Synthesis and biological activity of novel *N*-(5-((1*H*-1,2,4-triazol-1-yl)methyl)-4-*tert*-butylthiazol-2-yl)-4-carboxamide derivatives

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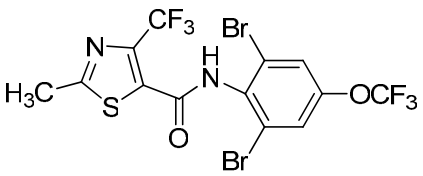
Abstract

Eleven new thiazol-containing 1*H*-1,2,4-triazole derivatives were designed and synthesized by utilizing 3,3-dimethylbutan-2-one as starting material. Their structures were characterized by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. Furthermore, some compounds' structures were confirmed with MS and X-ray diffraction and the biological activities of these compounds were evaluated, including *in vitro* fungicidal and plant-growth regulatory activities. The primary bioassay results indicated that these compounds showed low antifungal activities while exhibited promising plant-growth regulatory activities.

Keywords: 1*H*-1,2,4-Triazole, thiazole, antifungal activity, plant-growth regulatory activity

Introduction

The thiazole moiety plays a vital role in many biological activities, and molecules containing thiazole ring systems are extensively found in the field of agrochemicals,[1] such as commercial agricultural fungicides trifluzamide and ethaboxam.[2] Because of its low toxicity, excellent biological activity as well as readily access of diverse derivatives, this class of *N*-heterocyclic derivatives are widely studied.[3] On the other hand, 1*H*-1,2,4-triazole-containing derivatives which possess anti-inflammatory,[4] antiviral, anticonvulsant,[5] antimicrobial,[6] antitumorial,[7] analgesic,[8] antihypotensive,[9] antiparasitic, fungicidal, insecticidal, herbicidal and plant-growth regulatory activities[10] have been paid much attention during the last few decades. For example, triadimefon, tebuconazole, uniconazole are well known as commercial agricultural fungicides. Besides, some 1*H*-1,2,4-triazole-containing derivatives, such as uniconazole and paclobutrazol have also found to show significant plant-growth regulatory activity (Scheme 1).[11]



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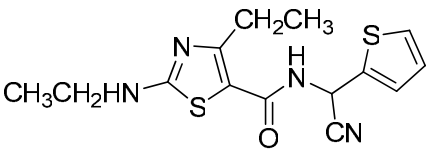
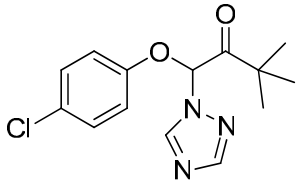
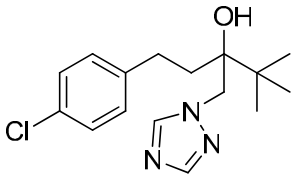


