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Annelation of the 1,2,4-Triazine Core to 2,3-Benzodiazepine

Abstract

A one-pot, stepwise method for the annelation of the 1,2,4-triazine core to the seven-membered 2,3-benzodiazepine ring *via* the interaction of the corresponding 2,3-benzodiazepin-1-yl- or 2,3-benzodiazepin-4-ylhydrazines with α-ketoesters has been developed. It has been found that a stepwise formation of an azomethine intermediate followed by solvent replacement and subsequent cyclization enables the desired compounds to be obtained in high yields. Derivatives of a new heterocyclic system of [1,2,4]triazino[3,4-*a*][2,3]benzodiazepine have been synthesized.

Keywords: 2,3-benzodiazepine; α-ketoester; 1,2,4-triazine; annelation

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Анелювання 1,2,4-триазинового ядра до 2,3-бензодіазепіну

Анотація

Розроблено однореакторний метод анелювання 1,2,4-триазинового ядра до семичленного циклу 2,3-бензодіазепіну шляхом взаємодії відповідних 2,3-бензодіазепін-1-іл- або 2,3-бензодіазепін-4-ілгідразинів і α-кетоестерів. З'ясовано, що поетапне утворення азометинового інтермедіату та подальша циклізація після заміни розчинника дозволяють отримувати бажані сполуки з високими виходами. Синтезовано похідні нової гетероциклічної системи [1,2,4]триазино[3,4-*a*]-[2,3]бензодіазепіну.

Ключові слова: 2,3-бензодіазепін; α-кетоестер; 1,2,4-триазин; анелювання

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■ Introduction

2,3-Benzodiazepines have been in the focus of organic and medicinal chemistry for over 50 years since the advent of the anxiolytic Grandaxin. Extensive studies of 2,3-benzodiazepine derivatives have revealed therapeutic applications for the central nervous system, pain, metabolic syndrome, urology, gastrointestinal, and cardiovascular systems (Talampanel) [1], cancer treatment [2], and as AMPAA and AMPAR antagonists [3]. Despite the absence of recent novel medical drugs based on 2,3-benzodiazepine, one of the latest reviews states that "the benzodiazepine saga continues to develop as the number and diversity of agents that modulate GABAA receptors allosterically increases seemingly exponentially. Such modulators are much sought after for their potential subtype selectivity as a result of the greater structural diversity of allosteric sites as distinct from the orthosteric GABA binding sites" [4]. 2,3-Benzodiazepine derivatives are attractive due to their large number of biological activities and their capacity to produce a more subtle effect on various receptors than 1,4- and 1,5-benzodiazepine derivatives [5]. Thus, Grandaxin exerts anxiolytic activity but lacks sedative, amnestic, anticonvulsant, or muscle-relaxant

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properties, and does not bind to the benzodiazepine binding site [6]. At present, there is a number of effective synthetic strategies for the construction, functionalization, and heteroannelation of the 1,2-diazepine core. New condensed heterocyclic systems with a 1,2-diazepine core have been synthesized, and their structures, stabilities, and biological activities have been studied. Most biomedical studies of 2,3-benzodiazepines have been performed on binuclear derivatives, but some studies have shown that the annelation of an additional heterocyclic ring to the seven-membered ring could enhance activity or exhibit a new property. It has been demonstrated that the addition of an azole ring to the seven-membered 2,3-benzodiazepine moiety at N3-C4 atoms provides a high activity of the molecule as an AMPA antagonist and imparts a whole spectrum of activity to the molecule in relation to the central nervous system [7]. The annelation of the imidazole ring retains a high level of the neurotropic activity, emphasizing the anticonvulsant and neuroprotective components in the pharmacological profile [8].

In most fused heterocyclic systems with the 2,3-benzodiazepine fragment, the additional heterocycle is formed at N3-C4 atoms using available 2,3-benzodiazepine-4-thiones or the corresponding hydrazines. Before our studies, only one instance of a fused 2,3-benzodiazepine system with a heterocycle at C(1)-N(2) atoms was reported [9].

