

Short Note

## 2-(6-Methoxynaphthalen-2-yl)propionic acid (1,3-dimethyl-butylidene)hydrazide

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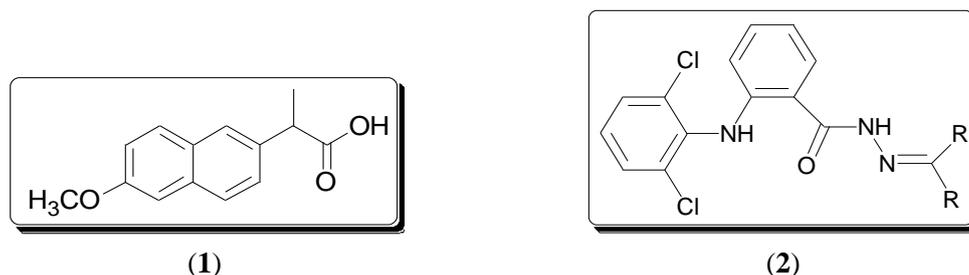
**Abstract:** The title compound, 2-(6-methoxynaphthalen-2-yl)propionic acid (1,3-dimethyl-butylidene)hydrazide was synthesized in high yield by the reaction of 2-(6-methoxynaphthalen-2-yl)propionic acid hydrazide and 4-methylpentan-2-one in PEG 400. This compound was fully characterized by IR, <sup>1</sup>H NMR, mass spectra and elemental analysis. The *in vitro* antibacterial activity of this compound was evaluated against gram positive and gram negative bacteria.

**Keywords:** 2-(6-methoxynaphthalen-2-yl)propionic acid hydrazide; 4-methylpentane-2-one

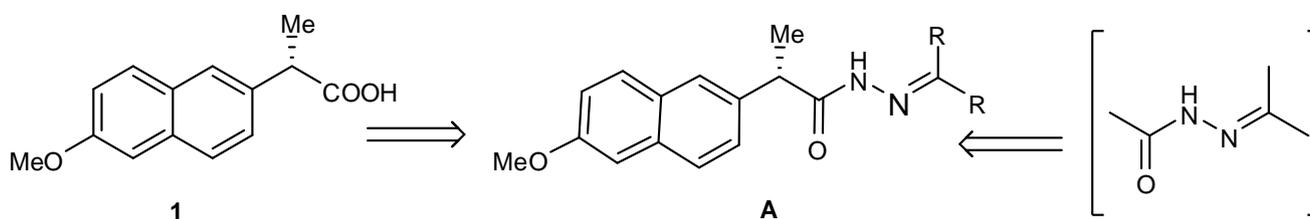
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Naproxen (**1**, **Figure 1**), [1] one of the most regularly used propionic acid derivatives for the treatment of pain, joint swelling and symptoms of arthritis, is believed to work by blocking the action of cyclooxygenase (COX) involved in the production of prostaglandins that are produced in response to injury or certain diseases and cause pain, swelling and inflammation. However its use is associated with some gastrointestinal side effects possibly caused by the free acidic group present. Masking of this free acidic group therefore was thought to be a possible solution to this problem.

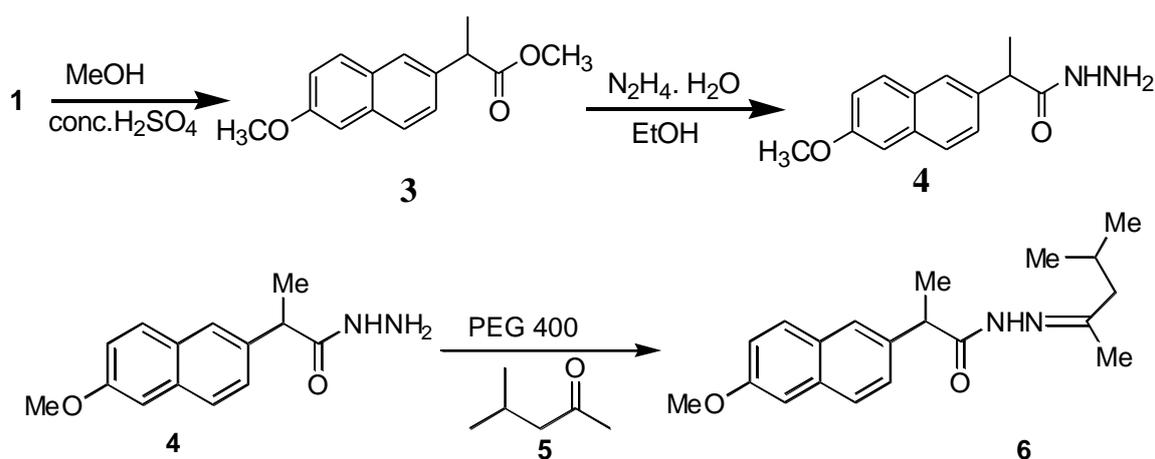
Because of their distinctive structural features (characterized by the presence of an azomethine hydrogen) and wide range of pharmacological activities, hydrazones have attracted enormous interest especially in medicinal chemistry [2]. This is exemplified by the synthesis and pharmacological evaluation of a large number of hydrazone derivatives against various pharmacological targets [3-5]. Hydrazones derived from diclofenac acid hydrazide (**2**, **Figure 1**) and naproxen have shown antimycobacterial activities when tested *in vitro* [6,8].

