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# Facile one-pot synthesis of 4-substituted semicarbazides†

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A diverse library of twenty-five 4-mono- and disubstituted semicarbazides was prepared in a one-pot two-step approach. The method includes formation of a carbamate from bis(2,2,2-trifluoroethyl)carbonate or 2,2,2-trifluoroethylchloroformate and a primary or secondary amine and subsequent interaction of the carbamate with hydrazine to result in a semicarbazide. The approach allowed to obtain 4-substituted semicarbazides on a large scale in good yield and high purity.

## Introduction

A semicarbazide motif is widespread in agrochemistry, drug discovery, and organic synthesis (Fig. 1).[1–5]

Methods for obtaining 4-substituted semicarbazides, common building blocks to introduce the semicarbazide motif into molecules, include reactions of hydrazine with (a) isocyanates, (b) N-substituted carbamoyl chlorides, and (c) carbamates (Scheme 1).[6–26]

Several disadvantages, however, can be noted for the existing synthetic approaches. Isocyanates are toxic and available with limited number of substituents (less than 300 substances are listed in *eMolecules* database), which decreases diversity of the semicarbazide motifs. N-substituted carbamoyl chlorides are effective reagents for the synthesis of 4-substituted semicarbazides; but they are derived from phosgene or triphosgene that are toxic, inconvenient in handling, and may result in side products in the reactions with functionalized amines. Commonly utilized ethyl, phenyl and *p*-nitrophenyl carbamates or "blocked isocyanates"[27,28] that are synthesized from the corresponding carbonates or chloroformates provide a facile approach to diverse semicarbazides.

Reactivity of the carbamate is related to a p$K_a$ value of the released alcohol:[29] ethyl carbamates (p$K_a$(ethanol) ≈ 16) poorly react with hydrazine resulting in longer time of the reaction; phenyl and *p*-nitrophenyl carbamates (p$K_a$(phenol) ≈ 10, p$K_a$(*p*-nitrophenol) ≈ 7) are very reactive substrates and can easily form symmetrical ureas with active amines during the synthesis of the carbamate, which complicates a one-pot transformation of the carbonate to 4-substituted semicarbazide.

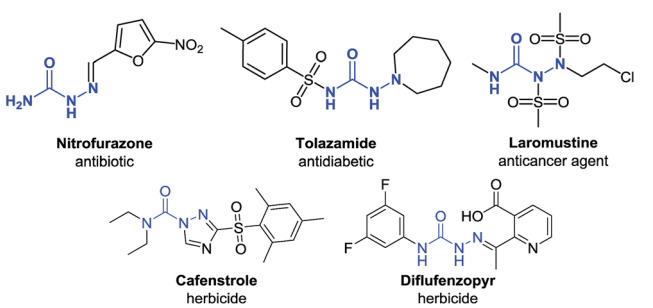
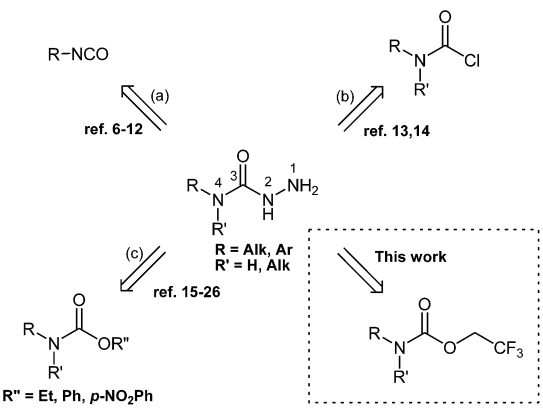



Fig. 1 Drugs and agrochemicals bearing the semicarbazide motif.[4,5]




Scheme 1 Synthetic approaches to 4-substituted semicarbazides.[6–26]

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† Electronic supplementary information (ESI) available: $^1$H and $^{13}$C NMR spectra of the synthesized compounds. See DOI: 10.1039/c4ra12425a

Recently we have successfully employed bis(2,2,2-trifluoroethyl)carbonate (**1**) and 2,2,2-trifluoroethyl-chloroformate (**2**) in the one-pot synthesis of unsymmetrical ureas[30,31] (Scheme 2), where a preformed carbamate **3** interacted with a primary or secondary alkyl amine to produce a di- or trisubstituted urea **4**, respectively. The moderate reactivity of the 2,2,2-trifluoroethyl carbamates (p$K_a$(2,2,2-trifluoroethanol) $\approx$ 12) compared with the ethyl and the phenyl carbamates prevented formation of symmetrical ureas during the carbamate synthesis and allowed for rapid interaction of the carbamate with the nucleophile resulting in a desirable product and a volatile and easily separable by-product, 2,2,2-trifluoroethanol.

