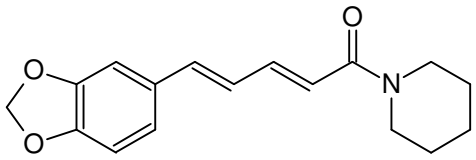
2.1 INTRODUCTION

As described in chapter 1, there is currently no cure for vitiligo; however there are various treatments available and none of these treatments are particularly successful and various side effects such as skin cancer and skin blistering make all these treatments problematic. Thus, there is a need for a new and more effective treatment for vitiligo.

As mentioned in chapter 1, the hair follicles are the sources of melanocytes available for repigmentation of vitiligo patches (Falabella, 1997). Ultraviolet radiation (UVR) has the ability to stimulate melanocytes present in hair follicles and PUVA can stimulate proliferation of the melanocytes from outer sheath of hair follicles as well as melanocytes in the border of vitiliginous lesions. Hence it is important aspect to search for compounds which can stimulate the proliferation of melanocytes and assist in migration of the melanocytes to vitiligo lesions in order to achieve repigmentation.

Previous studies from our laboratory showed that *Piper nigrum* and its main alkaloid piperine **(5)** possess the ability to stimulate melanocyte proliferation. Piperine was found to be selective to melan-a cell line and it possess melanoma inhibitory activity (Lin, 1999). Various pharmacological uses of piperine are well known; however, the melanocyte proliferative action of piperine is a novel observation and may be mediated by the protein kinase C (PKC) pathway (Lin *et al.,* 1999a). It is interesting that the chemical structure of piperine is not similar to TPA which stimulates proliferation of melanocytes through the PKC pathway. Since *Piper nigrum* extract showed melanocyte proliferation stimulatory activity, there is a possibility for certain compounds, which are structurally similar to piperine, share the stimulant activity. In this study we have attempted to identify compounds which are more potent than piperine.



(5)

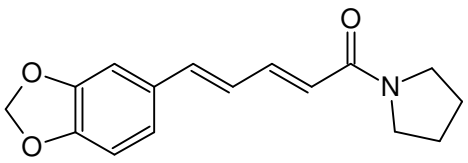
To investigate the chemical structure responsible for the proliferant activity, eight different series of compounds were prepared by using standard synthetic routes. They are listed below.

1. Variation on the nitrogen substitution
2. Substitution of an amide by an ester group
3. Variation in the connecting chain length
4. Substitution of an amide group with modification in the connecting chain length
5. Variation of the aromatic nuclei
6. Variation of the aromatic nuclei and connecting chain length
7. Modification of the degree of saturation of connecting chain
8. Removal of the amide formation

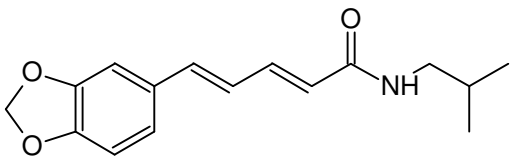
2.2 SYNTHESIS OF PIPERINE ANALOGUES

2.2.1 VARIATION ON THE NITROGEN SUBSTITUTION

In order to determine the amide group's involvement in the proliferation activity, aliphatic amines (C_1-C_6), aromatic amines and heterocyclic amines were used to synthesise related amides (Table 2.1). The naturally occurring alkaloids, trichostachine **(8a)** which is found to be present in *Piper nigrum* and piperlonguminine **(8f)** which although absent in *Piper nigrum,* is found to be present in other Piper species (Parmar *et al.,* 1997), have both been synthesised.



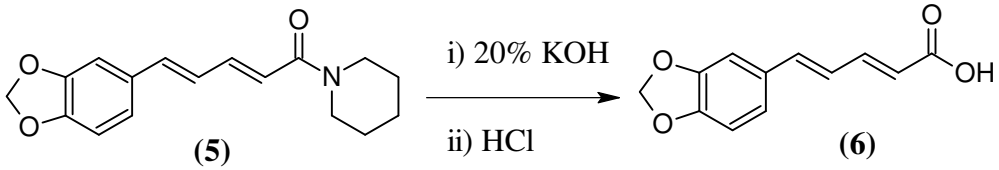
(8a)



(8f)

2.2.1.1 Preparation of piperinic acid (RV-A00 or 6)

Piperinic acid **(6)** was used as a starting material to synthesise various amide derivatives and ester derivatives of piperine analogues. Piperinic acid was obtained by basic hydrolysis of piperine. Piperine **(5)** was refluxed in methanolic KOH for 24h. The resulting solid was dissolved in water and acidified to give piperinic acid **(6)**. The pure acid was obtained after recrystallisation (Chatterjee and Dutta, 1967).



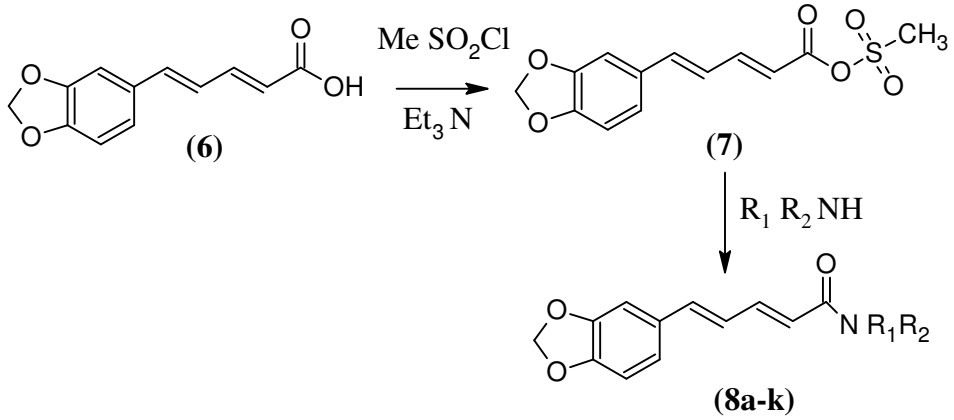
2.2.1.2 Synthesis of piperine amide analogues

Synthesis of amide - method I: Piperinic acid **(6)** was converted to an ester intermediate **(7)** by reacting with methane sulfonyl chloride and triethylamine at 0^0C for 30 min. By reacting this intermediate *in situ* with the desired amine, the corresponding amides **(8a-k)** was made (Scheme 2.1) (Nakamura *et al*., 1988). The amide was recrystallised to give a yield in the range of 30-60%.

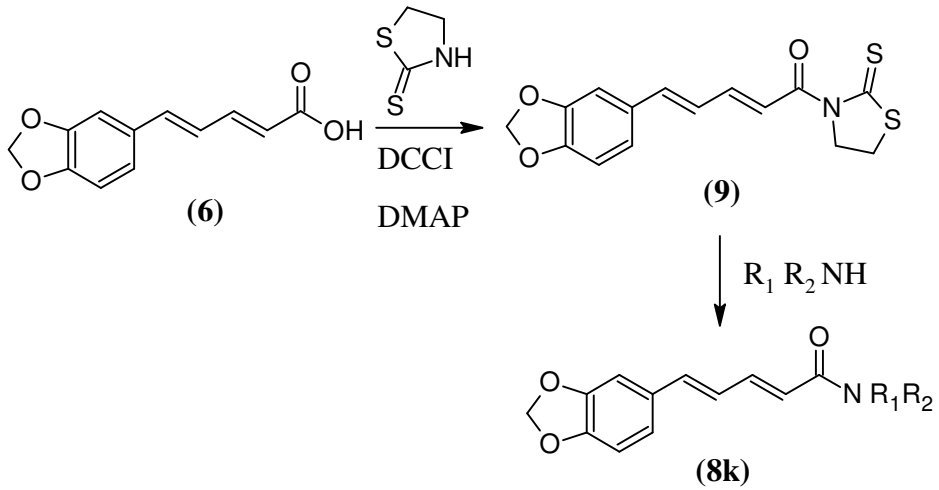
Synthesis of amide – method II: The 2-mercaptothiazolidine derivative of piperinic acid **(9)** was synthesised by adding dicyclohexylcarbodiimide (DCCI) followed by 2-mercaptothiazolidine and dimethylaminopyridine (DMAP). The reaction mixture was stirred overnight at room temperature. The corresponding amide formation was carried out by reaction between the resulting 2-mercaptothiazolidine derivative of piperinic acid **(6)** and the desired amine (Scheme 2.2). After purification by column chromatography, the desired amide (**8f**) was isolated with a typical yield of 20%.

Initially, both the above methods were compared by investigating their efficiency in the synthesis piperlonguminine (RV-A06). Method I was demonstrated to possess more advantages over method II, thus the reaction time for method I is 4h and the purification of the product can generally be achieved by recrystallisation where as in

method II reaction time is longer and column chromatography is necessary to remove DCU contamination. Thus, method I was generally adapted for the synthesis of various amide derivatives of piperinic acid. Piperine amide analogues are presented in Table 2.1.

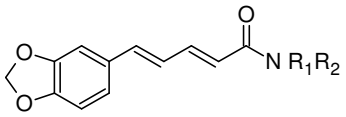
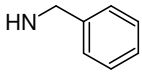
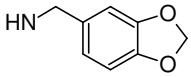
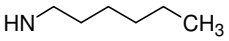
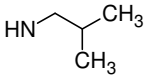
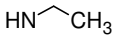
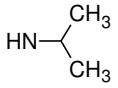
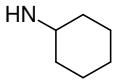
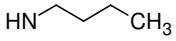


Scheme 2.1 Synthesis of amide derivatives of piperinic acid



Scheme 2.2 Synthesis of amide derivatives of piperinic acid

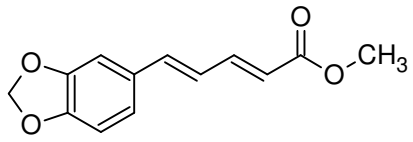
Table 2.1: Piperine amide analogues

	**- N R_1R_2**	**Molecular weight**	**Melting point ^{0}C**	**m.p (Lit) ^{0}C**	**C H N**
RV-A01 (**8a**)		271	142.9-143	147 (Koul *et al.,* 2000)	√
RV-A02 (**8b**)		287	161.8-162.5		√
RV-A03 (**8c**)		307	177-178		√
RV-A04 (**8d**)		351	190.5-191.7		√
RV-A05 (**8e**)		301	149.5-149.8	139-141 (de Paula *et al.,* 2000)	√
RV-A06 (**8f**)		273	161.2-161.7	156-160 (Nakumara *et al.,* 1988)	√
RV-A07 (**8g**)		231	181.2-182.4	186 (Gokhale *et al.,* 1948)	√
RV-A08 (**8h**)		245	158.5-159.9	162-164 (de Paula *et al.,* 2000)	
RV-A09 (**8i**)		259	169-169.4	171-173 (de Paula *et al.,* 2000)	√
RV-A10 (**8j**)		299	196.4-197.3	199-200 (de Paula *et al.,* 2000)	√
RV-A11 (**8k**)		273	144.2-145.6	144-145 (de Paula *et al.,* 2000)	√

Lit – Literature, m.p – melting point, C-carbon, H-hydrogen, N-nitrogen

2.2.2 SUBSTITUTION OF AN AMIDE BY AN ESTER GROUP

The amide functional group was replaced by an ester group in order to determine the effect of presence of an ester group on melanocytes. This group of compounds provided an idea of an importance of the presence of the amide group in the basic structure of piperine for the proliferation stimulatory activity. Interestingly, 5-(3,4-methylenedioxyphenyl)-penta-2*E*,4*E*-dienoic acid methyl ester **(10a)** has been isolated from Piper species (Parmar *et al.,* 1997).



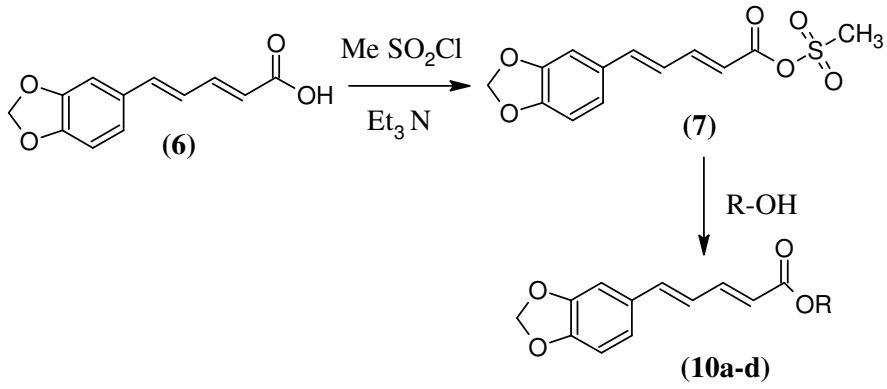
(10a)

2.2.2.1 Preparation of piperinic acid (RV-A00 or 6)

Piperinic acid was prepared as discussed in section 2.2.1.1

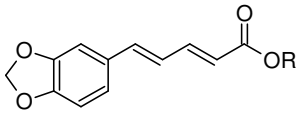
2.2.2.2 Synthesis of piperine ester analogues

Piperinic acid **(6)** was converted to an ester intermediate **(7)** by reacting with methane sulfonyl chloride and triethylamine at 0^0C for 30 min. By reacting this intermediate *in situ* with the desired alcohol the corresponding ester **(10a-d)** was made (Scheme 2.3). The ester was further purified by recrystallisation to give a yield in the range of 45-67%. Piperine ester analogues are shown in Table 2.2.



Scheme 2.3 Synthesis of ester derivatives of piperinic acid

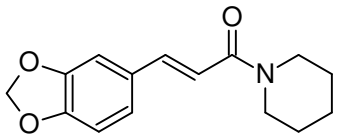
Table 2.2: Piperine ester analogues

	**-R**	**Molecular weight**	**Melting point ^{0}C**	**m.p (Lit) ^{0}C**	**C H N**
RV-AB1 (**10a**)	CH_3	232	142.9-143	143 (Banerji *et al.*, 1984)	√
RV-AB2 (**10b**)	CH_2CH_3	246	43.1-44	45 Dehmlow and Shamout (1980)	√
RV-AB4 (**10c**)	$CH_2CH_2CH_3$	260	119-120		√
RV-AB6 (**10d**)	$CH_2CH_2CH_2CH_3$	274			√

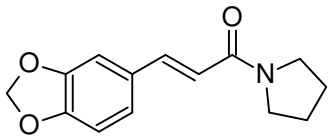
Lit – Literature, m.p – melting point, C-carbon, H-hydrogen, N-nitrogen

2.2.3 VARIATION OF THE CONNECTING CHAIN LENGTH

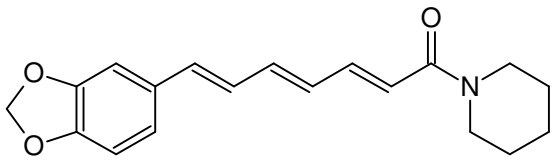
This group of compounds was designed to investigate the effect of the length of an unsaturated carbon and amide group on melanocyte proliferation. Compounds with one double bond (C_n, n=2) in the connecting chain was synthesised along with changes on nitrogen substitution (Table 2.3). Ilepcimide **(12a)** and 3,4-methylenedioxycinnamoyl pyrrolidine **(12b)** have been isolated in *Piper amalgo*. Piperettine (C_n, n=6) **(14)** is an alkaloid present in *Piper nigrum* and was also synthesised.



