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New efficient synthesis, spectroscopic characterization, and X-ray analysis of novel β -enaminocarboxamide derivatives

Yousra Ouafa Bouone¹ · Abdeslem Bouzina¹ · Nour-Eddine Aouf¹ · Malika Ibrahim-Ouali²

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Abstract

A new series of β -enaminocarboxamide was synthesized via the addition of chlorosulfonyl isocyanate to β -enaminones. The prepared intermediates were converted to corresponding β -enaminocarboxamides by removal of the chlorosulfonyl group using methanol. The resulting compounds were obtained in excellent yields in the range of (80–92%) and were characterized by ¹H, ¹³C, HMBC, HSQC NMR spectroscopy, and IR spectroscopy as well as elemental analysis. ¹H-NMR spectrum showed a non-equivalence of the primary amide protons which was due to H-bonding. β -enaminocarboxamide **5h** was obtained as a crystal and was subjected to X-ray analysis. Results showed that **5h** crystallizes in the monoclinic crystal system with C2/c space group and the ORTEP confirmed the presence of intramolecular H-bonds.

Keywords β -Enaminocarboxamide · β -Enaminone · Chlorosulfonyl isocyanate · Carboxamidation · Crystallographic study

Introduction

β -enaminone is an enamine linked to a carbonyl group that can be obtained through the condensation of an amine with a β -dicarbonyl compound [1]. Enaminones are recognized for their high reactivity related to their special structure containing the conjugated system N=C–C=O that combines both the nucleophilicity of the enamine group with two electron-rich sites and the electrophilicity of the

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α,β -unsaturated ketone with two electron-deficient sites. That is what made them very useful as intermediates in the synthesis of acyclic, cyclic, and heterocyclic systems [2–6]. Besides their use as precursors, β -enaminone-containing molecules have also been employed for medical purposes and remained very useful, showing several activities such as antibacterial [7], antitubercular [8], anti-inflammatory [9], anti-convulsant [10], antitumoral [11], antinociceptive [12], and antidepressant activities [13]. More recently, they have been identified as non-classical inhibitors of carbonic anhydrase [14] (Fig. 1).

On the other hand, amide-based compounds represent an extensive class of molecules known for their applications in various fields. Amide group derivatives have been widely reported in the literature for their uses in synthesis as intermediates leading to interesting products [15, 16], as well as in the industry as raw materials for lubricants, detergents, intensifiers of perfume, anti-block reagents, and color pigments for inks [17–19].

In addition, the amide group (CONH_2) has an important place in medicinal chemistry as an efficient pharmacophore and constitutes an integral part in many synthetic and natural active compounds [20–23]. These derivatives have shown interesting therapeutic properties such as: anticonvulsant [24], antitubercular [25], antimicrobial [26], analgesic and anti-inflammatory [27], insecticide [28], anticancer [29], fibrinolytic [30], nootropic [31], and antihypertensive [32] (Fig. 2).

In the literature, the introduction of the amide group into β -enaminones has been described and have interesting biological properties [33, 34]. In Fig. 3, the

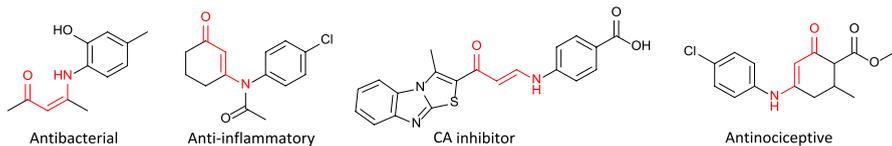


Fig. 1 Structure of diverse β -enaminone derivatives with interesting biological activities

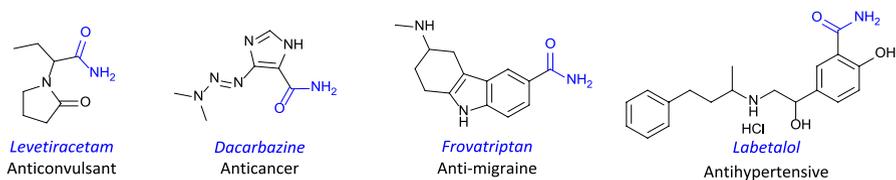


Fig. 2 Structure of diverse amide-based drugs

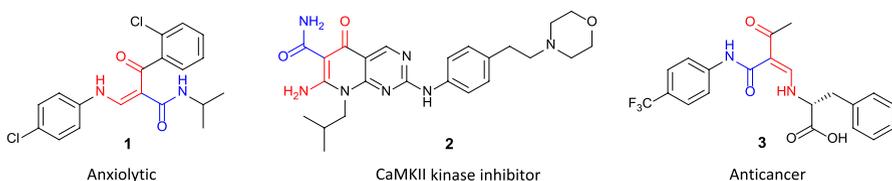


Fig. 3 Structure of diverse β -enaminone-amide group derivatives with interesting biological activities

structures of bifunctional (β -enaminone-amide group) compounds are depicted. Hogenkamp et al. [35]. demonstrated in their study that several analogues of β -enaminone-amide **1** are potent allosteric GABA_A receptors modulators, the N-isopropylamide **1** was orally active and showed central nervous system depressant effects including an anxiolytic activity. Enaminone compounds involving a primary amide group such as compound **2** were evaluated as Ca²⁺/calmodulin-dependent protein kinase II inhibitors which can be used in the treatment and prevention of several CaMKII-related pathologies especially cardiovascular diseases [36]. Subramamiam and coworkers have reported a series of amide substituted (*Z*)- β -enaminones as promising agents in the treatment of breast cancer, compound **3** was one of the most active derivatives against the human breast cancer cell line MCF-7 [37].

The development of new potentially active compounds containing important pharmacophores has nowadays become a necessity. Therefore, in the present work, our attention has been focused on the design, synthesis, and characterization of β -enaminone-amide derivatives, also called enaminocarboxamides.

Experimental

Chemicals and methods

All chemicals and solvents were purchased from Sigma-Aldrich and Thermo-Fisher Scientific and were used as received without any further purification. All reactions were monitored by TLC on silica Merck 60 F₂₅₄ percolated aluminum plates and were developed by spraying with ninhydrin solution (10% in EtOH). Proton nuclear magnetic resonance (¹H-NMR) spectra were recorded on a Brücker spectrometer at 400 MHz. Chemical shifts are reported in δ units (ppm) with TMS as reference (δ 0.00). All coupling constants (*J*) are reported in Hertz. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet), dd (doublet of doublet), dt (doublet of triplet). Carbon nuclear magnetic resonance (¹³C-NMR) spectra were recorded on a Brücker at 100 MHz. Chemical shifts are reported in δ units (ppm) relative to CDCl₃ or DMSO (δ 77.0 and 39.0–40.0). Infrared spectra were recorded on a PerkinElmer 600 spectrometer. Microanalysis spectra were performed by Elemental Analyser (Euro E.A. 3000-V3.0-single-2007), and the determined values were within the acceptable limits of the calculated values. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

Ultrasound assisted reactions were carried out using a FUNGILAB ultrasonic bath with a frequency of 40 kHz and a nominal power of 250 W. The reactions were carried out in an open glass tube (diameter 25 mm; thickness 1 mm; volume 20 mL).

