# 3-Hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one and 4-(formyl)-1,2,3,4,10-pentahydropyrido[2,1-b]-quinazolin-10-one - new sintons for obtaining of 3,4-dihydroisoquinolines

SH. N. ZHURAKULOV, V. I. VINOGRADOVA

S. Yu. Yunusov Institute of the Chemistry of Plant Substances,
Academy of Sciences of the Republic of Uzbekistan, Tashkent,
Corresponding author: j.sherzod.78@mail.ru.

## Abstract

*The reaction of 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazoline-9-one (3) and 4-(formyl-1,2,3,4,10-pentahydropyrido[2,1-b]-quinazoline-10-one (4) amination with homoverathryl- (5a) and homopyperanilamine (5b) studied. New heterocyclic derivatives of quinazolines 3-(3,4-dimethoxyphenylethylamino)-methylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (6a), 3-(3,4-methylene dioxypheny lethylamino) -methylidene-1,2,3,9-tetra hydropyrrolo[2,1-b]-quinazolin-9-one (6b), 4-(3,4-di methoxy phenyl ethylamino) -methylidene-1,2,3,4,10 –penta hydropyrido[2,1-b]-quinazolin-10-one (6c), 4-(3,4-methylenedioxyphenylethylamino)-methylidene-1,2,3,4,10-pentahydropyrido[2,1-b]-quinazolon-10-one (6d) synthesized. Interaction of the obtained heterocyclic derivatives 6a-d to trifluoroacetic acid gave the corresponding 3, 4-dihydroisoquinolines (7a, b), deoxyvasicinone (1) and mackinazolinone (2) instead of expected products of cyclization.*

**Keywords**: deoxyvasicinone, mackinazolinone, 3-hydroxymethylidene-1,2,3,9-tetra hydro pyrrolo[2,1-b] -quinazoline-9-one, 4-(formyl)-1,2,3,4,10-penta hydropyrido[2,1-b]-quinazoline -10-one, phenylethylamines, amination

## Introduction

Tricyclic quinazoline alkaloids are the most interesting group of quinazoline alkaloids found in *Peganum, Adhatoda, Waleda, Walium, Nitraria* and other plants[1].

Deoxyvasicinone (**1**) and mackinazolinone (**2**) are the most promising substances for obtaining of quinazoline derivatives. Deoxyvasicinone (1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one) isolated from *Peganum harmala* shown an antimicrobial and anti-inflammatory activity[2]. Mackinazolinone was the first alkaloid isolated from the plant *Mackilaya subulata* Philipson[3].

Despite the occurrence of these alkaloids in plants several effective methods of **1** and **2** synthesis developed[4-9]. One of the available methods is a condensation of anthranylic acid and lactams which allowed to obtain good yield of deoxyvasicinone, mackinazolinone and to implement deoxypeganine alkaloid into medical practice[10-11].

The presence of several reaction centers in these compounds promoted the synthesis of a large number of derivatives by the reaction of electrophylic, nucleophylic displacement or combination[12-16].

### Material and Methods

IR spectra were recorded in KBr pellets on an FTIR System 2000 instrument (Perkin-Elmer). PMR spectra were recorded on a Unity-400+ spectrometer (400 MHz, $CDCl_3$, $CD_3OD$ solvent, Hexamethyldisilane (HMDS) internal standard). The $R_f$-values were determined on LS 5/40 silicagel plates (Czechoslovakia) using $CHCl_3$:MeOH (system 1, 4:1; system 2, 14:1) and $C_6H_6$:MeOH (system 3, 12:1). 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 $CaCl_2$. Melting points of all synthesized compounds were determined on a "Boetius" microstage.

## Synthesis

Deoxyvasicinone (**1**), mackinazolinone (**2**), 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (**3**) and 4-(formyl)-1,2,3,4,10-pentahydropyrido [2,1-b]-quinazoline-10-one (**4**) obtained by the method[11].

**3-Hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one** (**3**). Yield is 4.8 g (81 %), mp 214-218°C ($CHCl_3$).

**4-(Formyl)-1,2,3,4,10-pentahydropyrido[2,1-b]quinazolin-10-one (4)**. Yield is 12.55 g (91%)**,** mp 201-203°C ($C_6H_{14}$).

***Interaction of 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (3) to homoveratrylamine and homopiperanylamine. General procedure.***

A solution of phenyl ethylamine (4.99 mol) in 10 mL of methanol was added to 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (**3,** 4.99 mol) and heated on water bath at 95-98°C for 5 hours. The obtained products were identified by TLC. The reaction mixture was cooled and crystalls were washed by methanol for 3 times and dried on air, then re-crystallized from methanol.

