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ORIGINAL PAPER

# Heterocyclic compounds derived from cyclohexane-1,4-dione: synthesis of tetrahydro-4*H*-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-4*H*-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-2*H*-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'-*O*MTases 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-4*H*-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

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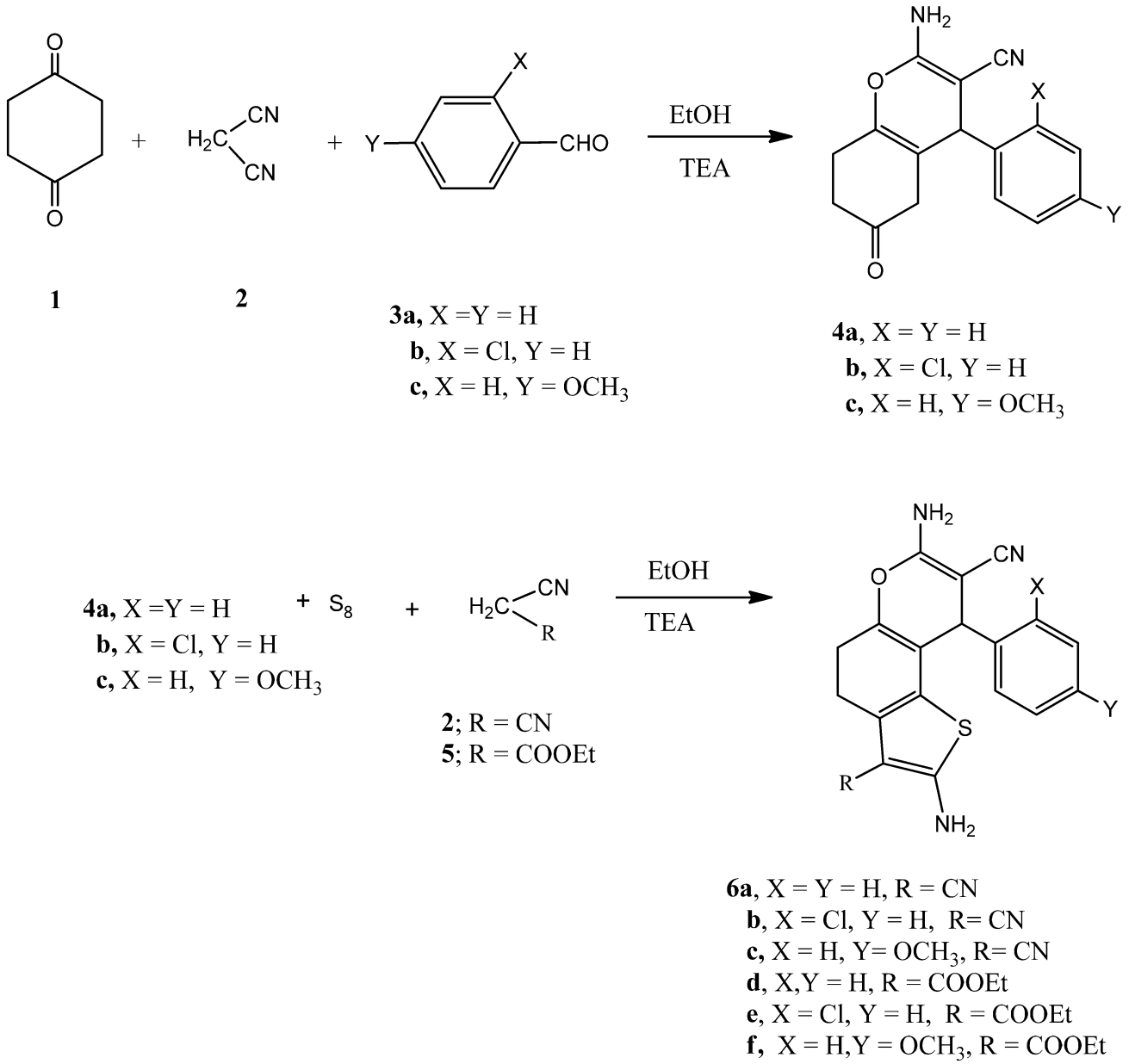
readily provide greater atom-economic access to a diverse spectrum of compounds and their libraries for screening. Recently, our research group was involved through the studying the multi-component reactions of cyclohexandiones [25–28]. As a continuation of this program we are presenting in this work 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 cyclohexandione 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'-*O*MTases 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** 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 δ3.05 ppm integrating for four hydrogens of the $CH_2$-$CH_2$ moiety and another multiplet at δ7.23–7.62 ppm corresponding to the aromatic protons. Moreover, the presence of a singlet at δ4.05 ppm for the active methylene moiety located between the carbonyl group and the $sp^2$ carbon and another singlet at δ6.69 ppm for the pyran *H*-4, beside a third singlet at δ3.31 ppm ($D_2O$ exchangeable) corresponding to the $NH_2$ group. In addition, the $^{13}$C NMR data revealed the appearance of signals at δ22.6 ($CH_2$), 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 ($C_6H_5$, pyran), 161.8 (CO).

Compounds **4a-c** containing the α-oxomethylene moiety 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-*f*]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.

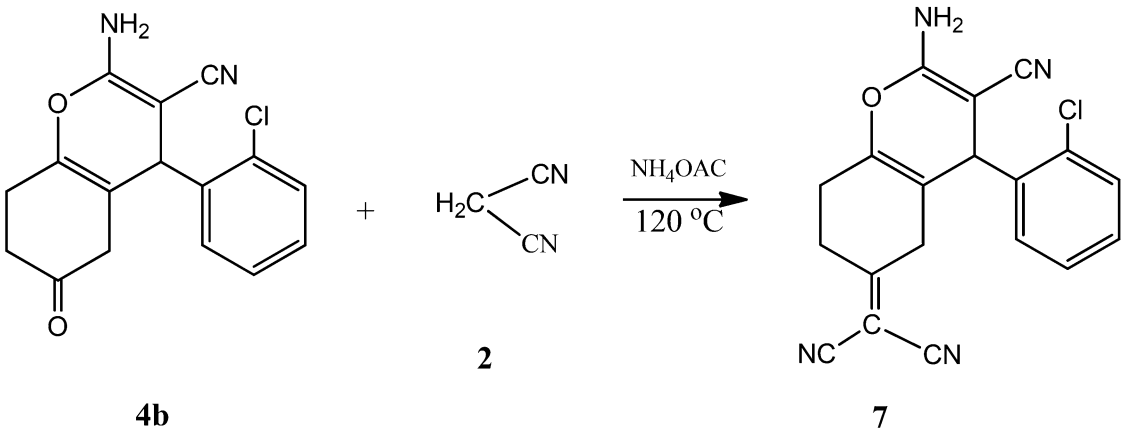
Recently, our research group was involved through a comprehensive program aiming to synthesis thiazole and thiophene derivatives through the reaction of phenylisothiocyanate with active methylene reagent in basic dimethylformamide solution to give the corresponding intermediate potassium sulfide salt. Heterocyclization of the latter intermediate with α-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 thiazole derivative **15**. On the other hand, the intermediate **13** reacted with α-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(7*H*)-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-2*H*-chromeno[6,5-*d*]thiazole derivatives **23a-d**, respectively (Scheme 4).

