Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2012, 4(8):3924-3928

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis of novel 1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one analogs by using lithiation-intramolecular electrophilic reaction

Azimvand J

Organic Chemistry Research Laboratory, Chemistry Department, Faculty of Science, Payame Noor University, Tehran, Iran

---

ABSTRACT

An efficient synthesis of the 4(3H)-quinazolinone-based alkaloids , 1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one has been achieved in good overall yields by using the strategy of regioselective lithiation-intramolecular electrophilic reaction as a key–step. Both the molecules have been synthesized in just two-steps from readily available starting materials. Several synthetic analogs of natural product 1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one , an alkaloid containing quinazolinone moiety are being reported in this communication. Novel synthetic method for the synthesis of 1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one analogs are reported. Final products were supported by FTIR , ^{1}H NMR , ^{13}C NMR and Mass spectroscopic measurements and possess moderate to good antifungal and antibacterial activities.

Keywords: 4(3H)-quinazolinone , [2,1-b]quinazoline-5-one , Deoxyvasicinone

---

INTRODUCTION

4(3H)-Quinazolinone is a building block for approximately 150 naturally occurring alkaloids isolated to date from a number of families of the plant kingdom, from animals, and from microorganisms [1-5]. All the 4(3H)-quinazolinone based natural products have interesting biological activities and have therefore been extensively investigated for pharmaceutical activities. The 4(3H)-quinazolinone ring is regarded as a privileged structure' in combinatorial synthesis [6-9] . These are structures which represent molecules that are capable of binding at multiple sites with high affinity and facilitate more rapid discovery of useful medicinally active compounds [10-13]. 1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one which is also called by the name of Deoxyvasicinone , is an alkaloid isolated from the aerial parts of Adhatoda vasica (from the family Acanthacea, Sankrit-Vasaka), an evergreen sub-herbaceous bush, used extensively in indigenous medicine for cold, cough, bronchitis, and asthma[14]. Deoxyvasicinone possesses antimicrobial , anti-inflammatory and antidepressant activities[15] . In addition, deoxyvasicinone is very important key intermediate for the synthesis of various natural products such as vasicinone [16], isaindigotone , and luotonin A [17] .

deoxyvasicinone has been synthesized using various methods. It includes intramolecular aza- Wittig reaction[19] , reductive N-heterocyclization[20] , azido-reductive cyclization[16] , solid-phase synthesis[21] , microwave-assisted domino reactions[22] , polymer-supported reagents[23] , radical cyclization[18] , and many other methods[24] . Among these none have employed the strategy of regioselective lithiation at C-2 of quinazolinone followed by reaction with an electrophile in an intramolecular fashion forming C-C bond to generate the cyclized product. As a

part of our interest on the synthesis of biologically active N-heterocycles[25-26]. we became interested in the synthesis of deoxyvasicinone using the above- mentioned strategy.

EXPERIMENTAL SECTION

General Procedures

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-200 spectrometer in $CDCl_3$ using TMS as internal standard. Infrared spectra were recorded with ATI MATT-SON RS-1 FTIR spectrometer using KBr pellets. Elemental analyses were obtained using a flash EA 1112 thermoFinnigan instrument and were carried out at the National Chemical Laboratory, Pune. Melting points were recorded in open capillary on Büchi melting Point B-540 apparatus. All solvents and chemicals were of research grade and were used as obtained from Merck and Lancaster. The progress of the reaction was monitored by TLC. Column chromatography was performed using silica gel (60–120 mesh size). Petroleum has boiling point 60-80 °C. RT denotes room temperature.

