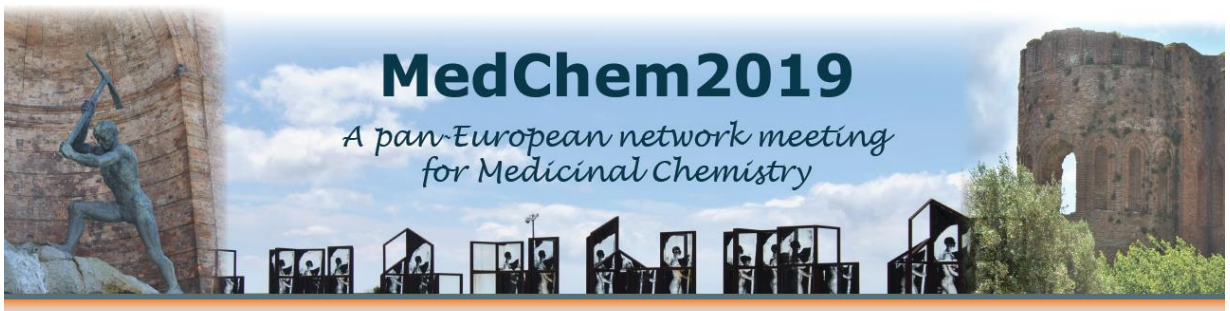
Net4Science multimedia poster session



Complesso Monumentale San Giovanni - Catanzaro (Italy), June 13th – 15th

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X-ray crystal structure of carbonic anhydrase XII complexed with a theranostic monoclonal antibody fragment

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X-ray crystal structure of carbonic anhydrase XII complexed with a theranostic monoclonal antibody fragment

Vincenzo Alterio

PC_1

Background

hCA XII is a membrane-associated CA isoform which is over-expressed in many tumors and associated with cancer progression and metastasis.

6A10 is a hCA XII inhibitory mAb, able to reduce the growth of cancer cells *in vitro* and in human xenograft lung cancer model.

Here we report on the development of a 6A10 Fab fragment, termed **Fab6A10**, and on its functional and structural characterization.

Conclusions

The X-ray structure of the hCA XII/Fab6A10 complex provides insights into the inhibition mechanism of Fab6A10, showing that it obstructs the substrate access to the active site and blocks His64 in an inactive conformation. Our data clearly indicate Fab6A10 as a new promising tool for the treatment of hCA XII-positive cancers.

Results and discussion

In vitro and *in vivo* binding of Fab6A10 to hCA XII

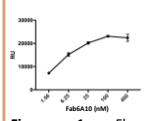

Figure 1. Flow cytometry binding assay of Fab6A10 to hCA XII-positive cells.

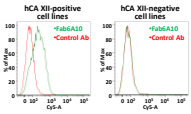

Figure 2. Flow cytometry binding specificity of Fab6A10 to hCA XII.

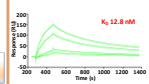

Figure 3. Surface Plasmon Resonance binding assay of Fab6A10 to hCA XII.

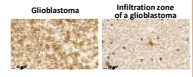

Figure 4. Frozen sections of human tissues immunostained with Fab6A10.

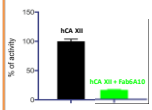

Figure 5. Inhibition of hCA XII esterase activity by Fab6A10

Isoform	K_I (nM)
hCA XII	6.6 ± 0.12
hCA I	>10000
hCA II	>10000

Table 1. Inhibition of CO_2 hydration activity of hCAs by Fab6A10

Structural characterization of the hCA XII/Fab6A10 complex

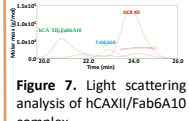

Figure 7. Light scattering analysis of hCAXII/Fab6A10 complex.

Figure 8. Crystals of hCA XII/Fab6A10 complex.

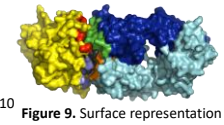

Figure 9. Surface representation of Fab6A10/hCA XII complex structure.

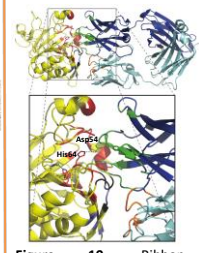

Figure 10. Ribbon representation of Fab6A10/hCA XII complex structure. Fab6A10 is reported in blue (heavy chain) and cyan (light chain), whereas hCA XII is reported in yellow.

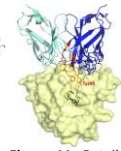

Figure 11. Detail of the hCA XII/Fab6A10 complex.

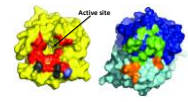

Figure 12. Fab6A10/hCA XII epitope and paratope as open-book representation.

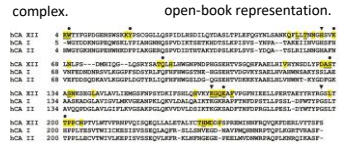

Figure 13. Structure-based sequence alignment of hCAs XII, I and II. (▼ salt bridges, ● h-bonds, _ hydrophobic interactions, ■ buried residues at the complex interface).

Compounds Targeting the RNA-Binding Protein HuR. Structure-Based Design, Synthesis and Interaction Studies.

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Compounds Targeting the RNA-Binding Protein HuR. Structure-Based Design, Synthesis and Interaction Studies.

Francesca Alessandra Ambrosio

PC_2

Background

HuR is a RNA-binding protein belongs to the family of the Embryonic Lethal Abnormal Vision proteins. HuR is a nucleic protein and its overexpression is associated with tumor progression and poor prognosis in various cancer types.

Material and Methods

✓ ***Receptor***
4ED5 pdb code[1] - Protein Preparation Wizard[2] - Molecular Dynamics simulation.[2]
✓ ***Ligands***
LigPrep Tools[2] pH 7.4.
✓ ***Docking simulations***
Glide SP[2] v. 6.7

Results and discussion

The compounds were ranked by the Docking Scores; the best docking pose of each compound was subjected to Molecular Mechanism Generalized Born Suface Area (MM-GBSA).[2] Our Molecular modeling studies are in agreement with STD, NMR experimental analysis.

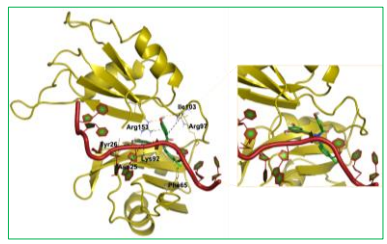

Figure 1. 3D representation of HuR−4 interactions. RNA and HuR are represented as a brown and yellow cartoon, respectively. Compound 4 is shown in green sticks. The interactions are showed as colored dashed lines.

Compounds	Docking score kcal/mol	MMGBSA dG Bind kcal/mol
1	-5,923	-43,62
2	-5.687	-55,32
3	-7,159	-55,7
4	-6.952	-47,08

Table 1. Docking Score and predicted binding-free energies (MMGBSA dG Bind) values of compounds with respect to the HuR protein.

Conclusions

Combining STD, NMR and in silico studies, we provide a guide for further research on the development of new effective HuR−RNA complex interfering compounds as new potential pharmacological tool in the treatment of several pathologies, such as cancer, inflammation and neurodegeneration, in which ELAV-RNA complexes play a pivotal role.

References:
1. Wang, H. et Al. *Acta Crystallographic Section D Structural Biology* **2013**. *69*,373-80
2. Schrödinger, LLC, New York, NY, 2017.

Benzothienoquinazolinones as new inhibitors of Topoisomerases and Tubulin

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Benzothienoquinazolinones as new inhibitors of Topoisomerases and Tubulin

Alexia Barbarossa

PC_3

Background

Benzothienoquinazolinones are Ellipticine's derivatives that showed a promising anti-proliferative activity toward two breast cancer cell lines. Molecular docking studies were also performed on Tubulin, Topoisomerase I and II and demonstrated that the compounds are able to bind them with a relatively high affinity.

Material and Methods

Molecular docking studies were performed on crystallographic enzyme structures of Tubulin, Topoisomerase I and II. Anti-proliferative activity was evaluated using MTT assay toward two breast cancer cell lines: Human estrogen receptor (ER)-positive MCF-7 and triple negative MDA-MB-231.

Results and discussion

The aim of this work was to study a new library of benzothienoquinazolinones, analogues of Ellipticine, in which both the carbazole moiety and the pyridine ring were substituted with a dibenzothiophene- and a pyrimidine moiety, respectively, through a simple one pot reaction.
The biological evaluation were performed in order to analyze the capability of these compounds to arrest cancer cells growth. Promising results have been obtained for these derivatives that exhibited an interesting anti-proliferative activity, mostly against highly metastatic MDA-MB-231. cells. To predict the mechanism of action molecular docking studies have been carried out. They pointed out that the tested compounds are able to bind Tubulin, Topoisomerases I and II at least in the low micromolar range.

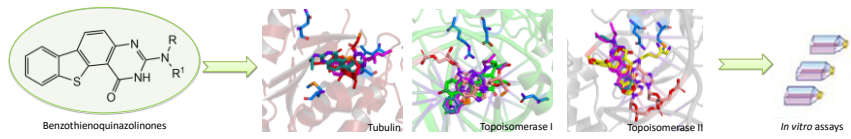

Figure 1. Docking studies and biological evaluation of new benzothienoquinazolinones

Conclusions

Discussed data give us the hope to consider the new synthetized compounds as promising tools for the cancer-fighting. However other *in vitro* assays are in progress to confirm *in silico* results.

Design, synthesis and pharmacological characterization of novel potent non-steroidal agonists of the farnesoid X receptor

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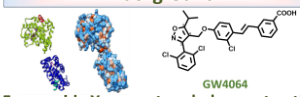
Design, synthesis and pharmacological characterization of novel potent non-steroidal agonists of the farnesoid X receptor

Giuliana Baronissi

PC_4

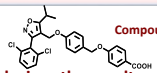
Background



GW4064

Farnesoid X receptor belongs to the super-family of nuclear receptor. FXR is expressed in the liver, kidney and intestine cells, and regulate the homeostasis and metabolism of the bile acids.[1, 2] The most potent endogenous FXR activator is chenodeoxycholic acid (CDCA), with a steroidal structure. In recent years, with the discovery of GW4064, a non-steroidal FXR agonist, new molecules active on FXR have been synthesized but with improved pharmacokinetics and toxicity.

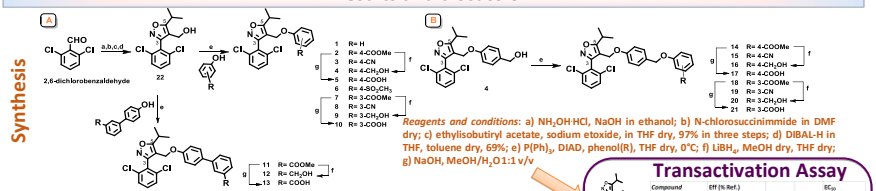
Conclusions

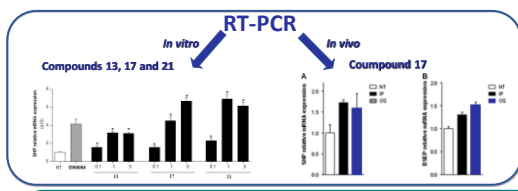


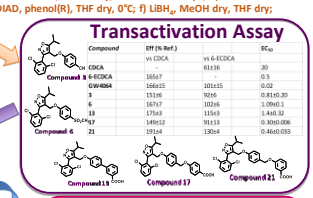
Compound 17

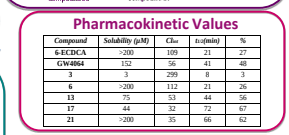
In conclusion, the results obtained showed that, modifications on the GW4064 scaffold, allowed to obtain a library of non-steroidal FXR agonists among which compound 17 was the most promising, also in the treatment of APAP liver toxicity.

Results and discussion

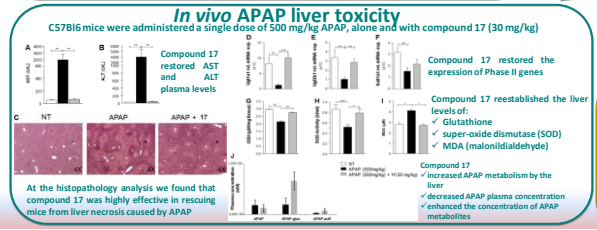


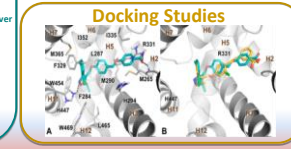






Compound	Solubility (μM)	Cl_{int}	$t_{1/2}$(min)	%
6-ECDCA	>200	109	21	27
GW4064	152	56	41	48
3	3	299	8	3
6	>200	112	21	26
13	75	53	44	56
17	44	52	72	67
21	>200	35	66	62





Hydroxypyridin-4-ones are a versatile scaffold to develop copper(II)-chelating COMT inhibitors with neuroprotective properties

Tiago Silva[a,b], Carlos Fernandes[b] , Lisa Sequeira[b], Vera Silva[b,c], Renata Silva[c], Patrício Soares-da-Silva[e] and Fernanda Borges[b]

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Presenting Author: Tiago Barros Silva

PC_5

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Hydroxypyridin-4-ones are a versatile scaffold to develop copper(II)-chelating COMT inhibitors with neuroprotective properties

Tiago Barros Silva

PC_5

Background

Catechol O-methyltransferase (COMT) inhibitors are valuable co-adjuvant drugs in the clinical management of Parkinson's disease. Standard COMT inhibitors based on the nitrocatechol scaffold, which chelates the Mg co-factor within COMT and lead to a tight-binding inhibition mechanism. While effective, these drugs have been linked to drug-induced hepatotoxicity and poor brain bioavailability. In our study, we explored alternative scaffolds that mimic the pharmacological behavior of nitrocatechols under physiological conditions and focused our strategy on hydroxypyridin-4-ones. The rationale for this approach is to develop COMT inhibitors lacking the nitro group, circumventing the risk of nitrocatechol-induced toxicity.

Material and Methods

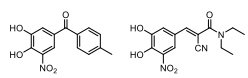
Hydroxypyridinones were synthesized from kojic acid according to the synthetic strategy depicted in the results section. All derivatives were characterized by NMR and EI-MS. *In vitro* COMT inhibition at a fixed concentration of 30 µM was evaluated in rat liver homogenates by measuring the formation of metanephrine by HPLC. Metal chelation was evaluated by recording a full UV/Vis scan of a solution of the test compounds in phosphate buffer (pH 7.4) and observing spectral alterations when the compounds are incubated with aq. MCl_2. SH-SY5Y cells were cultured in DMEM high glucose 10% FBS, seeded onto 96-well plates (25000 cells/cm^2) and differentiated with retinoic acid 10 µM.

Conclusions

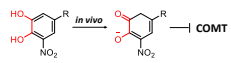
Our results show that **TS22** is a promising **hit** for further development as a **COMT inhibitor** with potential **neuroprotective** activity and increased **safety** over standard COMT inhibitor tolcapone.

Results and discussion

Standard COMT inhibitors



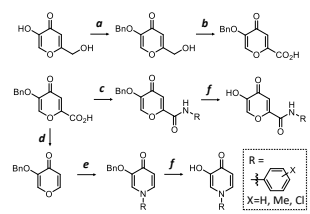
Tolcapone Hepatotoxic — **Entacapone** Low BBB permeability



3-hydroxypyridin-4-ones

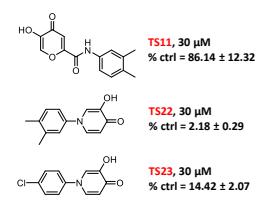
- **Mimic** nitrocatechols *in vivo*
- C-O$^-$ ionised without **NO_2 group**
- **Lower risk** of hepatotoxicity

Synthesis of 3-hydroxypyridin-4-ones



a BnCl, MeOH, NaOH, reflux, 6h; ***b*** Jones 2.5 M, acetone, rt, overnight; ***c*** 1. $POCl_3$, DMF, rt, 30', 2. RNH_2, MW, 120ºC, 5'; ***d*** Ph2O, 250ºC, 10'; ***e*** RNH_2, HCl 0.38 M, EtOH, 100ºC, 1h; ***f*** 1. BBr_3, DCM anhydrous, -80C, 6 h, 2. H_2O, 30', rt.

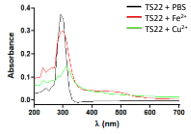
COMT inhibition & preliminary SAR



SAR

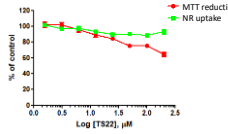
- **C2-amides** are **not** well tolerated
- ***N*-phenyl** ring is **well tolerated**
- ***N*-PhMe** groups **increase** activity

Interaction of TS22 with metals

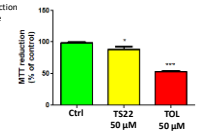


- **TS22** interacts **selectively** with **Cu^{2+}**

Cytotoxicity of TS22 in SH-SY5Y cells

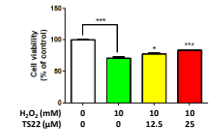


- **TS22** is **not toxic** up to **100 µM (MTT)**



- **TS22** is **safer** than **tolcapone**

Neuroprotection



- **Dose-dependent tendency**

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Study of pyrazolo[3,4-*b*]pyridin-6-one and pyrazolo[3,4-*b*]pyridine scaffolds as MNK inhibitors

Elisabeth Bou-Petit [a], Helena Alarcón [a], Pedro Jesús Guijarro [b], Marta Emperador [b], Stefan Hümmer [b], Roger Estrada-Tejedor [a], Santiago Ramon y Cajal [b] and José I. Borrell [a].

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PC_6

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PERSONA CIÈNCIA EMPRESA
UNIVERSITAT RAMON LLULL

Vall d'Hebron
Institut de Recerca

Study of pyrazolo[3,4-*b*]pyridin-6-one and pyrazolo[3,4-*b*]pyridine scaffolds as MNK inhibitors

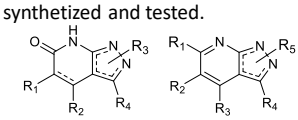
Elisabeth Bou-Petit

PC_6

Background

Phosphorylation of eIF4E by MNK1/2 is essential for oncogenesis but dispensable for normal development. Thus, pharmacological inhibition of MNKs may offer an effective and non-toxic anti-cancer therapeutic strategy.

Here we study the suitability of two new scaffolds as MNK inhibitors. Up to 5 families of compounds derivates of such structures have been synthetized and tested.

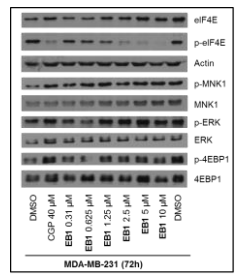


Conclusions

Compound **EB1** is a type II inhibitor that selectively inhibits eIF4E phosphorylation a low micromolar ranges and shows promising results in combination with chemotherapy.

Results and discussion

Biological activity: Compound **EB1** completely and selectively inhibits MNKs between 2.5 and 5 µM (EC_{50} = 1.2 µM) with no cell toxicity. Selectivity of **EB1** was tested in a panel of 320 kinases.



