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Green synthesis of structural analogs of favipiravir†

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A series of 3-hydroxy-5-arylpyrazine-2-carboxamides, structural analogs of favipiravir, have been successfully synthesized using a green and sustainable method through a one-pot condensation reaction of arylglyoxals **1a–i** and 2-aminopropanediamide **2** in an alkaline solution under heating conditions. The reaction is temperature-sensitive; when conducted at 80 °C, 5-aryl substituted pyrazine derivatives were predominantly obtained. In reactions with arylglyoxals **1a**, **1d**, **1h**, and **1i**, temperatures exceeding 80 °C produced a mixture of two regioisomeric pyrazine derivatives with significant efficiency. This method is highly desirable due to its short reaction time, simple purification of products, and the use of water as an eco-friendly solvent.

1. Introduction

Viruses, as microscopic infectious agents, are small obligate intracellular parasites that possess either an RNA or DNA genome and an outer protein shell, which may be enveloped by a lipid layer.[1] Viral infections and their resulting epidemics, and pandemics are among the primary causes of high mortality.[2] RNA viruses, such as the influenza virus (H1N1),[3] the highly pathogenic avian influenza virus (H5N1),[4,5] Zika,[6] the Ebola virus (EBOV),[7,8] severe acute respiratory syndrome coronavirus (SARS-CoV-1),[9] and COVID-19 (SARS-CoV-2)[10–13] are highly transmissible and lead to significant public health issues, along with considerable morbidity and mortality. Thus, to prevent the further spread of RNA viruses, the development of more potent therapeutic agents with activity against a broad spectrum of such pathogens is essential.

1,4-Pyrazine-3-carboxamide-based antiviral compounds have been under intensive study for the last 20 years.[2,14] Favipiravir (6-fluoro-3-hydroxypyrazine-2-carboxamide, T-705), a synthetic analog of 1,4-pyrazine-3-carboxamide, is an antiviral drug that inhibits the RNA-dependent RNA polymerase of influenza virus. It is effective against a variety of RNA viruses but not against DNA viruses.[2,15–20] In recent years, favipiravir has also been actively used against COVID-19.[21]

Favipiravir, a 3-OH substituted pyrazine derivative, exhibits acidic properties and can tautomerize to the keto form, as shown in Scheme 1.[22] Favipiravir, a nucleobase analog, is a prodrug; its active form is favipiravir-RTP, a nucleoside analog. The nucleobase analog favipiravir first undergoes metabolic activation through phosphoribosylation to form ribofuranosyl-5′-monophosphate (Favipiravir-RMP, T-705-RMP), which is then converted through intracellular phosphorylation into its ribofuranosyl-5′-triphosphate metabolite (Favipiravir-RTP, T-705-RTP), most likely by a series of intracellular enzymes (Scheme 1).[23–25] The fluoro group in the structure enhances favipiravir's binding energy with RNA polymerase.[26] Literature suggests that the nitrogen atom undergoing phosphoribosylation is a promising target for structural modifications (Fig. 1).[23] However, attempts to obtain the favipiravir riboside or the monophosphate revealed that its bond is prone to cleavage and the compound exhibited poor solubility.[27]

Favipiravir (T-705) was first synthesized by Furuta and coworkers[28] (Japanese Toyama Chemical Co., Ltd) in 2000 in a seven-step process from 3-aminopyrazine-2-carboxylic acid. This approach had a poor overall yield of 0.44% (Scheme 2), but a second approach starting with aminomalonic acid diethyl ester and proceeding through a series of sequential reactions, improved the yield to 17%.[29] Current research is focused on finding more efficient and practical ways to synthesize favipiravir (Scheme 3).[30–46] Classical synthetic methods for producing favipiravir are thoroughly detailed in three recent reviews by Y. Titova,[27] N. Al Bujuq,[43] and N. Qin.[46]

Structural analogs of favipiravir are also under study for antiviral activity. Of particular interest are the non-fluorinated T-705 analog (T-1105; 3-hydroxy-2-pyrazinecarboxamide) and it's active nucleoside 5′-triphosphate form (T-1105-RTP) (Fig. 1). T-1105 has shown promising results in the treatment of influenza virus H1N1and other RNA viruses.[47–49] The antiviral activity of T-1105 and it's activated form T-1105-RTP depends on the cell lines. For example, T-1105 showed higher antiviral activity in MDCK cells. However, antiviral activity of T-1105-RTP was not detected in the three cell lines, A549, Vero cells HEK293T cells.[49] Also its ribonucleoside analog T-1106 (3,4-dihydro-3-oxo-4-β-d-ribofuranosyl-2-pyrazinecarboxamide) has showed potent

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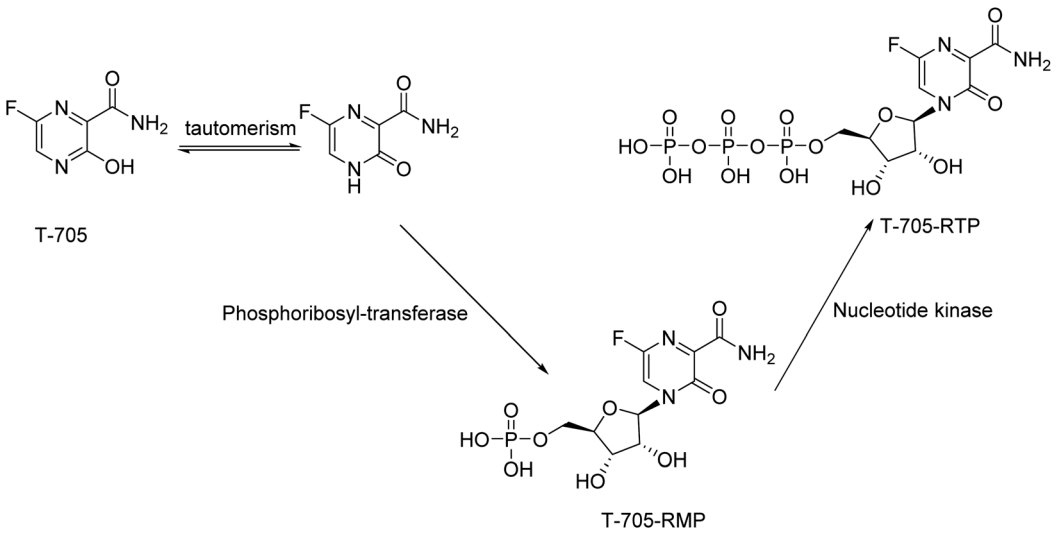


Scheme 1 Formation of the active metabolite of favipiravir (T-705-RTP) from favipiravir (T-705).

