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CHEMISTRY RESEARCH ARTICLE

# Synthesis, Characterization of 6-(4-hydroxy-1-methyl-1H-benzo[d]imidazol-6-yl) pyrimidine-2, 4(1H, 3H)-Dione

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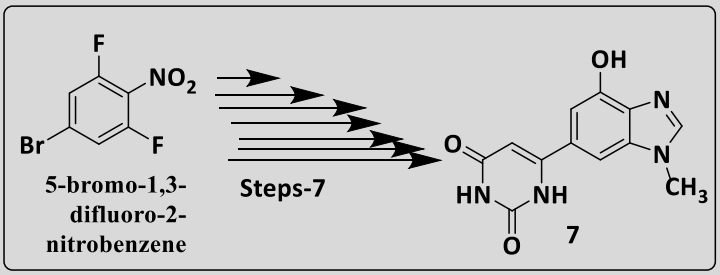
**ABSTRACT**

A concise synthetic route was developed for the preparation of 6-(4-hydroxy-1-methyl-1H-benzo[d]imidazol-6-yl)pyrimidine-2,4(1H,3H)-dione (Target 7) from 5-bromo-1,3-difluoro-2-nitrobenzene. The synthesis commenced with selective methoxylation using KOH in methanol, followed by nucleophilic substitution with methylamine to furnish the corresponding N-methyl intermediate. Reduction of the nitro functionality using Zn/$NH_4Cl$ afforded the required diamine, which underwent cyclo-condensation with triethyl orthoformate in the presence of PTSA to construct the N-methyl benzimidazole scaffold. The aryl bromide was subsequently converted into a boronate ester through Pd-catalyzed Miyaura borylation using bis(pinacolato)diboron. Suzuki–Miyaura cross-coupling with a brominated dimethoxy pyrimidine derivative efficiently established the key benzimidazole–pyrimidine carbon–carbon linkage. Finally, sequential $BBr_3$-mediated demethylation and acidic hydrolysis with concentrated HCl in methanol furnished the desired hydroxy-substituted pyrimidine-2,4-dione. This seven-step strategy provides a systematic and synthetically versatile approach to the target heterocyclic scaffold for further biological and medicinal chemistry investigations. (**Scheme I**)

**Key words:** Benzimidazole; Pyrimidine-2,4-dione; Suzuki–Miyaura coupling; Miyaura borylation; Palladium catalysis; Heterocyclic synthesis.




**Graphical Abstract**

## 1. INTRODUCTION

Due to their extensive application in functional materials, medicines, and agrochemicals, nitrogen-containing heterocyclic compounds are among the most significant types of organic molecules. Imidazole derivatives have garnered significant interest among these heterocycles due to their wide range of biological actions, which include enzyme inhibitory, antibacterial,

antifungal, anticancer, and anti-inflammatory qualities.[1–3] Imidazole-based scaffolds are also present in numerous clinically approved drugs owing to their excellent pharmacokinetic behavior and versatile binding characteristics. [4] The 1, 2, 3-triazole ring is another privileged heterocyclic that has emerged as an indispensable structural motif in medicinal chemistry. The remarkable stability, hydrogen-bonding capability, dipole moment, and bioisosteric nature of triazoles significantly enhance receptor binding affinity and metabolic stability. [5–6]

Molecular hybridization, involving the combination of two or more pharmacologically active heterocyclic scaffolds, benzo-imidazol within a single molecular framework, has become an effective strategy in modern drug discovery. Imidazole–triazole hybrids have demonstrated promising antibacterial, antifungal, antiviral, anticancer, and anti-inflammatory activities because the two heterocyclic systems often exhibit synergistic pharmacological effects.[8–10]

Cross-coupling reactions, particularly the Suzuki–Miyaura reaction, represent one of the most versatile carbon–carbon bond-forming methodologies for constructing functionalized aromatic compounds.[11] the incorporation of aryl substituents through Suzuki coupling considerably enhances molecular diversity and facilitates structure–activity relationship (SAR) studies.[12]. Considering the significant biological importance of imidazole and triazole pharmacophores, the present work describes an efficient synthetic strategy involving N-propargylation of 4-bromoimidazole, Suzuki cross-coupling with phenylboronic acid, and subsequent azide-mediated cyclization to afford a novel imidazole–triazole hybrid [13–15].

