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# SYNTHESIS AND BIOLOGICAL EVALUATION OF A NOVEL SERIES OF 2-(2'-ISOPROPYL-5'-METHYLPHENOXY) ACETYL AMINO ACIDS AND DIPEPTIDES

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**ABSTRACT.** A series of new 2-(2'-isopropyl-5'-methylphenoxy)acetyl amino acids and peptides have been synthesized by coupling the 2-(2'-isopropyl-5'-methylphenoxy)acetic acid with amino acid methyl esters/dipeptides using DCC as coupling agent and TEA as base. The structures were elucidated by elemental analyses as well as FTIR, $^{1}$H NMR, $^{13}$C NMR and MS spectral data. The newly synthesized compounds were also evaluated for antibacterial and antifungal activities. Compounds (**2**, **6** and **15**) were found to exhibit potent antibacterial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus* and compounds (**13**, **14** and **16**) were found to be potent antifungal agents against pathogenic *Candida albicans*.

**KEY WORDS:** Phenoxy acetic acid, Amino acids, Dipeptides, Antibacterial activity, Antifungal activity.

## INTRODUCTION

Phenoxy acetic acid is among the most vital moieties which are associated with potent antifungal activities. Much work has been done on synthesis of potent phenoxy acetic acid derivatives with diverse bioactivities and also reports have been received regarding attachment of phenoxy acetic acid derivatives with peptides [1-6]. The review of literature has suggested that incorporation of amino acids and peptides into the aromatic and heterocyclic congeners have resulted in compounds with potent bioactivities [7-10]. Thus keeping in view the biological potency of phenoxy acetic acids as well as taking advantage of biodegradability and biocompatibility of amino acids and peptides, a novel series of 2,5-disubstitutedphenoxy acetic acid derivatives of amino acids and peptides have been synthesized with an anticipation to get potent agents of more therapeutic efficacy with negligible side effects.

### *Chemistry*

2-(2'-Isopropyl-5'-methylphenoxy)acetic acid (**1**) was prepared by phenoxylation of thymol by using chloroacetic acid in alkaline conditions. Dipeptides Boc-Gly-Gly-OMe, Boc-Pro-Pro-OMe and Boc-Ala-Leu-OMe were prepared from the corresponding amino acid methyl esters and Boc-amino acids using DCC as the coupling agent. 2-(2'-Isopropyl-5'-methylphenoxy)acetyl amino acid esters (**2-6**) and dipeptides esters (**7-9**) were prepared by coupling (**1**) with amino acid methyl ester hydrochlorides/dipeptides which were hydrolysed to get 2-(2'-isopropyl-5'-methylphenoxy)acetyl amino acids (**10-14**) and dipeptides (**15-17**) [Scheme A].

Structures of all the newly synthesized compounds were confirmed by FTIR and $^{1}$H NMR. $^{13}$C NMR and Mass spectra were recorded for selected representative samples. Elemental analysis of the novel compounds was performed for carbon, hydrogen and nitrogen content.

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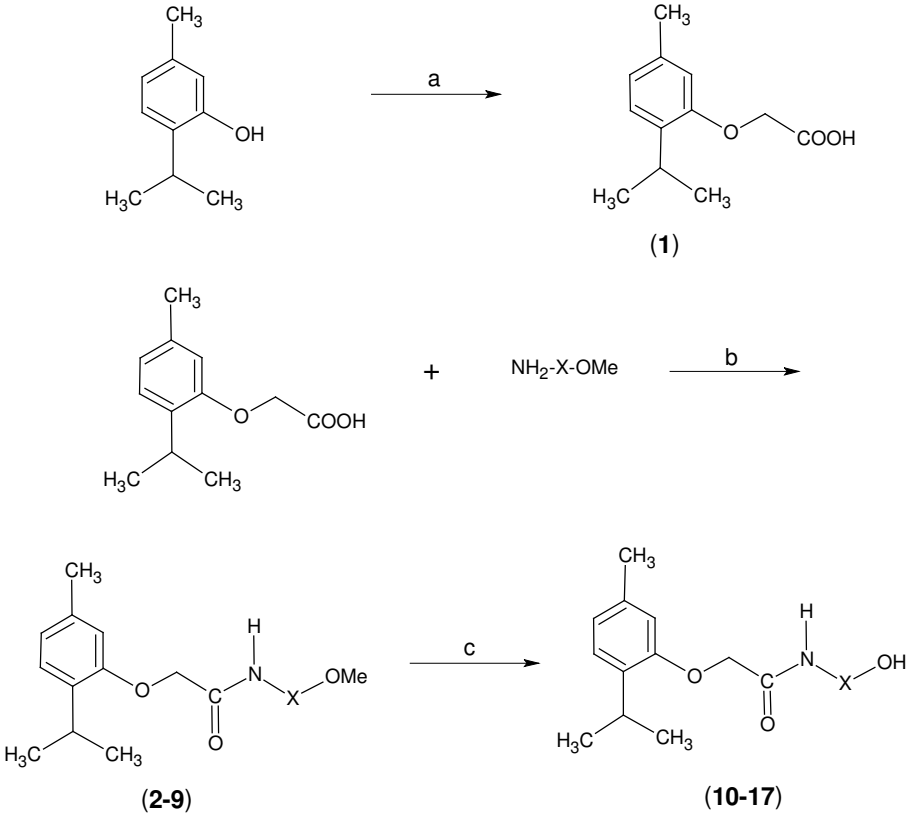


Where

a = $ClCH_2COOH$, NaOH, reflux, 1 h

X = L-Phe, L-Val, L-Ile, L-($N_4$-nitro)Arg, L-Try, Glygly, L-Pro-L-Pro, L-Ala-L-Leu

b = DCC, TEA, RT, 24 h

c = THF : $H_2O$ ( 1 : 1 ), LiOH, RT, 1 h

Scheme A

*Pharmacology*

All the synthesized compounds were screened for *in vitro* antimicrobial activity against gram positive bacteria *Bacillus subtilis* and *Staphylococcus aureus*, gram negative bacteria *Pseudomonas aeruginosa* and *Escherichia coli*, cutaneous fungi *Microsporum audouinii* and *Trichophyton mentagrophytes*, diamorphic fungi *Candida albicans* using modified Kirby-Bauer disk diffusion method [11]. The results are shown in Table 1.

