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Unveiling the synthesis and spectral characterizations of novel (E)-furan-2-yl acrylohydrazides: an exploration in molecular design

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ABSTRACT

In this study, we present the synthesis of novel derivatives of 3-furan-2-yl acrylohydrazide using a meticulous three-step reaction sequence. The synthesis ends up in the condensation of (E)-3-(furan-2-yl) acrylohydrazide (**3**) with diverse benzaldehyde and acetophenone derivatives. Comprehensive characterization of the synthesized compounds was achieved through 1D nuclear magnetic resonance spectroscopic analyses (^{1}H and ^{13}C NMR), 2D nuclear magnetic resonance spectroscopy (HSQC, NOESY), and high-resolution mass spectrometry (HRMS). The investigation of ^{1}H NMR data at room temperature in deuterated dimethyl sulfoxide (DMSO-d_6) unveiled the existence of (*E*)-3-(furan-2-yl) acrylohydrazide derivatives (**4a–h**) in a conformational equilibrium, manifesting as a mixture of *syn*periplanar *E* (sp *E*) and *anti*periplanar *E* (ap *E*), Notably, compounds **4a** and **4b** predominantly adopted the sp E conformer (*E*c=c sp $E_{C=N}$), while the remaining compounds (**4c–h**), favored the antiperiplanar conformation (*E*c=c ap $E_{C=N}$) even if for the **4g** compound it was challenging to determine the $E_{C=N}$ conformer. These findings contribute valuable insights into the conformational dynamics of this class of compounds, holding significance for applications in diverse scientific domains.

Subjects Spectroscopy, Synthetic Organic Chemistry
Keywords (E)-3-(furan-2-yl)acrylohydrazide, Acylhydrazone, Conformational analysis, NMR spectroscopy

INTRODUCTION

N-acylhydrazones (NAH) are distinguished by the presence of an azomethine fragment (CO-NH-N=CH), which, when integrated or connected into a heterocyclic scaffold, frequently yields compounds exhibiting noteworthy biological activities, (*Popiołek et al., 2020*; *Coulibaly et al., 2023*; *Popiołek, 2021*) including anticancer, (*Zheng et al., 2009*; *Terzioglu & Gürsoy, 2003*) antibacterial, (*Cardoso et al., 2014*) and antidepressant properties (*Salgin-Goksen et al., 2021*). Acrylohydrazides, a distinct class within these organic compounds, have recently garnered attention due to their multifunctional

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Additional Information and Declarations can be found on page 16

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properties (*Yan & Mihail, 2016*). Among them, (*E*)-3-(furan-2-yl) acrylohydrazides stand out, featuring the conjugated furan-2-yl scaffold linked to a hydrazide function. This unique combination of structures holds considerable potential for diverse applications, encompassing bioactive functionalities (*Ge et al., 2014*).

Building upon our prior studies, (*Achi et al., 2022*; *Ablo et al., 2022*) which consistently established the stable (*E*) conformation of N-acylhydrazones in various solvents, particularly the prevalence of the *syn* conformation in solvents like DMSO-d_6, we identified conditions favoring the *anti* conformation, including less polar solvents (*e.g.*, $CDCl_3$), intramolecular hydrogen bonding, or steric hindrance. The persistent dominance of the *syn* conformation, where crucial substituents adopt specific spatial orientations, suggests a structural regularity with promising implications for the design of novel molecules tailored for specific purposes.

Aligned with our previous investigations characterizing benzimidazoles N-acylhydrazones and acylhydrazones derived from nitroimidazo[1,2-a]pyridine, intimately linked to (*E*)-3-(furan-2-yl) acrylohydrazides by their fundamental structure, this study endeavors to comprehensively explore the preferential conformation of these newly synthesized molecular entities. Employing a rigorous synthetic approach coupled with structural analyses, encompassing NMR, and HRMS, our objective is to delve into the conformational properties of (*E*)-3-(furan-2-yl) acrylohydrazides. Ultimately, this research aspires to make a significant contribution to the understanding of molecular conformation, thereby laying the foundation for potential applications in the field of materials science.

MATERIALS AND METHODS

Material

Portions of this text were previously published as part of a preprint in ChemRxiv. 2024; doi:10.26434/chemrxiv-2024-f8gtf. Unless otherwise stated, ^{1}H et ^{13}C NMR spectra were recorded at 500 and 126 MHz, at 400 MHz for ^{1}H and 101 MHz for ^{13}C, respectively, in $CDCl_3$, Methanol-d_4, and DMSO-d_6 solutions provided by Eurisotop, using TMS as an internal reference. Chemical shifts are reported in ppm on the δ scale. Multiplicities are denoted as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet), and coupling constants (J) are reported in Hz. High-resolution mass spectra (HRMS) were acquired in electrospray ionization (ESI) mode using an LC-MSD TOF mass analyzer. The infrared analyses were conducted using a SHIMADZU FTIR spectrometer equipped with an ATR stage featuring a diamond crystal. Data acquisition involved performing 20 scans in the range of 4000 to 400 cm^{-1}. Reaction monitoring and compound purity were assessed by thin-layer chromatography (TLC) on silica gel plates (Merck Kisselgel $60F_{254\ nm}$, silica thickness 0.2 mm) revealed under UV-Vis light (λ = 254 and 365 nm). Product purification was carried out using silica gel column chromatography (Kisselgel SI60, 40–63).

Solid compound melting points were determined using a Köpfler melting point apparatus with a temperature range of 44–266 °C.

The required reagents for the synthesis protocols were procured from suppliers. Triphenylphosphine, 3-fluoroacetophenone, 4-fluoroacetophenone, furan-2-

carbaldehyde, thiophene-2-carbaldehyde, and pyridine-2-carbaldehyde were sourced from Sigma Aldrich. Hydrazine monohydrate and pyrrole carboxaldehyde were obtained from Thermo Scientific Chemicals. Additionally, sodium hydrogenocarbonate was sourced from Chem Lab. All solvents utilized in the experiments were provided by Polychimie Côte d'Ivoire, ensuring high quality and consistency throughout the experimental procedures.

Methods

Synthesis procedure for (E)-ethyl 3-(furan-2-yl) acrylate (2)

In a 100 mL round-bottom flask (rbf) fitted with a magnetic stirrer, a reaction mixture comprising triphenylphosphine (PPh_3, 1.5 eq., 36.46 mmol, 9,48 g), a saturated solution of sodium bicarbonate ($NaHCO_3$) (50 mL), ethyl 2-chloroacetate (1.8 eq, 43.40 mmol, 4.80 mL), and furan-2-carbaldehyde (1 eq, 24.10 mmol) was stirred at ambient temperature for a duration of 24 h. The reaction was monitored using thin-layer chromatography (TLC), and the completion of the reaction is indicated by TLC analysis. At the end of the reaction, the reaction mixture was extracted with dichloromethane (DCM), and the resulting organic layer was dried using magnesium sulfate ($MgSO_4$) before undergoing concentration under reduced pressure. Subsequently, diethyl ether (Et_2O) was introduced to induce the precipitation of triphenylphosphine oxide ($O=PPh_3$), which was subsequently separated *via* filtration. The obtained crude product undergoes purification *via* column chromatography on silica gel, using cyclohexane or hexane as the eluent, resulting in the isolation of a brown oil with a purity of 77% (3.07 g).

(E)-Ethyl-3-(furan -2-yl) acrylate (2); **brown oil, yield = 77% (3.07 g) (E/Z-ratio:88/12)**

^{1}H NMR (500 MHz, $CDCl_3$) δ: *E* (major): 7.42 (d, *J* = 1.9 Hz, 1H, HAr), 7.38 (d, *J* = 15.8 Hz, 1H, HC=), 6.55 (d, *J* = 3.4 Hz, 1H, HAr), 6.41 (dd, *J* = 3.4, 1.9 Hz, 1H, HAr), 6.27 (d, *J* = 15.8 Hz, 1H, =CH), 4.18 (q, *J* = 7.1 Hz, 2H, -CH_2-), 1.26 (t, *J* = 7.1, Hz, 3H, -CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.00, 150.95, 144.69, 130.95, 115.94, 114.62, 112.24, 60.40, 14.28.

1H NMR (500 MHz, $CDCl_3$) δ: *Z* (minor): 7.64 (d, *J* = 3.6 Hz, 1H, HAr), 6.73 (d, *J* = 13.0 Hz, 1H), 7.47 (d, *J* = 1.9 Hz, 1H, HAr), 6.45 (ddd, *J* = 3.6, 1.9, 0.8 Hz, 1H, HAr), 5.69 (d, *J* = 13.0 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.96, 150.83, 143.89, 130.35, 117.01, 114.39, 112.58, 60.11, 14.25.

