

Synthesis of Ethyl 2-Amino-6-hydroxy-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate and Ethyl 6-(Acetyloxy)-2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate

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Molbank **2026**, 2026(2), M2144; <https://doi.org/10.3390/M2144>

Submission received: 30 January 2026 / Revised: 24 February 2026 /

Accepted: 27 February 2026 / Published: 4 March 2026

(This article belongs to the Section **Organic Synthesis and Biosynthesis**)

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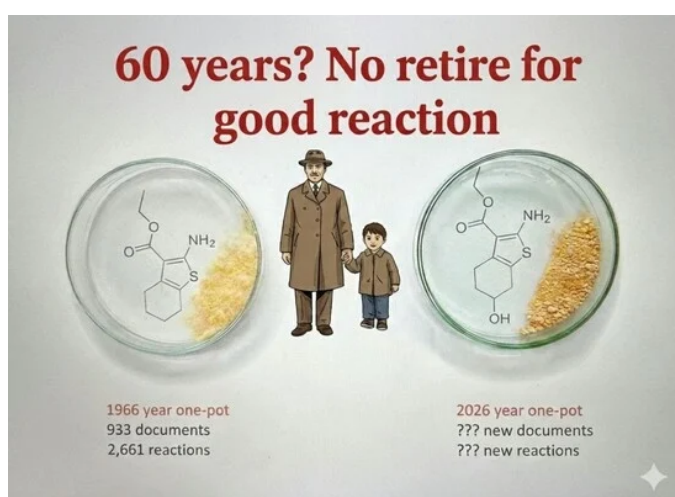
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Versions Notes

Abstract

An effective one-step synthetic procedure for preparation of hydroxylated analogues of ethyl 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate as novel promising multifunctional building blocks for drug discovery based on the Gewald procedure was developed.

Keywords: thiophene; hydroxylation; cyclohexane; metabolism; Gewald synthesis



Introduction

Since the discovery of an effective procedure to synthesize 2-aminothiophene by Kar Gewald [1,2], it remains useful and opens up new horizons for drug discovery. This reactor made a variety of 2-aminothiophene-3-carboxylic acid derivatives available; among them, the simplest but by no means the least useful is ethyl 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate **1**, which is the product of the Gewald reaction of cyclohexanone with ethyl cyanoacetate. According to Reaxsys, this molecule is cited in 933 documents and 2661 reactions as the starting compound. In the period 2020–2026, 94 papers were published mentioning this compound. Many of them are about the discovery of new biologically active substances like anticancer [3,4,5], antibacterial [3,6,7,8,9], anti-inflammatory [10,11,12], anthelmintic [13], anti-plasmodia [14] and multitarget anti-Alzheimer agents [15,16]. This derivative of 2-aminothiophene is also a precursor for the preparation of antivirals [17], α -glucosidase inhibitors [18], and antimalarial agents [19].

The popularity of ethyl 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate is explained by its structure; as a matter of fact, cyclohexane is a structural fragment of many useful drugs [20,21,22,23,24,25,26] (**Figure 1**).

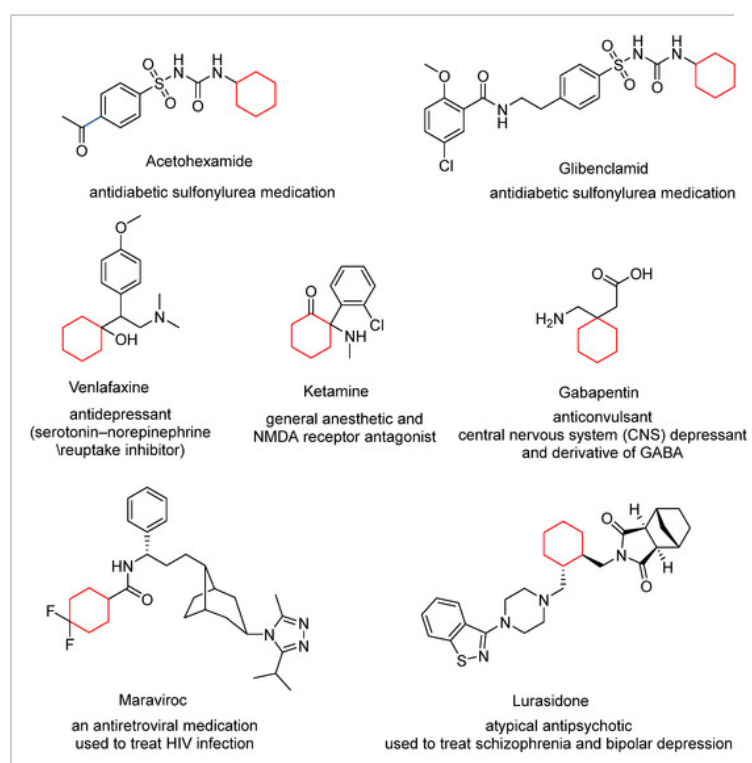


Figure 1. Modern medicines with cyclohexane ring.

