Update on Cancer Therapeutics: Chemotherapy, Enzymes & Immunotherapy

Najim A. Al-Masoudi, Ph.D. (UK), Disting. Scientist (WHO)
Professor of Organic & Medicinal Chemistry
Scientific Consultant, Konstanz (Germany)

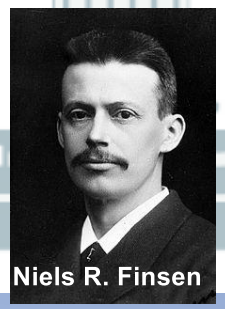
Cancer therapy

Surgery

التداخل الجراحي

Radio-therapy

التشعيع



Niels R. Finsen

Anti cancer drugs

المعالجة الكيماوية

بظمنها المعالجة بالانزيمات

Immune checkpoint therapy

المعالجة بالاستجابة المناعية

Cancer Cell Reproduction

Step. 1
Healthy Cell

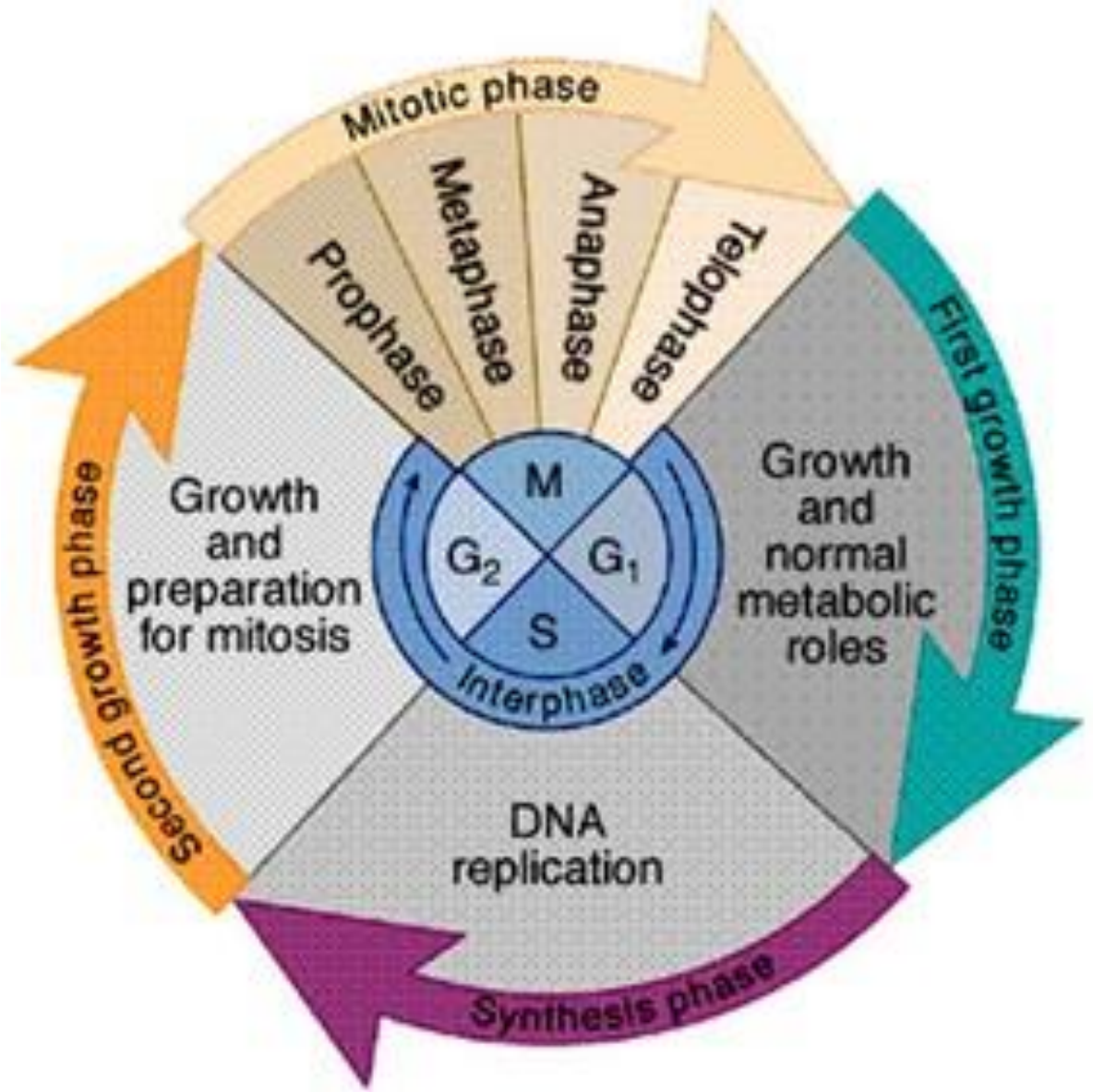
Step. 2
Damaged DNA in Cell

Step. 3
Cell becomes Mutated

Step. 4
Mutated Cell Begins Unchecked Reproduction

Step. 5
Mutated Cells Grown in number

Metastasis ?



Metastatic Breast Cancer & Therapy

1. Lysyl Oxidase
2. [Poly(Adenosine Diphosphate)Ribose] Polymerase (PARP)
3. Aromatase
4. Kinase

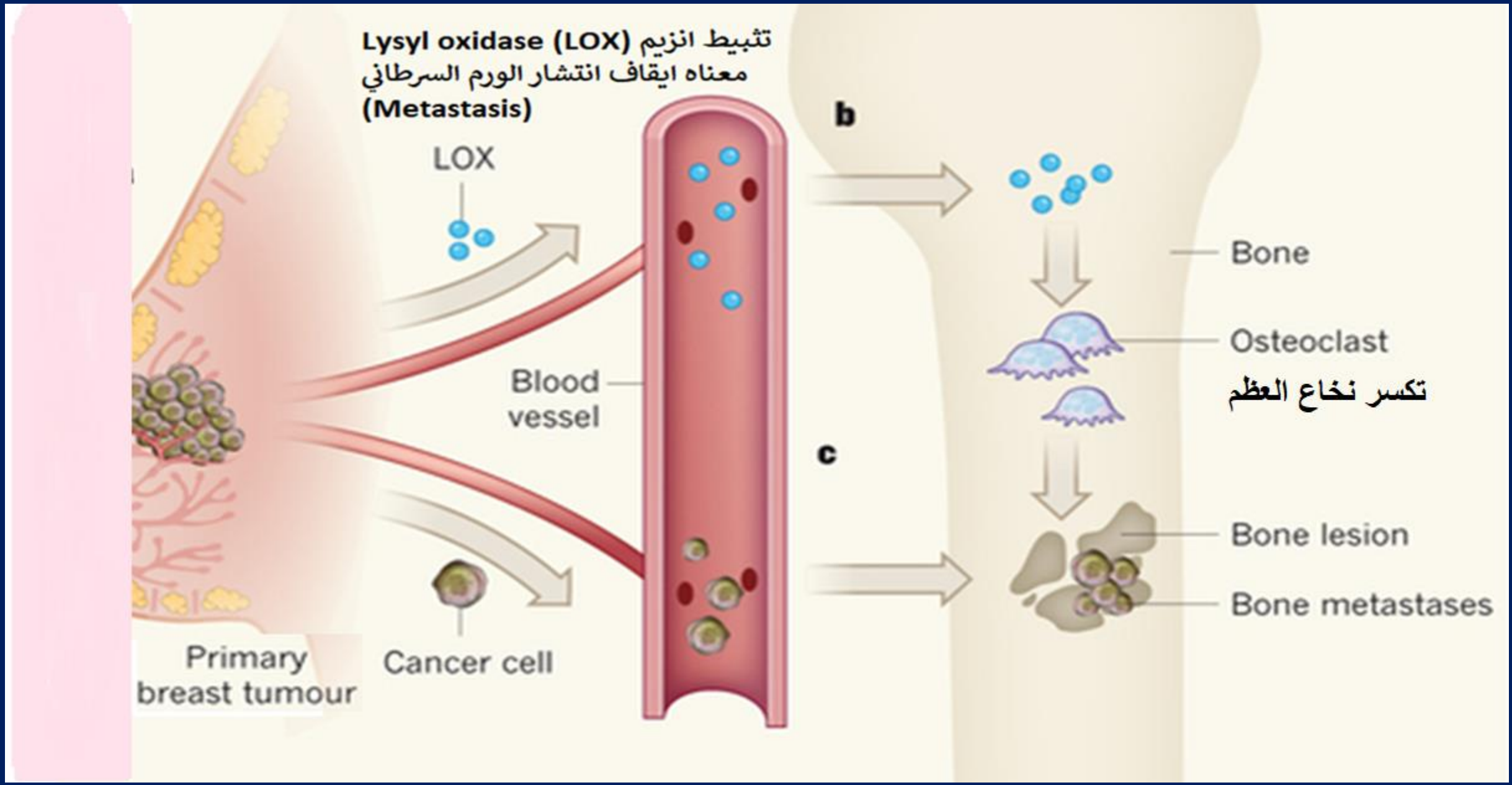
Lysyl Oxidase (LOX), a Targetable Secreted Molecule Involved in Cancer Metastasis.

Cox TR, Gartland A, Erler JT , ***Cancer Res.*** **2016**, 76:188-192.

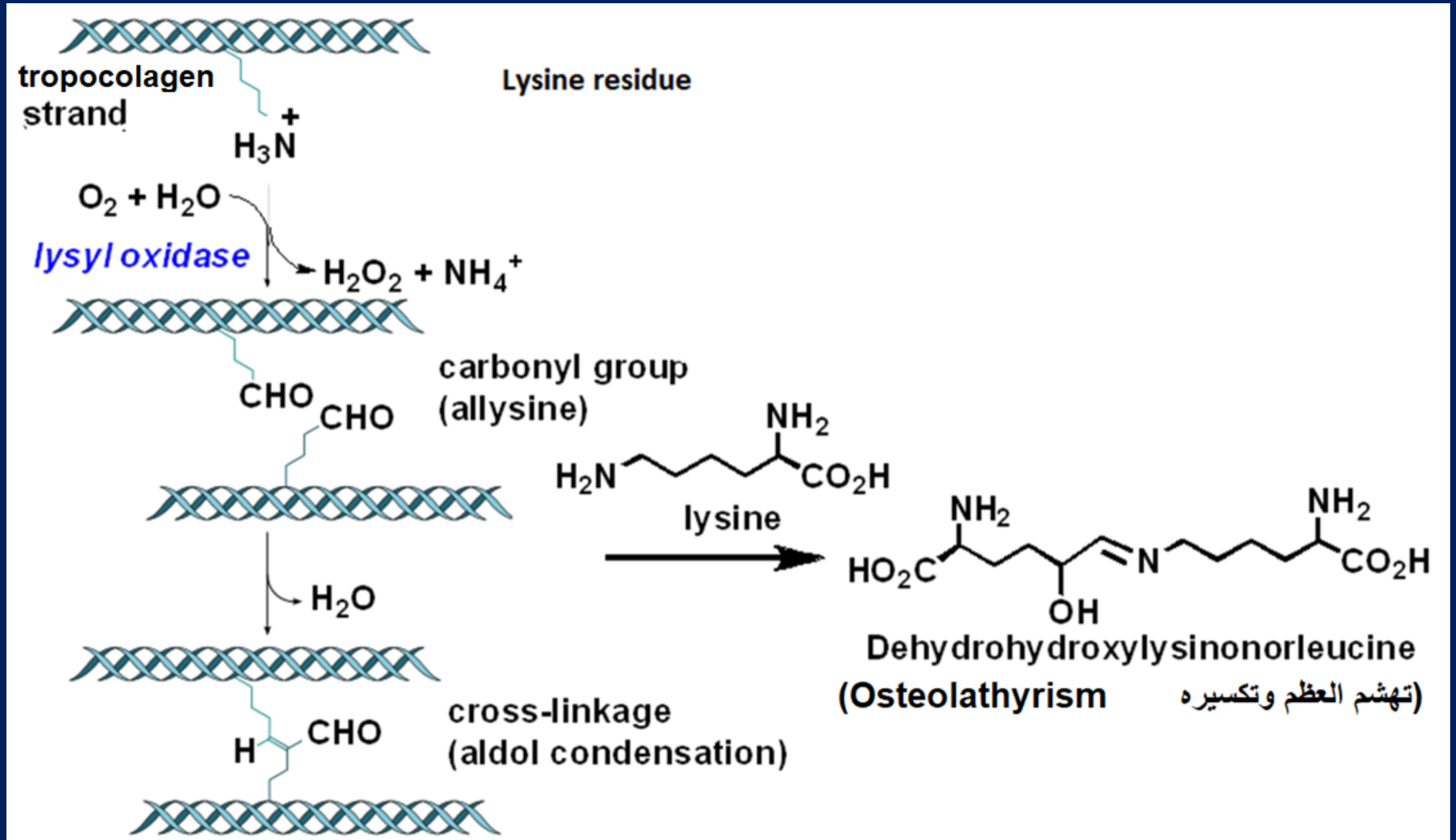
•**Abstract**

•**In breast cancer, 100% of deaths are attributed to metastasis. At present, there are "NO cures" for secondary metastatic cancer of any form and there is an urgent unmet clinical need to improve the tools available in our arsenal against this disease, both in terms of treatment, but also prevention.**

Lysyl oxidase (LOX) & metastatic breast cancer

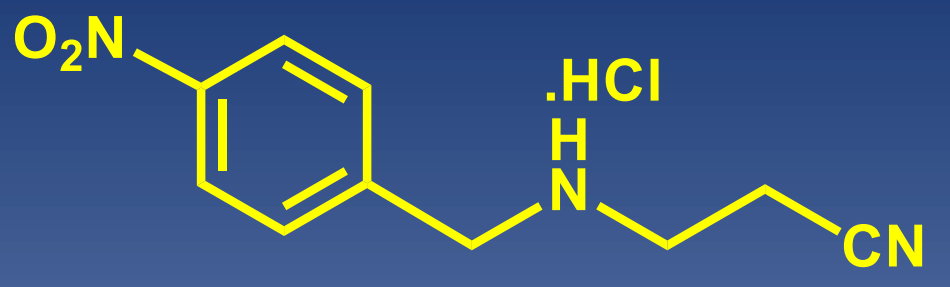


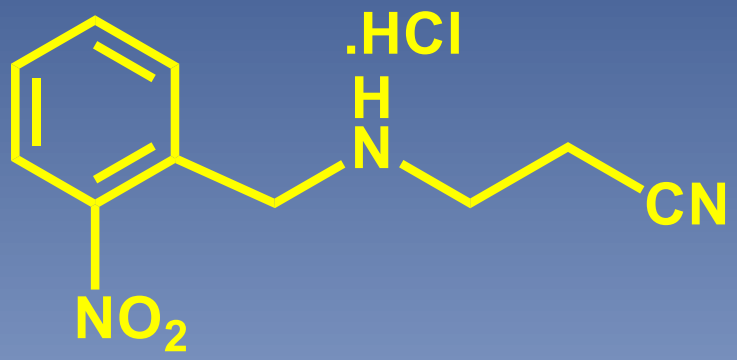
The Role of Lysyl Oxidase Enzyme in M. Breast Cancer

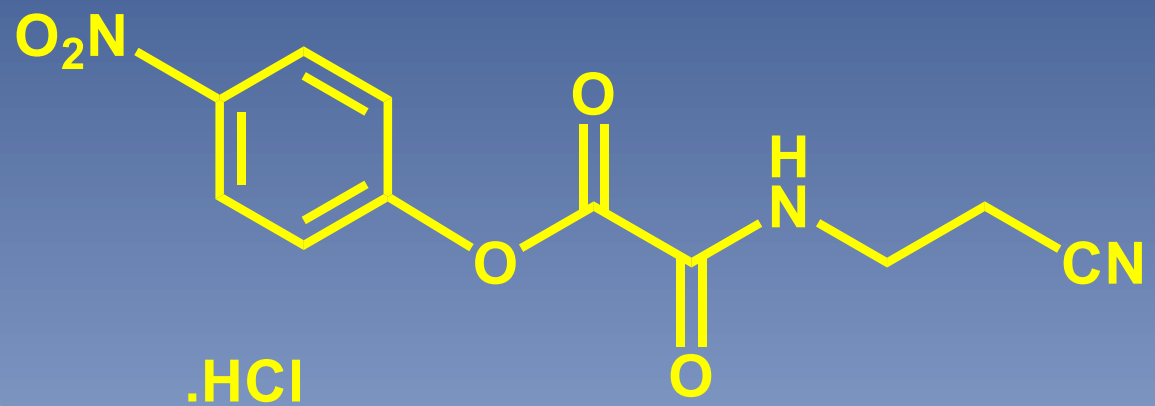


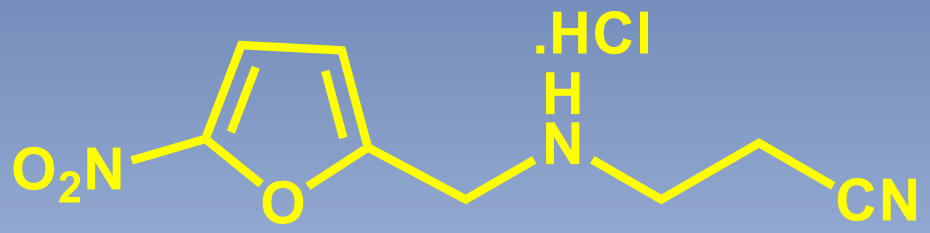
Inhibition of Lysyl oxidase (LOX) in breast cancer cells by small-molecule inhibitors

3-aminopropanenitrile hydrochloride (BNPA)









The inhibitors LP-1-2 for LOX enzyme

Prof. Janine Erler, University of Copenhagen

Prof. Alison Gartland, University of Sheffield, UK

hypoxia-activated prodrugs

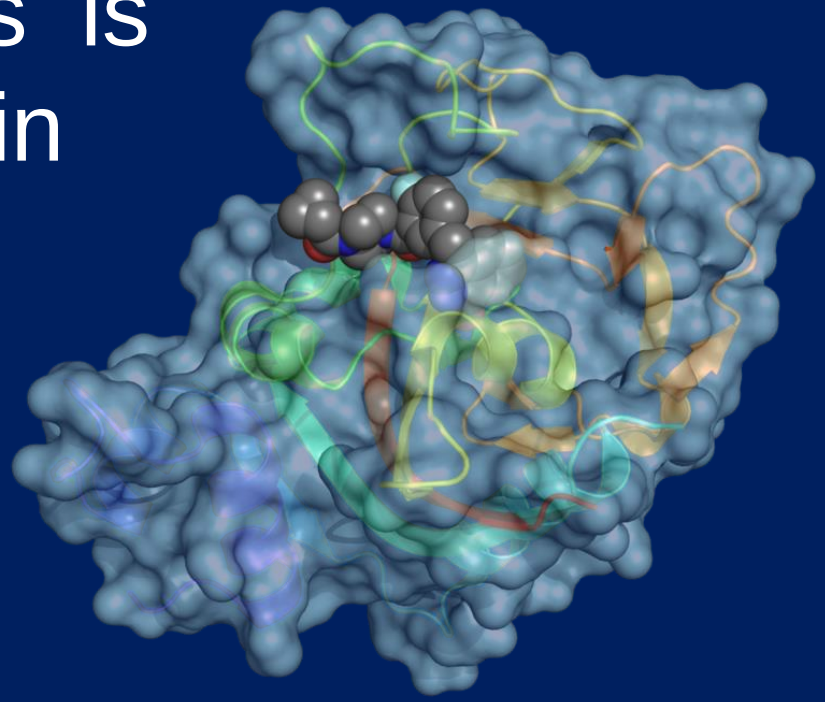
C. Granchi, T. Funaioli, **J. T. Erler**, A. J. Giaccia, M. Macchia, F. Minutolo, *ChemMedChem*. **2009**, *4*, 1590–1594.

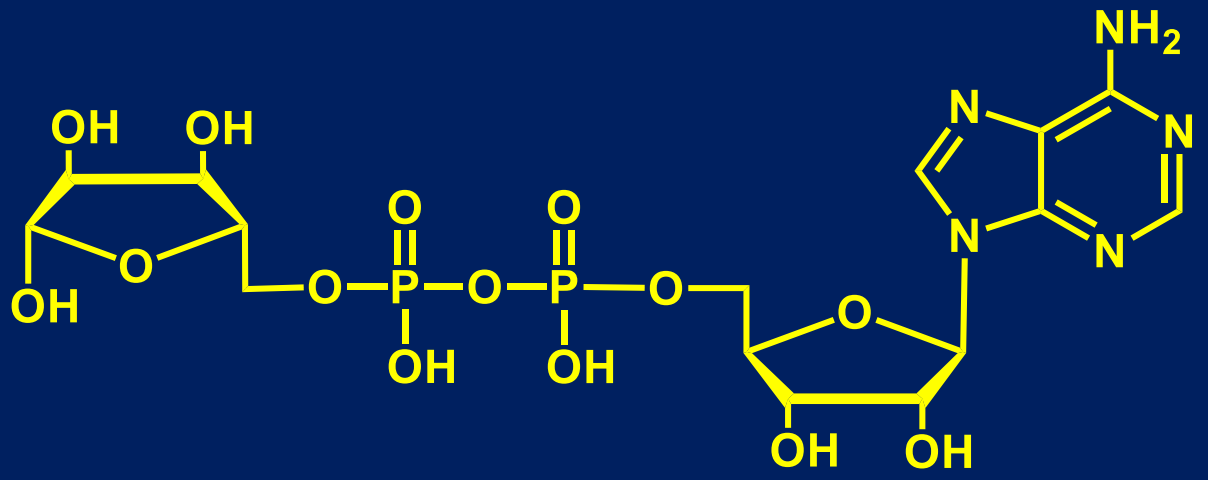
[Poly(Adenosine Diphosphate)Ribose]-Polymerase (PARP) inhibitors

PARP is a family of proteins involved in a number of cellular processes such as DNA repair, genomic stability, and programmed cell death.

Activity of PARP in Breast Cancer

When the gene for one of some proteins is mutated, the change can lead to errors in DNA repair that can eventually cause **breast cancer**

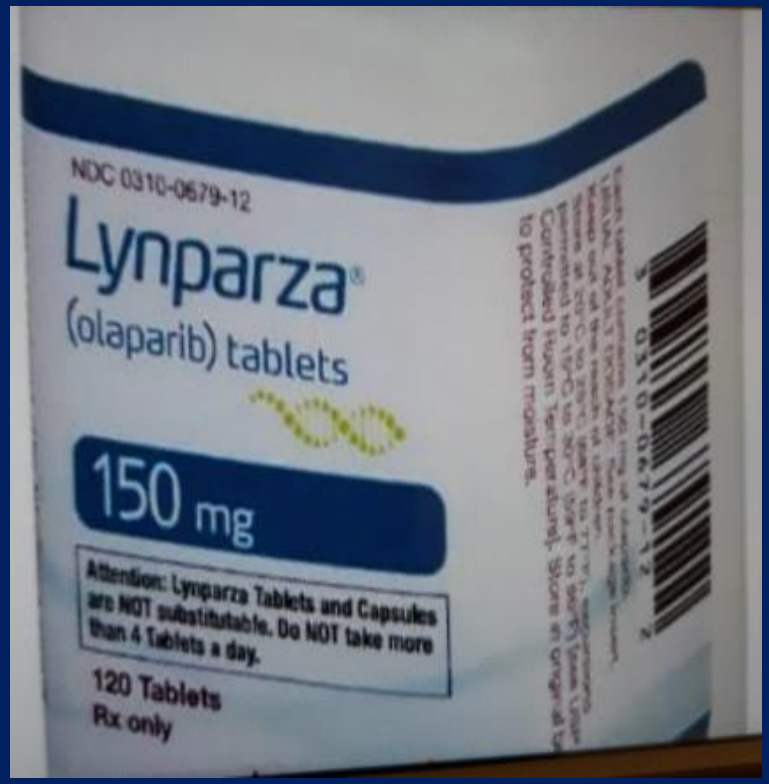




Poly-[Adenosine Diphosphate-Ribose] (ADP-ribose) Polymerase

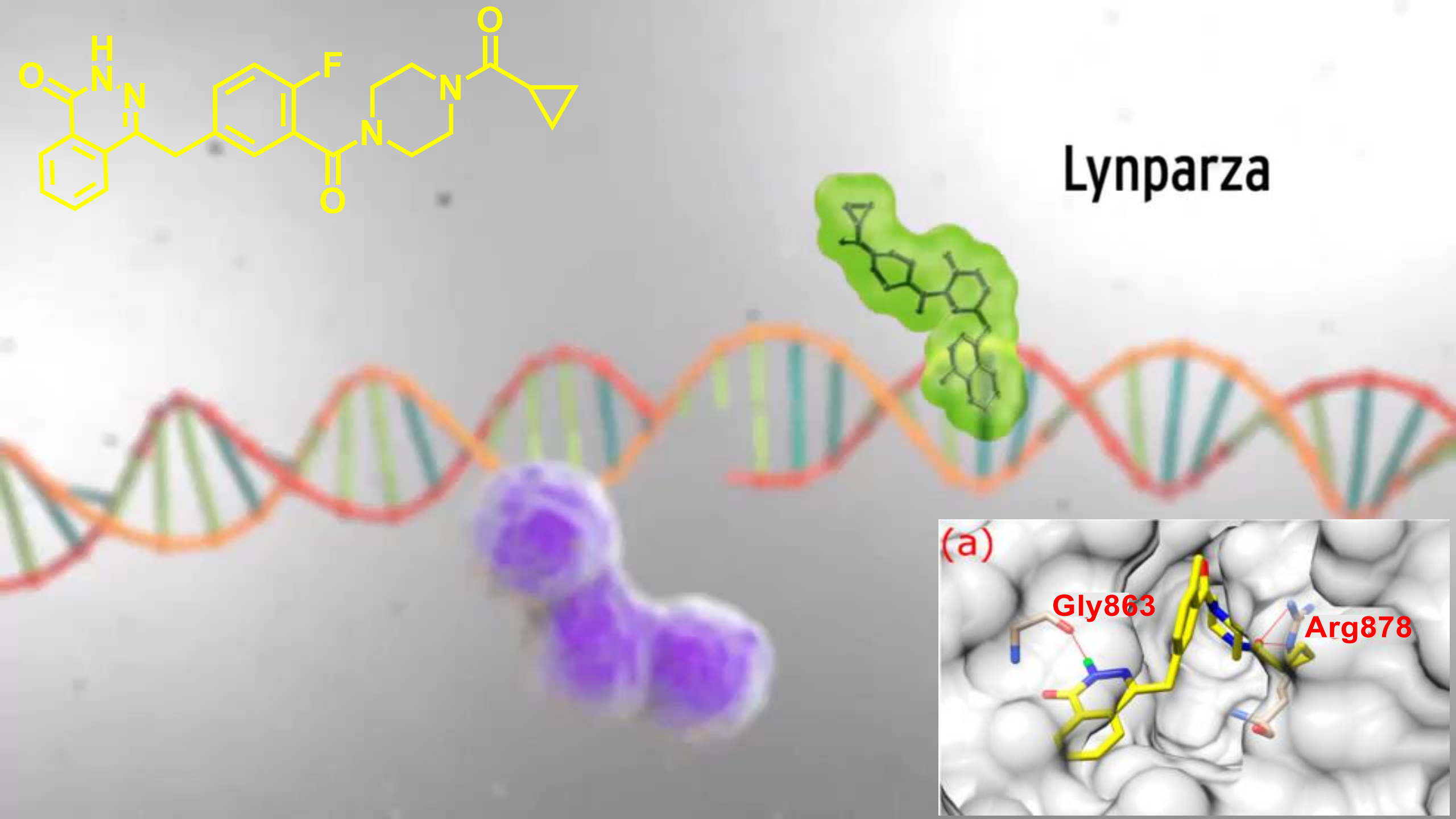
PARP inhibitors: A New Generation of Cancer Drugs

Lynparza (Olaparib)

