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Article

Synthesis and Anti-TMV Activity of Dialkyl/dibenzyl 2-((6-Substituted-benzo[d]thiazol-2-ylamino)(benzofuran-2-yl)methyl) Malonates

Han Xiao [1,2,*], Pengcheng Zheng [1], Chenghao Tang [1], Ying Xie [1], Fang Wu [1], Jie Song [1], Jun Zhao [1], Zhining Li [1] and Meichuan Li [1]

[1] Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China; E-Mails: zhengpc1986@163.com (P.Z.); chtang1122@163.com (C.T.); xieying0020@126.com (Y.X.); fangwu90@126.com (F.W.); songjie277@yeah.net (J.S.); zhaojun0020@126.com (J.Z.); aning072@126.com (Z.L.); lmcuvhn1987@163.com (M.L.)

[2] School of Chemistry and Environmental Science, Guizhou Minzu University, Guiyang 550025, China

* Author to whom correspondence should be addressed; E-Mail: hanx@gzmu.edu.cn; Tel./Fax: +86-0851-829-2090.

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Abstract: Starting from benzofuran-2-methanal, 6-substituted benzothiazole-2-amines and malonic esters, sixteen title compounds were designed and synthesized seeking to introduce anti-TMV activity. The structures of the newly synthesized compounds were confirmed by ^{1}H-NMR, ^{13}C-NMR, IR spectra, and MS (HREI) analysis. The bioassays identified some of these new compounds as having moderate to good anti-TMV activity. The compounds **5i** and **5m** have good antiviral activity against TMV with a curative rate of 52.23% and 54.41%, respectively, at a concentration of 0.5 mg/mL.

Keywords: benzofuran; benzothiazole; β-amino acid ester; anti-TMV activity

1. Introduction

Benzothiazoles have varied biological activities [1–3]. They are widely found in bioorganic and medicinal chemistry with applications in drug discovery and are still of great scientific interest

nowadays [4]. Benzothiazole moieties are part of compounds showing numerous biological activities such as anti-bacterial, anti-microbial, anthelmintic, antitumor, anti-inflammatory properties [5–8]. Compounds containing benzofuran moieties are also widespread in Nature, with a broad spectrum of physiological bioactivities, used as pesticidal, anti-bacterial, insecticide, anti-tumor, anti-inflammatory [9–11], and so on.

β-Amino ester derivatives are key intermediate in the synthesis of β-lactam antibiotics, which are important components of many natural products and therapeutic agents [12–14]. Therefore, the asymmetric synthesis of β-amino ester derivatives has become a field of increasing interest in organic synthetic chemistry over the past few years [15–20].

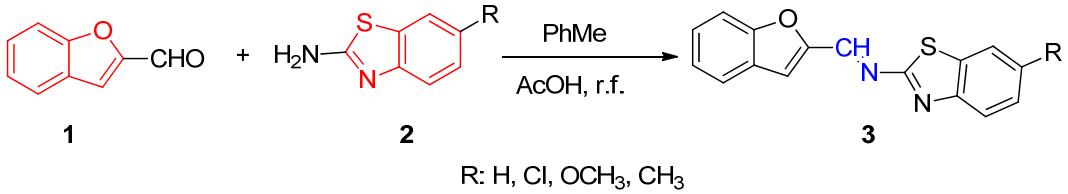
As an extension study of our group's research [19,21], we have now synthesized a series of novel β-amino ester derivatives containing benzofuran and benzothiazole units. The structures of these newly synthesized compounds were confirmed by ^{1}H-NMR, ^{13}C-NMR, IR spectra, and MS (HREI) analysis. Bioassays identified these new compounds as possessing weak to good antiviral activities.

2. Results and Discussion

2.1. Experimental Condition Optimization

Our strategy is outlined in Scheme 1. Benzofuran-2-methanal (**1**) reacted with 6-substituted benzothiazoles **2a**–**d** under reflux conditions in toluene, with some acetic acid as catalyst affording the imines **3a**–**d**. After recrystallization by ethanol, the final compounds were isolated in good yields. All products **3a**–**d** were characterized by spectroscopic methods.

Scheme 1. Synthesis of imines.



According to the Scheme 2, we tested the influence of the reaction temperature, solvent, and reaction times. The reaction temperature had a pronounced effect on the yield, solvents such as THF, acetone, and toluene showed lower yields compared to DCM (Table 1). According to an optimized procedure, the best result was achieved at 35 °C in DCM.

Scheme 2. Screening of the reaction conditions.

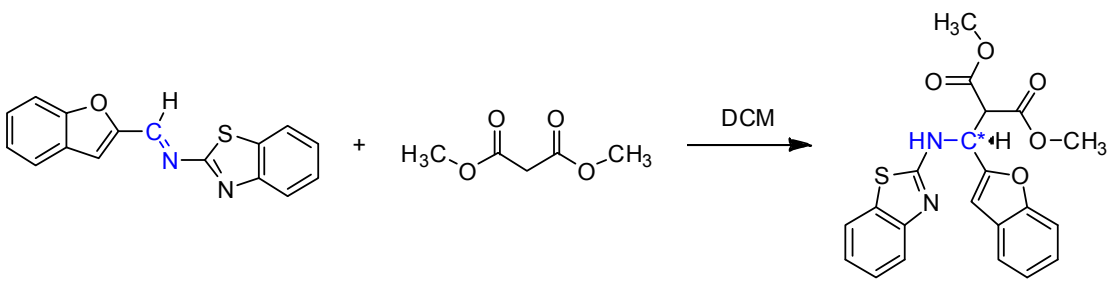
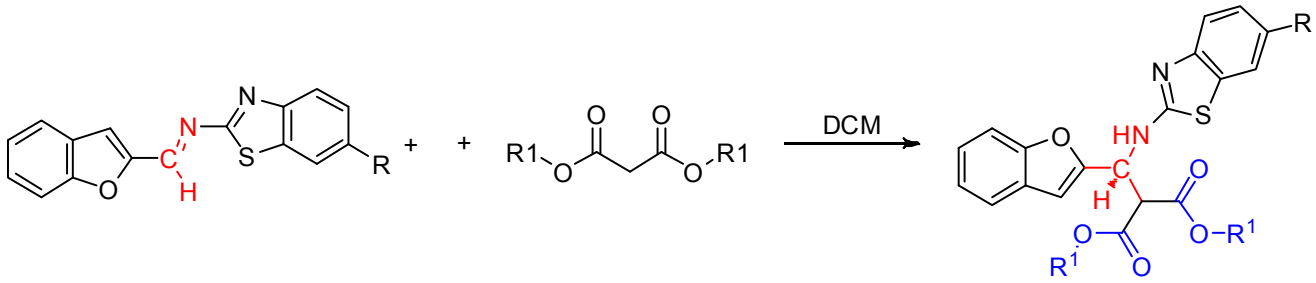


Table 1. The optimization of reaction conditions.

Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	THF	r.t.	24	34
2	THF	r.f.	12	38
3	PhMe	r.t.	24	46
4	PhMe	r.f.	12	72
5	DCM	r.t.	24	62
6	DCM	35	10	78

Having established the ideal reaction conditions, the synthetic scope of the reaction was evaluated with different imines and malonic esters (Scheme 3). The results of our studies are summarized in Table 2. It can be seen that the reactions afforded good yields.

Scheme 3. Synthesis of compounds **5a**–**p**.



4 **5**

R: H, Cl, OCH_3, CH_3

R1: CH_3, C_2H_5, C_3H_7, $CH_2C_6H_5$

Table 2. The yields of the Mannich reactions of imines and malonic esters.

Entry	5	R	R^1	Time(h)	Yield(% [a])
1	**5a**	6-H	$-CH_3$	12	82
2	**5b**	6-H	$-C_2H_5$	12	80
3	**5c**	6-H	$-C_3H_7$	12	78
4	**5d**	6-H	$-CH_2C_6H_5$	24	62
5	**5e**	6-Cl	$-CH_3$	12	85
6	**5f**	6-Cl	$-C_2H_5$	12	86
7	**5g**	6-Cl	$-C_3H_7$	12	82
8	**5h**	6-Cl	$-CH_2C_6H_5$	24	67
9	**5i**	6-OCH_3	$-CH_3$	12	81
10	**5j**	6-OCH_3	$-C_2H_5$	12	80
11	**5k**	6-OCH_3	$-C_3H_7$	12	79
12	**5l**	6-OCH_3	$-CH_2C_6H_5$	24	60
13	**5m**	6-CH_3	$-CH_3$	12	81
14	**5n**	6-CH_3	$-C_2H_5$	12	76
15	**5o**	6-CH_3	$-C_3H_7$	12	76
16	**5p**	6-CH_3	$-CH_2C_6H_5$	24	64

[a] Isolated yield after chromatographic purification.

