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Synthesis and Characterization of Novel Functionally Substituted Planar Pyrimidothienoisoquinolines and Nonplanar (3a*R*, 4*S*, 9a*S*)-pyrazolo[3,4-*g*]isoquinolines

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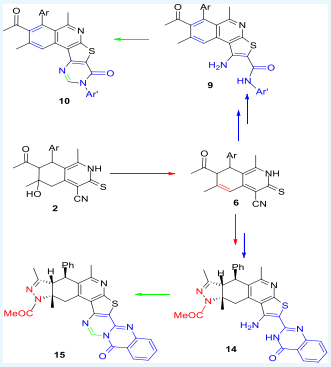
ABSTRACT: 7-Acetyl-8-aryl-4-cyano-1,6-dimethyl-6-hydroxy-5,6,7,8-tetrahydroisoquinolin-3(2*H*)-thiones **2a**,**b** are prepared and dehydrated to give 7-acetyl-8-aryl-4-cyano-1,6-dimethyl-6-hydroxy-7,8-dihydrodroisoquinolin-3(2*H*)-thiones **6a**,**b** via a novel method by heating with acetyl chloride in acetic acid. The reaction of both compounds **2a**,**b** and **6a**,**b** with *N*-aryl-2-chloroacetamides **7a**−**c** under two different conditions gave the same corresponding products, 7-acetyl-8-aryl-3-(*N*-aryl)carbamoylmethylsulfanyl-4-cyano-1,6-dimethyl-7,8-dihydroisoquinolines **8a**−**e**, in high yields. On treatment of compounds **8a**,**b**,**e** in methanol with a slightly excess molar amount of sodium methoxide, they underwent intramolecular Thorpe−Ziegler cyclization followed by spontaneous aromatization, providing the planar 7-acetyl-1-amino-6-aryl-2-(*N*-aryl)carbamoyl-5,8-dimethyl-8,9-dihydrothieno[2,3-*c*] isoquinolines **9a**,**b**,**e** in good yield. Cyclocondensation reactions of **6a**,**b** with phenyl hydrazine, thiosemicarbazide, or hydrazine hydrate led to the formation of nonplanar (3a*R*, 4*S*, 9a*S*)-pyrazolo[3,4-*g*]isoquinolines **11a**, **11b**, and **13**, respectively. The reaction of compound **13** with 2-chloromethylquinazolin-4(3*H*)-one in the presence of anhydrous sodium acetate gave the expected thienopyrazoloisoquinolone **14**. Heating the latter compound (**14**) with triethyl orthoformate in glacial acetic acid afforded the fused heptacyclic compound **15**. All of the synthesized compounds were characterized based on their full spectral analyses such as IR, ^{1}H nuclear magnetic resonance (NMR), and mass spectrometry (MS). Moreover, the crystal structure of compound **6a** was elucidated by X-ray diffraction analysis.



INTRODUCTION

Isoquinoline and its derivatives are an essential class of heterocyclic compounds that may be found in several naturally occurring alkaloids.[1,2] Isoquinoline derivatives show a wide range of biological activities. Some of them show antihypertensive, anti-inflammatory, anti-oxidant, antipyretic, analgesic, antibacterial, antifungal, and antimalarial activities.[3−7] Others may act as antidepressants and antipsychotic agents.[8] Several isoquinolines were found to exhibit antitumor or antiproliferative activity.[9−12] In particular, the isoquinoline ring constitutes an important molecular part of the topical anesthetic drug quinisocaine (A), whereas the tetrahydroisoquinoline moiety is found in the structure of the antihypertensive drugs quinapril (B) and debrisoquine (C) (Figure 1).[13] Also, many tetrahydroisoquinolines are considered as antitumor,[14,15] anticonvulsant, antithrombotic,[16] analgesic,[17] anti-inflammatory,[18] antifungal, and antibacterial agents.[19] In particular, some tetrahydrothieno[2,3-*c*]-isoquinolines were synthesized and reported to possess considerable antibacterial and antifungal activities.[20,21] Pyrazoloisoquinolines are tricyclic compounds with important biological and medicinal properties and are used as B-Raf^{V600E} inhibitors,[22] mu opioid receptor (μ-OR) agonists,[23] and p38 kinase inhibitors.[24] The pyrazole ring of the pyrazoloisoquinolines is commonly fused to the pyridine ring at bond (c)[25,26] or bond (a).[27−29] The literature reporting on compounds that contain a pyrazole ring fused with the carbocyclic ring of the isoquinoline systems is sparse since there are only two published patents[24,30] on the chemistry and applications of pyrazolo[3,4-*f*]isoquinolines, which exhibited important medicinal properties.

In view of all aforementioned findings, the current project was planned to design, synthesize, and characterize novel functionally substituted dihydroisoquinolines, planar pyrimidothienoisoquinolines, and nonplanar (3a*R*, 4*S*, 9a*S*)-tetrahydropyrazolo[3,4-*g*]isoquinolines with the hope that these compounds will prove to be of good biological and medicinal importance owing to the incorporation of different pharmacophores in their framework.

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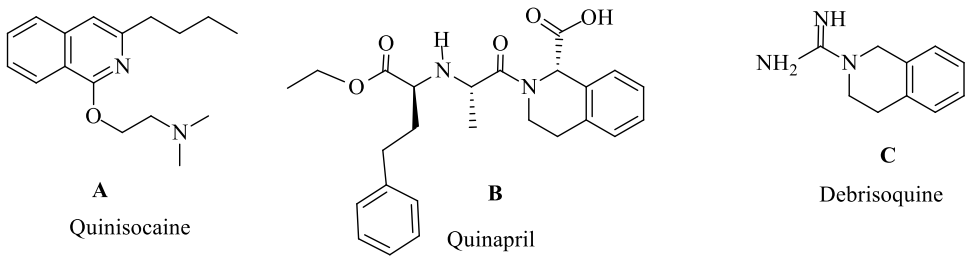
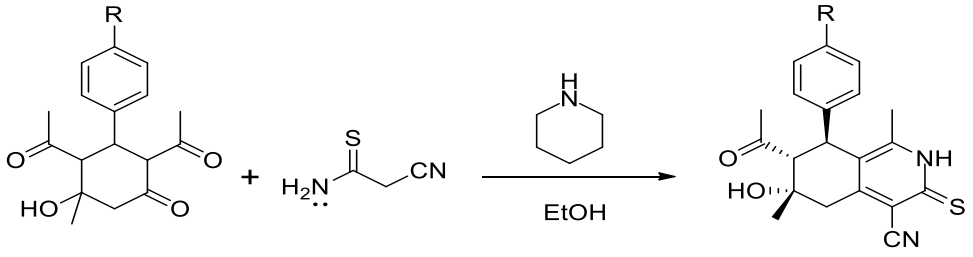
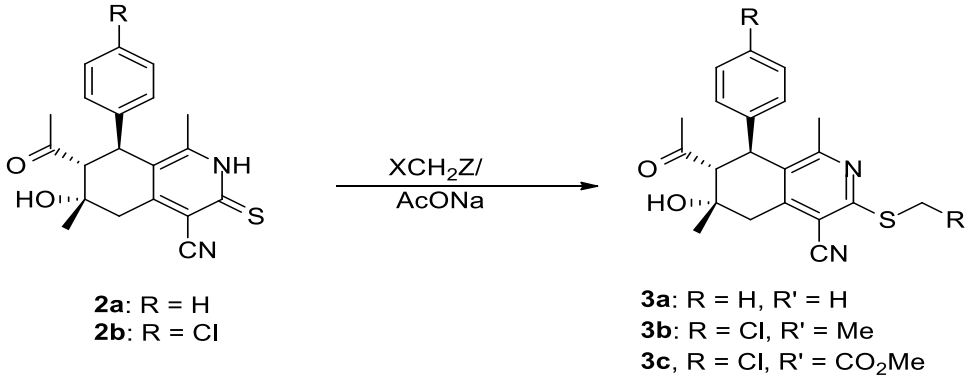


Figure 1. Structure of the topical anesthetic drug quinisocaine (A) and antihypertensive drugs quinapril (B) and debrisoquine (C).

