Microwave-assisted synthesis and antibacterial activity of unsymmetrical indolyl/aryl bis-thiosemicarbazones

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A series of nine novel unsymmetrical bis-thiosemicarbazones were prepared in high yield by condensation of aromatic aldehyde thiosemicarbazones with indole-3-carboxaldehyde using microwave irradiation. The structures of the new compounds were characterised. Six of the compounds displayed varying levels of antibacterial activity against *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Keywords: unsymmetrical bis-thiosemicarbazone, indole, microwave irradiation, antibacterial activity

Indole, as a basic subunit, plays a significant role in various natural products and synthetic compounds,[1] resulting from its many-electron aromatic structure.[2] Attention has focused on the indole derivatives to identify potent therapeutic agents,[3] specifically on five-membered heterocyclic ring,[4–5] due to their biological activity.[6] Indole molecules with 3-position functionality are highly reactive in electrophilic substitution.[7] Thus, indole-3-carboxaldehyde is an attractive raw material for producing 3-indole derivatives in medicinal chemistry.[8]

Thiosemicarbazones have been widely studied because of their physiological activities, such as antibacterial, antifungal, antiviral, antitumour and antimalarial properties.[9–13] It has been thought that superposition of two functional groups with different activities might create new compounds with improved activities. Alhough there have been a large number of reports of thiosemicarbazones and their pharmacological properties,[14–15] few efforts have been made to study the indole-3-carboxaldehyde unsymmetrical bis-thiosemicarbazones and their relative activities. Hence, we have considered the preparation and the bacteriostatic activity of indole-3-carboxaldehyde unsymmetrical bis-thiosemicarbazone derivatives.

Microwave irradiation (MWI) has advantages in chemical synthesis such as short-time, energy saving, higher yield, higher reaction selectivity and low-waste.[16–20] It thus also conforms to the idea of green chemistry.[21]

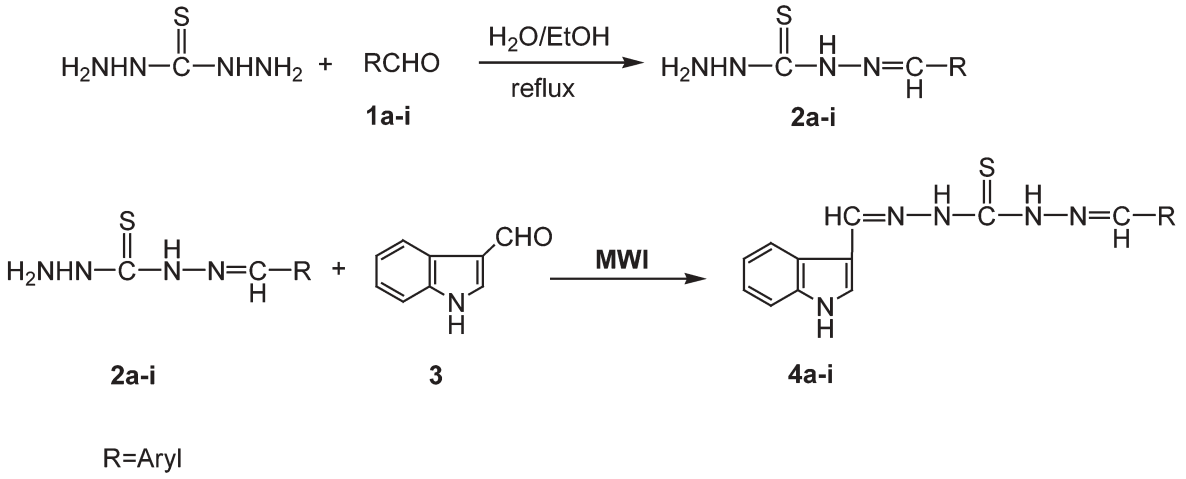
We have already synthesised a sequence of compounds containing Schiff-base structure using MWI.[22–24] The targets underwent antibacterial activity tests and mostly exhibited promising results, leading to a promising theoretical basis for indole-3-carboxaldehyde unsymmetrical bis-thiosemicarbazone synthesis.