(12a)



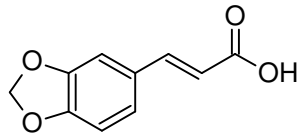
(12b)



(14)

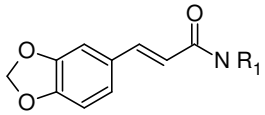
2.2.3.1 Synthesis of short chain piperine amide analogues

Short chain piperine amide analogues were synthesised utilising the same methodology (Section 2.2.1.2; method I) as that for preparation of piperine amide derivatives. 3,4-methylenedioxycinnamic acid **(11)** was used as the starting material in this method. The corresponding amide **(12a-c)** was obtained by reacting an ester intermediate of 3,4-methylenedioxycinnamic acid with desired amine. The short chain piperine amide derivatives **(12a-c)** are shown in Table 2.3.



(11)

Table 2.3 Short chain piperine amide analogues

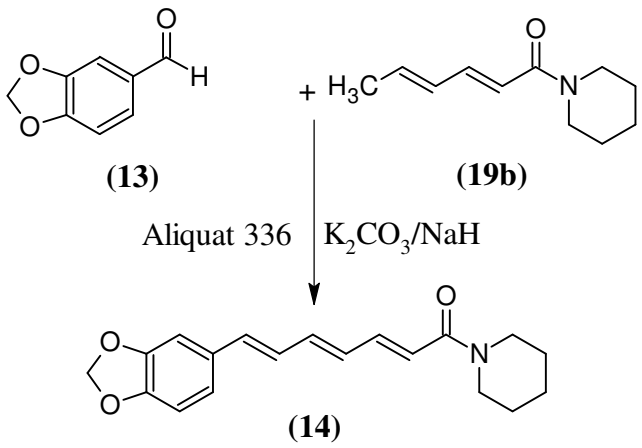
	**- N R_1**	**Molecular weight**	**Melting point ^{0}C**	**m.p (Lit) ^{0}C**	**C H N**
RV-B01 **(12a)**		259	80.1-82	89 Koul *et al.* (2000)	√
RV-B02 **(12b)**		245	152.5-153	146 Koul *et al.* (2000)	√
RV-B03 **(12c)**		261	160-160.4		√

Lit – Literature, m.p – melting point, C-carbon, H-hydrogen, N-nitrogen

2.2.3.2 Preparation of 7-(3,4-methylenedioxyphenyl)-hepta-2*E*,4*E*,6*E*-trienoyl piperidine (PIPERETTINE)

Piperettine was synthesised by a slightly modified method of Dehmlow and Shamout (1980). 2,4-hexadienoyl piperidine **(19b)**, piperonal **(13)**, and aliquat 336 were dissolved in toluene and anhydrous potassium carbonate and sodium hydride were added and refluxed under nitrogen for 6h at 90^{0}C. The reaction mixture was poured into water and extracted with dicholoromethane. The organic layer was dried over anhydrous sodium sulphate, filtered and rotary evaporated to dryness. The mixture is purified by column chromatography using hexane:ethylacetate (1:9) as an eluent to

yield yellow solid. Recrystallisation from ethylacetate and petroleum spirit yielded yellow needles of piperettine **(14)** (Scheme 2.4).



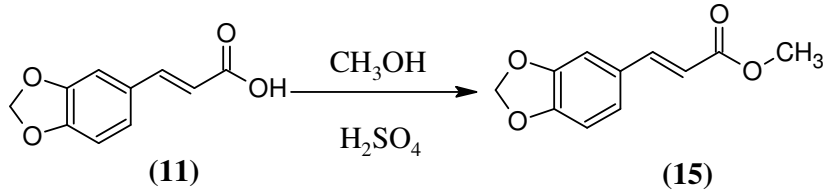
Scheme 2.4 Synthesis of piperettine

2.2.4 SUBSTITUTION OF AMIDE GROUPS WITH ESTER AND MODIFICATION IN THE CONNECTING CHAIN LENGTH

A compound with one double bond (C_n, n=2) in the connecting chain and an ester group instead of amide group was proposed. Only one compound was synthesised to investigate the structure-activity relationship. The type of variation proposed in this method of synthesis is changing chain length and substituting the ester group. A different method was attempted from previous methods to synthesis ester derivative.

2.2.4.1 Synthesis of short chain piperine ester analogue

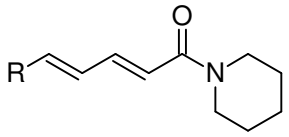
To 3,4-methylenedioxycinnamic acid **(11)**, methanol was added followed by adding few drops of sulphuric acid. The reaction was refluxed overnight yielding 3,4-(methylenedioxy)-cinnamic acid methyl ester **(15)** (Scheme 2.5).

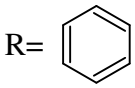


Scheme 2.5 Synthesis of 3,4-(methylenedioxy)-cinnamic acid methyl ester

2.2.5 VARIATION OF THE AROMATIC NUCLEI

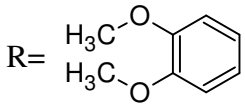
This group of compounds was synthesised to determine the importance of methylenedioxy group in the stimulation of melanocyte proliferation activity. The amide functional group was not modified but the 3,4-methylenedioxyphenyl group was removed by substituting with phenyl **(19a)**, methyl **(19b)** and dimethoxyphenyl **(21)** groups. None of these compounds have been isolated from Piper species.





(19a)

R=CH_3 **(19b)**

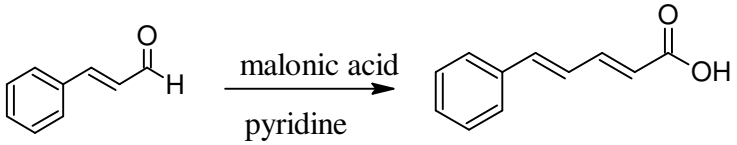


(21)

The variation is proposed to synthesise amide derivative by altering phenyl substitution group.

2.2.5.1 Preparation of 5-phenyl-penta-2*E*, 4*E*-dienoic acid

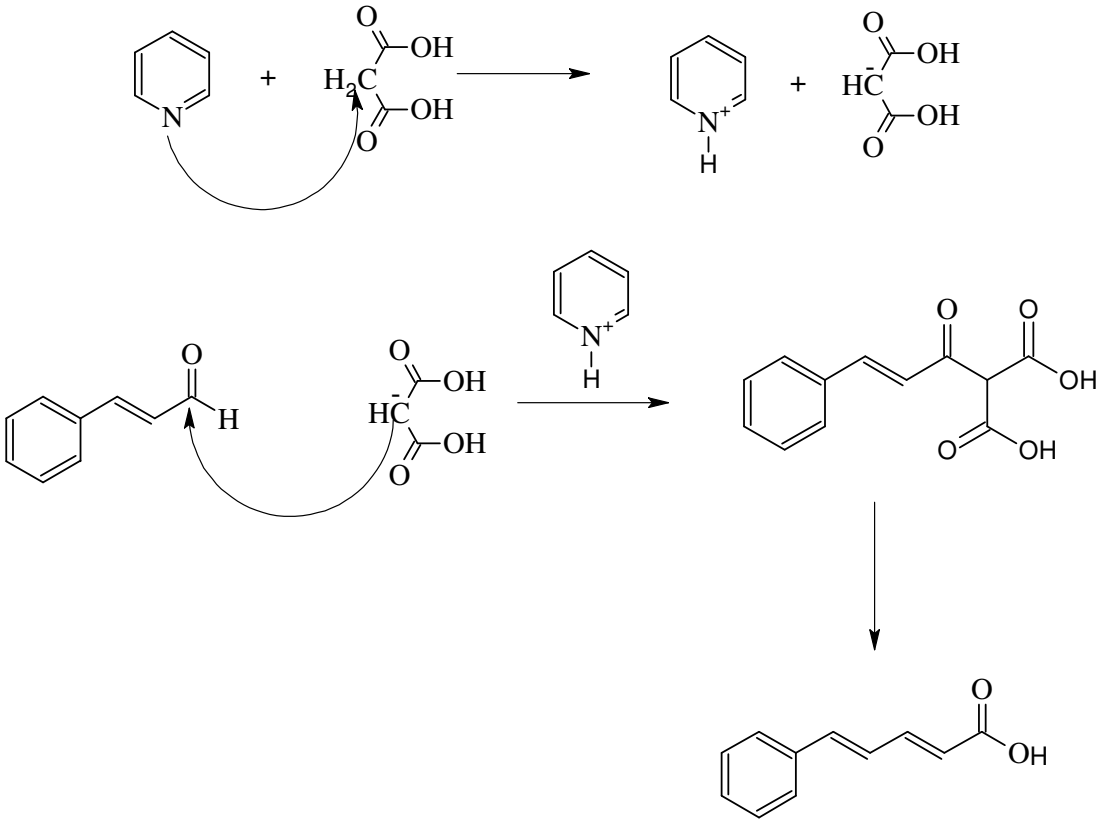
In order to remove 3,4-methylenedioxy moiety in piperine, 5-phenyl-penta-2*E*,4*E*-dienoic acid **(17a)** was prepared by refluxing malonic acid and cinnamaldehyde **(16)** in pyridine solution at 90^0C for overnight (Scheme 2.6) (Crombie and Crombie, 1994).



(16) **(17a)**

Scheme 2.6 Synthesis of 5 -phenyl-penta-2*E*, 4*E*-dienoic acid

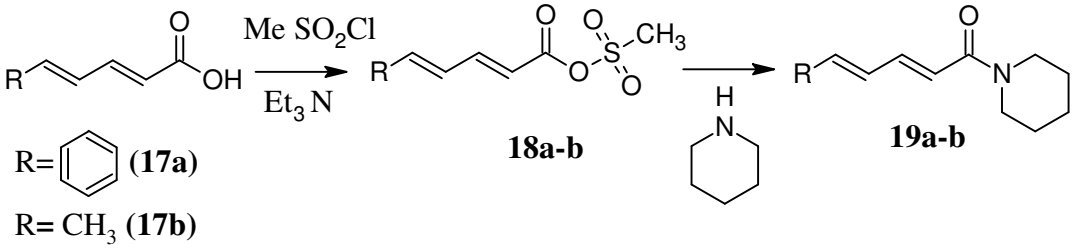
The proposed reaction mechanism of 5-phenyl-penta-2*E*-4*E*-dienoic acid is shown below (Scheme 2.7).



Scheme 2.7 The proposed mechanism for the formation of acid

2.2.5.2 Synthesis of aromatic substituted piperine amide analogues

In this synthesis the methylenedioxyphenyl group is substituted with either methyl group or phenyl group. Amides were prepared from the corresponding acid **(17a-b)**. The amide derivatives **(19a-b)** were obtained using a similar method (section 2.2.1.2 method I). The acid was converted to an ester intermediate **(18a-b)** by addition of triethylamine and methane sulfonyl chloride at 0^0C for 30min. By reacting the desired amine with the ester intermediate, the corresponding amide **(19a-b)** was produced (Scheme 2.8).

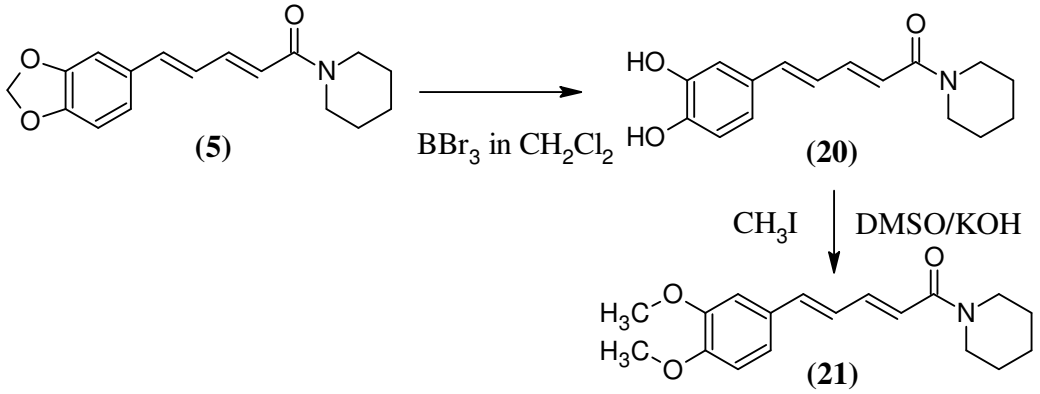


Scheme 2.8 The reaction scheme of aromatic substituted piperine analogues

2.2.5.3 Preparation of Piperidine-5-(3,4-dimethoxyphenyl)-2*E*,4*E*-pentadienoic acid amide

Piperine **(5)** was dissolved in dichloromethane and BBr_3 in dichloromethane was added and stirred at room temperature for 2 days. After the completion of reaction, solid residue was washed with DCM and the acid **(20)** was obtained by recrystallisation.

Alkylation was easily achieved by reaction of alkyl halide with solid KOH and DMSO (Johnstone and Rose, 1979). This method was effectively used for alkylation of amides. Potassium hydroxide was added to dimethylsulfoxide and stirred under nitrogen atmosphere. 5-(3,4-dihydroxyphenyl)-penta-2*E*,4*E*-dienoic acid **(20)** was added to the mixture followed by iodomethane, the mixture was poured into water and extracted with dichoromethane. The residue was recrystallised to yield yellow crystals of piperidine-5-(3,4-dimethoxyphenyl)-penta-2*E*,4*E*-dienoic acid amide **(21)** (Scheme 2.9).



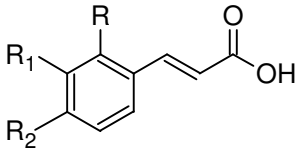
Scheme 2.9 Synthesis of 5-(3,4-dimethoxyphenyl)-penta-2*E*,4*E*-dienoic acid piperidine amide

2.2.6 VARIATION OF THE AROMATIC NUCLEI AND CONNECTING CHAIN LENGTH

A methoxyphenyl group was substituted instead of a 3,4-methylenedioxy group and unsaturated carbon (C_n, n=2) was reduced from the original structure of piperine. The position of methoxy group has been changed in this group of compounds to determine the effect of this compound on melanocytes.

