Synthesis and fungicidal activity of *N*-2-(3-methoxy-4-propargyloxy) phenethyl amides. Part 3: stretched and heterocyclic mandelamide oomyceticides†

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Abstract: Novel analogues of mandipropamid have been designed and prepared. The synthetic approach to these stretched and heterocyclic mandelamides is outlined. Biological data demonstrate their high efficacy against important plant diseases like tomato and potato late blight (*Phytophthora infestans* De Bary) and grape downy mildew (*Plasmopara viticola* Berliner & de Toni). Structure–activity relationship studies are discussed.

Keywords: mandipropamid; fungicide; *Phytophthora infestans*; *Plasmopara viticola*; glyceric acid amide; Passerini reaction

1 INTRODUCTION

The distinguished activity of mandelamides with dialkoxylated phenethylamine moieties against fungal diseases was first discovered in the field of human pathogens by Yu and Van Scott in the mid-1980s.[1] They found that **1** (Fig. 1), which is the acetylated adduct of mandelic acid and homoveratrylamine, has significant activity against skin disorders such as fungal mycosis and psoriasis. In the early 1990s, this structural motif was taken up by chemists at Agrevo (now Bayer), who found that the mandelamide SX 623 509 (**2**) has activity against plant pathogens, especially oomycetes diseases.[2,3] At Novartis (now Syngenta), the replacement of the ethoxy group of **2** by a propargyloxy function resulted in the mandelamide **3** with enhanced fungicidal efficacy.[4] Similar experiences, that the replacement of methoxy or ethoxy groups by propargyloxy leads to increases in biological activity, have also been reported in the pharmaceutical literature for compounds with antibacterial[5] and leishmanicidal[6] activity. The introduction of a further propargyl group into the mandelic acid moiety increased the fungicidal activity dramatically, leading finally to Syngenta's new oomycete fungicide mandipropamid (**4**),[7,8] which is the first derivative of the chemical class of mandelamide fungicides to be commercialized. Mandipropamid is highly effective against most foliar oomycete pathogens such as the economically important plant diseases *Phytophthora infestans* De Bary (potato and tomato late blight), *Plasmopara viticola* Berliner & de Toni (grape downy mildew) and *Pseudoperonospara cubensis* Rostow (cucumber downy mildew). Mandipropamid is highly active against spore germination, but it also inhibits mycelial growth and sporulation.[8] Locking rapidly and tightly to the wax layer of the plant surface,[9] mandipropamid provides a rainfast and long-lasting barrier to fungal diseases. It is reported here that mandipropamid analogues with a spacer in between the 4-chlorophenyl ring and the 2-propargyloxyacetamide function ('stretched mandelamides'), such as **5**, and with a aromatic heterocycle replacing the phenyl ring of the mandelic acid moiety ('heterocyclic mandelamides'), such as **6**, display strong fungicidal activity against oomycetes diseases.

2 MATERIALS AND METHODS

2.1 Chemical synthesis

The synthetic pathways used to prepare the stretched mandelamide **5** are shown in Fig. 2. 4-Chlorophenol (**7**) is alkyated with 3-chlorolactic acid without protection of the acid's hydroxy and carboxy functions.[10] The resulting glyceric acid derivative **8** is then transformed into the α-hydroxy amide **12** by peptide coupling with the phenethylamine **9**,[7] Castro's reagent and Hünig's base. Finally, **12** can be converted into the desired stretched mandelamide **5** by alkylation with propargyl bromide under basic conditions. In an alternative synthesis of **5**, 4-chlorophenol (**7**) is reacted with bromoacetaldehyde diethyl acetal, which after