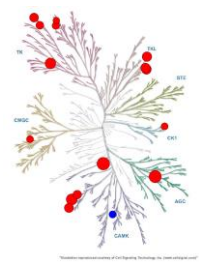


Figure 1. Activity of **EB1** tested by western blot and the kinome showing its selectivity

Binding mode: Active and inactive models of MNK1 were used to study the interaction mode of the hits. **EB1** is a type II inhibitor that inhibits the inactive form of the MNK1 kinase.

Combination with chemotherapy: Co-treatment with **EB1** increases the sensitivity of MB-MDA-231 cells to doxorubicin improving the efficacy of the drug in inhibiting cell growth.

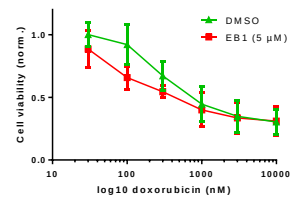


Figure 2. IC_{50} of doxorubicin with **EB1** or control (DMSO)

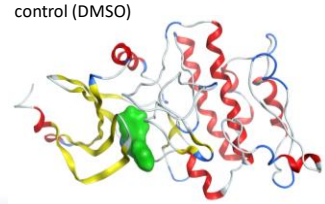


Figure 3. Model of MNK1 inactive with **EB1**

3'-Deoxy-3'-fluoro-7-deazapurine nucleosides: synthesis and evaluation against kinetoplastid parasites

Jakob Bouton,[a] Fabian Hulpia,[a] Louis Maes,[b] Guy Caljon[b] and Serge Van Calenbergh,[a]

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PC_7

3'-Deoxy-3'-fluoro-7-deazapurine nucleosides: synthesis and evaluation against kinetoplastid parasites

Bouton

PC_7

Background

- Kinetoplastid parasites are the causative agents of several neglected tropical diseases
- The purine salvage pathway is an attractive target
- Previously: several potent 7-deazapurine ribonucleoside hits

Combining a 7-deazapurine nucleobase with 3'-deoxy-3'-fluororibose

Conclusions

13.2 shows potent antileishmanial activity & no toxicity

Further evaluation in early curative hamster model

Results and discussion

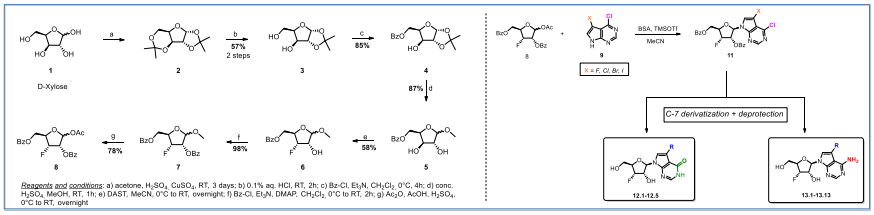
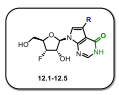
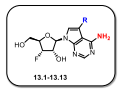


Figure 1. Synthesis





Compound	R =	MRC-5 (µM)	*T.cruzi* (µM)	*L. Inf.* (µM)	*T. b. brucei* (µM)	*T. b. rhod* (µM)	PMM cytotox (µM)
12.1	H	> 64,0	> 64,0	> 64,0	> 64,0	> 64,0	> 64,0
12.2	F	> 64,0	> 64,0	> 64,0	> 64,0	> 64,0	> 64,0
12.3	Br	> 64,0	> 64,0	> 64,0	> 64,0	> 64,0	> 64,0
12.4	I	> 64,0	> 64,0	> 64,0	> 64,0	> 64,0	> 64,0
12.5	Ph	> 64,0	> 64,0	> 64,0	> 64,0	> 64,0	> 64,0
13.1	F	> 64,0	0,21	2,00	0,43	0,04	> 64,0
13.2	Cl	22,63	0,09	0,08	0,13	0,03	0,13
13.3	Br	40,99	0,05	0,71	0,03	0,03	2,00
13.4	I	4,39	0,03	1,50	0,03	0,007	2,00
13.5	CN	1,32	9,67	2,03	10,48	0,38	2,00
13.6	$CONH_2$	2,38	7,10	32,46	2,34	0,12	32,00
13.7	ethynyl	0,19	0,04	0,13	0,04	0,02	0,13
13.8	vinyl	27,86	0,80	50,80	0,86	0,32	> 64,0
13.9	Me	> 64,0	18,87	12,70	0,61	0,12	> 64,0
13.10	Et	40,32	> 64,0	> 64,0	20,49	21,26	> 64,0
13.11	Ph	> 64,0	9,14	50,80	32,00	32,69	> 64,0
13.12	4-Cl-Ph	16,93	0,74	12,70	7,02	5,18	32,00
13.13	4-OMe-Ph	14,11	8,61	32,46	43,62	25,72	32,00
13.14	3,4-diCl-Ph	4,14	0,22	2,83	2,70	1,55	8,00

Figure 2. Antikinetoplastid activity

Development of new antibiotics based on natural scaffolds

Fernando Cagide,[a] Catarina Oliveira,[a] Sofia Benfeito,[a] Carlos Fernandes,[a] Alexandra Gaspar[a] and Fernanda Borges[a]

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PC_8

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Development of new antibiotics based on natural scaffolds

Fernando Cagide Fagin

PC_8

Background

Nowadays, antibiotics are indispensable to treat bacterial infections. However, resistance of bacteria to conventional antimicrobial (antibacterial, antiparasitic and antifungal) drugs is a fast-growing problem, causing millions of deaths every year and demanding seeking new antibiotics.

In this context, in 2017, the World Health Organization (WHO) issued a global priority pathogen list to guide efforts to find new antibiotics against the current public health bacterial threats. Gram-positive bacterial pathogens, such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Enterococcus faecium*, are responsible for community-acquired and hospital-associated infections and are an increasing public health threat. For these reasons, there is an urgent need for new antimicrobial and therapeutic strategies to deal with the ever-evolving antimicrobial resistance among the most prevalent bacterial pathogens.

Therefore, the aim of this project has been focused on the design and synthesis of innovative phosphonium salts as antibiotics. In order to achieve this goal, structural changes were performed in natural phenolic antioxidants present in human diet (as benzoic and cinnamic acids) by inserting an aliphatic carbon chain spacers and a triphenylphosphonium cation (TPP$^+$). The natural scaffolds are widely distributed in plants and fruits and display a great structural variety. In addition, a wide range of pharmacological activities of these natural compounds as well as of some quaternary phosphonium salts, as antimicrobial and/or enzymatic inhibitors[1-3] have been reported.

[1] Oliveira, C.; Cagide, F.; Teixeira, J.; Amorim, R.; Sequeira, L.; Mestil, F.; Silva, T.; Garrido, J.; Remião, F.; Vilar, S.; Uriarte, E.; Oliveira, P.J.; Borges, F., Frontiers in Chemistry, 2018, 6, 126.
[2] Teixeira, J.; Oliveira, C.; Amorim, R.; Cagide, F.; Garrido, J.; Ribeiro, J.A.; Pereira, C.M.; Silva, A.F.; Andrade, P.B.; Oliveira, P.J.; Borges, F., Scientific Reports, Nature, 2017, 7, 6842.
[3] Benfeito, S.; Oliveira, C.; Soares, P.; Fernandes, C.; Silva, T.; Teixeira, J.; Borges, F., Mitochondrion, 2013, 13, 427-435.

Conclusions

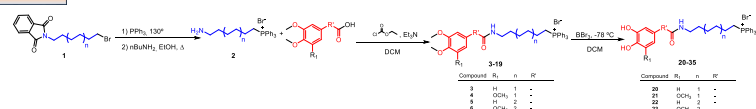
- A library of novel 17 cationic compounds was synthesized;
- Compounds **24**, **25**, **29-33** are inhibitors of *Methicillin-Resistant Staphylococcus aureus* (MRSA);
- Compounds **25**, **29-32**, **34** are inhibitors of *Cryptococcus neoformans var. grubii*;
- Compounds **29**, **31-33** are inhibitors of *Candida albicans*;
- Compound **33** does not display toxicity in human embryonic kidney cells or haemolytic activity.
- Mechanistic studies are on progress for the best candidates

Acknowledgments

This project was supported by FEDER/COMPETE POCI-01-0145-FEDER-028397 and Norte-01-0145-FEDER-000028 We thank CO-ADD (The Community for Antimicrobial Drug Discovery), funded by the Wellcome Trust (UK) and The University of Queensland (Australia) for performing antimicrobial screening of compounds.

Results and discussion

Synthesis



Compound	R_1	n	R'
3	H	1	-
4	OCH_3	1	-
5	H	2	-
6	OCH_3	2	-
7	H	3	-
8	OCH_3	3	-
9	OCH_3	2	CH=CH
10	H	1	CH_2CH_2
11	H	2	CH_2
12	OCH_3	2	CH=CH
13	OCH_3	3	CH_2
14	H	3	CH=CH
15	H	3	CH_2CH_2
16	H	3	CH_2
17	OCH_3	1	CH=CH
18	OCH_3	1	CH_2CH_2
19	OCH_3	1	CH_2

Compound	R_1	n	R'
20	H	1	-
21	OCH_3	1	-
22	H	2	-
23	OCH_3	2	-
24	H	3	-
25	OCH_3	2	-
26	OCH_3	2	CH=CH
27	H	1	CH_2CH_2
28	H	1	CH_2
29	OCH_3	2	CH=CH
30	OCH_3	3	CH_2
31	H	3	CH=CH
32	H	3	CH_2CH_2
33	H	3	CH_2
34	OCH_3	1	CH=CH
35	OCH_3	1	CH_2CH_2
36	OCH_3	1	CH_2

- ✓ **A four-step synthetic strategy was established;**
- ✓ **Simple and effective work-ups;**
- ✓ **A diverse and concise library of cationic compounds was obtained.**

Biological data

Preliminary screening

Antimicrobial activity of phosphonium salts (20-36) at 32 μg/mL

Compound	Sa*	Ec*	Kp*	Pa*	Ab*	Ca*	Cn *
20	25,78	19,83	20,41	3,19	-16,77	-1,51	3,56
21	61,08	39,45	25,12	30,59	40,29	0,52	-11,65
22	49,07	27,56	22,4	21,21	27,17	3,28	-36,8
23	71,05	50,66	31,72	30,3	50,77	2,5	-20,38
24	92,34	47,4	24,72	46,65	32,78	3,07	-39,52
25	93,52	56,87	34,72	43,11	43,77	7,43	-36,96
26	84,06	37,15	39,05	68,45	30,54	16,88	-23,2
27	63,94	22,14	17,07	14,84	1,11	0,07	23,44
28	41,24	15,81	21,68	10,6	6,94	7,12	22,49
29	83,42	39,31	44,67	63,24	43,13	99,13	89,44
30	92,32	88,75	37,7	71,03	51,76	6,83	18,99
31	85,54	32,13	26,02	60,81	14,94	60,52	91,04
32	94,26	59,31	35,71	49,91	35,86	99,73	104,5
33	94,87	53,8	27,21	35,06	16,56	4,55	98,67
34	52,51	32,76	33,13	65,19	15,1	5,43	-7,69
35	77,7	57,45	37,61	74,21	40,86	9,86	57,44
36	68,59	40,09	32,31	67,16	16,16	4,56	26,47

*Sa (*Staphylococcus aureus* (MRSA), ATCC BAA-1717), Ec (*Escherichia coli*), Kp (*Klebsiella pneumoniae*), Ab (*Acinetobacter baumannii*), Pa (*Pseudomonas aeruginosa*), Ca (*Candida albicans*), Cn (*Cryptococcus neoformans var. grubii*), Hk (human embryonic kidney cells), Hm (human erythrocytes)

Subsequent screening

Antimicrobial (MIC, μg/mL), cytotoxic (CC_{50}) and haemolytic (HC_{10}) outline of phosphonium salts (20-36)

Compound	Sa*	Ec*	Kp*	Pa*	Ab*	Ca*	Cn *	Hk*	Hm*
20	>32	>32	>32	>32	>32	>32	>32	>32	>32
21	>32	>32	>32	>32	>32	>32	>32	20,79	>32
22	-	-	-	-	-	-	-	-	-
23	32	>32	>32	>32	>32	>32	>32	>32	>32
24	8	>32	>32	>32	>32	>32	>32	9,07	>32
25	16	>32	>32	>32	>32	>32	>32	>32	>32
26	32	>32	>32	>32	>32	>32	16	>32	>32
27	32	>32	>32	>32	>32	>32	>32	>32	>32
28	>32	>32	>32	>32	>32	>32	>32	>32	>32
29	16	>32	>32	>32	>32	16	4	>32	6,00
30	8	>32	>32	>32	>32	>32	32	>32	>32
31	8	>32	>32	>32	>32	16	16	10,74	11,87
32	4	>32	>32	>32	>32	16	32	20,54	>32
33	8	>32	>32	>32	>32	32	>32	31,16	>32
34	>32	>32	>32	>32	>32	>32	16	>32	>32
35	32	>32	>32	>32	>32	>32	>32	>32	>32
36	32	>32	>32	>32	>32	>32	>32	>32	>32

*Sa (*Staphylococcus aureus* (MRSA), ATCC BAA-1717), Ec (*Escherichia coli*), Kp (*Klebsiella pneumoniae*), Ab (*Acinetobacter baumannii*), Pa (*Pseudomonas aeruginosa*), Ca (*Candida albicans*), Cn (*Cryptococcus neoformans var. grubii*), Hk (human embryonic kidney cells), Hm (human erythrocytes)

Metabolites prediction at the Mu.Ta.Lig. Chemotheca

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PC_9

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Metabolites prediction at the Mu.Ta.Lig. Chemotheca

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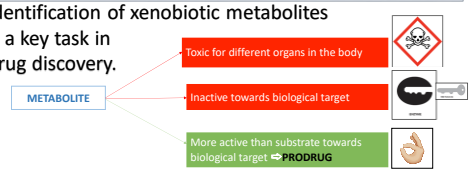
PC_9

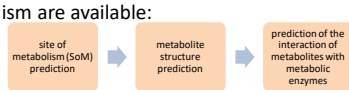
Background

Identification of xenobiotic metabolites is a key task in drug discovery.



Material and Methods

Different approaches for predicting xenobiotic metabolism are available:



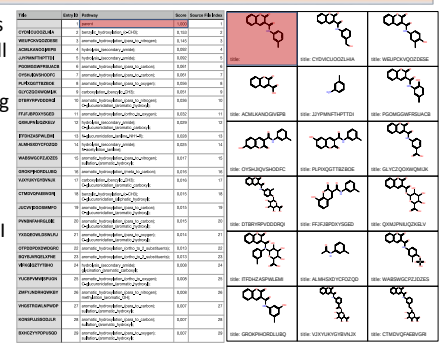
SyGMa (Systematic Generation of potential Metabolites), developed by Organon (now Schering-Plough) and released as open source code, is a reaction rules based approach.

Conclusions

Because rule-based methods ignore the role of specific interactions and orientation in enzymes that catalyze the reaction, the quality of the predictions will be measured also in terms of the ability to reproduce experimental metabolites by lipidomic analysis.

Results and discussion

SyGMa predicts metabolites by systematically applying all metabolic rules to a parent molecule, thereby generating all possible metabolites. The metabolite structures are reported and scored. This software is currently used to calculate the phase I and II metabolites of the Mu.Ta.Lig. Chemotheca stored molecules.



The Mu.Ta.Lig. Chemotheca was developed within the COST ACTION CA15135[4] framework. Chemotheca. Metabolites prediction is going to be implemented in the Chemotheca as new additive molecular descriptor.

chemotheca.unicz.it

Interesting biological properties of Anchusa azurea Mill. (Boraginaceae) methanol extract

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PC_10

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Interesting biological properties of *Anchusa azurea Mill.* (Boraginaceae) methanol extract

Jessica Ceramella

PC_10

Background

Anchusa azurea Mill. (Boraginaceae family) is distributed in the Mediterranean region and it was used in traditional medicine for its wide biological properties (anti-arthritic, anti-rheumatic, cathartic, diuretic, stimulant, etc.). In this work we report the chemical composition, the anti-cancer activity toward different cancer cell lines and the antioxidant properties of the *A. azurea* aerial parts methanol extract.

Material and Methods

The aerial parts of *A. azurea* were collected in Cosenza and extracted with methanol at RT. Phenols, anthocyaninis and flavonoids content was evaluated by using the Folin-Ciocalteu, pH-differential and aluminium chloride colorimetric assays, respectively. *In vitro* antioxidant activity was evaluated by ABTS, DPPH, FRAP and β-Carotene bleaching tests and ROS protection assay on 3T3-L1 cell lines. The anti-proliferative activity was evaluated toward 4 cell lines (MCF-7, MDA-MB-231, RKO, R_2C) using MTT assay. TUNEL assay, immunofluorescence and immunoblotting were used to evaluate the molecular mechanism.

Results and discussion

The phytochemical profile evidences that chlorogenic acid, catechin, caffeic acid, and astragalin are the main abundant constituents. Thanks to a rich phenolic content, *A. azurea* extract possess a promising antioxidant activity and protects 3T3-L1 mouse cells from oxidative stress. Furthermore, it exhibits a good antitumor activity, mostly toward the human colorectal RKO cells, highly aggressive and metastatic, with very low toxicity. This property relies on the ability of *A. azurea* extract to induce the activation of the intrinsic apoptotic pathway, acting as a cell cytoskeleton interfering agent.

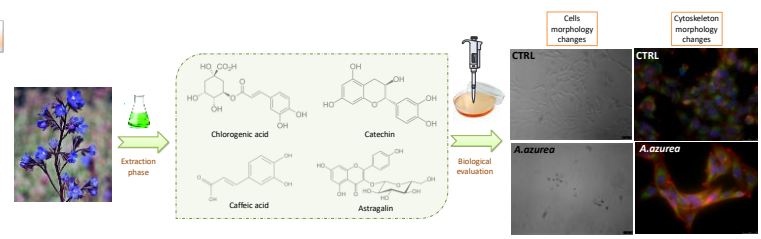

Figure 1. Chemical composition and biological properties of *A. azurea Mill.* methanol extract

Conclusions

The promising biological activities of *A. azurea* methanol extract suggest that it may represent an interesting resource for the developing of new anticancer agents.

Upcoming targets in neurodegenerative diseases: a molecular recognition study.

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PC_11

Upcoming targets in neurodegenerative diseases: a molecular recognition study.

Adriana Coricello

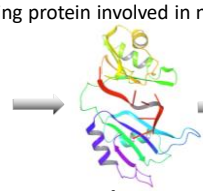
PC_11

Background

HuD is an RNA-binding protein involved in neurodegerative disorders.[1]

mRNA stabilization

Translation improvement



Neurogenesis

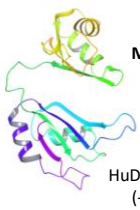
Axonal regeneration

Figure 1. 3D representation of HuD-RNA complex. PDB ID: 1FXL.[2]

Material and Methods

- Ligand Preparation (75808 compounds) pH 7.4 – LigPrep Tools.
- 500 ns MD simulation (NPT, explicit water) – Desmond v 3.8.[3]
- Structure-based virtual screening (SP)– Glide v 5.0 .[4]
- HuD-ligands STD-NMR experimets performed on the best *hits* (Bruker Avance spectrometer, 600 MHz).

