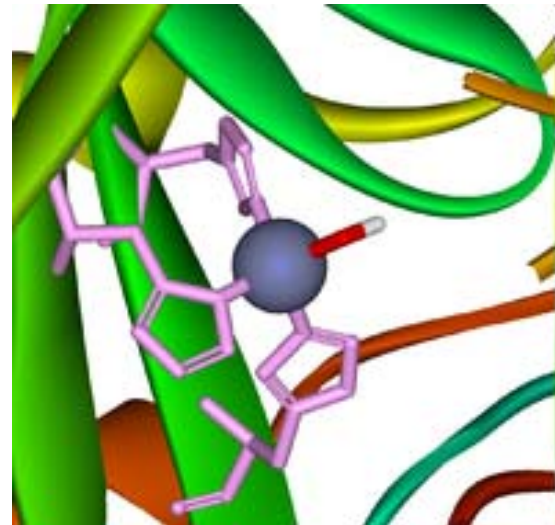




# **Jauni multi mērķu Zn enzīmu inhibitori**

**Pēteris Trapencieris**

**Latvijas Organiskās sintēzes institūts**

**Kleisti, 130627**

# **Multimērķu zāles** **(*multitarget drug design concept*)**

## **CNS aktīvās vielas**

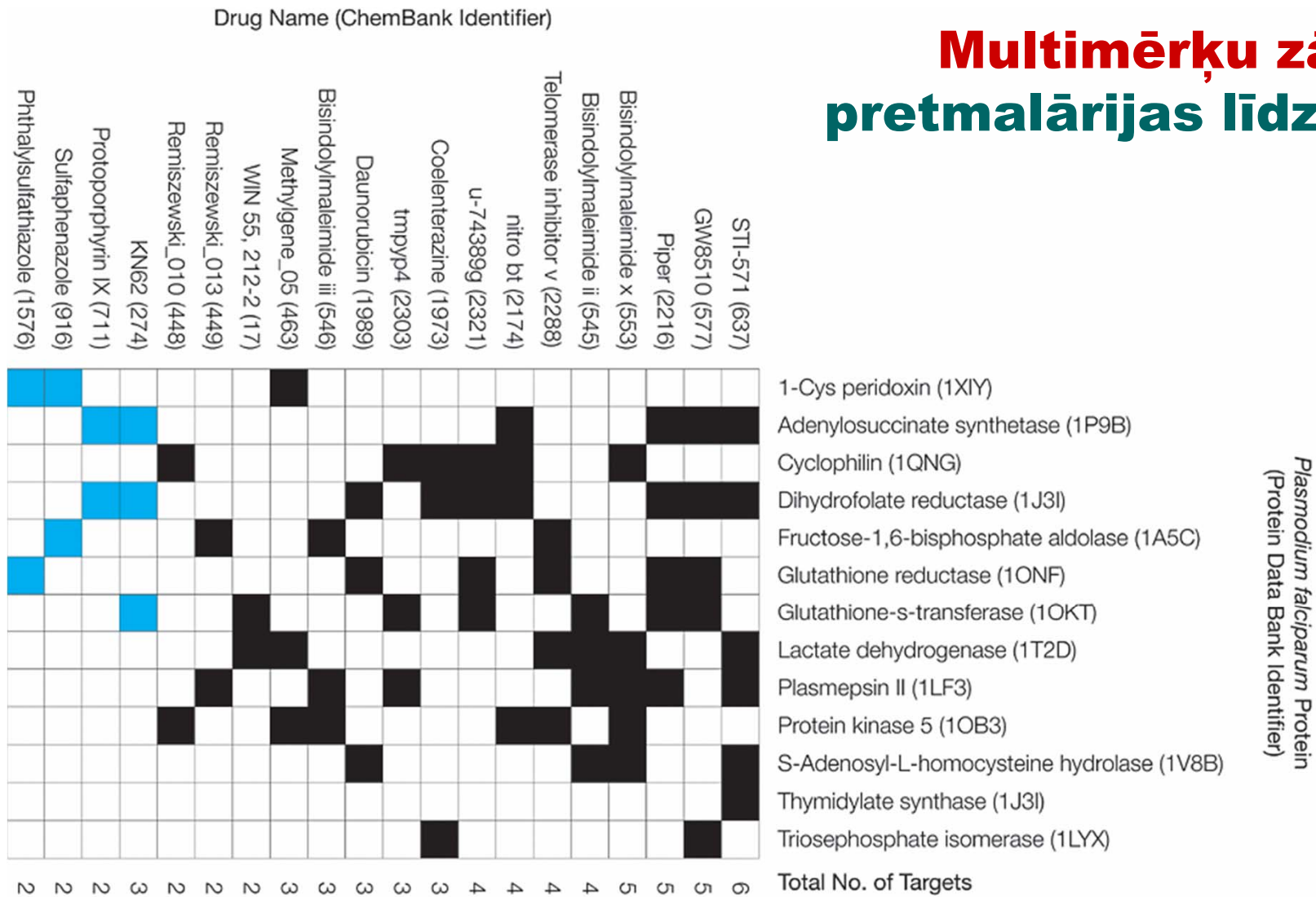
*J. Med. Chem.* 2007, 50, 4882;  
*J. Med. Chem.* 2007, 50, 6446;  
*J. Med. Chem.* 2008, 51, 347;  
*Bioorg. Med. Chem. Lett.*, 2008, 18, 2905;  
*J. Med. Chem.* 2009, 52, 559;  
*J. Med. Chem.* 2009, 52, 2727;  
*J. Med. Chem.* 2010, 53, 1338;

## **Zn-saturošās proteases (MMPs and CAs)**

*J. Med. Chem.* 2008, 51, 7968;  
*J. Med. Chem.* 2008, 51, 2279;  
*Bioorg. Med. Chem. Lett.*, 2006, 16, 4316.

.

# Multimērķu zāles pretmalārijas līdzekļi



Saistība 4 atļautām (zili) and 16 eksperimentālām (melni) multimērķu zālēm  
13 *Plasmodium falciparum* proteīni

