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Short Communication

Synthesis and Antimycobacterial Activity of New 2-Hydroxy-*N*-(3-oxo-1-thia-4-azaspiro[4.4]non-4-yl)/(3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-2,2-diphenylacetamide Derivatives

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Summary. 2-Hydroxy-2,2-diphenylacetohydrazide (**2**), cyclic ketones, and mercaptoalkanoic acids were converted into 2-hydroxy-*N*-(3-oxo-1-thia-4-azaspiro[4.4]non/[4.5]dec-4-yl)-2,2-diphenylacetamide derivatives (**3**, **4**) in a one pot procedure. Compounds **3** and **4** were tested for *in vitro* antimycobacterial activity against *M. tuberculosis* H37Rv. The compounds were found to provide 0–86% inhibition of mycobacterial growth in the primary screen conducted at 6.25 $\mu g/cm^3$.

Keywords. Spirothiazolidinones; Synthesis; Antimycobacterial activity.

Introduction

Tuberculosis (TB) is a contagious disease with high mortality worldwide. About 32% of the world's population is currently infected with TB. Every year, approximately eight to nine million of these infected people develop clinical pulmonary tuberculosis leading to nearly three million deaths annually [1]. In order to control the rapid spread of tuberculosis and to overcome resistance, there is an urgent need to develop new antimycobacterial agents with unique modes of action to replace the current regimens.

4-Thiazolidinones and their spiroheterocyclic analogs have been shown to possess antibacterial [2, 3], antifungal [4, 5], and antituberculosis [6–8] activities.

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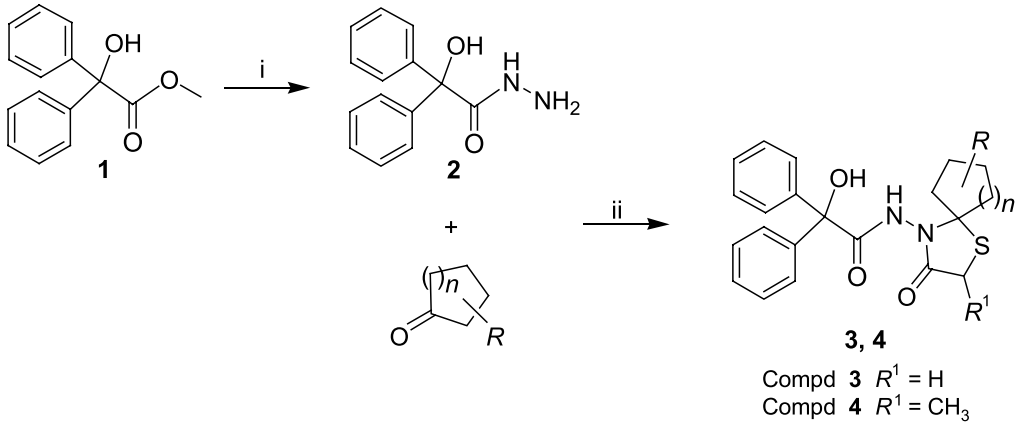
With the aim of obtaining new and more potent antituberculosis compounds which can improve the current chemotherapeutic antituberculosis treatments, we have synthesized and evaluated sixteen new 2-hydroxy-*N*-(3-oxo-1-thia-4-azaspiro[4.4]-non-4-yl)/(3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-2,2-diphenylacetamide derivatives, incorporating the thiazolidinone substructure, as potential antimycobacterials.

Results and Discussion

In an attempt to investigate the effects of modification of the ring substituents of the spiroheterocyclic system on biological activity and to get an insight into the substitution pattern required for the highest potencies, a series of 2-hydroxy-*N*-(3-oxo-1-thia-4-azaspiro[4.4]non-4-yl)/(3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-2,2-diphenylacetamides was prepared as described in the Scheme. Thus 2-hydroxy-2,2-diphenylacetohydrazide (**2**), an appropriate cyclic ketone, and mercaptoacetic acid or α-mercaptopropionic acid were refluxed in dry benzene using a *Dean-Stark* water separator to afford **3** and **4** in an efficient one-pot nucleophilic addition and cyclodehydration reaction.

