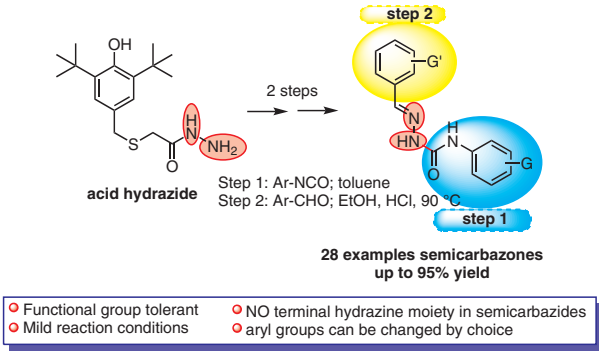
Synthesis A. R. Nath, W. A. Yehye Paper

Acid Hydrazide: A Potential Reagent for the Synthesis of Semicarbazones

Amit R. Nath
Wageeh A. Yehye*

Nanotechnology & Catalysis Research Centre (NANOCAT), University of Malaya, Block 3A, Institute of Postgraduate Studies, Kuala Lumpur 50603, Malaysia
wdabdoub@um.edu.my



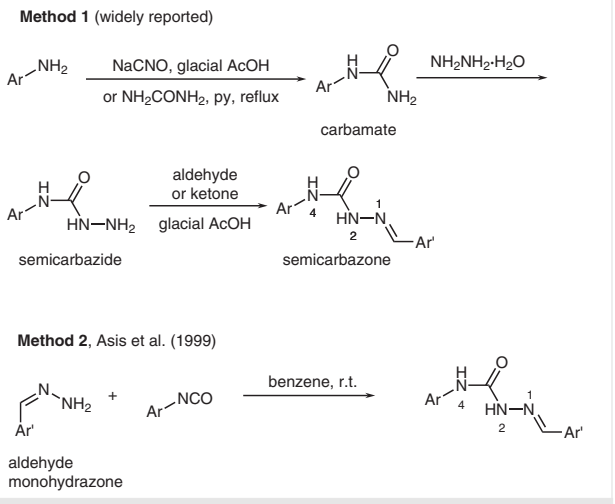
Received: 06.05.2018
Accepted after revision: 15.06.2018
Published online: 07.08.2018
DOI: 10.1055/s-0037-1609557; Art ID: ss-2018-z0312-op

Abstract Complex semicarbazone derivatives were successfully synthesized from substituted semicarbazides in acidic ethanol upon heating in the presence of aldehyde. The reaction is functional group tolerant and chemoselective because no terminal hydrazine moiety is present in the substituted semicarbazides. Thus, functional groups such as esters and acetyls, which are prone to reaction with hydrazine, can also be used in this reaction because the terminal hydrazine moiety of the acid hydrazide was protected by aryl isocyanates in order to prepare substituted semicarbazides. In addition, neither of the aryl groups of semicarbazone are dependent on the starting materials (acid hydrazide) and can be changed upon demand. Thus, this reaction protocol provides a simple and effective alternative for the preparation of a wide variety of semicarbazones that could not be synthesized by utilizing conventional methods.

Key words semicarbazones, substituted semicarbazides, acid hydrazide, hydrazine, nucleophilic substitution reaction

The development of effective routes to nitrogen-bearing molecules is a priority, considering that more than 90% of pharmaceutical products have at least one nitrogen atom in their framework and because one reaction out of six accomplished in the pharmaceutical industries is associated with the construction of a carbon–nitrogen bond.[1] Semicarbazone derivatives have attracted interest in both medicinal and pharmaceutical fields because of their broad spectrum of biological activities such as anticonvulsant, antitumor, and anticancer properties.[2,3] Its metal complexes also exhibit significant activity against bacteria, fungi, and viruses, which extends the versatility of the application.[4] Moreover, substituted semicarbazones can be used as a platform chemical to prepare benzotriazepin compounds, which are also an important class of drug because of their psychostimulant, antidepressant, anorexigenic, and antihypertensive properties.[5]

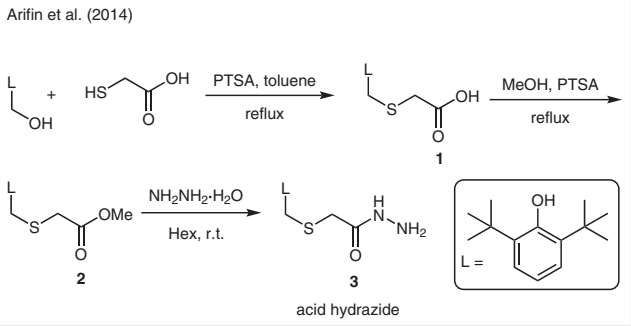
The well-known synthetic route to semicarbazones is a reaction between semicarbazides and aldehyde in which the semicarbazide compound is obtained by the treatment of carbamate compounds with hydrazine, as seen in Scheme 1.[6] Unfortunately, formation of the desired semicarbazides has proved challenging and most are not commercially available. Consequently, Asis et al. reported another method to prepare semicarbazones involving the reaction between appropriate monohydrazone and isocyanate.[7] However, this widely reported method[3,7] is limited by some functional groups such as ester or acyl group. Semicarbazone derivatives bearing these functional groups on an aromatic ring attached with N-4 (Scheme 1) could not be synthesized easily because of the reactivity of NH_2 of urea, hydrazine and aromatic aldehyde monohydrazone towards some active functional groups such as ester,



Scheme 1 Conventional methods for the preparation of semicarbazone

oxadiazole, and other carbonyl compounds.[8] Moreover, the yield of most of the semicarbazones achieved by using such synthetic techniques is poor. Garland et al. also reported the preparation of semicarbazone and hydrazone derivatives from common semicarbazones and hydrazones, respectively, via imino-isocyanates, wherein various amines and anilines were used as nucleophiles with hydrazones.[9] However, this protocol required a simple semicarbazone as starting material; the N-4 part of the semicarbazone was only replaced by amines or anilines as nucleophiles via nucleophilic substitution reaction to form a complex semicarbazone derivative.

Therefore, there remains a need to develop a robust synthetic route to prepare new semicarbazones that offers better functional group tolerance as well as chemoselectivity. Hence, in this study we outlined a viable synthetic technique and developed a potential reaction route. An effective and facile approach was adopted in this research to prepare diverse semicarbazones containing ester or acetyl groups on an aromatic ring attached at N-4. Acid hydrazide **3** was a prerequisite precursor, which was prepared according to a reported method showed in Scheme 2.[10]



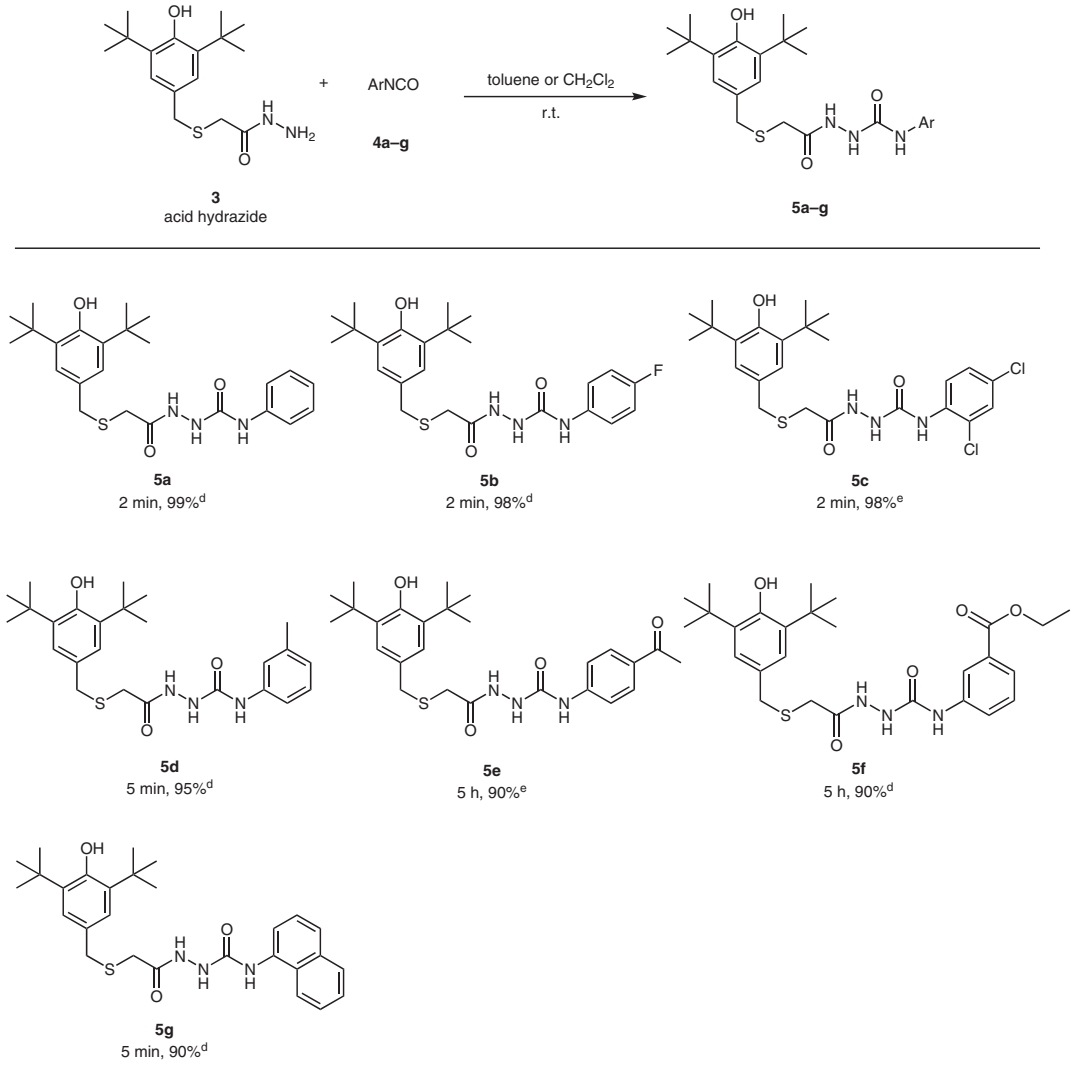
Scheme 2 Preparation of acid hydrazide **3**

The newly employed synthetic technique involved the preparation of substituted semicarbazides to protect the free hydrazine moiety of the acid hydrazides. To our knowledge, this is the first report of a reaction protocol for the synthesis of semicarbazones from free hydrazine moiety protected substituted semicarbazide. Functional groups that are very reactive to free hydrazine could be used in this reaction because no free hydrazine moiety was present in the substituted semicarbazides. This is one of the main advantages of this reaction over the existing methods. In addition, the by-product of this reaction (3,5-di-*tert*-butyl-4-hydroxybenzylsulfanyl)acetic acid ethyl ester proved the involvement of the solvent in the reaction. A diverse range of semicarbazone derivatives were synthesized to validate the reaction protocol by using seven different substituted semicarbazides containing reactive functional groups such as acetyl, ester etc.

