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Development of novel cyclohexanecarboxamido hydrazones: synthesis, characterization, and functional group tolerance

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Abstract: Cyclohexanecarboxamido hydrazones constitute a promising new class of therapeutic candidates exhibiting notable antioxidant, antibacterial, anticancer, and anti-inflammatory activities. In contrast to conventional hydrazones, these compounds combine the versatile hydrazone pharmacophore with a drug-like cyclohexyl amide moiety, a structural feature that may improve bioavailability, metabolic stability, and overall therapeutic performance. This study shows that, a series of sixteen novel derivatives. 2-(1-(4-chlorophenyl)cyclohexane-carboxamido)-N′-arylidenoacetohydrazides (**8a–8p**), were synthesized through a six-step pathway starting from 2-(4-chlorophenyl)acetic acid. The key hydrazide intermediate was condensed with various substituted aromatic aldehydes, affording the target hydrazones in good to excellent yields (72–86%). Structures of all compounds were confirmed by ^{1}H NMR, ^{13}C NMR, IR, LC-MS, and elemental analysis. The synthetic methodology demonstrated broad functional group tolerance, thus providing a reliable platform for generating structurally diverse analogues in consistently high yields.

Keywords: Hydrazones; substituted aldehydes; multistep synthesis; cyclohexane carboxamides.

1. Introduction

Nitrogen-containing compounds are prevalent in natural products and pharmacologically active substances, serving essential functions in various domains, including materials science, agrochemicals, and medicines.[1] Hydrazides are acknowledged as favoured scaffolds in diverse biological active molecules with synthetic versatility and exhibit a broad spectrum of applications in medicinal chemistry, biochemical processes, material chemistry, and the pharmaceutical industry.[2,3] These chemicals, notably hydrazides and hydrazones, constitute the structural foundation of various medicinal medicines, including Nifuroxazide[4], Isoniazid[5], Iproniazide, and Isocarboxazide. In recent years, significant advancements have been achieved in enhancing their synthetic utility and medicinal potential.

Hydrazides have become significant pharmacophores in the development of novel therapeutic drugs, demonstrating significant efficacy against diseases such as tuberculosis, viral and fungal infections, convulsions, depression, malaria, bacterial infections, and cancer (Figure 1).[6-14] The hydrazone functional group has attracted increased attention for combinatorial library design owing to its capacity to produce structurally varied and physiologically active compounds. Structural alterations of aromatic moieties within these frameworks have demonstrated improvements in biological efficacy, antioxidant capacity, and mitochondrial transport activities.

Hydrazone derivatives have attracted considerable attention from medicinal chemists and biologists due to their diverse biological activities. In this work, 2-(1-(4-chlorophenyl)cyclohexanecarboxamido)acetohydrazide was prepared from methyl 2-(4-

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chlorophenyl)acetate and subsequently coupled with various aromatic aldehydes to yield a series of hydrazone derivatives. Despite extensive research in this area, the development of new hydrazide-based compounds remains essential to address emerging therapeutic challenges. The present synthetic strategy represents a valuable approach for the preparation of novel, densely functionalized hydrazide derivatives with potential biological significance.

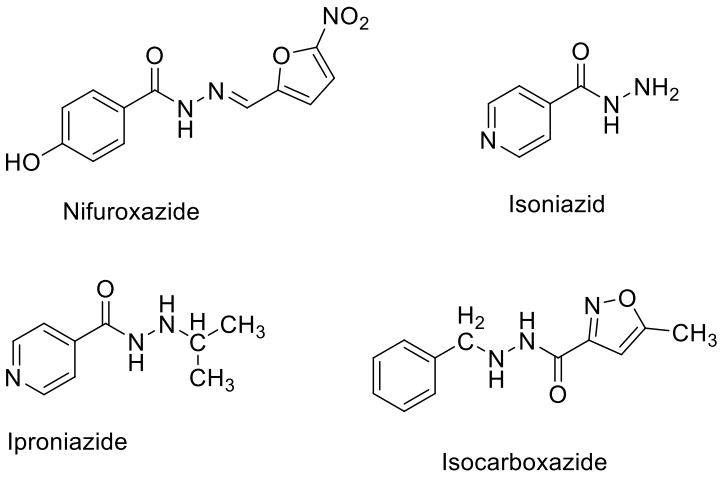


Figure 1. Pharmaceutically active hydrazone derivatives

Cyclohexanecarboxamido hydrazones possess substantial biological and pharmacological potential as next-generation antioxidant, antibacterial, anticancer, and anti-inflammatory agents. Distinct from standard hydrazones, these compounds integrate the versatile hydrazone pharmacophore with a drug-like cyclohexyl amide moiety, potentially enhancing bioavailability, metabolic stability, and therapeutic efficacy. By combining the cyclohexyl scaffold with hydrazone pharmacology, these molecules provide a promising foundation for new lead discovery. Moreover, cyclohexyl analogues may overcome microbial resistance mechanisms commonly associated with aromatic hydrazones. In continuation of our research on bioactive hydrazones,[15–17] we here in report the design and synthesis of a new series of cyclohexanecarboxamido-based acylhydrazones (**8a–8p**). The core scaffold, 2-(1-(4-chlorophenyl)cyclohexanecarboxamido)acetohydrazide, was synthesized and subsequently condensed with a range of aromatic aldehydes to generate structurally diverse derivatives. All compounds were thoroughly characterized, and the methodology was evaluated for its functional group tolerance.

2. Experimental

2.1. Materials and Methods

All reagents and solvents utilized in this work were of analytical grade and were from commercial suppliers (Merck). The melting points were determined with a Meltemp device and are uncorrected. Thin-layer chromatography (TLC) was conducted with Merck silica gel 60 F254 plates, with spots seen under ultraviolet light. Microwave-assisted reactions were performed with a Biotage 300-Watt microwave reactor. Infrared (IR) spectra were obtained with a Perkin-Elmer FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were obtained using a Varian (EM-360) spectrometer functioning at 300/400 MHz and 100 MHz, respectively, with $CDCl_3$ and DMSO-*d6* as the solvent. Chemical shifts (δ) are expressed in parts per million (ppm). Mass spectra were acquired with an Agilent 1100 series LC-MS equipment and a Shimadzu GC-MS-QP 5000. Elemental analysis was conducted using a Perkin Elmer 2400 CHNSO analyzer, yielding results within ±0.4% of theoretical values.

