Synthesis of amino acid derivatives of indole-3-acetic acid

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Amino acid derivatives of a modified indole-3-acetic acid have been synthesised. Fourteen new dipeptide-like compounds **3–4** were obtained and their structures were elucidated based on the IR, ^{1}H NMR, MS spectra.

Keywords: indole-3-acetic acid, amino acid, dipeptide-like compound

Indole-3-acetic acid derivatives have been found to exhibit biological activity and are used in pesticide and medicine.[1-5] Recently, 5, 6-difluoroindole-3-acetic acid was used as a new fluoroindole auxin;[1] indole-3-acetamide derivatives were used as antioxidant.[2]

In this paper, we report the synthesis of novel amino acid derivatives of indole-3-acetic acid. In title compounds **3** and **4**, there are indole fragment and amino acid residue in the structure. Which may serve as potential lead compounds for drug discovery.

The starting materials were glycine ethylester hydrochloride, alanine methylester hydrochloride, serine methylester hydrochloride, phenylalanine methylester hydrochloride and 5-methoxy-2-methyl-1H-indole-3-acetic acid **1**. Compound **1** was alkylated on the indole nitrogen by forming the sodium salt with sodium hydride and treating this with halogenated hydrocarbon followed by acidification. 5-Methoxy-2-methyl-1-substituted-1H-indole-3- acetic acids **2-I** and **2-II** were obtained. **2-I** or **2-II** reacted with amino acid ester hydrochlorides, to give the amino acid esters derivatives of indole-3-acetic acid **3**. Finally, **4** was prepared by hydrolysis of **3**. The procedure is shown in Scheme 1.

The elemental analyses and spectral data of compounds **3** and **4** were consistent with their assigned structures. Their IR spectra showed a characteristic strong absorptions at 3278–33670 cm^{-1} and 3282–3397 cm^{-1} due to N–H stretching vibration of compounds **3** and **4**, respectively. Both phenylalanine methylester **3d, 3h** have higher value than phenylalanines **4d, 4h**, other compounds **3** have lower value than their corresponding acid. The presence of an absorption in the range 1579–1754 cm^{-1} corresponded to carbonyl stretching absorptions. In ^{1}H NMR spectra, the peaks of all 2-methyl protons of indole are singlets at 2.10–2.37 ppm. The peaks of 5-methoxy protons of indole of compounds **3** are singlets, ranging from 3.82 to 3.85 ppm. The peaks of 5-methoxy protons of indole of compounds **4** are singlets in the range from 3.74 to 3.79 ppm.The methylene protons of –CH_2CONH– resonated between 3.54 and 3.75 ppm. Benzene ring protons appeared as multiplet line, appeared at 6.65–7.27 ppm. Mass spectra of compounds **4** showed the expected molecular peaks, for example, the molecular peaks of **4a** is 366(17 %), **4d** is 456(6 %).

Preliminary bioassay study showed that some compounds possess biological activity.

The method reported here will be useful to the synthesis of other dipeptide-like compounds.

Experimental

Melting points were obtained on an X6 apparatus and are uncorrected. IR spectra were recorded on a Nicolet Magna-IR 750 spectrometer with a Nic-Plan IR microscope-54183. Mass spectra were recorded on a VG-ZAB-HS spectrometer. ^{1}H NMR spectra were measured on a Brucker APX 400 spectrometer using TMS as internal standard.

The reagents and solvents were available commercially and purified according to conventional methods.

General procedure for the preparation of 5-methoxy-2-methyl-1-(phenylmethyl)1H-indole-3- acetic acid (**2-I**)