Scheme 1. Synthesis of Tetrahydroisoquinolines 2a,b



Scheme 2. Synthesis of Substituted Methylsulfanytetrahydroisoquinolines 3a−c



RESULTS AND DISCUSSION

The starting compounds, 7-acetyl-8-aryl-4-cyano-1,6-dimethyl-6-hydroxy-5,6,7,8-tetrahydroisoquinolin-3(2*H*)-thiones **2a,b**, are prepared by the reaction of acetylcyclohexanones **1a,b** with cyanothioacetamide according to the reported method[31] (Scheme 1).

Alkylation of **2a,b** with methyl iodide,[32] ethyl iodide,[33] or methyl chloroacetate,[34] by refluxing in ethanol containing the appropriate base, is reported to give the *S*-alkylated derivatives **3a−c** (Scheme 2).

The structure of tetrahydroisoquinolines **2a,b** and **3a−c** contains three chiral centers at C-6,7,8. Accordingly, there are eight possible isomers for each compound. Modern physical techniques such as spectral analyses and chromatography have proved strongly that all of the obtained compounds exist in one isomeric form. The absolute configurations of the three chiral centers of this isomer are detected by studying the X-ray diffraction of the single crystal of compounds **3a−c**. The previous studies confirmed 6*S*, 7*R*, and 8*S* configurations for the three chiral centers of compounds **3a−c**.[32−34]

Its interesting to note that since the alkylation process takes place far away from the chiral centers of **2a,b**, the configuration of these centers is similar to that of their alkylated products, i.e., 6*S*, 7*R*, and 8*S*.[32−34]

The acetyl group of compounds **2a,b** may possess low or no activity toward some reagents such as hydrazine hydrate, thiosemicarbazide, or phenylhydrazine because of the steric hindrance caused by its neighboring groups and its formation of hydrogen bonding with the *tert* hydroxyl group wherein the two groups (COMe and OH) are in the same direction as the cyclohexene ring.[32−34]

An attempt to increase the reactivity of the acetyl group of compounds **2a,b** via dehydration of these compounds has succeeded. The dehydration was achieved by heating with an excess amount of acetyl chloride in glacial acetic acid. Based on the spectral data, the structure of the dehydrated products was assigned as **6a,b** rather than **5a,b**; i.e., the elimination of the water molecule occurs between C-6 and C-5.

The pathway of the latter dehydration process is given in Scheme 3. Thus, the OH group of the compounds **2a,b** firstly reacted with acetyl chloride to form the corresponding esters **4a,b**, which undergo in situ pericyclic reaction of the six-membered ring to afford 7,8-dihydroisoquinolines **6a,b** under the acidic catalytic effect of acetic acid or liberated HCl.

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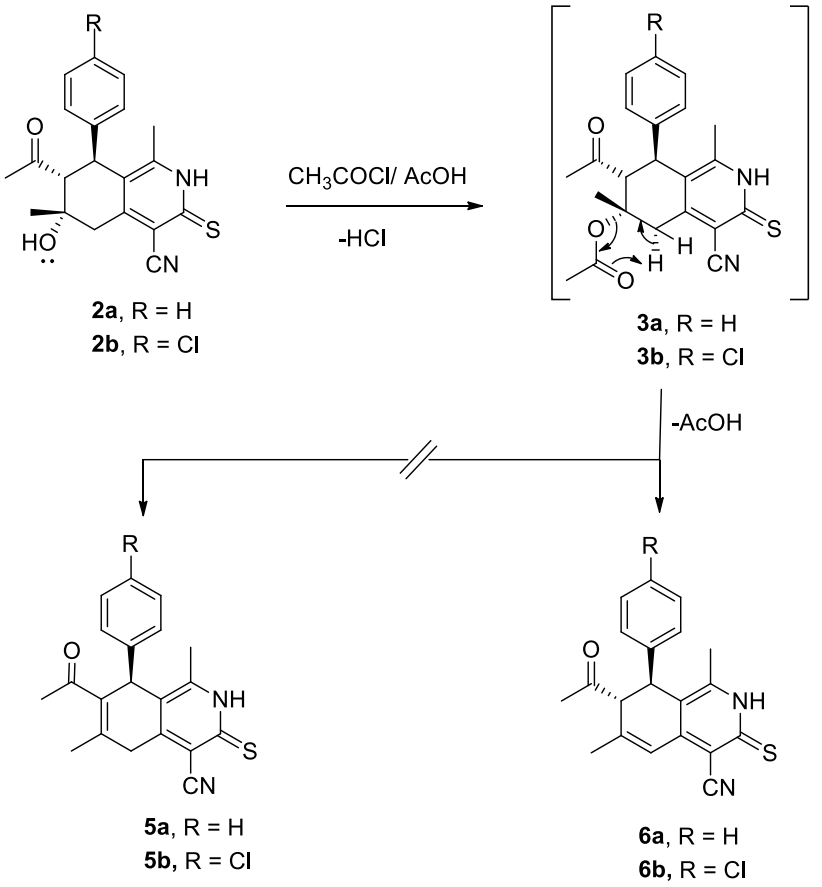
Scheme 3. Dehydration of Compounds 2a,b and Synthesis of Dihydroisoquinolines 5a,b



