Facile and Convenient Synthesis of N'^1,N'^3-Dialkyl-N'^1,N'^3-bis(arylcarbonothioyl)malonohydrazides via Propylphosphonic Anhydride Coupling

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Dedicated to Professor Chengye Yuan and Professor Li-Xin Dai of the Shanghai Institute of Organic Chemistry (CAS) on the occasion of their 90th birthdays

Abstract: A facile and convenient synthetic method for the anticancer agent elesclomol and its analogues, N'^1,N'^3-dialkyl-N'^1,N'^3-bis(arylcarbonothioyl)malonohydrazides, by the direct coupling of *N*-alkyl-*N*-(substituted)benzothiohydrazides and substituted malonic acids using propylphosphonic anhydride (T3P®) under very mild conditions has been developed.

Key words: propylphosphonic anhydride, elesclomol, analogues, synthesis, anticancer agents

Discovered by serendipity screening and medicinal chemistry optimization,[1] elesclomol [STA-4783, N'^1,N'^3-dimethyl-N'^1,N'^3-bis(phenylcarbonothioyl)malonohydrazide] is an anticancer drug that has received both fast track and orphan drug status from the U.S. FDA and has been evaluated in various stages of clinical trials together with Taxol® in humans for the treatment of metastatic melanoma or other refractory solid tumors.[2–5] Potent anticancer activities against a broad range of cancer cell lines including multidrug resistant (MDR) cell lines have also been demonstrated for elesclomol and its derivatives, N'^1,N'^3-dialkyl-N'^1,N'^3-bis(arylcarbonothioyl)malonohydrazides.[2,3,6a] Previously, we first reported the synthesis of elesclomol and its derivatives via the cyclization of malonyl hydrazide in perchloric acid followed by thionation with sodium sulfide then acidic hydrolysis or, alternatively, by the *N*,*N*′-dicyclohexylcarbodiimide-mediated coupling of malonic acid with α-thioacylhydrazides.[6] In order to avoid the use of explosive perchloric acid and the well-known drawbacks associated with *N*,*N*′-dicyclohexylcarbodiimide coupling, recently we also developed a method using malonyl chloride for the synthesis of elesclomol and its copper(II) complex that was plausible for the current good manufacturing practice.[7] However, the limited scope and the fact that malonyl chloride has to be freshly distilled in order to obtain a satisfactory yield of elesclomol are the undesirable aspects of this approach and limit its general application for the synthesis of elesclomol derivatives. In addition to that, this procedure also requires very low temperature (–20 °C or below) in order to avoid formation of inseparable byproducts and to achieve satisfactory yields. Herein, we wish to report a very facile and convenient synthetic procedure for this type of anticancer agent by using propylphosphonic anhydride (T3P®) as a coupling reagent. Since its first introduction by Wissmann and Kleiner in 1980, T3P® has become a more and more versatile reagent for the formation of C–N and C–O bonds, and other synthetic applications, due to its low toxicity and potential to minimize epimerization and facilitate product purification.[8] Besides peptide C–N bond formation, T3P® has also been widely used for the syntheses of various types of heterocyclic compounds, such as cyclic phosphinic acids,[9] pyrazolones,[10] tetrahydro-β-carbolines,[11] Weinreb amides,[12] imidazo[1,2-*a*]pyridines,[13] 4-thiazolidinones,[14] thienopyrimidines,[15] coumarins,[16] and benzothiazoles,[17] as well as for the Fischer indolization of arylhydrazines.[18] However, to the best of our knowledge, there is no precedence reporting the use of T3P® for the synthesis of malonic thiohydrazides via the direct coupling of malonic acid with a thiohydrazide. As demonstrated in Table 1, by employing this benign coupling reagent, a variety of elesclomol derivatives can be synthesized in moderate to high yields under very mild conditions by simply mixing a thiohydrazide **1**, a substituted malonic acid **2**, and T3P® with a base **3** in *N*,*N*-dimethylformamide at room temperature.