The structures of the new compounds were confirmed by elemental analysis, IR, ^{1}H NMR, HSQC, ^{13}C NMR(APT), and atmospheric pressure chemical ionization [APCI(-)] mass spectrometry.

The IR spectra exhibited OH/N–H and C=O bands in the 3435–3230 and 1685–1665 cm^{-1} regions attributed to the common OH/NH and CONHN functions of **3** and **4** [10]. The characteristic lactam C=O absorptions of **3** and **4** were observed in the 1731–1704 cm^{-1} region [4, 9].



Compd 3, 4	a	b	c	d	e	f	g	h
R	H	H	6-CH_3	7-CH_3	8-CH_3	8-C_2H_5	8-C_3H_7	8-C_6H_5
n	1	2	2	2	2	2	2	2

Scheme 1. Reagents and conditions: i) hydrazine hydrate, EtOH, reflux, 6 h; ii) mercaptoacetic acid/α-mercaptopropionic acid, dry benzene, reflux, 6 h

The ^{1}H NMR spectra of **3** and **4** displayed singlets and quartets attributed to the methylene (SCH_2) and methine ($SCHCH_3$) ring protons at 2-position of the spiroheterocyclic system at about $\delta = 3.54$–3.88 ppm [11]. The C–OH and CONH protons were observed at about $\delta = 6.78$–6.84 and 9.93–10.33 ppm, respectively [10].

Further structural confirmation was provided by the HSQC spectrum of **3f** which showed the expected ^{13}C–^{1}H correlations. Existence of cross peaks connecting 8-CH_2CH_3 ($\delta = 12.02$ ppm) and C_8 ($\delta = 37.97$ ppm) with the triplet at $\delta =$ 0.83 ppm; 8-CH_2CH_3 ($\delta = 29.38$ ppm) with the quintet at $\delta = 1.16$ ppm and C_2 ($\delta = 28.63$ ppm) with the singlet at $\delta = 3.54$ ppm was decisive evidence for unambigous assignment. Cross peaks connecting spirodecane $C_{7,9}$ ($\delta = 29.61$ ppm) with the multiplet at $\delta = 1.01$–1.09 ppm assigned to the axial protons and with the doublet at $\delta = 1.65$ ppm assigned to the equatorial protons on $C_{7,9}$ were also observed. Cross peaks existed also between $C_{6,10}$ ($\delta = 37.28$ ppm) and the doublets at $\delta = 1.65$ and 1.75 ppm assigned to the axial and equatorial protons on $C_{6,10}$. Carbon resonances at $\delta = 73.44$, 81.60, 168.01, and 173.39 ppm showed no cross peaks and were thus assigned to C_5, C–OH, CONH, and C_3 (lactam C=O) carbons, respectively.

The ^{13}C NMR(APT) spectra of **3b**, **4e**, and **4g** also supported the anticipated cyclization and showed the common spirodecane C_2, C_3 (lactam C=O), and C_5 resonances at about $\delta = 28.64$–37.47, 173.27–173.40, and 71.74–73.30 ppm, respectively [6, 12, 13]. The CONH and the $(C_6H_5)_2C$–OH resonances were observed at about $\delta = 167.98$–170.67 and 81.57–81.61 ppm.

$(M–H)^-$ ions with 100% relative abundance observed in the atmospheric pressure chemical ionization [APCI(-)] mass spectra of **4e** and **4h** provided further confirmation for the formation of the expected structures [14]. MS/MS clearly showed the $[(M–H)\text{-}SCH_2CO]^-$ fragments cited for the 4-thiazolidinone system in the literature [9]. Further spectral details are presented in the experimental section.

The *in vitro* antimycobacterial activity evalution of **3** and **4** against *M. tuberculosis* H37Rv (ATCC 27294) was initially carried out using the microplate alamar blue assay (MABA) at a concentration of 6.25 $\mu g/cm^3$ at the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) (Table) [15].

