We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

CLARIVATE ANALYTICS

BOOK CITATION INDEX

INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter

Therapeutic Significance of 1,4-Dihydropyridine Compounds as Potential Anticancer Agents

Tangali Ramanaik Ravikumar Naik

Abstract

A series of 1,4-dihydropyridines have been prepared from a three-component one-pot condensation reaction of β-diketonates, an aromatic aldehyde, and ammonium acetate under microwave irradiation. The reaction is performed using crystalline nano-ZnO in ethanol under microwave irradiation (CEM discover). A wide range of functional groups was tolerated in the developed protocol. The present methodology offers several advantages such as simple procedure, greener condition, excellent yields and short reaction time. The synthesized compounds were evaluated for DNA photocleavage, SAR analysis and molecular docking studies. The compound (**4b, 4c, 4 h, 4i, 4n** and **4o**) showed potent DNA cleavage activities compared to other derivatives. The molecular interactions of the active compounds within the binding site of B-DNA were studied through molecular docking simulations; the compound (**4b, 4c, 4 h, 4i, 4n** and **4o**) showed good docking interaction with minimum binding energies. All synthetic compounds were characterized by different spectroscopic techniques.

Keywords: 1,4-Dihydropyridines, DNA photocleavage, molecular docking, SAR analysis, ZnO nanoparticle

1. Introduction

Facile and efficient synthesis of biological active molecules is one of the main objectives of organic and medicinal chemistry. In recent years, multicomponent reactions have become one of the important tools in the synthesis of structurally diverse chemical libraries of drug-like polyfunctional organic molecules [1–4]. Furthermore, MCRs offer the advantage of simplicity and synthetic efficiency over conventional chemical reactions in several aspects. MCRs allow the construction of combinatorial libraries of complex organic molecules for an efficient lead structure identification and optimization in drug discovery [5–10].

In continuation of our ongoing research work on microwave assisted synthesis of nano materials [11, 12] we have found that, nano-crystalline metal oxides have attracted considerable attention of synthetic and medicinal chemists because of their high catalytic activity and reusability [13–25]. Zinc oxide is an inexpensive, moisture stable, reusable, commercially available and is non-toxic, insoluble in polar as well as non-polar solvents [26–31]. A wide range of organic reactions that include Beckmann rearrangements [32], N-benzylation [33], acylation [34], dehydration of oximes [35], nucleophilic ring opening reactions of epoxides [36],

synthesis of cyclic urea [37], N-formylation of amines [38]. In particular crystalline nano-ZnO oxide exhibit better catalytic activity compared to their bulk sized counterparts [29, 39–42].

In recent years, much attention has been directed toward the synthesis of dihydropyridine compounds owing to their tremendous application in various research fields including biological science and medicinal chemistry [43, 44]. Many DHPs are already commercial products such as: amlodipine, felodipine, isradipine, lacidipine, nicardipine, nitrendipine, nifedipine and nimodipine B, of which nitrendipine and nemadipine B exhibit potent calcium channel blocking activities [45–49] (**Figure 1**) and have emerged as one of the most important classes of drugs for the treatment of cardiovascular diseases [50, 51]. Moreover dihydropyridine derivatives possess a variety of biological activities like, geroprotective, hepatoprotective, anti-atherosclerotic, antitumor, and antidiabetic activities [46, 52, 53]. Widespread studies have uncovered that dihydropyridine unit containing compounds exhibit various medicinal functions such as neuroprotectant, platelet anti-aggregatory activity, cerebral anti ischemic activity in the treatment of Alzheimer's disease, chemosensitizer in tumor therapy [54–56]. Drug-resistance modifiers [57], antioxidants [58] and a drug for the treatment of urinary urge incontinence [59].

In order to model and understand these biological properties and to develop new chemotherapeutic agents based upon the 1,4-DHP compounds, significant effort has been devoted to establish effective methods for their synthesis. Generally, 1,4-DHPs were synthesized by Hantzsch method [60], which involves cyclocondensation of an aldehyde, a β-ketoester and ammonia either in acetic acid or under reflux in alcohols for long reaction times which typically leads to low yields [46, 61, 62]. Other methods comprise the use of microwaves [63–65], high temperatures at reflux [66–69], organocatalysts [70] and metal triflates [71].

Recently, DNA is an important drug target and it regulates many biochemical processes that occur in the cellular system. Small-molecule interactions with DNA continue to be intensely and widely studied for their usefulness as probes of cellular replication and transcriptional regulation and for their potential as pharmaceuticals [72–75]. In particular, designing of the compound based on their ability to cleave DNA is of great importance not only from the primary biological point of view
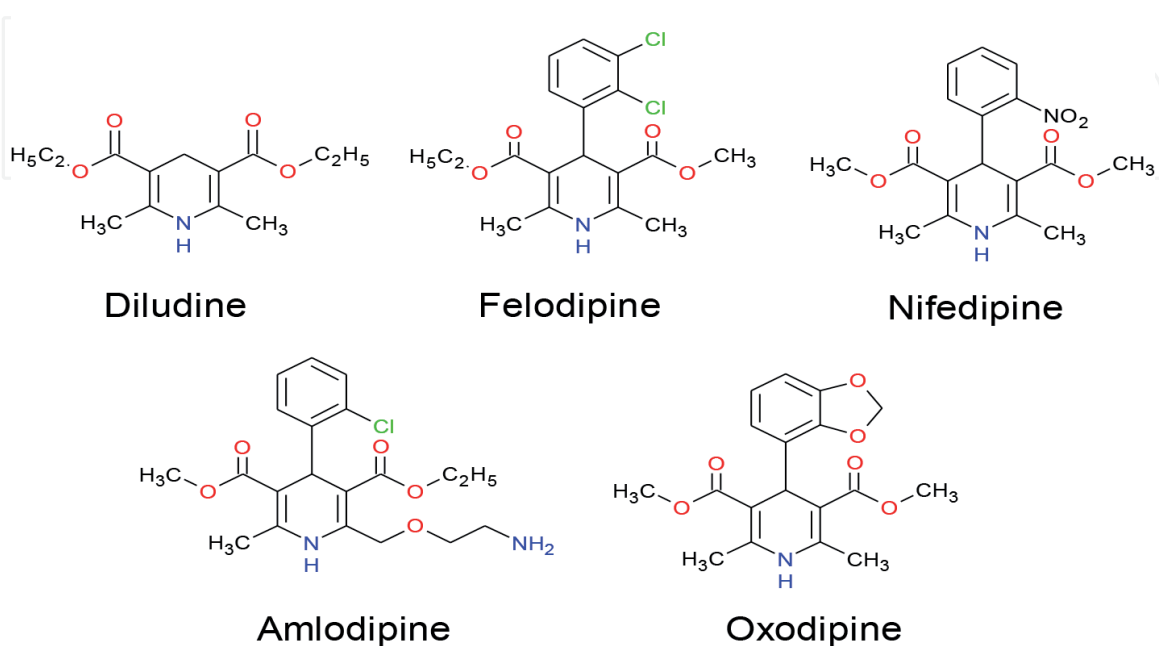

Figure 1.
Drugs containing 1,4-DHP moieties.

but also in terms of photodynamic therapeutic approach to develop potent drugs [72–75]. 1,4-Dihydropyridine derivatives have attracted the attention of the chemists because of their diverse biological applications [76]. The biological significance of this class of compounds impelled us to extend this series by working on the synthesis and DNA photocleavage studies of 1,4-dihydropyridine derivatives. In this communication, synthesis of 1,4-dihydropyridine derivatives and their DNA photocleavage studies and molecular docking have been reported.

In literature, there are several methods known for the synthesis of 1,4-dihydropyridine derivatives. In continuation of our program on the chemistry of nano material, herein we report an efficient microwave method for the synthesis of crystalline ZnO-NPs. The ZnO used in this work was synthesized according to a modified method. The prepared crystalline ZnO-nano-particle was characterized using powder XRD, SEM, EDX (**Figure 2**). Our synthetic approach started with the condensation of 1 equiv. of benzaldehyde **1a** with 2 equiv. of ethyl acetoacetate **2a** and 2 equiv. of NH_4OAc **3a** in the presence of ZnO-Nps resulted in the formation of Hantzsch 1,4-dihydropyridine **4a** (**Figure 3**). The reaction was complete in 5 min under microwave irradiation and the product was isolated by the usual work-up, in 90% yield and high purity. Under similar conditions, various substituted aromatic aldehydes carrying either electron-donating or -withdrawing substituents reacted with 1,3-diketones to form 1,4-DHPs in good to excellent yields, and the results are summarized in **Table 1**.

