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Practical one-pot synthesis of semicarbazone derivatives via semicarbazide, and evaluation of their antibacterial activity

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Abstract New series of 2-(aryl or alkyl)-*N*-phenylhydrazine-1-carboxamides **1a–j** were synthesized through one-pot reactions of aldehyde or ketones, hydrazine hydrate, and phenylisocyanate in MeOH. The structure of products was confirmed by Fourier transform infrared (FT-IR), proton nuclear magnetic resonance (^{1}H NMR), and ^{13}C NMR spectra. Minimum inhibitory concentration (MIC) of antibacterial activity of **1a–j** was screened against five bacterial strains. Compound **1f** showed antibacterial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Keywords Semicarbazone · Hydrazine hydrate · Phenyl isocyanate · One-pot reaction · Antibacterial

Introduction

Semicarbazones are urea derivatives and have recently been the subject of a great number of studies. Semicarbazone derivatives have versatile biological activities, making their study interesting: anticonvulsant [1–3], antimicrobial [4, 5], antioxidant [6], antiangiogenic [7], anticancer [8], antiproliferative [9], antimalarial [10], and antiprotozoal [11]. In addition, steroidal semicarbazone derivatives have shown antiproliferative activity [12], indole semicarbazones exhibited antimicrobial activity [13], and semicarbazone derivatives of calix[4]arene have been used for removal of Cr(VI) ions [14]. Moreover, semicarbazones have been used as organic

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corrosion inhibitors [15]. Metaflumizone, under the brand name ProMeris, is a semicarbazone derivative with eco-friendly insecticide activity [16] (Fig. 1).

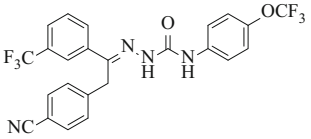
Moreover, semicarbazones behave as chelating ligands due to their N and O atoms and electron delocalization along the semicarbazone moiety. Various semicarbazone complexes have been synthesized that exhibit biological activities, for example, nickel(II) complexes of 3-thiophene aldehyde semicarbazone, 2,3-thiophene dicarboxaldehyde bis(semicarbazone) have shown antifungal activity [17]; antioxidant and anticancer activity of ruthenium(II) complexes of semicarbazone bearing 9,10-phenanthrenequinone moiety have been studied [18]; anticancer activity of copper(II), vanadium(IV/V), iron(II)/(III), and gallium(III) complexes of salicylaldehyde semicarbazone and its bromo derivative have been reported [19]; Cu(II), Zn(II), Ni(II) complexes of 3-carbaldehyde-chromone semicarbazone have DNA binding properties and antioxidant activities [20]; organotin(IV) complexes of semicarbazone derived from 4-hydroxy-3-methoxybenzaldehyde have shown antimicrobial activity [21]. In addition, palladium complexes of semicarbazones have been used as catalysts in Suzuki and Sonogashira cross-coupling reactions [22].

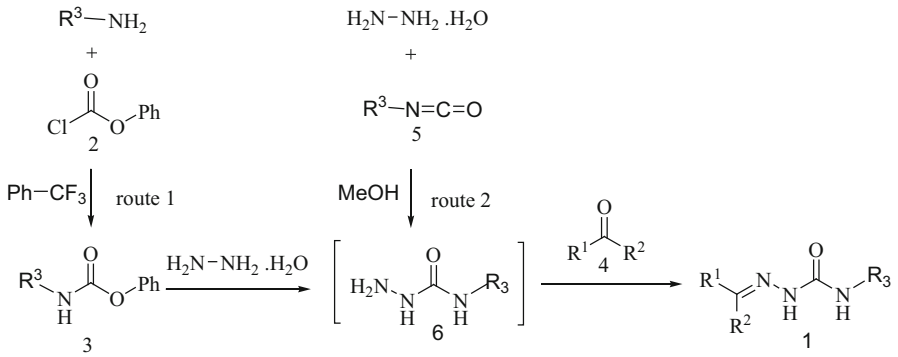
In addition, semicarbazone derivatives are versatile intermediates for synthesis of heterocyclic compounds. The key feature of these intermediates is obtaining different products from semicarbazone in acidic or basic media, e.g. oxadiazole derivatives obtained from 4-substituted phenyl semicarbazones in acidic media [23], while the reaction of aryl semicarbazones in alkaline media afforded 1,2,4-triazoles [24].