As can be seen in the Table, the compounds were found to provide 0–86% inhibition of mycobacterial growth of *M. tuberculosis* H37Rv in the primary screen conducted at 6.25 $\mu g/cm^3$.

Generally compounds bearing a methyl function at 2-position of the spiroheterocyclic system (**4**) showed higher inhibition when compared to the unsubstituted entries (**3**). The highest inhibition (86%) was demonstrated by **4h**, the 2-methyl and 8-phenyl substituted derivative.

These preliminary results confirm the fact that the 3-oxo-1-thia-4-azaspiro [4.4]nonane/[4.5]decane derivatives which may be considered as spirothiazolidinones have antimycobacterial potential. It is thus concluded that the new compounds described in this work, especially **4h**, deserve further investigation for the development of more potent antitubercular agents for therapeutic use.

Table 1. Formulas, physical constants, elemental analysis, and primary *in vitro* antimycobacterial activity evaluation of **3a–3h**, **4a–4h** against *M. tuberculosis* H37Rv

Compd.	Formula (MW)	Yield (%)	Mp (°C)	Analysis (%) (calcd./found)			*GI* (%)[a]
				C	H	N	
3a	$C_{21}H_{22}N_2O_3S$	52	201–3	65.95	5.80	7.32	0
	(382.474)			65.87	5.97	6.90	
3b	$C_{22}H_{24}N_2O_3S$	47	220–2	66.64	6.10	7.07	1
	(396.494)			66.21	6.22	6.69	
3c	$C_{23}H_{26}N_2O_3S$	28	126–8	67.29	6.38	6.82	0
	(410.524)			66.98	6.76	6.50	
3d	$C_{23}H_{26}N_2O_3S$	34	182–3	67.29	6.38	6.82	4
	(410.524)			66.99	6.50	6.85	
3e	$C_{23}H_{26}N_2O_3S$	54	174–6	67.29	6.38	6.82	0
	(410.524)			67.05	6.61	6.85	
3f	$C_{24}H_{28}N_2O_3S$	47	154–6	67.90	6.65	6.60	26
	(424.544)			67.78	6.65	6.62	
3g	$C_{25}H_{30}N_2O_3S$	15	175–6	68.46	6.89	6.39	38
	(438.574)			67.97	6.73	6.37	
3h	$C_{28}H_{28}N_2O_3S$	46	195–7	71.16	5.97	5.93	31
	(472.584)			71.25	5.92	6.03	
4a	$C_{22}H_{24}N_2O_3S$	49	185–7	66.64	6.10	7.07	0
	(396.494)			66.46	6.30	6.67	
4b	$C_{23}H_{26}N_2O_3S$	53	198–9	67.29	6.38	6.82	0
	(410.524)			67.62	6.50	6.49	
4c	$C_{24}H_{28}N_2O_3S$	48	182–5	67.90	6.65	6.60	38
	(424.544)			68.27	6.89	6.24	
4d	$C_{24}H_{28}N_2O_3S$	40	180–1	67.90	6.65	6.60	1
	(424.544)			67.57	6.76	6.46	
4e	$C_{24}H_{28}N_2O_3S$	34	210–1	67.90	6.65	6.60	36
	(424.544)			67.73	6.50	6.50	
4f	$C_{25}H_{30}N_2O_3S$	44	174–5	68.46	6.89	6.39	53
	(438.574)			68.83	6.72	6.17	
4g	$C_{26}H_{32}N_2O_3S$	23	196–8	69.00	7.13	6.19	64
	(452.604)			68.88	7.06	6.05	
4h	$C_{29}H_{30}N_2O_3S$	29	199–200	71.58	6.21	5.76	86
	(486.614)			71.18	6.11	5.41	

[a] Growth Inhibition of virulent H37Rv strain of *M. tuberculosis* ($MIC > 6.25\,\mu g/cm^3$); *MIC* of rifampin: $0.125\,\mu g/cm^3$ *versus M. tuberculosis H37Rv* (97% inhibition)

