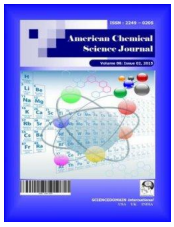

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Synthesis of Novel Methylidene Bridged Quinazoline-Isoquinoline Alkaloids

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Authors' contributions

The work was carried out in collaboration between all authors. Author SNZ carried out the synthesis. Author VIV provided analysis of the study, and spectroscopic evaluation. Author BZE did the collation of the date and editing of the write-up. All authors read and approved the final manuscript.

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ABSTRACT

Interaction of 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (2) with 1H(aryl)-6,7-dimethoxytetrahydroisoquinolines (3a-f) leads to the formation of novel methylidene bridged quinazoline-isoquinoline alkaloids. By results of IR- and ^{1}H-NMR – spectroscopy are shown that the synthesized products have enamine form and *E*-configuration.

Keywords: 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one; 1H(aryl)-6,7-dimethoxytetrahydroisoquinolines; nucleophilic substitution reactions; E-configuration.

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1. INTRODUCTION

Interest to quinazoline [1-9] and isoquinoline [10-16] alkaloids are caused by a wide spectrum of application of these heterocycles as biological active compounds (BAC). Alkaloid deoxyvasicinone (1,2,3,9-tetrahydropyrrolo [2,1-b]- quinazolin- 9-one, 1), which was isolated from plant *Peganum harmala* possesses antimicrobial and anti-inflammatory activities [9]. Natural and synthetic isoquinolines are a part of a number of drugs (papaverine, morphine, no-spa, etc.).

Modern approaches for creation of numerous series of synthetic derivatives are based on the simple reactions in implementation having wide opportunities for synthesis of the perspective compounds in high yields. Earlier developed amination methods [17-19] of 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2, 1-b]-quinazolin-9-one (2) with amines which allowed us to synthesize the methylidene bridged heterocyclic systems, consisting quinazoline part and various isoquinoline fragments. Similar structures are interesting; as they allow to combine various alkaloid fragments like bis-compounds and to investigate “structure-activity” relationships.

2. MATERIALS AND METHODS

2.1 General Conditions

2.1.1 Experimental

^{1}H-NMR spectra were recorded in $CDCl_3$+CD_3OD on Varian 400-MR spectrometer operating accordingly at 400 MHz. Hexamethyldisilane (HMDS) was used as internal standard, chemical shifts δ of ^{1}H were recorded in ppm.

Mass spectra were acquired on a Kratos MS-90 spectrometer. Mps were measured on a Boethius apparatus and was uncorrected. IR spectra were recorded on IR Fury System 2000 (Perkin-Elmer) as KBr pellets. The reaction process was monitored by TLC on LS 5/40 silica gel plates (Czech. SSR) using $CHCl_3$: MeOH (12:1 and 14:1) 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 $CaCl_2$.

2.2 Synthesis

1,2,3,9-Tetrahydropyrrolo[2,1-b]-quinazolin-9-one (1) was obtained by modified method, which was developed by *Elmuradov* [20].

3-Hydroxymethylidene-1,2,3,9-tetrahydropyrrolo [2,1-b]-quinazolin-9-one (2) was synthesized according to the method [21].

To the solution of 4.5 g (0.062 mol) absolute dimethylformamide at vigorous stirring and cooling (ice bath) 5.4 ml (0.062 mol) of phosphorus oxychloride was added drop wise, stirred for 20 min. and 5 g (0.027 mol) of 1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (1) was added on portions. Reactionary mixture was mixed for 2 hours at the room temperature (20°C) and was left for 14 hours. Then the mixture was heated for 2 hours on the water bath at 95-98°C, was cooled, and decomposed with distilled water (15 ml), neutralized by concentrated aqueous solution of sodium acetate, and stirred at the room temperature (20°C) for 3-4 hours. The formed white precipitate was filtered off, washed with water (3-4 times) and dried. Yield: 4.8 g (81%), mp 214-218°C (chloroform).

1H(Aryl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (3a-f) were prepared by methods [22,23].