2.2.6.1 Synthesis of short chain aromatic substituted piperine amide analogues

A mixture of monomethoxycinnamic acid **(22a-c)** and triethylamine in dichloromethane was stirred at 0^0C. To this mixture methane sulfonyl chloride was added at 0^0C. Amide was obtained on addition of piperidine. The product was purified by chromatography on silica gel using ethylacetate/petroleum spirit (2:8) as an eluent with typical yield of these compounds **(23a-c)** falling in the range of 25-42%. The piperidine amide of 3,4 dimethoxycinnamic acid **(23d)** was also prepared in the same way using dimethoxycinnamic acid **(22d).** The chemical structures of the amide derivatives are shown in Table 2.4.



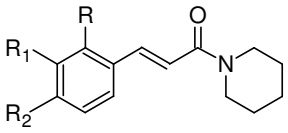
R = OCH_3, R = H , R = H **(22a)**

R = H, R = OCH_3 , R = H **(22b)**

R = H, R = H, R = OCH_3 **(22c)**

R = H, R = OCH_3 , R = OCH_3 **(22d)**

Table 2.4 Short chain aromatic substituted piperine analogues

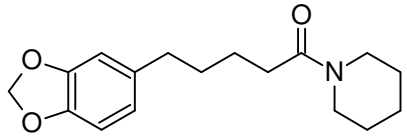


	R	R_1	R_2	**Molecular weight**	**Melting point ^{0}C**	**m.p (Lit) ^{0}C**	**C**	**H**	**N**
RV-G01 **(23a)**	OCH_3	H	H	245					
RV-G02 **(23b)**	H	OCH_3	H	245	68-70				√
RV-G03 **(23c)**	H	H	OCH_3	245					√
RV-G04 **(23d)**	H	OCH_3	OCH_3	275					

Lit – Literature, m.p – melting point, C-carbon, H-hydrogen, N-nitrogen

2.2.7 MODIFICATION OF DEGREE OF SATURATION OF CONNECTING CHAIN

Piperine possesses unsaturated carbons in the structure in the aliphatic side chain. Since this compound tends to form isomers when in solution and makes this compound less stable. Hence we have proposed to synthesise saturated analogues of piperine and other analogues and test them for melanocyte proliferation stimulatory activity. Piperine was reduced to synthesise 5-(3,4-methylenedioxyphenyl)-pentanoyl-piperidine or tetrahydropiperine **(25).**

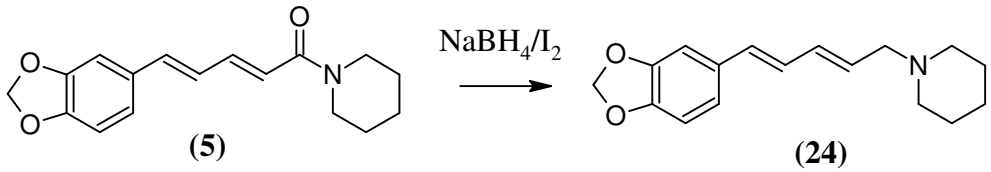


Tetrahydropiperine **(25)**

Synthesis of these types of compounds is to varying the connecting chain by subjecting them for reduction.

2.2.7.1 Synthesis of 5-(3,4-methylenedioxyphenyl)-penta-2*E*,4*E*-dienyl-piperidine

This compound was produced during an attempt to reduce only one double bond of piperine according to the method of Das *et al.* (1998). No double bond reduction was observed despite changing the proportion of reagents to that given in the method below. Piperine **(5)** and $NaBH_4$ was stirred in THF at 0^0C under nitrogen atmosphere. Iodine was added drop wise to the mixture and the reaction was quenched with methanol till the effervescence ceased (Scheme 2.10). The solvent containing mixture was rotary evaporated to yield a residue. This residue was purified by column chromatography. The product was further purified by recrystallisation yielding 120mg of 5-(3,4-methylenedioxyphenyl)-penta-2*E*,4*E*-dienyl-piperidine **(24)**.

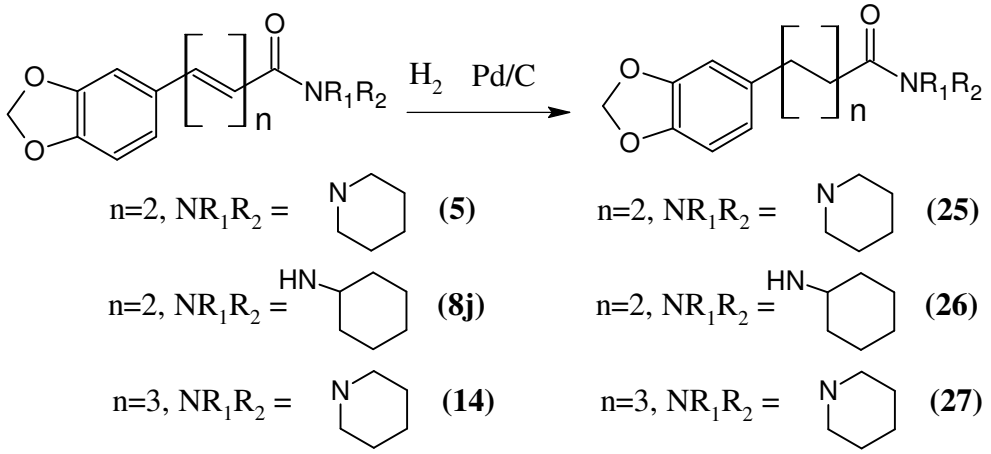


(5) **(24)**

Scheme 2.10 Synthesis of 5-(3,4-methylenedioxyphenyl)penta-2*E*,4*E*-dienyl-piperidine

2.2.7.2 Synthesis of saturated piperine amide analogues

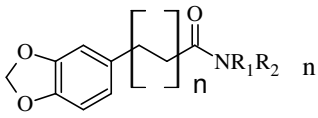
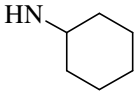
The hydrogenation method was used to reduce corresponding amides **(5, 8j, 14)**. The compound was hydrogenated in ethanol over 5% Pd-C under a pressure of hydrogen at 10 PSI for 30mins (Scheme 2.11) to give the products (**25,26,27**) with yield in the range of 65-85%.



Scheme 2.11 Reaction scheme of saturated amide derivatives

The chemical structure of the reduced compounds are shown in Table 2.5

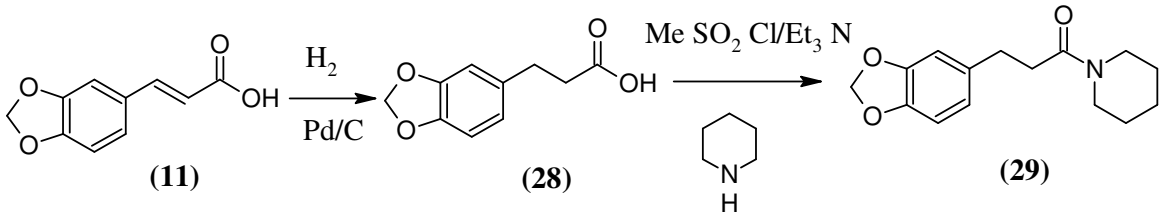
Table 2.5 Saturated piperine amide analogues

	n	- N R_1R_2	Molecular weight	Melting point ^{0}C	m.p (Lit) ^{0}C	C	H	N
RV-C02 (**25**)	2		289					√
RV-C04 (**26**)	2		303	145.5-146.3				√
RV-C05 (**27**)	3		317					

Lit – Literature, m.p – melting point, C-carbon, H-hydrogen, N-nitrogen

2.2.7.3 Synthesis of 3-(3,4-methylenedioxyphenyl)-propionoyl piperidine

The 3,4-methylenedioxycinnamic acid **(11)** was hydrogenated in ethanol over 5% Pd-C under a pressure of hydrogen at 10 PSI for 40mins to give 3-(3,4-methylenedioxyphenyl)-propionic acid **(28)** as a solid. To synthesise the amide derivative **(29)**, the method was adapted from that reported for amide derivatives of piperinic acid (section 2.2.1.2 method I) but utilising 3,4-methylenedioxypropionic acid and piperidine as the acid and amine components respectively (Scheme 2.12).

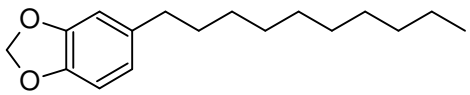


(11) **(28)** **(29)**

Scheme 2.12 Synthesis of 3-(3,4-methylenedioxyphenyl)-propionoyl piperidine

2.2.8 REMOVAL OF THE AMIDE FUNCTION

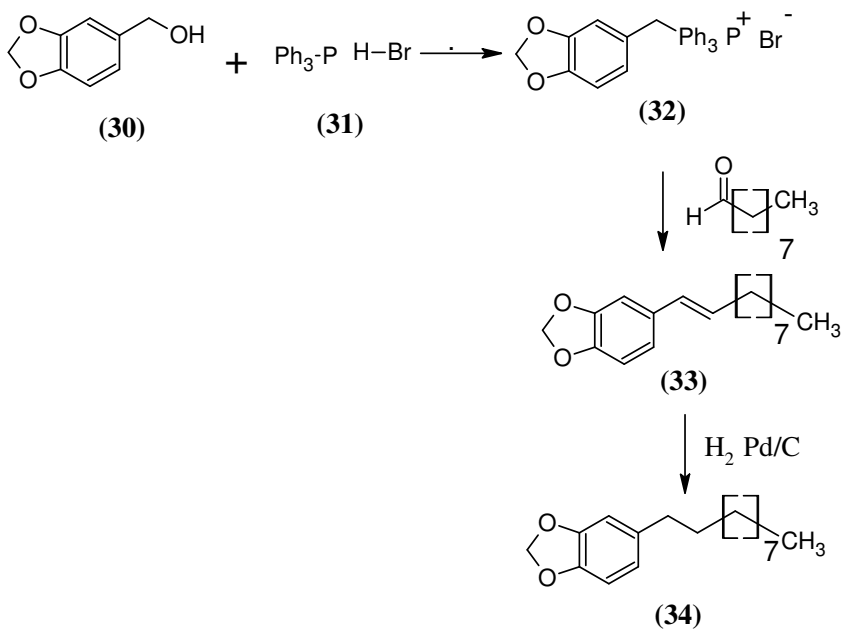
Various long hydrocarbon chain containing N-isobutyl amides were isolated from Piper species. Some of these analogues were isolated in our laboratory and were found to be less effective than piperine in stimulation of proliferation of melanocytes (Lin, 1999). The amide functional group was replaced to investigate long hydrocarbon chain on stimulation of melanocyte proliferation. Thus this group of compounds is synthesised by introducing long chain alkane (C_{10}) **(34)**.



3,4-methylenedioxy decane **(34)**

2.2.8.1 Synthesis of 3,4-methylenedioxyphenyl decane

Piperinyl alcohol **(30)** was reacted with triphenylphosphine hydrobromide **(31)** to yield piperinyl triphenyl phosphine bromine salt **(32)**. The salt was reacted with nonaldehyde under basic condition to give 3,4-methylenedioxy-9-trans-deca-8ene **(33).** Further hydrogenation of this compound yields 3,4-methylenedioxydecane **(34)** (Scheme 2.13)



Scheme 2.13 Synthesis of 3,4-methylenedioxyphenyl decane

2.3 EXPERIMENTAL

GENERAL METHOD

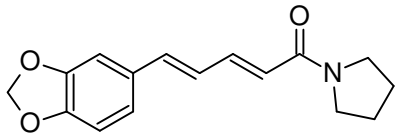
2.3.1 PREPARATION OF PIPERINIC ACID

20% methanolic KOH (100mL) was added to piperine **(5)** (2g, 0.7mmol, 1eq), and refluxed for 2days. After completion of the hydrolysis, methanol was removed under reduced pressure and a yellow coloured oily solid was obtained. This residue was dissolved in water (50mL) and acidified with 6N HCl to pH <1 yielding a yellowish precipitate of piperinic acid **(6).** Recrystallization from methanol gave yellow needles (0.9g, 60% yield). m.p. 206^0-208^0C. Lit m.p. 217^0-218^0C (Chatterjee and Dutta, 1967).

2.3.2 SYNTHESIS OF PIPERINE AMIDE ANALOGUES

A mixture of piperinic acid **(6)** (200mg, 0.9mmole, 1eq) and triethylamine (0.25mL, 1.8mmole, 2eq) in dichloromethane (50mL) was stirred for 15min at 0^0C. To this mixture methane sulfonylchloride (0.1mL, 1.3mmole, 1.5eq) was added and stirred for further 30 min at 0^0C. The amine (1.5eq) was added to the mixture and stirred for 1h at 0^0C and 2h at room temperature. Dichloromethane (50mL) was added to the mixture, which was then washed with 5% HCl (3x100mL), saturated aqueous $NaHCO_3$ (3x100mL) and water (3x100mL). The organic fraction was dried over anhydrous sodium sulphate, filtered and the filtrate was rotary evaporated to yield a solid residue. Recrystallisation from ethylacetate and petroleum spirit gave crystals of amide **(8a-k)**.