For novel C(1)-N(2) heterocyclic fused derivatives of 2,3-benzodiazepine, we used 2,3-benzodiazepinehydrazines-1 converted in moderate to high yields to [1,2,4]triazolo[3,4-*a*][2,3]benzodiazepines by the action of carboxylic acids, acid chlorides, and triethyl orthoformate [10] (**Figure 1**). The nitrosation in acetic acid forms the tetrazolo[5,1-*a*]-[2,3]benzodiazepine heterocyclic system [11]. In addition to five-membered heterocycles, we were also interested in the annelation of six-member heterocycles, including 1,2,4-triazine. Heterocyclic systems with the 1,2,4-triazine core exhibit a high anticancer activity [12, 13]. Thus, we investigated the possibility of adding a 1,2,4-triazine ring to 2,3-benzodiazepines by reacting the 2,3-benzodiazepine hydrazines with 2-ketoesters.

■ Results and discussion

As reported earlier, reactions of 1,3-dicarbonyl compounds with 4-aryl-2,3-benzodiazepin-1-ylhydrazines did not yield annelation products [11]. In contrast, Rosaria Gitto's group obtained products of the triazine ring annelation at N(3)-C(4) atoms by the action of oxalyl chloride on 1-aryl-4-hydrazino-2,3-benzodiazepine [7]. Therefore, we studied the interaction of 2,3-benzodiazepine-1-hydrazines with α-ketoesters (**Scheme 1**). As a result of the interaction of hydrazine derivative **1** with methyl phenylglyoxylate (**2a**) in boiling 2-ethoxyethanol, the expected 7-(4-methoxyphenyl)-3-phenyl[1,2,4]triazino[3,4-*a*][2,3]benzodiazepin-4(8*H*)-one (**3a**) was obtained in 28% yield.

Increasing the cyclization temperature by heating hydrazine **1** and ketoester **2a** in 2-butoxyethanol decreased the yield of cyclization product **3a** to 20%. To improve the yields of cyclization products, we studied the reaction stages of the azomethine **A** formation and the cyclization involving the ester group and the N(2) atom of

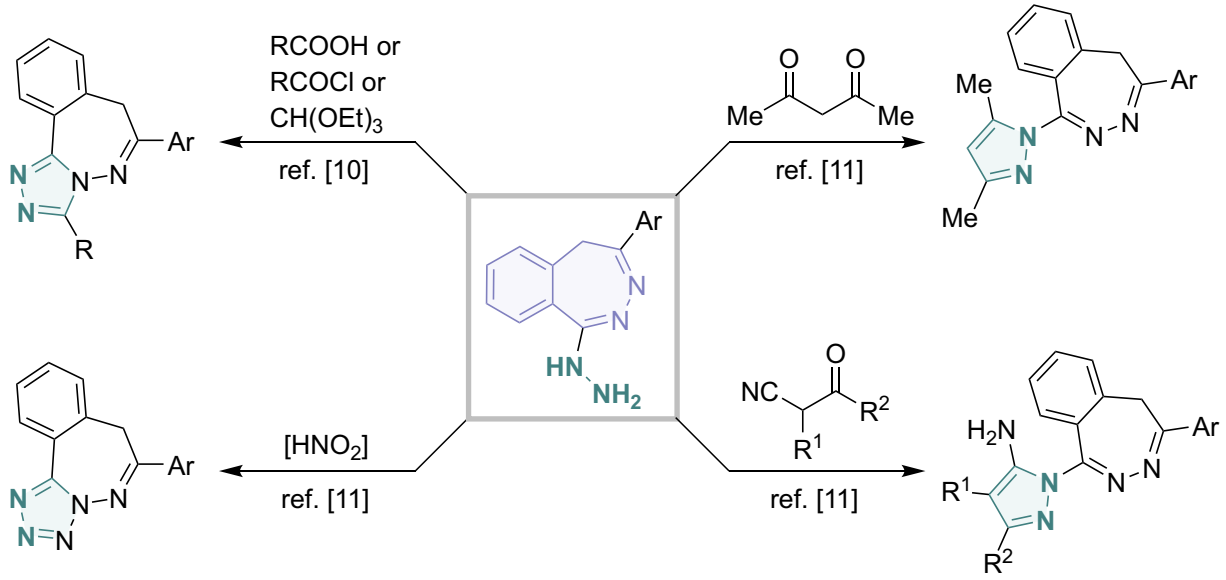
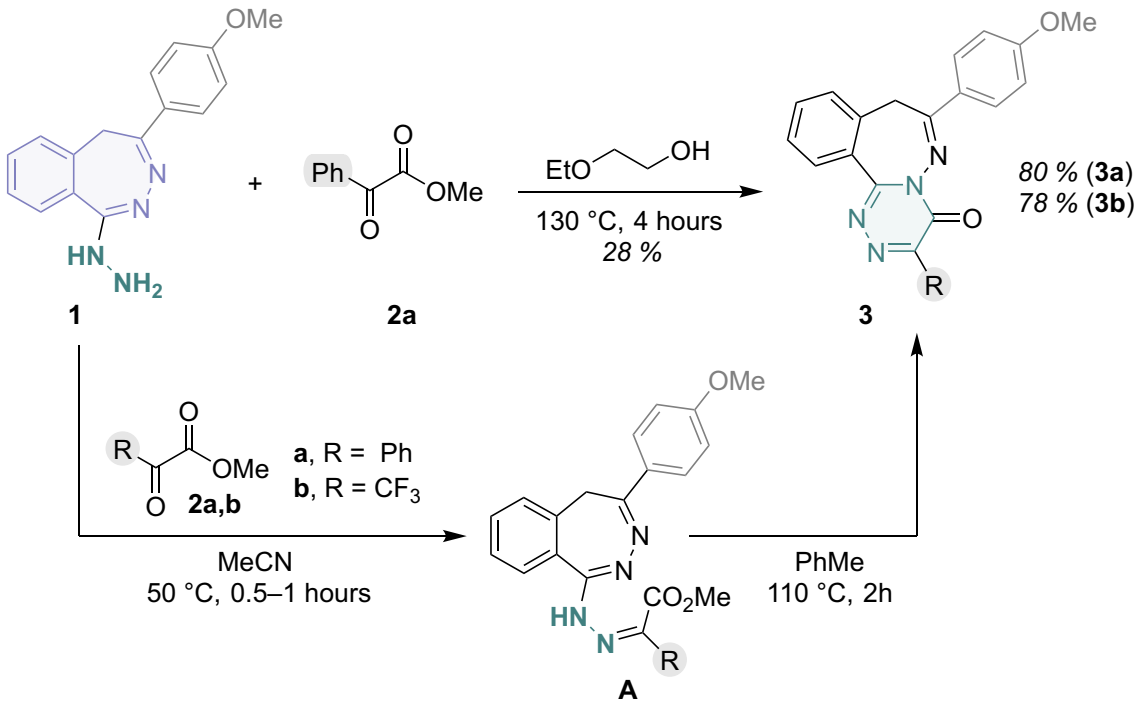