For the selection of base **3**, besides Hünig's base (*N*,*N*-diisopropylethylamine, DIPEA), some inorganic bases such as sodium carbonate and potassium carbonate were also screened but lower yields resulted. Comparable yields were achieved when triethylamine was used as the base (Table 1, entries 2, 11, 14, and 15). When coupling with malonic acid (**2a**), *N*-methyl-substituted phenylhydrazide **1a** afforded the highest yield (81%; Table 1, entry 1). Sterically more hindered thiohydrazides such as the ethyl **1b**, *n*-propyl **1d**, and *n*-butyl **1e** derivatives resulted in lower yields (Table 1, entries 4–6; 59%, 53%, and 51% yield, respectively). Besides malonic acid, methyl-, ethyl-, isopropyl-, and *n*-butylmalonic acid can also couple with thiohydrazides in a similar manner to provide the products in comparable yields (Table 1, entries 2, 3, and 13–18). Electron-rich arylhydrazides (Table 1, entries 8, 12, and 17) usually afforded better yields than the electron-deficient counterparts (Table 1, entries 9, 10, and 18). In addition to arylhydrazides (R = Ar) as listed in Table 1, the

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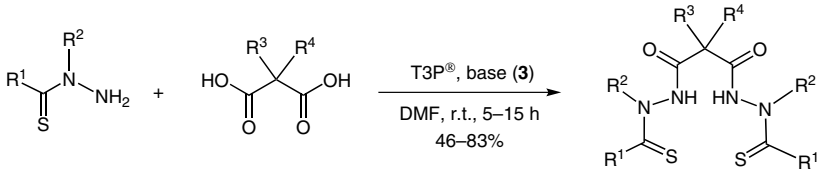
synthetic method can also be applied to the corresponding alkylhydrazides (R = alkyl). However, as we have reported previously,[6a] unlike the arylhydrazide counterparts, the corresponding products from alkylhydrazides are chemically labile which limits the potential therapeutic application of such derivatives.

Thus, elesclomol (**4a**) can be readily synthesized in high yield by simply mixing two equivalents of *N*-methylbenzothiohydrazide[19] (**1a**) and one equivalent of malonic acid (**2a**) with T3P® and *N*,*N*-diisopropylethylamine in *N*,*N*-dimethylformamide at room temperature (Table 1, entry 1). The desired product was readily precipitated out of the solution by pouring the reaction mixture into acidified ice–water and the pure product, N'^1,N'^3-dimethyl-N'^1,N'^3-bis(phenylcarbonothioyl)malonohydrazide (**4a**), was obtained conveniently by recrystallization from acetone–heptane or tetrahydrofuran–hexane. No silica gel column chromatography was needed. The proton NMR spectrum of compound **4a** (elesclomol) is complicated by the existance of tautomers, due to the presence of different forms of the compound that create hindered rotation around one of the nitrogen-containing bonds and result in slight inequivalence of the corresponding protons. These additional peaks were first thought to be due to impurities, but other purity tests (LC-MS, HPLC, and elemental analyses) did not indicate the presence of any impurity present at such a high level. Therefore, a variable temperature ^{1}H NMR experiment was conducted. Consequently, the ^{1}H NMR spectrum of elesclomol (40 mg/mL in DMSO-d_6) at 100 °C or higher shows the coalescence of the minor and major peaks for such corresponding protons present in the molecule.

Table 1 Synthesis of Elesclomol and Analogues via T3P® Coupling[a]



1 **2** **4**

Entry	Substrates	R	R^1	R^2	R^3	Product	Yield[b] (%)
1	**1a**, **2a**	Ph	Me	H	H	**4a**	81
2	**1b**, **2b**	Ph	Et	Me	H	**4b**	75[c]
3	**1c**, **2c**	Ph	Ph	Me	Me	**4c**	60
4	**1b**, **2a**	Ph	Et	H	H	**4d**	59
5	**1d**, **2a**	Ph	*n*-Pr	H	H	**4e**	53
6	**1e**, **2a**	Ph	*n*-Bu	H	H	**4f**	51
7	**1f**, **2a**	4-$N_3C_6H_4$	Me	H	H	**4g**	69
8	**1g**, **2a**	4-$MeOC_6H_4$	Me	H	H	**4h**	78
9	**1h**, **2a**	4-ClC_6H_4	Me	H	H	**4i**	60
10	**1i**, **2a**	4-NCC_6H_4	Me	H	H	**4j**	58
11	**1j**, **2a**	3-$Me_2NC_6H_4$	Me	H	H	**4k**	46[c]
12	**1k**, **2a**	2,5-$(MeO)_2C_6H_3$	Me	H	H	**4l**	75
13	**1a**, **2b**	Ph	Me	Me	H	**4m**	82
14	**1a**, **2d**	Ph	Me	Et	H	**4n**	74[c]
15	**1a**, **2e**	Ph	Me	*i*-Pr	H	**4o**	68[c]
16	**1a**, **2f**	Ph	Me	*n*-Bu	H	**4p**	51
17	**1l**, **2b**	2,3-$(MeO)_2C_6H_3$	Me	Me	H	**4q**	83
18	**1i**, **2b**	4-NCC_6H_4	Me	Me	H	**4r**	51