Results and discussion

The synthetic route used is shown in Scheme 1. In the first step, an aromatic aldehyde **1** is condensed with thiocarbohydrazide in EtOH–H_2O to yield an aromatic aldehyde semithiocarbohydrazone **2**, as previously described.[23,25–26] In the second step, **2** is reacted with indole-3-carboxaldehyde **3** in acetic acid, either at 80 °C or under MWI, to give the indolyl/aryl bis-thiosemicarbazones **4**.

As depicted in Table 1, we can see MWI largely reduced the reaction time from 150–240 min to 3–5 min. However, the yields were increased from 46–69% to 85–96%. Consequently, microwave technology allows rapid and efficient procedures in organic synthesis.

Compounds **4a–i** were confirmed by IR, Mass, ^{1}H NMR and elementary analysis. Their mass spectra showed the expected molecular peaks in high intensity. Their IR spectra exhibited a characteristic strong absorption at 3058–3686 cm^{-1} due to N–H stretching vibration. The disappearance of strong bands in the region 1710–1725 cm^{-1} and appearance of strong absorption peak at 1604–1620 cm^{-1} indicated C=O of indole-3-carboxaldehyde had been replaced by C=N; The strong absorption bands falling within the range of 1222–1247 cm^{-1} were assigned to C=S. In the ^{1}H NMR spectra, the singlet peaks between δ 11.24 and 11.61 ppm should be assigned to indole-NH protons, and singlet peaks due to the other two NH protons were observed at δ 11.47–11.71 ppm and δ 11.56–11.93 ppm respectively. In addition, the double peaks between δ 8.38 and 8.56 ppm were characteristic of the protons in =CH of indole structure. The singlet peaks at δ 8.01–8.47 ppm and δ 8.62–8.76 ppm were characteristic of the protons in the other two =CH moieties.



Scheme 1 The synthetic route of indolyl/aryl thiosemicarbazones.

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Table 1 Comparison of microwave irradiation with conventional heating for the efficiency of synthesis of indolyl/aryl thiosemicarbazones **4a–i** from aryl thiosemicarbazones **2a–i** (Scheme 1)

Compd	RCHO (R)	Conventional method		Microwave method		t_C/t_{MW}[a]
		t/min	Yield/%	t/min	Yield/%	
4a	C_6H_5	200	59	5.0	88	40
4b	2-Cl-C_6H_4	160	66	3.0	90	53
4c	4-Br-C_6H_4	220	69	5.0	92	44
4d	4-MeO-C_6H_4	240	46	5.0	87	48
4e	4-F-C_6H_4	160	58	3.5	96	46
4f	2,4-2F-C_6H_3	150	57	3.0	95	50
4g	3-Br-C_6H_4	200	61	4.0	85	50
4h	2,4-2(OH)-C_6H_3	230	65	4.5	91	51
4i	4-N$(CH_3)_2$-C_6H_4	180	62	4.0	90	45

t_C = conventional method time; t_{MW} = microwave method time.

In vitro *antibacterial activity*

The *in vitro* antibacterial activity of compounds **4a–i** were tested using cultures of *E. coli*, *B. subtilis*, *P. aeruginosa* and *S.aureus*. Amoxicillin (2.56 mg) and ciprofloxacin (2.56 mg) were used as the standard drugs. The MIC was evaluated by the double dilution method in tubes employing standard inoculums of 10^5 CFU mL^{-1}. Successive dilutions of the test compounds, dissolved in 1 mL DMSO beforehand were prepared to final concentrations of 256, 128, 64, 32, 16, 8, 4, 2, 1, 0.5 and 0.25 μg mL^{-1}. 1 mL bacterial fluid of 0.5 McFarland standard was added to each tube. The MIC was determined by inhibition of the visible bacteria growth after incubation for 16 h at 37°C. Meanwhile, the IC_{50} was evaluated by the inhibition zone test employing standard inoculums of 10^5 CFU mL^{-1}. Serial dilutions of the test compounds, previously dissolved in 2 mL DMSO were prepared to final concentrations of 640, 320, 160, 80, 40, 20, 10 and 5 μg mL^{-1}. Bacteria fluid of 0.5 McFarland standard was grown on bouillon medium and then filter papers (diameter of 6 mm) saturated with the compound dilutions were placed on top of the growing bacteria. Incubation at 37°C for 16 h gave the diameter of the inhibition zone which allowed us to evaluate theIC_{50} value. The results of MIC and IC_{50} are presented in Table 2.

