1st Molecules Medicinal Chemistry Symposium

Faculty of Pharmacy and Food Sciences

University of Barcelona, Spain

8 September 2017

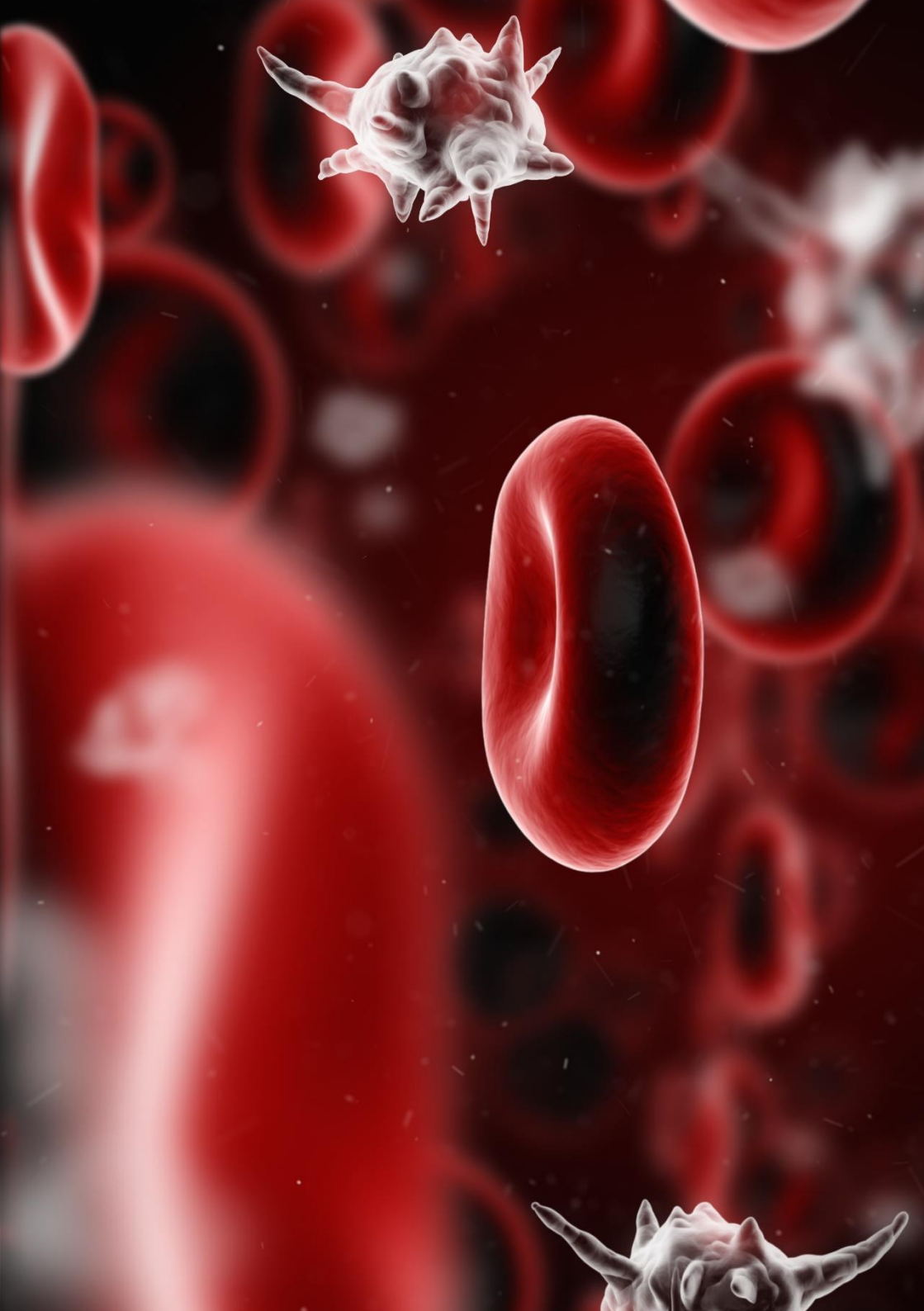
Conference Chair

Diego Muñoz-Torrero

Organised by

Conference Secretariat

Antonio Peteira	Matthias Burkhalter
Jiahua Zhang	Nikoleta Kiapidou
Jing Gao	Pablo Velázquez
Kristjana Xhuxhi	Sara Martínez
Lucia Russo	Sarai Rodríguez



CONTENTS

Symposium Programme

Morning Session

08:00 – 08:45	Check-in
08:45 – 09:00	Introduction by Conference Chair
	Chair: Diego Muñoz-Torrero
09:00 – 09:45	Kelly Chibale, "Cell-based medicinal chemistry optimization of high-throughput screening hits towards orally active antimalarial and antituberculosis agents"
09:45 – 10:30	Maria Laura Bolognesi, "Sustainable multi-target drugs for neglected tropical diseases caused by trypanosomatids: dream or reality?"
10:30 – 11:00	Coffee Break
	Chair: Kelly Chibale
11:00 – 11:45	Benoît Laleu, "Current pipeline of antimalarial therapies"
11:45 – 12:00	Rodolfo Lavilla, "Multicomponent reactions with heterocycles: a source of novel scaffolds for antiparasitic and antiviral agents"
12:00 – 12:15	Lakindu Samaranayake, "Structure guided design of *Xanthomonas oryzae* pv. *oryzae* topoisomerase I inhibitors"
12:15 – 12:30	Caterina Pont, "Design of potential antimalarial agents based on a homology model of *Plasmodium falciparum* glucose-6-phosphate dehydrogenase"
12:30 – 14:00	Lunch & Poster Session

Afternoon Session

Chair: Kelly Chibale

14:00 – 14:45	John M. Kelly, "Highly sensitive bioluminescence imaging models for Chagas disease drug discovery"
14:45 – 15:00	Fernando Albericio, "Structure–activity relationship of Arg_{10}–teixobactin: A recently discovered antimicrobial peptide"
15:00 – 15:15	Andrea Trabocchi, "Diversity-oriented synthesis and chemical genetics of peptidomimetics to address lead discovery of anti-infective agents"
15:15 – 15:30	Alicia Boto, "The search of new antimicrobial agents, by site-selective peptide modification"
15:30 – 16:00	Coffee Break

Chair: Diego Muñoz-Torrero

16:00 – 16:45	Jean-Marie Pagès, "Antibiotic translocation and membrane barrier: New insights to combat bacterial resistance"
16:45 – 17:00	Florenci González Adelantado, "Design and synthesis of cysteine protease inhibitors"
17:00 – 17:15	Ramon Eritja, "Lipid–oligonucleotide conjugates forming G-quadruplex (lipoquads) as potent inhibitors of HIV entry"
17:15 – 17:30	Nataliya Sanina, "Nitrosyl [2Fe-2S] ferredoxin mimetics as new nitric oxide donating antibacterial agents"
17:30 – 17:45	Hazem Sawalha, "Cultivated and natural plant flora with antibacterial action collected from Palestine"
17:45 – 18:00	Closing Remarks & Awards Ceremony

Welcome by Diego Muñoz-Torrero

Dear participants,

It is with great pleasure that we welcome you to the first scientific symposium organized by the Medicinal Chemistry Section of the MDPI journal *Molecules*. In this initial endeavor, we have opted for a one-day monographic symposium with a rather limited audience, dealing with one of our most urgent global health issues that needs a continuous intensive research. At the *1st Molecules Medicinal Chemistry Symposium* (MMCS) "Emerging Drug Discovery Approaches against Infectious Diseases", we want to provide a forum for discussion from novel biological targets and resistance mechanisms to the design and synthesis of new structural classes or the implementation of innovative therapeutic approaches against bacterial, protozoan, viral, and fungal infections. The MMCS will gather together experts in the field of medicinal chemistry of anti-infective agents from more than 15 countries of 3 continents, mostly from academia but also from pharmaceutical industry and product development partnerships, thereby offering a very interesting platform for international networking in this field.

The MMCS will be held at the noblest room of the Faculty of Pharmacy and Food Sciences of the University of Barcelona, the *Aula Magna*, which will provide a pleasant and relaxing atmosphere for the dissemination of research results and, hopefully, to bring about international research collaborations. We hope the MMCS will be a unique frame to share and increase your knowledge on anti-infective drug discovery, while enjoying the charm of the cosmopolitan city of Barcelona.

We look forward to seeing you in Barcelona!

Prof. Diego Muñoz-Torrero
Editor-in-Chief of the Medicinal Chemistry Section of Molecules
MMCS Chair

General Information

Molecules (ISSN 1420-3049, CODEN: MOLEFW) is an open access journal covering all aspects of organic chemistry. Originally conceived as a forum for papers on synthetic organic chemistry and natural product chemistry, like the field, Molecules has evolved over its 20 years, with increasing numbers of papers on more theoretical subjects, physical organic chemistry, nanomaterials and polymer chemistry and applied studies. All articles are peer-reviewed and published continously upon acceptance. Molecules is published by MDPI, Basel, Switzerland.

Editor-in-Chief: Dr. Derek J. McPhee: Senior Director, Technology Strategy, Amyris, Inc., 5885 Hollis St, Suite 100, Emeryville, CA 94608, USA.

Journal Webpage: www.mdpi.com/journal/molecules
Impact Factor: 2.861

The **1st Molecules Medicinal Chemistry Symposium (MMCS)** will be held at the School of Pharmacy and Food Sciences of the University of Barcelona (Spain) on September 8th, 2017.

This 1st MMCS seeks to gather together experts in the field of medicinal chemistry of anti-infective agents, and aims to provide a forum for discussion regarding novel drug structural classes, therapeutic approaches, biological targets, and resistance mechanisms, which can pave the way for the development of optimized therapies against bacterial, protozoan, viral, and fungal infections.

Conference Venue

Faculty of Pharmacy and Food Sciences

University of Barcelona

Spain

Registration Desk

The desk for registration, information and distribution of documents will be open from 8:00, 8 September 2017.

Certificate of Attendance

The Symposium participants will receive an electronic Certificate of Attendance by email once the event is concluded.

Barcelona and Catalonia

Catalonia has become one of the favourite tourist destinations of Spain, mainly because of Barcelona, a city that never sleeps and knows how to please the big majority. With a history among the oldest in Europe, Barcelona offers a mixture of inland and seaside charms that panders the interests of everybody. The variety of artistic treasures, Romanesque churches and the works of famous artists such as Dali, Gaudi, Miro or Picasso will make of your visit to the city a remarkable experience.

Parc Güell (Source: www.viajero-turismo.com)

Barcelona is the capital and largest city of Catalonia and Spain's second largest city, with a population of over one and half million people (over five million in the whole province). This city, bathed by the Mediterranean Sea, has become one of most cosmopolitan cities of Europe which has transformed it into the very modern, yet incredibly old city. This beautiful city is full of what European cities are known for (outdoor markets, restaurants, shops, museums and churches) and which makes it the perfect scenario to get lost in its pictouresque streets and avenues. Moreover, Barcelona's extensive and reliable Metro system will take you to more far-flung destinations. The core centre of the town, focused around the *Ciutat Vella* ("Old City"), provides days of enjoyment for those looking to experience the life of Barcelona while the beaches the city was built upon provide sun and relaxation during the long periods of agreeably warm weather. [Source: www.wikitravel.org]

Plaza España (Source: www.viajero-turismo.com)

The University of Barcelona

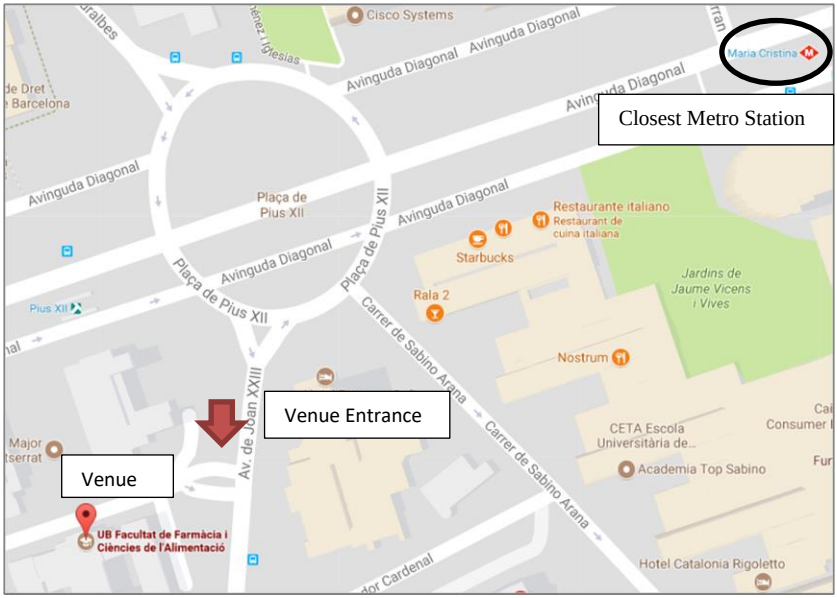
The University of Barcelona (UB) is the most formidable public institution of higher education in Catalonia, catering to the needs of the greatest number of students and delivering the broadest and most comprehensive offering in higher educational courses. The UB is also the principal centre of university research in Spain and has become a European benchmark for research activity, both in terms of the number of research programmes it conducts and the excellence these have achieved.

Having been founded in 1450, the University's own history is closely tied to the history of Barcelona and Catalonia, it combines the values of tradition with its position as an institution dedicated to innovation and teaching excellence: a university that is as outward-looking and cosmopolitan as the city from which it takes its name. For these reasons, it plays a direct and active part in the urban fabric of Barcelona, becoming a hub of cultural activity for the city itself. [Source: www.ub.edu]

Faculty of Pharmacy and Food Sciences
(Source: https://www.ub.edu/portal/web/farmacia-en/)

How to Reach the Venue

Address: Campus Diagonal, Av. de Joan XXIII, 27-31, 08028 Barcelona



Venue Location (Source: https://maps.google.com/)

Contact persons during the event

Antonio Peteira

Email: antonio.peteira@mdpi.com

Phone number: +34 639485613

Pablo Velázquez

Email: pablo.velazquez@mdpi.com

Phone number: +34 620189526

Sara Martínez

Email: sara.martinez@mdpi.com

Phone number: +34 676 671 885

Emergency Information

All emergencies in Spain: 112 (no area code needed)

Ambulance (Ambulancia) and health emergencies: 061 or 112

Fire brigade (Cuerpo de bomberos): 080 or 112

Spanish National Police (Policía nacional): 091

Tropical Medicine and Infectious Disease

Tropical Medicine and Infectious Disease (ISSN 2414-6366) is an international, scientific, open access journal of tropical medicine and infectious disease published quarterly online by MDPI. It is the official journal of The Australasian College of Tropical Medicine (ACTM, https://www.tropmed.org/) and its Joint Faculties of Travel Medicine (http://www.travelmedicine.org.au/) and Expedition and Wilderness Medicine. Tropical Medicine and Infectious Disease publishes on all tropical diseases of global significance, as well as neglected tropical diseases as defined from time-to-time by the World Health Organization.

Editor-in-Chief: Assoc. Prof. John Frean, Centre for Opportunistic, Tropical and Hospital Infections, National Institute for Communicable Diseases, University of the Witwatersrand, Johannesburg, South Africa

Journal Webpage: http://www.mdpi.com/journal/tropicalmed

Abstracts

Invited Speakers

Cell-Based Medicinal Chemistry Optimization of High Throughput Screening Hits towards Orally Active Antimalarial and Antituberculosis Agents

Kelly Chibale

Department of Chemistry,University of Cape Town, Cape Town, South Africa

It has recently been demonstrated, from a number of antimalarial and antituberculosis drug discovery programmes, that phenotypic whole cell screening can uncover cell permeable and active drug leads with potentially novel modes of action. In this regard, several series of antiplasmodial and antimycobacterial actives were identified by phenotypic whole cell high-throughput screening of small molecule libraries. Following validation, hit molecules demonstrating good in vitro antiplasmodial and antimycobacterial activity against the respective causative agents, *Plasmodium falciparum* and *Mycobacterium tuberculosis*, with low cytotoxicity were prioritized for hit to lead and lead optimization medicinal chemistry progression.

This talk will describe the drug discovery process that led to the identification of lead candidates with good oral in vivo pharmacokinetics. Target identification aspects will also be presented.

NOTES

Sustainable Multi-Target Drugs for Neglected Tropical Diseases Caused by Trypanosomatids: Dream or Reality?

