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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and urease inhibitory activities of benzophenone semicarbazones/thiosemicarbazones

Arshia Arshia[1] · Ajmal Khan[1,2] · Khalid Mohammed Khan[1] · Syed Muhammad Saad[1] · Nida Iqbal Siddiqui[3] · Sumaira Javaid[1] · Shahnaz Perveen[4] · M. Iqbal Choudhary[1,5]

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Abstract Twenty-five benzophenone semicarbazones and thiosemicarbazones **3**–**27** were synthesized starting from benzophenones via hydrazones treated with different aryl isocyanates and isothiocyantes under reflux. All synthetic derivatives were evaluated for their urease inhibitory potential. Good to moderate inhibition trend against urease was observed with the IC_{50} values in the range of 8.7–119.5 μM, when compared with the standard thiourea ($IC_{50} = 21.2 \pm 1.3$ μM). Compound **15** showed better inhibition than the standard having the IC_{50} value of 8.7 ± 0.6 μM. Compounds **3**, **4**, **8**, **11**–**14**, **16**, and **17** with the IC_{50} values within the range of 26.1 to 43.6 μM, demonstrated good to moderate activities while compound **9** ($IC_{50} = 119.5 \pm 1.6$ μM) displayed very weak activity. The enzyme kinetic studies on the most active compounds **15** and **17** were performed to deduce their modes of inhibition and dissociation constants K_i.

Keywords Benzophenone · Semicarbazone · Thiosemicarbazone · Ureases inhibition · Structure-activity relationship

✉ Khalid Mohammed Khan
khalid.khan@iccs.edu
iqbal.choudhary@iccs.edu

✉ M. Iqbal Choudhary
khalid.khan@iccs.edu
iqbal.choudhary@iccs.edu

[1] H. E. J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi 75270, Pakistan

[2] Department of Chemistry, COMSATS Institute of Information Technology, Abbottabad 22060, Pakistan

[3] Department of Chemistry, Federal Urdu University of Arts, Sciences and Technology, Gulshan-e-Iqbal, Science Campus, Karachi 75300, Pakistan

[4] PCSIR Laboratories Complex, Karachi, Shahrah-e-Dr Salimuzzaman Siddiqui, Karachi 75280, Pakistan

[5] Department of Biochemistry, Faculty of Sciences, King Abdulaziz University, Jeddah 21412, Saudi Arabia

Introduction

Semicarbazones and thiosemicarbazones are organic compounds having the general formulae $R^1R^2C{=}N{-}NH(C{=}O)NH_2$ and $R^1R^2C{=}N{-}NH(C{=}S)NH_2$, respectively. These moieties are formally synthesized by condensation of aldehyde or ketone with semicarbazide and thiosemicarbazide, respectively. Benzophenone molecules are extensively used in the field of agriculture and many fungicides, like flumorph (Yuan et al., 2006), have been reported to contain benzophenone as a key skeleton. This skeleton is associated with many pharmacological activities such as anticancer (Hsieh et al., 2003), antimicrobial (Sujarani and Ramu, 2013), anti-inflammatory (Khanum et al., 2010), anti-human immunodeficiency virus (HIV; Ma et al., 2011; Piccinelli et al., 2005), and antioxidant (Stanojević et al., 2013). Thiosemicarbazone nuclei have wide spectrum of applications in coordination chemistry (Singh and Prakash, 1992) and have multiple medicinal features like antimalarial (de Oliveira et al., 2008), anticonvulsant (Taroua et al., 1996), antimicrobial (Kasuga et al., 2003), and anti-HIV (Mishra et al., 1998). Benzophenone semicarbazones and thiosemicarbazones are classes of pharmacologically active

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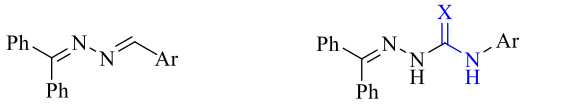
compounds, which show broad spectrum of medicinal properties such as anti-asthmatics (Kim et al., 2003), cathepsin L inhibitors (Kumar et al., 2010), antimalarial (Pingaew et al., 2010), and anticonvulsant activities (Yogeeswari et al., 2005). Benzophenone containing molecules are also involved in adhesive and coatings, photo-initiators as well as in optical fibers (Karahan et al., 2014; Wang et al., 2010; Wang et al., 2014; Wang et al., 2009). These properties mainly arise due to variation in stereochemistry and modes of bondings through oxygen and azomethine nitrogen atoms of benzophenone semicarbazones and thiosemicarbazones. As these molecules coordinate to metal centre, both as neutral or as anionic ligands, hence study of these molecules is a subject of interest to the chemists (Reena et al., 2008).

Urease (EC 3.5.1.5), also called urease aminohydrolase, is a two nickel-containing metalloenzyme. It is found in bacteria, fungi, and higher plants (Matongo and Nwodo, 2014; Uddin et al., 2013; Weber et al., 2008). Urease catalyzes the degradation of urea into ammonia and carbon dioxide. This results in localized increase in pH. *Helicobacter pylori* is a ureolytic bacterium that survives in low pH of human stomach due to urease activity. It is the main cause of gastric and duodenal ulcers which may lead to cancer. High secretion of stomach acid in response of *H. pylori* colonization destroys mucosal membrane and causes gastric ulcers (Kato et al., 2012; Millo et al., 2012). Ureolytic bacteria are also responsible for kidney stones and pyelonephritis (Mobley, 1996). It also contributes to the gastroduodenal inflammation (Blaser, 1990).

In order to resolve urease-hyperactivity based complications, our research group has been involved in designing urease inhibitors since last decade. In this connection, we have synthesized several classes of organic compounds for their urease inhibitory potential assesment. One of our synthesized urea derivatives, *N*-4-nitrophenyl-*N*′-4′-nitrophenylurea showed excellent urease inhibition potential against the standard thiourea (Perveen et al., 2008). Among the library of synthetic biscoumarins, 3,3′-methylene*bis*-(4-hydroxycoumarin) was found to be the most active analog (Khan et al., 2004). Working on oxadiazoles, we explored 5-(hydroxybenzyl)-2-(4-methylphenyl)amino-1,3,4-oxadiazole as an excellant urease inhibitor (Akhtar et al., 2010). Some acridine and piperidine analogs were also found to have promising biological activity for the urease inhibition (Khan et al., 2007; Khan et al., 2006). Pyridine and triazole nuclei, such as, 4,6-*bis*(4-methoxyphenyl)-5,6-dihydropyridin and 4-amino-3-[1-(4-methylbenzenesulfon-amido)-2-methylpropyl]-5-thioxo-1*H*,4*H*-1,2,4-triazole displayed the urease inhibitory potential comparable to the standard thiourea (Hameed et al., 2013; Akhtar et al., 2008). A class of arylidene barbiturates was also subjected to urease inhibition. Regioisomeric fluorinated



Benzophenone hydrazones Benzophenone (thio)semicarbazones

Fig. 1 Benzophenone hydrazones and benzophenone (thio)semicarbazones **3–27**

analogs demonstrated the encouraging results (Khan et al., 2011).

Recently, we have reported benzophenone hydrazones as a new class of uresae inhibitors (Khan et al., 2015). Incorporation of a carboxoamidic (CONH) or carbothioamidic (CSNH) functional group in these molecules may result in better urease inhibitory potentials (Fig. 1). Therefore, in the present study, we synthesized 25 benzophenone semicarbazones and thiosemicarbazones (**3–27**) and evaluated their inhibitory potential against urease in vitro (Table 1). Encouraging results were found and are discussed in forthcoming paragraphs. Compounds **5–9**, **12–17**, and **19–27** were found to be new compounds; while compounds **2a**, **2b**, **3**, **4**, **10**, **11**, and **18** were identified as previously reported compounds (Barton et al., 1962; Ferraz et al., 2012; Glinma et al., 2014; Pearson et al., 1953; Joshi et al., 1981; Singh et al., 2011).

Results and discussion

Chemistry

Twenty-five derivatives of benzophenone semicarbazones/thiosemicarbazones (**3–27**) were prepared in two-steps (Scheme 1). First of all, benzophenones (**1a** and **1b**) were reacted with hydrazine hydrate to have corresponding hydrazones (**2a** and **2b**). These hydrazones were later condensed with different aryl isocyanates and isothiocyantes to build a library of benzophenone semicarbazones/thiosemicarbazones. Chemical structures of these derivatives were confirmed by ^{1}H-nuclear magnetic resonance (NMR), ^{13}C-NMR, electron impact mass spectra (EI-MS) and infrared (IR) spectroscopy. All synthesized compounds gave agreeable elemental analyses and high-resolution electron ionization mass spectrometry (HREI-MS) data.

*Characteristic spectral feature of representative compound **15***

^{1}H- and ^{13}C-NMR spectra of compound **15** were recorded in deuterated dimethyl sulfoxide (DMSO) on a Bruker AM 400 MHz instrument. In ^{1}H-NMR spectrum, signals at δ_H

10.05 and 10.41 ppm indicated the presence of amidic protons in the molecule. The hydroxyl proton showed a signal at δ_H 9.03 ppm. Three aromatic rings are present in the structure; among them the most deshielded singlet at δ_H 7.85 ppm was due to H-2′′ (Ring C). The electron-withdrawing effect of neighboring N–C=S substituent is apparently responsible of downfield chemical shift of H-2′′. C-4 proton (Ring B) appeared as a doublet at δ_H 7.72 ppm ($J_{4,3} = J_{4,5} = 6.8$ Hz). Protons on the aromatic ring A having the hydroxy substituent at C-4′ appeared at upfield region in the range of δ_H 6.78–7.56 ppm. This is because of the electron-donating effect of hydroxyl group. The remaining aromatic protons appeared between δ_H 7.65–7.30 ppm (Fig. 2).

In the ^{13}C-NMR spectrum, a total 16 carbons appeared including 9 methine and 7 quarternary carbons. The most downfield signals at δ_C 175.5 and 159.5 ppm corresponded to iminic and thiocarbonylic carbons, respectively. Aromatic carbon directly attached to electronegative oxygen i.e., C-4′ (ring A) also appeared downfield at δ_C 150.9 ppm. The C-3′ and C-5′ adjacent to hydroxy group, resonated upfield at δ_C 115.2 ppm due to the mesomeric effect of the *ortho* hydroxy group. All remaining aromatic carbons appeared in the usual aromatic range of δ_C 140.5–116.4 ppm (Fig. 3).