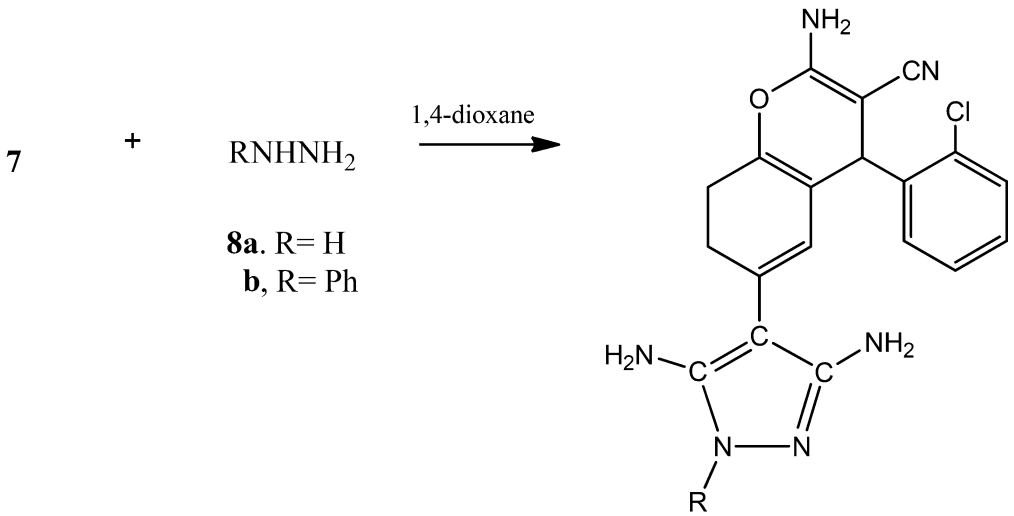
## RNA methyltransferase activity assays

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'-*O*MTases 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'-*O*MTases 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,

