



# Article Efficient Electrocatalytic Approach to Spiro[Furo[3,2-b]pyran-2,5'-pyrimidine] Scaffold as Inhibitor of Aldose Reductase

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Abstract: A continuously growing interest in convenient and 'green' reaction techniques encourages organic chemists to elaborate on new synthetic methodologies. Nowadays, organic electrochemistry is a new useful method with important synthetic and ecological advantages. The employment of an electrocatalytic methodology in cascade reactions is very promising because it provides the combination of the synthetic virtues of the cascade strategy with the ecological benefits and convenience of electrocatalytic procedures. In this research, a new type of the electrocatalytic cascade transformation was found: the electrochemical cyclization of 1,3-dimethyl-5-[[3-hydroxy-6-(hydroxymethyl)-4-oxo-4H-pyran-2-yl](aryl)methyl]pyrimidine-2,4,6(1H,3H,5H)-triones was carried out in alcohols in an undivided cell in the presence of sodium halides with the selective formation of spiro[furo[3,2*b*]pyran-2,5'-pyrimidines] in 59-95% yields. This new electrocatalytic process is a selective, facile, and efficient way to create spiro[furo[3,2-b]pyran-2,5'-pyrimidines], which are pharmacologically active heterocyclic systems with different biomedical applications. Spiro[furo[3,2-b]pyran-2,5'-pyrimidines] were found to occupy the binding pocket of aldose reductase and inhibit it. The values of the binding energy and Lead Finder's Virtual Screening scoring function showed that the formation of protein-ligand complexes was favorable. The synthesized compounds are promising for the inhibition of aldose reductase. This makes them interesting for study in the treatment of diabetes or similar diseases.

**Keywords:** electrochemistry; electrocatalysis; electrolysis; mediators; undivided cell; cyclization; electrosynthesis; spiro[furo[3,2-*b*]pyran-2,5'-pyrimidine]

# 1. Introduction

Privileged structures or scaffolds have become an important way to produce pharmaceutically active compounds [1]. Merck researchers were the first, who used this definition in the study on benzodiazepines [2]. These privileged scaffolds generally have a rigid heterocyclic system with a special orientation of the functional substituents for target recognition.

Cascade reactions or domino reactions are often used as efficient strategies in the synthesis of complex organic molecules since they ensure multiple transformations via a series of one-pot reactions. The design and development of cascade reactions is a rapidly expanding area of research in the field of organic synthesis [3].

The elaboration of convenient and efficient methods of synthesis of privileged scaffolds in one-pot cascade reactions is one of the important aims of organic chemistry.

Organic electrochemical synthesis has become a useful method with important synthetic and ecological advantages in the last few decades [4–6]. However, the usage of the electrochemical methods is generally limited by equipment complexity and long reaction times.



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**Copyright:** © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). One of the most useful electrochemical synthetic methods is the electrocatalytic oxidation of organic compounds in the presence of mediators [7]. Among a variety of mediators, the redox halide anion/halogen pair is the pair most often used for electroorganic transformations [8]. Electrolysis in an undivided cell in the presence of alcohols as solvents and alkali metal halides as mediators affords the simultaneous generation of a base (alkoxide anion) at the cathode and a halogen at the anode, which then initiates a chemical cascade of the oxidative transformations in solution.

C–H acids are well-known and useful starting compounds for electrocatalytic transformations using alkali metal halides as mediators [9–13]. The electrocatalytic processes with C–H acids are often carried out in an undivided electrolyzer with alkali metal halides as mediators. The electrocatalytic synthesis of functionally substituted cyclopropanes and related spirocyclopropanes is a special class of such electrocatalytic processes [14–16]. Electrocatalytic reactions of heterocyclic C–H acids [17] have also been intensively studied, as they afford the synthesis of different classes of heterocyclic compounds with a wide range of bioactivity [18].

Barbiturates (pyrimidine-2,4,6-triones) are well known in medicinal chemistry as a class of nitrogen- and oxygen-containing compounds that act as central nervous system depressants [19]. Recently, it has been established that barbiturates possess anti-AIDS and anticancer activity [20–22].

Moreover, kojic acid (5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one) is a known fungal metabolite and chelation agent that is produced by several species of fungi, especially *Aspergillus oryzae*, as a by-product in the fermentation process of rice [23]. It is widely used for averting enzymatic browning in food production and as a skin-lightening agent in the cosmetic field [24]. In the last few decades, it has been established that kojic acid and its derivatives reveal antibacterial [25], anti-inflammatory [26], antimicrobial [13], antiviral [27], and anti-HIV activities [28], and inhibit human neutrophil's elastase [29].

In addition, spirocyclic organic compounds are also known as active compounds in medicinal chemistry [30]. Spirocyclic compounds possess enough conformational stiffness together with flexibility. Therefore, the special orientation of the functional substituents facilitates the recognition of bioactive targets [30]. Spirobarbiturates have the special attention of the pharmaceutical community due to their broad spectrum of biological properties [31]. They exhibit useful neuropharmacological effects [32]. Spirobarbiturates are known as inhibitors of matrix metalloproteinase 13 (MMP)-13 [33] and dihydroorotate dehydrogenase (DHODase) [34]. 1-Phenyl-5,7-diazaspiro [2.5]octane-4,6,8-trione acts as a tumor necrosis factor alpha (TNF- $\alpha$ ) and is used in the treatment of various inflammatory, infectious, immunological, or malignant diseases [35].

In continuation of our research on electrocatalytic cascade transformations of carbonyl compounds and C–H acids into different types of spirocyclic compounds [36–40], and taking into consideration the biomedical applications of spirocyclic barbiturates given above, we were prompted to design a facile and efficient electrocatalytic one-pot cascade methodology for the conversion of 1,3-dimethyl-5-[[3-hydroxy-6-(hydroxymethyl)-4-oxo-4H-pyran-2-yl](aryl)methyl]pyrimidine-2,4,6(1H,3H,5H)-triones 1 into spiro[furo[3,2-*b*]pyran-2,5'-pyrimidines] **2**.

