ISSN 2409-9066. Sci. innov. 2015, 11(6): 68—74 doi: http://dx.doi.org/10.15407/scine11.06.068

Bogza, S.L.

L.M. Litvinenko Institute of Physical, Organic and Coal Chemistry, the NAS of Ukraine, Kyiv

NEW HETEROCYCLIC SYSTEMS FOR NEW PHARMACEUTICALS

The researches in the field of heterocyclic and medicinal chemistry carried out by the Department of Biologically Active Compounds of the L.M. Litvinenko Institute of Physical Organic and Coal Chemistry of the NAS of Ukraine have been reviewed. The results of search of new pharmaceuticals with basic β-carboline structures, its S- and O- isosteres, and isoquinoline have been showed.

Keywords: organic synthesis, drug, carbolines, isoquinoline, tranquilizer, and oncolitic products.

The importance of providing the population with accessible medicinal products and the necessity of huge investments into research and development of new effective pharmaceuticals are doubtless. The development of new medicinal product and its commercialization are very long-term and resource-intensive processes that starts with organic synthesis.

The IPOCC in cooperation with Ukrainian pharmacologists and pharmacists successfully deals with the creation of new molecules precursors of pharmaceuticals and original medicinal products.

SEARCH OF NEW PSYCHOTROPIC PRODUCTS AMONG β-CARBOLINES AND THEIR ISOSTERES

For decades, β-carbolines attracted the attention of chemists and biologists due to the presence of these alkaloids in many natural objects. Natural alkaloids – harmine, harman, and their derivatives are of particular interest. Pharmacological effects of harmine and harman have been known for almost 100 years; alkaloids of Harmala family have been therapeutically used for 80 years. Recently, the β-carbolines have become an important tool for studying the neurobiology of benzodiazepine receptors.

The long-term studies have showed that β-carbolines are a promising class of heterocyclic substances for creating new drugs having properties of tranquilizers, anxiolytics, nootropics, and stress-protectors.

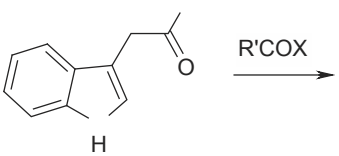
To simulate the biological properties of synthesized molecules, pharmaceutical chemistry uses the theory of *isosteres*, according to which the compounds with a similar structure have similar biological properties. The theory does not exclude new or opposite biological properties as a result of changing molecule's element composition. Therefore, it is important to synthesize and to study the biological properties of S- and O-isosteres of β-carboline, which also have a high biological activity. Tests of benzothiophene analogs of harmine and harmaline as MAO inhibitors *in vitro* have demonstrated that harmine and S-harmine have similar strength, while the activity of S-harmaline 50 times exceeds that of harmaline. The sulfur analogues of Harmala alkaloids have a high lipid solubility, a shorter biological half-life, and a weaker bond with tissues as compared with their nitrogen analogue.

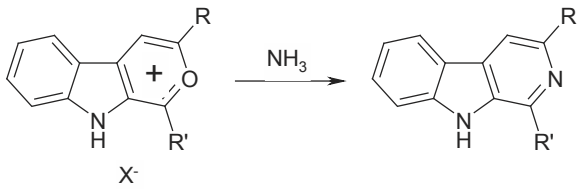
Last 45 years, the majority of researches were aimed at improving the methods for annulation of

pyridine ring to the indole, benzo[*b*]thiophene and benzo[*b*]furan using classic approaches based on the Bischler-Napieralski, the Pictet-Gams, the Pomeranz-Fritsch, and the Schlitter-Mueller reactions. Each method has some disadvantages: low yield (the Pomeranz-Fritsch and the Schlitter-Muller methods), necessary dehydrogenation of the intermediate 3,4-dihydro-derivatives (the Bischler-Napieralski method), and multi-stage synthesis of the starting compounds (the Pictet-Gams method).

In contrast to the above methods, the IPOCC researchers have developed an approach to the synthesis of annulated pyridines via corresponding pyrylium salts is remarkable for mild reaction conditions and high yields. The condensed pyrylium salts transform into the corresponding pyridines as result of pyran ring recyclization under the action of ammonia or ammonium acetate in alcohols or acetic acid. The synthesis of pyridine bases from pyrylium salts enables varying the substituents in both the pyridine and the carbocyclic parts of molecules. This paper summarizes the results of IPOCC research concerning the synthesis, transformations and pharmacological studies of β-carbolines and their isosteres.