Synthesis procedure for (E)-3-(furan-2-yl) acrylohydrazide (3)

In a 50 mL round bottom flask equipped with a magnetic stirrer, 1 g (1 eq, 6.00 mmol) of (E)-ethyl-3-(furan-2-yl) acrylate was dissolved in 2 mL of ethanol, followed by the addition of 1.5 mL (5 eq, 30.00 mmol) of hydrazine monohydrate (H_2N-NH_2.H_2O). The mixture was stirred for 3 h at room temperature. TLC, indicative of reaction completion, was performed. Upon cessation of the reaction, the reaction medium was extracted using DCM. The organic layer was washed multiple times with water (H_2O), then dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was

purified by column chromatography on silica gel, using cyclohexane/ethyl acetate 80/20 as the eluent, yielding a beige powder (0.48 g, 52%).

***(E)-3-(furan-2-yl) acrylohydrazide (3)*, beige powder, yield = 52% (480 mg), m. p = 72–74 °C**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 15.5 Hz, 1H, HC=), 7.43 (d, *J* = 1.9 Hz, 1H, HAr), 7.19 (s, 1H, NH), 6.55 (d, *J* = 3.6 Hz, 1H, HAr), 6.44 (dd, *J* = 3.6, 1.9 Hz, 1H, HAr), 6.27 (d, *J* = 15.5 Hz, 1H, =CH), 4.05 (s, 2H, NH_2).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.16, 151.23, 144.31, 128.60, 115.69, 114.33, 112.33.

General procedure for the synthesis of hydrazide-hydrazone derivatives (4a–h)

In a 10 mL Schlenk equipped with a magnetic stirrer, a mixture was prepared by combining 0.21 mmol (1 eq) of 3-(furan-2-yl) acrylohydrazide, 0.23 mmol (1.1 eq) of acetophenone or aldehyde derivatives, 1.5 mL of ethanol, and two drops of concentrated hydrochloric acid (HCl). The resulting mixture was stirred at room temperature (r.t) for 3 h. Subsequently, the reaction medium was concentrated under reduced pressure and subjected to purification *via* silica gel chromatography, using a DCM/MeOH mixture (95/5) as eluent. The isolated product was obtained from this process.

***(2E, N'E)-N′-(1-(3-fluorophenyl) ethylidene)-3-(furan-2-yl) acrylohydrazide (4a)*, gold yellow powder, yield = 54% (23.90 mg), m.p = 172-174 °C**

3-(furan-2-yl) acrylohydrazide (1 eq, 31.80 mg), 3-fluoroacetophenone (1.1 eq, 28 µL) were used in the procedure.

^{1}H NMR (500 MHz, Methanol-d_4) δ 7.74 (dt, *J* = 10.8, 1.9 Hz, 1H, HAr), 7.69_{sp}, 7.65_{ap} (dd, *J* = 7.9, 1.9 Hz, 1H, HAr), 7.67_{ap}, 7.63_{sp} (d, *J* = 1.9 Hz, 1H, HAr), 7.56_{sp}, 7.55_{ap} (d, *J* = 15.4 Hz, 1H, HC=), 7.40 (td, *J* = 7.9, 5.9 Hz, 1H, HAr), 7.13 (td, *J* = 7.9, 2.6 Hz, 1H, HAr), 6.78 (d, *J* = 15.4 Hz, 1H, =CH), 6.77_{ap}, 6.75_{sp} (d, *J* = 3.5 Hz, 1H, HAr), 6.56 (dd, *J* = 3.5, 1.9 Hz, 1H, HAr), 2.36_{sp}, 2.30_{ap} (s, 3H, -CH_3).

^{13}C NMR (126 MHz, Methanol-d_4) δ 168.38_{ap}, 164.43_{sp} (C=O), 162.94_{ap}, 162.90_{sp} (d, *J* = 243.9 Hz, =C-F), 152.47 (d, *J* = 3.1 Hz, C), 151.62_{ap}, 151.44_{sp} (CAr), 145.01_{ap}, 144.78_{sp} (CH), 140.53 (d, *J* = 7.7 Hz, CAr), 129.87_{ap}, 129.69_{sp} (d, *J* = 8.4 Hz, CH Ar), 129.63_{ap}, 129.04_{sp} (CH), 122.43_{sp}, 121.83_{ap} (d, *J* = 3.0 Hz, CH Ar), 115.92_{sp}, 115.58_{ap} (d, *J* = 21.8 Hz, CH Ar), 115.94_{sp}, 114.86_{ap} (CH), 114.50_{sp}, 113.84_{ap} (CH), 113.12_{sp}, 112.40_{ap} (d, *J* = 23.4 Hz, CH Ar), 112.08 (CH), 12.90_{sp}, 12.08_{ap} (s, CH_3).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74_{ap}, 10.69_{sp} (s, 1H, NH), 7.86_{ap}, 7.83_{sp} (s, 1H, HAr), 7.61 (m, 2H, HAr), 7.50 (m, 1H, HAr), 7.43_{sp}, 7.35_{ap} (d, *J* = 15.7 Hz, 1H, HAr), $7.24_{(sp+ap)}$ (t, *J* = 8.5 Hz, 1H, HAr), 6.93_{ap}, 6.86_{sp} (d, *J* = 3.5 Hz, 1H, HAr), 6.83 (d, *J* = 15.7 Hz, 1H, =CH), $6.62_{(sp+ap)}$ (d, *J* = 2.0 Hz, 1H), 2.31_{sp}, 2.29_{ap} (s, 3H, N=C(CH_3)).

FT-IR (ATR) cm^{-1}: 3,186.40 (NH), 2,978.09 (N=CH), 2,885.51 (CH), 1,651.07 (C=O), 1,620.21 (C=N), 1,325.10 (C-O-C), 1,014.56 (N-N), 966.34 (HC=CH).

***(2E, N'E)-N′-(1-(4-fluorophenyl) ethylidene)-3-(furan-2-yl) acrylohydrazide (4b)*, gold yellow powder, yield = 41% (21.70 mg), m.p = 178–180 °C**

3-(furan-2-yl) acrylohydrazide (1 eq, 30.00 mg), 4-fluoroacetophenone (1.1 eq, 26 µL) were used in the procedure.

^{1}H NMR (500 MHz, Methanol-d_4) δ 7.95_{sp}, 7.86_{ap} (dd, *J* = 9.0, 5.4 Hz, 2H, HAr), 7.65_{ap}, 7.62_{sp} (d, *J* = 2.1 Hz, 1H, HAr), 7.54_{sp}, 7.49_{ap} (d, *J* = 15.9 Hz, 1H, =CH), 7.15_{ap}, 7.11_{sp} (t, *J* = 9.0 Hz, 2H, HAr), 6.76_{sp} (d, *J* = 15.9 Hz, 1H, HC=), 6.76_{ap}, 6.74_{sp} (d, *J* = 3.3 Hz, HAr), 6.55 (dd, *J* = 3.3, 2.1 Hz, 1H, HAr), 2.36_{sp}, 2.30_{ap} (s, 3H, $-CH_3$).

^{13}C NMR (126 MHz, Methanol-d_4) δ 169.73_{ap}, 165.76_{sp} (C=O), 165.44_{ap}, 165.18_{sp} (d, *J* = 248.7 Hz, =C-F), 154.48_{sp}, 153.05_{ap} (C Ar), 152.85_{ap}, 149.38_{sp} (C Ar), 146.31_{ap} 146.13_{sp} (CH Ar), 135.94_{ap}, 135.77_{sp} (d, *J* = 3.4 Hz, C Ar), 130.89_{ap}, 130.27_{sp} (HC=), 130.16_{sp}, 129.42_{ap} (d, *J* = 8.4 Hz, 2CH Ar), 117.42_{ap}, 116.16_{ap} (=CH), 116.19_{sp}, 115.38_{ap} (CH Ar), 116.16_{ap}, 113.46_{sp} (CH Ar), 115.90 (d, *J* = 28.1 Hz, 2 CH Ar), 14.36_{sp}, 13.51_{ap} (CH_3).

FT-IR (ATR) cm^{-1}: 3,161.33 (NH), 3,020 (N=CH), 2,960 (CH), 1,658.78 (C=O), 1,625 (C=N), 1,384.99 (C-O-C), 1,016.49 (N-N), 972.12 (HC=CH)

HRMS (ESI): Calc. $C_{15}H_{14}N_2O_2F$ [M+H] = 273.1039 found = 273.1033.

Calc. $C_{15}H_{13}N_2O_2F$ [M–H] = 271.0883 found = 271.0895.