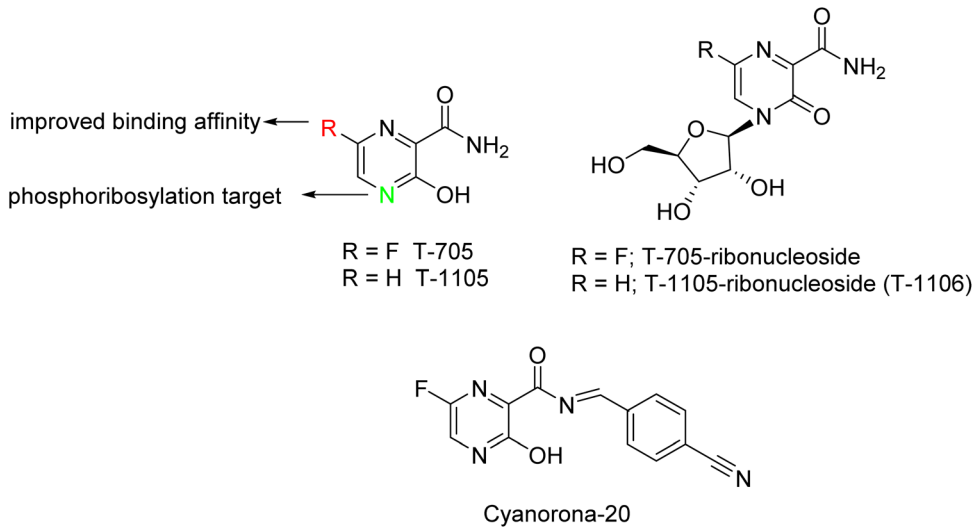
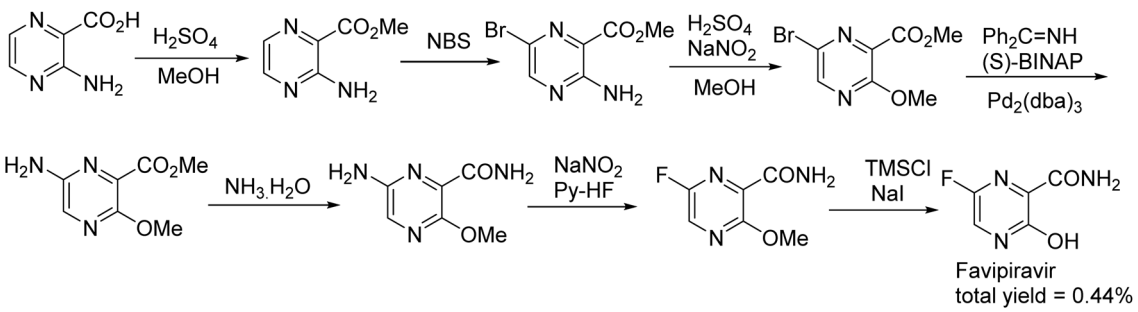
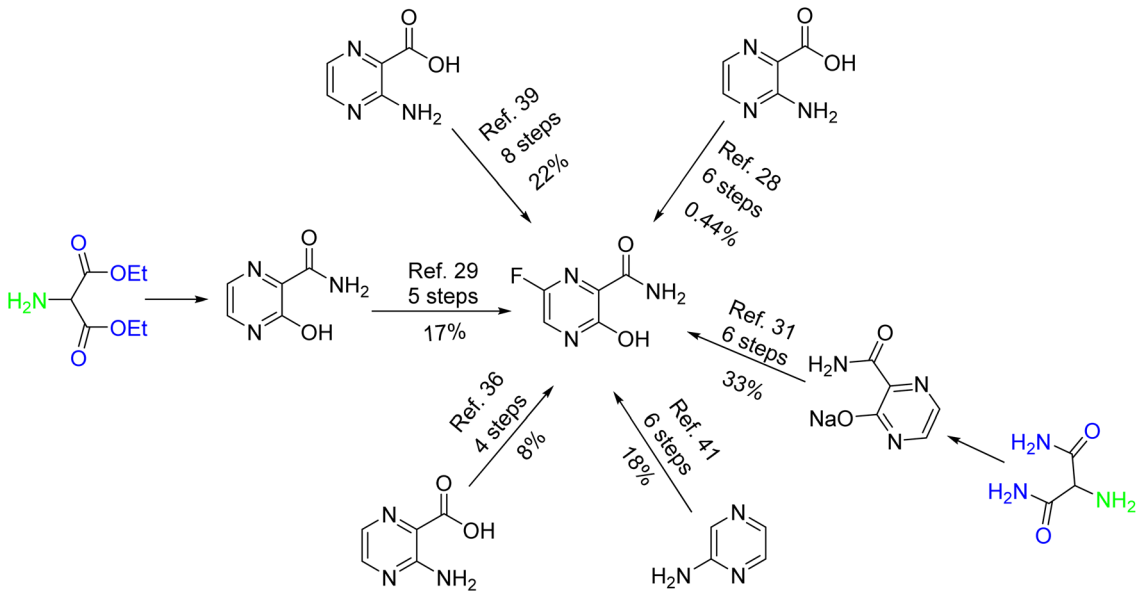


Fig. 1 Structural analogs of favipiravir.

