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Microwave synthesis of some *N*-phenylhydrazine-1-carbothioamide Schiff bases

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ABSTRACT

We have synthesized and characterized a series of carbothioamide derivatived molecules, obtained by reaction of aromatic aldehyde (Anisaldehyde, 9-anthraldehyde, cinnamaldehyde, indole-3-carboxaldehyde, 1-naphthaldehyde and o-vanillin) with an equimolar amount of 4-phenylthiosemicarbazide with microwave irradiation. The synthesized compounds have been characterized by FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy. Quantum calculations of the physical properties, based on density functional theory method at B3LYP/6-31+G(d,p) level of theory, were performed, by means of the Gaussian 09W set of programs. The theoretical ^{1}H NMR chemical shift results of the studied compounds have been calculated at B3LYP method and standard 6-31+G(d,p) basis set using the standard Gauge-Independent Atomic Orbital approach. The calculated values are also compared with the experimental data available for these molecules. A good linear relationship between the experimental and calculated data has been obtained.

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1. Introduction

Thiosemicarbazide and their Schiff bases have been extensively investigated due to their wide range of application including antibacterial and anticorrosion activities [1-4]. Schiff bases are important intermediates for the synthesis of many bioactive compounds such as β-lactams and thizolodone [2]. They have been prepared by various methods [5], one of the most popular one is by refluxing in a protic solvent a mixture of aldehydes or ketones with primary amines aldehydes. Some cases the reaction need long reaction time and in most cases a catalyst required. During the last decade, the microwave promoted organic synthesis has been used either in especial microwave oven or in domestic ovens, in these ovens despite the power level which commonly fluctuates as a result of the on-off cycles and heterogeneous energy [6]. We selected 4-phenyl-3-thiosemicarbazide as a working compound which is used as pesticide and antibacterial agent [1]. In this study, as part of our research program, we report herein an efficient synthesis of some new functionalized Schiff bases derived from 4-phenyl-3-thiosemicarbazones. In addition, quantum calculations of the physical properties, based on density functional theory method at B3LYP/6-31+G(d,p) level of theory, were performed for the prepared molecules, by means of the Gaussian 09W set of programs.

2. Experimental

2.1. Materials

4-Phenylthiosemicarbazide was purchased from Sigma Chemical Company. *o*-Vanillin and cinnamaldehyde were purchased from Fluka Chem. Company. Anisaldehyde, 9-anthraldehyde and 1-naphthaldehyde were purchased from BDH Chem. Company. Indol-3-caboxaldehyde was purchased from Himedia Chem. Company. All solvents used were of analytical grade commercially available and used without further purification.

2.2. Instrumentations

Microwave irradiation was carried out in a Kenwood microwave oven, model MW303, operating at 800 W. Melting points were recorded on Thermo Fisher Scientific apparatus. FT-IR spectra were recorded as KBr pellets on Shimadzu Inst. in the range from 400-4000 cm^{-1}.

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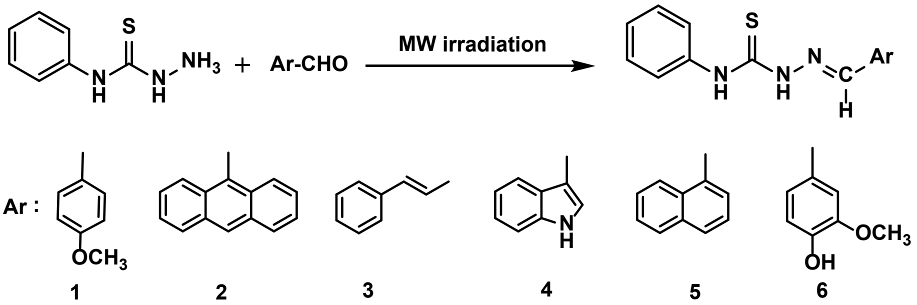


Scheme 1

^{1}H- and ^{13}C-NMR spectra were recorded on Bruker 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) using $CDCl_3$ or DMSO-d_6 as a solvent, TMS as internal reference.