***3-(3,4-Dimethoxy phenyl ethylamino) –methylidene -1,2,3,9-tetra hydropyrrolo[2,1-b] -quinazolin -9-one (6a)***

Obtained from 0.903 g (4.99 mmol) 3,4-dimethoxyphenylethylamine (**5a)** and 1.068 g (4.99 mmol) 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (**3**). Yield is 1.55 g (82%), mp 179-181°C ($CH_3OH$), $R_f$ 0.64 (system 2).

IR spectrum (KBr, ν, $cm^{-1}$): 3437(NH), 2934($CH_2$), 1693(C=O), 1626(C=N), 1573, 1518(C=C), 1482(C-H), 1375, 1325(C-N), 1275, 1238, 1204(C-O).

PMR spectrum (400 MHz, $CDCl_3$ + $CD_3OD$, δ, ppm, J/Hz): 2.77(2H, t, J=8.2, H-2), 2.87(2H, t, J=7.2, H-7′), 3.62(2H, t, J=7.1, H-8′), 3.76(3H, s, 3′-$OCH_3$), 3.82(3H, s, 4′-$OCH_3$), 4.17(2H, t, J=8.2, H-1), 6.72(3H, d, J=7.9, H-5′), 6.76(1H, d, J=5.8, H-6′), 6.78(1H, s, H-2′), 7.30(1H, t, J=7.5, H-7), 7.65(1H, t, J=7.6, H-6), 7.73(1H, t, J=8.2, H-5), 8.03(1H, t, J=7.9, H-8), 8.69(1H, s, H-11),

***3-(3,4-Methylenedioxyphenylethylamino)-methylidene-1,2,3,9-tetrahydropyrrolo [2,1-b]-quinazolin -9-one (6b)***

Obtained from 0.23 g (1.39 mmol) 3,4-methylendioxyphenylethylamine (**5b)** and 0.3 g (1.39 mmol) 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (**3**). Yield is 0.39 g (77%), mp 182-185°C (from $CH_3OH$), $R_f$ 0.75 (system 2).

IR spectrum (KBr, ν, $cm^{-1}$): 3411, 3169(NH), 2706(CH2), 1682(C=O), 1630(C=N), 1578, 1531(C=C), 1480, 1436(C-H), 1347, 1331(C-N), 1285, 1241(C-O).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz ): 2.60(2H, t, J=8.2, H-2), 2.73(2H, t, J=6.8, H-7′), 3.41(2H, t, J=8.6, H-8′), 4.12(2H, t, J=8.0, H-1), 5.89(2H, s, 3′-$OCH_2O$-4′), 6.62-6.72(3H, m, Ar-H), 7.19(1H, t, J=8.1, H-7), 7.43(1H, d, J=8.6, H-6), 7.54(2H, t, J=8.5, H-5, 8), 8.13(1H, d, J=8.2, H-11).

***Interaction of 4-(formyl)-1,2,3,4,10-pentahydropyrido[2,1-b]-quinazolin-10-one (4) to homoveratrylamine and homopiperanylamine. General procedure.***

A solution of phenyl ethylamine (4.99 mol) in 10 mL of chloroform was added to 4-(formyl)-1,2,3,4,10-pentahydropyrido[2,1-b]-quinazoline-10-one (**4,** 4.99 mol) and heated on water bath at 95-98°C for 4 hours. The obtained products were identified by TLC. The reaction mixture was cooled, chloroform removed by vacuum evaporationcrystalls and methanol: chloroform 10:1 mixture added. Obtained crystals were filtered, washed by methanol for 4 times and dried on air.

***4-(3,4-Dimethoxyphenylethylamino)-methylidene-1,2,3,4,10-pentahydropyrido[2,1-b]-quinazolin-10-one (6c)***

Obtained from 0.903 g (4.99 mol) of 3,4-dimethoxyphenylethylamine (**5a)** and 1.068 g (4.99 mol) of 4-(formyl)-methylidene-1,2,3,4,10-pentahydropyrido[2,1-b]-quinazolin-10-one **(4)**. Yield is 1.30 g (87%), mp 147-149°C (from $CH_3OH$:$CHCl_3$ 10:1), $R_f$ 0.46 (system 3).

