Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 20, pp. 2665-2668, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)10045-2

INHIBITION OF NEMATODE INDUCED ROOT DAMAGE BY DERIVATIVES OF METHYLENECYCLOPROPANE ACETIC ACID

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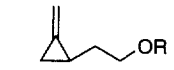
Abstract. Methylenecyclopropane acetic acid (MCPA), an inhibitor of fatty acid oxidation, and several derivatives were shown to be potent inhibitors of root galling induced by the nematode pest *Meloidogyne incognita.* © 1997 Elsevier Science Ltd.

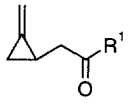
Economic control of plant parasitic nematodes with environmentally benign chemicals represents a significant unmet challenge for the agrochemical industry. Chemicals in use today include both fumigants and very toxic inhibitors of acetylcholinesterase, which are applied at high rates to achieve acceptable control.[1] The environmental and toxicological issues associated with the use of fumigants such as methyl bromide, dibromochloropropane, and ethylene dibromide have raised the possibility that these nematode treatments may not always be available to growers. Conceptually, a foliarly applied nematotoxic agent that is capable of being transported to the root zone should be effective at much lower doses than agents currently in use. Carboxylic acids in the appropriate pKa and log P ranges are known to be capable of movement in plant phloem.[2] Therefore, nematotoxic carboxylic acids could represent a useful starting point in the search for a commercially viable phloem mobile nematicide.[3] Recent work by Monsanto scientists using certain fluorinated amino acid derivatives nicely illustrates this approach.[4] By investigating potential utility of inhibitors of β–oxidation of fatty acids we found that methylenecyclopropane acetic acid (MCPA) exhibited interesting levels of nematicidal activity. We are not aware of any report describing pesticidal activity of MCPA and so present here the results of testing a short series of MCPA derivatives.

Synthesis. MCPA was prepared according to a literature report.[5] Derivatives were prepared as illustrated below.[6] Deprotection of tetrahydropyranyl ether **1a** afforded the racemic alcohol **1b** which was converted to MCPA (**2**) by Jones oxidation. MCPA was converted to amide **3** via aminolysis (NH_3 gas) of the N-hydroxysuccinimide derivative (DCC, DMAP, CH_2Cl_2). Esters **4** and **5** were also prepared by analogous DCC coupling. Alcohol **1b** was converted to amine **6c** through the three step sequence (a) MsCl, Et_3N, CH_2Cl_2 (to mesylate **6a**); (b) KNPhth, DMF, 80 °C (to phthalimide **6b**); (c) 2-aminoethanol, 25 °C. The mesylate **6a** was converted to thiazoline **7** by reaction with 2-mercaptothiazoline (NaOMe, methanol, reflux). Benzoate ester **8** was obtained from the reaction of **1** with 4-ethoxybenzoyl chloride (Et_3N, CH_2Cl_2). Saturated analog **9** was obtained by hydrogenation (H_2, Pd/C) of **2**. Preparation of the fluorinated derivative of MCPA presented a challenge, as there is scant literature on fluorinated methylenecyclopropanes.[7] After much experimentation, we found that direct difluorocyclopropanation of readily available allenic ester **10**,[8] although low yielding, was the most expedient route to ester **11**. Slow addition of a diglyme solution of a fivefold

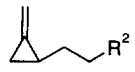
excess of NaO_2CCF_2Cl to a diglyme solution of ester **10** at 160 °C provided the difluoromethylenecyclopropane **11** in 11% yield, isolated by flash chromatography. Also isolated was an equivalent yield of a mixture of tetrafluorospiropentanes **12**. Hydrolysis (2 N NaOH, EtOH) afforded the target carboxylic acid **13**. Acid **13** was converted to ester derivatives **14** and **15** (DCC, CH_2Cl_2) to allow comparison with **4** and **5**.



