“Biomedicinal Chemistry and Drug Research” at CICS-UBI: From drug discovery to the development of novel pharmaceutical formulations

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Biomedicinal Chemistry and Drug Research (BCDR) group | Main Aims

To characterize the chemical composition, bioactivity and medicinal application of herbal products and natural mineral waters.

To design, synthesize and assess the bioactivity of small molecules.

To study microbial ecology, epidemiology, virulence and resistance.

To evaluate and improve the use of medicines in different clinical settings.

To develop pharmaceutical formulations and perform pharmacodynamic and pharmacokinetic-based studies.

To develop bioanalytical methods for identification and quantification of drugs, and other compounds in food, biological samples and herbal extracts.

To evaluate and improve the use of medicines in different clinical settings.
Biomedicinal Chemistry and Drug Research (BCDR) group | Main Research Lines

Main Research Lines:

1) Obtaining, characterizing, evaluating of natural products, and their application to the development of innovative products;

2) Discovery of synthetic new drug candidates and development of novel pharmaceutical formulations;

This communication intends to focus on ongoing or recently developed works related to the second line of research, which uses different models, from *in silico* to *in vivo*, and specific analytical methods, developed to support these studies.
Biomedicinal Chemistry and Drug Research (BCDR) group

Discovery of synthetic new drug candidates and development of novel pharmaceutical formulations;

**DISCOVERY OF NEW ANTICONVULSANT COMPOUNDS FROM CHEMICAL DIVERSITY**

**Virtual High Throughput Screening (HTS)**

- Number of candidates
- Candidate information
- Tools complexity
- Specificity

**Number of candidates**

- 11,586,640 non reactive and in stock compounds (ZINC15)
- 6,175,762 leadlike compounds
- 2,013,851 "CNS ready" compounds with acceptable ADMET properties
- 1,985,585 unique 2D molecular representations
- 608,617 compounds containing relevant substructures
- 1,246 compounds with putative anticonvulsant activity
- 50 commercially available candidates considered

**Candidate information**

- MOE filtering of duplicates, non-leadlike, reactive/mutagenic, MW ≤ 150 Da, rare elements and rotatable bonds ≤ 7
- CNS-MPO calculation and selection of compounds with SCORE ≥ 5 (maximum score of 6)
- Removal of isomers containing compounds and stereoisomers
- Privileged-substructure searching using 95 Klekowske-Roth fragments highly associated with anticonvulsant activity
- Fingerprint similarity search and EANNIE models prediction of activity, respecting the applicability domains
- Ranking, clustering and selection of representatives

**Tools complexity**

**Specificity**

Novel compounds with interesting properties were obtained

6-Hz Seizure model at 44 mA (M)
Maximal electroshock seizure test (M)
Motor impairment by Rotarod (M) [Screening]
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Discovery of synthetic new drug candidates and development of novel pharmaceutical formulations;

Three main unsolved medical problems of society:

- **Cancer**
- **Infectious diseases** (mainly MDR strains)
- **Metabolic problem**, (including uric acid accumulation)

Development of new drug candidates - including *barbituric and thiobarbituric acid derivatives*.

Wide range of biological activities!
1,3,5-trisubstituted barbiturates and thiobarbiturates were prepared and their activity as xanthine oxidase inhibitors, antioxidants, antibacterial agents and as anti-proliferative compounds was evaluated \textit{in vitro}:
Biomedicinal Chemistry and Drug Research (BCDR) group

Discovery of synthetic new drug candidates and development of novel pharmaceutical formulations;

Thirty-five compounds synthesized in moderate to excellent yields:

\[ \text{IC}_{50} = 13.3 \text{ μM}, \text{MCF-7 cells} \]

low cytotoxicity against the non-tumoral NHDF cells
**Biomedicinal Chemistry and Drug Research (BCDR) group**

**Discovery of synthetic new drug candidates and development of novel pharmaceutical formulations;**

**Thirty-five** compounds synthesized in moderate to excellent yields:

Novel compound classes bearing:

- xanthine oxidase inhibitory activity,
- antioxidant effects
- anti-proliferative action
- inhibition of the growth of *Acinetobacter baumannii*

Can be starting points to further:

- pharmacological and toxicological studies;
- structural improvements to improve their potency and selectivity.

