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Short Note

N-(3-Cyano-4,5,6,7-tetrahydrobenzothiophen-2-yl)-2-[[5-[(1,5-dimethyl-3-oxo-2-phenylpyrazol-4-yl)amino]-1,3,4-thiadiazol-2-yl]sulfanyl]acetamide

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Abstract: The small pyrazolone-bearing molecules attract attention and are widely explored in drug design as pharmacological agents. The new pyrazolone-thiadiazole hybrid molecule *N*-(3-cyano-4,5,6,7-tetrahydrobenzothiophen-2-yl)-2-[[5-[(1,5-dimethyl-3-oxo-2-phenylpyrazol-4-yl)amino]-1,3,4-thiadiazol-2-yl]sulfanyl]acetamide (**3**) has been synthesized following a two-stage protocol using simple, convenient transformations and cheap, commercially available reagents. The compound's structure was confirmed using ^{1}H, ^{13}C nuclear magnetic resonance (NMR), and liquid chromatography–mass spectrometry (LC–MS) spectra. The anti-inflammatory potency of **3** was evaluated in silico using molecular docking. The docking studies results suggest that title compound **3** is of great interest for further structure optimization and in-depth studies as a possible 5-lipoxygenase (5-LOX) inhibitor.

Keywords: antipyrine; 1,3,4-thiadiazole; hybrid molecules; NSAIDs; molecular docking; COX-2; 5-LOX

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1. Introduction

Antipyrine (1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one) structural motif is an important and valuable tool in modern medicinal chemistry [1–3]. Historically associated with antipyretic and anti-inflammatory properties, nowadays antipyrine-bearing molecules have been successfully studied and developed as potential modulators for the correction of various pathological processes [4,5]. Among them, the most successful example is Edaravone (brand names Radicava, Radicut), a close structural analog of antipyrine, which was was approved by the Food and Drug Administration (FDA) in 2017 as a neuroprotective antioxidant drug for used to help with recovery following a stroke and to treat amyotrophic lateral sclerosis and is considered by the FDA as a first-in-class medication [6,7] (Figure 1).

Despite the breakthrough in the development of potential non-steroidal anti-inflamm atory drugs (NSAIDs) in the second half of the last century this issue still remained a direction in modern drug design [8,9].The antipyrine-containing molecules attract much attention and have been widely explored for the design of new potential NSAIDs for more than 100 years. The new small molecules with antipyrine scaffold as possible multi-target and polypharmacological anti-inflammatory agents have been synthesized following the molecular hybrid-pharmacophore approach and have been reported recently [10–13] (Figure 1). It should be noted that currently potential NSAIDs are intensively evaluated as a promising medications for improving/treatment of pathological conditions associated with inflammatory processes such as neuro- and oncology diseases [14,15].