A microwave irradiation-assisted process very often minimizes the formation of byproducts and requires much less time than thermal methods. The main benefits of performing reactions under controlled conditions in sealed vessels are the significant rate enhancements and the higher product yields that can frequently be achieved. Therefore, in continuation of our studies on microwave synthesis of nano-materials [77–81], we have attempted to develop a rapid, microwave-assisted protocol for the synthesis of 1,4-DHPs using crystalline ZnO-nano catalyst (**Figure 3**).

The DNA cleavage of 1,4-DHP derivatives were studied by agarose gel electrophoresis. When circular plasmid DNA was subjected to electrophoresis, relatively fast migration was observed for the intact supercoiled DNA (type I). If scission occurs on one strand (nicking), the supercoiled DNA will relax to generate a slower moving open circular form (type II). If both strands are cleaved, a linear form
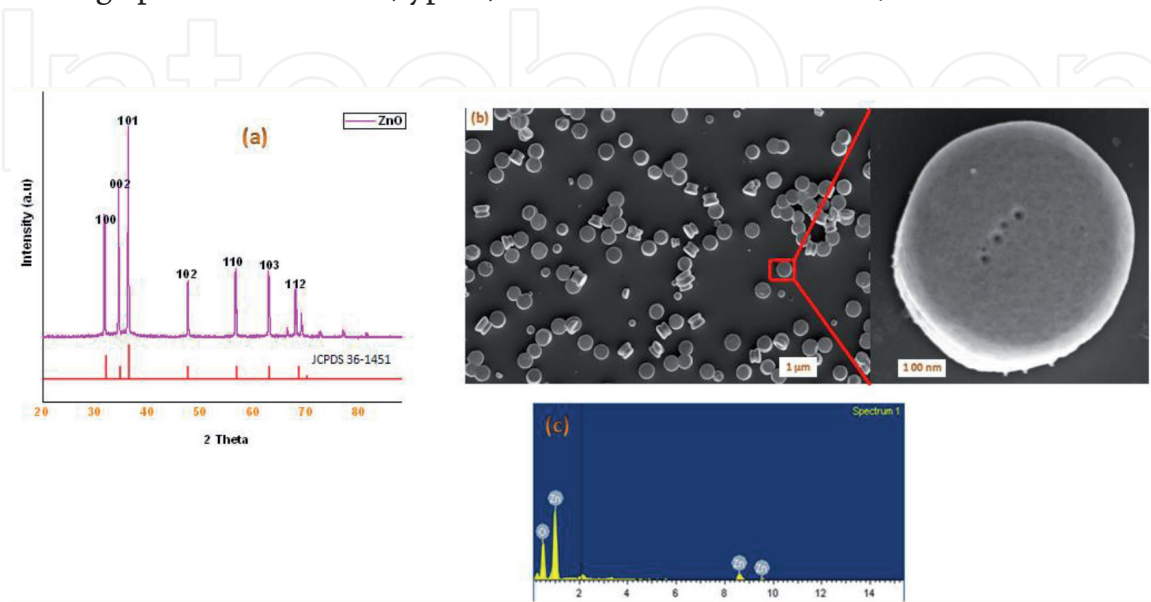

Figure 2.
(a) Powder XRD of obtained ZnO nano particles by microwave method; (b) SEM images of ZnO-NPs;
(c) EDX analysis spectrum of obtained ZnO nano particles by microwave method.
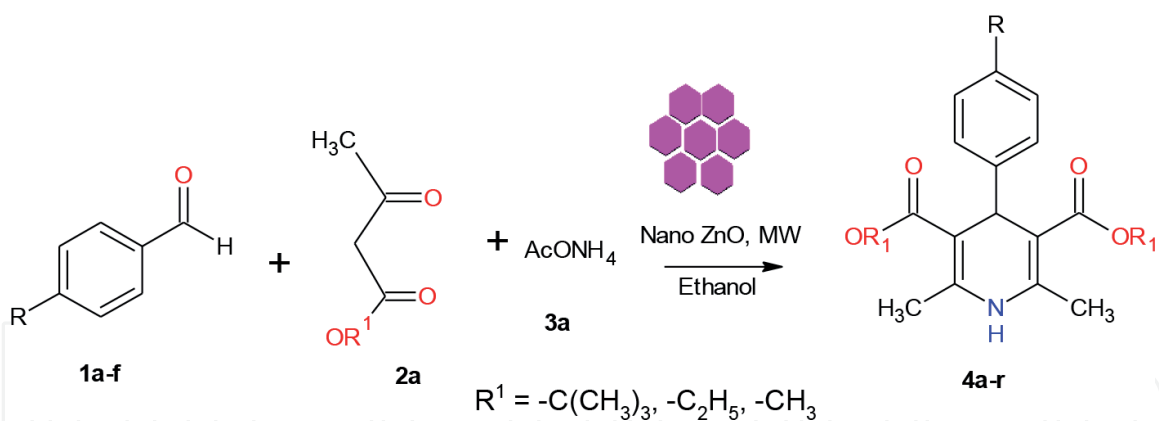
Figure 3.
Synthesis of 1,4-dihydropyridines.

Entry[a]	R	R[1]	Products	Entry[a]	Yield (%)[b]
1	C_6H_5	*t*-Bu	**4a**	1	90
2	4-MeO-C_6H_5	*t*-Bu	**4b**	2	95
3	4-OH-C_6H_5	*t*-Bu	**4c**	3	95
4	4-F-C_6H_5	*t*-Bu	**4d**	4	95
5	4-Cl-C_6H_5	*t*-Bu	**4e**	5	90
6	4-NO$_2$-C_6H_5	*t*-Bu	**4f**	6	95
7	C_6H_5	Et	**4 g**	7	90
8	4-MeO-C_6H_5	Et	**4 h**	8	95
9	4-OH-C_6H_5	Et	**4i**	9	92
10	4-F-C_6H_5	Et	**4j**	10	92
11	4-Cl-C_6H_5	Et	**4 k**	11	90
12	4-NO$_2$-C_6H_5	Et	**4 l**	12	90
13	C_6H_5	Me	**4 m**	13	90
14	4-MeO-C_6H_5	Me	**4n**	14	87
15	4-OH-C_6H_5	Me	**4o**	15	90
16	4-F-C_6H_5	Me	**4p**	16	90
17	4-Cl-C_6H_5	Me	**4q**	17	90
18	4-NO$_2$-C_6H_5	Me	**4r**	18	90

[a]*All the products were characterized by 1H NMR and 13C NMR studies and compared with the literature mps.*
[b]*Yields of isolated products*

Table 1.
Synthesis of 1,4-dihydropyridines.

(type III) that migrates between type I and type II will be generated [82–85]. The conversion of type I (supercoiled) to type II (nicked circular) was observed with different concentration of 1,4-DHP and irradiated for 2 h, in 1:9 DMSO/trisbuffer (20 μM, pH- 7.2) at 365 nm. No DNA cleavage was observed for the control in which 1,4-DHP was absent (lane 1) (**Figure 4**). With increasing concentration of these 1,4-DHP the amount of type I of pUC 19 DNA diminished gradually, whereas type II increased (**Figure 4**).