Table 1. Antimicrobial activity data (at 50 μg/mL level).

| Compound No. | Zone of inhibition (in mm) | | | | | | |
|---|---|---|---|---|---|---|---|
| | *B. sub.* | *E. coli* | *S. aur.* | *P. aeru.* | *M. audo.* | *T. menta.* | *C. alb.* |
| (**1**) | 8 | 7 | 9 | 10 | 10 | 9 | 10 |
| (**2**) | 7 | 10 | 20 | 26 | 11 | 10 | 11 |
| (**3**) | – | 9 | 10 | 14 | 9 | – | 12 |
| (**4**) | – | 9 | – | 13 | – | 9 | 10 |
| (**5**) | 9 | – | 8 | 15 | 10 | 8 | 12 |
| (**6**) | 10 | 11 | 19 | 28 | 11 | 9 | 11 |
| (**7**) | – | 10 | – | 12 | 9 | 8 | 10 |
| (**8**) | 7 | 8 | 7 | 13 | 10 | 7 | 11 |
| (**9**) | – | 8 | – | 10 | 9 | 7 | 11 |
| (**10**) | 9 | 10 | – | 13 | 11 | 12 | 13 |
| (**11**) | – | 7 | 8 | – | 10 | – | 11 |
| (**12**) | 8 | – | 7 | – | – | 8 | 12 |
| (**13**) | 8 | 10 | 9 | 14 | 13 | 12 | 25 |
| (**14**) | 10 | 9 | 7 | 17 | 11 | 11 | 20 |
| (**15**) | – | 12 | 21 | 25 | 12 | 12 | 13 |
| (**16**) | – | 10 | 7 | 15 | 12 | 11 | 23 |
| (**17**) | 9 | 11 | – | 10 | 13 | 11 | – |
| Ciprofloxacin | 18 | 22 | 19 | 20 | – | – | – |
| Griseofulvin | – | – | – | – | 15 | 14 | 16 |

## EXPERIMENTAL

*General*

All the coupling reactions requiring anhydrous conditions were conducted in oven-dried apparatus. Melting points were determined by open capillary method and are uncorrected. Amino acids, di-tert-butylpyrocarbonate ($Boc_2O$), dicyclohexylcarbodiimide (DCC), trifluoroacetic acid (TFA) and triethylamine (TEA) were obtained from Spectrochem Limited, Mumbai, India. IR spectra were recorded on Shimadzu 8700 Fourier Transform infrared spectrophotometer using a thin film supported on KBr pellets for all synthesized compounds. $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker AC NMR spectrometer (300 MHz) using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded on Jeol JMS DX 303 Mass spectrometer operating at 70 eV. Elemental analyses of all compounds were performed on Elementar vario EL III. Optical rotation was measured on Polarimeter (Optics Technology) in a 2 dm tube at 25 °C using sodium lamp. Purity of all the compounds was checked by TLC on precoated silica gel G plates.

*Preparation of dipeptides*

Amino acid methyl ester hydrochloride/dipeptide methyl ester (10 mmol) was dissolved in $CHCl_3$ (20 mL). To this, TEA (21 mmol) was added at 0 °C and the reaction mixture was stirred for 15 min. Boc-amino acid (10 mmol) in $CHCl_3$ (20 mL) and DCC (10 mmol) were added with stirring. After 24 h, the reaction mixture was filtered and the residue was washed with $CHCl_3$ (30 mL) and added to the filtrate. The filtrate was washed with 5% $NaHCO_3$ and saturated NaCl solutions. The organic layer was dried over anhydrous $Na_2SO_4$, filtered and evaporated in vacuum. The crude product was recrystallized from a mixture of chloroform and petroleum ether followed by cooling at 0 °C. Resulting Boc-dipeptide methyl ester (10 mmol) was

dissolved in $CHCl_3$ (15 mL) and treated with trifluoroacetic acid (20 mmol). The mixture was stirred at room temperature for 1 h and washed with saturated $NaHCO_3$ solution. The resulting organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Finally, crude product was purified by recrystallization with $CHCl_3$ and petroleum ether to get the deprotected dipetide methyl ester.

For protecting the amino group of L-amino acids, $Boc_2O$ was used. The carboxyl group of L-amino acids was protected by esterification with methanol using $SOCl_2$. Peptides were prepared by Bodanszky method with certain modifications [12]. Furthermore, trifluoroacetic acid was used for the removal of Boc group and ester group was removed by alkaline hydrolysis with lithium hydroxide.

*$^t$Butyloxycarbonylglycylglycine methyl ester*

Semisolid mass, yield 73%. $^1$H NMR ($CDCl_3$, 300 MHz) δ: 7.5 (1H, br s, -NH), 6.22 (1H, br s, -NH), 4.25-4.24 (2H, d, J = 4.8 Hz, $CH_2$ of Gly$^2$), 3.70-3.68 (2H, d, J = 4.7 Hz, $CH_2$ of Gly$^1$), 3.5 (3H, s, $OCH_3$), 1.55 (9H, s, $^t$Butyl group). Anal. calcd. for $C_{10}H_{18}N_2O_5$: C, 48.77; H, 7.37; N, 11.38. Found: C, 48.64; H, 7.85; N, 11.24.

*$^t$Butyloxycarbonylprolylproline methyl ester*

Semisolid mass, yield 69%. $^1$H NMR ($CDCl_3$, 300 MHz) δ: 4.18-4.08 (2H, m, α-protons of Pro$^2$ and Pro$^1$), 3.63 (3H, s, $OCH_3$), 3.60-3.52 (2H, t, J = 5.9 Hz, δ-protons of Pro$^2$), 3.25-3.20 (2H, t, J = 5.8 Hz, δ-protons of Pro$^1$), 2.60-2.52 (2H, m, β-protons of Pro$^1$), 2.10-1.95 (4H, m, β- and γ-protons of Pro$^2$), 1.93-1.85 (2H, m, γ-protons of Pro$^1$), 1.5 (9H, s, $^t$butyl group). Anal. calcd. for $C_{16}H_{26}N_2O_5$: C, 58.86; H, 8.03; N, 8.58. Found: C, 58.87; H, 8.34; N, 8.57.

*$^t$Butyloxycarbonylalanylleucine methyl ester*

Semisolid mass, yield 70%. $^1$H NMR ($CDCl_3$, 300 MHz) δ: 7.0 (1H, br s, -NH), 6.75 (1H, br s, -NH), 4.62-4.52 (1H, q, α-H of Ala), 4.14-4.05 (1H, m, α-H of Leu), 3.6 (3H, s, $OCH_3$), 1.55 (9H, s, $^t$butyl group), 1.54-1.44 (1H, m, γ-H of Leu), 1.34-1.32 (3H, d, J = 7.4 Hz, β-protons of Ala), 1.28-1.22 (2H, t, β-protons of Leu), 0.95-0.93 (6H, d, J = 7.1 Hz, γ-$CH_3$ of Leu). Anal. calcd. for $C_{15}H_{28}N_2O_5$: C, 56.94; H, 8.92; N, 8.85. Found: C, 56.64; H, 9.03; N, 8.86.