1-*E,E*-piperinoyl-pyrrolidine (RV-A01) (8a):

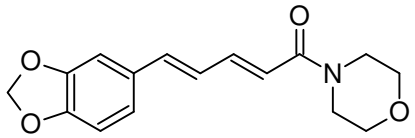


Yield : 186mg (49.2%)

^{1}H-NMR ($CDCl_3$) δ: 6.26 (d, 1H, J=14.7, CH=CH-CH=**CH),** 7.43 (dd, 1H, J=9.5, 14.7, CH=CH-**CH**=CH), 6.73 (dd, 1H, J=15.3, 9.5, CH=**CH**-CH=CH), 6.78 (d, 1H, J=15.3 **CH**=CH-CH=CH), 6.98 (d,1H J=1.6, Ar-**H**), 6.77 (d,1H J=8.0, Ar-**H**), 6.89

(dd, 1H J=1.6, 8.0 Ar-**H**), 5.97 (s, 2H, **O-CH$_2$-O**), 3.57 (t, 2H, J=4.0 N- **CH$_2$** (pyrrolidine)) 3.54 (t, 2H, J=4.0 N- **CH$_2$** (pyrrolidine) 1.90 (m, 2H, CH$_2$-**CH$_2$**(pyrrolidine)) 1.87 (m, 2H, **CH$_2$**.CH$_2$(pyrrolidine)) ^{13}C-NMR ($CDCl_3$) : 24.3 (**CH$_2$**), 26.1 (**CH$_2$**), 45.9 (**CH$_2$**), 46.4 (**CH$_2$**), 101.2 (**CH$_2$**), 105.7 (**CH**), 108.4 (**CH**), 121.4 (**CH**), 122.5 (**CH**), 125.2 (**CH**), 130.9 (**C**), 138.7 (**CH**), 141.7 (**CH**), 148.1 (**C**), 148.2 (**C**), 164.9 (**C**) MS m/z (%) : 271 (M^+ 78), 201 (100), 173 (30), 172 (15), 171 (13) 143 (13), 115 (27), IR (KBr) : ν_{max} (carbonyl group)cm^{-1} 1637 Calculated for $C_{16}H_{17}NO_3$ C 70.83, H 6.31, N 5.16% Found: C 70.90, H 6.99, N 4.58%

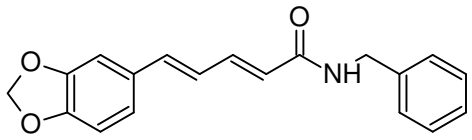
1-*E,E*-piperinoyl-morpholine (RV-A02) (8b):



Yield : 113mg (44.1%)
m.p. 161.8^0-162.5^{0}C

^{1}H-NMR ($CDCl_3$) δ: 6.37 (d, 1H, J=14.6, CH=CH-CH=**CH),** 7.45 (dd, 1H, J=10.2, 14.6, CH=CH-**CH**=CH), 6.72 (dd, 1H, J=15.5, 10.2, CH=**CH**-CH=CH), 6.79 (d, 1H, J=15.5 **CH**=CH-CH=CH), 6.98 (d,1H J=1.5, Ar-**H**), 6.80 (d,1H J=8.0, Ar-**H**), 6.89 (dd, 1H J=1.5, 8.0 Ar-**H**), 5.98 (s, 2H, **O-CH$_2$-O**), 3.70 (t, 4H, J=4.0 **CH$_2$**-N- **CH$_2$** (morpholine)) 3.60 (t, 4H, J=4.0 **CH$_2$**-O- **CH$_2$** (morpholine)) ^{13}C-NMR ($CDCl_3$) : 42.3 (**CH$_2$**), 46.1(**CH$_2$**), 66(**CH$_2$**), 66(**CH$_2$**), 101.3 (**CH$_2$**), 106.5 (**CH**), 108.5 (**CH**), 118.7 (**CH**), 122.7 (**CH**), 124.9 (**CH**), 130.8 (**C**), 139.1 (**CH**), 143.4 (**CH**), 148.2 (**C**), 148.3 (**C**), 165.6 (**C**)MS m/z (%) : 287 (M^+ 57), 201 (100), 173 (25), 171 (10) 143 (10), 115 (30) IR (KBr): ν_{max} (carbonyl group) cm^{-1} 1641 Yield : 113mg (44.1%) Calculated for $C_{16}H_{17}NO_4$ C 66.88, H 5.96, N 4.84% Found: C 66.47, H 5.78, N 4.79%

1-*E,E*-piperinoyl-benzylamine RV-A03 (8c):

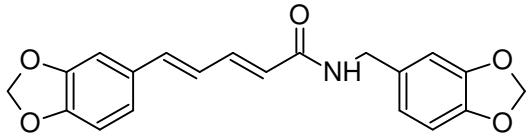


Yield : 214mg (50.1%)
m.p. 177^0-178^{0}C

^{1}H-NMR ($CDCl_3$) δ: 6.15 (d, 1H, J=15.0, CH=CH-CH=**CH),** 7.19 (dd, 1H, J=10.2, 15.0, CH=CH-**CH**=CH), 6.92 (dd, 1H, J=15.5, 10.2, CH=**CH**-CH=CH), 6.85 (d, 1H, J=15.5 **CH**=CH-CH=CH), 7.22 (d,1H J=1.4, Ar-**H**), 6.89 (d,1H J=8.0, Ar-**H**), 6.98 (dd, 1H J=1.4, 8.0 Ar-**H**), 6.03(s, 2H, **O-CH$_2$-O**), 4.36(d,2H, J=5.96, Ph-**CH$_2$**), 7.2-

7.3 (m, 5H, **Ar**) 8.55(t,1H, J=5.96 **NH**) ^{13}C-NMR ($CDCl_3$) : 43.8 (**CH_2**), 101.8 (**CH_2**), 106.0 (**CH**), 108.8 (**CH**), 123.1 (**CH**), 123.2 (**CH**), 125.1 (**CH**), 127.6 (**CH**), 128.0 (**CH**), 128.9 (**CH**), 139.6 (**CH**), 141.7 (**CH**), 148.7 (**C**), 148.8 (**C**), 167.6 (**C**) MS m/z (%) : 307 (M^+100), 216 (13), 202 (28) 201 (26), 174 (36), 173 (49), 172 (16), 144 (10), 143 (13), 115 (26), 91 (25) IR (KBr) : ν_{max} (carbonyl group) cm^{-1} 1637 Calculated for $C_{19}H_{17}NO_3$ C 74.23, H 5.58, N 4.56% Found: C 74.18, H 5.35, N 4.53%

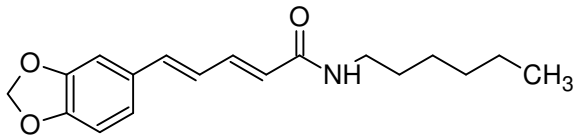
1-*E,E*-piperinoyl-3,4-methylenedioxyphenyl methylamine RV-A04 (8d):



Yield : 157mg (50.1%)
m.p. 190.5^0-191.7^0C

^{1}H-NMR ($CDCl_3$) δ: 5.98(d, 1H, J=14.9, CH=CH-CH=**CH),** 7.34 (dd, 1H, J=10.7, 14.9, CH=CH-**CH**=CH), 6.73 (dd, 1H, J=15.5, 10.7, CH=**CH**-CH=CH), 6.79 (d, 1H, J=15.5 **CH**=CH-CH=CH), 6.98 (d,2H J=1.5, Ar-**H**), 6.78 (d,2H J=8.0, Ar-**H**), 6.89 (dd, 2H J=1.6, 8.0 Ar-**H**), 5.98 (s, 2H, **O-CH_2-O**), 5.93 (s, 2H, **O-CH_2-O**), 4.40 (d, 2H, **CH_2** N) 3.57 (br, 1H, N**H**) ^{13}C-NMR ($CDCl_3$) : 43.4 (**CH_2**), 101.1 (**CH_2**), 101.4 (**CH_2**), 105.8 (**CH**), 108.3(**CH**) 108.5 (**CH**), 108.6 (**CH**), 121.2 (**CH**), 122.8 (**CH**), 124.7 (**CH**), 130.9 (**CH**), 132.2 (**CH**) 139.9 (**CH**), 141.6 (**C**), 147.0 (**C**) 147.9 (**C**)148.3 (**C**), 148.4(**C**), 166.9 (**C**) MS m/z (%) : 351 (M^+81), 216 (15), 203 (12), 202 (53) 201 (29), 174 (31), 173 (22), 150 (23) 144 (11), 143 (10), 135 (100), 116 (12) 115(29) Calculated for $C_{20}H_{17}NO_5$: C 68.37, H 4.88, N 3.99% Found: C 68.27, H 4.66, N 3.86%

1-*E,E*-piperinoyl-hexylamine RV-A05 (8e):

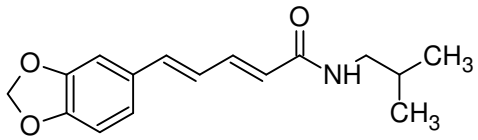


Yield : 168mg, (40.1%)
m.p. 149.5^0-149.8^0C

^{1}H-NMR ($CDCl_3$) δ: 5.90 (d, 1H, J=14.8, CH=CH-CH=**CH),** 7.35 (dd, 1H, J=10.6, 14.8, CH=CH-**CH**=CH), 6.66 (dd, 1H, J=15.4, 10.6, CH=**CH**-CH=CH), 6.76 (d, 1H, J=15.4 **CH**=CH-CH=CH), 6.97 (d,1H J=1.4, Ar-**H**), 6.77 (d,1H J=8.0, Ar-**H**), 6.88 (dd, 1H J=1.5, 8.0 Ar-**H**), 5.97 (s, 2H, **O-CH_2-O**), 3.34 (q, 2H, **CH_2** - CH_2- CH_2- CH_2- CH_2) 1.54 (m, 2H, CH_2 - **CH_2**- CH_2- CH_2- CH_2) 1.32 (m, 6H, CH_2 - CH_2- **CH_2- CH_2- CH_2**) 0.88 (t, 3H, **CH_3**), 5.54 (br, **NH**) ^{13}C-NMR ($CDCl_3$) : 14.3 (**CH_3**), 22.5

(**CH_2**), 26.6 (**CH_2**), 29.6 (**CH_2**), 31.5 (**CH_2**), 39.7 (**CH_2**), 101.3 (**CH_2**), 105.7 (**CH**), 108.5 (**CH**), 122.5 (**CH**), 123.2 (**CH**), 124.6 (**CH**), 130.8 (**C**), 138.7 (**CH**), 140.9 (**CH**) 148.2 (**C**), 148.2 (**C**), 166.0 (**C**) MS m/z (%) : 301(M^+94), 202 (18) 201 (73), 174 (40), 173 (100), 172 (31), 171 (15) 143 (24), 115 (63) IR (KBr) : ν_{max} (carbonyl group) cm^{-1} 1641 Yield : 168mg, (40.1%) Calculated for $C_{18}H_{23}NO_3$ C 71.72, H 7.69, N 4.64% Found: C 71.09, H 7.81, N 4.56%

1-*E,E*- piperinoyl-isobutylamine (RV-A06) (8f):

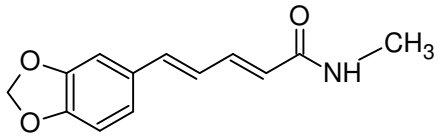


Yield : 120mg, (32%)

m.p. 161.2^0-161.7^0C

^{1}H-NMR ($CDCl_3$) δ: 5.96 (d, 1H, J=14.8, CH=CH-CH=**CH),** 7.36 (dd, 1H, J=10.5, 14.8, CH=CH-**CH**=CH), 6.66 (dd, 1H, J=15.4, 10.5, CH=**CH**-CH=CH), 6.76 (d, 1H, J=15.4 **CH**=CH-CH=CH), 6.96 (d,1H J=1.6, Ar-**H**), 6.76 (d,1H J=8.0, Ar-**H**), 6.87 (dd, 1H J=1.6, 8.0 Ar-**H**), 5.97 (s, 2H, **O-CH_2-O**), 3.18 (t, 2H, J=6.5 **CH_2** -CH), 1.83 (m, 1H, J=6.5 CH_2 -**CH**), 0.94(d, 6H, J=6.5, (**CH_3**) **$_2$**), 5.82 (t, 1H, **NH** J=5.3) ^{13}C-NMR ($CDCl_3$) : 20.4 (**CH_3**), 29.4 (**CH**), 47.3 (**CH_2**), 102.2 (**CH_2**), 106.2 (**CH**), 109.1 (**CH**), 123.3(**CH**), 125.5 (**CH**), 126.0 (**CH**), 132.0 (**C**), 138.0 (**CH**), 140.4 (**CH**), 148.9 (**C**), 149.2 (**C**), 166.2 (**C**) MS m/z (%) : 273 (M^+ 98), 216 (20), 201 (100), 174 (25), 173 (65), 172 (23), 171 (17) 143 (20), 115 (40), 96 (11). IR (KBr) : ν_{max} (carbonyl group) cm^{-1} 1644 Yield : 120mg, (32%) Calculated for $C_{16}H_{19}NO_3$ C 70.29, H 7.01, N 5.12% Found: C 69.79, H 7.02, N 5.01%

1-*E,E*-piperinoyl-methylamine (RV-A07) (8g):



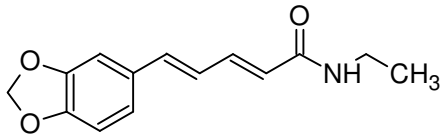
Yield : 155mg (48.2%)

m.p. 181.1^0-182.4^0C

^{1}H-NMR ($CDCl_3$) δ: 5.91 (d, 1H, J=14.8, CH=CH-CH=**CH),** 7.36 (dd, 1H, J=10.7, 14.8, CH=CH-**CH**=CH), 6.66 (dd, 1H, J=15.4, 10.6, CH=**CH**-CH=CH), 6.77 (d, 1H, J=15.4 **CH**=CH-CH=CH), 6.97 (d,1H J=1.5, Ar-**H**), 6.77 (d,1H J=8.0, Ar-**H**), 6.88 (dd, 1H J=1.6, 8.0 Ar-**H**), 5.97 (s, 2H, **O-CH_2-O**), 2.91(t, 3H, **CH_3**), 5.61 (br, **NH**) ^{13}C-NMR ($CDCl_3$) : 26.9 (**CH_3**), 101.7 (**CH_2**), 106.1 (**CH**), 108.9 (**CH**), 123.0 (**CH**), 123.3 (**CH**), 125.0 (**CH**), 131.2 (**C**), 139.2 (**CH**), 141.4 (**CH**), 148.6 (**C**), 148.6

(**C**)167.2 (**C**) MS m/z (%) : 231(M^+89), 201 (42), 173 (67), 172 (32), 171 (17), 143 (27), 116 (21)115 (100), 89 (12) Calculated for $C_{13}H_{13}NO_3$ C 67.50, H 5.66, N 6.01% Found: C 66.96, H 5.61, N 5.90%

1-*E,E*-piperinoyl-ethylamine (RV-A08) (8h):

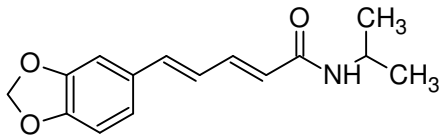


Yield : 156mg (45.6%)

m.p. 158.5^0-159.9^0C

^{1}H-NMR (CD_3OD) δ: 6.14 (d, 1H, J=15.0, CH=CH-CH=**CH),** 7.37 (dd, 1H, J=10.2, 15.0, CH=CH-**CH**=CH), 6.93 (dd, 1H, J=15.7, 10.6, CH=**CH**-CH=CH), 6.87 (d, 1H, J=15.7 **CH**=CH-CH=CH), 6.97 (d,1H J=1.5, Ar-**H**), 6.77 (d,1H J=8.0, Ar-**H**), 6.88 (dd, 1H J=1.6, 8.0 Ar-**H**), 5.97 (s, 2H, **O-CH_2-O**), 3.39(m, 2H, J= 6.2,**CH_2**),1.22(t, 3H, J= 6.1,**CH_3**), ^{13}C-NMR ($CDCl_3$) : 14.7 (**CH_3**), 36.9(**CH_2**), 103.2 (**CH_2**), 107.2 (**CH**), 109.8 (**CH**), 121.2 (**CH**), 124.9 (**CH**), 125.9 (**CH**), 132.4 (**C**), 142.9 (**CH**), 145.2 (**CH**), 150.2 (**C**), 150.6 (**C**),170 (**C**)MS m/z (%) : 245(M^+78), 218 (34), 201 (71), 200 (49), 174 (64),173 (80), 172 (76), 171 (65), 143 (75), 116 (68),115 (100).