Synthesis of 3-(3-Bromopropyl)-3,4-dihydro-4-quinazolinone (3) :

To a well stirred solution of 4(3H)-quinazolinone (1) (0.29 g, 2 mmol) and potassium carbonate (0.30 g, 2.2 mmol) in dry DMF (10mL) at RT was added 1,3-dibromopropane (2) (0.44 g, 2.2 mmol) dropwise over 15 min andreaction mixture was stirred at RT for 4 h . The progress of the reaction was monitored by TLC. After completion of reaction, the solvent was evaporated under vacuum to obtain solid to which water (20 mL) was added and product was extracted using ethyl acetate (3x15 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo to give crude product which was purified by column chromatography with petroleum:ethyl acetate (6:4) as the eluent to afford 0.46 g of the pure 3-(3-Bromopropyl)-3,4-dihydro-4-quinazolinone (3).

mp 178-180 °C; IR (KBr, cm^{-1}) 2931, 2854, 1681, 1561, 1450; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.33-2.45 (m, J = 6.66, 6.15 Hz, 2H, $NCH_2\underline{CH_2}CH_2$), 3.45 (t, J = 6.15 Hz, 2H, $NCH_2CH_2\underline{CH_2}Br$), 4.19 (t, J = 6.66 Hz, 2H, $N\underline{CH_2}CH_2CH_2$), 7.48-7.56 (m, 1H, ArH), 7.70-7.82(m, 2H, ArH), 8.12 (s, 1H, $C_2\underline{H}$ quinazolinone), 8.31 (dd, J = 7.96, 1.02 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.7, 31.0, 45.4, 121.8, 126.5, 127.3, 134.3, 146.5, 147.8, 160.9; Anal Calcd for $C_{11}H_{11}BrN_2O$: C, 49.46; H, 4.15; N, 10.49%. Found: C, 49.53; H, 4.09; N, 10.57%.

Synthesis of 1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one (4) :

To a freshly prepared solution of LDA (0.16 g, 1.5 mmol) in anhydrous THF (8 mL) at -78 °C under nitrogen atmosphere was added dropwise a solution of 3-(3-Bromopropyl)-3,4-dihydro-4-quinazolinone (3) (0.28 g, 1 mmol) dissolved in dry THF (5 mL). The reaction mixture was stirred at -78 °C for additional 2 h followed by stirring at RT for 2 h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate (3x15 mL). The combined organic layer was washed with brine solution. The solvent was dried over anhydrous sodium sulfate and evaporated in vacuo to give crude product which was purified by column chromatography with petroleum:ethyl acetate (2:8) to afford 0.12 g of the pure 1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one (4).

Mp 196-197 (lit.25a 196-198); IR (KBr, cm^{-1}) 2931, 2855, 1679, 1600, 1556, 1455; 1H NMR ($CDCl_3$, 200 MHz) δ 2.21-2.36 (m, J = 7.94, 7.21 Hz, 2H, NCH2CH2CH2), 3.18 (t, J = 7.94 Hz, 2H, NCH2CH2CH2), 4.21 (t, J = 7.21 Hz, 2H, NCH2CH2CH2), 7.40-7.48 (m, 1H, ArH), 7.62-7.77 (m, 2H, ArH), 8.26 (dd, J = 8.00, 1.14 Hz, 1H, ArH); 13C NMR ($CDCl_3$, 50 MHz) δ 19.4, 32.4, 46.4, 120.4, 126.2, 126.3, 126.7, 134.1, 149.0, 159.4, 160.9; Anal Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04%. Found: C, 71.02; H, 5.38; N, 15.17%.

Synthesis of 7-Nitro-1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one (4a) :

To a mixture of nitric acid and sulfuric acid (7 ml) 1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one (4)(4.5g, 0.024 mmol) was added at ice cold temperature and stirred for 2 h followed by dilution with water and extraction with dichloromethane. The dichloromethane layer was dried over anhyd. Sodium sulfate and concentration provided 7-Nitro-1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one (4g, 0.165mmol).