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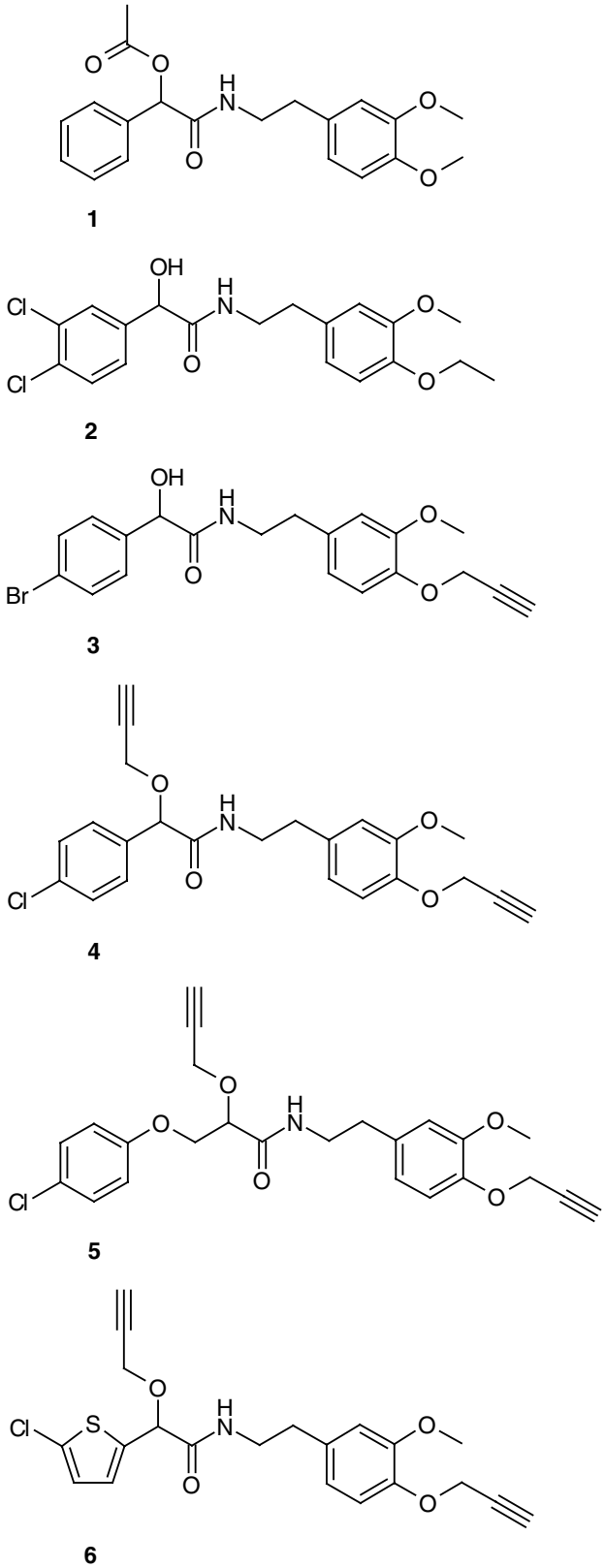


Figure 1. Fungicidal mandelamides and other α-hydroxycarboxamides.

acidic workup leads to the aryloxyacetaldehyde **10**.[11] This aldehyde is then further transformed with the formamide **11**,[7,12] triphosgene, triethylamine and titanium tetrachloride, using Seebach's modification[13,14] of the Passerini reaction,[15,16] into the α-hydroxy amide **12**, which can be propargylated to **5** as described above. This special multicomponent condensation was also applied to the concise synthesis of heterocyclic mandelamides, such as **6**, starting from the corresponding heterocyclic aldehydes. The stereoselective synthesis of enantiopure stretched or heterocyclic mandelamides would be possible via the diastereoselective Passerini reaction with a galacturonic acid derivative as acid component.[17]

2.1.1 3-(4-Chlorophenoxy)-2-hydroxypropionic acid (8)

A mixture of 4-chlorophenol (**7**, 9.3 g, 72 mmol) and 3-chlorolactic acid (5.0 g, 40 mmol) in 40 mL of 3.3 M aqueous sodium hydroxide solution was heated to reflux for 2 h. The mixture was cooled to room temperature and acidified to pH 3 with concentrated aqueous hydrochloric acid. The resulting crystals were filtered and dissolved in hot water and the hot solution was adjusted to pH 1 with concentrated sulfuric acid. Upon cooling, the product was collected in crystalline form. Yield: 4.8 g (22 mmol, 55%). ^{1}H NMR (d_6-DMSO): δ 3.93 (d, 2H, OCH_2), 4.14 (t, 1H, CHOH), 6.76 (d, 2H, CH arom.), 7.12 (d, 2H, CH arom.).

