4-CHLORO-1-ETHYL-1*H*-2,1-BENZOTHIAZINE-3-CARBALDEHYDE 2,2-DIOXIDE IN SYNTHESIS OF 2-AMINO-4*H*-PYRANS

Kolodiazhna T. I., Shemchuk L. A.
Scientific supervisor: assist. Lega D. A.
National University of Pharmacy, Kharkiv, Ukraine
legus.211288@gmail.com

Introduction. 2-Amino-4*H*-pyrans represent famous class of biologically active compounds. Our previous investigations have been dedicated to exploring 1-ethyl-1*H*-2,1-benzothiazin-4-(3*H*)-one 2,2-dioxide reactivity in the reaction with aldehydes and active methylene nitriles. In most cases this interaction resulted into condensed 2-amino-4*H*-pyrans. Formylation of the benzothiazine under the Vilsmeier–Haack reaction conditions gave 4-chloro-1-ethyl-1*H*-2,1-benzothiazine-3-carbaldehyde 2,2-dioxide. Application of the latter as aldehyde component in the abovementioned reaction might lead to 2-amino-4*H*-pyrans containing 1*H*-2,1-benzothiazine 2,2-dioxide core in the position 4.

Aim. To study the interaction of 4-chloro-1-ethyl-1*H*-2,1-benzothiazine-3-carbaldehyde 2,2-dioxide with malononitrile and carbonyl compounds aiming to synthesize 2-amino-4*H*-pyrans □-linked to 1*H*-2,1-benzothiazine 2,2-dioxide core.

Materials and methods. 4-Chloro-1-ethyl-1*H*-2,1-benzothiazine-3-carbaldehyde 2,2-dioxide, malononitrile and series of compounds containing CH_2CO moiety were used in the research as starting materials. While carrying out the research standard methods of organic synthesis were applied.

Results and discussion. It was found out that the three-component reaction (way 1) of 4-chloro-1-ethyl-1*H*-2,1-benzothiazine-3-carbaldehyde 2,2-dioxide 1 with malononitrile 2 and carbonyl compounds 3 in most cases yielded 2-amino-*4H*-pyran-3-carbonitriles 5. Unexpected outcome of the reaction occurred when 3-methyl-1*H*-pyrazol-5(4*H*)-one was utilized and compound 6 comprising novel condensed heterocyclic system of 7,10-dihydro-5*H*-benzo[*c*]pyrazolo[4',3':5,6]pyrano[2,3-*e*][1,2]thiazine 6,6-dioxide was isolated. It was also applied two-component format (way 2) towards 5 and 6 which turned out to be more convenient.

Conclusions. Series of 2-amino-4*H*-pyrans □-linked to 1*H*-2,1-benzothiazine 2,2-dioxide core was obtained. New product type of the reaction was isolated.

AMINOMETHYLQUINOLONES: A PROMISING CLASS OF NEW PSYCHOACTIVE SUBSTANCES

Kravchenko I. V.
Scientific supervisor: ass. prof. Podolsky I. M.
National University of Pharmacy, Kharkiv, Ukraine
medchem@nuph.edu.ua

Introduction. Our research focused on the class of new biologically active molecules – 3-aminomethylsubstituted 2-methylquinolin-4-ones. Initially, aminomethylquinolones were synthesized in National University of Pharmacy and considered as potential psychotropic agents because of their certain structural similarity with molecule of 5-hydroxytryptamine (5-HT).

Aim. Present study was undertaken to implement the *in vivo* profiling of psycho- and neurotropic properties of new 3-(N-R,R'-aminomethyl)-2-methyl-1H-quinolin-4-ones and reveal the possible «structure-activity relationships» (SAR) features for these derivatives.

Materials and methods. 3-(N-R,R'-Aminomethyl)-2-methyl-1H-quinolin-4-ones was synthesized from 2-methyl-1H-quinolin-4-one *via* aminomethylation and further interaction of the Mannich base obtained with the corresponding amines. N-Benzoylated derivatives were obtained by acylation of 2-methyl-3-(phenylaminomethyl)-1H-quinolin-4-one with benzoyl chloride or *o*-chlorobenzoyl chloride in the appropriate conditions. The identity of the compounds synthesized was confirmed by 1H-NMR spectroscopy.