2.2. Anti-TMV Activity

The antiviral activity of compound **5** against TMV was assayed by the reported method [9]. As it can be seen from the results presented in Table 3, some compounds possess good anti-TMV activity, such as the curative rates against TMV of compounds **5i** and **5m** which were 52.23% and 54.41%. These values are close to that of the the commercial control ningnanmycin (curative rate 55.27%).

Table 3. The *in vivo* antiviral activity towards TMV of the new compounds at 0.5 (mg/mL).

Entry	Compound	Protection Effect %	Curative Effect %	Inhibition Effect %
1	**5a**	57.95	48.27	39.72
2	**5b**	63.08	47.18	43.42
3	**5c**	62.11	43.83	33.29
4	**5d**	48.58	49.17	28.45
5	**5e**	58.67	46.28	33.50
6	**5f**	68.32	48.34	43.98
7	**5g**	56.76	48.27	46.77
8	**5h**	49.77	44.20	44.21
9	**5i**	59.79	52.23	40.98
10	**5j**	58.76	48.03	39.27
11	**5k**	40.20	46.73	41.04
12	**5l**	52.34	35.53	29.08
13	**5m**	68.75	54.41	46.88
14	**5n**	66.04	48.09	39.70
15	**5o**	58.97	47.93	42.33
16	**5p**	46.36	38.46	45.96
17	**Ningnanmycin**	82.03	55.27	52.16

3. Experimental

3.1. Instruments and Chemicals

Melting points were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., Beijing, China) and were not corrected. IR spectra were recorded on a Bruker VECTOR 22 spectrometer in KBr disks. ^{1}H- and ^{13}C-NMR spectral analyses (solvent $CDCl_3$ or DMSO-d_6) were performed on a JEOL-ECX 500 NMR spectrometer at room temperature using TMS as an internal standard. Elemental analyses were performed on an Elementar Vario-III CHN analyzer. MS spectra were recorded with a VG Autospec-3000 spectrometer. Analytical TLC was performed on silica gel GF254. Column chromatographic purification was carried out using silica gel GF254. Commercial reagents were used as received, unless otherwise indicated. Reactions were performed under a positive pressure of dry argon in oven-dried or flame-dried glassware equipped with a magnetic stir bar. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. All reagents were of analytical reagent grade or chemically pure. All solvents were dried, deoxygenated and redistilled before use.

3.2. Synthesis

3.2.1. General Synthetic Methods for **3a**–**d**

To a magnetically stirred solution of 6-substituted benzothiazole (6.80 mmol) in toluene (5 mL) benzofuran-2-methanal (6.80 mmol) dissolved in toluene (5 mL) was added dropwise at room temperature. After attaching a Dean Stark trap, the reaction was allowed to reflux after adding acetic acid (0.5 mL). Complete consumption of starting materials was observed after 24 h. After recrystallization from ethanol the final compounds **3a**–**d** were isolated in good yields.

3.2.2. Characterization of **3a**–**d**

N-(Benzofuran-2-ylmethylene)benzo[d]thiazol-2-amine (**3a**): yellow solid; mp:173–174 °C; yield: 77%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.11 (d, 1H, *J* = 5 Hz, 11-C<u>H</u>), 7.98 (d, 1H, *J* = 5 Hz, 9-C<u>H</u>), 7.89 (d, 1H, *J* = 5 Hz, 6-C<u>H</u>), 7.77 (d, 1H, *J* = 10 Hz, 17-C<u>H</u>), 7.61–7.54 (m, 2H, 7-C<u>H</u>, 8-C<u>H</u>), 7.52 (s, 1H, 20-C<u>H</u>), 7.47–7.46 (m, 2H, 18-C<u>H</u>, 19-C<u>H</u>), 7.43-7.39 (m, 1H, 14-C<u>H</u>); ^{13}C-NMR (DMSO-d_6) δ (ppm): 171.5 (2-<u>C</u>), 156.4 (16-<u>C</u>), 154.8 (4-<u>C</u>), 151.8 (11-<u>C</u>), 135.1 (12-<u>C</u>), 129.8 (5-<u>C</u>), 129.4 (15-<u>C</u>), 128.0 (8-<u>C</u>), 127.4 (7-<u>C</u>), 125.9 (19-<u>C</u>), 124.7 (18-<u>C</u>), 123.9 (6-<u>C</u>), 123.3 (9-<u>C</u>), 120.2 (17-<u>C</u>), 113.0 (20-<u>C</u>), 112.6 (14-<u>C</u>); IR (KBr, cm^{-1}) ν: 3049, 608, 1556, 1546, 1417, 1309, 1116, 954, 813, 750, 729; MS (ESI): *m/z* = 279 ([M+H]$^+$), 301 ([M+Na]$^+$).

N-(Benzofuran-2-ylmethylene)-6-chlorobenzo[d]thiazol-2-amine (**3b**): yellow solid; mp: 209–212 °C; yield: 76%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 9.17 (s, 1H, 6-C<u>H</u>), 8.23 (s, 1H, 11-C<u>H</u>), 7.96 (s, 1H, 17-C<u>H</u>), 7.91 (d, 1H, *J* = 5 Hz, 9-C<u>H</u>), 7.84 (d, 1H, *J* = 5 Hz, 8-C<u>H</u>), 7.72 (s, 1H, 20-C<u>H</u>), 7.54–7.54 (m, 2H, 18-C<u>H</u>, 19-C<u>H</u>), 7.36 (s, 1H, 14-C<u>H</u>); ^{13}C-NMR (DMSO-d_6) δ (ppm): 172.5 (2-<u>C</u>), 156.5 (16-<u>C</u>), 155.3 (4-<u>C</u>), 152.2 (11-<u>C</u>), 150.6 (6-<u>C</u>), 136.5 (12-<u>C</u>), 130.2 (5-<u>C</u>), 129.5 (15-<u>C</u>), 129.2 (8-<u>C</u>), 127.8 (7-<u>C</u>), 124.7 (19-<u>C</u>), 124.4 (18-<u>C</u>), 123.9 (9-<u>C</u>), 122.7 (17-<u>C</u>), 120.6 (20-<u>C</u>), 112.7 (14-<u>C</u>); IR (KBr, cm^{-1}) ν: 3086, 1598, 1539, 1425, 1330, 1294, 1166, 1122, 950, 812, 802, 738, 704, 605; MS (ESI): *m/z* = 313 ([M+H]$^+$), 335 ([M+Na]$^+$).

N-(Benzofuran-2-ylmethylene)-6-methoxybenzo[d]thiazol-2-amine (**3c**): yellow solid; mp: 147–150 °C; yield: 64%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 9.09–9.07 (m, 1H, 11-C<u>H</u>), 7.88 (d, 1H, *J* = 5 Hz, 17-C<u>H</u>), 7.81 (t, 2H, *J* = 15 Hz, 6-C<u>H</u>, 8-C<u>H</u>), 7.70 (t, 1H, *J* = 15 Hz, 9-C<u>H</u>), 7.62 (d, 1H, *J* = 5 Hz, 20-C<u>H</u>), 7.51 (d, 1H, *J* = 5 Hz, 19-C<u>H</u>), 7.34 (s, 1H, 14-C<u>H</u>), 7.09-7.07 (m, 1H, 18-C<u>H</u>), 3.81 (s, 3H, 22-C O$C\underline{H}_3$); ^{13}C-NMR (DMSO-d_6) δ (ppm): 168.9 (2-<u>C</u>), 157.9 (16-<u>C</u>), 156.3 (4-<u>C</u>), 153.5 (11-<u>C</u>), 152.4 (6-<u>C</u>), 146.1 (12-<u>C</u>), 136.5 (5-<u>C</u>), 129.1 (15-<u>C</u>), 128.0 (8-<u>C</u>), 124.6 (7-<u>C</u>), 124.0 (19-<u>C</u>), 123.7 (18-<u>C</u>), 119.4 (9-<u>C</u>), 116.6 (17-<u>C</u>), 112.5 (20-<u>C</u>), 105.6 (14-<u>C</u>), 56.2 (22-<u>C</u>); IR (KBr, cm^{-1}) ν: 3093, 1598, 1556, 1541, 1485, 1452, 1429, 1263, 1226, 1120, 1056, 1024, 954, 908, 833, 817, 756, 609; MS (ESI): *m/z* = 309 ([M+H]$^+$), 331 ([M+Na]$^+$).