2.2. Chemistry

*2.2.1 Procedure for the Preparation of methyl 2-(4-chlorophenyl)acetate (**2**)*

In a round bottom flask, to a stirred solution of compound **1** (25 g, 0.146 mol) in acetone (200 mL) was added potassium carbonate (81 g, 0.146 mol) and methyl iodide (166.4 g, 0.293 mol). The reaction mixture was refluxed for 8 hours and reaction progress monitored by TLC and on completion of reaction, the mixture was filtered, and the filtrate solvent was evaporated under reduced pressure to obtain compound **2** as a pale-yellow liquid (yield: 24 g, 89%) (see Scheme 1).

*2.2.2. Procedure for the Preparation of methyl 1-(4-chlorophenyl) cyclohexanecarboxylate (**3**)*

Sodium hydride (5.2 g, 0.216 mol) was suspended in THF (200 mL) under argon at 0 °C and compound **2** (20 g, 0.108 mol) in THF was added dropwise, and the mixture was stirred until gas evolution ceased. A solution of 1,5-dibromopentane (49.81 g, 0.216 mol) in THF (100 mL) was added to the reaction mixture and was stirred overnight at room temperature. The reaction mass was quenched with dry silica, filtered, and concentrated. The crude product was purified by flash chromatography (33% EtOAc/heptane) to yield compound **3** (25.3 g, 93%) as a yellow oil. (see Scheme 1).

2.2.3. Procedure for the Preparation of 1-(4-chlorophenyl)cyclohexanecarboxylic acid[19] *(**4**)*

Compound **3** (15.0 g, 0.059 mol) was dissolved in mixture of solvent THF/H_2O (2:1, 300 mL), and LiOH (2.85 g, 0.118 mol) was added slowly. The mixture was then stirred at 40 °C for 2 hours. After THF evaporation, the aqueous phase was extracted with ether solvent, acidified to pH of about 6 with 1 M HCl, and filtered. The solid was washed with water and dried to give compound **4** (12.6 g, 89%).

*2.2.4. Procedure for the Preparation of ethyl 2-(1-(4-chlorophenyl) cyclohexanecarboxamido) acetate (**5**)*

To a stirred solution of carboxylic acid **4** (10.0 g, 0.042 mol) in dichloromethane (100 mL), oxalyl chloride (7.0 g, 0.054 mol) was introduced at ambient temperature. Subsequently, a catalytic amount of dimethylformamide (0.5 mL) was added, and the mixture was stirred at ambient temperature for 30 minutes under a nitrogen atmosphere. The advancement of the reaction was verified through TLC for conversion from compound **4** to compound **5a**. The reaction mixture was concentrated to eliminate dichloromethane and any surplus oxalyl chloride. Subsequently, the resulting acid chloride residue was dissolved in 100 mL of fresh dry dichloromethane, to which trimethylamine (12.75 g, 0.126 mol) was introduced. Glycine ethyl ester hydrochloride (7.0 g, 0.050 mol) was gradually introduced to the reaction mixture at 0 °C, followed by stirring at room temperature for a duration of 8 hours. The reaction mixture was quenched with water (100 mL) and subsequently extracted with dichloromethane (2 x 100 mL). The combined organic layer underwent washing with water (100 mL) and brine solution (50 mL), followed by drying over Na_2SO_4. After filtration, the mixture was concentrated to yield compound 5 (12.2 g, 90%) as a white solid.

*2.2.5. Procedure for the Preparation of 2-(1-(4-chlorophenyl) cyclohexanecarboxamido)-acetohydrazide (**6**)*

A solution of the ethyl ester of carboxylic acid **5** (0.04 mol) in ethanol (130 mL) was treated with hydrazine monohydrate (0.044 mol) and subsequently refluxed for a duration of 3 hours. The reaction mixture was reduced to one-third of its original volume and subsequently allowed to cool to room temperature. Subsequently, the substance was subjected to filtration, followed by drying and recrystallization from ethanol (40 mL), resulting in the formation of the title compound **6** (10.8 g, 87%) as an off-white solid.

*Compound **3***: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34-7.31 (m, 2 H), 7.30-7.26 (m, 2 H), 3.63 (s, 3 H), 2.43 (m, 2 H), 1.71-0.80 (m, 8 H); ^{13}C NMR (100 MHz, DMSO- *d6*) δ: 174.3, 142.5, 131.4, 128.3,

127.5, 60.2, 51.8, 34.5, 34.0, 24.7, 2 3.0, 13.7; IR (KBr, cm^{-1}): 2935, 2859, 1728, 1493, 1449, 1217, 1130, 1012; ESI-MS: *m/z* 253.20 $[M+H]^+$; $C_{14}H_{17}ClO_2$; Anal. Calcd. for $C_{14}H_{17}ClO_2$: Found: C, 66.55; H, 6.79; Cl, 14.05; O, 12.67%; Calcd: C, 66.53; H, 6.78; Cl, 14.03; O, 12.66%;

Compound ***4***: Melting point: 155-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39-7.36 (m, 2 H), 7.32-7.26 (m, 2 H), 2.41 (m, 2 H), 1.75-1.50 (m, 7 H), 1.26 (m, 1H); ^{13}C NMR (100 MHz, DMSO- *d6*) δ: 175.5, 143.0, 131.2, 128.2, 127.7, 49.7, 33.9, 24.8, 23.2; IR (KBr, cm^{-1}): 2934, 2861, 1740, 1682, 1491, 1449, 1368, 1233, 1098, 1014; ESI-MS: m/z 237.15 $[M-H]^-$; $C_{13}H_{15}ClO_2$; Anal. Calcd. for $C_{13}H_{15}ClO_2$ (238): Found: C, 65.43; H, 6.35; Cl, 14.86; O, 13.42%; Calcd: C, 65.41; H, 6.33; Cl, 14.85; O, 13.40%;

Compound ***5***: Melting point: 157-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.38-7.35 (m, 2H), 7.34-7.26 (m, 2H), 5.80 (brs, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.93 (d, *J* = 5.6 Hz, 2H), 2.31-2.26 (m, 2H), 1.98-193 (m, 2H), 1.64-1.53 (m, 5H), 1.39 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-*d6*) *δ*: 173.8, 169.7, 144.1, 130.9, 127.9, 60.1, 49.6, 41.2, 34.2, 25.0, 22.8, 13.9; IR (KBr, cm^{-1}): 3340, 2937, 1745, 1643, 1535, 1368, 1200, 1092, 1020; ESI-MS: *m/z* 324.15 $[M+H]^+$; $C_{17}H_{22}ClNO_3$; Anal. Calcd. for $C_{17}H_{22}ClNO_3$: Found: C, 63.08; H, 6.87; Cl, 10.96; N, 4.34; O, 14.83%; Calcd: C, 63.06; H, 6.85; Cl, 10.95; N, 4.33; O, 14.82%;

