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Synthesis and Antifungal Activity of (±)-4-Methoxy Decanoic Acid and Its Novel Amide Derivatives[1]

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Abstract—A simple synthetic route has been developed for fatty acid, (±)-4-methoxy decanoic acid (**1**), in 4 steps with 42% overall yield. The novel amide derivatives of **1** are synthesized. The in vitro antifungal activity of **1** and its novel amide derivatives **1a–1f** has been evaluated against different organisms. Compounds **1e**, **1f** exhibited antifungal activity higher than the parent compound **1** against *macrophomina phaseolina*, and **1a, 1d** exhibited antifungal activity against *sclerotium rolfsii*.

Keywords: 1,2-epoxyoctane, Grignard reaction, methylation, oxidation, 4-methoxy decanoic acid, antifungal agent

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INTRODUCTION

Fungal pathogens acquired resistance frequently hampers effective treatment strategies [1]. Hydroxy-alkanoic and mid chain methylated fatty acids are known to exhibit antifungal activity [2–4]. Among those is (±)-4-methoxy decanoic acid (**1**) [5]. In the current study we synthesized 4-methoxy decanoic acid in 4 steps with overall yield 42% and its novel amide derivatives **1a–1f**.

RESULTS AND DISCUSSION

Synthesis of (±)-4-methoxy decanoicacid **1** started with treatment of 1,2-epoxy octane **2** by vinyl magnesium bromide at –10°C and formation of allylic alcohol **3** with high yield (Scheme 1). Methylation of **3** by NaH and MeI gave the corresponding methylated olefin **4** [5–7]. Treatment of **4** with BH_3–DMS, followed by addition of 30% H_2O_2 and 3N NaOH led to alcohol **5** [6]. Finally, oxidation of alcohol by TEMPO and BAIB in CH_3CN : H_2O (1 : 1) yielded the corresponding decanoic acid **1** [8, 9] with the overall yield 42%. Further the acid was treated with different amines **a–f** and gave the corresponding amides **1a–1f** [10] (Scheme 2, Table 1). All products were characterized by ^1H and ^{13}C NMR, IR and Mass spectral data.

Antifungal activity. Antifungal activity was tested by the dual culture method. Soil born plant pathogenic fungi (*Macrophomina phaseolina* and *Sclerotium rolfsii*) were grown on PDA. An agar block (five mm diameter) was cut from an actively growing (96 h old) fungal culture and placed on the surface of fresh agar medium at the centre of a Petri dish. A 24 h old culture of each bacterium was streaked in a straight line on one edge of a 90 mm diameter Petri dish. Dishes inoculated with the same fungus without bacteria were used as control. The dishes were incubated at 30°C and the inhibition zone was measured 5 days after inoculation. Three replications were carried out for each test, reduction in radial growth was measured and percent inhibition over control was calculated.

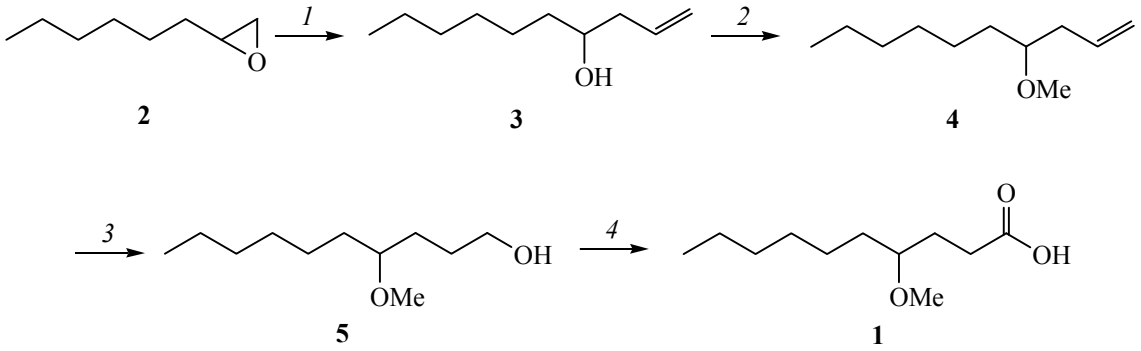
Some of the synthesized compounds were found to exhibit high antifungal activity (Table 2) with inhibition ranging from 75 to 80% in comparison to the standard reference flucanazole (I = 87.5%). The compounds **1e** and **1f** demonstrated antifungal activity higher than the parent compound **1** against *Macrophomina phaseolina* and could be considered as potent antifungal agents.

EXPERIMENTAL

All reagents and solvents were purchased from commercial sources. TLC was performed on Merck pre-coated 60 F254 silica gel plates and visualized by

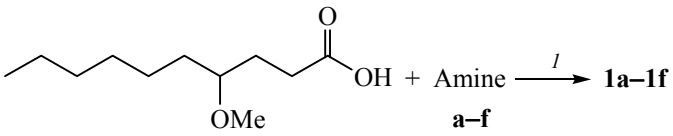
[1] The text was submitted by the authors in English.