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.67_{ap}, 10.63_{sp} (s, 1H, NH), 7.85 (m, 3H), 7.50_{ap}, 7.42_{sp} (d, *J* = 15.8 Hz, =CH), 7.34_{ap}, 6.83_{sp} (d, *J* = 15.8 Hz, HC=), 7.27 (m, 2H), 6.93_{ap}, 6.85_{sp} (d, *J* = 3.6 Hz, 1H, HAr), 6.64_{ap}, 6.62_{sp} (dd, *J* = 3.6, 1.7 Hz, 1H), 2.31_{sp}, 2.28_{ap} (s, 3H, $-CH_3$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 165.25_{sp}, 162.73_{ap} (d, *J* = 363.8 Hz, =C-F), 161.88_{sp}, 161.85_{ap} (C=O), 151.16 (C Ar), 150.55_{sp}, 147.02_{ap} (C Ar), 145.53_{ap}, 145.17_{sp} (CH Ar), 134.78 (C Ar), 129.06_{ap}, 127.49_{sp} (HC=), 128.58_{sp}, 128.21_{ap} (d, *J* = 8.6 Hz, 2 CH Ar), 117.92_{ap}, 117.87_{sp} (=CH), 115.44_{ap}, 115.24_{sp} (d, *J* = 21.3 Hz, 2CH Ar), 114.66_{sp}, 114.46_{ap} (CH Ar), 112.70_{ap}, 112.62_{sp} (CH Ar), 14.16_{sp}, 13.87_{ap} (CH_3).

***(2E, N'E)′-3-(furan-2-yl)-N'-(thiophen-2-ylmethylene) acrylohydrazide (4c)*, Brown solid, yield = 23% (11.47 mg), m.p = 216–218 °C**

3-(furan-2-yl) acrylohydrazide (1 eq, 31.10 mg), thiophene-2-carbaldehyde (1.1 eq, 21 µL) were used in the procedure.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.60_{ap}, 11.47_{sp} (s, 1H, NH), 8.45_{ap}, 8.23_{sp} (s, 1H, N=CH), 7.87_{sp}, 7.82_{ap} (d, *J* = 1.9 Hz, 1H, HAr), 7.66_{ap}, 7.63_{sp} (d, *J* = 5.0 Hz, 1H, HAr), 7.47_{ap}, 7.41_{sp} (m, 1H), 7.43_{sp}, 7.41_{ap} (d, *J* = 15.7 Hz, 1H, =CH), 7.21_{sp}, 6.46_{ap} (d, *J* = 15.7 Hz, 1H, HC=), $7.13_{(sp\ +\ ap)}$ (m, 1H, HAr), 6.91_{sp}, 6.86_{ap} (d, *J* = 3.5 Hz, 1H, HAr), 6.64_{sp}, 6.62_{ap} (dd, *J* = 3.5, 1.9 Hz, 1H, HAr).

^{13}C NMR (126 MHz, DMSO-d_6) δ 165.49_{sp}, 161.18_{ap} (C=O), 151.02_{sp}, 150.85_{ap} (C-O), 145.49_{sp}, 145.19_{ap} (CH Ar), 141.79_{sp}, 138.17_{ap} (N=CH), 139.10_{ap}, 138.92_{sp} (C -S), 130.87_{ap}, 130.19_{sp} (CH Ar), 128.89_{ap}, 128.21_{sp} (CHAr), 128.85_{sp}, 127.59_{ap} (HC=), 127.90_{sp}, 127.82_{ap} (CH Ar), 117.21_{ap}, 113.79_{sp} (=CH), 115.39_{sp}, 114.74_{ap} (CH Ar), 112.60_{sp}, 112.55_{ap} (CH Ar).

FT-IR (ATR) cm^{-1}: 3,200 (NH), 2,989 (N=CH), 1,670 (C=O), 1,610 (C=N), 1,328.95 (C-O-C), 1,016.49 (N-N), 961 (HC=CH).

***(2E, N'E)′-N'-((1H pyrrol-2-yl) methylene)-3-(furan-2-yl) acrylohydrazide (4d)*, green powder, yield = 48% (36.00 mg), m.p = 236–238 °C**

3-(furan-2-yl) acrylohydrazide (1 eq, 50.00 mg), pyrrole-2-carbaldehyde (1.1 eq, 34.39 mg) were used in the procedure.

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 11.50$_{ap}$, 11.44$_{sp}$ (s, 1H, NH $_{pyrrole}$), 11.32$_{ap}$, 11.16$_{sp}$ (s, 1H, NH), 8.07$_{ap}$, 7.88$_{sp}$ (s, 1H, N=CH), 7.84$_{sp}$, 7.80$_{ap}$ (d, *J* = 1.9 Hz, 1H, HAr), 7.42 (d, *J* = 1.9 Hz, 1H, HAr) 7.37 (d, *J* = 15.5 Hz, 1H, =CH), 6.93$_{sp}$, 6.90$_{ap}$ (m 1H), 6.90$_{ap}$, 6.82$_{sp}$ (d, *J* = 3.5 Hz, 1H, HAr), 6.64$_{sp}$, 6.61$_{ap}$ (dd, *J* = 3.5, 1.9 Hz, 1H, HAr), 6.47 (d, *J* = 15.5 Hz, 1H, HC=), 6.42$_{sp}$, 6.13$_{ap}$ (m, 1H).

^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 165.36$_{sp}$, 160.75$_{ap}$ (C=O), 151.40$_{sp}$, 150.99$_{ap}$ (C-O), 145.11$_{sp}$, 144.99$_{ap}$ (CH Ar), 139.72$_{ap}$, 136.09$_{sp}$ (N=CH), 128.35$_{ap}$, 115.11$_{sp}$ (CH Ar), 127.11$_{sp}$, 127.02$_{ap}$ (C-N, C Ar), 126.94$_{ap}$, 127.03$_{sp}$ (=CH), 122.52$_{ap}$, 121.86$_{sp}$ (CH Ar), 117.74, 113.30 (HC=), 114.56$_{sp}$, 114.26$_{ap}$ (CH Ar), 112.58, 112.50$_{sp}$, 112.48$_{ap}$ (CH Ar), 109.25$_{ap}$, 109.14$_{sp}$ (CH Ar).

FT-IR (ATR) cm^{-1}: 3,415.93 (NH), 3,211.48 (NH), 2,987.74 (N=CH), 2,889.37 (CH), 1,656.85 (C=O), 1,600.92 (C=N), 1,328.95 (C-O-C), 1,016.49 (N-N), 968.27 (HC=CH).

***(2E, N'E)′-3-(furan-2-yl)-N'-(furan-2-ylmethylene) acrylohydrazide (4e)*, beige powder, yield = 56% (44.00 mg), m.p = 224–226 °C**

3-(furan-2-yl) acrylohydrazide (1 eq, 50.00 mg), furane-2-carbaldehyde (1.1 eq, 30 µL) were used in the procedure.

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 11.59$_{ap}$, 11.44$_{sp}$ (s, 1H, NH), 8.13$_{ap}$, 7.94$_{sp}$ (s, 1H, N=CH), 7.84$_{(ap + sp)}$ (td, *J* = 8.35, 2.1 Hz, 2H, HAr), 7.45$_{sp}$, 7.43$_{ap}$ (d, *J* = 15.8 Hz, 1H, =CH), 7.24$_{sp}$, 6.45$_{ap}$ (d, *J* = 15.8 Hz, 1H, HC=), 6.92$_{sp}$, 6.62$_{ap}$ (m, 3H) 6.89$_{sp}$, 6.86$_{ap}$ (d, *J* = 3.5 Hz, 1H, HAr).

^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 165.68$_{sp}$, 161.27$_{ap}$ (C=O), 151.05$_{sp}$, 150.85$_{ap}$ (C-O), 149.41$_{ap}$, 149.16$_{sp}$ (C-O), 145.44$_{ap}$, 144.90$_{sp}$ (CH Ar), 145.21$_{ap}$, 145.14$_{sp}$ (CH Ar), 136.41$_{ap}$, 133.14$_{sp}$ (N=CH), 128.80$_{sp}$, 127.65$_{ap}$ (HC=), 117.17$_{ap}$, 113.95$_{sp}$ (=CH), 115.32$_{sp}$, 114.74$_{ap}$ (CH Ar), 113.51$_{ap}$, 113.36$_{ap}$ (CH Ar), 112.60$_{sp}$, 112.55$_{ap}$ (CH Ar), 112.17$_{ap}$, 112.05$_{sp}$ (CH Ar).

FT-IR (ATR) cm^{-1}: 3,126.61 (NH), 2,989.66 (N=CH), 2,887.44 (CH), 1,651.07 (C=O), 1,606.70 (C=N), 1,338.60 (C-O-C), 1,014.56 (N-N), 968.27 (HC=CH).