Results and discussion



HuD *closed* conformation (-8810.5 Kcal/mol).

Molecular Docking simulations → **ADMET and PAINS filters** → ***8 HITS*** → **STD-NMR Experiments**

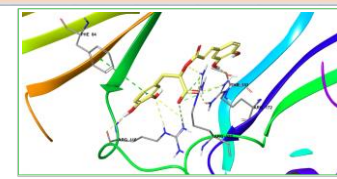


Figure 2. Binding mode of the best hit in HuD binding site. The protein and the ligand are showed as cartoon and sticks, respectively.

Conclusions

The predictive Molecular Modeling results were confirmed by STD-NMR analyses. Further studies will be carried out in order to investigate new therapeutic opportunities to counteract neurodegenerative diseases.

References:
1 Good, PJ. *Proceedings of the National Academy of Sciences*. **1995**; 92:4557-4561.
2 Wang , X et al. *Nature Structural Biology*. **2001**; 8:141-145.
3 Bowers, KJ et al. Proceedings of the ACM/IEEE Conference on Supercomputing (SC06), Tampa, Florida, **2006**, November 11-17.
4 Friesner, RA et al., *Journal of Medicinal Chemistry*, **2004**; 47:1739-1749.

New donepezil-like multi-target directed ligands for Alzheimer's Disease based on hydroxytyrosol

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New donepezil-like multi-target directed ligands for Alzheimer's Disease based on hydroxytyrosol

Paola Costanzo

PC_12

Background

Recently it was revealed that polyphenolic component of extra virgin olive oil, in particular hydroxytyrosol (HTy), could be neuroprotective against Aβ-induced neurotoxicity in neuroblastoma N2a cells [1]. Considering the multi-factorial nature of AD and basing on our previous experience [2], donepezil modifications to develop novel Multi-Target Direct Ligands (MTDL) have been carried out. Then, we propose to combine the antioxidant/free radical scavenging activity of the Hty with the acetyl cholinesterase inhibition activity of Donepezil (Figure 1).

References

[1] St-Laurent-Thibault et. al., *Current Alzheimer Research* **2011,** *8*, 543-551. **[2]** Costanzo et al., *ACS Medicinal Chemistry Letters* **2016,** *7(5),* 470-475.

Results and discussion

Different synthetic strategies were tested in order to conjugate the two different synthons in good yields.

Natural polyphenols, nitro and acetylated derivatives were obtained.

For all the novel derivatives will be assessed:

- AChE/BuChE, COMT and MAO inhibitory activity,
- ROS scavenging activity and ORAC test,
- chelating properties
- potential cytotoxicity.

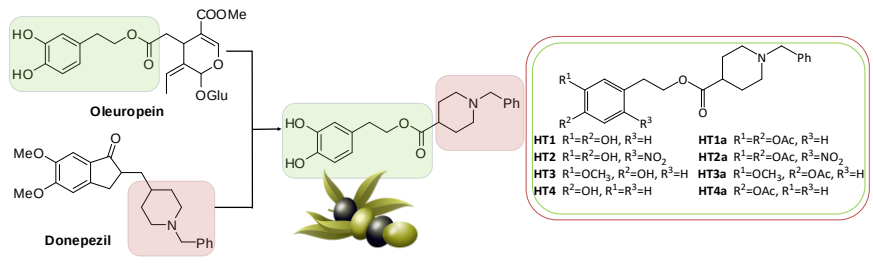

Figure 1. Chemical structure of designed MTDL donepezil-like.

Conclusion

The design, synthesis, characterization and preliminary biological tests of donepezil-Hydroxytyrosol hybrids are described.

Exploring conformational variability of benzoxaborole derivatives for the development of selective carbonic anhydrase inhibitors

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Exploring conformational variability of benzoxaborole derivatives for the development of selective carbonic anhydrase inhibitors

Anna Di Fiore

PC_13

Background

Human carbonic anhydrases (hCAs) have been recognized as drug targets. However, the limitation of CA inhibitors (CAIs) as therapeutics are related to their poor selectivity. Recently, a novel CAI class containing the benzoxaborole moiety has been investigated.

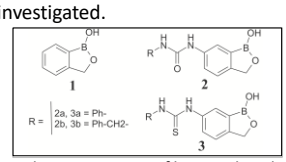

Figure 1. Schematic picture of benzoxaborole CAIs

Conclusions

Our data show that urea- and thiourea-benzoxaborole derivatives are an interesting class of versatile CAIs. X-Ray analysis combined with theoretical calculations highlight how the residue in position 131 plays a key role in determining the different binding mode for these inhibitors to the hCA active site.

Results and discussion

Inhibition Studies

Benzoxaboroles are selective CAIs.

CAI	K_i (nM)			
	hCA I	hCA II	hCA IX	hCA XII
1	5690	8180	>50000	>50000
2a	654	730	1060	240
2b	557	439	925	184
3a	548	1148	436	76
3b	380	1305	610	42

X-Ray Crystallography

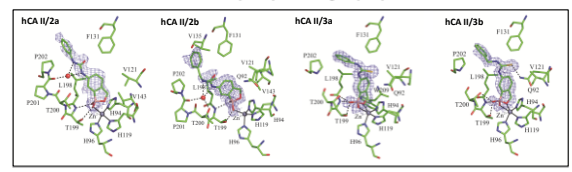

Figure 2. hCA II/inhibitor adducts

Notably, even if compounds **2a** and **2b** differ from **3a** and **3b** only for one atom, their conformational arrangement is completely different: **2a** and **2b** have a *trans-trans* geometry of the urea moiety, whereas **3a** and **3b** have a *trans-cis* geometry of the thiourea.

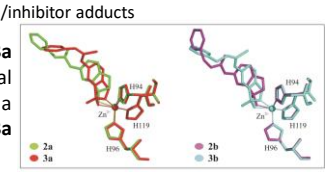

Figure 3. Superposition of urea- and thiourea-benzoxaborole analogues

Binding Free Energy Calculations

Per-residue decomposition of the binding free energy was evaluated for hCA II/inhibitor adducts by using the MM/GBSA method. These calculations indicate that interactions of urea and thiourea moieties with Phe131 modulate the binding conformation of the inhibitors within the enzyme active site.

	hCA II/2a	hCA II/2b	hCA II/3a	hCA II/3b	Δ3a¶	Δ3b‡
ΔG_{bind}-Gln92	-1,059	-1,555	-1,690	-3,772	-0,044	-0,135
ΔG_{bind}-Phe131	-1,224	-2,349	-2,295	-2,165	15,054	1,486
ΔG_{bind}-Val135	-1,622	-1,500	-1,243	-1,483	0,409	-0,075
ΔG_{bind}-Val143	-0,863	-1,493	-1,752	-1,614	-0,001	0,005
ΔG_{bind}-Leu198	-7,392	-7,211	-7,292	-7,062	-0,106	0,110
ΔG_{bind}-Thr199	-3,374	-2,879	-3,350	-3,238	0,009	0,043
ΔG_{bind}-Thr200	-2,611	-1,883	-3,683	-3,616	-0,050	-0,111
ΔG_{bind}-Pro202	-2,775	-1,886	-1,647	-2,456	-0,080	-0,011

¶ hCA II/**3a*** - hCA II/**2a**; ‡ hCA II/**3b*** - hCA II/**2b**

Pentafluorosulfanyl (SF_5) moiety as promising substituent in synthesis and design of novel D_2 and D_3 receptors ligands

Milica Elek,[a] Annika Frank,[a] Nemanja Djokovic,[b] Slavica Oljacic,[b] Aleksandra Zivkovic,[a] Katarina Nikolic,[b] and Holger Stark [a]

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PC_14

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Pentafluorosulfanyl (SF_5) moiety as promising substituent in synthesis and design of novel D_2 and D_3 receptors ligands

Milica Elek [a] Annika Frank,[a] Nemanja Djokovic, [b] Slavica Oljacic,[b] Aleksandra Zivkovic,[a] Katarina Nikolic,[b] and Holger Stark [a]

PC_14

Background

The **pentafluorosulfanyl moiety** displays high electronegativity and lipophilicity, while being thermally stable[1] and more resistant to hydrolysis in comparison to those of CF_3 or OCF_3 groups.[2] Therefore, SF_5 substituents were introduced in previously described dopamine D_2/D_3 receptor (D_2R/D_3R) pharmacophores (**Fig.1**).[3]

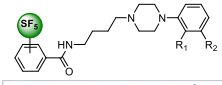

Fig. 1: Structural blueprint of newly synthesized SF_5 containing D_2R/D_3R ligands.

Material and Methods

Four compounds have been synthesized (**Fig. 2**). For in silico data were obtained using molecular docking Gold 5.6.3 and Gaussian 09 software.[4,5] Radioligand displacment assays were performed as described previously.[6]

Conclusions

In silico results obtained correlate with in vitro obtained pK_i values. Ligands demonstrated **similar binding modes** as those of known D_2R/D_3R antagonists. **SF_5 substituent is a promising tool.**

Results and discussion

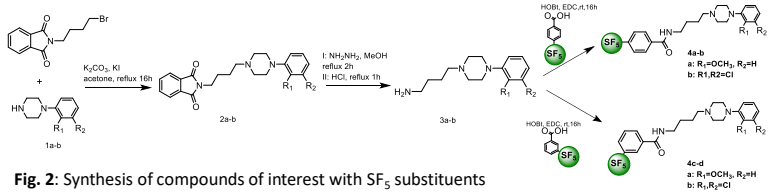

Fig. 2: Synthesis of compounds of interest with SF_5 substituents

Binding modes (with corresponding coefficients of determination: R^2 =0.917 (D_3R) and R^2=0.318 (D_2R)) indicate that phenylpiperazinyl moiety binds to orthosteric binding site (OBS), while arylamide tail extending to the extracellular vestibule (D_3R) and extended binding pocket (D_2R) (**Fig. 3**). All ligands showed affinities at D_2R and D_3R in nanomolar concentrations (**Fig. 4**) with slight preference for D_3R.

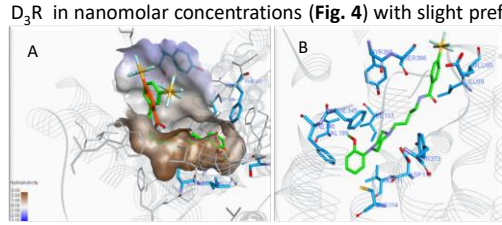

Fig. 3: Binding modes of ligands; **A) 4a** (red sticks) and **4c** (green sticks) in D_2R.[7]; **B) 4a** in D_3R.[8]

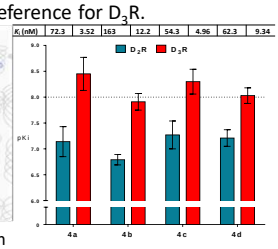

Fig. 4: In vitro D_2R/D_3R binding data.

[1] Das, P.; Tokunaga, E., Shibata, N., Recent advancements in the synthesis pentafluorosulfanyl (SF5)-containing heteroaromatic compounds. *Tetrahedron Lett.*, **2017**, 58 (52), 4803-4815. [2] Vida, N.; Václavík, J., Beier, P., Synthesis and reactivity of aliphatic sulfur pentafluorides from substituted (pentafluorosulfanyl)benzenes. *Beilstein J. Org. Chem.*, **2016**, 12 (1), 110-1. [3] Hackling AE; Stark H., Dopamine D3 receptor ligands with antagonist properties. *ChemBioChem.* **2002**, 3 (10), 946-61. [4] Jones G et al., Development and validation of a genetic algorithm for flexible docking. *J. Mol. Biol.*, **1997**, 267 (3), 727-48. [5] Cambridge Soft Corporation. 2013. ChemBio3D Ultra, Version 13.0. Cambridge, MA, USA. [6] Frank A; Kiss DJ, Keserü GM, Stark H., Binding kinetics of cariprazine and aripiprazole at the dopamine D3 receptor. *Sci. Rep.*, **2018**, 8 (1), 12505. [7] Wang S et al., Structure of the D2 dopamine receptor bound to the atypical antipsychotic drug risperidone. *Nature*. **2018**, 555 (7695), 269. [8] Chen EY et al., Structure of the human dopamine D3 receptor in complex with a D2/D3 selective antagonist. Science. **2010**, 330 (6007), 1091-5.

A novel binuclear hydrazone-based Cd(II) complex is a strong pro-apoptotic inducer with significant activity against 2D and 3D pancreatic cancer stem cells

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PC_15

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- Additional information:

Research interests

- Rational design and synthesis of MDR tumors targeting compounds
- Small molecule/biomacromolecule interactions

A novel binuclear hydrazone-based Cd(II) complex is a strong pro-apoptotic inducer with significant activity against 2D and 3D pancreatic cancer stem cells

Nenad Filipović

PC_15

Background

- Cd was classified as a human carcinogen.
- A paradoxical effect in the cancer treatment:
  stable Cd compounds may exert apoptosis, DNA damaging and inhibition of cancer relevant targets.

Material and Methods

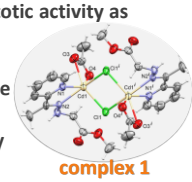
- MCF-7 cancer and AsPC-1 cancer stem cells (apoptosis, cell cycle, caspase inhibition, Mito SOx, growth inhibition on 3D tumor models)
- DNA and HSA interactions and docking studies.

Conclusions

Complex 1 is an excellent proapoptotic inducer in both cell lines and displays substantial activity against highly resistant pancreatic cancer stem cells.

Results and discussion

- **1 has superior pro-apoptotic activity as compared to CDDP**
- **1 is a strong inducer of mitochondrial superoxide generation**
- **1 shows a mighty activity on 3D CSC models**



complex 1

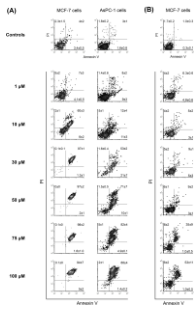


Figure 1. Incidences of apoptotic and necrotic deaths in cells treated with 1 (A) and CDDP (B).

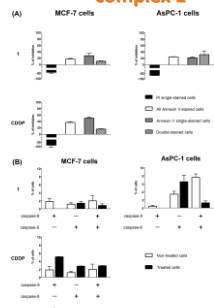


Figure 2. Caspase-dependency of cell death: co-incubation with pan-caspase inhibitor (A); % cells with activated caspases (B).

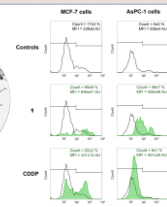


Figure 3. Mito Sox generation.

Figure 5. The most favorable docking solution for **1**-DNA interaction.

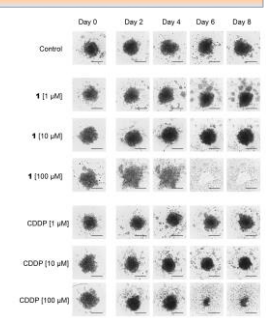


Figure 4. Changes in size and morphology of MCF-7 3D spheroids over the 8 days.

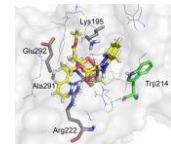


Figure 6. Complex **1** docked into IIA binding site of HSA.

Heterocyclic amides as selective inhibitors of HRV-B replication

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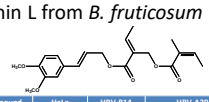
Heterocyclic amides as selective inhibitors of HRV-B replication

Benedetta Fois

PC_16

Morinin L from *Bupleurum fruticosum* is an anti-HRV-A capsid binder

Human Rhinovirus (HRVs) are the most common viral infectious agents and HRV infections have been reported to lead to worsening of chronic obstructive pulmonary disease and cystic fibrosis [1]. In a previous work, we identified Morinin L from *B. fruticosum* as anti-HRV-A capsid binder [2].



Compound	HeLa CC_{50} (μM)	HRV-B14 EC_{50} (μM)	HRV-A39 EC_{50} (μM) (SI)
Morinin L	20.3 ± 1.8	> 20.3	2.4 ± 0.04 (8.4)
Pleconaril	131 ± 1.2	0.2 ± 0.01	0.1 ± 0.01

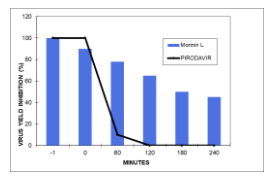
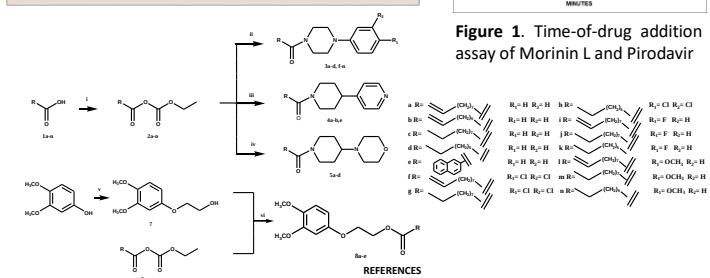


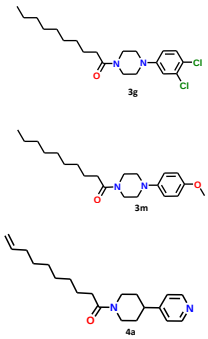
Figure 1. Time-of-drug addition assay of Morinin L and Pirodavir

Synthesis of Morinin L Analogues



Results and discussion

Compound	HeLa CC_{50} (μM)	HRV-B14 EC_{50} (μM)	HRV-A02 EC_{50} (μM) (SI)
3a	81.75 ± 3.1	11.85 ± 1.1	>100
3b	>100	45.0 ± 2.4	>100
3c	79.23 ± 2.2	5.7 ± 0.1	>100
3d	>100	>100	>100
3f	98.25 ± 4.8	4.0 ± 0.1	>75
3g	98.00 ± 3.3	1.4 ± 0.08	>75
3h	88.28 ± 3.8	>15	>15
3i	77 ± 1.7	6.6 ± 0.1	>100
3j	75.4 ± 5.1	3.1 ± 0.08	>100
3k	>100	>100	>100
3l	>100	2.9 ± 0.05	>100
3m	>100	1.0 ± 0.02	>100
3n	>100	>100	>100
4a	81.1 ± 6.0	1.4 ± 0.07	>75
4b	>100	>100	>100
4e	>100	>100	>100
5a	96.1 ± 3.9	>96.1	>96.1
5b	>34.0	>34.0	>34.0
5c	385.2	>385.2	>385.2
5d	209.1	>209.1	>209.1
8a	>100	>100	>100
8b	>100	>100	>100
8c	>100	>100	>100
8d	>100	>100	>100
8e	>100	24.6 ± 1.7	15.3 ± 0.1
Pleconaril	> 100	0.2 ± 0.01	0.3 ± 0.02



Conclusions

- Some compounds inhibited the replication of HRV-14 with EC_{50} values in the low micromolar range with low citotoxicity.
- In contrast with the natural compound, all synthetic active derivatives showed a reversal of selectivity towards the viral species B (HRV-14).

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[1] Jacobs, E.S.; Lamson, D.M.; Walsh T.J., *Clinical Microbiology Reviews* **2013**, *26*, 135-162.

[2] Fois, B.; Bianco, G.; Sonar, V.P.; Distinto, S.; Maccioni, E.; Meleddu, R.; Melis,C.; Marras,L.; Pompei, R.; Floris,C.; Caboni,P.; Cottiglia,F., *Journal of Natural Products* **2017**, *80*, 2799-2806.