Compound ***6***: Melting point: 65-68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.44 (brs, 1H), 7.34-7.31 (m, 4H), 6.10 (brs, 1H), 3.83 (t, *J* = 5.3 Hz, 2H), 2.28-2.23 (m, 2H), 1.98-193 (m, 2H), 1.54-142 (m, 6H); ^{13}C NMR (100 MHz, DMSO- *d6*) *δ*: 173.7, 168.5, 144.1, 130.9, 128.0, 49.7, 39.7, 34.24, 25.1, 22.8; IR (KBr, cm^{-1}): 3302, 3021, 2944, 1740, 1368, 1222, 1018; ESI-MS: *m/z* 310.1 $[M+H]^+$; $C_{15}H_{20}ClN_3O_2$; Anal. Calcd. for $C_{15}H_{20}ClN_3O_2$: Found: C, 58.15; H, 6.53; Cl, 11.45; N, 13.57; O, 10.35%; Calcd: C, 58.16; H, 6.51; Cl, 11.44; N, 13.56; O, 10.33%;

2.2.6. General experimental procedure for the synthesis of Compound ***8a-8p*** (Figure 2)

To a solution of carboxylic acid hydrazide **(6)** in 10–20 mL of ethanol was added 0.011 mol of aromatic aldehydes (**7a-7p**) and then heated under reflux for 3-6 hours. After that the solution was allowed to cool at room temperature and filtered off and recrystallized from ethanol to obtain corresponding hydrazone derivatives **8a-8p** (yields, 72-86%).

*2-(1-(4-chlorophenyl)cyclohexanecarboxamido)-N'-benzylideneaceto hydrazide (**8a**):* To a solution of carboxylic acid hydrazide **6** (309 mg, 1.0 mmol) in ethanol (15 mL), benzaldehyde **7a** (116 mg, 1.1 mmol) was introduced. The reaction mixture was subjected to heating at reflux temperature for duration of three hours. The completion of the reaction was tested by the analysing thin-layer chromatography. Subsequently, the solution was permitted to cool to ambient temperature, and the resulting precipitate was subjected to filtration. The residue was then recrystallized in 10 mL of ethanol and dried under vacuum, yielding the corresponding hydrazone derivative **8a** (305 mg, 77%) as an off-white solid.

2-(1-(4-chlorophenyl)cyclohexanecarboxamido)-N'-benzylideneaceto hydrazide ***8a***: Melting point: 166-170 °C. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.2 (brs, 1H, -N=CH), 7.6 (m, 1H), 7.44 (m, 2H, -NH), 7.34-7.31 (m, 7H, aromatic), 6.10 (m, 1H, aromatic), 4.40 (s, 2H), 2.28-2.23 (m, 2H), 1.98-193 (m, 2H), 1.54-142 (m, 6H); ^{13}C NMR (100 MHz, DMSO- *d6*) *δ*: 173.7, 170.2, 165.5, 146.1, 144.2, 143.0, 134.0, 130.8, 129.8, 128.6, 126.9, 126.6, 49.7, 41.5 34.3, 25.1, 22.8; IR (KBr, cm^{-1}): 3302, 3021, 2944, 1740, 1368, 1222, 1018; ESI-MS: *m/z* 310.1 $[M+H]^+$; $C_{22}H_{24}ClN_3O_2$; Anal. Calcd. for $C_{22}H_{24}ClN_3O_2$ (397): Found: C, 66.43; H, 6.10; Cl, 8.92; N, 10.55; O, 8.01%; Calcd: C, 66.41; H, 6.08; Cl, 8.91; N, 10.56; O, 8.04%;

*2-(1-(4-chlorophenyl)cyclohexanecarboxamido)-N'-(2-fluorobenzylidene) acetohydrazide (**8b**):* Off white solid (340.3 mg, 82%). Melting point: 189-192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.35 (brs, 1H, N=CH), 7.95 (brs, 1H, -NH), 7.40 (m, 1H, -NH), 7.38 (d, *J* = 8.2 Hz, 2H), 7.31 (m, 3H), 7.06 (m, 2H), 6.25 (s, 1H), 4.42 (d, *J* = 4.8 Hz, 2H), 2.31 (m, 2H), 1.97 (m, 2H), 1.61-1.56 (m, 5H), 1.41 (m, 1H); ^{13}C NMR (100 MHz, DMSO- *d6*) *δ*: 173.9, 170.4, 165.6, 161.7, 159.3, 144.3, 138.8, 131.7, 130.8, 127.9, 126.2, 124.8, 121.6, 115.9, 49.8, 49.7, 34.3, 25.1, 22.8; IR (KBr, cm^{-1}): 3346, 2942,

2859, 1740, 1660, 1423, 1364, 1305, 1228, 1091; ESI-MS: *m/z* 416.2 $[M+H]^+$; $C_{22}H_{23}ClFN_3O_2$. Anal. Calcd. for $C_{22}H_{23}ClFN_3O_2$: Found: C, 63.55; H, 5.58; Cl, 8.53; F, 4.56; N, 10.11; O, 7.70%; Calcd. C, 63.54; H, 5.57; Cl, 8.52; F, 4.57; N, 10.10; O, 7.69%;

*2-(1-(4-chlorophenyl)cyclohexanecarboxamido)-N'-(4-fluorobenzylidene) acetohydrazide (**8c**)*: Off white solid (332 mg, 80%). Melting point: 140-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.17 (brs, 1H), 7.61 (m, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.26 (s, 2H), 7.08(m, 2H), 6.29 (s, 1H), 4.42 (d, *J* = 4.8 Hz, 2H), 2.34-2.27 (m, 2H), 1.99-1.94 (m, 2H), 1.62-1.56 (m, 5H), 1.41 (m, 1H); ^{13}C NMR (400 MHz, DMSO-*d6*) *δ*: 173.9, 170.3, 165.5, 164.0, 161.7, 144.9, 130.8, 128.9, 127.9, 115.9, 49.8, 41.4, 34.3, 25.1, 22.8; IR (KBr, cm^{-1}): 3302, 2930, 2861, 1740, 1604, 1539, 1364, 1305, 1228, 1095; ESI-MS: *m/z* 416.2 $[M+H]^+$; $C_{22}H_{23}ClFN_3O_2$; Anal. Calcd. for $C_{22}H_{23}ClFN_3O_2$ (415): Found: C, 63.56; H, 5.59; Cl, 8.53; F, 4.56; N, 10.11; O, 7.71%; Calcd: C, 63.54; H, 5.57; Cl, 8.52; F, 4.57; N, 10.10; O, 7.69%;