[a] DIPEA was used as the base, unless otherwise indicated.
[b] Isolated yield.
[c] Et_3N was used as the base.

In conclusion, a facile and very convenient synthetic method was developed for the novel anticancer agent elesclomol and its derivatives by employing T3P® as a coupling reagent. Moderate to high yields were obtained for a wide range of substituted malonic acids and thiohydrazides. The facile and environment-friendly reaction conditions and easy isolation of products makes the synthesis of a wide range of elesclomol analogues feasible for further biological evaluation and other mechanistic studies.

Melting points were obtained with a Mel-Temp II apparatus (Laboratory Devices, Inc., Holliston, MA, USA) or a TA Instruments Q100 DSC (with heating ramp 10.0 °C/min, nitrogen purge), and are uncorrected. ^{1}H NMR data were obtained with a Bruker instrument at 400 MHz using TMS as an internal standard; ^{13}C NMR data were recorded at 100 MHz. FTIR analysis was performed on a Perkin Elmer Spectrum 1000 FTIR spectrometer (Norwalk, CT, USA). HPLC analyses were performed on a Hewlett-Packard Series 1100 reversed-phase liquid chromatograph equipped with a UV detector (254 nm) and an Agilent Eclipse XDB-C18 (150 mm × 4.6 mm) 5-μm column. LC-MS data were acquired on a Finnigan LCQ LC-MS system (equipped with an Agilent Series 1100 HPLC). Microanalyses were conducted by Atlantic Microlab, Inc., Norcross, GA, USA. All reagents and solvents were commercially available with the highest possible purity supplied and were used without further purification, unless otherwise stated. *N*-Alkyl-substituted benzothiohydrazides **1** were prepared according to literature procedures.[6,19]

N'^1,N'^3-Dimethyl-N'^1,N'^3-bis(phenylcarbonothioyl)malonohydrazide (Elesclomol, 4a); Typical Procedure

To a stirred solution of malonic acid (**2a**; 1.04 g, 10 mmol) and *N*-methyl-*N*-thiobenzoylhydrazine[19] (**1a**; 3.32 g, 20 mmol) in DMF (25 mL) and DIPEA (10 mL) was added T3P® (50% solution in DMF, 12 mL, 20 mmol) slowly at r.t. The resultant red solution was stirred at r.t. for 12 h (monitored by LC-MS). With stirring, the reaction mixture was then poured into ice–H_2O (350 mL) containing 6 N HCl (20 mL). The resultant yellow solid was collected by filtration and dried in vacuo to provide **4a** as a yellow powder; yield: 3.25 g (81%). An analytically pure sample was obtained by recrystallization (acetone–heptane); mp 190–192 °C (Lit.[6a] 191–193 °C).

HPLC: t_R = 13.73 min (98.7% purity).

FTIR (KBr): 3205 (N–H stretching), 1688 (C=O stretching), 1297 (C–N stretching), 1247 (C=S stretching) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.6–3.0 (m, 2 H), 3.2–3.6 (m, 6 H), 7.2–7.5 (m, 10 H), 11.0–11.2 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 40.1, 43.1, 125.9, 127.4, 128.9, 141.7, 163.2, 202.5.

LC-MS: m/z = 400 [M]$^+$; t_R = 3.97 min.

Compounds **4b**–**4r** were prepared from the corresponding malonic acids and thiohydrazides in a similar manner as described for **4a**.

N'^1,N'^3-Diethyl-2-methyl-N'^1,N'^3-bis(phenylcarbonothioyl)malonohydrazide (4b)

Yellow solid; yield: 3.32 g (75%); mp 208–210 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.3 (d, J = 8.0 Hz, 3 H), 1.0–1.4 (m, 6 H), 2.5 (m, 1 H), 3.6–4.5 (m, 4 H), 7.1–7.5 (m, 10 H), 10.9 (br, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.5, 40.5, 48.6, 125.5, 127.2, 128.6, 142.1, 166.2, 195.0.

