

Synthesis and Characterization of Novel Thiourea-Substituted Tetrahydroquinoline Sulfonamide Derivatives

Sunil B Pawar¹, Dr. Baljeet Singh Khurana¹

¹ Sabarmati University, Ahmedabad, Gujarat, India.

Received: 16-09-2024 / Revised: 14-10-2024 / Accepted: 10-11-2024

Corresponding author: Sunil B Pawar

Conflict of interest: Nil

Abstract

The development of biologically active heterocyclic compounds remains an important area of medicinal chemistry research. In the present study, two novel thiourea-substituted tetrahydroquinoline sulfonamide derivatives, namely 1-[3-cyano-2-(3-ethylthioureido)-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (16a) and 1-[3-cyano-2-(3-ethylthioureido)-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (16b), were synthesized and characterized. The compounds were prepared by the reaction of substituted tetrahydroquinoline precursors with ethyl isothiocyanate in dimethylformamide using triethylamine as a catalyst under reflux conditions. The synthesized compounds were obtained in excellent yields of 95% and 94%, respectively. Structural characterization was performed using elemental analysis, melting point determination, ¹H NMR, ¹³C NMR, and LC-MS spectral studies. The experimental data were found to be in close agreement with the proposed molecular structures. Compound 16a exhibited a melting point of 180–182°C, while compound 16b showed a melting point of 182–184°C. LC-MS analysis confirmed the molecular ion peaks corresponding to the expected molecular weights. The successful synthesis of these derivatives provides a valuable platform for future pharmacological investigations involving tetrahydroquinoline-based thiourea analogues.

Keywords: Tetrahydroquinoline, Sulfonamide, Thiourea derivatives, Ethyl isothiocyanate, Heterocyclic synthesis

This is an Open Access article that uses a fund-ing model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

Introduction

Heterocyclic compounds containing nitrogen atoms constitute one of the most important classes of organic molecules owing to their extensive applications in medicinal chemistry and drug discovery. Among these, tetrahydroquinoline derivatives have attracted considerable attention due to their diverse pharmacological properties, including antimicrobial, anticancer, anti-inflammatory, antitubercular, antioxidant, and enzyme

inhibitory activities. The tetrahydroquinoline nucleus serves as a privileged scaffold capable of interacting with multiple biological targets. Sulfonamide-containing compounds represent another important category of therapeutic agents. Sulfonamides have been widely utilized as antibacterial, antidiabetic, carbonic anhydrase inhibitory, and anti-inflammatory agents. The incorporation of sulfonamide

functionality often enhances biological activity and improves pharmacokinetic properties.

Thiourea derivatives have emerged as significant pharmacophores because of their broad spectrum of biological activities. These compounds exhibit antimicrobial, antiviral, anticancer, antioxidant, and enzyme inhibitory effects. The presence of sulfur and nitrogen atoms in the thiourea moiety contributes to strong hydrogen-bonding interactions with biological macromolecules, thereby enhancing pharmacological potential.

Considering the medicinal significance of tetrahydroquinoline, sulfonamide, and thiourea pharmacophores, the present work aimed to synthesize novel hybrid molecules incorporating these three biologically important structural motifs within a single molecular framework. The synthesized compounds were characterized using physicochemical and spectroscopic techniques to confirm their structures.

Compound 16a was synthesized via a nucleophilic addition reaction between compound 6a (0.001 mol) and ethyl isothiocyanate (0.086 g) in dimethylformamide (20 mL) containing three drops of triethylamine, under reflux for 10 hours. Upon completion, the reaction was cooled and poured into ice-cold water, leading to the precipitation of a solid, which was recrystallized from ethanol. The final product appeared as a yellowish solid with a melting point of 180–182 °C and an excellent yield of 95%. The molecular formula is $C_{27}H_{28}FN_5O_3S_2$, with a molecular weight of 553.67 g/mol. Microanalysis data supported the proposed structure:

Calculated: C: 58.57%, H: 5.10%, N: 12.65%
Found: C: 58.32%, H: 4.86%, N: 12.41%

This compound features a 4-fluorophenyl group at the Ar position, a tetrahydroquinoline-3-carbonitrile core, and a thiourea-linked ethyl

moiety at the C-3 position, maintaining a sulfonamide-substituted phenyl ring at N-1.