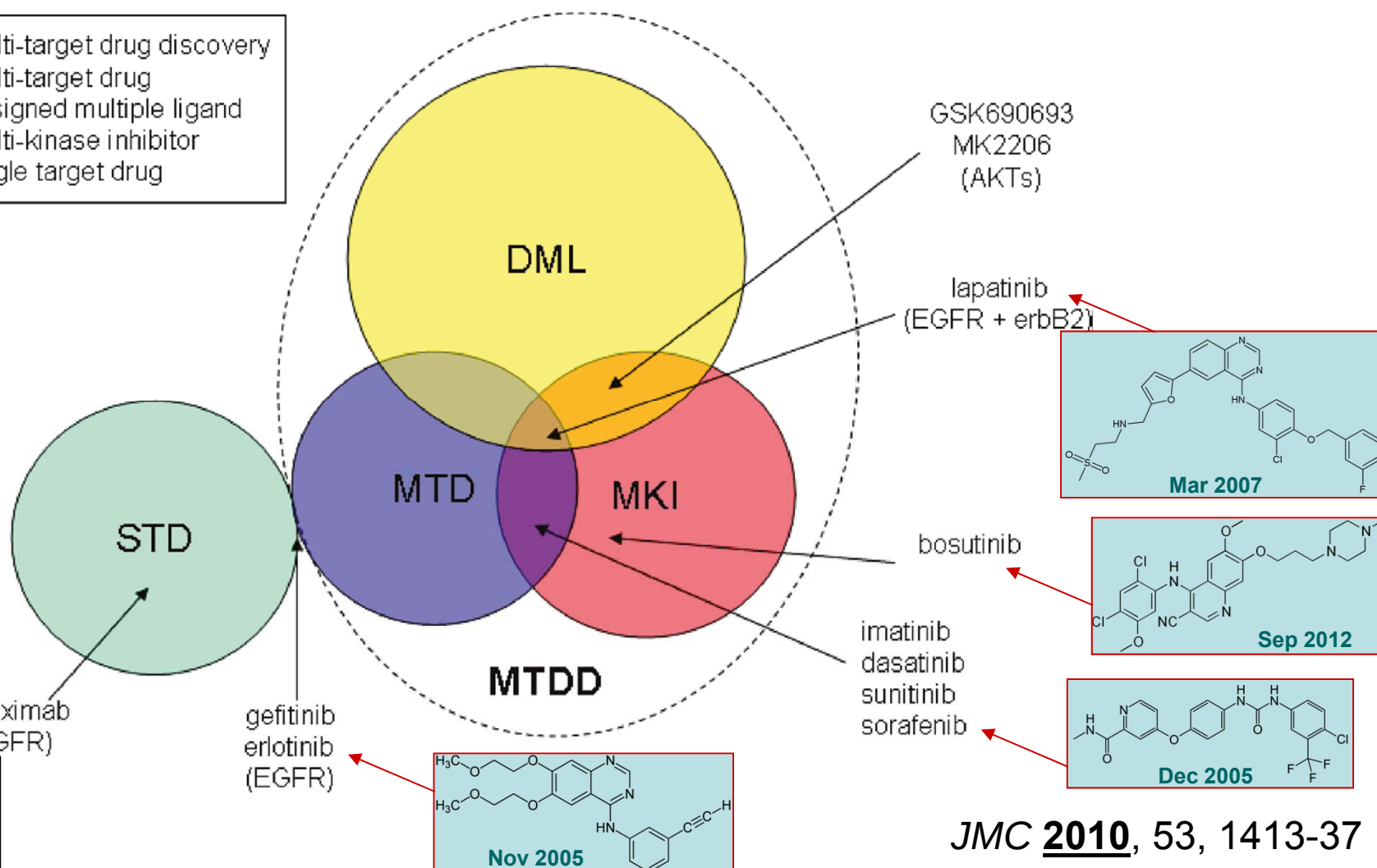
Augsta afinitāte uz 2-6 proteīnu aktīvajiem centriem

JAMA, 2005, 294(12), 1487-1491

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# Multimērķu zāles pretvēža līdzekļi

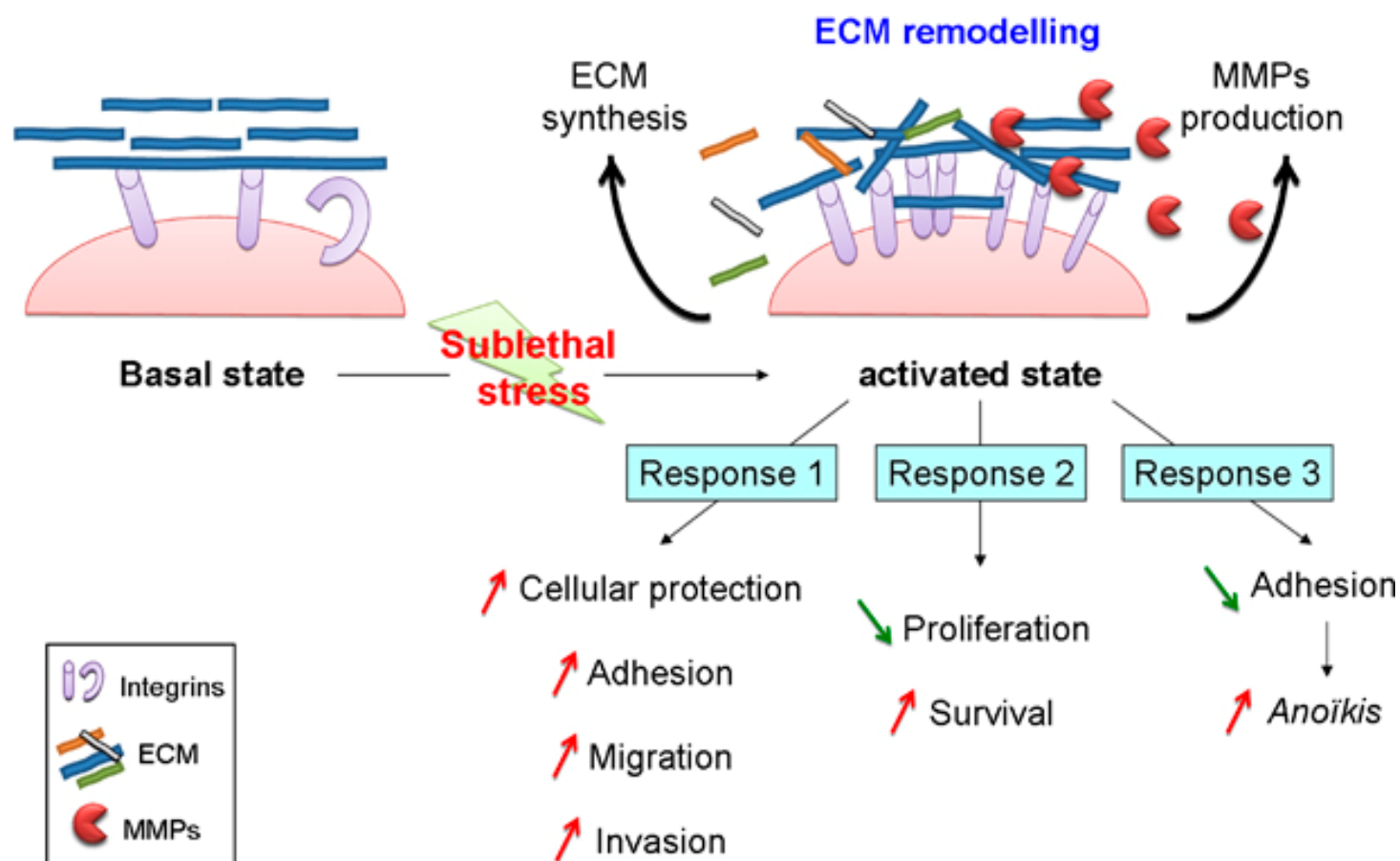
MTDD = multi-target drug discovery  
 MTD = multi-target drug  
 DML = designed multiple ligand  
 MK I = multi-kinase inhibitor  
 STD = single target drug