Reaction between acid hydrazide and aryl isocyanates is a straightforward reaction at room temperature that has been reported by many researchers.[11] Herein, we carried out this reaction between prepared acid hydrazide **3** and phenyl isocyanate at ambient temperature utilizing three different solvents: toluene, dichloromethane (DCM), and ethanol. Interestingly, although the reaction proceeded in all the solvents, the reaction products started to form almost instantly in toluene whereas in dichloromethane and ethanol it required around 10 and 20 minutes, respectively, for the product solid to be visible. Thus, most of the reactions were performed in toluene but a few aryl isocyanates were insoluble in this media and, in this case, the reaction was performed in DCM. The results of the reaction are summarized in Scheme 3. The time required for the reaction to reach completion was very short for semicarbazides substituted with phenyl isocyanate **4a**, 4-fluorophenyl isocyanate **4b**, 2,4-dichlorophenyl isocyanate **4c**, *m*-tolyl isocyanate **4d**, and naphthyl isocyanate **4g**, but in the case of 4-acetylphenyl isocyanate **4e** and 3-(ethoxycarbonyl)phenyl isocyanate **4f**, the required reaction time was noticeably longer (5 hours). This is possibly because of the nature of the substituents on benzene ring of the aryl isocyanates, which determines their reactivity.

It was observed that the reaction time was markedly shortened in the presence of a weakly electron-withdrawing body such as F or Cl (**4b**, **4c**) or even in the absence of any substituents (**4a** and **4g**) on the benzene or naphthyl ring of the aryl isocyanate. Likewise, in the presence of groups such as Ac and CO_2Et, which moderately deactivate the benzene ring, the reaction took approximately 5 hours to complete. This can probably be attributed to the resonance effect of the benzene ring bearing an acyl or ester group. For further investigations, *m*-tolyl isocyanate was utilized in the reaction to examine the effect of a ring activating group. Interestingly, this reaction also reached completion in a short time. However, the product yields of all the substituted semicarbazide derivatives (≥ 90%) were greatly increased.

With compounds **5a–g** in hand, we performed the reaction with substituted semicarbazides and benzaldehyde as shown in Scheme 4. Best turnover was found at around 90 °C in the presence of a catalytic amount of HCl in ethanol as solvent. The physical properties of the synthesized semicarbazones **7a–g**, outlined in Scheme 4, show that N^1-benzylidene-N^4-phenyl-semicarbazone (**7a**) was obtained with 90% yield along with (3,5-di-*tert*-butyl-4-hydroxybenzylsulfanyl)acetic acid ethyl ester (**8**) by this method; Asis et al. achieved 32% yield of **7a** by using their reported method.[7] Semicarbazones bearing 4-fluoro (**7b**), 2,4-dichloro (**7c**) and 3-methyl (**7d**) substitution of the benzene ring attached at *N*-4 provided about 90% yield. Gratifyingly, semicarbazones with N^4-(3-ethoxycarbonylphenyl) (**7f**) and N^4-(4-acetylphenyl) (**7e**) moiety were also synthesized with more than 80% yields.



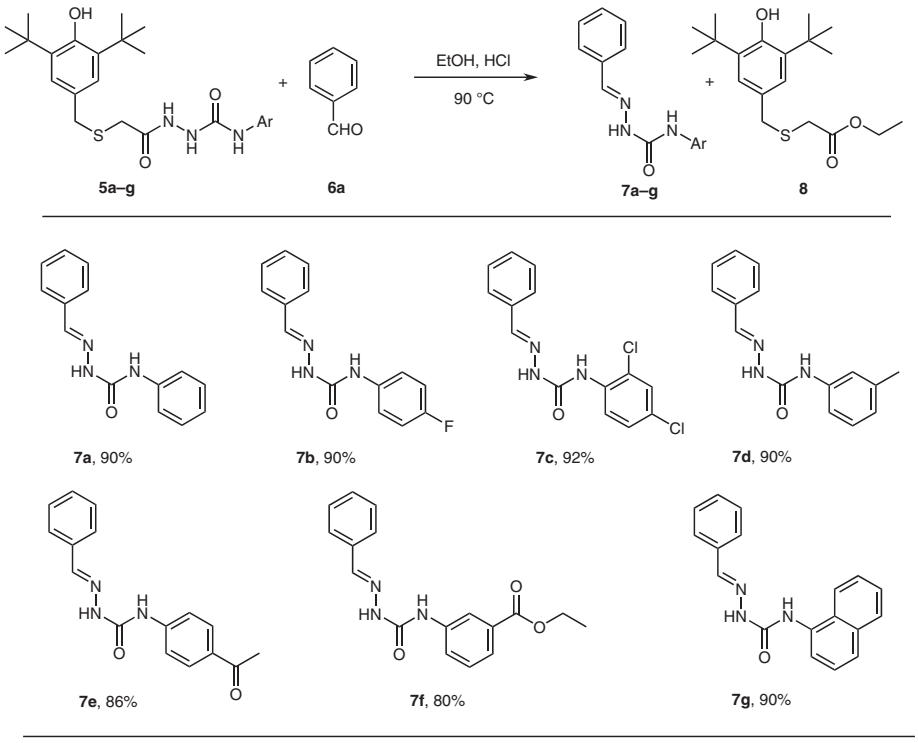
Scheme 3 Evaluation of the reaction of substituted semicarbazides formation. [a] *Reagents and conditions*: **3** (3.12 mmol), **4a–g** (3.12 mmol), room temperature. [b] Reaction completion time. [c] Isolated yield. [d] toluene was used as solvent. [e] Dichloromethane was used as solvent.

In case of compound **7g**, the N^1-benzylidene-N^4-naphthalene semicarbazone was isolated with 90% yield by using the current method, whereas Asis et al.[7] reported 20% yield for this product and Azam et al.[12] achieved 79% yields by utilizing the broadly reported method. In the earlier reported procedure the N^4-phenyl ring of semicarbazone depended upon the phenyl amine that was taken as starting materials in the initial step. For instance, it was extremely troublesome to obtain N^4-(alkoxycarbonylphenyl) semicarbazones starting from the ester substituted phenyl amine because of the high reactivity of hydrazine towards the ester moiety in the second step.[8]

To examine the versatility of this method, three benzaldehydes having electron-donating and electron-withdrawing groups were used. We carried out this reaction with *m*-anisaldehyde, 4-fluorobenzaldehyde, and cuminaldehyde to prepare semicarbazones containing different substituents on the N^1-benzylidene ring under the same reaction conditions; the results are outlined in Scheme 5.

To begin with, we endeavored to prepare semicarbazones with a N^1-(4-fluorobenzylidene) ring. Gratifyingly, the use of 4-fluorobenzaldehyde generated the expected semicarbazones with better yields, reacting with all substituted semicarbazides (**5a–g**). Phenyl (**7a$_1$**), 4-fluorophenyl (**7b$_1$**), and 2,4-dichlorophenyl (**7c$_1$**) semicarbazone with N^1-(4-fluorobenzylidene) ring were obtained with 92, 95, and 90% yield, respectively.

Though N^1-(4-fluorobenzylidene)-N^4-naphthyl-semicarbazone (**7g$_1$**) was isolated with 80% yield by using the earlier reported method,[12] interestingly, yields increased to



Scheme 4 Evaluation of N^1-benzylidene-N^4-(substituted phenyl) semicarbazone. [a] *Reagents and conditions*: **5a–g** (0.65 mmol), benzaldehyde **6a** (0.65 mmol), HCl (1.6 mmol), ethanol (10 mL), 90 °C. [b] Isolated yield.

90% by the reaction of 2-(2-(3,5-di-*tert*-butyl-4-hydroxybenzylthio)acetyl)-*N*-naphthylhydrazinecarboamide (**5g**) with 4-fluorobenzaldehyde.