# 2. Experimental Section

All melting points were measured with a Gallenkamp melting point apparatus (London, UK) and were uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in DMSO- $d_6$  with Bruker Avance II 300 and Bruker DRX 500 spectrometers (Billerica, MA, USA) at ambient temperature. Chemical shift values are relative to Me<sub>4</sub>Si. <sup>1</sup>H–<sup>13</sup>C HSQC and <sup>1</sup>H–<sup>13</sup>C HMBC 2D NMR spectra were recorded in DMSO- $d_6$  with a Bruker AV400 spectrometer (Billerica, MA, USA) at ambient temperature. IR spectra were recorded with a Bruker ALPHA-T FTIR spectrometer (Billerica, MA, USA) in KBr pellets. Mass spectra (EI = 70 eV) were obtained directly with a Kratos MS-30 spectrometer (Bremen, Germany). High-resolution mass spectra were obtained on a Bruker micrOTOF II instrument using electrospray ionization.

X-ray diffraction data were collected at 100K on a Bruker Quest D8 diffractometer (Billerica, MA, USA) equipped with a Photon-III area detector (graphite monochromator, shutterless  $\varphi$ - and  $\omega$ -scan technique) using Mo K $\alpha$  radiation. The intensity data were integrated using the SAINT program [41] and were corrected for absorption and decay using SADABS [42]. The structure was solved via direct methods using SHELXT [43] and refined on F2 using SHELXL-2018 [44]. All non-hydrogen atoms were refined with individual anisotropic displacement parameters. The location of atom H5 was found from the electron density difference map; it was refined with an individual isotropic displacement parameter. All other hydrogen atoms were placed in ideal calculated positions and refined as riding atoms with relative isotropic displacement parameters. The SHELXTL program suite1 was used for molecular graphics.

1,3-Dimethyl-5-[[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl](aryl)methyl]p yrimidine-2,4,6(1*H*,3*H*,5*H*)-triones **1** were obtained in one step from the arylaldehydes, N,N'-dimethylbarbiturate and kojic acid according to the literature procedure [45].

General Procedure for the Electrocatalytic Synthesis of Spiro[furo[3,2-b]pyran-2,5'pyrimidines 2: 1,3-Dimethyl-5-[[3-hydroxy-6-(hydroxymethyl)-4-oxo-4H-pyran-2-yl] (aryl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione 1 (5 mmol) and sodium iodide (3 mmol) in methanol (20 mL) was electrolyzed in an undivided cell equipped with a magnetic stirrer, a graphite anode (5 cm<sup>2</sup>), and an iron cathode (5 cm<sup>2</sup>) at 20 °C under a constant current density of 100 mA/cm<sup>2</sup> until the quantity of 2.8 F/mol of electricity was passed. After the electrolysis was finished, the reaction mixture was concentrated to a volume of 4 mL and cooled to 0 °C to crystallize the solid product, which was then filtered out, twice rinsed with an ice-cold ethanol/water solution (1:1, 4 mL), and dried under reduced pressure.

5-(Hydroxymethyl)-1',3'-dimethyl-3-phenyl-2'H-spiro[furo[3,2-b]pyran-2,5'-pyrimi dine]-2',4',6',7(1'H,3H,3'H)-tetraone 2a: (white powder, 1.56 g, 81%), mp 222–223 °C (decomp.) (from MeOH). FTIR (KBr) cm<sup>-1</sup>: 3366, 1712, 1694, 1675, 1632, 1427, 1369, 1259, 1035, 699. <sup>1</sup>H-NMR (300 MHz, DMSO- $d_6$ ) δ 2.39 (s, 3H, CH<sub>3</sub>), 3.22 (s, 3H, CH<sub>3</sub>), 4.22–4.30 (m, 2H, CH<sub>2</sub>), 5.57 (s, 1H, CH), 5.73 (t, <sup>3</sup>J = 6.1 Hz, 1H, OH, exchange with D<sub>2</sub>O), 6.47 (s, 1H, CH), 7.04–7.14 (m, 2H, 2 CH Ar), 7.32–7.43 (m, 3H, 3 CH Ar) ppm. <sup>13</sup>C-NMR (126 MHz, DMSO- $d_6$ ) δ 28.1, 29.5, 56.9, 59.7, 87.5, 113.5, 129.1 (2C), 129.6 (2C), 129.7, 132.5, 144.9, 148.7, 150.6, 164.1, 166.5, 168.8, 168.9 ppm. MS (EI, 70 eV) *m*/*z* (%): 283 [M-C<sub>4</sub>H<sub>4</sub>O<sub>3</sub>-H]<sup>+</sup> (17), 256 (28), 199 (16), 151 (5), 137 (45), 101 (40), 69 (66), 57 (73), 43 (100), 41 (83). HRMS–ESI: [M + H]<sup>+</sup>, calcd for C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>O<sub>7</sub> 385.1030, found 385.1025.