Despite these various properties and applications of semicarbazones, surprisingly there are limited one-pot straightforward procedures for their synthesis. In the present work, we planned to produce intermediate semicarbazide **6** [25] in one pot, and then in the same pot, incorporate it to the several different aliphatic, alicyclic, and aromatic ketones and aldehydes **4** to produce semicarbazone **1** (route 2) (Scheme 1). Key intermediate semicarbazides **6** [26, 27] prepared via route 1 involved the reaction of amines with phenyl chloroformate **2** to create the corresponding carbamates **3**, consequently under hydrazinolysis by hydrazine hydrate to **6** [26–28] (Scheme 1). The newly synthesized **1** were screened for their antibacterial activity against five bacteria strains, including *Bacillus cereus* (*B. cereus*) ATCC 11778, *Enterococcus fecalis* (*E. fecalis*) ATCC 29212, *Escherichia coli* (*E. coli*) ATCC 25922, *Pseudomonas aeruginosa* (*P. aeruginosa*) ATCC 27853, and *Staphylococcus aureus* (*S. aureus*) ATCC 25923.

The relative stability of salicylaldehyde semicarbazone derivatives has been previously investigated by Xi et al. [29]. They have compared the theoretic and experimental results to confirm the stability order of conformers. Accordingly, we have decided to confirm the stability of our interested compounds using the theoretical and experimental methods.

Fig. 1 Metaflumizone





Scheme 1 Synthetic routes to one-pot synthesis of semicarbazones

Experimental

The ^{1}H NMR spectra were obtained at room temperature on a Bruker Avance 400-MHz spectrometer.^{13}C NMR spectra were recorded at room temperature on a Bruker 100 MHz instrument. DMSO-d_6 used as solvent. FT-IR spectra were measured at room temperature with a Shimadzu IR-470 spectrophotometer. Melting points are uncorrected and were determined using a MettlerFp5 apparatus.

General procedure for synthesis of 1a–j

Hydrazine hydrate (1 mmol) was added dropwise to a methanolic solution of aldehydes or ketones **4a–i** (1 mmol) and stirred for 30 min, then phenylisocyanate **5** (1 mmol) was added dropwise to this mixture. The mixture was stirred well for the required time. The process of reaction was monitored by TLC (*n*-hexane:EtOAc 6:3). After completion of the reaction, the solution was kept at room temperature for evaporation to dryness, then recrystallized with EtOH. All reported yield was evaluated after recrystallization.

Theoretical

For the synthesized compounds **1a–j**, there are more stable conformers on their internal rotation potential energetic surfaces (PES) about the N–N and C–N single bonds. These conformers, called *cis–cis*, *cis–trans*, and *trans–trans*, have close potential energy on their potential energy surface (PES). One target from each category of compounds (**1b**, **1f**, and **1j)** was selected for theoretical calculations. The structures of selected compounds were optimized at B3LYP/6-311++G(d,p) level of theory. Vibrational frequency analysis was performed at the previously mentioned level for stationary states to obtain vibrational zero point vibrational energy (ZPVE) and to validate that the found structures corresponded to the energy minima or transition states.

2-(3,4-Dihydronaphthalen-1(2*H*)-ylidene)-*N*-phenylhydrazine-1-carboxamide 1a

White solid, yield: 98 %, m.p. 208–210 °C, FT-IR (KBr, ν cm^{-1}): 3359, 3201 (stretch N–H), 3109 (stretch C–H Ar.), 2934 (stretch C–H ali.), 1684 (stretch C=O, amide), 1597, 1528 (stretch C=C), 1442 (bending CH_2), 1299, 1129 (stretch C–N), 751, 622 (OOP. C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 9.72 (*s*, 1H, NH, H_e), 8.89 (*s*, 1H, NH, H_d), 8.29 (*d*, $J = 6.8$ Hz, 1H, H_l), 7.64 (*d*, $J = 7.6$ Hz, 2H, H_c), 7.32–7.19 (*m*, 5H, H_b, H_i, H_j, H_k), 7.02 (*t*, $J = 7$ Hz, 1H, H_a), 2.74 (*s*, 2H, H_h), 2.63 (*s*, 2H, H_f), 1.84 (*s*, 2H, H_g) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ;. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 158.1 (C=O), 142.7 (C=N), 139.0, 138.9, 130.1, 128.0, 128.4, 126.9, 125.7, 122.4, 121.7, 119.5, 119.4 (10 C), 28.0 (Cg), 26.9 (C_f) ppm.

2-(2,3-Dihydronaphthalen-1*H*-inden-1-ylidene)-*N*-phenylhydrazine-1-carboxamide 1b

White solid, yield: 98 %, m.p. 222–224 °C, FT-IR (KBr, ν cm^{-1}): 3362, 3193 (stretch N–H), 3085 (stretch C–H Ar.), 2914 (stretch C–H ali.), 1681 (stretch C=O, amide), 1597, 1537 (stretch C=C), 1442 (bending CH_2), 1313, 1127 (stretch C–N), 750, 688, 619 (OOP. C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 9.69 (*s*, 1H, NH, H_e), 8.91 (*s*, 1H, NH, H_d), 7.97 (*d*, $J = 7.6$ Hz, 1H, H_k), 7.67 (*d*, $J = 8.2$, 1.2 Hz, 2H, H_c), 7.38–7.28 (*m*, 5H, H_b, H_j, H_i, H_h), 7.01 (*t*, $J = 7.4$ Hz, 1H, H_a), 3.08 (*t*, $J = 6.4$ Hz, 2H, H_g), 2.82–2.79 (*m*, 2H, H_f) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 155.1 (C=O), 147.9 (C=N), 139.0, 137.8, 129.9, 128.4, 126.7, 125.5, 122.2, 121.7, 119.4, 119.3 (10 C), 28.0 (C_g), 26.9 (C_f) ppm.

