The First Example of a Regioselective Biginelli-Like Reaction Based on 3-Alkylthio-5-amino-1,2,4-triazole

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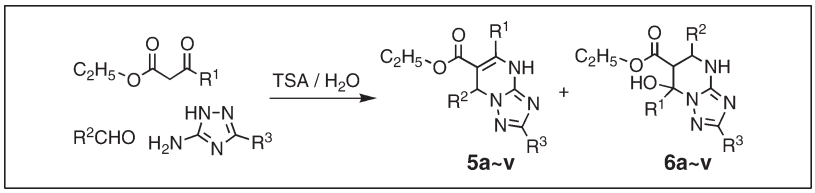

The three-component condensation of 3-amino-5-alkylthio-1,2,4-triazoles with aromatic aldehydes and β-ketoester was studied to develop a regioselective Biginelli-like reaction. The results indicated that the reaction solvent and the properties of the β-ketoester component displayed great influence on the regioselectivity. This is the first report about the regioselectivity of the aminotriazole-based Biginelli-like reaction.

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INTRODUCTION

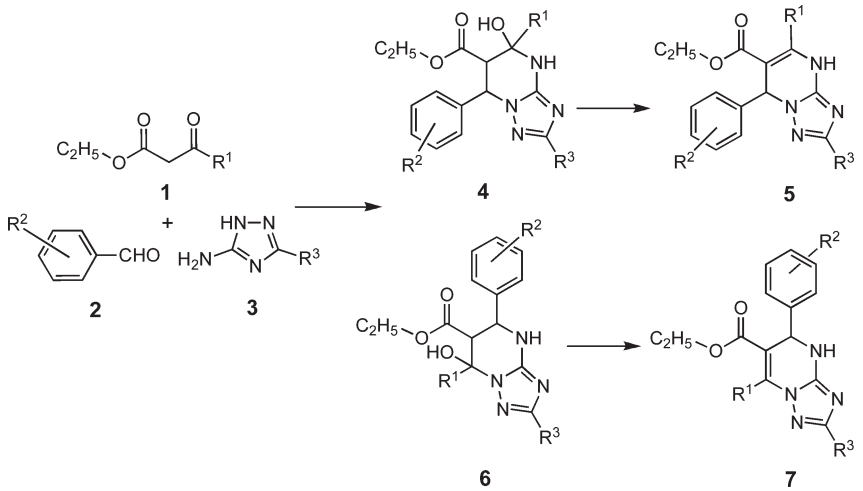
In the last decades, dihydropyrimidinones (DHPMs) and their sulfur analogs have attracted much attention because of their wide range of biological activities. For example, many DHPMs were reported to be calcium or/and potassium channel blockers and openers [1], antihypertensive agents [2], α-adrenergic antagonists [3], neuropeptide Y (NPY) antagonists [4], and HIV gp-120-CD4 inhibitors [5]. The most important and direct method for the synthesis of DHPMs is based on the Biginelli reaction reported first in 1893 [6]. The classical Biginelli reaction of an aldehyde, a β-ketoester, and urea or thiourea requires strongly acidic conditions. Recently, the Biginelli reaction was extended to the synthesis of dihydrotriazolo-pyrimidine by replacing the urea component with 5-amino-1,2,4-triazole [7–12]. Because the β-ketoester and 5-amino-1,2,4-triazole are asymmetric, four possible products (**4**, **5**, **6**, and **7**) could be obtained theoretically (Scheme 1) according to the mechanism of the traditional Biginelli reaction. However, so far no attention has been paid to the regioselectivity of the aminoazole-based Biginelli reaction.

The existing results about the aminoazole-based Biginelli-like reaction indicated that only product **5** was obtained or only product **4** was obtained at first, which then suffered subsequent dehydration to afford product **5** [7–12]. No reports about the formation of products **6** or **7** could be found in the existing literature. As a continuation of our systematic research work on the synthesis and biological activity of triazolopyrimidines [13–16], we report herein the first example of regioselective Biginelli-like reactions based on 3-alkylthio-5-amino-1,2,4-triazole, in which products **5** and **6** could be produced by regioselectivity depending on the reaction conditions.

RESULTS AND DISCUSSION

First, the reaction of ethyl acetoacetate, 4-methoxybenzaldehyde, and 3-methylthio-5-amino-1,2,4-triazole was selected as a model reaction. Some reported catalysts or additives, such as H_3BO_3 [17], *p*-toluene sulfonic acid (TSA) [18], $FeCl_3$ [19], $InCl_3$ [20], and HCl [21], and solvents, such as C_2H_5OH, DMF, H_2O, THF, HOAc, CH_2Cl_2, and $CHCl_3$, were screened. As shown in Table 1, the TSA/H_2O system was found to give almost equivalent amounts of products **5a** and **6a** with a moderate overall yield (**5a** and **6a**, 69%). Then, this system was extended to other substrates, and the results are listed in Table 2. As shown in Table 2, when ethyl acetoacetate and ethyl chloroacetoacetate acted as β-ketoester components, two isomers were isolated in all cases. Interestingly, only one isomer was isolated for the reaction of ethyl trifluoroacetoacetate and 4-substituted benzaldehyde. For example, the reactions of 4-methoxybenzaldehyde (Table 2, entry 15), 4-chlorobenzaldehyde (Table 2, entry 16), 4-chlorobenzaldehyde (Table 2, entry 17), 3,4-dichlorobenzaldehyde (Table 2, entry 18), and 4-nitrobenzaldehyde (Table 2, entry 19) afforded isomers **5o–s** in isolated yields of 40, 48, 49, 51, and 55%, respectively. However, the reactions of benzaldehyde (Table 2, entry 21) and 4-methylbenzaldehyde (Table 2, entry 22) afforded product **6u-v** in isolated yields of 80% and 60%, respectively. However, the reactions of 2-fluorobenzaldehyde (Table 2, entry 20) also

Scheme 1

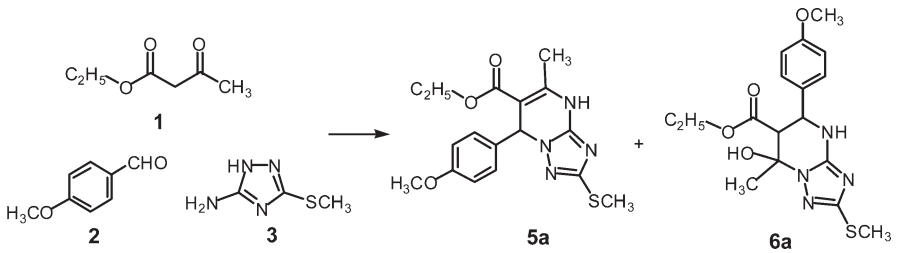


afforded product **6t**. From these results, we can conclude that the electronic property and the position of the R^1 group has the most important effect on the regioselectivity of the aminotriazole-based Biginelli reaction in H_2O solution. Additionally, the effect of R^2 group on the regioselectivity is complex, whereas the R^3 group seems to have no obvious effect on the regioselectivity.

In addition, as shown in Table 1, the reaction under the system of HCl/C_2H_5OH afforded regioselectivity isomer **5a** in a yield of 32%, a little higher than that in DMF solution. Then, we studied the extension of this reaction system to other substrates, and the results are listed in Table 3. Additionally, microwave irradiation has been proven to be a powerful technique for promoting a variety of chemical reactions [22–25]. The main benefits of performing reactions under microwave irradiation conditions are significant rate enhancements and higher yields. Recently, the technique of microwave irradiation was also applied to improve the yields and shorten the reaction time of Biginelli reactions [26–28]. So, the results in C_2H_5OH solution under microwave irradiation were compared with those under conventional heating as listed in Table 3, which indicated that the yields under microwave irradiation were improved as

Table 1

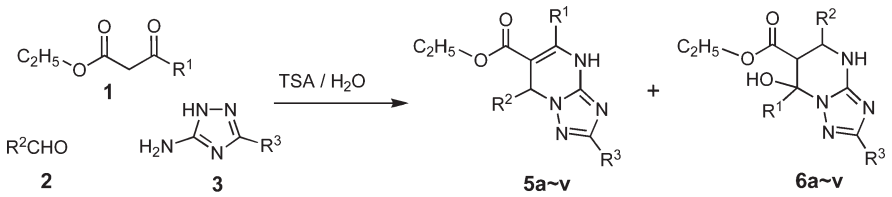
Results of the model reaction under various conditions.



