I.I.21: Streamlining Anti-Inflammatory Lead Discovery by Aligning *in silico* and *in vivo* Screening. Prediction, Synthesis and Biological Assay of Novel Metal Based Chelates

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Inflammation: a major life-threatening human condition

➤ Anti-inflammatory drugs (AIDs) have an important clinical role in the control of a response and resolution of excessive acute or chronic inflammatory processes.

➤ Existing AIDs exhibit severe undesired side effects among other limitations
➤ The *ToMoCoMD–CARDD* (*TO*pological *MO*lecular *COM*puter Design-*C*omputer *A*ided *R*ational *D*rug *D*esign) was used in this research for new and safer AIDs

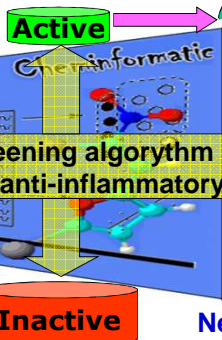## ToMoCoMD–CARDD as strategy for the discovery of a new antiinflammatory chemotype

Molecular entities: Training set, Test set and NMEs

General algorithm used for designing the training and test sets throughout *k*-MCA:

Active → In vivo testing of high-scoring molecules

Sreening algorithm P = anti-inflammatory

Inactive

New anti-inflammatory chemotypes

➤ Non stochastic and stochastic atom-based quadratic fingerprinting were used to codify the antiinflammatory-related chemical structure information from a comprehensive data set of 1213 organic compounds (587 Ais and 626 non-Ais) having a great structural variability.
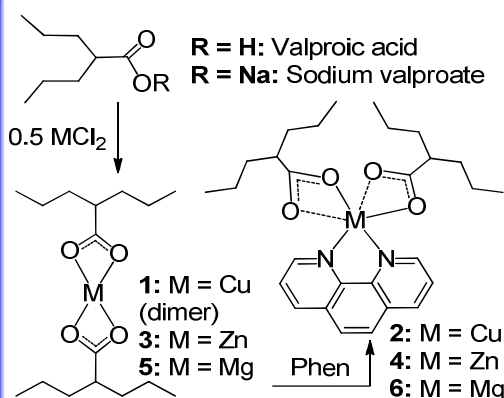➤ The *ToMoCoMD–CARDD* models were best in predicting antiinflammatory activity when compared with six of the most recent models reported so far.

➤ The fusion model was used for the identification of novel AI compounds using virtual screening of 200 molecules available in our in-house library. Of these, six metal-based complexes were selected, synthesized and tested in an *in vivo* anti-inflammatory test using *Danio r.* (zebrafish) larvae.
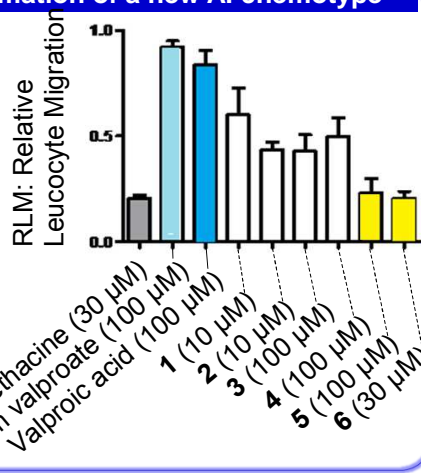
Synthesis of the chelates

R = H: Valproic acid
R = Na: Sodium valproate

0.5 MCl₂

1: M = Cu (dimer)
3: M = Zn
5: M = Mg

Phen

2: M = Cu
4: M = Zn
6: M = Mg

Zebrafish model for AI evaluation : Confirmation of a new AI chemotype

➤The biological evaluation was assayed by using an in vivo model of acute inflammation: Complete tail transection of transgenic zebrafish *fli*-1 EGFP larvae from 4 dpf and 10 µM LPS caused leukocyte migration to the wound. 10 larvae per well were placed using 10 µM, 30 µM and 100 µM of test compound in the medium. Fixed larvae were stained post 20h incubation and leukocytes numbered (in triplicate)

RLM: Relative Leucocyte Migration

Indomethacine (30 µM)
Sodium valproate (100 µM)
Valproic acid (100 µM)
1 (10 µM)
2 (10 µM)
3 (100 µM)
4 (100 µM)
5 (100 µM)
6 (30 µM)

1. Y. Marrero-Ponce, D. Siverio-Mota, M. Galvez-Llompart et al. *Eur. J. Med. Chem.* **2011**, *46*, 5736. **2.** F. Dumas, M. Sylla-Iyarreta Veitia, G. Morgant PCT/FR2009/051077. **3.** M. Sylla-Iyarreta Veitía, F. Dumas, G. Morgant, J.R.J. Sorenson, Y. Frapart, A. Tomas, *Biochimie*, **2009**, *91*, I286. **4.** Zon L.I., Peterson R.T. *Nat Rev Drug Discov* **2005**, *4*, 35. **5**. D. Siverio-Mota, M. Sylla-Iyarreta-Veitía, F. Dumas, Y. Herrera Pis, F. Pérez-Giménez, A. D. Crawford, P. de Witte, F. Torrens, Y. Marrero-Ponce, *revision.*

Conclusion & perspectives

➤ These results offer an attractive possibility to obtain new anti-inflammatory compounds by using ensemble LDA-assisted QSAR-classifier models, thereby significantly reducing the number of synthesized and tested compounds.
➤ The present study indicates that magnesium-valproic acid complexes 5 and 6 may represent an important therapeutic alternative for the treatment of inflammatory conditions. Work is in progress to develop these compounds.