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Microwave-Assisted Solvent-Free Arylation of Amino acids with Halogenobenzenes

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Abstract
The solventless microwave-assisted arylation and heteroarylation of different aliphatic and cyclic amino acids **2a–e** were carried out on activated, substituted *o*-nitrohalogenobenzenes **1a–h** and 2-chloro-3-nitropyridine **1i**, in the presence of potassium carbonate and potassium fluoride for 0.5 h at 70 W, to give substituted *N*-(*o*-nitrophenyl)amino-2-carboxylic acid **3–16** and *N*-(*m*-nitropyridyl)amino-2-carboxylic acid **17–18** adducts in yields ranging from 5–98% .

Keywords: amino acids, arylation, halogenobenzenes, microwave synthesis

Introduction

The *N*-functionalisation of amino acids with aryl compounds continues to have great utility in organic syntheses and drug discovery as well as in the pharmaceutical and agrochemical industries and materials science. Arylated natural amino acid derivatives are employed as inexpensive chiral building blocks whilst the incorporation of functionalised amino acids in peptides and proteins has propelled peptidomimetics and chemical biology by allowing, for instance, the development of new methods for the study of protein structures and functions.[1–3] *N*-Aryl amino acids are also important chimeras in the synthesis of poly-condensed nitrogen heterocycles with marked activities in many biological systems.[4]

The *N*-(hetero)arylation of amino acids with heteroaryl and aryl halides have been previously carried out using copper and palladium catalysts with different types of ligands and *N*-heterocyclic carbenes.[2] Nucleophilic aromatic substitution and hypervalent iodine chemistry have also been attempted.[1] In spite of the successes of the foregoing procedures, they suffer drawbacks, such as: high temperatures, long reaction times, racemisation, air- and moisture-sensitivity, high cost of catalysts, generation of wastes, limited substrate scope and the use of highly polar solvents, amongst others.[2,5,6]

It is well known that the rotational states of molecules undergo excitation with electromagnetic radiation. This effect is utilised in household microwave ovens to heat up food, for example; the water molecule being the focal action point of the microwave oven in the home. As with molecules with a dipole, water absorbs microwave radiation, which is typically 2.45 GHz in household microwave units.[7] The microwave region is located between the infrared and radiowave regions of the electromagnetic spectrum,[8] with frequencies of 1,000–100,000 MHz and short wavelengths.[9] Microwaves are being used for rapid organic syntheses based on the reactivity of organic substrates on irradiation.[10–12] Considerable rate increases (5–1000 folds) have been observed for all investigated transformations when compared to classical thermal reflux conditions.[12] The cross-coupling of amines under microwave conditions have been reported in good yields.[13] Some organic reactions involving the use of the microwave technique include: the synthesis of (*E*)-*β*-arylvinylbromide,[14] some non-natural *N*-aryl-*α*-amino acids[15] and the one-pot regioselective synthesis of 2-alkyl-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines[16] as well as the microwave-promoted rapid nitration of phenolic compounds with calcium nitrate.[17]

Solvent-free syntheses are becoming commonplace in order to meet the need for environmentally friendly reactions. Organic reactions requiring no solvents to proceed reduce the risk of hazardous explosions when reactions are conducted in closed vessels or ovens. Teflon, polystyrene and glass are used in the manufacture of microwave reaction vessels because they are transparent to microwave radiation.[18]

A solvent-free Knoevenagel condensation of aldehydes with ethyl cyanoacetate (or malono-

nitrile) catalysed by triphenylphosphine to afford olefins in excellent yields with *E*-geometries has been improved upon using microwave irradiation.[19] The synthesis of dioxolane has also been achieved in 4–30 mins using microwave technology. This reaction is much faster under microwave irradiation in comparison to the classical methods requiring 4–7 h.[20] Other examples include the synthesis of 2,3-dihydroimidazo[1,2-*b*]isoquinolin-5[*1H*]-one,[21] the one-pot synthesis of 2-amino-3-cyanopyridine derivatives via solvent-free microwave irradiation[22] and the ring-opening of a fatty epoxide, tetradecyloxirane, to furnish a lactone.[20]

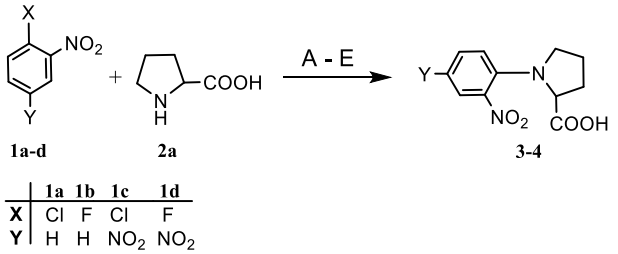
The sources of microwave irradiation for organic syntheses are usually purpose-built microwave reactors but their high costs have rendered their acquisition beyond the reach of many chemists. Consequently, the modification and adaptation of the domestic microwave oven for organic syntheses has become imperative as a veritable alternative.[23] Reported herein, therefore, is the successful application of the microwave technology to the arylation of aliphatic and cyclic amino acids using substituted *o*-nitrohalogenobenzenes.

Results and Discussion

The microwave-assisted synthesis of *N*-aryl and *N*-heteroaryl amino acids was embarked upon with a view to shortening the reaction times as well as reducing/eliminating the use of solvents without deleterious effects on product yield. The microwave protocol also has the advantage of offering simple work-up procedures and producing minimal wastes. In this work, potassium fluoride (KF) was chosen as the heat absorbent because of its high decomposition temperature while aluminium oxide (Al_2O_3) served as solid support with potassium carbonate (K_2CO_3) as base.

During the exploratory phase of this synthetic strategy, 1-chloro-2-nitrobenzene **1a** was reacted with L-proline **2a** (Scheme 1), mediated by K_2CO_3, KF and Al_2O_3 without solvent, in a microwave oven at different power settings to determine an optimum of 70 W. At 210 W, a charred reaction mixture resulted within seconds of commencing the reaction. Different reaction times were also investigated; after 10 mins. TLC indicated an incomplete reaction whereas a completed reaction was observed after 30 mins. of microwave irradiation.

