# Quinolone Analogues 9. Synthesis of 7-Methylsulfanyl- and 7-Methanesulfonylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones



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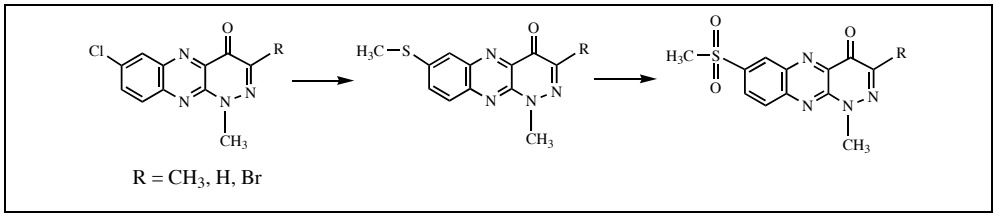


The reaction of 7-chloro-1-methylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones **3a-5a** with sodium methylthiolate gave 1-methyl-7-methylsulfanylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones **8a-c**, whose reaction with *m*-chloroperbenzoic acid afforded the 7-methanesulfonyl-1-methylpyridazino[3,4-*b*]-quinoxalin-4(1*H*)-ones **9a-c**, respectively. The above substituent change at the 7-position resulted in the activity alteration to microorganisms.

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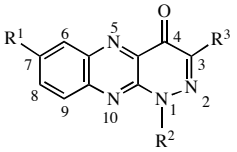
## INTRODUCTION

In previous papers [1-8], we reported the synthesis of the 1-methylpyridazino[3,4-*b*]quinoxalines **1-7** as candidates of antimicrobial quinolone analogues (Chart 1). Since the antibacterial activities of the 3-carboxyl derivatives **1** and **2** were not so good, the 3-substituent was converted into various functional groups in order to search for potent homologues, leading to the synthesis of compounds **3-7**. As the result, the 3-alkyl, 3-H, and 3-halogeno derivatives **3-5** showed good antibacterial and antifungal activities [3-6,9] (Tables 1 and 2), while the 3-heteroaryl and 3-amino derivatives **6** and **7** did not exhibit antimicrobial activities to microorganisms shown in Tables 1 and 2. Thus, the 3-alkyl, 3-H, and 3-halogeno derivatives **3-5** were found to be excellent candidates in the C3-homologues. In continuation of the above studies, we further undertook the modification of the C7-position of the 1-methyl-pyridazino[3,4-*b*]quinoxalin-4(1*H*)-one nucleus to seek for new candidates. As the first trial, we planned the introduction of the S-function at C7-position. Since some papers have already been provided concerning the

**Chart 1**



$R^1$ = Cl, H ; $R^2$ = $CH_3$, $C_2H_5$

**1** : $R^3$ = COOH
**2** : $R^3$ = $CH_2COOC_2H_5$, $(CH_2)_3COOH$
**3** : $R^3$ = $CH_3$, $C_2H_5$ , $CF_3$
**4** : $R^3$ = H
**5** : $R^3$ = Br, Cl
**6** : $R^3$ = 2-Furyl, 2-Thienyl, 3-Thienyl
**7** : $R^3$ = $NH_2$, $NHCOOR^4$

**Table 1.** *In vitro* Antifungal Activity of **3a**-**5a**.

| | | | Minimum Inhibitory Concentration (μg / ml) | | | | | |
|---|---|---|---|---|---|---|---|---|
| Compound | $R^1$ | $R^3$ | *Can. alb.* | *Can. kru.* | *Asp. fla.* | *Asp. fum.* | *Tri. men.* | *Tri. rub.* |
| **3a** | Cl | $CH_3$ | 4 | 4 | 8 | 8 | 2 | 2 |
| **4a** | Cl | H | 4 | 2 | 4 | 4 | 1 | 0.5 |
| **5a** | Cl | Br | 4 | 2 | – | – | 1 | 1 |

*Can. alb.* ---*Candida albicans*
*Can. kur.* --- *Candida krusei*
*Asp. fla.* --- *Aspergillus flavus*
*Asp. fum.* --- *Aspergillus fumigatus*
*Tri. men.* --- *Tricophyton mentagrophytes*
*Tri. rub.* --- *Tricophyton rubrum*