# Ekstracellulārā Matrica

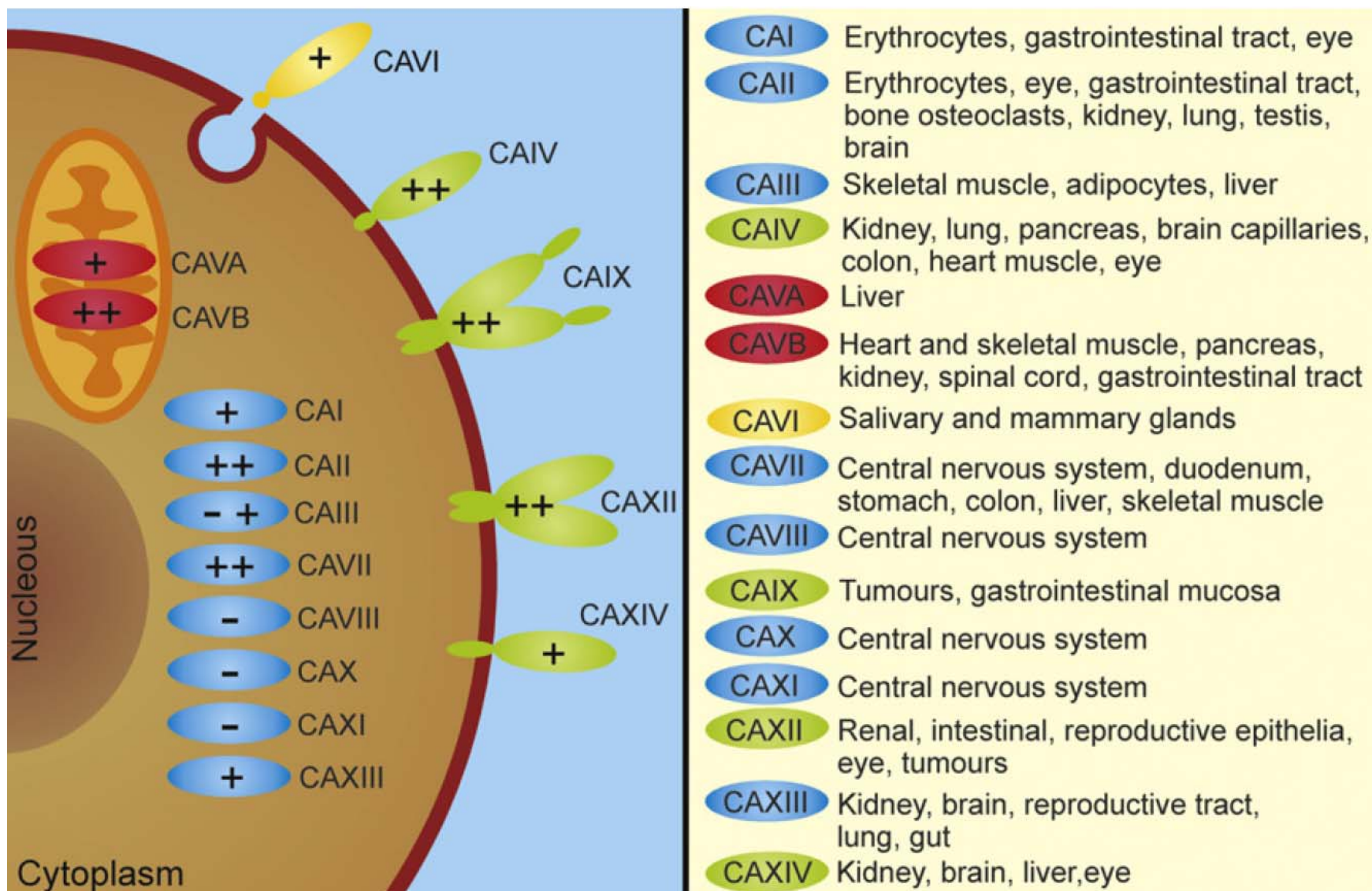
## Matricu metālproteināzes (MMP)

Stresa ietekme uz ekstracellulāro matricu un integrīnu bioloģiju:  
Trīs šūnu atbilžu iespējas

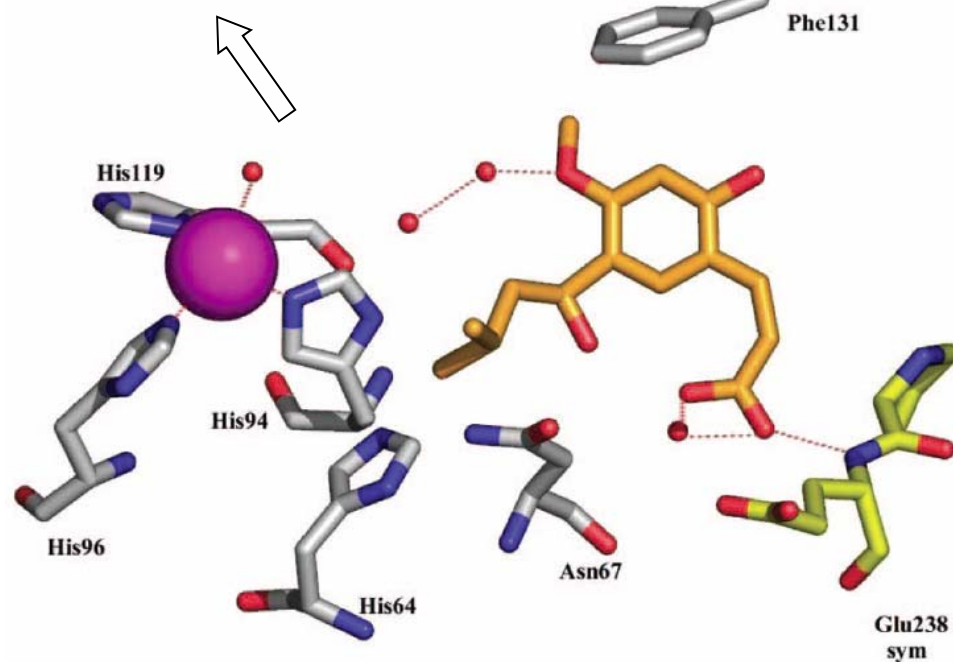
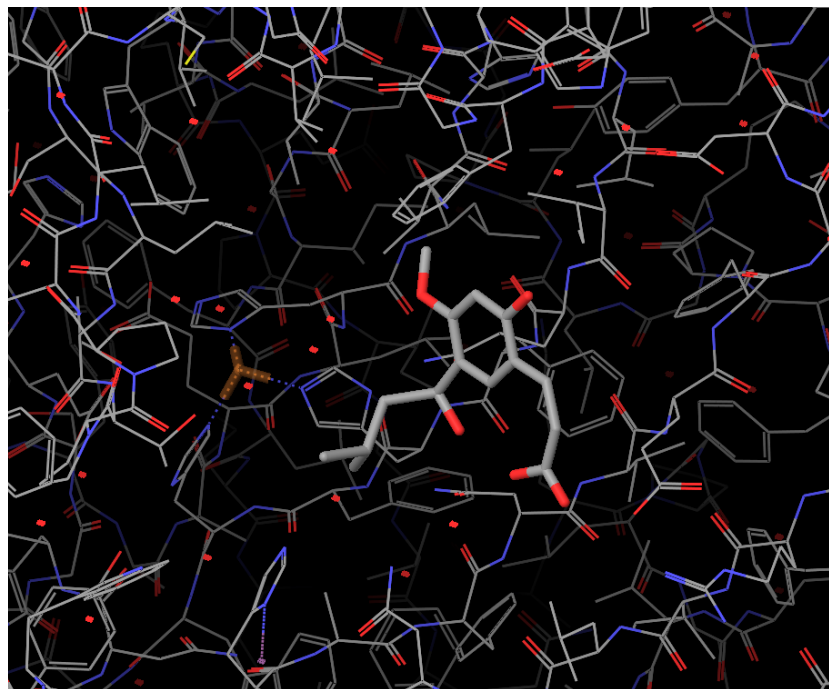
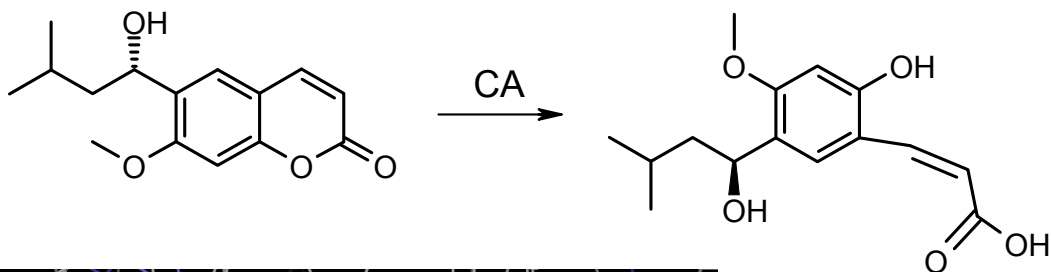




