Heterocyclic compounds derived from cyclohexane-1,4-dione: synthesis of tetrahydro-4H-chromene and tetrahydrobenzo[d]thiazole derivatives as target SARS-CoV-2 main protease (Mpro) and potential anti-Covid-19

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Abstract
Tetrahydro-4H-chromene-3-carbonitrile derivatives 4a-c where prepared from the reaction of 1,4-cyclohexane dione (1), malononitrile (2) and either of benzaldehyde (3a), 2-chlorobenzaldehyde (3b) or 4-methoxybenzaldehyde (3c) in ethanol containing triethylamine. Compound 4b was used to prepare pyrazole, pyrimidine and thiazole derivatives. Moreover, tetrahydrobenzo[d]thiazole derivative 18 was prepared from the reaction of 1,4-cyclohexane dione (1) with elemental sulfur followed by phenyl isothiocyanate (12) in absolute ethanol containing triethylamine. The latter compound reacted with ethyl orthoformate and either malononitrile or ethyl cyanoacetate in 1,4-dioxane in the presence of triethylamine to produce the 9-ethoxy-2H-chromeno[6,5-d]thiazole derivatives 20a,b. In addition, fused thiophene and pyran derivatives were synthesized starting from compound 18. The screened compounds were designed as mimics of the transition state of RNA2'-O-methylation were screened against several viral RNA 2'-OMTases from SARS-CoV (nsp10/nsp16 complex), Zika, West Nile, dengue, vaccinia (VP39) viruses. At the same time, the compounds were tested against human RNA N7-MTase (hRNMT) and selected viral N7-MTases such as SARS-CoV nsp14 and vaccinia D1-D12 complex to evaluate their specificity. Compounds 4a, 4b, 6b, 6c, 6e, 9a, 9b, 15, 16, 21b, and 23b showed high % inhibitions against SARs-Cov nsp 14 with values 93.42, 87.49, 98.23, 88.15, 89.24, 96.31, 93.28, 89.25, 89.20, 87.24, and 94.49, respectively.

Keywords Cyclohexane-1,4-dione · Tetrahydro-4H-chromene · Tetrahydrobenzo[d]thiazole · Anti SARS-CoV

Introduction
Heterocycles constitute the largest diversity of organic molecules of chemical, biomedical, and industrial significance [1–8]. They widely exist in numerous natural products, such as vitamins, hormones, antibiotics, alkaloids, herbicides, and dyes [9–12]. They are also among the most frequently encountered scaffolds in numerous drugs and pharmaceutically relevant substances [13–16]. In the past several decades, a significant number of efforts have been made on the discovery and development of more efficient pharmaceuticals, pesticides, insecticides, rodenticides, and weed killers by following well studied natural models and biochemical pathways in living cells [17, 18]. In addition, a series of libraries consisting of heterocycles have been successfully established for the structure–activity relationship studies (SAR) for drug design and synthesis [19]. Meanwhile, the diversity oriented synthesis (DOS) continues to be an area of importance at the interface of organic synthesis and chemical biology [20–22]. While DOS plays an important role in searching for new bioactive small molecules with functional and stereochemical diversity [23], more efficient multi-component domino reactions (MDRs) for the synthesis of a series of heterocycles, particularly functionalized multi-heterocycles, have been in high demand. In the past several years, the development of new multi-component domino reactions has become an active and challenging topic in modern organic chemistry [24]; they can
readily provide greater atom-economic access to a diverse spectrum of compounds and their libraries for screening. Recently, our research group was involved through the studying the multi-component reactions of cyclohexanediones [25–28]. As a continuation of this program we are presenting in this work the multi-component reaction of cyclohexan-1,4-dione [29, 30] followed by further heterocyclization of the products to afford biologically active fused derivatives.

**Results and discussion**

As a continued work through the uses of cyclohexan-dione to produce heterocyclic compounds characterized by their high anti-proliferative activities. In the present work, we demonstrated the use of cyclohexan-1,4-dione to synthesis novel fused heterocyclic compounds and study their activities against several viral RNA 2′-OMTases from SARS-CoV. The reactions were demonstrated through Schemes 1–4. Thus, the reaction of cyclohexan-1,4-dione with malononitrile and either of benzaldehyde,

![Scheme 1](image)

*Scheme 1* Synthesis of compounds 4a-c and 6a-f
2-chlorobenzaldehyde or 4-methoxybenzaldehyde in ethanol containing a catalytic amount of triethylamine gave the 4-H pyran derivatives 4a-c. Structures of the latter products were based on their respective analytical and spectral data. Thus, the $^1$H NMR spectrum of 4a (as an example) showed the presence of a multiplet at $\delta 3.05$ ppm integrating for four hydrogens of the CH$_2$-CH$_2$ moiety and another multiplet at $\delta 7.23$–7.62 ppm corresponding to the aromatic protons. Moreover, the presence of a singlet at $\delta 4.05$ ppm for the active methylene moiety located between the carbonyl group and the sp$^2$ carbon and another singlet at $\delta 6.69$ ppm for the pyran $H$-4, beside a third singlet at $\delta 3.31$ ppm (D$_2$O exchangeable) corresponding to the NH$_2$ group. In addition, the $^{13}$C NMR data revealed the appearance of signals at $\delta 22.6$ (CH$_2$), 50.3(CH$_2$), 66.3(CH$_2$), 96.9 (pyran-C4), 116.2 (CN), 118.4, 120.8, 121.0, 121.7, 125.4, 126.1, 128.9, 130.0 (C$_6$H$_5$, pyran), 161.8 (CO).

Compounds 4a-c containing the $\alpha$-oxomethylene moieties that capable for the Gewald’s thiophene synthesis [31–33]. Thus, the reaction of either of compounds 4a, 4b or 4c with elemental sulfur and either of malononitrile (2) or ethyl cyanoacetate (5) in absolute ethanol solution containing triethylamine gave the thieno[2,3-]chromene-8-carbonitrile derivatives 6a-f, respectively (Scheme 1).

Moreover, compound 4b underwent the Knoevenagel condensation reaction when was heated in an oil bath at 120 °C in the presence of ammonium acetate to give the condensation product 7 the structure of which was confirmed on the basis of its analytical and spectral data (see experimental section). Compound 7 reacted with either hydrazine hydrate (8a) or phenylhydrazine (8b) to give the pyrazole derivatives 9a,b, respectively. On the other hand, compound 7 reacted with thiourea (10) in sodium ethoxide solution to afford the pyrimidine-2-thione derivative 11 (Scheme 2). The structures of these compounds were confirmed by studying their spectral data as discussed in the experimental section.

