



# Design, synthesis and bioactivity of benzimidazole-2-carbamates as soil-borne anti-fungal agents

Thuraya Al-Harthy, Abdullah M. Al-Sadi, Wajdi Zoghaib, Ebrahim Saedian Moghadam, Raphael Stoll and Raid Abdel-Jalil



## Introduction

- Soil-borne fungi is one of the most important causes of widespread and serious plant diseases.
- Cucumber (*Cucumis sativus*) is the most important greenhouse crop in Oman.
- Soilborne diseases, i.e. damping-off and vine decline, limit cucumber growth and production.





- Losses due to these diseases have been reported to exceed 70% in some greenhouses\*.
- Damping-off and vine decline diseases are caused by different pathogens, including *Pythium*, *Rhizoctonia* and *Fusarium* species.
- *Pythium aphanidermatum* is the most common causal agent of damping-off disease of cucumber in Oman.

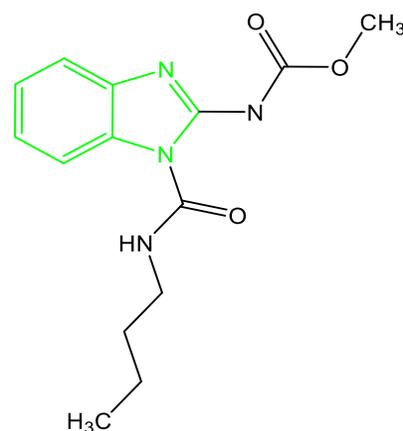
\*Al-Sadi, A. M.; Al-Said, F. A.; Al-Kiyumi, K. S.; Al-Mahrouqi, R. S.; Al-Mahmooli, I. H.; Deadman, M. L. Etiology and characterization of cucumber vine decline in Oman. *Crop Protection* **2011**, *30*, 192-197



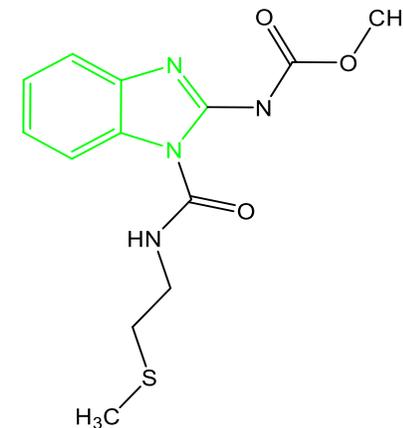
- **Management of *Pythium*-induced diseases of cucumber has relied on the use of imported fungicides, biological control and cultural practices:**
  - Mefenoxam and hymexazol are two common fungicides for the management of *Pythium*-induced diseases in Oman.
  - Some biocontrol agents have been isolated from Omani soils and plants and tested against *Pythium* damping-off disease. These include the use of *Pseudomonas aeruginosa*, *Aspergillus terreus*, *Talaromyces* spp. and *Trichoderma* spp.



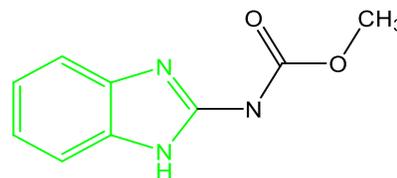
- Examples of some reported benzimidazole derivatives as fungicide.
- Due to limitations in these management methods, it is important to search for new fungicide formulations that can be used to control these diseases.