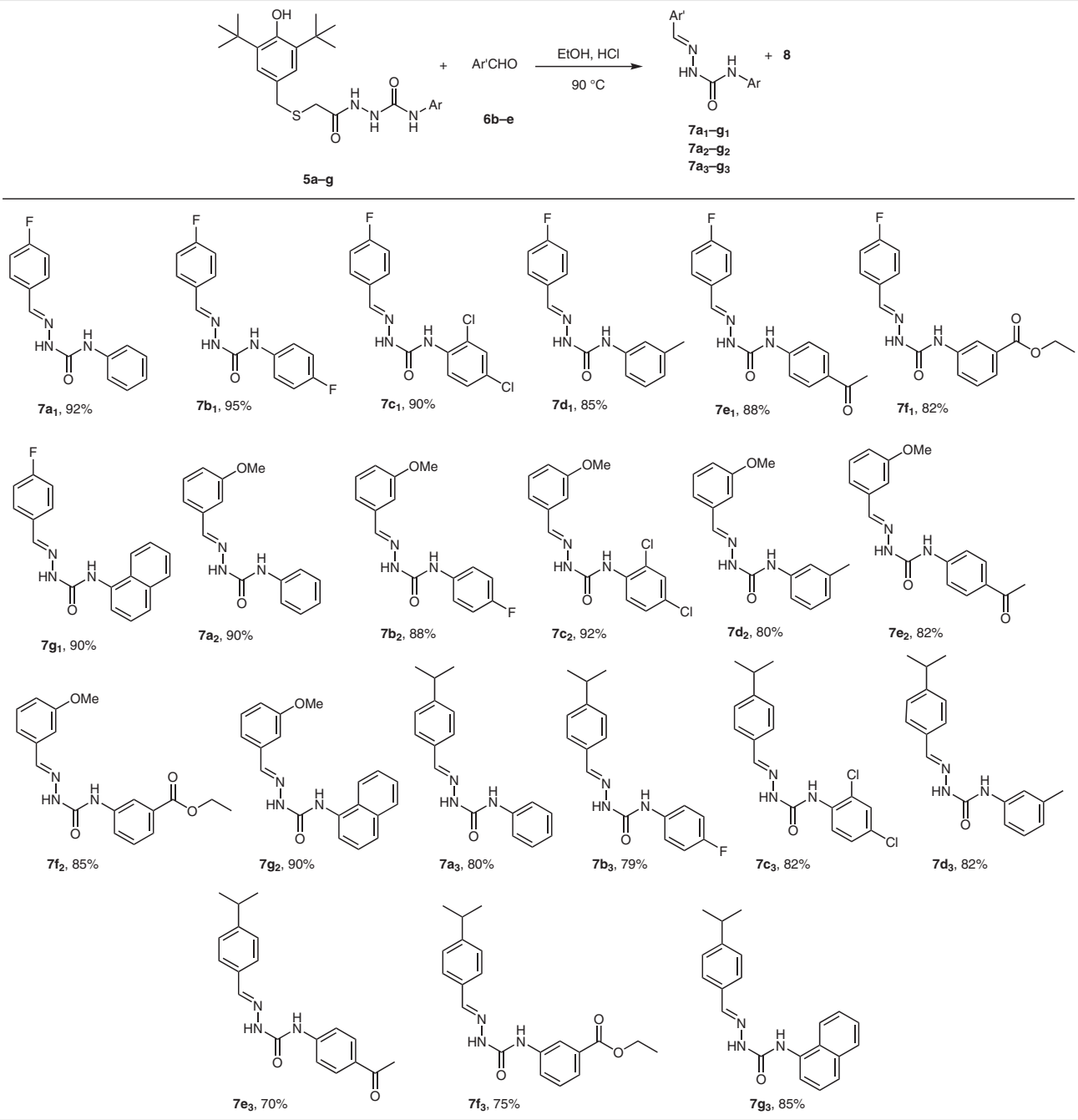
We then assembled semicarbazones containing the N^1-(3-methoxybenzylidene)-ring by treating 3-methoxybenzaldehyde with pre-prepared substituted semicarbazides **5a–g**. Phenyl (**7a$_2$**), 4-fluoro (**7b$_2$**), 2,4-dichloro (**7c$_2$**), and naphthyl (**7g$_2$**) semicarbazones were accessed with around 90% yield; for the rest (**7d$_2$–7f$_2$**) turnovers were found to be more than 80%. As noted in Scheme 5, the yield of compounds **7e$_3$** and **7f$_3$**, bearing a N^1-(4-(2-isopropyl)benzylidene) ring was around 70%, and for phenyl (**7a$_3$**), 4-fluorophenyl (**7b$_3$**), 2,4-dichloro (**7c$_3$**), *m*-tolyl (**7d$_3$**) and naphthyl (**7g$_3$**) semicarbazones were obtained with 80% yield.

The formation of substituted semicarbazide from acid hydrazide and aryl isocyanate by a nucleophilic addition mechanism is shown in Scheme 6. The hydrazine moiety of acid hydrazide **3** might attack the carbonyl carbon of isocyanate, forming an intermediate with two positive charges.

In the subsequent step, the positively charged nitrogen of the hydrazine part releases a proton to become a stable ion and, on the other hand, the nitrogen of the aryl isocyanate moiety might be attracted by this roaming proton and formed N–H bond. It could be anticipated from the different reaction times that the resonance of the aromatic ring of the aryl isocyanate bearing a different functional group affects the action of the nitrogen. Thus, formation of compounds **5e** and **5f** took longer than the other substituted semicarbazides.

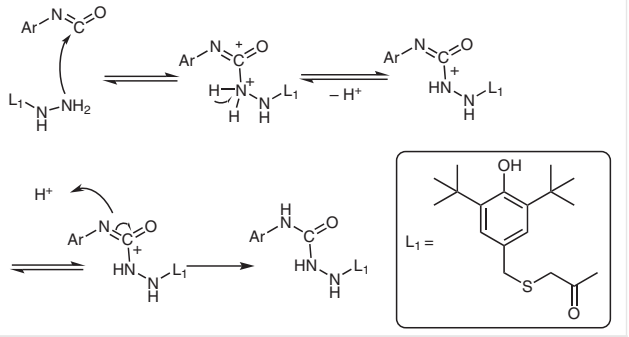
The observation that (3,5-di-*tert*-butyl-4-hydroxybenzylsulfanyl)acetic acid ethyl ester (**8**) was found as a reaction product along with semicarbazones in every reaction, indicates that solvent ethanol also participated in the reaction as a substrate and this product **8** could be used in the preparation of acid hydrazide **3** according to Scheme 7. Taking this into account, a plausible mechanism was drawn for the formation of semicarbazones in the Scheme 7. Protonation and nucleophilic attack of ethanol might occur at the same carbonyl carbon of substituted semicarbazides then the neighboring nitrogen might attack the protonated aldehyde, resulting in the formation of intermediate **i**. The latter intermediate released compounds **8** and is again protonated. In the last step semicarbazone is formed by giving up a hydronium ion.

The widely used semicarbazones preparation (Scheme 1) begins with reaction of aniline with the urea in the presence of pyridine or sodium cyanate in glacial acetic acid, and results in the formation of a carbamate compound, which is then reacted with hydrazine to give semicarbazide. Condensation of semicarbazide with aromatic aldehyde in the presence of glacial acetic acid provides semicarbazone.



Scheme 5 Evaluation of semicarbazones from three different benzaldehydes. [a] *Reagents and conditions*: **5a–g** (0.65 mmol), **6b–e** (0.65 mmol), HCl (1.6 mmol), ethanol (10 mL), 90 °C. [b] Isolated yield. **$7a_1$–g_1** reaction performed with 4-fluorobenzaldehyde. **$7a_2$–g_2** reaction performed with *m*-anisaldehyde. **$7a_3$–g_3** reaction performed with cuminaldehyde.

Although this method is more common in the synthesis of semicarbazones, unfortunately the use of aniline and a terminal amino group in carbamate greatly limits its use for the preparation of diverse semicarbazones. For instance, certain carbamates bearing ester or acetyl group are very difficult to synthesize because urea or cyanate molecules are more susceptible to react with other reactive functional groups instead of an amino group, which leads the unwanted product instead of carbamate.[7] In addition, formation of semicarbazide in the second step by the reaction of carbamate bearing ester or acetyl group with hydrazine is more problematic because hydrazine is very reactive to carbonyl or ester groups. In another method (Scheme 1, Method 2), aromatic aldehyde mono hydrazone, a key molecule in the

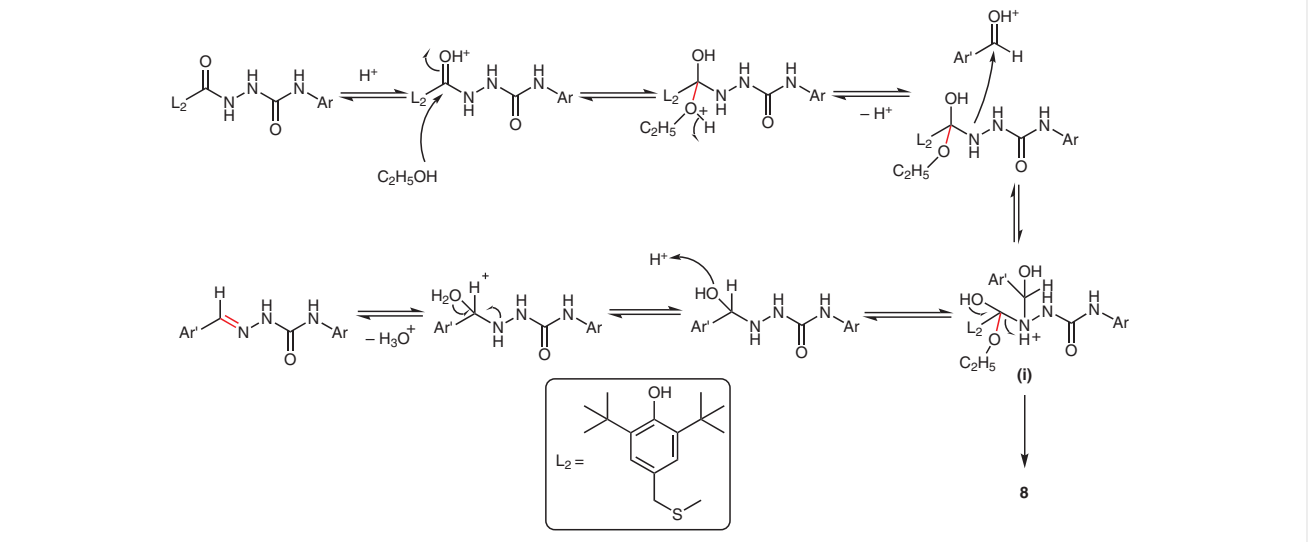


Scheme 6 Proposed mechanism for the formation of substituted semicarbazide

preparation of semicarbazone obtained from the reaction of aldehyde with hydrazine, also experiences similar problems due to the unwanted reactions between hydrazine molecule and other functional groups. Furthermore, the reaction of hydrazone with isocyanate is not functional group compatible. The above limitations are due to the presence of the terminal amino group, which prevents both methods from offering a wide variety of semicarbazones. Interestingly, the problem has been solved in this work by protecting the terminal hydrazine moiety of acid hydrazide with aryl isocyanates, which led to substituted semicarbazides bearing several active functional groups. Treatment of the substituted semicarbazides with aldehyde in acidic ethanol led to a substitution reaction in which the semicarbazones and (3,5-di-*tert*-butyl-4-hydroxybenzylsulfanyl)acetic acid ethyl ester (**8**) are generated in greater yields than those obtained with existing methods.