5-(Hydroxymethyl)-3-(2-hydroxyphenyl)-1',3'-dimethyl-2'H-spiro[furo[3,2-b]-pyran -2,5'-pyrimidine]-2',4',6',7(1'H,3H,3'H)-tetraone 2b: (white powder, 1.30 g, 65%), mp 242–243 °C (decomp.) (from MeOH). FTIR (KBr) cm<sup>-1</sup>: 3235, 1715, 1691, 1622, 1584, 1463, 1374, 1215, 1043, 768. <sup>1</sup>H-NMR (300 MHz, DMSO- $d_6$ ) δ 2.84 (s, 3H, CH<sub>3</sub>), 3.15 (s, 3H, CH<sub>3</sub>), 3.85–4.18 (m, 2H, CH<sub>2</sub>), 5.43 (s, 1H, CH), 5.66 (br s, 1H, OH, exchange with D<sub>2</sub>O), 6.31 (s, 1H, CH), 6.88–7.46 (m, 4H, 4 CH Ar), 9.87 (br s, 1H, OH, exchange with D<sub>2</sub>O) ppm. <sup>13</sup>C-NMR (126 MHz, DMSO- $d_6$ ) δ 28.6, 29.4, 52.9, 59.5, 87.4, 109.4, 110.2, 122.1, 122.5, 126.0, 130.2, 142.8, 145.0, 150.8, 160.2, 165.4, 167.7, 168.5, 173.3 ppm. MS (EI, 70 eV) *m/z* (%): 400 [M<sup>+</sup>] (1), 299 (8), 272 (3), 215 (3), 186 (3), 145 (20), 101 (27), 89 (80), 31 (100), 15 (41). HRMS–ESI: [M + H]<sup>+</sup>, calcd for C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>O<sub>8</sub> 401.0985, found 401.0980.

5-(Hydroxymethyl)-3-(4-methoxyphenyl)-1',3'-dimethyl-2'H-spiro[furo[3,2-b]-pyran -2,5'-pyrimidine]-2',4',6',7(1'H,3H,3'H)-tetraone 2c: (white powder, 1.26 g, 61%), mp 217–218 °C (decomp.) (from MeOH). FTIR (KBr) cm<sup>-1</sup>: 3464, 1696, 1632, 1613, 1514, 1431, 1371, 1259, 1035, 748. <sup>1</sup>H-NMR (300 MHz, DMSO- $d_6$ ) δ 2.46 (s, 3H, CH<sub>3</sub>), 3.21 (s, 3H, CH<sub>3</sub>), 3.74 (s, 3H, OCH<sub>3</sub>), 4.20-4.30 (m, 2H, CH<sub>2</sub>), 5.50 (s, 1H, CH), 5.73 (br s, 1H, OH, exchange with D<sub>2</sub>O), 6.46 (s, 1H, CH), 6.92 (d, <sup>3</sup>J = 8.1 Hz, 2H, 2 CH Ar), 7.01 (d, <sup>3</sup>J = 8.1 Hz, 2H, 2 CH Ar) ppm. <sup>13</sup>C-NMR (126 MHz, DMSO- $d_6$ ) δ 28.3, 29.5, 55.7, 56.5, 59.6, 59.7, 87.5, 113.5, 114.5 (2C), 124.2, 130.9 (2C), 144.7, 149.0, 150.7, 160.3, 164.2, 166.5, 168.8 ppm. MS (EI, 70 eV) m/z (%): 414 [M<sup>+</sup>] (1), 355 (1), 313 (10), 286 (6), 229 (2), 201 (2), 172 (12), 101 (18), 55 (71), 15 (100). HRMS–ESI: [M + H]<sup>+</sup>, calcd for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>8</sub> 415.1141, found 415.1137. 5-(Hydroxymethyl)-1',3'-dimethyl-3-(p-tolyl)-2'H-spiro[furo[3,2-b]pyran-2,5'-pyri midine]-2',4',6',7(1'H,3H,3'H)-tetraone 2d: (white powder, 1.75 g, 88%), mp 227–228 °C (decomp.) (from MeOH). FTIR (KBr) cm<sup>-1</sup>: 3367, 1716, 1696, 1676, 1631, 1426, 1369, 1258, 1075, 746. <sup>1</sup>H-NMR (500 MHz, DMSO- $d_6$ ) δ 2.30 (s, 3H, CH<sub>3</sub>), 2.42 (s, 3H, CH<sub>3</sub>), 3.22 (s, 3H, CH<sub>3</sub>), 4.25 (d, <sup>2</sup>J = 15.7 Hz, 1H, CH<sub>2</sub>), 4.28 (d, <sup>2</sup>J = 15.7 Hz, 1H, CH<sub>2</sub>), 5.52 (s, 1H, CH), 5.61–5.90 (br s, 1H, OH, exchange with D<sub>2</sub>O), 6.47 (s, 1H, CH), 6.97 (d, <sup>3</sup>J = 8.0 Hz, 2H, 2 CH Ar), 7.19 (d, <sup>3</sup>J = 8.0 Hz, 2H, 2 CH Ar) ppm. <sup>13</sup>C-NMR (126 MHz, DMSO- $d_6$ ) δ 21.2, 28.2, 29.5, 56.7, 59.6, 87.5, 113.5, 129.5 (3C), 129.6 (2C), 139.3, 144.8, 148.9, 150.7, 164.1, 166.5, 168.8, 168.9 ppm. MS (EI, 70 eV) *m*/*z* (%): 339 [M-C<sub>2</sub>H<sub>3</sub>O<sub>2</sub>]<sup>+</sup> (1), 297 (7), 270 (7), 213 (9), 201 (7), 156 (88), 115 (100), 101 (41), 69 (60), 28 (67). HRMS–ESI: [M + H]<sup>+</sup>, calcd for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>7</sub> 399.1187, found 399.1182.