Maria Laura Bolognesi

Department of Pharmacy and Biotechnology, Alma Mater Studiorum - University of Bologna, Bologna, Italy

The development of nifurtimox-eflornithine combination therapy (NECT) has been a major and emboldening advance towards more effective and simple medications in the field of neglected tropical diseases (NTD) caused by Trypanosomatids. In this context, novel prospects for curing such diseases are offered by the strategy of developing single chemical entities able to modulate multiple targets simultaneously, namely the multi-target-directed ligands (MTDLs).[1] Similarly to that observed in the anti-cancer field, we argue that NTD therapy might also benefit from the potential of reduced resistance, improved efficacy, and reduction of dosage and treatment length. Thus, the MTDLs could offer a simpler and more cost-effective treatment [1]. In this context, we have reported on the hit compound 2-phenoxy-1,4-naphthoquinone (B6), with a remarkable activity against *Trypanosoma brucei rhodesiense* in a phenotypic assay (IC50 = 80 nM) and a promising selectivity index [2]. Particularly, B6 showed a multitarget mechanism of action, including radical production and covalent inhibition of *Trypanosoma brucei* glyceraldehyde 3-phosphate dehydrogenase (TbGAPDH) enzyme.[3]

As a further step, we recently explored the possibility to discover new MTDLs based on inexpensive resources. Particularly, we were attracted by the opportunity of using food waste products as sustainable starting materials. Towards this aim, we have developed a series of novel MTDLs obtained by combining the 2-phenoxy-1,4-naphthoquinone scaffold with those of phenolic constituents from the cashew nut shell liquid (CNSL), which is an agro waste from cashew nut processing factories.

We envisage that such hybrid compounds, obtained from renewable and inexpensive material, might be promising bio-based, sustainable MTDLs for antitrypanosomatid drug discovery.

References:

1.Cavalli, A. & Bolognesi M.L. *J. Med. Chem.* 2009, 52, 7339–59.

2.Pieretti, S. et al. *PLOS Negl. Trop. Dis*. 2013, 7, e2012; Prati, F. et al. *J. Med. Chem.* 2015, 58, 6422–34.

3.Bruno, S. et al. *Chem. Biol. Drug Des*. 2017, doi: 10.1111/cbdd.12941.

NOTES

Current Pipeline of Antimalarial Therapies

Benoît Laleu

Medicines for Malaria Venture (MMV), Department ICC, University of Geneva, Geneva, Switzerland

Malaria is a devastating disease affecting millions of people each year yet, surprisingly, apart from the Artemisinin Combination Therapies (ACTs) there are relatively few effective treatments for *Plasmodium falciparum* and only one complete treatment for *Plasmodium vivax.*

Medicines for Malaria Venture (MMV) has the mission to reduce the burden of malaria in disease-endemic countries by discovering, developing and facilitating the delivery of new, effective and affordable antimalarial drugs in collaboration with international partners.

MMV manages a significant antimalarial pipeline and this has been strengthened in recent years with the delivery of new products, new clinical candidates and early stage discovery projects. The challenges that need to be overcome will be detailed as well as the strategy adopted to control and eradicate the disease, including definitions of target product and candidate profiles necessary for asexual blood stage cures (including single dose combination treatment), transmission blocking, *vivax* and chemoprotection.

MMV is also proud to lead open-source initiatives such as the Pathogen Box project to catalyze drug discovery for malaria and neglected diseases. The data, findings and results emanating from these initiatives are as rich as the connections and collaborations they inspire.

NOTES

Highly Sensitive Bioluminescence Imaging Models for Chagas Disease Drug Discovery

John M. Kelly, Amanda F. Francisco, Shiromani Jayawardhana, Martin C. Taylor, Michael D. Lewis

London School of Hygiene and Tropical Medicine, London, UK

Chagas disease is caused by the insect-transmitted protozoan *Trypanosoma cruzi*, and is the most important parasitic infection in Latin America. As a result of migration, it is also emerging as a public health issue in non-endemic regions, particularly in the US and Europe. Infections with *T. cruzi* are life-long, and lead to cardiomyopathy in 20–30% of cases. A causal link between cardiac infection and pathology has been difficult to establish because of a lack of robust methods to detect scarce focally distributed parasites within tissues. By combining highly sensitive bioluminescence imaging and fluorescence technology, we have developed procedures which have allowed us to track infection dynamics, quantify tissue-specific parasite loads, and provide new insights into parasite biology in predictive murine models. These approaches have identified the gut as the major reservoir site during chronic infections. In this presentation, we review the parameters of the imaging systems and describe how these experimental models can be incorporated into drug-development programmes as a valuable tool for assessing efficacy against both acute and chronic *T. cruzi* infections.

NOTES

Antibiotic Translocation and Membrane Barrier: New Insights to Combat Bacterial Resistance

Jean-Marie Pagès

UMR_MD1, TMCD2, Aix-Marseille Univ, IRBA, Marseille, France

Introduction: The increasing prevalence of antibacterial resistance is a worrying health concern. A challenge in antibacterial research is to better understand membrane permeation of antibiotics in infective bacteria: passing the membrane barrier to reach the threshold of active concentration inside the bacterium is a pivotal step for all antibiotics. This is particularly acute for Gram-negative bacteria that have two membranes, the outer and the inner membranes that strongly limit the transport and the intracellular accumulation of antibiotics. A key point is to determine the real concentrations of antibiotics inside bacterial cells to determine the parameters modulating this internal accumulation.
Methods: Recently, new concepts, RTC2T and SICAR (Masi et al, *Nat. Microbiol.* 2, 17001 (2017) have been proposed to evaluate the relationship between membrane permeability and antibiotic accumulation. A spectrofluorimetric methodology has been developed to detect fluoroquinolones in bacterial population and inside individual Gram-negative bacterial cells. The antibiotic accumulation was studied in cells expressing various levels of efflux pumps.
Results and Discussion: The assays allow the determination of the intracellular concentration of the fluoroquinolones to study the relationships between the level of efflux activity and the antibiotic accumulation, and finally to evaluate the impact of fluoroquinolone structures in this process. This clearly validates the recently proposed "Structure Intracellular Concentration Activity Relationship" (SICAR) concept.
Conclusion: The combination of these studies that include drug imaging studies, evaluation of antibacterial activity and determination of membrane permeability, represents a promising research strategy. This strongly stimulates the molecular understanding of resistance mechanisms and the development of a future rational antibacterial chemotherapy.

References:
1. Masi, M., Réfregiers, M., Pos, K. M. & Pagès, J.M. Mechanisms of envelope permeability and antibiotic influx/efflux in Gram negative bacteria. *Nat. Microbiol,* **2017,** 17001.
2. Zgurskaya, H.I., López, C.A. & Gnanakaran, S. Permeability barrier of Gram-negative cell envelopes and approaches to bypass it. *ACS Infect. Dis.* ***2015****,* 1, 512-522.
3. Cinquin, B. *et al.* Microspectrometric insights on the uptake of antibiotics at the single bacterial cell level. *Sci Rep.* **2015,** 5:17968.
4. Nikaido, H. & Pagès, J.M. Broad-specificity efflux pumps and their role in multidrug resistance of Gram-negative bacteria. *FEMS Microbiol. Rev.* **2012**, 36, 340–363.
5. Kaščáková, S., Maigre, L., Chevalier, J., Réfrégiers, M. & Pagès, J.M. Antibiotic transport in resistant bacteria: synchrotron UV fluorescence microscopy to determine antibiotic accumulation with single cell resolution. *PLoS One*. **2012**, 7, (6):e38624.

NOTES

pharmaceuticals

Pharmaceuticals (ISSN 1424-8247) is an international scientific journal of medicinal chemistry and related drug sciences. The journal's aim is to publish updated reviews as well as research articles with comprehensive theoretical and experimental details. It welcomes manuscripts covering a wide range of aspects involved in drug discovery and development. All articles are peer-reviewed and published continously upon acceptance. Molecules is published by MDPI, Basel, Switzerland.

Editor-in-Chief: Dr. Jean Jacques Vanden Eynde, formerly head of the Department of Organic Chemistry (FS), University of Mons-UMONS, 7000 Mons, Belgium

Journal Webpage: http://www.mdpi.com/journal/pharmaceuticals

Citescore (Scopus): 4.90

Abstracts

Selected Speakers

Multicomponent Reactions with Heterocycles: A Source of Novel Scaffolds for Antiparasitic and Antiviral Agents

Rodolfo Lavilla

Department of Pharmacology, Toxicology and Therapeutical Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona, Spain

We disclose a reaction discovery approach, based on novel multicomponent reactions (MCRs) upon heterocyclic substrates, especially azines, that yields a variety of scaffolds amenable to straightforward diversification. In just one step, we could jump from one generation of compounds to the next one by mere modification of the reagents. This feature greatly helps in the tuning of the biological properties and has allowed the formation of two classes of anti-infectious agents: antiparasitic and antiviral compounds. First, the silyl-promoted addition of isocyanides to azines yields pyridoimidazolium salts which are potent anti-trypanosoma agents. Next, we discuss the multiple multicomponent reaction approach on diaminodiazines using the Groebke–Blackburn–Bienaymé MCR as a source of new antiviral compounds, also featuring specific DNA affinity.
Details on the chemistry and biology related to these processes will be discussed.

NOTES

Structure Guided Design of *Xanthomonas oryzae* pv. *oryzae* *T*opoisomerase I Inhibitors

Lakindu Samaranayake

Department of Zoology, University of Colombo, Colombo, Sri Lanka

Topoisomerase inhibitors initiate the cell killing process by either stabilizing or increasing the amount of the covalent complex formed between the enzyme and cleaved DNA. In our study, we have attempted to identify structure based *Xanthomonas oryzae* pv. *oryzae(Xoo)* topoI inhibitors by in silico analysis of the binding affinities (BA) of a set of small ligands with the protein. In order to identify novel inhibitors of topoisomeraseI, a 3D model of the *Xoo* topoisomerase is created based on the *Mycobacterium tuberculosis* (PDB ID-5d5h) by using the SWISS-MODEL workspace. The final model is obtained in high quality as assessed by SAVeS server, which shows that the refined model is reliable. With this model, a flexible docking with screen compounds from MayBridge and known topoisomeraseI inhibitors such as Tn5 and ofloxacin were performed by AutoDock in PyRx Virtual Screening tool. The resulted BA were ordered and the top hundred molecules were selected. The binding pockets in the protein were assessed by POCASA1.1 and the active-site of the modelled protein was predicted. Out of the top hundred molecules, two molecules named HTS09044 and HTS11914 were bound with the assumed active-site with a better BA than Tn5 or ofloxacin. The binding interactions of the compound with the active-site of the model suggested that the amino acid residues (tyr495, asp546, pro492, arg491, thr265 and ser267) play a key role in drug design. The pharmacological properties were predicted and these two selected compounds showed a good drug profile. Hence, they would represent an intriguing step towards the development of potent inhibitor molecules against *Xoo* topoI.

NOTES

Design of Potential Antimalarial Agents Based on a Homology Model of *Plasmodium falciparum* Glucose-6-Phosphate Dehydrogenase

Caterina Pont[1], Nelson Alencar[2], Irene Sola[1], María Linares[3], Luca Di Palma[1], Carla Barbaraci[1], Cristina Sampedro[1], Jordi Juárez-Jiménez[2], Paloma Abad[3], Susana Pérez-Benavente[3], Jerónimo Lameira[4], José M. Bautista[3], F. Javier Luque[2], Diego Muñoz-Torrero[1]

[1] Laboratory of Pharmaceutical Chemistry (CSIC Associated Unit), Faculty of Pharmacy and Food Sciences and Institute of Biomedicine (IBUB), University of Barcelona (UB), Barcelona, Spain
[2] Department of Nutrition, Food Science and Gastronomy, Faculty of Pharmacy and Food Sciences, and IBUB, UB, Santa Coloma de Gramenet, Spain
[3] Departamento de Bioquímica y Biología Molecular IV and Instituto de Investigación Hospital 12 de Octubre, Universidad Complutense de Madrid, Madrid, Spain
[4] Laboratório de Planejamento e Desenvolvimento de Fármacos-LPDF, Instituto de Ciências Exatas e Naturais- ICEN, Universidade Federal do Pará – UFPA, Belém-Pará, Brazil

There currently exists a dire need for safe and inexpensive new antimalarial drugs, which are effective against multiple life cycle stages of *Plasmodium falciparum*, and act through mechanisms that differ from those of the available drugs to prevent drug resistance. The enzyme glucose-6-phosphate dehydrogenase (G6PD) of *P. falciparum* has emerged as a promising target for antimalarial drug discovery, due to its key role in parasite development and survival and its protective effect against malaria infection observed under human G6PD deficiency conditions. Here, we describe the construction of a homology model of *Pf*G6PD, which has enabled the identification of key structural differences as compared with the human enzyme. We have exploited these changes to rationally design a novel family of substrate analog-based inhibitors that can be endowed with selectivity towards *Pf*G6PD. Several compounds display micromolar affinity, good selectivity, and low cytotoxicity, but weak antiplasmodial activity in phenotypic assays, likely as a result of a poor internalization of the compounds in the parasite cell. Future hit optimization should focus on improving the physicochemical/pharmacokinetic properties of this class of compounds.

NOTES

Structure–Activity Relationship of Arg_{10}–Teixobactin: A Recently Discovered Antimicrobial Peptide

Fernando Albericio[1, 2], Shimaa A. H. Abdel Monaim[3], Yahya E Jad[3], Gerardo A. H. Acosta[2], Estelle J Ramchuran[3], Ayman El-Faham[4], Thavendran Govender[3], Hendrik G Kruger[3], Beatriz G de la Torre[5]

[1] School of Chemistry and Physics, University of KwaZulu-Natal, Durban, South Africa
[2] Department of Organic Chemistry, University of Barcelona, Barcelona, Spain
[3] School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa
[4] Department of Chemistry, College of Science, King Saud University, Riyadh, Saudi Arabia
[5] School of Laboratory of Medicine and Medical Sciences, University of KwaZulu-Natal, Durban, South Africa

The emergence of multidrug resistant bacteria has a direct impact on global public health due to the reduced potency of existing antibiotics against pathogens [1]. Hence, there is a pressing need for new drugs with different modes of action that can kill microorganisms. Antimicrobial peptides (AMPs) can be regarded as an alternative tool for this purpose since they are proven to have therapeutic effects with broad-spectrum activities [2].

In this regard, Teixobactin is a recently discovered antimicrobial cylcodepsipeptide with good activity against Gram-positive bacteria but not Gram-negative bacteria [3]. Teixobactin has been isolated from Eleftheria terrae, a non-culturable Gram-negative bacteria that belongs to the class of beta-proteobacteria. Teixobactin is the first new antibiotic to be discovered for several decades, attracting attention not only for its great activity against Gram-positive bacteria and mycobacterium tuberculosis. Teixobactin is an 11-mer peptide containing a cyclotetradepsipeptide unit in its structure. It contains five unnatural amino acid residues: D-NMe-Phe, D-Gln, D-allo-Ile, D-Thr and L-allo-enduracididine.

Recently, taking the Arg_{10}–Teixobactin as a base—published by our group at the end of 2015 [4]—where the Arg substituted the non-proteinoenic residue L-allo-enduracididine, Lys scanning allowed us to identify the importance of keeping the balance between the hydrophilic and hydrophobic amino acids for the antimicrobial activity of this peptide family. Thus, the substitution of the four Ile present in the natural sequence by Lys led to a total loss of activity. On the other hand, the substitution of the polar non-charged residues and the Ala by Lys allowed the antimicrobial activity to be kept and in some cases improved [5].

Herein, the latest results in the structure–activity relationship of Arg_{10}–Teixobactin will be discussed as well as some insights regarding the mode of action of this intriguing compound.

References:
1. Mali, S.N., Sapkai, P.M. *J. Pharmacy Pharm. Res*. **2015,** 4, 184
2. Ramesh, S. et al. *J. Peptide Sci*. **2016**, 22, 438.
3. Ling, L.L. et al. *Nature*. **2015**, 517, 455-459.
4. Jad, Y.E. et al. *Org. Lett*. **2015**, 17, 6182.
5. Abdel Monaim, S.A.H. et al. *ACS Omega.* **2016**, **1,** 1262.

