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# Synthesis and Characterization of 2-methylindolizino[1,2-b]quinolin-9(11H)-one

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**Abstract:**
Camptothecin is a natural quinoline alkaloid, initially extracted from the bark of the Chinese tree *Camptotheca acuminata*, which acts as a powerful anti-cancer agent by inhibiting DNA topoisomerase I. Number of Camptothecin analogs synthesized by researchers to find potent anticancer drug. Camptothecin drug having Quinoline and 2-pyrodone moiety in their structure have biological activity and their derivatives are used in number of drugs. In present work a Tetracyclic (ABCD) ring core of camptothecin was synthesized by simple method using simple starting material like aniline derivatives and 2-pyridone in six steps. The intermediates were confirmed and characterized by FT-IR, LC-MS and $^1$HNMR.

**Keywords:** Camptothecin, Quinoline, 2-pyridone

## 1. Introduction:

Camptothecin, a pentacyclic alkaloid isolated from the Chinese tree *Camptotheca acuminata* by Wall and Wani in 1966 [1], is one of the outstanding lead compounds in anticancer drug development. It has also been isolated from *Ophiorrhiza pumila* and *Mapia foetida.* It is a member of the quinoline alkaloid group. It consists of a pentacyclic ring structure that includes a pyrrole quinoline moiety and one asymmetric centre within the α-hydroxy lactone ring with 20(S) configuration (ring E). It consists of four planar rings (ABCD) and one boat conformational ring (E) (Figure **1**).

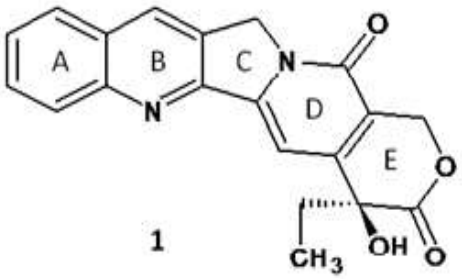


**Figure 1:** 20(S) - camptothecin

Camptothecin occurs in different plant parts like the roots, twigs and leaves. Camptothecin as such was not ideal for pharmaceutical development, mostly due to its toxicity, poor solubility and the unstable nature of the lactone ring, which opens rapidly to an inactive hydroxy acid at the physiological conditions.

Some members of this Camptothecin family [2], **2-8** are shown in Figure 2. They possess highly conjugated polycyclic quinoline core (11H-indolizino[1,2-b]quinoline-9-one, (Figure. 3)

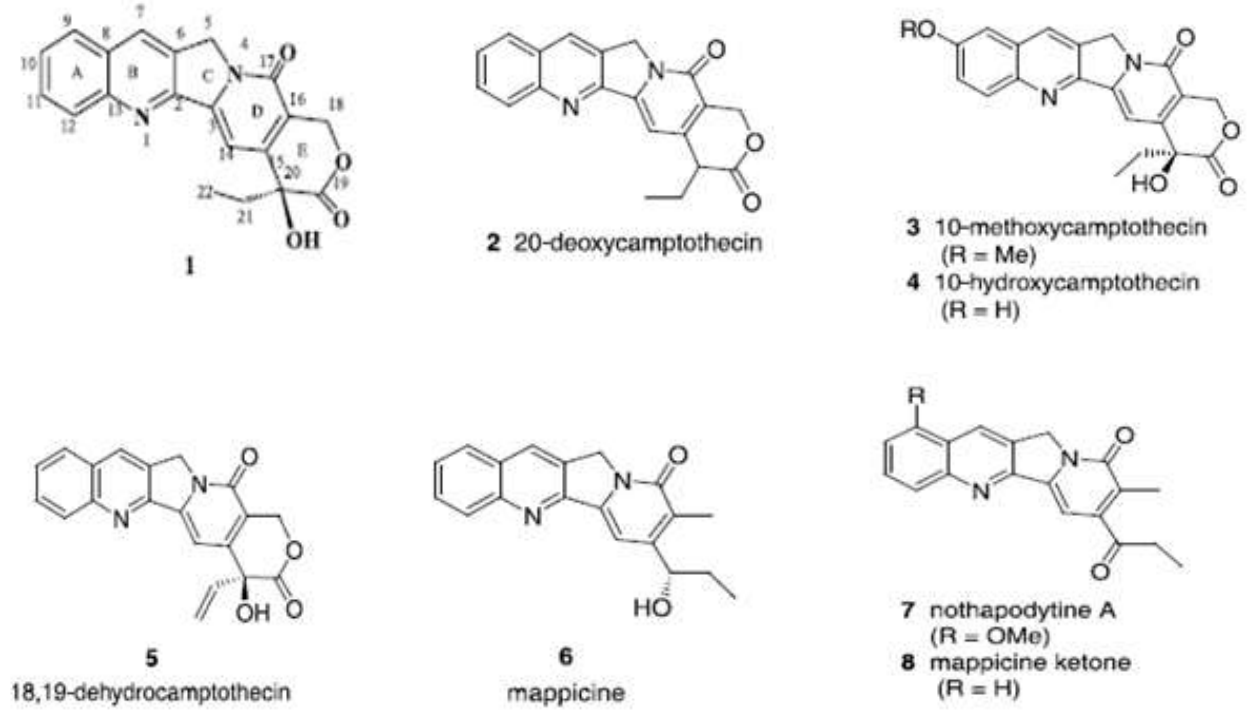


**Figure 2: Some natural products of camptothecin family.**

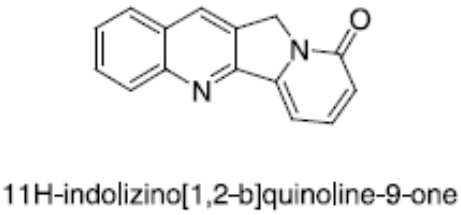


**Figure 3: The conjugated polycyclic quinoline core of camptothecins.**

Two successful camptothecin derivatives namely topotecan, **9** and irinotecan, **10** are in clinical practice and several other compounds in various stages of clinical trials, **11-14**.

