Microwave-assisted synthesis of benzothiazoleurea derivatives

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A simple and efficient method has been developed for the synthesis of 1-substituted-3-(4-chlorobenzo[*d*]thiazol-2-yl) ureas (**5**), from substituted aromatic or aliphatic amino compounds and phenyl 4-chlorobenzo[*d*]thiazol-2-yl carbamate **4** using microwave irradiation without phosgene in good yields. The title products were characterised by ^{1}H NMR, ESI-MS, and elemental analysis.

Keywords: benzothiazole urea; microwave irradiation; synthesis; biological activity, phenyl 4-chlorobenzo[*d*]thiazol-2-yl carbamate

Heterocyclic compounds play a key role in the research and development of new drugs because of their special chemical structures and special physical properties. They are important in medicine and for agriculture. Benzothiazole is an important heterocycle and has a wide range of applications in the pesticide, medicinal and other fields. Its aromaticity makes it relatively stable, although as a heterocycle it has reactive sites which allow for functionalisation. Benzothiazole compounds are also important raw materials in the production of fluorescent whitening agents, fluorescent dye such as Thioflavin[1] and pharmaceutical drugs, such as Riluzole which blocks TTX sensitive sodium channels.[2] Benzothiazole compounds can also be used as inhibitors of p56lck (Lck) in the T-cell proliferation[3] and inhibitors of HIV-1 protease with improved potency and antiviral activities.[4]

Benzothiazole ureas have also been previously reported to be local anaesthetics, potential hypoglycaemic agents and antibacterials.[5] In recent years benzothiazole-type compounds have attracted considerable attention in anticancer research.[6–12] Modified benzothiazole derivatives having additional functional groups may have enhanced the biological activity.

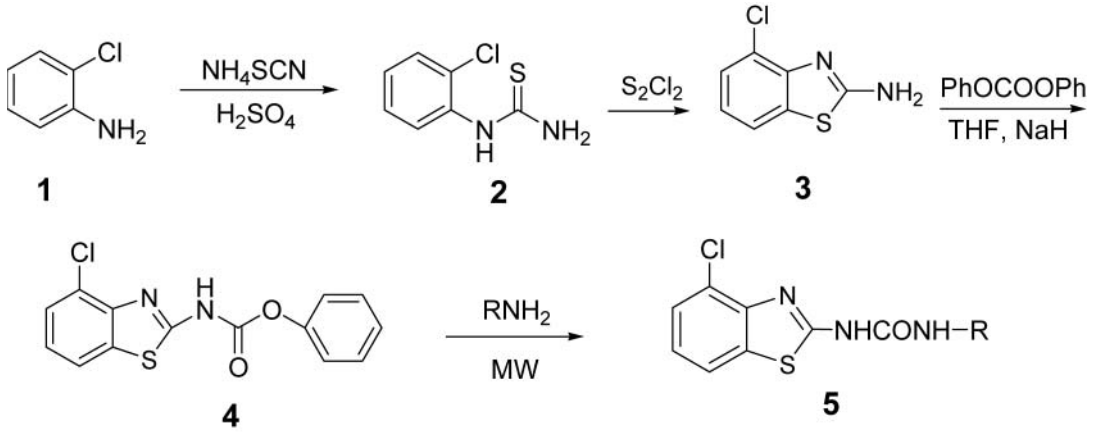
Microwave-assisted organic chemistry (MAOC) has become a valuable method in chemistry research during the past 20 years,[13–18] and been widely accepted. [19–22] The development of commercial microwave systems specifically designed for synthesis makes this technique more convenient and accesible. It gives improved opportunities for reproducibility, rapid synthesis, rapid reaction optimisation and the potential discovery of new chemistry.[23–25] The beneficial effects of microwave irradiation have become more important, especially when ordinary reactions require forcing conditions or prolonged reaction times.[26,27]

Although there are many feasible routes for the synthesis of heterocyclic asymmetric urea derivatives, but these methods are almost limited to addition of substituted amines to heterocyclic isocyanates from phosgene. To develop multifunctional libraries of 1, 3-disubstituted asymmetric urea derivatives and optimise the structure of urea derivatives to find a new lead compound, we here report a facile method without phosgene to synthesise the novel asymmetric urea derivative, benzothiazole heterocycle ureas, from substituted amino compounds and phenyl 4-chlorobenzo[*d*]thiazol-2-yl carbamate using MAOC conditions. Preliminary tests of their biological activities were then carried out.

Results and discussion

We have used microwave irradiation to prepare the title compounds and our results show that most reactions can be finished within 30 min in good yields. Products can be isolated by filtering or recrystallisation and rarely is silica gel column chromatography necessary. The reaction temperature was set up at 120–180 °C, and the time was 15–25 min. The synthetic route of the title compounds **5** is outlined in Scheme 1.

