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# Novel cycloalkylthiophene–imine derivatives bearing benzothiazole scaffold: Synthesis, characterization and antiviral activity evaluation

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ABSTRACT

A series of novel cycloalkylthiophene–imine derivatives containing benzothiazole unit were designed, synthesized and evaluated for their anti-viral activities. The bio-evaluation results indicated that some of the target compounds (such as **5g**, **5i**, **5u**) exhibited good to moderate antiviral effect on CVB5, ADV7 and EV71 viruses, however, these compounds did not have inhibition activity against H1N1 virus. Especially, the compounds **4c** and **4d** also exhibited high antiviral activities, which provide a new and efficient approach to evolve novel multi-functional antiviral agents by rational integration of active pharmacophores.



Benzothiazoles are an important class of heterocyclic scaffold that consist of a five-membered 1,3-thiazole ring fused to a benzene ring. Many compounds derived from this heterocycle exhibit diverse pharmacological and synthetic interest due to their extensive bioactivities, in particular, which also are extremely versatile building blocks for the manufacture of various bioactive compounds in medicinal and industrial fields.[1–6] Notably, among all these benzothiazole derivatives, 2-substituted benzothiazoles (Fig. 1) are privileged heterocyclic systems because of their broad applications range from medicinal agents, agrochemicals, materials to chemsensors.[7–18]

On the other hand, cycloalkylthiophene units have also attracted considerable attention for decades.[19,20] Very recently, many examples bearing this moiety have been reported to confirm that the introduction of these pharmacophores can result in high activity and broader activity spectra.[21–25] Meanwhile, the flexible properties and itself characteristics of imine (C=N) group make it present important chemical and biological significance,[26–28] and which is always the focus field to researchers due to its lone electron pair and better coordination properties. Recently, the extensive applications of imine compounds have also been demonstrated,[29–35] and many commercial medicines and agrochemicals all contain this unit, and so which has played significantly important role in pharmaceutical industry.

Thus, based on the aforementioned statements, this work focused on the design, convenient synthesis, and antiviral evaluation of novel series of cycloalkylthiophene–imine derivatives bearing benzothiazole unit. We utilized cycloalkylthiophene scaffold as key prototype structural unit and planed for the integration of benzothiazole and imine pharmacophores to the core structure as shown in Figure 2, and these novel three-block conjugations were not yet reported in the literature, which might be developed as lead compounds for novel antiviral agents.

The general procedures for the preparation of novel cycloalkylthiophene–imine derivatives **5a**–**y** are outlined in Scheme 1.

The key building blocks 2-(benzo[*d*]thiazol-2-yl)acetonitrile **1a**, **b** were constructed by cyclization reaction of 2-aminobenzenethiol and malononitrile, which were conveniently transferred to the corresponding cycloalkylthiophene derivatives **4a**–**d** via classical Gewald three components reaction. The following condensation reactions of intermediates **4a**–**d** were treated with various aldehydes resulting in cycloalkylthiophene–imine derivatives **5a**–**y**. All target compounds gave satisfactory chemical analyses, and the chemical structures of the synthesized compounds were summarized in Table 1.

The in vitro cytotoxic effects of these cycloalkylthiophene–imine derivatives **5a**–**y** on RD (rhabdomyosarcoma), HepG2 (hepatocellular liver carcinoma), Hela (cervical cancer), and MDCK (dog kidney) cell lines were evaluated by the standard MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay.[36] However, most of these compounds showed almost no toxic to the tested cell lines, and the preliminary results were summarized in the following Table 2.