# Ogļskābes anhidrāžu (CA) veidi



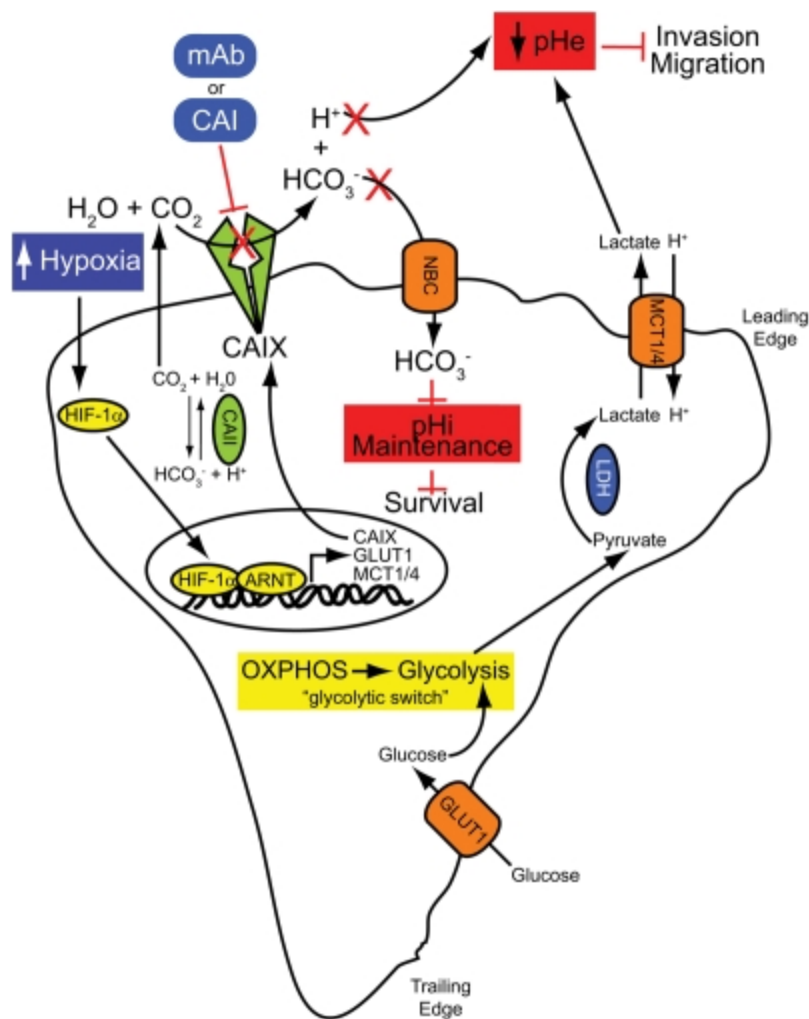
# $\alpha$ -Ogļskābes anhidrāžu ( $\alpha$ -CA) inhibitori **Kumarīni**



Supuran, *J. Am. Chem. Soc.* **2009**, 131, 3057

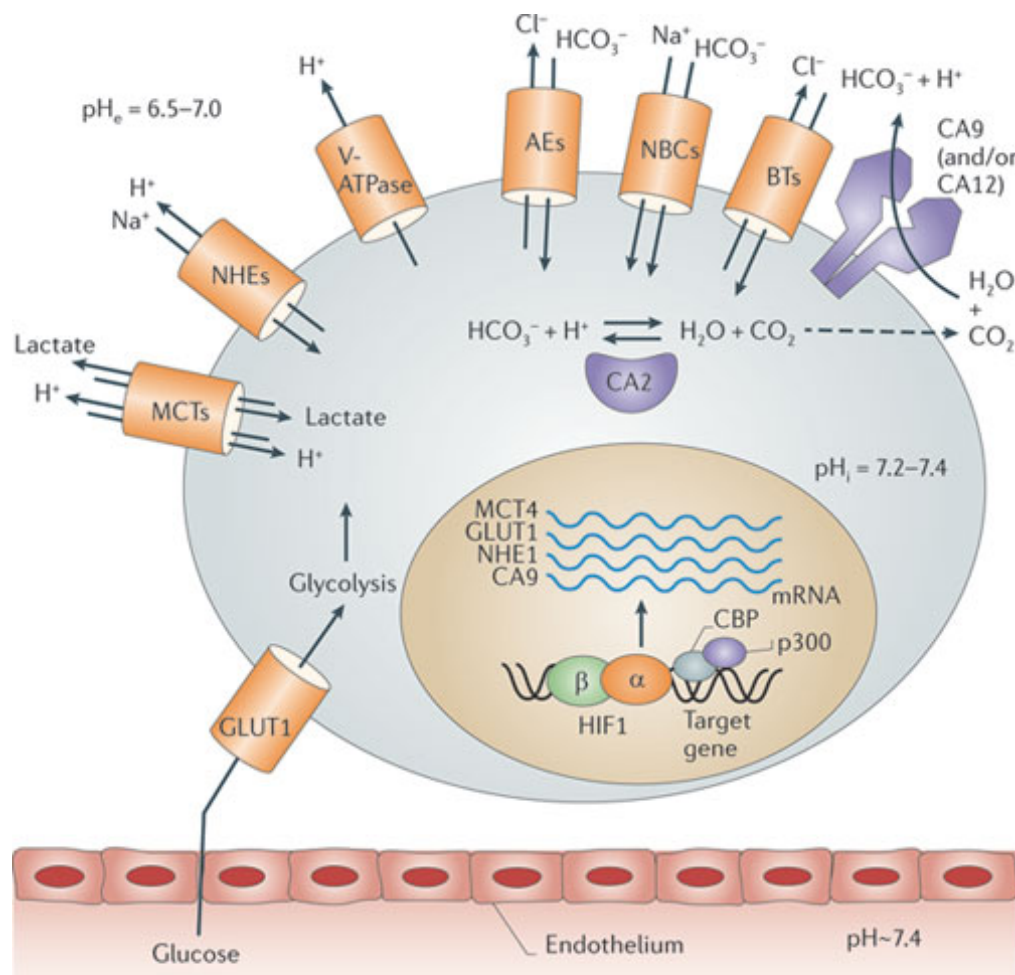
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# CAIX farmakoloģiskā inhibīcija samazina vēža šūnu izdzīvošanu un invāziju





# CAIX farmakoloģiskā inhibīcija samazina vēža šūnu izdzīvošanu un invāziju

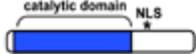


Proteīni, kas regulē audzēju šūnu pH monocarboxylate transporters (MCTs), Na<sup>+</sup>/H<sup>+</sup> apmaiņa (NHEs); plasmā membrānu protonu sūkņi *vacuolar ATPase* (V-ATPase); anion exchangers (AEs); Na<sup>+</sup>/HCO<sub>3</sub><sup>-</sup> co-transporters (NBCs); CA2, CA9 and/or CA12).