Crystallography

Crystallographic data for the studied compound 2-((4-methoxyphenyl)amino)-6-oxocyclohex-1-ene-1-carboxamide (**5h**) were collected on a SuperNova, Dual, Cu at home/near, AtlasS2 four-circle diffractometer equipped with an AtlasS2 CCD

detector using Mo K α (micro-focus sealed tube) radiation ($\lambda = 0.71073 \text{ \AA}$), the crystal was kept at a temperature of 295 K during data collection.

The crystallographic data and experimental details for structural analysis are summarized in Table 1. The reported structure was solved with the SHELXT-2014/5 [38] solution program by Intrinsic Phasing with Olex2 [39] as the graphical interface. The model was refined with SHELXL-2018/3 [40] using full matrix least-squares minimization on F^2 . All absorption corrections were performed with the CrysAlisPro 1.171.42.51a [41] using spherical harmonics implemented in SCALE3 ABSPACK scaling algorithm. Crystal structure visualization and construction of crystal packing diagrams were performed using Mercury 4.0 software [42].

CCDC Number: 2217011 contains the supplementary crystallographic data for compound **5h**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Typical experimental procedure for the synthesis of β -enaminones

The synthesis of β -enaminones was done according to the method described by Redjemia et al. [43].

In a glass tube (diameter 25 mm; thickness 1 mm; volume 20 mL) was taken a mixture of a dicarbonyl compound (1 mmol), an amine (1 mmol), and CuBr (0.05 mmol). The reaction mixture was subjected to the ultrasonication irradiation with a frequency of 40 kHz for appropriate time at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, EtOAc (5 mL) or DCM (5 mL) was added. The catalyst was recovered from the residue,

Table 1 Crystallographic data and refinement parameters of compound **5h**

Formula	C ₁₄ H ₁₆ N ₂ O ₃	Absorption coefficient (mm ⁻¹)	0.094
Formula weight (g.mol ⁻¹)	260.29	F(000)	1104.0
Crystal habit, color	Prism, colorless	Crystal size (mm)	0.4 × 0.18 × 0.14
Crystal system	Monoclinic	θ range for data collection (°)	2.160—32.400
Space group	C2/c	Reflections collected	33,156
<i>a</i> (Å)	14.2517(5)	Independent reflections	4531
<i>b</i> (Å)	9.7694(3)	R_{int}	0.0353
<i>c</i> (Å)	19.1925(7)	Number of parameters	182
α (°)	90	Goodness-of-fit on F^2	1.046
β (°)	100.784(4)	Final <i>R</i> indices [$I \geq 2\sigma(I)$]	$R_1 = 0.0578$, $wR_2 = 0.1570$
γ (°)	90	<i>R</i> indices [all data]	$R_1 = 0.0731$, $wR_2 = 0.1695$
Volume (Å ³)	2624.99(16)	Largest difference peak and hole (Å ³)	0.272, -0.260
<i>Z</i> , <i>Z'</i>	8, 0	CCDC deposition no	CCDC 2,217,011
Density (calculated) (g.cm ⁻³)	1.317		

and the filtrate was concentrated. A (1/1) mixture of diethyl ether and n-hexane was added to the reaction mixture, and pure product was crystallized to 6 °C overnight. The product was finally filtered and dried. This procedure was followed for the preparation of all the β -enaminones used in the synthesis of β -enaminocarboxamides.

Typical experimental procedure for the synthesis of β -enaminocarboxamides

A solution of β -enaminones (1 mmol) in anhydrous CH_2Cl_2 (5 mL) was added to a stirring solution of chlorosulfonyl isocyanate (CSI) (1.1 mmol) in (5 mL) of anhydrous CH_2Cl_2 at 0 °C dropwise over a period of 3 min. The solution was stirred at room temperature for less than 2 h, and then, 5 mL of methanol was added to the stirring mixture. The formation of the desired compound was monitored in TLC, silica gel; dichloromethane/methanol (94:06). The solution was concentrated in *vacuo*, and the residue was purified by silica gel column chromatography eluted with a (96:04) ratio of dichloromethane/methanol to give β -enaminocarboxamides in excellent yields.

6-oxo-2-(propylamino)cyclohex-1-ene-1-carboxamide (Table 2, Entry 5a)

White powder; 85% Yield; m.p=164–166 °C; R_f =0.34 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 94:06). IR (KBr, cm^{-1}) ν 3283.15, 2933.71, 1709.67, 1618.06, 1574.80, 1455.34, 1427.35; $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ =0.93 (t, 3H, J =7.4 Hz, $\text{CH}_2\text{-CH}_3$), 1.53–1.62 (m, 2H, $\text{CH}_2\text{-CH}_3$), 1.74–1.80 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}_2$), 2.27 (t, 2H, J =7.1 Hz, $\text{CH}_2\text{-C}$), 2.64 (t, 2H, J =6.3 Hz, $\text{CH}_2\text{-CO}$), 3.30 (q, 2H, J =7 Hz, $\text{CH}_2\text{-NH}$), 6.74 (bs, 1H, CO-NH^a), 9.50 (bs, 1H, CO-NH^b), 12.37 (s, 1H, NH); $^{13}\text{C-NMR}$ (101 MHz, DMSO-d_6): δ =11.16, 19.37, 22.20, 26.02, 37.29, 44.31, 98.07, 172.03, 173.61, 193.90. Anal. Calc. for $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_2$ C, 61.20; H, 8.22; N, 14.27; Found C, 61.27; H, 8.16; N, 14.23.

6-oxo-2-((1-phenylethyl)amino)cyclohex-1-ene-1-carboxamide (Table 2, Entry 5b)

Cristal 82% Yield; m.p=160–162 °C; R_f =0.37 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 94:06). IR (KBr, cm^{-1}) ν 3419.15, 3244.70, 2924.45, 1713.47, 1573.52, 1455.58; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ =1.28 (s, 3H, CH_3), 1.63 (s, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}_2$), 2.39 (s, 2H, $\text{CH}_2\text{-CH}_2\text{-C}$), 2.63 (d, 2H, J =14.9 Hz, $\text{CH}_2\text{-CH}_2\text{-CO}$), 4.78 (s, 1H, CH), 5.52 (bs, 1H, CO-NH^a), 7.29–7.40 (m, 5H, 5CH_{Ar}), 9.86 (bs, 1H, CO-NH^b), 12.76 (s, 1H, NH); $^{13}\text{C-NMR}$ (101 MHz, DMSO-d_6): δ =19.49, 24.79, 29.76, 37.73, 54.04, 101.07, 125.60, 127.80, 129.24, 142.01, 173.12, 173.50, 195.32. Anal. Calc. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2$ C, 69.74; H, 7.02; N, 10.84; Found C, 69.70; H, 7.07; N, 10.89.

