Synthesis of Dipeptides and Ruthenium-Phenanthroline Derivative for Photo Redox Studies

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Abstract: This paper describes the synthesis and characterization of a dipeptides and ruthenium phenanthroline-amine for the study of photoinitiated electron transfer (ET) in dipeptides were described.

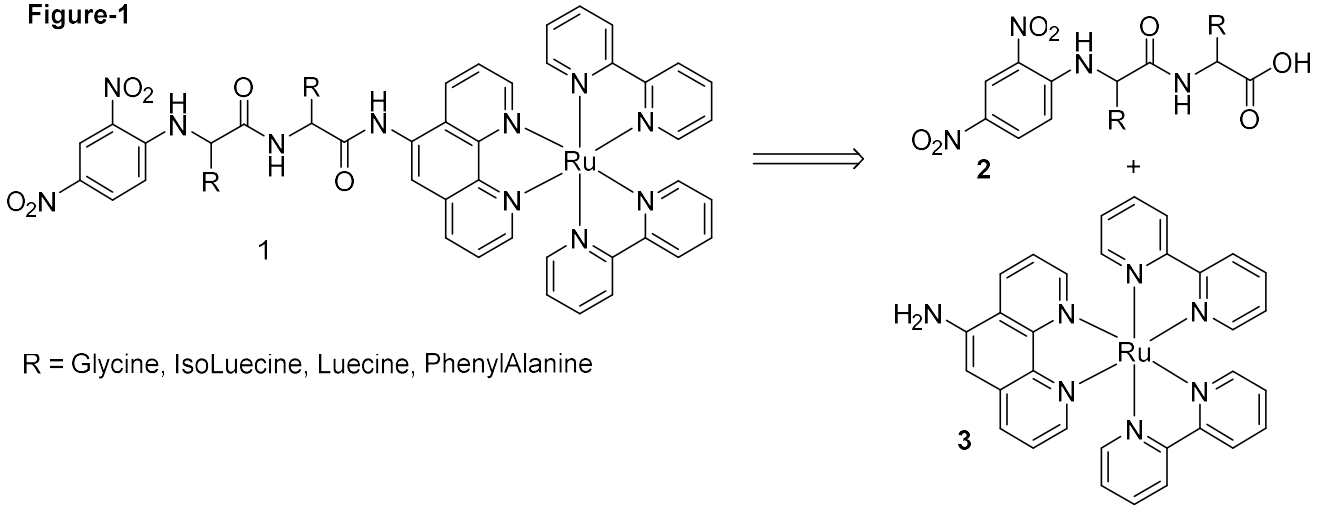
Key words: Photoredox, Ruthenium-phenanthroline-amine, Dipeptides, Electron Transfer.

Introduction: Photo physical properties of ruthenium complexes are much attention in recent years for its wide application is the study of electron transfer[1,2], molecular assemblies[3,4] and amide bridges containing peptides and proteins. groups[5,6]. A key feature of these applications is the electron distribution of ruthenium complexes measured by its acid dissociation constants of the ground and excited states. Several research group[7,8,9,10] explored excited-state charge distribution and electron transfer (ET) in ruthenium complexes especially in combination with proteins and polypeptides

Present work: In continuing our work on photoredox, we succeeded in synthesizing the Fluorescence Probe[11] to investigate cytochrome *c* folding kinetics and Synthesizing the photoredox ruthenium bipyridyl were linked with biomolecules having oxidative quencher,

viologen[12], herein we disclosed design of Ruthenium-Dipeptide molecule **1** (figure-1) which allows for many variations of the ruthenium Phenanthroline-5-Amine **3** and dipeptide structures **2**, The synthetic routes are straightforward and very manageable, it is possible to use commercially available L-amino acids as enantiomerically enriched starting materials.

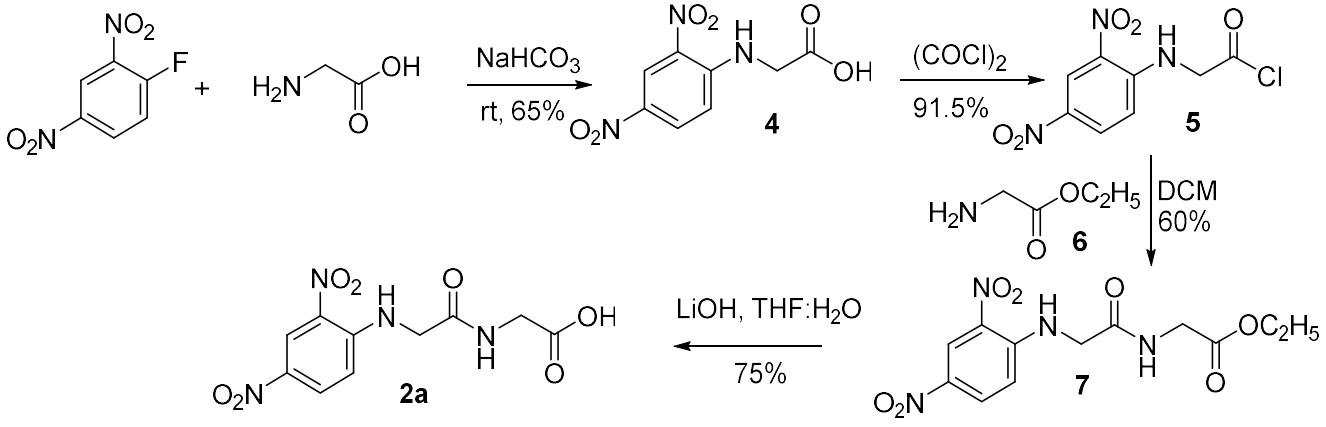
Figure-1



R = Glycine, IsoLuecine, Luecine, PhenylAlanine

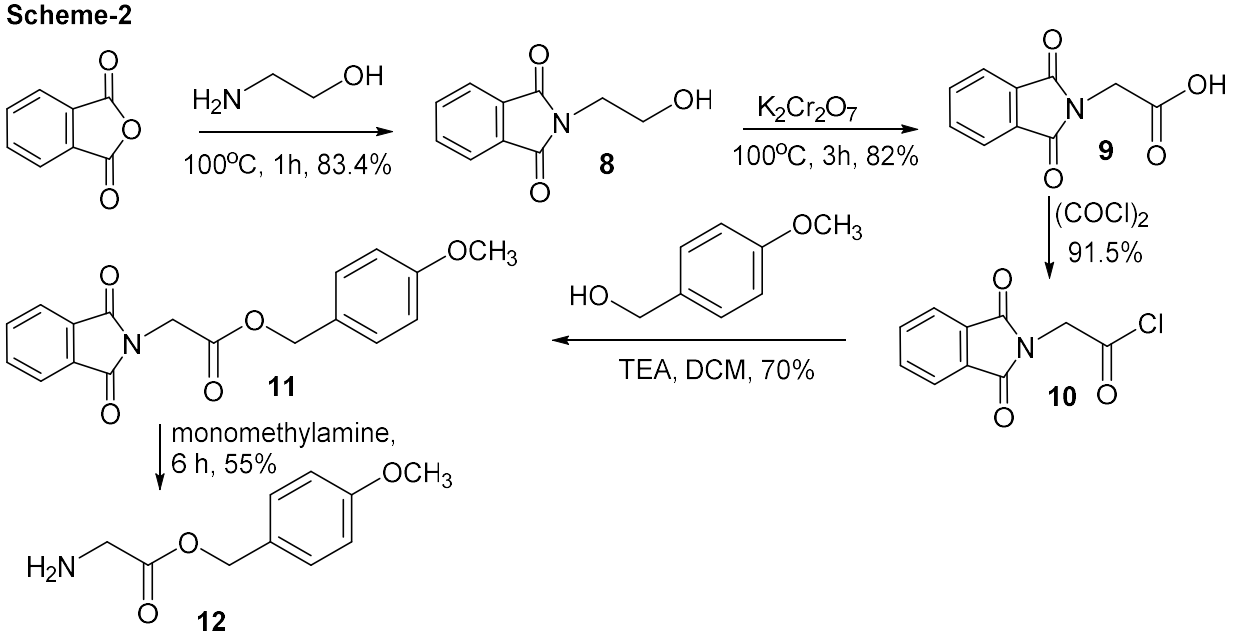
Synthesis Part: The dinitro-fluorobenzene were treated with glycine under base condition to get product[13] **4**, which is treated with oxalyl chloride to get acid chloride product[14] **5.** The free glycine ester[15] **6** is prepared with base treatment in 90 yield. On combining the **5** with **6** to gives the dipeptide[16] ester **7** in 60 % yield. The diester **7** on saponification gives dipeptide[17] **2a** in 75% yield. (scheme-1)

