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# Phase Transfer Catalyzed Synthesis and Antibacterial Activity of Water-soluble *S*-Triazolo[3,4-b][1,3,4]thiadiazoles Containing Piperazine Group

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**Abstract:** 6/3-(4-Chlorophenyl)-*s*-triazolo[3, 4-*b*][1, 3, 4]thiadiazoles (**2a-e)** and (**5a-e)** were synthesized respectively by intermolecular cyclization of 5-aryl / 4-chlorophenyl-4-amino-3-mercapto-1, 2, 4-triazoles (**1a-e**) and (**4**) with 4-chlorobenzoic acid / aryl acids, which were condensed with piperazine under phase transfer catalyst TBAB to yield the corresponding free bases of monopiperazine derivatives and followed to form water-soluble salts (**3a-e**) and (**6a-e)** with hydrochloric acid in good yields. The *in vitro* biological results showed that piperazine group conjugated with the above fused heterocycles played an important role in antibacterial activity. The structures of novel compounds were confirmed by IR, $^1$H NMR, MS and elemental analysis.

**Keywords**: *s*-Triazolo[3,4-b][1,3,4]thiadiazole, piperazine, water-soluble, antibacterial activity.

Recently, *s*-triazolo[3,4-*b*][1,3,4]thiadiazole heterocycles have been paid attractive attention due to their significantly biological activities[1-4], including antibacterial, antifungal, anticancer, relaxing vascular activities. However, the disadvantages of these compounds with alkyl and aryl substituent at 3 and 6 positions have weak polarity and low water solubility. Many chemotherapeutic agents such as antimicrobial agents norfloxacin and ciprofloxacin[5], antifungal drugs ketoconazole and itraconazole[6], antimalarials piperaquine[7], tuberculostatics rifampicin and rifapentine[8] *etc*. all have this basic structure, in which the basic piperazine group played an important role in enhancing water solubility and bioactivity. In order to search better antibacterial agents with good water solubility, on the bases of our former research[9], we designed and synthesized new water soluble fused heterocycles of triazolothiadiazole piperazine derivatives.

3-Aryl-6-(4-chlorophenyl)-*s*-triazolo[3,4-*b*][1,3,4]thiadiazoles **2a-e** were synthesized *via* cyclization of 5-aryl-4-amino-3-mercapto-1,2,4-triazoles **1a-e**[10] with 4-chlorobenzoic acid under phase transfer catalyst (PTC) of tetrabutylaminium bromide (TBAB) in 80% yield (50% without PTC). Condensation of compounds **2a-e** with piperazine in the presence of PTC the chlorine atom in the above fused heterocycles was replaced to

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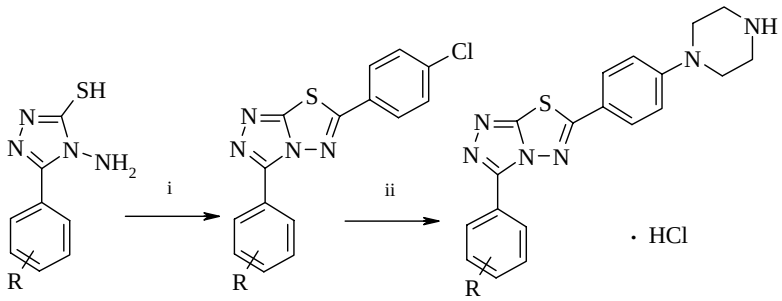
form the corresponding free bases of triazolothiadiazole monopiperazine derivatives, which followed to form water soluble salts **3a-e** with hydrochloric acid in ethanol (**Scheme 1**).

According to the above same procedure, 3-(4-chlorophenyl)-6-aryl-*s*-triazolo [3,4-*b*] [1,3,4] thiadiazoles **5a-e** were also prepared by cyclocondensation of 5-(4-chlorophenyl)-4-amino-3-mercapto-1,2,4-triazoles **4a-e**[10] with various substituted benzoic acids, which were treated with piperazine to form the free bases of triazolothiadiazole monopiperazines followed by treating with dilute hydrochloric acid to form the water soluble salts **6a-e** (**Scheme 2**).

**Scheme 1**

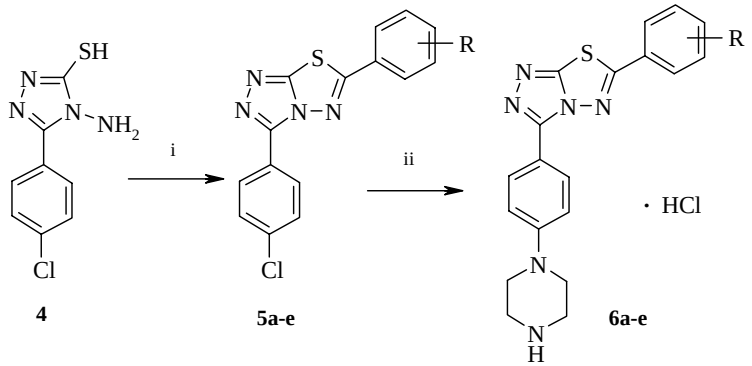



**1a-e** **2a-e** **3a-e**

R: H (**a**); *p*-$CH_3O$ (**b**); *m*-$CH_3O$ (**c**); *p*-$CH_3$ (**d**); *o*-$CH_3$ (**e**)

