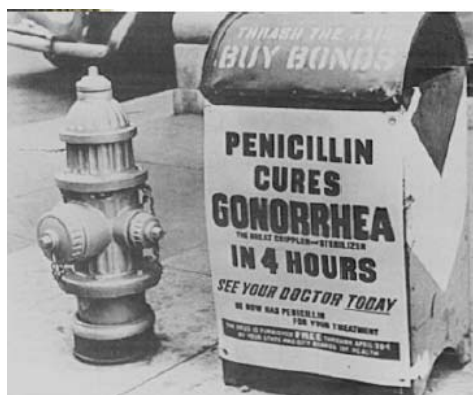
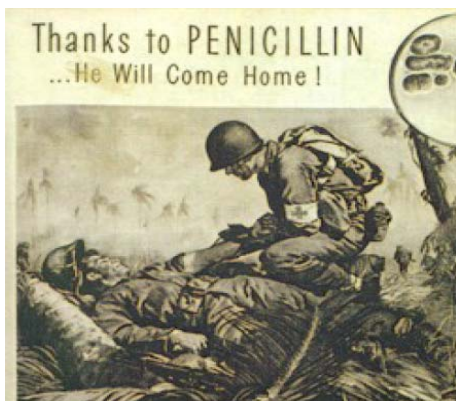


Medicines from the Sea



Medicines from Nature

The nature has provided the basis for medicines like penicillin (from the fungus *Penicillium chrysogenum*) or Aspirin (from the bark of *Salix alba*), also gave us the base of the best treatments against cancer:



Compound	Source
Paclitaxel (TAXOL)	<i>Taxus brevifolia</i>
Vincristine (ONCOVIN)	<i>Vinca rosea</i>
Irinotecan o CPT-11 (CAMPTOSAR)	<i>Camptotheca acuminata</i>
Etoposide (VEPESID)	<i>Podophyllum peltatum</i>
Doxorubicin (ADRIAMYCIN)	<i>Streptomyces peucetius</i>
Bleomycin (BLENOXANE)	<i>Streptomyces verticillus</i>
Mitomycin C (MITOMYCIN)	<i>Streptomyces caespitosus</i>



Vinca rosea



Vincristine approved for:

Leukemia

Lymphoma

Multiple myeloma

Sarcoma

Thyroid cancer

Wilms' tumor

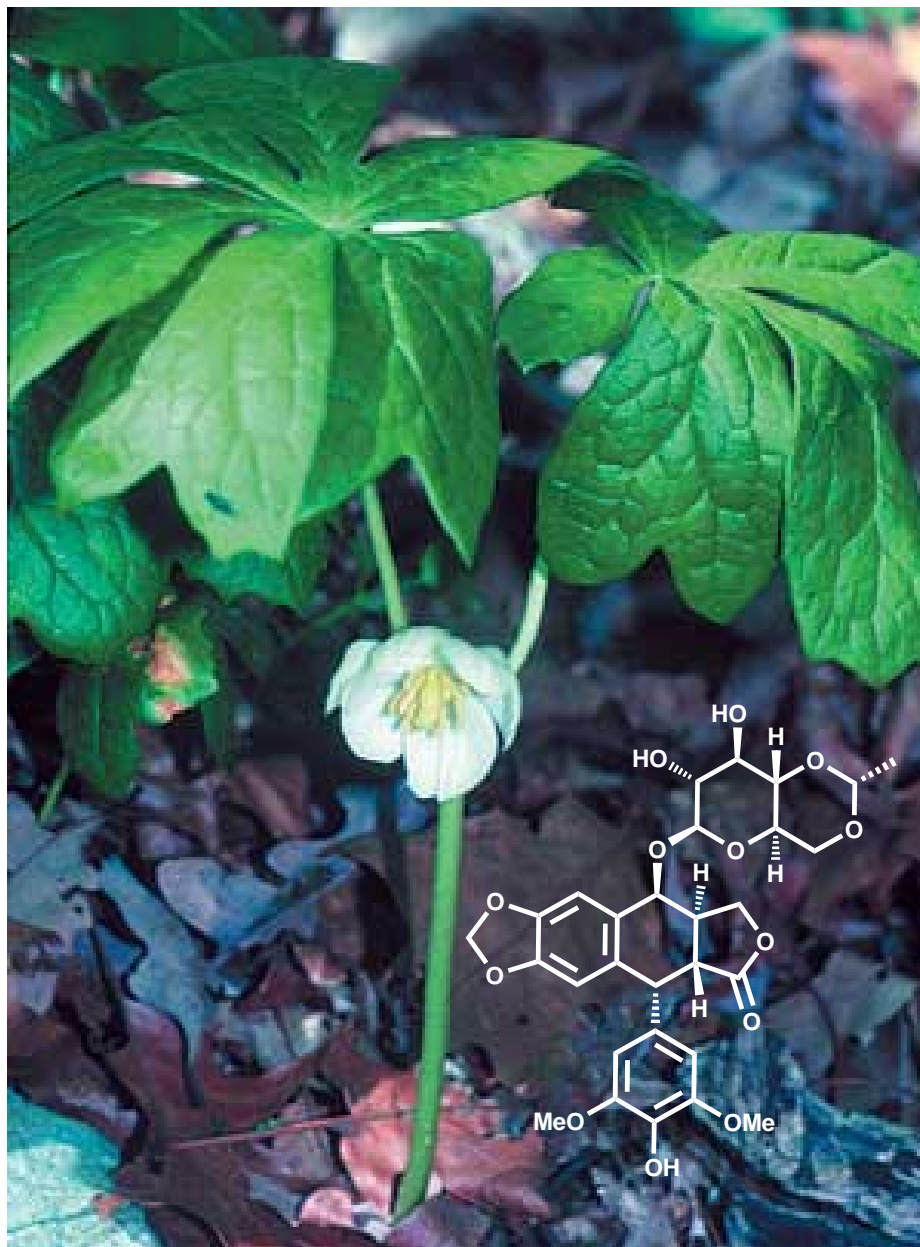
Taxus brevifolia

Paclitaxel approved for:

- Breast cancer**
- Ovarian cancer**
- Non Small Cell Lung cancer**
- Kaposi's Sarcoma**



Podophyllum peltatum



Etoposide approved for:

Lymphomas

Acute Leukemia

Small Cell Lung cancer

Breast cancer

Testicular cancer

Placental tumors

Camptotheca acuminata



Irinotecan (analog of camptothecin)
approved for:

Colorectal cancer

Small Cell Lung cancer

Streptomyces peucetius



Doxorubicin approved for:

