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Research Article

Synthesis and Single Crystal X-Ray Structure of New (2*E*)-2-[3-(1*H*-Imidazol-1-yl)-1-phenylpropylidene]-*N*-phenylhydrazinecarboxamide

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Synthesis, spectroscopic characterization and X-ray crystal structure of a new (2*E*)-2-[3-(1*H*-imidazol-1-yl)-1-phenylpropylidene]-*N*-phenylhydrazinecarboxamide (**4**) are reported. The stereochemistry of the title compound **4**, $C_{19}H_{19}N_5O$, about the imine bond [1.296 (4) Å] was assigned to have (*E*)-configuration. In the urea moiety, the N–H entities are *trans* to each other, and one of these forms is an intramolecular N–H···H hydrogen bond. The compound crystallizes in the monoclinic space group $P2_1/c$ with a = 5.8093 (2) Å, b = 20.5575 (6) Å, c = 14.0355 (5) Å, α = 90.00°, β = 97.365° (2), γ = 90.00°, V = 1662.36 (10) Å^3, and Z = 4. The molecules are packed in crystal structure by weak intermolecular hydrogen interactions.

1. Introduction

Epilepsy is the most prevalent neurological disorder, affecting nearly 50 million of mankind [1]. Despite significant advances that have been made in epilepsy research, estimates suggest that convulsions in about 30% of epileptics are still inadequately controlled by the available antiepileptic medications [2]. Additionally, the patients often suffer side effects from the currently used antiepileptics, such as nausea, headache, anorexia, hepatotoxicity, gingival hyperplasia, and hirsutism [3–5]. Accordingly, there is a substantial demand for the development of more effective and safer antiepileptic therapies.

An evaluation of the literature exposed the emergence of structurally distinct anticonvulsants, namely, aralkylimidazoles. Nafimidone (**I**) and danzimol (**II**) (Figure 1) are two representatives of this class of anticonvulsants that are independently discovered. Moreover, compounds **I** and **II** displayed anticonvulsant profile similar to that of phenytoin or carbamazepine, but more distinguished than that of barbiturates and valproic acid [6–9].

It has been well documented that arylsemicarbazones **III** (Figure 1) are a promising pharmacophore for anticonvulsants, and a number of arylsemicarbazone derivatives showed anticonvulsant potential [10, 11]. Accordingly, we report herein a synthetic pathway to achieve arylsemicarbazones incorporating imidazole moiety as hybrid structures which can be screened as new anticonvulsant leads. Additionally, the (*E*)-configuration of the title compound **4**, namely, (2*E*)-2-[3-(1*H*-imidazol-1-yl)-1-phenylpropylidene]-*N*-phenylhydrazinecarboxamide (**4**), was established *via* its single crystal X-ray structure.

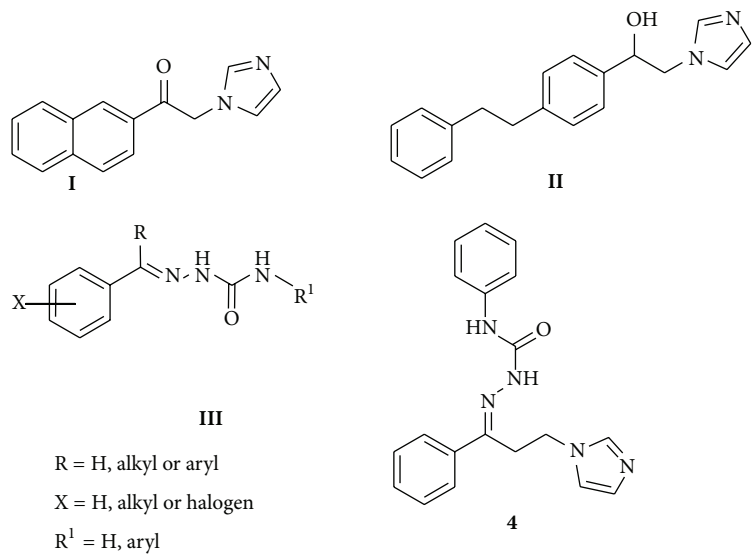


Figure 1: Chemical structures of nafimidone (**I**), denzimol (**II**), arylsemicarbazones **III**, and the target compound **4**.