Recently, our research group was involved through a comprehensive program aiming to synthesis thiazole and thiophene derivatives through the reaction of phenylisothiocyanate with active methylene reagent in basic dimethylformamide solution to give the corresponding intermediate potassium sulfide salt. Heterocyclization of the latter intermediate with $\alpha$-halocarbonyl compounds afford thiophene and/or thiazole derivatives [34, 35] depending on the nature of the active methylene reagent used. As a continuation of this program, compound 4b reacted with phenylisothiocyanate in DMF/KOH solution to give the intermediate potassium sulfide salt 13, the latter reacted with chloroacetone (14a) to give the thioazole derivative 15. On the other hand, the intermediate 13 reacted with $\alpha$-chloroethyl acetate (14b) to give the thioether derivative 16 (Scheme 3). Our trials to re-cyclize compound 16 were unsuccessful under different conditions. Structures of compounds 15 and 16 were based on the obtained analytical and spectral data (see experimental section).

Next, we moved toward studying Hantzsch reaction for thiazole synthesis. Thus, the reaction of cyclohexan-1,4-dione (1) with elemental sulfur and phenylisothiocyanate in 1,4-dioxane solution containing triethylamine gave the 3-phenyl-2-thioxo-2,3,4,5-tetrahydrobenzo[d]thiazol-6(7H)-one (18). The $^1$H NMR and $^{13}$C NMR spectra of compound 18 were in agreement with its structure (see experimental section). Compound 18 was capable to form fused heterocyclic compounds through its multi-component reactions. Thus, the reaction of compound 18 with ethyl orthoformate (19) and either malononitrile (5a) or ethyl cyanoacetate (5b) in 1,4-dioxane solution containing triethylamine afforded the chromeno[6,5-d][thiazole derivatives 20a and 20b, respectively. On the other hand, the reaction of compound 18 with elemental sulfur and either malononitrile (5a) or ethyl cyanoacetate (5b) in 1,4-dioxane containing triethylamine gave the thieno[2',3':3,4]benzo[1,2-d]thiazole derivatives 21a and 21b, respectively. Finally, the multi-component reactions of compound 18 with either benzaldehyde (3a) or 4-chlorobenzaldehyde (22) gave the tetrahydro-2H-chromeno[6,5-d]thiazole derivatives 23a-d, respectively (Scheme 4).

**RNA methyltransferase activity assays**

Twenty-two compounds were tested for their ability to inhibit them ethylation of the RNA cap structure. The inhibition induced by each compound (50 μM) was determined by a radioactive MTase (methyltransferase) assay (filter binding assay) which consists in measuring the [3H] radiolabeled methyl transferred from the methyl donor SAM onto RNA substrate (GpppAC4) synthetized by using T7 primase [36]. The screened compounds were designed as mimics of the transition state of RNA2’-O-methylation were screened against several viral RNA 2’-OMTases from SARS-CoV (nsp10/nsp16 complex), Zika, West Nile, dengue, vaccinia (VP39) viruses. At the same time, the compounds were tested against human RNA N7-MTase (hRNMT) and selected viral N7-MTases such as SARS-CoV nsp14 and vaccinia D1-D12 complex to evaluate their specificity (Table 1). Unexpectedly, all the bisubstrate compounds were barely active against the 2’-OMTases of flaviviruses or coronavirus SARS-CoV. In contrast, most of the compounds displayed inhibition of N7-MTases (methyltransferase).

It is clear from Table 1 that 4a, 4b, 6b, 6c, 6e, 9a, 9b, 15, 16, 21b, and 23b showed high % inhibitions against SARS-CoV nsp 14 with values 93.42, 87.49, 98.23, 88.15, 89.24, 96.31, 93.28, 89.25, 89.20, 87.24, and 94.49, respectively.

On the other hand, compounds 4a, 4b, 6a, 6b, 6c, 6e, 9a, 9b, 15, 16, 21b, and 23b revealed high activity on vaccinia virus D1-D12 with % of inhibitions 89.35, 98.27, 79.27,
Scheme 2  Synthesis of compounds 7, 9a,b, and 11
93.42, 92.21, 92.52, 95.45, 96.12, 90.41, and 96.28, respectively. Whereas, compounds 4a, 4b, 6a, 6b, 6c, 6e, 9a, 9b, 15, 16, 21b, and 23b showed high inhibitions on hRNMT. It is of a great value to mention that compounds with high inhibitions toward SARs-Cov nsp 14 containing in most cases the electronegative halogen and/or electronegative moiety. Considering the pyran derivatives 4a-c it was obvious that compounds 4a (X = Y = H) and 4b (X = Cl, Y = H) in all cases were characterized by high percentage of viral inhibition. On the other hand, compound 4c (X = H, Y = OCH3) exhibited low inhibitions. Similarly, for the thieno[2,3-f]chromene derivatives 6a-f where compounds 6a (X = Y = H, R = CN), 6b (X = Cl, Y = H, R = CN), 6c (X = H, Y = OCH3, R = CN), and 6e (X = Cl, Y = H, R = COOEt) exhibited high percentage of inhibitions. It was surprisingly that compound 6c showed high inhibitions although it contain the electron donating OCH3 group as it seemed that in this case other factors enhance inhibitions like the fused thiophene and pyran moieties beside the CN moiety. It was very interesting that the pyrazole derivatives 9a (R = H), 9b (R = Ph), the thiazole derivative 15, and the thioether derivative 16 exhibited high viral inhibitions. On the other hand, the thiazole derivatives 18 and 20a,b exhibited low inhibitions. Considering the thieno[2',3':3,4]benzo[1,2-d]thiazole derivatives 21a and 21b, it was clear from Table 1 that compound 21b (R = COOEt) showed higher inhibitions than 21a (R = CN). Finally, for the tetrahydro-2H-chromeno[6,5-d]thiazole 23a-d, it was clear that only compound 23b (R = CN, Y = Cl) exhibited the highest inhibitions among the four compounds.

It is clear from Table 2 that most of the tested compounds showed IC50’s indicated that they are active toward Cov nap14. Compounds 4a, 4b, 6e, 9a, 9b, 16, 23b, and 23d showed IC50’s < 1.0 μM. In addition, most of the
Scheme 4  Synthesis of compounds 18, 20a,b, 21a,b, and 23a-d
tested compounds were not active toward hRNMT. Interestingly, some compounds like 4a, 6c, 9a, 23b, and 23d showed IC$_{50}$'s $< 0.05$ against hRNMT.