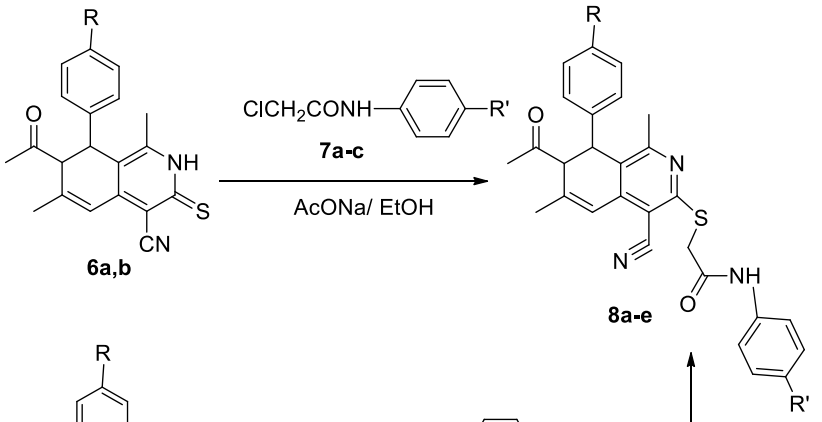
2a, R = H
2b, R = Cl

3a, R = H
3b, R = Cl

5a, R = H
5b, R = Cl

6a, R = H
6b, R = Cl

Scheme 4. Synthesis of Dihydroisoquinoline Derivatives 8a−e



6a,b

8a-e

2a,b

7	R'
a	H
b	Cl
c	Me

8	R	R'
a	H	H
b	H	Cl
c	H	Me
d	Cl	Cl
e	Cl	Me

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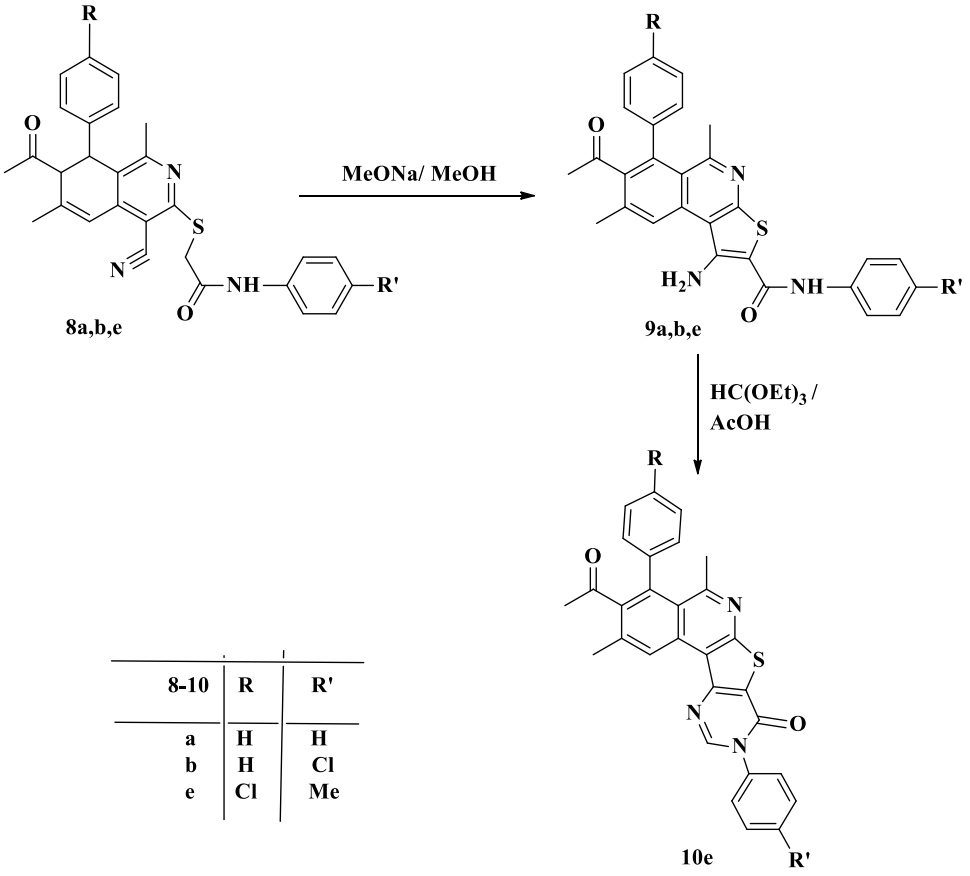
Scheme 5. Synthesis of Thienoisoquinolines 9a,b,e and Pyrimidothienoisoquinoline 10e



8-10	R	R'
a	H	H
b	H	Cl
e	Cl	Me

The IR spectrum of compound **6a** showed the presence of characteristic absorption bands at 3170 cm^{-1} for (NH), 2219 cm^{-1} for (C≡N), and 1718 cm^{-1} for (C═O, acetyl), and the absence of the alcoholic band at 3450 cm^{-1} of compound **2a**.[31] The ^{1}H nuclear magnetic resonance (NMR) spectrum of compound **6a** revealed the disappearance of the two signals at 2.85 and 3.04, which is equivalent to the CH_2 group of the cyclohexene ring of compound **2a**,[31] and the presence of three singlets at 6.77, 4.42, and 3.34, which correspond to the three CH groups of the cyclohexadiene ring besides the other signals, in agreement with its proposed structure. The mass spectrum of compound **6a** showed a molecular ion peak at m/z 334 (2.5%), which is in accordance with its molecular formula. Similar results were obtained for compound **6b** (cf. Experimental Section).

The reaction of dihydroisoquinolines **6a**,**b** with *N*-aryl-2-chloroacetamides **7a**−**c** by refluxing in ethanol, in the presence of slightly excess molar amounts of sodium acetate, for 1 h gave the corresponding 7-acetyl-8-aryl-3-(*N*-arylcarbamoyl-methyl-sulfanyl)-4-cyano-1,6-dimethyl-7,8-dihydroisoquinolines **8a**−**e**. In a creative reaction, an attempt to synthesize the latter compounds (**8a**−**e**) by heating tetrahydroisoquinolines **2a**,**b** with the appropriate *N*-aryl-2-chloroacetamides **7a**−**c** under neat conditions succeeded, wherein both the substitution reaction and regioselective dehydration occurred (Scheme 4). The structures of compounds **8a**−**e** were characterized and confirmed on the basis of their elemental analysis and spectroscopic data. Their elemental analyses gave satisfactory results within ±0.4 of the calculated values (cf. Experimental Section). The IR spectrum of compound **8a** exhibited absorption bands at 3256 cm^{-1} specific for (N−H, amide); at 2215 cm^{-1} for (C≡N); at 1706 cm^{-1} for (C═O, acetyl); and at 1660 cm^{-1} for (C═O, amide). ^{1}H NMR of compound **8a** showed two singlet signals at δ 9.46 and 4.06 specific for the NH and SCH_2 groups, respectively. Similar results were obtained for compounds **8b**−**e** (cf. Experimental Section).

On stirring of compounds **8a**,**b**,**e** in absolute methanol with slightly excess molar amounts of sodium methoxide for 40 min at room temperature, they underwent intramolecular Thorpe−Ziegler cyclization followed by aromatization, providing the corresponding 7-acetyl-1-amino-6-aryl-2-*N*-(arylcarbamoyl)-5,8-dimethyl-8,9-dihydrothieno[2,3-*c*]isoquinolines **9a**,**b**,**e** in nearly quantitative yield. Heating of compound **9e** with triethyl orthoformate in glacial acetic acid resulted in the formation of pyrimidothienoisoquinoline derivative **10e** (Scheme 5). The structures of compounds **9a**,**b**,**e** were characterized and confirmed on the basis of their spectroscopic data. The IR spectrum of compound **9a** revealed the presence of characteristic absorption bands at 3418, 3309, 3229 cm^{-1} for NH_2 and NH, at 1704 cm^{-1} for the acetyl group and at 1670 cm^{-1} for the amide carbonyl group. The ^{1}H NMR spectrum of compound **9a** displayed a singlet at δ 9.63 for NH and a broad singlet at δ 7.47 for NH_2 together with an aryl proton. Similar results were obtained for compounds **9b**,**e** (cf. Experimental Section). The IR spectrum of compound **10e** showed a band at 1702 characteristic of (C═O, acetyl group) and a band at 1684 for (C═O, pyrimidinone). The ^{1}H NMR spectrum of compound **10e** displayed a singlet at δ 9.63 corresponding to the CH of the pyrimidine ring.

Compound **6a** contains an important functional group, which is β,γ-unsaturated ketone with the double bond inside the carbocyclic ring of the isoquinoline system. This

