

Synthesis, Characterization, and Crystal Structure of Some New Tetrahydroisoquinolines and Related Tetrahydrothieno[2,3-*c*]isoquinolines

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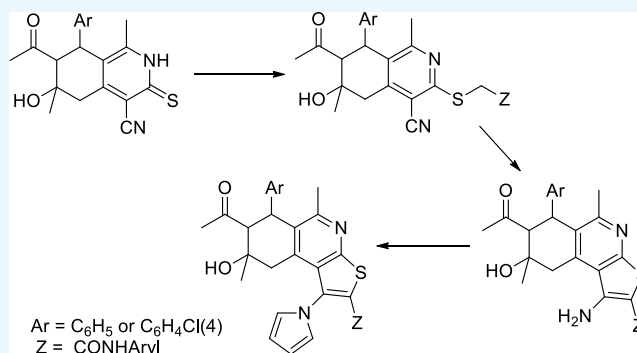


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ABSTRACT: The starting compounds 7-acetyl-8-aryl-4-cyano-1,6-dimethyl-6-hydroxy-5,6,7,8-tetrahydroisoquinoline(2*H*)-3-thiones **3a,b** were synthesized and reacted with some *N*-aryl-2-chloroacetamides **4a–e** in the presence of sodium acetate to produce 7-acetyl-8-aryl-3-(*N*-arylcarbamoylmethylsulfanyl)-4-cyano-1,6-dimethyl-6-hydroxy-5,6,7,8-tetrahydroisoquinolines **5a–g**. Upon heating in ethanol containing sodium ethoxide, they underwent intramolecular Thorpe–Zeigler cyclization, affording the corresponding 7-acetyl-1-amino-6-aryl-2-(*N*-arylcarbamoyl)-5,8-dimethyl-8-hydroxy-6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinolines **6a–g**. Compounds **6c,g,f** were converted into the corresponding 1-(1-pyrrolyl) derivatives **7a–c** by heating with 2,5-dimethoxytetrahydrofuran in glacial acetic acid. Structures of all synthesized compounds were characterized by elemental and spectral analyses. Also, the crystal structure of compounds **5a** was determined by X-ray diffraction analysis.



1. INTRODUCTION

Tetrahydroisoquinoline derivatives have important biological and pharmacological activities. Some of them are reported to possess antitumor,¹ antimicrobial,² and dopaminergic ligand activity.³ Others were used as starting materials in the synthesis of pharmacologically active constrained conformations of *N*-substituted-2-aminopyridines as antinociceptive agents⁴ and constrained conformations of nicotine to improve nicotine vaccines.^{5–7} Also, certain tetrahydroisoquinolines are included in the main skeleton of conformationally constrained compounds analogous to epibatidine and (–)-cytisine.⁸ Moreover, tetrahydroisoquinoline derivatives have important medicinal characteristics as potent, selective, and orally active aldosterone synthase (CYP11B2) inhibitors.⁹ There are many natural products and modified natural products that contain annulated pyridine motifs such as fatty acid binding protein inhibitors, (–)-oxerine, (–)-actinidine, indicaine, and other compounds that are derived from (*S*)-(–)-perillaldehyde (flavoring agent) and (1*R*)-myrtenal (flavoring agent).¹⁰ In C–H activation reactions, the pyridine ring acts as the directing group.¹¹

The thienopyridine modifiers also have important pharmacological activities including as antiplatelet drugs for the treatment of acute coronary syndromes,^{12,13} antibacterial activity against a drug-resistant *Staphylococcus epidermidis* clinical strain,¹⁴ and cytotoxic activity against human

hepatocellular liver carcinoma (HepG2).¹⁵ It is well known that the biological properties of most compounds usually improve as their solubility increases. The above observations prompted us to synthesize and characterize some new heterocyclic compounds containing 5,6,7,8-tetrahydroisoquinolines and/or 6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinoline frameworks with other new substituents, hoping to obtain new compounds with good solubility and hence enhanced biological and medicinal applications. Also, the crystal structure of compound **5a** was determined by X-ray diffraction analysis.

2. RESULTS AND DISCUSSION

2.1. Synthesis. The starting compounds 7-acetyl-8-aryl-4-cyano-1,6-dimethyl-6-hydroxy-5,6,7,8-tetrahydroisoquinoline-3(2*H*)-thiones **3a,b** were prepared by the reaction of acetyl-cyclohexanone derivatives **1a,b** with cyanothioacetamide (**2**) according to the reported method (Scheme 1).¹⁶

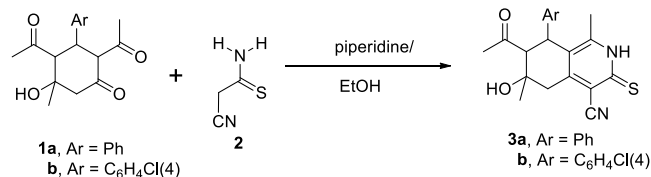
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Scheme 1. Synthesis of Compounds 3a,b



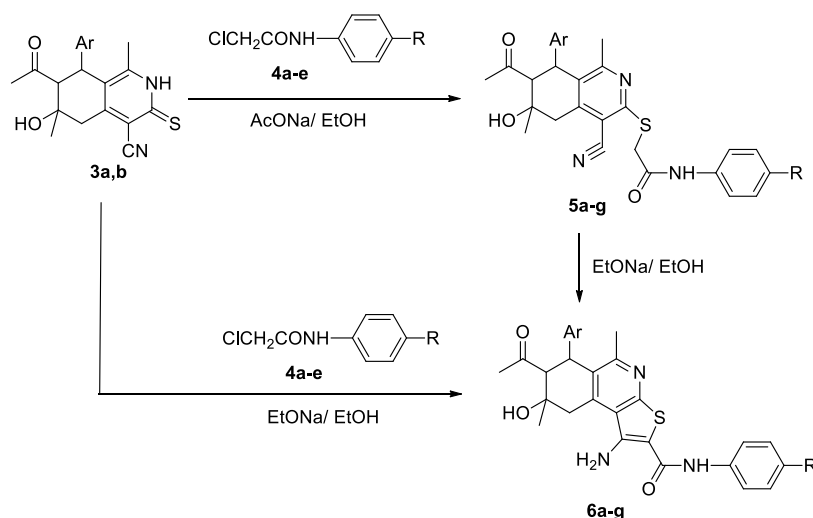
The reaction of compounds 3a,b with *N*-aryl-2-chloroacetamides 4a–e by refluxing in ethanol, in the presence of slightly excess molar amounts of sodium acetate, for 1 h gave 7-acetyl-8-aryl-3-(*N*-arylcarbamoyl-methylsulfanyl)-4-cyano-1,6-dimethyl-6-hydroxy-8-phenyl-5,6,7,8-tetrahydroisoquinolines 5a–g. On heating the latter compounds in abs. ethanol containing catalytic amounts of sodium ethoxide, they underwent intramolecular Thorpe–Ziegler cyclization, affording the corresponding isomers 7-acetyl-1-amino-6-aryl-2-(*N*-arylcarbamoyl)-5,8-dimethyl-8-hydroxy-6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinolines 6a–g in nearly quantitative yield. Compounds 6a–g were also synthesized via the reaction of 3a,b with the respective *N*-aryl-2-chloroacetamides 4a–e in the presence of slightly excess molar amounts of sodium ethoxide (Scheme 2).