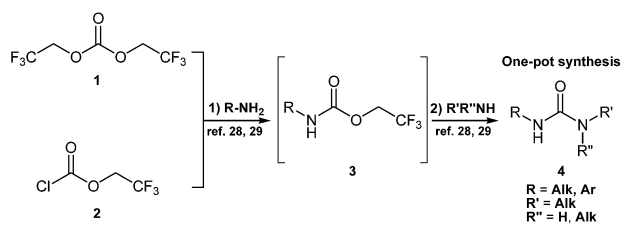
Herein, we present our results on utilization of this strategy for a one-pot synthesis of 4-substituted semicarbazides.

## Results and discussion

To test our approach, we decided to synthesize on a large scale a diverse library of 4-substituted semicarbizides utilizing 25 amines: alkyl and aryl, primary and secondary, simple and functionalized (Table 1). The approach consists of two steps: (1) *in situ* preparation of the carbamate and (2) the subsequent interaction of the carbamate with hydrazine (Scheme 3). We found that bis(2,2,2-trifluoroethyl)carbonate (**1**) smoothly reacted with alkyl amines in the presence of a base at room temperature producing carbamates **3** but showed no reactivity with less nucleophilic aryl amines. More active 2,2,2-trifluoroethylchloroformate (**2**), however, formed the carbamates under similar conditions with aryl amines. Reagents **1** and **2** can be synthesized simultaneously in the same reaction between triphosgene and 2,2,2-trifluoroethanol[31] which makes them available for both types of amines.

In the first step, reagent **1** or **2** was mixed with an alkyl or aryl amine in dichloromethane at 0 °C in the presence of triethylamine. Continuous stirring of the reaction mixture for 3 or 6 hours (for aryl or alkyl amines, respectively) at room temperature gave carbamates **3** in high purity according to the $^1$H NMR of the crude material. After removing the solvent under vacuum, by-product 2,2,2-trifluoroethanol, and unreacted **1** or **2**, an alcohol solution of hydrazine hydrate was added to the crude carbamate and the resulting mixture was heated at reflux for 1.5 hours.

Our results indicated that the higher nucleophilicity of hydrazine compared with amines allowed for a direct interaction with the carbamates in cases where a transient isocyanate




Scheme 2 One-pot synthesis of unsymmetrical ureas from reagents **1** and **2**.[30,31]

Table 1 Synthesized 4-substituted semicarbazides

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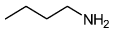
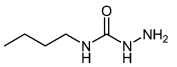
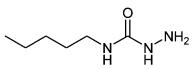
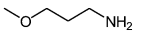
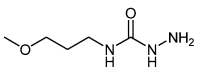
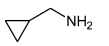
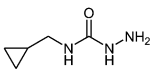
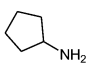
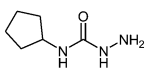
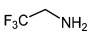
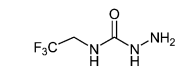
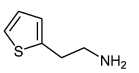
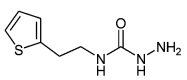
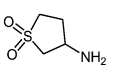
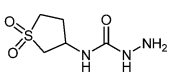
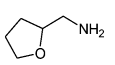
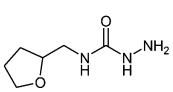
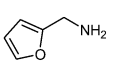
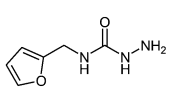
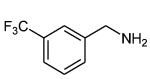
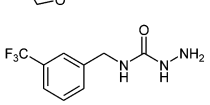
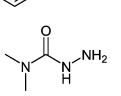
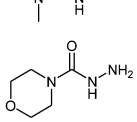
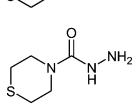
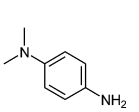
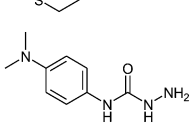
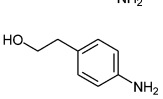
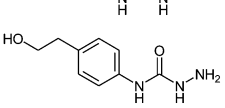
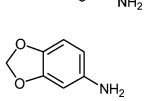
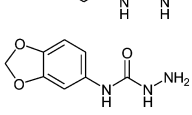
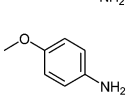
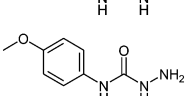
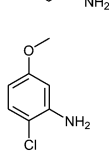
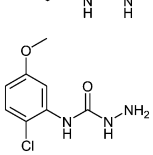
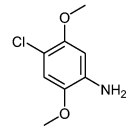
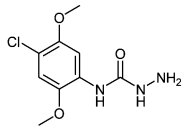
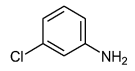
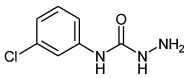
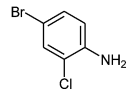
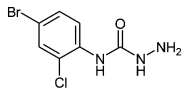
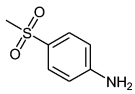
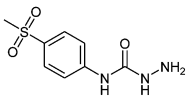
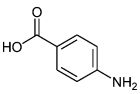
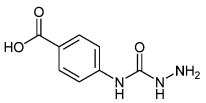
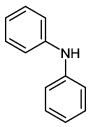
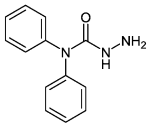
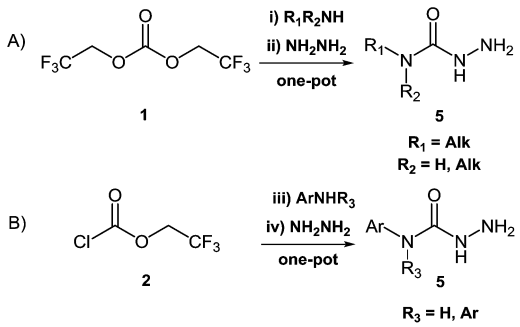
| **5.1** |  |  | 85 |
| **5.2** |  |  | 83 |
| **5.3** |  |  | 81 |
| **5.4** |  |  | 87 |
| **5.5** |  |  | 90 |
| **5.6** |  |  | 73 |
| **5.7** |  |  | 74 |
| **5.8** |  |  | 86 |
| **5.9** |  |  | 78 |
| **5.10** |  |  | 72 |
| **5.11** |  |  | 80 |
| **5.12** |  |  | 49 |
| **5.13** |  |  | 38 |
| **5.14** |  |  | 35 |
| **5.15** |  |  | 57 |
| **5.16** |  |  | 53 |
| **5.17** |  |  | 50 |
| **5.18** |  |  | 55 |
| **5.19** |  |  | 51 |