At 40 μM concentration, the Compound (**4c**) can promote only 30% conversion of DNA from type I to II (**Figure 5**). At the concentration of 80 μM, compound (**4c**)
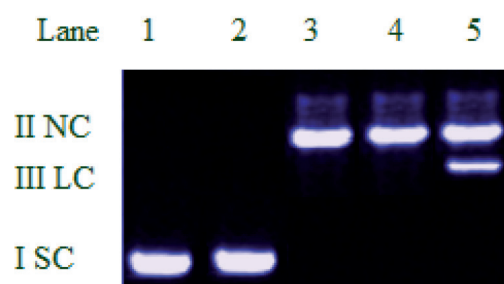
Figure 4.
*Light-induced DNA cleavage by 1,4-DHP. The 1,4-DHP was irradiated with UV light at 365 nm. Lane; 1: Control DNA (with out compound), lane; 2: 20 μM (**4c**), lane; 3: 40 μM (**4c**), lane; 4: 60 μM (**4c**), lane; 5: 80 μM (**4c**).*
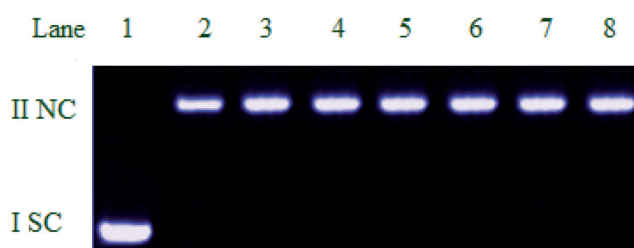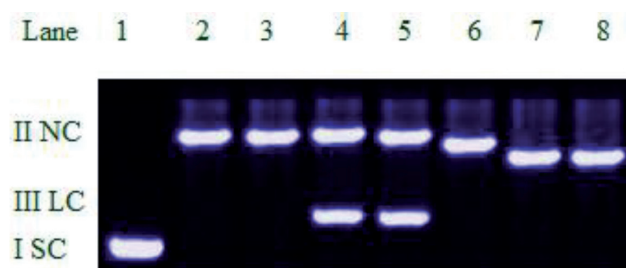

Figure 5.
*Light-induced DNA cleavage by 1,4-DHP. The 1,4-DHP was irradiated with UV light at 365 nm. Lane; 1: Control DNA (with out compound), lane; 2: 40 μM (**4a**), lane; 3: 40 μM (**4b**), lane; 4: 40 μM (**4c**), lane; 5: 40 μM (**4d**), lane; 5: 40 μM (**4e**), lane; 5: 40 μM (**4f**), lane; 5: 40 μM (**4 g**).*

can almost promote the about 80% conversion of DNA from type I to II (**Figure 5**). The cleavage potential of the test compounds were assessed by comparing the bands appeared in control and test compounds at 80 μM concentration. However, other derivatives exhibits much lower cleaving efficiency for pUC 19 DNA. Even at the concentration of 80 μM, it can promote only 40% conversion of DNA from type I to II (**Figure 5**).

But at higher concentrations around 130 μM, the compounds get precipitated and there is no moment in the DNA. The image (**Figure 6**) clearly demonstrates that compounds (**4b, 4c, 4d, 4e, 4f** and **4 g**) shows DNA cleavage of pUC19 DNA at 80 μM concentration. The results indicated that compounds bearing –OCH$_3$ and –OH at -*para* position of phenyl ring (C-6) did cleave the DNA completely, other compounds have displayed nearly complete cleavage of DNA. Overall, it indicates that, the alkoxy groups are highly reactive radicals, which abstracts hydrogen atoms efficiently at C-4′ of 2-deoxyribose. It is of interest to note that hydroxyl group has been reported to bring about oxygen radical mediated DNA damage in the presence of photoirradiation [86].

The structure–activity relationship studies of 1,4-DHPs with regard to DNA photocleavage studies shows that, the changes in the substitution pattern at C-3, C-4, and C-5 positions alter the 1,4-DHP ring. Osiris Property Explorer is one such knowledge based activity prediction tool which predicts drug likeliness, drug score and undesired properties such as mutagenic, tumorigenic, irritant and reproductive effect of novel compounds based on chemical fragment data of available drugs and non-drugs as reported (**Table 2**) [87]. It was observed that, the compounds having aliphatic groups such as –CH$_3$, –COOCH$_3$, –COOC$_2$H$_5$ and –COOC(CH$_3$)$_3$, attached to C-2 and C-3 of 1,4-DHP exhibited good activity. Other derivatives possessing, an electron-donating substituent, such as hydroxy and methoxy group on the phenyl ring (C-6) increases DNA photocleavage activity. A lone pair of electrons on oxygen atom of methoxy group delocalizes into the π space of benzene ring,

Figure 6.
*Light-induced DNA cleavage by 1,4-DHP. The 1,4-DHP was irradiated with UV light at 365 nm. Lane; 1: Control DNA (with out compound), lane; 2: 80 μM (**4a**), lane; 3: 80 μM (**4b**), lane; 4: 80 μM (**4c**), lane; 5: 80 μM (**4d**), lane; 5: 80 μM (**4e**), lane; 5: 80 μM (**4f**), lane; 5: 80 μM (**4 g**).*

Compounds	Mol. wt	C log P	Drug-likeness	Drug-score	Toxicity risks[a]			
					M[b]	T[c]	I[d]	R[e]
4a	329	3.29	2.41	0.77	(+)	(+)	(+)	(+)
4b	359	3.22	2.34	0.75	(+)	(+)	(+)	(+)
4c	345	2.94	2.48	0.79	(+)	(+)	(+)	(+)
4d	347	3.39	1.65	0.70	(+)	(+)	(+)	(+)
4e	419	5.37	−17.92	0.22	(+)	(+)	(+)	(+)
4f	430	4.17	−19.36	0.10	(−)	(+)	(+)	(−)
4 g	301	2.48	4.04	0.87	(+)	(+)	(+)	(+)
4 h	331	2.41	3.87	0.51	(+)	(+)	(+)	(+)
4i	317	2.13	4.08	0.53	(+)	(+)	(+)	(+)
4j	319	2.58	3.29	0.50	(+)	(+)	(+)	(+)
4k	363	3.89	3.33	0.68	(+)	(+)	(+)	(+)
4 l	374	2.69	1.92	0.25	(−)	(+)	(+)	(−)
4 m	269	2.98	4.09	0.50	(+)	(+)	(+)	(+)
4n	299	2.91	3.94	0.49	(+)	(+)	(+)	(−)
4o	285	2.63	4.14	0.51	(+)	(+)	(+)	(+)
4p	287	3.08	3.42	0.47	(+)	(+)	(+)	(−)
4q	335	3.08	4.97	0.48	(+)	(+)	(+)	(−)
4r	346	1.88	3.50	0.30	(−)	(+)	(+)	(−)

[a]Ranking as (+) no bad effect, (+/−) medium bad effect, (−) bad effect.
[b]M (mutagenic effect);
[c]T (tumorigenic effect);
[d]I (irritant effect);
[e]R (reproductive effect).

Table 2.
Drug likeliness properties of 1,4-dihydro pyridines according to Osiris property explorer tool.

thereby increasing the activity. Similarly, electron-withdrawing substituent's, such as 4-fluorophenyl, 4-chloro phenyl of 1,4-DHP lower the activity. These results indicate that, the alkoxy substituent's and nitrogen of pyridine ring in the 1,4-DHP structure are the responsible for DNA cleavage.

In order to rationalize the observed spectroscopic results and to get more insight into the intercalation modality, the 1,4-DHP (**4a–r**) were successively docked [88–90] within the DNA duplex of sequence d(CGCGAATTCGCG)$_2$ dodecamer

(PDB ID: 1BNA) in order to predict the chosen binding site along with preferred orientation of the ligand inside the DNA minor groove. All synthesized 1,4-DHP derivatives were drawn in ChemSketch and structures were saved in .mol format. Afterwards the .mol format was used in Hyperchem-7, to adjust their fragments, followed by total energy minimization of ligands so that they can attain a stable conformation and the file was saved in .pdb format.

Protein 3D structure of B-DNA was obtained from RCSB PDB (an information portal to biological macromolecular structures). The water molecules were removed from the file, and the protein was protonated in 3D to add polar hydrogen's. Binding pocket was identified using site finder, and the respective residues were selected. Docking parameters were set default values and scoring algorithm, the docking runs were retained to 30 conformations per ligand. The docked protein structures were saved in .pdb format, and ligand's conformations were investigated one by one. Complexes with best conformations were selected on the basis of highest score, lowest binding energy and minimum RMSD values [91].

The synthesized organic compounds perform their biological activity more efficiently by binding respective protein or DNA at their specific binding site. Identification of interacting residues with ligands is a necessary step toward rational drug designing, understanding of molecular pathway and mechanistic action of protein.

