

## Synthesis and Biological Screening of a Novel Series of 3,4,5-Trisubstituted Phenoxyacetic Acid Analogs

Rajiv Dahiya and Ramninder Kaur

Department of Pharmaceutical Chemistry, Rajiv Academy for Pharmacy,  
Mathura-281 001 (UP), India.

**Abstract:** Present investigation describes the synthesis of a novel series of 3,4,5-trisubstituted phenoxy acetyl amino acids and peptides by coupling the 2-(4-chloro-3,5-dimethylphenoxy)acetic acid with different amino acid methyl ester hydrochlorides/peptide methyl esters using dicyclohexylcarbodiimide (DCC) as the coupling agent and N-methylmorpholine (NMM) as the base. The structures of peptide derivatives were elucidated by elemental analysis as well as FTIR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and mass spectral data. The newly synthesized compounds were also evaluated for their antibacterial, antifungal and anthelmintic potential. Compounds 6, 10 and 12 were found to possess potent anthelmintic activity against *M. konkanensis*, *P. corethruses* and *Eudrilus* sp. and compound 13 displayed better activity against pathogenic fungus *C. albicans*, in addition to potent antibacterial activity exhibited by compounds 8 and 10 against gram negative bacteria *P. aeruginosa*.

**Keywords:** phenoxy acetic acid; amino acids; peptides; antimicrobial activity; anthelmintic activity

### INTRODUCTION

Phenoxyacetic acid is among the most vital moieties which are associated with potent fungicidal activities. Aryloxyacetic acid derivatives possess a wide array of diverse bioactivities including antimycobacterial (Ali and Shaharyar, 2007; Shaharyar *et al.*, 2006), anti-inflammatory and antioxidant (Kunsch *et al.*, 2005), antibacterial (Iqbal *et al.*, 2007), analgesic (Sato *et al.*, 2002), antisickling (Abraham *et al.*, 1989), antilipaeamic and antiplatelet (Perez-Pasten *et al.*, 2006; Metz and Specker, 1980), nonprostanoid prostacyclin (PGI<sub>2</sub>) mimetics (Meanwell *et al.*, 1993), gastrin/cholecystokinin (CCK)-B receptor antagonistic activity (Takeda *et al.*, 1998), inhibitory activity of cathepsin K and aldose reductase (Shinozuka *et al.*, 2006; Van Zandt *et al.*, 2004), diuretic (Kitagawa *et al.*, 1991; Bicking *et al.*, 1976) and growth regulators (Osborne *et al.*, 1955). Further, the review of literature has suggested that incorporation of amino acids and peptides into the aromatic and heterocyclic congeners have resulted in analogs exhibiting potent pharmacological activities (Poojary *et al.*, 2003; Himaja *et al.*, 2003). Thus keeping in view the biological potency of phenoxy acetic acids as well as taking advantage of biodegradability and biocompatibility of peptides and further, in continuation of our work on synthesizing potent heterocyclic and other aromatic analogs of amino acids/peptides (Dahiya and Pathak, 2007; Dahiya *et al.*, 2006; Dahiya and Pathak 2006; Dahiya and Pathak 2006a), a novel series of 2-(4-chloro-3,5-dimethylphenoxy)acetic acid derivatives of amino acids and peptides was synthesized with an anticipation to get novel compounds with more therapeutic efficacy and fewer side effects.

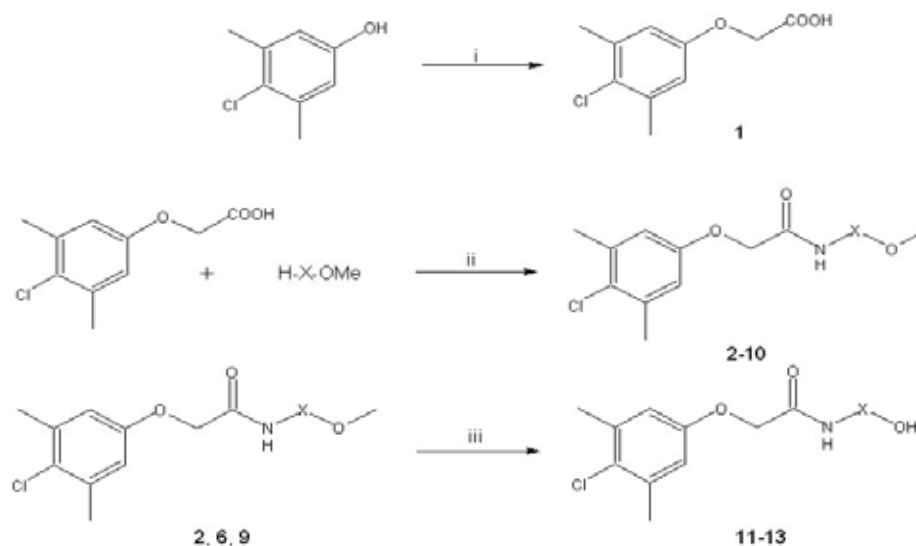
2-(4-Chloro-3,5-dimethylphenoxy)acetic acid 1 was prepared by phenoxylation of 4-chloro-3,5-dimethylphenol with monochloroacetic acid in presence of alkali. Dipeptides Boc-L-Pro-L-Phe-OMe, Boc-Gly-Gly-OMe, Boc-L-His-L-Leu-OMe were prepared by coupling of Boc-protected amino acids viz. Boc-L-Pro-OH, Boc-Gly-OH and Boc-L-His-OH with respective amino acid methyl ester hydrochlorides such as L-Phe-OMe.HCl, Gly-OMe.HCl and L-Leu-OMe.HCl using DCC and triethylamine (TEA) as the base. Similarly, tripeptides Boc-L-Try-L-nitro(Arg)-L-Try-OMe and Boc-L-Pro-L-Pro-L-Pro-OMe were prepared by coupling dipeptide methyl esters L-nitro(Arg)-L-Try-OMe and L-Pro-L-Pro-OMe with Boc-L-Try-OH and Boc-L-Pro-OH respectively.