2.3. Synthesis

General procedure: A mixture of 4-phenylthiosemicarbazide (2 mmol) and aromatic aldehyde (Anisaldehyde, 9-anthraldehyde, cinnamaldehyde, indole-3-carboxaldehyde, 1-naphthaldehyde or *o*-vanillin; 2 mmol) in a flask was inputted into microwave oven and irradiated for 2-15 min. The progress of the reactions were monitored by TLC using hexane:ethylacetate solvent mixture (7:3, *v*:*v*). The obtained crude product was recrystallized from suitable solvent (Scheme 1).

2-(4-Methoxybenziylidene)-N-phenylhydrazine-1-carbothioamide (**1**): Time: 2 min. Power: 100%. Recryst. solvent: Methanol. Color: Yellow. Yield: 73%. R_f: 0.62. M.p.: 167-169 °C. FT-IR (KBr, ν, cm^{-1}): 3416 (Ph-NH), 3279 (NH), 1204 (C=S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.90 (s, 3H, OCH_3), 6.98-7.82 (m, 9H, Ar-H), 8.63 (1H, HC=N), 11.91 (s, 1H, N-NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 55.35 (OCH_3), 114.00-130.01 (Ar-C), 161.03 (Azomethine carbon), 175.18 (C=S). Anal. calcd. for $C_{15}H_{15}N_3OS$: C, 63.13; H, 5.30; N, 14.73. Found: C, 63.41; H, 5.18; N, 15.11%.

2-(Anthracen-9-ylmthylene)-N-phenylhydrazinecarbothioamide (**2**): Time: 12 min. Power: 100%. Recryst. solvent: Acetonitrile. Color: Orange. Yield: 81%. R_f: 0.48. M.p.: 201-202 °C. FT-IR (KBr, ν, cm^{-1}): 3274 (NH), 1205 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.25-8.86 (m, 14H, Ar-H), 9.07 (s, 1H, HC=N), 10.19 (s, 1H, Ph-NH), 11.94 (s, 1H, N-NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 123.00-150.02 (Ar-C), 161.26 (Azomethine carbon), 176.40 (C=S). Anal. calcd. for $C_{22}H_{17}N_3S$: C, 74.34; H, 4.84; N, 11.82. Found: C, 74.82; H, 4.97; N, 11.63%.

N-Phenyl-2-(3-phenylallylidene)hydrazine-1-carbothioamide (**3**): Time: 4 min. Power: 50%. Recryst. solvent: Ethanol. Color: Pale-yellow. Yield: 78%. R_f: 0.58. M.p.: 172-174 °C. FT-IR (KBr, ν, cm^{-1}): 3269 (N-H), 1624 (C=N), 1205 (C=S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 6.86 (dd, 1H, C=C-*Ha*), 6.94 (dd, 1H, Ph-C-*Hb*), 7.20-7.70 (m, 10H, Ar-H), 7.75 (d, 1H, HC=N), 9.17 (br, 1H, N-NH), 9.75 (s, 1H, Ph-NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 175.38 (C=S), 144.61 (HC=N), 124.00-140.90 (Ar-C), 126.0, 135.6 (CH=CH). Anal. calcd. for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.81; H, 5.22; N, 14.78%.

2-((1H-Indol-3-yl)methylene)-N-phenylhydrazine-1-carbothioamide (**4**): Time: 8 min. Power: 100%. Recryst. solvent: Ethanol. Color: Pale-yellow. Yield: 62%. R_f: 0.41. M.p.: 259-261 °C. FT-IR (KBr, ν, cm^{-1}): 3377, 3308 (N-H), 3246 (NH indole), 1614 (C=N), 1246 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.20-8.88 (m, 10H, Ar-H), 8.41(s, 1H, HC=N), 9.61 (s, 1H, N-NH), 11.58 (s, 1H, Ph-NH), 11.68 (s, 1H, NH indole). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 111.00-141.00 (Ar-C), 165.01 (Azomethine carbon), 174.80 (C=S). Anal. calcd. for $C_{16}H_{14}N_4$: C, 65.28; H, 4.79; N, 19.03. Found: C, 65.41; H, 4.91; N, 19.41%.