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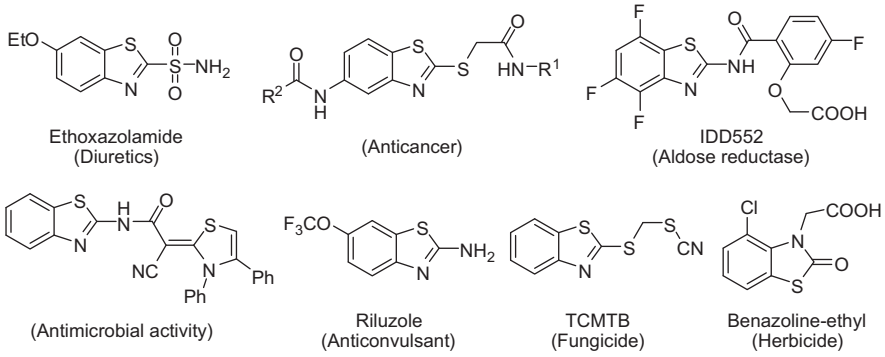



**Figure 1.** Representative compounds containing benzothiazole unit.

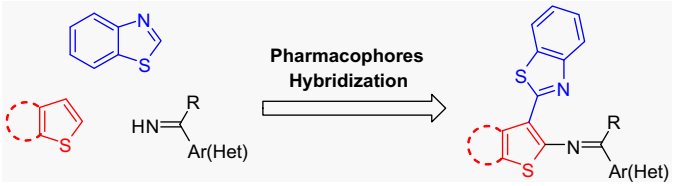


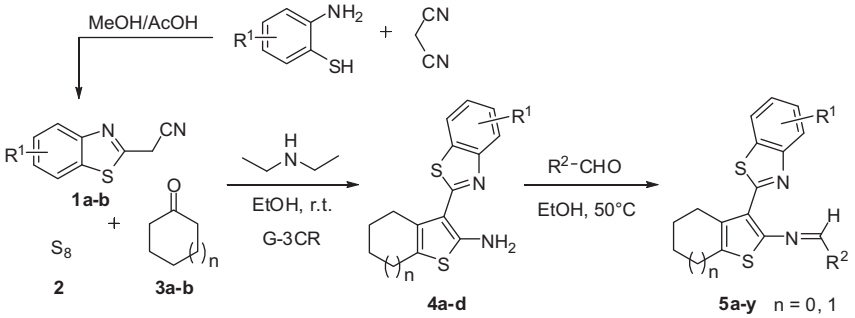

**Figure 2.** Design strategy of benzothiazole–cycloalkylthiophene–imine conjugations.

Based on the former results, the antiviral activities of synthesized compounds were further evaluated by using the above cell-based method. Generally, as shown in Figure 3, the prepared compounds (**5a**–**y**) displayed moderate to good inhibition activities against the tested viruses at the concentration of 32 μg/mL. We also can find that the different substituent at the periphery of the molecules **5a**–**y** can lead to the obviously different activities. Most cycloalkylthiophene derivatives containing six-member ring ($n = 1$) are more potent than that of five-member ring ($n = 0$). Notably, the compounds **5g**, **5i**, **5l**, and **5u** exhibited significant antivirus activities against all tested viruses except H1N1 with 60–95% inhibition activities at 32 μg/mL. Also, it is interesting to note that compounds **5g** and **5u** having a 2-OH-Ph unit showed comparatively good antiviral activities, which can be further demonstrated from the activities of compound **5x**. From Figure 3, compounds **5a** and **5t** exhibit the selective antiviral activities against CVB5 virus, however, compounds **5h**, **5q** and **5s** have obviously selective activities against EV71 virus respectively.

In addition, the preliminary bioassay indicated that some of the target compounds displayed good inhibitory activities, so in order to further investigate the potential antiviral activities, the $EC_{50}$ values were also evaluated and the commercial Ribavirin was used as positive control. The antiviral activities expressed as $EC_{50}$ values for the target compounds are presented in Table 2, and which further testify that some of the designed cycloalkylthiophene–imine deivatives **5a**–**y** exhibited higher antiviral activity than the commercial Ribavirin under the same conditions. As indicated in Table 2, compounds **5i**, **5u**,**4c** and **4d** displayed the strongest antiviral effect on EV71, CVB5 and ADV7, with a lower $EC_{50}$ values and higher SI values, respectively. We also can find that compounds **5l** and **5o** have the selective antiviral activities, the selective index value for compound **5l** against ADV7 virus is 26.5, and that for compounds **5o** and **5t** against CVB5 virus are 35 and 31.6, respectively.