Scheme-1



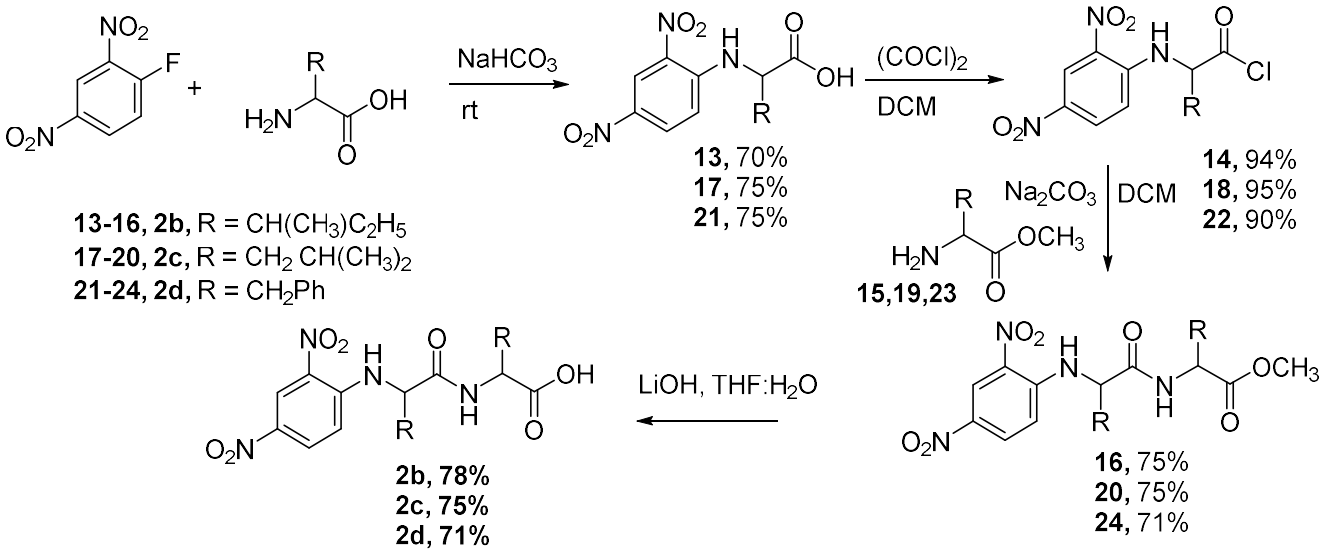
Alternatively, dipeptide acid **2a** was prepared from phthalimido ethanol[18] **8**, which on oxidation to acid product[19] **9** followed by acid chloride[20] conversion gives **10** in 91% yield, which was esterified to MPM ester[21] **11** by using MPM-OH, the phthalide group is cleaved by 40% monomethyl amine to get glycine MPM ester[22] **12** in 55% yield.(scheme-2)

Scheme-2



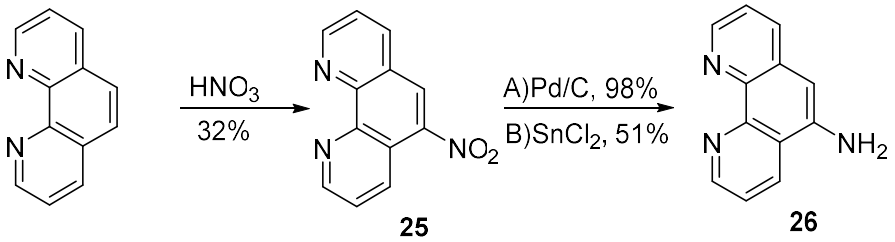
Similarly, corresponding symmetrical dipeptides from isoleucine[23,24], leucine[25-27] and phenylalanine[28-30] were synthesized in four steps each to get **2b**, **2c**, and **2d** respectively.

Scheme-3



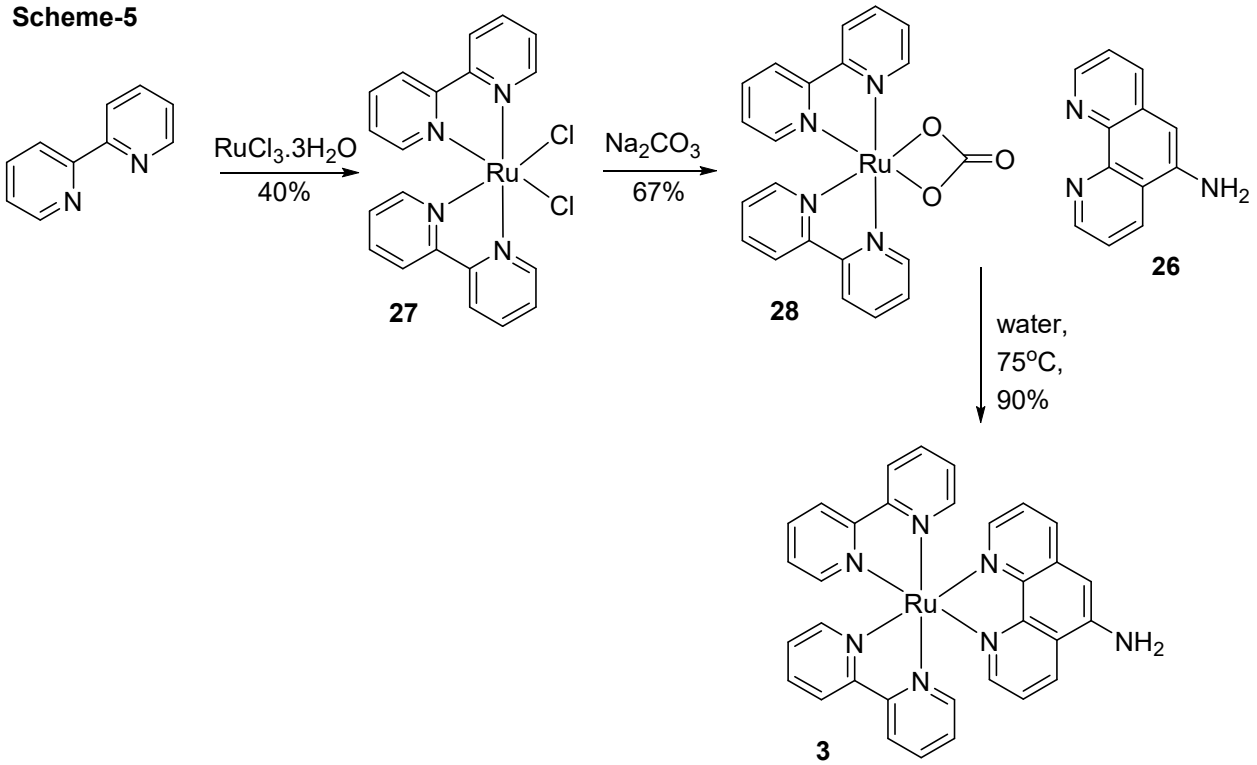
The phenanthrene was on nitration gives phenthroline-5-nitro[31] in 32% yield. The corresponding amine was synthesized in two different methods, palladium/charcoal[32] and stannous chloride[33] in 90% and 51% respectively. (scheme-4)

Scheme-4



Ruthenium carbonate is prepared in two steps by treating 2,2-bipyridyl with ruthenium trichloride to obtained intermediate product[34] in 40% yield, which on treated with sodium carbonate under Argon atmosphere gives ruthenium carbonate[35] in 67% yield. Ruthenium carbonate on treated with compounds **26** under heating condition to obtained the pure product[36] in 90% yield. (scheme-5).