LC-MS: m/z = 443.2 [M + 1]$^+$; t_R = 4.23 min.

Anal. Calcd for $C_{22}H_{26}N_4O_2S_2$: C, 59.70; H, 5.92; N, 12.66. Found: C, 59.33; H, 6.15; N, 12.43.

2,2-Dimethyl-N'^1,N'^3-diphenyl-N'^1,N'^3-bis(phenylcarbonothioyl)malonohydrazide (4c)

Yellow solid; yield: 3.31 g (60%); mp 218–220 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.4–1.8 (m, 6 H), 6.8–7.6 (m, 20 H), 11.1–11.3 (m, 2 H).

LC-MS: m/z = 552.1 [M]$^+$; t_R = 4.6 min.

Anal. Calcd for $C_{31}H_{28}N_4O_2S_2$: C, 67.36; H, 5.11; N, 10.14. Found: C, 67.01; H, 5.36; N, 10.05.

N'^1,N'^3-Diethyl-N'^1,N'^3-bis(phenylcarbonothioyl)malonohydrazide (4d)

Yellow solid; yield: 2.52 g (59%); mp 183–185 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.0–1.4 (m, 6 H), 2.9–4.3 (m, 6 H), 7.1–7.5 (m, 10 H), 10.8–11.1 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.6, 48.7, 99.5, 125.7, 127.3, 128.8, 142.0, 163.0, 202.0.

LC-MS: m/z = 428 [M]$^+$; t_R = 4.15 min.

Anal. Calcd for $C_{21}H_{24}N_4O_2S_2$: C, 58.85; H, 5.64; N, 13.07. Found: C, 58.47; H, 5.39; N, 12.89.

N'^1,N'^3-Bis(phenylcarbonothioyl)-N'^1,N'^3-dipropylmalonohydrazide (4e)

Yellow solid; yield: 2.42 g (53%); mp 141–143 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.7–1.0 (m, 6 H), 1.5–1.8 (m, 4 H), 2.8–4.2 (m, 6 H), 7.2–7.5 (m, 10 H), 10.8–11.2 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 11.09, 18.65, 54.79, 125.62, 125.70, 127.79, 128.65, 142.07, 162.91, 202.67.

LC-MS: m/z = 456 [M]$^+$; t_R = 4.37 min.

Anal. Calcd for $C_{23}H_{28}N_4O_2S_2$: C, 60.50; H, 6.18; N, 12.27. Found: C, 60.21; H, 6.38; N, 12.05.

N'^1,N'^3-Dibutyl-N'^1,N'^3-bis(phenylcarbonothioyl)malonohydrazide (4f)

Yellow solid; yield: 2.47 g (51%); mp 146–148 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.6–1.0 (m, 6 H), 1.1–1.8 (m, 8 H), 2.8–4.3 (m, 6 H), 7.2–7.5 (m, 10 H), 10.9–11.2 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.6, 19.1, 23.8, 25.0, 52.8, 125.5, 127.2, 128.6, 141.9, 162.8, 202.6.

LC-MS: m/z = 484 [M]$^+$; t_R = 4.57 min.

Anal. Calcd for $C_{25}H_{32}N_4O_2S_2$: C, 61.95; H, 6.65; N, 11.56. Found: C, 61.54; H, 6.93; N, 11.38.

N'^1,N'^3-Bis[(4-azidophenyl)carbonothioyl]-N'^1,N'^3-dimethylmalonohydrazide (4g)

Yellow solid; yield: 3.33 g (69%); mp 173–175 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.6–3.7 (m, 8 H), 7.0–7.6 (m, 8 H), 11.0–11.3 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 39.2, 43.1, 118.1, 128.0, 138.3, 140.1, 163.2, 202.5.

LC-MS: m/z = 482 [M]$^+$; t_R = 4.25 min.

Anal. Calcd for $C_{19}H_{18}N_{10}O_2S_2$: C, 47.29; H, 3.76; N, 29.03. Found: C, 46.90; H, 3.97; N, 28.83.