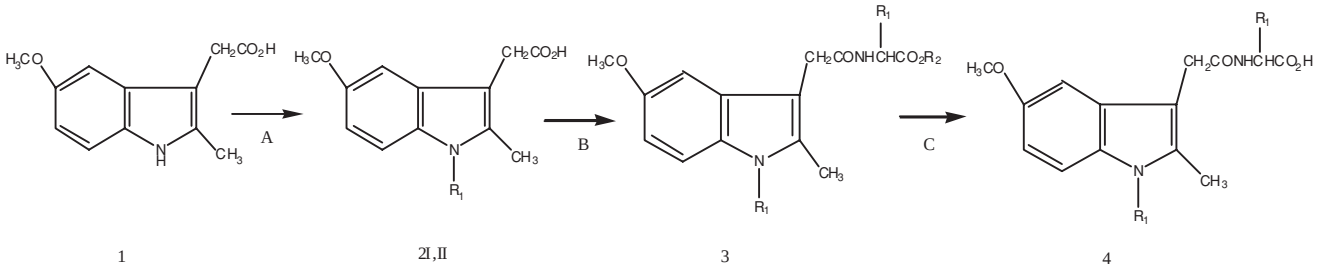
50 % NaH (2.0 g, 41.7 mmol) was added to 2.19 g (10 mmol) of **1** in 50 ml of DMF. The mixture was stirred for 30 min, 1.5 ml (13 mmol) of benzyl chloride was added, and the mixture was stirred for 8h. NaOH (2 mol/l, 20 ml) was added to the mixture and it was stirred for 1h, and extracted by ether. The water layer was acidified to pH=1 with 10 % HCl, and a white precipitate resulted. The precipitate was filtered off, washed with water and finally recrystallised from EtOH to give 2.46 g of the desired product **2–I**, corresponding to 80 % yield, m.p. 175–176 °C; IR (KBr) 3446(br,CO_2H), 1698(C=O) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): 2.30 (s, 3H, 2-C**H$_3$**), 3.73 (s, 2H, 3-C**H$_2$**), 3.84 (s, 3H, 5-OC**H$_3$**), 5.26 (s, 2H, 1-C**H$_2$**Ph), 6.73–7.27 (m, 8H, Ar); MS: *m/z* 309 (M^+,63), 264 (84), 251 (10), 174 (16), 131 (9), 91 (100). *Anal.* calcd. for $C_{19}H_{19}NO_3$ (309.35): C, 73.83; H, 6.26; N, 4.41. Found: C, 73.78; H, 6.27; N, 4.45.

2-II was prepared in the same method of **2-I**.

2-II, 5-methoxy-2-methyl-1-(decyl)1H-indole-3- acetic acid, white powder, m.p.123–125 °C, yield 37 %; IR(KBr) 2630 (CO_2H), 1744 (C=O) cm^{-1}; ^{1}H NMR (400 MHz,DMSO-d_6): 0.87 (t,3H,$(CH_2)_9$C**H$_3$**), 1.21–1.30,1.69–1.71 (m,16H,(C**H$_2$**)$_8$), 2.35 (s,3H,2-C**H$_3$**), 3.69 (s,2H,C**H$_2$**COOH), 3.84 (s,3H,5-OC**H$_3$**), 3.99 (t,2H,NC**H$_2$**$(CH_2)_8CH_3$), 6.78–7.26 (m,3H,Ar**H**), 9.4–10.9 (w,1H,COO**H**). *Anal.* calcd.for $C_{22}H_{33}NO_3$ (359.51): C, 73.50; H, 9.25; N, 3.90. Found: C, 73.07; H, 8.86; N, 3.81.

General procedure for the preparation of ethyl 2-(2-(1-benzyl-5-methoxy-2-methyl-1H-indol-3-yl) acetamido) acetate (**3a**)

2-I (0.618 g, 2 mmol), HOBt (0.272 g, 2 mmol) and glycine ethylester hydrochloride (0.279 g, 2 mmol) were dissolved in dry



1 2I,II 3 4

Scheme 1 A:NaH, $PhCH_2Cl$, DMF, HCl; B:$NH_2CHR_1CO_2R_2$.HCl, HOBt, NMM, EDC, DMF; C:NaOH, HCl

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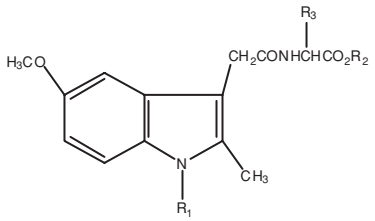