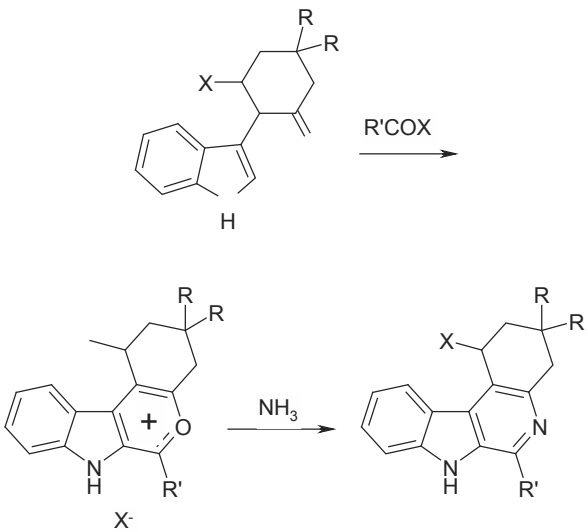
The synthesis of indole [2,3-c]-pyrylium salt is based on an acid-catalyzed hetero-cyclization reaction — acylation of 3-(oxoacyl)indoles by anhydrides of aliphatic carboxylic acids in the presence of perchloric acid or Lewis acids. The first examples of obtaining β-carbolines from indole[2,3-c]-pyrylium salts with 10–20% yield of indolopyrylium perchlorates have been described in [5, 6]. Later, improved techniques have enabled obtaining the desired products with up to 90% yield. Using this approach, a substantial amount of indolo[2,3-c]-pyrylium salts with various substituents in the heterocyclic and the benzene nuclei has been obtained. These salts have been transformed into β-carboline derivatives (Scheme 1) [7—9].





Scheme 1

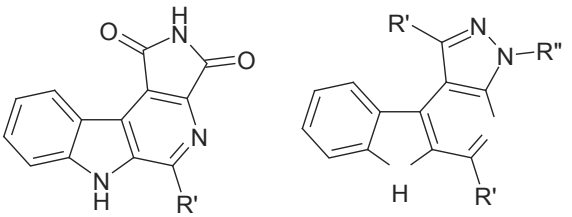
The study of acylation of 2-(3-indolyl)cycloalkane-1,3-dione and 2-(3-indolyl)cycloalkanes was very useful for creating new anxiolytics and antidepressants. Anhydrides of acetic, propionic, butyric, isobutyric, valeric, and trifluoroacetic acids, benzoyl- and phenylacetyl chlorides were used as acylating agents. Tetracyclic perchlorates of indolopyrylium were transformed into β-carbolines [10, 11]. Similarly, pentacyclic pyrylium salts and corresponding β-carboline derivatives were obtained from 2-(1-ethylindole-3)indandion [10]. An indolopyrylium salt with a high yield was obtained by acylation of 2-(3-indolyl)dimedone by chloranhydride of 3-trichlorogermylpropionic acid. The recyclization of this salt by ammonia and subsequent treatment with triethanolamine resulted in obtaining a β-carboline (19) with a germantran fragment (Scheme 2) [12].



Scheme 2

This approach has been successfully applied to the synthesis of β-carboline derivatives from in-

dolyl-substituted heterocyclic rings. 2-hydroxy-3-(3-indolyl)maleimide reacts with acyl-perchlorates forming dioxypropyrroloindolopyrylium that is easily transformed into pyrroloindolopyridine obtained by counter synthesis — acylation of 2-amino-3-(3-indolyl)maleimide (Scheme 3) [13].



Scheme 3

The formation of azole-condensed β-carbolines by acylation of indolyl-substituted aminoheterocyclic rings was effective as well: 4-(3-indolyl)-5-aminopyrazole is easily transformable into perchlorate indole[2,3-c]pyrazol[5,4-e]pyridinium formed as base by treatment with triethylamine. A new method for synthesizing azole-β-carbolines with unsubstituted carbon atom of pyridine ring by cyclization of N-azolylformamidines is promising as well [14].