^{1}HNMR ($CDCl_3$): 2.23(q , 2H , N-CH_2-$\underline{CH_2}$-CH_2-) , 3.14(t , 2H , N-CH_2-CH_2-$\underline{CH_2}$-) , 4.12(t , 2H , N-$\underline{CH_2}$-CH_2-CH_2-) , 7.83 (d , 1H , Ar) , 8.52 (d , 1H , Ar) , 8.76 (s , 1H , Ar) ; MS (m/z): 231

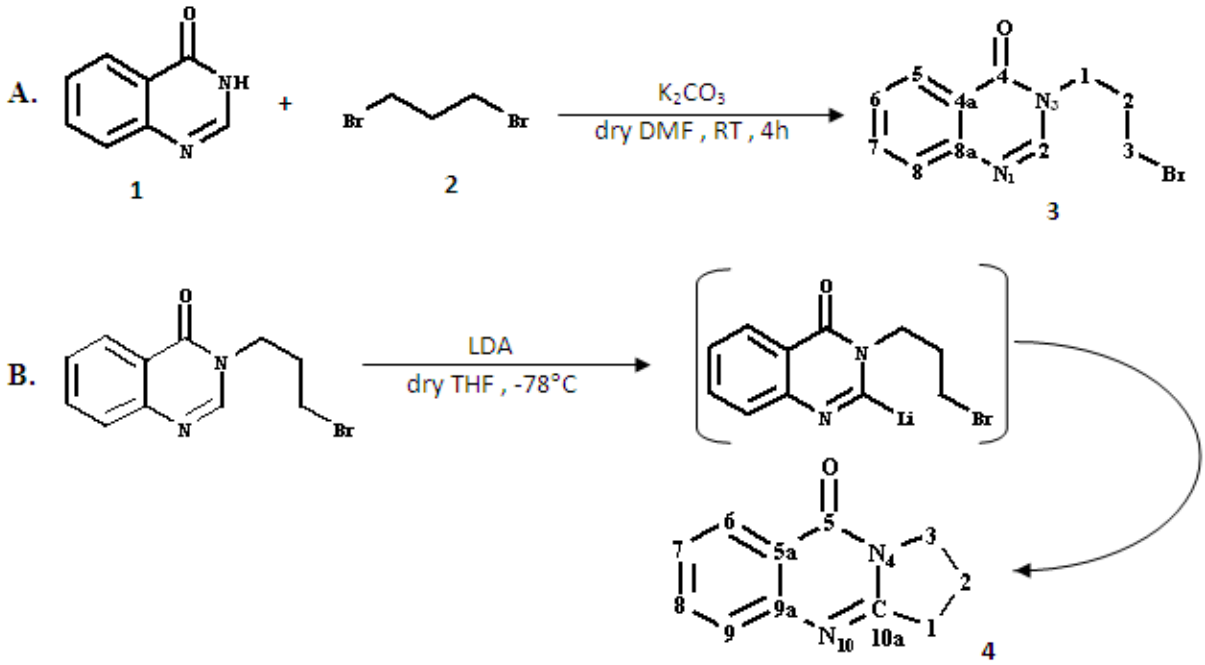
Synthesis of 7-Amino-1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one (4b) :
To 7-Nitro-1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one (4a) (3g, 0.0129 mmol) in 15 ml of hydrochloric acid, tin (8.0 g) was added and heated at reflux for 2 h. Filtration, neutralization followed by extraction with dichloromethane, drying over anhydrous sodium sulfate, concentration provided 7-Amino-1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one (2.1g, 0.01 mmol).

^{1}HNMR ($CDCl_3$): 2.23(q , 2H , N-CH_2-$\underline{CH_2}$-CH_2-) , 3.14(t , 2H , N-CH_2-CH_2-$\underline{CH_2}$-) , 3.82(s , 2H , -NH_2) , 4.12(t , 2H , N-$\underline{CH_2}$-CH_2-CH_2-) , 7.64 (d , 1H , Ar) , 7.67 (d , 1H , Ar) , 7.77 (s , 1H , Ar) ; MS (m/z): 201

Synthesis of 7- phenylsulfonilamylamino-1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one (4c) :
To 7-Amino-1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one (4b)(1.5g, 0.007mmol) in pyridine (2.5ml) was added phenylsulfonyl chloride (2ml,0.012mol) and heated to 50 deg C for 2 h followed by dilution with water and extraction with dichloromethane, drying and concentration, followed by chromatographic purification provided sulfonamide derivative (0.9 g, 0.0026mol).