Table 1 Physical constants and elemental analyses of compounds **3** and **4**

No.	Formula	Fw	MS (M^+)	R_1	R_2	R_3	M.p./°C	Yield/%	Elemental analyses (calc./%)		
									C	H	N
3a	$C_{23}H_{26}N_2O_4$	394.5		CH_2Ph	CH_2CH_3	H	103–105	80	69.82(70.03)	6.74(6.64)	7.06(7.10)
3b	$C_{23}H_{26}N_2O_4$	394.5		CH_2Ph	CH_3	CH_3	138–139	55	69.93(70.03)	6.56(6.64)	7.16(7.10)
3c	$C_{23}H_{26}N_2O_5$	410.5		CH_2Ph	CH_3	CH_2OH	116–118	68	66.98(67.30)	6.47(6.38)	6.76(6.82)
3d	$C_{29}H_{30}N_2O_4$	470.6		CH_2Ph	CH_3	CH_2Ph	78–79	28	73.76(74.02)	6.16(6.43)	5.91(5.95)
3e	$C_{26}H_{40}N_2O_4$	444.6		$(CH_2)_9CH_3$	CH_2CH_3	H	88–90	25	70.15(70.24)	9.25(9.07)	6.32(6.30)
3f	$C_{26}H_{40}N_2O_4$	444.6		$(CH_2)_9CH_3$	CH_3	CH_3	112–113	48	69.92(70.24)	9.19(9.07)	6.23(6.30)
3g	$C_{26}H_{40}N_2O_5$	460.6		$(CH_2)_9CH_3$	CH_3	CH_2OH	118–119	60	67.67(67.80)	8.90(8.75)	5.77(6.08)
3h	$C_{32}H_{44}N_2O_4$	520.7		$(CH_2)_9CH_3$	CH_3	CH_2Ph	64–65	53	73.42(73.81)	8.62(8.52)	5.22(5.38)
4a	$C_{21}H_{22}N_2O_4$	366.4	366	CH_2Ph	H	H	209–210	43	68.57(68.84)	6.41(6.06)	7.53(7.65)
4c	$C_{22}H_{24}N_2O_5$	396.4	396	CH_2Ph	H	CH_2OH	157–159	57	66.61(66.66)	5.97(6.10)	7.34(7.07)
4d	$C_{28}H_{28}N_2O_4$	456.6	456	CH_2Ph	H	CH_2Ph	104–105	32	73.70(73.66)	6.49(6.18)	5.90(6.14)
4e	$C_{24}H_{36}N_2O_4$	416.6	416	$(CH_2)_9CH_3$	H	H	180–181	58	69.02(69.20)	8.66(8.71)	6.53(6.72)
4f	$C_{25}H_{38}N_2O_4$	430.6		$(CH_2)_9CH_3$	H	CH_3	121–123	31	69.42(69.74)	9.02(8.90)	6.41(6.51)
4g	$C_{25}H_{38}N_2O_5$	446.6	446	$(CH_2)_9CH_3$	H	CH_2OH	134–135	55	67.00(67.23)	8.45(8.58)	5.94(6.27)