The compound **3**, which was obtained from 2-chloroaniline in two steps according to literature[28] with some modification, was treated with diphenyl carbonate and NaH in anhydrous THF to give phenyl-4-chlorobenzo[*d*]thiazol-2-ylcarbamate **4** in acceptable yield. The title compounds **5** were produced by aminolysis of compound **4** by various amines under microwave irradiation. Meanwhile, compound **5a**, **5l** and **5w** were



Scheme 1

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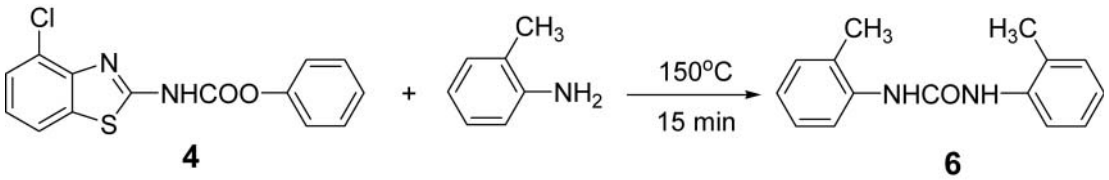

Scheme 2

selected to be prepared by conventional heating conditions and microwave irradiation. The results show that the reactants must be refluxed in THF or toluene for 24 h to give acceptable yields of 80%, 75% and 83%, respectively. So in these reactions, microwave irradiation can accelerate reaction rate and reduce the reaction time.

In the above reaction, when R is substituted phenyl, and the mole ratio of amine to intermediate **4** is 1.5–3, at a temperature higher than 120 °C, the title compound was not obtained and the symmetric urea substituted by the aniline was isolated. For example, when 2-methylaniline was reacted with intermediate **4**, the symmetric urea **6** was obtained, the structure of which was determined by ^{1}H NMR and ESI-MS. ^{1}H NMR [DMSO, 400M Hz] δ = 8.21 (s, 2H, 2×NH), 7.78–7.76 (dd, *J* = 6.2 Hz, 1.8 Hz, 2H), 7.15–7.08 (dt, *J* = 4.8 Hz, 7.7 Hz, 4H), 6.92–6.89 (m, 2H), 2.23 (s, 6H, 2×CH_3); ESI-MS (M^+): Calcd $C_{15}H_{16}N_2O$ 240.3; found 241.3 (100%, M+1).

Eventually we found that when reaction temperature was set at 120 °C, the ratio of 2-methylaniline to **4** was 1:1 and irradiation was for 25 min, the desired product in 50% yield.

The structures of all the title compounds were confirmed by elemental analysis, ^{1}H NMR, and ESI-MS. The structure of compound **5a** has also been confirmed by X-ray diffraction.[29]

The molecular structure shows that the N3–C9 bond distance indicates a typical single bond, but the N2–C7 (1.365Å) bond is much shorter than the N3–C9 (1.453Å) bond and shows something of the character of a C–N double bond. This is presumably due to the overlap of the non-bonding orbital of the imino N2 atom with the π orbital of the thiazole ring. The water molecules link with the urea derivative molecules via O—H----O and N—H---O hydrogen bonding, which helps to stabilise the crystal structure.

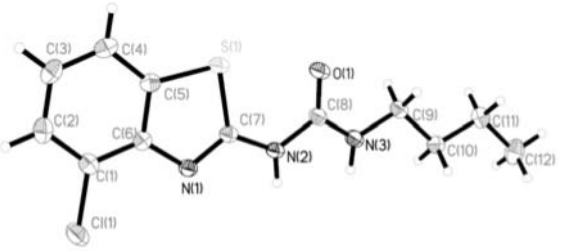

Fig. 1 The molecular structure of compound **5a**.

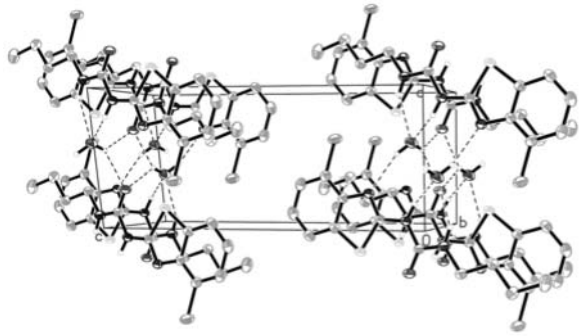

Fig. 2 The unit cell of compound **5a**.

To evaluate the biological usefulness of the title compounds, we are testing the insecticidal, herbicidal, fungicidal and plant growth regulation activities. The results show that some title compounds have good plant growth regulation and fungicidal activities. Detailed studies are in progress.

In conclusion, we report a rapid, mild and efficient procedure under microwave conditions for the synthesis of 1-substituted-3-(4-chlorobenzo[*d*]thiazol-2-yl) ureas from substituted aromatic or aliphatic amino compounds and phenyl 4-chlorobenzo[*d*]thiazol-2-yl carbamate **4** in good yields, avoiding the use of phosgene. Preliminary results suggest that the title compounds possess good fungicidal and plant growth regulation activities.

Experimental

Microwave irradiation was conducted using an Initiator 8 (Biotage)reactor. Melting points were determined using an X-4 digital microscope melting point apparatus (Beijing Taike Co. Ltd.) and were uncorrected. NMR spectra were recorded on a Varian Mercury Plus 400 NMR or Bruker Avance-300 NMR instrument in $CDCl_3$ or $(CD_3)_2SO$. Chemical shifts (δ_H) are reported in parts per million (ppm), relative to TMS as internal standard. Elemental analyses were carried out on an MF-3 automatic analyser instrument.Mass measurements were performed on a Polaris-Q GC-MS instrument from Finnigan using negative ion electrospray (values for ^{35}Cl and ^{79}Br quoted) Flash-column chromatography was performed using commercial grades of silica gel 200~300 mesh. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates, and spot visualization was accomplished by UV light (254 nm) or phosphomolybdic acid solution. Solvents were obtained from commercial sources and purified according to the literature[30] if necessary.

