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BASIC APPROACHES TO THE SYNTHESIS OF 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 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

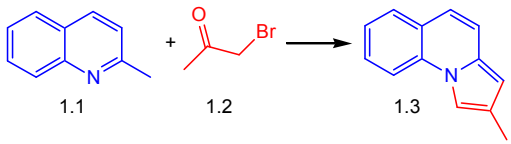
One of the main directions of the development of chemistry is the search for substances with high biological effect, which can become the base for the creation of new biologically active substances that would be competitive as potential medicines in the market of imported and domestic products. Nitrogen-containing 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 C_2) 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 benzoindolizine (1927) [19].

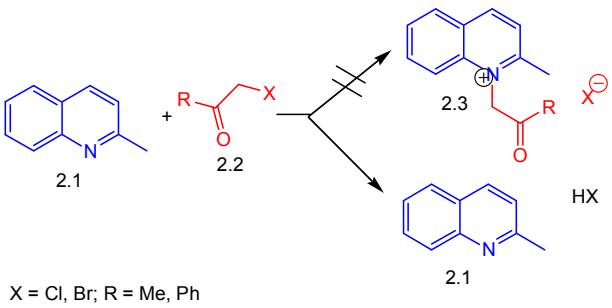
Despite the fact that the reaction of haloketones with quinaldine (2-methylquinoline) proceeds easily, homologs of benzoindolizin can be obtained only in the form of non-crystallizing resins; such resins can be polymers of already formed compounds (Scheme 1). The reaction occurs in alcohol, followed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

processing the product with a solution of sodium bicarbonate [20].



Scheme 1

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).



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.

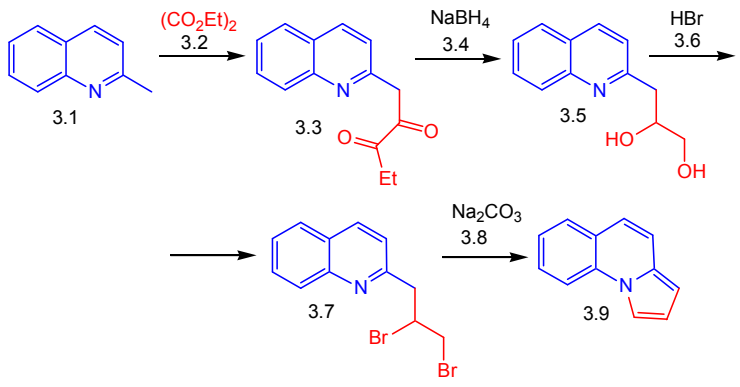
Pyrrolo[1,2-a]quinoline was prepared from quinaldine (3.1) bypass via oxalic acid derivatives (Scheme 3) [21].

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 C_4. 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 C_4 atom. This can lead to an increase in the nucleophilic properties of the heteromolecule [22].

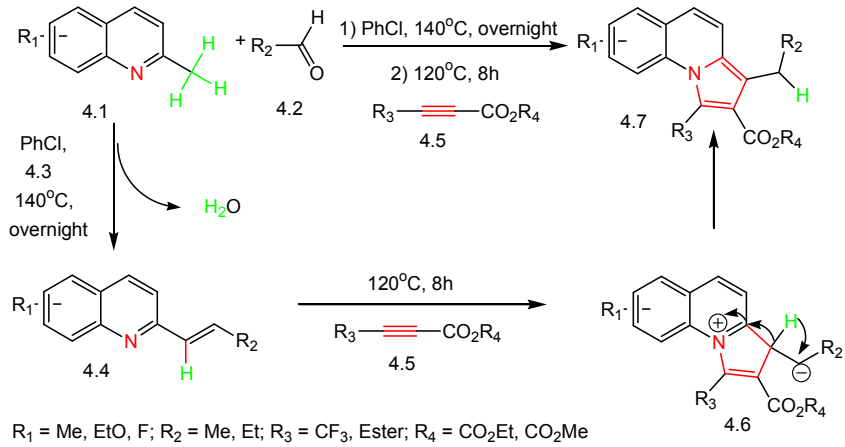
A further direction of research was developed in the study of complexes of transition metals, such as Pd [23–25], Cu [26–31], Cu/Pd [32], Rh [33], Ir [34], Pt [35], Fe/Au [36], Sm [37], Ce [38], etc. They are used as catalysts for the derivation of pyrrolo[1,2-a]quinoline derivatives; however, despite 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 using for the synthesis of pyrrolo[1,2-a]quinoline derivatives, I_2/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-ynedioate 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

