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Design, Synthesis and Bioactivity of Benzimidazole–2–Carbamates as Soil–Borne Anti–Fungal Agents †

Thuraya Al–Harthy [1], Abdullah M. Al-Sadi [2], Wajdi Zoghaib [3], Ebrahim Saeedian Moghadam [3], Raphael Stoll [4] and Raid Abdel-Jalil [3],*

[1] Department of Basic Sciences, College of Health and Applied Sciences, A'Sharqiyah University, Ibra, Oman; email1@gmail.com
[2] Department of Crop Sciences, College of Agricultural and Marine Sciences, Sultan Qaboos University, Muscat, Oman; email2@gmail.com
[3] Chemistry Department, College of Science, Sultan Qaboos University, Muscat, Oman; email3@gmail.com (W.Z.); email4@gmail.com (E.S.M.)
[4] Biomolecular NMR, Ruhr University of Bochum, D-44780 Bochum, Germany; email5@gmail.com
* Correspondence: jalil@squ.edu.om

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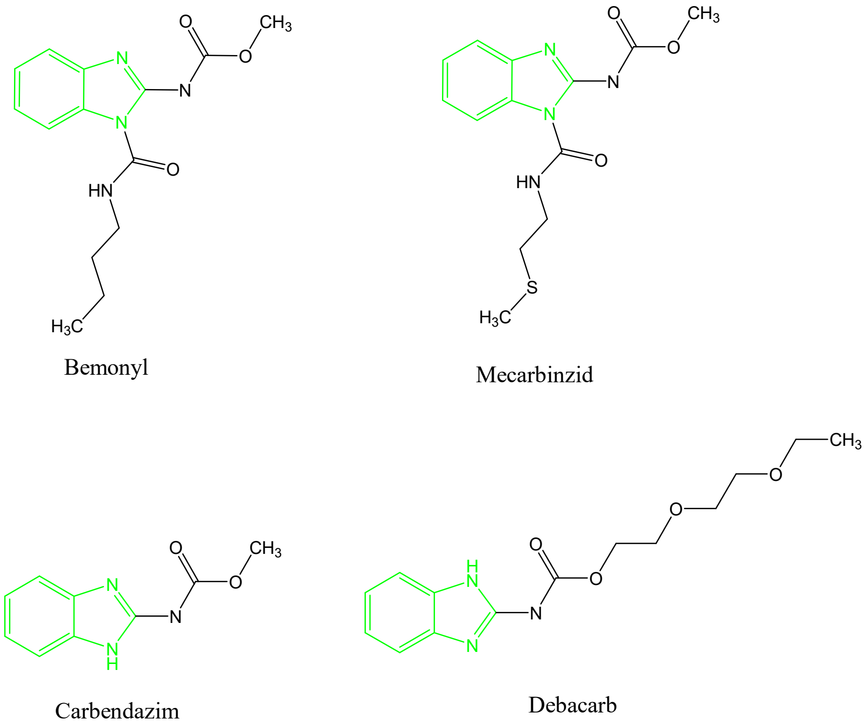
Abstract: Design and synthesis of new, safe and potent molecules to apply against soil-borne pathogens is a critical goal for organic and bio-medicinal chemists. Herein, we designed and synthesized a series of benzimidazole based carbamate derivatives **7a**–**f**, as soil-born antifungals. All **7a**–**f** were synthesized in multistep reactions with acceptable yields. Structures of all **7a**–**f** identified and characterized using ^{1}H-NMR, IR, HRMS, and melting point. Final compounds were tested on five soil-borne pathogens. Results of bioassays showed that compounds **7a**-**3**, **7a**-**2**, **7b**-**2**, 7a-1 and 7b-1 significantly affected the growth of *Pythium aphanidermatum*, a serious pathogen of vegetable crops worldwide. Compounds **7a**-**1** & **7b**-**1** was the most efficacious, which resulted in 96% growth inhibition in *Pythium* at 100 mg L^{-1}. In conclusion, we reported the potent carbamate derivatives as soil-born antifungals and synthesis of more derivatives related to the current scaffold would be beneficial.