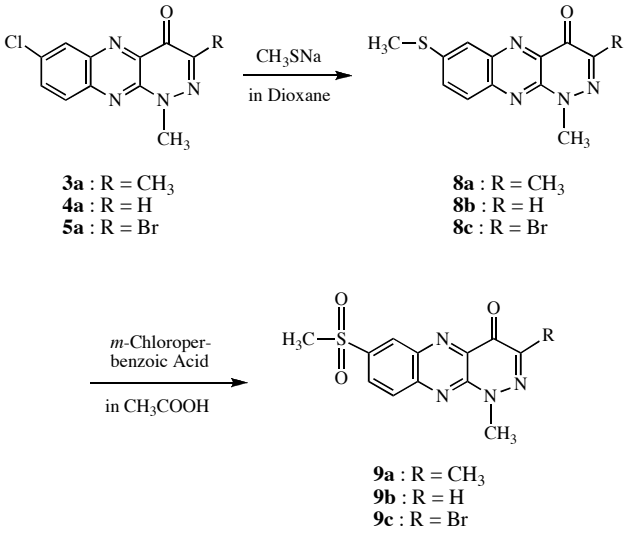
**Table 2.** *In vitro* Antimicrobial Activity of **3a-5a**, **8a-c** and **9a-c**.

| Compound | $R^1$ | $R^3$ | Minimum Inhibitory Concentration (μg / ml) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | *M. l.* | *C. g.* | *B. s.* | *S. a.* | *C. c.* | *A. p.* | *A. f.* |
| **3a** | Cl | $CH_3$ | 3.9 | < 2.0 | 2.0 | < 2.0 | 3.9 | 15.6 | – |
| **8a** | $CH_3S$ | $CH_3$ | < 2.0 | < 2.0 | 7.8 | – | – | – | < 2.0 |
| **9a** | $CH_3SO_2$ | $CH_3$ | 15.6 | 6.3 | 3.9 | 7.8 | – | – | – |
| **4a** | Cl | H | – | – | 2.0 | – | – | – | – |
| **8b** | $CH_3S$ | H | < 2.0 | < 2.0 | 7.8 | 7.8 | 7.8 | 7.8 | – |
| **9b** | $CH_3SO_2$ | H | 7.8 | 6.3 | 3.9 | < 2.0 | – | – | < 2.0 |
| **5a** | Cl | Br | < 2.0 | < 2.0 | < 2.0 | < 2.0 | < 2.0 | < 2.0 | – |
| **8c** | $CH_3S$ | Br | < 2.0 | < 2.0 | 2.0 | 31.3 | – | – | 31.3 |
| **9c** | $CH_3SO_2$ | Br | 7.8 | < 2.0 | 3.9 | 3.9 | – | – | < 2.0 |

**Bacteria** *M. l.* --- *Micrococcus luteus* *S. a.* --- *Staphylococcus aureus*
*C. g.* --- *Chaetonium globosum* *C. c.* --- *Cladosporium Cladosporioides*
*B. s.* --- *Bacillus subtilis* *A. p.* --- *Aureobacididium pullulans*
**Algae** *A. f.* --- *Ankistroidesmus falcatus*

synthesis of aromatic thioethers by the substitution of unactivated aryl halides with thiolate ions [10-12], we adopted this method for the synthesis of the 7-methylsulfanyl derivatives **8a-c** starting from the potent 3-methyl, 3-H, and 3-bromo derivatives **3a-5a**, respectively (Scheme 1). Good yields of compounds **8a-c** enabled us to obtain the 7-methanesulfonyl derivatives **9a-c** as novel candidates. The screening data clarified that compounds **8a** and **9b,c** acquired algicidal activity instead of diminishing antifungal activities (Tables 1 and 2). Moreover, compounds **8b** and **9b** showed improved antibacterial activities to a few kinds of bacteria (Table 2).