2-(cyclohexylamino)-6-oxocyclohex-1-ene-1-carboxamide (Table 2, Entry 5c)

White powder 90% Yield; m.p=179–181 °C; R_f =0.46 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 94:06). IR (KBr, cm^{-1}) ν 3357.11, 2854.15, 1621.80, 1561.11, 1456.34; $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ =1.22–1.41 (m, 5H, $2\text{CH}_2\text{-CH}_2(\text{cyclohexyl})$), 1.51–1.55

Table 2 Physicochemical properties of synthesized β -enaminocarboxamides 5a–q

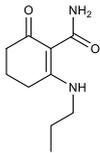
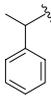
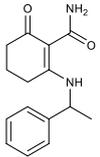
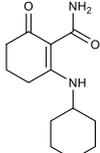
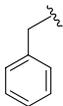
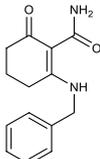
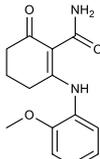
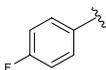
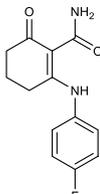
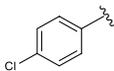
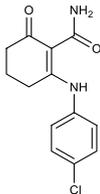
Entry	R ₁	R ₂	Structure	Yield %	m. p. °C
5a	H			85	164–166
5b	H			82	160–162
5c	H			90	179–181
5d	H			91	144–146
5e	H			86	215–217
5f	H			92	194–196
5g	H			84	214–216

Table 2 (continued)

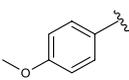
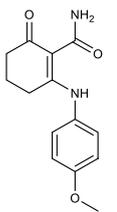
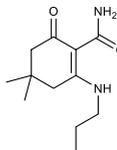
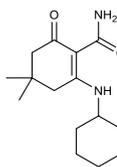
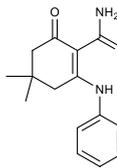
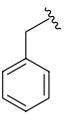
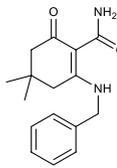
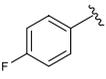
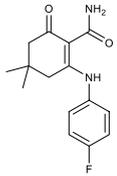
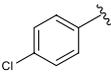
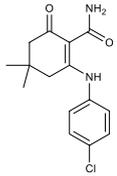
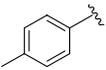
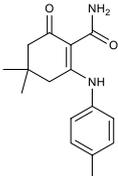
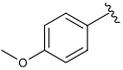
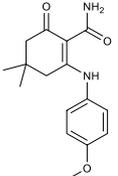
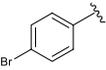
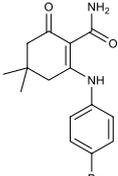
Entry	R ₁	R ₂	Structure	Yield %	m. p. °C
5h	H			80	186–188
5i	CH ₃			82	172–174
5j	CH ₃			80	166–168
5k	CH ₃			87	222–224
5l	CH ₃			85	136–138
5m	CH ₃			84	192–194
5n	CH ₃			81	214–216

Table 2 (continued)

Entry	R ₁	R ₂	Structure	Yield %	m. p. °C
5o	CH ₃			80	187–189
5p	CH ₃			88	144–146
5q	CH ₃			89	228–230

(m, 1H, CH₂(cyclohexyl)), 1.62–1.67 (m, 2H, CH₂–CH₂–CO), 1.73–1.84 (m, 4H, 2CH₂(cyclohexyl)), 2.26 (t, 2H, *J* = 8 Hz, CH₂–C), 2.68 (t, 2H, *J* = 6.3 Hz, CH₂–CO), 3.58–3.67 (m, 1H, CH–NH), 6.3 (bs, 1H, CO–NH^a), 7.72 (bs, 1H, CO–NH^b), 12.55 (d, 1H, *J* = 8.4 Hz, NH); ¹³C–NMR (101 MHz, DMSO-*d*₆): δ = 19.58, 23.62, 24.81, 25.83, 32.68, 37.37, 50.91, 97.91, 172.13, 172.34, 193.98. Anal. Calc. for C₁₃H₂₀N₂O₂ C, 66.07; H, 8.53; N, 11.85; Found: C, 66.13; H, 8.60; N, 11.79.

2-(benzylamino)-6-oxocyclohex-1-ene-1-carboxamide (Table 2, Entry 5d)

Yellow powder 91% Yield; m.p. = 144–146 °C; *R*_f = 0.44 (CH₂Cl₂/MeOH, 94:06). IR (KBr, cm⁻¹) ν 3297.75, 3034.85, 2936.18, 1612.17, 1563.23, 1454.43; ¹H–NMR (400 MHz, DMSO-*d*₆): δ = 1.74–1.80 (m, 2H, CH₂–CH₂–CH₂), 2.28 (t, 2H, *J* = 7.2 Hz, CH₂–C), 2.67 (t, 2H, *J* = 6.3 Hz, CH₂–CO), 4.62 (d, 2H, *J* = 5.7 Hz, CH₂–NH), 6.88 (1H, d, *J* = 5.0 Hz, CO–NH^a), 7.31–7.35 (m, 3H, 3CH_{Ar}), 7.38–7.42 (m, 2H, 2CH_{Ar}), 9.49 (d, 1H, *J* = 5.1 Hz, CO–NH^b), 12.64 (1H, s, NH); ¹³C–NMR (101 MHz, DMSO-*d*₆): δ = 19.34, 26.26, 37.27, 46.38, 98.63, 127.24, 127.48, 128.77, 137.36, 171.88, 173.78, 194.21. Anal. Calc. for C₁₄H₁₆N₂O₂ C, 68.83; H, 6.60; N, 11.47; Found: C, 68.80; H, 6.55; N, 11.51.

2-((2-methoxyphenyl)amino)-6-oxocyclohex-1-ene-1-carboxamide (Table 2, Entry 5e)

Brown powder 86% Yield; m.p. = 215–217 °C; *R*_f = 0.39 (CH₂Cl₂/MeOH, 94:06). IR (KBr, cm⁻¹) ν 3291.48, 2925.55, 1619.13, 1591.05, 1566.70, 1502.77, 1434.37; ¹H–NMR (400 MHz, DMSO-*d*₆): δ = 1.71–1.77 (m, 2H, CH₂–CH₂–CH₂), 2.35 (t,

2H, $J=6.5$ Hz, CH₂-C), 2.56 (t, 2H, $J=6.2$ Hz, CH₂-CO), 3.83 (s, 3H, O-CH₃), 7.00 (td, 1H, $J_1=7.6$, $J_2=1.3$ Hz, CH_{Ar}), 7.15 (dd, 2H, $J_1=8.3$, $J_2=1.3$ Hz, 2CH_{Ar}), 7.25–7.35 (m, 2H, 1CH_{Ar}, CO-NH^a), 9.5 (s, 1H, CO-NH^b), 13.92 (s, 1H, NH); ¹³C-NMR (101 MHz, DMSO-d₆): $\delta=19.89, 27.61, 37.67, 55.71, 99.49, 112.12, 120.47, 125.70, 126.56, 128.18, 153.21, 171.81, 172.93, 195.03$. Anal. Calc. for C₁₄H₁₆N₂O₃ C, 64.60; H, 6.20; N, 10.76; Found: C, 64.54; H, 6.16; N, 10.70.