3-(4-Ethylphenyl)-5-(hydroxymethyl)-1',3'-dimethyl-2'H-spiro[furo[3,2-b]pyran-2,5' -pyrimidine]-2',4',6',7(1'H,3H,3'H)-tetraone **2e**: (white powder, 1.38 g, 67%), mp 140–141 °C (from MeOH). FTIR (KBr) cm<sup>-1</sup>: 3544, 1677, 1648, 1611, 1568, 1458, 1424, 1382, 1246, 1041. <sup>1</sup>H-NMR (500 MHz, DMSO- $d_6$ )  $\delta$  1.16 (t, <sup>3</sup>*J* = 7.5 Hz, 3H, CH<sub>3</sub>), 2.58 (q, <sup>3</sup>*J* = 7.5 Hz, 2H, CH<sub>2</sub>), 3.01 (s, 3H, CH<sub>3</sub>), 3.06 (s, 3H, CH<sub>3</sub>), 4.16–4.26 (m, 2H, CH<sub>2</sub>), 5.04 (s, 1H, CH), 6.31 (s, 1H, CH), 7.14 (d, <sup>3</sup>*J* = 7.8 Hz, 2H, 2 CH Ar), 7.20 (d, <sup>3</sup>*J* = 7.8 Hz, 2H, 2 CH Ar) ppm. <sup>13</sup>C-NMR (126 MHz, DMSO- $d_6$ )  $\delta$  15.9, 28.2, 28.4, 28.6, 45.5, 59.7 (2C), 109.5, 128.1 (2C), 129.3 (2C), 133.7, 143.3 (2C), 147.7, 151.9, 167.3, 167.5, 167.6, 173.7 ppm. MS (EI, 70 eV) m/z (%): 414 [M + 2H]<sup>+</sup> (2), 313 (7), 259 (11), 230 (9), 201 (9), 156 (34), 143 (16), 115 (23), 69 (27), 42 (100). HRMS-ESI: [M + H]<sup>+</sup>, calcd for C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>O<sub>7</sub> 413.1349, found 413.1342.

3-(4-Chlorophenyl)-5-(hydroxymethyl)-1',3'-dimethyl-2'H-spiro[furo[3,2-b]pyran-2,5'-pyrimidine]-2',4',6',7(1'H,3H,3'H)-tetraone 2f: (beige powder, 1.98 g, 95%), mp 170–171 °C (decomp.) (from MeOH). FTIR (KBr) cm<sup>-1</sup>: 3380, 1716, 1697, 1631, 1596, 1427, 1368, 1264, 1075, 747. <sup>1</sup>H-NMR (500 MHz, DMSO- $d_6$ )  $\delta$  2.49 (s, 3H, CH<sub>3</sub>), 3.22 (s, 3H, CH<sub>3</sub>), 4.20-4.32 (m, 2H, CH<sub>2</sub>), 5.62 (s, 1H, CH), 6.48 (s, 1H, CH), 7.14 (d, <sup>3</sup>*J* = 8.3 Hz, 2H, 2 CH Ar), 7.47 (d, <sup>3</sup>*J* = 8.3 Hz, 2H, 2 CH Ar) ppm. <sup>13</sup>C-NMR (126 MHz, DMSO- $d_6$ )  $\delta$  28.2, 29.5, 55.9, 59.6, 87.2, 113.5, 129.2 (2C), 131.5 (2C), 131.6, 134.6, 145.0, 148.3, 150.6, 164.0, 166.3, 168.8, 169.0 ppm. MS (EI, 70 eV) *m*/*z* (%): 290 [M-C<sub>6</sub>H<sub>4</sub>Cl-H<sub>2</sub>O]<sup>+</sup> (1), 277 (1), 264 (1), 235 (1, <sup>37</sup>Cl), 233 (3, <sup>35</sup>Cl), 178 (7, <sup>37</sup>Cl), 176 (20, <sup>35</sup>Cl), 136 (15), 101 (54), 75 (21), 69 (100), 42 (87). HRMS–ESI: [M + H]<sup>+</sup>, calcd for C<sub>19</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>7</sub> 419.0641, found 419.0632.

Crystal Data for **2f**: orthorhombic, space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, a = 5.68820(10) Å, b = 11.4345(2) Å, c = 27.5456(6) Å,  $\alpha = \beta = \gamma = 90^{\circ}$ , V = 1791.61(6) Å<sup>3</sup>, Z = 4, T = 100(2) K,  $\mu$ (Mo K $\alpha$ ) = 0.262 mm<sup>-1</sup>, Dcalc = 1.553 g/cm<sup>3</sup>, 35,956 reflections measured (2.09°  $\leq 2\Theta \leq 34.65^{\circ}$ ), 4446 unique (Rint = 0.0618), which were used in all calculations. The final R1 was 0.0339 [I>2sigma(I)] and wR2 was 0.0727. CCDC 2,049,440 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk (accessed on 24 May 2021).

3-(3-Bromophenyl)-5-(hydroxymethyl)-1',3'-dimethyl-2'H-spiro[furo[3,2-b]pyran-

2,5'-pyrimidine]-2',4',6',7(1'H,3H,3'H)-tetraone 2g: (beige powder, 1.74 g, 75%), mp 151–152 °C (decomp.) (from MeOH). FTIR (KBr) cm<sup>-1</sup>: 3432, 1772, 1700, 1675, 1623, 1436, 1371, 1269, 1080, 695. <sup>1</sup>H-NMR (500 MHz, DMSO- $d_6$ )  $\delta$  2.49 (s, 3H, CH<sub>3</sub>), 3.22 (s, 3H, CH<sub>3</sub>), 4.24–4.31 (m, 2H, CH<sub>2</sub>), 5.62 (s, 1H, CH), 6.49 (s, 1H, CH), 7.10 (d, <sup>3</sup>J = 7.7 Hz, 1H, CH Ar), 7.32–7.41 (m, 2H, 2 CH Ar), 7.61 (dd, <sup>3</sup>J = 7.7 Hz, <sup>4</sup>J = 1.1 Hz, 1H, CH Ar) ppm. <sup>13</sup>C-NMR (126 MHz, DMSO- $d_6$ )  $\delta$  28.2, 29.5, 55.8, 59.6, 87.2, 113.6, 122.2, 128.7, 131.3, 132.2, 132.6, 135.2, 145.1, 148.1, 150.6, 163.9, 166.1, 168.8, 169.0 ppm. MS (EI, 70 eV) m/z (%): 362 [M-C<sub>4</sub>H<sub>4</sub>O<sub>3</sub>-H]<sup>+</sup> (1, <sup>81</sup>Br), 360 [M-C<sub>4</sub>H<sub>4</sub>O<sub>3</sub>-H]<sup>+</sup> (1, <sup>79</sup>Br), 336 (3, <sup>81</sup>Br), 334 (3, <sup>79</sup>Br), 323 (1, <sup>81</sup>Br), 321 (1, <sup>79</sup>Br), 279 (3, <sup>81</sup>Br), 277 (3, <sup>79</sup>Br), 222 (28, <sup>81</sup>Br), 220 (30, <sup>79</sup>Br), 182 (9), 126 (25), 101 (91), 69 (100), 28 (71). HRMS–ESI: [M + H]<sup>+</sup>, calcd for C<sub>19</sub>H<sub>15</sub>BrN<sub>2</sub>O<sub>7</sub> 463.0141, found 463.0133.