Breast cancer

Small Cell Lung cancer

Sarcoma

Ovarian cancer

Thyroid cancer

Bladder cancer

Gastric cancer

Hepatocarcinoma

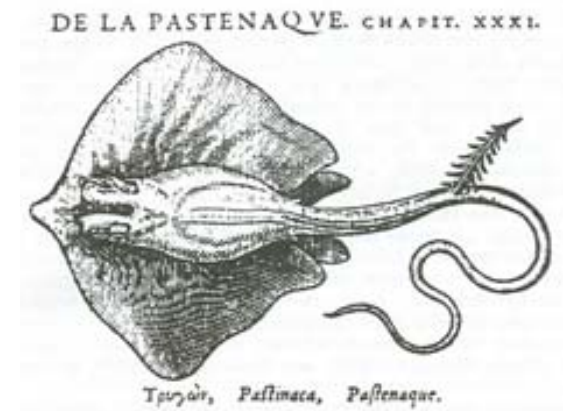
Neuroblastoma

Wilm's tumor

Lymphoma

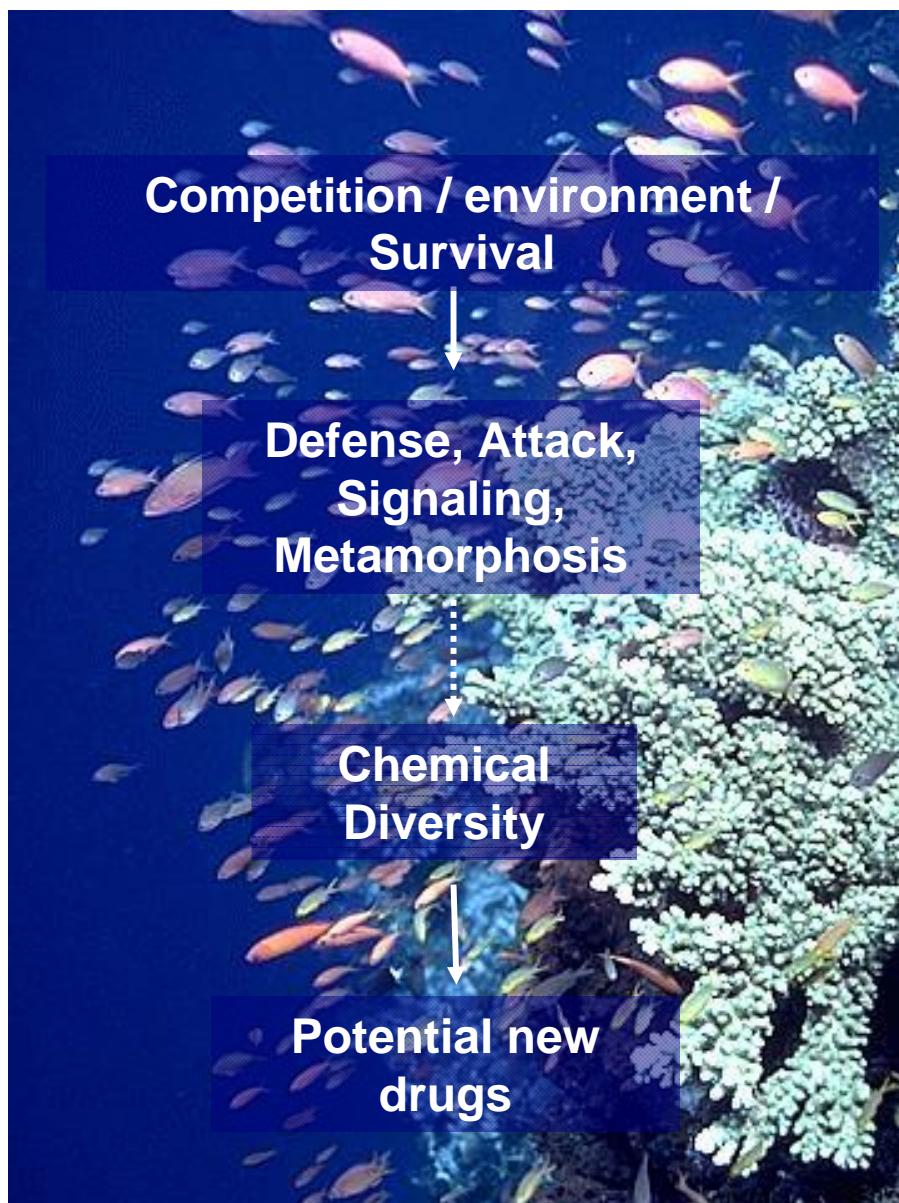
Leukemia

The Sea as Source of New Medicines



“Nature distributed medicines everywhere” *Pliny the Elder - 77 A.D*

Biodiversity: Sea vs Earth



Biodiversity: Marine > Terrestrial

“...1.8% of extracts from marine animals have shown anticancer activity...
0.4% from terrestrial plants ...”

US National Cancer Institute

Opportunity:
The sea has not been explored

John W. Blunt et al. *Nat. Prod. Report* **2006**, 23, 26-78.

Selective Collecting from the Oceans

Close collaboration with local communities and academic centers

Selective sampling by expert marine biologists

Exclude protected organisms and avoid depletion

Small samples (10-100 g) are sufficient for R&D

Simultaneous taxonomic studies



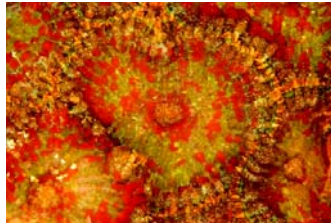
Worldwide Marine Expeditions



A Collection of 100.000 Marine Organisms



Dendrophyllia gracilis



Discosoma sp.



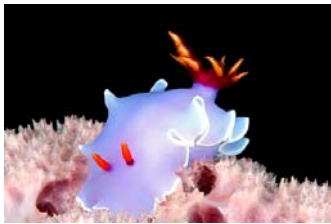
Haliclona sp.



Helofungia actiniformis



Clavularia sp.



Hypselodoris bullockii



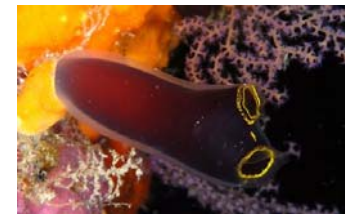
Sabella spallanzanii



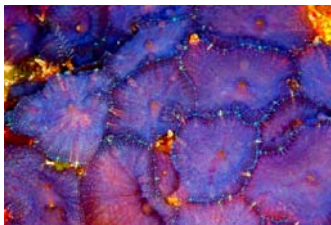
Spirobranchus giganteus



Waminoa sp.



Rhopalaea sp.



Discosoma sp.



Clathria sp.



Pseudoceros bedfordi



Fungia fungites



Clathria sp.



Archidistoma sp.



Dendronephthya sp.



Echinotrix calamaris



Gossodoris rufomarginata



Sycozoa sp.

A Collection of 100.000 Marine Organisms



Actinodendrum sp.



Urticina sp.



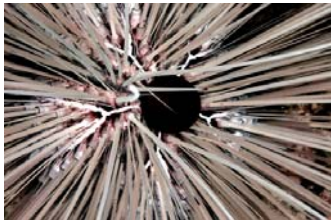
Pentaceraster regulus



Notodoris minor



Caulerpa racemosa



Diadema antillarum



Spirobranchus giganteus



Myriapora truncata



Umbellullifera sp.



Sycozoa sp.



Himerometra sp.



Chromodoris leopardus



Haliclona mediterranea



Rhopalaea sp.