*2.1.2 3-(4-Chlorophenoxy)-2-hydroxy-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)ethyl]propionamide (**12**)*

(Benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate (BOP, Castro's reagent, 9.5 g, 21 mmol) was added slowly to a solution of **8** (4.3 g, 20 mmol), 2-(3-methoxy-4-prop-2-ynyloxyphenyl)ethylamine hydrochloride[7] (**9**, 5.0 g, 21 mmol) and *N*-ethyldiisopropylamine (10 g, 78 mmol) in 70 mL of *N*,*N*-dimethylformamide. This reaction mixture was stirred at room temperature for 16 h, poured into water and extracted 3 times with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate + hexane, 7 + 3 by volume). Yield: 7.4 g (18 mmol, 93%). ^{1}H NMR ($CDCl_3$): δ 2.52 (t, 1H, C≡CH), 2.83 (t, 2H, CH_2CH_2), 3.61 (q, 2H, CH_2CH_2), 3.89 (s, 3H, OCH_3), 4.15 (d, 2H, OCH_2), 4.43 (t, 1H, CHOH), 4.76 (d, 2H, $CH_2C{\equiv}C$), 6.72–7.30 (m, 7H, CH arom.).

*2.1.3 (4-Chlorophenoxy)acetaldehyde (**10**)*

A mixture of 4-chlorophenol (**7**, 13 g, 0.1 mol) in 15 mL of *N*,*N*-dimethylformamide was added dropwise to a vigorously stirred suspension of sodium hydride (2.6 g, 0.11 mol) in 50 mL of *N*,*N*-dimethylformamide. After 20 min at room temperature, bromoacetaldehyde diethyl acetal (20 g, 0.1 mol) was added and the resulting mixture was heated to 90 °C for 4 h. The reaction mixture was poured on water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate and evaporated. The residue was taken up in 250 mL of a mixture of acetone