In conclusion, a variety of substituted semicarbazides were easily accessed by a straightforward reaction of acid hydrazide with aryl isocyanate bearing different substituents in order to protect the free hydrazine moiety of the acid hydrazide. A nucleophilic substitution reaction of substituted semicarbazides with diverse substituted benzaldehyde has been established by which an extensive range of semicarbazone compounds were synthesized with notable yield. Since the hydrazine moiety is not free in the substituted semicarbazides, it can easily be converted into diverse complex semicarbazone compounds bearing different reactive functional groups such as ester and acetyl groups. Again, the obtained by-product **8** proved the involvement of ethanol in the reaction, and this by-product could also be used in the preparation of acid hydrazide, which would be another interesting aspect of this method. Thus, this reaction protocol pointedly offers a simple and robust alternative for the preparation of diverse semicarbazone derivatives, resolving the limitations of conventional methods. This reaction can also help to obtain distinct substitution derivatives of semicarbazides forming more carbon–nitrogen bonds, the development of which is under way.

All starting materials were of analytical grade, and double-distilled water was used throughout the experiments. The solvents and reagents were supplied by Sigma–Aldrich and Merck, Malaysia and used without further purification. Pre-coated silica gel plates (0.25 mm) was utilized to observe the reaction by analytical thin-layer chromatography and imagined by UV light. Column chromatography was done on Silica Gel 60 (particle size: 0.040–0.063 mm). IR spectra were recorded using FTIR-ATR of the solid samples. Melting points were approximated. 600 MHz and 150 MHz NMR spectrometers were used for ^{1}H and ^{13}C NMR analysis, respectively, and tetramethylsilane was used as a reference. Chemical shifts (δ) are reported in ppm with respect to the residual solvent peak ($CHCl_3$, δ = 7.26 ppm; DMSO-d_6, δ =



Scheme 7 Proposed mechanism for semicarbazone formation via substitution reaction

2.5 ppm for proton spectra; $^{13}CDCl_3$, δ = 77.0 ppm; DMSO-d_6, δ = 40 ppm for carbon spectra). High-resolution mass spectra were recorded with a time-of-flight Q-TOF LCMS system.

Synthesis of 2-((3,5-Di-*tert*-butyl-4-hydroxybenzyl)thio)acetohydrazide (3)

2-((3,5-Di-*tert*-butyl-4-hydroxybenzyl)thio)acetohydrazide was synthesized according to a previously described method.[10] The compound was solid and was stored at ambient temperature.

Synthesis of Substituted Semicarbazides 5a–g (Gram Scale); General Procedure A

Acid hydrazide (1 g, 3.12 mmol) was stirred in toluene (20 mL) then an equimolar amount of aryl isocyanate was introduced and the reaction was monitored by TLC. All the substituted semicarbazides formed white precipitates during the reaction, which were filtered and washed several times with toluene. Dichloromethane (CH_2Cl_2) was used for compounds **5c** and **5e** since 2,4-dichlorophhenylisocyanate and 4-acylphenylisocyanate are not soluble in toluene. Compound structures were confirmed by IR, ^{13}C NMR, ^1H NMR and HRMS analyses.

2-(2-(3,5-Di-*tert*-butyl-4-hydroxybenzylthio)acetyl)-*N*-phenylhydrazinecarboxamide (5a)

Yield: 1.42 g (99%); white solid; mp 128–130 °C.

FTIR (ATR): 3619, 3252, 2960, 1605 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 10.10 (s, 1 H), 9.67 (s, 1 H), 9.60 (b, 1 H), 7.45 (s, 2 H), 7.34 (t, *J* = 6 Hz, 1 H), 7.17 (t, *J* = 6 Hz, 1 H), 7.08 (s, 2 H), 6.90 (s, 1 H), 3.79 (s, 2 H), 3.17 (s, 2 H), 1.38 (s, 18 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 181.4, 169.4, 153.3, 139.6, 139.5, 128.9, 128.6, 126.1, 125.7, 125.5, 36.7, 34.9, 33.4, 30.8.

HRMS (Q-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{33}O_3N_3SNa^+$: 466.2140; found: 466.2161.

2-(2-(3,5-Di-*tert*-butyl-4-hydroxybenzylthio)acetyl)-*N*-4-(fluorophenyl)hydrazinecarboxamide (5b)

Yield: 1.41 g (98%); white solid; mp 160–162 °C.

FTIR (ATR): 3634, 3292, 2955, 1656 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 9.81 (s, 1 H), 8.76 (s, 1 H), 8.15 (s, 1 H), 7.47 (dd, *J* = 6 Hz, 2 H), 7.10 (t, *J* = 6 Hz, 2 H), 7.07 (s, 2 H), 6.89 (s, 1 H), 3.78 (s, 2 H), 3.12 (s, 2 H), 1.37 (s, 18 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 169.5, 158.6, 157.1, 153.3, 136.4, 139.6, 128.9, 120.7, 115.6, 115.5, 36.5, 34.9, 32.9, 30.8.

HRMS (Q-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{32}FO_3N_3SNa^+$: 484.2046; found: 484.2051.

2-(2-(3,5-Di-*tert*-butyl-4-hydroxybenzylthio)acetyl)-*N*-(2,4-dichlorophenyl)hydrazinecarboxamide (5c)

Yields: 1.56 g (98%); white solid; mp 106–108 °C.

FTIR (ATR): 3644, 3184, 2956, 1591 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 10.00 (s, 1 H), 8.91 (s, 1 H), 8.33 (b, 1 H), 8.11 (d, *J* = 6 Hz, 1 H), 7.62 (d, *J* = 2.4 Hz, 1 H), 7.37 (dd, *J* = 3, 6 Hz, 2 H), 7.07 (s, 2 H), 6.89 (s, 1 H), 3.78 (s, 2 H), 3.13 (s, 2 H), 1.37 (s, 18 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 169.4, 155.1, 153.3, 139.6, 135.5, 129.1, 128.8, 128.1, 126.8, 125.7, 123.3, 122.6, 36.5, 34.9, 32.6, 30.8.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{31}O_3N_3Cl_2SNa^+$: 534.1355; found: 534.1373.

2-(2-(3,5-Di-*tert*-butyl-4-hydroxybenzylthio)acetyl)-*N*-(3-methylphenyl)hydrazinecarboxamide (5d)

Yield: 1.35 g (95%); white solid; mp 106–108 °C.

FTIR (ATR): 3361, 2916, 2853, 1607 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 9.80 (s, 1 H), 8.63 (s, 1 H), 8.10 (s, 1 H), 7.29 (s, 1 H), 7.25 (d, *J* = 7.8 Hz, 1 H), 7.15 (t, *J* = 7.8 Hz, 1 H), 7.08 (s, 2 H), 6.88 (s, 1 H), 6.79 (d, *J* = 7.2 Hz, 1 H), 3.78 (s, 2 H), 3.13 (s, 2 H), 2.26 (s, 3 H), 1.38 (s, 18 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 169.5, 155.7, 153.3, 139.9, 139.6, 138.3, 128.9, 128.9, 125.7, 123.1, 119.4, 116.1, 36.5, 34.9, 32.9, 30.8, 21.7.

HRMS (Q-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{35}O_3N_3SNa^+$: 480.2291; found: 480.2312.

2-(2-(3,5-Di-*tert*-butyl-4-hydroxybenzylthio)acetyl)-*N*-(4-acetylphenyl)hydrazinecarboxamide (5e)

Yield: 1.36 g (90%); white solid; mp 147–149 °C.

FTIR (ATR): 3368, 3092, 2918, 2850, 1613 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 9.88 (s, 1 H), 9.83 (s, 1 H), 9.15 (s, 1 H), 8.33 (s, 1 H), 7.88 (d, *J* = 9 Hz, 2 H), 7.60 (d, *J* = 8.4 Hz, 2 H), 7.08 (s, 2 H), 6.88 (s, 1 H), 2.53 (s, 3 H), 1.38 (s, 18 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 196.8, 169.7, 153.3 144.8, 139.7, 131.0, 130.1, 129.9, 128.9, 125.7, 117.9, 36.5, 34.9, 32.9, 30.8, 26.8.

HRMS (Q-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{36}O_4N_3SNa^+$: 486.2421; found: 486.2435.

2-(2-(3,5-Di-*tert*-butyl-4-hydroxybenzylthio)acetyl)-*N*-(3-ethoxycarbonylphenyl)hydrazinecarboxamide (5f)

Yield: 1.45 g (90%); white solid; mp 157–159 °C.