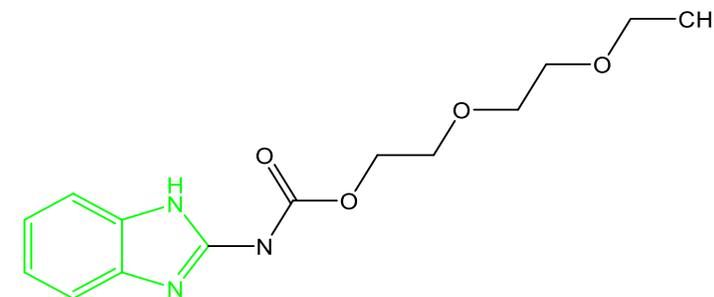
Bemonyl



Mecarbinzid



Carbendazim

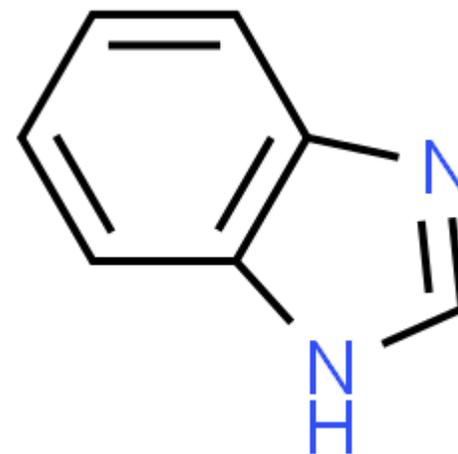


Debacarb



## Benzimidazole system

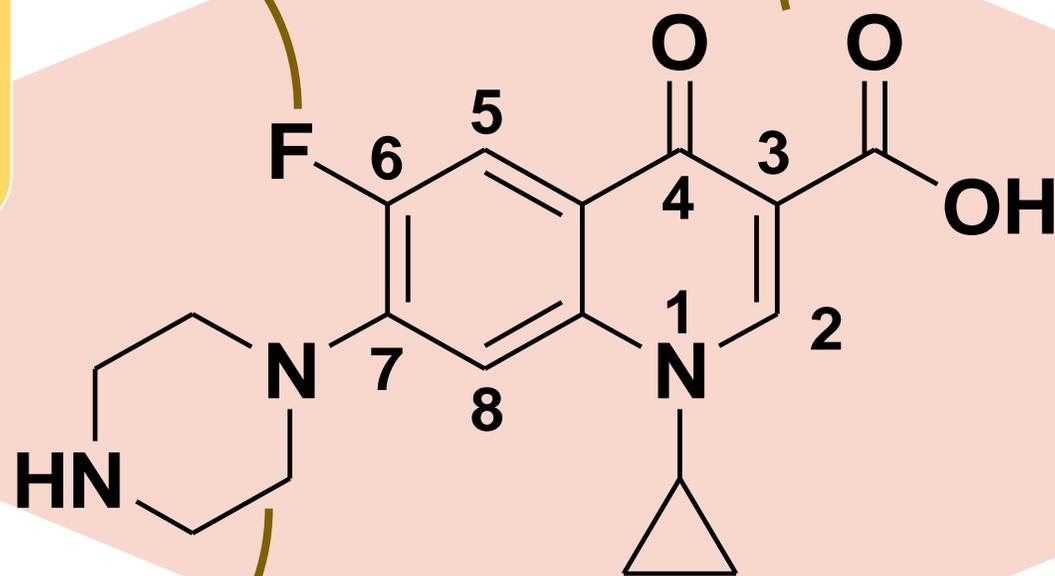
- Bicyclic aromatic ring system
- Comprises of benzene fused with azole
- Relatively stable system





