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

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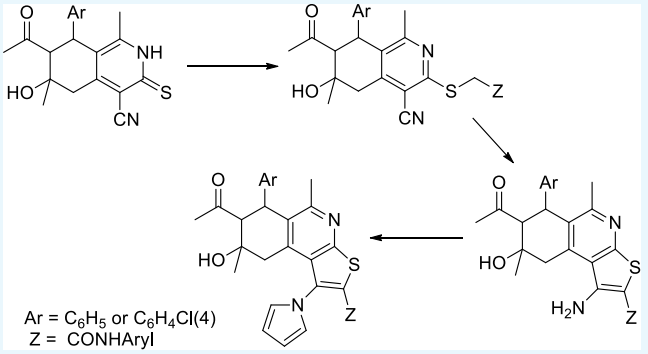
ABSTRACT: The starting compounds 7-acetyl-8-aryl-4-cyano-1,6-dimethyl-6-hydroxy-5,6,7,8-tetrahydroisoquinoline(2*H*)-3-thiones **3a,b** were synthesized and reacted with some *N*-aryl-2-chloroacetamides **4a−e** in the presence of sodium acetate to produce 7-acetyl-8-aryl-3-(*N*-arylcarbamoylmethylsulfanyl)-4-cyano-1,6-dimethyl-6-hydroxy-5,6,7,8-tetrahydroisoquinolines **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 agents[4] 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-tetrahyroisoquinolines and/or 6,7,8,9-tetrahyrothieno[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 acetylcyclohexanone derivatives **1a,b** with cyanothioacetamide (**2**) according to the reported method (Scheme 1).[16]

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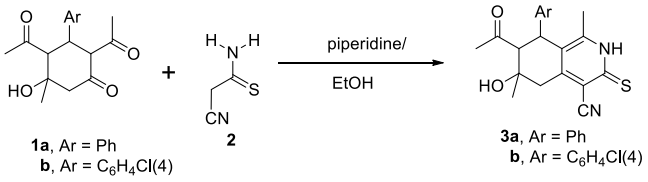
Scheme 1. Synthesis of Compounds 3a,b



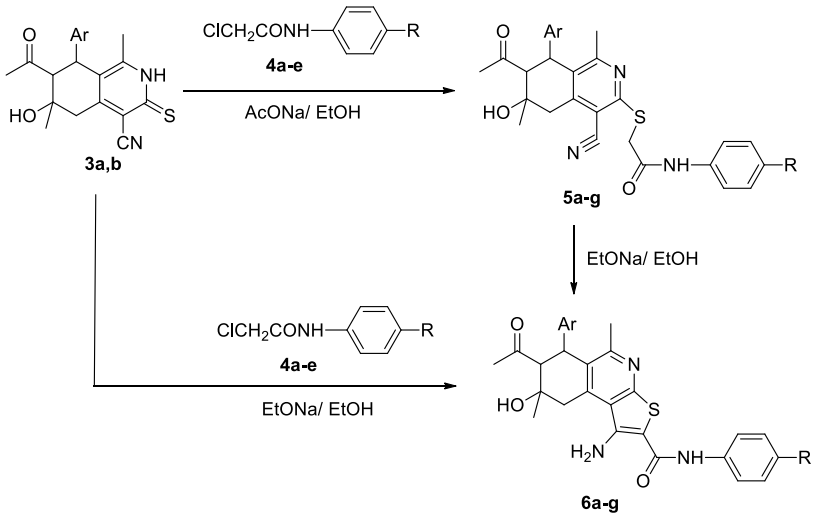
The reaction of compounds **3a,b** with *N*-aryl-2-chloroacetamides **4a−e** by refluxing in ethanol, in the presence of slightly excess molar amounts of sodium acetate, for 1 h gave 7-acetyl-8-aryl-3-(*N*-arylcarbamoyl-methylsulfanyl)-4-cyano-1,6-dimethyl-6-hydroxy-8-phenyl-5,6,7,8-tetrahydroisoquinolines **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). ^{1}H NMR spectra of compounds **5a−g** showed the presence of a double doublet signal[16] that corresponds to the SCH_2 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, NH_2, 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. ^{1}H 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 SCH_2 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 ^{1}H 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. ^{1}H 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	$C_6H_4Cl(4)$	H
b	C_6H_5	Me
c	$C_6H_4Cl(4)$	OMe
d	C_6H_5	Cl
e	C_6H_5	NO_2
f	$C_6H_4Cl(4)$	Cl
g	$C_6H_4Cl(4)$	NO_2

