Patented molecules that counteract the effect of the most common anticoagulant drug

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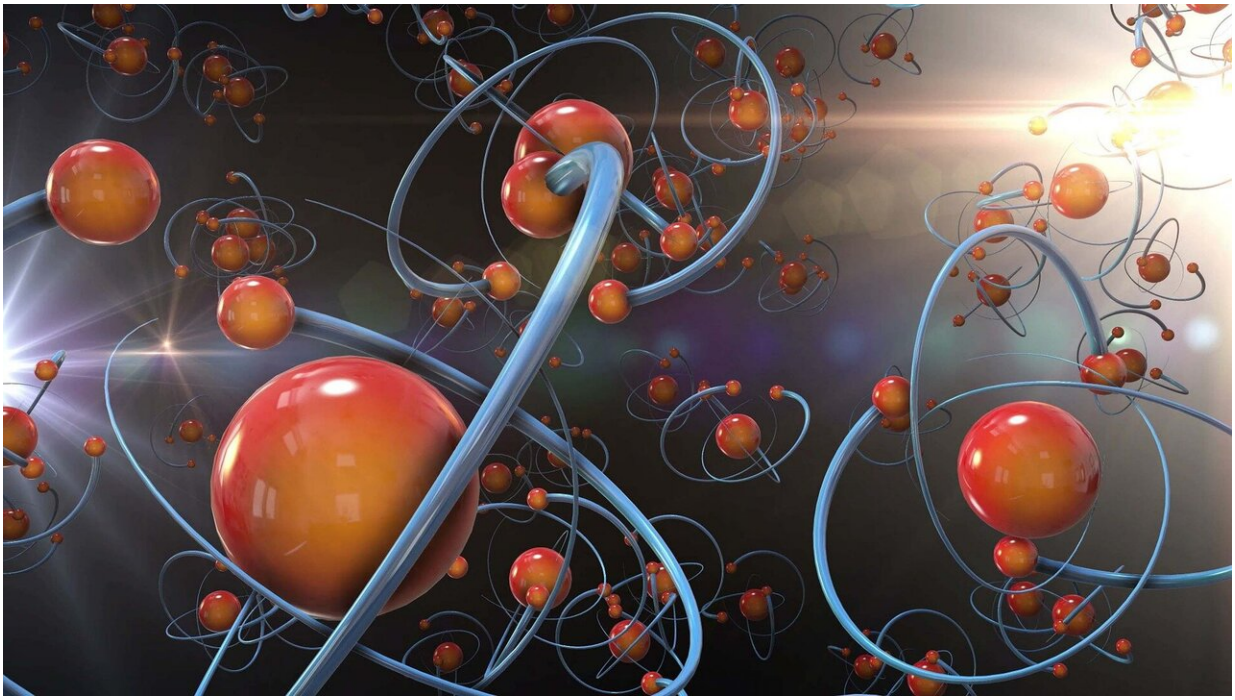

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A study performed by researchers from the Institute for Advanced Chemistry of Catalonia (IQAC-CSIC) from the Spanish National Research Council (CSIC) has discovered and synthesized several molecules that inhibit the effect of the most common anticoagulant drug. This drug is very useful for treating patients at risk of thrombi, but on many occasions it is essential to block its action when these patients face

surgical interventions to avoid uncontrolled bleeding. Two of these molecules have been tested, with very good results, in assays with mice, which could be the first step to design possible drugs. These results have been patented and published in *The Journal of Medicinal Chemistry* (*ACS*).

The proof of concept was published in 2018 as a hot paper in the journal *Angewandte Chemie International Edition*, in which the researchers used Dynamic Combinatorial Chemistry (DCC) systems and achieved a simple molecule that inhibited in vitro the effect of heparin, the most widely used anticoagulant drug. In this work, the team led by Ignacio Alfonso, from the Institute for Advanced Chemistry of Catalonia, has used the same methodology for a broader screening, which has led them to discover molecules with greater potential that have been tested in ex vivo and in vivo with mice. "Coagulation tests with mice show that the optimized molecules are powerful antidotes with potential use as heparin reversal drugs," explains the researcher.

Heparin is widely used in clinical, mainly as an anticoagulant, but also as an antiviral and anticancer agent. In addition, its use has been revitalized even more with the covid-19 pandemic, since it is currently being used as a preventive treatment for clots produced in coronavirus patients and pregnant women. "Although it is one of the most common anticoagulant drugs, it is not free of dangers, and it is essential to have an efficient and varied battery of antidotes," says Alfonso.

"Heparin treatment is very common in patients at risk of blood clots. However, in some cases there are allergic reactions or overdose, which cause the appearance of significant bruising or even uncontrolled bleeding," highlights the researcher. "This is especially critical in patients under heparin treatment who need urgent or unexpected surgery (for example, after severe trauma or a cardiovascular accident). In these cases, the inhibition of circulating heparin in the bloodstream is essential

to avoid complications due to excessive bleeding," adds Alfonso.

Protamine sulfate is currently the antidote that exists to neutralize the action of heparin, but it is a high molecular weight drug, so it can have disadvantages. To date, there is no small molecule on the market that inhibits the anticoagulant effect of heparin. "The search for heparin antidotes based on small molecules continues to be a challenge due to the physicochemical properties of this anionic polysaccharide," says Alfonso.

In this work, the methodology based on dynamic combinatorial chemistry has been used again, which combines the selection, identification and preparation of molecules for a specific application in a single process, accelerating the development of new functional compounds. The limited structural information and the heterogeneity of the heparin molecule make it a good candidate as a model in dynamic combinatorial chemistry, since this methodology does not require detailed knowledge of the structure of the target molecule.

"The results obtained from this research underline the success of this methodology. In addition, an excellent correlation between screening results and heparin inhibition has been found with in vitro enzymatic assays, from which a small collection of molecules with good activity was obtained. From this battery of molecules, two of them showed significantly better in vitro activities than those obtained in 2018, and therefore, were tested in vivo, obtaining excellent results," explains the researcher. "This study represents a definitive validation of our approach," Alfonso concludes.

Therefore, dynamic combinatorial chemistry methodology proves to be a very powerful tool for discovering new milestones in future drug development where conventional approaches have found it very difficult to succeed.

More information: Daniel Carbajo et al, Dynamic Combinatorial Optimization of In Vitro and In Vivo Heparin Antidotes, *Journal of Medicinal Chemistry* (2022). DOI: 10.1021/acs.jmedchem.1c02054