# An update on natural products with carbonic anhydrase inhibitory activity

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Carbon (C) is essential in biology as it forms up to four bonds per atom in an endless variety of complex organic molecules, which are the basis of living cells and viruses (DNA, RNA, proteins, etc.). In biology the carbon cycle is mainly regulated by the hydration of CO2.

Such a reaction is however too slow to meet the physiological needs (pH homeostasis, respiration, bone calcification, tumorigenesis and progression, gluconeogenesis, lipogenesis, ureagenesis and pathogenic switches in microorganisms). This is why all living organisms on earth have developed efficient enzymes, named the carbonic anhydrases (CAs, EC 4.2.1.1), speeding up the reaction by 10,000 times. They represent a typical example of enzymatic convergent evolution, and six genetically unrelated families have been reported so far.

Karioti et al., in their research article on natural and semi-synthetic CA inhibitors (or CAIs) recently published in Curr Pharm Des. 2016; 22; 1570-9, examine the mechanisms of CAI action at the molecular level. Natural products (NPs) represent an excellent source of scaffolds in terms of diversity, specificity and binding efficiency with biological targets, such as the CAs. To date, coumarins are the main NP classes acting as CA modulators.[1, 2] Other NPs include naturally occurring phenols, polyphenols, polyamines and terpenes.

The paper presents a systematic and comprehensive overview of each NP group acting as CAI and their mechanisms of action at molecular level. On the whole, this study represents a valid starting point for

approaching new chemotypes present in NPs which have not yet been adequately explored.

Prof. Supuran's research team is involved in several projects related to CA inhibitors as antiglaucoma, antitumor/antimetastatic, antiobesity/antiepileptic and antineuropathic pain agents. Their studies reveal that several different human enzyme isoforms are involved in CA inhibition and this explains why the pharmacology of the CA inhibitors is so complex. For instance, the antiglaucoma agents target isoforms CA II and XII; the antitumor/antimetastatic agents target isoforms CA IX and XII; the anti-obesity agents target the mitochondrial isoforms CA VA and VB, the antiepileptics are believed to target CA II, VII and XIV. Supurun's team also researches CAs in other organisms to learn more about potential CAI targets.

While synthetic sulfonamides have been introduced nearly 70 years ago as antimicrobial agents, the sulfonamide CAI SLC-0111 (discovered by two of the authors of the Curr Pharm Des paper discussed here) entered Phase I clinical trials for the treatment of solid tumors only recently in 2014. Supuran hopes his team can find adequate non-toxic CAIs which can better help patients suffering from serious ailments.

**More information:** Anastasia Karioti et al, An Update on Natural Products with Carbonic Anhydrase Inhibitory Activity, *Current Pharmaceutical Design* (2016). DOI: 10.2174/1381612822666151211094235

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