New complexes of platinum(II): effects on sensitive and resistant cells

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New complexes of platinum(II): effects on sensitive and resistant cells

Mariafrancesca Hyeraci

PC_17

Background

Cisplatin-based therapies suffer from the occurrence of resistance, a multifactorial event that involves reduced intracellular uptake, increased intracellular repair of DNA damage, increased deactivation of platinum species, enhanced drug efflux and the failure of apoptotic pathways.

Material and Methods

Antiproliferative activity:

- A2780 (ovarian cancer)
- A2780cis (resistant ovarian cancer)

ICP-AES: quantitative determination of P and Pt to DNA and in cells

Cytofluorimetric determinations

Conclusions

A3 and **B2** show the ability to overcome cisplatin resistance

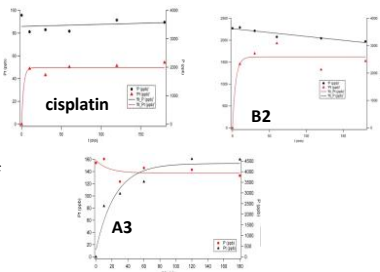
The binding of **A3** to DNA is comparable to that of the drug, while for **B2** it is significantly lower.

A3 and **B2** are accumulated by resistant cells more efficiently than cisplatin, and induce mitochondrial depolarisation.

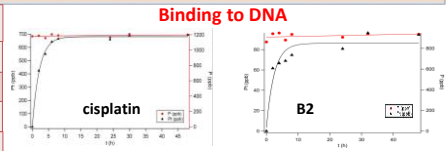
Results and discussion

	GI_{50} (μM)	
Complex	A2780	A2780cis
A3	2.45±0.33	1.60±0.35
B2	0.31±0.03	1.38±0.55
cisPt	0.80±0.06	7.23±0.26

A2780cis - cell uptake

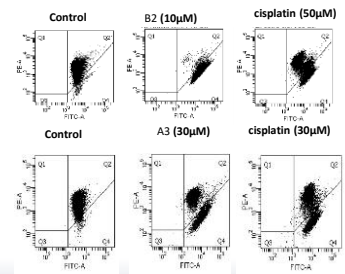


Binding to DNA



Complex	Structure
A3	
B2	

A2780cis – mitochondrial depolarisation



Design, synthesis and biological evaluation of pyrazine derivatives

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  - Project was financially supported by SVV 260-401.

Design, synthesis and biological evaluation of pyrazine derivatives

Martin Juhás, Jan Zitko and Martin Doležal

PC_18

Background

Alanyl-racemase (Alr) is a well-known bacterial target. Many of the recognized inhibitors disrupt its activity by blocking Alr cofactor pyridoxal-5-phosphate (PLP). We prepared a series of amino acid substituted **pyrazinamide** (PZA) derivatives, related to structure of PLP-alanine (PLP-Ala in **Fig. 1**) and tested the inhibition of (myco)bacterial growth.

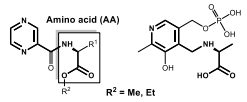
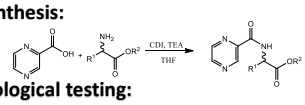


Fig. 1 Proposed derivatives vs. PLP-Ala

Material and Methods

***In silico* design:** docking in MOE 2019.01

Synthesis:



Biological testing:

microdilution broth method (MABA).

This project was financially supported by SVV 260-401.

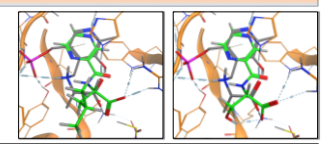
Results and discussion

Docking

Mycobacterium tuberculosis Alr, PDB ID: **1xfc**

Score of PLP-Ala = -10, majority of derivatives = -7 to -6

Poses compared to pose of PLP-Ala



Synthetic, *in silico* results and biological activities

Code	R¹/AA	Yield	Docking score		*Mycobacteria* spp. MIC (μg/ml)						Selected bacteria and fungi MIC (μM)			
			Ester	Acid	*M.smeg.*	*M.aurum*	*M.kansasii*	*M.avium*	*Mtb* H37Ra	*Mtb* H37Rv	*SE*	*CK*	*CT*	*TI*
PC-D-Ser	Ser	20%		-6.3	≥500	≥500	>100	>100	≥500	>100	>500	>500	>500	**500**
PC-D-Ala	Ala	26%		-5.9	≥500	≥500	>100	>100	≥500	>100	>500	>500	>500	>500
PC-DL-Ala-Me	Ala	17%	NA	NA	NA	NA	NA	NA	NA	NA	>500	**250**	>500	>500
PC-MeAcr	R¹: =CH₂	11%	-5.7	-6.4	**31.25**	**62.5**	**100**	>100	**15.625**	**50**	>125	>125	>125	>125
PC-Gly	Gly	10%		-6	**≥500**	≥500	>100	>100	≥500	>100	>500	**500**	>500	>500
PC-Gly-Et	Gly	22%	-5.8		**250**	≥500	NA	NA	≥500	NA	>500	>500	>500	>500
PC-DL-Val-Et	Val	31%	NA	NA	**250**	≥500	>100	>100	≥500	>100	>500	>500	>500	>500
PC-L-Val-Me	Val	76%	>-5.0	-6.2	**250**	≥500	NA	NA	≥500	NA	>500	>500	>500	>500
PC-D-Val-Me	Val	34%	-6.7	-6.2	**≥500**	≥500	NA	NA	≥500	NA	>500	>500	>500	>500
PC-DL-Leu-Et	Leu	83%	NA	NA	**250**	**250**	>100	>100	**250**	**100**	>500	>500	>500	>500
PC-L-Leu-Me	Leu	66%	-6.4	-6.8	**250**	**≥500**	>100	>100	**250**	**100**	**500**	>500	>500	>500
PC-D-Leu-Me	Leu	85%	>-5.0	>-5.0	**250**	**≥500**	>100	>100	**≥500**	**>100**	>500	>500	>500	>500
PC-D-Pgl-Me	Pgl	55%	-6.5	-6.5	NA	NA	NA	NA	NA	NA	>500	>500	**500**	>500
PC-DL-Phe-Et	Phe	94%	NA	NA	**250**	≥500	>100	>100	**250**	>100	**500**	>500	>500	>500
PC-CPC-Et	R¹: cycloPe	10%	-6.5	-6.8	≥500	≥500	>100	>100	≥500	>100	>500	>500	>500	>500
PC-L-Asp-diEt	Asp	25%	-6.9	>-5.0	≥500	≥500	NA	NA	≥500	NA	**500**	>500	>500	>500
INH					7.81	3.91	25	25	0.25	0.39				

***Mtb**-Mycobacterium tuberculosis, **SE**-S. epidermidis, **CK**-Candida krusei, **CT**-C. tropicalis, **TI**-Trichophyton interdigitale, **NA**–not available*

Conclusions

Mild activity, mainly antimycobacterial, was noted for the lipophilic derivatives (Val, Leu, Phe). Esters seem to be more active than free acids. No activity was seen in most G+, G- bacteria and fungi (some not presented). Differences were observed in activities of stereoisomers, L-antipods were more active *e.g.* in Val and Leu-derivatives.

Conjugates of tuftsin-based peptide carriers and phenolic antitubercular molecules

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- **e-mail:** martin.kratky@faf.cuni.cz
- **Additional information:** This work was supported by the Czech Science Foundation project No. 17-27514Y and by the project EFSA-CDN (No. CZ.02.1.01/0.0/0.0/16_019/0000841) co-funded by ERDF.

Conjugates of tuftsin-based peptide carriers and phenolic antitubercular molecules

Martin Krátký

PC_19

Background

- Global spread of tuberculosis-TB
- Increasing drug-resistance
- Latent TB and its reactivation
- Complicated treatment
- Disadvantages of current drugs
- Potential solutions
  - new drugs
  - drug delivery systems (DDSs)

Material and Methods

- Synthesis of small molecules
- Synthesis of tuftsin-based peptide DDSs (solid-phase)
- Their mutual conjugation
- Biological evaluation
- Stability study

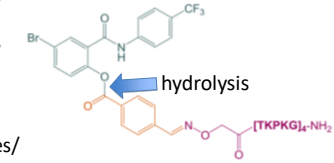
Results and discussion

Small molecules (salicylanilides, triclosan, their esters and carbamates)

- Comparatively simple synthesis (up to four steps) with high yields
- High activity against *Mycobacterium tuberculosis* and atypical mycobacteria (MIC ≥1 μM) including drug-resistant strains
- Considerable cytotoxicity and low intracellular activity (phenols)
- Esters and carbamates: predominantly **improved activity** and **lower toxicity**

Oligotuftsin peptide carriers ($[TKPKG]_n$)

- A library of various carriers was obtained using solid-phase synthesis (Fmoc/t-Bu strategy)
  - various length, substituents to control lipophilicity, modification at N-terminus and/or lysine side chain ε-amino group
- **Non-toxic**, **immunostimulating**, **targeting of macrophages**
- Stable under *in vitro* evaluation conditions



Conjugates

- Synthesis mainly by oxime ligation (in solution)
- The activity/toxicity identical with parent free salicylanilides/ triclosan (!), worse than esters/carbamates used for conjugation with DDSs
- Experimentally detected rapid hydrolysis of ester/carbamate bond (x stability of esters)

Conclusions

- Phenols were converted to esters/carbamates to be coupled with peptide DDSs → enhanced anti-TB activity, lower toxicity
- Conjugation with tuftsin analogues – successful synthesis
  - Previous results: conjugates – improved solubility, cellular uptake, intracellular activity, decreased toxicity of small molecules
  - Surprisingly in this study – no improvement of biological activity → a quick hydrolysis of ester/carbamate bond found
- Ester/carbamate bond is inapplicable for this type of compounds, carbonyl group should be attached directly to the anti-TB scaffold

The CD98hc oncoprotein as a target of novel anticancer therapeutic approaches

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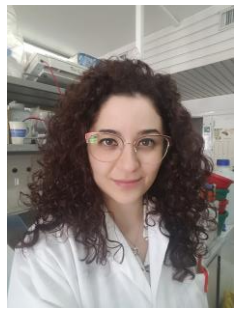

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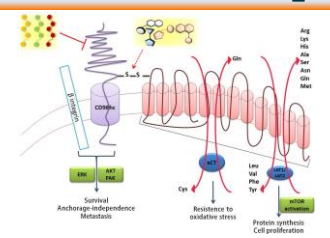
The CD98hc oncoprotein as a target of novel anticancer therapeutic approaches

Delia Lanzillotta

PC_20

Background

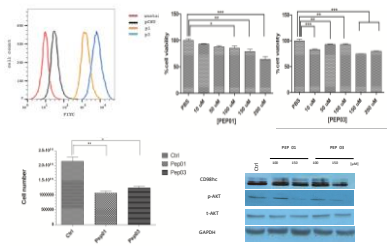
The oncoprotein CD98hc is a very interesting candidate for the development of innovative targeted drugs. CD98hc, representing the heavy chain of a transmembrane aminoacids transporter, is overexpressed in several human cancers. CD98hc is linked to light chains (LATs, xCT) by disulfide bridge. The light chain confers substrate specificity and ERK, AKT, FAK and mTOR pathways are involved in downstream signals. Moreover, CD98hc is a co-receptor of b-integrins and it is involved in cell proliferation, migration and invasion. Very recently, as candidate CD98hc inhibitors we identified two peptides and 15 small molecules (putatively targeting the disulfide bridge) by means of phage display and *in silico* screenings, respectively.



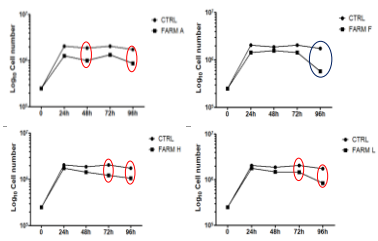
Mechanism of action of compounds on CD98hc

Results

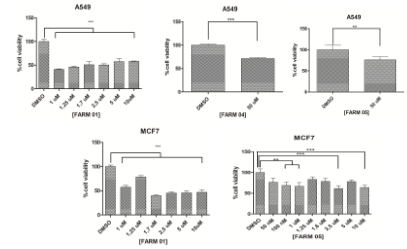
CD98hc-interacting peptides



Co-treatment with peptide 03+small molecules



CD98hc-interacting small molecules



Conclusions

Taken together, our observations encourage a deeper characterization of these candidate anticancer molecules to develop potentially new drugs to be used in a combinatorial approach for the treatment of cancer patients.

Discovery of pyrrolo[2,3-*b*]pyridine nucleoside analogues as anti-*Trypanosoma cruzi* agents

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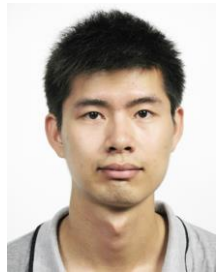

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PC_21

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Discovery of pyrrolo[2,3-*b*]pyridine nucleoside analogues as anti-*Trypanosoma cruzi* agents

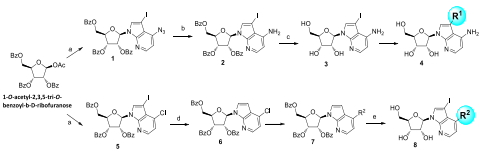
Cai Lin,[x] Fabian Hulpia,[x] Kristof Van Hecke, Louis Maes, Guy Caljon, Maria de Nazaré C. Soeiro,and Serge Van Calenbergh

PC_21

Background

➢ Chagas disease (CD) is a neglected tropical disease caused by *Trypanosoma cruzi.*
➢ *T.cruzi* relies on the salvage of host purines → purine-nucleoside analogs as promising candidates.
➢ Previous work: 7-deazapurine modification
➢ This work: 1,7-dideazapurine nucleosides analogs.

Chemistry



Conclusions

Results and discussion

R^1	*T.cruzi* EC_{50} (μM)	MRC-5 EC_{50} (μM)	SI
H	*2.27*	17.9 ± 4.4	7.9
F	8.8 ± 2.4	>64.0	>7.3
Cl	0.19 ± 0.051	>64.0	>337
Br	0.20 ± 0.020	>64.0	>320
I	**0.040 ± 0.013**	**>64.0**	**>1600**
CF_3	1.56 ± 0.85	0.73 ± 0.12	0.47
NO_2	*47.7*	*>64.0*	>1.3
CN	4.00 ± 0.00	18.5 ± 15.2	4.6
Methyl	1.14 ± 0.61	51.6 ± 12.4	45
Ethyl	>64.0	>64.0	--
Vinyl	0.81 ± 0.27	>64.0	>79
E-styryl	>64.0	>64.0	--
Ethynyl	**0.080 ± 0.026**	**59.01 ± 4.99**	**738**
Phenylethynyl	>64.0	>64.0	--
Phenyl	>64.0	>64.0	--
4-Chlorophenyl	>64.0	>64.0	--
2-Thienyl	36.9 ± 0.75	>64.0	>1.7
2-Pyridyl	>64.0	>64.0	--
Cyclohexen-1-yl	>64.0	>64.0	--
Cyclohexyl	>64.0	>64.0	--
Benznidazole	2.36 ± 0.14	N.D.	--

Structure	*T.cruzi* EC_{50} (μM)	MRC-5 EC_{50} (μM)	SI
	0.040 ± 0.013	>64.0	>1600
	1.75 ± 0.99	52.9 ± 11.2	>30.2
	7.98 ± 2.83	2.29 ± 1.71	0.29
	2.14	*2.18*	*1.0*
	0.80 ± 0.025	5.35 ± 0.31	6.7
	>64.0	>64.0	--
	>64.0	>64.0	--
	>64.0	>64.0	--
	>64.0	>64.0	--

➢ Small groups as C-7 substituents preferred
➢ 7-Iodo and ethynyl derivatives: subnanomolar EC_{50}-values
➢ 6-Amino group is essential for the potent activity
➢ 2-', 3' and 5'-deoxygenation → activity↓

Design and synthesis of new potential theranostic agents targeting tumor-expressed carbonic anhydrase IX and XII

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PC_22

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Design and synthesis of new potential theranostic agents targeting tumor-expressed carbonic anhydrase IX and XII

Francesca Mancuso

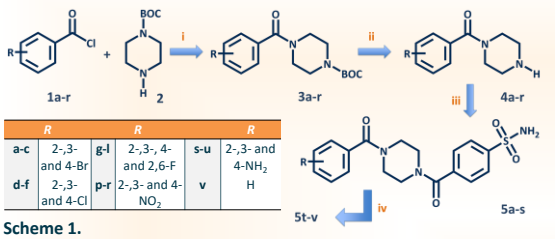
PC_22

Background

Human carbonic anhydrases (hCAs) are a family of metalloenzymes that catalyze the hydration of CO_2 to $^{-}HCO_3$ and H^+. To obtain new theranostic tools in cancer therapy an attractive strategy is focused on the development of selective molecules targeting hCA IX/XII.

Material and Methods

a. Chemistry



R		R		R	
a-c	2-,3- and 4-Br	g-l	2-,3-, 4- and 2,6-F	s-u	2-,3- and 4-NH_2
d-f	2-,3- and 4-Cl	p-r	2-,3- and 4-NO_2	v	H

Scheme 1.
(i) DCM, EDIPA, rt, 3h; (ii) DCM, TFA, rt, 4 h; (iii) DMF, HBTU, 4-Sulfamoylbenzoic acid, DIPEA, rt, overnight; (iv) EtOH, NH_2-NH_2·H_2O, Pd/C, reflux, 1 h.

b. Docking studies: Gold **c. hCAs inhibition:** Stopped-flow CO_2 hydrase assay

Results and discussion

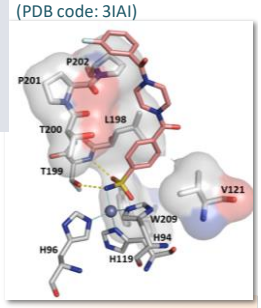
1 Synthesis of a small library of the benzene-sulfonamides **5a-v**

2 Evaluation of inhibitory activity against selected hCAs

Cmp	*hCA I*	*hCA II*	*hCA IX*	*hCA XII*	*hCA I/hCA IX*	*hCA II/hCA IX*
5b	460.0	0.6	16.2	8.5	28.39	0.04
5h	0.84	0.41	3.8	29.1	0.22	0.11
5q	93.8	28.6	2.2	8.2	42.6	13.0
5t	404.9	51.1	15.2	7.7	26.64	3.36
5v	69.1	3.7	37.1	8.5	0.32	0.41
AAZ	250.0	12.1	25.8	5.7	9.70	0.47

3 Investigation of binding mode by molecular docking

Figure 1. Derivative **5h** bound to the active site of hCA IX (PDB code: 3IAI)



Conclusions

-New 4-(4-benzoylpiperazine-1-carbonyl)-benzenesulfonamide derivatives **5a-t** were synthesized
-They displayed K_i values in the nM range towards tumor associated hCAs
- Some compounds showed a favorable *selectivity ratio* for hCA IX (e.g. **5q** and **5t**).
-Docking studies suggested the main interactions within hCA IX

New strategies for the multistep synthesis of Oleocanthal

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New strategies for the multistep synthesis of Oleocanthal

Mancuso Stefano

PC_23

Background

Literature describes **Oleocanthal** (**OC**) as the major phenolic compound in extra-virgin olive oil with broad functional and health benefits through its capacity to interact with different specific disease targets.
Nowadays it is very problematic to find a ways to extract it.