High-resolution EI-MS of compound **15** showed M^+ at *m/z* 425.0188 with a composition of $C_{20}H_{16}BrN_3OS$ (calcd 425.0197). The isotopic [M^++2] peak at *m/z* of 427 indicated the presence of a bromine (98 % isotopic relative abundance) and sulfur (4.4 % isotopic relative abundance) atoms in a molecule. Neutral losses in the forms of H_2S, 3-Br-C_6H_4-NCS, 3-Br-C_6H_4-NH_2, and (3-OH-C_6H_4)(Ph)C=NNH_2 yielded signals at *m/z* of 391, 212, 254, and 213, respectively. Cleavage of N–N bond resulted in nitrenium ion at *m/z* of 196 as the base peak. Cleavage of adjacent

Table 1 Urease inhibitory activity of benzophenone semicarbazones and thiosemicarbazones **3–27**

Compounds	Structure			$IC_{50} \pm SEM$ (μM)
	X	R	Ar	
3	S	H	Phenyl	41.2 ± 0.9
4	S	H	3′′-Chlorophenyl	43.6 ± 0.5
5	S	H	2′′,3′′-Dichlorophenyl	NA
6	S	H	2′′,5′′-Dichlorophenyl	NA
7	S	H	3′′,4′′-Dichlorophenyl	NA
8	S	H	3′′-Bromophenyl	35.8 ± 0.2
9	S	H	4′′-Bromophenyl	119.5 ± 1.6
10	S	H	4′′-Nitrophenyl	NA
11	S	OH	Phenyl	28.0 ± 0.2
12	S	OH	2′′,3′′-Dichlorophenyl	38.0 ± 1.3
13	S	OH	2′′,4′′-Dichlorophenyl	31.1 ± 0.1
14	S	OH	2′′,5′′-Dichlorophenyl	29.9 ± 1.7
15	S	OH	3′′-Bromophenyl	8.7 ± 0.6
16	S	OH	4′′-Bromophenyl	28.7 ± 0.8
17	S	OH	4′′-Nitrophenyl	26.1 ± 0.2
18	O	H	Phenyl	NA
19	O	H	3′′-Chlorophenyl	NA
20	O	H	3′′-(Trifluoromethyl)phenyl	NA
21	O	H	4′′-(Trifluoromethyl)phenyl	NA
22	O	H	2′′-Chloro-5′′-(trifluoromethyl)phenyl	NA
23	O	H	4′′-Chloro-2′′-(trifluoromethyl)phenyl	NA
24	O	OH	3′′-Chlorophenyl	NA
25	O	OH	4′′-(Trifluoromethyl)phenyl	NA
26	O	OH	2′′-Chloro-5′′-(trifluoromethyl)phenyl	NA
27	O	OH	4′′-Chloro-2′′-(trifluoromethyl)phenyl	NA

Standard: Thiourea, $IC_{50} \pm SEM = 21.2 \pm 1.3$ μM

SEM standard error of the mean, *NA* not active

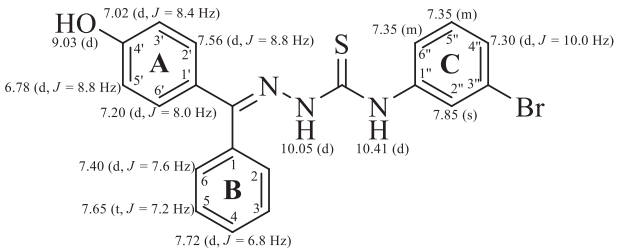
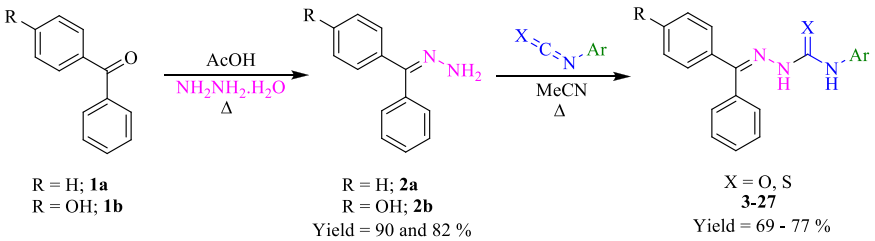


Fig. 2 ^{1}H-NMR analysis of compound **15**



Scheme 1 Synthesis of benzophenone semicarbazones and thiosemicarbazones **3–27**

N–C bond generated a cation at *m/z* of 211. Peak at *m/z* 348 was due to stable aromatic (triazolethione) cation arose through the removal of phenyl radical, followed by intramolecular cyclization. Loss of a mercapto radical from the parent molecule yielded an oxonium ion at *m/z* 392 having diaziridine ring in the middle (Fig. 4).

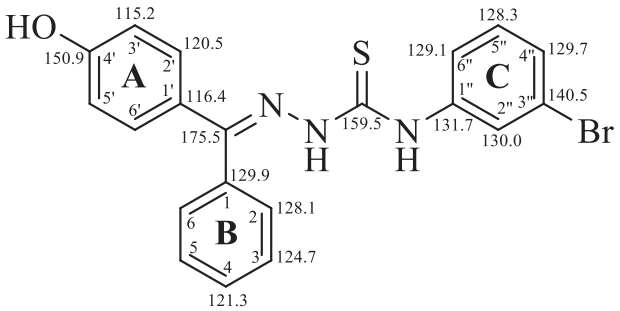


Fig. 3 ^{13}C-NMR analysis of compound **15**

The presence of the main functionalities of compound **15** was further justified with the help of fourier transform infrared (FT-IR) spectroscopy. The FT-IR spectrum showed the stretching vibrations at 3555 and 3283 cm^{-1} that corresponded to the O–H and N–H bonds, respectively. The iminic (C=N) and aromatic (C=C) bonds vibrated at 1583 and 1533 cm^{-1}, respectively. Vibrational stretching of thiocarbonylic bond (C=S) appeared at 1277 cm^{-1} (Fig. 5).

Enzyme inhibitory studies

Survey on limited SAR studies of 25 synthetic derivatives of benzophenone semicarbazones/thiosemicarbazones (**3**–**27**) suggested that substituting different groups on the aryl, as well as CONH/CSNH parts of the molecules are responsible for urease inhibitorty activity of the compounds (Fig. 6).

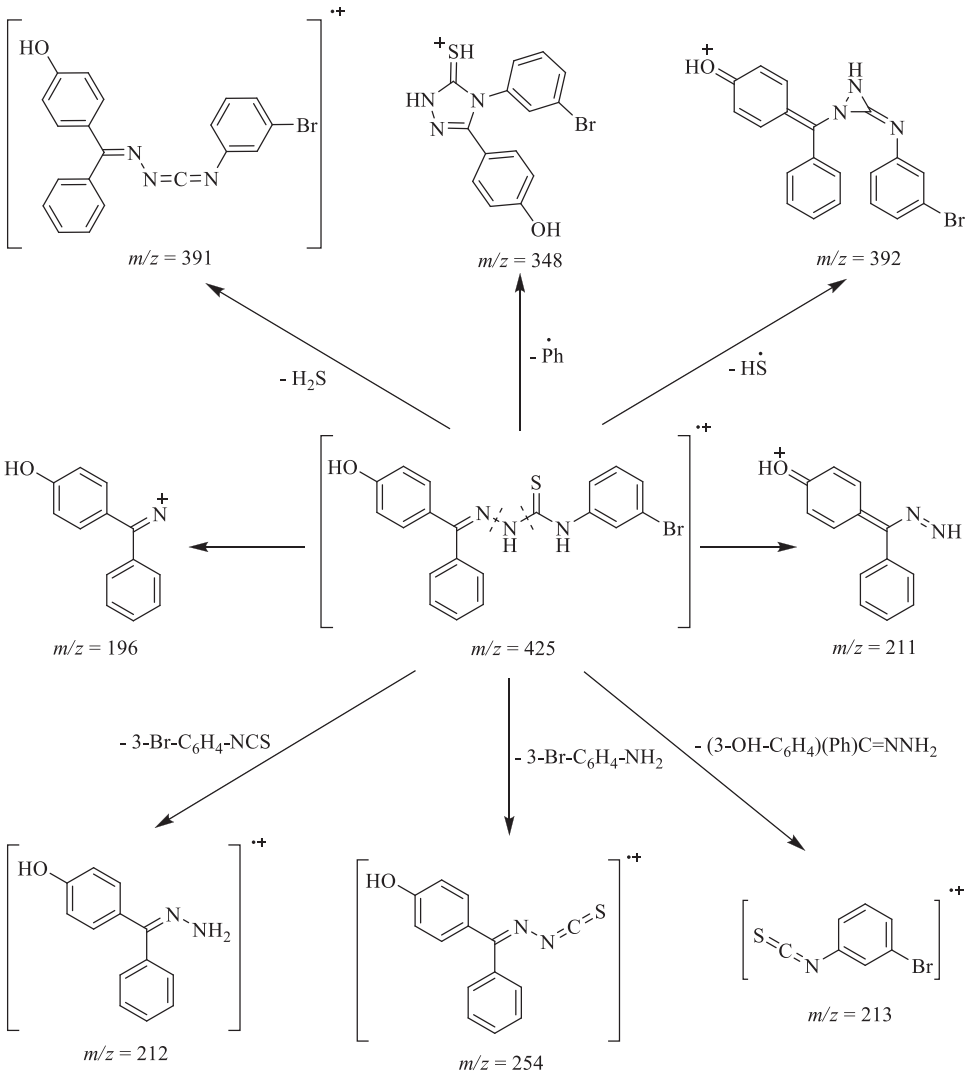


Fig. 4 EI-MS fragmentation pattern of compound **15**

Compounds **3**,**4**, **8**, **9**, and **11**–**17** displayed varying inhibitory potential of enzyme having IC_{50} values in the range of 8.7 ± 0.6–119.5 ± 1.6 μM, in comparison with the standard thiourea ($IC_{50} = 21.2 \pm 1.3$ μM). Nonetheless, compounds **5**–**7**, **10**, and **18**–**27** were identified as entirely inactive.

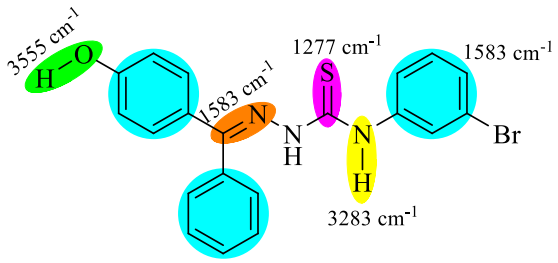


Fig. 5 FT-IR analysis of compound **15**

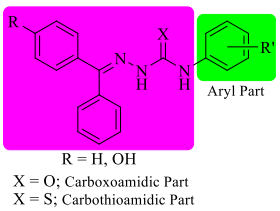


Fig. 6 Benzophenone semicarbazones and thiosemicarbazones **3**–**27**

Among the library of synthesized 25 compounds, compound **15** ($IC_{50} = 8.7 \pm 0.6$ μM) demonstrated the highest urease inhibition. It is about threefolds more active than the standard urea. The attachment of bromo group at C-3″ and hydroxyl group at C-4′ of aryl thiosemicarbazone provide the best configuration mode to interact with the active site of the enzyme. Migration of this bromo group to C-4″, as in compound **16** ($IC_{50} = 28.7 \pm 0.8$ μM), suppressed the inhibition to three times. Similar trend was observed when the bromo group changed with hydrogen as in compound **11** ($IC_{50} = 28.0 \pm 0.2$ μM).