As shown in Table 2, **4b**, **4c**, **4e** and **4f** has better inhibitory activities against *E.coli* than amoxicillin with **4f** as the best; **4b**, **4c**, **4e**, **4f**, **4g** and **4h** could inhibit *B.subtilis*; **4b**, **4c** and **4e** had almost the same effect as that of amoxicillin; **4b**, **4c**, **4e** and **4f** could suppress *P.aeruginosa*, **4c** and **4e** worked better than amoxicillin while **4b** and **4f** had almost the same effect as amoxicillin; **4b**, **4c** and **4e** had a better effect on *S.aureus* than did amoxicillin, and **4c** had even better antimicrobial effects of ciprofloxacin against *S.aureus*. The remaining compounds had no effect on the bacteria. We can conclude that addition of electron withdrawing group especially a halogen atom has the potential for bacteria depression. More antibacterial activities are under study.

Table 2 Antibacterial activity of indolyl/aryl thiosemicarbazones **4a–i** and two positive controls (ciprofloxacin and amoxicillin)

Compd	*E. coli*		*B. subtilis*		*P. aeruginosa*		*S. aureus*	
	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}
Ciprofloxacin	0.25	0.18	0.125	0.1	0.5	0.41	3.12	1.82
Amoxicillin	16	7.3	2	1	4	2.5	16	6.4
4a	–	–	–	–	–	–	–	–
4b	4	2.66	2	1.48	4	2.54	4	2.53
4c	2	1.48	2	1.60	2	1.64	2	1.65
4d	–	–	–	–	–	–	–	–
4e	4	1.92	2	1.55	2	1.69	4	1.72
4f	2	1.43	8	3.52	4	2.32	–	–
4g	–	–	16	12.35	–	–	–	–
4h	–	–	16	10.18	–	–	–	–
4i	–	–	–	–	–	–	–	–

–, Not able to inhibit bacteria.

In summary, we report the synthesis using MWI of new novel indole bis-thiosemicarbazone derivatives and their antibacterial activities. This method is efficient, environmental-friendly, has a simple reaction set-up, and a high product yield. The novel compounds might be useful for designing more potent antibacterial agents for biological and pharmacological uses.

Experimental

Melting points were determined on a micro-melting point apparatus and the thermometer was uncorrected. IR spectra were obtained on 1700 PerkinElmer FTIR using KBr disks. ^{1}H NMR spectra were recorded on a Varian INOVA 400 MHz spectrometer using DMSO-d_6 as solvent and TMS as internal standard. Mass spectra were determined on FinniganLCQ^{DECA} instrument. Elemental analysis was performed on a Carlo-Erba-1106 auto analyser. All reactions were performed in a commercial microwave reaction (XH-100A, 100-1000W, Beijing XiangHu Science and Technology Development Co. Ltd, Beijing, P.R. China). The disinfection of apparatus and reagents used *in vitro* antimicrobial activity test was conducted in a portable stainless steel pressure steam steriliser (YX280A, Shanghai Sanshen Medical Instrument Co., Ltd, Shanghai, P. R. China). Sterile operation was carried out on a super clean bench (DL-CJ-1N, Donglian Elactronic & Technology Develepment Co.Ltd, Beijing, P.R. China). Bacterial culture was grown in a biological constant temperature incubator (ECA-9272, Beijing ECOA Science & Development Co., Ltd, Beijing, P.R. China). All the chemicals and solvents were dried and purified before use.

Synthesis of thiosemicarbazones **4a–i**; *general procedure*

Conventional method: Indole-3-carboxaldehyde (**3**) (0.138 g, 0.95 mmol), an aromatic aldehyde thiocarbohydrazone[23,25–26] (**2a–i**) (1 mmol) was dissolved in glacial acetic acid (5 mL). The mixture was stirred for 2.5–4h at 80 °C. The liquid phase was filtrated at a high temperature immediately, and the pure product was recrystallised from a mixed solvent of methanol and ethanol in 46–69% yields.