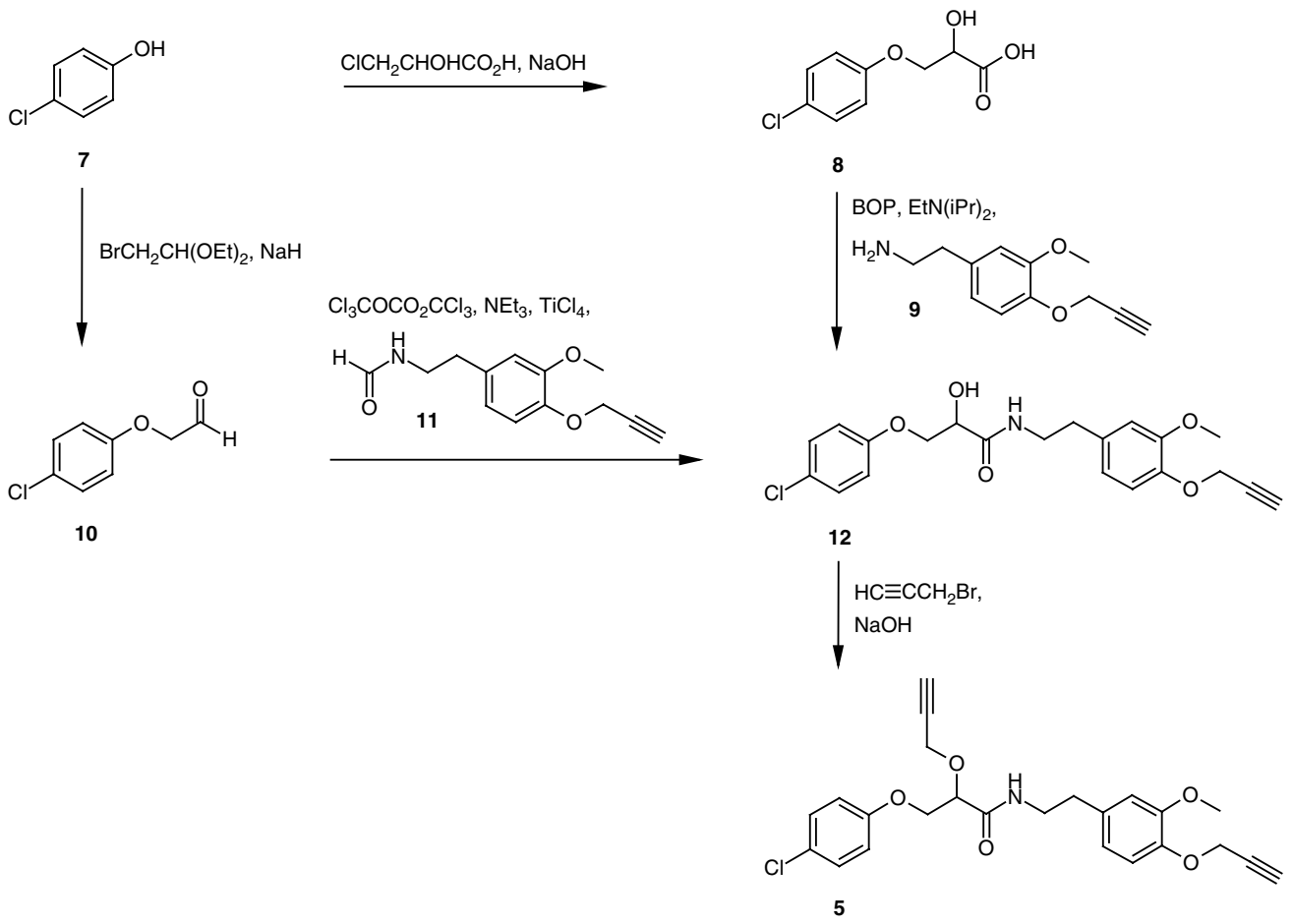


Figure 2. Different synthetic approaches to the stretched mandelamide **5**.

and water. Concentrated sulfuric acid (0.75 g) was added and the mixture was heated to reflux for 16 h. After cooling, the reaction mixture was poured on ice and extracted 3 times with dichloromethane. The combined organic layer was washed with 50 g L^{-1} aqueous sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the solvent delivered the product, which could be transformed in the next step without further purification. Yield: 13 g (78 mmol, 78%). ^{1}H NMR ($CDCl_3$): δ 4.42 (d, 2H, OCH_2), 6.87–7.33 (m, 4H, CH arom.), 9.71 (t, 1H, CHO).

*2.1.4 3-(4-chlorophenoxy)-2-hydroxy-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)ethyl]propionamide (**12**)*

To a solution of *N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)ethyl]formamide[7,12] (**11**, 7.3 g, 31 mmol) in 80 mL of dichloromethane was added triethylamine (7.6 g, 75 mmol). The mixture was cooled to 0–5 °C and a solution of bis(trichloromethyl) carbonate (triphosgene, 3.7 g, 12 mmol) in 40 mL of dichloromethane was added dropwise at 5 °C. After the addition was complete, the reaction was stirred for 4 h at 5 °C. Subsequently, the reaction was cooled down to −75 °C and a solution of titanium tetrachloride (6.5 g, 35 mmol) in 60 mL of dichloromethane was added dropwise in such a way that the reaction temperature did not exceed −70 °C. After completion of the addition, the reaction mixture was stirred for 2 h at −40 °C. A solution of **10** (5.6 g, 33 mmol) in 40 mL of dichloromethane was added dropwise at −40 °C and the reaction mixture was stirred for 16 h at room temperature. Subsequently the mixture was quenched with 20 mL of 5 M hydrochloric acid and stirred for 30 min at room temperature. The phases were separated, the aqueous phase was extracted 3 times with dichloromethane and the combined organic layer was washed with brine, dried over magnesium sulfate and evaporated. The remaining oil was purified by chromatography (ethyl acetate + hexane, 1 + 4 by volume). Yield: 9.0 g (22.5 mmol, 72%). ^{1}H NMR ($CDCl_3$): δ 2.52 (t, 1H, C≡CH), 2.83 (t, 2H, CH_2CH_2), 3.61 (q, 2H, CH_2CH_2), 3.89 (s, 3H, OCH_3), 4.15 (d, 2H, OCH_2), 4.43 (t, 1H, CHOH), 4.76 (d, 2H, $CH_2C{\equiv}C$), 6.72–7.30 (m, 7H, CH arom.).