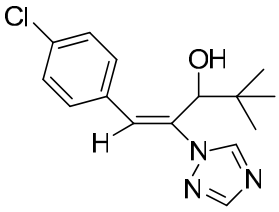
ethaboxam



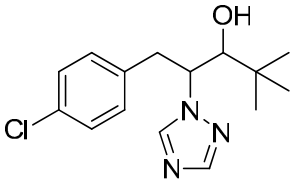
triadimefon



tebuconazole



uniconazole



paclobutrazol

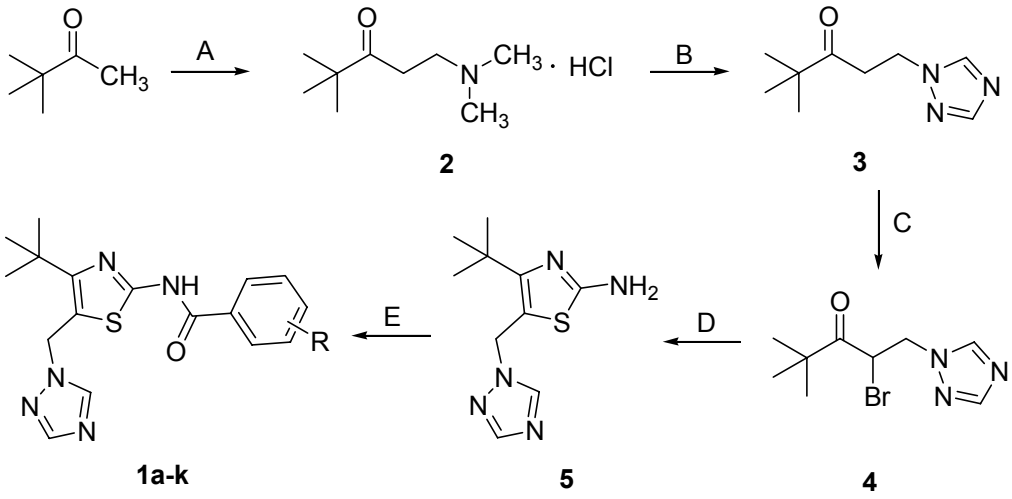
Scheme 1. Commercial thiazolyl- and 1*H*-1,2,4-triazolyl-containing agrochemicals.

Promoted by the above observations and in continuation of our study on the biological activities of thiazole derivatives, we designed and synthesized some new thiazole derivatives by incorporating the 1*H*-1,2,4-triazole unit into the title compounds, and such molecules are expected to exhibit improving biological activity. We herein report the synthesis and structure of a series of novel *N*-(5-((1*H*-1,2,4-triazol-1-yl)methyl)-4-*tert*-butylthiazol-2-yl)-4-carboxamide derivatives, which have been characterized by spectral data and elemental analysis.

Results and Discussion

Chemistry

Synthetic route of the title compounds is outlined in Scheme 2. Compounds **2**-**4** were synthesized according to the literature methods.[12-13] The key intermediate compound **5** was obtained by the condensation of compound **4** with thiourea via a typical Hantzsh reaction.[14] Synthetic conditions of compound **5** were examined including temperature, time and solvent. The best yield was reached when compound **4** reacted with thiourea in ethanol at 50 °C for 8 h. Compound **5** reacted readily with substituted benzoyl chlorides in 1,2-dichloroethane to afford the title compounds **1a-k** in high purity and yields.



Scheme 2. Synthesis of the title compounds 1a-k. Reagents and conditions: (A) $(CH_2O)n/Me_2NH{\cdot}HCl$, C_2H_5OH; (B) 1*H*-1,2,4-triazole/H_2O; (C) $Br_2/CH_3COOH,CH_3COONa$; (D) thiourea/C_2H_5OH; (E) substituted benzoyl chlorides/1,2-dichloroethane/pyridine.

Biological activity

The title compounds **1a-k** were screened for their biological activities *in vitro* against five selected fungi including *Gibberella zeae*, *Alternaria solani*, *Cercospora arachidicola*, *Physalospora piricola* and *Cladosporium cucumerinum* according to procedures described previously.[15] At the concentration of 50 mg/L, the relative inhibitory ratios (%) against these fungi were listed in Table 2. Disappointedly, compared with known commercial antifungal analog (Triadimenfon), the antifungal activities of most of this type of compounds were not encouraging, except that compound **1a** showed higher activity against *A. solani* and **1a**, **1c**, **1e** exhibited higher activity against *G. zeae* than Triadimenfon. To the best of our knowledge, a linkage between the triazole ring and the aryl group via a carbon-carbon single or double bond is essential for fungicidal activities. In addition, it has been proved that an extended carbon backbone linking the triazole cycle and the aryl group in an almost linear fashion possesses higher activity than a distorted backbone.[15] The X-ray structure of (**1f**) shows that, because of the bulkiness of thiazole, the triazole cycle and the aryl group are not connected in such a way, but via a bent linkage (Figure 1). As a result, the fungicidal activities of title compounds **1a–k** were depressed. This implies that a bulky group close to the triazole cycle is not a wise choice for the generation of compounds with fungicidal activities.