^{1}HNMR ($CDCl_3$): 2.23(q , 2H , N-CH_2-$\underline{CH_2}$-CH_2-) , 3.14(t , 2H , N-CH_2-CH_2-$\underline{CH_2}$-) , 4.12(t , 2H , N-$\underline{CH_2}$-CH_2-CH_2-) , 5.89 (s , 1H , -$\underline{NH}$-SO2-) , 7.29 (d , 1H , Ar) , 7.42 (t , j=7.44 , 2H , Ar) , 7.44 (t , j- 8.02 , 2H , Ar) , 7.55 (t , j=7.44 , 1H , Ar) , 7.74 (d , 1H , Ar) , 7.87 (s , 1H , Ar) ; MS (m/z): 341.

Scheme 1



RESULTS AND DISCUSSION

Deoxyvasicinone (4) (1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one) was synthesized employing the strategy of regioselective lithiation-intramolecular electrophilic reaction. The synthesis of deoxyvasicinone (4) was initiated with the formation of 3-(3-Bromopropyl)-3,4-dihydro-4-quinazolinone (3), obtained by alkylation of 4(3H)-quinazolinone (1) with 1,3-dibromopropane (2) , and potassium carbonate in dry DMF at room temperature. The unknown compound 3 is fully characterized. The absence of band in IR spectra in the region 3300-3400 cm-1 corresponding to -NH and presence of band in the region 2800-3000 cm^{-1} corresponding to methyl group suggest the formation of N-alkyl derivative. The ^{1}H NMR of 9 shows peaks at δ ppm 2.33-2.45 (m, 2H), 3.42-3.48 (t, 2H), 4.16-4.22 (t, 2H) corresponding to the group (-$CH_2CH_2CH_2$-) suggests the presence of a propyl group. Furthermore, the ^{13}C NMR spectrum of 3 showing peaks at δ 29.7, 31.0, 45.4 ppm respectively for the carbon of propyl group confirmed the structure. Very similar to tryptanthrin, the regioselective lithiation of 3 at C-2 was achieved by using

LDA which proceeded readily at -78 °C in dry THF under inert atmosphere to form lithiated anion which subsequently reacted with the electrophile viz. methylene bromide in an intramolecular fashion by forming C-C bond to afford the cyclized product, deoxyvasicinone (4) (Scheme 1). Thus, by this way we have successfully achieved the synthesis of deoxyvasicinone also in only two-steps. The structure of deoxyvasicinone (4) was confirmed by mp, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The ^{1}H NMR spectrum of 4 with the absence of peak as singlet at δ 8.12 ppm corresponding to hydrogen at C-2 of quinazolinone supports its formation. Furthermore, ^{13}C NMR spectra of 4 shows a peak at δ 159.0 ppm indicating that C-alkylation has taken place at the 2-position of 4(3H)-quinazolinone. For known compounds, the values were in good agreement with those reported in literature.