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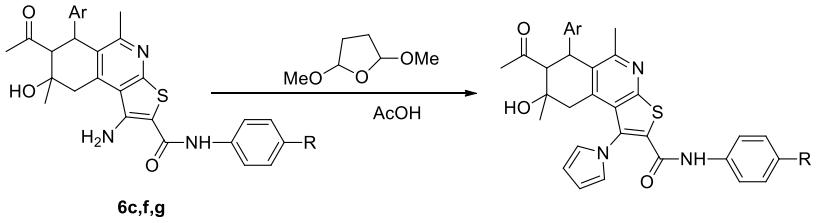
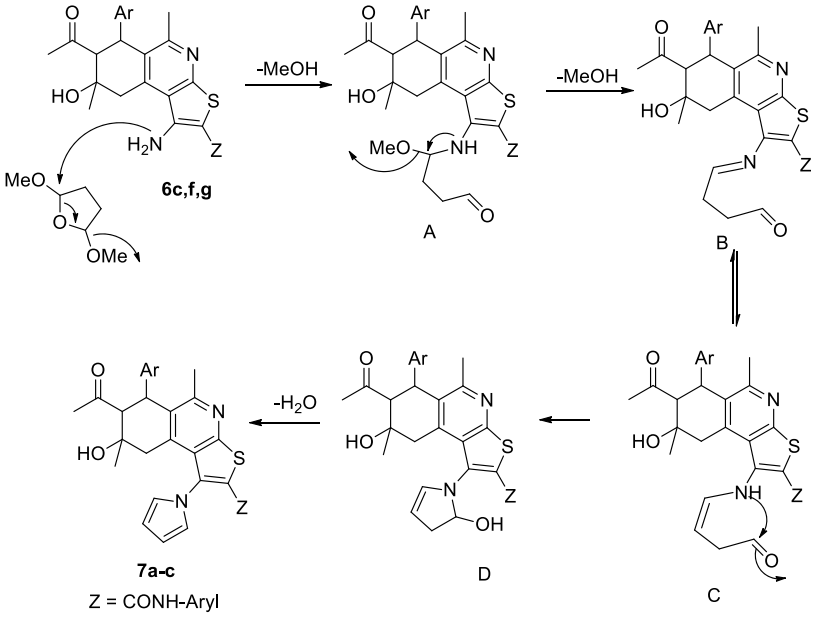
Scheme 3. Synthesis of Compounds 7a−c



7	Ar	R
a	$C_6H_4Cl(4)$	OMe
b	$C_6H_4Cl(4)$	Cl
c	$C_6H_4Cl(4)$	NO_2

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 mm^3) using a Bruker-AXS Smart APEX diffractometer and Mo Kα radiation (λ = 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 tetrahydroisoquinoxaline 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 analysis[21] of the C1···C5/C9 ring gave the parameters Q = 0.530(3) Å, θ = 54.3(3)°, and φ = 93.5(4)°. 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 (1*H*)-2-thiones **3a,b**, we have synthesized three new series of heterocyclic compounds with expected biological activities, substituted methylsulfanylisoquinolines **5a−g**, thieno[2,3-*c*]isoquinolines