**Experimental**

**Chemistry**

$^{13}$C NMR and $^{1}$H NMR spectra were measured on Bruker DPX300 instrument in DMSO with TMS as an internal standard for protons and solvent signals as internal standard for carbon spectra. Chemical shift values are mentioned in δ (ppm). Mass spectra were recorded on EIMS (Shimadzu) and ESI-esquire 3000 Bruker Daltonics instrument. Elemental analyses were obtained using by the Microanalytical Data Unit at Cairo University.

The progress of all reactions was observed by TLC on $2 \times 5$ cm pre-coated silica gel 60 F254 plates of thickness of 0.25 mm (Merck).

**Synthesis of 5,6,7,8-tetrahydro-4H-chromene derivatives (4a-c)**

A mixture of compound 1,4-cyclohexane dione (1) (1.12 g, 0.01 mol), malononitrile (2) (0.66 g, 0.01 mol) and either of benzaldehyde (3a) (1.06 g, 0.01 mol), 2-chlorobenzaldehyde (3b) (1.4 g, 0.01 mol) or 4-methoxybenzaldehyde (3c) (1.36 g, 0.01 mol) in ethanol (40 mL) containing triethylamine (0.5 g) was heated under reflux for 3–4 h. The reaction mixture was left to cool to room temperature, poured onto ice/water, and neutralized by hydrochloric acid. The precipitated solid was collected by filtration, washed with water, and dried.

**Table 1** Screening for inhibitory activity of sinefungin and compounds 4a-23d at 50 μM on N7-MTases

| Compd | % of inhibition at 50 μM (%)<sup>a</sup> | SARS-CoV nsp 14 | Vaccinia virus | hRNMT |
|-------|--------------------------------|-----------------|---------------|-------|
|       |                                | D1-D12          |               |       |
| 4a    | 93.42 ± 3.68                   | 89.35 ± 7.89    | 92.26 ± 5.41  |       |
| 4b    | 87.49 ± 8.21                   | 98.27 ± 5.42    | 94.62 ± 7.68  |       |
| 4c    | 34.59 ± 4.62                   | 49.38 ± 6.92    | 51.68 ± 4.62  |       |
| 6a    | 68.21 ± 4.53                   | 79.27 ± 5.37    | 80.26 ± 3.74  |       |
| 6b    | 98.23 ± 6.51                   | 93.42 ± 6.75    | 92.58 ± 4.68  |       |
| 6c    | 88.15 ± 4.26                   | 92.21 ± 5.22    | 92.21 ± 5.22  |       |
| 6d    | 42.63 ± 4.65                   | 36.3 ± 5.22     | 40.29 ± 6.27  |       |
| 6e    | 89.24 ± 8.27                   | 92.52 ± 6.90    | 80.2 ± 6.28   |       |
| 6f    | 58.32 ± 3.65                   | 44.78 ± 5.08    | 62.49 ± 5.84  |       |
| 9a    | 96.31 ± 2.4                    | 95.45 ± 3.23    | 93.62 ± 3.71  |       |
| 9b    | 93.28 ± 4.17                   | 96.12 ± 2.48    | 90.26 ± 5.20  |       |
| 15    | 89.25 ± 5.83                   | 90.41 ± 5.68    | 87.29 ± 6.42  |       |
| 16    | 89.20 ± 6.58                   | 84.30 ± 6.29    | 90.32 ± 4.66  |       |
| 18    | 56.42 ± 5.73                   | 63.72 ± 7.08    | 65.45 ± 4.80  |       |
| 20a   | 49.22 ± 6.73                   | 53.52 ± 8.25    | 70.41 ± 5.90  |       |
| 20b   | 36.12 ± 6.83                   | 41.37 ± 4.93    | 39.48 ± 6.83  |       |
| 21a   | 49.25 ± 6.73                   | 57.83 ± 5.82    | 60.29 ± 5.37  |       |
| 21b   | 87.24 ± 5.36                   | 90.41 ± 6.53    | 88.25 ± 5.38  |       |
| 23a   | 56.58 ± 6.72                   | 45.80 ± 6.38    | 42.68 ± 5.88  |       |
| 23b   | 94.49 ± 6.83                   | 96.28 ± 9.2     | 96.42 ± 7.24  |       |
| 23c   | 64.26 ± 5.53                   | 70.39 ± 5.63    | 59.28 ± 4.68  |       |
| 23d   | 57.68 ± 4.26                   | 72.26 ± 5.58    | 68.59 ± 6.42  |       |
| Sinefungin | 98.36 ± 0.23                  | 99.80 ± 0.18    | 99.80 ± 0.26  |       |

<sup>a</sup>Values are the mean of three independent experiments. The MTase activity was measured using a filter binding assay. Assays were carried out in reaction mixture [40 mMTris-HCl (pH 8.0), 1 mM DTT, 1 mM MgCl$_2$, 2 μM SAM and 0.1 μM 3H-SAM] in the presence of 0.7 μM GpppAC4 synthetic RNA and incubated at 30 °C. SARS-CoVnsp14 (50 nM), vaccinia virus capping enzyme (D1-D12) (41 U), human RNA N7MTase (hRNMT) (50 nM). Compounds were previously dissolved in 100% DMSO. n.i.: no inhibition detected at 50 μM

**Table 2** IC$_{50}$ values of the newly synthesized compounds on SARS-CoV nsp14 and human RNMT activities

| Compd | SARS-CoV nsp14 IC$_{50}$ (μM) | hRNMT IC$_{50}$ (μM) |
|-------|------------------------------|----------------------|
| 4a    | 0.63 ± 0.32                  | <0.05                |
| 4b    | 0.62 ± 0.32                  | 0.41 ± 0.26          |
| 4c    | 16.37 ± 2.70                 | 32.60 ± 1.70         |
| 6a    | 26.41 ± 3.57                 | 36.52 ± 0.27         |
| 6b    | 0.39 ± 0.25                  | 80.42 ± 2.27         |
| 6c    | 0.45 ± 0.19                  | <0.05                |
| 6d    | 26.73 ± 5.73                 | 10.52 ± 2.69         |
| 6e    | 0.39 ± 0.25                  | 0.29 ± 0.08          |
| 6f    | 36.42 ± 4.51                 | 1.26 ± 0.58          |
| 9a    | 0.42 ± 0.19                  | <0.05                |
| 9b    | 0.36 ± 0.20                  | 1.91 ± 1.32          |
| 15    | 22.59 ± 3.58                 | 4.91 ± 2.34          |
| 16    | 0.53 ± 0.18                  | 1.29 ± 0.98          |
| 18    | 53.29 ± 5.62                 | 26.49 ± 0.28         |
| 20a   | 42.36 ± 5.63                 | 58.27 ± 4.95         |
| 20b   | 32.64 ± 3.80                 | 18.82 ± 5.36         |
| 21a   | 18.53 ± 2.68                 | 56.31 ± 4.62         |
| 21b   | 1.08 ± 0.58                  | 0.94 ± 0.36          |
| 23a   | 32.42 ± 4.58                 | 24.68 ± 5.47         |
| 23b   | 0.35 ± 0.15                  | <0.05                |
| 23c   | 28.43 ± 3.26                 | 70.35 ± 5.30         |
| 23d   | 0.49 ± 0.13                  | <0.05                |
| Sinefungin | 0.36                      | <0.05                |

<sup>a</sup>Concentration inhibiting MTase activity by 50%; mean value from three independent experiments.