Control gyrase and bacterial potency

Controls potency spectrum and pharmacokinetics

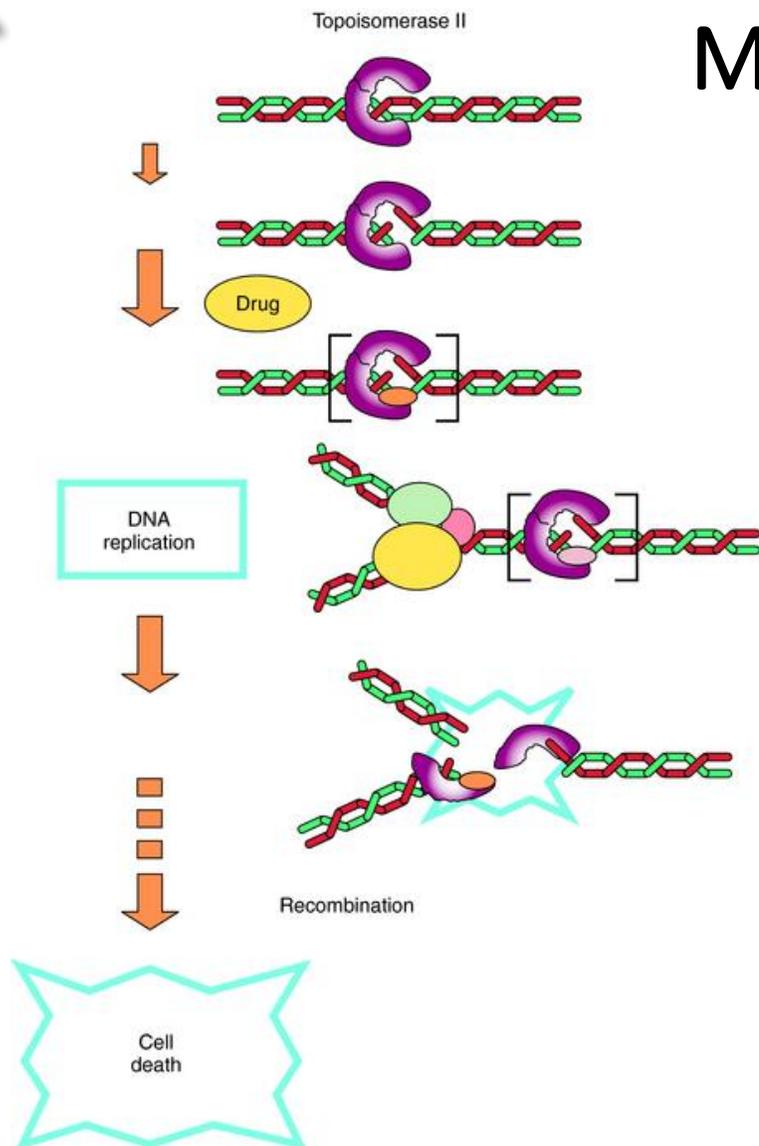


Essential for gyrase binding and bacterial transport

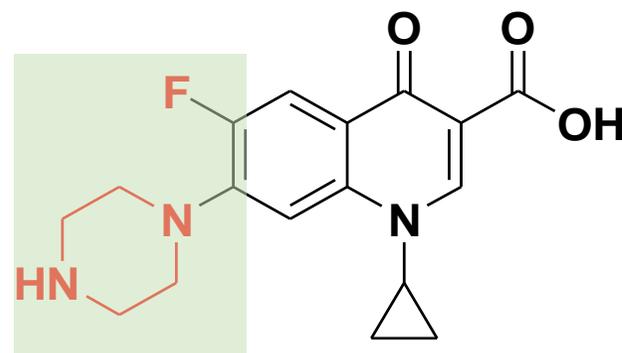
Control potency



# Mechanism of action of quinolones



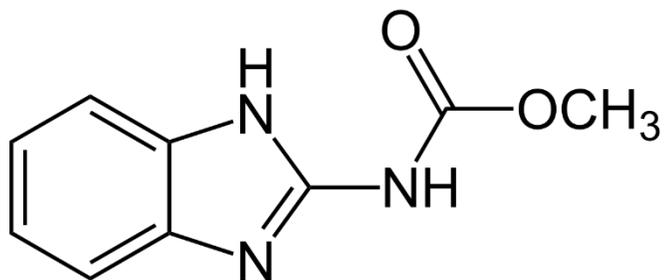
Binding to enzyme



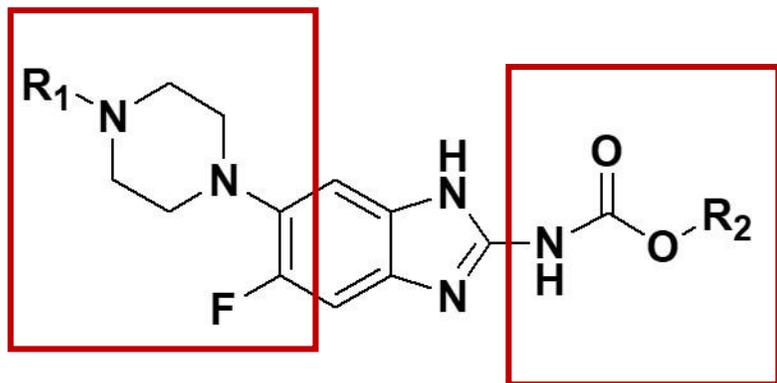
Ciprofloxacin



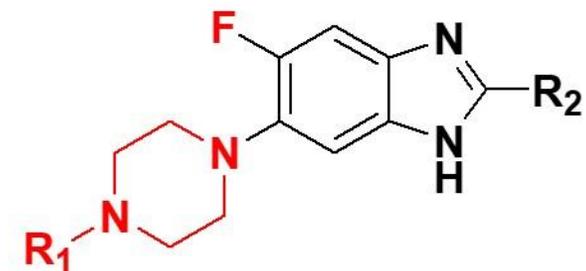
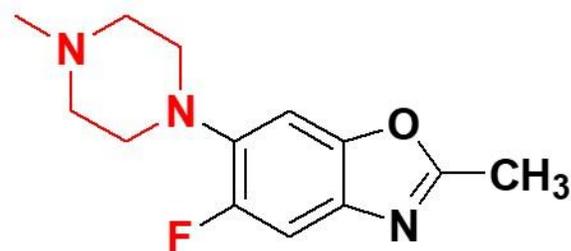
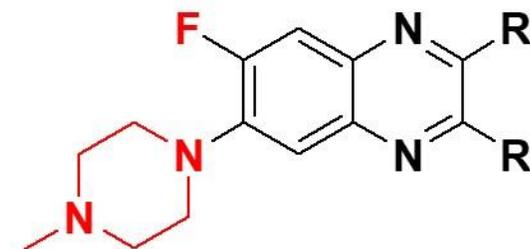
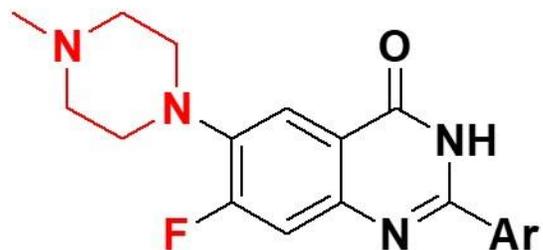
- We hypothesize that quinolone can be replaced by benzimidazole since both are bioisosteres of nucleotides thereby grant similar biological activities.
- The moieties like fluorine at position-6 and piperazine at position-7 has a role in the binding interaction with the topoisomerase.
- Thus, having benzimidazole as core structure in addition of fluorine and piperazine may elicit similar or better antimicrobial activity as reported for the ciprofloxacin.