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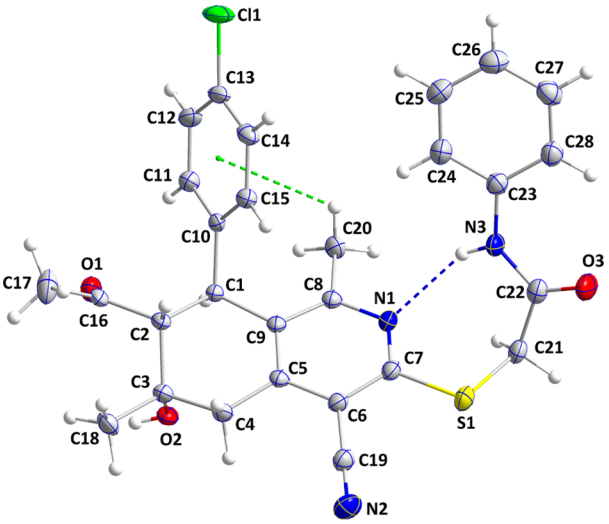

Figure 1. Perspective view of **5a** with a labeling scheme and 50% probability ellipsoids. The intramolecular N−H···N hydrogen bond and C−H···π(ring) interactions are depicted, respectively, by blue and green dashed lines.

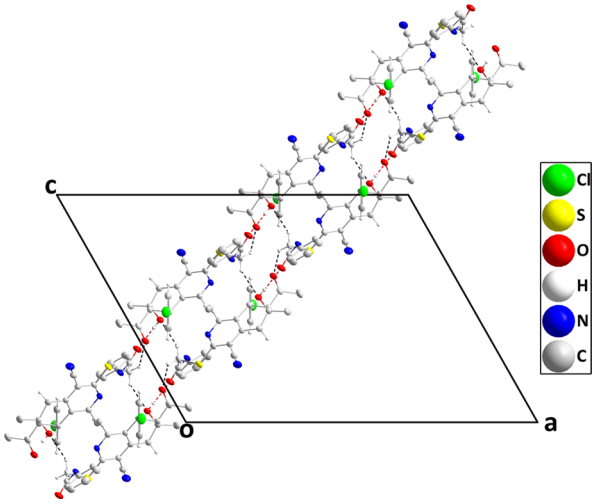

Figure 2. Portion of one double chain viewed along the *b*-axis direction, with O−H···O and C−H···O hydrogen bonds depicted, respectively, by red and black dashed lines.

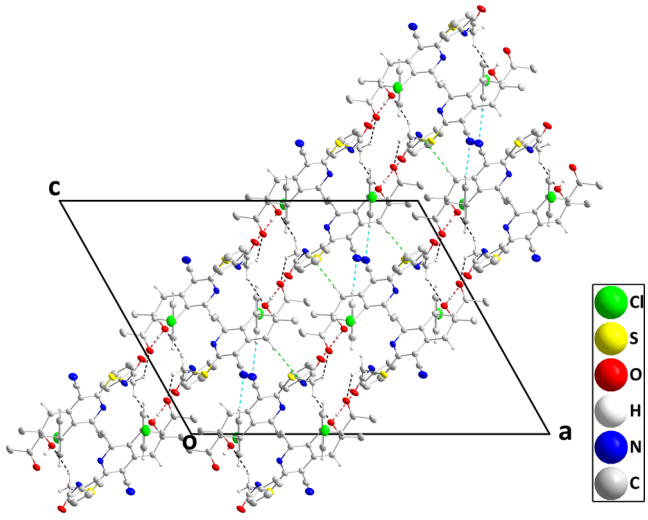

Figure 3. Portion of two adjacent chains viewed along the *b*-axis direction showing the C−H···N hydrogen bonds (light blue dashed lines) and C−H···π(ring) interactions (green dashed lines) binding them together.

