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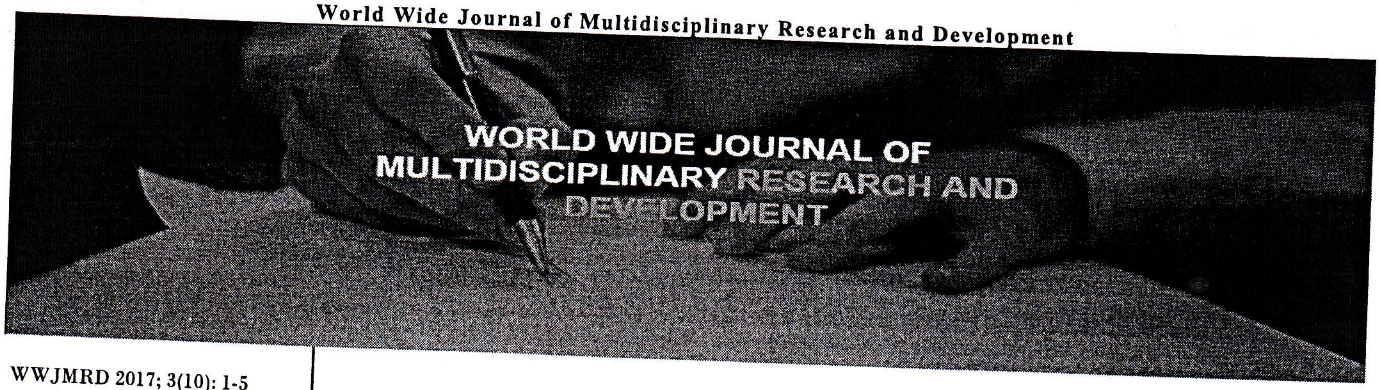

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Selective Bromination of Tricyclic Quinazolones

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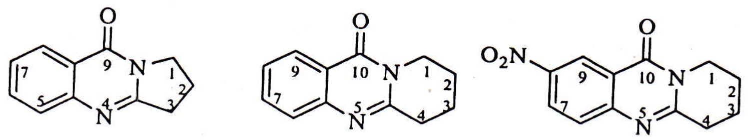
Abstract
Bromination of the tricyclic quinazolones – deoxyvasicinone (1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-9-one, 1), mackinazolinone (2,3,4,10-tetrahydropyrido[2,1-b]quinazolin-10-one, 2), 8-nitromackinazolinone (8-nitro-2,3,4,10-tetrahydropyrido[2,1-b]quinazolin-10-one, 3) and their some analogues have been systematically studied. It was found that depending on the reaction conditions and structures of the starting compounds takes place bromination on the aromatic ring, on N1=C2 double bound of pyrimidine ring or on methylene groups of the α-position (C-4). Selective bromination of 8-nitromackinazolinone (3) was investigated by N-bromosuccinimide (NBS) in the presence of benzoyl peroxide (BZP) in anhydrous tetrachloromethane. It was developed the method for monobromination of initial compound. The synthesized optical isomers of (*R, S*)-4-bromo-8-nitromackinazolinone (16) are quantitatively separated on HPLC column, consisting chiral adsorbent. Bromination direction and a course of the reactions with inorganic bromates, molecular bromine and N-bromosuccinimide were discussed. It was revealed that using allylic bromination method (*Wohl-Ziegler Reaction*) for compound 3 gives exclusively and in high yield targeted chiral compound - (*R, S*)-4-bromo-8-nitromackinazolinones (16).

Keywords: 8H (nitro)-mackinazolinones, activated methylene group, selective bromination, optical isomers, chiral column.

Introduction

Tricyclic quinazoline alkaloids (deoxyvasicinone, 1; mackinazolinone, 2) are widely distributed in nature [1-4]. There are many review articles, which covered bi- and tricyclic quinazoline alkaloids [5-10] and their substituted derivatives. These compounds have different reaction centers: nitrogen atoms, carbonyl and activated methylene groups, a benzene ring [12] (Fig. 1).



1 2 3

Fig. 1: Starting tricyclic quinazoline alkaloids.

