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Details including Project Title

Natural product hybrids of Withaferin-A as NF-κB inhibitors via 1,3 dipolar cycloaddition reaction: Experimental and computational approach towards their anti-cancer/ inflammatory activities.

Project summary

Natural products play an important role in the development of drugs, especially for the treatment of infections, cancer and immunosuppressant. The number of natural products is limited but millions of hybrids as combinations of parts of different natural products can be prepared. This new approach seems to be very promising in the development of leads for both medicinal and agrochemical applications, as the bioactivity of several new hybrids exceeds that of the parent compounds. The advantage of this concept over a combinatorial chemistry approach is the high diversity and the inherent biological activity of the hybrids.

Deregulation of NF-κB activity is often observed and can lead to chronic inflammatory diseases as well as cancer. Blocking NF-κB can cause tumour cells to stop proliferating, to die, or to become more sensitive to the action of anti-tumour agents. Thus, NF-κB is the subject of much active research as a target for anti-cancer therapy. Various research concepts focus on the development of therapeutics that targets the NF-κB activation pathway. Suppression of NF-κB not only limits the proliferation of cancer cells but also a key player in the inflammatory response. Hence methods of inhibiting NF-κB signaling have potential therapeutic application in cancer and inflammatory diseases.

Many natural products that have been promoted to have anti-cancer and anti-inflammatory activity have also been shown to inhibit NF-κB. One such concept is with withaferin-A (WA), a poly functional steroidal lactone based on ergostane framework, has made WA work as an antiangiogenic compound by inhibiting both Sp1 and NF-κB transcription factor activity. In a plethora of reports described the NF-kB inhibiting, anti-inflammatory capacity of withaferin- A, either in vitro as well as in vivo and out of 46,000 small molecular inhibitors withaferin-A was reported as best inhibitor.

Isoxazolidines and spirooxindole scaffold are of great interest in modern organic, medicinal, and natural product chemistry. This type of framework has been found as a core structure of

many alkaloids with promising pharmacological activity like antiviral, antibiotic, local anaesthetics, anti-amnestic, anti-stress activities, antitumoural and inhibitors of human NK-1 receptor etc, such as pyrinodemin A, aerothionin, Subereamolline A, horsfiline, gelsemine, mitraphylline, spirotryprotatins A, B, and others. The [3+2] cycloaddition reaction of azomethine yilide/ nitrones with alkenes is a powerful synthetic method applied for the synthesis of isoxazolidines and Spirooxindole. I contemplated to prepare the natural product hybrids containing withaferin-A and isoxazolidine/ pyrrolizidino/ thiapyrrolizidino spiro-oxinddolo/ acenapthyleno ring system/ via 1,3-Dipolar azomethine yilide/ nitrone cycoaddion. I presume the advantage of this concept over a combinatorial chemistry approach would be the high diversity and the inherent biological activity of the hybrids.