The present invention relates to novel intermediate compounds of formula (Ia) and its salts thereof, wherein R is an amino protecting group, R1 is selected from the group consisting of hydrogen, an alkyl, aralkyl, hydroxyethyl, carboxymethyl, acetyloxymethyl, trialkylsilyl or an N-substituted alkyl amine where nitrogen forms the linking atom. The invention also relates to the use of these novel intermediate compounds of formula (Ia) for the preparation of camptothecan analogues and its salts, more particularly the anti-cancer drug irinotecan and its pharmacetically accepted salts.
NOVEL INTERMEDIATES FOR THE PREPARATION OF CAMPTOTHECIN ANALOGUES

Field of the invention:

The present invention relates to a process for the preparation of camptothecin analogues useful as anti-cancer drugs, in particular camptothecin analogue irinotecan and its salts thereof. More particularly, the invention relates to novel intermediate compound of formula (Ia) and its use in the process for the preparation of camptothecin analogues and its salts thereof.

Background of the invention:

US Patent No. 6,121,451 reveals a process for preparing antineoplastic drug 7-ethyl-10-hydroxy camptothecin 10-[1',4'-carboxylate] or CPT-II (V) free base. In the described process a compound therein identified as 14CPT (I) is first reacted with compound of formula (II) to form an intermediate of formula (III), which is further reacted with 4-piperidino piperidine carbomyl chloride of formula (IV) to produce CPT-II free base (V) as shown below.
WO 03/089413 reveals the novel compound of formula (VI).

![Formula (VI)](image)

and its use in the preparation of camptothecin analogues and particularly irinotecan free base and its pharmaceutically acceptable salts.

Alternative materials and methods for preparing irinotecan and camptothecin analogues are described in the prior art. The prior art processes reported for the preparation of irinotecan and its salts involves chromatographic purification step at one or the other stage of the process. However, in the process of present invention for the preparation of irinotecan and its salt the tedious step of chromatographic purification has been totally eliminated. Thus the process of present invention is economical and easily viable for the commercial scale preparation of the anticancer drug. This provides an added advantage to the process of present invention over the prior art processes.

**Objects of the invention:**

An object of the invention is to provide novel intermediate compounds of formula (Ia)

Another object of the invention is to provide process for the preparation of compounds of formula (Ia)

Yet another object of the invention is to use novel intermediate compounds of formula (Ia) for the preparation of Camptothecin analogues and its salts thereof.

Still another object of the invention is to provide a process using novel intermediate compound of formula (Ia, Ri= C$_2$Hs) for the preparation of anti cancer drug irinotecan and its pharmaceutically acceptable salts thereof.

Still yet another object of the invention is to provide a process for the preparation of Camptothecin analogues without involving chromatography purification at any stage of the process, more particularly for the preparation of irinotecan and its salts thereof.

An objective of the invention is to provide an easy and economically viable process for the commercial scale preparation of irinotecan and its pharmaceutically acceptable salts.
Summary of the invention:
The present invention provides novel intermediate compounds of formula (Ia) and its salts thereof.

Wherein R is amino protecting group defined as -CO (CH₂)n CH₃ (n = 0 to 4); -CO (CH₂)n CH₂X (X = Halogen; n = 0 to 4); -COCX₃ (X = Halogen) and R₁ is hydrogen, alkyl, araalkyl, hydroxy methyl, carboxymethyl, acyloxy methyl or N-substituted alkyl amine -CH₂-N-R₂ where N is a linking nitrogen atom, wherein R₂ and R₃ substituents on the N-atom may be defined as follows.

i) R₂ and R₃ are each independently selected from hydrogen, alkyl, alkenyl, hydroxyalkyl, acyloxyalkyl or acyloxy alkyl substituted group.

ii) R₂ and R₃ together with the nitrogen linking atom can form heterocyclic unit

The novel intermediate compounds of the invention are useful in the preparation of anti-cancer camptothecin analogues and in particular irinotecan and their pharmaceutically acceptable salts thereof.

The compounds of the invention are useful in the preparation of camptothecin analogues of formula (VII)

Wherein R₁ is as defined above.
Detailed description of the Invention:

An embodiment of the invention provides intermediate compounds of formula (Ia), its salt and its use in the preparation of camptothecin analogues of formula (VII).

In a preferred embodiment Rj is an ethyl group. Accordingly this embodiment provides a novel intermediate compound of formula (Ia, Ri = C₂H₅) which is useful in the preparation of Irinotecan (formula VII, Rj = C₂H₅) and its salts thereof.

In an another embodiment of the invention provides a process comprising step of contacting compounds of (formula Ia) with the compound of formula (I) above to yield Camptothecin analogues.