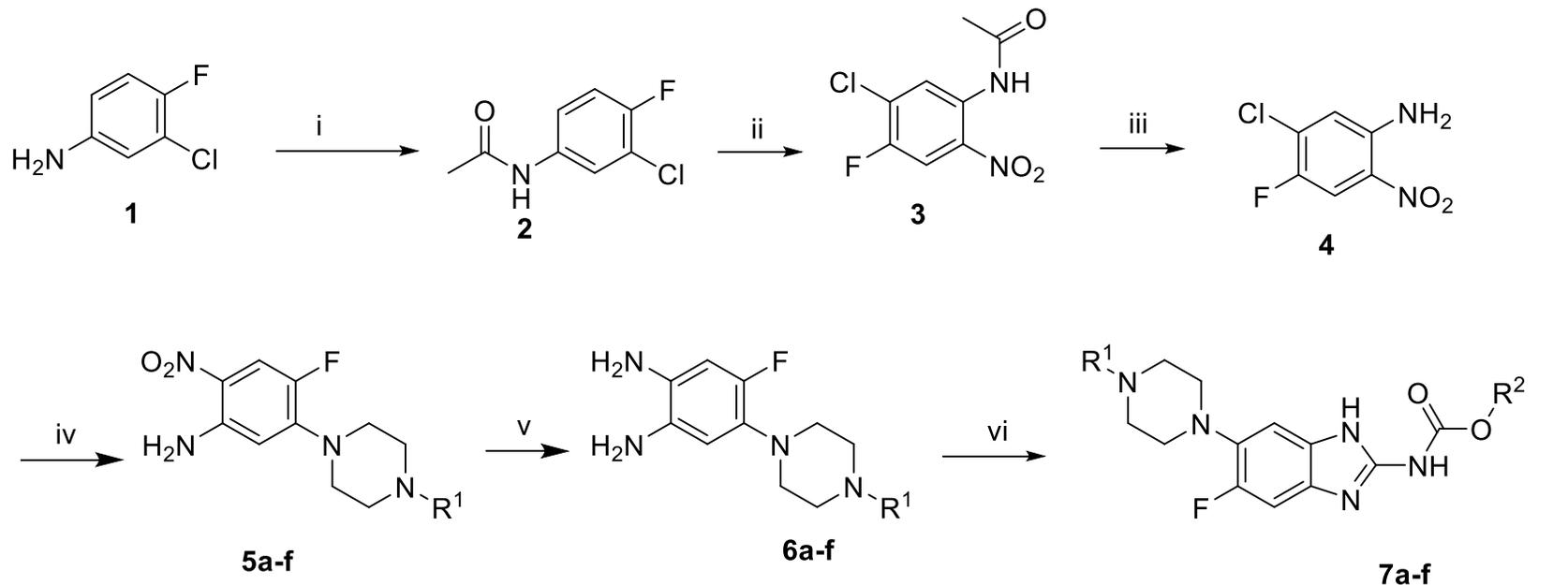
Carbendazim



Current work



Previous work of heterocycles incorporating fluorine and piperazine moieties.



