SYNTHESIS OF PENTACYCLIC ALKALOID HYBRIDES

Máté Bubenyák, Miklós Boros, József Kökösi, Béla Noszál

Semmelweis University, Department of Pharmaceutical Chemistry
Hőgyes Endre u. 9. Budapest, H-1092 Hungary

Two groups of natural alkaloids – rutaecarpine and its derivates (*Evodia rutaecarpa*) and luotonin A and B (*Peganum nigellastrum*) – exhibit potent antitumor activity by activation of the caspase cascade and inhibition of the topoisomerase I. Both alkaloids are used as components of traditional Chinese folk medicines. *Evodia rutaecarpa* (Chinese name:Wu-Chu-Yu) has been used as a remedy for gastrointestinal disorders (abdominal pain, dysentery), headache, amenorrhea, and postpartum hemorrhage in Chinese medical practice for a long time. Rutaecarpine, a quinazolinocarboline alkaloid is the major component isolated from the fruit of *Evodia* species and has been shown to possess interesting pharmacological activity by having antiplatelet, vasodilator, diuretic, selective COX-2 inhibitor, cytochrome P450 activator properties. The plant *Peganum nigellastrum* is used for the treatment of rheumatism, inflammation and abscesses. Examination of the chemical components of this plant led to isolation of luotonine (A, B, E) alkaloids containing a pyrroloquinazolinoquinoline ring system.

The structural similarity and potent anticancer activity of these alkaloids promted us to synthesize hybrid compounds containing common structural features of rutaecarpine and luotonines.

Two alternative reaction routes have been developed for the synthesis of pentacyclic compounds, in which the key step is the Fischer indolization of the different phenylhydrazono-quinazolone derivatives. Starting from natural tricyclic alkaloid vasicinone the dimethylamino-methylene derivative was prepared by Vilsmeier-Haack reaction using DMF and $POCl_3$. Japp-Klingemann reaction of the product by coupling of different aryldiazonium salts led to the arylhydrazone derivatives of vasicinone. Fischer indolization of the phenylhydrazone has provided 8-nor-rutaecarpine (14-nor-luotonine A).

These bioisosteric analogues are the first representatives of a new heterocyclic ring system, indolopyrroloquinazoline.

In an alternative way indolyl-quinazolone was prepared starting from 2-alkyl-quinazolone via bromination, substitution with phenylhydrazine and indolization. Vilsmeier-Haack reaction of the indolyl-quinazolone and acid catalysed ring closure reaction of the formyl derivatives led to 14-nor-luotonine B(7-hydroxy-8-nor-rutaecarpine).

The 8-nor-rutaecarpines incorporate the structural elements of these two efficient herbal alkaloids, so they are promising lead molecules for our pharmacological researches.

The new compounds are characterized by UV, IR, ^{1}H, ^{13}C NMR, MS spectroscopy.