Figure 1. Selected studies in the formation of heterocyclic systems based on 2,3-benzodiazepin-1-yl-hydrazine



Scheme 1. The synthesis of 7-(4-methoxyphenyl)-3-R-[1,2,4]triazino[3,4-*a*][2,3]benzodiazepin-4-ones **3a,b**

the seven-membered ring. In the ^{1}H NMR experiment using hydrazine **1** and methyl trifluoropyruvate (**2b**) as an example, it was found that azomethine A formed quantitatively in acetonitrile at 30 °C within 30 min (**Figure 2***B*). The cyclization of azomethine **A** in boiling acetonitrile was extremely slow (**Figure 2***C*). After removing acetonitrile from the reaction mixture, we successfully carried out the cyclization step in boiling toluene. Under preparative conditions, we performed a stepwise synthesis of azomethine **A** and cyclized it *via* solvent exchange. As a result, 3-(trifluoromethyl)-7-(4-methoxyphenyl)-8*H*-[1,2,4]-triazino[3,4-*a*][2,3]benzodiazepin-4-one (**3b**) was isolated in 78% yield after the crystallization step (**Figure 2***D*).

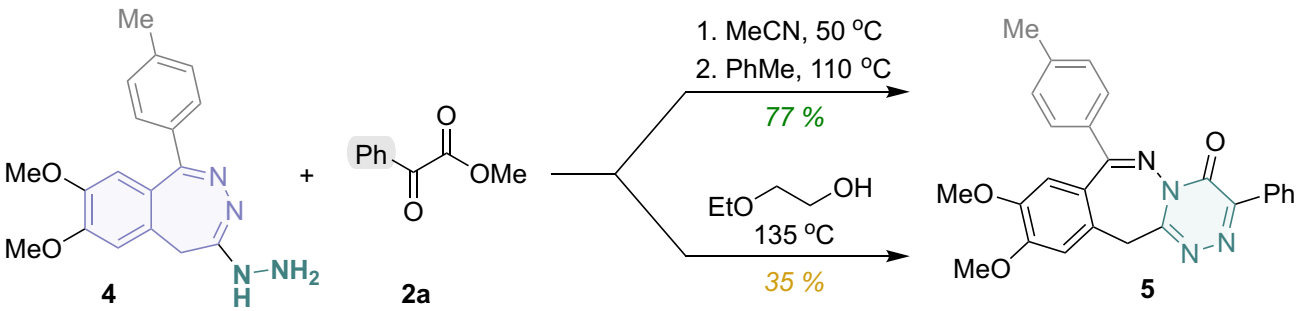
The increase in yield is probably also due to the removal of methanol released during the cyclization from the reaction zone. Triazinodiazepine **3a** was obtained by this method in 80% yield.