2-((4-fluorophenyl)amino)-6-oxocyclohex-1-ene-1-carboxamide (Table 2, Entry 5f)

White powder 92% Yield; m.p.=194–196 °C; $R_f=0.25$ (CH₂Cl₂/MeOH, 94:06). IR (KBr, cm⁻¹) ν 3406.65, 3258.70, 1707.12, 1606.04, 1541.39, 1504.73; ¹H-NMR (400 MHz, CDCl₃): $\delta=1.88$ –1.94 (m, 2H, CH₂-CH₂-CH₂), 2.62 (t, 2H, $J=6.3$ Hz, CH₂-C), 2.72 (t, 2H, $J=6.4$ Hz, CH₂-CO), 6.97–7.22 (m, 5H, 4CH_{Ar}, CO-NH^a), 11.54 (s, 1H, CO-NH^b), 13.24 (s, 1H, NH); ¹³C-NMR (101 MHz, CDCl₃): $\delta=19.73, 28.61, 34.01, 94.45, 116.83, 117.06, 127.59, 127.68, 132.12, 172.13, 173.18, 196.79$. Anal. Calc. for C₁₃H₁₃FN₂O₂ C, 62.90; H, 5.28; N, 11.28; Found: C, 62.85; H, 5.20; N, 11.22.

2-((4-chlorophenyl)amino)-6-oxocyclohex-1-ene-1-carboxamide (Table 2, Entry 5g)

Yellow powder 84% Yield; m.p.=214–216 °C; $R_f=0.46$ (CH₂Cl₂/MeOH, 94:06). IR (KBr, cm⁻¹) ν 3303.24, 1620.03, 1551.41, 1489.38; ¹H-NMR (400 MHz, CDCl₃): $\delta=1.82$ –1.88 (m, 2H, CH₂-CH₂-CH₂), 2.46 (t, 2H, $J=6.8$ Hz, CH₂-C), 2.55 (t, 2H, $J=6$ Hz, CH₂-CO), 5.7 (bs, 1H, CO-NH^a), 7.08 (d, 2H, $J=8.8$ Hz, 2CH_{Ar}), 7.36 (d, 2H, $J=6.8$ Hz, 2CH_{Ar}), 9.97 (bs, 1H, CO-NH^b), 13.89 (s, 1H, NH); ¹³C-NMR (101 MHz, CDCl₃): $\delta=20.41, 28.69, 38.01, 98.89, 127.71, 129.68, 131.85, 136.37, 172.40, 173.58, 193.87$. Anal. Calc. for C₁₃H₁₃ClN₂O₂ C, 58.99; H, 4.95; N, 10.58; Found: C, 58.92; H, 4.99; N, 10.55.

2-((4-methoxyphenyl)amino)-6-oxocyclohex-1-ene-1-carboxamide (Table 2, Entry 5h)

Cristal 80% Yield; m.p.=186–188 °C; $R_f=0.44$ (CH₂Cl₂/MeOH, 94:06). IR (KBr, cm⁻¹) ν 3346.63, 3221.60, 2839.86, 1613.74, 1584.99, 1565.90, 1508.67, 1460.55; ¹H-NMR (400 MHz, CDCl₃): $\delta=1.79$ –1.86 (m, 2H, CH₂-CH₂-CH₂), 2.45 (t, 2H, $J=6$ Hz, CH₂-C), 2.51 (t, 2H, $J=6.3$ Hz, CH₂-CO), 3.60 (s, 3H, O-CH₃), 5.59 (bs, 1H, CO-NH^a), 6.89 (d, 2H, $J=8.8$ Hz, 2CH_{Ar}), 7.05 (d, 2H, $J=8.8$ Hz, 2CH_{Ar}), 9.16 (bs, 1H, CO-NH^b), 13.67 (s, 1H, NH); ¹³C-NMR (101 MHz, CDCl₃): $\delta=20.37, 28.63, 38.05, 55.62, 99.78, 114.66, 127.15, 130.20, 158.73, 172.66, 173.00, 195.72$. Anal. Calc. for C₁₄H₁₆N₂O₃ C, 64.60; H, 6.20; N, 10.76; Found: C, 64.54; H, 6.27; N, 10.80.

4,4-dimethyl-6-oxo-2-(propylamino)cyclohex-1-ene-1-carboxamide (Table 2, Entry 5i)

Cristal 82% Yield; m.p.=172–174 °C; $R_f=0.39$ (CH₂Cl₂/MeOH, 94:06). IR (KBr, cm⁻¹) ν 3312.48, 2963.24, 1632.23, 1564.46, 1443.18; ¹H-NMR (400 MHz, CDCl₃): $\delta=0.99$ (t, 3H, $J=7.3$ Hz, CH₂-CH₃), 1.04 (s, 6H, 2CH₃), 1.61–1.71 (m,

2H, CH₂-CH₃), 2.27 (s, 2H, CH₂-C), 2.39 (s, 2H, CH₂-CO), 3.26 (q, 2H, $J=7.1$ Hz, CH₂-NH), 5.41 (bs, 1H, CO-NH^a), 9.82 (bs, 1H, CO-NH^b), 12.30 (s, 1H, NH); ¹³C-NMR (101 MHz, CDCl₃): $\delta=11.12, 22.22, 28.00, 30.27, 39.27, 44.71, 50.28, 95.63, 171.86, 172.39, 193.03$. Anal. Calc. for C₁₂H₂₀N₂O₂ C, 64.26; H, 8.99; N, 12.49; Found: C, 64.19; H, 8.92; N, 12.55.

2-(cyclohexylamino)-4,4-dimethyl-6-oxocyclohex-1-ene-1-carboxamide (Table 2, Entry 5j)

Powder 80% Yield; m.p.=166–168 °C; $R_f=0.32$ (CH₂Cl₂/MeOH, 94:06). IR (KBr, cm⁻¹) ν 3244.18, 3059.89, 2935.15, 1755.94, 1712.67, 1572.47, 1547.02, 1468.43, 1452.64; ¹H-NMR (400 MHz, CDCl₃): $\delta=1.07$ (s, 6H, 2CH₃), 1.23–1.33 (m, 3H, CH₂-CH₂(cyclohexyl)), 1.51–1.64 (m, 3H, CH₂-CH₂(cyclohexyl)), 1.73 (m, 2H, CH₂(cyclohexyl)), 1.78–1.93 (m, 2H, CH₂(cyclohexyl)), 2.53 (s, 2H, CH₂-C), 2.60 (s, 2H, CH₂-CO), 4.11 (q, 1H, $J=7$ Hz, CH-NH), 5.71 (bs, 1H, CO-NH^a), 7.84 (bs, 1H, CO-NH^b), 8.65 (bs, 1H, NH); ¹³C-NMR (101 MHz, CDCl₃): $\delta=14.89, 24.44, 24.79, 28.52, 31.58, 32.56, 43.32, 46.61, 53.50, 55.50, 63.73, 93.64, 171.12, 172.79, 186.70$. Anal. Calc. for C₁₅H₂₄N₂O₂ C, 68.15; H, 9.15; N, 10.60; Found: C, 68.10; H, 9.21; N, 10.67.

