At the present stage of the development of organic and bioorganic chemistry, several basic approaches to the synthesis of pyrrolo[1,2-a]quinolines are known. These compounds are of interest to the researches primarily as bioregulators with a wide spectrum of biological activity. This review is an attempt to systematize and generalize literary data relating to the chemistry of pyrrolo[1,2-a]quinoline and its derivatives as important synthetic substrates and precursors for the design of biologically active substances. The main approaches to the synthesis of these compounds, consisting in various preparative methods for constructing a tricyclic base of pyrrolo[1,2-a]quinolone, were considered. The search for biologically active substances of this series is important and has a practical and theoretical significance.

Keywords: synthesis, quinolone, indolizine, pyrrolo[1,2-a]quinolone, biologically active substances.

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Introduction

One of the main directions of the development of chemistry is the search for substances with high biological effect, which can become the base for the creation of new biologically active substances that would be competitive as potential medicines in the market of imported and domestic products. Nitrogen-containing heterocyclic compounds are known as natural and synthetic molecules [1,2] that exhibit a wide range of biological effects [3–5]. Among various N-heterocycles, pyrrolo[1,2-a]quinoline derivatives attract considerable attention due to their unique biological activity [6–12]. It is well known that these substances show a wide spectrum of activities such as antibacterial, antifungal, antispasmodic and anti-inflammatory effects, tumor growth inhibitors, etc. [13]. Pyrrolo[1,2-a]quinoline derivatives are activators of caspases and inducers of apoptosis and are also used as therapeutically effective anticancer agents [14,15]. Due to these characteristics, functional derivatives of pyrrolo[1,2-a]quinolines draw considerable synthetic interest and various synthetic ways for their preparation were developed [16–18]. This review is an attempt to summarize literary sources on the synthetic and biological potential of pyrrolo[1,2-a]quinoline derivatives. At the present stage of the development of chemistry of nitrogen-containing heterocycles, several major approaches to the synthesis of the pyrrolo[1,2-a]quinoline heterocyclic system are known. Heterocyclic systems containing pyrrolo[1,2-a]quinoline core have a rich synthetic history and they are characterized by a wide range of synthesis methods. The production of this heterocycle is carried out in various ways, using quinoline, indolizin and their derivatives as a basis, and constructing a tricyclic structure by embedding a pyridine ring in a compound already containing two rings. Considering the relevance of the research of pyrrolo[1,2-a]quinolones and the positive tendency for their further development, it was expedient to systematize and generalize literary sources on the methods of their synthesis.

Synthesis based on quinoline and its derivatives

One of the common methods for the synthesis of pyrrolo[1,2-a]quinoline is the production on the basis of quinoline and its derivatives (via the nitrogen atom or via C₂) as a result of the alkylation reaction. For the first time, the pyrrolo[1,2-a]quinoline system was obtained by Chichibabin in the form of homologues of benzoindolizin (1927) [19].

Despite the fact that the reaction of haloketones with quinaldine (2-methylquinoline) proceeds easily, homologs of benzoindolizin can be obtained only in the form of non-crystallizing resins; such resins can be polymers of already formed compounds (Scheme 1). The reaction occurs in alcohol, followed by
processing the product with a solution of sodium bicarbonate [20].

However, later it was found that the interaction of quinaldine with chloroacetone or phenacyl bromide results in the formation of quinaldine hydrohalides, and not 1-acylalkyl-2-methylquinolinium halides (Scheme 2).

Further studies had shown that the nature of substituents in the quinoline cycle is significantly influenced by the yield of intermediate N-alkyl derivatives.

Pyrrolo[1,2-a]quinoline was prepared from quinaldine (3.1) bypass via oxalic acid derivatives (Scheme 3) [21].

Quantum-chemical calculations for 2-R-substituted quinoline and their 4-chloro-derivatives showed the effect of substituents on charges of carbon atom (in positions 2 and 4) and on endocyclic nitrogens and their changes when chlorine is entered in position C4. Thus, when the methyl group is entered in the 2nd position of the heterocycle, the value of the negative charge on the nitrogen atom is changed, the main properties of the quinoline cycle are increased. The chlorine atom in the 4th position increases the electronegativity of the nitrogen atom and the electron deficiency on the C4 atom. This can lead to an increase in the nucleophilic properties of the heteromolecule [22].

A further direction of research was developed in the study of complexes of transition metals, such as Pd [23–25], Cu [26–31], Cu/Pd [32], Rh [33], Ir [34], Pt [35], Fe/Au [36], Sm [37], Ce [38], etc. They are used as catalysts for the derivation of pyrrolo[1,2-a]quinoline derivatives; however, despite their potential utility, none of these procedures can directly provide end products with a lack of heavy metal admixtures [39–42].

When transition metals are used for the synthesis of pyrrolo[1,2-a]quinoline derivatives, I2/acids/carbonates were used as additives [43–46]. These studies have made a significant contribution to the synthesis of more efficient, simpler and more environmentally friendly techniques that are still needed for the synthesis of pyrrolo[1,2-a]quinolines. A highly efficient synthesis of pyrrolo[1,2-a]quinolines without catalysts was reported through dehydration, [3+2] cyclization of aldehydes and alkylating agents directly to 2-methylquinoline (Scheme 4) [47–51].