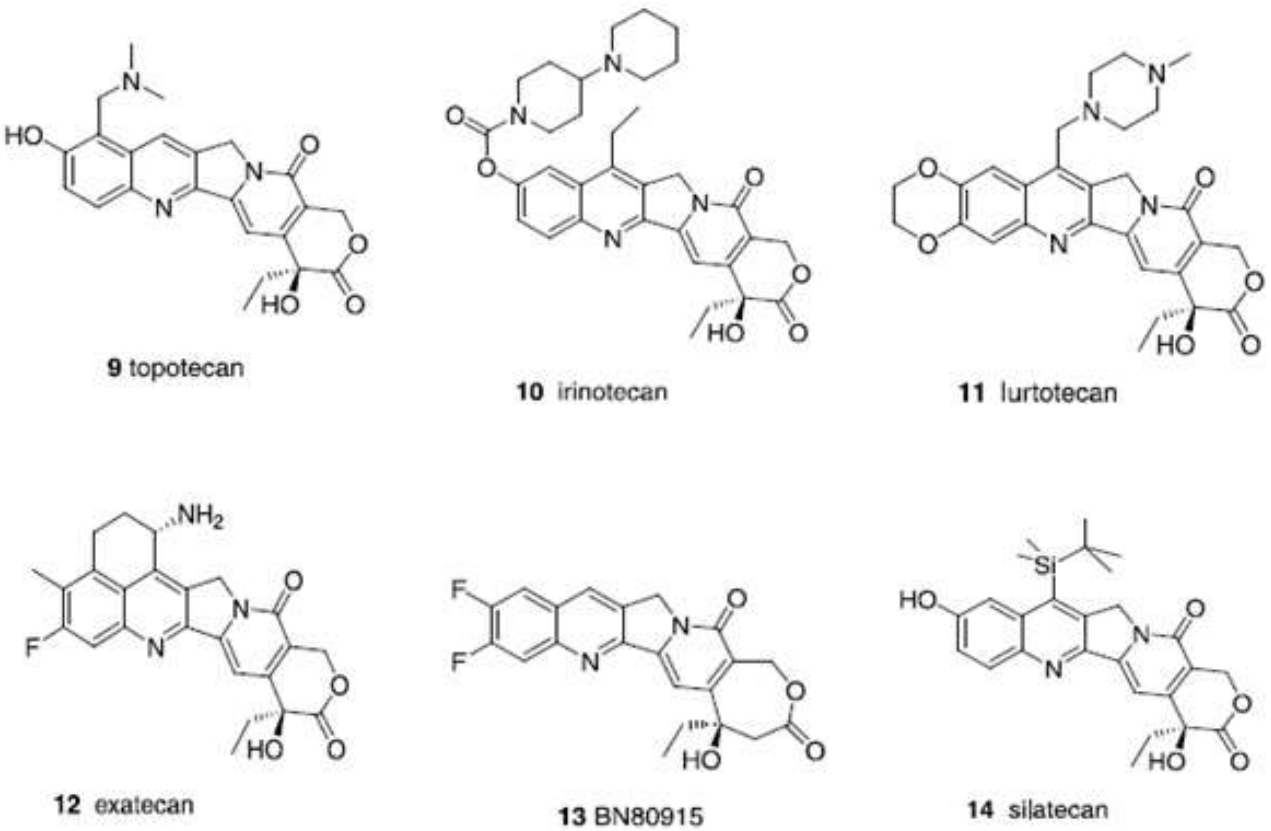


**Figure 4: Anticancer drugs and some drug candidates for camptothecin family.**

To date, a number of syntheses of camptothecin have been reported. Yadav *et al*, (1999) [3] established a convergent total synthesis of mappicine ketone which belongs to camptothecin family. Mappicine ketone has recently been identified as an antiviral agent with selective activities against HSV-1, HSV-2, and human cytomegalovirus.

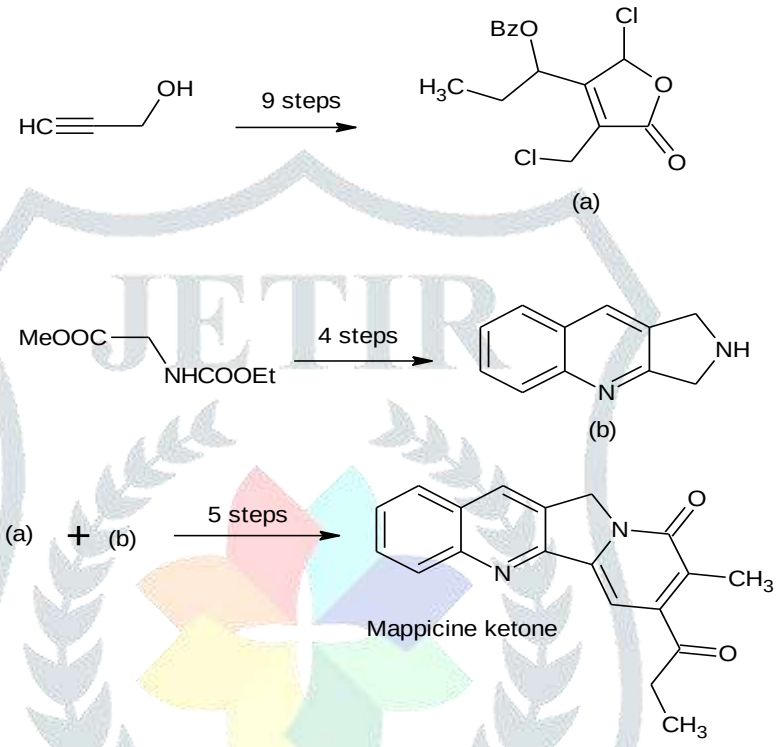


**Figure 5: Synthesis scheme given by Yadav *et al.***

Yu *et al*, (2004) [4] reported Synthesis of (±)-camptothecin using a [3+2] nitrone cycloaddition to construct the CDE ring moiety. Synthesis to camptothecin was achieved by Friedlander condensation of o-aminobenzaldehyde **(b)** with tricyclic ketone **(a)**.