Among the dichlorinated analogs, keeping the CSNH part constant (when OH group at C-4′), different positions of both chlorine groups on the aryl part of molecule are responsible for increasing or decreasing inhibitory pattern which is *para* (Compound **14**; $IC_{50} = 29.9 \pm 1.7$ μM), *meta* (Compound **13**; $IC_{50} = 31.1 \pm 0.1$ μM), and *ortho* (Compound **12**; $IC_{50} = 38.0 \pm 1.3$ μM). Interestingly, when hydroxyl at C-4′ of

Table 2 Kinetic data of most potent benzophenone thiosemicarbazones **15** and **17**

Compounds	$K_i \pm$ SEM (μM)	Type of inhibition
15	6.76 ± 0.002	Mixed
17	14.18 ± 0.002	Mixed

K_i dissociation constant, *SEM* standard error of the mean

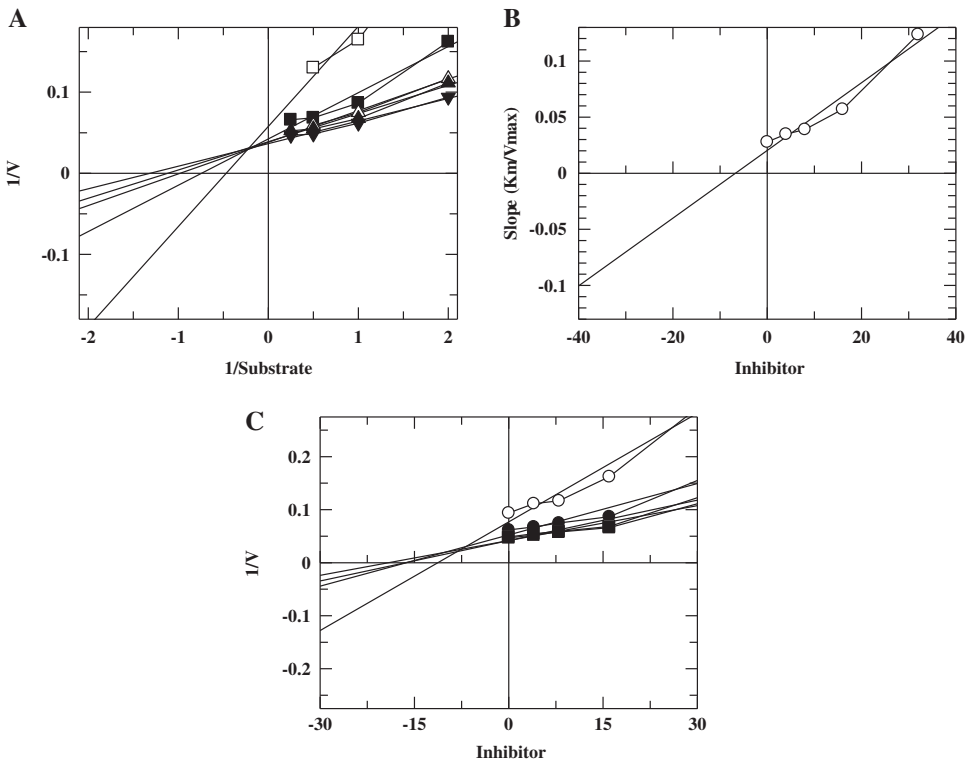


Fig. 7 The mode of inhibition of urease by compound **15**, **a** is the Lineweaver–Burk plot of reciprocal rate of reaction (velocities) versus reciprocal of substrate (urea) in the absence (▼), and in the presence of 4 (▲), 8 (Δ), 16 (■), 32 μM (□) of compound **15**. **b** Is secondary replot of Lineweaver–Burk plot between the slopes of each line on Lineweaver–Burk plot versus different concentrations of compound **15** and **c** is Dixon plot of reciprocal rate of reaction (velocities) versus different concentrations of compound **15**

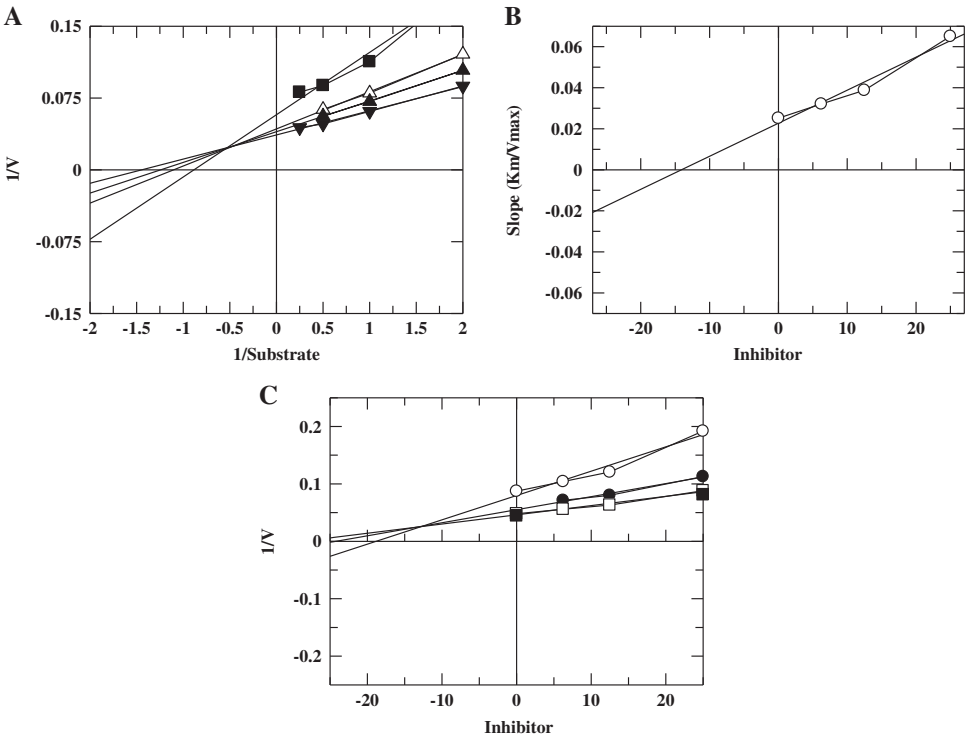


Fig. 8 The mode of inhibition of urease by compound **17**, **a** is the Lineweaver–Burk plot of reciprocal rate of reaction (velocities) versus reciprocal of substrate (urea) in the absence (▼), and in the presence of 6.25 (▲), 12.5(Δ), and 25 μM (■) of compound **17**. **b** Is secondary replot of Lineweaver–Burk plot between the slopes of each line on Lineweaver–Burk plot versus different concentrations of compound **17** and **c** is Dixon plot of reciprocal rate of reaction (velocities) versus different concentrations of compound **17**

CSNH part was replaced with hydrogen keeping the positions of chlorines intact as in compounds **5**, **6**, and **7**, the activitity of compounds was dramatically diminished.

However, among the monohalogenated analogs for the non-hydroxylated thiosemicarbazones, inhibitory activity was observed. Compound **8** ($IC_{50} = 35.8 \pm 0.2$ μM) with bromo group at C-3′′ was found to be modertaely active. Bromo group at C-4′′ lowered the activity to threefolds as in compound **9** ($IC_{50} = 119.5 \pm 1.6$ μM). A slight decline in activity was observed when bromo group in compound **8** was replaced by a chloro group as in compound **4** ($IC_{50} = 43.6 \pm 0.5$ μM).

Nitro group at *para* position was not sufficient enough to display activity until it is hydroxylated at C-4′ as in compound **17** ($IC_{50} = 26.1 \pm 0.2$ μM). An inactivity may be seen in compound **10** which lacks hydroxy group at C-4′ but has nitro group at C-4′′.

All activities discussed so far must have some connection with sulphur as well. The clear-cut non-compatibilty with the enzyme may be seen when the sulphur was replaced with oxygen (semicarabazone derivatives **18**–**27**). However, thiosemicarbazone derivatives rendered varied inhibitory potential that may be correlated with combination of sulphur, hydroxy at C-4′, and different substitutions on the aryl part.

Kinetic studies

Type of inhibition by most active compounds **15** and **17** was determined by kinetic studies using various concentrations of substrate urea (0.5–4.0 mM). Inhibition type was deduced by Lineweaver–Burk plots, where the reciprocal of the rates of the reaction were plotted against the reciprocal of substrate concentration to monitor the effect of inhibitor on both K_m and V_{max}. The K_i values were determined by secondary re-plot of Lineweaver–Burk plots where the slope of each line in the Lineweaver–Burk plots was plotted against different concentrations of inhibitor. The K_i values were deduced by Dixon plot where the reciprocal of the rate of reaction were plotted against different concentrations of inhibitors (Table 2). Kinetic studies showed that compounds **15** and **17** inhibited urease in mixed modes as both K_m and V_{max} was found to be affected (Figs. 7 and 8). This indicates that these compounds could interact at the allosteric site or active site of the enzyme.

Conclusion

We have synthesized 25 differently substituted benzophenone semicarbazones and thiosemicarbazones and screened them against urease. Compound **15** was found to have IC_{50} value below the standard thiourea. While compounds, **3**, **4**, **8**, **9**, **11**–**14**, **16**, and **17** displayed good to moderate IC_{50} values within the range of 26.1–43.6 μM. Further studies may help in the development of these molecules as a potential leads for the urease-hyperactivity based complications.

Experimental

Material and methods

Acetic acid, hydrazine hydrates, benzophenones, and different aryl isocyanates/isothiocyantes, type IX Jack bean urease (EC 3.5.1.5), urea, thiourea, di-sodium hydrogen phosphate, mono-sodium di-hydrogen phosphate, and phenol were purchased from Sigma-Aldrich (USA). Acetonitrile was dried by charging it with 3 Å molecular sieves. All chemicals were used as acquired without purification.

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Avance Bruker AM 300 and 400 MHz machines. EI-MS were run on a Finnigan MAT-311A (Germany) Mass Spectrometer. Melting points of the compounds were recorded on Stuart® SMP10 melting point apparatus. IR spectra (KBr discs) were recorded on a FTS 3000 MX, Bio-RAD Merlin (Excalibur Model) spectrophotometer. CHN analyses were operated on a Carlo Erba Strumentazione-Mod-1106, Italy. Thin layer chromatography (TLC) analyses were performed on pre-coated silica gel aluminum plates (Kieselgel 60, 254, E. Merck, Germany). TLC chromatograms were visualized under ultraviolet lamp at 254 and 365 nm.

Assay for urease inhibitory activity

The urease inhibition assay was performed spectrophotometrically. In the 96-well plate, 25 µL of urease solution (1 U/well) was incubated with 5 µL of test compound (250 µM) for 15 minutes, at 30 °C. Thereafter, 55 µL of urea (substrate) with concentration of 100 mM, was added and the plate was again incubated for 10 min at 30 °C. After incubation, 45 µL of phenol (1 % w/v phenol and 0.005 % w/v sodium nitroprusside), and 70 µL of alkali reagents (0.5 % w/v sodium hydroxide and 0.1 % sodium hypochlorite) were added to each well. The plate was again incubated for 50 min at 30 °C. Urease activity was measured with the rate of production of ammonia continuously following the method of Weatherburn (Weatherburn, 1967), and change in absorbance was monitored at 630 nm on a ELISA plate reader (Spectra Max M2, Molecular Devices, CA, USA). Thiourea was used as a standard compound.

Kinetic studies protocol

Mechanistic studies were carried out to determine the mechanism of inhibitors, binding to enzyme. Inhibitors could bind enzyme in a competitive, non-competitive, mixed, or uncompetitive way. Briefly the enzyme solution (1 U/200 µL) was incubated with different concentrations of inhibitor for 15 min at 30 °C. The reaction was then started by adding different concentrations of substrate (0.5–4.0 mM). Production of ammonia was measured continuously at 630 nm for 50 min on an ELISA plate reader, after the addition of phenol and alkali reagent.

