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ORIGINAL PAPER

ZnO nanoparticles in the synthesis of AB ring core of camptothecin

Selvaraj Mohana Roopan, Fazlur Rahman Nawaz Khan*

Organic & Medicinal Chemistry Research Laboratory, Organic Chemistry Division, School of Advanced Sciences, VIT University, Vellore, India

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For the first time, synthesis of AB ring core of camptothecin synthons such as (2-chloroquinolin-3-yl)methanols (*Va–Vg*) using zinc oxide nanoparticles is reported. The desired attractive products were obtained in high yields, short reaction time, using a simple work-up procedure with the purification of products by non-chromatographic methods.

Keywords: ZnO nanoparticles, camptothecin synthons, (2-chloroquinolin-3-yl)methanol

Introduction

The search for new anticancer drugs from nature continues to be a fruitful activity as evidenced by the successes of natural products as pharmaceutical agents (Rath et al., 2009; Niizuma et al., 2009). Camptothecin (CPT), a pentacyclic alkaloid isolated from the Chinese tree *Camptotheca acuminata* (Wall et al., 1966), is an outstanding lead compounds in anticancer drug development. Due to its toxicity, poor solubility and unstable nature of the lactone ring, camptothecin was not ideal for pharmaceutical use. Substituted quinolines are a common structural feature in a number of biologically active alkaloids, see for example camptothecin (*I*) and its derivatives such as Diflomotecan (*II*) and S39625 (*III*) (Fig. 1).

Reaction of the AB ring core of camptothecin with DE rings in the Comins synthetic approach (Comins et al., 1994) (Fig. 2) has been used by several research groups for the assembly of camptothecin.

In view of the on going active analogue development programs of CPT in our laboratory, it is apt to mention the synthesis of synthons (AB ring core). Reduction of different derivatives of 2-chloroquinoline-3-carbaldehyde by the catalytic hydrogenation method in the presence of zinc oxide nanoparticles provides a convenient method for the preparation of the corresponding alcohols. Synthetic chemists continue to explore new methods of chemical transformations. One such method includes reactions on the surface of solids with high product yield and purity, which is more desirable compared to reactions proceeding in a solution. Several classes of solids have commonly been

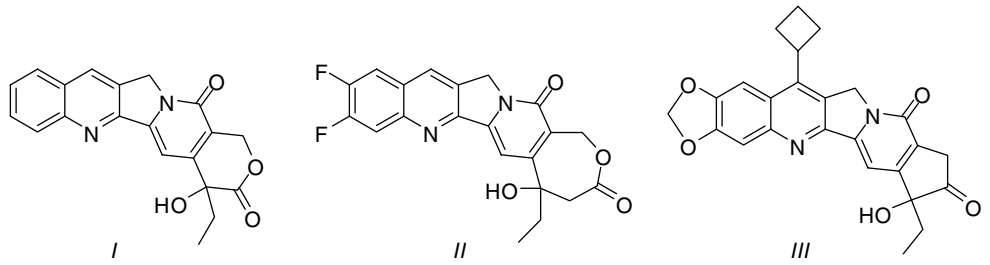


Fig. 1. Biologically active alkaloids.

*Corresponding author, e-mail: nawaz_f@yahoo.co.in

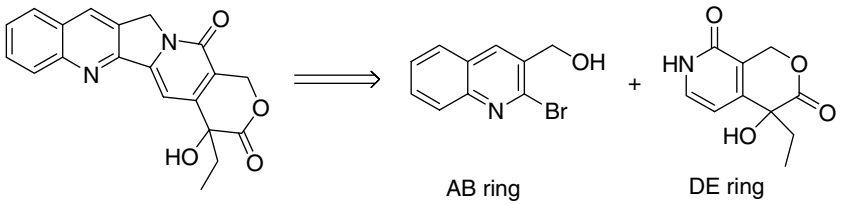


Fig. 2. Retrosynthesis of the Comins approach for camptothecin construction.

used for surface organic chemistry including alumina, silica gels, and clays.