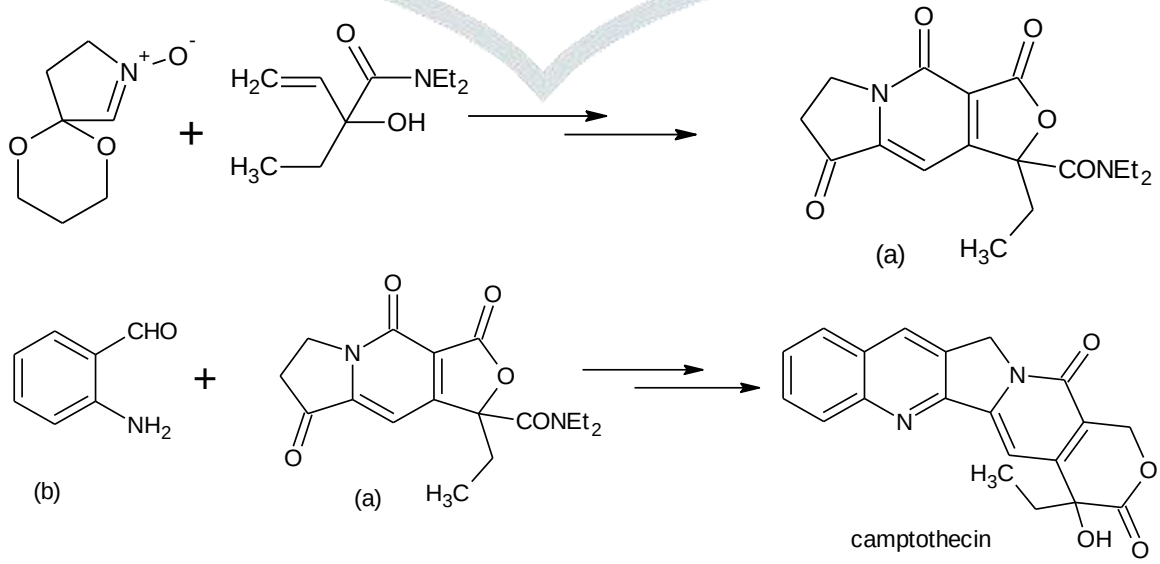


**Figure 6: Synthesis scheme given by Yu *et al.***

Chavan *et al*, (2004) [5] reported synthesis of camptothecin via ring-closing metathesis strategy.

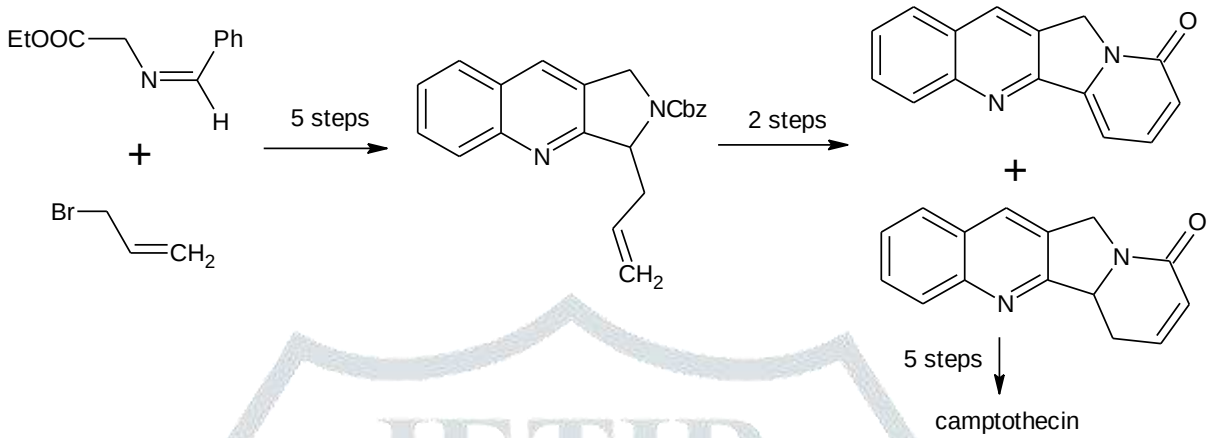


**Figure 7: Synthesis scheme given by Chavan *et al.***

In spite of continued interest on camptothecin and its analogues, though many syntheses have been achieved still there is an evident need for the development of a new synthetic route amenable to camptothecin and its analogues. Due to Camptothecin and their derivatives low availability, high demand, potential application in clinical field, our group has been interested in developing a simple and practical synthesis of camptothecin and its analogues. The major objective of the research is to synthesize quinoline ring cores (ABCD ring of Camptothecin) in few steps from simpler starting materials such as aniline. Other objectives include characterization of the synthesized compounds by FT-IR, $^{1}$HNMR, LC / MS spectral techniques.