NOTES

Diversity-Oriented Synthesis and Chemical Genetics of Peptidomimetics to Address Lead Discovery of Anti-Infective Agents

Elena Lenci[1], Irene Stefanini[2], Antonio Guarna[1], Gloria Menchi[1], Duccio Cavalieri[1], Andrea Trabocchi[1]

[1] Department of Chemistry "Ugo Schiff", University of Florence, Florence, Italy
[2] Department of Biomedical Sciences, University of Warwick, Warwick, UK

Modern advances in Chemical Biology include the improvement of screening methods, the introduction of bioinformatic methods to unravel biological pathways, and the generation of high-quality chemical libraries. Diversity-Oriented Synthesis (DOS) has gathered interest to systematically explore the chemical space by generating high-quality small-molecule collections as probes to investigate biological pathways. DOS consists of generating structurally diverse compounds from a complexity-generating reaction followed by cyclization steps and appendage diversity. Also, chemical genetics emerged as a tool in chemical biology due to its role in selecting small molecules capable of inducing a biological phenotype or interacting with a gene product. Our efforts in this field are focused on the generation of diversity-oriented molecules of peptidomimetic nature as tool addressing protein–protein interactions, taking advantage of amino acid- and sugar-derived polyfunctional building blocks to be applied in couple-pair synthetic approaches. Also, we are applying peptidomimetic scaffolds to biological evaluation using cell growth as a phenotypic screening on yeast deletant strains to identify hit compounds in the discovery of novel antifungal and anticancer agents, and to dissect their mode of action.

NOTES

The Search for New Antimicrobial Agents, by Site-Selective Peptide Modification

A. Boto[1], C. González, D. Hernández, I. Romero-Estudillo, N. Rodriguez-Paz, and J. M. Pérez de la Lastra

[1] CSIC Instituto de Productos Naturales y Agrobiologia, Santa Cruz de Tenerife - Canary Islands, Spain

Antimicrobial peptides (AMPs) have been used by animals and plants for millions of years for defence against pathogens, and present important advantages as potential drugs, such as a broad spectrum of activity, no induction of resistances, and synergic action with conventional antibiotics [1].
However, many natural antimicrobial peptides present problems due to in vivo degradation or biodisponibility issues. The production of synthetic analogues would allow the discovery of antimicrobials with improved selectivity, stability, and biodisponibility. The site-selective modification of peptides would allow the fast, efficient generation of libraries of such peptides from a few "parent" peptides, saving time and materials in the discovery processes [2].
We describe two "customizable units" that allow the production of peptides “à la carte”, with many different lateral chains and functional groups, and their evaluation as antimicrobials for human and animal health, and as crop protection agents.

References:
1. Kastin, A. J. Handbook of Biologically Active Peptides, Academic Press, San Diego, USA, 2006; Chapters 10 (systemins), 11 (defensins), 12 (cathelicidins), 45 (dermaseptins), 46 (temporins).
2. Romero-Estudillo, I; Boto, A**.** Domino Process Achieves Site-Selective Peptide Modification with High Optical Purity. Applications to Chain Diversification and Peptide Ligation. J. *Org. Chem*. **2015,** *80*, 9379-9391.

NOTES

Design and Synthesis of Cysteine Protease Inhibitors

Florenci Vicent Gonzalez Adelantado

Department de Química Inorgànica i Orgànica, Universitat Jaume I, Castelló, Spain

We have been preparing new dipeptidyl inhibitors against parasitic cysteine proteases cruzain (related to Chagas disease) and rhodesain (related to Sleeping Sickness disease), and against human cathepsins. Inhibitors display new warheads embedded into a dipeptidic framework. Dipeptidyl epoxyesters [1] and Dipeptidyl enoates [2] are highly potent irreversible inhibitors of cruzain and rhodesain. We also prepared an oxidized version of well-known Vinylsulfones (Epoxysulfones [3]) as inhibitors of human cathepsins. Recently, we have reported the synthesis of Dipeptidyl nitroalkenes [4] as a new type of highly potent covalent reversible inhibitors of cysteine proteases exhibiting certain selectivity for the parasitic cysteine proteases rhodesain and cruzain.

References:
1. F. V. González, J. Izquierdo, S. Rodríguez, J. H. McKerrow, E. Hansell *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6697-6700.
2. S. Royo, S. Rodríguez, T. Schirmeister, J. Kesselring, M. Kaiser, F. V. González *Chem. Med. Chem.* **2015**, *10*, 1484-1487.
3. A. Latorre, S. Rodríguez, F. V. González, B. I. Florea, H. S. Overkleeft *J. Org. Chem.* **2015**, *80*, 7752 -7756.
4. A. Latorre *et al ACS Chem. Med. Lett.* **2016**, *12*, 1073-1076.

NOTES

Lipid–Oligonucleotide Conjugates Forming G-Quadruplex (Lipoquads) as Potent Inhibitors of HIV Entry

Sebastien Lyonnais[1], Santiago Grijalvo[2], Carmen Alvarez-Fernández[1], Eric Fleta[3], Javier Martínez[3], Andreas Meyerhans[3], Tula Ester Saison-Behmoaras[4], Sonsoles Sánchez-Palomino[1], Gilles Mirambeau[1], Ramon Eritja[2]

[1] AIDS Research group / IDIBAPS, Hospital Clínic de Barcelona / Faculty of Medecine, Barcelona, Spain
[2] IQAC-CSIC, CIBER-BBN, Barcelona, Spain
[3] Infection Biology Laboratory, Virology Unit DCEXS, Universitat Pompeu Fabra, Barcelona, Spain
[4] Museum National d'Histoire Naturelle, `Paris, France

Molecules that block virus entry by interfering with the actions of viral fusion proteins are of primary concern in the search for antiviral drugs. We present here the synthesis and antiviral activities of lipid–oligonucleotide conjugates (Lipoquads) forming a highly stable tetramolecular parallel G-quadruplex. We show that these molecules block HIV-1 and HIV-2 entry with submicromolar activites, demonstrating the great advantage of targeting both viral envelope glycoprotein and lipid rafts—a key platform in virus entry. Because the behavior of envelope proteins is similar in several other enveloped viruses, Lipoquads may have broader activities against enveloped viruses.

NOTES

Nitrosyl [2Fe-2S] Ferredoxin Mimetics as New Nitric Oxide Donating Antibacterial Agents

Nataliya Sanina, Galina Kozub, Tat'yana Kondrat'eva, Viktoriya Mumyatova, Alexei Terent'ev

Institute of Problems of Chemical Physics Russian Academy of Sciences, Chernogolovka, Moscow, Russia

Nitric oxide (NO) therapy is the newest approach to the treatment of socially important diseases all over the world. Nitric oxide (NO) is a multi-functional molecule able to interact with many cellular targets. Both direct and indirect NO effects (through the formation of reactive nitrogen species) have been shown in many investigations. Considerable experimental material has been accumulated, which demonstrates that NO participates both in the development of pathologic processes, and in their correction by chemotherapeutic methods [1]. In addition to many studies aimed at the search for compounds-traps for the excess NO, interest is growing in the search for new classes of compounds that generate NO, which could be the base for a new generation of medications easily delivering NO to biologic targets. Fundamentals for the creation of a new class of NO donors have been developed based on a detailed study of the chemical nature of Fe–S and Fe–N bonds of nitrosyl ferredoxin active sites. Nitrosyl binuclear iron complexes with pharmacologically active sulfur-containing ligands $[Fe_2(SR)_2(NO)_4]$ were isolated in the crystalline state. Heterocyclic functional thiols having a high coordination activity were used for the isolation of these complexes. Basic research of the structures and properties of these compounds in the solid phase and in the solutions was performed [2].

The functions of nitrogen oxide (NO) in the regulation of the reversible processes of Fe–S cluster assembly in proteins and the formation of *E. coli* biofilms have been investigated for the first time. Cationic [2Fe–2S] tetranitrosyl complex with cysteamine at physiological concentrations suppressed the formation of mature biofilms, and the activity of these compounds was comparable to that of antibiotic ciprofloxacine as a positive control. The study of the antibacterial activity of a series of neutral [2Fe–2S] tetranitrosyl iron complexes with nitro- and amino-thiophenolyls was carried out also by the serial dilutions method by determining the minimum concentration suppressing the growth of the microorganisms in culture. Double consecutive dilutions of the concentrations of the test compounds in a suspension of Gram-negative bacteria *E. coli* (strain BB) at a concentration of 106 cfu/ml were used. Evaluation of antibacterial activity was carried out 24 hours after the application of the test compounds. The greatest antibacterial activity was shown by compounds with 4-nitro-thiophenolyl and 3-hydroxythiophenolyl at a concentration of 250 μM and 125 μM, respectively. This, apparently, is due to the more effective NO-donating activity of these complexes.

References:
1. Batler, R. Nicholson. Life, Death and Nitric Oxide, *The Royal Society of Chemistry*, Cambridge, UK, 2003.
2. M. Aldoshin, N.A. Sanina. "Fundamental sciences for medicine: Biophysical medical technologies", Moscow, MAKS Press. 2015. 72-102.

NOTES

Cultivated and Natural Plant Flora with Antibacterial Action Collected from Palestine

Hazem Diab Sawalha and Saed Khaseeb

Department of Biology & Biotechnology. Faculty of Arts & Sciences/Arab American University, Jenin, Palestine

This research was conducted to study the antibacterial activity of some Palestinian plants against seven human pathogenic bacteria using the agar disk-diffusion method. Evaluation of the antibacterial activities of plant saps based on the width of the bacterial inhibition revealed that *Eucalyptus camaldulensis* (0.3 cm), *Allium sativum* (0.2 cm), *Ceratonia siliqua* (0.15 cm) and *Amygdalus communis* (0.15 cm) have the best antimicrobial activities against the bacterial mixture compared with the other fourteen tested plants. Furthermore, *E. camaldulensis* showed the strongest antimicrobial activity among the four plants. Also, *A. sativum* has the maximum anti-microbial action against all types of the tested bacteria. In addition, saps of *E. camaldulensis* and the mixture of *E. camaldulensis* and *A. sativum* have a strong ability to kill all types of the tested bacteria followed by the mixture of *C. siliqua* and *A. sativum*; the mixture of *C. siliqua*, *A. sativum* and *E. camaldulensis;* and the mixture of *A. communis, A. sativum* and *E. camaldulensis* that have significant results as anti-microbial agents against most types of the tested bacteria. The results showed that *A. sativum* and the mixture of *A. sativum* and *C. siliqua* have the maximum antimicrobial affectivity against *Staphylococcus aureus,* whereas, *Micrococcus luteus* was strongly inhibited by *E. camaldulensis; A. sativum;* the mixture of *E. camaldulensis* and *C. siliqua;* the mixture of *E. camaldulensis* and *A. sativum;* and the mixture of *E. camaldulensis, A. sativum* and *C. siliqua*. *Escherichi. coli* was efficiently inhibited by *A. communis, A. sativum,* and *E. camaldulensis* and also by the mixture of *A. sativum* and *E. camaldulensis. Pseudomonas aeruginosa* was inhibited in a significant amount by *E. camaldulensis* and *A. sativum*, whereas, *Proteus vulgaris* was strongly inhibited by *A. sativum*. *Bacillus subtilis* was strongly inhibited by *A. sativum*, while, for the *Klebsiella pneumoniae*, most saps revealed an intermediate inhibition except *A. communis,* which showed the lowest inhibition value.

Therefore, the current study elucidated that *E. camaldulensis*, *A. sativum*, *C. siliqua* and *A. communis* are the best tested Palestinian plants containing antibacterial agents against the tested bacterial types.

NOTES

Abstracts

Poster Exhibition

Docking Study on *T. cruzi* Trypanothione Reductase and Iron-Superoxide Dismutase Isoforms of a Series of Imidazole-Based Derivatives as an Approach towards the Design of New Potential Inhibitors

Iván Beltrán-Hortelano[1,2,3], María Font [1,3], Silvia Galiano[1,2], Silvia Pérez-Silanes[1,2]

[1] *Instituto de Salud Tropical (ISTUN), Universidad de Navarra, Pamplona, Spain*
[2] *Departamento de Química Orgánica y Farmacéutica, Sección Síntesis Orgánica, Facultad de Farmacia y Nutrición, Universidad de Navarra, Pamplona, Spain*
[3] *Departamento de Química Orgánica y Farmacéutica, Sección Modelización Molecular, Facultad de Farmacia y Nutrición, Universidad de Navarra, Pamplona, Spain*

Chagas disease (CD) or American trypanosomiasis is a widespread parasitic disease throughout the world. It is part of the group of 17 Neglected Tropical Diseases (NTD), classified by the World Health Organization (WHO) [1]. CD is caused by the flagellate protozoan parasite *Trypanosoma cruzi* (*T. cruzi*), which is mainly transmitted to humans by the faeces of blood-sucking *Triatomine* insects. Nowadays, CD is one of the most significant health problems in Central and South America in terms of epidemiological and human health repercussions. CD is potentially lethal (12,000 deaths/year), so it involves significant socioeconomic repercussions for the concerned countries [2]. Currently, only two drugs are available to treat CD in the acute phase: Nifurtimox (NFX) and Benznidazol (BNZ). However, both of them have significant toxic effects and variable clinical efficacy during the chronic phase of CD [3]. For those reasons, there is an urgent necessity to find new compounds that are safer, more effective and more affordable than the existing ones to eradicate *T. cruzi*, preventing the progression and reducing the risk of transmission of this disease.

Despite efforts, actions and strategies by the WHO and several organizations, the research of new potential treatments against CD remains a challenge in drug discovery programmes [4]. Nowadays, one of the strategies is based on the search for molecules enabling interference with enzymes that are involved in the survival of the parasite. Thus, many enzymes have been studied and reported as potential targets for the discovery and design of new compounds for the treatment of CD [5].

Due to the intracellular nature of the parasite, it is highly sensitive to Reactive Oxygen Species (ROS), so our research group focuses on two targets that protect it against oxidative damage: trypanothione reductase (TR) and iron-superoxide dismutases (Fe-SODs) isoforms (one cytosolic and one mitochondrial). Therefore, we design and synthesize new potential inhibitors against these two targets for the therapy of CD [6]. In this context, we carried out a docking study of a new series of imidazole-based derivatives with the ability to inhibit these two exclusive targets that regulate *T. cruzi* redox metabolism.

References:

1. World Health Organization (WHO). Neglected Tropical Diseases. http://www.who.int/neglected_diseases/diseases/en/ (Accessed on 25 May 2017).

2. WHO. Chagas disease (American trypanosomiasis)/Fact sheet March 2017. http://www.who.int/mediacentre/factsheets/fs340/es/ (Accessed on 25 May 2017).
3. Bermúdez, J.; Davies, C.; Simonazzi, A.; Real, J.P.; Palma, S. Current drug therapy and pharmaceutical challenges for Chagas disease. *Acta Trop.* **2016**, *156*, 1–16.
4. Paucar, R.; Moreno-Viguri, E.; Pérez-Silanes, S. Challenges in Chagas Disease Drug Discovery: A Review. *Curr. Med. Chem.* **2016**, *23*, 1–17.
5. Beltrán-Hortelano, I.; Pérez-Silanes, S.; Galiano, S. Trypanothione Reductase and Superoxide Dismutase as Current Drug Targets for *Trypanosoma cruzi*: An Overview of Compounds with Activity against Chagas Disease. *Curr. Med. Chem.* **2017***, 24,* 1066–1138.
6. Moreno-Viguri, E.; Jiménez-Montes, C.; Martín-Escolano, R.; Santivañez-Veliz, M.; Martín-Montes, A.; Azqueta, A.; Jimenez_Lopez, M.; Zamora-Ledesma, S.; Cirauqui, N.; López de Cerain, A.; Marín, C.; Sánchez-Moreno, M.; Pérez-Silanes, S. *In Vitro* and *in Vivo* Anti-*Trypanosoma cruzi* Activity of New Arylamine Mannich Base-Type Derivatives. *J. Med. Chem.* **2016**, *59*, 10929–10945.

NOTES

Synthesis of 2-(5-(2-((5-(Cyclohexylamino)-1,3,4-Thiadiazol-2-yl)thio) ethyl)-1,3,4-Oxadiazol-2-yl) Derivatives and Their Antimicrobial Activity

Serkan Levent[1, 2], Betül Kaya Çavuşoğlu[1], Yusuf Özkay[1, 2], Zafer Asım Kaplancıklı[1]

[1] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Anadolu University, Eskişehir, Turkey
[2] Doping and Narcotic Compounds Analysis Laboratory, Faculty of Pharmacy, Anadolu University, Eskişehir, Turkey

The rate of invasive fungal infections has increased since the 1980s, particularly in the vast populace of immunocompromised patients as well as those hospitalized with serious underlying disease [1]. The type of infections caused by Candida can be classified under two headings: superficial or systemic. Superficial diseases of the cutaneous or mucocutaneous tissues incorporate oropharyngeal candidiasis vaginitis, conjunctivitis, esophagitis, or gastrointestinal candidiasis. Systemic infections include endocarditis, pyelonephritis, esophagitis, meningitis, and disseminated candidiasis [2]. It is reported separately that oxadiazole, thiadiazole and cyclohexylamine have antimicrobial activity [3–5]. In light of this information, a skeleton composed of oxadiazole, thiadiazole and hexylamine was designed and 18 different novel derivatives were synthesized. All synthesized compounds were characterized by spectroscopic analysis such as FT-IR, ^{1}H-NMR, ^{13}C-NMR, and HRMS and screened for in vitro anticandidal activity against Candida species by broth microdiluation methods. Also, inhibition of ergosterol biosynthesis was measured by quantification of ergosterol amount in *C. albicans* by optimizing the LC-MS-MS method.