Scheme-5

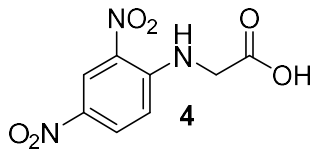


Conclusion: In summary, A manageable synthetic route for dipeptides and ruthenium-phenanthrene-amine was established. This work provides valuable information for the discovery of novel strategies in exploring novel molecules having combined properties of electronic channel and photoredox properties of ruthenium and its amide coupling with dipeptides suitable for biological applications.

Experimental parameters: All reagents were purchased from commercial sources and used without any further purification. Technical solvents were used unless otherwise stated. Anhydrous solvents were obtained by passing solvent through columns of molecular sieves in a solvent purification system. Flash chromatography employed 230-400 mesh silica gel. Solvents used for chromatography are quoted as volume/volume ratios. Analytical thin layer chromatography was performed using silica gel plates precoated with silica gel 60 F254 (0.2 mm) using UV light and 10% ethanolic solution phosphomolybdic acid dip to visualize the products. ^{1}H NMR spectra were recorded at 298 K unless otherwise stated using Varian VXR (200 MHz) spectrometers. Data is expressed in parts per million (ppm) downfield shift from tetramethyl silane with residual solvent as an internal reference (δ 7.26 ppm for chloroform) and is reported as position (δ in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet = multiplet), coupling constant (J in Hz) and integration (number of protons). ^{13}C NMR spectra were recorded at 298 K unless otherwise stated using Bruker Avance III 100 MHz spectrometers with complete proton decoupling. Data is expressed in parts per million (ppm) downfield shifts relative to the internal reference (δ 77.2 ppm for the central peak of deuterated chloroform) and is reported as position (δ in ppm). IR spectra were recorded on a Perkin Elmer 688 spectrometer. Mass spectra were obtained on a Shimadzu QP 1000 spectrometer. High resolution mass spectra (HRMS) were recorded using

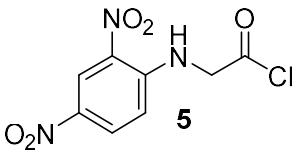
electrospray ionization on a Time of Flight (TOF) mass spectrometer at National Taiwan University.

(2,4-Dinitro-phenylamino)-acetic acid: (4) Dissolved 6.0 g (79 mmol) of glycine in 100 mL of 0.1 M sodium bicarbonate solution in a beaker. Added 160 mmol (3.0 g/2.0 mL) of 2,4-dinitrofluorobenzene solution (in 10 mL of acetone) over a period of 5 minutes. Stir for 4 hours at room temperature. Distilled to half of its volume to get residue and neutralized with 2.0 M HCl (30 mL) and filtered, washed the yellow solid with water (10 mL X 2) followed by hexane (10 mL X 2). Transferred the solid to single neck flask and add benzene (10 mL X 2), concentrated on rota evaporator under pressure to obtain 2.5 g of yellow solid product **4** in 65% yield. Melting point is 192-196°C. ^{1}H NMR (200 MHz, acetone-d_6): 9.02 (d, 1H, *J* = 2.6 Hz), 8.37-8.31 (dd, 1H, *J* = 2.8 & 6.6 Hz), 7.18 (d, 1H, *J* = 9.2 Hz), 4.48-4.45 (dis-d, 2H, *J* = 2.6 & 7.2 Hz). Mass: m/z. 241 (M+).



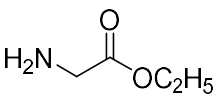
4

(2,4-Dinitro-phenylamino)-acetyl chloride: (5): Suspended 5.0 g (24.3 mmol) of N-(2,4-Dintrophenyl)-Glycine in benzene (50 mL), Added 24.3 mmol (3.1 g / 2.2 mL) of oxalyl chloride drop wise over a period of 5 minutes under nitrogen atmosphere. Stirred at room temperature for 2 hours. Concentrated on rota evaporator to get 5.0 g of reddish solid product **5** in 91.5% yield. Melting point is 82-84°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.17 (d, 1H, *J* = 2.6 Hz), 9.17-9.16 (m, 1H, NH), 8.39-8.37 (dd, 1H, *J* = 2.0 & 6.2 Hz), 6.75 (d, 1H, *J* = 9.2 Hz), 4.65 (d, 2H, *J* = 6.2 Hz).



5

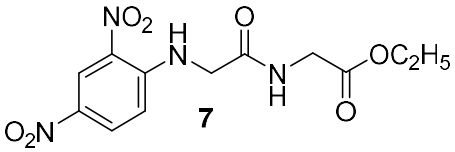
Ethyl-2-aminoacetate: (6): Dissolve 5.0 g (35.8 mmol) of ethyl 2-aminoacetate HCl salt in 100 mL of 1.0 M solution of sodium carbonate in a beaker. Stirred the reaction mixture at room temperature for one hour. Extracted with DCM



6

(100 mL X 2), Washed the organic layer with brine solution (200 mL), dried over $MgSO_4$ and filter. Concentrated under reduced pressure to get 1.8 g of product **6** in 50% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.16 -4.11 (m, 2H), 3.33 (d, 2H, *J* = 2.0 Hz), 1.23-1.14 (m, 3H).

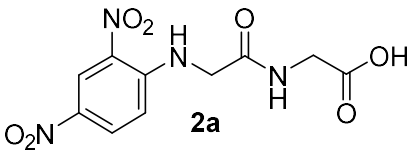
[2-(2,4-Dinitro-phenylamino)-acetylamino]-acetic acid ethyl ester: (7): Suspended 1.74 g



7

(12.4 mmol) of ethyl ester **6** in dichloromethane (30 mL) under nitrogen atmosphere. Cool to 0^{o}C and add 2.0 g (19.0 mmol) of sodium carbonate at 0^{o}C and stir for 1 h. Drop wise addition of 2.5 g (9.6 mmol) of acid chloride **5** solution (10 mL of dichloromethane) over a period of 15 minutes. Maintained at room temperature for 6 hours and poured the reaction mass into beaker containing 250 mL of water. Extracted with dichloromethane (50 mL x2). Washed the combined organic layer with saturated $NaHCO_3$ solution, brine solution, dried over $MgSO_4$, and filtered. Concentrated under reduced pressure and purified by column chromatography to obtain the 1.8 g of product **7** in 60% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.15 (d, 1H, *J* = 2.8 Hz), 8.95 (m, 1H, NH), 8.34-8.28 (dd, 1H, *J* = 6.2 & 13.0 Hz), 6.80 (d, 1H, *J* = 8.8 Hz), 6.36 (m, 1H, NH), 4.22-4.02 (t, 2H, *J* = 5.2 & 6.6 Hz), 1.30-1.23 (t, 3H, *J* = 7.2 & 14.2 Hz). Mass m/z: 326 (M+).

[2-(2,4-Dinitro-phenylamino)-acetylamino]-acetic acid. (2a): Method-A: Dissolved 1.5 g



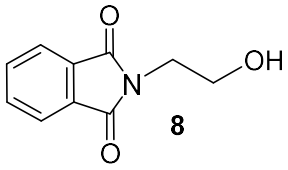
2a

(4.5 mmol) of ethyl ester **7** in THF: water 10 mL: 5 mL. Added 386 mg (12.0 mmol) of lithium hydroxide portion wise over a period of 10 minutes. Stirred at room temperature for 4 hours. Initially it was dark red which gradually turns to pale red (after 2 hours) and yellow (after 4 hours). Concentration on rota evaporator under reduced pressure to remove the THF. Dissolved the residue in 15 mL of water and neutralize with conc. HCl (5 mL) and filtered, washed the yellow solid with water (10 mL X 2) followed by hexane (10 mL X 2). Transferred

the solid to single neck flask and added benzene (10 mL X 2), concentrated on rota evaporator under pressure to obtain 1.0 g of yellow solid **2a** in 75% yield. Melting point is 194-195°C. ^{1}H NMR (200 MHz, Acetone-d_6): δ 9.26 (m, 1H, NH), 8.99 (d, 1H, *J* = 2.6 & 6.6 Hz), 8.35-8.29 ((dd, 1H, *J* = 2.6 & 6.6 Hz), 7.88 (m, 1H, NH), 7.07 (d, 1H, *J* = 9.4 Hz), 4.37 (dd, 2H, *J* = 2.8 & 6.6 Hz), 4.05 (d, 2H, *J* = 5.6 Hz). Mass m/z: 298 (M+).

