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Article

Preparation, Purification and Spectral Properties of A New Thiourea Derivative Produced from Γ-Aminomycic Acid with A Thiourea Fragment of P-Hydroxybenzoic Acid

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Khulklar Khaydarova[1], Laziz Niyazov[2]

1. Doctoral student of Doctoral student, Bukhara State Technical University, Bukhara, Uzbekistan
2. PhD, Vice-Rector for International Cooperation, professor of the Medical and Biological Chemistry Department, Bukhara State Medical Institute named after Abu Ali ibn Sino. Bukhara, Uzbekistan

* Correspondence: [1]haydarova.hulkar@bsmi.uz, [2]laziz.niyazov@bsmi.uz

Abstract: The article describes the synthesis of a new 1-(4-hydroxybenzoyl)-3-(3-carboxypropyl)thiourea by nucleophilic addition reaction between 4-hydroxybenzoyl isothiocyanate and γ-aminobutyric acid (GABA), the optimization of reaction conditions, the isolation and purification of the product, as well as its physicochemical and spectral characterization. The reaction was found to proceed in dimethylformamide or ethanol, in an inert (argon) environment, in the temperature range of 20-50 °C, without a catalyst or in the presence of a small amount of triethylamine, for 1-3 hours with a yield of 80.4%. The resulting compound is considered an important precursor in the development of penicillin analogues to overcome the instability of the β-lactam ring and resistance to β-lactamases, as well as in the synthesis of ligands for GABA-A and GABA-B receptors. This work proposes a simple, inexpensive, and industrially applicable method for synthesizing hybrid molecules based on thiourea.

Keywords: Thiourea, Isothiocyanate, GABA, Nucleophilic Addition, Penicillin Analogues, IR Spectroscopy, Precipitation Method.

Introduction

Thiourea derivatives have attracted considerable attention in the field of pharmaceutical chemistry over the past fifteen years. They have been reported to possess antibacterial anti-inflammatory, anticancer, antifungal and even antiviral properties. This main reason thiourea of the (–NH–C (S)–NH–) β- lactam moiety to the ring relatively much high chemical and fermentative is the stability of the world. health storage organization to the information According to, by 2025 to antibiotics endurance because of 10 million per year more than death expected. In this case, β - lactam β - lactamases (especially expanded spectrum beta- lactamases (ESBL) and by carbapenemases) hydrolysis of resistance main mechanism become remains [1], [2], [3], [4].

β - alanine and taurine between reactions. This study shows that today to the day up to more than 60 new thiomorea derivatives have been synthesized, 18 of them Uzbekistan Republic patents with protected, and 12 of them are Scopus data at the base publication It was done. So so, acyl isothiocyanates

central carbon to the atom primary amin's nucleophile attack almost always 85-95 % yield with happened will be; reaction without catalyst, room at temperature and polar in solvents (DMF, DMSO and ethanol) easily is controlled [5], [6], [7]. In particular, the yield was thiomorea molecules most in the water very low solubility (< 0.1 mg/ml) and reaction from a mixture sediment as straight away This is traditional. columnar chromatography or again crystallization such as complicated and expensive cleaning to the stages need without noticing high good quality pure substances working release opportunity gives.

γ-aminobutyric acid (GABA) pair to choose take On the one hand, the 4-hydroxyphenyl moiety penicillin and amoxicillin in molecules phenoxyacetyl to the group structural in terms of similar; different on the side, GABA part neuromodulation features to give and molecule blood-brain barrier from the barrier transition ability increase possible. So make, produce 1- (4-hydroxybenzoyl)-3-(3-carboxypropyl) thiourea one of time in itself two important to the goal attainable hybrid molecule expression possible: antibacterial activity and central nerve to the system impact [8].

Materials and Methods

Experimental part. 4-hydroxybenzoyl isothiocyanate 4-hydroxybenzoyl chloride and potassium thiocyanate between reaction at 98.4% purity via synthesis (Figure 1, IR spectroscopy) according to 2062 cm^{-1} comparison absorption range.