*Preparation of 2-(2'-isopropyl-5'-methylphenoxy)acetic acid (**1**)*

Thymol (0.024 mol) was dissolved in 20 mL of 33% NaOH solution (0.165 mol). To the above mixture, 15 mL of 50% chloroacetic acid solution (0.079 mol) was added. The reaction mixture was refluxed on gently boiling water bath for 1 h. After cooling, water (50-60 mL) was added and whole mixture was acidified to congo red with dil. HCl and finally extracted with ether (150 mL). Etheral extract was washed with water (50 mL) and shaken twice with 5% $Na_2CO_3$ solution (75 mL). Crude acid was precipitated out by acidifying the $Na_2CO_3$ extract with dil. HCl. The separated solid was collected by filtration, washed with cold water and finally crystallized from aq. ethanol to get the title compound.

Light brown crystals, m.p. 135-136 ºC, yield 68%. IR (KBr) cm$^{-1}$: 3288-2495 (m/br, -OH str, -COOH), 3077, 3043 (w, -CH str, arom. ring), 2962, 2928 (m, -CH str, asym, $CH_3$ and $CH_2$), 2870 (m, -CH str, sym, $CH_3$), 1715 (m, -C=O str, -COOH), 1594, 1487 (m, skeletal bands, arom. ring), 1464 (m, -CH bend (scissoring), $CH_2$), 1407 (m, C-O-H bend, -COOH), 1385, 1372 (s, -CH bend, isopropyl group), 1262 (s, C–O–C str, asym), 1125, 1112 (m, -CH bend, in plane, arom. ring), 1062 (s, C–O–C str, sym), 925 (w, $CH_3$ rocking, isopropyl group), 887, 805 (s, -CH

bend, out-of-plane, arom. ring). $^1$H NMR ($CDCl_3$, 300 MHz) δ: 7.06 (1H, s, -COOH), 7.00-6.97 (1H, d, J = 6.8 Hz, *m*-H of phenoxy ring), 6.90 (1H, s, *o*-H of phenoxy ring), 6.54-6.51 (1H, d, J = 6.8 Hz, *p*-H of phenoxy ring), 4.39 (2H, s, -$OCH_2CO$-), 3.12-2.98 (1H, m, *o*-(α-H) of phenoxy ring), 1.99 (3H, s, *m*-$CH_3$ of phenoxy ring), 1.12-1.10 (6H, d, J = 6.9 Hz, *o*-(α-$CH_3$) of phenoxy ring) ppm. Anal. calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.15; H, 7.76.

*Preparation of 2-(2'-isopropyl-5'-methylphenoxy)acetyl amino acid and peptide methyl esters*

2-(2'-Isopropyl-5'-methylphenoxy)acetyl amino acid and peptide methyl esters were prepared by coupling 2-(2'-isopropyl-5'-methylphenoxy)acetic acid (1) with amino acid methyl ester hydrochlorides/ peptide methyl esters in the presence DCC, TEA and DMF by following the same procedure as that adopted for dipeptide synthesis to get the compounds (**2-9**) which were hydrolysed with LiOH to get the corresponding free acids (**10-17**). For deprotection of the carboxyl group, protected peptide derivative (10 mmol) was dissolved in THF:$H_2O$ (1:1) and LiOH (15 mmol) was added to the solution at 0 ˚C. The resulting mixture was stirred at room temperature for 1 h and then acidified to pH 3.5 with 1 N $H_2SO_4$. The aqueous layer was extracted with $Et_2O$ (2 x 15 mL) and the combined organic extracts were dried over $Na_2SO_4$ and concentrated under reduced pressure to get the deprotected compound.

*2-(2'-Isopropyl-5'-methylphenoxy)acetylphenylalanine methyl ester (**2**)*

Light brown solid, m.p. 167-168 ºC, $[\alpha]_D$ +7.8˚, yield 72%. IR (KBr) $cm^{-1}$: 3125 (m, -NH str, amide), 3073, 3052 (w, -CH str, arom. rings), 2965, 2927 (m, -CH str, asym, $CH_3$ and $CH_2$), 2871, 2854 (m, -CH str, sym, $CH_3$ and $CH_2$), 2825 (m, -CH str, $OCH_3$), 1745 (s, -C=O str, ester), 1642 (s, -C=O str, 2˚ amide), 1588, 1480 (m, skeletal bands, arom. rings), 1535 (m, -NH bend, 2˚ amide), 1463 (m, -CH bend (scissoring), $CH_2$), 1382, 1371 (s, -CH bend, isopropyl group), 1270 (s, C–O str, ester), 1244 (s, C–O–C str, asym), 1035 (s, C–O–C str, sym), 905, 811 (s, -CH bend, out-of-plane, tri substi. ring), 725, 689 (s, -CH bend, out-of-plane, mono substi. ring). $^1$H NMR ($CDCl_3$, 300 MHz) δ: 7.3 (1H, br. s, -NH), 7.23-7.20 (1H, d, J = 6.8 Hz, *m*-H of phenoxy ring), 7.13-7.07 (1H, t, J = 7.2 Hz, *p*-H of Phe), 7.02-6.98 (2H, tt, *m*-protons of Phe), 6.86-6.84 (2H, dd, *o*-protons of Phe), 6.68 (1H, s, *o*-H of phenoxy ring), 6.46-6.44 (1H, d, J = 6.8 Hz, *p*-H of phenoxy ring), 4.74-4.67 (1H, m, α-H of Phe), 4.45 (2H, s, -$OCH_2CO$-), 3.54 (3H, s, $OCH_3$), 3.15-2.80 (3H, m, *o*-(α-H) of phenoxy ring and β-protons of Phe), 1.96 (3H, s, *m*-$CH_3$ of phenoxy ring), 1.12-1.10 (6H, d, J = 6.9 Hz, *o*-(α-$CH_3$) of phenoxy ring) ppm. Anal. calcd. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.25; H, 7.45; N, 3.85.