*2-(1-(4-chlorophenyl)cyclohexanecarboxamido)-N'-(2,5-difluoro-benzylidene) acetohydrazide (**8d**)*: Off white solid (368 mg, 85%). Melting point: 193-197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.35 (brs, 1H), 7.95 (s, 1H), 7.40 (m, 1H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.06 (m, 2H), 6.25 (s, 1H), 4.42 (d, *J* = 4.8 Hz, 2H), 2.31 (m, 2H), 1.97 (m, 2H), 1.61-1.56 (m, 5H), 1.41 (m, 1H); ^{13}C NMR (400 MHz, DMSO- *d6*) *δ*: 173.9,170.6, 165.8, 159.5, 157.9, 155.5, 144.3, 137.8, 134.8, 130.8, 127.9,123.2, 118.2, 117.6, 111.8, 49.8, 49.7, 34.3, 25.1, 22.8; IR (KBr, cm^{-1}): 3347, 2942, 2862, 1740, 1684, 1637, 1527, 1485, 1439, 1363, 1208, 1096; ESI-MS: *m/z* 434.15 $[M+H]^+$; $C_{22}H_{22}ClF_2N_3O_2$; Anal. Calcd. for $C_{22}H_{22}ClF_2N_3O_2$: Found: C, 60.91; H, 5.12; Cl, 8.18; F, 8.75; N, 9.66; O, 7.35%; Calcd. C, 60.90; H, 5.11; Cl, 8.17; F, 8.76; N, 9.68; O, 7.38%;

*2-(1-(4-chlorophenyl)cyclohexanecarboxamido)-N'-(3,4-difluorobenzylidene)acetohydrazide (**8e**)*: Off white solid (350 mg, 81%). Melting point: 136-140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.17 (brs, 1H), 7.65 (s, 1H), 7.52 (m, 1H) 7.40 (m, 1H), 7.38 (m, 3H), 7.20-7.17 (m, 1H), 7.06 (m, 1H), 6.25 (brs, 1H), 4.41 (d, *J* = 4.8 Hz, 2H), 2.31 (m, 2H), 1.97 (m, 2H), 1.61-1.56 (m, 5H), 1.41 (m, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) *δ*: 173.9, 170.4, 165.7, 151.4, 148.8, 144.2, 140.7, 132.1, 130.8, 127.9, 124.2, 117.6, 111.8, 49.8, 49.7, 34.3, 25.1, 22.8; IR (KBr, cm^{-1}): 3313, 2929, 2860, 1740, 1688, 1649, 1535, 1364, 1280, 1218, 1017; ESI-MS (Fig. 36): *m/z* 434.20 $[M+H]^+$; $C_{22}H_{22}ClF_2N_3O_2$; Anal. Calcd. for $C_{22}H_{22}ClF_2N_3O_2$: Found: C, 60.92; H, 5.10; Cl, 8.16; F, 8.74; N, 9.65; O, 7.35%; Calcd: C, 60.90; H, 5.11; Cl, 8.17; F, 8.76; N, 9.68; O, 7.38%;

*2-(1-(4-chlorophenyl)cyclohexanecarboxamido)-N'-(5-fluoro-2-nitrobenzylidene)acetohydrazide (**8f**)*: Off white solid (363 mg, 79%). Melting point: 161-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.44 (s, 1H), 8.48 (s,1H), 8.14 (q, *J* = 7.8 Hz, 1H), 7.77 (dd, *J* = 8.3, 7.8 Hz, 1H), 7.40 (m, 2H), 7.31 (m, 2H), 7.25-7.20 (m, 1H), 6.26 (m, 1H), 4.41 (d, *J* = 4.8 Hz, 2H), 2.34 (m, 2H), 1.98 (m, 2H), 1.64-1.59 (m, 5H), 1.41 (m, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) *δ*: 173.9 (2C), 170.7, 166.1, 165.2, 162.6, 144.3, 140.7, 137.5, 131.8, 130.8, 127.9, 117.5, 114.2, 113.9, 113.7, 49.8, 49.7, 34.3, 25.1, 22.8; IR (KBr, cm^{-1}): 3358, 2935, 2862, 1740, 1653, 1517, 1416, 1361, 1297, 1226, 1090, 1017; ESI-MS: *m/z* 461.20 $[M+H]^+$; $C_{22}H_{22}ClFN_4O_4$; Anal. Calcd. for $C_{22}H_{22}ClFN_4O_4$: Found: C, 57.34; H, 4.82; Cl, 7.71; F, 4.13; N, 12.15; O, 13.87%; Calcd. C, 57.33; H, 4.81; Cl, 7.69; F, 4.12; N, 12.16; O, 13.89%;

*2-(1-(4-chlorophenyl)cyclohexanecarboxamido)-N'-(2-nitrobenzylidene)acetohydrazide (**8g**)*: Off white solid (367 mg, 83%). Melting point:.160-164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.80 (s, 1H), 8.39 (s,1H), 8.08 (m, 1H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.41 (m, 2H), 7.31-7.26 (m, 3H), 6.33 (s, 1H), 4.42 (d, *J* = 4.8 Hz, 2H), 2.34 (m, 2H), 2.04 (m, 2H), 1.80-1.57 (m, 5H), 1.39 (m, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) *δ*: 173.9, 170.5, 165.9, 147.9, 144.3, 141.6, 138.4, 133.6, 130.8, 128.0, 127.9, 124.6, 124.4, 49.7, 41.5, 34.3, 25.1, 22.8; IR (KBr, cm^{-1}): 3358, 2942, 2860, 1738, 1659, 1520, 1416, 1342, 1293, 1229, 1090, 1014; ESI-MS: *m/z* 443.15 $[M+H]^+$; $C_{22}H_{23}ClN_4O_4$; Anal. Calcd. for $C_{22}H_{23}ClN_4O_4$: Found: C, 59.67; H, 5.25; Cl, 8.02; N, 12.66; O, 14.44%; Calcd: C, 59.66; H, 5.23; Cl, 8.00; N, 12.65; O, 14.45%.