Molecular docking was carried out between rigid receptor protein and the flexible ligands. **Table 3** shows the details of the docking results including RMSD and binding energy values of protein–ligand complexes. The ligands (**4b, 4c, 4 h, 4i, 4n** and **4o**) bind strongly to B-DNA as inferred by their minimum binding energy values, that is, −13.8, −12.9 and − 12.3 kcal/mol, respectively (**Figure 7**).

Figure 8 shows the position of active site in the helical structure of DNA and it also shows that all docked ligands clustered inside the pocket. **Figure 8** exhibited

Products	Docking energy (Kcal/mol)	Inhibition constant (M)	RMSD
4a	−6.23	4.35×10^{-7}	2.5
4b	−24.12	1.81×10^{-16}	1.1
4c	−21.74	1.96×10^{-16}	1.5
4d	−5.72	5.96×10^{-7}	3.4
4e	−7.24	6.31×10^{-7}	3.4
4f	−6.85	4.88×10^{-7}	3.8
4 g	−7.41	4.51×10^{-7}	2.0
4 h	−22.35	1.92×10^{-16}	1.0
4i	−19.81	2.32×10^{-16}	1.0
4j	−6.34	5.88×10^{-7}	2.1
4 k	−6.68	6.76×10^{-7}	2.1
4 l	−8.22	5.18×10^{-7}	2.4
4 m	−7.55	4.68×10^{-7}	2.3
4n	−22.64	1.96×10^{-16}	1.1
4o	−20.36	2.18×10^{-16}	1.0
4p	−6.78	6.20×10^{-7}	1.5
4q	−6.52	7.15×10^{-7}	1.8
4r	−7.89	6.32×10^{-7}	1.5

Table 3.
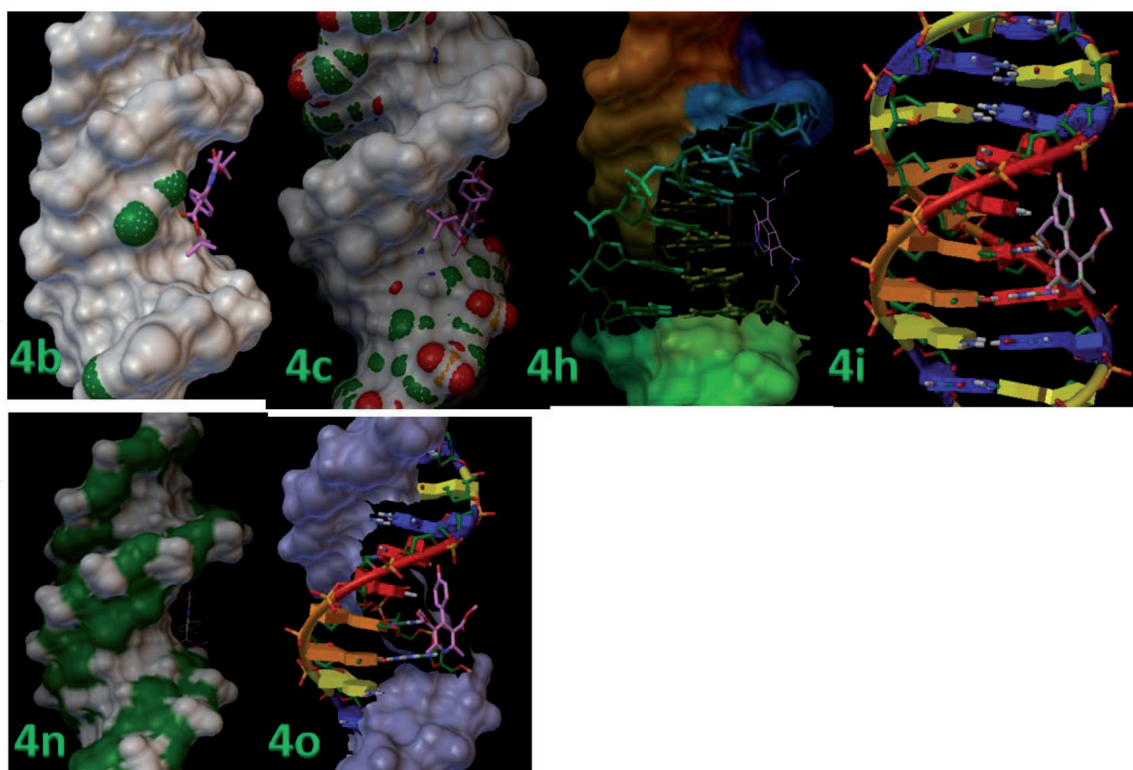*Molecular docking studies of 1,4-dihydropyridines.*

Figure 7.
1,4-DHP was successively docked within the DNA duplex of sequence d(CGCGAATTCGCG)$_2$ dodecamer (PDB ID: 1BNA).
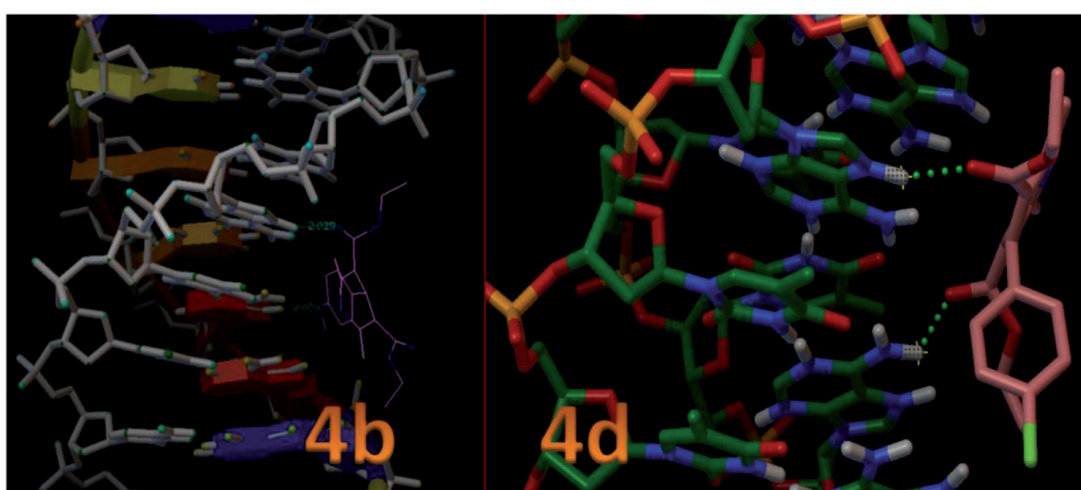

Figure 8.
Interaction of 1,4-DHP with DNA duplex of sequence d(CGCGAATTCGCG)$_2$ dodecamer (PDB ID: 1BNA).

the hydrogen bond interaction of **4c** and **4d** with key residues in active site inside the helical structure of DNA. In this model, it is clearly indicated that the compound **4c** formed hydrogen bonded between the –OH and N1 of thymine, which is DT7 and DT19 with the bond length of 2.02 and 2.05 Å respectively. Moreover, the other derivatives of 1,4-DHP formed less H-bond interaction with the DNA due to the orientation of aromatic ring involved in van der Waals interactions (Wireframe model) and flat hydrophobic regions of the binding sites of DNA (**Table 3**). These results demonstrated the in silico molecular docking studies of 1,4-DHPs with B-DNA suggested that 1,4-DHPs possess the potential to disturb hydrophobic and H-bond interactions thereby affecting the stability of attachment of B-DNA, and may be effective for cancer cell lines.

2. Experimental

2.1 Materials and method

All the chemicals used in the present study are of AR grade. Whenever analytical grade chemicals were not available, laboratory grade chemicals were purified and used. $AlCl_3$, $ZnCl_2$, $Yb(OTF)_3$, $FeCl_3$ and Zinc acetate obtained from Merck chemicals and are directly used without further purification. Melting points were recorded on an open capillary tube with a Buchi melting point apparatus and are uncorrected. ^{1}H- NMR spectra were obtained using a 400 MHz on a Bruker spectrometer (chemical shifts in δ ppm).