A rapid and effective synthetic pathway has not been developed yet; the synthesis of OC shows low yields with a huge numbers of steps.

Conclusions

We propose a short new semi-synthetic green strategy for the synthesis of oleocanthal.

Results and discussion

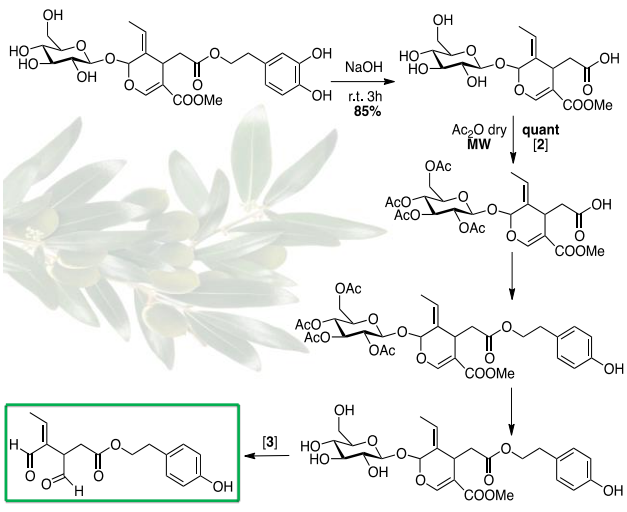

Figure 1. Strategy of synthesis of Oleocanthal

- ✓ This is the first approach for a new green semi-synthetic way to get OC [**1**].
- ✓ Oleuropein was first hydrolyzed, acetylated and then esterificated by a green Mitsunobu method.
- ✓ After deacetylation and Krapcho decarboxylation, OC can be obtained in only five steps.

References

[**1**] Samara et al., *Eur J Med Chem* **2017**, 137, 11-29. [**2**] Oliverio et al. *BJOC* **2016**, 12, 2222-2223. [**3**] Costanzo et al., *Food Chem* **2018**, 245, 410-414

Toxicological profile of phenethylamine-based psychoactive drugs

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Toxicological profile of phenethylamine-based psychoactive drugs

DANIEL MARTINS

PC_24

Background

The consumption of highly potent psychedelic drugs such as *N*-(2-methoxy)benzylphenethylamine (NBOMe) derivatives have been associated with several cases of acute and severe intoxications. The literature regarding the toxicity of these compounds is scarse and limited to case studies of poison centers.

Therefore, this project is focused on the synthesis of selected phenethylamine and corresponding *N*-benzylphenethylamine derivatives and the evaluation of their *in vitro* cytotoxicity. The log D (at pH=7.4) was also determined from the chromatographic hydrophobicity index (CHI).

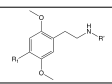
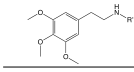
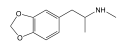
Material and Methods

Phenethylamine derivatives were synthesized via nitrostyrene (Henry reaction) and further reduction with lithium aluminum hydride. *N*-benzylation was achieved through reductive amination. All derivatives were characterized by NMR and EI-MS. Neuronal cells (SH-SY5Y) were seeded onto 96-well plates (25000 cells/cm^2) with DMEM high glucose, and differentiated with retinoic acid (10 μM) and TPA (80 nM). LOG D values were calculated from CHI data obtained by HPLC.

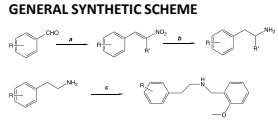
Conclusions

The results show that *N*-benzyl derivatives of phenethylamine-based psychedelic drugs are **more cytotoxic** and **more lipophilic** than the primary amines, which can be associated with their clinical toxicity profile.

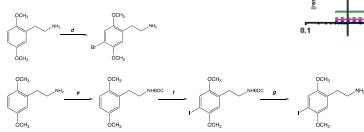
Results and discussion

STRUCTURE	COMPOUND	R	CELL-DEATH CURVE PARAMETERS				CHI Log D (7.4)
			EC_{50} (μM)	Top (%)	Bottom (%)	Hillslope (%)	
	**1. 2C-I**	R_1=I; R'=H	146.3	75.4	8.7	2.2	0.642
	2. 2C-I-NBOMe	R_1=I; R'=2-methoxybenzyl	16.6	80.0	1.6	2.7	1.676
	3. 2C-B	R_1=Br; R'=H	180.2	77.0	8.9	2.1	0.050
	4. 2C-B-NBOMe	R_1=Br; R'=2-methoxybenzyl	69.9	82.6	1.6	10.5	0.094
	**5. Mescaline**	R'=H	-	15.0	2.8	3.6	-0.135
	6. Mescaline-NBOMe	R'=2-methoxybenzyl	632.7	~100.0	4.0	2.5	1.070
	**7. MDMA**	-	-	18.6	-0.2	~13.2	0.094

GENERAL SYNTHETIC SCHEME

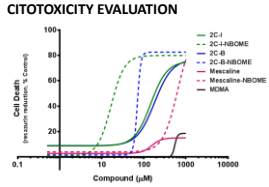


HALOGENATION STRATEGY

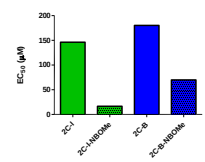


a R'NO_2, NH_4CH_3COO, 110°C; ***b*** $LiAlH_4$, THF, 60°C; ***c*** 2-MeO-Benzaldehyde, Et_3N, $NaHB_4$, EtOH, rt.; ***d*** Br_2, CH_3COOH, rt.; ***e*** BOC_2O, DCM, Et_3N, rt.; ***f*** CH_3COOH, ICl, rt.; ***g*** HCl, IPA, rt.

CITOTOXICITY EVALUATION



Concentration-response (cell death) curves obtained after exposure of differentiated SH-SY5Y cells to the tested compounds (0-1000 μM) for 24 h evaluated by the resazurin reduction assay.



N-Benzyl derivatives have lower values of EC_{50} and higher Log D values than the corresponding free amine compounds.

This project was supported by FEDER/COMPETE POCI-01-0145-FEDER-028397 and Norte-01-0145-FEDER-000028. Daniel Martins was supported by a PhD fellowship (PD/BD/135122/2017) from The Foundation for Science and Technology (FCT, Portugal).

Computational methods to identify bioactive food constituents with potential Multi-Targeting profile

Annalisa Maruca, [a,b] Raffaella Catalano, [a,b] Roberta Rocca, [a,b] Antonio Lupia, [a,b] Domenica M. Corigliano, [a] Federica Moraca, [a,b] Giosuè Costa, [a,b] Anna Artese, [a,b] Francesco Ortuso, [a,b] Antonio Brunetti, [a] and Stefano Alcaro[a,b]

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PC_25

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Computational methods to identify bioactive food constituents with potential Multi-Targeting profile

Annalisa Maruca

PC_25

Background

Foods are naturally rich in bioactive components that affect several biological processes in our organism. Therefore, they attract great interest from the scientific community for their health benefits or desirable physiological effects. Unfortunately, their mechanisms of action are often unknown or have not been enough investigated in their complexity.

Material and Methods

SCHRÖDINGER.

- **Database Building:** LigPrep module using pH 7.4;
- **Targets Preparation and Clustering:** Protein Preparation Wizard;
- **Virtual Screening:** Docking protocol;
- **Molecular Dynamics Simulations;**
- Biological evaluation.

Results and discussion

1 The food database, derived from different healthy foods, was virtually screened against macromolecular targets involved in **metabolic**, **neurodegenerative** and **inflammatory diseases** (Figure 1).

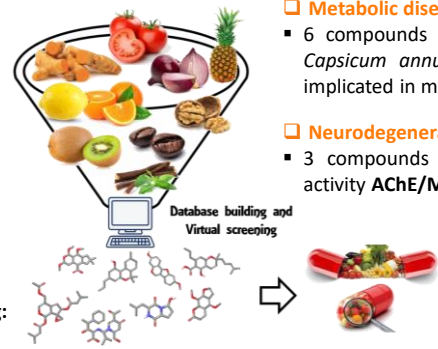

Figure 1. Database building and virtual screening of natural products.

❑ **Metabolic diseases**

- 6 compounds extracted from *Carum carvi L.*, *Zea mays* and *Capsicum annum* present a good binding affinity *vs* targets implicated in metabolic diseases: **PPAR-γ, PPAR-α and cAMP-PK**

❑ **Neurodegenerative disorders**

- 3 compounds extracted from *Piper nigrum,* present a dual activity **AChE/MAO-B**

❑ **Inflammatory**

- 2 compounds extracted from *Carum Carvi L.* and *Arachis Hypogaea* present a dual activity **COX-2/Glucocorticoid R**

2 The best hits were subjected to **Molecular Dynamic Simulations**, in order to evaluate the target-ligand stability.

Conclusions

In this work the main interactions between ligand and targets were described in order to understand the polypharmacological profile of the food extracts and to suggest a design strategy of new multi-target agents.

Identification of potent and selective MAO-B inhibitors

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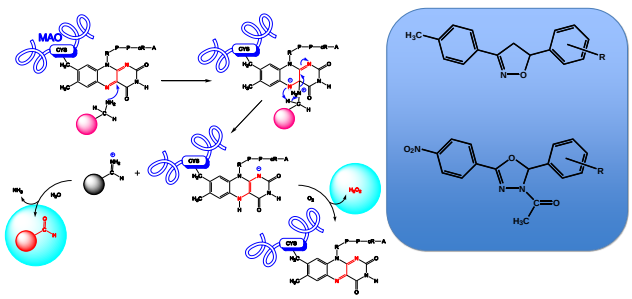
Identification of potent and selective MAO-B inhibitors

Rita Meleddu

PC_26

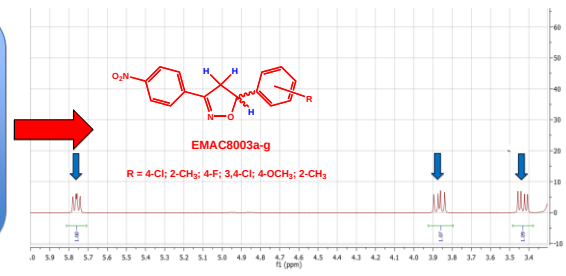
Background



MAO induced neurotoxicity

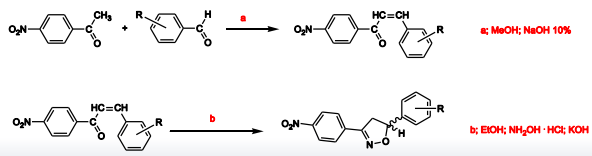
Previous inhibitors

Results and discussion



New inhibitors family (best activity of racemic mixture ~ 2 nM)

Material and Methods



Conclusions

- ✓ Synthesis, characterisation of new MAO-B selective inhibitors;
- ✓ no activity toward MAO-A at the tested concentrations;
- ✓ ongoing enantiomers separation;
- ✓ ongoing studies on the mechanism of action;
- ✓ ongoing studies on the binding mode.

Design, synthesis and biological evaluation of Exemestane derivatives as potent inhibitors of Aromatase

Federica Moraca,[a,b,c] Giosuè Costa,[a,b] Anna Caterina Procopio,[a] Antonio Lupia,[a,b] Elisiário J. Tavares da Silva,[d] Fernanda M.F. Roleira,[d] and Stefano Alcaro [a,b]

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PC_27

Design, synthesis and biological evaluation of Exemestane derivatives as potent inhibitors of Aromatase

Federica Moraca

PC_27

Background

Breast cancer is nowadays one of the most prevalent and hormone-dependent cancer. Aromatase is a CYP19A1 enzyme responsible of biosynthesis of estrogens by catalyzing the aromatization of androgens into estrogens (Figure 1C). For this reason, this enzyme, is a very valuable therapeutic target for the selective treatment of estrogen-dependent breast cancer.

Exemestane is an irreversible, steroidal aromatase inhibitor (AI) of type I of clinical use. Here, a series of Exemestane derivatives are reported as potent AI.

Material and Methods

FLAPdock software was used to perform GRID MIFs docking.

Conclusions

Among the designed AI, compound **13** showed a potency and affinity to aromatase similar to Exemestane.

Results and discussion

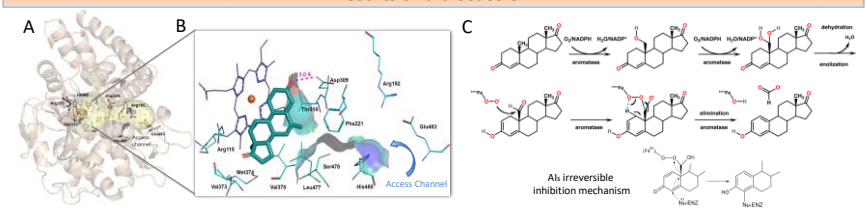

Figure 1. (A) The ligand binding pocket (yellow surface) of aromatase (light-orange cartoon). **(B)** The irreversibile AI Exemestane complexed within aromatase. **(C)** Details of the aromatization mechanism.

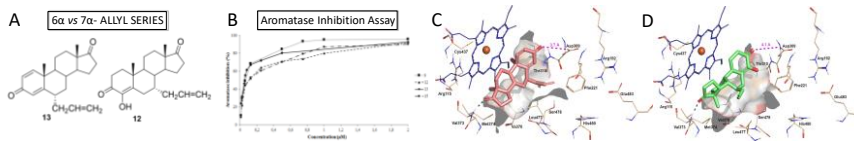

Figure 2. (A) The synthesized C6α and C7α derivatives (**13** and **12**); **(B)** Aromatase inhibition assay; **(C-D)** FLAPdock best S-score pose of **13** and **12**, respectively.

In this study it was disclosed that the C6α position is the best to be functionalized to reach a potent aromatase inhibition. In particular, **13** showed a potency and affinity to aromatase similar to exemestane and molecular modelling studies guided GRID MIFs docking demonstrated that **13** shares very similar binding geometries to Exemestane especially as concerns the 3-keto oxygen atom of the A-ring. This study is a base to develop new AIs against breast cancer.

Synthesis of a new cross-bridged cyclam radiotracer for PET detection of PD-L1 cancer expression

Paolo Novelli,[a] Rosina Paonessa,[a] Sonia Bonacci,[b] Manuela Oliverio,[b] Giuseppe Lucio Cascini,[a] and Antonio Procopio[b]

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PC_28

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Synthesis of a new cross-bridged cyclam radiotracer for PET detection of PD-L1 cancer expression

Paolo Novelli

PC_28

Background

^{64}Cu has been largely studied in PET imaging and target cancer radiotherapy due to its intrinsic teranostic qualities.

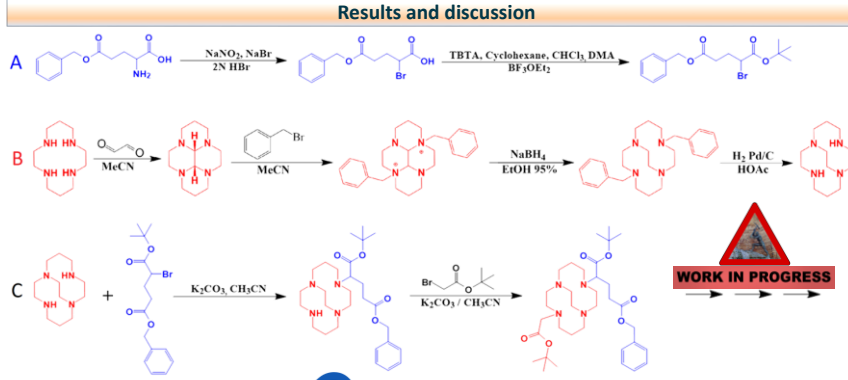
^{64}Cu-CB-TE2A complex has shown high stability, efficient complexation and a very low *in vivo* transchelation.

In recent years **PD-L1**, an overexpressed protein in many type of cancer providing immune evasion mechanisms, is a preferred target for cancer immunotherapy.

Conclusions

A new selective and non-invasive **PET radiotracer** that combines a specific peptide ligand for PD-L1 with an efficient copper CB-TE2A chelator, by the way of an appropriate linker, is under synthesis.

Results and discussion



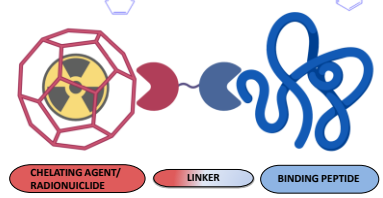


Figure 1. Scheme of final radiotracer for preclinical studies.

A) Synthesis of first building block.
B) Synthesis of second building block.
C) Coupling reaction to obtain the radiotracer precursor.

- C. Andrew Boswell et all, Bioconjugate Chem. **2008**, (19), 1476–1484.
- Samit Chatterjee et all, Biochemical and Biophysical Research Communications **2017**, (483), 258-263.

3D pharmacophore modeling of DHODH as an antimalarial target using LigandScout

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For my PhD thesis, I am working on the design of new antimalarial drugs using pharmacophore modeling in combination with various chemoinformatic methods.

3D pharmacophore modeling of DHODH as an antimalarial target using LigandScout

Domen Oblak

PC_29

Background

DHODH is an enzyme involved in de novo biosynthesis of pyrimidines which are essential metabolites for many biochemical processes. This enzyme catalyzes the oxidation of dihydroorotate into orotate, with the help of two bonded cofactors – FMN and Ubiquinone. With the binding of a ligand into the Ubiquinone hydrophobic pocket we can stop the biosynthesis. In humans, the de novo biosynthesis of pyrimidines is only one of the sources of pyrimidines, while in *P. falciparum* this is the only source.

Methodology

3D pharmacophore modeling using LigandScout:

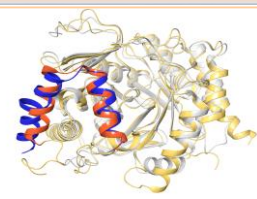
Structure Based → Ligand based → best models

After modeling, we performed virtual screening of several databases and molecular docking of hits.

Conclusions

The main results are several (8) selective pharmacophore models for DHODH that are useful for data mining, lead optimization, and understanding of key features of DHODH inhibitors associated with their inhibitory effects.

Results and discussion



Difference between PfDHODH (orange) and hDHODH (blue) – hydrophobic pocket

There is a significant difference in the Ubiquinone binding pocket between human (hDHODH) and *P. falciparum* (PfDHODH), as shown left. We decided to exploit that fact in designing selective 3D pharmacophore models.

We obtained several pharmacophore models that differ in the level of specificity, and with the combination of general and selective models we can get new compounds that could serve as inhibitors of DHODH and as such be potentially active against malaria and other DHODH dependent diseases.