**Scheme 1**




We report herein the synthesis and antimicrobial activities of compounds **8a-c** and **9a-c** as quinolone analogues. Moreover, we describe the $^{13}C$ nmr spectral data of the above 1-alkylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-ones **8a,b** and **9a,b**, since the carbon chemical shifts of compounds **1-6** have seldom been reported up to date. The data on the carbon chemical shifts of compounds **8a,b** and **9a,b** in deuteriochloroform and deuteriotrifluoroaccetic acid suggested the N5-deuteronation of the 7-methylsulfanyl derivatives **8a,b** in deuteriotrifluoroacetic acid.

## RESULTS AND DISCUSSION

**Synthesis of Quinolone Analogues 8a-c and 9a-c.** In the conversion of unactivated aryl halides into aryl thioethers, hexamethylphosphoric triamide was reported to be a better solvent than *N,N*-dimethylformamide or dimethyl sulfoxide [10-12]. However, the boiling point of hexamethylphosphoric triamide is high so that we searched a substitutional solvent for our reaction. As a result, dioxane was found to be suitable for our objective.

The reaction of 7-chloro-1-methylpyridazino[3,4-*b*]-quinoxalines **3a-5a** with sodium methylthiolate in dioxane effected a smooth replacement to give the 7-methylsulfanyl derivatives **8a-c**, respectively, in good yields. Compounds **3a-5a** include the pyridazinone ring and electron deficient pyrazine ring, which would provide an advantage for the above substitution reaction producing the 7-methylsulfanyl derivatives **8a-c** in comparison with the case of unactivated aryl halides such as chlorobenzene derivatives. The reaction of compounds **8a-c** with *m*-chloroperbenzoic acid afforded the 7-methanesulfonyl derivatives **9a-c**, respectively (Scheme 1). The analytical and spectral data supported the structure of compounds **8a-c** and **9a-c**.

**Antimicrobial Activities of Compounds 8a-c and 9a-c.** Compounds **3a-5a** exhibited the antifungal activities (Table 1) which were found to be reduced considerably in compounds **8a-c** and **9a-c** from the screening data. The antibacterial activities of compounds **3a-5a**, **8a-c**, and **9a-c** are shown in Table 2. In the 3-methyl and 3-bromo series of compounds, the 7-methylsulfanyl and 7-methanesulfonyl derivatives **8a,c** and **9a,c** were inferior to the 7-chloro derivatives **3a** and **5a** in the antibacterial activities. In the 3-H series of compounds, however, the 7-

methylsulfanyl and 7-methanesulfonyl derivatives **8b** and **9b** were superior to the 7-chloro derivative **4a** in the antibacterial activities against *Micrococcus luteus, Chaetonium globosum,* and *Staphylococcus aureus*. Moreover, compounds **8a**, **9b**, and **9c** showed the algicidal activity against *Ankistroidesmus falcatus* at the concentration of below 2.0 μg/ml, while compounds **3a**-**5a** had not so good algicidal activity against the above algae.

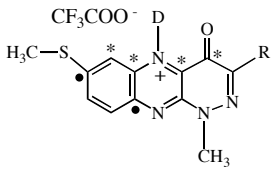
**$^{13}$C NMR Spectral Data.** The HMBC and HMQC spectra of compounds **8a,b** and **9a,b** were measured in deuteriochloroform and deuteriotrifluoroacetic acid, and the carbon signals of compounds **8a,b** and **9a,b** were assigned as shown in Table 3. In the 7-methylsulfanyl derivatives **8a,b**, the signals of the C4, C4a, C5a, and C6 carbons in deuteriotrifluoroacetic acid shifted to higher magnetic field in comparison with those in deuteriochloroform, while the signals of C7 and C9a carbons in deuteriotrifluoroacetic acid moved to lower magnetic field in comparison with those in deuteriochloroform (Table 3, Chart 2). From these data, the N5-deuteronation was suggested for compounds **8a,b** in deuteriotrifluoroacetic acid. Namely, it has been well known that the α-carbons (C2 and C6) of protonated pyridine are shielded (7.8 ppm) in comparison with those of pyridine, while the β-carbons (C3 and C5) and γ-carbon (C4) of protonated pyridine are deshielded [β-carbons (5.1 ppm), γ-carbon (12.4 ppm)] when compared with those of pyridine [13] (Chart 2). Similar results were obtained in the 4*H*-1,3,4-thiadiazino-[5,6-*b*]quinoxaline derivatives (Chart 2) [14]. On the contrary, enough information was not obtained in the 7-methanesulfonyl derivatives **9a,b** to support which site was deuteronated, since only C5a and C9a carbon signals slightly shifted to lower and higher magnetic field, respectively.