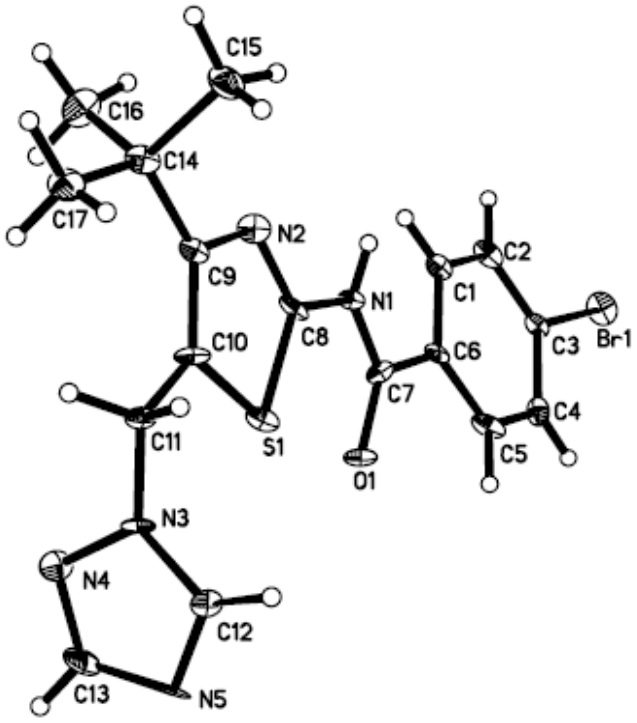


Figure 1. Molecular structure and crystallographic numbering scheme for compound **1f**. X-ray crystallography shows that compound **1f** contains two independent molecules, whose coordination environments are completely the same. The molecular structure of **1f** contains the following three-plane subunit: the substituted phenyl ring C1-C6 (*p1*), the thiazole ring (*p2*), and the triazole ring (*p3*). The dihedral angles between *p1* and *p2* and between *p2* and *p3* are 10.9 and 80.2, respectively. Some of their selected bond lengths and angles are listed in Table 1.

Table 1. Selected bond lengths and angles of compound **1f**

Bond lengths (Å)		bond angles (°)	
Br(1)-C(3)	1.924(9)	C(8)-S(1)-C(10)	89.7(5)
S(1)-C(8)	1.720(9)	C(7)-N(1)-C(8)	124.1(8)
S(1)-C(10)	1.721(10)	C(8)-N(2)-C(9)	113.0(8)
O(1)-C(7)	1.259(11)	C(13)-N(4)-N(3)	103.0(9)
N(1)-C(7)	1.308(11)	N(3)-C(11)-C(10)	112.3(8)
N(1)-C(8)	1.377(12)	O(1)-C(7)-N(1)	121.3(8)
N(3)-C(11)	1.417(11)	O(1)-C(7)-C(6)	119.3(8)
N(3)-N(4)	1.355(12)	C(4)-C(3)-Br(1)	116.4(7)
N(5)-C(13)	1.319(15)	C(1)-C(6)-C(7)	122.7(9)
N(2)-C(9)	1.410(12)	O(1)-C(7)-N(1)	121.3(8)
C(9)-C(14)	1.485(14)	N(2)-C(8)-S(1)	114.3(7)

Table 2. Fungicidal activity of title compounds 1a-k (c = 50 mg/L)

Compound	R	Fungicidal activity (relative inhibitory ratio, %)				
		G. zeae	*A. solani*	*C. ara*	*P. piricola*	*C. cucum*
1a	2-Cl	13.0	46.2	0	0	0
1b	2-F	0	7.7	0	0	0
1c	2-Et	13.0	23.1	0	0	0
1d	3-F	0	15.4	0	0	0
1e	4-Cl	13.0	7.7	20.0	0	0
1f	4-Br	0	7.7	0	0	0
1g	4-F	0	0	0	0	0
1h	4-Me	0	7.7	0	0	0
1i	4-NO_2	0	0	0	0	0
1j	2,4-Cl_2	4.3	23.1	0	0	0
1k	3,4-Cl_2	0	7.7	0	0	0
triadimefon		7.7	44	61.1	44.4	53.3