Statistical analysis

All experiments were carried out in triplicate. The results were processed via Softmax Pro Software (Molecular Devices, CA, USA). The percentage of inhibition was calculated using the formula given below.

$$\%\,\text{Inhibition} = 100 - (\text{Absorbance of test compound}/\text{Absorbance of control}) \times 100$$

The IC_{50} of the active compounds was evaluated by measuring the effect of different concentrations of inhibitors on production of ammonia. The IC_{50} values were deduced via EZ-Fit enzyme kinetics program (Perellela Scientific, Inc., Amherst, USA). To determine the mechanism of inhibitor binding to enzyme, Lineweaver–Burk plot, secondary plot, and Dixon plot were plotted by using Grafit 7 software (Erithacus Software Limited, UK). Grafit 7 program was used to evaluate different kinetic parameters.

General procedure for the synthesis of compounds 2a and 2b

Benzophenone or 4′-hydroxybenzophenone (1 mmol) was taken in hydrazine hydrate (10 mL) and refluxed for 6 h catalyzed by acetic acid (2 mL; Scheme1). Progress of chemical reaction was periodically monitored by TLC analysis. When the reaction completed, water was added until precipitation. These precipitates were filtered and dried under vacuum.

General procedure for the synthesis of compounds 3–27

Benzophenone semicarbazones and thiosemicarbazones **3**–**27** were synthesized by refluxing benzophenone hydrazones (**2a** or **2b**; 2 mmol) and substituted aryl isocyanates or isothiocyanates (2 mmol) in acetonitrile (15 mL) for 24 h. When TLC analysis suggested the completion of reaction, the mixtures were left at room temperature to be cooled down which resulted in precipitation. The precipitates were filtered and dried under vacuum at 40 °C to afford good yields of the title compounds.

*(Diphenylmethylene)hydrazine (**2a**)*

Yield: 90 %; White solid; m.p. 99–100 °C (lit. 97–98 °C; Barton et al., 1962); R_f: 0.35 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 7.56 (t, 2H, $J_{3(2,4)} = J_{5(4,6)} = 7.6$ Hz, H-3, H-5), 7.48 (t, 1H, $J_{4(3,5)} = 7.2$ Hz, H-

4), 7.33 (d, 2H, $J_{2,3} = J_{6,5} = 7.2$ Hz, H-2, H-6), 7.28 (t, 2H, $J_{3'(2',4')} = J_{5'(4',6')} = 7.2$ Hz, H-3′, H-5′), 7.22 (m, 3H, H-2′, H-4′,H-6′), 6.22(s, 2H, NH_2); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 144.4 (C=N), 138.8 (C-1), 133.0 (C-1′), 129.3 (C-2, C-6), 128.6 (C-2′, C-6′), 128.4 (C-4), 128.0 (C-4′), 127.1 (C-3, C-5), 125.3 (C-3′, C-5′); EI-MS: *m/z* (rel. abund. %), 196 $[M]^+$ (72.6), 180 (76.1), 165 (91.4), 105 (26.1), 77 (100.0); HREI-MS: *m/z* calcd for $C_{13}H_{12}N_2$ $[M]^+$ 196.1000 found 196.1003; IR (KBr, cm^{-1}): 3430 (N–H), 1630 (C=N), 1550 (C=C); Anal. calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27; Found: C, 79.58; H, 6.15; N, 14.29.

*(E)-[(4′-Hydroxyphenyl)(phenyl)methylene]hydrazine (**2b**)*

Yield: 82 %; White solid; m.p. 130–132 °C (lit. 150 °C; Joshi and Hari, 1981); R_f: 0.28 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 9.69 (s, 1H, OH), 7.33 (d, 2H, $J_{2,3} = J_{6,5} = 7.6$ Hz, H-2, H-6), 7.28 (m, 3H, H-3, H-4, H-5), 7.02 (d, 2H, $J_{2',3'} = J_{6',5'} = 8.4$ Hz, H-2′, H-6′), 6.92 (d, 2H, $J_{3',2'} = J_{5',6'} = 8.4$ Hz, H-3′, H-5′), 6.12 (s, 2H, NH_2); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 157.4 (C-4′), 144.7 (C=N), 139.3 (C-1), 129.9 (C-2, C-6), 127.9 (C-4), 127.0 (C-3, C-5), 125.5 (C-2′, C-6′), 123.0 (C-1′), 116.0 (C-3′, C-5′); EI-MS: *m/z* (rel. abund. %), 212 $[M]^+$ (100.0), 196 (25.2), 181 (25.2), 152 (15.6), 77 (38.8); HREI-MS: *m/z* calcd for $C_{13}H_{12}N_2O$ $[M]^+$ 212.0950 found 212.0952; IR (KBr, cm^{-1}): 3465 (O–H), 3428 (N–H), 1635 (C=N), 1560 (C=C); Anal. calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20; O, 7.54; Found: C, 73.52; H, 5.73; N, 13.21.

2-(Diphenylmethylene)-N-*phenylhydrazinecarbothioamide (**3**)*

Yield: 71 %; Brown solid; m.p. 164–166 °C (lit. 160–162 °C; Singh et al., 2011); R_f: 0.56 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.44 (s, 1H, NH), 8.81 (s, 1H, NH), 7.73 (d, 2H, $J_{2,3} = J_{6,5} = 6.3$ Hz, H-2, H-6), 7.67 (m, 3H, H-2′′, H-6′′, H-4′′), 7.54 (d, 2H, $J_{2',3'} = J_{6',5'} = 7.8$ Hz, H-2′, H-6′), 7.43 (m, 1H, H-4), 7.41 (m, 6H, H-3, H-5, H-3′, H-5′, H-3′′, H-5′′), 7.25 (m, 1H, H-4′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 176.1 (C=S), 149.8 (C=N), 138.8 (C-1′′), 136.2 (C-1), 131.3 (C-1′), 130.0 (C-2, C-6), 129.8 (C-2′, C-6′), 128.3 (C-4), 128.1 (C-4′), 127.8 (C-3, C-5), 125.9 (C-3′, C-5′), 125.7 (C-3′′, C-5′′), 124.3 (C-4′), 123.5 (C-2′′, C-6′′); EI-MS: *m/z* (rel. abund. %), 331 $[M]^+$ (13.0), 298 (17.6), 254 (45.5), 197 (61.8), 180 (61.1); HREI-MS: *m/z* calcd for $C_{20}H_{17}N_3S$ $[M]^+$ 331.1143 found 331.1146; IR (KBr, cm^{-1}): 3435 (N–H), 1636 (C=N), 1542 (C=C), 1386 (C–N), 1290 (C=S); Anal. calcd for $C_{20}H_{17}N_3S$: C, 72.48; H, 5.17; N, 12.68; S, 9.67; Found: C, 72.46; H, 5.19; N, 12.67.

N-*(3′′-Chlorophenyl)-2-(diphenylmethylene) hydrazinecarbothioamide (**4**)*

Yield: 72 %; White solid; m.p. 128–130 °C; R_f: 0.37 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.47 (s, 1H, NH), 8.98 (s, 1H, NH), 7.72 (m, 3H, H-2, H-6, H-4), 7.64 (s, 1H, H-2′′), 7.62 (d, 2H, $J_{2',3'} = J_{6',5'} = 7.8$ Hz, H-2′, H-6′), 7.57 (d, 1H, $J_{4'',5''} = 8.1$ Hz, H-4′′), 7.44 (m, 1H, H-5′′), 7.42 (m, 3H, H-3′, H-4′, H-5′), 7.37 (m, 2H, H-3, H-5), 7.30 (d, 1H, $J_{6'',5''} = 9.0$ Hz, H-6′′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 176.0 (C=S), 150.4 (C=N), 140.3 (C-3′′), 136.1 (C-1′′), 132.2 (C-2′′), 131.3 (C-1), 130.0 (C-1′), 129.8 (C-4′′), 129.7 (C-2, C-6), 128.8 (C-2′, C-6′), 128.3 (C-6′′), 128.0 (C-3, C-5), 127.9 (C-3′, C-5′), 125.3 (C-5′′), 125.2 (C-4), 124.2 (C-4′); EI-MS: *m/z* (rel. abund. %), 367 $[M^+{+}2]$ (5.6), 365 $[M]^+$ (14.0), 238 (24.2), 195 (21.3), 180 (100.0), 166 (66.5); HREI-MS: *m/z* calcd for $C_{20}H_{16}ClN_3S$ $[M]^+$ 365.0753, found 365.0756; IR (KBr, cm^{-1}): 3475 (N–H), 1587 (C=N), 1542 (C=C), 1298 (C–N), 1286 (C=S); Anal. calcd for $C_{20}H_{16}ClN_3S$: C, 65.65; H, 4.41; Cl, 9.69; N, 11.48; S, 8.76; Found: C, 65.67; H, 4.43; N, 11.45.

*N-(2′′,3′′-Dichlorophenyl)-2-(diphenylmethylene) hydrazinecarbothioamide (**5**)*

Yield: 71 %; Yellow solid; m.p. 178–180 °C; R_f: 0.32 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.49 (s, 1H, NH), 9.15 (s, 1H, NH), 7.71 (d, 2H, $J_{2,3} = J_{6,5} = 6.6$ Hz, H-2, H-6), 7.66 (d, 2H, $J_{2',3'} = J_{6',5'} = 7.5$ Hz, H-2′, H-6′), 7.62 (m, 2H, H-3, H-5), 7.45 (m, 7H, H-4′′, H-5′′, H-6′′, H-3′, H-5′, H-4′, H-4); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 176.9 (C=S), 150.3 (C=N), 138.5 (C-2′′), 136.2 (C-3′′), 131.6 (C-1′′), 131.3 (C-1), 130.0 (C-1′), 129.8 (C-4′′), 129.7 (C-2, C-6), 128.9 (C-2′, C-6′), 129.6 (C-6′′), 128.4 (C-5′′), 128.3 (C-3, C-5), 127.8 (C-3′, C-5′), 127.7 (C-4, C-4′); EI-MS: *m/z* (rel. abund. %), 364 $[M^+$-Cl] (87.0), 238 (19.1), 195 (40.8), 180 (99.0), 133 (29.2), 77 (100.0); IR (KBr, cm^{-1}): 3413 (N–H), 1579 (C=N), 1531 (C=C), 1311 (C–N), 1215 (C=S); Anal. calcd for $C_{20}H_{15}Cl_2N_3S$: C, 60.00; H, 3.78; Cl, 17.71; N, 10.50; S, 8.01; Found: C, 60.02; H, 3.76 N, 10.52.

*N-(2′′,5′′-Dichlorophenyl)-2-(diphenylmethylene) hydrazinecarbothioamide (**6**)*

Yield: 75 %; White solid; m.p. 168–170 °C; R_f: 0.39 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.42 (s, 1H, NH), 9.27 (s, 1H, NH), 7.86 (d, 1H, $J_{4'',6''} =$ 2.4 Hz, H-4′′), 7.68 (m, 2H, H-3, H-3′), 7.62 (d, 3H, $J_{2,3} = J_{2',3'} = J_{3'',4''} = 6.3$ Hz, H-2, H-2′, H-3′′), 7.57 (s, 1H, H-6′′), 7.43 (m, 6H, H-6, H-6′, H-5, H-5′, H-4, H-4′); ^{13}C-NMR: (100 MHz, DMSO-d_6):δ_C 176.6 (C=S), 150.5

(C=N), 137.6 (C-2′′), 136.2 (C-5′′), 131.3 (C-1′′), 131.0 (C-6′′), 130.6 (C-1), 130.0 (C-1′), 129.6 (C-3′′), 129.2 (C-5′′), 128.9 (C-2, C-6), 128.5 (C-2′, C-6′), 128.4 (C-3, C-5), 127.8 (C-3′, C-5′), 127.7 (C-4, C-4′); EI-MS: *m/z* (rel. abund. %), 364 [M^+-Cl] (87.0), 238 (14.0), 195 (38.5), 180 (94.3), 77 (100.0); IR (KBr, cm^{-1}): 3414 (N–H), 1581 (C=N), 1529 (C=C), 1311 (C–N), 1257 (C=S); Anal. calcd for $C_{20}H_{15}Cl_2N_3S$: C, 60.00; H, 3.78; Cl, 17.71; N, 10.50; S, 8.01; Found: C, 60.01; H, 3.75 N, 10.51.