4,4-dimethyl-6-oxo-2-(phenylamino)cyclohex-1-ene-1-carboxamide (Table 2, Entry 5k)

White powder 87% Yield; m.p.=222–224 °C; $R_f=0.44$ (CH₂Cl₂/MeOH, 94:06). IR (KBr, cm⁻¹) ν 3295.90, 3065.79, 2945.99, 1615.50, 1552.84, 1494.15, 1434.52; ¹H-NMR (400 MHz, CDCl₃): $\delta=1.00$ (s, 6H, 2CH₃), 2.33 (s, 2H, CH₂-C), 2.41 (s, 2H, CH₂-CO), 5.62 (bs, 1H, CO-NH^a), 7.12–7.42 (m, 5H, 5CH_{Ar}), 9.78 (bs, 1H, CO-NH^b), 13.91 (s, 1H, NH); ¹³C-NMR (101 MHz, CDCl₃): $\delta=28.02, 31.22, 42.17, 51.60, 99.73, 126.16, 127.42, 129.60, 137.50, 171.31, 173.26, 193.24$. Anal. Calc. for C₁₅H₁₈N₂O₂ C, 69.74; H, 7.02; N, 10.84; Found: C, 69.79; H, 7.09; N, 10.90.

2-(benzylamino)-4,4-dimethyl-6-oxocyclohex-1-ene-1-carboxamide (Table 2, Entry 5l)

Cristal 85% Yield; m.p.=136–138 °C; $R_f=0.25$ (CH₂Cl₂/MeOH, 94:06). IR (KBr, cm⁻¹) ν 3220.96, 3030.97, 2956.32, 1733.09, 1707.80, 1590.07, 1494.75; ¹H-NMR (400 MHz, CDCl₃): $\delta=1.00$ (s, 6H, 2CH₃), 2.10 (s, 2H, CH₂-C), 2.18 (s, 2H, CH₂-CO), 4.19 (s, 2H, CH₂-NH), 5.12 (s, 1H, CO-NH^a), 5.49 (bs, 1H, CO-NH^b), 7.19–7.30 (m, 5H, 5CH_{Ar}). Anal. Calc. for C₁₆H₂₀N₂O₂ C, 70.56; H, 7.40; N, 10.29; Found: C, 70.61; H, 7.43; N, 10.33.

2-((4-fluorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-ene-1-carboxamide (Table 2, Entry 5m)

Yellow powder 84% Yield; m.p.=192–194 °C; $R_f=0.34$ (CH₂Cl₂/MeOH, 94:06). IR (KBr, cm⁻¹) ν 3313.14, 2952.60, 1692.51, 1615.88, 1601.67, 1551.65, 1507.25, 1435.64; ¹H-NMR (400 MHz, CDCl₃): $\delta=1.00$ (s, 6H, 2CH₃), 2.33 (s, 2H, CH₂-C),

2.35 (s, 2H, CH₂-CO), 5.73 (bs, 1H, CO-NH^a), 7.11 (d, 4H, *J*=6.8 Hz, 4CH_{Ar}), 9.80 (bs, 1H, CO-NH^b), 13.78 (s, 1H, NH); ¹³C-NMR (101 MHz, CDCl₃): δ=28.04, 31.22, 41.72, 51.53, 99.11, 116.48, 127.24, 127.99, 128.39, 130.64, 133.45, 134.05, 160.42, 162.88, 171.58, 172.65, 195.37. Anal. Calc. for C₁₅H₁₇FN₂O₂ C, 65.20; H, 6.20; N, 10.14; Found: C, 65.24; H, 6.26; N, 10.19.

2-((4-chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-ene-1-carboxamide (Table 2, Entry 5n)

White powder 81% Yield; m.p.=214–216 °C; *R_f*=0.39 (CH₂Cl₂/MeOH, 94:06). IR (KBr, cm⁻¹) ν 3375.77, 3344.35, 3206.22, 2870.05, 1633.35, 1541.56, 1491.96, 1437.79; ¹H-NMR (400 MHz, CDCl₃): δ=1.00 (s, 6H, 2CH₃), 2.33 (s, 2H, CH₂-C), 2.38 (s, 2H, CH₂-CO), 5.51 (bs, 1H, CO-NH^a), 7.05–7.09 (m, 2H, 2CH_{Ar}), 7.36–7.39 (m, 2H, 2CH_{Ar}), 10.06 (bs, 1H, CO-NH^b), 13.92 (s, 1H, NH); ¹³C-NMR (101 MHz, CDCl₃): δ=28.03, 31.29, 41.75, 51.54, 99.33, 127.43, 129.79, 133.16, 136.05, 171.11, 172.39, 195.34. Anal. Calc. for C₁₅H₁₇ClN₂O₂ C, 61.54; H, 5.85; N, 9.57; Found: C, 61.49; H, 5.90; N, 9.51.

4,4-dimethyl-6-oxo-2-(*p*-tolylamino)cyclohex-1-ene-1-carboxamide (Table 2, Entry 5o)

Yellow powder 80% Yield; m.p. 187–189 °C; *R_f*=0.41 (CH₂Cl₂/MeOH, 94:06). IR (KBr, cm⁻¹) ν 3377.54, 3347.54, 3206.57, 3046.73, 2961.44, 1631.36, 1514.14, 1512.60, 1438.18; ¹H-NMR (400 MHz, CDCl₃): δ=0.99 (s, 6H, 2CH₃), 2.32 (s, 2H, CH₂-C), 2.37 (s, 3H, CH₃), 2.39 (s, 2H, CH₂-CO), 5.47 (bs, 1H, CO-NH^a), 7.01 (d, 2H, *J*=4.3 Hz, 2CH_{Ar}), 7.20 (d, 2H, *J*=7.9 Hz, 2CH_{Ar}), 9.95 (bs, 1H, CO-NH^b), 13.81 (s, 1H, NH); ¹³C-NMR (101 MHz, CDCl₃): δ=21.24, 28.03, 31.18, 41.68, 51.59, 98.90, 125.97, 130.18, 134.82, 137.43, 171.53, 172.55, 195.23. Anal. Calc. for C₁₆H₂₀N₂O₂ C, 70.56; H, 7.40; N, 10.29; Found: C, 70.50; H, 7.45; N, 10.34.

2-((4-methoxyphenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-ene-1-carboxamide (Table 2, Entry 5p)

Powder 88% Yield; m.p.=144–146 °C; *R_f*=0.53 (CH₂Cl₂/MeOH, 94:06). IR (KBr, cm⁻¹) ν 3335.32, 2937.94, 1617.08, 1554.53, 1432.68; ¹H-NMR (400 MHz, CDCl₃): δ=0.98 (s, 6H, 2CH₃), 2.31 (s, 2H, CH₂-C), 2.35 (s, 2H, CH₂-CO), 3.82 (s, 3H, O-CH₃), 5.53 (bs, 1H, CO-NH^a), 6.89–6.93 (m, 2H, 2CH_{Ar}), 7.02–7.06 (m, 2H, 2CH_{Ar}), 9.87 (bs, 1H, CO-NH^b), 13.69 (s, 1H, NH); ¹³C-NMR (101 MHz, CDCl₃): δ=27.41, 31.11, 41.05, 52.01, 54.50, 98.80, 115.83, 126.43, 129.29, 159.56, 171.82, 172.95, 195.55. Anal. Calc. for C₁₆H₂₀N₂O₃ C, 66.65; H, 6.99; N, 9.72; Found: C, 66.60; H, 6.93; N, 9.69.