***(2E, N'E)′-3-(furan-2-yl)-N'-(pyridin-2-ylmethylene) acrylohydrazide (4f)*, yellow powder, yield = 96% (47.17 mg), m.p = 104–106 °C**

3-(furan-2-yl) acrylohydrazide (1 eq, 31.00 mg), pyridine-2-carbaldehyde (1.1 eq, 21 µL) were used in the procedure.

^{1}H NMR (500 MHz, Methanol-*d*$_4$) δ 8.56 (m, 1H), 8.27$_{ap}$, 8.05$_{sp}$ (d, *J* = 7.8 Hz, 1H, HAr), 8.19$_{ap}$, 8.05$_{sp}$ (s, 1H, N=CH), 7.90$_{sp}$, 7.88$_{ap}$ (t, *J* = 7.8 Hz, 1H, HAr), 7.67$_{sp}$, 7.63$_{ap}$ (d, *J* = 1.8 Hz, 1H, HAr), 7.58$_{ap}$, 7.52$_{sp}$ (d, *J* = 15.4 Hz, 1H, HC=), 7.42 (dd, *J* = 7.4, 4.8 Hz, 1H, HAr), 6.81$_{sp}$, 6.77$_{ap}$ (d, *J* = 3.3 Hz, 1H, HAr), 6.56$_{ap}$, 6.39$_{sp}$ (dd, *J* = 3.3, 1.8 Hz, 1H, HAr), 6.52 (d, *J* = 15.4 Hz, 1H, =CH).

^{13}C NMR (126 MHz, Methanol-*d*$_4$) δ 169.37$_{sp}$, 165.46$_{ap}$ (C=O), 154.47$_{ap}$, 154.39$_{sp}$ (C-N), 153.02$_{sp}$, 152.59$_{ap}$ (C-O), 150.26$_{sp}$, 150.15$_{ap}$ (CH), 148.29$_{ap}$, 143.96$_{sp}$ (CH), 146.39$_{ap}$, 144.62$_{sp}$ (N=CH), 138.89$_{sp}$, 138.60$_{ap}$ (CH), 131.32$_{sp}$, 130.93$_{ap}$ (CH), 125.97$_{ap}$, 125.71$_{sp}$ (CH), 122.30$_{ap}$, 121.92$_{sp}$ (CH), 116.68$_{sp}$, 116.31$_{ap}$ (CH), 114.77$_{sp}$, 113.53$_{ap}$ (CH).

HRMS (ESI): Calc. $C_{13}H_{12}N_3O_2$ [M+H] = 242.0929 found = 242.0924.

Calc. $C_{13}H_{10}N_3O_2$ [M–H] =240.0773 found = 240.0781.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89$_{ap}$, 11.72$_{sp}$ (s, 1H, NH), 8.61$_{(sp + ap)}$ (d, *J* = 4.9 Hz, 1H, HAr), 8.23$_{ap}$, 8.10$_{sp}$ (s, 1H, N=CH), 7.96$_{sp}$, 7.94$_{ap}$ (d, *J* = 3.5 Hz, 1H, HAr), 7.89 $_{(sp + ap)}$ (td, *J* = 7.5, 1.9 Hz, 1H, HAr), 7.88$_{ap}$, 7.84$_{sp}$ (d, *J* = 1.9 Hz, 1H, HAr), 7.51$_{sp}$, 7.47$_{ap}$ (d, *J* = 15.5 Hz, =CH), 7.42$_{(sp + ap)}$ (dd, *J* = 7.5, 4.9 Hz, 1H, HAr), 7.31$_{sp}$, 6.50$_{ap}$ (d, *J* = 15.5 Hz, 1H, HC=), 6.98$_{sp}$, 6.89$_{ap}$ (d, *J* = 3.5 Hz, 1H, HAr), 6.65$_{sp}$, 6.64$_{ap}$ (dd, *J* = 3.5, 1.9 Hz, 1H, HAr).

^{13}C NMR (101 MHz, DMSO-d_6) δ 166.01$_{sp}$, 161.55$_{ap}$ (C=O), 153.17$_{ap}$, 152.97$_{sp}$ (C-N), 151.05$_{sp}$, 150.79$_{ap}$ (C-O), 149.51$_{ap}$, 146.82$_{sp}$ (CHAr), 145.57$_{ap}$, 145.40$_{sp}$ (CH), 143.68$_{sp}$, 136.91$_{ap}$ (CH), 129.30$_{sp}$, 128.19$_{ap}$ (CH), 124.35$_{ap}$, 124.19$_{sp}$ (CH), 119.93$_{ap}$, 119.61$_{sp}$ (CH), 116.90$_{ap}$, 115.51$_{sp}$ (CH), 115.13$_{ap}$, 113.73$_{sp}$ (CH), 112.68$_{ap}$, 112.65$_{sp}$ (CH).

FT-IR (ATR) cm^{-1}: 3,180.62 (NH), 2,990 (N=CH), 2,866.22 (CH), 1,660.71 (C=O), 1,624.09 (C=N), 1,556.55 (C=N), 1,323.17 (C-O-C), 1,014.56 (N-N), 968.27 (HC=CH).

***(2E, N'E)-N′-(1-(4chloro-3-nitrobenzylidene)-3-(furan-2-yl) acrylohydrazide (4g)*, yellow powder, yield = 70% (44.80 mg), m.p = 98–100 °C**

3-(furan-2-yl) acrylohydrazide (1 eq, 30.60 mg), 4-chloro-3-nitrobenzaldehyde (1.1 eq, 41.00 mg) were used in the procedure.

^{1}H NMR (500 MHz, Methanol-d_4) δ 8.43$_{ap}$, 8.23$_{sp}$ (d, *J* = 2.0 Hz, 1H, HAr), 8.17$_{ap}$, 8.03$_{sp}$ (s, 1H, N=CH), 8.03$_{ap}$, 8.00$_{sp}$ (dd, *J* = 8.4, 2.0 Hz, 1H, HAr), 7.74$_{sp}$, 7.71$_{ap}$ (d, *J* = 8.4 Hz, 1H, HAr), 7.69$_{sp}$, 7.65$_{ap}$ (d, *J* = 2.0 Hz, 1H, HAr), 7.57$_{ap}$, 7.53$_{sp}$ (d, *J* = 15.5 Hz, =CH), 6.82$_{sp}$, 6.78$_{ap}$ (d, *J* = 3.5 Hz, 1H, HAr), 6.59$_{sp}$, 6.58$_{ap}$ (dd, *J* = 3.5, 2.0 Hz, 1 H, HAr), 6.50 (d, *J* = 15.5 Hz, HC=).

^{13}C NMR (126 MHz, Methanol-d_4) δ 169.20$_{sp}$, 165.40$_{ap}$ (C=O), 152.93$_{sp}$, 152.56$_{ap}$ (C-O), 149.99$_{ap}$ (C-NO$_2$), 146.45$_{sp}$, 146.39$_{ap}$ (CH), 145.60$_{ap}$, 142.08$_{sp}$ (CH), 136.28 (C Ar), 133.35$_{sp}$, 133.19$_{ap}$ (CH), 132.71$_{ap}$, 131.87$_{sp}$ (CH), 131.35$_{sp}$, 130.90$_{ap}$ (CH), 128.26$_{ap}$, 127.99$_{sp}$ (C-Cl), 124.86$_{ap}$, 124.52$_{sp}$ (CH), 116.59$_{ap}$, 116.44$_{sp}$ (CH), 116.34$_{ap}$, 114.55$_{sp}$ (CH), 113.53 (CH).

HRMS (ESI) Calc. $C_{14}H_{11}ClN_3O_4$ [M+H] = 320.0438 found = 320.0427

Calc. $C_{14}H_9ClN_3O_4$ [M−H] = 318.0281 found = 318.0284

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.93$_{ap}$, 11.75$_{sp}$ (s, 1H, NH), 8.38$_{ap}$, 8.37$_{sp}$ (d, *J* = 2.1 Hz, HAr), 8.29$_{ap}$, 8.11$_{sp}$ (s, 1H, N=CH), 8.03$_{(ap + sp)}$ (m, 1H), 7.88$_{sp}$, 7.83$_{ap}$ (s, 1H, HAr), 7.86$_{ap}$, 7.84$_{sp}$ (s, 1H, HAr), 7.50$_{sp}$, 7.46$_{ap}$ (d, *J* = 15.5 Hz, 1H, =CH), 7.31$_{sp}$, 6.51$_{ap}$ (d, *J* = 15.5 Hz, HC=), 6.97$_{sp}$, 6.89$_{ap}$ (d, *J* = 3.5 Hz, 1H, HAr), 6.65$_{sp}$, 6.64$_{ap}$ (dd, *J* = 3.5, 2.1 Hz, HAr).