The current work describes an effective synthetic strategy that novel imidazole–pyrimidine hybrid, given the significant biological importance of both imidazole and triazole pharmacophores. The presented technology provides an effective pathway to heterocyclic conjugates with a variety of structures that could be useful models for further research in medicinal chemistry.

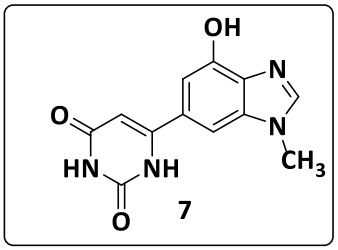



**Fig: 1 Designed Target 7**

## 2. EXPERIMENTAL

Melting points were determined using a Cintex melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed by using Merck silica gel 60 F254 precoated plates (0.25 mm) and column chromatography was performed by using Silica gel (particle size 100-200 mesh). $^1$H NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer, 400MHz for $^1$HNMR spectra. Chemical shift values were given in ppm (δ) with TMS as an internal standard. Mass spectra were determined on Agilent LC-1100 (LC-MS) series instrument. Elemental analyses were performed on a Carlo Erba 106 and Perkin Elmer model 240 analyzers.

## 3. RESULTS AND DISCUSSION

**Step 1: synthesis of 5-bromo-1-fluoro-3-methoxy-2-nitrobenzene 1**

To a stirred solution of 5-bromo-1, 3-difluoro-2-nitrobenzene (12.60 mmol) in MeOH (30 mL) was added KOH (11.34 mmol) and stirred the reaction mixture at reflux temperature for 1 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to RT; the solvent was concentrated under reduced pressure. The obtained residue was dissolved in water, extracted with DCM. The combined organic layer was washed with brine, dried over *anhydrous* sodium sulphate and concentrated under reduced pressure. The crude compound was purified by column chromatography to afford 5-bromo-1-fluoro-3-

methoxy-2-nitrobenzene **1** as off white solid (2.7 g, 85.7% yield). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.57 (dd, J = 9.4, 1.8 Hz, 1H), 7.50 (br-s, 1H), 3.96 (s, 3H).

**Step 2: synthesis of 5-bromo-3-methoxy-N-methyl-2-nitroaniline 2**

To a stirred solution of 5-bromo-1-fluoro-3-methoxy-2-nitrobenzene (4.8 mmol) in THF was added 2M Methylamine in THF (19.2 mmol) and stirred the reaction mixture in a seal tube at 70 °C temperature for 2 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to RT, solvent was concentrated under reduced pressure to afford 5-bromo-3-methoxy-N-methyl-2-nitroaniline 2 as yellow solid (1.2 g, 96%, crude wt.). The crude compound was used in the next step without any purification. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 6.60 (d, J = 1.8 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 6.48 (m, 1H), 3.81 (s, 3H), 2.72 (d, J = 4.7 Hz, 3H).

**Step 3: synthesis of 5-bromo-3-methoxy-N1-methylbenzene-1, 2-diamine 3**

To a stirred solution of 5-bromo-3-methoxy-N-methyl-2-nitroaniline (4.59 mmol) in THF/$H_2O$ (2:1 v/v) was added Zn dust (45.97 mmol), $NH_4Cl$ (22.98 mmol) at 0 °C and stirred the reaction mixture at RT for 1 h. The progress of the reaction was monitored by TLC. The reaction mixture was filtered through a pad of celite, celite pad washed with EtOAc, combined organic layer was washed with water, and aqueous layer was extracted with EtOAc. The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound was purified by column chromatography to afford 5-bromo-3-methoxy-N1-methylbenzene-1, 2-diamine 3 as brown solid (900 mg, 85% yield). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 6.43 (d, J = 2.1 Hz, 1H), 6.22 (d, J = 2.0 Hz, 1H), 4.93 (br-s, 1H), 4.12 (s, 2H), 3.72 (s, 3H), 2.68 (d, J = 3.7 Hz, 3H).

**Step 4: synthesis of 6-bromo-4-methoxy-1-methyl-1H-benzo[d]imidazole 4**

To a stirred solution of 5-bromo-3-methoxy-N1-methylbenzene-1, 2-diamine (3.89 mmol) in Toluene was added Triethyl orthoformate (4.28 mmol), pTSA (catalytic amount) and stirred the reaction mixture at reflux temperature for 2 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to RT; the solvent was concentrated under reduced pressure. The obtained residue was dissolved in water, extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound was purified by column chromatography to afford 6-bromo-4-methoxy-1-methyl-1H-benzo[d]imidazole 4 as off white solid (800 mg, 85% yield). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.07 (s, 1H), 7.42 (d, J = 1.8 Hz, 1H), 6.85 (d, J = 1.8 Hz, 1H), 3.93 (s, 3H), 3.77 (s, 3H).