2-((4-bromophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-ene-1-carboxamide (Table 2, Entry 5q)

Powder 89% Yield; m.p.=228–230 °C; *R_f*=0.43 (CH₂Cl₂/MeOH, 94:06). IR (KBr, cm⁻¹) ν 3345.77, 3210.23, 2958.32, 1709.61, 1634.80, 1566.89, 1492.92, 1437.85;

$^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta=0.99$ (s, 6H, 2CH_3), 2.32 (s, 2H, $\text{CH}_2\text{-C}$), 2.34 (s, 2H, $\text{CH}_2\text{-CO}$), 5.54 (bs, 1H, CO-NH^a), 7.09 (d, 2H, $J=1.1$ Hz, 2CH_{Ar}), 7.10 (d, 2H, $J=1.1$ Hz, 2CH_{Ar}), 9.79 (bs, 1H, CO-NH^b), 13.86 (s, 1H, NH); $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): $\delta=28.00$, 31.18, 41.64, 51.51, 99.14, 116.41, 128.00, 133.48, 160.33, 162.80, 171.46, 172.43, 195.24. Anal. Calc. for $\text{C}_{15}\text{H}_{17}\text{BrN}_2\text{O}_2$ C, 53.43; H, 5.08; N, 8.31; Found: C, 53.39; H, 5.14; N, 8.36.

Results and discussion

Synthesis

The most reactive isocyanate, chlorosulfonyl isocyanate (CSI), has been extremely useful in organic and pharmaceutical synthesis processes due to the presence of two excellent electrophile sites: carbonyl of cyanate and chlorosulfonyl groups. The CSI is involved in the formation of a wide range of bioactive compounds, including lactams [44, 45], sulfonylureas [46], ureas [47, 48], carbonates [49], sulfamides [50, 51], and cyclosulfamides [52]. CSI is also used in carboxamidation reactions [53, 54].

In this work, and to satisfy the ongoing need for new synthetic potentially active compounds, we were interested to synthesis of a new series of β -enaminocarboxamides. The preparation of the enaminocarboxamide was carried out in two steps.

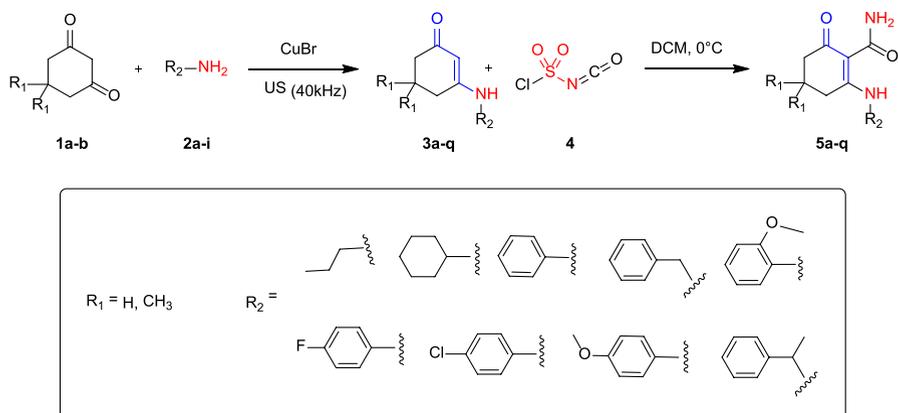
The first step; we have synthesized the various β -enaminones. The following method to realize this step is described by our group. Prepared β -enaminones were easily obtained in excellent yields via the green condensation of cyclohexanedione/dimedone and different primary amines under ultrasound irradiation (Scheme 1).

In the second step, the resulting β -enaminones were reacted with CSI in anhydrous dichloromethane as a solvent at 0 °C. The special conjugated ‘push–pull’ system of the β -enaminone played a key role in the obtention of the desired compounds since it has an increased nucleophilicity in C(β) of the olefin in which the CSI is added. Hence, CSI when reacted to β -enaminones gave N-chlorosulfonyl intermediates which were easily converted to the corresponding primary amide in the presence of methanol as a proton donor (Scheme 1).

A range of 17 new β -enaminocarboxamides **5a–q** obtained in excellent yields (80–92%) after purification through column chromatography. The results of these studies are presented in Table 2.

The structures of obtained compounds were determined using ^1H , ^{13}C , HSQC, and HMBC NMR techniques as well as IR spectroscopy, elemental analysis, and X-ray crystallography (Fig. 6).

IR spectrum showed bands of weak to moderate intensities in the range between 3419 and 3206 cm^{-1} which are representative of stretching absorption bands corresponding to N–H in both primary amide and secondary amine groups. Intense sharp bands appearing between 1755 and 1606 cm^{-1} showed the presence of carbonyl C=O of the primary amide and the α,β -unsaturated ketone functions. The conjugated double bond C=C absorbed at 1591–1541 cm^{-1} .



Scheme 1. Synthesis of β -enaminocarboxamides

In $^1\text{H-NMR}$ spectrum, signals for two protons of the primary amide group appeared separately in different regions of the spectrum as two singlets at 11.54–7.72 ppm and 7.31–5.41 ppm (Table 3). It can be assumed that the non-equivalence of primary amide protons in the $^1\text{H-NMR}$ spectrum is essentially due to the presence of hydrogen bonding which is consistent with the previously reported study of gorobets et al. [55] in which the authors suggested that a large chemical shifts differences ($\Delta\delta$) between each protons signals of a primary amide is related to the fact that one hydrogen is implicated in hydrogen bonding and these values could be employed as a numeric tool to estimate H-bonds strengths. Based on these observations, we calculated the $\Delta\delta$ values of amide protons for the synthesized β -enaminocarboxamides, the results are presented in Table 3. It can be noticeable that $\Delta\delta$ reached significant values on most compounds, the highest one was observed for compound **5n** (4.55 ppm). Signals of secondary amine protons have been localized in deshielded shifts of the spectrum 13.92–12.30 ppm, it appears that protons resonances for N–H linked to aromatic rings were more downfield than the ones linked to aliphatic chains (Fig. 4).

$^{13}\text{C-NMR}$ spectrum can also confirm our structures by the presence of the C=O (ketone) and C=O (amide) at 196.91–186.70 ppm and 173.78–171.79 ppm, respectively. And the double bond is characterized by two peaks at 101.07–93.64 ppm and 173.12–171.11 ppm.

Crystal characterization.

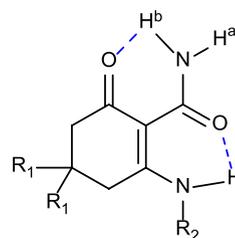
Since compound **5h** was obtained as suitable single crystals, it was further analyzed by X-ray diffraction methods for a complete structure elucidation.

Structural resolution revealed that the asymmetric unit consists of one molecule of 2-((4-methoxyphenyl)amino)-6-oxocyclohex-1-ene-1-carboxamide which crystallizes in the monoclinic crystal system with $C2/c$ space group (Table 1).