**2. Material and Methods:**

**Retro synthesis of ABCD ring core:**

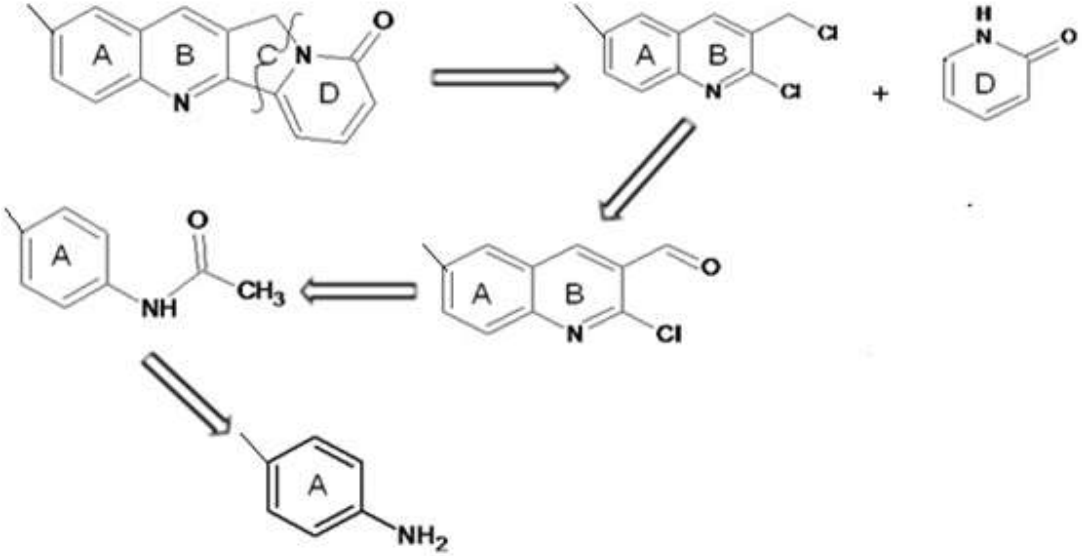


**Figure 8: Retro synthesis of ABCD ring core**

Tetracyclic aromatic ring core when disconnected from C ring, AB & D rings will be obtained. ABCD ring can be formed by coupling of AB & D ring. Whereas AB rings core can be synthesized from aniline derivatives in four steps.

**Synthesis of ABCD ring core:**

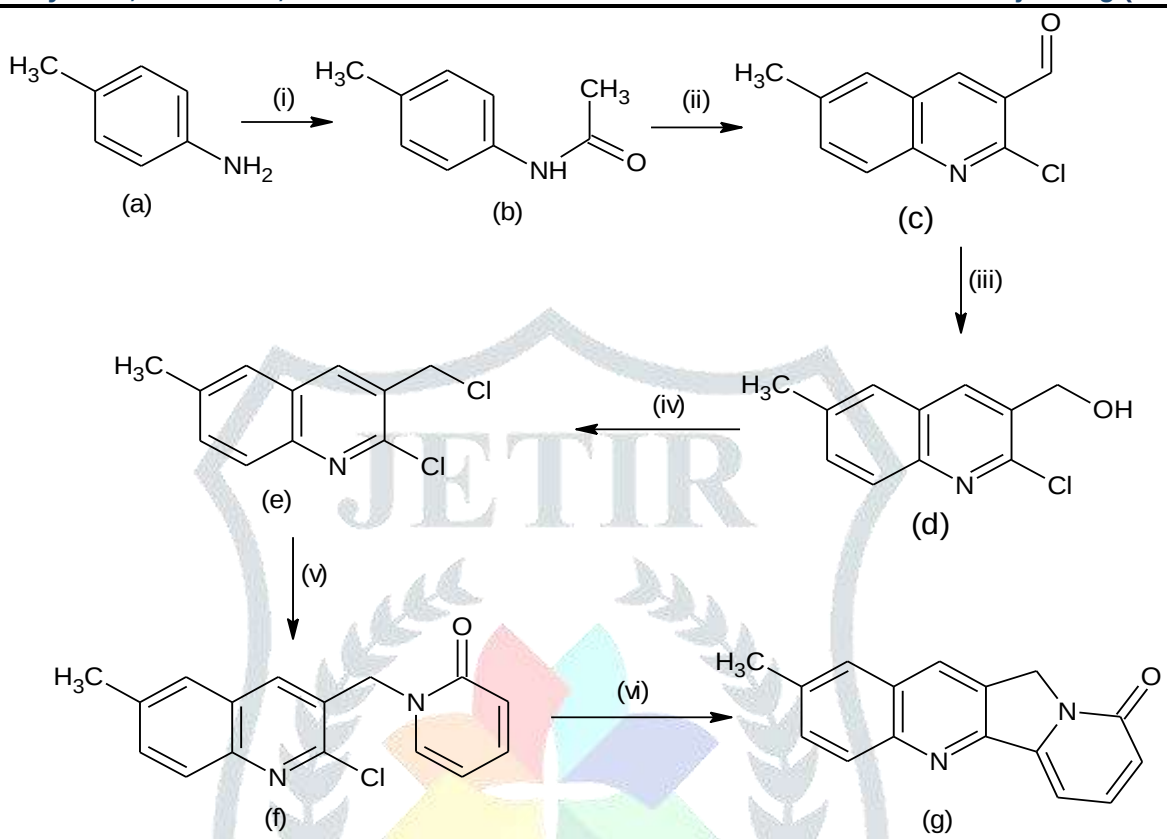


**Figure 9: Synthetic scheme**

***Reagents and Conditions:*** (i) Acetic anhydride, 70-80 °C, 2 hr, (ii) DMF, $POCl_3$, 80-90 °C, 6-16 hr (iii) $NaBH_4$, 0-25 °C, 1-2 hr (iv) $SOCl_2$, 80-90 °C, 1-2 hr (v) DMF, 2-pyridone, THF, tBuOK, $Bu_4NBr$, rt, 5-6hr (vi) DMF, $CH_3COOK$, $Bu_4NBr$, Pd(II), 5-6 hr, 90 °C.

Starting materials were obtained from commercial sources or prepared using known procedures. Melting points were measured by open capillary technique and were corrected with reference to benzoic acid, the temperature was expressed in degree Celsius. All solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80 ºC. In case where chromatographic purification was done unless mentioned silica gel (60-120 mesh size) was used as stationary phase. The reaction progress was monitored by the thin layer plates coated with silica gel (Himedia) and visualized by fluorescence quenching or iodine. The IR spectra were recorded on AVATAR 330-FT-IR and IR absorbance is expressed in $cm^{-1}$. The $^1H$ NMR spectra were recorded on Bruker AVANCE III 500 MHz (AV 500) multi nuclei solution NMR. $^1H$ NMR spectra are reported in ppm. All the new experiments were repeated two or more times.