Furthermore, the dose–response analysis of virus growth inhibition activity for representative compounds **5i**, **5u**, **4c** and **4d** have been outlined in Figure 4, which indicated that the antiviral effects on cell lines of target compounds showed obvious concentration-dependent manner. Compound **5u** exhibited high potent antivirus activities against CVB5, ADV7 and EV71 virus with the $EC_{50}$ values of 5.4 ± 0.9, 10.8 ± 1.0, and 2.0 ± 0.7 μg/mL (Table 2), respectively, which was better than the control compound Ribavirin. Especially, the intermediates **4c** and **4d** also displayed high antivirus activities against CVB5, ADV7 and EV71 virus, which can be used as novel lead compounds for further optimization.

In conclusion, a series of novel cycloalkylthiophene–imine derivatives have been designed and synthesized as potential antiviral agents. Bio-evaluation indicated that some of the newly synthesized compounds exhibited moderate to good antiviral activities. Especially, the most potent compounds **5i** and **5u** showed higher antiviral activity compared to commercial Ribavirin, which is characterized by $EC_{50}$ values in the low μM range. This work provides a novel approach to develop multi-functional antiviral agents from previously reported agents.




**Scheme 1.** General synthetic route for cycloalkylthiophene–imine derivatives bearing benzothiazole scaffold.

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**Table 1**
The chemical structure of cycloalkylthiophene–amine derivatives **5a–y**

| Entry | Compd no. | Substituents | | | Yield[a] (%) | Appearance | Mp (°C) |
|---|---|---|---|---|---|---|---|
| | | *n* | $R^1$ | $R^2$ | | | |
| 1 | **5a** | 0 | H | 4-F-Ph | 63 | Yellowish crystal | 187–189 |
| 2 | **5b** | 0 | H | 4-Cl-Ph | 87 | Yellowish powder | 217–218 |
| 3 | **5c** | 0 | H | 2-F-Ph | 91 | Yellowish floccule | 179–180 |
| 4 | **5d** | 0 | H | 2-Cl-Ph | 87 | Yellowish floccule | 210–211 |
| 5 | **5e** | 0 | H | 2,4-$Cl_2$-Ph | 84 | Orange powder | 213–214 |
| 6 | **5f** | 0 | H | 3,4-$OCH_2O$-Ph | 70 | Orange powder | 231–232 |
| 7 | **5g** | 0 | H | 2-OH-Ph | 65 | Yellowish brown powder | 197–198 |
| 8 | **5h** | 0 | H | PhCH=CH- | 95 | Orange powder | 186–188 |
| 9 | **5i** | 1 | H | 4-F-Ph | 63 | Reddish brown crystal | 166–167 |
| 10 | **5j** | 1 | H | 4-Cl-Ph | 71 | Yellow powder | 186–187 |
| 11 | **5k** | 1 | H | 2,4-$Cl_2$-Ph | 91 | Yellowish floccule | 198–200 |
| 12 | **5l** | 1 | H | Ph | 86 | Yellowish powder | 163–165 |
| 13 | **5m** | 1 | H | 2-F-Ph | 86 | Orange powder | 174–176 |
| 14 | **5n** | 1 | H | 2-Cl-Ph | 84 | Yellowish powder | 168–169 |
| 15 | **5o** | 1 | H | 2-$NO_2$-Ph | 77 | Carmine powder | 165–166 |
| 16 | **5p** | 1 | H | 4-$NO_2$-Ph | 81 | Carmine powder | 232–233 |
| 17 | **5q** | 1 | H | 4-$CF_3$-Ph | 87 | Yellowish floccule | 196–198 |
| 18 | **5r** | 1 | H | 3,4,5-$(MeO)_3$-Ph | 95 | Orange powder | 225–227 |
| 19 | **5s** | 1 | H | 3,4-$OCH_2O$-Ph | 78 | Yellowish powder | 215–217 |
| 20 | **5t** | 1 | H | PhCH=CH- | 89 | Orange powder | 179–180 |
| 21 | **5u** | 1 | H | 2-OH-Ph | 68 | Reddish brown crystal | 153–154 |
| 22 | **5v** | 0 | 4-Cl | 2-OH-Ph | 71 | Orange yellow powder | 220–222 |
| 23 | **5w** | 0 | 4-Cl | PhCH=CH- | 75 | Orange powder | 207–209 |
| 24 | **5x** | 1 | 4-Cl | 2-OH-Ph | 91 | Yellowish powder | 227–229 |
| 25 | **5y** | 1 | 4-Cl | PhCH=CH- | 87 | Orange yellow powder | 190–192 |