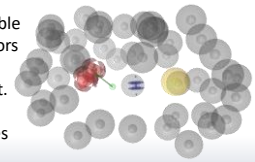
Testing pharmacophore models with virtual screening:

1) hDHODH library of very active (IC50 < 10nm) and inactive molecules (IC50 > 10µM)

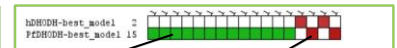
Hitrate: **50%** of very actives and **0,3%** of inactives

Best 3D model for hDHODH, with features:

- 1 negative ionisable
- 2 H-bond acceptors
- 1 H-bond donor
- 1 hydrophobic int.
- 1 aromatic int.
- exclusion volumes



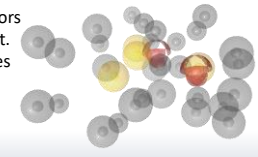
2) PfDHODH library of very active (IC50 < 30nm) and inactive molecules (IC50 > 10 µM)



Hitrate: **44%** of very actives and **0,8%** of inactives

Best 3D model for PfDHODH, with features:

- 2 H-bond acceptors
- 4 hydrophobic int.
- exclusion volumes



Lipid lowering and antiglycaemic properties of Tacle® by *in vitro* and *in vivo* investigation

Maria Antonietta Occhiuzzi,[a] Fedora Grande,[a] Bruno Rizzuti,[b] Teresa Casacchia,[a] Michele De Luca,[a] Maria Concetta Granieri,[c] Carmine Rocca,[c] Alfonsina Gattuso,[c] Jessica Ceramella,[a] Giuseppina Ioele,[a] Tommaso Angelone,[c] Antonio Garofalo[a] and Giancarlo Statti.[a]

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- PhD student

Maria Antonietta Occhiuzzi

PC_30

Lipid lowering and antiglycaemic properties of Tacle® by *in vitro* and *in vivo* investigation

Maria Antonietta Occhiuzzi

PC_30

Background

Tacle® (TC), a hybrid citrus cultivar obtained from the crossbreeding of Clementine and Tarocco, recently gained an increasing interest due to its nutraceutical properties. Experimental evidences indicate remarkable protective properties of TC extract against oxidative toxic agents, consequent to a high content in polyphenols.

Material and Methods

TC samples were collected from Calabrian cultivars. Total polyphenol and flavonoid content has been determited. Antioxidant activity, pancreatic lipase and α-amylase inhibition as well as cytotoxic profile have been evaluated by specific *in vitro* assays. Molecular docking was performed on the crystallographic structures of HPL and HPA. Anthropometric parameters have been *in vivo* assessed on rats.

Results and discussion

After a preliminary investigation, naringin and hesperidin have been recognized as the most abundant polyphenol glycoside components of TC extracts,. Thus, the TC beneficial effects including antioxidant, lipid lowering and hypoglycemic activities, were attributed to the noteworthy presence of these compounds, as confirmed by specific *in vitro* assays. The aglycones of naringin and hesperidin, namely naringenin and hesperetin, have been docked into amylase and lipase enzyme active sites (Figure 1). As a result, both compounds proved to be able to easily accommodate into the active site of both enzymes. The influence of TC extracts on anthropometric values, on a rat model of obesity and metabolic syndrome was measured by *in vivo* studies.

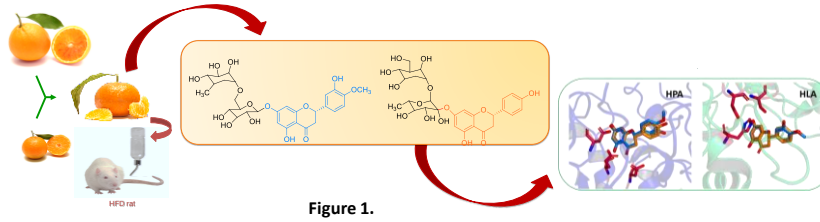

Figure 1.

Conclusions

The collected overall results showed an enhanced nutraceutical profile of TC with respect to citrus parent fruits, suggesting that a dietary enrichment with its extract could be useful in the management of metabolic disorders such as obesity and diabetes.

Benzoic acid-derived nitrones: a new class of acetylcholinesterase inhibitors and potential neuroprotective agents

Catarina Oliveira,[a] Donatella Bagetta,[b,c] Fernando Cagide,[a] José Teixeira,[a,d] Ricardo Amorim,[d] Tiago Silva,[a] Jorge Garrido,[a,e] Fernando Remião,[f] Eugenio Uriarte,[g] Paulo J. Oliveira,[d] Stefano Alcaro,[b,c] Francesco Ortuso,[b,c] and Fernanda Borges[a]

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[f] *UCIBIO-REQUIMTE, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal;*
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PC_31

Benzoic acid-derived nitrones: a new class of acetylcholinesterase inhibitors and potential neuroprotective agents

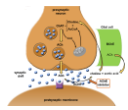
Catarina Oliveira

PC_31

Background

Alzheimer's disease (AD) is a multi-factorial disease deeply associated with impaired **cholinergic transmission** and **oxidative stress**, a process that is related with a failure in the antioxidant protective system and/or an increment in reactive species production/accumulation. In this context, the discovery of new chemical entities endowed with potent and selective acetylcholinesterase (AChE) and/or butyrylcholinesterase (BChE) inhibitory activity is still a relevant subject for Alzheimer's disease therapy.

Therefore, a small library of benzoic based amide nitrones, a class of compounds known as spin traps (compounds **24** to **42**) was synthesized and screened toward cholinesterase enzymes (AChE and BChE).



Conclusions

- A small library of non-cytotoxic benzoic based amide nitrones was obtained;
- Only nitrones with *tert*-butyl moiety effectively and selectively inhibited AChE;
- Molecular docking studies provided insights into the enzyme-inhibitor interactions;
- Compound **33** is highlighted as a non-competitive toward AChE (IC_{50} = 8.3 ± 0.3 μM; K_i 5.2 μM);
- Compound **33** was able to prevent *t*-BHP-induced oxidative stress in SH-SY5Y differentiated cells.

ACKNOWLEDGEMENTS

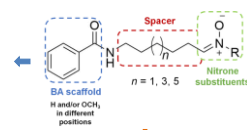
This work was funded by FEDER funds through the Operational Programme Competitiveness Factors-COMPETE and national funds by FCT – Foundation for Science and Technology under research grants (QUI/UI0081/2013, NORTE-01-0145-FEDER-000028, POCI-01-0145-FEDER-016659, and PTDC/DTP-FTO/2433/2014). C. Oliveira (SFRH/BD/88732/2012, NORTE-01-0145-FEDER-000028), F. Cagide (SFRH/BPD/74492/2010, NORTE-01-0145-FEDER-000028), J. Teixeira (PTDC/DTP-FTO/2433/2014, NORTE-01-0145-FEDER-000028) grants are supported by FCT, POPH and QREN.

Results and discussion

Benzoic acid and derivatives

- Benzoic acid (BA) is the simplest aromatic carboxylic acid;
- It is naturally present in plants (e. g. fruit, vegetables and grains) and animal tissues;
- It is industrially used as preservative and/or flavouring agent in food, cosmetic, and pharmaceutical products.

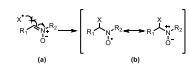
Limited therapeutic application



Goal - Design multi-target drug candidates
- ChE inhibitory activity
- Antioxidant/Cytoprotective properties

Nitrones

- Nitrones, a class of compounds known as spin traps, were described as having the ability to stabilize or trap free radicals and reduce the damage associated with unbalanced production of radical reactive species.

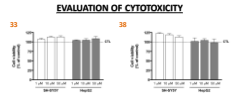


ACETYL AND BUTYRYLCHOLINESTERASE INHIBITION

Compound	Structure	IC_{50} (μM ± SD) AChE	BChE
27		27.2 ± 2.9	*
30		26.1 ± 2.7	*
33		8.3 ± 0.3	*
36		12.2 ± 0.4	*
37		12.6 ± 0.6	*
38		17.2 ± 1.3	*
41		16.9 ± 1.3	*
42		11.8 ± 0.8	*
Donepezil		0.025 ± 0.001	2.2 ± 0.2

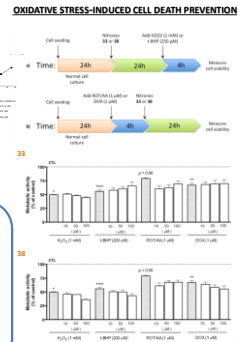
* Inactive at 50 μM (highest concentration tested).

EVALUATION OF CYTOTOXICITY

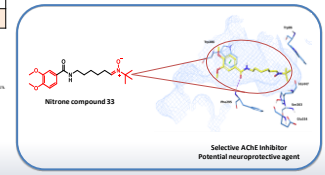


ENZYME-INHIBITION MECHANISM

OXIDATIVE STRESS-INDUCED CELL DEATH PREVENTION



SELECTION OF A MULTI-TARGET LEAD CANDIDATE



Arsenous acid-platinum(II) a new dual pharmacophore anti-cancer agent: computational insights

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Presenting Author: Angela Parise

PC_32

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Arsenous acid-platinum(II) a new dual pharmacophore anti-cancer agent: computational insights

Angela Parise, Tiziana Marino, and Nino Russo

PC_32

Abstract

We have explored at theoretical level the aquation process of the arsenous acid–platinum(II) anticancer complex in comparison with the well known cis-platinum. Furthermore, the role of arsenic was also evaluated in the DNA metalation process[1]. Recently, it was observed that arsenous acid-platinum can act as dual pharmacophore anticancer agent [2] due to its interaction with specific amino acid residues (Cys and His) present in hen egg white lysozyme (HEWL) and bovine pancreatic ribonuclease (RNase A) implicated in the RNA hydrolysis. A mechanistic study has been undertaken, at the density functional theory level, with the aim to give insights on the metalation process of the HEWL and RNaseA (PDB code 5NJ1 and 5NJ7 respectively).

References

[1] Marino T., Parise A., Russo N., Physical Chemistry Chemical Physics **2017,** 19 (2), 1328.
[2] Miodragović et al.. Am. Chem. Soc. **2019**, 141 (16), 6453.

Results and discussion

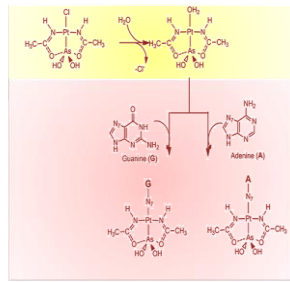


Figure 1. Proposed mechanism for the As-Pt complex acquation and its interaction with DNA.

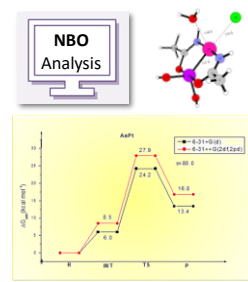


Figure 2. The calculated B3LYP free energy profile for acquation process of As-Pt.

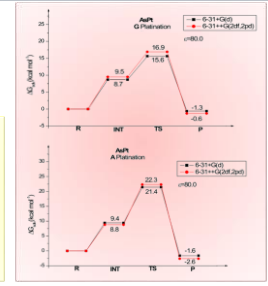


Figure 3. Calculated B3LYP free energy profile for the DNA purine bases metalation process.

Not just DNA...

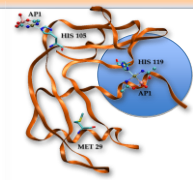
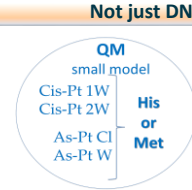
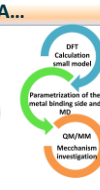


Figure 4. Binding sites of the AP-1 moieties of RNase A (PDB code 5NJ7).





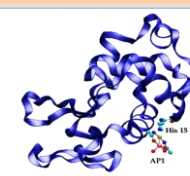


Figure 5. Binding site AP-1- HEWL adduct (PDB code 5NJ1).

Molecular docking and design of novel 2, 3-aryl-thiazolidin-4-ones as potent NNRTIs inhibitors

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[b] *InterBioscreen, Moscow, Russia*
[c] *BogaR Laboratories LLC, Suwanee, USA*
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- Additional information:

Molecular docking and design of novel 2, 3-aryl-thiazolidin-4-ones as potent NNRTIs inhibitors

Anthi Petrou, Athina Geronikaki, Victor Kartsev, Ramesh Boga , and Giovanni Maga

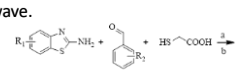
PC_33

Background

This work presents and discusses the design, synthesis and biological evaluation of sixteen novel 2, 3-aryl-thiazolidin-4-ones, with increased activity against human immunodeficiency virus (HIV) based on docking evaluation and PASS prediction.

Material and Methods

PASS program was used for the prediction of activity spectra of the designed compounds. For docking calculations AutoDock 4.2 was used. Synthesis was performed by one pot method as well as by microwave.



Scheme 1.
(a) toluene, reflux 18–32 h
(b) 100 °C, power 100 W, 30′

Compounds were characterized by TLC and spectroscopic methods (IR, ^{1}H-NMR, ^{13}C-NMR) and the radioisotope method was used for the evaluation of the HIV-1 Reverse Transcriptase Activity.

Results and discussion

Taking into account the best features of the available NNRTIs we designed a series of novel compounds that collect the number of necessary characteristics for possible strong inhibition of RT HIV-1 enzyme. Molecular docking studies were performed on the allosteric site of RT. Interactions with the residues were studied and from the originally amount of designed compounds 16 compounds that showed the best docking scores and the favorable binding position were chosen for the synthesis and biological evaluation (table 1). The results obtained from the RT assay were in accordance with the docking scores and validate the method (table 2). Docking analysis revealed that the majority of the compounds adopt a confirmation similar to that of etravirine in a butterfly-like conformation in the crystalized complex. The best docking score was predicted for compound **c1** which seems to be the most potent inhibitor with the lowest IC_{50}=3 ± 3,5μM . Based on the docking results, **c1** formed two hydrogen bonds with the residues Lys101 and Pro126. The H-bonding interaction with the residue Lys101 is a common characteristic of NNRTIs.

Table 1. Molecular docking scores.

N.	R_1	R_2	Est. binding energy	Binding affinity score	I-H	Residues
c1	6-Cl	4-F	-12.30	-33.22	2	Lys101, Pro126
j5	4-(pyridin-2-yl)thiazole	2-F, 6-Cl	-10.12	-30.81	2	Lys101, Tyr181
j6	5-ethyl-4-methylthiazole	2-F, 6-Cl	-8.45	-28.74	1	Lys101
k1	6-CN	4-F	-9.27	-29.96	2	Lys101, Ile180
k2	6-CN	4-NO_2	-10.95	-31.49	2	Lys101, Lys172
k3	6-CN	2-F, 6-Cl	-8.49	-28.04	1	Lys101
k4	6-CN	2,6-di-F	-9.15	-29.11	2	Lys101
k5	6-CN	2,6-di-Cl	-7.84	-26.13	1	Lys103
k6	6-CN	2,4-di-Cl	-7.13	-25.40	-	-
m1	6-Ad	2,6-di-Cl	-8.76	-28.15	1	Lys101
m2	6-Ad	2,6-di-F	-9.13	-29.16	2	Lys101, Lys103
m3	6-Ad	2-F, 6-Cl	-9.76	-30.25	2	Lys101
l1	6-CF_3	2,6-di-Cl	-7.12	-25.43	-	-
l2	6-CF_3	2,6-di-F	-9.32	-28.93	2	Lys101, Lys103
l3	6-CF_3	2-F, 6-Cl	-9.55	-29.48	2	Lys101
n2	4-CH_2, 6-Ad	2,6-di-F	-9.02	-29.05	2	Lys101
	Nevirapine		-11.95	-34.72	2	Lys101, Lys103

Table 2. *In vitro* RT assay

N	MW (g/mol)	Weight (mg)	IC_{50} μM
c1**	365.5	2.7	3 ± 3,5**
J5	391.5	8 (x2)	> 132
J6	400.5	8 (x2)	40.9 ± 22.8
k1	355	6 (x2)	> 33
k2	382	6 (x2)	4.4 ± 2.9
k3	388.5	6 (x2)	> 132
k4	373	6 (x2)	> 132
k5	405	6 (x2)	> 132
k6	405	6 (x2)	> 132
m1	514	3	> 132
m2	482	2.83	> 132
m3	498.5	2.98	69,5 ± 79,4
l1	448	3	> 132
l2	416	2.35	> 132
l3	431.5	3	> 132
n2	496	3	> 132

** low solubility*
*** 7 days after dissolution the compound lost its solubility in both DMSO 50% and 100%*

Reaction conditions: 5′ pre-incubation on ice (Buffer + RT + Mg^{2+} + compound) +20′ at 37°C
Substrate: ^{3}H-TTP (10 μM); Template: poly(rA)-oligo(dT) (0.2 μM)

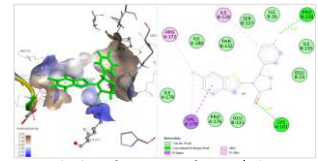


Figure 1. Docked conformation of comp/nd **c1** in HIV-1 RT.

Conclusions

Molecular docking studies were carried out to enable the design of new HIV-1 RT inhibitors. The binding free energies of compounds to HIV-1 RT were found to have a good correlation with the experimental inhibitory activities. The most favorable binding mode of top-ranking compounds will be useful in designing new NNRTIs.

Synthesis and evaluation of novel antimycobacterial isoniazid analogues

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PC_34

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- **Additional information:** This work was supported by the Czech Science Foundation project No. 17-27514Y and SVV 260 401.

Synthesis and evaluation of novel antimycobacterial isoniazid analogues

Václav Pflégr

PC_34

Background

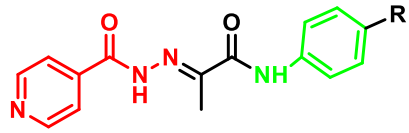
- Tuberculosis (TB)
- Latest status of the TB epidemic
- TB treatment
  - Isoniazid (INH)
- Drug-resistant TB
- Current trends in TB therapy
- Possible solutions

Material and Methods

- Compound library synthesis
- Evaluation
  - *In vitro* antimycobacterial activity
  - Selectivity
  - SAR

Results and discussion

The best activity against *Mtb.* showed 2-(2-isonicotinoylhydrazineylidene)-*N*-phenylpropanamides substituted by an electron-withdrawing group at anilide ring (4-OCF_3, MIC ≤0.03 μM), an additional aromatic ring or a long alkyl at anilide ring and also 2-napthylamide (MIC values from ≤0.25 μM). The highest efficacy against nontuberculous mycobacteria (MIC from ≤1 μM) exhibited 2-(2-isonicotinoylhydrazineylidene)-*N*-(4-phenoxyphenyl)propanamide. Importantly, the presented compounds are selective, non-toxic for mammalian cells (HepG2, MonoMac6) and several of them are comparable or significantly superior (up to more than 17×) to parent INH. Their activity against multidrug- and extensively drug-resistant tubercular strains is currently under investigation.



R
OCF_3
O-C_6H_5
n-octyl

Figure 1. 2-(2-Isonicotinoylhydrazineylidene)-*N*-phenylpropanamide

Conclusions

More than one hundred derivatives with the presented structural motif (**Fig. 1**) have been designed, prepared and tested within this project. Some of them exhibited interesting inhibition activities against various mycobacterial strains in basic bioscreening. The synthesis of small molecules as potential antituberculotics is a promising direction in the development of new prodrugs and drugs with a new mechanism of action. The next aim is to determine the mechanism of action of the most potent molecules.