All computational parameters of compounds, such as molar weight (MW), the number of hydrogen bond donors (HBD) and acceptors (HBA), the fraction of sp3-hybridized carbons (Fsp3), topological polar surface area (TPSA), pKa, clogP and clogS were calculated using a Chemicalize free online service by ChemAxon. This computational study of «drug-likeness» properties preceded pharmacological tests to reveal violations of Lipinski's "Rule of 5".

The open field test, the elevated plus maze, the rotarod test, the tail suspension test, the passive avoidance test and acute normobaric hypoxia with hypercapnia were used as pharmacological methodological basis.

Results and discussion. Taking into account the modest scope of testing the impressive conclusions concerning SAR regularities cannot be made. Furthermore, doubts are cast upon feasibility of the activity profile prediction for 3-(N-R,R'-aminomethyl)-2-methyl-1H-quinolin-4-ones due to complicated results obtained in behavioural tests. These facts indicate the delicacy of the mechanism of action and sensitivity to minor modifications of the chemical structure. However, certain SAR features were revealed.

It became absolutely apparent that compounds with the phenylaminomethyl fragment have pronounced mnemotropic effects against scopolamine-induced amnesia. Substitution of this fragment with the heterocyclic moiety or N-benzoylation leads to the action weakening. Being the most structurally similar to atristamine, 3-[[(2-methylphenyl)amino]methyl]-2-methyl-1H-quinolin-4-one has the same profile of activity. But, if other substituents are present in the phenyl moiety, there is rather large dispersion of results in behavioural tests. According to the data obtained, N-benzoylation of basic structure results in appearance of the potent anti-anxiety action, but an ambiguous influence on depressive behaviour at the same time. It should be emphasized that the methoxy group in position 6 of the quinolone fragment causes great differences in the profile of the biological activity compared to atristamine. This fact correlates well with the results for 3-(dimethylaminomethyl)-6-methoxy-2-methyl-1H-quinolin-4-one in the previous study, i.e. a high physiological activity without valuable outcomes for drug development.

Conclusions. The psycho- and neurotropic profiling of novel 3-(N-R,R'-aminomethyl)-2-methyl-1H-quinolin-4-ones *in vivo* was carried. Certain regularities of the «structure – activity relationships» revealed have been discussed. Some compounds that deserve a deeper and more detailed pharmacological study have been found. 3-[[(4-Methoxyphenyl)amino]methyl]-2-methyl-1H-quinolin-4-one exhibiting a specific sedative effect and a considerable antiamnesic activity, as well as N-[(2-methyl-4-oxo-1H-quinolin-3-yl)methyl]-N-phenylbenzamide, which combines the anti-anxiety action, anti-amnesic activity and antihypoxic effect, are among them as promising psychoactive agents**.** The results of this study expand current knowledge about pharmacological properties of this class of compounds and allow us to outline directions for the further purposeful searches of promising psycho- and neurotropic agents among 3-(N-R,R'-aminomethyl)-2-methyl-1H-quinolin-4-ones.

SYNTHESIS OF CHLORO-SUBSTITUTED 2-YLIDENE-1,3-DITHIOLANES

Lipin K.V.
I.N. Ulianov Chuvash State University, Cheboksary, Russia
lipinkost@mail.ru

Introduction. Five-membered 1,3-dithioheterocycles are often found in the synthesis of substances with valuable electronic and optical properties. Compounds with 2-ylidene-1,3-dithiolene fragment absorbing near ultraviolet and narrow ranges of visible light are described, while having light stability and stability. Based on these substances, materials have already been created that are used for optical recording of information and the production of protective coatings from ultraviolet radiation.

Aim. Previously reported on the development of methods for the synthesis of some representatives of 2-ylidene-1,3-dithiolanes. Of greatest interest is a one-pot method of preparation, consisting of the interaction of a methylene active compound, carbon disulfide and dichloroethane (Scheme 1). With further study of this transformation, it was decided to extend the one-reactor synthesis method to more complex objects.