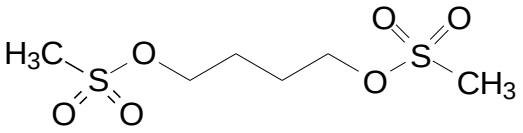


carboquone

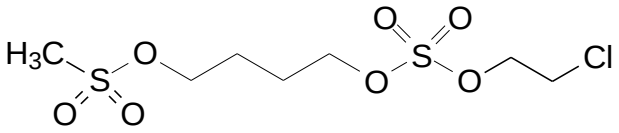


diazoquone

methanesulfonates



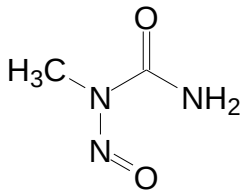
busulfan

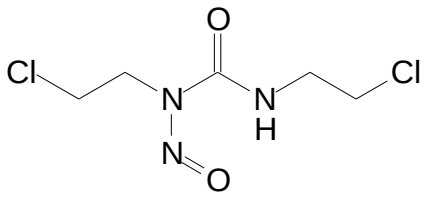


clomesone

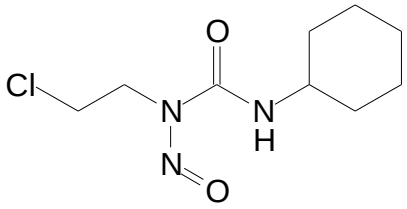
nitrosoureas

Ένωση-οδηγός,
Χαμηλής δραστικότητας

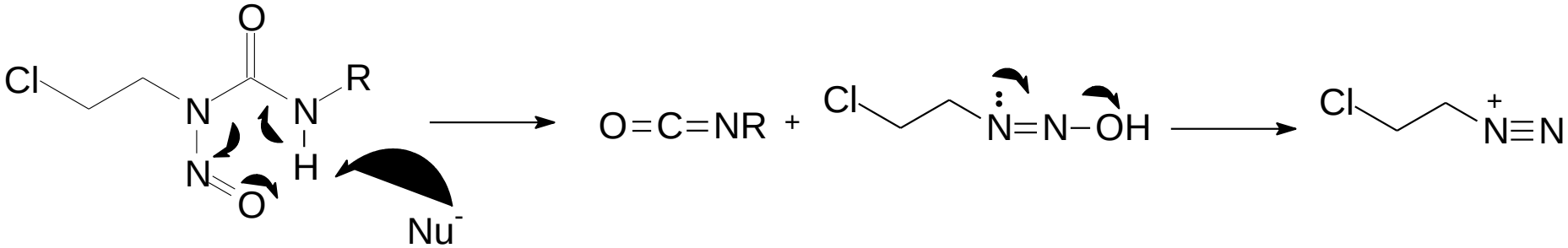


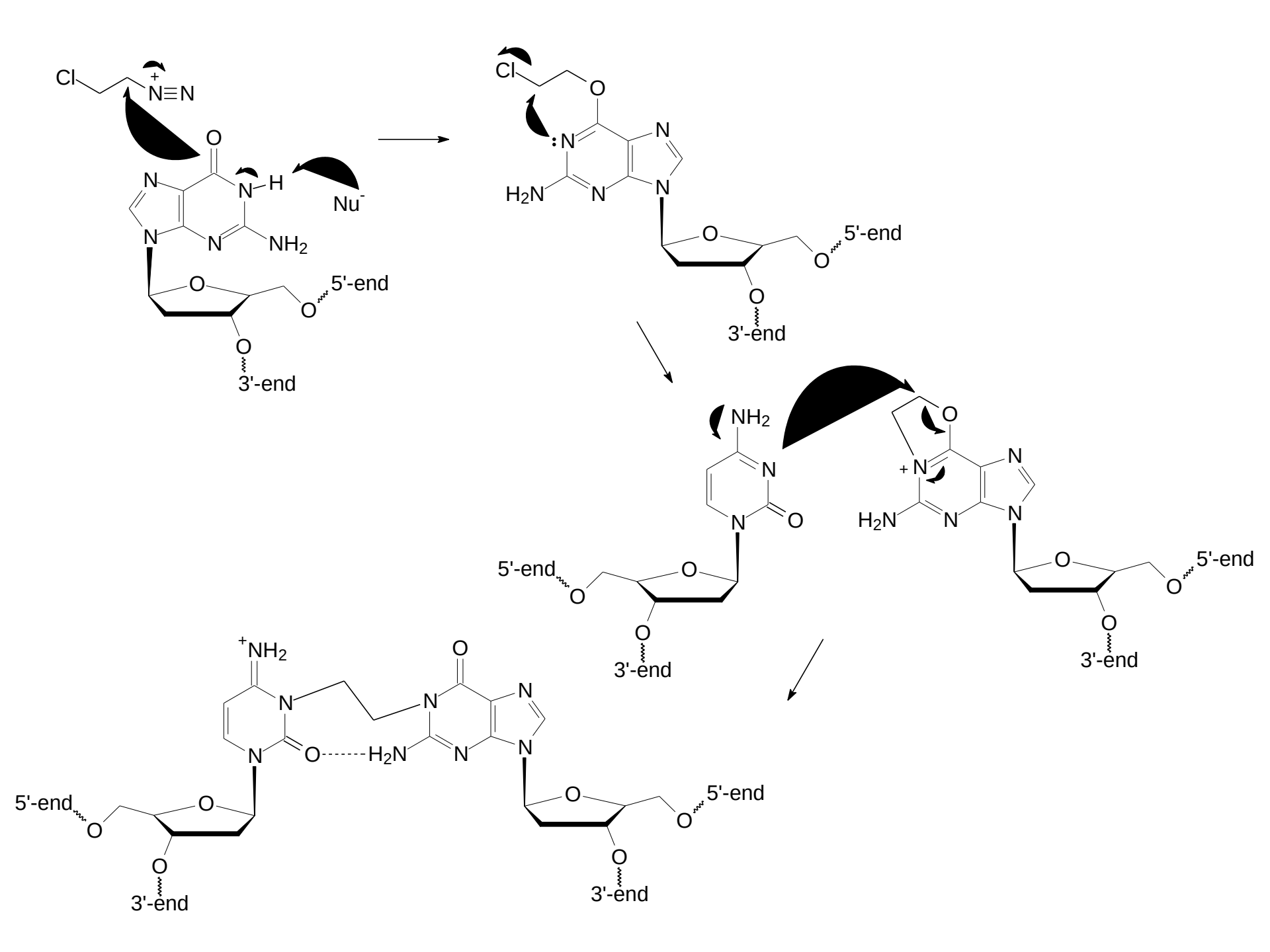


carmustine

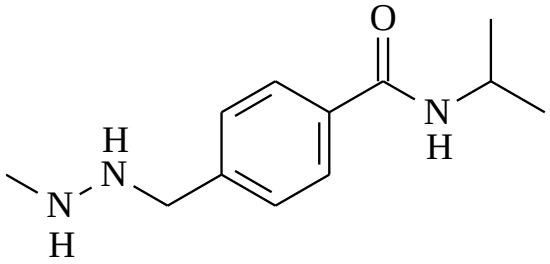