Preparation of 2-amino-4-chlorobenzothiazole **3**[28]

In a 100 mL four-necked flask equipped with a thermometer, mechanical stirrer and condenser, were placed 2-chlorobenzenamine (7.65 g, 0.06 mmol, 1.0 equiv) and water (6 mL). To the mixture, was added dropwise 5.64 g 98% concentrated sulfuric acid with the temperature at about 50 °C. After addition, ammonium thiocyanate (4.7 g, 0.06 mmol, 1.0 equiv) was added partially, and the mixture was stirred at 45–50 °C for 2 h. When the solid had disappeared completely, the mixture was heated to 70–80 °C for 5 h. Then 1 mL of water was added and the mixture was heated for a further 8 h. After cooling the mixture to room temperature, 20 mL of water was added and the solid was filtered, washed with water and dried to obtain the light yellow powder **2**, 9.85 g, yield 78%.

The solid **2** (8.5 g, 0.046 mmol) was added to sulfur chloride (50 mL) and heated to reflux for 3h. After cooling to room temperature, the mixture was filtered and washed with dichloromethane. The solid was dissolved again in boiled water, and the pH was adjusted to 9.0 with ammonia to precipítate a light yellow solid. This was filtered off and dried to give the desired product **3**, 6.7 g, yield 78%, m.p. 201 °C (lit[28], 201–202 °C).

Preparation of phenyl 4-chlorobenzothiazole -2-yl carbamate **4**[31]

To dry THF (100 mL), was added NaH (3.6 g, 0.150 mol, 3 equiv) cooling with an ice-water bath and stirring for 30 min. Then 2-amino-4-chlorobenzo[*d*]thiazole (9.25 g, 0.05 mmol, 1equiv) in 100 mL dry THF was added dropwise to the above mixture. After stirring for 1h, diphenyl carbonate (21.4 g, 0.1 mmol, 2 equiv) was added and the mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was diluted with ethyl acetate (150 mL), washed with brine (50 mL × 3), and dried over Na_2SO_4. The solvent was evaporated and the residue was separated by flash silica gel column chromatography to give a white solid 7.3 g, yield 48%. ^{1}H

NMR [$CDCl_3$, 400 MHz]: δ = 10.86 (brs, 1H, NH), 7.70 (d, 1H, *J* = 7.9 Hz), 7.46 (d, 1H, *J* = 7.9 Hz), 7.40 (t, 2H, *J* = 7.9Hz), 7.28–7.20 (m, 4H).

Preparation of title compounds; typical procedure:
A mixture of phenyl 4-chlorobenzo[*d*]thiazol-2-yl carbamate **4** (1 equiv) and the aliphatic or aromatic amine (1~1.5 equiv) in THF was placed in a microwave synthetic reactor and treated at a certain temperature, absorption level (usually high) and time. When the solution was cooled, the precipitate from the reactant was filtered off and washed with a mixture of hexane and ethyl acetate. The filtrate was concentrated and recrystallised from ethyl acetate or purified by flash silica gel column chromatography (hexane and ethyl acetate mixtures as eluent), to yield another portion of product.

1-butyl-3-(4-chlorobenzo[d]thiazol-2-yl) urea ($C_{12}H_{14}ClN_3OS$) **(5a):** White solid, yield 86%, m.p. 188–189 °C, ^{1}H NMR [$CDCl_3$, 400M Hz]: δ = 0.91 (t, *J* = 7.2 Hz, 3H, CH_3), 1.36–1.43 (m, 2H, CH_2), 1.63–1.68 (m, 2H, CH_2), 3.34 (d, *J* = 6.0 Hz, 2H, CH_2), 7.13 (t, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 10.52 (s, 1H, NH). ESI-MS: $(M-1)^-$ *m/z*(%) = 282(100). Elemental Anal. Calcd for $C_{12}H_{14}ClN_3OS$ (283.78): C, 50.79; H, 4.97; N, 14.81. Found: C, 50.52; H, 4.71; N, 14.80%.

1-(4-chlorobenzo[d]thiazol-2-yl)-3-(naphthalen-1-yl)urea ($C_{18}H_{12}ClN_3OS$) **(5b):** White solid, yield 85%, m.p. 242–245 °C, ^{1}H NMR[DMSO, 400M Hz]: δ = 7.22 (t, *J* = 15.6 Hz, 1H), 7.63–7.47 (m, 4H), 7.73 (d, *J* = 8.4 Hz, 1H), 8.10–7.89 (m, 4H), 9.24 (s, 1H), 11.57 (s, 1H, NH). ESI-MS: $(M-1)^-$ *m/z*(%) = 352(100). Elemental Anal. Calcd for $C_{18}H_{12}ClN_3OS$ (351.83): C, 61.10; H, 3.42; N, 11.88. Found: C, 61.07; H, 3.49; N, 11.70%.