Considering the example of the interaction of 2-methylquinoline, benzaldehyde and diethylbut-2-yneedioate on the substrate and using a screening model with a series of measurements, the effect of the solvent and the reaction temperature on the yield of the reaction products was determined. It was shown that the most optimal solvent is PhCl and a...
Georgescu et al. [53] proposed another way of synthesizing pyrrolo[1,2-a]quinolines, which includes the 1,3-dipolar cyclic-addition reaction of heterocyclic N-ylides with electron deficient alkynes or alkenes. The key components of this multi-stage process are derivatives of quinoline (5.1), various bromoacetophenones (5.2), asymmetric electron deficiency alkynes (5.3) and 1,2-epoxypropane (Scheme 5). The last acts as a solvent and an acceptor of protons. Generally, the synthesis of pyrrolo[1,2-a]quinolines by quinoline of N-ylides requires the preparation and separation of quinoline salts in the first stage. Further, quinoline salts are converted into pyrrolo[1,2-a]quinoline by the treatment with an alkali that generates the corresponding quinoline N-ylide.

In this multi-stage process, the reaction mechanism involves the formation of intermediate of quinoline salt from the corresponding quinoline and 2-bromoacetophenone. In the next stage, the bromide salt ion is attacked by an oxyran ring 1,2-epoxypropane, as a result of which the ring is opened and the generation of N-ylide is carried out by an alkoxide. N-ylide reacts with activated (5.3), which makes it possible to obtain the corresponding dihydropyrroloquinoline. Finally, pyrroloquinolines are formed by dehydration of the intermediate compound of dihydropyrroloquinoline (Scheme 5) [53].

Catalysts CuNPS@ZnO–PTh are also used for the synthesis of pyrrolo[1,2-a]quinolone. The general catalytic system CuNPS@ZnO–PTh for the synthesis of various pyrrolo[1,2-a]quinolines by reactions between different substrates such as quinoline-2-carboxaldehyde, phenylacetylenes and secondary amines was studied to optimize the reaction conditions (Scheme 6) [54].

Practical methods are very desirable due to the complex requirements for the above-mentioned reactions. Thus, in one of the methods, a reaction was chosen which involves the interaction of easily accessible 2-alkylazoarenes with the use of methylene and nitroolefins of cerium (III) chloride as a catalyst under mild conditions. Optimization of the condensation reaction was accomplished by changing catalysts and solvents (Scheme 7).

The general scheme for the synthesis of pyrrolo[1,2-a]quinolines is presented in Scheme 8 [38].

Getting from arylalkins and N-arylpyrroles
Cheeseman et al. [55] reported the first reaction from arylalkines and N-arylpyrroles. It was found that (9.1) may act as a precursor of pyrrolo[1,2-
a]quinolone (Scheme 9). Accordingly, it was treated with chloromethylaldehyde with triethylphosphite (to activate chloromethyl halide), and then the intermediate phosphonate was reacted with sodium ethoxide. The main product formed in this process was pyrroloquinoline, which was isolated only in sequential quantities. The best outcomes were observed in the synthesis of 5-diethoxyphosphoryl derivatives (Scheme 9) [55].

In the case of N-unprotected pyrrole derivatives, it can be expected that the nitrogen atom acts as a nucleophile, and there is an exclusive carbocyclization form 1H-benzo[g]indoles. The simple path is opened for the formation and access to the skeleton of the pyrrolo[1,2-a]quinoline containing the heteroatom at the base. For comparison, different catalysts were selected, which acted on the substrate with substituents (R = H; C_6H_13). It was stated that PtCl_2 is the most effective catalyst for these reactions (Scheme 10) [56].

Mamane et al. [57] determined the effect of catalysts (PtCl_2, GaCl_3, and InCl_3) and substituents (R = H, Me, Ph, C_6H_13, and SiMe_3) on the yield of the target compounds. The smallest yield of the reaction product was observed at R=H when PtCl_2 was used as a catalyst, whereas InCl_3 (at R=C_6H_13) provided the highest yield (91%).

Hulcoop and Lautens [58] offered a way to obtain pyrroloquinolines using the synthesis of Retro-Diels-Alder products. The reaction proceeds with the formation of an intermediate products, it is selective and can be used to prepare compounds...
with different substituents ($R_1=CH_3$, $R_2=CHO$). The adding of the 2-position of the Ph group leads to a slight increase in the output of the target products (from 81% to 84%) (Scheme 11) [58].

An interesting method for the synthesis of 1-(2-bromophenyl)-1H-pyrrole/1-(2,6-dibromophenyl)-1H-pyrrole and N,N-diisopropylethylamine (DIPEA) with aromatic alkynes in the presence of catalytic amounts of rhodamine 6G (Rh-6G) with a blue light irradiation followed by an internally molecular cyclization leads to the formation of pyrrolo[1,2-a]quinolones [59]. The ring of pyrrolo[1,2-a]quinoline was obtained with a 60% yield and the reaction time of 24 hours. The high reduction power of an excited stable radical anion Rh-6G, prepared by photoradiation of xanthos dye nitrogen with visible light in the presence of DIPEA is used in this synthetic approach (Scheme 12). The reaction proceeds in visible light and at room temperature [59].

**Synthesis based on derivatives of pyridine or indolizine**

A fundamentally different approach to the synthesis of pyrrolo[1,2-a]quinolines is a synthesis based on derivatives of pyridine or indolizine. Most methods for the synthesis of indolizine include the 1,3-dipolar cyclocondensation of pyridine N-methylides with electron deficient alkins or alkenes and intramolecular catalysts, transition metals, and cyclizomerization of pyridines with specific C–2 functionalities.

However, these methods often require multi-stage synthesis. Thus, common and convenient methods for the synthesis of indolizines from simple and easily available precursors are still important (Scheme 13) [16,60–63].