Glikozes transportieris GLUT1 (aktivēts lielākajā vēža šūnu)

Nature Reviews | Drug Discovery

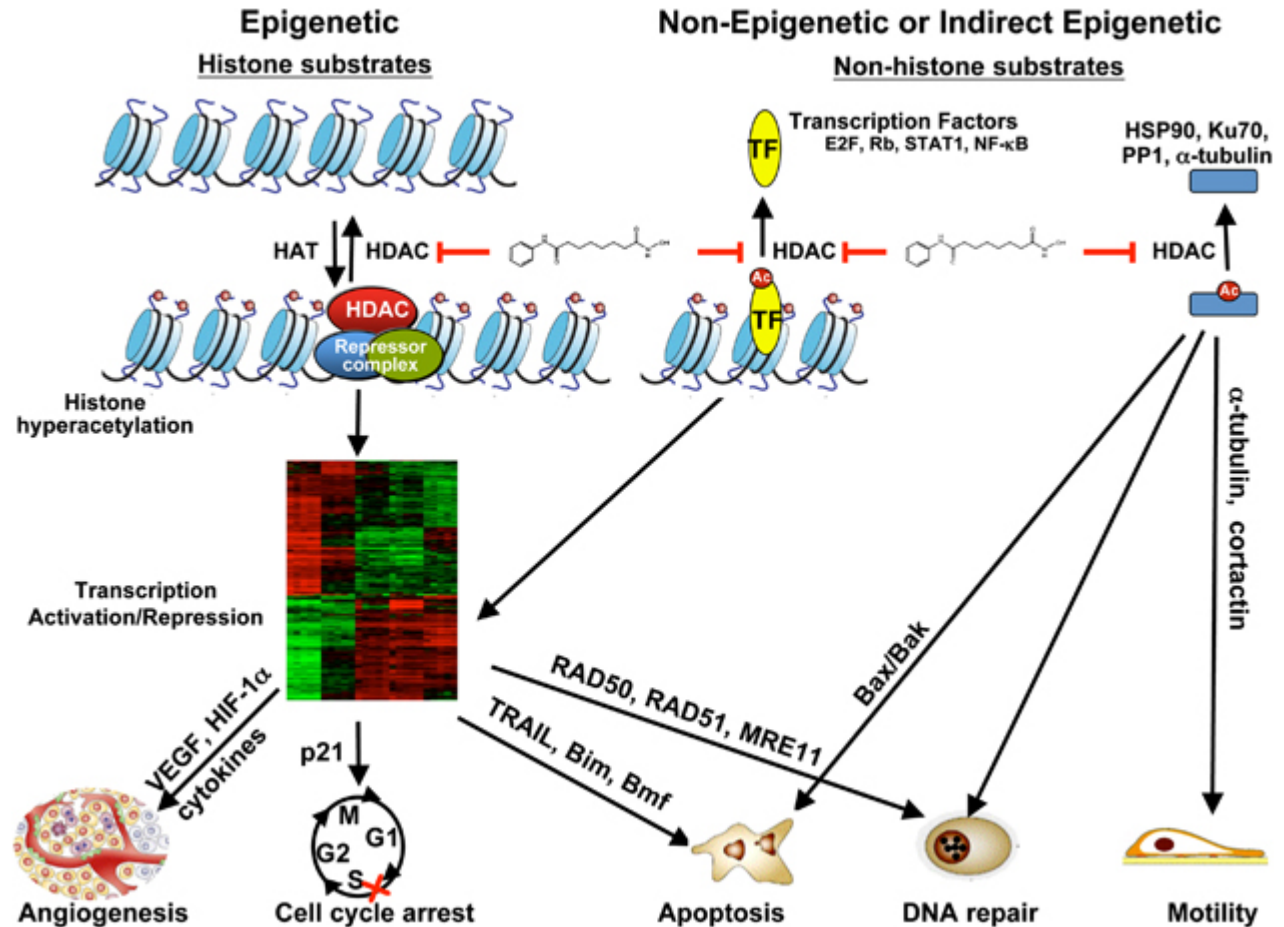
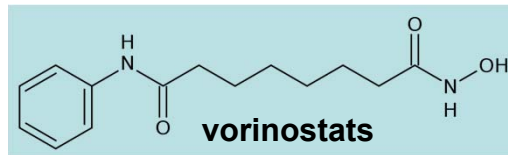
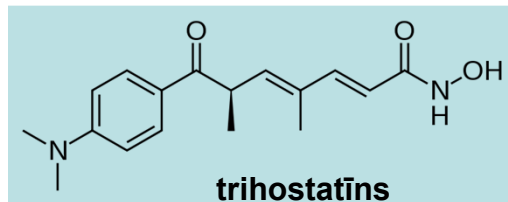
# Histona deacilāžu (HDAC) veidi

|                                                                                     | Class  | Cancer Relevance                                                                                                                                                                                                                                                                                                                                                                                                      | References                                                                                                                                                                                                                                                                                                                                            |
|-------------------------------------------------------------------------------------|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    | HDAC1  | <p>Overexpressed in gastric, pancreatic, colorectal, prostate, hepatocellular cancers and correlates with poor prognosis.</p> <p>Mutated in colon cancer, overexpressed in esophageal, prostate, non-small cell lung, gastrointestinal, oral cancers.</p> <p>Expression correlates with poor prognosis in gastric, prostate, colorectal cancers.</p> <p>Expression correlates with poor outcome in neuroblastoma.</p> | <p>Choi et al 2001, Fritzsche et al 2008, Miyake et al 2008, Rikimaru et al 2007, Weichert et al 2008, Zhang et al 2005.</p> <p>Chang et al 2009, Fritzsche et al 2008, Ropero et al 2006, Weichert et al 2008</p> <p>Fritzsche et al 2008, Krusche et al 2005, Moreno et al 2010, Weichert et al 2008</p> <p>Moreno et al 2010, Oehme et al 2009</p> |
|    | HDAC2  |                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                       |
|    | HDAC3  |                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                       |
|    | HDAC8  |                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                       |
|    | HDAC4  | <p>Mutated in breast cancer.</p> <p>Low expression in lung cancer associated with poor prognosis, upregulated in colon cancer.</p> <p>Highly expressed in colorectal cancer.</p> <p>Not known.</p>                                                                                                                                                                                                                    | <p>Ozdag et al 2006</p> <p>Osada et al 2004, Ozdag et al 2006</p> <p>Moreno et al 2010</p>                                                                                                                                                                                                                                                            |
|    | HDAC5  |                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                       |
|    | HDAC7  |                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                       |
|    | HDAC9  |                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                       |
|    | HDAC6  | <p>Low expression in lymphoma, high expression in oral squamous cell cancer and correlates with stage.</p> <p>Low expression in lung cancer associated with poor prognosis.</p>                                                                                                                                                                                                                                       | <p>Gloghini et al 2009, Moreno et al 2010, Sakuma et al 2006</p> <p>Osada et al 2004</p>                                                                                                                                                                                                                                                              |
|    | HDAC10 |                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                       |
|  | HDAC11 | Not known.                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                       |