These centers can react with electrophilic and nucleophilic reagents, resulting in different derivatives of tricyclic quinazoline alkaloids [13-17]. Tricyclic quinazolines exhibit different properties [18-21]; it is often found that several of the quinazoline compounds possess more significant biological activity than the corresponding quinazolones. Along with this, the number of methylene groups have a positive effect on the biological activity; so increasing of the number of the methylene groups (2, 3-tri → 2, 3-tetra → 2, 3-penta → 2, 3-hexamethylene quinazolines) increases the biological activity of the compounds [22].

Materials and Methods

Research objects of this work are tricyclic quinazolones, in particular deoxyvasicinone (1), mackinazolinone (2) and 8-nitromackinazolinone (3) and their analogues. Research methods are organic synthesis reaction, such as cyclization, nitration, electrophilic substitution (mono-, and dibromination); NBS is used as selective brominating agent; structural analysis of the synthesized compounds by IR, ^{1}H and ^{13}C NMR spectra, qualitative separation of optical isomers using column chromatography (HPLC) in presence of chiral adsorbent.

Synthesized new (*R, S*)-4-bromo-8-nitromackinazolinone (16) was screened by HPLC (Agilent 1100 Series, USA) using a column with chiral adsorbent - amylose *tris*-[(*S*)-α-methyl-benzylcarbamate] coated on 10μm silica-gel (ChiralPak® AS 0.46cm *ф* x25cm, DAIC 20025, Daicel Chemical Industries, LTD, France), and mobile phase A - ACN, and B - i-PrOH in gradient mode: 0-10min B2% to 10% and 10-15min B10%.

^{1}H-NMR spectra were recorded in $CDCl_3$ on Varian 400-MR spectrometer operating accordingly at 400 MHz. Tetramethylsilane (TMS) was used as internal standard, chemical shifts δ of ^{1}H were recorded in ppm. Mps were measured on a Boethius and MEL-TEMP apparatus manufactured by Branstead international (USA) and were uncorrected. IR spectra were recorded on Shimadzu FTIR-8400 and IR Fury System 2000 (Perkin-Elmer) as KBr pellets. HPLC analysis was acquired on a Agilent 1200 series. The reaction process was monitored by TLC on Sorbfil and Whatman UV-254 percoated aluminum plates using C_6H_6/CH_3OH (7:1) solvent system and developed plates were visualized under UV lamp, and/or iodine tank where necessary. Solvents were purified by standard procedures. Organic solutions were dried over anhydrous Na_2SO_4 or with the dried $CaCl_2$.

Deoxyvasicinone (1), mackinazolinone (2) and 8-nitromackinazolinone (3) were prepared by the literature method [23].

Deoxyvasicinone (1): Yield 75 %, mp=110-111°C (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.25 (q, *J*=7.8 Hz, 2H, CH_2-2), 3.15 (t, *J*=7.8 Hz, 2H, CH_2-3), 4.20 (t, *J*=7.4 Hz, 2H, CH_2-1), 7.40 (td, *J*=1.2 Hz, J=8.0 Hz, 1H, H-7), 7.60 (d, *J*=8.0 Hz, 1H, H-5), 7.71 (td, *J*=1.3 Hz, *J*=8.0 Hz, 1H, H-6), 8.22 (dd, *J*=1.2 Hz, *J*=8.0 Hz, 1H, H-8) ppm.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.0 (C-2), 32.1 (C-3), 46.2 (C-1), 119.6 (C-7), 125.1 (C-8a), 126.1 (C-5), 126.6 (C-8), 133.3 (C-6), 147.4 (C-4a), 158.7 (C-9), 160.1 (C-3a) ppm.

Mackinazolinone (2): Yield 85 %, mp=98-99°C (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.28 (dd, *J*=1.28 Hz, *J*=7.92 Hz, 1H, H-9), 7.74 (td, *J*=1.56 Hz, *J*=8.4 Hz, 1H, H-7), 7.62 (d, *J*=7.92 Hz, 1H, H-6), 7.44 (td, *J*=1.04 Hz, J=8.04 Hz, 1H, H-8), 4.1 (t, *J*=6.12 Hz, 2H, CH_2-1), 3.00 (t, *J*=6.72 Hz, 2H, CH_2-4), 2.05-1.96 (m, 4H, CH_2-2,3) ppm.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.3 (C-3), 22.1 (C-2), 31.9 (C-4), 42.3 (C-1), 120.4 (C-8), 126.1 (C-9a), 126.4 (C-6), 126.6 (C-9), 134.2 (C-7), 147.4 (C-5a), 154.9 (C-10), 162.2 (C-4a) ppm.