Compound 1 was coupled with amino acid methyl ester hydrochlorides L-Tyr-OMe.HCl, L-Ile-OMe.HCl, L-Val-OMe.HCl, L-Try-OMe.HCl and deprotected di/tripeptides using DCC and NMM to yield novel 2-(4-chloro-3,5-dimethylphenoxy)acetyl amino acids/peptide methyl esters (2-10). Selected ester derivatives 2, 6 and 9 were further hydrolyzed using lithium hydroxide to get respective free acids 11-13 (Fig. 1).

**Corresponding Author:** Rajiv Dahiya, Assistant Professor, Department of Pharmaceutical Chemistry, Rajiv Academy for Pharmacy, NH#2, Delhi-Mathura Bypass Road, PO Chattikara, Mathura-281 001, Uttar Pradesh (UP), India.

Tel: 09897417450, 0565 6531680.

E-mail: rajivdahiya04@yahoo.co.in, rajivdahiya77@rediffmail.com



X = L-Tyr (**2**), L-Ile (**3**), L-Val (**4**), L-Try (**5**), L-Pro-L-Phe (**6**), Gly-Gly (**7**), L-His-L-Leu (**8**),  
 L-Try-L-nitro(Arg)-L-Try (**9**), L-Pro-L-Pro-L-Pro (**10**), L-Try (**11**), L-Pro-L-Phe (**12**),  
 L-Try-L-nitro(Arg)-L-Try (**13**)

i = ClCH<sub>2</sub>COOH, NaOH, reflux, 1 h

ii = DCC, NMM, RT, 24 h

iii = LiOH, THF:H<sub>2</sub>O (1:1), RT, 1 h

Fig. 1: Synthetic pathway for novel 3,4,5-trisubstituted phenoxyacetic acid analogs.

Structures of all the newly synthesized compounds 2-13 were confirmed by FTIR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and mass spectra. Elemental analysis of the novel compounds was performed for carbon, hydrogen and nitrogen content. Physical characterization data of the synthesized peptide derivatives is compiled in Table 1.

**Table 1:** Physical characterization of compounds 1-13.

Compd.	Mol. formula (Mol. wt.)	M.p. (°C)	Yield (%)	R <sub>f</sub> value <sup>#</sup>	[α] <sub>D</sub> Value*	% Analysis [calcd. (found)]		
						C	H	N
1	C <sub>10</sub> H <sub>11</sub> ClO <sub>3</sub> (214)	79-80	81	0.76	+11.8	55.96 (55.95)	5.17 (5.19)	-
2	C <sub>20</sub> H <sub>25</sub> ClNO <sub>5</sub> (391)	68-69	74	0.62	-73.9	61.30 (61.34)	5.66 (5.65)	3.57 (3.55)
3	C <sub>17</sub> H <sub>24</sub> ClNO <sub>4</sub> (341)	59-60	67	0.59	+104.3	59.73 (59.76)	7.08 (7.05)	4.10 (4.10)
4	C <sub>16</sub> H <sub>22</sub> ClNO <sub>4</sub> (327)	142-143	86	0.68	+37.9	58.63 (58.63)	6.76 (6.75)	4.27 (4.29)
5	C <sub>22</sub> H <sub>23</sub> ClN <sub>2</sub> O <sub>4</sub> (414)	175-177	72	0.52	-122.5	63.69 (63.65)	5.59 (5.62)	6.75 (6.78)
6	C <sub>25</sub> H <sub>29</sub> ClN <sub>2</sub> O <sub>5</sub> (472)	-	82	0.83	-43.7	63.49 (63.48)	6.18 (6.20)	5.92 (5.94)
7	C <sub>13</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>5</sub> (342)	102-103	80	0.86	+2.4	52.56 (52.59)	5.59 (5.62)	8.17 (8.15)
8	C <sub>23</sub> H <sub>31</sub> ClN <sub>4</sub> O <sub>5</sub> (478)	-	76	0.66	-113.2 <sup>2</sup>	57.68 (57.70)	6.52 (6.55)	11.70 (11.69)
9	C <sub>39</sub> H <sub>44</sub> ClN <sub>9</sub> O <sub>8</sub> (802)	197-198	84	0.55 <sup>1</sup>	-75.9	58.39 (58.38)	5.53 (5.55)	15.71 (15.74)
10	C <sub>26</sub> H <sub>34</sub> ClN <sub>5</sub> O <sub>6</sub> (520)	-	78	0.80 <sup>1</sup>	-5.7 <sup>2</sup>	60.05 (59.98)	6.59 (6.60)	8.08 (8.08)
11	C <sub>19</sub> H <sub>20</sub> ClNO <sub>5</sub> (377)	114-115	86	0.55	-52.3	60.40 (60.38)	5.34 (5.35)	3.71 (3.74)
12	C <sub>24</sub> H <sub>27</sub> ClN <sub>2</sub> O <sub>5</sub> (458)	-	74	0.65	-92.6	62.81 (62.80)	5.93 (5.95)	6.10 (6.12)
13	C <sub>38</sub> H <sub>42</sub> ClN <sub>9</sub> O <sub>8</sub> (788)	160-162	88	0.73 <sup>1</sup>	-23.2	57.90 (57.90)	5.37 (5.35)	15.99 (16.03)

<sup>#</sup>(CHCl<sub>3</sub>:MeOH / 8:2), <sup>1</sup>(CHCl<sub>3</sub>:MeOH / 9:1)

\* (c, 0.3 in MeOH), <sup>2</sup>(c, 1 in DMF)