Experimental

All chemicals were purchased from E. Merck (Darmstadt, Germany). Melting points were measured in open capillary tubes with a Büchi 530 melting point apparatus and are uncorrected. IR (KBr) spectra were recorded using a Perkin-Elmer 1600 FTIR spectrophotometer. ^{1}H NMR, HSQC, and ^{13}C NMR(APT) spectra were recorded on a Varian^{UNITY}INOVA 500 MHz spectrometer. Elemental analyses were performed on a Carlo Erba Model 1106 elemental analyzer. Mass spectra (LC/MS-APCI) were recorded on a Finnigan^{TM} LCQ^{TM} Mass Spectrometer in the negative ionization mode.

2-Hydroxy-2,2-diphenylacetohydrazide (**2**)
Methyl 2-hydroxy-2,2-diphenylacetate (0.05 mol) and 12 cm^3 hydrazine hydrate (98%) were heated under reflux for 12 h. The reaction mixture was transferred to a crystallizing dish and left aside until crystallization. The crude product thus obtained was recrystallized from ethanol.

2-Hydroxy-N-(3-oxo-1-thia-4-azaspiro[4.4]non-4-yl)/(3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-2,2-diphenylacetamides **3 and 4** *(General Procedure)*
A mixture of **2** (0.005 mol), an appropriate cyclic ketone (0.005 mol), and mercaptoacetic acid or α-mercaptopropionic acid (0.02 mol) was refluxed in 20 cm^3 dry benzene for 5–6 h using a *Dean-Stark* water separator. Excess benzene was evaporated *in vacuo*. The resulting residue was triturated with saturated $NaHCO_3$ solution until CO_2 evolution ceased and was allowed to stand overnight or in some cases refrigerated until solidification. The solid thus obtained was washed with water, dried, and recrystallized from ethanol.

2-Hydroxy-N-(3-oxo-1-thia-4-azaspiro[4.4]non-4-yl)-2,2-diphenylacetamide (**3a**)
IR(KBr): $\bar{\nu} = 3353$ (O–H/N–H), 1682, 1729 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 500 MHz): $\delta =$ 1.41–1.49 (m, 4H, spn[b]), 1.69–1.73 (m, 2H, spn), 2.03 (s, 2H, spn), 3.61 (s, 2H, C_2–H_2), 6.82 (s, 1H, COH), 7.28–7.35 (m, 6H, Ar–H), 7.43–7.44 (m, 2H, Ar–H), 7.45–7.46 (m, 2H, Ar–H), 10.31 (s, 1H, CONH) ppm.

2-Hydroxy-N-(3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-2,2-diphenylacetamide (**3b**)
IR(KBr): $\bar{\nu} = 3354$ (O–H/N–H), 1685, 1726 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 500 MHz): $\delta = 0.80$–1.07 (m, 1H, spd[c]), 1.34–1.38 (m, 2H, spd), 1.49–1.63 (m, 5H, spd), 1.73, 1.76 (2s, 2H, spd), 3.54 (s, 2H, C_2–H_2), 6.81 (s, 1H, COH), 7.28–7.35 (m, 6H, Ar–H), 7.46 (s, 2H, Ar–H), 7.47–7.48 (m, 2H, Ar–H), 10.21 (s, 1H, CONH) ppm; ^{13}C NMR(APT) (*DMSO*-d_6, 125 MHz): $\delta = 23.56$ ($C_{7,9}$ spd), 24.83 (C_8 spd), 28.64 (C_2 spd), 37.61 ($C_{6,10}$ spd), 73.30 (C_5 spd), 81.61 (C–OH), 128.05, 128.25, 128.30 (ar CH), 144.40 (ar C), 167.98 (amide C=O), 173.40 (lactam C=O) ppm.