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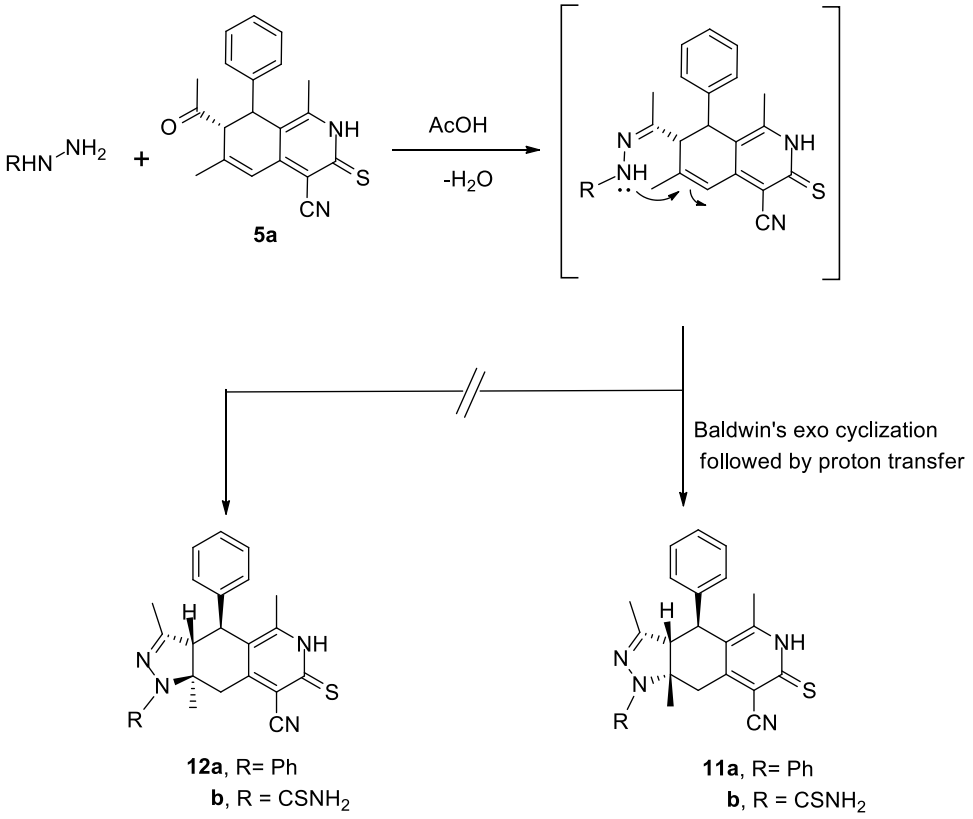
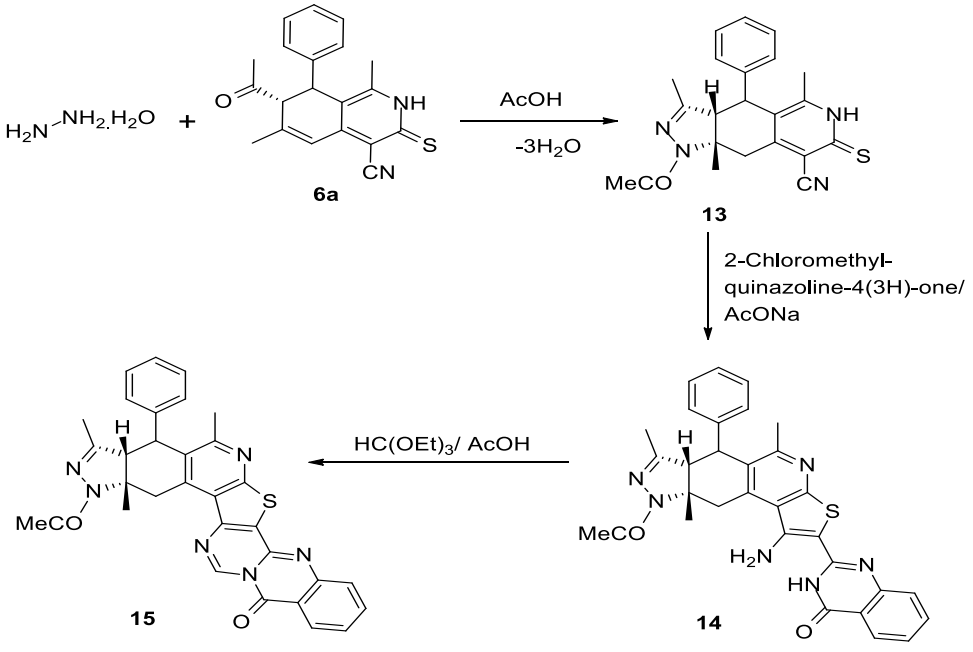
Scheme 6. Synthesis of Tetrahydropyrazoloisoquinolines 11a,b



Scheme 7. Synthesis of Tetrahydropyrazololsoquinolines 13−15



construction leads to the formation of a fused ring with the carbocyclic ring when allowed to react with some reagent molecules with binucleophiles such as phenyl hydrazine and thiosemicarbazide, where the amino group of these molecules is condensed with the reactive acetyl group and the other nucleophilic group is added to the double bond by Baldwin's exocyclization to afford a fused pyrazole ring with the carbocyclic ring of the isoquinoline system as shown in Scheme 6.

Thus, heating compound **6a** with an equimolar amount of phenyl hydrazine or thiosemicarbazide in glacial acetic acid at reflux temperature for 1 h led to the formation of pyrazoloisoquinolines **11a,b** rather than **12a,b**. The IR spectrum of compound **11a** showed characteristic absorption bands at 3181 for NH and at 2230 for the C≡N group. The

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^{1}H NMR spectrum of compound **11a** displayed a singlet at δ 13.99 specific for NH, a singlet at δ 4.61 for the CH at C-4, a singlet at δ 4.06 for CH at C-3a, a doublet at δ 3.46−3.49 for the CH of CH_2 at C-9, a singlet at δ 2.35 for CH_3 at C-5, a doublet at δ 2.29−2.32 for the CH of CH_2 at C-9, a singlet at δ 1.96 for CH_3 at C-3, and a singlet at δ 1.24 for CH_3 at C-9a. The mass spectrometry (MS) of compound **11a** showed a molecular ion at m/z = 424.27 (84%), which is in accordance with its molecular formula. Similar results were obtained for compound **11b** (cf. Experimental Section).

In the same manner, compound **5a** was reacted with hydrazine hydrate by refluxing in glacial acetic acid for 2 h to furnish *N*-acetylpyrazoloisoquinoline **13**. The presence of 4-cyano-3(2*H*)-thione function in the structure of compound **13** was chemically confirmed via its reaction with 2-chloromethylquinazolin-4(3*H*)-one in the presence of anhydrous sodium acetate, wherein the expected thienopyrazoloisoquinolone **14** was obtained. Heating the latter compound with triethyl orthoformate in glacial acetic acid afforded the fused heptacyclic compound **15** (Scheme 7). The IR spectrum of compound **13** showed characteristic absorption bands at 3183 for NH, at 2223 for C≡N, and at 1647 for C═O. The ^{1}H NMR spectrum of compound **13** exhibited a singlet at δ 14.04 specific for NH, a singlet at δ 4.62 for CH at C-4, a singlet at δ 4.10 for CH at C-3a, a doublet at δ 2.94−2.97 for the CH of CH_2 at C-9, a doublet at 2.34−2.37 for the CH of CH_2 at C-9, a singlet at δ 2.34 for CH_3 attached to the pyridine ring, a singlet at δ 1.95 for CH_3 at C-3a, a singlet at δ 1.98 for $COCH_3$, and a singlet at δ 1.39 for CH_3 at C-9a. The IR spectrum of compound **14** showed characteristic absorption bands at 3371−3289 for the NH_2 group, at 3187 for NH at 1677, and at 1647 for two C═O groups. The ^{1}H NMR spectrum of compound **14** displayed a singlet at δ 11.86 specific for the NH of the quinazoline system and a singlet at δ 7.55 for NH_2. The IR spectrum of compound **15** showed two absorption bands at 1719 and 1650 characteristic of the two C═O groups. The ^{1}H NMR spectrum of compound **15** displayed a singlet at δ 9.39 specific for the CH of the pyrimidine ring.

According to the crystal structure data provided by Dyachenko et al.[32] and Mague et al.,[33,34] for compounds **3a−c**, the cyclohexene ring presented in half chair conformation and both acetyl and hydroxyl groups were in the same direction. Hence, the condensation of the acetyl group of compound **6a** with hydrazine derivatives may give the corresponding hydrazone intermediates **A**, which undergo intramolecular cycloaddition reaction according to the Felkin−Ahn model to give pyrazoloisoquinolines **11a,b** rather than **12a,b**. The pyrazoloisoquinolines **11a,b** are non-planar, wherein the pyrazole is located at an angle to the carbocyclic ring of the isoquinoline scaffold because the pyrazole ring is located in place of the acetyl and alcoholic groups of compounds **2a,b**, which are situated at an angle to the plane of the cyclohexene ring.

Crystal Structure. A yellow plate-like crystal of **6a** (0.11 × 0.18 × 0.18 mm^3) was used for collection of the X-ray intensity data on a Bruker D8 VENTURE PHOTON 100 CMOS diffractometer at 150 K using Cu Kα radiation (λ = 1.541787 Å) using the APEX3 software.[35] The raw data were converted to F^2 values with SAINT,[35] while an empirical absorption correction and merging of equivalent reflections were performed with *SADABS*.[36] The structure was solved by dual space methods (SHELXT)[37] and refined by full-matrix, least squares procedures (SHELXL)[38] with hydrogen atoms refined freely except for those of the methyl groups, which were included as riding contributions in idealized positions.