i: Acetic Anhydride, RT, 3h

ii: H<sub>2</sub>SO<sub>4</sub>, HNO<sub>3</sub>, 0°C - RT, 3h

iii: Ethanol, conc HCl, Reflux, 3h

iv: Piperazine derivatives, DMSO, Reflux, 2h

v: HCl, SnCl<sub>2</sub>, RT, 2h

vi: 1,3-dicarbalkoxy-S-methylisothiurea derivatives, Ethanol, Reflux, overnight

**5a,6a:** R<sup>1</sup>:Me

**5b,6b:** R<sup>1</sup>:Et

**5c,6c:** R<sup>1</sup>:But

**5d,6d:** R<sup>1</sup>:Ph

**5e,6e:** R<sup>1</sup>:4-F-Ph

**5f,6f:** R<sup>1</sup>:2-F-Ph

**7a-1:** R<sup>1</sup>:Me, R<sup>2</sup>:Bn

**7a-2:** R<sup>1</sup>:Me, R<sup>2</sup>:t-But

**7a-3:** R<sup>1</sup>:Me, R<sup>2</sup>:Me

**7b-1:** R<sup>1</sup>:Et, R<sup>2</sup>:Bn

**7b-2:** R<sup>1</sup>:Et, R<sup>2</sup>:t-But

**7b-3:** R<sup>1</sup>:Et, R<sup>2</sup>:Me

**7c-1:** R<sup>1</sup>:But, R<sup>2</sup>:Bn

**7c-2:** R<sup>1</sup>:But, R<sup>2</sup>:Me

**7d-1:** R<sup>1</sup>:Ph, R<sup>2</sup>:Bn

**7d-2:** R<sup>1</sup>:Ph, R<sup>2</sup>:t-But

**7d-3:** R<sup>1</sup>:Ph, R<sup>2</sup>:Me

**7e-1:** R<sup>1</sup>:4-F-Ph, R<sup>2</sup>:Bn

**7e-2:** R<sup>1</sup>:4-F-Ph, R<sup>2</sup>:t-But

**7e-3:** R<sup>1</sup>:4-F-Ph, R<sup>2</sup>:Me

**7f-1:** R<sup>1</sup>:2-F-Ph, R<sup>2</sup>:Bn

**7f-2:** R<sup>1</sup>:2-F-Ph, R<sup>2</sup>:t-But

**7f-3:** R<sup>1</sup>:2-F-Ph, R<sup>2</sup>:Me

### Scheme 1: Synthetic pathway to target compounds **7a-f**\*

\* Thuraya Al-Harthy, Abdullah M. Al-Sadi, Wajdi Zoghaib, Ebrahim Saeedian  
Moghadam, Raphael Stoll and Raid Abdel-Jalil: non-published work