No.	Reaction conditions	Products
1	HBO_3 (cat.), HOAc, reflux	Very complex
2	$FeCl_3$ (10%), THF, reflux	Very complex
3	$AlCl_3$ (cat.), THF, reflux	Very complex
4	$InCl_3$ (20%), THF, reflux	Very complex
5	HCl (cat.), H_2O, reflux	Very complex
6	TSA, CH_2Cl_2, reflux	No reaction
7	TSA, $CHCl_3$, reflux	No reaction
8	TSA, H_2O, reflux	**5a**, 34%; **6a**, 35%
9	HCl (cat.), C_2H_5OH, reflux	**5a**, 32%
10	DMF, reflux	**5a**, 30%

Table 2

Results of the Biginelli-like reaction in H_2O solution using TSA as catalyst.



No.	R^1	R^2	R^3	Isolated yields of products (%)	
1	CH_3	4-$CH_3OC_6H_4$	SCH_3	**5a** (34)	**6a** (35)
2	CH_3	4-$CH_3C_6H_4$	SCH_3	**5b** (25)	**6b** (~5)[a]
3	CH_3	4-ClC_6H_4	SCH_3	**5c** (36)	**6c** (~5)[a]
4	CH_3	2,4-$Cl_2C_6H_3$	SCH_3	**5d** (32)	**6d** (24)
5	CH_3	4-Pyridyl	SCH_3	**5e** (48)	**6e** (~5)[a]
6	CH_3	4-$CH_3C_6H_4$	SCH_2Ph	**5f** (32)	**6f** (19)
7	CH_3	4-$CH_3OC_6H_4$	SCH_2Ph	**5g** (41)	**6g** (~5)[a]
8	CH_3	4-ClC_6H_4	SCH_2Ph	**5h** (29)	**6h** (39)
9	$ClCH_2$	4-$CH_3C_6H_4$	SCH_3	**5i** (36)	**6i** (20)
10	$ClCH_2$	4-$CH_3OC_6H_4$	SCH_3	**5j** (31)	**6j** (~5)[a]
11	$ClCH_2$	4-ClC_6H_4	SCH_3	**5k** (43)	**6k** (~5)[a]
12	$ClCH_2$	4-$CH_3C_6H_4$	SCH_2Ph	**5l** (35)	**6l** (~5)[a]
13	$ClCH_2$	4-$CH_3OC_6H_4$	SCH_2Ph	**5m** (30)	**6m** (25)
14	$ClCH_2$	4-ClC_6H_4	SCH_2Ph	**5n** (28)	**6n** (35)
15	CF_3	4-$CH_3OC_6H_4$	SCH_3	**5o** (40)	**6o** (0)
16	CF_3	4-ClC_6H_4	SCH_3	**5p** (48)	**6p** (0)
17	CF_3	4-ClC_6H_4	SCH_2Ph	**5q** (49)	**6q** (0)
18	CF_3	3,4-$Cl_2C_6H_3$	SCH_3	**5r** (51)	**6r** (0)
19	CF_3	4-$NO_2C_6H_4$	SCH_3	**5s** (55)	**6s** (0)
20	CF_3	2-FC_6H_4	SCH_3	**5t** (0)	**6t** (54)
21	CF_3	C_6H_5	SCH_3	**5u** (0)	**6u** (80)
22	CF_3	4-$CH_3C_6H_4$	SCH_3	**5v** (0)	**6v** (60)

[a] Detected by HPLC, but unable to be isolated.

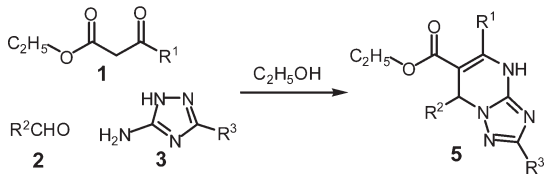
expected by 3–10%, and the reaction time was also shortened from 18 h to 30 min.

The structures of compounds **4–7** correspond to the direction of the interaction established earlier in the reactions between 3-amino-5-alkylthio-1,2,4-triazoles and arylidenacetoacetates (**8**) (Scheme 2). Formation of the pyrimidine ring with the participation of the arylidene derivatives (**8**) occurs *via* interaction of the β-carbon atom of the acetoacetate with the carbonyl group of the aldehydes. For example, in H_2O solution with TSA as catalyst, the reaction proceeded first with the participation of $N_{(2)}$ or 3-NH_2 of the 3-amino-5-alkylthio-1,2,4-triazoles to afford regioselectivity ethyl 7-aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo-[1,5-*a*]pyrimidine-6-carboxylate (**5**) or ethyl-7-hydroxy-7-alkyl-5-aryl-2-alkylthio-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxylate (**6**) depending on the property of the aromatic aldehydes when ethyl trifluoroacetoacetate was used as the β-ketoester component. When ethyl acetoacetate and ethyl chloroacetoacetate acted as β-ketoester components, the reaction always produced two isomers **5** and **6**. However, the reactions in C_2H_5OH solution always proceeded first with the participation of $N_{(2)}$ to produce regioselectivity of the isomer **5**.

Recently, Chebanov *et al*. reported the three-component condensation of 3-amino-5-alkylthio-1,2,4-triazoles with aromatic aldehydes and acetoacetamides in C_2H_5OH solution under microwave irradiation without any catalyst [12]. Prompted by these results, we also examined the microwave-assisted aminoazole-based Biginelli-like reaction in C_2H_5OH solution without any catalyst. The results shown in Table 3 indicated that the yields were improved significantly compared with those in the presence of HCl as catalyst. Further, it should be noted that different from the situation in H_2O solution using TSA as catalyst, only isomer **5** was formed using C_2H_5OH as reaction solvent no matter what β-ketoester component was used. Additionally, the properties of the R^1 and R^2 group displayed great effects on the yields of product **5**. Ethyl trifluoroacetoacetate always gave higher yields than ethyl acetoacetate and ethyl chloroacetoacetate. Benzaldehydes with electron-withdrawing group

Table 3

Results of the Biginelli-like reaction in C_2H_5OH solution.