We have observed the presence of intramolecular interactions which consists of two H-bonds **N1-H1B...O1** and **N2-H2...O2** with lengths of 1.98 and 1.80 Å, respectively (Fig. 5). These results are in agreement with the studied $^1\text{H-NMR}$

Table 3 Chemical shifts of amides protons for synthesized compounds **5a–q**

Compounds	Chemical shifts δ (ppm)		
	H ^a	H ^b	$\Delta\delta$ (H ^b – H ^a)
5a	6.74	9.50	2.76
5b	5.52	9.86	4.34
5c	6.30	7.72	1.42
5d	6.87	9.48	2.61
5e	7.31	9.50	2.19
5f	7.07	11.54	4.47
5g	5.70	9.97	4.27
5h	5.59	9.16	3.57
5i	5.41	9.82	4.41
5j	5.71	7.84	2.09
5k	5.62	9.78	4.16
5l	5.12	5.49	0.37
5m	5.73	9.80	4.07
5n	5.51	10.06	4.55
5o	5.47	9.95	4.48
5p	5.53	9.87	4.34
5q	5.54	9.79	4.25

Fig. 4 Representation of intramolecular interactions and formed hydrogen bonds in the general structure of β -enamino-carboxamides

data above (Table 3). Two identical intermolecular H-bonds **N1–H1A...O2** with a length of 2.15 Å are formed between every two molecules of compound **5h** (Fig. 5) forming dimers which is a common phenomenon occurring in primary and secondary amides [56–58]. This combination engenders the formation of a ring with $R^2_2(8)$ graph-set motif. The crystal structure is also supported by other intermolecular interactions C–H... π and C–H...O (H...A distances are in the range of 2.68–2.86 Å) (Table 4). All these interactions link the components together and reinforce the cohesion of the structure.

Further, the present product adopts a non-planar conformation since the plane of the phenyl group is almost perpendicular to the plane of the substituted cyclohexenone with a dihedral angle equal to 113.35°. However, amide group and secondary amine group are both almost planar to the cyclohexenone ring

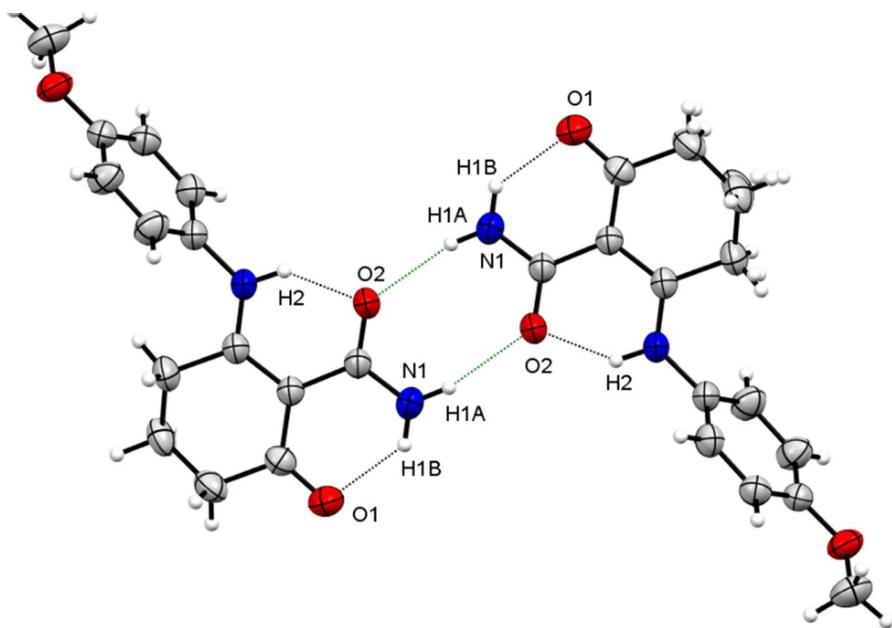


Fig. 5 View of the dimer structure of compound **5h** (intramolecular and intermolecular H-bonds are shown as black and green dashed sticks, respectively)

Table 4 Distances (Å) and angles (°) of hydrogen bond for compound **5h**

D-H...A	<i>d</i> (D-H)	<i>d</i> (H...A)	<i>d</i> (D-A)	D-H-A	Symmetry
N1-H1B...O1	0.860	1.980	2.648	139.89	<i>x, y, z</i>
N2-H2...O2	0.860	1.800	2.519	139.89	<i>x, y, z</i>
N1-H1A...O2	0.860	2.151	2.992	165.81	<i>x, y, z, 1-x, 2-y, 1-z</i>
C9-H9...O3	0.930	2.687	3.396(2)	133.7	<i>x, y, z, 1.5-x, -1/2+y, 1/2-z</i>
C13-H13...O1	0.930	2.685	3.600(2)	168.0	<i>x, y, z, 1-x, 1-y, 1-z</i>
C5A-H5AA...C11	0.970	2.854	3.692(2)	145.2	<i>x, y, z, -1/2+x, -1/2+y, z</i>
C12-H12...C7	0.930	2.794	3.665(2)	156.3	<i>x, y, z, -1/2+x, 1/2+y, z</i>
C5A-H5AB...C10	0.970	2.837	3.664(2)	143.6	<i>x, y, z, 1-x, y, 1/2-z</i>

with torsion angles of 0.17° and 2.63°, respectively. In the presence of H-bonding, it forms two planar six-membered pseudocycles with S(6) graph-set motifs (Fig. 5).

The ORTEP diagram of compound **5h** is shown in Fig. 6.

The arrangement of the molecules in the crystal is represented through crystal packing diagrams viewed along axis *a* and *b* appearing in Fig. 7.

Mechanistic proposal

A proposition of the reaction mechanism is presented in Scheme 2. The nitrogen doublet in the β -enaminone **1** activates the double bond by isomerization, and a nucleophilic attack occurs in the isocyanate functional group to give an amide attached to a chlorosulfonyl group **2**. This step is followed by reformation of the enamine moiety after being converted to imine in the previous attack. Then, methanol is added to intermediate **3** according to an addition–elimination mechanism in which compound **4** is formed. We obtained the β -enaminocarboxamide after liberation of SO_3 and MeCl molecules.

Conclusions

In summary, we developed an efficient route to easily synthesize of novel β -enaminocarboxamides by carboxamidation of β -enaminones using chlorosulfonyl isocyanate. We obtained the desired compounds in excellent yields within short time, avoiding high temperature and refluxing conditions. A spectral characterization of the structures was done using IR, ^1H , ^{13}C , HSQC and HMBC NMR spectroscopy as well as elemental analysis, the structure of compound **5h** was completely elucidated via single-crystal X-ray diffraction. Analysis of the results showed the tendency of primary amide protons to have different chemical shifts due to intramolecular H-bonds formation.