Keyworeds: antifungal; benzimidazole; carbamate; synthesis; soil-born pathogen

1. Introduction

Heterocyclic chemistry plays critical role in design and synthesis bioactive compounds. One of the most important heterocycles is benzimidazole and its derivatives. The properties of benzimidazole and its derivatives have been studied over more than one hundred years. Benzimidazole derivatives are useful intermediates/subunits for the development of molecules of pharmaceutical or biological interest. Substituted benzimidazole derivatives have found applications in diverse therapeutic areas such as anti-cancer, anti-bacterial, anti-fungal, anti-inflammatory, analgesic agents, anti-HIV, anti-oxidant, anti-convulsant, anti-tubercular, anti-diabetic, anti-leishmanial, anti-histaminic, anti-malarial agents, and other medicinal agents [1–8]. One of the most important applications of benzimidazole derivatives is using as anti-fungal agent in plants. Soil-borne fungi is one of the most important causes of widespread and serious plant diseases. Spores or mycelium of many of these fungi can overwinter or survive adverse conditions in soil or on plant debris, and once an area has become infested with soilborne fungi, it is generally difficult to get rid of them. There are many reported benzimidazole derivatives as fungicide (Figure 1) [9].

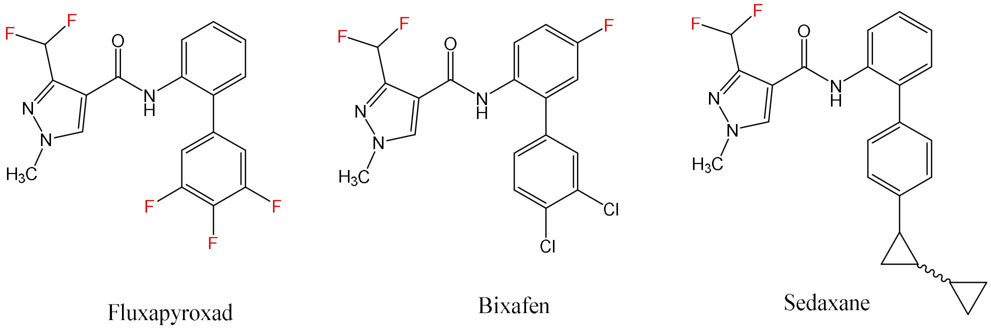


Bemonyl Mecarbinzid

Carbendazim Debacarb

Figure 1. Benzimidazole derivatives as fungicide.

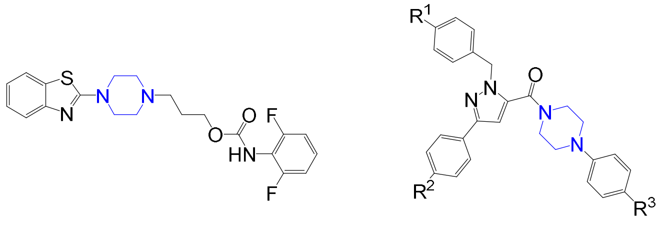
In parallel with benzimidazole containing fungicide, a series of fungicide involving fluorine atom have been developed. Fluorinated heterocycles have attracted attention due to the ability of fluorine to act as polar hydrogen or hydroxyl mimic. The introduction of fluorine at a strategic position of a molecule is a powerful and versatile tool for the development of organic molecules which have potential biological activities by changing the steric and electronic parameters. The inclusion of fluorine into organic molecules can affect the lipophilicity and thus enhance the rate of cell penetration and transport of a drug to an active site (Figure 2) [10–13].



Fluxapyroxad Bixafen Sedaxane

Figure 2. Fluorine containing fungicides.

Except addition of fluorine atom in the structure of some molecules for exerting antifungal activity, using piperazine moiety also led to emerging antifungal activities in some structures (Figure 3) [14–19].

