Chinese Chemical Letters Vol. 16, No. 6, pp 723-726, 2005
http://www.imm.ac.cn/journal/ccl.html


# Synthesis and Antibacterial Activity of 8-Substituted Phenyl-1-pyridin-3-yl-5H-bis[1, 2, 4]triazolo[3, 4-b; 4′, 3′-d][1, 3, 4] thiadiazines

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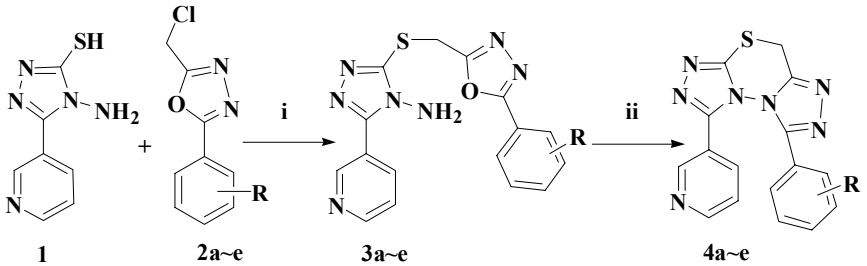
**Abstract**: To find new structural leading compounds for the research of the multidrug resistant of antibacterial agents, five novel 8-substituted phenyl-1-pyridin-3-yl-5H-bis[1, 2, 4] triazolo[3, 4-b; 4′, 3′-d] thiadiazines were prepared from the corresponding intermediates of 3-(5-substituted phenyl[1,3,4]oxadiazol-2-ylmethylsulfanyl)-5-pyridin-3-yl-[1,2,4]triazol-4-ylamines *via* intramolecular cyclization and the antibacterial activity *in vitro* against Gram-postive ($G^+$) and Gram negative ($G^-$) bacteria was primarily evaluated.

**Keywords**: Antibiotics, triazole, thiadiazine, synthesis, antibacterial agent.

1,2,4-Triazole derivatives, such as 1, 2, 4-triazolo[3, 4-*b*]thiadiazoles and 1, 2, 4- triazolo [3,4-*b*]thiadiazolines, as potent antibacterial agents have been widely investigated[1-4]. Chemically, their structures mainly focus on bi-fused heterocycles, but tri-fused derivatives have not been reported. In continuing our previous works[5-8] on finding better antibacterial agents, we herein reported the synthesis and pharmacological evaluation for completely new class of compounds **4a~e** with antibacterial activity (**Scheme 1**).

**Scheme 1**




R: **a,** H; **b**, *p*-$CH_3O$; **c**, 3,4,5-$(CH_3O)_3$; **d**, *p*-$CH_3C_6H_4$; **e**, *p*-Cl
reagents and conditions: i, MeOH, $H_2O$, NaOH, rt, 6 h; ii, acetic acid, $CH_3COONa$, reflux, 5 h

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## Experimental

Melting points were determined with sealed capilly and the thermometer was uncorrected. $^1$H NMR was measured on a Bruker DR 500 spectrometer. Mass spectra were recorded on an HP 1100 instrument. Elemental analysis (EA) was carried out on a Carlo Erba 1106 instrument.

*General procedure for synthesis of the intermediates **3a~e***

To a solution of compound **1**[5] (1.93 g, 10 mmol) in aqueous methanol (30 mL, 50 %) containing NaOH (0.4 g, 10 mmol) and polyethylene glycol 600 (0.5 mL) was added the equal mole of compounds **2** [9]. The reaction mixture was refluxed for 2 h. The solvent was removed *in vacuo* and the precipitate was collected, crystallized from the mixed solvent of EtOH and DMF to give the corresponding intermediates **3a~e**.

*General procedure for the preparation of the title compounds **4a~e***

Compounds **3** (5 mmol) was dissolved in acetic acid (15 mL) containing anhydrous sodium acetate (1.6 g, 10 mmol), stirred and refluxed for 3 h. After removing the solvent, water (30 mL) was added. The precipitate was collected, and crystallized from DMF to give the corresponding title compounds **4a~e**.

The MIC values of compounds **4a~e** were tested by the standard agar dilution method. The activity of **4a** and **4b** against *Staphylococcus aureus* is comparable to that of norfloxacin at the same condition, compounds **4d** and **4e** show the evidently antibacterial activity against *Escherichia.coli* and *Proteus vulgaris* at 1.0 mg•L$^{-1}$, but compound **4c** show no effect or poor activity against the above bacterial strains.