Table 1 (*Contd.*)

| | Amine | Semicarbazide | Yield[a] (%) |
|---|---|---|---|
| **5.20** |  |  | 50 |
| **5.21** |  |  | 52 |
| **5.22** |  |  | 55 |
| **5.23** |  |  | 52 |
| **5.24** |  |  | 55 |
| **5.25** |  |  | 39 |

[a] Isolated yield in respect to the quantity of the starting amine.




Scheme 3 One-pot synthesis of 4-substituted semicarbizides. Reagents and conditions: (A) (i) alkyl amine, triethylamine, stirring at room temperature for 6 hours; (ii) hydrazine hydrate, heating under reflux for 1–2 hours; (B) (iii) aryl amine, triethylamine, stirring at room temperature for 3 hours; (iv) hydrazine hydrate, heating under reflux for 1–2 hours.

can't be formed[32,33] which resulted in 4-disubstituted semicarbazides **5.12–5.14** and **5.25** (Table 1). In the reaction between disubstituted carbamate and hydrazine, however, secondary amine, a better leaving group than a primary amine, can be easily substituted with hydrazine under reaction conditions to produce carbohydrazide. Therefore, we monitored the progress of the reaction using $^1$H NMR to decrease the formation of this side product.

The synthesized semicarbazides typically precipitated out from the solution and were easily separated by filtration. The products were obtained in moderate to high yields; the identity and purity of them were confirmed by means of $^1$H, $^{13}$C NMR spectroscopy and LC-MS analysis. The yields for 4-disubstituted semicarbazides were generally lower than those for the monosubstituted analogs. $^1$H NMR spectra of the compounds recorded in DMSO-$d_6$ contained characteristic broad peaks for NH groups (in most cases three for **5.1–5.11** and **5.15–5.24** and two for **5.12–5.14** and **5.25**) and one set of signals for each alkyl or aryl group.

The experimental results showed advantages of reagents **1** and **2** over the commonly used reagents. The synthesized semicarbazides were obtained as solids except for compound **5.3** in high purity with no need for further purification. Semicarbazide **5.17** derived from 3,4-(methylenedioxy)aniline was obtained in good yield utilizing the above procedure, but the experiment with phenyl chloroformate failed because substantial amount of the symmetrical urea formed. Additional functionalities (hydroxyl in **5.16** and carboxylic in **5.24**) were tolerated under the reaction conditions.

## Conclusions

We employed bis(2,2,2-trifluoroethyl) carbonate (**1**) and 2,2,2-trifluoroethyl chloroformate (**2**) in a facile one-pot synthesis of twenty five 4- mono and disubstituted semicarbazides. The approach allows to prepare the semicarbazides derived from alkyl and aryl amines in moderate to good yields and high purity. The developed approach makes possible to generate diverse 4-substituted semicarbazides under conditions of parallel synthesis, which would expand availability of the compounds with the semicarbazide structural motif.

## Experimental

### Materials and methods

All amines and solvents were obtained from commercially available sources (Aldrich, Enamine Ltd.) and used without further purification. Bis(2,2,2-trifluoroethyl)carbonate and 2,2,2-trifluoroethyl chloroformate were prepared as previously described.[31] IR spectra were recorded on Perkin-Elmer Spectrum BX II. NMR spectra were acquired on Bruker Avance DRX 500 spectrometer using $CDCl_3$ or DMSO-$d_6$ as a solvent and tetramethylsilane (TMS) as an internal standard. Melting points were determined on a Buchi melting point apparatus and are uncorrected. LC-MS data were obtained on Agilent 1100 HPLC equipped with diode-matrix and mass-selective detector Agilent LC/MSD SL. According to the LC-MS data all the synthesized compounds have purity over 95%. Elemental analysis was done on a Vario MICRO Cube (Elementar) Elemental Micro-Analyzer.