1-*E,E*-piperinoyl-isopropylamine (RV-A09) (8i):

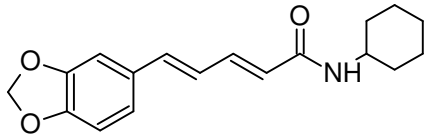


Yield : 188mg (52%)

m.p. 169^0-169.4^0C

^{1}H-NMR ($CDCl_3$) δ: 5.87 (d, 1H, J=14.8, CH=CH-CH=**CH),** 7.36 (dd, 1H, J=10.7, 14.8, CH=CH-**CH**=CH), 6.66 (dd, 1H, J=15.4, 10.6, CH=**CH**-CH=CH), 6.76 (d, 1H, J=15.2 **CH**=CH-CH=CH), 6.97 (d,1H J=1.6, Ar-**H**), 6.77 (d,1H J=8.0, Ar-**H**), 6.88 (dd, 1H J=1.6, 8.0 Ar-**H**), 5.97 (s, 2H, **O-CH_2-O**), 4.15(m, 1H, J=6.6, **CH**), 5.36 (d, 1H, J=7.3 **NH**), 1.19 (d, 6H, J=6.6, (**CH_3**)$_2$) ^{13}C-NMR ($CDCl_3$) : 23.2 (**CH_3**)$_2$, 41.9 (**CH**),101.9 (**CH_2**), 106.4 (**CH**), 108.9 (**CH**), 123.0 (**CH**), 123.8 (**CH**), 124.1 (**CH**), 131.3 (**C**), 140.2 (**CH**), 141.2 (**CH**), 148.8 (**C**), 148.6 (**C**)165.6 (**C**) MS m/z (%) : 259(M^+80), 201 (62), 174 (34), 173 (74), 172 (31), 171 (15), 143 (30), 116 (16), 115 (100) Calculated for $C_{15}H_{17}NO_3$ C 69.46, H 6.61, N 5.40% Found: C 69.13, H 6.34, N 5.24%

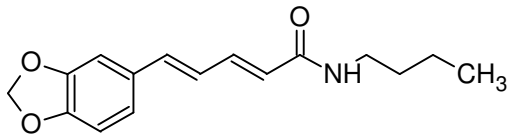
1-*E,E*-piperinoyl-cyclohexylamine (RV-A10) (8j):



Yield : 239mg (57.4%)
m.p. 196.4^0-197.3^0C

^{1}H-NMR ($CDCl_3$) δ: 5.93 (d, 1H, J=14.8, CH=CH-CH=**CH),** 7.35 (dd, 1H, J=10.6, 14.8, CH=CH-**CH**=CH), 6.66 (dd, 1H, J=15.3, 10.6, CH=**CH**-CH=CH), 6.76 (d, 1H, J=15.4 **CH**=CH-CH=CH), 6.96 (d,1H J=1.6, Ar-**H**), 6.76 (d,1H J=8.0, Ar-**H**), 6.87 (dd, 1H J=1.6, 8.0 Ar-**H**), 5.97 (s, 2H, **O-CH_2-O**), 3.87 (m, 1H, **CH** (cyclohexyl)) 1.99 (m, 2H, **CH_2**(cyclohexyl)) 1.65 (m, 4H, **CH_2-CH_2**(cyclohexyl) 1.39 (m, 2H, **CH_2**(cyclohexyl)) 1.18 (m, 2H, **CH_2**(cyclohexyl)) 5.48 (d,J=8.0 **NH**) ^{13}C-NMR ($CDCl_3$) : 25.3 ((**CH_2**)$_2$), 25.9 (**CH_2**) , 33.6 ((**CH_2**)$_2$), 48.6 (**CH**), 101.7 (**CH_2**), 101.7 (**CH**), 106.1 (**CH**), 108.9 (**CH**), 123.0 (**CH**), 124.0 (**CH**), 125.1 (**CH**),131.3 (**C**), 139.0 (**CH**), 141.2 (**CH**) 148.5 (**C**), 148.5 (**C**), 165.5 (**C**) MS m/z (%) : 299(M^+56), 259 (48) 216 (33), 201 (60),174 (33), 173 (61), 172 (18), 171 (16) 143 (17), 115 (100) Calculated for $C_{18}H_{21}NO_3$ C 72.20, H 7.07, N 4.68% Found: C 72.14, H 6.90, N 4.61%

1-*E,E*-piperinoyl-butylamine (RV-A11) (8k):



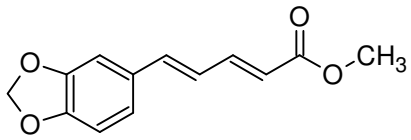
Yield : 146mg (38.4%)
m.p. 144.2^0-145.6^0C

^{1}H-NMR ($CDCl_3$) δ: 5.97 (d, 1H, J=14.8, CH=CH-CH=**CH),** 7.35 (dd, 1H, J=10.7, 14.8, CH=CH-**CH**=CH), 6.66 (dd, 1H, J=15.4, 10.6, CH=**CH**-CH=CH), 6.76 (d, 1H, J=15.4 **CH**=CH-CH=CH), 6.97 (d,1H J=1.6, Ar-**H**), 6.77 (d,1H J=8.0, Ar-**H**), 6.89 (dd, 1H J=1.5, 8.0 Ar-**H**), 5.97 (s, 2H, **O-CH_2-O**), 3.36 (q, 2H, **CH_2** - CH_2- CH_2-) 1.54 (m, 2H, CH_2 - **CH_2**- CH_2) 1.39 (m, 6H, CH_2 - CH_2- **CH_2**) 0.93 (t, 3H, **CH_3**), 5.47 (br, **NH**) ^{13}C-NMR ($CDCl_3$): 14.2 (**CH_3**), 20.5 (**CH_2**), 32.2 (**CH_2**), 39.8 (**CH_2**), 101.7 (**CH_2**), 106.1 (**CH**), 108.9 (**CH**), 123.0 (**CH**), 123.6 (**CH**), 125.0 (**CH**), 131.3 (**C**), 139.2 (**CH**), 141.3 (**CH**) 148.6 (**C**), 148.6 (**C**), 166.4 (**C**) Yield : 146mg (38.4%) Calculated for $C_{16}H_{19}NO_3$ C 70.29, H 7.01, N 5.12% Found: C 70.16, H 6.56, N 4.78%

2.3.3 SYNTHESIS OF PIPERINE ESTER ANALOGUES

A mixture of piperinic acid **(6)** (200mg, 0.9mmole, 1eq) and triethylamine (0.25mL, 1.8mmole, 2eq) in dichloromethane (50mL) was stirred for 15min at 0^0C. To this mixture methane sulfonylchloride (0.1mL, 1.3mmole, 1.5eq) was added and stirred for further 30 min at 0^0C. A desired alcohol (10mL) was added to the mixture and stirred for 1h at 0^0C and 2h at room temperature. Dichloromethane (50mL) was added to the mixture, which was then washed with water (3x100mL), 5% $NaHCO_3$ (3x100mL) and water (3x100mL). The organic fraction was dried over anhydrous sodium sulphate, filtered and rotary evaporated to yield a brownish solid residue. Recrystallisation from ethylacetate and petroleum spirit gave piperinic acid esters **(10a-d).**

5-(3,4-Methylenedioxyphenyl)-penta-2*E*,4*E*-dienoic acid methyl ester (RV-AB1) (10a):

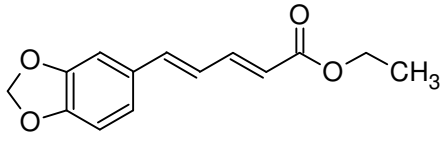


Yield : 117mg (56.2%)

m.p. 142.9^0-143^0C m.p.

^{1}H-NMR ($CDCl_3$) δ: 5.94 (d, 1H, J=15.2, CH=CH-CH=**CH),** 7.41 (dd, 1H, J=10.8, 15.2, CH=CH-**CH**=CH), 6.70 (dd, 1H, J=15.4, 10.8, CH=**CH**-CH=CH), 6.81 (d, 1H, J=15.7 **CH**=CH-CH=CH), 6.99 (d,1H J=1.6, Ar-**H**), 6.79 (d,1H J=8.1, Ar-**H**), 6.91 (dd, 1H J=1.5, 8.1 Ar-**H**), 5.98 (s, 2H, **O-CH_2-O**), 3.57 (t, 3H, br, **OCH_3** J=4.7) ^{13}C-NMR ($CDCl_3$) :51.5(**CH_3**), 101.8 (**CH_2**), 106.2 (**CH**) 108.9 (**CH**), 120.0 (**CH**), 123.4 (**CH**)124.7 (**CH**), 130.8 (**CH**), 140.9 (**C**), 145.5 (**CH**), 148.6 (**C**), 148.9 (**C**), 168.9 (**C**) MS m/z (%) : 232 (M^+ 69), 201 (19), 174 (12), 173 (100), 172 (39), 171 (12) 143 (33), 116 (11), 115 (53) 101 (15), 100 (12) Calculated for $C_{13}H_{12}O_4$ C 67.22, H 5.21% Found: C 66.91, H 5.21%

5-(3,4-Methylenedioxyphenyl)-penta-2*E*,4*E*-dienoic acid ethyl ester (RV-AB2)(10b):



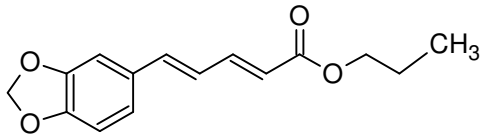
Yield : 120mg 55%

m.p 43.1^0-44^0 C m.p

^{1}H-NMR ($CDCl_3$) δ: 5.94 (d, 1H, J=15.2, CH=CH-CH=**CH),** 7.41 (dd, 1H, J=10.8, 15.3, CH=CH-**CH**=CH), 6.70 (dd, 1H, J=15.4, 10.8, CH=**CH**-CH=CH), 6.81 (d, 1H,

J=15.5 **CH**=CH-CH=CH), 6.99 (d,1H J=1.6, Ar-**H**), 6.78 (d,1H J=8.1, Ar-**H**), 6.91 (dd, 1H J=1.6, 8.1 Ar-**H**), 5.98 (s, 2H, **O-CH_2-O**), 4.22 (q, 2H, **OCH_2** J=7.2) 1.31 (t, 3H, **CH_3** J=7.2) ^{13}C-NMR ($CDCl_3$) :14.7(**CH_3**), 60.7(**CH_2**),101.6 (**CH_2**), 106.3 (**CH**) 108.9 (**CH**), 120.8 (**CH**), 123.3 (**CH**)124.9 (**CH**), 131.0 (**C**), 140.5 (**CH**), 145.1 (**CH**), 148.7 (**C**), 148.9(**C**), 167.6 (**C**) MS m/z (%) : 246 (M^+ 83), 201 (26), 174 (14), 173 (100), 143 (15), 115 (53)Calculated for $C_{14}H_{14}O_4$ C 68.27 H 5.73% Found C 68.61 H 5.54%

5-(3,4-Methylenedioxyphenyl)-penta-2*E*,4*E*-dienoic acid propyl ester (RV-AB5) (10c):

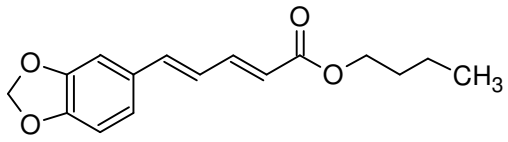


Yield : 84mg 34%

m.p. 119^0-120^0C

^{1}H-NMR ($CDCl_3$) δ: 5.94 (d, 1H, J=15.2, CH=CH-CH=**CH),** 7.41 (dd, 1H, J=10.7, 15.2, CH=CH-**CH**=CH), 6.70 (dd, 1H, J=15.4, 10.8, CH=**CH**-CH=CH), 6.76 (d, 1H, J=15.4 **CH**=CH-CH=CH), 6.99 (d,1H J=1.6, Ar-**H**), 6.78 (d,1H J=8.1, Ar-**H**), 6.91 (dd, 1H J=1.5, 8.0 Ar-**H**), 5.98 (s, 2H, **O-CH_2-O**), 4.12 (t, 2H, **OCH_2** J=6.7) 1.69 (m, 2H, **CH_2** J=7.3) 0.97 (t, 3H, **CH_3** J=7.4) ^{13}C-NMR ($CDCl_3$) :10.9(**CH_3**), 22.5(**CH_2**), 66.3(**CH_2**),101.8 (**CH_2**), 106.2 (**CH**) 108.9 (**CH**), 120.9 (**CH**), 123.3 (**CH**)124.9 (**CH**), 131.0 (**C**), 140.5 (**CH**), 145.1 (**CH**), 148.7 (**C**), 148.9(**C**), 167.7 (**C**) MS m/z (%) : 260 (M^+ 59), 201 (26), 174 (18), 173 (100), 172 (39), 171 (14) 143 (34), 116 (16), 115 (73),100 (12) Calculated for $C_{15}H_{16}O_4$ C 69.20, H 6.19% Found: C 69.04, H 6.49%

5-(3,4-Methylenedioxyphenyl)-penta-2*E*,4*E*-dienoic acid butyl ester(RV-AB6) (10d)



Yield : 102mg 41.4%

Obtained as oil

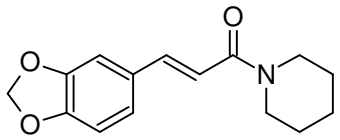
^{1}H-NMR ($CDCl_3$) δ: 5.94 (d, 1H, J=15.2, CH=CH-CH=**CH),** 7.40 (dd, 1H, J=10.7, 15.3, CH=CH-**CH**=CH), 6.70 (dd, 1H, J=15.4, 10.8, CH=**CH**-CH=CH), 6.76 (d, 1H, J=15.4 **CH**=CH-CH=CH), 6.99 (d,1H J=1.6, Ar-**H**), 6.78 (d,1H J=8.0, Ar-**H**), 6.91 (dd, 1H J=1.5, 8.0 Ar-**H**), 5.98 (s, 2H, **O-CH_2-O**), 4.12 (t, 2H, **OCH_2** J=6.7) 1.69 (m,

2H, **CH_2** J=7.3) 1.69 (m, 2H, **CH_2** J=7.6), 0.95 (t, 3H, **CH_3** J=7.5) MS m/z (%) : 274 (M^+ 50), 201 (15), 174 (14), 173 (100), 172 (30), 171 (14) 143 (21), 115 (55) Calculated for $C_{16}H_{18}O_4$ C 70.04, H 6.61% Found: C 69.56, H 6.27 %