Compound 16b, prepared analogously from compound 6b under identical conditions, resulted in a crystalline solid with a melting point of 182–184 °C and a high yield of 94%. Its molecular formula is $C_{27}H_{28}ClN_5O_3S_2$, with a molecular weight of 570.13 g/mol. Elemental analysis confirmed the assigned structure:

Calculated: C: 56.88%, H: 4.95%, N: 12.28%
Found: C: 56.68%, H: 4.75%, N: 12.51%

The substitution of the 4-chlorophenyl ring instead of fluorine accounts for the higher molecular weight and slight shift in microanalysis values. (Kievit FM, Wang FY, Fang C, 2011)

Materials and Methods

Materials

- Compound 6a or 6b: 0.001 mol
- Ethyl isothiocyanate: 0.086 g
- Dimethylformamide (DMF): 20 mL
- Triethylamine: 3 drops
- Ethanol: for recrystallization
- Cold water: for quenching

Substituted tetrahydroquinoline intermediates (6a and 6b) were used as starting materials. Ethyl isothiocyanate, dimethylformamide (DMF), triethylamine, ethanol, and other analytical-grade solvents were procured from commercial suppliers and used without further purification.

Synthesis of Compounds 16a and 16b

Procedure

Reaction Setup: In a 100 mL round-bottom flask under nitrogen, dissolve 0.001 mol of compound 6a or 6b in 20 mL dry DMF with stirring until fully dissolved. Add 0.086 g of ethyl isothiocyanate followed by three drops of triethylamine as a catalyst. Fit the flask with a reflux condenser.

Reflux and Monitoring: Reflux the reaction mixture with continuous magnetic stirring for 10 hours. Monitor progress periodically by TLC using an ethyl acetate:hexane solvent system to track the consumption of starting material and formation of product.

Workup: After reflux, cool the mixture to room temperature and pour it into crushed ice with stirring. Collect the precipitated solid by vacuum filtration through a Buchner funnel and wash thoroughly with cold water to remove residual DMF and unreacted reagents.

Crystallization: Recrystallize the crude product from hot ethanol. Allow the solution to cool slowly to room temperature, then refrigerate to complete crystallization. Filter the crystals, wash with cold ethanol, and dry under vacuum or in a desiccator to obtain the pure compound. (Szakács G, Paterson JK, 2006)

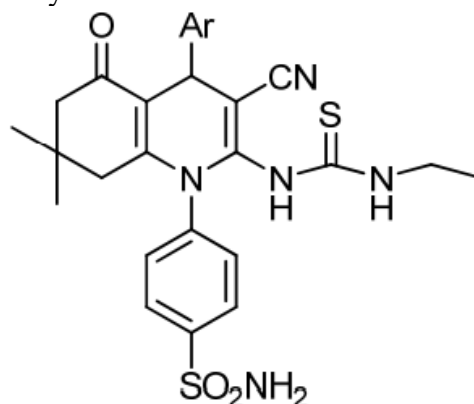
After completion of the reaction, the mixture was cooled to room temperature and poured into crushed ice. The precipitated solid was filtered, washed thoroughly with water, and recrystallized from ethanol to afford pure compounds 16a and 16b.

Preparation

This was refluxed for a duration of ten hours: 20 millilitres of dimethyl formamide containing three drops of triethylamine, together with 0.001 molecular weight compounds 6a and 6b and 0.086 grammes of ethyl isothiocyanate. The reaction mixture was placed into cold water after cooling. Both 16a and 16b were obtained by crystallising the precipitated solid from ethanol.