Microwave irradiation method: Indole-3-carboxaldehyde (**3**) (0.138 g, 0.95 mmol), aromatic aldehyde thiocarbohydrazones (**2a–i**) (1 mmol) and glacial acetic acid (5 mL) were placed in a round-bottom flask (25 mL). After being shaken, the flask was placed into a microwave oven. The radiant power was set to 200–550W for 3–5 min. The output was filtered while hot and the filtrate was reserved. The pure targets was recrystallised from a mixed solvent of methanol and ethanol in 85–96% yields. The physical and spectra data of the compounds **2f** and **4a–i** are as follows.

1-(2,4-Difluorobenzylidene)thiocarbonohydrazide (**2f**): White solid (79%), m.p. 169–170 °C (EtOH). IR: 3409, 3356, 3265, 2930, 2791, 1615, 1564, 1507, 1429, 1283, 1253, 1141, 1077, 1018, 848, 611 cm^{-1}; ^{1}H NMR δ: 11.53 (s, 1H, NH), 9.96 (s, 1H, NH), 8.39–8.45 (m, 1H, ArH), 8.17 (s, 1H, =CH), 7.27–7.33 (m, 1H, ArH), 7.15 (dd, J_1 = 6.4, J_2 = 8.4 Hz, 1H, ArH), 4.88 (s, 2H, NH_2); ESI-MS *m/z* (%): 231 ([M+1]$^+$, 100). Ana1. Calcd for $C_8H_8F_2N_4S$: C, 41.73; H, 3.50; N, 24.33; Found: C, 41.78; H, 3.48; N, 24.35%.

2′-(Benzylidene)-2-[(1H-indol-3-yl)methylidene]hydrazine-1-thiocarbohydrazide (**4a**): Pale yellow solid (88%), m.p. 232–234 °C (MeOH and EtOH); IR: 3422, 3281, 1610, 1535, 1483, 1222, 1104, 1059, 748, 663 cm^{-1}; ^{1}H NMR δ: 7.15–7.23 (m, 2H, ArH), 7.38–7.42 (dd, J_1 = 5.6 Hz, J_2 = 8.4 Hz, 3H, ArH), 7.78–7.79 (d, *J* = 6.4 Hz, 1H, ArH), 7.82–7.84 (d, *J* = 4.4 Hz, 1H, ArH), 7.85–7.88 (d, *J* = 12.0 Hz, 2H, ArH), 8.13 (s, 1H, NCH), 8.44 (d, *J* = 7.2 Hz, 1H, indole-CH in 2-moiety), 8.75 (s, 1H, NCH), 11.41 (s, 1H, indole-NH), 11.58 (s, 1H, NH), 11.72 (s, 1H, NH); ESI-MS *m/z* (%): 665 ([2M+Na]$^+$, 100). Ana1. Calcd for $C_{17}H_{15}N_5S$: C, 63.53; H, 4.70; N, 21.79. Found: C, 63.50; H, 4.68; N, 21.81%.

2′-(2-Chlorobenzylidene)-2-[(1H-indol-3-yl)methylidene]hydrazine-1-thiocarbohydrazid-e **4b**: bright yellow solid (90%), m.p. 198–200 °C (MeOH and EtOH); IR: 3284, 3130, 1612, 1576, 1426, 1362, 1243, 747, 658 cm^{-1}; ^{1}H NMR δ: 7.16–7.23 (m, 2H, ArH), 7.44–7.46 (d, *J* = 8.0 Hz, 4H, ArH), 7.46–7.53 (m, 1H, ArH), 7.78–7. 82 (m, 1H,

ArH), 8.47 (s, 1H, NCH), 8.54(d, *J* = 7.2 Hz, 1H, indole-CH in 2-moiety), 8.75 (s, 1H, NCH), 11.48 (s, 1H, indole-NH), 11.59 (s, 1H, NH), 11.90 (s, 1H, NH); ESI-MS *m/z* (%): 733 ([2M+Na]$^+$, 100). Ana1. Calcd for $C_{17}H_{14}ClN_5S$: C, 57.38; H, 3.97; N, 19.68. Found: C, 57.42; H, 3.95; N, 19.65%.