In addition, plant-growth regulatory activity of title compounds **1a–k** was screened using cucumber cotyledon rhizogenesis method according to procedures described previously.[16] At the concentration of 10 mg/L, the plant-growth regulatory activity data for compounds **1a–k** is shown in **Table 3**. To our delight, although these novel triadimefon analogues exhibited lower antifungal activities against selected fungi than control triadimefon, screening data displayed that most of them had potent plant-growth regulatory activity. The title compounds **1a–k** obviously promoted cotyledon rhizogenesis of cucumber seed at a concentration of 10 mg/L. In comparison with control triadimefon, compounds **1i** and **1j** showed lower activity than the parent triadimefon, while compounds **1a**, **1b**, **1d**, **1g** and **1h** displayed more highly promoting activity. These data show that efficacy is strongly influenced by the nature of the substitutes and their position on the benzene ring. The structure-activity relationships for the phenyl group were elucidated. In general, the presence of halo groups such as fluorine and chlorine atom at position 2 or 4 of phenyl ring enhanced the plant-growth regulatory activity. However, the substituted group of chlorine atom at both 2-position and 4-position of benzene ring caused a decrease of the activity. The presence of a strong electron-withdrawing group like nitro-group led to decrease in activity. From the result, we notice that the presence of fluorine atom at position 2, 3, 4 of phenyl ring all exhibited excellent plant-growth regulatory activities, so we can draw the conclusion that the fluorine atom connected to the phenyl ring contributes most to the plant-growth regulatory activity among these compounds, such as **1b**, **1d** and **1g**.

Table 3. Plant growth regulatory activity of title compounds 1a-k (c = 10 mg/L)

Compound	R	Plant growth regulatory activity (Relative Ratio, %)	Active Grade[a]
1a	2-Cl	238.8	+++
1b	2-F	211.1	+++
1c	2-Et	105.5	++
1d	3-F	211.1	+++
1e	4-Cl	100.0	++
1f	4-Br	116.6	++
1g	4-F	205.5	+++
1h	4-Me	150.5	+++
1i	4-NO_2	22.2	-
1j	2,4-Cl_2	33.3	-
1k	3,4-Cl_2	88.8	+
triadimefon		80.7	+

[a] Active grade : +++ ≥150□ ++ ≥100□ + ≥50□ - □50□

With respect to ineffective antifungal activity and promising plant-growth regulatory activity of these novel triadimefon analogues, it could be inferred that these triazole derivatives might share different action mechanism between fungicidal activity and plant-growth regulator activity. The mode of action about this class of plant-growth regulators still remains unknown.[17] To disclose these details, further chemical and biological investigation is needed to clarify action modes of these novel thiazole-containing triadimefon analogues.

Conclusions

In search of potentially biological molecules containing thiazole and 1*H*-1,2,4-triazole moieties, a series of new carboxamide derivatives was synthesized and their antifungal and plant-growth regulatory activity assayed. These thiazole-substituted 1*H*-1,2,4-triazole carboxamide derivatives showed lower antifungal activity than parent triadimefon, while exhibiting promising plant-growth regulatory activity.

Experimental Section

General Procedures. Melting points were measured by using a RY-1 melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian-300 spectrometer using TMS as an internal reference. Chemical shift values (δ) were given in ppm. Infrared spectra were obtained on a Bio-Rad spectrophotometer using potassium bromide pellets or as

neat oils and are reported as wave numbers (cm^{-1}). Mass spectra (ESI) were obtained on a LCQ Advantage instrument from Thermo Finnigan company. Elemental analysis was determined on a Yanaco CHN Corder elemental analyzer. X-ray diffraction data were recorded at 293 K on a Bruker Smart 1000 diffractometer (graphite-monochromatized Mo Kα radiation,λ= 0.71073 Å). The biological activity of the title compounds were assayed at the Biological Assay Centre, Nankai University.

