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Full Paper

Synthesis, Analgesic and Anti-Inflammatory Activity of 4-(2-Phenoxyphenyl)semicarbazones

Ardeshir Rineh[1], Nosratollah Mahmoodi[1], Mohammad Abdollahi[2], Alireza Foroumadi[3], Maedeh Sorkhi[3], and Abbas Shafiee[3]

[1] Department of Chemistry, University of Guilan, Rasht, Iran
[2] Department of Pharmacology and Toxicology, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran
[3] Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

A series of 4-(2-phenoxyphenyl)semicarbazones was synthesized and evaluated for their analgesic and anti-inflammatory activities. Several compounds (e.g. **10h**, **10i**, and **11i**) were found to be more potent than the reference drug mefenamic acid in the formalin test. Based on the results of an anti-inflammatory study, 1-(1-(2,5-dimethoxyphenyl)ethylidene)-4-(2-phenoxyphenyl)semicarbazide **11i** was the most active compound.

Keywords: Analgesic activity / Anti-inflammatory activity / Semicarbazones

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Introduction

Non steroidal anti-inflammatory drugs (NSAID's) are widely used in the treatment of pain and inflammation. NSAID's reduce the pain and swelling associated with arthritis by blocking the metabolism of arachidonic acid (AA) through the enzyme cyclooxygenase (COX) and thereby the production of prostaglandins, e.g. PGE_2, which sensitizes nociceptors at nerve fiber terminals [1, 2].

Additionally, the 5-lipoxygenase (5-LO) products such as leukotriene B_4 (LTB_4) also contributes to the hyperalgesia seen during inflammation by decreasing the mechanical and thermal thresholds of C fibers [3]. Leukotrienes, especially LTB_4 together with prostaglandins are implicated in the acute ulceration induced by NSAID's [4]. For these reasons, compounds that achieve dual inhibition of the enzymes COX and 5-LO reduce side effects and improved the efficacy in the combat of pain in inflammatory diseases [5]. Compound **1** (Fig. 1) was described as a dual COX/5-LO inhibitor [6, 7]. Furthermore, there are several reports about the synthesis and pharmacological evaluation of new bioactive *N*-aroylarylhydrazones acting at the AA cascade enzyme level (Fig. 1, compounds **2** – **4**) [8 – 10]. As a part of our ongoing research program [11 – 13] to find novel anti-inflammatory and analgesic compounds, herein, we describe the synthesis, analgesic and anti-inflammatory activity of 4-(2-phenoxyphenyl)semicarbazones.

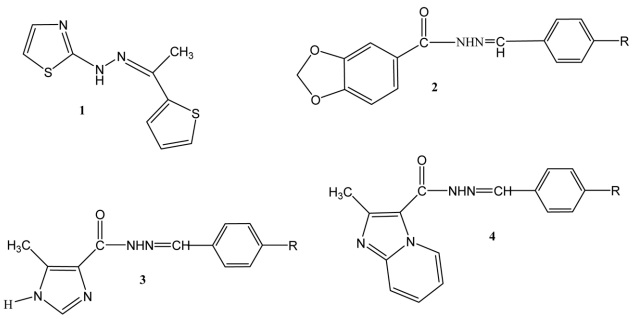
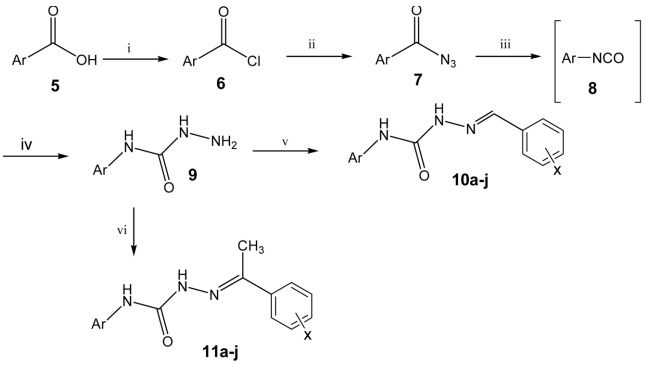


Figure 1. Structures of hydrazones **1** – **4**.

Correspondence: Abbas Shafiee, Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, 14174 Iran.
E-mail: ashafiee@ams.ac.ir
Fax: +98 21 664-61178

Abbreviations: arachidonic acid (AA), cyclooxygenase (COX); leukotriene B_4, (LTB_4); 5-lipoxygenase (5-LO); non steroidal anti-inflammatory drugs (NSAID's)



Ar = 2-phenoxyphenyl

Reagents and conditions: (i) $SOCl_2$, C_6H_6/reflux, 3 h; (ii) NaN_3 /PhN(Et)$_2$, C_6H_6; (iii) $C_6H_6\Delta$/; (iv) $NH_2NH_2 \times H_2O$, diethyl ether/r.t.; (v) substituted benzaldehyde, EtOH; (vi) substituted acetophenone, EtOH.

Scheme 1 Synthesis route of compounds **5–11**.

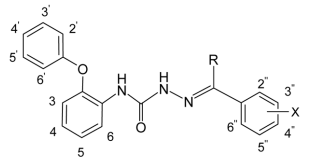
Chemistry

The designed compounds were synthesized according to Scheme 1. Reaction of 2-phenoxybenzoic acid **5** with thionyl chloride followed by sodium azide afforded azido(2-phenoxyphenyl)methanone **7**. Heating of compound **7** in dry benzene gave 2-phenoxybenzeneisocyanate **8** as an intermediate. Reaction of hydrazine hydrate with compound **8** afforded 4-(2-phenoxyphenyl)semicarbazide **9** in high yield. Reaction of compound **9** with various benzaldehydes and acetophenones in ethanol yielded the corresponding semicarbazones **10** and **11**, respectively (Table 1).

Pharmacology

All the tested compounds were initially dissolved in DMSO and diluted with H_2O. The final concentration of DMSO was 5%. Male NMRI mice weighing 20–25 g and male Wistar rats weighing 200–250 g (from the animal house of the Faculty of Pharmacy, TUMS) were used for the formalin test and the carrageenan-induced paw edema, respectively. The animals were housed in colony cages, conditions of constant temperature (22 ± 2°C), a 12 h light/dark schedule, and allowed free access to standard diet and tap water except during the experiment. The animals were allowed to habituate to the laboratory environment for 2 h before the experiments were initiated. All ethical manners for use of laboratory animals were considered carefully and the protocol of study was approved by TUMS ethical committee. The compounds were administered intraperitoneally (ip.) (30 mg/kg; 0.2 mL/20g) as a suspension in saline and tween 80 (5% w/v) 30 min before formalin injection. Mefenamic acid (Hakim Pharmaceutical Co., Tehran, Iran) (30 mg/kg, ip.) was used as standard drug under the same conditions. The control group received vehicle (0.2 mL/20g, ip.) alone.