2.3.4 SYNTHESIS OF MODIFIED CONNECTING CHAIN PIPERINE AMIDE ANALOGUES

A mixture of 3,4-methylenedioxycinnamic acid **(11)** (500mg,0.0026mole,1eq) and triethylamine (0.54ml,3.9mmole,1.5eq) in dichloromethane (50mL) was stirred for 15min at 0^0C. To this mixture methane sulfonylchloride (0.3mL,3.9mmole,1.5eq) was added and stirred for further 30 min at 0^0C. The amine (1.5eq) was added to the mixture and stirred for 2h at 0^0C and 1h at room temperature. Dichloromethane (50mL) was added to the mixture, which was then washed with water (3x100mL), 5% $NaHCO_3$ (3x100mL) and water (3x100mL). The organic fraction was dried over anhydrous sodium sulphate, filtered and the filtrate was rotary evaporated to yield a brownish solid residue. Recrystallisation from ethylacetate and petroleum spirit gave short chain piperinic acid amides **(12a-c).**

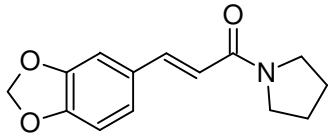
1-(3,4-Methylenedioxy-cinnamoyl)-piperidine (RV-B01) (12a)



Yield :328mg (58.2%)
m.p. 80.1^0-82^0C

^{1}H-NMR ($CDCl_3$) δ: 7.56 (d, 1H, J=15.3, CH=**CH),** 6.73 (d, 1H, J=15.3, **CH**=CH), 7.03 (d,1H J=1.5, Ar-**H**), 6.79 (d,1H J=8.0, Ar-**H**), 6.99 (dd, 1H J=1.6, 8.0 Ar-**H**), 5.98 (s, 2H, **O-CH_2-O**), 3.57 (br, 2H, CH_2-N-**CH_2**), 3.65 (br, 2H, **CH_2**-N-CH_2(piperidine)), 1.65 (m, 6H, **CH_2**- **CH_2**- **CH_2**- (piperidine)) ^{13}C-NMR ($CDCl_3$) : 24.8 (**CH_2**), 25.6 (**CH_2**), 26.7 (**CH_2**), 43.3 (**CH_2**), 46.9 (**CH_2**), 101.3 (**CH_2**), 106.7 (**CH**), 108.4 (**CH**), 115.6 (**CH**), 123.5 (**CH**), 129.9 (**C**), 141.9 (**CH**) 148.1 (**C**), 148.8 (**C**), 165.4 (**C**) Calculated for $C_{15}H_{17}O_3N$ C 69.47, H 6.60 N 5.40% Found: C 69.56, H 6.58, N 5.39 %

1-(3,4-Methylenedioxy-cinnamoyl)-pyrrolidine (RV-B02) (12b)

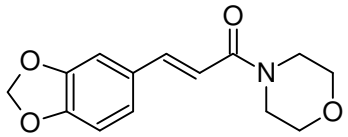


Yield : 280mg (44.1%)

m.p. 152.5^0-153^0C

^{1}H-NMR ($CDCl_3$) δ: 7.60 (d, 1H, J=15.2, CH=**CH),** 6.73 (d, 1H, J=15.3, **CH**=CH), 7.04 (d,1H J=1.5, Ar-**H**), 6.80 (d,1H J=8.0, Ar-**H**), 7.01 (dd, 1H J=1.5, 8.0 Ar-**H**), 5.99 (s, 2H, **O-CH_2-O**), 3.61 (br, 2H, CH_2-N- **CH_2** (pyrrolidine)), 3.57 (br, 2H, **CH_2**-N- CH_2(pyrrolidine)), 1.99 (4H, **CH_2**- **CH_2**(pyrrolidine)), ^{13}C-NMR ($CDCl_3$) : 24.3 (**CH_2**), 26.1 (**CH_2**) 46.0 (**CH_2**), 46.5 (**CH_2**), 101.4 (**CH_2**), 106.4 (**CH**), 108.5 (**CH**), 116.8 (**CH**), 123.8 (**CH**), 129.7 (**C**), 141.0 (**CH**) 148.1 (**C**), 148.9 (**C**), 164.8 (**C**) MS m/z (%) : 245(M^+ 62), 176 (41) 175 (100) 145 (36), 117 (11), 89 (14).Calculated for $C_{14}H_{15}NO_3$ C 68.54, H 6.16, N 5.71% Found: C 68.02, H 6.26, N 5.74%

1-(3,4-Methylenedioxy-cinnamoyl)-morpholine (RV-B03) (12c)

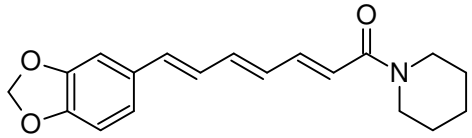


Yield : 339mg (50.1%)

m.p. 160^0-160.3^0C

^{1}H-NMR ($CDCl_3$) δ: 7.61 (d, 1H, J=15.3, CH=**CH),** 6.73 (d, 1H, J=15.3, **CH**=CH), 7.03 (d,1H J=1.4, Ar-**H**), 6.80 (d,1H J=8.0, Ar-**H**), 7.01 (dd, 1H J=1.4, 8.0 Ar-**H**), 5.99 (s, 2H, **O-CH_2-O**), 3.72 (br, 4H, **CH_2**-N- **CH_2** (morpholine)), 3.67 (br, 4H, **CH_2**-O- CH_2(morpholine)), ^{13}C-NMR ($CDCl_3$) : 42.6 (**CH_2**), 46.2 (**CH_2**), 66.8 (**CH_2**), 46.5 (**CH_2**), 101.4 (**CH_2**), 106.3 (**CH**), 108.5 (**CH**), 114.4 (**CH**), 123.9 (**CH**), 129.5 (**CH**), 143.0 (**CH**) 148.2 (**C**), 148.9 (**C**), 149.1 (**C**), 165.6 (**C**) MS m/z (%) : 261(M^+ 60), 176 (24) 175 (100) 145 (30), 117 (10), 89 (11).Calculated for $C_{14}H_{15}NO_4$ C 64.34, H 5.78, N 5.36% Found: C 64.20, H 5.88, N 5.38%

7-(3,4-methylenedioxyphenyl)-hepta2*E*,4*E*,6*E*-trienoyl piperidine (14)



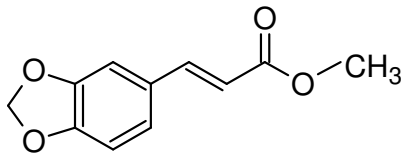
1-[(2*E*,4*E*)-Hexadienoyl]-piperidine (**19b**) (500mg, 2.79mmol) piperonal (**13**) (419mg, 2.69mmol) and aliquat 336 (50mg) were dissolved in toluene and anhydrous potassium carbonate (100mg) and sodium hydride (20mg) was added and refluxed

under nitrogen for 6h at 90^0C. The reaction mixture was poured into water and extracted with dichloromethane (3x100mL). The organic layer was dried over anhydrous sulphate, filtered and the filtrate was rotary evaporated to yield a solid residue. The mixture was purified by column chromatography using hexane: ethylacetate (1:9) as an eluent to give yellow solid. Yield 45.6% m.p 144.3-145.6^{0}C

^{1}H-NMR ($CDCl_3$) δ: 6.95 (d,1H J=1.6, Ar-**H**), 6.76 (d,1H J=8.0, Ar-**H**), 6.85 (dd, 1H J=1.6, 8.0 Ar-**H**), 6.37 (d,1H J=14.6, CH=CH-CH=CH-CH**=CH**), 6.42 (dd,1H J=11.4, 14.0, CH=CH-CH=**CH**-CH**=**CH), 7.35 (dd,1H J=11.4, 14.6, CH=CH-CH=CH-**CH=**CH), 6.59 (d,1H J=15.0, **CH**=CH-CH=CH-CH**=**CH), 6.66 (dd,1H J=15.0, 10.0, CH=**CH**-CH=CH-CH**=**CH), 6.63 (dt,1H J=10.0, 14.0, CH=CH-**CH**=CH-CH**=**CH), 5.96 (s, 2H, O-**CH_2**-O), 3.51 (br s, 2H, CH_2-N-**CH_2**) 3.62 (br s, 2H, J=5.7, (**CH_2**-N- CH_2) 1.54-1.59 (m, 4H, CH_2-**CH_2-CH_2** (Piperidine)) 1.60-1.68 (m, 2H, **CH_2**-CH_2-CH_2-(Piperidine)) ^{13}C-NMR ($CDCl_3$) : 25.0(**CH**), 26.0 (**CH**),27.1 (**CH**), 43.6 (**CH**), 47.3(**CH**), 101.6 (**CH_2**), 105.8 (**CH**), 108.8 (**CH**), 120.4 (**CH**), 122.4 (**CH**), 127.0 (**CH**), 130.8(**CH**), 135.8 (**CH**), 139.5 (**CH**), 142.7 (**CH**), 135.9 (**C**), 148.1 (**C**), 148.5 (**C**), 165.8 (**C**), MS m/z (%) : 311 (M^+ 99), 301 (18), 227 (27), 217 (21), 199 (42), 182 (30) 169 (59), 149 (29), 141 (100), 127 (86), 115 (43),84(81),69(43)

2.3.5 SYNTHESIS OF SHORT CHAIN PIPERINE ESTER ANALOGUE

3-(3,4-Methylenedioxy)-cinnamic acid methyl ester (RV-BB1) (15)

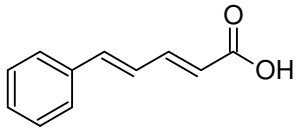


Methanol (4mL, 10eq) was added to 3,4-methylenedioxycinnamicacid(**11)** (2g, 0.01mole, 1eq). 0.2mL of sulphuric acid was added to the methanolic solution and refluxed overnight. The solvent containing mixture was rotary evaporated to a yield solid residue. This residue was dissolved in ether and washed with water (2x100mL) and 5%$NaHCO_3$ (3x100mL) and with water (2x100mL). The organic fraction was dried over anhydrous sodium sulphate, filtered and the filtrate was and rotary evaporated to yield a white solid. Recrystallisation from ethylacetate/petroleum spirit yielded crystals (1.42g, 69.4% yield) m.p. 133.7^0-134.2^0C (Lit m.p.134^0C).

^{1}H-NMR ($CDCl_3$) δ: 7.59 (d, 1H, J=15.9, CH=**CH),** 6.26 (d, 1H, J=15.9, **CH**=CH), 7.03 (d,1H J=1.5, Ar-**H**), 6.81 (d,1H J=8.0, Ar-**H**), 7.01 (dd, 1H J=1.5, 8.0 Ar-**H**), 6.00 (s, 2H, **O-CH_2-O**), 3.79 (s, 3H, **OCH_3**) ^{13}C-NMR ($CDCl_3$) : 51.6 (**CH_3**), 101.5 (t **CH_2**), 106.5 (**CH**), 108.5 (**CH**), 115.7 (**CH**), 124.4 (**CH**), 128.8 (**CH**), 144.5 (**CH**) 148.3 (**C**), 148.6 (**C**), 148.2 (**C**), 167.6 (**C**) MS m/z (%) : 206(M^+ 100), 175 (68) 175 (100) 145 (27), 117 (10), 89 (11).

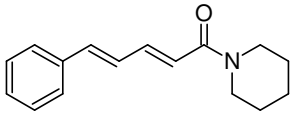
2.3.6 SYNTHESIS OF AROMATIC SUBSTITUTED PIPERINE ANALOGUES

5-Phenyl-penta-2*E*,4*E*-dienoic acid (17a)



Cinnamaldehyde **(16)** (1mL, 0.0075mole, 1eq) and malonic acid (1.56g, 0.015mole, 2eq) was stirred in pyridine (15mL) for 10min and refluxed for overnight. Mixture was boiled for 15min. Mixture is cooled and acidified with 1N HCl yielding a yellowish precipitate of a mixture of 5-phenyl-penta-2,4-dienoic acid. Recrystallisation from chloroform gave 5-phenyl-penta-2*E*,4*E*-dienoic acid **(17a)** (56.2% yield). m.p. 164.5^0-165^{0}c. (Lit m.p. 164^0-165^{0}c)

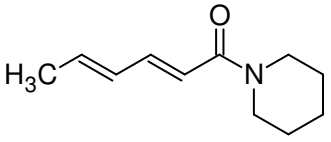
5-Phenyl-penta-2*E*,4*E*-dienoyl piperidine (19a)



A mixture of 5-phenyl)-penta-2*E*,4*E*-dienoic acid (**17a)** (200mg, 0.0011mole, 1eq) and triethylamine (0.3mL, 0.0022mole, 2eq) in dichloromethane (50mL) was stirred for 15min at 0^{0}C. To this mixture methane sulfonylchloride (0.12mL, 0.0016mole, 1.5eq) was added and stirred for further 30 min at 0^{0}C. Piperidine (0.16mL, 0.0016mole, 1.5eq) was added to the mixture and stirred for 1h at 0^{0}C and 1h at room temperature. Dichloromethane (50mL) was added to the mixture which was then washed with 5% HCl (3x100mL), saturated aqueous $NaHCO_3$ (3x100mL) and water (3x100mL). The organic fraction was dried over anhydrous sodium sulphate, filtered and rotary evaporated to yield a yellowish solid residue. Recrystallisation from ethylacetate/ether yielded white crystals of 5-(phenyl)-penta-2*E*,4*E*-dienoyl piperidine (**19a**) (36% yield) m.p 73-75^{0}C (Lit m.p. 77^{0}C).