N-(Benzofuran-2-ylmethylene)-6-methylbenzo[d]thiazol-2-amine (**3d**): yellow solid; mp: 185–190 °C; yelid: 78%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.37-8.36 (m, 2H, 11-C<u>H</u>, 6-C<u>H</u>), 8.05–8.00 (m, 2H, 9-C<u>H</u>, 17-C<u>H</u>), 7.92–7.90 (m, 2H, 18-C<u>H</u>, 19-C<u>H</u>), 7.51–7.47 (m, 2H, 14-C<u>H</u>, 20-C<u>H</u>), 7.46-7.40 (m, 1H, 8-C<u>H</u>), 2.43 (s, 3H, 21-$C\underline{H}_3$); ^{13}C-NMR (DMSO-d_6) δ (ppm): 181.4 (2-<u>C</u>), 170.5 (16-<u>C</u>), 166.2 (4-<u>C</u>), 154.3

(11-C), 129.8 (6-C), 129.3 (12-C), 128.8 (5-C), 126.9 (15-C), 124.7 (8-C), 123.8 (7-C), 122.9 (19-C), 122.5 (18-C), 121.3 (9-C), 120.0 (17-C), 117.9 (20-C), 112.9 (14-C), 21.7 (22-C); IR (KBr, cm^{-1}) ν: 3028, 1602, 1579, 1562, 1473, 1433, 1361, 1305, 1213, 1186, 1120, 956, 916, 858, 825, 750, 740, 686, 609; MS (ESI): *m/z* = 293 ($[M+H]^+$), 315 ($[M+Na]^+$).

3.2.3. General Synthetic Methods for **5a**–**p**

To a magnetically stirred solution of imines (0.50 mmol) in DCM (5 mL) malonic ester (0.7 mmol) was added dropwise at room temperature. The reaction was allowed to reach 35 °C, and complete consumption of starting materials was observed after 12–24 h. After removing the solvent by reduced pressure distillation, the mixture was subjected to column chromatography on silica gel (EA/PE = 1:7) to afford compounds **5a**–**p**.

Dimethyl 2-((Benzo[d]thiazol-2-ylamino)(benzofuran-2-yl)methyl) malonate (**5a**): white solid; mp: 70–72 °C; yield 82%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.61–7.58 (m, 2H, 24-CH, 27-CH), 7.52–7.47 (m, 1H, 14-CH), 7.45–7.41 (m, 1H, 17-CH), 7.33–7.26 (m, 2H, 25-CH, 26-CH), 7.24–7.18 (m, 1H, 16-CH), 7.15-7.09 (m, 1H, 15-CH), 6.71 (s, 1H, NH), 6.75 (d, 1H, *J* = 15 Hz, 11-CH), 6.07 (d, 1H, *J* = 10 Hz, 8-CH), 4.37–4.33 (m, 1H, 2-CH), 3.76 (s, 6H, 28-CH_3, 29-CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 168.4 (20-C), 167.1 (1-C), 165.8 (3-C), 155.0 (10-C), 154.1 (13-C), 152.1 (22-C), 131.0 (23-C), 128.1 (12-C), 126.1 (15-C), 124.5 (16-C), 123.1 (25-C), 122.3 (26-C), 121.3 (24-C), 121.0 (27-C), 119.7 (14-C), 111.3 (17-C), 104.7 (11-C), 53.9 (8-C), 53.8 (2-C), 53.1 (28-C), 52.8 (29-C); MS (ESI): *m/z* = 411 ($[M+H]^+$), 433 ($[M+Na]^+$); MS (HREI): $C_{21}H_{18}N_2O_5S$ Na for +, calculated 410.0940, found 410.0940; IR (KBr, cm^{-1}) ν 3385, 2951, 1745, 1732, 1595, 1539, 1452, 1435, 1355, 1259, 1207, 1172, 1014, 966, 750, 725.

Diethyl 2-((Benzo[d]thiazol-2-ylamino)(benzofuran-2-yl)methyl) malonate (**5b**): white solid; mp: 110–112 °C; yield 80%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.59 (d, 2H, *J* = 5 Hz, 24-CH, 27-CH), 7.50 (s, 1H, 14-CH), 7.43 (s, 1H, 17-CH), 7.31–7.26 (m, 3H, 25-CH, 26-CH, 16-CH), 7.20 (s, 1H, 15-CH), 7.12 (s, 1H, NH), 6.75 (s, 1H, 11-CH), 6.08 (s, 1H, 8-CH), 4.33 (d, 1H, *J* = 5 Hz, 2-CH), 4.25–4.17 (m, 4H, 28-CH_2, 30-CH_2), 1.21 (s, 6H, 29-CH_3, 31-CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 168.1 (20-C), 166.7 (1-C), 165.9 (3-C), 155.0 (10-C), 154.3 (13-C), 152.1 (22-C), 131.0 (23-C), 128.1 (12-C), 126.0 (15-C), 124.5 (16-C), 123.1 (25-C), 122.2 (26-C), 121.3 (24-C), 120.9 (27-C), 119.6 (14-C), 111.2 (17-C), 104.7 (11-C), 62.5 (28-C), 62.1 (30-C), 54.1 (8-C), 52.8 (2-C), 14.1 (29-C), 14.0 (31-C); MS (ESI): *m/z* = 439 ($[M+H]^+$), 461 ($[M+Na]^+$); MS (HREI): $C_{23}H_{22}N_2O_5S$ Na for +, calculated 438.1249, found 438.1253; IR (KBr, cm^{-1}) ν 3369, 1739, 1718, 1537, 1485, 1454, 1286, 1242, 1201, 1184, 1176, 1018, 947, 802, 758.

Dipropyl 2-((Benzo[d]thiazol-2-ylamino)(benzofuran-2-yl)methyl) malonate (**5c**): white solid; mp: 127–129 °C; yield 78%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.59–7.55 (m, 2H, 24-CH, 27-CH), 7.48 (d, 1H, *J* = 5 Hz, 14-CH), 7.42 (d, 1H, *J* = 5 Hz, 17-CH), 7.30–7.23 (m, 2H, 25-CH, 26-CH), 7.19 (t, 1H, *J* = 5 Hz, 16-CH), 7.09 (t, 1H, *J* = 5 Hz, 15-CH), 6.73 (d, 1H, *J* = 5 Hz, 11-CH), 6.07 (s, 1H, NH), 4.35–4.32 (m, 1H, 8-CH), 4.13-4.09 (m, 4H, 28-CH_2, 29- CH_2), 3.40 (d, 1H, *J* = 5 Hz, 2-CH), 1.61–1.56 (m, 4H, 30-CH_2, 31-CH_2), 0.87-0.82 (m, 6H, 32-CH_3, 33-CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 168.3 (20-C), 166.8 (1-C),

165.7 (3-C), 155.0 (10-C), 154.4 (13-C), 152.2 (22-C), 131.0 (23-C), 128.1 (12-C), 126.0, (15-C) 124.4 (16-C), 123.1 (25-C), 122.2 (26-C), 121.3 (24-C), 120.9 (27-C), 119.7 (14-C), 111.2 (17-C), 104.6 (11-C), 68.0 (28-C), 67.7 (29-C), 54.0 (8-C), 52.8 (2-C), 21.9 (30-C), 21.8 (31-C), 10.3 (32-C), 10.2 (33-C); MS (ESI): *m/z* = 467 ($[M+H]^+$), 489 ($[M+Na]^+$); MS (HREI): $C_{25}H_{26}N_2O_5S$ Na for +, calculated 438.1249, found 466.1550; IR (KBr, cm^{-1}) ν 3356, 2962, 1751, 1724, 1600, 1564, 1548, 1454, 1442, 1386, 1313, 1271, 1176, 1136, 1053, 925, 815, 759, 754.