*2-(2'-Isopropyl-5'-methylphenoxy)acetylvaline methyl ester (**3**)*

Brown crystals, m.p. 124-125 ºC, $[\alpha]_D$ -4.5˚, yield 69%. IR (KBr) $cm^{-1}$: 3138 (m, -NH str, amide), 3068 (w, -CH str, arom. ring), 2997, 2993 (m, -CH str, -CH), 2962, 2925 (m, -CH str, asym, $CH_3$ and $CH_2$), 2872 (m, -CH str, sym, $CH_3$), 2812 (m, -CH str, $OCH_3$), 1742 (s, -C=O str, ester), 1639 (s, -C=O str, 2˚ amide), 1594, 1489 (m, skeletal bands, arom. ring), 1528 (m, -NH bend, 2˚ amide), 1380, 1362 (s, -CH bend, isopropyl group), 1282 (s, C–O str, ester), 1258 (s, C–O–C str, asym), 921 (w, -CH bend (rocking), isopropyl group), 895, 805 (s, -CH bend, out-of-plane, tri substi. ring), 486 (w, C–C bend, aliphatic). $^1$H NMR ($CDCl_3$, 300 MHz) δ: 7.24-7.21 (1H, d, J = 6.7 Hz, *m*-H of phenoxy ring), 6.99 (1H, br s, -NH), 6.70 (1H, s, *o*-H of phenoxy ring), 6.48-6.46 (1H, d, J = 6.8 Hz, *p*-H of phenoxy ring), 4.60 (2H, s, -$OCH_2CO$-), 4.12-4.07 (1H, t, J = 5.9 Hz, α-H of Val), 3.48 (3H, s, $OCH_3$), 3.10-2.98 (1H, m, *o*-(α-H) of phenoxy ring), 2.23-2.09 (1H, m, β-H of Val), 2.97 (3H, s, *m*-$CH_3$ of phenoxy ring), 1.10-1.08

(6H, d, J = 6.9 Hz, *o*-(α-$CH_3$) of phenoxy ring), 0.80-0.78 (6H, d, J = 6.2 Hz, β-$CH_3$ of Val). Anal. calcd. for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 66.94; H, 8.85; N, 4.34.

*2-(2'-Isopropyl-5'-methylphenoxy)acetylisoleucine methyl ester (**4**)*

Light brown crystals, m.p. 140-142 ºC, $[\alpha]_D$ -12.5˚, yield 73%. IR (KBr) $cm^{-1}$: 3145 (m, -NH str, amide), 3072, 3055 (w, -CH str, arom. ring), 2995 (m, -CH str, -CH), 2959, 2932 (m, -CH str, asym, $CH_3$ and $CH_2$), 2869, 2852 (m, -CH str, sym, $CH_3$ and $CH_2$), 2815 (m, -CH str, $OCH_3$), 1755 (s, -C=O str, ester), 1644 (s, -C=O str, 2˚ amide), 1599, 1480 (m, skeletal bands, arom. ring), 1533 (m, -NH bend, 2˚ amide), 1466 (m, -CH bend (scissoring), $CH_2$), 1449 (m, -CH bend, $CH_3$), 1382, 1360 (s, -CH bend, isopropyl group), 1282 (s, C–O str, ester), 1262 (s, C–O–C str, asym), 898, 810 (s, -CH bend, out-of-plane, tri substi. ring), 496, 489 (w, C–C bend, aliphatic). $^1$H NMR ($CDCl_3$, 300 MHz) δ: 7.23-7.20 (1H, d, J = 6.8 Hz, *m*-H of phenoxy ring), 6.69 (1H, s, *o*-H of phenoxy ring), 6.45-6.43 (1H, d, J = 6.8 Hz, *p*-H of phenoxy ring), 6.2 (1H, br s, -NH), 4.5 (2H, s, -$OCH_2CO$-), 4.24-4.20 (1H, t, J = 8.3 Hz, α-H of Ile), 3.50 (3H, s, $OCH_3$), 3.13~2.99 (1H, m, *o*-(α-H) of phenoxy ring), 2.07-1.94 (1H, m, β-H of Ile), 1.98 (3H, s, *m*-$CH_3$ of phenoxy ring), 1.74-1.38 (2H, m, γ-$CH_2$ of Ile), 1.11-1.09 (6H, d, J = 6.9 Hz, *o*-(α-$CH_3$) of phenoxy ring), 0.97-0.90 (6H, m, β-$CH_3$ and γ-$CH_3$ of Ile) ppm. Anal. calcd. for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 67.65; H, 8.85; N, 4.14.

*2-(2'-Isopropyl-5'-methylphenoxy)acetyl($N_4$-nitro)arginine methyl ester (**5**)*

Brown solid, m.p. 125-127 ºC, $[\alpha]_D$ +14.6˚, yield 68%. $^1$H NMR ($CDCl_3$, 300 MHz) δ: 7.22-7.19 (1H, d, J = 6.8 Hz, *m*-H of phenoxy ring), 7.15 (1H, br s, -NH), 6.66 (4H, s, *o*-H of phenoxy ring and imino protons of guanidino group), 6.46-6.44 (1H, d, J = 6.7 Hz, *p*-H of phenoxy ring), 4.45 (2H, s, -$OCH_2CO$-), 4.35-4.24 (1H, m, α-H of $N_4$-nitro(Arg)), 3.87-3.83 (2H, t, J = 8.0 Hz, δ-protons of $N_4$-nitro(Arg)), 3.65 (3H, s, $OCH_3$), 3.10-2.96 (1H, m, *o*-(α-H) of phenoxy ring), 1.99 (3H, s, *m*-$CH_3$ of phenoxy ring), 1.96-1.60 (4H, m, β- and γ-protons of $N_4$-nitro(Arg)), 1.09-1.07 (6H, d, J = 6.9 Hz, *o*-(α-$CH_3$) of phenoxy ring) ppm. Mass: m/z (relative intensity) 15 (1.1), 29 (8.7), 31 (7.8), 39 (8.9), 41 (11.7), 43 (10.4), 51 (24.2), 59 (14.8), 77 (35.4), 88 (1.9), 103 (11.2), 149 (2.8), 163 (100), 191 (4.9), 320 (5.3), 335 (5.7), 364 (15.3), 392 (23.5), 423 ($M^+$, 8.4), 424 ($M^+$+1, 0.8). Anal. calcd. for $C_{19}H_{29}N_5O_6$: C, 53.89; H, 6.90; N, 16.54. Found: C, 53.74; H, 7.14; N, 16.55.