## hHDAC grupa:

uzrāda domeinu struktūru un iedarbību uz ļaundabīgajiem audzējiem  
iedala pēc struktūras līdzībām  
zilā krāsa rāda katalītisko domeinu  
zvaigznīte rāda lokalizācijas signālu vietu kodolā

# HDAC inhibitoru loma



## HDACi:

novērš histonu deacetilēšanos (vorinostats)  
 noved pie transkripcijas aktivācijas vai represijas  
 var ietekmēt transkripcijas faktoru (E2F, NF-κB, Stats) acetilēšanas statusu  
 var ietekmēt citus bioloģiski svarīgu funkciju proteīnus (α-tubulin, Ku70, Hsp90)

*Oncogene* **2012**, 31, 537-551 (review)

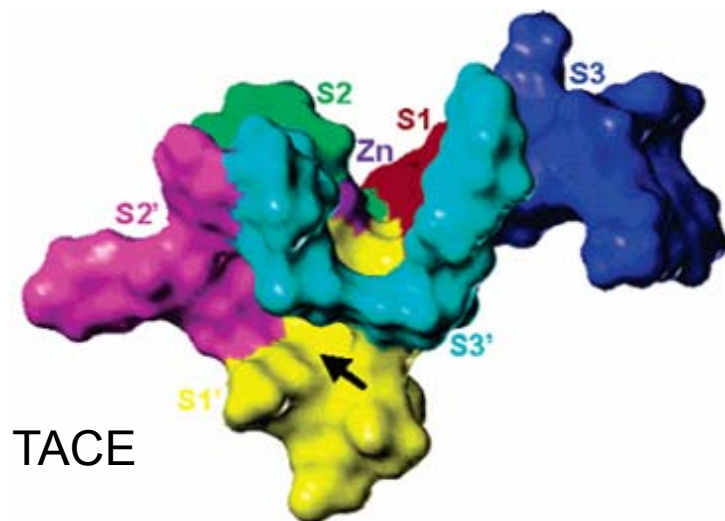
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## TACEi

# TACE Inhibitoru selektivitāte

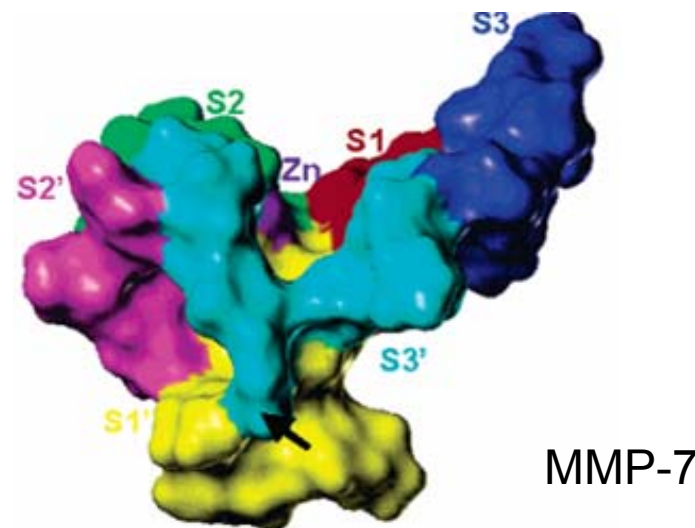
**TACE = ADAM 17**

*A disintegrin and metalloproteinase family*



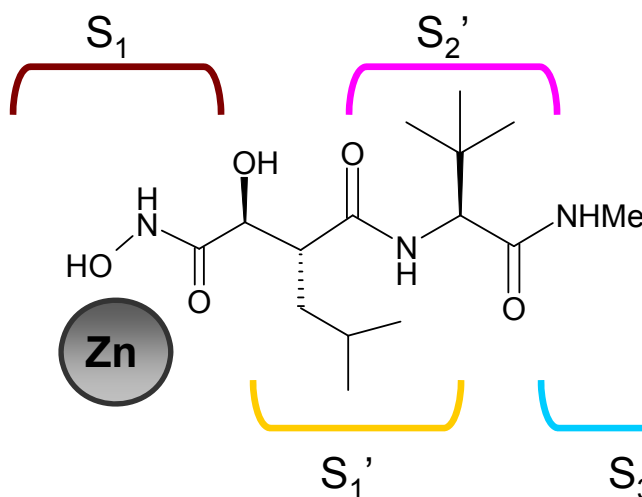
**MMPs**

*Matrix metalloproteinase family*



**Pirmās paaudzes  
TACE inhibitori**

*Marimastat un tā analogi*



**Neselektīvi  
TACE/ MMP inhibitori**

Muskuloskeletāli  
blakus efekti

**A.Jirgensonas grupa**

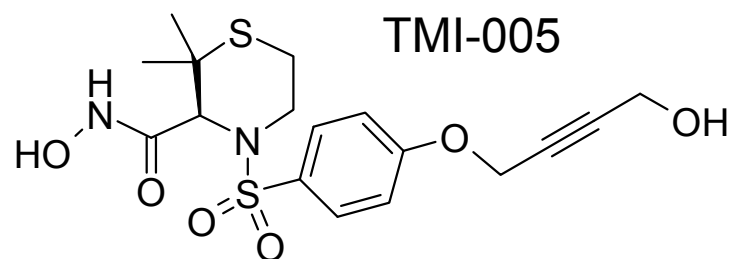
**Kleisti, 130627**



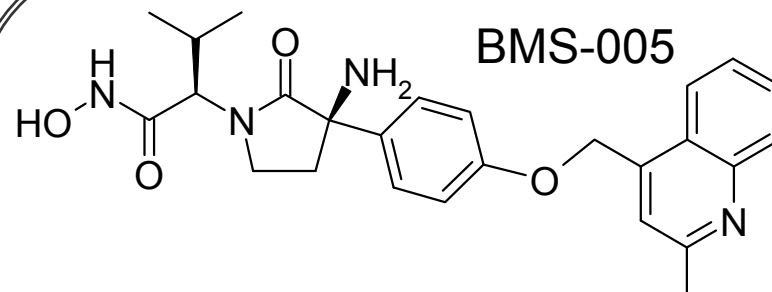
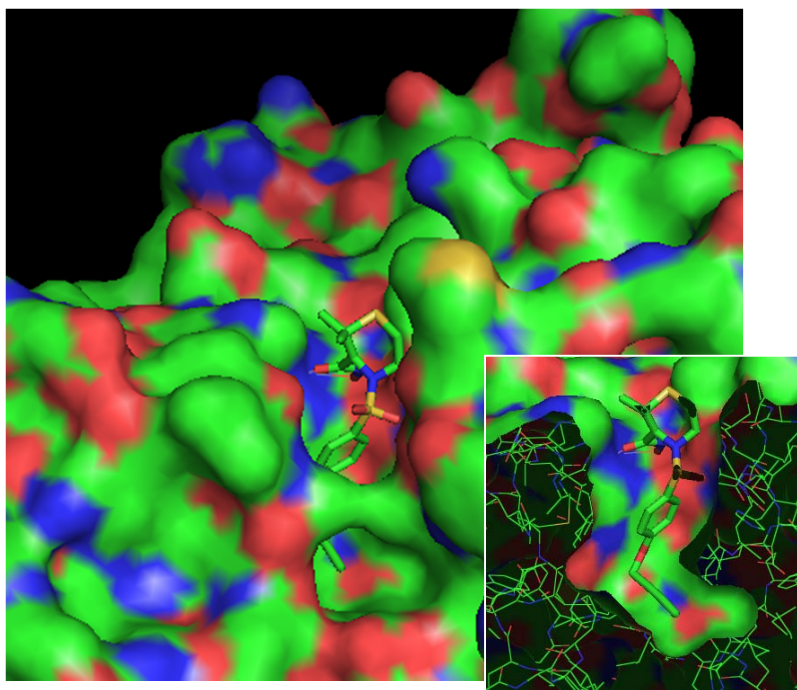
## TACEi