Dibenzyl 2-((Benzo[d]thiazol-2-ylamino)(benzofuran-2-yl)methyl) malonate (**5d**): white solid; mp: 110–112 °C; yield 62%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.57 (d, 1H, *J* = 10 Hz, 24-CH), 7.54 (d, 1H, *J* = 10 Hz, 27-CH), 7.44 (d, 1H, *J* = 10 Hz, 14-CH), 7.34–7.32 (m, 10H, 31-CH, 32-CH, 33-CH, 34-CH, 35-CH, 37-CH, 38-CH, 39-CH, 40-CH, 41-CH), 7.25 (s, 1H, NH), 7.19–7.18 (m, 1H, 17-CH), 7.16–7.15 (m, 2H, 25-CH, 26-CH), 7.13–7.11 (m, 2H, 15-CH, 16-CH), 6.65 (s, 1H, 11-CH), 5.17 (s, 4H, 28-CH_2, 29-CH_2), 4.44 (d, 1H, *J* = 5 Hz, 8-CH), 3.48 (s, 1H, 2-CH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 167.9 (20-C), 166.4 (1-C), 166.3 (3-C), 165.5 (10-C), 155.0 (13-C), 154.1 (22-C), 152.1 (30-C), 135.3 (36-C), 134.8 (23-C), 134.7 (32-C), 131.1 (34-C), 128.7 (38-C), 128.6 (40-C), 128.5 (12-C), 128.5 (31-C), 128.4 (35-C), 128.3 (37-C), 128.2 (41-C), 128.1 (39-C), 126.0 (33-C), 124.5 (15-C), 123.1 (26-C), 122.2 (25-C), 121.3 (16-C), 120.9 (24-C), 119.7 (17-C), 111.3 (27-C), 104.7 (14-C), 67.4 (11-C), 54.1 (28-C), 54.0 (29-C), 52.6 (8-C), 41.7 (2-C); MS (ESI): *m/z* = 563 ($[M+H]^+$), 585 ($[M+Na]^+$); MS (HREI): $C_{33}H_{26}N_2O_5S$ Na for +, calculated 562.1562, found 562.1569; IR (KBr, cm^{-1}) ν 3352, 2922, 1747, 1716, 1537, 1454, 1444, 1348, 1249, 1172, 954, 750, 727.

Dimethyl 2-(Benzofuran-2-yl((6-chlorobenzo[d]thiazol-2-yl)amino)methyl) malonate (**5e**): white solid; mp: 115–117 °C; yield 85%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.53 (s, 1H, 24-CH), 7.49 (d, 1H, *J* = 5 Hz, 27-CH), 7.46 (d, 1H, *J* = 5 Hz, 14-CH), 7.42 (d, 1H, *J* = 5 Hz, 17-CH), 7.26 (d, 1H, *J* = 5 Hz, 25-CH), 7.22–7.17 (m, 2H, 26-CH, 15-CH), 6.73 (d, 1H, *J* = 5 Hz, 11-CH), 6.03 (s, 1H, NH), 5.29 (d, 1H, *J* = 5 Hz, 8-CH), 4.32-4.31 (m, 1H, 2-CH), 3.73 (s, 6H, 29-CH_3, 30-CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 168.4 (20-C), 167.0 (1-C), 165.9 (3-C), 155.0 (10-C), 153.8 (13-C), 150.8 (22-C), 132.2 (23-C), 128.0 (12-C), 127.4 (15-C), 126.5 (16-C), 124.6 (25-C), 123.2 (26-C), 121.4 (24-C), 120.6 (27-C), 120.3 (14-C), 111.3 (17-C), 104.7 (11-C), 53.7 (8-C), 53.4 (2-C), 53.1 (29-C), 52.7 (30-C); MS (ESI): *m/z* = 445 ($[M+H]^+$), 467 ($[M+Na]^+$); MS (HREI): $C_{21}H_{17}ClN_2O_5S$ Na for +, calculated 444.0547, found 444.0547; IR (KBr, cm^{-1}) ν 3340, 2954, 1745, 1593, 1537, 1483, 1436, 1359, 1226, 1161, 1138, 1037, 974, 954, 875, 812, 759.

Diethyl 2-(Benzofuran-2-yl((6-chlorobenzo[d]thiazol-2-yl)amino)methyl) malonate (**5f**): white solid; mp: 92–94 °C; yield 86%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.53 (s, 1H, 24-CH), 7.49 (d, 1H, *J* = 5 Hz, 27-CH), 7.45 (d, 1H, *J* = 5 Hz, 14-CH), 7.42 (d, 1H, *J* = 5 Hz, 17-CH), 7.26 (d, 1H, *J* = 5 Hz, 26-CH), 7.22–7.17 (m, 2H, 15-CH, 16-CH), 6.94 (s, 1H, 11-CH), 6.72 (s, 1H, 8-CH), 6.05 (s, 1H, NH), 4.28 (d, 1H, *J* = 5 Hz, 2-CH), 4.24–4.13 (m, 4H, 28-CH_2, 30-CH_2), 1.21–1.16 (m, 6H, 29-CH_3, 31-CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 168.1 (20-C), 166.6 (1-C), 165.9 (3-C), 155.0 (10-C), 154.1 (13-C), 150.8 (22-C), 132.2 (23-C), 128.0 (12-C), 127.3 (15-C), 126.5 (16-C), 124.5 (25-C), 123.1 (26-C), 121.3 (24-C), 120.6 (27-C), 120.3 (14-C), 111.3 (17-C), 104.7 (11-C), 62.5 (28-C), 62.2 (30-C), 54.0 (8-C), 52.7 (2-C), 14.1 (29-C), 14.0 (31-C); MS (ESI): *m/z* = 473 ($[M+H]^+$), 495 ($[M+Na]^+$); MS (HREI): $C_{23}H_{21}ClN_2O_5S$ Na for +,

calculated 472.0860, found 472.0850; IR (KBr, cm^{-1}) ν 3346, 2974, 1741, 1718, 1537, 1483, 1396, 1367, 1301, 1242, 1172, 1029, 974, 812, 763.

Dipropyl 2-(Benzofuran-2-yl((6-chlorobenzo[d]thiazol-2-yl)amino)methyl) malonate (**5g**): white solid; mp: 88–90 °C; yield 82%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.54 (s, 1H, 24-C<u>H</u>), 7.49 (d, 1H, *J* = 5 Hz, 27-C<u>H</u>), 7.45 (d, 1H, *J* = 5 Hz, 14-C<u>H</u>), 7.42 (d, 1H, *J* = 5 Hz, 17-C<u>H</u>), 7.27–7.22 (m, 2H, 25-C<u>H</u>, 26-C<u>H</u>), 7.20-7.17 (m, 1H, 15-C<u>H</u>), 6.93 (s, 1H, 11-C<u>H</u>), 6.72 (s, 1H, 8-C<u>H</u>), 6.05 (s, 1H, N<u>H</u>), 4.31 (d, 1H, *J* = 5 Hz, 2-C<u>H</u>), 4.14-4.06 (m, 4H, 29-C<u>H</u>$_2$, 30-C<u>H</u>$_2$), 1.61–1.57 (m, 4H, 31-C<u>H</u>$_2$, 32-C<u>H</u>$_2$), 0.87–0.83 (m, 6H, 33-C<u>H</u>$_3$, 34-C<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 168.3 (20-<u>C</u>), 166.7 (1-<u>C</u>), 165.8 (3-<u>C</u>), 155.0 (10-<u>C</u>), 154.1 (13-<u>C</u>), 150.8 (22-<u>C</u>), 132.2 (23-<u>C</u>), 128.1 (12-<u>C</u>), 127.3 (15-<u>C</u>), 126.5 (16-<u>C</u>), 124.5 (25-<u>C</u>), 123.1 (26-<u>C</u>), 121.3 (24-<u>C</u>), 120.6 (27-<u>C</u>), 120.3 (14-<u>C</u>), 111.3 (17-<u>C</u>), 104.7 (11-<u>C</u>), 68.0 (29-<u>C</u>), 67.7 (30-<u>C</u>), 54.0 (8-<u>C</u>), 52.7 (2-<u>C</u>), 21.9 (31-<u>C</u>), 21.8 (32-<u>C</u>), 10.4 (33-<u>C</u>), 10.3 (34-<u>C</u>); MS (ESI): *m/z* = 501 ($[M+H]^+$), 523 ($[M+Na]^+$); MS (HREI): $C_{25}H_{25}ClN_2O_5S$ Na for +, calculated 500.1173, found 500.1171; IR (KBr, cm^{-1}) ν 3357, 2966, 1747, 1720, 1593, 1533, 1483, 1446, 1392, 1354, 1290, 1238, 1197, 1172, 1053, 945, 812, 759.