## 3. Results and Discussion:

### 3.1. Synthesis of N-(4-methylphenyl)acetamide:

To 4-methylaniline (a) (0.1M) at 0-5 °C with stirring acetic anhydride (0.1M) was added drop wise. After that 1 ml glacial acetic acid added and solution was kept for reflux for 2hr. at 70-80 °C. The completion of reaction was monitored by TLC using 3:17 ratios of ethylacetate and petroleum ether as eluent. The mixture was poured into crushed ice, stirred for five min and the resulting solid filtered, washed well with water and dried. Yield: 67%, Melting point: 148-150 °C.

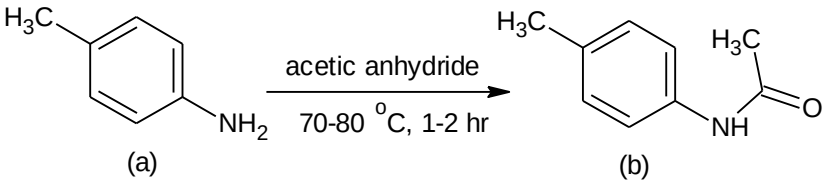


**Figure 10: Scheme for Synthesis of N-(4-methylphenyl)acetamide**

### 3.2. Synthesis of 2-chloro-6-methylquinoline-3-carbaldehyde [6]:

To dry DMF (0.15M) maintained at 0-5 °C with stirring $POCl_3$ (0.35M) was added drop wise and mixture was stirred for 30 min. Compound N-(4-methylphenyl)acetamide (b) (0.05M) was added to this mixture and refluxed for 6-16 hr at 80-90 °C. The completion of reaction was monitored by TLC using 3:17 ratios of ethylacetate and petroleum ether as eluent. The mixture was poured into crushed ice, stirred for five min and the resulting solid filtered, washed well with water and dried. The compound was purified by column chromatography. Yield: 66%, Melting point: 123-125 °C, FT-IR (KBr): ν 2876 (C-H), 1691 (C=O), 1623 (N=C), 1579 (C=C), 822 (C-Cl) $cm^{-1}$.

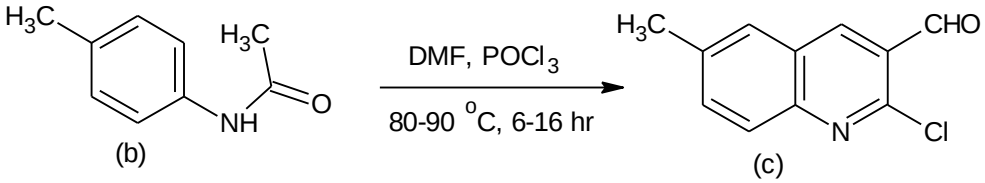


**Figure 11: Scheme for Synthesis of 2-chloro-6-methylquinoline-3-carbaldehyde**

**3.3. Synthesis of (2-chloro-6-methylquinolin-3-yl)methanol:**

To a solution of compound 2-chloro-6-methylquinoline-3-carbaldehyde (c) (3.0mM) in methanol maintained at 0 °C with stirring solution of $NaBH_4$ (2.5mM) in methanol was added dropwise and stirred for 1 hr. The completion of reaction was monitored by TLC using 1:4 ratios of ethylacetate and petroleum ether as eluent. The mixture was poured into crushed ice, stirred for five min and the resulting solid filtered, washed well with water and dried. Yield: 96%, Melting point: 140-142 °C, FT-IR (KBr) ν: 3293 (O-H), 2915 (C-H), 1598 (N=C), 1566 (C=C), 819 (C-Cl) $cm^{-1}$, Mass spectra (positive mode): m/z 208 ($M^{+\cdot}$+1), 209 ($M^{+\cdot}$+2).

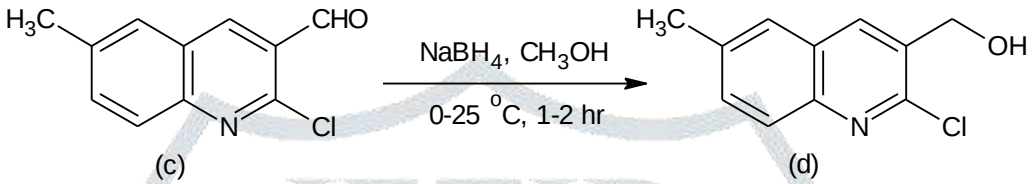


**Figure 12: Scheme for Synthesis of (2-chloro-6-methylquinolin-3-yl)methanol**

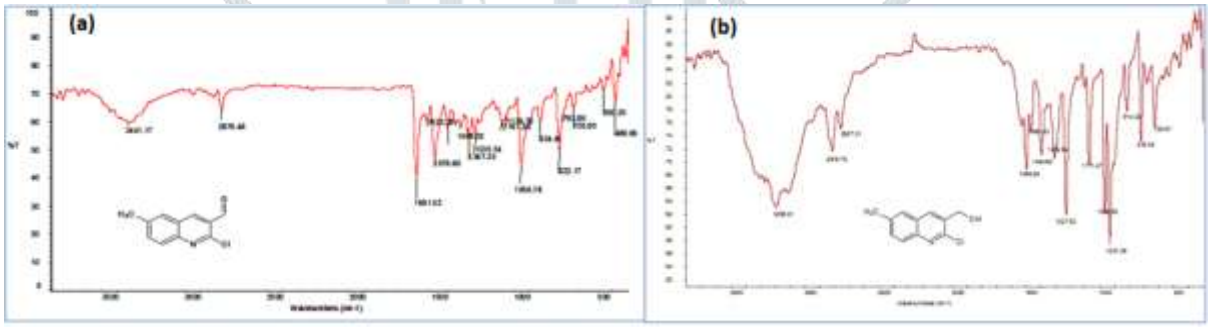


**Figure 13: (a) FT-IR spectra of 2-chloro-6-methylquinoline-3-carbaldehyde (b) FT-IR spectra of (2-chloro-6-methylquinolin-3-yl)methanol**