2-(Naphthalene-1-ylmethylene)-N-phenylhydrazinecarbothioamide (**5**): Time: 5 min. Power: 100%. Recryst. solvent: Methanol. Color: Orange. Yield: 63%. R_f: 0.43. M.p.: 198-200 °C. FT-IR (KBr, ν, cm^{-1}): 3217 (N-H), 1611 (C=N), 1238 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.20-8.87 (m, 12H, Ar-H), 9.10 (s, 1H, HC=N), 10.20 (1H, Ph-NH), 11.98 (s, 1H, CS-NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 121.01-144.01 (Ar-C), 160.05 (Azomethine carbon), 175.80 (C=S). Anal. calcd. for $C_{18}H_{15}N_3S$: C, 70.79; H, 4.95; N, 13.76. Found: C, 70.22; H, 5.01; N, 13.81%.

2-(2-Hydroxy-3-methoxybenzylidene)-N-phenylhydrazine-1-carbothioamide (**6**): Time: 2 min. Power: 70%. Recryst. solvent: Ethanol. Color: Pale-yellow. Yield: 73%. R_f: 0.68. M.p.: 205-207 °C. FT-IR (KBr, ν, cm^{-1}): 3337 (OH), 3302 (N-H), 1595 (C=N), 1543 (NH), 1211 (C=S), 1066 (C-O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.96 (s, 3H, OCH_3), 6.94-7.69 (m, 8H, Ar-H), 8.16 (s, 1H, HC=N), 9.53 (s, 1H, Ph-NH), 11.54 (s, 1H, N-NH), 13.21 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm):56.10 (OCH_3), 121.00-150.20 (Ar-C), 156.10 (Azomethine carbon), 176.00 (C=S). Anal. calcd. for $C_{15}H_{15}N_3O_2S$: C, 59.78; H, 5.02; N, 13.94. Found: C, 59.63; H, 5.13; N, 14.02%.

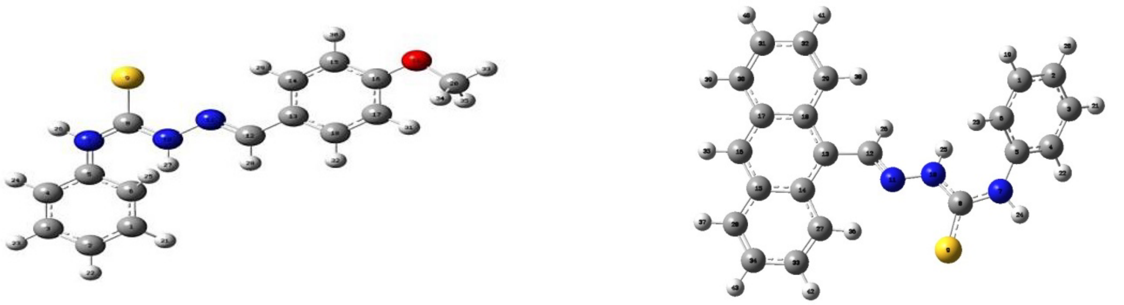
2.4. Computational study

All computational studies were performed with the Gaussian 09W program [7]. Density functional theory (DFT) with B3LYP method was used in present work to perform theoretical calculations on the studied compounds. The geometry of all prepared compounds was optimized at the B3LYP level of theory along with standard 6-31+G(d,p) basis set. The electronic properties were calculated using B3LYP/6-31+G(d,p) based on the optimized structures [8-10]. Mulliken atomic charges have been calculated in same level of theory. Also, the theoretical ^{1}H NMR chemical shift have been calculated at B3LYP method and standard 6-31+G(d,p) basis set using the standard GIAO (Gauge-Independent Atomic Orbital) approach. The magnetic shielding tensor of the protons of the studied compounds has been determined.