No.	R^1	R^2	R^3	Conventional heating: Isolated yields (%)		Conventional heating: Reaction time (h)	Microwave irradiation: Isolated yields (%)	Microwave irradiation: Reaction time (min)
1	CH_3	4-$CH_3OC_6H_4$	SCH_3	**5a**	30	18	36[a]/52[b]	30
2	CH_3	4-$CH_3C_6H_4$	SCH_3	**5b**	36	18	39[a]/55[b]	30
3	CH_3	4-ClC_6H_4	SCH_3	**5c**	40	18	45[a]/60[b]	30
4	CH_3	2,4-$Cl_2C_6H_3$	SCH_3	**5d**	40	18	48[a]/62[b]	30
5	CH_3	4-Pyridyl	SCH_3	**5e**	70	18	80[a]/82[b]	30
6	CH_3	4-$CH_3C_6H_4$	SCH_2Ph	**5f**	40	18	46[a]/60[b]	30
7	CH_3	4-$CH_3OC_6H_4$	SCH_2Ph	**5g**	34	18	40[a]/54[b]	30
8	CH_3	4-ClC_6H_4	SCH_2Ph	**5h**	45	18	49[a]/53[b]	30
9	$ClCH_2$	4-$CH_3C_6H_4$	SCH_3	**5i**	39	18	34[a]/50[b]	30
10	$ClCH_2$	4-$CH_3OC_6H_4$	SCH_3	**5j**	31	18	35[a]/51[b]	30
11	$ClCH_2$	4-ClC_6H_4	SCH_3	**5k**	43	18	47[a]/61[b]	30
12	$ClCH_2$	4-$CH_3C_6H_4$	SCH_2Ph	**5l**	42	18	44[a]/60[b]	30
13	$ClCH_2$	4-$CH_3OC_6H_4$	SCH_2Ph	**5m**	37	18	41[a]/56[b]	30
14	$ClCH_2$	4-ClC_6H_4	SCH_2Ph	**5n**	48	18	53[a]/67[b]	30
15	CF_3	4-$CH_3OC_6H_4$	SCH_3	**5o**	51	18	56[a]/61[b]	30
16	CF_3	4-ClC_6H_4	SCH_3	**5p**	61	18	68[a]/75[b]	30
17	CF_3	4-ClC_6H_4	SCH_2Ph	**5q**	63	18	70[a]/78[b]	30
18	CF_3	3,4-$Cl_2C_6H_3$	SCH_3	**5r**	61	18	66[a]/72[b]	30
19	CF_3	4-$NO_2C_6H_4$	SCH_3	**5s**	60	18	69[a]/73[b]	30
20	CF_3	2-FC_6H_4	SCH_3	**5t**	64	18	67[a]/68[b]	30
21	CF_3	C_6H_5	SCH_3	**5u**	68	18	72[a]/79[b]	30
22	CF_3	4-$CH_3C_6H_4$	SCH_3	**5v**	59	18	63[a]/68[b]	30

[a] Yields of the reactions without any catalyst under conventional heating.
[b] Yields of the reactions without any catalyst under microwave irradiation.

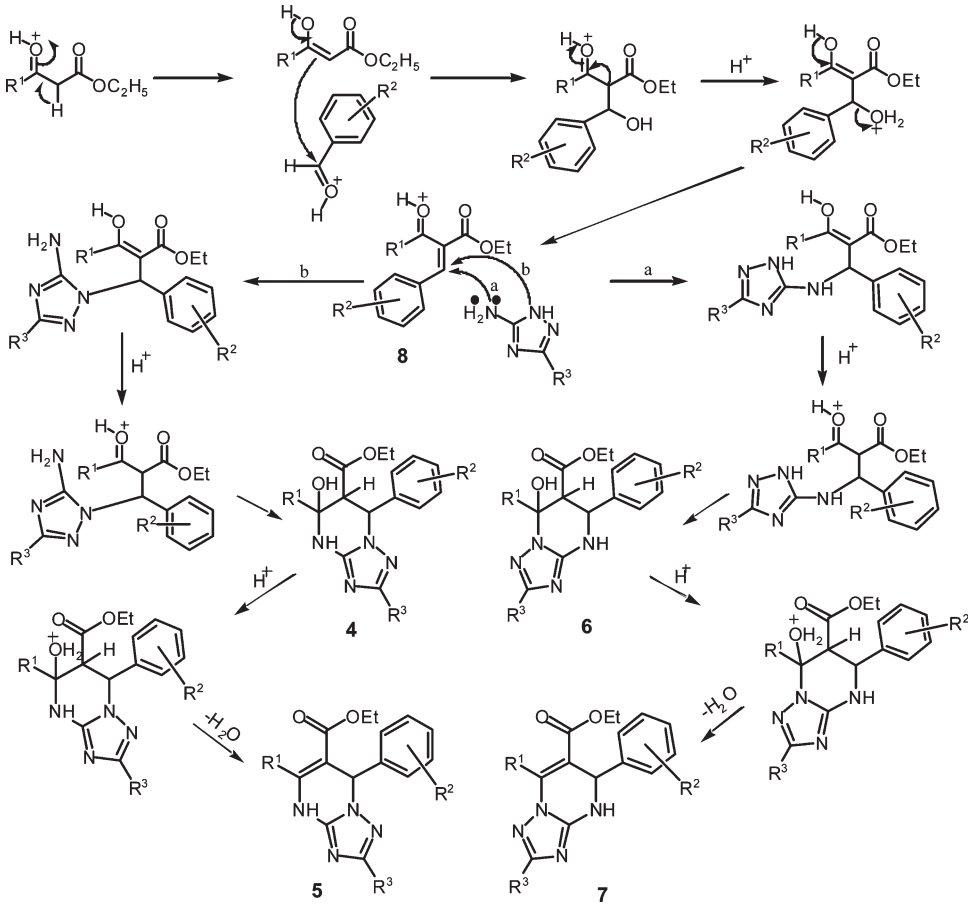
always afforded higher yields of products than benzaldehydes with electron-donating groups. For example, the reaction of 4-pyridylaldehyde (entry 5, Table 3) gave the highest yield (80% in the presence of HCl, 82% without any catalyst) among eight aromatic aldehydes used in this study.

Structure determination. As shown in Scheme 1, four possible products could be obtained theoretically, but only two isomers, compounds **5** and **6**, were identified in this study. The structures of **5** and **6** were assigned by ^1H NMR, ^{13}C NMR, MS, and X-ray diffraction analysis to be ethyl 7-aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxylate and ethyl 7-hydroxy-7-alkyl-5-aryl-2-alkylthio-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxylate, respectively. For example, compound **5d** displayed two single peaks at 6.77 and 10.90 ppm for 7-CH and 4-NH, respectively, whereas an obvious AB system at 3.44 and 5.62 ppm for 5-CH and 6-CH was observed in the ^1H NMR spectrum of compound **6d**. The peak for the 4-NH of compound **6d** appeared at 6.88 ppm. Ultimately, the structures of **5d** and **6d** were established on the basis of a X-ray analysis as shown in Figure 1.

CONCLUSIONS

In summary, the three-component condensation of 3-amino-5-alkylthio-1,2,4-triazoles with aromatic aldehydes and β-ketoester was studied. The obtained results showed that the reaction solvent and the properties of the β-ketoester components had a great influence on the regioselect. In H_2O solution with TSA as catalyst, the reaction proceeded first with the participation of $N_{(2)}$ or 3-NH_2 of the 3-amino-5-alkylthio-1,2,4-triazoles to afford regioselectivity ethyl 7-aryl-2-alkylthio-4,7-

Scheme 2. The hypothetic mechanism of reaction.



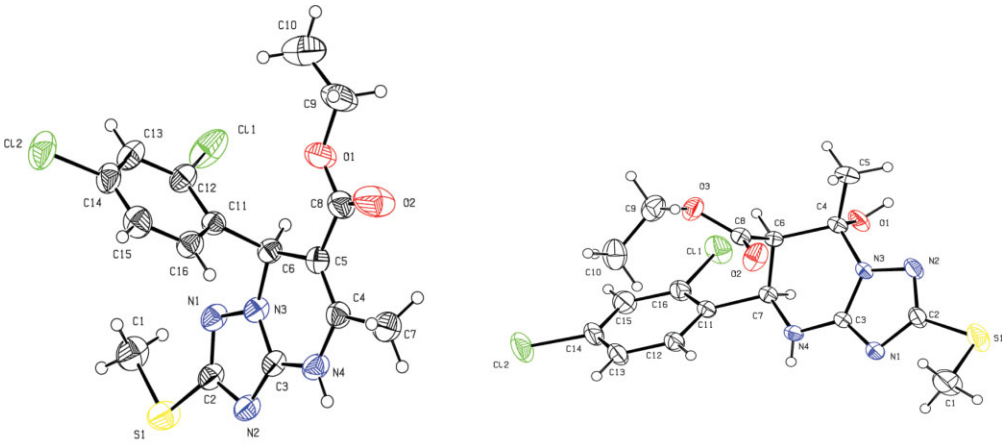
dihydro-1,2,4-triazolo-[1,5-*a*]pyrimidine-6-carboxylate (**5**) or ethyl-7-hydroxy-7-alkyl-5-aryl-2-alkylthio-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxylate (**6**) depending on the property of the aromatic aldehydes when ethyl trifluoroacetoacetate was used as the β-ketoester component. When ethyl acetoacetate and ethyl chloroacetoacetate acted as β-ketoester components, the reaction always produced two isomers **5** and **6**. However, the reactions in C_2H_5OH solution always proceeded first with the participation of $N_{(2)}$ to produce regioselectivity isomer **5**. The yields of the reaction in C_2H_5OH solution in the absence of any catalyst were improved significantly when compared with those in the presence of HCl as catalyst. Additionally, compared with the conventional heating, microwave irradiation improved the yields of the reaction in C_2H_5OH solution and shortened the reaction time to a great extent. To our knowledge, this is the first report about the regioselectivity of aminotriazole-based Biginelli-like reactions.