Table 1. The optimization of reaction conditions for the cyclocondensation of hydrazines **1** and **4** with ketoesters **2a,b**

Reagents	Solvent	T, °C	Product	Yield, %
1 + **2a**	2-Ethoxyethanol	135	**3a**	28
1 + **2a**	2-Butoxyethanol	170	**3a**	20
1 + **2a**	MeCN → PhMe	50 → 110	**3a**	80
4 + **2a**	2-Ethoxyethanol	135	**5**	35
1 + **2b**	MeCN → PhMe	50 → 110	**3b**	78
4 + **2a**	MeCN → PhMe	50 → 110	**5**	77

The reaction scheme does not require the isolation of the azomethine intermediate (**Table 1**).

This approach is also effective for the 1,2,4-triazine annelation at the N(3)-C(4) 2,3-benzodiazepine bond. The reaction of 1-aryl-2,3-benzodiazepin-4-ylhydrazine (**4**) with ketoester **2a** led to the isomeric heterocyclic structure of 9,10-dimethoxy-7-(4-methylphenyl)-3-phenyl[1,2,4]triazino[4,3-*c*][2,3]benzodiazepin-4(12*H*)-one with 77% yield (**Scheme 2**).



Scheme 2. The synthesis of [1,2,4]triazino[4,3-*c*][2,3]benzodiazepin-4-one **5**

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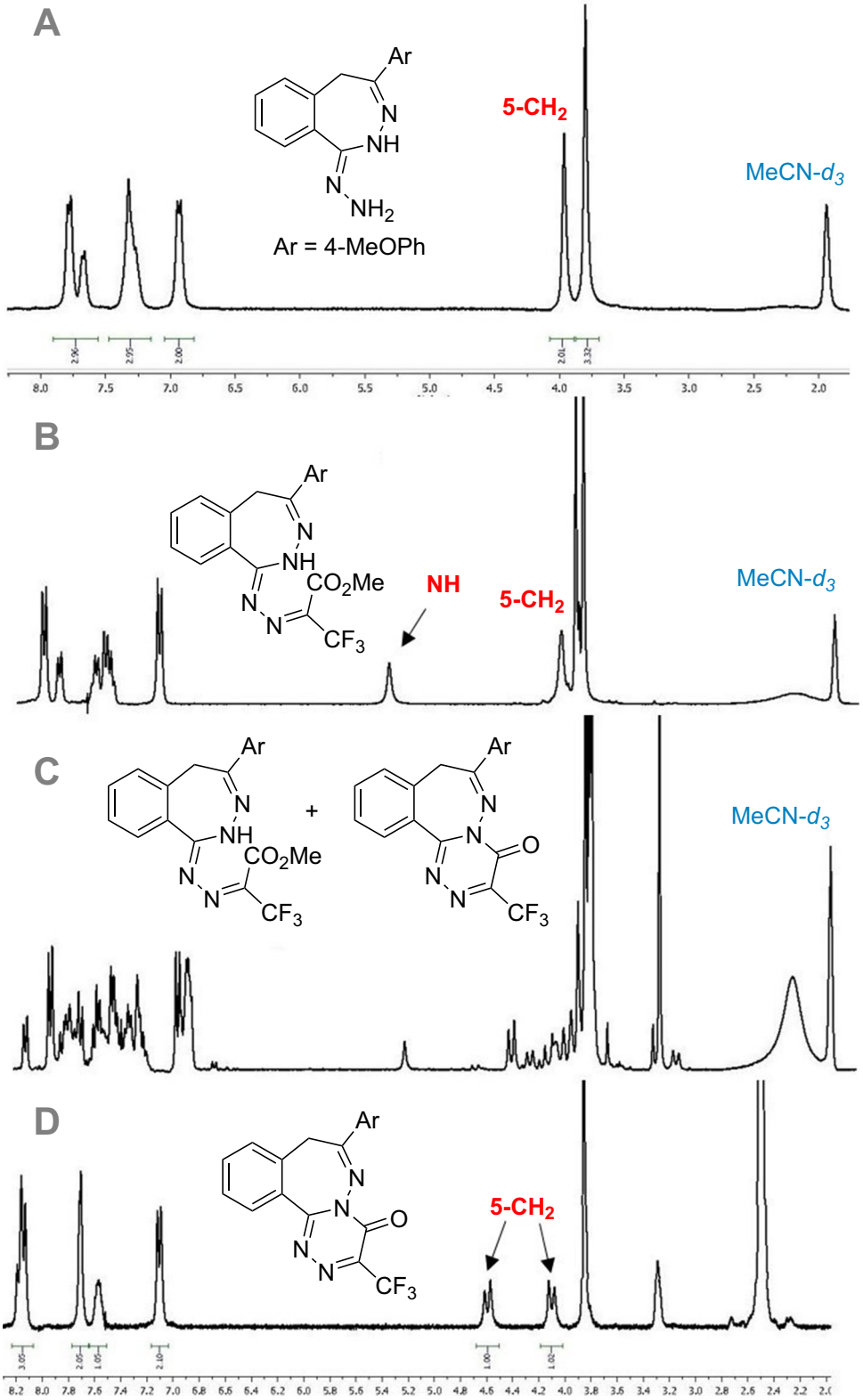