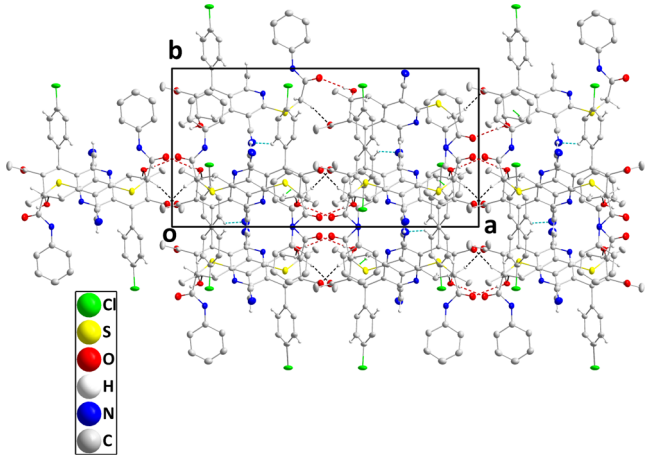

Figure 4. Packing viewed along the *c*-axis direction, with intermolecular interactions depicted as in Figures 2 and 3.

6a−g, and pyrrolylthieno[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 cm^2 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 ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer using $CDCl_3$ or dimethyl sulfoxide (DMSO)-d_6 as a solvent and tetramethylsilane (TMS) as the reference standard. Coupling constants (J values) are given in Hertz (Hz). ^{1}H 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**.

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*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). ^{1}H 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, SCH_2), 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, $COCH_3$); 1.93 (s, 3H, CH_3 attached to a pyridine ring); 1.28 (s, 3H, CH_3). Anal. calcd for $C_{28}H_{26}ClN_3O_3S$ (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). ^{1}H NMR (400 MHz, $CDCl_3$): 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, SCH_2); 3.33 (br.s, 1H, OH); 3.05−3.09, 2.86−2.91 (dd, 2H, CH_2 of a cyclohexene ring); 3.00−3.03 (d, *J* = 12 Hz, 1H, CH at C-7); 2.19 (s, 3H, CH_3 of the 4-tolyl group); 1.97 (s, 3H, $COCH_3$); 1.73 (s, 3H, CH_3 attached to a pyridine ring); 1.29 (s, 3H, CH_3). Anal. calcd for $C_{29}H_{29}N_3O_3S$ (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). ^{1}H 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, SCH_2); 3.71 (s, 3H, OCH_3); 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, $COCH_3$); 1.93 (s, 3H, CH_3 attached to a pyridine ring); 1.27 (s, 3H, CH_3). Anal. calcd For $C_{29}H_{28}ClN_3O_4S$ (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 by 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).^{1}H 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, SCH_2); 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, $COCH_3$); 1.89 (s, 3H, CH_3 attached to a pyridine ring); 1.28 (s, 3H, CH_3). Anal. calcd for $C_{28}H_{26}ClN_3O_3S$ (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). ^{1}H NMR (400 MHz, $CDCl_3$): 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, SCH_2); 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, $COCH_3$); 1.75 (s, 3H, CH_3 attached to a pyridine ring); 1.31 (s, 3H, CH_3). Anal. calcd for $C_{28}H_{26}N_4O_5S$ (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). ^{1}H 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, SCH_2); 2.87−2.93 (m, 3H: CH_2 at C-5 and CH at C-7); 2.14 (s, 3H, $COCH_3$); 1.91 (s, 3H, CH_3 attached to a pyridine ring); 1.28 (s, 3H, CH_3). Anal. calcd For $C_{28}H_{25}Cl_2N_3O_3S$ (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). ^{1}H 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, SCH_2); 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, $COCH_3$); 1.86 (s, 3H, CH_3 attached to a pyridine ring); 1.27 (s, 3H, CH_3). Anal. calcd For $C_{28}H_{25}ClN_4O_5S$ (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