The conversion of the amino group of compounds 6c,f,g into a pyrrolyl ring was achieved by their interaction with 2,5-dimethoxytetrahydrofuran in refluxing glacial acetic acid for 1 h, wherein 7-acetyl-6-aryl-2-(*N*-arylcarbamoyl)-5,8-dimethyl-8-hydroxy-1-(pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinolines 7a–c were isolated in good yields (Scheme 3).

The aforementioned reaction may proceed via the Paal–Knorr reaction for pyrrole synthesis, and its mechanism is depicted in Scheme 4.¹⁷

2.2. Characterization. The structures of newly synthesized compounds were characterized and confirmed on the basis of their elemental analysis and spectroscopic data (cf. [Experimental Section](#)). The elemental analyses give satisfactory results within ± 0.4 of the calculated values. The spectral analyses of compounds 3a,b are in agreement with those reported before.¹⁶ IR spectra of compounds 5a–g showed characteristic absorption bands in the regions 3556–3427 cm⁻¹ for (OH), 3351–3260 cm⁻¹ for (NH), 2221–2215 cm⁻¹ for (C≡N), 1712–1694 cm⁻¹ for (C=O, acetyl), and 1682–1666 cm⁻¹ (C=O, amide). ¹H NMR spectra of compounds 5a–g showed the presence of a double doublet signal¹⁶ that corresponds to the SCH₂ group at a δ value of around 4.0, and a singlet signal at a δ value ranging from 8.99 to 10.95 corresponds to the NH group. IR spectra of compounds 6a–g revealed the disappearance of the carbonitrile band and the presence of four absorption bands in the region 3517–3314 cm⁻¹ characteristic of the (OH, NH₂, and NH) group in addition to two other bands in the regions 1705–1698 and 1651–1624 cm⁻¹ corresponding to the acetyl group and amidic carbonyl group, respectively. ¹H NMR spectra of compounds 6a–g showed the presence of a broad singlet signal corresponding to the amino group at a δ value ranging from 6.90 to 7.14 instead of the signal of the SCH₂ group that exists in the spectra of compounds 5a–g. The spectral data of compounds 7a–c revealed the conversion of the amino group of compounds 6c,f,g into a pyrrole ring. The presence of a tertiary alcoholic group in all compounds was ascertained from their ¹H NMR spectra, which possess a singlet signal at a δ value ranging from 4.56 to 4.89 equivalent to one proton of the (OH) group. ¹H NMR spectra of all compounds displayed characteristic signals at certain δ values that are equivalent to

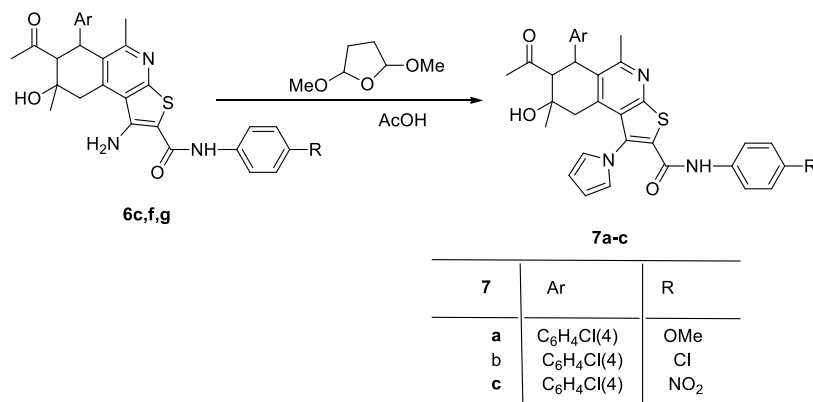
Scheme 2. Synthesis of Compounds 5a–g and 6a–g



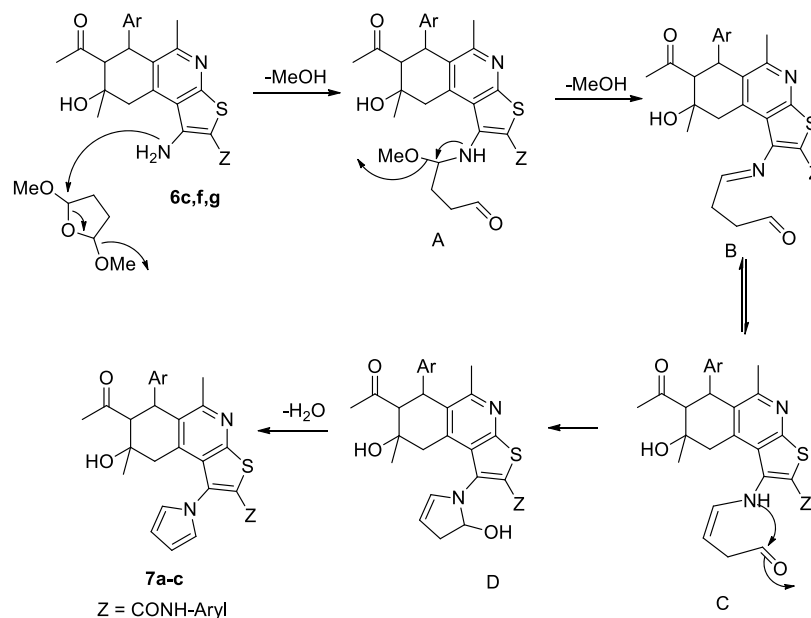
4	R
a	H
b	Me
c	OMe
d	Cl
e	NO ₂

5,6	Ar	R
a	C ₆ H ₄ Cl(4)	H
b	C ₆ H ₅	Me
c	C ₆ H ₄ Cl(4)	OMe
d	C ₆ H ₅	Cl
e	C ₆ H ₅	NO ₂
f	C ₆ H ₄ Cl(4)	Cl
g	C ₆ H ₄ Cl(4)	NO ₂

Scheme 3. Synthesis of Compounds 7a–c



Scheme 4. Mechanism of Formation of Compounds 7a–c



the protons of the cyclohexene ring and in accordance with those reported before.¹⁶

2.3. Crystal Structure. For compound 5a, X-ray intensity data were collected at 150 K from a colorless crystal (0.206 × 0.292 × 0.397 mm³) using a Bruker-AXS Smart APEX diffractometer and Mo K α radiation ($\lambda = 0.71073$ Å) under control of APEX3 software.¹⁸ Conversion of the raw data into F^2 values was performed with SAINT,¹⁸ and an empirical absorption correction and merging of equivalent reflections were carried out with TWINABS.¹⁹ The structure was solved by dual space methods (SHELXT)²⁰ and refined by full-matrix, least-squares procedures (SHELXL).²⁰ H atoms were included as riding contributions in idealized positions with isotropic displacement parameters 1.2–1.5 times those of the attached atoms. The final model was refined as a three-component twin.