A perspective view of **6a** is shown in Figure 2 with the dashed line depicting the intramolecular C15−H15···π (ring)

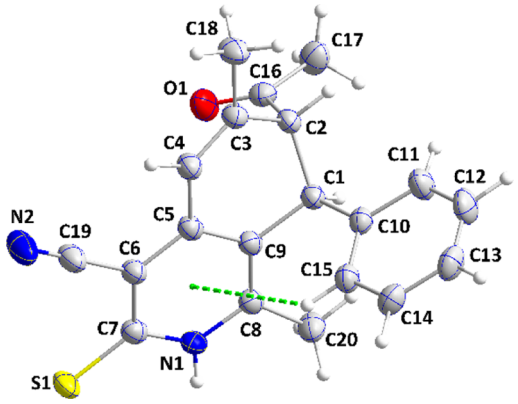

Figure 2. Title molecule with labeling scheme and 50% probability ellipsoids. The intramolecular C−H···π (ring) interaction is shown by a dashed line.

interaction (H16···centroid = 2.96(2) Å, C15−H15···centroid = 131.8(16)°). The C5/C6/C7/N1/C8/C9 ring is planar to within 0.0099(11) Å (rms deviation = 0.0074) and the dihedral angle between it and the plane of the C10···C15 benzene ring is 88.55(5)°. This is partially determined by the C16−H16···π (ring) interaction noted above. A puckering analysis[38] of the C1···C5/C9 ring gave the parameters Q = 0.4511(17) Å, θ = 114.62(2)°, and φ = 207.8(2)°. The phenyl and acetyl substituents are trans to one another (Figure 2) and all bond distances and interbond angles appear as expected for the given formulation. In the crystal, inversion dimers are formed by N1−H1A···S1 hydrogen bonds (H1A···S1 = 2.34(3) Å, N1−H1A···S1 = 175(2)°) and are connected to layers parallel to (101) by C13−H13···O1 hydrogen bonds (H13···O1 = 2.48(3) Å, C13−H13···O1 = 155(2)°) and C12−H12···π (ring) (H12···centroid = 2.94(3) Å, C12−H12···centroid = 169(2)°) interactions (Figures 3 and 4).

CONCLUSIONS

In the current paper, we have concluded a facile approach for synthesis of new substituted methylsulfanyldihydroisoquinolines, related planar dihydrothieno[2,3-*c*]isoquinolines, and pyrimidothieno[2,3-*c*]isoquinolines based on various reactions of 7-acetyl-8-aryl-4-cyano-1,6-dimethyl-7,8-dihydroisoquinolin-3(2*H*)-thiones **6a,b**. Also, some novel non-planar 1*H*-pyrazolo[3,4-*g*]isoquinolines were synthesized starting from compound **6a**. The isolated products were easily purified by recrystallization from the proper solvents. All synthesized compounds were characterized based on their full spectral analyses such as IR, ^{1}H NMR, and MS. Moreover, the crystal structure of compound **6a** was elucidated by X-ray diffraction analysis. Finally, this sophisticated strategy can be utilized for synthesis of similar compounds, which are medicinally and pharmaceutically significant too.

EXPERIMENTAL SECTION

Melting points were determined on a Gallan−Kamp apparatus and are uncorrected. The IR spectra were recorded on a

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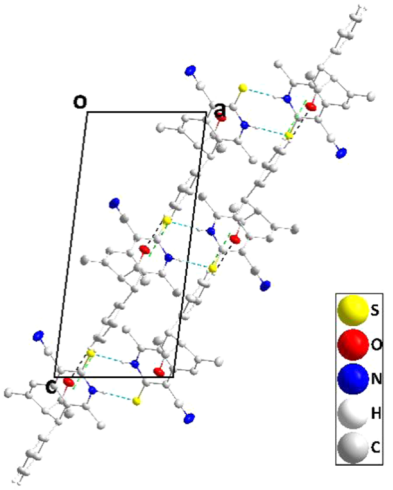

Figure 3. Elevation view of one layer seen along the *b*-axis direction, with C−H···O and N−H···S hydrogen bonds depicted, respectively, by black and light blue dashed lines. The intermolecular C−H···π (ring) interactions are depicted by green dashed lines.

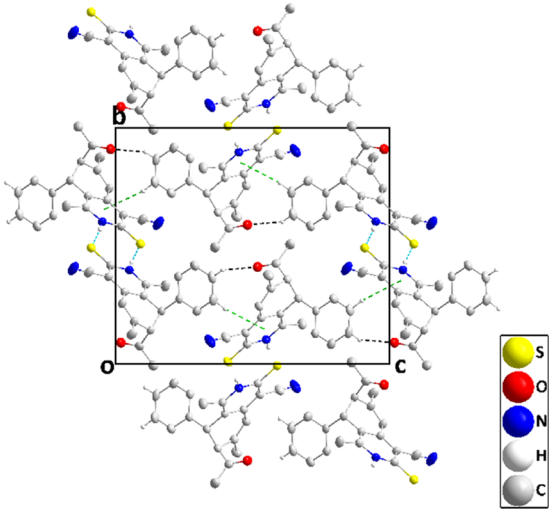

Figure 4. Packing viewed along the *a*-axis direction with intermolecular interactions depicted as in Figure 3.

Shimadzu 470 IR-spectrophotometer (KBr; ν_{max} in cm^{-1}). The NMR spectra were taken on a Bruker 400 MHz spectrometer or on a Joel 500 MHz spectrometer using $CDCl_3$ or dimethyl sulfoxide (DMSO)-d_6 as a solvent and tetramethylsilane (TMS) as internal 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 multiples (m). MS analyses were performed on a Thermo Scientific single quadrupole mass spectrometer (Model: ISQ 7000).

Synthesis of (7*R*, 8*S*)-7-acetyl-4-cyano-1,6-dimethyl-8-aryl-7,8-dihydroisoquinoline-2(2*H*)-thiones 6a,b: General Procedure. A mixture of compound **2a,b** (10 mmol) and acetyl chloride (7 mL, 100 mmol) in glacial acetic acid (100 mL) was heated under reflux for 2 h and then allowed to cool. The solid that formed was collected by filtration, dried in air, and recrystallized from ethanol to give compounds **6a,b** in the form of orange needle crystals.

*(7R, 8S)-7-acetyl-4-cyano-1,6-dimethyl-8-phenyl-7,8-dihydroisoquinoline-3(2H)-thione (**6a**).* **6a** was synthesized by using compound **2a** in the above general procedure; yield 93%; m.p.: 268−270 °C. IR: 3171 (N−H); 3057 (C−H, aromatic); 2859−2933 (C−H, aliphatic); 2219 (C≡N); 1718 (C═O, acetyl group). ^{1}H NMR (400 MHz, $CDCl_3$): 7.19−7.21 (t, 3H, Ar H); 6.90−6.92 (d, 2H, *J* = 8 Hz, Ar H); 6.77 (s, 1H, CH at C-5); 4.42 (s, 1H, CH at C-8); 3.34 (s, 1H, CH at C-7); 2.27 (s, 3H, $COCH_3$); 2.16 (s, 3H, CH_3 attached to the pyridine ring); 1.99 (s, 3H, CH_3 at C-6). EI-MS: (*m*/*z*): 334 (M^+, 2.5%), 291 (M^+ −$COCH_3$, 5.0%); 215 [M^+ − (ethenone + phenyl cation), 8.9%]; 77 (phenyl radical, 0.8%); 44 (cationic radical of acetaldehyde, 2.1%); 43 (acetyl cation, 2.9%); 32 (sulfur cation, 13%).