The yield obtained from the condensation reaction of 1-chloro-2-nitrobenzene **1a** with L-proline **2a** was poor (about 10%). This result necessitated the replacement of 1-chloro-2-nitrobenzene **1a** with 1-fluoro-2-nitrobenzene **1b**, which, fortunately, was better-yielding. Next, 1-chloro-2,4-dinitrobenzene **1c** was reacted with L-proline **2a** (Scheme 1). It was posited that since the condensation reaction proceeded via aromatic nucleophilic substitution, the presence of a second nitro group would further activate the benzene ring to favour the formation of the expected *N*-aryl amino acid adduct **4**.

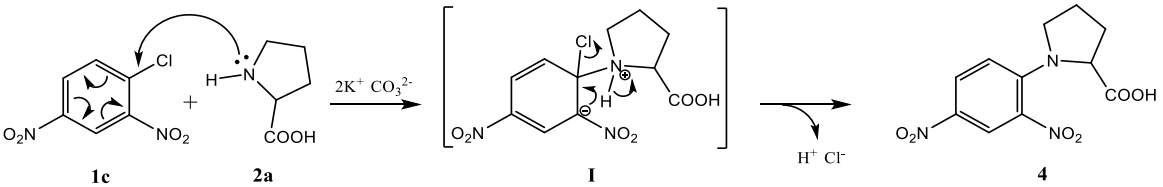


	1a	1b	1c	1d
X	Cl	F	Cl	F
Y	H	H	NO_2	NO_2

Scheme 1: Optimisation reactions for the synthesis of *N*-aryl-L-proline

The reaction of 1-chloro-2,4-dinitrobenzene **1c** with L-proline **2a** yielded *N*-(2,4-dinitrophenyl) pyrrolidine-2-carboxylic acid **4** in 96% in the presence of K_2CO_3, KF and Al_2O_3, solvent-free. The reaction mixture was quenched with water and taken up in CH_2Cl_2 to remove unreacted inorganics and organics, respectively. The disappearance of the strong C–Cl stretching frequency at 845 cm^{-1} in the IR spectrum of **4** as well as the upfield shifts of the aryl protons in its ^{1}H-NMR spectrum were good indicators of a successful reaction. A mechanism is proposed in Scheme 2.

Following a typical nucleophilic aromatic substitution S_NAr (addition–elimination) mechanism, the nitrogen lone pair of L-proline **2a**, enabled by the basic K_2CO_3, attacks the carbon atom bonded to chlorine. The chloride carbon has



Scheme 2: Proposed mechanism for the condensation reaction of aryl halide [1] and amino acid [2]

an adjacent carbon atom with localised excess electrons by virtue of its *ortho* and *para* positions to two nitro groups, which are S_NAr activators and *meta*-directing. The existence of the ring carbanion in the intermediate **I** (Scheme 2) favours the *ipso*-carbon *C–N* bond formation with the prolyl ion, which leads to the breaking of the *C–Cl* bond. The leaving Cl^- then picks up the proton eliminated by the prolyl ion to form hydrogen chloride, which is given off to afford the *N*-aryl amino acid **4**. The second step is fast because it involves a good leaving group whereas the first step, which involves the formation of the intermediate **I** is slow and rate-determining.

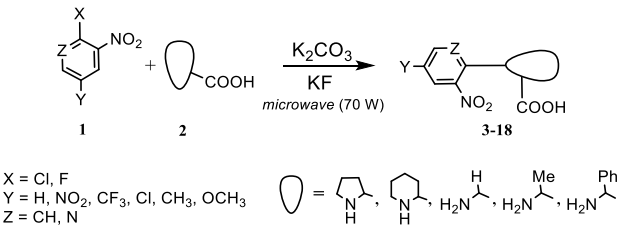
As part of the optimisation process for this reaction, model experiments, with varying conditions of reaction: **A**–**G** (Table 1), were carried out in order to determine the effect(s) of each of the reagents employed on the reaction of 1-chloro-2,4-dinitro benzene **1c** with L-proline **2a** (Scheme 1). In the design of this arylation reaction, the well-known, inexpensive and easily available K_2CO_3 was chosen as the base[24] while KF and Al_2O_3 served as the reaction heat absorbent and solid support, respectively. The results of varying the combination of reagents for the condensation reaction of **1c** (1.0 mmole) with **2a** (1.2 mmole) at 70 W, without solvent, for 30 mins. are summarised in Table 1.

Table 1: Optimisation of reaction conditions at 70 W

	Reaction Conditions	Reagents			
		Al_2O_3	K_2CO_3 (mmole)	KF	Yield (%)
1.	**A**	2.0	2.0	2.0	96
2.	**B**	2.0	2.0	0	83
3.	**C**	2.0	0	2.0	73
4.	**D**	0	2.0	2.0	98
5.	**E**	0	0	2.0	6
6.	**F**	0	2.0	0	90
7.	**G**	2.0	0	0	5

Table 1 gives the mole equivalents of each of the reagents used and highlights the effect of using different combinations of reagents on the yield of the reaction products. A combination of the 3 reagents resulted in an excellent product yield of 96% (**A**) but afforded a slightly higher yield of 98% without Al_2O_3 (**D**). Using only K_2CO_3 in the reaction gave 90% (**F**) of the product **4** whereas KF and Al_2O_3 gave 6% (**E**) and 5% (**G**), respectively. It is therefore safe to surmise that the arylation reaction is better without Al_2O_3 and that, of the 3 reagents, K_2CO_3 is the most important contributor.

The scope of this reaction was also extended as delineated in Scheme 3. Differently substituted (het)aromatic halides **1** were reacted with cyclic and non-cyclic amino acids **2**, with the aid of a solvent-free microwave irradiation protocol at 70 W, to afford the required *N*-aryl amino acid adducts **3**–**18**, in the presence of K_2CO_3 and KF.