References:

1. Sardi, J.C.O.; Scorzoni, L.; Bernardi, T.; Fusco-Almeida A. M.; Mendes Giannini M. J. S. Candida species: current epidemiology, pathogenicity, biofilm formation, natural antifungal products and new therapeutic options. *Journal of Medical Microbiology*, **2013**, *62*, 10–24.
2. Jenkinson H.F.; Douglas L.J. Interactions between Candida Species and Bacteria in Mixed Infections. In *Polymicrobial Diseases;* Brogden KA, Guthmiller JM, Eds. ASM Press: Washington, DC, USA, 2002; Chapter 18. Available from: https://www.ncbi.nlm.nih.gov/books/NBK2486/
3. Onkol ,T.; Doğruer, D.S.; Uzun, L.; Adak, S.; Ozkan, S.; Sahin, M.F. Synthesis and antimicrobial activity of new 1,2,4-triazole and 1,3,4-thiadiazole derivatives. *J Enzyme Inhib Med Chem.* **2008**, *23*, 277–284. doi: 10.1080/14756360701408697
4. Desai, N.C.; Dodiya, A.M.; Rajpara, K.M.; Rupala, Y.M. Synthesis and antimicrobial screening of 1,3,4-oxadiazole and clubbed thiophene derivatives. *Journal of Saudi Chemical Society*, **2014**, *18*, 255–261.
5. Yurttas, L.; Çavuşoğlu, B.K.; Cankılıç, M.Y.; Levent, S. New Cyclohexylamine-Dithiocarbamate Derivatives as Potential Antimicrobial Agents. *Letters in Drug Design & Discovery*, **2017**, *14*, 1–8.

NOTES

Antimicrobial Peptides Derived from the Genome Mining of Animals Living in Pathogenic Environments

J.M. Pérez de la Lastra, C. Garrido-Orduña, C.L. Borges, A.A. Borges and A. Boto

Instituto de Productos Naturales y Agrobiología (IPNA), Consejo Superior de Investigaciones Científicas (CSIC), Tenerife, Spain

Antimicrobial peptides (AMPs) have been used on animals for millions of years. However, AMPs lack any specific consensus amino-acid sequences that are associated with biological activity, although most of them maintain certain common features, such as containing a positive charge and relatively hydrophobic and amphipathic structure. With the increasing number of genomes sequenced and available in the public domain, one alternative methodology to obtain novel AMPs is to analyse genes and proteins from genomic databases to predict and identify amino acid sequences that share similarities and molecular features with natural bioactive peptides. Cathelicidins are found in varying numbers in numerous different vertebrate species. A remarkable degree of molecular diversity has been noted within this gene family. However, a well-conserved feature across evolutionary distant species is an N-terminal cathelin-domain. Using this domain, we have found novel cathelicidins from the genome mining of vertebrates from avian, aquatic and terrestrial environments. The in silico structural analysis of the peptides indicated that all of them were alpha helical, had a positive net charge, with a hydrophobicity around 50% and a Boman index between 1.33 kcal/mol and 3.64 kcal/mol. We have derived 12 peptides from different animals and have studied their in vitro antimicrobial activity, together with the haemolytic activity as a measure of their potential toxicity. All peptides showed remarkably antimicrobial activity and lower toxicity. We believe that newly characterized molecules from several species have inspired molecular designs for the creation of therapeutics, and will continue to do so as more are discovered, because these are based on antimicrobial strategies that have proven efficacious over millennia. Every species harbours a unique, specific collection of antimicrobial peptides, tuned to defend the organism against microorganisms that it will predictably encounter. Therefore, a more detailed analysis of antimicrobial peptides structure and function from pathogen-resistant species will aid our understanding of antimicrobial peptides recognition and neutralization of pathogens, yielding a potentially large number of effective therapeutics. We hope that our preliminary investigation with these novel peptides could provide novel treatment opportunities based on antimicrobial peptides.

NOTES

Machine-Learning QSAR Model for Predicting Activity against Malaria Parasite's Ion Pump PfATP4 and In Silico Binding Assay Validation

Angela Lopez-del Rio[1,2], Laura Llorach-Parés[1,3], Alexandre Perera-Lluna[2,4], Conxita Avila[3], Alfons Nonell-Canals[1], Melchor Sanchez-Martinez[1]

[1] Mind the Byte S.L., Barcelona, Spain
[2] Department of ESAII, Center for Biomedical Engineering Research, Universitat Politècnica de Catalunya (UPC), Barcelona, Spain
[3] Department of Evolutionary Biology, Ecology, and Environmental Sciences, Faculty of Biology and Biodiversity Research Institute (IrBIO), Universitat de Barcelona, Barcelona, Spain
[4] Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Madrid, Spain

Malaria is a mosquito-borne infectious disease caused by parasitic protozoans of the genus Plasmodium. Although different effective antimalarial medicines have been developed, there is serious concern that parasites are developing widespread resistance to these drugs. To avoid this, now the efforts are concentrated on treating the malaria inside the Anopheles mosquito.
Several academic groups and companies are working worldwide to develop new compounds that fight the disease without provoking drug resistance. Within this context and making use of the Open Source Malaria project (http://opensourcemalaria.org/) which provides a large collection of molecules and 3D models of the targets with which they interact, we developed a machine learning-based QSAR model that predicts which molecules will block the malaria parasite's ion pump, PfATP4. The model was then employed to screen and classify the DrugBank database molecules and compounds coming from a proprietary marine molecules library. Finally, by means of an in silico binding assay, the predicted behavior was validated in the positive cases.
Summarizing, we have created a new set of repositioned drugs and marine molecules against malaria, establishing a good starting point for further studies and highlighting the key role that computational methods can have in the rational design of new drugs against infectious diseases.

NOTES

Synthesis and Antimicrobial Activity Evaluation of New Benzimidazole–Thiazole Derivatives

Zafer Asim Kaplancikli[1], Serkan Levent[1,2], Derya Osmaniye[1,2], Yusuf Özkay[1,2]

[1] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Anadolu University, Eskişehir, Turkey
[2] Doping and Narcotic Compounds Analysis Laboratory, Faculty of Pharmacy, Anadolu University, Eskişehir, Turkey

Antibiotic resistance which was expedited by the use of antimicrobial drugs has been a significant global challenge for public health [1]. In addition to this, candidiasis is the most common fungal infection worldwide, causing important morbidity and mortality, especially in immunocompromised patients [2].
A literature survey has uncovered that the various derivatives of benzimidazole have been synthesized for their pharmalogical activities and many of them supported the finding that benzimidazole derivatives are potent against various microorganism strains [3]. On the other hand, benzimidazoles are a class of synthetic remedial agents; for example, chlormidazole and carbendazim are used with a view to curing patients infected with fungus species.
The compounds that include thiazole on the same structure have significant antimicrobial activity; Sulfathiazole, which is an antimicrobial drug, includes a thiazole moiety [4].
From this point of view, in the present study, new benzimidazole–thiazole derivatives were synthesized. The structures of the synthesized compounds were elucidated using FT-IR, ^{1}H-NMR, ^{13}C-NMR, and HRMS spectral data. The synthesized compounds were screened for in vitro antimicrobial activity against pathogenic strains bacteria and candida. The effects of the selected compounds against ergosterol biosynthesis were observed by the LC-MS-MS method, which is based on quantification of the ergosterol level in *C. albicans*.

References:
1. Zhang, H.Z.; He, S.C.; Peng, Y.J.; Zhang, H.J.; Gopala, L.; Reddy Tangadanchu, V.K.; Gan, L.L.; Zhou, C.H. Design, synthesis and antimicrobial evaluation of novel benzimidazole-incorporated sulfonamide analogues, European Journal of Medicinal Chemistry, 2017, 136, 165–183.
2. Tang, H.; Wub, J.; Zhang, W.; Zhao, L.; Zhang, Y.H.; Shen, C.W. Design, Synthesis and Biological Evaluation of Novel Non-Azole Derivatives as Potential Antifungal Agents. *Chinese Chemical Letters*, **2015**, *26*, 1161–1164.
3. Salahuddin; Shaharyar, M.; Mazumder, A. Benzimidazoles: A biologically active compounds, *Arabian Journal of Chemistry*, **2017**, *10*, 157–173.
4. Ayati, A.; Emami, S.; Asadipour, A.; Shafiee, A.; Foroumadi, A. Recent applications of 1,3-thiazole core structure in the identification of new lead compounds and drug discovery. *European Journal of Medicinal Chemistry,* **2015**, *97*, 699–718.

NOTES

Synthesis and In Vitro Antiparasitic Activity of Novel Arylamine Mannich Base-Type Derivatives against *Trypanosoma cruzi* and *Leishmania* spp.

Rocio Paucar-Bernabé[1], Rubén Martin-Escolano[2], Elsa Moreno-Viguri[1], Manuel Sánchez-Moreno[2], Silvia Pérez-Silanes[1]

[1] Departamento de Química Orgánica y Farmacéutica, Instituto de Salud Tropical, Universidad de Navarra, Pamplona, Spain
[2] Departamento de Parasitología, Instituto de Investigación Biosanitaria (ibs.GRANADA), Universidad de Granada, Granada, Spain

Chagas disease and Leishmaniasis are trypanosomatid diseases considered as neglected tropical diseases by the WHO. These diseases are caused by *T. Cruzi* and *Leishmania* spp that affect hundreds of millions of people all over the world [1]. Although the number of people affected has decreased, these infections are still threatening to human life. Governmental and non-governmental organizations have proposed big challenges with the commitment to meet the needs of these patients. One of the most important challenges is the search for new, safe, effective and affordable drugs to combat these diseases as the current therapeutic arsenal is inadequate and insufficient [2].

In this context, our research group has been working on the discovery of new Mannich base-type derivative compounds as promising molecules for new anti-trypanosomatid agents [3].

Considering the target product profile of these diseases and the results found to date, we persist in the search of potentially trypanocidal compounds; therefore, thirty-three new derivatives have been synthesized by different, simple and cheap synthetic routes.

All compounds have been tested in vitro against the epimastigote form in three different *T. cruzi* strains (SN3, Arequipa and Tulahuen) for Chagas disease and in the promastigote form in *L. braziliensis, L. donovani* and *L. infantum*. The cytotoxicity has also been determined using Vero and THP-1 mammalian cell lines to establish their selectivity index (SI). Subsequently, the activity of the selected compounds is being carried out in the intracellular forms of the parasites. The results obtained from this evaluation will be shown in this Symposium.

References:

1. http://www.who.int/mediacentre/factsheets/fs387/en/ (Accessed on 20 March 2017).
2. Paucar, R., et al. Challenges in Chagas Disease Drug Discovery: A Review. *Med. Chem*. **2016**, *23*, 3154-3170.
3. Moreno-Viguri, E., et al. In Vitro and in Vivo Anti-*Trypanosoma Cruzi* Activity of New Arylamine Mannich Base-Type Derivatives. *J. Med. Chem*. **2016**, *59*, 10929-10945.

NOTES

Synthesis and Anticandidal Activity of New Imidazole Derivatives

Derya Osmaniye[1,2], Betül Kaya Çavuşoğlu[1], Begüm Nurpelin Sağlık[1,2], Yusuf Özkay[1,2], Zafer Asım Kaplancıklı[1,2]

[1] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Anadolu University, Eskişehir, Turkey
[2] Doping and Narcotic Compounds Analysis Laboratory, Faculty of Pharmacy, Anadolu University, Eskişehir, Turkey

During the last few years, there has been an increased awareness of morbidity and mortality related to invasive and systemic fungal disease because of resistant fungi and immunocompromised infections, for instance, AIDS. Due to this reason, various antifungal drugs have been improved in an attempt to reduce the effect of fungal infections. Azoles in the form of amphotericin B, 5-fluorocytosine, and caspofungin have been used based on their antifungal impact [1,2].

Azoles are administered against C14α-demethylase in the ergosterol pathway. The subsequent ergosterol exhaustion and accumulation of 14α-methylsterols intervene in the function of ergosterol as the determinant cellular membrane ingredient [3]. Azoles including fluconazole, miconazole, itraconazole, clotrimazole, and econazole, are used for treatment of patients who are affected by different Candida species [4].

By virtue of the above consequence, in the present study, new imidazole derivatives were synthesized. The structures of the synthesized compounds were elucidated using FT-IR, ^{1}H-NMR, ^{13}C-NMR, and HRMS spectral data. The target compounds were screened for in vitro anticandidal activity against Candida species by broth microdiluation methods. The effects of the selected compounds against ergosterol biosynthesis were observed by the LC-MS-MS method, which is based on quantification of the ergosterol level in *C. albicans*.

References:

1. Tang, H., Wub, J., Zhang, W., et al. Design, Synthesis and Biological Evaluation of Novel Non-Azole Derivatives as Potential Antifungal Agents. *Chinese Chemical Letters*, **2015**, *26*, 1161–1164.
2. Canuto, M.M., Rodero, F.G. Antifungal Drug Resistance to Azoles and Polyenes. *Infectious Diseases*, **2002**, *2*, 550-563.
3. Lupetti, A., Danesi, R., Campa, M. et al. Molecular basis of resistance to azole antifungals. *Molecular Medicine*, **2002**, *8*, 77-81.
4. Niimi, M., Firth, N.A., Cannon, R.D. Antifungal drug resistance of oral fungi. *Odontology*, **2010**, *98*, 15–25.

NOTES

Biological Evaluation of Arylamine Mannich Base Derivatives with Potent In Vivo Activity as Potent Antichagasic Agents

Rocio Paucar-Bernabé[1], Elsa Moreno-Viguri[1], Rubén Martin-Escolano[2], Mery Santivañez-Veliz[1], Amaya Azqueta[3,4], Nuria Cirauqui[5], Manuel Sánchez-Moreno[2], Silvia Pérez-Silanes[1]

[1] Departamento de Química Orgánica y Farmacéutica, Instituto de Salud Tropical, Universidad de Navarra, Pamplona, Spain
[2] Departamento de Parasitología, Instituto de Investigación Biosanitaria (ibs.GRANADA), Universidad de Granada, Granada, Spain
[3] Departamento de Farmacología y Toxicología, Universidad de Navarra, Pamplona, Spain
[4] Navarra Institute for Health Research, IdiSNA, Recinto de Complejo Hospitalario de Navarra, Pamplona, Spain
[5] Departamento de Fármacos, Facultade do Farmacia, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Chagas disease (CD) is a neglected tropical disease caused by the parasite *Trypanosoma cruzi* [1]. About 6–7 million people are infected worldwide, mainly in Latin America [1]. Benznidazole and Nifurtimox are the only available drugs for this disease but the problems with those drugs are related to their variable antiparasitic activity, the undesired side effects and long treatment duration among others [2]. Therefore, there is a great need for the development of new, effective, safe and affordable drugs for the treatment of CD.

In this context, our group is focused on identifying new agents to fight against CD. So, twenty new derivatives were synthetized and tested in epimastigote, amastigote and trypomastigote forms in three different *T. cruzi* strains (SN3, Arequipa and Tulahuen). The cytotoxicity was also determined to establish their selectivity index (SI). The lead compound showed in vitro SI ranging from 99 to 258 times higher than Benznidazol in the amastigote form and from 333 to 2810 in the trypomastigote form of the parasites. The tested compounds in the SOS/umu screening test were non-genotoxic, whereas the reference drugs showed genotoxicity in the tested conditions. Regarding the studies of their mechanism of action, it seems that this family could be inhibitors of the Fe-SOD exclusive antioxidant defense trypanosomatids.

According to their in vitro biological activity and preliminary toxicological studies, four out of twenty derivatives were selected for an in vivo assay in a murine mice model. The in vivo acute model showed that the compounds decrease the parasitemia from the beginning of the treatment and parasites were not detected from day 25 post-infection. Moreover, none of the compounds showed reactivation after immunosuppression with the dose used with the reference drug (100 mg/kg) and the lead compounds showed no reactivation also at 50 mg/kg [3]. Considering the in vivo results, three out of four derivatives were selected for their mutagenicity evaluation and were non-mutagenic in the Ames test. Moreover, the absorption, distribution, metabolism, and excretion (ADME)/Tox and

Pharmacokinetic (PK) evaluations are ongoing and the results will be presented in this congress.