*(7R, 8S)-7-acetyl-8-(4-chlorophenyl)-4-cyano-1,6-dimethyl-7,8-dihydroisoquinoline-3(2H)-thione (**6b**).* **6b** was synthesized by using compound **2b** in the above general procedure; m.p.: 278−280 °C; yield: 90%. IR: 3292 (N−H); 3048 (C−H, aromatic); 2971 (C−H, aliphatic); 2223 (C≡N); 1688 (C═O, acetyl group). ^{1}H NMR (500 MHz, DMSO-d_6): 13.69 (s, 1H, NH); 7.29−7.31 (d, *J* = 10 Hz, 2H, Ar H); 7.12−7.14 (d, *J* = 10 Hz, 2H, Ar H); 6.60 (s, 1H, CH at C-5), 4.52 (s, 1H, CH at C-8); 3.67 (s, 1H, CH at C-7); 2.27 (s, 3H, $COCH_3$); 2.13 (s, 3H, CH_3 attached to the pyridine ring); 1.89 (s, 3H, CH_3 at C-6).

Synthesis of (7*R*, 8*S*)-7-acetyl-8-aryl-3-(*N*-arylcarbamoylmethylsulfanyl)-4-cyano-1,6-dimethyl-7,8-dihydroisoquinolines 8a−e: General Procedure. *Method (**A**).* A mixture of compound **6a,b** (10 mmol), the respective *N*-aryl-2-chloroacetamide **7a−c** (10 mmol), and sodium acetate trihydrate (1.50 g, 11 mmol) in ethanol (60 mL) was heated under reflux for 1 h. The precipitate that formed after standing at room temperature overnight was collected by filtration, washed with water, dried in air, and then recrystallized from ethanol to give compounds **8a−e** in the form of white needle crystals.

*(7R, 8S)-7-acetyl-4-cyano-1,6-dimethyl-8-phenyl-3-(N-phenyl)carbamoylmethyl-sulfanyl-7,8-dihydroisoquinoline (**8a**).* **8a** was synthesized by reacting compound **6a** with *N*-phenyl-2-chloroacetamide (**7a**) as described in the above general procedure; yield: 91%; m.p.: 172−173 °C. IR: 3256 (N−H, amide); 3083 (C−H, aromatic); 2922 (C−H, aliphatic); 2215 (C≡N); 1706 (C═O, acetyl); 1660 (C═O, amide). ^{1}H NMR (500 MHz, DMSO-d_6) showed the following signals: 9.46 (s, 1H, NH); 7.45−7.47 (d, *J* = 8 Hz, 2H, Ar H); 7.27−7.29 (m, 4H, Ar H); 7.07−7.11 (t, 1H, Ar H); 7.01−7.02 (d, *J* = 4 Hz, 2H, Ar H); 6.84 (s, 1H, CH at C-5); 4.65 (s, 1H, CH at C-8); 4.06 (s, 2H, SCH_2); 3.40 (s, 1H, CH at C-7); 2.49 (s, 3H, $COCH_3$); 2.24 (s, 3H, CH_3 attached to the pyridine ring); 2.07 (s, 3H, CH_3 at C-6).

*(7R, 8S)-7-acetyl-3-[N-(4-chlorophenyl)-carbamoylmethylsulfanyl]-4-cyano-1,6-dimethyl-8-phenyl-7,8-dihydroisoquinoline (**8b**).* **8b** was synthesized by reacting compound **6a** with *N*-(4-chlorophenyl)-2-chloroacetamide (**7b**) as described in the above general procedure; yield: 89%. m.p.: 176−178 °C. IR: 3302 (N−H, amide); 3063 (C−H, aromatic); 2919 (C−H, aliphatic); 2214 (C≡N); 1702 (C═O, acetyl); 1686 (C═O, amide). ^{1}H NMR (500 MHz, DMSO-d_6): 9.41 (s, 1H, NH); 7.35−7.36 (d, *J* = 5 Hz, 2H, Ar H); 7.26−7.28 (m, 3H, Ar H); 7.21−7.23 (d, *J* = 10 Hz, 2H, Ar H); 6.97−6.99 (d, *J* = 10 Hz, 2H, Ar H); 6.80 (s, 1H, CH at C-5); 4.62 (s, 1H, CH at C-8); 3.90−3.97 (dd, 2H, SCH_2); 3.36 (s, 1H, CH at C-7); 2.43 (s, 3H, $COCH_3$); 2.22 (s, 3H, CH_3 attached to the pyridine ring); 2.04 (s, 3H, CH_3 at C-6).

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*(7R, 8S)-7-acetyl-3-[N-(4-tolyl)carbamoylmethylsulfanyl]-4-cyano-1,6-dimethyl-8-phenyl-7,8-dihydroisoquinoline (**8c**).* **8c** was synthesized by reacting compound **6a** with *N*-(4-tolyl)-2-chloroacetamide (**7c**) as described in the above general procedure; yield: 87%. m.p: 180−182 °C. IR: 3304 (N−H, amide); 3054 (C−H, aromatic); 2918 (C−H, aliphatic); 2215 (C≡N); 1701 (C═O, acetyl); 1682 (C═O, amide). ^{1}H NMR (500 MHz, DMSO-d_6): δ: 9.23 (s, 1H, NH); 7.26−7.29 (m, 5H, Ar H); 7.05−7.07 (d, J = 10 Hz, 2H, Ar H); 6.97−6.99 (d, J = 10 Hz, 2H, Ar H); 6.80 (s, 1H, CH at C-5); 4.62 (s, 1H, CH at C-8); 3.94 (s, 2H, SCH_2); 3.35 (s, 1H, CH at C-7); 2.43 (s, 3H, $COCH_3$); 2.27 (s, 3H, CH_3 attached to the pyridine ring); 2.21 (s, 3H, CH_3 at C-6); 2.03 (s, 3H, CH_3 of the tolyl group).

*(7R, 8S)-7-acetyl-3-[N-(4-chlorophenyl)-carbamoylmethylsulfanyl]-4-cyano-1,6-dimethyl-8-(4-chlorophenyl)-7,8-dihydroisoquinoline (**8d**).* **8d** was synthesized by reacting compound **6b** with *N*-(4-chlorophenyl)-2-chloroacetamide (**7b**) as described in the above general procedure; yield: 86%; m.p.: 188−190 °C. IR: 3271, (N−H, amide); 3064 (C−H, aromatic); 2916 (C−H, aliphatic); 2217 (C≡N); 1704 (C═O, acetyl); 1667 (C═O, amide). ^{1}H NMR (400 MHz, DMSO-d_6): 9.45 (s, 1H, N−H); 7.40−7.42 (d, J = 8 Hz, 2H, Ar H); 7.24−7.28 (t, 4H, Ar H); 6.93−6.95 (d, J = 8 Hz, 2H, Ar H); 6.83 (s, 1H, aliphatic, CH at C-5); 4.64 (s, 1H, CH at C-8); 4.04 (dd, 2H, SCH_2); 3.34 (s, 1H, CH at C-7); 2.46 (s, 3H, $COCH_3$); 2.24 (s, 3H, CH_3 attached to pyridine ring); 2.09 (s, 3H, CH_3 at C-6).

*(7R, 8S)-7-acetyl-3-[N-(4-tolyl)carbamoylmethylsulfanyl]-4-cyano-1,6-dimethyl--8-(4-chloro-phenyl)-7,8-dihydroisoquinoline (**8e**).* **8e** was synthesized by reacting compound **6b** with *N*-(4-tolyl)-2-chloroacetamide (**7c**) as described in the above general procedure; yield: 92%. m.p.: 190−192 °C. IR: 3251(N−H, amide); 3055 (C−H, aromatic); 2923 (C−H, aliphatic); 2216 (C≡N); 1709 (C═O, acetyl); 1672 (C═O, amide). ^{1}H NMR (500 MHz, DMSO-d_6): 9.14 (s, 1H, NH); 7.27−7.29 (d, J = 10 Hz, 2H, Ar H); 7.23−7.25 (d, J = 10 Hz, 2H, Ar H); 7.07−7.08 (d, J = 5 Hz, 2H, Ar H); 6.90−6.92 (d, J = 10 *Hz*, 2H, Ar H); 6.80 (s, 1H, aliphatic CH at C-5); 4.61 (s, 1H, CH at C-8); 3.94 (s, 2H, SCH_2); 3.28 (s, 1H, CH at C-7); 2.42 (s, 3H, $COCH_3$); 2.28 (s, 3H, CH_3 attached to the pyridine ring); 2.20 (s, 3H, CH_3, CH_3 of the tolyl group); 2.05 (s, 3H, CH_3 at C-6).