2′-(4-Bromobenzylidene)-2-[(1H-indol-3-yl)methylidene]hydrazine-1-thiocarbohydrazid-e (**4c**): Pale yellow solid (92%), m.p. 208–210 °C (MeOH and EtOH); IR: 3272, 3156, 3058, 1615, 1547, 1485, 1441, 1324, 1246, 1069, 819, 784 cm^{-1}; ^{1}H NMR δ: 7.16–7.23 (m, 2H, ArH), 7.43 (d, *J* = 8.0 Hz, 1H, ArH), 7.65 (d, *J* = 8.4 Hz, 3H, ArH), 7.85(d, *J* = 7.2 Hz, 2H, ArH), 8.09 (s, 1H, NCH), 8.47 (d, *J* = 7.2 Hz, 1H, indole-CH in 2-moiety), 8.75 (s, 1H, NCH), 11.44 (s, 1H, indole-NH), 11.59 (s, 1H, NH), 11.78 (s, 1H, NH); ESI-MS *m/z* (%): 823 ([2M+Na]$^+$, 100). Ana1. Calcd for $C_{17}H_{14}BrN_5S$: C, 51.01; H, 3.53; N, 17.50. Found: C, 51.06; H, 3.50; N, 17.53%.

2′-(4-Methyloxybenzylidene)-2-[(1H-indol-3-yl)methylidene]hydrazine-1-thiocarbohydr-azide (**4d**): Pale yellow solid (87%), m.p. 204–206 °C (MeOH and EtOH); IR: 3292, 3248, 1606, 1535, 1498, 1387, 1247, 831, 799 cm^{-1}; ^{1}H NMR δ: 3.82 (s, 3H, –OCH_3), 7.01 (d, *J* = 8.0 Hz, 2H, ArH), 7.17–7.24 (m, 2H, ArH), 7.44 (d, *J* = 8.0 Hz, 1H, ArH), 7.81 (d, *J* = 8.8 Hz, 3H, ArH), 8.09 (s, 1H, NCH), 8.50 (d, *J* = 7.2 Hz, 1H, indole-CH in 2-moiety), 8.76 (s, 1H, NCH), 11.34 (s, 1H, indole-NH), 11.58 (s, 1H, NH), 11.62 (s, 1H, NH); ESI-MS *m/z* (%): 725 ([2M+Na]$^+$, 100). Ana1. Calcd for $C_{18}H_{17}N_5OS$: C, 61.52; H, 4.88; N, 19.93. Found: C, 61.49; H, 4.89; N, 19.95%.

2′-(4-Fluorobenzylidene)-2-[(1H-indol-3-yl)methylidene]hydrazine-1-thiocarbohydrazide (**4e**): Pale yellow solid (96%), m.p. 211–213 °C (MeOH and EtOH); IR: 3271, 3130, 1607, 1530, 1439, 1235, 1118, 1076, 835 cm^{-1}; ^{1}H NMR δ: 7.16–7.24 (m, 2H, ArH), 7.44 (d, *J* = 8.0 Hz, 1H, ArH), 7.51 (d, *J* = 8.0 Hz, 3H, ArH), 7.93 (d, *J* = 7.2 Hz, 2H, ArH), 8.12 (s, 1H, NCH), 8.48 (d, *J* = 7.2 Hz, 1H, indole-CH in 2-moiety), 8.76 (s, 1H, NCH), 11.45 (s, 1H, indole-NH), 11.59 (s, 1H, NH), 11.78 (s, 1H, NH); ESI-MS *m/z* (%): 701 ([2M+Na]$^+$, 100). Ana1. Calcd for $C_{17}H_{14}FN_5S$: C, 60.16; H, 4.16; N, 20.64. Found: C, 60.18; H, 4.19; N, 20.62%.

2′-(2,4-Difluorobenzylidene)-2-[(1H-indol-3-yl)methylidene]hydrazine-1-thiocarbohydr-azide (**4f**): White solid (95%), m.p. 219–221 °C (MeOH and EtOH); IR: 3275, 3244, 3170, 1612, 1539, 1236, 1124, 896, 842, 752 cm^{-1}; ^{1}H NMR δ: 7.16 (d, *J* = 7.2 Hz, 1H, ArH), 7.20–7.26 (m, 3H, ArH), 7.35–7.39 (dd, J_1 = 10.0 Hz, J_2 = 9.2 Hz, 1H, ArH), 7.44 (d, *J* = 8.0 Hz, 1H, ArH), 7.81 (s, 1H, ArH), 8.31 (s, 1H, NCH), 8.47 (d, *J* = 7.2 Hz, 1H, indole-CH in 2-moiety), 8.74 (s, 1H, NCH), 11.47 (s, 1H, indole-NH), 11.60 (s, 1H, NH), 11.84 (s, 1H, NH); ESI-MS *m/z* (%): 737 ([2M+Na]$^+$, 100). Ana1. Calcd for $C_{17}H_{13}F_2N_5S$: C, 57.13; H, 3.67; N, 19.60. Found: C, 57.18; H, 3.64; N, 19.62%.