Nembrotha guttata



Catalaphyllia sp.



Predaea



Rhopalaea sp.

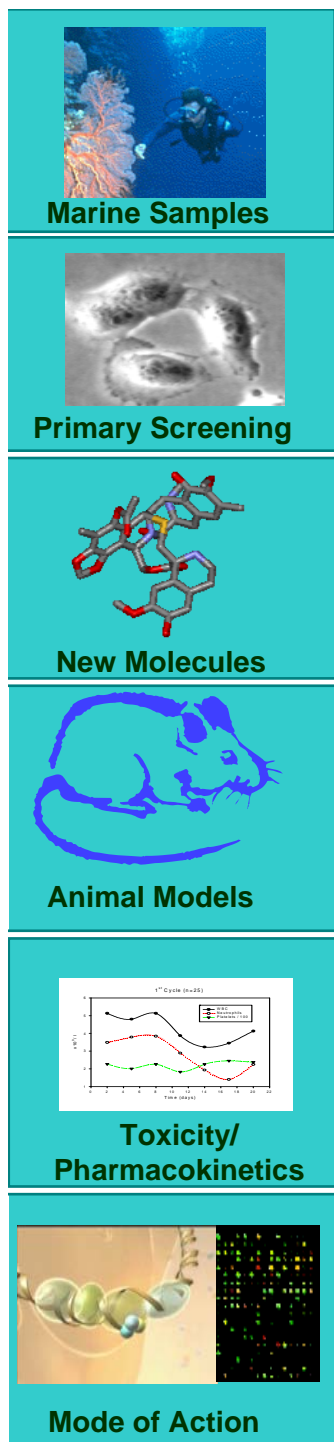


Clavelina sp.

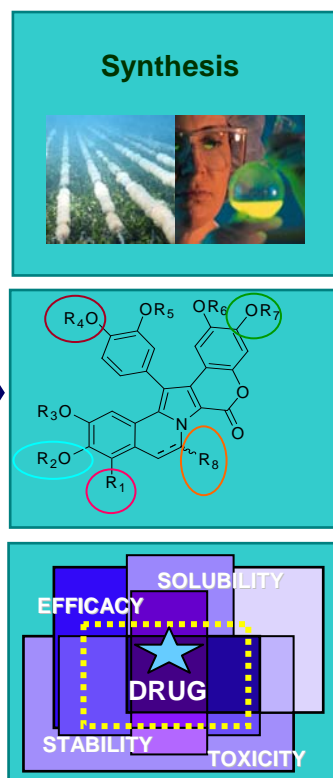


Reteporellina denticulata

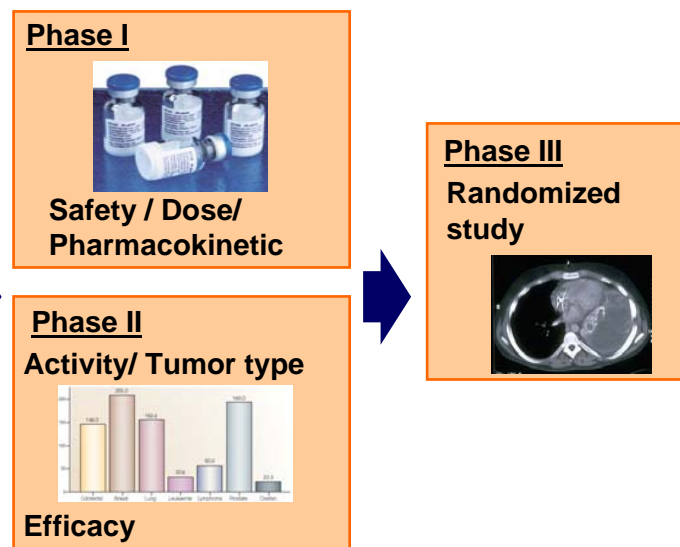
Our R & D Process



PRECLINICAL



CLINICAL



MARKET



NDA (US) *New Drug Approval*
MAA (UE) *Marketing Author. Applic.*

IND (US) *Investigational New Drug*
IMPDP *Investigational Medicinal Product Dossier*
CTD *Common Technical Document*

Strong Oncology Pipeline



Ecteinascidia turbinata

Yondelis®

12.000 treated patients

Soft Tissue Sarcoma (STS) – 2nd/3rd line

Relapsed ovarian cancer (Yondelis+Doxil)

STS with translocations-1st line

Paediatrics

Breast

Prostate

Patient selection: molecular signature of sensitivity to Yondelis



Aplidium albicans

Aplidin®

800 treated patients

Relapsed/refractory multiple myeloma

Relapsed/refractory T-cell lymphoma

Mielofibrosis

Combination studies



Jorunna funebris

Zalypsis®

160 treated patients

Cervix
Endometrial

Ewing sarcoma

Bladder

Combination studies



Elysia rufescens

Irvalec®

140 treated patients

Lung

Esophageal
gastric

Combination studies

PM01183

31 treated patients

Solid tumours

Phase I

Phase II

Phase III

Regulatory

Market

Ecteinascidia turbinata



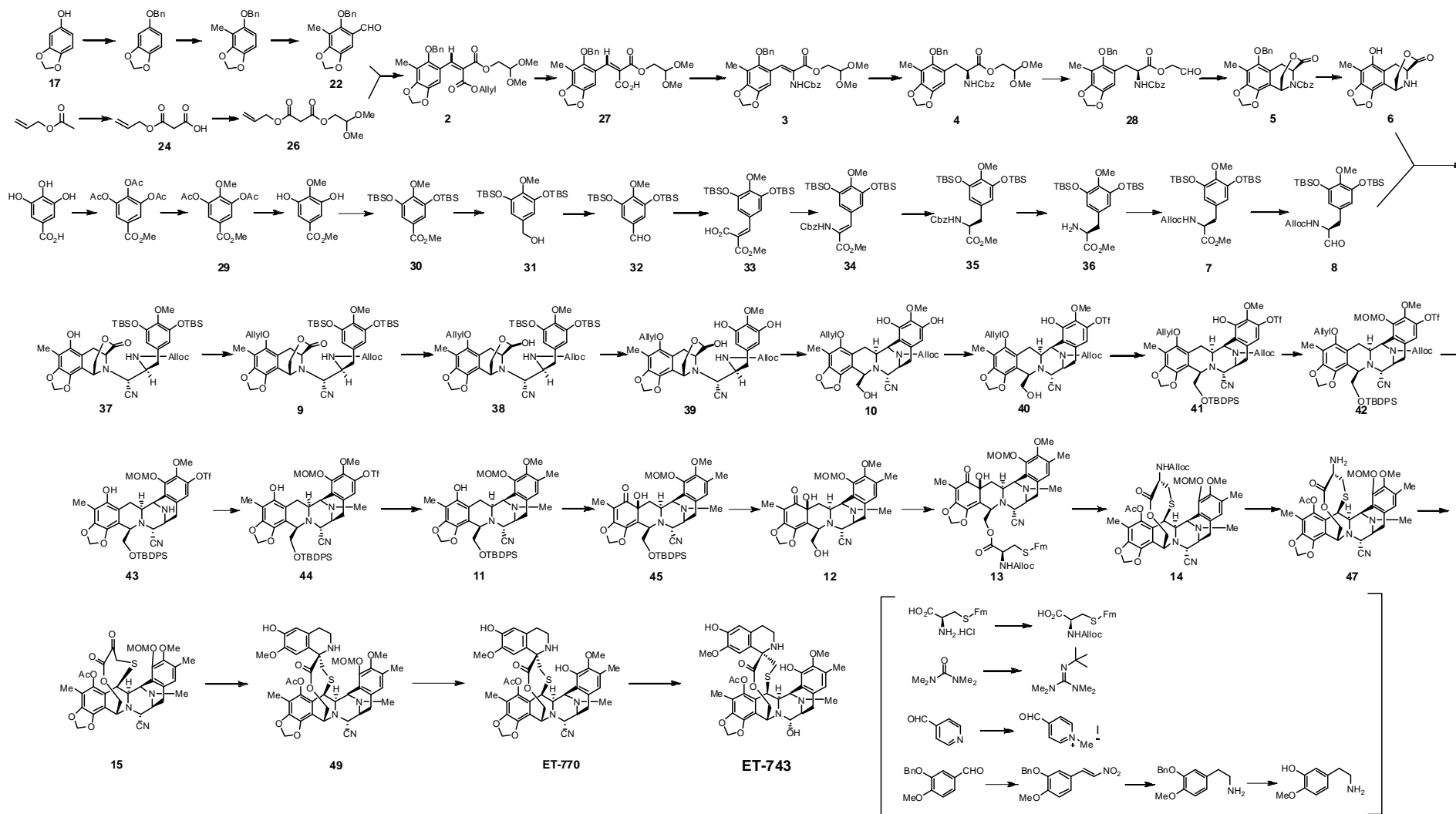
Yondelis® approved for:
Soft Tissue Sarcoma
Ovarian cancer

