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The Synthesis and Tuberculostatic Activity of Benzenesulfonohydrazide Derivatives

Krystyna Wisterowicz,[1] Katarzyna Gobis,[1] Henryk Foks,[1] and Ewa Augustynowicz-Kopeć[2]

[1]*Department of Organic Chemistry, Medical University of Gdansk, 107 Gen. Hallera, 80-416 Gdansk, Poland*

[2]*Department of Microbiology, Institute of Tuberculosis and Pulmonary Diseases, 26 Płocka, 01-138 Warszawa, Poland*

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ABSTRACT: *The series of novel* N′*-aminocarbonothioyl-benzenesulfonohydrazides were synthesized in a reaction of benzenesulphonyl chlorides with various aminocarbothiohydrazides. The structures were confirmed by IR and NMR spectra as well as elemental analysis. All of the obtained compounds were screened in vitro for their tuberculostatic activity. Preliminary results indicated that some target compounds exhibited promising results, especially toward* Mycobacterium tuberculosis *(Mtb) resistant strain 210.* © 2011 Wiley Periodicals, Inc. Heteroatom Chem 23:99–104, 2012; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20743

INTRODUCTION

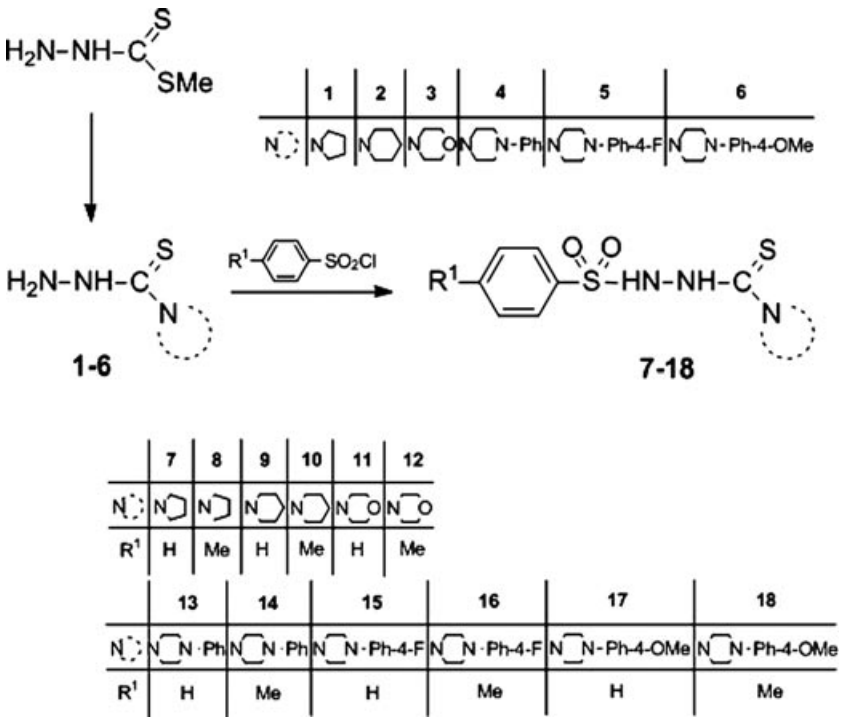
Tuberculosis (TB) remains one of the most serious infectious diseases. It persists as a major public health problem. There is a growing number of *Mycobacterium tuberculosis* (Mtb) strains, which are now resistant to the commonly used first-line anti-TB drugs such as rifampicine (RMF) and isoniazid (INH) [1]. TB is a leading cause of morbidity and mortality in adults infected with HIV worldwide [2]. Unfortunately, the most effective chemotherapeutics rapidly induce multidrug resistance (MDR) and cause serious side effects, such as hepatotoxicity, neurotoxicity, acute pancreatitis, and hypersensitivity reactions [3,4]. Therefore, tuberculostatic agent screening and TB drug development are still the priority tasks undertaken by many research programs and scientific groups [5].

One of the first-line chemotherapeutics in the treatment of TB is morinamide (MZA), which, from a chemical point of view, is morpholinothioamide. It is worth noting that this compound includes a cyclic amine in its structure. In the chemical literature, examples of other thioamides and thiosemicarbazides exhibiting significant tuberculostatic activity can be found. Examples might be 4-cyclohexylthiobenanilides and 4-phenylsulfonylbenzoylhydrazinecarbothioamides [6] as well as 1-benzoyl-isothiosemicarbazides [7]. Previously, our research team proved high tuberculostatic activity (MIC 6.2 μg/mL) of benzoylhydrazinecarbothioamides [8].