8-Nitromackinazolinone (3).

In 8 ml (95.72%, ρ=1.835 g/cm^3) of concentrated sulfuric acid with vigorous stirring and cooling (ice bath) dissolved 4 g (20 mmol) mackinazolinone (**1**), then at the temperatu below 2°C was added drop wise nitrating mixtur consisting of 3 ml nitric (59.69%, ρ=1.365g/cm^3) and 3 n of sulfuric (ρ=1.835 g/cm^3) acids. After that mixture w stirred at the temperature of 5-10°C and 1 h at roo temperature. Reaction mixture treated by ice and th formed yellow precipitates filtered off, washed with wat to neutral medium and dried.

Yield 4.55 g, 92 %, mp 183-184°C (methanol).

^{1}H NMR (400 MHz, $CDCl_3$): δ= 9.15 (d, *J*=2.6 Hz, 1H, H 9), 8.51 (dd, *J*=2.68 Hz, *J*=8.96 Hz, 1H, H-7), 7.71 (*J*=9.0 Hz, 1H, H-6), 4.12 (t, *J*=6.16 Hz, 2H, CH_2-1), 3.0 (t, *J*=6.72 Hz, 2H, CH_2-4), 2.1-1.9 (m, 4H, CH_2-2,3) ppm.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.1 (C-3), 21.9 (C-2 32.2 (C-4), 42.9 (C-1), 120.3 (C-8), 123.5 (C-9a), 128.0 (C 6), 128.2 (C-9), 145.1 (C-7), 151.5 (C-5a), 158.7 (C-10 161.1 (C-4a) ppm.

General procedure for selective bromination: Synthesi of (*R, S*)-4-bromo-8-nitro-mackinazolinone (16)

The reaction mixture, consisting 0.5 g (2 mmol) of 8 nitromackinazolinone (3), 0.43 g (2.4 mmol) of NBS an 0.04 g (0.2 mmol) of benzoyl peroxide in 15 ml o tetrachloromethane refluxed for 8 h and was left overnigh The formed precipitate of succinimide was filtered off, an solvent was evaporated in vacuo. The residue was treate with water and the resulting crystals were filtered of washed with water and dried. 0.61 g (92%) product **(16** has been synthesized, mp 136-137°C (ethanol), Rf=0. (benzene:methanol – 7:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.10 (d, *J*=2.2 Hz, 1H, H 9), 8.43 (dd, *J*=2.2 Hz, *J*=8.8 Hz, 1H, H-7), 7.60 (d, *J*=8. Hz, 1H, H-6), 4.09 (t, *J*=6.0 Hz, 2H, CH_2-1), 3.0 (t, *J*=6. Hz, 1H, CH_2-4), 1.97-1.90 (m, 4H, CH_2-2,3) ppm.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.6 (C-3), 20.8 (C-2) 31.3 (C-4), 41.7 (C-1), 119.4 (C-8), 121.4 (C-9a), 127.3 (C 6), 127.8 (C-9), 144.3 (C-7), 150.4 (C-5a), 157.5 (C-10) 160.5 (C-4a) ppm.

IR, ν (cm^{-1}): 2956 (C-H), 1670 (CO), 1580 (C=N), 155 (C-N), 1505 (NO_2), 672 (C-Br).

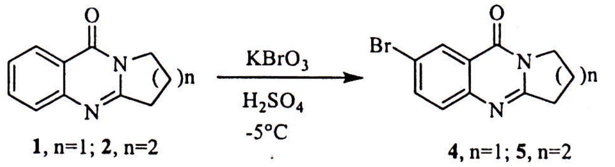
Results and discussion

Aromatic and heterocyclic compounds containing bromine atom in the ring are of considerable importance fo organic synthesis.

It is known, that sodium or potassium bromates are powerful brominating agents for aromatic compounds tha contain deactivating substituents [24].

Bromination of tricyclic quinazolines by differen brominating agents (sodium/or potassium bromates molecular bromine, NBS) has been studied.