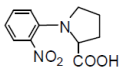
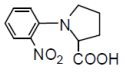
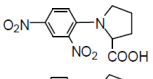
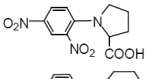
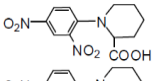
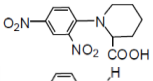
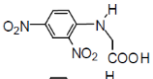
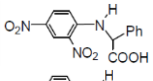
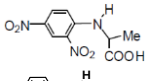
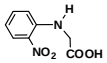
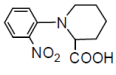
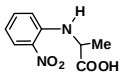
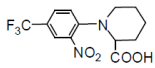
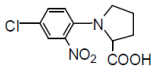
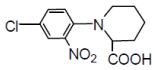
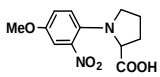
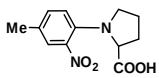
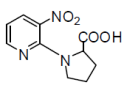
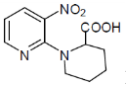
Scheme 3: Synthesis of *N*-aryl amino acids

The synthesis of substituted *N*-(*o*-nitrophenyl) amino-2-carboxylic acid **3–16** and *N*-(*m*-nitro pyridyl)amino-2-carboxylic acid **17–18** adducts was achieved, in poor to excellent yields of 5–98%, by condensing different substituted *o*-nitrohalogeno benzenes **1a–h** and 2-chloro-3-nitropyridine **1i** with other cyclic (**2a**–**b**) and aliphatic (**2c**–**e**) amino acids (Table 2).

As would be expected, the *o,p*-dinitrohalogeno benzenes (entries 3–9) were generally better-yielding than the *o*-nitrohalogenobenzenes (entries 1–2, 10–12). This supports the proposed S_NAr mechanism where *o,p*-dinitrobenzene halides are most predisposed to activate aromatic nucleophilic substitution at the *ipso*-carbon atom. In the same vein, electron-withdrawing substituents (e.g., CF_3, Cl) and electron-donating groups (e.g., OCH_3, CH_3) *para* to the *ipso* halide carbon are more likely to, respectively, activate and deactivate the *o*-nitro-halogenobenzenes towards S_NAr. The results in Table 2 are in agreement with the foregoing; the synthesis of adduct **13** was better yielding (43%) than adducts **15** (25%) and **16** (28%).

The high yield of 97% obtained for **17** underlines the propensity of 2-chloro-3-nitropyridine **1i** to undergo nucleophilic substitution.[25] The moderate yield (45%) of 3-nitro-2-*N*-pipecolinylpyridine **18** was, therefore, surprising. This result may be attributable to steric factor due to the flexible 6-membered amino acid **2b**. In fact in all of the reactions where L-proline **2a** and D,L-pipecolinic acid **2b** were coupled to the same aryl halide, **2b** gave lower-yielding products (entries 1 v 11, 3 v 5, 4 v 6, 14 v 15 and 18 v 114 vs. 159). This has been previously observed, under similar conditions, by Alo *et al*.[26]

Table 2: Synthesis of substituted *N*-aryl amino acid adducts [3–18]

entry	*o*-NO_2PhX	amino acid	adduct	yield
1.	**1a**	**2a**	 **3**	13%
2.	**1b**	**2a**	 **3**	77%
3.	**1c**	**2a**	 **4**	98%
4.	**1d**	**2a**	 **4**	98%
5.	**1c**	**2b**	 **5**	76%
6.	**1d**	**2b**	 **5**	63%
7.	**1d**	**2c**	 **6**	71%
8.	**1c**	**2d**	 **7**	39%
9.	**1c**	**2e**	 **8**	32%
10.	**1b**	**2c**	 **9**	75%
11.	**1a**	**2b**	 **10**	6%
12.	**1a**	**2e**	 **11**	31%
13.	**1e**	**2b**	 **12**	40%
14.	**1f**	**2a**	 **13**	43%
15.	**1f**	**2b**	 **14**	7%
16.	**1g**	**2a**	 **15**	25%
17.	**1h**	**2a**	 **16**	28%
18.	**1i**	**2a**	 **17**	97%
19.	**1i**	**2b**	 **18**	45%

1a; 1-chloro-2-nitrobenzene, **1b**; 1-fluoro-2-nitrobenzene, **1c**; 1-chloro-2,4-dintrobenzene, **1d**; 1-fluoro-2,4-dintro-benzene, **1e**; 1-chloro-4-trifluoromethyl-2-nitrobenzene, **1f**; 1,4-dichloro-2-nitrobenzene, **1g**; 4-chloro-3-nitroanisole, **1h**; 4-chloro-3-nitrotoluene, **1i**; 2-chloro-3-nitropyridine, **2a**; L-proline, **2b**; D,L-pipecolinic acid, **2c**; glycine, **2d**; phenyl glycine, **2e**; methyl glycine.

Furthermore, the *N*-arylation of the cycloamino acids **2a**–**b** generated products (**3**–**5**, **10**, **12**–**18**) at higher yields in comparison to those (**7**–**9**, **11**) synthesised from aliphatic amino acids **2c**–**e**, except for **6** (entry 7) and **9** (entry 10), which were prepared from the reaction of glycine **2c** with 1-fluoro-2,4-dintrobenzene **1d** and 1-fluoro-2-nitrobenzene **1b**, respectively. Incidentally, **1b** and **1d** are fluoroarenes, which might be responsible for their higher reactivity towards S_NAr compared to chloroarenes. It is well-established that fluorine is a much better leaving group than chlorine.[25] Fluoroarenes herein consistently afforded better-yielding products than their chloro- analogues, except in the case of **5** (entries 5 & 6) where the converse was the case. Comparing the aliphatic amino acids **2c**–**e** (entries 7–9), glycine **2c** gave the product with the highest yield (71%), followed by phenyl glycine **2d** (39%) and then methyl glycine **2e** (32%).

In conclusion, a microwave-assisted protocol for the synthesis of *N*-(hetero)aryl amino acids has been developed and executed. The method involves the use of 70 W microwave irradiation on suitably activated (het)aromatic halides and amino acids in the presence of a solvent-free mixture of K_2CO_3 and KF for 30 mins. It has been shown to be robust, efficient and environmentally benign, reducing reaction time, work-up stress and wastes.

