RESEARCH ARTICLE

In Silico Design, Synthesis, and Characterization of Ibuprofen Derivative as Potential Antitumor Agent

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ABSTRACT

Background: Numerous animal studies and clinical trials in cancer have shown that ibuprofen reduces the incidence of and mortality from cancer. Synthesis of a novel conjugate of ibuprofen with the 2-phenyl amino pyrimidine derivative (to mimic small molecules kinase inhibitor anti-cancers) exhibits significant increase, as compared to free ibuprofen, potential to inhibit proliferation of cancer cells.

Methods: The docking study was performed with GOLD software supplied by the Cambridge Crystallographic Data Centre. Thereafter, chemical synthesis was established. The chemical structures of this study were confirmed by spectral instrumentation; infrared, differential scanning calorimeter thermal analyzer, proton and carbon-13 nuclear magnetic resonance.

Results and Discussions: The docking process was successfully conducted, and the chemical synthesis yielded a good percent. The spectral interpretations show a characteristic identification of the target chemical compound.

Keywords: ^{1}H-NMR,^{13}C-NMR, Antitumor, Docking, DSC, Ibuprofen acid chloride, IR.

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Ethical Clearance: No ethical concerns are encountered.

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to reduce inflammation and as analgesics by inhibition of cyclooxygenase-2.[1-3] At higher concentrations, some NSAIDs inhibit proliferation and induce apoptosis of cancer cells. This was found with ibuprofen, which is considered one of the most common and potent anti-inflammatory and analgesic drugs that can be utilized to treat mild to severe pains.[4-7] It has been reported that ibuprofen possesses an antiproliferative effect against colon and breast cell lines.[8] In this work, the authors, aim to design and synthesize a new ibuprofen derivative with potential antiproliferative effect.

MATERIALS AND INSTRUMENTATION

Chemicals and reagents

- 6-methyl-N1-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine was purchased from BLDpharm (China).
- Dichloromethane HPLC-grade and n-Hexane were purchased from GCC (UK).
- Ethyl acetate HPLC-grade was purchased from GCC, UK.
- Ibuprofen acid chloride was gifted by Dr. Zaid M. Al-Obaidi, Department of Pharmaceutical Chemistry, College of Pharmacy, University of Kerbala.
- Methanol (HPLC grade), was purchased from Biosolve Chimie SARL (France).
- Sodium hydrogen carbonate was purchased from Himedia (India)
- THF and Potassium carbonate were purchased from SCR (China).
- Triethylamine was purchased from Thermo (Canada).

Instrumentation

- 1-stage vacuum pump 5 Pa ¼ HP Wenling Aitcool (China).
- 4-digit balance Sartorius Lab (Germany).
- DSC (Differential Scanning Calorimeter) Thermal

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Analyzer Shimadzu (Japan).
- Hotplate stirrer LabTech (Korea).

Docking study

The X-ray crystallographic structure of Tyrosine-protein kinase ABL1 (PDB ID 3k5v) was downloaded from the Protein Data Bank that was uploaded with X-ray diffraction method at a resolution of 1.74 Å. Thereafter, the water molecules and ligands were removed from the protein structure. The addition of hydrogen atoms to the protein macromolecule was performed by the aid of Mercury software version 4.1.2.

On the other hand, the ligand molecular structure was designed, and energy minimized utilizing the ChemBioDraw Ultra version 14.0 and the ChemBio3D Ultra version 14.0 software. Finally, the GOLD software version 5.7.2 was utilized to establish the docking study. The GOLD program was run, and the resulted solutions were saved and visualized, as seen in the result section.

Chemistry

Synthesis of 2-(4-isobutylphenyl)-N-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)propanamide[9]

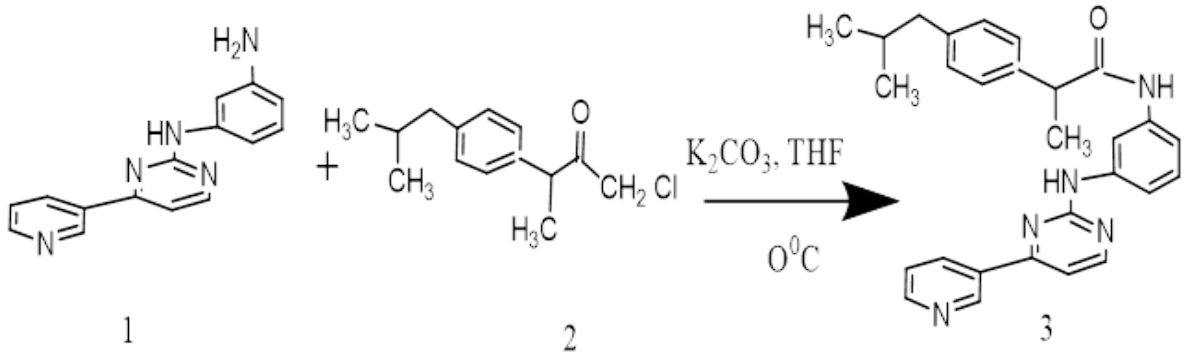
To a stirred solution of 6-methyl-N1-(4-(pyridin-3-yl) pyrimidin-2-yl)benzene-1,3-diamine ((compound 1) (500 mg, 1.8 mmol)) and potassium carbonate (1.24 g, 9 mmol) in THF (20 mL) at 0°C was added ibuprofen acid chloride 2 (493 mg, 2.2 mmol) and the reaction mixture was stirred at 0°C for 45 min. The reaction mixture was added dropwise to a cold, stirring solution of 10% NaHCO3 (20 mL) and stirred at the same temperature (0°C) for 30 min. A yellowish solid precipitated out, which was isolated by filtration. The solid was washed with cold water, hexane, and dissolved in a mixture of methanol/dichloromethane (50:50, 10 mL) and concentrated under reduced pressure. The residue obtained was suspended in cold water (20 mL), Et3N was added to it, and it was extracted with ethyl acetate (2 x 20 mL). The combined ethyl acetate extract was washed with water (10 mL), concentrated under reduced pressure in a desiccator to get the title compound 3 (697 mg, 83%) (Scheme 1). The IR spectra (υ, cm-1) were as follows; 1625 (str. vib. C=O, amide) and the disappearance of 3500 (str. vib.NH, NH2).