Up to now, these results have encouraged us to propose these compounds as promising molecules for developing new anti-Chagas agents and they will be transferred to an in vivo bioluminescence model in collaboration with the London School of Hygiene and Tropical Medicine.

References:

1. World Health Organization (WHO). Chagas disease (American trypanosomiasis) / Fact sheet N°340. http://www.who.int/mediacentre/factsheets/fs340/en/ (Accessed on 6 March 2017).
2. Paucar, R., Moreno-Viguri, E., Pérez-Silanes, S. Challenges in Chagas Disease Drug Discovery: A Review. *Current Medicinal Chemistry*, **2016**, *23*, 3154-3170.
3. Moreno-Viguri, E., Jiménez-Montes, C., Martín-Escolano, R. et al. In Vitro and in Vivo Anti-*Trypanosoma cruzi* Activity of New Arylamine Mannich Base-Type Derivatives. *Journal of Medicinal Chemistry*, **2016**, *59*, 10929-10945.

NOTES

Activity of 2-benzyl-1-(2-hydroxyethyl)-5-nitroindazolin-3-one on *Trypanosoma cruzi* Bloodstream Trypomastigotes (Y strain): In Vitro and In Vivo Studies

Cristina Fonseca-Berzal[1], Cristiane França da Silva[2], Marcos Meuser Batista[2], Francisca Hildemagna Guedes-da-Silva[2], Mariane Vasconcelos[2], Kelly C. Demarque[2], José A. Escario[1], Vicente J. Arán[3], Maria de Nazaré C. Soeiro[2] and Alicia Gómez-Barrio[1]

[1] Departamento de Parasitología, Facultad de Farmacia, Universidad Complutense de Madrid (CEI Campus Moncloa UCM-UPM and CSIC), Madrid, Spain
[2] Laboratório de Biologia Celular, Instituto Oswaldo Cruz, Fiocruz, Rio de Janeiro, Brazil
[3] Instituto de Química Médica (IQM), CSIC, Madrid, Spain

Benznidazole and nifurtimox, the currently available drugs for the specific treatment of Chagas disease, show limited effectiveness and high toxicity that prompt the identification of therapeutic alternatives. In this context, our group has proposed 5-nitroindazole derivatives as antichagasic prototypes, according to their activity in vitro and in vivo [1–5]. The lack of cytoxicity and outstanding activity on the replicative forms of *Trypanosoma cruzi* (i.e., epimastigotes and intracellular amastigotes) previously shown by 2-benzyl-1-(2-hydroxyethyl)-5-nitroindazolin-3-one [5], encouraged assaying this compound in vitro on bloodstream trypomastigotes of Y strain (DTU TcII) and then, moved it to murine models of toxicity and infection. After confirming NOAEL >25 mg/kg and no signs of acute toxicity (i.e., normal weight, organs appearance, hemogram and biochemistry), infected mice were treated on the 5th and 8th dpi with doses of 25, 12.5 or 6.25 mg/kg/day. The results obtained in this acute model of *T. cruzi* infection in mice showed that this compound achieved ca. 30% of parasitemia reduction on the 8th dpi when administered either at 25 mg/kg/day p.o. or 6.25 mg/kg/day ip. Accordingly, new treatment schemes and molecule optimization are now considered for further analysis in vivo, aiming to contribute to the identification of novel alternative therapies for Chagas disease.

References:

1. Vega, M.C., Rolón, M., Montero-Torres, A. et al. Synthesis, biological evaluation and chemometric analysis of indazole derivatives. 1,2-Disubstituted 5-nitroindazolinones, new prototypes of antichagasic drug. *Eur. J. Med. Chem.* **2012**, *58*, 214-227.
2. Fonseca-Berzal, C., Escario, J.A., Arán, V.J. et al. Further insights into biological evaluation of new anti-*Trypanosoma cruzi* 5-nitroindazoles. *Parasitol. Res.* **2014**, *113*, 1049-1056.
3. Fonseca-Berzal, C., da Silva, P.B., da Silva, C.F. et al. Exploring the potential activity spectrum of two 5-nitroindazolinone prototypes on different *Trypanosoma cruzi* strains. *Parasitology Open*, **2015**, *e10*, doi:10.1017/pao.2015.4.
4. Fonseca-Berzal, C., da Silva, C.F., Menna-Barreto, R.F.S. et al. Biological approaches to characterize the mode of action of two 5-nitroindazolinone prototypes on *Trypanosoma cruzi* bloodstream trypomastigotes. *Parasitology* **2016**, *143*, 1469-1478.
5. Fonseca-Berzal, C., Ibáñez-Escribano, A., Reviriego, F. et al. Antichagasic and trichomonacidal activity of 1-substituted 2-benzyl-5-nitroindazolin-3-ones and 3-alkoxy-2-benzyl-5-nitro-2H-indazoles. *Eur. J. Med. Chem.* **2016**, *115*, 295-310.

NOTES

Anti-Bacterial and Anti-Fungal Activity of Xanthones Obtained via Semi-Synthetic Modification of α-Mangostin from *Garcinia mangostana*

Imad Abu-Yousef[1], Narasimhan Srinivasan[2], Amin Majdalawieh[1], Shanmugam Maheshwaran[2], Janarthanam Rethavathi[2], Prince Das[2], Palmiro Poltronieri[3]

[1] Department of Biology, Chemistry and Environmental Sciences, American University of Sharjah, Sharjah, United Arab Emirates
[2] Asthagiri Herbal Research Foundation, Perungudi Industrial Estate, Perungudi, Chennai, India
[3] Institute of Sciences of Food Productions, CNR-ISPA, Lecce, Italy

Microbial contamination in food packaging has been a major concern that has paved the way to the search for novel, natural anti-microbial agents, such as modified α-mangostin. In the present study, twelve synthetic analogues were obtained through semi-synthetic modification of α-mangostin (I) by Ritter reaction; reduction by palladium-carbon (Pd-C); alkylation; and acetylation. The evaluation of the anti-microbial potential of the synthetic analogues showed higher bactericidal activity than the parent molecule. The anti-microbial studies proved that (II) showed high anti-bacterial activity whereas (III) showed the highest anti-fungal activity. Due to their microbicidal potential, modified α-mangostin derivatives could be utilized as active anti-microbial agents in materials for the biomedical and food industry.

NOTES

Anti-Fungal Potential of Novel Chiral Schiff Bases and Their Reduction Products

Amin Majdalawieh[1], Mohamed Abouleish[1], Imad Abu-Yousef[1], Srinivasan Narasimhan[2]

[1] *Department of Biology, Chemistry and Environmental Sciences, American University of Sharjah, United Arab Emirates*
[2] *Asthagiri Herbal Research Foundation, Chennai, India*

Anti-fungal agents have been used for agricultural protection and are still in use worldwide. This study aims at assessing the anti-fungal activity of novel chiral Schiff bases and their reduction products against several plant fungal pathogens. Such compounds were synthesized using various salicylaldehydes and naturally-occurring amino acid L-valine. The anti-fungal activity was assessed in vitro using the Poisoned Food Technique (PFT). Our findings reveal that these novel Schiff base derivatives and their reduction products, at 25 ppm, display differential anti-fungal activities against four common plant fungal pathogens (e.g., *Rhizoctonia solani*, *Colletotrichum capsici*, *Phyllosticta sp.*, and *Curvularia lunata*). At 100 ppm, many Schiff base derivatives cause more potent % inhibition. At 1000 ppm, some Schiff bases' derivatives caused 100% inhibition against *Rhizoctonia solani* and *Colletotrichum capsici*. Additionally, the Schiff base derivatives and their reduction products demonstrated fungicidal efficacy against common food fungal pathogens including *Rhizopus sp.*, *Fusarium sp.*, *Penicillium sp.*, and *Botrytis cinerea* at 50–100 ppm concentration. The minimum inhibitory concentration (MIC) values of the studied Schiff base derivatives and their reduction products against the respective fungal pathogens were determined. In sum, our study clearly demonstrates that the studied novel Schiff base derivatives and their reduction products possess potent fungicidal activity against several plant and food fungal pathogens at concentrations as low as 50 ppm. We anticipate that such novel compounds will be employed in the future as alternative, ecologically-friendly, broad-spectrum fungicidal agents against common plant and food fungal pathogens including *Rhizoctonia solani*, *Colletotrichum capsici*, *Phyllosticta sp.*, *Curvularia lunata*, *Rhizopus sp.*, *Fusarium sp.*, *Penicillium sp.*, and *Botrytis cinerea*.

NOTES

Antimicrobial Activity of Amino Acid Analogues and Their Derivatives

Dácil Hernández Mesa, Carlos Saavedra, Carmen Carro, Alicia Boto, and José Manuel Pérez de Lastra

CSIC Instituto de Productos Naturales y Agrobiologia, San Cristóbal de La Laguna, Spain

Libraries of compounds containing unnatural amino acids or amino acid analogues were prepared from inexpensive substrates using sustainable processes. The compounds were evaluated for antimicrobial activity against different pathogens.

References:
1. Saavedra, C. J.; Boto, A.; Hernández, R. *Org. Lett.* **2012**, *14*, 3788-91.
2. Boto, A.; Hernández, D.; Hernández, R. *Eur. J. Org. Chem.* **2010**, 6633-42.

NOTES

Antimycobacterial Activity of New 1,4-Benzoxazine-2-One Derivatives and Its 2-(Arylamino)-4-Oxobut-2-Enoate, Ring-Open Analogues

Daniele Zampieri[1], Maria Grazia Mamolo[1], Alessandro De Logu[2]

[1] Department of Chemistry and Pharmaceutical Sciences, University of Trieste, Trieste, Italy
[2] Department of Life Sciences and Development, University of Cagliari, Cagliari, Italy

Menaquinone is one of the essential components of the electron transport chain in many pathogens and consequently enzymes in its biosynthesis pathway are potential drug targets for the development of novel antibacterial agents. A few years ago, Li et al. [1] identified several 1,4-benzoxazine-2-one derivatives, that target MenB (1,4-dihydroxy-2-naphtoyl-CoA synthase), endowed with high antibacterial activity against *Mycobacteria tuberculosis* $H_{37}Rv$ with MIC values of 0.6 µg/ml. By these assumptions, we designed and synthesized some analogous compounds in order to investigate the SAR and to discover new potent antimycobacterial derivatives. First of all, we tried to check the activity of several benzoxazine-3-one isosters and, in our case, the derivative showed low antimycobacterial activity (32->64 mg/ml), contradicting the bioisosterism principle. Then, we tried to modify the substituents on the original 1,4-benzoxazin-2-one core and we found some interesting data that will be presented. Moreover, we synthesized some 2-(arylamino)-4-oxobut-2-enoate derivatives as analogues of O-Succylbenzoate (OSB), a precursor in the menaquinone biosynthetic pathway. Details on antitubercular activity will be presented.

References:
1. Li, X.; Liu, N.; Zang, H. et al. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6306-09.

NOTES

Arginine and Lysine Conjugated Rhamnolipids

Anderson Ramos[1], Aurora Pinazo[2], Ana M Marqués[1], Ángeles Manresa[1], Lourdes Pérez[2]

[1] Microbiology, Department of Biology, Healthcare and Environment, Faculty of Pharmacy, University of Barcelona, Spain.
[2] Department of Chemical Surfactants Technology, Institute of Advanced Chemistry od Catalonia (IQAC-CSIC), Barcelona, Spain.

The rapid increase of multiple drug resistant bacteria and fungi poses a serious threat to society. Therefore, there is an urgent need to design new antimicrobial compounds that impede the development of acquired resistance. One possible strategy is the preparation of new antimicrobial compounds with novel modes of action and different targets.
Biosurfactants are surface active molecules that are produced by a variety of different microorganisms. Rhamnolipids produced by *Pseudomonas aeruginosa* are a mixture of mono-rhamnolipids and di-rhamnolipids. Mono-rhamnolipids and di-rhamnolipids consist of one or two molecules of rhamnose functionalized with one or two hydroxy fatty acids of different length. Rhamnolipids have the two main properties of surfactants, that is, strong surface activity and self-assembly in water. With the aim of obtaining new antimicrobial compounds, we have synthesized new molecules that structurally consist of one molecule of rhamnolipid linked to one arginine or lysine. A simple procedure was used to obtain the new molecules. The new molecules were prepared by linking the α-NH_2 of the methilated arginine or lysine to the carboxyl terminus of the rhamnolipids. The introduction of the amino acids gives cationic character to the new rhamnolipid derivatives. After the synthesis, these compounds were assayed to ascertain their antimicrobial and hemolytic activity.

NOTES

Aryl Sulfonamides as a New Antitubercular Series: Discovery, Optimization and Target Identification

Arancha Pérez García

[1] *GSK, Tres Cantos, Madrid, Spain*

Tuberculosis (TB) remains a major global health problem. An estimated one-third of the world's population is infected with *Mycobacterium tuberculosis* (*Mtb*), the causative agent of tuberculosis. In 2015, 1.8 million people died from the disease. The development of new anti-TB therapeutics is urgently needed due to the emergence of multi-drug resistant strains (MDR and XDR-TB) as well as the co-infection with other pathogens (e.g., VIH).

A Whole Cell HTS with GSK´s two million compound collection using *Mycobacterium bovis* BCG as a surrogate of *Mycobacterium tuberculosis* and subsequent confirmation of the obtained hits in *Mtb* was performed. As a result, several families with interesting antitubercular features were identified. An aryl sulfonamide series presenting a particularly promising profile was prioritized for optimization.

Details of the phenotypic screen, the initial Hit profile, preliminary SAR, Medicinal Chemistry activities and identification of the biological target will be presented.

References:

1. World Health Organization. Global tuberculosis report. 2016. Available at http://www.who.int/tb/publications/global_report/en/

NOTES

Computational Approach to Structural and Conformational Characterization of Viral Surface Glycoproteins of HIV-2

Patricia Serra[1], Andreia Martins[1], Nuno Taveira[1, 2], Rita C. Guedes[1]

[1] iMed.ULisboa, Research Institute for Medicines and Faculty of Pharmacy, University of Lisbon, Portugal
[2] Instituto Superior de Ciências da Saúde Egas Moniz (ISCSEM), Quinta da Granja, Portugal

The efficacy of some of the available antiretroviral drugs is very limited against HIV-2 and, most importantly, none of the current drugs effectively prevents entry into the cells. HIV envelope glycoproteins mediate binding to the receptor CD4 and to CCR5 and/or CXCR4 co-receptors at the surface of the target cell, enabling fusion with the cell membrane and viral entry [1,2]. We are using computational tools to infer the structure of HIV-2 variable regions, and discover new compounds that bind to these regions and prevent cell entry. In the absence of a complete crystallographic structure of HIV-2 envelope gp125 comprising variable domains, computer aided modulation is crucial to identify structural features in the region that correlate with HIV-2 tropism and susceptibility to antibody neutralization [3].
A 3D structure of the C2V3C3 domain of HIV-2_{ROD} gp125 was generated by homology modelling. HIV-2_{ROD} is an X4 T-cell adapted isolate naturally resistant to antibody neutralization. To disclose the importance of the main structural features and compare with experimental results, 3D-models of six V3 mutants were also generated (H18L, H23Δ + Y24Δ, K29T, H18L+ H23Δ + Y24Δ, H18L+ K29T and H18L+ H23Δ + Y24Δ+ K29T). These mutations in V3 revealed a selective impact. The 3D structures were submitted to molecular dynamics procedures. Energy minimization and molecular dynamic simulations were performed using Gromacs 2016.01 packages.
The results were associated with higher resistance to antibody neutralization and acquisition of macrophage tropism. These new insights into the structure–function relationship will help in the design of better vaccine immunogens.

References:
1. Uchtenhagen, H.; Friemann, R.; Raszewski, G. et al. *PLoS One* **2011**, *6*, e18767.
2. Mascola, J. *Science* **2015**, *349*, 139; 3.
3. Davenport, Y.; West, A.; Bjorkman, P. *J. Virol.* **2016**, *90*, 2112.