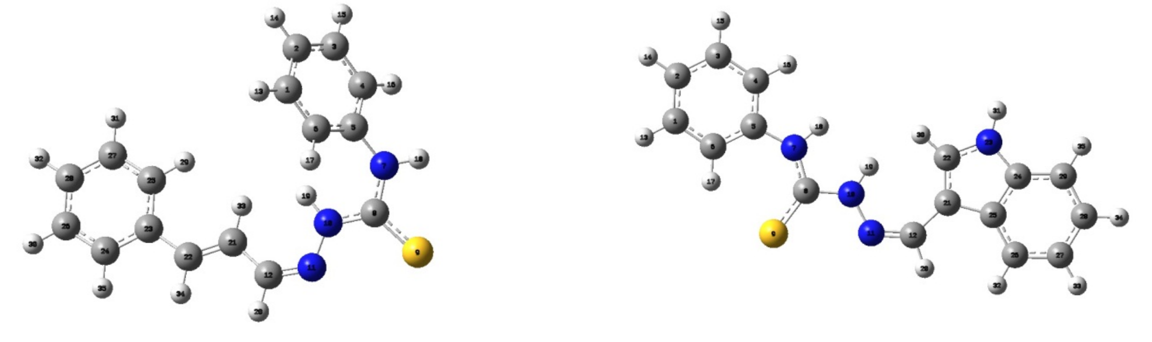
3. Results and discussion

3.1. Synthesis

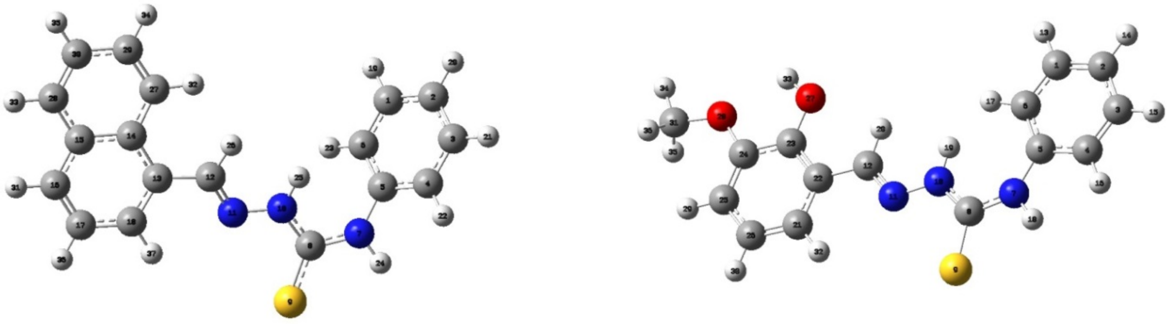
The preparation and purification procedures are simple and it gives good yields within a few minutes. The synthesized compounds are crystalline solids stable in air, most of them soluble in DMF and DMSO and sparingly soluble in methanol, ethanol, hexane, acetonitrile and benzene. The proposed molecular formulas for prepared compounds are in agreement with analytical data (C, H and N) together with spectroscopic data namely IR, ^{1}H NMR and ^{13}C NMR.



Compound 1 **Compound 2**



Compound 3 **Compound 4**



Compound 5 **Compound 6**

Figure 1. The optimized structure of compounds **1**-**6** within numbering of atoms.

The IR spectra provide valuable information regarding the formation of Schiff bases. All compounds show a strong bands at 1640 to 1611 cm^{-1} attributed azomethine (-C=N-)stretching vibration also all compounds shows a bands at 1267-1264 cm^{-1} and at 3217 and 3377 cm^{-1}which attributed to C=S and NH stretching vibration, respectively. The totally absence of SH stretching vibration together with strong band of C=S gives good evidence that these compounds existed in thione-amine form.