Table 1. Physical properties of compounds **10a–j** and **11a–j**.



Compound No.	R	X	Mp. (°C)	Yield (%)	Formula[a)]
10a	H	2-Cl	150–152	85	$C_{20}H_{16}ClN_3O_2$
10b	H	3-Cl	160–162	75	$C_{20}H_{16}ClN_3O_2$
10c	H	4-Cl	189–190	80	$C_{20}H_{16}ClN_3O_2$
10d	H	2-OH	202–204	60	$C_{20}H_{17}N_3O_3$
10e	H	3-OH	197–200	55	$C_{20}H_{17}N_3O_3$
10f	H	4-OH	194–196	55	$C_{20}H_{17}N_3O_3$
10g	H	2-NO_2	160–162	85	$C_{20}H_{16}N_4O_4$
10h	H	3-NO_2	175–177	80	$C_{20}H_{16}N_4O_4$
10i	H	4-NO_2	235–236	80	$C_{20}H_{16}N_4O_4$
10j	H	4-Me	187–189	90	$C_{21}H_{19}N_3O_2$
11a	CH_3	2-NO_2	214–216	75	$C_{21}H_{18}N_4O_4$
11b	CH_3	3-NO_2	240–243	70	$C_{21}H_{18}N_4O_4$
11c	CH_3	4-NO_2	236–238	70	$C_{21}H_{18}N_4O_4$
11d	CH_3	2-Cl	166–168	70	$C_{21}H_{18}ClN_3O_2$
11e	CH_3	3-Cl	210–212	65	$C_{21}H_{18}ClN_3O_2$
11f	CH_3	4-Cl	214–216	65	$C_{21}H_{18}ClN_3O_2$
11g	CH_3	3-Br	198–200	60	$C_{21}H_{18}BrN_3O_2$
11h	CH_3	4-Br	215–217	60	$C_{21}H_{18}BrN_3O_2$
11i	CH_3	2,5-OMe	166–168	55	$C_{23}H_{23}N_3O_4$
11j	CH_3	4-OMe	176–178	70	$C_{22}H_{21}N_3O_3$

[a)] All compounds were analyzed for C, H, N. Analytical results obtained for these elements were within ± 0.4% of the calculated value for the formula shown.

Formalin-induced test

All final compounds (**10** and **11**) were tested in the formalin-induced pain test. Twenty-five microliters of formalin (0.5%) was injected subcutaneously into the dorsal surface of the right hind paw of the mouse using a micro syringe with a 26-gauge needle. Immediately after the formalin injection, animals were placed individually in glass cylinder (20 cm wide, 25 cm long) and a glass door and a mirror were arranged at a 45° angle under the cylinder to allow clear observation of the paws of the animals. The total time in seconds that the animal spent licking or biting the injected paw during the period of 0–10 min was considered as indicator of neurogenic pain (early phase) and during the 10–30 min (late phase) represented the inflammatory pain [14].

Anti-inflammatory activity

The anti-inflammatory activity was determined *in vivo* using the carrageenan-induced rat paw edema test [10, 15]. A solution of 0.1 mL of 1% carrageenan (Sigma-Aldrich, Dorset, UK) in saline was injected subplantarly in the right hind paw of the rats 1 h after ip. administration of the compounds. The paw thickness was measured from the ventral to the dorsal surfaces using a dial caliper immediately prior to carrageenan injection and then at each hour, up to 4 h after the subplantar injection. The edema was calculated as the thickness variation between the carrageenan- and saline-treated paw. Anti-inflammatory activity was expressed as percent of inhibition of the edema when compared with the control group.

Statistics

The results are expressed as the mean ± SEM of four animals per group. The data were statistically analyzed by one-way analysis of Variance (ANOVA) followed by Tukey multi-comparison test. Differences with $P < 0.05$ between experimental groups were considered statistically significant.

Results and discussion

The analgesic effects of aldehyde and acetophenone semicarbazones **10a–10j** and **11a–11j** are shown in Table 2. As it could be seen from Table 2, all compounds except **10f** showed significant reduction of formalin-induced nociception. This effect was comparable or better than the reference drug mefenamic acid. In aldehyde series, compounds **10g**, **10h**, and **10i** were more potent that mefenamic acid. In this series, all isomeric nitrophenyl analogues were active and the order of analgesic activity was 3-NO_2 ≥ 4-NO_2 > 2-NO_2. The same order of analgesic activity was observed in the nitro-analogues of acetophenone series, compounds **11b**, **11c**, and **11a**. In addition, it seems that OH substituent caused the decrease or elimination of activity, compounds **10d**, **10e** and **10f**. All halogenated derivatives, **11d–11h** also showed moderate analgesic activity. In the acetophenone series, compounds **11a**, **11b**, **11c, 11g**, and **11i** were more active than mefenamic acid and the order of activity was **11i** > **11g** > **11b** > **11c** > **11a**. In general, aldehydes were more active than ketones. The anti-inflammatory activity of the synthesized compounds is summarized in Table 3. Comparison of the anti-inflammatory activity of all tested compounds revealed that compound **11i** was the most active compound in both aldehyde and acetophenone semicarbazone series. As can be seen from Table 3, both, 3-nitro phenyl analogues of aldehyde or acetophenone, **10h** and **11b,** were also potent anti-inflammatory agents in comparison to indomethacin as the reference drug. Among aldehydes, the tested compounds **10g**, **10h**, and **10i** showed significant anti-inflammatory activity. The most active compound was **10h** which was comparable to indomethacin as the reference drug. Among acetophenones, compounds **11b**, **11g**, and **11i** showed a significant anti-inflammatory effect. Compound **11i** was the most potent in this series. In contrast to the good analgesic activity of halogenated derivatives, all halogenated analogues, except **11g**, showed no anti-inflammatory activity. In summary, the analgesic activity of the synthesized compounds was better than anti-inflammatory activity.

Table 2. Analgesic activity of 4-(2-phenoxyphenyl)semicarbazones.

Compound	Dose (mg/kg)[a]	Nociception (mean ± SEM)	Inhibition (%)[b]	Relative Activity[c]
Control	–	83 ± 6.72	–	–
Mefenamic acid	30	34.75 ± 2.66	58.13	1**
10a	30	32.5 ± 5.12	60.84	1.04**
10b	30	32 ± 4.41	61.44	1.05**
10c	30	35 ± 5.58	57.83	0.99**
10d	30	40 ± 4.46	51.80	0.89**
10e	30	38 ± 5.21	54.21	0.93**
10f	30	80.5 ± 7.59	3.01	0.05
10g	30	25 ± 7.26	69.88	1.20**
10h	30	12.5 ± 4.48	84.93	1.46**
10i	30	14 ± 3.10	83.13	1.43**
10j	30	38 ± 3.24	54.21	0.93**
11a	30	29.75 ± 5.80	64.15	1.10*
11b	30	22.25 ± 7.05	73.19	1.26**
11c	30	22.50 ± 4.53	72.89	1.25**
11d	30	36 ± 10.52	56.62	0.97*
11e	30	42.75 ± 3.81	48.49	0.83**
11f	30	31.75 ± 6.30	61.75	1.06*
11g	30	20.5 ± 3.2	75.30	1.29**
11h	30	34.25 ± 11.27	58.73	1.01*
11i	30	16.5 ± 2.33	80.12	1.37**
11j	30	50.0 ± 13.52	39.75	0.68*

[a] Number of animals in each group n = 4.
[b] Percentage if inhibition obtained by comparison with vehicle control group.
[c] Analgesic activity relative to mefenamic acid. * and ** differed from control group $P < 0.05$ and $P < 0.01$, respectively.