lomustine

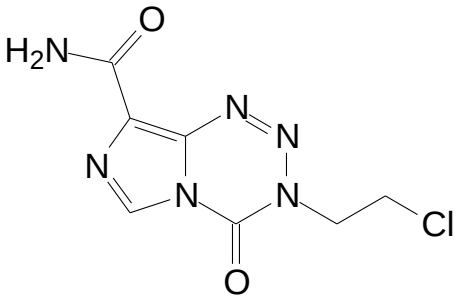



Cl
+
N≡N
O
N
N
H
Nu-
N
N
NH2
O
5'-end
O
O
3'-end
Cl
O
N
N
H2N
N
N
O
5'-end
O
O
3'-end
NH2
N
O
N
5'-end
O
O
3'-end
+
N
N
H2N
N
N
O
5'-end
O
O
3'-end
+NH2
N
O
N
O
H2N
N
N
5'-end
O
O
3'-end
O
5'-end
O
O
3'-end

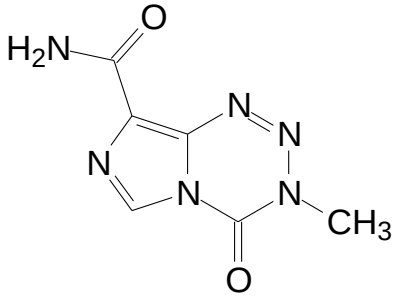
procarbazine



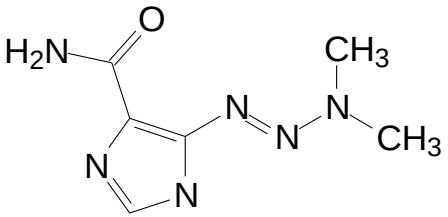
triazenes



mitozolomide

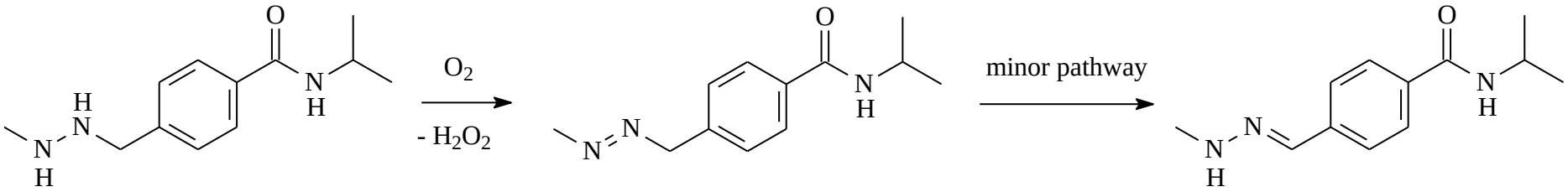


temozolomide (TMZ)