*2-(2'-Isopropyl-5'-methylphenoxy)acetyltryptophan methyl ester (**6**)*

Light brown solid, m.p. 130 ºC, $[\alpha]_D$ -61.5˚, yield 72%. $^1$H NMR (CDCl3, 300 MHz) δ: 8.95 (1H, s, α-NH of Try), 7.52 (1H, s, β-H of Try), 7.22-7.19 (1H, d, J = 6.8 Hz, *m*-H of phenoxy ring), 7.17-7.01 (4H, m, δ-, ε-, ζ-, η-protons of Try), 6.67 (1H, s, *o*-H of phenoxy ring), 6.50-6.48 (1H, d, J = 6.8 Hz, *p*-H of phenoxy ring), 6.31 (1H, br s, -NH), 4.98-4.91 (1H, m, γ-(β'-H) of Try), 4.44 (2H, s, -$OCH_2CO$-), 3.58 (3H, s, $OCH_3$), 3.27-2.97 (3H, m, *o*-(α-H) of phenoxy ring and γ-(α'-$CH_2$) of Try), 1.99 (3H, s, *m*-$CH_3$ of phenoxy ring), 1.10-1.08 (6H, d, J = 6.9 Hz, *o*-(α-$CH_3$) of phenoxy ring) ppm. $^{13}$C NMR ($CDCl_3$, 300 MHz) δ: 176.3 (s, C=O, amide), 170.5 (s, C=O, ester), 156.2 (s, C1, phenoxy ring), 138.1 (s, C5, phenoxy ring), 136.3 (s, C2, phenoxy ring), 136.0 (s, C8, Try), 127.5 (s, C3, Try), 122.8 (s, C1, Try), 122.2 (s, C4, phenoxy ring), 121.9 (s, C6, Try), 119.5 (s, C5, Try), 118.4 (s, C3, phenoxy ring), 118.2 (s, C4, Try), 114.6 (s, C2, Try), 113.6 (s, C6, phenoxy ring), 111.4 (s, C7, Try), 68.5 (s, -$OCH_2$-), 53.0 (s, α-C, Try), 50.3 (s, -$OCH_3$, ester), 27.4 (s, 2-(α-C), phenoxy ring), 23.1 (s, 2-(β-2C), phenoxy ring), 21.4 (s,

5-($CH_3$), phenoxy ring), 18.8 (s, β-C, Try) ppm. Anal. calcd. for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.34; H, 7.16; N, 6.84.

*2-(2'-Isopropyl-5'-methylphenoxy)acetylglycylglycine methyl ester (**7**)*

Light brown solid, m.p. 170-172 ºC, $[\alpha]_D$ -116˚, yield 81%. $^1$H NMR ($CDCl_3$, 300 MHz) δ: 8.84 (1H, br s, -NH), 8.63 (1H, br s, -NH), 7.21-7.18 (1H, d, J = 6.8 Hz, *m*-H of phenoxy ring), 6.70 (1H, s, *o*-H of phenoxy ring), 6.46-6.44 (1H, d, J = 6.7 Hz, *p*-H of phenoxy ring), 4.59 (2H, s, -$OCH_2CO$-), 4.04-4.02 (2H, d, J = 4.8 Hz, $CH_2$ of Gly$^2$), 3.92-3.90 (2H, d, J = 4.7 Hz, $CH_2$ of Gly$^1$), 3.52 (3H, s, $OCH_3$), 3.10-2.97 (1H, m, *o*-(α-H) of phenoxy ring), 1.98 (3H, s, *m*-$CH_3$ of phenoxy ring), 1.12-1.10 (6H, d, J = 6.9 Hz, *o*-(α-$CH_3$) of phenoxy ring). $^{13}$C NMR ($CDCl_3$, 300 MHz) δ: 172.8 (s, C=O, amide), 169.6 (s, C=O, ester), 165.6 (s, C=O, amide), 156.9 (s, C1, phenoxy ring), 140.5 (s, C5, phenoxy ring), 134.3 (s, C2, phenoxy ring), 122.2 (s, C4, phenoxy ring), 118.6 (s, C3, phenoxy ring), 115.6 (s, C6, phenoxy ring), 68.3 (s, -OCH2-), 52.4 (s, -$OCH_3$, ester), 40.3 (s, $CH_2$, Gly$^2$), 39.6 (s, $CH_2$, Gly$^1$), 27.3 (s, 2-(α-C), phenoxy ring), 22.9 (s, 2-(β-2C), phenoxy ring), 21.4 (s, 5-($CH_3$), phenoxy ring) ppm. Anal. calcd. for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.45; H, 7.35; N, 8.32.

*2-(2'-Isopropyl-5'-methylphenoxy)acetylprolylproline methyl ester (**8**)*

Brown solid, m.p. 205 ºC, $[\alpha]_D$ +123˚, yield 89%. $^1$H NMR ($CDCl_3$, 300 MHz) δ: 7.22-7.19 (1H, d, J = 6.9 Hz, *m*-H of phenoxy ring), 6.66 (1H, s, *o*-H of phenoxy ring), 6.48-6.46 (1H, d, J = 6.8 Hz, *p*-H of phenoxy ring), 4.57 (2H, s, -$OCH_2CO$-), 4.32-4.20 (2H, m, α-protons of Pro$^1$ and Pro$^2$), 3.75-3.70 (2H, t, J = 6.1 Hz, δ-protons of Pro$^2$), 3.59 (3H, s, $OCH_3$), 3.50-3.45 (2H, t, J = 6.0 Hz, δ-protons of Pro$^1$), 3.15-3.01 (1H, m, *o*-(α-H) of phenoxy ring), 2.70-2.64 (2H, q, β-protons of Pro$^1$), 2.10-1.86 (6H, m, β-protons of Pro$^2$ and γ-protons of Pro$^1$ and Pro$^2$), 1.99 (3H, s, *m*-$CH_3$ of phenoxy ring), 1.10-1.08 (6H, d, J = 6.9 Hz, *o*-(α-$CH_3$) of phenoxy ring). Mass: m/z (relative intensity) 15 (1.5), 29 (9.2), 31(8.8), 39 (8.9), 41 (12.3), 43 (11.2), 51 (29.3), 59 (13.7), 77 (37.3), 149 (3.4), 163 (100), 191 (4.6), 261 (15.2), 288 (7.7), 358 (17.8), 387 (6.1), 416 ($M^+$, 7.2), 417 ($M^+$+1, 0.4). Anal. calcd. for $C_{23}H_{32}N_2O_5$: C, 66.32; H, 7.74; N, 6.73. Found: C, 68.09; H, 8.01; N, 6.85.

