Synthesis of New 1,2,4-Triazoles Containing Oxadiazole Moiety: Potential Intermediates for Preparation of Ribavirin Analogues

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Authors' contributions

This work was carried out in collaboration between all authors. All authors designed the study and performed the literature search. Authors SB and TS performed the experiments. Authors SB and MD wrote the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

In this paper, we report synthesis of the new biheterocycles containing 1,2,4-triazole and 1,2,4-oxadiazole or 1,3,4-oxadiazole moiety. Oxadiazole ring is bioisosteric replacement of carboxamide group. In future, these compounds will be used for enzymatic synthesis of ribavirin analogues. Structures of the final biheterocycles were confirmed by spectral and elemental analysis.

Keywords: 1,2,4-triazole; 1,2,4-oxadiazole; 1,3,4-oxadiazole; bioisosteric replacement; ribavirin.

1. INTRODUCTION

Antiviral properties of ribavirin (Fig. 1) were known since 1972 year [1]. Initially, it demonstrated activity against broad-spectrum of DNA and RNA viruses [1], that's why it has been widely used in medicine. Currently, it used for treatment of influenza, severe respiratory syncytial virus (RSV) infection, Lassa fever virus infection, SARS coronavirus infections [2,3]. In
combination with interferon-α, it is used for therapy of hepatitis C virus (HCV) infection - major cause of cirrhosis and hepatocellular carcinoma [4]. However, side effects, including hemolytic anemia, and resistance of some viruses significantly limited its application [5,6].

Synthesis of new ribavirin structural analogues is most common strategy to overcome described limits. There are two routes of modification: carboxamide group of heterocyclic moiety or glycoside moiety. Phosphorylation of primary hydroxyl group is the main glycoside moiety modification [7]. The hydrazones, amidines, ketones and α-imino esters were obtained as a result of carboxamide group transformation [8,9].

![Heterocyclic moiety](image)

![Glycoside moiety](image)

2. EXPERIMENTAL DETAILS

2.1 General

The starting reagents and solvents were obtained from Sigma-Aldrich Company and used without further purification. The reactions were monitored by high-performance liquid chromatography (HPLC). Analysis was performed on Shimadzu LC 20 Prominence apparatus and Waters Xbridge C18, 50 mm x 4.6 mm column with water-acetonitrile eluent. The purity of compounds was also determined by HPLC.

2.2 Synthesis of the Starting Compounds

The compounds 3, 4, 6, 7 were prepared from 1,2,4-triazolecarboxylic acid 2 according to literature methods [12,13].

Methyl 1H-1,2,4-triazole-3-carboxylate (3)

Yield: 88%, m.p.: 185-186°C. ¹H NMR (DMSO-d₆): 4.33 (s, 3H, CH₃), 8.51 (s, 1H, CH).

1H-1,2,4-triazole-3-carboxamide (4)

Yield: 85%, m.p.: 224-228°C. ¹H NMR (DMSO-d₆): 7.49 (s, 1H, NH), 7.73 (s, 1H, NH), 8.63 (s, 1H, CH).

1H-1,2,4-triazole-3-carbonitrile (6)

Yield: 68%, m.p.: 186-188°C. ¹H NMR (DMSO-d₆): 8.87 (s, 1H, CH).

1H-1,2,4-triazole-3-carbamidoxime (7)

Yield: 89%, m.p.: 215-216°C. ¹H NMR (DMSO-d₆): 7.94 (s, 2H, NH₂), 8.25 (s, 1H, CH), 9.96 (s, 1H, OH).

The data of all compounds are in accordance with the published [12,13].

2.3 Synthesis of 1H-1,2,4-triazole-3-carbohydrazide (5)

At stirring to 0.4 mol of hydrazine hydrate was added 0.1 mol of 1,2,4-triazole-3-carboxylic acid methyl ester 3. The reaction mixture was refluxed for 30 min, cooled to 40°C, and concentrated at reduced pressure. The resulting suspension was cooled to 0-5°C over 2 h and filtered.

Yield: 89%, m.p.: 241-244°C, ¹H NMR (DMSO-d₆): 5.21 (s, 2H, NH₂), 7.67 (s, 1H, NH), 8.55 (s, 1H, CH).

2.4 General Procedure for the Synthesis of 3-alkyl-5-(1H-1,2,4-triazole-3-yl)-1,2,4-oxadiazoles (8a-c)

To 0.011 mol of acid 2 in 20 mL of 1.4-dioxane was added 0.015 mol of EDC and resulted mixture was stirred for 30 min at RT. Further, 0.01 mol of amidoxime was added. Reaction mixture was stirred for 3 h at RT and for 6 h at 100 °C. Solvent was evaporated at reduced pressure, and then 50 mL of dichloromethane was added to the residue. Organic layer was separated, washed with 10% solution of sodium bicarbonate (1 x 25 mL) and water (2 x 25 mL), dried with sodium sulfate and evaporated at reduced pressure.
Yield: 71%. ^1^H NMR (DMSO-d6): 2.63 (s, 3H, CH3), 8.63 (s, 1H, CH). ^13^C NMR (DMSO-d6): 11.5, 144.9, 157.5, 159.2, 163.1. Found, %: C 39.78; H 4.00; N 46.31. Calculate, %: C 39.74; H 3.98; N 46.34.