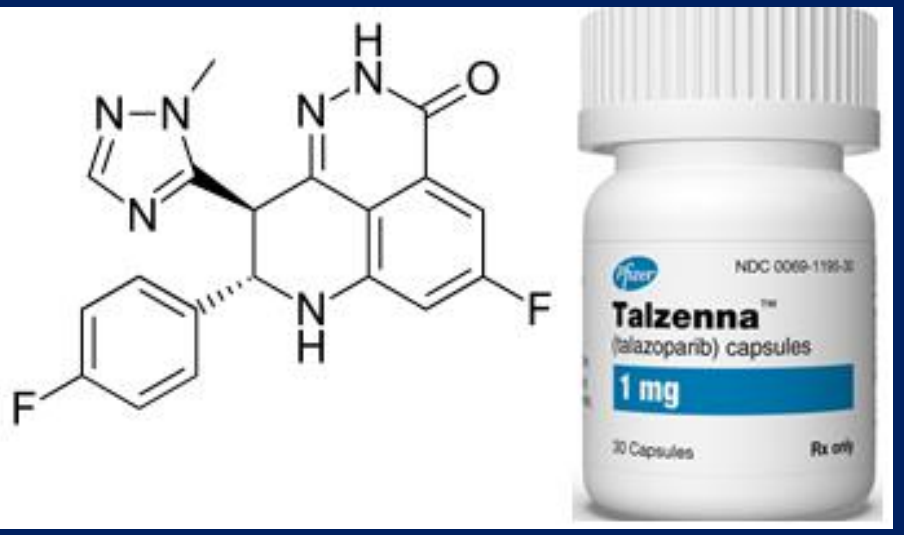


50 mg / 112 cap. 3,391.24 $
100-150 mg / 60 Tab. 7,257.24 $

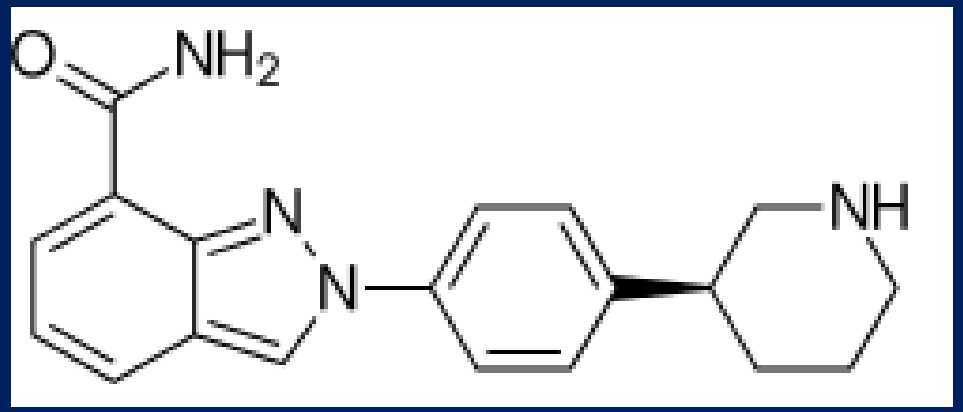
Prof. Stephen Philip Jackson, Nottingham, England


Lynparza
(a)
Gly863
Arg878

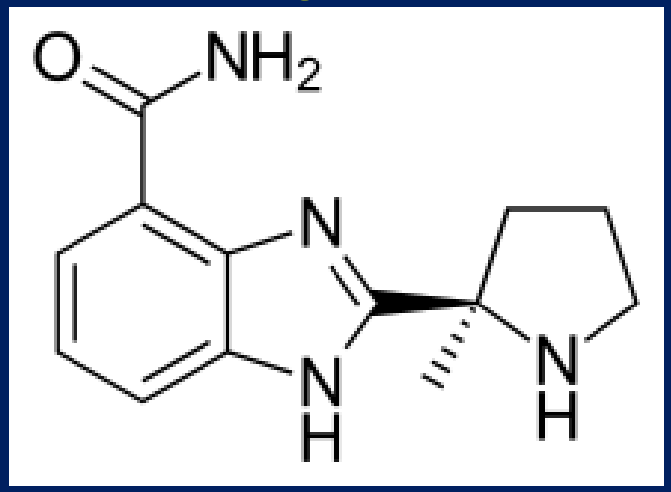
Other PARP Inhibitors for Treatment of MBC



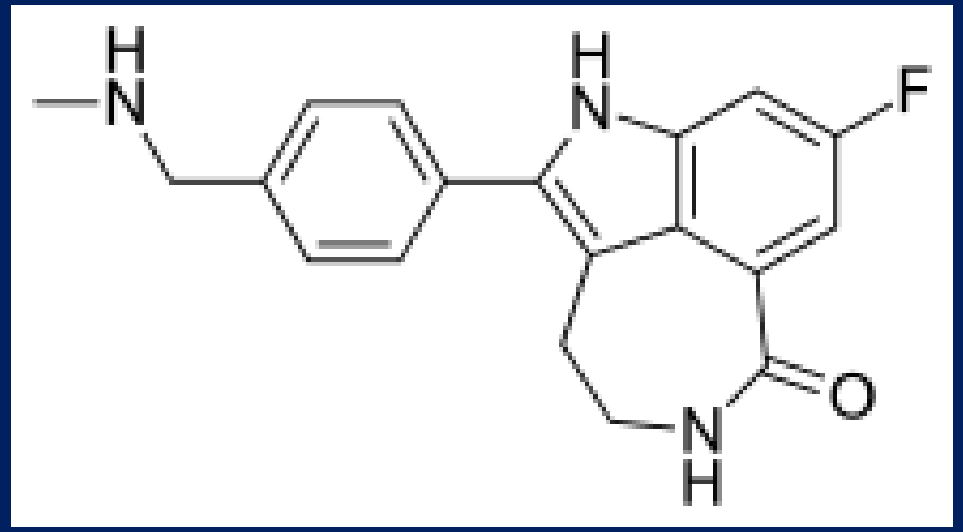
Talazoparib



Niraparib



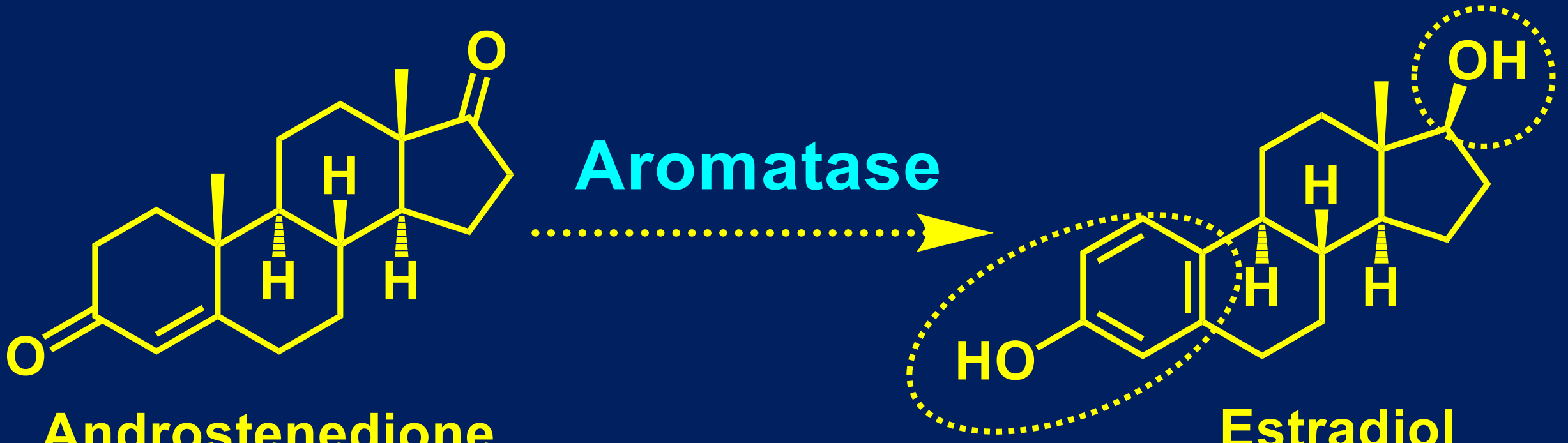
Veliparib



Rucaparib

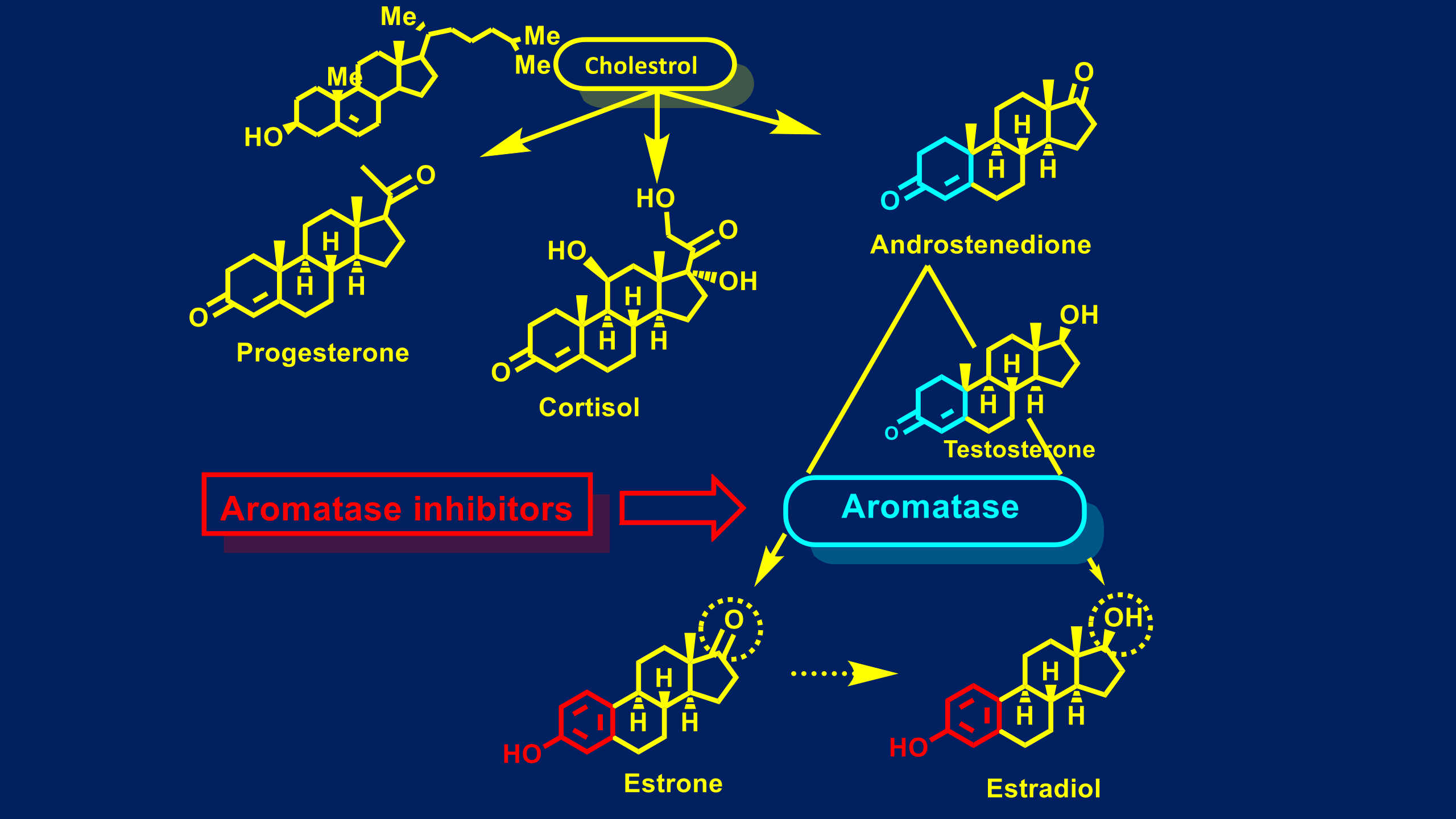
Aromatase Inhibitors for Treatment of Breast Cancer

- AI's inhibit the enzyme aromatase, which is responsible for converting androgens (produced by women in the adrenal glands) to estrogens.

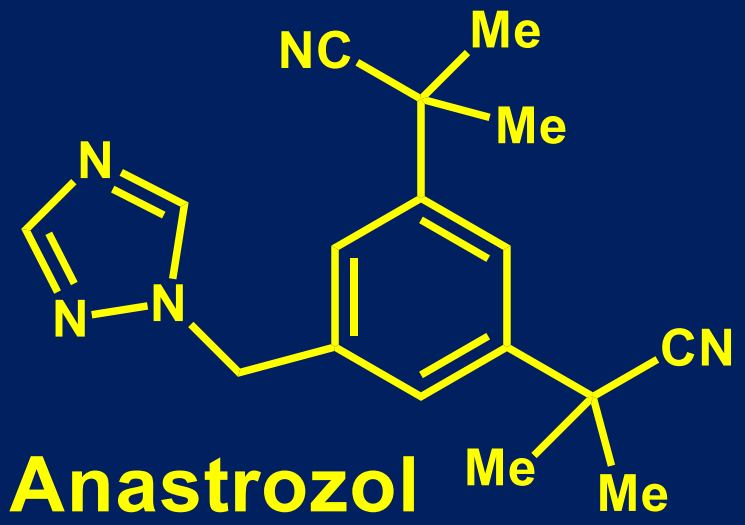


Androstenedione

Estradiol

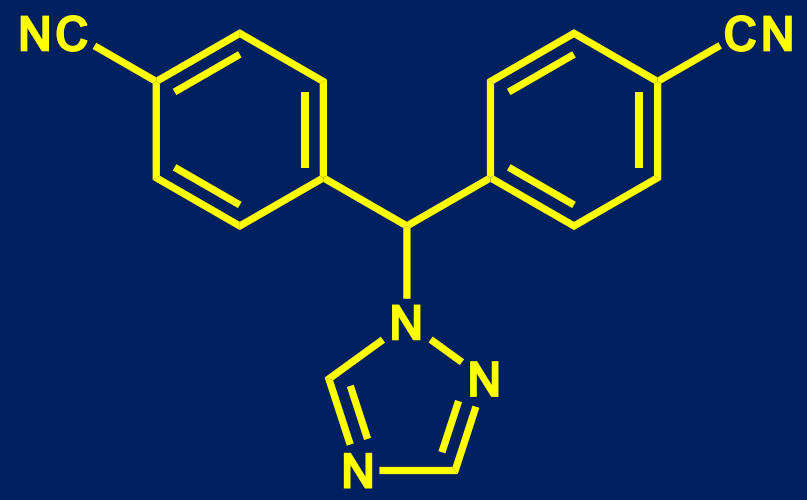

Cholestrol
Progesterone
Cortisol
Androstenedione
Testosterone
Aromatase inhibitors
Aromatase
Estrone
Estradiol

Aromatase Inhibitors for Breast Cancer



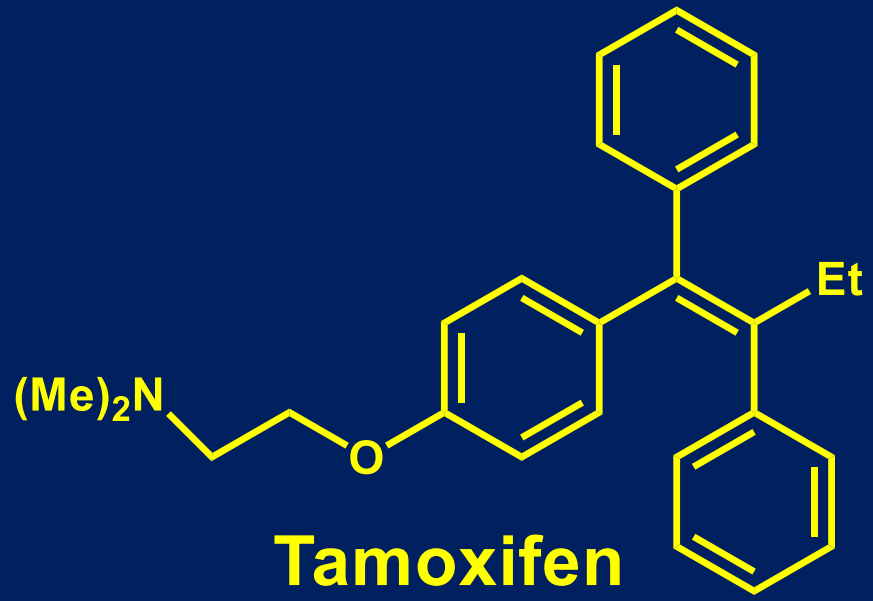
Anastrozol

J. F. R. Robertson, et al., *J. Clin. Oncol*. 2009, *27*: 4530-4535.



Letrozole

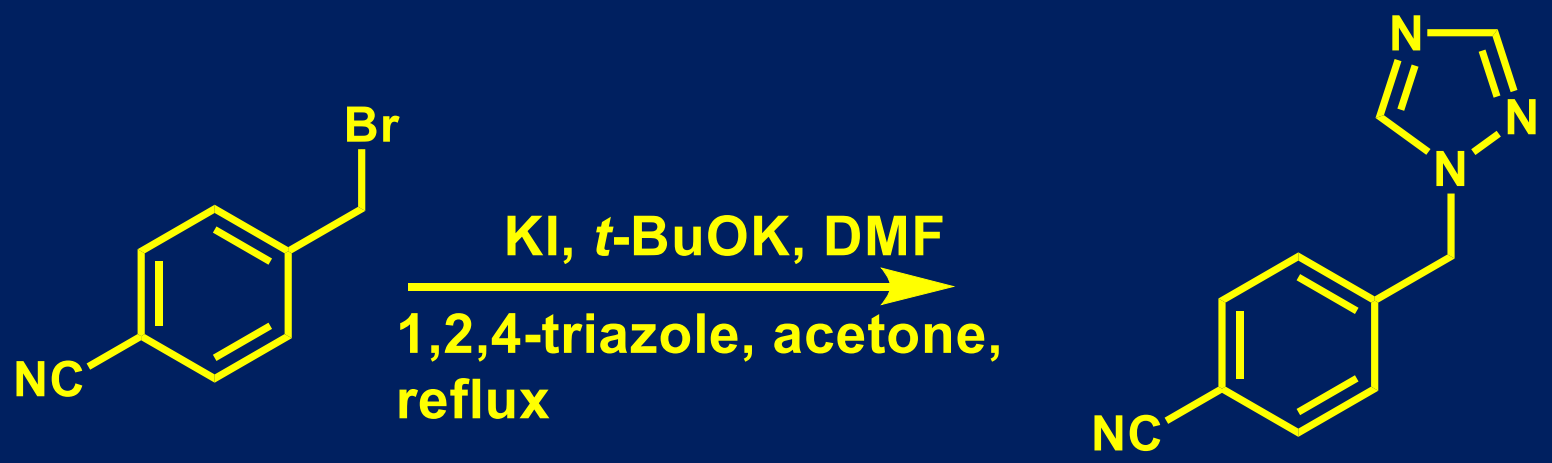
J. K. Fowler, et al., *Nucl. Med. Biol*. 2009, *36*:215-223



Tamoxifen

Howell A, et al., *J. Clin. Oncol.* 2004, *22*:1605

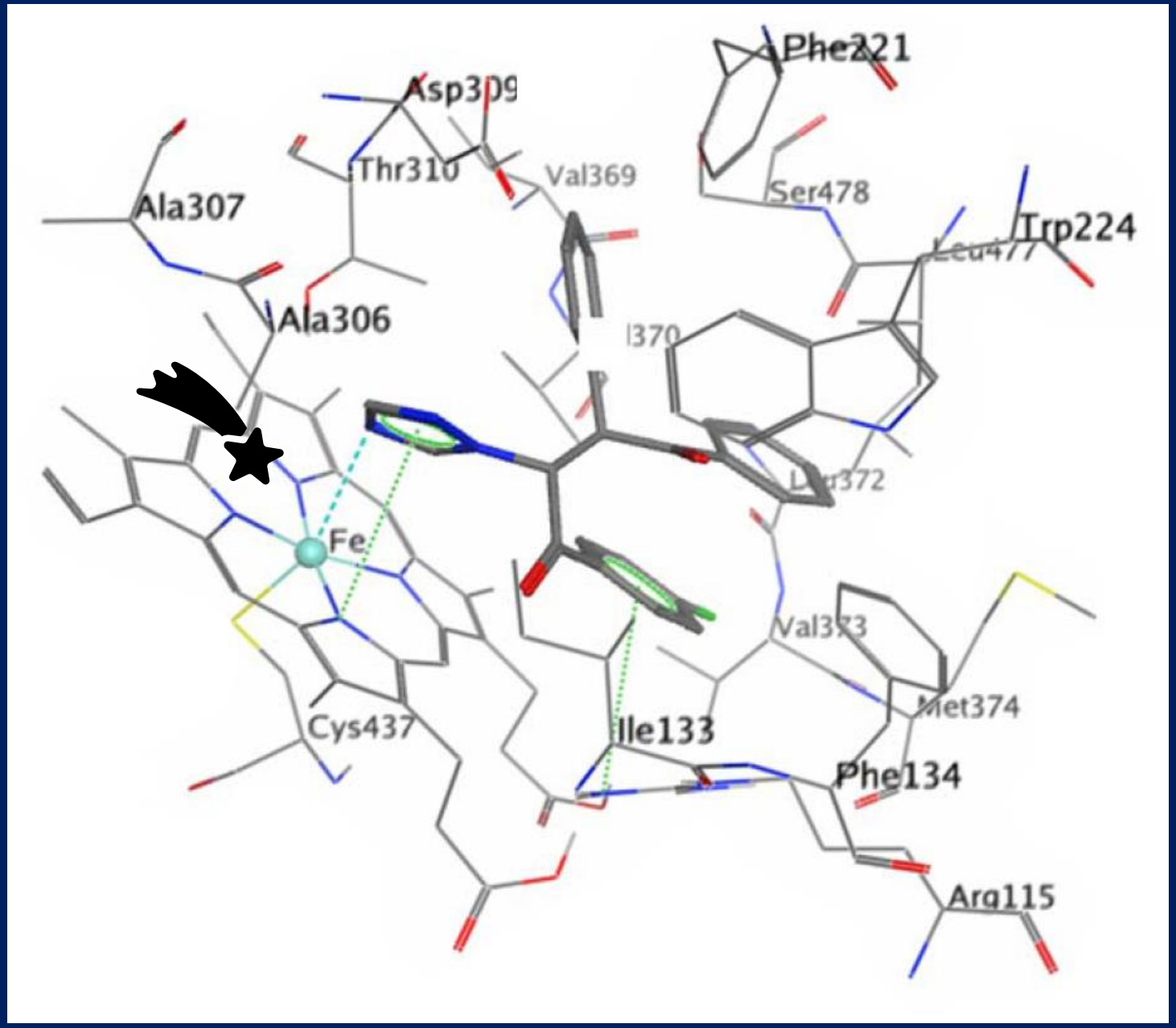
Synthesis of Letrozole

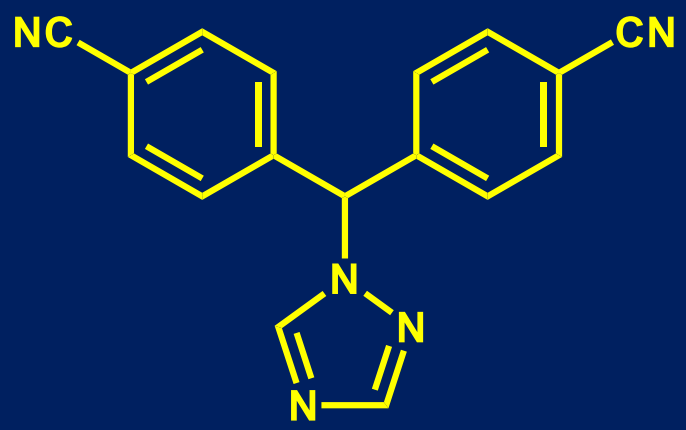


Letrozole

Fowler, *et al.*, *Nuc. Med. Biol.* 2009, *36*, 215-223

Molecular Docking of Letrozole with Aromatase Enzyme





Letrozole

N4 of triazole coordinated to Fe of HEM + pi-cation interactions to pophyrin

Z. Rezaei, et al., *Res. Pharm. Sci.* 2017, *12*, 21-30

Which test should be done for breast cancer diagnosis

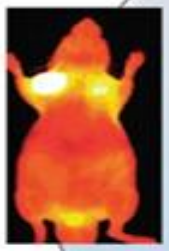
Blood Marker Test:

- **CA 15.3:** used to find breast and ovarian cancers.
- **TRU-QUANT and CA 27.29:** may mean that breast cancer is present.