*Method (**B**).* A mixture of compound **2a**,**b** (10 mmol) and appropriate *N*-aryl-2-chloroacetanide **7a**−**c** (10 mmol) was fused at melting temperature for 10 min. The reaction mixture was triturated with ethanol (30 mL) and refluxed for further 10 min and then left to cool. The white precipitate was collected and recrystallized from ethanol to give the compounds **8a**,**b**,**e** in the form of white needle crystals (yield: 76−87%). These products are identical to those reported before in all aspects.

Synthesis of 7-acetyl-1-amino-2-(*N*-aryl)carbamoyl-5,8-dimethyl-8-phenyl-6,7-thieno [2,3-*c*]isoquinolines 9a,b,e: General Procedure. To a suspension of compound **8a**,**b**,**e** (10 mmol) in methanol (20 mL), a methanolic sodium methoxide solution (0.23 g sodium in 40 mL methanol) was added. The resulting mixture was stirred at room temerature for 40 min. The product that precipitated on dilution with water (20 mL) was collected by filtration, dried in air, and crystallized from methanol to give compounds **9a**,**b**,**e**.

*7-Acetyl-1-amino-5,8-dimethyl-6-phenyl-2-[N-(phenyl)-carbamoyl]thieno[2,3-c] isoquinoline (**9a**).* **9a** is obtained from **8a** as a yellow amorphous substance; yield: 64%; m.p.: 287−289 °C. IR: 3309, 3418 (NH_2); 3229 (NH, amide); 2924 (CH, aliphatic); 1704 (C═O, acetyl). ^{1}H NMR (400 MHz, DMSO-d_6): 9.63 (s, 1H, NH); 8.67 (s, 1H, CH at C-9); 7.72−7.74 (d, J = 8 Hz, 2H, Ar H); 7.47 (broad s, 3H: NH_2 and Ar H); 7.31−7.35 (m, 4H, Ar H); 7.10−7.12 (d, J = 8 Hz, 2H, Ar H); 2.32 (s, 3H, $COCH_3$); 2.05 (s, 3H, CH_3 attached to the pyridine ring); 1.89 (s, 3H,CH_3 at C-8).

*7-Acetyl-1-amino-2-[N-(4-chlorophenyl)carbamoyl]-5,8-dimethyl-6-phenylthieno[2,3-c]isoquinoline (**9b**).* **9b** is obtained from **8b** as a yellow amorphous substance; yield: 57%; m.p.: 280−282 °C. IR: 3173, 3222 (NH_2); 3154 (NH); 1691 (C═O, acetyl group). ^{1}H NMR (500 MHz, DMSO-d_6): 9.73 (s, 1H, NH); 7.72−7.74 (d, J = 8 Hz, 2H, Ar H); 7.42−7.44 (m, 4H: NH_2 and Ar H); 7.35−7.37 (d, J = 10 Hz, 2H, Ar H); 7.25−7.27 (d, J = 10 Hz, 2H, Ar H); 2.27 (s, 3H, $COCH_3$); 2.00 (s, 3H, CH_3 attached to the pyridine ring); 1.84 (s, 3H, CH_3 at C-8).

*7-Acetyl-1-amino-6-(4-chlorophenyl)-5,8-dimethyl-2-[N-(4-tolyl)carbamoyl]thieno[2,3-c]isoquinoline (**9e**).* **9e** is obtained from **8e** as a yellow amorphous substance; yield: 61%; m.p.: 277−279 °C. IR: 3221, 3413 (NH_2); 3300 (N−H); 2923 (C−H, aliphatic); 1703 (C═O, acetyl). ^{1}H NMR (500 MHz, DMSO-d_6): 9.53 (s, 1H, NH); 8.64 (s, 1H, CH at C-9); 7.53−7.55 (m, 4H, Ar H); 7.41 (broad s, 2H, NH_2); 7.35−7.37 (d, J = 10 Hz, 2H, Ar H); 7.11−7.13 (d, J = 10 Hz, 2H, Ar H); 2.26 (s, 3H, $COCH_3$); 2.25 (s, 3H, CH_3 attached to the pyridine ring); 2.08 (s, 3H,CH_3 of the tolyl group); 1.97 (s, 3H, CH_3 at C-8).

Synthesis of 3-acetyl-4-(4-chlorophenyl)-2,5-dimethyl-9-(4-tolyl)pyrimido [4′,5′:4,5] thieno[2,3-*c*]-isoquinolin-8(9*H*)-one (10e). A mixture of compound **9e** (0.52 g, 1 mmol) and triethyl orthoformate (0.5 mL, 3 mmol) in glacial acetic acid (20 mL) was heated under reflux for 20 min. The product that precipitated while hot was collected and recrystallized from ethanol to afford compound **10e** in the form of fine colorless crystals; yield: 86%; m.p: 360 °C. IR: 3028 (C−H, aromatic); 2919 (C−H, aliphatic); 1702 (C═O, acetyl group); 1684 (C═O, amide). ^{1}H NMR (500 MHz, DMSO-d_6): 9.63 (s, 1H, CH of the pyrimidine ring); 8.71 (s, 1H, CH at C-1); 7.54−7.56 (d, J = 10 Hz, 2H, Ar H); 7.48−7.50 (d, J = 10 Hz, 2H, Ar H); 7.38−7.40 (m, J = 10 Hz, 4H, Ar H); 2.47 (s, 3H, $COCH_3$); 2.40 (s, 3H, CH_3 attached to the pyridine ring); 2.16 (s, 3H, CH_3 at C-2); 2.01 (s, 3H, CH_3 of the tolyl group).

Synthesis of (3a*R*, 4*S*, 9a*S*)-8-cyano-3,5,9a-trimethyl-1,4-diphenyl-3a,4,9,9a-tetrahydro-1*H*-pyrazolo[3,4-*g*]-isoquinoline-7(6*H*)-thione (11a). A mixture of compound **6a** (3.34 g, 10 mmol) and phenyl hydrazine (1 mL, 10 mmol) in glacial acetic acid (40 mL) was heated under reflux for 1 h. On cooling, a yellow crystalline solid precipitated. It was collected and recrystallized from acetic acid to give compound **11a** in the form of yellow needle crystals; yield: 89%; m.p.: 254−257 °C. IR: 3181 (N−H); 3057 (C−H aromatic); 2970 (C−H aliphatic); 2230 (C≡N). ^{1}H NMR (500 MHz, DMSO-d_6): 13.99 (s, 1H, NH); 7.31−7.34 (t, 2H, Ar H); 7.23−7.25 (t, 1H, Ar H); 7.20−7.21 (d, J = 5 Hz, 1H, Ar H); 7.15−7.18 (t, 2H, Ar H); at δ 7.01−7.02 (d, J = 5 Hz, 2H, Ar H); 6.81−6.84 (t, 1H, Ar H); 4.61 (s, 1H, CH at C-4); 4.06 (s, 1H, C-3a); 3.46−3.49 (d, J = 15 Hz, 1H, CH_2 at C-9); 2.35 (s, 3H, CH_3 at C-5); 2.29−2.32 (d, J = 15 Hz, 1H, CH_2 at C-9); 1.96 (s, 3H, CH_3 at C-3); 1.24 (s, 3H, CH_3 at C-9a). EI-MS: (m/z): 424.27 [M^+, 84%], 409.23 [M^+ − Me, 46%].