2.2.1 General method for the synthesis of compounds 4a-f

The solution of 1H(aryl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (3a-f, 0.467 mol) and 3- hydroxymethylidene-1,2,3,9-tetrahydropyrrolo [2,1-b]-quinazolin-9-one (2, 0.467 mol) in MeOH (10 mL) was refluxed for 4-5 h (TLC monitoring), and cooled. The formed precipitate was filtered off, washed with MeOH, dried on air. The crude product was crystallized from methanol.

2.2.1.1 *3-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinol-2-yl)-methylidene-1,2,3,9-tetrahydropyrrolo-[2,1-b] quinazolin-9-one (4a)*

From 0.1 g (0.51 mmol) compound 3a and 0.11 g (0.51 mmol) 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-9-one was prepared 0.15 g (71%) 4a, mp 211–213°C

(MeOH), $C_{23}H_{23}N_3O_3$, R_f =0.83 ($CHCl_3$/MeOH - 12:1, at RT). IR (KBr) cm^{-1}: 1659 (C=O), 1641 (C=N), 1567, 1548, 1513 (C=C), 1462 (C-H), 1373 (C-N), 1268, 1171, 1116 (C-O). ^{1}H-NMR ($CDCl_3$ +CD_3OD) δ: 2.79 (2H, t, J=5.8, H-2), 3.12 (2H, t, J=8.1, H-4´), 3.61 (2H, t, J=5.8, H-1), 3.80 (3H, s, 7´-OCH_3), 3.81(3H, s, 6´-OCH_3), 4.09 (2H, t, J=8.1, H-3´), 4.56 (2H, s, H-1´), 6.49 (1H, s, H-8´), 6.56 (1H, s, H-5´), 7.14 (1H, t, J=8.0, H-6), 7.40 (1H, d, J=8.0, H-5), 7.51 (1H, s, H-11), 7.53 (1H, t, J=7.7, H-7), 8.09 (1H, dd, J=1.0, 7.8, H-8).

2.2.1.2 3-(1'-Phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinol-2-yl)-methylidene-1,2,3,9-tetrahydropyrrolo[2,1-b] quinazolin-9-one (4b)

Analogously from 0.126 g (0.461 mmol) of 3b and 0.1 g (0.467mmol) of 2 was synthesized 0.165 g (76%) of 4b, mp 219–221°C (MeOH), $C_{29}H_{27}N_3O_3$, R_f =0.88 ($CHCl_3$/MeOH - 12:1, at RT). IR spectrum (KBr) cm^{-1}: 1669 (C=O), 1641 (C=N), 1566, 1547,1515 (C=C), 1466 (C-H), 1373 (C-N), 1226, 1112 (C-O). ^{1}H-NMR ($CDCl_3$ +CD_3OD) δ: 2.68 (1H, m, H_a-4´), 2.99 (1H, m, H_e-3´), 3.11 (2H, m, H-2), 3.45 (1H, m, H_e-4´), 3.71 (1H, m, H_a-3´), 3.76 (3H, s, 7´-OCH_3), 3.84 (3H, s, 6´-OCH_3), 4.11 (2H, m, H-1), 5.74 (1H, s, H-1´), 6.49 (1H, s, H-8´), 6.63 (1H, s, H-5´), 7.16-7.30 (6H, m, H-7, Ar-H), 7.43 (1H, d, J=8.1, H-5), 7.54 (1H, t, J=7.7, H-6), 7.76 (1H, s, H-11), 8.12 (1H, d, J=7.8, H-8).

2.2.1.3 3-[1'-(2''-Hydroxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinol-2-yl)]–methylidene--1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-9-one (4c)