FTIR (ATR): 3375, 3092, 2918, 2850 1620 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 9.83 (s, 1 H), 9.02 (s, 1 H), 8.23 (s, 1 H), 8.12 (s, 1 H), 7.75 (d, *J* = 7.8 Hz, 1 H), 7.57 (d, *J* = 7.8 Hz, 1 H), 7.41 (t, *J* = 7.8 Hz, 1 H), 6.87 (s, 1 H), 7.08 (s, 2 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 1.38 (s, 18 H), 1.32 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 169.6, 166.2, 155.7, 153.3, 140.5, 140.4, 139.6, 130.8, 129.6, 129.5, 128.9, 125.7, 123.1, 119.4, 61.2, 36.6, 34.9, 32.9, 30.8, 14.7.

HRMS (Q-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{37}O_5N_3SNa^+$: 538.2346; found: 538.2363.

2-(2-(3,5-Di-*tert*-butyl-4-hydroxybenzylthio)acetyl)-*N*-(1-naphthyl)hydrazinecarboxamide (5g)

Yield: 1.42 g (92%); white solid; mp 123–125 °C.

FTIR (ATR): 3639, 3302, 2961, 1610 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 9.96 (s, 1 H), 8.79 (s, 1 H), 8.43 (s, 1 H), 8.06 (d, *J* = 12 Hz, 1 H), 7.92 (m, 1 H), 7.80 (br s, 1 H), 7.67 (d, *J* = 6 Hz, 1 H), 7.53 (m, 2 H), 7.46 (t, *J* = 6 Hz, 1 H), 7.08 (s, 2 H), 6.90 (s, 1 H), 3.80 (s, 2 H), 3.16 (s, 2 H), 1.36 (s, 18 H).

^{13}C NMR (600 MHz, DMSO-d_6): δ = 169.6, 156.4, 153.3, 139.7, 134.6, 134.2, 128.9, 128.7, 126.4, 126.2, 126.2, 125.7, 124.2, 122.4, 119.4, 36.6, 34.9, 32.9, 30.8.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{36}O_3N_3S^+$: 494.2472; found: 494.2473.

Synthesis of Semicarbazone; General Procedure B

Substituted semicarbazide (0.65 mmol) and an equimolar quantity of aldehyde were mixed together in EtOH (ca. 10 mL) in a round-bottom flask. The reaction mixture was then stirred at 90 °C for 4–5 hours in the presence a catalytic amount of HCl (1.6 mmol) until the disappearance of the starting materials spot was observed by thin-layer chromatography. The reaction mixture was then warmed to ambient temperature, and stirred for ca. 30 min. In most of the reactions, the target compounds formed a solid precipitate during stirring at ambient temperature. The precipitate was filtered and washed with hexane several times. The resultant products were then dried and either recrystallized from hexane or purified by column chromatography. On the other hand, when no precipitate was observed, the reaction mixture was concentrated and residue was purified by column chromatography on silica gel with hexane/EtOAc mixture as eluent.

(3,5-Di-*tert*-butyl-4-hydroxybenzylsulfanyl)acetic Acid Ethyl Ester (8)

Yield: 0.77–0.88 g (70–80%); brown gummy liquid; R_f 0.35 (hexane/EtOAc, 1:1).

FTIR (ATR): 3564, 2955, 2914, 2873, 1728 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 7.03 (s, 1 H), 6.92 (s, 1 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 3.71 (s, 2 H), 3.18 (s, 2 H), 1.37 (s, 18 H), 1.20 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 170.5, 153.4, 139.7, 128.6, 125.7, 61.1, 36.3, 34.9, 32.7, 30.8, 14.5.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{31}O_3S^+$: 338.1916; found: 338.1912.

***N*^{1}-(Benzylidene)-*N*^{4}-phenylsemicarbazone (7a)**

Yield: 139.9 mg (90%); white solid; mp 178–180 °C; R_f 0.58 (hexane/EtOAc, 2:1).

FTIR (ATR): 3371, 3198, 3094, 2973, 2889, 1680 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 10.76 (s, 1 H), 8.91 (s, 1 H), 7.97 (s, 1 H), 7.87 (d, *J* = 6.6 Hz, 2 H), 7.66 (d, *J* = 7.8 Hz, 2 H), 7.44 (t, *J* = 6.6, 7.8 Hz, 2 H), 7.40 (t, *J* = 7.2 Hz,1 H), 7.30 (t, *J* = 7.8, 8.4 Hz, 1 H),7.02 (t, *J* = 7.2 Hz, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 153.5, 141.3, 139.5, 134.9, 129.9, 129.5, 128.9, 127.5, 122.9, 120.4.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}N_3O^+$: 240.1131; found: 240.1149.

***N*^{1}-(Benzylidene)-*N*^{4}-(4-fluorophenyl)semicarbazone (7b)**

Yield: 150.4 mg (90%); white solid; mp 172–174 °C; R_f 0.52 (hexane/EtOAc, 2:1).

FTIR (ATR): 3377, 3193, 3102, 2958, 2832, 1680 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 10.75 (s, 1 H), 8.96 (s, 1 H), 7.96 (s, 1 H), 7.86 (d, *J* = 7.2 Hz, 2 H), 7.67 (dd, *J* = 3.6, 5.4 Hz, 2 H), 7.44 (t, *J* = 7.2 Hz, 2 H), 7.40 (t, *J* = 7.2 Hz, 1 H), 7.14 (t, *J* = 9, 8.4 Hz, 2 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 159.1, 157.5, 153.7, 141.3, 135.9, 134.9, 129.9, 129.1, 127.5, 122.3, 115.3.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}FN_3O^+$: 258.1037; found: 258.1052.

***N*^{1}-(Benzylidene)-*N*^{4}-(2,4-dichlorophenyl)semicarbazone (7c)**

Yield: 183.5 mg (92%); white solid; mp 222–223 °C; R_f 0.57 (hexane/EtOAc, 2:1).

FT-IR (ATR): 3341, 3190, 3093, 2962, 2864, 1689.

^1H NMR (600 MHz, DMSO-d_6): δ = 11.17 (s, 1 H), 8.94 (s, 1 H), 8.19 (d, *J* = 9 Hz, 1 H), 8.01 (s, 1 H), 7.73 (d, *J* = 7.2 Hz, 2 H), 7.70 (d, *J* = 2.4 Hz, 1 H), 7.47 (t, *J* = 7.2 Hz, 2 H), 7.45 (d, *J* = 2.4 Hz, 1 H), 7.43 (t, *J* = 3 Hz, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 152.7, 142.2, 134.9, 134.4, 130.3, 129.4, 129.1, 128.3, 127.4, 127.2, 124.3, 122.7.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{12}Cl_2N_3O^+$: 308.0352; found: 308.0364.

***N*^{1}-(Benzylidene)-*N*^{4}-(3-methylphenyl)semicarbazone (7d)**

Yield: 148 mg (90%); white solid; mp 165–167 °C; R_f 0.54 (hexane/EtOAc, 2:1).

FTIR (ATR): 3356, 2916, 2853, 1628 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 10.73 (s, 1 H), 8.80 (s, 1 H), 7.96 (s, 1 H), 7.85 (d, *J* = 7.2 Hz, 2 H), 7.48 (s, 1 H), 7.47 (d, *J* = 6 Hz, 1 H), 7.43 (t, *J* = 6.6, 7.8 Hz, 2 H), 7.40 (t, *J* = 7.2 Hz, 1 H), 7.18 (t, *J* = 7.8 Hz, 1 H), 6.84 (d, *J* = 7.8 Hz, 1 H), 2.30 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 153.5, 141.2, 139.4, 138.1, 134.9, 129.9, 129.1, 128.8, 127.5, 123.7, 120.8, 117.4, 21.6.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}N_3O^+$: 254.1288; found: 254.1306.

***N*^{1}-(Benzylidene)-*N*^{4}-(4-acetylphenyl)semicarbazone (7e)**

Yield: 157 mg (86%); white solid; mp 180–182 °C; R_f 0.55 (hexane/EtOAc, 2:1).

FTIR (ATR): 3361, 3200, 3099, 2957, 2857, 1693 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 10.93 (s, 1 H), 9.24 (s, 1 H), 7.99 (s, 1 H), 7.93 (d, *J* = 9 Hz, 2 H), 7.88 (d, *J* = 6 Hz, 2 H), 7.85 (d, 2 H), 7.45 (m, *J* = 7.8 Hz, 2 H), 7.42 (t, *J* = 7.2 Hz, 1 H), 2.54 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 196.9, 153.2, 144.2, 142.0, 134.7, 131.4, 130.1, 129.7, 129.1, 127.6, 119.1, 22.7.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}N_3O_2^+$: 282.1237; found: 282.1248.

***N*^{1}-(Benzylidene)-*N*^{4}-(3-ethoxycarbonylphenyl)semicarbazone (7f)**

Yield: 161.8 mg (80%); white solid; mp 126–128 °C; R_f 0.59 (hexane/EtOAc, 2:1).

FTIR (ATR): 3361, 3193, 3058, 2917, 2850, 1633 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 9.18(s, 1 H), 10.84 (s, 1 H), 7.96 (d, *J* = 6.8 Hz, 1 H), 7.62 (d, *J* = 7.2 Hz, 1 H), 8.34 (s, 1 H), 7.98 (s, 1 H), 7.45 (dt, *J* = 1.8, 8.4 Hz, 3 H), 7.41 (t, *J* = 6.6 Hz, 1 H), 7.45 (t, *J* = 7.2 Hz, 2 H), 7.88 (d, *J* = 7.2 Hz, 2 H), 4.33(q, *J* = 7.2 Hz, 2 H), 1.33(t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 193.7, 166.3, 153.8, 153.6, 141.6, 140.1, 134.8, 129.9, 129.1, 127.7, 125.1, 123.6, 120.9, 61.2, 14.7.