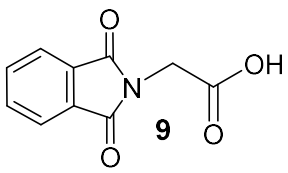
Method-B: Suspended 1.0 g (5.1 mmol) of MPM-ester **12** in dichloromethane (30 mL) under nitrogen atmosphere. Cool to 0°C and add 1.1 g (10.2 mmol) of sodium carbonate at 0°C and stir for 1 h. Drop wise addition of 1.2 g (4.6 mmol) of acid chloride **5** solution (10 mL of dichloromethane) over a period of 15 minutes. Maintained at room temperature for 6 hours and poured the reaction mass into beaker containing 250 mL of water. Extracted with dichloromethane (50 mL x 2). Added 10 ml of trifluoro acetic acid and stirred for 2 hours at room temperature. Concentrated to get residue. Extracted with dichloromethane (50 mL x 2). Washed the combined organic layer with saturated $NaHCO_3$ solution, brine solution, dried over $MgSO_4$, and filtered. Concentrated under reduced pressure and purified by column chromatography to obtain the 760 mg of product **7** in 50% yield.

2-(2-Hydroxy-ethyl)-isoindole-1,3-dione: (8): Charged 37 g (250 mmol) of phthalic anhydride in a 1L-R.B. equipped with reflux condenser. Poured 15 g (250 mmol) of 2-amino ethanol. Heated at 90-100°C. Initially the reaction is vigorous and turns from pasty to liquid. Stirred for 1 hour at same temperature. Poured 100 mL of water and increase the temperature to 110-120°C. Maintained for 30 minutes. Poured the hot liquid mass into beaker, allowed cooling to RT. Filtered and washed with water (250 mL) to obtain the product 40 g of product **8** in 83.4% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.88-7.77 (m, 2H), 7.75-7.70 (m, 2H), 3.92 (m, 4H). Mass: 191 (M+).



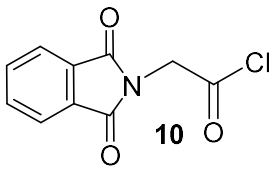
8

1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetic acid: (9): Charged 25 g (131 mol) of 2-Phthalimino ethanol **8** in a 3N-1L-RB equipped reflux. Poured 400 mL of water, 10 mL of glacial acetic acid. Added 30.1 g of $K_2Cr_2O_7$ and stirred for 15 minutes. Dropwise addition of dilute sulfuric acid (25.5 g in 100 mL of water) over 30 minutes. Heated the reaction mass at 70°C –100°C for 1 hour. (Initially it is suspension which turns to clear solution). Maintained at 100°C for 3 hours. Allowed cooling to RT. Concentrated to half off its volume, filtered and washed with water, dry in vacuum for 3 hours to obtain 22 g of white powder solid **9** in 82% yield. Melting point is 193-196°C. Product is soluble in EtOAc, ether, acetone, methanol and Insoluble in DCM, chloroform, benzene, toluene, hexane, and water. ^{1}H NMR (200 MHz, CD_3OD): δ 7.32-7.25 (m, 4H), 3.68 (s, 2H). Mass: 205 (M+).



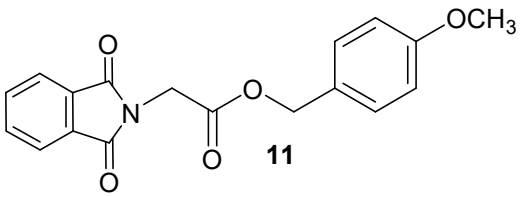
9

(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetyl chloride: (10): Charged 5 g (24 mmol) of 2-Phthalimido acetic acid in a R.B. flask and add toluene under nitrogen atmosphere. drop wise addition 2.2 ml/3.1 g (24 mmol) of oxalyl chloride for 5 minutes. Add one drop of DMF. Stirred at RT for 2 hours. Homogenous solution is formed. Concentrated on rota evaporator to get residue, which slowly turns to reddish solid 5 g of product **10** is obtained in 91.5 yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.94-7.81 (m, 2H), 7.79-7.25 (m, 2H), 4.82 (s, 2H). Mass: 223 (M+).



10

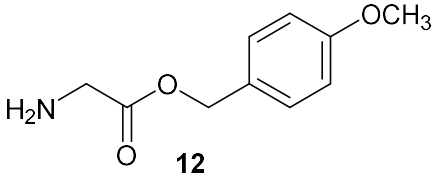
(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetic acid 4-methoxy-benzyl ester: (11): Charged 2.76 g (20 mmol, 0.9 eq) of 4-methoxy benzyl alcohol in a R.B flask and cooled to 0°C and added 75 mL of DCM. Drop wise addition of 4.37mL/3.33g, (33 mmol,



11

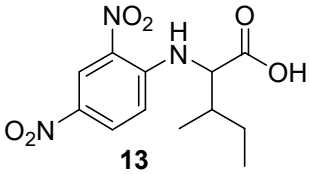
1.5 eq) of TEA over a period 5 minutes. Stirred for 1 hour at RT and cool to 0°C. Drop wise addition of 5.0 g (23 mmol) of acid chloride **10** over a period of 15 minutes. Stir for 0°C-RT for 3 hours. Quenched with water and extracted with DCM, Washed the organic layer with 10%$NaHCO_3$, brine solution, dried over $MgSO_4$ and filtered. Concentrated and Column chromatography purification give 5 g of product **11** in 70% yield. Rf value of MPMOH (0.3) Product (0.6) in 40% EtOAc in hexane. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.89-7.86 (m, 2H), 7.76-7.72 (m, 2H), 7.30 (d, 2H, *J* = 8.8 Hz), 6.86 (d, 2H, *J* = 8.8 Hz), 5.13 (s, 2H), 4.45 (s, 2H), 3.80 (s, 3H). Mass: 325 (M+).

Amino-acetic acid 4-methoxy-benzyl ester: (12): Charged 5 g (15.3 mmol) of MPM ester **11** in a R.B. flask and added 50 mL of chloroform. Added 25 mL of 40% of monomethylamine and stir at RT for 6 hours. Extracted with DCM (50 ml X 2), washed the combined organic layer with 10%$NaHCO_3$, brine solution, dried over $MgSO_4$ and filtered. Concentrated and column purification give 1.65 g of product **12** in 55% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.45 (br-d, 2H, NH), 7.29 (d, 2H, *J* = 8.2 Hz), 6.89 (d, 2H, *J* = 8.2 Hz), 5.28 (s, 2H), 3.79 (s, 3H), 3.31 (d, 2H, *J* = 3.8 Hz).



12

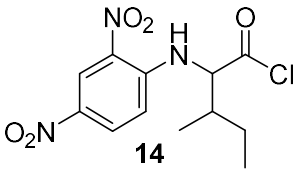
2-(2,4-Dinitro-phenylamino)-3-methyl-pentanoic acid: (13): Dissolved 10.0 g (76 mmol) of Isoluecine in 250 mL of 0.2 M sodium bicarbonate solution in a beaker. Add 52 mmol (9.64 g / 6.5 mL) of 2,4-dinitrofluorobenzene solution (in 20 mL of acetone) over a period of 5 minutes. Stir for 4 hours at room temperature. Distilled to half of its volume to get residue and neutralize with 2.0 M HCl (30 mL) and filtered, washed the yellow solid with water (10 mL X 2) followed by hexane (10 mL X 2). Transferred the solid to single neck flask and add benzene (10 mL X 2), concentrated on rota evaporator under pressure to obtain 10.75 g of yellow solid product **13** in 70% yield.