The molecule adopts a chairlike conformation, with the tetrahydroisoquinoline unit forming the seat, the hydroxyl and acetyl substituents forming stubby legs, and the two phenyl rings forming the back. This conformation is partly determined by the intramolecular N3–H3...N1 hydrogen bond (H3...N1 = 2.19 Å; N3–H3...N1 = 147°) and the C–H... π (ring) interaction between C20–H20A and the C23...C28 ring (H...centroid = 2.97 Å; C–H...centroid = 121°)

(Figure 1). The N1/C5...C9 ring is somewhat twisted, with C8 0.0432(18) Å to one side of the mean plane (rms deviation = 0.0139) and C9 the same distance to the opposite side. A puckering analysis²¹ of the C1...C5/C9 ring gave the parameters $Q = 0.530(3)$ Å, $\theta = 54.3(3)^\circ$, and $\varphi = 93.5(4)^\circ$. In the crystal, O2–H2A...O3 (H2A...O3 = 2.16 Å; O2–H2A...O3 = 177°) and C21–H21A...O1 (H21A...O1 = 2.39 Å; C21–H21A...O1 = 136°) hydrogen bonds form chains parallel to (10–1). These are joined into pairs by C21–H21B...O2 (H21B...O2 = 2.42 Å; C21–H21B...O2 = 152°) hydrogen bonds (Figure 2), and the resulting ribbons are linked into layers parallel to the ac plane by pairwise C15–H15...N2 (H15...N2 = 2.55 Å; C15–H15...N2 = 147°) hydrogen bonds and C12–H12...Cg4 (Cg4 is the centroid of the C23...C28 benzene ring; H12...Cg4 = 2.72 Å; C12–H12...Cg4 = 134°) interactions (Figures 3 and 4).

3. CONCLUSIONS

Starting from readily available 7-acetyl-8-aryl-4-cyano-1,6-dimethyl-6-hydroxy-5,6,7,8-tetrahydroisoquinoline (1H)-2-thi-ones 3a,b, we have synthesized three new series of heterocyclic compounds with expected biological activities, substituted methylsulfanyloquinolines 5a–g, thieno[2,3-c]isoquinolines

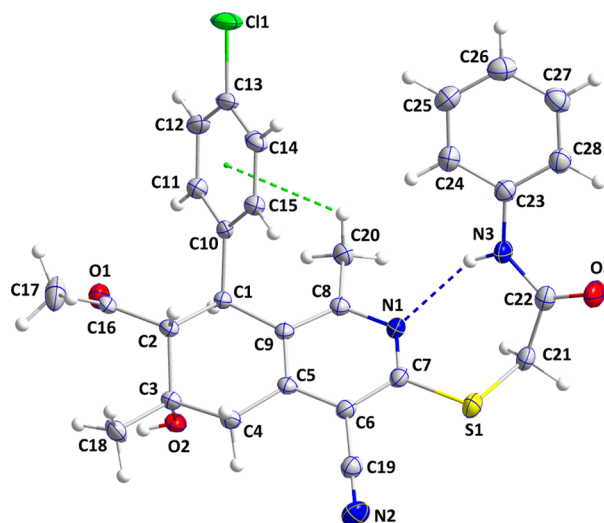


Figure 1. Perspective view of **5a** with a labeling scheme and 50% probability ellipsoids. The intramolecular N–H...N hydrogen bond and C–H... π (ring) interactions are depicted, respectively, by blue and green dashed lines.

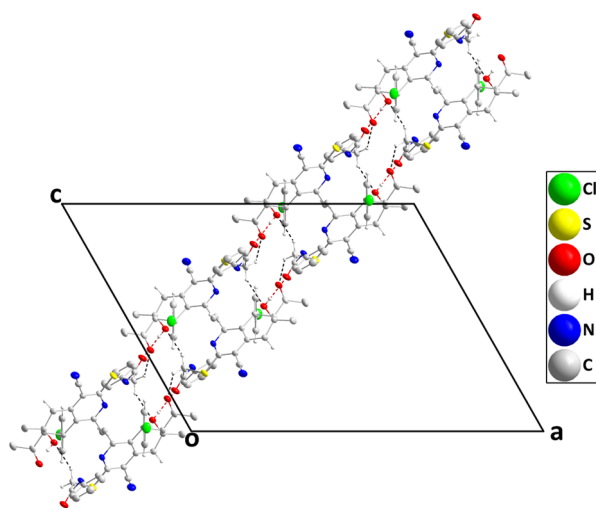


Figure 2. Portion of one double chain viewed along the *b*-axis direction, with O–H...O and C–H...O hydrogen bonds depicted, respectively, by red and black dashed lines.

6a–g, and pyrrolythieno[2,3-*c*]isoquinolines **7a–c**, which might have biological and medicinal value. Characterization of all new compounds was performed based on their elemental and modern spectral analyses. Also, the crystal structure of compounds **5a** was determined by X-ray diffraction analysis.

4. EXPERIMENTAL SECTION

4.1. Instrumentation and Chemicals. All reagents and solvents were purchased from commercial sources and used without further purification. Organic solvents were dried by standard methods. TLC was performed using 2.5 × 5 cm² aluminum plates coated with silica gel of 0.25 mm thickness; visualization was performed with iodine and under a UV lamp. Melting points were determined on a Gallan–Kamp apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu 470 IR-spectrophotometer (KBr; ν_{\max} in cm⁻¹). The ¹H NMR spectra were recorded on a Bruker 400 MHz spectrometer using CDCl₃ or dimethyl sulfoxide (DMSO)-*d*₆

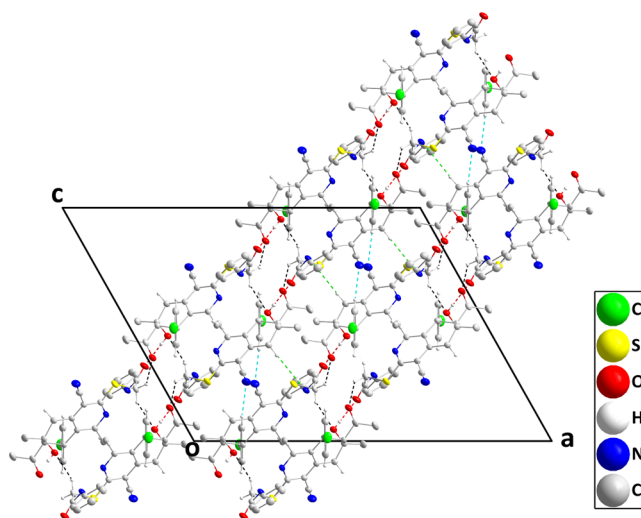


Figure 3. Portion of two adjacent chains viewed along the *b*-axis direction showing the C–H...N hydrogen bonds (light blue dashed lines) and C–H... π (ring) interactions (green dashed lines) binding them together.

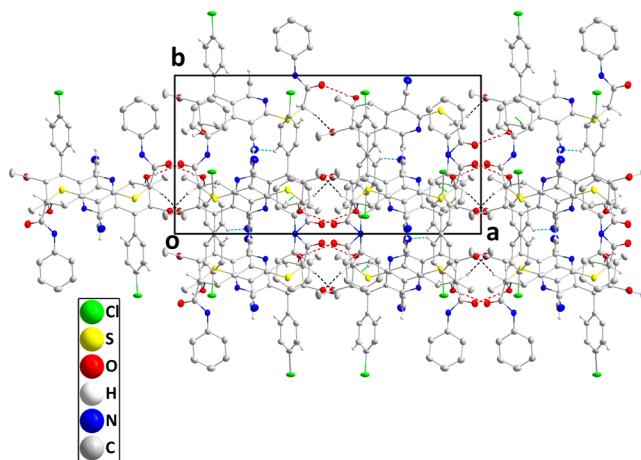


Figure 4. Packing viewed along the *c*-axis direction, with intermolecular interactions depicted as in Figures 2 and 3.

as a solvent and tetramethylsilane (TMS) as the reference standard. Coupling constants (*J* values) are given in Hertz (Hz). ¹H NMR splitting patterns are designated as singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q), or multiplet (m).