5-(Hydroxymethyl)-1',3'-dimethyl-3-(4-nitrophenyl)-2'H-spiro[furo[3,2-b]pyran-2,5' -pyrimidine]-2',4',6',7(1'H,3H,3'H)-tetraone 2h: (white powder, 1.27 g, 59%), mp 194–195 °C (decomp.) (from MeOH). FTIR (KBr) cm<sup>-1</sup>: 3491, 1764, 1690, 1650, 1602, 1524, 1446, 1346, 1266, 1027. <sup>1</sup>H-NMR (300 MHz, DMSO- $d_6$ )  $\delta$  2.47 (s, 3H, CH<sub>3</sub>), 3.22 (s,

3H, CH<sub>3</sub>), 4.23-4.30 (m, 2H, CH<sub>2</sub>), 5.80 (s, 1H, CH), 6.55 (s, 1H, CH), 7.42 (d,  ${}^{3}J$  = 8.2 Hz, 2H, 2 CH Ar), 8.24 (d,  ${}^{3}J$  = 8.2 Hz, 2H, 2 CH Ar) ppm.  ${}^{13}$ C-NMR (126 MHz, DMSO- $d_{6}$ )  $\delta$  28.2 (2C), 59.9 (2C), 109.6, 124.0 (2C), 131.0 (2C), 140.4, 142.4, 148.5, 150.2 (2C), 166.4, 169.7, 175.2, 187.3 (2C) ppm. MS (EI, 70 eV) m/z (%): 328 [M-C<sub>4</sub>H<sub>4</sub>O<sub>3</sub>-H]<sup>+</sup> (1), 312 (1), 282 (1), 244 (1), 187 (18), 156 (8), 141 (20), 101 (31), 69 (51), 42 (100). HRMS–ESI: [M + H]<sup>+</sup>, calcd for C<sub>19</sub>H<sub>15</sub>N<sub>3</sub>O<sub>9</sub> 430.0887, found 430.0881.

*Methyl* **4**-(5-(*hydroxymethyl*)-1',3'-*dimethyl*-2',4',6',7-*tetraoxo*-1',3,3',4',6',7-*hexah ydro*-2'*H*-*spiro*[*furo*[3,2-*b*]*pyran*-2,5'-*pyrimidin*]-3-*yl*)*benzoate* **2i**: (white powder, 1.88 g, 85%), mp 227–228 °C (decomp.) (from MeOH). FTIR (KBr) cm<sup>-1</sup>: 3442, 1768, 1699, 1676, 1629, 1436, 1373, 1287, 1117, 1039. <sup>1</sup>H-NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  2.56 (s, 3H, CH<sub>3</sub>), 3.37 (s, 3H, CH<sub>3</sub>), 4.01 (s, 3H, COOCH<sub>3</sub>), 4.37–4.47 (m, 2H, CH<sub>2</sub>), 5.85 (s, 1H, CH), 6.64 (s, 1H, CH), 7.42 (d, <sup>3</sup>*J* = 7.3 Hz, 2H, 2 CH Ar), 8.10 (d, <sup>3</sup>*J* = 7.3 Hz, 2H, 2 CH Ar) ppm. <sup>13</sup>C-NMR (126 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  28.2, 29.5, 52.8, 56.2, 59.6, 87.2, 113.5, 129.8 (2C), 130.1 (2C), 130.7, 137.8, 145.1, 148.3, 150.6, 163.9, 166.1, 166.2, 168.8, 169.0 ppm. MS (EI, 70 eV) *m/z* (%): 442 [M<sup>+</sup>] (1), 383 (1), 314 (24), 283 (5), 257 (6), 200 (23), 156 (14), 101 (20), 69 (36), 42 (100). HRMS–ESI: [M + H]<sup>+</sup>, calcd for C<sub>21</sub>H<sub>18</sub>N<sub>2</sub>O<sub>9</sub> 443.1091, found 443.1084.

# 3. Results and Discussion

In this paper, we report the data on the selective and efficient cascade electrocatalytic cyclization of 1,3-dimethyl-5-[[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl](aryl) methyl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones **1a**–**i** into substituted spiro[furo[3,2-*b*]pyran-2,5'-pyrimidines] **2a**–**i** in alcohols in an undivided cell in the presence of alkali metal halides (Scheme 1, Tables 1 and 2).



**Scheme 1.** Electrocatalytic cyclization of 1,3-dimethyl-5-[[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl](aryl)methyl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones **1a**–**i**.

