

Natural Compounds in Drug Discovery: New Trends in the Chemistry of Isoquinoline Alkaloids

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Among many thousands of modern drugs, about 40% are of natural origin. The most wide spectrum of pharmacological action is exhibited by alkaloids (especially, isoquinoline ones). In this lecture various aspects of synthesis and modification of plant isoquinoline alkaloids, such as stephaglabrine, salsoline, pancrotine, noscapine, cotarnine, etc. are discussed. Special attention is given to recent (2000–2003) studies performed in terms of the research programs on modification of natural compounds initiated and developed by InterBioScreen Ltd. First of all, it will concern new trends in the chemistry of cotarnine, one of most promising and inadequately studied alkaloids. While cotarnine is being used as hemostatic agent, the spectrum of biological activity of other isoquinoline alkaloids is much wider.

The alkaloids ambelline, pancratistatine (from *Pancratium littorale*), cyclopeltine, and methyltelobine-N are known to exhibit pronounced citostatic activity. Recently, the alkaloids zephyrantine (from *Zephyranthes carinata*) and narcyclasine-glucoside were found to exhibit antitumor activity. Narcyclasine, dihydronarcyclasine and the secocepharantine (*Stephania sasakii*) exhibit a marked antiviral effect. Macrolide isoquinoline alkaloids are known as anti-parasites and antibacterials e.g. the protozoacide obamegine and tuberculostatic phytoncide tetrandrine. Alkaloids micrantine and daphnoline are being used in curing various cardiovascular pathologies. Alkaloid anhalinine is known as psychomimetic, dimethylbromide of cycleanine is a relaxant and hypotensive agent, while the alkaloids tritoqualine and altoqualine are being used as effective anti-histamine preparations, protectors of H1-receptors, antagonists of serotonin, and inhibitors of histidinedecarboxylase with a pronounced anti-allergic effect.

Analysis of WDI/WDA (Derwent) and other databases shows that chemical modification of natural compounds may either improve a specific biological action or give rise to new, earlier unpredicted biological properties. This principle made a basis for the research programs of InterBioScreen, Ltd. oriented to a search for new routes to modification of natural compounds to be used as new pharmaceuticals. The results of these programs on new chemical transformations of isoquinoline alkaloids are discussed along with some results on total synthesis and new synthetic routes to alkaloids and their mimetics by reactions of molecular self-assembling.

1. J. Mann, R.S. Davidson, J.B. Hobbs *et al.*, *Natural Products: Their Chemistry and Biological Significance*, London: Longman, 1993.
2. V.G.Kartsev, *Nitrogen Containing Heterocycles and Alkaloids*, Moscow: Iridium Press, 2001, v.1, p.110-117, 543; v.2, p.152, 416.