[a] Isolated yields.

**Table 2**
Cytotoxicity and antiviral activity of compounds **5a–y** against Enterovirus 71 (EV71), Coxsackievirus B5 (CVB5), Adenovirus type 7 (ADV7) and Influenza A virus (H1N1)

| Entry | Compds | EV71 (RD) | | | CVB5 (HepG-2) | | | ADV7 (Hela) | | | H1N1 (MDCK) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $CC_{50}$[a] (μg/mL) | $EC_{50}$[b] (μg/mL) | SI[c] | $CC_{50}$[a] (μg/mL) | $EC_{50}$[b] (μg/mL) | SI[c] | $CC_{50}$[a] (μg/mL) | $EC_{50}$[b] (μg/mL) | SI[c] | $EC_{50}$[b] (μg/mL) |
| 1 | **5a** | 289.5 ± 1.7[d] | —[e] | — | 302.3 ± 1.3 | 15.5 ± 0.7 | 19.4 | 372.3 ± 6.0 | — | — | — |
| 2 | **5b** | 342.4 ± 7.2 | — | — | 430.5 ± 3.5 | — | — | 380.2 ± 4.4 | — | — | — |
| 3 | **5c** | 270 ± 5.2 | — | — | 394.2 ± 1.9 | — | — | 355.2 ± 3.6 | — | — | — |
| 4 | **5d** | 123.1 ± 3.1 | — | — | 180.2 ± 0.8 | — | — | 138.4 ± 3.9 | — | — | — |
| 5 | **5e** | 159.6 ± 4.0 | — | — | 310.1 ± 2.0 | — | — | 345.3 ± 1.2 | — | — | — |
| 6 | **5f** | 309.8 ± 2.8 | — | — | 356.2 ± 0.7 | — | — | 449 ± 1.3 | — | — | — |
| 7 | **5g** | 100.1 ± 1.9 | 7.9 ± 0.8 | 12.6 | 155.8 ± 5.2 | 11.1 ± 0.8 | 13.8 | 167.9 ± 0.3 | 17.4 ± 1.1 | 9.6 | — |
| 8 | **5h** | 122.4 + 2.1 | — | — | 214.6 ± 1.8 | — | — | 100 ± 0.9 | — | — | — |
| 9 | **5i** | 229.9 ± 1.3 | 6.9 ± 1.4 | 32.8 | 324.1 ± 1.4 | 9.7 ± 0.9 | 33.2 | 276.9 ± 2.5 | 21.1 ± 2.6 | 13.1 | — |
| 10 | **5j** | 367.3 ± 2.8 | — | — | 396.8 ± 5.7 | — | — | 430.7 ± 1.9 | — | — | — |
| 11 | **5k** | 56.6 ± 0.2 | — | — | 383.5 ± 4.8 | — | — | 541.8 ± 4.9 | — | — | — |
| 12 | **5l** | 71.1 ± 2.4 | 14.2 ± 0.8 | 4.9 | 307.6 ± 1.8 | 32.9 ± 2.7 | 9.3 | 333.4 ± 2.2 | 12.5 ± 2.1 | 26.5 | — |
| 13 | **5m** | 318.9 ± 5.2 | — | — | 398.4 ± 3.3 | — | — | 426.4 ± 5.2 | — | — | — |
| 14 | **5n** | 331.7 ± 0.2 | — | — | 369.7 ± 4.4 | — | — | 407.4 ± 3.8 | — | — | — |
| 15 | **5o** | 255.4 ± 6.2 | — | — | 393.1 ± 1.5 | 11.2 ± 0.5 | 35 | 369 ± 9.5 | — | — | — |
| 16 | **5p** | 316.4 ± 5.9 | — | — | 453.6 ± 1.3 | — | — | 356.8 ± 4.5 | — | — | — |