HRMS (Q-TOF): *m*/*z* M + H]$^+$ calcd for $C_{17}H_{18}N_3O_3^+$: 312.1343; found: 312.1357.

***N*^{1}-(Benzylidene)-*N*^{4}-(1-naphthyl)semicarbazone (7g)**

Yield: 169.2 mg (90%); white solid; mp 196–198 °C; R_f 0.43 (hexane/EtOAc, 2:1).

FTIR (ATR): 3410, 3199, 3109, 2965, 2868, 1701 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.84 (s, 1 H), 9.19 (s, 1 H), 8.03 (s, 1 H), 7.98 (d, J = 8.4 Hz, 1 H), 7.96 (d, J = 7.8 Hz, 1 H), 7.88 (d, J = 7.2 Hz, 2 H), 7.77 (d, J = 8.4 Hz, 1 H), 7.72 (d, J = 7.2 Hz, 1 H), 7.57 (t, J = 6.6 Hz, 1 H), 7.55 (t, J = 7.2 Hz, 1 H), 7.52 (t, J = 7.8 Hz, 1 H), 7.44 (t, J = 7.2 Hz, 2 H), 7.40 (t, J = 7.2 Hz, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 154.4, 141.2, 135.0, 134.4, 134.2, 129.8, 129.1, 129.1, 128.6, 127.4, 126.4, 126.4, 126.1, 125.3, 122.9, 122.3.

HRMS (Q-TOF): m/z [M + H]$^+$ calcd for $C_{18}H_{16}N_3O^+$: 290.1288; found: 290.1303.

N^1-(4-Fluorobenzylidene)-N^4-phenylsemicarbazone (7a$_1$)

Yield: 153.8 mg (92%); white solid; mp 160–162 °C; R_f 0.45 (hexane/EtOAc, 2:1).

FTIR (ATR): 3377, 3193, 3102, 2958, 2832, 1680 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.75 (s, 1 H), 8.92 (s, 1 H), 7.95 (s, 1 H), 7.93 (d, J = 6, 2.4 Hz, 2 H), 7.65 (d, J = 7.8 Hz, 2 H), 7.30 (t, J = 7.8 Hz, 2 H), 7.27 (d, J = 9 Hz, 2 H), 7.03 (t, J = 7.2 Hz, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 162.4, 153.5, 140.1, 139.5, 131.5, 129.6, 128.9, 122.9, 120.4, 115.9.

HRMS (Q-TOF): m/z [M + H]$^+$ calcd for $C_{14}H_{13}N_3FO^+$: 258.1037; found: 258.1052.

N^1-(4-Fluorobenzylidene)-N^4-(4-fluorophenyl)semicarbazone (7b$_1$)

Yield: 169.8 mg (95%); white solid; mp 170–172 °C; R_f 0.57 (hexane/EtOAc, 2:1).

FTIR (ATR): 3368, 2917, 2850, 1633 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.74 (s, 1 H), 8.98 (s, 1 H), 7.95 (s, 1 H), 7.92 (d, J = 3, 5.4 Hz, 2 H), 7.66 (dd, J = 1.8, 5.4 Hz, 2 H), 7.26 (t, J = 9 Hz, 2 H), 7.14 (t, J = 9 Hz, 2 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 162.4, 157.5, 153.7, 140.2, 135.9, 131.5, 129.6, 122.3, 115.9, 115.3.

HRMS (Q-TOF): m/z [M + H]$^+$ calcd for $C_{14}H_{11}N_3F_2O^+$: 276.0943; found: 276.0961.

N^1-(4-Fluorobenzylidene)-N^4-(2,4-dichlorophenyl)semicarbazone (7c$_1$)

Yield: 190.2 mg (90%); white solid; mp 235–237 °C; R_f 0.54 (hexane/EtOAc, 2:1).

FTIR (ATR): 3341, 3197, 3086, 2962, 2831, 1689 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.17 (s, 1 H), 8.93 (s, 1 H), 8.16 (d, J = 9.0 Hz, 1 H), 8.01 (s, 1 H), 7.81 (dd, J = 3, 6 Hz, 2 H), 7.70 (d, J = 2.4 Hz, 1 H), 7.43 (dd, J = 2.4, 6.6 Hz, 1 H), 7.30 (d, J = 9 Hz, 2 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 162.6, 152.7, 141.1, 134.9, 131.1, 129.3, 129.1, 128.3, 127.5, 124.6, 122.9, 116.5.

HRMS (Q-TOF): m/z [M + H]$^+$ calcd for $C_{14}H_{11}N_3Cl_2FO^+$: 326.0258; found: 326.0263.

N^1-(4-Fluorobenzylidene)-N^4-(3-methylphenyl)semicarbazone (7d$_1$)

Yield: 149.8 mg (85%); white solid; mp 152–154 °C; R_f 0.47 (hexane/EtOAc, 2:1).

FTIR (ATR): 3365, 2916, 2848, 1628 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.72 (s, 1 H), 8.82 (s, 1 H), 7.95 (s, 1 H), 7.92 (dd, J = 3, 6 Hz, 2 H), 7.48 (d, J = 4.2 Hz, 1 H), 7.46 (s, 1 H), 7.26 (d, J = 9 Hz, 2 H), 7.18 (t, J = 7.8 Hz, 1 H), 6.84 (d, J = 7.2 Hz, 1 H), 2.29 (s, 1 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 162.4, 153.5, 140.0, 139.4, 138.1, 131.5 129.6, 128.8, 123.7, 120.9, 117.5, 115.9, 21.6.

HRMS (Q-TOF): m/z [M + H]$^+$ calcd for $C_{15}H_{15}N_3FO^+$: 272.1194; found: 272.1209.

N^1-(4-Fluorobenzylidene)-N^4-(4-acetylphenyl)semicarbazone (7e$_1$)

Yield: 171 mg (88%), white solid; mp 232–233 °C; R_f 0.55 (hexane/EtOAc, 2:1).

FTIR (ATR): 3368, 3200, 3099, 2964, 2857, 1693 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.93 (s, 1 H), 9.26 (s, 1 H), 7.98 (s, 1 H), 7.95 (d, J = 5.4 Hz, 2 H), 7.92 (d, J = 8.4 Hz, 2 H), 7.86 (d, J = 9 Hz, 2 H), 7.28 (t, J = 9 Hz, 2 H), 2.54 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 196.9, 164.1, 162.5, 153.2, 144.3, 140.9, 131.4, 131.3, 129.8, 129.7, 119.1, 116.1, 26.9.

HRMS (Q-TOF): m/z [M + H]$^+$ calcd for $C_{16}H_{15}N_3FO_2^+$: 300.1143; found: 300.1158.

N^1-(4-Fluorobenzylidene)-N^4-(3-ethoxycarbonylphenyl)semicarbazone (7f$_1$)

Yield: 175.4 mg (82%); white solid; mp 142–144 °C; R_f 0.58 (hexane/EtOAc, 2:1).

FTIR (ATR): 3374, 3200, 3085, 2964, 1680 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.82 (s, 1 H), 9.18 (s, 1 H), 7.96 (s, 1 H), 7.95 (d, J = 5.4 Hz, 2 H), 7.95 (d, J = 5.4 Hz, 1 H), 7.63 (d, J = 7.8 Hz, 1 H), 7.45 (t, J = 7.8 Hz, 1 H), 7.28 (d, J = 9 Hz, 2 H), 4.33 (q, J = 7.2 Hz, 2 H),1.33 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 166.3, 164.1, 162.4, 153.6, 140.5 131.5, 130.7, 129.8, 129.2, 125.1, 123.6, 120.8, 115.9, 61.2, 14.7.

HRMS (Q-TOF): m/z [M + H]$^+$ calcd for $C_{17}H_{17}N_3FO_3^+$: 330.1248; found: 330.1264.

N^1-(4-Fluorobenzylidene)-N^4-(1-naphthyl)semicarbazone (7g$_1$)

Yield: 179.7 mg (90%); white solid; mp 212–214 °C; R_f 0.39 (hexane/EtOAc, 2:1).

FTIR (ATR): 3320, 3193, 2959, 2862, 1641 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.85 (s, 1 H), 9.23 (s, 1 H), 8.01 (s, 1 H), 7.99 (d, J = 7.8 Hz, 1 H), 7.97 (m, J = 4.2 Hz, 1 H), 7.95 (d, J = 6 Hz, 1 H), 7.79 (d, J = 7.8 Hz, 1 H), 7.69 (d, J = 7.2 Hz, 1 H), 7.57 (t, J = 8.4 Hz, 2 H), 7.53 (t, J = 7.8 Hz, 1 H), 7.28 (d, J = 9 Hz, 2 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 154.5, 139.9, 134.5, 134.2, 131.7, 129.5, 129.2, 128.6, 126.3, 126.1, 125.4, 123.1, 122.71, 116.0.

HRMS (Q-TOF): m/z [M + H]$^+$ calcd for $C_{18}H_{15}N_3FO^+$: 308.1194; found: 308.1208.

N^1-(3-Methoxybenzylidene)-N^4-phenylsemicarbazone (7a$_2$)

Yield: 157.4 mg (90%); white solid; mp 130–132 °C; R_f 0.55 (hexane/EtOAc, 2:1).

FTIR (ATR): 3371, 3193, 3094, 2963, 2832, 1680 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.74 (s, 1 H), 8.91 (s, 1 H), 7.93 (s, 1 H), 7.65 (d, *J* = 7.2 Hz, 2 H), 7.45 (s, 1 H), 7.35 (d, *J* = 7.8 Hz, 1 H), 7.32 (t, *J* = 7.8 Hz, 1 H), 7.29 (t, *J* = 7.8 Hz, 2 H), 7.01 (t, *J* = 7.2 Hz, 1 H), 6.95 (dd, *J* = 1.2, 6.6 Hz, 1 H), 3.83 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 160.02, 153.5, 141.2, 139.5, 136.3, 130.2, 128.9, 123.0, 120.4, 115.9, 115.9, 112.1, 55.7.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}N_3O_2^+$: 270.1237; found: 270.1252.