EXPERIMENTAL

Melting points are uncorrected. Mass spectra were measured on a Finnigan Trace MS spectrometer. NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 400 spectrometer, and resonances are given in ppm (δ) relative to TMS. HPLC analyses were performed on an Agilent 1100 MWD instrument. Microwave irradiation reactions were carried out on a Smith-synthesizer^{TM} instrument.

General procedure for the three-component reaction in H_2O solution. A solution of β-ketoester (1 mmol), aromatic aldehyde (1 mmol), and 3-amino-5-alkylthio-1,2,4-triazoles (1 mmol) in H_2O (3 mL) containing a catalytic amount of TSA was heated under 80°C for 10 h. The resulting mixture was extracted with CH_2Cl_2 (10 mL × 3), and then the extract was dried over sodium sulfate and filtered. The filtrate was condensed under reduced pressure, and the residue was purified by chromatography on SiO_2 ($V_{acetone}/V_{petroleum\ ether}$ = 1/10) to afford products **5** and **6**.

General procedure for the three-component reaction in C_2H_5OH solution using HCl as catalyst. A solution of β-ketoester (1 mmol), aromatic aldehyde (1 mmol), and 3-amino-5-alkylthio-1,2,4-triazoles (1 mmol) in EtOH (3 mL)



5d **6d**

Figure 1. Crystal structures of products **5d** and **6d**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

containing 10 μL of concentrated HCl (37%) were refluxed for 18 h. The reaction mixture was cooled to room temperature, and the precipitate was filtered and recrystallized from ethanol to give pure product **5**.

General procedure for the three-component reaction in C_2H_5OH solution using HCl as catalyst under microwave irradiation. A mixture of β-ketoester (1 mmol), aromatic aldehyde (1 mmol), and 3-amino-5-alkylthio-1,2,4-triazoles (1 mmol) in EtOH (3 mL) containing 10 μL of concentrated HCl (37%) was added into a microwave tube. The sealed tube was placed in a Smithsynthesizer™ and irradiated at 150°C for 30 min. The reaction mixture was cooled to room temperature, and the precipitate was filtered and recrystallized from ethanol to give pure product **5**.

General procedure for the reaction in C_2H_5OH solution without any catalyst under microwave irradiation. A mixture of β-ketoester (1 mmol), aromatic aldehyde (1 mmol), and 3-amino-5-alkylthio-1,2,4-triazoles (1 mmol) in EtOH (3 mL) was added into a microwave tube. The sealed tube was placed in a Smithsynthesizer™ and irradiated at 150°C for 30 min. The reaction mixture was cooled to room temperature, and the precipitate was filtered and recrystallized from ethanol to give pure product **5**.

Determination of the X-ray crystal structure of compounds 5d and 6d. Crystals of **5d** and **6d** were grown by slowly evaporating an acetone solution at room temperature. Compound **5d**, $C_{16}H_{16}Cl_2N_4O_2S$ (Mr = 399.29), Monoclinic space group *Pbca*, $Z = 4$, $a = 10.7044(10)$ Å, $b = 22.128(2)$ Å, $c = 8.2341(8)$ Å, $\alpha = 90°$, $\beta = 110.663(2)°$, $\gamma = 90°$, $V = 1824.9(3)$ Å^3, Mo Kα radiation, $1.84° < \theta < 26.99°$, 15129 measured reflections, $T = 292(2)$ K on a Brucker-Nonius kappa CCD. The structure was solved using direct methods (SHELXS 97) and refined with SHELXK 97 final R [$F^2 > 2\sigma(F^2)$] = 0.066 and $wR = [w = 1/[\sigma^2(F_o^2) + (0.0737P)^2 + 1.1468P]$, where $P = (F_o^2 + 2F_c^2)/3$. Compound **6d**, $C_{16}H_{18}Cl_2N_4O_3S$ (Mr = 417.30), Monoclinic space group *Pbca*, $Z = 4$, $a = 11.9765(10)$ Å, $b = 8.7314(8)$ Å, $c = 18.7954(16)$ Å, $\alpha = 90°$, $\beta = 91.3200(10)°$, $\gamma = 90°$, $V = 1824.9(3)$ Å^3, Mo Kα radiation, $2.00° < \theta < 25.99°$, 13069 measured reflections, $T = 292(2)$ K on a Brucker-Nonius kappa CCD. The structure was solved using direct methods (SHELXS 97) and refined with SHELXK 97 final R [$F^2 > 2\sigma(F^2)$] = 0.064 and $wR = [w = 1/[\sigma^2(F_o^2) + (0.0865P)^2 + 1.8162P]$, where $P = (F_o^2 + 2F_c^2)/3$.

CCDC 639763 and 639764 contain the supplementary crystallographic data for compounds **5d** and **6d**, respectively, from this article. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk/data_request/cif.

Data for characterizations of 5 and 6.

Compound 5a. White solid, mp 219–220; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.15 (t, 3H, $J = 6.8$ Hz), 2.50 (s, 3H), 2.60 (s, 3H), 3.78 (s, 3H), 4.07 (q, 2H, $J = 6.8$ Hz), 6.32 (s, 1H), 6.82–7.23 (m, 4H), 10.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 14.10, 14.41, 19.30, 55.19, 59.45, 60.01, 99.36, 113.68, 128.55, 133.65, 145.74, 148.26, 158.95, 159.32, 165.72; EI-MS (70Ev, *m/z*) (relative intensity %): 362 (20), 360 (M^+, 99), 345 (25), 331 (66), 313 (100), 287 (57), 259 (26), 253 (98), 240 (31), 225 (67), 207 (15), 180 (12), 179 (28), 159 (19), 143 (12), 127 (15), 115 (36), 108 (31); Elemental *Anal.* Calcd. for $C_{17}H_{20}N_4O_3S$: C, 56.65; H, 5.59; N, 15.54; Found: C, 56.89; H, 5.32; N, 15.79.

Compound 5b. White solid, mp 227–228; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.16 (t, 3H, $J = 7.2$ Hz), 2.31 (s, 3H), 2.49 (s, 3H), 2.62 (s, 3H), 4.07 (q, 2H, $J = 7.2$ Hz), 6.33 (s, 1H), 7.19–7.22 (m, 4H), 10.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 14.10, 14.43, 19.32, 21.15, 59.78, 60.03, 99.49, 127.24, 129.10, 137.88, 138.38, 145.75, 148.28, 158.97, 165.67; EI-MS (70Ev, *m/z*) (relative intensity %): 346 (20), 344 (M^+, 94), 315 (45), 297 (100), 271 (30), 253 (99), 225 (86), 207 (11), 179 (26), 161 (10), 141 (12), 128 (18), 115 (17); Elemental *Anal.* Calcd. for $C_{17}H_{20}N_4O_2S$: C, 59.28; H, 5.85; N, 16.27; Found: C, 59.55; H, 5.64; N, 16.40.