**Step 5: synthesis of 4-methoxy-1-methyl-6-(4, 4, 5, 5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole 5**

To a stirred solution of 6-bromo-4-methoxy-1-methyl-1H-benzo[d]imidazole (3.31 mmol) in Dioxane was added Bis (pina-colato) diborane (3.31 mmol), Potassium acetate (9.95 mmol) and the reaction mixture was degassed with Argon gas. After 10 min $PdCl_2$ (dppf) $CH_2Cl_2$ (0.16 mmol, Catalyst) was added and stirred the reaction mixture at 100 °C for 16 h. The reaction mixture was cooled to RT; filtered through a pad of celite with EtOAc; organic layer was washed with water (20 mL). Aqueous layer was extracted with EtOAc. The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound was purified by column chromatography to afford 4-methoxy-1-methyl-6-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1H-benzo[d]imidazole 5 as pale-yellow solid (500 mg, 52% yield). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.11 (s, 1H), 7.47 (s, 1H), 6.93 (s, 1H), 3.93 (s, 3H), 3.83 (s, 3H), 1.31 (s, 12H).

**Step 6: 6-(2, 6-dimethoxypyrimidin-4-yl)-4-methoxy-1-methyl-1H-benzo[d]imidazole 6**

To a stirred solution of 4-methoxy-1-methyl-6-(4, 4, 5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole (1.73 mmol), 4-bromo-2, 6-dimethoxypyrimidine (2.08 mmol) in Dioxane/water (4:1 v/v) was added $NaHCO_3$ (3.47 mmol) and the reaction mixture was

degassed with Argon gas. After 10 min $PdCl_2$ (dppf) $CH_2Cl_2$ (0.08 mmol, catalyst) was added and stirred the reaction mixture at 100 °C for 16 h. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to RT; the catalyst was filtered through a pad of celite with EtOAc; organic layer was washed with water. Aqueous layer was extracted with EtOAc. The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound was purified by column chromatography to afford 6-(2,6-dimethoxypyrimidin-4-yl)-4-methoxy-1-methyl-1H-benzo[d]imidazole as yellow liquid (380 mg, 80.5% yield). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.43 (s, 1H), 8.09 (s, 1H), 7.28 (d, J = 1.3 Hz, 1H), 6.85 (d, J = 1.3 Hz, 1H), 4.00-3.90 (m, 9H), 3.81 (s, 3H).

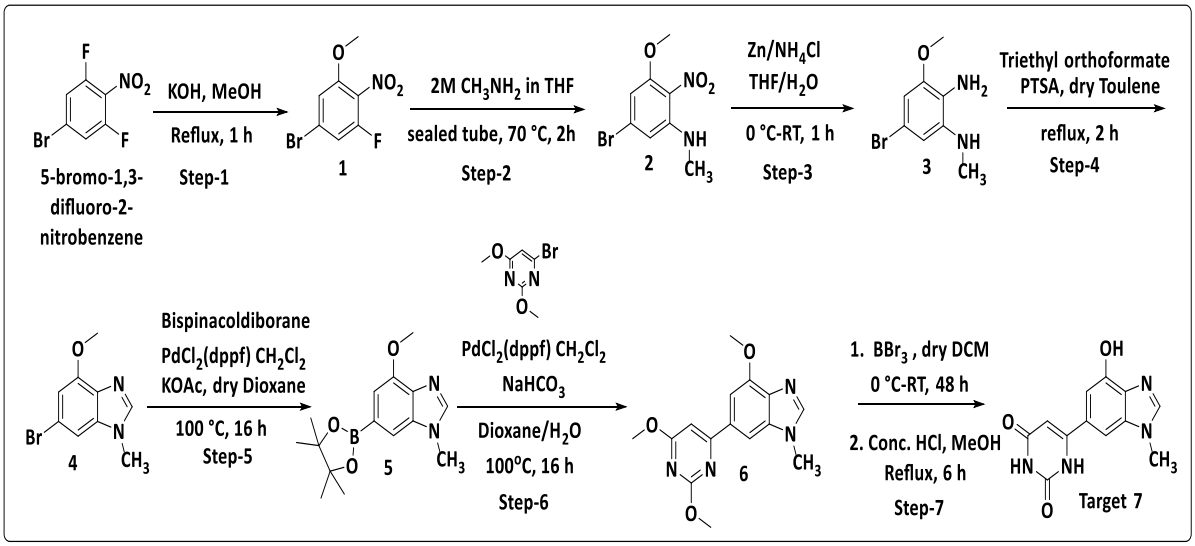
**Step 7: synthesis of 6-(4-hydroxy-1-methyl-1H-benzo[d]imidazol-6-yl) pyrimidine-2, 4(1H, 3H)-Dione 7**