There are also many reports about the pharmacological activity of benzenesulfonohydrazides and their derivatives. Among others, they exhibit antimycotic [9,10], antiinflammatory [11], and antibacterial [12,13] activity. Antineoplastic action of that chemical group has also been reported [14].

Although it is difficult to find reports on the tuberculostatic activity of sulfonohydrazides in the chemical literature, no doubt such action has been described for sulfonamides [15,16]. Other authors

Correspondence to: Katarzyna Gobis; e-mail: kgobis@gumed.edu.pl.



SCHEME 1

described antimalarian activity [17] and γ–secretase inhibition [18] caused by sulfonamide derivatives bearing cyclic amine moiety in their structures.

On the basis of all the above considerations and as an extension of our studies on the development of novel benzoylhydrazinecarbothioamide antitubercular agents, we decided to synthesize the new *N′*-aminocarbonothioyl-benzenesulfonohydrazides as their sulfonic analogs containing sulfonohydrazide and thioamide group with cyclic amine moiety fused in thiosemicarbazide system.

RESULTS AND DISCUSSION

The synthetic route of target compounds was outlined in Scheme 1. Starting methyl hydrazinecarbodithioate was obtained by the method of Klayman et al. from hydrazine, potassium hydroxide, carbon disulfide, and methyl iodide in a water-isopropanol solution [19].

Cycloaminocarbothiohydrazides (**1–6**), the intermediates for the syntheses of corresponding *N′*-aminocarbonothioyl-benzenesulfonohydrazides (**7–18**), were prepared by the procedure described earlier [20]. The various amines, such as pyrrolidine, piperidine, morpholine, 1-phenylpiperazine, 1-(4-methoxyphenyl)piperazine, and 1-(4-fluorophenyl)piperazine, that were used for nucleophilic substitution of which thiomethyl group in a methyl hydrazinecarbodithioate, were commercially obtained. For the amines with lower molecular weights, water was a suitable solvent, but for 1-phenylpiperazine and its derivatives, reactions were carried out in ethanol. The yields of the reactions were not very high, although amines were used in triple excess to thioester.

Aminocarbothiohydrazides (**1–6**) were treated with benzenesulfonyl chloride or 4-toluenesulfonyl chloride to give the corresponding *N′*-aminocarbonothioyl-benzenesulfonohydrazides (**7–18**). The reactions were carried out in dry pyridine for 24 h. However, their yields were rather average; 4-toluenesulfonohydrazides seemed to form more easily.

All the newly synthesized compounds were characterized by IR and NMR spectra as well as the elemental analysis (Table 1) listed in the Experimental Section. The spectral analyses were in accordance with the assigned structures. In ^{1}H NMR spectra of compounds (**7–11**) and (**13–17**), the signal of one NH group proton was visible in the form of a multiplet common with aromatic protons in the range of 7.20 to 7.93 ppm as a rule. Only in the case of compounds (**12,18**), the signal of the NH group proton appeared in the form of a well-separated singlet at 7.18 (**12**) and 7.85 ppm (**18**). Signals occurring as multiplets common with aromatic protons in the spectra of compounds (**7–11**) and (**13–17**) undoubtedly came

TABLE 1 Characteristics of Newly Synthesized *N′*-Aminobenzenesulfonohydrazides 7–18