### General procedure for the one-pot synthesis of 4-substituted alkyl (method A) and aryl (method B) semicarbazides (5)

To a chilled stirred solution of an amine (0.1 mol) and triethylamine (0.11 mol, method A, 0.2 mol, method B) in

dichloromethane (70 mL) was added dropwise 0.11 mol of bis(2,2,2-trifluoroethyl)carbonate (**1**) (method A) or 2,2,2-trifluoroethyl chloroformate (**2**) (method B). Care was taken to maintain temperature below 0 °C during the addition. The obtained mixture was stirred for 3 hours (6 hours in case of method B) at room temperature; then, the solvent, triethylamine and unreacted **1** or **2** were removed under reduced pressure. To a solution of the crude carbamate **3** in ethanol (100 mL) hydrazine hydrate (0.5 mol, method A and 0.75 mol, method B) was added. The reaction mixture was heated under reflux for approximately 1.5 hours. For carbamates **5.12–5.14** and **5.25**, derived from secondary amines, the reaction was monitored by $^1$H NMR to prevent formation of the symmetrical side product, carbonohydrazide. Most semicarbazides precipitated out upon cooling down the solution to room temperature. In other cases, the solvent was evaporated under reduced pressure and the remained crude product **5** was treated with diethyl ether to form solid or viscous oil (**5.3**). The product was separated by filtration and dried in vacuum.

**4-Butyl semicarbazide (5.1).** Yield: 11.2 g, 85%, white solid, Mp 45–47 °C. IR (KBr): 3500, 3358, 3338, 3316, 3215 (NH), 2963, 2932, 2873, 2861, 2852 (CH), 1662 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 0.87$ (t, $^3J = 7.2$ Hz, 3H, $CH_3$), 1.27 (m, 2H, $CH_2$), 1.36 (m, 2H, $CH_2$), 3.02 (q, $^3J = 6.5$ Hz, 2H, $NCH_2$), 4.07 (br. s, 2H, $NH_2$), 6.29 (br. s, 1H, NH), 6.90 (s, 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta = 14.2$, 20.0, 32.7, 39.0, 160.8 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_5H_{14}N_3O$ 132.1, found 132.2. Anal. calcd for $C_5H_{13}N_3O$: C, 45.78; H, 9.99; N, 32.03; found C, 45.69; H, 10.08; N, 31.95%.

**4-Penthyl semicarbazide (5.2).** Yield: 12 g, 83%, white solid, Mp 66–68 °C. IR (KBr): 3395, 3293, 3220 (NH), 2955, 2930, 2872, 2860 (CH), 1663 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 0.87$ (t, $^3J = 7.2$ Hz, $CH_3$), 1.27 (m, 4H, $CH_2$), 1.39 (m, 2H, $CH_2$), 3.01 (q, $^3J = 6.7$ Hz, $CH_2$), 4.05 (br. s, 2H, $NH_2$), 6.28 (br. s, 1H, NH), 6.85 (s, 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta = 14.4$, 22.4, 29.1, 30.3, 39.3, 160.7 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_6H_{16}N_3O$ 146.1, found 146.1. Anal. calcd for $C_6H_{15}N_3O$: C, 49.63; H, 10.41; N, 28.94; found C, 49.57; H, 10.50; N, 28.83%.

**4-(3-Methoxypropyl)semicarbazide (5.3).** Yield: 11.9 g, 81%, colorless viscous oil. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 1.62$ (m, 2H, $CH_2$), 3.07 (q, $^3J = 6.5$ Hz, 2H, $CH_2$), 3.22 (s, 3H, $OCH_3$), 3.33 (t, $^3J = 6.2$ Hz, 2H, $CH_2$), 3.99 (br. s, 2H, $NH_2$), 6.37 (br. s, 1H, NH), 6.91 (s, 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta =$ 30.6, 36.9, 58.4, 70.5, 160.8 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_5H_{14}N_3O_2$ 148.1, found 148.2%.

**4-(*C*-Cyclopropyl-methyl)semicarbazide (5.4).** Yield: 11.2 g, 87%, whitish solid, Mp 54–56 °C. IR (KBr): 3370, 3353, 3326, 3298 (NH), 3005, 2972, 2929, 2874 (CH), 1660 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 0.15$ (m, 2H, $CH_2$), 0.38 (m, 2H, $CH_2$), 0.91 (m, 1H, CH), 2.91 (t, $^3J = 6.2$ Hz, 2H, $CH_2$), 4.10 (br. s, 2H, $NH_2$), 6.36 (br. s, 1H, NH), 6.90 (s, 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta = 3.1$, 11.7, 43.4, 160.3 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_5H_{12}N_3O$ 130.1, found 130.2. Anal. calcd for $C_5H_{11}N_3O$: C, 46.50; H, 8.58; N, 32.53; found C, 46.47; H, 8.63; N, 32.48%.