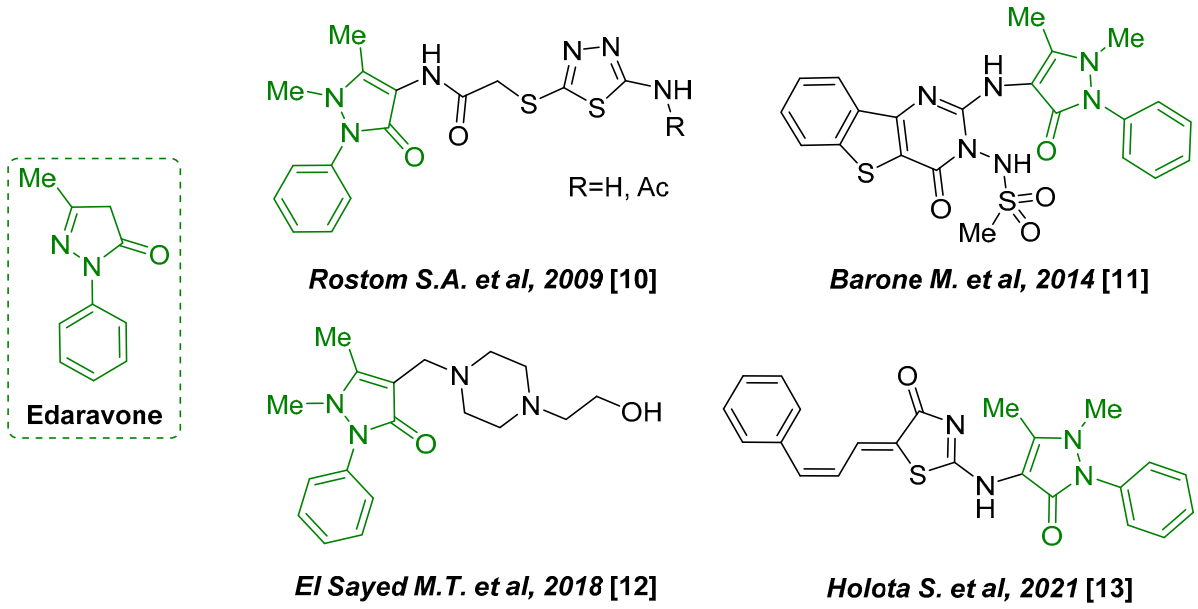
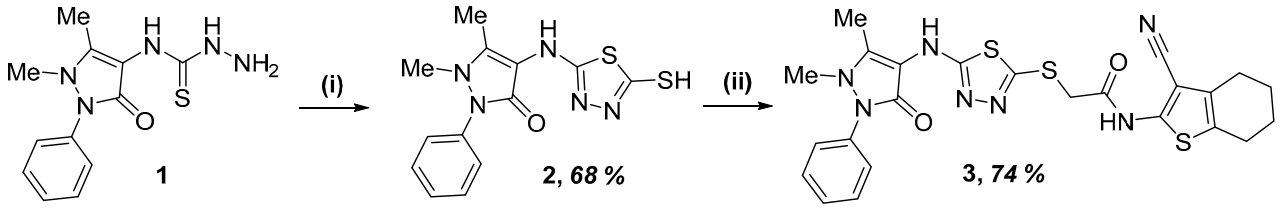


Figure 1. Structures of edaravone and antipyrine-heterocycle hybrid molecules with anti-inflammatory properties.

In view of all the above reasons, the aim of the present work was to develop a facile and cheap synthetic pathway to new antipyrine-thiadiazole-bearing hybrid molecules as possible potential non-steroidal anti-inflammatory agents. Herein the synthesis of *N*-(3-cyano-4,5,6,7-tetrahydrobenzothiophen-2-yl)-2-[[5-[(1,5-dimethyl-3-oxo-2-phenyl-pyrazol-4-yl)amino]-1,3,4-thiadiazol-2-yl]sulfanyl]acetamide **3** (Scheme 1), its structure characterization, and its in silico evaluation as a potential anti-inflammatory agent, are described.



Scheme 1. Synthesis of title compound **3**. Reagents and conditions: (**i**)—**1** (10 mmol), K_2CO_3 anhyd. (5 mmol), CS_2 (10 mmol), ethanol (15 mL), reflux 4 h; (**ii**)—**2** (10 mmol), KOH (10 mmol), 2-chloro-*N*-(3-cyano-4,5,6,7-tetrahydrobenzothiophen-2-yl)acetamide (11 mmol), KI (traces), ethanol (10 mL), reflux 1.5 h.

2. Results and Discussion

2.1. Synthesis of the Title Compound **3**

The title compound **3** was synthesized following a two-stage protocol using simple and convenient transformations (Scheme 1). The 1-amino-3-(1,5-dimethyl-3-oxo-2-phenylpyrazol-4-yl)thiourea (**1**), which can be easily prepared from cheap and commercially available 4-aminoantipyrine, hydrazine hydrate, and carbon disulfide accordingly to the method described in [16], was used as starting reagent. The reflux (for 4 h) of **1** with an equimolar amount of carbon disulfide in the presence of a base (potassium carbonate anhydrous) led to the 1,5-dimethyl-2-phenyl-4-[(5-sulfanyl-1,3,4-thiadiazol-2-yl)amino]pyrazol-3-one (**2**) with good yield (68%). In the next stage the one-pot process took place; initially potassium 5-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)amino)-1,3,4-thiadiazole-2-thiolate was generated in situ by heating for 15 min derivative **2** with an ethanol solution of potassium hydroxide. Then, to the reaction mixture, the 10% excess amount of 2-chloro-*N*-(3-cyano-4,5,6,7-tetrahydrobenzothiophen-2-yl)acetamide was added and refluxed (for 1.5 h) in the presence of potassium iodide traces. The target

compound **3** was obtained in satisfactory yield (74%) and was purified by recrystallization from a mixture of dimethylformamide (DMF)-ethanol (1:4).