  CA125: may signal ovarian cancer,
  recurrence of breast and ovarian cancer recurrence.
- **CEA (carcinoembryonic antigen):** metastatic factor

- **HER2 (Human Epidermal Growth) receptor test.**

Optical Imaging



Advantages:
- High sensitivity
- Multicolor imaging
- Activatable

Disadvantages:
- Low spatial resolution
- Poor tissue penetration

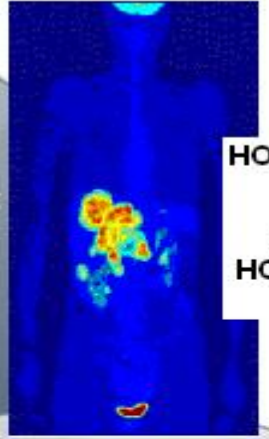
Detection : Fluorescence

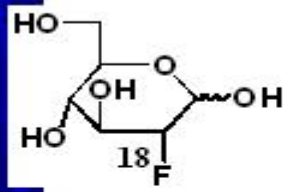
PET Imaging

Advantages:
- High sensitivity
- No tissue penetrating limit
- Quantitative
- Whole-body scanning

Disadvantages:
- Radiation risk
- High cost

Detection : γ-ray



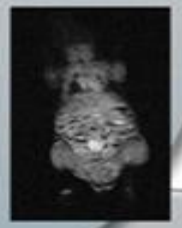


MR Imaging

Advantages:
- High spatial resolution
- No tissue penetrating limit

Disadvantages:
- Relatively low sensitivity
- High Cost
- Long imaging time

Detection : Magnetic field (Radiowave)



TARGET

SPECT Imaging

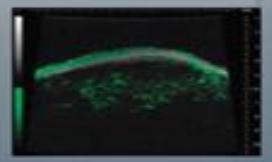
Advantages:
- High sensitivity
- No tissue penetrating limit

Disadvantages:
- Radiation risk
- Low spatial resolution

Detection : γ-ray

US Imaging

Advantages:
- Real-time
- Low cost



Disadvantages:
- Low resolution
- Operator dependent analysis

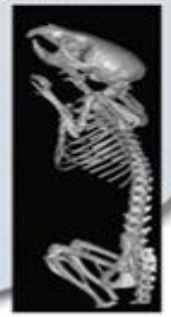
Detection : Ultrasonic waves

CT Imaging

Advantages:
- High spatial resolution
- No tissue penetrating limit

Disadvantages:
- Radiation risk
- Not quantitative

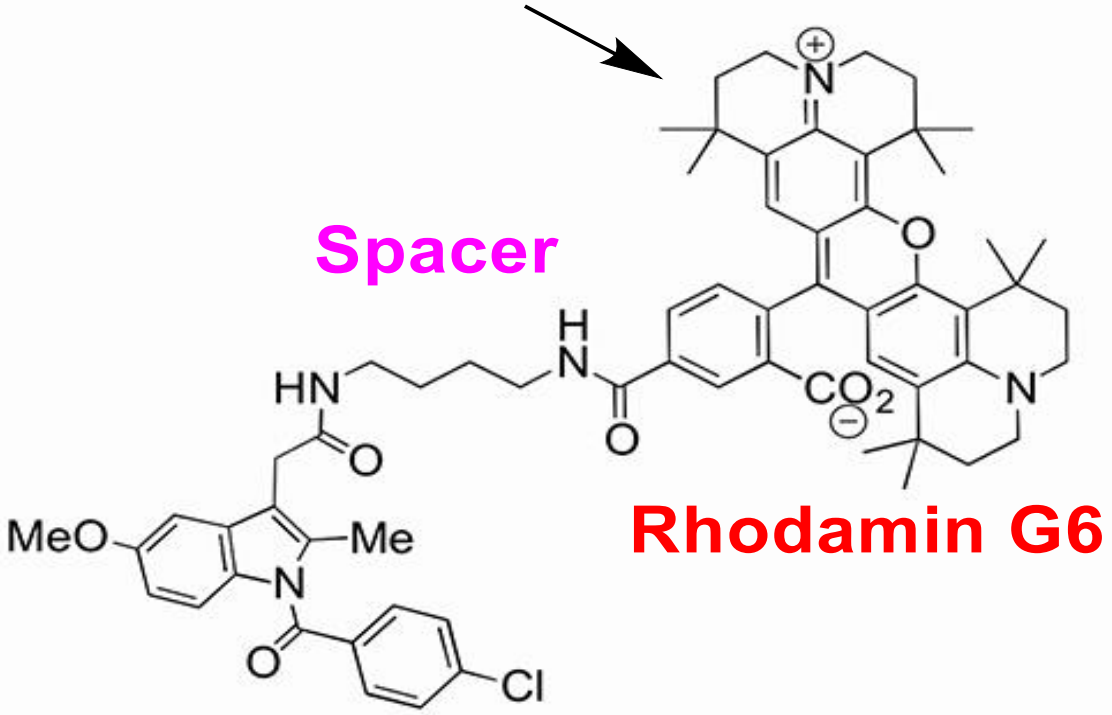
Detection : X-ray

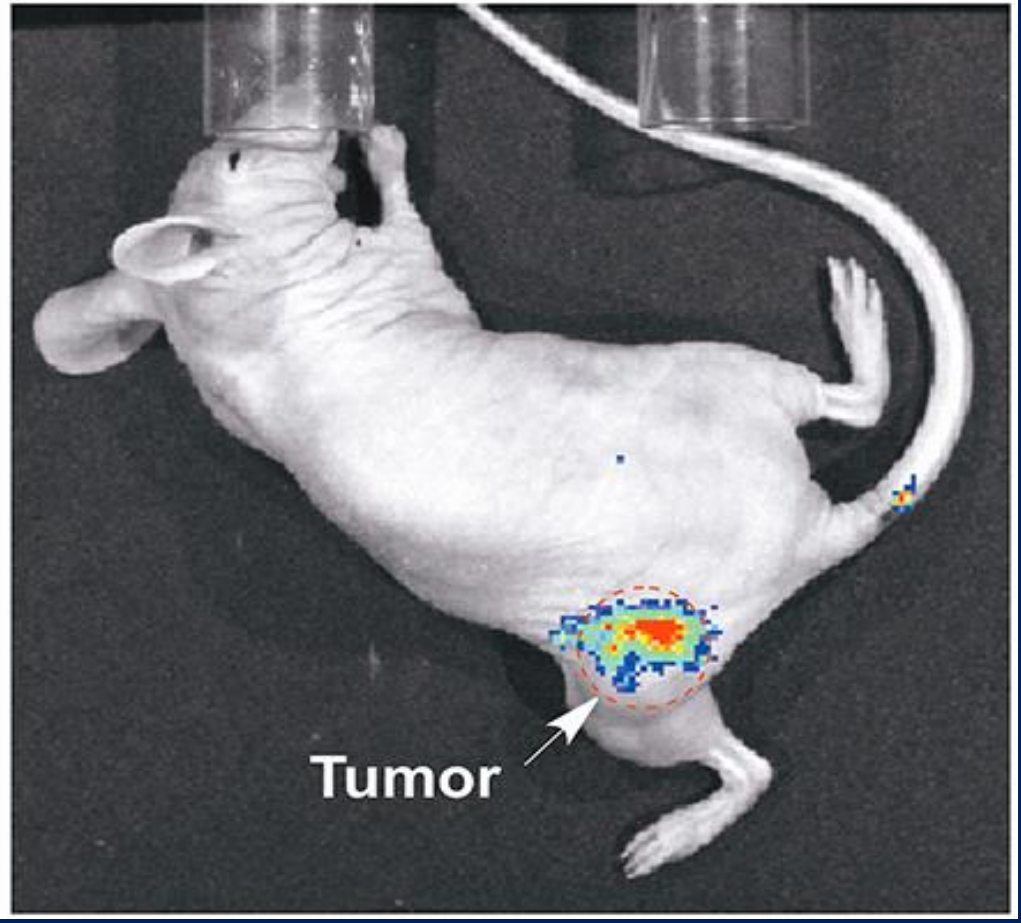


Early Tumor Diagnosis By Fluorescence Imaging Technique

COX-2-Targeted Imaging Agents

Quantum Yield = 0.95





L. J. Marnett et al., ***Bioconjucate Chem*. 2013**, 24, 712-723


20ml
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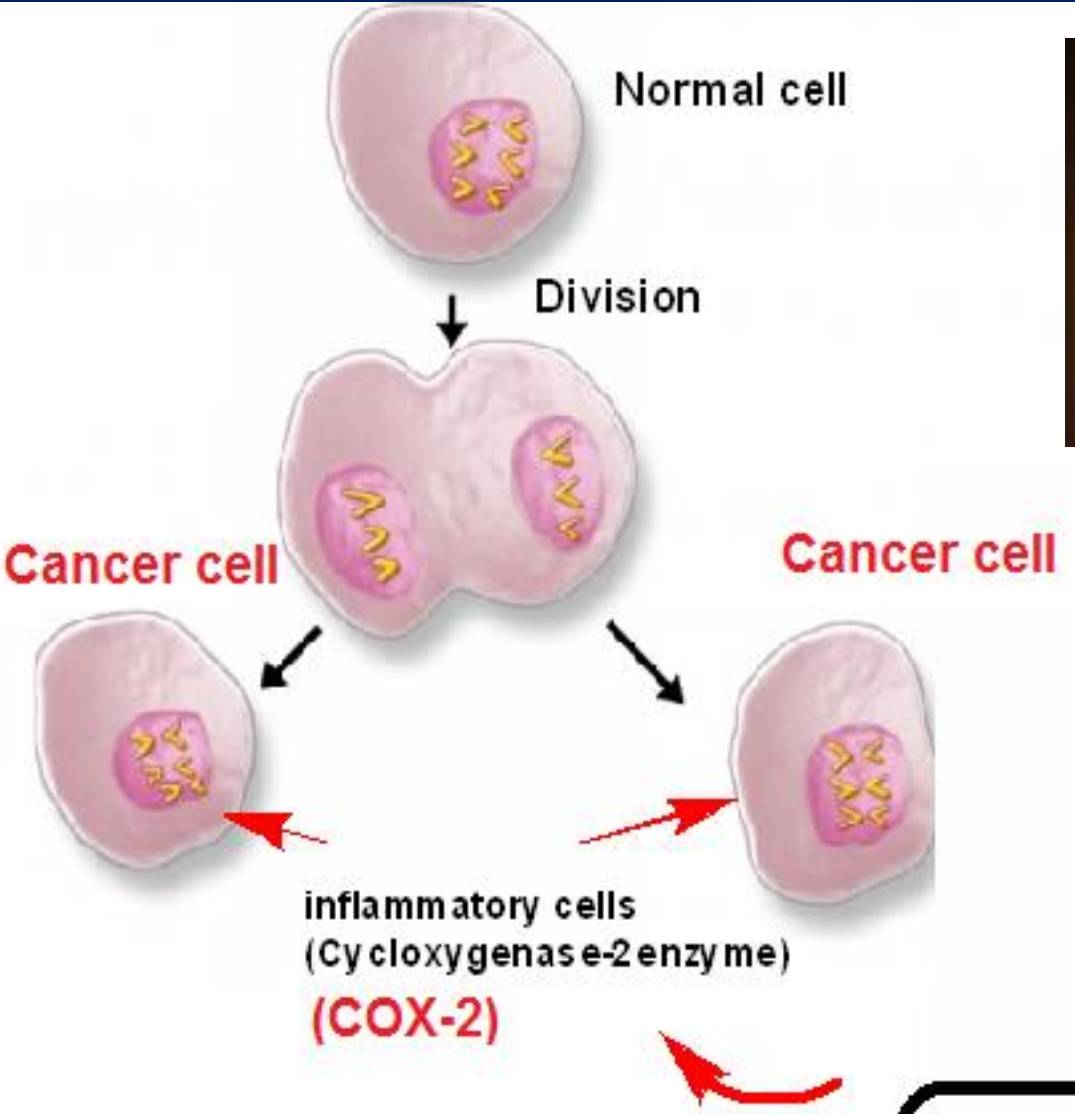
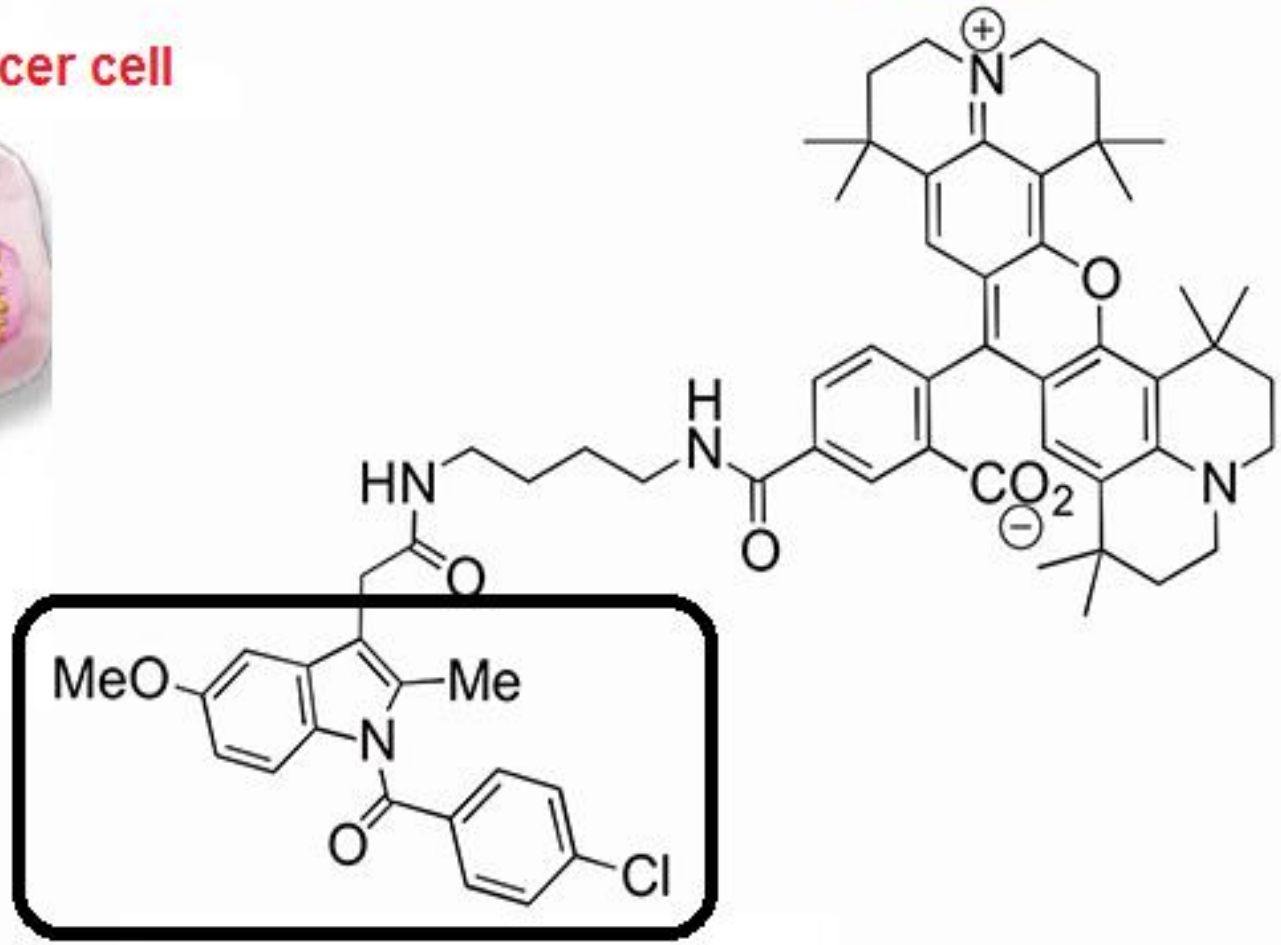
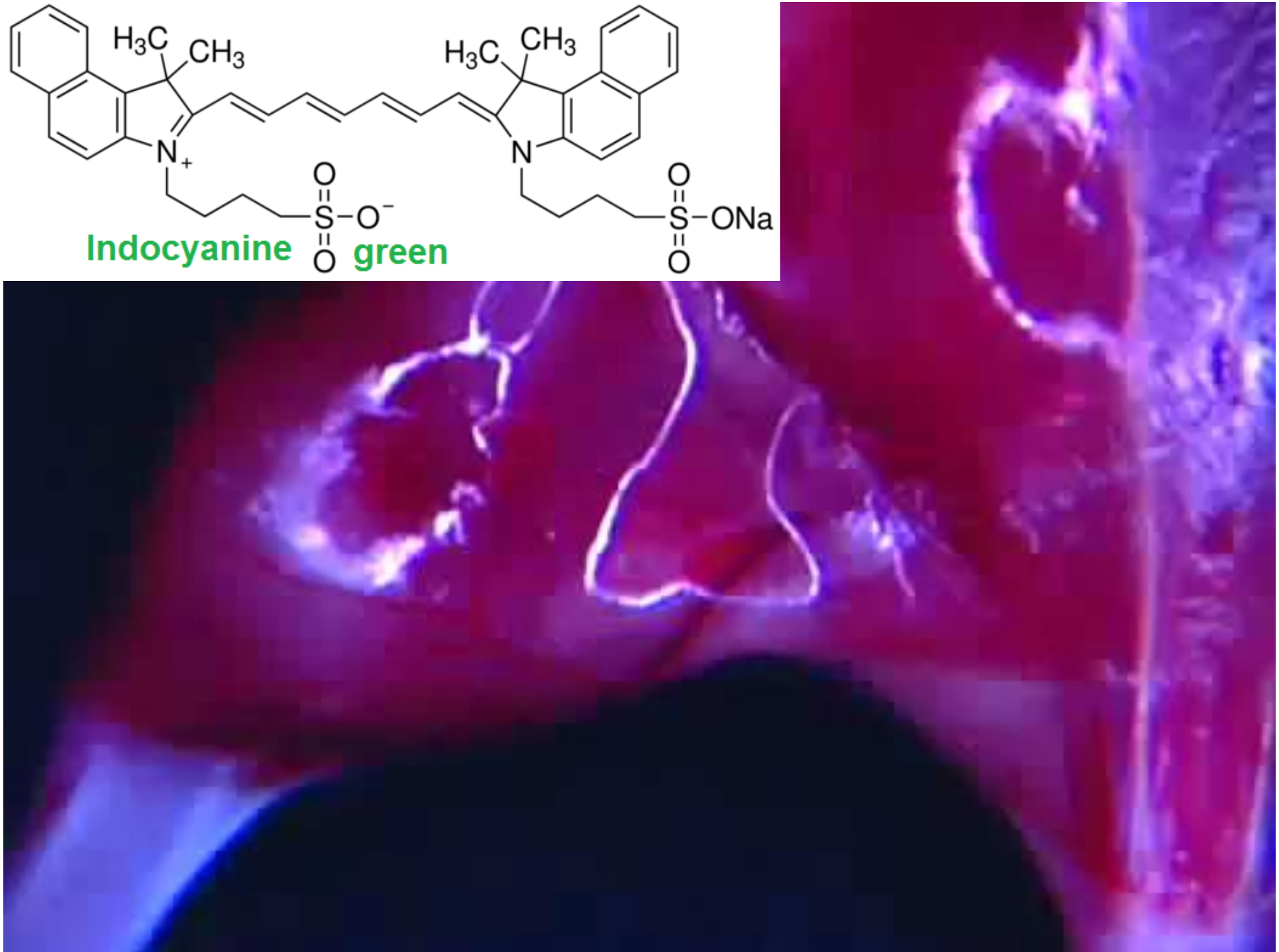
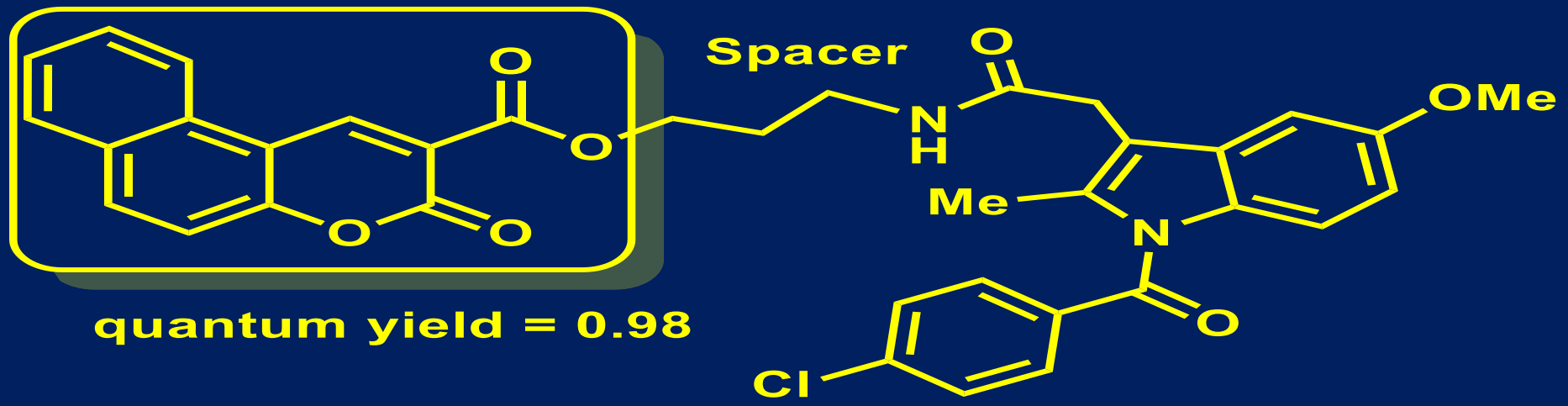
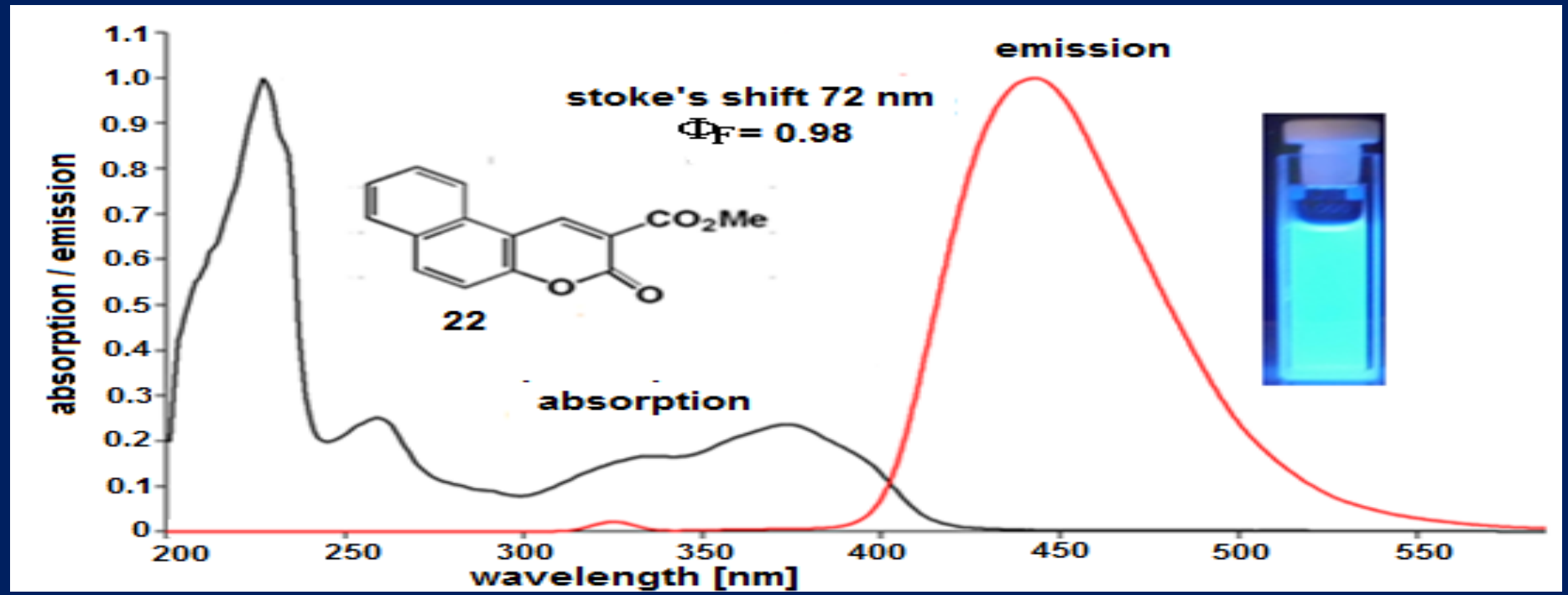

Normal cell
Division
Cancer cell
Cancer cell
inflammatory cells
(Cycloxygenase-2 enzyme)
(COX-2)


HN
H
N
O
O
CO2
N
O
MeO
Me
N
O
Cl


H3C CH3
H3C CH3
N+
N
O
S
O−
O
O
S
ONa
O
Indocyanine green



quantum yield = 0.98



N. A. Al-Masoudi, N. J. Al-Salihi, Y. A. Marich, T. Markus
J. Fluorescence 25, 1847 – 1854 **(2015)**

N. A. Al-Masoudi, N. J. Al-Salihi, Y. A. Marich, *J. Fluorescence 26*, 31 – 35 **(2016)**

- **Prostate Cancer Therapy**

Cell Lines of Prostate Cancer

The most common PC cell lines are:

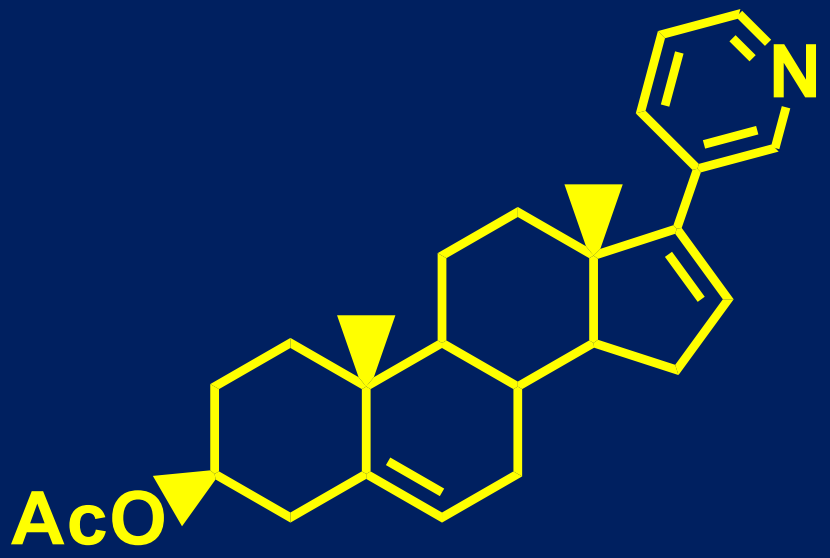
PC-93, PC-3, DU-135, TSU-Pr1, LNCaP, Cytochrome P450 17A1 (CYP 17A1).

Important antigens expressed by prostate cancer cells include prostate-specific antigen (PSA) (≤ 2.0 ng), which has been used both for screening for prostate cancer and for management of patients with the disease.

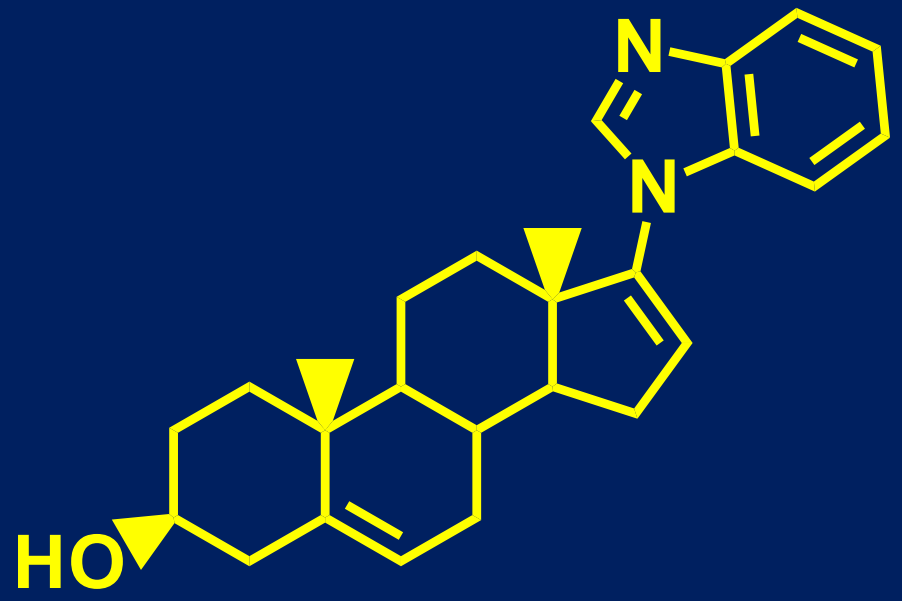
D. M. Peehl, *Cancer Suppl.* 1995, *75*, 2021-2026.

CYP 17A1 Inhibitors for treatment of PC

Cytochrome P450 17α-hydroxylase, C17,20-lyase (CYP17) is at the crossroads of androgen and corticoid biosynthesis and has become a valuable target in prostate cancer (PC) treatment.