4.2. Synthesis of 7-Acetyl-8-aryl-4-cyano-1,5-dimethyl-6-hydroxy-5,6,7,8-tetrahydroisoquinoline-3(2*H*)-thiones **3a,b.** These compounds were prepared according to the reported method.¹⁶

4.3. Reaction of 7-Acetyl-8-aryl-4-cyano-1,5-dimethyl-6-hydroxy-5,6,7,8-tetrahydroisoquinoline-3(2*H*)-thiones **3a,b with *N*-Aryl-2-chloroacetamides **4a–e**, Synthesis of Compounds **5a–g**, and General Procedure.** A mixture of compound **3a,b** (10 mmol), respective *N*-aryl-2-chloroacetamides **4a–e** (10 mmol), and sodium acetate (1.0 g, 12 mmol) in ethanol (100 mL) was heated under reflux for 1 h. The precipitate that formed after it was allowed to stand at room temperature overnight was collected, washed with water, dried in air, and then recrystallized from the proper solvent to give compounds **5a–g**.

4.3.1. 7-Acetyl-8-(4-chlorophenyl)-4-cyano-1,6-dimethyl-6-hydroxy-3-(*N*-phenyl-carbamoylmethylsulfanyl)-5,6,7,8-tetrahydroisoquinoline (5a). It was obtained from the reaction of **3b** with *N*-phenyl-2-chloroacetamide (**4a**) as colorless needles (methanol). Yield: 86%; m.p.: 192–193 °C. IR (cm⁻¹): 3439 (OH); 3260 (NH); 3074, 3030 (C–H, aromatic); 2963, 2916 (C–H, aliphatic); 2215 (C≡N); 1706 (C=O, acetyl); 1682 (C=O, amide). ¹H NMR (DMSO-*d*₆): 10.24 (s, 1H, NH); 7.53–7.55, 7.29–7.31 (dd, *J* = 8 Hz, 4H, Ar–H); 7.25–7.27, 7.06–7.08 (dd, *J* = 8 Hz, 4H, Ar–H); 7.03 (m, 1H, Ar–H); 4.89 (s, 1H, OH); 4.55 (d, 1H, CH at C-8); 4.10–4.19 (dd, 2H, SCH₂), 3.25 (d, 1H, CH at C-5); 2.90–2.92 (m, 2H: CH at C-5 and CH at C-7), 2.15 (s, 3H, COCH₃); 1.93 (s, 3H, CH₃ attached to a pyridine ring); 1.28 (s, 3H, CH₃). Anal. calcd for C₂₈H₂₆ClN₃O₃S (519.13): C, 64.67; H, 5.04; N, 8.08; S, 6.16%. Found: C, 64.38; H, 5.01; N, 8.00; S, 6.29%.

4.3.2. 7-Acetyl-4-cyano-1,6-dimethyl-6-hydroxy-8-phenyl-3-[*N*-(4-tolyl)carbamoylmethylsulfanyl]-5,6,7,8-tetrahydroisoquinoline (5b). It was obtained from the reaction of **3a** with *N*-(4-tolyl)-2-chloroacetamide (**4b**); yield: 84%; m.p.: 151–153 °C (ethanol). IR (cm⁻¹): 3482 (OH); 3335 (NH); 3030 (C–H, aromatic); 2971, 2938 (C–H, aliphatic); 2221 (C≡N); 1702 (C=O, acetyl); 1666 (C=O, amide). ¹H NMR (400 MHz, CDCl₃): 8.99 (s, 1H, NH); 7.19–7.24 (m, 3H, Ar–H); 7.12–7.14 (d, *J* = 8 Hz, 2H, Ar–H); 6.94–6.96 (d, *J* = 8 Hz, 2H, Ar–H); 6.88–6.90 (d, *J* = 8 Hz, 2H, Ar–H); 4.28–4.31 (d, *J* = 12 Hz, 1H, CH at C-8); 3.78–3.88 (dd, *J* = 14 Hz, 2H, SCH₂); 3.33 (br.s, 1H, OH); 3.05–3.09, 2.86–2.91 (dd, 2H, CH₂ of a cyclohexene ring); 3.00–3.03 (d, *J* = 12 Hz, 1H, CH at C-7); 2.19 (s, 3H, CH₃ of the 4-tolyl group); 1.97 (s, 3H, COCH₃); 1.73 (s, 3H, CH₃ attached to a pyridine ring); 1.29 (s, 3H, CH₃). Anal. calcd for C₂₉H₂₉N₃O₃S (499.19): C, 69.72; H, 5.85; N, 8.41; S, 6.42. Found: C, 69.49; H, 5.80; N, 8.59; S, 6.43.

4.3.3. 7-Acetyl-8-(4-chlorophenyl)-4-cyano-1,5-dimethyl-6-hydroxy-3-(*N*-(4-methoxyphenyl)-carbamoylmethylsulfanyl)-5,6,7,8-tetrahydroisoquinoline (5c). It was obtained from the reaction of **3b** with *N*-(4-methoxyphenyl)-2-chloroacetamide (**4c**); yield: 81%; m.p.: 139–140 °C (methanol). IR (cm⁻¹): 3490 (OH); 3303 (NH); 3051 (C–H, aromatic); 2970, 2936, 2836 (C–H, aliphatic); 2219 (C≡N); 1701 (C=O, acetyl); 1666 (C=O, amide). ¹H NMR (DMSO-*d*₆): 10.09 (s, 1H, NH); 7.42–7.44 (d, *J* = 8 Hz, 2H, Ar–H); 7.30–7.32 (d, *J* = 8 Hz, 2H, Ar–H); 7.06–7.08 (d, *J* = 8 Hz, 2H, Ar–H); 6.84–6.86 (d, *J* = 8 Hz, 2H, Ar–H); 4.89 (s, 1H, OH); 4.55–4.57 (d, *J* = 8 Hz, 1H, CH at C-8); 4.09–4.11 (dd, 2H, SCH₂); 3.71 (s, 3H, OCH₃); 3.24–3.28 (d, 1H, CH at C-5); 2.87–2.91 (m, 2H: CH at C-5 and CH at C-7); 2.14 (s, 3H, COCH₃); 1.93 (s, 3H, CH₃ attached to a pyridine ring); 1.27 (s, 3H, CH₃). Anal. calcd For C₂₉H₂₈ClN₃O₄S (550.07): C, 63.32; H, 5.13; N, 7.64; S, 5.83%. Found: C, 63.13; H, 5.15; N, 7.55; S, 5.72%.

