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MEETING
ABSTRACTS

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SancaMedChem - The São Carlos Special Medicinal Chemistry Meeting

November 25th to 27th, 2019

São Carlos Institute of Chemistry (IQSC), University of São Paulo (USP)

São Carlos – SP, Brazil

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SUMMARY

2,2,2-Trifluoroethylamine as a Peptidic Bond Bioisostere in Reversible Covalent Inhibitors of Cysteine Proteases

Rafael da Fonseca Lameiro[1,*], Anwar Shamim[1], Carlos Alberto Montanari[1]

[1] Grupo de Estudos em Química Medicinal – NEQUIMED, São Carlos Institute of Chemistry – University of São Paulo, São Carlos, São Paulo, Brazil.
**E-mail: rafael.lameiro@usp.br*

Field: Organic Synthesis

Keywords: *Bioisosteric replacement, Cysteine protease, 2,2,2-Trifluoroethylamine*

Cysteine proteases (CPs) are involved in the pathogenicity of various parasitosis, such as Chagas disease and leishmaniasis. Selective inhibitors for this class of enzymes can be developed from peptides, which are their natural substrate. However, the peptidic bond is a metabolic instability site that can decrease the substance's bioavailability when used as a drug. In this work, we used the bioisosteric replacement of the peptidic bond by a *2,2,2*-trifluoroethylamine group to develop more stable and bioavailable cysteine protease inhibitors. The method employed was adapted from the literature[1, 2], and it begins with the formation of an imine between an (*S*)-amino ester and a substituted *2,2,2*-trifluoroacetophenone. The imines are reduced using stereoselective reactions that yield both (*R,S*)- and (*S,S*)-trifluoromethylamino acids, which can finally be coupled to a substituted aminonitrile. The peptidomimetic compounds synthesized are reversible CP inhibitors that can covalently bind to the cysteine residue at the active site of the enzymes. Inhibition constants (K_i) were measured for three different CPs (*T. cruzi* cruzain, *Leishmania* CPB and human cathepsin L), and inhibitory activities ranged from 2.5 µM to 16 nM. **Figure 1** shows pK_i comparisons for two molecular pairs (Neq0976 + Neq0997) and (Neq0997 + Neq1001). The profile indicates that the modifications in the molecular structures proposed were able to increase affinity and selectivity for cathepsin L.

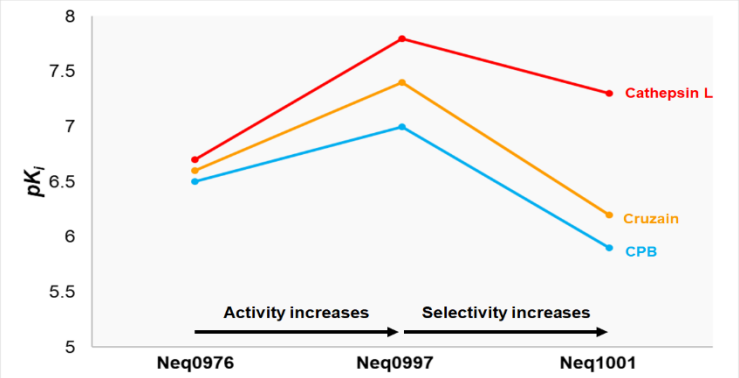

Figure 1. Comparison of CP inhibition activities (*pKi*) for three selected compounds.

Acknowledgments: São Paulo Research Foundation (FAPESP Process n° 2013/18009-4, 2018/03279-0 and 2018/03985-1) and National Council for Scientific and Technological Development (CNPq).

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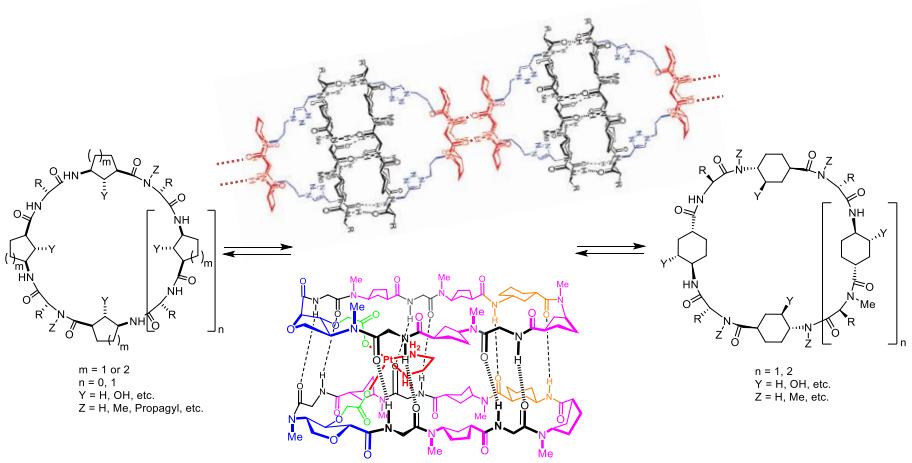
Cyclic Peptide Nanotubes: Designs for materials and biological applications

M. Amorín, A. Fuertes, A. Lamas, M. Vilela, F. Novelli, E. González, M. Panciera, J. R. Granja

Singular Research Centre in Chemical Biology and Molecular Materials, (CIQUS), Organic Chemistry Department, University of Santiago de Compostela (USC), 15782 Santiago de Compostela, Spain.
E-mail: manuel.amorin@usc.es

The construction of tubular structures of nanometric dimensions has a wide range of applications. One of the more powerful strategies toward this end is based in the self assembly of cyclic peptides.[1] The combination of natural and non-natural amino acids allows the modification of the external and internal properties, while at the same time, the control over the internal diameter.[2] Here, we show a variety of designs and their potential applications in the biological and the material field.[3]



Acknowledgements: This work was supported by the Spanish Agencia Estatal de Investigación (AEI) and the ERDF (CTQ2013-43264-R, CTQ2016-78423-R), and by the Xunta de Galicia and the ERDF (EM2014/011, ED431C 2017/25 and Centro singular de investigación de Galicia accreditation 2016-2019, ED431G/09). We also thank the ORFEO-CINCA network and Mineco (CTQ2016-81797-REDC).

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Development and validation of an analytical method for the quantification of a dipeptidyl nitrile in the extracellular medium using HPLC-UV

Pedro Henrique Jatai Batista[1] and Andrei Leitão[1]

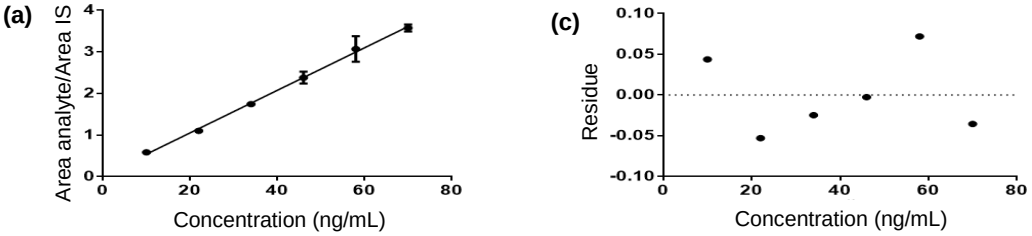
[1]Medicinal Chemistry Group (NEQUIMED), São Carlos Institute of Chemistry (IQSC), University of São Paulo, São Carlos, Brazil
E-mail: pedrojatai@hotmail.com

