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DOI: 10.1039/C4RA06772J

Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Green Chemical Approach: Microwave assisted, titanium dioxide nanoparticles catalyzed, convenient and efficient C-C bond formation in the synthesis of highly functionalized quinolines and quinolinones

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

Highly efficient titanium dioxide nanoparticles (TiO_2 Nps) catalyzed, C-C bond formation under microwave irradiation and solvent less condition provided the highly functionalized quinolines and quinolinones in excellent yields

Introduction

The quinolines and quinolinones are nitrogen heterocylces[1] (Fig 1) which possess a wide range of biological activities including antibacterial[2], antifungal and analgesic,[3-9] antituberculosis,[10-16] antimalarial,[17-20] anti-inflammatory,[21] anticancer,[22] antibiotic,[23] anti-hypertensive,[24] and anti-HIV activities.[25-27] The halogen containing quinolines are a great source for further structural modifications[28-34]. Similarly the 2,3-position substituted quinolines have shown *in vivo* activities against *Leishmania donovani*[35-37] and are in preclinical development.[38-41] They display substantial antiviral activity in HIV-infected cells,[42-47] anticancer,[48-52] antimalarial activities.[53-65] In spite of their potential pharmacological activities and numerous synthetic reports,[66-75] including Combes[76], Camps, Knorr, Pfitzinger, Doebner-von Miller, Friedlander synthesis[77], Aza-Diels-Alder reactions, Lewis acids and organomatalic catalysis involving $BF_3.OEt_2$[78], $Yb(OTf)_3$[79], $RuCl_3.nH_2O/3PPh_3$[80], $SnCl_2.2H_2O$[81], $IrCl_3.3H_2O$/BINAP[82], still there is a continuous demand for their simple, convenient and environmentally benign synthetic approaches.

In recent years, a non conventional method such as microwave assisted solid support-solvent free organic synthesis is more attractive. And has shown tremendous advantages including simple reaction and easy work up procedure, rapid conversion, ambient reaction condition, eco-friendly, improved yields in comparison to conventional methods.[83] With our enormous interest in quinoline chemistry and environmentally benign synthesis,[84-97] in the present study the titanium dioxide nanoparticles, TiO_2 NP_s has been explored as a solid support in the C-C bond formation for the synthesis of highly functionalized quinolines and quinolinones (Scheme 1). The methodology also included the solvent free microwave irradiation to afford the desired products in high purity and yield in a short time.

Results and Discussion

Initially, the condensation of the quinolinone ketones (QNK), **1** or quinoline ketones (QK), **2** and aryl aldehydes, **3** or quinolines aldehydes, **4** was attempted using 5% ethanolic KOH under magnetic stirring at room temperature. The results indicated that 2-oxo-3-acetylquinoline, **1** and benzaldehyde, **3** have efficiently condensed to offer the desired quinolinone-aryl enones (QNAE), **5, 6** in good yield however in overnight stirring condition. Similarly, when the 2-methyl-3-acetyl quinoline, **2** was reacted with benzaldehyde, **3** the desired quinoline-arylenone (QNE), **7** was obtained in less yield even after long reaction period. Similar observations were inferred when QNK, **1** or QK, **2** reacted with 2-chloro-3-formyl quinoline, **4** to afford the desired quinolinone-quinoline enone (QNQE)**, 9** or quinoline-quinoline (QQE), **8, 10**.

Further, the above reactions were explored in the presence of other solvents including methanol, THF, DMF, 1, 4 - Dioxane or toluene and the weak inorganic bases including NaOH, K_2CO_3, Na_2CO_3, $CeCO_3$, KO*t*Bu or NaOMe. However, there is no improvement in the product yield. The reactions were then investigated using organic bases including piperidine, triethylamine, Cy_2NMe or diethyl amino pyridine. In solvents comprising of THF, DCM, 1,4-Dioxane, toluene or DMF at room temperature or under heating condition, the tested reactions offered desired product in a poor yield.

The 2-methyl-3-acetylqinoline was also reacted with benzaldehyde in the presence of $RuCl_3.nH_2O$ in solvents including ethanol, toluene, DMF, 1,4-dioxane, CH_3CN, isopropanol, n-butanol, isobutanol, etc. and the reaction did not offer better yield, though there was good conversion/improvement in the reaction. In order to further increase the product yield and increase the scope of the reaction, microwave irradiation has been utilized; however no good results were achieved.