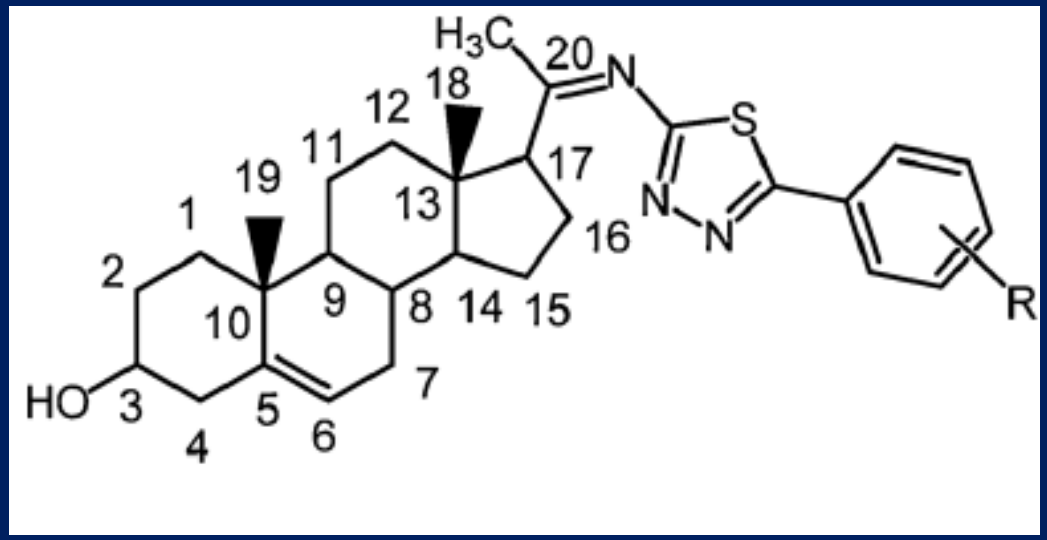


Abiraterone acetate

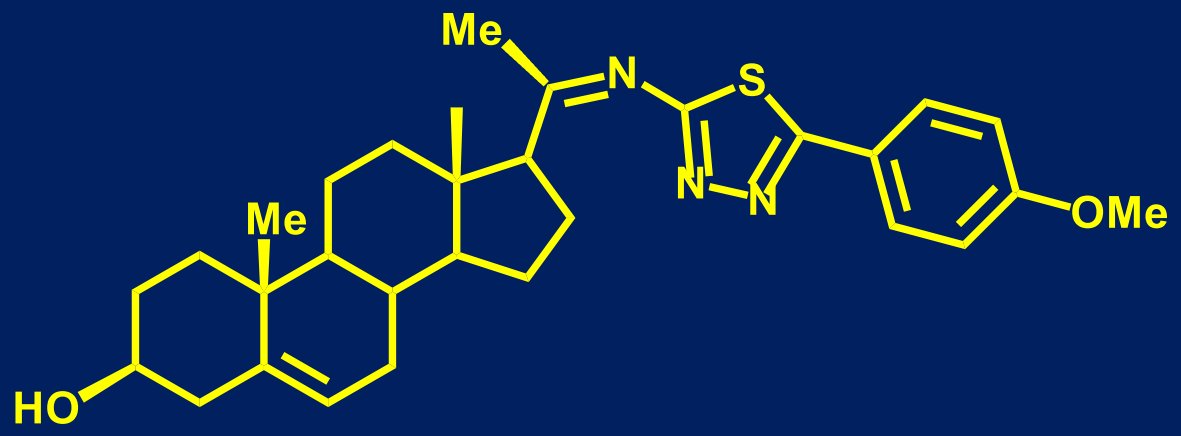


Galeterone TOK-001

Our recent work on CYP 17 Inhibitors



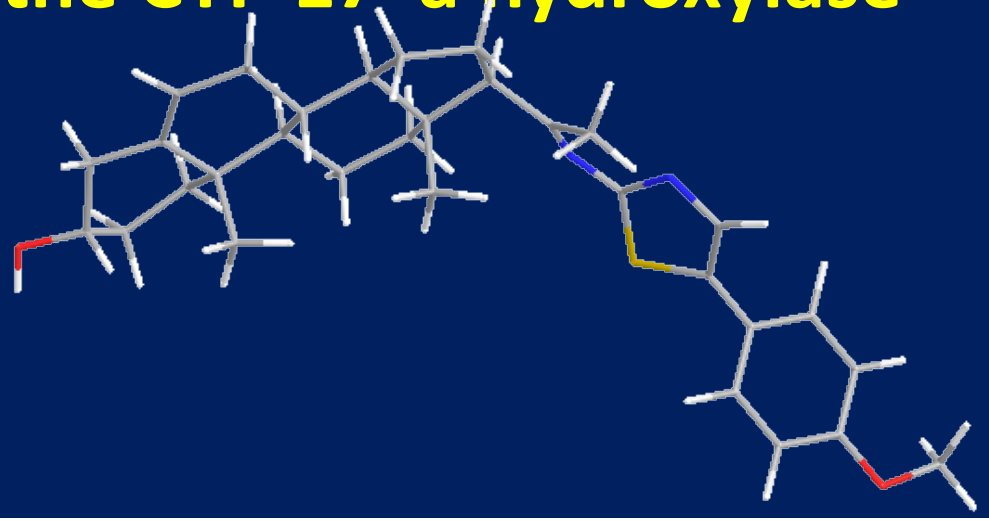
	R
6, 11	H
7, 12	4-OMe
8, 13	4-Br
9, 14	4-Cl
10, 15	4-NO_2

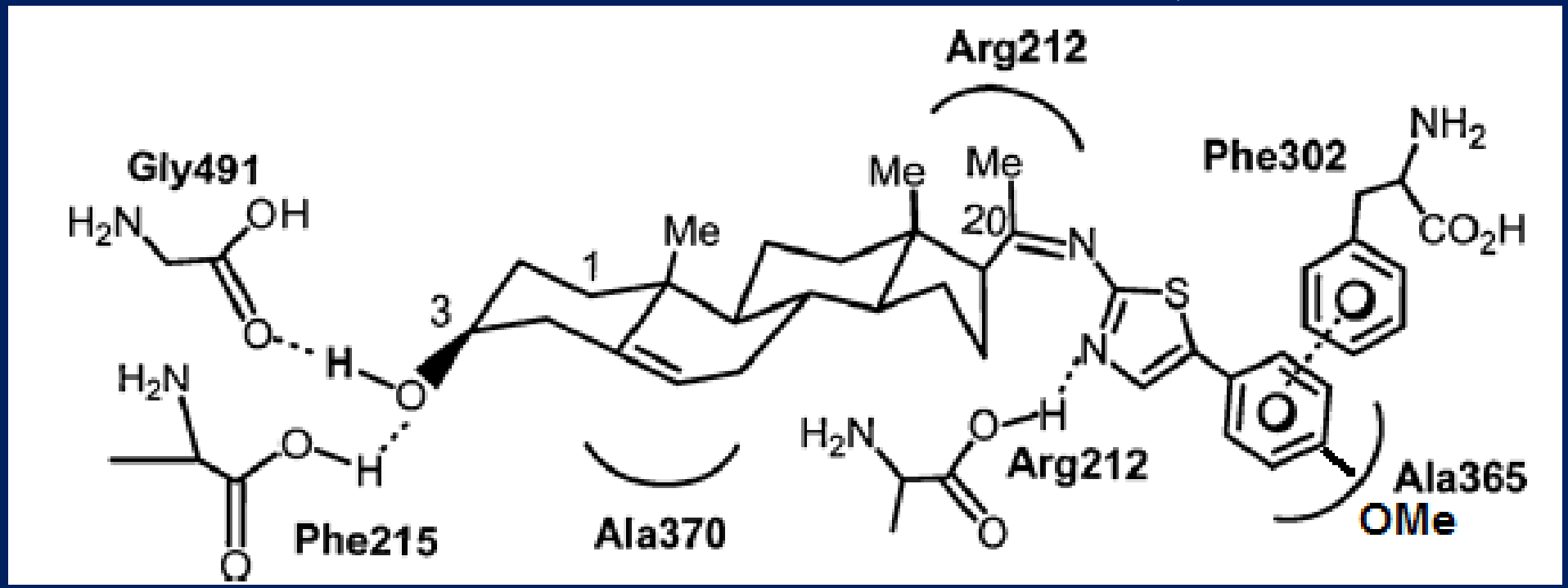


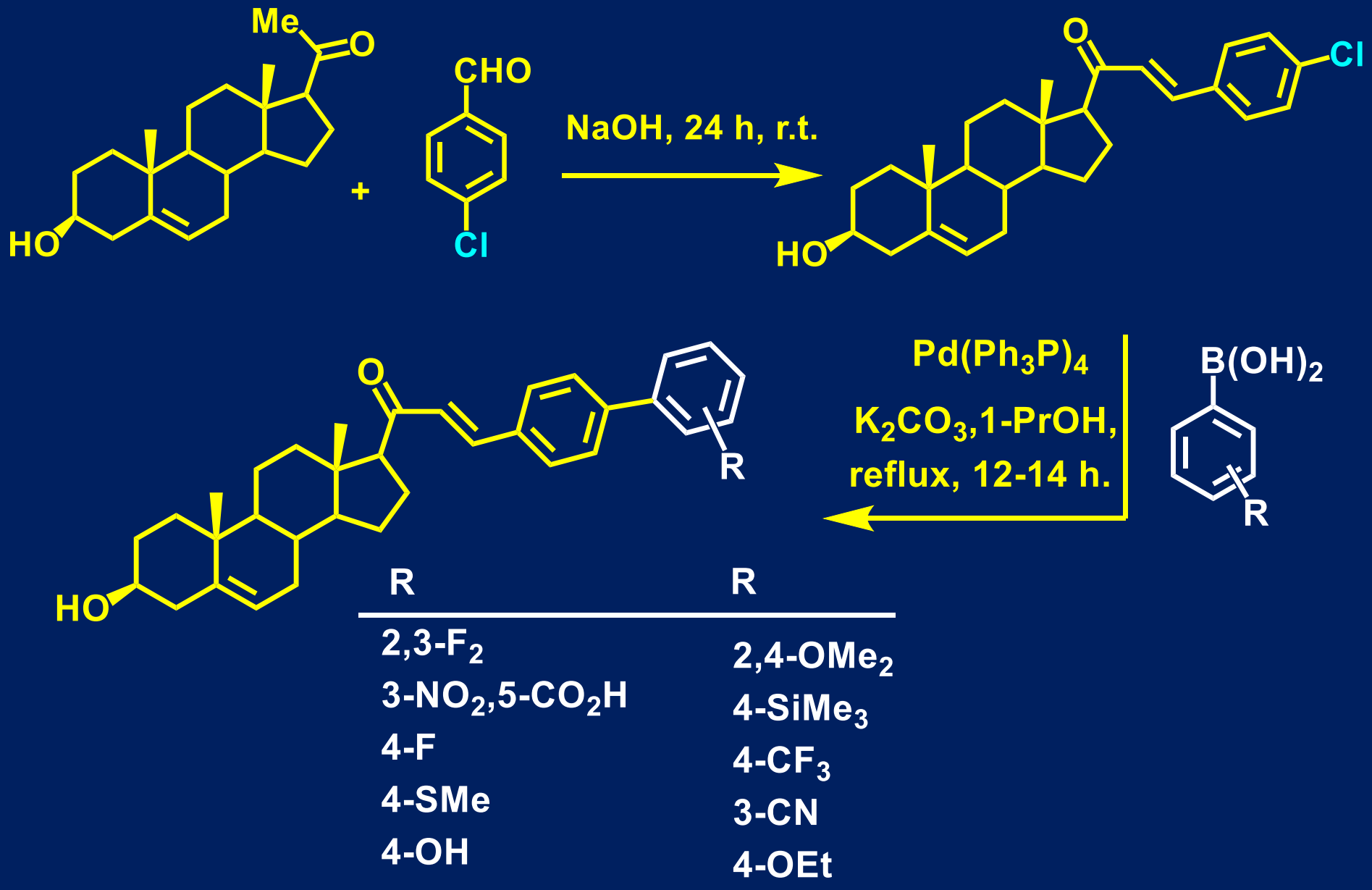
IC_{50} = 2.5 ± 0.0 μM, Inhibition % = 78.6 ± 3

N. A. Al-Masoudi, D. S. Ali, B. Saeed, R. W. Hartmann, M. Engel, S. Rashid, B. A. Saeed, ” *Archiv der Pharmazie-life Science* 2014, *347*, 896 – 907

Molecular Modeling Study of Thiazolyl- pregnenolone analogue with the amino acids of the CYP 17 a hydroxylase







N. A. Al-Masoudi, R. A. Kadhim, N. A. Abdul-Rida, B. A. Saeed, M. Engel, *Steroids* 2015, *101*, 43 – 50

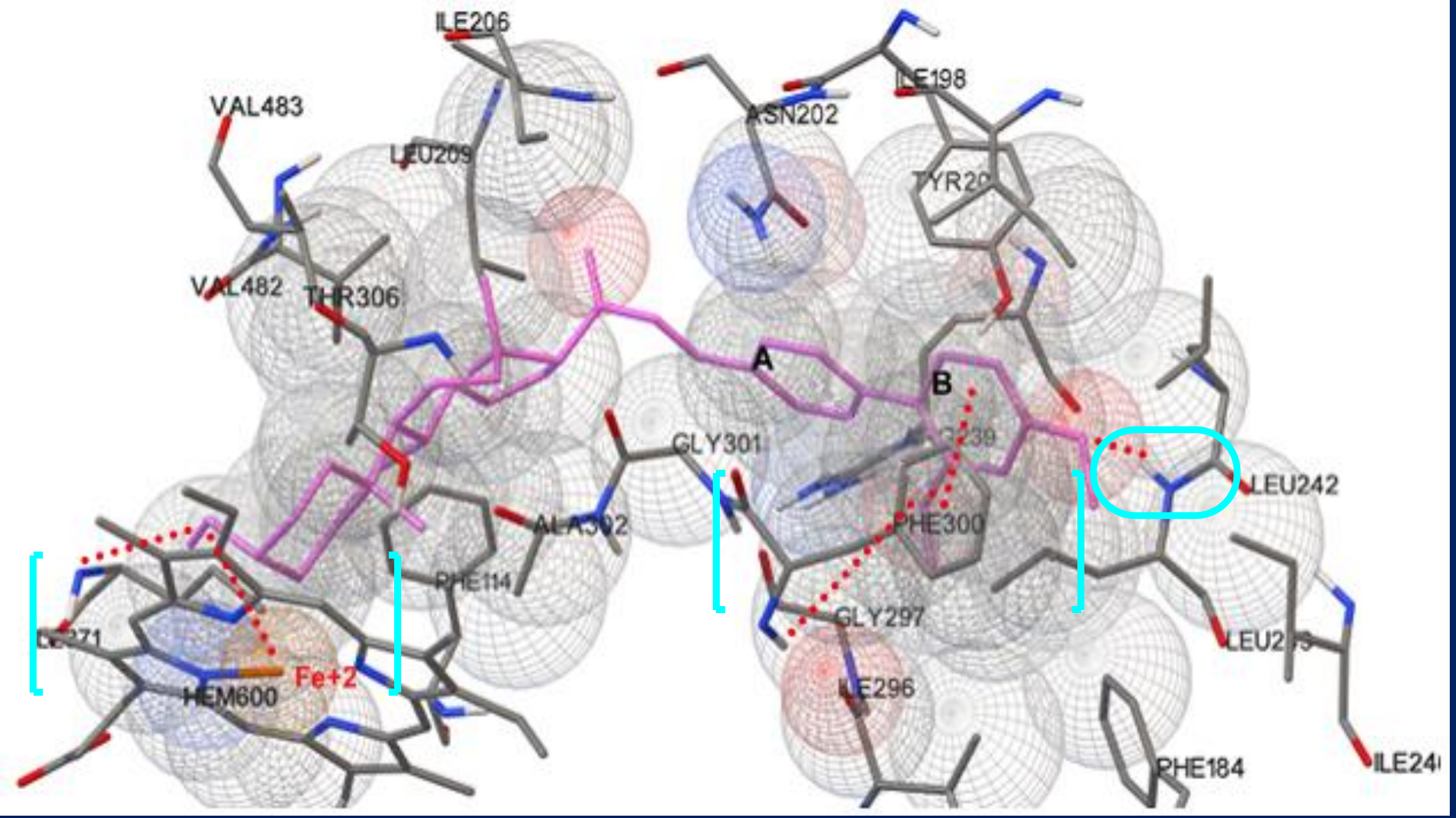
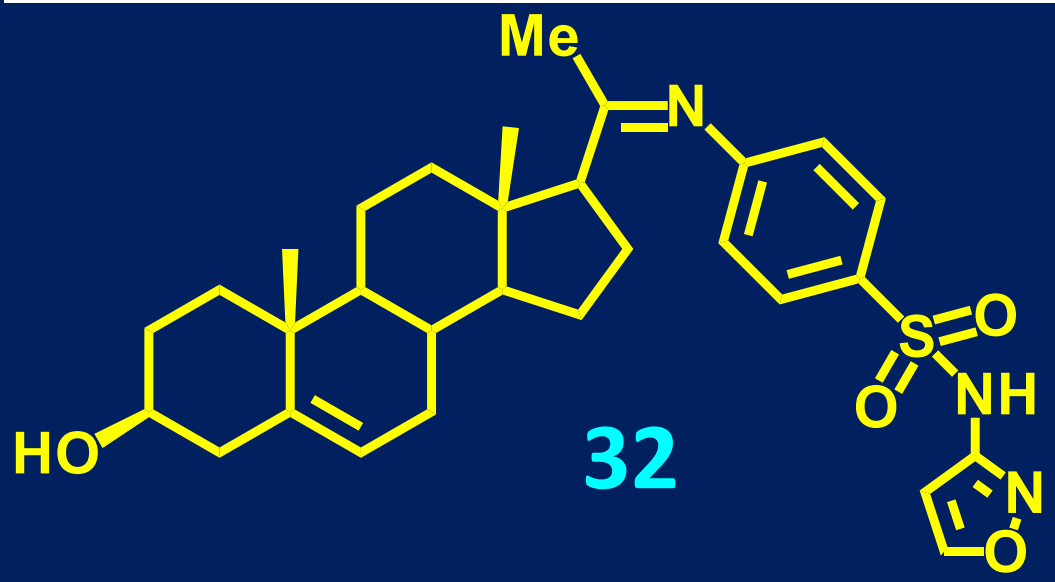


Fig. Computer model of human CYP17 (pdbid: 3ruk) with 21. Complexation of heme-Fe^{+2} (*brown*) with lone pair of oxygen atom of OH group at C-3. Three hydrogen bonds are shown: Ile371 with OH at C-3; Gly297 and Leu242 with 2'' and 4''-OMe groups of phenyl moiety (B). In addition, a hydrophobic interaction between phenyl group B and Phe300 of the CYP17 enzyme amino acid residues is observed.

Inhibition activity of CYP17 hydroxylase by pregnenolone derivatives.

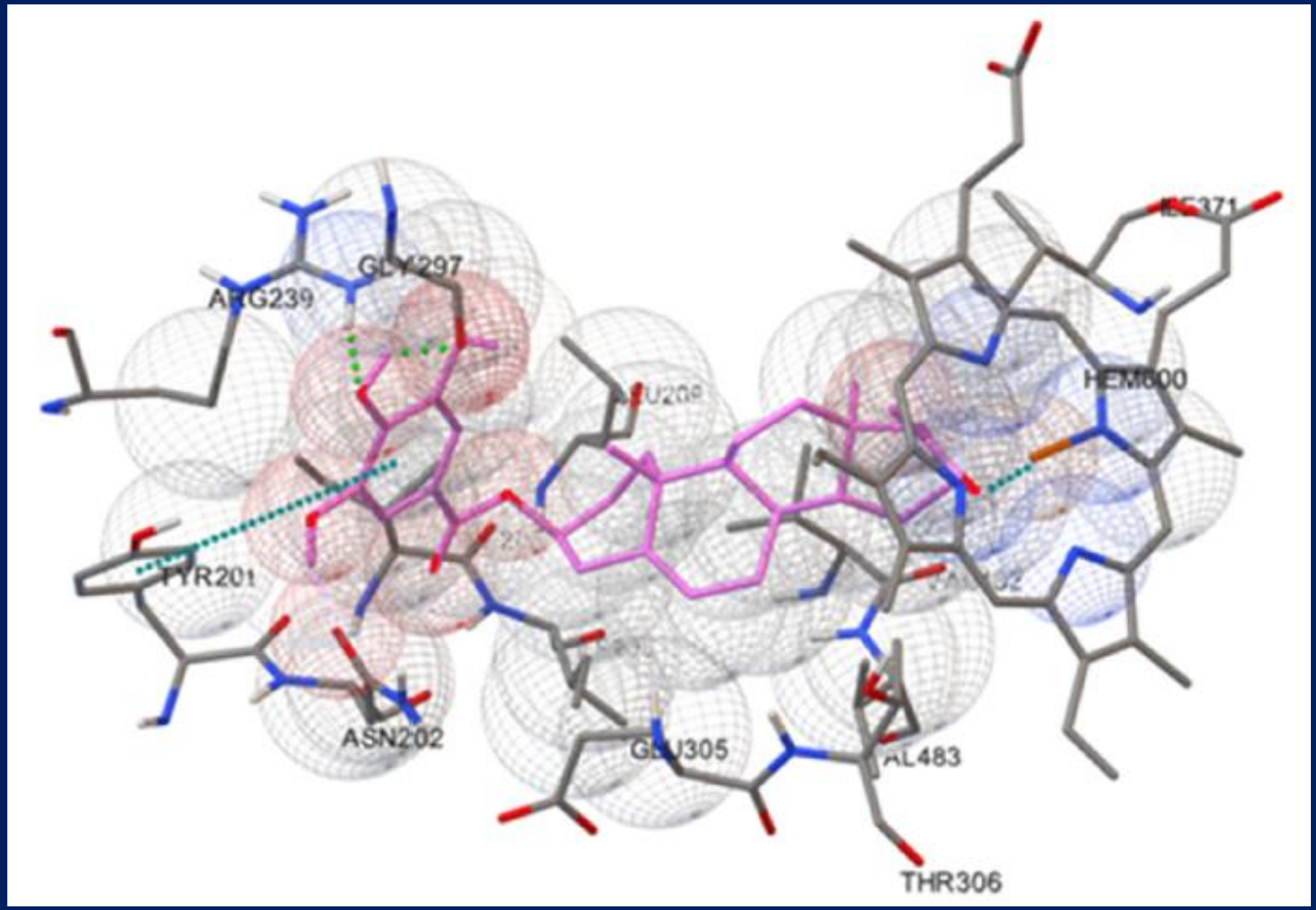
Compd.	Inhibition [%][a]	IC_{50} [μM][b]	Compd.	Inhibition [%]	IC_{50} [μM][b]
16	53.44	34.2	**26**	62.52	18.59
17	49.34	nd	**27**	81.99	2.38
18	55.23	nd	**28**	78.61	3.29
19	43.34	nd	**29**	16.27	nd
20	49.21	nd	**30**	56.23	nd
21	40.02	nd	**31**	48.37	26.8
22	39.38	nd	**32**	81.78	2.11
23	8.37	nd	**37**	83.21	1.29
24	57.10	19.8	**38**	45.50	24.7
25	78.84	3.11	**39**	41.34	22.2
ABT[c]	85.38	0.072	**40**	43.27	nd



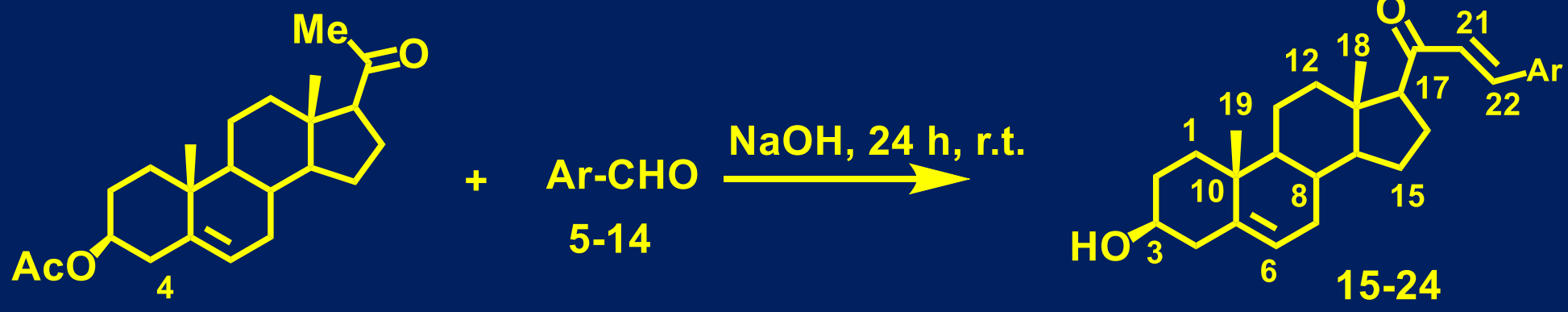
32

IC_{50} = 2.11 μM as inhibitor for CYP 17 hydroxylase

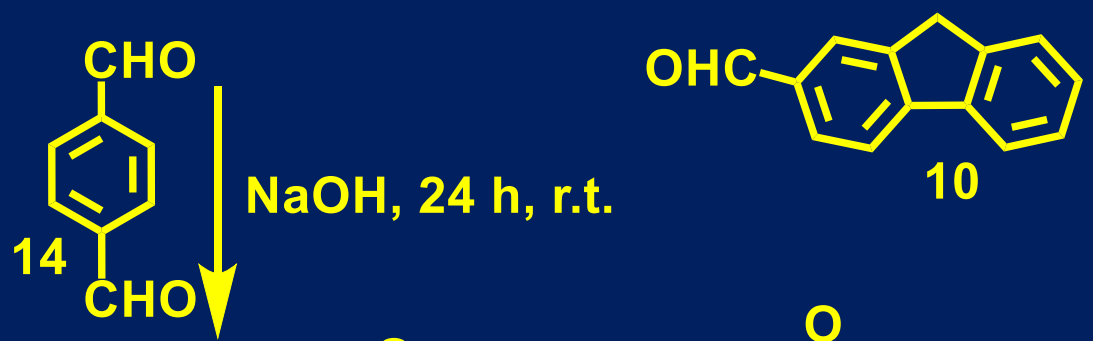
Binding of Steroid 32 with Fe^{+2} & amino acids of hydroxylase enzyme



New chalconyl steroids, their pyrazoline and oxime analogues for treatment of prostate cancer