*2-(1-(4-chlorophenyl)cyclohexanecarboxamido)-N'-(4-fluoro-3-(trifluoromethyl) benzylidene) aceto-hydrazide (**8h**)*: Light brown solid (415 mg, 86%). Melting point: .173-175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.22 (s, 1H), 7.95-7.85 (m, 3H), 7.40 (t, J = 8.2 Hz, 2H), 7.33 (m, 3H), 6.23 (brs, 1H), 4.43 (d, J = 4.8 Hz, 2H), 2.34 (m, 2H), 2.04 (m, 2H), 1.80-1.57 (m, 5H), 1.39 (m, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ: 173.9, 170.5, 165.9, 157.9, 144.3, 140.4, 133.4, 131.4, 127.9, 125.8, 123.7, 121.0, 117.9, 49.7, 41.5, 34.3, 25.1, 22.8; IR (KBr, cm^{-1}): 3018, 2940, 1740, 1368, 1221, 1130, 1090, 1014; ESI-MS: *m/z* 484.15 $[M+H]^+$; $C_{23}H_{22}ClF_4N_3O_2$; Anal. Calcd. for $C_{23}H_{22}ClF_4N_3O_2$: Found: C, 57.10; H, 4.59; Cl, 7.35; F, 15.72; N, 8.69; O, 6.63%; Calcd. C, 57.09; H, 4.58; Cl, 7.33; F, 15.70; N, 8.68; O, 6.61%;

*(2-(1-(4-chlorophenyl)cyclohexanecarboxamido)-N'-(3-(trifluoromethyl)benzylidene) acetohydrazide (**8i**)*: Off white solid (376 mg, 81%). Melting point: 137-141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.12 (s, 1H), 7.85 (m, 2H), 7.76 (m, 1H), 7.67 (m, 1H), 7.52 (m, 1H), 7.39 (t, J = 8.4 Hz, 2H), 7.33 (m, 2H), 6.25 (brs, 1H), 4.43 (d, J = 4.8 Hz, 2H), 2.35 (m, 2H), 1.97 (m, 2H), 1.80-1.57 (m, 5H), 1.25 (m, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ: 173.9, 170.5, 165.8, 144.2, 141.4, 135.4, 130.8, 129.8, 127.9, 127.8, 126.0, 122.9, 122.6, 49.7, 41.5, 34.3, 25.1, 22.8; IR (KBr, cm^{-1}): 3465, 2937, 2861, 1740, 1717, 1528, 1214, 1121, 1073, 1014; ESI-MS: *m/z* 466.20 $[M+H]^+$; $C_{23}H_{23}ClF_3N_3O_2$; Anal. Calcd. for $C_{23}H_{23}ClF_3N_3O_2$: Found: C, 59.30; H, 4.99; Cl, 7.63; F, 12.25; N, 9.05; O, 6.88%; Calcd. C, 59.29; H, 4.98; Cl, 7.61; F, 12.23; N, 9.02; O, 6.87%;

*2-(1-(4-chlorophenyl)cyclohexanecarboxamido)-N'-(2-fluoro-6-methoxybenzylidene) acetohydrazide (**8j**)*: Off white solid (347 mg, 78%). Melting point: 178-182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77 (brs, 1H), 7.96 (s, 1H), 7.76 (m, 2H), 7.30 (m, 3H), 6.73 (q, J = 8.3 Hz, 2H), 6.28 (brs, 1H), 4.43 (d, J = 4.8 Hz, 2H), 3.87 (s, 3H), 2.33 (m, 2H), 1.97 (m, 2H), 1.80-1.57 (m, 5H), 1.25 (m, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ: 173.8, 170.2, 165.3, 161.3, 158.9, 144.2, 139.2.4, 136.0, 131.2, 127.9, 110.8, 108.6, 107.5, 56.3, 49.8, 41.5, 34.3, 25.1, 22.8; IR (KBr, cm^{-1}): 3463, 2939, 2868, 1740, 1681, 1608, 1469, 1386, 1270, 1219, 1070, 1015; ESI-MS: *m/z* 446.20 $[M+H]^+$; $C_{23}H_{25}ClFN_3O_3$; Anal. Calcd. for $C_{23}H_{25}ClFN_3O_3$: Found: C, 61.94; H, 5.66; Cl, 7.97; F, 4.26; N, 9.44; O, 10.78%; Calcd. C, 61.95; H, 5.65; Cl, 7.95; F, 4.26; N, 9.42; O, 10.76%;

*2-(1-(4-chlorophenyl)cyclohexanecarboxamido)-N'-(4-fluoro-3-methoxybenzylidene) acetohydrazide (**8k**)*: Off white solid (356 mg, 80%). Melting point: 142-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83 (brs, 1H), 7.65 (s, 1H), 7.40 (m, 2H), 7.32 (m, 3H), 7.11-7.04 (m, 2H), 6.31 (brs, 1H), 4.43 (d, J = 4.8 Hz, 2H), 3.93 (s, 3H), 2.34 (m, 2H), 1.98 (m, 2H), 1.64-1.57 (m, 5H), 1.39(m, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ: 173.9, 165.6, 153.6, 147.5, 145.2, 139.2, 136.0, 127.9, 120.6, 116.1, 110.8, 55.9, 49.8, 34.3, 25.1, 22.8; IR (KBr, cm^{-1}): 3459, 2936, 1740, 1672, 1506, 1466, 1366, 1219, 1104, 1023; ESI-MS: *m/z* 446.20 $[M+H]^+$; $C_{23}H_{25}ClFN_3O_3$; Anal. Calc. for $C_{23}H_{25}ClFN_3O_3$: Found C, 61.94; H, 5.66; Cl, 7.97; F, 4.28; N, 9.45; O, 10.77%; Calc: C, 61.95; H, 5.65; Cl, 7.95; F, 4.26; N, 9.42; O, 10.76%;

*2-(1-(4-chlorophenyl)cyclohexanecarboxamido)-N'-(2-methoxybenzylidene)acetohydrazide (**8l**)*: Off white solid (363 mg, 85%). Melting point: 196-200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (brs, 1H), 8.14 (s, 1H), 7.86 (dd, J = 8.6, 6.2 Hz, 1H), 7.40-7.26 (m, 5H), 6.96 (t, J = 7.8 Hz, 1H), 6.88 (d, 1H), 6.33 (brs, 1H), 4.43 (d, J = 4.8 Hz, 2H), 3.85 (s, 3H), 2.35 (m, 2H), 1.98 (m, 2H), 1.64-1.57 (m, 5H), 1.40 (m, 1H); ^{13}C NMR (100 MHz, DMSO- *d6*) δ: 173.9, 170.1, 165.3, 157.6, 157.5, 144.3, 141.6, 138.7, 131.3, 125.3, 122.1, 120.6, 111.7, 55.6, 49.8, 34.3, 25.1, 22.8; IR (KBr, cm^{-1}): 3460, 2939, 1740, 1670, 1468, 1369, 1221, 1094, 1016; ESI-MS: *m/z* 428.20 $[M+H]^+$; $C_{23}H_{26}ClN_3O_3$; Anal. Calcd. for $C_{23}H_{26}ClN_3O_3$: Found: C, 64.56; H, 6.13; Cl, 8.29; N, 9.83; O, 11.25%; Calcd. C, 64.55; H, 6.12; Cl, 8.28; N, 9.82; O, 11.22%;