## Results and Discussion

The intermolecular condensation of compound **1** with compound **2** gave the corresponding amino sulfuric ethers **3** in good yields, and followed by intramolecular cyclocondensation to afford triheterocyclic thiadiazines **4a~c** in moderate yields, while the yields of **4d~e** were poor. These results showed that increase bulk of the substituted group R or with electronic donoting substituent resulted in decrease of the yields of compounds **4**. The structures of all novel compounds were confirmed by elemental analysis and spectral analysis[10].

The antibacterial activity *in vitro* of compounds **4** demonstrated that the bulk and the electronic character of substituent R in compounds **4** could obviously affect on pharmacological activity and antibacterial spectrum, the bulky substituents, *e .g*. phenyl ring, could make compound **4** weaken or lose the antibacterial activity.

The above conclusions were made just preliminarly, the further studies on their synthesis, antibacterial activity and structure activity relationship (SAR) are in progressing.

## Acknowledgment

We appreciate that this project is supported by the National Natural Science Foundation of China (No. 30070861) and the Science Foundation of Henan University (XK02041).

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10. *3-(5-Phenyl-[1, 3, 4]oxaiazole-2-ylmethylsulfanyl)-5-pyridin-3-yl-[1, 2, 4] triazol-4-ylamine **3a***. White powders, yield 92 %, mp 189~190℃. $^1$H NMR (DMSO-$d_6$, $\delta$ ppm): 9.26 (s, 1H), 8.70 (d, 1H, *J*=4.7 Hz), 8.36 (d d, 1H, *J*=1.5 and 8.0 Hz), 7.98~7.56 (m, 6H), 6.38 (s, 2H), 4.79 (s, 2H). MS *m/z*: 352 (M+1), calcd. 351. EA calcd. for $C_{16}H_{13}N_7OS$: C, 54.69; H, 3.73; N, 27.69. Found C, 54.76; H, 3.68; N, 28.12.
*3-[5-(4-Methoxyphenyl)-[1,3,4]oxadiazol-2-ylmethylsulfanyl]-5-pyridin-3-yl-[1,2,4]triazol-4-ylamine **3b***. White powders, yield 86 %, mp 175~176℃. $^1$H NMR (DMSO-$d_6$, $\delta$ ppm): 9.26 (s, 1H), 8.74 (d, 1H, *J*=4.5 Hz), 8.37 (d, 1H, *J*=5.5 Hz), 8.05~7.48 (m, 5H), 6.27 (s, 2H), 4.74 (s, 2H), 3.86 (s, 3H). MS *m/z*: 382 (M+1), calcd. 381. EA calcd. for $C_{16}H_{15}N_7O_2S$: C, 53.53; H, 3.96; N, 25.71. Found C, 53.66; H, 4.12; N, 25.84.
*3-[5-(3,4,5-Trimethoxyphenyl)-[1,3,4]oxadiazol-2-ylmethylsulfanyl]-5-pyridin-3-yl-[1,2,4]triazol-4-ylamine **3c***. White powders, yield 78 %, mp 168~170℃. $^1$H NMR (DMSO-$d_6$, $\delta$ ppm): 9.28 (s, 1H), 8.83 (d, 1H, *J*=4.5 Hz), 8.41 (dd, 1H, *J*=2.0 and 8.0 Hz), 8.15~7.24 (m, 3H), 6.20 (s, 2H), 4.86 (s, 2H), 3.86 (s, 6H), 3.88 (s, 3H). MS *m/z*: 442 (M+1), calcd. 441. EA calcd. for $C_{19}H_{19}N_7O_4S$:: C, 51.69; H, 4.34; N, 22.21. Found C, 51.76; H, 4.22; N, 22.36.
*3-[5-(4-Methylphenyl)-[1,3,4]oxadiazol-2-ylmethylsulfanyl]-5-pyridin-3-yl-[1,2,4]triazol-4-ylamine **3d***. White powders, yield 90 %, mp 184~186℃. $^1$H NMR (DMSO-$d_6$, $\delta$ ppm): 9.27 (s, 1H), 8.78 (d, 1H, *J*=4.5 Hz), 8.26 (d, 1H, *J*=5.0 Hz), 8.07~7.54 (m, 5H), 6.26 (s, 2H), 4.82 (s, 2H), 2.45 (s, 3H). MS *m/z*: 366 (M+1), calcd. 365. EA calcd. for $C_{17}H_{15}N_7OS$: C, 55.88; H, 4.14; N, 26.83. Found C, 55.94; H, 4.21; N, 26.76.
*3-[5-(4-Chlorophenyl)-[1,3,4]oxadiazol-2-ylmethylsulfanyl]-5-pyridin-3-yl-[1,2,4]triazol-4-ylamine **3e***. White powders, yield 91 %, mp 189~190℃. $^1$H NMR (DMSO-$d_6$, $\delta$ ppm): 9.27 (s, 1H), 8.88 (d, 1H, *J*=4.5), 8.38 (d, 1H, *J*=5.0 Hz), 8.13~7.56 (m, 5H), 6.23 (s, 2H), 4.78 (s, 2H). MS *m/z*: 386 (M+1), calcd. 385. EA calcd. for $C_{16}H_{12}ClN_7OS$: C, 49.81; H, 3.13; N, 25.41. Found C, 49.74; H, 3.26; N, 25.60.
*8-Phenyl-1-pyridin-3-yl-5H-bis[1, 2, 4] triadiazolo[3, 4-b; 4', 3'-d] thiadiazine **4a.*** Yellow powders, yield 67 %, mp 236~238℃. $^1$H NMR (DMSO-$d_6$, $\delta$ ppm): 9.17 (s, 1H), 8.86 (d, 1H, *J*=5.0 Hz), 8.40 (d d, 1H, *J*=2.0 and 7.5 Hz), 7.76~7.54 (m, 6H), 4.42 (s, 2H). MS *m/z*: 334 (M+1), calcd. 333. EA calcd. for $C_{16}H_{11}N_7S$: C, 57.65; H, 3.33; N, 29.41. Found C, 57.81; H, 3.26; N, 29.56.
*8-(4-Methoxyphenyl)-1-pyridin-3-yl-5H-bis[1, 2, 4] triadiazolo[3, 4-b; 4', 3'-d] thiadiazine **4b.*** Yellow powders, yield 72 %, mp 204~206℃. $^1$H NMR (DMSO-$d_6$, $\delta$ ppm): 9.22 (s, 1H), 8.81 (d, 1H, *J*=4.5 Hz), 8.46 (d, 1H, *J*=5.0 Hz), 8.12~ 7.56 (m, 5H), 4.48 (s, 2H), 3.88 (s, 3H). MS *m/z*: 364 (M+1), calcd. 363. EA calcd. for $C_{16}H_{13}N_7OS$: C, 56.19; H, 3.61; N,