Synthesis of 5-((1*H*-1,2,4-triazol-1-yl)methyl)-4-*tert*-butylthiazol-2-amine (5). Thiourea was added to the solution of compound **4** (9.918 mmol) in ethanol (15 mL), the mixture was heated to 50 °C and stirred for 8 h to form the hydrobromide salt of **5** which precipitated out. The reaction mixture was then cooled and vacuum filtered. The solid was then stirred for 1 h with saturated solution of sodium bicarbonate. The precipitated product was collected by filtration, and dried to give compound **5** in high purity, yield 75%, white crystalline solid, mp 187-189 °C. IR (KBr, cm^{-1}) ν: 1646 (m, sh, NH), 1282 (m, sh, CN). ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm): 1.30 (s, 9H, *t*-butyl), 5.49 (s, 2H, CH_2), 6.82 (s, 2H, NH_2), 7.97 (s, 1H, TrH), 8.49 (s, 1H, TrH); ^{13}C NMR (300 MHz, DMSO) δ(ppm): 161.8 (s), 156.8 (s), 151.3 (d), 143.4 (d), 110.7 (s), 44.9 (t), 35.7 (s), 30.8 (q). Anal. Calc. (%) for $C_{10}H_{15}N_5S$: C, 50.61; H, 6.37; N, 29.51. Found: C, 50.45; H, 6.30; N, 29.78.

General preparation of the title compounds 1a-k

To the solution of compound **5** (2 mmol) in 1,2-dichloroethane (15 mL) was added appropriate benzoyl chloride (2.4 mmol) and pyridine (2.4 mmol). The reaction mixture was stirred and refluxed for 2-5 h (tracked with thin-layer chromatography, TLC). The solvent was evaporated under the reduced pressure, the residue was purified by flash chromatography (ethyl acetate/petroleum ether (v/v□3:2)) to afford the title compounds **1a-k** in high purity.

***N*-(5-((1*H*-1,2,4-Triazol-1-yl)methyl)-4-*tert*-butylthiazol-2-yl)-2-chlorobenzamide (1a).** Yield, 62%, white crystalline solid, mp 178-180 °C. IR (KBr, cm^{-1}) ν: 3432 (m, br, NH), 2958 (m, sh, CH), 1668 (s, sh, CO), 1566 (s, sh, CC). ^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 1.31 (s, 9H, *t*-butyl), 5.55 (s, 2H, CH_2), 7.31-7.36 (m, 1H, ArH), 7.40-7.42 (m, 2H, ArH), 7.76 (q, 1H, ArH), 7.88 (s, 1H, TrH), 7.97 (s, 1H, TrH). ^{13}C NMR (300MHz, $CDCl_3$) δ(ppm): 163.9 (s), 157.8 (s), 155.0 (s), 151.7 (d), 142.5 (d), 132.7 (s), 132.5 (d), 131.3 (s), 130.6 (d), 130.4 (d), 127.2 (d), 116.2 (s), 45.6 (t), 36.2 (s), 30.7 (q). Anal. calcd for $C_{17}H_{18}ClN_5OS$: C 54.32, H 4.83, N 18.63; found C 54.21, H 4.96, N 18.29.

***N*-(5-((1*H*-1,2,4-Triazol-1-yl)methyl)-4-*tert*-butylthiazol-2-yl)-2-fluorobenzamide (1b).** Yield, 39%, white crystalline solid, mp 173-175 °C. IR (KBr, cm^{-1}) ν: 3460 (w, br, NH), 2954 (s, br, CH), 1662 (s, sh, CO), 1575 (s, sh, CC). ^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 1.41 (s, 9H, *t*-butyl), 5.63 (s, 2H, CH_2), 7.24 (q, 1H, ArH), 7.36 (t, 1H, ArH), 7.57-7.64 (m, 1H, ArH), 7.98 (s, 1H, TrH), 8.05 (s, 1H, TrH), 8.15-8.21 (m, 1H, ArH). ^{13}C NMR (300MHz, $CDCl_3$) δ(ppm): 162.2 (s), 160.7 (s), 158.9 (s), 157.9 (s), 154.5 (s), 152.0 (d), 142.6 (d), 134.9 (d), 132.2 (d), 125.3 (d), 119.2 (s), 116.5 (d), 45.5 (t), 36.3 (s), 30.7 (q). Anal. calcd for $C_{17}H_{18}FN_5OS$: C 56.81, H 5.05, N 19.49; found C 56.65, H 5.16, N 19.42.