Experimental

Chemicals were purchased from Merck Chemical Company (Darmstadt, Germany). Melting points were taken on a Kofler hot stage apparatus (Reichert, Vienna, Austria) and are uncorrected. ^{1}H-NMR spectra were obtained using a Brucker FT-80 and a Brucker FT-500 spectrometer (Brucker, Rheinstetten, Germany). Tetramethylsilane was used as an internal standard.

Table 3. Anti-inflammatory activity of 4-(2-phenoxyphenyl)semicarbazones.

Compound	Time (h)	Dose (mg/kg)[a)]	Thickness variation (mm)[b)]	Inhibition (%)[c)]
Control	1	–	0.8 ± 0.24	–
	2	–	1.62 ± 0.09	–
	3	–	1.78 ± 0.15	–
	4	–	1.52 ± 0.27	–
Indomethacin	1	30	0.58 ± 0.45	7.5*
	2	30	0.94 ± 0.43	41.98**
	3	30	0.81 ± 0.33	54.49**
	4	30	0.36 ± 0.25	76.32**
10b	1	30	1.12 ± 0.49	−40.0
	2	30	1.48 ± 0.44	8.65
	3	30	2.1 ± 0.26	−17.97
	4	30	1.95 ± 0.34	−28.29
10c	1	30	0.87 ± 0.37	−8.75
	2	30	1.59 ± 0.51	1.85
	3	30	2.23 ± 0. 66	−25.28
	4	30	2.27 ± 0. 59	−49.34
10g	1	30	0.68 ± 0.17	15.0*
	2	30	0.93 ± 0.17	42.60**
	3	30	0.88 ± 0.23	50.56**
	4	30	0.93 ± 0.45	38.82**
10h	1	30	0.52 ± 0.07	35.0*
	2	30	0.68 ± 0.05	58.02**
	3	30	0.67 ± 0.16	62.36**
	4	30	0.58 ± 0.2	61.84**
10i	1	30	0.66 ± 0.26	17.5*
	2	30	0.96 ± 0.40	40.74**
	3	30	0.91 ± 0.29	48.88**
	4	30	0. 88 ± 0.19	42.11**
10j	1	30	1.02 ± 0.13	−27.5
	2	30	1.55 ± 0.24	4.32
	3	30	1.74 ± 0.22	2.24
	4	30	1.67 ± 0.32	−9.87
11a	1	30	0.75 ± 0.11	6.25
	2	30	1.16 ± 0.13	28.39
	3	30	1.24 ± 0.09	30.34
	4	30	1.14 ± 0.03	25.00
11b	1	30	0.53 ± 0.11	33.75*
	2	30	0.83 ± 0.10	48.77**
	3	30	0.82 ± 0.15	53.93**
	4	30	0.67 ± 0.11	55.92**
11c	1	30	0.86 ± 0.05	−7.5
	2	30	1.21 ± 0.06	25.30
	3	30	1.48 ± 0.04	16.85
	4	30	1.47 ± 0.11	3.28
11d	1	30	1.10 ± 0.23	−37.5
	2	30	1.50 ± 0.10	7.40
	3	30	1.72 ± 0.11	3.37
	4	30	1.53 ± 0.35	−0.65
11e	1	30	0.90 ± 0.09	−12.5
	2	30	1.38 ± 0.10	14.81
	3	30	1.66 ± 0.10	−6.74
	4	30	1.67 ± 0.06	−9.86
11f	1	30	0.77 ± 0.12	3.75
	2	30	1.19 ± 0.15	26.54
	3	30	1.34 ± 0.1	24.72
	4	30	1.16 ± 0.04	23.68
11g	1	30	0.64 ± 0.10	20.0*
	2	30	0.82 ± 0.05	49.38**
	3	30	0.78 ± 0.08	56.18**
	4	30	0.71 ± 0.05	53.29**
11h	1	30	0.96 ± 0.10	−20
	2	30	1.57 ± 0.14	3.08
	3	30	1.90 ± 0.09	−6.74
	4	30	1.93 ± 0.13	−26.97
11i	1	30	0.46 ± 0.04	42.5**
	2	30	0.65 ± 0.04	59.88**
	3	30	0.63 ± 0.04	64.61**
	4	30	0.55 ± 0.03	63.82**
11j	1	30	1.13 ± 0.48	−41.25
	2	30	1.51 ± 0.43	6.79
	3	30	2.18 ± 0.34	−22.47
	4	30	1.96 ± 0.33	−28.94

a) Number of animals in each group n = 4.

b) Thickness variation is the difference between the thickness of the carrageenan-treated paw and the saline-treated paw.

c) Percentage of inhibition obtained by comparison with the vehicle. * and ** differed from control group $P < 0.05$ and $P < 0.01$, respectively.

Mass spectra were obtained using a Finnigan Mat TSQ-70 spectrometer at 70 eV (Finnigan Mat, Bremen, Germany). The IR spectra were obtained using Nicolet FT-IR Magna 550 spectrographs (KBr disks) (Nicolet, Madison, WI, USA). The purity of compounds was confirmed by TLC using different mobile phases. The results of the elemental analyses (C, H, N) were within ± 0.4% of theoretical values for C, H and N.

2-Phenoxybenzoyl chloride 6

To a stirring solution of 2-phenoxybenzoic acid 5 (1 mmol) in benzene (50 mL), thionyl chloride (2 mmol) was added. The reaction contents were heated under reflux for 3 h and the solvent was removed under reduced pressure. The residue was crystallized from *n*-heptane to give compound **6**. Yield 85%; mp. 35–8°C. IR (KBr): ν cm^{-1} 1774 (C=O). ^{1}H-NMR ($CDCl_3$): δ = 7.85 (dd, *J* = 7.8, 1.7 Hz, 1H, H_6), 7.59 (dt, *J* = 7.8, 1.7 Hz, 1H, H_4), 7.34 (t, *J* = 7.8 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.29 (t, *J* = 7.8 Hz, 1H, $H_{4'}$), 7.07 (t, *J* = 7.8 Hz, 1H, H_5), 7.06 (d, *J* = 7.8 Hz, 1H, H_3), 6.89 (d, *J* = 7.8 Hz, 2H, $H_{2'}$, $H_{6'}$). MS: *m/z* (%) 234 [M^++2] (5), 232 [M^+] (15), 196 (100), 192 (20), 167 (10), 114 (25), 76 (85), 49 (60). Anal. Calcd. for $C_{13}H_9ClO_2$: C, 67.11; H, 3.90. Found: C, 66.93; H, 3.98.