*N-(3′′,4′′-Dichlorophenyl)-2-(diphenylmethylene) hydrazinecarbothioamide (**7**)*

Yield: 72 %; Yellow solid; m.p. 216–218 °C; R_f: 0.39 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.39 (s, 1H, NH), 9.15 (s, 1H, NH), 7.74 (m, 2H, H-2, H-6), 7.70 (m, 3H, H-3, H-4, H-5), 7.66 (m, 2H, H-2′, H-6′), 7.48 (dd, 1H, $J_{6'',5''} = 6.6$ Hz, $J_{6'',2''} = 1.8$ Hz, H-6′′), 7.41 (m, 5H, H-2′′, H-5′′, H-3′, H-4′, H-5′); ^{13}C-NMR: (100 MHz, DMSO-d_6):δ_C 176.9 (C=S), 150.3 (C=N), 136.1 (C-3′′), 135.6 (C-4′′), 131.8 (C-1′′), 131.4 (C-6′′), 131.2 (C-2′′), 131.0 (C-1), 130.3 (C-1′), 130.0 (C-5′′), 129.6 (C-2, C-6), 128.8 (C-2′, C-6′), 128.4 (C-3, C-5), 128.3 (C-3′, C-5′), 127.7 (C-4), 127.3 (C-4′); EI-MS: *m/z* (rel. abund. %), 364 [M^+-Cl] (21.3), 238 (2.4), 195 (12.1), 180 (100.0), 166 (73.0), 77 (36.2); IR (KBr, cm^{-1}): 3415 (N–H), 1631 (C=N), 1525 (C=C), 1363 (C–N), 1255 (C=S); Anal. calcd for $C_{20}H_{15}Cl_2N_3S$: C, 60.00; H, 3.78; Cl, 17.71; N, 10.50; S, 8.01; Found: C, 60.02; H, 3.73 N, 10.54.

*N-(3′′-Bromophenyl)-2-(diphenylmethylene) hydrazinecarbothioamide (**8**)*

Yield: 74 %; White solid; m.p. 226–228 °C; R_f: 0.52 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.47 (s, 1H, NH), 8.98 (s, 1H, NH), 7.84 (br. s, 1H, H-2′′), 7.72 (d, 2H, $J_{2,3} = J_{6,5} = 6.9$ Hz, H-2, H-6), 7.67 (t, 2H, $J_{3(2,4)} = J_{5(6,4)} = 7.2$ Hz, H-3, H-5), 7.62 (d, 2H, $J_{2',3'} = J_{6',5'} = 8.7$ Hz, H-2′, H-6′), 7.42 (m, 6H, H-4′′, H-5′′, H-3′, H-4′, H-5′, H-4), 7.33 (d, 1H, $J_{6'',5''} = 7.8$ Hz, H-6′′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 176.7 (C=S), 156.8 (C=N), 153.2 (C-3′′), 136.5 (C-1′′), 131.9 (C-2′′), 130.2 (C-4′′), 130.0 (C-1, C-1′), 129.6 (C-6′′), 128.4 (C-5′′), 127.8 (C-2, C-6, C-4, C-2′, C-6′, C-4′), 127.6 (C-3, C-5, C-3′, C-5′); EI-MS: *m/z* (rel. abund. %), 412 [M^++2] (3.4), 410 $[M]^+$ (3.9), 376 (4.7), 332 (7.7), 239 (7.5), 180 (100.0), 166 (95.3), 155 (3.5), 77 (44.9); HREI-MS: *m/z* calcd for $C_{20}H_{16}BrN_3S$ $[M]^+$ 409.0248, found 409.0245; IR (KBr, cm^{-1}): 3418 (N–H), 1627 (C=N), 1521 (C=C), 1325 (C–N), 1245 (C=S); Anal. calcd for $C_{20}H_{16}BrN_3S$: C, 58.54; H, 3.93; Br, 19.47; N, 10.24; S, 7.81; Found: C, 58.54; H, 3.93, N, 10.24.

*N-(4′′-Bromophenyl)-2-(diphenylmethylene) hydrazinecarbothioamide (**9**)*

Yield: 72 %; White solid; m.p. 240–242 °C; R_f: 0.56 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.62 (s, 1H, NH), 9.34 (s, 1H, NH), 7.76 (m, 2H, H-2, H-6), 7.58 (m, 4H, H-2′, H-6′, H-3′′ ,H-5′′), 7.43 (m, 2H, H-3, H-5), 7.35 (m, 4H, H-3′, H-5′, H-2′′, H-6′′), 7.30 (m, 1H, H-4), 6.89 (m, 1H, H-4′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 173.8 (C=S), 154.8 (C=N), 139.7 (C-1′′), 136.4 (C-4′′), 131.0 (C-1), 130.0 (C-1′), 129.7 (C-2′′, C-6′′), 129.5 (C-3′′, C-5′′), 128.5 (C-2, C-6), 128.4 (C-2′, C-6′), 128.3 (C-3, C-5), 128.1 (C-3′, C-5′), 127.2 (C-4), 127.0 (C-4′); EI-MS: *m/z* (rel. abund. %), 409 $[M]^+$ (Absent), 238 (24.0), 196 (28.9), 180 (100.0), 77 (67.8); IR (KBr, cm^{-1}): 3473 (N–H), 1625 (C=N), 1531 (C=C), 1321 (C–N), 1288 (C=S); Anal. calcd for $C_{20}H_{16}BrN_3S$: C, 58.54; H, 3.93; Br, 19.47; N, 10.24; S, 7.81; Found: C, 58.53; H, 3.92; N, 10.22.

*2-(Diphenylmethylene)-N-(4′′-nitrophenyl) hydrazinecarbothioamide (**10**)*

Yield: 69 %; Yellow solid; m.p. 198–200 °C (lit. 197–199 °C; Singh et al., 2011); R_f: 0.36 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.71 (s, 1H, NH), 9.36 (s, 1H, NH), 8.26 (d, 2H, $J_{3'',2''} = J_{5'',6''} = 6.9$ Hz, H-3′′, H-5′′), 8.03 (d, 2H, $J_{2,3} = J_{6,5} = 6.9$ Hz, H-2, H-6), 7.69 (m, 5H, H-2′, H-6′, H-3, H-5, H-4), 7.45 (d, 2H, $J_{2'',3''} = J_{6'',5''} = 6.3$ Hz, H-2′′, H-6′′), 7.41 (m, 3H, H-3′, H-5′, H-4′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 175.7 (C=S), 151.3 (C=N), 145.1 (C-1′′), 143.6 (C-4′′), 136.2 (C-3′′, C-5′′), 131.4 (C-1), 130.1 (C-1′), 130.0 (C-2, C-6), 129.6 (C-2′, C-6′), 128.5 (C-2′′, C-6′′), 128.3 (C-3, C-5), 128.0 (C-3′, C-5′), 124.6 (C-4), 123.7 (C-4′); EI-MS: *m/z* (rel. abund. %), 376 $[M]^+$ (33.4), 299 (17.6), 238 (53.6) 195 (43.2), 180 (100.0), 77 (14.5); HREI-MS: *m/z* calcd for $C_{20}H_{16}N_4O_2S$ $[M]^+$ 376.0994, found 376.0993; IR (KBr, cm^{-1}): 3415 (N–H), 1598 (C=N), 1546 (C=C), 1517 (N=O), 1332 (C–N), 1282 (C=S); Anal. calcd for $C_{20}H_{16}N_4O_2S$: C, 63.81; H, 4.28; N, 14.88; O, 8.50; S, 8.52; Found: C, 63.82; H, 4.27; N, 14.88.

*(E)-2-[(4′-Hydroxyphenyl)(phenyl)methylene]-N-phenylhydrazine carbothioamide (**11**)*

Yield: 75 %; Yellow solid; m.p. 171–173 °C; R_f: 0.40 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.35 (d, 1H, NH), 8.90 (s, 1H, NH), 8.60 (s, 1H, OH), 7.73 (d, $J_{2',3'} = 7.5$ Hz, 1H, H-2′), 7.65 (d, $J_{6',5'} = 7.8$ Hz, 1H, H-6′), 7.55 (d, $J_{2,3} = J_{6,5} = 7.2$ Hz, 2H, H-2, H-6), 7.39 (m, 4H, H-3, H-5, H-3′′, H-5′′), 7.21 (m, 2H, H-4, H-4′′), 7.02 (d, 2H, $J_{2'',3''} = J_{6'',5''} = 8.4$ Hz, H-2′′, H-6′′), 6.92 (d, $J_{3',2'}$

= 8.4 Hz, 1H, H-3′), 6.77 (d, $J_{5',6'}$ = 8.7 Hz, 1H, H-5′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 159.3 (C=S), 129.9 (C=N), 129.8 (C-4′), 129.7 (C-1′′), 129.6 (C-1), 128.3 (C-2′′, C-6′′), 128.2 (C-2, C-6), 128.1 (C-3′′, C-5′′), 127.9 (C-3, C-5), 125.8 (C-4′′), 124.3 (C-4), 123.5 (C-2′, C-6′), 116.4 (C-1′), 115.3 (C-3′, C-5′); EI-MS: *m/z* (rel. abund. %): 347 $[M]^+$ (6.7), 254 (31.2), 212 (28.4), 196 (100.0), 181 (19.1), 77 (16.0); HREI-MS: *m/z* calcd for $C_{20}H_{17}N_3OS$ $[M]^+$ 347.1092, found 347.1096; IR (KBr, cm^{-1}): 3413 (O–H), 3328 (N–H), 1510 (C=N), 1537 (C=C), 1311 (C–N), 1274 (C=S); Anal. calcd for $C_{20}H_{17}N_3OS$: C, 69.14; H, 4.93; N, 12.09; O, 4.61; S, 9.23; Found: C, 69.12; H, 4.94; N, 12.07.