2-Cyclohexylidene-*N*-phenylhydrazine-1-carboxamide 1c

White solid, yield: 98 %, m.p. 207–208 °C, FT-IR (KBr, ν cm^{-1}): 3289, 3135 (stretch N–H), 3086 (stretch C–H Ar.), 2934, 2859 (stretch C–H ali.), 1656 (stretch C=O, amide), 1601, 1550, 1499 (stretch C=C), 1442 (bending CH_2), 1309, 1213 (stretch C–N), 758, 642 (OOP. C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 9.60 (*s*, 1H, NH, H_e), 8.73 (*s*, 1H, NH, H_d), 7.64 (*d*, $J = 7.6$ Hz, 2H, H_c), 7.32 (*d*, $J = 7.8$ Hz, 2H, H_b), 7.03 (*t*, $J = 7.2$ Hz, 1H, H_a), 2.42 (*s*, 2 h, H_f or $H_{f'}$), 2.35 (*t*, $J = 7.4$ Hz, 2H, $H_{f'}$ or H_f), 1.70 (*s*, 2H, H_h), 1.62 (*m*, 4H, H_g) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 153.6 (C=N), 139.2 (C=O), 139.1, 128.4, 122.0, 119.0, 118.9, 34.7, 26.8, 26.5, 25.5, 25.1 ppm.

2-Cyclopentylidene-*N*-phenylhydrazine-1-carboxamide 1d

White solid, yield: 98 %, m.p. 178–180 °C, FT-IR (KBr, ν cm^{-1}): 3348, 3193 (stretch N–H), 3082 (stretch C–H Ar.), 2961, 2874 (stretch C–H ali.), 1677 (stretch C=O, amide), 1600, 1532 (stretch C=C), 1443 (bending CH_2), 1188 (stretch C–N), 751, 612 (OOP. C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 9.23 (*s*, 1H, NH, H_e), 8.65 (*s*, 1H, NH, H_d), 7.57 (*d*, $J = 7.6$ Hz, 2H, H_c), 7.25 (*t*, $J = 8.0$ Hz, 2H, H_b), 6.97 (*t*, $J = 7.4$ Hz, 1H, H_a), 2.37 (*t*, $J = 7.2$ Hz, 2H, H_f or H_i), 2.28 (*t*, $J = 7.2$ Hz,

2H, H_i or H_f), 1.76 (*m*, 2H, H_g or H_h), 1.68 (*m*, 2H, H_h or H_g) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 160.3 (C=N), 153.4 (C=O), 139.2, 128.4, 122.0, 119.0, 118.9 (5C), 32.8, 28.1, 24.5, 24.4 (4C aliphatic) ppm.

2-Cycloheptylidene-*N*-phenylhydrazine-1-carboxamide 1e

White solid, yield: 97 %, m.p. 185–186 °C, FT-IR (KBr, ν cm^{-1}): 3378, 3190 (stretch N–H), 3112 (stretch C–H Ar.), 2916, 2848 (stretch C–H ali.), 1682 (stretch C=O, amide), 1596, 1532 (stretch C=C), 759, 685, 606 (OOP. C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 9.24 (*s*, 1H, NH, H_e), 8.72 (*s*, 1H, NH, H_d), 7.58 (*d*, $J = 8.2$ Hz, 2H, H_c), 7.25 (*t*, $J = 8.0$ Hz, 2H, H_b), 6.97 (*t*, $J = 7.4$ Hz, 1H, H_a), 2.47 (*t*, $J = 5.4$ Hz, 2H, H_f or H_c), 2.38 (*t*, $J = 6$ Hz, 2H, H_k or H_f), 1.66–1.53 (*m*, 8H, H_g, H_h, H_i, H_j) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 156.3 (C=N), 153.4 (C=O), 139.1, 128.5, 122.0, 119.0 (4C), 36.3, 30.3, 29.8, 29.8, 27.2, 23.9 (5C aliphatic) ppm.