Experimental

General Details

All reactions were conducted in a domestic LG microwave oven (ECN:MS-1924SN/01). Melting points were determined using a Gallenkamp melting point apparatus. All chemicals and solvents (reagent or analytical grade) were purchased from Sigma–Aldrich Germany. All extractions were carried out using dichloromethane and organic extracts were dried over anhydrous sodium sulphate. The progress of reactions was monitored by TLC on Merck silica gel 60 F_{254} precoated plates, in ethyl acetate, dichloromethane and ethanol solvent systems as appropriate, and visualised under a UV lamp. NMR spectra were recorded on Bruker AMX400 or AVANCE 400 MHz spectrometers in $CDCl_3$ or DMSO-d_6 at 303 K using tetramethylsilane (TMS) and deuterated solvent signals as internal standards. Infrared spectra were recorded on a Perkin Elmer FT-IR spectrum 2000 instrument at Rhodes University, Grahamstown, South Africa.

Preparation of Adducts

General Procedure

o-Nitrohalogenobenzenes **1** (1.00 mmol), amino acids **2** (1.20 mmol), potassium carbonate (2.00 mmol) and potassium fluoride (2.00 mmol) were weighed into a

clean, dry 50 mL beaker and crushed thoroughly with a glass rod. A colour change in the reaction mixture was observed in some cases. The beaker was then placed in a microwave oven at 70 watts for 30 mins. After which the reaction mixture was allowed to cool to ambient temperature and quenched with distilled water (15 mL). Unreacted materials were taken up in CH_2Cl_2 (5 mL) and the resulting aqueous layer was acidified with 6*M* HCl solution and washed with brine (10 mL). The solution was subsequently extracted into CH_2Cl_2 (10 mL x 3) and the organic layer was dried over anhydrous Na_2SO_4 and filtered. The solvent was then evaporated to afford the adducts **3**–**18**. Recrystallisation was carried out in petroleum ether (40–60 ^oC) where necessary.

***N*-(2-Nitrophenyl)pyrrolidine-2-carboxylic acid [3]**
1-Chloro-2-nitrobenzene **1a** (0.50 g, 3.17 mmol), **L**-proline **2a** (0.44 g, 3.81 mmol), potassium carbonate (0.87 g, 6.34 mmol) and potassium fluoride (0.37 g, 6.34 mmol) were reacted to give **3** as a red oil (0.10 g, 13%).

Also, 1-fluoro-2-nitrobenzene **1b** (1.0 g, 7.09 mmol), **L**-proline **2a** (0.98 g, 8.50 mmol), potassium carbonate (1.96 g, 14.18 mmol) and potassium fluoride (0.82 g, 14.18 mmol) gave **3** as a red oil (1.29 g, 77%).

IR (neat) ν_{max} (cm^{-1}): 3500–2250 (O–H str.), 2974 (C–H str.), 1721 (C=O str.), 1607 (aryl C=C str.), 1508 (antisym. C-NO_2 str.), 1353 (sym. C-NO_2 str.), 1276 (aryl C–N str.), 1217 (C–O str.), 1181 (C–N str.), 757 (aryl C–H def.). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.01 (broad s, COO<u>H</u>, 1H), 8.56–8.52 (m, phenyl, 1H), 8.14–8.11 (m, phenyl, 1H), 7.71–7.69 (m, phenyl, 1H), 7.38–7.36 (m, phenyl, 1H), 5.15 (s, -C<u>H</u>-COOH, 1H), 4.49–4.47 (m, -*N*-C<u>H</u>$_2$-, 2H), 2.16–2.13; 1.99–1.96 (m, C-C<u>H</u>$_2$-C<u>H</u>$_2$-C, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 177.5 (-<u>C</u>OOH), 141.2; 138.7; 133.2; 126.5; 118.0; 116.7 (phenyl), 61.7 (-<u>C</u>H-COOH), 51.7 (-*N*-<u>C</u>H$_2$-), 30.9 (C-CH$_2$-<u>C</u>H$_2$-C), 24.8 (C-<u>C</u>H$_2$-CH$_2$-C).

***N*-(2,4-Dinitrophenyl)pyrrolidine-2-carboxylic acid[4]**
1-Chloro-2,4-dinitrobenzene **1c** (0.64 g, 3.17 mmol), **L**-proline **2a** (0.44 g, 3.80 mmol), potassium carbonate (0.87 g, 6.34 mmol) and potassium fluoride (0.37 g, 6.34 mmol) were reacted to give **4** as a yellow solid (0.87 g, 98%) on recrystallisation from petroleum ether (40–60 ^oC).

Also, 1-fluoro-2,4-nitrobenzene **1d** (1.32 g, 7.14 mmol), **L**-proline **2a** (0.99 g, 8.57 mmol), potassium carbonate (1.97 g, 14.30 mmol) and potassium fluoride (0.83 g, 14.30 mmol) gave **4** as a yellow solid (1.97 g, 98%).

m.p. 125–127 ^oC. IR (neat) ν_{max} (cm^{-1}): 3550–2550 (O–H str.), 2937 (C–H str.), 1721 (C=O str.), 1607 (aryl C=C str.), 1522 (antisym. C-NO_2 str.), 1328 (sym. C-NO_2 str.), 1181 (C–O str.), 1147 (C–N str.), 743 (aryl C–H def.). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.07 (broad s, COO<u>H</u>, 1H), 8.56–8.52 (m, phenyl, 1H), 8.14 (d, J = 2.4 Hz, phenyl, 1H), 7.38 (dd, J = 2.2 Hz; 9.4 Hz, phenyl, 1H), 5.18 (s, -C<u>H</u>-COOH, 1H), 4.53–4.51 (m, -*N*-C<u>H</u>$_2$-, 2H), 2.21–2.18; 2.01–1.97 (m, C-C<u>H</u>$_2$-C<u>H</u>$_2$-C, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 177.5 (-<u>C</u>OOH), 144.2; 141.7; 136.2; 129.5; 121.8; 119.7 (phenyl), 61.7 (-<u>C</u>H-COOH), 51.7 (-*N*-<u>C</u>H$_2$-), 30.9 (C-CH$_2$-<u>C</u>H$_2$-C), 24.0 (C-<u>C</u>H$_2$-CH$_2$-C).