*2-(1-(4-chlorophenyl)cyclohexanecarboxamido)-N'-(2,3-dimethoxybenzylidene)acetohydrazide (**8m**)*: Off white solid (370 mg, 81%). Melting point: 162-166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.78 (brs, 1H), 8.08 (s, 1H), 7.47 (dd, J = 8.2, 6.8 Hz, 1H), 7.40-7.37 (m, 2H), 7.34 (m, 2H), 7.08 (t, J = 8.4 Hz, 1H), 6.96 (m, 1H), 6.32 (brs, 1H), 4.43 (d, J = 4.8 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 2.35 (m, 2H), 1.98 (m, 2H), 1.64-1.57 (m, 5H), 1.38 (m, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ: 173.9, 173.7, 170.1, 165.4, 152.6, 147.8, 147.7, 144.3, 141.6, 138.8, 130.8, 127.9, 124.2, 116.8, 116.7, 114.1, 113.9,

61.0, 55.7, 49.8, 41.5, 34.3, 25.1, 22.8; IR (KBr, cm^{-1}): 3334, 2938, 1740, 1688, 1634, 1542, 1470, 1369, 1226, 1072, 1009; ESI-MS: *m/z* 458.20 $[M+H]^+$; $C_{24}H_{28}ClN_3O_4$; Anal. Calcd. for $C_{23}H_{26}ClN_3O_3$: Found: C, 62.96; H, 6.18; Cl, 7.75; N, 9.19; O, 13.98%; Calcd. C, 62.95; H, 6.16; Cl, 7.74; N, 9.18; O, 13.97%.

*2-(1-(4-chlorophenyl)cyclohexanecarboxamido)-N'-(4-methoxybenzylidene) acetohydrazide (**8n**)*: Off white solid (341 mg, 80%). Melting point: 200-204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.97 (brs, 1H), 7.66 (s, 1H), 7.57 (dd, *J* = 8.2, 6.2 Hz, 2H), 7.40-7.38 (m, 2H), 7.34 (m, 3H), 6.96 (m, 2H), 6.33 (brs, 1H), 4.43 (d, *J* = 4.8 Hz, 2H), 3.84 (s, 3H), 2.35 (m, 2H), 1.98 (m, 2H), 1.64-1.57 (m, 5H), 1.38 (m, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ: 173.8, 173.7, 170.1, 165.3, 160.7, 145.9, 144.3, 142.9, 130.8, 128.4, 127.9, 126.7, 126.6, 114.2, 55.2, 49.8, 41.5, 34.3, 25.1, 22.8; IR (KBr, cm^{-1}): 3317, 2937, 1740, 1683, 1640, 1604, 1532, 1366, 1242, 1020; ESI-MS: *m/z* 428.20 $[M+H]^+$; $C_{23}H_{26}ClN_3O_3$; Anal. Calcd. for $C_{23}H_{26}ClN_3O_3$: Found: C, 64.56; H, 6.14; Cl, 8.29; N, 9.83; O, 11.25%; Calcd. C, 64.55; H, 6.12; Cl, 8.28; N, 9.82; O, 11.22%;

*2-(1-(4-chlorophenyl)cyclohexanecarboxamido)-N'-((pyridin-3-yl)methylene) acetohydrazide (**8o**)*: Off white solid (276 mg, 72%). Melting point: 144-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.22 (brs, 1H), 8.7 (m, 1H), 8.64 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.76 (s, 1H), 7.40-7.33 (m, 5H), 6.26 (brs, 1H), 4.43 (d, *J* = 4.8 Hz, 2H), 2.35 (m, 2H), 1.98 (m, 2H), 1.64-1.57 (m, 5H), 1.41 (m, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ: 173.8, 173.7, 170.4, 165.7, 150.5, 148.5, 144.3, 135.9, 133.2, 130.8, 129.9, 127.9, 123.8, 49.8, 41.5, 34.3, 25.1, 22.8; IR (KBr, cm^{-1}) 3465, 3306, 2931, 1740, 1688, 1640, 1367, 1278, 1221, 1015; ESI-MS: *m/z* 399.20 $[M+H]^+$; $C_{21}H_{23}ClN_4O_2$; Anal. Calcd. for $C_{21}H_{23}ClN_4O_2$: Found: C, 63.25; H, 5.83; Cl, 8.90; N, 14.06; O, 8.05%; Calcd. CC, 63.23; H, 5.81; Cl, 8.89; N, 14.05; O, 8.02%;

*2-(1-(4-chlorophenyl)cyclohexanecarboxamido)-N'-(3,4,5-trimethoxybenzylidene)acetohydrazide (***8p**): Off white solid (399 mg, 82%). M.P.: 120-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (brs, 1H), 7.60 (s, 1H), 7.41 (dd, *J* = 8.4, 6.0 Hz, 2H), 7.35 -7.33 (m, 2H), 6.94 (s, 2H), 6.32 (brs, 1H), 4.43 (d, *J* = 4.8 Hz, 2H), 3.89 (s, 9H), 2.35 (m, 2H), 1.98 (m, 2H), 1.64-1.57 (m, 5H), 1.41 (m, 1H); ^{13}C NMR (100 MHz, DMSO- *d6*) δ: 173.7, 170.2, 165.5, 153.1, 146.0, 144.2, 139.0, 130.8, 129.6, 127.9, 104.2, 60.0, 55.9, 49.7, 41.5, 34.3, 25.1, 22.8; IR (KBr, cm^{-1}): 3321, 2934, 1738, 1688, 1644, 1498, 1407, 1364, 1228, 1128, 1009; ESI-MS: *m/z* 488.20 $[M+H]^+$; $C_{25}H_{30}ClN_3O_5$; Anal. Calcd. for $C_{25}H_{30}ClN_3O_5$: Found: C, 61.54; H, 6.22; Cl, 7.25; N, 8.63; O, 16.41%; Calcd. C, 61.53; H, 6.20; Cl, 7.27; N,8.61; O,16.39%.