1-(2-Oxoindolin-3-ylidene)-4-phenylsemicarbazide 1f

Orange solid, yield: 95 %, m.p. 196–198 °C, reported 193–196 °C [30], FT-IR (KBr, ν cm^{-1}): 3331 (stretch N–H), 3060 (stretch C–H Ar.), 2921, 2867 (stretch C–H ali.), 1675 (stretch C=O, amide), 1598, 1506 (stretch C=C), 825, 752, 588 (OOP. C–H).

2-(Anthracen-9-ylmethylene)-*N*-phenylhydrazine-1-carboxamide 1g

Orange solid, yield: 98 %, m.p. 285–287 °C, FT-IR (KBr, ν cm^{-1}): 3391, 3200 (stretch N–H), 3033 (stretch C–H Ar.), 2971, 2890 (stretch C–H ali.), 1691 (stretch C=O, amide), 1595, 1534 (stretch C=C), 1297, 1150 (stretch C–N), 738, 574 (OOP. C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 10.99 (*s*, 1H, NH, H_e), 9.13 (*s*, 1H, NH, H_d), 8.82 (*s*, 1H, H_k), 8.71 (*s*, 1H, H_f), 8.53 (*d*, $J = 8.4$ Hz, 2H, H_j), 8.16 (*d*, $J = 8.0$ Hz, 2H, H_g), 7.65–7.58 (*m*, 6H, H_c, H_h, H_i), 7.28 (*t*, $J = 8.0$ Hz, 2H, H_b), 7.00 (*d*, $J = 7.6$ Hz, 1H, H_a) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 139.7, 139.7, 138.8, 130.8, 129.4, 128.8, 128.7, 128.5, 126.9, 125.9, 125.5, 124.8, 122.4, 119.6, 119.4 ppm.

2-(1-(3-Nitrophenyl)ethylidene)-*N*-phenylhydrazine-1-carboxamide 1h

Orange solid, yield: 98 %, m.p. 249–251 °C, FT-IR (KBr, ν cm^{-1}): 3381, 3197 (stretch N–H), 3098 (stretch C–H Ar.), 1683 (stretch C=O, amide), 1599 (stretch C=C), 1536, 1342 (stretch NO_2), 892, 796, 749 (OOP. C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 9.98 (*s*, 1H, NH, H_e), 8.99 (*s*, 1H, NH, H_d), 8.60 (*t*, $J = 2$ Hz, 1H, H_j), 8.41 (*d*, $J = 8.4$ Hz, 1H, H_i), 8.23 (*d*, $J = 8.4$, 1.4 Hz, 1H, H_g), 7.71 (*t*, $J = 8.0$ Hz, 1H, H_h), 7.61 (*d*, $J = 8.2$, 1.2 Hz, 2H, H_c), 7.32 (*t*, $J = 7.4$ Hz, 2H, H_b), 7.04 (*t*, $J = 10$ Hz, 1H, H_a), 2.33 (*s*, 3H, H_f) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 148.0 (C=O), 143.7 (C=N), 139.7, 138.8, 132.6, 129.7, 128.5, 123.1, 122.6, 120.6, 119.9, 119.8 (10C), 13.7 (1C aliphatic) ppm.

2-(1-(4-Methoxyphenyl)ethylidene)-*N*-phenylhydrazine-1-carboxamide 1i

Pale green solid, yield: 96 %, m.p. 163–165 °C, FT-IR (KBr, ν cm^{-1}): 3350, 3200 (stretch N–H), 3100 (stretch C–H Ar.), 2950, 2800 (stretch C–H ali.), 1680 (stretch C=O, amide), 1600, 1540, 1520, 1500 (stretch C=C), 1250, 1030 (stretch C–N), 830, 800, 750, 680 (OOP. C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 9.68 (*s*, 1H, NH, H_e), 8.82 (*s*, 1H, NH, H_d), 7.87 (*d*, $J = 9.2$ Hz, 2H, H_g), 7.63 (*d*, $J = 8.0$ Hz, 2H, H_c), 7.03 (*t*, $J = 8.0$ Hz, 2H, H_b), 7.02 (*t*, $J = 7.4$ Hz, 1H, H_a), 6.96 (*d*, $J = 6.8$, 2.2 Hz, 2H, H_h), 3.79 (*s*, 3H, H_i, OCH_3), 2.23 (*s*, 3H, H_f, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 159.8, 153.5 (C=O), 145.8 (C=N), 139.0, 130.4, 128.4, 127.7, 122.3, 119.6, 119.5, 113.5 (8C), 55.1 (OCH_3), 13.6 (CH_3) ppm.