# TACE Inhibitoru selektivitāte

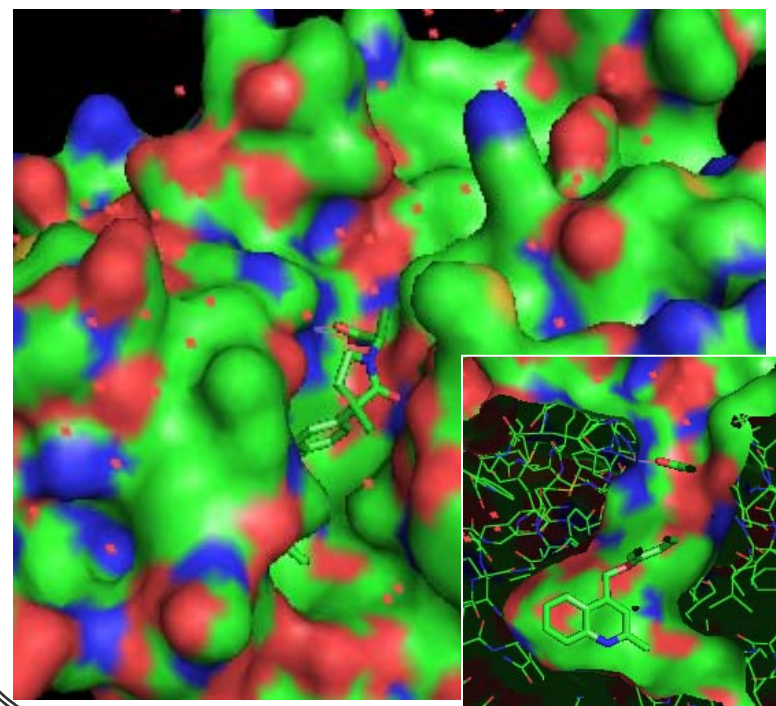
## Otrās paaudzes TACE inhibitori - selektīvi pret MMP



Wyett, II klīn. fāze



Bristol-Myers Squibb, II klīn. fāze

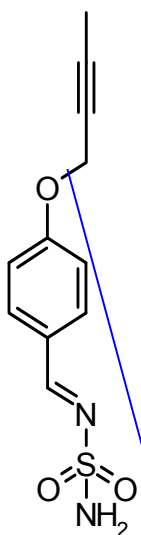
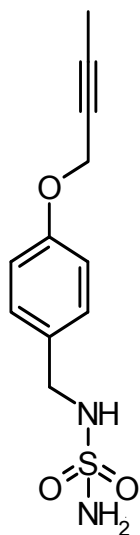
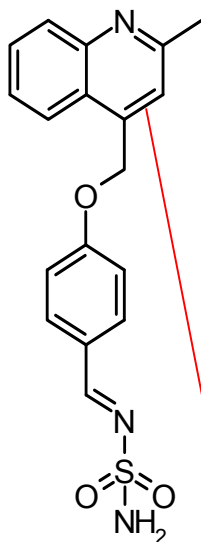
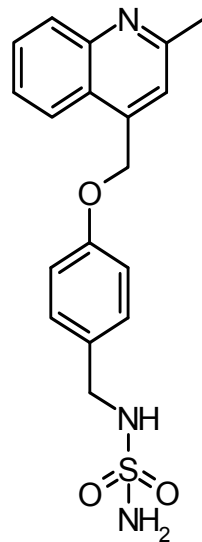
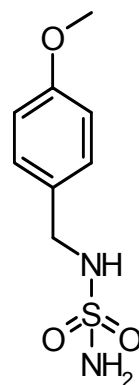
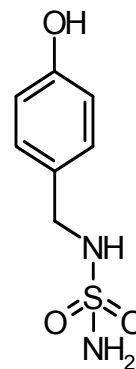