The synthesized derivative **3** was characterized by ^{1}H, ^{13}C nuclear magnetic resonance (NMR) and liquid chromatography–mass spectrometry (LC–MS) spectra (copies of spectra are presented in Supplementary). The ^{1}H NMR spectrum exhibited all the characteristic protons of antipyrine and tetrahydrobenzothiophen moieties as well as the amide, amine and methylene groups. The protons of NH groups appeared as singlets at 11.84 and 9.23 ppm and were assigned to the amide and secondary amine groups, respectively. The protons of the phenyl group in the antipyrine moiety resonated as two multiplets at 7.48–7.54 and 7.32–7.37 ppm. Then, the singlet signal at 4.19 ppm was assigned to protons of the methylene group of acetamide moiety whereas eight protons ($(CH_2)_4$) of tetrahydrobenzothiophen moiety appeared as a multiplet at 2.53–2.61 ppm and as a singlet at 1.74 ppm. The protons of two methyl groups appeared as singlets at 3.09 and 2.20 pm. In the ^{13}C NMR, the signals of C=O group carbons were assigned at 171.7 and 161.7 ppm. The remaining carbon signals appeared in the corresponding aromatic and aliphatic regions as expected. The molecular ion peak observed at *m/z* value of 538.2 $[M+H]^+$ in positive ionization mode in the mass spectrum confirmed the formation of the title compound **3**.