2-Hydroxy-N-(8-methyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-2,2-diphenylacetamide (**3e**)
IR(KBr): $\bar{\nu} = 3435$, 3230 (O–H/N–H), 1682, 1704 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 500 MHz): $\delta = 0.83$ (d, 3H, $J = 4.88$ Hz, 8-CH_3 spd), 1.06 (t, 4H, $J = 7.07$ Hz, spd), 1.58–1.63 (m, 4H, spd), 1.71–1.74 (m, 1H, spd), 3.54 (s, 2H, C_2–H_2), 6.80 (s, 1H, COH), 7.28–7.36 (m, 6H, Ar–H), 7.44–7.45 (m, 2H, Ar–H), 7.46–7.47 (m, 2H, Ar–H), 10.20 (s, 1H, CONH) ppm.

2-Hydroxy-N-(8-ethyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-2,2-diphenylacetamide (**3f**)
IR(KBr): $\bar{\nu} = 3337$ (O–H/N–H), 1665, 1723 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 500 MHz): $\delta = 0.83$ (t, 4H, $J = 7.56$ Hz, 8-CH_2CH_3 and C_8-*H* spd), 1.01–1.09 (m, 2H, $C_{7,9}$-H_{ax} spd), 1.16 (quint, 2H, $J = 7.32$ Hz, 8-CH_2CH_3), 1.65 (d, 4H, $J = 12.20$ Hz, $C_{6,10}$-H_{ax} and $C_{7,10}$-H_{eq} spd), 1.75 (d, 2H, $J =$ 13.67 Hz, $C_{6,10}$-H_{eq} spd), 3.54 (s, 2H, C_2–H_2), 6.81 (s, 1H, COH), 7.28–7.36 (m, 6H, Ar–H), 7.46–7.48 (m, 4H, Ar–H), 10.21 (s, 1H, CONH) ppm; ^{13}C NMR(HSQC) (*DMSO*-d_6, 125 MHz): $\delta = 12.02$ (8-CH_2CH_3 spd), 28.63 (C_2 spd), 29.38 (8-CH_2CH_3 spd), 29.61 ($C_{7,9}$ spd), 37.28 ($C_{6,10}$ spd), 37.97 (C_8 spd), 73.344 (C_5 spd), 81.60 (C–OH), 128.03, 128.24, 128.28, 128.36 (ar CH), 144.45 (ar C), 168.01 (amide C=O), 173.39 (lactam C=O) ppm.

2-Hydroxy-N-(2,6-dimethyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-2,2-diphenylacet-amide (**4c**)
IR(KBr): $\bar{\nu} = 3335$ (O–H/N–H), 1679, 1731 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 500 MHz): $\delta = 0.93$ (t, 3H, $J = 6.83$ Hz, 6-CH_3), 0.95–1.10 (m, 1H, spd), 1.11–1.14 (m, 1H, spd), 1.19–1.27 (m, 1H, spd),

[b] spn = spirononane
[c] spd = spirodecane

1.41 (t, 3H, $J = 7.32$ Hz, 2-CH_3), 1.45–1.67 (m, 5H, spd), 1.83–1.87 (m, 1H, spd), 3.77, 3.85 (2q, 1H, $J = 6.83$ Hz, C_2–H), 6.78 (s, 1H, COH), 7.26–7.31 (m, 2H, Ar–H), 7.33–7.35 (m, 4H, Ar–H), 7.45–7.49 (m, 4H, Ar–H), 9.93, 10.05 (2s, 1H, CONH) ppm.

2-Hydroxy-N-(2,8-dimethyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-2,2-diphenylacetamide (**4e**)
IR(KBr): $\bar{\nu} = 3365$ (O–H/N–H), 1682, 1722 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 500 MHz): $\delta = 0.83$ (d, 3H, $J = 5.86$ Hz, 8-CH_3), 1.05–1.12 (m, 3H, spd), 1.42 (d, 3H, $J = 5.85$ Hz, 2-CH_3), 1.60 (d, 3H, $J = 11.23$ Hz, spd), 1.70 (d, 3H, $J = 8.79$ Hz, spd), 3.83 (q, 1H, $J = 6.99$ Hz, C_2–H), 6.80 (s, 1H, COH), 7.28–7.36 (m, 6H, Ar–H), 7.46–7.49 (m, 4H, Ar–H), 10.25 (s, 1H, CONH) ppm; ^{13}C NMR(APT) (*DMSO*-d_6, 125 MHz): $\delta = 20.39$ (2-CH_3 spd), 22.49 (8-CH_3 spd), 31.39 (C_8 spd), 31.89 (C_7 spd), 32.39 (C_9 spd), 37.44 (C_6 spd), 37.47 (C_2 spd), 38.23 (C_{10} spd), 71.74 (C_5 spd), 81.60 (C–OH), 128.04, 128.07, 128.23, 128.26, 128.29, 128.32 (ar CH), 144.43, 144.47 (ar C), 170.67 (amide C=O), 173.30 (lactam C=O) ppm; LC/MS: $m/z = 423$ $(M–H)^-$.