1-(4-chlorobenzo[d]thiazol-2-yl)-3-isopropylurea ($C_{11}H_{12}ClN_3OS$) **(5c):** White solid, yield 90%, m.p. 178–180 °C, ^{1}H NMR [$CDCl_3$, 400M Hz]: δ = 1.24 (d, *J* = 6.4 Hz, 6H), 4.00–4.05 (m, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 10.51 (s, 1H, NH). ESI-MS: $(M-1)^-$ *m/z*(%) = 268(100). Elemental Anal. Calcd for $C_{11}H_{12}ClN_3OS$ (269.75): C, 48.98; H, 4.48; N, 15.58. Found: C, 48.70; H, 4.58; N, 15.40%.

1-(4-chlorobenzo[d]thiazol-2-yl)-3-propylurea ($C_{11}H_{12}ClN_3OS$) **(5d):** White solid, yield 87%, m.p. 200–202 °C, ^{1}H NMR [DMSO, 400M Hz]: δ = 0.84 (t, *J* = 7.2 Hz, 3H), 1.38–1.51 (m, 2H), 3.06–3.12 (m, 2H), 6.59 (s, 1H), 7.16 (t, *J* = 8 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8 Hz, 1H), δ = 11.17 (s, 1H, NH). ESI-MS: $(M-1)^-$ *m/z*(%) = 268(100). Elemental Anal. Calcd for $C_{11}H_{12}ClN_3OS$ (269.75): C, 48.98; H, 4.48; N, 15.58. Found: C, 48.71; H, 4.27; N, 15.39%.

1-(4-chlorobenzo[d]thiazol-2-yl)-3-(4-methylpyridin-2-yl)urea ($C_{14}H_{11}ClN_3OS$) **(5e):** White solid, yield 84%, m.p. 273–275 °C, ^{1}H NMR [DMSO, 400M Hz]: δ = 2.3 (s, 3H, CH_3), 6.96 (d, *J* = 4.8 Hz, 1H), δ7.27 (t, *J* = 7.8 Hz, 1H), 7.35 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0, 1H), 8.21 (d, *J* = 4.0 Hz, 1H, NH), 9.87 (s, 1H, NH). ESI-MS: $(M-1)^-$ *m/z*(%) = 317(100). Elemental Anal. Calcd for $C_{14}H_{11}ClN_4OS$(318.78): C, 52.75; H, 3.48; N, 17.58. Found: C, 52.62; H, 3.40; N, 17.60%.

1-(4-chlorobenzo[d]thiazol-2-yl)-3-(5-bromopyridin-2-yl)urea ($C_{13}H_8BrClN_3OS$) **(5f):** White solid, yield 86%, m.p. 288–289 °C, ^{1}H NMR[DMSO, 400M Hz]: δ = 7.26–7.32 (m, 1H), 7.40 (t, *J* = 4 Hz, 1H), 7.76 (d, *J* = 8.4, 1H), 7.94–7.98 (m, 1H), 8.04 (t, *J* = 7.8 Hz, 1H), 8.43–8.49 (m, 1H), 9.74 (s, 1H, NH), 11.80 (s, 1H, NH). ESI-MS: $(M-1)^-$ *m/z*(%) = 381(100). Elemental Anal. Calcd for $C_{13}H_8BrClN_4OS$ (383.65): C, 40.70; H, 2.10; N, 14.60. Found: C, 40.51; H, 2.16; N, 14.47%.

1-(4-chlorobenzo[d]thiazol-2-yl)-3-(6-methylpyridin-2-yl)urea ($C_{14}H_{11}ClN_4OS$) **(5g):** White solid, yield 82%, m.p. 260–262 °C, ^{1}H NMR[DMSO, 400M Hz]: δ = 2.44 (s, 3H, CH_3), 6.97 (d, *J* = 7.6 Hz, 1H), 7.23–7.26 (m, *J* = 4.0 Hz, 1H), 7.50 (d, *J* = 8 Hz, 2H), 7.71 (t, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 9.71 (s, 1H, NH). ESI-MS: $(M-1)^-$ *m/z*(%) = 317(100). Elemental Anal. Calcd for $C_{14}H_{11}ClN_4OS$ (318.78): C, 52.75; H, 3.48; N, 17.58. Found: C, 52.96; H, 3.45; N, 17.53%.

1-(4-chlorobenzo[d]thiazol-2-yl)-3-(5-chloropyridin-2-yl)urea ($C_{13}H_8Cl_2N_4OS$) **(5h):** White solid, yield 88%, m.p. 275–276 °C, ^{1}H NMR[DMSO, 400M Hz] δ = 7.24 (t, *J* = 7.3, 1H), 7.48 (t, *J* = 6.6 Hz, 1H), 7.79 (d, *J* = 4.0 Hz, 1H), 7.90–7.94 (m, *J* = 3.4 Hz, 2H), 8.40 (s, 1H), 9.74 (s, 1H, NH), 11.80 (s, 1H, NH). ESI-MS: $(M-1)^-$ *m/z*(%) = 337(100). Elemental Anal. Calcd for $C_{13}H_8Cl_2N_4OS$ (339.2): C, 46.03; H, 2.38; N, 16.52. Found: C, 46.0; H, 2.40; N, 16.30%.