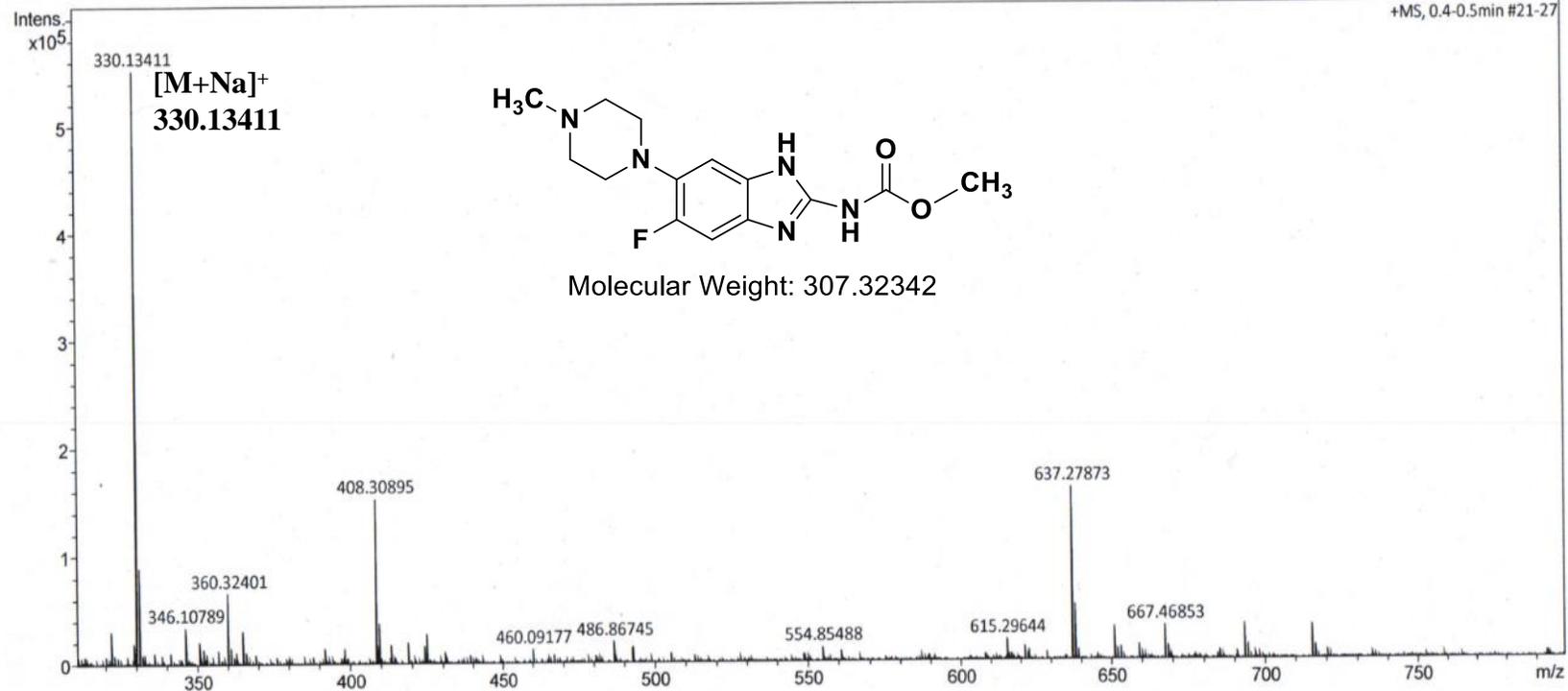
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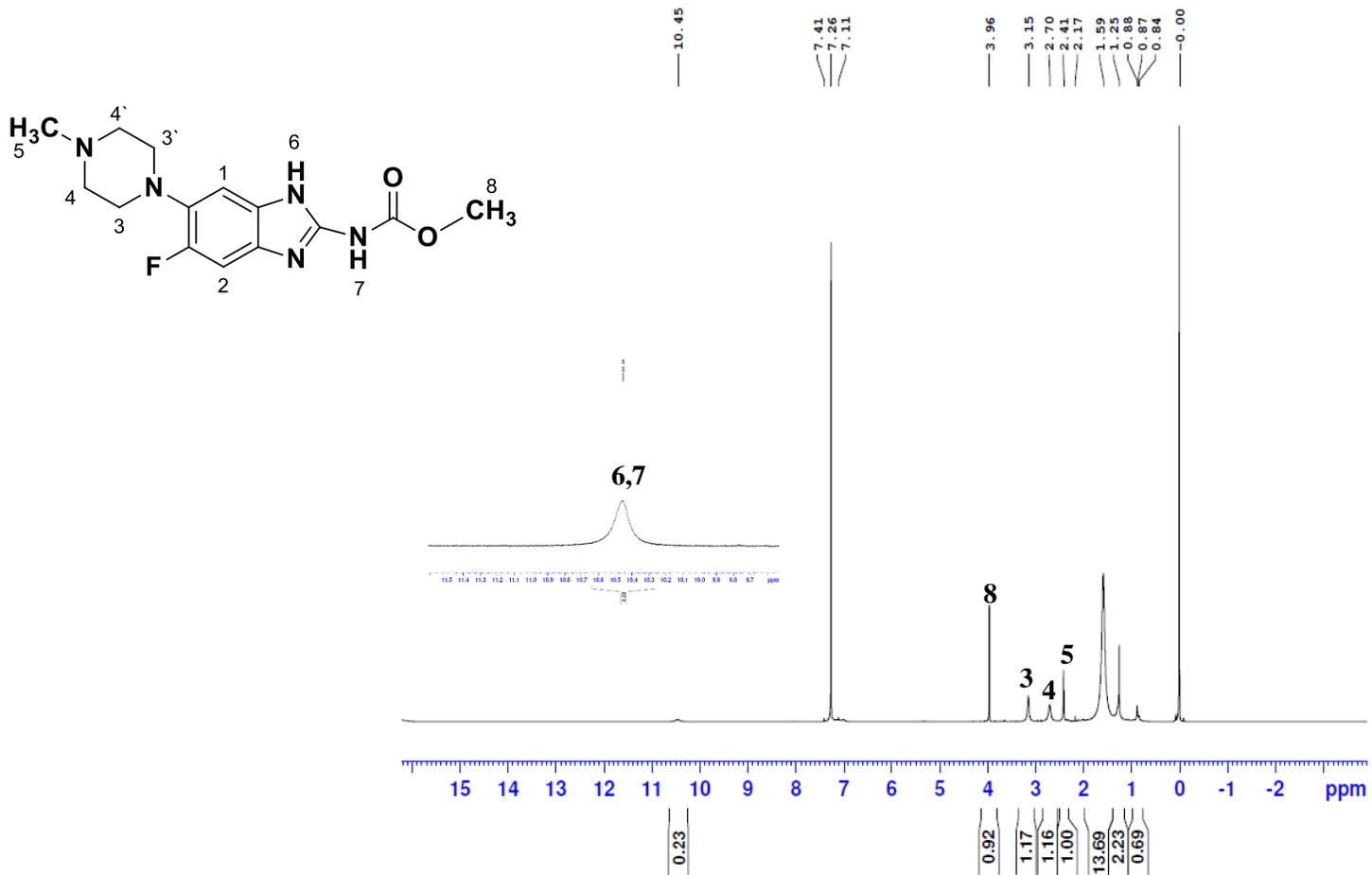
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Focus Not active  
Scan Begin 80 m/z  
Scan End 1000 m/z