**Table 3.** Carbon Chemical Shifts (δ) for Compounds **8a,b** and **9a,b**.

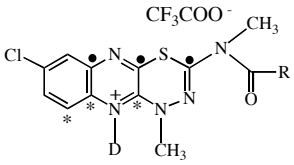
| Carbon | in $CDCl_3$ **8a** | in TFA-$d_1$ [a] **8a** | Shift [b] | in $CDCl_3$ **8b** | in TFA-$d_1$ [a] **8b** | Shift [b] | in $CDCl_3$ **9a** | in TFA-$d_1$ [a] **9a** | Shift [b] | in $CDCl_3$ **9b** | in TFA-$d_1$ [a] **9b** | Shift [b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C3 | 149.4 | 153.0 | | 140.7 | 141.6 | | 150.3 | 150.0 | | 141.6 | 139.8 | |
| C4 | 172.9 | 164.8 | ∗ 8.1 | 172.8 | 165.5 | ∗ 7.3 | 172.7 | 171.1 | | 172.6 | 173.5 | |
| C4a | 132.9 | 118.3 | ∗ 14.6 | 134.3 | 120.6 | ∗ 13.7 | 134.2 | 133.3 | | 135.7 | 133.9 | |
| C5a | 142.6 | 133.1 | ∗ 9.5 | 142.5 | 133.3 | ∗ 9.2 | 141.1 | 147.5 | ● 6.4 | 141.8 | 147.4 | ● 5.6 |
| C6 | 122.2 | 108.7 | ∗ 13.5 | 121.7 | 108.8 | ∗ 12.9 | 132.4 | 131.6 | | 132.3 | 131.8 | |
| C7 | 143.7 | 164.9 | ● 21.2 | 144.4 | 165.8 | ● 21.4 | 140.0 | 142.3 | | 140.3 | 142.2 | |
| C8 | 134.2 | 137.9 | | 134.2 | 138.3 | | 129.7 | 130.4 | | 130.0 | 130.4 | |
| C9 | 127.8 | 128.9 | | 127.6 | 129.0 | | 130.1 | 131.8 | | 130.2 | 131.8 | |
| C9a | 143.1 | 150.3 | ● 7.2 | 142.8 | 150.7 | ● 7.9 | 145.6 | 141.2 | ∗ 4.4 | 145.5 | 141.2 | ∗ 4.3 |
| C10a | 145.2 | 144.2 | | 144.9 | 144.3 | | 146.6 | 146.0 | | 146.6 | 146.4 | |
| N1-$CH_3$ | 40.8 | 41.6 | | 41.0 | 42.0 | | 40.7 | 41.4 | | 41.1 | 41.2 | |
| S-$CH_3$ | 15.3 | 14.2 | | 15.0 | 14.4 | | - | - | | - | - | |
| $SO_2$-$CH_3$ | - | - | | - | - | | 44.2 | 42.8 | | 44.2 | 42.9 | |
| C3-$CH_3$ | 17.4 | 15.4 | | - | - | | 17.1 | 15.5 | | - | - | |

[a] Deuteriotrifluoroacetic acid.
[b] ● Mark means shift to lower magnetic field in deuteriotrifluoroacetic acid.
[b] ∗ Mark means shift to higher magnetic field in deuteriotrifluoroacetic acid.

**Chart 2**

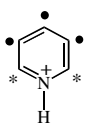


**8a** : R = $CH_3$ , **8b** : R = H
**in $CF_3COOD$**



R = $CH_3$ , $CF_3$ [Ref. 14]
**in $CF_3COOD$**

● Mark means shift to lower magnetic field in deuteriotrifluoroacetic acid.
∗ Mark means shift to higher magnetic field in deuteriotrifluoroacetic acid.