Up-to-date synthetic methods require high and specific ligands, optimal temperature and the use of transition metals as catalysts; they are multi-stage processes. In some cases, the presence of cyclized and non-cyclized products formed during the reaction does not allow them to be effectively separated. Transition-metal-free catalysis in visible light is a selective and effective alternative method for the synthesis of pyrrolo[1,2-a]quinolines.
Conclusions
In conclusion, it is clear that pyrrolo[1,2-a]quinolines and their derivatives occupy an important place in the synthesis of heterocycles. Various approaches to the synthesis of pyrrolo[1,2-a]quinolines are presented in this article. New developments in the synthesis of pyrrolo[1,2-a]quinoline may be expected in the future.

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REFERENCES
1. Dragmacidins G and H, bisindole alkaloids tethered by a guanidino ethylthiopyrazine moiety, from a Lipastrotethya sp. marine sponge / Hitora Y., Takada K., Ise Y., Okada S., Matsunaga S. // J. Nat. Prod. – 2016. – Vol.79. – P.2973-2976.
2. Lamellarins and related pyrrole-derived alkaloids from marine organisms / Fan H., Peng J.G., Hamann M.T., Hu J.F. // Chem. Rev. – 2008. – Vol.108. – P.264-287.
3. Nauclea latifolia: biological activity and alkaloid phytochemistry of a West African tree / Boucherle B., Haudecoeur R., Queiroz E.F., de Waard M., Wolfender J.L., Robins R.J., Boumendjel A. // Nat. Prod. Rep. – 2016. – Vol.33. – P.1034-1043.
4. Legros J., Figadere B. Iron-promoted C–C bond formation in the total synthesis of natural products and drugs // Nat. Prod. Rep. – 2015. – Vol.32. – P.1541-1555.
5. A hexacycle, iboga-derived monoterpenoid indole with a contracted tetrahydroazepine C-ring and incorporation of an isoxazolidine moiety, a seco-corynanthean, an aspidosperma-aspidosperma bisindole with anticancer properties, and the absolute configuration of the pyridopyrimidine indole alkaloid, vemavosine // Nge C.E., Sim K.S., Lim S.H., Thomas N.F., Low Y.Y., Kam T.S. // J. Nat. Prod. – 2016. – Vol.79. – P.2709-2717.
6. Fluorescence and UV/Vis spectroscopic behaviour of novel biindolizines / Sonnenschein H., Henrich G., Resch-Genger U., Schulz B. // Dyes Pigm. – 2000. – Vol.46. – P.23-27.
7. Synthesis, ABTS-radical scavenging activity, and antiproliferative and molecular docking studies of novel pyrrolo[1,2-a]quinoline derivatives / Nanjappa C., Hanumanthappa S.K.T., Nagendarappa G., Ganapathy P.S.S., Shruthi S.D., More S.S., Jose G., Sommyna H.B.V., Kulkarni R.S. // Synth. Commun. – 2015. – Vol.45. – P.2529-2545.
8. Ravna A.W., Sager G. Molecular model of the outward facing state of the human multidrug resistance protein 4 (MRP4/ABCC4) // Bioorg. Med. Chem. Lett. – 2009. – Vol.18. – P.3481-3483.
9. Discovery of 1-benzoyl-3-cyanopyrrolo[1,2-a]quinolines as a new series of apoptosis inducers using a cell- and caspase-based high-throughput screening assay. Part 1: Structure–activity relationships of the 1- and 3-positions / Kemnitzer W., Kuemmerle J., Jiang S.C., Zhang H.Z., Sirisoma N., Kasibhatla S., Crogan-Grundy C., Tseng B., Drews J., Cai S.X. // Bioorg. Med. Chem. Lett. – 2008. – Vol.18. – P.6259-6264.
10. Amberlite–IRA-402 (OH) ion exchange resin mediated synthesis of indolizines, pyrrolo[1,2-a]quinolines and isoquinolines: Antibacterial and antifungal evaluation of the products / Hazra A., Mondal S., Maity A., Naskar S., Saha P., Pain R., Sahu K.B., Paina P., Ghosh S., Sinha C., Samanta A., Banerjee S., Mondal N.B. // Eur. J. Med. Chem. – 2011. – Vol.46. – P.2132-2140.
11. Reformatsky reactions with N-arylpyrrolidine-2-thiones: synthesis of tricyclic analogues of quinolone antibacterial agents / Michael J.P., de Koning C.B., Hosken G.D., Stanbury T.V. // Tetrahedron. – 2001. – Vol.57. – P.9635-9648.

Basic approaches to the synthesis of pyrrolo[1,2-a]quinolines derivatives: a review
12. Synthesis and antileukemic activity of bis[[carbamoyl]oxymethyl]-substituted pyrrolo[2,1-a]quinolines, pyrrolo[1,2-a]quinolines, pyrrolo[2,1-a]isobenzazepines, and pyrrolo[1,2-a]benzazepines / Anderson W.K., Heider A.R., Raju N., Yucht J.A. // J. Med. Chem. – 1988. – Vol.31. – P.2097-2102.

13. Pyrrolo[1,2-a]quinoxalines: novel synthesis via annulation of 2-alkylquinoxalines / Ammermann S., Hrib C., Jones P.G., du Mont W.-W., Kowalsky W., Johannes H.-H. // Org. Lett. – 2012. – Vol.14. – P.5900-5093.

14. Kianmehr E., Estiri H., Bahreman A. Efficient synthesis of pyrrolo[2,1-a]isoquinoline and pyrrolo[1,2-a]quinoline derivatives in aqueous media / J. Heterocycl. Chem. – 2009. – Vol.46. – P.7158-7174.

Addressing functionalized indolizines via copper-catalyzed annihilation of structurally diverse polyfunctional pyrrolo[1,2-a]quinolines and pyrrolo[1,2-a]quinoline derivatives by sequential iron-catalyzed three-component reactions // Chin. J. Chem. – 2012. – Vol. 30. – P.590-596.