*(E)-N-(2′′,3′′-Dichlorophenyl)-2-[(4′hydroxyphenyl) (phenyl)methylene] hydrazine carbothioamide (**12**)*

Yield: 77 %; White solid; m.p. 150–152 °C; R_f: 0.30 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.42 (d, 1H, NH), 10.03 (d, 1H, NH) , 9.16 (d, 1H, OH), 7.71 (d, $J_{4'',5''}$ = 7.6 Hz, 1H, H-4′′), 7.66 (m, 3H, H-3, H-5, H-5′′), 7.60 (d, $J_{6'',5''}$ = 8.4 Hz, 1H, H-6′′), 7.54 (d, $J_{2',3'}$ = 8.8 Hz, 1H, H-2′), 7.42 (m, 3H, H-2, H-6, H-4), 7.22 (d, $J_{6',5'}$ = 8.4 Hz, 1H, H-6′), 7.02 (d, $J_{3',2'}$ = 8.4 Hz, 1H, H-3′), 6.77 (d, $J_{5',6'}$ = 8.7 Hz, 1H, H-5′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 159.4 (C=N), 150.7 (C=S), 138.5 (C-4′), 131.6 (C-2′′), 130.0 (C-3′′), 129.9 (C-1′′), 129.6 (C-1), 128.7 (C-4′′), 128.6 (C-6′′), 128.3 (C-5′′), 128.2 (C-2, C-6), 127.9 (C-3, C-5), 127.7 (C-4), 127.6 (C-2′, C-6′), 116.4 (1′), 115.2 (C-3′, C-5′); EI-MS: *m/z* (rel. abund. %), 381 $[M^+$-Cl] (11.0), 253 (32.4), 196 (100.0), 161 (87.1), 90 (15.0), 77 (16.6); IR (KBr, cm^{-1}): 3429 (O–H), 3413 (N–H), 1589 (C=N), 1541 (C=C), 1357 (C–N), 1215 (C=S); Anal. calcd for $C_{20}H_{15}Cl_2N_3OS$: C, 57.70; H, 3.63; Cl, 17.03; N, 10.09; O, 3.84; S, 7.70; Found: C, 57.71; H, 3.61; N, 10.08.

*(E)-N-(2′′,4′′-Dichlorophenyl)-2-[(4′-hydroxyphenyl) (phenyl)methylene]hydrazine carbothioamide (**13**)*

Yield: 71 %; White solid; m.p. 170–172 °C; R_f: 0.30 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.32 (d, 1H, NH), 10.03 (d, 1H, NH), 9.18 (d, 1H, OH), 7.72 (m, 3H, H-3′′, H-3, H-5), 7.64 (d, 2H, $J_{2,3} = J_{6,5}$ = 7.2 Hz, H-2, H-6), 7.53 (d, $J_{2',3'}$ = 8.7 Hz, 1H, H-2′), 7.47 (d, $J_{5'',6''}$ = 8.4 Hz, 1H, H-5′′), 7.40 (d, $J_{6'',5''}$ = 7.8 Hz, 1H, H-6′′), 7.37 (m, 1H, H-4), 7.21 (d, $J_{6',5'}$ = 8.4 Hz, 1H, H-6′), 7.01 (d, $J_{3',2'}$ = 8.4 Hz, 1H, H-3′), 6.77 (d, $J_{5',6'}$ = 8.7 Hz, 1H, H-5′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 176.3 (C=N), 159.5 (C=S), 158.7 (C-4′), 150.8 (C-2′′), 136.7 (C-4′′), 135.8 (C-3′′), 131.6 (C-1′′), 131.1 (C-1), 131.0 (C-5′′), 130.0 (C-6′′), 129.9 (C-2, C-6), 129.6 (C-3, C-5), 128.8 (C-4), 128.4 (C-2′, C-6′), 128.3 (C-1′), 127.9 (C-3′, C-5′); EI-MS: *m/z* (rel. abund. %), 381 $[M^+$-Cl] (2.8), 254 (17.2), 212 (6.6), 196 (100.0), 161 (68.1), 77 (20.8); IR (KBr, cm^{-1}): 3473 (O–H), 3413 (N–H), 1531 (C=N), 1537 (C=C), 1321 (C–N), 1288 (C=S); Anal. calcd for $C_{20}H_{15}Cl_2N_3OS$: C, 57.70; H, 3.63; Cl, 17.03; N, 10.09; O, 3.84; S, 7.70; Found: C, 57.72; H, 3.62; N, 10.07.

*(E)-N-(2′′,5′′-Dichlorophenyl)-2-[(4′-hydroxyphenyl) (phenyl)methylene]hydrazine carbothioamide (**14**)*

Yield: 73 %; Yellow solid; m.p. 120–122 °C; R_f: 0.38 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.37 (d, 1H, NH), 10.04 (d, 1H, NH), 9.31 (d, 1H, OH), 7.93 (d, 1H, $J_{6'',4''}$ = 2.4 Hz, H-6′′), 7.69 (d, 1H, $J_{3'',4''}$ = 7.5 Hz, H-3′′), 7.64 (d, 1H, $J_{4'',3''}$ = 7.5 Hz, H-4′′), 7.61 (m, 2H, H-3, H-5), 7.52 (d, $J_{2',3'}$ = 8.7 Hz, 1H, H-2′), 7.43 (m, 3H, H-2, H-4, H-6), 7.21 (d, $J_{6',5'}$ = 8.4 Hz, 1H, H-6′), 7.01 (d, $J_{3',2'}$ = 8.4 Hz, 1H, H-3′), 6.78 (d, $J_{5',6'}$ = 8.7 Hz, 1H, H-5′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 176.3 (C=N), 159.5 (C=S), 158.8 (C-4′), 151.0 (C-2′′), 137.6 (C-5′′), 131.6 (C-1′′), 131.0 (C-6′′), 130.6 (C-1), 130.1 (C-3′′), 129.9 (C-4′′), 129.6 (C-2, C-6), 128.7 (C-3, C-5), 128.4 (C-4), 128.0 (C-2′, C-6′), 116.3 (C-1′), 115.2 (C-3′, C-5′); EI-MS: *m/z* (rel. abund. %), 381 $[M^+$-Cl] (24.7), 254 (70.2), 196 (100.0), 161 (90.5), 77 (41.5); IR (KBr, cm^{-1}): 3413 (O–H), 3319 (N–H), 1581 (C=N), 1532 (C=C), 1357 (C–N), 1269 (C=S); Anal. calcd for $C_{20}H_{15}Cl_2N_3OS$: C, 57.70; H, 3.63; Cl, 17.03; N, 10.09; O, 3.84; S, 7.70; Found: C, 57.73; H, 3.66; N, 10.05.

*(E)-N-(3′′-Bromophenyl)-2-[(4′-hydroxyphenyl)(phenyl) methylene]hydrazine carbothioamide (**15**)*

Yield: 69 %; Yellow solid; m.p. 160–162 °C; R_f: 0.42 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 10.41 (d, 1H, NH), 10.05 (d, 1H, NH), 9.03 (d, 1H, OH), 7.85 (s, 1H, H-2′′), 7.72 (d, $J_{4(3,5)}$ = 6.8 Hz, 1H, H-4), 7.65 (t, $J_{3(4,2)} = J_{5(4,6)}$ = 7.2 Hz, 2H, H-3, H-5), 7.56 (d, $J_{2',3'}$ = 8.8 Hz, 1H, H-2′), 7.40 (d, $J_{2,3} = J_{6,5}$ = 7.6 Hz, 2H, H-2, H-6), 7.35 (m, 2H, H-5′′, H-6′′), 7.30 (d, $J_{4'',5''}$= 10.0 Hz, 1H, H-4′′), 7.20 (d, $J_{6',5'}$ = 8.0 Hz, 1H, H-6′), 7.02 (d, $J_{3',2'}$ = 8.4 Hz, 1H, H-3′), 6.78 (d, $J_{5',6'}$ = 8.8 Hz, 1H, H-5′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 175.5 (C=N), 159.5 (C=S), 150.9 (C-4′), 140.5 (C-3′′), 131.7 (C-1′′), 130.0 (C-2′′), 129.9 (C-1), 129.7 (C-4′′), 129.1 (C-6′′), 128.3 (C-5′′), 128.1 (C-2, C-6), 124.7 (C-3, C-5), 121.3 (C-4), 120.5 (C-2′, C-6′), 116.4 (C-1′), 115.2 (C-3′, C-5′); EI-MS: *m/z* (rel. abund. %), 427 $[M^+$+2] (12.1), 425 $[M]^+$ (12.4), 392 (2.9), 391 (1.1), 348 (2.5), 254 (70.3), 213 (15.3), 212 (11.7), 211 (22.4), 196 (100.0); HREI-MS: *m/z* calcd for $C_{20}H_{16}BrN_3OS$ $[M]^+$ 425.0197, found 425.0188; IR (KBr, cm^{-1}): 3555 (O–H), 3283 (N–H), 1583 (C=N), 1533 (C=C), 1313 (C–N), 1277 (C=S); Anal. calcd for $C_{20}H_{16}BrN_3OS$:C, 56.34; H, 3.78; Br, 18.74; N, 9.86; O, 3.75; S, 7.52; Found: C, 56.32; H, 3.79; N, 9.87.

*(E)-N-(4′′-Bromophenyl)-2-[(4′-hydroxyphenyl)(phenyl) methylene]hydrazine carbothioamide (**16**)*

Yield: 72 %; Yellow solid; m.p. 230–232 °C; R_f: 0.38 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (400 MHz, DMSO-d_6): δ_H 10.31 (d, 1H, NH), 9.90 (d, 1H, NH), 8.72 (d, 1H, OH), 7.72 (m, 1H, H-4), 7.65 (d, $J_{2',3'} = 7.2$ Hz, 1H, H-2′), 7.55 (m, 4H, H-3′′, H-5′′, H-2, H-6), 7.53 (m, 2H, H-3, H-5), 7.40 (m, 2H, H-2′′, H-6′′), 7.20 (d, $J_{6',5'} = 8.4$ Hz, 1H, H-6′), 7.02 (d, $J_{3',2'} = 8.4$ Hz, 1H, H-3′), 6.77 (d, $J_{5',6'} = 8.7$ Hz, 1H, H-5′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 175.8 (C=N), 159.4 (C=S), 158.7 (C-4′), 150.7 (C-4′′), 138.3 (C-1′′), 136.7 (C-1), 130.9 (C-3′′, C-5′′), 129.7 (C-2′′, C-6′′), 128.3 (C-2, C-6), 128.0 (C-3, C-5), 127.8 (C-4), 121.3 (C-3′, C-5′), 116.4 (C-1′), 115.2 (C-2′, C-6′); EI-MS: *m/z* (rel. abund. %), 425 $[M]^+$ (Absent), 254 (21.9), 212 (55.6), 196 (100.0), 181 (28.2), 77 (13.8); IR (KBr, cm^{-1}): 3417 (O–H), 3278 (N–H), 1697 (C=N), 1593 (C=C), 1353 (C–N), 1257 (C=S); Anal. calcd for $C_{20}H_{16}BrN_3OS$: C, 58.54; H, 3.93; Br, 19.47; N, 10.24; S, 7.81; Found: C, 58.53; H, 3.94; N, 10.23.