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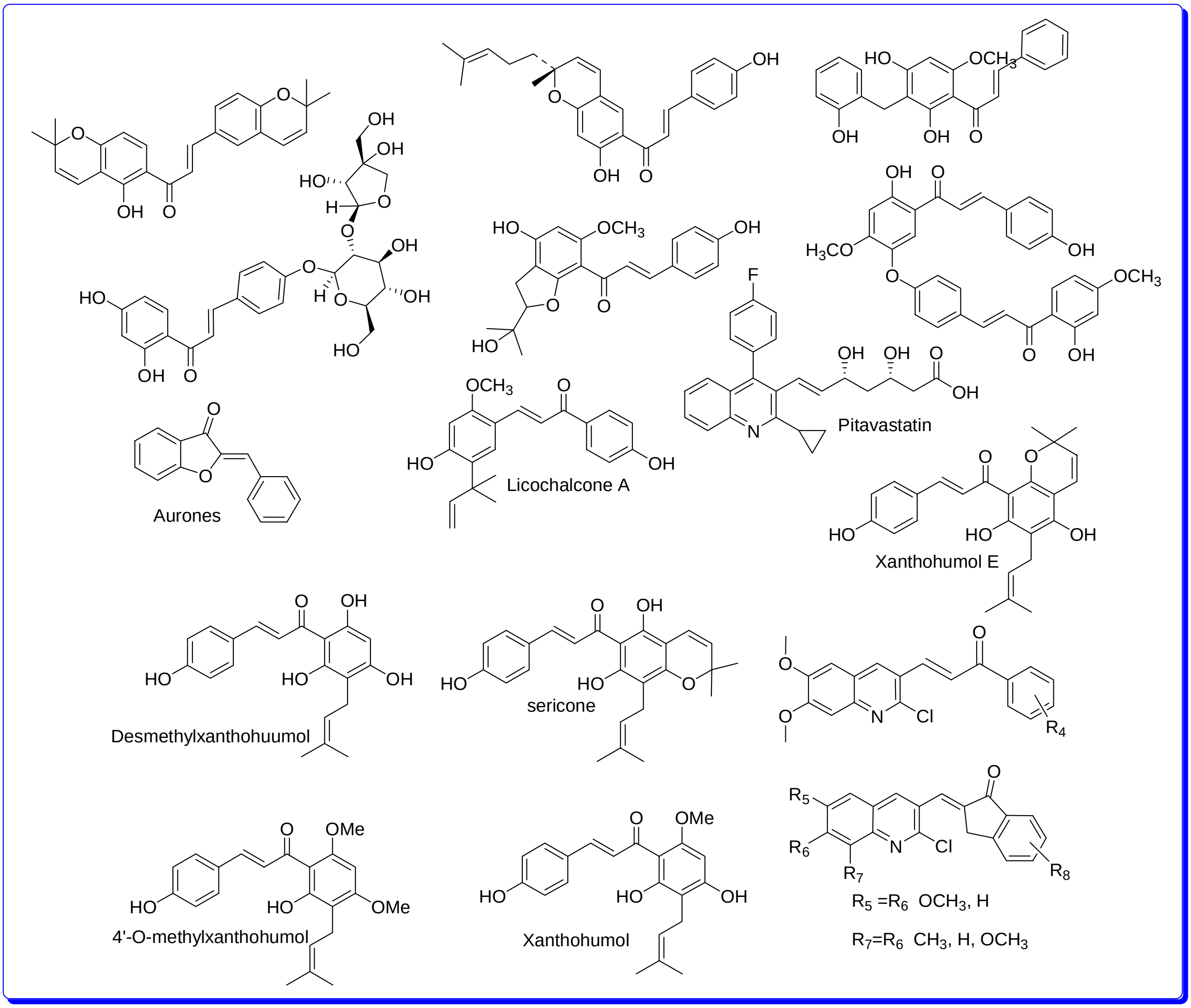