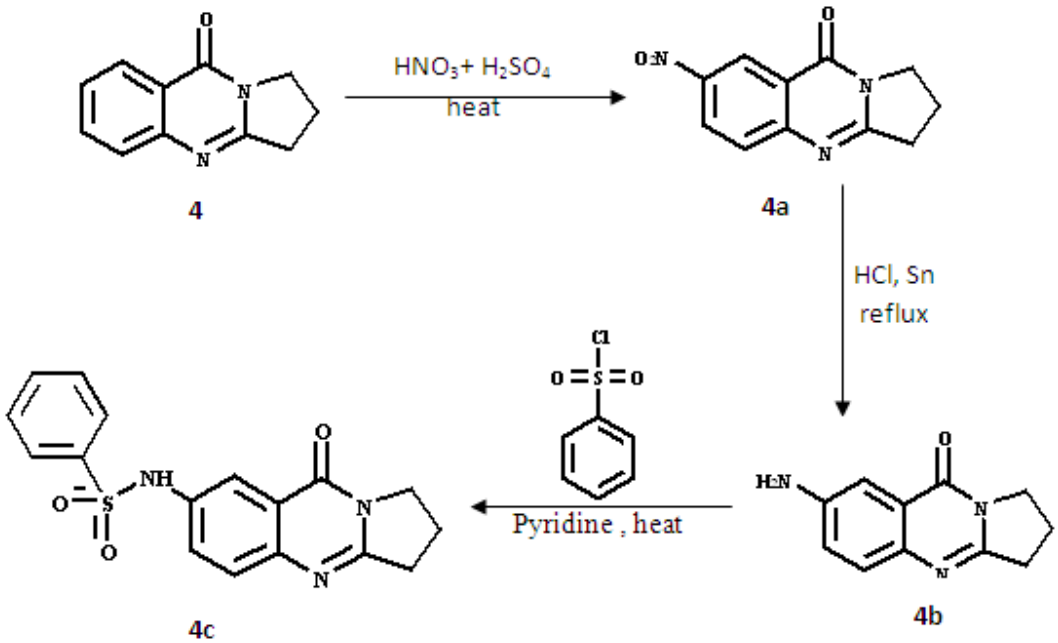
Table 1 shows the yield value of the synthesized compounds .

Table 1 . synthesis of 1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one derivatives

Compound	R	Molecular formula	Yield value(%)
3	-	$C_{11}H_{11}BrN_2O$	91
4	-	$C_{11}H_{10}N_2O$	89
4a	7-NO_2	$C_{11}H_9N_3O_3$	94
4b	7-NH_2	$C_{11}H_{11}N_3O$	96
4c	7- $NHSO_2$-ph	$C_{17}H_{15}N_3O_3S$	86

Also in Scheme 2 , is shown the method of preparing a 1,2,3,5-tetrahydropyrrolo[2,1-b]quinazoline-5-one (4) compound of derivatives.

Scheme 2



CONCLUSION

In conclusion, we have achieved the synthesis of 3-(3-Bromopropyl)-3,4-dihydro-4-quinazolinone (3) and deoxyvasicinone (4) in only twosteps in good overall yields of 91 and 89% respectively. The key-step for the reaction is the regioselective lithiation at 2-position of 4(3H)-quinazolinone followed by subsequent reaction of the lithiated intermediate with the respective electrophiles in an intramolecular fashion to afford the corresponding cyclized product. The advantage of this method is the access to both bio-active molecules, deoxyvasicinone and

drivitives from readily available starting materials in only two-steps using a common protocol. The methodology can be extended to the synthesis of other natural products and their mimics to prove its generality.