All synthesized compounds were screened for their antimicrobial activity (Bauer *et al.*, 1966) against four bacterial strains *Bacillus subtilis* (MUMC 408), *Staphylococcus aureus* (MUMC 377), *Pseudomonas aeruginosa* (MUMC 266) and *Escherichia coli* (MUMC 106) and three fungal strains *Microsporium audouinii* (MUMC 545), *Trichophyton mentagrophytes* (MUMC 665) and *Candida albicans* (MUMC 29) at 12.5-6 mg mL<sup>-1</sup> concentration. MIC values of test compound were determined by tube dilution technique. The solvents DMF/DMSO were used as negative controls and ciprofloxacin/griseofulvin were used as standards. Anthelmintic activity studies were carried out against three different species of earthworms *Megascoplex konkanensis* (ICARBC 211), *Pontoscotex corethruses* (ICARBC 117) and *Eudrilus sp.* (ICARBC 042) at 2 mg mL<sup>-1</sup> concentration using tween 80 (0.5 %) in distilled water as control and mebendazole as reference compound (Garg and Atal, 1963). The results of biological activity studies are tabulated in Table 2 and 3.

**Table 2:** Antimicrobial activity data for compounds 2-13.

Compd.	Zone of inhibition (in mm)						
	<i>B. subtilis</i>	<i>E. coli</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>M. audouinii</i>	<i>T. mentagro.</i>	<i>C. albicans</i>
2	8	12	-	11	10	11	14
3	9	11	7	17	12	10	13
4	8	13	7	15	-	11	15
5	7	13	-	12	8	11	19
6	9	-	9	11	16	18	12
7	7	14	14	16	12	14	11
8	7	16	14	28	11	13	16
9	8	12	9	13	11	-	20
10	7	16	7	26	13	11	11
11	10	13	-	13	13	12	16
12	11	--	10	15	17	19	14
13	10	14	11	16	13	--	24
Ciprofloxacin	20	19	20	25	--	--	--
Griseofulvin	-	-	-	-	17	20	20

**Table 3:** Anthelmintic activity data for compounds 2-13.

Compd.	Earthworm species					
	<i>M. konkanensis</i>		<i>P. corethruses</i>		<i>Eudrilus sp.</i>	
	Mean paralyzing time (min)*	Mean death time (min)*	Mean paralyzing time (min)	Mean death time (min)	Mean paralyzing time (min)	Mean death time (min)
2	28.10 ± 0.22	39.11 ± 0.39	34.54 ± 0.21	46.56 ± 0.42	30.55 ± 0.43	48.30 ± 0.60
3	27.05 ± 0.58	37.50 ± 0.55	35.65 ± 0.42	47.22 ± 0.27	35.67 ± 0.52	49.55 ± 0.12
4	31.04 ± 0.29	41.45 ± 0.34	37.10 ± 0.38	47.40 ± 0.53	38.73 ± 0.40	54.04 ± 0.23
5	29.26 ± 0.11	40.29 ± 0.40	41.25 ± 0.52	52.18 ± 0.12	36.49 ± 0.32	51.09 ± 0.14
6	10.08 ± 0.22	16.28 ± 0.21	14.24 ± 0.60	20.44 ± 0.32	13.30 ± 0.52	23.59 ± 0.60
7	15.21 ± 0.41	23.55 ± 0.31	19.22 ± 0.22	31.07 ± 0.42	17.50 ± 0.41	27.50 ± 0.55
8	16.11 ± 0.52	25.09 ± 0.22	19.58 ± 0.42	33.22 ± 0.50	17.22 ± 0.39	25.42 ± 0.37
9	20.24 ± 0.29	30.22 ± 0.12	26.61 ± 0.11	34.30 ± 0.20	23.60 ± 0.21	35.24 ± 0.25
10	13.58 ± 0.24	22.51 ± 0.29	17.44 ± 0.49	30.02 ± 0.11	13.44 ± 0.59	24.11 ± 0.28
11	25.18 ± 0.27	35.46 ± 0.28	33.04 ± 0.29	45.20 ± 0.28	29.02 ± 0.36	44.32 ± 0.49
12	09.13 ± 0.32	14.22 ± 0.46	12.41 ± 0.28	19.05 ± 0.32	13.08 ± 0.56	23.45 ± 0.40
13	19.33 ± 0.21	28.43 ± 0.80	23.33 ± 0.33	32.02 ± 0.17	20.52 ± 0.35	33.45 ± 0.18
Control	-	-	-	-	-	-
Mebendazole	13.55 ± 0.64	22.58 ± 0.53	17.52 ± 0.83	29.54 ± 0.20	13.42 ± 0.45	24.05 ± 0.32

\* Data are given as mean ± S.D. (n = 3)

## MATERIALS AND METHODS

All the coupling reactions requiring anhydrous conditions were conducted in flame dried apparatus. Melting points were determined by open capillary method and are uncorrected. Amino acids, di-tert-butylpyrocarbonate (Boc<sub>2</sub>O), DCC, TFA, TEA and NMM 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/CHCl<sub>3</sub> as solvent for the synthesized compounds. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on Bruker AC NMR spectrometer (300 MHz) using CDCl<sub>3</sub> 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. Purity of all the compounds was checked by TLC on precoated silica gel G plates.

**Preparation of Boc-di/tripeptide Methyl Esters:**

L-amino acid methyl ester hydrochloride / dipeptide methyl ester (10 mmol) was coupled with Boc-L-amino acid (10 mmol) using DCC (10 mmol) as coupling agent and TEA (21 mmol) as base according to the Bodanzsky and Bodanzsky procedure with certain modifications (Dahiya, 2007) to get Boc-protected di/tripeptide methyl esters which were deprotected at amino terminal using TFA (Dahiya, 2007a) prior to coupling with compound 1.