Scheme 1. Synthesis of 4-methoxy decanoic acid **1**.



Reagents and conditions: (*1*) vinylmagnesium bromide, THF, –10°C, 2 h, 85%; (*2*) NaH, MeI, THF, 0°C–room temperature, 4 h, 87%; (*3*) BH_3DMS, MeOH, 20% NaOH, 30% H_2O_2, THF, 6 h, 75%; (*4*) TEMPO, BAIB, CH_3CN : H_2O (1 : 1), 4 h, 76%.

Scheme 2. Synthesis of novel amide derivatives **1a–1f.**



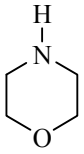
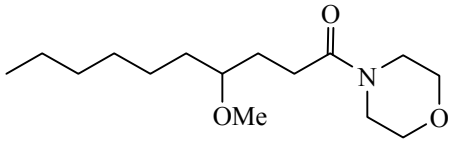
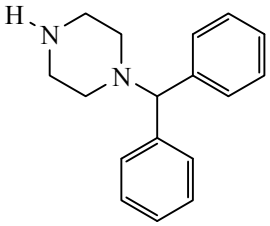
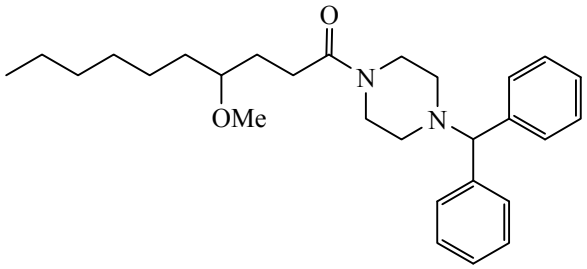
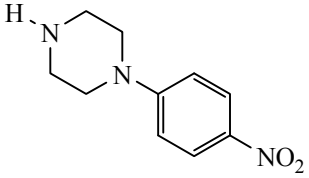
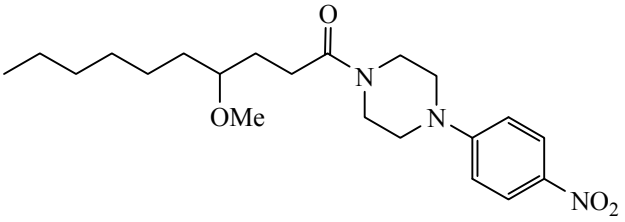
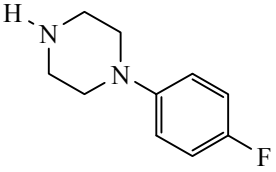
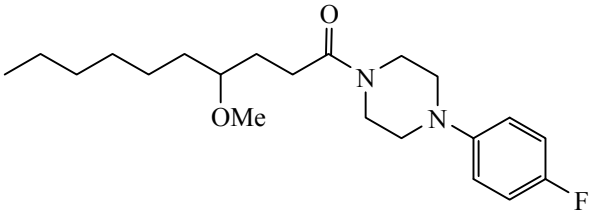
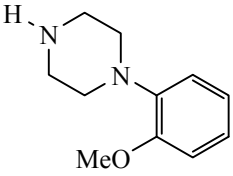
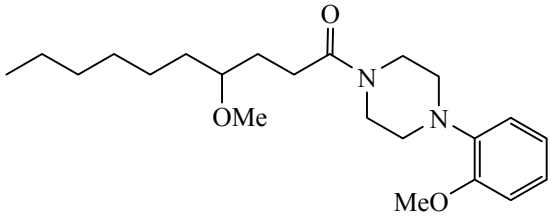
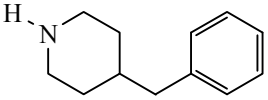
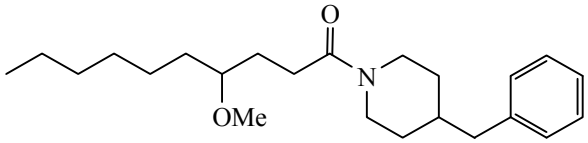
Reagents and conditions: (*1*) EDC·HCl, HOBT, Et_3N, CH_2Cl_2, room temperature.

iodine vapour, stain solutions and UV. IR spectra of compounds (neat) were recorded on a Shimadzu FT-IR 8400 S spectrophotometer. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ on a Bruker AVANCE-500 spectrometer using TMS as an internal standard. Mass spectra were measured on a Shimadzu GCMS-QP 1000.