RESULTS AND DISCUSSIONS

The docking of the compound (3) ligand with the target protein is shown in Figure 1.

The docking study shows good fitness for the receptor, which may potentiate its ex-vivo effect.[8]

The IR spectrum of compound 3 is shown in Figure 2



Scheme 1: The chemical synthesis of 2-(4-isobutylphenyl)-N-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)propanamide.

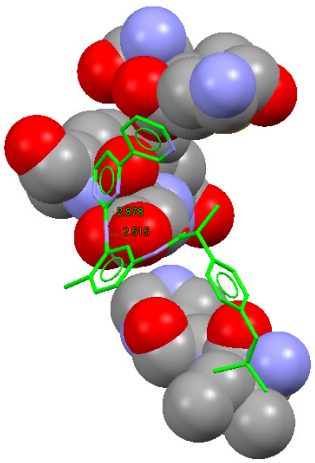


Figure 1: This figure shows the interaction between the ligand (compound 3) and the Tyrosine-protein kinase ABL1 (PDB ID 3k5v).

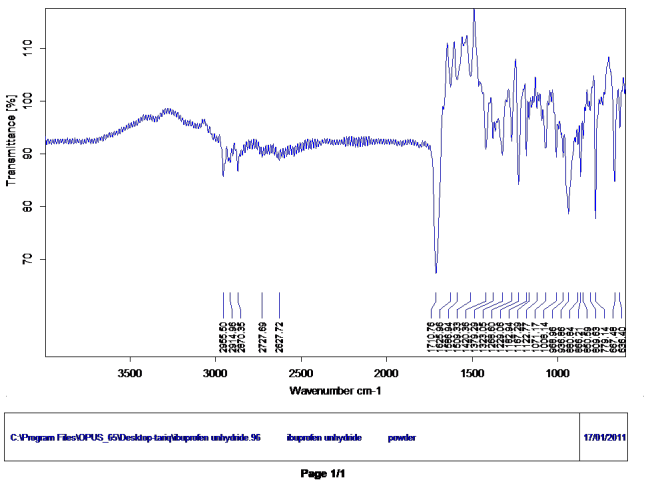


Figure 2: The IR spectrum of compound (3) shows its characteristic peaks.

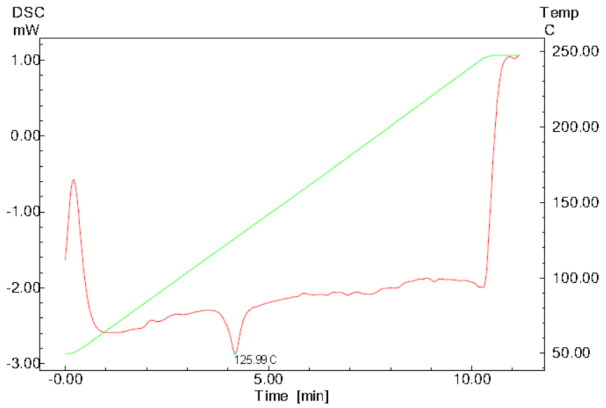


Figure 3: This figure reveals the melting point of compound (3), as indicated with 125.99°C.