Entry	Solvent	Mediator	Time (min)	Electricity (F/mol)	Yield of 2a (%)
1	MeOH	LiBr	64	2.0	59
2	MeOH	NaBr	64	2.0	65
3	MeOH	KBr	64	2.0	62
4	MeOH	LiI	64	2.0	63
5	MeOH	NaI	64	2.0	70
6	MeOH	KI	64	2.0	66
7	MeOH	$NH_4I$	64	2.0	53
8	EtOH	NaI	64	2.0	64
9	<i>n</i> -PrOH	NaI	64	2.0	60
10	MeOH	NaI	70	2.2	74
11	MeOH	NaI	77	2.4	77
12	MeOH	NaI	83	2.6	80
13	MeOH	NaI	90	2.8	82
14	MeOH	NaI	96	3.0	78

$\mathbf{u}_{\mathbf{u}}$	Table 1. Electrocata	lytic cyclization c	of <b>1a</b> into spiro	[furo[3,2-b]p	vran-2,5'-p	vrimidine]	2a
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Electrolysis conditions: 1,3-dimethyl-5-[[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl]-(phenyl)methyl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **1a** (5 mmol), mediator (3 mmol), alcohol (20 mL), iron cathode (5 cm<sup>2</sup>), graphite anode (5 cm<sup>2</sup>), undivided cell, constant current density 50 mA/cm<sup>2</sup>, 20 °C.



Table 2. Electrocatalytic cyclization of 1a-i into spiro[furo[3,2-b]pyran-2,5'-pyrimidines] 2a-i.

Electrolysisconditions:1,3-Dimethyl-5-[[3-hydroxy-6-(hydroxymethyl)-4-oxo-4H-pyran-2-yl]-(aryl)methyl]pyrimidine-2,4,6(1H,3H,5H)-trione 1a (5 mmol), NaI (3 mmol), MeOH (20 mL), iron cathode (5 cm²),graphite anode (5 cm²), undivided cell, constant current density 50 mA/cm², 20 °C.

In the first step, to estimate the synthetic potential of the electrocatalytic method and improve the electrochemical conditions, the electrocatalytic cyclization of 1,3-dimethyl-5-[[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl](phenyl)-methyl]pyrimidine-2,4,6

(1*H*,3*H*,5*H*)-trione **1a** in alcohols as a solvent in an undivided cell in the presence of alkali metal halides was specially studied (Scheme 1, Table 1).

Thus, at the beginning of our study, MeOH was used as a solvent and alkali metal bromides were used as mediators. Under these electrolysis conditions in an undivided cell after 2 F/mol of electricity were passed, spiro[furo[3,2-*b*]pyran-2,5'-pyrimidine] **2a** was obtained in 59–65% yields (Entries 1–3, Table 1). Under these electrolysis conditions with iodides as mediators, the yields of spiro[furo[3,2-*b*]pyran-2,5'-pyrimidine] **2a** were in the range of 53–70% (Entries 4–7, Table 1). The best yield of spiro[furo[3,2-*b*]pyran-2,5'-pyrimidine] **2a** in this series of experiments was obtained with NaI as a mediator was 70% (Entry 5, Table 1).

Other alcohols, namely ethanol, and *n*-propanol, were less efficient as solvents compared with methanol such that the yields of **2a** were 64% and 60% (Entries 8 and 9, Table 1). The increase of the amount of electricity passed through the cell up to 2.8 F/mol led to the best yield of spiro[furo[3,2-*b*]pyran-2,5'-pyrimidine] **2a** (Entry 13, Table 1) with 82%.

Under the optimal conditions thus found, spiro[furo[3,2-*b*]pyran-2,5'-pyrimidines] **2a–i** were obtained in 59–95% yields as a result of the electrocatalytic cyclization of 1,3dimethyl-5-[[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl](aryl)methyl]pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-triones **1a–i** (Scheme 1, Table 2).

In all these electrocatalytic processes, after the electrolysis had ended, the reaction mixture was concentrated to a volume of 4 mL and cooled to 0 °C to crystallize the solid product, which was then filtered out, twice rinsed with an ice-cold ethanol/water solution (1:1 v/v, 4 mL), and dried under reduced pressure.

The structure of all new compounds **2a–i** was confirmed using <sup>1</sup>H, <sup>13</sup>C NMR, and IR spectroscopy, as well as mass spectrometry data. For all compounds, only one set of signals was observed in the <sup>1</sup>H and <sup>13</sup>C NMR spectra.

The structure of the compound **2a** was additionally confirmed via NMR spectroscopy using 2D <sup>1</sup>H–<sup>13</sup>C HSQC and <sup>1</sup>H–<sup>13</sup>C HMBC experiments. The assignment of <sup>1</sup>H and <sup>13</sup>C signals in the NMR spectra was carried out and the chemical shifts correlated well with the structure of **2a**. It should be noted that the carbon atoms of the amide group, as well as the signals of protons and carbons of methyl residues, had chemically nonequivalent natures; therefore, they had different chemical shifts. Key interactions are indicated by arrows in Figure 1. Complete correlation of signals:



Figure 1. Key HMBC and HSQC interactions for 2a.

<sup>1</sup>H-NMR (400 MHz, DMSO- $d_6$ )  $\delta$  2.39 (s, 3H, NCH<sub>3</sub>), 3.22 (s, 3H, NCH<sub>3</sub>), 4.27 (s, 2H, CH<sub>2</sub>), 5.58 (s, 1H, H<sup>3</sup>), 5.71 (s, 1H, OH), 6.48 (s, 1H, H<sup>6</sup>), 7.13–7.03 (m, 2H, H<sup>o</sup>), 7.43–7.33 (m, 3H, H<sup>m</sup>, H<sup>p</sup>) ppm.

<sup>13</sup>C-NMR (101 MHz, DMSO- $d_6$ ) δ 27.6 (NCH<sub>3</sub>), 29.0 (NCH<sub>3</sub>), 56.4 (C<sup>3</sup>), 59.2 (CH<sub>2</sub>), 87.0 (C<sup>2</sup>), 113.0 (C<sup>6</sup>), 128.6 (C<sup>m</sup>), 129.1 (C<sup>o</sup>), 129.2 (C<sup>p</sup>), 132.0 (C<sup>i</sup>), 144.4 (C<sup>7a</sup>), 148.2 (C<sup>3a</sup>), 150.1 (NC(O)N), 163.6 (NCO), 166.0 (NCO), 168.3 (C<sup>7</sup>), 168.4 (C<sup>5</sup>) ppm.