EIMS (Shimadzu) and ESI-esquire 3000 Bruker Daltonics instrument. Elemental analyses were obtained using by the Microanalytical Data Unit at Cairo University. The progress of all reactions was observed by TLC on 2×5 cm pre-coated silica gel 60 F254 plates of thickness of 0.25 mm (Merck).
Green crystals from ethanol, yield: 75%; m.p.: 210–213 °C; IR (KBr, v max cm⁻¹): 3433, 3220(NH₂), 2949 (CH aliphatic), 2211 (CN), 1702 (CO), 1530 (C=C); ¹H NMR (300 MHz, DMSO-d₆): δ3.05 (m, 4H, CH₂-CH₂), 3.31 (s, 2H, D₂O exchangeable, NH₂), 4.05 (s, 2H, CH₂), 6.69 (s, 1H, pyran H-4), 7.23–7.62 (m, 5H, C₆H₅); ¹³C NMR (DMSO-d₆): δ22.6 (CH₂), 50.3 (CH₂), 66.3 (CH₂), 96.9 (pyran C-4), 116.2 (CN), 118.4, 120.8, 121.0, 125.4, 126.5, 128.7, 130.8 (C₆H₄, pyran), 161.8 (CO); EIMS (m/z, %): 266 (M⁺, 84). Anal. Calcd. For C₁₆H₁₄N₂O₂ (266.29): C, 72.16; H, 5.30; N, 10.52%. Found: C, 72.34; H, 5.08; N, 10.39%.

2-Amino-6-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4a)

2-Amino-6-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4a)

Pale brown crystals from ethanol, yield: 82%; m.p.: 145–147 °C; IR (KBr, v max cm⁻¹): 3433, 3228 (NH₂), 2981 (CH aliphatic), 2199 (CN), 1698 (CO), 1588 (C=C); ¹H NMR (300 MHz, DMSO-d₆): δ6.03 (m, 4H, CH₂-CH₂), 3.31 (s, 2H, D₂O exchangeable, NH₂), 3.98 (s, 2H, CH₂), 6.65 (s, 1H, pyran H-4), 7.28–7.57 (m, 4H, CH₂), ¹³C NMR (DMSO-d₆): δ23.2 (CH₂), 49.6 (CH₂), 97.1 (pyran C-4), 116.6 (CN), 118.0, 119.7, 121.4, 121.9, 126.2, 126.7, 128.5, 129.4  (C₆H₄, pyran and thiophene); EIMS (m/z, %): 295 (M⁺, 34). Anal. Calcd. for C₁₉H₁₄N₂O₂ (307.34): C, 63.90; H, 4.36; N, 9.31%. Found: C, 63.58; H, 4.16; N, 9.63%.

2-Amino-4-(2-chlorophenyl)-6-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6b)

Green crystals from 1,4-dioxane, yield: 95%; m.p.: 205–207 °C; IR (KBr, v max cm⁻¹): 3448–3223 (NH₂), 2959 (CH aliphatic), 2210, 2192 (2CN), 1548 (C=C); ¹H NMR (300 MHz, DMSO-d₆): δ3.05 (m, 4H, CH₂-CH₂), 3.36, 6.53 (2 s, 4H, D₂O exchangeable, 2NH₂), 6.79 (s, 1H, pyran-H4), 7.15–7.60 (m, 5H, C₆H₅) 13C NMR (DMSO-d₆): δ23.0 (CH₂), 49.7 (CH₂), 98.1 (pyran C-4), 115.9, 116.5 (2CN), 119.0, 120.4, 121.5, 124.8, 125.6, 126.7, 127.9, 132.9, 136.8, 138.4 (C₆H₄, pyran and thiophene); EIMS (m/z, %): 346 [M⁺, 34]. Anal. Calcd. for C₁₉H₁₄N₂O₂ (346.41): C, 65.88; H, 4.07; N, 16.17; S, 9.26%. Found: C, 65.64; H, 4.34; N, 15.92; S, 9.49%.

2,7-Diamino-9-phenyl-5,9-dihydro-4H-thieno[2,3-f]chromene-3,8-dicarbonitrile (6b)

Yellow crystals from ethanol, yield: 93%; m.p.: 155–157 °C; IR (KBr, v max cm⁻¹): 3437–3229 (2NH₂), 2923 (CH aliphatic), 2219, 2207 (2CN), 1577 (C=C); ¹H NMR (300 MHz, DMSO-d₆): δ3.05 (m, 4H, CH₂-CH₂), 3.36, 6.55 (2 s, 4H, D₂O exchangeable, 2NH₂), 6.82 (s, 1H, pyran H-4), 7.24–7.76 (m, 4H, C₆H₄); ¹³C NMR (DMSO-d₆): δ23.0 (CH₂), 49.3 (CH₃), 98.5 (pyran C-4), 116.1, 116.9 (2CN), 118.3, 119.6, 120.8, 121.7, 123.9, 125.9, 126.4, 128.1, 129.4, 131.8, 138.2 (C₆H₄, pyran and thiophene); EIMS (m/z, %): 380 [M⁺, 57]. Anal. Calcd. for C₁₉H₁₄N₂O₂ (380.85): C, 59.92; H, 3.44; N, 14.71; S, 8.42%. Found: C, 60.14; H, 3.34; N, 14.69; S, 8.09%.