Figure 2. The ^{1}H NMR study of the reaction of hydrazine **1** and **2a**. ^{1}H NMR spectra of **1** in MeCN-d_3 (**A**); ^{1}H NMR spectra of **1** and **2b** in MeCN-d_3, in 30 min at 30 °C (**B**); ^{1}H NMR spectra of **1** and **2b** in MeCN-d_3, 4 h at 80 °C (**C**); ^{1}H NMR spectra of **3b** in DMSO-d_6, after 2 h in toluene refluxing (**D**)

■ Conclusions

In summary, we report an easy approach to the 1,2,4-triazine ring annelation to the "A" or "C" bond of 2,3-benzodiazepine. Unlike the known method [7], the method described allows for the introduction of various substituents into the triazine ring. Considering the availability of the starting reagents and high yields of the final compounds, we propose this simple and convenient method for the 1,2,4-triazine ring annelation to 2,3-benzodiazepines and relative compounds.

■ Experimental part

The solvents were purified according to the standard procedures. The initial hydrazines **1** and **4** were synthetized as described in [10, 11], α-ketoesters **2a,b** were received from commercial sources. The melting points were determined on a Fisher-Johns apparatus. ^{1}H, ^{13}C and ^{19}F NMR spectra were measured in the DMSO-d_6 solution on a Bruker Avance II 400 (400 MHz for protons, 100 MHz for carbon, and 376 MHz for fluorine atoms, respectively) and a Varian Mercury+ (300 MHz on protons and 76 MHz on carbon atoms, respectively) at 25 °C. Tetramethylsilane for ^{1}H and ^{13}C and hexafluorobenzene for ^{19}F were used as internal standards [14]. HPLC-MS spectra were recorded using the chromatography/mass-spectrometric system consisting of an Agilent 1100 high-performance liquid chromatograph equipped with a diode-matrix and mass-selective detector. The parameters of the chromatography-mass analysis were the column SUPELCO Ascentis Express C18, 2.7 μm 4.6 mm×15 cm. The elemental analysis was carried out in the Analytical Laboratory of the Institute of Organic Chemistry, NAS of Ukraine.

The cyclization of 2,3-benzodiazepin-1-yl- (1) and 2,3-benzodiazepin-4-yl-hydrazine (4) with ethyl phenylglyoxylate (*Method A*)

Hydrazine **1** or **4** (3 mmol) and ethyl phenylglyoxylate (3.3 mmol) were refluxed in 10 mL of 2-ethoxyethanol for 4 h. After cooling the mixture, water was added, the precipitated product was filtered, washed with water and recrystallized.

