

Note

A simple two-step synthesis of avenanthramides, constituents of oats (*Avena sativa L*)[†]

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A simple two-step general procedure has been developed to prepare naturally occurring and synthetic avenanthramides, constituents of oats (*Avena sativa L*). Reaction of anthranilic acid **1** with Meldrum's acid **2** gives half amide of malonic acid **3** which on condensation with different benzaldehyde derivatives **4a-m** gives avenanthramides **5a-m** of which **5a-d** are natural, **5e-g** are their methyl ethers and **5h-m** are synthetic.

Keywords: Oats, *Avena sativa*, antioxidants, avenanthramides, anthranilic acid, Meldrum's acid, 2-[(carboxyacetyl)amino]-benzoic acid

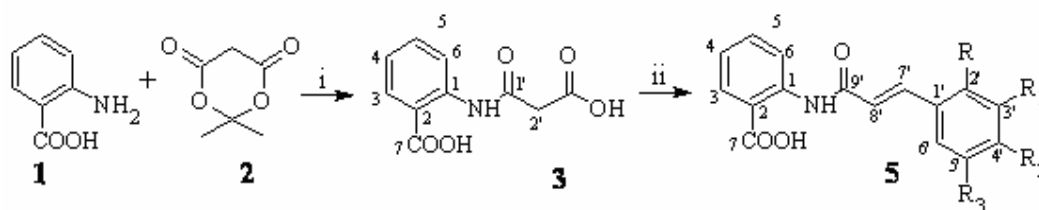
Oats have been considered to be a good source of antioxidants for a long time¹ and recently it has been shown that, this antioxidant activity and the fresh taste of oat products is mainly due to the presence of a group of amides called avenanthramides². Chemically avenanthramides are substituted *N*-cinnamoylanthranilate derivatives. They are phytoalexins and are produced when oat leaves are infected or inoculated with an incompatible race of crown rust fungus^{3,4}. Although avenanthramides have also been isolated from oat groats and hulls⁵, none appear to be present in healthy leaves prior to inoculation with pathogens⁶. It has been demonstrated by administering labelled putative precursors to oat leaf segments that avenanthramides are *de novo* synthesized from primary metabolites and phenylpropanoid metabolism is involved in their biosynthesis⁶.

Avenanthramides have been prepared in milligram quantities mainly for the purpose of identification in oat extracts^{2,5}, structure-antioxidant activity studies² and for providing support to the structure assigned⁵. For example avenanthramides **5a-d** have been synthesized² in about 40% yields by the acid catalyzed aldol reactions of 2-methylbenzoxazin-4-

ones^{4,7} with substituted benzaldehyde derivatives followed by hydrolysis. On the other hand, satisfactory yields of avenanthramides **5a** and **5b** have been obtained⁵ by using a modification of the Bain and Smalley's procedure⁸ in which substituted cinnamoyl chlorides are condensed with anthranilic acid in presence of pyridine^{3,5}. However, these^{2,5} methods involve additional protection and deprotection steps.

We have developed a simple two-step procedure for the synthesis of cinnamyl esters by condensation of monomalonates with substituted benzaldehyde derivatives in the presence of pyridine⁹. These monomalonates are obtained in high yields by simply heating Meldrum's acid **2** with alcohols or phenols¹⁰ in benzene⁹ or toluene¹¹. On similar lines, reaction of **2** with anthranilic acid **1** in refluxing toluene gave the half amide of malonic acid, 2-[(carboxyacetyl)amino]benzoic acid **3** in 90% yield (**Scheme I**). To our knowledge compound **3** and its preparation is being reported for the first time. It was fully characterized on the basis of its spectral data (IR, ¹H and ¹³C NMR) and elemental analysis. In the ¹H NMR spectrum of **3** the singlet at δ 3.44 integrated for 2H indicated the presence of the methylene group flanked by two carbonyls, one of the carboxyl and the other of the amide group. This was further confirmed by DEPT experiments. The remaining four aromatic protons are seen as doublet of doublets between δ 7.08 to 8.56. Further condensation of **3** with benzaldehyde and its derivatives **4a-m** in the presence of dry pyridine and β -alanine using a Verley-Doebner modification of Knoevenagel condensation¹² gave avenanthramides **5a-m** (**Table I**) in yields ranging from 65-95%. The avenanthramides **5a-d** have been isolated from oats⁵ while **5e-g** are their methyl ethers and **5h-m** are synthetic. The structures of **5a-d** were confirmed by comparison of their m.p. and spectroscopic data with that reported in the literature^{2,5} and hence their reported data is not included in the experimental. The structure of each new avenanthramide was confirmed by ¹H, ¹³C NMR spectroscopy and MS spectrometry. Although preparation of avenanthramides **5c**, **5e** and **5h** has been reported by Ashok Kumar and coworkers¹³, the melting point and the ¹H NMR data on **5c** (ref.13)