N'^1,N'^3-Bis[(4-methoxyphenyl)carbonothioyl]-N'^1,N'^3-dimethylmalonohydrazide (4h)

Yellow solid; yield: 3.59 g (78%); mp 176–178 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.0–3.8 (m, 14 H), 6.7–7.4 (m, 8 H), 10.9–11.2 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 39.2, 41.5, 53.4, 110.4, 126.3, 131.7, 157.8, 161.2, 200.2.

LC-MS: m/z = 460 [M]$^+$; t_R = 4.02 min.

Anal. Calcd for $C_{21}H_{24}N_4O_4S_2$: C, 54.76; H, 5.25; N, 12.16. Found: C, 54.70; H, 5.33; N, 11.77.

N'^1,N'^3-Bis[(4-chlorophenyl)carbonothioyl]-N'^1,N'^3-dimethylmalonohydrazide (4i)
Yellow solid; yield: 2.81 g (60%); mp 194–196 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.6–3.6 (m, 8 H), 7.2–7.4 (m, 8 H), 11.0–11.3 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 39.3, 42.7, 127.4, 127.6, 133.4, 140.3, 163.1, 200.7.

LC-MS: m/z = 469.1 $[M + 1]^+$; t_R = 4.29 min.

Anal. Calcd for $C_{19}H_{18}Cl_2N_4O_2S_2$: C, 48.62; H, 3.87; Cl, 15.11; N, 11.94. Found: C, 48.23; H, 3.99; Cl, 15.03; N, 11.65.

N'^1,N'^3-Bis[(4-cyanophenyl)carbonothioyl]-N'^1,N'^3-dimethylmalonohydrazide (4j)
Yellow solid; yield: 2.61 g (58%); mp 146–148 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.6–4.0 (m, 8 H), 7.4–7.9 (m, 8 H), 11.1 (br, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 42.6, 111.1, 118.1, 126.2, 131.7, 145.7, 163.1, 200.1.

LC-MS: m/z = 450 $[M]^+$; t_R = 4.02 min.

Anal. Calcd for $C_{21}H_{18}N_6O_2S_2$: C, 55.98; H, 4.03; N, 18.65. Found: C, 55.59; H, 4.15; N, 18.37.

N'^1,N'^3-Bis{[3-(dimethylamino)phenyl]carbonothioyl}-N'^1,N'^3-dimethylmalonohydrazide (4k)
Isolated by silica gel chromatography eluting gradiently with a mixture of CH_2Cl_2–MeOH.

Red solid; yield: 2.24 g (46%); mp 119–121 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.6–3.0 (m, 12 H), 3.2–3.7 (m, 8 H), 6.5–6.7 (m, 6 H), 7.1–7.2 (m, 2 H), 10.9–11.1 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 39.7, 43.1, 109.4, 112.9, 113.9, 128.0, 142.4, 149.0, 163.4, 203.6.

LC-MS: m/z = 486.1 $[M]^+$; t_R = 3.65 min.

Anal. Calcd for $C_{23}H_{30}N_6O_2S_2$: C, 56.76; H, 6.21; N, 17.27. Found: C, 56.65; H, 6.18; N, 16.92.

N'^1,N'^3-Bis[(2,5-dimethoxyphenyl)carbonothioyl]-N'^1,N'^3-dimethylmalonohydrazide (4l)
Dark yellow solid; yield: 3.90 g (75%); mp 166–168 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.4–3.8 (m, 20 H), 6.8–8.0 (m, 6 H), 10.7–11.1 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 41.9, 55.1, 56.0, 96.6, 111.8, 113.1, 114.5, 115.2, 130.8, 131.7, 143.3, 146.9, 152.2, 153.1, 163.3, 199.3.

LC-MS: m/z = 520.1 $[M]^+$; t_R = 4.05 min.

Anal. Calcd for $C_{23}H_{28}N_4O_6S_2$: C, 53.06; H, 5.42; N, 10.76. Found: C, 53.45; H, 5.14; N, 10.37.

N'^1,N'^3,2-Trimethyl-N'^1,N'^3-bis(phenylcarbonothioyl)malonohydrazide (4m)
Yellow solid; yield: 3.40 g (82%); mp 213–214 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.4 (d, J = 8.0 Hz, 3 H), 2.6–2.7 (m, 1 H), 3.1–4.7 (m, 6 H), 7.2–7.5 (m, 10 H), 10.9–11.0 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 12.9, 42.6, 125.5, 127.2, 128.6, 141.6, 166.4, 202.8.