1-(4-chlorobenzo[d]thiazol-2-yl)-3-(5-methylpyridin-2-yl)urea ($C_{14}H_{11}ClN_4OS$) **(5i)**: White solid, yield 82%, m.p. 270–271 °C, ^{1}H NMR [DMSO, 400M Hz]: δ = 2.23 (s, 3H, CH_3), 7.24 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 8.20 (s, 1H), 9.76 (s, 1H, NH), 12.30 (s, 1H, NH). ESI-MS: $(M-1)^-$ *m/z*(%) = 317 (100). Elemental Anal. Calcd for $C_{14}H_{11}ClN_4OS$ (318.78): C, 52.75; H, 3.48; N, 17.58; Found: C, 52.52; H, 3.48; N, 17.70%.

1-(4-chlorobenzo[d]thiazol-2-yl)-3-(4-methylpyrimidin-2-yl)urea ($C_{13}H_{10}ClN_5OS$) **(5j)**: White solid, yield 35%, m.p. 252–254 °C, ^{1}H NMR [DMSO, 400M Hz]: δ = 2.45 (s, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.0 Hz, 1H), 7.73 (t, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 10.90 (s, 1H, NH), 13.1 (s, 1H, NH). ESI-MS: $(M-2)^-$ *m/z*(%) = 317(100).

1-(4-chlorobenzo[d]thiazol-2-yl)-3-(pyridin-3-yl)urea ($C_{13}H_9ClN_4OS$) (**5k**): White solid, yield 81%, m.p. 250–251 °C, ^{1}H NMR[DMSO, 400M Hz]: δ = 7.17–7.22 (m, *J* = 4.1 Hz, 1H), 7.40 (t, *J* = 4.1 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.91–8.09 (m, *J* = 10 Hz, 2H), 8.30 (s, 1H), 8.60 (s, 1H), 9.20 (s, 1H, NH), 11.50 (s, 1H, NH). ESI-MS:

Table 1 The preparation conditions of the title compounds **5**

Compound	R	Temperature/°C	Time/min	Yield/%
5a	n-Butyl	150	30	86
5b	α-Naphthalenyl	160	25	85
5c	i-Propyl	150	25	90
5d	n-Propyl	150	25	87
5e	4-Methylpyridin-2-yl	180	15	84
5f	5-Bromopyridin-2-yl	180	15	86
5g	6-Methylpyridin-2-yl	160	25	82
5h	5- Chloropyridin- 2-yl	180	15	88
5i	5-Methylpyridin-2-yl	160	25	82
5j	4-Methylpyrimidin- 2-yl	180	15	35
5k	Pyridin-3-yl	180	15	81
5l	Phenyl	120	20	79
5m	Benzyl	120	25	35
5n	4-Methylphenyl	120	20	89
5o	2-Methylphenyl	120	10	85
5p	4-Chlorophenyl	120	20	86
5q	2-Chlorophenyl	120	20	83
5r	3-Chlorophenyl	120	20	73
5s	4-Bromophenyl	120	20	82
5t	4-Nitrophenyl	120	20	89
5u	2-Bromophenyl	120	25	86
5v	Piperidin-1-yl	120	25	83
5w	Pyridin-2-yl	150	20	86
5x	Pyrimidin-2-yl	150	20	86

(M-1)$^-$ *m/z*(%) = 303(100). Elemental Anal. Calcd for $C_{13}H_9ClN_4OS$ (304.75): C, 51.23; H, 2.98; N, 18.38. Found: C, 51.08; H, 3.11; N, 18.53%.

1-(4-chlorobenzo[d]thiazol-2-yl)-3-phenylurea ($C_{14}H_{10}ClN_3OS$) (**5l**): White solid, yield 79%, m.p. 285–286 °C, ^{1}H NMR[DMSO, 300M Hz]: δ = 7.07 (t, *J* = 9.8 Hz, 1H), 7.24 (t, *J* = 10.4 Hz, 1H), 7.34 (t, *J* = 10.4 Hz, 2H), 7.42–7.60 (m, *J* = 4.0 Hz, 3H), 7.91 (d, *J* = 10.4 Hz, 1H), 9.01 (s, 1H, NH), 11.28 (s, 1H, NH). ESI-MS: (M-1)$^-$ *m/z*(%) = 302(100). Elemental Anal. Calcd for $C_{14}H_{10}ClN_3OS$(303.77): C, 55.36; H, 3.32; N, 13.83; Found: C, 55.49; H, 3.10; N, 13.63%.

1-benzyl-3-(4-chlorobenzo[d]thiazol-2-yl)urea ($C_{15}H_{12}ClN_3OS$) (**5m**):White solid, yield 35%, m.p. 199–200 °C, ^{1}H NMR[DMSO, 400M Hz]: δ = 4.35 (d, *J* = 5.2 Hz, 2H, CH_2), 7.09 (s, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 5.6 Hz, 1H), 7.34–7.28 (m, 4H), 7.42 (d, *J* = 11.6 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 11.36 (s, 1H, NH). ESI-MS: (M-1)$^-$ *m/z*(%) = 316(100).