To a stirred solution of 6-(2, 6-dimethoxypyrimidin-4-yl)-4-methoxy-1-methyl-1H-benzo[d]imidazole (0.66 mmol) in dry DCM was added BBr3 (3.33 mmol) at 0 °C and stirred the reaction mixture at RT for 48 h. The progress of the reaction was monitored by LCMS. The reaction mixture was concentrated under reduced pressure. The residue was washed with diethyl ether and dried under vacuum to afford 6-(6-hydroxy-2-methoxypyrimidin-4-yl)-1-methyl-1H-benzo[d]imidazol-4-ol as brown solid. The compound was used in the next step without any purification. The crude compound in MeOH was

added Conc. HCl at RT and stirred the reaction mixture at reflux temperature for 6 h. The progress of the reaction was monitored by LCMS. The reaction mixture was cooled to RT and concentrated under reduced pressure. The obtained solid was purified by prep HPLC to afford 6-(4-hydroxy-1-methyl-1H-benzo[d]imidazol-6-yl) pyrimidine-2, 4(1H, 3H)-Dione **7** as white solid (87 mg, 66% yield).$^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.33 (s, 1H, $D_2O$ exchangeable), 11.28 (d, J = 5.6 Hz, 1H, D2O exchangeable), 10.86 (br-s, 1H, $D_2O$ exchangeable), 9.15 (s, 1H), 7.70 (d, J = 5.9 Hz, 1H), 7.42 (s, 1H), 7.18 (s, 1H), 3.95 (s, 3H).

## CONCLUSION

In the current study, we have synthesized 6-(4-hydroxy-1-methyl-1H-benzo[d]imidazol-6-yl) pyrimidine-2, 4(1*H*, 3*H*)-Dione with an excellent yields and high purity. **(Scheme I)**




**Scheme I** Synthesis of 6-(4-hydroxy-1-methyl-1*H*-benzo[d]imidazol-6-yl) pyrimidine-2, 4(1*H*, 3*H*)-Dione

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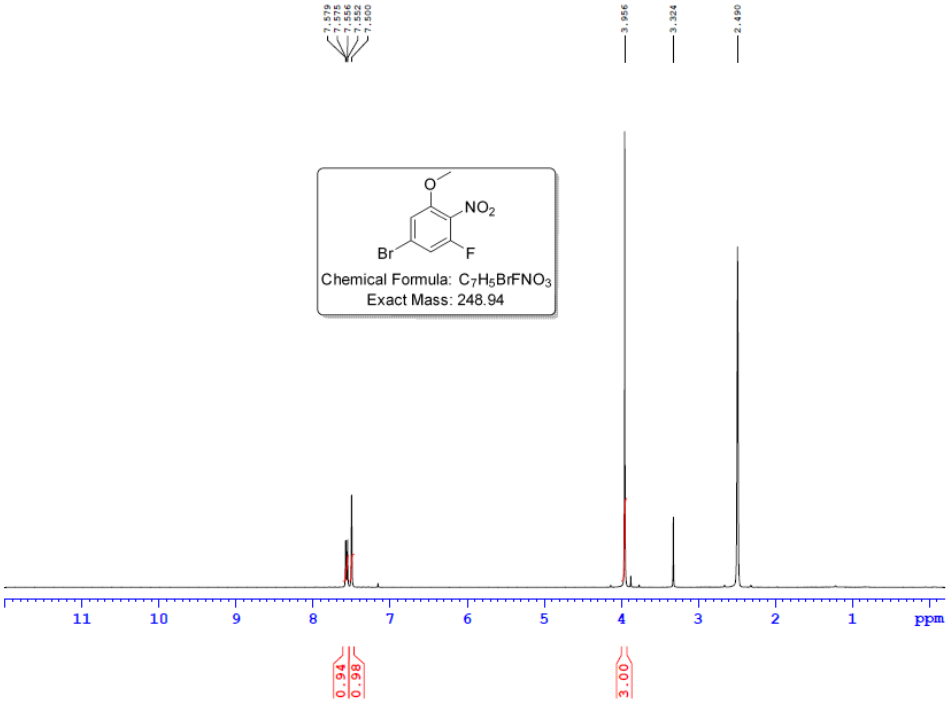