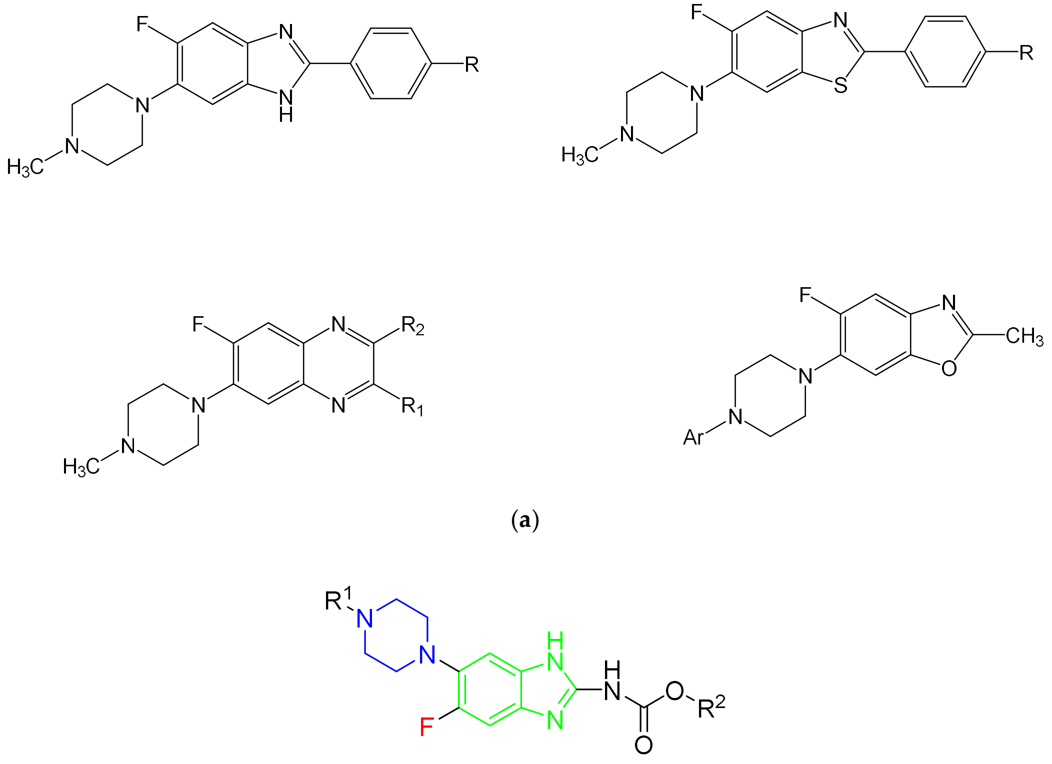


A **B** **C**

Figure 3. Structures containing piperazine ring with antifungal activities.

With respect to above explanations and in continue of our efforts in design and synthesis of novel antimicrobial agents containing fluorine and piperazine substituents (Figure 4a), here in, we reported synthesis of a series of benzimidazole derivatives and their bioactivity as antifungal agents (Figure 4b).

Cucumber (*Cucumis sativus*) is the most important greenhouse crop in Oman [20–21]. However, 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 [22–24]. Damping-off and vine decline diseases are also limiting factors to the production of cucumber and other cucurbits in different parts of the world [25–28].



(**a**)

(**b**)

Figure 4. (**a**) Previous works, (**b**) Current work.

Damping-off and vine decline diseases are caused by different pathogens, including *Pythium*, *Rhizoctonia* and *Fusarium* species [27,29–31]. *Pythium aphanidermatum* is the most common causal agent of damping-off disease of cucumber in Oman [32–34]. It is also among the two most common pathogens associated with cucumber vine decline [23]. The pathogen is tolerant to heat and has been found associated with cucumber root diseases during most times of the year.

Management of *Pythium*-induced diseases of cucumber has relied on the use of imported fungicides, biological control and cultural practices [27,35–38]. Mefenoxam and hymexazol are two common fungicides for the management of Pythium-induced diseases in Oman. Despite their use in different farms, mefenoxam suffers from rapid biodegradation in soil while resistance has been reported among Pythium species to hymexazol [39–42]. Biological control is a new area of research 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. [43–47]. However, the efficacy of these biocontrol agents is limited. Due to limitations in these management methods, it is important to search for new fungicide formulations that can be used to control these diseases.