2,7-Diamino-9-(2-chlorophenyl)-5,9-dihydro-4H-thieno[2,3-f]chromene-3,8-dicarbonitrile (6c)

Off white crystals from 1,4-dioxane, yield: 94%; m.p.: 230–232 °C; IR (KBr, v max cm⁻¹): 3435–3227(2NH₂), 2942 (CH aliphatic), 2234, 2210 (2CN), 1626 (C=C); ¹H NMR (300 MHz, DMSO-d₆): δ3.01 (m, 4H, CH₂-CH₂), 3.34, 6.72 (2 s, 4H, D₂O exchangeable, 2NH₂), 3.89 (s, 3H, OCH₃), 6.68(s, 1H, pyran H-4), 6.92–7.36 (m, 6H, C₆H₄); ¹³C NMR (DMSO-d₆): δ23.6 (CH₂), 48.1 (CH₃), 55.0 (OCH₃), 97.8 (pyran-C₄), 116.4, 117.0 (2CN), 118.1, 119.6, 121.2, 123.3, 124.9, 125.3, 127.4, 128.5, 130.1, 133.4, 137.8, 139.7.
Ethyl 2,7-diamino-8-cyano-9-phenyl-5,9-dihydro-4H-thieno[2,3-f]chromene-3-carboxylate (6d)

Green crystals from 1,4-dioxane, yield: 60%; m.p.: 190–193 °C; IR (KBr, υ max cm⁻¹): 3438–3244 (2NH₂), 2931 (CH aliphatic), 2209 (CN), 1701 (CO), 1529 (C = C); ¹H NMR (300 MHz, DMSO-d₆): δ 1.15 (t, 3H, J = 7.5 Hz, OCH₂CH₃), 3.05 (m, 4H, CH₂-CH₂), 3.36, 6.51 (2 s, 4H, D₂O exchangeable, 2NH₂), 4.05 (q, 2H, J = 7.5 Hz, OCH₂CH₃), 4.21 (q, 2H, J = 7.5 Hz, OCH₂CH₃), 6.82 (s, 1H, pyran H-4), 6.94–7.31 (m, 4H, C₆H₄); ¹³C NMR (DMSO-d₆): δ 15.6 (CH₃) 22.9 (CH₂), 49.6 (CH₂), 54.1 (CH₂), 98.4 (pyran C-4), 116.1(CN), 118.5, 119.8, 121.7, 122.0, 124.8, 125.1, 126.3, 127.5, 129.1, 132.9, 135.9, 139.4 (C₆H₄, pyran and thiophene), 163.1 (CO); EIMS (m/z, %): 376 [M+, 29]. Anal. Calcd. for C₂₁H₂₀ClN₃O₃S (427.90): C, 58.94; H, 4.24; N, 9.81; S, 7.37%.

Synthesis of 2-(2-amino-4-(2-chlorophenyl)-3-cyano-7,8-dihydro-4H-chromen-6(5H)-ylidene)malononitrile (7)

Malononitrile (5a) (0.66 g, 0.01 mol) and ammonium acetate (1.00 g) were added to a dry solid of compound 4b (3.0 g, 0.01 mol). The reaction mixture was heated in an oil bath at 120 °C for 1 h then left to cool. The remaining product was triturated with ethanol, and the formed solid product was filtered and dried.

Pale brown crystals from ethanol, yield: 84%; m.p.: 185–187 °C; IR (KBr, υ max cm⁻¹): 3435–3235 (3NH₂, NH), 2931 (CH aliphatic), 2226–2210 (3CN),1593 (C = C); ¹H NMR (300 MHz, DMSO-d₆): δ 3.18 (m, 4H, CH₂CH₂), 3.38 (s, 2H, D₂O exchangeable, NH₂), 4.01 (s, 2H, CH₂), 6.89 (s, 1H, pyran H-4), 7.26–7.67 (m, 4H, C₆H₄); ¹³C NMR (DMSO-d₆): δ 24.6 (CH₂), 46.0 (CH₂), 66.4 (CH₂), 95.1 (pyran C-4), 108.4, 111.6 (C = C), 115.4, 116.2, 116.8 (3CN), 118.4, 121.7, 122.9, 124.5, 127.3, 129.9, 131.2, 133.8 (C₆H₄, pyran C); EIMS (m/z, %): 348 [M⁺, 52]. Anal. Calcd. for C₁₉H₁₈ClN₃O₄S (414.44): C, 58.94; H, 4.24; N, 9.82; S, 7.49%. Found: C, 59.17; H, 4.01; N, 9.61; S, 7.37%.

Ethyl 2,7-diamino-9-(2-chlorophenyl)-8-cyano-5,9-dihydro-4H-thieno[2,3-f]chromene-3-carboxylate (6e)

Yellow crystals from ethanol, yield: 70%; m.p.: 145–147 °C; IR (KBr, υ max cm⁻¹): 3435–3236 (2NH₂), 2974 (CH aliphatic), 2209 (CN), 1732 (CO), 1584 (C = C); ¹H NMR (300 MHz, DMSO-d₆): δ 1.16 (t, 3H, J = 7.5 Hz, OCH₂CH₃), 3.08 (m, 4H, CH₂-CH₂), 3.35, 6.55 (2 s, 4H, D₂O exchangeable, 2NH₂), 4.14 (q, 2H, J = 7.5 Hz, OCH₂CH₃), 6.85 (s, 1H, pyran H-4), 7.26–7.75 (m, 4H, C₆H₄); ¹³C NMR (DMSO-d₆): Δ 15.6 (CH₂) 22.9 (CH₂), 49.6 (CH₂), 54.1 (CH₂), 98.4 (pyran C-4), 116.6 (CN),118.1, 119.5, 120.8, 122.7, 124.5, 125.4, 126.8, 127.1, 129.9, 132.8, 133.5, 139.7 (C₆H₄, pyran and thiophene C), 163.1 (CO); EIMS (m/z, %): 423 [M⁺, 47]. Anal. Calcd. for C₂₁H₁₈N₃O₃S (423.46): C, 64.10; H, 4.87; N, 10.68; S, 8.15%. Found: C, 63.89; H, 4.58; N, 14.88; S, 8.52%.
for C_{19}H_{17}ClN_{6}O (380.83): C, 59.92; H, 4.50; N, 22.07%. Found: C, 59.68; H, 4.23; N, 21.79%.