				Calcd/Found					
No	*Yield [%]*	*mp. [°C] Solvent*	*Formula MW*	*C*		*H*		*N*	
7	29	145–146 H_2O/EtOH	$C_{11}H_{15}N_3O_2S_2$285.39	46.29	46.38	5.30	5.29	14.72	14.68
8	33	150–153 H_2O/EtOH	$C_{12}H_{17}N_3O_2S_2$299.41	48.14	48.09	5.72	5.73	14.03	14.00
9	30	134–137 EtOH	$C_{12}H_{17}N_3O_2S_2$299.41	48.14	48.11	5.72	5.71	14.03	14.08
10	35	131–134 AcOH	$C_{13}H_{19}N_3O_2S_2$313.44	49.81	49.85	6.11	6.10	13.41	13.46
11	45	150–154 H_2O/EtOH	$C_{11}H_{15}N_3O_3S_2$301.39	43.84	43.77	5.02	5.03	13.94	13.72
12	59	127–129 H_2O/EtOH	$C_{12}H_{17}N_3O_3S_2$315.41	45.70	45.75	5.43	5.44	13.32	13.28
13	15	146–148 AcOH	$C_{17}H_{20}N_4O_2S_2$376.50	54.23	54.29	5.35	5.36	14.88	14.91
14	10	165–169 AcOH	$C_{18}H_{22}N_4O_2S_2$390.52	55.36	55.42	5.68	5.69	14.36	14.41
15	27	136–138 AcOH	$C_{17}H_{19}FN_4O_2S_2$394.49	51.76	51.81	4.85	4.86	14.20	14.17
16	57	158–160 AcOH	$C_{18}H_{21}FN_4O_2S_2$408.51	52.92	52.86	5.18	5.19	13.71	13.73
17	35	155–157 AcOH	$C_{18}H_{22}N_4O_3S_2$406.52	53.18	53.21	5.45	5.46	13.78	13.79
18	52	148–151 AcOH	$C_{19}H_{24}N_4O_3S_2$420.55	54.26	54.33	5.75	5.76	13.32	13.29

from an NH group. Addition of D_2O resulted in an exchange of an NH proton and the partial extinction of the multiplets.

Tuberculostatic Activity

The newly synthesized *N′*-aminocarbonothioylbenzenesulfonohydrazides (**7–18**) were examined in vitro for their tuberculostatic activity against the Mtb H_{37}Rv strain and two "wild" strains isolated from tuberculotic patients: one (Spec. 210) resistant to p-aminosalicylic acid (PAS), isonicotinic acid hydrazide (INH), etambutol (ETB), and rifampicine (RFP) and the other (Spec. 192) fully sensitive to the administered tuberculostatics (Table 2). Investigations were performed by a classical test-tube method of successive dilution in a Proskauer and Beck modification with a Youmans liquid medium containing 10% of bovine serum [21,22]. Bacterial suspensions were prepared from 14-day-old cultures of slowly growing strains and from 48 h old cultures of saprophytic strains [23,24]. Solutions of compounds in ethylene glycol were tested. Stock solutions contained 10 mg of compounds in 1 mL. Dilutions (in geometric progression) were prepared in a Youmans medium. The medium containing no investigated substances and containing isoniazid (INH) as a reference drug was used for comparison. Incubation was performed at 37°C. The MIC values were determined as minimum concentration inhibiting the growth of tested tuberculous strains in relation to the probe with no tested compound.

The results of tuberculostatic activity indicated that some of the title compounds showed moderate activity against tested strains in vitro and were much less active than when INH was used as a reference drug. The MIC values for most of the tested compounds ranged from 25 to 50 μg/mL and from 0.5 to 1.1 μg/mL for INH. All compounds exhibited low activity against susceptible strain 192 (MICs 50 μg/mL) and moderate activity against standard strain H_{37}Rv (MICs 25 μg/mL). Unexpectedly, the most sensitive to the tested compounds was the resistant strain 210. The MIC values determined for most of the tested compounds against that strain were 25 μg/mL. The pyrrolidine derivative (**7**) and two 4-methoxyphenylpiperazine derivatives (**17,18**) were the most active against strain 210 with MIC values of 12.5 μg/mL. These results allowed us to include the obtained compound, *N′*-aminocarbonothioyl-benzenesulfonohydrazides

TABLE 2 In Vitro Tuberculostatic Activity of Novel Benzenesulfonohydrazide Derivatives **7–18**[a,b,c]

	MIC [μg/mL]		
Compound Number	*R_{37}Rv*	*Spec. 192*	*Spec. 210*
7	25	50	12.5
8	25	50	25
9	25	50	25
10	25	50	25
11	25	50	25
12	25	50	25
13	50	50	25
14	25	50	25
15	25	50	25
16	25	50	25
17	25	50	12.5
18	25	50	12.5
INH	0.5	0.5	1.1
PZA	25	25	>400

[a]Minimum inhibitory concentrations for mycobacterial strains were detrmined by a two-fold classical test-tube method of successive dilution.
[b]INH–isoniazid, PZA–pyrazinamid.
[c]*M. tuberculosis* H_{37}Rv, Spec. 192 and Spec. 210.

among the compounds of moderate tuberculostatic activity.