Synthesis of dec-1-en-4-ol (3). To a stirred solution of epoxide compound **2** (1.0 g, 7.81 mmol) in THF (10 mL) were added 9.35 mL of vinylmagnesium bromide (1 M solution in THF) at –10°C and maintained stirring at the same temperature. Progress of the reaction was monitored by TLC. After completion of the process (2 h), the reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate (2×10 mL). The organic layer was washed with water (10 mL), $NaHCO_3$ solution (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (60–120 mesh silica gel) to afford the product **3** (1.04 g, 85%) as light yellow liquid. IR spectrum (neat), ν, cm^{-1}: 3450, 2924, 2855, 1744, 1627, 1462, 1372, 1264, 1158, 766. ^1H NMR spectrum, δ, ppm: 0.88 t (3H, J = 6.6, 7.0 Hz), 1.37–1.23 m (8H), 1.50–1.41 m (2H), 1.63 br.s (1H), 2.17–2.11 m (1H), 2.34–2.28 m (1H), 3.67–3.62 m (1H), 5.12 s (1H), 5.15 d (1H, J = 3.4 Hz), 5.88–5.79 m (1H). ^{13}C NMR spectrum, δ, ppm: 14.1, 22.6, 25.6, 29.3, 31.8, 36.8, 41.9, 70.7, 118.0, 134.9. EI-MS: 157 $[M + H]^+$.

Synthesis of 4-methoxy dec-1-ene (4). To a stirred solution of NaOH (0.38 g, 9.61 mmol) in dry THF (10 mL) was slowly added the compound **3** (1 g, 6.41 mmol), which was dissolved in dry THF (10 mL) at 0°C. After 30 min stirring at the same temperature was added methyl iodide (0.44 mL, 7.05 mmol). The resulting reaction mixture was stirred for 1 h at room temperature. Progress of the reaction was monitored by TLC. After completion of the process (TLC), the reaction mixture was quenched with saturated ammonium chloride solution. Then, the solvent was removed under reduced pressure and the mixture was extracted with ethyl acetate (2×20 mL). The combined ethyl acetate layers was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60–120 mesh), to afford the compound **4** (0.95g, 87%) as a light yellow liquid. IR spectrum, ν, cm^{-1}: 3448, 2925, 2856, 1641, 1434, 1215, 1090, 761. ^1H NMR spectrum, δ, ppm:

Table 1. Synthesis of amide derivatives **1a–1f** with different amines **a–f**

Amine no.	Formula	Amide no.	Formula
a		**1a**	
b		**1b**	
c		**1c**	
d		**1d**	
e		**1e**	
f		**1f**	

0.88 t (3H, J = 6.4, 7.0 Hz), 1.39–1.23 m (8H), 1.50–1.42 m (1H), 2.26 t (2H, J = 5.9, 6.9 Hz), 3.32–3.18 m (1H), 3.34 s (3H), 5.10–5.03 m (2H), 5.86–5.77 m (1H). ^{13}C NMR spectrum, δ, ppm: 14.1, 22.6, 25.2, 29.4, 31.8, 33.4, 37.7, 56.5, 80.5, 116.7, 135.0. ESI-MS: 171 $[M + H]^+$.

Synthesis of 4-methoxydecan-1-ol (5). To a solution of compound **4** (0.9 g, 5.29 mmol) in dry THF, was added BH_3–DMS (0.75 mL, 7.94 mmol) in THF (10 mL) over a period of 15 min, at 0°C. The reaction mixture was stirred for 3 h at room temperature. Progress of the reaction was monitored by TLC. After completion of process, the reaction mixture was quenched with MeOH at 0°C. Then, the mixture was treated with 20% aq NaOH (slow addition) at 0°C until the mixture became basic. To this, was added H_2O_2 (1.19 mL, 30% aqueous solution, 10.5 mmol)

and stirring continued for 3 h. The reaction mixture was extracted with ethyl acetate (2×10 mL). The combined ethyl acetate layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60–120 mesh), to afford the compound **5** (0.75 g, 75%) as a light yellow liquid. IR spectrum, ν, cm^{-1}: 3448, 2925, 2856, 1641, 1434, 1215, 1090, 761. ^{1}H NMR spectrum, δ, ppm: 0.88 t (3H, J = 6.4, 7.0 Hz), 1.39–1.23 m (8H), 1.50–1.42 m (1H), 2.26 t (2H, J = 5.9, 6.9 Hz), 3.32–3.18 m (1H), 3.34 s (3H), 5.10–5.03 m (2H), 5.86–5.77 m (1H). ^{13}C NMR spectrum, δ, ppm: 14.1, 22.6, 25.2, 29.4, 31.8, 33.4, 37.7, 56.5, 80.5, 116.7, 135.0. ESI-MS: 189 $[M + H]^+$, 211 $[M + Na]^+$.