Field: Analytical Chemistry

Keywords: Analytical Method; Antiparasitic Compound; Dipeptidyl Nitrile

Neglected diseases, such as Chagas disease and Leishmaniasis, are being tackled by the discovery of inhibitors for macromolecular targets, including cruzain[1]. Among these inhibitors, dipeptidyl nitriles inhibit cruzain and present therapeutic potential[2]. This work reports the development and validation of a method for the analysis of the extracellular medium with a dipeptidyl nitrile (Neq0570) synthesized by the Medicinal Chemistry Group (NEQUIMED) using HPLC-UV with Odanacatib as an internal standard (IS). The sample was prepared by liquid-liquid extraction with three sequential steps using *tert*-butyl methyl ether in a 1:1 ratio. The method was set as a linear gradient of 15-85% acetonitrile in 14 min, under a 1.0 $mL.min^{-1}$ flow, 35°C and 5 µL of injection. The analyte shows 225 nm as the maximum absorbance, while it is at 265 nm for Odanacatib. The chromatographic column used for this work was a Gemini® Column-C18, Phenomenex® (150x4.6 mm, 5 µm). The validation was based on the ANVISA guideline, and presented accuracy, good linearity within the range of 10-70 $ng.mL^{-1}$ (Figure 1), without the matrix effect. The matrix was composed by the compound (administered *in vitro* at 10 µM) and incubated for 5 days with the culture medium *in vitro*. The method quantified 22.1% (2.21 µM) of the initial concentration of the parental compound administered in the cell-based assay. The next steps involve the quantification of the compound in the intracellularly and to detect the metabolites and degradation products. All data together will provide a clear picture of the pharmacokinetic profile for the dipeptidyl nitrile in the same conditions of the *in vitro* studies made to the anti-chagasic compounds.

Figure 2. Linear regression of Neq0570 (a), equation (b) and the distribution of the residues (c).



(b) $A_{Neq0570}/A_{PI} = 0.0169*X + 0.00252$ R = 0.9978

Acknowledgments: The authors want to acknowledge the FAPESP (grant #2013/18009-4, #2018/15904-6) and CNPq (grant #142422/2016-9).

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Disclosing the molecular determinants of bioactive compounds: From chemical structure to mechanisms of drug action

Javier Luque, PhD
Universidade de Barcelona

Drug design relies on the concept that a small molecule interacts with a physiological target in such a way that the strength of the interaction (affinity) is the main determinant of the therapeutic response. This assumption resides at the heart of structure-based drug design strategies, by which the chemical structure of a given compound with moderate but promising properties is subsequently modified in order to obtain a *lead* candidate. Despite the efforts spent in developing a wide range of structure-based approaches and the integration within multidisciplinary research that combines molecular biology, biophysics, combinatorial chemistry, high-throughput screening and genomics, it is paradoxical that the number of chemical entities released along the last years has risen only slightly in spite of the substantial increase in development investment.[1] This situation reflects our still limited understanding of the molecular determinants of drug activity and the complexity of biological systems.[2] In this context, this talk will highlight several challenging aspects of the molecular modeling of ligand-target interactions. Specifically, attention will be paid to the relationships between specific structural and physicochemical features of small molecules, the molecular mechanism that underlye the recognition and binding at their macromolecular targets, and the modulation of the bioactive response.

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Falcipain-2 loop involved in the capture of Human Hemoglobin as target for inhibitor design

Sudbrack, T. P., Juliano, M. A., Riske, K. A., Perez, K. R., Juliano L.,
Departamento de Biofísica, Escola Paulista Medicina, Universidade Federal de São Paulo

Malaria is responsible for hundreds of thousands of deaths per year worldwide caused mainly by *Plasmodium falciparum*. Cysteine proteases play essential role in malaria parasites life cycle, and among them falcipain-2 (PF2) and falcipain-3 (PF3) received more attention due to their peculiar hemoglobinase activity. FP2 and FP3 have an unusual beta-hairpin motif of 10-amino acids that protrudes out from the protein and is distant from the enzyme active site. FP2 utilizes this motif for interaction with hemoglobin, which hydrolysis depends on the presence of this motif (Pandey et al, 2005). In order to explore the effect on hemoglobin of this beta-hairpin motif we synthesized the peptide corresponding to this segment (EIVNPLTKKG) and evaluated its effects on hemoglobin type A (HbA) by UV-visible spectroscopy, circular dichroism (CD), differential scanning calorimetry (DSC) and isothermal titration calorimetry (ITC) techniques. The interaction of the peptide with HbA causes spectral UV-visible modifications at peptide/HbA ratio 169 or higher. The typical CD spectrua of a β-helix-rich structure, characteristic of hemoglobin, underwent significant reduction as observed by the extinction of the 195 nm positive band, evidencing HbA denaturation. The obtained thermograms from DSC measurements confirm that the interaction of the peptide with HbA induces its denaturation. Isothermal titration calorimetry (ITC) showed an exothermic component followed by an endothermic one that may be associated with the binding of peptides to HbA with its consequent denaturation. Similar studies were done with HbS obtained from sickle cell disease patients and very significant resistance to denaturation by EIVNPLTKKG was observed. This is also in according to the well-known resistance to malaria of these patients.
Cathepsins are drug target for several diseases and several active site-directed inhibitors have shown high efficacy in clinical trials. However, they have various safety concerns. One drawback of these inhibitors is that they inhibit the degradation of the entire substrate spectrum of the target protease or even other of the same family, which might lead to side effects. Using crystallographic and biochemical approaches, Brömme et al. (2019) demonstrate that so-called ectosteric inhibitors bind at multiple sites on CatK remote from its active sites and depending on their sites show the selective inhibition of individual substrates. These ectosteric inhibitors present a novel enzyme inhibitory approach which promises higher substrate specificity and fewer side effects, could be used for PF2 and/or PF3 focusing the interaction of its beta-hairpin motif EIVNPLTKKG with hemoglobin.

Acknowledgement: FAPESP-Project 12/50191-4R, and CNPq-Projects 471340/2011-1 and 470388/2010-).

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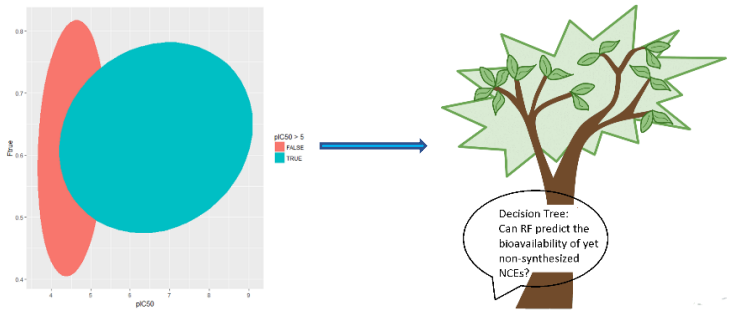
How NEQUIMED/IQSC/USP's Using Machine Learning to Aid Drug Discovery

Carlos A. Montanari & Lorenzo Cianni

Department of Chemistry and Molecular Physics, University of Sao Paulo, São Carlos, Brazil
E-mail: Carlos.Monanari@usp.br

Field: Computational chemistry

Keywords: Artificial intelligence, Machine Learning, Accelerating Drug Discovery



Different methods of machine learning are used successfully in various areas of artificial intelligence research, such as molecular drug candidate design. Despite this, a particular method of machine learning may outperform another, and therefore, the use of orthogonal methods may be an alternative to overcome such toil and improve the prediction result. Our research group has routinely used methods such as artificial neural networks (ANN), vector support machines (SVM) and random forests (RF) for the molecular design of new bioactive chemical entities (BioNCEs). In this work,[1] such methods were applied to aid prediction-power of cysteine protease inhibitors. Navigation through chemical spaces made up of a myriad of molecules will occur through the supervised method followed by the unsupervised one to identify previously unknown patterns.