13

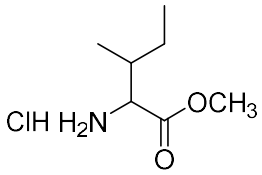
Product is freely soluble in methanol, ethanol, ethyl acetate, dichloromethane, chloroform, and hot benzene. ^{1}H NMR (200 MHz, CD_3OD): δ 8.76 (d, 1H, *J* = 2.8 Hz), 7.98-7.92 (dd, 1H, *J* = 2.8 & 6.8 Hz), 6.60 (d, 1H, *J* = 10.0 Hz), 3.80 (d, 1H, *J* = 5.4 Hz), 1.82-1.52 (m, 1H), 1.41-1.21 (m, 1H), 1.18-0.99 (m, 1H), 0.80-0.67 (m, 6H). Mass m/z: 297 (M+).

2-(2,4-Dinitro-phenylamino)-3-methyl-pentanoyl chloride (14): Suspended 2.0 g (4 mmol) of N- (2,4-Dintrophenyl)-Isoleucine in benzene (20 mL), Added 5 mmol (0.63 g/0.4mL) of oxalyl chloride drop wise over a period of 5 minutes under nitrogen atmosphere. Stir at room temperature for 2 hours. Concentrated on rota evaporator to get 2.0 g of reddish solid product **14** in 94.3% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.08 (d, 1H, *J* = 2.6 Hz), 8.72 (d, 1H, *J* = 7.0 Hz), 8.27-8.21 (dd, 1H, J = 2.6 & 6.8 Hz), 6.68 (d, 1H, *J* = 10.6 Hz), 4.31-4.24 (dd, 1H, *J* = 6.2 & 14.0 Hz), 2.20-2.10 (m, 1H), 1.82-1.62 (m, 1H), 1.40-1.20 (m, 1H), 1.09 (d, 3H, *J* = 1.8 & 5.2 Hz), 0.97-0.89 (t, 3H, *J* = 7.2 & 14.6 Hz).



14

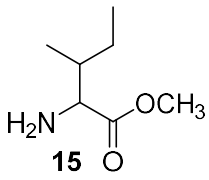
2-Amino-3-methyl-pentanoic acid methyl ester-HCl: (15-HCl): Dissolved 5.0 g (38 mmol) of Isoleucine in 50 mL of methanol and cool to 0^{o}C. Added 95 mmol (11.35 g / 10.0 mL) of thionyl chloride drop wise over a period of 5 minutes. The solution was refluxed for 4 hours until clear is clear solution. And the solvent was evaporated giving the crude methyl ester-HCl, which was triturated with ether at 0^{o}C. The resulting solid product was collected and the dried under high vacuum to yield 85% crude methyl ester HCl. The crude material was recrystallized from 25 mL of hot methanol by slow addition of 100 mL ether followed by cooling at 0^{o}C. The crystals were collected, washed twice with 5:1 of ether: methanol solution and dried under high vacuum to obtained 6 g of pure product in 68%. ^{1}H NMR (200 MHz,



15-HCl

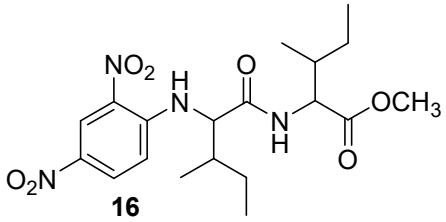
$CDCl_3$): δ 8.95-8.75 (br-s, 2H, NH), 4.05 (t, 1H, *J* = 3.8 & 7.2 Hz), 3.80 (s, 3H), 2.20-2.15 (m, 1H), 1.60-1.35 (m, 2H), 1.10 (d, 3H, *J* = 7.0 Hz), 0.92 (t, 3H, *J* = 7.2 & 14.6 Hz).

2-Amino-3-methyl-pentanoic acid methyl ester: (15): Dissolved 6 g of salt in 100 mL of 1.0 M solution of sodium carbonate in a beaker. Stir the reaction mixture at room temperature for one hour. Extracted with DCM (50 mL X 2), washed the combine organic layer with water (10 mL), brine solution (100 mL), dried over $MgSO_4$ and filtered. Concentrated under reduced pressure to obtain 4.3 g of product **15** as residual oil in 78% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.78 (s, 3H), 3.34 (d, 1H, *J* = 4.8 Hz), 1.75 (m, 1H), 1.45-1.35 (m, 1H), 1.25-1.15 (m, 1H), 0.98-0.78 (m, 6H).



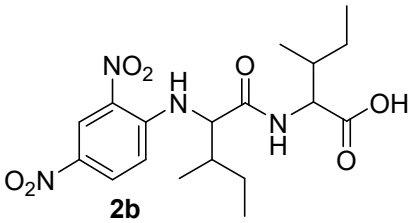
15

2-[2-(2,4-Dinitro-phenylamino)-3-methyl-pentanoylamino]-3-methyl-pentanoic acid methyl ester: (16): Dissolved 1.0 g of methyl ester **15** in dichloromethane (10 mL) under nitrogen atmosphere. Cool to 0^{o}C and 2.0 g of acid chloride **14** solution (in dichloromethane, 10 mL) was added drop wise over a period of 5 minutes. Maintained at room temperature for 6 h and pour the reaction mass into beaker containing 50 mL of water. Extracted with dichloromethane (100 mL). Washed the organic layer with saturated $NaHCO_3$ solution, brine solution, dried over $MgSO_4$, and filtered. Concentration under reduced pressure and column chromatographic purification to obtain the 2.0 g of product **16** in 74.62% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.17-9.15 (dd, 1H, *J* = 0.8 & 1.8 Hz), 8.84 (d, 1H, NH, *J* = 6.2 Hz), 8.30-8.24 (dd, 1H, *J* = 2.6 & 7.0 Hz), 6.81 (d, 1H, *J* = 8.4 Hz), 6.42 (d, 1H, *J* = 8.0 Hz), 4.61-4.55 (dd, 1H, *J* = 4.2 & 4.0 Hz), 4.03-4.00 (t, 1H, *J* = 5.6 & 11.4 Hz), 3.71 (s, 3H), 2.20-1.80 (m, 1H), 1.80-1.60 (m, 1H), 1.45-1.25 (m, 1H), 1.05-0.90 (m, 6H). Mass m/z: 424 (M+).



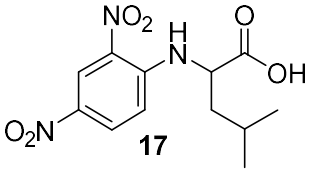
16

2-[2-(2,4-Dinitro-phenylamino)-3-methyl-pentanoylamino]-3-methyl-pentanoic acid: (2b): Dissolved 1.0 g (2.3 mmol) of methyl ester **16** (2.3 mmol) in THF: water 10 mL: 5 mL. Added 280 mg (12 mmol) of lithium hydroxide portion wise over a period of 10 minutes. Stirred at room temperature for 12 hours. Initially it was dark red which gradually turns to pale red (after 2 hours) and yellow (after 4 hours). Concentrated on rota evaporator under reduced pressure to remove the THF. Dissolved the residue in 15 mL of water and neutralized with conc. HCl (5 mL) and filtered, washed the yellow solid with water (10 mL X 2) followed by hexane (10 mL X 2). Transferred the solid to single neck flask and add benzene (10 mL X 2), concentrated on rota evaporator under pressure to obtain 750 mg of yellow solid **2b** in 78% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.14 (d, 1H, *J* = 2.4 Hz), 8.81 (d, 1H, NH, *J* = 5.4 Hz), 8.22 (dd,1H, *J* = 7.2), 6.86 (d, 1H, *J* = 8.4 Hz), 6.37 (d, 1H, NH, *J* = 8.6 Hz), 4.61-4.56 (dd, 1H, *J* = 4.2 & 9.2 Hz), 4.07-4.05 (t, 1H, *J* = 4.2 & 9.2 Hz), 2.10-2.05 (m, 1H), 2.05-1.95 (m, 1H), 1.90-1.65 (m, 1H), 1.45-1.25 (m,2H), 1.15-0.95 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 175.7, 170.3, 147.8, 137.4, 131.6, 130.6, 124.0, 115.2, 63.5, 56.5, 37.8, 37.2, 28.8, 25.2, 24.9, 15.8, 15.5, 11.4. Mass m/z: 410 (M+).