4.3.4. 7-Acetyl-3-[*N*-(4-chlorophenyl)-carbamoylmethylsulfanyl]-4-cyano-1,6-dimethyl-6-hydroxy-8-phenyl-5,6,7,8-tetrahydroisoquinoline (5d). It was obtained from the reaction of compound **3a** with *N*-(4-chlorophenyl)-2-chloroacetamide (**4d**) in the form of colorless cubic crystals; yield: 88%; m.p.: 189–190 °C (isopropanol). IR (cm⁻¹): 3460 (OH); 3290 (NH); 2217 (C≡N); 1700 (C=O, acetyl); 1671 (C=O, amide). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.33 (s, 1H, NH); 7.55–7.57 (d, *J* = 8 Hz, 2H, Ar–H); 7.31–7.33 (d, *J* = 8 Hz, 2H, Ar–H); 7.18–7.25 (m,

3H, Ar–H); 7.01–7.03 (d, *J* = 8 Hz, 2H, Ar–H); 4.83 (s, 1H, OH); 4.51–4.53 (d, *J* = 8 Hz, 1H, CH at C-8); 4.08–4.17 (dd, 2H, SCH₂); 3.24–3.29 (d, 1H, CH at C-5); 2.93–2.96 (m, 2H: CH at C-5 and CH at C-7); 2.11 (s, 3H, COCH₃); 1.89 (s, 3H, CH₃ attached to a pyridine ring); 1.28 (s, 3H, CH₃). Anal. calcd for C₂₈H₂₆ClN₃O₃S (519.13): C, 64.67; H, 5.04; N, 8.08; S, 6.16. Found: C, 64.37; H, 5.00; N, 8.43; S, 6.22.

4.3.5. 7-Acetyl-4-cyano-1,6-dimethyl-6-hydroxy-3-[*N*-(4-nitrophenyl)carbamoylmethylsulfanyl]-8-phenyl-5,6,7,8-tetrahydroisoquinoline (5e). It was obtained from the reaction of compound **3a** with *N*-(4-nitrophenyl)-2-chloroacetamide (**4e**) Yellow fine crystals, yield: 87%; m.p.: 220–222 °C (methanol). IR (cm⁻¹): 3427 (OH); 3273 (NH); 3074 (C–H, aromatic); 2970 (C–H, aliphatic); 2217 (C≡N); 1712 (C=O, acetyl); 1693 (C=O, amide). ¹H NMR (400 MHz, CDCl₃): δ 9.66 (s, 1H, NH); 8.01–8.03 (d, 2H, Ar–H); 7.41–7.44 (d, 2H, Ar–H); 7.20–7.25 (m, 3H, Ar–H); 6.90–6.91 (d, 2H, Ar–H); 4.30–4.33 (d, 1H, CH at C-8); 3.83–3.93 (dd, 2H, SCH₂); 3.03–3.11 (m, 2H: CH at C-5 and CH at C-7); 2.89–2.93 (d, 1H, CH at C-5); 2.01 (s, 3H, COCH₃); 1.75 (s, 3H, CH₃ attached to a pyridine ring); 1.31 (s, 3H, CH₃). Anal. calcd for C₂₈H₂₆N₄O₅S (530.16): C, 63.38; H, 4.94; N, 10.56; S, 6.04. Found: C, 63.21; H, 4.92; N, 10.44; S, 6.11.

4.3.6. 7-Acetyl-8-(4-chlorophenyl)-4-cyano-1,5-dimethyl-6-hydroxy-3-(*N*-(4-chlorophenyl)carbamoylmethylsulfanyl)-5,6,7,8-tetrahydroisoquinoline (5f). It was obtained from the reaction of **3b** with *N*-(4-chlorophenyl)-2-chloroacetamide (**4d**); yield: 91%; m.p.: 218–220 °C (methanol). IR (cm⁻¹): 3492 (OH); 3286 (NH); 2218 (C≡N); 1690 (C=O, acetyl); 1661 (C=O, amide). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.50 (s, 1H, NH); 7.58–7.60 (d, *J* = 8 Hz, 2H, Ar–H); 7.36–7.39 (d, *J* = 8 Hz, 2H, Ar–H); 7.29–7.31 (d, 2H, Ar–H); 7.05–7.07 (d, *J* = 8 Hz, 2H, Ar–H); 4.90 (s, 1H, OH); 4.67–4.69 (d, *J* = 8 Hz, 1H, CH at C-8); 4.10–4.20 (dd, 2H, SCH₂); 2.87–2.93 (m, 3H: CH₂ at C-5 and CH at C-7); 2.14 (s, 3H, COCH₃); 1.91 (s, 3H, CH₃ attached to a pyridine ring); 1.28 (s, 3H, CH₃). Anal. calcd For C₂₈H₂₅Cl₂N₃O₃S (553.10): C, 60.65; H, 4.54; N, 7.58; S, 5.78. Found: C, 60.34; H, 4.57; N, 7.68; S, 5.97.

4.3.7. 7-Acetyl-8-(4-chlorophenyl)-4-cyano-1,5-dimethyl-6-hydroxy-3-(*N*-(4-nitrophenyl)carbamoylmethylsulfanyl)-5,6,7,8-tetrahydroisoquinoline (5g). It was obtained from the reaction of **3b** with *N*-(4-nitrophenyl)-2-chloroacetamide (**4e**); yield: 84%; m.p.: 191–193 °C (isopropanol). IR (cm⁻¹): 3557 (OH); 3351 (NH); 3086 (C–H, aromatic); 2968, 2914 (C–H, aliphatic); 2215 (C≡N); 1694 (C=O, acetyl); 1667 (C=O, amide). ¹H NMR (DMSO-*d*₆): 10.95 (s, 1H, NH); 8.17–8.24 (m, 2H, Ar–H); 7.79–7.81 (d, 2H, Ar–H); 7.26–7.32 (m, 2H, Ar–H); 7.03–7.05 (d, 2H, Ar–H); 4.88 (s, 1H, OH); 4.53–4.55 (d, 1H, CH at C-8); 4.19–4.20 (dd, 2H, SCH₂); 3.24–3.29 (d, 1H, CH at C-5); 2.87–2.90 (m, 2H: CH at C-5 and CH at C-7); 2.13 (s, 3H, COCH₃); 1.86 (s, 3H, CH₃ attached to a pyridine ring); 1.27 (s, 3H, CH₃). Anal. calcd For C₂₈H₂₅ClN₄O₅S (565.04): C, 59.52; H, 4.46; N, 9.92; S, 5.67. Found: C, 59.77; H, 4.36; N, 9.80; S, 5.51.

4.4. 7-Acetyl-1-amino-6-aryl-2-(*N*-arylcarbamoyl)-5,8-dimethyl-8-hydroxy-6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinolines 6a–g. **4.4.1. Method A: Cyclization of 5,6,7,8-Tetrahydroisoquinolines 5a–g and General Procedure.** Compounds **5a–g** (10 mmol) were suspended in sodium ethoxide solution (0.10 g of sodium in 30 mL of abs. ethanol) and heated under reflux for 2 min. The yellow

precipitate that formed after cooling was collected and recrystallized from dioxane to give compounds **6a–g**.

4.4.1.1. 7-Acetyl-1-amino-6-(4-chlorophenyl)-5,8-dimethyl-8-hydroxy-2-[N-phenyl-carbamoyl]-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline (6a). It was obtained by cyclization of compound **5a**; yield: 87%; m.p.: 307–309 °C. IR (cm⁻¹): 3424 (OH); 3394, 3327 (NH₂, NH); 2967, 2917 (C–H, aliphatic); 1698 (C=O, acetyl); 1624 (C=O, conjugated amide). ¹H NMR (DMSO-*d*₆): 9.37 (s, 1H, NH); 7.69–7.71 (d, 2H, Ar–H); 7.31–7.35 (m, 4H, Ar–H); 7.02–7.11 (m, 5H: NH₂ and Ar–H); 4.72 (s, 1H, OH); 4.66–4.68 (d, 1H, CH at C-6); 3.57–3.62, 3.38–3.43 (dd, 2H, CH₂ of a cyclohexene ring); 2.85–2.88 (d, 1H, CH at C-7); 2.18 (s, 3H, COCH₃); 2.04 (s, 3H, CH₃ attached to a pyridine ring); 1.32 (s, 3H, CH₃). C₂₈H₂₆ClN₃O₃S (520.04): C, 64.67; H, 5.04; N, 8.08; S, 6.16. Found: C, 64.33; H, 5.01; N, 8.00; S, 6.52%.

