Alkaloids Derived from Anthranilic Acid

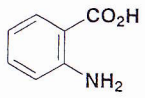
Quinoline, Acridone, and Quinazoline Alkaloids

Anthranilic acid is the starting unit of various groups of alkaloids: simple quinolines (rare), simple and prenylated 2- and 4-quinolones, furo-and pyranoquinolines, simple acridones and their prenylated derivatives, furo- and pyranoacridines, quinazolidones, pyrroloquinazolines, and more.

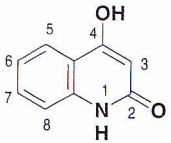
It is also the precursor of the 1,4-benzoxazin-3-ones, which are metabolites involved in the resistance of the Poaceae to predators (fungi, bacteria, insects) and in their allelopathic effects. Note also that this acid is the origin of benzodiazepines, which are elaborated by certain fungi, but have rarely been found in higher plants.

Biosynthesis. The condensation of anthranilic acid with one acetate unit leads to 4-hydroxy-2-quinolinone; upon prenylation at C-3 by dimethylallyl pyrophosphate, followed by cyclization involving the oxygenated function at C-2 or C-4, the latter leads to a logical series of compounds: the hydroxyisopropyldihydrofuroquinolines and related compounds, furo- and pyranoquinolines, linear or angular, derivatives of quinolinone, and more. It is plausible that the 2-alkyl-4-hydroxyquinolines arise from the condensation of one molecule of anthranilic acid with an acyl-CoA (or its equivalent in the case of 2-arylalkyl derivatives).

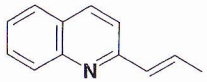
In the case of the acridones, anthranilic acid is the origin of only one of the two benzene rings, since the other arises from three acetate units (i.e., three molecules of malonyl-CoA): almost all of them have oxygenated functions at C-1 and C-3. Many acridones are isoprenylated at C-2, or C-4, or both, and they can also form



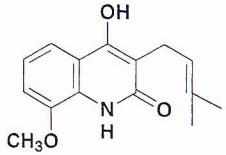
Anthranilic acid



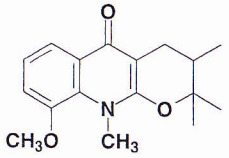
4-Hydroxy-2-quinolinone



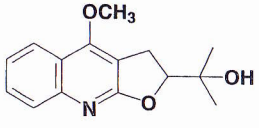
Chimanine B



Glycophylone

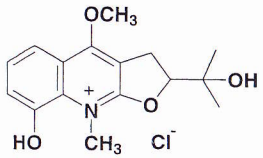


Isobalfourodine

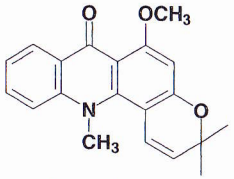


Platydesmine

Dictamnine



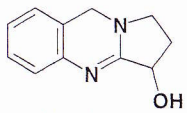
Pteleatinium chloride



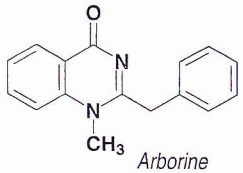
Acronycine

dimers. The quinazolines are a special case: most often, it is an amino acid that reacts with anthranilic acid to form the alkaloids (e.g., phenylalanine in the case of arborine, ornithine [or aspartic acid] in the case of vasicine).

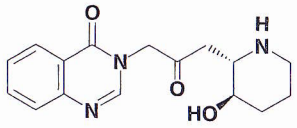
Distribution. The distribution of these compounds is fairly limited and centered on the family Rutaceae. This is true for the simple structures (*Eisenbeckia*, *Galipea*) as well as for those that incorporate an isoprene unit (e.g., *Choisya*, *Dictamnus*, *Haplophyllum*, *Ptelea*, *Zanthoxylum*). The acridones are also characteristic of Rutaceae. Quinazolines, on the other hand, have been found in several families: Acanthaceae (*Adhatoda*), Rutaceae (*Glycosmis*, *Zanthoxylum*), Scrophulariaceae (*Linaria*), Zygophyllaceae (*Peganum*), Araliaceae, Fabaceae, and more.



Vasicine



Arborine



Febrifugine

Properties. Although a large number of alkaloids has been identified to date, their pharmacological interest appears to be low (except for the abortive properties of vasicine); none of them is currently used clinically (in Europe).

Regarding the pharmacological potential of the quinolines, note the antimicrobial properties of a traditional North American drug, *Ptelea trifoliata* L. which are due to pteleatinium chloride. Related derivatives are cytotoxic. Note also that some simple quinolines (2-alkyl- and 2-arylquinolines) act as leishmanicides in mice; that acronycine, an acridone, has antimitotic properties; and that furoquinolines such as skimmianine or dictamnine are phototoxic, like the furocoumarins.

Not much more is known of the activity of the quinazolines: it is known, however, that the antipyretic properties of a drug considered an antimalarial in Chinese medicine, namely *Dichroa febrifuga* Lour. (Saxifragaceae) are due to febrifugine, an *N*3-substituted quinazolin-4-one.

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