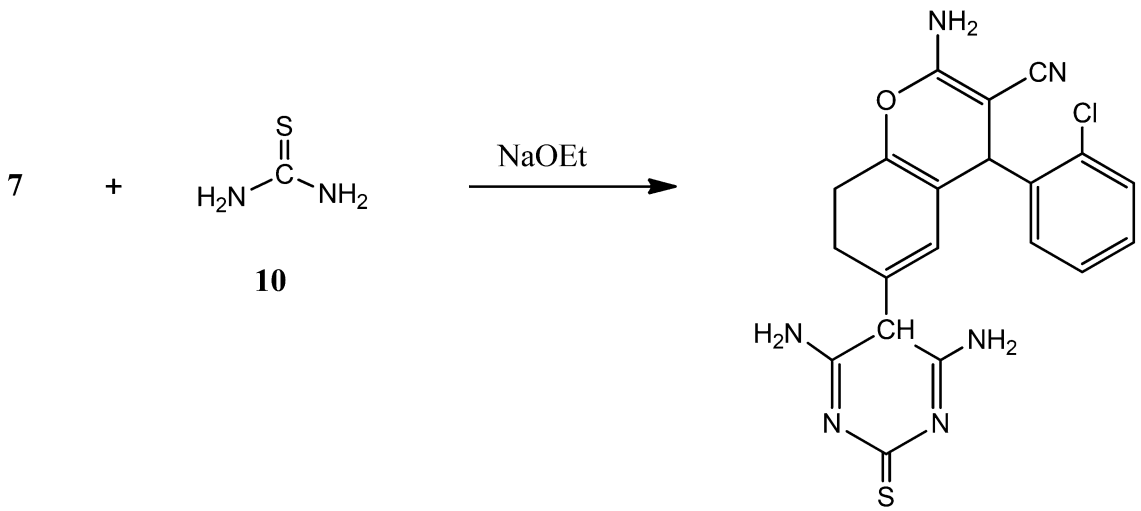



**4b** **2** **7**




**8a**. R= H
**b**, R= Ph

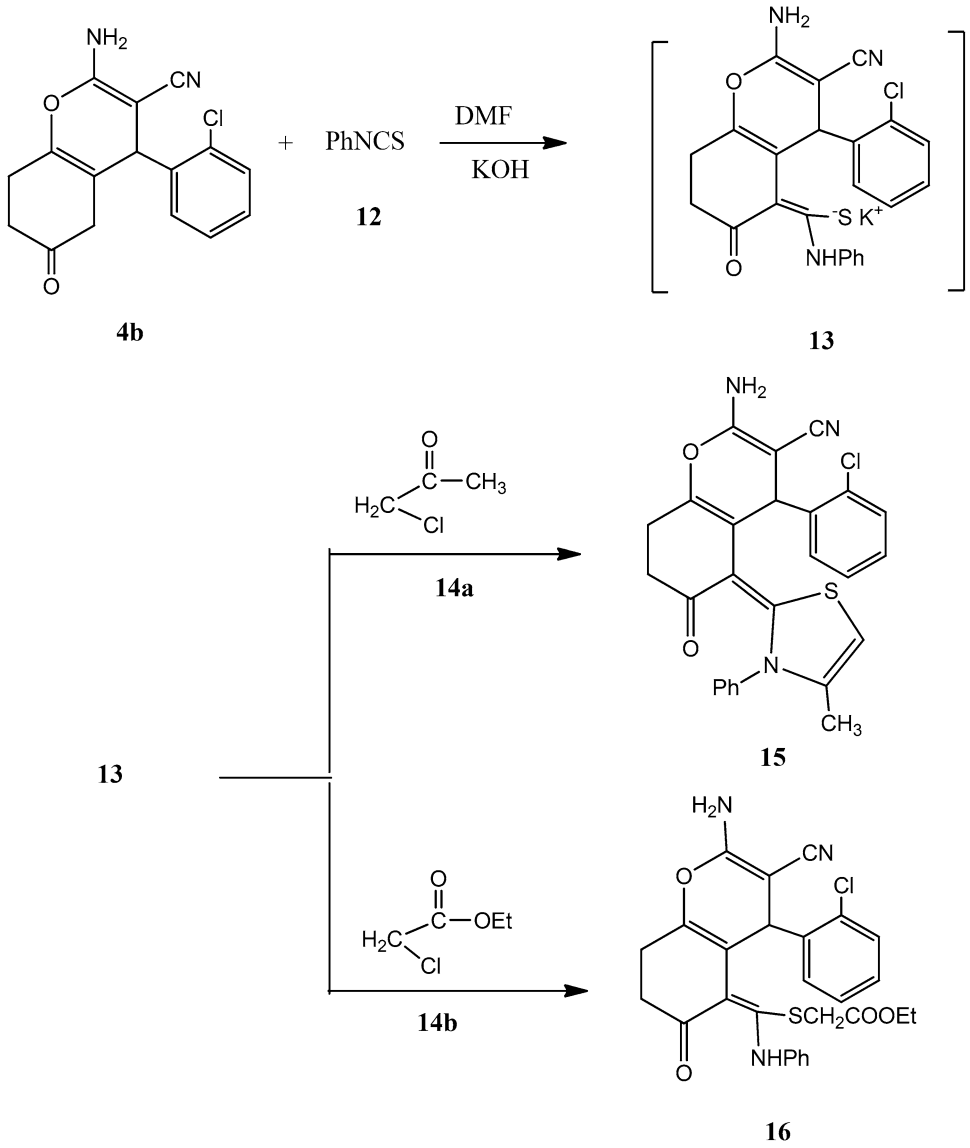
**9a**, R= H
**b**, R= Ph




**10** **11**

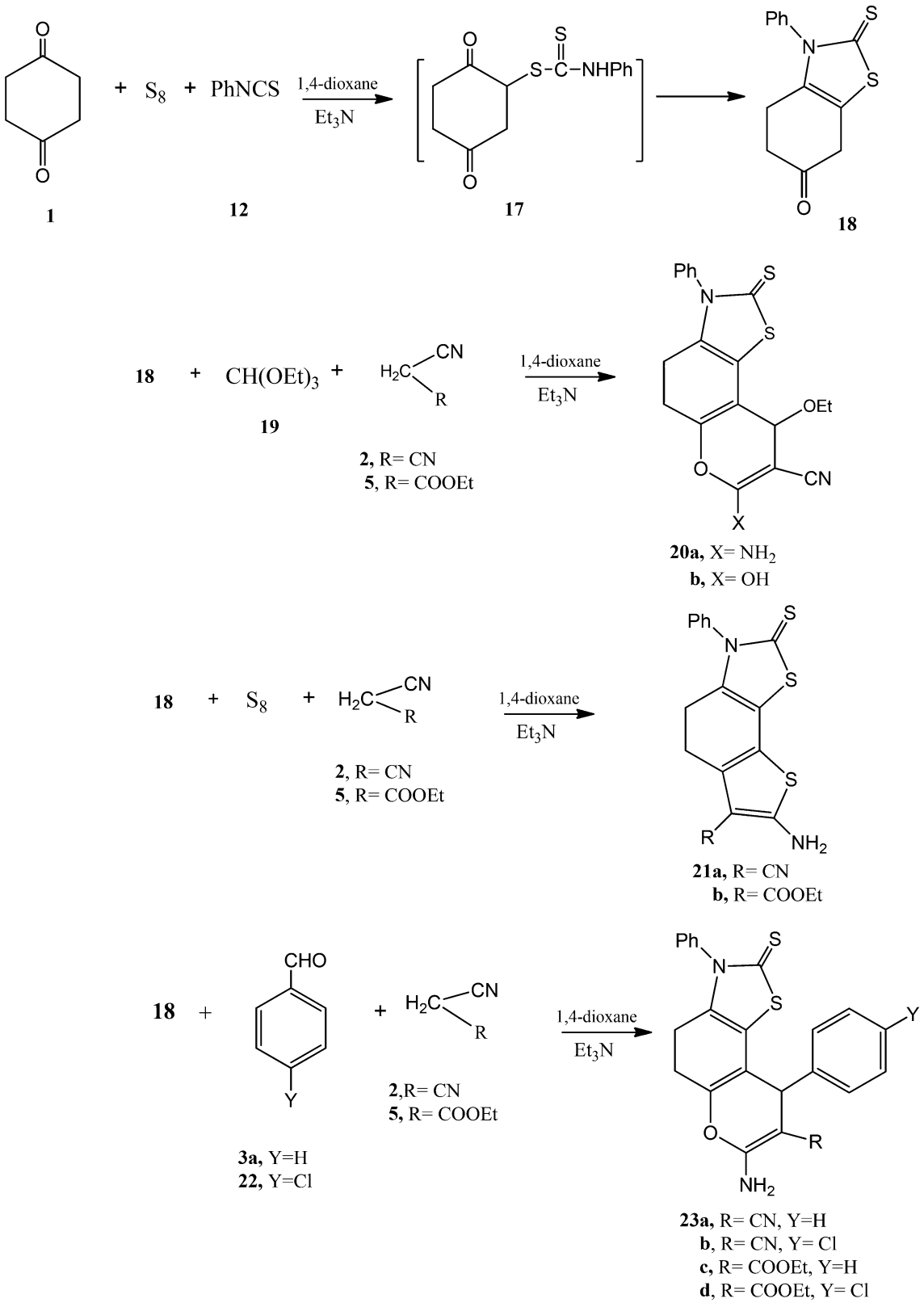
**Scheme 2** Synthesis of compounds **7**, **9a,b,** and **11**

**Scheme 3** Synthesis of compounds **15** and **16**




93.42, 92.21, 92.52, 95.45, 96.12, 90.41, 84.30, 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 = $OCH_3$) 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 = $OCH_3$, 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 $OCH_3$ 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 $IC_{50}$'s indicated that they are active toward Cov nap14. Compounds **4a**, **4b**, **6c**, **6e**, **9a**, **9b**, **16**, **23b,** and **23d** showed $IC_{50}$'s < 1.0 μM. In addition, most of the




**Scheme 4** Synthesis of compounds **18, 20a,b, 21a,b,** and **23a-d**

**Table 1** Screening for inhibitory activity of sinefungin and compounds **4a-23d** at 50 μMonN7-MTases

| Compd | % of inhibition at 50 μM (%)[a] | | |
|---|---|---|---|
| | SARs-Cov nsp 14 | Vaccinia virus | |
| | | D1-D12 | hRNMT |
| 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 ± 8.92 | 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 |

[a]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

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

**Table 2** $IC_{50}$ values of the newly synthesized compounds on SARS-Cov nap14 and human RNMT activities

| Compd | SARS-Cov nap14 $IC_{50}$[a] (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 ± 6.27 |
| 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 ± 6.28 |
| 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 ± 3.80 |
| 23d | 0.49 ± 0.13 | < 0.05 |
| Sinefungin[b] | 0.36 | < 0.05 |

[a]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).