IR spectrum (KBr, ν, cm–1): 3349(NH), 1650(C=O), 1609(C=N), 1516(C=C), 1467(C-H), 1336, 1309(C-N), 1261, 1230(C-O).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz ): 1.86(2H, kv, J=6.2, H-2), 2.39(2H, t, J=6.0, H-3), 2.79(2H, t, J=6.4, H-8′), 3.47(2H, t, J=6.4, H-7′), 3.72(3H, s, 3′-$OCH_3$), 3.81(3H, s, 4′-$OCH_3$), 3.95(2H, t, J=8.2, H-1), 6.58(1H, d, J=12.2, H-12), 6.70(1H, d, J=1.8, H-2′), 6.72(1H, dd, J=1.8, 8.0, H-6′), 6.75(1H, d, J=8.0 H-5′), 6.91(1H, d, J=8.2, H-6), 7.13(1H, t, J=8.0, H-8), 7.46(1H, t, J=8.2, H-7), 8.08(1H, d, J=8.0, H-9), 9.86(1H, dt, J=6.0, 12.2, NH),

***4-(3,4-Methylenedioxyphenylethylamino)-methylidene-1,2,3,4,10-pentahydropyrido[2,1-b]-quinazolin-10-one (6d)***

Obtained from 0.23 g (1.39 mol) 3,4-methylendioxyphenylethylamime (**5b)** and 0.3 g (1.39 mol) 4-(formyl)-1,2,3,4,10-pentahydropyrido[2,1-b]-quinazoline-10-one **(4)**. Yield is 1.82 g (98%), mp 136-139°C (from $CH_3OH$:$CHCl_3$ 10:1), $R_f$ 0.5 (system 3).

IR spectrum (KBr, ν, cm–1): 3437, 3350(NH), 1646(C=O), 1626(C=N), 1607, 1520(C=C), 1469, 1449(C-H), 1340, 1308(C-N), 1245, 1181(C-O).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz ): 1.86(2H, kv, J=6.0, H-2), 2.39(2H, t, J=6.0, H-3), 2.76(2H, t, J=6.6, H-8′), 3.44(2H, dd, J=6.2, 6.4, H-7′), 3.95(2H, t, J=6.0, H-1), 5.84(2H, s, 3′-$OCH_2O$-4′), 6.68(1H, d, J=12.0, H-12) 6.64(1H, dd, J=1.6, 8.0 H-6′), 6.66(1H, d, J=1.2, H-2′), 6.71(1H, d, J=8.0 H-5′), 6.97(1H, d, J=8.2, H-6), 7.13(1H, t, J=8.0, H-8), 7.46(1H, t, J=8.2, H-7), 8.08(1H, d, J=8.0, H-9), 9.83(1H, dt, J=6.1, 12.2, NH),

***Interaction of 3-(3,4-dimethoxyphenylethylamino)-, 3-(3,4-methylenedioxyphenylethylamino)-methylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (6a, b) and 4-(3,4-dimethoxyphenylethylamino)-, 4-(3,4- methylenedioxyphenylethylamino)-methylidene-1,2,3,4,10-pentahydropyrido[2,1-b]-quinazolin-10-one (6c, d) to $CF_3CO_2H$. General procedure.***

A solution of 0.3 g 3-(3,4-dimethoxyphenylethylamino)-,(3,4-methylenedioxyphenylethylamino)-methylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (**6a, b**) or 4-(3,4-dimethoxyphenylethylamino)- ,(3,4-methylenedioxyphenylethylamino)-methylidene-1,2,3,4,10-pentahydropyrido[2,1-b]-quinazolin-10-one (**6c, d**) was dissolved in 5 mL trifluoroacetic acid and heated at 95-98°C on water bath for 3 hours. The obtained products were identified by TLC. Then the reaction mixture was cooled and alkalinized by ammonia till pH 9-10, amine was exhaustively extracted with chloroform. The crude product was purified on silicagel column using chloroform: methanol (100:1→100:5).

***6,7-Dimethoxy-3,4-dihydroisoquinoline (7a)***[17].

Obtained from 0.3 g (0.79 mol) 3-(3,4-dimethoxyphenylethylamino)-methylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (**6a**). Yield is 0.13 g (89%), oil, mp 198-202°C of hydrochloride, $R_f$ 0.63 (system 1).

Obtained from 0.25 f (0.11 mM) 4-(3,4-dimethoxyphenylethylamino)-methylidene-1,2,3,4,10-pentahydropyrido[2,1-b]-quinazolin-10-one (**6c**). Yield is 0.11 g (90%).