REFERENCES

[1] Yang C. Wu; Mann J. Hour; Wing C. Leung; Chi Y. Wu; Wen Z. Liu; Yu H. Chang; Hong Z. Lee , J. Pharmacol. Exp. Ther., **2011**, 338(7) ,942 - 951.
[2] Kai Chen; Ketai Wang; Agop M. Kirichian; Ayman F. Al Aowad; Lakshmanan K. Iyer, S. James Adelstein; Amin I. Kassis , Mol. Cancer Ther., **2006**, 5(12) , 3001 - 3013.
[3] S S Carroll; M Stahlhut; J Geib; D B Olsen , J. Biol. Chem., **1994**, 269(4) , 32351 - 32357.
[4] Akinori Iwashita; Nobuteru Tojo; Shigeru Matsuura; Syunji Yamazaki; Kazunori Kamijo, J. Pharmacol. Exp. Ther., **2004**, 310(16) ,425 - 436.
[5] Sung Hee Hwang; Antonina Rait; Kathleen F. Pirollo; Qi Zhou, Mol. Cancer Ther., **2008**, 7(27) , 559 - 568.
[6] Metabolic Activation ; Enzyme Kinetics ; Hao Chen; Weiqi Chen; Liang-Shang Gan; Abdul E. Mutlib , Drug Metab. Dispos., **2003**, 31(12) , 122-136.
[7] Akinori Iwashita; Syunji Yamazaki; Kayoko Mihara; Kouji Hattori; Hirofumi Yamamoto; Junya Ishida; Nobuya Matsuoka; Seitaro Mutoh , J. Pharmacol. Exp. Ther., **2004**, 309(18) ,1067 - 1078.
[8] Jennifer Carroll; Lisa Adams; Donna Rogers; John Clifford; Heather Kleiner, AACR Meeting Abstracts., **2009**,21(4) , 4674- 4695.
[9] E. Myles Glenn; Stanley C. Lyster; Norman A. Rohloff , Exp Biol Med., **1971**, 138(4) , 244 - 248.
[10] R. J. Ericsson ; Exp Biol Med, **1971**, 137(24) , 532 - 535.
[11] S. S. Samudre; F. A. Lattanzio; Jr., A. Hosseini; P. B. Williams ; Invest. Ophthalmol. Vis. Sci., **2008**,49(18) , 3401-3415.
[12] Lyn M. Moir; Thomas Trian; Qi Ge; Peter R. Shepherd; Janette K. Burgess; Brian G. G. Oliver, Judith L. Black ; J. Pharmacol. Exp. Ther., **2011**, 337(2) , 557 - 566.
[13] Liquan Yang; Anja Seifert; Daifei Wu; Xiaoqian Wang; Vladan Rankovic, Mol. Pharmacol., **2010**, 78(4) , 105 - 113.
[14] Kh. M. Shakhidoyatov; T. F. Ibragimov ; N. S. Mukhamedov , Chemistry of Natural Compounds., **2010** , 46 (9) , 598-599.
[15] V. N. Plugar'; Ya. V. Rashkes ; N. Tulyaganov , Chemistry of Natural Compounds., **1981** ,17 (4) ,158-162.
[16] K. K. Turgunov; B. Tashkhodzhaev; L. V. Molchanov ; Kh. N. Aripov , Chemistry of Natural Compounds., **1995** , 31 (6) , 714-718.
[17] Kh. M. Shakhidoyatov ; Ch. Sh. Kadyrov , Chemistry of Natural Compounds., **1977** , 13 (7) ,554-556.
[18] E. L. Kristallovich; A. G. Eshimbetov; N. D. Chuvylkin; L. I. Belen'kii ; Kh. M. Shakhidoyatov , Chemistry of Natural Compounds., **2003** , 39(11) , 495-500.
[19] V. N. Plugar'; Ya. V. Rashkes; A. Karimov; M. V. Telezhenetskaya ; S. Yu. Yunusov, Chemistry of Natural Compounds., **1983** , 19(4) , 64-68.
[20] É. O. Oripov; K. A. Zakhidov ; Kh. M. Shakhidoyatov ,Chemistry of Natural Compounds., **1991** , 27 (12) ,341-342.
[21] T. S. Tulyaganov; R. Sh. Atadzhanov; N. D. Abdullaev; É. L. Kristallov ; Z. Osmanov , Chemistry of Natural Compounds., **1993** , 29 (2) , 509-511.
[22] Kh. M. Shakhidoyatov ; I. K. Kaisarov , Chemistry of Natural Compounds., **1998**, 34 (7) , 59-61.
[23] B. D. Kabulov ,Chemistry of Natural Compounds., **1991** , 27 (4) , 256-257.
[24] Zh. E. Turdibaev; B. Zh. Elmuradov; M. M. Khakimov ; Kh. M. Shakhidoyatov , Chemistry of Natural Compounds., **2011** , 47 (17) , 600-603.
[25] E. L. Kristallovich; A. G. Eshimbetov; N. I. Mukarramov ; Kh. M. Shakhidoyatov ,Chemistry of Natural Compounds., **2002** , 38 (4) , 589-594.
[26] Kh. M. Shakhidoyatov; M. Ya. Yamankulov ; Ch. Sh. Kadyrov , Chemistry of Natural Compounds., **1977** , 13 (15) , 461-463.