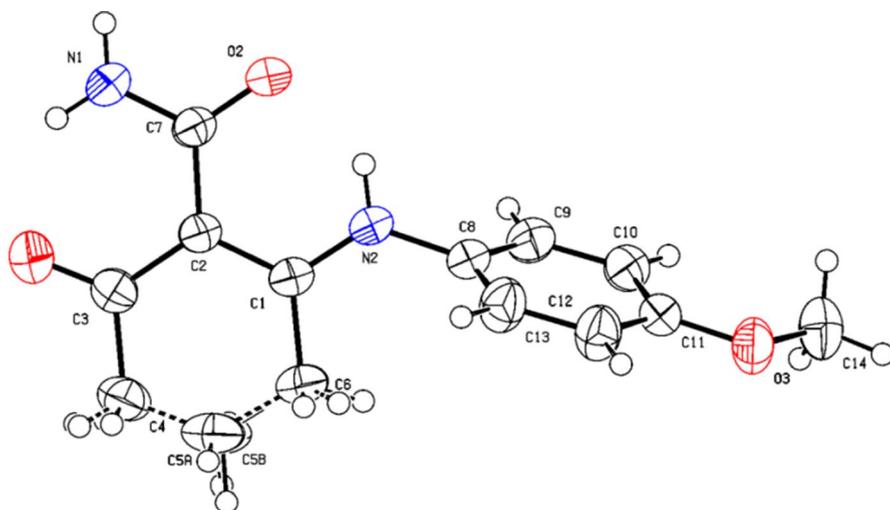
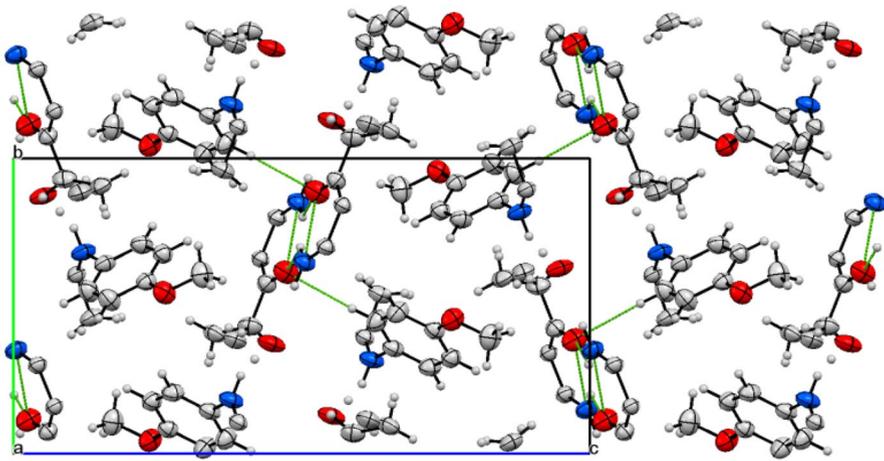
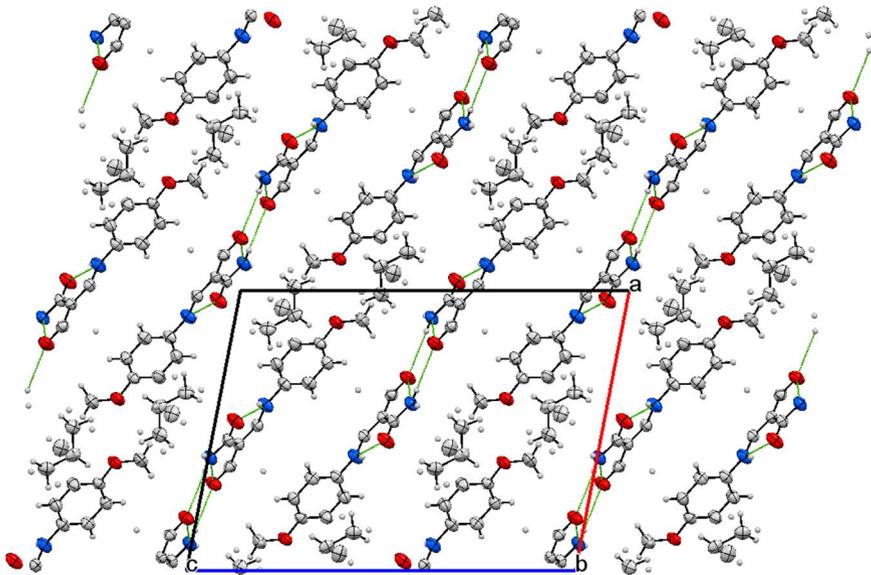


Fig. 6 The ORTEP diagram of compound **5h**, displacement ellipsoids are drawn at the 50% probability level. H atoms are represented as small spheres of arbitrary radius

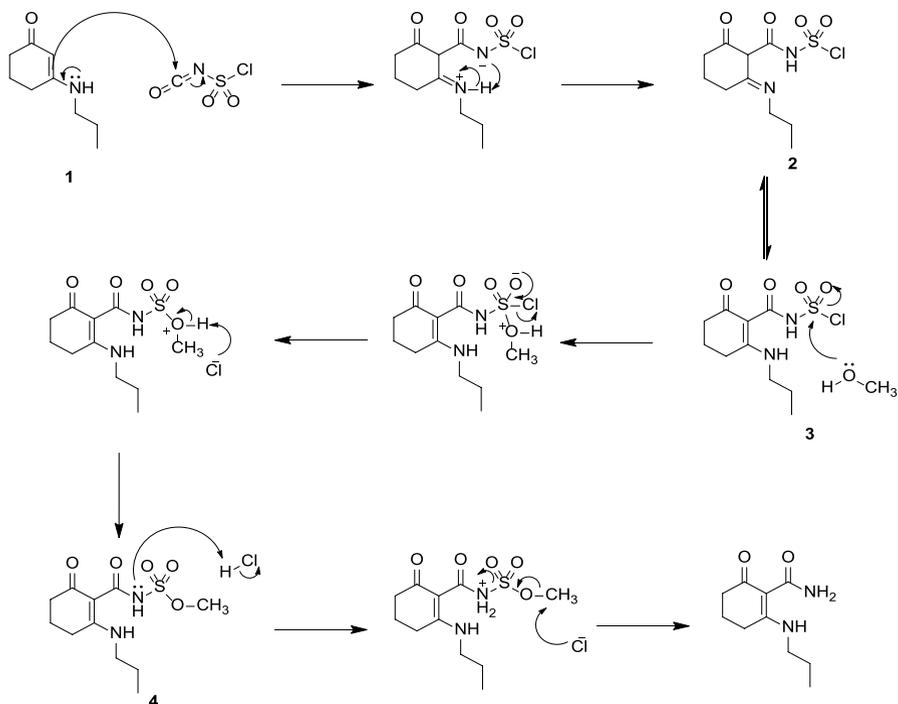


(a)



(b)

Fig. 7 Crystal packing of compound **5h** viewed along the *a* axis (a) and the *b* axis (b). H-bonds are shown as green dashed sticks



Scheme 2. Proposed mechanism for the formation of β -aminocarboxamides

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Author contributions YOB was involved in the synthesis and characterization of most compounds, contributing to the writing of the paper, AB was responsible for the idea, synthesis of some molecules, and manuscript writing, NEA assisted in the characterization of some compounds, contributing to the writing of the paper, and MIO analyzed/interpreted the crystallography data and provided a critical review of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declarations

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

Ethical approval Not applicable.

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