2-Amino-4-(2-chlorophenyl)-6-(3,5-diamino-1-phenyl-1H-pyrazol-4-yl)-7,8-dihydro-4H-chromene-3-carbonitrile (9b)

Yellow crystals from ethanol, yield: 74%; m.p.: 212-214 °C; IR (KBr, v max cm⁻¹): 3438–3226 (3NH₂), 2929 (CH aliphatic), 2208 (CN), 1597 (C = N); ¹H NMR (300 MHz, DMSO-d₆): δ3.03 (m, 4H, CH₂-CH₂), 3.31, 6.47, 6.63 (3 s, 6H, D₂O exchangeable, 3NH₂), 6.87 (s, 1H, pyran-H₄), 7.09 (s, 1H, CH = C), 7.29–7.74 (m, 9H, C₆H₅, C₆H₄); ¹³C NMR (DMSO-d₆): δ24.6 (CH₂), δ35.0 (CH₂), 76.1 (pyrimidine C-5), 95.1 (pyran C-4), 108.4, 111.6 (C = C), 115.7 (CN), 118.4, 119.1, 121.9, 122.3, 123.9, 124.7, 125.2, 127.2, 128.4, 129.8, 131.5, 134.8, 136.8, 140.1 (C₆H₅,C₆H₄, pyran, pyrazole), 172.2 (C = N); EIMS (m/z, %): 456  [M+, 56]. Anal. Calcd. for C₂₅H₂₁ClN₆O (456.93): C, 65.71; H, 4.63; N, 18.39%. Found: C, 65.58; H, 4.44; N, 18.16%.

Synthesis of 2-amino-4-(2-chlorophenyl)-6-(4,6-diamino-2-thioxo-2,5-dihydropyrimidin-5-yl)-7,8-dihydro-4H-chromene-3-carbonitrile (11)

A mixture of compound 7 (3.48 g, 0.01 mol) and thiourea (10) (0.76 g, 0.01 mol) in absolute ethanol (30 mL) containing sodium ethoxide (0.02 mol) [prepared by dissolving metallic sodium (0.46 g, 0.02 mol) in absolute ethanol (20 mL)] was heated under reflux for 4 h. the reaction mixture was left to cool, poured onto ice/water containing few drops of hydrochloric acid. The formed solid product was collected by filtration and dried.

2-Amino-4-(2-chlorophenyl)-5-(4-methyl-3-phenylthiazol-2(3H)-ylidene)-6-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (15)

Yellow crystals from 1,4-dioxane, yield: 73%; m.p.: 185-187 °C; IR (KBr, v max cm⁻¹): 3419-3214 (NH₂, NH), 2980 (CH aliphatic), 2216 (CN), 1718 (CO), 1550 (C = C); ¹H NMR (300 MHz, DMSO-d₆): δ2.17 (s, 3H, CH₃), 3.07 (m, 4H, CH₂-CH₂), 3.32 (s, 2H, D₂O exchangeable,NH₂), 5.03 (s, 1H, thiazole H-5), 6.89 (s, 1H, pyran H-4), 7.07–7.61 (m, 9H, C₆H₅, C₆H₄); ¹³C NMR (DMSO-d₆): δ16.5 (CH₃), 25.9 (CH₂), 45.0 (CH₂), 89.1 (thiazole C-5), 95.1 (pyran C-4), 103.4, 110.6 (C = C), 116.7(CN), 118.1, 119.5, 121.6, 122.4, 123.8, 127.1, 129.7, 128.2, 131.4, 133.9, 140.5 (C₆H₅, C₆H₄, pyran, thiazole C), 162.1 (C = O); EIMS (m/z, %): 473 [M⁺, 31]. Anal. Calcd. for C₂₅H₂₁ClN₃O₂S (473.97): C, 63.12; H, 4.25; N, 8.87; S, 6.56%. Found: C, 65.59; H, 4.52; N, 8.72; S, 6.58%.

Ethyl 2-(((2-amino-4-(2-chlorophenyl)-3-cyano-6-oxo-7,8-dihydro-4H-chromen-5(6H)-ylidene)(phenylamino)methyl)thio)acetate (16)

Yellow crystals from 1,4-dioxane, yield: 79%; m.p.: 155–157 °C; IR (KBr, v max cm⁻¹): 3419–3214(NH₂, NH), 2980 (CH aliphatic), 2215 (CN), 1733, 1699 (2CO), 1621 (C = C); ¹H NMR (300 MHz, DMSO-d₆): δ8.10, 10.10 (3H, J = 6.6 Hz, OCH₂CH₃), 3.01 (m, 4H, CH₂-CH₂), 3.31 (s, 2H, D₂O exchangeable,NH₂), 4.31 (q, 2H, J = 6.6 Hz, OCH₂CH₃), 4.93 (s, 2H, CH₂), 6.93 (s, 1H, pyran H-4), 7.24–7.73 (m, 9H, C₆H₅, C₆H₄), 8.81 (s, 1H, D₂O exchangeable, NH), ¹³C NMR (DMSO-d₆): δ14.2 (CH₃), 26.3 (CH₃), 45.8 (CH₂), 55.8 (CH₂), 66.5 (CH₂), 97.1 (pyran C-4), 101.3, 109.1 (C = C), 116.4 (CN), 119.1, 120.5, 121.3, 122.9, 123.5, 126.9, 127.4, 127.9, 128.8, 130.8, 131.3, 133.2 (C₆H₅, C₆H₄, pyran C), 162.1, 164.5 (2C = O); EIMS (m/z, %): 522 [M⁺, 31]. Anal. Calcd. for C₂₇H₂₃ClN₄O₂S (522.02): C, 62.12; H, 4.63; N, 8.05; S, 6.14%. Found: C, 62.34; H, 4.77; N, 8.26; S, 6.42%.

3-Phenyl-2-thioxo-2,3,4,5-tetrahydrobenzo[d]thiazol-6(7H)-one (18)

Elemental sulfur (0.32 g, 0.01 mol) followed by phenylisothiocyanate (1.35 mL, 0.01 mol) were added to a solution of cyclohexane1,4-dione (1.12 g, 0.01 mol) in absolute ethanol...
(30 mL) containing triethylamine (0.50 mL). The whole reaction mixture was heated under reflux for 2 h, then left to cool and the formed solid product was filtered and dried.

Yellow crystals from ethanol, yield: 65%; m.p.: 155–157 °C; IR (KBr, v max cm⁻¹): 3049 (CH aromatic), 2920 (CH aliphatic), 1699 (CO), 1644 (C = C), 1207 (C = S); ¹H NMR (300 MHz, DMSO-d₆): δ 3.17 (m, 4H, CH₂-CH₂), 4.04 (s, 2H, CH₂), 7.09–7.30 (m, 5H, CH₃), 7.12–7.56 (m, 6H, pyran H-4 and C₆H₅); ¹³C NMR (DMSO-d₆): δ 22.6 (CH₂), 45.3 (CH₂), 66.3 (CH₂), 124.1, 124.8, 128.9, 130.4, 139.4, 142.3 (C₆H₅ thioene C), 161.8 (CO), 180.1 (C = S); EIMS (m/z, %): 261 [M⁺, 65]. Anal. Calcd. for C₁₉H₁₇N₃O₂S₂ (383.49): C, 59.51; H, 4.28; N, 10.96; S, 24.54%. Found: C, 59.69; H, 4.41; N, 5.74; S, 24.30%.