***N*-(2,4-Dinitrophenyl)piperidine-2-carboxylic acid [5]**
1-Chloro-2,4-dinitrobenzene **1c** (0.27 g, 1.34 mmol), **D**,**L**-pipecolinic acid **2b** (0.21 g, 1.60 mmol), potassium carbonate (0.37 g, 2.68 mmol) and potassium fluoride (0.16 g, 2.68 mmol) were reacted to give **5** as a yellow powder (0.30 g, 76%).

1-Fluoro-2,4-dinitrobenzene **1d** (0.25 g, 1.34 mmol), **D**,**L**-pipecolinic acid **2b** (0.21 g, 1.60 mmol), potassium carbonate (0.37 g, 2.68 mmol) and potassium fluoride (0.16 g, 2.68 mmol) were also reacted and the product was recrystallised to give **5** as a yellow crystals (0.25 g, 63%).

m.p. 129–131 ^oC (Lit.[27]: 130–131 ^oC). IR (neat) ν_{max} (cm^{-1}): 3550–2550 (O–H str.), 2937 (C–H str.), 1731 (C=O str.), 1617 (aryl C=C str.), 1538 (antisym. C-NO_2 str.), 1334 (sym. C-NO_2 str.), 1191 (C–O str.), 1167 (C–N str.), 745 (aryl C–H def.). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 12.03 (broad s, COO<u>H</u>, 1H), 8.95–8.92 (m, phenyl, 1H), 8.44 (d, J = 2.4 Hz, phenyl, 1H), 7.25 (dd, J = 2.4 Hz; 9.4 Hz, phenyl, 1H), 4.96 (s, -C<u>H</u>-COOH, 1H), 4.54–4.52 (m, -*N*-C<u>H</u>$_2$-, 2H), 2.22–2.18; 2.10–2.03; 1.99–1.97 (m, C-C<u>H</u>$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$-C, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.8 (<u>C</u>OOH), 148.9; 145.0; 140.3; 138.8; 130.6; 123.9 (phenyl), 66.4 (-<u>C</u>H-COOH), 48.5 (-*N*-<u>C</u>H$_2$-), 27.3 (C-CH$_2$-CH$_2$-<u>C</u>H$_2$-C), 24.8 (C-<u>C</u>H$_2$-CH$_2$-CH$_2$-C), 21.7 (C-CH$_2$-<u>C</u>H$_2$-CH$_2$-C).

***N*-(2,4-Dinitrophenyl)glycine [6]**
1-Fluoro-2,4-dinitrobenzene **1d** (1.10 g, 5.94 mmol), glycine **2c** (0.53 g, 7.12 mmol), potassium carbonate (1.64 g, 11.9 mmol) and potassium fluoride (0.69 g, 11.9 mmol) were reacted to give **6** as a yellow powder (1.02 g, 71%). m.p. 170–172 ^oC. IR (neat) ν_{max} (cm^{-1}): 3500–2500 (O–H str.), 3343 (N–H str.), 2885 (C–H str.), 1713 (C=O str.), 1607 (aryl C=C str.), 1527 (antisym. C-NO_2 str.), 1449 (antisym. C–H def.), 1379 (sym. C–H def.), 1338 (sym. C-NO_2 str.), 1243 (C–O str.), 1132 (C–N str.), 739 (aryl C–H def.). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.11 (broad s, COO<u>H</u>, 1H), 8.99–8.96 (m, phenyl, 1H), 8.85 (d, J = 2.4 Hz, phenyl, 1H), 8.25 (dd, J = 2.4 Hz; 9.6 Hz, phenyl, 1H), 7.10 (s, -N<u>H</u>-, 1H), 4.30 (d, J = 5.6 Hz, -C<u>H</u>$_2$-COOH, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 172.0 (-<u>C</u>OOH), 149.5; 137.0; 131.7; 129.9; 118.0; 111.5 (phenyl), 44.9 (-<u>C</u>H$_2$-COOH).

***N*-(2,4-Dinitrophenyl)phenyl glycine [7]**
1-Chloro-2,4-dinitrobenzene **1c** (0.50 g, 2.47 mmol), phenyl glycine **2d** (0.22 g, 2.93 mmol), potassium carbonate (0.68 g, 4.94 mmol) and potassium fluoride (0.29 g, 4.94 mmol) were reacted to give **7** (0.31 g, 39%, yellow oil). IR (neat) ν_{max} (cm^{-1}): 3550–2550 (O–H str.),

3342 (N–H str.), 2844 (C–H str.), 1713 (C=O str.), 1625 (aryl C=C str.), 1522 (antisym. C-NO_2 str.), 1320 (sym. C-NO_2 str.), 1283 (aryl C–N str.), 1217 (C–O str.), 1096 (C–N str.), 744 (aryl C–H def.). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.11 (broad s, COOH, 1H), 8.87–8.84 (m, phenyl, 1H), 8.76 (d, J = 2.2 Hz, phenyl, 1H), 8.27 (dd, J = 2.3 Hz; 9.5 Hz, phenyl, 1H), 7.35–7.16 (m, phenyl, 5H), 6.10 (s, -NH-, 1H), 4.29 (d, J = 5.6 Hz, -CH-COOH, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 170.5 (-COOH), 151.2; 139.3; 135.6; 131.7; 129.7; 129.1; 127.5; 125.9; 118.0; 114.4 (phenyl), 63.3 (-CH-COOH).

***N*-(2,4-Dinitrophenyl)methyl glycine [8]**

1-Chloro-2,4-dinitrobenzene **1c** (0.50 g, 2.47 mmol), methyl glycine **2e** (0.26 g, 2.96 mmol), potassium carbonate (0.68 g, 4.94 mmol) and potassium fluoride (0.29 g, 4.94 mmol) were reacted to give **8** (0.20 g, 32%, yellow powder). m.p. 136–138 ^{o}C. IR (neat) ν_{max} (cm^{-1}): 3500–2550 (O–H str.), 3314 (N–H str.), 2889 (C–H str.), 1710 (C=O str.), 1621 (aryl C=C str.), 1533 (antisym. C-NO_2 str.), 1456 (antisym. C–H def.), 1379 (sym. C–H def.), 1331 (sym. C-NO_2 str.), 1118 (C–O str.), 1059 (C–N str.), 721 (aryl C–H def.). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.06 (broad s, COOH, 1H), 8.97 (s, -NH-, 1H), 8.84 (d, J = 2.4 Hz, phenyl, 1H), 8.26 (dd, J = 2.0 Hz; 9.2 Hz, phenyl, 1H), 7.09 (d, J = 9.6 Hz, phenyl, 1H), 4.00 (d, J = 5.4 Hz, -CH-COOH, 1H), 1.52 (s, -CH$_3$, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 171.0 (-COOH), 159.7; 137.2; 135.0; 130.8; 120.8; 115.2 (phenyl), 52.0 (-CH-COOH), 18.4 (-CH$_3$).