2. Experimental

2.1. General. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared (IR) spectrawere recorded as KBr disks using the Perkin Elmer FT-IR Spectrum BX apparatus. NMR spectra were measured in DMSO-d_6 on a Bruker NMR spectrometer operating at 500 MHz for ^{1}H and 125.76 MHz for ^{13}C at the Research Center, College of Pharmacy, King Saud University, Saudi Arabia. Chemical shifts are expressed in δ-values (ppm) relative to TMS as an internal standard. Mass spectra were measured on Agilent Triple Quadrupole 6410 QQQ LC/MS with ESI (electrospray ionization) source. The X-ray diffraction measurements of compound **4** were performed using Bruker SMART APEXII CCD diffractometer. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center (supplementary publication number CCDC-933941).

2.2. Preparation of (2E)-2-[3-(1H-Imidazol-1-yl)-1-phenylpropylidene]-N-phenylhydrazinecarboxamide (4). A solution of **2** (1.51 g, 10 mmol), ketone **3** (2.00 g, 10 mmol), and few drops of glacial acetic acid in ethanol (15 mL) was stirred at room temperature for 18 h. The reaction mixture was evaporated under reduced pressure, and the residue was crystallized from ethanol to give 2.16 g (65%) of **4** as colorless crystals m.p. 176–178°C.

IR (KBr): ν (cm^{-1}) 3480, 3216 (NH), 1652 (C=O), 1594 (C=N); ^{1}H NMR (DMSO-d_6): δ: 3.33 (t, J = 7.6 Hz, 2H, –C$\underline{H}_2$–CH$_2$–N), 4.13 (t, J = 7.6 Hz, 2H, –CH$_2$–C$\underline{H}_2$–N), 6.87 (s, 1H, –N–C$\underline{H}$=CH–N=), 7.05 (t, J = 7.35 Hz, 1H, Ar–H), 7.29 (s, 1H, –N–CH=C$\underline{H}$–N=), 7.32 (t, J = 8.0 Hz, 2H, Ar–H), 7.41–7.43 (m, 3H, –N–C$\underline{H}$=N–, Ar–H), 7.65 (d, J = 8.3 Hz, 3H, Ar–H), 7.85-7.86 (m, 2H, Ar–H), 8.88 (s, 1H, NH), 10.27 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ: 28.3 (–$\underline{C}$H$_2$–CH$_2$–N), 42.1 (–CH$_2$–$\underline{C}$H$_2$–N), 119.4 (–N–$\underline{C}$H=CH–N=), 119.9, 122.6, 126.4, 128.3, 128.4, 128.5, 128.9 (–N–CH=$\underline{C}$H–N=, Ar–CH), 136.8, 137.3 (Ar–C), 138.9 (–N–$\underline{C}$H=N–), 145.1 (C=O), 153.6 (C=N); MS m/z (ESI): 334.2 [M + 1]$^+$.

2.3. Crystal Structure Determination. Slow evaporation of pure semicarbazone **4** in DMSO furnished the colorless single crystals. A colorless single crystal of suitable size, 0.42 mm × 0.11 mm × 0.09 mm, was selected for X-ray diffraction analysis. Data were collected on a Bruker APEX-II CCD area diffractometer equipped with graphite monochromatic Cu Kα radiation (λ = 1.54178 Å) at 296 K. Cell refinement and data reduction were done by Bruker SAINT [12]; program used to solve structure and refine structure is SHELXS-97 [13]. The final refinement was performed by full-matrix least-squares techniques with anisotropic thermal data for nonhydrogen atoms on F^2. All the hydrogen atoms were placed in calculated positions and constrained to ride on their parent atoms. Multiscan absorption correction was applied by use of SADABS software [12]. The crystallographic data and refinement information are summarized in Table 1.

3. Results and Discussion

3.1. Chemistry. The intermediate semicarbazide **2** was prepared according to our previously developed methodology [14] as outlined in Scheme 1. Thus, aniline was allowed to react with ethyl chloroformate to give the carbamate ester **1** which was subsequently reacted with hydrazine hydrate to furnish semicarbazide **2**.

The imidazole-containing ketone **3** was synthesized from acetophenone in two steps according to the previously

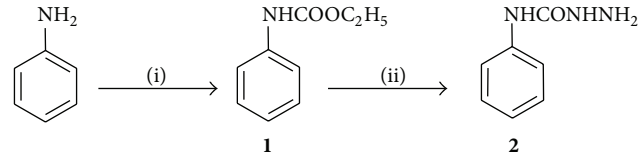
Table 1: Crystallographic data and refinement information.