**3.4. Synthesis of 2-chloro-3-(chloromethyl)-6-methylquinoline:**

$SOCl_2$ (2.5mM) was added to compound (2-chloro-6-methylquinolin-3-yl)methanol (d) (2.5mM) and kept on reflux for 1-2 hr at 80-90 °C. The completion of reaction was monitored by TLC using 1:4 ratios of ethylacetate and petroleum ether as eluent. The mixture was poured into crushed ice, stirred for five min and the resulting solid filtered, washed well with water and dried. Yield: 95%, Melting point: 135-137 °C, FT-IR (KBr) ν: 2923 (C-H), 1597 (C=C) $cm^{-1}$, $^1H$ NMR: (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.9 (d, 1H), 7.58 (d, 2H), 4.82 (s, 2H, $CH_2$), 2.53 (s, 3H, $CH_3$), Mass spectra (positive mode): m/z 226 ($M^{+\cdot}$), 228 ($M^{+\cdot}$+2), 229 ($M^{+\cdot}$+3).

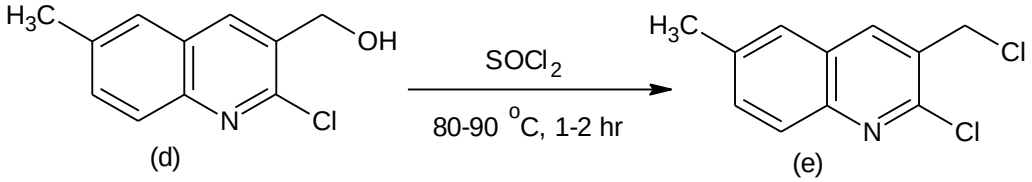


**Figure 14: Scheme for synthesis of 2-chloro-3-(chloromethyl)-6-methylquinoline**

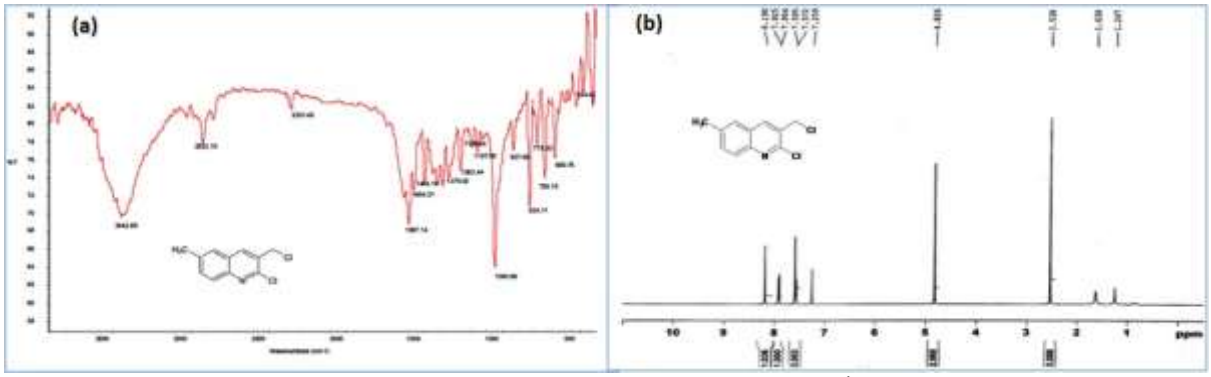


**Figure 15: (a) FT-IR spectra of 2-chloro-3-(chloromethyl)-6-methylquinoline (b) $^1H$ NMR, 2-chloro-3-(chloromethyl)-6-methylquinoline, ($CDCl_3$, 500MHz)**

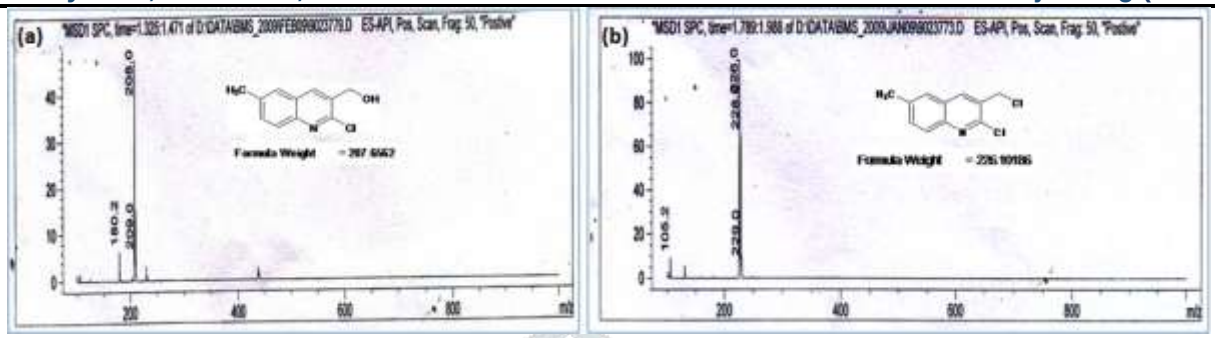

**Figure 16: (a) LC/MS report of (2-chloro-6-methylquinolin-3-yl)methanol (b) LC/MS report of 2-chloro-3-(chloromethyl)-6-methylquinoline**