***N*-(2-Nitrophenyl)glycine [9]**

1-Fluoro-2-nitrobenzene **1b** (1.10 g, 5.94 mmol), glycine **2c** (0.53 g, 7.12 mmol), potassium carbonate (1.64 g, 11.9 mmol) and potassium fluoride (0.69 g, 11.9 mmol) were reacted to give **9** as a yellow powder (0.87 g, 75%). m.p. 170–172 ^{o}C. IR (neat) ν_{max} (cm^{-1}): 3550–2550 (O–H str.), 3342 (N–H str.), 2886 (C–H str.), 1713 (C=O str.), 1606 (aryl C=C str.), 1537 (antisym. C-NO_2 str.), 1338 (sym. C-NO_2 str.), 1234 (C–O str.), 1135 (C–N str.), 739 (aryl C–H def.). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.98 (broad s, COOH, 1H), 8.35–8.34 (m, phenyl, 1H), 7.75–7.72 (m, phenyl, 1H), 7.59–7.54 (m, phenyl, 2H), 6.56 (s, -NH-, 1H), 4.29 (d, J = 5.2 Hz, -CH$_2$-COOH, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.0 (-COOH), 145.0; 135.6; 131.7; 125.9; 118.0; 111.5 (phenyl), 44.9 (-CH$_2$-COOH).

***N*-(2-Nitrophenyl)piperidine-2-carboxylic acid [10]**

1-Chloro-2-nitrobenzene **1a** (0.20 g, 1.27 mmol), **D,L**-pipecolinic acid **2b** (0.19 g, 1.47 mmol), potassium carbonate (0.35 g, 2.54 mmol) and potassium fluoride (0.15 g, 2.54 mmol) were reacted to give **10** (0.02 g, 6%, yellow oil). IR (neat) ν_{max} (cm^{-1}): 3500–2600 (O–H str.), 2896 (C–H str.), 1717 (C=O str.), 1614 (aryl C=C str.), 1533 (antisym. C-NO_2 str.), 1342 (sym. C-NO_2 str.), 1195 (C–O str.), 1172 (C–N str.), 741 (aryl C–H def.). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 12.05 (broad s, COOH, 1H), 8.86–8.84 (m, phenyl, 1H), 8.45–8.43 (m, phenyl, 1H), 8.01–7.97 (m, phenyl, 1H), 7.68–7.66 (m, phenyl, 1H), 4.98 (s, -CH-COOH, 1H), 4.54–4.52 (m, -*N*-CH$_2$-, 2H), 2.20–2.18; 2.10–2.03; 1.96–1.94 (m, C-CH$_2$-CH$_2$-CH$_2$-C, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.3 (COOH), 143.9; 141.0; 135.0; 126.0; 119.9; 110.5 (phenyl), 66.4 (-CH-COOH), 48.5 (-*N*-CH$_2$-), 27.3 (C-CH$_2$-CH$_2$-CH$_2$-C), 25.5 (C-CH$_2$-CH$_2$-CH$_2$-C), 21.7 (C-CH$_2$-CH$_2$-CH$_2$-C).

***N*-(2-Nitrophenyl)methyl glycine [11]**

1-Chloro-2-nitrobenzene **1a** (0.50 g, 3.18 mmol), methyl glycine **2e** (0.34 g, 3.81 mmol), potassium carbonate (0.88 g, 6.36 mmol) and potassium fluoride (0.37 g, 6.36 mmol) were reacted to give **11** (0.21 g, 31%, yellow oil). IR (neat) ν_{max} (cm^{-1}): 3550–2550 (O–H str.), 3342 (N–H str.), 2888 (C–H str.), 1709 (C=O str.), 1621 (aryl C=C str.), 1537 (antisym. C-NO_2 str.), 1378 (sym. C-NO_2 str.), 1120 (C–O str.), 1063 (C–N str.), 720 (aryl C–H def.). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 12.13 (broad s, COOH, 1H), 9.10 (s, -NH-, 1H), 8.41–8.38 (m, phenyl, 1H), 7.85–7.83 (m, phenyl, 1H), 7.65–7.61 (m, phenyl, 2H), 3.86 (d, J = 5.4 Hz, -CH-COOH, 1H), 1.43 (s, 3H). ^{13}C-NMR (100 MHz $CDCl_3$) δ 171.0 (-COOH), 152.8; 137.2; 135.0; 130.8; 121.8; 115.2 (phenyl), 52.0 (-CH-COOH), 19.1 (-CH$_3$).

***N*-(4-Trifluoromethyl-2-nitrophenyl)piperidine-2-carboxylic acid [12]**

1-Chloro-4-trifluoromethyl-2-nitrobenzene **1e** (1.00 g, 4.43 mmol), **D,L**-pipecolinic acid **2b** (0.69 g, 5.32 mmol), potassium carbonate (1.22 g, 8.86 mmol) and potassium fluoride (0.51 g, 8.86 mmol) were reacted to give **12** as a yellow powder in 40% yield (0.56 g). m.p. 122–124 ^{o}C. IR (neat) ν_{max} (cm^{-1}): 3550–2500 (O–H str.), 2937 (C–H str.), 1713 (C=O str.), 1625 (aryl C=C str.), 1537 (antisym. C-NO_2 str.), 1328 (sym. C-NO_2 str.), 1125 (C–F str.), 744 (aryl C–H def.). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.07 (broad s, COOH, 1H), 8.06–8.05 (m, phenyl, 1H), 7.39–7.36 (m, phenyl, 1H), 7.14–7.12 (m, phenyl, 1H), 4.78 (s, -CH-COOH, 1H), 4.04–4.01 (m, -*N*-CH$_2$-, 2H), 1.70–1.68; 1.60–1.54; 1.46–1.44 (m, C-CH$_2$-CH$_2$-CH$_2$-C, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 177.6 (COOH), 148.3; 140.9; 130.1; 130.0; 123.9; 122.8 (phenyl), 61.1 (-CH-COOH), 48.4 (-*N*-CH$_2$-), 27.3 (C-CH$_2$-CH$_2$-CH$_2$-C), 24.9 (C-CH$_2$-CH$_2$-CH$_2$-C), 20.5 (C-CH$_2$-CH$_2$-CH$_2$-C).