**Development of future lead compounds!**
Biomedicinal Chemistry and Drug Research (BCDR) group

Discovery of synthetic new drug candidates and development of novel pharmaceutical formulations;

**Acinetobacter baumannii** - an important nosocomial pathogen:

- infectious outbreaks caused by multidrug-resistant strains increasing worldwide.

New antibacterial treatments for multidrug-resistant A. baumannii strains are clearly needed.

A series of 5-hydrazinylethylidene.pyrimidines were synthesized and evaluated against sensitive and multidrug-resistant *A. baumannii* strains:

5-Hydrazinylethylidene.pyrimidines effective against multidrug-resistant *Acinetobacter baumannii*: Synthesis and *in vitro* biological evaluation of antibacterial, radical scavenging and cytotoxic activities

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Discovery of synthetic new drug candidates and development of novel pharmaceutical formulations;

Chemical synthesis, taking into account the previously reported anti-A. baumannii effects of 5-hydrazinylethylidenepyrimidines and SAR data:

Relevant antibacterial effects against A. baumannii, including two MDR A. baumannii isolates (AcB 13/10 and AcB 73/10) resistant to several antibiotics:

Compounds 3a and 3c: similar antibacterial activity in both resistant strains
Discovery of synthetic new drug candidates and development of novel pharmaceutical formulations;

5-Hydrazinylethylidenepyrimidines 3a and 3c demonstrated bacteriostatic activity:

Studies on combinations with known antibiotic classes (checkerboard assay) – additive effect:

- against the AcB 13/10 strain in the combinations 3a+gentamicin, 3c+gentamicin, 3a+rifampicin, 3a+polymyxin B and 3c+polymyxin B
- against the AcB 73/10 strain in the combinations: 3a+rifampicin and 3c+rifampicin

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<tr>
<th>Fractional inhibitory concentration indices (FICI) of 3a and 3c combined with gentamicin, polymyxin B or rifampicin against two different strains of MDR A. baumannii.</th>
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<tbody>
<tr>
<td><strong>FICI</strong></td>
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<tr>
<td>3a</td>
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<tr>
<td>Gentamicin</td>
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<tr>
<td>A. baumannii AcB 13/10</td>
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<tr>
<td>A. baumannii AcB 73/10</td>
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Discovery of synthetic new drug candidates and development of novel pharmaceutical formulations;

Further in vitro studies:

Xanthine oxidase inhibition and radical scavenging activity, at 30 µM:

Cytotoxicity in NHDF cells (30 µM, 72h, MTT assay):

Compound 3a has important and selective effects against sensitive and multidrug-resistant A. baumannii strains!
Biomedicinal Chemistry and Drug Research (BCDR) group

Discovery of synthetic new drug candidates and development of novel pharmaceutical formulations;

- Intranasal administration
- Direct nose-to-brain transport (neuronal pathway)

↑ Efficacy of treatment of neurodegenerative diseases
↓ Systemic side effects
Discovery of synthetic new drug candidates and development of novel pharmaceutical formulations;

Phenytoin
- Antiepileptic drug
- Low aqueous solubility

Fosphenytoin
- Phosphate ester prodrug
- High aqueous solubility

Pires et al. International of Pharmaceutics, accepted for publication
Biomedicinal Chemistry and Drug Research (BCDR) group

Discovery of synthetic new drug candidates and development of novel pharmaceutical formulations;

Phenytoin (low aqueous solubility) + Fosphenytoin (high aqueous solubility) → Nanoemulsions with immediate or prolonged drug release profiles

Phenytoin - Antiepileptic drug
- Low aqueous solubility

Fosphenytoin - Phosphate ester prodrug
- High aqueous solubility

Phenytoin + Fosphenytoin microemulsion
vs.
Fosphenytoin microemulsion

Discovery of synthetic new drug candidates and development of novel pharmaceutical formulations;
BCDR
Biomedical Chemistry and Drug Research

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