Supply

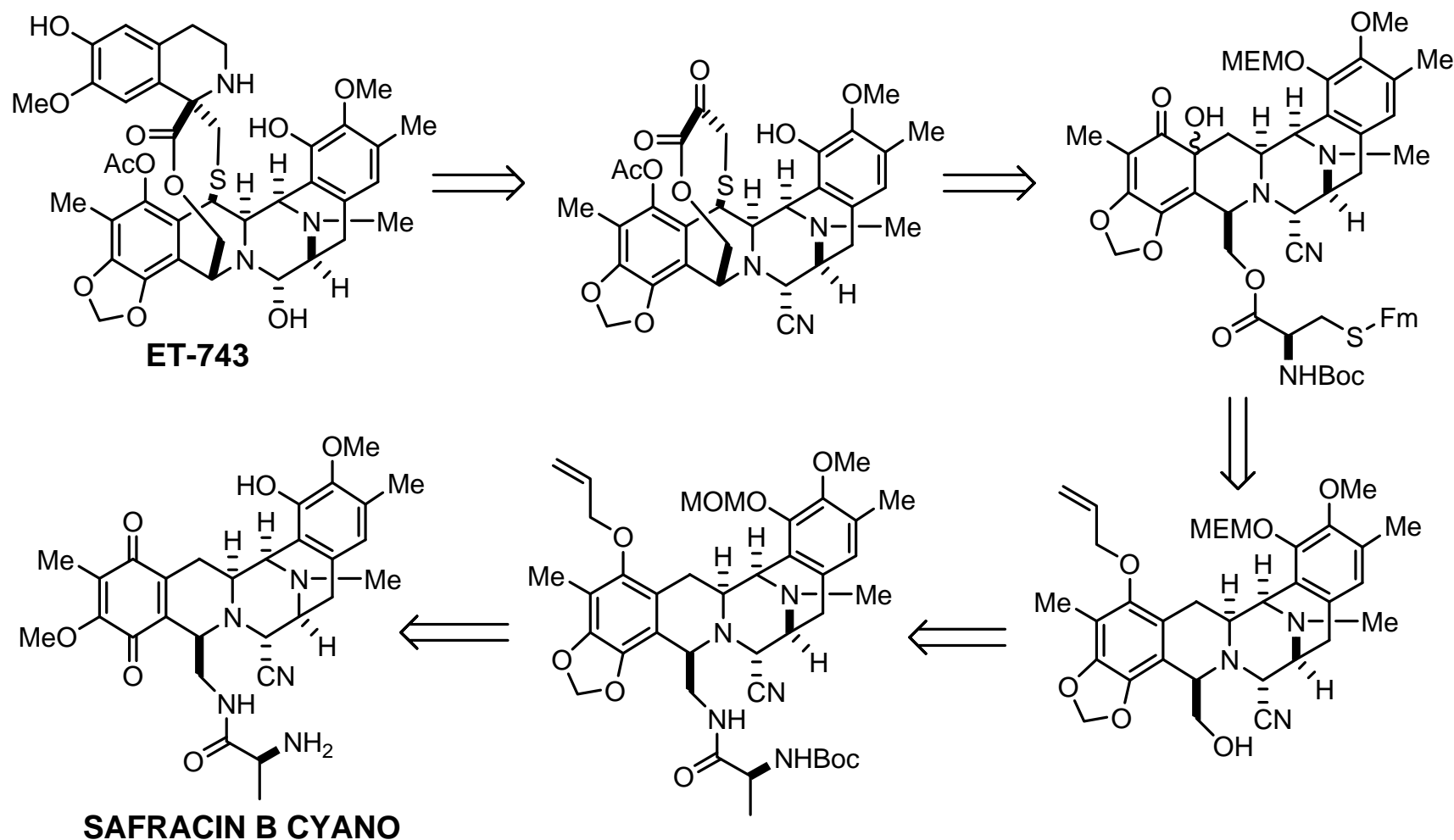
Yondelis® Production. *Ecteinascidia turbinata* Aquaculture



Total Synthesis (44 steps)