CONCLUSION

In summary, a series of novel *N′*-aminocarbonothioyl-benzenesulfonohydrazides with different cyclic amine moieties were synthesized successfully in reaction of cycloaminocarbothiohydrazides with benzenesulphonyl chlorides. All these new compounds were confirmed by IR and NMR spectra as well as through elemental analysis. Their tuberculostatic activity was evaluated against *M. tuberculosis* $H_{37}Rv$ standard strain, sensitive strain 192, and resistant strain 210 to commonly administered drugs (PAS, INH, ETB, RFP). MIC values were determined using the two-fold serial diluting technique. The results showed that most of the synthesized benzenesulfonohydrazide derivatives exhibited moderate tuberculostatic activity in vitro. The most susceptible to tested compounds was resistant strain 210. The pyrrolidine derivative (**7**) and two 4-methoxyphenylpiperazine derivatives (**17,18**) were the most active against strain 210 with MIC values of 12.5 μg/mL. These results allowed us to include the obtained compound, wording, *N′*-aminocarbonothioyl-benzenesulfonohydrazides among the compounds of promising tuberculostatic activity toward resistant Mtb.

EXPERIMENTAL

Melting points were determined with Boethius apparatus (Franz Küstner Nachf. KG, Dresden, Germany) and were uncorrected. IR spectra were taken on the Satellite FT-IR spectrophotometer (Mattson Instruments, Madison, WI) (KBr pellets). NMR spectra were taken in $CDCl_3$ on the Varian Gemini (200 MHz) instrument (Varian, Palo Alto, CA). The results of elemental analysis (% C, H, N) for all of the obtained compounds were in agreement with calculated values within a range of ± 0.3%. Reaction details and physicochemical data for newly synthesized *N′*-aminocarbonothioyl-benzenesulfonohydrazides are given in Table 1. Methyl hydrazinecarbodithioate, which was required for further syntheses, was obtained according to the method described earlier by Klayman et al. [19].

General procedure for the synthesis of cycloaminocarbothiohydrazides (1-6). Methyl hydrazinecarbodithioate (2.44 g, 20 mmol) was dissolved in 20 mL water. The solution was treated with the appropriate amount of cyclic amine (60 mmol). The mixture was refluxed for 6 h until the evolution of methyl mercaptan had ceased almost completely. Methyl mercaptan was detected by the yellow color it imparted to the moisten $Pb(OAc)_2$ paper, which was placed at the mouth of the reflux condenser. In the case of 1-phenylpiperazine and its derivatives, the reactions were carried out in ethanol. Then the solution was neutralized with AcOH. Furthermore, cooling yielded the desired amount of aminocarbothiohydrazide, which was filtered off and recrystallized. Compounds **1–4** have already been described [20].

4-(4-Fluorophenyl)piperazine-1-carbothiohydrazide (5). This compound was obtained as colorless needles. Yield: 2.74 g (54%). Crystallization from ethanol; mp 169–171°C. IR: 3430, 3268 (ν N—H), 2923, 2854 (ν C—H), 1513 (δ N—H), 815 (γ C—H) cm^{-1}. ^1H NMR δ: 3.12–3.26 (s, 4H, $2NCH_2$), 3.97–4.07 (m, 4H, $2NCH_2$), 5.93 (brs, 2H, NH_2), 6.88 (d, 2H, Ph, *J* 7.8 Hz), 7.82 (t, 2H, Ph, *J* 7.8 Hz), 8.28 (s, 1H, NH) ppm. Anal Calcd. for $C_{11}H_{15}FN_4S$ (mw 254.33): C, 51.95; H, 5.94; N, 22.03. Found: C, 51.82;H, 5.95; N, 21.98.