NOTES

Design, Synthesis and Activity of New Polymyxins

Francesc Rabanal[1], Roser Segovia[1], Aina Coll[1], Judith Solé[1], Maria Garcia-Subirats[1], Angeles Manresa[2], Yolanda Cajal[3,4]

[1] Section of Organic Chemistry, Department of Inorganic and Organic Chemistry, Faculty of Chemistry, University of Barcelona, Spain
[2] Laboratory of Microbiology, Faculty of Pharmacy, University of Barcelona, Spain
[3] Department of Physical Chemistry, Faculty of Pharmacy, University of Barcelona, Spain
[4] Institute of Nanoscience and Nanotechnology (IN2UB), University of Barcelona, Spain

Antibiotic resistance is a daunting challenge for public health systems worldwide. A major goal to fight resistant bacteria involves the design, discovery and development of new antibiotics, particularly against multi-drug-resistant strains. Currently, there is renewed interest in polymyxins, an old class of antimicrobial cyclic lipopeptides, highly potent against therapeutically relevant Gram-negative bacteria. Polymyxins are now used as last resort antibiotics in hospitals because of their nephrotoxicity and neurotoxicity that requires careful monitoring of the patient. Our group has embarked on a project to design and develop new polymyxins devoid of toxicity problems using a versatile and chemically accessible scaffold structure [1,2]. Compounds show excellent activity against Gram-negative bacteria. Synergistic and antibiofilm activities have also been recently described in combination with imipenem [3]. Herein, the latest results of our recently designed polymyxin analogs will be presented.

References:

1. Rabanal, F.; Grau-Campistany, A.; Vila-Farrés, X. et al. A bioinspired peptide scaffold with high antibiotic activity and low in vivo toxicity. *Sci. Rep.* **2015**, *5*, 10558.
2. Rabanal, F.; Cajal, Y. Recent advances and perspectives in the design and development of polymyxins. *Nat. Prod. Rep.* **2017**, in press, DOI: 10.1039/c7np00023e.
3. Rudilla, H.; Fusté, E.; Cajal, Y. et al. Synergistic Antipseudomonal Effects of Synthetic Peptide AMP38 and Carbapenems. *Molecules* **2016**, *21*, 1223.

NOTES

Design, Synthesis and Structure–Activity Relationships of a Phenotypic Small Library against Protozoan Infections

Elisa Uliassi[1], Lorna Piazzi[1], Federica Belluti[1], Marcel Kaiser[2], Reto Brun[2], Sheraz Gul[3], Bernhard Ellinger[3], Carolina B. Moraes[4], Lucio H. Freitas-Junior[4], Chiara Borsari[5], Maria Paola Costi[5], Maria Laura Bolognesi[1]

[1] Department of Pharmacy and Biotechnology, Alma Mater Studiorum - University of Bologna, Bologna, Italy
[2] Swiss Tropical and Public Health Institute; University of Basel, Basel, Switzerland
[3] Fraunhofer Institute for Molecular Biology and Applied Ecology Screening Port, Hamburg, Germany
[4] Laboratório Nacional de Biociências (LNBio), Centro Nacional de Pesquisa em Energia e Materiais (CNPEM), Campinas, Brazil
[5] Department of Life Sciences, University of Modena and Reggio Emilia, Modena, Italy

Protozoan infections (*Plasmodium* spp., *Leishmania* spp., and *Trypanosoma* spp.) remain one of the most pressing global health concerns, affecting billions of people and producing unsustainable economic burdens [1]. Current pharmacotherapy is inadequate, and appropriate technologies should be exploited to identify novel drug candidates in a cost- and time-effective manner. Accordingly, an effective strategy could exploit privileged structures to generate libraries of high-quality compounds, combined with the feasibility of a phenotypic assay, and the early evaluation of the ADME-tox profile.

On these bases, we generated an 18-membered combinatorial library by fast assembling phenothiazine, biphenyl and phenylpiperazine anti-protozoan privileged scaffolds via a Huisgen cycloaddition. Thanks to NMTrypI [2] and SPHTI [3] screening facilities, we tested 1–18 against *T. brucei* and *cruzi*, *L. infantum* and *donovani*, and *P. falciparum*, and counter-screened selectivity against mammalian cells (L6 and A549). In parallel, ADME-tox properties were assessed by testing hERG, CYP inhibition, and mitochondrial viability.

Despite the small number of synthesized compounds, this strategy led to the successful identification of interesting hits with promising profiles. Particularly, 4 and 9 showed IC_{50} values of 3.8 and 3.4 μM against *T. cruzi,* together with an excellent selectivity (SI (IC_{50} (L6)/IC_{50} (*Tc*)) >48 and % A549 cell growth at 10 μM >100%).

References:

1. Field, M.C. et al. *Nat Rev Microbiol* **2017**, *15*, 217–31.
2. The anti-parasitic activity and the early-toxicity profiling of the compounds were developed within the international collaborative effort of the European Union's Seventh Framework Programme under grant agreement n° 603240 (NMTrypI—New Medicines for Trypanosomatidic Infections) (http://fp7-nmtrypi.eu).
3. SPHTI - Swiss Tropical & Public Health Institute, Parasite Chemotherapy Unit (https://www.swisstph.ch/en/).

NOTES

Design, Synthesis Molecular Docking Study and Antifungal Activity Evaluation of New Benzimidazole–Triazole Derivatives

Büşra Korkut[1], Ulviye Acar Çevik[2, 3], Yusuf Özkay[2, 3], Özlem Atlı[1]

[1] Anadolu University, Faculty of Pharmacy, Department of Pharmaceutical Toxicology, Eskişehir, Turkey
[2] Anadolu University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Eskişehir, Turkey
[3] Anadolu University, Faculty of Pharmacy, Doping and Narcotic Compounds Analysis Laboratory, Eskişehir, Turkey

Lanosterol 14α-demethylase (CYP51) is an essential enzyme in the fungal life cycle and also an important target for antifungal drug development. Selective inhibition of the enzyme would cause depletion of ergosterol and accumulation of lanosterol and result in the growth inhibition of the fungal cell [1].

In this study, a series of benzimidazole derivatives containing a triazole ring that are structurally related to the famous antifungal azole pharmacophore were synthesized and their structures were characterized by spectral (IR, ^{1}H-NMR, ^{13}C-NMR, and MS spectra) analyses. Compounds 5i and 5s showed the most promising antifungal activity with a MIC_{50} value of 0.39 ug/mL against *Candida* species. Molecular docking studies were performed to investigate the mode of action towards the fungal lanosterol 14α-demethylase. ADME studies were carried out and a connection between activities and physicochemical properties of the target compounds was determined. The effect of the active compounds against ergosterol biosynthesis was observed by the LC-MS-MS method.

References:

1. Morrison, A. M. S.; Goldstone, J. V.; Lamb, D. C. et al. Identification, modeling and ligand affinity of early deuterostome CYP51s, and functional characterization of recombinant zebrafish sterol 14α-demethylase. *Biochimica et biophysica acta (BBA)-General subjects* **2014**, *1840*, 1825-36.

NOTES

Designing Novel Hydrazinecarbothioamides as Potential HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors

Hong Yin[1], Zhengyong Wan[1], Ge Meng[1], Fen-Er Chen[1, 2], Erik De Clercq[3], Christophe Pannecouque[3], Jan Balzarini[3]

[1] Department of Chemistry, Fudan University, Shanghai, People's Republic of China
[2] Institute of Biomedical science, Fudan University, Shanghai, People's Republic of China
[3] Rega Institute for Medical Research, KU Leuven, Leuven, Belgium

Reverse transcriptase (RT), the key enzyme in the HIV life cycle of HIV, is one of the main targets for the antiretroviral chemotherapy. Nonnucleoside reverse transcriptase inhibitors (NNRTIs), including HEPT, DABO, TIBO, DATA, and DAPY, are the main drugs for treating AIDS efficiently. Among them, DAPYs were regarded as one of the most successful NNRTI members including Etravirine (TMC125) as the FDA approved drugs showing the improved potency against many drug resistance mutations. The newly approved Rilpivirine (TMC278) possessed a higher genetic barrier to oppose various clinically relevant RT mutations than Etravirine. However, the rapid emergence of the drug resistance and the serious side effects of the long-term clinical drugs impelled the medicinal chemists to develop the structure diversified NNRTIs. As indicated in the previous papers, our program in NNRTIs led to the modifications on DAPY derivatives with hydroxyl, cyano, chlorine, and hydrazone groups attached to the CH_2-linker between the left benzene ring and the central pyrimidine ring, which showed the excellent activity against HIV-1 replication. Moreover, the docking results show that these groups could fill the Val179-including active binding pocket (Lys101/Glu138/Val179) of HIV-1 RT, which provide some possibilities to generate the suitable electrostatic interactions with the amino acid residues at the wall of the active site. On the other hand, thiosemicarbazone derivatives have been evaluated for their inhibitor activity against antiviral, as well as the effects against human immunodeficiency virus (HIV).

Based on the SAR analysis of these NNRTIs and the structure feature of HIV-1 RT NNIBP, we postulate that introducing a thiosemicarbazone group might be well accommodated in the open position in front of Lys101/Glu138/Val179, which is considered as the entrance channel for the NNRTIs. Therefore, we designed and synthesized a new series of CR_2-DAPYs featuring a thiosemicarbazone group at the CH_2 linker between wing I and the central pyrimidine ring in order to evaluate their biological activities against HIV-1 RT for the further structure–activity relationship (SAR) studies.

The HIV-1 reverse transcriptase assay of the synthesized compounds also indicates that the target of these compounds is HIV-1 RT. Most of these target compounds displayed anti-HIV-1 activity at the level of micromolar EC_{50} values in infected MT-4 cells. Compound 1e exhibited the most potent activity with an EC_{50} value of 0.0047μM on HIV-1 RT enzymatic assay screening test. However, almost all of the

target compounds lost the potency against the mutant type virus and HIV-2, except for compound 1a, which showed both the potent anti-HIV-1 activity with IC_{50} values of 0.038 μM against wild type and the inhibitory activity with an EC_{50} value of 0.082μM against the mutant type virus (Y181C). In addition, the molecular docking result revealed that introducing a small thiosemicarbazone group into CH_2 linker occupied the binding space in the hydrophobic cavity lined with Tyr181, Tyr188, Phe227, Trp229 of NNIBP, and the bulky thiosemicarbazone group tailed with phenyl ring was docked in front of the Y181-Val179 binding pocket. Both of the two interaction modes retained the low cellular inhibitory potencies. Further, SAR analysis showed that the thiosemicarbazone moiety played the more important role on enhancing the inhibition potency than other skeleton moiety does. However, as the length of the thiosemicarbazone attaching group increased, the inhibition activity against the mutant type of HIV-1 decreased accordingly.

References:

1. Schafer, J.J.; Short, W.R. Rilpivirine, a novel non-nucleoside reverse transcriptase inhibitor for the management of HIV-1 infection: a systematic review. *Antivir. Ther.* **2012**, *17,* 1495-502.
2. Ge M.; Yang L.; Aqun Z. et al. Design and synthesis of a new series of modified CH-diarylpyrimidines as drug-resistant HIV *non*-nucleoside reverse transcriptase inhibitors. *Eur. J. Med. Chem.* **2014**, *82*, 600-11.
3. Meng, Q.; Chen, X.; Kang, D. et al. Design, synthesis and evaluation of novel HIV-1 NNRTIs with dual structural conformations targeting the entrance channel of the NNRTI binding pocket. *Eur. J. Med. Chem.* **2016**, *115*, 53.

NOTES

Discovery of Biphenyl-Substituted Diarylpyrimidines as New Non-Nucleoside HIV-1 Reverse Transcripttase Inhibitors

Kaijun Jin[1], Ge Meng[1], Fen-Er Chen[1, 2], Erik De Clercq[3], Jan Balzarini[3], Christophe Pannecouque[3]

[1] Department of Chemistry, Fudan University, Shanghai, People's Republic of China
[2] Institute of Biomedical science, Fudan University, Shanghai, People's Republic of China
[3] Rega Institute for Medical Research, KU Leuven, Leuven, Belgium

Although Rilpivirine (RPV, TMC278) was approved by the FDA in 2011 as a non-nucleoside HIV-1 reverse transcriptase inhibitor to treat Human Immunodeficiency Virus (HIV) [1] for its potent activity against many clinically relevant wild-type (WT) and mutant HIV-1 strains, the corresponding dosing complexity, drug–drug interactions and long-term toxicity of this drug have severely compromised its efficacy [2].

To solve the above problem, herein a novel series of biphenyl-substituted diarylpyrimidine analogues (DAPYs) was designed, synthesized to evaluate the in vitro activity against HIV-1 in MT-4 cells. Some of these compounds exhibited excellent activity with the low nanomolar EC_{50} to wild-type (WT), single-mutant, and double-mutant HIV-1 strains. The most potent compound 2a displayed an EC_{50} value of 1 nM against HIV-1 ⅢB, 1.3 nM against L100I, 0.84 nM against K103N, 1.5 nM against Y181C, 11 nM against Y188L, 2 nM against E138K, 10 nM against K103N+Y181C, nearly 110 nM against F227L+V106 with a selectivity index (SI) value above 2059.

To investigate the possible interaction model between the new chemical entity and the biological target, compound 2a was docked into the allosteric non-nucleoside bind pocket (NNIBP) of HIV-1 RT (PDB code: 2ZD1) [3] by using Sybyl-X 1.2. Compound 2a exhibited a series of well-known kinds of interactions: the biphenyl moiety fitted well into the aromatic-rich sub-pocket consisting of amino acid residues including Tyr181, Tyr188, Phe227 and Trp229, showing the positive face-to-face π–π stacking interactions with the amino acid residues of Tyr181, Tyr188 and Trp229, excluding Phe227. The *p*-cyano group is protruding toward a tunnel formed by Phe227 and Trp229, indicating a possible polar interaction. The right aromatic ring extended to a solvent exposure region, which was surrounded by amino acid residues His235, Pro236 and Try 318. Additionally, two hydrogen bonds between compound 2a and NNIBP of HIV-1 RT were formed altogether; one is between the *NH*-linker and the oxygen atom of the carbonyl group on the back-bone of Lys101, another is between the 1-nitrogen atom on pyrimidine between the terminal amino group of Lys101.

Deep SAR analysis of the anti-HIV-1 profile of all the compounds showed that beside keeping the 2,6-dimethyl groups on the left ring of DAPY analogues, introducing a *para*-substituted cyano group on the second phenyl ring (B) on the biphenyl group might be crucial for enhancing the biological activity against both wild-type and mutant-type HIV-1. This important discovery on the biphenyl-

substituted DAPY analogs might guide the further structural modification of our ongoing project of HIV-1 RT inhibitors.

References:
1. Chen, X.; Zhan, P.; Li, D. et al. Recent Advances in DAPYs and Related Analogues as HIV-1 NNRTIs. *Curr. Med. Chem.* **2011**, *18*, 359.
2. Rimsky, L.; Vingerhoets, J.; Van Eygen, V. et al. Genotypic and phenotypic characterization of HIV-1 isolates obtained from patients on rilpivirine therapy experiencing virologic failure in the phase 3 ECHO and THRIVE studies: 48-week analysis. *J. Acquir. Immune. Defic. Syndr.* **2012**, *59*, 39-46.
3. Lansdon, E.B.; Brendza, K.M.; Hung, M. et al. Crystal Structures of HIV-1 Reverse Transcriptase with Etravirine (TMC125) and Rilpivirine (TMC278): Implications for Drug Design. *Med. Chem.* **2010**, *53,* 4295.

NOTES

Edelfosine (ET-18-0CH_3) a Promising Alkylphospholipid against Resistant *Trichomonas vaginalis*

Alexandra Ibáñez-Escribano[1], Jose Antonio Escario[1], Faustino Mollinedo[2], Alicia Gómez-Barrio[1]

[1] Departamento de Parasitología, Facultad de Farmacia, Universidad Complutense de Madrid, Madrid, Spain.
[2] Laboratorio de Muerte Celular y Terapia del Cáncer, Centro de Investigaciones Biológicas (CIB-CSIC), Madrid, Spain.

Edelfosine (ET-18-OCH_3) is an alkylphospholipid with an analogous structure to miltefosine. Both molecules are active against kinetoplastids (*Leishmania* spp., *Trypanosoma cruzi* and *Trypanosoma brucei*). However, its trichomonacidal effect has never been studied. For this purpose, edelfosine has been evaluated in vitro against the common sexually transmitted parasite *Trichomonas vaginalis* following a standardized fluorimetric procedure. The results show an IC_{50}=19.8 μM against metronidazole-sensitive isolates and a remarkable IC_{50}=7.6 μM against the metronidazole-resistant IR78. This enhanced effect against the resistant isolate suggests another possible mode of action in comparison with the reference drug. Moreover, *T. vaginalis* exhibits a different growth rate due to the metabolic modifications according to its resistant trait. These results are in consonance with the trichomonacidal effect observed by other authors using the analog miltefosine against resistant samples, provoking membrane alterations and apoptosis. It is estimated that 2.5–10% of clinical cases of trichomonosis are produced by resistant isolates. The absence of pharmacological alternatives to the unique two 5-nitroimidazole drugs approved by the FDA makes necessary the incorporation of novel trichomonacidal drugs with a different mode of action. Taken together, our results, in consonance with previous reports, suggest the promising use of these alkylphospholipids as an alternative trichomonacidal drug against resistant cases.