Reaction carried out analogously to synthesis of compound 4a. From 0.185 g (0.649 mmol) 3c and 0.139 g (0.649 mmol) 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo [2,1-b]-quinazolin-9-one 0.215 g (70%) product 4c was synthesized, mp 260–261°C (MeOH), $C_{29}H_{27}N_3O_4$, R_f =0.69 ($CHCl_3$/MeOH - 14:1, at RT). IR (KBr), cm^{-1}: 3126 (OH), 1650 (C=O), 1636 (C=N), 1566, 1549, 1515 (C=C), 1453 (C-H), 1372 (C-N), 1284, 1257, 1187 (C-O). ^{1}H-NMR ($CDCl_3$ +CD_3OD) δ: 2.76 (1H, m, H_a-4´), 2.99-3.16 (3H, m, H_a-3´, H-2), 3.47 (1H, m, H_e-4´), 3.66 (3H, s, 7´-OCH_3), 3.79 (1H, m, H_e-3´), 3.83 (3H, s, 6´-OCH_3), 4.06 (2H, m, H-1), 6.12 (1H, s, H-1´), 6.43 (1H, s, H-8´), 6.62 (1H, s, H-5´), 6.63-6.64 (2H, m, H-3´´,4´´), 6.83 (1H, d, J=8.0, H-6´´), 7.08 (1H, t, J=7.5, H-5´´), 7.15 (1H, t, J=7.5, H-6), 6.83 (1H, d, J=7.9, H-8), 7.53 (1H, t, J=7.7, H-7), 7.93 (1H, s, H-11), 8.03 (1H, dd, J=1.3, 8.2, H-5).

2.2.1.4 3-[1'-(4''-Nitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinol-2-yl)]-methylidene-1,2,3,9-tetrahydropyrrolo [2,1-b]quinazolin-9-one (4d)

Prepared from 0.164 g (0.522 mmol) 3d and 0.122 g (0.522 mmol) 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (2). Yield: 0.22 g (82%), mp 189–192°C (MeOH), $C_{29}H_{26}N_4O_5$, R_f =0.81 ($CHCl_3$/MeOH - 14:1, at RT). IR (KBr), cm^{-1}: 1668 (C=O), 1645 (C=N), 1566, 1544, 1518 (C=C), 1464, 1440 (C-H), 1347 (C-N), 1243, 1220 (C-O). ^{1}H-NMR ($CDCl_3$ +CD_3OD) δ: 2.67 (1H, dt, J=3.3, 16.0, H_a-4´), 2.99 (1H, dtd, J=6.0, 5.6, 5.5, H_a-3´), 3.10 (2H, m, H-2), 3.35 (1H, ddd, J=4.7, 7.1, H_e-4´), 3.76 (3H, s, 7´-OCH_3), 3.78 (1H, m, H_e-3´), 3.84 (3H, s, 6´-OCH_3), 4.14 (2H, m, H-1), 5.74 (1H, s, H-1´), 6.44 (1H, s, H-8´), 6.65 (1H, s, H-5´), 7.18 (1H, t, J=7.5, H-7), 7.35 (2H, d, J=8.7, H-2´´,6´´), 7.43 (1H, d, J=8.2, H-5), 7.56 (1H, t, J=7.6, H-6), 7.73 (1H,s, H-11), 8.12 (3H, d, J=8.5, H-3´´, 5´´, 8).

2.2.1.5 3-[1'-(3,''4''-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinol-2-yl)]-methylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-9-one (4e)

The reaction carried out analogously to the above mentioned method; from 0.159 g (0.485 mmol) 3e and 0.104 g (0.485 mmol) compound 2 have been synthesized 0.18 g (72%) 4e, mp 133–135°C (MeOH), $C_{31}H_{31}N_3O_5$, R_f =0.53 ($CHCl_3$/MeOH - 14:1, at RT). IR (KBr), cm^{-1}: 1646 (C=O), 1608 (C=N), 1568, 1550, 1514 (C=C), 1467, 1439 (C-H), 1374 (C-N), 1233, 1102, 1025 (C-O). ^{1}H-NMR ($CDCl_3$ +CD_3OD) δ: 2.66 (1H, m, H_a-4´), 2.99 (1H, dtd, J=6.0, 5.2, H_a-3´), 3.11 (2H, m, H-2), 3.41 (1H, ddd, J=6.7, 4.3, 4.4, H_e-4´), 3.72 (1H, m, H_e-3´), 3.74 (3H, s, 7´-OCH_3), 3.75 (3H, s, 6´-OCH_3), 3.80 (3H, s, 3´´-OCH_3), 3.83 (3H, s, 4´´-OCH_3), 4.12 (2H, m, H-1), 5.66 (1H, s, H-1´), 6.46 (1H, s, H-8´), 6.59 (1H, dd, J=1.5, 8.4, H-6´´), 6.61 (1H, s, H-5´), 6.72 (2H, dd, J=2.5, 7.9, H-2´´,5´´), 7.16 (1H, t, J=7.7, H-7), 7.41 (1H, d, J=8.3 H-5), 7.54 (1H, t, J=8.3, H-6), 7.76 (1H, s, H-11), 8.11 (1H, d, J=7.8, H-8).