4-(4-Methoxyphenyl)piperazine-1-carbothiohydrazide (6). This compound was obtained as colorless crystals. Yield: 2.62 g (49%). Crystallization from ethanol; mp 151–153°C. IR: 3399, 3284 (ν N—H), 2931, 2849 (ν C—H), 1528 (δ N—H), 1231, 1035 (ν C—O), 842 (γ C—H) cm^{-1}. ^1H NMR δ: 3.08–3.18 (m, 4H, NCH_2), 3.85 (s, 3H, OCH_3), 3.88–3.96 (m, 4H, $2NCH_2$), 5.85 (brs, 2H, NH_2), 7.08 (d, 2H, Ph, *J* 8.8 Hz), 7.81 (d, 2H, Ph, *J* 8.8 Hz), 8.55 (s, 1H, NH) ppm. Anal. Calcd. for $C_{12}H_{18}N_4OS$ (mw 266.36): C, 54.11; H, 6.81; N, 21.03. Found: C, 54.23; H, 6.79; N, 20.98.

General procedure for the synthesis of *N′*-benzenesulfonohydrazides (7–18). To a solution of benzenesulphonyl or 4-toluenesulphonyl chloride (5 mmol) in 5 mL of dry pyridine, an appropriate amount of aminocarbothiohydrazide (5 mmol) was added. The mixture was stirred at room temperature for 24 h. Then 20 mL of ice cold water was added. The precipitate was filtered off and recrystallized from a suitable solvent (Table 1).

***N′*-(Pyrrolidine-1-carbonothioyl)benzenesulfonohydrazide (7).** IR: 3314 (ν N—H), 3107, 2987, 2869 (ν C—H), 1528 (δ N—H), 1445 (δ C—H), 1337, 1165 (ν SO_2), 738 cm^{-1}. ^1H NMR δ: 2.25–2.36 (m, 4H, $2CH_2$), 2.39–2.50 (m, 4H, $2NCH_2$), 7.46–7.66 (m, 4H, 3H Ph and 1H NH + D_2O exchangeable), 7.90–7.99 (m, 2H, Ph), 8.60 (s, 1H, NH + D_2O exchangeable) ppm. ^{13}C NMR: δ 25.6, 51.9, 127.3, 129.0, 131.9, 136.7, 179.2 ppm.

4-Methyl-*N′*-(pyrrolidine-1-carbonothioyl) benzenesulfonohydrazide (8). IR: 3287 (ν N—H), 3080, 2959, 2873 (ν C—H), 1596 (δ N—H), 1443 (δ C—H), 1339 (ν SO_2), 710 cm^{-1}. ^1H NMR δ: 1.93 (brs, 4H,

$2CH_2$), 2.40 (s, 3H, CH_3), 3.43–3.57 (m, 4H, $2NCH_2$), 7.20–7.25 (m, 3H, 2H Ph and 1H NH + D_2O exchangeable), 7.39 (s, 1H, NH + D_2O exchangeable), 7.75–7.79 (m, 2H, Ph) ppm. ^{13}C NMR: δ 22.3, 26.2, 53.4, 128.7, 129.7, 133.4, 137.3, 181.5 ppm.

***N′*-(Piperidine-1-carbonothioyl)benzenesulfonohydrazide (9).** IR: 3269 (ν N—H), 3002, 2939, 2854 (ν C—H), 1525 (δ N—H), 1439 (δ C—H), 1377, 1161 (ν SO_2), 755 cm^{-1}. ^1H NMR δ: 1.45-1.57 (m, 2H, CH_2), 1.59-1.70 (m, 4H, $2CH_2$), 3.62–3.76 (m, 4H, $2NCH_2$), 7.43–7.65 (m, 4H, 3H Ph and 1H NH + D_2O exchangeable), 7.92 (d, 2H, Ph, *J* 7.3 Hz), 8.89 (s, 1H, NH + D_2O exchangeable) ppm. ^{13}C NMR: δ 25.1, 26.3, 55.2, 128.3, 130.1, 132.5, 137.4, 181.3 ppm.

4-Methyl-*N′*-(piperidine-1-carbonothioyl)benzenesulfonohydrazide (10). IR: 3245 (ν N—H), 3008, 2940, 2853 (ν C—H), 1595 (δ N-H), 1438 (δ C—H), 1331, 1161 (ν SO_2), 713 cm^{-1}. ^1H NMR δ: 1.52-1.64 (m, 6H, $3CH_2$), 2.42 (s, 3H, CH_3), 3.67-3.73 (m, 4H, $2NCH_2$), 7.24–7.28 (m, 3H, 2H Ph and 1H NH + D_2O exchangeable), 7.55 (s, 1H, NH + D_2O exchangeable), 7.78 (d, 2H, Ph, *J* 8.3 Hz) ppm. ^{13}C NMR: δ 22.1, 25.3, 26.7, 55.3, 129.5, 130.8, 134.2, 139.5, 181.1 ppm.