IR spectrum (KBr, ν, cm–1): 2938, 2837($CH_2$), 1630, 1605(C=N), 1574, 1518(C=C), 1457(C-H), 1351, 1325(C-N), 1280, 1120(C-O).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz ): 2.62(2H, t, J=7.6, H-4), 3.67(2H, t, J=6.1, H-3), 3.84(3H, s, 7-$OCH_3$), 3.86(3H, s, 6-$OCH_3$), 6.61(1H, s, H-8), 6.75(1H, s, H-5), 8.18(1H, s, H-1).

***6,7-Methylenedioxy-3,4-dihydroisoquinaline (7b).***

Obtained from 0.15 g (0.41 mol) 3-(3,4-methylenedioxyphenylethylamino)-methylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (**6b**) and 4 ml of trifluoroacetic acid. Yield is 0.05 g (68%), oil, $R_f$ 0.59 (system 1).

Obtained from 0.1 g (0.26 mol) 3-(3,4-methylenedioxyphenylethylamino)-methylidene-1,2,3,9,10-pentahydropyrido[2,1-b]-quinazolin-10-one (**6d**) и and 3 ml of trifluoroacetic acid. Yield is 0.039 g (84%).

IR spectrum (KBr, ν, $cm^{-1}$): 2924, 2853($CH_2$), 1738, 1672(C=N), 1596, 1541(C=C), 1463(C-H), 1378(C-N), 1272, 1245(C-O).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz ): 2.66(2H, t, J=7.9, H-4), 3.67(2H, t, J=7.7, H-3), 5.94(2H, s, 6-$OCH_2O$-7), 6.60(1H, s, H-8), 6.75(1H, s, H-5), 8.23(1H, s, H-1).

***Deoxyvasicinone (1).***

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz ): 2.23(2H, dt, J=7.9, 15.3, H-2), 3.12(2H, t, J=7.9, H-1), 4.15(2H, t, J=7.4, H-3), 7.38(1H, t, J=7.8, H-6), 7.58(1H, d, J=8.0, H-5), 7.66(1H, t, J=7.5, H-7), 8.21(1H, d, J=8.0, H-8)[15].

***Mackinazolinone (2).***

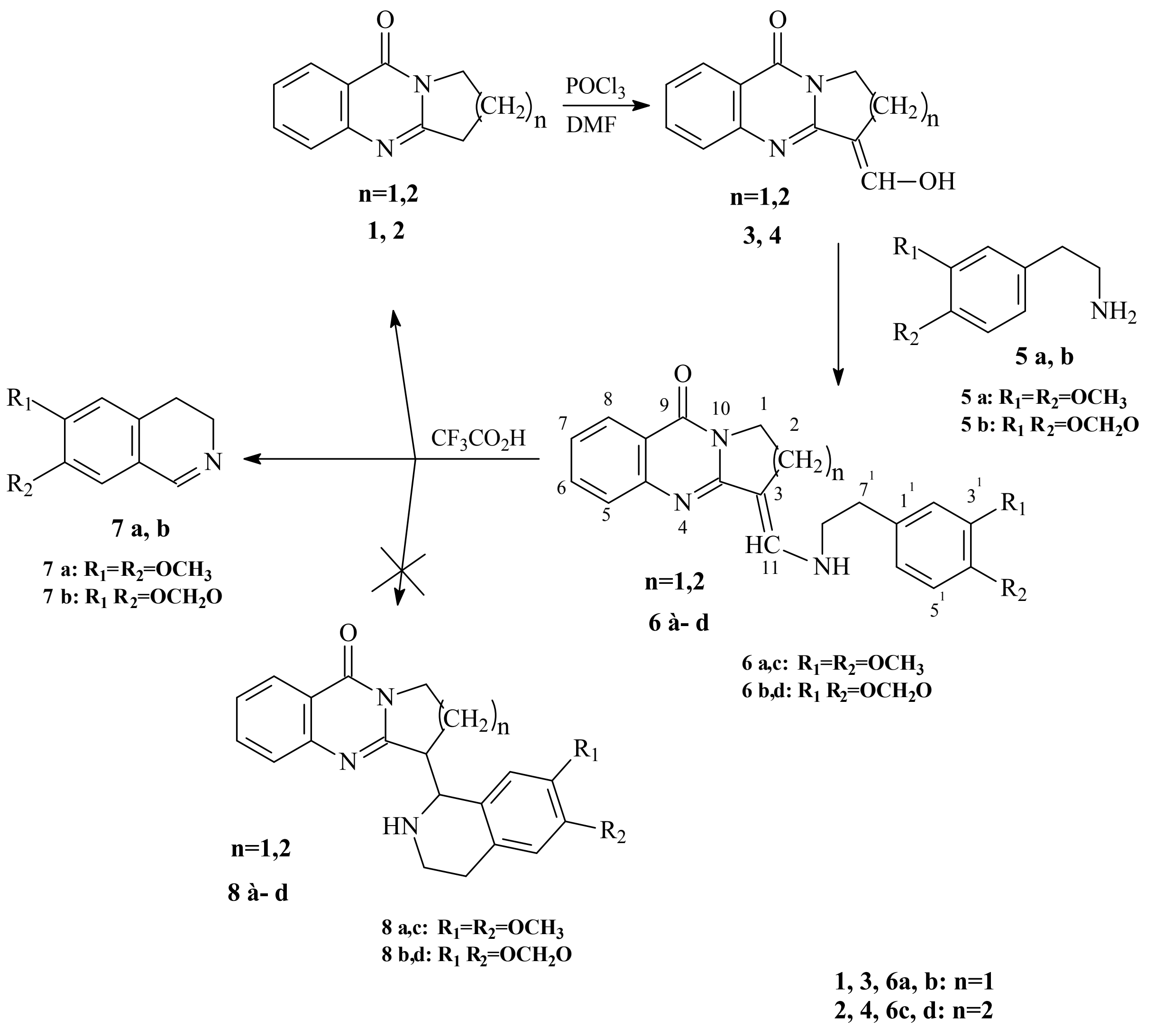
PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz ): 1.91(4H, m, H-2, 3), 2.94(2H, t, J=6.7, H-1), 4.02(2H, t, J=6.2, H-4), 7.36(1H, t, J=8.4, H-7), 7.53(1H, d, J=8.2, H-6), 7.65(1H, t, J=8.3, H-8), 8.21(1H, d, J=8.0, H-9)[16].