**3.5. Synthesis of 1-[(2-chloro-6-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one[7]:**

t-BuOK (2.5mM) and n-$Bu_4NBr$ (0.1mM) were added to a cooled solution (0 °C) of 2-pyridone (2.0mM) in DMF (5 ml) and the resulting reaction mixture was stirred at 0 °C for 15 min. After that a solution of compound 2-chloro-3-(chloromethyl)-6-methylquinoline (e) (2.0mM) in THF was added and resulting reaction mixture was left stirring for 6-10 hr at room temperature. The completion of reaction was monitored by TLC using 2:3 ratios of ethylacetate and petroleum ether as eluent. The mixture was concentrated in vacuo, and ice water was added in concentrated mixture and extracted with ethylacetate. The compound was purified by column chromatography. Yield: 65%, Melting point: 163-165 °C, FT-IR (KBr) ν: 3029 (C-H), 2924 (C-H), 1662 (C=O), 1597 (N=C), 1537 (C=C) $cm^{-1}$, $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.88 (d, 1H), 7.55 (d, 2H), 7.46 (d, 1H), 7.38 (t, 1H), 6.65 (d, 1H), 6.22 (t, 1H), 5.36 (s, 2H, $CH_2$), 2.50 (s, 3H, $CH_3$).

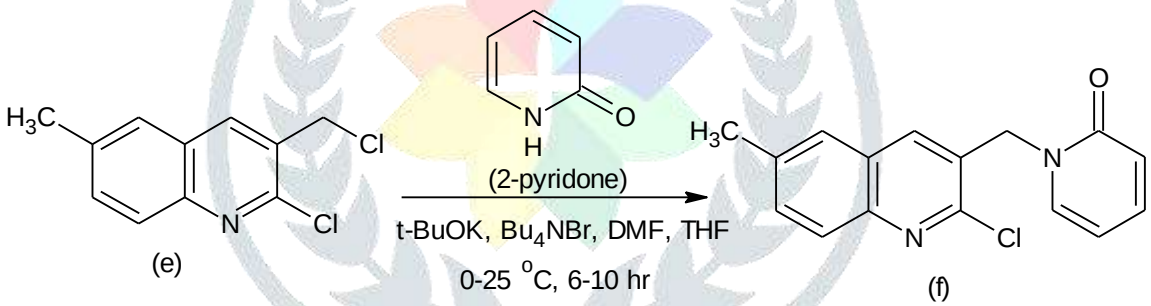


**Figure 17: Scheme for Synthesis of 1-[(2-chloro-6-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one**

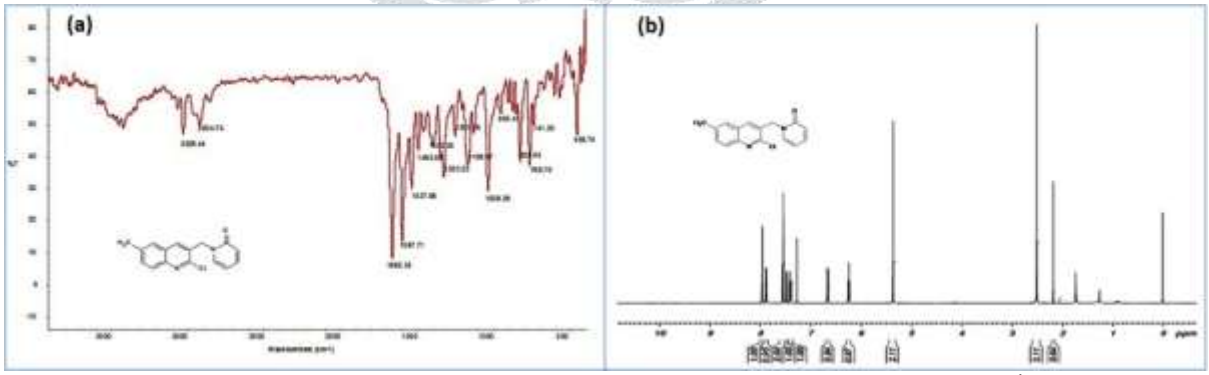


**Figure 18: (a) FT-IR spectra of 1-[(2-chloro-6-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one (b) $^1H$ NMR, 1-[(2-chloro-6-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one, ($CDCl_3$, 500MHz)**

**3.6. Synthesis of 2-methylindolizino[1,2-b]quinolin-9(11H)-one [8]:**

KOAc (0.6mM), n-$Bu_4NBr$ (20% of 0.5mM) and $Pd(OAc)_2$ (10% of 0.5mM) were added to a solution of compound 1-[(2-chloro-6-methylquinolin-3-yl)methyl]pyridin-2(1*H*)-one (f) (0.5mM) in DMF (2 ml) and resulting mixture was kept on reflux at 90 °C for 12-16 hr. The completion of reaction was monitored by TLC using 1:1 ratios of ethylacetate and petroleum ether as eluent. The mixture was poured into crushed ice, stirred for five min and extracted with ethylacetate. The compound was purified by column chromatography. Yield: 62%, Melting point: 225-227 °C, FT-IR (KBr) ν: 1658 (C=O), 1582 (N=C), 1532 (C=C) $cm^{-1}$, $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.86 (d, 1H), 7.3 (m, 2H), 7.16 (d, 1H), 6.56 (d, 1H), 6.16 (t, 1H), 5.13 (s, 2H, $CH_2$), 2.18 (s, 3H, $CH_3$).