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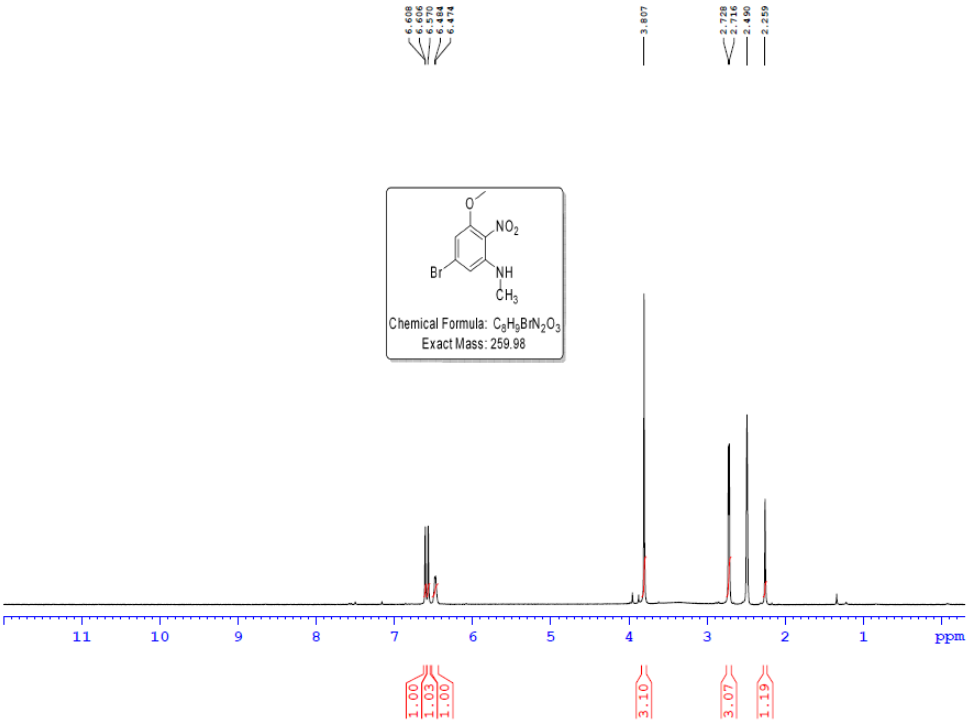

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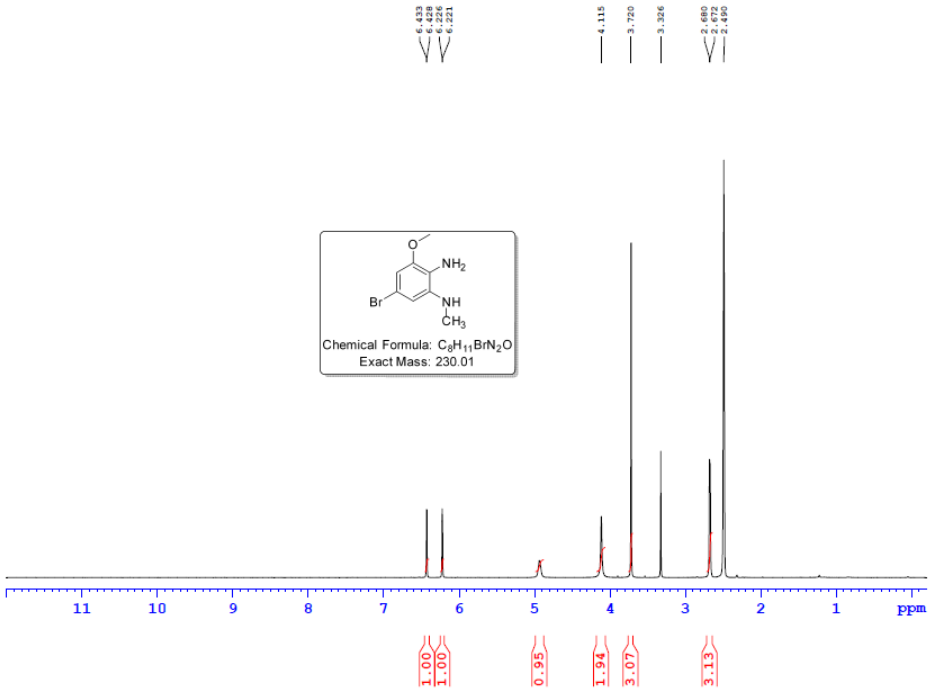