***N′*-(Morpholine-4-carbonothioyl)benzenesulfonohydrazide (11)**. IR: 3216 (ν N—H), 3079, 2921, 2865 (ν C—H), 1584 (δ N—H), 1464 (δ C—H), 1335, 1170 (SO_2), 736 cm^{-1}. ^1H NMR δ: 3.61 (t, 4H, $2NCH_2$, *J* 5.5 Hz), 3.74 (t, 4H, $2OCH_2$, *J* 5.4 Hz), 7.45–7.67 (m, 3H, Ph), 7.85–7.93 (m, 3H, 2H Ph and 1H, NH + D_2O exchangeable), 8.50–9.20 (brs, 1H, NH + D_2O exchangeable) ppm. ^{13}C NMR: δ 50.1, 66.8, 128.1, 129.7, 132.3, 137.4, 174.5 ppm.

4-Methyl-*N′*-(morpholine-1-carbonothioyl) benzenesulfonohydrazide (12). IR: 3303 (ν N—H), 3049, 2914, 2871 (ν C—H), 1595 (δ N—H), 1466 (δ C—H), 1333, 1164 (ν SO_2), 709 cm^{-1}. ^1H NMR δ: 2.42 (s, 3H, CH_3), 3.58-3.76 (m, 8H, $4CH_2$), 7.18 (s, 1H, NH + D_2O exchangeable), 7.26 (d, 2H Ph *J* 7.8 Hz), 7.74 (d, 2H, Ph, $J = 8.3$ Hz), 8.11 (s, 1H, NH + D_2O exchangeable) ppm. ^{13}C NMR: δ 22.4, 50.2, 67.1, 128.9, 130.0, 134.2, 137.9, 174.7 ppm.

***N′*-(4-Phenylpiperazine-1-carbonothioyl)benzenesulfonohydrazide (13)**. IR: 3298 (ν N—H), 3060, 2917, 2842 (ν C—H), 1579 (δ N—H), 1448 (δ C—H), 1326, 1167 (ν SO_2), 732 cm^{-1}. ^1H NMR δ: 3.17 (t, 4H, $2NCH_2$, *J* 5.1), 3.93 (t, 4H, $2NCH_2$, *J* 5.1 Hz), 6.91–6.98 (m, 3H, Ph), 7.25–7.69 (m, 6H, 4H Ph and 2H 2NH + D_2O exchangeable), 7.88–7.94 (m, 2H, Ph), 8.79 (d, 1H, Ph, *J* 8.1 Hz) ppm. ^{13}C NMR: δ 54.6, 57.4, 115.3, 122.8, 128.1, 129.9, 130.3, 132.7, 137.5, 150.2, 175.6 ppm.

4-Methyl-*N′*-(4-phenylpiperazine-1-carbonothioyl)benzenesulfonohydrazide (14). IR: 3268 (ν N—H), 3037, 2956, 2855 (ν C—H), 1598 (δ N—H), 1427 (δ C—H), 1331, 1161 (ν SO_2), 715 cm^{-1}. ^1H NMR δ: 2.38 (s, 3H, CH_3), 3.18 (t, 4H, NCH_2, *J* 5.0 Hz), 3.94 (t, 4H, $2NCH_2$, *J* 5.0 Hz), 6.91–6.98 (m, 3H, Ph), 7.22-7.77 (m, 5H, 4H Ph and 1H NH + D_2O exchangeable), 8.12 (s, 1H, NH + D_2O exchangeable), 8.79 (d, 1H, Ph, *J* 8.2 Hz) ppm. ^{13}C NMR: δ 22.7, 54.3, 57.2, 115.7, 122.4, 129.7, 129.8, 130.7, 134.6, 138.1, 150.4, 175.8 ppm.