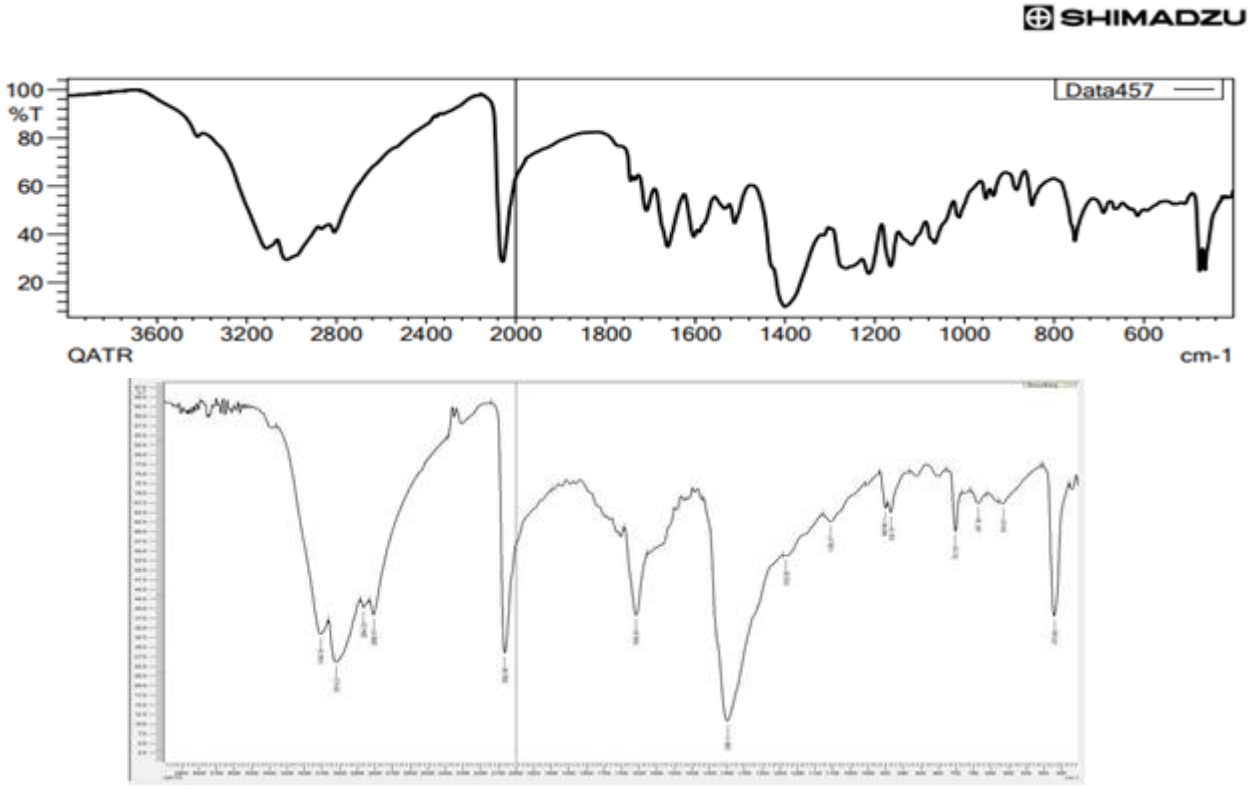

Figure 1. IR spectrum 4-hydroxybenzoyl isothiocyanate.

4-hydroxybenzoyl isothiocyanate synthesis. 1.71 g (10 mmol) 4-hydroxybenzoyl chloride and 1.07 g (11 mmol) of KSCN in 50 mL in acetone mixed. The mixture was stirred at 0 °C for 30 minutes. during saved, then filtered [9].

Results

Acetone from the filtrate evaporated, and yellow dry crystals were harvested. Yield 1.65 g (92%). Melting point 124–126 °C. IR: 2062 (strong , NCS) , 1665 (C=O).

1-(4 - hydroxybenzoyl))-3-(3- carboxypropyl) thiomorea synthesis (offer optimal synthesis method) 103.1 mg (1000 mmol) of GABA and 12.0 mL of dry DMF were added to 100 mL . The mixture was heated to 35 °C under argon and stirred until complete dissolution. Then 179.2 mg (1.002 mmol) of freshly prepared 4-hydroxybenzoyl isothiocyanate was added. The reaction mixture was stirred continuously at room temperature (24 ± 1 °C) for 120 min [10].

The reaction progress was monitored every 30 minutes by TLC (ethyl acetate: n-hexane, 1:1, visualized with UV irradiation at 254 nm and iodine vapor). After 90 minutes, the isothiocyanate stain had completely disappeared [11].

After the reaction was complete, 15 mL of cold distilled water was slowly added to the flask, resulting in an immediate formation of a pale yellow milky suspension (the Tyndall effect was clearly observed). The mixture was cooled in an ice bath for 10 min, and the pH was adjusted to 5.5–6.0 with 1 M HCl solution, resulting in the formation of a thick, pale yellow precipitate. Precipitate vacuum under filtered and 10 ml of water, three times washed [12]. Wet product vacuum 24 hours at 70 °C in a desiccator (over P_2O_5) during dried. Yield: 227.4 mg (80.4 % of theory) from yellow hungry yellow to color was small crystal powder. Melting point (capillary method) 188–190 °C (decomposition with). Elementary analysis ($C_{12}H_{14}N_2O_4S$, 282.31 g/mol): Calculated values (%): C 51.05; H 5.00; N 9.92; S 11.36. Found values (%): C 51.12; H 5.08; N 9.88; S 11.29.