26.98. Found C, 56.24; H, 3.52; N, 27.12.

*8-(3,4,5-Trimethoxyphenyl)-1-pyridin-3-yl-5H-bis[1,2,4]triadiazolo[3,4-b; 4',3'-d] hiadiazine* ***4c.*** Yellow powders, yield 53 %, mp 187~189℃. $^1$H NMR (DMSO-$d_6$, $\delta$ ppm): 9.18 (s, 1H), 8.80 (d, 1H, *J*=4.5 Hz), 8.41 (d d, 1H, *J*=2.0 and 7.0 Hz), 8.15~7.44 (m, 3H), 4.46 (s, 2H), 3.85 (s, 6H), 3.88 (s, 3H). MS *m/z*: 424 (M+1), calcd. 423. EA calcd. for $C_{19}H_{17}N_7O_3S$: C, 53.89; H, 4.05; N, 23.15. Found C, 53.82; H, 4.13; N, 23.38.

*8-(Methylphenyl)-1-pyridin-3-yl-5H-bis[1, 2, 4] triadiazolo[3, 4-b; 4', 3'-d] thiadiazine* ***4d.*** Yellow powders, yield 43 %, mp 212~214℃. $^1$H NMR (DMSO -$d_6$, $\delta$ ppm): 9.21 (s, 1H), 8.84 (d, 1H, *J*=4.5 Hz), 8.42 (d, 1H, *J*=5.0 Hz), 8.16~7.62 (m, 5H), 4.46 (s, 2H), 2.43 (s, 3H). MS *m/z*: 348 (M+1), calcd. 347. EA calcd. for $C_{17}H_{13}N_7S$: C, 58.78; H, 3.77; N, 28.22. Found C, 58.94; H, 3.64; N, 28.36.

*8-(Chlorophenyl)-1-pyridin-3-yl-5H-bis[1, 2, 4] triadiazolo[3, 4-b; 4', 3'-d] thiadiazoline* ***4e.*** Yellow powders, yield 40 %, mp 217~218℃. $^1$H NMR (DMSO -$d_6$, $\delta$ ppm): 9.20 (s, 1H), 8.84 (d, 1H, *J*=4.2 Hz), 8.26 (d, 1H, *J*=5.0 Hz), 8.10~7.47 (m, 5H), 4.62 (s, 2H). MS *m/z*: 368, 370 (M+1), calcd. 367. EA calcd. for $C_{16}H_{10}ClN_7S$: C, 52.25; H, 2.74; N, 26.66. Found C, 52.38; H, 2.70; N, 26.72.

Received 8 June, 2004