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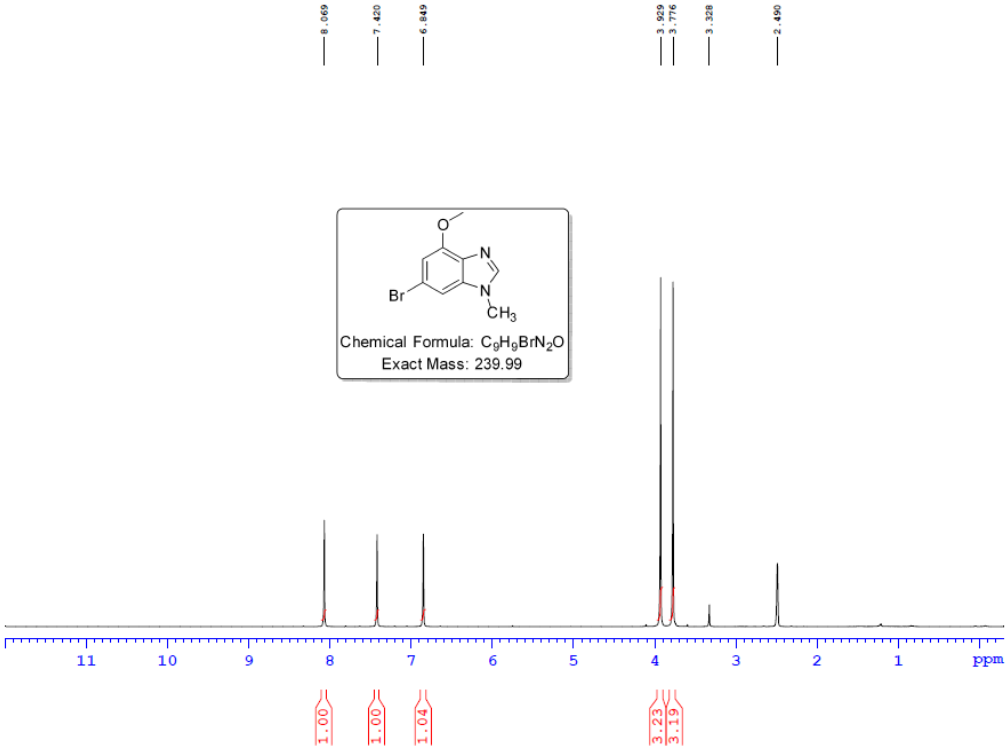