Azido(2-phenoxyphenyl)methanone 7

To a stirring solution of 2-phenoxybenzoyl chloride (2.32 g, 0.01 mol) in benzene (30 mL) at −5°C was added a solution of sodium azide (0.65 g, 0.01 mol) in water (24 mL) and *N,N*-diethylanilline (1.49 g, 0.01 mol). After the addition was completed, the mixture was stirred at room temperature overnight. The organic layer was washed with 10% aqueous hydrochloric acid, 10% sodium carbonate solution and water. The organic layer was dried (Na_2SO_4) and filtered. The solvent was evaporated and the residue was crystallized from absolute ethanol to give 1.91 g of **7** (80%); mp. 53 – 55°C. IR (KBr): ν max cm^{-1} 2136 (N_3), 1716 (C=O). ^{1}H-NMR ($CDCl_3$): δ = 7.85 (d, *J* = 7.7 Hz, 1H, H_6), 7.41-6.68 (m, 8H, aromatic). MS: *m/z* (%) 239 [M^+] (25), 211 (10), 183 (100), 76 (85). Anal. Calcd. for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.18; H, 3.99; N, 17.72.

4-(2-Phenoxyphenyl)semicarbazide 9

A solution of compound **7** (2.39 g, 0.01 mol) in benzene (10 mL) was refluxed and the progress of the reaction was followed by TLC. After the rearrangement was complete (about 2 h) the solvent was evaporated. The residue was dissolved in diethyl ether (20 mL) and hydrazine hydrate (500 mg, 0.01 mol) was added to it. The mixture was stirred for 4 h at room temperature. The white solid was filtered and crystallized from ethanol to give 2.31 g of **9** (95%); mp. 124 – 125°C. IR (KBr): ν max cm^{-1} 3243, 3350 (NH_2), 1678 (C=O). ^{1}H-NMR ($CDCl_3$): δ = 8.95 (bs, 1H, NH), 8.31 (d, *J* = 7.8 Hz, 1H, H_6), 7.69 (s, 1H, NH), 7.39 (dt, *J* = 7.6, 0.8 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.14 (t, *J* = 7.6 Hz, 1H, $H_{4'}$), 7.10 (t, *J* = 7.8 Hz, 1H, H_4), 7.00 (dd, *J* = 7.6, 0.8 Hz, 2H, $H_{2'}$, $H_{6'}$), 6.93 (t, *J* = 7.8 Hz, 1H, H_5), 6.88 (d, *J* = 7.8 Hz, 1H, H_3), 4.48 (bs, 2H, NH_2). MS: *m/z* (%) 243 [M^+] (95), 211 (100), 168 (30), 154 (55), 128 (32), 77 (85). Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.28; H, 5.25; N, 17.09.

General procedure for the preparation of compounds 10a – j and 11a – j

To a stirring solution of aldehyde or ketone (0.01 mol) in absolute ethanol (25 mL) compound **9** (2.43 g, 0.01 mol) was added. The progress of the reaction was followed by TLC. After the completion of the reaction, the precipitate was filtered and the residue was crystallized from a suitable solvent.

*1-(2-Chlorobenzylidene)-4-(2-phenoxylphenyl)semicarbazide **10a***

Mp. 150 – 152°C. IR (KBr): ν max cm^{-1} 3365 (NH), 1695 (C=O). ^{1}H-NMR (DMSO-d_6): δ = 11.19 (bs, 1H, NH), 8.70 (bs, 1H, NH), 8.28 (d, *J* = 7.6 Hz, 1H, H_6), 8.27 (s, 1H, HC=N), 7.53 (d, *J* = 7.6 Hz, 1H, $H_{6''}$), 7.49 (d, *J* = 7.6 Hz, 1H, $H_{3''}$), 7.41 (t, *J* = 7.6 Hz, 3H, $H_{3'}$, $H_{5'}$, $H_{5''}$), 7.32 (t, *J* = 7.6 Hz, 1H, $H_{4''}$), 7.23 (t, *J* = 7.6 Hz, 1H, H_4), 7.12 (t, *J* = 7.6 Hz, 1H, $H_{4'}$), 7.11 (t, *J* = 7.6 Hz, 1H, H_5), 7.09 (d, *J* = 7.6 Hz, 1H, H_3), 7.02 (d, 2H, *J* = 7.6 Hz, $H_{2'}$, $H_{6'}$). MS: *m/z* (%) 367 [M^++2] (35), 365 [M^+] (100), 330 (45), 275 (20), 216 (60), 211 (28), 184 (98), 152 (75), 135 (50), 119 (95), 109 (80), 93 (65). Anal. Calcd. for $C_{20}H_{16}ClN_3O_2$: C, 65.67; H, 4.41; N, 11.49. Found: C, 65.82; H, 4.36; N, 11.78.

*1-(3-Chlorobenzylidene)-4-(2-phenoxyphenyl)semicarbazide **10b***

Mp. 160 – 162°C. IR (KBr): ν max cm^{-1} 3365 (NH), 1685 (C=O). ^{1}H-NMR (DMSO-d_6): δ = 11.10 (s, 1H, NH), 8.72 (bs, 1H, NH), 8.27 (d, *J* = 8.1 Hz, 1H, H_6), 7.94 (s, 1H, HC=N), 7.88 (s, 1H, $H_{2''}$), 7.86 (d, *J* = 7.6 Hz, 1H, $H_{6''}$), 7.61 (d, *J* = 7.6 Hz, $H_{4''}$), 7.56 (t, *J* = 7.6 Hz, 1H, $H_{5''}$), 7.44 (t, *J* = 7.5 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.39 (t, *J* = 8.1 Hz, 1H, H_4), 7.22 (t, *J* = 8.1 Hz, 1H, H_5), 7.11 (t, *J* = 7.5 Hz, 1H, $H_{4'}$), 7.09 (d, *J* = 7.5 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.04 (d, *J* = 8.1 Hz, 1H, H_3). MS: *m/z* (%) 367 [M^++2] (32), 365 [M^+] (100), 308 (10), 255 (15), 211 (55), 185 (75), 136 (55), 93 (20), 83 (15). Anal. Calcd. for $C_{20}H_{16}ClN_3O_2$: C, 65.67; H, 4.41; N, 11.49. Found: C, 65.59; H, 4.30; N, 11.61.