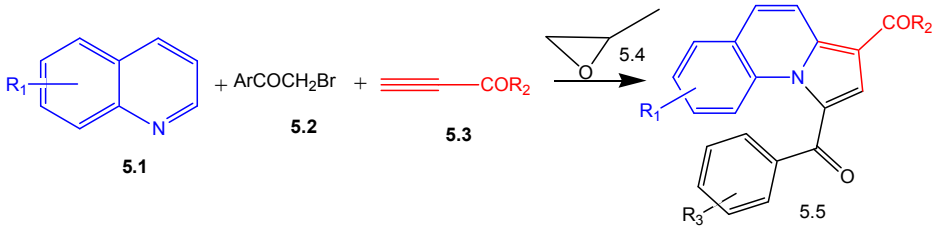


Scheme 3



R_1 = Me, EtO, F; R_2 = Me, Et; R_3 = CF_3, Ester; R_4 = CO_2Et, CO_2Me

Scheme 4



R_1 = H, Me; R_2 = OEt, Me, Ph; R_3 =H, 4-F, 4-Cl, 4-Br, 3-MeO, 4-MeO, 3-NO_2, 4-Ph, 4-Me, 3-Br, 4-CN

Scheme 5

temperature is 120°C (89%) [52].

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 dehydrification of the intermediate compound of dihydropyrroloquinoline (Scheme 5) [53].

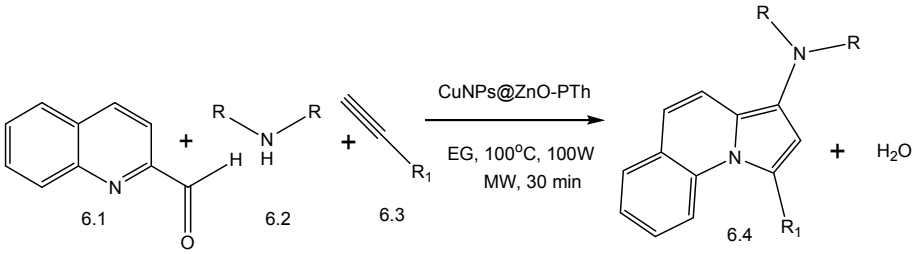
Catalysts CuNPS@ZnO–PTh are also used for the synthesis of pyrrolo[1,2-a]quinolone. The general catalytic system CuNPS@ZnO–PTh for the synthesis of various pyrrolo[1,2-a]quinolines by reactions between different substrates such as quinoline-2-carboxaldehyde, phenylacetylenes and secondary amines was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

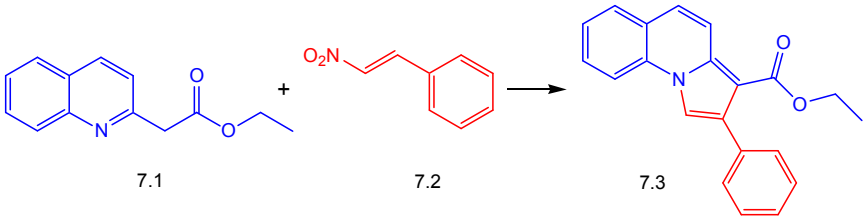
Getting from arylalkins and N-arylpyrrols

Cheeseman et al. [55] reported the first reaction from arylalkines and N-arylpyrrole. It was found that (9.1) may act as a precursor of pyrrolo[1,2-

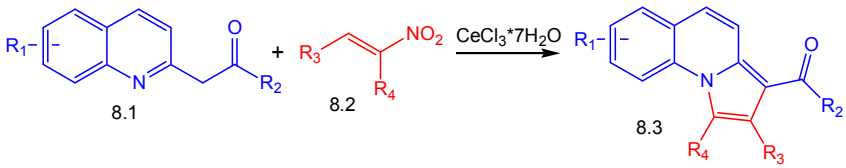


R=Piperidine, Pyrrolidin, Morpholine
R_1=Ph, C_3H_5, 4-Br-C_6H_4, 4-OCH_3-C_6H_4, 4-CH_3-C_6H_4

Scheme 6



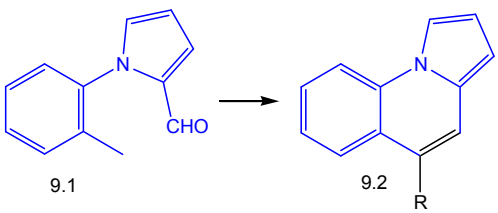
Scheme 7



R_1 = H, 7-OCH_3, 7-Cl, 7-Br, 7-CF_3; R_2 = OEt, Ph; R_3 = Ph, $C_6H_4CH_3$, $C_6H_4NH_2$; R_4 =H.

Scheme 8

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].



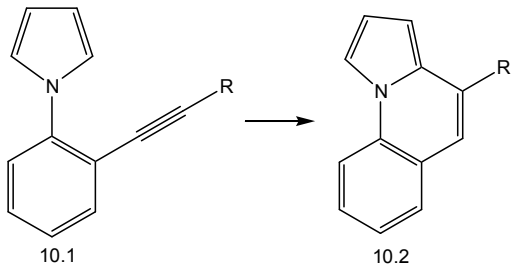
R = H, O-P[OC_2H_5]2

Scheme 9

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



R = H, Me, COOMe, C_6H_4OMe

Scheme 10

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].