***N*-(5-((1*H*-1,2,4-Triazol-1-yl)methyl)-4-*tert*-butylthiazol-2-yl)-2-ethylbenzamide (1c).** Yield, 61%, white crystalline solid, mp 176-178 °C. IR (KBr, cm^{-1}) ν: 3456 (m, br, NH), 2966 (m, sh, CH), 1663 (s, sh, CO), 1612 (s, sh, CC). ^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 1.28 (t, 3H, *J* = 7.6 Hz, CH_3), 1.39 (s, 9H, *t*-butyl), 2.74 (q, 2H, *J* = 7.6 Hz, CH_2), 5.62 (s, 2H, CH_2), 7.35 (d, 2H, *J* = 8.2 Hz, ArH), 7.87 (d, 2H, *J* = 8.2 Hz, ArH), 7.98 (s, 1H, TrH), 8.04 (s, 1H, TrH). ^{13}C NMR (300MHz, $CDCl_3$) δ(ppm): 164.7 (s), 157.5 (s), 155.9 (s), 152.0 (d), 150.0 (s), 142.6 (d), 129.2 (s), 128.4 (d), 127.8 (d), 115.9 (s), 45.6 (t), 36.2 (s), 30.8 (q), 28.9 (t), 15.2 (q). MS (ESI), m/z 370.06 ($[M+1]^+$, 100). Anal. calcd for $C_{19}H_{23}N_5OS$: C 61.76, H 6.27, N 18.95; found C 61.69, H 6.48, N 18.83.

***N*-(5-((1*H*-1,2,4-Triazol-1-yl)methyl)-4-*tert*-butylthiazol-2-yl)-3-fluorobenzamide (1d).** Yield, 32%, white crystalline solid, mp 133-135 °C. IR (KBr, cm^{-1}) ν: 3468 (s, br, NH), 2958 (s, sh, CH), 1667 (s, sh, CO), 1557 (s, sh, CC). ^{1}H NMR ($CDCl_3$, 300MHz) δ(ppm): 1.39 (s, 9H, *t*-butyl), 5.62 (s, 2H, CH_2), 7.29-7.36 (m, 1H, ArH), 7.47-7.57 (m, 1H, ArH), 7.69-7.79 (m, 2H, ArH), 7.99 (s, 1H, TrH), 8.06 (s, 1H, TrH). MS (ESI), m/z 360.05 ($[M+1]^+$, 100). Anal. calcd for $C_{17}H_{18}FN_5OS$: C 56.81, H 5.05, N 19.49; found C 56.58, H 5.24, N 19.41.

***N*-(5-((1*H*-1,2,4-Triazol-1-yl)methyl)-4-*tert*-butylthiazol-2-yl)-4-chlorobenzamide (1e).** Yield, 61%, white crystalline solid, mp 198-200 °C. IR (KBr, cm^{-1}) ν: 3413 (m, br, NH), 2952 (w, sh, CH), 1665 (s, sh, CO), 1596 (s, sh, CC). ^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 1.42 (s, 9H, *t*-butyl), 5.63 (s, 2H, CH_2), 7.51 (d, 2H, *J* = 8.5 Hz, ArH), 7.97 (d, 2H, *J* = 8.5 Hz, ArH), 7.99 (s, 1H, TrH) ,8.09 (s, 1H, TrH). ^{13}C NMR (300MHz, $CDCl_3$) δ(ppm): 164.0 (s), 162.3 (s), 156.8 (s), 152.0 (d), 142.6 (d), 139.4 (s), 131.4 (d), 130.2 (s), 129.2 (d), 116.3 (s), 45.6 (t), 36.4 (s), 30.7 (q). Anal. calcd for $C_{17}H_{18}ClN_5OS$: C 54.32, H 4.83, N 18.63; found C 54.15, H 5.01, N 18.44.