Yield: 72%. ^1^H NMR (DMSO-d6): 1.45 (d, J = 7.2 Hz, 6H, CH3), 3.46-3.52 (m, 1H, CH), 8.55 (s, 1H, CH). ^13^C NMR (DMSO-d6): 20.3, 26.8, 144.1, 157.7, 160.9, 162.1. Found, %: C 46.97; H 5.11; N 39.02. Calculate, %: C 46.92; H 5.06; N 39.09.

**2.6 General Procedure for the Synthesis of 5-alkyl-3-(1H-1,2,4-triazole-3-yl)-1,2,4-oxadiazoles (10a-c)**

0.011 mol of acyl chloride was added to 0.01 mol of amidoxime 7 in 10 mL of pyridine at 0°C. Reaction mixture was stirred for 30 min at RT and then for 4 h at 100°C. Reaction mixture was cooled to RT and diluted by 70 mL of water. Resulting solution was extracted with dichloromethane (3 x 20 mL). Organic layer was washed with water (2 x 25 mL), dried with sodium sulfate and evaporated at reduced pressure.

Yield: 65%. ^1^H NMR (DMSO-d6): 2.72 (s, 3H, CH3), 8.67 (s, 1H, CH). ^13^C NMR (DMSO-d6): 12.3, 145.2, 158.8, 159.7, 163.2. Found, %: C 39.80; H 4.01; N 46.30. Calculate, %: C 39.74; H 3.98; N 46.34.

Yield: 77%. ^1^H NMR (DMSO-d6): 1.51 (d, J = 7.0 Hz, 6H, CH3), 3.47-3.54 (m, 1H, CH), 8.69 (s, 1H, CH). ^13^C NMR (DMSO-d6): 20.6, 27.4, 144.8, 158.1, 159.3, 161.7. Found, %: C 46.98; H 5.10; N 39.04. Calculate, %: C 46.92; H 5.06; N 39.09.

Yield: 79%. ^1^H NMR (DMSO-d6): 1.29-1.36 (m, 2H, CH3), 1.43-1.46 (m, 2H, CH2), 2.55 (m, 1H, CH), 8.61 (s, 1H, CH). ^13^C NMR (DMSO-d6): 7.5, 10.6, 144.2, 157.8, 158.6, 160.9. Found, %: C 47.53; H 4.02; N 39.46. Calculate, %: C 47.46; H 3.98; N 39.53.
3. RESULTS AND DISCUSSION

As part of our idea to replace the carboxamide group by 1,2,4- or 1,3,4-oxadiazole moiety, we synthesized 9 biheterocyclic compounds (8a-c, 9a-c, 10a-c). Route of synthesis is shown in Scheme 1 above. At first, we converted starting 1,2,4-triazolecarboxylic acid 2 into ester 3 and amide 4 by well-known methods. Further, hydrazide 5 and nitrile 6 were obtained from compounds 3 and 4 respectively. Treatment of the nitrile 6 with hydroxylamine hydrochloride alcohol solution and sodium bicarbonate was led to amidoxime 7.

3-Alkyl-5-(1H-1,2,4-triazole-3-yl)-1,2,4-oxadiazoles 8a-c were obtained by the reaction between aliphatic amidoximes with 1,2,4-triazolecarboxylic acid 2 in 1,4-dioxane. Starting acid 2 was activated by EDC, and amidoximes was added at resulting isoacylurea. Further, reaction mixture was refluxed, and 1,2,4-oxadiazoles 8 was formed via cyclodehydration of intermediate O-acylamideoximes.

Isomeric 1,2,4-oxadiazoles 10a-c were synthesized by heating amidoxime 7 with acyl chlorides in pyridine.

1,3,4-Oxadiazoles 9a-c were prepared by two-step method. In the first step, hydrazide 5 was acylated with previously described acyl chlorides in the presence of sodium bicarbonate in acetone at room temperature. In the second step, obtained dihydrazides were heated with two equivalents of phosphorus oxychloride.

Structure of all synthesized compounds was confirmed by $^1$H NMR data, and they purity’s was determined by HPLC. Moreover, final biheterocycles were characterized by $^{13}$C NMR spectroscopy and elemental analysis.

In future, all synthesized biheterocycles will be used for enzymatic synthesis of ribavirin analogues.

4. CONCLUSION

In this work, we report the synthesis of series of 9 new biheterocyclic compounds (8a-c, 9a-c, 10a-c), in which oxadiazole moiety is bioisosteric replacement of carboxamide group. In future, these compounds will be used for preparation of ribavirin analogues.
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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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