Acknowledgments: FAPESP #2013/18009-4.

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Hydrogen bonding and drug design

Peter Kenny

São Carlos Institute of Chemistry (IQSC), University of São Paulo, São Carlos, Brazil

I will discuss drug design in terms of what a drug needs to do, stressing the need to control exposure and summarizing the nature of drug design. The importance of molecular interactions in drug design will be highlighted and two approaches to quantifying the strength and importance of hydrogen bonding will be presented. Drug design can be also be considered in terms of beating water at hydration and I will conclude the lecture by discussing tactics for achieving this.

Lead-Optimization of 1-(4-aryl)cyclohexyl-4-(3-pyridyl)piperazine as TRPV6 Inhibitors

Micael R. Cunha,[1,3] Rajesh Bhardwaj,[2] Roberto Parise-Filho,[1]* Matthias A. Hediger,[2]* Jean-Louis Reymond.[3]*

[1]Department of Chemistry and Biochemistry, University of Bern, Switzerland
[2]Department of Nephrology and Hypertension, University Hospital Bern, Switzerland
[3]Department of Pharmacy, University of São Paulo, Brazil
E-mail: micaelrc@gmail.com

Field: Chemical synthesis

Keywords: Capsaicin, Bioisosterism, TRPV Channel

Capsaicin is a substance produced by *Capsicum* peppers with extensive biological activity reported in the literature. Among these studies, it was suggested that the anti-tumor activity is related with modulation of the Transient Potential Receptor Vanilloid (TRPV) channels [1,2]. Capsaicin is known to bind with very high affinity to TRPV1 (IC_{50} ≈ 7 nM), triggering the burning sensation followed by analgesia. However, recent studies have suggested that the pro-apoptotic effects of capsaicin are TRPV6-mediated [3-4]. Herein we report the development of a novel inhibitor of the TRPV6 using two different strategies for compounds design. We generated series of direct and chimeric capsaicinoids based on the literature compounds, capsaicin and *cis*-22a [5,6]. These analogues were probed against HEK-*h*TRPV6 and HEK-*h*TRPV1 and the hits were further optimized. Based on the previous SAR and chemical optimization, we found **56h**, named MRC-130, a derivative that remarkably inhibited TRPV6 in nanomolar range (IC_{50} = 83 ± 4 nM), possess high selectivity and stability *in vitro,* and lesser *h*ERG inhibition compared to the reference compound, *cis*-22a. It is expected that these new molecules would contribute significantly for the study on TRPV6 function and its role in tumor pathophysiology.

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Mapping the S1 and S1' subsites of cysteine proteases for the synthesis of new dipeptidyl nitriles as trypanocidal agents

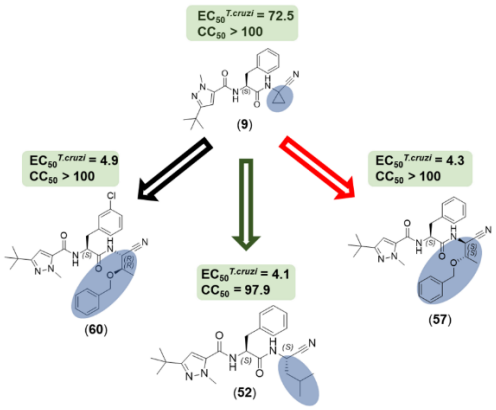
Lorenzo Cianni, **Carlos A. Montanari**

Medicinal Chemistry Group, Institute of Chemistry of São Carlos, University of São Paulo, Avenue Trabalhador San carlense, 400, 23566-590, São Carlos/SP, Brazil
E-mail: lorenzo.cianni@usp.br

Field: Synthetic and Medicinal Chemistry

Keywords: *T.cruzi*, Cruzain, Structure-Activity Relationship

The cysteine protease cruzipain is considered to be a validated target for therapeutic intervention in the treatment of Chagas disease[1]. A series of 26 new compounds was designed, synthesized and tested against the recombinant cruzain (Cz) to map its S1/S1´ subsites. The same series was tested on a panel of four human cysteine proteases (CatB, CatK, CatL, CatS)[2] and *Leismania mexicana* CPB[3], which is a potential target for the treatment of cutaneous leishmaniasis. The synthesized compounds are dipeptidyl nitriles formed by the most promising combinations of different moieties in P1 (ten), P2 (six) and P3 (four). In P1, different natural and non-natural amino acids were chosen as building blocks. Eight compounds exhibited a K_i smaller than 20.0 nM for Cz, whereas 3 compounds met this criteria for LmCPB. Furthermore, the same set of compounds displayed a one-digit nanomolar affinity for CatK and CatL. The most potent of these inhibitors display a degree of non-additivity in the SAR illustrating how the S1-P1 interaction is driven by the S2-P2 interaction. 30 inhibitors were also evaluated for their anti-trypanosomal (*T. cruzi*, amastigote) effects and an EC_{50} value of ca. 4 μM was observed for three of them, resulting to be equipotent with benznidazole (current drug for the treatment of CD) with no observable cytotoxicity.



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Marinoquinolines as antimalarial agents: Design of new highly active and selective derivatives

Patrícia Santos Barbosa[1], Ítalo Caetano Canevari da Silva[1], Gilberto Gaspar Duarte Ortin[1], Rebeca Monique Capitão[1], Eric Francisco Simão dos Santos[1], Rafael Dias do Espírito Santo[1], Michele Panciera[1], Guilherme Eduardo de Souza[2], Anna Caroline Campos Aguiar[2], Rafael Victório Carvalho Guido[2] and Carlos Roque Duarte Correia[1]

[1]Chemistry Institute, UNICAMP, Campinas, Brazil
[2]Physics Institute of São Carlos, USP, São Carlos, Brazil
E-mail: patriciasbarb@gmail.com

Field: Synthetic chemistry

Keywords: quinoline compounds, malaria, plasmodium.

Marinoquinolines represent a new class of natural and unnatural compounds containing the uncommon 3H-pyrrolo[2,3-c]quinoline scaffold which has rarely been studied. In 2012, our research group reported the total synthesis of the natural marinoquinolines A, B, C and E, and this synthetic procedure allowed the synthesis of new unnatural derivatives. In light of these results, we have been working on the synthesis of new analogues in order to find a new drug candidate for malaria. The synthetic route evolves as key-reactions the Suzuki-Miyaura cross-coupling reaction and the Pictet-Spengler reaction. We created a library of marinoquinolines containing compounds with different substituents.