**tert-Butyloxycarbonyl-L-tryptophanyl-L-nitro(arginyl)-L-tryptophan Methyl Ester:**

Semisolid mass; Yield 79 %;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz): d 176.2, 174.9, 172.7 (3C, -C=O, try-1, try-2 and arg), 161.7 (C=NH, arg), 156.0 (-C=O, boc), 139.3, 137.1 (2C, C- $\beta'$ , indole-1 and indole-2), 129.1, 128.4 (2C, C- $\gamma'$ , indole-2 and indole-1), 125.5, 123.2 (2C, C- $\beta$ , indole-2 and indole-1), 122.1 (C- $\zeta$ , indole-2), 121.5, 121.0, 120.4 (3C, C- $\varepsilon$ , C- $\delta$  and C- $\zeta$ , indole-1), 119.8, 117.2 (2C, C- $\varepsilon$  and C- $\delta$ , indole-2), 113.0, 112.3 (2C, C- $\eta$ , indole-1 and indole-2), 110.2, 107.8 (2C, C- $\gamma$ , indole-2 and indole-1), 79.8 (C- $\alpha$ , boc), 67.3, 54.5 (2C, C- $\alpha$ , indole-1 and indole-2), 51.1 ( $\text{OCH}_3$ ), 46.7 (C- $\alpha$ , arg), 38.8 (C- $\delta$ , arg), 30.1 (C- $\beta$ , indole-1), 28.9 (3C, C- $\beta$ , boc), 27.6 (C- $\beta$ , arg), 26.4 (C- $\beta$ , indole-2), 21.1 (C- $\gamma$ , arg) ppm; Anal. Calcd. for  $\text{C}_{34}\text{H}_{43}\text{N}_9\text{O}_8$  (705): C, 57.86; H, 6.14; N, 17.86. Found: C, 57.90; H, 6.15; N, 17.88 %.

**L-Tryptophanyl-L-nitro(arginyl)-L-tryptophan Methyl Ester:**

Semisolid mass; Yield 71 %;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz): d 175.4, 173.6, 169.6 (3C, -C=O, arg, try-2 and try-1), 160.5 (C=NH, arg), 138.9, 137.6 (2C, C- $\beta'$ , indole-2 and indole-1), 129.7, 128.5 (2C, C- $\gamma'$ , indole-2 and indole-1), 125.1, 123.0 (2C, C- $\beta$ , indole-2 and indole-1), 123.2, 121.6 (2C, C- $\zeta$ , indole-2 and indole-1), 119.9 (C- $\varepsilon$ , indole-2), 120.7, 119.0 (2C, C- $\delta$  and C- $\zeta$ , indole-1), 117.1 (C- $\delta$ , indole-2), 111.9, 111.1 (2C, C- $\eta$ , indole-1 and indole-2), 109.1, 107.5 (2C, C- $\gamma$ , indole-2 and indole-1), 59.8, 55.3 (2C, C- $\alpha$ , indole-1 and indole-2), 52.3 (C- $\alpha$ , arg), 51.6 ( $\text{OCH}_3$ ), 38.6 (C- $\delta$ , arg), 31.3 (C- $\beta$ , indole-1), 27.2 (C- $\beta$ , arg), 26.5 (C- $\beta$ , indole-2), 23.0 (C- $\gamma$ , arg) ppm; Anal. Calcd. for  $\text{C}_{29}\text{H}_{35}\text{N}_9\text{O}_6$  (605): C, 57.51; H, 5.82; N, 20.81. Found: C, 57.50; H, 5.79; N, 20.84 %.

**tert-Butyloxycarbonyl-L-prolyl-L-prolyl-L-proline Methyl Ester:**

Semisolid mass; Yield 81 %;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz): d 4.38-4.35 (1H, t, H- $\alpha$ , pro-2), 4.27-4.24 (1H, t, H- $\alpha$ , pro-3), 4.19-4.16 (1H, t, H- $\alpha$ , pro-1), 3.75-3.72 (2H, t, H- $\delta$ , pro-3), 3.64 (3H, s, - $\text{OCH}_3$ , ester), 3.54-3.51 (2H, t, H- $\delta$ , pro-2), 3.25-3.22 (2H, t, H- $\delta$ , pro-1), 2.72-2.67 (2H, q, H- $\beta$ , pro-2), 2.59-2.54 (2H, q, H- $\beta$ , pro-1), 2.09-2.05 (2H, q, H- $\beta$ , pro-3), 1.99-1.83 (6H, m, H- $\gamma$ , pro-1, pro-2 and pro-3), 1.52 (9H, s, butyl-*t*) ppm; Anal. Calcd. for  $\text{C}_{21}\text{H}_{33}\text{N}_3\text{O}_6$  (423): C, 59.56; H, 7.85; N, 9.92. Found: C, 59.60; H, 7.87; N, 9.89 %.

**L-Prolyl-L-prolyl-L-proline Methyl Ester:**

Semisolid mass; Yield 77 %;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz): d 6.82 (1H, br. s, -NH, pro-1), 4.30-4.23 (2H, m, H- $\alpha$ , pro-2 and pro-3), 3.77-3.73 (2H, t, H- $\delta$ , pro-3), 3.65 (3H, s, - $\text{OCH}_3$ , ester), 3.61-3.58 (1H, t, H- $\alpha$ , pro-1), 3.45-3.41 (2H, t, H- $\delta$ , pro-2), 2.80-2.76 (2H, t, H- $\delta$ , pro-1), 2.73-2.69 (2H, q, H- $\beta$ , pro-2), 2.05-1.98 (4H, m, H- $\beta$  and H- $\gamma$ , pro-3), 1.95-1.90 (2H, m, H- $\gamma$ , pro-2), 1.89-1.85 (2H, q, H- $\beta$ , pro-1), 1.78-1.73 (2H, m, H- $\gamma$ , pro-1) ppm; Anal. Calcd. for  $\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}_4$  (323): C, 59.43; H, 7.79; N, 12.99. Found: C, 59.45; H, 7.77; N, 13.00 %.