In yet another embodiment of the invention provides a process for the preparation of compound of formula (Ia). Wherein Rj is an ethyl group i.e. 4-amino protected-3-propionyl phenyl-1,4'-bipiperidine-1'-carboxylate comprising a step of contacting compound of formula (Ha) with 4-piperidino piperidine carbamyl chloride of formula (IV) or its hydrochloride salt under suitable reaction condition. A person skilled in the art by appropriate modifications of compound of formula (Ha) may derive other compounds of formula (Ia).

The present invention provides compounds of formula (Ia), wherein R, Ri, R₂, and R₃ are as defined above. Also, provided in the present invention salts of formula (Ia).

The compounds of formula (Ia) can exist as free base and also as their salts. The salts are acid addition salt prepared by contacting free base of compound of formula (Ia) with an acid selected from the group consisting of hydrochloric, hydrobromic, benzoic, tartaric, citric, fumaric, maleic and alkyl monocarboxylic and alkyl dicarboxylic acid having C₁-C₄ alkyl chain

In a typical example compound of formula (Ia) wherein R is an amino protecting group, Rj being ethyl or its salt thereof is contacted with ¹⁴CPT (I) to yield Irinotecan base, which is subsequently converted into its salt by adopting conventional methods.
can be carried out by heating a mixture of compound of formula (Ia) and 14CPT (I) in a suitable solvent (s), for example an acid or mixture of protic solvent and / or acid.

In an embodiment of the invention, the drug substance Irinotecan may comprise of most preferably not more than 0.1% compound of formula (Ia), which provides an evidence for the preparation of irinotecan by

a) process involving compound of formula (Ia) as reactant, or
b) a process involving compounds (Ha) and (IV) as reactants under suitable reaction conditions enabling these compounds to react to form compound of formula (Ia).

A drug substance comprising therapeutically effective amount of irinotecan and/ or its salt thereof and a compound of formula (Ia) and /or its atleast one salt thereof in a detectable amount.

The drug substance comprising therapeutically effective amount of irinotecan and/ or its salt thereof and a compound of formula (Ia) and /or its atleast one salt thereof is present in an amount not more than 1%.

The drug substance comprising therapeutically effective amount of irinotecan and/ or its salt thereof and a compound of formula (Ia) and /or its atleast one salt thereof is present in an amount not more than 0.5%.

The drug substance comprising therapeutically effective amount of irinotecan and/ or its salt thereof and a compound of formula (Ia) and /or its atleast one salt thereof is present in an amount not more than 0.1%.

A drug substance comprising therapeutically effective amount of irinotecan and/ or its salt thereof and 7-ethyl-10-hydroxy-camptothecin and /or its at lease one salt thereof in a detectable amount.

The drug substance comprising therapeutically effective amount of irinotecan and/ or its salt thereof and 7-ethyl-lO-hydroxy-camptothecin and /or its at least one salt thereof is present in an amount, not more than 1%.

The drug substance comprising therapeutically effective amount of irinotecan and/ or its salt thereof, and 7-ethyl-lO-hydroxy-camptothecin and /or its at least one salt thereof is present in an amount, not more than 0.5%.

The drug substance comprising therapeutically effective amount of irinotecan and/ or its salt thereof and 7-ethyl-lO-hydroxy-camptothecin and /or its at least one salt thereof is present in an amount, not more than 0.1%.

A drug substance comprising therapeutically effective amount of irinotecan and /or its salt thereof and a compound of formula (Ia) and /or its at least one salt thereof and 7-ethyl-10-
hydroxy-camptothecin and /or its atleast one salt thereof each present in an amount not more than 1%.

A drug substance comprising therapeutically effective amount of irinotecan and /or its salt thereof and a compound of formula (Ia) and /or its atleast one salt thereof and 7-ethyl-10-hydroxy-camptothecin and /or its atleast one salt thereof each present in an amount not more than 0.5%.

A drug substance comprising therapeutically effective amount of irinotecan and /or its salt thereof and a compound of formula (Ia) and /or its atleast one salt thereof and 7-ethyl-10-hydroxy-camptothecin and /or its atleast one salt thereof each present in an amount not more than 0.1%.

The schematic representation of the process of present invention is depicted herein below:
The invention is illustrated with the following examples and should not be construed to limit the scope of the present invention. The features of the present invention will become more apparent from the following description of the inventive concept and the description of the preferred embodiments and appended claims.