**4-(Cyclopenthyl)semicarbazide (5.5).** Yield: 12.9 g, 90%, white solid, Mp 123–125 °C. IR (KBr): 3373, 3306, 3299 (NH), 2958, 2869 (CH), 1631 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 1.33$ (m, 2H, $CH_2$), 1.50 (m, 2H, $CH_2$), 1.61 (m, 2H, $CH_2$), 1.78 (m, 2H, $CH_2$), 3.87 (m, 1H, CH), 4.05 (br. s, 2H, $NH_2$), 6.12 (m, 1H, NH), 6.82 (s, 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta =$ 23.3, 33.0, 50.7, 160.0 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_6H_{14}N_3O$ 144.1, found 144.2. Anal. calcd for $C_6H_{13}N_3O$: C, 50.33; H, 9.15; N, 29.35; found C, 50.30; H, 9.21; N, 29.32%.

**4-(2,2,2-Trifluoroethyl)semicarbazide (5.6).** Yield: 11.5 g, 73%, whitish solid, Mp 72–74 °C. IR (KBr): 3366, 3311, 3230 (NH), 3007, 2974, 2925 (CH), 1630 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta =$ 3.80 (m, 2H, $CH_2$), 4.22 (br. s, 2H, $NH_2$), 6.90 (s, 1H, NH), 7.36 (s, 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta =$ 40.8 (q, $^2J_{C,F} = 34$ Hz), 125.7 (q, $^1J_{C,F} = 279$ Hz), 160.0 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_3H_7F_3N_3O$ 158.1, found 158.1. Anal. calcd for $C_3H_6F_3N_3O$: C, 22.94; H, 3.85; N, 26.75; found C, 22.90; H, 3.90; N, 26.73%.

**4-(2-Thiophen-2yl-ethyl)semicarbazide (5.7).** Yield: 13.7 g, 74%, yellowish solid, Mp 90–92 °C. IR (KBr): 3379, 3355, 3243 (NH), 3071, 2969, 2933, 2860 (CH), 1648 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 2.92$ (t, $^3J = 7.2$ Hz, 2H, $CH_2$), 3.29 (q, $^3J = 7.0$ Hz, 2H, $CH_2$), 4.09 (s, 2H, $NH_2$), 6.49 (s, 1H, NH), 6.88 (m, 1H, Het), 6.96 (m, 1H, Het), 7.00 (s, 1H, NH), 7.33 (m, 1H, Het) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta =$ 30.9, 41.2, 124.3, 125.5, 127.4, 142.4, 160.6 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_7H_{12}N_3OS$ 186.1, found 186.3. Anal. calcd for $C_7H_{11}N_3OS$: C, 45.39; H, 5.99; N, 22.68; found C, 45.37; H, 6.05; N, 22.64%.

**4-(1,1-Dioxo-tetrahydro-1λ$^6$-thiophen-3-yl)semicarbazide (5.8).** Yield: 16.6 g, 86%, yellowish solid, Mp 167–168 °C. IR (KBr): 3363, 3343, 3295, 3234 (NH), 3007, 2947 (CH), 1666 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 2.11$ (m, 1H, $CH_2$), 2.31 (m, 1H, $CH_2$), 3.02 (m, 1H, $CH_2$), 3.12 (m, 1H, $CH_2$), 3.27 (m, 2H, $CH_2$), 4.14 (s, 2H, $NH_2$), 4.38 (m, 1H, CH), 6.79 (br. s, 1H, NH), 7.18 (s, 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta =$ 29.7, 46.8, 51.4, 56.0, 159.9 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_5H_{12}N_3O_3S$ 194.1, found 194.2. Anal. calcd for $C_5H_{11}N_3O_3S$: C, 31.08; H, 5.74; N, 21.75; found C, 31.05; H, 5.78; N, 21.72%.

**4-(*C*-(Tetrahydro-furan-2-yl)-methyl)semicarbazide (5.9).** Yield: 12.4 g, 78%, yellowish solid, Mp 80–81 °C. IR (KBr): 3309, 3226, 3090 (NH), 2943, 2871 (CH), 1662 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 1.49$ (m, 1H, $CH_2$), 1.83 (m, 3H, $CH_2$), 3.03 (m, 1H, $CH_2$), 3.17 (m, 1H, $CH_2$), 3.60 (m, 1H, $CH_2$), 3.80 (m, 2H, CH + $CH_2$), 4.1 (br. s, 2H, $NH_2$), 6.32 (s, 1H, NH), 6.97 (s, 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta =$ 25.8, 28.7, 43.4, 67.6, 78.3, 160.7 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_6H_{14}N_3O_2$ 160.1, found 160.2. Anal. calcd for $C_6H_{13}N_3O_2$: C, 45.27; H, 8.23; N, 26.40; found C, 45.23; H, 8.30; N, 26.38%.