Fig 1 Biologically important 2- or 2,4-disubstituted quinolines and enones

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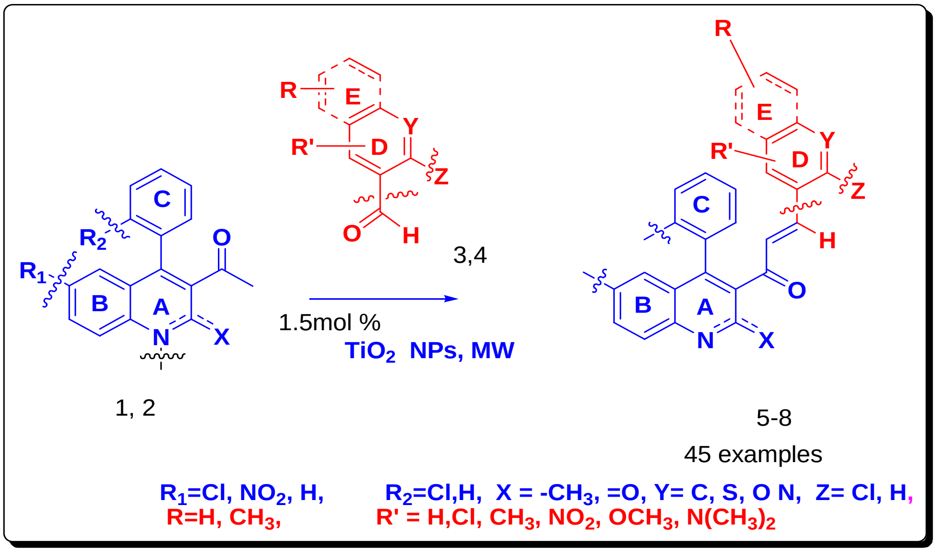

Scheme 1. General scheme for the highly functionalized quinolines and quinolinones

Further, the reactions were screened in the presence of catalysts including commercial TiO_2, ZnO, SnO or Ag_2O catalysts and 1mg NaOH in different solvents including toluene, DMF, 1,4-dioxane, ethanol, isopropanol, n-butanol or isobutanol under conventional heating conditions. Interestingly, among the tested catalyst, TiO_2 in ethanol was found to be the better catalyst-solvent system, however not satisfactory yield was obtained (Table 1, entry 1-7). With these result in hand, non-conventional approaches including microwave irradiation, mechano-chemical methods have been investigated. The result indicated that the microwave condition has found to increase the desired product.

Further studies on this commercial TiO_2 in different stoichiometric amount and 1mg NaOH in solvents including ethanol, isopropanol, n-butanol, 1,4-dioxane or methanol under refluxing condition as well as solvent free microwave irradiation has showed only negligible improvement in the reaction (Table 1, entry 1-7 in parentheses).The solvent free microwave assisted reaction using bulk TiO_2 catalysis was not impressive.

It is well known that in comparison to bulk TiO_2, their corresponding nanoparticles possess high surface area, uniform pore size and find tremendous applications in photocatalysis[98], solar cells[99], lithium-ion batteries[100], sensors[101] and catalyst supports as well as in many fields.

Hence we made further investigation on synthesized TiO_2 Nanoparticles in the conventional solvent refluxing condition and non-conventional microwave irradiation.

With the above objective in mind, the TiO_2 nanoparticles required for the present study were obtained through sol–gel process, employing 8 mL titanium (IV) tetraisopropoxide ($Ti[OCH(CH_3)_2]_4$; TIP) precursor. The precursor was slowly added drop wise to a mixture of 34.5 mL ethanol, 0.1 mL of nitric acid with continued magnetic stirring for 10 minutes. The mixture in turn was added drop wise to 150 mL distilled water with continued vigorous magnetic stirring at room temperature for 30 minutes for gelation. The gels were then washed with distilled water, dried at 80 °C, grinded to obtain nanocrystalline titania.

The as-obtained dried TiO_2 nanoparticles were characterized by powder X-ray diffraction (XRD), scanning electron microscopy (SEM), energy dispersive X-ray analysis (EDX), and high resolution transmission electron microscopy (HRTEM), selected area electron diffraction (SAED) and X-ray Photoelectron Spectroscopy (XPS) (Fig. 2).

Powder XRD pattern was collected using a Bruker/D8 advance X-ray diffractometer equipped with 2.2 KW Cu anode, ceramic X-ray tube (λ 1.5406 A). The crystalline anatase phases were confirmed by XRD patterns at 2θ = 25.43 (101), 37.80 (004), 47.90 (200), 54.54 (105) and 63.00. The lattice spacing (*d* spacing) i.e. 0.349, 0.238, 0.189 and 0.169 nm are in good agreement with the expected spacing for the (101), (004), (200) and (211) anatase planes. The broadening of the diffraction peaks is indicative of the small size of the obtained nanoparticles

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The SEM images were collected using a field-emission scanning electron microscope (Supra 55, Carl Zeiss) operated at an accelerating voltage of 5 kV. The SEM images reveal the crystalline, anatase titanium dioxide nanoparticles of 45-50nm.

The crystalline structure and morphology of nanocrystals have been investigated by high resolution transmission electron microscopy (HRTEM; Jem 2011, Jeol cop.) equipped with CCD 4k x 4k camera (Ultra Scan 400SP, gatan cop.) in the Busan KBSI. HR-TEM image showed agglomerated particles consisting of both large and average particles of diameter of 50-80 nm and 50 nm respectively. The clear lattice fringes confirm the crystalline nature and the lattice spacing (*d* spacing) of 0.34 nm confirms (101) plane of the anatase phase titania.