*1-(4-Chlorobenzylidene)-4-(2-phenoxyphenyl)semicarbazide **10c***

Mp. 189 – 190°C. IR (KBr) ν: max cm^{-1} 3354 (NH), 1690 (C=O). ^{1}H-NMR (DMSO-d_6): δ = 11.04 (s, 1H, NH), 8.66 (bs, 1H, NH), 8.28 (d, *J* = 7.8 Hz, 1H, H_6), 7.93 (s, 1H, HC=N), 7.91 (d, *J* = 8.5 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.59 (d, *J* = 8.5 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.43 (t, *J* = 7.6 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.24 (t, *J* = 7.8 Hz, 1H, H_4), 7.13 (t, *J* = 7.6 Hz, 1H, $H_{4'}$), 7.11 (t, *J* = 7.8 Hz, 1H, H_5), 7.10 (d, *J* = 7.8 Hz, 1H, H_3), 7.02 (d, *J* = 7.6 Hz, 2H, $H_{2'}$, $H_{6'}$). MS: *m/z* (%) 367 [M^++2] (21), 365 [M^+] (65), 272 (30), 210 (25), 185 (45), 176 (90), 153 (60), 119 (100), 109 (55), 93 (40), 82 (10). Anal. Calcd. for $C_{20}H_{16}ClN_3O_2$: C, 65.67; H, 4.41; N, 11.49. Found: C, 65.35; H, 4.56; N, 11.71.

*1-(2-Hydroxybenzylidene)-4-(2-phenoxyphenyl)semicarbazide **10d***

Mp. 202 – 204°C. IR (KBr): ν max cm^{-1} 3416 (OH), 3331 (NH), 1685 (C=O). ^{1}H-NMR (DMSO-d_6): δ = 10.88 (s, 1H, NH), 10.05 (bs, 1H, OH), 8.71 (bs, 1H, NH), 8.31 (d, *J* = 8.4 Hz, 1H, H_6), 8.20 (s, 1H, HC=N), 7.41 (t, *J* = 7.7 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.30 (d, *J* = 7.7 Hz, 1H, $H_{6''}$), 7.22 (t, *J* = 8.4 Hz, 1H, H_4), 7.19 (dd, *J* = 8.2, 7.7 Hz, 1H, $H_{4''}$), 7.13 (t, *J* = 7.7 Hz, 1H, $H_{4'}$), 7.08 (t, *J* = 8.4 Hz, 1H, H_5), 7.07 (t, *J* = 8.4 Hz, 1H, H_3), 7.02 (d, *J* = 7.7 Hz, 2H, $H_{2'}$, $H_{6'}$), 6.86 (d, *J* = 8.2 Hz, 1H, $H_{3''}$), 6.77 (t, *J* = 7.7 Hz, 1H, $H_{5''}$). MS: *m/z* (%) 347 [M^+] (30), 272 (25), 295 (27), 239 (40), 212 (12), 185 (60), 135 (100), 106 (35), 77 (30). Anal. Calcd. for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.32; H, 4.87; N, 12.04.

*1-(3-Hydroxybenzylidene)-4-(2-phenoxyphenyl)semicarbazide **10e***

Mp. 197 – 200°C. IR (KBr): ν max cm^{-1} 3397 (OH), 3336 (NH), 1678 (C=O). ^{1}H-NMR (DMSO-d_6): δ = 10.91 (s, 1H, NH), 9.58 (bs, 1H, OH), 8.68 (s, 1H, NH), 8.30 (d, *J* = 8.2 Hz, 1H, H_6), 7.80 (s, 1H, HC=N), 7.46 (d, *J* = 7.8 Hz, 1H, $H_{6''}$), 7.41 (t, *J* = 7.6 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.22 (t, *J* = 8.2 Hz, 1H, H_4), 7.16 (t, *J* = 7.8 Hz, 1H, $H_{5''}$), 7.11 (t, *J* = 7.6 Hz, 1H, $H_{4'}$), 7.09 (t, *J* = 8.2 Hz, 1H, H_5), 7.07 (d, *J* = 8.2 Hz, 1H, H_3), 7.04 (d, *J* = 7.6 Hz, 2H, $H_{2'}$, $H_{6'}$), 6.94 (s, 1H, $H_{2''}$), 6.88 (d, *J* = 7.8 Hz, 1H, $H_{4''}$). MS: *m/z* (%) 347 [M^+] (30), 272 (20), 239 (100), 211 (40), 185 (50), 136 (85), 134 (40), 120 (20), 77 (98). Anal. Calcd. for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.02; H, 4.96; N, 11.89.

*1-(4-Hydroxybenzylidene)-4-(2-phenoxyphenyl)semicarbazide **10f***

Mp. 194 – 196°C. IR (KBr): ν max cm^{-1} 3457 (OH), 3344 (NH), 1670 (C=O). ^{1}H-NMR (DMSO-d_6): δ = 10.76 (s, 1H, NH), 9.85 (s, 1H, OH), 8.69 (s, 1H, NH), 8.32 (d, *J* = 8.2 Hz, 1H, H_6), 7.78 (s, 1H, HC=N), 7.41 (t, *J* = 7.6 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.24 (d, *J* = 8.6 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.25 (t, *J* = 7.7 Hz, 1H, H_4), 7.13 (dd, *J* = 8.2, 7.7 Hz, 1H, H_5), 7.10 (d, *J* = 7.7 Hz, 1H, H_3), 7.09 (t, *J* = 7.6 Hz, 1H, $H_{4'}$), 7.02 (d, *J* = 7.6 Hz, 2H, $H_{2'}$, $H_{6'}$), 6.75 (d, *J* =8.6 Hz, 2H, $H_{3''}$, $H_{5''}$). MS: *m/z* (%) 347 [M^+] (5), 239 (15), 211 (50), 185 (100), 135 (25), 77 (20). Anal. Calcd. for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 68.82; H, 5.09; N, 12.45.

1-(2-Nitrobenzylidene)-4-(2-phenoxyphenyl)semicarbazide ***10g***

Mp. 160–162°C. IR (KBr): ν max cm^{-1} 3385 (NH), 1695 (C=O), 1531, 1337 (NO_2), ^{1}H-NMR (DMSO-d_6): δ = 11.29 (s, 1H, NH), 8.67 (s, 1H, NH), 8.31 (s, 1H, HC=N), 8.26 (dd, *J* = 7.6, 1.4 Hz, 1H, H_6), 8.04 (d, *J* = 8.0 Hz, 1H, $H_{3''}$), 7.70 (t, *J* = 8.0 Hz, 1H, $H_{5''}$), 7.67 (d, *J* = 8.0 Hz, 1H, $H_{6''}$), 7.63 (t, *J* = 8.0 Hz, 1H, $H_{4''}$), 7.39 (t, *J* = 7.6 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.23 (dt, *J* = 7.6, 1.4 Hz, 1H, H_4), 7.12 (t, *J* = 7.6 Hz, 1H, $H_{4'}$), 7.09 (d, *J* = 7.6 Hz, 1H, H_3), 7.08 (t, *J* = 7.6 Hz, 1H, H_5), 7.02 (d, *J* = 7.6 Hz, 2H, $H_{2'}$, $H_{6'}$). MS: *m/z* (%) 376 [M^+] (15), 298 (70), 251 (25), 211 (85), 185 (100), 108 (18), 77 (20). Anal. Calcd. for $C_{20}H_{16}N_4O_4$: C, 63.82; H, 4.28; N, 14.89. Found: C, 64.12; H, 4.49; N, 14.71.