***N*-(5-((1*H*-1,2,4-Triazol-1-yl)methyl)-4-*tert*-butylthiazol-2-yl)-4-bromobenzamide (1f).** Yield, 70%, white crystalline solid, mp 204-205 °C. IR (KBr, cm^{-1}) ν: 3410 (w, br, NH), 2959 (s, sh, CH), 1663 (s, sh, CO), 1592 (s, sh, CC). ^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 1.43 (s, 9H, *t*-butyl), 5.64 (s, 2H, CH_2), 7.69 (d, 2H, *J* = 8.6 Hz, ArH), 7.88 (d, 2H, *J* = 8.4 Hz, ArH), 8.00 (s, 1H, TrH), 8.09 (s, 1H, TrH). MS (ESI), m/z 442.63 ($[M+23+1]^+$, 90), 419.95($[M+1]^+$, 100), 417.93 ($[M-1]^+$, 100). Anal. calcd for $C_{17}H_{18}BrN_5OS$: C 48.58, H 4.32, N 16.66; found C 48.31, H 4.38, N 16.60. CCDC 711849 contains the crystallographic data for compound **1f**. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/deposit, or from the Cambridge Crystallographic Data Centre,12 Union Road, Cambridge CB2 EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

***N*-(5-((1*H*-1,2,4-Triazol-1-yl)methyl)-4-*tert*-butylthiazol-2-yl)-4-fluorobenzamide (1g).** Yield, 49%, white crystalline solid, mp 190-192 °C. IR (KBr, cm^{-1}) ν: 3405 (w, br, NH), 2948 (s, sh, CH), 1661 (s, sh, CO), 1603 (s, sh, CC). ^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 1.32 (s, 9H, *t*-butyl), 5.55 (s, 2H, CH_2), 7.15 (q, 2H, *J* = 8.5 Hz, ArH), 7.94 (q, 2H, ArH), 7.91 (s, 1H, TrH), 8.00 (s, 1H, TrH). ^{13}C NMR (300MHz, $CDCl_3$) δ(ppm): 167.3(s), 163.7 (s), 162.3 (s), 157.5 (s), 155.5 (s), 151.9 (d), 142.6 (d), 130.0 (d), 128.2 (s), 116.2 (d), 45.6 (t), 36.2 (s), 30.8 (q). Anal. calcd for $C_{17}H_{18}FN_5OS$: C 56.81, H 5.05, N 19.49; found C 56.70, H 5.17, N 19.30.

***N*-(5-((1*H*-1,2,4-Triazol-1-yl)methyl)-4-*tert*-butylthiazol-2-yl)-4-methylbenzamide (1h).** Yield, 53%, white crystalline solid, mp 200-201 °C. IR (KBr, cm^{-1}) ν: 3390 (w, br, NH), 2948 (s, sh, CH), 1661 (s, sh, CO), 1603 (s, sh, CC). ^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 1.38 (s, 9H, *t*-butyl), 2.44 (s, 3H, CH_3), 5.62 (s, 2H, CH_2), 7.32 (d, 2H, *J* = 8.1 Hz, ArH), 7.84 (d, 2H, *J* = 8.1 Hz, ArH), 7.97 (s, 1H, TrH), 8.04 (s, 1H, TrH). ^{13}C NMR (300MHz, $CDCl_3$) δ(ppm): 164.6 (s), 157.5 (s), 155.7 (s), 151.9 (d), 143.7 (s), 142.6 (d), 129.6 (d), 129.0 (s), 127.5 (d), 115.9 (s), 45.6 (t), 36.2 (s), 30.7 (q), 21.5 (q). Anal. calcd for $C_{18}H_{21}N_5OS$: C 60.82, H 5.95, N 19.70; found C 60.66, H 6.11, N 19.56.