^{13}C NMR (126 MHz, DMSO-d_6) δ 166.09$_{sp}$, 161.63$_{ap}$ (C=O), 151.03$_{sp}$, 150.80$_{ap}$ (C-O), 148.05$_{sp}$, 147.86$_{ap}$ (C-NO$_2$), 145.61$_{sp}$, 145.41$_{ap}$ (CH Ar), 143.16$_{ap}$, 140.00$_{sp}$ (N=CH), 135.04$_{ap}$, 134.82$_{sp}$ (C Ar), 132.15$_{ap}$, 131.46$_{sp}$ (CH Ar), 130.98 (CH Ar), 129.44$_{sp}$, 128.24$_{ap}$ (HC=), 125.66$_{ap}$, 125.29$_{sp}$ (C-Cl), 123.58$_{ap}$, 123.37$_{sp}$ (CH Ar), 116.85$_{ap}$, 113.63$_{sp}$ (=CH), 115.56$_{sp}$, 115.17$_{ap}$ (CH Ar), 112.74$_{sp}$, 112.65$_{ap}$ (CH Ar).

FT-IR (ATR) cm^{-1}: 3,429.43 (NH), 3,000 (N=CH), 2,889.37 (CH), 1,658.78 (C=O), 1,606.70 (C=N), 1,531.48 (NO$_2$), 1,328.95 (C-O-C), 1,016.49 (N-N), 968.27 (HC=CH).

***(2E, N'E)-N′-(3-(benzyloxy) benzylidene)-3-(furan-2-yl) acrylohydrazide (4h)*, yellow powder, yield = 40% (28.10 mg), m.p = 116–118 °C**

3-(furan-2-yl) acrylohydrazide (1 eq, 30.06 mg), 3-benzyloxybenzaldehyde (1.1 eq, 47.00 mg) were used in the procedure.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (s, NH), 7.78 (s, 1 H, N=CH), 7.62 (d, *J* = 15.8 Hz, 1H, =CH), 7.51 (d, *J* = 15.8 Hz, 1H, HC=), 7.46 (d, *J* = 7.3 Hz, 2H, HAr), 7.40 (t, *J* = 7.3 Hz, 4H, HAr), 7.34 (t, *J* = 7.7 Hz, 2H, HAr), 7.28 (d, *J* = 1.4 Hz, 1H, HAr), 7.03 (dd, *J* = 7.5, 1.9 Hz, 1H, HAr), 6.67 (d, *J* = 3.5 Hz, 1H, HAr), 6.50_{ap}, 6.47_{sp} (dd, *J* = 3.5, 1.9 Hz, 1H, HAr), 5.15 (s, 2H, -CH_2-).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.88 (C=O), 159.21 (C-O), 151.93 (C-O), 144.71 (CH Ar), 143.77 (N=CH), 136.93 (C Ar), 135.42 (C Ar), 130.28 (HC=), 129.94 (=CH), 128.81 (2C, CH Ar), 128.26 (CH Ar), 127.77 (2C, CH Ar), 120.75 (CH Ar), 117.11 (CH Ar), 115.00 (CH Ar), 114.35 (CH Ar), 112.87 (CH Ar), 112.47 (CH Ar), 70.30 (CH_2).

HRMS (ESI) Calc. $C_{21}H_{19}N_2O$ [M+H] = 347, 13,957 found = 347, 13,864

Calc. $C_{21}H_{17}N_2O$ [M–H] = 345.12391 found = 345.12466

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70_{ap}, 11.53_{sp} (s, 1H, NH), 8.19_{ap}, 8.01_{sp} (s, 1H, N=CH), 7.85 (d, *J* = 15.4 Hz, 1H, =CH), 7.48 (m, 3H), 7.37 (m, 6H), 7.27_{ap}, 7.08_{sp} (d, *J* = 7.7 Hz, 1H, HAr), 6.95_{sp}, 6.85_{ap} (d, *J* = 3.5 Hz, 1H, HAr), 6.65_{sp}, 6.63_{ap} (dd, *J* = 3.5, 1.9, 1H, HAr), 6.50 (d, *J* = 15.4 Hz, 1H, HC=), 5.18_{sp}, 5.15_{ap} (s, 2H, -CH_2-).

^{13}C NMR (101 MHz, DMSO-d_6) δ 165.84_{sp}, 161.34_{ap} (C=O), 158.64_{ap}, 158.61_{sp} (C-O), 151.10_{sp}, 150.87_{ap} (C-O), 146.45_{ap}, 145.48_{sp} (CH Ar), 145.24_{ap}, 142.98_{sp} (N=CH), 136.96_{sp}, 136.90_{ap} (CAr), 135.77_{ap}, 135.57_{sp} (CAr), 130.02_{sp}, 129.93_{ap} (CH), 128.97 (CH), 128.45_{sp}, 128.42_{ap} (CH Ar, 2C), 127.85 (CH), 127.73_{sp}, 127.68_{ap} (CH Ar, 2C), 120.02_{ap}, 119.50_{sp} (CH), 117.27_{ap}, 116.81_{sp} (CH), 116.48_{sp}, 115.27_{ap} (CH), 114.81_{ap}, 114.06_{sp} (CH), 112.64_{sp}, 112.59_{ap} (CH), 112.47 (CH), 69.27 (CH_2).

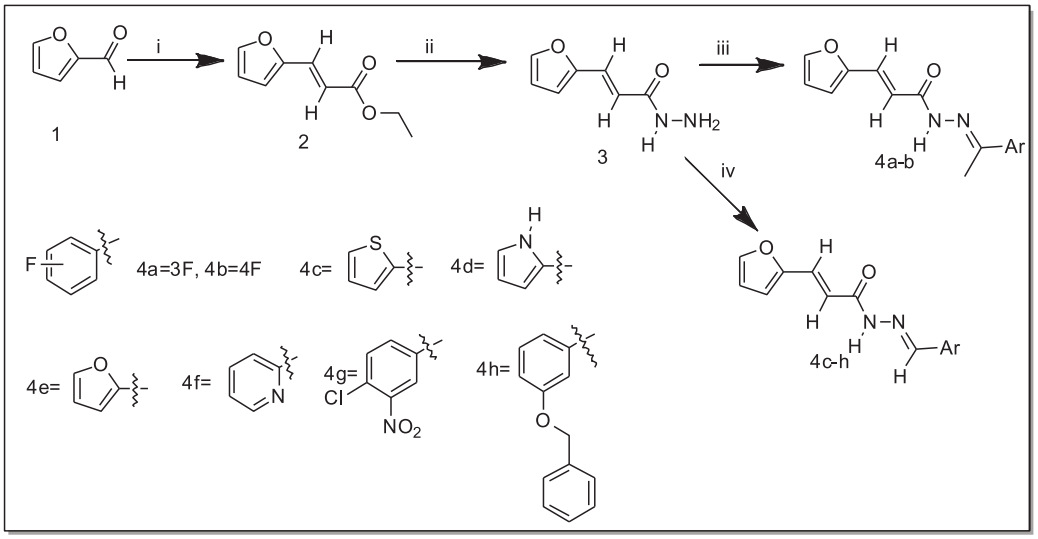
FT-IR (ATR) cm^{-1}: 3,200 (NH), 2,947.23 (N=CH), 2,931.80 (CH), 1,660.71 (C=O), 1,620.21 (C=N), 1,328.49 (C-O-C), 1,016.49 (N-N), 972.12 (HC=CH).

RESULTS AND DISCUSSION

Chemical synthesis

The N-acylhydrazone derivatives (**4a–h**) were obtained through a three-step synthetic pathway starting from furan-2-carbaldehyde (**1**). The initial step involved the addition of ethyl chloroacetate to aldehyde (**1**) in the presence of triphenylphosphine (PPh_3) under basic conditions, employing the Wittig reaction (*El-Batta et al., 2007*). Consequently, the ester (**2**) was obtained with a yield of 77%. Subsequently, the ester (**2**) reacted with hydrazine monohydrate (H_2N-NH_2.H_2O) in ethanol at room temperature to yield the corresponding hydrazide (**3**) with a yield of 52%. Finally, a series of acrylohydrazide derivatives (**4a–h**) was synthesized with yields ranging from 23% to 96% (Table 1). This was achieved by condensing hydrazide (**3**) with various derivatives of benzaldehyde and acetophenone in ethanol at room temperature for 3 h, in the presence of a catalytic amount of concentrated hydrochloric acid (HCl) (Scheme 1).