2′-(3-Bromobenzylidene)-2-[(1H-indol-3-yl)methylidene]hydrazine-1-thiocarbohydrazide (**4g**): Pale yellow solid (85%), m.p. 203–205 °C (MeOH and EtOH); IR: 3437, 3265, 3145, 1610, 1518, 1470, 1246, 1055, 787, 748, 681 cm^{-1}; ^{1}H NMR δ: 7.16–7.22 (m, 3H, ArH), 7.44–7.46 (d, *J* = 7.6 Hz, 1H, ArH), 7.73 (t, *J* = 7.6 Hz, 1H, ArH), 8.25 (d, *J* = 9.2 Hz, 2H, ArH), 8.33 (s, 1H, NCH), 8.49 (d, *J* = 7.2 Hz, 1H, indole-CH in 2-moiety), 8.73 (s, 1H, NCH), 8.78 (s, 1H, ArH), 11.61 (s, 1H, indole-NH), 11.64 (s, 1H, NH), 11.93 (s, 1H, NH); ESI-MS *m/z* (%): 823 ([2M+Na]$^+$, 100). Ana1. Calcd for $C_{17}H_{14}BrN_5S$: C, 51.01; H, 3.53; N, 17.50. Found: C, 51.09; H, 3.50; N, 17.48%.

2′-(2,4-Dihydroxybenzylidene)-2-[(1H-indol-3-yl)methylidene]hydrazine-1-thiocarbohy-drazide (**4h**): White solid (91%), m.p. 198–200 °C (MeOH and EtOH); IR: 3686, 3413, 3290, 1620, 1503, 1232, 1165, 882, 741, 658 cm^{-1}; ^{1}H NMR δ: 6.28–6.38 (m, 2H, ArH), 7.19–7.25 (m, 3H, ArH), 7.44 (d, *J* = 7.6 Hz, 1H, ArH), 7.90 (s, 1H, ArH), 8.34 (s, 1H, NCH), 8.38 (d, *J* = 7.2 Hz, 1H, indole-CH in 2-moiety), 8.62 (s, 1H, NCH), 9.94 (s, 2H, OH), 11.36 (s, 1H, indole-NH), 11.71 (s, 1H, NH), 11.84 (s, 1H, NH); ESI-MS *m/z* (%): 729 ([2M+Na]$^+$, 100). Ana1. Calcd for $C_{17}H_{15}N_5O_2S$: C, 57.78; H, 4.28; N, 19.82. Found: C, 57.75; H, 4.30; N, 19.83%.

2′-(4-Dimethylaminobenzylidene)-2-[(1H-indol-3-yl)methylidene]hydrazine-1-thiocarbo-hydrazide (**4i**): Yellow solid (90%), m.p. 199–201 °C (MeOH and EtOH); IR: 3394, 3277, 1604, 1526, 1437, 1364, 1226, 1175, 812 cm^{-1}; ^{1}H NMR δ: 2.99 (s, 6H, -$N(CH_3)_2$), 6.74 (d, *J* = 8.4 Hz, 2H, ArH), 7.16–7.23 (m, 3H, ArH), 7.43 (d, *J* = 8.0 Hz, 1H, ArH), 7.67 (d, *J* = 8.4 Hz, 2H, ArH), 8.01 (s, 1H, NCH), 8.48 (d, *J* = 7.2 Hz, 1H, indole-CH in 2-moiety), 8.73 (s, 1H, NCH), 11.24 (s, 1H, indole-NH), 11.47 (s, 1H, NH), 11.56 (s, 1H, NH); ESI-MS *m/z* (%): 751 ([2M+Na]$^+$, 100). Ana1. Calcd for $C_{19}H_{20}N_6S$: C, 62.61; H, 5.53; N, 23.06. Found: C, 62.64; H, 5.50; N, 23.03%.

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