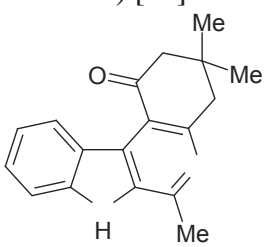
The approach to the synthesis of condensed pyridine bases from respective pyrylium salts was designed by the IPOCC researchers and has been used successfully for obtaining benzothieno[2,3-c]pyridines, benzofuro[2,3-c]pyridines [15, 16], and isomeric thienothiopheno[2,3-c]pyridines [17]. Tetracyclic benzothieno-, benzoselenopheno- and benzofuro[2,3-c]pyridines [18] were obtained in a similar way.

Further studies of β-carbolines deals with chemical properties of condensed pyridine bases, introduction of functional groups into the benzene ring of hetarylpyridines and various functional group transformation in polyheterocyclic rings. The reactions of nitration and acylation of tetracyclic β-carbolines, their isosteres, tricyclic benzothieno- and benzofuropyridines have been studied [19—21]. Mononitropyridines or dinitro-derivatives were obtained at various conditions. Direction of heterapyridine acylation depends on the type of heterocycle central core and the acylhalogenide structure.

BIOCTIVITY OF β-CARBOLINES AND THEIR ISOSTERES

Preclinical studies of β-carbolines obtained and their isosteres have been carried out at the Department of Pharmacology of the Donetsk State Medical University. As the pharmacological tests have showed, new derivatives of harman and harmine have properties of antidepressants, tranquilizers, anxiolytics, and nootropics, with their effect depending on available substituents. The tricyclic derivatives of harman and harmine have properties of antidepressants [25] and stress-protectors [9]. A distinctive feature of all these compounds tested is the lack of narcosis potentiating action inherent in benzodiazepine tranquilizers. Among the hundreds of new compounds tested, the highest activity has been reported for 1-oxo-3,3,6-trimethyl-1,2,3,4-tetrahydroindole[2,3-c]quinoline (9) (R1=R2=Me), a day-time tranquilizer [26] that has been clinically tested and recommended for use in medicine. Further tests showed that this drug has properties and a powerful stress- and neuroprotective effect 50 times exceeding the action of piracetam (Nootropil) [27]. In 1994, a drug called carbocetam was approved for clinical use as nootropic agent. Pyrrole β-carboline has been studied and recommended for clinical trials (27). It has stronger nootropic properties and is significantly more active than piracetam.

Benzothieno[2,3-c]pyridines have a spectrum of action that coincides with that of antipsychotic drugs [28]. A similar spectrum of action is inherent in thieno[2,3: 5,4]thieno[2,3-c]pyridine (31). Derivatives of benzofuro[2,3-c]pyridines have showed pharmacological properties of tranquilizers (see Scheme 4) [29].



Scheme 4

HETEROCONDENSED ISOQUINOLINE

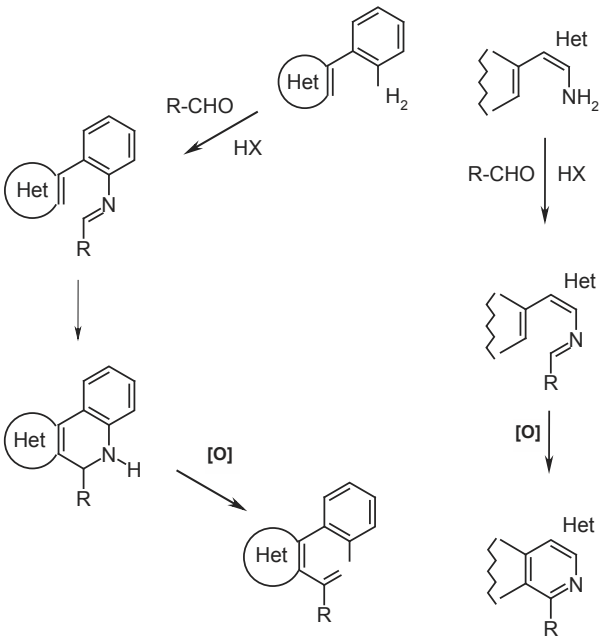
Isoquinolines condensed with azole and other heterocyclic rings on the «c» face has recently become popular targets of medicinal chemistry. The Institute has been dealing with the development of methods for their synthesis for several years. Especially popular are isoquinolines condensed with azole rings. A convenient method for their preparation is based on modified Pictet-Spengler reaction [30, 31].