The ^{1}H NMR and ^{13}C NMR data of compounds recorded at room temperature in DMSO-d_6 or $CDCl_3$. The NH signal in all compounds is solvent dependent where appear down field in DMSO-d_6 compared with $CDCl_3$. All the other signals appear at expected region. The ^{1}H NMR spectrum of compound **1** in $CDCl_3$ showed two singlet signals for methoxy protons at δ 3.90 ppm and for azomethine proton at δ 8.63 ppm along with multiplet in the region δ 6.98-7.82 ppm for aromatic protons. The ^{1}H NMR spectrum of compound **3** in $CDCl_3$ showed two doublets of doublet signals for olefinic protons at δ 6.86 and 6.94 ppm. The azomethine proton signal appears at 7.75 ppm.^{13}C NMR spectrum of compound **3** showed a signals at δ 175.38 ppm attributed to C=S, 144.61 ppm for azomethine carbon. ^{1}H NMR spectrum of compound **4** (in DMSO-d_6) showed five signals at 11.68 ppm as abroad band attributed to NH of indole moiety [11]. Singlet at δ 11.58 for Ph-NH, singlet at 9.61 ppm N-NH, singlet at δ 8.41 ppm for azomethine proton and multiplet in the region δ 7.20-8.88 ppm attributed to aromatic protons.

3.2. Computational study

Theoretical investigations were performed using the Density Functional Theory at B3LYP level of theory at 6-31+G(d,p) in the Gaussian 09W program. The optimized structure of compound **1** with labeling of atoms is given in Figure 1 as an example. Figure 1 shows the compound in the ball and stick model.

3.2.1. Mulliken population analysis

Dipole moment, molecular polarizability and bond properties are affected by atomic charges, therefore, the Mulliken atomic charge calculation has an important role [11-13].

Table 1. The Mulliken atomic charge (a.u.) distribution of some atoms of the synthesized compounds.

Atoms	Compound					
	1	2	3	4	5	6
1C	0.0157	0.0109	0.1390	-0.5600	0.0281	-0.3150
2C	0.0075	-0.0104	-0.0355	0.0980	-0.0158	0.0559
3C	-0.1200	-0.1164	-0.0872	-0.1500	-0.1095	-0.0620
4C	-0.4895	-0.5747	-0.4400	0.0510	-0.5258	0.2665
5C	0.1562	0.1357	0.1429	-0.6990	0.1934	-0.7610
6C	0.5746	0.7094	0.4152	1.1540	0.6018	0.7539
7N	0.0349	0.0432	0.0255	0.1840	0.0265	0.0558
8C	-0.1715	-0.2227	-0.1727	-0.2810	-0.2018	0.1004
9S	-0.0298	-0.0492	-0.0778	0.0980	-0.0390	-0.1530
10N	-0.1740	0.0693	0.1115	0.0710	-0.0838	0.1180
11N	0.3709	0.1460	-0.0219	-0.0040	0.3031	0.0696
12C	0.1593	-0.2352	-0.4941	-0.4910	0.0305	0.3305
13C	0.3539	0.2050	0.0761	0.8430	0.2070	0.5146
14C	0.3924	0.4929	0.0481	0.1860	-0.4809	0.9277
20 H	0.1246	0.1497	0.1144	0.1387	0.1226	0.1597

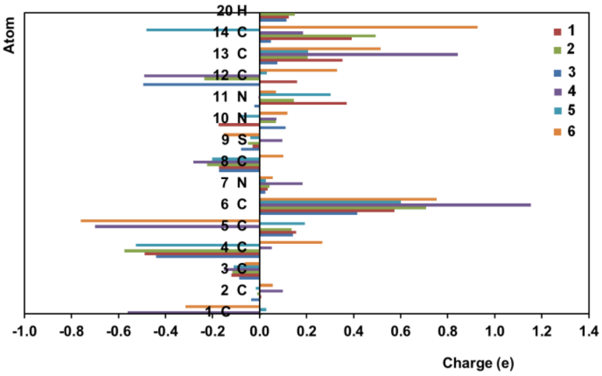


Figure 2. The Mulliken atomic charge distribution of some atoms of the synthesized compounds.