***N*-(4-Chloro-2-nitrophenyl)pyrrolidine-2-carboxylic acid [13]**

1,4-Dichloro-2-nitrobenzene **1f** (1.0 g, 5.20 mmol), **L**-proline **2a** (0.72 g, 6.25 mmol), potassium carbonate (1.44 g, 10.4 mmol) and potassium fluoride (0.60 g, 10.4 mmol) were reacted to give **13** (0.61 g, 43%, brown oil). IR (neat) ν_{max} (cm^{-1}): 3550–2550 (O–H str.), 3026 (aryl C–H str.), 2870 (C–H str.), 1717 (C=O str.), 1610 (aryl C=C str.), 1511 (antisym. C-NO_2 str.), 1346 (sym. C-NO_2 str.), 1221 (C–O str.), 754 (C–Cl str.). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.5 (broad s, COOH, 1H), 7.66–7.64 (m, phenyl, 1H), 7.01–6.98 (m, phenyl, 1H), 6.74–6.71 (m, phenyl, 1H), 4.38 (s, -CH-COOH, 1H), 3.54–3.52 (m, -*N*-CH$_2$-, 2H), 1.84–1.79; 1.58–1.54 (m, C-CH$_2$-

$C\underline{H}_2$-C, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 177.5 (C<u>O</u>OH), 139.9; 138.2; 133.1; 125.9; 122.2; 117.9 (phenyl), 61.7 (-C<u>H</u>-COOH), 51.7 (-*N*-$C\underline{H}_2$-), 30.9 (C-CH_2-$C\underline{H}_2$-C), 24.6 (C-$C\underline{H}_2$-CH_2-C).

***N*-(4-Chloro-2-nitrophenyl)piperidine-2-carboxylic acid [14]**

1,4-Dichloro-2-nitrobenzene **1f** (0.10 g, 0.52 mmole), **D**,**L**-pipecolinic acid **2b** (0.08 g, 0.63 mmol), potassium carbonate (0.15 g, 1.05 mmol) and potassium fluoride (0.06 g, 1.05 mmol) were reacted to give **14** (0.01 g, 7%, brown oil). IR (neat) ν_{max} (cm^{-1}): 3550–2550 (O–H str.), 2880 (C–H str.), 1712 (C=O str.), 1610 (aryl C=C str.), 1517 (antisym. C-NO_2 str.), 1342 (sym. C-NO_2 str.), 1226 (C–O str.), 752 (C–Cl str.). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.72 (broad s, COO<u>H</u>, 1H), 7.86–7.83 (m, phenyl, 1H), 7.31–7.28 (m, phenyl, 1H), 7.02–6.99 (m, phenyl, 1H), 4.56 (s, -C<u>H</u>-COOH, 1H), 3.34–3.31 (m, -*N*-$C\underline{H}_2$-, 2H), 1.90–1.88; 1.80–1.74; 1.66–1.64 (m, C-$C\underline{H}_2$-$C\underline{H}_2$-$C\underline{H}_2$-C, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 177.6 (<u>C</u>OOH), 146.3; 142.9; 133.5; 132.0; 125.9; 120.8 (phenyl), 62.1 (-<u>C</u>H-COOH), 49.4 (-*N*-$\underline{C}H_2$-), 28.3 (C-CH_2-CH_2-$\underline{C}H_2$-C), 25.4 (C-$\underline{C}H_2$-CH_2-CH_2-C), 21.5 (C-CH_2-$\underline{C}H_2$-CH_2-C).

***N*-(2-Nitro-4-methoxyphenyl)pyrrolidine-2-carboxylic acid [15]**

4-Chloro-3-nitroanisole **1g** (1.01 g, 5.40 mmol), **L**-proline **2a** (0.75 g, 6.48 mmol), potassium carbonate (1.49 g, 10.80 mmol) and potassium fluoride (0.63 g, 10.80 mmol) were reacted to give **15**, which on recrystallisation from petroleum ether (40–60 ^{o}C) gave a yellow powder (0.36 g, 25%). m.p. 119–120 ^{o}C. IR (neat) ν_{max} (cm^{-1}): 3550–2550 (O–H str.), 2977 (C–H str.), 1720 (C=O str.), 1645 (aryl C=C str.), 1537 (antisym. C-NO_2 str.), 1334 (sym. C-NO_2 str.), 1120 (C–O str.), 749 (aryl C–H def.). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.0 (broad s, COO<u>H</u>, 1H), 7.20–7.19 (m, phenyl, 1H), 7.10–7.08 (m, phenyl, 1H), 7.01–6.98 (m, phenyl, 1H), 5.00 (s, -C<u>H</u>-COOH, 1H), 4.54–4.52 (m, -*N*-$C\underline{H}_2$-, 2H), 3.87 (s, -OC<u>H</u>$_3$, 3H), 2.18–2.15; 1.98–1.95 (m, C-$C\underline{H}_2$-$C\underline{H}_2$-C, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.5 (-<u>C</u>OOH), 153.0; 138.5; 135.2; 125.9; 121.0; 116.0 (phenyl), 75.2 (-<u>C</u>H-COOH), 56.4 (-O<u>C</u>H$_3$), 50.3 (-*N*-$\underline{C}H_2$-), 28.9 (C-CH_2-$\underline{C}H_2$-C), 26.8 (C-$\underline{C}H_2$-CH_2-C).