N^1-(3-Methoxybenzylidene)-*N*^{4}-(4-fluorophenyl)semicarbazone (7b$_2$)

Yield: 164.2 mg (88%); white solid; mp 125–127 °C; R_f 0.41 (hexane/EtOAc, 2:1).

FTIR (ATR): 3314, 3240, 2998, 2957, 2836, 1673 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.76 (s, 1 H), 9.00 (s, 1 H), 7.93 (s, 1 H), 7.67 (dd, *J* = 1.8, 5.4 Hz, 2 H), 7.45 (s, 1 H), 7.36 (d, *J* = 7.2 Hz, 1 H), 7.34 (t, *J* = 7.2 Hz, 1 H), 7.14 (t, *J* = 9 Hz, 2 H), 6.97 (dd, *J* = 1.2, 6.6 Hz, 1 H), 3.82 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 160.01, 157.6, 153.7, 141.2, 136.3, 135.9, 130.1, 122.4, 120.4, 115.9, 115.3, 112.1, 55.7.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}N_3FO_2^+$: 288.1143; found: 288.1155.

N^1-(3-Methoxybenzylidene)-*N*^{4}-(2,4-dichlorophenyl)semicarbazone (7c$_2$)

Yield: 201.6 mg (92%); white solid; mp 200–201 °C; R_f 0.61 (hexane/EtOAc, 2:1).

FTIR (ATR): 3360, 3203, 3099, 2969, 2831, 1696 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.76 (s, 1 H), 9.00 (s, 1 H), 8.21 (d, *J* = 9 Hz, 1 H), 7.98 (s, 1 H), 7.70 (s, 1 H), 7.44 (dd, *J* = 2.4, 6 Hz, 1 H), 7.37 (t, *J* = 7.8 Hz, 1 H), 7.33 (s, 1 H), 7.28 (d, *J* = 7.8 Hz, 1 H), 7.00 (dd, *J* = 2.4, 5.4 Hz, 1 H), 3.80 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 160.0, 152.9, 141.9, 135.9, 134.9, 130.5, 129.1, 128.4, 127.4, 124.2, 122.6, 120.1, 116.6, 111.1, 55.5.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}N_3Cl_2O_2^+$: 338.0458; found: 338.0464.

N^1-(3-Methoxybenzylidene)-*N*^{4}-(3-methylphenyl)semicarbazone (7d$_2$)

Yield: 147.2 mg (80%); white solid; mp 142–144 °C; R_f 0.50 (hexane/EtOAc, 2:1).

FTIR (ATR): 3371, 3193, 3083, 2952, 2837, 1680 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.75 (s, 1 H), 8.85 (s, 1 H), 7.93 (s, 1 H), 7.50 (s, 1 H), 7.46 (d, *J* = 8.4 Hz, 1 H), 7.44 (s, 1 H), 7.37 (d, *J* = 7.8 Hz, 1 H), 7.34 (t, *J* = 7.8 Hz, 1 H), 7.18 (t, *J* = 7.8 Hz, 1 H), 6.97 (dd, *J* = 1.2, 6.6 Hz, 1 H), 6.85 (d, *J* = 7.8 Hz, 1 H), 3.82 (s, 3 H), 2.30 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 160.0, 153.5, 141.1, 139.4, 138.1, 136.3, 130.2, 128.7, 123.7, 120.9, 120.3, 117.6, 115.8, 112.1, 55.7, 21.7.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}N_3O_2^+$: 284.1394; found: 284.1407.

N^1-(3-Methoxybenzylidene)-*N*^{4}-(4-acetylphenyl)semicarbazone (7e$_2$)

Yield: 157.3 mg (82%); white solid; mp 129–131 °C; R_f 0.52 (hexane/EtOAc, 2:1).

FTIR (ATR): 3354, 3185, 3082, 2951, 2837, 1693 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.96 (s, 1 H), 9.29 (s, 1 H), 7.96 (d, *J* = 9 Hz, 1 H), 7.93 (d, *J* = 9 Hz, 2 H), 7.86 (d, *J* = 9 Hz, 2 H), 7.48 (s, 1 H), 7.39 (d, *J* = 7.2 Hz, 1 H), 7.36 (t, *J* = 7.8 Hz, 1 H), 6.99 (dd, *J* = 1.2, 6.6 Hz, 1 H), 3.83 (s, 3 H), 2.53 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 196.9, 160.0, 153.3, 144.3, 141.9, 136.1, 131.4, 130.2, 129.7, 120.5, 119.1, 116.0, 112.3, 55.7, 26.9.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_3O_3^+$: 312.1343; found: 312.1355.

N^1-(3-Methoxybenzylidene)-*N*^{4}-(3-ethoxycarbonylphenyl)semicarbazone (7f$_2$)

Yield: 188.5 mg (85%); white solid; mp 104–106 °C; R_f 0.57 (hexane/EtOAc, 2:1).

FTIR (ATR): 3394, 3193, 3092, 2978, 1687 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.85 (s, 1 H), 9.21 (s, 1 H), 8.35 (s, 1 H), 7.95 (s, 1 H), 7.93 (d, *J* = 1.8 Hz, 1 H), 7.62 (d, *J* = 7.2 Hz, 1 H), 7.48 (s, 1 H), 7.45 (t, *J* = 7.8 Hz, 1 H), 7.40 (d, *J* = 7.8 Hz, 1 H), 7.35 (t, *J* = 7.8 Hz, 1 H), 6.98 (dd, *J* = 1.8, 6.6 Hz, 1 H), 4.33 (q, *J* = 7.2 Hz, 2 H), 3.83 (s, 3 H),1.33 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 166.3, 160.0, 153.6, 141.5, 140.0, 136.2, 130.7, 130.1, 129.2, 125.1, 123.6, 120.9, 120.4, 115.8, 112.3, 61.2, 55.7, 14.7.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}N_3O_4^+$: 342.1448; found: 342.1458.

N^1-(3-Methoxybenzylidene)-*N*^{4}-(1-naphthyl)semicarbazone (7g$_2$)

Yield: 186.7 mg (90%); white solid; mp 194–196 °C; R_f 0.57 (hexane/EtOAc, 2:1).

FTIR (ATR): 3380, 3187, 3091, 2959, 2868, 1683 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.88 (s, 1 H), 9.24 (s, 1 H), 8.00 (d, *J* = 3.6 Hz, 1 H), 7.99 (s, 1 H), 7.97 (d, *J* = 7.2 Hz, 1 H), 7.79 (d, *J* = 8.4 Hz, 1 H), 7.73 (d, *J* = 7.2 Hz, 1 H), 7.56 (dt, *J* = 1.2, 2.4 Hz, 2 H), 7.53 (t, *J* = 7.2 Hz, 1 H), 7.52 (s, 1 H), 7.36 (d, *J* = 5.4 Hz, 1 H), 7.34 (t, *J* = 7.8 Hz, 1 H), 6.98 (d, *J* = 2.4, 6.6 Hz, 1 H), 3.83 (s, 3 H), 2.53 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 160.1, 154.4, 141.0, 136.4, 134.4, 134.2, 130.2, 129.1, 128.6, 126.4, 126.3, 126.1, 125.3, 122.3, 120.4, 116.1, 111.4, 55.7.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{18}N_3O_2^+$: 320.1394; found: 320.1402.

N^1-(4-Isopropylbenzylidene)-*N*^{4}-phenylsemicarbazone (7a$_3$)

Yield: 146.2 mg (80%); white solid; mp 140–142 °C; R_f 0.65 (hexane/EtOAc, 2:1).

FTIR (ATR): 3377, 3193, 3089, 2952, 2863, 1675 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.67 (s, 1 H), 8.85 (s, 1 H), 7.93 (s, 1 H), 7.76 (d, *J* = 7.8 Hz, 2 H), 7.66 (d, *J* = 7.8 Hz, 2 H), 7.30 (d, *J* = 7.8 Hz, 2 H), 7.30 (t, *J* = 7.8 Hz, 2 H), 7.02 (t, *J* = 7.8 Hz, 1 H), 2.93 (m, *J* = 7.2 Hz, 1 H), 1.22 (d, *J* = 7.2 Hz, 6 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 153.5, 150.4, 141.3, 139.5, 132.6, 128.9, 127.6, 127.0, 122.9, 120.3, 33.8, 24.2.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{20}N_3O^+$: 282.1601; found: 282.1615.

N^1-(4-Isopropylbenzylidene)-*N*^{4}-(4-fluorophenyl)semicarbazone (7b$_3$)

Yield: 153.6 mg (79%); white solid; mp 114–116 °C; R_f 0.50 (hexane/EtOAc, 2:1).

FTIR (ATR): 3368, 2917, 2850, 1633 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 10.70 (s, 1 H), 8.94 (s, 1 H), 7.93 (s, 1 H), 7.76 (d, *J* = 7.8 Hz, 2 H), 7.67 (dd, *J* = 4.8 Hz, 2 H), 7.30 (d, *J* = 7.8 Hz, 2 H), 7.14 (t, *J* = 9 Hz, 2 H), 2.92 (m, *J* = 7.2 Hz, 1 H), 1.22 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 157.4, 153.7, 150.4, 141.4, 135.9, 132.6, 127.6, 127.0, 122.2, 115.3, 33.8, 24.2.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{19}N_3FO^+$: 300.1507; found: 300.1519.

N^1-(4-Isopropylbenzylidene)-*N*^{4}-(2,4-dichlorophenyl)semicarbazone (7c$_3$)

Yield: 186 mg (82%); white solid; mp 191–193 °C; R_f 0.55 (hexane/EtOAc, 2:1).