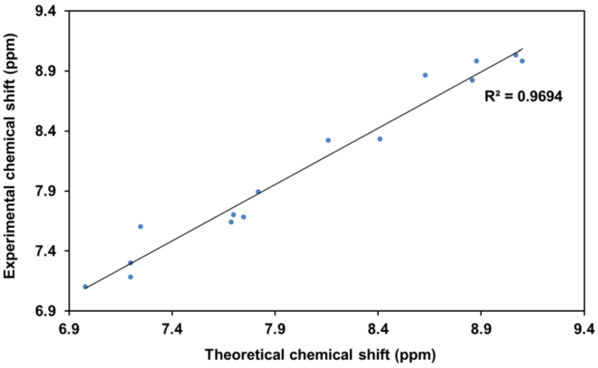


Figure 3. Experimental values *vs.* theoretical ^{1}H NMR chemical shifts for azomethine proton of studied molecules.

Mulliken population analysis was performed at the same level of theory. Illustration of atomic charges plotted for some atoms of studied compound obtained by Mulliken population is shown in Figure 2. As can be seen in Table 1, all the hydrogen atoms have a net positive charge. The obtained atomic charge shows that 20 H atom of compound **6** has bigger positive atomic charge (0.1597) than the other same hydrogen atoms in the studied compound. The C12 atom of compound **3** has bigger negative atomic charge (-0.4941) than the other same carbon atoms in the studied compound and C5 atom of compound **6** (-0.7610).

3.2.2. NMR analysis

The NMR calculations are widely use to complement experimental measurements to solve structural problems [14]. The theoretical ^{1}H NMR chemical shift results of the studied compounds have been calculated at B3LYP methods and standard 6-31+G(d,p) basis set using the standard GIAO (Gauge-Independent Atomic Orbital) approach. The calculated values are compared with the experimental data available for these molecules. A good linear relationship between the experimental and calculated data has been obtained shown in Figure 3.

The magnetic shielding tensor can be used as a probe of intermolecular structure. The magnetic nucleus becomes a sensitive probe of the local electron distribution, providing information about molecular structure. Moreover, the shielding tensor is affected when a molecule is brought from an ideal gas into a condensed phase [15]. The magnetic shielding tensor of the studied compounds has been determined using DFT at B3LYP methods and standard 6-31+G(d,p) basis set using the standard GIAO approach (Table 2).

Table 2. Experimental, theoretical chemical shifts and calculated ^{1}H shielding with B3LYP/6-31+G(d,p)/ GIAO approach for azomethine proton of studied molecules.

Compounds	Chemical shielding azomethine proton		^{1}H Chemical shift	
	Isotropic	Anisotropic	Experimental	Calculated
1	23.1259	7.6718	8.63	8.86
2	22.3670	10.9716	9.07	9.03
3	24.4444	5.4940	7.75	7.68
4	23.8280	8.6557	8.41	8.33
5	22.8982	10.7818	9.10	8.98
6	24.2332	11.7370	8.16	8.32

4. Conclusions

We have synthesized and characterized six carbothioamide derivatives (2-(4-methoxybenziylidene)-*N*-phenylhydrazine-1-carbothioamide, 2-(anthracen-9-ylmthylene)-*N*-phenylhydrazinecarbothioamide, *N*-phenyl-2-(3-phenylallylidene)hydrazine-1-carbothioamide, 2-((1*H*-indol-3-yl)methylene)-*N*-phenylhydrazine-1-carbothioamide, 2-(naphthalene-1-ylmethylene)-*N*-phenylhydrazine carbothioamide and 2-(2-hydroxy-3-methoxybenzylidene)-*N*-phenyl hydrazine-1-carbothioamide). The prepared compounds primarily investigated by performing density functional theory calculations. The theoretical ^{1}H NMR chemical shift results of the studied compounds have been calculated at B3LYP methods and standard 6-31+G(d,p) basis set using the standard Gauge-Independent Atomic Orbital approach. The calculated values are also compared with the experimental data available for these molecules. A good linear relationship between the experimental and calculated data has been obtained.

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Disclosure statement

Conflict of interests: The author declares that she has no conflict of interest.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

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