| 17 | **5q** | 250.3 ± 1.2 | — | — | 360.9 ± 1.7 | — | — | 368.5 ± 1.9 | — | — | — |
| 18 | **5r** | 381.4 ± 3.2 | — | — | 301.3 ± 0.7 | — | — | 447.6 ± 2.1 | — | — | — |
| 19 | **5s** | 299.0 ± 0.9 | 32.6 ± 6.7 | 9.1 | 329.4 ± 2.1 | — | — | 568.4 ± 0.4 | — | — | — |
| 20 | **5t** | 206.9 ± 3.9 | — | — | 467 ± 2.6 | 14.7 ± 1.2 | 31.6 | 389 ± 2.9 | — | — | — |
| 21 | **5u** | 42.36 ± 1.1 | 2.0 ± 0.7 | 20.3 | 114.2 ± 0.5 | 5.4 ± 0.9 | 20.8 | 121.9 ± 2.1 | 10.8 ± 1.0 | 11.1 | — |
| 22 | **5v** | 269 ± 1.2 | 13.9 ± 0.9 | 19.2 | 210.0 ± 3.2 | — | — | 250.8 ± 2 | — | — | — |
| 23 | **5w** | 122.4 ± 1.0 | — | — | 14.9 ± 1.3 | — | — | 200.4 ± 3.1 | — | — | — |
| 24 | **5x** | 183.6 ± 7.0 | 21.7 ± 1.2 | 8.4 | 220.3 ± 1.8 | 6.8 ± 1.2 | — | 235.8 + 0.6 | 35.7 ± 4.6 | 6.5 | — |
| 25 | **5y** | 211.5 ± 0.2 | — | — | 113.8 ± 4.2 | — | — | 150.4 ± 1.2 | — | — | — |
| 26 | **4b** | 252.8 ± 1.9 | 14.1 ± 4.2 | 17.8 | 163.2 ± 1.2 | 14.5 ± 3.3 | 11.9 | 475.4 ± 1.1 | — | — | — |
| 27 | **4c** | 59.1 ± 0.6 | 1.2 ± 1.1 | 46.9 | 67.8 + 0.7 | 6.4 ± 1.6 | 10.4 | 75.1 ± 3.3 | 9.8 ± 1.2 | 7.6 | — |
| 28 | **4d** | 43.5 ± 2.3 | 1.3 ± 1.4 | 33.7 | 93.7 + 0.1 | 3.5 ± 1.4 | 26.7 | 106.7 ± 0.8 | 5.0 ± 1.2 | 20.9 | — |
| 29 | Ribavirin[f] | >500 | 49.2 ± 5.8 | >10 | >500 | 22.3 ± 3.3 | >20 | >500 | 27.8 ± 3.8 | >15 | ND[g] |

The compounds were added 48 h after infection and total infectivity was determined by the crystal violet staining method.
[a] Concentration of the compound at which cell viability was reduced by 50% when compared to the 0.1% DMSO-treated cells, which served as a mock control.
[b] Inhibitory concentration that reduced viral replication by 50%.
[c] The selective index was calculated as the ratio of $CC_{50}$ versus $EC_{50}$, SI (Selective index) = $CC_{50}/EC_{50}$.
[d] Data are expressed as mean ± SD of results from three independent experiments.
[E] —, activity that lower than 50% inhibition.
[f] Ribavirin, used as a positive control.
[g] ND, not done.