2.1.1 General procedure for the preparation of ZnO-Nps

In a typical synthesis process, zinc acetate dihydrate (1.1 g, 0.01 M) was dissolved in 20 mL of ethanol with constant stirring for 20 min. Then KOH (0.178 M) was added into the above mixed solution. After further stirring for 5 min, the reaction mixture was put into a CEM microwave synthesizer to irradiate for 10 min with the power set at 150 W, Temperature at 150°C and Pressure 150 C^0. After completion of reaction, the white precipitate was collected by centrifugation, washed twice with deionized water, ethanol and dried in vacuum oven at 60°C for 5 h.

Crystalline structure of the prepared ZnO-Nps was determined by powder X-ray diffraction (XRD). The strong intensity and narrow width of diffraction peaks indicate the high crystallinity of the prepared ZnO-Nps (**Figure 2a**). The peaks are indexed as 31.82° (100), 34.54° (002), 36.42° (101), 47.46° (102), 56.74° (110), 62.92° (103), 66.06° (200), 68.42° (112), 69.06° (201) and 78.82° (202) respectively. This revealed that the resultant nanoparticles were pure ZnO with a hexagonal structure (JCPDS 36-1451). No impurities could be detected in this pattern, which implies hexagonal phase ZnO nanoparticles could be obtained under the current microwave method. X-ray diffraction shows that metal oxide is pure ZnO having hexagonal structure. Sharpness of the peaks shows good crystal growth of the oxide particles. Average particle sizes of the ZnO have been calculated using from high intensity peak using Image J.

2.1.2 General procedure for the synthesis of 1,4-DHP by microwave method

A mixture of aromatic aldehydes **1a** (5 mmol), ethyl acetoacetate **2** (10 mmol), and ammonium acetate **3** (10 mmol) and ZnO (10 mol %) was taken in ethanol (20 mL) and the mixture was heated at microwave irradiation for 5 min (monitored by TLC after 5 min. interval). After 5 min, the reaction mixture was cooled to room temperature and then it was poured into cold water. The product was extracted with ethyl acetate. The organic layer was washed with brine, water and dried over anhydrous Na_2SO_4. The crude product thus obtained was recrystallized from EtOH to obtain desired product (**Figure 3**, **Table 1**).

4a. Di-tert-Butyl — 1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate

Solid: MP 180–182°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 18H), 2.30 (s, 6H), 4.83 (s, 1H), 5.58 (brs, 1H), 7.05-7.10 (m, 1H), 7.10-7.20 (m, 2H), 7.23-7.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.0, 28.4, 40.0, 80.0, 105.5, 125.6, 127.5, 128.5, 129.2, 143.0, 147.5, 167.3.

4b. Di-tert-butyl 4-(4-methoxyphenyl)-l,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate

Solid: MP 168–170°C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.40 (s, 18H), 2.25 (s, 6H), 3.86 (s, 3H), 4.81 (s, 1H), 5.51 (brs, 1H), 7.10-7.20 (d, 2H), 7.40-7.50 (d, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 19.8, 30.0, 41.0, 56.0, 81.0, 106.1, 125.6, 127.8, 135.0, 146.4, 153.2, 160.0, 167.5.

4c. Di-tert-butyl 4-(4-hydroxy-phenyl)-l,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate

Solid: MP 230–232°C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.36 (s, 18H), 2.28 (s, 6H), 4.90 (s, 1H), 5.56 (brs, 1H), 6.86-6.90 (d, 2H), 7.10-7.20 (d, 2H), 10.10 (s, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 24.5, 32.8, 45.3, 88.0, 108.4, 128.3, 131.0, 134.2, 134.6, 136.8, 148.4, 154.6, 172.6.

4d. Di-tert-butyl – 4-(4-fluorophenyl)-l,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate

Solid: MP 150–152°C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.43 (s, 18H), 2.30 (s, 6H), 4.81 (s, 1H), 5.50 (brs, 1H), 6.90-6.96 (d, 2H), 7.15-7.20 (d, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 20.0, 21.3, 38.9, 40.0, 79.8, 106.0, 114.2, 113.7, 125.4, 126.8, 129.2, 142.5, 143.2, 160.0, 162.5, 167.1.

4e. Di-tert-butyl 4-(4-chlorophenyl)-l,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate

Solid: MP 188–190°C; ^{1}U NMR (500 MHz, CDCl$_3$) δ 1.38 (s, 18H), 2.25 (s, 6H), 4.85 (s, 1H), 5.50 (brs, 1H), 6.80-6.85 (d, 2H), 7.00-7.08 (d, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 24.3, 33.4, 45.1, 86.2, 108.8, 128.9, 130.4, 133.5, 134.3, 136.1, 148.6, 151.6, 172.4.

4 f. Di-tert-butyl – 4-(4-nitrophenyl)-l,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate

Solid: MP 176–178°C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.38 (s, 18H), 2.30 (s, 6H), 4.86 (s, 1H), 5.55 (brs, 1H), 7.00–7.10 (d, 2H), 7.15–7.25 (d, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 20.5, 22.4, 38.6, 40.1, 79.6, 107.0, 114.5, 114.6, 126.2, 126.8, 129.6, 142.6, 144.6, 161.0, 167.1.

4 g. 2,6-Dimethyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester

Solid: MP 158–160°C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.20 (t, J = 9.7 Hz, 6H, 2CH$_3$CH$_2$), 2.28 (s, 6H, 2CH$_3$), 4.10 (q, J = 6 Hz, 4H, 2CH$_3$CH$_2$), 5.00 (s, 1H, CH), 5.75 (s, 1H, NH), 7.10–7.50 (m, 5H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 14.20 (C-3″), 19.5 (C-1″), 39.6 (C-4), 59.5 (C-2″), 104.1 (C-3 and C-5), 126.0 (C-4′), 127.8 (C-3′ and C-5′), 130.0 (C-2′ and C-6′), 143.8 (C-2 and C-6), 148.0 (C-1′), 168.0 (C-4″).

4 h. 2,6-Dimethyl-4-(4-methoxy-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester

Solid: MP 160–162°C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.21 (t, J = 7.0 Hz, 6H), 2.30 (s, 6H), 3.78 (s, 3H), 4.10 (q, J = 6.3 Hz, 4H), 4.95 (s, 1H), 5.60 (s, 1H), 6.80

(d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 14.2, 19.6, 38.8, 55.2, 59.8, 104.0, 115.0, 128.8, 140.0, 145.3, 156.7, 168.0.

4i. 2,6-Dimethyl-4-(4-hydroxy-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester

Solid: MP 238–240°C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.18 (t, J = 7.2 Hz, 6H), 2.28 (s, 6H), 4.05 (q, J = 6.6 Hz, 4H), 4.90 (s, 1H), 5.61 (s, 1H), 6.70 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 9.90 (s, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 14.0, 18.9, 39.0, 59.0, 103.0, 114.2, 128.3, 139.4, 144.2, 154.1, 167.6.

4j. 2,6-Dimethyl-4-(4-fluoro-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester

Solid: MP 152–154°C; 1H NMR (CDCl$_3$, 400 MHz): δ 1.10 (t, J = 7.2 Hz, 6H), 2.25 (s. 6H), 4.00 (q, J = 5.7 Hz, 4H), 4.88 (s, 1H), 5.68 (s, 1H), 6.80 (m, 2H), 7.15(m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 14.3, 19.7, 39.6, 60.1, 104.2, 114.4, 129.4, 129.7, 130.0, 143.5, 147.0, 167.5.

4 k. 2,6-Dimethyl-4-(4-chloro-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester

Solid: MP 153–155°C; 1H NMR (CDCl$_3$, 400 MHz): δ 1.12 (t, J = 7.2 Hz, 6H), 2.35 (s. 6H), 4.12 (q, J = 5.7 Hz, 4H), 5.10 (s, 1H), 5.82 (s, 1H), 7.50 (d, 2H), 8.16 (d, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 14.2, 18.6, 39.6, 60.0, 101.6, 116.8, 127.8, 129.3, 130.2, 144.8, 147.2, 166.8.

4 l. 2,6-Dimethyl-4-(4-nitro-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester

Solid: MP 178–180°C; 1H NMR (CDCl$_3$, 400 MHz): δ 1.26 (t, J = 7.2 Hz, 6H), 2.35 (s. 6H), 4.06 (q, J = 5.7 Hz, 4H), 5.08 (s, 1H), 5.76 (s, 1H), 7.48 (m, 2H), 8.02 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 14.2, 19.5, 39.6, 59.6, 104.2, 121.3, 1234.0, 128.4, 136.8, 144.5, 147.8, 148.8, 167.5.