The newly synthesized compounds (**4a–h**) were fully characterized using various analytical methods, notably NMR, which revealed the presence of a dynamic equilibrium between two isomers for each compound in the N-acrylohydrazone series (**4a–h**). The results of this stereochemical study will be discussed in the following section.



Scheme 1 **Synthesis of acrylohydrazide derivatives.** i. PPh_3, ethyl chloroacetate, $NaHCO_3$, ii. H_2NNH_2, EtOH, iii. EtOH, HCl, acetophenone derivatives, iv. EtOH, HCl, aldehydes.
Full-size DOI: 10.7717/peerj-ochem.11/scheme-1

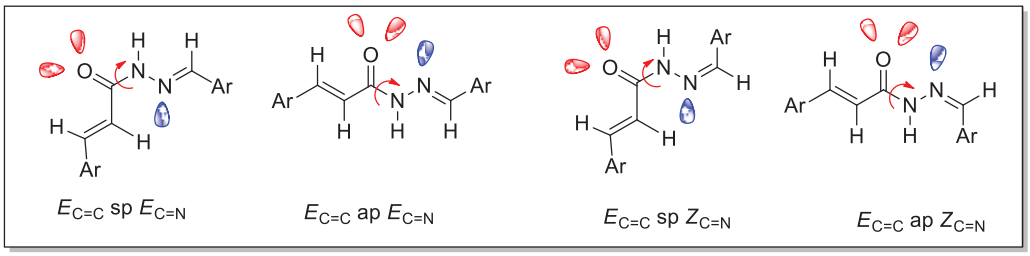
Spectral analysis

The examination of the ^{1}H NMR spectrum for compound (**2**) reveals the presence of two distinct *E* and *Z* isomers, with an approximate ratio of 88/12 (*E*/*Z*). Each isomer exhibits characteristic doublet signals. In the predominant E isomer, a doublet is observed at 6.27 ppm, corresponding to the alpha (α) proton adjacent to the carbonyl CO, while another doublet is detected at 7.38 ppm, indicative of the beta (β) proton. Conversely, in the minor *Z* isomer, the alpha (α) proton resonates at 5.69 ppm, while the beta (β) proton is discerned at 7.73 ppm.

The pronounced mesomeric attractive effect between the alkene and the carbonyl bonds results in notable deshielding of the beta (β) proton in the vicinity of the carbonyl. Furthermore, a quadruplet, integrating for two protons around 4.18 ppm, and a triplet, integrating for three protons at 1.26 ppm, are evident, corroborating the presence of the methyl group of the ester function. In the ^{13}C NMR spectrum, discernible peaks at 167 ppm (*E* isomer) and 165.96 ppm (*Z* isomer) confirm the presence of the carbonyl carbon in both forms.

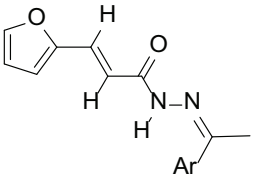
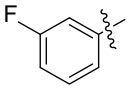
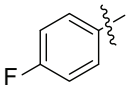
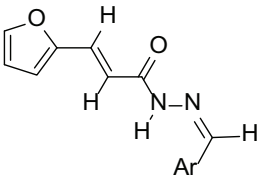
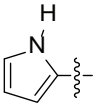
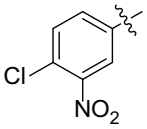
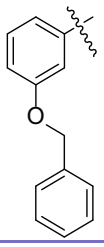
The scrutiny of the ^{1}H NMR spectrum for compound (**3**) reveals the disappearance of signals attributed to the ethoxy group (OCH_2CH_3) and the emergence of broad singlets at 4.05 and 7.19 ppm. These singlets correspond to the NH protons of the NH_2 and C(O)-NH groups, respectively. Even if compound (**2**) was initially utilized, consisting of a mixture of *E* and *Z* isomers in an 88/12 ratio, only the *E* isomer was successfully isolated for compound (**3**).

The ^{1}H NMR spectra of the ultimate compounds (**4a–h**), acquired in DMSO-d_6, exhibit a marked duplication of signals pertaining to three neighboring atom groups within the amide fragment: NH, N=CH or N=C(CH_3), and CH=CH(CO) (Figs. 1–4). Table 2 provides the chemical shift data for the duplicated proton signals of the amide function, as



Scheme 2 **The various possible conformers of the acrylohydrazides derivatives.**
Full-size DOI: 10.7717/peerj-ochem.11/scheme-2

Table 1 **Acrylohydrazide derivatives obtained.**

Compounds	Structure	Ar	Yield (%)
4a			54
4b			41
4c			23
4d			48
4e			56
4f			96
4g			70
4h			40

well as the azomethine (N=CH) and azoethylidine (N=C(CH_3)) fragments. Additionally, a systematic duplication of signals is discernible in the ^{13}C NMR spectra for all compounds (**4a–h**). Table 3 compiles the chemical shift values for the duplicated carbons of the amide carbonyl function, and the N=CH and N=C(CH_3) fragments.

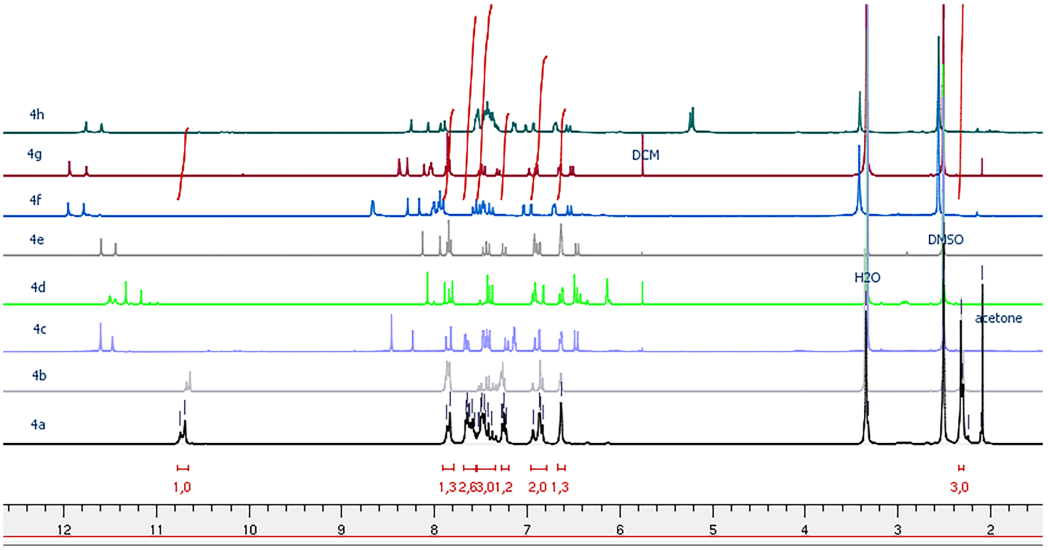


Figure 1 **^{1}H NMR spectra of compounds 4a–h.** Full-size DOI: 10.7717/peerj-ochem.11/fig-1

Comparison of the ^{1}H NMR spectra (Fig. 3) for compound (**4h**) recorded in deuterated chloroform ($CDCl_3$) and deuterated dimethyl sulfoxide (DMSO-d_6) reveals the presence of two conformers characterized by the splitting of the NH function signal, one at 11.70 ppm and the other at 11.53 ppm in the DMSO-d_6 spectrum. In contrast, the $CDCl_3$ spectrum indicates a singular conformer with the NH function signal appearing at 9.33 ppm. Notably, the chemical shift of NH is reduced in the $CDCl_3$ spectrum compared to the DMSO-d_6 spectrum. This observation aligns with the findings reported by *Palla et al. (1986)*, suggesting that the marginal chemical shifts observed in the $CDCl_3$ spectra may be attributed to intramolecular hydrogen bonding.

Comparative analysis of the ^{1}H NMR spectra for compounds **4b** and **4g**, recorded in deuterated methanol (Methanol-d_4) and DMSO-d_6 (Figs. 2 and 4) indicates signal duplication for various protons. However, the NH signal is absent in the spectrum recorded in Methanol-d_4, and the duplicated signals exhibit lower intensity compared to the ^{1}H NMR spectrum recorded in DMSO-d_6. The duplicated NH signals manifest at 11.75 ppm and 11.93 ppm for compound (**4g**) and 10.63 ppm and 10.67 ppm for compound (**4b**). The absence of the NH signal in the spectra recorded in Methanol-d_4 may be ascribed to proton exchange with deuterium from the solvent.

Stereochemical analysis of Acrylohydrazide derivatives (4a–h)

The duplication of characteristic signals for NH and N=CH groups observed in both ^{1}H and ^{13}C NMR spectra (Tables 2 and 4) of the acrylohydrazides (compounds **4a–h**) indicates the presence of two distinct isomers. Considering the structure of acrylohydrazide, this signal duplication could be attributed to the geometric stereoisomerism (*Z* or *E*) of the azomethine (N=CH) or azoethylidine (N=C(CH_3)) fragment, or the ethylenic (CH=CH) group, or to a slow rotation around the N-N or N-C=O bond (Scheme 2).

