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Short Note

N-(3-Methoxyphenethyl)-2-propylpentanamide

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Abstract

Herein, we present the synthesis of *N*-(3-methoxyphenethyl)-2-propylpentanamide, a derivative of valproic acid. The compound has been thoroughly characterized through melting-point determination, ^{1}H and ^{13}C NMR spectroscopy, infrared spectroscopy, and mass spectrometry. The comprehensive analytical data obtained from these techniques confirm the successful preparation and structural integrity of the newly synthesized molecule.

Keywords: hybrid molecule; valproic acid; 2-(3-methoxyphenyl)ethan-1-amine; amide; epilepsy; neuropsychiatric disorders; anticonvulsant

1. Introduction

Valproic acid (VPA) is a widely used medication with diverse therapeutic applications across numerous neurological and psychiatric conditions. It is prescribed to control various forms of epilepsy, manage bipolar disorder, and prevent migraines [1]. Chemically, it is known as 2-propylpentanoic acid—a short-chain fatty acid and structural analog of valeric acid, which occurs naturally in *Valeriana officinalis* [2]. In addition to its use in epilepsy, VPA is utilized for migraine prophylaxis, the management of bipolar disorder, and experimentally as a protective agent in diabetic neuropathy [2]. Despite its strong efficacy, the clinical use of VPA is constrained by rare but serious adverse effects—including hepatotoxicity, teratogenicity, and neural tube defects, particularly in pregnant women—necessitating stringent monitoring and regulatory oversight [3]. The pharmacologically active form of the drug is the valproate anion, which predominates at physiological pH and is responsible for its therapeutic effects [4].

2-Phenylethylamine (PEA) is an endogenous trace amine present throughout the brains of both vertebrate and invertebrate species [5,6]. The term "trace amine" refers to a class of amines that occur at much lower intra- and extracellular concentrations than the chemically and functionally related biogenic amines [7]. Alterations in the metabolism of 2-phenylethylamine can contribute to a variety of central nervous system disorders, including schizophrenia, Tourette's syndrome, and attention deficit disorder, among others [8]. PEA is a small molecule that has very intriguing and yet at the same time quite different from each other functions—it has the role of a neurotransmitter and is also used in food processing [7].

Many methoxy (OCH_3)-containing compounds arise in nature through the action of O-methylating enzymes on hydroxylated substrates, making methoxy groups a common feature in naturally derived drugs [8]. It improves drug binding, physicochemical properties, and metabolic behavior, making it a valuable tool for medicinal chemists in drug design and optimization [8].

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Academic Editor: Rodrigo Abonia

Received: 20 November 2025
Revised: 10 December 2025
Accepted: 16 December 2025
Published: 17 December 2025

Citation: Dimitrova, D.; Barakova, Y.; Trifonov, I.; Ivanov, I.; Bojilov, D.; Manolov, S. *N*-(3-Methoxyphenethyl)-2-propylpentanamide. *Molbank* **2025**, *2025*, M2114. https://doi.org/10.3390/M2114

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Given the broad therapeutic relevance of VPA (given in red at Figure 1) and the important neuroactive functions of PEA (given in blue at Figure 1), designing a hybrid molecule **1** (Figure 1) that incorporates structural features of both compounds presents a promising strategy for developing novel CNS-active agents.

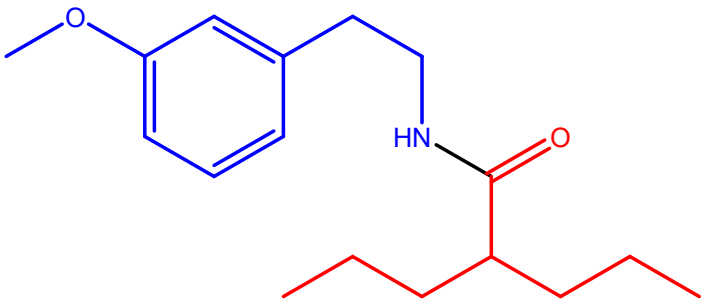
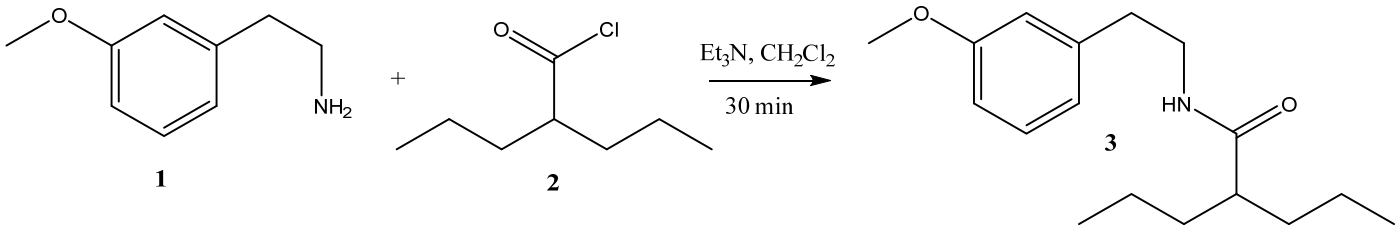