De-risking tolcapone hepatotoxicity for repurposing therapy using a nanotechnological approach

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De-risking tolcapone hepatotoxicity for repurposing therapy using a nanotechnological approach

Miguel Pinto, Carlos Soares, Carlos Fernandes, Fernanda Borges

PC_35

Background

Tolcapone is an iCOMT FDA authorized drug for the treatment of PD, and a potential candidate for the treatment of neuroblastoma[1] and FAP's.[2] Despite its efficiency, the drug has a highly hepatotoxic profile, which has led to restrictions and concerns about its application.[3] Therefore, the aim of this work was to encapsulate tolcapone within PEGylated PLGA nanoparticles to overcome its hepatotoxicity issues.

Material and Methods

Tolcapone loaded PEGylated PLGA nanoparticles were prepared by nanoprecipitation.

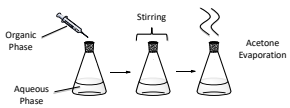

Fig. 1 – Schematic representation of nanoprecipitation method.

Conclusions

- ✓ Formulation F4 displays physicochemical features suitable for biologically effective application;
- ✓ It also displays controlled release features.

Results and discussion

Optimization of Nanoparticle Synthetic Conditions

Formulation	Coating	(m/m_{PLGA}) Coating	(m/m_{PLGA}) Tolcapone	Acetone (mL)	Organic/Aqueous Phase ratio	EE (%)	DLC (%)
F1	mPEG	10%	5%	5 ml	1:2	40.56 ± 9.20	5.14 ± 1.18
F2	mPEG	10%	10%	5 ml	1:2	25.94 ± 7.47	8.89 ± 1.43
F3	P188	100%	5%	5 ml	1:2	35.33 ± 3.79	3.47 ± 0.80
F4	P188	100%	10%	5 ml	1:2	40.12 ± 3.31	6.37 ± 0.47

Table 1 – Synthetic conditions of nanoprecipitation optimization process of loaded PLGA particles, and corresponding EE% (entrapment efficiency) and DLC% (drug loading capacity). All quantifications were run in triplicate and presented as mean ± SD.

NP's Physicochemical Characterization

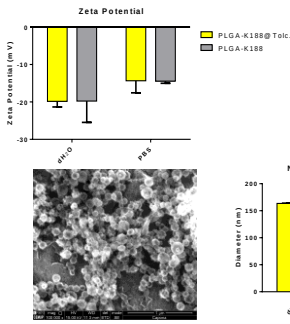

Fig. 2 – Determination of physicochemical nanoparticle features in different dispersion (dH_2O or PBS) media. Size and Z-potential values obtained by Dynamic Light Scattering and Laser Doppler Anemometry, respectively (Mean ± SD, n=3). NPs morphology was confirmed by SEM.

In Vitro Release Study

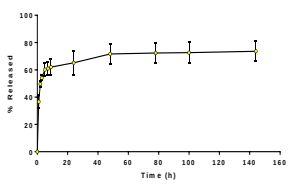

Fig. 3 – In vitro release profile of F5. Each point represents the mean ± SD with n = 3.

1. Olanow CW, Panel TA. Arch Neurol-Chicago 2000; **57**(2): 263-7.
2. Sant'Anna R, Gallego P, Robinson LZ, et al. *Nat Commun* 2016; **7**: 10787.
3. Maser T, Rich M, Hayes D, et al. *Cancer med-US* 2017; **6**(6): 1341-52.

Acknowledgments: This project was supported by the Foundation for Science and Technology (FCT) and FEDER/COMPETE (Grants UID/QUI/00081/2013, POCI-01-0145-FEDER-006980, POCI-01-0145-FEDER-029164, PTDC/DTP-FTO/2433/2014, and NORTE-01-0145-FEDER-000028). M. Pinto and C. Fernandes were supported by NORTE 2020 funds.

In silico identification of new aromatase inhibitors

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Presenting Author: Anna Caterina Procopio

PC_36

In silico identification of new aromatase inhibitors

Anna Caterina Procopio

PC_36

Background

The aromatase is a microsomal enzyme belonging to the superfamily of the cytochromes p450, which catalyzes the aromatization reaction from androgens to estrogens. An over-expression of such enzyme leads to overproduction of estrogens tipical in breast cancer.

Material and Methods

A library of drugs was downloaded from Drugbank, and has been prepared with LigPrep. These drugs has been screened with molecular docking and the hits was submitted to molecular dynamics.

Conclusions

Molecular dynamics analysis confirmed that the identified compounds are promising aromatase inhibitors characterized by innovative non-steroideal scaffolds, a fundamental element in order to avoid side effects. Subsequently these drugs will be submitted to further studies, such as enzymatic assays.

Results and discussion

In this study three hits were identified which interact with important aminoacids of the active site of the enzyme. In particular the interactions with aminoacids crucial in aromatization reaction were taken into account.

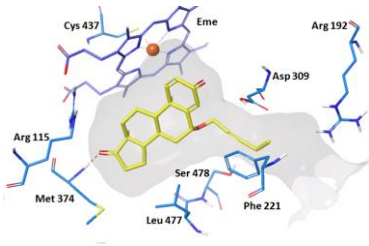

Figure 1. Binding mode of the co-crystalized ligand inside the active site.

Table 1. Glide score of the best hits submitted to molecular dynamics (MD) simulation.

COMPOUNDS	Gscore (Kcal/mol)
Hit1	-8.856
Hit2	-8.411
Hit3	-8.229

Table 2. The active site aminoacids interacting more than 80% of MD simulation time are highlighted (+).

	Asp 309	Phe 221	Met 374	Leu 372	Arg 192	Ser 478
Hit 1	+	+	+	+	-	-
Hit 2	+	+	-	-	+	-
Hit 3	-	+	-	-	-	+

An in vivo biologically active pyrido[2,3-*d*]pyrimidine as a KRAS and tyrosine kinase inhibitor for the potential treatment of lung cancer

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An *in vivo* biologically active pyrido[2,3-*d*]pyrimidine as a KRAS and tyrosine kinase inhibitor for the potential treatment of lung cancer

Raimon Puig de la Bellacasa

PC_37

Background

Oncogenic mutations of KRAS are frequently identified in pancreatic, colorectal and lung cancers. After 30 years of intensive research, there is not yet an effective clinical drug against this target. Our group with a large experience in synthesis of pyrido[2,3-*d*]pyrimidines has decided to properly substitute this structure to get a compound with activity against KRAS.

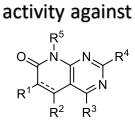

Figure 1. Pyrido[2,3-*d*]-pyrimidine scaffold

Conclusions

A new compound, **IQS080**, has been synthesized and its good activity against KRAS and some key protein kinases has been shown. This work also demonstrate the interaction IQS080-KRAS at the GTP binding site.

Results and discussion

Among several synthesized pyrido[2,3-*d*]pyrimidine compounds, **IQS080** has shown promising results as a KRAS and protein kinase inhibitor:

- **Enzimatic assay**: **Inhibition** of key kinases involved in cancer, such as **EGFR**, **ERK1/2** and **p-38**.
- ***In vitro* assay**: **Good IC_{50}** against different cell lines.

Table 1. IC_{50} determination

Cell line	IC_{50} IQS080
H2286 (μM)	0,73
HCC 366 (μM)	2,16
H520 (μM)	1,05

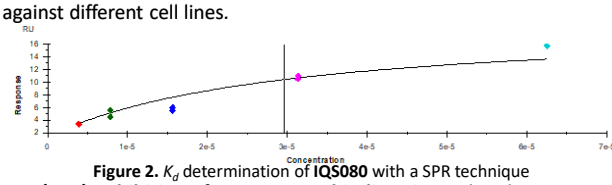

Figure 2. K_d determination of **IQS080** with a SPR technique

- **Surface Plasmon Resonance (SPR): Inhibition** of **KRAS** at **GTP binding site** with a dissociation constant (K_d) = 29.6 μM, better than a described reference (0375-0604 K_d = 702 μM).
- **In vivo assay**: **Stop** of the **tumour growth**.
- **Computational studies**: Interaction at **GTP binding site**.

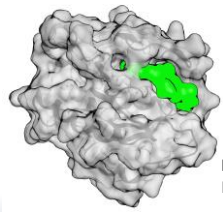

Figure 4. Docking of **IQS080** with KRAS

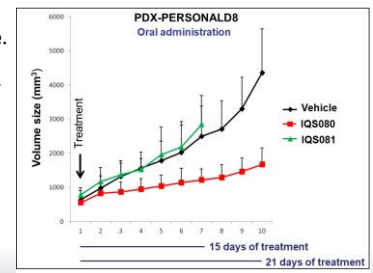

Figure 3. Stop of the tumour growth after the treatment with **IQS080**, vehicle or an inactive pyrido[2,3-*d*]pyrimidine (IQS081)

Can boron-containing compounds be considered new structural scaffolds for the treatment of Alzheimer's disease?

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Can boron-containing compounds be considered new structural scaffolds for the treatment of Alzheimer's disease?

Alessandra G. Ritacca

PC_38

Background

Alzheimer's disease is a lethal neurological disease with a faceted pathogenesis. To date, only five drugs have been approved by FDA for its treatment. A novel series of boron-containing compounds has been proposed, exhibiting multi-functional activity: they inhibit self-induced Aβ aggregation, act as antioxidants and as biometal chelators.

Material and Methods

- *Ab initio* geometry optimization: SMD(ε=78)/M052X/6-311+G**.

Conclusions

- Antioxidant activity of 17c is better than 17h, according to experiments. Boron improves antioxidant ability for both species.
- The most stable structures have squared planar geometry. Anionic 17h is the best complexating ligand.
- Further studies are in progress for experimental data support.

Results and discussion

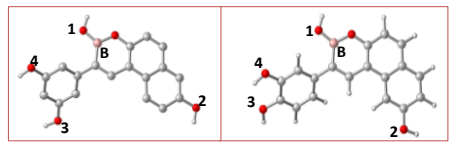

Figure 1. 17c and 17h

Metal-chelating properties towards CuII. ΔG_f in kcal/mol, solvent=H2O $[Cu^{2+}(H_2O)_6$ + ligand]

Complex	17c	$(17c)^-$	Complex	17h	$(17h)^-$
Squared planar			Squared planar		
1:1a	-5,7		1:1°	-12,5	
1:1a'		-24,4	1:1a'		-29,7
1:1b	-5,5		1:1a''		-22,7
Octahedral			1:1b	-6,0	
1:1c	-10,6		1:1c	-6,9	
			Octahedral		
			1:1d	-2,4	

➢ The different positions of OH groups on the phenyl moiety confer to 17h better chelating ability. At pH=7.4 also the anionic form of the ligands exists.

Antioxidant activity towards ·OOH. ΔG and ΔG≠ in kcal/mol, solvent=H2O

Channel	17c		17h	
	ΔG	ΔG≠	ΔG	ΔG≠
HT(1)	12,5		30,1	
$HT_{(2)}$	-2,2	barrierless	25,2	
$HT_{(3)}$	1,1		-8,0	17,3
$HT_{(4)}$	1,3		-5,5	barrierless
SET	25,3		22,0	
RAF	>0		>0	
RAF (B)	-1,5	barrierless	-3,1	14,9

➢ Boron has an empty orbital so it can accept the OOH's unpaired electron and promotes radical adduct formation reaction. Although this latter occurs for both species, only for 17c it is favoured both kinetically and thermodynamically. Hydrogen transfer is also one of the most probable mechanism of action and 17c works better than 17h.

Lu, C.-J.; Hu, J.; Wang, Z.; Xie, S.; Pan, T.; Huang, L.; Li, X, *Med. Chem. Commun*. **2018**, 9, 1862

Identification of small molecules with specific interference to lncRNA activity through different computational approaches

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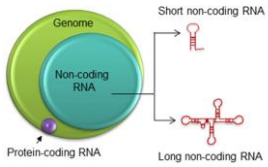
Identification of small molecules with specific interference to lncRNA activity through different computational approaches

Roberta Rocca

PC_39

Background

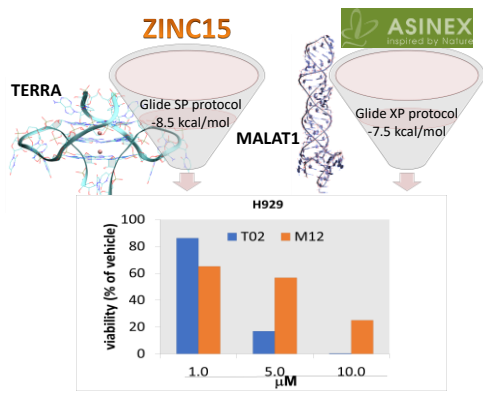
Aberrant long-ncRNAs (lncRNAs) expression is crucial in the metastatic process. They are transcripts longer than 200 nucleotides that are not translated into proteins and are involved in chromatin remodeling, transcriptional regulation, RNA processing, and many others.



Material and Methods

A Structure-Based Virtual Screening (SBVS) approach was pursued on TERRA and MALAT1 3D structures (pdb code 2KBP and 4PLX, respectively). In particular, two different compounds libraries were screened: ZINC Natural compounds and Asinex database. The best hits were tested *in vitro.*

Results and discussion



Accurate and hard-working *in silico* studies led us to identify a promising lead compound for both TERRA (**T02**) and MALAT1 (**M12**). Indeed, in biological essays they showed good anti-proliferative activity on cell lines of multiple myeloma .

In particular, we demonstrated the binding of **T02** to unimolecolar G4 structure through Circular Dichroism .

Instead, biophysical essays are in progress for the complex of Malat1 with **M12**.

Conclusions

Complex tertiary structures and dynamic forms of RNAs have recently gained particular attention. Specifically, before unfolding to single-stranded sequences, their 3D-conformation structurally resemble proteins, offering potential targeting sites for small molecules (SMs). Collectively, our preliminary results prompt us to further investigate TERRA AND MALAT1 in *in vivo* essays.

Mechanistic insights of hydrolytic activity into a *de novo* functional protein framework

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Mechanistic insights of hydrolytic activity into a *de novo* functional protein framework

Isabella Romeo

PC_40

Background

The reaction mechanism of an artificial esterase obtained by engineering the functional catalytic triad (**Cys-His-Glu**) into a fully de novo designed coiled-coil homo-heptameric peptide assembly (**CC-Hept**) is proposed on the basis of a combined molecular dynamics (**MD**) and hybrid quantum mechanics/molecular mechanics (**QM/MM**) investigation.

Conclusions

- For **A** and **B** channels the rate-limiting step (RDS) corresponds to the hydrolysis of the thioester intermediate.
- This result well compares with the barrier obtained by converting the experimental k_{cat} (17-20 kcal mol^{-1}).[1]
- Path **B** results more favorable from both thermodynamic and kinetics point of view.

Reference

1. Burton, A.J.; Thomson, A.R., Dawson, W.D., Brady, R.L. & Woolfson, D.N. Nat. Chem. 8, 837-844 (2016).

Results and discussion

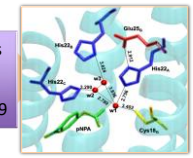
PDB code:5EZC

200 ns of apo-form MDs by using Amber package

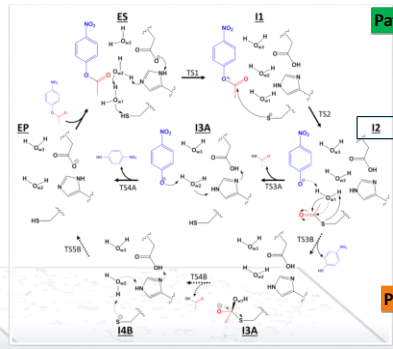
Clustering analysis and Molecular docking by using AutoDock

3 x 200 ns of bound-form MDs by using Amber package

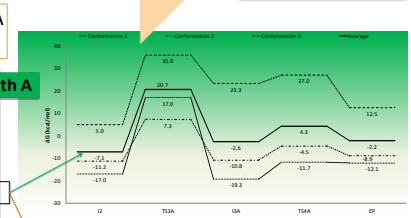
3 conformations for QM/MM calculations by using Gaussian 09



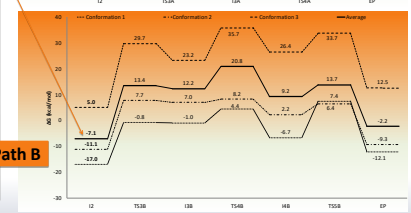
Two proposed reaction mechanisms of *p*NPA hydrolysis catalyzed by *de novo* protein.



Path A



Path B



Synthesis of furochromone derivatives with potential anticancer activity

Lisa Sequeira,[a] Rita Meleddu,[a] and Elias Maccioni,[a]
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Sequeira Lisa

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Synthesis of furochromone derivatives with potential anticancer activity

Lisa Sequeira

PC_41

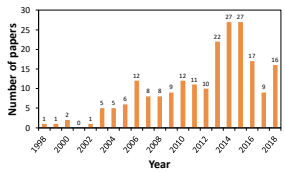
Background

Metalloenzymes envolved in several physiologic processes

Carbonic Anhydrases

CA IX and XII are associated with and overexpressed in tumors

16 different isoforms in mammals

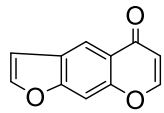


CAs become an increasing interest to researchers

Chromones

O-heterocycles present in nature

Wide range of biological activities



Methods

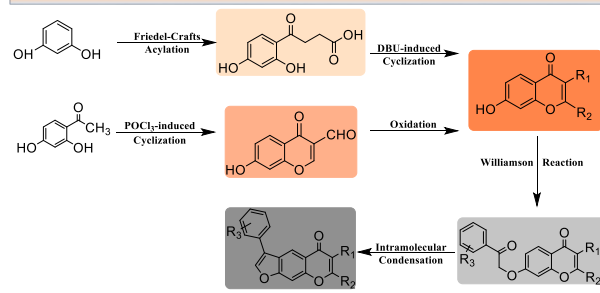


Figure 1. Synthetic strategy for the development of furochromones.

Conclusions and Future Work

✓ Several furochromones were already synthesized by the group with selective inhibition of CA IX and XII.

✓The Friedel-Craft acylation and the $POCl_3$-induced cyclization were tested and are being optimized.

➢ The compounds will be isolated and characterized by ^1H and ^{13}C nuclear magnetic ressonance;

➢ Two families of furochromones of eleven compounds each will be synthesized.

Computational conception and chemical synthesis of dual BTK-TCL1 inhibitors

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- Additional information:

Computational conception and chemical synthesis of dual BTK-TCL1 inhibitors

Simona Sestito

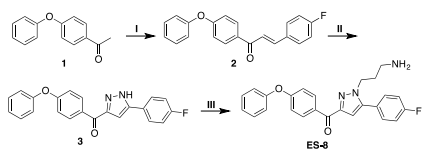
PC_42

Background

The Bruton tyrosine kinase (BTK) inhibitor Ibrutinib has been approved by the FDA for the treatment of many lymphomas and chronic lymphocytic leukemia (CLL). However, T-cell leukemia/ lymphoma 1 (TCL1) is investigated as innovative therapeutic target due to its central role in lymphomagenesis.
In this light, following a multitarget approach, we designed and synthesized a small series of novel BTK/TCL1 inhibitors that proved to target, at least in silico study, both proteins.