2.2.1.6 3-[1′-(3″,4″-Methylenedioxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinol-2-yl)]–methylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-9-one (4f)

Analogously from 0.146 g (0.466 mmol) 3f and 0.1g (0.466 mmol) 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (2) was prepared 0.186 g (78%) product 4f, mp 202–205°C (MeOH), $C_{33}H_{27}N_3O_5$, R_f =0.72 ($CHCl_3$/MeOH - 14:1, at RT). IR (KBr), cm^{-1}: 1672 (C=O), 1648 (C=N), 1569, 1549, 1515 (C=C), 1487, 1467 (C-H), 1375 (C-N), 1241, 1230, 1121 (C-O). ^{1}H-NMR ($CDCl_3$ +CD_3OD) δ: 2.66 (1H, m, H_a-4′), 2.97 (1H,dtd, J=6.1, 5.1, H_a-3′), 3.10 (2H, m, H-2), 3.44 (1H, ddd, J=4.6, 7.8, 4.6, H_e-4′), 3.71 (1H, m, H_e-3′), 3.75 (3H, s, 7′-OCH_3), 3.83 (3H, s, 6′-OCH_3), 4.14 (2H, m, H-1), 5.63 (1H, s, H-1′), 5.89 (2H, s, 3′′-OCH_2O-4′′), 6.44 (1H, s, H-8′), 6.58 (1H, dd, J=1.5, 8.0, H-6′′), 6.60 (1H, s, H-5′), 6.63 (1H, d, J=1.5, H-2′′), 6.69 (2H, d, J=8.0, H-5′′), 7.17 (1H, t, J=1.0, 7.5, H-7), 7.41 (1H, d, J=8.1 H-5), 7.54 (1H, t, J=1.2, 8.0, H-6), 7.71 (1H, s, H-11), 8.11 (1H, dd, J=1.4, 8.0, H-8).

3. RESULTS AND DISCUSSION

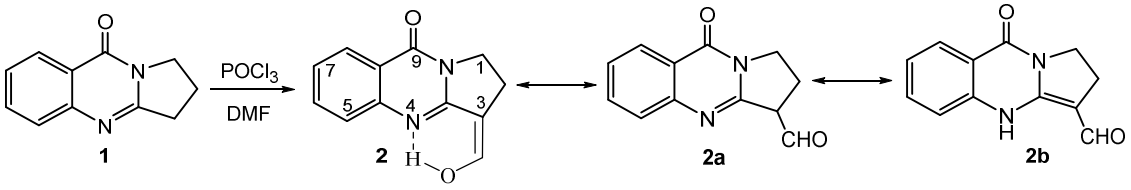
3.1 Chemistry

Heterocyclic compounds, consisting reactive formyl (or hydroxymethylidene) groups are very important starting synthons for creation of new condensation products. With purpose studying nucleophilic substitution reaction, we synthesized the 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (2) by formylation of 1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (1) with Vilsmeier–Haack reagent ($POCl_3$+DMF) [21] (see Scheme 1).

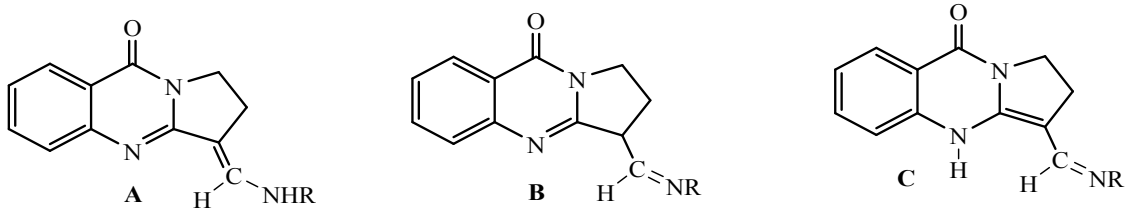
It was determined (by the UV- and IR-spectroscopy) that compound 2 has three tauromeric forms: enol (2), aldehyde (2a) and enaminoaldehyde (2b). The enol form of compound 2 was stable due to conjugation of ^{4}N=C and ^{3}C=CH-OH bonds, also formation of intramolecular hydrogen bonds between the hydrogen atom of hydroxyl group and ^{4}N nitrogen atom [21,24].