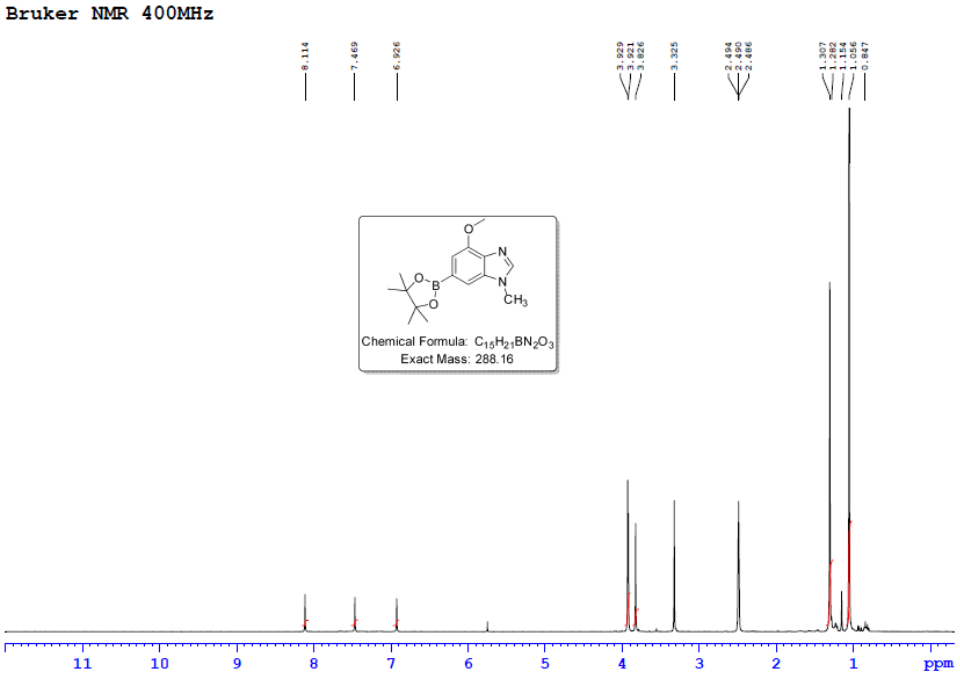
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1.282
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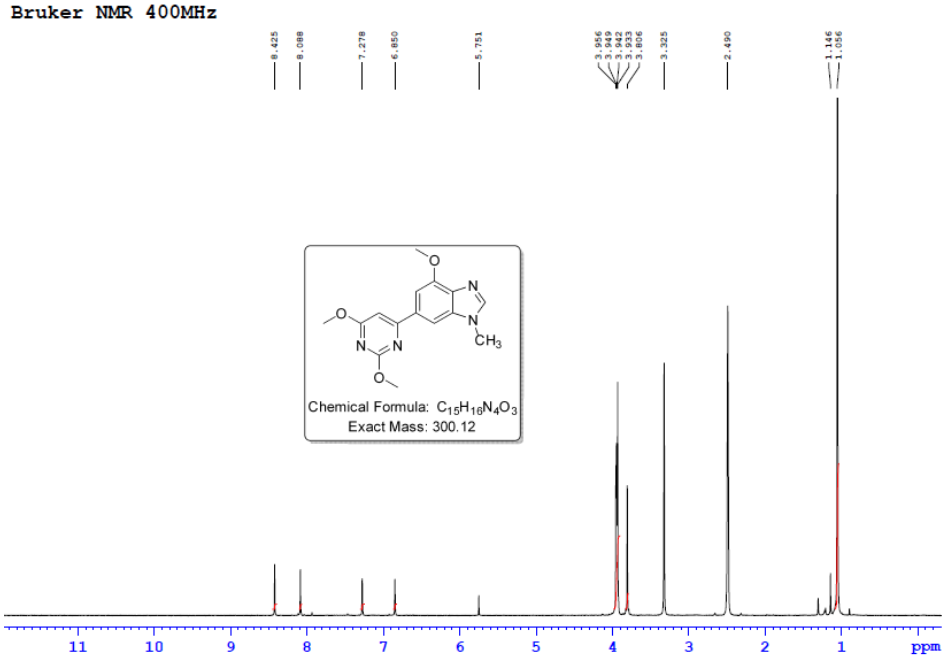
2
1
ppm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3.325
2.490
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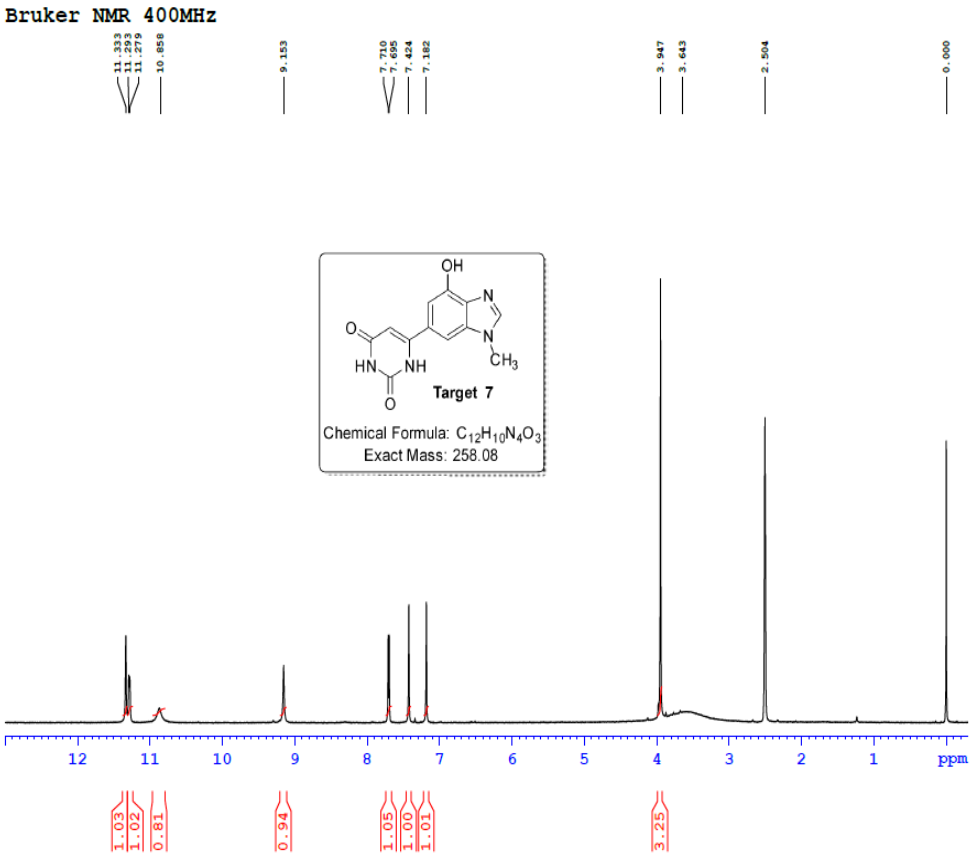