### Synthesis of 5,6,7,8-tetrahydro-4*H*-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.

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

Green crystals from ethanol, yield: 75%; m.p.: 210–213 °C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3438, 3240($NH_2$), 2949 (CH aliphatic), 2211 (CN), 1702 (CO), 1530 (C = C); $^1$H NMR (300 MHz, DMSO-$d_6$): δ3.05 (m, 4H, $CH_2$-$CH_2$), 3.31 (s, 2H, $D_2O$ exchangeable, $NH_2$), 4.05 (s, 2H, $CH_2$), 6.69 (s, 1H, pyran *H*-4), 7.23–7.62 (m, 5H, $C_6H_5$); $^{13}$C NMR (DMSO-$d_6$):δ22.6 ($CH_2$),50.3 ($CH_2$), 66.3 ($CH_2$), 96.9 (pyran C-4),116.2 (CN),118.4, 120.8, 121.0, 121.7, 125.4, 126.1, 128.9, 130.0 ($C_6H_5$, pyran), 161.8 (CO); EIMS (m/z, %): 266 [$M^+$, 84]. Anal. Calcd. For $C_{16}H_{14}N_2O_2$ (266.29): C, 72.16; H, 5.30; N, 10.52%. Found: C, 72.34; H, 5.08; N, 10.39%.

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

Pale brown crystals from ethanol, yield: 82%; m.p.: 145–147 °C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3433, 3228 ($NH_2$), 2981 (CH aliphatic), 2199 (CN), 1698 (CO), 1588 (C = C);$^1$H NMR (300 MHz, DMSO-$d_6$): δ3.06 (m, 4H, $CH_2$-$CH_2$), 3.31 (s, 2H, $D_2O$ exchangeable, $NH_2$), 3.98 (s, 2H, $CH_2$), 6.65 (s, 1H, pyran *H*-4), 7.28–7.57 (m, 4H, $C_6H_4$); $^{13}$C NMR (DMSO-$d_6$): δ23.2 ($CH_2$),49.6 ($CH_2$), 65.9 ($CH_2$), 97.1 (pyran C-4),116.6 (CN), 118.0, 119.7, 121.4, 121.9, 126.2, 126.7, 128.5, 129.4 ($C_6H_4$, pyran), 162.3 (CO); EIMS (m/z, %): 300 [$M^+$, 61]. Anal. Calcd. For $C_{16}H_{13}ClN_2O_2$ (330.74): C, 63.90; H, 4.36; N, 9.31%. Found: C, 63.58; H, 4.16; N, 9.63%.

### 2-Amino-4-(4-methoxyphenyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4c)

Green crystals from 1,4-dioxane,yield: 76%; m.p.: 180–183 °C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3433, 3369 ($NH_2$), 2945 (CH aliphatic), 2200 (CN), 1695 (CO), 1606 (C = C); $^1$H NMR (300 MHz, DMSO-$d_6$): δ3.07 (m, 4H, $CH_2$-$CH_2$), 3.31 (s, 2H, $D_2O$ exchangeable, $NH_2$), 3.86 (s, 3H, $OCH_3$), 3.97 (s, 2H, $CH_2$), 6.81 (s, 1H, pyran *H*-4), 7.14, 7.85 (2d, 4H, $C_6H_4$); $^{13}$C NMR (DMSO-$d_6$):δ22.1 ($CH_2$),50.8 ($CH_2$), 55.3 ($OCH_3$), 66.0 ($CH_2$), 97.6 (pyran C-4), 116.7 (CN), 118.1, 120.4, 121.3, 121.8, 125.0, 126.5, 128.7, 130.8 ($C_6H_4$, pyran), 162.8 (CO); EIMS (m/z, %): 296 [$M^+$, 42]. Anal. Calcd. for $C_{17}H_{16}N_2O_3$ (296.32): C, 68.91; H, 5.44; N, 9.45%. Found: C, 68.72; H, 5.19; N, 9.77%.

### Synthesis of 4*H*-thieno[2,3-*f*]chromene derivatives 6a-f

Elemental sulfur (0.32 g, 0.01 mol) and either malononitrile (**2**) (0.66 g, 0.01 mol) or ethyl cyanoacetate (**5b**) (1.07 g, 0.01 mol) were added to a solution of either compound **4a** (2.66 g, 0.01 mol), **4b** (3.0 g, 0.01 mol) or **4c** (2.96 g, 0.01 mol) in absolute ethanol (40 mL) containing triethylamne (0.50 mL). The reaction mixture was heated under reflux for 3 h, then neutralized by ice/water mixture containing a few drops of hydrochloric acid. The precipitated product was filtered off, washed, and dried.

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

Green crystals from 1,4-dioxane, yield: 95%; m.p.: 205–207 °C; IR (KBr, υ max cm-1): 3448–3223 ($2NH_2$), 2959 (CH aliphatic), 2210, 2192 (2CN),1548 (C = C); $^1$H NMR (300 MHz, DMSO-$d_6$): δ3.05 (m, 4H, $CH_2$-$CH_2$), 3.36, 6.53 (2 s, 4H, $D_2O$ exchangeable, $2NH_2$), 6.79 (s, 1H, pyran-H4), 7.15–7.60 (m, 5H, $C_6H_5$); $^{13}$C NMR (DMSO-$d_6$): δ23.0 ($CH_2$), 49.7 ($CH_2$), 98.1 (pyran C-4), 115.9, 116.5 (2CN), 119.0, 120.4, 121.5, 122.3, 124.8, 125.6, 126.7, 127.9, 129.7, 132.9, 136.8, 138.4 ($C_6H_5$, pyran and thiophene); EIMS (m/z, %): 346 [$M^+$, 34]. Anal. Calcd. For $C_{19}H_{14}N_4OS$ (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-(2-chlorophenyl)-5,9-dihydro-4*H*-thieno[2,3-*f*]chromene-3,8-dicarbonitrile (6b)