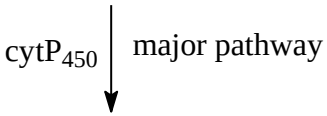


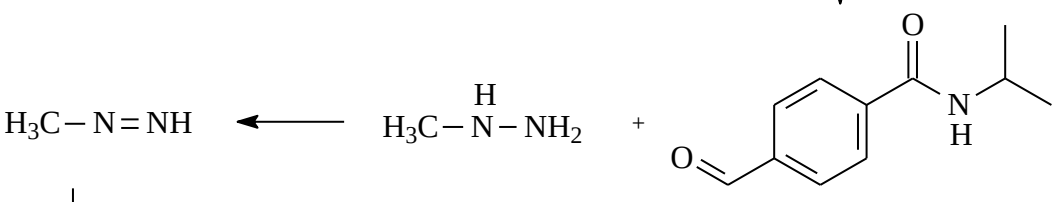
dacarbazine

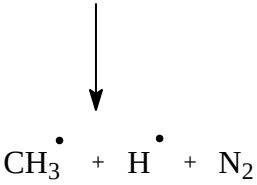
procarbazine

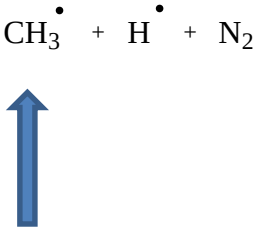


azoprocarbazine



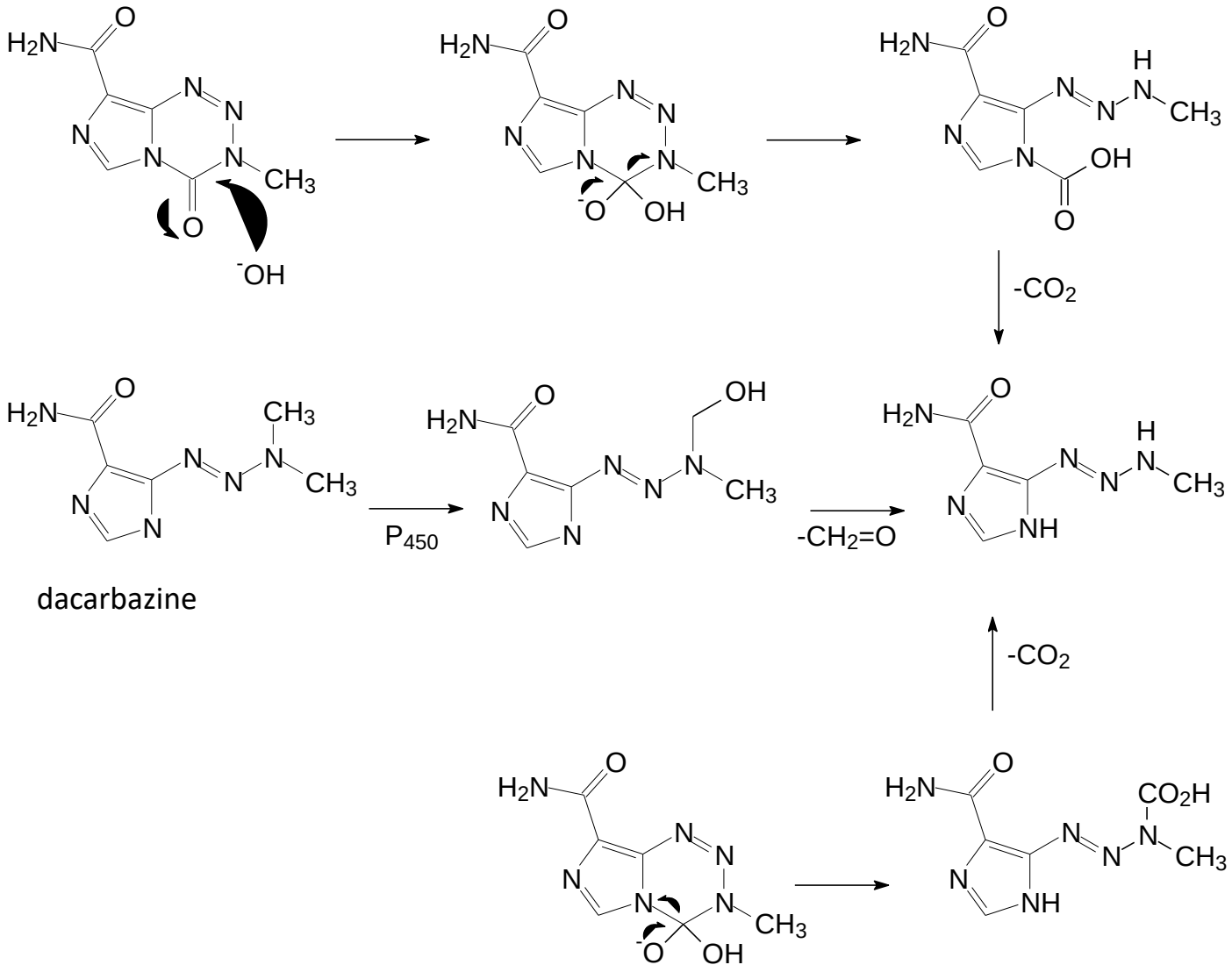


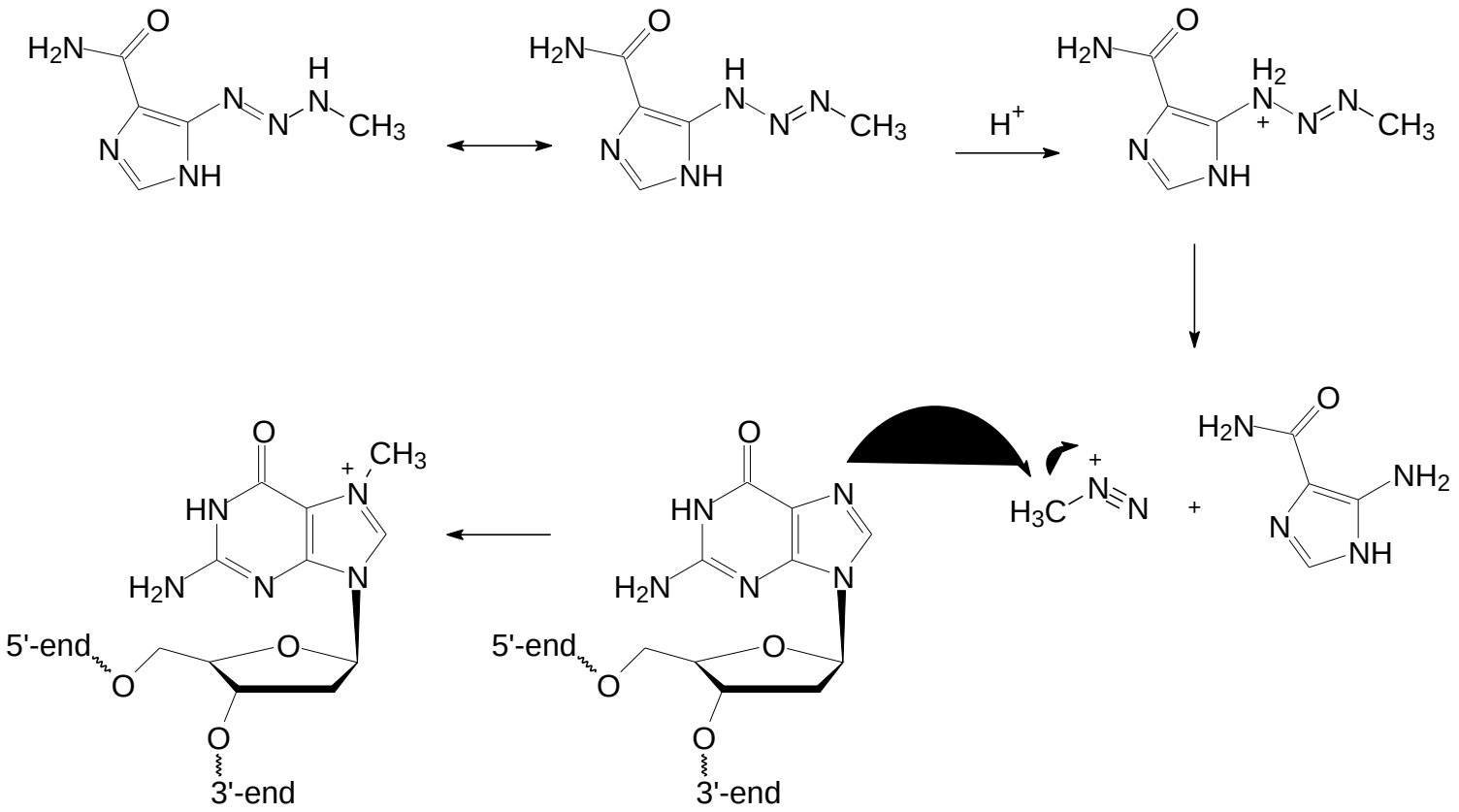


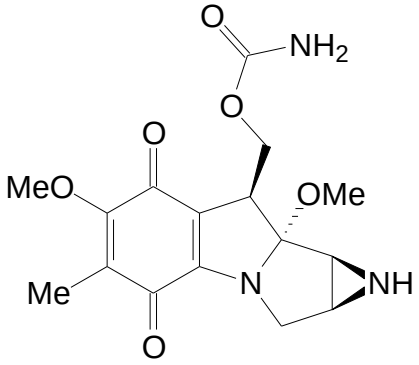


guanine O^6, or N^7

temozolomide (TMZ)




H2N
O
N
H
N
N
CH3
NH
H+
H2
+
NH2
HN
5'-end
O
3'-end

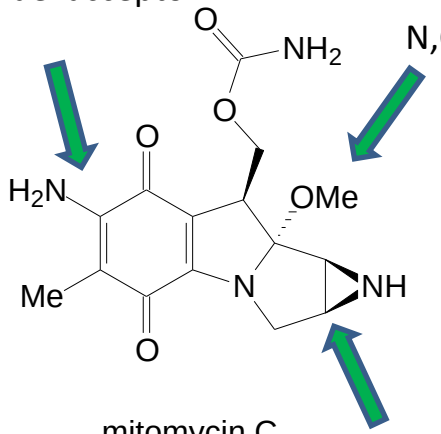


mitomycin A

Απομονώθηκε το 1956 από *Streptomyces caespitosus*.
Διευκρινίστηκε η δομή το 1962.

Είναι γνωστά 17 παράγωγα, 16 από τα οποία βιολογικώς δραστικά (αντιβιοτική, αντικαρκινική δράση).