2b

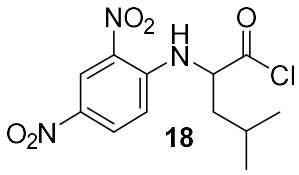
2-(2,4-Dinitro-phenylamino)-4-methyl-pentanoic acid: (17): Dissolved 10.0 g (76 mmol) of L-Leucine in 250 mL of 0.1 M sodium bicarbonate solutions in a beaker. Add 76 mol (8.51g/5.73mL) of 2,4-dinitrofluorobenzene solution (in 30 mL of acetone) over a period of 5 minutes. Stirred for 4 hours at room temperature. Distilled to half of its volume to get residue and neutralize with 2.0 M HCl (30 mL) and filtered, washed the yellow solid with water (10 mL X 2) followed by hexane (10 mL X 2). Transferred the solid to single neck flask and add benzene (10 mL X 2), concentrated on rota evaporator under pressure to obtain 10.75 g of yellow solid **17** in 75%



17

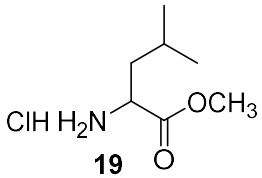
yield. Melting point is 100-101°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.16-9.14 (dd, 1H, *J* = 2.6 & 1.4 Hz), 8.72 (d, 1H, *J* = 7.2 Hz), 8.32-8.26 (dd, 1H, *J* = 1.8 & 5.4 Hz), 6.86 (d, 1H, *J* = 9.6 Hz), 4.40-4.29 (q, 1H, *J* = 7.0 & 7.4 Hz), 1.98-1.70 (m, 3H), 1.06-0.96 (dd, 6H, *J* = 6.0 & 9.6 Hz). Mass m/z: 297 (M+).

2-(2,4-Dinitro-phenylamino)-4-methyl-pentanoyl chloride: (18): Suspended 10.0 g (33 mmol) of N-(2,4-Dintrophenyl)-Leucine **17** in benzene (100 mL), Add 40 mmol (5.12 g / 3.6 mL) of oxalyl chloride drop wise over a period of 5 minutes under nitrogen atmosphere. Stir at room temperature for 2 hours. Concentrate on rota evaporator to get 10 g of reddish solid product **18** in 95% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.19 (d, 1H, *J* = 2.8 Hz), 8.69 (d, 1H, *J* = 7.8 Hz), 8.38-8.32 (dd, 1H, *J* = 2.6 & 7.6 Hz), 6.82 (d, 1H, *J* = 9.6 Hz), 4.57-4.46 (m, 1H), 2.05-1.70 (m, 3H), 1.10-0.99 (dd, 6H, *J* = 7.2 & 4.8 Hz).



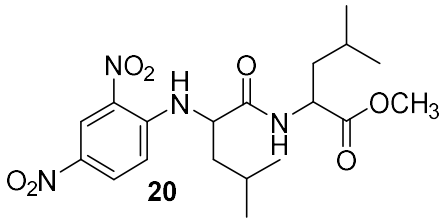
18

2-Amino-4-methyl-pentanoic acid methyl ester (19): Dissolved 20.0 g (152 mmol) of L-Leucine in 100 mL of methanol and cool to 0°C. Added 182 mmol (21.76 g / 15 mL) of thionyl chloride drop wise over a period of 15 minutes. Similar to compound **15**. After workup obtained 25.0 g of salt **19** in 90% yield.



19

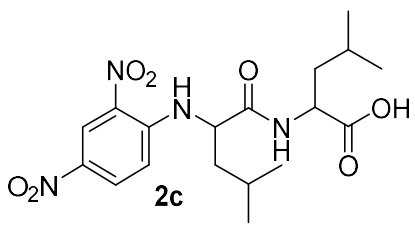
2-[2-(2,4-Dinitro-phenylamino)-4-methyl-pentanoylamino]-4-methyl-pentanoic acid methyl ester: (20): Suspend 6.9 g (37.9 mmol) of methyl ester HCl salt **19** in dichloromethane (100 mL) under nitrogen atmosphere. Cool to 0°C and add 5.3 g (63.0 mmol) of sodium carbonate at 0°C and stir for 1 hour. Drop wise addition of 10.0 g (31.5 mmol) of acid chloride **18** solution (10 mL of dichloromethane,) over a period of 15 minutes. Maintained at room temperature for 6 h and pour the reaction



20

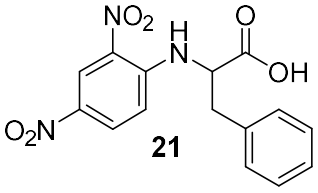
mass into beaker containing 250 mL of water. Extracted with dichloromethane (50 mL x 2). Washed the combined organic layer with saturated $NaHCO_3$ solution, brine solution, dried over $MgSO_4$, and filtered. Concentrated under reduced pressure and purified by column chromatography to obtain the 10.0 g of product **20** in 75% yield. ^1H NMR (200 MHz, $CDCl_3$): δ 9.17 (d, 1H, *J* = 2.8 Hz), 8.63 (d, 1H, NH, *J* = 5.6 Hz), 8.33-8.27 (dd, 1H, *J* = 2.6 & 7.2 Hz), 6.89 (d, 1H, *J* = 9.6 Hz), 6.32 (d, 1H, NH, *J* = 8.4 Hz), 4.65-4.55 (m, 1H), 4.15-4.00 (m, 1H), 3.65 (s, 3H), 1.95-1.70 (m, 3H), 1.06-1.03 (d, 3H, *J* = 6.0 Hz), 0.96-0.91 (m, 9H). Mass m/z: 424 (M+).

2-[2-(2,4-Dinitro-phenylamino)-4-methyl-pentanoylamino]-4-methyl-pentanoic acid: (2c): Dissolved 2.0 g (4.6 mmol) of methyl ester **20** in THF: water 20 mL: 10 mL. Added 280 mg (12 mmol) of lithium hydroxide portion wise over a period of 10 minutes. Stirred at room temperature for 4 hours. Initially it was dark red which gradually turns to pale red (after 2 hours) and yellow (after 4 hours). Concentrated on rota evaporator under reduced pressure to remove the THF. Dissolved the residue in 15 mL of water and neutralize with conc. HCl (5 mL) and filtered, washed the yellow solid with water (10 mL X 2) followed by hexane (10 mL X 2). Transfer the solid to single neck flask and added benzene (10 mL X 2), concentrated on rota evaporator under pressure to obtain 1.45 g of yellow solid **2c** in 75% yield. ^1H NMR (200 MHz, acetone-d_6): δ 9.09 (d, 1H, *J* = 2.6 Hz), 8.60 (d, 1H, NH, *J* = 5.4 Hz), 8.24-8.19 (dd, 1H, *J* = 2.6 & 7.0 Hz), 6.91 (d, 1H, *J* = 9.6 Hz), 6.49 (br-s, 1H, NH), 4.65-4.56 (dis-d, 1H, *J* = 8.8 & 17.6 Hz), 4.16-4.07 (d, 1H, *J* = 6.0 Hz), 1.98-1.70 (m, 4H), 1.06-1.03 (d, 3H, *J* = 5.8 Hz), 0.96-0.91 (m, 9H). Mass m/z: 410 (M+).