**4-(*C*-Furan-2-yl-methyl)semicarbazide (5.10).** Yield: 11.2 g; 72%, yellowish solid, Mp 88–89 °C. IR (KBr): 3403, 3338, 3217, 3137 (NH), 3082, 2951, 2930 (CH), 1663 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 4.14$ (s, 2H, $NH_2$), 4.23 (d, $^3J = 6.0$ Hz, 2H, $CH_2$), 6.19 (m, 1H, Het), 6.37 (m, 1H, Het), 7.01 (m, 1H, NH),

7.09 (m, 1H, NH), 7.55 (s, 1H, Het) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ = 36.5, 106.6, 110.8, 142.2, 154.2, 160.4 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_6H_{10}N_3O_2$ 156.1, found 156.2. Anal. calcd for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08; found C, 46.41; H, 5.90; N, 27.05%.

**4-(3-Trifluoromethyl-benzyl)semicarbazide (5.11).** Yield: 18.6 g, 80%, whitish solid, Mp 87–90 °C. IR (KBr): 3395, 3364, 3325, 3244 (NH), 3079, 2957, 2928 (CH), 1668 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 4.20 (br. s, 2H, $NH_2$), 4.33 (d, $^3J$ = 6.1 Hz, 2H, $CH_2$), 7.07 (s, 1H, NH), 7.15 (s, 1H, NH), 7.57 (m, 4H, Ar) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ = 42.6, 123.6 (q, $^3J_{C,F}$ = 4.6 Hz), 124.0 (q, $^3J_{C,F}$ = 4.2 Hz), 124.8 (q, $^1J_{C,F}$ = 272 Hz), 129.4 (q, $^2J_{C,F}$ = 33 Hz), 129.6, 131.7, 143.3, 160.8 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_9H_{11}F_3N_3O$ 234.1, found 234.2. Anal. calcd for $C_9H_{10}F_3N_3O$: C, 46.36; H, 4.32; N, 18.02; found C, 46.32; H, 4.40; N, 17.97%.

***N*,*N*-Dimethyl semicarbazide (5.12).** Yield: 5.1 g, 49%, white solid, Mp 86–88 °C. IR (KBr): 3424, 3338 (NH), 2936, 2886 (CH), 1641 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 2.85 (s, 6H, $2CH_3$), 3.80 (br. s, 2H, $NH_2$), 6.28 (br. s, 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ = 35.6, 160.3 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_3H_{10}N_3O$ 104.1, found 104.2. Anal. calcd for $C_3H_9N_3O$: C, 34.94; H, 8.80; N, 40.75; found C, 34.80; H, 8.92; N, 40.69%.

**Morpholine-4-carbohydrazide (5.13).** Yield: 5.5 g, 38%, yellowish solid, Mp 121–122 °C. IR (KBr): 3320, 3230 (NH), 2987, 2959, 2933, 2917, 2903, 2864 (CH), 1651 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 3.25 (m, 4H, $2CH_2$), 3.53 (m, 4H, $2CH_2$), 3.91 (br. s, 2H, $NH_2$), 7.71 (br. s, 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ = 44.2, 66.4, 160.4 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_5H_{12}N_3O_2$ 146.1, found 146.2. Anal. calcd for $C_5H_{12}N_3O_2$: C, 41.37; H, 7.64; N, 28.95; found C, 41.32; H, 7.72; N, 28.90%.

**Thiomorpholine-4-carbohydrazide (5.14).** Yield: 5.6 g, 35%, white solid, Mp 130–131 °C. IR (KBr): 3340, 3332, 3323, 3237 (NH), 2963, 2921, 2910, 2897 (CH), 1646 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 2.50 (m, 4H, $2CH_2$), 3.57 (m, 4H, $2H_2$), 3.92 (br. s, 2H, $NH_2$), 7.68 (s. 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ = 26.6, 46.7, 159.7 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_5H_{12}N_3OS$ 162.1, found 162.2. Anal. calcd for $C_5H_{11}N_3OS$: C, 37.25; H, 6.88; N, 26.06; found C, 37.21; H, 6.92; N, 26.03%.

**4-(4-Dimethylamino-phenyl)semicarbazide (5.15).** Yield: 11.1 g, 57%, beige solid, Mp 141–143 °C. IR (KBr): 3351, 3337, 3232 (NH), 3083, 3045, 2898, 2861 (CH), 1663 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 2.81 (s, 6H, $NMe_2$), 4.31 (br. s, 2H, $NH_2$), 6.66 (d, $^3J$ = 8.8 Hz, 2H, Ar), 7.21 (s, 1H, NH), 7.32 (d, $^3J$ = 8.7 Hz, 2H, Ar), 8.30 (s, 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ = 41.3, 113.6, 120.5, 130.5, 146.7, 158.2 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_9H_{15}N_4O$ 195.1, found 195.0. Anal. calcd for $C_9H_{14}N_4O$: elemental analysis: C, 55.65; H, 7.27; N, 28.85; found C, 55.60; H, 7.33; N, 28.80%.