2-(1-(Naphthalene-2-yl)ethylidene)-*N*-phenylhydrazine-1-carboxamide 1j

Pink solid, yield: 87 %, m.p. 200–201 °C, FT-IR (KBr, ν cm^{-1}): 3371, 3196 (stretch N–H), 3098 (stretch C–H Ar.), 1691 (stretch C=O, amide), 1597, 1535 (stretch C=C), 747, 601 (OOP. C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 9.87 (*s*, 1H, NH, H_e), 8.94 (*s*, 1H, NH, H_d), 8.31–8.29 (*m*, 2H, H_g, H_h), 8.00 (*d*, $J = 5.6$, 4.2 Hz, 1H, H_m), 7.92 (*d*, $J = 9.2$, 4.4 Hz, 2H, H_i, H_j), 7.55–7.53 (*m*, 2H, H_k, H_l), 7.57 (*d*, $J = 7.6$ Hz, 2H, H_c), 7.32 (*t*, $J = 7.8$ Hz, 2H, H_b), 7.04 (*t*, $J = 7.4$ Hz, 1H, H_a), 2.39 (*s*, 3H, H_f, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ; 153.4 (C=O), 145.7 (C=N), 138.9, 135.3, 133.0, 132.7, 128.5, 128.4, 127.5, 127.4, 126.5, 125.8, 124.0, 122.5, 119.9, 119.8 (14C), 13.5 (CH_3) ppm.

2,2′-(((Butane-1,4-diylbis(oxy))bis(3,1-phenylene))bis(ethan-1-yl-1-ylidene))bis(*N*-phenylhydrazine-1-carboxamide) 8

Hydrazine hydrate **5** (2 mmol) was added dropwise to a 10-mL methanolic solution of bis-ketones **7** (0.374 g, 1 mmol) and stirred for 2 days at 40 °C, then phenylisocyanate **5** (2 mmol) was added dropwise to this mixture. The mixture was stirred well for 1 day. The process of reaction was monitored by TLC (*n*-hexane:EtOAc 6:3), and after completion of the reaction, the solution was kept at room temperature for evaporation to dryness, then recrystallized from EtOH. Forty-two percent (0.25 g) of 8 was recovered.

Pink opaque solid, yield: 42 %, m.p. 204–206 °C, FT-IR (KBr, ν cm^{-1}): 33,751, 3199 (stretch N–H), 3072 (stretch C–H Ar.), 2941 (C–H aliphatic), 1684 (stretch C=O, amide), 16057, 1515 (stretch C=C), 826, 750 (OOP. C–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ; 9.78 (*s*, 1H, NH, H_e), 8.88 (*s*, 1H, NH, H_d), 7.62–7.61 (*m*, 2H, H_g, H_h), 7.47–7.43 (*m*, 2H, H_m), 7.31–7.29 (*m*, 3H), 7.01–6.99 (*m*, 2H), 4.14–4.05 (*m*, 2H, O–CH_2), 2.25 (*s*, 3H, CH_3), 1.99–1.93 (*m*, 1H, CH_2) ppm.

Antibacterial activity using MIC

Minimum inhibitory concentration is defined as the lowest concentration of tested compound that can inhibit bacterial growth. Cultures were prepared according to manufacturers' instructions. Stock solutions of tested compounds were prepared at a

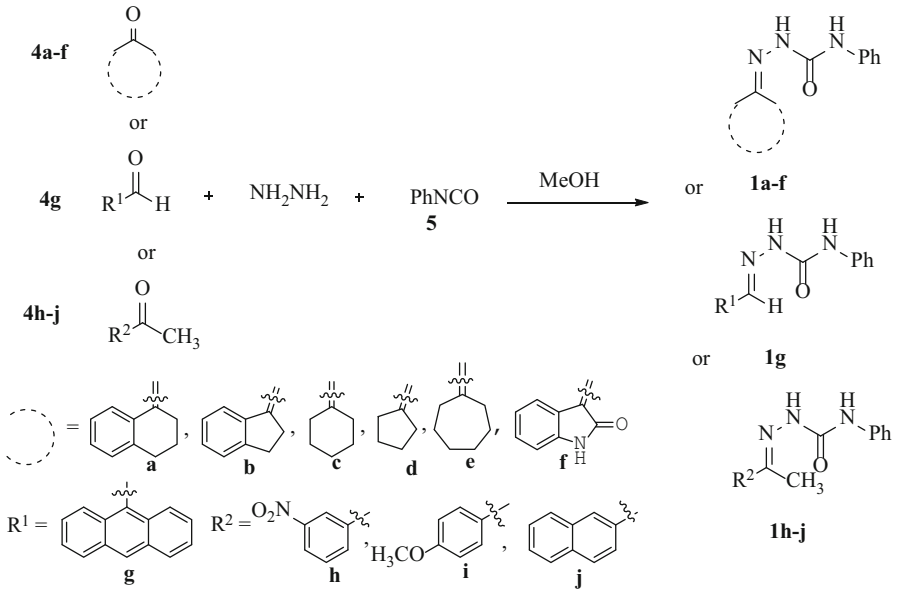
concentration of 1000 μg/mL in DMSO. DMSO was used as negative control. Twofold serial dilutions from stock solutions were used to determine MIC.