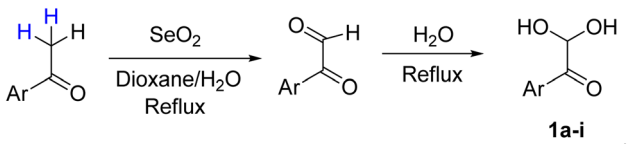


Scheme 2 Favipiravir synthesis according to the strategy developed by Y. Furuta *et al.* (Toyama Chemical Co., Ltd).[28]

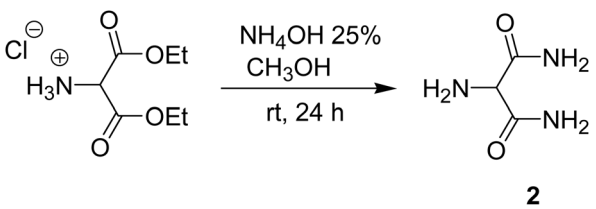
antiviral activity against RNA viruses without significant toxicity to mammalian cells.[50–55] A number of *in vitro* and *in vivo* studies have shown an even higher efficacy of T-1105 and T-1106 compared to that of favipiravir.[17,56] Synthesis of the new bioactive derivative of favipiravir, (*E*)-*N*-(4-cyanobenzylidene)-6-fluoro-3-hydroxypyrazine-2-carboxamide (cyanorona-20), was



Scheme 3 Synthetic methods for the preparation of favipiravir (T-705).



Scheme 4 Synthesis of arylglyoxalmonohydrates.



Scheme 5 Synthesis of 2-aminopropanediamide.

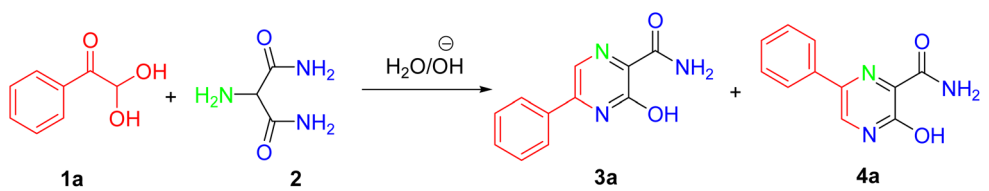
reported in 2021. Cyanorona-20 exhibited very significant anti-COVID-19 activity and interestingly demonstrated approximately 209- and 45-fold anti-SARS-CoV-2 selectivity/potency compared to favipiravir and remdesivir, respectively.[57]

In this study, we present the synthesis of novel structural analogs of favipiravir through an eco-friendly one-pot condensation reaction involving arylglyoxal monohydrates and 2-aminopropanediamide.