Figure 1. Structural formula of *N*-(3-methoxyphenethyl)-2-propylpentanamide.

VPA provides well-established anticonvulsant and mood-stabilizing properties, while PEA, as an endogenous trace amine, plays a modulatory role in neurotransmission and is implicated in several neuropsychiatric disorders. Introducing a methoxy group at the 3-position further enhances this design rationale, as methoxy substituents commonly improve binding affinity, physicochemical properties, and metabolic stability in drug candidates. Therefore, a hybrid structure combining VPA with 3-methoxy-substituted PEA may yield a molecule with synergistic or improved pharmacological effects, potentially reducing adverse effects while expanding therapeutic potential within neurological and psychiatric disorders.

2. Results and Discussion

In this work, we describe the successful synthesis of *N*-(3-methoxyphenethyl)-2-propylpentanamide. For this purpose, the carboxyl functional group of valproic acid was initially transformed into its corresponding acyl chloride derivative, which was then allowed to react with 2-(3-methoxyphenyl)ethan-1-amine (Scheme 1).



Scheme 1. Synthesis of compound **3**.

The structure of the synthesized compound was confirmed through comprehensive spectral analysis, including melting-point determination, ^{1}H and ^{13}C NMR, IR, and mass spectrometry.

The ^{1}H NMR spectrum confirms the presence of all 27 expected protons (Supplementary Material Figure S1). The two methyl groups appear at 0.81 ppm as a triplet integrating for six protons. The methylene resonances originating from the valproic acid moiety are observed as multiplets corresponding to four, two, and two protons within the 1.09–1.41 ppm region. The methine (CH) proton is detected between 2.13 and 2.05 ppm. The two methylene groups of the PEA fragment are observed as a quartet and a triplet, each integrating for two protons at 3.29 and 2.68 ppm, respectively. A sharp singlet at 3.73 ppm corresponds to the methoxy group. In the aromatic region, the four aromatic

protons produce characteristic signals, and the amino proton appears as a triplet at 7.85 ppm. The ^{13}C NMR spectrum further confirms both the presence and the expected number of carbon atoms within the molecular structure (Figure S2).

The IR spectrum (Figure S3) clearly exhibits the characteristic absorption bands corresponding to the principal functional groups of the compound. In both the solid and liquid phases, secondary amides typically present a strong absorption band at approximately 3289 cm^{-1}. A methoxy group attached to an aromatic ring usually gives rise to a sharp isolated band near 2835 cm^{-1}. An alkoxy on an aromatic ring usually gives rise to two correlatable bands, 1310–1210 and 1050–1010 cm^{-1} [9].

3. Materials and Methods

All reagents and chemicals were purchased from commercial suppliers (Sigma-Aldrich S.A. and Riedel-de Haën, Sofia, Bulgaria) and were used without further purification. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance II + 600 spectrometer (BAS-IOCCP—Sofia, Bruker, Billerica, MA, USA), operating at 600 MHz for ^{1}H and 150.9 MHz for ^{13}C. Spectra were acquired in DMSO-d_6, with chemical shifts (δ) referenced to tetramethylsilane (TMS, δ = 0.00 ppm) and coupling constants (J) reported in hertz (Hz). All NMR measurements were performed at ambient temperature (approximately 295 K). Melting points were determined using a Boetius hot-stage apparatus (Plovdiv University; Boetius, Germany) and are reported uncorrected. Infrared (IR) spectra were obtained on a Bruker Alpha II FTIR spectrometer (Plovdiv University; Bruker, Billerica, MA, USA). High-resolution mass spectrometry (HRMS) analyses were conducted using a Q Exactive Plus mass spectrometer equipped with a heated electrospray ionization (HESI-II) source (Thermo Fisher Scientific, Bremen, Germany) and coupled to a Dionex Ultimate 3000RSLC UHPLC system (Thermo Fisher Scientific, Waltham, MA, USA). Thin-layer chromatography (TLC) was carried out on 0.2 mm silica gel 60 plates (Fluka, Merck KGaA, Darmstadt, Germany).