^{1}H-NMR ($CDCl_3$) (60mHZ) δ: 7.1-7.4 (1H ArH)**,** 7.25 (1H ArH), 6.78 (2H ArH) 6.45 (1H, ArH) 3.4-3.6 (br, 4H, CH_2- N- CH_2 (piperidine)) 1.5-1.8 (m, 6H, CH_2.CH_2 CH_2 (piperidine))

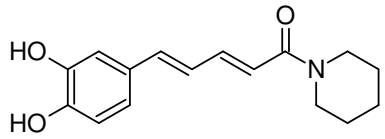
1-[(2*E*,4*E*)-Hexadienoyl]-piperidine (RV-E01) (19b)



A mixture of 2,4-hexadienoic acid **(17b)** (300mg, 0.0026mole, 1eq) and triethylamine (0.7mL,0.0052mole, 2eq) in dichloromethane (50mL) was stirred for 15min at 0^0C. To this mixture methane sulfonylchloride (0.3mL, 0.0039mole, 1.5eq) was added and stirred for further 30 min at 0^0C. Piperidine (0.23mL, 0.0039mole, 1.5eq) was added to the mixture and stirred for 1h at 0^0C and 1h at room temperature. Dichloromethane (50mL) was added to the mixture which was then washed with 5% HCl (3x100mL), saturated aqueous $NaHCO_3$ (3x100mL) and water (3x100mL). The organic fraction was dried over anhydrous sodium sulphate, filtered and the filtrate was rotary evaporated to yield a yellowish solid residue. Recrystallisation from ethylacetate/ether yielding colourless crystals of 1-[(2*E*,4*E*)-hexadienoyl]-piperidine **(19b)** (58.3% yield). m.p. 79.2^0-81.2^0C (Lit m.p. 83-84^0C)

^{1}H-NMR ($CDCl_3$) δ: 6.23 (d, 1H, J=15.7, CH=CH-CH=**CH),** 7.25 (dd, 1H, J=10.7, 15.7, CH=CH-**CH**=CH), 6.73 (dd, 1H, J=15.3, 9.5, CH=**CH**-CH=CH), 6.78 (d, 1H, J=15.3 **CH**=CH-CH=CH), 3.61 (br, 2H, N- **CH_2** (piperidine)) 3.48 (br, 2H, N- **CH_2** (piperidine)) 1.65 (m, 2H, **CH_2.**CH_2 CH_2 (piperidine)) 1.57 (m, 4H, **CH_2.CH_2** CH_2 (piperidine)) 1.83 (d, 3H, J=6.6, **CH_3**) ^{13}C-NMR ($CDCl_3$) : 18.5 (**CH_3**), 24.6 (**CH_2**), 25.6 (**CH_2**), 26.7 (**CH_2**), 43.1(**CH_2**), 46.8(**CH_2**), 118.3 (**CH**), 130.0 (**CH**), 137.0 (**CH**), 142.6 (**CH**), 165.7 (**C**) MS m/z (%) : 179(M^+ 5), 168 (100), 167 (14), 138 (12), 112 (11), 85 (18), 83 (31), 69 (10), 47 (11) Calculated for $C_{11}H_{17}ON$ C 73.70, H 9.55, N7.81% Found: C 72.95, H 9.34, N7.81 %

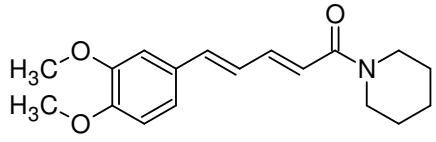
Piperidine-5-(3,4-dihydroxyphenyl)penta-2*E*,4*E*-dienoic acid amide (20)



Piperine **(5)** (500mg, 1.75mmole, 1eq) was dissolved in dichloromethane (DCM, 10mL) and BBr3 in dichloromethane (0.7mL, 8.7mmole, 5eq) was added and stirred at room temperature for 2 days. After the completion of reaction, DCM was removed under reduced pressure and a yellow solid was obtained. The yellow solid was washed with DCM and filtered to give a product (354mg, 76.2%).

^{1}H-NMR (MeOD) δ: 6.54 (d, 1H, J=14.6, CH=CH-CH=**CH),** 7.32 (dd, 1H, J=9.5, 14.6, CH=CH-**CH**=CH), 6.78 (dd, 1H, J=13.2, 9.5, CH=**CH**-CH=CH), 6.75 (d, 1H, J=13.2 **CH**=CH-CH=CH), 6.98 (d,1H J=1.9, Ar-**H**), 6.74 (d,1H J=8.2, Ar-**H**), 6.85 (dd, 1H J=1.9, 8.2 Ar-**H**), 3.59 (br, 4H, **CH_2**.N- **CH_2** ((piperidine)) 1.59 (m, 6H, **CH_2.CH_2.CH_2**(piperidine)) ^{13}C-NMR (MeOD) : 25.9 (**CH_2**), 27.3 (**CH_2**), 28.2 (**CH_2**), 45.1 (**CH_2**), 48.6 (**CH_2**), 114.8 (**CH**), 116.9 (**CH**), 119.7 (**CH**), 121.7 (**CH**), 125.5 (**CH**), 141.7 (**CH**), 145.7 (**CH**), 147.0 (**C**), 148.3 (**C**), 148.3 (**C**), 168.3(**C**)

Piperidine-5-(3,4-dimethoxyphenyl)penta-2*E*,4*E*-dienoic acid amide (21)



Potassium hydroxide (328mg) was added to dimethylsulfoxide (5mL, DMSO) and stirred under nitrogen atmosphere for 5mins at room temperature. The compound **(20)** (200mg) was added to the mixture and followed by iodomethane (0.3mL) and stirred for another 30 min at same temperature. The mixture was poured into water 50ml and extracted with dichoromethane (3x30mL). The combined extracts were washed with water (50mL) and dried under sodium sulphate, filtered and the filtrate was rotary evaporated to yield a solid. Recrystallisation from using petroleum spirit and ethylacetae yielded pure greenish crystals (122mg, 58%).

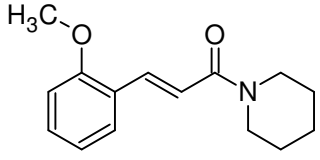
^{1}H-NMR ($CDCl_3$) δ: 6.46 (d, 1H, J=14.6, CH=CH-CH=**CH),** 7.25-7.46 (m, 1H, CH=CH-**CH**=CH), 6.78 (1H, CH=**CH**-CH=CH), 6.80 (d, 1H, J=14.6 **CH**=CH-CH=CH), 6.98 (d,1H J=1.8, Ar-**H**), 6.83 (d,1H J=8.1, Ar-**H**), 7.0 (dd, 1H J=1.6, 8.1

Ar-**H**), 3.89 and 3.91 (2s, 6H, (**O-CH$_3$-)$_2$**), 3.63 (br, 2H, N- **CH$_2$** ((piperidine)) 3.52 (b, 2H, N- **CH$_2$** (piperidine) 1.64 (m, 2H, CH$_2$-**CH$_2$**(piperidine)) 1.87 (m, 4H, **CH$_2$-CH$_2$**CH$_2$ (piperidine)) ^{13}C-NMR ($CDCl_3$) : 23.3 (**CH$_2$**), 24.2 (**CH$_2$**), 25.3 (**CH$_2$**), 41.8 (**CH$_2$**), 45.5 (**CH$_2$**), 54.4 (O**CH$_3$**), 54.5 (O**CH$_3$**), 107.5 (**CH**), 109.7 (**CH**), 118.4 (**CH**), 123.8 (**CH**), 137.0 (**CH**), 141.2 (**CH**), 147.6 (**C**), 148.2 (**C**), 148.2 (**C**), 164.0(**C**), MS m/z (%) : 301 (M^+ 71), 218 (27), 217 (81), 188 (52), 182 (34) 148 (17), 140 (52), 127 (100), 115 (22), 84 (40)

2.3.7 SYNTHESIS OF AROMATIC SUBSTITUETED SHORT CHAIN PIPERINE ANALOGUES

A mixture of monomethoxycinnamic acid **(22a-c)** (200mg, 0.89mmole, 1eq) and triethylamine (2.4mL, 1.78mmole, 2eq) in dichloromethane (50mL) was stirred for 15min at 0^{0}C. To this mixture methane sulfonyl chloride (1.02mL, 1.33mmole, 1.5eq) was added and stirred for further 30 min at 0^{0}C. Piperidine (0.23mL, 1.33mmole, 1.5eq) was added to the mixture and stirred for 1h at 0^{0}C and 1h at room temperature. Then dichloromethane (50mL) was added to the mixture which was then washed with 5% HCl (3x100mL), saturated aqueous $NaHCO_3$ (3x100mL) and water (3x100mL). The organic fraction was dried over anhydrous sodium sulphate, filtered and rotary evaporated to yield an oil. This oil is purified by chromatography on silica gel using ethylacetate/petroleum spirit (2:8) as an eluent (**23a-c**).The piperidine amide of 3,4 dimethoxycinnamic acid **(22d)** was prepared in the same way utilising 200mg of the acid **(23d)**.

1-(2-methoxy-cinnamoyl)-piperidine (RV-G01) (23a)



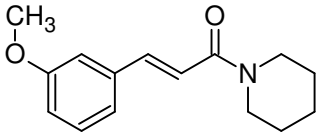
Yield : 55mg (25.5%)

m.p 68-70^{0}C

^{1}H-NMR ($CDCl_3$) δ: 7.56 (d, 1H, CH=CH)**,** 7.29 (d, 1H, J=7.8 Ar-**H**), 7.12(d, 1H, J=7.6 Ar-**H**) 7.0 (dd 1H, J=1.8 Ar-**H**) 6.86-6.90 (m,Ar-**H**), 6.88 (d, 1H, J=15.4 **CH**=CH), 3.58-3.66 (br, 4H, **CH$_2$**-N- **CH$_2$** (piperidine)) 1.56-1.71 (m, 6H, **CH$_2$-CH$_2$ CH$_2$** (piperidine)) 3.83 (s, 3H, **OCH$_3$**) ^{13}C-NMR ($CDCl_3$) : 25.7 (**CH$_2$**), 26.0 (**CH$_2$**), 27.1 (**CH$_2$**), 43.7(**CH$_2$**), 47.4(**CH$_2$**), 55.7(**CH$_3$**), 113.4 (**CH**),115.3 (**CH**), 118.5

(**CH**),120.6 (**CH**),130.1 (**CH**),142.4 (**CH**), 137.3 (**C**), 160.2 (**C**), 165.6 (**C**)MS m/z (%) : 245(M^+ 28), 162 (22), 161 (100), 133 (20), 118 (24), 113 (14), 84 (51) Yield : 55mg (25.5%) m.p 68-70^{0}C

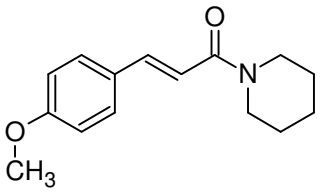
1-(3-methoxy-cinnamoyl)-piperidine (RV-G02) (23b)



Yield : 68mg, (31.4%)

^{1}H-NMR ($CDCl_3$) δ: 7.60 (d, 1H, J=15.4, CH=**CH),** 7.29 (d, 1H, J=7.8 ArH), 7.12(d, 1H, J=7.6 Ar-**H**) 7.0 (dd 1H, J=1.8 Ar-**H**) 6.86-6.90 (m,Ar-**H**), 6.88 (d, 1H, J=15.4 **CH**=CH), 3.58-3.66 (br, 4H, **CH_2**-N- **CH_2** (piperidine)) 1.56-1.71 (m, 6H, **CH_2.CH_2 CH_2** (piperidine)) 3.83 (s, 3H, **OCH_3**)^{13}C-NMR ($CDCl_3$) : 25.7 (**CH_2**), 26.0 (**CH_2**), 27.1 (**CH_2**), 43.7(**CH_2**), 47.4(**CH_2**), 55.7(**CH_3**), 113.4 (**CH**),115.3 (**CH**), 118.5 (**CH**),120.6 (**CH**),130.1 (**CH**),142.4 (**CH**), 137.3 (**C**), 160.2 (**C**), 165.6 (**C**) MS m/z (%) : 245(M^+ 77), 162 (65), 161 (100), 133 (20), 118 (24), 113 (14), 84 (51) m.p. 68^0-70^{0}C Yield : 68mg, (31.4%) Calculated for $C_{15}H_{19}NO_2$ C 73.42, H 7.81, N 5.71% Found: C 73.37, H 7.96, N 5.86%

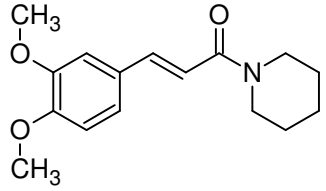
1-(4-methoxy-cinnamoyl)-piperidine (RV-G03) (23c)



Yield : 79.1mg (36.3%)

^{1}H-NMR ($CDCl_3$) δ: 7.61 (d, 1H, J=15.4, CH=**CH),** 7.47 (d, 2H, J=7.8 Ar-**H**), 6.87-6.90 (m,2H,Ar-**H**), 6.77 (d, 1H, J=15.4 **CH**=CH), 3.58-3.65 (br, 4H, **CH_2**-N- **CH_2** (piperidine)) 1.52-1.69 (m, 6H, **CH_2.CH_2 CH_2** (piperidine)) 3.82 (s, 3H, **OCH_3**) ^{13}C-NMR ($CDCl_3$) : 25.6 (**CH_2**), 26.0 (**CH_2**), 26.4 (**CH_2**), 43.7(**CH_2**), 47.4(**CH_2**), 55.7(**CH_3**), 114.5 (**CH**),115.6 (**CH**), 118.5 (**CH**),121.9 (**CH**),129.6 (**CH**),142.2 (**CH**), 132.8 (**C**), 161.0 (**C**), 166.0 (**C**) MS m/z (%) : 245(M^+ 71), 162 (17), 161 (100), 133 (26), 118 (12), 113 (14), 84 (24), 77 (36) Yield : 79.1mg (36.3%) Calculated for $C_{15}H_{19}NO_2$ C 73.44, H 7.80, N 5.71% Found: C 73.49, H 7.63, N 5.89

1-(3,4-dimethoxy-cinnamoyl)-piperidine (RV-G04) (23d)

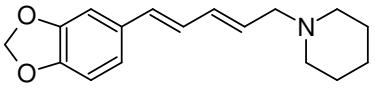


Yield : 111mg (42.3%)

^{1}H-NMR ($CDCl_3$) 60MHz δ: 7.61 (1H, CH=CH**),** 7.23 (1H, Ar-**H**), 6.98(1H, Ar-**H**) 6.82 (1H, J=1.8 Ar-**H**) 6.68 (1H, CH=CH), 3.58-3.65 (br, 4H, **CH_2**-N- **CH_2** (piperidine)) 1.5-1.8 (6H, **CH_2.CH_2 CH_2** (piperidine)) 3.91 (s, 6H, **OCH_3) $_2$**) MS m/z (%) : 275(M^+ 62), 192 (48), 191 (100), 161 (18), 118 (11), 84 (26), 77 (12) Yield : 111mg (42.3%)

2.3.8 VARIATION ON THE CONNECTING CHAIN

5-(3,4-Methylenedioxyphenyl)penta-2*E*,4*E*-dienyl-piperidine (RV-C01) (24)

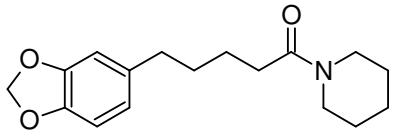


Piperine **(5)** (1g, 3.5mmol) and NaBH4 (0.35g, 8.75mmol) was stirred in THF (20mL) at 0^0C under nitrogen atmosphere. Iodine (0.65g, 2.62mmol) was added dropwise to the mixture and left for 2 days. The reaction was quenched with methanol till the effervescence ceased. The solvent was rotary evaporated to yield a residue (0.9g). This residue was purified by column chromatography on silica gel (31cm/10mm) using petroleum spirit/ethylacetate as an eluent. Recrystallisation of the fraction from methanol gave white crystals **(24)** (120mg, 13%). m.p. 126.7^0-127.3^0C.