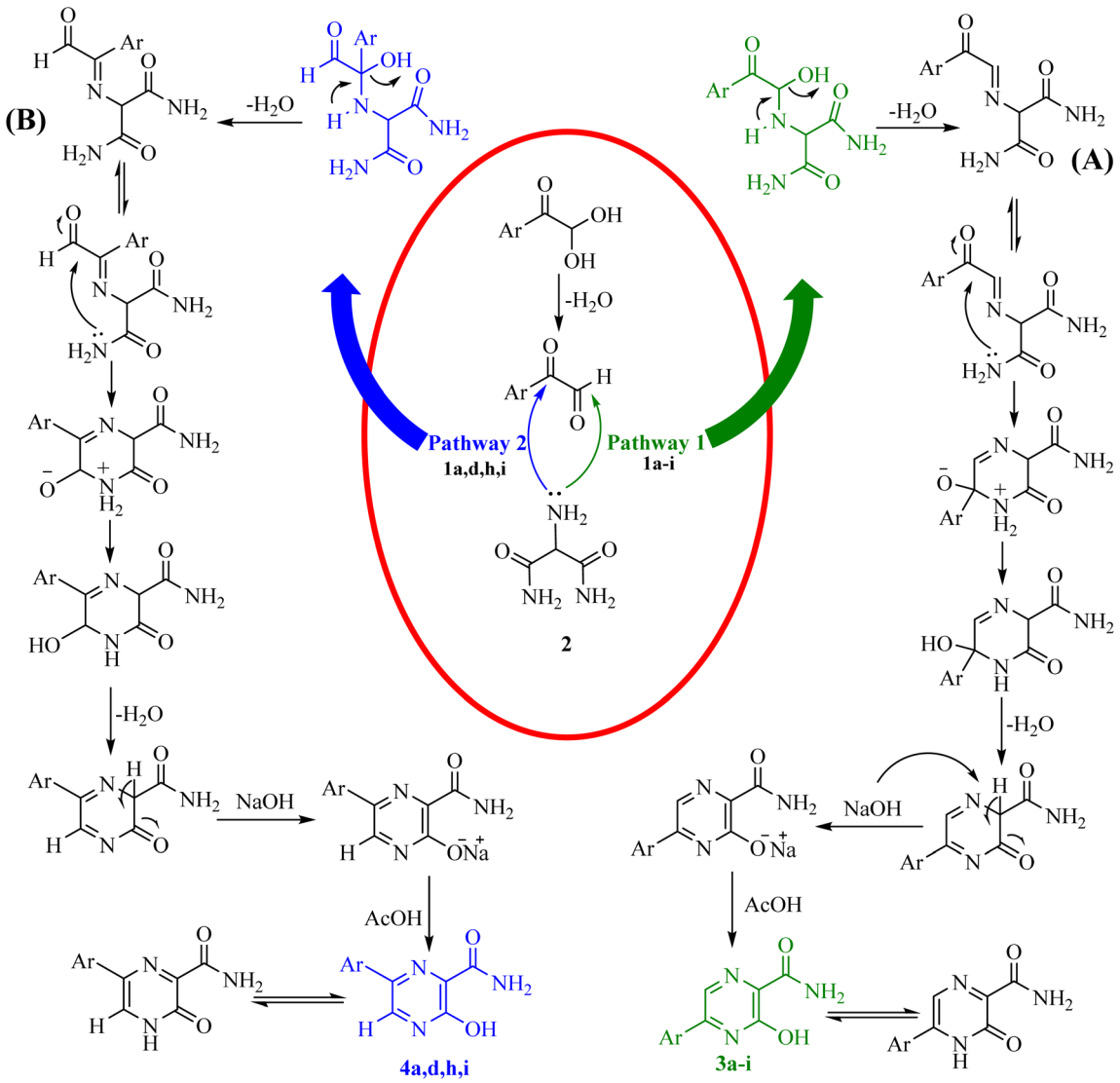
2. Results and discussion

Development of convenient protocols for synthesis of biologically active pyrazine scaffolds from simple raw materials is a key research area in heterocyclic chemistry and especially drug discovery programs. Synthetic routes for pyrazines may include different building blocks or conditions. In this work, we tried to synthesize the pyrazine ring, the central core of favipiravir, from the condensation reaction of arylglyoxalmonohydrates **1** with 2-

Table 1 Optimization of the reaction temperature



Entry	Temperature (°C)	Time (h)	Yield (%) **3a**	Yield (%) **4a**
1	70	2	40	—
2	80	2	55	10
3	90	2	30	30

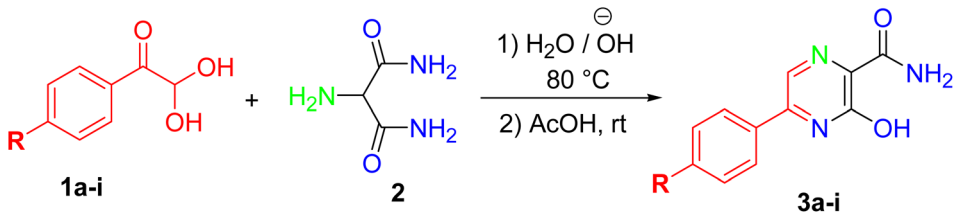


Scheme 6 Plausible mechanism for the synthesis of 3-hydroxy-(5-aryl and 6-aryl) pyrazine-2-carboxamide derivatives.

aminopropanediamide **2** in the presence of aqueous sodium hydroxide solution.

For this purpose, the arylglyoxalmonohydrates **1a–i** were prepared by oxidation of corresponding aryl methyl ketones with selenium dioxide according to standard literature procedure (Scheme 4).[58] 2-Aminopropanediamide **2** was synthesized using modified literature methods *via* the ammonolysis of the ester groups of diethylaminomalonate hydrochloride salt with a 25% ammonia solution at room temperature in methanol (Scheme 5).[59,60]

Next, the reaction of phenylglyoxalmonohydrate (**1a**), and 2-aminopropanediamide (**2**) was selected as a model reaction. The condensation reaction of phenylglyoxalmonohydrate **1a** (1.6 mmol), and 2-aminopropanediamide **2** (1.7 mmol) was carried out in water in the presence of sodium hydroxide under heating conditions. The reaction of **1a** and **2** under basic



Scheme 7 Synthesis of 3-hydroxy-5-arylpyrazine-2-carboxamide derivatives in aqueous solution.

Table 2 One-pot synthesis of 3-hydroxy-5-arylpyrazine-2-carboxamides[a]