2c

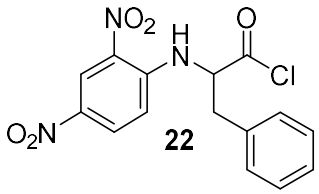
2-(2,4-Dinitro-phenylamino)-3-phenyl-propionic acid: (21): Dissolved 5.0 g (30 mmol) of Phenyl alanine in 100 mL of 0.1 M sodium bicarbonate solution in a



21

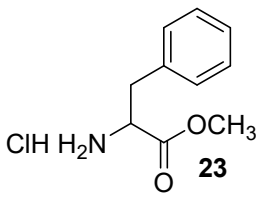
beaker. Add 18 mol (3.3 g/2.2 mL) of 2,4-dinitrofluorobenzene solution (in 10 mL of acetone) over a period of 5 minutes. Stir for 4 hours at room temperature. Distilled to half of its volume to get residue and neutralize with 2.0 M HCl (30 mL) and filtered, washed the yellow solid with water (10 mL X 2) followed by hexane (10 mL X 2). Transferred the solid to single neck flask and add benzene (10 mL X 2), concentrated on rota evaporator under pressure to obtain 7.5 g of yellow solid **21** in 75% yield. The product is soluble in methanol, ethanol, ethyl acetate, dichloromethane, chloroform and hot benzene. ^{1}H NMR (200 MHz, Acetone d_6): δ 9.00 (d, 1H), *J* = 2.8 Hz), 8.91 (d, 1H, NH, *J* = 7.2 Hz), 8.31-8.26 (dd, 1H, *J* = 2.8 & 6.8 Hz), 7.35-7.27 (m, 6H), 5.10-5.01 (dd, 1H, *J* = 5.8 & 7.6 Hz), 3.48-3.24 (m, 2H). ^{1}H NMR (200 MHz, $CDCl_3$ one drop of acetone d_6): δ 8.88 (d, 1H, *J* = 1.4 Hz), 8.70 (d, 1H, NH, *J* = 7.6 Hz), 8.02-7.96 (dd, 1H, *J* = 2.4 & 7.2 Hz), 7.09-7.00 (m, 5H), 6.62 (d, 1H, *J* = 8.4 Hz), 4.55-4.45 (m, 1H), 3.30-3.20 (dd, 1H, *J* = 5.0 & 9.0 Hz), 3.13-3.03 (dd, 1H, *J* = 7.0 & 6.8 Hz). Mass m/z: 331 (M+).

2-(2,4-Dinitro-phenylamino)-3-phenyl-propionyl chloride: (22): Suspended 5.0 g (15 mmol) of N- (2,4-Dintrophenyl)-Phenylalanine **21** in benzene (50 mL), Add 18 mmol (2.3 g/2.0 mL) of oxalyl chloride drop wise over a period of 5 minutes under nitrogen atmosphere. Stirred at room temperature for 2 hours. Concentrated on rota evaporator to get 4.75 g of product **22** in 90% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.09 (d, 1H, *J* = 2.8 Hz), 8.84 (d, 1H, NH, *J* = 7.2 Hz), 8.30-8.24 (dd, 1H, *J* = 2.6 & 6.8 Hz), 7.40-7.20 (m, 5H), 6.75 (d, 1H, *J* = 8.4 Hz), 4.89-4.81 (m, 1H), 3.60-3.40 (m, 2H).



22

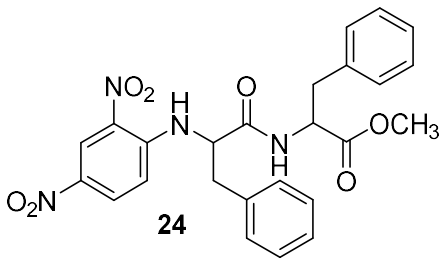
2-Amino-3-phenyl-propionic acid methyl ester-HCl (23): Dissolved 5.0 g (30 mmol) of L-Phenylalanine in 100 mL of methanol and cool to 0°C. Added 36 mmol (4.32 g / 4.0 mL) of thionyl chloride drop wise over a period of 5 minutes.



23

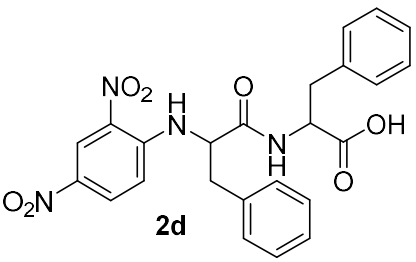
Similar to compound **15**. After workup obtained 5.8 g of salt **23** in 90% yield.

2-[2-(2,4-Dinitro-phenylamino)-3-phenyl-propionylamino]-3-phenyl-propionic acid methyl ester: (24): Suspended 3.5 g (16.3 mmol) of methyl ester HCl salt **23** in dichloromethane (50 mL) under nitrogen atmosphere. Cool to 0°C and add 2.88 g (27 mmol) of sodium carbonate at 0°C and stir for 1 hour. Drop wise addition of 4.75 g (13 mmol) of acid chloride **22** solution (10 mL of dichloromethane,) over a period of 15 minutes. Maintained at room temperature for 6 hours and pour the reaction mass into beaker containing 250 mL of water. Extracted with dichloromethane (50 mL x 2). Washed the combined organic layer with saturated $NaHCO_3$ solution, brine solution, dried over $MgSO_4$, and filtered. Concentrated under reduced pressure and purified by column chromatography to obtain the 4.75 g of product **24** in 71% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.09 (d, 1H, *J* = 2.8 Hz), 8.74 (d, 1H, NH, *J* = 6.8 Hz), 8.25-8.20 (dd, 1H, NH, *J* = 2.8 & 6.8 Hz), 7.41-7.20 (m, 9H), 6.95-6.90 (m, 1H), 6.77 (d, 1H, *J* = 8.4 Hz), 6.42 (d, 1H, *J* = 8.0 Hz), 4.91-4.86 (q, 1H, *J* = 2.2 & 3.6 Hz), 4.35-4.30 (q, 1H, *J* = 1.8 & 5.6 Hz), 3.86 (s, 3H), 3.41-3.20 (m, 4H). ^{1}H NMR (200 MHz, acetone-d_6): δ 8.93 (d, 1H, *J* = 2.8 Hz), 8.17-8.11 (dd, 1H, *J* = 2.6 & 7.0 Hz), 7.38-7.25 (m, 10H), 6.87 (d, 1H, *J* = 9.6 Hz) 4.84-4.75 (m, 2H), 3.66 (s, 3H), 3.66-2.92 (m, 4H). Mass m/z: 492 (M+).



24

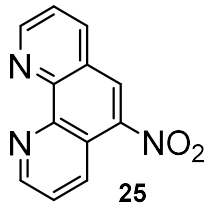
2-[2-(2,4-Dinitro-phenylamino)-3-phenyl-propionylamino]-3-phenyl-propionic acid: (2d): Dissolved 1.0 g (2 mmol) of methyl ester **24** in THF: water 10 mL: 5 mL. Add 240 mg (10 mmol) of lithium hydroxide portion wise over a period of 10 minutes. Stirred at room temperature for 4 hours. Initially it was dark red which gradually turns to



2d

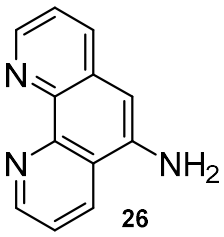
pale red (after 2 hours) and yellow (after 4 hours). Concentrated on rota evaporator under reduced pressure to remove the THF. Dissolved the residue in 15 mL of water and neutralize with conc. HCl (5 mL) and filtered, washed the yellow solid with water (10 mL X 2) followed by hexane (10 mL X 2). Transferred the solid to single neck flask and add benzene (10 mL X 2), concentrated on rota evaporator under pressure to obtain 0.69 g of yellow solid **2d** in 71% yield. ^{1}H NMR (200 MHz, acetone-d_6): δ 8.90 (d, 1H, *J* = 2.6 Hz), 8.86 (d, 1H, NH, *J* = 7.2 Hz), 8.12-8.06 (dd, 1H, *J* = 2.2 & 7.4 Hz), 7.96 (d, 1H, *J* = 8.2 Hz), 7.18-7.08 (m, 10H), 6.81(d, 1H, *J* = 9.6 Hz), 4.89-4.74 (m, 2H), 3.42-2.98 (m, 4H). Mass m/z: 478 (M+).