For many of these drugs, metabolic transformations were studied, and it was found that they undergo hydroxylation of the cyclohexane ring [27,28,29,30].

Among good examples of the metabolite application of cyclohexane hydroxylation in drug discovery is the introduction of paliperidone to the pharmaceutical market (**Figure 2**) [31,32,33]. This compound was first identified as metabolite of risperidone with an almost identical pharmacological profile. That gave an opportunity to introduce paliperidone palmitate under the brand name Invega Sustenna[®] as an alternative to risperidone with the possible development of long-acting injectable dosage forms [34,35].

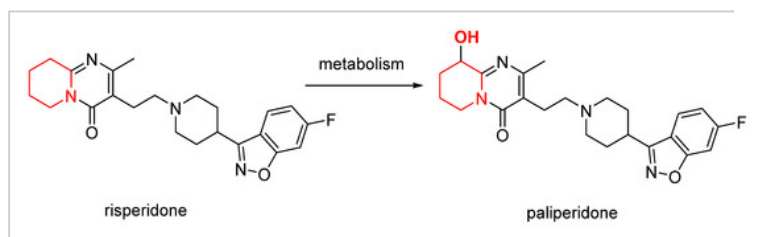


Figure 2. Transformation of risperidone to paliperidone.

In view of the importance of aminoester **I** as a building block for biologically active compounds and much information about the hydroxylation of the cyclohexane ring as a key metabolic transformation for cyclohexane-containing xenobiotics, we focused our efforts on the preparation of previously unknown hydroxylated analogues **3a** and **3b**, with either a free or acetylated hydroxyl group (**Figure 3**).

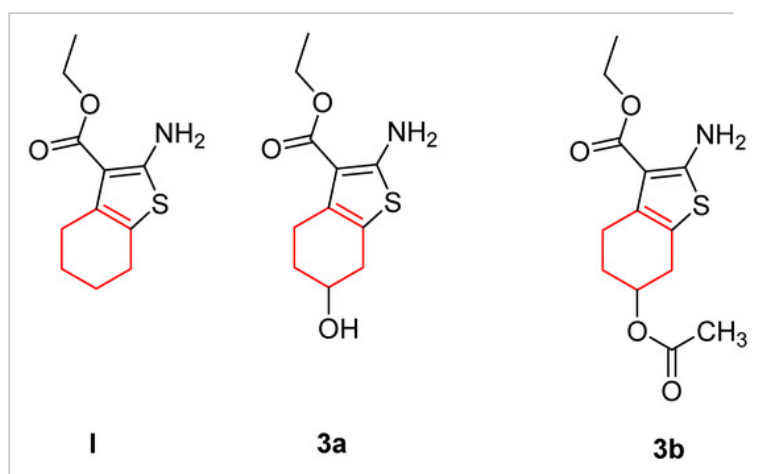
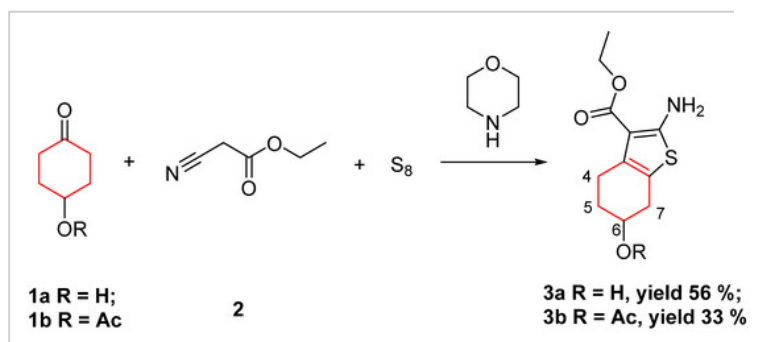


Figure 3. The target compounds with a hydroxylated cyclohexane ring.