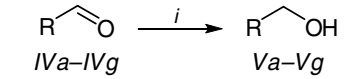
Zinc oxide (Kim & Varma, 2004; Maghsoodlou et al., 2007; Roopan & Khan, 2010) is certainly one of the most interesting of these solids because its surface properties suggest that many organic reactions can occur there. The majority of aldehydes reduction was done using reagents transferring a hydride from boron or aluminum such as sodium borohydride, lithium borohydride in the presence of an organic solvent medium. Some inorganic clay materials such as montmorillonite have been used as the catalyst for organic reactions and they are superior to classical acids due to their strong acidity, non-corrosive nature, cheapness, mild reaction conditions, high yields and selectivity, and the simplicity of the process set-up and work-up. In continuation of our work (Roopan et al., 2008, 2009, 2010; Roopan & Khan, 2008), nanoparticles were utilized in our synthesis as nanoparticle catalysts have offered great opportunities for a wide range of applications in organic synthesis (Sapkal et al., 2009; Kidwai et al., 2009; Chaicharoenwimolkul et al., 2008).

Experimental

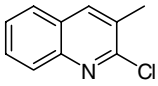
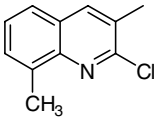
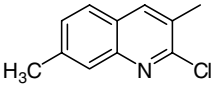
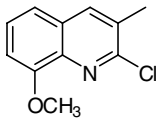
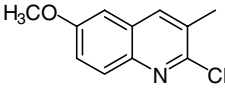
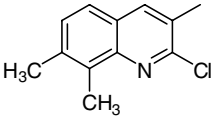
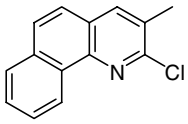
Chemicals used for the reaction were purchased from Sigma–Aldrich Co. (India). The substances were used as provided without purification. Melting points were taken in open capillary tubes and are corrected with reference to benzoic acid. FTIR spectra in KBr pellets were recorded on a Nucon Infrared spectrophotometer. ^{1}H (400 MHz and 500 MHz) and ^{13}C (100 MHz and 125 MHz) NMR spectra were recorded on Bruker Spectrospin Avance DPX400 and Bruker AVANCE III (AV 500) spectrometers, respectively, using TMS as an internal reference. High resolution scanning electron microscope (HRSEM) spectra were recorded on a FEI Quanta FEG 200. Mass spectra were recorded on a Finnigan Mat 8230 mass spectrometer.

(2-Chloroquinolin-3-yl)methanols (*Va–Vg*) were synthesized using the following general procedure. Starting 2-chloroquinoline-3-carbaldehyde derivative (*IVa–IVg*, 1 mmol) (Srivastava & Singh, 2005), sodium borohydride (1 mmol), zinc oxide nanoparticles (5 mole %), and distilled water (0.1 mL) were well mixed in a beaker and then kept for about 1 min at room temperature to give the corresponding (2-chloroquinolin-3-yl)methanol derivative (*Va–Vg*, Table 1). Ethyl acetate was added to the reaction mixture and the catalyst was recovered by filtration. Filtrate and catalyst were washed with saturated NH_4Cl solution to remove unreacted sodium borohydride. The organic layer was dried and the solvent was evaporated to give products (Table 1). Structures of all products were confirmed by FTIR,

Table 1. Synthesis of some AB ring cores of camptothecin using S-ZONPs



IVa–IVg *Va–Vg*

Compound	R	Time/s	M.p./°C	Yield/%[a]
Va		56	161	99
Vb		58	137	96
Vc		64	146	92
Vd		110	190	88
Ve		82	124	92
Vf		62	246	97
Vg		55	173	94

a) Isolated yield; reaction conditions: *i*) 1 mmol of aldehyde *IVa–IVg*, 1 mmol of $NaBH_4$, 0.1 mL of H_2O, 5 mole % of S-ZONPs, room temperature.

Table 2. Spectral data of newly prepared compounds

Compound	Spectral data
Vf	IR, $\tilde{\nu}$/cm^{-1}: 3315 (OH) ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.16 (s, 1H), 7.57 (dt, J = 8.0 Hz, 1H), 7.37 (dt, J = 8.4 Hz, 1H), 4.90 (s, 2H), 2.65 (s, CH_3, 3H), 2.49 (s, CH_3, 3H), 2.20 (s, 1H) ^{13}C NMR (100 MHz, $CDCl_3$), δ: 148.02, 146.27, 138.21, 136.54, 133.78, 130.70, 129.98, 125.73, 124.40, 62.24 (CH_2), 20.68 (CH_3), 13.36 (CH_3) LCMS, m/z (I_r): 222 (M^+ + 1); HRMS, m/z (found/calc.): 221.1002/221.6827 (M^+, $C_{12}H_{12}ClNO$)
Vg	IR, $\tilde{\nu}$/cm^{-1}: 3435 (OH) ^{1}H NMR (500 MHz, $CDCl_3$), δ: 9.22 (s, 1H), 8.33 (s, 1H), 7.93 (t, 1H), 7.86 (dt, J = 9.0 Hz, 1H), 7.72–7.77 (m, 3H), 5.00 (s, 2H, CH_2), 2.23 (s, 1H, OH) ^{13}C NMR (125 MHz, $CDCl_3$), δ: 147.96, 145.54, 136.19, 133.73, 132.76, 130.36, 128.61, 128.37, 127.80, 127.32, 125.56, 124.62, 124.59, 62.11 HRMS, m/z (found/calc.): 243.3570/243.6883 (M^+, $C_{14}H_{10}ClNO$)