*2-(2'-Isopropyl-5'-methylphenoxy)acetylalanylleucine methyl ester (**9**)*

Light brown crystals, m.p. 166-167 ºC, $[\alpha]_D$ -92.4˚, yield 68%. IR (KBr) cm$^{-1}$: 3145 (m, -NH str, amide), 3066, 3045 (w, -CH str, arom. ring), 2994, 2990 (m, -CH str, -CH), 2959, 2929 (m, -CH str, asym, $CH_3$ and $CH_2$), 2872, 2853 (m, -CH str, sym, $CH_3$ and $CH_2$), 2815 (m, -CH str, $OCH_3$), 1748 (s, -C=O str, ester), 1642, 1635 (s, -C=O str, 2˚ amide), 1605, 1493 (m, skeletal bands, arom. ring), 1538 (m, -NH bend, 2˚ amide), 1388, 1367 (s, -CH bend, isopropyl group), 1285 (s, C–O str, ester), 1269 (s, C–O–C str, asym), 1022 (s, C–O–C str, sym), 922 (w, $CH_3$ rocking, isopropyl group), 898, 803 (s, -CH bend, out-of-plane, arom. ring), 495, 486 (w, C–C bend, aliphatic). $^1$H NMR ($CDCl_3$, 300 MHz) δ: 7.92 (1H, br s, -NH), 7.25-7.22 (1H, d, J = 6.8 Hz, *m*-H of phenoxy ring), 6.67 (1H, s, *o*-H of phenoxy ring), 6.46-6.44 (1H, d, J = 6.8 Hz, *p*-H of phenoxy ring), 5.82 (1H, br s, -NH), 4.60 (2H, s, -$OCH_2CO$-), 4.43-4.37 (1H, m, α-H of Ala), 3.61 (3H, s, $OCH_3$), 3.57-3.46 (1H, m, α-H of Leu), 3.09-2.95 (1H, m, *o*-(α-H) of phenoxy ring), 1.98 (3H, s, *m*-$CH_3$ of phenoxy ring), 1.50-1.47 (3H, d, J = 7.3 Hz, α-$CH_3$ of Ala), 1.46-1.25 (3H, m, β-($CH_2$) and γ-(CH) of Leu), 1.10-1.08 (6H, d, J = 6.9 Hz, *o*-(α-$CH_3$) of phenoxy ring), 0.94-0.92 (6H, d, J = 7.1 Hz, γ-$CH_3$ of Leu). Anal. calcd. for $C_{22}H_{34}N_2O_5$: C, 65.00; H, 8.43; N, 6.89. Found: C, 64.93; H, 8.56; N, 6.84.

*2-(2'-Isopropyl-5'-methylphenoxy)acetylphenylalanine (**10**)*

Light brown crystals, m.p. 154-155 ºC, $[\alpha]_D$ +9.0˚, yield 68%. IR (KBr) $cm^{-1}$: 3290-2498 (m/br, -OH str, -COOH), 3128 (m, -NH str, amide), 3072, 3054 (w, -CH str, arom. rings), 2967, 2925 (m, -CH str, asym, $CH_3$ and $CH_2$), 2872, 2857 (m, -CH str, sym, $CH_3$ and $CH_2$), 1720 (m, -C=O str, -COOH), 1640 (s, -C=O str, 2˚ amide), 1590, 1484 (m, skeletal bands, arom. rings), 1528 (m, -NH bend, 2˚ amide), 1462 (m, -CH bend (scissoring), $CH_2$), 1402 (m, C-O-H bend, -COOH), 1382, 1371 (s, -CH bend, isopropyl group), 1241 (s, C–O–C str, asym), 1152, 1125 (s, -CH bend, in plane, arom. rings), 1035 (s, C–O–C str, sym), 908, 812 (s, -CH bend, out-of-plane, tri substi. ring), 724, 689 (s, -CH bend, out-of-plane, mono substi. ring). $^1$H NMR ($CDCl_3$, 300 MHz) δ: 12.05 (1H, s, -COOH), 7.23-7.20 (1H, d, J = 6.8 Hz, *m*-H of phenoxy ring), 7.10-6.92 (5H, m, *o*-, *m*- and *p*-protons of Phe), 6.70 (1H, s, *o*-H of phenoxy ring), 6.55 (1H, br s, -NH), 6.50-6.45 (1H, d, J = 6.9 Hz, *p*-H of phenoxy ring), 4.90-4.83 (1H, m, α-H of Phe), 4.45 (2H, s, -$OCH_2CO$-), 3.10-2.83 (3H, m, *o*-(α-H) of phenoxy ring and β-protons of Phe), 2.01 (3H, s, *m*-$CH_3$ of phenoxy ring), 1.11-1.09 (6H, d, J = 6.9 Hz, *o*-(α-$CH_3$) of phenoxy ring). Anal. calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.93; H, 7.16; N, 3.83.

*2-(2'-Isopropyl-5'-methylphenoxy)acetylvaline (**11**)*

Brown solid, m.p. 110-112 ºC, $[\alpha]_D$ -2.7˚, yield 77%. IR (KBr) $cm^{-1}$: 3303-2519 (m/br, -OH str, -COOH), 3140 (m, -NH str, amide), 3067 (w, -CH str, arom. ring), 2997, 2992 (m, -CH str, -CH), 2963, 2924 (m, -CH str, asym, $CH_3$ and $CH_2$), 2872 (m, -CH str, sym, $CH_3$), 1719 (m, -C=O str, -COOH), 1640 (s, -C=O str, 2˚ amide), 1594, 1490 (m, skeletal bands, arom. ring), 1530 (m, -NH bend, 2˚ amide), 1402 (m, C-O-H bend, -COOH), 1382, 1360 (s, -CH bend, isopropyl group), 1259 (s, C–O–C str, asym), 922 (w, -CH bend (rocking), isopropyl group), 898, 803 (s, -CH bend, out-of-plane, tri substi. ring), 488 (w, C–C bend, aliphatic). $^1$H NMR ($CDCl_3$, 300 MHz) δ: 11.09 (1H, s, -COOH), 7.49 (1H, br s, -NH), 7.21-7.18 (1H, d, J = 6.8 Hz, *m*-H of phenoxy ring), 7.01 (1H, s, *o*-H of phenoxy ring), 6.50-6.48 (1H, d, J = 6.8 Hz, *p*-H of phenoxy ring), 4.47 (2H, s, -$OCH_2CO$-), 4.33-4.28 (1H, t, J = 6.0 Hz, α-H of Val), 3.11-2.97 (1H, m, *o*-(α-H) of phenoxy ring), 2.35-2.23 (1H, m, β-H of Val), 2.01 (3H, s, m-$CH_3$ of phenoxy ring), 1.14-1.12 (6H, d, J = 6.9 Hz, *o*-(α-$CH_3$) of phenoxy ring), 0.90-0.88 (6H, d, J = 5.9 Hz, β-$CH_3$ of Val). Anal. calcd. for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56. Found: C, 66.34; H, 8.22; N, 4.52.