4 m. 2,6-Dimethyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid dimethyl ester

Solid: MP 194–196°C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.30 (s, 6H, 2CH$_3$), 3.66 (s, 6H, 2CH$_3$), 5.00 (s, 1H, CH), 5.80 (b, 1H), 7.20-7.56 (m, 5H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 19.7, 38.7, 50.5, 105.5, 126.2, 127.0, 128.0, 144.1, 147.1, 168.2.

4n. 2,6-Dimethyl-4-(4-methoxy-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid dimethyl ester

Solid: MP 185–187°C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.28 (s, 6H, 2CH$_3$), 3.60 (s, 6H, 2CH$_3$), 3.78 (s, 3H), 4.89 (s, 1H, CH), 5.30 (b, 1H), 6.80–7.10 (m, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 19.5, 38.7, 55.1, 51.8, 104.4, 113.2, 128.9, 140.4, 143.4, 158.0, 167.7.

4o. 2,6-Dimethyl-4-(4-hydroxy-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid dimethyl ester

Solid: MP 228–230°C; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.26 (s, 6H, 2CH3), 3.63 (s, 6H, 2CH$_3$), 5.00 (s, 1H, CH), 5.40 (b, 1H), 6.95–7.20 (m, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 18.4, 38.4, 51.8, 103.1, 114.2, 128.4, 139.0, 144.2, 155.0, 167.6.

4p. 2,6-Dimethyl-4-(4-fluoro-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid dimethyl ester.

Solid: MP 170–172°C; 1H NMR (CDCl$_3$, 400 MHz): δ 2.32 (s, 6H, 2CH$_3$), 3.64 (s, 6H, 2CH$_3$), 4.98 (s, 1H, CH), 5.78 (b, 1H), 7.10 (t, 2H), 7.32 (t, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 19.5, 40.0, 51.0, 104.1, 114.4, 129.3, 130.0, 144.1, 145.3, 160.5, 162.3, 167.6.

4q. 2,6-Dimethyl-4-(4-chloro-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid dimethyl ester

Solid: MP 194–196°C; 1H NMR (CDCl$_3$, 400 MHz): δ 2.30 (s, 6H, 2CH$_3$), 3.66 (s, 6H, 2CH$_3$), 4.95 (s, 1H, CH), 5.76 (b, 1H), 7.15 (m, 2H), 7.36 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 19.5, 39.6, 51.1, 103.6, 113.8, 128.2, 130.0, 144.4, 146.2, 160.4, 167.8.

4r. 2,6-Dimethyl-4-(4-nitro-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid dimethyl ester

Solid: MP 210–212°C; 1H NMR (CDCl$_3$, 400 MHz): δ 3.00 (s, 6H, 2CH$_3$), 3.61 (s, 6H, 2CH$_3$), 5.08 (s, 1H, CH), 5.86 (b, 1H), 7.30 (m, 2H), 7.62 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 19.7, 40.1, 51.2, 103.2, 114.4, 128.7, 145.0, 146.1, 156.2, 167.6.

3. Conclusion

In conclusion, the present study describes the ZnO-NPs catalyzed synthesis of 1,4-dihydropyridines (**4a–r**) under microwave irradiation, giving excellent yields in shorter reaction time as compared to conventional method. All the synthesized compounds were evaluated for DNA photocleavage, SAR and DNA docking studies. DNA cleavage by gel electrophoresis method revealed that compounds (**4b** and **4c**) were found to cleave the DNA completely. The preliminary SAR study revealed that the –OCH$_3$ and –OH substituted compounds, were more favorable for activity, particularly at *-para* position of the phenyl ring. Docking studies indicated that one of the ester moieties of these compounds played a key role in their interactions with the DNA. However, the nature of reactive intermediates involved in the DNA cleavage by the 1,4-dihydropyridines has not been clear. Needless to say, further understanding the mechanism of biological action are still required in order to fully develop these compounds as potent anticancer drugs.

Acknowledgements

Author details

Tangali Ramanaik Ravikumar Naik
Vijayanagara Srikrishna Devaraya University (VSKU), Ballari, Karnataka

*Address all correspondence to: naikravi7@gmail.com

IntechOpen

References

[1] Raman DJ, Yus M. Asymmetric multicomponent reactions (AMCRs): The new frontier. Angewandte Chemie, International Edition. 2005;**44**:1602

[2] Domling A. Recent developments in isocyanide based multicomponent reactions in applied chemistry. Chemical Reviews. 2006;**106**:17

[3] Domling A, Ugi I. Multicomponent Reactions with Isocyanides. Angewandte Chemie, International Edition. 2000;**39**:3168

[4] Zhu J, Bienayme H, editors. Multicomponent Reaction. Weinheim: Wiley-VCH; 2005

[5] Tanaka K, Toda F. Solvent-free organic synthesis. Chemical Reviews. 2000;**100**:1025

[6] Li C-J. Organic reactions in aqueous media with a focus on carbon-carbon bond formations: A decade update. Chemical Reviews. 2005;**105**:3095

[7] Paul S, Bhattacharyya P, Das AR. One-pot synthesis of dihydropyrano[2,3-*c*] chromenes via a three component coupling of aromatic aldehydes, malononitrile, and 3-hydroxycoumarin catalyzed by nano-structured ZnO in water: A green protocol. Tetrahedron Letters. 2011;**52**:4636-4641

[8] Ghosh PP, Das AR. Nano crystalline ZnO: A competent and reusable catalyst for one pot synthesis of novel benzylamino coumarin derivatives in aqueous media. Tetrahedron Letters. 2012;**53**:3140

[9] Bhattacharyya P, Pradhan K, Paul S, Das AR. Nano crystalline ZnO catalyzed one pot multicomponent reaction for an easy access of fully decorated 4*H*-pyran scaffolds and its rearrangement to 2-pyridone nucleus in aqueous media. Tetrahedron Letters. 2012;**53**:4687

[10] Ghosh PP, Pal G, Paul S, Das AR. Design and synthesis of benzylpyrazolyl coumarin derivatives via a four-component reaction in water: Investigation of the weak interactions accumulating in the crystal structure of a signified compound. Green Chemistry. 2012;**14**:2691

[11] Jena A, Vinu R, Shivashankar SA, Giridhar M. Microwave assisted synthesis of nanostructured titanium dioxide with high photocatalytic activity. Industrial and Engineering Chemistry Research. 2010;**49**(20):9636-9643

[12] Sai R, Kulkarni SD, Vinoy KJ, Bhat N, Shivashankar SA. ZnFe$_2$O$_4$: Rapid and sub-100°C synthesis and anneal-tuned magnetic properties. Journal of Materials Chemistry. 2012;**22**:2149-2156

[13] Reddy KH, Reddy VVP, Shankar J, Madhav B, Kumar BSPA, Nageswar YVD. Copper oxide nanoparticles catalyzed synthesis of aryl sulfides via cascade reaction of aryl halides with thiourea. Tetrahedron Letters. 2011;**52**:2679-2682

[14] Cristau H-J, Cellier PP, Spindler J-F, Taillefer M. Highly efficient and mild coppercatalyzed N- and C-arylations with aryl bromides and iodides. Chemistry. 2004;**10**(22):5607-5622

[15] Mittapelly N, Reguri BR, Mukkanti K. Copper oxide nanoparticles-catalyzed direct Nalkylation of amines with alcohols. Der Pharma Chemica. 2011;**3**:180-189

[16] Chassaing S, Kumarraja M, Sido ASS, Pale P, Sommer J. Click chemistry in CuI-zeolites: The Huisgen [3 + 2]-cycloaddition. Organic Letters. 2007;**9**:883-886

[17] Hudson R, Feng Y, Varma RS, Moores A. Bare magnetic nanoparticles:

Sustainable synthesis and applications in catalytic organic transformations. Green Chemistry. 2014;**16**:4493-4505

[18] Meldal M, Tornoe CW. Cu-catalyzed azide-alkyne cycloaddition. Chemical Reviews. 2008;**108**:2952-3015