[Ref. 13]

Chemical Shift (δ)

| Carbon | Pyridinium | Pyridine | Shift (ppm) |
|---|---|---|---|
| C2, C6 | 142.4 | 150.2 | 7.8 |
| C3, C5 | 129.0 | 123.9 | 5.1 |
| C4 | 148.3 | 135.9 | 12.4 |

## EXPERIMENTAL

All melting points were determined on a Yazawa micro melting point BY-2 apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a JASCO FT/IR-200 spectrophotometer. The nmr spectra were measured with a Varian XL-400 spectrometer at 400 MHz. The chemical shifts are given in the δ scale. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

**1,3-Dimethyl-7-methylsulfanylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-one (8a).** A solution of compound **3a** (4 g, 15.4 mmoles) and sodium methylthiolate (15% solution, 12.9 g, 27.7 mmoles) in dioxane (200 ml) was refluxed with stirring for 2 hours to precipitate reddish orange crystals of compound **8a**. After the

solvent was evaporated *in vacuo*, the reddish orange crystals of compound **8a** were triturated with water and then collected by filtration (3.52 g, 84%). Recrystallization from *N,N*-dimethylformamide/ethanol/water afforded reddish orange needles, mp 239-240°; ir ν $cm^{-1}$ 1630; ms: m/z 272 ($M^+$) ; nmr (deuteriotrifluoroacetic acid): 7.91 (d, J = 9.5 Hz, 1H, C9-H), 7.78 (dd, J = 2.0, 9.5 Hz, 1H, C8-H), 7.69 (d, J = 2.0 Hz, 1H, C6-H), 4.27 (s, 3H, N-$CH_3$), 2.54 (s, 3H, S-$CH_3$), 2.38 (s, 3H, C3-$CH_3$). *Anal.* Calcd. for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.44; N, 20.57. Found: C, 57.18; H, 4.53; N, 20.53.

**1-Methyl-7-methylsulfanylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-one** (**8b**). A solution of compound **4a** (5 g, 16.2 mmoles) and sodium methylthiolate (15% solution, 13.63 g, 29.2 mmoles) in dioxane (200 ml) was refluxed with stirring for 2 hours to precipitate reddish brown crystals of compound **8b**, which were collected by filtration (2. 58 g). Evaporation of the filtrate *in vacuo* gave reddish brown crystals of compound **8b**, which were triturated with acetic acid/water and then collected by filtration (1.02 g), total yield, 3.60 g (86%). Recrystallization from *N,N*-dimethylformamide/ethanol provided brick red needles, mp 230-231°; ir ν $cm^{-1}$ 1620; ms: m/z 258 ($M^+$) ; nmr (deuteriotrifluoroacetic acid ): 8.22 (s, 1H, C3-H) 7.93 (d, J = 10.0 Hz, 1H, C9-H), 7.81 (dd, J = 2.0, 10.0 Hz, 1H, C8-H), 7.69 (d, J = 2.0 Hz, 1H, C6-H), 4.28 (s, 3H, N-$CH_3$), 2.54 (s, 3H, S-$CH_3$). *Anal*. Calcd. for $C_{12}H_{10}N_4OS$: C, 55.80; H, 3.90; N, 21.69. Found: C, 55.78; H, 3.91; N, 21.52.

**3-Bromo-1-methyl-7-methylsulfanylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-one 8c.** A solution of compound **5a** (3 g, 9.22 mmoles) and sodium methylthiolate (15% solution, 7.74 g, 16.6 mmoles) in dioxane (150 ml) was refluxed with stirring for 2 hours to precipitate reddish orange crystals of compound **8c**. After the solvent was evaporated *in vacuo*, the reddish orange crystals of compound **8b** were triturated with water and then collected by filtration (2.17 g, 70%). Recrystallization from *N,N*-dimethylformamide/ethanol/water afforded reddish orange needles, mp 256-257°; ir ν $cm^{-1}$ 1650; ms: m/z 336 ($M^+$), 338 ($M^+$ + 2); nmr (deuteriotrifluoroacetic acid): 7.99 (d, J = 9.0 Hz, 1H, C9-H), 7.88 (dd, J = 2.0, 9.0 Hz, 1H, C8-H), 7.77 (d, J = 2.0 Hz, 1H, C6-H), 4.34 (s, 3H, N-$CH_3$), 2.62 (s, 3H, S-$CH_3$). *Anal*. Calcd. for $C_{12}H_9BrN_4OS$: C, 42.74; H, 2.69; N, 16.62. Found: C, 42.56; H, 2.73; N, 16.75.