15. Substituted 1-benzoyl-3-cyano-pyrrolo[1,2-a]quinolines and analogs as activators of caspases and inducers of apoptosis / Cai S.X., Drewe J.A., Jiang S., Kasibhatla S., Santarem M., Vanucci-Bacque C., Lhommet G. // Angew. Chem. Int. Ed. – 2001. – Vol.40. – P.1516-1518.

16. A novel and highly stereoselective intramolecular formal [3+2] cycloaddition reaction of vinloxygous amides tethered with α,β-unsaturated aldehydes: a formal total synthesis of (+)-gephyrotoxin / Wei L.L., Hsung R.P., Sklenicka H.M., Gerasyuto A.I. // Chem. Commun. – 2010. – Vol.46. – P.6341-6343.

17. Santarem M., Vanucci-Bacque C., Lhommet G. Formal total synthesis of (+)-gephyrotoxin / J. Org. Chem. – 2008. – Vol.73. – P.6466-6469.

18. Pearson W.H., Fang W.K. Synthesis of benzo-fused 1-azabicyclo[m.n.0]alkanes via the Schmidt reaction: a formal synthesis of gephyrotoxin / J. Org. Chem. – 2005. – Vol.70. – P.7158-7174.

19. Tschitschibabin A.E. Tautomerie in der Pyridin-Reihe. // Ber. Dtsch. Chem. Ges. (A and B Ser.). – 1927. – Vol.60. – P.1607-1617.

20. Tschitschibabin A.E. Patent DE464481, 1928.

21. Kochergin P.M., Druzhinina A.A. Synthesis of pyrrole-containing heteroaromatic systems with a bridging nitrogen atom / Ed. by Kartsev V.G. // Selected methods for the synthesis and modification of heterocyclics. – M.: IBS PRESS, 2003. - P.300-313.

22. Brazhko O.A., Yeveled A.S. Synthesis of pyrrolo[2,1-a]quinolines based on 4-substituted quinolone // Abstracts of the VII Ukrainian conference «Dombrowsky chemical readings-2017». – Ivano-Frankivsk: Ivano-Frankivsk National Medical University, 2017. - 92 p.

23. Palladium-catalyzed regioselective [3+2] annihilation of internal alkynes and iodo-pyranooquinolines with concomitant ring opening / Aggarwal T., Jha R.R., Tiwari, R.K., Kumar S., Kotla S.K.R., Kumar S., Verma A.K. // Org. Lett. – 2012. – Vol.14. – P.5184-5187.

24. Tandem synthesis of pyrroloacridones via [3+2] alkyne annulation/ring opening with concomitant intramolecular aldol condensation / Verma A.K., Kotla S.K.R., Aggarwal T., Kumar S., Nimesh H., Tiwari R.K. // J. Org. Chem. – 2013. – Vol.78. – P.5372-5384.

25. An efficient preparation of indolizines through a tandem palladium-catalyzed cross-coupling reaction and cyclosomerization / Kim H., Lee K., Kim S., Lee P.H. // Chem. Commun. – 2010. – Vol.46. – P.6341-6343.

26. Ligand-free Cu-catalyzed [3 + 2] cyclization for the synthesis of pyrrolo[1,2-a]quinolines with ambient air as terminal oxidant / Yu Y., Liu Y., Liu A., Xie H., Li H., Wang W. // Org. Biomol. Chem. – 2016. – Vol.14. – P.7455-7458.

27. Copper-catalyzed C–H alkylation/intramolecular cyclization cascade for the first synthesis of trifluoromethylated pyrrolo[1,2-a]quinolines / Xu Z., Ni F., Han J., Tao L., Deng H., Shao M., Chen J., Zhang H., Cao W. // Eur. J. Org. Chem. – 2016. – Vol.2016. – No. 17. – P.2959-2965.

28. Albaladejo M.J., Alonso F., Yus M. Synthesis of indolizines and heterocyclic chalcones catalyzed by supported copper nanoparticles // Chem. Eur. J. – 2013. – Vol.19. – P.5242-5245.

29. Efficient one-pot synthesis of pyrrolo[2,1-a]isoquinoline and pyrrolo[1,2-a]quinoline derivatives / Liu Z.M., Wu L., Sun J., Yan C.G. // Chem. Res. Chin. Univ. – 2012. – Vol.28. – P.990-993.

30. Synthesis of functionalized indolizines via copper-catalyzed annulation of 2-alkylazaarenes with α,β-unsaturated carboxylic acids / Yang Y., Xie C., Xie Y., Zhang Y. // Org. Lett. – 2012. – Vol.14. – P.957-959.

31. Indolizine synthesis via oxidative cross-coupling/cyclization of alkynes and 2-(pyridin-2-yl)acetate derivatives / Liu R.R., Hong J.J., Lu C.J., Xu M., Gao J.R., Jia Y.X. // Org. Lett. – 2015. – Vol.17. – P.3050-3053.

32. Wu L., Sun J., Yan C.G. Efficient synthesis of pyrrolo[2,1-a]isoquinoline and pyrrolo[1,2-a]quinoline derivatives via one-pot two-step metal-catalyzed three-component reactions // Chin. J. Chem. – 2012. – Vol. 30. – P.590-596.

33. Shen B., Li B., Wang B. Rh(III)-catalyzed oxidative annulation leading to substituted indolizolines by cleavage of C(sp3)–H/C(sp3)–H bonds // Org. Lett. – 2016. – Vol.18. – P.2816-2819.