Results and discussion

Continuing our studies of the synthesis of novel compounds bearing heteroatoms [31–36] here, synthesis of a new series of 2-(aryl or alkyl)-*N*-phenylhydrazine-1-carboxamide **1a–j** via one-pot reaction is completed. The products **1a–j** were obtained through the reaction of anthracene carbaldehyde **4g** or cyclic aliphatics **4a–f**, or aromatic ketones **4h–j** with hydrazine hydrate and phenyl isocyante **5** in MeOH under reflux condition (Scheme 2).

For optimization of reaction conditions, the reaction of α-tetralone **4a**, hydrazine hydrate, and phenyl isocyanate **5** was selected as the model reactions. The results are summarized in Table 1. The lowest yield was obtained in $CHCl_3$ as solvent at room temperature (Table 1, entry 2); however, MeOH led to the highest yield at room temperature (Table 1, entry 5). Moreover, while the reaction was performed under reflux in MeOH the lower yield of product, but in shorter reaction time was obtained. TLC monitoring shows that reflux conditions also will lead to the formation of several by-products (Table 1, entry 8). Thus, the product was obtained in higher yield at 45 °C in MeOH (Table 1, entry 9).

The structure of compounds has been characterized by FT-IR, ^{1}H NMR, and ^{13}C NMR spectra. All spectral data are in accordance with the expected structures. In FT-IR spectra, N–H stretching appeared in 3391–3289 and 3201–3135 cm^{-1}; the



Scheme 2 Synthesis of 2-(aryl or alkyl)-*N*-phenylhydrazine-1-carboxamide **1a–j**

Table 1 Optimization of the reaction condition for synthesis of **11a**

Entry	Solvent	Temperature (°C)	Time (h)	Yield %
1	EtOH	r.t.	9	89
2	$CHCl_3$	r.t.	12	45
3	THF	r.t.	12	59
4	DMF	r.t.	14	81
5	MeOH	r.t.	12	90
6	CH_2Cl_2	r.t.	12	87
7	CH_3CN	r.t.	14	39
8	MeOH	Reflux	6	45
9	MeOH	45	6	96

band in 1691–1659 cm^{-1} is due to the C=O group of amide, and the other stretching and bending vibrations appeared in expected frequencies.

The ^1H NMR spectral data were consistent with the assigned structures; the signals of the respective protons of the synthesized compounds **1a–j** were confirmed on the basis of their chemical shifts, multiplicities, and coupling constants. Protons of C=N–NH and NH–C=O appeared as singlets at 10.99–9.23 and 9.13–8.65 ppm, respectively. Aromatic protons appeared at 8.82–6.96 ppm. Protons of the HC=N of compound **1f** was observed as a sharp singlet at 8.71 ppm. Aliphatic protons appeared at 3.79–1.53 ppm.

The ^{13}C NMR spectra of **1a–j** are in agreement with their structures. Presence of chemical shifts of C=N and C=O at low field confirmed the formation of products. Aromatic carbons, C=N and C=O appeared at 160.3–113.5 ppm, and aliphatic carbons were observed at 55.1–13.5 ppm.

In the ^1H and ^{13}C NMRs of **1c–e** different protons and carbons for cyclic derivatives have been observed. ^1H NMR of **1c** showed four kinds of protons and in ^{13}C NMR of **1c** five kinds of carbon appeared in aliphatic region. Also, for **1d**, four types of protons appeared in the high field of ^1H NMR, and four resonances for four aliphatic carbons in ^{13}C NMR (Fig. 2). ^{13}C NMR of compound **1e** showed seven types of carbons in aliphatic region.

In the other attempt in contribution to our previous bis-synthesis [38–41], 0.5 equivalents of prepared diketone **7**, upon reaction with one equivalent of **5** and one equivalent of $H_2N–NH_2·H_2O$ via in situ prepared intermediate **8,** in one pot led to the formation of 2,2′-(((butane-1,4-diylbis(oxy))bis(3,1-phenylene))bis(ethan-1-yl-1-ylidene))bis(*N*-phenylhydrazine-1-carboxamide) **9** (Scheme 3).

The ZPVE corrected energy of conformers and vibrational frequency for three categories as depicted in Fig. 3 are given in Table 3. As can be seen in Table 2, the *trans–trans* conformer is most stable in each category.

The order of stability of conformers is *cis–cis* < *cis–trans* < *trans–trans*. In addition, the results show that there is a good agreement between the calculated frequency and experimental one. It is clear that vibrational frequency of the C=O group increases on going from *cis–cis* to *cis–trans* and then *trans–trans*, with the exceptional *trans–trans* form of **1f** due to the presence of NH···OC H-bonding.