Reagents and conditions: (i) 4-chlorobenzoic acid, $POCl_3$, TBAI, reflux, 6 h; (ii) a) piperazine, DMSO, $K_2CO_3$, 120℃, 12 h; b) HCl

**Scheme 2**




**4** **5a-e** **6a-e**

R: H (**a**); *p*-$CH_3O$ (**b**); *m*-$CH_3O$ (**c**); *p*-$CH_3$ (**d**); *o*-$CH_3$ (**e**)

Reagents and conditions: (i) substituted benzoic acids, $POCl_3$, TBAI, reflux, 6 h; (ii) a) piperazine, DMSO, $K_2CO_3$, 120℃, 12 h; b) HCl

The antibacterial activity of compounds **3a-e** and **6a-e** against *S. aureus*, *E. coli* and *P. vulgaris in vitro* demonstrated strong inhibitory activity comparable to that of ciprofloxacin at the concentration of 0.1 mg/L, but compounds **2a-e** and **5a-e** at the same concentration only displayed weak or poor activity. From those facts, we may draw a

conclusion that piperazine substituent exert an important role in the inhibitory activity of the tested compounds. The further synthesis and study of structure-activity relationships (SAR) are in progress.

The structures of the intermediates **2a-e**, **5a-e** and the title compounds **3a-e**, **6a-e** were confirmed by elemental analysis (EA), $^1$H NMR, IR and MS[11].

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11. The typically analytic data of intermediate **2a**: yield 87 %, mp 195-197℃. IR (KBr)$\upsilon$: 3108, 1604, 1475, 1265 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$, $\delta$ ppm): 7.82-7.34 (m, 9H, Ph-H); EIS-MS (70ev) *m/z:* Found 313 (M+H), Calcd. 312.78 ($M^+$). Anal. (Calcd. for $C_{15}H_9ClN_4S$): C 57.60, H 2.90, N 17.91; Found C 57.81, H 2.88, N 18.04. **5b**: yield 85 %, mp 225-226℃. IR (KBr)$\upsilon$: 3045, 1557, 1450, 1267 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$, $\delta$ ppm): 8.22-7.54 (m, 8H, Ph-H), 3.89 (s, 3H, $CH_3O$); EIS-MS (70ev) *m/z:* Found 343 (M+H), Cacld. 342.81 ($M^+$). Anal. (Calcd. for $C_{16}H_{11}$ $ClN_4OS$): C 56.06, H 3.23, N 16.34; Found C 56.17, H 3.25, N 16.50.

    The analytic data of other intermediates **2b-e**, **5a** and **5c-e** were deposited in the Editorial Office of CCL.