Compound 5c. White solid, mp 254–255; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.15 (t, 3H, $J = 7.2$ Hz), 2.49 (s, 3H), 2.63 (s, 3H), 4.07 (q, 2H, $J = 7.2$ Hz), 6.33 (s, 1H), 7.25–7.30 (m, 4H), 10.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 14.10, 14.37, 19.43, 59.49, 60.23, 99.06, 128.68, 128.81,

134.09, 139.60, 145.98, 147.97, 159.13, 165.38; EI-MS (70Ev, *m/z*) (relative intensity %): 366 (30), 364.5 (M^+, 94), 349 (10), 337 (22), 335 (48), 318 (100), 289 (23), 275 (11), 253 (71), 244 (11), 225 (46), 207 (8), 179 (17), 154 (4), 127 (13), 111 (5); Elemental *Anal.* Calcd. for $C_{16}H_{17}ClN_4O_2S$: C, 52.67; H, 4.70; N, 15.36; Found: C, 52.78; H, 4.92; N, 15.09.

Compound 5d. White solid, mp 242–243; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.12 (t, 3H, J = 7.2 Hz), 2.48 (s, 3H), 2.65 (s, 3H), 4.04 (q, 2H, J = 7.2 Hz), 6.77 (s, 1H), 7.18–7.38 (m, 3H), 10.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 14.10, 14.32, 19.39, 56.84, 60.19, 97.94, 127.52, 129.63, 130.71, 134.18, 134.53, 137.27, 146.9, 147.9, 159.2, 165.2; EI-MS (70Ev, *m/z*) (relative intensity %): 403 (10), 401 (16), 399 (M^+, 32), 398 (87), 371 (52), 369 (80), 363 (55), 353 (25), 333 (9), 325 (12), 317 (8), 287 (15), 253 (100), 225 (56), 207 (12), 179 (19), 161 (17), 126 (7); Elemental *Anal.* Calcd. for $C_{16}H_{16}Cl_2N_4O_2S$: C, 48.13; H, 4.04; N, 14.03; Found: C, 48.32; H, 3.86; N, 14.29.

Compound 5e. White solid, mp 243–244; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.17 (t, 3H, J = 7.2 Hz), 2.49 (s, 3H), 2.66 (s, 3H), 4.10 (q, 2H, J = 7.2 Hz), 6.36 (s, 1H), 7.27 (d, 2H, J = 6.4 Hz), 8.59 (d, 2H, J = 6.0 Hz), 11.15 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 14.10, 14.22, 19.43, 58.87, 60.33, 97.49, 122.34, 147.21, 148.38, 149.50, 149.92, 159.39, 165.23; EI-MS (70Ev, *m/z*) (relative intensity %): 333 (10), 331 (M^+, 60), 287 (35), 253 (100), 225 (59), 207 (24), 180 (29), 159 (19), 143 (12), 127 (36), 115 (29); Elemental *Anal.* Calcd. for $C_{15}H_{17}N_5O_2S$: C, 54.36; H, 5.17; N, 21.13; Found: C, 54.59; H, 5.46; N, 21.44.

Compound 5f. White solid, mp 165–166; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.15 (t, 3H, J = 7.2 Hz), 2.24 (s, 3H), 2.56 (s, 3H), 4.06 (q, 2H, J = 6.8 Hz), 4.14 (d, 1H, J = 12.8 Hz), 4.26 (d, 1H, J = 12.8 Hz), 6.33 (s, 1H), 7.19–7.22 (m, 9H), 10.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 14.09, 19.40, 21.17, 36.49, 59.92, 60.03, 99.26, 127.24, 127.29, 128.37, 128.97, 129.12, 137.35, 137.86, 138.40, 145.82, 148.13, 157.45, 165.67; EI-MS (70Ev, *m/z*) (relative intensity %): 422 (18), 420 (M^+, 100), 387 (58), 376 (10), 359 (5), 341 (26), 329 (42), 297 (45), 283 (9), 269 (15), 251 (11), 239 (8), 224 (11), 205 (16), 169 (11), 141 (15), 128 (15), 123 (39), 115 (14); Elemental *Anal.* Calcd. for $C_{23}H_{24}N_4O_2S$: C, 65.69; H, 5.75; N, 13.32; Found: C, 65.37; H, 5.96; N, 13.54.

Compound 5g. White solid, mp 191–192; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.15 (t, 3H, J = 6.8 Hz), 2.57 (s, 3H), 3.80 (s, 3H), 4.07 (q, 2H, J = 6.8 Hz), 4.14 (d, 1H, J = 12.8 Hz), 4.27 (d, 1H, J = 12.8 Hz), 6.33 (s, 1H), 7.19–7.22 (m, 9H), 10.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 14.11, 19.41, 36.47, 55.26, 59.65, 60.07, 99.48, 113.80, 127.27, 128.39, 128.60, 128.98, 133.56, 137.33, 145.47, 147.89, 157.41, 159.49, 165.65; EI-MS (70Ev, *m/z*) (relative intensity %): 438 (31), 436 (M^+, 100), 403 (44), 389 (7), 357 (12), 345 (38), 329 (11), 313 (35), 285 (10), 267 (8), 241 (5), 229 (8), 197 (8), 185 (6), 159 (6), 123 (17); Elemental *Anal.* Calcd. for $C_{23}H_{24}N_4O_3S$: C, 63.28; H, 5.54; N, 12.83; Found: C, 63.04; H, 5.28; N, 13.06.

Compound 5h. White solid, mp 204–205; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.14 (t, 3H, J = 7.2 Hz), 2.58 (s, 3H), 4.06 (q, 2H, J = 7.2 Hz), 4.12 (d, 1H, J = 13.2 Hz), 4.26 (d, 1H, J = 13.2 Hz), 6.32 (s, 1H), 7.19–7.30 (m, 9H), 10.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 14.10, 19.47, 36.28, 59.57, 60.19, 98.62, 127.34, 128.37, 128.65, 128.81, 128.91, 134.02, 137.20, 139.75, 146.23, 148.00, 157.71, 165.43; EI-MS (70Ev, *m/z*) (relative intensity %): 444 (6), 442 (25), 440 (M^+, 100), 407 (60), 395 (5), 361 (19), 349 (26), 329 (21), 317 (21), 289 (11), 275 (5), 247 (9), 207 (12), 189 (10), 163 (10), 123 (43); Elemental *Anal.* Calcd. for $C_{22}H_{21}ClN_4O_2S$: C, 59.92; H, 4.80; N, 12.71; Found: C, 60.23; H, 4.51; N, 12.84.

Compound 5i. White solid, mp 292–293; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.17 (t, 3H, J = 6.8 Hz), 2.32 (s, 3H), 2.51 (s, 3H), 4.11 (q, 2H, J = 7.2 Hz), 4.95 (d, 1H, J = 12.4 Hz), 5.14 (d, 1H, J = 12.4 Hz), 6.36 (s, 1H), 7.11–7.22 (m, 4H), 10.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.94, 14.50, 21.19, 40.21, 59.82, 60.90, 101.76, 127.25, 129.34, 137.22, 138.50, 142.39, 147.19, 159.34, 164.38; EI-MS (70Ev, *m/z*) (relative intensity %): 381 (32), 379 (M^+, 99), 342 (100), 331 (19), 313 (51), 297 (20), 287 (69), 267 (37), 255 (36), 223 (29), 194 (9), 177 (11), 153 (8), 141 (14) 126 (13), 115 (21); Elemental *Anal.* Calcd. for $C_{17}H_{19}ClN_4O_2S$: C, 53.89; H, 5.05; N, 14.79; Found: C, 54.13; H, 5.28; N, 14.91.

Compound 5j. White solid, mp 286–287; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.17 (t, 3H, J = 7.2 Hz), 2.52 (s, 3H), 3.78 (s, 3H), 4.11 (q, 2H, J = 7.2 Hz), 4.95 (d, 1H, J = 12.0 Hz), 5.13 (d, 1H, J = 12.0 Hz), 6.36 (s, 1H), 6.83–7.27 (m, 4H), 10.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.9,7 14.58, 40.19, 55.25, 59.55, 60.850, 101.72, 126.98, 128.62, 132.57, 142.51, 147.38, 159.56, 159.73, 164.46; EI-MS (70Ev, *m/z*) (relative intensity %): 397 (13), 395 (M^+, 100), 358 (99), 329 (36),313 (29), 287 (62), 271 (41), 251 (27), 240 (15), 222 (27), 194 (14), 177 (10), 158 (9), 145 (10), 115 (14), 108 (18), 77 (10); Elemental *Anal.* Calcd. for $C_{17}H_{19}ClN_4O_3S$: C, 51.71; H, 4.85; N, 14.19; Found: C, 51.93; H, 5.07; N, 14.43.