Earlier interaction of 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (2) with aliphatic primary and secondary amines (diamines) [17], isomeric aminophenols and aminobenzoic acids [18] and 4-substituted piperazines [19] were studied and it was revealed that depending on basicity, structure and reaction conditions corresponding condensation products – heterocyclic enamines (A) or imines (azomethines B and C) have been synthesized (see Scheme 2).

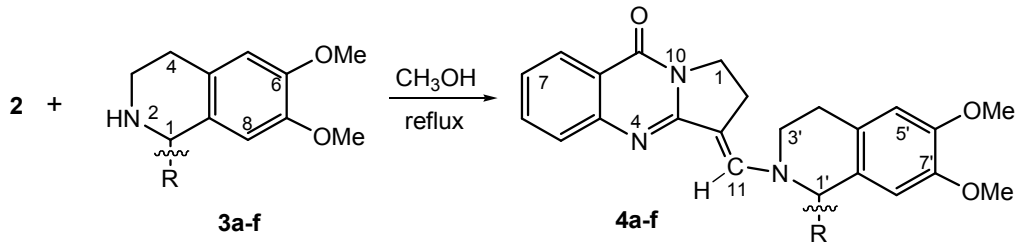
In present work nucleophilic substitution reactions of 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazolin-9-one (2) with different 1H(aryl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (3a-f) have been studied. The substituted isoquinolines, consisting electron donating or electron withdrawing groups react with compound 2 similar each other. Reactions carried out in methanol by refluxing for 4-5 hours and compounds 4a-f were synthesized in good yields (70-82%) (see Scheme 3).



Scheme 1. Formylation of 1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-9-one (1)



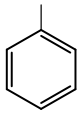
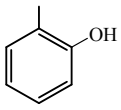
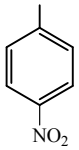
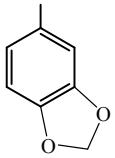
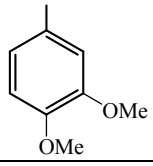
Scheme 2. Imine-enamine tautomeric forms of targeted compounds



3a-f 4a-f

Scheme 3. Synthesis of methylidene bridged quinazoline-isoquinoline alkaloids

Table 1. Yields and R in compounds 4a-4f

No	Starting compounds		R	Product	Yield, %
1	2	3a	H	4a	71
2	2	3b		4b	76
3	2	3c		4c	70
4	2	3d		4d	82
5	2	3e		4e	72
6	2	3f		4f	78

The structure of the obtained compounds were confirmed by data of IR- and ^{1}H-NMR spectroscopy.

In IR-spectra valence vibrations of the OH and NH groups aren't found at 3350-3600 cm^{-1} and 3200-3300 cm^{-1}. In ^{1}H-NMR spectrum of products the chemical shifts of aromatic protons of quinazoline part found – at 6.44-8.12 ppm, signals isoquinoline fragments – at 6.43-6.65 ppm, 1-aryl cycles – at 6.58-8.12 ppm. Chemical shifts of other groups (methoxy, methylene) were determined in corresponding fields (see experimental part). Signals of olefinic protons H-11 have chemical shifts at 7.51-7.93 ppm as one protonic singlets (1H, s). It means that reaction products have enamine form (A) and *E*-configuration.

4. CONCLUSION

It was found that by nucleophilic substitution of 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo [2,1-b]-quinazolin-9-one with 1H(aryl)-6,7-dimethoxytetrahydroisoquinolines are formed a novel methylidene bridged quinazoline-isoquinoline alkaloids. The structure of the synthesized compounds investigated by the IR- and ^{1}H-NMR spectroscopy and it was shown that the obtained substances have *E*-configuration. Researches in this direction will be continued.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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