2. Results and Discussion

We tested the Gewald protocol of synthesis, similarly to the reported for more active malononitrile [36,37], with 4-hydroxycyclohexanone in ethanol, applying morpholine as the catalyst suitable to be extracted with water during the isolation procedure (**Scheme 1**). According to LC-MS monitoring, the product was formed to a high extent. The main challenging task was the isolation of the product as, unlike its cyclohexyl analog **I**, **3a** did not precipitate from the reaction mixture even upon cooling. We performed the extraction of water-soluble ethanol and morpholine.



Scheme 1. Synthesis of the target hydroxylated derivatives **3a** and **3b**.

For purification of the product **3a**, simple flash chromatography was enough for isolation of the pure product. For acetylated product **3b**, an additional chromatographic purification round was needed. The oily **3b** product obtained was additionally crystallized from acetonitrile.

The products **3** were isolated in 56% for **3a** and 33% for **3b** yields; the set of analytical data confirmed their purity, and the structure was recorded.

In the ^1H NMR spectrum of **3a** (see [Supplementary Materials](#)), the signal of the amino group is observed at 7.18 ppm, and the carboethoxy group displays two signals: the methyl group at 1.22 ppm and the methylene group at 4.12 ppm. The signal of the secondary OH group for compound **3a** is observed at 3.83 ppm and it has the splitting pattern, which confirms its proximity to the CH group at position 6 with the signal at 4.77 ppm. The compound **3b** has a very similar pattern of signals in the ^1H NMR spectrum, but the signal of OH is not observed, while the signal of the CH group at position 6 is shifted to 5.01 ppm.

3. Materials and Methods

All solvents were purified according to the standard procedures. All starting materials were obtained from Enamine Ltd. (Enamine Ltd., Kyiv, Ukraine) and used without additional purification. Analytical TLC was performed using ALUGRAM Xtra SIL G UV254, (Macherey-Nagel GmbH, Duren, Germany). Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) (Merck KGaA, Darmstadt, Germany) as the stationary phase. ^1H and ^{13}C NMR spectra were recorded at 500 MHz or 400 MHz, and 126 MHz or 101 MHz, respectively. LC-MS spectra were obtained on the Shimadzu 10-AV LC (Shimadzu Corporation, Kyoto Japan), Gilson-215 (Gilson, Inc., Middleton, WI, USA), equipped with autosampler, with the following detectors: UV (215 and 254 nm), electrospray ionization mass spectrometer (AP 150EX) (Agilent, Santa Clara, CA, USA), ELS detectors. HRMS spectra were acquired with the Agilent 6200 Series TOF (Agilent, Melbourne, Australia) and 6500 Series Q-TOF LC/MS System. IR spectra were taken on an IR5 FTIR spectrometer (Edinburgh Instruments, Livingston Scotland, UK). AI was used for the preparation of the graphic abstract.

The starting of 4-oxocyclohexyl acetate **1b** was achieved by the reported procedures from 4-hydroxycyclohexanone and acetyl chloride [38,39].

Preparation of ethyl 2-amino-6-hydroxy-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate **3a**.

To the stirred mixture of 20 mL (0.175 mol) of 4-hydroxycyclohexanone, 20 mL (0.175 mol) of ethyl cyanoacetate, 5.6 g (0.175 mol) of sulfur and 20 mL of ethanol in a conical 1000 mL flask, 20 mL of morpholine was added. The reaction mixture was stirred at 60 °C till the sulfur powder was dissolved and additionally for 2 h at the same temperature. The reaction mixture was left with stirring overnight for 10 h at ambient temperature. The reaction mixture was quenched with 700 mL of water, which was then removed. The oily mass was washed with 500 mL of water three times. The oily residue was dissolved in the minimal amount of ethyl acetate and the organic extract was dried over anhydrous sodium sulfate and filtered through the 100 mm pad of silica on the 500 mL Schott filter funnel. Ethyl acetate was used as the eluent. The obtained ethyl acetate solution of the product was evaporated at reduced pressure till crystallization occurred. The yellow mass solid was additionally dried at 60 °C in the oven.

Yellow crystalline powder, yield 56%. m.p. 98 °C.

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ : 7.18 (m, J = 9.6 Hz, 2H), 4.77 (d, J = 4.0 Hz, 1H), 4.12 (dtt, J = 9.7, 4.8, 2.7 Hz, 2H), 3.83 (br.s, 1H), 2.75 (dt, J = 17.7, 5.3 Hz, 1H), 2.62 (dd, J = 15.5

5.0 Hz, 1H), 2.53 (q, J = 8.9, 8.1 Hz, 1H), 2.31–2.20 (m, 1H), 1.79 (dd, J = 12.6, 6.2 Hz, 1H) 1.59–1.44 (m, 1H), 1.22 (td, J = 7.1, 2.0 Hz, 3H).