4.4.1.2. 7-Acetyl-1-amino-5,8-dimethyl-8-hydroxy-6-phenyl-2-[N-(4-tolyl)carbamoyl]-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline (6b). It was synthesized by cyclization of **5b**; yield: 92%; m.p.: 306–308 °C. IR (cm⁻¹): 3500 (OH); 3424–3324 (NH₂, NH); 3027 (C–H, aromatic); 2918–2965 (C–H, aliphatic); 1703 (C=O, acetyl); 1640 (C=O, conjugated amide). ¹H NMR (400 MHz, DMSO-*d*₆): 9.29 (s, 1H, NH); 7.57–7.59 (d, *J* = 8 Hz, 2H, Ar–H); 7.24–7.27 (t, 2H, Ar–H); 7.19–7.20 (d, 1H, Ar–H); 7.13–7.15 (d, *J* = 8 Hz, 2H, Ar–H); 6.98–7.00 (d, *J* = 8 Hz, 2H, Ar–H); 7.02 (broad s, 2H, NH₂); 4.66 (s, 1H, OH); 4.62–4.64 (d, 1H, CH at C-8); 3.57–3.61 (d, 1H, CH₂); 3.39–3.44 (d, 1H, CH₂); 2.88–2.91 (d, 1H, CH at C-7); 2.29 (s, 3H, CH₃ of the tolyl group); 2.14 (s, 3H, COCH₃); 2.02 (s, 3H, CH₃ attached to a pyridine ring); 1.31 (s, 3H, CH₃). Anal. calcd for C₂₉H₂₉N₃O₃S (499.19): C, 69.72; H, 5.85; N, 8.41; S, 6.42%. Found: C, 69.54; H, 5.81; N, 8.09; S, 6.32%.

4.4.1.3. 7-Acetyl-1-amino-6-(4-chlorophenyl)-5,8-dimethyl-8-hydroxy-2-[N-(4-methoxyphenyl)carbamoyl]-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline (6c). It was obtained by cyclization of compound **5c**; yield: 93%; m.p.: 295–298 °C. IR (cm⁻¹): 3420 (OH); 3391, 3323 (NH₂, NH); 2915, 2834 (C–H aliphatic); 1701 (C=O, acetyl); 1630 (C=O, conjugated amide). ¹H NMR (DMSO-*d*₆): 9.28 (s, 1H, NH); 7.57–7.59 (d, 2H, Ar–H); 7.31–7.33 (d, 2H, Ar–H); 6.90–7.04 (m, 6H: NH₂ and Ar–H); 4.72 (s, 1H, OH); 4.65–4.68 (d, 1H, CH at C-6); 3.76 (s, 3H, OCH₃); 3.57–3.61, 3.39–3.43 (dd, 2H, CH₂ of a cyclohexene ring); 2.85–2.87 (d, 1H, CH at C-7); 2.18 (s, 3H, COCH₃); 2.04 (s, 3H, CH₃ attached to a pyridine ring); 1.32 (s, 3H, CH₃). Anal. calcd For C₂₉H₂₈ClN₃O₄S (550.07): C, 63.32; H, 5.13; N, 7.64; S, 5.83%. Found: C, 63.59; H, 5.20; N, 7.53; S, 5.66%.

4.4.1.4. 7-Acetyl-1-amino-2-[N-(4-chlorophenyl)-carbamoyl]-5,8-dimethyl-8-hydroxy-6-phenyl-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline (6d). It was obtained by cyclization of compound **5d**; yield: 90%; pale yellow amorphous substance; m.p.: 299–300 °C. IR (cm⁻¹): 3408–3323 (OH, NH₂, NH); 3026 (C–H, aromatic); 2963, 2916 (C–H, aliphatic); 1704 (C=O, acetyl); 1640 (C=O, conjugated amide). ¹H NMR (DMSO-*d*₆): 9.52 (br. s, 1H, NH); 7.74–7.76 (d, *J* = 8 Hz, 2H, Ar–H); 7.36–7.38 (d, *J* = 8 Hz, 2H, Ar–H); 7.17–7.27 (m, 3H, Ar–H); 7.08 (br. s, 2H, NH₂); 6.98–7.00 (d, *J* = 8 Hz, 2H, Ar–H); 4.70 (broad s, 1H, OH); 4.62–4.64 (d, 1H, CH at C-6); 3.57–3.61, 3.39–3.43 (dd, 2H, CH₂ of a cyclohexene ring); 2.88–2.91 (d, 1H, CH at C-7); 2.14 (s, 3H, COCH₃); 2.02 (s, 3H, CH₃ attached to a

pyridine ring); 1.32 (s, 3H, CH₃). Anal. calcd For C₂₈H₂₆ClN₃O₃S (520.04): C, 64.67; H, 5.04; N, 8.08; S, 6.16%. Found: C, 64.48; H, 5.20; N, 8.16; S, 6.09%.

4.4.1.5. 7-Acetyl-1-amino-5,8-dimethyl-8-hydroxy-2-[N-(4-nitrophenyl)carbamoyl]-6-phenyl-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline (6e). It was obtained by cyclization of compound **5e**; yield: 92%; m.p.: 302–303 °C. IR (cm⁻¹): 3430, 3324 (OH, NH₂, NH); 3026 (C–H, aromatic); 2962, 2917 (C–H, aliphatic); 1702 (C=O, acetyl); 1640 (C=O, amide). ¹H NMR (DMSO-*d*₆): 9.90 (br. s, 1H, NH); 8.09–8.11 (d, *J* = 8 Hz, 2H, Ar–H); 7.82–7.84 (d, *J* = 8 Hz, 2H, Ar–H); 7.25–7.27 (d, *J* = 8 Hz, 2H, Ar–H); 6.98–7.27 (m, 3H: NH₂ and Ar–H); 4.60–4.63 (d, 2H: OH and CH at C-6); 3.55–3.59, 3.42–3.46 (dd, 2H, CH₂ of a cyclohexene ring); 2.87–2.90 (d, 1H, CH at C-7); 2.14 (s, 3H, COCH₃ of acetyl); 2.00 (s, 3H, CH₃ attached to a pyridine ring); 1.31 (s, 3H, CH₃). Anal. calcd for C₂₈H₂₆N₄O₅S (530.16): C, 63.38; H, 4.94; N, 10.56; S, 6.04%. Found: C, 63.49; H, 4.97; N, 10.36; S, 5.84%.