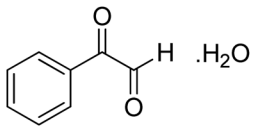
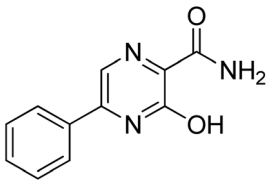
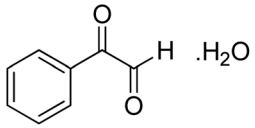
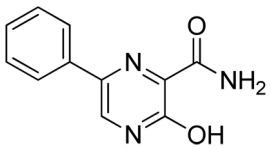
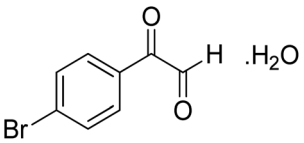
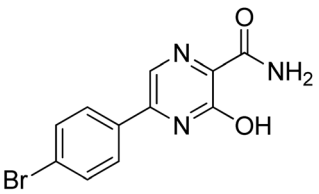
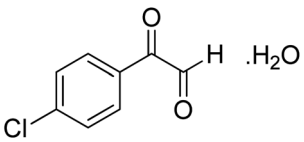
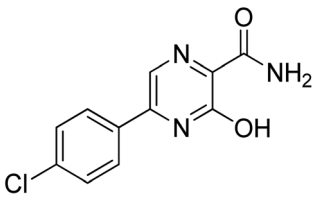
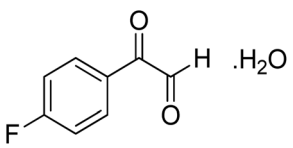
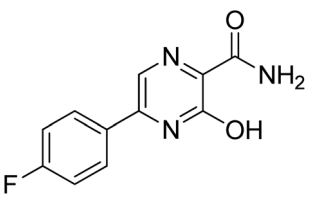
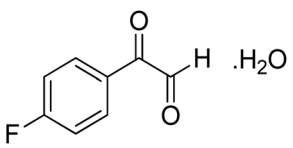
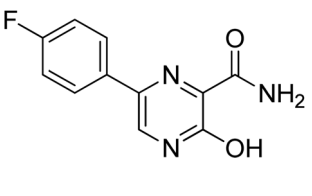
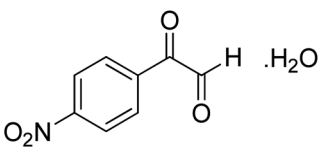
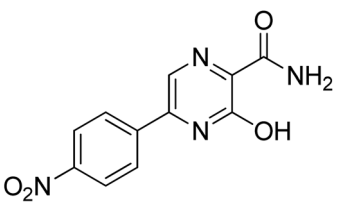
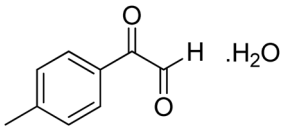
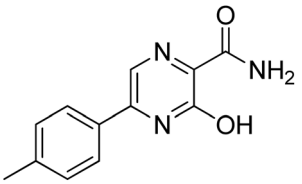
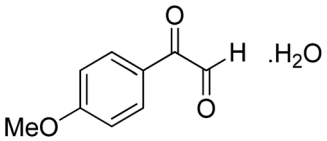
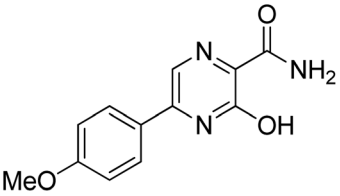
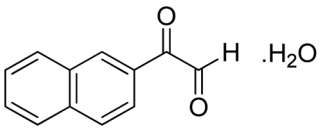
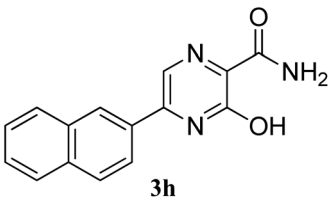
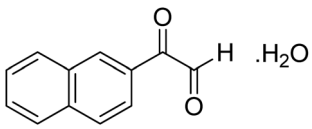
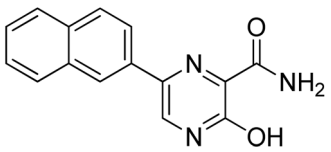
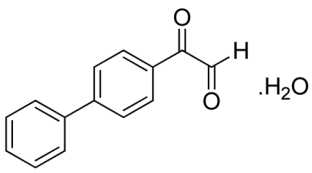
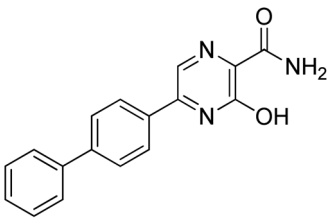
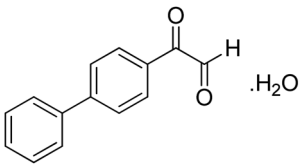
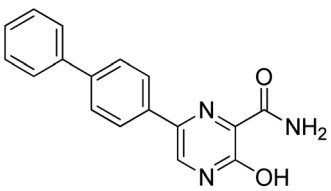
Entry	Reactant	Product[b]	Time (h)	Yield[c] (%)	m.p. (°C)
1		 **3a**	2	55	256–257
2		 **4a**	2	30[b]	210–213 (ref. 60 213–216)
3		 **3b**	2	65	238–240
4		 **3c**	2	60	254–255 (Dec.)[d]
5		 **3d**	2	45	219–220
6		 **4d**	2	15[b]	236–238 (Dec.)[d]
7		 **3e**	2.5	48	275–278

Table 2 (*Contd.*)

Entry	Reactant	Product[b]	Time (h)	Yield[c] (%)	m.p. (°C)
8		 **3f**	2	72	269–270 (Dec.)[d]
9		 **3g**	2	68	266–270 (Dec.)[d]
10		 **3h**	2	48	217–220
11		 **4h**	2	15[b]	200–204
12		 **3i**	2	50	225–226 (Dec.)[d]
13		 **4i**	2	12[b]	198–199

[a] Reaction conditions: arylglyoxalmonohydrates (1.6 mmol), aminomalonamide (1.7 mmol), aqueous sodium hydroxide solution (12.5 N, 1 mL), 6 mL water at 80 °C, then glacial acetic acid (1 mL). [b] Yield of products **4a**, **4d**, **4h**, and **4i** at reaction temperature above 80 °C. [c] Yield of the isolated product after recrystallization. [d] Decompose before melting.

conditions at 70 °C leads to the formation of sodium salt of **3a**. Then acidification by acetic acid to afford **3a** in 40% yield. We were pleased to find that this reaction is temperature-sensitive (Table 1). At 80 °C, the reaction also favors the formation of 3-hydroxy-5-phenylpyrazine-2-carboxamide **3a** as main product in higher yield 55% (Table 1, entry 2), while temperatures exceeding 80 °C lead to a mixture of two possible regioisomeric pyrazine compounds with significant efficiency. At 90 °C, two

regioisomeric compounds **3a** and **4a** were obtained in equal amounts (Table 1, entry 3). This indicates that temperature significantly affects the regioselectivity of the reaction. Two compounds were separated through crystallization from ethanol. The melting point of one of the products is in agreement with the value reported for the 3-hydroxy-6-phenylpyrazine-2-carboxamide (**4a**) with a melting point of 213 °C in the literature.[60] Consequently, another regioisomeric compound, with a melting point of 257 °C, corresponds to 3-hydroxy-5-phenylpyrazine-2-carboxamide (**3a**).

The electron-withdrawing ketone group in arylglyoxals enhances the electrophilicity of the aldehyde carbonyl group. This increased electrophilicity results in a quicker reaction of the aldehyde carbonyl with the more nucleophilic NH_2 group under kinetic conditions, favoring the formation of the product **3a**. However, under thermodynamic conditions, both products **3a** and **4a** are generated as the reaction can progress to a more stable equilibrium. The proposed mechanism for the synthesis of 3-hydroxy-(5-aryl/6-aryl) pyrazine-2-carboxamides is shown in Scheme 6. The formation of product **3a** *versus* **4a** *via* two pathways depends not only on the relative electrophilicity of two carbonyl groups but also on the stability of the imine intermediates (**A**) and (**B**). Pathway 1, leading to product **3a**, involves a less stable imine derivative (**A**), while pathway 2, leading to product **4a**, proceeds through a more stable aryl imine (**B**).