The *Pictet—Spengler* reaction is one of the most widely used in heterocyclic chemistry for the construction of various alkaloids and their analogs, new heterocycles with potential biological activity and other useful and interesting properties. It is based on the acid-catalyzed condensation of aldehyde or ketone with 2-aryl(hetaryl) ethylamine whose aromatic fragment is capable of electrophilic attack and subsequent cyclization between C-nucleophile of (hetero)aromatic nucleus and iminium ion, which leads to the formation of a new C—C bond and nitrogen-containing heterocyclic ring.

However, despite the attractiveness of this strategy, its use is limited to tryptamine/tryptophan, histamine/histidine, and dopamine/tyramine as amine substrates, which invariably leads to the formation of heterocycles with basic structures of tetrahydro-β-carboline, tetrahydroimidazopyridine, and tetrahydroisoquinoline.

For a long time, despite a huge amount of researches using the *Pictet—Spengler* reaction, the synthesis strategy remained unchanged. Even in the solid phase, the use of which has opened up new opportunities in heterocyclic chemistry, the *Pictet—Spengler* reaction is limited to only the above-mentioned formation of classical systems.

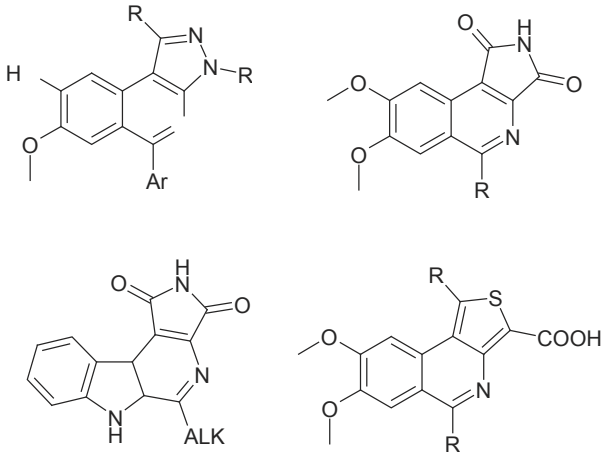
In the last 10 years, one can see a revival of this reaction: the use of so-called *Pictet—Spengler substrates* of the second generation will significantly expand the range of nitrogen-containing heterocyclic systems. The new approach is based on using the aromatic and heterocyclic amines (orthohetaryl-substituted anilines, ortho-aryl or orthohetaryl-substituted aminoheterocycles) instead of the aliphatic ones for cyclization (Scheme 5):



Scheme 5

These starting compounds cannot be directly attributed to the Pictet—Spengler reaction substrates by the structure and depth of transformation, with their cyclization being new acid-catalyzed reactions. The IPOCC research works on the synthesis of new heterocyclic structures have become the basis for the search of new drugs having very different actions, as illustrated by the following examples.

Derivatives of pyrazol[3,4-c]isoquinoline have been the most widely used for searching new inhibitors of anaplastic lymphoma kinase [32—34]. They have been patented as compounds capable of enhancing the effectiveness of chemotherapeutic drugs and antibiotics, promoting detoxification of cells and tissues, and regulating the transport of multidrug complex systems through the blood-brain and the placental barriers [35, 36]. Pyrazol[3,4-c] isoquinolines have a low toxicity of LD_{50} 1500—2500 mg/kg (Scheme 6) [34].



Scheme 6

Pyrrole[3,4-c]isoquinolin-2,5diones [37, 38] are inhibitors of glycogen synthase kinase 3 (GSK 3) as well as activators of W_{nt} signaling pathway [39], which is important for proliferation, differentiation and apoptosis. Pyrrole[3,4-c]-β-carboline-1,3-diones [39] are studied as a new class of inhibitors of tyrosine kinases [40]. Derivatives of heterocyclic system of thieno[3,4-c]isoquinoline synthesized for the first time several years ago in the IPOCC [38] are studied as promising inhibitors of $NF_{kappa}B$ receptor [41, 42]. Therefore, new drug substances with the heterocondensed isoquinoline structure are very likely to appear in the near future. To this end, the development of alternative methods of synthesis and functionalization of azole- and other condensed isoquinolines remains relevant for medicinal chemistry.