For example: it was studied aromatic bromination o tricyclic quinazolones (1, 2) in sulfuric acid, and was revealed that in this case takes place aromatic electrophilic substitution in benzene ring [21] (Scheme 1):

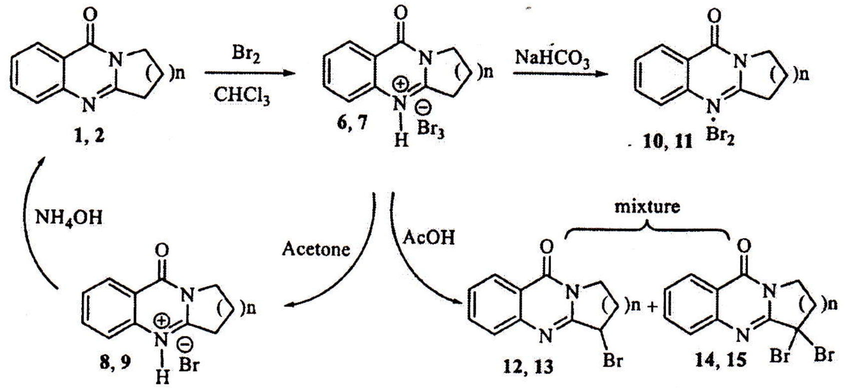


1, n=1; **2**, n=2

4, n=1; **5**, n=2

Scheme 1: Bromination by inorganic bromates.

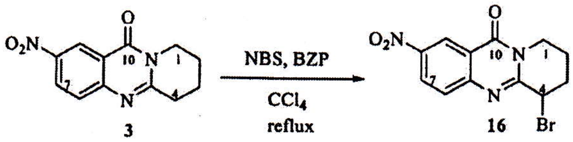
We previously studied the interaction of some tricyclic quinazolones with molecular bromine. Reaction goes on C=N double bond and are formed appropriate perbromides. Reaction carried out in the ratio of reagents 1:2 in dry chloroform at 0-5°C and corresponding perbromides (6, 7) have been synthesized. Conducted chemical transformations of the obtained perbromides under the influence of sodium bicarbonate and acetone; wherein hydrobromides (8, 9) and bromine complexes (10, 11) are received [25] (Scheme 2):



Scheme 2: Bromination by molecular bromine and modification of formed perbromides.

The received perbromides when stored under normal conditions loss of bromine molecule and turn into hydrobromides. Treating of perbromides with acetone takes place bromination of acetone and occurs with formation of bromacetone and are formed the precipitates of the corresponding hydrobromides (8, 9), which under the action of aqueous ammonia is easily transferred to the starting compounds 1, 2. Perbromides 6, 7 easily converted into bromine complexes (10, 11) under the action of 5% sodium bicarbonate. Heating of perbromides in aqueous acetic acid are formed a mixture of the mono- (12, 13) and dibromo- (14, 15) derivatives.

To obtain the targeted monobromo – derivatives, which contain asymmetrical centre we studied the reaction of 8-nitromackinazolinone with N-bromosuccinimide. The reaction carried out in dried tetrachloromethane in the presence of benzoyl peroxide (BZP) by refluxing for 8 h of mixture of NBS and 8-nitromackinazolinone (3). As a result of this reaction exclusively and in high yield (92%) of monobromo derivative - 4-bromo-8-nitromackinazolinones (16) have been synthesized (Scheme 3):



Scheme 3: Allylic bromination of quinazolones.

N-Bromosuccinimide (NBS) is a brominating agent that is used as source for bromine in radical reactions (for example: allylic bromination - *Wohl-Ziegler Reaction*) and various electrophilic additions. The bromination of allylic positions with N-bromosuccinimide (NBS) follows a radical pathway.

The synthesized compound 16 can be in two forms of optical isomers, as 4-(*R*)- 16a and 4-(*S*)-bromo-8-nitromackinazolinones (16b) (Fig. 2):

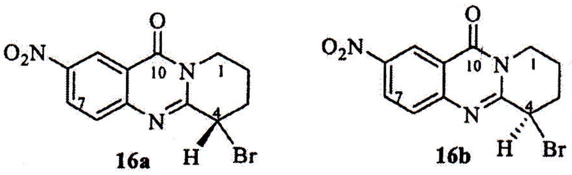


Fig. 2: Optical isomers of compound 16.