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Novel Cathepsin B Inhibitors with Inversely Oriented Warheads

Michael Gütschow

Pharmaceutical Institute, University of Bonn, An der Immenburg 4, 53121 Bonn, Germany
guetschow@uni-bonn.de

Cathepsin B, a papain-like cysteine protease, is involved in various physiological processes. In tumor cells, it adopts a peripheral distribution and affects the extracellular matrix either directly by extracellular proteolytic degradation of its components or indirectly via activation of other proteases. The breakdown of the extracellular matrix remodels the tumor environment, promotes tumor invasion, and enables angiogenesis and metastasis. The crucial roles of cathepsin B at multiple points of the tumor development have been established in several in vitro and in vivo models and cathepsin B was proposed to be a prognostic marker in patients with various types of cancer [1,2]. The typical feature of peptidic inhibitors of cysteine proteases includes an N-capped peptide structure bearing an electrophilic warhead (e.g. a nitrile [3-7], aldehyde, halomethyl or acyloxymethyl ketone or Michael acceptor) in place of the scissile peptide bond. A linker can direct a carboxylic group to the S' region to allow for an advantageous salt bridging with the histidine residues of the occluding loop of cathepsin B, thus enhancing cathepsin B selectivity [8]. In E-64-derived epoxysuccinyl derivatives, a peptide part can bind along the S subsites of cathepsin B, while a dipeptide moiety is oriented towards the S' sites [9,10]. We have designed cathepsin B inhibitors with dipeptide portions directed towards the occluding loop and equipped with fine-tuned, inversely oriented warhead structures which are cleaved upon the action of the active site cysteine leading to irreversible inhibition. Kinetic data at four human cathepsins obtained for an extended series of around 200 unpublished representatives of this chemotype demonstrated their selectivity for cathepsin B, supported the exciting mode of action and allowed to draw detailed structureactivity relationships. The synthesis and the biochemical characterization of these novel cysteine protease inhibitors will be presented. The tailored structure of our new inhibitors allows the design of PET ligands and (in continuation of our previous studies [11-13]) linker connection for the assembly of activity-based probes.

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Predicting the $\Delta\Delta G_{bind}$ of halogenated reversible covalent inhibitors of hCatL through computer simulation

Jerônimo Lameira,[1,2] Vinícius Bonatto,[2] Lorenzo Cianni,[2] Fernanda dos Reis Rocho,[2] Andrei Leitão,[2] Carlos A. Montanari[2]

[1] On leave from Universidade Federal do Pará, Belém-PA, Brazil
[2] Instituto de Química de São Carlos, Universidade de São Paulo, São Carlos-SP, Brazil
E-mail: vbonatto@usp.br

Field: Computational Chemistry

Keywords: Computational Chemistry, Molecular Dynamics, Free Energy Perturbation

The cysteine protease human Cathepsin L (hCatL) are expressed in different types of cancer, then the inhibition of this enzyme may be important to discovery of novel therapeutics. In this study five nitrile-based inhibitors analogs of the prototypical **Neq0570** were studied. All of them are halogenated reversible covalent inhibitor of hCatL. To describe the halogen bonding interaction in active site of hCatL, we applied an extra point (EP) of charge in the halogen atom to represent the σ-hole. We used molecular dynamics calculation to verify the distance between the halogen atom and the oxygen atom from Gly61. To evaluate the overall relative binding free energy of these inhibitors, we used alchemical free energy calculations of two-state binding model: noncovalent and covalent state. The results show that EP improve the average of halogen bond and the use of free energy perturbation (FEP) can predict the hCatL binding affinities of the compounds with a close agreement with experimental results, as shown in Table 1.

Table 1: Relative binding free energy of hCatL inhibitors, all values in kcal/mol. Note that $\Delta\Delta G_{bind}$ corresponds to the sum of the relative binding free energy of covalent and noncovalent states.

Transformation	Mutation	$\Delta\Delta G_{bind}$ (FEP)	$\Delta\Delta G_{bind}$ (exp)	$\lvert\Delta x^a\rvert$
Neq0570 → 0802	H → F	-0.49	0.22	0.71
Neq0570 → 0710	H → Cl	-1.59	-0.82	0.77
Neq0570 → 0803	H → Br	-1.51	-1.54	0.03
Neq0570 → 0804	H → I	-1.80	-1.99	0.19

[a]**Absolute error between the calculated and experimental values**

Acknowledgments: FAPESP (2013/18009-4 and 2018/21749-3) and CAPES.

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Protein-Ligand Docking using DockThor: Pose and Binding Affinity Prediction

Laurent E. Dardenne
Laboratório Nacional de Computação Científica – LNCC/MCTIC, Petrópolis, RJ, Brazil

Protein-ligand docking is an important tool for structure-based rational drug design studies. This method aims to predict the experimental binding mode and affinity of a small molecule within the binding site of the protein target of interest. The DockThor program, developed by our group GMMSB/LNCC, uses a grid-based methodology and was implemented to deal with highly flexible ligands using a multiple-solution steady-state genetic algorithm. The pose prediction scoring function is based on the MMFF94S classical force field, and, recently, our group developed linear and non-linear affinity scoring functions (general and target-specific). In this talk, we will show some recent methodological developments associated with the DockThor program and comparative analyses for pose and affinity predictions with other state-of-the-art docking programs. We will also discuss some DockThor developments under progress. The DockThor-VS portal (freely available for the scientific community at www.dockthor.lncc.br) utilizes the computational facilities provided by the SINAPAD Brazilian High-performance Platform and the petaflop supercomputer Santos Dumont.

Quantitative Dissection of Proteolytic Networks Governing Tissue Remodeling

Manu O. Platt, Ph.D.
Georgia Tech and Emory University

In many tissue engineering strategies and tissue-destructive disease progression, mechanisms of proteolytic remodeling of extracellular matrix and tissue structure are implicated. This talk will discuss complex variability and non-intuitive cell behaviors and enzyme kinetics when targeting cysteine cathepsins, the most potent mammalian collagenases and elastases, that has led to failure of cathepsin pharmacological inhibitors to pass human clinical trials in the United States. Cysteine cathepsins are proteases capable of cathepsin cannibalism, where one cathepsin hydrolyzes another with substrate present, and cathepsin inhibitors continue to fail clinical trials due to side effects, not efficacy, motivating greater understanding of multiple proteases working in a proteolytic network. During this seminar, Dr. Platt will discuss 1) experimental and computational tools he has developed to better quantify and model the proteolytic network's role in tissue remodeling, 2) fundamental insights and consequences of proteolytic network perturbation on extracellular matrix remodeling, and 3) applications for personalized medicine strategies and identification of new targets for pharmacological targeting.

Structure-activity relationship using cell-based assay for dipeptidyl nitriles in MIA PaCa-2 pancreatic cancer cells

BOTELHO, S. M.; LEITÃO, A.