LC-MS: m/z = 414.1 $[M]^+$; t_R = 4.07 min.

Anal. Calcd for $C_{20}H_{22}N_4O_2S_2$: C, 57.95; H, 5.35; N, 13.52. Found: C, 58.02; H, 5.25; N, 13.46.

2-Ethyl-N'^1,N'^3-dimethyl-N'^1,N'^3-bis(phenylcarbonothioyl)malonohydrazide (4n)
Yellow solid; yield: 3.17 g (74%); mp 190–192 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.1–1.8 (m, 5 H), 2.9–3.6 (m, 7 H), 7.2–7.4 (m, 10 H), 10.96 (s, 2 H).

LC-MS: m/z = 428 $[M]^+$; t_R = 4.15 min.

Anal. Calcd for $C_{21}H_{24}N_4O_2S_2$: C, 58.85; H, 5.64; N, 13.07. Found: C, 58.81; H, 5.53; N, 13.02.

2-Isopropyl-N'^1,N'^3-dimethyl-N'^1,N'^3-bis(phenylcarbonothioyl)malonohydrazide (4o)
Yellow solid; yield: 3.01 g (68%); mp 208–210 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.1–1.7 (m, 7 H), 2.3–3.6 (m, 7 H), 7.2–7.4 (m, 10 H), 10.96 (s, 2 H).

LC-MS: m/z = 442 $[M]^+$; t_R = 4.22 min.

Anal. Calcd for $C_{22}H_{26}N_4O_2S_2$: C, 59.70; H, 5.92; N, 12.66. Found: C, 59.57; H, 5.72; N, 12.57.

2-Butyl-N'^1,N'^3-dimethyl-N'^1,N'^3-bis(phenylcarbonothioyl)malonohydrazide (4p)
Yellow solid; yield: 2.33 g (51%); mp 181–183 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.3–1.6 (m, 9 H), 3.2–3.6 (m, 7 H), 7.2–7.3 (m, 10 H), 10.96 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 11.9, 22.6, 26.4, 31.8, 40.9, 45.9, 124.3, 125.4, 127.1, 140.4, 164.1, 202.3.

LC-MS: m/z = 456.1 $[M]^+$; t_R = 4.33 min.

Anal. Calcd for $C_{23}H_{28}N_4O_2S_2$: C, 60.50; H, 6.18; N, 12.27. Found: C, 60.13; H, 6.39; N, 12.02.

N'^1,N'^3-Bis[(2,3-dimethoxyphenyl)carbonothioyl]-N'^1,N'^3,2-trimethylmalonohydrazide (4q)
Dark yellow solid; yield: 4.44 g (83%); mp 178–180 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.3–1.7 (m, 3 H), 2.5–2.6 (m, 1 H), 3.0–3.8 (m, 18 H), 6.5–7.1 (m, 6 H), 10.3–11.1 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 12.9, 55.4, 59.8, 112.4, 117.7, 123.2, 136.7, 141.9, 151.7. 167.1, 199.1.

LC-MS: m/z = 534.7 $[M]^+$; t_R = 4.18 min.

Anal. Calcd for $C_{24}H_{30}N_4O_6S_2$: C, 53.92; H, 5.66; N, 10.48. Found: C, 53.57; H, 5.94; N, 10.28.

N'^1,N'^3-Bis[(4-cyanophenyl)carbonothioyl]-N'^1,N'^3,2-trimethylmalonohydrazide (4r)
Dark yellow solid; yield: 2.37 g (51%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.4–0.95 (m, 3 H), 2.6–2.8 (m, 1 H), 3.2–3.6 (m, 6 H), 7.3–7.9 (m, 8 H), 11.0 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 12.9, 42.4, 110.8, 118.4, 126.2, 131.5, 145.7, 166.4, 200.1.

LC-MS: m/z = 464.1 $[M]^+$; t_R = 4.07 min.

Anal. Calcd for $C_{22}H_{20}N_6O_2S_2 \cdot 0.45H_2O$: C, 55.90; H, 4.46; N, 17.78. Found: C, 56.12; H, 4.42; N, 17.82.

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