Using HPLC equipped with a chiral column, we qualitatively separated two optical isomers with RT 7.187 (51.5579%) and 7.468 (47.2074%), respectively (Fig. 3)

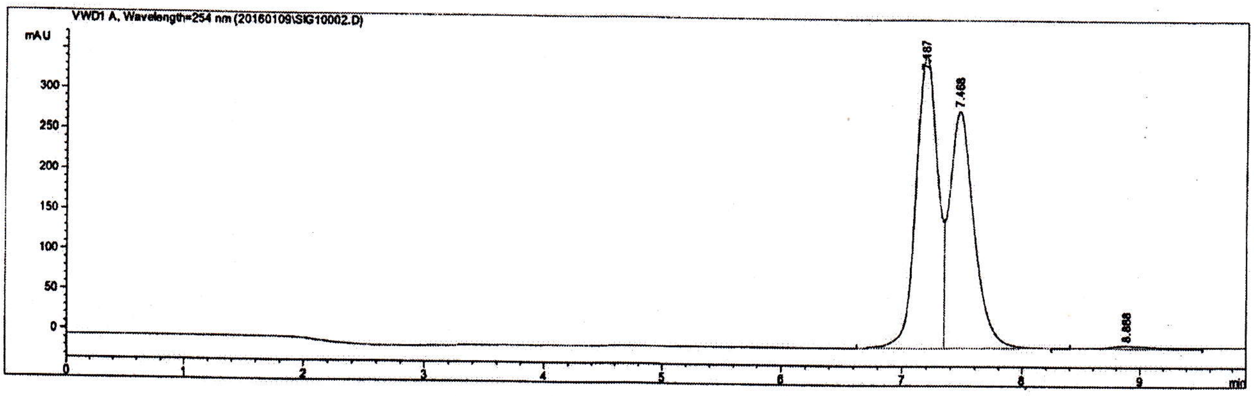


Fig. 3: HPLC results of the separated optical isomers.

Conclusion

Comparative bromination of the tricyclic quinazolines (**1-3**) and their some analogues with different bromating agents - inorganic bromates, molecular bromine and N-bromosuccinimide (NBS) have been studied and discussed. It was found that depending on the reaction conditions and structures of the starting compounds and bromating agents takes place bromination on the aromatic ring, on N1=C2 double bound of pyrimidine ring or on methylene groups of the α-position (C-4). Targeted bromination of 8-nitromackinazolinone (**3**) was investigated by N-bromosuccinimide (NBS) in the presence of benzoyl peroxide (BZP) in anhydrous tetrachloromethane and was developed the method for monobromination. Such selective monobromination of 8-nitromackinazolinone in the participation only of α-CH_2 group was shown. The synthesized optical isomers of (*R,S*)-4-bromo-8-nitromackinazolinone is quantitatively separated on HPLC column, consisting chiral adsorbent. It was revealed that using allylic bromination method (*Wohl-Ziegler Reaction*) for compound **3** gives exclusively and in high yield targeted chiral compound - (*R,S*)-4-bromo-8-nitromackinazolinone (**16**).