Yellow crystals from ethanol, yield: 93%; m.p.: 155–157 °C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3437–3229 ($2NH_2$), 2923 (CH aliphatic), 2219, 2207 (2CN),1577 (C = C); $^1$H NMR (300 MHz, DMSO-$d_6$): δ3.05 (m, 4H, $CH_2$-$CH_2$), 3.36, 6.55 (2 s, 4H, $D_2O$ exchangeable, $2NH_2$), 6.82 (s, 1H, pyran *H*-4), 7.24–7.76 (m, 4H, $C_6H_4$); $^{13}$C NMR (DMSO-$d_6$): δ23.4 ($CH_2$), 49.3 ($CH_2$), 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, 138.8, 139.2 ($C_6H_4$, pyran and thiophene); EIMS (m/z, %): 380 [$M^+$, 57]. Anal. Calcd. for $C_{19}H_{13}ClN_4OS$ (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-(4-methoxyphenyl)-5,9-dihydro-4*H*-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, $\upsilon_{max}$ $cm^{-1}$): 3435–3227($2NH_2$), 2942 (CH aliphatic), 2234, 2210 (2CN),1626 (C = C); $^1$H NMR (300 MHz, DMSO-$d_6$): δ3.01 (m, 4H, $CH_2$-$CH_2$), 3.34, 6.72 (2 s, 4H, $D_2O$ exchangeable, $2NH_2$), 3.89 (s, 3H, $OCH_3$), 6.86(s, 1H, pyran *H*-4), 6.92–7.36 (m, 4H, $C_6H_4$); $^{13}$C NMR (DMSO-$d_6$): δ23.6 ($CH_2$),48.1 ($CH_2$), 55.0 ($OCH_3$), 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

($C_6H_4$, pyran and thiophene); EIMS (m/z, %): 376 [$M^+$, 29]. Anal. Calcd. for $C_{20}H_{16}N_4O_2S$ (376.45): C, 63.81; H, 4.28; N, 14.88; S, 8.52%. Found: C, 63.59; H, 4.52; N, 15.12; S, 8.37%.

### Ethyl 2,7-diamino-8-cyano-9-phenyl-5,9-dihydro-4*H*-thieno[2,3-*f*]chromene-3-carboxylate (6d)

Green crystals from 1,4-dioxane, yield: 60%; m.p.: 190–193 °C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3438–3244 ($2NH_2$), 2951 (CH aliphatic), 2209 (CN), 1701 (CO), 1529 (C = C); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.15 (t, 3H, $J$ = 7.5 Hz, $OCH_2\underline{CH_3}$), 3.05 (m, 4H, $CH_2$-$CH_2$), 3.30, 6.51 (2 s, 4H, $D_2O$ exchangeable, $2NH_2$), 4.05 (q, 2H, $J$ = 7.5 Hz, $O\underline{CH_2}CH_3$), 6.74 (s, 1H, pyran *H*-4), 7.18–7.64 (m, 5H, $C_6H_5$); $^{13}$C NMR (DMSO-$d_6$):δ 15.9 ($CH_3$), 24.6 ($CH_2$),48.9 ($CH_2$), 53.4 ($CH_2$), 97.5 (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, 139.1 ($C_6H_5$, pyran and thiophene), 163.1(CO); EIMS (m/z, %): 393 [$M^+$, 47]. Anal. Calcd. for $C_{21}H_{19}N_3O_3S$ (393.46): C, 64.10; H, 4.87; N, 10.68; S, 8.15%. Found: C, 63.89; H, 4.58; N, 10.42; S, 8.37%.

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

Yellow crystals from ethanol, yield: 70%; m.p.: 145–147 °C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3435–3236 ($2NH_2$), 2974 (CH aliphatic), 2209 (CN), 1732 (CO), 1584 (C = C); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.16 (t, 3H, $J$ = 7.5 Hz, $OCH_2\underline{CH_3}$), 3.08 (m, 4H, $CH_2$-$CH_2$), 3.35, 6.55 (2 s, 4H, $D_2O$ exchangeable, $2NH_2$), 4.14 (q, 2H, $J$ = 7.5 Hz, $O\underline{CH_2}CH_3$), 6.85 (s, 1H, pyran *H*-4), 7.26–7.75 (m, 4H, $C_6H_4$); $^{13}$C NMR (DMSO-$d_6$):δ 15.6 ($CH_3$) 22.9 ($CH_2$), 49.6 ($CH_2$), 54.1 ($CH_2$), 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, 135.3, 139.7 ($C_6H_4$, pyran and thiophene C), 163.1 (CO); EIMS (m/z, %): 427 [$M^+$, 52]. Anal. Calcd. for $C_{21}H_{18}ClN_3O_3S$ (427.90): 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-8-cyano-9-(4-methoxyphenyl)-5,9-dihydro-4*H*-thieno[2,3-*f*]chromene-3-carboxylate (6f)

Green crystals from 1,4-dioxane, yield: 75%; m.p.: 195–198 °C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3434–3230 ($2NH_2$), 2942 (CH aliphatic), 2205 (CN), 1711 (CO), 1535 (C = C);$^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.15 (t, 3H, $J$ = 7.5 Hz, $OCH_2\underline{CH_3}$), 3.17 (m, 4H, $CH_2$-$CH_2$), 3.36, 6.51 (2 s, 4H, $D_2O$ exchangeable, $2NH_2$), 3.89 (s, 3H, $OCH_3$),4.21 (q, 2H, $J$ = 7.5 Hz, $O\underline{CH_2}CH_3$), 6.82 (s, 1H, pyran *H*-4), 6.94–7.31 (m, 4H, $C_6H_4$); $^{13}$C NMR (DMSO-$d_6$):δ 15.4 ($CH_3$) 24.7 ($CH_2$),48.5 ($CH_2$), 52.0 ($CH_2$), 55.8 ($OCH_3$), 98.2 (pyran C-4), 116.7(CN),118.8, 120.8, 121.3, 122.7, 124.1, 125.7, 126.5, 127.3, 130.9, 132.8, 135.6, 139.5 ($C_6H_4$, pyran and thiophene), 163.6 (CO); EIMS (m/z, %): 423 [$M^+$, 43]. Anal. Calcd. for $C_{22}H_{21}N_3O_4S$ (423.48): C, 62.40; H, 5.00; N, 9.92; S, 7.57%. Found: C, 62.59; H, 4.82; N, 10.12; S, 7.34%.

### Synthesis of 2-(2-amino-4-(2-chlorophenyl)-3-cyano-7,8-dihydro-4*H*-chromen-6(5*H*)-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, $\upsilon_{max}$ $cm^{-1}$): 3438, 3223 ($NH_2$), 2920 (CH aliphatic), 2226–2210 (3CN),1593 (C = C); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 3.18 (m, 4H, $CH_2$-$CH_2$), 3.38 (s, 2H, $D_2O$ exchangeable, $NH_2$), 4.01 (s, 2H, $CH_2$), 6.89 (s, 1H, pyran *H*-4), 7.26–7.67 (m, 4H, $C_6H_4$); $^{13}$C NMR (DMSO-$d_6$):δ 24.6 ($CH_2$), 46.0 ($CH_2$), 66.4 ($CH_2$), 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 ($C_6H_4$, pyran C); EIMS (m/z, %): 348 [$M^+$, 59]. Anal. Calcd. for $C_{19}H_{13}ClN_4O$ (348.79): C, 65.43; H, 3.76; N, 16.06%. Found: C, 65.59; H, 3.52; N, 15.92%.