Example I

**Step I: Preparation of 2-Acetimido-5-hydroxy-propiophenone (Ia; R= -C0CH3, R1=C2H5)**

Charge acetic anhydride (30ml) into a reactor, add 2-Amino-5-hydroxy-propiophenone (AHP) (10g) to it. The mixture is heated to 130°C and maintained at this temperature for 2-3 hr. Monitor the reaction mixture by HPLC for the disappearance of AHP. Work up the reaction mixture by pouring on to crushed ice water (300ml) with stirring and continued stirring between 0°C-5°C for at least an hour. Filter the precipitated solid, wash with water (100ml) to yield step 1 product (11g); HPLC purity not less than 99.00%.

**Step II: Preparation of ^acetimidoS-propionylphenyl-l^'-bipiperidine-l'-carboxylate (Ia; R=-C0CH3 and R1=C2H5)**

Dissolve Step-I product (10g) in dry pyridine (160ml). Add 4-Dimethylamino pyridine (23.3g), followed by 4-piperidino piperidine carbomylchloride (25.3g) to it. Stirred the mixture at room temperature for 48h-60h. Monitor the reaction mixture by HPLC. Work up the reaction mixture when step-I product is NMT 3.0% by adding water (60ml). Extract with ethylacetate (200ml). Separate layers, evaporate ethyl acetate layer to dryness. Dissolve the residue in chloroform (215ml), washed with 10% aqueous sodium bicarbonate solution (6x215ml), followed by water (6x215ml). Dry the washed chloroform over anhydrous sodium sulphate, filter and evaporate to dryness to yield step-II product (11.5g), HPLC purity not less than 95.00%.

**Step III: Preparation of Irinotecan base (VII, Rf=C2H5)**

Dissolve Step-II product (1.5) in ethyl alcohol (115ml), added conc. HCl (25.4ml), glacial acetic acid (115ml), 14CPT (10.62g) and heat the mixture to 110°C-115°C for a period of 24 hrs. Evaporate the reaction mixture to dryness, add water (345ml) and stir for 10-15 mih and filter the aqueous solution through celite bed. The filtered aqueous solution is extracted with chloroform (4x85ml). Separated organic and aqueous layer. Aqueous layer is evaporated to dryness under vacuum. Add ethyl alcohol (80ml) to dissolve the residue, add activated charcoal (1.15g) and heat to 70°C with string for an hour. Filter the hot solution and cool to room temperature with stirring and then to 0°C for an overnight. The precipitated pale yellow
solid is filtered to obtain is step- III product (10.4g) having HPLC purity of not less than 98.00%.

Step IV: Preparation of Irinotecan Hydrochloride Trihydrate
Take Step- III (10.4g) product in DM H₂O (93.6ml) and add cone. HCl (19.80ml). Heat the mixture to 60° when a pale yellow solution is obtained. Add activated charcoal (1.04g) and continue to maintain the mixture at this temperature for further 30 min and filter. Cool the filtered solution to room temperature and then to 0°C with stirring for an overnight. Filter the separated solid, dry the solid under high vacuum to yield irinotecan hydrochloride trihydrate (6.13g); HPLC purity 99.65%

Example II
Step I: Preparation of 2-propionimido-5-hydroxy-propiophenone (Ia; R= COCH₂ CH₃, RrC₂H₃)
Charge chloroacetic anhydride (27ml) into a reactor, add 2- Amino-5-hydroxy -propiophenone [AHP] (9g) to it. The mixture is heated to 130°C and maintained at this temperature for 2-3 hr. Monitor the reaction mixture by HPLC for the disappearance of AHP. Work up the reaction mixture by pouring on to crushed ice water (270ml) with stirring and continued stirring between 0°-5°C for at least an hour. Filter the precipitated solid, wash with water (100ml), dried and crystallised to yield step - I product (13.5g); HPLC purity not less than 98.00%.

Step II: Preparation of 4- propionimido -3-propionylphenyl-1,4'-bipiperiditie-l'-carboxylate (Ia; R = COCH₂CH₃ and R'; C₂H₅)
Dissolve Step- I product (12g) in dry pyridine (192ml). Add 4-Dimethylamino pyridine (24), followed by 4, piperidino piperidine carbonyl chloride (26.4g) to it. Stirred the mixture at room temperature for 48h-60h. Monitor the reaction mixture by HPLC. Work up the reaction mixture when step- I product is NMT 3.0% by adding water (72ml). Extract with ethylacetate (240ml). Separate layers, evaporate ethyl acetate layer to dryness. Dissolve the residue in chloroform 260ml), washed with 10% aqueous sodium bicarbonate solution (6x 260ml), followed by water (6x 260ml). Dry the washed chloroform over anhydrous sodium sulphate, filter and evaporate to dryness to yield step- II product (11.5g), HPLC purity not less than 94.00%.