Compound 5k. White solid, mp 270–271; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.17 (t, 3H, J = 7.2 Hz), 2.51 (s, 3H), 4.12 (q, 2H, J = 7.2 Hz), 4.96 (d, 1H, J = 12.0 Hz), 5.12 (d, 1H, J = 12.0 Hz), 6.37 (s, 1H), 7.26–7.31 (m, 4H), 10.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.95, 14.57, 39.80, 59.39, 60.98, 100.81, 128.79, 128.84, 134.45, 138.76, 143.67, 147.60, 159.68, 164.16; EI-MS (70Ev, *m/z*) (relative intensity %): 402 (11), 400 (44), 399 (M^+, 21), 398 (81), 362 (80), 353 (10), 333 (36), 317 (17), 287 (100), 275 (45), 259 (23), 251 (10), 223 (22), 208 (5), 194 (5), 177 (9), 162 (7), 149 (10), 140 (6), 127 (9); Elemental *Anal.* Calcd. for $C_{16}H_{16}Cl_2N_4O_2S$: C, 48.13; H, 4.04; N, 14.03; Found: C, 47.87; H, 4.27; N, 13.86.

Compound 5l. White solid, mp 297–298; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.16 (t, 3H, J = 6.8 Hz), 2.34 (s, 3H), 4.12 (q, 2H, J = 7.2 Hz), 4.16 (d, 1H, J = 12.8 Hz), 4.27 (d, 1H, J = 12.8 Hz), 4.88 (d, 1H, J = 12.0 Hz), 5.09 (d, 1H, J = 12.0 Hz), 6.36 (s, 1H), 7.11–7.23 (m, 9H), 10.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.93, 21.18, 36.67, 39.87, 59.86, 60.79, 101.31, 127.25, 127.29, 128.36, 128.97, 129.29, 137.22, 137.49, 138.31, 143.25, 147.64, 157.94, 164.43; EI-MS (70Ev, *m/z*) (relative intensity %): 456 (19), 454 (M^+, 59), 418 (59), 385 (20), 363 (10), 357 (13), 339 (12), 327 (11), 297 (6), 267 (8), 227 (6), 212 (6), 168 (4), 141 (8), 123 (12); Elemental *Anal.* Calcd. for $C_{23}H_{23}ClN_4O_2S$: C, 60.72; H, 5.10; N, 12.31; Found: C, 60.54; H, 4.87; N, 12.09.

Compound 5m. White solid, mp 293–294; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.17 (t, 3H, J = 6.8 Hz), 3.80 (s, 3H), 4.11 (q, 2H, J = 6.8 Hz), 4.16 (d, 1H, J = 12.8 Hz),

4.28 (d, 1H, J = 12.8 Hz), 4.90 (d, 1H, J = 12.0 Hz), 5.07 (d, 1H, J = 12.0 Hz), 6.35 (s, 1H), 6.84–7.24 (m, 9H), 10.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.95, 36.67, 39.83, 55.25, 59.56, 60.77, 101.29, 113.91, 127.26, 128.36, 128.64, 128.97, 132.71, 137.22, 143.25, 147.61, 157.84, 159.64, 164.44; EI-MS (70Ev, *m/z*) (relative intensity %): 472 (10), 470 (M^+, 40), 462 (7), 434 (70), 401 (16), 373 (10), 355 (12), 327 (12), 313 (21), 283 (24), 267 (23), 241 (22), 228 (25), 197 (20), 185 (20), 172 (14), 158 (12), 123 (28), 115 (10), 91 (100); Elemental *Anal*. Calcd. for $C_{23}H_{23}ClN_4O_3S$: C, 58.65; H, 4.92; N, 11.90; Found: C, 58.88; H, 5.12; N, 12.05.

Compound 5n. White solid, mp > 300; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.16 (t, 3H, J = 7.2 Hz), 4.11 (q, 2H, J = 7.2 Hz), 4.15 (d, 1H, J = 13.6 Hz), 4.27 (d, 1H, J = 13.6 Hz), 4.92 (d, 1H, J = 12.0 Hz), 5.07 (d, 1H, J = 12.0 Hz), 6.36 (s, 1H), 7.17–7.32 (m, 9H), 10.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.95, 36.54, 39.80, 59.52, 60.95, 100.63, 127.34, 128.37, 128.81, 128.86, 128.92, 134.46, 137.12, 138.87, 143.75, 147.59, 158.28, 164.18; EI-MS (70Ev, *m/z*) (relative intensity %): 478 (14), 476 (54), 474 (M^+, 73), 438 (57), 405 (31), 391 (23), 377 (10), 362 (17), 327 (9), 288 (10), 258 (13), 246 (14), 228 (9), 162 (7), 149 (8), 133 (34), 105 (22), 91 (100); Elemental *Anal*. Calcd. for $C_{22}H_{20}Cl_2N_4O_2S$: C, 55.58; H, 4.24; N, 11.79; Found: C, 55.41; H, 4.51; N, 11.63.

Compound 5o. White solid, mp 154–155; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.16 (t, 3H, J = 7.2 Hz), 2.46 (s, 3H), 3.79 (s, 3H), 4.12 (m, 2H), 6.38 (s, 1H), 6.86–7.26 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.60, 14.16, 55.21, 60.11, 61.66, 106.45, 114.11, 115.73, 118.48, 121.22, 123.97, 128.78, 130.15, 130.52, 130.87, 147.11, 159.98, 160.76, 163.17; EI-MS (70Ev, *m/z*) (relative intensity %): 416 (5), 414 (M^+, 100), 385 (25), 367 (78), 341 (44), 325 (12), 294 (10), 279 (16), 233 (6), 213 (9), 170 (4), 85 (4); Elemental *Anal*. Calcd. for $C_{17}H_{17}F_3N_4O_3S$: C, 49.27; H, 4.13; N, 13.52; Found: C, 49.42; H, 4.36; N, 13.69.

Compound 5p. White solid, mp 188–189; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.17 (t, 3H, J = 7.2 Hz), 2.45 (s, 3H), 4.13 (m, 2H), 6.40 (s, 1H), 7.25–7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.60, 14.12, 60.02, 61.87, 92.29, 105.74, 115.60, 118.36, 121.11, 123.86, 128.87, 129.09, 130.83, 131.20, 131.57, 135.05, 136.76, 147.06, 161.17, 162.92; EI-MS (70Ev, *m/z*) (relative intensity %): 420 (29), 418 (M^+, 100), 389 (32), 371 (62), 349 (32), 307 (21), 279 (17), 263 (3), 233 (8), 217 (5), 182 (3), 111 (5); Elemental *Anal*. Calcd. for $C_{16}H_{14}ClF_3N_4O_2S$: C, 45.88; H, 3.37; N, 13.38; Found: C, 45.62; H, 3.47; N, 13.11.

Compound 5q. White solid, mp 160–161; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.16 (t, 3H, J = 7.2 Hz), 4.12 (m, 2H), 4.12 (d, 1H, J = 13.2 Hz), 4.24 (d, 1H, J = 13.2 Hz), 6.39 (s, 1H), 7.18–7.34 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.59, 35.77, 59.99, 61.84, 105.47, 115.57, 118.32, 121.07, 123.82, 127.22, 128.27, 128.90, 129.07, 129.82, 130.94, 131.31, 131.68, 132.04, 135.01, 136.77, 146.96, 159.64, 162.94; EI-MS (70Ev, *m/z*) (relative intensity %): 496 (32), 494 (M^+, 100), 461 (65), 449 (4), 415 (12), 403 (6), 390 (4), 217 (3), 172 (4), 121 (7), 91 (99); Elemental *Anal*. Calcd. for $C_{22}H_{18}ClF_3N_4O_2S$: C, 53.39; H, 3.67; N, 11.32; Found: C, 53.62; H, 3.84; N, 11.08.