The objectives of this study were:

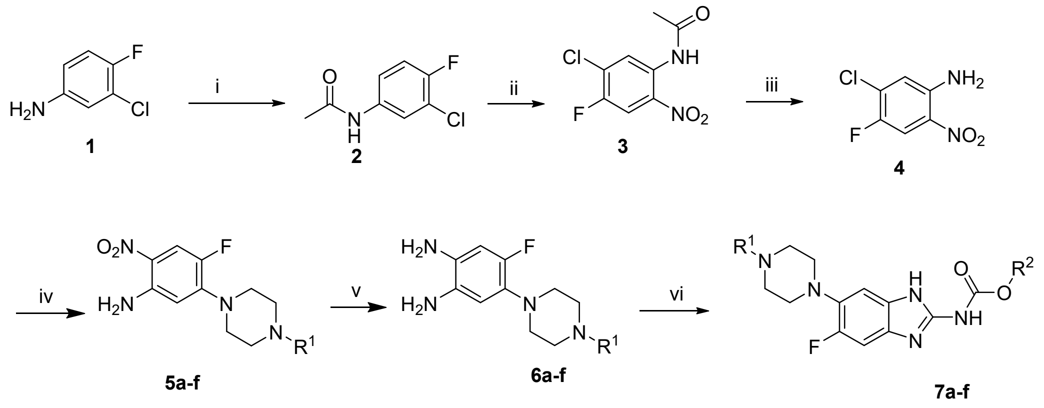
1. To synthesize a novel class of 2-carbamate benzimidazoles.
2. To investigate the efficacy of the new fungicide formulations in suppressing growth of the most common soil borne pathogens.

2. Results and Discussion

2.1. Chemistry

The synthetic scheme for the target compounds **7a**–**f** is outlined in Scheme 1. The synthetic strategy involved multi-step synthesis. The 2-carbamate benzimidazole derivatives **7a**–**f** were prepared from the *o*-phenylenediamine **6a**–**f** in one-pot procedure by reacting with 1,3-bis(substitutedoxycarbonyl)-2-methyl-2-thiopseudourea to produce new nine compounds of 2-carbamatebenzimidazoles. The yields of the cyclization reaction were ranged from excellent to good yield.

The chemical structures of the new series of 2-carbamate benzimidazoles **7a**–**f** were elucidated utilizing HRMS, ^{1}H NMR, FTIR, and Mp. For all known intermediates related references reported and novel intermediates also identified using ^{1}H NMR, ^{13}C NMR and IR. In the case of intermediates **6a**–**f**, were not separated and the crude mixture was used directly for next step to synthesis final products. The HRMS spectra of the newly prepared molecules displayed molecular ion peaks at appropriate *m*/*z* values. In FTIR, the (NHC=O) shown as sharp band in the range of 1743–1716 cm^{-1}. The main characterization techniques for the target carbamates **7a**–**f** are HRMS and ^{1}H NMR spectroscopy.



i:Acetic Anhydride, RT, 3h
ii:H_2SO_4, HNO_3, 0°C - RT, 3h
iii:Ethanol, conc HCl, Reflux, 3h
iv:Piperazine derivatives, DMSO, Reflux ,2h
v: HCl, $SnCl_2$, RT, 2h
vi:1,3-dicarbalkoxy-S-methylisothiourea derivatives, Ethanol, Reflux, overnight

5a,6a: R^1:Me
5b,6b: R^1:Et
5c,6c: R^1:But
5d,6d: R^1:Ph
5e,6e: R^1:4-F-Ph
5f,6f: R^1:2-F-Ph

7a-1: R^1:Me, R^2:Bn
7a-2: R^1:Me, R^2:t-But
7a-3: R^1:Me, R^2:Me
7b-1: R^1:Et, R^2:Bn
7b-2: R^1:Et, R^2:t-But
7b-3: R^1:Et, R^2:Me
7c-1: R^1:But, R^2:Bn
7c-2: R^1:But, R^2:Me

7d-1: R^1:Ph, R^2:Bn
7d-2: R^1:Ph, R^2:t-But
7d-3: R^1:Ph, R^2:Me
7e-1: R^1:4-F-Ph, R^2:Bn
7e-2: R^1:4-F-Ph, R^2:t-But
7e-3: R^1:4-F-Ph, R^2:Me
7f-1: R^1:2-F-Ph, R^2:Bn
7f-2: R^1:2-F-Ph, R^2:t-But
7f-3: R^1:2-F-Ph, R^2:Me

Scheme 1. Synthetic pathway to target compounds **7a**–**f**.