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Synthesis of (3a*R*, 4*S*, 9a*S*)-8-cyano-1-thiocarbamoyl-3,5,9a-trimethyl-4-phenyl-3a,4,9,9a-tetrahydro-1*H*-pyrazolo[3,4-*g*]isoquinoline-7(6*H*)-thione (11b). A mixture of compound **6a** (3.34 g, 10 mmol) and thiosemicarbazide (0.91 g, 10 mmol) in glacial acetic acid (40 mL) was heated under reflux for 1 h. The product that precipitated while hot was collected by filtration, dried in air, and then purified by boiling in ethanol to afford fine bright yellow crystals of compound **11b**; yield: 83%; m.p.: 306−308 °C. IR: 3295, 3407 (NH_2); 3154 (N−H); 3107 (C−H aromatic); 2970, 2926 (C−H aliphatic); 2234 (C≡N). ^{1}H NMR (500 MHz, DMSO-d_6): δ 14.02 (s, 1H, NH); 7.60 (broad s, 2H, NH_2); 7.30−7.33 (t, 2H, Ar H); 7.22−7.25 (t, 1H, Ar H); at δ 7.16−7.18 (d, J = 10 Hz, 1H, Ar H); 4.97−5.01 (d, J = 20 Hz, 1H, CH_2 at C-9); 4.63 (s, 1H, CH at C-4); 4.19 (s, 1H, CH at C-3a); 2.33 (s, 3H, CH_3 attached to the pyridine ring); 2.11−2.14 (d, J = 15 Hz, 1H, CH_2 at C-9); 1.98 (s, 3H, CH_3 at C-3); 1.66 (s, 3H, CH_3 at C-9a).

Synthesis of (3a*R*, 4*S*, 9a*S*)-1-acetyl-8-cyano-3,5,9a-trimethyl-4-phenyl-3a,4,9,9a-tetrahydro-1*H*-pyrazolo-[3,4-*g*]isoquinolin-7(6*H*)-thione (13). A mixture of compound **6a** (3.34 g, 10 mmol) and hydrazine hydrate 99% (1 mL, 10 mmol) in glacial acetic acid (40 mL) was heated under reflux for 2 h. The solid that precipitated on cooling was collected and recrystallized from ethanol to give large cubic yellow crystals of compound **13**; yield: 93%; m.p.: 310−314 °C. IR: 3430 (OH of the crystallized ethanol molecule); 3183 (N−H); 3091 (C−H aromatic); 2972 cm (C−H aliphatic); 2223 (C≡N). ^{1}H NMR (500 MHz, DMSO-d_6): 14.04 (s, 1H, NH); 7.30−7.33 (t, 2H, Ar H); 7.22−7.25 (t, 1H, Ar H); 7.18−7.20 (d, J = 10 Hz, 1H, Ar H); 4.62 (s, 1H, CH at C-4); 4.10 (s, 1H, CH at C-3a); 2.94−2.97 (d, J = 15 Hz, 1H, CH_2 at C-9); 2.34−2.37 (d, J = 15 Hz, 1H, CH_2 at C-9); 2.34 (s, 3H, CH_3 attached to the pyridine ring); 1.95 (s, 3H, CH_3 at C-3a); 1.98 (s, 3H, $COCH_3$); 1.39 (s, 3H, CH_3 at C-9a). One ethanol molecule obtained from the crystallization has three bands appearing at δ: 4.34 (s broad, 1H, OH); 3.38−3.43 (p, 2H, CH_2); and 1.01−1.03 (t, 3H, CH_3).

Synthesis of (6*S*, 6a*R*, 9a*S*)-9-acetyl-1-amino-2-(3,4-dihydro-4-oxoquinazolin-2-yl)-5,7,9a-trimethyl-6-phenyl-6a,9,9a,10-tetrahydro-6*H*-pyrazolo[3,4-*g*]thieno-[2,3-*c*]isoquinoline (14). To a mixture of compound **13** (1.17 g, 2 mmol) and 2-chloromethylquinazoline-3(4*H*)-one (0.40 g, 2.1 mmol) in methanol (50 mL), anhydrous sodium acetate (0.50 g, 6 mmol) was added. The reaction mixture was heated under reflux for 3 h and then left to cool. The precipitated solid was collected, dried in air, and recrystallized from methanol to afford yellowish green crystals of compound **14**; yield: 78%; m.p.: 352−354 °C. IR: 3289−3371 (NH_2); 3187 (N−H, quinazolinone); 2925 (C−H, aliphatic); 1677 (C═O, quinazoline); 1647 (C═O, acetyl). ^{1}H NMR (500 MHz, DMSO-d_6): 11.86 (s, 1H, NH of the quinazoline system); 8.05−8.06 (d, 2H, J = 5 Hz, Ar H); 7.74−7.77 (t, 1H, Ar H); 7.69−7.71 (d, J = 10 Hz, 1H, Ar H), 7.55 (s, 2H, NH_2); 7.37−7.41 (t, 1H, Ar H); 7.28−7.32 (t, 2H, Ar H); 7.21−7.24 (t, 1H, Ar H); 7.06−7.08 (d, J = 10 Hz, 2H, Ar H); 4.85 (s, 1H, CH at C-6); 4.71−74 (d, J = 15 Hz, 1H, CH_2 at C-9); 4.17 (s, 1H, CH at C-6′); 3.14 (s, 1H, of 0.33 the crystallized methanol molecule); 2.52 (s, 3H, $COCH_3$); 2.27−2.31 (d, J = 20 Hz, 1H, CH_2 at C-10); 2.06 (s, 3H, CH_3 attached to the pyridine ring); 1.91 (s, 3H, CH_3 at C-7); 1.50 (s, 3H, CH_3 at C-9′).

Synthesis of (3*S*, 3a*R*, 6a*S*)-6-acetyl-2,4,6a-trimethyl-3-phenyl-3a,6,6a,7-tetrahydro-3*H*-pyrazolo-[3″′,4″′:6″,7″]isoquinolino[4″,3″:4′,5′]thieno[3′,2′:4,5]-pyrimido[6,1-*b*] quinazoline-11-one (15). To a suspension of compound **14** (0.55 g, 1 mmol) in glacial acetic acid (20 mL), triethyl orthoformate (0.5 mL, 3 mmol) was added. The resulting mixture was heated under reflux for 20 min and then left to cool. The product that precipitated was collected and recrystallized from ethanol to give compound **15** in the form of a canary amorphous substance; yield: 88%; m.p.: 385−360 °C. IR: 3063 (C−H, aromatic); 2915, 2970 (C−H, aliphatic); 1719 (C═O, quinazolinone), 1650 (C═O, acetyl). ^{1}H NMR (500 MHz, DMSO-d_6): 9.39 (s, 1H, CH of the pyrimidine ring); 8.26−8.28 (d, 1H, J = 10 Hz, Ar H); 7.93−7.97 (t, 1H, Ar H); 7.78−7.79 (d, J = 5 Hz, 1H, Ar H), 7.53−7.56 (t, 1H, Ar H); 7.30−7.33 (t, 2H, Ar H); 7.23−7.35 (t, 1H, Ar H); 7.09−7.11 (d, 2H, Ar H); 5.69−5.72 (d, J = 15 Hz, 1H, CH_2 at C-7); 4.97 (s, 1H, CH at C-3); 4.19 (s, 1H, CH at C-3′); 2.60 (s, 3H, CH_3 attached to the pyridine ring); 2.24−2.27 (d, J = 20 Hz, 1H, CH_2 at C-7); 2.00 (s, 3H, CH_3 at $COCH_3$); 1.83 (s, 3H, CH_3 at C-4); 1.52 (s, 3H, CH_3 at C-6′).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c00601.

FTIR, ^{1}H NMR, and EI-MS data (PDF)

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Notes

The authors declare no competing financial interest.

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