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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 (NH_2, 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: NH_2 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, CH_2 of a cyclohexene ring); 2.85−2.88 (d, 1H, CH at C-7); 2.18 (s, 3H, $COCH_3$); 2.04 (s, 3H, CH_3 attached to a pyridine ring); 1.32 (s, 3H, CH_3). $C_{28}H_{26}ClN_3O_3S$ (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 (NH_2, 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, NH_2); 4.66 (s, 1H, OH); 4.62−4.64 (d, 1H, CH at C-8); 3.57−3.61 (d, 1H, CH_2); 3.39−3.44 (d, 1H, CH_2); 2.88−2.91 (d, 1H, CH at C-7); 2.29 (s, 3H, CH_3 of the tolyl group); 2.14 (s, 3H, $COCH_3$); 2.02 (s, 3H, CH_3 attached to a pyridine ring); 1.31 (s, 3H, CH_3). Anal. calcd for $C_{29}H_{29}N_3O_3S$ (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 (NH_2, 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: NH_2 and Ar−H); 4.72 (s, 1H, OH); 4.65−4.68 (d, 1H, CH at C-6); 3.76 (s, 3H, OCH_3); 3.57−3.61, 3.39−3.43 (dd, 2H, CH_2 of a cyclohexene ring); 2.85−2.87 (d, 1H, CH at C-7); 2.18 (s, 3H, $COCH_3$); 2.04 (s, 3H, CH_3 attached to a pyridine ring); 1.32 (s, 3H, CH_3). Anal. calcd For $C_{29}H_{28}ClN_3O_4S$ (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, NH_2, 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, NH_2); 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, CH_2 of a cyclohexene ring); 2.88−2.91 (d, 1H, CH at C-7); 2.14 (s, 3H, $COCH_3$); 2.02 (s, 3H, CH_3 attached to a pyridine ring); 1.32 (s, 3H, CH_3). Anal. calcd For $C_{28}H_{26}ClN_3O_3S$ (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, NH_2, 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: NH_2 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, CH_2 of a cyclohexene ring); 2.87−2.90 (d, 1H, CH at C-7); 2.14 (s, 3H, $COCH_3$ of acetyl); 2.00 (s, 3H, CH_3 attached to a pyridine ring); 1.31 (s, 3H, CH_3). Anal. calcd for $C_{28}H_{26}N_4O_5S$ (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, NH_2, 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, NH_2); 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, CH_2 of a cyclohexene ring); 3.23−3.25 (d, 1H, CH at C-7); 2.18 (s, 3H, $COCH_3$); 2.05 (s, 3H, CH_3 attached to a pyridine ring); 1.34 (s, 3H, CH_3). Anal. calcd For $C_{28}H_{25}Cl_2N_3O_3S$ (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 (NH_2, 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, NH_2); 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, CH_2 of a cyclohexene ring); 2.84−2.87 (d, J = 12 Hz, 1H, CH at C-7); 2.18 (s, 3H, $COCH_3$); 2.03 (s, 3H, CH_3 attached to a pyridine ring); 1.32 (s, 3H, CH_3). $C_{28}H_{25}ClN_4O_5S$ (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%.

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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). ^{1}H 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, CH_3, OCH_3); 2.86−2.89 (d, 1H, CH at C-7); 2.77−2.81, 2.13−2.18 (dd, 2H, CH_2 of a cyclohexene ring); 2.10 (s, 3H, $COCH_3$); 2.09 (s, 3H, CH_3 attached to a pyridine ring); 1.02 (s, 3H, CH_3). Anal. Cacld. For $C_{33}H_{30}ClN_3O_4S$ (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). ^{1}H 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, CH_2 of a cyclohexene ring); 2.10 (s, 3H, $COCH_3$); 2.09 (s, 3H, CH_3 attached to a pyridine ring); 1.01 (s, 3H, CH_3). Anal. calcd. For $C_{32}H_{27}Cl_2N_3O_3S$ (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). ^{1}H 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, CH_2 of a cyclohexene ring); 2.11 (s, 3H, $COCH_3$); 2.10 (s, 3H, CH_3 attached to a pyridine ring); 1.02 (s, 3H, CH_3). Anal. calcd For $C_{32}H_{27}ClN_4O_5S$ (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

Supporting Information

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

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

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Notes

The authors declare no competing financial interest.

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