Medicinal Chemistry Group, The São Carlos Institute of Chemistry, University of São Paulo (NEQUIMED-IQSC-USP)
E-mail: sabrina.botelho@usp.br

Field: Biological Assay

Keywords: cysteine protease inhibitors, phenotypic study, enzymatic activity

Pancreatic cancer is still a deadly disease, with a high occurrence of metastasis and infective treatment. Therefore, the work analyzed the activity of dipeptidyl nitrile derivatives using pancreatic cancer lineage (MIA PaCa-2)[1], by viability assay, migration, colony formation, and inhibition of cell cysteine protease activity. The homologous series of (*S*)-N-(1-((1-cyanocyclopropyl)amino)-1-oxo-3-henylpropan-2-yl)benzamide was assayed against MIA PaCa-2 cells cultured in standard conditions with DMEM medium. It was found that Neq0709 and Neq0712 inhibited cysteine protease activity, while just Neq0709 led to colony reduction above the 50% threshold. All compounds were inactive in the wound healing assay. In short, the compound containing *o*-Cl was active in two of the three assays (Neq0709), while the *m*-CH_3 derivative (Neq0712) only inhibited proteolysis. Other chlorine-containing derivatives (*meta* and *para*) were inactive. These results demonstrated that the *o*-chlorine in ortho-position is essential for bioactivity.

Acknowledgments: FAPESP (13/18009-4, 18/15904-6, 18/09365-5), CAPES (139/2015), and CNPq.

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Synthesis and study of *L*-cysteine-arylamides derivatives as protease inhibitors

Aline S. Serralbo[1], Marghuel A. V. Silveira[2], Débora N. Okamoto[3], Luiz S. Longo Jr.[3], Suzan P. Vasconcellos[3], Maria A. Juliano[2], Adriana K. C. A. Reis[1]
[1]*Department of Chemistry, Federal University of São Paulo, Diadema, Brazil.*
[2]*Department of Biophysics, Institute of Pharmacology and Molecular Biology, Federal University of São Paulo, São Paulo, Brazil.*
[3]*Pharmaceutical Sciences Department of Pharmaceutical Sciences, Federal University of São Paulo, Diadema, Brazil*
E-mail: alinesserralbo@gmail.com

Field: Synthetic Organic Chemistry and Medicinal Chemistry

Keywords: *drug design, arylamides, protease inhibitors.*

HIV-protease and renin are aspartyl proteases with many structural similarities. Since patients on highly active antiretroviral therapy (HAART) are at a high risk of developing some irreversible side effects, such as hypertension, this project aims the drug design for the development of potential inhibitors bearing dual activity towards these proteases. The synthesis of *L*-cysteine-derived arylamides using more sustainable methodologies were studied. The methodologies employing the coupling reagent CDI in neat conditions and/or using green solvents proved to be quite efficient and very clean, with yields between 80%-90%. Screening *in vitro* assays have been played with cysteine, serine and aspartyl proteases in order to verify the inhibitory action of these compounds. Results are promising, and some arylamides used at concentrations around 0.5 μM showed complete inhibition of these proteases, being smaller than those found in the literature.[1]

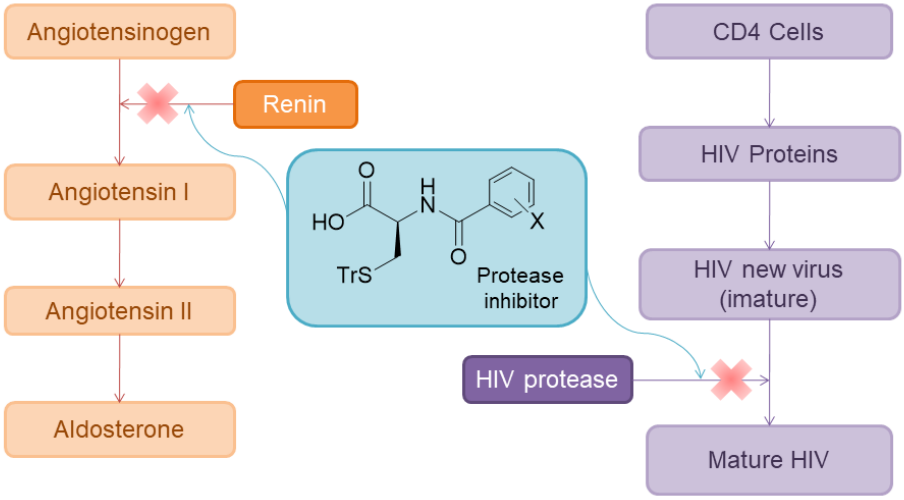

Figure 3. General scheme of the action of the arylamides (Protease Inhibitors) on the enzymatic reactions of the renin-angiotensin-aldosterone system (responsible for blood pressure control) and maturation of the HIV virus, respectively.

Acknowledgments: PPG-CTS, FAPESP, CNPq and CAPES.

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Synthesis and study of the anti-inflammatory activity of amides derived from NSAIDs

Daniel de Carvalho Santos[1*], Hugo P. Monteiro[2], Elaine G. Rodrigues[3] and Adriana Karla C. A. Reis[1*]

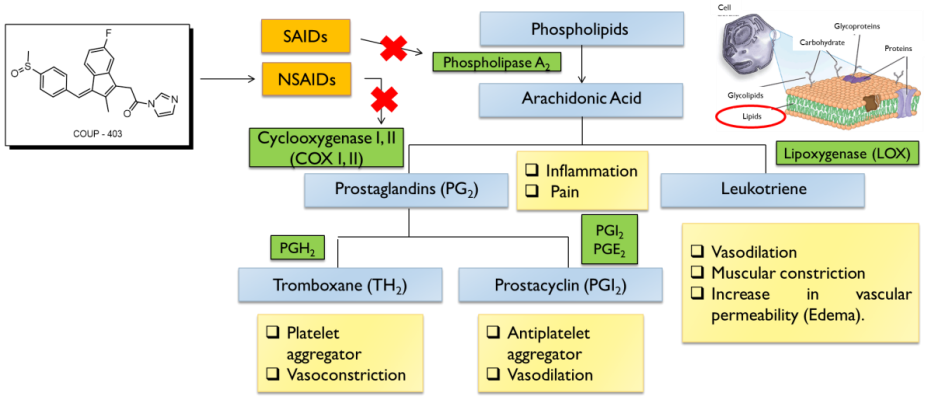
[1]Chemistry Department, Federal University of São Paulo, Diadema, SP, Brazil.
[2] Biochemistry Department, *Federal University of São Paulo, São Paulo, SP, Brazil.*
[3]*Microbiology, Immunology and Parasitology Department, Federal University of São Paulo, São Paulo, SP, Brazil.*
**e-mail: carvalho.daniiel@gmail.com; adrianakarla.amorim@gmail.com*

Field: Organic Chemistry, Medicinal Chemistry

Keywords: *Non steroidal anti-inflammatory drugs, S-Nitrosothiols, coupling reactions.*

This project aims the synthesis and study of amides derived from nonsteroidal anti-inflammatory drugs (NSAIDs). These compounds are potential prodrugs with less side effects, and appropriate selectivity to the different cyclooxygenase isoforms. The anti-inflammatory activity of those compounds has being evaluated *in vitro* through reduction of IL (interleukine)-12 levels produced by macrophages previously activated with interferon-gamma and lipopolysaccharide. Amides were prepared reacting the NSAIDs with heterocyclic aromatic amines and with *L*-cysteine ethyl ester hydrochloride by coupling reactions with carbodiimiides and CDI, in classical and sustainable methods. *In silico* analysis are being carried out for this molecules. Results obtained for the *in vitro* assays for anti-inflammatory activity are showing positive results. The use of environmentally friendly methodologies for the coupling reactions is providing very promising results. These methodologies are becoming a relevant alternative for the preparation of the compounds of interest.