**4-(4-(2-Hydroxy-ethyl)-phenyl)semicarbazide (5.16).** Yield: 11.4 g, 53%, white solid, Mp 149–150 °C. IR (KBr): 3364, 3320, 3247 (NH), 3095, 3040, 2945, 2927, 2883, 2858 (CH), 1668 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 2.66 (t, $J$ = 7.0 Hz, 2H, $CH_2$), 3.58 (t, $J$ = 6.5 Hz, 2H, $CH_2$), 4.35 (s, 2H, $NH_2$), 4.51 (s, 1H, OH), 7.08 (d, $^3J$ = 8.0 Hz, 2H, Ar), 7.35 (s, 1H, NH), 7.41 (d, $^3J$ = 8.2 Hz, 2H, Ar), 8.54 (s, 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ = 38.9, 62.9, 118.7, 129.4, 132.9, 138.3, 158.0 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_9H_{14}N_3O_2$ 196.1, found 196.2. Anal. calcd for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52; found C, 55.32; H, 6.80; N, 21.48%.

**4-(Benzo[1,3]dioxol-5-yl)semicarbazide (5.17).** Yield: 9.8 g, 50%, brown solid, Mp 163–165 °C. IR (KBr): 3357, 3334, 3222, 3177 (NH), 3088, 3006, 2937, 2909, 2893 (CH), 1681 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 4.33 (br. s, 2H, $NH_2$), 5.94 (s, 2H, $CH_2$), 6.78 (d, $^3J$ = 8.5 Hz, 1H, Ar), 6.88 (d, $^3J$ = 8 Hz, 1H, Ar), 7.28 (s, 1H, Ar), 7.34 (br. s, 1H, NH), 8.54 (s, 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ = 101.1, 101.3, 108.4, 111.3, 135.0, 142.1, 147.5, 158.0 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_8H_{10}N_3O_3$ 196.1, found 196.2. Anal. calcd for $C_8H_9N_3O_3$: C, 49.23; H, 4.65; N, 21.53; found C, 49.18; H, 4.74; N, 21.45.

***N*-(4-Methoxyphenyl)hydrazinecarboxamide (5.18).** Yield: 9.8 g, 55%, beige solid, Mp 146–148 °C. IR (KBr): 3363, 3356, 3311, 3259 (NH), 3156, 3090, 3036, 3005, 2975, 2835 (CH), 1680 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 3.70 (s, 3H, $OCH_3$), 4.32 (br. s, 2H, $NH_2$), 6.83 (d, $^3J$ = 7 Hz, 2H, Ar), 7.29 (s, 1H, NH), 7.42 (d, $^3J$ = 7 Hz, 2H, Ar), 8.46 (br. s, 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ = 55.6, 114.3, 120.4, 133.6, 154.7, 158.1 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_8H_{12}N_3O_2$ 182.1, found 182.2. Anal. calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19; found C, 52.94; H, 6.26; N, 23.04%.

***N*-(2-Chloro-5-methoxyphenyl)hydrazinecarboxamide (5.19).** Yield: 11.0 g, 51%, whitish solid, Mp 159–161 °C. IR (KBr): 3345, 3319, 3240 (NH), 3117, 3094, 3070, 3037, 2876 (CH), 1675 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 3.73 (s, 3H, $OCH_3$), 4.71 (br. s, 2H, $NH_2$), 6.57 (d, $^3J$ = 7.5 Hz, 1H, Ar), 7.32 (d, $^3J$ = 7.5 Hz, 1H, Ar), 7.92 (s, 1H, Ar), 8.01 (br. s, 1H, NH), 9.15 (br. s, 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ = 55.8, 105.2, 108.2, 112.7, 129.7, 137.3, 156.9, 159.0 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_9H_{13}ClN_3O_3$ 246.1, found 246.0. Anal. calcd for $C_9H_{12}ClN_3O_3$: C, 44.00; H, 4.92; N, 17.10; found C, 43.95; H, 5.05; N, 17.02%.

***N*-(4-Chloro-2,5-dimethoxyphenyl)hydrazinecarboxamide (5.20).** Yield: 12.3 g, 50%, whitish solid, Mp 168–170 °C. IR (KBr): 3347, 3304, 3275 (NH), 3110, 3001, 2963, 2936 (CH), 1688, 1652 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 3.77 (s, 3H, $OCH_3$), 3.83 (s, 3H, $OCH_3$), 4.60 (br. s, 2H, $NH_2$), 7.06 (s, 1H, Ar), 7.78 (s, 1H, NH), 8.16 (s, 1H, Ar), 8.95 (br. s, 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ = 56.8, 57.0, 103.3, 112.2, 112.9, 129.2, 142.0, 149.0, 157.2 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_8H_{11}ClN_3O_2$ 216.1, found 216.0. Anal. calcd for $C_8H_{10}ClN_3O_2$: C, 44.00; H, 4.92; N, 17.10; found C, 43.95; H, 5.05; N, 17.02%.