The yield of triazinodiazepine **3a** was 28%, the yield of triazinodiazepine **5** was 35%.

The [1,2,4]triazine ring annelation to 2,3-benzodiazepin-1-yl- and 2,3-benzodiazepin-4-yl-hydrazines (*Method B*)

To hydrazine **1** or **4** (3 mmol) in 50 mL of acetonitrile, α-ketoester **2** (3.15 mmol) was added, and the solution was stirred at 40–50 °C until complete conversion in 0.5–1 h (^{1}H NMR control). The solvent was removed under reduced pressure to dryness, 20 mL of toluene was added, and the mixture was refluxed for 2 h. The solvent was removed under reduced pressure to dryness, and the residue was crystallized.

7-(4-Methoxyphenyl)-3-phenyl[1,2,4]triazino[3,4-*a*][2,3]benzodiazepin-4(8*H*)-one (3a)

Small light-yellow crystals. Yield 0.94 g (80%). M. p. 209–211 °C (methanol). Anal. Calcd for $C_{24}H_{18}N_4O_2$, %: C 73.08; H 4.60; N 14.20. Found, %: C 73.2; H 4.6; N 14.3. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.88 (3H, s, CH_3O); 4.00 (1H, d, J = 13.2 Hz), 4.52 (1H, d, J = 13.2 Hz), 7.02 (2H, d, J = 8.8 Hz), 7.53–7.50 (4H, m), 7.65–7.55 (2H, m), 8.14 (2H, d, J = 8.8 Hz), 8,21 (1H, d, J = 7.76 Hz), 8.36–8.30 (2H, m). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 33.7, 55.3, 114.1, 125.1, 126.6, 127.5, 127.6, 127.8, 128.7, 129.0, 129.9, 130.1, 130.2, 132.3, 133.5, 138.9, 149.1, 151.3, 152.8, 172.0.

7-(4-Methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazino[3,4-*a*][2,3]benzodiazepin-4(8*H*)-one (3b)

Small white crystals. Yield 0.9 g (78%). M. p. 183–185 °C (propanol-2). Anal. Calcd for $C_{19}H_{13}F_3N_4O_2$, %: C 59.07; H 3.39; F 14.75; N 14.50. Found, %: C 58.95; H 3.35; F 14.84; N 14.67. ^{1}H NMR (300 MHz, DMSO-d_6), δ, ppm: 3.86 (3H, s, CH_3O), 4.10 (1H, d, J = 12 Hz, 5-CH_2), 4.59 (1H, d, J = 12 Hz, 5-CH_2), 7.10 (2H, d, J = 9 Hz), 7.52–7.63 (1H, m), 7.71 (2H, d, J = 9 Hz), 8.13–8.19 (3H, m). ^{13}C NMR (76 MHz, DMSO-d_6), δ, ppm: 33.31, 55.66, 114.66, 124.52, 127.83, 128.13, 130.63, 130.89, 133.90, 139.88, 155.76, 163.10, 172.96. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6), δ, ppm: -66.88. LC-MS (EI), m/z: 387 $[M+H]^+$.

9,10-Dimethoxy-3-phenyl-7-(p-tolyl)-12H-[1,2,4]triazino[4,3-*c*][2,3]benzodiazepin-4-one (5)

Small light-yellow crystals. Yield 1.0 g (77%). M. p. 245–247 °C (propanol-2). Anal. Calcd for $C_{26}H_{22}N_4O_3$, %: C 71.3; H 5,1; N 12.7. Found, %: C 71.22; H 5.06; N 12.78. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.41 (3H, s, CH_3), 3.63 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.06 (2H, dd, 5-CH_2, J = 14, 6.5 Hz), 6.75 (1H, s), 7.37 (3H, m), 7.49 (3H, m), 7.69 (2H, d, J = 6.8 Hz), 8.05 (2H, d, J = 6.8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 23.1, 38.1, 57.7, 58.0, 113.2, 114.7, 114.8, 120.7, 122.6, 130.0, 130.7, 130.8, 131.3, 132.2, 132.4, 134.3, 135.1, 135.8, 144.3, 150.0, 151.2, 154.8, 156.6, 157.5, 170.0.

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