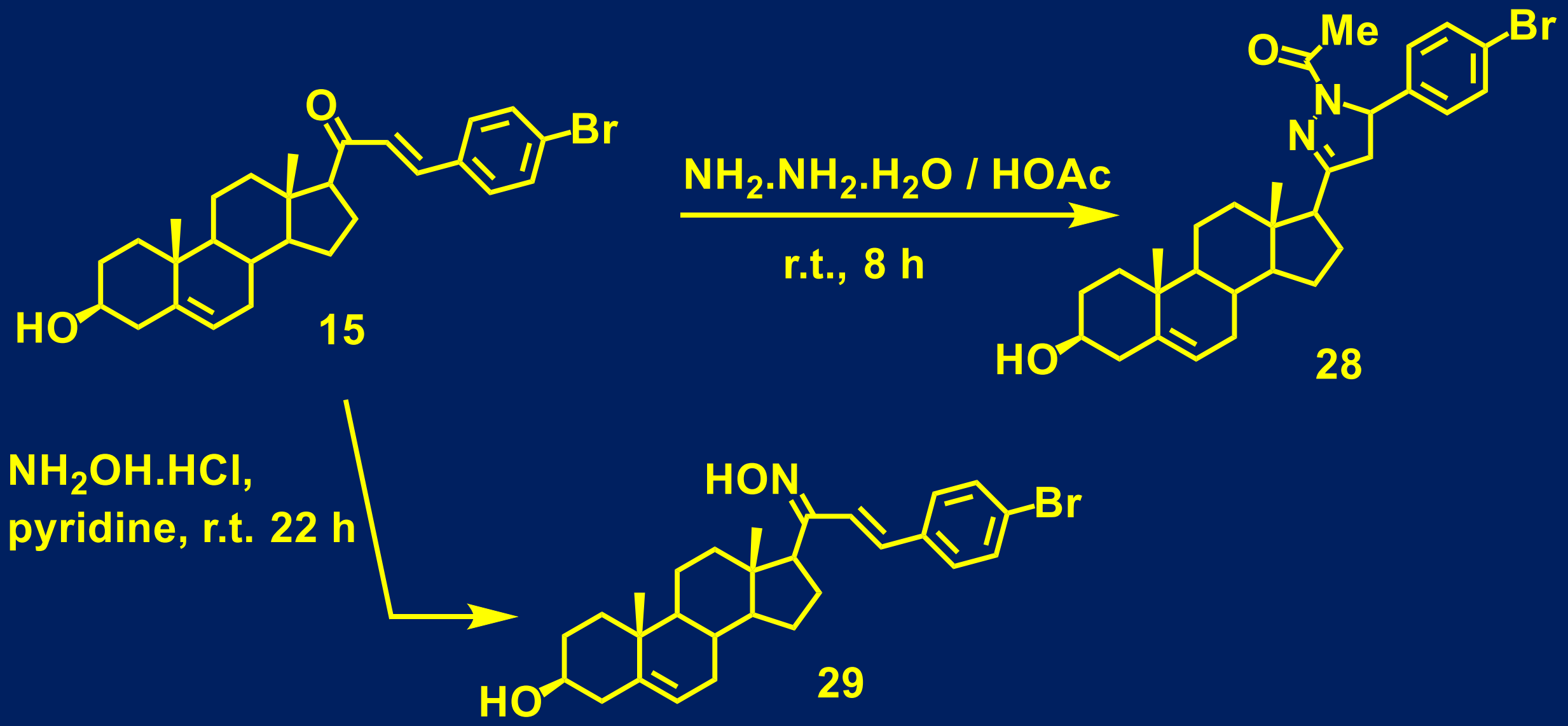


15-24

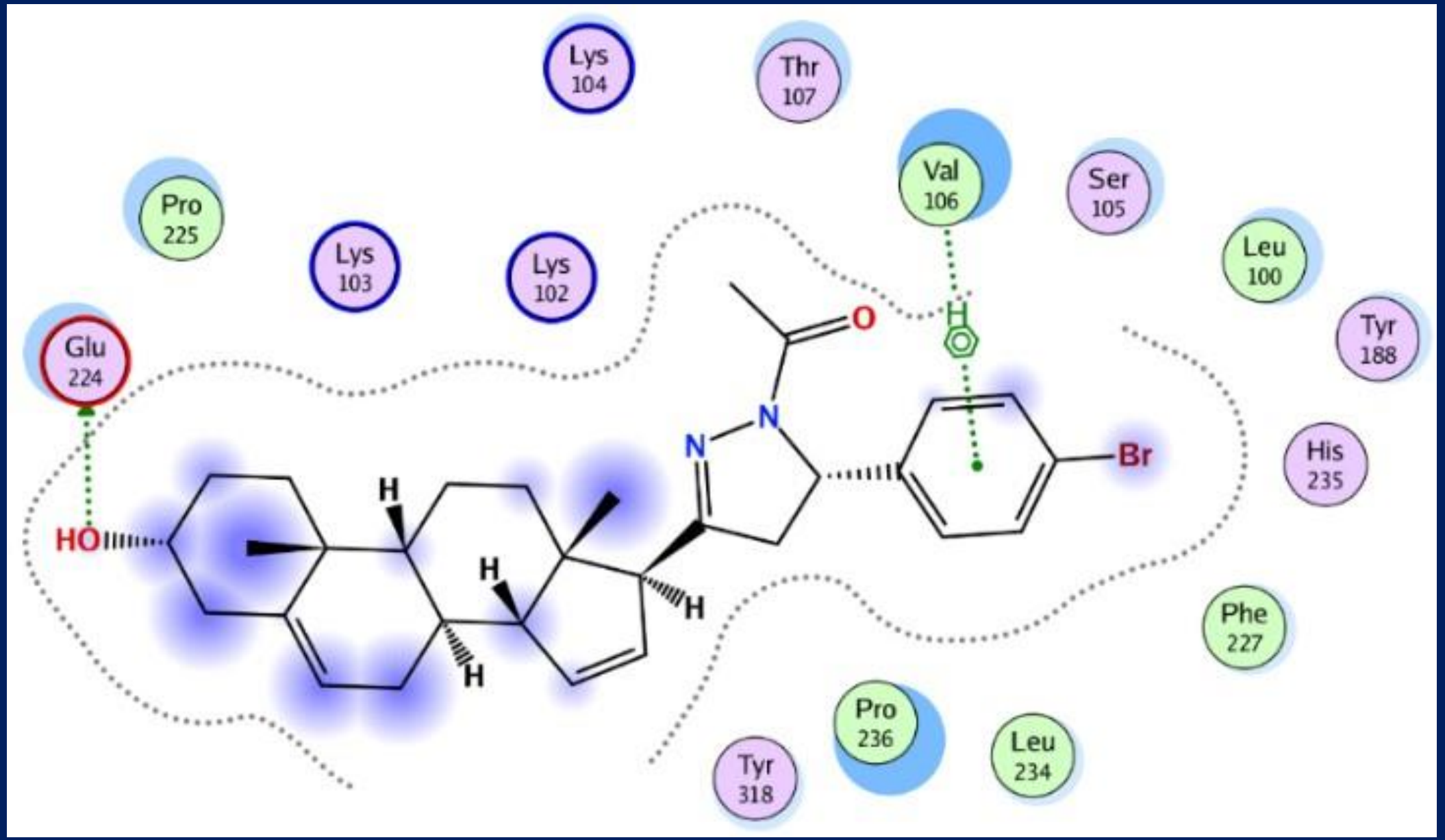


	Ar
5,15	4-Br-C_6H_4
6,16	4-CF_3-C_6H_4
7,17	4-Me-C_6H_4
8,18	5-Br-2-OH-C_6H_3
9,19	2-Cl-4-$(NMe)_2$-C_6H_3
10,20	2-(9*H*-fluorene)
11,21	2-furan
12,22	2-thiophene
13,23	2-CO_2H-C_6H_4

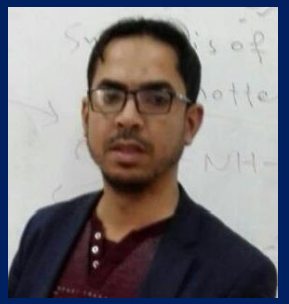
W. A. Al-Masoudi, **N. A. Al-Masoudi,*** B. A. Saeed, R. Winter, C. Pannecouque, ***Serb. J. Chem.*** ***accepted*****, 2019**


O
Br
HO
15
$NH_2.NH_2.H_2O$ / HOAc
r.t., 8 h
Me
O
N
N
Br
HO
28
$NH_2OH.HCl$,
pyridine, r.t. 22 h
HON
Br
HO
29

Molecular Docking Study of the Steroidal pyrazole



New Steroids for treatment of prostate cancer (PC-3 & LNCAP-A1): Synthesis and QSAR



(Mnoxprol)

NjNAA-22

% Cytotoxicity = 79.8% against prostate cancer (**PC-3 cell line**)

= 64.7% against prostate cancer (**LNCaP-A1 cell line**)

< 1% against prostate cell (**RWPE1**)

A. Farhan, N. A. Abdul-Rida, N. A. Al-Masoudi, W. A. Al-Masoudi, Z. A. Shahab, ***Patent, submitted,*** **2019**

NjNAA-18

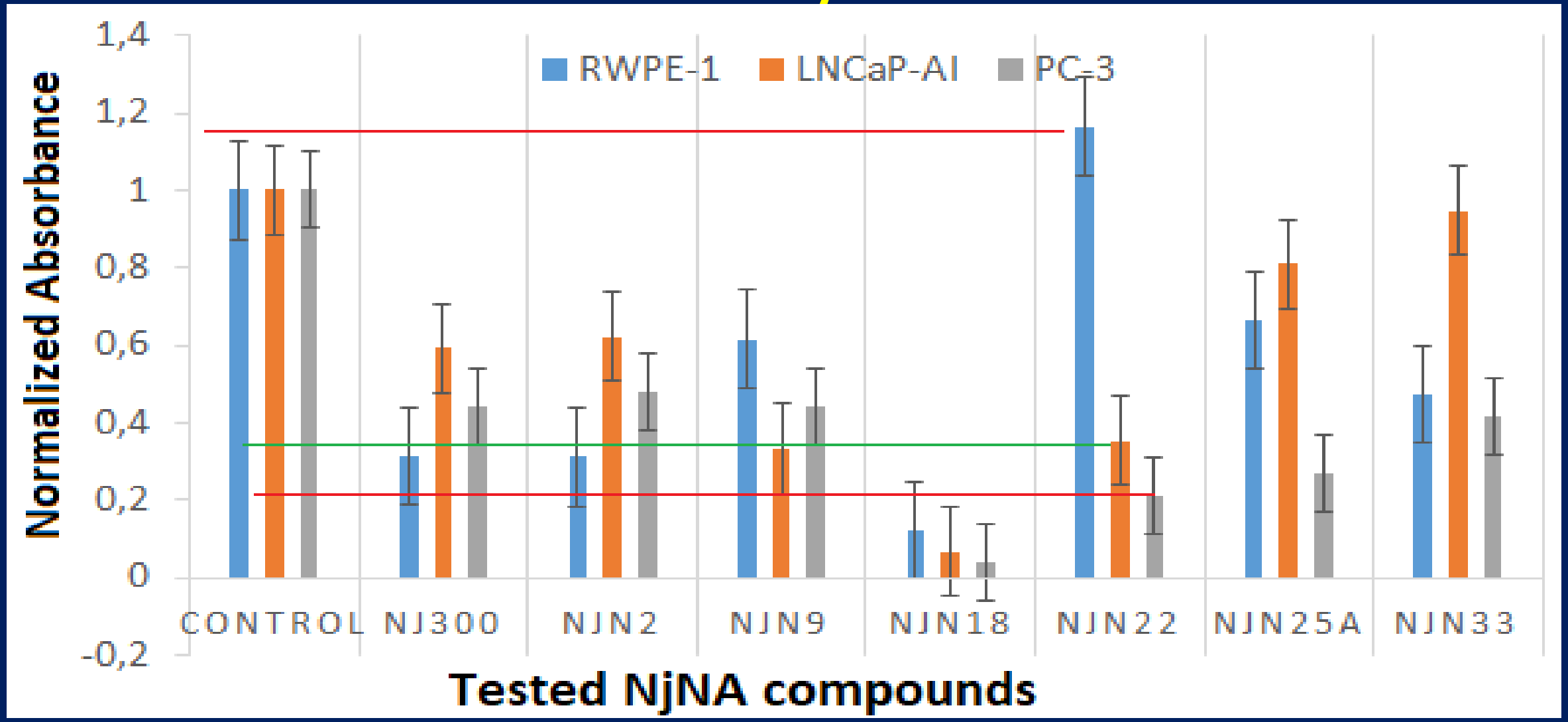
N-(4-(4-((4-(4-Aminophenoxy)phenyl)sulfonyl)phenoxy) phenyl)-3-((5-pregnen-3b,17-diol-15-yl)thio)propan amid

% Cytotoxicity = 96.2% against prostate cancer (PC-3 cell line)

= 93.6% against prostate cancer (LNCaP-A1 cell line)

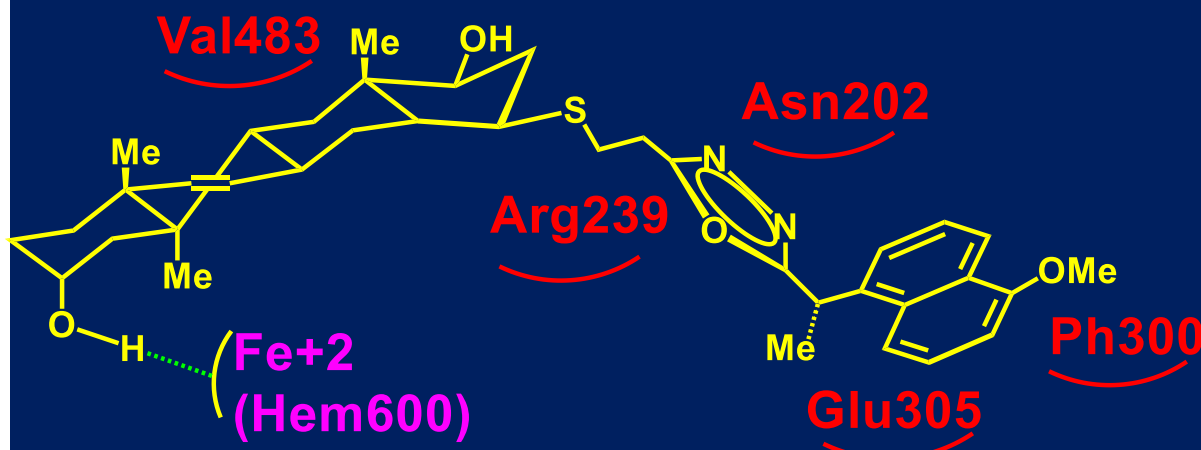
= 87.9% against prostate cell (RWPE1)

Optical density of tested NjNA steroids against PC cell lines by MTT assay

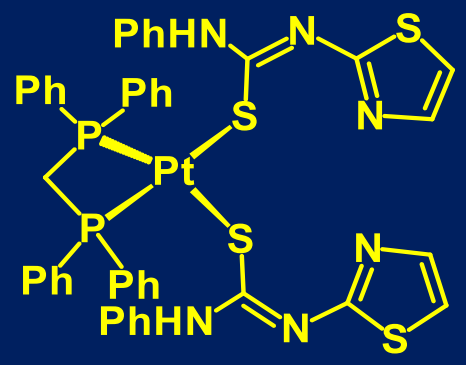


At concentrations: 1.0 & 10 μM, 72 h., N = 3x3

Molecular Docking Study of NjNA-22(14) with Prostate cancer

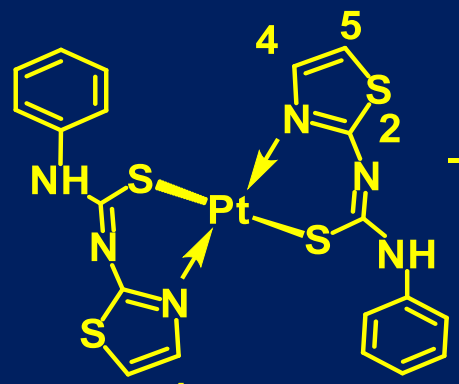


New Platinum(II) Complexes as Anti-prostate cancer



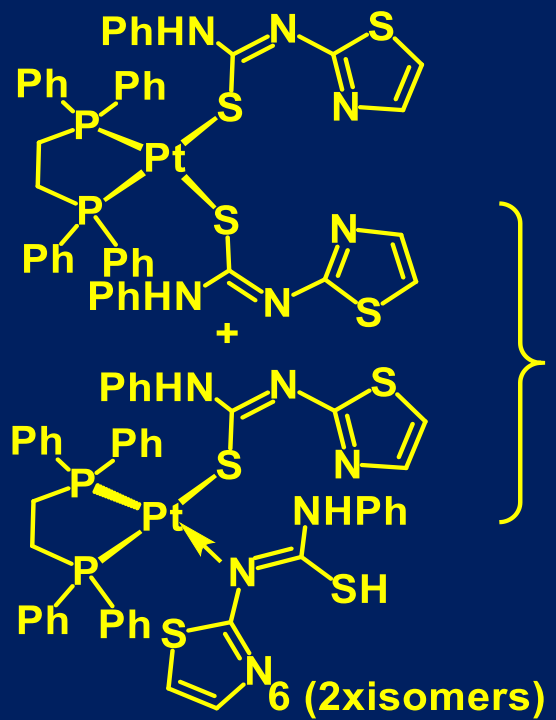
5

dppm



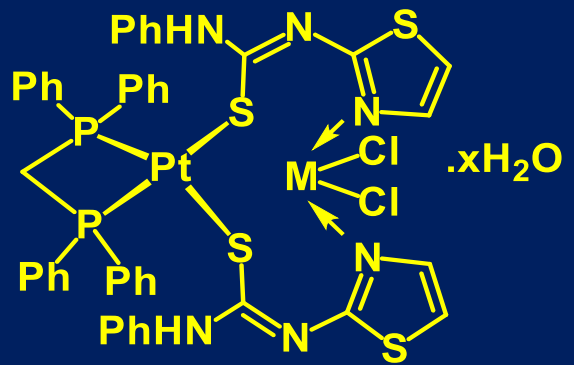
4

dppe



6 (2xisomers)

$MCl_2.xH_2O$



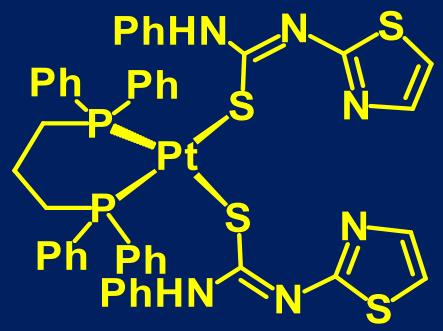
$.xH_2O$

8: M = Ni(II), X = 2

9: M = Pd(II), X = 0

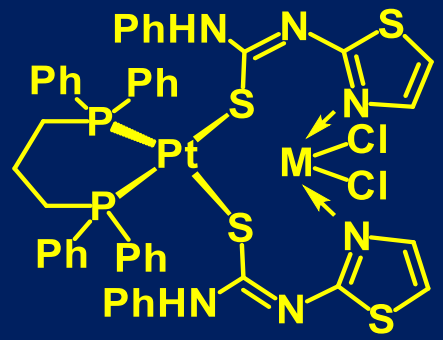
10: M = Pt(II), X = 0

dppp



7

$MCl_2.xH_2O$

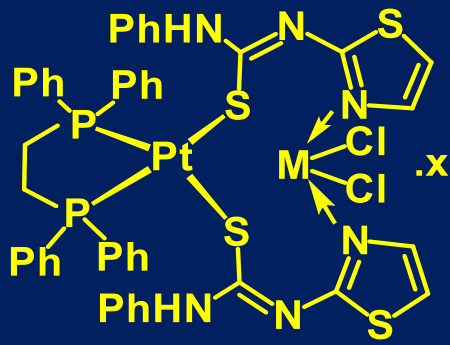


14: M = Ni(II)

15: M = Pd(II)

16: M = Pt(II)

$MCl_2.xH_2O$

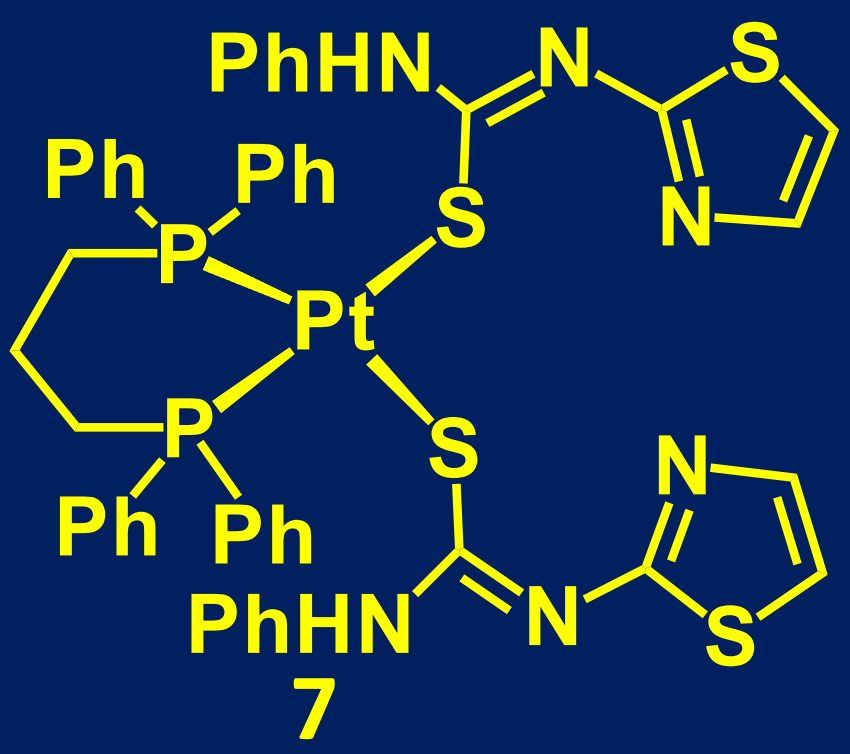


$.xH_2O$

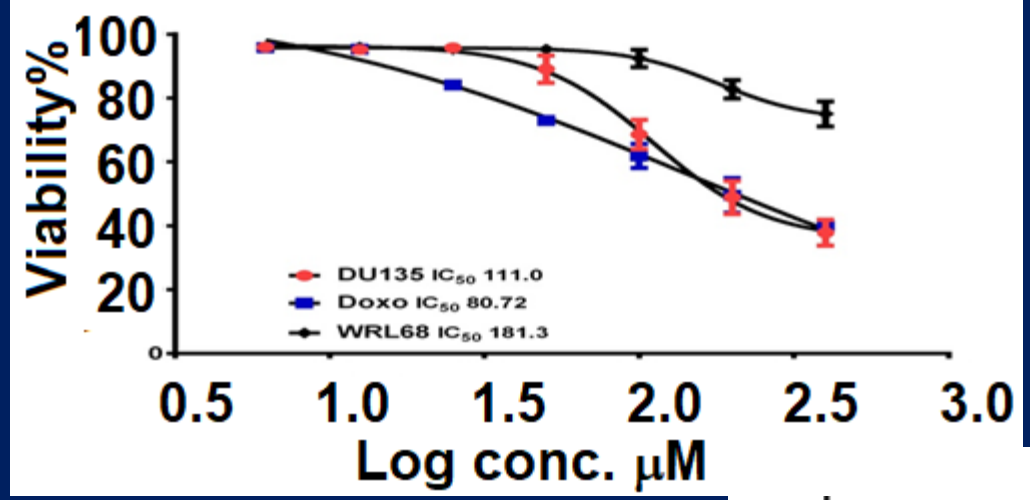
11: M = Ni(II), X = 2

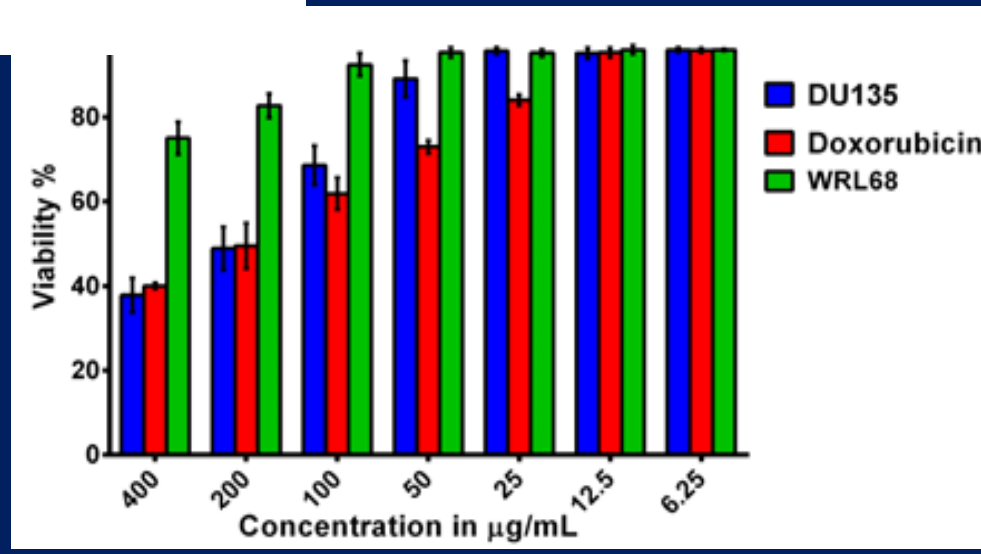
12: M = Pd(II), X = 0

13: M = Pt(II), X = 0



7





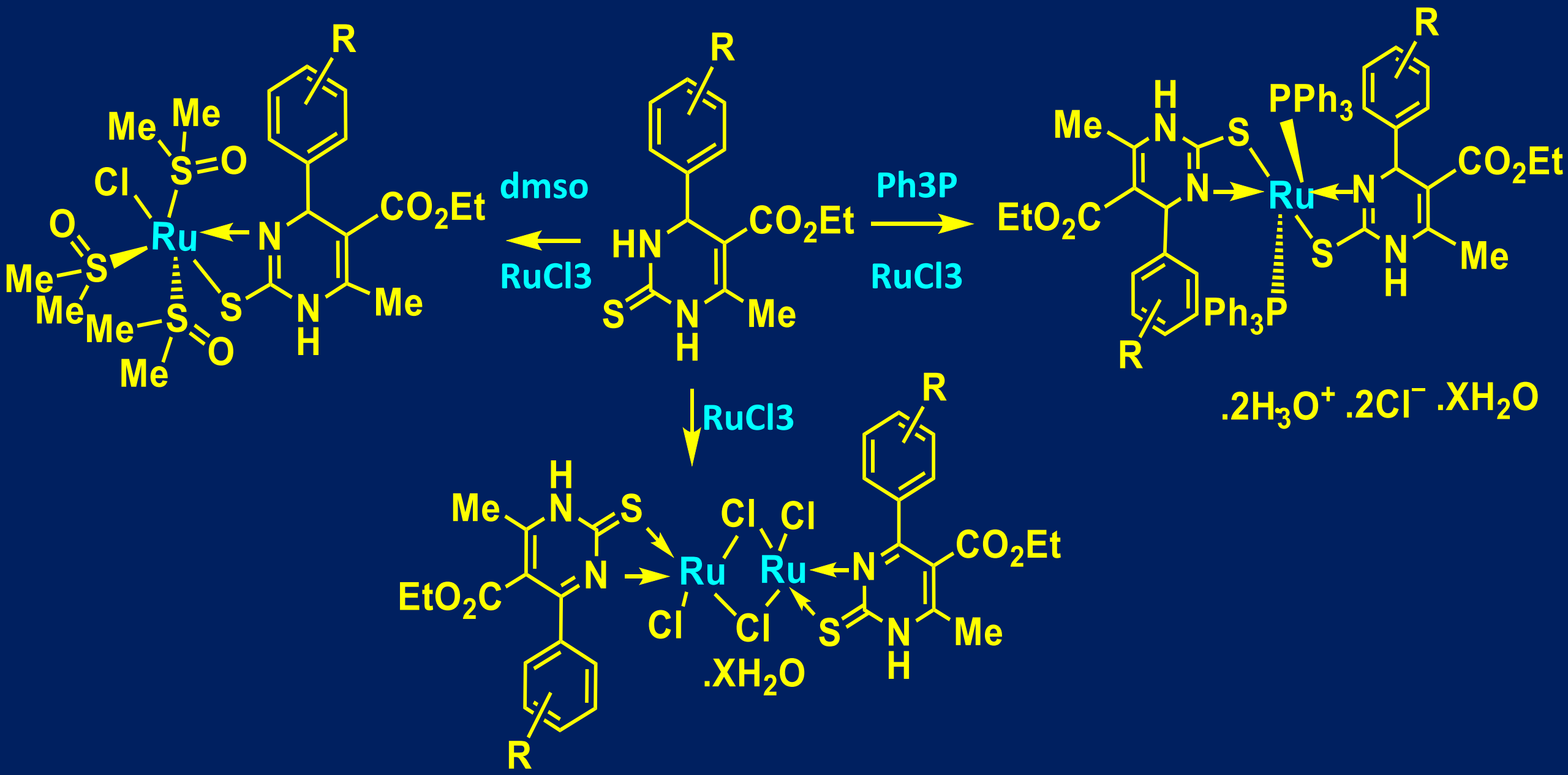
IC_{50} = 69.66 µM against breast cancer (MCF-7 cell line)

= 69.10 µM against prostate cancer (DU-135 cell line)

= 298.7 µM against healthy breast cell (WRL68)

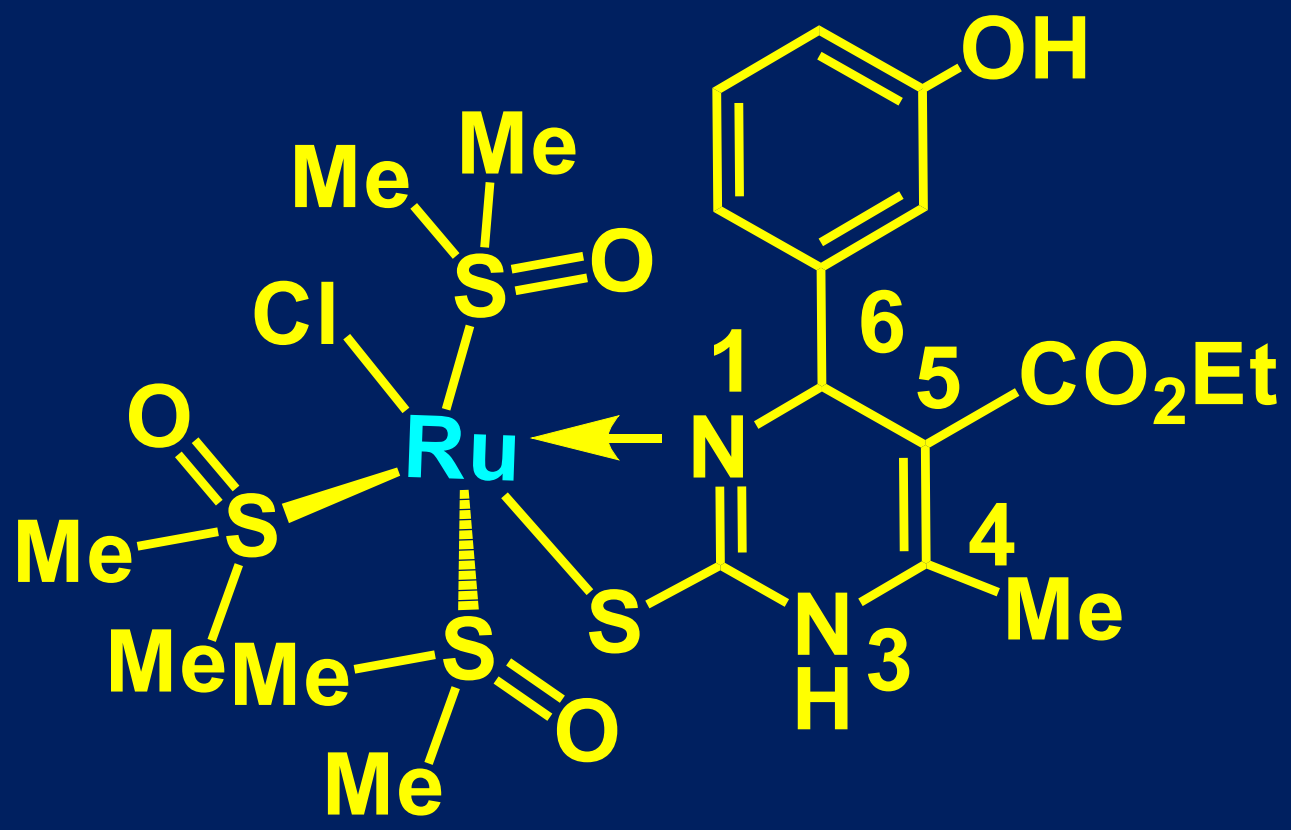
IC_{50} (Doxouribicine) = 80.72 µM against prostate cancer (DU-135 cell line)