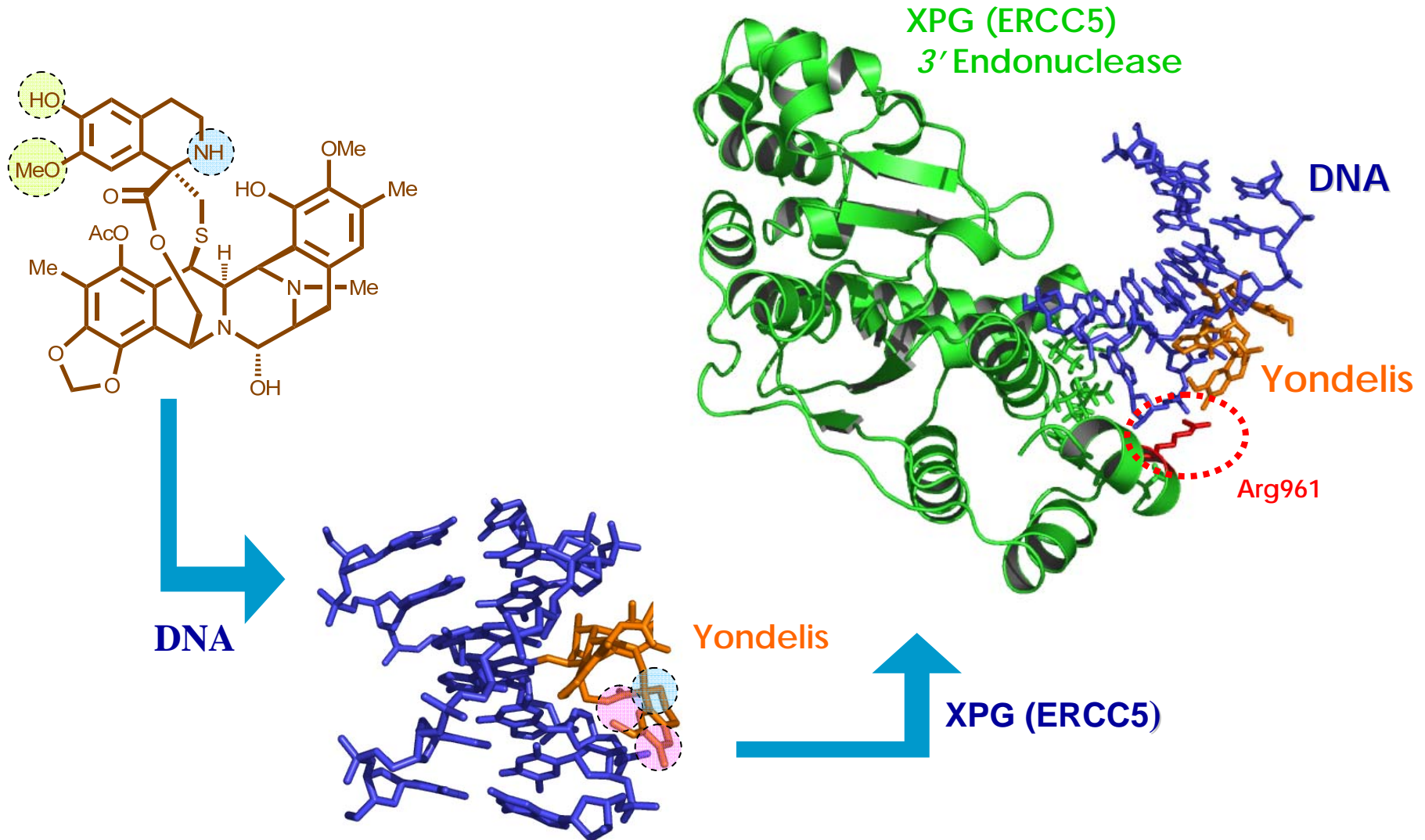


PharmaMar Semisynthesis (18 steps)

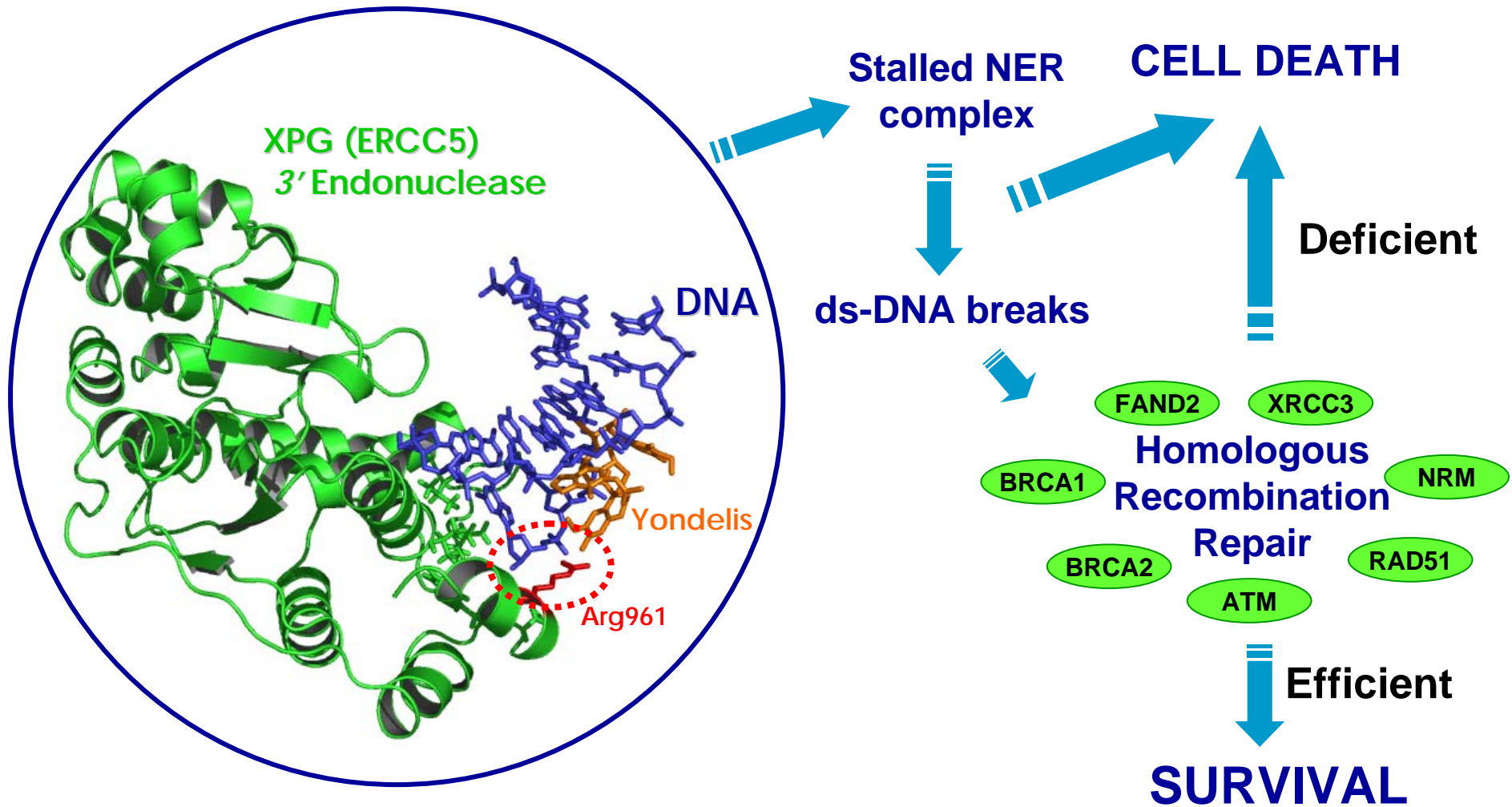


Unique MoA (*First in Class Drug*)