The structure of compound 2f was confirmed using an X-ray diffraction study (Supplementary Material (Figures S19 and S20) and Figure 2).



Figure 2. The general view of compound 2f in crystalline form. Atoms are represented using thermal displacement ellipsoids (p = 50%).

Given all the above results and taking into consideration the data on electrocatalytic reactions mediated by iodides [46–48], the following mechanism for the electrocatalytic cyclization of 1,3-dimethyl-5-[[3-hydroxy-6-(hydroxymethyl)-4-oxo-4H-pyran-2-yl](aryl)methyl]pyrimidine-2,4,6(1H,3H,5H)-triones 1 into substituted spiro[furo[3,2-b]pyran-2,5'-pyrimidines] 2 was suggested (Scheme 2).

Cathode: 
$$2 \text{ MeOH} + 2 \text{ e} \longrightarrow 2 \text{ MeO}^{\ominus} + \text{ H}_2$$
  
Anode:  $2 \stackrel{\ominus}{\text{I}} - 2 \text{ e} \longrightarrow \text{ I}_2$ 

In solution:



Scheme 2. Electrocatalytic cyclization of 1,3-dimethyl-5-[[3-hydroxy-6-(hydroxymethyl)-4-oxo-4H-pyran-2yl](aryl)methyl]pyrimidine-2,4,6(1H,3H,5H)-triones 1.

The evolution of hydrogen was the cathodic process, which was accompanied by methoxide anion generation. The formation of iodine was an anodic process and the corresponding iodine color was observed at the anode when the electrolysis was conducted without stirring of the reaction mixture.

The reaction in solution between a methoxide ion and 6-hydroxy-5-[(2-hydroxy-6-oxocyclohex-1-en-1-yl)(aryl)methyl]-1,3-dimethyl-pyrimidine-2,4-(1*H*,3*H*)-dione **1** led to the anion of 6-hydroxy-5-[(2-hydroxy-6-oxocyclohex-1-en-1-yl)-(aryl)methyl]-1,3-dimethyl-pyrimidine-2,4-(1*H*,3*H*)-dione **A** formation. Then, the iodination of anion **A** resulted in iodinated 6-hydroxy-5-[(2-hydroxy-6-oxocyclohex-1-en-1-yl)-(aryl)methyl]-1,3-dimethyl-pyrimidine-2,4-(1*H*,3*H*)-dione **3** formation, which, by the action of the next methoxide anion, was cyclized into spiro[furo[3,2-*b*]pyran-2,5'-pyrimidine] **2** with the regeneration of the iodine ion.

Aldose reductase catalyzes the reduction of aldehydes and acids. It participates in glucose into sorbitol transformation [49], which is the first step in fructose formation. Inhibitors of aldose reductase are employed for the treatment of diabetic peripheral neuropathy [50]. Computational chemistry, docking in particular, is a tool that is applied in drug development [51]. It allows for getting insights into protein–ligand interactions and reduces the time and effort directed toward the development of potential drugs [51,52].

In this research, the investigation of substituted spiro[furo[3,2-*b*]pyran-2,5'-pyrimidines] and aldose reductase interactions was conducted in Flare 3.0.0. [53–58]. The protein structure was downloaded from RCSB (pdb code: 2NVD) [44]. Build Model was used for the protein preparation, the water molecules out of 6A from the binding site were removed, then docking was performed with a co-crystallized ligand as a template molecule in very high precision mode. The Lead Finder's energy and Virtual Screening scoring functions were used for benchmarking [53–58].

The cavity of aldose reductase is divided by Trp111 into the catalytic subpocket and the specificity pocket. The catalytic pocket is related to the catalytic mechanism and is represented by Tyr48, Lys77, and His110 residues [59–61]. However, almost all inhibitory activity is related to Trp20 and, in several cases, Leu300 enhances the intercalation of inhibitor between these two residues [51].

In docking studies, all synthesized compounds, with the exception of spiro[furo[3,2b]pyran-2,5'-pyrimidine] **2d**, intercalated near Trp20 (Table 3). Other structures interacted with Val47, Tyr48, His110, Trp111, Asn160, Tyr209, Ser210, Ser214, Cys298, and Leu300 (Table 3). Many of them are key residues for inhibitors, for example, the reference cocrystallized ligand interacts with Trp20, Tyr48, His110, Ser210, and Ser214 [51]. The diagrams of interaction, the interacting residues, the calculated values of binding energies (LFdG), and the Lead Finder's Virtual Screening Score (LFVS) are presented in Table 3.

Compound	LFdG (kcal/mol)	LFVS	Interaction	Residues	Remark
2a	-8.426	-9.520	Trabha Crasta Trabha Bar2tah	Trp20 Tyr209 Ser210	Formed an interaction with the key residue Trp20. Formed additional interactions with Tyr209 and Ser210 (which are binding residues in the reference ligand) [51].
2b	-8.301	-9.381	Tip20A Tip20A Tip20A Tip20A Tip20A Tip20A Tip20A Tip20A Tip20A Tip20A Tip20A Tip20A Tip20A Tip20A Tip20A Tip20A Tip20A Tip20A	Tyr20 Asn160 Tyr209	Formed an interaction with the key residue Trp20. Formed additional interactions with Asn160 and Cys298.
2c	-8.269	-9.951	Tryson Tryson	Trp20 Trp111 Asn160 Tyr209 Ser210 Cys298	Formed an interaction with the key residue Trp20. Formed additional interactions with Ser210 (which is a binding residue in the reference ligand), Trp111, Asn160, Tyr209, and Cys298.
2d	-7.874	-8.951	H- H- H- H- H- H- H- H- H- H- H- H- H- H	Ser210	The only interaction revealed was with Ser210.