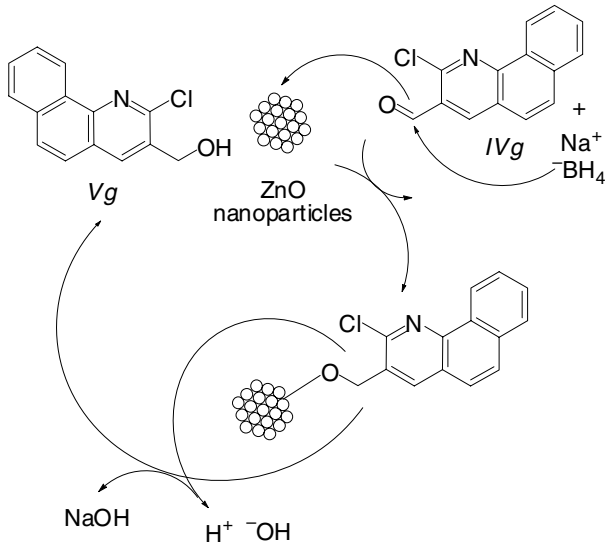


Fig. 3. Mechanistic pathway for the synthesis of AB ring core of camptothecin.

^{1}H and ^{13}C NMR, and LCMS and HRMS analyses. Spectral data of the new compounds, *Vf* and *Vg*, are given in Table 2. Data of compounds *Va*–*Ve* were identical with those already reported (Roopan & Khan, 2009). We proposed a mechanistic pathway to synthesize the AB ring core of camptothecin (Fig. 3).

Synthesis of ZnO nanoparticles

Zinc oxide nanoparticles (ZONPs) were prepared from zinc nitrate ($Zn(NO_3)_2 \cdot 6H_2O$) according to an already described method (Wu et al., 2006). Samples were used for the reduction of 2-chloroquinoline-3-carbaldehyde (*IVa*) with $NaBH_4$ as the reducing agent. Synthesized zinc oxide nanoparticles (S-ZONPs) were found to be superior compared to commercial zinc oxide nanoparticles (CM-ZONPs). The above results indicate that the efficiency of the catalytic activity is dependent on the particle size of ZnO.

Table 3. Selection of nanoparticles[a]

Nanoparticle	Catalyst/mole %	Time/s	Yield of *V*
Co(O)	5	> 60	nr
Fe(O)	5	> 60	nr
Ni–Fe	5	> 60	nr
Commercial ZnO	5	60	moderate
Synthesized ZnO	5	60	high

a) Reaction conditions: aldehyde *IV* (1 mmol), $NaBH_4$ (1 mmol), H_2O (0.1 mL), room temperature; nr – no reaction at given conditions.

Screening, optimization, and reutilization of nanoparticles

Selection of nanoparticles was done (Table 3) including Fe, Co, Ni–Fe, and ZnO (Fig. 4). The reduction of 2-chloroquinoline-3-carbaldehyde (*IVa*) was first studied. This compound was reduced fast to the corresponding alcohol in good isolated yield only in the presence of ZnO nanoparticles. Two different nanosized ZnO, one commercial and one synthesized in the range of < 100 nm, were screened.

Using this methodology, optimization of the catalyst amount was also done (Table 4). Substituted 2-chloroquinoline-3-carbaldehydes (*IVa–IVg*) (Table 1) were reduced fast to the corresponding alcohols in modest to good isolated yields. 2-Chloroquinoline-3-carbaldehyde (*IVa*) was used as a model substrate in order to optimize the amount of the catalyst (Table 4). The amount of 4 mole % of S-ZONPs showed to be effective to complete the conversion into (2-chloroquinolin-3-yl)methanol (*Va*) (Entry 5, Table 4). The reaction with 5 mole % of ZnO led also to the product in a relatively short time and high yield (Entry 6, Table 4).