Ternary complex XPG-Yondelis-DNA

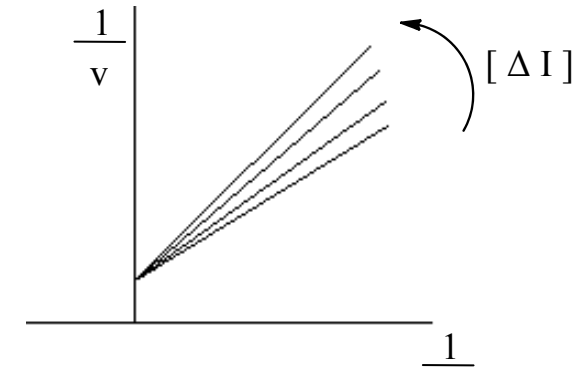
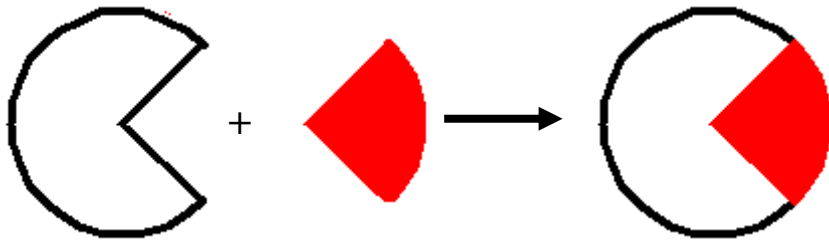


Unique MoA (*First in Class Drug*)

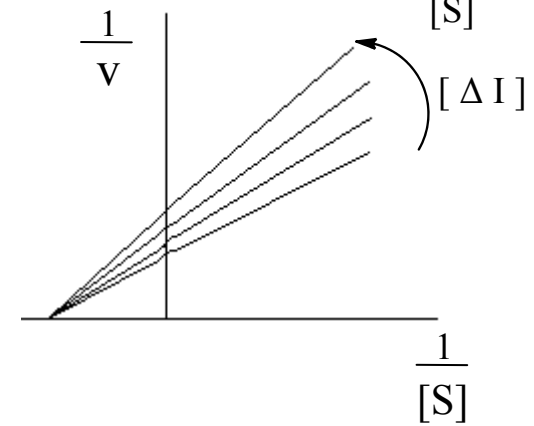
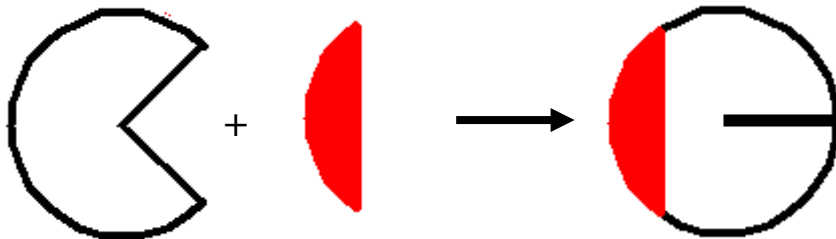


Enzymatic Inhibition Types

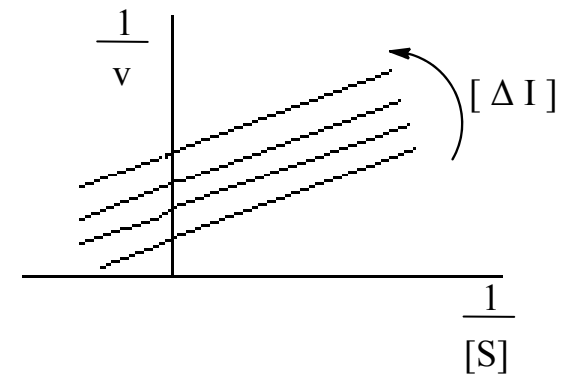
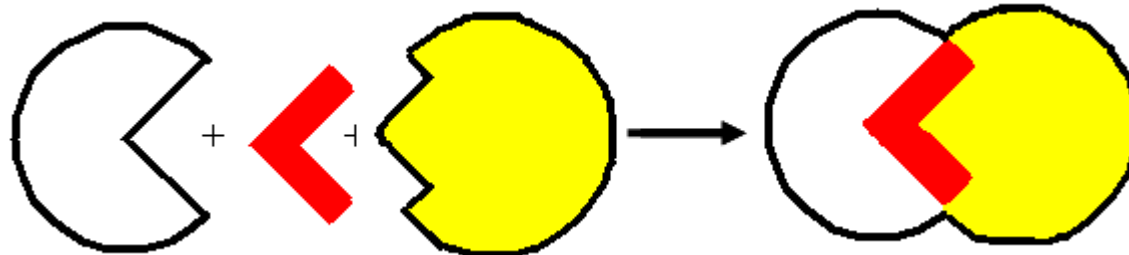
COMPETITIVE INHIBITION