Dibenzyl 2-(Benzofuran-2-yl((6-chlorobenzo[d]thiazol-2-yl)amino)methyl) malonate (**5h**): white solid; mp: 116–118 °C; yield 67%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.53 (s, 1H, 24-C<u>H</u>), 7.45 (d, 1H, *J* = 10 Hz, 27-C<u>H</u>), 7.42 (d, 1H, *J* = 5 Hz, 14-C<u>H</u>), 7.36–7.66 (m, 7H, 31-C<u>H</u>, 32-C<u>H</u>, 33-C<u>H</u>, 34-C<u>H</u>, 35-C<u>H</u>, 37-C<u>H</u>, 38-C<u>H</u>), 7.26–7.24 (m, 2H, 39-C<u>H</u>, 40-C<u>H</u>), 7.19–7.18 (m, 2H, 17-C<u>H</u>, 41-C<u>H</u>), 7.17–7.15 (m, 2H, 15-C<u>H</u>, 26-C<u>H</u>), 7.13–7.11 (m, 2H, 11-C<u>H</u>, 26-C<u>H</u>), 6.81 (s, 1H, N<u>H</u>), 6.11 (s, 1H, 8-C<u>H</u>), 5.17–5.14 (m, 4H, 28-C<u>H</u>$_2$, 29-C<u>H</u>$_2$), 3.47 (s, 1H, 2-C<u>H</u>); ^{13}C-NMR ($CDCl_3$) δ (ppm): 168.0 (20-<u>C</u>), 166.4 (1-<u>C</u>), 165.6 (3-<u>C</u>), 155.0 (10-<u>C</u>), 153.8 (13-<u>C</u>), 150.8 (22-<u>C</u>), 135.3 (30-<u>C</u>), 134.7 (36-<u>C</u>), 134.6 (23-<u>C</u>), 132.3 (32-<u>C</u>), 128.7 (34-<u>C</u>), 128.6 (38-<u>C</u>), 128.6 (40-<u>C</u>), 128.5 (12-<u>C</u>), 128.5 (31-<u>C</u>), 128.5 (35-<u>C</u>), 128.4 (37-<u>C</u>), 128.4 (41-<u>C</u>), 128.2 (39-<u>C</u>), 128.0 (33-<u>C</u>), 127.4 (15-<u>C</u>), 126.5 (26-<u>C</u>), 124.6 (25-<u>C</u>), 123.2 (16-<u>C</u>), 121.4 (24-<u>C</u>), 120.5 (17-<u>C</u>), 120.4 (27-<u>C</u>), 111.3 (14-<u>C</u>), 104.7 (11-<u>C</u>), 68.2 (28-<u>C</u>), 67.8 (29-<u>C</u>), 54.0 (8-<u>C</u>), 41.9 (2-<u>C</u>); MS (ESI): *m/z* = 597 ($[M+H]^+$), 619 ($[M+Na]^+$); MS (HREI): $C_{33}H_{25}ClN_2O_5S$ Na for +, calculated 596.1173, found 596.1189; IR (KBr, cm^{-1}) ν 3388, 2966, 1745, 1730, 1599, 1543, 1529, 1487, 1454, 1381, 1259, 1220, 1147, 1004, 817, 748, 694.

Dimethyl 2-(Benzofuran-2-yl((6-methoxybenzo[d]thiazol-2-yl)amino)methyl) malonate (**5i**): white solid; mp: 85–87 °C; yield 81%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.49–7.45 (m, 2H, 24-C<u>H</u>, 27-C<u>H</u>), 7.42 (d, 1H, *J* = 5 Hz, 14-C<u>H</u>), 7.27–7.23 (m, 1H, 17-C<u>H</u>), 7.20–7.17 (m, 1H, 25-C<u>H</u>), 7.11 (s, 1H, 26-C<u>H</u>), 6.89 (d, 1H, *J* = 5 Hz, 15-C<u>H</u>), 6.73 (d, 1H, *J* = 5 Hz, 11-C<u>H</u>), 6.64 (s, 1H, N<u>H</u>), 6.01 (s, 1H, 8-C<u>H</u>), 4.34–4.32 (m, 1H, 2-C<u>H</u>), 3.80 (s, 3H, 29-C-OC<u>H</u>$_3$), 3.73 (s, 6H, 30-C<u>H</u>$_3$, 31-C<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 168.4 (20-<u>C</u>), 167.1 (1-<u>C</u>), 164.1 (3-<u>C</u>), 155.6 (10-<u>C</u>), 154.9 (13-<u>C</u>), 154.2 (22-<u>C</u>), 146.3 (23-<u>C</u>), 132.0 (12-<u>C</u>), 128.1 (15-<u>C</u>), 124.5 (16-<u>C</u>), 123.1 (25-<u>C</u>), 121.3 (26-<u>C</u>), 120.0 (24-<u>C</u>), 113.7 (27-<u>C</u>), 111.3 (14-<u>C</u>), 105.3 (17-<u>C</u>), 104.7 (11-<u>C</u>), 56.1 (8-<u>C</u>), 53.9 (2-<u>C</u>), 53.3 (29-<u>C</u>), 53.1 (30-<u>C</u>), 52.8 (31-<u>C</u>); MS (ESI): *m/z* = 441 ($[M+H]^+$), 463 ($[M+Na]^+$); MS (HREI): $C_{22}H_{20}N_2O_6S$ Na for +, calculated 440.1042, found 440.1047; IR (KBr, cm^{-1}) ν 3377, 2953, 1745, 1724, 1604, 1544, 1483, 1471, 1454, 1436, 1359, 1247, 1170, 1058, 1029, 968, 815, 759.

Diethyl 2-(benzofuran-2-yl((6-methoxybenzo[d]thiazol-2-yl)amino)methyl) malonate (**5j**): white solid; mp: 85–88 °C; yield 80%; ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.50–7.45 (m, 2H, 24-C<u>H</u>, 27-C<u>H</u>), 7.42 (d, 1H, *J* = 5 Hz, 14-C<u>H</u>), 7.26–7.23 (m, 1H, 17-C<u>H</u>), 7.20–7.17 (m, 1H, 26-C<u>H</u>), 7.11 (s, 1H, 15-C<u>H</u>), 6.90–6.87 (m, 1H, 16-C<u>H</u>), 6.72 (s, 1H, 11-C<u>H</u>), 6.70 (s, 1H, N<u>H</u>), 6.02 (s, 1H, 8-C<u>H</u>), 4.29 (d, 1H, *J* = 5 Hz, 2-C<u>H</u>), 4.24–4.14 (m, 4H, 28-C<u>H$_2$</u>, 30-C<u>H$_2$</u>), 3.80 (s, 3H, 25-C-OC<u>H$_3$</u>), 1.21–1.17 (m, 6H, 29-C<u>H$_3$</u>, 31-C<u>H$_3$</u>); ^{13}C-NMR ($CDCl_3$) δ (ppm): 168.1 (20-<u>C</u>), 166.7 (1-<u>C</u>), 164.1 (3-<u>C</u>), 155.5 (10-<u>C</u>), 154.9 (13-<u>C</u>), 154.5 (22-<u>C</u>), 146.3 (23-<u>C</u>), 131.9 (12-<u>C</u>), 128.1 (15-<u>C</u>), 124.4 (16-<u>C</u>), 123.1 (25-<u>C</u>), 121.3 (26-<u>C</u>), 120.0 (24-<u>C</u>), 113.7 (27-<u>C</u>), 111.2 (14-<u>C</u>), 105.3 (17-<u>C</u>), 104.6 (11-<u>C</u>), 62.4 (28-<u>C</u>), 62.1 (30-<u>C</u>), 55.9 (8-<u>C</u>), 54.1 (25-C), 52.7 (2-<u>C</u>), 14.1 (29-<u>C</u>), 14.0 (31-<u>C</u>); MS (ESI): *m/z* = 469 ([M+H]$^+$), 491 ([M+Na]$^+$); MS (HREI): $C_{24}H_{24}N_2O_6S$ Na for +, calculated 468.1355, found 468.1336; IR (KBr, cm^{-1}) ν 3377, 2974, 1745, 1712, 1602, 1543, 1490, 1469, 1436, 1280, 1188, 1033, 981, 855, 825, 756.