A Ruthenium Complexes of Monastrol and its Pyrimidine



Cytotoxicity (CC_{50}) against MT-4 cell lines 0.21 µM

(For treatment of Leukemia)



$[RuCl(dmso)_3(N,S\text{-}L1)]$

Wasfi A. Al-Masoudi and Najim A. Al-Masoudi, *Phosphorus, Sulfur, Silicon & The Related Elements, 2019, in press. DOI:* org/10.1080/10426507.2019.1597362

Vitrakvi is the New Generation of Anticancer Drug

It is an inhibitor of **tropomyosin kinase receptors**

Dun, Lauren (27 Nov 2018). "FDA approves a new cancer drug targeted to genetic mutation,

OPEN ACCESS Freely available online

Vol. 7(10), e48208 (2012)

PLOS | ONE

Aspirin Inhibits Colon Cancer Cell and Tumor Growth and Downregulates Specificity Protein (Sp) Transcription Factors

Satya Pathi[1], Indira Jutooru[1], Gayathri Chadalapaka[1], Vijayalekshmi Nair[1], Syng-Ook Lee[2], Stephen Safe[1,2]*

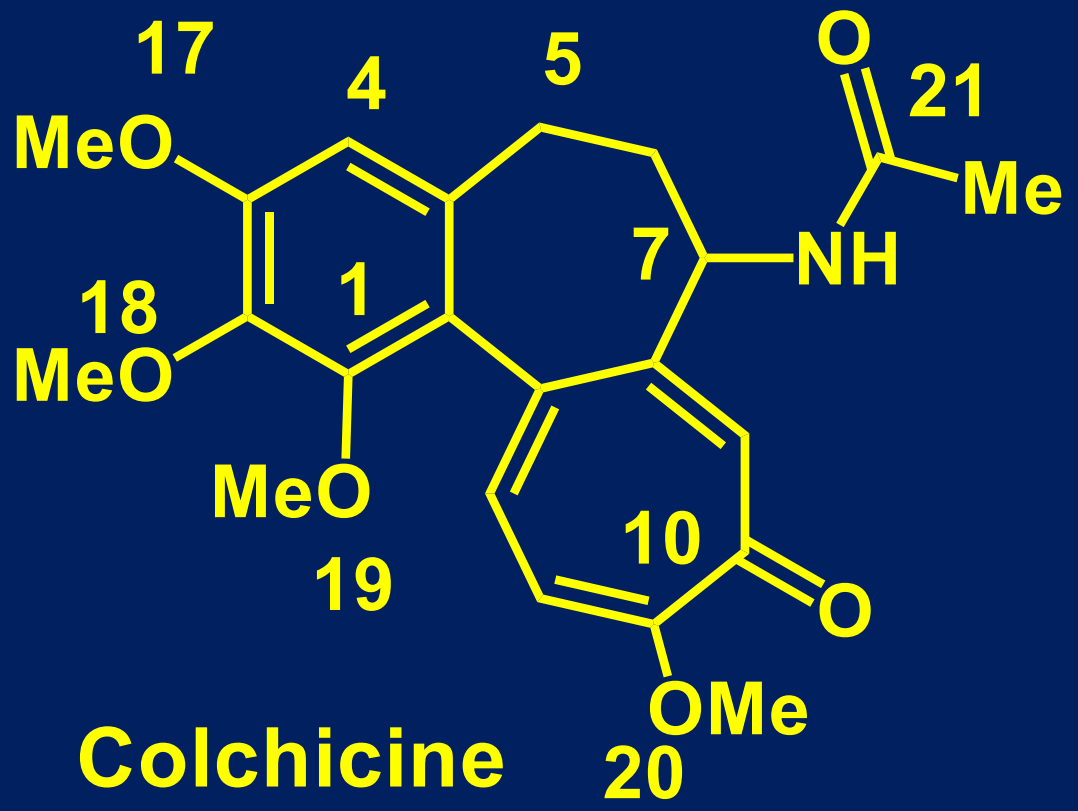
1 Department of Veterinary Physiology & Pharmacology, Texas A&M University, College Station, Texas, United States of America, 2 Institute of Biosciences and Technology, Texas A&M Health Science Center, Houston, Texas, United States of America

Abstract

Acetylsalicylic acid (aspirin) is highly effective for treating colon cancer patients postdiagnosis; however, the mechanisms of action of aspirin in colon cancer are not well defined. Aspirin and its major metabolite sodium salicylate induced apoptosis and decreased colon cancer cell growth and the sodium salt of aspirin also inhibited tumor growth in an athymic nude mouse xenograft model. Colon cancer cell growth inhibition was accompanied by downregulation of Sp1, Sp3 and Sp4 proteins and decreased expression of Sp-regulated gene products including bcl-2, survivin, VEGF, VEGFR1, cyclin D1, c-MET and p65 (NFκB). Moreover, we also showed by RNA interference that β-catenin, an important target of aspirin in some studies, is an Sp-regulated gene. Aspirin induced nuclear caspase-dependent cleavage of Sp1, Sp3 and Sp4 proteins and this response was related to sequestration of zinc ions since addition of zinc sulfate blocked aspirin-mediated apoptosis and repression of Sp proteins. The results demonstrate an important underlying mechanism of action of aspirin as an anticancer agent and, based on the rapid metabolism of aspirin to salicylate in humans and the high salicylate/aspirin ratios in serum, it is likely that the anticancer activity of aspirin is also due to the salicylate metabolite.

Anti-mitotic Activity of Aspirin compared to anti-mitotic drug Colchicine

Aspirin



Colchicine

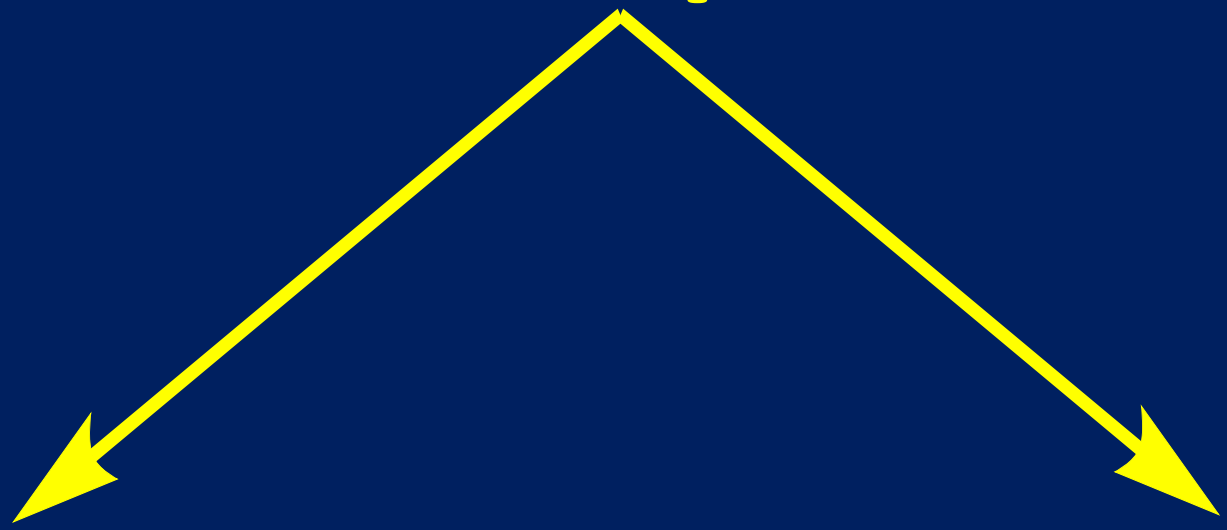
W. A. Al-Masoudi, N. A. Al-Masoudi, *in preparation*, 2019

Table 1. Effect of colchicine and aspirin on cell division

Material/cell division	Colchicine/cell	Aspirin/cell
Undivided cells	740	840
Devided cells	260	160
percentage of undivided cells	74%	84%
percentage of devided cells	26%	16%

N. A. Al-Masoudi, . W. A. Al-Masoudi, Zaynab A. Shahab, ***in preparation*, 2019**

Cancer Immunotherapy Developments



Enchancing the immune system and make it STRONGER

Using drugs that help inhibit the suppresive immune environment of the tumors

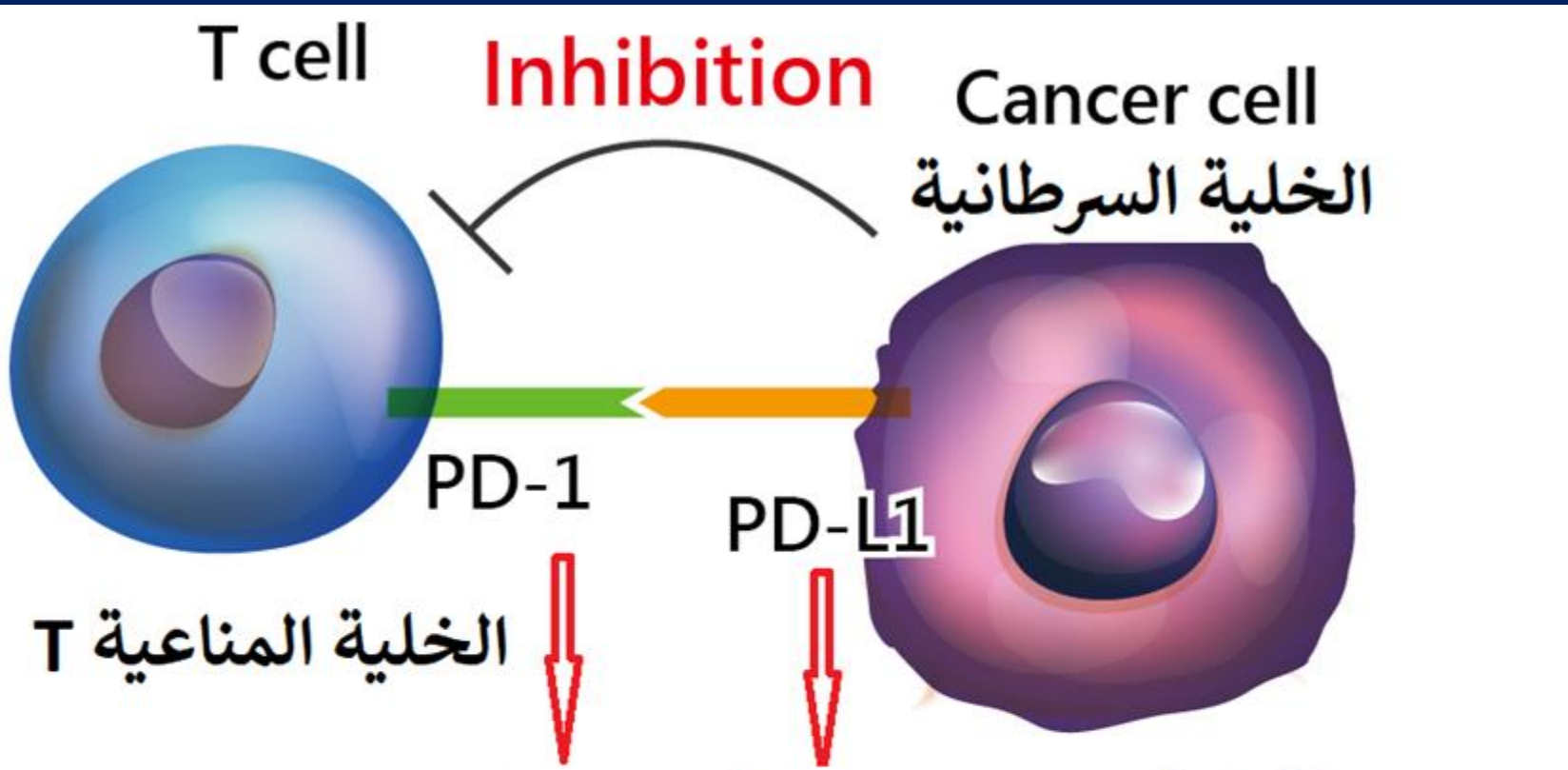
The Nobel Prize in Physiology or Medicine 2018 was awarded to James P. Allison and Tasuku Honjo" for their discovery of cancer therapy by inhibition of negative immune regulation (Immune checkpoint inhibitors)

Prof. J. P. Allison,
Immunology, born 1948,
Chair of Immunology at
University MD Aderson Cancer Center

Prof. T. Honjo
Immunology, born 1942,
Univ. of Kyoto, Japan

•Immune Checkpoint Inhibitor

•A type of drug that blocks certain proteins made by some types of immune system cells, such as T cells, and some cancer cells. These proteins keep immune responses in check and can keep T cells from killing cancer cells. When these proteins are blocked, the “brakes” on the immune system are released and T cells are able to kill cancer cells better. Examples of checkpoint proteins found on T cells or cancer cells include: PD-1 / PD-L1.

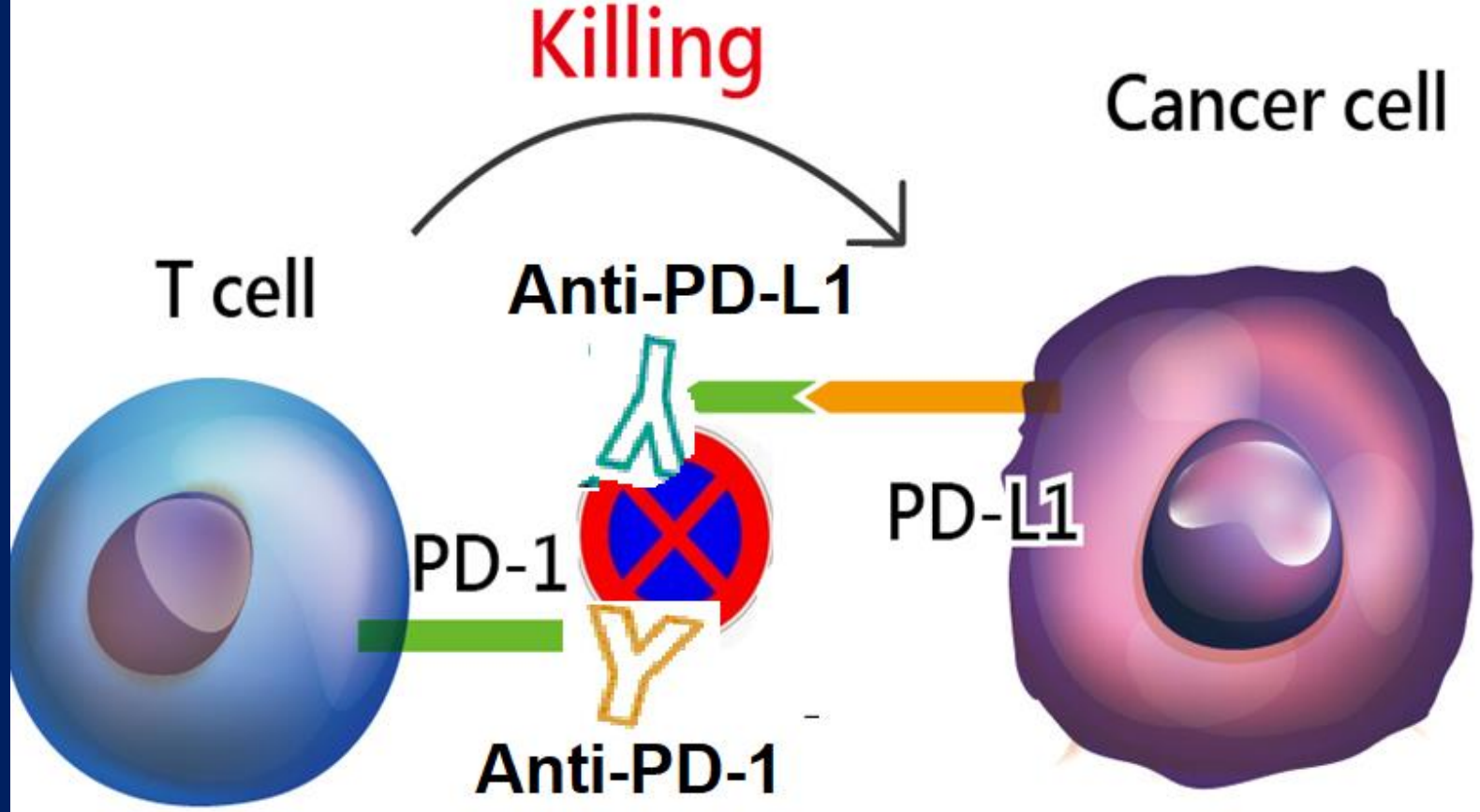


Programmed cell protein receptor-1

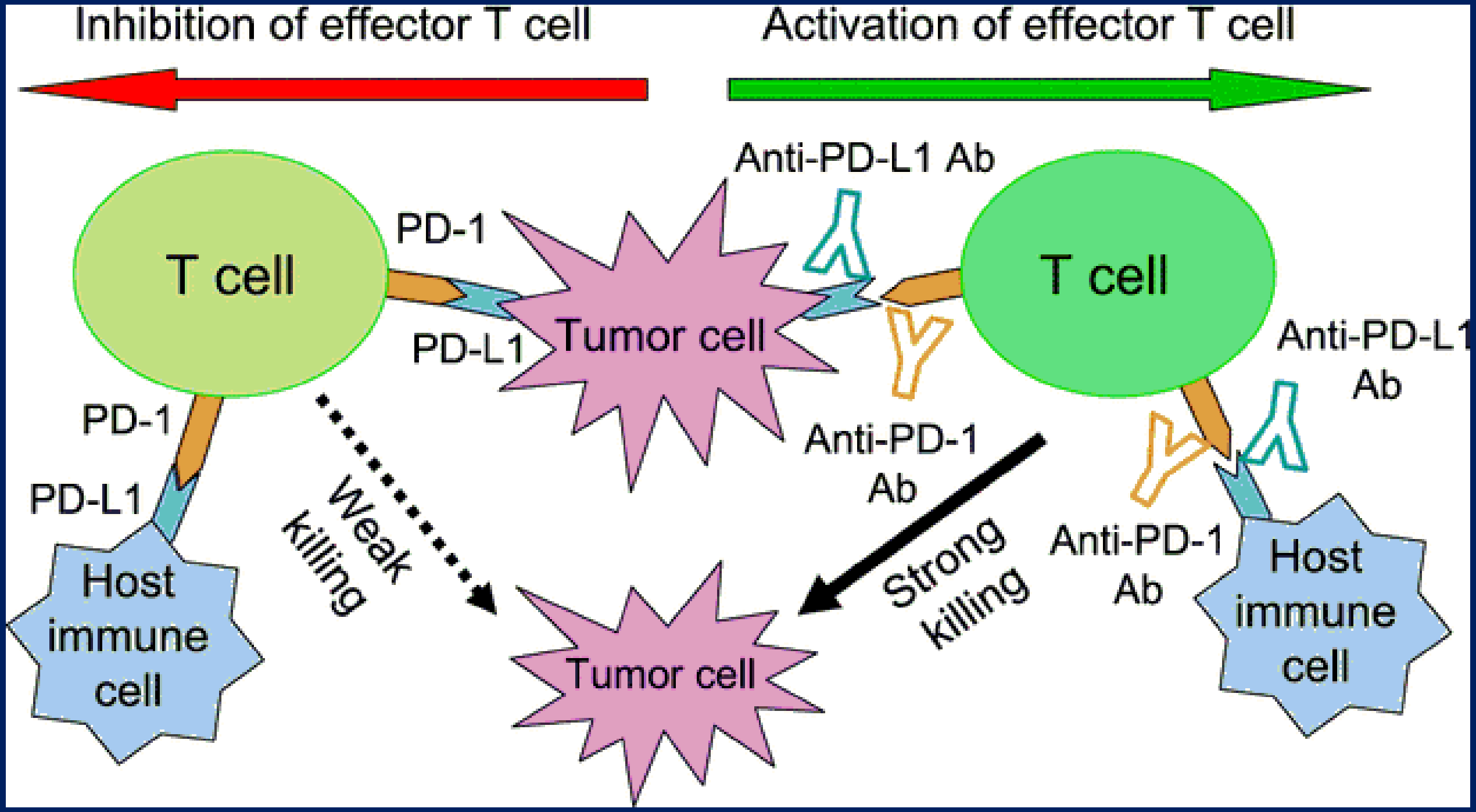
بروتين على سطح الخلية المناعية ومنظم لعمل الجهاز المناعي

Programmed cell death ligand -1 or (CD274 gene)

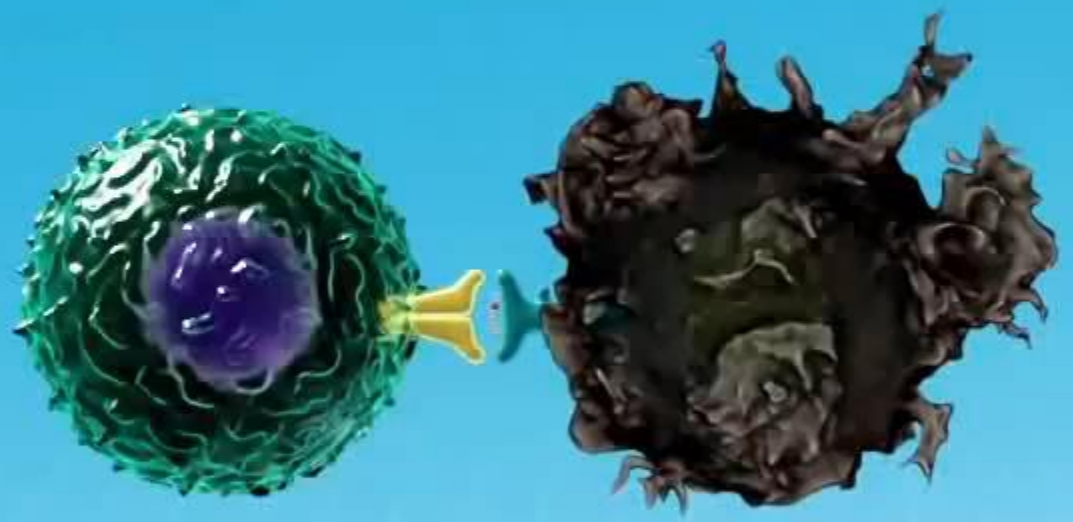
هي الجزيئة المثبطة للخلايا T والمتورطة في حماية الخلايا السرطانية من الهجوم المناعي

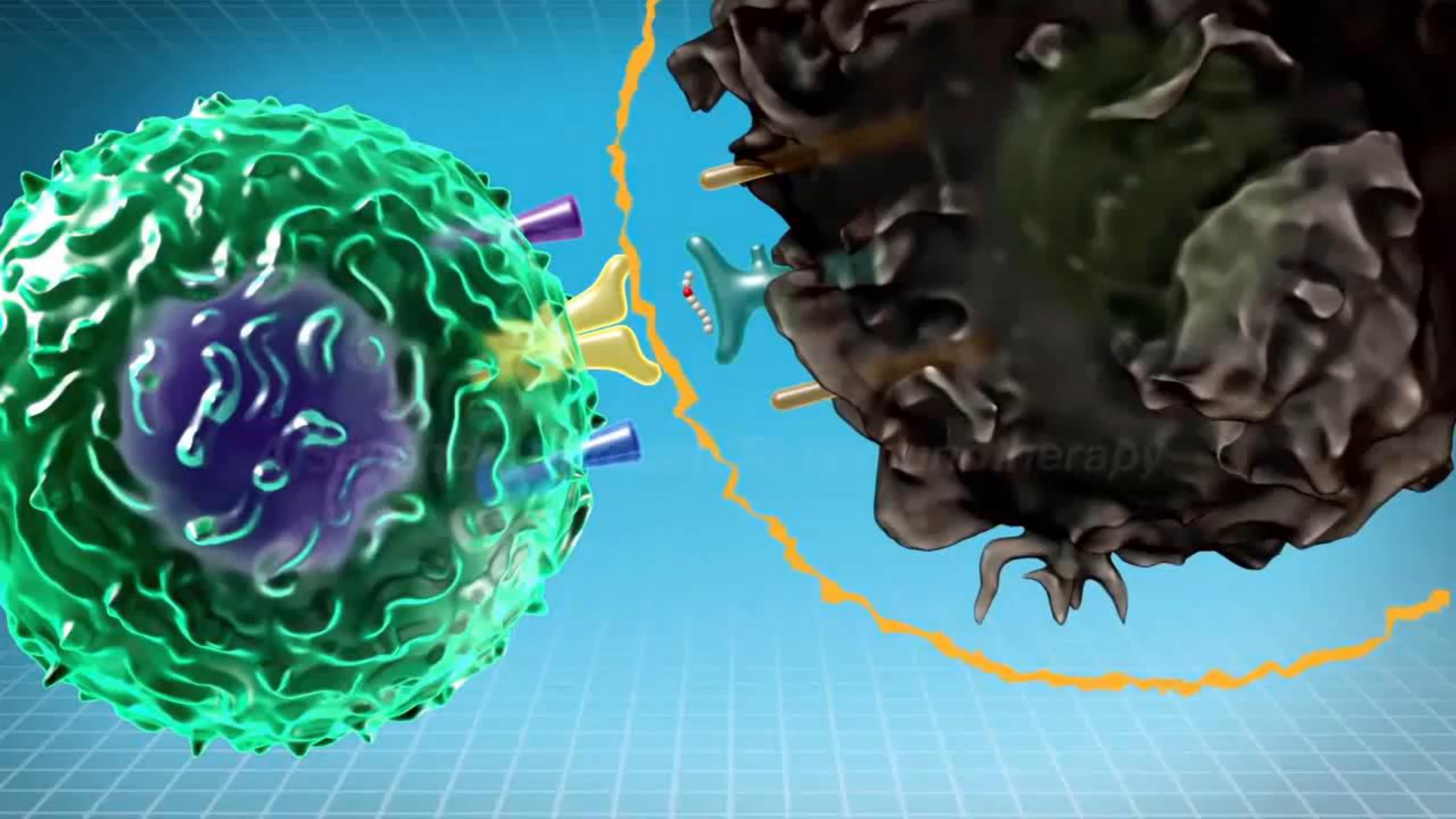


اذا تم منع التصاق PD-1 مع PDL-1 بواسطة inhibitor
فسينشط الجهاز المناعى وبالتالى ستهاجم الخلايا المناعية
النشطة الخلايا السرطانية وسيتم انتاج المزيد من Cytokine
المحفز للجهاز المناعي


Inhibition of effector T cell
Activation of effector T cell
T cell
PD-1
PD-L1
Tumor cell
Anti-PD-L1 Ab
T cell
Anti-PD-L1 Ab
PD-1
PD-L1
Host immune cell
Weak killing
Anti-PD-1 Ab
Strong killing
Anti-PD-1 Ab
Host immune cell
Tumor cell