Compound 5r. White solid, mp 188–189; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.20 (t, 3H, J = 7.2 Hz), 2.47 (s, 3H), 4.16 (m, 2H), 6.39 (s, 1H), 7.14–7.45 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.60, 14.11, 59.58, 61.92, 104.87, 114.19, 115.54, 118.33, 121.08, 123.79, 126.80, 129.61, 130.93, 131.37, 131.82, 132.22, 132.51, 133.03, 133.42, 138.44, 147.06, 161.54, 162.80; EI-MS (70Ev, *m/z*) (relative intensity %): 454 (100), 452 (M^+, 88), 423 (32), 405 (84), 383 (43), 359 (10), 307 (39), 279 (26), 251 (6), 233 (10), 201 (5), 165 (7), 109 (6); Elemental *Anal*. Calcd. for $C_{16}H_{13}Cl_2F_3N_4O_2S$: C, 42.40; H, 2.89; N, 12.36; Found: C, 42.50; H, 3.05; N, 12.05.

Compound 5s. Yellow solid, mp 209–210; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.19 (t, 3H, J = 7.2 Hz), 2.45 (s, 3H), 4.15 (m, 2H), 6.54 (s, 1H), 7.51–8.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.60, 14.02, 59.83, 62.14, 104.58, 115.49, 118.30, 120.87, 124.13, 128.61, 131.88, 132.22, 132.60, 132.93, 144.79, 147.20, 148.14, 161.73, 162.68; EI-MS (70Ev, *m/z*) (relative intensity %): 244 (3), 227 (2), 199 (2), 138 (20), 107 (33), 77 (100); Elemental *Anal*. Calcd. for $C_{16}H_{14}F_3N_5O_4S$: C, 44.76; H, 3.29; N, 16.31; Found: C, 45.02; H, 3.38; N, 16.05.

Compound 5t. White solid, mp 155–156; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.15 (t, 3H, J = 7.2 Hz), 2.45 (s, 3H), 4.04 (m, 2H), 6.65 (s, 1H), 7.03–7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.54, 14.10, 55.83, 61.68, 104.53, 115.56, 115.89, 116.22, 118.40, 121.13, 123.83, 124.44, 125.46, 125.60, 129.82, 130.87, 131.61, 131.92, 132.27, 132.58; EI-MS (70Ev, *m/z*) (relative intensity %): 402 (M^+, 53), 373 (13), 353 (27), 333 (22), 307 (12), 279 (9), 266 (10), 249 (22), 198 (14), 168 (99), 139 (100), 124 (92), 106 (32); Elemental *Anal*. Calcd. for $C_{16}H_{14}F_4N_4O_2S$: C, 47.76; H, 3.51; N, 13.92; Found: C, 48.02; H, 3.76; N, 14.15.

Compound 5u. White solid, mp 179–180; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.14 (t, 3H, J = 7.2 Hz), 2.46 (s, 3H), 4.04 (m, 2H), 6.43 (s, 1H), 7.30–7.38 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.60, 14.11, 60.58, 60.72, 61.74, 106.19, 115.68, 118.48, 121.19, 123.90, 127.43, 128.83, 129.04, 130.51, 130.79, 131.20, 131.57, 138.33, 147.29, 160.81, 163.10; EI-MS (70Ev, *m/z*) (relative intensity %): 385 (19), 384 (M^+, 100), 355 (20), 337 (50), 315 (19), 307 (25), 279 (19), 133 (8); Elemental *Anal*. Calcd. for $C_{16}H_{15}F_3N_4O_2S$: C, 50.00; H, 3.93; N, 14.58; Found: C, 50.08; H, 4.00; N, 14.30.

Compound 5v. White solid, mp 156–157; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.16 (t, 3H, J = 7.2 Hz), 2.33 (s, 3H), 2.46 (s, 3H), 4.12 (m, 2H), 6.38 (s, 1H), 7.15 (dd, 2H, J = 8.4 Hz), 7.19 (dd, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.60, 14.12, 21.17, 60.39, 61.57, 106.44, 115.73, 118.54, 121.16, 123.92, 127.33, 129.48, 130.41, 130.72, 131.14, 131.50, 135.45, 138.93, 147.23, 160.83, 163.12; EI-MS (70Ev, *m/z*) (relative intensity %): 400 (5), 398 (M^+, 100), 369 (25), 351 (81), 329 (28), 307 (30), 278 (31), 233 (8), 197 (4), 165 (3), 115 (7); Elemental *Anal*. Calcd. for $C_{17}H_{16}F_4N_4O_2S$: C, 49.04; H, 3.87; N, 13.46; Found: C, 49.25; H, 3.67; N, 13.19.

Compound 6a. White solid, mp 154–155; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.96 (t, 3H, J = 7.2 Hz), 1.89 (s, 3H), 2.43 (s, 3H), 3.04 (d, 1H, J = 11.2 Hz), 3.81 (s, 3H), 3.95 (m, 2H), 4.95 (d, 1H, J = 11.2 Hz), 5.93 (s, 1H), 6.87–7.34 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.71, 14.30, 25.69, 53.84, 55.33, 57.10, 61, 50, 81.83, 114.12, 129.08, 129.74, 153.14, 159.09, 160.10, 169.87; EI-MS (70Ev, *m/z*)

(relative intensity %): 379 (8), 378 (M^+, 32), 360 (12), 335 (7), 313 (9), 289 (8), 247 (100), 233 (41), 200 (38), 174 (24), 161 (64), 146 (61), 129 (64), 115 (23); Elemental *Anal*. Calcd. for $C_{17}H_{22}N_4O_4S$: C, 53.95; H, 5.86; N, 14.80; Found: C, 53.76; H, 6.04; N, 14.92.

Compound 6d. White solid, mp 151–152; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.97 (t, 3H, J = 7.2 Hz), 1.86 (s, 3H), 2.43 (s, 3H), 3.44 (d, 1H, J = 11.2 Hz), 4.01 (m, 2H), 5.62 (d, 1H, J = 11.2 Hz), 6.88 (s, 1H), 7.25–7.50 (m, 3H); ^{13} C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.69, 14.30, 24.38, 49.63, 52.14, 61.88, 82.10, 127.61, 129.67, 133.89, 139.11, 153.69, 159.52, 169.83; EI-MS (70Ev, *m/z*) (relative intensity %): 418 (4), 416 (M^+, 7), 373 (5), 327 (9), 287 (23), 251 (100), 223 (21),199 (15), 170 (8), 13 0 (28), 114 (8); Elemental *Anal*. Calcd. for $C_{16}H_{18}Cl_2N_4O_3S$: C, 46.05; H, 4.35; N, 13.43; Found: C, 46.33; H, 4.08; N, 13.80.

Compound 6f. White solid, mp 140–141; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.96 (t, 3H, J = 7.2 Hz), 1.80 (s, 3H), 2.31 (s, 3H), 3.05 (d, 1H, J = 11.2 Hz), 3.92 (m, 2H), 4.20 (d, 1H, J = 13.2 Hz), 4.27 (d, 1H, J = 13.2 Hz), 4.94 (d, 1H, J = 11.2 Hz), 5.86 (s, 1H), 7.13–7.37 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.60, 21.11, 25.69, 36.13, 54.33, 56.74, 61.48, 81.87, 127.21, 127.72, 128.44, 129.13, 129.49, 134.52, 137.47, 138.86, 152.90, 157.88, 170.12; EI-MS (70Ev, *m/z*) (relative intensity %): 438 (M^+, 5), 369 (2), 308 (50), 275 (30), 231 (27), 217 (72), 206 (65), 187 (21), 173 (24), 143 (28), 115 (51), 102 (16), 90 (100); Elemental *Anal*. Calcd. for $C_{23}H_{26}N_4O_3S$: C, 62.99; H, 5.98; N, 12.78; Found: C, 62.77; H, 6.17; N, 12.94.