Reusability of nanoparticles was explored by successive runs of reactions using recycled catalyst; i.e. after the first reaction, catalyst was recovered by washing with methanol, centrifuged, removed, and

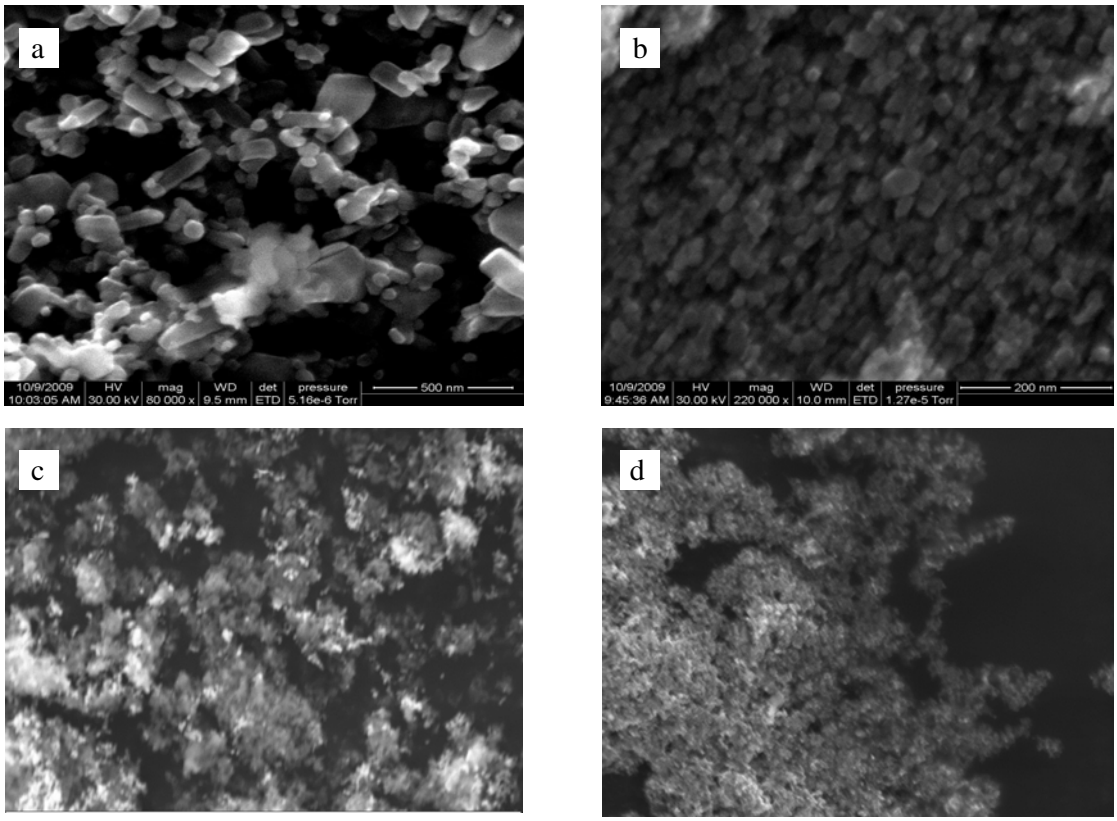


Fig. 4. SEM images of nanoparticles: CM-ZONPs (a), S-ZONPs (b), Ni–Fe (c), Co (d).

Table 4. Optimization of catalyst (CM-ZONPs, S-ZONPs) for the synthesis of AB ring core of camptothecin[a]

Entry	Optimized parameters		Yield/%[b]	Optimized parameters		Yield/%[b]
	CM-ZONPs/mole %	Time/s		S-ZONPs/mole %	Time/s	
1	None	> 150	23	None	> 150	23
2	1	90	83	1	84	87
3	2	83	85	2	78	88
4	3	73	86	3	65	92
5	4	72	87	4	58	95
6	5	72	87	5	56	99

a) Reaction conditions: aldehyde *IV* (1 mmol), $NaBH_4$ (1 mmol), H_2O (0.1 mL), room temperature; *b*) isolated and not optimized yield.

reused for four consecutive runs without any apparent loss of activity for the same reaction. It was noticed that the use of recycled catalyst in subsequent experiments resulted in similar yields (Table 5, Figs. 5 and 6). Thus, the catalyst did not leach.