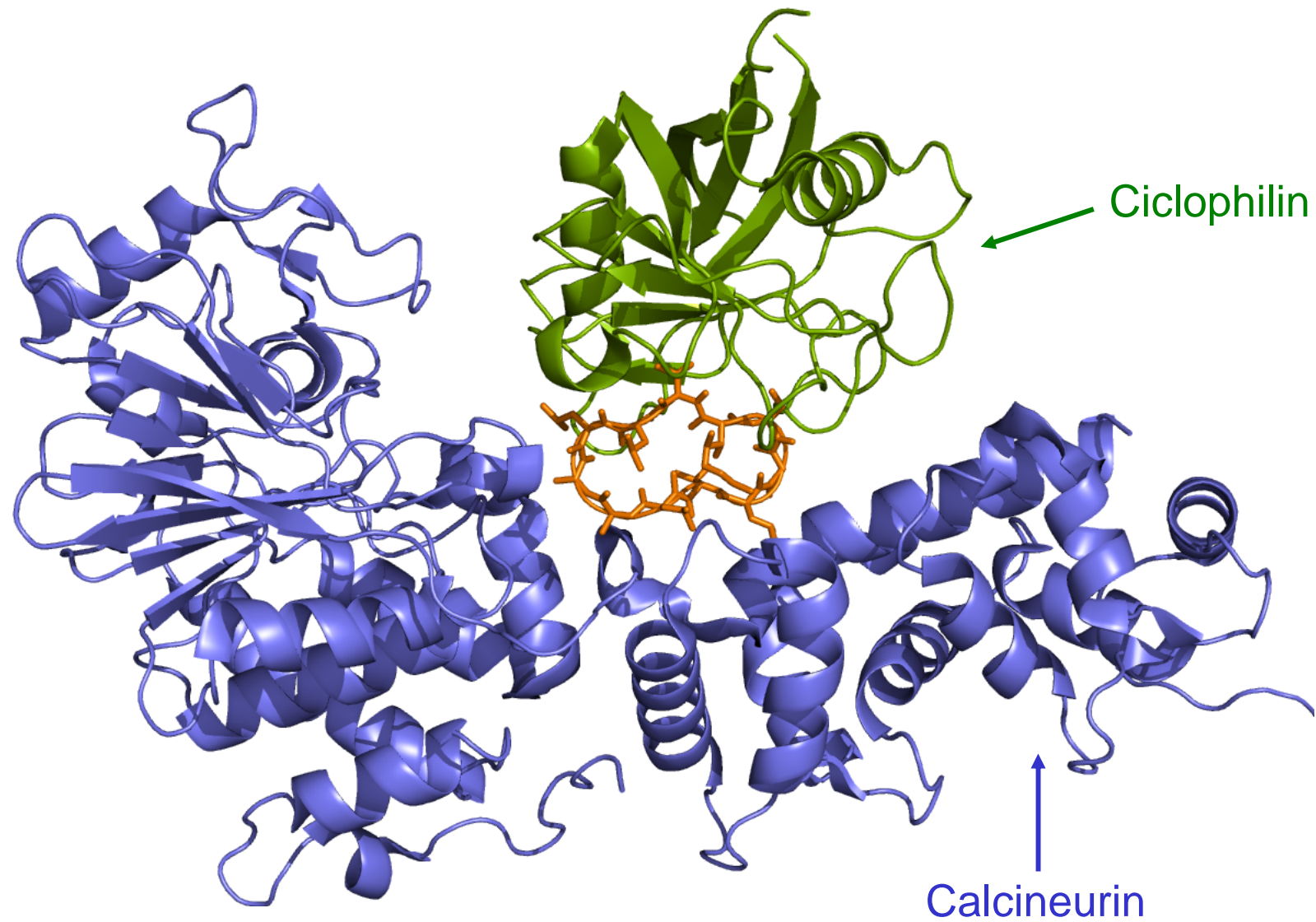
NON COMPETITIVE INHIBITION



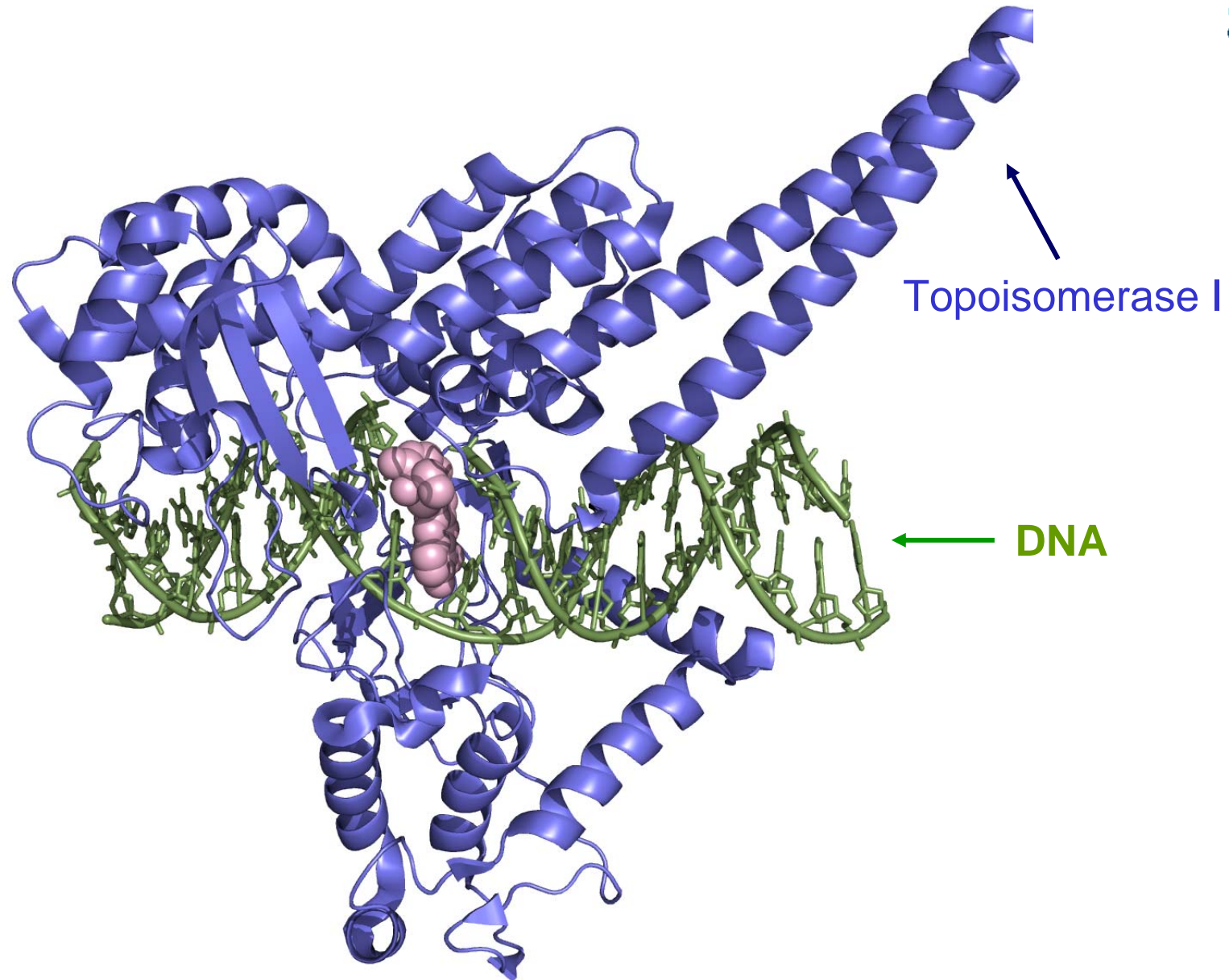
UNCOMPETITIVE INHIBITION



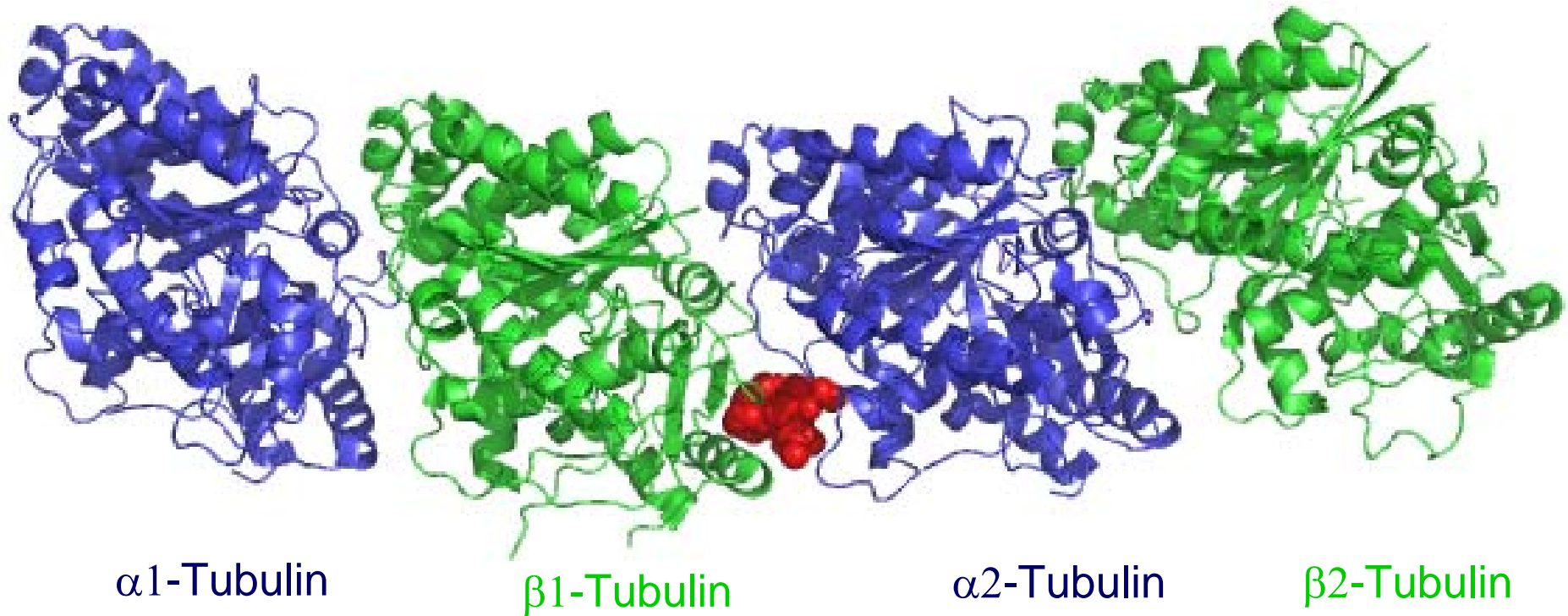
Cyclosporin Mechanism of Action



Camptothecin Mechanism of Action



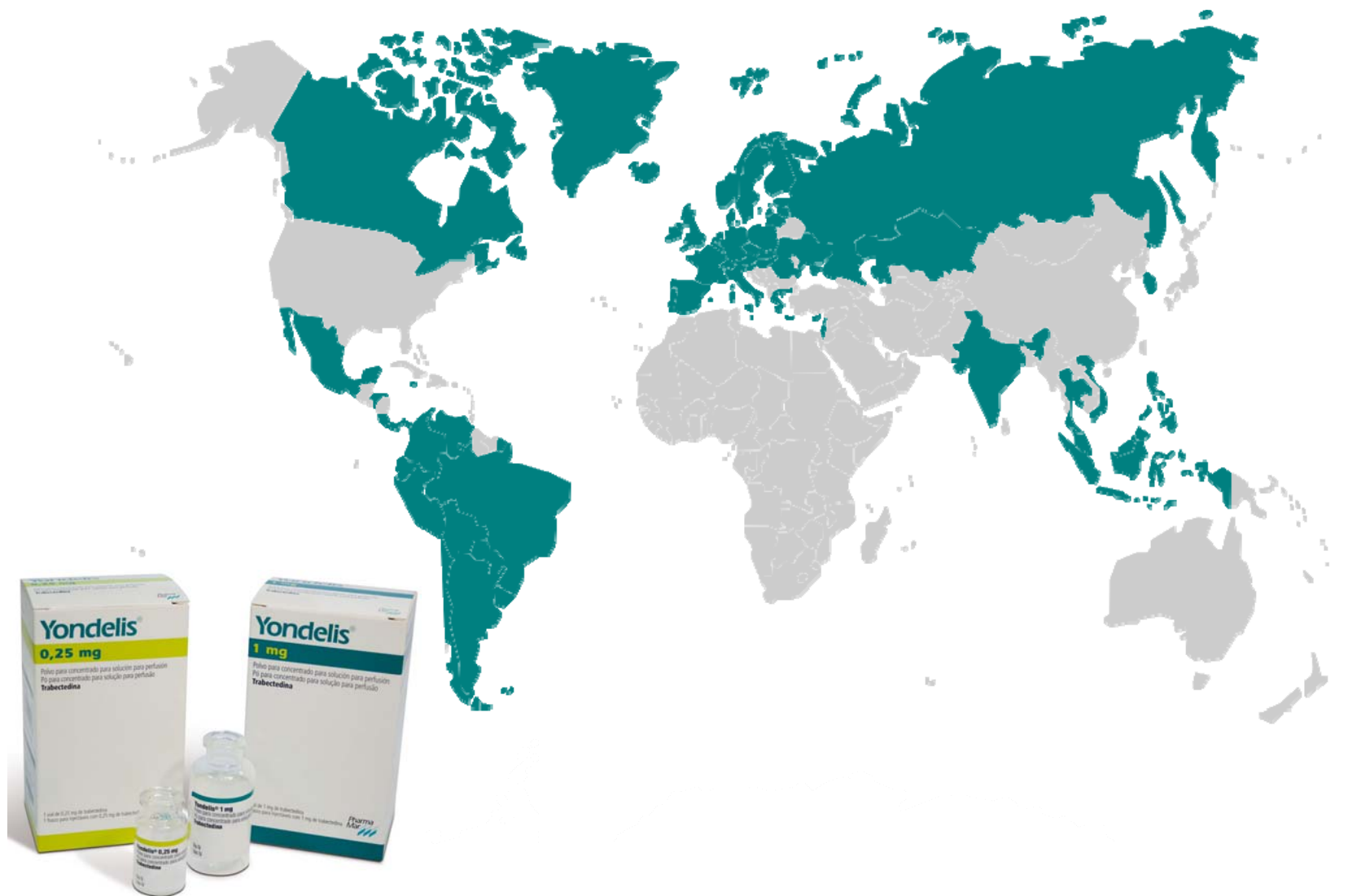
Vinblastine Mechanism of Action



Potential Interfacial Inhibitors of Nucleic Acid-Protein Interactions

Drug	Origin	Substrate	Mechanism
Doxorubicin (Adriamycin)	Micro organism	Topoisomerase II-DNA complex	Traps cleavage complexes by binding at the enzyme-DNA interface
Etoposide & Teniposide	Semi-synthetic	Topoisomerase II-DNA complex	Traps cleavage complexes by binding at the enzyme-DNA interface
Quinolones (Norfloxacin, ciprofloxacin)	Synthetic	Gyrase-DNA complexes	Traps cleavage complexes by binding at the gyrase A (and B) subunit-DNA interface
Actinomycin D	<i>Streptomyces antibioticus</i>	Pol I (+ other DNA processing enzymes)	Inhibits RNA synthesis
Ecteinascidin <u>Yondelis®</u>	Sea Squirt (<i>Ecteinascidia turbinata</i>)	Transcription-coupled nucleotide excision repair	Poisons the repair complex after incision of the DNA by preventing normal repair ligation
Aphidicolin	Micro organism (<i>Cephalosporium aphidicola</i>)	Replicative DNA polymerases	Inhibits dCTP incorporation
Cycloheximide	<i>Streptomyces griseus</i>	Eukaryotic ribosome	Blocks the translocation reaction on ribosomes
Diketo acids	Synthetic	HIV-1 integrase-DNA complexes	Metal chelation in the catalytic site of the integrase-DNA complex

Yondelis® Approved in more than 60 Countries





MOLECULES THAT CHANGED THE WORLD

K. C. NICOLAOU • T. MONTAGNON

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Pharma
Mar 
Grupo Zeltia

All the power
of the sea,
now against
cancer

Thank you

Dr. José María Fernández
Grupo Zeltia