Empirical formula	$C_{19}H_{19}N_5O$
Formula weight	333.39
Temperature (K)	296
Crystal system	Monoclinic
Space group	$P2_1/c$
Cu Kα radiation, λ	1.54178 Å
a (Å)	5.8093 (2)
b (Å)	20.5575 (6)
c (Å)	14.0355 (5)
α (°)	90.00
β (°)	97.365 (2)
γ (°)	90.00
V (Å^3)	1662.36 (10)
Z	4
F(000)	704
Theta range for data collection (°)	3.8–62.9
μ (mm^{-1})	0.70
Density (calc.) (g/cm^3)	1.332
Crystal shape and color	Needle, colorless
Crystal size (mm^3)	0.42 × 0.11 × 0.09
$h/k/l$	−4.6/−24.25/−16.16
Measured reflections	10883
Independent reflections	3009 [R_{int} = 0.074]
Reflections with $I > 2\sigma(I)$	1536
Goodness-of-fit on F^2	0.97
$R[F^2 > 2\sigma(F^2)]$	0.075
$wR(F^2)$	0.252
$\Delta\rho_{max}$ (e Å^{-3})	0.35
$\Delta\rho_{min}$ (e Å^{-3})	−0.28

reported procedure as shown in Scheme 2 [15]. Semicarbazide **2** was reacted with ketone **3** in ethanol in the presence of a catalytical amount of acetic acid at ambient temperature to yield the target semicabazone **4** in moderate yield (Scheme 2). The structure of compound **4** was confirmed *via* IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data.

X-ray crystallography is a decisive analytical tool which can confirm the configuration of the title semicarbazone **4**. Fortunately, we have succeeded to get single crystals of compound **4** which were suitable for X-ray crystallography, and hence the assigned (*E*)-configuration of compound **4** was established *via* its single crystal X-ray structure.

3.2. Crystal Structure of Compound 4. The crystal structure of the title compound **4** contains one molecule in the asymmetric unit. The labeled displacement ellipsoid plot of this molecule is shown in Figure 2. The selected bond lengths, bond angles, and bond torsion angles are listed in Table 2. The hydrogen-bonded interactions are listed in Table 3. Figure 3 depicts the packing of the molecules in the crystal structure. The crystal structure is stabilized by a three-dimensional framework structure by the combination of N–H···O and C–H···O intermolecular hydrogen bonds.



Scheme 1: Synthetic route for preparation of the semicarbazide **2**. Reagents and conditions: (i) $ClCOOC_2H_5$, CH_2Cl_2, RT, 0.5 h; (ii) $H_2N–NH_2·H_2O$, reflux, 24 h.

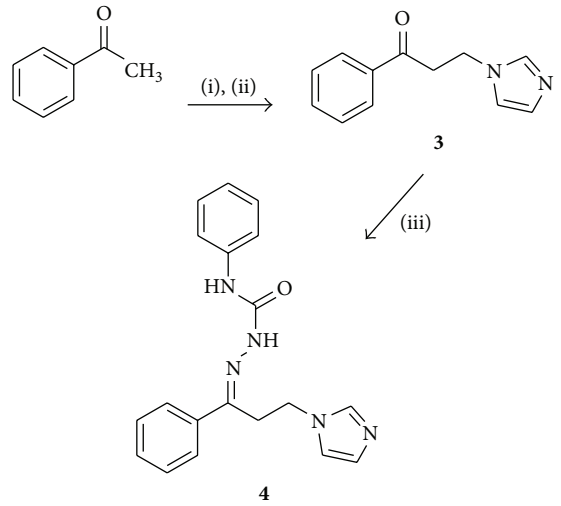
Table 2: Selected geometric parameters (Å, °).

O1–C13	1.227 (3)	N3–N4	1.384 (3)
N1–C11	1.368 (6)	N3–C7	1.296 (4)
N1–C12	1.311 (4)	N4–C13	1.365 (4)
N2–C9	1.450 (4)	N5–C13	1.355 (4)
N2–C10	1.362 (4)	N5–C14	1.418 (4)
N2–C12	1.348 (6)		
C11–N1–C12	103.9 (3)	N2–C9–C8	112.4 (2)
C9–N2–C10	128.0 (3)	N2–C10–C11	106.5 (3)
C9–N2–C12	126.3 (3)	N1–C11–C10	110.7 (3)
C10–N2–C12	105.7 (3)	N1–C12–N2	113.3 (4)
N4–N3–C7	118.9 (3)	O1–C13–N5	124.1 (3)
N3–N4–C13	118.7 (3)	N4–C13–N5	115.9 (3)
C13–N5–C14	124.0 (3)	O1–C13–N4	120.0 (3)
N3–C7–C8	125.8 (3)	N5–C14–C15	122.1 (3)
N3–C7–C6	114.4 (3)	N5–C14–C19	118.4 (3)

Table 3: Hydrogen-bond geometry (Å, °).