Table 5. Reutilization of ZONPs by hydrogen transfer reduction

Run	Yield	
	CM-ZONPs	S-ZONPs
1	92	99
2	90	99
3	86	97
4	82	96
5	68	89
6	66	88
7	58	86
8	52	78

Results and discussion

The required 2-chloroquinoline-3-carbaldehydes (*IVa–IVg*) were readily prepared from acetanilides with the Vilsmeier-Haack reagent at 80–90 ℃, which upon treatment with sodium borohydride and distilled water in the presence of zinc oxide nanoparticles afforded AB synthons such as (2-chloroquinolin-

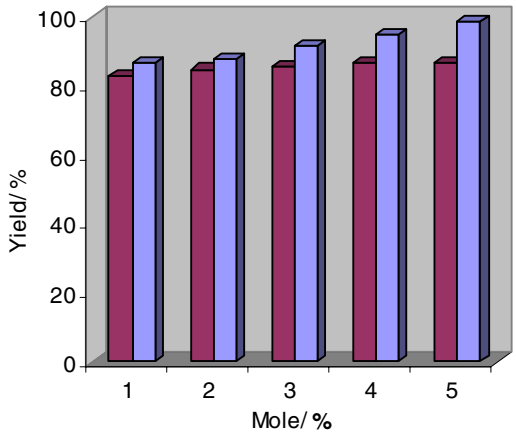


Fig. 5. Yield comparison between commercial (■ CM-ZONPs) and synthesized (■ S-ZONPs) ZnO nanoparticles.

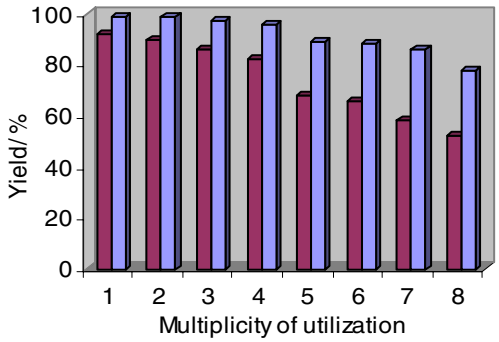


Fig. 6. Comparison of multiplicity of commercial (■ CM-ZONPs) and synthesized (■ S-ZONPs) ZnO nanoparticles utilization.

3-yl)methanols (*Va–Vg*). A number of methods for the reduction of aldehydes are available (Alonso et al., 2008; Khan et al., 2010a, 2010b). It is reported herein that ZONPs, receiving considerable attention nowadays, act as efficient heterogeneous hydrogenation catalysts. A preliminary study was carried out using 2-chloroquinoline-3-carbaldehyde (*IVa*) as a model substrate in the presence of different amounts of catalysts (Table 4). It is noteworthy that, under the conditions presented in Table 4, ZONPs were able to reduce 2-chloroquinoline-3-carbaldehyde (*IVa*) to the corresponding AB synthons of camptothecin such as (2-chloroquinolin-3-yl)methanol (*Va*). Blank experiment, in the absence of ZONPs, was also done and lower yield of the product was achieved (Table 4). These experimental results clearly suggest that the reaction involves a heterogeneous process and the catalysis may occur on the surface of the ZnO nanoparticles. Thus, H_2O-stabilized ZnO nanoparticles may undergo a reaction with 2-chloroquinoline-3-carbaldehyde (*IVa*) to give intermediates (Fig. 3) which can complete the catalytic cycle by the elimination of the reduced product *Va*.

From the HRSEM analysis of the ZnO sample it can be observed that the particles contain nanoparticles. Fig. 4a shows the HRSEM image of commercial zinc oxide nanoparticles where a fairly uniform particle size of (48 ± 0.5) nm is evident. Fig. 4b shows the particle size of (18 ± 0.5) nm of the synthesized ZnO nanoparticles. From the HRSEM image, the average particle size of the zinc oxide catalyst was found to be < 100 nm and the particles were spherical in nature. High yield of the product is based on the particle size of zinc oxide.

IR data were normalized to 100 % absorption for a peak at approximately 491.66 cm^{-1} for the pure form; after the reaction, the catalyst showed peaks at 491.05 cm^{-1} indicating non-leachability of the catalyst.

Conclusions

In conclusion, the application of catalytic zinc oxide nanoparticles as a catalyst for the reduction of several substituted 2-chloroquinoline-3-carbaldehydes at room temperature, a simple, economical, and environmentally benign method avoiding volatile and toxic organic solvents is reported for the first time.

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