2-Hydroxy-N-(8-propyl-2-methyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-2,2-diphenylacetamide (**4g**)
IR(KBr): $\bar{\nu} = 3388, 3276$ (O–H/N–H), 1682, 1722 (C=O); ^{1}H NMR (*DMSO*-d_6, 500 MHz): $\delta = 0.83$ (t, 3H, $J = 6.59$ Hz, 8-$CH_2CH_2CH_3$), 0.96–1.01 (m, 3H, spd), 1.10 (q, 2H, $J = 7.16$ Hz, 8-$CH_2CH_2CH_3$), 1.22–1.28 (m, 2H, 8-$CH_2CH_2CH_3$), 1.41 (d, 3H, $J = 9.02$ Hz, 2-CH_3), 1.64 (d, 3H, $J = 12.20$ Hz, spd), 1.69–1.71 (m, 3H, spd), 3.82 (q, 1H, $J = 6.99$ Hz, C_2–H), 6.79 (s, 1H, COH), 7.28–7.35 (m, 6H, Ar–H), 7.45–7.47 (m, 4H, Ar–H), 10.24 (s, 1H, CONH) ppm; ^{13}C NMR(APT) (*DMSO*-d_6, 125 MHz) $\delta = 14.82$ (8-$CH_2CH_2CH_3$ spd), 20.15 (8-$CH_2CH_2CH_3$ spd), 20.39 (2-CH_3 spd), 29.81 (C_7 spd), 30.29 (C_9 spd), 35.89 (C_8 spd), 37.39 (8-$CH_2CH_2CH_3$ spd), 37.46 (C_2 spd), 38.18 (C_6 spd), 39.01 (C_{10} spd), 72.03 (C_5 spd), 81.57 (C–OH), 128.02, 128.23, 128.25, 128.28, 128.30 (ar CH), 144.43, 144.47 (ar C), 170.65 (amide C=O), 173.27 (lactam C=O) ppm.

2-Hydroxy-N-(2-methyl-8-phenyl-3-oxo-1-thia-4-azaspiro[4.5]dec-4-yl)-2,2-diphenylacetamide (**4h**)
IR(KBr): $\bar{\nu} = 3395$ (O–H/N–H), 1683, 1721 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 500 MHz): $\delta = 1.44$ (d, 3H, $J = 6.84$ Hz, 2-CH_3), 1.49–1.71 (m, 3H, spd), 1.77–1.84 (m, 6H, spd), 3.88 (q, 1H, $J = 6.99$ Hz, C_2–H), 6.84 (s, 1H, COH), 7.16–7.19 (m, 3H, Ar–H), 7.26–7.32 (m, 4H, Ar–H), 7.34–7.37 (m, 4H, Ar–H), 7.49–7.51 (m, 4H, Ar–H), 10.33 (s, 1H, CONH) ppm; LC/MS: $m/z = 485$ $(M–H)^-$.

In Vitro Evaluation of Antituberculosis Activity
Primary screen was conducted at 6.25 $\mu g/cm^3$ against *Mycobacterium tuberculosis* H37Rv in BACTEC 12B medium using a broth microdilution assay: Microplate Alamar Blue Assay (MABA). Compounds effecting <90% inhibition in the primary screen (MIC > 6.25 $\mu g/cm^3$) were not evaluated further [15].

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