34. Iridium-catalyzed intramolecular asymmetric allylic dearomatization reaction of pyridines, pyrazines, quinolines and isquinolines / Yang Z.P., Wu Q.F., Shao W., You S.L. // J. Am. Chem. Soc. – 2015. – Vol.137. – P.15899-15906.

35. Pt-catalyzed cyclization/1,2-migration for the synthesis of indolizines, pyrrolones, and indolizinones // Smith C.R., Bunnelle E.M., Rhodes A.J., Sarpong R. // Org. Lett. – 2007. – Vol.9. – P.1169-1171.

36. Synthesis of structurally diverse polyfunctional pyrrolo[1,2-a]quinolines by sequential iron-catalyzed three-component coupling and gold-catalyzed hydroarylation reactions // Sarkar S., Bera K., Jalal S., Jana U. // Eur. J. Org. Chem. – 2013. – Vol.2013. – P.6055-6061.

37. Samarium(III)-catalyzed C(sp3)–H bond activation: synthesis of indolizines via C–C and C–N coupling between 2-alkylazaarenes and propargylic alcohols / Wang X., Li S.Y.,
Basic approaches to the synthesis of pyrrolo[1,2-a]quinolines derivatives: a review

Pan Y.M., Wang H.S., Liang H., Chen Z.F., Qin X.H. // Org. Lett. – 2014. – Vol.16. – P.580-583.

38. Cerium(III)-catalyzed cascade cyclization: an efficient approach to functionalized pyrrolo[1,2-a]quinolones / Feng C., Yan Y., Zhang Z., Xu K., Wang Z. // Org. Biomol. Chem. – 2014. – Vol.12. – P.4837-4840.

39. Zhang W.Z., Yang M.W., Lu X.B. Carboxylative cyclization of substituted propenyl ketones using CO\textsubscript{2}: transition-metal-free synthesis of α-pyrones // Green Chem. – 2016. – Vol.18. – P.4181-4184.

40. Garrett C.E., Prasad K. The art of meeting palladium specifications in active pharmaceutical ingredients produced by Pd-catalyzed reactions // Adv. Synth. Catal. – 2004. – Vol.346. – P.889-900.

41. Adsorben screening for metal impurity removal in pharmaceutical process research / Welch C.J., Albanez-Walker J., Leonard W.R., Biba M., Da Silva J., Henderson D., Laing B., Matthee D.J., Spencer S., Bu X., Wang T. // Org. Process Res. Dev. – 2005. – Vol.9. – P.198-205.

42. Balaram V. Recent advances in the determination of elemental impurities in pharmaceuticals – status, challenges and moving frontiers // TrAC, Trends Anal. Chem. – 2016. – Vol.80. – P.3-8.

43. 1-(2-Allylaryl)-1H-pyroles as building blocks for novel 4-methyl-3,5-di-hydropyrrolo[1,2-a]quinoline derivatives / Orejarena J.C., Gomez S.L., Palma A., Cobo J., Nogueras M. // Synlett. – 2014. – Vol.25. – P.243-246.

44. I,3-Dipolar cycloadditions of 4-acetoxy allenolates: access to 2,3-dihydropyrazoles, 2,3-dihydroisoxazoles, and indolizines / Li F., Chen J., Hou Y., Li Y., Wu X.Y., Tong X. // Org. Lett. – 2015. – Vol.17. – P.5376-5379.

45. Bakshi D., Singh A. Transition-metal-free synthesis of nitrogen containing heterocycles with fully substituted N-fused pyrrole rings // Asian J. Org. Chem. – 2016. – Vol.5. – P.70-73.

46. One-pot multicomponent synthesis of polysubstituted indolizines / Mao Z., Li X., Lin X., Lu P., Wang Y. // Tetrahedron. – 2012. – Vol.68. – P.85-91.

47. Cu(I)-catalyzed multicomponent cascade reactions of terminal alkynes, unactivated primary alkyl bromides, CO, and NaN\textsubscript{3} / Wu F.S., Tong W., Liang Y., Wang H.S., Teng Q.H., Pan Y.M. // RSC Adv. – 2016. – Vol.6. – P.63855-63858.

48. Transition metal-free synthesis of 3-alkynylpyrrole-2-carboxylates via Michael addition/intramolecular cyclodehydrations / Teng Q.H., Xu Y.L., Liang Y., Wang H.S., Wang Y.C., Pan Y.M. // Adv. Synth. Catal. – 2016. – Vol.358. – P.1897-1902.

49. A novel methodology for synthesis of dihydropyrazole derivatives as potential anticancer agents / Wang X., Pan Y.M., Huang X.C., Mao Z.Y., Wang H.S. // Org. Biomol. Chem. – 2014. – Vol.12. – P.2028-2032.

50. Catalyst-free synthesis of fused 1,2,3-triazole and isoindoline derivatives via an intramolecular azide–alkene cascade reaction / Xie Y.Y., Wang Y.C., He Y., Hu D.C., Wang H.S., Pan Y.M. // Green Chem. – 2017. – Vol.19. – P.656-659.

51. Palladium-catalyzed synthesis of benzoazoles by the cleavage reaction of carbon-carbon triple bonds with α-amino-phenol / Xie H.Z., Gao Q., Liang Y., Wang H.S., Pan Y.M. // Green Chem. – 2014. – Vol.16. – P.2132-2135.

52. Catalyst-free synthesis of pyrrolo[1,2-a]quinolines via dehydration/[3+2] cycloaddition directly from 2-methylquinolines, aldehydes, and alkyanoates / Wu F.S., Zhao H.Y., Xu Y.L., Hu K., Pan Y.M., Ma X.L. // J. Org. Chem. – 2017. – Vol.82. – P.4289-4296.