A.Jirgensona grupa

Kleisti, 130627



## Fragmenti no aktīviem savienojumiem CA skrīnings selektivitāšu uzlabošanai

GP1-53-5-2GP1-61-4-1GP1-52-5GP1-62-3GP1-58-3-3GP1-59-5-1

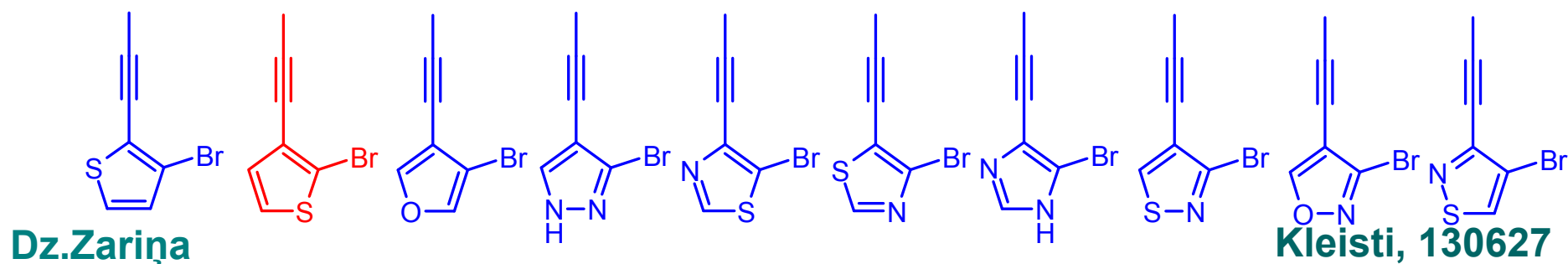
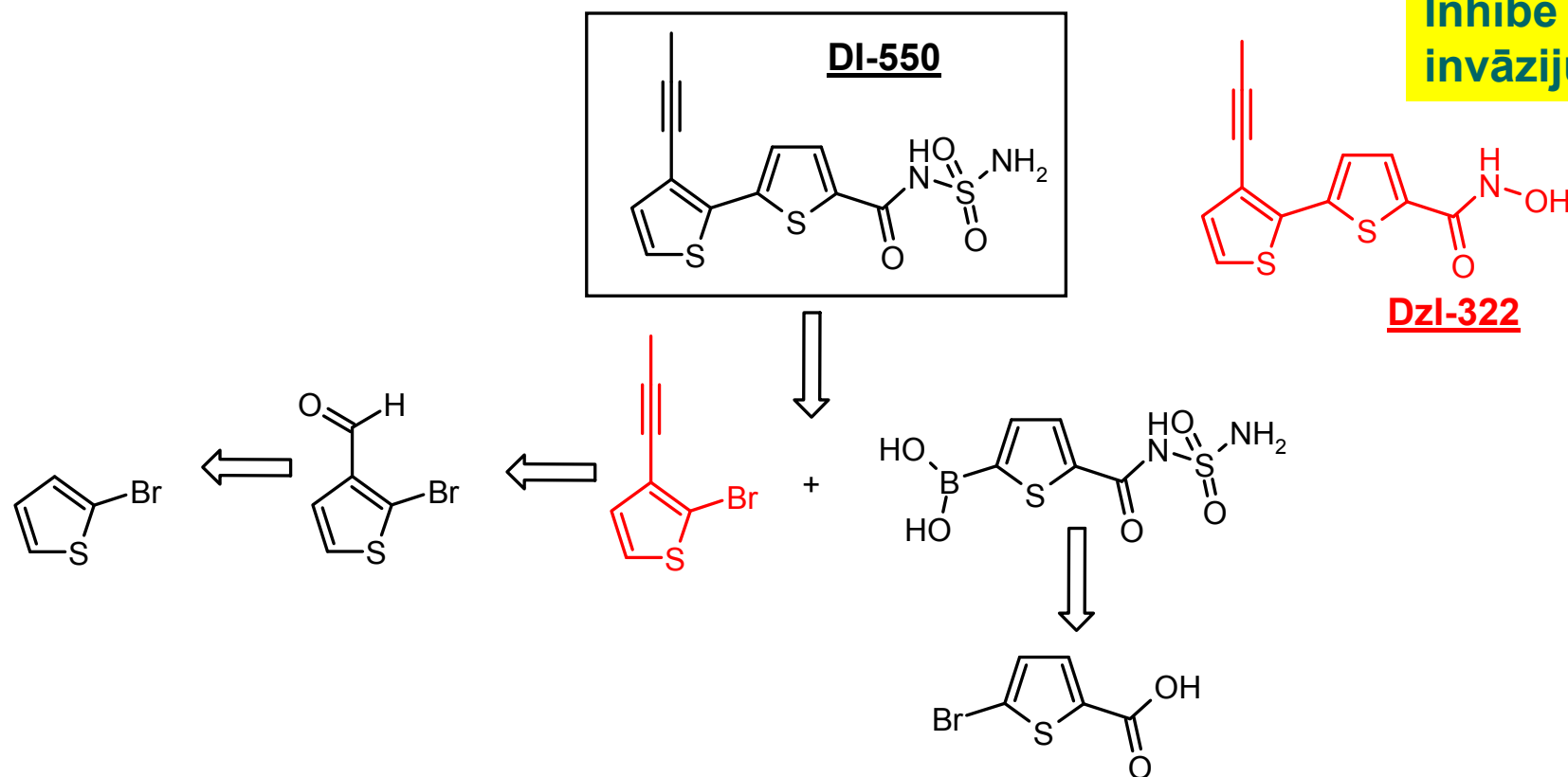
|               |               |
|---------------|---------------|
| hCAI 1940 nM  | hCAI 1810 nM  |
| hCAII 9.8 nM  | hCAII 9.5 nM  |
| hCAIX 59.1 nM | hCAIX 61.7 nM |
| hCAXII 9.4 nM | hCAXII 8.1 nM |

|               |               |
|---------------|---------------|
| hCAI 1650 nM  | hCAI 1440 nM  |
| hCAII 188 nM  | hCAII 43.3 nM |
| hCAIX 56.3 nM | hCAIX 62.1 nM |
| hCAXII 6.5 nM | hCAXII 6.6 nM |

|               |               |
|---------------|---------------|
| hCAI 4050 nM  | hCAI 2180 nM  |
| hCAII 134 nM  | hCAII 74.1 nM |
| hCAIX 60.0 nM | hCAIX 40.7 nM |
| hCAXII 6.6 nM | hCAXII 5.8 nM |

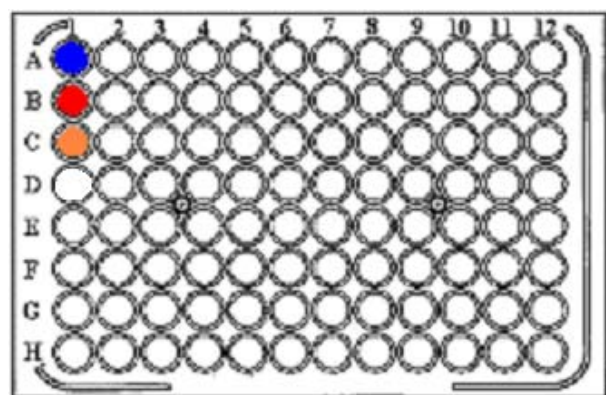
# Jauni Zn metaloproteināžu inhibitori balstīti uz kompjuāterdizainu

Inhibē  
invāziju



## HDAC inhibitoru atlase Paraugu sagatavošana

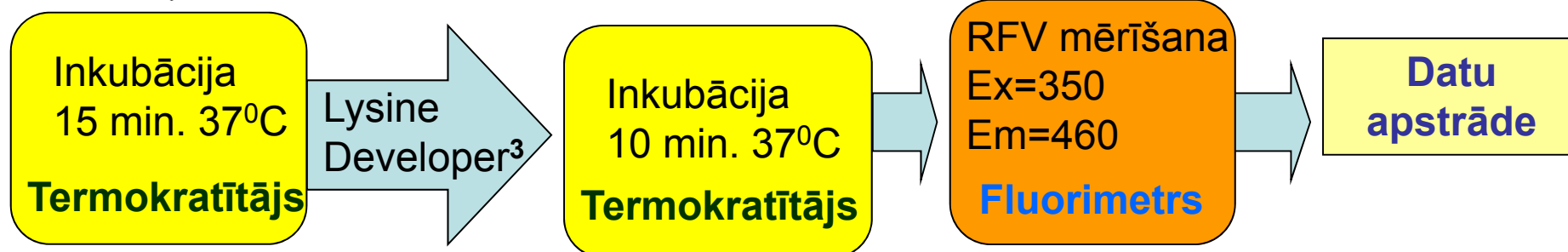
Potenciālo inhibitoru skrīningam tika izmantots  
*HDAC inhibitor Drug Screening Kit* no *Biovision*



**Kontrole:** ddH<sub>2</sub>O + buferis + HeLa kodola ekstrakts<sup>1</sup> + substrāts<sup>2</sup>

**Trihostatīns A (TSA):** ddH<sub>2</sub>O + TSA + buferis + HeLa kodola ekstrakts + substrāts

**Savienojums:** ddH<sub>2</sub>O + savienojums + buferis + HeLa kodola ekstrakts + substrāts



1. Hela - dzemdes kakla vēža šūnu līnija;
2. Substrāts – [Boc-Lys(Ac)-AMC];
3. Lysine Developer – [Boc-Lys-AMC].
4. TSA – universāls HDAC inhibitors

# Pateicības

## Sintēze

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**Kleisti, 130627**