*2-(2'-Isopropyl-5'-methylphenoxy)acetylisoleucine (**12**)*

Light brown solid, m.p. 141-142 ºC, $[\alpha]_D$ -112˚, yield 80%. IR (KBr) $cm^{-1}$: 3300-2545 (m/br, -OH str, -COOH), 3152 (m, -NH str, amide), 3056 (w, -CH str, arom. ring), 2998 (m, -CH str, -CH), 2961, 2938 (m, -CH str, asym, $CH_3$ and $CH_2$), 2872, 2855 (m, -CH str, sym, $CH_3$ and $CH_2$), 1722 (m, -C=O str, -COOH), 1648 (s, -C=O str, 2˚ amide), 1599, 1482 (m, skeletal bands, arom. ring), 1540 (m, -NH bend, 2˚ amide), 1469 (m, -CH bend (scissoring), $CH_2$), 1450 (m, -CH bend, $CH_3$), 1402 (m, C-O-H bend, -COOH), 1380, 1361 (s, -CH bend, isopropyl group), 1262 (s, C–O–C str, asym), 899, 808 (s, -CH bend, out-of-plane, tri substi. ring), 496, 490 (w, C–C bend, aliphatic). $^1$H NMR ($CDCl_3$, 300 MHz) δ: 12.50 (1H, s, -COOH), 7.21-7.18 (1H, d, J = 6.7 Hz, *m*-H of phenoxy ring), 6.71 (1H, s, *o*-H of phenoxy ring), 6.59 (1H, br s, -NH), 6.48-6.46 (1H, d, J = 6.8 Hz, *p*-H of phenoxy ring), 4.42 (2H, s, -$OCH_2CO$-), 4.18-4.13 (1H, t, J = 8.2 Hz, α-H of Ile), 3.11-2.96 (1H, m, *o*-(α-H) of phenoxy ring), 2.18-2.05 (1H, m, β-H of Ile), 1.97 (3H, s, *m*-$CH_3$ of phenoxy ring), 1.69-1.34 (2H, m, γ-protons of Ile), 1.11-1.09 (6H, d, J =

6.9 Hz, o-(α-$CH_3$) of phenoxy ring), 0.95-0.89 (6H, m, β-$CH_3$ and δ-protons of Ile). Anal. calcd. for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.23; H, 8.44; N, 4.48.

*2-(2'-Isopropyl-5'-methylphenoxy)acetyl($N_4$-nitro)arginine (**13**)*

Brown crystals, m.p. 181-183 ºC, $[\alpha]_D$ +77.7˚, yield 79%. $^1$H NMR ($CDCl_3$, 300 MHz) δ: 8.05 (4H, s, imino protons of guanidino group and -COOH), 7.44 (1H, br s, -NH), 7.21-7.18 (1H, d, J = 6.8 Hz, m-H of phenoxy ring), 6.69 (1H, m, *o*-H of phenoxy ring), 6.48-6.46 (1H, d, J = 6.9 Hz, *p*-H of phenoxy ring), 4.59-4.54 (1H, m, α-H of $N_4$-nitro(Arg)), 4.41 (2H, s, -$OCH_2$CO-), 3.84-3.80 (2H, t, J = 8.1 Hz, δ-protons of $N_4$-nitro(Arg)), 3.11-2.97 (1H, m, *o*-(α-H) of phenoxy ring), 2.11-1.78 (2H, m, β-protons of $N_4$-nitro(Arg)), 1.99 (3H, s, *m*-CH3 of phenoxy ring), 1.63-1.54 (γ-protons of $N_4$-nitro(Arg)), 1.10-1.08 (6H, d, J = 6.9 Hz, *o*-(α-$CH_3$) of phenoxy ring). $^{13}$C NMR ($CDCl_3$, 300 MHz) δ: 180.2 (s, C=O, acid), 170.0 (s, C=O, amide), 159.6 (s, C=NH, guanidino group), 156.9 (s, C1, phenoxy ring), 138.1 (s, C5, phenoxy ring), 137.3 (s, C2, phenoxy ring), 123.2 (s, C4, phenoxy ring), 119.4 (s, C3, phenoxy ring), 115.3 (s, $C_6$, phenoxy ring), 66.5 (s, -$OCH_2$-), 52.3 (s, α-C, $N_4$-nitro(Arg)), 39.3 (s, δ-C, $N_4$-nitro(Arg)), 27.7 (s, β-C, $N_4$-nitro(Arg)), 27.3 (s, 2-(α-C), phenoxy ring), 24.1 (s, γ-C, $N_4$-nitro(Arg)), 23.5 (s, 2-(β-2C), phenoxy ring), 21.4 (s, 5-($CH_3$), phenoxy ring). Anal. calcd. for $C_{18}H_{27}N_5O_6$: C, 52.80; H, 6.65; N, 17.10. Found: C, 52.74; H, 6.63; N, 17.14.

*2-(2'-Isopropyl-5'-methylphenoxy)acetyltryptophan (**14**)*

Light brown solid, m.p. 197-198 ºC, $[\alpha]_D$ -74.3˚, yield 72%. $^1$H NMR ($CDCl_3$, 300 MHz) δ: 10.50 (1H, s, -COOH), 10.47 (1H, s, α-NH of Try), 7.58 (1H, s, β-H of Try), 7.25-7.18 (3H, m, *m*-H of phenoxy ring and ε-, η-protons of Try), 7.10-7.04 (1H, t, ζ-H of Try), 6.98-6.96 (1H, d, J = 8.4 Hz, δ-H of Try), 6.68 (1H, s, *o*-H of phenoxy ring), 6.50-6.48 (1H, d, J = 6.8 Hz, *p*-H of phenoxy ring), 6.42 (1H, br s, -NH), 5.18-5.11 (1H, m, γ-(β'-H) of Try), 4.42 (2H, s, -$OCH_2$CO-), 3.35-2.97 (3H, m, *o*-(α-H) of phenoxy ring and γ-(α'-$CH_2$) of Try), 2.00 (3H, s, *m*-$CH_3$ of phenoxy ring), 1.10-1.08 (6H, d, J = 6.9 Hz, *o*-(α-$CH_3$) of phenoxy ring) ppm. Mass: m/z (relative intensity) 15 (0.8), 29 (9.9), 39 (9.7), 41 (12.6), 43 (9.8), 45 (1.8), 51 (32.4), 77 (37.9), 117 (3.7), 130 (45.8), 149 (3.5), 163 (100), 191 (5.3), 219 (2.3), 278 (6.4), 349 (8.3), 381 (15.5), 394 ($M^+$, 5.7), 395 ($M^+$+1, 0.4). Anal. calcd. for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 70.07; H, 6.68; N, 7.04.

*2-(2'-Isopropyl-5'-methylphenoxy)acetylglycylglycine (**15**)*

Brown crystals, m.p. 118 ºC, $[\alpha]_D$ -40.8˚, yield 70%. $^1$H NMR ($CDCl_3$, 300 MHz) δ: 11.61 (1H, s, -COOH), 8.83 (1H, br s, -NH), 8.14 (1H, br s, -NH), 7.21-7.18 (1H, d, J = 6.8 Hz, *m*-H of phenoxy ring), 6.69 (1H, s, *o*-H of phenoxy ring), 6.48-6.46 (1H, d, J = 6.8 Hz, *p*-H of phenoxy ring), 4.60 (2H, s, -$OCH_2$CO-), 4.19-4.17 (2H, d, J = 4.7 Hz, $CH_2$ of $Gly^2$), 3.94-3.93 (2H, d, J = 4.8 Hz, $CH_2$ of $Gly^1$), 3.11-2.97 (1H, m, *o*-(α-H) of phenoxy ring), 1.99 (3H, s, *m*-$CH_3$ of phenoxy ring), 1.12-1.10 (6H, d, J = 6.9 Hz, *o*-(α-$CH_3$) of phenoxy ring). Anal. calcd. for $C_{16}H_{22}N_2O_5$: C, 59.62; H, 6.88; N, 8.69. Found: C, 59.61; H, 6.84; N, 8.63.