Michael acceptor

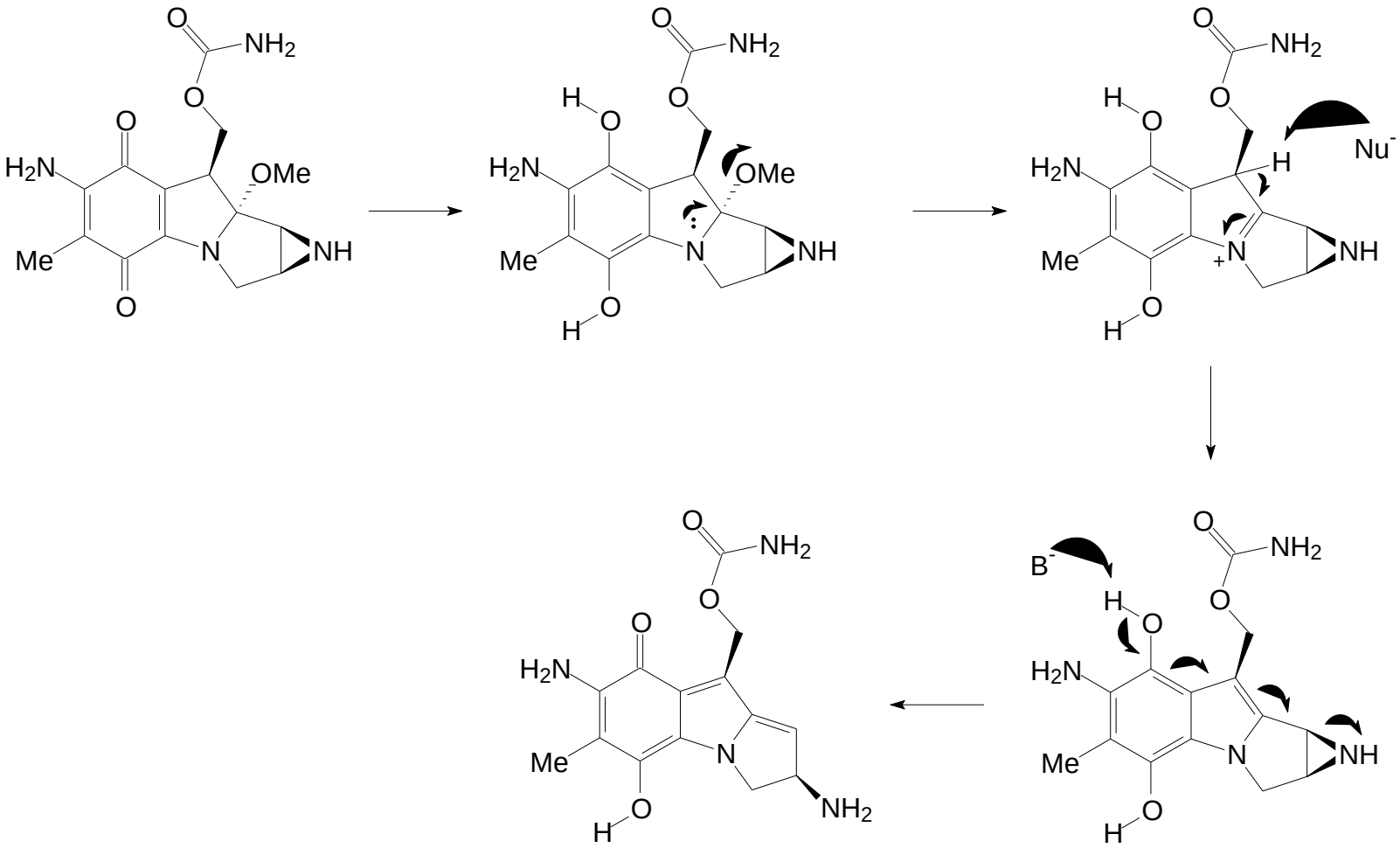


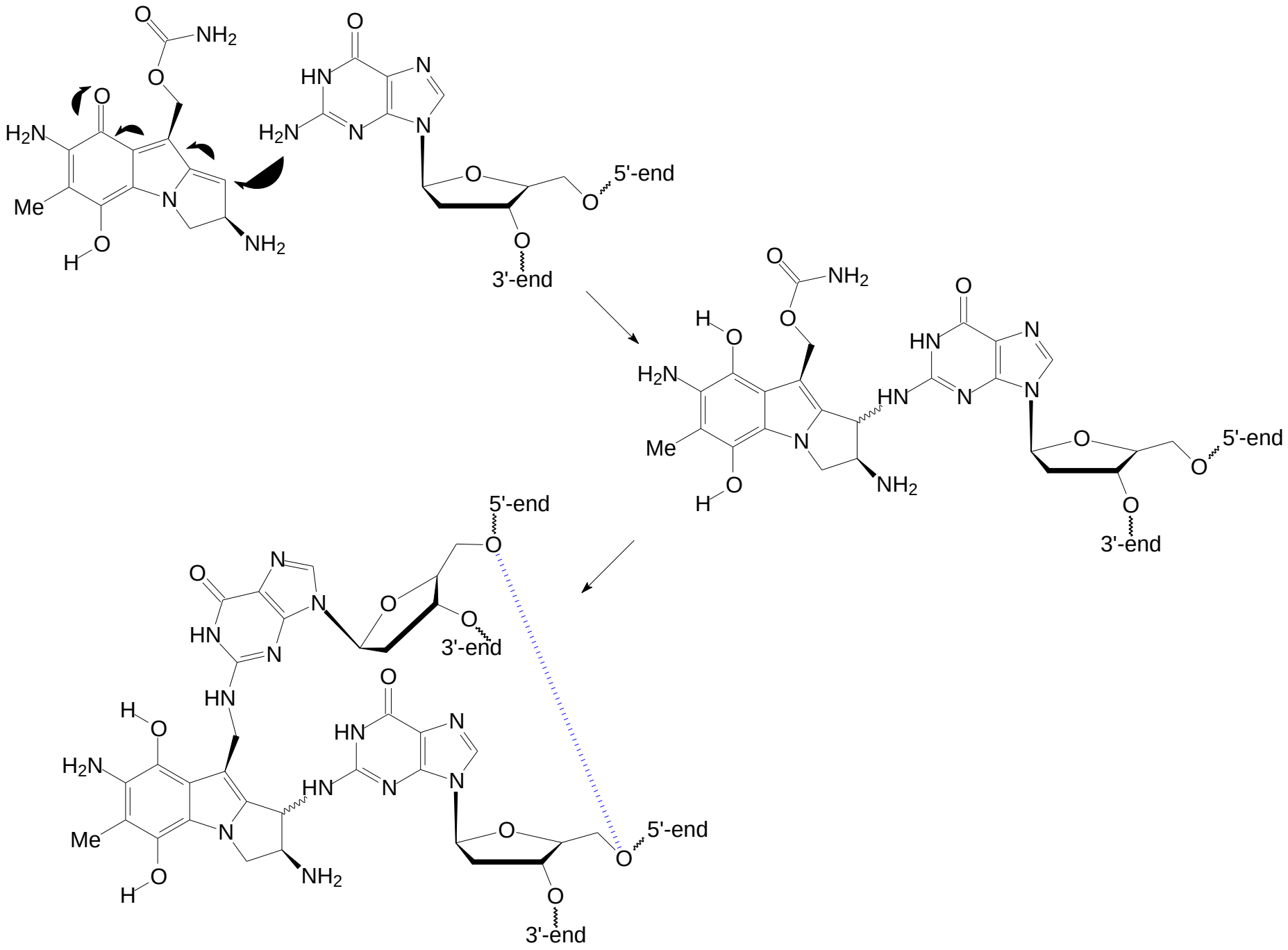
N,O-ακετάλη: εύκολη απόσπαση

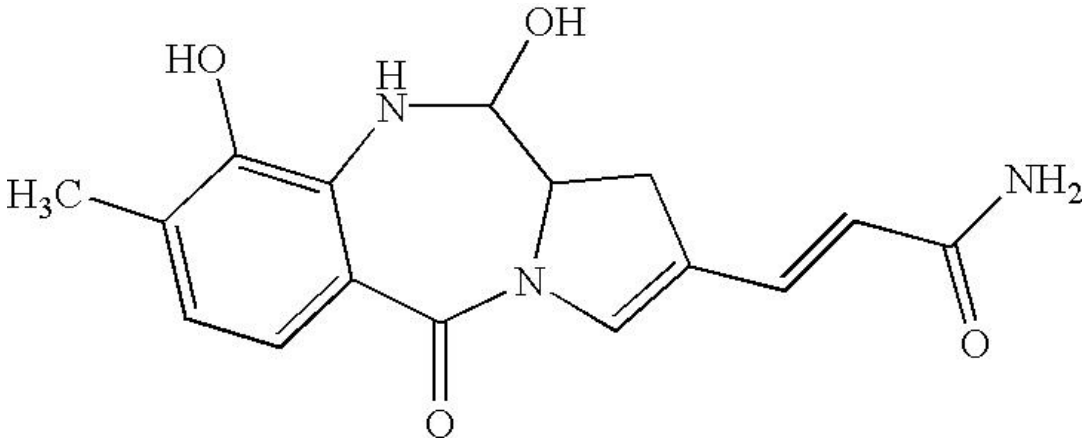
mitomycin C

Καλό ηλεκτρονιόφιλο
Διάνοιξη σε όξινο pH

Κυκλοφορεί για χρήση σε καρκίνους οισοφάγου, μαστού, παγκρέατος, ουροδόχου κύστεως.
Απομονώνεται από βακτήρια – δεν υπάρχει εμπορικά διαθέσιμη συνθετική μέθοδος.