Table 2 ^{1}H NMR data and IR data of compounds **3** and **4**

No	^{1}H NMR data (δ / ppm)	NH	C=O	OH
3a	1.21(t,3H,C**H$_3$**), 2.33(s,3H,2–C**H$_3$**), 3.74(s,2H, C**H$_2$**CONH), 3.85(s,3H, 5–OC**H$_3$**), 3.95(d,2H, NHC**H$_2$**COOEt), 4.13(q,2H,OC**H$_2$** CH_3), 5.30(s,2H, PhC**H$_2$**), 6.17(t,1H, N**H**), 6.78–7.29 (m,8H,Ar**H**)	3288	1662(**CO**NH), 1754(**CO**OEt)	
3b	1.26(d,3H,NHCHC**H$_3$**CO_2H), 2.31(s,3H,2–C**H$_3$**), 3.66(s,3H,CO_2C**H$_3$**), 3.70(s,2H,C**H$_2$**CONH), 3.85(s,3H,5–OC**H$_3$**), 4.57(m,1H,NHC**H**CH_3CO_2 CH_3), 5.32(s,2H,PhC**H$_2$**), 6.20(d,1H,CON**H**), 6.79–7.27 (m,8H,Ar**H**)	3318	1646(**CO**NHR), 1752(**CO**OMe)	
3c	2.32(s,3H,2–C**H$_3$**), 2.41(s,1H,O**H**), 3.69(s,3H,CO_2C**H$_3$**), 3.75(s,2H,C**H$_2$** CONH), 3.84(s,3H,5–OC**H$_3$**), 3.86(s,2H, NHCH(C**H$_2$**OH)CO_2H), 4.62(m, 1H,NHC**H**(CH_2OH)CO_2H), 5.31(s,2H, PhC**H$_2$**), 6.79(d,1H,CON**H**), 6.94–7.27 (m,8H,Ar**H**)	3338	1644(**CO**NHR), 1733(**CO**OMe)	3471(OH)
3d	2.18(s,3H,2–C**H$_3$**), 2.95(m,2H,NHCH(**CH$_2$**Ph)CO_2H), 3.61(s,3H,CO_2C**H$_3$**), 3.67(s,2H,C**H$_2$**CONH), 3.83(s,3H,5–OC**H$_3$**), 4.85(m,1H,NHC**H**(CH_2Ph)CO_2H) , 5.26(s,2H, 1–PhC**H$_2$**), 6.08(d,1H,CON**H**), 6.70–7.26 (m,13H,Ar**H**)	3321	1649(**CO**NHR), 1743(**CO**OMe)	
3e	0.87(t,3H,$(CH_2)_9$C**H$_3$**), 1.20(t,3H,$COOCH_2$C**H$_3$**), 1.23–1.32, 1.72(m,16H, (C**H$_2$**)$_8$), 2.37(s,3H,2–C**H$_3$**), 3.70(s,2H,C**H$_2$**CONH), 3.84(s,3H,5–OC**H$_3$**), 3.93(d,2H,NHC**H$_2$**COOEt), 4.04(t,2H,NC**H$_2$**$(CH_2)_8CH_3$), 4.12(q,2H, $COOCH_2CH_3$), 6.12(t,1H,CON**H**), 6.82–7.20 (m,3H,Ar**H**)	3293	1640(**CO**NHR), 1730(**CO**OEt)	
3f	0.87(t,3H,$(CH_2)_9$C**H$_3$**), 1.25(d,3H,NHCH(C**H$_3$**)$COOCH_3$), 1.30,1.73(m,16H, (C**H$_2$**)$_8$), 2.36(s,3H,2–C**H$_3$**), 3.65(s,2H,C**H$_2$**CONH), 3.66(s,3H,$COOCH_3$), 3.84(s,3H,5–OC**H$_3$**), 4.04(t,2H,NC**H$_2$**$(CH_2)_8CH_3$), 4.58(m,1H,NHC**H**(CH_3)CO OCH_3), 6.16(d,1H,CON**H**), 6.82–7.20 (m,3H,Ar**H**)	3278	1646(**CO**NHR), 1748(**CO**OMe)	
3g	0.87(t,3H,$(CH_2)_9$C**H$_3$**),1.25–1.31,1.68–1.74(m,16H,(C**H$_2$**)$_8$), 2.37(s,3H, 2–C**H$_3$**), 2.50(s,1H,OH), 3.69(s,3H,$COOCH_3$), 3.71(s,2H,C**H$_2$**CONH), 3.84 (s,3H,5–OC**H$_3$**), 3.85(s,2H,C**H$_2$**OH), 4.04(t,2H,NC**H$_2$**$(CH_2)_8CH_3$), 4.60(m,1H, NHC**H**(CH_2OH)$COOCH_3$), 6.54(d,1H,CON**H**), 6.81–7.19 (m,3H,Ar**H**)	3292	1650(**CO**NHR), 1724(**CO**OMe)	3501(OH)
3h	0.87(t,3H,$(CH_2)_9$C**H$_3$**), 1.25–1.65 (m,16H,(C**H$_2$**)$_8$), 2.22(s,3H,2–C**H$_3$**), 2.92 (m,2H,NHCH(C**H$_2$**Ph)$COOCH_3$), 3.63(s,2H,C**H$_2$**CONH), 3.64(s,3H, $COOCH_3$), 3.82(s,3H,5–OC**H$_3$**), 3.99(t,2H,NC**H$_2$**$(CH_2)_8CH_3$), 4.82(m,1H,NHC **H**(CH_2Ph)$COOCH_3$), 6.01(d,1H,CON**H**),7.20–6.66(m,8H,Ar**H**)	3302	1646(**CO**NHR), 1743(**CO**OMe)	
4a	2.30(s,3H,2–C**H$_3$**), 3.54(s,2H,C**H$_2$**CONH), 3.73(s,2H,NHC**H$_2$**COOH), 3.75 (s,3H,5–OC**H$_3$**), 5.35(s,2H,PhC**H$_2$**), 6.63–7.29 (m,8H,Ar**H**), 8.12(t,1H, CON**H**), 12.49(s,1H,COO**H**)	3367	1597(**CO**NHR), 1740(**CO**OH)	2512(CO**OH**)
4c	2.29(s,3H,2–C**H$_3$**), 3.57(s,2H,C**H$_2$**CONH), 3.51–3.55, 3.65– 3.74(m,2H,NHC H(C**H$_2$**OH)COOH), 3.74(s,3H,5–OC**H$_3$**), 4.13(m,1H,NHC**H**(CH_2OH)COOH), 5.35(s,2H,ArC**H$_2$**), 7.29–6.63(m,8H,Ar**H**),7.79(d,1H,CON**H**)	3397	1621(**CO**NHR), 1732(**CO**OH)	2527(CO**OH**), 3463(OH)