3. Results and Discussion

3.1. Chemistry

Although cyclohexane-based amido hydrazones are relatively uncommon, they exhibit structural and functional features distinct from the widely studied aromatic hydrazones. As opposed to aromatic rings, which are prone to oxidative metabolism, the cyclohexane ring confers both metabolic stability and structural flexibility. By integrating the hydrazone pharmacophore with a cyclohexyl moiety, these compounds may overcome limitations of aromatic hydrazones, such as poor solubility, reduced bioavailability, and undesired toxicity. Furthermore, the amido group enables additional derivatization, thereby facilitating structure–activity relationship (SAR) studies.

In order to generate the desired hydrazone derivatives (**8a–8p**), a systematic six-step synthetic route was designed and developed, starting from 2-(4-chlorophenyl)acetic acid (**1**) (Scheme 1). Methylation yielded the corresponding methyl ester (**2**) in 89%,[17] which was then cyclized with 1,5-dibromopentane in the presence of sodium hydride in THF to afford compound (**3**). The structure of compound (**3**) was confirmed using spectroscopic techniques, including ^{1}H NMR, ^{13}C NMR, and mass spectrometry.[18,19] In the ^{1}H NMR spectrum, characteristic signals at δ 2.43 (m, 2H) and δ 1.71–0.80 (m, 8H) were observed, corresponding to protons within the cyclohexyl ring.

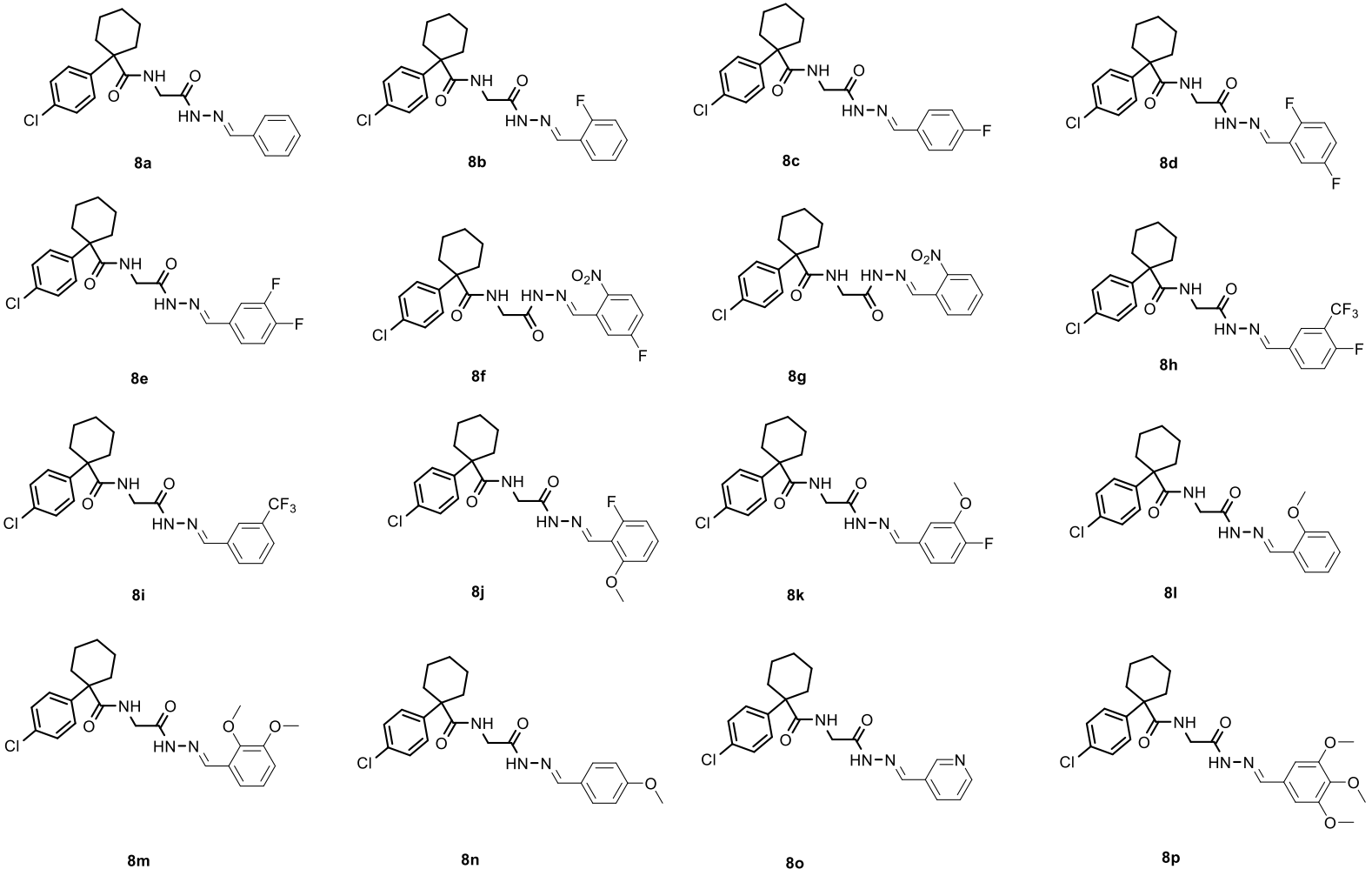
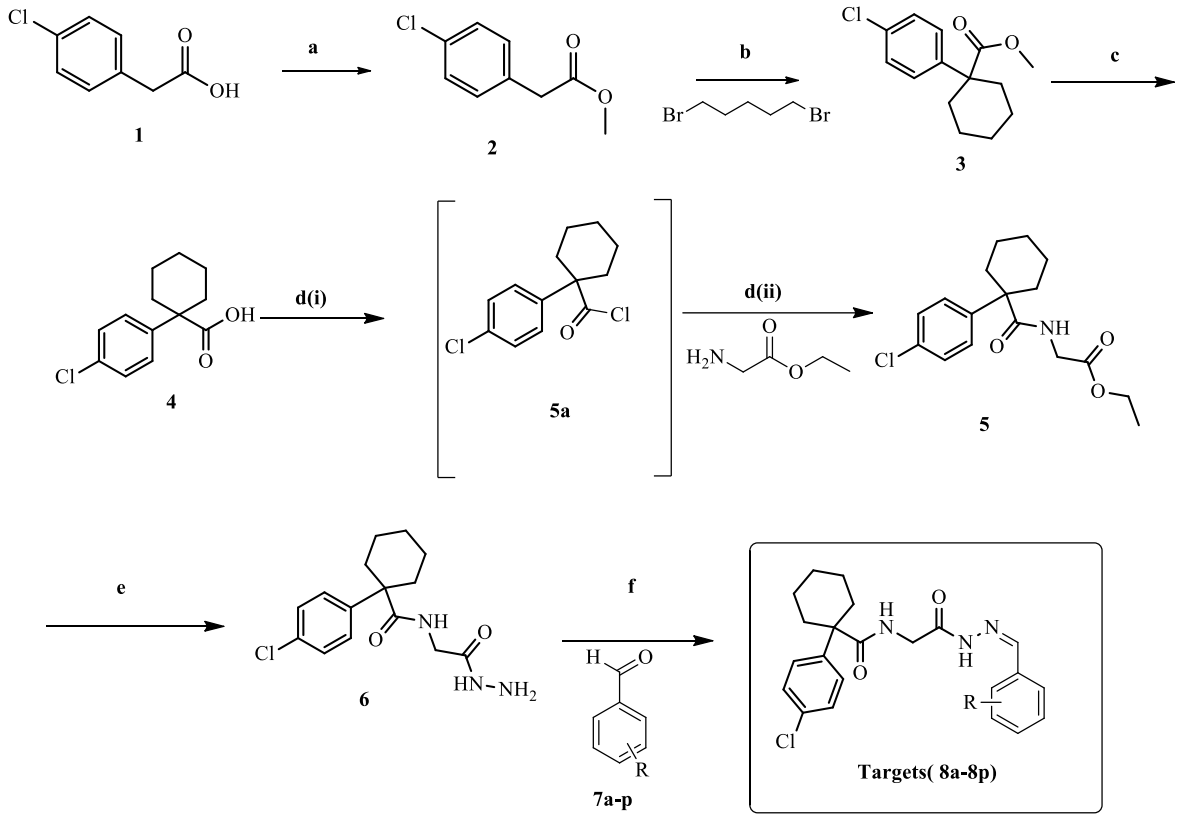