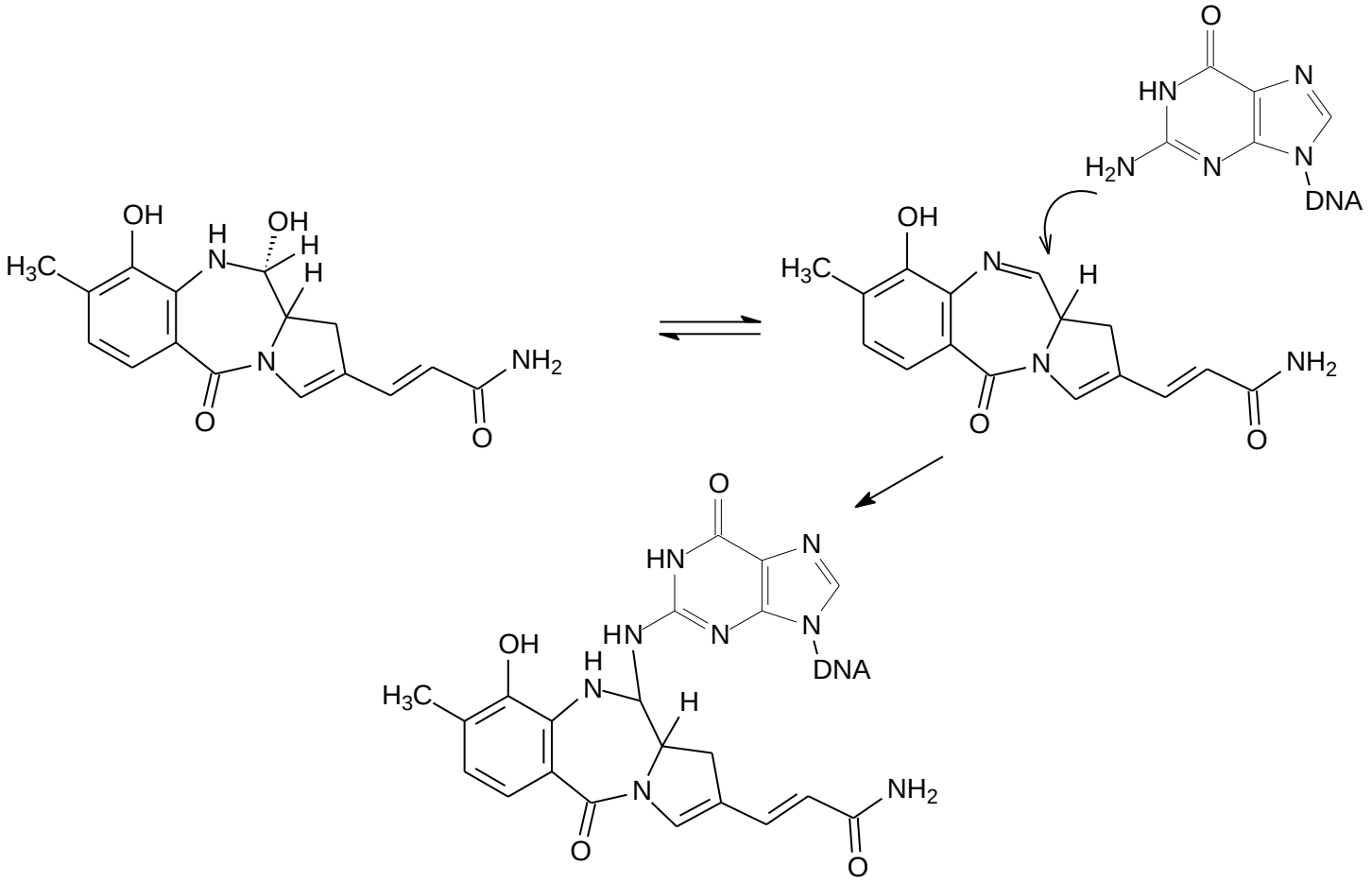

O
NH2
O
H2N
O
OMe
Me
N
NH
O
H
O
H2N
OMe
Me
N
NH
H
O
Nu-
H2N
H
Me
N+
NH
B-
NH2
Me
N
NH2


O
NH2
O
O
H2N
Me
N
NH2
H
O
HN
N
H2N
N
N
O
O
5'-end
O
3'-end
O
NH2
H
O
O
H2N
Me
N
NH2
H
O
HN
N
HN
N
N
O
O
5'-end
O
3'-end
5'-end
O
N
O
HN
N
O
3'-end
HN
H
O
O
HN
N
H2N
HN
N
N
Me
N
NH2
H
O
O
5'-end
O
3'-end

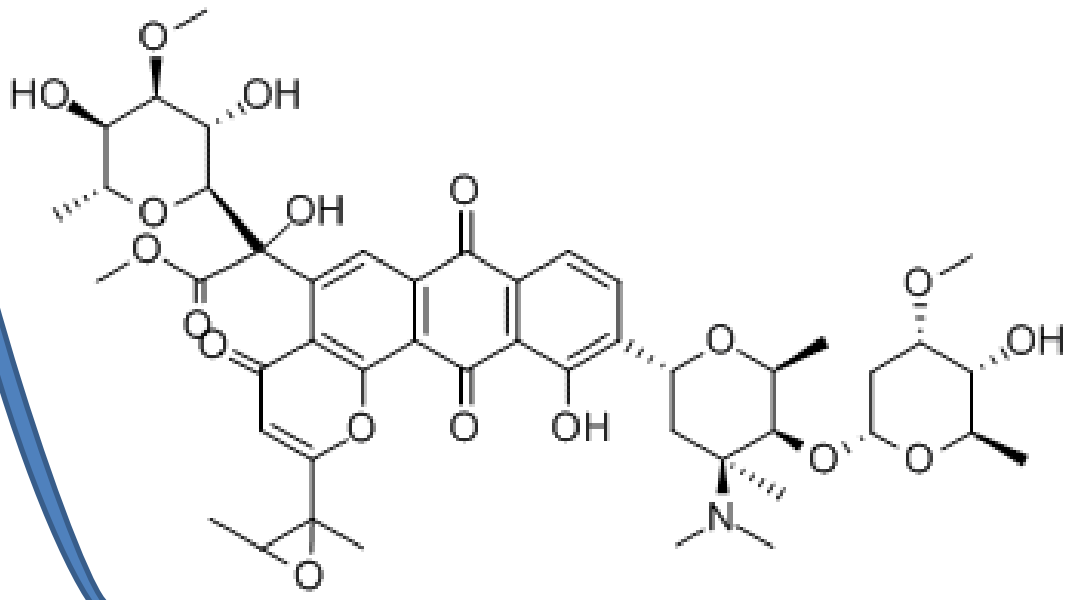


anthramycin

Sequence selectivity: 5’-PuGPu-3’