Compound 6h. White solid, mp 152–153; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.96 (t, 3H, J = 7.2 Hz), 1.78 (s, 3H), 3.01 (d, 1H, J = 11.2 Hz), 3.92 (m, 2H), 4.12 (d, 1H, J = 13.2 Hz), 4.20 (d, 1H, J = 13.2 Hz), 4.96 (d, 1H, J = 11.6 Hz), 6.63 (s, 1H), 7.23–7.35 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.70, 25.61, 35.92, 53.68, 56.84, 61.73, 81.85, 127.20, 128.44, 128.91, 129.04, 129.29, 134.77, 136.32, 137.28, 152.91, 157.83, 169.64; EI-MS (70Ev, *m/z*) (relative intensity %): 458 (M^+, 2), 328 (64), 295 (48), 251 (49), 237 (36), 217 (42), 206 (100), 189 (9), 173 (46), 165 (37), 141 (11), 115 (11), 101 (18); Elemental *Anal*. Calcd. for $C_{22}H_{23}ClN_4O_3S$: C, 57.57; H, 5.05; N, 12.21; Found: C, 57.82; H, 5.30; N, 12.09.

Compound 6i. White solid, mp 147–148; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.93 (t, 3H, J = 7.2 Hz), 2.36 (s, 3H), 2.39 (s, 3H), 3.55 (d, 1H, J = 11.6 Hz), 3.88 (d, 1H, J = 12.0 Hz), 3.94 (m, 2H), 4.36 (d, 1H, J = 11.6 Hz), 4.93 (d, 1H, J = 11.2 Hz), 5.82 (s, 1H), 7.17–7.34 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.52, 14.20, 21.24, 46.08, 51.73, 54.14, 61.88, 83.63, 127.81, 129.50, 134.08, 139.22, 153.91, 159.79, 169.90; EI-MS (70Ev, *m/z*) (relative intensity %): 396 (M^+, 6), 360 (2), 273 (3), 266 (6), 251 (6), 231 (100), 217 (53), 185 (5), 164 (4), 145 (13), 130 (36), 115 (47), 103 (9); Elemental *Anal*. Calcd. for $C_{17}H_{21}ClN_4O_3S$: C, 51.45; H, 5.33; N, 14.12; Found: C, 51.57; H, 5.05; N, 14.34.

Compound 6m. White solid, mp 147–148; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.94 (t, 3H, J = 7.2 Hz), 3.52 (d, 1H, J = 11.6 Hz), 3.76 (s, 3H), 3.87 (d, 1H, J = 12.0 Hz), 3.96 (m, 2H), 4.02 (d, 1H, J = 12.8 Hz), 4.16 (d, 1H, J = 12.8 Hz), 4.34 (d, 1H, J = 11.6 Hz), 4.91 (d, 1H, J = 11.6 Hz), 6.33 (s, 1H), 6.85–7.36 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.60, 35.82, 46.19, 51.89, 53.04, 55.22, 61.73, 83.61, 113.88, 127.11, 128.26, 128.86, 129.37, 137.24, 154.13, 158.30, 160.04, 169.11; EI-MS (70Ev, *m/z*) (relative intensity %): 324 (16), 291 (8), 282 (17), 233 (89), 206 (38), 189 (9), 173 (24), 161 (22), 137 (19), 115 (50), 91 (100); Elemental *Anal*. Calcd. for $C_{23}H_{25}ClN_4O_4S$: C, 56.49; H, 5.15; N, 11.46; Found: C, 56.78; H, 5.06; N, 11.57.

Compound 6n. White solid, mp 150–151; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.97 (t, 3H, J = 7.2 Hz), 3.51 (d, 1H, J = 11.2 Hz), 3.87 (d, 1H, J = 11.2 Hz), 3.94 (m, 2H), 4.03 (d, 1H, J = 13.2 Hz), 4.15 (d, 1H, J = 13.2 Hz), 4.34 (d, 1H, J = 11.2 Hz), 4.93 (d, 1H, J = 11.2 Hz), 6.78 (s, 1H), 7.23–7.39 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.60, 35.91, 45.86, 51.69, 53.40, 61.87, 83.73, 127.32, 128.45, 128.86, 129.02, 129.64, 135.03, 135.87, 137.11, 154.10, 158.50, 169.14; EI-MS (70Ev, *m/z*) (relative intensity %): 493 (M^+, 1), 419 (1), 366 (2), 328 (61), 295 (43), 286 (21), 251 (4), 237 (99), 206 (100), 190 (10), 173 (45), 165 (33), 136 (23), 115 (29), 101 (25); Elemental *Anal*. Calcd. for $C_{22}H_{22}Cl_2N_4O_3S$: C, 53.55; H, 4.49; N, 11.36; Found: C, 53.78; H, 4.72; N, 11.70.

Compound 6t. White solid, mp 158–159; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.88 (t, 3H, J = 7.2 Hz), 2.33 (s, 3H), 3.78 (d, 1H, J = 4.0 Hz), 3.84 (m, 2H), 5.44 (d, 1H, J = 4.0 Hz), 7.12–7.46 (m, 4H); ^{13}C NMR (DMSO, 100 MHz) δ (ppm): 13.54, 47.03, 48.10, 60.43, 60.61, 81.23, 81.46, 115.25, 115.44, 121.42, 123.74, 123.79, 124.23, 124.67, 127.88, 130.50, 153.93, 155.62, 157.67, 158.33, 159.40, 160.77, 164.65, 165.52; EI-MS (70Ev, *m/z*) (relative intensity %): 422 (6), 420 (M^+, 100), 401 (20), 373 (7), 353 (12), 277 (14), 235 (72), 217 (83), 184 (5), 149 (25), 134 (27), 115 (22); Elemental *Anal*. Calcd. for $C_{16}H_{16}F_4N_4O_3S$: C, 45.71; H, 3.84; N, 13.33; Found: C, 45.54; H, 4.05; N, 13.56.

Compound 6u. White solid, mp 143–144; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.88 (t, 3H, J = 7.2 Hz), 2.26 (s, 3H), 3.59 (d, 1H, J = 4.0 Hz), 3.85 (m, 2H), 5.10 (d, 1H, J = 4.4 Hz), 7.32–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.60, 14.22, 49.89, 54,14, 61.12, 81.87, 82.32, 121.24, 124.13, 126.65, 126.91, 136.14, 155.10, 160.83, 165.44; EI-MS (70Ev, *m/z*) (relative intensity %): 402 (M^+, 8), 369 (4), 272 (3), 230 (4), 217 (100), 203 (5), 184 (9), 171 (6), 139 (15), 115 (22); Elemental *Anal*. Calcd. for $C_{16}H_{17}F_3N_4O_3S$: C, 47.76; H, 4.26; N, 13.92; Found: C, 48.04; H, 4.02; N, 14.15.

Compound 6v. White solid, mp 153–154; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.92 (t, 3H, J = 7.2 Hz), 2.29 (s, 3H), 2.34 (s, 3H), 3.56 (d, 1H, J = 4.0 Hz), 3.87 (q, 2H, J = 7.2 Hz), 5.06 (d, 1H, J = 4.0 Hz), 7.07–7.24 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 13.22, 13.58, 14.20, 49.87, 53.90, 61.23, 81.91, 82.19, 118.22, 121.14, 123.88, 126.55, 127.64, 129.61, 132.88, 138.83, 139.74, 155.13, 160.89, 165.54; EI-MS (70Ev, *m/z*) (relative intensity %): 416 (M^+, 6), 286 (2), 271 (3), 231 (100), 217 (8), 184 (5), 139 (9), 130 (14), 115 (19); Elemental *Anal*. Calcd. for $C_{17}H_{19}F_3N_4O_3S$: C, 49.03; H, 4.60; N, 13.45; Found: C, 49.37; H, 4.63; N, 13.13.

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