Figure 2. Structure of compounds **8a-8p**



Reagents: (a) K_2CO_3, MeI, Acetone, reflux; (b) NaH, 1,5-dibromopentane, THF, 35 °C (c) LiOH, THF/H_2O, 40 °C; H_3O^+(d) (i) oxalyl chloride, DMF (ii) Glycine ethylester hydrochloride, triethylamine, 30 °C; (e) $NH_2NH_2.H_2O$, EtOH, reflux; (f) Aromatic aldehydes, EtOH, reflux.

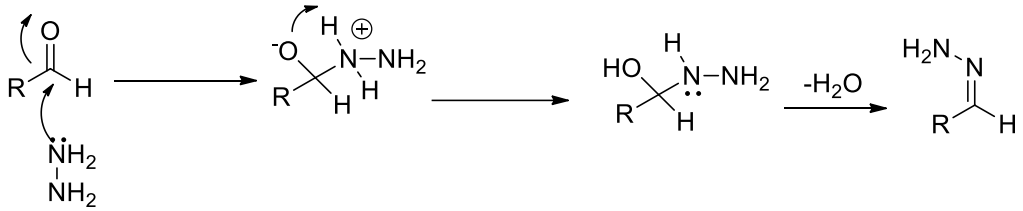
Scheme 1. Synthesis of hydrazone derivatives

Compound (**3**) was then subsequently hydrolyzed using mild basic conditions such as lithium hydroxide to produce the equivalent carboxylic acid (**4**).[20–21] The activation of compound (**4**) using oxalyl chloride to give the corresponding acid chloride (**5a**), followed by its coupling with glycine ethyl ester, yielded ethyl 2-(1-(4-chlorophenyl)cyclohexanecarboxamido)acetate (**5**). The intermediate underwent further treatment with hydrazine hydrate in boiling ethanol to provide the crucial hydrazide derivative 2-(1-(4-chlorophenyl)cyclohexanecarboxamido)acetohydrazide (**6**). The structure of the compound (**6**) was confirmed using NMR, elemental analysis, and mass spectrometry methods. The ^{1}H NMR spectrum exhibited signals at δ = 6.10 (brs, 1H) and 3.83 (t, 2H), indicative of the hydrazide protons. Finally, compound (**6**) was reacted with various substituted aromatic aldehydes (**7a–7p**) under reflux in ethanol, resulting in the formation of the corresponding hydrazone derivatives (**8a–8p**) with yields ranging from moderate to excellent (72–86%). The derivatives were structurally investigated using ^{1}H NMR, elemental analysis, and additional spectral approaches, with results corroborating their anticipated structures.

Moreover, the authors also evaluated the substrate scope using different aromatic aldehydes bearing various functional groups, such as –F, –CF_3, –OMe, and –NO_2. These modifications were well-tolerated by the developed scheme, which confirmed by the formation of desired hydrazones with satisfactory yields under the optimized conditions. In addition, the spectral and analytical data of all synthesized molecules (**8a-8p)** were consistent with their proposed structures.

On the basis of controlled experiments and previous literature reports, plausible mechanistic pathway is proposed as shown in Scheme 2. Hydrazones are generated by the condensation of hydrazine (**6**) with a carbonyl molecule (aldehyde (**7a-7p**), by eliminating water as the

only product. The reaction begins with the nucleophile of hydrazine attacking the electrophile's carbonyl carbon atom *via* proton catalysis. After proton transfer, a tetrahedral intermediate was produced. This intermediate undergoes dehydration *via* protonation of the hydroxyl group, subsequently elimination of water molecule to produce the hydrazone (**8a-8p**) derivatives.



Scheme 2. Plausible mechanistic pathway

4. Conclusion

In conclusion, we have effectively synthesized a unique series of sixteen hydrazone derivatives derived from a cyclohexanecarboxamidoacetohydrazide core using an efficient and adaptable multistep synthetic pathway. The approach accommodated various aryl aldehyde substituents, producing structurally varied products with good to outstanding yields. Thorough structural characterisation was accomplished *via* NMR, IR, mass spectrometry, and elemental analysis. This methodology is applicable for various substituted aromatic hydrazones with good to excellent yields. The advantage of this protocol is shorter reaction time, wide range substrate scope, easy workup procedures and scalability. These factors make the protocol highly beneficial in synthetic organic chemistry, the medicinal, material science and pharmaceutical industry.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

Author Contributions

Madhuri the principal author who carried out experiments; MP-Investigator; Suribabu P, Maheswara Rao G, who supported in establishing spectral characterization; Dr. HBB- supervised the work.

Conflicts of Interest

All the authors declare that this work has not received prior publication, and no portion of the work is under consideration for publication elsewhere in any medium. Further, the authors declare no conflict of interest.

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