Chemists propose new approach to the synthesis of ABCD ring system of alpkinidine

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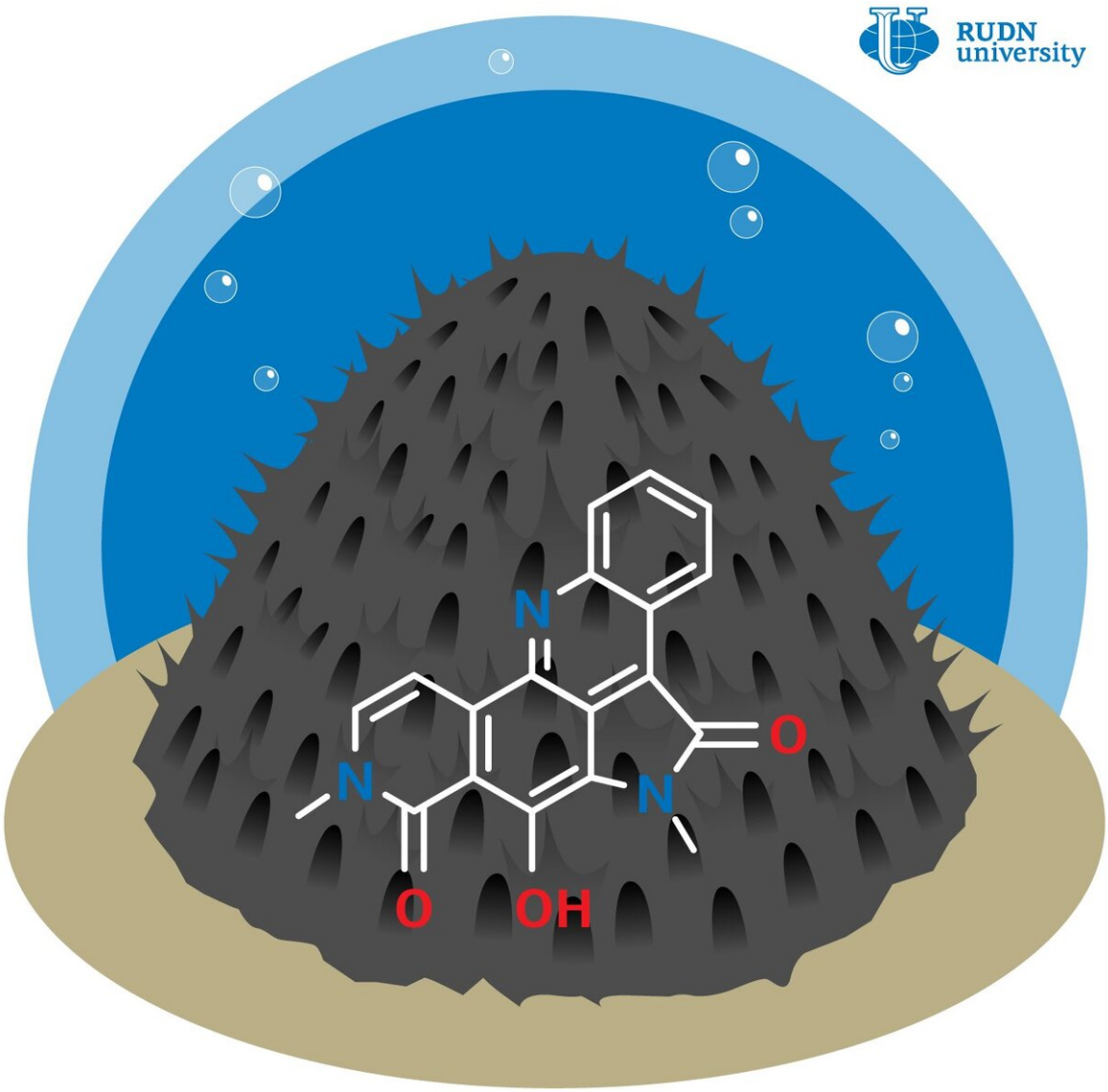

Credit: RUDN University

RUDN University chemists, together with Indian colleagues from Goa University, have synthesized an analog of alkaloid of alpkinidine, a substance with a signified cytotoxic effect. Before the team's research, there was no convenient way to synthesize such heterocycles. The authors were able to obtain an analog of alpkinidine using the Negishi reaction as a key stage (a palladium-catalyzed combination of aryl halides with organozincs) followed by annelation (completion) of an additional cycle to the resulting heterocyclic framework. The method could potentially become the basis for a scheme of the synthesis of alpkinidine. The article is published in *ChemistrySelect*.

Alpkinidine is a naturally occurring purple substance obtained from the sea sponge Xestospongia cf. carbonaria. A specific feature of its structure is the presence of a conjugated ABCDE five-ring system. Alpkinidine is not yet well studied in contrast to closely structurally related amphimedine and neoamphimedine. These substances are well-known for their antiviral, antiparasitic, antifungal and bactericidal activity. It is also known that neoamphimedine can show selective cytotoxicity to the cell lines of solid tumors. Neoamphimedine undergoes preclinical trials and could be an effective anticancer drug in the future.

The antitumor effect of neoamphimedine is due to its inhibitory effect on DNA topoisomerase—an enzyme that is responsible for regulating the topology of DNA. The development of anti-cancer drugs—topoisomerase inhibitors—is a promising field in pharmacology, since compounds with similar inhibitory properties show a very strong antitumor effect. Most of them are not used in clinical practice because of the strong toxic effect on healthy cells or unpredictable side effects of

therapy, so scientists are actively searching for analogs with similar useful properties and without a negative effect on the human body.

Alpkinidine is similar in structure to neoamphimedine, so it is assumed that it may demonstrate a similar range of biological properties, including powerful antitumor activity. However, simple approaches to the complete synthesis of this substance have not been developed previously. Synthesis of similar analogues in structure would help in the development of an effective scheme for the synthesis of alpkinidine.

Fedor Zubkov, Ph.D. in Chemistry, associate professor of the Department of Organic Chemistry of RUDN University, participated in planning the synthesis of an analog of alpkinidine and thus, together with scientists from the Goa University, proposed a new approach to the synthesis of the ABCD ring system of alpkinidine.

Chemists replaced the pyridine E-ring of a natural alkaloid with a benzene ring. At the same time, the system of five cycles remained conjugated so that the biological properties characteristic of alpkinidine were preserved. The synthesis of the simplified analog of alpkinidine was carried out in several stages. Using the Negishi reaction, the chemists obtained an intermediate compound with a yield of 94 percent. Then it was treated with sodium ethoxide and then using the alkylation of the nitrogen atom, the target analog of alpkinidine was obtained with an yield of 88 percent.

Thus, in the published research, a fundamentally new approach to the complete synthesis of compounds with the ABCD ring system of alpkinidine was developed on the basis of the synthesis of an analog of alpkinidine. In the future, scientists plan to use the developed method for the synthesis of alpkinidine. In the absence of negative effects on the human body, medicines based on it can become one of the powerful tools in the anticancer therapy.

More information: Prajesh S. Volvoikar et al. A Concise Approach for the Synthesis of the ABCD Ring System of Alpkinidine, *ChemistrySelect* (2019). DOI: 10.1002/slct.201900357