With optimized reaction conditions in hand (reaction in alkaline water at 80 °C), the scope of the reaction was explored with various arylglyoxalmonohydrates (Scheme 7 and Table 2).

The structure of novel 3-hydroxy-5-arylpyrazine-2-carboxamide derivatives was confirmed using FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. For example, the FT-IR spectrum of 3-hydroxy-5-arylpyrazine-2-carboxamide **3a** confirmed the presence of the functional groups OH and NH_2 at 3435, 3264, 3211 cm^{-1}, along with the amide carbonyl (NH–C=O) exhibiting a strong absorption band around 1666 cm^{-1}. The ^{1}H NMR spectrum of **3a** displayed the aromatic protons of phenyl ring at 7.59–8.17 ppm, the CH proton of pyrazine ring at 8.76 ppm, and the NH_2 protons at 8.42 and 8.82 ppm as two singlets, with the OH proton at 13.59 ppm. The partial double bond character of the carbon–nitrogen bond in the amide group results in restricted rotation, making the two NH_2 protons of chemically distinct and leading to separate NMR signals. On the other hand, the two NH NMR signals of ortho hydroxy carboxamide would likely appear at different chemical shifts due to intramolecular hydrogen bonding and the different environments of the amide protons. The ^{13}C NMR spectrum further confirmed the product by the presence of an amide carbonyl signal at 170.1 ppm, and C-3 of pyrazine ring at 168.6 ppm.

3. Conclusions

In summary, we presented a simple and eco-friendly method for synthesizing structural analogs of favipiravir through a one-pot condensation reaction of 2-aminopropanediamide and arylglyoxals in an aqueous alkaline solution upon heating. The reaction is sensitive to temperature. At 80 °C, the main product is 3-hydroxy-5-phenylpyrazine-2-carboxamide; however, in some instances, temperatures exceeding 80 °C result in a mixture of two regioisomeric pyrazine compounds with comparable efficiency.

4. Experimental

4.1. General

The ^{1}H and ^{13}C NMR spectra were recorded using Varian INOVA 500 MHz or Bruker 250 MHz NMR spectrometers. The IR spectra were recorded on a Bruker PS-15 spectrometer. The melting points were measured on an electrothermal 9100 apparatus in open capillaries without correction. The elemental analyses were performed on a Carlo-Erba 1104 CHN analyzer. All the commercial reagents were used without prior purification.

4.2. Preparation of 2-aminopropanediamide 2

Diethyl aminomalonate hydrochloride (1.5 g, 7 mmol) was dissolved in methanol (2 mL) and added to a 25% ammonia solution (14 mL) while kept in an ice bath (0 °C). The mixture was stirred for 15 min at 0 °C, followed by 24 h at room temperature. The resulting precipitate was filtered and washed with 25% ammonia solution. 2-Aminopropanediamide (aminomalonamide) was obtained as a white powder with a yield of 67% (0.56 g).

mp 188–189 °C (ref. 60 187–188 (Dec.)); IR (KBr): $\bar{\nu}$ = 3358, 3312, 3211 (NH_2), 2892 (C–H), 1686 (C=O), 1658, 1286 (C–N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 250 MHz): δ = 2.88 (s, 1H, CH), 3.74 (s, 2H, NH_2), 7.21 (s, 2H, (C=O)NH_2), 7.40 (s, 2H, (C=O)NH_2) ppm; ^{13}C NMR (DMSO-d_6, 62 MHz): δ = 58.6 (CH), 172.2 (C=O) ppm.

4.3. Typical procedure for the synthesis of 3-hydroxy-5-arylpyrazine-2-carboxamides 3a–i

Powdered aminomalonamide **2** (200 mg, 1.7 mmol) was added to a solution of phenylglyoxalmonohydrates **1a** (250 mg, 1.6 mmol) in water (6 mL) at 80 °C with stirring. Then, a 12.5 N aqueous sodium hydroxide solution (1 mL) was added dropwise to the reaction mixture. Within a few minutes of stirring, the semi-solid mixture was obtained. Upon completion of the reaction (1 h), the reaction mixture cooled to room temperature and glacial acetic acid (1 mL) was added drop-wise while stirring. After the reaction was complete, the precipitated solid was filtered, washed with water and acetone, respectively, and air-dried. Ethanol was then added to the crude solid product and refluxed. Part of the solid dissolved in ethanol, and the residue was separated by filtration. This compound, with a melting point of 257 °C, was consistent with 3-hydroxy-5-phenylpyrazine-2-carboxamide **3a**. The filtrate is also allowed to cool. The resulting crystals was filtered. This compound, with a melting point of 213 °C, was consistent with 3-hydroxy-6-arylpyrazine-2-carboxamide **4a**. In the reaction of arylglyoxalmonohydrates **1a**, **1d**, **1h**, and **1i** with aminomalonamide **2** at 80–85 °C, 6-aryl substituted pyrazine derivatives were obtained in significant yields, while in other cases, 6-aryl substituted pyrazine derivatives formed only in trace amounts.

4.3.1. 3-Hydroxy-5-phenylpyrazine-2-carboxamides 3a. Yield: 189 mg (55%); brown powder; mp 256–257 °C; IR (KBr): $\bar{\upsilon}$ = 3435, 3264, 3206 (NH_2, OH), 1666 (C=O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 7.54–7.55 (m, 3H, Ar–H), 8.15–8.16 (m, 2H, Ar–H), 8.42–8.82 (s, 2H, NH_2), 8.75 (s, 1H, pyrazine H), 13.59 (s, 1H, OH) ppm; ^{13}C NMR (62 MHz, DMSO-d_6): δ = 125.76, 127.41, 129.19, 130.25, 139.86, 142.78, 154.00, 168.64 (C–OH), 170.12 (C=O) ppm; anal. calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.42; H, 4.36; N, 19.80.