^{13}C NMR (101 MHz, DMSO- d_6) δ : 165.4 (C=O), 163.7 (C), 131.1 (C), 113.6 (C), 102.7 (C) 65.9 (CH), 59.0 (CH₂), 33.6 (CH₂), 31.5 (CH₂), 25.1 (CH₂), 14.8 (CH₃).

LCMS, positive mode, m/z : 241.0 [M + H]⁺.

HRMS (ESI): calcd. for C₁₁H₁₅NO₃S [M + H]⁺: 241.0773; found: 241.0763.

IR (ATR, neat), ν , cm⁻¹: 356, 375, 391, 430, 457, 491, 517, 556, 634, 677, 751, 778, 828 881, 957, 981, 1009, 1030, 1069, 1119, 1148, 1195, 1214, 1267, 1295, 1338, 1365, 1384, 1413 1439, 1482, 1588, 1639, 2840.88 VW; 2893.91 W; 2928, 2951, 2978, 3083, 3170, 3306, 3417.

Preparation of ethyl 6-(acetyloxy)-2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate **3b**.

The preparation was similar to the previous one, but for isolation of the individual product additional chromatography for the ethyl acetate extract was needed. First, it was filtered through the 100 mm pad of silica on the 500 mL Schott filter funnel and eluted with ethyl acetate–hexane 1:2 mixed eluent. The second purification round was performed on 2000 mL Schott filter funnel (1500 mL of silica gel) and elution of the desired compounds was successful with (ethyl acetate–hexane 1:5). The product was additionally crystallized from dry acetonitrile. The formed crystals were filtered off and dried at 60 °C in the oven.

Yellow crystalline powder, yield 33%. m.p. 119 °C.

^1H NMR (500 MHz, DMSO- d_6) δ : 7.24 (m, J = 9.6 Hz, 2H), 5.01 (dtd, J = 8.7, 5.4, 3.2 Hz 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.79 (dd, J = 16.1, 5.0 Hz, 1H), 2.68 (q, J = 5.7 Hz, 2H), 2.45 (d, J = 6.1 Hz, 1H), 1.98 (s, 3H), 1.90–1.76 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, DMSO- d_6) δ : 170.4 (C=O), 165.3 (C=O), 163.9 (C), 131.1 (C), 112.3 (C), 102.6 (C), 69.3 (CH), 59.2 (CH₂), 29.8 (CH₂), 27.2 (CH₂), 24.0 (CH₂), 21.5 (CH₃), 14.8 (CH₃).

LCMS, positive mode, m/z : 283.1 [M + H]⁺.

HRMS (ESI): calcd. for C₁₃H₁₇NO₄S [M + H]⁺: 283.0878; found: 283.0869.

IR (ATR, neat), ν , cm⁻¹: 355, 375, 384, 419, 473, 490, 526, 550, 607, 627, 656, 741, 779 832, 882, 921, 970, 996, 1030, 1102, 1138, 1158, 1251, 1308, 1337, 1365, 1380, 1413, 1431 1457, 1476, 1496, 1532, 1592, 1672, 1714, 2902, 2932, 2977, 3169, 3265, 3309, 3427.

Supplementary Materials

The following supporting information can be downloaded online: LCMS, ^1H , ^{13}C NMR DEPT, HRMS, IR spectra, of ethyl 2-aminothiophen-3-carboxylates **3a** and **3b**.

Author Contributions

Conceptualization, A.Y.M., S.V.V. and A.R.K.; Methodology, A.Y.M. and G.G.Y.; Software H.I.S.; Validation, A.Y.M. and S.V.V.; Formal Analysis, A.R.K.; Investigation, A.Y.M.; Resources A.Y.M., G.G.Y. and A.R.K.; Data Curation, A.Y.M. and S.V.V.; and Writing—Original Draft Preparation, A.Y.M. and H.I.S.; Writing—Review and Editing, A.Y.M. and H.I.S.; Visualization

A.Y.M. and G.G.Y.; Supervision, S.V.V.; Project Administration, S.V.V.; Funding Acquisition G.G.Y. and A.R.K. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Data Availability Statement

Data is contained within the article or the [Supplementary Material](#).

Acknowledgments

All the authors and contributors are truly grateful to Enamine Ltd. company for the research opportunities and analytical data like ^1H , ^{13}C NMR, LC-MS, IR and HRMS spectra.