[†] Dedicated to Prof S K Paknikar on his 72nd birthday



i) Toluene, reflux, 4 hr ii) **4a-m**, pyridine, β -alanine

Scheme I

Table I— Natural (**5a-d**) and synthetic (**5e-m**) avenanthramides

Aldehyde 4	R	R ₁	R ₂	R ₃	Avenanthramide 5	R	R ₁	R ₂	R ₃	
	a	H	H	OH	H	a	H	H	OH	H
	b	H	OH	OH	H	b	H	OH	OH	H
	c	H	OMe	OH	H	c	H	OMe	OH	H
	d	H	OMe	OH	OMe	d	H	OMe	OH	OMe
	e	H	H	OMe	H	e	H	H	OMe	H
	f	H	OMe	OMe	H	f	H	OMe	OMe	H
	g	H	OMe	OMe	OMe	g	H	OMe	OMe	OMe
	h	H	-O-CH ₂ -O-		H	h	H	-O-CH ₂ -O-		H
	i	OMe	H	OMe	H	i	OMe	H	OMe	H
	j	H	H	Cl	H	j	H	H	Cl	H
	k	Cl	H	H	H	k	Cl	H	H	H
	l	H	OH	H	H	l	H	OH	H	H
	m	H	H	H	H	n	H	H	H	H

clearly shows its non-identity with **5c** prepared in the present study as well as with that reported in the literature^{2,5}. Moreover, our attempts to prepare **5c** using the procedure of Ashok Kumar and co-workers¹³ did not work and instead gave the starting *N*-acetylanthranilic acid back with no trace of **5c**.

It may be noted that several phenolics such as *p*-hydroxybenzoic, protocatechuic, vanillic, syringic, *p*-coumaric, caffeic, ferulic, sinapic, etc. are also isolated as free acids or their esters from the bran layer of oat grains¹⁴. Moreover, the silica gel two dimensional TLC analysis of the mixture of avenanthramides isolated from oat groat extracts is found to contain at least 40 chromatographically distinct avenanthramides⁵ of which very few have been individually isolated and characterized as they are present in very small quantities. Our method can be efficiently used to prepare these remaining (not isolated but detected) avenanthramides in sufficient quantities and subsequently used to detect their presence in oat extracts and also study their bioactivity.

The major advantage of the present method is that the intermediate half amide of malonic acid **3** can be chemically separated and purified. Secondly, it does not involve any type of chromatography for separation and purification and as such it can be conveniently scaled up.

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on a Shimadzu 8101A FTIR spectrophotometer. ¹H and ¹³C NMR spectra were recorded on a Bruker WT 300 MHz FTNMR spectrophotometer in CDCl₃ and DMSO-*d*₆ with TMS as internal standard and chemical shifts are recorded in δ values. All yields refer to pure isolated products. Meldrum's acid **2** was prepared from malonic acid by using the procedure reported in the literature¹⁵.