^{1}H-NMR ($CDCl_3$) δ: 3.48 (d, 2H, J=7.4 CH=CH-CH=CH-**CH_2)** 6.1 (m, 1H, J=7.5,15.1, CH=CH-CH=**CH),** 6.35 (dd, 1H, J=15.1, 10.2, CH=CH-**CH**=CH), 6.67 (dd, 1H, J=10.2, 15.4, CH=**CH**-CH=CH), 6.48 (d, 1H, J=15.6 **CH**=CH-CH=CH), 6.94 (d,1H J=1.6, Ar-**H**), 6.76 (d,1H J=8.0, Ar-**H**), 6.82 (dd, 1H J=1.5, 8.0 Ar-**H**), 5.97 (s, 2H, **O-CH_2-O**), 3.57 (br, 2H, CH_2-N- **CH_2**), 3.65 (br, 2H, **CH_2**-N-CH_2(piperidine)),1.65(m,6H,**CH_2-CH_2-CH_2**-(piperidine))

^{13}CNMR($CDCl_3$):20.5(**CH_2**),20.5(**CH_2**),22.7(**CH_2**),53.0(**CH_2**),57.8(**CH_2**),101.2(**CH_2**) ,124.1(**CH**),108.4(**CH**),147.6(**C**),148.1(**C**),105.5(**CH**),131.3(**C**),133.5(**CH**),126.2(**C H**),137.1(**CH**),121.6(**CH**),57.78(**CH_2**) MS (m/z) 271 (M^+) 187, 157, 136, 110, 98, 84,55 Calculated for $C_{17}H_{21}NO_2.H_2O$ C 70.23, H 8.01, N 4.84% Found: C 69.79, H 7.72, N 4.47%

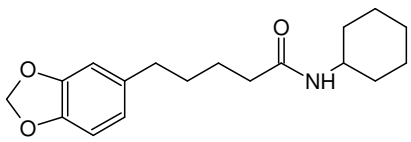
5-(3,4-Methylenedioxyphenyl)-pentanoyl-piperidine (RV-C02) (25)



Piperine **(5)** (2g, 7mmol) was hydrogenated in ethanol (50mL) over 5% Pd-C under a pressure of hydrogen at 10 PSI for 30min to give 5-(3,4-methylenedioxyphenyl)-pentanoyl piperidine (tetrahydropiperine) (1.59g, 78%) as an oil.

^{1}H-NMR ($CDCl_3$) δ: 2.55 (t, 4H, J=7.0 CH_2-CH_2- **CH_2-CH_2**), 2.32 (t, 4H, J=7.0 **CH_2-CH_2-** CH_2-CH_2) 6.66 (d,1H J=1.3, Ar-**H**), 6.70 (d,1H J=8.0, Ar-**H**), 6.61 (dd, 1H J=1.2, 8.0 Ar-**H**), 5.89 (s, 2H, **O-CH_2-O**), 3.53 (t, 2H, N- **CH_2** (piperidine)) 3.35 (t, 2H, N- **CH_2** (piperidine)) 1.63 (m, 2H, **CH_2-CH_2-**CH_2 (piperidine)) 1.54 (m, 2H, CH_2-CH_2-**CH_2**(piperidine)) ^{13}C-NMR ($CDCl_3$) : 24.5 (**CH_2**), 24.9 (**CH_2**), 25.5 (**CH_2**), 26.5 (**CH_2**), 31.4 (**CH_2**), 33.2 (**CH_2**), 35.4 (**CH_2**), 42.5(**CH_2**), 46.6(**CH_2**), 100.7 (**CH_2**), 108.0 (**CH**), 108.8 (**CH**), 109.0 (**CH**), 121.0 (**C**), 145.4 (**C**) 147.4 (**C**), 171.1 (**C**) MS m/z (%) : 289 (M^+ 71), 204 (31), 154 (23), 148 (22), 141 (23), 140 (38), 135 (28) 127 (100), 112 (23), 86 (12), 84 (24), 70 (10), 36 (11) Calculated for $C_{17}H_{23}NO_3$ C 70.54, H 8.01, N 4.84% Found: C 70.70, H 8.38, N 4.85%

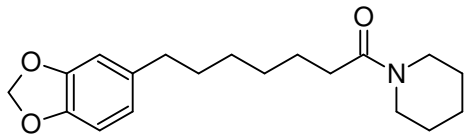
5-(3,4-methylenedioxy phenyl)-pentanoyl cyclohexylamine (RV-C04) (26)



5% Pd/C (30mg) was added to 5-(3,4-methylenedioxyphenyl)-penta-2*E*,4*E*-dienoyl cyclohexylamine **(8j)** (300mg) and hydrogenated the contents at 30 psi for 1h. The solution was filtered and rotary evaporated to yield a white solid. Recrystallisation from ethylacetate and petroleum spirit yielded pure white crystals (255mg, yield 84%). m.p. 145.4^0-146.3^0c

^{1}H-NMR ($CDCl_3$) δ: 6.65 (d,1H J=1.6, Ar-**H**), 6.71 (d,1H J=7.8, Ar-**H**), 6.60 (dd, 1H J=1.6, 8.0 Ar-**H**), 5.90 (s, 2H, **O-CH_2-O**), 5.43 (s, 1H, **NH**), 3.87 (m, 1H, **CH** (cyclohexyl amide)) 2.53 (t, 2H, J=7.7 (**CH_2**-CH_2-CH_2CH_2)) 2.14 (t, 2H, J=7.7 ((CH_2-CH_2-CH_2-**CH_2**)) 1.62-1.91 (m, 10H, CH_2-**CH_2.CH_2**-CH_2, **CH_2.CH_2.CH_2** (cyclohexyl amide) 1.07-1.30 (m, 4H, **CH_2**-CH-**CH_2** (cyclohexylamide)) ^{13}C-NMR ($CDCl_3$) : 25.3 ((**CH_2**) **$_2$**), 25.7 (**CH_2**),25.9 (**CH_2**), 31.3 (**CH_2**), 31.7 (**CH_2**), 33.6 (**CH_2**), 35.8 (**CH_2**), 37.3 (**CH_2**), 48.4 (**CH**), 101.1 (**CH_2**), 108.4 (**CH**), 109.2 (**CH**), 121.4 (**CH**), 136.4 (**C**), 145.8 (**C**), 147.8 (**C**), 172.2 (**C**) MS m/z (%) : 303 (M^+ 98), 204 (72), 176 (13), 168(16), 162 (12) 161 (14), 154 (27), 148 (66), 141 (61) 135 (100) 74 (24) 60 (60) Calculated for $C_{20}H_{17}NO_5$ C 71.24, H 8.31, N4.62% Found C 71.22, H 8.66, N 4.61%

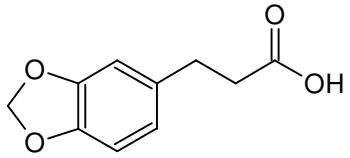
7-(3,4-methylenedioxy phenyl)-heptanoic acid piperidine amide (RV-C05) (27)



7-(3,4-Methylenedioxyphenyl)-hepta-2*E* 4*E*,6*E*-trienoyl piperidine (150mg) was dissolved in 30ml of ethanol. 5% Pd/C (15mg) was added and hydrogenated the contents at 30 psi. The solution was filtered and rotary evaporated to yield oil (83mg, 43.6%).

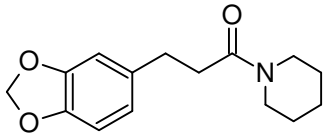
^{1}H-NMR ($CDCl_3$) δ: 6.66 (d,1H J=1.5, Ar-**H**), 6.71 (d,1H J=7.8, Ar-**H**), 6.60 (d, d, 1H J=1.6, 8.0 Ar-**H**), 5.90 (s, 2H, **O-CH_2-O**), 3.53 (t, 2H, J=5.4 CH_2-N-**CH_2**) 3.37 (t, 2H, J=5.7, (**CH_2**-N- CH_2) 2.51 (t, 2H, J=7.7 (**CH_2**-CH_2-CH_2-CH_2-CH_2-CH_2)) 2.33(t, 2H, J=7.7 ((CH_2-CH_2-CH_2-CH_2-CH_2-**CH_2**)) 1.52-1.65 (m, 10H, CH_2-CH_2-**CH_2.CH_2**-CH_2-CH_2, **CH_2-CH_2-CH_2** (Piperidine)) 1.34 (m, 4H, CH_2-**CH_2**-CH_2-CH_2-**CH_2**-CH_2) ^{13}C-NMR ($CDCl_3$) : 24.9 (**CH_2**), 25.8 (**CH_2**),25.9 (**CH_2**), 26.9 (**CH_2**), 29.3(**CH_2**), 29.7 (**CH_2**), 31.3 (**CH_2**), 31.9 (**CH_2**), 33.8 (**CH_2**), 42.9 (**CH_2**), 47.1 (**CH_2**), 101.8 (**CH_2**), 108.4 (**CH**), 109.2 (**CH**), 121.4 (**CH**), 137.0 (**C**), 145.7 (**C**), 147.8 (**C**), 171.8 (**C**), MS m/z (%) : 317 (M^+ 78), 232 (11), 204 (10), 183 (30), 182 (15), 154 (21) 148 (43), 141 (41), 127 (100), 112 (43), 85 (49)

3-(3,4-Methylenedioxyphenyl)-propionic acid (28)



3,4-methylenedioxycinnamic acid **(11)** (2g) was hydrogenated in ethanol (50mL) over 5% Pd-C under a pressure of hydrogen at 10 PSI for 40mins to give 3-(3,4-methylenedioxyphenyl)-propionic acid (1.67g, 80%yield) as a solid. m.p. 86.1^0-88.3^0C (Lit m.p. 87-88^0C)

3-(3,4-Methylenedioxyphenyl)-propionoyl piperidine (RV-C03)(29)



The method was adapted from that reported for piperlonguminine (section 2.2.1.1; method I) but using 3-(3,4-methylenedioxyphenyl)-propionic acid and piperidine as the acid and amine components respectively. A mixture of 3-(3,4-methylenedioxyphenyl)-propionic acid (200mg, 0.0026mole, 1eq) and triethylamine (0.27mL, 0.002mole, 2eq) in dichloromethane (50ml) was stirred for 15min at 0^0C. To this mixture methane sulfonyl chloride (0.11mL, 0.0015mole, 1.5eq) was added and stirred for further 30 min at 0^0C. Piperidine (0.15mL, 0.0015mole, 1.5eq) was added to the mixture and stirred for 1h at 0^0C and 1h at room temperature. Dichloromethane (50mL) was added to the mixture which was then washed with 5% HCl (3x100mL), saturated aqueous $NaHCO_3$ (3x100mL) and water (3x100mL). The organic fraction was dried over anhydrous sodium sulphate, filtered and the filtrate was rotary evaporated to yield brown oil (203mg, 65% yield).

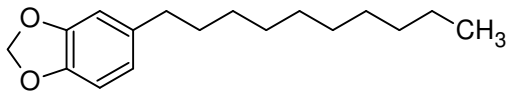
^{1}H-NMR ($CDCl_3$) δ: 2.87 (t, 2H, J=7.3 **CH_2**), 2.57 (t, 2H, J=7.0 CH_2-**CH_2**) 6.70 (d,1H J=1.5, Ar-**7H**), 6.72 (d,1H J=8.0, Ar-**10H**), 6.66 (dd, 1H J=1.2, 8.0 Ar-**11H**), 5.90 (s, 2H, **O-CH_2-O**), 3.55 (t, 2H, N- **CH_2** (piperidine)) 3.34 (t, 2H, N- **CH_2** (piperidine)) 1.62 (m, 2H, **CH_2-CH_2-**CH_2 (piperidine)) 1.49 (m, 2H, CH_2-CH_2-**CH_2**(piperidine)) ^{13}C-NMR ($CDCl_3$) : 25.7 (**CH_2**), 25.9 (**CH_2**), 26.6 (**CH_2**), 31.7 (**CH_2**), 35.8 (**CH_2**), 43.1(**CH_2**), 47.1(**CH_2**), 101.2 (**CH_2**), 109.2 (**CH**), 109.3 (**CH**), 121.5 (**CH**), 135.6 (**C**), 146.2 (**C**) 148.0 (**C**), 170.8 (**C**)

2.3.9 SYNTHESIS OF 3,4-METHYLENEDIOXYPHENYL DECANE

Piperinyl alcohol **(30)** (2g, 0.013mole, 1eq) and triphenylphosphine hydrobromide **(31)** (4.96g, 0.014mole, 1.1eq) were refluxed in anhydrous THF at 160^0C for 2hr.After cooling the reaction mixture the salt was filtered (3g). The salt was recrystallised from chloroform to give white crystals of 3,4-mehtylenedioxytriphenylphosphine bromine salt **(32)** (2g). The brominium salt (1.5g, 0.003mole, 1eq) and nonaldehyde (0.5mL, 0.003mole, 1eq) was stirred in 5ml of DMSO under nitrogen atmosphere at 0^0C for 15 min and tert-But-OK (0.41mL, 0.33mole, 1.1eq) was added. The reaction mixture was stirred at 0^0C for further 30 min. The mixture was poured into 100mL of water and extracted with ethylacetate (3x50mL). The organic layer was dried over anhydrous sodium sulphate, filtered and rotary evaporated to yield oil. The oil was further purified by silica gel column chromatography using hexane:dicholoromethane (9:1) as an eluant to yield oil **(33)** (400mg, 52.1%)

The compound **(33)** (100mg, 0.0038mmole, 1eq) was dissolved in ethanol and 5% Pd/C (10mg) was added and hydrogenated under hydrogen at 30 PSI for 30mins to yield 3,4-methylenedioxy decane **(34)** (75mg, 75% yield).

3,4-Methylenedixoyphenyl decane (RV-I02) (34)



^{1}H-NMR ($CDCl_3$) δ: 6.71 (d,1H J=7.8, Ar-**12-H**), 6.64 (d, d, 1H J=1.5, 7.8Ar-**16-H**), 6.60 (d,1H J=1.3, Ar-**15-H**), 5.90 (s, 2H, **O-CH_2-O**), 5.43 (s, 1H, **NH**), 2.54 (t, 2H, J=7.3 (**CH_2 aliphatic chain-10**) 1.55 (t, 2H, J=7.3 (**CH_2 aliphatic chain-9**) 1.14-1.54 (m, 14H, **aliphatic chain**) 0.83 (t, 3H, **CH_3**) ^{13}C-NMR ($CDCl_3$) : 14.14 (**CH_3**), 22.7 (**CH_2**), 29.2 (**CH_2**), 29.3 (**CH_2**), 29.5 (**CH_2**), 29.6 (**CH_2**), 29.7 (**CH_2**), 31.8 (**CH_2**), 31.9 (**CH_2**), 35.7 (**CH_2**), 100.6 (**CH_2**), 108.8 (**CH**), 108.6 (**CH**), 121.0 (**CH**), 136.8 (**C**), 145.3 (**C**) 147.2 (**C**)

MS m/z (%) : 262 (M^+ 70), 261 (45), 250 (32), 135 (100), 123 (65)

UV max 286, Calculated for $C_{17}H_{26}O_2$ C 78.77, H 9.55% Found: C 78.65, H 9.82%