***N*-(5-((1*H*-1,2,4-Triazol-1-yl)methyl)-4-*tert*-butylthiazol-2-yl)-4-nitrobenzamide (1i).** Yield, 69%, white crystalline solid, mp 216-218 °C. IR (KBr, cm^{-1}) ν: 3402 (s, br, NH), 2958 (s, sh, CH), 1697 (s, sh, CO), 1602 (s, sh, CC). ^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 1.49 (s, 9H, *t*-butyl), 5.67 (s, 2H, CH_2), 8.03 (s, 1H, TrH), 8.13 (s, 1H, TrH), 8.27 (d, 2H, *J* = 8.3 Hz, ArH), 8.41 (d, 2H, *J* = 8.8 Hz, ArH). ^{13}C NMR (300MHz, DMSO) δ(ppm): 163.9 (s), 161.8 (s), 155.5 (s), 151.6 (d), 149.5 (s), 143.8 (d), 137.9 (s), 129.7 (d), 123.4 (d), 118.3 (s), 44.5 (t), 35.7 (s), 30.6 (q). Anal. calcd for $C_{17}H_{18}N_6O_3S$: C 52.84, H 4.70, N 21.75; found C 52.64, H 4.85, N 21.49.

***N*-(5-((1*H*-1,2,4-Triazol-1-yl)methyl)-4-*tert*-butylthiazol-2-yl)-2,4-dichlorobenzamide (1j).** Yield, 74%, white crystalline solid, mp 186-188 °C. IR (KBr, cm^{-1}) ν: 3464 (s, br, NH), 2968 (s, sh, CH), 1667 (s, sh, CO), 1567 (s, sh, CC). ^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 1.38 (s, 9H, *t*-butyl), 5.63 (s, 2H, CH_2), 7.41 (q, 1H, *J* = 1.9 Hz, *J* = 8.4 Hz, ArH), 7.51 (d, 1H, *J* = 1.9 Hz, ArH), 7.82 (d, 1H, *J* = 8.4 Hz, ArH), 7.96 (s, 1H, TrH), 8.05 (s, 1H, TrH). ^{13}C NMR (300MHz, $CDCl_3$) δ(ppm): 162.7 (s), 157.5 (s), 154.9 (s), 151.9 (d), 142.5 (d), 138.4 (s), 132.2 (s), 131.8 (d), 130.6 (s), 130.5 (d), 127.8 (d), 116.6 (s), 45.6 (t), 36.3 (s), 30.7 (q). Anal. calcd for $C_{17}H_{17}Cl_2N_5OS$: C 49.76, H 4.18, N 17.07; found C 49.56, H 4.48, N16.79.

***N*-(5-((1*H*-1,2,4-Triazol-1-yl)methyl)-4-*tert*-butylthiazol-2-yl)-3,4-dichlorobenzamide (1k).** Yield, 49%, white crystalline solid, mp 204-206 °C. IR (KBr, cm^{-1}) ν: 3414 (w, br, NH), 2977 (s, sh, CH), 1668 (s, sh, CO), 1553 (s, sh, CC). ^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 1.34 (s, 9H, *t*-butyl), 5.56 (s, 2H, CH_2), 7.54 (d, 1H, *J* = 8.4 Hz, ArH), 7.8 (q, 1H, *J* = 1.9 Hz, *J* = 8.4 Hz, ArH), 7.93 (s, 1H, TrH), 8.02 (s, 1H, TrH), 8.03 (d, 1H, *J* = 2.0 Hz, ArH). ^{13}C NMR (300MHz, $CDCl_3$) δ(ppm): 162.8 (s), 162.3 (s), 155.6 (s), 152.0 (d), 142.6 (d), 137.6 (s), 133.6 (s), 131.7 (s), 131.0 (d), 129.6 (d), 126.7 (d), 116.6 (s), 45.6 (t), 36.3 (s), 30.7 (q). Anal. calcd for $C_{17}H_{17}Cl_2N_5OS$: C 49.76, H 4.18, N 17.07; found C 49.66, H 4.29, N 16.99.

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