2-[(carboxyacetyl)amino]benzoic acid 3. An equimolar mixture of Meldrum's acid **2** (1.44 g, 10 mmole) and anthranilic acid **1** (1.37 g, 10 mmole) in dry toluene (10 mL) was refluxed for 4 hr. On cooling

to room temperature, the half amide of malonic acid **3** separated out as white solid which was filtered and washed with water. It was then chemically purified by dissolving in saturated NaHCO₃ solution, regenerated using 1:1 HCl, filtered under suction, washed with water and dried at 100°C to give white solid (2.01 g, 90%). Recrystallization from hot water afforded white solid, m.p. 174°C; IR (KBr): 3118 (NH), 1720 (CH₂COOH), 1685 (NHCO), 1643 (Ar-COOH), 1608, 1591, 1296 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, MeOH in traces): δ 3.44 (s, 2H, C₂-H), 7.08 (dd, *J*=8.25, 7.2 Hz, 1H, C₅-H), 7.50 (dd, *J*=8.7, 7.1, 1.7 Hz, 1H, C₄-H), 8.03 (dd, *J*=8.0, 1.7 Hz, 1H, C₆-H), 8.56 (dd, *J*=8.4, 0.9 Hz, 1H, C₃-H); ¹³C NMR (75 MHz, CDCl₃, MeOH in traces): δ 116.1 (C-1), 120.1 (C-3), 122.8 (C-5), 131.0 (C-6), 133.7 (C-4), 140.1 (C-2), 164.9 (C-7), 169.0 (C-3'), 169.6 (C-1'). Found: C, 52.74; H, 4.17; N, 6.15 Calcd for C₁₀H₉NO₅.1/4H₂O: C, 52.96; H, 4.22; N, 6.27. %.

General procedure for the preparation of avenanthramides 5a-m. A mixture of 2-[(carboxy-acetyl)amino]benzoic acid **3** (0.45 mmole), the corresponding benzaldehyde derivatives **4a-m** (0.45 mmole) and catalytic amount of β-alanine (10 mg) was refluxed in pyridine (0.5 mL) for 110 min. For the hydroxybenzaldehydes **4a-d** and **4l**, the reaction mixtures were just kept in loosely stoppered Erlenmeyer flasks for two weeks. The reaction mass was cooled in ice and acidified with Conc HCl (1.0 mL). The solid product that separated out was filtered, washed with water and recrystallized using hot water-acetone mixture to give the title compounds.

***N*-[4'-hydroxy-(*E*)-cinnamoyl]anthranilic acid 5a.** Reaction of **3** (0.10 g, 0.45 mmole) and 4-hydroxybenzaldehyde **4a** (0.055 g, 0.45 mmole) gave pale yellow crystals from hot water-acetone mixture, m.p. 220°C (Lit. ref. 5, 219°C), yield: 0.110 g, 85%; IR (KBr): 3120 (NH), 1665 (NHCO), 1610 cm⁻¹; UV and ¹H NMR data of **5a** was found to be identical with that reported⁵.

***N*-[3',4'-dihydroxy-(*E*)-cinnamoyl]anthranilic acid 5b.** Reaction of **3** (0.10 g, 0.45 mmole) and 3,4-dihydroxybenzaldehyde **4b** (0.062 g, 0.45 mmole) gave yellow crystals from hot water-acetone, m.p. 230-34°C (Lit. ref. 2, 221-30°C), yield: 0.10 g, 75%; UV, IR and ¹H NMR data of **5b** was found to be identical with that reported².

***N*-[4'-hydroxy-3'-methoxy-(*E*)-cinnamoyl]anthranilic acid 5c.** Reaction of **3** (0.10 g, 0.45 mmole) and 4-hydroxy-3-methoxybenzaldehyde **4c** (0.069 g, 0.45 mmole) gave pale yellow crystals from hot

water-acetone mixture, m.p. 212°C (Lit. ref.5, 235°C), yield: 0.12 g, 85%; IR (KBr): 3515 (NH), 1660 (NHCO), 1600, 1520, 1270 cm⁻¹; UV and ¹H NMR data of **5c** was found to be identical with that reported⁵.