***N′*-(4-(4Fluorophenyl)piperazine-1-carbonothioyl)benzenesulfonohydrazide (15)**. IR: 3307 (ν N—H), 3056, 2960, 2842 (ν C—H), 1583 (δ N—H), 1448 (δ C—H), 1336, 1166 (ν SO_2), 731 cm^{-1}. ^1H NMR δ: 3.08–3.12 (m, 4H, $2NCH_2$), 3.96–4.00 (m, 4H, $2NCH_2$), 6.98–7.06 (m, 4H, Ph), 7.45-7.65 (m, 3H, 2H Ph and 1H NH + D_2O exchangeable), 7.91 (d, 2H, Ph, *J* 7.5 Hz), 8.05 (s, 1H, NH + D_2O exchangeable), 8.84 (d, 1H, Ph, *J* 7.2 Hz) ppm. 13C NMR: 55.1, 58.3, 116.3, 117.5, 128.0, 129.3, 132.1, 137.2, 146.0, 157.3, 176.1 ppm.

***N′*-(4-(4-Fluorophenyl)piperazine-1-carbonothioyl)-4-methylbenzenesulfonohydrazide (16).** IR: 3248 (ν N—H), 3002, 2927, 2819 (ν C—H), 1582 (δ N—H), 1430 (δ C—H), 1328, 1167 (ν SO_2), 709 cm^{-1}. ^1H NMR δ: 2.40 (s, 3H, CH_3), 3.03–3.22 (m, 4H, $2NCH_2$), 3.98–4.11 (m, 4H, $2NCH_2$), 7.05 (d, 2H, Ph, *J* 8.1 Hz), 7.25–7.29 (m, 3H, 2H Ph and 1H NH + D_2O exchangeable), 7.78 (d, 2H, Ph, *J* 8.1 Hz), 8.07 (s, 1H, NH + D_2O exchangeable), 8.76 (d, 2H, Ph, *J* 8.2 Hz) ppm. ^{13}C NMR: δ 23.1, 55.2, 58.1, 116.4, 118.2, 128.1, 129.2, 131.8, 137.1, 146.2, 157.8, 175.8 ppm.

***N′*-(4-(4-Methoxyphenyl)piperazine-1-carbonothioyl)benzenesulfonohydrazide (17).** IR: 3250 (ν N—H), 3033, 2938, 2838 (ν C—H), 1590 (δ N—H), 1449 (δ C—H), 1331, 1170 (ν SO_2), 752 cm^{-1}. ^1H NMR δ: 3.02–3.22 (brs, 4H, $2NCH_2$), 3.89 (s, 3H, OCH_3), 3.95–4.04 (m, 4H, $2NCH_2$), 6.91–7.17 (m, 3H, Ph), 7.15 (s, 1H, NH + D_2O exchangeable), 7.46–7.66 (m, 3H, Ph), 7.89–7.93 (m, 3H, 2H Ph and 1H NH + D_2O exchangeable), 8.79 (d, 1H, Ph, *J* 8.1 Hz) ppm. ^{13}C NMR: δ 54.2, 56.3, 57.3, 116.1, 116.9, 127.8, 129.3, 132.3, 134.0, 147.5, 153.4, 175.2 ppm.

***N′*-(4-(4-Methoxyphenyl)piperazine-1-carbonothioyl)-4-methylbenzenesulfonohydrazide (18).** IR: 3239 (ν N—H), 3032, 2942, 2840 (ν C—H), 1596 (δ N—H), 1499 (δ C—H), 1329, 1164 (ν SO_2), 746 cm^{-1}.^1H NMR δ: 2.41 (s, 3H, CH_3), 2.98-3.14 (m, 4H, $2NCH_2$), 3.88 (s, 3H, OCH_3), 3.93–4.02 (m, 4H, $2NCH_2$), 6.94 (d, 2H, Ph, J 8.0 Hz), 7.08 (s, 1H, NH + D_2O exchangeable), 7.27 (d, 2H, Ph, *J* 8.0 Hz), 7.78 (d, 2H Ph, *J* 8.3 Hz), 7.85 (s, 1H, NH + D_2O exchangeable), 8.83 (d, 2H, Ph, *J* 8.1 Hz) ppm. ^{13}C NMR: δ 22.8, 54.3, 56.2, 57.1, 116.7, 117.0, 128.9, 129.8, 134.2, 138.6, 147.2, 153.8, 175.5 ppm.

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