1-(4-chlorobenzo[d]thiazol-2-yl)-3-p-tolylurea ($C_{15}H_{12}ClN_3OS$) (**5n**): White solid, yield 89%, m.p. 289–292 °C, ^{1}H NMR[DMSO, 300M Hz]: δ = 2.27 (s 3H, CH_3), 7.15 (d, *J* = 11.2 Hz, 2H), 7.24 (t, *J* = 10.4 Hz, 1H), 7.40 (d, *J* = 10.8 Hz, 2H), 7.48 (d, *J* = 10.4 Hz, 1H), 7.91 (d, *J* = 10.0 Hz, 1H), 8.90 (s, 1H, NH), 11.24 (s, 1H, NH). ESI-MS: (M-1)$^-$ *m/z*(%) = 316(100). Elemental Anal. Calcd for $C_{15}H_{12}ClN_3OS$ (317.79): C, 56.69; H, 3.81; N, 13.22. Found: C, 56.50; H, 3.68; N, 13.05%.

1-(4-chlorobenzo[d]thiazol-2-yl)-3-o-tolylurea ($C_{15}H_{12}ClN_3OS$) (**5o**): White solid, yield 85%, m.p. 268–270 °C, ^{1}H NMR[DMSO, 300M Hz]: δ = 2.27 (s, 3H, CH_3), 7.04 (t, *J* = 9.6 Hz, 1H), 7.20–7.28 (m, 3H), 7.50 (d, *J* = 10.4 Hz, 1H),7.85 (d, *J* = 10.4 Hz, 1H), 7.92 (d, *J* = 6.4 Hz, 1H), 8.40 (s, 1H, NH), 11.61 (s, 1H, NH) ESI-MS: (M-1)$^-$ *m/z*(%) = 316(100). Elemental Anal. Calcd for $C_{15}H_{12}ClN_3OS$(317.79): C, 56.69; H, 3.81; N, 13.22. Found: C, 56.82; H, 3.80; N, 13.20%.

1-(4-chlorobenzo[d]thiazol-2-yl)-3-(4-chlorophenyl)urea ($C_{14}H_9Cl_2N_3OS$) (**5p**): White solid, yield 86%, m.p. 278–280 °C, ^{1}H NMR[DMSO, 300M Hz]: δ = 7.25 (t, *J* = 10.6 Hz, 1H), 7.40 (d, *J* = 11.6 Hz, 2H), 7.48–7.56 (m, *J* = 10.3 Hz, 3H), 7.92 (d, *J* = 9.6 Hz, 1H), 9.16 (s, 1H), 11.40 (s, 1H, NH). ESI-MS: (M-1)$^-$ *m/z*(%) = 336(100). Elemental Anal. Calcd for $C_{14}H_9Cl_2N_3OS$ (338.21): C, 49.72; H, 2.68; N, 12.42. Found: C, 49.71; H, 2.58; N, 12.33%.

1-(4-chlorobenzo[d]thiazol-2-yl)-3-(2-chlorophenyl)urea ($C_{14}H_9Cl_2N_3OS$) (**5q**): White solid, yield 83%, m.p. 282–285 °C, ^{1}H NMR [DMSO, 300M Hz]: δ = 7.14 (t, *J* = 10.2 Hz, 1H), 7.26 (t, *J* = 10.6 Hz, 1H), 7.37 (t, *J* = 9.0 Hz, 1H), 7.51 (t, *J* = 10.4 Hz, 2H), 7.93 (d, *J* = 10.4 Hz, 1H), 8.16 (d, *J* = 9.2 Hz, 1H), 8.78 (s, 1H, NH), 11.94 (s, 1H, NH). ESI-MS: (M-1)$^-$ *m/z*(%) = 336(100). Elemental Anal. Calcd for $C_{14}H_9Cl_2N_3OS$.(338.21): C, 49.72; H, 2.68; N, 12.42. Found: C, 49.71; H, 2.58; N, 12.33%.

1-(4-chlorobenzo[d]thiazol-2-yl)-3-(3-chlorophenyl)urea ($C_{14}H_9Cl_2N_3OS$) (**5r**): White solid, yield 73%, m.p. 282–285 °C, ^{1}H NMR[DMSO, 300M Hz]: δ = 7.12–7.15 (m, 1H), 7.26 (t, *J* = 10.6 Hz, 1H), 7.37 (d, *J* = 6.8 Hz, 2H), 7.50 (d, *J* = 10.0 Hz, 1H), 7.71 (s, 1H), 7.93 (d, *J* = 10.4 Hz, 1H), 9.20 (s, 1H, NH), 11.45 (s, 1H, NH). ESI-MS: (M-1)$^-$ *m/z*(%) = 336(100). Elemental Anal. Calcd for $C_{14}H_9Cl_2N_3OS$ (338.21): C, 49.72; H, 2.68; N, 12.42. Found: C, 49.59; H, 2.57; N, 12.26%.

1-(4-bromophenyl)-3-(4-chlorobenzo[d]thiazol-2-yl)urea ($C_{14}H_9BrClN_3OS$) (**5s**): Yellow solid, yield 82%, m.p. 282–285 °C, ^{1}H NMR[DMSO, 300M Hz]: δ = 7.24 (t, *J* = 10.6 Hz, 1H), 7.47–7.54 (m, 5H), 7.91 (d, *J* = 10.4 Hz, 1H), 9.15 (s, 1H, NH),11.40 (s, 1H, NH). ESI-MS: (M-1)$^-$ *m/z*(%) = 380(100). Elemental Anal. Calcd for $C_{14}H_9BrClN_3OS$ (382.66): C, 43.94; H, 2.37; N, 10.98.Found: C, 43.87; H, 2.21; N, 10.78.