[19] Hein JE, Fokin VV. Copper-catalyzed azide-alkyne cycloaddition (CuAAC) and beyond: New reactivity of copper(I) acetylides. Chemical Society Reviews. 2010;**39**:1302-1315

[20] Jin T, Yan M, Yamamoto Y. Click chemistry of alkyne-azide cycloaddition using nano-structured copper catalysts. ChemCatChem. 2012;**4**:1217-1229

[21] Zhou Y, He T, Wang Z. Nanoparticles of silver oxide immobilized on different templates: Highly efficient catalyst for three-component coupling of aldehydeamine-alkyne. ARKIVOC. 2008;**xiii**:80-90

[22] Zhou X, Lu Y, Zhai L-L, Zhao Y, Liu Q, Sun W-Y. Propargylamines formed from three-component coupling reactions catalyzed by silver oxide nanoparticles. RSC Advances. 2013;**3**:1732-1734

[23] Kwon SG, Hyeon T. Colloidal chemical synthesis and formation kinetics of uniformly sized nanocrystals of metals, oxides, and chalcogenides. Accounts of Chemical Research. 2008;**41**:1696

[24] Hu A, Yee GT, Lin W. Magnetically recoverable chiral catalysts immobilized on magnetite nanoparticles for asymmetric hydrogenation of aromatic ketones. Journal of the American Chemical Society. 2005;**127**:12486

[25] Kawamura M, Sato K. Magnetically separable phase-transfer catalysts. Chemical Communications. 2006;**45**:4718

[26] Xia YN, Yang PD, Sun YG, Wu YY, Mayers B, Gates B, et al. One-dimensional nanostructures: Synthesis, characterization, and applications. Advanced Materials. 2003;**15**:353-389

[27] Comparelli R, Fanizza E, Curri ML, Cozzoli PD, Mascolo G, Agostiano A. UV-induced photocatalytic degradation of azo dyes by organic-capped ZnO nanocrystals immobilized onto substrates. Applied Catalysis B: Environmental. 2005;**60**:1-11

[28] Moghaddam FM, Saeidian H. Controlled microwave-assisted synthesis of ZnO nanopowder and its catalytic activity for *O*-acylation of alcohol and phenol. Materials Science and Engineering B. 2007;**139**:265-269

[29] Mirjafary Z, Saeidian H, Sadeghi A, Moghaddam FM. ZnO nanoparticles: An efficient nanocatalyst for the synthesis of β-acetamido ketones/esters via a multi-component reaction. Catalysis Communications. 2008;**9**:299-306

[30] Gupta M, Paul S, Gupta R, Loupy A. ZnO: A versatile agent for benzylic oxidations. Tetrahedron Letters. 2005;**46**:4957-4960

[31] Lietti L, Tronconi E, Forzatti P. Surface properties of zno-based catalysts and related mechanistic features of the higher alcohol synthesis by FT-IR spectroscopy and TPSR. Journal of Molecular Catalysis. 1989;**55**:43-54

[32] Sharghi H, Hosseini M. Solvent-free and one-step beckmann rearrangement of ketones and aldehydes by zinc oxide. Synthesis. 2002:1057

[33] Dhakshinamoorthy A, Visuvamithiran P, Tharmaraj V, Pitchumani K. Clay encapsulated ZnO nanoparticles as efficient catalysts for N-benzylation of amines. Catalysis Communications. 2011;**16**:15-19

[34] Sarvari MH, Sharghi H. Reactions on a solid surface. A simple, economical

and efficient Friedel-Crafts acylation reaction over zinc oxide (ZnO) as a new catalyst. The Journal of Organic Chemistry. 2004;**69**:6953

[35] Sarvari MH. ZnO/CH3COCl: A new and highly efficient catalyst for dehydration of aldoximes into nitriles under solvent-free condition. Synthesis. 2005;**5**:787

[36] Sarvari MH. Synthesis of β-aminoalcohols catalyzed by ZnO. Acta Chimica Slovenica. 2008;**55**:440

[37] Kim YJ, Varma RS. Microwave assisted preparation of cyclic ureas from diamines in the presence of ZnO. Tetrahedron Letters. 2004;**45**:7205

[38] Sarvari MH, Sharaghi H. ZnO as a new catalyst for N-formylation of amines under solvent-free conditions. The Journal of Organic Chemistry. 2006;**71**:6652

[39] Zhang M, Wang L, Ji H, Wu B, Zenge X. Cumene liquid oxidation to cumene hydroperoxide over CuO nanoparticle with molecular oxygen under mild condition. Journal of Natural Gas Chemistry. 2007;**16**:393-417

[40] Beydoun D, Amal R, Low G, McEvoy S. Role of nanoparticles in photocatalysis. Journal of Nanoparticle Research. 1999;**1**:439-458

[41] Kassaee MZ, Masrouri H, Movahedi F. ZnO-nanoparticle-promoted synthesis of polyhydroquinoline derivatives via multicomponent Hantzsch reaction. Monatshefte für Chemie. 2010;**141**:317-322

[42] Prasad GK, Ramacharyulu PVRK, Singh B, Batra K, Srivastava AR, Ganesan K, et al. Sun light assisted photocatalytic decontamination of sulfur mustard using ZnO nanoparticles. Journal of Molecular Catalysis A: Chemical. 2011;**349**:55

[43] Evans BE, Rittle KE, Bock MG, Dipardo RM, Freidinger RM, Whitter WL, et al. Methods for drug discovery: Development of potent, selective, orally effective cholecystokinin antagonists. Journal of Medicinal Chemistry. 1998;**31**:2235

[44] Muller G. Medicinal chemistry of target family-directed masterkeys. Drug Discovery Today. 2003;**8**:681

[45] Bocker H, Guengerich FP. Oxidation of 4-aryl- and 4-alkyl-substituted 2,6-dimethyl-3,5-bis(alkoxycarbonyl)-1,4-dihydropyridines by human liver microsomes and immunochemical evidence for the involvement of a form of cytochrome P-450. Journal of Medicinal Chemistry. 1986;**29**(9):1596-1603

[46] Sausins A, Duburs G. Synthesis of 1,4-dihydropyridines by cyclocondensation reactions. Heterocycles. 1988;**27**:269-289

[47] Goldman S, Stoltefuss J. 1,4-dihydropyridines: Effects of chirality and conformation on the calcium antagonist and calcium agonist activities. Angewandte Chemie International Edition in English. 1991;**30**:559-1578

[48] Bossert F, Meyer H, Wehinger E. 4-Aryldihydropyridines, a new class of highly active calcium antagonists. Angewandte Chemie International Edition in English. 1981;**20**:762-769

[49] Bossert F, Vater W. 1,4-dihydropyridines--a basis for developing new drugs. Medicinal Research Reviews. 1989;**9**(3):291-324

[50] Buhler FR, Kiowski W. Calcium antagonists in hypertension. Journal of Hypertension. 1987;**5**(3):S3-S10

[51] Reid JL, Meridith PA, Pasanisi F. Clinical pharmacological

aspects of calcium antagonists and their therapeutic role in hypertension. Journal of Cardiovascular Pharmacology. 1985;**7**:S18-S20

[52] Godfaid T, Miller R, Wibo M. Calcium antagonism and calcium entry blockade. Pharmacological Reviews. 1986;**38**:321-327

[53] Mannhold R, Jablonka B, Voigdt W, Schoenafinger K, Schravan K. Calcium- and calmodulin-antagonism of elnadipine derivatives: Comparative SAR. European Journal of Medicinal Chemistry. 1992;**27**:229-235

[54] Boer R, Gekeler V. Chemosensitizer in tumor therapy: New compounds promise better efficacy. Drugs of the Future. 1995;**20**:499-509

[55] Bretzel RG, Bollen CC, Maester E, Federlin KF. Nephroprotective effects of nitrendipine in hypertensive type I and type II diabetic patients. American Journal of Kidney Diseases. 1993;**21**:54-63

[56] Bretzel RG, Bollen CC, Maester E, Federlin KF. Trombodipine platelet aggregation inhibitor antithrombotic. Drugs of the Future. 1992;**17**:465-468