53. One-pot, three-component synthesis of a library of new pyrrolo[1,2-a]quinoline derivatives / Georgescu E., Caira M.R., Georgescu F., Draghici B., Popa M.M., Dumitrascu F. // Synlett. – 2009. – Vol.11. – P.1795-1799.

54. Microwave assisted one pot three component synthesis of propargylamine, tetra substituted propargylamine and pyrrolo[1,2-a]quinolines using CuNPs@ZnO–PTh as a heterogeneous catalyst / Shah A.P., Sharma A.S., Jain S., Shimpi N.G. // New J. Chem. – 2018. – Vol.42. – P.8724-8737.

55. Cheseeman G.W.H., Eccleshall S.A., Thornton T. Some cyclisation reactions of 2,2-disubstituted-N-arylpyrroles // J. Heterocycl. Chem. – 1985. – Vol.22. – P.809-811.

56. Fuerstner A., Mamane V. Flexible synthesis of phenanthrenes by a PdC\textsubscript{11}-catalyzed cycloisomerization reaction // J. Org. Chem. – 2002. – Vol.67. – P.6264-6267.

57. Mamane V., Hannen P., Fuerstner A. Synthesis of phenanthrenes and polycyclic heteroarenes by transition-metal catalyzed cycloisomerization reactions // Chem. Eur. J. – 2004. – Vol.10. – P.4556-4575.

58. Hulcoop D.G., Lautens M. Palladium-catalyzed annulation of aryl heterocycles with strained alkenes // Org. Lett. – 2007. – Vol.9. – P.1761-1764.

59. Das A., Ghosh I., Konig B. Synthesis of pyrrolo[1,2-a]quinolines and ullazines by visible light mediated one- and twofold annulation of N-arylpyrroles with arylalkynes // Chem. Commun. – 2016. – Vol.52. – P.8695-8698.

60. On the electronic transport properties of pyrrolo[1,2-a][1,10]phenanthroline derivatives in thin films / Leontie L., Druta C., Balaram V., Hulcoop D.G., Lautens M. // Chem. Commun. – 2016. – Vol.52. – P.8695-8698.

61. Ahmed, S.A. Photochromism of dihydroindolizines. Part VI: synthesis and photochromic behavior of a novel type of IR-absorbing photochromic compounds based on highly conjugated dihydroindolizines // J. Phys. Org. Chem. – 2006. – Vol.19. – P.402-414.

62. Allocen and acetylenic spiropiperidine alkaloids from the neotropical frog, dendrobates histrionicus / Tokuyama T., Uenoyama K., Brown G., Daly J.W., Witkop B. // Helv. Chim. Acta. – 1974. – Vol.57. – P.2597-2604.

63. Fujimoto R., Kishi Y., Blount J.F. Total synthesis of (+-)-gephyrotoxin // J. Am. Chem. Soc. – 1980. – Vol.102. – P.7154-7156.

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PYRROLO[1,2-A]QUINOLINES DERIVATIVES: A REVIEW

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At the present stage of the development of organic and bioorganic chemistry, several basic approaches to the synthesis of pyrrolo[1,2-a]quinolines are known. These compounds are of interest to the researchers primarily as bioregulators with a wide spectrum of biological activity. This review is an attempt to systematize and generalize literary data relating to the chemistry of pyrrolo[1,2-a]quinoline and its derivatives as important synthetic substrates and precursors for the design of biologically active substances. The main approaches to the synthesis of these compounds, consisting in various preparative methods for constructing a tricyclic base of pyrrolo[1,2-a]quinolone, were considered. The search for biologically active substances of this series is important and has a practical and theoretical significance.

Keywords: synthesis; quinolone; indolizine; pyrrolo[1,2-a]quinolone; biologically active substances.

REFERENCES

1. Hitora Y., Takada K., Isé Y., Okada S., Matsunaga S. Dragmacidins G and H, bisindolylalkoids tethered by a guanidino ethyliptyropyrazine moiety, from a Lipastrotethya sp. marine sponge. Journal of Natural Products, 2015, vol. 78, pp. 6259-6264.

2. Fan H., Peng J.G., Hamann M.T., Hu J.F. Lamellarins ABCC4). Synthesis and antileukemic activity of pyrrolo[2,1-a]isoquinolines, pyrrolo[1,2-a]quinolines, pyrrolo[1,2-a]isobenzazepines, and pyrrolo[1,2-a]benzazepines. Journal of Medicinal Chemistry, 1988, vol. 31, pp. 2097-2102.

3. Boucherle B., Haudecoeur R., Queiroz E.F., de Waard M., Paira R., Sahu K.B., Paira P., Ghosh S., Sinha C., Samanta A., Banerjee S., Mondal N.B. Amberlite–IRA-402 (OH) ion exchange resin mediated synthesis of indolizines, pyrrolo[1,2-a]quinolines and isoquinolines: antibacterial and antifungal evaluation of the products. European Journal of Medicinal Chemistry, 2011, vol. 46, pp. 2132-2140.

4. Anderson W.K., Heider A.R., Raju N., Yucht J.A. Synthesis and antileukemic activity of bis[[(carbamoyl)oxy]methyl]-substituted pyrrolo[2,1-a]isoquinolines, pyrrolo[1,2-a]quinolines, pyrrolo[2,1-a]benzazepines, and pyrrolo[1,2-a]benzazepines. Journal of Medicinal Chemistry, 1988, vol. 31, pp. 2097-2102.