4.3.2. 3-Hydroxy-6-phenylpyrazine-2-carboxamide 4a. Yield: 35 mg (10%); yellow powder; mp 210–213 °C (ref. 60 213–216 °C); IR (KBr): $\bar{\upsilon}$ = 3433 (OH), 3266, 3210 (NH_2, OH), 1665 (C=O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 7.46–7.48 (m, 1H, Ar–H), 7.49–7.55 (m, 2H, Ar–H), 8.15–8.16 (m, 2H, Ar–H), 8.42 and 8.82 (s, 2H, NH_2), 8.76 (s, 1H, pyrazine H), 13.55 (s, 1H, OH) ppm; ^{13}C NMR (62 MHz, DMSO-d_6): δ = 127.69, 128.00, 129.41, 130.92, 135.74, 153.64, 162.62 (C–OH), 169.87(C=O) ppm; anal. calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.41; H, 4.32; N, 19.79.

4.3.3. 5-(4-Bromophenyl)-3-hydroxypyrazine-2-carboxamide 3b. Yield: 207 mg (65%); yellow powder; mp 238–240 °C; IR (KBr): $\bar{\upsilon}$ = 3566, 3248, 3211 (NH_2, OH), 1630 (C=O) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ = 7.69–7.73 (m, 2H, Ar–H), 8.06–8.10 (m, 2H, Ar–H), 8.39 (s, 1H, pyrazine H), 8.75 and 8.79 (s, 2H, NH_2), 13.60 (s, 1H, OH) ppm; ^{13}C NMR (62 MHz, DMSO-d_6): δ = 121.62, 125.13, 129.72, 131.89, 132.49, 134.33, 152.73, 161.43 (C–OH), 170.08 (C=O) ppm; anal. calcd for $C_{11}H_8BrN_3O_2$: C, 44.92; H, 2.74; N, 14.29. Found: C, 44.95; H, 2.89; N, 14.46.

4.3.4. 5-(4-Chlorophenyl)-3-hydroxypyrazine-2-carboxamide 3c. Yield: 202 mg (60%); green powder; mp 254–255 °C (Dec.); IR (KBr): $\bar{\upsilon}$ = 3442, 3278, 3211 (NH_2, OH), 1666 (C=O) $cm^{-1;}$ ^1H NMR (500 MHz, DMSO-d_6): δ = 7.60 (s, 1H, Ar–H), 7.62 (s, 1H, Ar–H), 8.19 (s, 1H, Ar–H), 8.20 (s, 1H, Ar–H), 8.44 and 8.84 (s, 2H, NH_2), 8.78 (s, 1H,pyrazine H), 13.58 (s, 1H, OH) ppm; ^{13}C NMR (62 MHz, DMSO-d_6): δ = 129.57, 132.90, 134.06, 136.23, 152.84, 161.51 (C–OH), 170.20 (C=O) ppm; anal. calcd for $C_{11}H_8ClN_3O_2$: C, 52.92; H, 3.23; N, 16.83. Found: C, 53.15; H, 3.38; N, 16.99.

4.3.5. 5-(4-Fluorophenyl)-3-hydroxypyrazine-2-carboxamide 3d. Yield: 154 mg (45%); orange powder; mp 219–220 °C; IR (KBr): $\bar{\upsilon}$ = 3445, 3277, 3211 (NH_2, OH),1673 (C=O) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ = 7.24–7.35 (m, 2H, Ar–H), 8.14–8.20 (m, 2H, Ar–H), 8.40 (s, 1H, pyrazine H), 8.71 and 8.85 (m, 2H, NH_2), 13.52 (s, 1H, OH) ppm; ^{13}C NMR (62 MHz, DMSO-d_6): δ = 116.63, 128.58, 130.18, 130.32, 132.68, 153.02, 162.26 (C–OH), 166.22 (C–F), 170.23 (C=O) ppm; anal. calcd for $C_{11}H_8FN_3O_2$: C, 56.65; H, 3.46; N, 18.02. Found: C, 56.72; H, 3.61; N, 18.25.

4.3.6. 6-(4-Fluorophenyl)-3-hydroxypyrazine-2-carboxamide 4d. Yield: 52 mg (15%); yellow powder; mp 236–238 °C (Dec.); IR (KBr): $\bar{\upsilon}$ = 3444, 3280, 3210 (NH_2, OH), 1671 (C=O) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ = 7.29–7.36 (m, 2H, Ar–H), 8.21 (s, 2H, Ar–H), 8.42 (s, 1H, pyrazine H), 8.76–8.80 (s, 2H, NH_2), 13.58 (s, 1H, OH) ppm; ^{13}C NMR (62 MHz, DMSO-d_6): δ = 116.68, 128.58, 130.35, 131.77, 132.73, 153.03, 161.51 (C–OH), 166.24 (C–F), 170.23 (C=O) ppm; anal. calcd for $C_{11}H_8FN_3O_2$: C, 56.65; H, 3.46; N, 18.02. Found: C, 56.68; H, 3.62; N, 18.32.

4.3.7. 3-Hydroxy-5-(4-nitrophenyl)pyrazine-2-carboxamide 3e. Yield: 158 mg (48%); dark brown powder; mp 275–278 °C; IR (KBr): $\bar{\upsilon}$ = 3418 (NH_2, OH), 1669 (C=O) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ = 7.50–8.54 (m, 7H, Ar–H, pyrazine H, NH_2), 8.89 (s, 1H, OH) ppm; ^{13}C NMR (62 MHz, DMSO-d_6): δ = 122.92, 125.31, 128.74, 130.83, 132.90, 154.60, 161.75 (C–OH), 167.14 (C–NO_2), 170.06 (C=O) ppm; anal. calcd for $C_{11}H_8N_4O_4$: C, 50.77; H, 3.10; N, 21.53. Found: C, 50.60; H, 3.20; N, 21.70.