**Synthesis of 9-ethoxy-2H-chromeno[6,5-d]thiazole derivatives 20a,b**

Triethylthioformate (1.48 mL, 0.01 mol) followed by either molononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 mL, 0.01 mol) were added to a solution of compound 18 (2.61 g, 0.01 mol) in absolute ethanol (30 mL) containing triethylamine (0.50 mL). The reaction mixture was refluxed for 2 h, then left to cool, and the formed solid product was filtered and dried.

9-Ethoxy-7-aminoo-3-phenyl-2-thioxo-2,3,4,5-tetrahydro-2H-chromeno[6,5-d]thiazole-8-carbonitrile (20a)

Light brown crystals from 1,4-dioxane, yield: 51%; m.p.: 129–131 °C; IR (KBr, v max cm⁻¹): 3435, 3378 (NH₂), 3059 (CH aromatic), 2929 (CH aliphatic), 1663 (C = C), 1205 (C = S); ¹H NMR (300 MHz, DMSO-d₆): δ 1.18 (t, 3H, J = 7.5 Hz, OCH₂CH₃), 3.17 (m, 4H, 2CH₂), 3.42 (q, 2H, J = 7.5 Hz, OCH₂CH₃), 6.75 (s, 2H, D₂O exchangeable, NH₂), 7.12–7.56 (m, 6H, pyran H-4 and C₆H₅); ¹³C NMR (DMSO-d₆): δ 23.2 (CH₂), 45.3 (CH₂), 55.7 (CH₂), 98.7 (pyrrole C-4), 116.4 (CN), 118.7, 122.8, 123.6, 124.4, 128.8, 129.1, 131.5, 132.9, 140.8, 149.7 (C₆H₅ pyran, thiazole C), 182.0 (C = S); EIMS (m/z, %): 383 [M⁺, 48]. Anal. Calcd. for C₁₆H₁₁N₃S₃ (341.49): C, 59.51; H, 4.47; N, 10.96; S, 16.72%. Found: C, 59.74; H, 4.28; N, 11.19; S, 16.60%.

**Synthesis of 2,3,4,5-tetrahydrothieno[2′,3′:3,4]benzo[1,2-d]thiazole derivatives 21a,b**

Elemental sulfur (0.32 g, 0.01 mol) followed by either molononitrile (5a) (0.66 g, 0.01 mol) or ethyl cyanoacetate (5b) (1.13 mL, 0.01 mol) were added to a solution of compound 18 (2.61 g, 0.01 mol) in absolute ethanol (30 mL) containing triethylamine (0.50 mL). The whole reaction mixture was refluxed for 2 h, then left to cool, and the formed solid product was filtered and dried.

7-Amino-3-phenyl-2-thioxo-2,3,4,5-tetrahydrothieno[2′,3′:3,4]benzo[1,2-d]thiazole-6-carbonitrile (21a)

Green crystals from ethanol, yield: 61%; m.p.: 144–146 °C; IR (KBr, v max cm⁻¹): 3407, 3202 (NH₂), 3026 (CH aromatic), 2926 (CH aliphatic), 2194 (CN), 1597 (C = C), 1197 (C = S); ¹H NMR (300 MHz, DMSO-d₆): 8 3.17 (m, 4H, CH₂, 2CH₂), 6.82 (s, 2H, D₂O exchangeable, NH₂), 116.3 (CN), 118.3, 121.7, 123.5, 127.9, 128.6, 129.1, 131.9, 134.5, 139.5 (C₆H₅ thiophene, thiazole C), 180.9 (C = S); EIMS (m/z, %): 341 [M⁺, 46]. Anal. Calcd. for C₁₈H₁₅N₃S₃ (341.47): C, 56.28; H, 3.25; N, 12.31; S, 28.17%. Found: C, 56.50; H, 3.38; N, 12.53; S, 28.31%.

Ethyl 7-amino-3-phenyl-2-thioxo-2,3,4,5-tetrahydrothieno[2′,3′:3,4]benzo[1,2-d]thiazole-6-carboxylate (21b)

Light brown crystals from ethanol, yield: 57%; m.p.: 130–132 °C; IR (KBr, v max cm⁻¹): 3447, 3205 (NH₂), 3026 (CH aromatic), 2926 (CH aliphatic), 1698(CO), 1592 (C = C), 1236 (C = S); ¹H NMR (300 MHz, DMSO-d₆): 8 1.24 (t, 3H, J = 6.9 Hz, OCH₂CH₃), 3.32 (m, 4H, 2CH₂), 6.82 (q, 2H, J = 6.9 Hz, OCH₂CH₃), 6.73 (s, 2H, D₂O exchangeable, NH₂), 7.09–7.59 (m, 5H, C₆H₅); ¹³C NMR (DMSO-d₆): 8 15.9 (CH₃), 23.2 (CH₂), 45.3 (CH₃), 55.8 (CH₂), 118.6, 119.7, 122.2, 123.5, 128.1, 128.9, 129.5, 132.1, 135.7, 139.9 (C₆H₅ thiophene, thiazole C), 161.4 (CO), 180.9 (C = S); EIMS (m/z, %): 388 [M⁺, 71]. Anal. Calcd. for C₁₈H₁₆N₃O₂S₃ (388.53): C, 55.64; H, 4.15; N, 7.21; S, 24.76%. Found: C, 55.53; H, 4.48; N, 7.39; S, 24.60%.
Synthesis of 3,4,5,9-tetrahydro-2H-chromeno[6,5-d]thiazole derivatives (23a-d)

A mixture of compound 18 (2.61 g, 0.01 mol), either malononitrile (5a) (0.66 g, 0.01 mol) or ethyl cyanoacetate (6b) (1.13, 0.01 mol) and either benzaldehyde (3a) (1.06 g, 0.01 mol) or 4-chlorobenzaldehyde (22) (1.4 g, 0.01 mol) in absolute ethanol (40 mL) containing triethylamine (0.5 mL) was heated under reflux for 3 h. The reaction mixture was left to cool to room temperature, poured onto ice/water, and neutralized by hydrochloric acid. The precipitated solid was filtered, washed with water, and dried.