Concerning the geometric stereoisomerism of the ethylenic fragment in acrylohydrazides, they all exhibit the $E_{c=c}$ configuration confirmed by the coupling

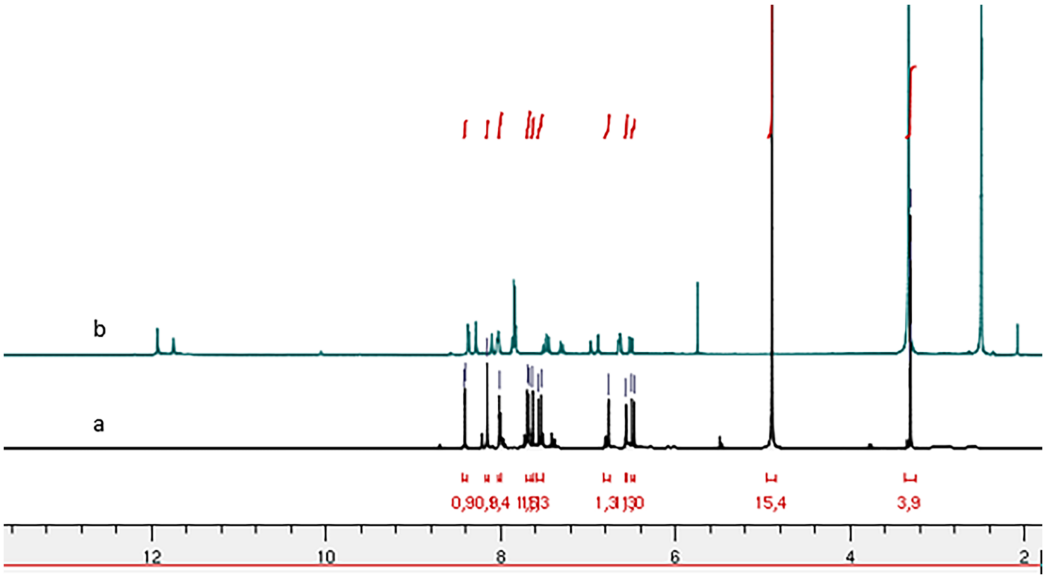


Figure 2 ^{1}H NMR spectrum of compound 4g: (A) in Methanol-d_4 and (B) in DMSO-d6.
Full-size DOI: 10.7717/peerj-ochem.11/fig-2

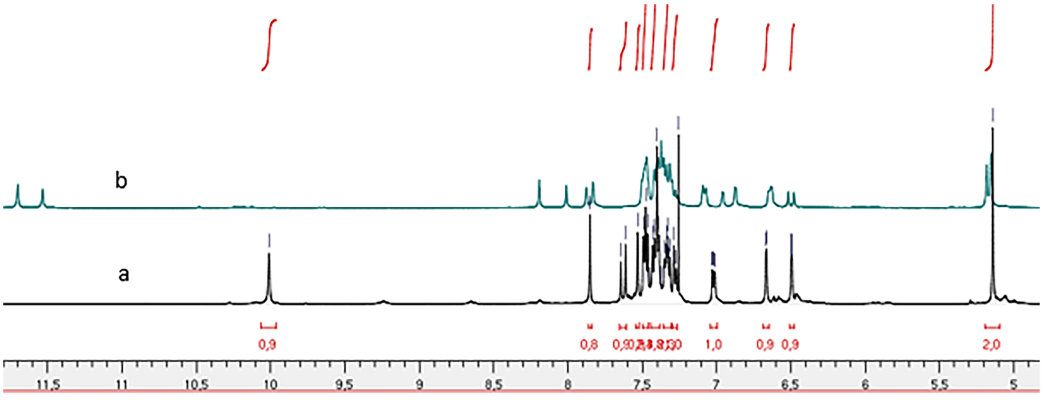


Figure 3 ^{1}H NMR spectrum of compound 4h: (A) in $CDCl_3$ and (B) in DMSO-d_6.
Full-size DOI: 10.7717/peerj-ochem.11/fig-3

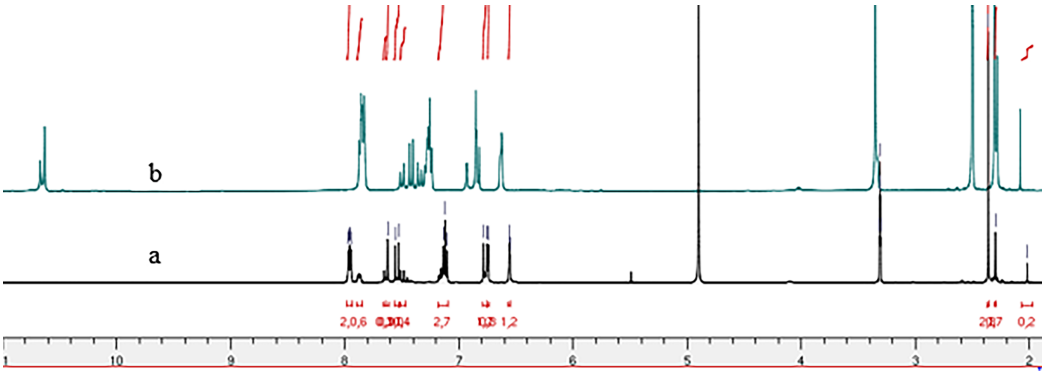


Figure 4 ^{1}H NMR spectrum of compound 4b: (A) in methanol-d_3 et (B) in DMSO-d_6.
Full-size DOI: 10.7717/peerj-ochem.11/fig-4

Table 2 Chemical shift of protons in compounds 4a–h.

Chemical shift δ (ppm)							
	C(O)-NH		N=C(CH_3) or N=CH		Ar	Ratio (%)	
Compounds	*Anti*	*Syn*	*Anti*	*Syn*		*Anti*	*Syn*
4a	10.74	10.69	2.29	2.31	3-F-C_6H_4	38	62
4b	10.67	10.63	2.28	2.30	4-F- C_6H_4	38	62
4c	11.60	11.47	8.46	8.23	C_4H_3S	62	38
4d	11.33	11.16	8.07	7.88	C_4H_4N	62	38
4e	11.59	11.43	8.12	7.93	C_4H_3O	53	47
4f	11.89	11.72	8.22	8.10	C_5H_4N	53	47
4g	11.93	11.74	8.29	8.10	3-Cl-4-NO_2- C_6H_3	56	44
4h	11.70	11.53	8.19	8.01	3-O-CH_2-C_6H_5	56	44

Table 3 Proportion of ratios relative to C(O)-NH in compounds 4a–h.

Compounds	Ratio (%) relative to C(O)-NH		Proportion
	Anti	*Syn*	
4a	38	62	1:1.6
4b	38	62	1:1.6
4c	62	38	1.6:1
4d	62	38	1.6:1
4e	53	47	1.1:1
4f	53	47	1.1:1
4g	56	44	1.3:1
4h	56	44	1.3:1

Table 4 Chemical shift of carbon in compounds 4a–h.

Chemical shift δ ppm (^{13}C)					
	C(O)-NH		N=C(CH_3) or N=CH		Ar
Compounds	*Anti*	*Syn*	*Anti*	*Syn*	
4a	164.43	168.38	13.62	14.45	3-F-C_6H_4
4b	165.77	169.74	13.66	14.51	4-F- C_6H_4
4c	161.18	165.49	141.79	138.92	C_4H_3S
4d	160.75	165.36	139.72	136.09	C_4H_4N
4e	161.27	165.68	136.41	133.14	C_4H_3O
4f	165.42	169.30	–	–	C_5H_4N
4g	161.63	166.09	143.16	140.00	3-Cl-4-NO_2- C_6H_3
4h	161.39	165.84	–	–	3-O-CH_2-C_6H_5