ppm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O
N
HN
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CH3
O
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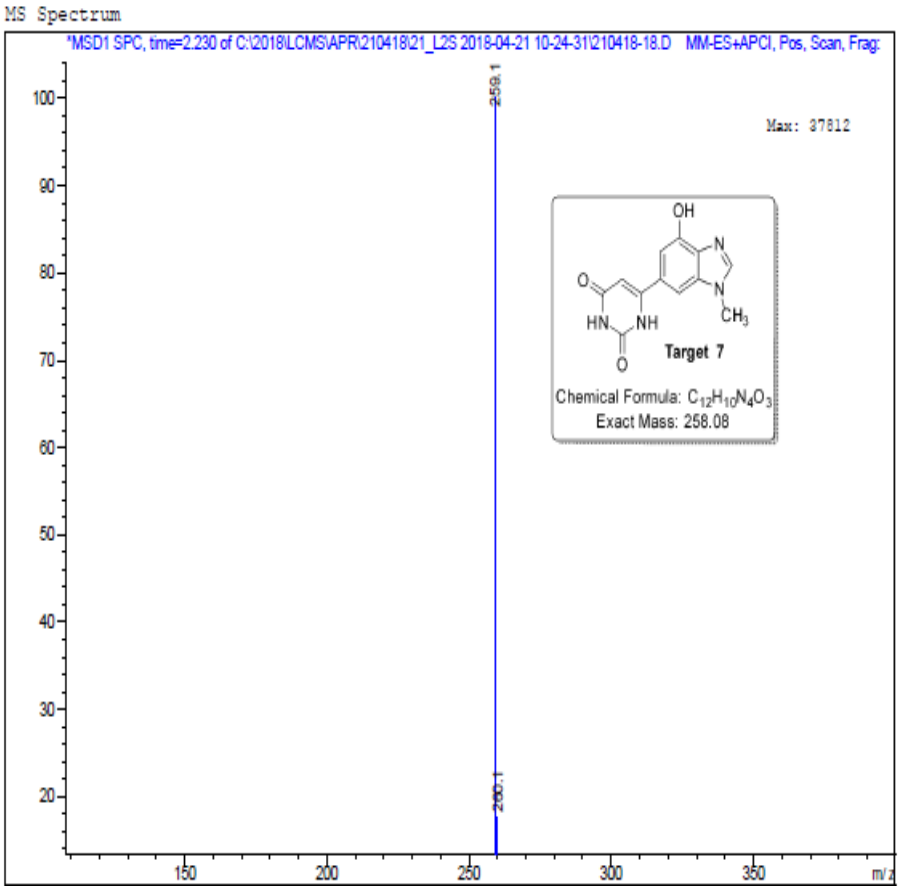
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