**7-Methanesulfonyl-1,3-dimethylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-one** (**9a**). A solution of compound **8a** (1 g, 3.68 mmoles) and *m*-chloroperbenzoic acid (70% purity, 2.27 g, 9.20 mmoles) in acetic acid (50 ml) was refluxed with stirring for 1 hour. The solution was allowed to stand overnight to precipitate reddish orange prismic needles of compound **9a**, which were collected by filtration and washed with ethanol/*n*-hexane to give analytically pure sample (770 mg). Evaporation of the filtrate *in vacuo* afforded reddish orange crystals of compound **9a**, which were collected by filtration (130 mg), total yield, 900 mg (80%). Compound **9a** had mp 285-286°; ir ν $cm^{-1}$ 1650; ms: m/z 304 ($M^+$); nmr (deuteriotrifluoroacetic acid): 8.96 (dd, J = 1.0, 1.5 Hz, 1H, C6-H), 8.46 (dd, J = 1.0, 10.0 Hz, 1H, C9-H), 8.24 (dd, J = 1.5, 10.0 Hz, 1H, C8-H), 4.55 (s, 3H, N-$CH_3$), 3,37 (s, 3H, $SO_2CH_3$), 2.68 (s, 3H, C3-$CH_3$). *Anal*. Calcd. for $C_{13}H_{12}N_4O_3S$•1/3 $H_2O$: C, 50.31; H, 4.11; N, 18.05. Found: C, 50.50; H, 4.05; N, 17.92.

**7-Methanesulfonyl-1-methylpyridazino[3,4-*b*]quinoxalin-4(1*H*)-one** (**9b**). A solution of compound **8b** (1 g, 3.87 mmoles) and *m*-chloroperbenzoic acid (70% purity, 2.38 g, 9.68 mmoles) in acetic acid (100 ml) was refluxed with stirring for 1 hour. Evaporation of the filtrate *in vacuo* gave orange crystals of compound **9b**, which were triturated with ethanol and then collected by filtration (920 mg, 82%). Recrystallization from acetic acid provided orange needles, mp above 300°; ir ν $cm^{-1}$ 1650; ms: m/z 290 ($M^+$); nmr (deuteriotrifluoroacetic acid): 8.80 (dd, J = 1.0, 1.8 Hz, 1H, C6-H), 8.34 (s, 1H, C3-H) 8.32 (dd, J = 1.0, 9.0 Hz, 1H, C9-H), 8.29 (dd, J = 1.8, 9.0 Hz, 1H, C8-H), 4.36 (s, 3H, N-$CH_3$), 3.22 (s, 3H, $SO_2CH_3$). *Anal*. Calcd. for $C_{12}H_{10}N_4O_3S$: C, 49.65; H, 3.47; N, 19.30. Found: C, 49.49; H, 3.50; N, 19.46.

**3-Bromo-7-methanesulfonyl-1-methylpyridazino[3,4-*b*]-quinoxalin-4(1*H*)-one** (**9c**). A solution of compound **8c** (1 g, 2.96 mmoles) and *m*-chloroperbenzoic acid (70% purity, 1.82 g, 7.40 mmoles) in acetic acid (50 ml) was refluxed with stirring for 1 hour. The solution was allowed to stand overnight to precipitate orange needles of compound **9c**, which were collected by filtration and washed with ethanol/*n*-hexane to give analytically pure sample (970 mg, 89%); mp 303-304°; ir ν $cm^{-1}$ 1670; ms: m/z 368 ($M^+$), 370 ($M^+$ + 2) ; nmr (deuteriotrifluoro-acetic acid ): 8.88 (s, 1H, C6-H), 8.30 (s, 2H, C8-H and C9-H), 4.33 (s, 3H, N-$CH_3$), 3,23 (s, 3H, $SO_2CH_3$). *Anal*. Calcd. for $C_{12}H_9BrN_4O_3S$: C, 39.04; H, 2.31; N, 15.33. Found: C, 39.13; H, 2.31; N, 15.33.

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