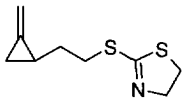
1a R = THP
1b R = H



2 R^1 = OH (MCPA)
3 $R^1 = NH_2$
4 $R^1 = O^nC_{16}H_{33}$
5 $R^1 = OCH_2C_6H_4$-m-OPh



6a R^2 = OMs
6b R^2 = NPhth
6c $R^2 = NH_2 \cdot HCl$



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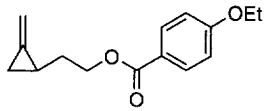

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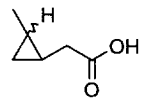

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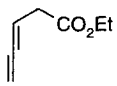

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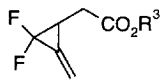
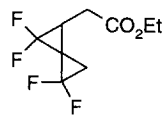


11 R^3 = Et
13 R^3 = H
14 $R^3 = {}^nC_{16}H_{33}$
15 $R^3 = CH_2C_6H_4$-*m*-OPh



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Results and Discussion. The CoA derivative of MCPA has been shown to act as an irreversible inhibitor of general acyl-CoA dehydrogenase enzymes.[9] (*R*)-(–)MCPA is also known as the toxic metabolite of hypoglycin A, the causative agent of Jamaican vomiting sickness.[10a] Derivatives of MCPA which are substituted on the ring with alkyl groups have been studied as potential agents for the treatment of non-insulin dependent diabetes.[11] Although a mechanistic hypothesis that the insecticidal activity exhibited by certain difluorocyclopropanes and fluorinated olefins may be the result of inhibition of fatty acid oxidation has been offered,[12] we aren't aware of any published work describing the effect of known inhibitors such as MCPA on agronomic pests.

Table 1 lists a series of MCPA derivatives and their activity in screening tests against the nematode pest *Meloidogyne incognita*. Compounds were dissolved in acetone and diluted with 20% acetone/water to the appropriate concentration. One milliliter of each concentration was added to one-ounce cups containing 20 g of either sand or soil and 20–30 foxtail millet (*Setaria italica*) seeds. After drying, a suspension of approx. 2000 eggs in 3.2 mL of water was added to each cup. The cups were capped and the plants allowed to germinate. The plants were then held in a growth chamber at 27 °C. After 14 d, roots of treated and untreated control plants were compared. Each dose was replicated 2–5 times depending on the compound, and activity was expressed as an average percent inhibition of nematode induced root galling.

MCPA derivatives **4–8** at 0.5 ppm exhibited moderate to excellent control of root galling in sand medium despite their apparent structural variation. All compounds were significantly less active in soil than in sand, suggesting the possibility of soil degradation. Since only carboxylic acids can be converted directly to the SCoA ester required for enzyme inhibition, the non-acids might be acting as pro-drugs for MCPA. Surprisingly, alcohol **1b**, an expected intermediate in a putative bioconversion of **8** into MCPA, was inactive in our test up to a concentration of 400 ppm. In a separate series of experiments, the THP ether **1a** gave 100% control of root galling at 6.25 ppm in sand. We believe that the high volatility of alcohol **1b**[5] is responsible for its inactivity. Because simple aliphatic carboxylic acids such as maleic and itaconic acid have been reported to exhibit nematicidal activity[3], we tested those acids as controls and found them to be ineffective at protecting roots up to a maximum dose of 400 ppm. As would be expected from the mechanism of enzyme inhibition, [9] the saturated analog **9** was much less active than MCPA. The novel fluorinated methylenecyclopropane **13** had activity comparable to MCPA in the soil assays; however, the two lipophilic analogs **14** and **15** appeared to be less active than their nonfluorinated counterparts **4** and **5**. MCPA and derivatives **4** and **7** had activity close to that of the standard nematicide aldicarb. Because of the challenges associated in working with this microscopic pest organism, the enzyme studies needed to demonstrate that MCPA actually inhibits fatty acid oxidation *in nematodes* have yet to be performed. However, these results suggest that this mode of action may have a role in pesticide discovery.

Table 1. Percent Inhibition of Nematode Induced Root Galling over a Dose Range.

Compound	0.5 ppm	7.8 ppm	125 ppm	Compound	0.5 ppm	7.8 ppm	125 ppm
2	90[a]/0[b]	100/15	100/80	**8**	100/0	100/0	100/100
3	0/0	100/0	100/100	**9**	0/0	100/0	100/0
4	100/0	100/50	100/100	**13**	NT[c]/0	NT/0	NT/100
5	50/0	100/0	100/50	**14**	NT/0	NT/0	NT/0
6c	25/0	100/0	100/75	**15**	NT/0	NT/0	NT/25
7	50/0	100/25	100/100	**aldicarb**	0.5 / 3.8[d]		

[a]In sand medium. [b]In soil medium. [c]Not tested. [d]Activity expressed as LC_{50}, in ppm, representing an average of numerous determinations.

Acknowledgment.

We thank Michelle Schlenz for the nematode screening data and Drs. Larry Larson and Joel Sheets for helpful discussions.

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(*Received in USA* 18 *July* 1997; *accepted* 18 *September* 1997)