7-Amino-3,9-diphenyl-2-thioxo-3,4,5,9-tetrahydro-2H-chromeno[6,5-d]thiazole-8-carbonitrile (23a)

Brown crystals from 1,4-dioxane, yield: 55%; m.p.: 115–117 °C; IR (KBr, ν max cm⁻¹): 3463, 3237 (NH₂), 3059 (CH aromatic), 2925 (CH aliphatic), 2208 (CN), 1590 (C = C), 1259 (C = S); ¹H NMR (300 MHz, DMSO-d₆): δ 2.33 (m, 4H, CH₂), 6.90 (s, 2H, D₂O exchangeable, NH₂), 7.09–7.59 (m, 11H, pyran-4 and 2C₆H₅); ¹³C NMR (DMSO-d₆): δ 24.5 (CH₂), 45.1 (CH₂), 98.4 (pyran-C-4), 116.1 (CN), 118.1, 118.6, 119.7, 121.0, 122.2, 122.8, 123.5, 124.9, 125.5, 128.9, 129.5, 132.1, 139.9, 143.6 (2C₆H₅, pyran and thiazole C), 181.4 (C = S); EIMS (m/z, %): 415 [M⁺, 58]. Anal. Calcd. for C₂₃H₁₅N₃O·0.5H₂O: C, 66.48; H, 4.12; N, 10.11; S, 15.60%. Found: C, 66.4; H, 4.3; N, 10.39; S, 15.49%.

7-Amino-9-(4-chlorophenyl)-3-phenyl-2-thioxo-3,4,5,9-tetrahydro-2H-chromeno[6,5-d]thiazole-8-carboxylate (23b)

Light brown crystals from ethanol, yield: 88%; m.p.: 98–100 °C; IR (KBr, ν max cm⁻¹): 3431, 3240 (NH₂), 3034 (CH aromatic), 2936 (CH aliphatic), 2192 (CN), 1595 (C = C), 1258 (C = S); ¹H NMR (300 MHz, DMSO-d₆): 83.32 (m, 4H, 2CH₃), 6.84 (s, 2H, D₂O exchangeable, NH₂), 7.09–7.59 (m, 10H, pyran H-4 and 2C₆H₅); ¹³C NMR (DMSO-d₆): δ 224.1 (CH₂), 42.2 (CH₂), 98.4 (pyran-C-4), 116.8 (CN), 118.5, 118.9, 119.6, 121.5, 122.7, 122.3, 123.8, 124.9, 125.8, 128.3, 129.1, 132.4, 140.9, 144.3 (C₆H₅, pyran, and thiazole C), 181.4 (C = S); EIMS (m/z, %): 462 [M⁺, 38]. Anal. Calcd. for C₂₅H₂₁ClN₂O₃S: 462.58: C, 64.6; H, 4.48; N, 6.06; S, 13.86%. Found: C, 64.73; H, 4.48; N, 5.89%; S, 14.10%.

Ethyl 7-amino-3-phenyl-2-thioxo-3,4,5,9-tetrahydro-2H-chromeno[6,5-d]thiazole-8-carboxylate (23c)

Reddish brown crystals from ethanol, yield: 51%; m.p.: 163–165 °C; IR (KBr, ν max cm⁻¹): 3433, 3205 (NH₂), 3022 (CH aromatic), 2952 (CH aliphatic), 1725 (CO), 1544 (C = C), 1235 (C = S); ¹H NMR (300 MHz, DMSO-d₆): δ 1.29 (t, 3H, J = 6.5 Hz, OCH₂CH₃), 3.31 (m, 4H, 2CH₂), 4.32 (q, 2H, J = 6.5 Hz, OCH₂CH₃), 6.61 (s, 2H, D₂O exchangeable, NH₂), 7.10–7.50 (m, 11H, pyran H-4 and 2C₆H₅); ¹³C NMR (DMSO-d₆): δ 16.9 (CH₃), 25.0 (CH₂), 44.7 (CH₂), 55.1 (CH₃), 98.0 (pyran-C-4), 117.9, 118.1, 119.9, 121.2, 122.0, 122.6, 123.9, 124.5, 125.7, 129.6, 134.3, 139.6, 142.1 (2C₆H₅, pyran and thiazole C), 161.6 (CO), 180.4 (C = S); EIMS (m/z, %): 462 [M⁺, 38]. Anal. Calcd. for C₃₂H₂₂N₂O₅S₂ (497.03): C, 70.41; H, 4.26; N, 5.64; S, 12.90%. Found: C, 70.53; H, 4.16; N, 5.38; S, 12.80%.

Conclusion

Tetrahydro-4H-chromene-3-carbonitrile derivatives 4a-c and tetrahydrobenzox[d]thiazole derivatives 18 were synthesized starting from 1,4-cyclohexane dione (1). Compounds 4b and 18 were used for further heterocyclization reactions to synthesize pyrazole, pyrimidine, thiazole, fused thiophene, and fused pyran derivatives. The screened compounds were designed as mimics of the transition state of RNA2'-O-methylation were screened against several viral RNA 2'-OMTases from SARS-CoV (nsp10/nsp16 complex), Zika, West Nile, dengue, vaccinia (VP39) viruses. At the same time, the compounds were tested against human RNA N7-MTase (hRNMT) and selected viral N7-MTases such as SARS-CoV nsp14 and vaccinia D1-D12 complex to evaluate their specificity. Compounds 4a, 4b, 6a, 6c, 6e, 9a, 9b, 15, 16, 21b, and 23b showed high % inhibitions against SARs-Cov nsp14 with values 93.42, 87.49, 98.23, 88.15, 89.24, 96.31, 93.28, 89.25, 89.20, 87.24, and 94.49, respectively. The obtained results through this work indicated that these
compounds were good candidates as anti-Covid-19 this will encourage further work in the future.

**Author contributions**

First author R.M. Mohareb had the idea of writing this article, and he performed the literature survey and data research. The second author N. Y. Abdo was responsible about revising the manuscript and writing the text and the references of this work.

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**Declarations**

**Conflict of interest**  The authors declare no conflict of interest, financial, or otherwise.

**Ethical Approval**  No related ethical issues.

**Informed consent**  Informed consent was obtained from all participants included in the study.

**Consent for Publication**  This work is consent for publication through the Journal formats.

**Consent to publish**  The authors promise that if the manuscript is accepted, it will not be published elsewhere in the same form, in English or in any other language, without the written consent of the Publisher. There are no conflicts of interest to declare.

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