**Preparation of 2-(4-Chloro-3,5-dimethylphenoxy)acetic Acid (1):**

Sodium hydroxide (0.9 g, 22.4 mmol) was dissolved in water (25 mL) and the alkaline solution was slowly added to another solution of 4-chloro-3,5-dimethylphenol (1.57 g, 10 mmol) and chloroacetic acid (0.94 g, 10 mmol) in water (25 mL) with stirring. The reaction mixture was heated to remove all the liquid and the residue was treated with water (30 mL). The mixture was cooled, filtered and acidified with dilute HCl. The aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $2 \times 25$  mL) and combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The crude product was crystallized from equimolar mixture of  $\text{EtOH-H}_2\text{O}$ .

1 :  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz): d 7.05 (1H, s, -COOH), 6.88 (2H, s, H-*o*, phenoxy ring (pnr)), 4.58 (2H, s,  $\text{CH}_2$ , acetyl), 2.12 (6H, s,  $\text{CH}_3$ -*m*, pnr) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz): d 173.2 (-C=O, -COOH), 155.6 (C-1, pnr), 137.5 (2C, C-3 and C-5, pnr), 125.9 (C-4, pnr), 116.4 (2C, C-2 and C-6, pnr), 69.1 ( $\text{CH}_2$ , acetyl), 18.2 (2C, 3- $\text{CH}_3$  and 4- $\text{CH}_3$ , pnr) ppm.

**Preparation of 2-(4-Chloro-3,5-dimethylphenoxy)acetyl Amino Acid and Peptide Methyl Esters:**

Compound 1 (2.14 g, 10 mmol) was dissolved in  $\text{CHCl}_3$  (25 mL) and added to a mixture of L-amino acid methyl ester hydrochloride/deprotected dipeptide/tripeptide methyl ester (10 mmol) in  $\text{CHCl}_3$  (25 mL) to which NMM (2.3 mL, 21 mmol) was previously added at 0 °C with stirring. To the above mixture, DCC (2.1 g, 10

mmol) was added and stirring was done for 24 h. The reaction mixture was filtered and filtrate was washed with 5 % NaHCO<sub>3</sub> and saturated NaCl solutions (25 mL each). Organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> followed by evaporation in vacuum. Crude product was crystallized from a mixture of chloroform and light petroleum ether (b.p. 40-60 °C) followed by cooling at 0 °C. Compounds 2, 6 and 9 were further subjected to alkaline hydrolysis using LiOH (Dahiya, 2007a) to get corresponding acid derivatives 11-13.

**2-(4-Chloro-3,5-dimethylphenoxy)acetyl-tyrosine Methyl Ester (2):**

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): d 7.23 (1H, br. s, -NH, tyr), 6.89-6.76 (4H, m, H-*m* and H-*o*, tyr), 6.65 (2H, s, H-*o*, pnr), 5.98 (1H, br. s, -OH, tyr), 4.72 (2H, s, CH<sub>2</sub>, acetyl), 4.65-4.61 (1H, q, H- $\alpha$ , tyr), 3.55 (3H, s, -OCH<sub>3</sub>, ester), 2.98-2.96 (2H, d, *J* = 5.5 Hz, H-*b*, tyr), 2.15 (6H, s, CH<sub>3</sub>-*m*, pnr) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 300 MHz): d 173.2 (C=O, acetyl), 170.5 (-C=O, tyr), 160.8 (C-1, pnr), 154.4 (C-*p*, tyr), 136.9 (2C, C-3 and C-5, pnr), 134.6, 129.7 (4C, C-*m* and C-*o*, tyr), 125.1 (C-4, pnr), 123.5 (C-*g*, tyr), 116.8 (2C, C-2 and C-6, pnr), 68.9 (CH<sub>2</sub>, acetyl), 56.4 (C- $\alpha$ , tyr), 52.3 (OCH<sub>3</sub>), 38.9 (C-*b*, tyr), 18.8 (2C, 3-CH<sub>3</sub> and 4-CH<sub>3</sub>, pnr) ppm.

**2-(4-Chloro-3,5-dimethylphenoxy)acetyl-isoleucine Methyl Ester (3):**

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 300 MHz): d 174.6 (-C=O, ile), 173.8 (C=O, acetyl), 159.6 (C-1, pnr), 137.2 (2C, C-3 and C-5, pnr), 125.4 (C-4, pnr), 116.2 (2C, C-2 and C-6, pnr), 69.3 (CH<sub>2</sub>, acetyl), 58.8 (C- $\alpha$  ile), 56.3 (OCH<sub>3</sub>), 39.1 (C-*b*, ile), 24.5 (C-*g*, ile), 19.3 (2C, 3-CH<sub>3</sub> and 4-CH<sub>3</sub>, pnr), 15.1 (C-*g'*, ile), 10.4 (C- $\delta$ , ile) ppm; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): d 6.68 (2H, s, H-*o*, pnr), 5.98 (1H, br. s, -NH, ile), 4.70 (2H, s, CH<sub>2</sub>, acetyl), 4.25-4.22 (1H, t, H- $\alpha$ , ile), 3.52 (3H, s, -OCH<sub>3</sub>, ester), 2.13 (6H, s, CH<sub>3</sub>-*m*, pnr), 2.05-1.96 (1H, m, H-*b*, ile), 1.69-1.65 (2H, m, H- $\gamma$ , ile), 0.95-0.92 (3H, t, H- $\delta$ , ile), 0.87-0.85 (3H, d, *J* = 5.3 Hz, H-*g'*, ile) ppm.

