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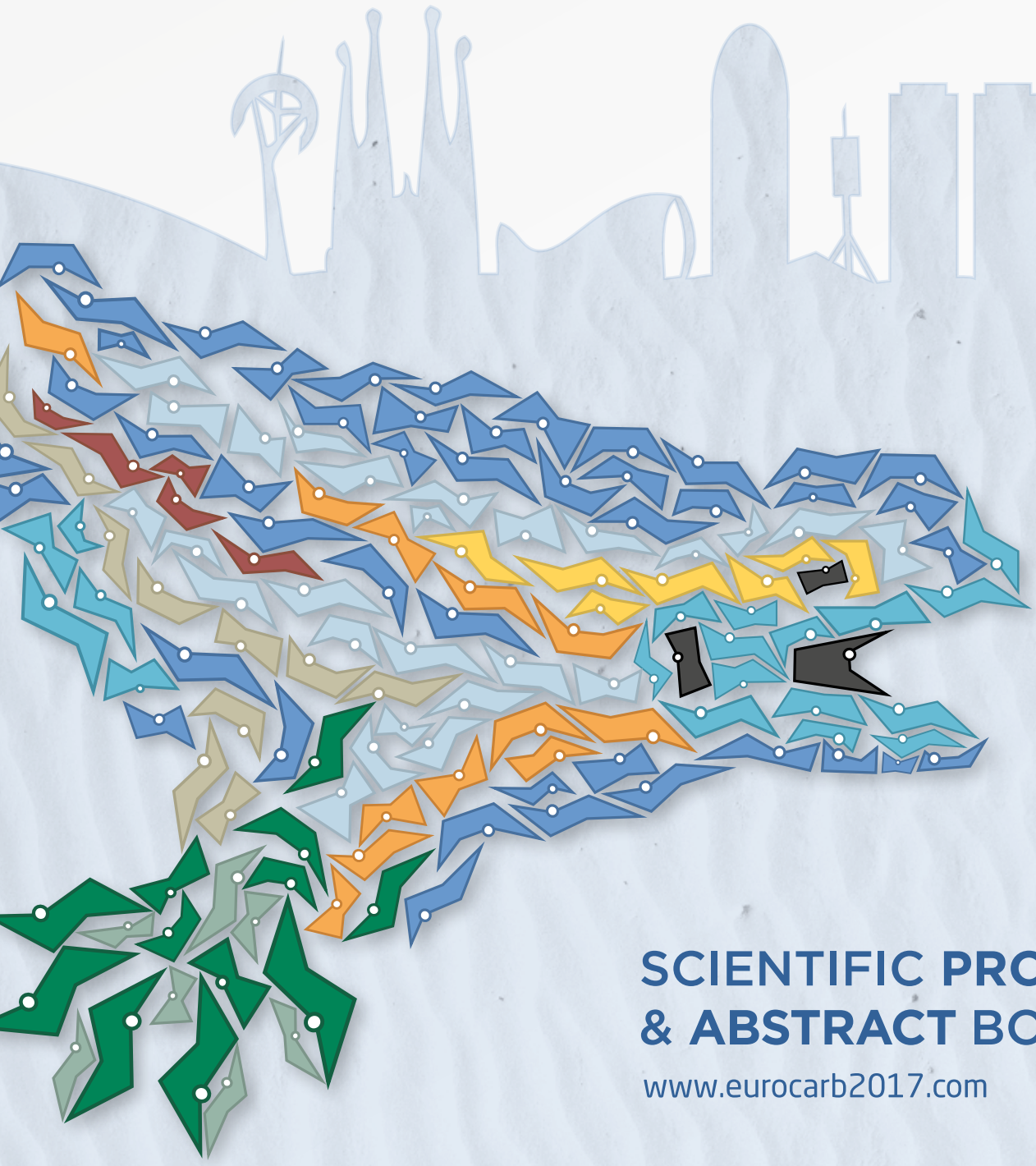

SCIENTIFIC PROGRAM & ABSTRACT BOOK

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AMINOGLYCOSIDES-RNA INTERACTION: MOLECULAR BASIS AND DESIGN OF NEW LIGANDS

Ester Jiménez-Moreno[1] and Juan Luis Asensio[2]

[1] Department of Chemistry, University of Cambridge, Lensfield Road, CB2 1EW Cambridge, United Kingdom
[2] Departamento de Química Bio-orgánica, Instituto de Química Orgánica General (CSIC), C/ Juan de la Cierva 3, 28006 Madrid (Spain).
e-mail: ej306@cam.ac.uk

Aminoglycosides are antibiotics of oligosaccharidic nature widely employed in clinics. They constitute, in turn, one of most important families of RNA ligands, being able to recognize specifically a great variety of viral or bacterial targets of biological relevance. Indeed, from a chemical-biology perspective, these compounds can be considered privileged architectures for the development of high affinity polyamine RNA ligands. Regarding their antibiotic activity, the emergence and dissemination of bacteria resistance phenomena has conferred to the search of new active compounds a character of urgency in the recent years.

Unfortunately, despite the efforts made within this field during the last 20 years, the progress obtained to date can be described as modest. In our opinion, there are two main reasons that have obstructed the development of new compounds with novel activities. On the one hand, from a fundamental perspective, our comprehension of the intermolecular forces that determine the affinity and selectivity of the RNA/ligand interaction is still limited. On the other hand, aminoglycoside synthesis is inherently difficult, which has supposed a considerable obstacle to chemical-biology efforts. In particular, the high polarity and structural complexity of these compounds, together with the presence of a large number of chemically equivalent positions, make the preparation of new derivatives a considerable synthetic challenge.

Here, we will address ways to overcome both limitations by employing new approaches based on dynamic combinatorial chemistry and NMR. It will be discussed the development of an experimental study of CH/π interactions in water that involved the design and synthesis of several compound libraries and the quantification of the stability of more than 100 complexes employing a dynamic combinatorial approach.[1] It will also be discussed the design of a novel methodology for the optimization of polyamine RNA ligands based on aminoglycosides using a combination of isotopic labelling and NMR techniques.[2]

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[2] (a) Jiménez-Moreno, E.; Gómez-Pinto, I.; Corzana, F.; Santana, A. G.; Revuelta, J.; Bastida, A.; Jiménez-Barbero, J.; González, C. and Asensio, J. L. Chemical Interrogation of Drug/RNA Complexes: From Chemical Reactivity to Drug Design. *Angew. Chem. Int. Ed.* **2013**, *52*, 3148–3151. (b) Jiménez-Moreno, E.; Montalvillo-Jiménez, L.; Gómez, A. M.; Jiménez-Osés, G.; Corzana, F.; Bastida, A.; Jimenez-Barbero, J.; Cañada F. J; Gomez-Pinto, I.; González, C. and Asensio, J. L. Finding the Right Candidate for the Right Position: A Fast NMR-assisted Combinatorial Method for Optimizing Nucleic Acids Binders. *J. Am. Chem. Soc.,* **2016**, *138*, 6463–6474