Conflicts of Interest

The authors Andrii Yu. Myshastyi, Sergiy V. Vlasov, Georgiy G. Yakovenko and Andrii R. Khairulin were employed by the company Enamine Ltd. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationship that could be considered a potential conflict of interest.

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Myshastyi, A.Y.; Vlasov, S.V.; Severina, H.I.; Yakovenko, G.G.; Khairulin, A.R. Synthesis of Ethyl 2-Amino-6-hydroxy-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate and Ethyl 6-(Acetyloxy)-2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate. *Molbank* **2026**, *2026*, M2144. <https://doi.org/10.3390/M2144>

AMA Style

Myshastyi AY, Vlasov SV, Severina HI, Yakovenko GG, Khairulin AR. Synthesis of Ethyl 2-Amino-6-hydroxy-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate and Ethyl 6-(Acetyloxy)-2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate. *Molbank*. 2026; 2026(2):M2144. <https://doi.org/10.3390/M2144>

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Myshastyi, Andrii Yu., Sergiy V. Vlasov, Hanna I. Severina, Georgiy G. Yakovenko, and Andrii R. Khairulin. 2026. "Synthesis of Ethyl 2-Amino-6-hydroxy-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate and Ethyl 6-(Acetyloxy)-2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate" *Molbank* 2026, no. 2: M2144. <https://doi.org/10.3390/M2144>

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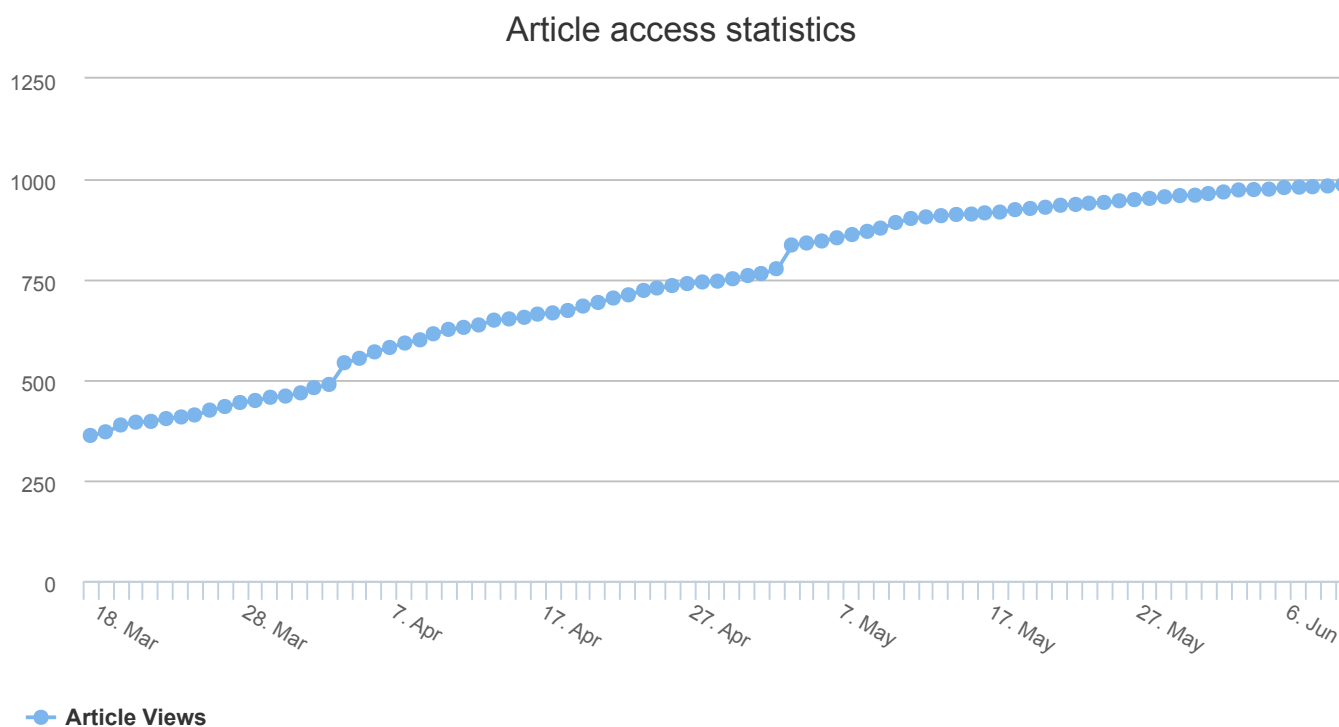
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