5. Nge C.E., Sim K.S., Lim S.H., Thomas N.F., Low Y.Y., Kam T.S. A hexacyclic, iboga-derived monoterpenoid iodide with a contracted tetrahydroazepine C-ring and incorporation of an oxazolodine moiety, a sec-o-corynanthean, an aspidosperma-aspidosperma bisindole with anticancer properties, and the absolute configuration of the pyridopyrimidine iodide alkald, vernavosine. Journal of Natural Products, 2016, vol. 79, pp. 2709-2717.

6. Sonnenschein H., Henrich G., Resch-Genger U., Schulz B. Fluorescence and UV/Vis spectroscopic behaviour of novel biindolizines. Dyes and Pigments, 2000, vol. 46, pp. 23-27.

7. Nanjappa C., Hanumanthappa S.K.T., Nagendrappa G., Ganapathy P.S.S., Shruthi S.D., More S.S., Joge G., Sowmya H.B.V., Kulkarni R.S. Synthesis, ABTS-radical scavenging activity, and antiproliferative and molecular docking studies of novel pyrrolo[1,2-a]quinoline derivatives. Synthetic Communications, 2015, vol. 45, pp. 2529-2545.

8. Ravna A.W., Sager G. Molecular model of the outward facing state of the human multidrug resistance protein 4 (MRP4/ABCC4). Bioorganic & Medicinal Chemistry Letters, 2008, vol. 18, pp. 3481-3483.

9. Kemnitzer W., Kueammerle J., Jiang S., Zhang H.Z., Sirisoma N., Kasibhatla S., Crogan-Grundy C., Tseng B., Drewes J., Cai S.X. Discovery of 1-benzoyl-3-cyanopyrrolo[1,2-a]quinolines as a new series of apoptosis inducers using a cell- and caspase-based high-throughput screening assay. Part 1: Structure-activity relationships of the 1- and 3-positions. Bioorganic & Medicinal Chemistry Letters, 2008, vol. 18, pp. 6259-6264.

10. Hazra A., Mondal S., Maity A., Naskar S., Saha P., Paire R., Sahu K.B., Paire P., Ghosh S., Sinha C., Samanta A., Banerjee S., Mondal N.B. Amberlite–IRA-402 (OH) ion exchange resin mediated synthesis of indolizines, pyrrolo[1,2-a]quinolines and isoquinolines: antibacterial and antifungal evaluation of the products. European Journal of Medicinal Chemistry, 2011, vol. 46, pp. 2132-2140.

11. Michael J.P., de Koning C.B., Hosken G.D., Stanbury T.V. Reformatsky reactions with N-arylpyrrolidine-2-thiones: synthesis of tricyclic analogues of quinolone antibacterial agents. Tetrahedron, 2001, vol. 57, pp. 9635-9648.

12. Anderson W.K., Heider A.R., Raju N., Yucht J.A. Synthesis and antileukemic activity of bis[[(carbamoyl)oxy]methyl]-substituted pyrrolo[2,1-a]isoquinolines, pyrrolo[1,2-a]quinolines, pyrrolo[2,1-a]benzazepines, and pyrrolo[1,2-a]benzazepines. Journal of Medicinal Chemistry, 1988, vol. 31, pp. 2097-2102.

13. Ammermann S., Heib C., Jones P.G., du Mont W.W., Kowalsky W., Johannes H.H. Pyrrolo[1,2-a]quinoloxalines: novel synthesis via annulation of 2-alkylquinoloxalines. Organic Letters, 2012, vol. 14, pp. 5090-5093.

14. Kianmehr E., Estiri H., Bahreman A. Efficient synthesis of pyrrolo[2,1-a]isoquinoline and pyrrolo[1,2-a]quinoline derivatives in aqueous media. Journal of Heterocyclic Chemistry, 2009, vol. 46, pp. 1203-1207.

O.A. Brazhko, A.S. Yevlash, M.P. Zavgorodnii, M.M. Kornet, O.O. Brazhko, A.V. Lagron
Basic approaches to the synthesis of pyrrolo[1,2-α]quinolines derivatives: a review

15. Cai S.X., Drewe J.A., Jiang S., Kasibhatla S., Kuenmerle J.D., Sirsoma N.S., Zhang H.-Z., Substituted 1-benzoyl-3-cyano-pyrrolo [1,2-α] quinolines and analogs as activators of caspases and inducers of apoptosis. Patent US, no. 7135480 B2, 2006.

16. Wei L.L., Huang R.P., Sklenicka H.M., Gerasyuto A.I. A novel and highly stereoselective intramolecular formal [3+3] cycloaddition reaction of vinylogous amides tethere d with α,β-unsaturated aldehydes: a formal total synthesis of (+)-gephyrotoxin. Angewandte Chemie International Edition, 2001, vol. 40, pp. 1516-1518.

17. Santarem M., Vanucci-Bacque C., Lhommet G. Formal total synthesis of (+)-gephyrotoxin. The Journal of Organic Chemistry, 2008, vol. 73, pp. 6466-6469.

18. Pearson W.H., Fang W.K. Synthesis of benzo-fused 1-azabicyclo[m.n.0]alkanes via the Schmidt reaction: a formal synthesis of gephrytoxin. The Journal of Organic Chemistry, 2000, vol. 65, pp. 7158-7174.

19. Tschitschibabin A.E. Tautomerie in der Pyridin-Reihe. Berichte der Deutschen Chemischen Gesellschaft (A and B Series), 1927, vol. 60, pp. 1607-1617 (in German).

20. Tschitschibabin A.E., Patent DE464481, 1928.

21. Kochergin P.M., Druzhinina A.A., Synthesis of pyrrole-containing heteroaromatic systems with a bridging nitrogen atom. In: Kartsev V.G. (ed.) Selected methods for the synthesis and modification of heterocycles. IBS PRESS, Moscow, 2003, pp. 300-313.