**2-(4-Chloro-3,5-dimethylphenoxy)acetyl-valine Methyl Ester (4):**

IR (KBr): 3125 (m, -NH str, amide), 3058 (w, -CH str, pnr), 2965, 2922 (m, -CH str, asym, CH<sub>3</sub> and CH<sub>2</sub>), 2873 (m, -CH str, sym, CH<sub>3</sub>), 1746 (s, -C=O str, ester), 1644 (s, -C=O str, 2° amide), 1585, 1477 (m, skeletal bands, pnr), 1533 (m, -NH bend, 2° amide), 1384, 1370 (s, -CH bend, propyl-*i*), 1269 (s, C-O str, ester), 1245 (s, C-O-C str, asym), 1088 (s, C-Cl str), 922 (w, CH<sub>3</sub> rocking, propyl-*i*), 852, 821 (s, -CH bend, out-of-plane (oop), pnr) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): d 6.64 (2H, s, H-*o*, pnr), 6.42 (1H, br. s, -NH, val), 4.73 (2H, s, CH<sub>2</sub>, acetyl), 4.15-4.12 (1H, t, H- $\alpha$ , val), 3.49 (3H, s, -OCH<sub>3</sub>, ester), 2.19-2.14 (1H, m, H-*b*, val), 2.10 (6H, s, CH<sub>3</sub>-*m*, pnr), 0.84-0.82 (6H, d, *J* = 4.6 Hz, H-*g*, val) ppm.

**2-(4-Chloro-3,5-dimethylphenoxy)acetyl-tryptophan Methyl Ester (5):**

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): d 8.92 (1H, br. s, -NH, indole), 7.50-7.48 (1H, d, *J* = 7.8 Hz, H-*b*, try), 7.22 (1H, br. s, -NH, try), 7.16-7.05 (4H, m, H-*d-h*, try), 6.66 (2H, s, H-*o*, pnr), 4.90-4.86 (1H, q, H- $\alpha$ , try), 4.68 (2H, s, CH<sub>2</sub>, acetyl), 3.56 (3H, s, -OCH<sub>3</sub>, ester), 3.26-3.24 (2H, d, *J* = 5.2 Hz, H-*b*, try), 2.13 (6H, s, CH<sub>3</sub>-*m*, pnr) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 300 MHz): d 175.4 (C=O, acetyl), 174.2 (C=O, try), 159.1 (C-1, pnr), 138.2 (2C, C-3 and C-5, pnr), 136.6 (C-*b $\phi$* , indole), 127.9 (C-*g $\phi$* , indole), 125.2 (C-4, pnr), 122.6 (C- $\beta$ , indole), 122.5, 120.7, 119.2 (3C, C-*d- $\zeta$* , indole), 116.0 (2C, C-2 and C-6, pnr), 112.2 (C-*h*, indole), 109.5 (C-*g*, indole), 67.7 (CH<sub>2</sub>, acetyl), 53.0 (C-*a*, try), 51.1 (-OCH<sub>3</sub>, ester), 28.8 (C-*b*, try), 20.3 (2C, 3-CH<sub>3</sub> and 4-CH<sub>3</sub>, pnr) ppm.

**2-(4-Chloro-3,5-dimethylphenoxy)acetyl-prolyl-phenylalanine Methyl Ester (6):**

IR (CHCl<sub>3</sub>): 3128 (m, -NH str, amide), 3056, 3033 (w, -CH str, rings), 2998-2986 (m, -CH str, CH<sub>2</sub>, pro), 2968, 2925 (m, -CH str, asym, CH<sub>3</sub> and CH<sub>2</sub>), 2875, 2852 (m, -CH str, sym, CH<sub>3</sub> and CH<sub>2</sub>), 1749 (s, -C=O str, ester), 1662, 1641 (s, -C=O str, 3° and 2° amide), 1589-1583, 1472 (m, skeletal bands, rings), 1530 (m, -NH bend, 2° amide), 1272 (s, C-O str, ester), 1242 (s, C-O-C str, asym), 1085 (s, C-Cl str), 849, 825, 712, 695 (s, -CH bend, oop, rings) cm<sup>-1</sup>; MASS: m/z (rel. int.) 15 (10), 31 (6), 42 (11), 59 (MeOCO<sup>+</sup>, 17), 65 (13), 91 (15), 155 (29), 169 (25), 197 (71), 266 (52), 294 (base peak, 100), 413 (15), 441 (M-31, 21), 472 (M<sup>+</sup>, 9), 473 (5), 474 (2).

**2-(4-Chloro-3,5-dimethylphenoxy)acetyl-glycyl-glycine Methyl Ester (7):**

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 300 MHz): d 176.2 (-C=O, gly-1), 175.0 (C=O, acetyl), 170.8 (-C=O, gly-2), 158.1 (C-1, pnr), 136.7 (2C, C-3 and C-5, pnr), 125.1 (C-4, pnr), 115.9 (2C, C-2 and C-6, pnr), 69.9 (CH<sub>2</sub>, acetyl), 54.8 (OCH<sub>3</sub>), 40.8, 39.5 (2C, C- $\alpha$ , gly-2 and gly-1), 20.2 (2C, 3-CH<sub>3</sub> and 4-CH<sub>3</sub>, pnr) ppm; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): d 8.80, 8.65 (2H, br. s, -NH, gly-1 and gly-2), 6.64 (2H, s, H-*o*, pnr), 4.75 (2H, s, CH<sub>2</sub>, acetyl), 4.05-4.03 (2H, d, *J* = 5.15 Hz, H- $\alpha$ , gly-2), 3.94-3.92 (2H, d, *J* = 5.2 Hz, H- $\alpha$ , gly-1), 3.52 (3H, s, OCH<sub>3</sub>), 2.12 (6H, s, CH<sub>3</sub>-*m*, pnr) ppm.