### Synthesis of 3,5-diamino-1*H*-pyrazol-4-yl)-7,8-dihydro-4*H*-chromene derivatives 9a,b

Either of hydrazine hydrate (**8a**) (0.50 mL, 0.01 mol) or phenyl hydrazine (**8b**) (1.08 mL, 0.01 mol) was added to a solution of compound **7** (3.48 g, 0.01 mol) in absolute ethanol (40 mL). The reaction mixture was heated under reflux for 2 h then left to cool. The solid product in each case was precipitated on cooling, filtered, washed, and dried.

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

Light brown crystals from ethanol, yield: 66%; m.p.: 199–201 °C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3435–3235 ($3NH_2$, NH), 2930 (CH aliphatic), 2207 (CN),1586 (C = C); $^1$H NMR (300 MHz, DMSO-$d_6$): δ3.05 (m, 4H, $CH_2$-$CH_2$), 3.32, 6.49, 6.61 (3 s, 6H, $D_2O$ exchangeable, $3NH_2$), 6.89 (s, 1H, pyran-H4), 7.04 (s, 1H, CH = C), 7.33–7.69 (m, 4H, $C_6H_4$), 9.81 (s, 1H, $D_2O$ exchangeable, NH); $^{13}$C NMR (DMSO-$d_6$): δ24.1 ($CH_2$),45.0 ($CH_2$), 97.3 (pyran-C4), 103.5, 110.1 (C = C), 116.8 (CN), 118.4, 121.7, 122.9, 124.5, 127.3, 129.9, 131.2, 133.8, 138.3, 141.6 ($C_6H_4$, pyran, pyrazole), 170.2 (C = N); EIMS (m/z, %): 380 [$M^+$, 78]. Anal. Calcd.

for $C_{19}H_{17}ClN_6O$ (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-1*H*-pyrazol-4-yl)-7,8-dihydro-4*H*-chromene-3-carbonitrile (9b)

Yellow crystals from ethanol, yield: 74%; m.p.: 212–214 °C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3438–3226 ($3NH_2$), 2929 (CH aliphatic), 2208 (CN), 1597 (C = C); $^1$H NMR (300 MHz, DMSO-$d_6$): δ3.03 (m, 4H, $CH_2$-$CH_2$), 3.31, 6.47, 6.63 (3 s, 6H, $D_2O$ exchangeable, $3NH_2$), 6.87 (s, 1H, pyran-H4), 7.09 (s, 1H, CH = C), 7.29–7.74 (m, 9H,$C_6H_5$, $C_6H_4$); $^{13}$C NMR (DMSO-$d_6$): δ24.6 ($CH_2$), 46.0 ($CH_2$), 95.1 (pyran-C4), 108.4, 111.6 (C = C), 116.3 (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, 138.6, 140.1 ($C_6H_5$,$C_6H_4$, pyran, pyrazole), 172.2 (C = N); EIMS (m/z, %): 456 [$M^+$, 56]. Anal. Calcd. for $C_{25}H_{21}ClN_6O$ (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.

Light brown crystals from 1,4-dioxane, yield: 79%; m.p.: 220 °C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3439–3237 ($3NH_2$), 2923 (CH aliphatic), 2210 (CN), 1576 (C = C); $^1$H NMR (300 MHz, DMSO-$d_6$): δ3.01 (m, 4H, $CH_2$-$CH_2$), 3.41 (s, 2H, $D_2O$ exchangeable,$NH_2$), 5.43 (s, 1H, pyrimidine H-5), 6.32, 6.56 (2 s, 4H, $D_2O$ exchangeable, $2NH_2$), 6.88 (s, 1H, pyran *H*-4), 6.97 (s, 1H, CH = C), 7.23–7.77 (m, 4H,,$C_6H_4$); $^{13}$C NMR (DMSO-$d_6$): δ24.6 ($CH_2$),35.0 ($CH_2$), 76.1 (pyrimidine C-5), 95.1 (pyran C-4), 103.4, 110.6 (C = C), 115.7 (CN), 123.4, 127.3, 127.8, 128.3, 128.5, 129.7, 131.3, 133.3 ($C_6H_4$, pyran C), 170.1, 172.9 (2C = N), 187.8 (C = S); EIMS (m/z, %): 424 [$M^+$, 84]. Anal. Calcd. for $C_{20}H_{17}ClN_6OS$ (429.91): C, 56.53; H, 4.03; N, 19.78; S, 7.55%. Found: C, 56.34; H, 4.31; N, 19.56; S, 7.78%.

#### Synthesis of 4*H*-chromene-3-carbonitrile derivatives 15, 16

A solution of compound **4b** (3.0 g, 0.01 mol) in dimethylformamide (30 mL) and phenyl isothiocyanate (**12**) (1.35 mL, 0.01 mol) in the presence of potasium hydroxide (0.5 gm) was left on cold overnight. Either α-chloro acetone (**14a**) (0.92 mL, 0.01 mol) or ethyl chloroacetate (**14b**) (1.22 mL, 0.01 mol) was added to the reaction mixture and left overnight. The reaction mixture was poured onto ice/water containing few drops of hydrochloric acid and 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-4*H*-chromene-3-carbonitrile (15)

Yellow crystals from 1,4-dioxane, yield: 73%; m.p.: 185–187 °C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3424, 3216 ($NH_2$), 2927 (CH aliphatic), 2216 (CN), 1718 (CO), 1550 (C = C); $^1$H NMR (300 MHz, DMSO-$d_6$): δ2.17 (s, 3H, $CH_3$), 3.07 (m, 4H, $CH_2$-$CH_2$), 3.32 (s, 2H, $D_2O$ exchangeable,$NH_2$), 5.03 (s, 1H, thiazole H-5), 6.89 (s, 1H, pyran *H*-4), 7.07–7.61 (m, 9H, $C_6H_5$, $C_6H_4$); $^{13}$C NMR (DMSO-$d_6$): δ16.5 ($CH_3$), 25.9 ($CH_2$), 45.0 ($CH_2$), 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, 127.9, 128.2, 128.7, 129.8, 131.4, 133.9, 140.5 ($C_6H_5$, $C_6H_4$, pyran, thiazole C), 162.1 (C = O); EIMS (m/z, %): 473 [$M^+$, 31]. Anal. Calcd. for $C_{26}H_{20}ClN_3O_2S$ (473.97): C, 65.89; H, 4.25; N, 8.87; S, 6.77%. 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-4*H*-chromen-5(6H)-ylidene)(phenylamino)methyl)thio)acetate (16)