22. Bzrehko O.A., Yevlash A.S., Synthesis of pyrrolo[1,2-α]quinolines based on 4-substituted quinoline. Abstracts of the VIII Ukrainian conference «Dombrovsky chemical readings-2017», Ukraine, Ivano-Frankivsk, 2017. 92 p.

23. Aggarwal T., Jha R.R., Tiwari, R.K., Kumar S., Kotla S.K.R., Verma A.K. Palladium-catalyzed regioselective [3+2] annulation of internal alkynes and iodo-pyranonoquinolines with concomitant ring opening. Organic Letters, 2012, vol. 14, pp. 5184-5187.

24. Verma A.K., Kotla S.K.R., Aggarwal T., Kumar S., Nimesh H., Tiwari R.K. Tandem synthesis of pyrroloacridones via [3+2] alkyne annulation/ring opening with concomitant intramolecular alld condensation. The Journal of Organic Chemistry, 2013, vol. 78, pp. 5372-5384.

25. Kim H., Lee K., Kim S., Lee P.H. An efficient preparation of indolizines through a tandem palladium-catalyzed cross-coupling reaction and cyclosomerization. Chemical Communications, 2010, vol. 46, pp. 6341-6343.

26. Yu Y., Liu Y., Liu A., Xie H., Li H., Wang W. Ligand-free Cu-catalyzed [3 + 2] cyclization for the synthesis of pyrrolo[1,2-α]quinolines with ambient air as terminal oxidant. Organic & Biomolecular Chemistry, 2016, vol. 14, pp. 7455-7458.

27. Xu Z., Ni F., Han J., Tao L., Deng H., Shao M., Chen J., Zhang H., Cao W. Copper-catalyzed C–H alkylation/ intramolecular cyclization cascade for the first synthesis of trifluoroacrylated pyrrolo[1,2-α]quinolines. European Journal of Organic Chemistry, 2016, vol. 2016, no. 17, pp. 2959-2965.

28. Albalaidejo M.J., Alonso F., Yus M. Synthesis of indolizines and heterocyclic chalcones catalyzed by supported copper nanoparticles. Chemistry – A European Journal, 2013, vol. 19, pp. 5242-5245.

29. Liu Z.M., Wu L., Sun J., Yan C.G. Efficient one-pot synthesis of pyrrolo[2,1-α]quinoline and pyrrolo[1,2-α]quinolines derivatives. Chemical Research in Chinese Universities, 2012, vol. 28, pp. 990-993.

30. Yang Y., Xie C., Xie Y., Zhang Y. Synthesis of functionalized indolizines via copper-catalyzed annulation of 2-alkylazaarenes with α,β-unsaturated carboxylic acids. Organic Letters, 2012, vol. 14, pp. 957-959.

31. Liu R.R., Hong J.J., Lu C.J., Xu M., Gao J.R., Jia Y.X. Indolizine synthesis via oxidative cross-coupling/ cyclization of alkenes and 2-(pyridin-2-yl)acetate derivatives. Organic Letters, 2015, vol. 17, pp. 3050-3053.

32. Wu L., Sun J., Yan C. Efficient synthesis of pyrrolo- [2,1-α]quinoline and pyrrolo[1,2-α]quinoline derivatives via one-pot two-step metal-catalyzed three-component reactions. Chinese Journal of Chemistry, 2012, vol. 30, pp. 590-596.

33. Shen B., Li B., Wang B. Rh(III)-catalyzed oxidative annulation leading to substituted indolizines by cleavage of C(sp2)–H/C(sp3)–H bonds. Organic Letters, 2016, vol. 18, pp. 2816-2819.

34. Yang Z.P., Wu Q.F., Shao W., You S.L. Iridium-catalyzed intramolecular asymmetric allylic dearmatization reaction of pyridines, pyrazines, quinolines and isoquinolines. Journal of the American Chemical Society, 2015, vol. 137, pp. 15899-15906.

35. Smith C.R., Bunnelle E.M., Rhodes A.J., Sarpong R. Pt-Catalyzed cyclization/1,2-migration for the synthesis of indolizines, pyrrolones, and indolizinones. Organic Letters, 2007, vol. 9, pp. 1169-1171.

36. Sarkar S., Bera K., Jalal S., Jana U. Synthesis of structurally diverse polyfunctional pyrrolo[1,2-α]quinolines by sequential iron-catalyzed three-component coupling and gold-catalyzed hydroarylation reactions. European Journal of Organic Chemistry, 2013, vol. 2013, no. 27, pp. 6055-6061.

37. Wang X., Li S.Y., Pan Y.M., Wang H.S., Liang H., Chen Z.F., Qin X.H. Samarium(III)-catalyzed C(sp3)–H bond activation: synthesis of indolizines via C–C and C–N coupling between 2-alkylazaarenes and propargylic alcohols. Organic Letters, 2014, vol. 16, pp. 580-583.

38. Feng C., Yan Y., Zhang Z., Xu K., Wang Z. Cerium(III)-catalyzed cascade cyclization: an efficient approach to functionalized pyrrolo[1,2-α]quinolines. Organic & Biomolecular Chemistry, 2014, vol. 12, pp. 4837-4840.

39. Zhang W.Z., Yang M.W., Lu X.B. Carboxylative cyclization of substituted propenyl ketones using CO2; transition-metal-free synthesis of α-pyrones. Green Chemistry, 2016, vol. 18, pp. 4181-4184.

40. Garrett C.E., Prasad K. The art of meeting palladium specifications in active pharmaceutical ingredients produced by Pd-catalyzed reactions. Advanced Synthesis & Catalysis, 2004, vol. 346, pp. 889-900.