REFERENCES

1. Andronati S.A., Javorskij A.S., Chepelev V.M. i dr. *Mehanizmy dejstvija anksioliticheskih, protivosudorozhnyh i snotvornyh sredstv*. Kyiv: Nauk. dumka, 1988 [in Russian].
2. Dulenko V.I., Komissarov I.V., Dolzhenko A.T. i dr. *β-Karboliny. Himija i nejrobiologija*. Kyiv: Nauk. dumka, 1992 [in Russian].
3. *Thornber C.W.* Isosterism and molecular modification in drug design. *Chemical Society Reviews*. 1979, 8(4): 563–580 .
4. Stradyn' Ja.P. Novye imennye reakcii v himii getierociklicheskih soedinenij. *HGS*. 1981, N 10: 1412 [in Russian].
5. Dorofeenko G.N., Dulenko L.V. Novyj metod pristrojki pirilievogo i piridinovogo ciklov k proizvodnym furana i indole. *HGS*. 1969, N 3: 417–421 [in Russian].
6. Dorofeenko G.N., Dulenko L.V., Semenov N.S. Soli 2-benzopirilija. Vzaimodejstvie s azotistymi osnovanijami. *HGS*. 1970, N 2: 245–249 [in Russian].
7. Komissarov I.V., Dulenko L.V., Dulenko V.I. Sintez i farmakologicheskie svojstva proizvodnyh garmana i garmina. *Him.-farmac. zhurn*. 1977, 11(5): 93–97 [in Russian].
8. Dulenko V.I., Semenov N.S., Nikoljukin Ju.A. i dr. Sintez kondensirovannyh proizvodnyh indolo2,3-s.pirilievyh solej i β-karbolinov. *HGS*. 1971, N 4: 568 [in Russian].
9. Komissarov I.V., Dulenko V.I., Dolzhenko A.T. i dr. Farmakologicheskie svojstva proizvodnyh garmina. *Him. farmac. zhurn*. 1985, 19(3): 172–176 [in Russian].
10. Dulenko V.I., Luk'janenko V.I., Kibal'nyj A.V. i dr. Sintez kondensirovannyh proizvodnyh indolo[2,3-c]pirilievyh solej i β-karbolinov. *HGS*. 1985, N 3: 363–366 [in Russian].
11. Komissarov I.V., Dulenko V.I., Dolzhenko A.T i dr. Sintez i farmakologicheskie svojstva 1-alkil-3,4-tetrametilen-beta-karbolinov. *Him.-farmac. zhurn*. 1989, 23(6): 674–678 [in Russian].
12. Tolkunov S.V. Kislotno-kataliticheskoe acetilirovanie N-metallil'nyh proizvodnyh laktamov i imidov. *HGS*. 1988, N 10: 1414–1419 [in Russian].
13. Bogza S.L., Nikoljukin Ju.A., Zubrickij M.Ju., Dulenko V.I. Sintez pirrolo[3,4-c]izohinolindionov i pirrolo[3,4-c]-β-karbolindiona. *ZhOrH*. 1993, 29(7): 1480–1484 [in Russian].
14. Bogza S.L., Kobrakov K.I., Dulenko V.I. Ciklodezaminirovanie N-azolil-formamidinov. Sintez poliazageterociklov so strukturnymi fragmentami izohinolina i indolo-[2,3-c]-piridina. *HGS*. 1997, N 1: 80–84 [in Russian].
15. Dulenko V.I., Tolkunov S.V., Alekseev N.N Sintez i reakcii solej benzoj.tieno[2,3-s]pirilija. *HGS*. 1981, N 10: 1351–1354 [in Russian].
16. Tolkunov S.V., Dulenko V.I. Sintez i reakcii solej benzofuro[2,3-s]pirilija. *HGS*. 1987, N 7: 889–893 [in Russian].
17. Tolkunov S.V., Alekseev N.N. Novye geterociklicheskie sistemy proizvodnye pirilija i piridinija na osnove tieno-[3,2-b]tiofena. *HGS*. 1979, N 10: 1424 [in Russian].
18. Tolkunov S.V., Hizhan A.I., Simonova S.I i dr. Kondensirovannye piridinovye osnovanija. Sintez nekotoryh proizvodnyh benzo[b]furo[2,3-c]-, benzo[b]tieno[2,3-c]- i benzo[b]selenofeno[2,3-c]hinolinov. *HGS*. 1994, N 3: 321–326 [in Russian].
19. Tolkunov S.V., Kal'nickij M.N., Dulenko V.I. Jelektrofil'noe zameshhenie v benzo[b]tieno[2,3-c]piridinah. Nitrovanie. *HGS*. 1993, N 5: 706–709 [in Russian].
20. Tolkunov S.V., Kal'nickij M.N., Dulenko V.I. Jelektrofil'noe zameshhenie v benzo[b]tieno[2,3-c]piridinah. Acilirovanie. *HGS*. 1994, N 5: 701–705 [in Russian].