Step III: Preparation of Irinotecan base (VII, R₁ = C₂H₅)
Dissolve Step- II product (11.5) in ethyl alcohol (115ml) , added con. HCl (25.4ml) , glacial acetic acid (115ml), 14CPT (10.62g) and heat the mixture to 110°- 115°C for a period of 24
Evaporate the reaction mixture to dryness, add water (345ml) and stir for 10-15 min and filter the aqueous solution through celite bed. The filtered aqueous solution is extracted with chloroform (4x85ml). Separated organic and aqueous layer. Aqueous layer is evaporated to dryness under vacuum. Add ethyl alcohol (80ml) to dissolve the residue, add activated charcoal (1.15g) and heat to 70°C with string for an hour. Filter the hot solution and cool to room temperature with stirring and then to 0°C for an overnight. The precipitated pale yellow solid is filtered to obtain is step- III product(10.0 g) having HPLC purity of not less than 98.00%.

**Step IV: Preparation of irinotecan Hydrochloride Trihydrate:**
Take Step- III (10.0g) product in DM H₂O (90.0ml) and add cone. HCl (19.00ml). Heat the mixture to 60°C when a pale yellow solution is obtained. Add activated charcoal (1.0Og) and continue to maintain the mixture at this temperature for further 30 min and filter. Cool the filtered solution to room temperature and then to 0°C with stirring for an overnight. Filter the separated solid, dry the solid under high vacuum to yield irinotecan hydrochloride trihydrate (5.9g); HPLC purity 99.60%

**Example H1**

**Step I: Preparation of 2-chloroacetimido-5-hydroxy-propiophenone (Ia; R= COCH₂Cl , R₁=C₂H₅**
Charge chloro acetic anhydride (30ml) into a reactor, add 2- Amino-5-hydroxy -propiophenone [AHP](1Og) to it. The mixture is heated to 130°C and maintained at this temperature for 2-3 hr. Monitor the reaction mixture by HPLC for the disappearance of AHP. Work up the reaction mixture by pouring on to crushed ice water (300ml) with stirring and continued stirring between 0°C-5°C for at least an hour. Filter the precipitated solid, wash with water (100ml), dried and crystallised to yield step - I product (Hg); HPLC purity not less than 98.50%.

**Step II: Preparation of 4-chloroacetimido-3-propionylphenyl-1,4’-bipiperidine-1’- carboxylate (Ia; R=COCH₂Cl and R₁=C₂H₅)**
Step- I product (1Og) in dry pyridine (160ml). Add 4-Dimethylamino pyridine (18.3g), followed by 4-piperidino piperidine carbomylchloride (2O.0g) to it. Stirred the mixture at room temperature for 48h-60h. Monitor the reaction mixture by HPLC. Work up the reaction mixture when step- I product is NMT 3.0% by adding water (60ml). Extract with ethylacetate (200ml) . Separate layers, evaporate ethyl acetate layer to dryness. Dissolve the residue in chloroform 215ml), washed with 10% aqueous sodium bicarbonate solution (6x 215ml),
followed by water (6x 215ml). Dry the washed chloroform over anhydrous sodium sulphate, filter and evaporate to dryness to yield step-II product (11.0g), HPLC purity not less than 95.00%.

**Step III: Preparation of Irinotecan base (VII, $R = C_2H_4$)**

Dissolve Step-II product (1.0g) in ethyl alcohol (110ml), added conc. HCl (24.2ml), glacial acetic acid (110ml), 14CPT (10.0g) and heat the mixture to 110°-115°C for a period of 24 hrs. Evaporate the reaction mixture to dryness, add water (345ml) and stir for 10-15 min and filter the aqueous solution through celite bed. The filtered aqueous solution is extracted with chloroform (4x85ml). Separated organic and aqueous layer. Aqueous layer is evaporated to dryness under vacuum. Add ethyl alcohol (80ml) to dissolve the residue, add activated charcoal (1.15g) and heat to 70°C with string for an hour. Filter the hot solution and cool to room temperature with stirring and then to 0°C for an overnight. The precipitated pale yellow solid is filtered to obtain is step-III product (1.0g) having HPLC purity of not less than 98.00%.