NOTES

Examination of Antimicrobial and Cytotoxic Activity of Naphthoquinone Rich Extracts from the Roots of *Onosma visianii* Clem

Milena Dejan Vukić[1], Nenad Vukovic[1], Dejan Baskic[2], Miroslava Kacaniova[3]

[1] *University of Kragujevac, Faculty of Science, Department of Chemistry, Kragujevac, Serbia*
[2] *University of Kragujevac, Faculty of Medical Sciences, Centre for Molecular Medicine and Stem Cell Research, Kragujevac, Serbia*
[3] *Department of Microbiology, Faculty of Biotechnology and Food Science, Slovak University of Agriculture in Nitra, Nitra, Slovakia*

In the present study, five root extracts of *Onosma visianii* Clem were investigated for their in vitro antibacterial and cytotoxic activity. On the basis of developed HPLC-PDA methodology for shikonin derivatives, these plants have proven to be a rich source of naphthoquinones as natural colorants for the food and cosmetic industries. From the obtained results, all investigated root extracts contain acetylshikonin, isobutyrylshikonin and alpha-methylbutyrylshikonin as major compounds. Among examined extracts, the best activity against six Gram-positive bacteria was observed for ethyl acetate extract. Methanol extract showed low activity toward test bacteria. Strong cytotoxic activity was observed for acetone, chloroform and ethyl acetate extracts. Those results indicate that examined extracts may serve for food coloring, with preservative function toward bacteria, and have a beneficial effect in the treatment of cancer.

NOTES

Identification of a Novel Anti-Mycobacterial Series

Esther Porras, Carlos Alemparte

GSK–TB DPU, Parque Tecnológico de Madrid, Spain

Tuberculosis (TB) is the biggest global killer in history. One of the main objectives for fighting TB is to find a shorter treatment and also to target multidrug-resistant (MDR) and extensively drug-resistant XDR strains. Nowadays, finding and developing new compounds that are active against tuberculosis constitutes a main objective for the Diseases of the Developing World (DDW) center of GlaxoSmithKline (GSK) at Tres Cantos. At our site, both target- and cell-based screens have been approached to identify new anti-TB compounds. *Mtb* phenotypic HTS represents the main source of new chemical entities, although the major challenge resides in their successful optimization and the elucidation of their mechanism of action (MoA).

In this work, we will present a new hit (GSK1) from a whole cell phenotypic screen and also Medicinal Chemistry efforts in the Hit Optimization program to overcome the risks associated with the Lead.

NOTES

In Vitro Primary Screening of a Synthetic Series of Chromenoazoldiones against *Trypanosoma cruzi*

Cristina Fonseca-Berzal[1], Paula Morales[2], José A. Escario[1], Nadine Jagerovic[2] and Alicia Gómez-Barrio[1]

[1] *Departamento de Parasitología, Facultad de Farmacia, Universidad Complutense de Madrid, Madrid, Spain.*
[2] *Instituto de Química Médica (IQM), CSIC, Madrid, Spain.*

Similarities between parasites and cancer have prompted parasitologists to take advantage of several approaches enabled by cancer research to identify antiparasitic agents [1]. Quinones generate reactive oxygen species (ROS), which not only results in their antitumor properties, but also in a mechanism for designing antichagasic drugs. Here, a synthetic series of seven chromenoazoldiones previously defined as potential antitumorals [2,3], has been assayed in vitro against *Trypanosoma cruzi* (CL-B5 *lacZ* strain) in a primary screening that evaluates activity over epimastigotes and toxicity on L929 cells [4,5]. Compounds PM199, PM203 and PM401 achieved higher IC_{50} values than that of the reference drug benznidazole (BZ): IC_{50} = 14.45 ± 1.90, 14.84 ± 4.49, 16.01 ± 9.06 and 36.47 ± 4.43 μM (PM199, PM203, PM401 and BZ, respectively). However, their higher cytotoxicity led to a lower selectivity (SI) on epimastigotes: SI_{PM199} = 5.83, SI_{PM203} = 7.03, SI_{PM401} = 5.27 and SI_{BZ} > 7.02. Only two compounds showed no cytotoxicity (LC_{50} > 256 μM) and thus, no derivative was further assayed against intracellular amastigotes. These chromenoazoldiones did not show relevant activity on *T. cruzi*. Their cytotoxicity, probably connected to ROS production in mammalian cells, encourages further optimization to apply them as trypanocidal templates.

References:
1. Oliveira, G. Cancer and parasitic infections: similarities and opportunities for the development of new control tools. *Rev. Soc. Bras. Med. Trop.* **2015**, *47*, 1-2.
2. Morales, P.; Vara, D.; Gómez-Cañas, M. et al. Synthetic cannabinoid quinones: preparation, *in vitro* antiproliferative effects and *in vivo* prostate antitumor activity. *Eur. J. Med. Chem.* **2013**, *70*, 111-119.
3. Morales, P.; Blasco-Benito, S.; Andradas, C. et al. Selective, nontoxic CB2 cannabinoid o-quinone with *in vivo* activity against triple-negative breast cancer. *J. Med. Chem.* **2015**, *58*, 2256-2264.
4. Fonseca-Berzal, C.; Arenas, D.R.M.; Bohórquez, A.R.R. et al. Selective activity of 2,4-diaryl-1,2,3,4 tetrahydroquinolines on *Trypanosoma cruzi* epimastigotes and amastigotes expressing β-galactosidase. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4851-4856.
5. Fonseca-Berzal, C.; Ibáñez-Escribano, A.; Reviriego, F. et al. Antichagasic and trichomonacidal activity of 1-substituted 2-benzyl-5-nitroindazolin-3-ones and 3-alkoxy-2-benzyl-5-nitro-2*H*-indazoles. *Eur. J. Med. Chem*. **2016**, *115*, 295-310.

NOTES

Investigation of In Vitro Antileishmanial Activity of Antimony, Paromomycin and Antimony–Paromomycin Combination on *Leishmania tropica* Promastigotes from an Antimony-Resistant Cutaneous Leishmaniasis Patient from Turkey

Ahmet Özbilgin[1], Alicem Nuraydın[1], Hande İpek[2], İbrahim Çavuş[1], Mehmet Harman[3]

[1]*Department of Parasitology, Faculty of Medicine, Celal Bayar University, Manisa, Turkey*
[2]*Faculty of Medicine, Celal Bayar University, Manisa, Turkey*
[3]*Department of Dermatology, Dicle University, Diyarbakır, Turkey*

Objective: This study aimed to evaluate the potential in vitro anti-leishmanial activities of three different drugs against *Leishmania tropica*: antimony, paromomycin and a combination of them. *Leishmania tropical* was clinically isolated from a cutaneous leishmaniasis patient from Turkey, who underwent antimony treatment four times but did not respond to it.
Methods: The in vitro effects of all agents were studied by using the microdilution method. For this purpose, serial dilutions of the aforementioned agents were prepared in concentrations between 500 µg/mL and 3.90 µg/mL. Afterwards, promastigotes incubated in suitable medium were counted with the hemocytometer and adjusted as having a final concentration of $1x10^7$ cells/mL in wells containing medium+antibiotic. After incubation, live promastigotes were counted with the hemocytometer and inhibitor concentrations (IC50) were determined by comparing with the control that contained no antibiotics.
Results: IC50 values of antimony, paromomycin and antimony–paromomycin combination were found to be 250 µg/mL, 67.5 µg/mL and 7.81 µg/mL, respectively.
Conclusion: As a result, paromomycin was found to be effective against antimony-resistant *L. tropica* promastigotes and antimony–paromomycin combination was found to be even more effective. Thus, these results suggested that antimony–paromomycin combination can be used for the treatment of antimony-resistant Cutaneous Leishmaniasis patients and the combination should be used as the first-line drug.

NOTES

Lipopeptide Antibiotics Derived from Polymyxin B with a Broad Spectrum of Activity: Membrane Interaction

Yolanda Cajal Visa[1], Roser Segovia[2], Angeles Manresa[3], Ariadna Grau-Campistany[4], Francesc Rabanal[2]

[1] Department of Pharmacy, Pharmaceutical Technology and Physical Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona; Institute of Nanoscience and Nanotechnology (IN2UB), University of Barcelona;
[2] Section of Organic Chemistry, Dept. of Inorganic and Organic Chemistry, Faculty of Chemistry
[3] Laboratory of Microbiology, Faculty of Pharmacy and Food Sciences, Barcelona, University of Barcelona.
[4] Department of Pharmacy, Pharmaceutical Technology and Physical Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona

Antimicrobial peptides offer a new class of therapeutic agents to which bacteria may not be able to develop genetic resistance, since they act on the lipid component of the cell membranes [1]. Among these compounds, polymyxin B (PxB) is acquiring new therapeutical relevance and is starting to be considered as a representative of a new class of antibiotics against multiresistant bacteria. PxB and other members of the polymyxin family such as colistin are drugs of last resort to treat Gram-negative multiresistant infections. We have designed new synthetic antimicrobial lipopeptides with Gram-positive and Gram-negative activity derived from the structure of the Gram-negative selective antibiotic PxB [2]. Biophysical studies with model membranes show that the peptides bind to zwitterionic and anionic membranes, but they require the presence of anionic lipids to disrupt the membrane. The inclusion of Arg residues instead of natural Dab favors the insertion in the bacterial lipid membrane and allows passage of the peptides across the bilayer. The presence of (D)Trp favors membrane interaction and confers the molecule intrinsic fluorescence properties that allow the determination of membrane binding. The substitution of Leu by the more flexible NLeu increases the permeabilizing and fusogenic capacity. The new lipopeptides described here are good candidates to become new antimicrobials, although further work needs to be done to ascertain their molecular mechanism of action.

References:

1. Rabanal, F.; Cajal, Y. Recent advances and perspectives in the design and development of polymyxins. *Nat.Prod. Rep.* **2017**, *34,* 886-908.
2. Grau-Campistany, A.; Manresa, A.; Pujol, M. et al. Tryptophan-containing lipopeptide antibiotics derived from polymyxin B with activity against Gram positive and Gram negative bacteria, *Biochem. Biophys. Acta*, **2016**, *1858*, 333-343.

NOTES

Novel Imidazole Derivatives as Antifungal Agents: Synthesis, Biological Evaluation, ADME Prediction and Molecular Docking Studies

Yusuf Özkay[1,2], Derya Osmaniye[1,2], Serkan Levent[1,2], Begüm Nurpelin Sağlık[1,2]

[1] Anadolu University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Eskişehir, Turkey
[2] Anadolu University, Faculty of Pharmacy, Doping and Narcotic Compounds Analysis Laboratory, Eskişehir, Turkey

The incidence of infection from opportunistic and pathogenic fungi has continued to rise in recent years. Azoles are an extensive and comparatively new class of synthetic compounds including imidazoles and triazoles and this group is most commonly applied in clinical treatment [1]. Azoles are administered against C14α-demethylase in the ergosterol pathway [2]. Ergosterol is a principal component of the fungal cell wall, which plays a significant role in membrane fluidity, enzyme activity, cell morphology, membrane permeability and cell cycle progression [3]. On the other hand, a literature review shows that the compounds that include dithiocarbamates have significant antifungal and anti-bacterial effects [4,5].

In light of the above findings, a series of compounds with imidazole and dithiocarbamate scaffolds was designed and synthesized. The structures of the synthesized compounds were elucidated using FT-IR, ^{1}H-NMR, ^{13}C-NMR, and HRMS spectral data. The target compounds were screened for in vitro anticandidal activity against Candida species by broth microdiluation methods. The results of in vitro anti-Candida activity, a docking study and ADME prediction revealed that the newly synthesized compounds have potential anti-Candida activity and evidenced the most active derivative, 5b, which can be further optimized as a lead compound.

References:

1. Iman, M.; Peroomian, T.; Davood, A. et al. Design, Synthesis and Evaluation of New Azoles as Antifungal Agents: A Molecular Hybridization Approach. *Pharm. Chem. J.* **2016,** *49*, 1354-1359.
2. Lupetti, A.; Danesi, R.; Campa, M. et al. Molecular basis of resistance to azole antifungals. *Trends Mol. Med.* **2002**, *8*, 77-81.
3. Jacob, K.S.; Ganguly, S.; Kumar, P. et al. Homology model, molecular dynamics simulation and novel pyrazole analogs design of *Candida albicans* CYP450 lanosterol 14 α-demethylase, a target enzyme for antifungal therapy. *J. Biomol. Struct. Dyn.* **2017**, *35,* 1446-1463.
4. Yurttaş, L.; Özkay, Y.; Duran, M. et al. Synthesis and antimicrobial activity evaluation of new dithiocarbamate derivatives bearing thiazole/benzothiazole rings. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2016**, *191*, 1166-1173.
5. Zou, Y.; Yu, S.; Li, R. et al. Synthesis, antifungal activities and molecular docking studies of novel 2-(2, 4-difluorophenyl)-2-hydroxy-3-(1H-1, 2, 4-triazol-1-yl) propyl dithiocarbamates. *Eur. J. Med. Chem.* **2014**, *74*, 366-374.

NOTES

Preparation of Antimicrobial Nitrogen Heterocycles Using Sustainable Processes

Concepción González-Martín[1], Jorge Juan Cabrera Trujillo[1], Emy André-Joyaux[2], Antonio Herrera[1], Nieves Rodríguez[1]

[1] CSIC Instituto de Productos Naturales y Agrobiologia, Spain
[2] Universität Bern, Bern, Switzerland.

Libraries of compounds containing heteroaromatic rings and other nitrogen heterocycles were prepared from sugars and other readily available substrates using sequential scission-addition processes, which save time and materials with respect to conventional processes. Some of these compounds displayed remarkable antimicrobial activity.

References:
1. Santana, A. G.; Paz, N. R.; Francisco, C. G. et al. Synthesis of Branched Iminosugars through a Hypervalent Iodine(III)-Mediated Radical-Polar Crossover Reaction. *J. Org. Chem.* **2013**, *78,* 7527-7543 and references cited therein.

NOTES

QSAR Analysis of Antibacterial and Antifungal Activity of Novel 2-Morpholinoquinoline Analogs

Strahinja Kovačević, Milica Karadžić, Lidija Jevrić, Sanja Podunavac-Kuzmanović

Faculty of Technology, University of Novi Sad, Serbia

The present study is focused on the chemometric QSAR analysis of antifungal and antibacterial activity of novel 2-morpholinoquinoline analogs and their molecular structure described by in silico molecular descriptors. The results of antifungal activity have taken into account *Aspergillus fumigatus* (MTCC 3008) and *Candida albicans* (MTCC 227), while antibacterial activity included Gram positive bacteria (*Clostridium tetani* MTCC 449, *Streptococcus pneumonia* MTCC 1936 and *Bacillus subtilis* MTCC441) and Gram negative bacteria (*Vibrio cholerae* MTCC 3906, *Salmonella typhi* MTCC 98 and *Escherichia coli* MTCC 443). The experimental results of the antimicrobial analysis of studied compounds have been taken from the literature [1]. In the QSAR modeling the chloramphenicol, ciprofloxacin, ampicillin and norfloxacin were used as the standard antibacterial therapeutics. The QSAR modeling has been carried out on the basis of the in silico molecular descriptors (physico-chemical, lipophilicity, topological and absorption, distribution, metabolism, excretion and toxicity—ADMET descriptors) applying linear and multiple linear regression methods, as well as a cross-validation approach. The obtained high-quality models can be considered useful in prediction of the antifungal and antibacterial activity of not yet synthesized structurally similar compounds as well as a contribution to the development of new antimicrobial agents. The studied compounds have been ranked by the sum of ranking differences (SRD) method on the basis of the reference ranking, which was based on the strongest antibacterial and antifungal activities in order to see which compounds express the most potent antimicrobial activity.

References:
1. Karad, S.C.; Purohit, V.B.; Thummar, R.P.; et al. *J. Med. Chem.* **2017**, 126, 894-909.