***N*-[4'-hydroxy-3',5'-dimethoxy-(*E*)-cinnamoyl]anthranilic acid 5d.** Reaction of **3** (0.10 g, 0.45 mmole) and 4-hydroxy-3,5-dimethoxybenzaldehyde **4d** (0.082 g, 0.45 mmole) gave bright yellow crystals from hot water-acetone, m.p. 214°C (Lit. ref.2, 199-200°C), yield: 0.10 g, 65%; UV, IR and ¹H NMR data of **5d** was found to be identical with that reported².

***N*-[4'-methoxy-(*E*)-cinnamoyl]anthranilic acid 5e.** Reaction of **3** (0.10 g, 0.45 mmole) and 4-methoxybenzaldehyde **4e** (0.061 g, 0.45 mmole) gave pale yellow crystals from hot water-acetone, m.p. 190°C (Lit. ref. 13, 123°C), yield: 0.093 g, 70%; UV (MeOH): 326, 301, 226, 211 nm; IR (KBr): 3310 (NH), 1670 (NHCO), 1600, 1255cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆): δ 6.70 (d, *J*=16 Hz, 1H, C₈-H), 6.98 (d, *J*=8.4 Hz, 2H, C₃ & C₅-H), 7.16 (t, *J*=7.5 Hz, 1H, C₅-H), 7.56 (d, *J*=16 Hz, 1H, C₇-H), 7.62 (d, *J*=8.1 Hz, 2H, C₂ & C₆-H), 7.67 (d, *J*=8.1 Hz, 1H, C₄-H), 8.00 (d, *J*=7.5 Hz, 1H, C₆-H), 8.58 (d, *J*=8.7 Hz, 1H, C₃-H), 11.28 (s, 1H, COOH); ¹³C NMR (75 MHz, CDCl₃): δ 56.2 (4'-OCH₃), 114.2 (C-3' & C-5'), 115.4 (C-1), 119.3 (C-8'), 120.2 (C-3), 122.4 (C-5), 127.3 (C-1'), 129.5 (C-2' & C-6'), 131.4 (C-6), 134.3 (C-4), 141.6 (C-2), 141.8 (C-7'), 161.1 (C-4'), 165.2 (C-7), 170.4 (C-9'); FAB HRMS: *m/z* 320.0898 [M + Na]⁺; Calcd for C₁₇H₁₅NO₄Na⁺: 320.0899.

***N*-[3',4'-dimethoxy-(*E*)-cinnamoyl]anthranilic acid 5f.** Reaction of **3** (0.10 g, 0.45 mmole) and 3,4-dimethoxybenzaldehyde **4f** (0.074 g, 0.45 mmole) gave yellow crystals from hot water-acetone, m.p. 184°C, yield: 0.109 g, 74%; UV (MeOH): 336, 299, 237, 208 nm; IR (KBr): 3200 (NH), 1687 (NHCO), 1597, 1260, 1192 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆): δ 6.77 (d, *J*=15.9 Hz, 1H, C₈-H), 7.00 (d, *J*=8.4Hz, 1H, C₅-H), 7.17 (d, *J*=7.5 Hz, 1H, C₆-H), 7.23 (d, *J*=8.4 Hz, 1H, C₅-H), 7.34 (s, 1H, C₂-H), 7.55 (d, *J*=15.9 Hz, 1H, C₇-H), 7.63 (d, *J*=7.5 Hz, 1H, C₄-H), 8.00 (d, *J*=7.2 Hz, 1H, C₆-H), 8.58 (d, *J*=8.4 Hz, 1H, C₃-H), 11.28 (s, 1H, COOH).

***N*-[3',4',5'-Trimethoxy-(*E*)-cinnamoyl]anthranilic acid 5g.** Reaction of **3** (0.10 g, 0.45 mmole) and 3,4,5-trimethoxybenzaldehyde **4g** (0.088 g, 0.45 mmole) gave yellow crystals from hot water-acetone, m.p. 168°C, yield: 0.104 g, 65%; UV (MeOH): 339, 239, 211 nm; IR (KBr): 3580 (NH), 1660 (NHCO), 1600, 1583, 1267 cm⁻¹; ¹H NMR (300 MHz, CDCl₃):