These results have been further confirmed by collecting a SAED pattern which shows discrete spots indicative of the presence of single-crystal nanocrystalline material. Similarly, the inter-planar spacing extracted from circles of most intense spots, are in good agreement with the expected spacing for the (101), (004), (200) and (211) anatase planes

The XPS study was performed using Thermo Fisher Scientific Inc (UK). Theta Probe XPS system equipped with monochromatic Al Kα X-ray source (hν=1486.6 eV) at a spot size of 400 m in diameter with charge compensation at Busan Center of Korea Basic Science Institute (KBSI). Emitted photoelectrons were detected by a multichannel detector at a takeoff angle of 90 ^{o} relative to the sample surface. The Avantage software provided by the manufacturer was used for controlling spectrometer and for analyzing the spectra. During the measurements, the base pressure in the ion-pumped analysis chamber was $4x10^{-10}$ mbar (UHV). Survey spectra were obtained at pass energy of 300 eV and a resolution of 1 eV, and high-resolution spectra were acquired at pass energy of 50 eV and a resolution of 0.1 eV. All of the obtained binding energy (BEs) was compensated with that of adventitious carbon (C1s) core level peak at 284.6 eV as a reference[102]

The XPS was employed for the identification of surface composition and the oxidation (valance) state analysis of the metals in the TiO_2 nanoparticles. The XPS spectrum of Ti 2p shows doublet peaks corresponding to the binding energy of Ti $2p_{1/2}$ and Ti $2p_{3/2}$ at 464.3 eV and 458.6 eV respectively. The splitting data (spin–orbital doublet splitting) between the Ti $2p_{1/2}$ and Ti $2p_{3/2}$ core levels is 5.7 eV, and an intensity ratio of 0.44 between the Ti $2p1_{/2}$ and Ti $2p_{3/2}$ is indicating a normal state of Ti^{4+} in the anatase $TiO_{2,}$ the peak of O 1s is centered at 529.9 eV, which is ascribed to O atoms bound to titanium (Ti^{4+}–O). The atomic percentage of Ti 2p and O 1s is found to be 33.78 and 66.22% respectively confirming the TiO_2 composition

Preliminary reaction was carried out using the TiO_2 Nps under convenient solvent refluxing condition. Among the tested solvents (DMF, DCM, toluene, ethanol, methanol, isopropanol, 1,4-dioxane, THF or CH_3CN), the toluene was found to be best solvent with a yield of 67%. Similarly under microwave irradiation condition, the toluene solvent offered 75% yield (Table 1, entry 7-22). However to our surprise, when the reaction was carried out under solvent free microwave irradiation in the presence of TiO_2 nanoparticles, offered the desired product with 85% yield (Table 1, entry 23). With this improvement in solvent free reaction condition, variation of TiO_2 nano loading was investigated next and an excellent yield of 95% desired product was obtained using the optimized amount of 1.5 mol% TiO_2 nanoparticles. The 500W was found to be the optimized microwave power (Table 2, entry 1-10)
.

This reaction involved a simple procedure and is scale upgradable as inferred from the tested 50g scale reaction which offered an excellent yield. The other advantages included are reusability of the catalyst (the catalyst was recovered by adding the excess of ethanol-ethyl acetate mixture after the completion of the reaction and filtering the catalyst, which was further cleaned by washing with ethyl acetate), lesser reaction time. The recycled catalyst was very much efficient for the successive 5 runs with negligible loss in product yield and catalytic activity. The crude products of the reaction were purified using column chromatography and are characterized by proton and carbon NMR, Mass and IR spectral techniques.

We were inspired by these interesting results under optimized conditions in the formation of enone from the reaction between quinolinone ketone, QK and aryl aldehyde. Further, an investigation of the reaction scope by changing the functional groups including heteroaryl aldehydes, chloroformyl quinolines containing substitutions at varied positions were attempted to afford the desired enones (Quinolinone-aryl enones, QNAE). Further, the differently substituted QNKs were examined for the TiO_2 catalyzed enone bond formation activated by NaOH (Table 3, quinolinone-aryl enones, QNAE quinolinone-quinoline enone, QNQE). Further, the 2-methyl quinoline ketones, QKs successfully finished the desired products quinoline-aryl enones, QAE and the quinoline-aryl enones, QQE in quantitative yields (Table 3, quinoline-aryl enones, QAE quinoline-quinoline enone, QQE).