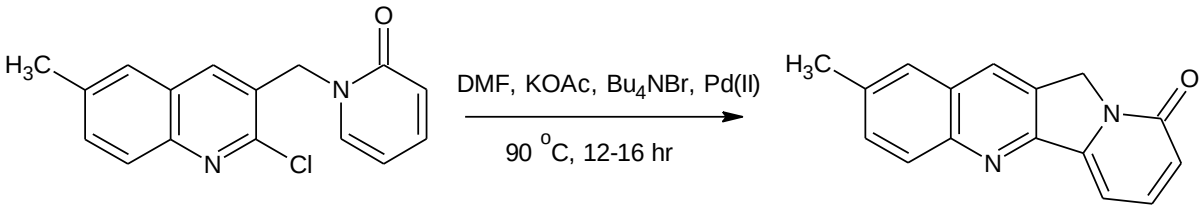


**Figure 19: Scheme for Synthesis of 2-methylindolizino[1,2-b]quinolin-9(11H)-one**

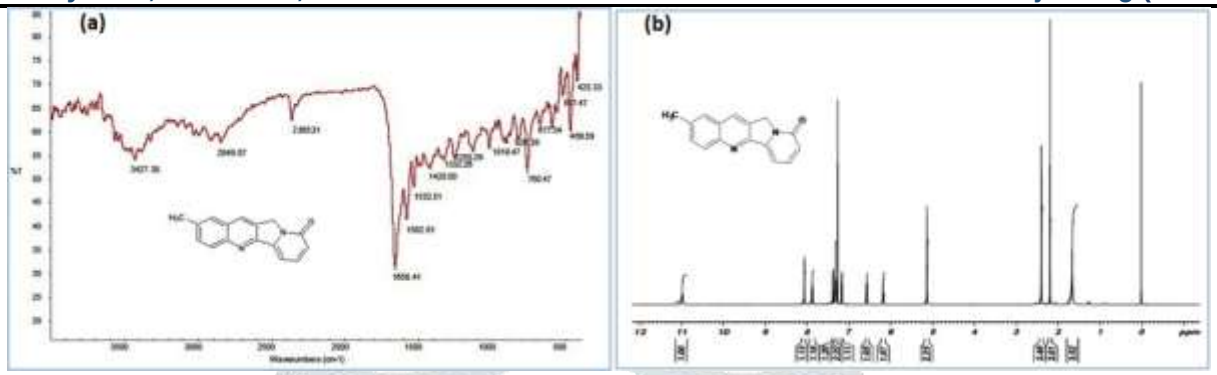


**Figure 20: (a) FT-IR spectra of 2-methylindolizino[1,2-b]quinolin-9(11H)-one (b) $^1$H NMR, 2-methylindolizino[1,2-b]quinolin-9(11H)-one , ($CDCl_3$, 500MHz)**

An acetanilide (b) derivative was synthesized with 67 % yield. Then they were converted into the 2-chloro-3-formylquinolines (c) 66 % yield. The chloroformyl derivative gave IR peaks corresponding to C=O (1682-1691cm$^{-1}$) and in $^1$H NMR a peak for CHO group at 10.55 ppm, 4 aromatic protons in range of 7.4-8.7 ppm. The chloroformyl derivative was then converted into the chloromethyl derivative in two steps by reduction and chlorination. The disappearance of aldehydic and OH peaks in IR and NMR and appearance of methylene protons is evident from the IR and NMR spectra of (e) i.e. 2 protons of $CH_2$ group appears at 4.8 ppm. The coupled product, (f) showed the presence of C=O (1662-1665 cm$^{-1}$) in IR spectra also in NMR aromatic protons in range of 6.2-8.1 ppm, 2 protons of $CH_2$ group at 5.3. Finally the cyclized compound, (g), (ABCD ring) were synthesized with 62 % yield. The disappearance of C-Cl bond and disappearance of one aromatic proton confirmed the products. All The intermediates were confirmed and characterized by FT-IR, LC-MS and $^1$HNMR.

**Conclusion:**

Synthesis of Tetracyclic (ABCD) ring cores of camptothecin was established by simple scheme using simple starting material like aniline and its derivatives in six steps. The intermediates were confirmed and characterized by FT-IR, LC-MS and $^1$HNMR. All the reactions were carried out on ordinary laboratory condition by employing cheaper, easily available chemicals and reagents in moderate to good yield.

**Acknowledgements:**

I am thankful to **TBI, VIT University, Vellore, T.N.** and **SAIF, IIT Madras, Chennai, T.N.** for their help in recording spectra.

**References:**

**[1]** Wall M. E., Wani M. C., Cook C. E., Palmer K. H., Mcphail A. T., Sim G. A., 1966. Plant Antitumor Agents. I. The Isolation and Structure of Camptothecin, a Novel Alkaloidal Leukemia and Tumor Inhibitor from Camptotheca acuminate. *Journal of American Chemical Society*, 88: 3888.

**[2]** Wu Du, 2003. Towards new anticancer drugs: a decade of advances in synthesis of camptothecins and related alkaloids. *Tetrahedron*, 59: 8649-8687.

**[3]** Yadav J.S., Sarkar S., Chandrasekhar S., 1999. A convergent total synthesis of mappicine ketone: A leading antiviral compound. *Tetrahedron*, 55 (17): 5449-5456.

**[4]** Yu J., DePue J., Kronenthal D., 2004. Synthesis of (±)-camptothecin using a [3+2] nitrone cycloaddition to construct the CDE ring moiety. *Tetrahedron Letters*, 45 (39): 7247-7250.

**[5]** Chavan S. P., Pasupathy K., Venkatraman M. S., Kale R. R., 2004. Formal total synthesis of camptothecin via ring-closing metathesis strategy. *Tetrahedron Letters*, 45: 6879–6882.

**[6]** Srivastava A., Singh R. M., 2005. Vilsmeier-Haack reagent: A facile synthesis of 2-chloro-3-formylquinolines from N-arylacetamides and transformation into different functionalities. *Indian Journal of Chemistry*, 44B: 1868-1875.

**[7]** Conreaux D., Bossharth E., Monteiro N., Desbordes P., Balme G., 2005. A practical procedure for the selective *N*-alkylation of 4-alkoxy-2-pyridones and its use in a sulfone-mediated synthesis of *N*-methyl-4-methoxy-2-pyridone, *Tetrahedron Letters*, 46 (46): 7917-7920.

**[8]** Comins D. L.., Baevsky M, F., Hong H., 1992. A 10-step, asymmetric synthesis of (S)-camptothecin, *Journal of American Chemical Society*, 114 (27): 10971–10972.