21. Tolkunov S.V., Kal'nickij M.N., Ljashhuk S.N., Dulenko V.I. Jelektrofil'noe zameshhenie v benzo[b]furo[2,3-c] piridinah. Nitrovanie, acilirovanie. *HGS*. 1995, N 5: 694–699 [in Russian].
22. Tolkunov S.V., Kal'nickij M.N., Ljashhuk S.N., Dulenko V.I. Kondensirovannye piridinovye osnovanija. Reakcii 1-okso-3,3,6-trimetil-1,2,3,4-tetragidrobenzo/b/furohinolinov s jelektrofil'nymi agentami. *HGS*. 1995, N 8: 1124–1130 [in Russian].
23. Dolzhenko A.T., Zin'kovskaja A.Ja., Komissarov I.V. Trankvilizirujushhaja aktivnost' garmana i 3-metilgarmana. *Him.-farmac. zhurn*. 1982, 16(12): 1474–1476 [in Russian].
24. *A.s. 803383 SSSR*. V.I. Luk'janenko, Ju.A. Nikoljukin, A.V. Kibal'nyj i dr. Gidrohlorid 3, 3, 6-trimetil-1, 2, 3, 4-tetragidroindolo2, 3 shinolina, obladajushhij antidepressantnoj aktivnost'ju [in Russian].
25. *A.s.1160709 SSSR*. A.V.Kibal'nyj, Ju.A.Nikoljukin, A.T. Dolzhenko i dr.Gidrohlorid 6-metil-1-okso-1,2,3,4-tetragidroindolo/2,3-s/hinolina [in Russian].
26. *A.s. 753093 SSSR*. V.I.Luk'janenko, I.V.Komissarov, T.F. Larina i dr. Gidrohlorid 1-metil-3, 4-(2, 2-dimetil-4-oksotetragidro benzo)-indolo-(2, 3-s)-piridina, projavljajushhij trakvilizirujushhuju aktivnost'; № 2754361/23-04 [in Russian].
27. *Pat. RF 2064793 A61K31/44*. Stressprotektivnoe sredstvo, obladajushhee antiamnesticheskim, antigipoksicheskim, protivotrevozhnym i protivoshokovym dejstviem. Komissarov I. V., Titievskij A. V., Abramec I. I., Dulenko V. I., Nikoljukin Ju. A., Kibal'nyj A. V., Groshevoj T. A., Suhovoj G. F. [in Russian].
28. Tadashi Nagatani, Tsuneyuki Yamamoto, Katsuyuki Takao, Shinji Hashimoto, Kenichi Kasahara, Taisuke Sugihara, Showa Ueki. Pharmacological profile of a potential anxiolytic: AP159, a new benzothieno-pyridine derivative. *Psychopharmacology*. 1991, 104(4): 432–438.
29. *A.s. 123580 SSSR*. V.I.Dulenko, S.V.Tolkunov, I.V. Komissarov i dr. Gidrohloridy benzotiofeno (2, 3)piridinov, obladajushhie nejtrolepticheskoj aktivnost'ju [in Russian].
30. Kobrakov K.I., Malienko A.A., Sujkov S.Yu. et al. The Improved One Pot Synthesis of 5-Unsubstituted Pyrazolo[5,4-c]Isoquinolines. *J. Heterocyclic Chem*. 2001, 38 (3): 523–525.
31. Kobrakov K.I., Malienko A.A., Perepichka I.F. et al. A versatile synthesis of pyrasolo[3,4-c]isoquinoline derivatives by reaction of 4-aryl-5-amino-pyrazoles with aryl/heteroaryl aldehydes: the effect of heterocycle on the reaction pathways. *Org.Biomol.Chem*. 2005, 3(5): 932–940.
32. Li R., Xue L., Zhu T. et al. Design and Synthesis of 5-Aryl-pyridone-carboxamides as Inhibitors of Anaplastic Lymphoma Kinase. *J. of Medicinal Chemistry*. 2006, 49(3): 1006–1015.
33. *Oncolytics*. Drug Data Report, 2007. 29(7): P. 644.
34. *Pat. US 7872014 1/ 5605, 657*. Anaplastic lymphoma kinase modulators and methods of use. Neel Kumar Anand, Charles M. Blazey, Owen Joseph Bowles, Joerg Bussenius, Simona Costanzo, Jeffry Kimo Curtis, Larisa Dubenko, Abigail R. Kennedy, Richard G. Khoury, Angie I. Kim, Jean-Claire L. Manalo, Csaba J. Peto, Kenneth D. Rice, Tsze H. Tsang.
35. Kondratov R.V., Komarov P.G., Becker Y. et al. Small molecules that dramatically alter multidrug resistance phenotype by modulating the substrate specificity of P –glycoprotein. *PNAS*. 2001, 98(24): 14078–14083.
36. Gudkov A., Kondratov R.. *Compounds capable of modulating the activity of multidrug transporters and therapeutic use of the same*. US 20030073611.
37. Nikoljukin Ju.A., Zubrickij M.Ju., Dulenko V.I. Sintez pirrolo[3,4-c]izohinolindionov i pirrolo[3,4-c] -β-karbolindiona. *Zh. org. himii*. 1993, 29(7): 1480–1484 [in Russian].
38. Zinchenko S.Yu., Efimenko R.A., Suikov S.Yu, K.I. Kobrakov. Acid cyclization of amino-substituted heterocycles. Synthesis of 1,3-dioxo-pyrrolo[3,4-c]- and thieno [3,4-c]isoquinolines and cinnolines. *Chem. of Heterocyclic Compounds*. 2009, 45(3): 365–369.
39. Zhong H. et al. Characterization and development of novel small-molecules inhibiting GSK3 and activating Wnt signaling. *Molecular BioSystems*, 2009. 5(11): p. 1356-1360,
40. Teller S. et al. Pyrrolo[3,4-c]-β-carboline-diones as a novel class of inhibitors of the platelet-derived growth factor receptor kinase. *European Journal of Medicinal Chemistry*, 2000. 35(4): p. 413–427.
41. *Pat US 7696221 B2*. Richard D. C., William F. F., Eugene J. T. Thienoisoquinoline-phenylsulfonamides and their use as ER-NFkappaB inhibitors. US7696221 B2, US200 60154875.
42 Wong, N.W.Y. and P. Forgione. A One-Pot Double C–H Activation Palladium Catalyzed Route to a Unique Class of Highly Functionalized Thienoisoquinolines. *Organic Letters*, 2012. 14(11): 2738–2741.