Yellow crystals from 1,4-dioxane, yield: 79%; m.p.: 155–157 °C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3419- 3214($NH_2$, NH), 2980 (CH aliphatic), 2215 (CN), 1733, 1699 (2CO), 1621 (C = C); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.10 (t, 3H, $J$ = 6.6 Hz, $OCH_2\underline{CH_3}$), 3.01 (m, 4H, $CH_2$-$CH_2$), 3.31 (s, 2H, $D_2O$ exchangeable, $NH_2$), 4.31 (q, 2H, $J$ = 6.6 Hz, $O\underline{CH_2}CH_3$), 4.93 (s, 2H, $CH_2$), 6.93 (s, 1H, pyran *H*-4), 7.24–7.73 (m, 9H,$C_6H_5$, $C_6H_4$), 8.81 (s, 1H, $D_2O$ exchangeable, NH); $^{13}$C NMR (DMSO-$d_6$): δ14.2 ($CH_3$), 26.3 ($CH_2$),45.8 ($CH_2$), 55.8 ($CH_2$), 66.5 ($CH_2$), 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 ($C_6H_5$, $C_6H_4$, pyran C), 162.1, 164.5 (2C = O); EIMS (m/z, %): 522 [$M^+$, 31]. Anal. Calcd. for $C_{27}H_{24}ClN_3O_4S$ (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(7*H*)-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, $\upsilon_{max}$ $cm^{-1}$): 3049 (CH aromatic), 2920 (CH aliphatic), 1699 (CO), 1644 (C=C), 1207 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 3.17 (m, 4H, $CH_2$-$CH_2$), 4.04 (s, 2H, $CH_2$), 7.09–7.30 ( m, 5H, $C_6H_5$); $^{13}$C NMR (DMSO-$d_6$):δ 22.6 ($CH_2$), 45.3 ($CH_2$), 66.3 ($CH_2$), 124.1, 124.8, 128.9, 130.4, 139.9, 142.3 ($C_6H_5$, thiophene C), 161.8 (CO), 180.1 (C=S); EIMS (m/z, %): 261 [$M^+$, 65]. Anal. Calcd. for $C_{13}H_{11}NOS_2$ (261.36): C, 59.74; H, 4.24; N, 5.36; S, 24.54%. Found: C, 59.69; H, 4.41; N, 5.74; S, 24.30%.

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

Triethylorthoformate (1.48 mL, 0.01 mol) followed by either malononitrile (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, cooled, and neutralized by ice/water containing few drops of hydrochloric acid, and the precipitated product was filtered off and dried.

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

Light brown crystals from 1,4-dioxane, yield: 51%; m.p.: 129–131 °C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3435,3378($NH_2$), 3059 (CH aromatic), 2929 (CH aliphatic), 2203 (CN), 1633 (C=C),1205 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.29 (t, 3H, $J$=6.9 Hz, $OCH_2\underline{CH_3}$), 3.17 (m, 4H, $2CH_2$), 3.42 (q, 2H, $J$=6.9 Hz, $O\underline{CH_2}CH_3$), 6.75 (s, 2H, $D_2O$ exchangeable, $NH_2$), 7.12–7.56 (m, 6H, pyran H-4 and $C_6H_5$); $^{13}$C NMR (DMSO-$d_6$): δ 16.3 ($CH_3$), 24.5 ($CH_2$), 46.9 ($CH_2$), 55.7 ($CH_2$), 98.7 (pyran 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 ($C_6H_5$, pyran, thiazole C), 182.0 (C=S); EIMS (m/z, %): 383 [$M^+$, 48]. Anal. Calcd. for $C_{19}H_{17}N_3O_2S_2$ (383.49): 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%.

### 9-Ethoxy-7-hydroxy-3-phenyl-2-thioxo-3,4,5,9-tetrahydro–2*H*-chromeno[6,5-*d*]thiazole-8-carbonitrile (20b)

Brown crystals from 1,4-dioxane, yield: 40%; m.p.: 156–158 °C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3423 (OH), 3051 (CH aromatic), 2930 (CH aliphatic), 2195 (CN), 1639 (C=C),1229 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.18 (t, 3H, $J$=7.5 Hz, $OCH_2\underline{CH_3}$),3.30 (m, 4H, $2CH_2$), 3.49 (q, 2H, $J$=7.5 Hz, $O\underline{CH_2}CH_3$), 6.93–7.46 (m, 6H, pyran *H*-4 and $C_6H_5$), 9.64 (s, 1H, $D_2O$ exchangeable, OH); $^{13}$C NMR (DMSO-$d_6$):δ 16.5 ($CH_3$), 24.9 ($CH_2$), 47.5 ($CH_2$), 56.3($CH_2$), 98.4 (pyran C-4), 116.1 (CN), 118.6, 122.2, 123.5, 124.8, 129.2, 129.5, 131.4, 132.1, 140.1, 148.3 ($C_6H_5$, pyran, thiazole C), 180.5 (C=S); EIMS (m/z, %): 384 [$M^+$, 56]. Anal. Calcd. for $C_{19}H_{16}N_2O_3S_2$ (384.47): C, 59.35; H, 4.19; N, 7.29; S, 16.68%. Found: C, 59.64; H, 4.38; N, 7.59; S, 16.80%.

### Synthesis of2,3,4,5-tetrahydrothieno[2',3':3,4]benzo[1,2-*d*]thiazole derivatives 21a,b

Elemental sulfur (0.32 g, 0.01 mol) followed by either malononitrile (**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, $\upsilon_{max}$ $cm^{-1}$): 3407, 3202 ($NH_2$), 3026 (CH aromatic), 2926 (CH aliphatic), 2194 (CN), 1597 (C=C), 1197 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$): δ3.32 (m, 4H, $2CH_2$), 6.82 (s, 2H, $D_2O$ exchangeable, $NH_2$),7.09–7.50 (m, 5H, $C_6H_5$); $^{13}$C NMR (DMSO-$d_6$): δ23.2 ($CH_2$), 45.3 ($CH_2$), 116.3 (CN), 118.3, 119.1, 121.7, 123.5, 127.9, 128.6, 129.1, 131.9, 134.5, 139.5 ($C_6H_5$, thiophene, thiazole C), 180.9 (C=S); EIMS (m/z, %): 341 [$M^+$, 46]. Anal. Calcd. for $C_{16}H_{11}N_3S_3$ (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, $\upsilon_{max}$ $cm^{-1}$): 3447, 3205 ($NH_2$), 3026 (CH aromatic), 2926 (CH aliphatic), 1698(CO), 1592 (C=C),1236 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.24 (t, 3H, $J$=6.9 Hz, $OCH_2\underline{CH_3}$),3.32 (m, 4H, $2CH_2$), 6.82 (q, 2H, $J$=6.9 Hz, $O\underline{CH_2}CH_3$), 6.73 (s, 2H, $D_2O$ exchangeable, $NH_2$), 7.09–7.59 (m, 5H, $C_6H_5$); $^{13}$C NMR (DMSO-$d_6$): δ 15.9 ($CH_3$), 23.2 ($CH_2$), 45.3 ($CH_2$), 55.8 ($CH_2$), 118.6, 119.7, 122.2, 123.5, 128.1, 128.9, 129.5, 132.1, 135.7, 139.9 ($C_6H_5$, thiophene, thiazole C), 161.4 (CO), 180.9 (C=S); EIMS (m/z, %): 388 [$M^+$, 71]. Anal. Calcd. for $C_{18}H_{16}N_2O_2S_3$ (388.53): C, 55.64; H, 4.15; N, 7.21; S, 24.76%. Found: C, 55.53; H, 4.28; N, 7.39; S, 24.60%.