δ 3.89 (s, OCH₃, 3H), 3.92 (s, OCH₃, 6H), 6.52 (d, $J=15.6$ Hz, 1H, C₈-H), 6.81 (s, 2H, C₂' & C₆-H), 7.15 (t, $J=7.8$ Hz, 1H, C₅-H), 7.65 (t, $J=4.5$ Hz, 1H, C₄-H), 7.69 (d, $J=15.6$ Hz, 1H, C₇-H), 8.15 (d, $J=7.8$ Hz, 1H, C₆-H), 8.90 (d, $J=8.7$ Hz, 1H, C₃-H), 11.25 (s, 1H, COOH); ¹³C NMR (75 MHz, CDCl₃): δ 56.1 (3',5'-OCH₃), 60.1 (4'-OCH₃), 105.3 (C-2' & C-6'), 115.3 (C-1), 120.3 (C-8'), 121.0 (C-3), 122.6 (C-5), 130.2 (C-1'), 131.5 (C-6), 134.6 (C-4), 139.8 (C-2), 141.8 (C-3' & C-5'), 142.2 (C-7'), 153.3 (C-4'), 164.7 (C-7), 171.0 (C-9'); FAB HRMS: m/z 380.1113 [M + Na]⁺; Calcd for C₁₉H₁₉NO₆Na⁺: 380.1110.

***N*-[3',4'-Methylenedioxy-(*E*)-cinnamoyl]anthranilic acid 5h.** Reaction of **3** (0.10 g, 0.45 mmole) and 3,4-methylenedioxybenzaldehyde **4h** (0.067 g, 0.45 mmole) gave pale yellow crystals from water-methanol, m.p. 202°C (dec), yield: 0.22 g, 71%; UV (MeOH): 337, 297, 234, 207 nm; IR (KBr): 1691 (NHCO), 1600, 1450, 1211 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆): δ 6.09 (s, 2H, -O-CH₂-O-), 6.77 (d, $J=15.6$ Hz, 1H, C₈-H), 6.97 (d, $J=8.1$ Hz, 1H, C₅-H), 7.16 (d, $J=7.2$ Hz, 1H, C₅-H), 7.21 (d, $J=8.1$ Hz, 1H, C₆-H), 7.45 (d, $J=1.2$ Hz, 1H, C₂-H), 7.55 (d, $J=15.6$ Hz, 1H, C₇-H), 7.62 (t, $J=7.2$ Hz, 1H, C₄-H), 8.01 (dd, $J=8.0$ Hz & 1.5 Hz, 1H, C₆-H), 8.62 (d, $J=8.4$ Hz, 1H, C₃-H), 11.30 (s, 1H, COOH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 101.0 (O-CH₂-O), 106.2 (C-2'), 108.0 (C-5'), 116.1 (C-1), 119.8 (C-8' & C-6'), 122.2 (C-3), 124.0 (C-5), 128.4 (C-1'), 130.6 (C-6), 133.5 (C-4), 140.5 (C-7'), 140.8 (C-2), 147.5 (C-3'), 148.5 (C-4'), 163.5 (C-7), 168.9 (C-9'); LCMS: m/z 334.2902 [M + Na]⁺; Calcd for C₁₇H₁₃NO₅Na⁺: 334.0691.