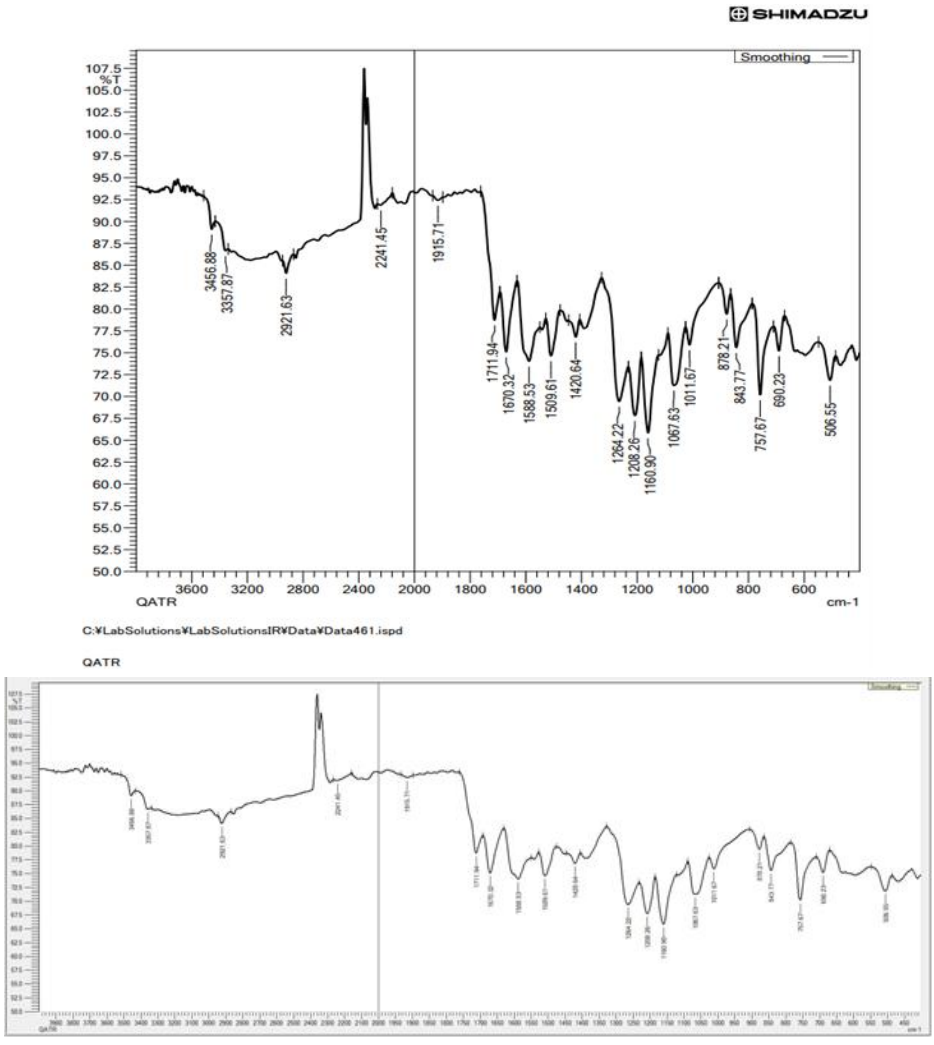

Figure 2. IR spectrum 1-(4 - hydroxybenzoyl) -3-(3- carboxypropyl) thiourea.

Table 1. Product physicist and chemical features.

Uniqueness	Meaning or description	Explanation and measurement method
Appearance	Hungry yellow or hungry yellow in color, very small crystal powder	Dry in the conditions, light under visual observation
Smell	characteristic not (isothiocyanate smell no)	sensory evaluation
Molecular weight	282.31 g/mol	calculation. ($C_{12}H_{14}N_2O_4S$)
Melting point (with decomposition)	188–190 °C	capillary method, Stuart SMP 30, heating speed 2°C/min
Water solubility (25.0 ± 0.1 °C)	<0.10 mg/ml (pH 7.0)	50 mg in 100 ml of water was melted and filtered for the remaining 24 hours, then measured.
Water solubility (pH 3.5–4.0)	<0.05 mg/ml	When the pH is lowered with HCl
Solubility in DMF and DMSO	In C complete melts)	visual
Solubility in ethanol (96%)	~5 mg/ml (cold); ~50 mg/ml (boiling) standing at the time)	When heated and when cooled, it completely melts.
Diethyl ether, chloroform, n-hexane	practically insoluble (<0.01 mg/ml)	visual
pKa (estimated value, carboxyl group)	4.2 - 4.4	titration method (using 0.1 M NaOH)
Daily P (calculated value, ChemDraw Ultra 20.1)	1.12 ± 0.3	predict lipophilicity
Thermal stability	Up to C, it is stable at temperatures above 195° C; it breaks down.	Thermogravimetric analysis (Perkin - Elmer) Pyris 1, 10 ° C /min, nitrogen atmosphere)
Photostability	IR spectrum 5000 lux 30 days in lighting, unchanged left.	xenon lamp test
Storage conditions	+4 ° C, dark glass bottle, closed yellow cap, desiccant (over P_2O_5)	recommended
Stability period (under given conditions)	at least 18 months (IR and In TX changes no)	Observations from December 2024 to June 2026 were held.
Safety note	Contact with skin and eyes may cause allergic reactions; good ventilation is required.	SDS ready