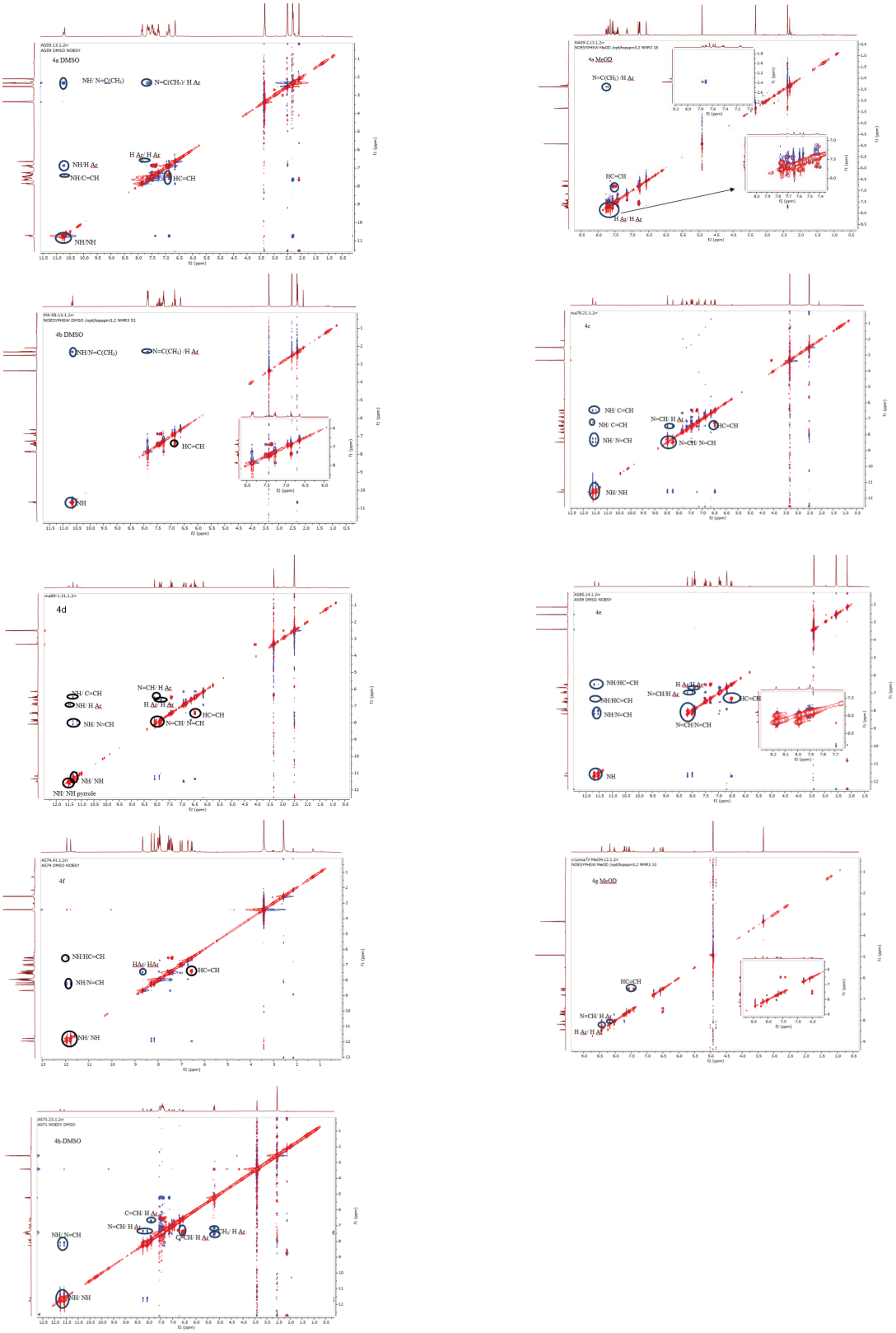


Figure 5 **NOESY spectra in DMSO-d_6 of compounds 4a–f, 4h.** Full-size DOI: 10.7717/peerj-ochem.11/fig-5

Table 5 Stereoisomerism of the obtained compounds (4a–h).

Compounds	Stereoisomerism
4a	Ec=c sp $E_{C=N}$
4b	Ec=c sp $E_{C=N}$
4c	Ec=c ap $E_{C=N}$
4d	Ec=c ap $E_{C=N}$
4e	Ec=c ap $E_{C=N}$
4f	Ec=c ap $E_{C=N}$
4g	Ec=c ap $E_{C=N}$
4h	Ec=c ap $E_{C=N}$

constant (J = 15.40–15.90 Hz) of the ethylenic proton signals ranging between 6.46 ppm and 7.62 ppm.

Due to the assembly of amide and imine functionalities, acrylohydrazides can exist as stereoisomers with a C=N double bond (geometric configurations *Z* or *E*) and as *syn*/*anti*periplanar conformers around the amide (C(O)-NH) bond (Scheme 2). In the ^{1}H NMR spectra, the maximum intensity difference for compounds (**4a–h**) confirms that both conformers were obtained with different ratios (Table 2).

Analysis of the various ratios among all possible conformers reveals that the *syn*periplanar (sp) conformer is predominant for compounds **4a–b**, while the *anti*periplanar (ap) conformer is favored for compounds **4c–d**. For compounds **4e–h**, the *syn*/*anti*-periplanar conformers are nearly in equal proportions.

Palla et al.'s *(1986)* previous work has demonstrated that the *Z* isomer of acrylohydrazides is characterized by a singlet around 14 ppm corresponding to the NH proton. The absence of a duplicated singlet around this chemical shift in the proton spectra (Fig. 1) suggests the absence of the *Z*(C=N) isomer. However, the correlation between the NH proton and the azomethine fragment in the NOESY spectrum of compounds **4h** and **4f** (Fig. 5) confirms the presence of the *E*(C=N) isomer, according to the findings of *Palla et al. (1986)*. Regarding compounds **4a–f** and **4h**, the emergence of a weak correlation between the NH proton and azomethine (N=CH) and azoethylidine (N=C(CH_3)) fragments in the NOESY spectrum (Fig. 2) confirms also the presence of the *E*(C=N) isomer. Table 3 summarizes the calculated ratios relative to the duplicated NH signal. These results indicate that the *syn* conformer is predominant for compounds **4a–b** (thus, the stereochemistry *E*c=c sp $E_{C=N}$), while for compounds **4c–h**, the *anti* conformer is favored (Table 5). It is noteworthy that the proportion of the *anti* conformer decreases in favor of the *syn* conformer when transitioning from compounds **4c–d** to **4g–h** and from **4g–h** to **4e–f**.

Comparing the ratios of different conformers between compounds **4c–h** and **4a–b** reveals a reversal of the *anti* conformer in favor of the *syn* conformer when transitioning from compounds **4c–h** to **4a–b**. This inversion of conformers could be explained by the

bulkier nature of the azoethylidine fragment (N=C(CH_3)) compared to the azomethine fragment (N=CH).

CONCLUSION

This study successfully synthesized eight new derivatives of (*E*)3-furan-2-yl acrylohydrazide. The obtained compounds were comprehensively characterized through spectroscopic analyses, including 1D and 2D NMR, as well as high-resolution mass spectrometry.

The analysis of ^{1}H NMR data unveiled significant conformational diversity among the synthesized compounds. Compounds 4a–b demonstrated an *E*c=c sp $E_{C=N}$ configuration, while all other compounds exhibited an *E*c=c ap $E_{C=N}$ configuration. Notably, compounds **4g** displayed an *E*c=c ap configuration and likely $E_{C=N}$, although confirmation of the latter was challenging.

Ultimately, this research contributes to the continuum of prior investigations on N-acylhydrazones, emphasizing the stability of (*E*)-3-(furan-2-yl) acrylohydrazides. This understanding of their conformation properties opens promising avenues for future applications in diverse fields, such as the design of new materials.

In our research, we have developed N-acylhydrazones featuring diverse passivation groups. The incorporation of these groups has the potential to significantly influence their utility in solar energy applications, and also could exhibit promising bioactive properties. Our preliminary studies with our synthesis compounds have demonstrated their efficacy in inhibiting the growth of *S. aureus*, motivating further investigation into their potential as treatments for methicillin-resistant *S. aureus* infections.

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Competing Interests

The authors declare that they have no competing interests.

Author Contributions

- Penayori Marie-Aimée Coulibaly conceived and designed the experiments, performed the experiments, analyzed the data, performed the computation work, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Souleymane Coulibaly conceived and designed the experiments, performed the experiments, analyzed the data, performed the computation work, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Evrard Ablo analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Seiny Roger N'Dri performed the computation work, authored or reviewed drafts of the article, and approved the final draft.
- Kassi Amian Brise Benjamin conceived and designed the experiments, prepared figures and/or tables, supervision, and approved the final draft.
- Drissa Sissouma analyzed the data, prepared figures and/or tables, supervision, and approved the final draft.
- Adjou Ané conceived and designed the experiments, performed the computation work, prepared figures and/or tables, and approved the final draft.

Data Availability

The following information was supplied regarding data availability:

The data is available at Zenodo: Coulibaly, S. (2024). Acrylohydrazides derivatives NMR for PeerJ [Data set]. Zenodo. https://doi.org/10.5281/zenodo.11199900.

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