1-(3-Nitrobenzylidene)-4-(2-phenoxyphenyl)semicarbazide ***10h***

Mp. 175–177°C. IR (KBr): ν max cm^{-1} 3283 (NH), 1685 (C=O), 1525, 1355 (NO_2). ^{1}H-NMR (DMSO-d_6): δ = 11.21 (s, 1H, NH), 8.72 (bs, 1H, NH), 8.42 (s, 1H, $H_{2''}$), 8.34 (d, *J* = 7.7 Hz, 1H, H_6), 8.26 (d, *J* = 8.0 Hz, 1H, $H_{4''}$), 8.03 (s, 1H, HC=N), 7.88 (d, *J* = 8.0 Hz, 1H, $H_{6''}$), 7.67 (t, *J* = 8.0 Hz, 1H, $H_{5''}$), 7.37 (t, *J* = 7.7 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.22 (t, *J* = 7.7 Hz, 1H, H_4), 7.10 (t, *J* = 7.7 Hz, 1H, $H_{4'}$), 7.07 (d, *J* = 7.7 Hz, 1H, H_3), 7.05 (t, *J* = 8.5 Hz, 1H, H_5), 7.04 (d, *J* = 8.5 Hz, 2H, $H_{2'}$, $H_{6'}$). MS: *m/z* (%) 376 [M^+] (35), 298 (85), 251 (17), 226 (5), 211 (75), 185 (100), 204 (20), 176 (98), 130 (19), 89 (20). Anal. Calcd. for $C_{20}H_{16}N_4O_4$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.55; H, 4.48; N, 14.62.

1-(4-Nitrobenzylidene)-4-(2-phenoxyphenyl)semicarbazide ***10i***

Mp. 235–236°C. IR (KBr): ν max cm^{-1} 3365 (NH), 1690 (C=O), 1527, 1347 (NO_2). ^{1}H-NMR (DMSO-d_6): δ = 11.30 (s, 1H, NH), 8.71 (s, 1H, NH), 8.38 (d, *J* = 8.7 Hz, 2H, $H_{3''}$, $H_{5''}$), 8.22 (d, *J* = 7.8 Hz, 1H, H_6), 8.17 (d, *J* = 8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.99 (s, 1H, HC=N), 7.41 (t, *J* = 7.8 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.25 (t, *J* = 7.8 Hz, 1H, H_4), 7.13 (t, *J* = 7.8 Hz, 1H, $H_{4'}$), 7.11 (t, *J* = 7.8 Hz, 1H, H_5), 7.09 (d, *J* = 7.8 Hz, 1H, H_3), 7.06 (d, *J* = 7.8 Hz, 2H, $H_{2'}$, $H_{6'}$). MS: *m/z* (%) 376 [M^+] (10), 298 (65), 251 (18), 211 (8), 176 (100), 130 (20), 103 (15), 58 (8). Anal. Calcd. for $C_{20}H_{16}N_4O_4$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.72; H, 4.15; N, 14.78.

1-(4-Methylbenzylidene)-4-(2-phenoxyphenyl)semicarbazide ***10j***

Mp. 187–189°C. IR (KBr): ν max cm^{-1} 3349 (NH), 1685 (C=O). ^{1}H-NMR (DMSO-d_6): δ = 10.91 (s, 1H, NH), 8.70 (bs, 1H, NH), 8.32 (d, *J* = 8.4 Hz, 1H, H_6), 7.85 (s, 1H, HC=N), 7.43 (t, *J* = 7.4 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.32 (d, *J* =7.9 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.23 (t, *J* = 8.4 Hz, 1H, H_4), 7.21 (d, *J* = 7.9 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.14 (t, *J* = 7.4 Hz, 1H, $H_{4'}$), 7.09 (t, *J* = 8.4 Hz, 1H, H_5), 7.07 (d, *J* = 8.4 Hz, 1H, H_3), 7.02 (d, *J* = 7.4 Hz, 2H, $H_{2'}$, $H_{6'}$), 2.33 (s, 3H, CH_3). MS: *m/z* (%) 345 [M^+] (15), 344 (18), 212 (25), 185 (15), 132 (100), 109 (15). Anal. Calcd. for $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17. Found: C, 72.83; H, 5.69; N, 12.32.

1-(1-(2-Nitrophenyl)ethylidene)-4-(2-phenoxyphenyl)semicarbazide ***11a***

Mp. 214–216°C. IR (KBr): ν max cm^{-1} 3375 (NH), 1690 (C=O), 1533, 1345 (NO_2). ^{1}H-NMR (DMSO-d_6): δ = 10.24 (s, 1H, NH), 8.58 (bs, 1H, NH), 8.31 (d, *J* = 8.2 Hz, 1H, H_6), 7.99 (d, *J* = 7.6 Hz, 1H, $H_{3''}$), 7.73 (t, *J* = 7.6 Hz, 1H, $H_{5''}$), 7.65 (t, *J* = 7.6 Hz, 1H, $H_{4''}$), 7.52 (d, *J* = 7.6 Hz, 1H, $H_{6''}$), 7.38 (t, *J* = 7.6 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.12 (t, *J* = 7.6 Hz, 1H, $H_{4'}$), 7.04 (t, *J* = 7.6 Hz, 1H, H_4), 7.00 (dd, *J* = 8.2, 7.6 Hz, 1H, H_5), 6.97 (d, *J* = 7.6 Hz, 1H, H_3), 6.85 (d, *J* = 7.6 Hz, 2H, $H_{2'}$, $H_{6'}$), 2.18 (s, 3H, CH_3). MS: *m/z* (%) 390 [M^+] (65), 297 (7), 212 (97), 188 (100), 168 (11), 157 (18), 149 (61), 132 (98), 105 (45), 91 (44), 76 (75), 65 (25), 51 (39), 43 (39). Anal. Calcd. for $C_{21}H_{18}N_4O_4$: C, 64.61; H, 4.65; N, 14.35. Found: C, 64.52; H, 4.49; N, 14.23.