## *Results and Discussion*

Previously we have obtained bimolecular quinazoline-isoquinoline derivatives by amination of 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (**3**) with 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines [18].

In this paper, we have continued to study of nucleophilic displacement reaction[19] of 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (**3**) and 4-(formyl)-1,2,3,4,10-pentahydropyrido[2,1-b]quinazolin-10-one (**4**) with phenyl ethylamine **5a, b,** and realized the cyclization of the obtained **6a-d** in trifluoroacetic acid medium. Interaction of **3** and **4** to amines **5a, b** at the conditions found previously[18] (equimolar substances ratio in chloroform boiled for 2-4 hours) proceeded successfully and led to formation of heterocyclic enamines **6a-d**, which was confirmed by IR and 1H NMR spectra. Reactions were carried out in methanol or chloroform boiled for 4-5 hours. All compounds (**6a-d**) were isolated as crystals with high yield (77-98%). Regardless of whether the ring C **3** and **4** in the initial tricyclic pyrido[2,1-b]-quinazoline alkaloids has five- or six atoms, the nucleophilic displacement reaction with primary amines were in high yield.

There are intense absorption bands of amine (3338-3437sm$^{-1}$) and carbonyl groups of quinazoline fragments (1646-1693sm$^{-1}$) in IR spectra of quinazoline derivatives **6a-d**. H-11 signals at δ 8.69 ppm **6 a**, at 8.13 ppm **6 b**, and H-12 at 6.58 ppm **6 c**, and at 6.68 ppm for **6 d** are presented in $^1$H NMR spectra. The structure of obtained compounds **6 a-d** is confirmed by the absence of signal H-3 for **6a,b** and H-4 for **6c, d**.




Scheme 1 General synthetic scheme: (**6 a-d**) and preparation of compounds (**7a,b**)

In our attempts in cyclization of **6a-d** in $CF_3CO_2H$ (TFA) environment instead of the expected bis-products of **8a-d** consisting of quinazolinone and isoquinoline molecules, we have obtained the corresponding 3,4-dihydroisoquinolines (**7a, b**) and initial deoxyivasicinone (**1**) and mackinazolinone (**2**). During the reaction molecular degradation **6a-d** occur in acidic medium providing the corresponding imine ion, which is cyclized to the 3,4-dihydroisoquinoline (**7a, b**). The structure of the obtained 3,4-dihydroisoquinolines (**7a, b**) was confirmed by IR and $^1$H-NMR spectra[17].

## Conclusions

Reactions were carried out in methanol or chloroform boiled for 4-5 hours. All compounds (**6a-d**) were isolated as crystals with high yield (77-98%). Regardless of whether the ring C **3** and **4** in the initial tricyclic pyrido[2,1-b]-quinazoline alkaloids has five- or six atoms, the nucleophilic displacement reaction with primary amines were in high yield.

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