Ion Polarity Positive  
Set Capillary 4500 V  
Set End Plate Offset -500 V  
Set Charging Voltage 0 V  
Set Corona 0 nA

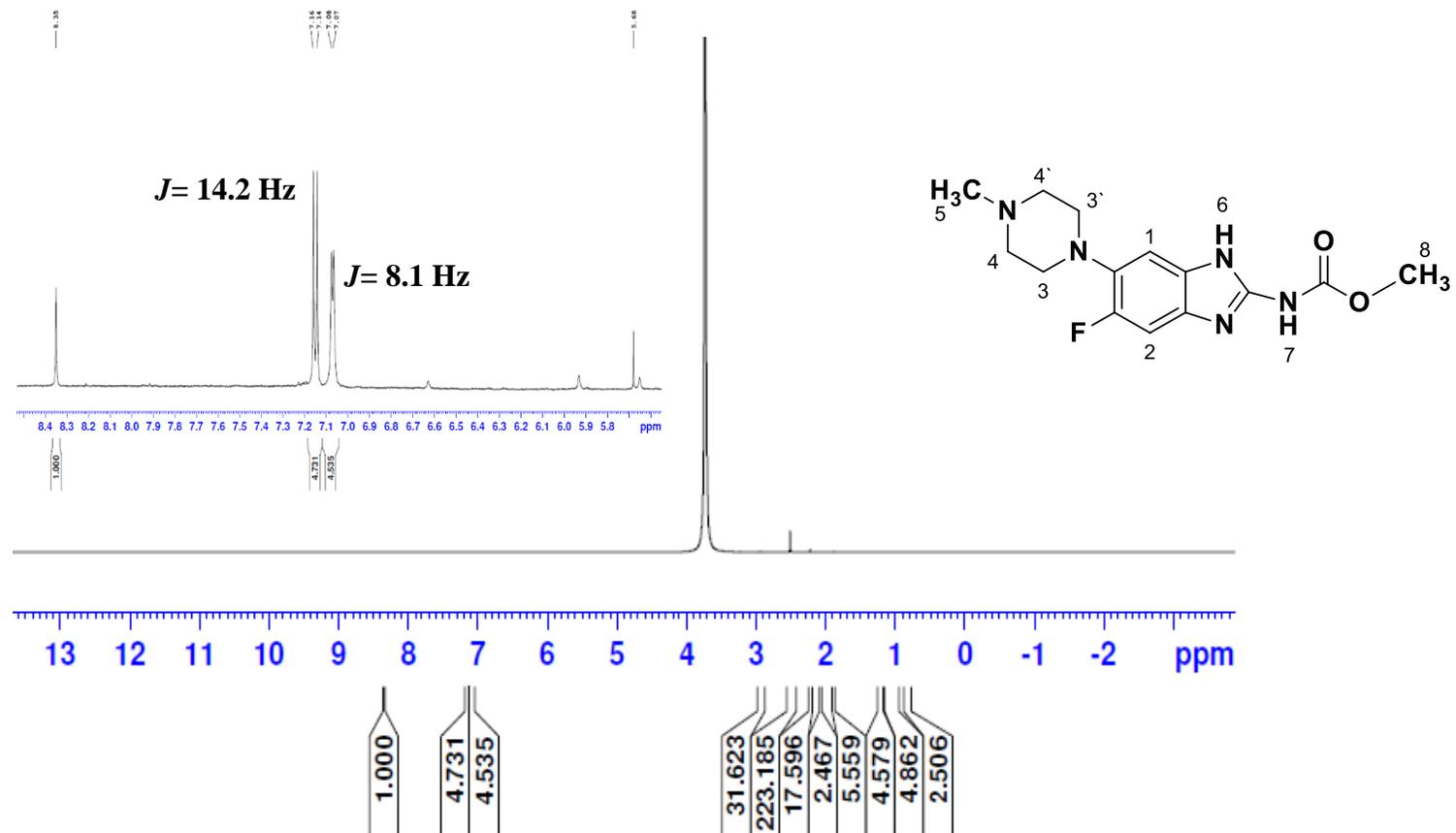
Set Nebulizer 1.2 Bar  
Set Dry Heater 200 °C  
Set Dry Gas 6.0 l/min  
Set Divert Valve Waste  
Set APCI Heater 0 °C