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References

1. Fitzgerald JS, Johns SR, Lamberton JA, Redcliffe AH. 6,7,8,9-Tetrahydropyrido-quinazolines, a new class of alkaloids from Mackinlaya species (Araliaceae). Australian Journal of Chemistry, 1966; 19: 151-155.
2. Cagir A, Jones SH, Eisenhauer BM, Gao R, Hecht SM. Synthesis and biological properties of E-ring modified luotonin A derivatives. Bioorganic and Medicinal Chemistry Letters, 2004; 14: 2051-2054.
3. Ma ZZ, Hano Y, Nomura T, Chen YJ. Novel quinazoline-quinoline alkaloids with cytotoxic and DNA topoisomerase II inhibitory activities, Bioorganic and Medicinal Chemistry Letters, 2004; 14: 1193-1196.
4. Mhaske SB, Argade NP. Concise and efficient synthesis of bioactive natural products pegamine, deoxyvasicinone, and (-)- vasicinone. Journal of Organic Chemistry, 2001; 66 (26): 9038-9040.
5. Michael JP. Quinoline, quinazoline and acridone alkaloids. Natural Product Reports, 1999; 16 (6): 697-709.
6. Michael JP. Quinoline, quinazoline and acridone alkaloids. Natural Product Reports, 2002; 19 (6): 742-760.
7. Michael JP. Quinoline, quinazoline and acridone alkaloids. Natural Product Reports, 2004; 21(5): 650-668.
8. Michael JP. Quinoline, quinazoline and acridone alkaloids, Natural Product Reports, 2005; 22 (5): 627-646.
9. Mhaske SB, Argade NP. Ficile zeolite induced Fisher-indole synthesis: A new approach to bioactive natural product rutaecarpine. Tetrahedron, 2004; 60: 3417-3420.
10. Nepali K, Sharma S, Ojha R, Dhar KL. Vasicine and structurally related quinazolines. Medicinal Chemistry Research, 2013; 22 (1): 1-15.
11. Shakhidoyatov KM, Elmuradov BZ. Tricyclic quinazoline alkaloids: isolation, synthesis, chemical modification and biological activity. Chemistry of Natural Compounds, 2014; 50 (5): 781-800.
12. Elmuradov BZ, Shakhidoyatov KM, Dräger G, Butenschön H. Tricyclic quinazoline alkaloids conjugated to ferrocene. Synthesis, structure, and redox behavior of ferrocenylmethylene substituted 7H-deoxyvasicinones. European Journal of Organic Chemistry, 2016; 483–492.
13. Abdurazakov AS, Elmuradov BZ, Turdibaev ZE, Shakhidoyatov KM. Reaction of 2,3-tetramethylene-3,4-dihydroquinazol-4-one and its derivatives with aromatic aldehydes and furfurol, Chemistry of Natural Compounds, 2009; 45: 402-408.
14. Shakhidoyatov KM, Elmuradov BZ, Levkovich MG, Abdullayev ND. Reactivity and H–D exchange rate of the α-methylene of deoxyvasicinone and its homologues, Chemistry of Natural Compounds, 2014; 50 (6): 1060-1065.
15. Levkovich MG, Elmuradov BZ, Shakhidoyatov KM, Abdullaev ND. Deuterium Exchange of the α-Methylene Group Protons in the Quinazolones. III. Environment Influence on the Exchange Rate. Journal of Basic and Applied Research, 2016; 2(2): 202-204.
16. Elmuradov BZ, Abdurazakov AS, Shakhidoyatov KM. Directions of reactions of 6-amino-, -acetylamino-, and – benzoylaminodeoxyvasicinones with aldehydes, Chemistry of Natural Compounds, 2010; 46 (2): 262-267.
17. Richers MT, Zhao C, Seidel D. Selective copper (II) acetate and potassium iodide catalyzed oxidation of aminals to dihydroquinazoline and quinazolinone alkaloids. Beilstein Journal of Organic Chemistry, 2013; 9: 1194-1201.
18. Yunusov SY, Tulyaganov N, Telezhenetskaya MV, Sadritdinov F, Khashimov K. USSR Pat. No. 605,614, Byull. Izobret., No.17, 1978.
19. Jafari E., Khajouei M. R., Khodarahmi G.A. Quinazolinone and quinazoline derivatives: recent structures with potent antimicrobial and cytotoxic activities. Research in Pharmaceutical Sciences, 2016; 11 (1): 1–14.
20. Al-Shamma A, Drake S, Flynn DL, Mitscher LA, Park YH, Rao GS, Simpson A, Swayze JK, Veysoglu T, Wu ST. Antimicrobial agents from higher plants. Antimicrobial agents from Peganum harmala seeds. Journal of Natural Products, 1981; 44(6): 745-747.
21. Shakhidoyatov KM. Quinazol-4-ones and their biological activity. Tashkent: Fan. 1988; 99-104 (in Russian).
22. Tulyaganov N. Pharmacological investigations of alkaloids of the Peganum harmala L. of quinazoline and quinazoline structure and their derivatives. Pharmacology of Natural Compounds, Tashkent: Fan, 1979; 71-80 (in Russian).
23. Elmuradov BZ, Abdurazakov AS, Shakhidoyatov KM. Synthesis and antibactericide activity of 6-H(nitro)-9-arylidendeoxyvasicinones and their perchlorates. Chemistry of Natural Compounds, 2008; 44 (4): 475-479.

24. Kumar L, Mahajan T, Agarwal D D. Bromination of Deactivated Aromatic Compounds with Sodium Bromide/Sodium Periodate under Mild Acidic Conditions. Industrial & Engineering Chemistry Research, 2012; 51 (36): 11593-11597.
25. Makhmadiyarova CE, Nasrullayev AO, Elmuradov BZ, Shakhidoyatov KM. Synthesis and reactions of 2,3-trimethylene-3,4-dihydroquinazoline perbromides and 2,3-trimethylene-3,4-dihydroquinazoline-4-thione. Uzbek Chem. Journal, 2011; Special issue: 48-50.