**2-(4-Chloro-3,5-dimethylphenoxy)acetyl-histidinyl-leucine Methyl Ester (8):**

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): d 9.12 (1H, br. s, -NH, imidazole (imz)), 7.95 (1H, br. s, -NH, his), 7.67 (1H, s, H-*d*, imz), 7.38 (1H, d, *J* = 8.0 Hz, H-*b*, imz), 7.79 (1H, br. s, -NH, leu), 6.66 (2H, s, H-*o*, pnr), 4.78-4.73 (1H, q, H-*a*, his), 4.72 (2H, s, CH<sub>2</sub>, acetyl), 3.61 (3H, s, OCH<sub>3</sub>), 3.56-3.52 (1H, q, H-*a*, leu), 2.99-2.97 (2H, d, *J* = 5.9 Hz, H-*β*, his), 2.10 (6H, s, CH<sub>3</sub>-*m*, pnr), 1.50-1.42 (3H, m, H-*β* and H-*γ*, leu), 0.95-0.93 (6H, d, *J* = 6.2 Hz, H-*δ*, leu) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 300 MHz): d 178.1 (-C=O, leu), 175.4 (C=O, acetyl), 174.6 (-C=O, his), 157.8 (C-1, pnr), 146.7 (C-2, imz), 135.4 (2C, C-3 and C-5, pnr), 131.5 (C-4, imz), 125.2 (C-4, pnr), 115.7 (2C, C-2 and C-6, pnr), 115.0 (C-*γ*, his), 70.3 (CH<sub>2</sub>, acetyl), 62.8 (C-*α*, his), 52.4 (OCH<sub>3</sub>), 49.2, 45.5 (2C, C-*α* and C-*β*, leu), 28.9 (C-*β*, his), 27.8 (C-*γ*, leu), 25.1 (2C, C-*δ*, leu), 20.1 (2C, 3-CH<sub>3</sub> and 4-CH<sub>3</sub>, pnr) ppm.

**2-(4-Chloro-3,5-dimethylphenoxy)acetyl-tryptophanyl-nitro(arginyl)-tryptophan Methyl Ester (9):**

MASS: m/z (rel. int.) 15 (11), 31 (9), 46 (13), 59 (MeOCO<sup>+</sup>,15), 116 (14), 117 (19), 130 (25), 131 (13), 145 (22), 155 (32), 169 (21), 197 (67), 355 (43), 383 (base peak, 100), 557 (58), 585 (22), 743 (39), 771 (M-31, 28), 802 (M<sup>+</sup>, 6), 803 (3), 804 (2).

**2-(4-Chloro-3,5-dimethylphenoxy)acetyl-prolyl-prolyl-proline Methyl Ester (10):**

IR (CHCl<sub>3</sub>): 3052 (w, -CH str, pnr), 2998-2983 (m, -CH str, CH<sub>2</sub>, pro), 2965, 2923 (m, -CH str, asym, CH<sub>3</sub> and CH<sub>2</sub>), 2875, 2850 (m, -CH str, sym, CH<sub>3</sub> and CH<sub>2</sub>), 1753 (s, -C=O str, ester), 1665-1659 (s, -C=O str, 3° amide), 1585, 1476 (m, skeletal bands, pnr), 1270 (s, C-O str, ester), 1244 (s, C-O-C str, asym), 1081 (s, C-Cl str), 848, 820 (s, -CH bend, oop, pnr) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): d 6.68 (2H, s, H-*o*, pnr), 4.75 (2H, s, CH<sub>2</sub>, acetyl), 4.30-4.22 (3H, m, H-*α*, pro-1-3), 3.75-3.72 (2H, t, H-*δ*, pro-3), 3.69-3.66 (2H, t, H-*δ*, pro-2), 3.62 (3H, s, OCH<sub>3</sub>), 3.35-3.32 (2H, t, H-*δ*, pro-1), 2.78-2.67 (4H, m, H-*β*, pro-1 and pro-2), 2.13 (6H, s, CH<sub>3</sub>-*m*, pnr), 2.05-1.96 (4H, m, H-*β* and H-*γ*, pro-3), 1.93-1.86 (4H, m, H-*γ*, pro-1 and pro-2) ppm.

**2-(4-Chloro-3,5-dimethylphenoxy)acetyl-tyrosine (11):**

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): d 8.97 (2H, br. s, -OH, tyr and -OH, -COOH), 7.45 (1H, br. s, -NH, tyr), 6.92-6.75 (4H, m, H-*m* and H-*o*, tyr), 6.67 (2H, s, H-*o*, pnr), 4.86-4.82 (1H, q, H-*a*, tyr), 4.68 (2H, s, CH<sub>2</sub>, acetyl), 2.91-2.89 (2H, d, *J* = 5.45 Hz, H-*b*, tyr), 2.13 (6H, s, CH<sub>3</sub>-*m*, pnr) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 300 MHz): d 173.5 (-C=O, tyr), 169.6 (C=O, acetyl), 154.7 (C-*p*, tyr), 162.2 (C-1, pnr), 135.5 (2C, C-3 and C-5, pnr), 133.9, 129.4 (4C, C-*m* and C-*o*, tyr), 125.2 (C-4, pnr), 122.6 (C-*g*, tyr), 117.0 (2C, C-2 and C-6, pnr), 69.5 (CH<sub>2</sub>, acetyl), 55.2 (C-*a*, tyr), 38.7 (C-*b*, tyr), 18.4 (2C, 3-CH<sub>3</sub> and 4-CH<sub>3</sub>, pnr) ppm.