Scheme 1. Action sites of steroidal and nonsteroidal anti-inflammatory drugs and a selected example of an amide derived from NSAIDs .



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Synthesis, characterization and evalution of potencial use of BioMOFs as veterinary *drug delivery* systems

Camila Juliane Lima[1] and Regina Célia Galvão Frem[2]

[1]Department General and Inorganic Chemistry, University State Paulista Julio de Mesquita Filho (UNESP), Araraquara, Brazil.
[2]Department General and Inorganic Chemistry, University State Paulista Julio de Mesquita Filho (UNESP), Araraquara, Brazil.
E-mail: camilajuliane@outlook.com

Field: Inorganic Chemistry.

Keywords: BioMOFs, *drug delivery.*

Metal-Organic Frameworks (MOFs) are coordinating polymers that have open structure containing potentially free pores. Because they are crystalline, light, have high specific area values and considerable thermal stability, this new class of compounds has been applied in several areas such as gas storage and separation, heterogeneous catalysis, drug delivery, chemical sensors, among others. The construction of these porous materials using bioelements and biocompatible organic binders gave rise to the BioMOFs (Biocompatible MetalOrganic Frameworks). These compounds have no cytotoxicity and are therefore suitable to be investigated as carriers acting on release mechanisms. In this context, the present project performed the synthesis and characterization of biocompatible MOFs to be used as controlled release systems of veterinary drugs, more specifically brucellosis antibiotics. The building blocks of porous matrices involve the metal ion Mg^{2+} and the organic binders: adenine, lactic acid. The characterization results obtained so far suggest that the synthesis process of BMMg material was successfully obtained. Infrared spectroscopy analysis presents characteristic bands that corroborate the coordination of organic ligands to the metal ion for BMMg material. X-ray powder diffraction analysis revealed well-defined peaks typical of crystalline materials. Scanning electron microscopy images show the material morphology aspects. In the case of BMMg material the analysis revealed surface porosity, suggesting potential for drug incorporation and release. Thermal analysis has shown that BMMg has a thermal stability of 381°C. Nitrogen adsorption-desorption measurements for the BMMg sample suggested that the material is porous (pore diameter 25-55 nm) and has a specific area of 46 m^2 g^{-1}. Thus, observing the characterizations and textural evaluations of the synthesized BMMg, it is possible to suggest that the work presents potential for the veterinary antibiotic *drug delivery* system [1].

Acknowledgments: CAPES, CNPQ, FAPESP.

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Synthesis of chalcones and β-ketoindoles as potential Mcl-1 inhibitors for the treatment of cancer

Ingrid Vieira Machado[1], Hérika Danielle Almeida Vidal[1], Bruno Neves[2], Lucas Brito[3], Claudia do Ó Pessoa[3] and Gilberto Lúcio Benedito de Aquino[1]

[1]Laboratório de Pesquisa em Bioprodutos e Síntese - LPBioS, Universidade Estadual de Goiás, Anápolis, Brasil
[2]Laboratory of Cheminformatics, Centro Universitário, Anápolis, Brasil
[3]Núcleo de Pesquisa e Desenvolvimento de Medicamentos - NPDM, Universidade Federal do Ceará, Fortaleza, Brasil
E-mail: Ingridvieiramachado09@gmail.com

Field: Synthesis of New Molecules with Potential Biological Activity

Keywords: Mcl-1 protein, Chalcone, Cancer.

Cancer is among the top ten causes of death worldwide, accounting for 9.6 million deaths in 2018[1]. Studies have showed that Mcl-1 protein is an important target for the discovery of new drugs to the treatment of different cancers, such as breast, colorectal and leukemia[2]. Consequently, potential Mcl-1 inhibitors may be promising agents against cancer that depends on Mcl-1 for survival. Chalcones and indolic derivatives have a number of biological activities, including anti-tumor[3]. Thus, the objective of this research was performed docking studies followed by the synthesis of new analogues of chalcones and β-ketoindoles as potential inhibitors of Mcl-1 protein and biological activity tests. Docking was performed using the OpenEye FRED program[4]. Was used PDB code protein 5FC4, high resolution during search and fit optimization and generated ten poses for each compound tested. After selecting the compounds, the organic synthesis and structural identification (MS, NMR and IR) were performed. The chalcones were synthesized by the condensation aldolic of Claisen-Schmidt. The β-ketoindoles were obtained by the alkylation reaction of Friedel-Crafts from the obtained chalcones. Seven chalcone derivatives and six indolic derivatives were synthesized with satisfactory purity and yield. The biological activity tests were performed by the MTT method with an incubation time of 72 hours in the non-tumor line L929, and in the tumor lines NCIH460, HCT116, HL60, PC3, and MDAMB231. The most promising compounds were chalcones 5b, 5c, 5e and 5g in the HCT116 strain with IC_{50}(μM) of 15.16; 15.33; 16.61 and 7.79 respectively. These compounds were tested for cell viability evaluation which these were able to reduce 90% of viable cells and cell morphology analyzes that showed accented cytotoxic activity, cells with membrane alteration (blebs) and cells with indications of apoptosis. QSAR studies must be performed in order to propose new substitutions to improve the activity.

Acknowledgments: LPBioS, PrP-UEG, FAPEG, CNPq, CAPES, NPDM.

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Synthesis of Covalent Reversible Inhibitors of Cysteine Protease CPB

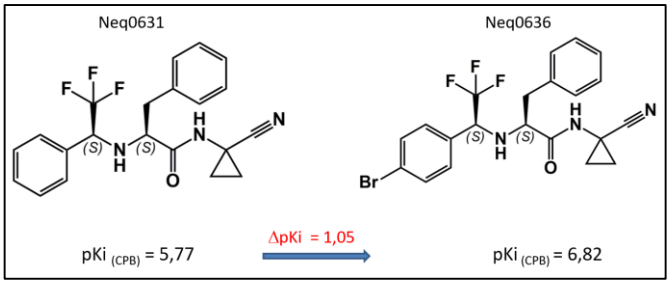
Matos, Thiago K. B*.; Leitão, Andrei

Medicinal Chemistry Group (NEQUIMED), The São Carlos Institute of Chemistry-University of São Paulo (IQSC-USP) São Carlos -SP - Brazil
**E-mail: britomatost@usp.com*

Field: Organic synthesis

Keywords: Dipeptidyl nitriles derivatives, Enzymatic inhibitors, Medicinal chemistry,

Medicinal Chemistry is an essential area for the discovery, development and planning of new chemical compounds that have therapeutic effects. Among the most diverse types of pathologies, the tropical neglected diseases present big predominance in countries such as Brazil where Leishmaniasis, a neglected disease, is endemic. A macromolecular target of therapeutic interest for antileishmanial substances is the cysteine protease B (CPB) enzyme. The Medicinal Chemistry Group (Nequimed)[1] study reversible covalent inhibitor of CPB with potential antileishmanial activity. In this study, the synthesis of dipeptidyl nitrile derivatives was performed, so that the potential inhibitory activity for CPB could be accessed through the corresponding enzymatic assays. A series of sixteen compounds that are derivatives and stereoisomers of dipeptidyl nitriles of the compound N-(1-cyanocyclopropyl)-3-phenyl-2-((2,2,2-trifluoro-1-phenylethyl)amino)propenamide were synthesized and characterized[2], one of which (Neq0930) had its absolute configuration determined by X-rays Crystallography. The stereoselectivity of the series was analyzed using biochemical assays against CPB. A Matched Molecular Pairs study (MMP) was performed with the results of the enzymatic assay and it could be concluded that the (S,S) isomers were the most potent. Moreover, an additive effect was observed for the substituents in positions P2 and P3. Finally, Neq0636 was the most potent CPB inhibitor of the whole series.