*(E)-2-[(4′-Hydroxyphenyl)(phenyl)methylene]-N-(4′′-nitrophenyl)hydrazine carbothioamide (**17**)*

Yield: 76 %; Yellow solid; m.p. 212–214 °C; R_f: 0.34 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.65 (d, 1H, NH), 10.04 (d, 1H, NH), 9.37 (d, 1H, OH), 8.25 (d, 2H, $J_{3'',2''} = J_{5'',6''} = 9.0$ Hz, H-3′′, H-5′′), 8.04 (d, 2H, $J_{2'',3''} = J_{6'',5''} = 9.0$ Hz, H-2′′, H-6′′), 7.70 (m, 3H, H-2, H-4, H-6), 7.54 (d, $J_{2',3'} = 8.4$ Hz, 1H, H-2′), 7.44 (m, 2H, H-3, H-5), 7.21 (d, $J_{6',5'} = 8.4$ Hz, 1H, H-6′), 7.01 (d, $J_{3',2'} = 8.4$ Hz, 1H, H-3′), 6.79 (d, $J_{5',6'} = 8.7$ Hz, 1H, H-5′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 175.8 (C=N), 159.4 (C=S), 158.7 (C-4′), 150.7 (C-1′′), 138.3 (C-4′′), 136.7 (C-3′′, C-5′′), 131.7 (C-1), 130.9 (C-2′′, C-6′′), 130.0 (C-2, C-6), 129.9 (C-3, C-5), 129.7 (C-4), 128.4 (C-2′, C-6′), 128.0 (C-1′), 127.8 (C-3′, C-5′); EI-MS: *m/z* (rel. abund. %), 392 $[M]^+$ (1.0), 254, (3.6), 196 (100.0), 138 (17.9), 77 (11.7); HREI-MS: *m/z* calcd for $C_{20}H_{16}N_4O_3S$ $[M]^+$ 392.0943, found 392.0945; IR (KBr, cm^{-1}): 3550 (O–H), 3415 (N–H), 1606 (C=N), 1548 (C=C), 1323 (C–N), 1276 (C=S); Anal. calcd for$C_{20}H_{16}N_4O_3S$: C, 61.21; H, 4.11; N, 14.28; O, 12.23; S, 8.17; Found: C, 61.22; H, 4.13; N, 14.26.

*2-(Diphenylmethylene)-N-phenylhydrazinecarboxamide (**18**)*

Yield: 73 %;White solid; m.p. 160–163 °C (lit. 163–164 °C; Pearson et al., 1953); R_f: 0.45 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 9.09 (s, 1H, NH), 8.69 (s, 1H, NH), 7.62 (m, 3H,H-2, H-6, H-4), 7.55 (m, 4H, H-3, H-5, H-3′,H-5′), 7.38 (m, 3H, H-4, H-3′′, H-5′′), 7.33 (d, 2H, $J_{2',3'} = J_{6',5'} = 8.1$ Hz, H-2′, H-6′), 7.27 (d, 2H, $J_{2'',3''} = J_{6'',5''} = 7.8$ Hz, H-2′′, H-6′′), 7.01 (t, 1H, $J_{4''(3'',5'')} = 7.2$ Hz, H-4′′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 152.2 (C=O), 149.2 (C=N), 137.1 (C-1′′), 135.0 (C-1), 133.2 (C-1′), 132.1 (C-2, C-6), 129.5 (C-2′, C-6′), 129.4 (C-4), 128 .5 (C-4′), 127.6 (C-3, C-5), 126.8 (C-3′, C-5′), 126.0 (C-3′′, C-5′′), 125.0 (C-4′), 121.4 (C-2′′, C-6′′); EI-MS: *m/z* (rel. abund.%):315 $[M]^+$ (24.4), 257 (5.0), 195 (100.0), 180 (31.6), 165 (56.5), 77 (33.1); EI-HRMS: *m/z* calcd for $C_{20}H_{17}N_3O$ $[M]^+$ 315.1372, found 315.1375; IR (KBr, cm^{-1}): 3354 (N–H), 1687 (C=O), 1593 (C=N), 1533 (C=C), 1307 (C–N); Anal. calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32; O, 5.07; Found: C, 76.15; H, 5.42; N, 13.31.

*N-(3′′-Chlorophenyl)-2-(diphenylmethylene) hydrazinecarboxamide (**19**)*

Yield: 73 %; White solid; m.p. 190–192 °C; R_f: 0.42 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 9.27 (s, 1H, NH), 8.79 (s, 1H, NH), 7.75 (s, 1H, H-2′′), 7.64 (d, 2H, $J_{2,3} = J_{6,5} = 6.0$ Hz, H-2, H-6), 7.57 (m, 3H, H-3, H-5, H-4), 7.38 (m, 4H, H-2′, H-6′, H-3′, H-5′), 7.32 (m, 3H, H-4′, H-5′′, H-6′′), 7.05 (d, 1H, $J_{4'',5''} = 9.0$ Hz, H-4′′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 138.5 (C-3′′), 135.8 (C-1′′), 132.7 (C-2′′), 131.0 (C-1), 128.3 (C-1′), 128.1 (C-4′′), 127.9 (C-2, C-6), 127.0 (C-2′, C-6′), 126.6 (C-6′′), 126.0 (C-3′, C-5′), 121.4 (C-3′′, C-5′′), 118.1 (C-3′, C-5′), 116.4 (C-4); EI-MS: *m/z* (rel. abund.%), 351 $[M^+ + 2]$ (1.8), 349 $[M]^+$ (7.5), 195 (99.0), 165 (57.4), 77 (100.0); EI-HRMS: *m/z* calcd for $C_{20}H_{16}ClN_3O$ $[M]^+$ 349.0982, found 349.0984; IR (KBr, cm^{-1}): 3267 (N–H), 1662 (C=O), 1616 (C=N), 1593 (C=C), 1305 (C–N); Anal. calcd for $C_{20}H_{16}ClN_3O$: C, 68.67; H, 4.61; Cl, 10.13; N, 12.01; O, 4.57; Found: C, 68.65; H, 4.60; N, 12.02.

*2-(Diphenylmethylene)-N-[3′′-(trifluoromethyl)phenyl] hydrazinecarboxamide (**20**)*

Yield: 74 %; White solid; m.p. 170–172 °C; R_f: 0.38 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 9.43 (s, 1H, NH), 8.82 (s, 1H, NH), 8.03 (s, 1H, H-2′′), 7.77 (d, 1H, $J_{6'',5''} = 7.8$ Hz, H-6′′), 7.64 (m, 3H, H-2, H-6, H-4), 7.53 (m, 2H, H-3, H-5), 7.51 (d, 1H, $J_{4'',5''} = 7.8$ Hz, H-4′′), 7.39 (m, 3H, H-2′, H-6′, H-4′), 7.33 (m, 3H, H-5′′, H-3′, H-5′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 152.1 (C=O), 148.8 (C=N), 139.9 (C-1′′), 137.1 (C-3′′), 132.1 (C-1), 129.7 (C-1′), 129.5 (C-2′′), 129.1 (C-6′′), 128.4 (C-4′′), 128.2 (C-5′′), 127.1 (C-2, C-6), 125.5 (C-2′, C-6′), 122.8 (C-3, C-5), 118.6 (C-3′, C-5′), 118.5 (C-4, C-4′), 115.2 (3′-CF_3); EI-MS: *m/z* (rel. abund.%), 383 $[M]^+$ (49.3), 325 (18.1), 248 (18.9), 195 (100.0), 165 (71.1), 77 (19.1); EI-HRMS: *m/z* calcd for $C_{21}H_{16}F_3N_3O$ $[M]^+$ 383.1245, found 383.1257; IR (KBr, cm^{-1}): 3352 (N–H), 1687 (C=O), 1618

(C=N), 1541 (C=C), 1317 (C–N); Anal. calcd for $C_{21}H_{16}F_3N_3O$: C, 65.79; H, 4.21; F, 14.87; N, 10.96; O, 4.17; Found: C, 65.77; H, 4.20; F, 14.85; N, 10.95.

*2-(Diphenylmethylene)-N-[4′′-(trifluoromethyl)phenyl] hydrazinecarboxamide (**21**)*

Yield: 72 %; White solid; m.p. 174–176 °C; R_f: 0.42 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 9.46 (s, 1H, NH), 8.90 (s, 1H, NH), 7.76 (d, 2H, $J_{3'',2''} = J_{5'',6''} = 8.7$ Hz, H-3′′, H-5′′), 7.64 (m, 5H, H-2, H-6, H-4, H-3, H-5), 7.53 (m, 2H, H-2′, H-6′), 7.39 (m, 3H, H-3′, H-5′, H-4′), 7.33 (d, 2H, $J_{2'',3''} = J_{6'',5''} = 7.5$ Hz, 2H, H-2′′, H-6′′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 151.8 (C=O), 148.9 (C=N), 142.9 (C-1′′), 137.2 (C-4′′), 132.2 (C-1), 129.5 (C-1′), 129.1 (C-2′′, C-6′′), 128.5 (C-3′′, C-5′′), 128.2 (C-2, C-6), 127.1 (C-2′, C-6′), 125.9 (C-3, C-5), 125.8 (C-3′, C-5′), 125.5 (C-4), 122.0 (C-4′), 118.7 (4′′-CF_3); EI-MS: *m/z* (rel. abund.%), 383 $[M]^+$ (25.3), 364 (7.2), 195 (100.0), 165 (96.3), 145 (27.8), 77 (39.0); EI-HRMS: *m/z* calcd for $C_{21}H_{16}F_3N_3O$ $[M]^+$ 383.1245, found 383.1247; IR (KBr, cm^{-1}): 3344 (N–H), 1691 (C=O), 1600 (C=N), 1533 (C=C), 1325 (C–N), 846 (C–F); Anal. calcd for $C_{21}H_{16}F_3N_3O$: C, 65.79; H, 4.21; F, 14.87; N, 10.96; O, 4.17; Found: C, 65.76; H, 4.22; N, 10.94.

*N-[2′′-Chloro-5′′-(trifluoromethyl)phenyl]-2-(diphenylmethylene)hydrazine carboxamide (**22**)*

Yield: 70 %; White solid; m.p. 200–202 °C; R_f: 0.31 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 9.67 (s, 1H, NH), 9.30 (s, 1H, NH), 8.55 (s, 1H, H-6′′), 7.76 (d, 1H, $J_{3'',4''} = 8.4$ Hz, H-3′′), 7.62 (m, 3H, H-2, H-6, H-4), 7.46 (m, 2H, H-3, H-5), 7.40 (m, 4H, H-2′, H-6′, H-3′, H-5′), 7.35 (m, 2H, H-4′, H-4′′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 152.2 (C=O), 149.2 (C=N), 137.1 (C-2′′), 135.0 (C-1′′), 133.2 (C-5′′), 132.1 (C-1), 129.6 (C-1′), 129.5 (C-6′′), 129.4 (C-3′′), 128.5 (C-4′′), 128.4 (C-2, C-6), 127.6 (C-2′, C-6′), 126.8 (C-3, C-5), 126.0 (C-3′, C-5′), 125.9 (C-4), 125.0 (C-4′), 121.4 (5′-CF_3); EI-MS: *m/z* (rel. abund.%): 419 $[M^+ + 2]$ (13.4), 417 $[M]^+$ (36.5), 382 (11.8), 195 (100.0), 165 (52.3), 77 (29.6); EI-HRMS: *m/z* calcd for $C_{21}H_{15}ClF_3N_3O$ $[M]^+$ 417.0856, found 417.0859; IR (KBr, cm^{-1}): 3415 (N–H), 1699 (C=O), 1666 (C=N), 1552 (C=C), 1330 (C–N), 887 (C–F); Anal. calcd for $C_{21}H_{15}ClF_3N_3O$: C, 60.37; H, 3.62; Cl, 8.49; F, 13.64; N, 10.06; O, 3.83; Found: C, 60.35; H, 3.61; N, 10.04.