*2-(2'-Isopropyl-5'-methylphenoxy)acetylprolylproline (**16**)*

Light brown solid, m.p. 165-166 ºC, $[\alpha]_D$ +117˚, yield 72%. IR (KBr) $cm^{-1}$: 3315-2530 (m/br, -OH str, -COOH), 3065 (w, -CH str, arom. ring), 2963 (m, -CH str, asym, $CH_3$), 2930, 2926, 2918 (m, -CH str, asym, cyclic $CH_2$), 2871 (m, -CH str, sym, $CH_3$), 2859, 2852 (m, -CH str,

sym, $CH_2$), 1710 (m, -C=O str, -COOH), 1675, 1664 (s, -C=O str, 3° amide), 1608, 1503 (m, skeletal bands, arom. ring), 1455, 1459 (m, -CH bend (scissoring), cyclic $CH_2$), 1423 (m, C-O-H bend, -COOH), 1384, 1368 (s, -CH bend, isopropyl group), 1270 (s, C–O–C str, asym), 1115, 1106 (s, -CH bend, in plane, arom. ring), 1062 (s, C–O–C str, sym), 894, 802 (s, -CH bend, out-of-plane, tri substi. ring). $^1$H NMR (CDCl3, 300 MHz) δ: 10.49 (1H, s, -COOH), 7.22-7.19 (1H, d, J = 6.7 Hz, *m*-H of phenoxy ring), 6.70 (1H, s, *o*-H of phenoxy ring), 6.46-6.44 (1H, d, J = 6.8 Hz, *p*-H of phenoxy ring), 4.59 (2H, s, -$OCH_2CO$-), 4.48-4.37 (1H, t, J = 5.9 Hz, α-protons of Pro$^2$), 4.10-4.08 (1H, t, J = 6.0 Hz, α-protons of Pro$^1$), 3.74-3.69 (2H, t, J = 6.2 Hz, δ-protons of Pro$^2$), 3.50-3.45 (2H, t, J = 6.1 Hz, δ-protons of Pro$^1$), 3.11-2.97 (1H, m, *o*-(α-H) of phenoxy ring), 2.70-2.64 (2H, q, β-protons of Pro$^1$), 2.08-1.89 (9H, m, β-protons of Pro$^2$, γ-protons of Pro$^1$ and Pro$^2$, *m*-$CH_3$ of phenoxy ring), 1.11-1.09 (6H, d, J = 6.9 Hz, *o*-(α-$CH_3$) of phenoxy ring) ppm. Anal. calcd. for $C_{22}H_{30}N_2O_5$: C, 65.65; H, 7.51; N, 6.96. Found: C, 65.63; H, 7.56; N, 6.93.

*2-(2'-Isopropyl-5'-methylphenoxy)acetylalanylleucine (**17**)*

Light brown crystals, m.p. 135-136 ºC, $[\alpha]_D$ -38.2°, yield 72%. IR (KBr) cm$^{-1}$: 3290-2500 (m/br, -OH str, -COOH), 3150 (m, -NH str, amide), 3074, 3044 (w, -CH str, arom. ring), 2995, 2990 (m, -CH str, -CH), 2960, 2930 (m, -CH str, asym, $CH_3$ and $CH_2$), 2871, 2853 (m, -CH str, sym, $CH_3$ and $CH_2$), 1712 (m, -C=O str, -COOH), 1640, 1634 (s, -C=O str, 2° amide), 1601, 1498 (m, skeletal bands, arom. ring), 1534 (m, -NH bend, 2° amide), 1405 (m, C-O-H bend, -COOH), 1384, 1367 (s, -CH bend, isopropyl group), 1270 (s, C–O–C str, asym), 926 (w, $CH_3$ rocking, isopropyl group), 899, 801 (s, -CH bend, out-of-plane, arom. ring), 495, 485 (w, C–C bend, aliphatic). $^1$H NMR ($CDCl_3$, 300 MHz) δ: 12.52 (1H, s, -COOH), 7.94 (1H, br s, -NH), 7.23-7.20 (1H, d, J = 6.8 Hz, *m*-H of phenoxy ring), 6.69 (1H, s, *o*-H of phenoxy ring), 6.47-6.45 (1H, d, J = 6.7 Hz, *p*-H of phenoxy ring), 5.71 (1H, br s, -NH), 5.47-5.38 (1H, m, α-H of Ala), 4.58 (2H, s, -$OCH_2CO$-), 3.70-3.63 (1H, m, α-H of Leu), 3.12-2.98 (1H, m, *o*-(α-H) of phenoxy ring), 2.00 (3H, s, *m*-$CH_3$ of phenoxy ring), 1.97-1.83 (1H, m, γ-H of Leu), 1.59-1.28 (5H, m, α-$CH_3$ of Ala and β-$CH_2$ of Leu), 1.11-1.09 (6H, d, J = 6.9 Hz, *o*-(α-$CH_3$) of phenoxy ring), 0.96-0.94 (6H, d, J = 7.1 Hz, γ-$CH_3$ of Leu). Anal. calcd. for $C_{21}H_{32}N_2O_5$: C, 64.26; H, 8.22; N, 7.14. Found: C, 64.23; H, 8.21; N, 7.16.

## RESULTS AND DISCUSSION

Synthesis of all novel compounds was carried out successfully with good yields. DCC was found to be a good coupling agent both economically as well as quantitatively. FTIR spectra of synthesized compounds showed characteristic absorption bands of the -CO-NH- moiety and $^1$H NMR spectra were found to be in agreement with respective structures. MS spectra showed molecular ion ($M^+$) peak at m/z values which were in consistent with the molecular formulas. Almost all the synthesized compounds were found to exhibit moderate antibacterial and antifungal activity. The compounds (**2**), (**6**) and (**15**) were found to be more potent than standard drug Ciprofloxacin against bacteria *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Compounds (**13**), (**14**) and (**16**) were found to be more potent than standard drug Griseofulvin against pathogenic fungus *Candida albicans*. Comparison of antimicrobial data has suggested that amino acid methyl ester derivatives (**2-6**) are more potent than dipeptide ester derivatives (**7-9**). Furthermore, derivatives of amino acids and peptides (**10-17**) were found to be more potent antifungal agents than their corresponding methyl ester derivatives (**2-9**). On passing

toxicity tests, these derivatives may prove good candidate for clinical studies and can be new antibacterial and antifungal agents of tomorrow.

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