Acknowledgments: CAPES grant (PROEX program: processes 1632465 and 139/2015), CNPq, and FAPESP grant (thematic project 13/18009-4).

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Synthesis of Dipeptidyl and Peptidomimetic Nitriles as Cruzain, CPB and Related Human Cathepsins Inhibitors

Anwar Shamim[1] and Carlos A. Montanari[1]

Nequimed - Grupo de Química Medicinal, Departamento de Química e Física Molecular, Instituto de Química de São Carlos, Universidade de São Paulo – NEQUIMED/IQSC/USP
E-mail: shamim.hej@gmail.com

Field: Synthetic Medicinal Chemistry

Keywords: Synthesis, peptidomimetic, cysteine proteases

Libraries of new dipeptidyl and related peptidomimetic nitriles have been synthesized and decorated with different moieties at P1, P2 and P3. These libraries consist of dipeptidyl nitriles (12 compounds), their sulfonamide (4 compounds) and trifluoroethyl amine (21 compounds) bioisosteres, and cyclohexane dicarboxamide nitrile (1 compound) figure 1. Most of the compounds synthesized are tested against cysteine proteases including cruzain (recombinant form of cruzipain – a validated target for Chagas disease),[1] CPB (target for Leishmaniasis) and a panel of four human cathepsins (Cat. B, Cat. K, Cat. L, Cat. S), while other compounds are under analysis. According to the assays, groups of structurally related compounds with high affinity and selectivity against the said enzymes have been developed. Four compounds have exhibited pKi >8 for cruzain, six with pKi 7-8 for cathepsin B with selectivity, and two compounds with pKi >9 for cathepsin L. Our approach is to complete these libraries of compounds to observe structure activity relationship studies based on their bioassays against the panel of cysteine proteases.

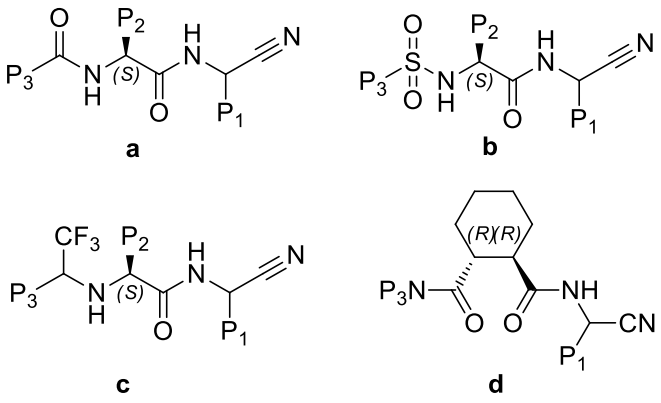

Figure 1. Basic backbone of dipeptidyl nitriles (a), and their sulfonamide (b) and trifluoroethyl amine bioisosteres, and cyclohexane dicarboxamide nitrile (d).

Acknowledgments: We thank SancaMedChem2019 and FAPESP (Thematic Project # 2013/18009-4 and project # 2018/03985-1) for the opportunities and funding.

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Synthesis of non-peptide nitrile cysteine protease inhibitors with bioisostere sulfonamides at position P3

Deborah A. dos Santos[1] and Carlos A. Montanari[1]

[1]São Carlos Institute of Chemistry, University of São Paulo, São Carlos-SP, Brazil
E-mail: deborah.araujo89@gmail.com

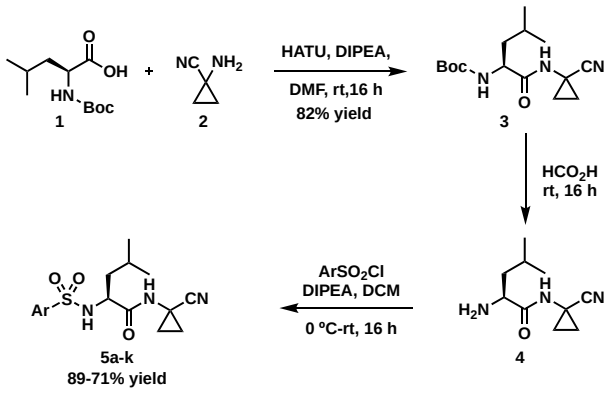
Field: Synthetic Chemistry

Keywords: Amide bioisostere, Sulfonamide, Cysteine protease inhibitors.

Dipeptidyl nitriles are known as cysteine protease covalent reversible inhibitors [1]. Our research group has been studying this scaffold with success in developing high-affintiy cruzain and cysteine cathepsins inhibitors [2]. To improve target affinity and selectivity, one strategy is the use of amide bioisoteres such as trifluoethylamine, terciary amide and sulfonamide, with interesting preliminary results.

Bioisosterism in medicinal chemistry is an important tool in terms of modulation of properties, such as metabolic stability, improvement of solubility and cell permeability [3]. Herein, we aim to evaluate the replacement of the amide function in P3 for arylsulfonamides moieties as a bioisostere in the inhibition of cruzain and other cysteine cathepsins.

The synthetic route adopted begins with the amide coupling reaction of *N*-Boc-L-leucine (**1**) and 1,1-aminocyclopropanecarbonitri-le (**2**) with HATU, followed by the Boc deprotection, giving the primary amine intermediate (**4**) that was employed in the second coupling reaction with a variety of arylsulfonyl chlorides, providing a small library of 11 compounds (**5a-k**) (Scheme1).



In general, the desired products were obtained in good yields and satisfactory purity (> 95 %). Kinetic assays on cruzain and cysteine cathepsins will be carried out to determine the structure-activity relationships.

Scheme 1. Synthesis of sulfonamide scaffolds.

Acknowledgments: The authors thank FAPESP (grants 2013/18009-4 and 2018/09961-7) and CAPES (Finance code 001).

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Synthesis of novel cysteine protease inhibitors and anti-*Trypanosoma cruzi* agents

Felipe Cardoso Prado Martins[1] and Carlos Alberto Montanari[1]

[1]Instituto de Química de São Carlos, Universidade de São Paulo, São Carlos, São Paulo, Brasil
E-mail: felipecpm@usp.br

Field: Organic Synthesis

Keywords:

Proteases are a class of enzymes that function by catalyzing the process of peptide bonds' hydrolysis. Many protease inhibitors are being developed for the treatment of bacterial, parasitic, viral, cancerous, neurodegenerative, autoinflammatory, and cardiovascular diseases[1]. Cruzain is the *T. cruzi* cruzipain's recombinant form, which is vital for the parasite's life management, being present in all its life cycle. With that in mind, cruzain is an attractive target for the development of new molecules capable of inhibiting the action of such enzyme and, consequently and ideally, interrupt the parasite's life cycle. Besides, cruzain has a highly similar amino acid sequence of human's cathepsins, which are also cysteine proteases[2], allowing for further exploration of such molecules as cysteine cathepsin inhibitors. Therefore, having in mind previous results from the NEQUIMED group[3], compounds were synthesized based on a cyclic scaffold and the addition of an extended carbon chain (Figure 1), in which some of them showed to be moderate cruzain and cysteine cathepsin inhibitors. Others have high cysteine protease affinities.