*N-[4′′-Chloro-2′′-(trifluoromethyl)phenyl]-2-(diphenylmethylene)hydrazine carboxamide (**23**)*

Yield: 69 %; White solid; m.p. 185–187 °C; R_f: 0.32 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 9.48 (s, 1H, NH), 9.06 (s, 1H, NH), 8.14 (d, 1H, $J_{5'',6''} = 7.8$ Hz, H-5′′), 7.77 (d, 1H, $J_{3'',5''} = 2.7$ Hz, H-3′′), 7.73 (m, 1H, H-6′′), 7.61 (m, 3H, H-2, H-6, H-4), 7.46 (m, 2H, H-3, H-5), 7.40 (m, 3H, H-2′, H-6′, H-4′), 7.34 (m, 2H, H-3′, H-5′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 151.9 (C=O), 148.7 (C=N), 140.6 (C-4′′), 137.1 (C-1′′), 132.9 (C-2′′), 132.1 (C-1), 130.1 (C-1′), 129.6 (C-3′′), 129.5 (C-5′′), 129.1 (C-6′′), 128.4 (C-2, C-6), 128.2 (C-2′, C-6′), 127.0 (C-3, C-5), 121.9 (C-3′, C-5′), 118.5 (C-4, C-4′), 117.5 (2′′-CF_3); EI-MS: *m/z* (rel. abund.%): 419 $[M^+ + 2]$ (1.0), 417 $[M]^+$ (13.0), 221 (23.6), 195 (100.0), 180 (31.3), 165 (45.6), 77 (37.6); EI-HRMS: *m/z* calcd for $C_{21}H_{15}ClF_3N_3O$ $[M]^+$ 417.0856, found 417.0858; IR (KBr, cm^{-1}): 3475 (N–H), 1699 (C=O), 1616 (C=N), 1583 (C=C), 1338 (C–N), 877 (C–F); Anal. calcd for $C_{21}H_{15}ClF_3N_3O$: C, 60.37; H, 3.62; Cl, 8.49; F, 13.64; N, 10.06; O, 3.83; Found: C, 60.36; H, 3.60; N, 10.05.

*(E)-N-(3′′-Chlorophenyl)-2-[(4′-hydroxyphenyl)(phenyl) methylene]hydrazine carboxamide (**24**)*

Yield: 72 %;White solid; m.p. 176–178 °C; R_f: 0.40 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 9.89 (s, 1H, NH), 9.25 (s, 1H, NH), 8.74 (s, 1H, OH), 7.75 (s, 1H, H-2′′), 7.55 (m, 2H, H-5′′, H-4′′), 7.42 (m, 3H, H-2, H-6, H-4), 7.31 (t, 2H, $J_{3(2,5)} = J_{5(6,4)} = 9.0$ Hz, H-3, H-5), 7.12 (d, 2H, $J_{2',3'} = J_{6',5'} = 8.4$ Hz, H-2′, H-6′), 7.04 (d, 1H $J_{4'',5'} = 8.4$ Hz, H-4′′), 6.98 (d, 2H, $J_{3',2'} = J_{5',6'} = 8.4$ Hz, H-3′, H-5′); ^{13}C-NMR: (100 MHz, DMSO-d_6):δ_C 158.3 (C=O), 151.9 (C=N), 149.0 (C-4′), 140.7 (C-3′′), 137.7 (C-1′′), 133.0 (C-2′′), 130.2 (C-1), 130.0 (C-4′′), 129.0 (C-6′′), 128.2 (C-5′′), 127.2 (C-2, C-6), 122.2 (C-3, C-5), 121.9 (C-4), 118.4 (C-2′, C-6′), 117.4 (C-1′), 116.3 (C-3′, C-5′); EI-MS: *m/z* (rel. abund.%): 367 $[M^+ + 2]$ (3.0), 365 $[M]^+$ (10.0), 239 (11.0), 211 (100.0), 181 (75.4), 127 (72.4), 77 (19.4); IR (KBr, cm^{-1}): 3415 (O–H), 3323 (N–H), 1689 (C=O), 1612 (C=N), 1566 (C=C); EI-HRMS: *m/z* calcd for $C_{20}H_{16}ClN_3O_2$ $[M]^+$ 365.0931, found 365.0934; Anal. calcd for $C_{20}H_{16}ClN_3O_2$:C, 65.67; H, 4.41; Cl, 9.69; N, 11.49; O, 8.75; Found: C, 65.66; H, 4.42; N, 11.48.

*(E)-2-[(4′-Hydroxyphenyl)(phenyl)methylene)-N-(4′′-(trifluoromethyl)phenyl) hydrazinecarboxamide (**25**)*

Yield: 69 %; White solid; m.p. 208–210 °C; R_f: 0.30 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 9.90 (s, 1H, NH), 9.44 (s, 1H, NH), 8.85 (s, 1H, OH), 7.75 (d, 2H, $J_{3'',2''} = J_{5'',6''} = 8.4$ Hz, H-3′′, H-5′′), 7.63 (d, 2H, $J_{2'',3''} = J_{6'',5''} = 8.7$ Hz, H-2′′, H-6′′), 7.58 (t, 2H, $J_{3(2,4)} = J_{5(6,4)} = 8.3$ Hz, H-3, H-5), 7.37 (d, 3H, $J_{2,3} = J_{6,5} = J_{4(3,5)} = 6.0$ Hz, H-2, H-6, H-4), 7.13 (d, 2H, $J_{2',3'} = J_{6',5'} = 8.4$ Hz, H-2′, H-6′), 6.98 (d, 2H, $J_{3',2'} = J_{5',6'} = 8.4$ Hz, H-3′, H-5′); ^{13}C-NMR: (100 MHz, DMSO-d_6):δ_C 158.7

(C=O), 151.9 (C=N), 149.4 (C-4′), 143.0 (C-4′′), 137.7 (C-1′′), 132.5 (C-1), 130.0 (C-2′′, C-6′′), 129.5 (C-2, C-6), 129.0 (C-3, C-5), 128.2 (C-4), 127.2 (C-2′, C-6′), 125.9 (C-1′), 118.7 (C-3′′, C-5′′), 116.3 (4′-CF_3), 115.1 (C-3′, C-5′); EI-MS: *m/z* (rel. abund.%) 399 $[M]^+$ (4.8), 211 (33.4), 196 (27.1), 181 (100.0), 165 (19.6), 77 (18.9); EI-HRMS: *m/z* calcd for $C_{20}H_{16}ClN_3O_2$ $[M]^+$ 399.1195, found 399.1198; IR (KBr, cm^{-1}): 3398 (O–H), 3350 (N–H), 1691 (C=O), 1656 (C=N), 1541 (C=C), 1325 (C–N), 840 (C–F); Anal. calcd for $C_{21}H_{16}F_3N_3O_2$: C, 63.16; H, 4.04; F, 14.27; N, 10.52; O, 8.01; Found: C, 63.15; H, 4.02; N, 10.51.

*(E)-N-[2′′-Chloro-5′′-(trifluoromethyl)phenyl]-2-[(4′-hydroxyphenyl)(phenyl) methylene]hydrazinecarboxamide (**26**)*

Yield: 70 %; White solid; m.p. 200–202 °C; R_f: 0.31 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 9.88 (s, 1H, NH), 9.57 (s, 1H, NH), 9.28 (s, 1H, OH), 8.56 (s, 1H, H-6′′), 7.75 (d, 1H $J_{4,3} = J_{4,5} = 8.4$ Hz, H-4), 7.58 (m, 2H, H-2, H-6), 7.42 (m, 4H, H-3, H-5, H-2′, H-6′), 7.15 (d, 2H, $J_{3',2'} = J_{5',6'} = 8.4$ Hz, H-3′, H-5′), 6.97 (d, 1H $J_{3'',4''} = 8.4$ Hz, H-3′′), 6.78 (d, 1H $J_{4'',3''} = 8.7$ Hz, H-4′′); ^{13}C-NMR: (100 MHz, DMSO-d_6):δ_C 158.4 (C=O), 152.0 (C=N), 149.9 (C-4′), 137.9 (C-2′′), 136.3 (C-5′′), 130.3 (C-1′′), 130.1 (C-6′′), 129.3 (C-1), 128.6 (C-3′′), 128.5 (C-4′′), 128.3 (C-2, C-6), 127.1 (C-3, C-5), 122.5 (C-4), 122.0 (C-2′, C-6′), 119.8 (C-1′), 116.1 (5′′-CF_3), 115.2 (C-3′, C-5′); EI-MS: *m/z* (rel. abund.%): 433 $[M]^+$ (10.4), 212 (51.6), 196 (34.6), 181 (100.0), 152 (28.7), 77 (15.2); EI-HRMS: *m/z* calcd for $C_{20}H_{16}ClN_3O_2$ $[M]^+$ 433.0805, found 433.0808; IR (KBr, cm^{-1}): 3411 (O–H), 3328 (N–H), 1678 (C=O), 1591 (C=N), 1539 (C=C), 1332 (C–N), 821 (C–F); Anal. calcd for $C_{21}H_{15}ClF_3N_3O_2$: C, 58.14; H, 3.49; Cl, 8.17; F, 13.14; N, 9.69; O, 7.38; Found: C, 58.12; H, 3.48; N, 9.68.

*(E)-N-[4′′-Chloro-2′′-(trifluoromethyl)phenyl]-2-[(4′-hydroxyphenyl)(phenyl) methylene]hydrazinecarboxamide (**27**)*

Yield: 69 %; White solid; m.p. 172–174 °C; R_f: 0.37 (ethyl acetate/hexanes, 2:8); ^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 9.85 (s, 1H, NH), 9.37 (s, 1H, NH), 9.15 (s, 1H, OH), 8.15 (s, 1H, H-3′′), 7.76 (d, 2H, $J_{2,3} = J_{6,5} = 9.0$ Hz, H-2, H-6), 7.56 (m, 5H, H-3, H-5, H-4, H-2′, H-6′), 7.29 (m, 1H, H-5), 7.15 (d, 2H, $J_{3',2'} = J_{5',6'} = 8.7$ Hz, H-3′, H-5′), 6.95 (d, 1H $J_{6'',5''} = 8.4$ Hz, H-6′′), 6.77 (d, 1H $J_{5'',6''} = 8.7$ Hz, H-5′′); ^{13}C-NMR: (100 MHz, DMSO-d_6): δ_C 158.4 (C=O), 152.2 (C=N), 149.7 (C-4′), 137.6 (C-4′′), 135.1 (C-2′′), 133.2 (C-1′′), 130.1 (C-3′′), 129.3 (C-1), 128.7 (C-5′′), 128.5 (C-6′′), 128.3 (C-2, C-6), 127.5 (C-3, C-5), 127.0 (C-4), 125.9 (C-2′, C-6′), 122.2 (C-1′), 116.1 (2′-CF_3), 115.2 (C-3′, C-5′); EI-MS: *m/z* (rel. abund.%): 433 $[M]^+$ (2.2), 416 (1.4), 221 (29.3), 211 (56.7), 195 (100.0), 175 (63.3), 43 (74.4); EI-HRMS: *m/z* calcd for $C_{20}H_{16}ClN_3O_2$ $[M]^+$ 433.0805, found 433.0808; IR (KBr, cm^{-1}): 3344 (O–H), 3278 (N–H), 1691 (C=O), 1589 (C=N), 1589 (C=C), 1311 (C–N), 839 (C–F); Anal. calcd for $C_{21}H_{15}ClF_3N_3O_2$: C, 58.14; H, 3.49; Cl, 8.17; F, 13.14; N, 9.69; O, 7.38; Found: C, 58.13; H, 3.47; N, 9.67.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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