Weak Immune System





PD-1 inhibitors:

- Pembrolizumab (Keytruda)
- Nivolumab (Opdivo)
- Cemiplimab (Libtayo)

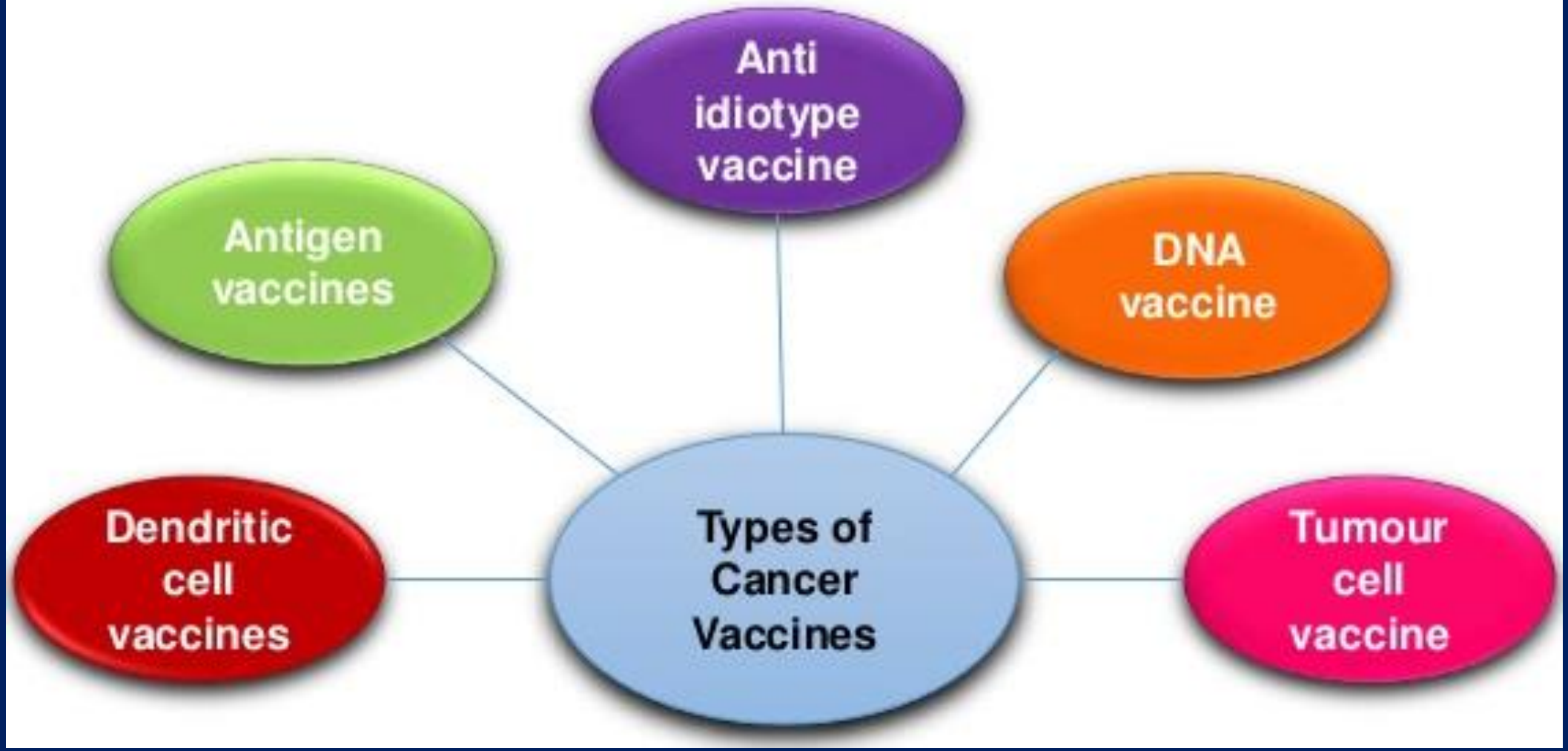
PD-L1 inhibitors:

Atezolizumab (Tecentriq)

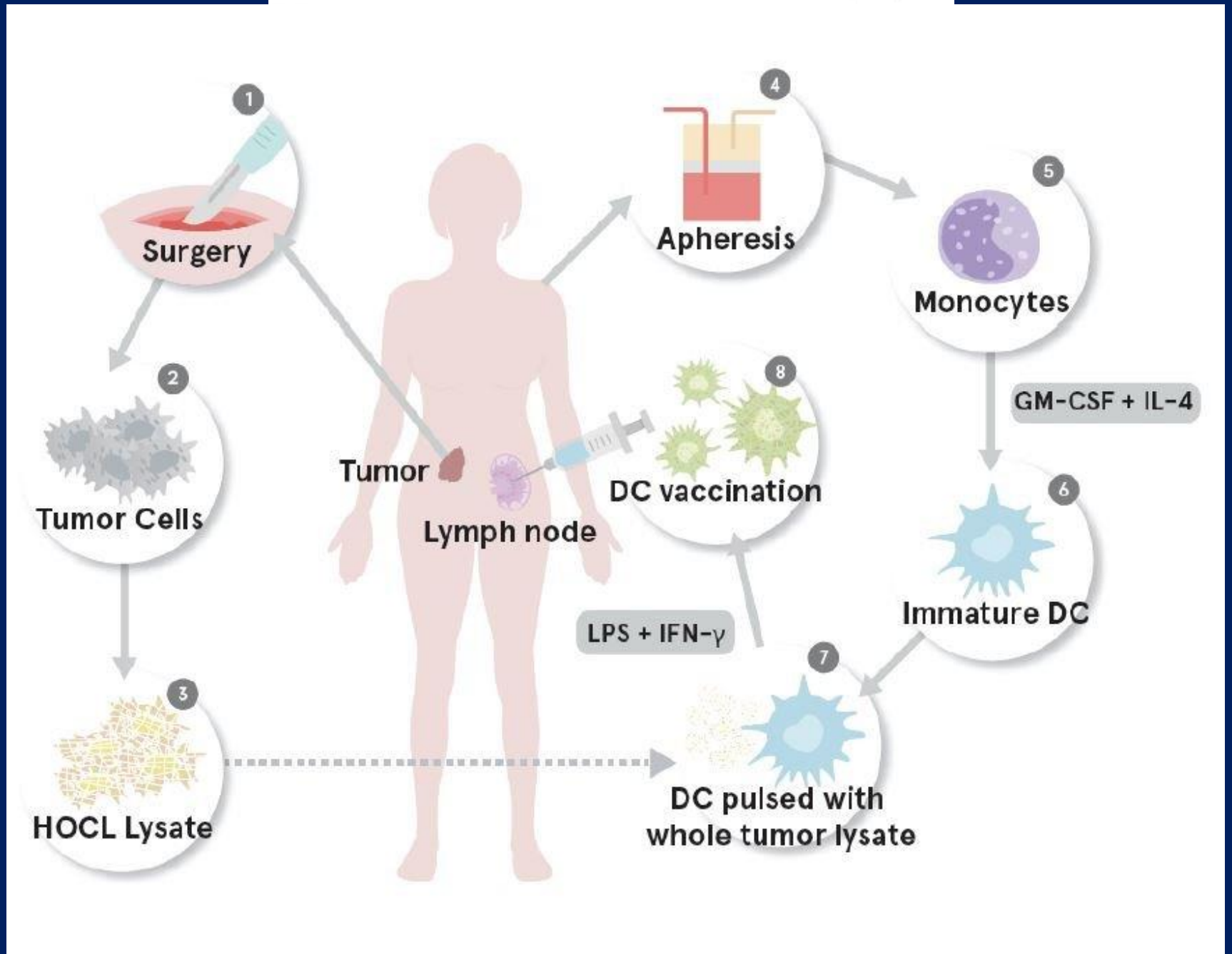
Avelumab (Bavencio)

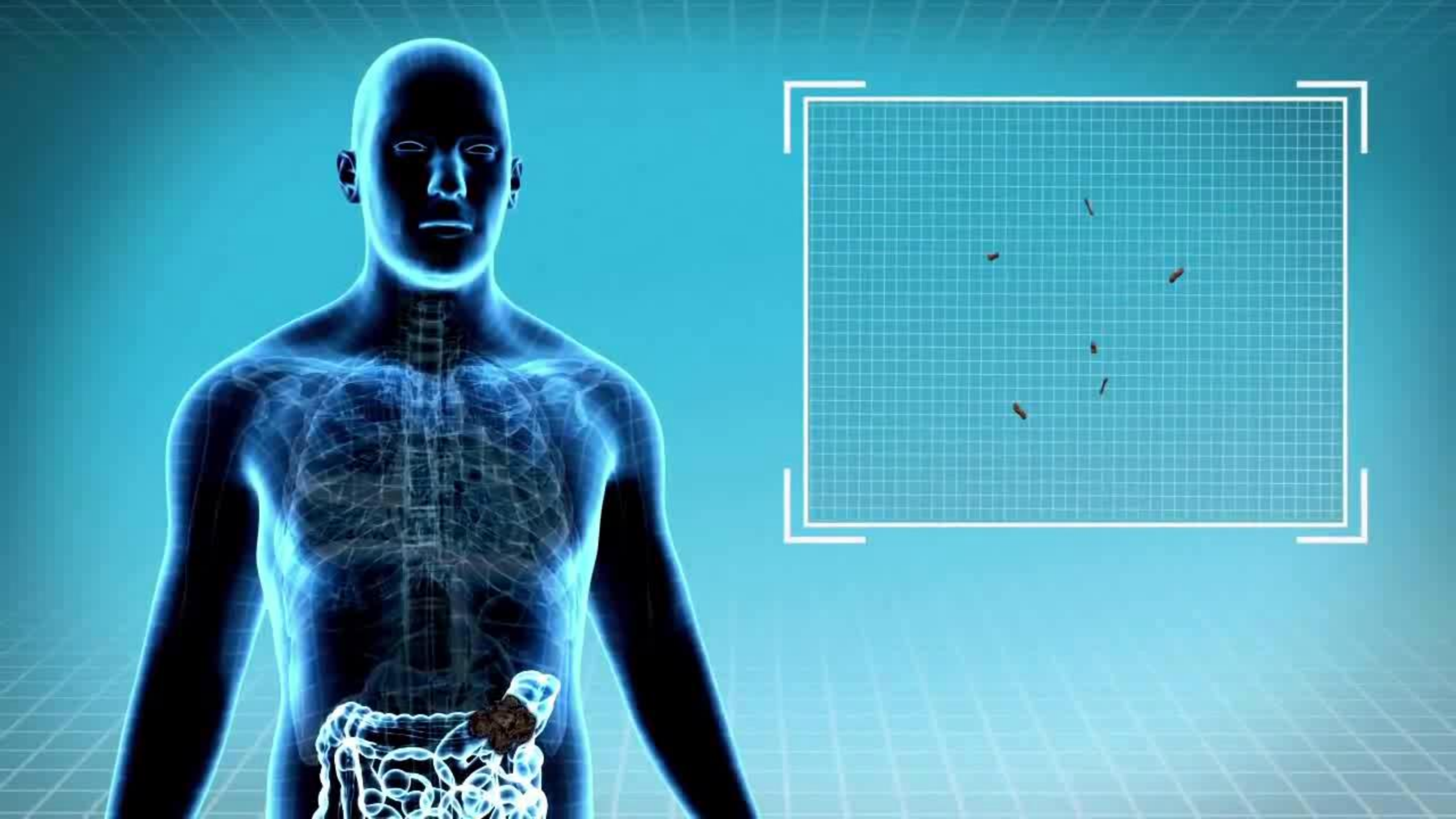
Durvalumab (Imfinzi)

TYPES OF CANCER VACCINES:



Dendritic Cell Vaccines

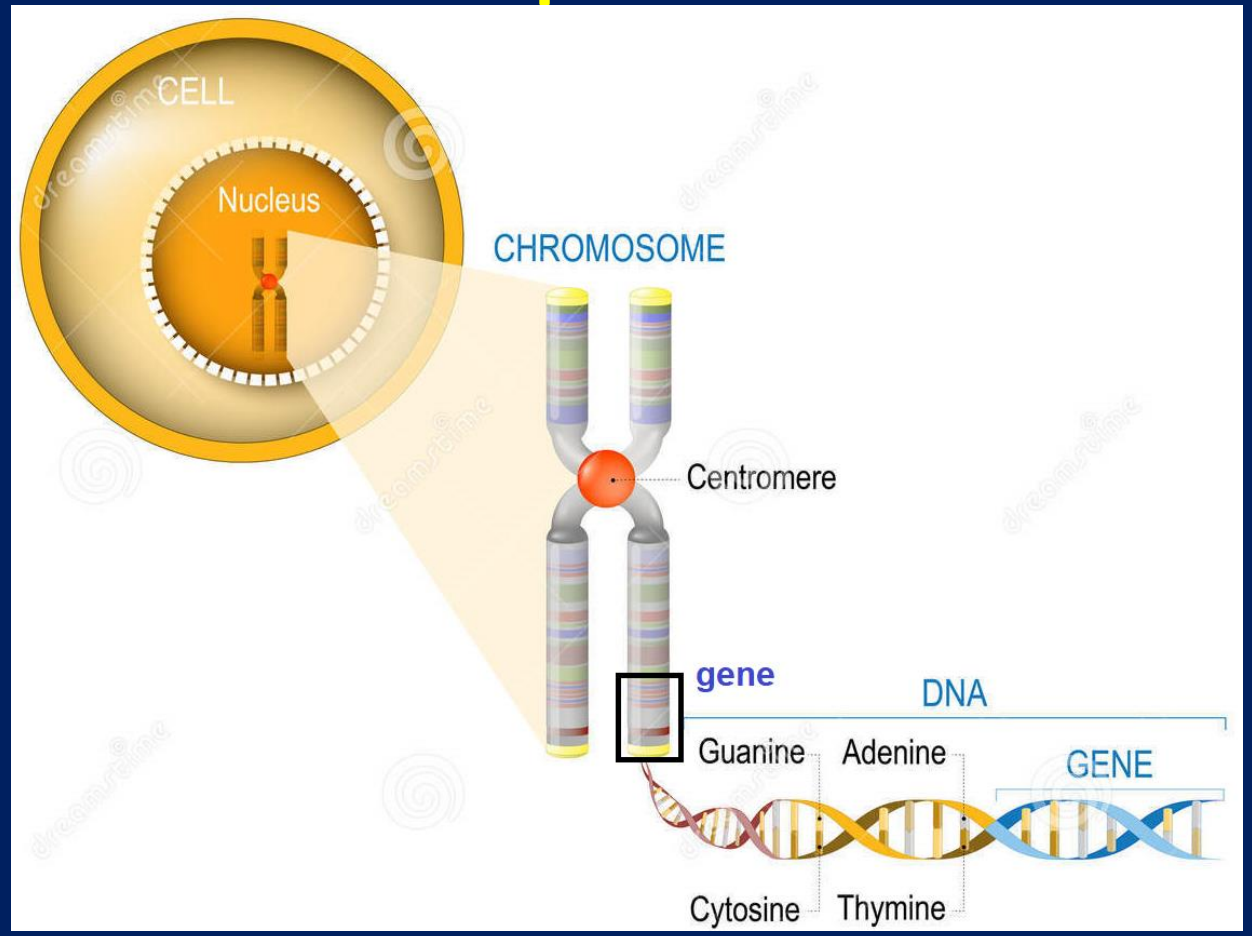


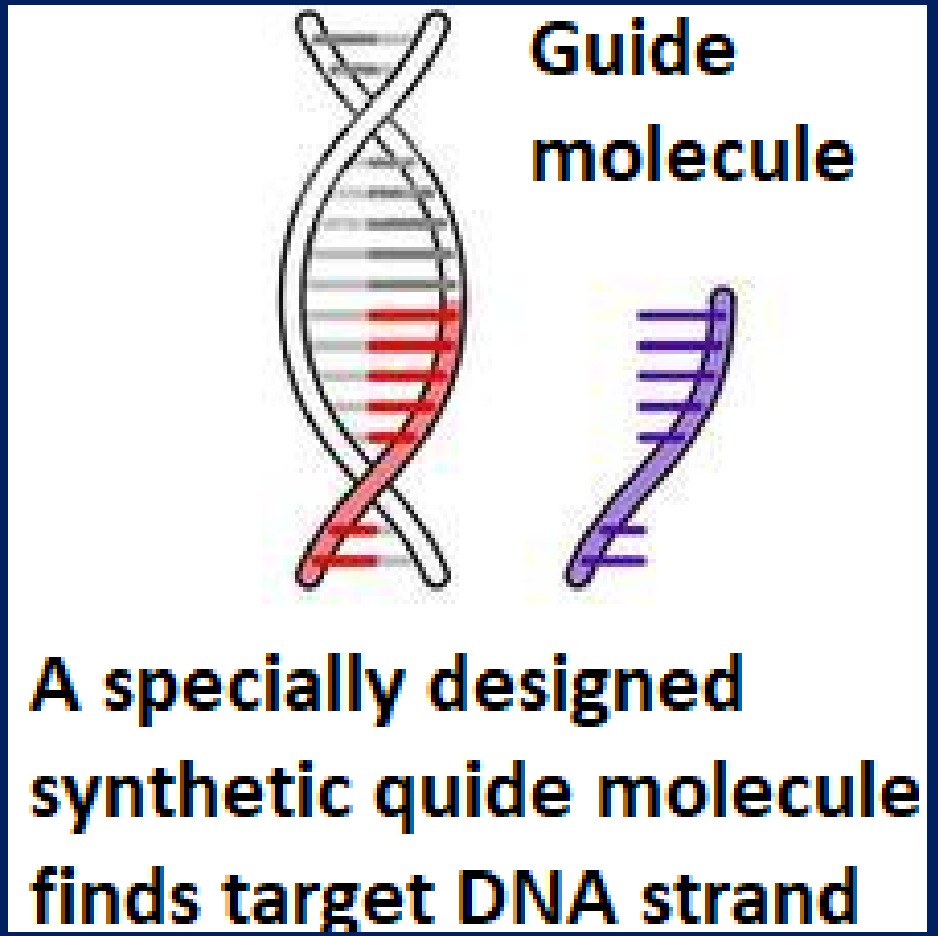


Gene Editing in Cancer Therapy (2016)

A **gene** editing techique, called CRISPR / Cas9, works as "find and replace" fuction

How the technique works:





Enzyme Cancer Therapy

3 PLANT BASED PROTEOLYTIC ENZYMES

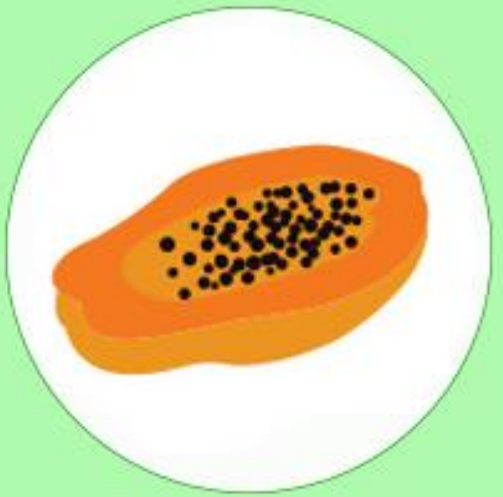
BROMELAIN

can be found
in pineapple juice &
the pineapple stem

RUTIN

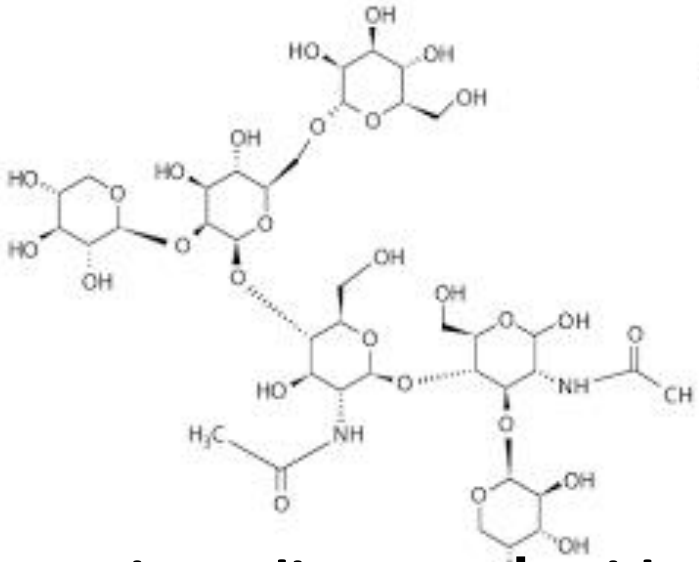
can be found in asparagus,
buckwheat, Japanese
pagoda tree, etc.

PAPAIN

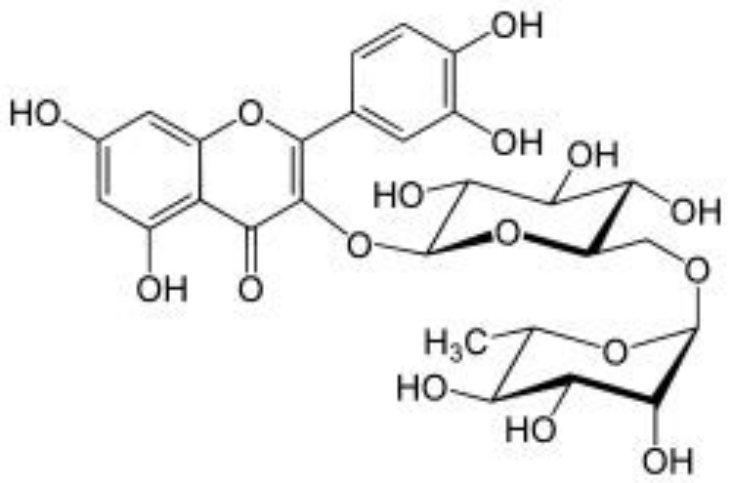


can be found in
papaya and
mountain papaya

cysteine protease



Glycoprotein + oligosaccharide



quercetin-3-O-rutinoside

Article

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Biomedical Nanotechnology
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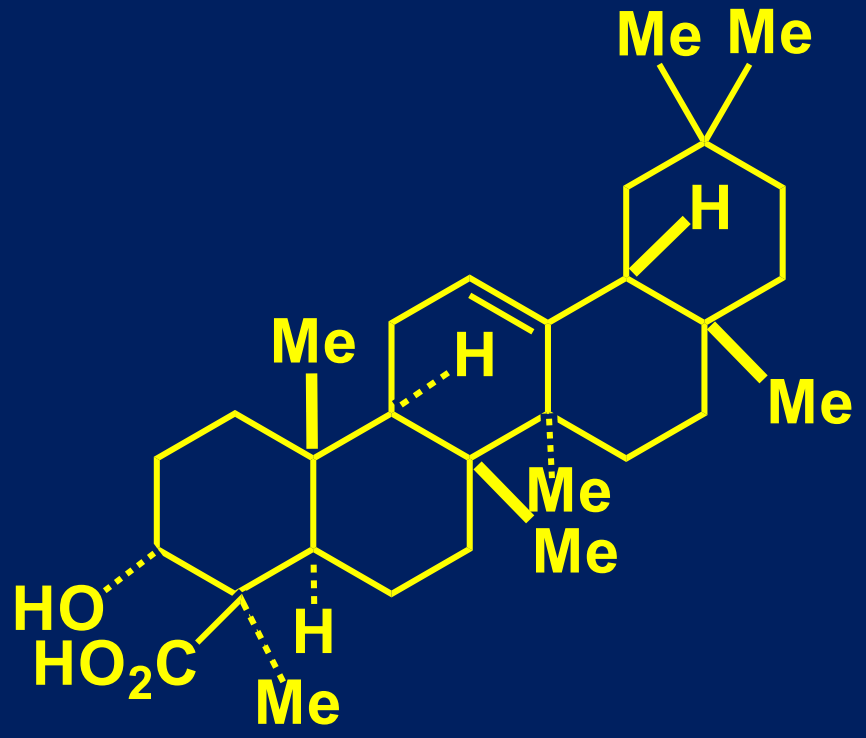
Anti-Cancer Activity of Bromelain Nanoparticles by Oral Administration

Priyanka Bhatnagar[1], Soma Patnaik[2], Amit K. Srivastava[3], Mohan K. R. Mudiam[3], Yogeshwer Shukla[3], Amulya K. Panda[2], Aditya B. Pant[3], Pradeep Kumar[1], and Kailash C. Gupta[1, 3, *]

[1] *CSIR-Institute of Genomics and Integrative Biology, Delhi University Campus, Mall Road, Delhi 110007, India*
[2] *Product Development Cell, National Institute of Immunology, Aruna Asaf Ali Marg, New Delhi 110067, India*
[3] *CSIR-Indian Institute of Toxicology Research, M.G. Marg, Post Box No. 80, Lucknow 226001, U.P., India*

Oral administration of anti-cancer drugs is an effective alternative to improve their efficacy and reduce undesired toxicity. Bromelain (BL) is known as an effective anti-cancer phyto-therapeutic agent, however, its activity is reduced upon oral administration. In addressing the issue, BL was encapsulated in Poly(lactic-co-glycolic acid) (PLGA) to formulate nanoparticles (NPs). Further, the NPs were coated with Eudragit L30D polymer to introduce stability against the gastric acidic. The resultant coated NPs were characterized for BL entrapment, proteolytic activity and mean particle size. The stability and release pattern of NPs were evaluated under simulated gastrointestinal tract pH conditions. Cytotoxicity studies carried out in human cell lines of diverse origin have shown significant dose advantage (~7–10 folds) with NPs in reducing the IC_{50} values compared with free BL. The cellular uptake of NPs in MCF-7, HeLa cells and Caco-2 cell monolayer was significantly enhanced several folds as compared to free BL ~~solution~~. Altered expression of marker proteins associated with apoptosis and cell death (P53, P21, Bcl2, Bax) also confirmed the enhanced anti-carcinogenic potential of formulated NPs. Oral administration of NPs reduced the tumor burden of Ehrlich ascites carcinoma (EAC) in Swiss albino mice and also increased their life-span (160.0±5.8%) when compared with free BL (24±3.2%). The generation of reactive oxygen species, induction of apoptosis and impaired mitochondrial membrane potential in EAC cells treated with NPs confirmed the suitability of Eudragit coated BL-NPs as a promising candidate for oral chemotherapy.