#### Synthesis of 3,4,5,9-tetrahydro-2*H*-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 (**5b**) (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-2*H*-chromeno[6,5-*d*]thiazole-8-carbonitrile (23a)

Brown crystals from 1,4-dioxane, yield: 55%; m.p.: 115–117 °C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3463, 3237 ($NH_2$), 3059 (CH aromatic), 2952 (CH aliphatic), 2208 (CN), 1590 (C = C), 1259 (C = S); $^1$H NMR (300 MHz, DMSO-$d_6$): δ3.33 (m, 4H, $2CH_2$), 6.89 (s, 2H, $D_2O$ exchangeable, $NH_2$), 7.10–7.61 (m, 11H, pyran *H*-4 and $2C_6H_5$); $^{13}$C NMR (DMSO-$d_6$): δ24.5 ($CH_2$), 45.1 ($CH_2$), 98.4 (pyran-C-4), 116.1 (CN), 118.1, 118.6, 119.7, 121.9, 122.2, 122.8, 123.5, 124.9, 125.5, 128.9, 129.5, 132.1, 139.9, 143.6 ($2C_6H_5$, pyran and thiazole C), 181.4 (C = S); EIMS (m/z, %): 415 [$M^+$, 58]. Anal. Calcd. for $C_{23}H_{17}N_3OS_2$ (415.53): C, 66.48; H, 4.12; N, 10.11; S, 15.43%. Found: C, 66.63; H, 4.30; N, 10.39; S, 15.60%.

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

Light brown crystals from ethanol, yield: 88%; m.p.: 98–100 °C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3431,3240($NH_2$), 3034 (CH aromatic), 2936 (CH aliphatic), 2192 (CN), 1585 (C = C),1258 (C = S); $^1$H NMR (300 MHz, DMSO-$d_6$): δ3.32 (m, 4H, $2CH_2$),6.84 (s, 2H, $D_2O$ exchangeable, $NH_2$), 7.09–7.59 (m, 10H, pyran *H*-4, $C_6H_5$ and $C_6H_4$); $^{13}$C NMR (DMSO-$d_6$): δ23.7 ($CH_2$), 44.2 ($CH_2$), 98.9 (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 ($C_6H_5$, $C_6H_4$, pyran, and thiazole C), 181.4 (C = S); EIMS (m/z, %): 449 [$M^+$, 47]. Anal. Calcd. for $C_{23}H_{16}ClN_3OS_2$ (449.98): C, 61.39; H, 3.58; N, 9.34; S, 14.25%. Found: C, 61.19; H, 3.79; N, 9.02; S, 14.10%.

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

Reddish brown crystals from ethanol, yield: 51%; m.p.: 163–165 °C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3433, 3205 ($NH_2$), 3022 (CH aromatic), 2952 (CH aliphatic), 1725 (CO), 1544 (C = C), 1235 (C = S); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.29 (t, 3H, *J* = 6.5 Hz, $OCH_2\underline{CH_3}$),3.31 (m, 4H, $2CH_2$),4.32 (q, 2H, *J* = 6.5 Hz, $O\underline{CH_2}CH_3$), 6.61 (s, 2H, $D_2O$ exchangeable, $NH_2$), 7.10–7.50 (m, 11H, pyran *H*-4 and $2C_6H_5$); $^{13}$C NMR (DMSO-$d_6$): δ 16.9 ($CH_3$), 25.0 ($CH_2$), 44.7 ($CH_2$), 55.1 ($CH_2$), 98.0 (pyran C-4), 117.9, 118.1, 119.9, 121.2, 122.0, 122.6, 123.9, 124.5, 125.7, 128.6, 129.4, 133.2, 139.6, 142.1 ($2C_6H_5$, pyran and thiazole C), 161.6 (CO), 180.4 (C = S); EIMS (m/z, %): 462 [$M^+$, 38]. Anal. Calcd. for $C_{25}H_{22}N_2O_3S_2$ (462.58): C, 64.91; H, 4.79; N, 6.06; S, 13.86%. Found: C, 64.73; H, 4.48; N, 5.89; S, 14.10%.

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

Brown crystals from 1,4-dioxane, yield: 86%; m.p.: 122–125 C; IR (KBr, $\upsilon_{max}$ $cm^{-1}$): 3425,3279 ($NH_2$), 3049 (CH aromatic), 2980 (CH aliphatic), 1702 (CO), 1592 (C = C), 1230 (C = S); $^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.15 (t, 3H, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 3.29 (m, 4H, $2CH_2$) 4.15, (q, 2H, J = 7.2 Hz, $O\underline{CH_2}CH_3$), 6.90 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.96–7.60 (m, 10H, pyran *H*-4, $C_6H_5$ and $C_6H_4$); $^{13}$C NMR (DMSO-$d_6$): δ 16.8 ($CH_3$), 24.5 ($CH_2$), 44.9 ($CH_2$), 55.8 ($CH_2$), 98.3 (pyran-C4), 118.0, 118.9, 119.6, 121.4, 122.1, 122.8, 123.7, 124.8, 127.6, 128.1, 130.0, 133.0, 139.6, 142.9 ($C_6H_5$, $C_6H_4$, pyran and thiazole C), 162.6 (CO), 180.1 (C = S); EIMS (m/z, %): 497 [$M^+$, 31]. Anal. Calcd. for $C_{25}H_{21}ClN_2O_3S_2$ (497.03): C, 60.41; H, 4.26; N, 5.64; S, 12.90%. Found: C, 60.53; H, 4.16; N, 5.38; S, 12.80%.

## Conclusion

Tetrahydro-4*H*-chromene-3-carbonitrile derivatives **4a-c** and tetrahydrobenzo[*d*]thiazole derivative **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'-*O*MTases 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. 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 participate** The authors promise that the work described has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out.

**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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