4.4.1.6. 7-Acetyl-1-amino-6-(4-chlorophenyl)-5,8-dimethyl-8-hydroxy-2-[N-(4-chlorophenyl)carbamoyl]-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline (6f). It was obtained by cyclization of compound **5f**; yield: 90%; m.p.: 315–316 °C. IR (cm⁻¹): 3408, 3327 (OH, NH₂, NH); 2967, 2915 (C–H, aliphatic); 1705 (C=O, acetyl); 1644 (C=O, amide). ¹H NMR (DMSO-*d*₆): 9.53 (s, 1H, NH); 7.74–7.76 (d, *J* = 8 Hz, 2H, Ar–H); 7.31–7.33 (d, *J* = 8 Hz, 2H, Ar–H); 7.27–7.29 (d, 2H, Ar–H); 7.10 (s, 2H, NH₂); 7.05–7.07 (d, *J* = 8 Hz, 2H, Ar–H); 4.75 (s, 1H, OH); 4.55–4.57 (d, 1H, CH at C-6); 3.45–3.60 (dd, 2H, CH₂ of a cyclohexene ring); 3.23–3.25 (d, 1H, CH at C-7); 2.18 (s, 3H, COCH₃); 2.05 (s, 3H, CH₃ attached to a pyridine ring); 1.34 (s, 3H, CH₃). Anal. calcd For C₂₈H₂₅Cl₂N₃O₃S (553.10): C, 60.65; H, 4.54; N, 7.58; S, 5.78%. Found: C, 60.80; H, 4.41; N, 7.63; S, 5.63%.

4.4.1.7. 7-Acetyl-1-amino-6-(4-chlorophenyl)-5,8-dimethyl-8-hydroxy-2-[N-(4-nitro-phenyl)carbamoyl]-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline (6g). It was obtained by cyclization of compound **5g**; yield: 87%; m.p.: 295–296 °C. IR (cm⁻¹): 3517 (OH); 3436, 3314 (NH₂, NH); 2980 (C–H, aliphatic); 1702 (C=O, acetyl); 1651 (C=O, amide). ¹H NMR (DMSO-*d*₆): 9.94 (s, 1H, NH); 8.12–8.14 (d, *J* = 8 Hz, 2H, Ar–H); 7.87–7.89 (d, *J* = 8 Hz, 2H, Ar–H); 7.30–7.32 (d, *J* = 8 Hz, 2H, Ar–H); 7.14 (broad s, 2H, NH₂); 7.02–7.04 (d, *J* = 8 Hz, 2H, Ar–H); 4.71 (s, 1H, OH); 4.64–4.67 (d, *J* = 12 Hz, 1H, CH at C-6); 3.56–3.60, 3.40–3.45 (dd, 2H, CH₂ of a cyclohexene ring); 2.84–2.87 (d, *J* = 12 Hz, 1H, CH at C-7); 2.18 (s, 3H, COCH₃); 2.03 (s, 3H, CH₃ attached to a pyridine ring); 1.32 (s, 3H, CH₃). C₂₈H₂₅ClN₄O₅S (565.04): C, 59.52; H, 4.46; N, 9.92; S, 5.67%. Found: C, 59.71; H, 4.43; N, 10.00; S, 5.43%.

4.4.2. Method B: Reaction of 2a,b with N-Aryl-2-chloroacetamides 4a-e in the Presence of Sodium Ethoxide and General Procedure. To a mixture of compound **3a,b** (10 mmol), the respective *N*-aryl-2-chloroacetamide **4a–e** (10 mmol) in ethanol, an ethanolic solution of sodium ethoxide, prepared by dissolving 0.30 g of sodium in 40 mL of ethanol, was added. The reaction mixture was heated under reflux for 5 min. The precipitate that formed while hot was collected, washed several times with water, dried in air, and then recrystallized from dioxane. The products that were obtained are identical to those reported above (**Method A**) in all aspects; yield: 73–82%.

4.5. Reaction of Compounds 6c,g,f with 2,5-Dimethoxytetrahydrofuran, Synthesis of 1-(Pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinolines 7a–c, and General Procedure. A mixture of compound 6c,g,f (2 mmole) and 2,5-dimethoxytetrahydrofuran (2 mL) in glacial acetic acid (10 mL) was heated under reflux for 1 h and then allowed to cool. The product that formed was collected and recrystallized from ethanol to give yellowish white crystals of 7a–c.

4.5.1. 7-Acetyl-6-(4-chlorophenyl)-5,8-dimethyl-8-hydroxy-2-[N-(4-methoxyphenyl) carbamoyl]-1-(pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline (7a). It was obtained by the reaction of compound 6c with 2,5-dimethoxytetrahydrofuran; yield: 68%; m.p.: 311–313 °C. IR (cm⁻¹): 3482 (OH), 3364 (NH); 3102 (C–H aromatic); 2969, 2934, 2836 (C–H aliphatic); 1702 (C=O, acetyl); 1632 (C=O, amide). ¹H NMR (DMSO-*d*₆): 8.18 (s, 1H, NH); 7.20–7.33 (m, 6H, Ar–H); 7.02–7.04 (d, 2H, pyrrole-H); 6.89–6.92 (d, 2H, pyrrole-H); 6.51 (m, 2H, Ar–H); 4.68–4.70 (d, 1H, CH at C-6); 4.56 (s, 1H, OH); 3.73 (s, 3H, CH₃, OCH₃); 2.86–2.89 (d, 1H, CH at C-7); 2.77–2.81, 2.13–2.18 (dd, 2H, CH₂ of a cyclohexene ring); 2.10 (s, 3H, COCH₃); 2.09 (s, 3H, CH₃ attached to a pyridine ring); 1.02 (s, 3H, CH₃). Anal. Calcd. For C₃₃H₃₀ClN₃O₄S (600.13): C, 66.05; H, 5.04; N, 7.00; S, 5.34. Found: C, 66.14; H, 5.02; N, 6.89; S, 5.00%.

4.5.2. 7-Acetyl-7-(4-chlorophenyl)-5,8-dimethyl-8-hydroxy-2-[N-(4-chlorophenyl) carbamoyl]-1-(pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline (7b). It was obtained by the reaction of compound 6g with 2,5-dimethoxytetrahydrofuran; yield: 79%; m.p.: 310–312 °C. IR (cm⁻¹): 3499 (OH); 3358 (NH); 2972 (C–H, aliphatic); 1702 (C=O, acetyl); 1641 (C=O, amide). ¹H NMR (DMSO-*d*₆): 8.60 (s, 1H, NH); 7.18–7.41 (m, 8H: pyrrole-H and Ar–H); 7.01–7.03 (d, 2H, Ar–H); 6.51 (s, 2H, pyrrole-H); 4.66–4.69 (d, 1H, CH at C-6); 4.56 (s, 1H, OH); 2.86–2.88 (d, 1H, CH at C-7); 2.77–2.82, 2.11–2.16 (dd, 2H, CH₂ of a cyclohexene ring); 2.10 (s, 3H, COCH₃); 2.09 (s, 3H, CH₃ attached to a pyridine ring); 1.01 (s, 3H, CH₃). Anal. calcd. For C₃₂H₂₇Cl₂N₃O₃S (604.55): C, 63.58; H, 4.50; Cl, 11.73; N, 6.95; S, 5.30. Found: C, 63.66; H, 4.46; N, 6.73; S, 5.18%.