**Table 3.** The results of docking studies of substituted spiro[furo[3,2-*b*]pyran-2,5'-pyrimidines] **2a–i**.

Compound	LFdG (kcal/mol)	LFVS	Interaction	Residues	Remark
2e	-9.124	-10.496	Trp20A	Tyr20 Asn160 Tyr209 Ser210	Formed an interaction with the key residue Trp20. Formed an additional interaction to Ser110 (which is a binding residue in the reference ligand). The selection of the best pose was performed manually.
2f	-8.424	-9.04	Cyu298A LeugooA R	Trp20 Leu300	Formed an interaction with the key residue Trp20. Formed an additional binding with Leu300.
2g	-9.588	-10.799	Try20A Try20A Try20A	Trp20 Tyr48 Trp111 Asn160 Tyr209	Formed an interaction with the key residue Trp20. Formed an additional interaction with Tyr48 (which is a binding residue in the reference ligand), Trp111, Asn160, and Tyr209.

#### Table 3. Cont.

Compound	LFdG (kcal/mol)	LFVS	Interaction	Residues	Remark
2h	-6.399	-7.686	Sec21AA	Trp20 Ser210 Ser214	Formed an interaction with the key residue Trp20. Formed additional interactions with Ser210 and Ser214 (which are binding residues in the reference ligand).
2i	-9.238	-10.634		Trp20 Val47 Tyr48	Formed an interaction with the key residue Trp20. Formed an additional interaction with Val47 and Tyr48 (which are binding residues in the reference ligand) [51].
Co-crystallized ligand	-8.545	-10.089	Sergitak Ser	Trp20 Tyr48 His110 Ser210 Ser214	The reference co-crystallized ligand [51].

Spiro[furo[3,2-*b*]pyran-2,5'-pyrimidines] **2e**, **2g**, and **2i** showed the best results in docking studies from a thermodynamic point of view. The binding energies of interaction with the protein were -9.124, -9.588, and -9.238 kcal/mol, respectively. The LFVS values were also high, where the values were -10.496, -10.799, and -10.634, respectively. Both the binding energy and LFVS values of **2e**, **2g**, and **2i** surpassed the same values of the co-crystallized ligand (-8.545 kcal/mol and -10.089). At the same time, **2e** and **2g** formed many interactions with the aldose reductase, namely **2e** formed  $\pi$ - $\pi$  intercalations with Trp20 and Tyr209 and two hydrogen bonds to Ser210 and Asn160, while spiro[furo[3,2-*b*]pyran-2,5'-pyrimidine] **2g** formed the similar intercalations with Trp20 and Tyr209 and two from the similar intercalations with Trp20 and Tyr209 and Tyr48, Asn160, and Trp111. As mentioned above, Tyr48 and Trp111, as well as Trp20, are considered key residues for inhibition [51,59–61].

Despite a good position and several hydrogen bonds forming with key amino acids (Cys298, Ser214, Ser210, Trp20), the nitro derivative **2h** showed the lowest binding energy among the examined compounds, which was -6.399 kcal/mol. The LFVS value was also moderate, which was -7.686. Nevertheless, because of the moderate value and the presence of a key interaction (Trp20), it may be interesting for further investigations in drug development.

Thus, according to docking studies, substituted spiro[furo[3,2-*b*]pyran-2,5'-pyrimidines] have conformations that may inhibit aldose reductase function. The values of the binding energy and Lead Finder's Virtual Screening scoring function found for this formation of protein–ligand complexes were favorable and, in several cases, it may surpass the co-crystallized inhibitor. Thus, substituted spiro[furo[3,2-*b*]pyran-2,5'-pyrimidines] are promising for the further investigation of their inhibitory activity related to aldose reductase as its inhibitors are applied in the treatment of diabetes or similar diseases.

#### 4. Conclusions

Thus, the new electrochemically induced and highly efficient cyclization of 6-hydroxy-5-[(2-hydroxy-6-oxocyclohex-1-en-1-yl)(aryl)methyl]-1,3-dimethylpyrimidine-2,4-(1*H*,3*H*)diones in methanol in the presence of sodium iodide as a mediator in the undivided cell resulted in the formation of the earlier unknown substituted spiro[furo[3,2-*b*]pyran-2,5'pyrimidines] in 59–95% yields.

This new electrocatalytic cyclization is a facile path to the earlier unknown substituted spiro[furo[3,2-*b*]pyran-2,5'-pyrimidines] containing both barbituric and kojic acid fragments, which are promising compounds for different biomedical applications, with anticonvulsants, anti-AIDS agents, and anti-inflammatory remedies among them.

This efficient electrocatalytic procedure utilizes simple equipment, an undivided cell, and an available and cheap mediator, namely, sodium iodide. It is easily carried out and the isolation procedure is very simple. Thus, this new method is valuable from the viewpoint of environmentally benign, diversity-oriented, large-scale processes. All these advantages make this method valuable for the synthesis of new potential drug libraries.

It was found that substituted spiro[furo[3,2-*b*]pyran-2,5'-pyrimidines] may occupy the binding pocket of aldose reductase to inhibit its action. The values of the binding energies and Lead Finder's Virtual Screening scoring functions showed that the formation of protein–ligand complexes was favorable. The synthesized compounds are promising for further investigation of their inhibitory activity related to aldose reductase, it makes them interesting for the treatment of diabetes or similar diseases.

**Supplementary Materials:** The following are available online at https://www.mdpi.com/article/10 .3390/electrochem2020021/s1, <sup>1</sup>H and <sup>13</sup>C Spectra of synthesized compounds **4a–i** (Figures S1–S18), 2D NMR Spectra of Compound **2a** (Figures S19 and S20), Single-crystal X-ray Diffraction Data for Compound **2f** (Tables S1–S7).

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