D–H···A	D–H	H···A	D···A	D–H···A
N5–H1N5···N3	0.95 (4)	2.19 (4)	2.622 (4)	106 (3)
N5–H1N5···N1^{i}	0.95 (4)	2.23 (4)	3.121 (4)	156 (4)
N4–H1N4···O1^{ii}	0.93 (4)	1.96 (4)	2.893 (3)	176 (4)
C8–H8A···O1^{ii}	0.9700	2.5100	3.198 (3)	128.00
C9–H9B···O1^{ii}	0.9700	2.5600	3.132 (3)	118.00
C15–H15A···O1	0.9300	2.5400	2.944 (5)	106.00

Symmetry codes: (i): $x, -y + 3/2, z + 1/2$; (ii): $-x + 1, -y + 1, -z$.



Scheme 2: Synthetic protocol of the target compound **4**. Reagents and conditions: (i) $HN(CH_3)_2 \cdot HCl$, $(CH_2O)_n$, conc. HCl, ethanol, reflux, 2 h; (ii) imidazole, water, reflux, 5 h; (iii) compound **2**, ethanol, acetic acid, RT, 18 h.

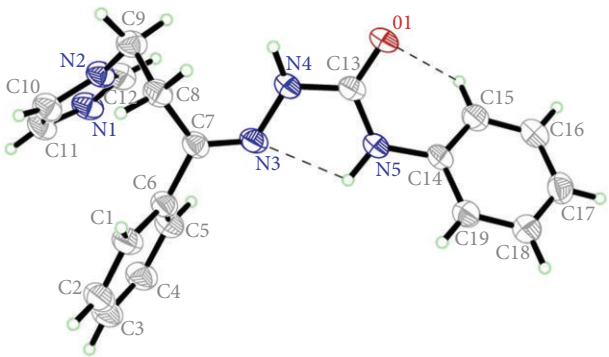


Figure 2: ORTEP diagram of the title compound **4** drawn at 50% ellipsoids for nonhydrogen atoms.

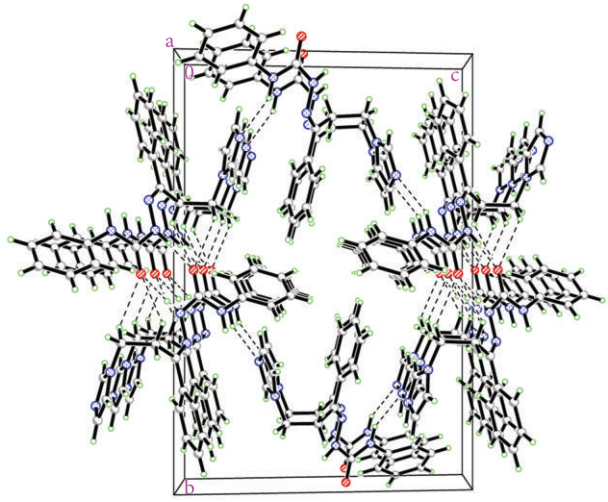


Figure 3: Crystal packing showing intermolecular N–H···O and C–H···O hydrogen bonds as dashed lines.

4. Conclusion

The synthesis and spectroscopic characterization of a new imidazole-containing arylsemicarbazone, namely, (2*E*)-2-[3-(1*H*-imidazol-1-yl)-1-phenylpropylidene]-*N*-phenylhydrazinecarboxamide (**4**), have been successfully achieved. The assigned (*E*)-configuration of the title compound **4** was confirmed *via* its single crystal X-ray structure. Results and analysis of the X-ray crystal structure of compound **4** are also reported. Compound **4** can be screened for anticonvulsant potential as it is a hybrid structure containing both arylsemicarbazone and imidazole pharmacophoric moieties of anticonvulsants.

Conflict of Interests

The authors have declared that there is no conflict of interests.

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