Synthesis of 4-methoxydecanoic acid (1). To a stirred solution of alcohol **5** (0.7 g, 3.72 mmol) in CH_3CN : H_2O (1 : 1) (40 mL) were added BAIB (3.59 g, 11.17 mmol) and TEMPO (0.116 g, 7.44 mmol) at room temperature. Upon completion of reaction, as indicated by TLC, acetonitrile was evaporated under reduced pressure and the residue was diluted with ethyl acetate. The mixture was washed with a saturated aqueous solution of $Na_2S_2O_3$ (25 mL) and extracted with ethyl acetate (2×25 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (60–120 mesh Silica gel,) to afford the product **1** (0.571 g, 76%) as a yellow liquid. IR spectrum, ν, cm^{-1}: 3425, 2927, 2857, 1712, 1460, 1168, 1094, 1020, 761. ^{1}H NMR spectrum, δ, ppm: 0.89 t (3H, J = 6.6, 7.2 Hz), 1.36–1.23 m (8H), 1.46–1.37 m (1H), 1.59–1.50 m (1H), 1.79–1.70 m (1H), 1.92–1.83 m (1H), 2.44 t (2H, J = 7.6, 7.5 Hz), 3.23–3.13 m (1H), 3.33 s (3H). ^{13}C NMR spectrum, δ, ppm: 14.0, 22.6, 25.1, 28.3, 29.4, 29.9, 31.8, 33.2, 56.5, 80.0, 179.5. ESI-MS: 203 $[M + H]^+$, 225 $[M + Na]^+$.

General procedure for amide derivatives. To a stirred solution of 4-methoxydecanoic acid **1** (0.08 g, 0.396 mmol) in CH_2Cl_2 (5 mL) were added HOBT (0.067 g, 0.435 mmol) and EDC.HCl (0.083 g, 0.435 mmol) at room temperature under the atmosphere of N_2. After 15 min of stirring, a solution of TEA (0.17 mL, 1.188 mmol) and an amine **a–f** (0.435 mmol) in CH_2Cl_2 (5 mL) were added at 0°C. Progress of the reaction was monitored by TLC. Upon completion of the process, the reaction mixture was quenched with saturated NH_4OH solution (5 mL). In 10 min it was diluted with CH_2Cl_2 (10 mL) and the organic layer was washed with water (5 mL), $NaHCO_3$ solution (5 mL) and brine (5 mL), dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography (60–120 mesh silica gel) to afford amides **1a–1f**.

Table 2. In vitro antifungal activity of compounds **1** and **1a-1f**

Compound	Inhibition, %	
	Macrophomina phaseolina	*Sclerotium rolfsii*
1	62.5	80.0
1a	–	75.0
1b	25.0	25.0
1c	–	50.0
1d	25.0	80.0
1e	75.0	37.5
1f	80.0	37.5
Flucanazole	87.5	87.5

The representative spectral data are listed below for the product **1a**.

4-Methoxy-1-morpholinodecan-1-one (1a). Light yellow liquid, yield 80%. IR spectrum, ν, cm^{-1}: 3450, 2927, 2857, 1647, 1433, 1222, 1114, 764. ^{1}H NMR spectrum, δ, ppm: 0.88 t (3H, J = 6.7, 7.2 Hz), 1.34–1.22 m (8H), 1.44–1.35 m (1H), 1.59–1.51 m (1H), 1.75–1.66 m (1H), 1.96–1.88 m (1H), 2.45–2.31 m (2H), 3.24–3.19 m (1H), 3.32 s (3H), 3.49 t (2H, J = 4.9, 4.7 Hz), 3.62 t (2H, J = 5.6, 3.2 Hz), 3.67 t (4H, J = 5.3, 4.6 Hz). ^{13}C NMR spectrum, δ, ppm: 14.1, 22.6, 25.2, 28.5, 29.5, 31.8, 33.2, 41.9, 45.9, 56.3, 66.7, 80.1, 117.8. ESI-MS: 272 $[M + H]^+$.

1-(4-Benzhydrylpiperazin-1-yl)-4-methoxydecan-1-one (1b). Yellow liquid, yield 70%.

4-Methoxy-1-[(4-nitrophenyl)piperazin-1-yl]decan-1-one (1c). Brown viscous liquid, yield 75%.

1-[4-(4-Fluorophenyl)piperazin-1-yl]-4-methoxydecan-1-one (1d). Brown liquid, yield 72%.

4-Methoxy-1-[4-(2-methoxyphenyl)piperazin-1-yl]decan-1-one (1e). Brown liquid, yield 71%.

1-(4-Benzylpiperadin-1-yl)-4-methoxydecan-1-one (1f). Light yellow liquid, yield 68%.

CONCLUSIONS

Synthesis of (±)-4-meyhoxy decanoic acid and its novel amide derivatives was developed. Antifungal activity of 4-methoxy decanoicacid and all synthesised amide derivatives has been evaluated against *Macrophomina phaseolina* and *Sclerotium rolfsii*. Several products demonstrated high activity.

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