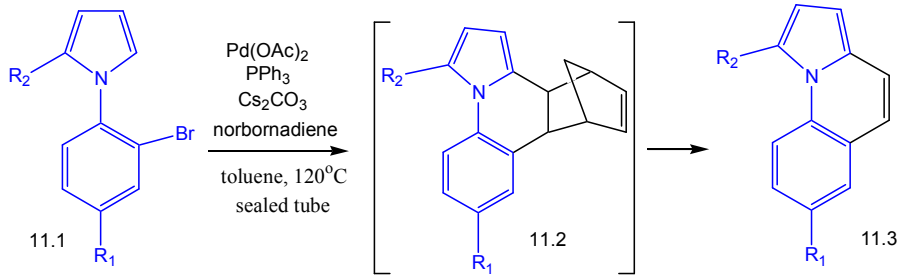
An interesting method for the synthesis of 1-(2-bromophenyl)-1H-pyrrole/1-(2,6-dibromofenyl)-1H-pyrrole and N,N-diisopropylethylamine (DIPEA) with aromatic alkynes in the presence of catalytic amounts of rhodamine 6G (Rh-6G) with a blue light irradiation followed by an internally molecular cyclization 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 cycloconduction of pyridine N-methylides with electron deficient alkins or alkenes and intramolecular catalysts, transition metals, and cyclizomerization of pyridines with specific C−2 functionalities.

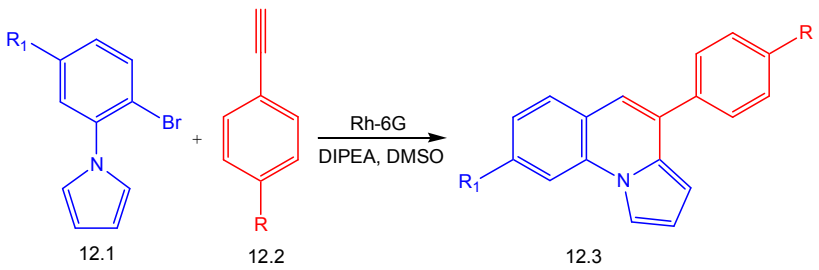
However, these methods often require multi-stage synthesis. Thus, common and convenient methods for the synthesis of indolizines from simple and easily available precursors are still important (Scheme 13) [16,60−63].

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.



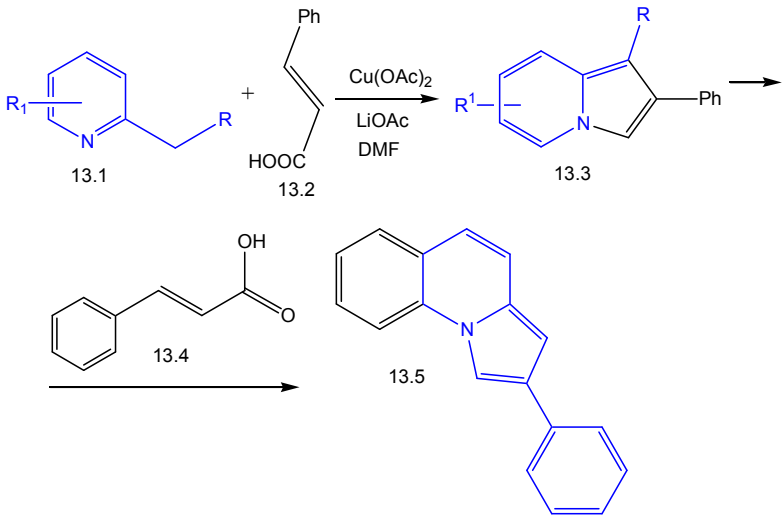
R_1 = H, Me, F, Cl; R_2 = H, CHO

Scheme 11



R = H, $COCH_3$, CF_3; R_1 = H, CH_3, OCH_3, F, Cl

Scheme 12



R= H, Me, n-C_4H_9, Ph, CN, COOEt; R^1= aryl, heteroaryl

Scheme 13

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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ОСНОВНІ ПІДХОДИ ДО СИНТЕЗУ ПОХІДНИХ ПІРРОЛО[1,2-А]ХІНОЛІНІВ: ОГЛЯД

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На сучасному етапі розвитку органічної та біоорганічної хімії відомо декілька основних підходів до синтезу піррол[1,2-а]хінолінів, які цікаві, у першу чергу, як біорегулятори з широким спектром біологічної активності. Дана оглядова стаття є спробою систематизувати та узагальнити літературні джерела, що стосуються хімії піррол[1,2-а]хіноліну, його похідних як важливих синтетичних субстратів і попередників для конструювання біологічно активних речовин. Розглянуто основні підходи до синтезу даної низки сполук, що полягають у різних препаративних методиках побудови трициклічної основи піррол[1,2-а]хіноліну. Пошук біологічно активних речовин у даній низці сполук є доцільним, має практичну і теоретичну значимість.

Ключові слова: синтез, хінолін, індолізин, піррол-[1,2-а]хінолін, біологічно активні речовини.

BASIC APPROACHES TO THE SYNTHESIS OF 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 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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