*2.1.5 3-(4-Chlorophenoxy)-*N*-[2-(3-methoxy-4-prop-2-ynyloxyphenyl)ethyl]-2-prop-2-ynyloxypropionamide (**5**)*

An 80% solution of propargyl bromide in toluene (1.7 g, 11 mmol) was added slowly at room temperature to a mixture of **12** (3.5 g, 8.7 mmol), 300 g L^{-1} aqueous sodium hydroxide solution (4.4 mL, 44 mmol) and catalytic amounts of tetrabutylammonium

bromide in 20 mL of dichloromethane. The reaction mixture was stirred for 16 h at 40 °C. Subsequently the mixture was evaporated and the residue was diluted with water and dichloromethane. The phases were separated and the aqueous layer was extracted 3 times with dichloromethane. The combined organic phases were washed with brine, dried over magnesium sulfate and evaporated. The remainder was purified by chromatography (ethyl acetate + hexane, 1 + 4 by volume). Yield: 1.8 g (4.1 mmol, 47%). ^{1}H NMR ($CDCl_3$): δ 2.39 (t, 1H, C≡CH), 2.43 (t, 1H, C≡CH), 2.72 (t, 2H, CH_2CH_2), 3.49 (q, 2H, CH_2CH_2), 3.80 (s, 3H, OCH_3), 4.01–4.33 (m, 5H, OCH_2, CH_2C≡C, CHO), 4.68 (d, 2H, CH_2C≡C), 6.67–7.19 (m, 7H, CH arom.).

2.2 Biological assays

2.2.1 Phytophthora infestans/*tomato (late blight on tomato)*

Three-week-old tomato plants (*Lycopersicon esculentum* Mill. cv. Roter Gnom) were treated with the formulated test compound in a spray chamber. Two days after application, plants were inoculated by spraying a sporangial suspension (2×10^4 sporangia mL^{-1}) on the test plants. After an incubation period of 4 days at 18 °C and 95% relative humidity (RH) in a growth chamber, disease incidence was assessed.

2.2.2 Plasmopara viticola/*grape (grape downy mildew)*

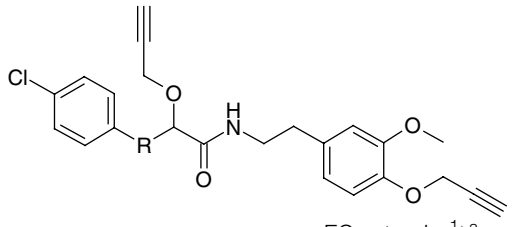
Five-week-old grape seedlings (*Vitis vinifera* L. cv. Gutedel) were treated with the formulated test compound in a spray chamber. One day after application, grape plants were inoculated by spraying a sporangial suspension (4×10^4 sporangia mL^{-1}) on their lower leaf surface. After an incubation period of 6 days at 22 °C and 95% RH in a greenhouse, disease incidence was assessed.

3 RESULTS AND DISCUSSION

3.1 Influence of the spacer between the phenyl ring and the 2-propargyloxyacetamide function in the mandelic acid moiety of mandipropamid (4) on anti-oomycetic activity

Table 1 compares EC_{80} values of mandipropamid (**4**) and its derivatives bearing different spacers between the 4-chlorophenyl ring and the 2-propargyloxyacetamide function on tomato late blight and grape downy mildew. One-atom carbon or oxygen spacers, as in **13** and **14**, generally seem to be unfavourable. However, the introduction of an additional linker atom leads to the highly active glyceric acid amide **5** with an OCH_2 bridge. Its impressive efficacy, especially against *P. infestans* down to 0.02 mg L^{-1}, was unrivalled by all other mandelamide derivatives, and it is also very active against *P. viticola*. The stretched mandelamide **17** with a three-atom spacer is still highly active on tomato late blight, but it has somehow lost the *P. viticola* efficacy. Four or more linker atoms, as in **18**, seem to be unsuitable.