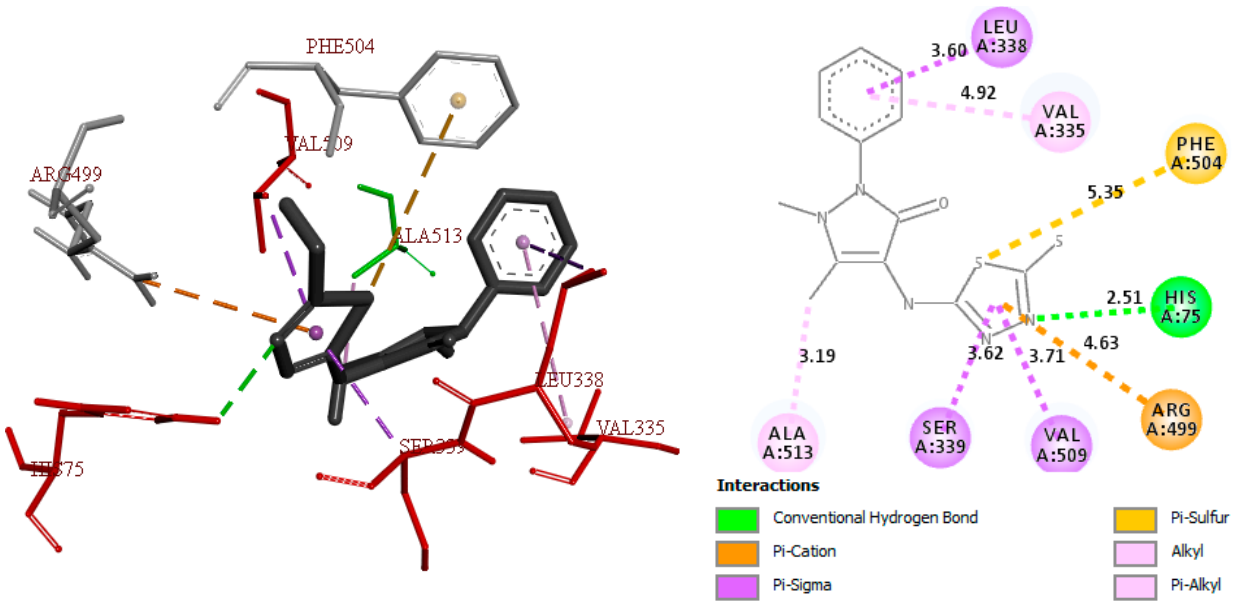
2.2. Molecular Docking

In order to explore anti-inflammatory properties of **2** and **3,** docking studies were performed. Cyclooxygenase-2 (COX-2) (PDB ID 3LN1) and 5-LOX (PDB ID 3V99) were chosen as targets proteins for in silico simulations. After docking simulations binding energies and inhibition constants were obtained, which allowed us to make suggestions about the anti-inflammatory potential of each compound. Docking simulations demonstrated good affinity of compound **2** to COX-2, nevertheless its binding energy was less compared to reference drug Celecoxib (Table 1 and Figure 2). The 1,3,4-thiadiazole core connects to an enzyme inside the allosteric site by hydrogen bond to HIS 75 with the length 2.51Å, Pi-Sigma to SER339 and VAL509, Pi-Cation and Pi-Sulfur to ARG499 and PHE504 respectively. Another part of the molecule also has a hydrophobic interaction with LEU338, VAL335 and ALA513, but the absence of strong hydrogen bonds, like in the interaction of the sulfonamide group of Celecoxib and COX-2, decreases the anti-inflammatory potential of compound **2**.

Table 1. The docking result for COX-2 and 5-LOX.

Compounds	COX-2 (PDB:3LN1)		5-LOX (PDB:3V99)	
	Binding Energy (Kcal/mol)	**Ki Inhibition Constant**	**Binding Energy (Kcal/mol)**	**Ki Inhibition Constant**
2	−8.5	807.43 nM	−6.5	11.77 uM
3	−3.6	925.65 μM	−9.0	243.23 nM
Celecoxib	−12.3	12.23 nM	-	-
Licofelone	-	-	-8.73	443.88 nM

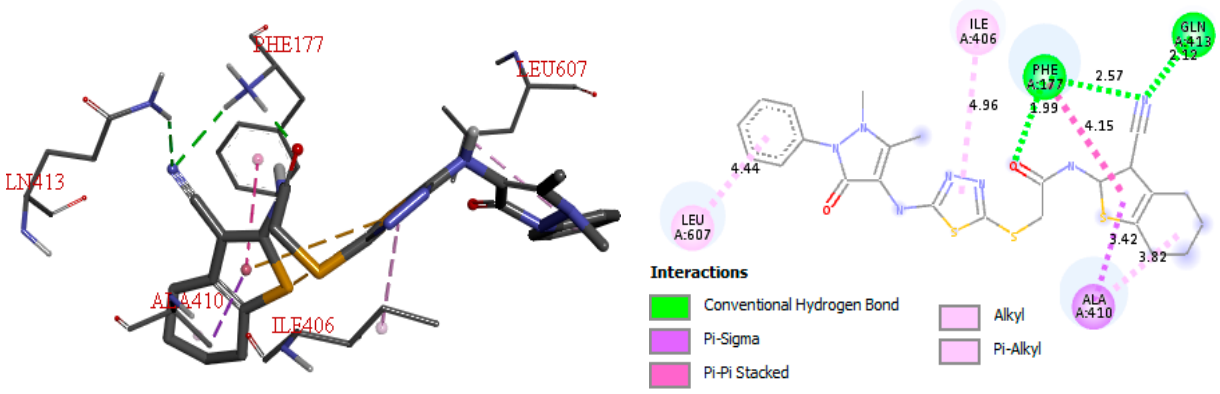
The promising binding energy close to the reference drug allows us to suggest that compound **2** possesses pronounced anti-inflammatory potential. Also, docking results demonstrate the selectivity of compound **2** to 5-LOX enzyme. Such selectivity decreases the total anti-inflammatory effect of the molecule, but increases its safety as COX-2 inhibition is also connected with cardiotoxicity [17]. Additionally, the impact on 5-LOX enzyme may have extra benefits like anticancer activity and the absence of ulcerogenic effects of «classical» NSAIDs.