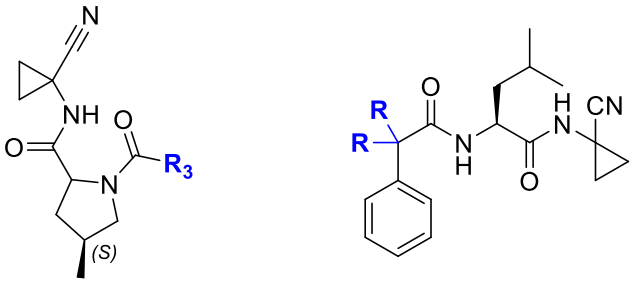

Figure 1. Schematic scaffold of the inhibitors synthesized.

Acknowledgments: FAPESP #2019/06271-2 and FAPESP #2013/18009-4.

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Synthesis of peptoids of nitriles as cruzain inhibitors

Luana Alves Galvão de Souza, Deborah Araujo dos Santos, Carlos A. Montanari, Andrei Leitão

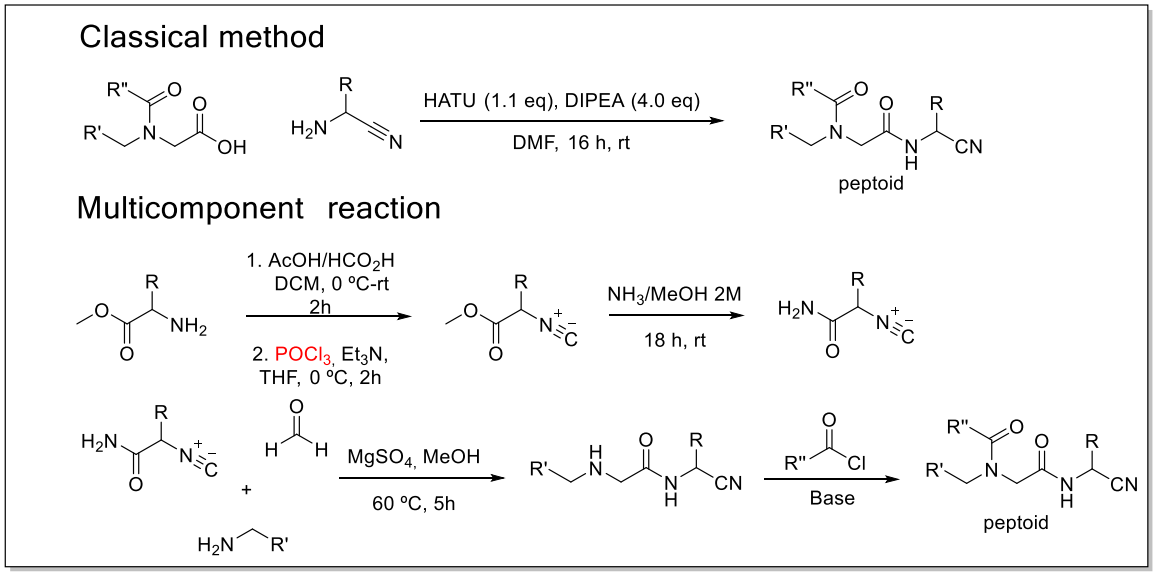
Medicinal Chemistry Group - NEQUIMED, São Carlos Institute of Chemistry (IQSC), São Carlos, Brazil
E-mail: luana_alves@usp.br

Field: Synthesis

Keywords: Chagas disease, cruzain inhibitors, peptoid

Chagas Disease is a Tropical Disease that affects about 6 million people, causing 12,000 deaths per year[1]. Only one drug (benznidazole) is for this condition, with high toxicity and limited use for patients[2,3]. This work aims to get a novel set of compounds via the synthesis of bioactive peptoids that act as reversible covalent inhibitors of cruzain. So far, 14 compounds have been synthesized using two different methods (Figure 1). After characterization, these compounds were tested and showed low potency against cruzain. SAR studies have shown that substitution at position P1 is not well accepted, whereas substitutions at P3 do not cause considerable change in inhibitory activity. The hypothesis that a spacer at position P1 may give the compound greater flexibility, thereby increasing its inhibitory activity, is currently being tested, which may lead to potent cruzain inhibitors.

Figure 4. Two synthetic approaches applied to produce the set of peptoids.



Acknowledgments: FAPESP (2013/18009-4, 2018/15904-6), CNPq, CAPES (139/2015).

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Total Synthesis of (±)-Brussonol and (±)-Komaroviquinone via a Regioselective Cross-Electrophile Coupling of Aryl Bromides and Epoxides

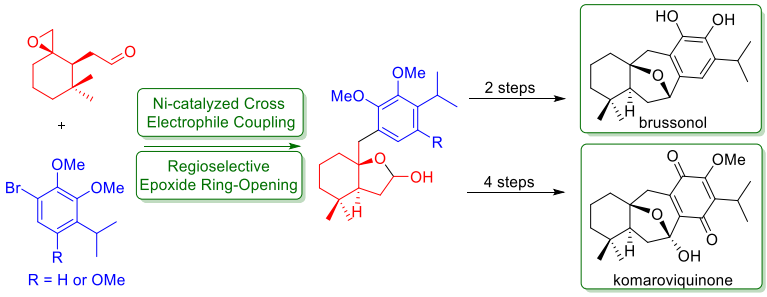
Anees Ahmad, Antonio C. B. Burtoloso*

*São Carlos Institute of Chemistry, University of São Paulo, 13560-970, São Carlos, SP, Brazil
E-mail: anees_chemist@yahoo.com, antonio@iqsc.usp.br*.

Field: Total Synthesis

Keywords: Icetexane diterpenes, Total Synthesis, Cross-Electrophile Coupling

The icetexane diterpenoids include a variety of bioactive and structurally interesting compounds. Its tricyclic skeleton comprises of cyclohexane ring, a central seven-membered ring and an aromatic ring (or a quinone). The significant biological activities possess by these diterpenes are, anti-Chagasic, anticancer, antibacterial, antifungal, and anti-Leishmania activities. Taking into account the biological importance, a number of different approaches to prepare such class of compounds, especially Brussonol and komaroviquinone are described in the literature. Herein, we report direct and short stereoselective convergent synthesis of natural products brussonol and Komaroviquinone via cross-electrophile coupling strategy. The chemistry features effective preparation of challenging acetal intermediate in a single step operation by Ni-catalyzed regiodivergent epoxide ring-opening with aryl halide followed by highly efficient $BF_3.OEt_2$ catalyzed Friedel-Crafts alkylation to construct tricyclic skeleton of brussonol. In case of komaroviquinone respected acetal was oxidized to lactone followed by intra-molecular nucleophilic cyclization to build tricyclic skeleton. The synthetic approach might offer a unified approach for the synthesis of varieties of natural products containing icetexane motifs.



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