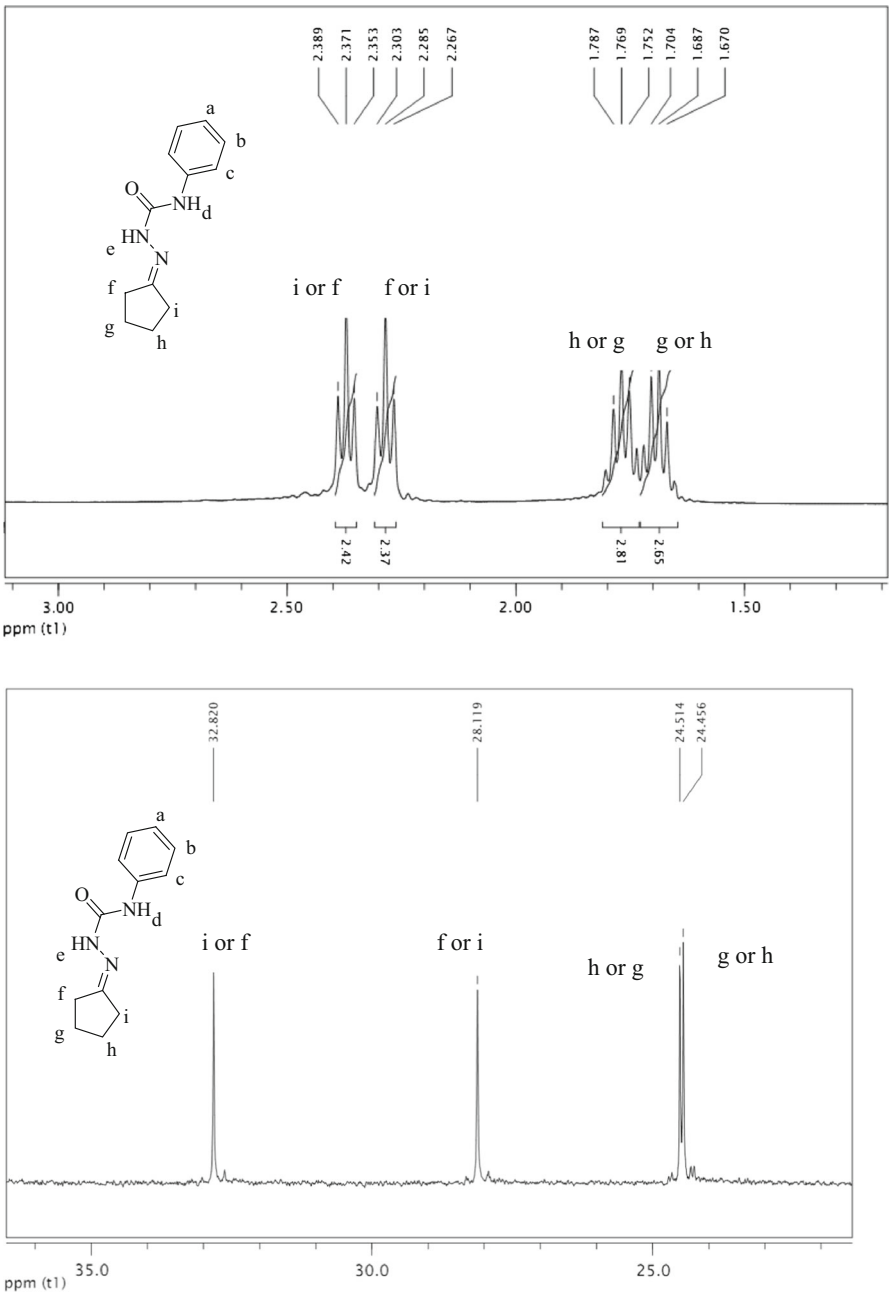
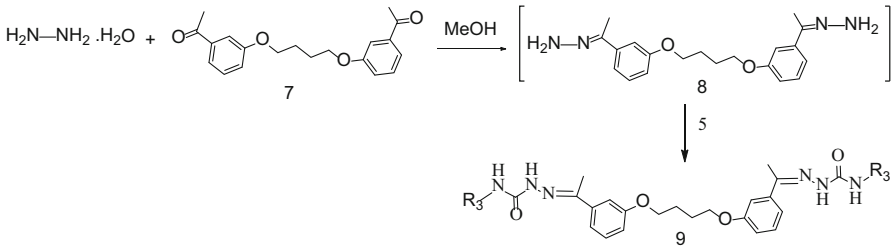


Fig. 2 ^{1}H NMR and ^{13}C NMR of aliphatic region for **1d**

The in vitro antibacterial activities of compounds **1a–j** were screened against five bacterial strains, including *Bacillus cereus* (*B. cereus*) ATCC 11778, *Enterococcus fecalis* (*E. fecalis*) ATCC 29212, *Escherichia coli* (*E. coli*) ATCC 25922,