Intens. x10<sup>5</sup>





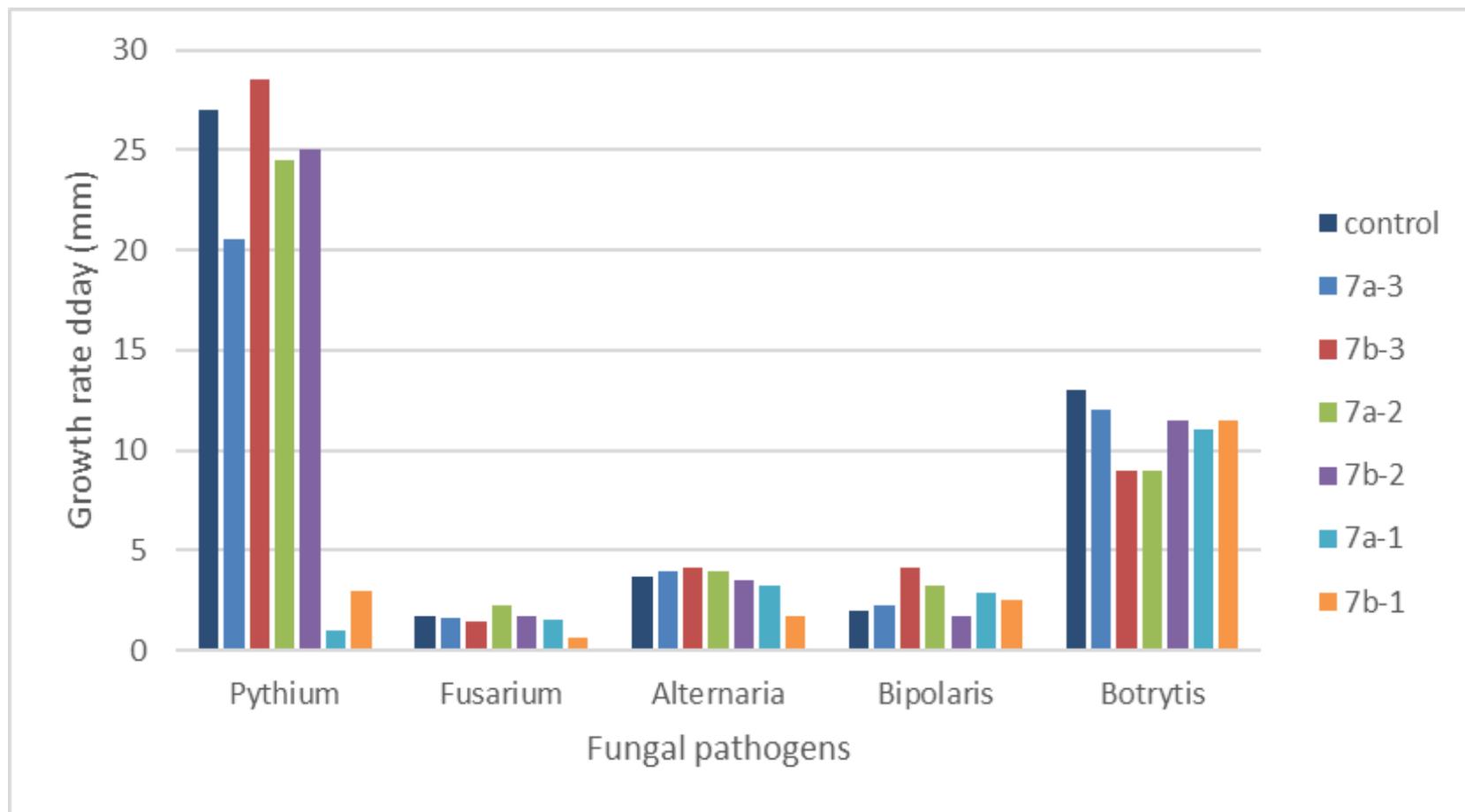
**Figure. 2** <sup>1</sup>H NMR of methyl (5-fluoro-6-(4-methylpiperazin-1-yl)-1H-benzo[d]imidazol-2-yl)carbamate (**74a**) in CDCl<sub>3</sub>



**Figure. 1**  $^1\text{H}$  NMR of methyl (5-fluoro-6-(4-methylpiperazin-1-yl)-1H-benzo[d]imidazol-2-yl)carbamate (**74a**) in DMSO



# Antifungal assay



**Figure 1.** Effect of six fungicide formulations on the growth rate of *Pythium*, *Fusarium*, *Alternaria*, *Bipolaris* and *Botrytis* species. Bars with the same letter in the same fungus category are not significantly different from each other at  $P < 0.05$  (Tukey's Studentized range test, SAS).



## Conclusion

- A novel class of benzimidazole based carbamate derivatives **7a-f** was designed and synthesized as soil-born antifungals.
- Structures of all **7a-f** identified and characterized using  $^1\text{H-NMR}$ , IR, HRMS, and melting point.
- Some derivatives significantly affected the growth of *Pythium aphanidermatum*.
- Compounds **7a-1** & **7b-1** was the most efficacious, which resulted in 96% growth inhibition in *Pythium* at  $100 \text{ mg L}^{-1}$ .