**2-(4-Chloro-3,5-dimethylphenoxy)acetyl-prolyl-phenylalanine (12):**

IR (CHCl<sub>3</sub>): 3298-2477 (m/br, -OH str, -COOH), 3127 (m, -NH str, amide), 3052, 3035 (w, -CH str, rings), 2996-2985 (m, -CH str, CH<sub>2</sub>, pro), 2969, 2922 (m, -CH str, asym, CH<sub>3</sub> and CH<sub>2</sub>), 2872, 2850 (m, -CH str, sym, CH<sub>3</sub> and CH<sub>2</sub>), 1712 (s, -C=O str, -COOH), 1660, 1644 (s, -C=O str, 3° and 2° amide), 1589-1582, 1476 (m, skeletal bands, rings), 1533 (m, -NH bend, 2° amide), 1405 (m, C-OH bend, -COOH), 1245 (s, C-O-C str, asym), 1087 (s, C-Cl str), 847, 826, 710, 695 (s, -CH bend, oop, rings) cm<sup>-1</sup>; MASS: m/z (rel. int.) 15 (11), 17 (6), 42 (14), 45 (COOH<sup>+</sup>,11), 65 (16), 91 (18), 155 (32), 169 (22), 197 (67), 266 (58), 294 (base peak, 100), 413 (M-45, 28), 441 (M-17, 16), 458 (M<sup>+</sup>, 7), 459 (3).

**2-(4-Chloro-3,5-dimethylphenoxy)acetyl-tryptophanyl-nitro(arginyl)-tryptophan (13):**

MASS: m/z (rel. int.) 15 (12), 45 (COOH<sup>+</sup>,15), 46 (18), 116 (18), 117 (13), 130 (32), 131 (19), 145 (20), 155 (38), 169 (25), 197 (69), 355 (41), 383 (base peak, 100), 557 (51), 585 (27), 743 (M-45, 25), 771 (M-17, 34), 788 (M<sup>+</sup>, 5), 789 (2).

## RESULTS AND DISCUSSIONS

Synthesis of 2-(4-chloro-3,5-dimethylphenoxy)acetic acid 1 was accomplished with good yield (> 80 %). Presence of free carboxylic group in compound 1 was clearly indicated by singlets at 173.2 and 7.05 ppm corresponding to carbonyl and hydroxyl portions of -COOH group in <sup>13</sup>C and <sup>1</sup>H NMR spectra. Prior to coupling, boc-di/tripeptide methyl esters were deprotected at amino terminal and their structures were confirmed by disappearance of singlet at 1.52 ppm (for nine protons of butyl-*t*) in <sup>1</sup>H NMR spectra and singlets at 156.0, 79.8, 28.9 ppm (for five carbons of boc) in <sup>13</sup>C NMR spectra of tripeptide methyl esters. All phenoxyacetic



acid derivatives 2-13 were synthesized successfully and DCC was found to be a good coupling agent providing 67-88 % yield of synthesized compounds. IR spectra of newly synthesized peptide derivatives showed characteristic Amide I and Amide II bands of the -CO-NH- moieties at 1665-1641 and 1533-1530  $\text{cm}^{-1}$  which clearly indicated the completeness of coupling reaction. This fact was further confirmed by appearance of singlets at 8.80-5.98 and 178.1-170.5 ppm corresponding to -CO-NH- moiety in  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of compounds 2-13. Presence of chloro functional group was indicated by a strong band at 1088-1087  $\text{cm}^{-1}$  in IR spectra of peptide derivatives. Further, presence of bands at 3298-2477 and 1712  $\text{cm}^{-1}$  (for -C(=O)-OH moiety) in IR spectra and broad singlet at 8.97 ppm (for -COOH moiety) in  $^1\text{H}$  NMR spectra of compounds 11-13 and disappearance of strong bands at 1749 and 1270  $\text{cm}^{-1}$  corresponding to C=O and C-O moiety (ester) in IR spectra and singlets at 52.3 and 3.55 ppm (for -OCH<sub>3</sub> moiety) in  $^{13}\text{C}$  and  $^1\text{H}$  NMR spectra of compounds 2, 6 and 9 further confirmed accomplishment of hydrolysis reaction. Moreover, mass spectrum of ester and corresponding acid derivatives showed characteristic fragment ion peaks (M-31 and MeOCO<sup>+</sup> - m/z 59) and (M-17, M-45 and COOH<sup>+</sup> - m/z 45) along with respective molecular ion peak (M<sup>+</sup>) and elemental analysis afforded values ( $\pm 0.04$ ), consistent with molecular composition of synthesized compounds.

All the synthesized compounds were found to exhibit moderate to good antifungal activity against pathogenic fungi. Compounds 5, 9 and 13 displayed significant activity against pathogenic *C. albicans*, most potent compound being 13 which displayed better activity than standard drug. Moreover, compound 6 and its hydrolyzed derivative 12 showed good activity against dermatophytes, comparable to reference compound - griseofulvin. Almost, all the synthesized compounds possessed moderate activity against gram negative bacteria, except compound 8 and 10 which displayed even more activity against *P. aeruginosa*, in comparison to standard drug - ciprofloxacin. No compound exhibited significant activity against gram positive bacteria except moderate level of activity for compounds 7 and 8 against pathogenic *S. aureus*. From analysis of anthelmintic activity data, it was concluded that dipeptide analogs 6-8, 12 possessed more activity in comparison to tripeptides 9 and 13 which in turn, exhibited more activity than amino acid derivatives 2, 3 and 11. Further, compounds 6 and 12 showed better activity against all three earthworm species, in comparison to standard drug - mebendazole and compound 10 displayed anthelmintic activity comparable to reference drug. *Eudrilus* sp. was found to be less sensitive towards the newly synthesized phenoxyacetic acid derivatives, in comparison to other two species *M. konkanensis* and *P. corethruses*. Comparison of antimicrobial and anthelmintic activity data suggested that hydrolyzed peptide derivatives 11-13 displayed better activity in comparison to corresponding ester derivatives 2, 6 and 9. On passing toxicity tests, these compounds may prove good candidates for clinical studies and can be new antimicrobial and anthelmintic agents of future.

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