***N*-(2-Nitro-4-methylphenyl)pyrrolidine-2-carboxylic acid [16]**

4-Chloro-3-nitrotoluene **1h** (1.00 g, 5.40 mmol), **L**-proline **2a** (0.75 g, 6.48 mmol), potassium carbonate (1.49 g, 10.8 mmol) and potassium fluoride (0.63 g, 10.8 mmol) were reacted to give **16** (0.38 g, 28%) as a red oil. IR (neat) ν_{max} (cm^{-1}): 3550–2550 (O–H str.), 2937 (C–H str.), 1720 (C=O str.), 1606 (aryl C=C str.), 1527 (antisym. C-NO_2 str.), 1327 (sym. C-NO_2 str.), 743 (aryl C–H def.). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.3 (broad s, COO<u>H</u>, 1H), 8.06–8.04 (m, phenyl, 1H), 7.51–7.48 (m, phenyl, 1H), 6.84–6.80 (m, phenyl, 1H), 5.20 (s, -C<u>H</u>-COOH, 1H), 4.51–4.99 (m, -*N*-$C\underline{H}_2$-, 2H), 3.15 (s, -C<u>H</u>$_3$, 3H), 2.17–2.14; 1.98–1.94 (m, C-$C\underline{H}_2$-$C\underline{H}_2$-C, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.6 (-<u>C</u>OOH), 140.5; 139.3; 133.0; 125.0; 123.9; 118.2 (phenyl), 74.5 (-<u>C</u>H-COOH), 49.3 (-*N*-$\underline{C}H_2$-), 28.3 (C-CH_2-$\underline{C}H_2$-C), 27.1 (C-$\underline{C}H_2$-CH_2-C) 23.1 (-<u>C</u>H$_3$).

***N*-[2-(3-Nitropyridyl)]pyrrolidine-2-carboxylic acid [17]**

2-Chloro-3-nitropyridine **1i** (0.50 g, 3.15 mmol), **L**-proline **2a** (0.44 g, 3.78 mmol), potassium carbonate (0.87 g, 6.30 mmol) and potassium fluoride (0.37 g, 6.30 mmol) were reacted to give **17** as a greenish-yellow powder in 97% yield (0.72 g). m.p. 135–137 ^{o}C (Lit.[18]: 137–138 ^{o}C). IR (neat) ν_{max} (cm^{-1}): 3550–2550; 3432 (O–H str.), 2923 (C–H str.), 1702 (C=O str.), 1603 (pyridyl C=C str.), 1463 (antisym. C-NO_2 str.), 1331 (sym. C-NO_2 str.), 1246 (C–O str.), 1052 (C–N str.), 750 (aryl C–H def.). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.07 (broad s, COO<u>H</u>, 1H), 8.26 (dd, *J* = 1.6 Hz; 4.4 Hz, pyridyl, 1H), 8.04 (dd, *J* = 1.6 Hz; 8.0 Hz, pyridyl, 1H), 6.72 (dd, *J* = 4.6 Hz; 8.2 Hz, pyridyl, 1H), 4.74 (dd, *J* = 5.2 Hz; 7.6 Hz, -C<u>H</u>-COOH, 1H), 3.31–3.27 (m, -*N*-C<u>H</u>H-, 1H), 3.22–3.18 (m, -*N*-CH<u>H</u>-, 1H), 2.35–2.33 (m, C-CH_2-CH<u>H</u>-C, 1H), 2.19–2.13 (m, C-CH<u>H</u>-C<u>H</u>H-C, 2H), 1.69–1.67 (m, C-C<u>H</u>H-CH_2-C, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 177.9 (-<u>C</u>OOH), 151.1; 149.3; 134.9; 132.5; 112.5 (pyridyl), 61.7 (-<u>C</u>H-COOH), 49.7 (-*N*-$\underline{C}H_2$-), 28.9 (C-CH_2-$\underline{C}H_2$-C), 25.1 (C-$\underline{C}H_2$-CH_2-C).

***N*-[2-(3-Nitropyridyl)]piperidine-2-carboxylic acid [18]**

2-Chloro-3-nitropyridine **1i** (0.50 g, 3.15 mmol), **D**,**L**-pipecolinic acid **2b** (0.49 g, 3.78 mmol), potassium carbonate (0.87 g, 6.30 mmol) and potassium fluoride (0.37 g, 6.30 mmol) were reacted to give **18** (0.36 g, 45%, yellow powder). m.p. 140–144 ^{o}C. IR (neat) ν_{max} (cm^{-1}): 3550–2200; 3424 (O–H str.), 2899 (C–H str.), 1710 (C=O str.), 1596 (pyridyl C=C str.), 1559 (antisym. C-NO_2 str.), 1463 (C–H def.), 1327 (sym. C-NO_2 str.), 1235 (C–O str.), 938 (pyridyl C–H def.). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.11 (broad s, COO<u>H</u>, 1H), 8.54 (dd, *J* = 1.6 Hz; 4.4 Hz, pyridyl, 1H), 8.14 (dd, *J* = 1.6 Hz; 8.0 Hz, pyridyl, 1H), 6.80 (dd, *J* = 4.8 Hz; 8.4 Hz, pyridyl, 1H), 5.28 (dd, *J* = 5.2 Hz; 7.6 Hz, -C<u>H</u>-COOH, 1H), 4.52–4.50 (m, -*N*-C<u>H</u>H-, 1H), 4.25–4.22 (m, -*N*-CH<u>H</u>-, 1H), 2.53–2.51 (m, C-CH_2-CH_2-CH<u>H</u>-C, 1H), 2.42–2.39 (m, C-CH_2-CH_2-C<u>H</u>H-C, 1H), 2.19–2.13 (m, C-$C\underline{H}_2$-CH_2-CH_2-C, 2H), 1.92–1.87 (m, C-CH_2-$C\underline{H}_2$-CH_2-C, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.1 (-<u>C</u>OOH), 152.1; 150.3; 135.7; 132.5; 113.5 (pyridyl), 59.7 (-<u>C</u>H-COOH), 51.4 (-*N*-$\underline{C}H_2$-), 27.9 (C-CH_2-CH_2-$\underline{C}H_2$-C), 26.1 (C-$\underline{C}H_2$-CH_2-CH_2-C), 21.9 (C-CH_2-$\underline{C}H_2$-CH_2-C).

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