Dipropyl 2-(Benzofuran-2-yl((6-methoxybenzo[d]thiazol-2-yl)amino)methyl) malonate (**5k**): white solid; mp: 67–70 °C; yield 79%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.49–7.45 (m, 3H, 24-C<u>H</u>, 27-C<u>H</u>, 14-C<u>H</u>), 7.25–7.06 (m, 3H, 17-C<u>H</u>, 25-C<u>H</u>, 26-C<u>H</u>), 6.89-6.81 (m, 1H, 15-C<u>H</u>), 6.72 (s, 1H, 11-C<u>H</u>), 6.62 (s, 1H, N<u>H</u>), 5.98 (s, 1H, 8-C<u>H</u>), 4.31–4.26 (m, 1H, 2-C<u>H</u>), 4.08–4.01 (m, 4H, 29-C<u>H$_2$</u>, 30-C<u>H$_2$</u>), 3.80 (s, 3H, 28-C-OC<u>H$_3$</u>), 1.60-1.52 (m, 4H, 31-C<u>H$_2$</u>, 32-C<u>H$_2$</u>), 0.87–0.77 (m, 6H, 33-C<u>H$_3$</u>, 34-C<u>H$_3$</u>); ^{13}C-NMR ($CDCl_3$) δ (ppm): 168.2 (20-<u>C</u>), 166.8 (1-<u>C</u>), 164.0 (3-<u>C</u>), 155.5 (10-<u>C</u>), 155.0 (13-<u>C</u>), 154.5 (22-<u>C</u>), 146.3 (23-<u>C</u>), 132.0 (12-<u>C</u>), 128.2 (15-<u>C</u>), 124.4 (16-<u>C</u>), 123.0 (25-<u>C</u>), 121.2 (26-<u>C</u>), 120.0 (24-<u>C</u>), 113.6 (27-<u>C</u>), 111.2 (14-<u>C</u>), 105.3 (17-<u>C</u>), 104.6 (11-<u>C</u>), 67.9 (29-<u>C</u>), 67.6 (30-<u>C</u>), 56.0 (8-<u>C</u>), 54.1 (2-<u>C</u>), 52.7 (28-<u>C</u>), 21.8 (31-<u>C</u>), 21.7 (32-<u>C</u>), 10.3 (33-<u>C</u>), 10.2 (34-<u>C</u>); MS (ESI): *m/z* = 497 ([M+H]$^+$), 519 ([M+Na]$^+$); MS (HREI): $C_{26}H_{28}N_2O_6S$ Na for +, calculated 496.1668, found 496.1669; IR (KBr, cm^{-1}) ν 3348, 2951, 1741, 1716, 1604, 1543, 1483, 1357, 1288, 1172, 1064, 947, 850, 806, 759.

Dibenzyl 2-(Benzofuran-2-yl((6-methoxybenzo[d]thiazol-2-yl)amino)methyl) malonate (**5l**): white solid; mp: 110–112 °C; yield 60%; ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.42 (d, 2H, *J* = 5 Hz, 27-C<u>H</u>, 24-C<u>H</u>), 7.35 (d, 1H, *J* = 5 Hz, 14-C<u>H</u>), 7.27–7.23 (m, 14H, 31-C<u>H</u>, 32-C<u>H</u>, 33-C<u>H</u>, 34-C<u>H</u>, 35-C<u>H</u>, 37-C<u>H</u>, 38-C<u>H</u>, 39-C<u>H</u>, 40-C<u>H</u>, 17-C<u>H</u>, 41-C<u>H</u>, 15-C<u>H</u>, 26-C<u>H</u>, 11-C<u>H</u>), 6.90–6.88 (m, 1H, 26-C<u>H</u>), 6.64 (s, 1H, N<u>H</u>), 6.01 (s, 1H, 8-C<u>H</u>), 5.19-5.06 (m, 4H, 28-C<u>H$_2$</u>, 29-C<u>H$_2$</u>), 4.43 (d, 1H, *J* = 5 Hz, 2-C<u>H</u>), 3.80 (s, 3H, 25-C-OC<u>H$_3$</u>); ^{13}C-NMR ($CDCl_3$) δ (ppm): 167.9 (20-<u>C</u>), 166.5 (1-<u>C</u>), 163.8 (3-<u>C</u>), 155.6 (10-<u>C</u>), 155.0 (13-<u>C</u>), 154.2 (22-<u>C</u>), 146.3 (30-<u>C</u>), 134.8 (36-<u>C</u>), 134.7 (23-<u>C</u>), 132.1 (32-<u>C</u>), 128.7 (34-<u>C</u>), 128.6 (38-<u>C</u>), 128.5 (40-<u>C</u>), 128.5 (12-<u>C</u>), 128.5 (31-<u>C</u>), 128.4 (35-<u>C</u>), 128.4 (37-<u>C</u>), 128.3 (41-<u>C</u>), 128.2 (39-<u>C</u>), 128.1 (33-<u>C</u>), 124.4 (15-<u>C</u>), 123.1 (26-<u>C</u>), 121.3 (25-<u>C</u>), 120.1 (16-<u>C</u>), 113.7 (24-<u>C</u>), 111.3 (17-<u>C</u>), 105.3 (27-<u>C</u>), 104.7 (14-<u>C</u>), 68.1 (11-<u>C</u>), 67.8, 67.8 (28-C, 29-<u>C</u>), 56.0 (25-C), 54.2 (8-<u>C</u>), 52.6 (2-<u>C</u>); MS (ESI): *m/z* = 593 ([M+H]$^+$), 615 ([M+Na]$^+$); MS (HREI): $C_{34}H_{28}N_2O_6S$ Na for +, calculated 592.1668, found 592.1687; IR (KBr, cm^{-1}) ν 3350, 2954, 1747, 1716, 1602, 1543, 1469, 1454, 1348, 1222, 1172, 1028, 954, 823, 750, 696.

Dimethyl 2-(Benzofuran-2-yl((6-methylbenzo[d]thiazol-2-yl)amino)methyl) malonate (**5m**): white solid; mp: 108–109 °C; yield 81%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.48 (d, 1H, *J* = 5 Hz, 24-C<u>H</u>), 7.45 (d, 1H, *J* = 5 Hz, 27-C<u>H</u>), 7.42 (d, 1H, *J* = 5 Hz, 14-C<u>H</u>), 7.38 (s, 1H, 17-C<u>H</u>), 7.25 (t, 1H, *J* = 15 Hz, 25-C<u>H</u>), 7.29 (t, 1H, *J* = 15 Hz, 26-C<u>H</u>), 7.10 (d, 1H, *J* = 5 Hz, 15-C<u>H</u>), 6.72 (s, 1H, 11-C<u>H</u>), 6.71 (s, 1H, N<u>H</u>),

6.01 (s, 1H, 8-C<u>H</u>), 4.43 (d, 1H, *J* = 5 Hz, 2-C<u>H</u>), 3.73 (s, 6H, 29-C<u>H</u>$_3$, 30-C<u>H</u>$_3$), 2.38 (s, 3H, 28-C<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 168.4 (20-<u>C</u>), 167.0 (1-<u>C</u>), 165.1 (3-<u>C</u>), 155.0 (10-<u>C</u>), 154.2 (13-<u>C</u>), 150.0 (22-<u>C</u>), 132.1 (23-<u>C</u>), 131.0 (12-<u>C</u>), 128.1 (15-<u>C</u>), 127.2 (16-<u>C</u>), 124.5 (25-<u>C</u>), 123.1 (26-<u>C</u>), 121.3 (24-<u>C</u>), 121.0 (27-<u>C</u>), 119.3 (14-<u>C</u>), 111.3 (17-<u>C</u>), 104.7 (11-<u>C</u>), 53.8 (8-<u>C</u>), 53.3 (2-<u>C</u>), 53.0 (29-<u>C</u>), 52.8 (30-<u>C</u>), 21.3 (28-<u>C</u>); MS (ESI): *m/z* = 425 ($[M+H]^+$), 447 ($[M+Na]^+$); MS (HREI): $C_{22}H_{20}N_2O_5S$ Na for +, calculated 424.1093, found 424.1097; IR (KBr, cm^{-1}) ν 3361, 2954, 1743, 1724, 1539, 1487, 1454, 1435, 1357, 1224, 1172, 1147, 1033, 972, 817, 759.