5-Nitro-[1,10]phenanthroline (25): Charged 30 g (166 mmol) of 1,10-Phenantranene in a R.B. and cool to 0^{o}C. Add 30% fuming sulfuric acid, over a period of 1 hour while maintaining the temperature. Drop wise addition of 90 mL of Conc. Nitric acid over a period of 1 hour, while maintaining the temperature. Removed cooling and stir at RT for 30 minutes. Heated at 130-140^{o}C for 4 hours. Cool to RT. Poured the reaction mixture into 2 L beaker containing 1 kg of crushed ice, neutralized with NaOH pellets (150 g) to adjust the pH = 8, ppt is formed, filtered, and washed the solid with water (1 L). Suspended the solid in chloroform (250 mL) and filtered to get 12 g of pure product **25** obtained in 32% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.37 (dd, 2H, *J* = 2.8 Hz & 4.4 Hz), 9.02 (dd, 1H, *J* = 1.6 & 7.0Hz), 8.70 (s, 1H), 8.42 (dd, 1H, *J* = 1.8 & 6.4 Hz), 7.86-7.75 (m, 2H). ^{1}H NMR (200 MHz, acetone-d_6): δ 9.31-9.24 (m, 2H), 8.90 (m, 2H), 8.80 (dd, 1H, *J* = 2.0 & 5.2 Hz), 7.98-7.90 (m, 2H). Mass: 225, GC-MS: 225, 5,6-DINITRO PHENANTHRANE (impurities). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.80 (dd, 2H, *J* = 1.2 Hz & 3.0 Hz), 8.02 (dd, 1H, *J* = 1.0 & 1.6 Hz), 7.95 (s, 2H), (dd, 1H, *J* = 4.0 & 8.0 Hz). PHEN-SM: NMR ^{1}H NMR (200 MHz, acetone-d_6): δ 9.13 (dd, 2H, *J* = 1.8 Hz & 2.6 Hz), 8.46 (dd, 2H, *J* = 1.8 & 13.2 Hz), 8.70 (s, 1H), 8.42 (dd, 1H, *J* = 1.8 & 6.4 Hz), 7.86-7.75 (m, 2H).



25

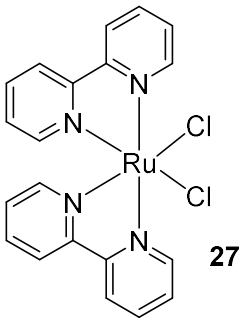
5-Amine[1,10]Phenanthroline (26): METHOD-A: Palladium charcoal slurry is prepared by adding 250 mg of palladium cautiously with spatula into a conical flask containing 100 mL of methanol. Dissolved 5 g (22.2 mol) of 5-Nitro-1,10-Phenantranene **25** in 50 mL of methanol in a single neck R.B. flask. Transferred the palladium slurry to R.B. flask containing the compound **25** solution. Washed the palladium slurry conical with additional 50 mL of methanol and transferred to R.B. flask. kept under Hydrogen atmosphere and stirred in hydrogen atmosphere until sm disappeared. (18 hours). Filtered through silica gel; wash the palladium with methanol and DCM. Concentrated the filtrate to get gummy material. Hexane was added and scratches with glass rod to form solid, filtered to obtained 4.3 g of product **26** in 98% yield. Rf value of sm 0.6 sm, product 0.4, polarity 9.5:0.5 Methanol: aqueous ammonia solution. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.21 (d, 1H, *J* = 4.0 Hz), 8.95 (d, 1H, *J* = 4.0 Hz), 8.30 (d, 1H, *J* = 8.0 Hz), 8.00 (d, 1H, *J* = 8.0 Hz), 7.68 (dd, 1H, *J* = 4.0 & 8.0 Hz), 7.50 (dd, 1H, *J* = 4.0 & 8.0 Hz), 6.95 (s, 1H). ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.05 (d, 1H, *J* = 4.0 Hz), 8.66 (m, 2H), 8.01 (d, 1H, *J* = 8.0 Hz), 7.71 (dd, 1H, *J* = 4.0 & 8.0 Hz), 7.46 (dd, 1H, *J* = 4.0 & 8.0 Hz), 6.86 (s, 1H). Mass m/z: 195 (M+).



26

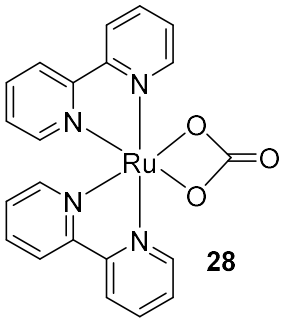
METHOD-B Dissolved 6.2 g, (27.5 mmol, 3.1 eq) stannous chloride dihydrate in 200 mL of ethanol in a single neck R.B. Added 2.0 g (8.89 mmol) of 5-Nitro-1,10-Phenantranene **25** heated at reflux for 8 hours. Removed solvent on rota evaporator to get residue. Cool to 0^{o}C, added slowly 1.0 M NaOH solution until pH = 13, ppt is formed. Filtered and washed with water. Transferred the solid into R.B. flask and added toluene (10 ml x 2). Concentrated on rota evaporator to get the 0.9 g of product **26** in 51% yield.

Ruthenium, bis(2,2'-bipyridine-kN1,kN1')dichloro (27): To a solution of 2.5 g (9.5 mmol,1.0 eq) of $RuCl_3.3H_2O$ and 2.75 g (61 mmol, 6.4 eq) of LiCl in 25 ml DMF was added 2.94 g (19 mmol, 2.0 eq) bipyridine at room temperature. Heated at reflux for 45 minutes, while continuously check the tlc for emission under uv lamp. Cool to RT. Poured into 100 mL of acetone. After cooling in freezer for 24 h, ppt is formed. Filtered and washed with water and acetone until pale color appeared. After 2 hours dry in vacuum, obtained 1.9 g of product **27** in 40% yield. Melting Point = 196-198^oC. Mass (m/z): 484 (M+).



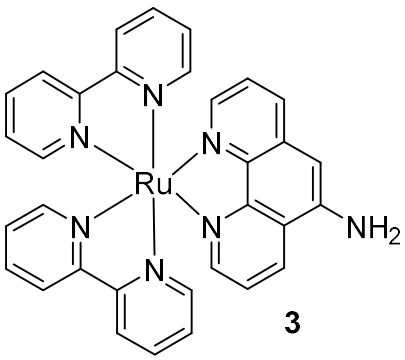
27

Ruthenium, bis(2,2'-bipyridine-kN1,kN1')[carbonato(2-)-kO,kO']-, (OC-6-22) (28): charged 2.0 g (4.13 mmol) of compound **27** in 50 ml of water, heated at reflux under argon atmosphere for 15 minutes. Added 6.6 g (6.3 mmol) of sodium carbonate and heated at reflux for 45 minutes. Cool to room temperature and filtered, washed the solid with water and dry in vacuum for 2 hours to obtained 1.3 g of product **28** in 67% yield. Mass: 474 (M+).



28

Ruthenium (2+), bis(2,2'-bipyridine-kN1,kN1')(1,10-phenanthrolin-5-amine-kN1,kN10)-, (OC-6-31)-, Perchlorate (3): To a 1.0 g (2.1 mmol) of Ruthenium bipyridine carbonate, **28** in a R.B. flask and added 412 mg (2.1 mmol) of 5-Amino, 1,10-phenantroline, **26** and 10 ml of water (10 mL). Heated at 75^oC for 45 minutes under nitrogen atmosphere. Observed the emission in UV lamp, cool to room temperature, poured into beaker containing 15 mL of



3

water. Added 1 g of sodium perchlorate solid while stirring, ppt formed. Filtered and washed with water, ether, and dry to get 1.7 of product **3** in 90% yield. Mass: 608 (M+), 709 (M+ClO_4), 829 (M+$[ClO_4]_2$+H_2O).

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■ **Competing interests:**

There is no Competing Interests pending.

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