NOTES

Synthesis and Antimicrobial Activity of Newly Synthesized 2-((5-(4-(5(6)fluoro-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-1,3,4-oxadiazol-2-yl)thio)-Derivatives

Abdullah Burak Karaduman[1], Ulviye Acar Çevik[2,3], Derya Osmaniye[2, 3], Yusuf Özkay[2,3], Sinem Ilgın[1, 3]

[1] *Department of Pharmaceutical Toxicology, Anadolu University, Eskişehir, Turkey*
[2] *Department of Pharmaceutical Chemistry, Anadolu University, Eskişehir, Turkey*
[3] *Doping and Narcotic Compounds Analysis Laboratory, Anadolu University Eskişehir, Turkey*

Benzimidazole derivatives have a great deal of interest in terms of antimicrobial therapy. Thus, in the present study, new benzimidazole derivatives were obtained to perform antimicrobial activity. The 4-(5(6)fluoro-1*H*-benzo[*d*]imidazol-2-yl)benzoate (1) obtained by 4-fluoro-o-phenylenediamine and methyl 4-formylbenzoate, was reacted with hydrazine hydrate to afford 4-(5(6)fluoro-1*H*-benzo[*d*]imidazol-2-yl)benzohydrazide (2). The reaction of compound 2 with CS_2 in the presence of NaOH gave 5-(4-(5(6)fluoro-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-1,3,4-oxadiazole-2-thiol (3), which was reacted with substituted bromide derivatives to obtain final compounds.

The structures of all the compounds were established on the basis of elemental and spectral analysis. Antimicrobial activities of the compounds against resistant human pathogenic microorganisms were evaluated according to the CLSI methods [1,2]. Final products were tested for their in vitro growth inhibitory activity against human pathogenic *Escherichia coli* (ATCC 35218), *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923), *Pseudomona aeuroginosa* (ATCC 27853), and yeast as *Candida albicans* (ATCC 90028), *Candida glabrata* (ATCC 90030), *Candida krusei* (ATCC 6258), and *Candida parapsilosis* (ATCC 22019). Chloramphenicol and ketoconazole were used as control drugs. The compound 4ı containing 3,4-dihydroxyphenyl moiety in its structure exhibited the highest activity against *Candida krusei* ATCC 6258, *Candida glabrata* ATCC 90030, and *Candida parapsilosis* ATCC 22019. Furthermore, the cytotoxic effects of the synthesized compounds were determined by in vitro activity tests.

References:

1. Clinical and Laboratory Standarts Institue (CLSI). *Methods for dilution antimicrobial sceptibilitytests for bacteria that grow aerobically*, *CLSI M7-A7*, 7th ed.; Clinical and Laboratory Standards Institute: Wayne, USA, 2006.
2. Clinical and Laboratory Standards Institute (CLSI), *Reference Method for Broth Dilution Antifungal SusceptibilityTesting of Yeast, Approved Standard*, *CLSI 27-A3,* 3rd ed.; Clinical and Laboratory Standards Institute: Wayne, USA, 2008.

NOTES

Synthesis, Anticandidal Activity and Molecular Docking Study of Some New Imidazole Derivatives

Begüm Nurpelin Sağlık[1,2], Ayşen Işık[1], Ulviye Acar Çevik[1,2], Yusuf Özkay[1,2], Serkan Levent[1, 2]

[1] *Department of Pharmaceutical Chemistry, Anadolu University, Eskişehir, Turkey*
[2] *Doping and Narcotic Compounds Analysis Laboratory, Anadolu University, Eskişehir, Turkey*

The azole pharmacophore is still regarded as a viable lead structure for the synthesis of more effective antifungal agents [1-3]. In this study, new 2-substituted-*N*-[4-(1*H*-imidazole-1-yl) phenyl] acetamide (5a–5g, 6a–6n) derivatives were synthesized and the antifungal activities of these compounds were evaluated. The synthesized compounds consisted of two novel series of imidazole derivatives containing dithiocarbamate (5a–g) and (benz)azolethiol (6a–6n) side chains that are structurally related to the famous antifungal azole pharmacophore. Their structures were characterized by spectral (IR, ^{1}H NMR, ^{13}C NMR, and MS spectra) analyses. The synthesized compounds were screened for in vitro antifungal activity against pathogenic strains of fungi. Theoretical ADME predictions were calculated for final compounds. A molecular docking study of the most active compound with target 'lanosterol 14α-demethylase' (CYP51) [4] was performed to unravel the mode of antifungal action. Compound 5e, which features imidazole and 4-methoxybenzyl piperazine scaffolds, showed the most promising antifungal activity with a MIC_{50} value of 0.78 ug/mL against *Candida krusei*. The effect of the compound 5e against ergosterol biosynthesis was observed by the LC-MS-MS method, which is based on quantification of the ergosterol level in *C. krusei*. Significant interactions were also observed between compound 5e and 14-α-sterol demethylase. In addition to good antifungal activity, all compounds in the series exhibited a good predicted pharmacokinetics profile.

References:

1. White, T.C.; Marr, K.A.; Bowden, R.A. Clinical, cellular, and molecular factors that contribute to antifungal drug resistance. *Clin. Microbiol. Rev.* **1998**, *11*, 382-402.
2. Shah, J.J.; Khedkar, V.; Coutinho, E.C.; et al. Design, synthesis and evaluation of benzotriazole derivatives as novel antifungal agents. *Bioorg. Med. Chem. Lett.* **2015**, 25, 3730-3737.
3. Wani, M.Y.; Ahmad, A.; Shiekh, R.A.; et al. Imidazole clubbed 1, 3, 4-oxadiazole derivatives as potential antifungal agents. *Bioorg. Med. Chem.* **2015**, 23, 4172-4180.
4. Larissa, M.P.; Thomas, L.P.; Michael, R. Crystal structure of cytochrome P450 14α-sterol demethylase (CYP51) from Mycobacterium tuberculosis in complex with azole inhibitors, *PNAS* **2001**, 98, 3068-3073.

NOTES

Thioridazine Exposed to UV Laser Radiation: A New Approach in Fighting against Infectious Diseases

Tatiana Tozar[1], Viorel Nastasa[1], Marcelica Popa[2], Carmen Chifiriuc[2], Ionut R. Andrei[1], Mihai L. Pascu[1]

[1] National Institute for Laser, Plasma and Radiation Physics, Magurele, Romania
[2] Research Institute of the University of Bucharest, Bucharest, Romania

A major global health concern is the development of multidrug resistance by Gram-positive and Gram-negative bacteria. The high number of antibiotic-resistant pathogens contribute to higher mortality, longer hospital stays, and increased treatment costs. An urgent need for developing new drugs exists. A solution could be phenothiazine derivatives which demonstrated enhanced antimicrobial activity and less toxicity when exposed to UV radiation.
Thioridazine at 2 mg/mL (in ultrapure water) was exposed to a 266 nm laser beam for up to 240 min. The antimicrobial activity was tested in vivo on Gram-positive and Gram-negative bacteria by determining the minimum inhibitory concentration and minimum biofilm eradication concentration. Afterwards, a mixture of photo-products that resulted during irradiation was evaluated by UV-Vis-NIR absorption, Thin Layer Chromatography, Laser Induced Fluorescence and FTIR.
MIC and MBEC values suggest that, during irradiation, new antimicrobial and antibiofilm species are generated. The spectroscopic studies showed the formation of photo-products that depend on laser exposure time intervals and on photo-reactions that occur during irradiation. This method could constitute a fast approach in developing new antimicrobial agents.

NOTES

Trichomonacidal Activity of 3,3'-Diindolylmethane (DIM) Is Additive to Metronidazole (MTZ) In *V*itro, Supporting Future Oral/Topical Use

Alexandra Ibáñez-Escribano[1], Leyre Pernaute Lau[1], Juan José Nogal-Ruiz[1], Alicia Gómez-Barrio[1], Jose Antonio Escario[1], Michael A. Zeligs[2]

[1] Departamento de Parasitología, Facultad de Farmacia, Universidad Complutense de Madrid, Spain.
[2] BioResponse, LLC, Boulder, Colorado, USA.

New, safe, well tolerated, and versatile anti-trichomonal agents for oral and topical use are needed to combat spreading resistance of *Trichomonas vaginalis* to metronidazole (MTZ). Diindolylmethane (DIM) is a non-toxic, cruciferous indole under pharmaceutical development for treatment of cervical and prostatic pre-cancers. Present work reports anti-trichomonal activity of DIM with IC_{50} hundreds of times below the DIM concentration provided in a clinic-ready, sustained-release, vaginal-topical formulation (BR-DIM-VC™2%) which has passed vaginal tolerance testing in rabbits. Present in vitro findings against *T. vaginalis* exhibit additive effects of DIM with MTZ, significantly reducing the IC_{50} for MTZ ($p<0.05$). Combinatorial activity with MTZ was demonstrated using DIM dissolved in DMSO and in a novel self-emulsifying lipid-based formulation, BR-9001, showing a statistically significant enhanced effect of BR-9001 over DIM (DMSO) ($p<0.05$). Improved bio-delivery of DIM from BR-9001 confirmed DIM's concentration-dependent trichomonacidal activity. Performed in triplicate, the anti-parasitic results are: $IC_{50\ DIM\text{-}DMSO}$=91.8 uM, $IC_{50\ BR\text{-}9001}$=30.65 uM*, $IC_{50\ MTZ}$= 2.34 uM, $IC_{50\ MTZ(0.75uM)+DIM(37.5uM)}$ = 1.6 uM* and $IC_{50\ MTZ(0.75uM)+BR9\text{-}001(37.5uM)}$ = 0.8 uM*, *=$p<0.05$. Considering the nonexistent therapeutic alternatives for trichomonosis treatment in patients with hypersensitivity to 5-nitroimidazoles or against resistant cases, the combined use of DIM+MTZ for oral and topical administration provides a promising new therapeutic opportunity.

NOTES

List of Participants

Abu-Yousef, Imad
American University of Sharjah, UAB
iabuyousef@aus.edu

Afonso, Margarida
Technical University of Lisbon, Portugal
margarida_afonso1995@hotmail.com

Albericio, Fernando
University of KwaZulu-Natal, South Africa
albericio@ukzn.ac.za

Almeida, Rita
Technical University of Lisbon, Portugal
ritalmeida1995@gmail.com

Barreto, Maria do Carmo
cE3c / FCT, Azores University, Portugal
maria.cr.barreto@uac.pt

Bolognesi, Maria-Laura
University of Bologna, Italy
marialaura.bolognesi@unibo.it

Boto, Alicia
Institute of Natural Products
and Agrobiology - CSIC, Spain
alicia@ipna.csic.es

Burgio, Noemi
University of Genoa, Italy
nomy_8@hotmail.it

Cajal Visa, Yolanda
University of Barcelona, Spain
ycajal@ub.edu

Chen, Fen'Er
Fudan University, China
rfchen@fudan.edu.cn

Chibale, Kelly
University of Cape Town, South Africa
Kelly.Chibale@uct.ac.za

De Boeck, Benoît
Janssen Research & Development, Belgium
bdboeck@its.jnj.com

Eritja, Ramon
Institute for Advanced Chemistry of
Catalonia (IQAC), CSIC, Spain
ramon.eritja@iqac.csic.es

Feliu, Lidia
LIPPSO - University of Girona, Spain
lidia.feliu@udg.edu

Fichman, Merav
The Hebrew University of Jerusalem, Israel
merav.fichman@mail.huji.ac.il

Fonseca Berzal, Cristina Rosa
Complutense University of Madrid, Spain
crfonseca@pdi.ucm.es

Giorgini, Simone
University of Genoa, Italy
simone.giorgini@gmail.com

Gonzalez Adelantado, Florenci V.
Jaume I University, Spain
fgonzale@uji.es

González-Martín, Concepción
Institute of Natural Products
and Agrobiology - CSIC, Spain
ccgm@ipna.csic.es

Hernández Mesa, Dácil
Institute of Natural Products
and Agrobiology - CSIC, Spain
dacilhernandezmesa@gmail.com

Huang, Zedu
Fudan University, China
huangzedu@fudan.edu.cn

Ibáñez Escribano, Alexandra
Complutense University of Madrid, Spain
alexandraibanez@ucm.es

Ipek, Hande
Celal Bayar University, Turkey
ipekkhande@gmail.com

Jin, Kaijun
Fudan University, China
kjjin14@fudan.edu.cn

Kaplancikli, Zafer
Anadolu University, Turkey
zakaplan@anadolu.edu.tr

Karaduman, Abdullah Burak
Anadolu University, Turkey
abkaraduman@anadolu.edu.tr

Kelly, John
London School of Hygiene and Tropical Medicine, UK
john.kelly@lshtm.ac.uk

Korkut, Büşra
Anadolu University, Turkey
busrakorkut@anadolu.edu.tr

Kovačević, Strahinja
University of Novi Sad, Serbia
strahko@uns.ac.rs

Laleu, Benoît
Medicines for Malaria Venture, Switzerland
laleub@mmv.org

Lavilla, Rodolfo
University of Barcelona, Spain
rlavilla@ub.edu

Levent, Serkan
Anadolu University, Turkey
serkanlevent@anadolu.edu.tr

López-del Rio, Ángela
Mind the Byte S.L., Spain
angela.lopez.delrio@gmail.com

Majdalawieh, Amin
American University of Sharjah, UAE
amajdalawieh@aus.edu

Manresa Presas, M. Ángeles
University of Barcelona, Spain
amanresa@ub.edu

Meng, Ge
Fudan University, China
mgfudan@fudan.edu.cn

Muñoz-Torrero, Diego
IBUB - University of Barcelona, Spain
dmunoztorrero@ub.edu

Mustaqeem, Muhammad
University of Sargodha, Pakistan
mustaqeem@uos.edu.pk

Oliveras, Ángel
LIPPSO – University of Girona, Spain
a.oliveras.rovira@gmail.com

Osmaniye, Derya
Anadolu University, Turkey
dosmaniye@anadolu.edu.tr

Özkay, Yusuf
Anadolu University, Turkey
yozkay@anadolu.edu.tr

Pagès, Jean-Marie
UMR MD1-TMCD2
Aix-Marseille University, France
jean-marie.pages@univ-amu.fr

Paucar-Bernabé, Rocio
University of Navarra, Spain
rpaucar@alumni.unav.es

Peng, Haihui
Fudan University, China
haihui_peng@fudan.edu.cn

Pérez de la Lastra, José Manuel
Institute of Natural Products and Agrobiology – CSIC, Spain
jm.perezdelalastra@csic.es

Pérez García, Arancha
GSK, Spain
arancha.g.perez@gsk.com

Pérez Silanes, Silvia
University of Navarra, Spain
sperez@unav.es

Planas, Marta
LIPPSO - University of Girona, Spain
marta.planas@udg.edu

Pont Masanet, Caterina
IBUB - University of Barcelona, Spain
aitak1989@gmail.com

Porras, Esther
GSK, Spain
esther.d.porras@gsk.com

Rabanal, Francesc
University of Barcelona, Spain
frabanal@ub.edu

Raboisson, Pierre
Janssen Pharmaceutica NV, Belgium
praboiss@its.jnj.com

Ramos de Silva, Anderson
University of Barcelona, Spain
anderson_ramos3@hotmail.com

Sağlık, Begüm Nurpelin
Anadolu University, Turkey
bnsaglik@anadolu.edu.tr

Samaranayake, Lakindu
University of Colombo, Sri Lanka
lakyspk@gmail.com

Sanina, Nataliya
Institute of Problems of Chemical Physics of the Russian Academy of Sciences, Russia
sanina@icp.ac.ru

Sawalha, Hazem
Arab American University, Palestine
hazem.sawalha@aauj.edu

Segovia Laserna, Roser
University of Barcelona, Spain
rosersegovia@ub.edu

Serra, Patricia
University of Lisbon, Portugal
patriciafaserra@gmail.com

Solé Solé, Judith
University of Barcelona, Spain
judsol@outlook.com

Tozar, Tatiana
National Institute for Laser, Plasma and Radiation Physics, Romania
tatiana.alexandru@inflpr.ro

Trabocchi, Andrea
University of Florence, Italy
andrea.trabocchi@unifi.it

Uliassi, Elisa
University of Bologna, Italy
elisa.uliassi3@unibo.it

Viñas, Miguel
University of Barcelona, Spain
mvinyas@ub.edu

Vukić, Milena
University of Kragujevac, Serbia
milena.vukic@kg.ac.rs

Wu, Yan
Fudan University, China
yanw@fudan.edu.cn

Zampieri, Daniele
University of Trieste, Italy
dzampieri@units.it

Acknowledgments

Organizer

MDPI Academic Open Access Publishing since 1996

Conference Sponsoring Journals

molecules www.mdpi.com/journal/molecules

Tropical Medicine and Infectious Disease http://www.mdpi.com/journal/tropicalmed

pharmaceuticals http://www.mdpi.com/journal/pharmaceuticals

Media Partners and Patronage

BarcelonaTurisme Convention Bureau

Universitat de Barcelona

TECHNOLOGY NETWORKS

medGadget