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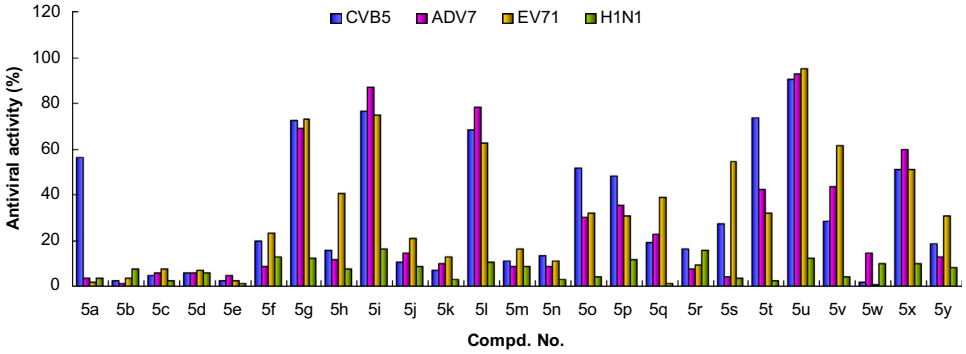


**Figure 3.** Inhibition activities against virus proliferation for all compounds. RD cells, HepG-2 cells, Hela cells and MDCK cells were infected with Enterovirus 71 (EV71), Coxsackievirus B5 (CVB5), Adenovirus type 7 (ADV7) and Influenza A virus (H1N1) for 48 h in the presence of the compounds at 32 μg/mL (compds **5i** and **5u** against EV71 were at 16 μg/mL). Antiviral efficacy was evaluated using the crystal violet staining method.

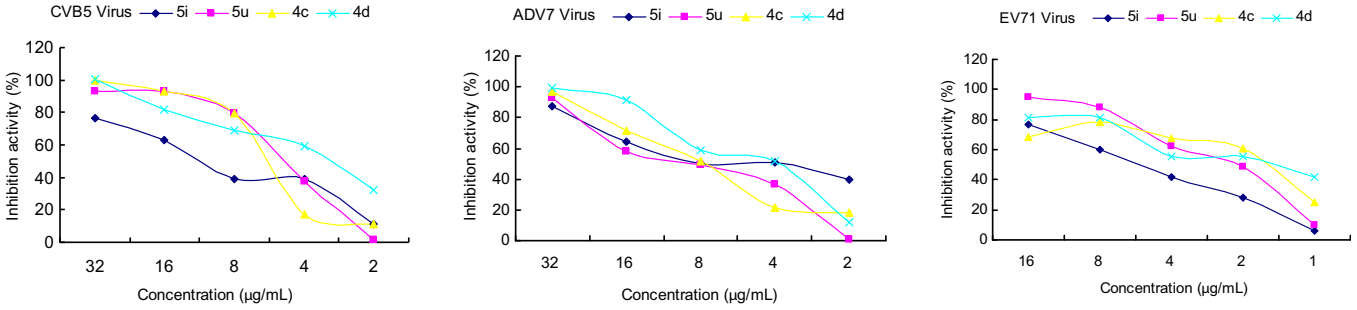


**Figure 4.** Dose–response analysis of virus inhibition activity for representative compounds **5i**, **5u**, **4c**, **4d** against Coxsackievirus B5 (CVB5), Adenovirus type 7 (ADV7), and Enterovirus 71 (EV71).

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.07.023.

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