Table 2 *Continued*

No	^{1}H NMR data (δ / ppm)	NH	C=O	OH
4d	2.10(s,3H,2–C**H$_3$**), 2.90–3.07(m,2H, NHCH(**CH$_2$**Ph)COOH), 3.67(s,2H,C**H$_2$**CONH), 3.79(s,3H,5–OC**H$_3$**), 4.75(m,1H,NHC**H**(CH$_2$Ph)COOH), 5.25(s,2H,NC**H$_2$**Ph), 6.08(d,1H,CON**H**), 6.73–7.26 (m,13H,Ar**H**)	3317	1640(**CO**NHR), 1744(**CO**OH)	2650(CO**OH**)
4e	0.84(t,3H,(CH$_2$)$_9$C**H$_3$**), 1.22–1.26 , 1.59 (m,16H,(C**H$_2$**)$_8$), 2.32(s,3H,2–C**H$_3$**), 3.33(s,2H,C**H$_2$**CONH), 3.71(d,2H,NHC**H$_2$**COOH), 3.75(s,3H,5–OC**H$_3$**), 4.02(t ,2H,NC**H$_2$(**CH$_2$)$_8$CH$_3$), 6.65–7.23 (m,3H,Ar**H**), 8.05(t,1H,CON**H**),12.46(s,1H, COO**H**)	3370	1591(**CO**NHR), 1740(**CO**OH)	2398(CO**OH**)
4f	0.85(t,3H,(CH$_2$)$_9$C**H$_3$**), 1.22(m,3H,NHCH(C**H$_3$**)COOH), 1.25–1.26, 1.59 (m,16H,(C**H$_2$**)$_8$), 2.32(s,3H,2–C**H$_3$**), 3.43(s,2H,C**H$_2$**CONH), 3.74(s,3H, 5–OC**H$_3$**), 4.03(t,2H,NC**H$_2$**(CH$_2$)$_8$CH$_3$), 4.17(m,1H,NHC**H**(CH$_3$)COOH), 6.65–7.22(m,3H,Ar**H**), 8.19(d,1H,CON**H**),12.50(s,1H,COO**H**)	3309	1579(**CO**NHR), 1742(**CO**OH)	
4g	0.84(t,3H,(CH$_2$)$_9$C**H$_3$**), 1.22–1.26, 1.59(m,16H,(C**H$_2$**)$_8$), 2.32(s,3H,2–C**H$_3$**), 3.34(s,2H,C**H$_2$**CONH), 3.53– 3.70 (m,2H,C**H$_2$**OH), 3.74(s,3H,5–OC**H$_3$**), 4.03(t,2H,NC**H$_2$(**CH$_2$)$_8$CH$_3$), 4.25(m,1H,NHC**H**(CH$_2$OH)COOH), 4.51– 5.60 (w,1H,O**H**), 6.64–7.22 (m,3H,Ar**H**), 7.97(d,1H,CON**H**),13.2–11.2(w,1H, COO**H**)	3377	1630(CONHR), 1742(COOH)	2540(CO**OH**), 3505(**OH**)

DMF (10 ml). The mixture was cooled to 0 °C with an ice-bath and added NMM (0.52 ml), and added EDC (0.471 g, 2.2 mmol) after the solid disappeared. After the mixture was stirred for 5h, the mixture was poured to water (70 ml) to give a white precipitate. The precipitate was filtered off, washed with water and finally recrystallised from CH_3CO_2Et. The desired product **3a** (0.78 g), corresponding to 82 % yield, was obtained.

Compounds **3b–h** were prepared in the similar method as **3a**.

General procedure for the preparation of 2-(2-(1-benzyl-5-methoxy-2-methyl-1H-indol-3-yl) acetamido) acetic acid (**4a**)

To a solution of **3a** (0.788 g, 2 mmol) in dry DMF (8 ml), NaOH (2N, 10 ml) was added. After the mixture was stirred at room temperature for 2h, water (20 ml) was added, then it was acidified to pH=1 with hydrochloric acid, to give a white precipitate. The precipitate was filtered off, washed with water and finally recrystallised from chloroform/petroleum ether. The desired product **4a** (0.222 g), corresponding to 30 %, was obtained.

Compounds **4c–g** were prepared in the similar method as **4a**.

Physical constants and elemental analyses of compounds **3** and **4** were shown in Table 1, ^{1}H NMR data and IR data of compounds **3** and **4** were shown in Table 2.

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