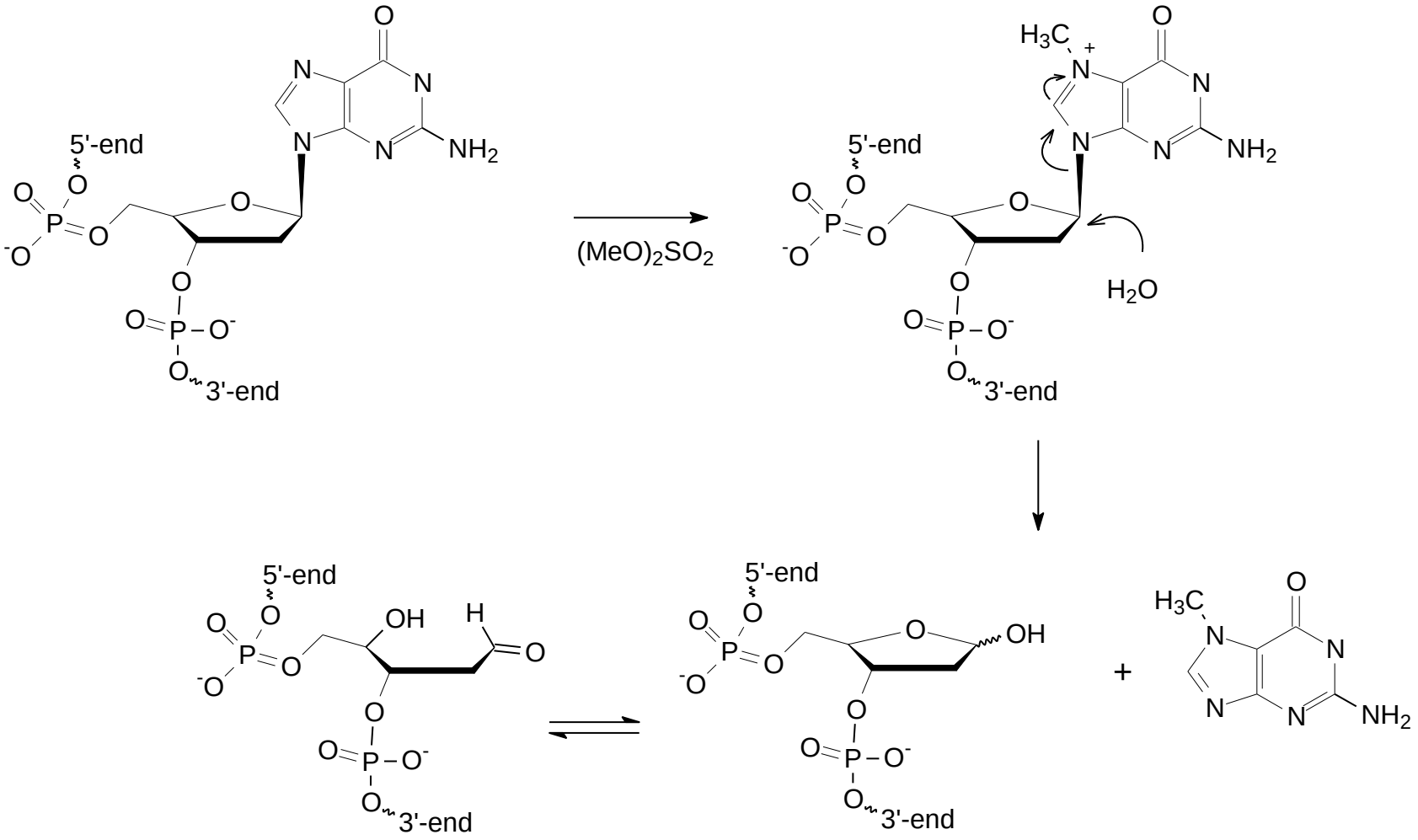
major
groove



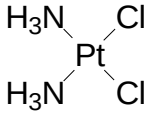
minor groove

altromycin B

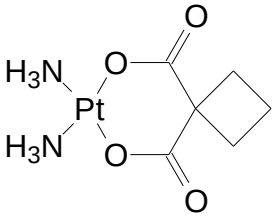
Αλκυλιωτικά αντιδραστήρια!!



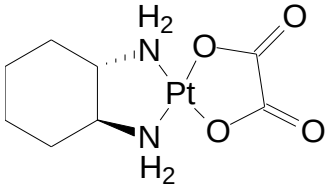
Platinum complexes



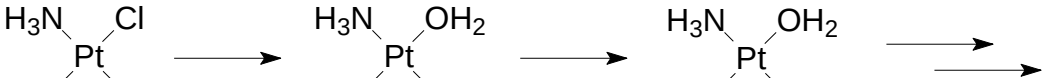
cisplatin

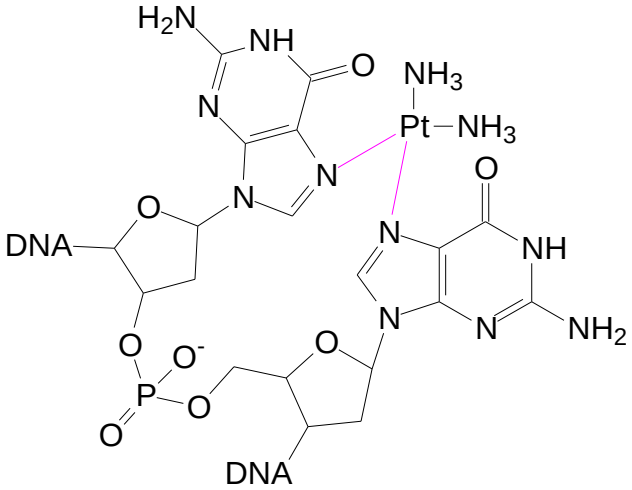


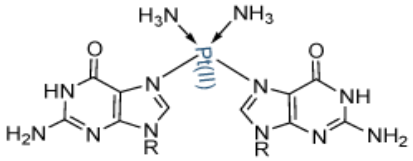
carboplatin



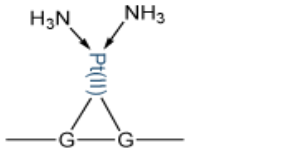
oxalilplatin



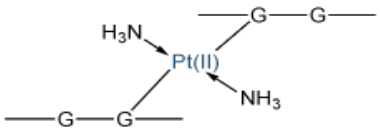




cisplatin reacts with *N*(7) of guanine



cisplatin forms intra-strand crosslinks:
poorly repaired



trans-platin forms inter-strand crosslinks:
repaired more efficiently