In general, all of the prepared carbamates **7a**–**f** have poor solubility in organic solvents though deuterated chloroform and DMSO show appropriate solubility for all to conduct the NMR measurements.

The new 2-carbamatebenzimidazoles **7a**–**f** have been converted to their hydrochloride salts in an attempt to enhance their aqueous solubility for the biological investigation.

In order to ensure that the structures maintained after conversion to hydrochloride salts, LC-MS was performed and showed the correct molecular ion peak.

2.2. Biologic Activity

The six fungicide formulations affected the growth of the five fungi at different rates. The growth of *Botrytis* and *Bipolaris* were not affected by any of the fungicide formulations at a concentration of 100 mg L^{-1}. However, the growth of *Pythium* was significantly affected by **7a**-**3**, **7a**-**2**, **7b**-**2**, **7a**-**1** and **7b**-**1** (Figure 1). The benzimidazoles with benzyl derivatives (**7a**-**1** & **7b**-**1**) were the most efficacious fungicide formulation in reducing the growth of *Pythium*, where it resulted in 96% growth inhibition in *Pythium* at 100 mg L^{-1}. *Fusarium* and *Alternaria* were only affected by **7b**-**1** fungicide formulation (Figure 1).

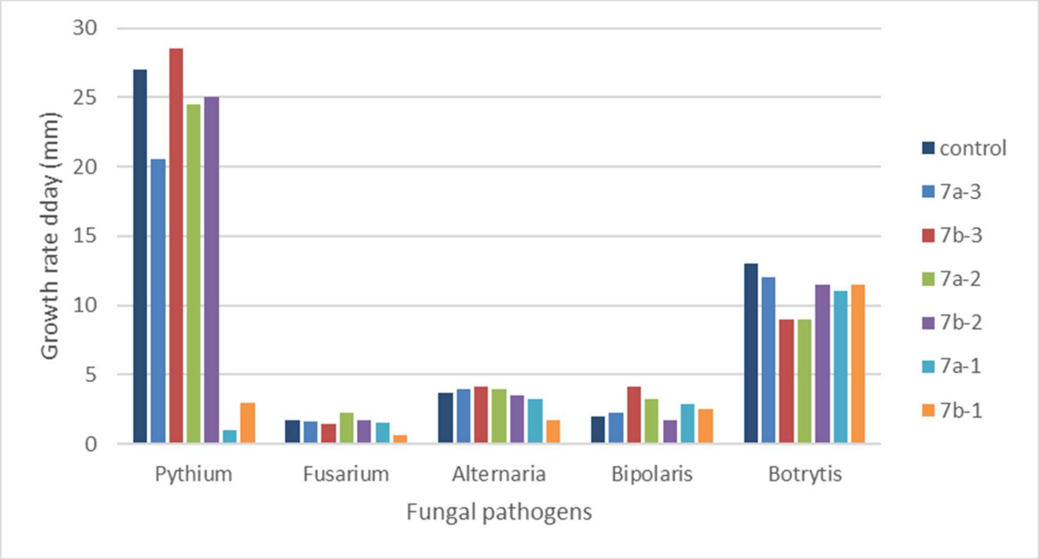


Figure 1. Effect of six fungicide formulations on the growth rate of *Pythium*, *Fusarium*, *Alternaria*, *Bipolaris* and *Botrytis* species. Bars with the same letter in the same fungus category are not significantly different from each other at $p < 0.05$ (Tukey's Studentized range test, SAS).

3. Conclusions

In conclusion, in this work we reported the synthesis and bioactivity of seventeen benzimidazole based carbamate derivatives **7a**–**f** as fungicides. Synthesized compounds exhibited acceptable activity against soil-borne pathogens. The benzimidazoles with benzyl derivatives (**7a**-**1** & **7b**-**1**) showed very high and promising results and was the most efficacious fungicide formulation in reducing the growth of *Pythium*. Future studies should focus on the efficacy of this fungicide on other soil borne pathogens.

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Conflicts of Interest: Authors declare that they have no conflict of interest.

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