Diethyl 2-(Benzofuran-2-yl((6-methylbenzo[d]thiazol-2-yl)amino)methyl) malonate (**5n**): white solid; mp: 105–107 °C; yield 76%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.48-7.47 (d, 1H, *J* = 5 Hz, 24-C<u>H</u>), 7.45 (d, 1H, *J* = 5 Hz, 27-C<u>H</u>), 7.42 (d, 1H, *J* = 5 Hz, 14-C<u>H</u>), 7.38 (s, 1H, 17-C<u>H</u>), 7.25 (t, 1H, *J* = 15 Hz, 26-C<u>H</u>), 7.20–7.17 (m, 1H, 15-C<u>H</u>), 7.10 (d, 1H, *J* = 5 Hz, 16-C<u>H</u>), 6.74 (s, 1H, N<u>H</u>), 6.72 (s, 1H, 11-C<u>H</u>), 6.03 (s, 1H, 8-C<u>H</u>), 4.29 (m, 1H, 2-C<u>H</u>), 4.24–4.14 (m, 4H, 28-C<u>H</u>$_2$, 30-C<u>H</u>$_2$), 2.38 (s, 3H, 25-C<u>H</u>$_3$), 1.21–1.16 (m, 6H, 29-C<u>H</u>$_3$, 31-C<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 168.1 (20-<u>C</u>), 165.1 (1-<u>C</u>), 155.0 (3-<u>C</u>), 154.5 (10-<u>C</u>), 150.0 (13-<u>C</u>), 133.7 (22-<u>C</u>), 132.0 (23-<u>C</u>), 131.0 (12-<u>C</u>), 128.1 (15-<u>C</u>), 127.2 (16-<u>C</u>), 124.4 (25-<u>C</u>), 123.0 (26-<u>C</u>), 121.3 (24-<u>C</u>), 121.0 (27-<u>C</u>), 119.2 (14-<u>C</u>), 111.2 (17-<u>C</u>), 104.6 (11-<u>C</u>), 62.4 (28-<u>C</u>), 62.1 (30-<u>C</u>), 54.1 (8-<u>C</u>), 52.8 (2-<u>C</u>), 21.3 (25-C), 14.1 (29-<u>C</u>), 14.0 (31-<u>C</u>); MS (ESI): *m/z* = 453 ($[M+H]^+$), 475 ($[M+Na]^+$); MS (HREI): $C_{24}H_{24}N_2O_5S$ Na for +, calculated 452.1406, found 452.1407; IR (KBr, cm^{-1}) ν 3352, 2976, 1743, 1720, 1600, 1560, 1541, 1487, 1456, 1336, 1301, 1238, 1172, 1029, 939, 858, 810, 763.

Dipropyl 2-(Benzofuran-2-yl((6-methylbenzo[d]thiazol-2-yl)amino)methyl) malonate (**5o**): white solid; mp: 76–78 °C; yield 73%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.48–7.43 (m, 3H, 24-C<u>H</u>, 27-C<u>H</u>, 14-C<u>H</u>), 7.41 (d, 1H, *J* = 10 Hz, 17-C<u>H</u>), 7.38 (s, 1H, 25-C<u>H</u>), 7.25–7.23 (m, 1H, 26-C<u>H</u>), 7.10–7.08 (m, 1H, 15-C<u>H</u>), 6.80 (s, 1H, 11-C<u>H</u>), 6.71 (s, 1H, N<u>H</u>), 6.04 (s, 1H, 8-C<u>H</u>), 4.33-4.32 (m, 1H, 2-C<u>H</u>), 4.13–4.06 (m, 4H, 29-C<u>H</u>$_2$, 30-C<u>H</u>$_2$), 2.38 (s, 3H, 28-CH_3), 1.61-1.56 (m, 4H, 31-C<u>H</u>$_2$, 32-C<u>H</u>$_2$), 0.87–0.82 (m, 6H, 33-C<u>H</u>$_3$, 34-C<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 168.2 (20-<u>C</u>), 166.8 (1-<u>C</u>), 165.1 (3-<u>C</u>), 155.0 (10-<u>C</u>), 154.5 (13-<u>C</u>), 150.0 (22-<u>C</u>), 132.0 (23-<u>C</u>), 131.0 (12-<u>C</u>), 128.1 (15-<u>C</u>), 127.2 (16-<u>C</u>), 124.4 (25-<u>C</u>), 123.0 (26-<u>C</u>), 121.3 (24-<u>C</u>), 121.0 (27-<u>C</u>), 119.2 (14-<u>C</u>), 111.2 (17-<u>C</u>), 104.6 (11-<u>C</u>), 68.0 (29-<u>C</u>), 67.6 (30-<u>C</u>), 54.1 (8-<u>C</u>), 52.8 (2-<u>C</u>), 21.9 (28-<u>C</u>), 21.8 (31-<u>C</u>), 21.3 (32-<u>C</u>), 10.3 (33-<u>C</u>), 10.2 (34-<u>C</u>); MS (ESI): *m/z* = 481($[M+H]^+$), 503 ($[M+Na]^+$); MS (HREI): $C_{26}H_{28}N_2O_5S$ Na for +, calculated 480.1719, found 480.1711; IR (KBr, cm^{-1}) ν 3365, 2966, 1747, 1722, 1535, 1483, 1456, 1354, 1290, 1172, 1055, 954, 808, 761.

Dibenzyl 2-(Benzofuran-2-yl((6-methylbenzo[d]thiazol-2-yl)amino)methyl) malonate (**5p**): white solid; mp: 126–128 °C; yield 64%; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.43–7.41 (m, 2H, 27-C<u>H</u>, 24-C<u>H</u>), 7.35–7.31 (m, 3H, 14-C<u>H</u>, 31-C<u>H</u>, 32-C<u>H</u>), 7.23–7.14 (m, 10H, 33-C<u>H</u>, 34-C<u>H</u>, 35-C<u>H</u>, 37-C<u>H</u>, 38-C<u>H</u>, 39-C<u>H</u>, 40-C<u>H</u>, 17-C<u>H</u>, , 41-C<u>H</u>, 15-C<u>H</u>), 7.12–7.08 (m, 3H, 26-C<u>H</u>, 11-C<u>H</u>, 26-C<u>H</u>), 6.64–6.62 (m, 1H, N<u>H</u>), 6.10 (s, 1H, 8-C<u>H</u>), 5.17–5.04 (m, 4H, 28-C<u>H</u>$_2$, 29-C<u>H</u>$_2$), 4.43-4.41 (m, 1H, 2-C<u>H</u>), 2.39–2.37 (s, 3H, 25-C<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 167.9 (20-<u>C</u>), 166.5 (1-<u>C</u>), 165.0 (3-<u>C</u>), 155.0 (10-<u>C</u>), 154.2 (13-<u>C</u>), 150.0 (22-<u>C</u>), 134.8 (30-<u>C</u>), 134.7 (36-<u>C</u>), 132.0 (23-<u>C</u>), 131.1 (32-<u>C</u>), 128.7 (34-<u>C</u>), 128.7 (38-<u>C</u>), 128.6 (40-<u>C</u>), 128.6 (12-<u>C</u>), 128.5 (31-<u>C</u>), 128.5 (35-<u>C</u>), 128.2 (37-<u>C</u>), 128.2 (41-<u>C</u>), 128.1 (39-<u>C</u>), 128.1 (33-<u>C</u>),

127.2 (15-C), 127.2 (26-C), 124.7 (25-C), 123.1 (16-C), 121.4 (24-C), 121.0 (17-C), 119.3 (27-C), 111.3 (14-C), 104.7 (11-C), 68.1 (28-C), 67.8 (29-C), 54.1 (8-C), 52.7 (2-C), 21.4 (25-C); MS (ESI): *m/z* = 577 ($[M+H]^+$), 599 ($[M+Na]^+$); MS (HREI): $C_{34}H_{28}N_2O_5S$ Na for +, calculated 576.1719, found 576.1702; IR (KBr, cm^{-1}) ν 3348, 2954, 1743, 1724, 1537, 1487, 1452, 1382, 1238, 1170, 1012, 910, 808, 731, 702.