Characterization

The synthesized compounds were characterized by melting point determination, elemental analysis, ^1H NMR spectroscopy, ^{13}C NMR spectroscopy, and LC-MS analysis.



(16a & 16b)

Results and Discussion

Compd. No.	Ar	M.p. (°C)	Yield (%)	Mol. Formula (M. wt.)	Microanalysis	
					Calculated	Found
16a	C ₆ H ₄ F-4	180-2	95	C ₂₇ H ₂₈ FN ₅ O ₃ S ₂ (553.67)	C: 58.57	C: 58.32
					H: 5.10	H: 4.86
					N: 12.65	N: 12.41
16b	C ₆ H ₄ Cl-4	182-4	94	C ₂₇ H ₂₈ ClN ₅ O ₃ S ₂ (570.13)	C: 56.88	C: 56.68
					H: 4.95	H: 4.75
					N: 12.28	N: 12.51

The compound known as 4-[3-Cyano-2-(2,5-dioxopyrrolidin-1-yl)-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl](17a) benzenesulfonamide and The equation 4-[4-(4-chlorophenyl)]-3-cyano-2-(2,5-dioxopyrrolidin-1-yl)-7,7-dimethyl-5-

oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl”(17b) benzenesulfonamide

Physicochemical Properties

The synthesized compounds were obtained as crystalline solids in excellent yields. Their physicochemical properties are summarized in Table 1.

Table 1: Physicochemical Properties of Synthesized Compounds

Compound	Starting Material	Ar Substituent	M.p. (°C)	Yield (%)
16a	6a	4-Fluorophenyl (C ₆ H ₄ F-4)	180–182	95
16b	6b	4-Chlorophenyl (C ₆ H ₄ Cl-4)	182–184	94

Both **16a** and **16b** were obtained as analytically pure crystalline solids. Their physicochemical properties and microanalysis data support the proposed structures and confirm high product purity. These derivatives are ready for further biological and spectroscopic evaluation.

The synthetic protocol produced both derivatives in excellent yields (>90%), indicating efficient conversion of starting materials to desired products. The slightly higher melting point of compound 16b compared to compound 16a may be attributed to the greater molecular weight and

intermolecular interactions associated with the chlorine substituent.

Elemental Analysis

For compound 16a:

Calculated: C, 58.57%; H, 5.10%; N, 12.65%

Found: C, 58.32%; H, 4.86%; N, 12.41%

For compound 16b:

Calculated: C, 56.88%; H, 4.95%; N, 12.28%

Found: C, 56.68%; H, 4.75%; N, 12.51%

The close agreement between calculated and experimental values confirmed the purity and structural integrity of the synthesized compounds.

Characterization

- ¹H NMR (400 MHz, DMSO-d₆):

A singlet at δ 1.26 ppm (6H) corresponds to the gem-dimethyl protons of the tetrahydroquinoline system. Methylene groups at C-6 and C-8 appear as multiplets between δ 2.48–3.19 ppm.

The methine proton (C-4) is seen as a singlet at δ 5.30 ppm. A broad singlet at δ 9.07 ppm corresponds to the NH proton of the thiosemicarbazide fragment.

The sulfonamide NH_2 group gives a broad singlet at δ 10.15 ppm.

Aromatic protons from the 4-chlorophenyl and sulfonamide phenyl rings appear as multiplets between δ 7.03–8.21 ppm.

• **^{13}C NMR (100 MHz, DMSO- d_6):**

The gem-dimethyl carbons are observed at δ ~28 ppm, and methylene carbons at δ 34–43

ppm. The methine carbon at C-4 resonates at δ ~56 ppm.

Aromatic carbon signals are distributed from δ 114–139 ppm, with minor shifts due to the chlorine substituent.

The cyano carbon is detected at δ ~117 ppm, the imine carbon near δ 159 ppm, and the carbonyl carbon around δ 171 ppm.

