Research & Reviews: Journal of Pharmaceutical Analysis

Extended Abstract
Vol. 8, Iss. 3
2019

MedChem & CADD 2016: Computer analysis of structure-activity relationships of the compounds of diterpenoid nature

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Diterpenoid alkaloids (DA) of different structural types, isolated from plant of the genus Aconitum, Delphinium and Consolida, - the most suitable candidates to find among them substance with antispasmodic action. We investigated spasmogenic activity of 82 compounds. C19 and C18 diterpenoid alkaloids have been investigated including types of aconitine, likoktonin, lappaconitin, lactone-containing alkaloids geteratizin type, C20 diterpenoid alkaloids napellin and denudatin types with their derivatives. Antispasmodic or spasmogenic effect of compounds studied in vitro experiments on isolated segments of the small intestine of rats and rabbits. The effect of DA on the smooth muscles of the small intestine of rats and rabbits can be divided into three groups:1) alkaloids, not significantly affecting the intestinal smooth muscle at concentrations up to 200mcM; 2) compounds having spazmogenic action, increase the tone, the frequency and amplitude of spontaneous contractions, and in high concentrations cause spasm of smooth muscle) alkaloids having myotropic antispasmodic effect, and lowering the tone, reducing the amplitude and preventing and relieving spasms caused by barium chloride, acetylcholine, and the compounds of mezakonitin, aconitine types. We designed optimal predictive models for diterpenoid alkaloids of different structural types. We proved the positive effect of pre-clustering the original data set, although not all of the classes show a valid statistics. The work confirms two well-known position of the correct design of QSAR models: the linearity of the equation gives a better interpretability, and the high value of the standard statistics provides the predictive efficiency of the model.

Diterpenes are a class of chemical compounds made up of four isoprene units, often with the molecular formula C20H32. Diterpenes are made up of four isoprene subunits. By plants, animals and fungi, they are biosynthesized via HMG-CoA reductase pathway. Diterpenes form the basis of biologically important compounds such as retinol, retina and phytol. They are known to be antimicrobial and anti-inflammatory.

Diterpenes are derived from the addition of an IPP unit to the FPP to form geranylgeranyl-pyrophosphate (GGPP). From GGPP, structural diversity is mainly obtained by two classes of enzymes: diterpenes synthases and cytocromes P450. Several diterpenes are produced by plants and cyanobacteria. GGPP is also the precursor of phytane synthesis through the action of the enzyme geranylgeranyl reductase. For the biosynthesis of tocopherols, this compound is utilized. In the formation of chlorophyll a, ubiquinones, plastoquinone and phylloquinone, the phytyl functional group is utilized.

Diterpenes are formally defined as hydrocarbons and therefore do not

This work is partly presented at 5th International Conference on Medicinal Chemistry & Computer Aided Drug Designing and Drug Deliver on December 05-07, 2016 at Phoenix, USA

contain heteroatoms. Although there is a wide range of terpene structures, few of them are biologically significant; on the other hand, the diterpenoids have a rich pharmacology and include important compounds such as retinol and phytol. Taxanes are a class of diterpenoids with a taxadiene ring. They are produced by plants of the genus Taxus (ifs) and are widely used as chemotherapy agents.

Natural diterpenoids cover a wide chemical diversity and include many compounds that are medically and industrially relevant. All diterpenoids are derived from a common substrate, (E, E, E) -geranylgeranyl diphosphate, which is cyclized to one of several scaffolds by diterpene synthase (DTS).

Diterpenoids are secondary metabolites containing 20 carbon atoms derived from the condensation of four isoprenyl units. Like other terpenoids, they are widespread in the plant kingdom, and most of them are biosynthetically derived from geranylgeranyl diphosphate, which forms acyclic (phytanes), bicyclic (labdanes, halimanes, clerodanes) etc. Diterpenoids are divided into more than 45 classes; they are also found in marine organisms, which provide interesting skeletons such as the Elisapterane.

The diterpenoids of the abietane and pimarane series, as well as the norabietane flavored diterpenoids, have been identified as having anti-tuberculosis activity. All of the compounds that have been studied include a fused, angular, three-membered carbocyclic ring structure. A number of ring oxygenations (e.g. C-12 phenolics or C-11, C-12 and / or C-14 ketones) provide easy oxidation sites which can generate radicals, which could provide an explanation of their anti-tuberculosis behavior. Seco-abietanes also exhibit significant anti-tuberculosis activity; these compounds share a similar

molecular architecture with their tricyclic cousins. In addition, labdanes have only a weak anti-tuberculosis activity.

Diterpenoids can be classified into linear, bicyclic, tricyclic, tetracyclic, pentacyclic or macrocyclic diterpenes based on their skeletal nucleus. In nature, they are commonly found in a polyoxygenated form with keto and hydroxyl groups, these are often esterified by small aliphatic or aromatic acids.

Diterpenoid alkaloids

Diterpenoid alkaloids are abundant in the Aconitum and Delphinium and are known to have anticancer activity. For example, lappaconitine causes the cell cycle G0 / G1 to stop, apoptosis and downregulation of the expression of the cyclin E1 gene from NSCLC (Sheng et al.). Taipeinin A, a C19 diterpenoid alkaloid from the roots of Aconitum taipeicum, regulates the expression of Bax proteins and caspase-3 upwards and regulates the expression of Bcl-2 and CCND1 (Zhang and al.). The cytotoxic activities of the diterpenoids Delphinium alkaloids were evaluated using the MTT method (Lin et al.), And the IC50 values against cancer cells A549 ranged from 12.03 to 52.79 μM. Their anticancer mechanisms await further studies.

3-isopropyl-tetrahydropyrrolo [1, 2-a] pyrimidine-2, 4 (1H, 3H) -dione (ITPD), isolated from A. Taipeicum, induces apoptosis and stopping the cell cycle in S phase (Zhang et al.) ITPD can mediate the mitochondrial pathway by activating caspase-3/9 and increasing the Bax / Bcl-2 ratio. Aconitine induces apoptosis in

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human pancreatic cancer via the NF-κB signaling pathway.

Aconitum szechenyianum (ASA) alkaloids upregulate the expression of phosphorylated p38 and p38 MAPK (Fan et al.), Suggesting that ASA-induced apoptosis is associated with the p38 MAPK-mediated pathway. ASA upregulates TNF-R1 and DR5 via activation of p38 MAPK, thereby activating caspase 8, revealing that the death receptor pathway is involved in apoptosis. ASA leads to a loss of the mitochondrial membrane potential, which regulates up p53, phosphorylated p53 and Bax, regulates down Bcl-2, causes the release of cytochrome c by the mitochondria and activates caspase-9 and - 3 in cell A549. This suggests that ASA may also induce apoptosis through the mitochondria.

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