4.3.8. 3-Hydroxy-5-(*p*-tolyl)pyrazine-2-carboxamide 3f. Yield: 249 mg (72%); light orange powder; mp 269–270 °C (Dec.); IR (KBr): $\bar{\upsilon}$ = 3428, 3274, 3212 (NH_2, OH), 1662(C=O) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ = 2.32 (s, 3H, CH_3), 7.24–7.27 (d, J = 7.5 Hz, 2H, Ar–H), 8.03–8.06 (d, J = 7.5 Hz, 2H, Ar–H), 8.37 (s, 1H, pyrazine H), 8.71–8.83 (m, 2H, NH_2) 13.38 (s, 1H, OH) ppm; ^{13}C NMR (62 MHz, DMSO-d_6): δ = 21.25 (CH_3), 126.23, 127.75, 130.11, 132.41, 138.75, 141.33, 159.79, 161.51 (C–OH), 170.22 (C=O) ppm; anal. calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.90; H, 4.94; N, 18.50.

4.3.9. 3-Hydroxy-5-(4-methoxyphenyl)pyrazine-2-carboxamide 3g. Yield: 229 mg (68%); green powder; mp 266–270 °C (Dec.); IR (KBr): $\bar{\upsilon}$ = 3450, 3271 (OH, NH_2), 1610 (C=O) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ = 3.81 (s, 3H, OCH_3), 6.97–7.00 (d, J = 7.5 Hz, 1H, Ar–H), 7.03–7.06 (d, J = 7.5 Hz, 1H, Ar–H), 8.07 (s, 1H, Ar–H), 8.11 (s, 1H, Ar–H), 8.30 (s, 1H, pyrazine H), 8.68–8.85 (m, 2H, NH_2), 13.34 (s, 1H, OH) ppm; ^{13}C NMR (62 MHz, DMSO-d_6): δ = 55.82 (OCH_3), 114.57, 128.15, 129.47, 131.63, 141.14, 153.76, 161.96 (C–OH), 169.42 (C–OCH_3), 170.30 (C=O) ppm; anal. calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.85; H, 4.67; N, 17.40.

4.3.10. 3-Hydroxy-5-(naphthalen-2-yl)pyrazine-2-carboxamide 3h. Yield: 158 mg (48%); light yellow powder; mp 217–220 °C; IR (KBr): $\bar{\upsilon}$ = 3439, 3275, 3213 (OH, NH_2), 1669 (C=O) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ = 7.56–7.58 (m, 3H, Ar–H), 7.97–8.06 (m, 4H, Ar–H), 8.30 (s, 1H, pyrazine H), 8.78 and 8.94 (s, 2H, NH_2), 13.49 (s, 1H, OH) ppm; ^{13}C NMR (62 MHz, DMSO-d_6): δ = 124.55, 125.23, 127.00, 127.30, 128.09, 128.78, 129.13, 132.86, 133.35, 134.36, 153.84, 161.74 (C–OH), 170.26 (C=O) ppm; anal. calcd for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84. Found: C, 67.95; H, 4.30; N, 15.98.

4.3.11. 3-Hydroxy-6-(naphthalen-2-yl)pyrazine-2-carboxamide 4h. Yield: 50 mg (15%); mustard yellow powder; mp 200–204 °C; IR (KBr): $\bar{\upsilon}$ = 3433, 3267, 3205 (OH, NH_2), 1671 (C=O) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ = 7.45–8.30 (m, 8H, pyrazine H, Ar–H), 8.81–8.95 (s, 2H, NH_2), 13.54 (s, 1H, OH) ppm; ^{13}C NMR (62 MHz, DMSO-d_6): δ = 124.53, 126.49, 129.74, 130.48, 130.95, 133.07, 134.36, 142.64, 153.84, 161.59 (C–OH), 170.25 (C=O) ppm; anal. calcd for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84. Found: C, 67.85; H, 4.28; N, 16.12.

4.3.12. 5-([1,1′-Biphenyl]-4-yl)-3-hydroxypyrazine-2-carboxamide 3i. Yield: 160 mg (50%); bright orange powder; mp 225–226 °C (Dec.); IR (KBr): $\bar{\upsilon}$ = 3444, 3282, 3058 (OH, NH_2), 1661(C=O) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ = 7.47 (m, 3H, Ar–H), 7.73–7.83 (m, 5H, Ar–H), 8.23 (s, 1H, pyrazine H), 8.79 and 9.02 (s, 2H, NH_2), 13.20 (s, 1H, OH) ppm; ^{13}C NMR (62

MHz, DMSO-d_6): δ = 126.15, 127.23, 127.66, 128.38, 129.49, 131.85, 134.92, 139.93, 140.45, 142.63, 154.63, 162.11 (C–OH), 170.09 (C=O) ppm; anal. calcd for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42. Found: C, 70.22; H, 4.65; N, 14.59.

4.3.13. 6-([1,1′-Biphenyl]-4-yl)-3-hydroxypyrazine-2-carboxamide 4i. Yield: 39 mg (12%); yellow powder; mp 198–199 °C; IR (KBr): $\bar{\upsilon}$ = 3441, 3279, 3056 (OH, NH_2), 1660 (C=O) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ = 7.47 (m, 4H, Ar–H), 7.73 (m, 5H, Ar–H), 8.00 (s, 1H, pyrazine H), 8.24–8.40 (m, 1H, NH_2), 8.84–8.93 (m, 1H, NH_2), 13.54 (s, 1H, OH) ppm; ^{13}C NMR (62 MHz, DMSO-d_6): δ = 126.49, 127.02, 129.41, 129.74, 130.48, 130.94, 134.36, 135.29, 142.64, 153.84, 161.59 (C–OH), 170.25 (C=O) ppm; anal. calcd for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42. Found: C, 70.12; H, 4.64; N, 14.66.

Data availability

The data supporting the findings of this study are included in the ESI file.† Additional data will be available upon request.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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