(**a**) (**b**)

Figure 2. The binding mode of compound **2** with COX-2 enzyme (PDB 3LN1): (**a**) 3D visualization; (**b**) ligand interaction diagram of compound **2** with COX-2.

Compound **3** demonstrated strong affinity to 5-LOX and very weak binding to COX-2 under in silico simulations, which allowed us to consider the selective mechanism of action with all the following advantages and disadvantages (Table 1 and Figure 3). The cyano-group in position 3 of 2-amino-4,5,6,7-tetrahydrobenzothiophene core forms two hydrogen bonds with PHE177 and GLN413 with the length 2.57 Å and 2.12Å. Additionally, the amide group also connects to PHE177 by a hydrogen bond (1.99 Å). Phenyl, 1,3,4-thiadiazole, and benzothiophene cores interact with a number of lipophilic amino acids (LEU4607, ILE406, ALA410). The high binding energy for title compound **3** suggests its further structure optimization and the need for in-depth studies as a possible 5-LOX inhibitor.



(**a**) (**b**)

Figure 3. The binding mode compound **3** with 5-LOX enzyme (PDB 3V99): (**a**) 3D visualization; (**b**) Ligand interaction diagram of the title compound **3** with 5-LOX.

3. Materials and Methods

3.1. General Information and Compound **3** *Synthesis*

Melting points were measured in open capillary tubes on a BÜCHI B-545 melting point apparatus (BÜCHI Labortechnik AG, Flawil, Switzerland) and are uncorrected. The elemental analyses (C, H, N) were performed using the Perkin–Elmer 2400 CHN

analyzer (PerkinElmer, Waltham, MA, USA) and were within ±0.4% of the theoretical values. The 400 MHz-^{1}H and 100 MHz-^{13}C spectra were recorded on Varian Unity Plus 400 (400 MHz) spectrometer (Varian Inc., Paulo Alto, CA, USA). All spectra were recorded at room temperature except where indicated otherwise and were referenced internally to solvent reference frequencies. Chemical shifts (δ) are quoted in ppm and coupling constants (*J*) are reported in Hz. LC–MS spectra were obtained on a Finnigan MAT INCOS-50 (Thermo Finnigan LLC, San Jose, CA, USA). The reaction mixture was monitored by thin layer chromatography (TLC) using commercial glass-backed TLC plates (Merck Kieselgel 60 F_{254}). Solvents and reagents that are commercially available were used without further purification. Compound **1** was prepared according to the protocol described in [16]. The 2-chloro-*N*-(3-cyano-4,5,6,7-tetrahydrobenzothiophen-2-yl)acetamide was obtained from 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile and 2-chloroacetyl chloride as was described in [18].

1,5-Dimethyl-2-Phenyl-4-[(5-Sulfanyl-1,3,4-Thiadiazol-2-yl)Amino]Pyrazol-3-One (**2**)

To the mixture of 1.0 mmol of compound **1** and 0.5 mmol of anhydrous potassium carbonate in the 15 mL of ethanol, the 1.0 mmol of carbon disulfide was added slowly. The obtained mixture was refluxed and mixed with magnetic stirring for 4 h. The process was monitored by TLC. After the synthesis was completed, the solvent was evaporated in a vacuum and 25 mL of distilled water was added to the residue and white precipitate of compound **2** formed, which was filtered, washed with water, dried, and recrystallized from a glacial acetic acid. Yield 86%, white powder, mp 238–240 °C (AcOH).

^{1}H NMR (400 MHz, dimethylsulfoxide (DMSO)-d_6, δ): 13.40 (s, 1H, SH), 8.95 (s, 1H, NH), 7.49–7.54 (m, 2H, arom.), 7.32–7.37 (m, 3H, arom.), 3.09 (s, 3H, CH_3), 2.21 (s, 3H, CH_3).

LCMS (Electrospray ionization (ESI+)) m/z 320.0 (100%, [M+H]+).

Anal. calc. for $C_{13}H_{13}N_5OS_2$: C 48.89%, H 4.10%, N 21.93%. Found: C 49.00%, H 4.30%, N 22.10%.