[57] Sridhar R, Perumal PT. A new protocol to synthesize 1,4-dihydropyridines by using 3,4,5-trifluorobenzeneboronic acid as a catalyst in ionic liquid: Synthesis of novel 4-(3-carboxyl-1*H*-pyrazol-4-yl)-1,4-dihydropyridines. Tetrahedron. 2005;**61**:2465

[58] Heravi MM, Behbahani FK, Oskooie HA, Shoar RH. Catalytic aromatization of Hantzsch 1,4-dihydropyridines by ferric perchlorate in acetic acid. Tetrahedron Letters. 2005;**46**:2775

[59] Moseley JD. Alternative esters in the synthesis of ZD0947. Tetrahedron Letters. 2005;**46**:3179

[60] Hantzsch A. Condensationprodukte aus aldehydammoniak und ketoniartigen verbindungen. Bernoulli. 1881;**14**:1637-1638

[61] Loev B, Snader KM. Oxidation dealkylation of certain dihydropyridines. The Journal of Organic Chemistry. 1965;**30**:1914

[62] Alajarin R, Vaquero JJ, Garcia JLN, Alvarez-Builla J. Synthesis of 1,4-dihydropyridines under microwave irradiation. Synlett. 1992:297

[63] Khadikar BM, Gaikar VG, Chitnavis AA. Aqueous hydrotrope solution as a safer medium for microwave enhanced Hantzsch dihydropyridine ester synthesis. Tetrahedron Letters. 1995;**36**:8083

[64] Ohberg L, Westman J. An efficient and fast procedure for the hantzsch dihydropyridine synthesis under microwave conditions. Synlett. 2001;**2001**(8):1296-1298

[65] Agarwal A, Chauhan PMS. Solid supported synthesis of structurally diverse dihydropyrido[2,3-*d*] pyrimidines using microwave irradiation. Tetrahedron Letters. 2005;**46**:1345

[66] Phillips AP. Hantzsch's pyridine synthesis. Journal of the American Chemical Society. 1949;**71**:4003

[67] Anderson GJR, Berkelhammer G. A study of the primary acid reaction on model compounds of reduced diphosphopyridine nucleotide. Journal of the American Chemical Society. 1958;**80**:992

[68] Dolly HS, Chimni SS, Kumar S. Acid catalysed enamine induced transformations of 1,3-dimethyl-5-formyluracil. A unique annulation reaction with enaminones. Tetrahedron. 1995;**51**:12775

[69] Breitenbucher JG, Figliozzi G. Solid-phase synthesis of 4-aryl-1,4-dihydropyridines via the Hantzsch three component condensation. Tetrahedron Letters. 2000;**41**:4311

[70] Kumar A, Maurya RA. Synthesis of polyhydroquinoline derivatives through unsymmetric Hantzsch reaction using organocatalysts. Tetrahedron. 2007;**63**:1946

[71] Wang L-M, Sheng J, Zhang L, Han J-W, Fan Z, Tian H, et al. Facile Yb(OTf)3 promoted one-pot synthesis of polyhydroquinoline derivatives through Hantzsch reaction. Tetrahedron. 2005;**61**:1539

[72] Ravikumar Naik TR, Bhojya Naik HS, Prakash Naik HR, Bindu PJ, Harish BG, Krishna V. Synthesis, DNA binding, docking and photoclevage studies of novel benzo[b][1,8] naphthyridines. Medicinal Chemistry. 2009;**5**(5):411

[73] Bindu PJ, Mahadevan KM, Ravikumar Naik TR. Sm(III)nitrate-catalyzed one-pot synthesis of furano[3,2c]-1,2,3,4-tetrahydroquinolines and DNA photocleavage studies. Journal of Molecular Structure. 2012;**1020**:142

[74] Bindu PJ, Mahadevan KM, Satyanarayan ND, Ravikumar Naik TR. Synthesis and DNA cleavage studies of novel quinoline oxime esters. Bioorganic & Medicinal Chemistry Letters. 2012;**22**(2):898

[75] Bindu PJ, Mahadevan KM, Naik TRR, Harish BG. Synthesis, DNA binding, docking and photocleavage studies of 2-chloro-3-quinolinyl-3-phenylpropen-2-ones. Medicinal Chemistry Communications. 2014;**5**:1708

[76] Ravikumar Naik TR, Shivashankar SA. Heterogeneous bimetallic ZnFe$_2$O$_4$ nanopowder catalyzed synthesis of Hantzsch 1,4-dihydropyridines in water. Tetrahedron Letters. 2016;**57**:4046-4049

[77] Janis RA, Silver PJ, Triggle DJ. Drug action and cellular calcium regulation. Aciv, Advances in Drug Research. 1987;**16**:309

[78] Lavilla R. Recent developments in the chemistry of dihydropyridines. Journal of the Chemical Society, Perkin Transactions 1. 2002:1141

[79] Kappe CO. Biologically active dihydropyrimidones of the Biginelli-type–a literature survey. European Journal of Medicinal Chemistry. 2000;**35**:1043

[80] Varache-Lemebge M, Nuhrich A, Zemb V, Devaux G, Vacher P, Vacher AM, et al. Synthesis and activities of a thienyl dihydropyridine series on intracellular calcium in a rat pituitary cell line (GH3/B6). European Journal of Medicinal Chemistry. 1996;**31**:547

[81] Alker D, Campbell SF, Cross PE, Burges RA, Carter AJ, Gardiner DG. Long-acting dihydropyridine calcium antagonists. 4. Synthesis and structure-activity relationships for a series of basic and nonbasic derivatives of 2-[(2-aminoethoxy)methyl]-1,4-dihydropyridine calcium antagonists. Journal of Medicinal Chemistry. 1990;**33**:585

[82] Reddy PR, Rao KS, Satyanarayana B. Synthesis and DNA cleavage properties of ternary Cu(II) complexes containing histamine and amino acids. Tetrahedron Letters. 2006;**47**(41):7311-7315

[83] Reddy DS, Hosamani KM, Devarajegowda HC. Design, synthesis of benzocoumarinpyrimidine hybrids as novel class of antitubercular agents, their DNA cleavage and X-ray studies. European Journal of Medicinal Chemistry. 2015;**101**:705-715

[84] Barton JK, Raphael AL. Photoactivated stereospecific cleavage of double-helical DNA by cobalt(III) complexes. Journal of the American Chemical Society. 1984;**106**:2466

[85] Sigman DS. Nuclease activity of 1,10-phenanthroline-copper ion. Accounts of Chemical Research. 1986;**19**:180

[86] Liu C, Zhou J, Xu H. Interaction of the copper(II) macrocyclic complexes with DNA studied by fluorescence quenching of ethidium. Journal of Inorganic Biochemistry. 1998;**71**:1-6

[87] Suvarna S, Krishna K, Kaushik SH, Rijesh K, Diwakar L, Reddy GC. Synthesis, anticancer and antioxidant activities of 2,4,5-trimethoxy chalcones and analogues from asaronaldehyde: Structureeactivity relationship. European Journal of Medicinal Chemistry. 2013;**62**:435-442

[88] Sun C, Aspland SE, Ballatore C, Castillo R, Smith AB, Castellino AJ. The design, synthesis, and evaluation of two universal doxorubicin-linkers: Preparation of conjugates that retain topoisomerase II activity. Bioorganic & Medicinal Chemistry Letters. 2006;**16**:104

[89] Zhang Y, Zheng W, Luo Q, Zhao Y, Zhang E, Liu S, et al. Dual-targeting organometallic ruthenium(ii) anticancer complexes bearing EGFR-inhibiting 4-anilinoquinazoline ligands. Dalton Transactions. 2015;**44**:13100-13111

[90] Tabassum S, Zaki M, Afzal M, Arjmand F. New modulated design and synthesis of quercetin-Cu(II)/Zn(II)-Sn2(IV) scaffold as anticancer agents: In vitro DNA binding profile, DNA cleavage pathway and Topo-I activity. Dalton Transactions. 2013;**42**(27):10029

[91] Taha M, Ismail NH, Khan A, Shah SAA, Anwar A, Halim SA, et al. Synthesis of novel derivatives of oxindole, their urease inhibition and molecular docking studies. Bioorganic & Medicinal Chemistry Letters. 2015;**25**(16):3285-3289