Scheme 3 Synthetic routes to one-pot bis *N*-phenylhydrazine-1-carboxamide **9** synthesis

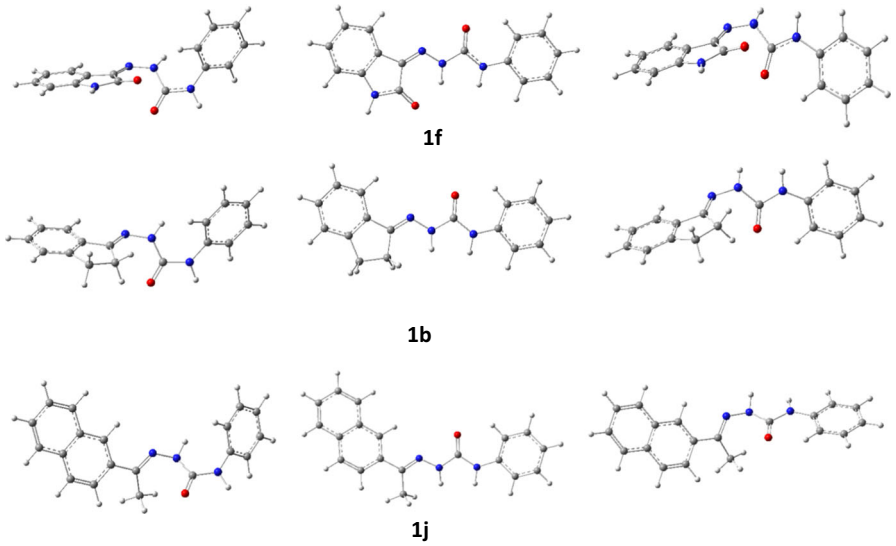


Fig. 3 The B3LYP/6-311++G(d,p) optimized structures of **1f**, **1b,** and **1J**

Table 2 The ZPVE-corrected relative energy and vibrational frequency of C=O group at B3LYP/6-311++G(d,p) level of theory

	Conformer	ZPVE/hartree	E_0/hartree	ΔE_0 (kJ/mol)	ν(CO)/cm^{-1}
1b	*cis–cis*	0.28241	−857.98624	0.00	1701.76178
	cis–trans	0.28239	−857.986933	−1.82	1716.47386
	trans–trans	0.28115	−857.987433	−3.13	1736.50939
1f	*cis–cis*	0.25203	−948.081867	0.00	1723.8299
	cis–trans	0.25232	−948.082606	−1.94	1731.28273
	trans–trans	0.25245	−948.099538	−46.35	1693.05068
1j	*cis–cis*	0.32155	−973.481805	0.00	1706.89165
	cis–trans	0.32187	−973.483786	−5.20	1722.57163
	trans–trans	0.32039	−973.484709	−7.62	1737.3805

Table 3 Antibacterial activity of **1f** using MIC

Compound	Microorganisms				
	B. cereus	*E. fecalis*	*E. coli*	*P. aeruginosa*	*S. aureus*
1f	–	–	–	512	128
Ciprofloxacin	62.5	62.5	62.5	62.5	62.5

Pseudomonas aeruginosa (*P. aeruginosa*) ATCC 27853, and *Staphylococcus aureus* (*S. aureus*) ATCC 25923. The minimum inhibitory concentrations (MIC) of compounds **1a–j** were evaluated. MIC values are expressed in μg/mL [33]. Compound **1f** showed activity against *P. aeruginosa* at a concentration of 512 μg/mL and *S. aureus* at a concentration of 128 μg/mL, while other compounds showed no activity against bacterial strains. Ciprofloxacin was used as positive control and showed antibacterial activity at concentration 62.5 μg/mL against all tested bacterial strains (Table 3).

Conclusion

New 2-(aryl or alkyl)-*N*-phenylhydrazine-1-carboxamide derivatives were synthesized in an efficient high yield, and semicarbazone derivatives can be prepared by this optimized reaction set-up. Synthesized carboxamide derivatives showed no antibacterial activity against tested bacterial strains except 1-(2-oxoindolin-3-ylidene)-4-phenylsemicarbazide. The results showed route2 in comparison to other reported syntheses of (thio)semicarbazones, e.g. route1, was more reliable, reproducible, economic, produced a high yield, showed no chromatographic separation, and was time consuming. The ZPVE corrected energy of conformers and vibrational frequency for three categories indicate that the *trans–trans* conformer is the most stable one in each category. The order of stability of conformers is *cis–cis* < *cis–trans* < *trans–trans*. Also, good agreement between the calculated frequency of C=O group and experimental one was observed.

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