1-(4-chlorobenzo[d]thiazol-2-yl)-3-(4-nitrophenyl)urea ($C_{14}H_9ClN_4O_3S$) (**5t**): Yellow solid, yield 89%, m.p. 270–272 °C, ^{1}H NMR[DMSO, 300M Hz]: δ = 7.27 (t, *J* = 10.6 Hz, 1H), 7.51 (d, *J* = 11.4 Hz, 1H), 7.77 (d, *J* = 12.0 Hz, 2H), 7.94 (d, *J* = 10.4 Hz, 1H), 8.24 (d, *J* = 12 Hz, 2H), 9.69 (s, 1H, NH), δ11.60 (s, 1H, NH). ESI-MS: (M-1)$^-$ *m/z*(%) = 347(100). Elemental Anal. Calcd for $C_{14}H_9ClN_4O_3S$ (348.76): C, 48.21; H, 2.60; N, 16.06. Found: C, 47.86; H, 2.66; N, 16.01.

1-(2-bromophenyl)-3-(4-chlorobenzo[d]thiazol-2-yl)urea ($C_{14}H_9BrClN_3OS$) (**5u**): White solid, yield 86%, m.p. 282–285 °C, ^{1}H NMR[DMSO, 300M Hz]: δ = 7.08 (t, *J* = 10.2 Hz, 1H), 7.26 (t, *J* = 10.4 Hz, 1H), 7.40 (t, *J* = 10.4 Hz, 1H), 7.50 (d, *J* = 10.4 Hz, 1H), 7.67 (d, *J* = 10.8 Hz, 1H), 7.93 (d, *J* = 10.8 Hz, 1H), 8.08 (d, *J* = 10.0 Hz, 1H), 8.58 (s, 1H, NH), 12.04 (s, 1H). ESI-MS: (M-1)$^-$ *m/z*(%) = 380(100). Elemental Anal. Calcd for $C_{14}H_9BrClN_3OS$ (382.66): C, 43.94; H, 2.37; N, 10.98. Found: C, 44.33; H, 2.04; N, 10.88%.

N-(4-chlorobenzo[d]thiazol-2-yl)piperidine-1-carboxamide ($C_{13}H_{14}ClN_3OS$) **(5v):** White solid, yield 83%, m.p. 148–150 °C, ^{1}H NMR[$CDCl_3$, 300M Hz]: δ = 1.49 (s, 6H), 3.40 (d, *J* = 6.4 Hz, 4H), 7.08 (t, *J* = 10.6 Hz, 1H), 7.30 (d, *J* = 10.4 Hz, 1H), 7.58 (d, *J* = 10.8 Hz, 1H), 10.08 (s, 1H, NH). ESI-MS: (M-1)$^-$ *m/z*(%) = 294(100). Elemental Anal. Calcd for $C_{13}H_{14}ClN_3OS$(295.79): C, 52.79; H, 4.77; N, 14.21. Found: C, 52.60; H, 4.54; N, 14.02%.

1-(4-chlorobenzo[d]thiazol-2-yl)-3-(pyridin-2-yl)urea ($C_{13}H_9ClN_4OS$) **(5w):** White solid, yield 86%, m.p. 278–280 °C, ^{1}H NMR[DMSO, 300M Hz]: δ = 7.13 (t, *J* = 8.2 Hz, 1H), 7.27 (t, *J* = 10.4 Hz, 1H), 7.51 (d, *J* = 10.0 Hz, 1H), 7.60 (d, *J* = 10.8 Hz, 1H), 7.82–7.87 (m, 1H), 7.93 (d, *J* = 10.0 Hz, 1H), 8.37 (d, *J* = 4.4 Hz, 1H), 9.89 (s, 1H, NH), 12.36 (s, 1H, NH). ESI-MS: (M-1)$^-$ *m/z*(%) = 303(100). Elemental Anal. Calcd for $C_{13}H_9ClN_4OS$ (304.75): C, 51.23; H, 2.98; N, 18.38. Found: C, 51.07; H, 2.87; N, 18.20%.

1-(4-chlorobenzo[d]thiazol-2-yl)-3-(pyrimidin-2-yl)urea ($C_{12}H_8ClN_5OS$) (5x): White solid, yield 86%, m.p. 285–287 °C, ^{1}H NMR[DMSO, 300M Hz]: δ = 7.26–7.32 (m, 2H), 7.52 (d, *J* = 10.4 Hz, 1H), 7.97 (d, *J* = 10.0 Hz, 1H), 8.80 (d, *J* = 6.4 Hz, 2H), 11.00 (s, 1H, NH), 12.93 (s, 1H, NH). ESI-MS: (M-1)$^-$ *m/z*(%) = 304(100). Elemental Anal. Calcd for $C_{12}H_8ClN_5OS$ (305.74): C, 47.14; H, 2.64; N, 22.91. Found: C, 47.07; H, 2.40; N, 22.78%.