KEYWORDS: *Bromelain, Eudragit, Nanoparticles, Oral Delivery, Apoptosis, Ehrlich's Ascites Carcinoma.*



β-Boswellic acid

β-Boswellic acid can directly inhibits 5-LOX with a half maximal inhibitory concentration as low as 1.5 μM

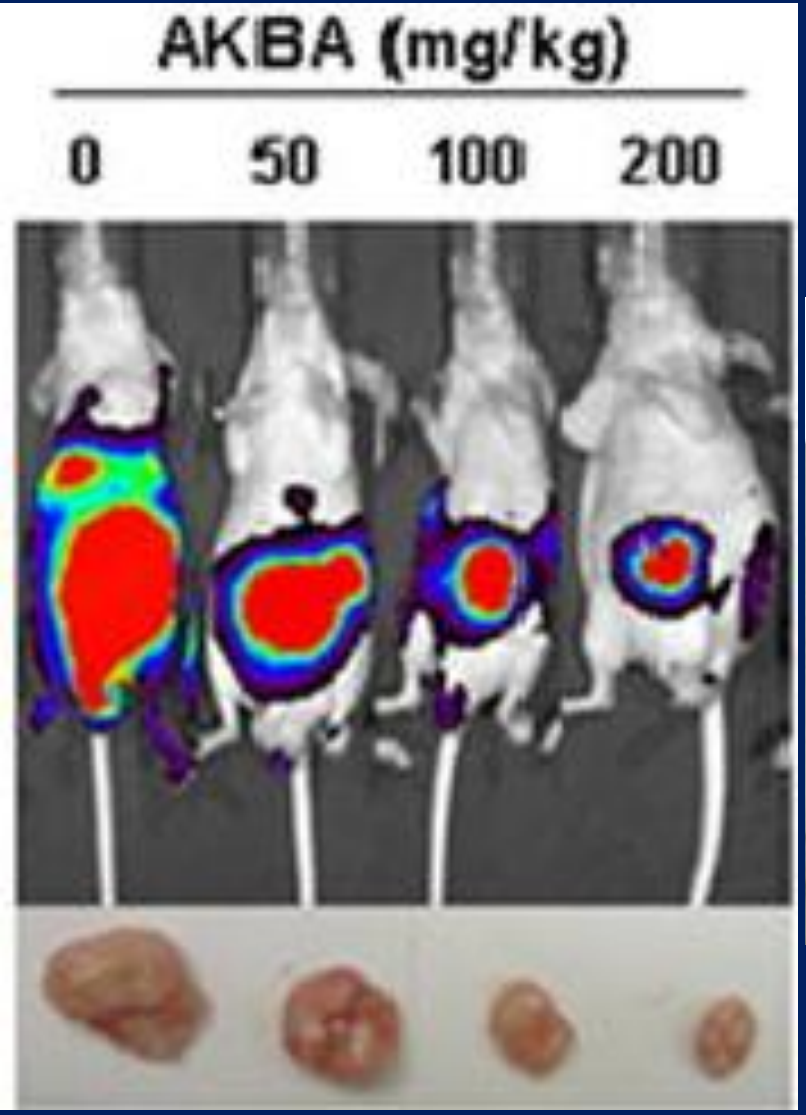
Safayhi H, et al., *Mol Pharmacol*. **1995**, 47:1212-6.

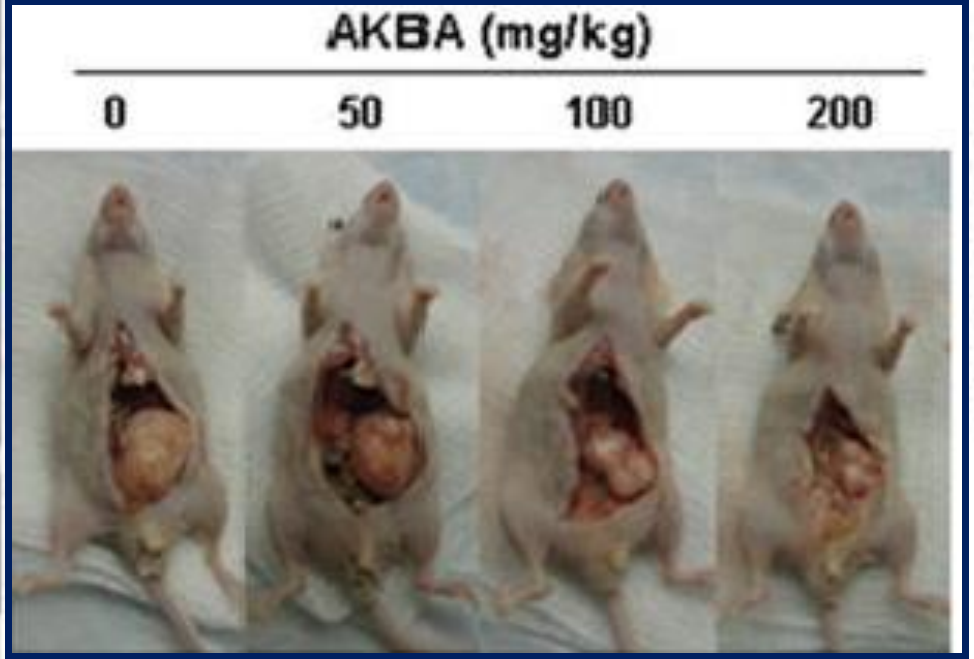
β-Boswellic acids

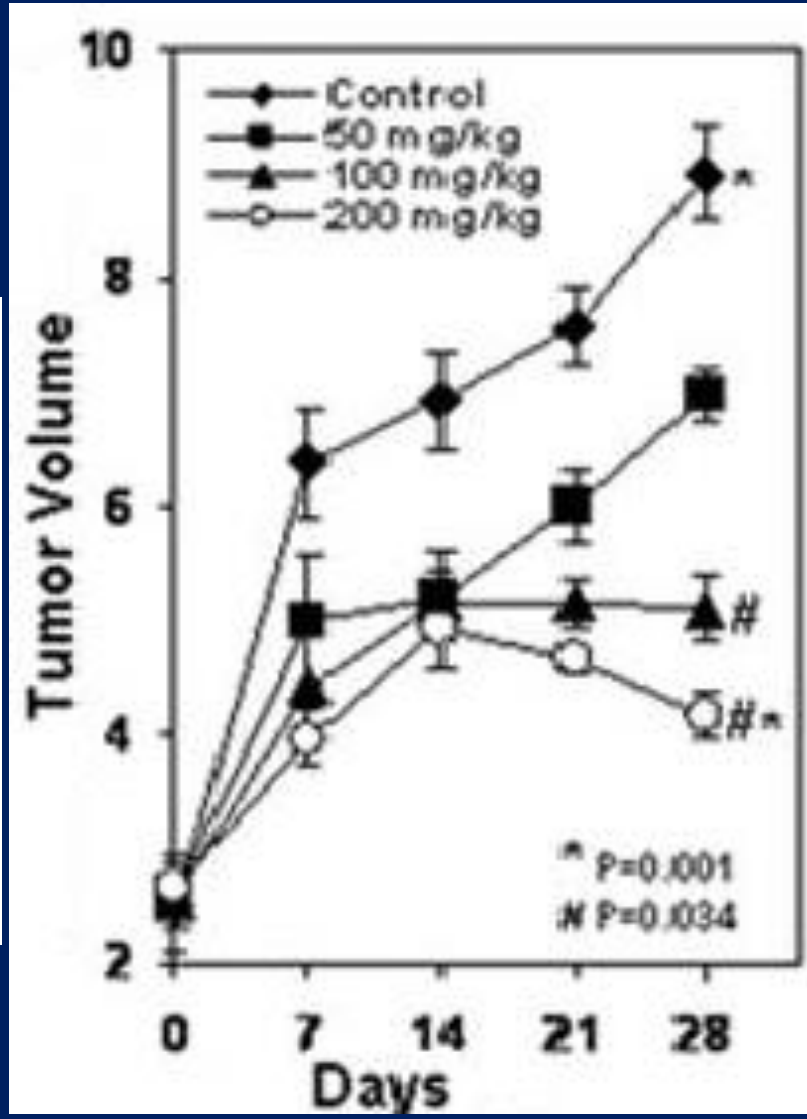
Boswellic acids are the effective components of gum resin of *Boswellia serrata* (علك بستج), which has anti-inflammatory properties. Recent study indicated that β-Boswellic acid, keto-β-boswellic acid, and acetyl-keto-β-boswellic acid (AKBA) have been indicated in apoptosis of cancer cells, in particular brain tumors and cells affected by leukemia or colon cancer

*Liu, J.-J.; Nilsson, A.; Oredsson, S.; Badmaev, V.; Zhao, W.; Duan, R. (**2002**) "Boswellic acids trigger apoptosis via a pathway dependent on caspase-8 activation but independent on Fas/Fas ligand interaction in colon cancer HT-29 cells". **Carcinogenesis**. **23**: 2087–93.*

80342- 5 MG Sigma-Aldrich 247.00 Euro





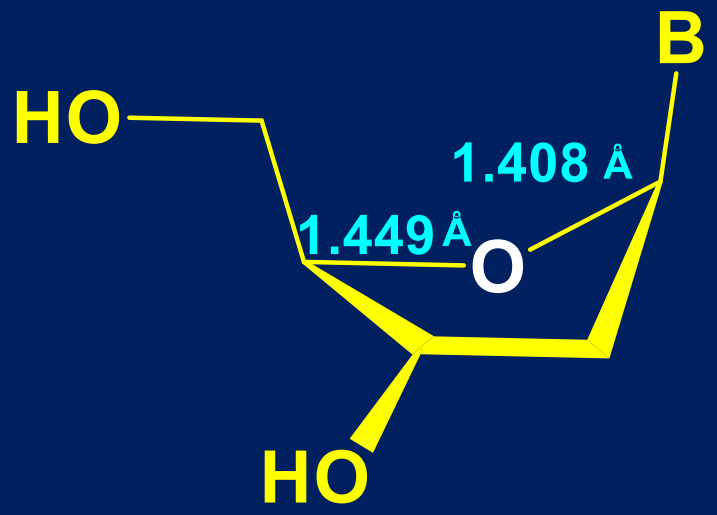


Aggrawal *et al*., Boswellic acid inhibits growth and metastasis of human colorectal cancer in orthotopic mouse model by downregulating inflammatory, proliferative, invasive, and angiogenic biomarkers, ***Int. J. Cancer***. **2012**, 130: 2176–2184.

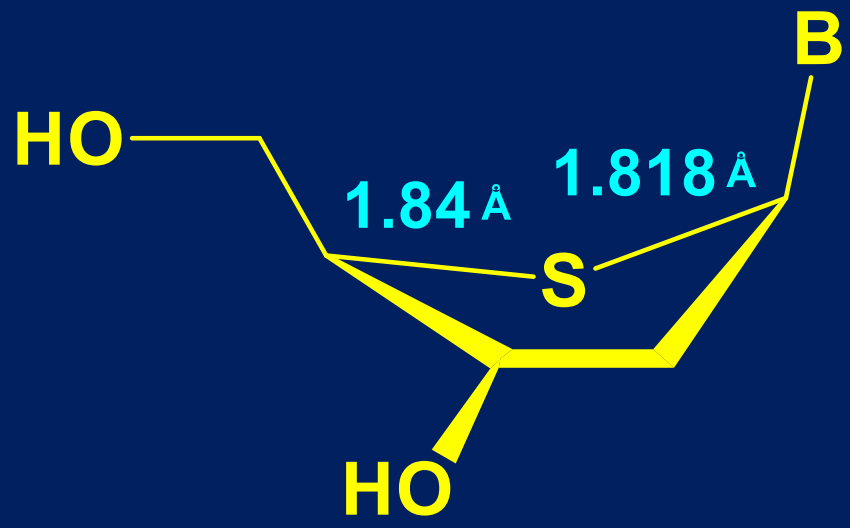
•Our Current Work & Ambition

•Synthesis of New Alternative DNA

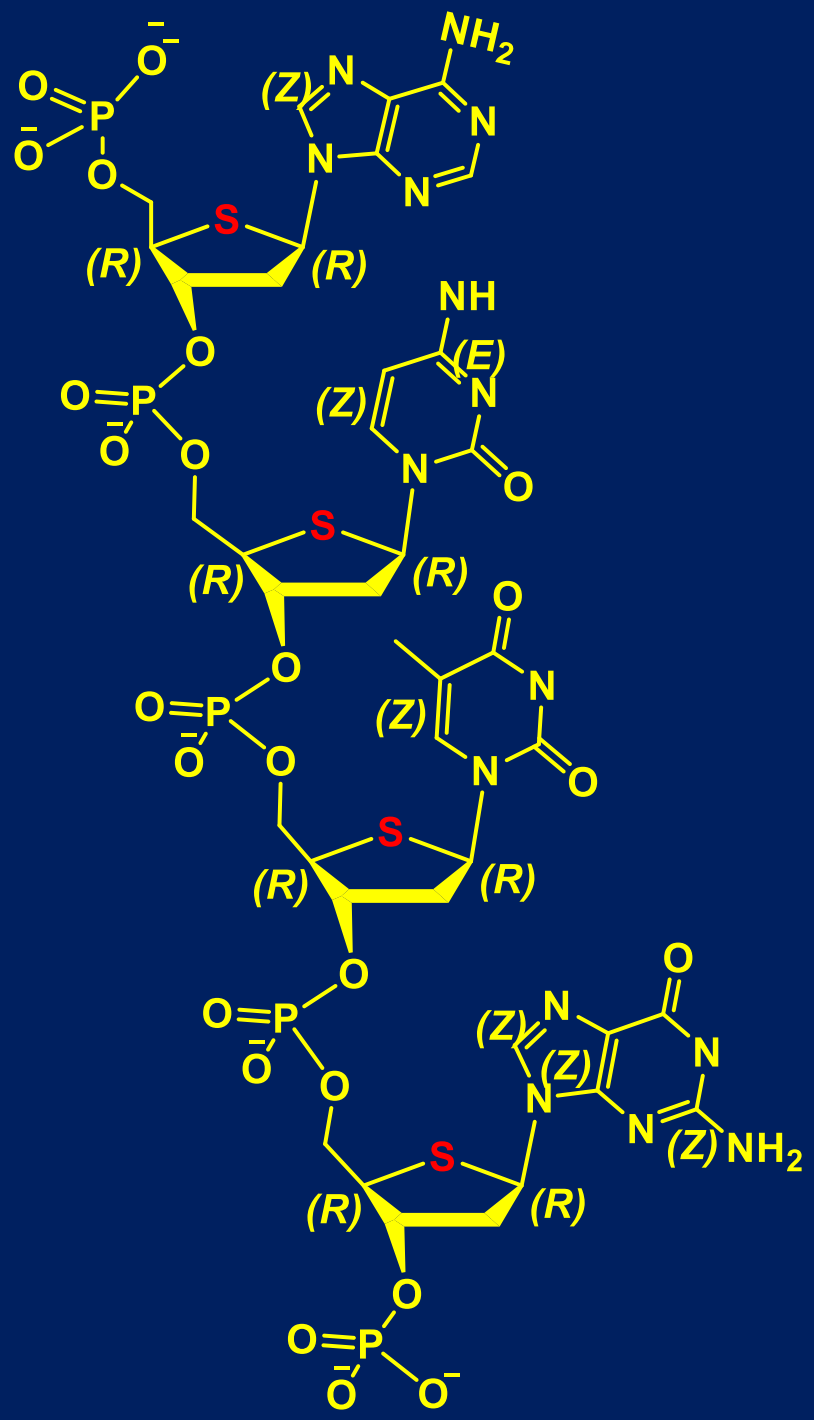
•Thio-DNA



2-Deoxy-D-ribonucleoside



2-Deoxy-4'-thio-D-ribonucleoside

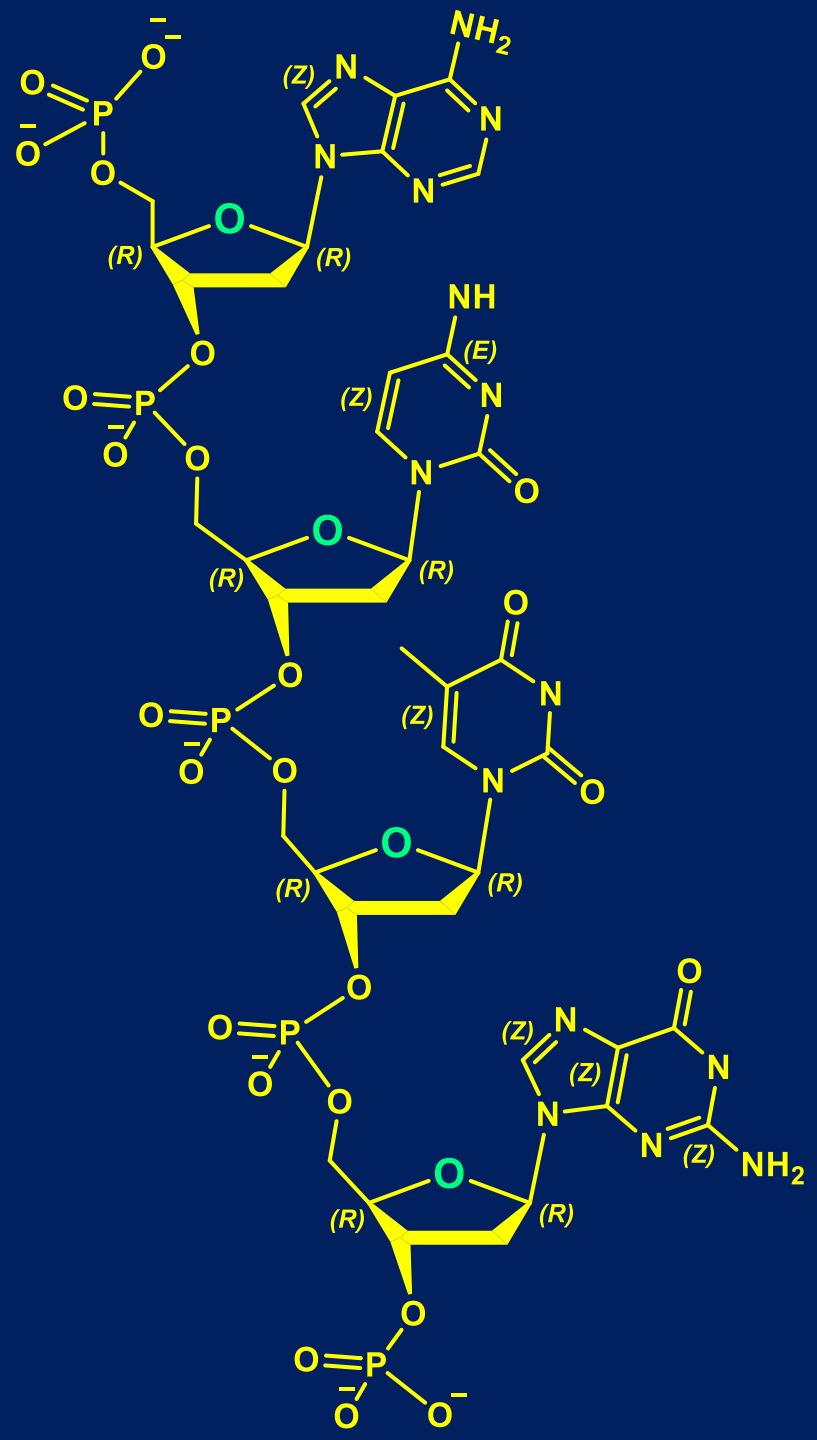


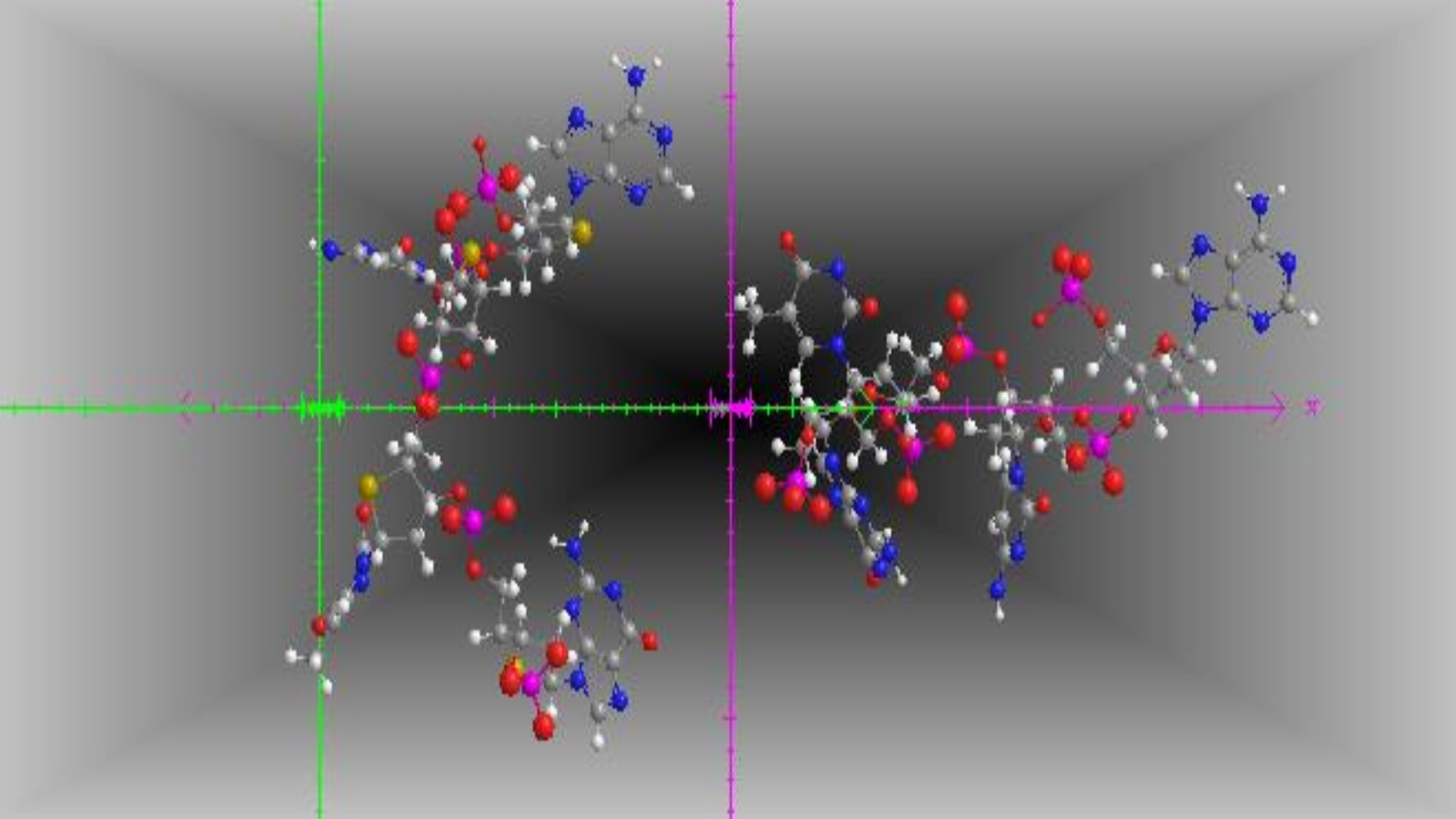
Adenosine

Cytidine

Thymidine

Guanidine





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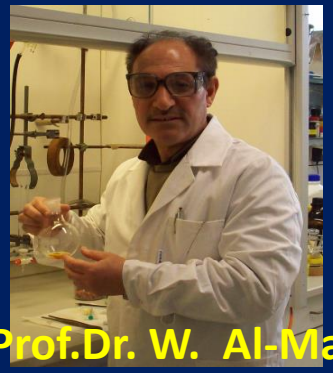
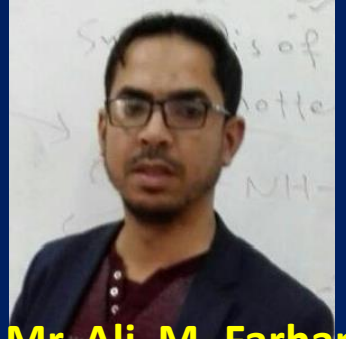
Al-Qadisiya Uni., Iraq



Prof.Dr. W. Al-Masoudi,
Basrah Uni., Iraq

Prof.Dr. Bahjat Saeed,
Basrah Uni., Iraq

Prof.Dr. Dawood S. Ali
Basrah Uni., Iraq



Mr. Ali M. Farhan ,
Ph.D. student
Al-Qadisiya Uni.,
Iraq

Prof. Ming-Fong Lin
Nebraska Medical
Center Nebraska Uni., USA

Prof. Pfleidrer, Dr. Geeta
Germany, 2006

Prof. C. Pannecouque,
Rega Medical Inst.,
Katholiek Uni, Belgium

Dr. M. Engel,
Sarrbrucken Uni,
Germany

Prof. Steiner, Dr. Geeta, Prof. Waldvogel
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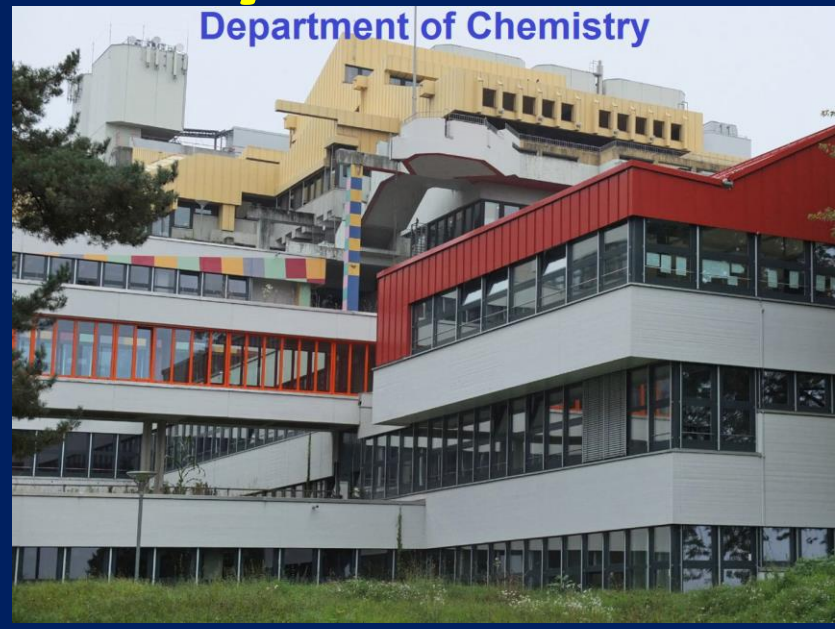
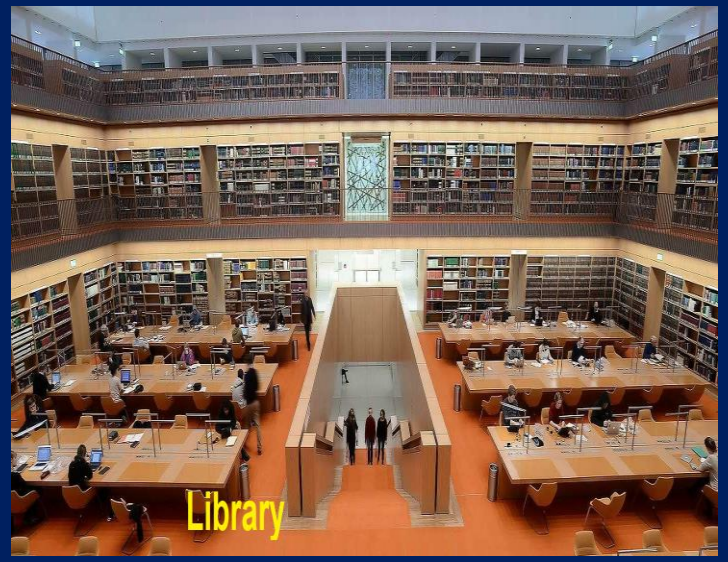
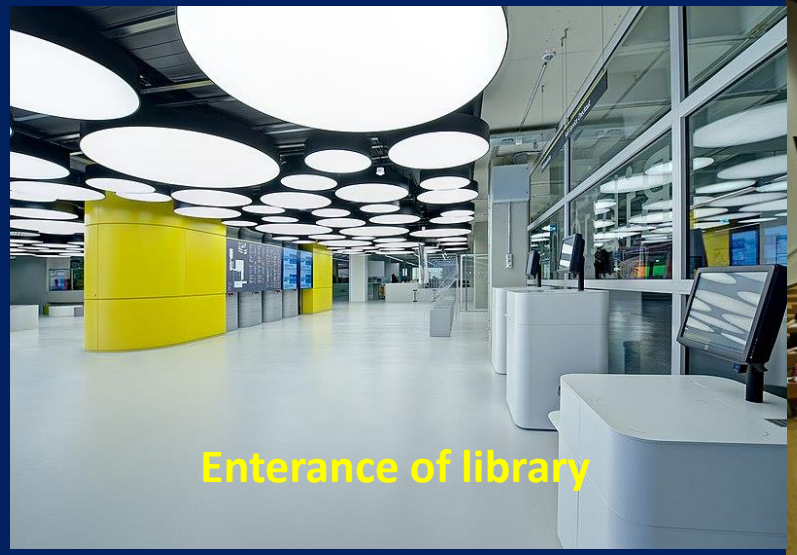
Prof. S. Hameed,
QA Uni., Islamabad
Pakistan

University of Konstanz, Germany







web:www.al-masoudi.de

https://www.researchgate.net/profile/Najim_Al-Masoudi2

Google: Najim Al-Masoudi