***N*-[2',4'-Dimethoxy-(*E*)-cinnamoyl]anthranilic acid 5i.** Reaction of **3** (0.10 g, 0.45 mmole) and 3,4-methoxybenzaldehyde **4i** (0.075 g, 0.45 mmole) gave orange crystals from water-methanol, m.p. 194-98°C (dec), yield: 0.281 g, 86%; UV (MeOH): 339, 299, 240, 208 nm; IR (KBr): 1693 (NHCO), 1660, 1598, 1288 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆): δ 3.82 (s, OCH₃, 3H), 3.89 (s, OCH₃, 3H), 6.60 (d, $J=8.6$ Hz, 1H, C₅-H), 6.64 (d, $J=1.53$ Hz, 1H, C₃-H), 6.70 (d, $J=15.7$ Hz, 1H, C₈-H), 7.16 (t, $J=8.0$ Hz, 1H, C₅-H), 7.61 (t, $J=8.0$ Hz, 1H, C₄-H), 7.69 (d, $J=8.5$ Hz, 1H, C₆-H), 7.80 (d, $J=15.7$ Hz, 1H, C₇-H), 8.00 (d, $J=7.9$ Hz, 1H, C₆-H), 8.61 (d, $J=8.4$ Hz, 1H, C₃-H), 11.3 (s, 1H, COOH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 55.0 (2'-OCH₃), 55.3 (4'-OCH₃), 97.9 (C-3'), 105.6 (C-5'), 115.2 (C-6'), 116.1 (C-1), 119.1 (C-3), 119.7 (C-8'), 122.1 (C-5), 129.3 (C-1'), 130.6 (C-6), 133.5 (C-4), 135.7 (C-7'), 140.6 (C-2), 158.8 (C-2'), 161.9 (C-4'),

163.9 (C-7), 169.0 (C-9'); LCMS: m/z 350.6357 [M + Na]⁺; Calcd for C₁₈H₁₇NO₅Na⁺: 350.1004.

***N*-[4'-Chloro-(*E*)-cinnamoyl]anthranilic acid 5j.** Reaction of **3** (0.10 g, 0.45 mmole) and 4-chlorobenzaldehyde **4j** (0.063 g, 0.45 mmole) gave pale yellow crystals from water-methanol, m.p. 220°C (dec), yield: 0.223 g, 74%; UV (MeOH): 317, 297, 289, 247, 208 nm; IR (KBr): 3329 (NH), 1672 (NHCO), 1608, 1531, 1259 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆): δ 6.83 (d, $J=15.6$ Hz, 1H, C₈-H), 7.14 (t, $J=8.4$ Hz, 1H, C₅-H), 7.43 (d, $J=8.4$ Hz, 2H, C₃' & C₅-H), 7.57 (t, $J=8.0$ Hz, 1H, C₄-H), 7.60 (d, $J=15.6$ Hz, 1H, C₇-H), 7.71 (d, $J=8.4$ Hz, 2H, C₂' & C₆-H), 8.00 (d, $J=7.8$ Hz, 1H, C₆-H), 8.61 (d, $J=8.4$ Hz, 1H, C₃-H), 11.44 (s, 1H, COOH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 115.9 (C-1), 119.6 (C-8'), 122.1 (C-3), 122.5 (C-5), 128.3 (C-2' & C-6'), 129.1 (C-3' & C-5'), 130.5 (C-6), 132.7 (C-1'), 133.3 (C-4'), 134.0 (C-4), 139.3 (C-7'), 140.4 (C-2), 162.9 (C-7), 169.0 (C-9'); LCMS: m/z 324.0379 [M + Na]⁺; Calcd for C₁₆H₁₂NO₃ClNa⁺: 324.0403.

***N*-[2'-Chloro-(*E*)-cinnamoyl]anthranilic acid 5k.** Reaction of **3** (0.10 g, 0.45 mmole) and 2-chlorobenzaldehyde **4k** (0.063 g, 0.45 mmole) gave white crystals from water-methanol, m.p. 200°C (dec), yield: 0.196 g, 65%; UV (MeOH): 318, 287, 247, 214 nm; IR (KBr): 3064 (NH), 1678 (NHCO), 1608, 1531, 1228 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆): δ 6.95 (d, $J=16.0$ Hz, 1H, C₈-H), 7.21 (t, $J=8.0$ Hz, 1H, C₅-H), 7.43 (t, $J=8.0$ Hz, 2H, C₄' & C₅-H), 7.54 (d, $J=8.0$ Hz, 1H, C₆-H), 7.64 (t, $J=8.0$ Hz, 1H, C₃-H), 7.93 (d, $J=16.0$ Hz, 1H, C₇-H), 8.00 (d, $J=8.0$ Hz, 1H, C₄-H), 8.01 (d, $J=8.0$ Hz, 1H, C₆-H), 8.60 (d, $J=8.0$ Hz, 1H, C₃-H), 11.43 (s, 1H, COOH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 117.3 (C-1), 120.7 (C-8'), 123.3 (C-3), 125.7 (C-5), 127.9 (C-5'), 128.4 (C-6'), 130.2 (C-6), 131.4 (C-4'), 131.7 (C-3'), 132.3 (C-1'), 133.9 (C-2'), 134.2 (C-4), 136.3 (C-7'), 140.8 (C-2), 163.5 (C-7), 169.7 (C-9'); LCMS: m/z 324.0572 [M + Na]⁺; Calcd for C₁₆H₁₂NO₃ClNa⁺: 324.0403.