FTIR (ATR): 3350, 3193, 3115, 2959, 1689 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 11.11 (s, 1 H), 8.94 (s, 1 H), 8.24 (d, *J* = 12 Hz, 1 H), 7.98 (s, 1 H), 7.70 (d, *J* = 2.4 Hz, 1 H), 7.64 (d, *J* = 7.8 Hz, 2 H), 7.42 (dd, *J* = 2.4, 6.6 Hz, 1 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 2.92 (m, *J* = 6.6 Hz, 1 H), 1.21 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 152.7, 151.0, 142.3, 134.9, 132.1, 129.0, 128.4, 127.4, 127.2, 124.0, 122.3, 33.8, 24.2.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_3Cl_2O^+$: 350.0821; found: 350.0831.

N^1-(4-Isopropylbenzylidene)-*N*^{4}-(3-methylphenyl)semicarbazone (7d$_3$)

Yield: 157.3 mg (82%); white solid; mp 146–148 °C; R_f 0.68 (hexane/EtOAc, 2:1).

FTIR (ATR): 3377, 3188, 3089, 2958, 2853, 1680 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 10.67 (s, 1 H), 8.77 (s, 1 H), 7.92 (s, 1 H), 7.75 (d, *J* = 7.8 Hz, 2 H), 7.49 (s, 1 H), 7.46 (d, *J* = 8.4 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 2 H), 7.17 (t, *J* = 7.8 Hz, 1 H), 6.83 (d, *J* = 7.8 Hz, 1 H), 2.90 (m, *J* = 7.2 Hz, 1 H), 2.30 (s, 3 H), 1.22 (d, *J* = 7.2 Hz, 6 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 153.5, 150.4, 141.3, 139.4, 138.1, 132.6, 128.8, 127.5, 127.0, 123.6, 120.7, 117.4, 33.8, 24.2, 21.6.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{22}N_3O^+$: 296.1757; found: 296.1770.

N^1-(4-Isopropylbenzylidene)-*N*^{4}-(4-acetylphenyl)semicarbazone (7e$_3$)

Yield: 147.1 mg (70%); white solid; mp 136–138 °C; R_f 0.48 (hexane/EtOAc, 2:1).

FTIR (ATR): 3365, 3180, 3018, 2964, 2857, 1673 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 10.90 (s, 1 H), 9.25(s, 1 H), 8.00 (s, 1 H), 7.98 (d, *J* = 9 Hz, 2 H), 7.91 (d, *J* = 9 Hz, 1 H), 7.83 (d, *J* = 8.4 Hz, 1 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 2.98 (m, *J* = 6.6 Hz, 1 H), 2.59 (s, 3 H), 1.28 (d, *J* = 7.2 Hz, 6 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 197.0, 153.2, 150.6, 144.3, 140.1, 132.4, 131.4, 129.7), 127.7, 127.0, 119.1, 33.8, 26.8, 24.2.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}N_3O_2$: 324.1707; found: 324.1718.

N^1-(4-Isopropylbenzylidene)-*N*^{4}-(3-ethoxycarbonylphenyl)semicarbazone (7f$_3$)

Yield: 172.2 mg (75%); white solid; mp 120 °C; R_f 0.57 (hexane/EtOAc, 2:1).

FTIR (ATR): 3448, 3193, 3092, 2957, 2884, 1664 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 10.75 (s, 1 H), 9.13 (s, 1 H), 8.33 (s, 1 H), 7.96 (s, 1 H), 7.95 (s, 1 H), 7.78 (d, *J* = 8.4 Hz, 2 H), 7.62 (d, *J* = 7.8 Hz, 1 H), 7.44 (t, *J* = 7.8 Hz, 1 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 4.33 (q, *J* = 7.2 Hz, 2 H), 2.92 (m, *J* =6.6 Hz, 1 H), 1.33 (t, *J* = 7.2 Hz, 3 H), 1.22 (d, *J* = 7.2 Hz, 6 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 166.3, 153.6, 150.5, 141.7, 140.1, 132.5, 130.7, 129.2, 127.7, 127.0, 124.9, 123.5, 120.9, 61.2, 33.8, 24.2, 14.7.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{24}N_3O_3^+$: 354.1812; found: 354.1824.

N^1-(4-Isopropylbenzylidene)-*N*^{4}-(1-naphthyl)semicarbazone (7g$_3$)

Yield: 183 mg (85%); white solid; mp 171–173 °C; R_f 0.72 (hexane/EtOAc, 2:1).

FTIR (ATR): 3350, 3195, 3110, 2960, 1689 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 10.85 (s, 1 H), 9.18 (s, 1 H), 8.01 (s, 1 H), 8.00 (s, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 7.77 (d, *J* = 7.8 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 1 H), 7.58 (t, *J* = 8.4 Hz, 1 H), 7.54 (t, *J* = 7.2 Hz, 1 H), 7.51 (t, *J* = 7.8 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 2.92 (m, *J* = 6 Hz, 1 H), 1.22 (d, *J* = 6 Hz, 6 H).

^{13}C NMR (600 MHz, DMSO-d_6): δ = 154.4, 150.4, 141.3, 134.4, 134.2, 132.7, 128.7, 128.6, 127.4, 127.1, 126.4, 126.1, 125.1, 122.8, 121.8, 33.8, 24.2.

HRMS (Q-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}N_3O^+$: 332.1752; found: 332.1773.

Funding Information

Grand Challenge (GC001C-14AET), PPP Grant PG208-2015B provided by the University of Malaya and Ministry of Higher Education, Malaysia (MOHE).

Acknowledgment

The authors would like to thank the University of Malaya and the Ministry of Higher Education, Malaysia for their cordial support in completing this work. We also thank Dr. Rauful Alam (Postdoc Researcher, University of Pennsylvania) for his valuable suggestions.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609557.

References

(1) (a) Dugger, R. W.; Ragan, J. A.; Ripin, D. H. B. *Org. Process Res. Dev.* **2005**, *9*, 253. (b) Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C. J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740.

(2) (a) Pandeya, S. N. *Acta Pharm.* **2012**, *62*, 263. (b) Liu, Z.; Wu, S.; Wang, Y.; Li, R.; Wang, J.; Wang, L.; Zhao, Y.; Gong, P. *Eur. J. Med. Chem.* **2014**, *87*, 782. (c) Yogeeswari, P.; Sriram, D.; Pandeya, S. N.; Stables, J. P. *Farmaco* **2004**, *59*, 609. (d) Dimmock, J.; Baker,

G. *Epilepsia* **1994**, *35*, 648. (e) Mishra, V.; Pandeya, S. N.; Pannecouque, C.; Witvrouw, M.; De Clercq, E. *Arch. Pharm.* **2002**, *335*, 183.

(3) (a) Yogeeswari, P.; Sriram, D.; Veena, V.; Kavya, R.; Rakhra, K.; Ragavendran, J. V.; Mehta, S.; Thirumurugan, R.; Stables, J. *Biomed. Pharmacother.* **2005**, *59*, 51. (b) Yogeeswari, P.; Thirumurugan, R.; Kavya, R.; Samuel, J. S.; Stables, J.; Sriram, D. *Eur. J. Med. Chem.* **2004**, *39*, 729.

(4) (a) Pelosi, G.; Bisceglie, F.; Bignami, F.; Ronzi, P.; Schiavone, P.; Re, M. C.; Casoli, C.; Pilotti, E. *J. Med. Chem.* **2010**, *53*, 8765. (b) Noblía, P.; Baran, E. J.; Otero, L.; Draper, P.; Cerecetto, H.; González, M.; Piro, O. E.; Castellano, E. E.; Inohara, T.; Adachi, Y. *Eur. J. Inorg. Chem.* **2004**, 322.

(5) Douchez, A.; Lubell, W. D. *Org. Lett.* **2015**, *17*, 6046.

(6) (a) Yogeeswari, P.; Sriram, D.; Thirumurugan, R.; Raghavendran, J. V.; Sudhan, K.; Pavana, R. K.; Stables, J. *J. Med. Chem.* **2005**, *48*, 6202. (b) Jung, M. E.; Chamberlain, B. T.; Ho, C.-L. C.; Gillespie, E. J.; Bradley, K. A. *ACS Med. Chem. Lett.* **2014**, *5*, 363. (c) Pandeya, S. N.; Yogeeswari, P.; Stables, J. P. *Eur. J. Med. Chem.* **2000**, *35*, 879. (d) Jafri, L.; Ansari, F. L.; Jamil, M.; Kalsoom, S.; Qureishi, S.; Mirza, B. *Chem. Biol. Drug Des.* **2012**, *79*, 950.

(7) Asís, S. E.; Bruno, A. M.; Martínez, A. R.; Sevilla, M. a. V.; Gaozza, C. H.; Romano, A. M.; Coussio, J. D.; Ciccia, G. *Farmaco* **1999**, *54*, 517.

(8) Saravanan, S.; Sridharan, V.; Muthusubramanian, S. *Synth. Commun.* **2006**, *36*, 849.

(9) Garland, K.; Gan, W.; Depatie-Sicard, C.; Beauchemin, A. M. *Org. Lett.* **2013**, *15*, 4074.

(10) Ariffin, A.; Rahman, N. A.; Yehye, W. A.; Alhadi, A. A.; Kadir, F. A. *Eur. J. Med. Chem.* **2014**, *87*, 564.

(11) (a) Majumdar, P.; Pati, A.; Patra, M.; Behera, R. K.; Behera, A. K. *Chem. Rev.* **2014**, *114*, 2942. (b) Drummond, J. T.; Johnson, G. *J. Heterocycl. Chem.* **1988**, *25*, 1123.

(12) Azam, F.; El-gnidi, B. A.; Alkskas, I. A. *Eur. J. Med. Chem.* **2010**, *45*, 2817.