3.1. Obtaining of 2-Propylpentanoyl Chloride **2**

Valproic acid (1.0 mmol, 0.1442 g) was dissolved in toluene (20 mL), after which thionyl chloride in excess (1.2 mmol, 0.087 mL) was added to the solution. The mixture was refluxed at 110–115 °C for 2 h to promote conversion of the carboxylic acid to the corresponding acid chloride. Upon completion, excess toluene and volatile byproducts were removed under reduced pressure using rotary evaporation. The resulting residue was then dissolved in dichloromethane for use in the subsequent reaction step, without further purification.

3.2. Synthesis of N-(3-Methoxyphenethyl)-2-propylpentanamide **3**

A solution of 3-methoxyphenylethylamine (1 mmol, 0.1512 g) in dichloromethane (20 mL) was prepared. To this solution, 2-propylpentanoyl chloride (1 mmol, 0.1626 g) was added. The resulting mixture was stirred at room temperature for 10 min, after that triethylamine (Et_3N, 0.168 mL, 1.2 mmol) was added dropwise to neutralize the hydrochloric acid byproduct and facilitate amide bond formation. The reaction was stirred continuously on an electromagnetic stirrer for 30 min. Progress of the reaction was monitored by thin-layer chromatography (petroleum ether/diethyl ether 1:1 (v/v)), confirming complete consumption of the amine starting material. Upon completion, the reaction mixture was washed with dilute aqueous hydrochloric acid ($HCl:H_2O$ = 1:4), saturated aqueous sodium carbonate (Na_2CO_3), and brine. The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified

by short-column chromatography on neutral aluminum oxide (Al_2O_3) using CH_2Cl_2 as the eluent to afford the new hybrid molecule **3**.

N-(3-methoxyphenethyl)-2-propylpentanamide **3**

White solid (m.p. 88–90 °C), yield 96% (0.266 g), R_f = 0.45 (petroleum ether/diethyl ether = 1/1 *v*/*v*), ^{1}H NMR (600 MHz, DMSO) δ 7.85 (t, *J* = 5.3 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 6.80–6.73 (m, 3H), 3.73 (s, 3H), 3.29 (q, 2H), 2.68 (t, *J* = 7.2 Hz, 2H), 2.13–2.05 (m, 1H), 1.41 (ddt, *J* = 12.4, 9.3, 6.8 Hz, 2H), 1.23–1.17 (m, 2H), 1.16–1.09 (m, 4H), 0.81 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (151 MHz, DMSO) δ 175.18 (C=O), 159.69 (Ar), 141.58 (Ar), 129.65 (Ar), 121.35 (Ar), 114.72 (Ar), 111.94 (Ar), 55.30 (OCH_3), 45.70 (CH), 40.22 (CH_2CH_2NH), 35.75 ($ArCH_2CH_2NH$), 35.35 ($2xCHCH_2CH_2CH_3$), 20.63 ($2xCH_2CH_3$), 14.46 ($2xCH_3$). IR (KBr) $\nu_{max.}$, cm^{-1}: 3289, 3085 ν(N-H), 1626 ν(C=O), 2832 ν_s ($O–CH_3$), 1310, 1050 δ(C_{sp^3}–O–C_{sp^2}), Electrospray ionization (ESI) *m*/*z* calculated for $[M + Na]^+$ $C_{17}H_{27}NNaO_2^+$ = 300.1934 found 300.1924 (mass error Δm = −3.33 ppm).

Supplementary Materials: The following supporting information can be downloaded online. Figure S1: ^{1}H NMR spectrum of compound **3**; Figure S2: ^{13}C NMR spectrum of compound **3**; Figure S3: IR spectrum of compound **3**; Figure S4: ESI-HRMS of compound **3**.

Author Contributions: Conceptualization, I.I. and S.M.; methodology, S.M.; software, S.M. and D.B.; validation, I.I., S.M. and D.B.; formal analysis, D.D., Y.B. and I.T.; investigation, S.M.; resources, I.I.; data curation, S.M.; writing—original draft preparation, S.M.; writing—review and editing, S.M.; visualization, S.M. and D.B.; supervision, I.I.; project administration, S.M.; funding acquisition, I.I. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: The data presented in this study are available in this article and supporting Supplementary Materials.

Acknowledgments: The authors thank the Faculty of Chemistry at "Paisii Hilendarski" University of Plovdiv.

Conflicts of Interest: The authors declare no conflicts of interest.

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