**Figure 1.** Naproxen and diclofenac acid hydrazide-derived hydrazones.

We anticipated that combination of structural features of naproxen (**1**) with substituted hydrazones in a single molecule (**A**,  $R \neq H$ ) (**Scheme 1**) would provide novel agents of potential pharmacological interest.

**Scheme 1.** Design of hybrid molecule.

As solvents play a vital role in performing the majority of organic transformations, we used a simple and widely available nontoxic, non-ionic (aprotic) liquid, inexpensive, less volatile and biologically acceptable polymer, polyethylene glycol (PEG) as alternative solvent medium for our purpose. Performing reactions in such a solvent generally does not produce toxic waste products.

**Scheme 2.** Synthesis of the title compound (**6**).

We report the synthesis of 1-aroyle-2-(alkenyl/aryl)idenehydrazine (**6**) as hybrid molecule derived from naproxen (**1**) by straightforward condensation of a key intermediate *i.e.*, naproxen based N-acylhydrazine with the commercially available carbonyl compound, 4-methylpentane-2-one (**5**). Thus, esterification [7] of **1** with methanol in the presence of catalytic amounts of concentrated sulphuric acid followed by treating the resulting ester (**3**) with hydrazine hydrate in methanol gave

compound **4** in 96% yield [8]. The final condensation was performed by stirring an equimolar mixture of 4-methylpentane-2-one (**5**) (1.1 g, 0.011 mol) and 2-(6-methoxynaphthalen-2-yl)propionic acid hydrazide (**4**) (2.44 g, 0.01 mol) in PEG 400 (10 mL) at room temperature for 5 h to afford the solid compound (**6**). The solid was filtered, dried and purified by column chromatography to yield 2.60 g (80%) of compound **6**. The compound exists as a mixture of two rotamers at room temperature as evident from  $^1\text{H}$  NMR spectra [8]. While the present reaction was carried out using PEG 400 as a solvent, the use of other solvents was also examined. The use of solvents like DMF, DMSO, and THF decreased the product yield. Although use of 1,4-dioxane as a solvent afforded the product in 70% yield after 6 h, its use is not advisable as it is carcinogenic. The synthesized hybrid molecule **6** was tested *in vitro* against various Gram negative and Gram positive bacteria using Amikacin as a standard. The concentration of compound used was 1 mg per mL.

Yield of the title compound: 80%; mp: 118–120 °C;  $R_f$  0.6 (hexane/ethyl acetate, 6:4).

IR (KBr  $\text{cm}^{-1}$ ): 3198, 3055, 2876, 1673 ( $\text{CO}_{\text{amide I}}$ ), 1608 (C=N).

MS (ES):  $m/z$  327 ( $\text{M}^+$ , 99%).

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  10.01 (10.00\*, s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable), 7.74 (m, ArH, 4H), 7.40 (m, ArH, 1H), 7.26 (m, ArH, 1H), 4.78 (4.00\*, q, 1H,  $J = 8.0$  Hz), 3.86 (s,  $\text{OCH}_3$ , 3H), 2.05 (d, 2H,  $J = 7.0$  Hz), 1.90 (m, 1H), 1.80 (1.78\*, s, 3H), 1.42 (m, 3H), 0.82 (0.80\*, d, 6H,  $J = 7.2$  Hz).

[chemical shift ( $\delta$ ) values of rotameric  $\pm$  hydrogens whenever identified are presented within the parentheses by assigning an asterisk (\*) along with that of other form].

$^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  175.2, 169.7, 158.5, 157.0, 151.8, 137.1, 133.1, 133.0, 129.1, 128.9, 128.4, 128.3, 126.8, 126.6, 126.5, 125.7, 125.3, 118.6, 118.4, 105.6, 55.1, 47.5, 47.4, 43.1, 40.4, 25.4, 25.2, 22.4, 22.3, 22.7, 22.1, 18.6, 18.3, 18.2, 16.3, 15.8.

Anal. calc. for  $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_2$ : C, 73.59, H, 8.03, N, 8.58. Found: C, 73.84, H, 8.31, N, 8.34.

**Table 1.** Antibacterial activity of compound **6** against Gram positive and Gram negative bacteria, using Amikacin as standard.

Code	Escherichia Coli	Klebsiella pneumonia	Bacillus subtilis	Staphylococcus aureus	Staphylococcus epidermis
<b>6</b>	+++	+++	+++	++	++
Control	++++	++++	++++	++++	++++

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