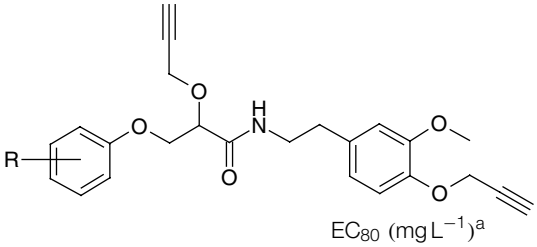
Table 1. Variation of the spacer between the phenyl ring and the α-propargyloxy-carboxamide function in the mandelic acid moiety of mandipropamid (**5**)



Compound	R	EC_{80} (mg L^{-1})[a] *Phytophthora infestans* (tomato late blight)	*Plasmopara viticola* (grape downy mildew)
4	–	0.1	1.2
13	CH_2	26.3	18.6
14	O	>200	>200
5	OCH_2	0.02	0.6
15	SCH_2	33.2	20.7
16	$CH(CH_3)CH_2$	28.8	100.5
17	CH_2OCH_2	0.3	20.4
18	$CH_2CH_2OCH_2$	32.0	45.9

[a] Concentration showing 80% activity in greenhouse trials.

Table 2. Variation of the phenyl substituent in the mandelic acid moiety of stretched mandelamides



Compound	R	EC_{80} (mg L^{-1})[a] *Phytophthora infestans* (tomato late blight)	*Plasmopara viticola* (grape downy mildew)
19	H	7.8	2.0
20	2-Cl	38.7	38.7
21	3-Cl	26.3	19.8
5	4-Cl	0.02	0.6
22	4-F	10.5	1.6
23	4-Br	15.8	5.1
24	4-CH_3	0.1	1.8
25	3-CF_3	41.6	53.7
26	3-F-4-Cl	18.6	42.8
27	3-CH_3-4-Cl	17.8	48.1
28	3-CH_3-4-Br	14.8	2.9
29	4-CH_3CH_2	56.2	5.3
30	4-CH_3S	40.0	34.6
31	4-CH_3O	32.0	60.4

[a] Concentration showing 80% activity in greenhouse trials.

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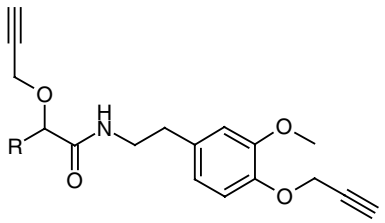
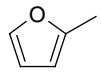
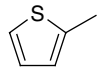
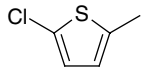
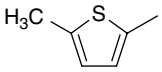
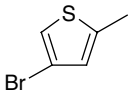
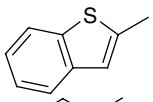
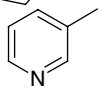
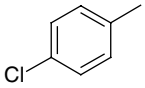
Table 3. Replacement of the phenyl ring in the mandelic acid moiety of mandelamides by a heterocycle



Compound	R	EC_{80} (mg L^{-1})[a] *Phytophthora infestans* (tomato late blight)	*Plasmopara viticola* (grape downy mildew)
32		17.5	12.4
33		2.1	1.4
6		1.7	1.2
34		24.9	1.8
35		133.9	>200
36		>200	>200
37		186.3	>200
4		0.1	1.2

[a] Concentration showing 80% activity in greenhouse trials

3.2 Influence of the phenyl substituent in the acid moiety of glyceric acid amides on anti-oomycetic activity

The introduction of small lipophilic groups such as halogen (**5** and **22**) or alkyl (**24**) into the *para* position of the glyceric acid phenyl ring was essential for excellent biological activity (Table 2). As was already the case for mandelamides, in the class of glyceric acid amides the 4-chloro substituent (**5**) gave the best results.

3.3 Influence of the heterocycle replacing the phenyl ring in the acid moiety of mandipropamid (4) on anti-oomycetic activity

The 4-chlorophenyl ring of mandipropamid (**4**) can be replaced by a five-membered ring heterocycle with preservation of anti-oomycetic activity (Table 3). In particular, thiophene (**6** and **33**) gave the best results. Six-membered ring heterocycles (**37**) and annelated bicyclic ring systems (**36**) lead to inactive compounds.

4 CONCLUSION

The introduction of a spacer between the phenyl ring and the 2-propargyloxyacetamide function in the mandelic acid moiety of mandipropamid (**4**) leads to stretched mandelamides, some of which possess high fungicidal activity. In particular, the application of an OCH_2 two-atom linker, converting the mandelamide into a glyceric acid amide, results in extremely potent oomyceticides. The replacement of the 4-chlorophenyl ring of mandipropamid by different heterocycles delivers heterocyclic mandelamides, of which mainly the five-membered ring derivatives display the best biological efficacy.

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