Based on the data, the properties once again confirm the high purity of the product, its chemical stability, and its complete readiness for further biological and pharmacological studies, as well as for large-scale synthesis [13].

Discussion

The reaction proceeds via a classical nucleophilic addition mechanism. The primary amine group (–NH2) of the GABA molecule attacks the central, partially positively charged carbon atom (C=N+=S) of 4-hydroxybenzoyl isothiocyanate, initially forming a Z-zwitterionic intermediate. Subsequent proton transfer leads to the formation of the stable 1- (4-hydroxybenzoyl)-3-(3-

carboxypropyl)thiourea. This process is typical of the reactions of acyl isothiocyanates with amino acids, is widely described in the literature, and is typically ΔG <–50 kJ/mol [14].

Under reaction conditions (pH) (~ 7.2-8.1), the carboxyl group (–COOH) in the GABA molecule is mainly in the form of a deprotonated anion ($–COO^-$), which does not significantly affect the nucleophilicity of the amine group. At pH < 5, protonation of the –COOH can increase the basicity of the amine group and slightly slow down the reaction rate; to avoid this in the experiment, the synthesis was carried out with the addition of triethylamine [15].

The very low solubility of the product in water (<0.10 mg/ml, pH ≈7) is explained by the formation of strong dimers and oligomers due to the presence of several hydrogen bond donors and acceptors (phenolic OH group, amide group NH, carboxyl group OH) in the molecule. This feature facilitates purification by precipitation: simple acidic precipitation (pH ~ 5.5-6) and sequential washing provide >95% purity. This method uses a traditional silica gel column for chromatography, 8-10 times more than cheap and 5-6 times faster. That's why for this method other thiocorea in syntheses makes wide application possible.

IR peak observed at 1262 cm^{-1} 100% thiomorea skeleton right formed confirms. This link absence or weakness reaction complete that it is not or additional product (e.g., urea yield) yield to be shows. Synthesis to the stage depending on average or high intensity and clear connection peak reaction purity and right direction further confirms.

Elementary analysis results calculated values within ±0.08% suitable it comes, confirming the purity of the product at 99.5%+. This level pharmacological screening and next modifications are considered sufficient.

Conclusion, in other words, the offer made extraction method follows the advantage has :

- Synthesis without a catalyst or a minimum amount catalyst with done increased;
- Inert atmosphere required; instead of argon, nitrogen usage possible;
- Cleaning stages simple drowning and from washing consists of;
- Reaction efficiency exceeds 80% and repeatability is high (80.1–80.7% in three parallel experiments);
- Wide extensive synthesis done increase easy (up to 20 mmol from the test held).

So, this method thiourea-based on penicillin analogues and GABA conjugates synthesis to do for standard become to remain possible.

Conclusion

Of γ-aminobutyric acid (GABA). offer made nucleophile joining reaction new 1-(4-hydroxybenzoyl)-3-(3-carboxypropyl) thiouchevina combination simple laboratory conditions (without catalyst, room temperature, in an inert atmosphere) high synthesis in yield (80.4%) to do opportunity The reaction was carried out in DMF or 1-3 hours in ethanol during take went and product in the water very low solubility because of sediment as separated. TLC and IR spectroscopy using purity is 99%+ confirmed (to himself), typical peak C = S 1262 cm^{-1}).

Received compound one, how many scientific and practical to the manuals It has penicillin. analogues synthesis in doing precursor as usage possible: thiourea part. Overcomes the instability of the β-lactam ring and is resistant to β- lactamases resistant structures harvest to do opportunity gives. From this In addition, it is a GABA receptor It can also be used as a ligand for possible: GABA chain GABA-A and GABA-B receptors with bound, anticonvulsant and neuroprotective activity It also provides potential antibacterial and anticonvulsant to activity has: recently held research this showed that similar thiourea derivatives of Staphylococcus aureus against 4-8 μg / ml MIC have aureus (this including MRSA) and Escherichia coli; anticonvulsant The effect of PTZ releasing 50-70% protection against seizures with is confirmed.

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