***N*-(3-Chlorophenyl)hydrazinecarboxamide (5.21).** Yield: 9.6 g, 52%, whitish solid, Mp 107–109 °C. IR (KBr): 3358, 3225 (NH), 3096, 2962, 2940, 2909, 2829 (CH), 1679 (C=O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 4.40 (br. s, 2H, $NH_2$), 6.95 (d, $^3J$ = 7.5 Hz, 1H, Ar), 7.24 (dd, $^3J$ = 7.5 Hz, $^3J$ = 5.5 Hz, 1H, Ar), 7.41 (d, $^3J$ = 5.5 Hz, 1H, Ar), 7.56 (br. s, 1H, NH), 7.81 (s, 1H, Ar), 8.85 (s, 1H, NH) ppm. $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ = 117.1, 118.0, 121.4, 130.6, 133.5, 142.1, 157.7 ppm. MS (APCI) $m/z$ $[M + H]^+$

calculated for $C_7H_8ClN_3O$ 186.0, found 186.0. Anal. calcd for $C_7H_7ClN_3O$: C, 44.56; H, 4.67; N, 19.49; found C, 44.50; H, 4.75; N, 19.44%.

***N*-(4-Bromo-2-chlorophenyl)hydrazinecarboxamide (5.22).** Yield: 14.5 g, 55%, white solid, Mp 130–131 °C. IR (KBr): 3364, 3332, 3220 (NH), 3103, 3046, 2913 (CH), 1702 (C=O) $cm^{-1}$. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_7H_8BrClN_3O$ 264.0, found 264.0. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta = 4.73$ (br. s, 2H, $NH_2$), 7.46 (d, $^3J = 9$ Hz, 1H, Ar), 7.67 (s, 1H, NH), 7.98 (s, 1H, Ar), 8.28 (m, 1H, Ar), 9.18 (br. s, 1H, NH) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta = 113.1$, 120.8, 122.3, 131.1, 131.4, 136.2, 156.8 ppm. Anal. calcd for $C_7H_7BrClN_3O$: C, 31.79; H, 2.67; N, 15.89; found C, 31.71; H, 2.77; N, 15.82%.

***N*-(4-(Methylsulfonyl)phenyl)hydrazinecarboxamide (5.23).** Yield: 11.9 g, 52%, white solid, Mp 104–106 °C. IR (KBr): 3376, 3364, 3260 (NH), 3020, 3003, 2925 (CH), 1684 (C=O) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta = 3.14$ (s, 3H, $CH_3SO_2$), 4.45 (br. s, 2H, $NH_2$), 7.71 (m, 5H, Ar + NH), 9.15 (s, 1H, NH) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta = 117.2$, 130.5, 143.1, 158.0, 170.3 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_8H_{12}N_3O_3S$ 230.1, found 230.2. Anal. calcd for $C_8H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33; found C, 41.85; H, 4.90; N, 18.24%.

**4-(4-Carboxy-phenyl)semicarbazide (5.24).** Yield: 10.7 g, 55%, whitish solid, Mp 198–200 °C. IR (KBr): 3336, 3288, 3223 (NH), 3044, 2884 (CH), 1677 (C=O) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta = 5.5$–6.7 (s, 3H, $NH_2$ + COOH), 7.55 (d, $^3J = 8.0$ Hz, 2H, Ar), 7.83 (d, $^3J = 8.0$ Hz, 2H, Ar), 8.0–8.7 (m, 1H, NH), 9.0–10.0 (s, 1H, NH) ppm. $^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta = 44.5$, 118.2, 128.5, 130.1, 145.3, 157.4 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_8H_{10}N_3O_3$ 196.2, found 196.1. Anal. calcd for $C_8H_9N_3O_3$: C, 49.23; H, 4.65; N, 21.53; found C, 49.20; H, 4.70; N, 21.50%.

***N*,*N*-Diphenyl semicarbazide (5.25).** Yield: 8.9 g, 39%, yellowish solid, Mp 141–143 °C. IR (KBr): 3318, 3281, 3220 (NH), 3090, 3058, 3010 (CH), 1672 (C=O) $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta = 4.42$ (br. s, 8H, NH + $NH_2$ + $H_2O$), 7.16 (m, 6H, Ar), 7.34 (m, 4H, Ar) ppm. $^{13}C$ NMR (APT, 125 MHz, $CDCl_3$-$d_6$): $\delta = 125.9$, 127.4, 129.5, 143.6, 158.8 ppm. MS (APCI) $m/z$ $[M + H]^+$ calculated for $C_{13}H_{14}N_3O$ 228.3, found 228.2. Anal. calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49; found C, 68.65; H, 5.85; N, 18.42%.

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