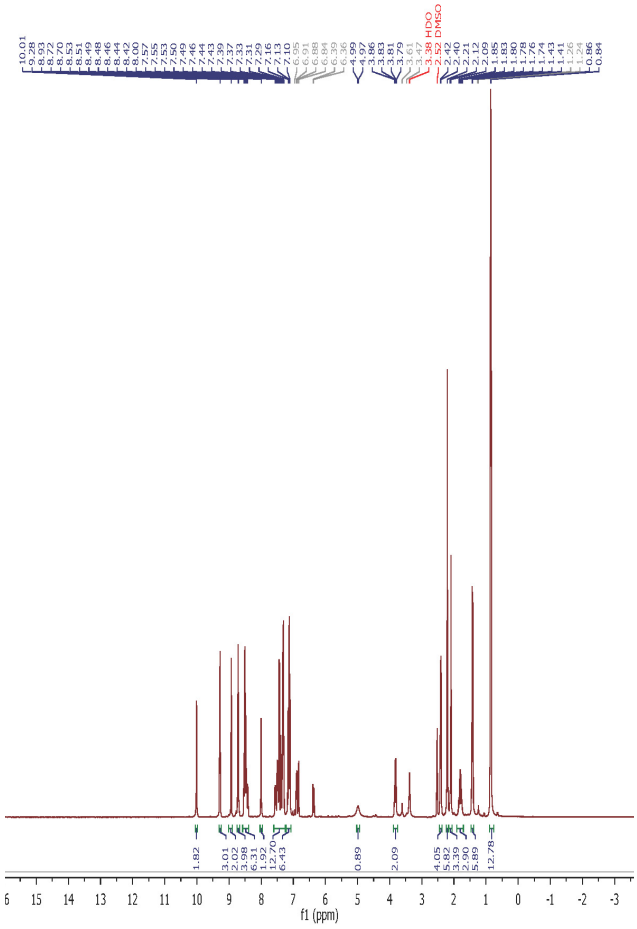


Figure 4: The proton nuclear magnetic resonance of compound (3).

The IR spectrum shows very clearly the appearance of the carbonyl group, which is correlated to the amide bond formation.[8]

The Differential Scanning Calorimeter (DSC) Thermal Analyzer was utilized in the characterization of the melting point, as seen in Figure 3.

The ability of the Differential Scanning Calorimeter to register enthalpies and transition temperatures constrain

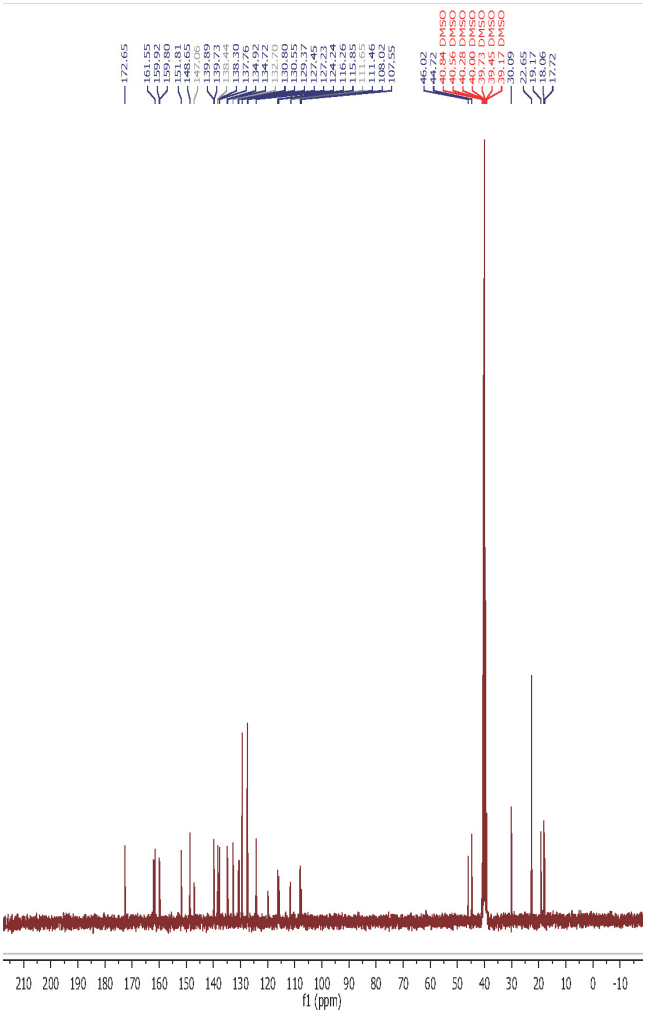


Figure 5: The carbon-13 nuclear magnetic resonance of compound (3).

the acceptance of the DSC as a valuable technique in the observation of specific and sensitive melting points for the target analyte.[10] In this work, the melting point of compound (3) is found to be 125.99°C.

The proton nuclear magnetic resonance of compound (3) is shown in Figure 4.

The following data was extracted from figure (4); 0.8 ∂ (6 H, triplet) $(CH_3)_2$, 1.4 ∂ (3H, triplet) CH_3

1.9 ∂ (2H, septet) CH_2, 2.1 and 2.2 ∂(1H, singlet) R_2NH, 2.4 ∂(1H,quartet)CH-C=O, 6.8-7.5∂ (multiplet) aromatics.

The carbon-13 nuclear magnetic resonance of compound (3) is shown in Figure 5.

The following data was extracted from figure (5); 175∂ C=O amide, 100-160∂ aromatic, 50∂ CH-C=O, 40∂ CH_2, 30∂ CH_3-CH, 22∂ $CH(CH_3)_2$, 18∂$(CH_3)_2$.

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