***N*-[3'-Hydroxy-(*E*)-cinnamoyl]anthranilic acid 5l.** Reaction of **3** (0.10 g, 0.45 mmole) and 3-hydroxybenzaldehyde **4l** (0.055 g, 0.45 mmole) gave white shiny crystals from hot water-acetone, m.p. 242°C (dec), yield: 0.269 g, 95%; UV (MeOH): 322, 289, 238, 216, 207 nm; IR (KBr): 3169 (NH), 1693 (NHCO), 1612, 1514, 1288 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆): δ 6.76 (d, $J=15.7$ Hz, 1H, C₈-H), 6.83 (dd, $J=7.9$ Hz & 1.6 Hz, 1H, C₅-H), 7.06 (s, 1H, C₂-H), 7.26-7.12 (m, 3H, C₄, C₅, C₆-H), 7.52 (d, $J=15.7$

Hz, 1H, C₇-H), 7.62 (dt, $J=7.9$ Hz & 1.5 Hz, 1H, C₄-H), 8.00 (dd, $J=7.9$ Hz & 1.6 Hz, 1H, C₆-H), 8.56 (d, $J=8.4$ Hz, 1H, C₃-H), 11.30 (s, 1H, COOH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 113.9 (C-2'), 116.6 (C-1), 116.8 (C-4'), 118.7 (C-5'), 120.0 (C-8'), 121.7 (C-3), 122.5 (C-5), 129.5 (C-6'), 130.6 (C-1'), 133.5 (C-6), 135.2 (C-4), 140.2 (C-2), 141.0 (C-7'), 157.2 (C-3'), 163.3 (C-7), 168.9 (C-9'); LCMS: m/z 306.0243 [M + Na]⁺; Calcd for C₁₆H₁₃NO₄Na⁺: 306.0742.

N-(E)-cinnamoylanthranilic acid 5m. Reaction of **3** (0.10 g, 0.45 mmole) and benzaldehyde **4m** (0.048 g, 0.45 mmole) gave light green flakes from hot water-acetone, m.p. 188°C (Lit. ref. 13, 136°C), yield: 0.080 g, 66%; UV (MeOH): 311, 211 nm; IR (KBr): 3141 (NH), 1668 (NHCO), 1611, 1548, 1223 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆): δ 6.63 (d, $J=15.6$ Hz, 1H, C₈-H), 7.16 (t, $J=7.5$ Hz, 1H, C₅-H), 7.40-7.64 (m, 5H, Ar-H), 7.66 (t, $J=7.8$ Hz, 1H, C₄-H), 7.80 (d, $J=15.6$ Hz, 1H, C₇-H), 8.12 (d, $J=8.1$ Hz, 1H, C₆-H), 8.91 (d, $J=8.4$ Hz, 1H, C₃-H), 11.23 (s, 1H, COOH); ¹³C NMR (75 MHz, CDCl₃): δ 114.1 (C-1), 120.9 (C-8'), 121.8 (C-3), 122.9 (C-5), 128.2 (C-2' & C-6'), 128.9 (C-3' & C-5'), 130.2 (C-4'), 131.9 (C-1'), 134.7 (C-6), 135.7 (C-4), 142.3 (C-2), 142.8 (C-7'), 164.9 (C-7), 171.9 (C-9'); FAB HRMS: m/z 290.0791 [M + Na]⁺; Calcd for C₁₆H₁₃NO₃Na⁺: 290.0793.

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