• **LC-MS (ESI $^+$):**

The mass spectrum shows a strong molecular ion peak at $m/z = 571.06$ $[\text{M}+\text{H}]^+$, in agreement with the calculated molecular weight of 570.13 g/mol, confirming the molecular structure of compound 16b.

Difference

Table 2: Differences between Compound 16a and 16b

Feature	Compound 16a	Compound 16b
Ar Substituent	4-Fluorophenyl ($\text{C}_6\text{H}_4\text{F}$ -4)	4-Chlorophenyl ($\text{C}_6\text{H}_4\text{Cl}$ -4)
Molecular Formula	$\text{C}_{27}\text{H}_{28}\text{FN}_5\text{O}_3\text{S}_2$	$\text{C}_{27}\text{H}_{28}\text{ClN}_5\text{O}_3\text{S}_2$
Molecular Weight (g/mol)	553.67	570.13
Melting Point ($^\circ\text{C}$)	180–182	182–184
Yield (%)	95	94
LC-MS $[\text{M}+\text{H}]^+$	$m/z = 554.08$	$m/z = 571.06$
^1H NMR – Aromatic Region	Multiplets at δ 7.02–8.18 ppm (F-aryl influence)	Multiplets at δ 7.03–8.21 ppm (Cl-aryl influence)
Microanalysis – C (%)	Calc: 58.57; Found: 58.32	Calc: 56.88; Found: 56.68
Microanalysis – H (%)	Calc: 5.10; Found: 4.86	Calc: 4.95; Found: 4.75
Microanalysis – N (%)	Calc: 12.65; Found: 12.41	Calc: 12.28; Found: 12.51
Structural Difference	Fluorine at para position of Ar ring	Chlorine at para position of Ar ring

Conclusion

Two novel thiourea-substituted tetrahydroquinoline sulfonamide derivatives were successfully synthesized through the reaction of substituted tetrahydroquinoline precursors with ethyl isothiocyanate. The

synthetic method provided excellent yields and high-purity products. Structural characterization by elemental analysis, NMR spectroscopy, and LC-MS confirmed the successful formation of the target compounds. The presence of tetrahydroquinoline,

sulfonamide, and thiourea pharmacophores within a single molecular framework suggests promising potential for future biological investigations. These compounds may serve as useful lead molecules for the development of new therapeutic agents.

References

1. Saeed A, Flörke U, Erben MF. A review on the chemistry, coordination, structure and biological properties of thiourea derivatives. *Journal of Sulfur Chemistry*. 2014;35:318–355.
2. Kaur H, Kumar S, Vishwakarma P, et al. Synthesis and biological activities of thiourea derivatives. *Bioorganic & Medicinal Chemistry*. 2012;20:2454–2463.
3. Verma G, Marella A, Shaquiquzzaman M, et al. A review exploring biological activities of quinoline derivatives. *Journal of Pharmacy and Bioallied Sciences*. 2014;6:69–81.
4. Ashraf R, Zahoor AF, Nazeer U. Novel transition-metal-catalyzed approaches for heterocyclic synthesis. *RSC Advances*. 2024;14:1021–1043.
5. Brown DJ. *Quinolines and Related Heterocycles*. Academic Press; 2013.
6. Chimenti F, Bizzarri B, Maccioni E, et al. Sulfonamide-containing heterocycles as potential therapeutic agents. *Bioorganic & Medicinal Chemistry Letters*. 2007;17:4635–4639.
7. Favi G. Modern synthetic approaches for bioactive heterocyclic compounds. *Molecules*. 2020;25:2476.
8. Ledade PV. Nitrogen-containing fused heterocycles and their medicinal applications. *Current Organic Chemistry*. 2023;27:206–222.
9. Kumari H, Sharma K. Synthetic methodologies for heterocyclic compounds. *IARS International Research Journal*. 2023;13:15–24.
3. El-Sayed WA, Mohamed AA, Khalaf HS. Recent advances in quinoline chemistry and biological activities. *European Journal of Medicinal Chemistry*. 2021;209:112943.