**Step IV: Preparation of Irinotecan Hydrochloride Trihydrate**

Take Step-III (10.0 g) product in DM H$_2$O (90.0ml) and add cone. HCl (19.0ml). Heat the mixture to 60° when a pale yellow solution is obtained. Add activated charcoal (1.04g) and continue to maintain the mixture at this temperature for further 30 min and filter. Cool the filtered solution to room temperature and then to 0°C with stirring for an overnight. Filter the separated solid, dry the solid under high vacuum to yield irinotecan hydrochloride trihydrate (6.03g); HPLC purity 99.62%
We* Claim:
1. A compound of formula (Ia) and its salts thereof.

   \[
   \text{Formula (Ia) } \quad R
   \]

Wherein R is amino protecting group defined as -CO (CH\(_n\)) CH\(_3\) (n = 0 to 4); -CO (CH\(_2\)) \(_n\) CH\(_2\) X (X = Halogen; n = 0 to 4); -COCX\(_3\) (X = Halogen) and R1 is hydrogen, alkyl, aminokyl, hydroxy methyl, carboxymethyl, acyloxy methyl silyl or N-substituted alkyl amine -CH\(_2\)-N-R, where N is a linking nitrogen atom, wherein R\(_2\) and R\(_3\) substituents on the N-atom may be defined as follows.

i) R\(_2\) and R\(_3\) are each independently selected from hydrogen, alkyl, alkemyl, hydroxyalkyl, acyloxyalkyl or acycloxy alkyl substituted group.

ii) R\(_2\) and R\(_3\) together with the nitrogen linking atom can form heterocyclic unit

2. A compound of claim 1, wherein R is an ethyl group.

3. A compound of claim 1 that is an acid addition salt of compound of formula (Ia) with an acid selected from hydrochloric, hydrobromic, benzoic, tartaric, citric, fumaric, maleic, alkyl monocarboxylic acid and alkyl dicarboxylic acid having C\(_1\)-C\(_4\) alkyl chain.

4. A process for the preparation of camptothecin analogues or its salts thereof, the said process comprising first step of contacting compound of formula (Ia)

   \[
   \text{Formula (Ia) } \quad R
   \]

with compound of formula (I)
and a second step of preparing a salt of camptothecin analogues thus obtained.

5. A process of claim 4, wherein irinotecan or its salt thereof is prepared by contacting compound of formula (Ia, R1=C2H5) or its salt thereof with compound of formula (I).

6. A process for preparing compounds of formula (Ia) comprising step of contacting compound of of formula (Ha) with 4-piperidinopiperidine carbamyl chloride (IV).

7. A drug substance comprising therapeutically effective amount of irinotecan and/or its salt thereof and compound of formula (Ia) and/or its atleast one salt thereof in a detectable amount.

8. The drug substance of claim 7, wherein compound of formula (Ia) and/or its atleast one salt thereof present in an amount not more than about 1%.

9. The drug substance of claim 7, wherein compound of formula (Ia) and/or its atleast one salt thereof present in an amount not more than about 0.5%.

10. The drug substance of claim 7, wherein compound of formula (Ia) and/or its atleast one salt thereof present in an amount not more than about 0.1%.

11. A drug substance comprising therapeutically effective amount of irinotecan and/or its salt thereof and 7-ethyl-10-hydroxy-camptothecin and/or its atleast one salt thereof in a detectable amount.

12. The drug substance of claim 11, wherein 7-ethyl-1 O-hydroxy-camptothecin and/or its atleast one salt thereof present in an amount not more than about 1%.

13. The drug substance of claim 11, wherein 7-ethyl-1 O-hydroxy-camptothecin and/or its atleast one salt thereof present in an amount not more than about 0.5%.

14. The drug substance of claim 11, wherein 7-ethyl-1 O-hydroxy-camptothecin and/or its atleast one salt thereof present in an amount not more than about 0.1%.

15. A drug substance comprising therapeutically effective amount of irinotecan and/or its salt thereof and compound of formula (Ia) and/or its atleast one salt thereof and 7-ethyl-10-hydroxy-camptothecin and/or its atleast one salt thereof each present in a detectable amount.

16. The drug substance of claim 15, wherein compound of formula (Ia) and/or its atleast one salt thereof and 7-ethyl-1 O-hydroxy-camptothecin and/or its atleast one salt thereof each present in an amount not more than 1%.

17. The drug substance of claim 15, wherein compound of formula (Ia) and/or its atleast one salt thereof and 7-ethyl-1 O-hydroxy-camptothecin and/or its atleast one salt thereof each present in an amount not more than 0.5%.
18. The drug substance of claim 15 wherein compound of formula (Ia) and/or its at least one salt and/or 7-ethyl-10-hydroxy-camptothecin and/or its at least one salt thereof each present in an amount not more than 0.1%.

19. Compounds of claim 1, process for preparation and its use in the process of preparation of camptothecin analogues as herein substantially described with reference to the detailed description and examples.