3.3. Anti-TMV Activity Section

3.3.1. Purification of Tobacco Mosaic Virus

Using Gooding's method [21], the upper leaves of *Nicotiana tabacum* inoculated with TMV were selected and ground in phosphate buffer and then filtered through double-layer pledget. The filtrate was centrifuged at 10,000 *g*, treated with PEG twice, and centrifuged again. The whole experiment was processed at 4 °C. Absorbance value was estimated at 260 nm by ultraviolet spectrophotometer:

$$\text{virus concn} = (A_{260} \times \text{dilution ratio}) / E_{1cm}^{0.1\%,260} \quad (1)$$

3.3.2. Inhibition Effect of Compound on TMV *in Vivo* [22]

The virus was inhibited by mingling with the compound solution at the same volume for 30 min. The mixture was then inoculated on the left side of the leaves of *N. tabacum L.*, whereas the right side of the leaves was inoculated with the mixture of solvent and the virus for control. The local lesion numbers were recorded 3–4 days after inoculation [10]. Three repetitions were conducted for each compound.

3.3.3. Curative Effect of Compounds on TMV *in Vivo* [22]

The leaves of *N. tabacum L.* growing at the same ages were selected. TMV at a concentration of 6×10^{-3} mg/mL was dipped and inoculated on the whole leaves. Then the leaves were washed with water and dried. The compound solution was smeared on the left side, and the solvent was smeared on the right side for control. The local lesion numbers were then recorded 3–4 days after inoculation. For each compound, three repetitions were conducted to ensure the reliability of the results.

3.3.4. Protective Effect of Compounds on TMV *in Vivo* [22]

The leaves of *N. tabacum L.* growing at the same ages were selected. The compound solution was smeared on the left side for 12 h and the solvent was smeared on the right side for control. The TMV at a concentration of 6×10^{-3} mg/mL was inoculated on the whole leaves. The local lesion numbers were then recorded 3–4 days after inoculation. For each compound, three repetitions were conducted to ensure the reliability of the results:

$$\text{inhibition rate}(\%) = \frac{\text{av local lesion numbers of control (not treated with compound)} - \text{av local lesion numbers without drugs}}{\text{av local lesion numbers without drugs}}$$

4. Conclusions

Sixteen novel β-amino ester derivatives containing benzofuran and benzothiazole units were designed and synthesized seeking anti-TMV activity. The bioassays identified these new compounds as possessing weak to good antiviral activities. The bioassay test results showed that compounds **5i** and **5m** have good antiviral activity against TMV, with curative rates of 52.23% and 54.41% at a concentration of 0.5 mg/mL.

Supplementary Materials

Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/18/11/13623/s1.

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Conflicts of Interest

The authors declare no conflict of interest.

References

1. Sawada, Y.; Yanai, T.; Nakagawa, H. Synthesis and insecticidal activity of benzoheterocycil analofues of N`-benzoheterocyclic analogues of N`-benzoyl-*N*-(tert-butyl)benzohydrazide: Patr 1. Design of benzoheterocyclic analogues. *Pest Manag. Sci.* **2003**, *59*, 25–35.
2. Mahran, M.A.; El-nassry, S.M.F.; Allam, S.R. Synthesis of some new benzothiazole derivatives as potential antimicrobial and antiparasitic agents. *Pharmazie* **2003**, *58*, 527–530.
3. Khanitha, P.; Kazuki, K.; Hiroki, Te. Synthesis of three classes of rhodacyanine dyes and ebalitation of their *in vitro* and *in vivo* antimalarial activity. *Bioorg. Med. Chem.* **2006**, *14*, 8550–8563.
4. Victor, F.; Raisa, R.; Claudia, R.B.G.; Thatyana, R.A.V. Chemistry and Biological Activities of 1,3-Benzothiazoles. *Mini Rev. Org. Chem*. **2012**, *9*, 44–53.
5. Charris, J.; Monasterios, M.; Domingguez, J. Synthesis of some 5-nitro-2-furfurylidene derivatives and their antibacterial and antifungal activities. *Heterocycl. Commun.* **2002**, *8*, 275–280.
6. Helal, M.H.M.; Salem, M.A.; El-Gaby, M.S.A.; Aljahdali, M. Synthesis and biological evaluation of some novel thiazole compounds as potential anti-inflammatory agents. *Eur. J. Med. Chem.* **2013**, *65*, 517–526.
7. Sidoova, E.; Loos, D.; Bujdakova, H. New Anticandidous 2-Alkylthio-6-aminobenzothiazoles. *Molecules* **1997**, *2*, 36–42.
8. Hassan, M.; Chohan, Z.H.; Supuran, C.T. Antibacterial Co (II) and Ni (II) complexes of benzothiazole-dereved Schiff bases. *Synth. Reactiv. Inorg. Metal Org. Chem.* **2002**, *32*, 1445–1461.
9. Albert, W.B.; Leonard, R.W. Coumarone. *Organic Synth.* **1973**, *5*, 251.

10. Muthu, K.K.; Amol, B.S.; Aparna, S.C.; Prashik, B.D.; Rahul, P.W.; Maheshwar, S.M.; Sandeep, G. The biology and chemistry of antifungal agents: A review. *Bioorg. Med. Chem.* **2012**, *20*, 5678–5698.
11. Benaim, G.; Paniz, M.; Alberto, E. The emerging role of amiodarone and dronedarone in Chagas disease. *Nat. Rev. Cardiol*. **2012**, *9*, 605–609.
12. Giannis, A. Peptidomimetics for receptor ligands-discovery, development, and medical perspectives. *Angew. Chem. Int. Ed.* **1993**, *32*, 1244–1267.
13. Goody, R.S.; Alexandrov, K.; Engelhard, M. Combining chemical and biological techniques to produce modified proteins. *ChemBioChem* **2002**, *3*, 399–403.
14. Wang, L.; Schultz, P.G. Expanding the genetic code. *Chem. Commun.* **2002**, *2002*, 1–11.
15. Simon, S.; Markus, W.; Thomas, I.; Irina, S.; Harald, G. Kinetic investigation of a solvent-free, chemoenzymatic reaction sequence towards enantioselective synthesis of a β-amino acid ester. *Biotechnol. Bioeng.* **2012**, *109*, 1479–1489.
16. Eusebio, J.; Delia, Q.; Jaime, E. Enantioselective Synthesis of *beta*-Amino Acids. *Aldrichimica Acta* **1994**, *27*, 3–11.
17. Jerry, D.C.; Gerald, A.W.; Keithm, A.; Pierre, J.C. Pilot Plant Preparation of an α v β 3 Integrin Antagonist. Part 1. Process Research and Development of a (S)-β-Amino Acid Ester Intermediate: Synthesis via a Scalable, Diastereoselective Imino-Reformatsky Reaction. *Org. Process Res. Dev.* **2004**, *8*, 51–61.
18. Bai, S.; Liang, X.P.; Bhadury, P.; Hu, D.H.; Yang, S. Asymmetric Mannich reactions catalyzed by cinchona alkaloid thiourea: Enantioselective one-pot synthesis of novel β-amino ester derivatives. *Tetrahedron* **2011**, *22*, 518–523.
19. Dockichev, T.V.; Latypova, D.R.; Shakirov, R.R.; Biglova, R.Z.; Talipov, R.F. Catalyzed synthesis of β-amino acids esters. *Russ. J. Organ. Chem.* **2010**, *46*, 755–757.
20. Zhang, K.K.; Liang, X.P.; He, M.; Wu, J.; Zhang, Y.P.; Xue, W.; Jin, L.H.; Yang, S.; Hu, D.Y. One-Pot Synthesis of Novel Chiral β-Amino Acid Derivatives by Enantioselective Mannich Reactions Catalyzed by SquaramideCinchona Alkaloids. *Molecules* **2013**, *18*, 6142–6152.
21. Gooding, G.V.; Hebert, T.T. A simple technique for purification of tobacco mosaic virus in large quantities. *Phytopathology* **1967**, *57*, 1285–1290.
22. Li, S.Z.; Wang, D.M.; Jiao, S.M. *Pesticide Experiment Methods-Fungicide Sector*; Agriculture Press of China: Beijing, China, 1991; pp. 93–94.

Sample Availability: Samples of the compounds **5a**–**5p** are available from the authors.