N-(3-Cyano-4,5,6,7-Tetrahydrobenzothiophen-2-yl)-2-[[5-[(1,5-Dimethyl-3-Oxo-2-Phenyl -Pyrazol-4-yl)Amino]-1,3,4-Thiadiazol-2-yl]Sulfanyl]Acetamide (**3**)

A solution of 1.0 mmol of **2** in 10 mL of ethanol and a solution of 1.0 mmol of KOH in 5 mL of ethanol were mixed and refluxed for 15 min. Then the 1.1 mmol of 2-chloro-*N*-(3-cyano-4,5,6,7-tetrahydrobenzothiophen-2-yl)acetamide and several crystals of potassium iodide were added to the reaction mixture and refluxed for 1.5 h. The process was monitored by TLC. After the synthesis has been completed, the reaction mixture was cooled and poured into distilled water, and yellow precipitate of compound **3** formed, which was filtered, washed with water, dried, and recrystallized from a mixture of DMF-ethanol (1:4). Yield 74 %, yellow powder, mp 213–215 °C (ethanol–DMF 4:1).

^{1}H-NMR (400 MHz, DMSO-d_6, δ): 11.84 (s, 1H, NH), 9.23 (s, 1H, NH), 7.48–7.54 (m, 2H, arom.), 7.32-7.37 (m, 3H, arom.), 4.19 (s, 2H, CH_2), 3.09 (s, 3H, CH_3), 2.53–2.61 (m, 4H, $(CH_2)_4$), 2.20 (s, 3H, CH_3), 1.74 (s, 4H, $(CH_2)_4$).

^{13}C-NMR (100 MHz, DMSO-d_6, δ): 171.7, 166.3, 161.7, 152.7, 150.9, 146.6, 135.3, 131.3, 129.6, 128.1, 127.1, 124.4, 114.5, 110.5, 93.5, 37.7, 36.1, 24.0, 23.8, 23.0, 22.1, 11.0.

LCMS (ESI+) *m*/*z* 538.2 (100%, $[M+H]^+$).

Anal. calc. for $C_{24}H_{23}N_7O_2S_3$: C 53.61%, H 4.31%, N 18.24%. Found: C 53.80%, H 4.50%, N 18.40%.

3.2. Molecular Docking

Under the preparing procedures all ligands, cofactors and water molecules were removed, polar hydrogen atoms were added, and non-polar hydrogen atoms were merged. Also, Gasteiger charges were added to the residues. Three-dimensional structures of 1 and 2 were created by Hyperchem 7.5 through energy minimizations using the MM+ and PM3 quantum techniques, respectively. The Auto Dock Tool was used for calculation of the binding free energy which includes all types of interaction (hydrogen bonds, Van

Der Waals force, etc.) Lamarckian Genetic Algorithm (LGA) parameters were used as a default, which includes 150 runs, 150 conformational possibilities, 50 populations and 2,500,000 energy evaluations [19]. The validations of selected docking parameters were performed by redocking of the initial ligand Celecoxib for COX-2 and Licofelone [20] for 5-LOX. Visualization and interpretation of the data obtained were performed by Discovery Studio Visualizer of Dassault Systemes Biovia®.

4. Conclusions

In this work, we have presented the efficient synthesis of a new antipyrine-thiadiazole-bearing hybrid molecule. The compound's structure was characterized and confirmed by NMR spectroscopy and LC–MS spectrometry analysis. The in silico studies using molecular docking predicted that the title compound has anti-inflammatory potency through the 5-LOX inhibition and presented interest for in-depth in vitro and in vivo studies.

Supplementary Materials: The following are available online. Figures S1–S3: NMR and LC–MS spectra of compound **3**.

Author Contributions: Conceptualization was done by S.H. and R.L.; Methodology and experimental works were done by S.H., I.Y., D.K., R.V.; Data Analysis was done by S.H., I.Y., D.K., R.V., R.L.; writing, review and editing the paper were done by S.H., I.Y., D.K., R.L.; Project administration and supervision was done by R.L. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data presented in this study are available in this article.

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

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