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References

1 H. LeVine, *Amyloid, prions, and other protein aggregates*, ed. R. Wetzel, 1999, Academic Press, San Diego, Vol.309, 274.
2 J.H. Song, C.S. Huang, K. Nagata, J.Z. Yeh and T. Narahashi, *J. Pharmacol. Exp. Ther.*, 1997, **282**, 707.
3 J. Das, J. Lin, R.V. Moquin, Z. Shen, S.H. Spergel, J. Wityak, A.M. Doweyko, H.F. DeFex, Q. Fang, S. Pang, S. Pitt, D.R. Shen, G.L. Schieven and J.C. Barrish, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2145.
4 S.R. Nagarajan, G.A. De Crescenzo, D.P. Getman, H.F. Lu, J.A. Sikorski, J.L. Walker, J.J. McDonald, K.A. Houseman, G.P. Kocan, N. Kishore, P.P. Mehta, C.L. Funkes-Shippy and L. Blystone, *Bioorg. Med. Chem.*, 2003, **11**, 4769.
5 C.J. Paget, K. Kisner, R.L. Stone and D.C. DeLong, *J. Med. Chem.*, 1969, **12**, 1016.
6 K. Yamazaki, Y. Kaneko, K. Suwa, S. Ebara, K. Nakazawa and K. Yasuno, *Bioorg. Med. Chem.*, 2005, **13**, 2509.
7 E. Brantley, S. Antony, G. Kohlhagen, L.H. Meng, K. Agama, S.F. Stinson, E.A. Sausville and Y. Pommier, *Cancer Chemother. Pharmacol*., 2006, **58**, 62.
8 C.J. Lion, C.S. Matthews, G. Wells, T.D. Bradshaw, M.F.G. Stevens and A.D. Westwell, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5005.
9 I. Hutchinson, S.A. Jennings, B.R. Vishnuvajjala, A.D. Westwell and M.F.G. Stevens, *J. Med. Chem.*, 2002, **45**, 744.
10 S.E. O'Brien, H.L. Browne, T.D. Bradshaw, A.D. Westwell, M.F.G. Stevens and C.A. Laughton, *Org. Biomol. Chem*., 2003, **1**, 493.
11 M. Yoshida, C. Hayakawa, N. Hayashi, T. Agatsuma, Y. Oda, F. Tanzawa, S. Iwasaki, K. Koyama, H. Furukawa, S. Kurakata and Y. Sugano, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3328.
12 E.Y. Song, N. Kaur, M.Y. Park, Y. Jin, K. Lee, G. Kim, K.Y. Lee, J.S. Yang, J.H. Shin, K.Y. Nam, K.T. No and G. Han, *Eur. J. Med. Chem*., 2008, **43**, 1519.
13 K.I. Mahan, T.A. Foderaro, T.L. Garza, R.M. Martinez, G.A. Maroney, M.R. Trivisonno and E.M. Willging, *Anal. Chem.,* 1987, **59**, 938.
14 C.M. Chen, M. Chen, F.C. Leu, S.Y. Hsu, S.C. Wang, S.C. Shi and C.F. Chen, *Diamond Relat. Mater.*, 2004, **13**, 1182.
15 S. Chatti, M. Bortolussi and A. Loupy, *Tetrahedron Lett.*, 2000, **41**, 3367.
16 G. Bram, A. Loupy and M. Majdoub, *Synth. Commun.*, 1990, **20**, 125.
17 M. Majdoub, A. Loupy, A. Petit and S. Roudesli, *Tetrahedron*, 1996, **52**, 617.
18 J.C. Ding, H.J. Gu, J.Z. Wen and C.Z. Lin, *Synth. Commun.*, 1994, **24**, 301.
19 R.J. Giguere, T.L. Bray, S.M. Duncan and G. Majetich, *Tetrahedron Lett.*, 1986, **27**, 4945.

20 R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge and J. Rousell, *Tetrahedron Lett.*, 1986, **27**, 279.
21 H.K. Lee and T.M. Rana, *J. Comb. Chem.*, 2004, **6**, 504.
22 G. Bashiardes, I. Safir, A.S. Mohamed, F. Barbot and J. Laduranty, *Org. Lett.*, 2003, **5**, 4915.
23 G.L. Kad, I. Kaur, M. Bhandari, J. Singh and J. Kaur, Org. Process. *Res. Dev.,* 2003, **7**, 339.
24 L.B.D. Barbier-Baudry, A. Cretu, R. Gattin, A. Loupy and D. Stuerga, *Environ. Chem. Lett*., 2003, **1**, 19.
25 B. Martin, H. Sekljic and C. Chassaing, *Org. Lett.*, 2003, **5**, 1851.
26 L. Perreux, A. Loupy and F. Volatron, *Tetrahedron*, 2002, **58**, 2155.
27 P.M. Bendale and C.M. Sun, *J. Comb. Chem.*, 2002, **4**, 359.
28 J. Long, W. Liu, D. Xu, S. Du, *Jingxi Huagong Zhongjianti*, 2003, **33**(6), 31.
29 K.J. Li, S.R. Ban, X.F. Cheng, H.J. Liu and W.B. Chen, *Acta Crystallogr. Sec. E: Struct Rep Online*, 2006, **62**, O2755.
30 L.F.A. Wilfred and L.L.C. Christina, *Purification of laboratory chemicals*, 5th edn, 2003.