    **3a**: yield 76 %, mp 254-256℃. IR (KBr)$\upsilon$: 3317, 1623, 1557, 1268 cm$^{-1}$; $^1$H NMR ($D_2O$, $\delta$ ppm): 8.23-7.65 (m, 9H, Ph-H), 3.67-3.42 (m, 8H, piperazine-H); EIS-MS (70ev) *m/z:* Found 363 (M+H), Cacld. 362.46 ($M^+$). Anal. (Calcd. for $C_{19}H_{18}N_6S$•HCl): C 57.21, H 4.80, N 21.07; Found C 57.44, H 4.68, N 21.33. **3b**: yield 72 %, mp 260-263℃. IR (KBr)$\upsilon$: 3315, 1617, 1265 cm$^{-1}$; $^1$H NMR ($D_2O$, $\delta$ ppm): 8.14 -7.63 (m, 8H, Ph-H), 3.88 (s, 3H, $CH_3O$), 3.84-3.46 (m, 8H, piperazine-H); EIS-MS (70ev) *m/z:* Found 393 (M+H), Cacld. 392.49 ($M^+$). Anal. (Calcd. for $C_{20}H_{20}N_6OS$•HCl): C 56.00, H 4.93, N 19.59; Found C 56.25, H 5.10, N 19.68. **3c**: yield 68 %, mp 248-250℃. IR (KBr)$\upsilon$: 3317, 1557, 1268 cm$^{-1}$; $^1$H NMR ($D_2O$, $\delta$ ppm): 8.06-7.51 (m, 8H, Ph-H), 3.86 (s, 3H, $CH_3O$), 3.84-3.42 (m, 8H, piperazine-H); EIS-MS (70ev) *m/z:* Found 393 (M+H), Cacld. 392.49 ($M^+$). Anal. (Calcd. for $C_{20}H_{20}N_6OS$•HCl): C 56.00, H 4.93, N 19.59; Found C 56.31, H 5.02, N 19.49. **3d**: yield 74 %, mp 238-240℃. IR (KBr)$\upsilon$: 3028, 2986, 1554, 1264 cm$^{-1}$; $^1$H NMR ($D_2O$, $\delta$ ppm): 8.14-7.46 (m, 8H, Ph-H), 3.82-3.47 (m, 8H, piperazine-H), 2.46 (s, 3H, $CH_3$); EIS-MS (70ev) *m/z:* Found 377 (M+H), Cacld. 377.49 (M+H). Anal. (Calcd. for $C_{20}H_{20}N_6S$•HCl): C 58.17, H 5.13, N 20.35; Found C 58.25, H 5.17, N 20.46. **3e**: yield 71 %, mp 247-258℃. IR (KBr)$\upsilon$: 3034, 2995, 1568, 1267 cm$^{-1}$; $^1$H NMR ($D_2O$, $\delta$ ppm): 8.07-7.52 (m, 8H, Ph-H), 3.80-3.43 (m, 8H, piperazine-H), 2.42 (s, 3H, $CH_3$); EIS-MS (70ev) *m/z:* Found 377 (M+H), Cacld 376.49 ($M^+$). Anal. (Calcd. for $C_{20}H_{20}N_6S$ •HCl): C 58.17, H 5.13, N 20.35; Found C 58.32, H 5.26, N 20.48. **6a**: yield 62 %, mp 268-271℃(dec). IR (KBr)$\upsilon$: 3326, 1618, 1450, 1267 cm$^{-1}$; $^1$H NMR ($D_2O$, $\delta$ ppm): 8.17-7.55 (m, 9H, Ph-H), 3.68-3.45 (m, 8H,

piperazine-H); EIS-MS (70ev) *m/z:* 363 (M+H), Cacld. 362.46 ($M^+$). Anal. (Calcd. for $C_{19}H_{18}N_6S$•HCl): C 57.21, H 4.80, N 21.07; Found C 57.38, H 4.60, N 21.23. **6b**: yield 71 %, mp 257-260℃. IR (KBr)$\upsilon$: 3324, 1608, 1264 $cm^{-1}$; $^1H$ NMR ($D_2O$, $\delta$ ppm)*:* 8.24-7.55 (m, 8H, Ph-H), 3.86 (s, 3H, $CH_3O$), 3.87-3.42 (m, 8H, piperazine-H); EIS-MS (70ev) *m/z:* Found 393 (M+H), Cacld. 392.49 ($M^+$). Anal. (Calcd. for $C_{20}H_{20}N_6OS$ •HCl): C 56.00, H 4.93, N 19.59; Found C 56.22, H 5.13, N 19.62. **6c**: yield 65 %, mp 238-240℃. IR (KBr)$\upsilon$: 3315, 1561, 1267 $cm^{-1}$; $^1H$ NMR ($D_2O$, $\delta$ ppm)*:* 8.17-7.44 (m, 8H, Ph-H), 3.86 (s, 3H, $CH_3O$), 3.84-3.46 (m, 8H, piperazine-H); EIS-MS (70ev) *m/z:* Found 393 (M+H), Cacld. 392.49 ($M^+$). Anal. (Calcd. for $C_{20}H_{20}N_6OS$•HCl): C 56.00, H 4.93, N 19.59; Found C 56.20, H 5.12, N 19.77. **6d**: yield 74 %, mp 226-228℃. IR (KBr)$\upsilon$: 3314, 1600, 1557, 1264 $cm^{-1}$; $^1H$ NMR ($D_2O$, $\delta$ ppm)*:* 8.32-7.38 (m, 8H, Ph-H), 3.88-3.45 (m, 8H, piperazine-H), 2.37 (s, 3H, $CH_3$); EIS-MS (70ev) *m/z:* Found 377 (M+H), Cacld. 377.49 (M+H). Anal. (Calcd. for $C_{20}H_{20}N_6S$ •HCl): C 58.17, H 5.13, N 20.35; Found C 58.24, H 5.30, N 20.44. **6e**: yield 71 %, mp 237-240℃. IR (KBr)$\upsilon$: 3334, 3005, 1560, 1263 $cm^{-1}$; $^1H$ NMR ($D_2O$, $\delta$ ppm)*:* 8.17-7.56 (m, 8H, Ph-H), 3.85-3.44 (m, 8H, piperazine-H), 2.41 (s, 3H, $CH_3$); EIS-MS (70ev) *m/z:* Found 377 (M+H), Cacld. 377.49 (M+H). Anal. (Calcd. for $C_{20}H_{20}N_6S$•HCl): C 58.17, H 5.13, N 20.35; Found C 58.21, H 5.27, N 20.48.

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