1-(1-(3-Nitrophenyl)ethylidene)-4-(2-phenoxyphenyl)semicarbazide ***11b***

Mp. 240–243°C. IR(KBr): ν max cm^{-1} 3365 (NH), 1695 (C=O), 1536, 1347 (NO_2). ^{1}H-NMR (DMSO-d_6): δ = 10.32 (s, 1H, NH), 8.94 (s, 1H, NH), 8.42 (s, 1H, $H_{2''}$), 8.32 (d, *J* = 7.8 Hz, 1H, H_6), 8.21 (d, *J* = 7.8 Hz, 1H, $H_{4''}$), 8.00 (d, *J* = 7.8 Hz, 1H, $H_{6''}$), 7.60 (t, *J* = 7.8 Hz, 1H, $H_{5''}$), 7.35 (t, *J* = 7.7 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.20 (t, *J* = 8.0 Hz, 1H, H_4), 7.10 (t, *J* = 8.0 1H, H_5), 7.09 (d, *J* = 8.0 Hz, 1H, H_3), 7.06 (t, *J* = 7.7 Hz, 1H, $H_{4'}$), 7.01 (d, *J* = 7.7 Hz, 2H, $H_{2'}$, $H_{6'}$), 2.30 (s, 3H, CH_3). MS: *m/z* (%) 390 [M^+] (10), 389 (10), 325 (100), 310 (75), 263 (18), 212 (5), 203 (15), 162 (25), 115 (98), 74 (96). Anal. Calcd. for $C_{21}H_{18}N_4O_4$: C, 64.61; H, 4.65; N, 14.35. Found: C, 64.82; H, 4.59; N, 14.42.

1-(1-(4-Nitrophenyl)ethylidene)-4-(2-phenoxyphenyl)semicarbazide ***11c***

Mp. 236–238°C. IR (KBr): ν max cm^{-1} 3375 (NH), 1695 (C=O), 1536, 1337 (NO_2). ^{1}H-NMR (DMSO-d_6): δ = 10.42 (s, 1H, NH), 8.99 (s, 1H, NH), 8.32 (d, *J* = 8.4 Hz, 2H, $H_{3''}$, $H_{5''}$), 8.22 (d, *J* = 7.8 Hz, 1H, H_6), 7.82 (d, *J* = 8.4 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.40 (t, *J* = 7.5 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.22 (t, *J* = 7.2 Hz, 1H, H_4), 7.14 (t, *J* = 7.5 Hz, 1H, $H_{4'}$), 7.07 (dd, *J* = 7.8, 7.2 Hz, 1H, H_5), 6.98 (d, *J* = 7.2 Hz, 1H, H_3), 6.93 (d, *J* = 7.5 Hz, 2H, $H_{2'}$, $H_{6'}$), 2.33 (s, 3H, CH_3). MS: *m/z* (%) 390 [M^+] (65), 212 (100), 177 (40), 132 (30), 104 (35), 75 (98), 55 (38). Anal. Calcd. for $C_{21}H_{18}N_4O_4$: C, 64.61; H, 4.65; N, 14.35. Found: C, 64.62; H, 4.32; N, 14.08.

1-(1-(2-Chlorophenyl)ethylidene)-4-(2-phenoxyphenyl)semicarbazide ***11d***

Mp. 166–168°C. IR (KBr): ν max cm^{-1} 3354 (NH), 1695 (C=O). ^{1}H-NMR (DMSO-d_6): δ = 10.19 (s, 1H, NH), 8.83 (bs, 1H, NH), 8.32 (d, *J* = 8.0 Hz, 1H, H_6), 7.48 (d, *J* = 7.6 Hz, 1H, $H_{6''}$), 7.41 (t, *J* = 7.6 Hz, 1H, $H_{5''}$), 7.34 (t, *J* = 7.6 Hz, 1H, $H_{4''}$), 7.27 (t, *J* = 7.6 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.26 (d, *J* = 7.6 Hz, 1H, $H_{3''}$), 7.19 (t, *J* = 7.7 Hz, 1H, H_4), 7.08 (t, *J* = 7.6 Hz, 1H, $H_{4'}$), 7.04 (dd, *J* = 8.0, 7.7 Hz, 1H, H_5), 7.00 (d, *J* = 7.7 Hz, 1H, H_3), 6.85 (d, *J* = 7.7 Hz, 2H, $H_{2'}$, $H_{6'}$), 2.21 (s, 3H, CH_3). MS: *m/z* (%) 381 [M^++2] (23), 379 [M^+] (70), 377 (60), 287 (10), 209 (18), 188 (100), 165 (98), 131 (96), 101 (55), 75 (98), 50 (98). Anal. Calcd. for $C_{21}H_{18}ClN_3O_2$: C, 66.40; H, 4.78; N, 11.06. Found: C, 66.31; H, 4.92; N, 11.31.

1-(1-(3-Chlorophenyl)ethylidene)-4-(2-phenoxyphenyl)semicarbazide ***11e***

Mp. 210–212°C. IR (KBr): ν max cm^{-1} 3375 (NH), 1690 (C=O). ^{1}H-NMR (DMSO-d_6): δ = 10.23 (s, 1H, NH), 9.00 (bs, 1H, NH), 8.35(dd, *J* = 8.2, 1.3 Hz, 1H, H_6), 7.70 (s, 1H, $H_{2''}$), 7.53 (d, *J* = 7.8 Hz, 1H, $H_{6''}$), 7.40 (d, *J* = 7.8 Hz, 1H, $H_{4''}$), 7.38 (t, *J* = 7.4 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.33 (t, *J* = 7.8 Hz, 1H, $H_{5''}$), 7.19 (dt, *J* = 7.4, 1.3 Hz, 1H, H_4), 7.12 (t, *J* = 7.4 Hz, 1H, $H_{4'}$), 7.08 (dd, *J* = 7.4, 8.2 Hz, 1H, H_5), 7.04 (d, *J* = 7.4 Hz, 2H, $H_{2'}$, $H_{6'}$), 6.99 (d, *J* = 7.4 Hz, 1H, H_3), 2.23 (s, 3H, CH_3). MS: *m/z* (%) 381 [M^++2] (20), 379 [M^+] (65), 186 (40), 168 (100), 165 (98), 131 (96), 129 (28), 76 (75), 52 (38). Anal. Calcd. for $C_{21}H_{18}ClN_3O_2$: C, 66.40; H, 4.78; N, 11.06. Found: C, 66.58; H, 4.70; N, 10.84.