С.Л. Богза

Інститут фізико-органічної хімії і вуглехімії
ім. Л.М. Литвиненка НАН України, Київ

НОВІ ГЕТЕРОЦИКЛІЧНІ СИСТЕМИ ДЛЯ НОВИХ ЛІКІВ

Подано огляд досліджень відділу хімії біологічно активних сполук Інституту фізико-органічної хімії і вуглехімії ім. Л.М. Литвиненка НАН України в галузі хімії гетероциклічних сполук та медичної хімії. Викладено результати пошуку нових лікарських препаратів з базовими структурами β-карболіна, його S- і O-ізостерів, ізохінолiну.

Ключові слова: органічний синтез, лікарський засіб, карболіни, ізохінолін, транквілізатор, онколітік.

С.Л. Богза

Институт физико-органической химии и углехимии
им. Л.М. Литвиненко НАН Украины, Киев

НОВЫЕ ГЕТЕРОЦИКЛИЧЕСКИЕ СИСТЕМЫ ДЛЯ НОВЫХ ЛЕКАРСТВ

Представлен обзор исследований отдела химии биологически активных соединений Института физико-органической химии и углехимии им. Л.М. Литвиненко НАН Украины в области химии гетероциклических соединений и медицинской химии. Изложены результаты поиска новых лекарственных препаратов с базовыми структурами β-карболина, его S- и O- изостеров, изохинолина.

Ключевые слова: органический синтез, лекарственное средство, карболин, изохинолин, транквилизатор, онколитик.

Received 25.08.15