Results and discussion

The initial proposed hit compound, namely "12R", and its synthesized derivatives (ES1-10) have been evaluated *in silico* for their binding energy versus the two putative targets, BTK and TCL1. Interestingly, some optimized compounds showed higher affinity versus BTK than ibrutinib (Fig. 1). The affinity versus TCL1 could not be compared with any competitors, since there are not available TCL1 inhibitors. The most interesting compound namely ES8 showed anti-proliferative activity (IC50 ≤ 10 μM) in a panel of four lymphoma cell lines (Table 1).



Reagents and conditions: **I.** NaOH, EtOH, rt, 2h; **II.** NH_2NH_2, reflux, 12h; **III.** 3-Chloropropylamine, EtOH, reflux, 12h.

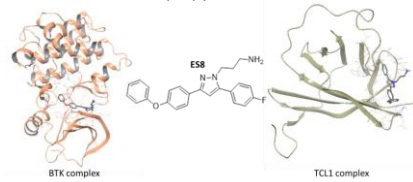


Figure 1. The 2D structure of the most interesting compound ES8 and its best complexes with BTK and TCL1, respectively.

cell line	cell of origin	ES8 (μM)
OCI-LY-10	ABC-DLBCL	7
OCI-LY-3	ABC-DLBCL	7
SU-DHL-2	ABC-DLBCL	>10
RI-1	ABC-DLBCL	>10
KARPAS 422	GCB-DLBCL	7
PFEIFFER	GCB-DLBCL	9
OCI-LY-8	GCB-DLBCL	>10
OCI-LY-1	GCB-DLBCL	>10

Table 1. Anti-tumor activity of ES8 in lymphoma cell lines. IC50s were calculated after 72h of drug exposure by MTT assay.

Material and Methods

BTK and TCL1 3D structures were downloaded by Protein Data Bank (pdb code 4RFZ and 1JSG, respectively). Ligand 3D strcutures were built using Maestro GUI and then submitted to docking simulations using SP Glide protocol. Finally, the best docking poses were selected according to thermodynamical evaluation results.

Conclusions

Collectively, these preliminary results prompt us to further investigate ES8 in both cell-free and in *in vitro* assays to validate the multitarget approach as promising strategy to fight lymphoma.

New route for the synthesis of 1-(arylimidazolin-2-yl)-3-arylureas

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New route for the synthesis of 1-(arylimidazolin-2-yl)-3-arylureas

Dominik Straszak, Dariusz Matosiuk

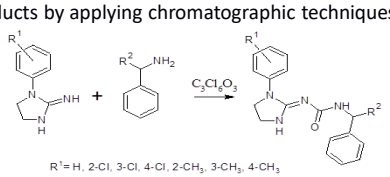
PC_43

Background

Series of 1-(arylimidazolin-2-yl)-3-arylureas synthesized by Matosiuk and co-authors showed analgesic properties. Their high affinity towards μ opioid receptor was evaluated on radioligand binding assay tests. Behavioral tests on animals confirmed their great antinociceptive activity and low toxicity. Moreover, the compounds did not show side effects typical for opiates. Pharmacological examination suggested that this new compounds may have other mechanism of activation of μ receptors than morphine-like analgesics

Material and methods

The main aim of this work was to synthesize a novel derivatives of 1-(arylimidazolin-2yl)-3-arylureas using new method. In a multi-step reaction, the primary arylamines were treated with triphosgene in the presence of triethylamine to form arylisocyanates. Further, nucleophilic substitution with appropriate 1-aryl-2-iminoimidazolines-2 led to formation of 1-(arylimidazolin-2-yl)-3-arylureas (Scheme 1). The final products had been purified from byproducts by applying chromatographic techniques.



R^1= H, 2-Cl, 3-Cl, 4-Cl, 2-CH_3, 3-CH_3, 4-CH_3

R^2= H, CH_3

Scheme 1

Results and discussion

Structural analysis of compounds was confirmed with elemental analysis, API-MS and 1H-NMR spectroscopy. Spectral characteristic revealed:

- two double doublet signals of H2 and H3 in H-NMR spectra at ca. 3,5 and 4 ppm;
- widely separated signals of the hydrogens in the aromatic ring between 7,2-7,8 ppm;
- N-H signal at ca. 8,2-8,6 ppm;
- $CH_{2benzyl}$/CH_{benzyl} signals between 4,2-5 ppm.

Conclusions

The synthesis of 1-(arylimidazolin-2-yl)-3-arylureas was completed successfully. The obtained compounds were sent for further *in vitro* studies (involving affinity to μ-opioid receptor, G protein activation and beta-arrestin recruitment assays) to provide more information about their activity and selectivity.

Combined Ultrasound/Microwave Chemocatalytic Method for Selective Conversion of Cellulose into Lactic Acid

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Combined Ultrasound/Microwave Chemocatalytic Method for Selective Conversion of Cellulose into Lactic Acid

Sofia Tallarico

PC_44

Background

Lactic acid (LA) is a chiral α-hydroxy acid referred as ***platform chemical*** [1], with the potential to become a precursor for the synthesis of α-amino acids, opening to new sustainable chemical routes for the production of proteins from biomass [2].

In this work, we present an alternative combined US/MW chemocatalytic method to realize the ***selective hydrothermal conversion of cellulose into LA***, under mild reaction conditions in presence of $ErCl_3$ grafted on MCM-41 silica surface.

Results and discussion

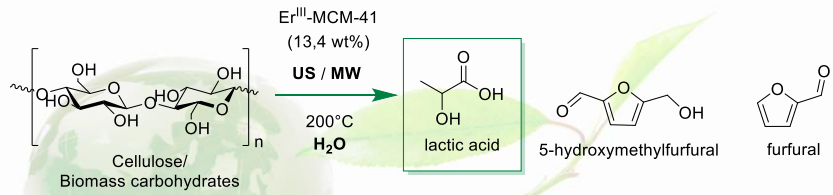

Figure 1. Catalytic hydrothermal conversion of cellulose and biomass carbohydrates.

- This chemocatalytic route allowed realizing biomass hexoses conversion to LA in only ten minutes with ***good yields*** and ***selectivity.***
- Concerning cellulose, an additional US pre-treatment was necessary to lower its crystallinity degree, thus activating its conversion.
- The method is efficient and selective: MW assistance allowed mild reaction temperatures, safely operational conditions and good scaling-up performances.

References

[1] M. Dusselier et all., Energy Environ. Sci., **2013**, 6, 1415-1442
[2] W. Deng et all., PNAS, **2018**, 115 (20), 5093-5098

Conclusions

We were able to realize selective conversion to LA in ***relatively mild and safe conditions*** with respect to the literature, thus demonstrating the efficiency of the proposed chemocatalytic MW-assisted route.

Biological activity of toluquinol derivatives

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[a] *Departamento Biología Molecular y Bioquímica, Facultad de Ciencias e IBIMA, Universidad de Málaga, Andalucía Tech, Málaga, España,*
[b] *Universidad de Málaga, Andalucía Tech, Departamento de Química Orgánica, Facultad de Ciencias, Málaga, España,*
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Biological activity of toluquinol derivatives

Jose Antonio Torres Vargas

PC_45

Background

Angiogenesis, one of the hallmarks of cancer is required for both tumor progression and metastasis. Our group has described the antiangiogenic effect of toluquinol, a methylhydroquinone produced by marine fungus able to inhibit the growth of endothelial and tumor cells, the capillary tube formation on Matrigel and migratory capabilities of the endothelial cells, all in the micromolar range.

In this study we have examined the activity of several toluquinol derivatives, to study how certain structural modifications of toluquinol would produce significant changes in the toxicity against cancer and endothelial cells, and also in the antiangiogenic effect in vitro as compared to the original compound.

Material and Methods

Cell proliferation assay
Cells was treated during 72h with several compounds and concentrations, and MTT colorimetric method was used to determinate IC50 for endothelial and tumor cell lines.

Endothelial tube formation on Matrigel
Endothelial cell (BAEC) were plated on Matrigel with the presence of compound to determinate the minimal concentration of compound that inhibited the cords formation.

Endothelial cell migration
The migratory activity of BAEC cells was assessed using a wound migration assay; confluent monolayers were wounded with pipette tips. After washing, complete medium was added either in the presence of tested compounds. Wounded areas were photographed at 7h.

Conclusions

Some of the toluquinol derivatives exhibited a decreased effect on the growth of endotelial and tumor cells, whereas they maintained a similar antiangiogenic activity, as compared to the original compound. This suggest that the structural modification of toluquinol could improve their therapeutic potential by reducing the citotoxicity. Additional assays are necesary to fully determinate the biological activity of toluquinol derivatives and their mechanism of action.

Results and discussion

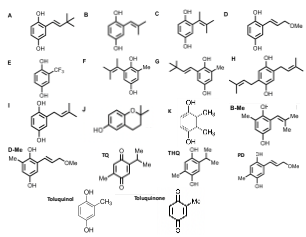

Figure 1: Molecular structures of toluquinol and derivatives.

Table 1: Biological evaluation of compounds A-J

	BAEC	MDA-MB	HL-60	U87-MG	HT-1080	HT-29	Tubes	Migration
	IC50 [a] (µM)						MIC [b] (µM)	
Toluquinol	2,26 ± 1,72	2,30 ± 0,80	1,69 ± 0,49	5,56 ± 1,49	1,38 ± 0,58	4,07 ± 0,37	2,5	10
A	31,12 ± 5,00	6,65 ± 1,83	6,29 ± 1,34	15,91 ±4,37	6,11 ± 2,47	12,25 ± 2,51	5	25
B	13,94 ± 1,73	4,06 ± 1,13	2,95 ± 0,69	10,40 ± 3,59	3,66 ± 1,81	7,87 ± 0,13	2,5	25
C	11,69 ± 2,68	3,92 ± 1,50	5,32 ± 2,00	29,69 ± 4,89	8,44 ± 1,39	15,45 ± 4,46	2,5	25
D	6,07 ± 1,35	4,21 ± 1,85	6,17 ± 1,66	8,81 ± 0,83	3,21 ± 1,87	9,81 ± 3,18	2.5	10
E	37,83 ± 2,48	14,48 ± 1,81	13,92 ± 1,10	31,68 ± 5,59	21,32 ± 9,67	29,66 ± 7,10	25	50
F	6,98 ± 2,71	2,63 ± 1,31	3,64 ± 1,51	15,76 ± 2,25	5,50 ± 1,96	14,23 ± 4,34	5	10
G	14,26 ± 2,22	3,15 ± 1,18	4,70 ± 0,78	15,98 ± 1,27	5,00 ± 1,46	17,57 ± 1,19	10	25
H	67,87 ± 8,05	>100	7,03 ± 1,23	>100	>100	>100	25	>50
I	>100	>100	50,04 ± 3,41	>100	>100	>100	25	>50
J	>100	>100	82 ± 5,94	>100	>100	>100	25	>50
Bme	2,87 ± 1,03	2,19 ± 0,29	3,06 ± 1,66	9,96 ± 2,15	3,30 ± 0,09	8,11 ± 0,65	2,5	5
Dme	3,03 ± 1,04	2,44 ± 0,25	3,10 ± 1,25	9,55 ± 1,32	2,89 ± 1,01	7,68 ± 1,63	2,5	10
TQ	2,50 ± 0,98	1,02 ± 0,05	2,03 ± 0,88	15,05 ± 3,24	3,96 ± 0,88	12,87 ± 1,64	2,5	5
THQ	2,17 ± 0,87	0,98 ± 0,12	1,56 ± 0,54	10,19 ± 2,04	2,03 ± 1,10	8,20 ± 1,36	2,5	10
Toluquinone	2,50± 1,27	3,39 ± 0,12	5,57 ± 1,94	8,79 ± 0,88	4,87 ± 1,66	9,46 ± 0,54	2,5	5
PD	2,17 ± 0,30	1,61 ± 0,48	2,90 ± 1,37	5,19 ± 1,24	1,13 ± 0,19	7,85 ± 1,97	2,5	10
K	2,19 ± 0,50	2,03 ± 0,30	3,21 ± 1,59	5,07 ± 0,40	1,58 ± 0,33	6,53 ± 2,63	2,5	5

[a]Data are means ± SD of at least three independent experiment with quadruplicate samples each.
[b]Minimal inhibitory concentration of compounds (MIC) on BAEC, cell diferentation (tube formation) or migration.

Wound migration assay

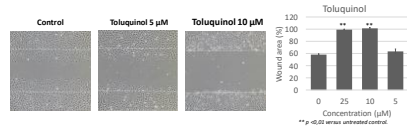

Figure 2: Wounded areas were photographed at 7h. The assay was performed with all the compounds, and the dose was reduced until show no significant difference respect to control. Only the results of one representative compound are shown.

Endothelial tube formation on Matrigel

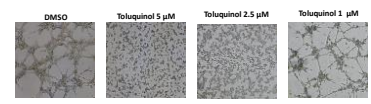

Figure 3: Images shown several concentrations tested with BAEC, in Matrigel tube formation assay. The assay was performed with all the compounds, and the dose was reduced until show no significant difference respect to control. Only the results of one representative compound are shown.

In silico studies for the discovery of MUC1/CIN85 protein-protein interaction inhibitors as anti-metastatic agents

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In silico studies for the discovery of MUC1/CIN85 protein-protein interaction inhibitors as anti-metastatic agents

Serena Vittorio

PC_46

Background

MUC1 is a transmembrane glycoprotein overexpressed in most epithelial cancers. CIN85, a multifunctional adaptor protein, interacts with the tumor form of MUC1 through its SH3 domains and this association promotes the invasiveness of cancer cells (Cascio S.,2013).

Material and Methods

CHARMM ➡ MD simulation

fpocket ➡ Binding pocket detection

AutoDock Vina ➡ Docking

Conclusions

An *in silico* approach was applied to design MUC1/CIN85 PPI inhibitors. The most promising compounds were purchased. Biological studies are ongoing.

Results and discussion

AIM: design molecules able to bind CIN85 SH3 domain thus preventing its interaction with MUC1.

400ns MD simulation CIN85 SH3A domain (PDB 2BZ8) → Clustering&Binding Pocket prediction → **Druggable binding pocket between 170-230 ns**

Asinex PPI library (Non-Macrocyclic) → **Molecular docking studies**

MD simulation of the protein-ligand complex for the 30 best scored hits → **Best results: 18 hits** → **Biological studies in progress…**

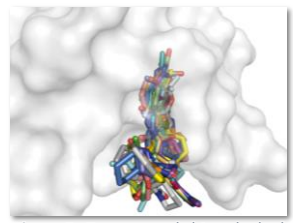

Figure.2 Best scored hits docked into the identified pocket.

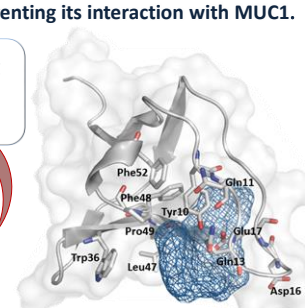

Figure.1 Putative ligand binding pocket (blue mesh) identified on CIN85 SH3A domain.

A NEW SYNTHESIZED AChE INHIBITOR INDUCES H_2S FORMATION IN THE BRAIN

Nazlıcan Belen[a], Elif Alancay[a], Gulnur Sevin[a], Sulunay Parlar[b], Vildan Alptuzun[b] and Gunay Yetik Anacak[a]
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[b]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ege University, Izmir, Turkey*

Presenting Author: Gunay Yetik Anacak

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A NEW SYNTHESIZED AChE INHIBITOR INDUCES H_2S FORMATION IN THE BRAIN

Nazlıcan Belen, Elif Alancay, Gulnur Sevin, Sulunay Parlar, Vildan Alptuzun and Gunay Yetik Anacak

PC_47

Background

Oxidative stress is implicated in several mental disorders including alzheimer, depression, anxiety disorders, schizophrenia and bipolar disorder. Plasma H2S levels were found to significantly lower in patients with schizophrenia. Thus we investigated whether oxidative stress decreases H_2S formation and pharmacological tools that can stimulate H_2S formation in brain.

Material and Methods

Methylene Blue Assay

We investigated the effect of oxidative stress induced by pyrogallol and/or our new synthesized AchE inhibitor; C1 (10-5 M, 30 min.) in the absence or presence of inhibitor of H2S synthesis enzymes; CSE and/or CBS on H2S formation in mice brain homogenates by methylene blue assay.

Conclusions

We suggest that decreased level of H2S may contribute to the mental disorders where oxidative stress is decreased such as depression, alzheimer diseases and schizophrenia. Since the neuroprotective role of H2S has been confirmed, our result suggest additional therapeutical potential of the new synthesized compound C1 in such mental disorders including oxidative stress through inducing H2S formation.

Results and Discussion

Oxidative stress caused a strong inhibition of H_2S formation (P<0.001, unpaired t test, n=9) and C1 can reverse it in brain (P<0.01, unpaired t test, n=9). The effect of C1 is inhibited by CSE inhibitor PAG slightly but with CSE+CBS inhibitor AOAA strongly (P<0.001, unpaired t test, n=9). These results suggest the dominant role of CBS in the stimulator effect of C1 on H_2S formation.

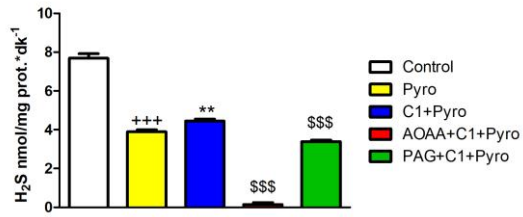

Figure 1: The effect of C1 on oxidative stress induced by pyrogallol in mice brain homogenates in the presence and absence of inhibitors. C1 augmented the decreased H_2S formation. AOAA reversed this augmentation back stronger than PAG. ^{+++}P<0.001 compared to control, $^{**}P$<0.01 compared to pyro, $^{\$\$\$}P$<0.001 compared to C1+Pyro, Unpaired t-test

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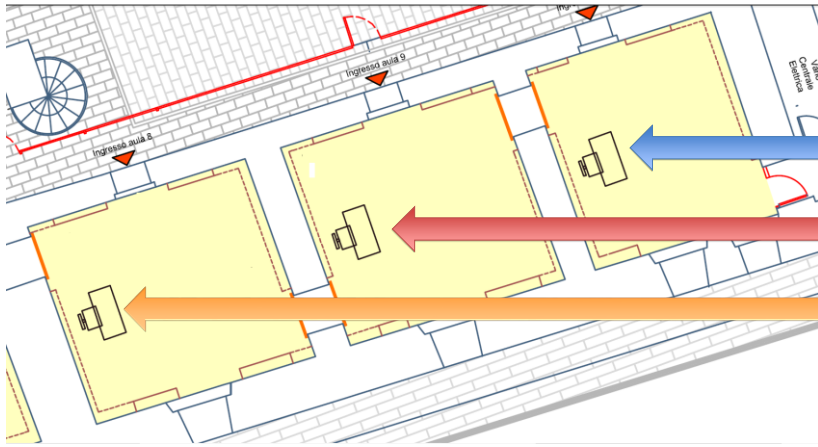
LOCATION OF THE MULTIMEDIA POSTER SESSION

COMPLESSSO MONUMENTALE SAN GIOVANNI BASIN FLOOR



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