1-(1-(4-Chlorophenyl)ethylidene)-4-(2-phenoxyphenyl)semicarbazide ***11f***

Mp. 214 – 216°C. IR (KBr): ν max cm^{-1} 3375 (NH), 3216 (NH), 1700 (CO). ^{1}H-NMR (DMSO-d_6): δ = 10.19 (s, 1H, NH), 8.98 (bs, 1H, NH), 8.35 (d, *J* = 8.3 Hz, 1H, H_6), 7.58 (d, *J* = 8.4 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.40 (t, *J* = 7.6 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.35 (d, *J* = 8.4 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.22 (t, *J* = 7.4 Hz, 1H, H_4), 7.13 (t, *J* = 7.6 Hz, 1H, $H_{4'}$), 7.06 (dd, *J* = 8.3, 7.4 Hz, 1H, H_5), 7.05 (d, *J* = 7.4 Hz, 1H, H_3), 7.03 (d, *J* = 7.6 Hz, 2H, $H_{2'}$, $H_{6'}$), 2.22 (s, 3H, CH_3). MS: *m/z* (%) 381 [M^++2] (19), 379 [M^+] (55), 186 (30), 165 (90), 132 (100), 128 (20), 91 (18), 75 (40). Anal. Calcd. for $C_{21}H_{18}ClN_3O_2$: C, 66.40; H, 4.78; N, 11.06. Found: C, 66.46; H, 4.57; N, 11.16.

1-(1-(3-Bromophenyl)ethylidene)-4-(2-phenoxyphenyl)semicarbazide ***11g***

Mp. 198 – 200°C. IR (KBr): ν max cm^{-1} 3359 (NH), 3221 (NH), 1705 (C=O). ^{1}H-NMR (DMSO-d_6): δ = 10.22 (s, 1H, NH), 8.98 (bs, 1H, NH), 8.34 (d, *J* = 8.0 Hz, 1H, H_6), 7.85 (s, 1H, $H_{2''}$), 7.57 (d, *J* = 7.7 Hz, 1H, $H_{6''}$), 7.55 (d, *J* = 7.7 Hz, 1H, $H_{4''}$), 7.37 (t, *J* = 7.7 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.27 (t, *J* = 7.7 Hz, 1H, $H_{5''}$), 7.19 (t, *J* = 7.7 Hz, 1H, H_4), 7.12 (t, *J* = 7.7 Hz, 1H, $H_{4'}$), 7.05 (dd, *J* = 8.0, 7.7 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.04 (dd, *J* = 8.0, 7.7 Hz, 1H, H_5), 6.99 (d, *J* = 7.7 Hz, 1H, H_3), 2.23 (s, 3H, CH_3). MS: *m/z* (%) 425 [M^++2] (37), 423 [M^+] (38), 211 (100), 184 (30), 132 (25), 126 (18), 75 (60), 50 (27). Anal. Calcd. for $C_{21}H_{18}BrN_3O_2$: C, 59.45; H, 4.28; N, 9.90. Found: C, 59.27; H, 4.41; N, 10.20.

1-(1-(4-Bromophenyl)ethylidene)-4-(2-phenoxyphenyl)semicarbazide ***11h***

Mp. 215-217°C. IR (KBr): ν max cm^{-1} 3385 (NH), 1705 (C=O). ^{1}H-NMR (DMSO-d_6): δ = 10.19 (s, 1H, NH), 8.98 (bs, 1H, NH), 8.34 (d, *J* = 7.9 Hz, 1H, H_6), 7.51 (d, *J* = 8.8 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.49 (d, *J* = 8.8 Hz, 2H, $H_{3''}$, $H_{5''}$), 7.40 (t, *J* = 7.5 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.22 (t, *J* = 7.6 Hz, 1H, H_4), 7.13 (t, *J* = 7.5 Hz, 1H, $H_{4'}$), 7.06 (dd, *J* = 7.9, 7.4 Hz, 1H, H_5), 7.05 (d, *J* = 7.6 Hz, 1H, H_3), 7.03 (d, *J* = 7.5 Hz, 1H, $H_{2'}$, $H_{6'}$), 2.21 (s, 3H, CH_3); MS: *m/z* (%) 425 [M^++2] (52), 423 [M^+] (55), 210 (100), 183 (45), 153 (30), 126 (45), 101 (47), 78 (68), 74 (98). Anal. Calcd. for $C_{21}H_{18}BrN_3O_2$: C, 59.45; H, 4.28; N, 9.90. Found: C, 59.67; H, 3.98; N, 9.78.

1-(1-(2,5-Dimethoxyphenyl)ethylidene)-4-(2-phenoxyphenyl)semicarbazide ***11i***

Mp. 166 – 168°C. IR (KBr): ν max cm^{-1} 3365 (NH), 1690 (C=O). 1H-NMR (DMSO-d_6): δ = 10.02 (s, 1H, NH), 8.90 (s, 1H, NH), 8.33 (d, *J* = 8.2 Hz, 1H, H_6), 7.28 (t, *J* = 7.8 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.16 (t, *J* = 7.4 Hz, 1H, H_4), 7.09 (t, *J* = 7.8 Hz, 1H, $H_{4'}$), 7.01 (dd, *J* = 8.2, 7.4 Hz, 1H, H_5), 6.99 (d, *J* = 8.6 Hz, 1H, $H_{3''}$), 6.94 (d, *J* = 7.4 Hz, 1H, H_3), 6.93 (d, *J* = 7.8 Hz, 2H, $H_{2'}$, $H_{6'}$), 6.92 (dd, *J* = 8.6, 3.0 Hz, 1H, $H_{4''}$), 6.79 (d, *J* = 3.0 Hz, 1H, $H_{6''}$), 3.72 (s, 3H, OMe), 3.61 (s, 3H, OMe), 2.15 (s, 3H, CH_3). MS: *m/z* (%) 405 [M^+] (50), 211 (17), 195 (53), 193 (70), 161 (100), 103 (30), 89 (45), 77 (98). Anal. Calcd. for $C_{23}H_{23}N_3O_4$: C, 68.13; H, 5.72; N, 10.36. Found: C, 68.40; H, 5.57; N, 10.61.

1-(1-(4-Methoxyphenyl)ethylidene)-4-(2-phenoxyphenyl)semicarbazide ***11j***

Mp. 176 – 178°C. IR (KBr): ν max cm^{-1} 3370 (NH), 1690 (C=O). ^{1}H-NMR (DMSO-d_6): δ = 10.02 (s, 1H, NH), 9.05 (bs, 1H, NH), 8.38 (d, *J* = 8.1 Hz, 1H, H_6), 7.51 (d, *J* = 8.7 Hz, 2H, $H_{2''}$, $H_{6''}$), 7.41 (t, *J* = 7.6 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.22 (t, *J* = 7.4 Hz, 1H, H_4), 7.14 (t, *J* = 7.6 Hz, 1H, $H_{4'}$), 7.08 (dd, *J* = 8.1, 7.4 Hz, 1H, H_5), 7.03 (d, *J* = 7.6 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.0 (d, *J* = 7.4 Hz, 1H, H_3), 6.83 (d, *J* = 8.7 Hz, 2H, $H_{3''}$, $H_{5''}$), 3.74 (s, 3H, OMe), 2.19 (s, 3H, CH_3). MS: *m/z* (%) 375 [M^+] (40), 211 (11), 184 (45), 163 (100), 92 (12), 75 (25). Anal. Calcd. for $C_{22}H_{21}N_3O_3$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.08; H, 5.84; N, 11.43.

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