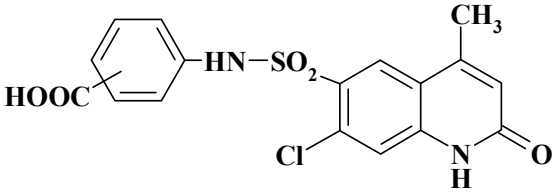
DEVELOPMENT OF NOVEL QUINOLINE DERIVATIVES WITH DIURETIC ACTIVITY

Zebari Havar Rashid, Tsapko T.A., Galuzinskaya L.V.
The National University of Pharmacy, Kharkiv, Ukraine
medchem@nuph.edu.ua

Thiazides are effective antihypertensives with long track records and low cost. The most popular agent in this class, hydrochlorothiazide, was traditionally used in doses of 50 to 100 mg per day. These doses were associated with metabolic and electrolyte complications. Therefore, low-dose therapy has been applied and demonstrated to be efficacious and to have a much lower incidence of side effects. The other way to solve thiazides disadvantages is to use thiazide-like diuretics, for example, chlorthalidone, that have been shown to provide a greater antihypertensive effect comparing with hydrochlorothiazide and, more importantly, to reduce mortality. Accordingly, thiazide-like diuretics development for edema and essential hypertension treatment is actual problem of pharmaceutical science.

The aim of this work was to search for new chemical scaffold of thiazide-like diuretics. To reach the goal, a series of new 7-chloro-4-methyl-1,2-dihydroquinoline-2-ones with sulfonamide moiety bearing different substituents has been synthesized. The procedure includes sulfochlorination of 7-chloro-4-methyl-1,2-dihydroquinoline-2-one and further amidation of corresponding 7-chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfochloride with various aromatic amines.

Obtained substances (for example, I) contain basic pharmacophores of thiazide and thiazide-like drugs, in particular, essential sulfonamide group with halogen atom in *ortho*-position and amino group in *para*-position of aromatic ring.



I

Synthesized substances have been tested for their diuretic activity in rats. According to the results of the screening, derivatives with carboxylic group in the benzene ring (I) posses 37.9-71.6% of hydrochlorothiazide activity. The higher activity was found for 4-(7-chloro-4-methyl-2-oxo-1,2-dihydroquinolin-6-yl-sulfonylamino)benzoic acid (I, *para*-COOH). Thus, polar carboxylic group in *para*-position doubled diuretic activity in comparison with corresponding *ortho*- and *meta*-substituted derivatives.