4.5.3. 7-Acetyl-6-(4-chlorophenyl)-5,8-dimethyl-8-hydroxy-2-[N-(4-nitrophenyl) carbamoyl]-1-(pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline (7c). It was obtained by the reaction of compound 6f with 2,5-dimethoxytetrahydrofuran; yield: 79%; m.p.: 315–317 °C. IR: 3492 (OH); 3356 (NH); 2967, 2920 (C–H, aliphatic); 1701 (C=O, acetyl); 1667 (C=O, amide). ¹H NMR (DMSO-*d*₆): 9.19 (s, 1H, NH); 8.22–8.24 (d, 2H, Ar–H); 7.02–7.64 (m, 8H: pyrrole-H and Ar–H); 6.46 (s, 2H, pyrrole-H); 4.67–4.70 (d, 1H, CH at C-6); 4.57 (s, 1H, OH); 2.88–2.90 (d, 1H, CH at C-7); 2.81–2.85, 2.12–2.17 (dd, 2H, CH₂ of a cyclohexene ring); 2.11 (s, 3H, COCH₃); 2.10 (s, 3H, CH₃ attached to a pyridine ring); 1.02 (s, 3H, CH₃). Anal. calcd For C₃₂H₂₇ClN₄O₃S (615.10): C, 62.49; H, 4.42; N, 9.11; S, 5.21%. Found: C, 62.17; H, 4.29; N, 9.00; S, 5.45%.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.1c00050>.

IR, ¹H NMR, and ¹³C NMR spectra of all newly synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- Scott, J. D.; Williams, R. M. Chemistry and biology of the tetrahydroisoquinoline antitumor antibiotics. *Chem. Rev.* **2002**, *102*, 1669–1730.
- Bernan, V. S.; Montenegro, D. A.; Korshalla, J. D.; Maiese, W. M.; Steinberg, D. A. M. J.; Greenstein, M. Bioalcalomycins new antibiotics produced by the marine Streptomyces spp. LL-31F508: taxonomy and fermentation. *J. Antibiot.* **1994**, *47*, 1417–1424.
- Andujar, S.; Suvire, F.; Berenguer, I.; Cabedo, N.; Marin, P.; Moreno, L.; Ivorra, M. D.; Cortes, D.; Enriz, R. D. Tetrahydroisoquinolines acting as dopaminergic ligands. A molecular modeling study using MD simulations and QM calculations. *J. Mol. Model.* **2012**, *18*, 419–431.
- Dukat, M.; Taroua, M.; Dahdouh, A.; Siripurapu, U.; Damag, M. I.; Martin, B. R.; Glennon, R. A. 8-Amino-5,6,7,8-tetrahydroisoquinolines as novel antinociceptive agents. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3651–3654.
- Xu, R.; Dwoskin, L. P.; Grinevich, V.; Sumithran, S. P.; Crooks, P. A. Synthesis and evaluation of conformationally restricted pyridine N-alkylated nicotine analogs as nicotinic acetylcholine receptor antagonists. *Drug Dev. Res.* **2002**, *55*, 173–186.
- Meijler, M. M.; Matsushita, M.; Altobelli, L. J.; Wirsching, P.; Janda, K. D. A New Strategy for Improved Nicotine Vaccines Using Conformationally Constrained Haptens. *J. Am. Chem. Soc.* **2003**, *125*, 7164–7165.
- Carroll, F. I.; Robinson, T. P.; Brieady, L. E.; Atkinson, R. N.; Mascarella, S. W.; Damaj, M. I.; Martin, B. R.; Navarro, H. A. Synthesis and nicotinic acetylcholine receptor binding properties of bridged and fused ring analogues of epibatidine. *J. Med. Chem.* **2007**, *50*, 6383–6391.

(8) Demers, S.; Stevenson, H.; Candler, J.; Bashore, C. G.; Arnold, E. P.; O'Neill, B. T.; Coe, J. W. Pyridine analogs of (-)-cytisine and varenicline: cholinergic receptor probes. *Tetrahedron Lett.* **2008**, *49*, 3368–3371.

(9) Martin, R. E.; Lehamann, J.; Alzieu, T.; Lenz, M.; Corrales, M. A. C.; Aebi, J. D.; Marki, H. P.; Kuhn, B.; Amrein, K.; Mayweg, A. V.; Britton, R. Synthesis of annulated pyridines as inhibitors of aldosterone synthase (CYP11B2). *Org. Biomol. Chem.* **2016**, *14*, 5922–5927.

(10) Uredi, D.; Motati, D. R.; Watkins, E. B. A Simple, Tandem Approach to the Construction of Pyridine Derivatives under Metal-free Conditions: A One-step Synthesis of the Monoterpene Natural Product, (-)-Actinidine. *Chem. Commun.* **2019**, *55*, 3270–3272.

(11) Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. Recent advances in directed C–H functionalizations using monodentate nitrogen-based directing groups. *Org. Chem. Front.* **2014**, *1*, 843–895.

(12) Bundhoo, S. S.; Anderson, R. A.; Sagan, E.; Dada, J.; Harris, R.; Halcox, J. P.; Lang, D.; James, P. E. Direct Vasoactive Properties of Thienopyridine-Derived Nitrosothiols. *J. Cardiovasc. Pharmacol.* **2011**, *58*, 550–558.

(13) Peters, R. J. G.; Mehta, S. R.; Fox, K. A. A.; Zhao, F.; Lewis, B. S.; Kopecky, S. L.; Diaz, R.; Commerford, P. J.; Valentin, V.; Yusuf, S. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation* **2003**, *108*, 1682–1687.

(14) Leal, B.; Afonso, I. F.; Rodrigues, C. R.; Abreu, P. A.; Garrett, R.; Pinheiro, L. C. S.; Azevedo, A. R.; Borges, J. C.; Vegi, P. F.; Santos, C. C. C.; da Silveira, F. C. A.; Cabral, L. M.; Frugulhetti, I. C. P. P.; Bernardino, A. M. R.; Santos, D. O.; Castro, H. C. Antibacterial profile against drug-resistant *Staphylococcus epidermidis* clinical strain and structure–activity relationship studies of 1H-pyrazolo-[3,4-b]pyridine and thieno[2,3-b]pyridine derivatives. *Bioorg. Med. Chem.* **2008**, *16*, 8196–8204.

(15) Hassan, A. Y.; Sarg, M. T.; Said, M. M.; El-Sebaey, S. A. Utility of thieno[2,3-b] pyridine derivatives in the synthesis of some condensed heterocyclic compounds with expected biological activity *Univers. Org. Chem.* 2013, DOI: 10.7243/2053-7670-1-2.

(16) Ozols, A. I.; Pelcher, Y. E.; Kalme, Z. A.; Popelis, Y. Y.; Turovskis, I. V.; Duburs, G. Y. Synthesis and chemical properties of 8-aryl-7-acyl-1,6-dimethyl-6-hydroxy-4-cyano-5,6,7,8-tetrahydro-3(2H)-isoquinolinones and isoquinolinethiones. *Chem. Heterocycl. Compd.* **1996**, *32*, 52–58.

(17) Amarnath, V.; Anthony, D. C.; Amarnath, K.; Valentine, W. M.; Wetterau, L. A.; Graham, D. G. Intermediates in the Paal-Knorr synthesis of pyrroles. *J. Org. Chem.* **1991**, *56*, 6924–6931.

(18) APEX3; Bruker-AXS: Madison, WI, 2015.

(19) Sheldrick, G. M. TWINABS; University of Göttingen: Göttingen, Germany, 2009.

(20) (a) Sheldrick, G. M. SHELXT. *Acta Cryst.* **2015**, *A71*, 3.

(b) Sheldrick, G. M. Crystal structure refinement with SHELXL. *Acta Cryst.* **2015**, *C71*, 3–8.

(21) Cremer, D.; Pople, J. A. A General Definition of Ring Puckering Coordinates. *J. Am. Chem. Soc.* **1975**, *97*, 1354–1358.