It is noteworthy that when the QKs were microwave irradiated in the presence of 2-chloro-3-formylquinolines, water and TiO_2 NPs the quinoline-quinolinone enones, QQNE were obtained. This may be ascribed due to the initial hydrolysis of the 2-chloro-3-formylquinolines to 2-hydroxy-3-formylquinolines which underwent tautomerisation to 2-oxoquinolines as facilitated by the TiO_2 NPs. The oxo-derivative in turn condensed with the quinoline ketones to afford the quinoline-quinolinone enones, QQNE. Similarly we have recognized the chemoselectivity of the reaction as emplified in the formation of the E isomer in every case.

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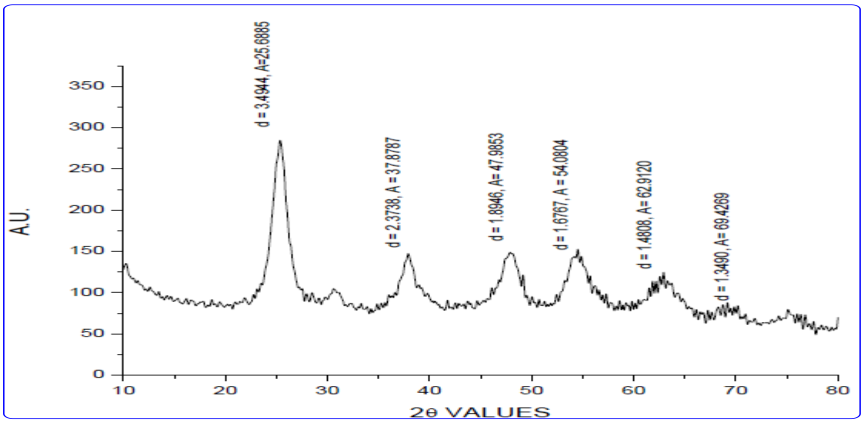

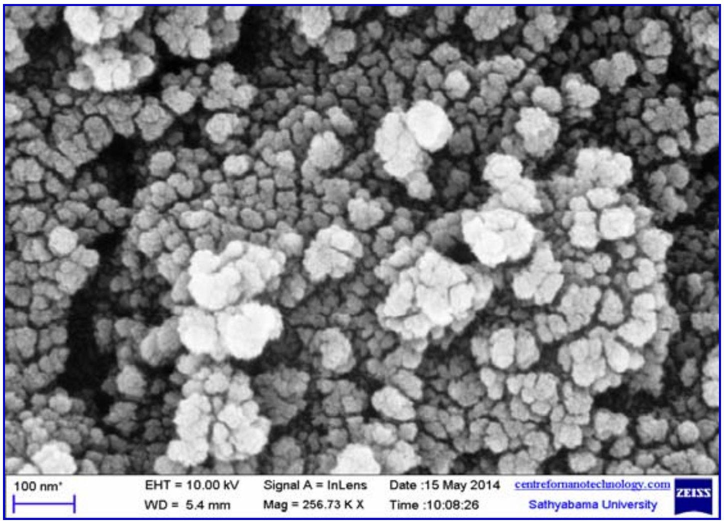

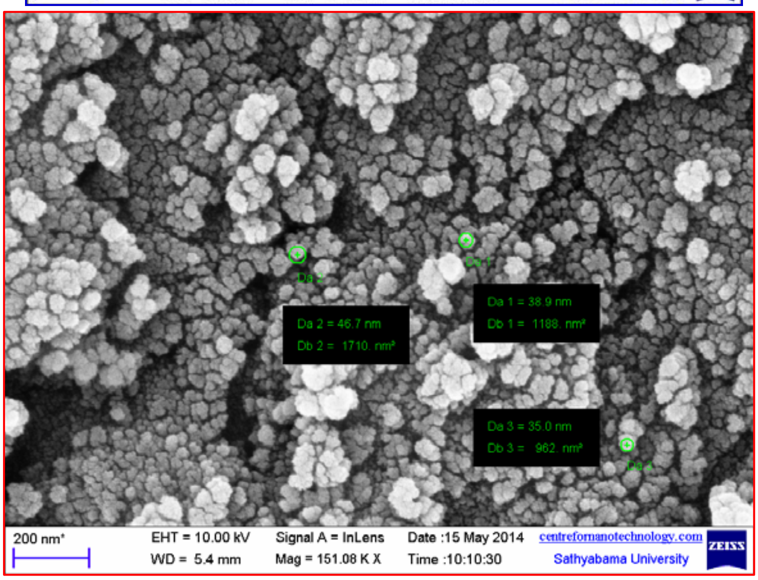

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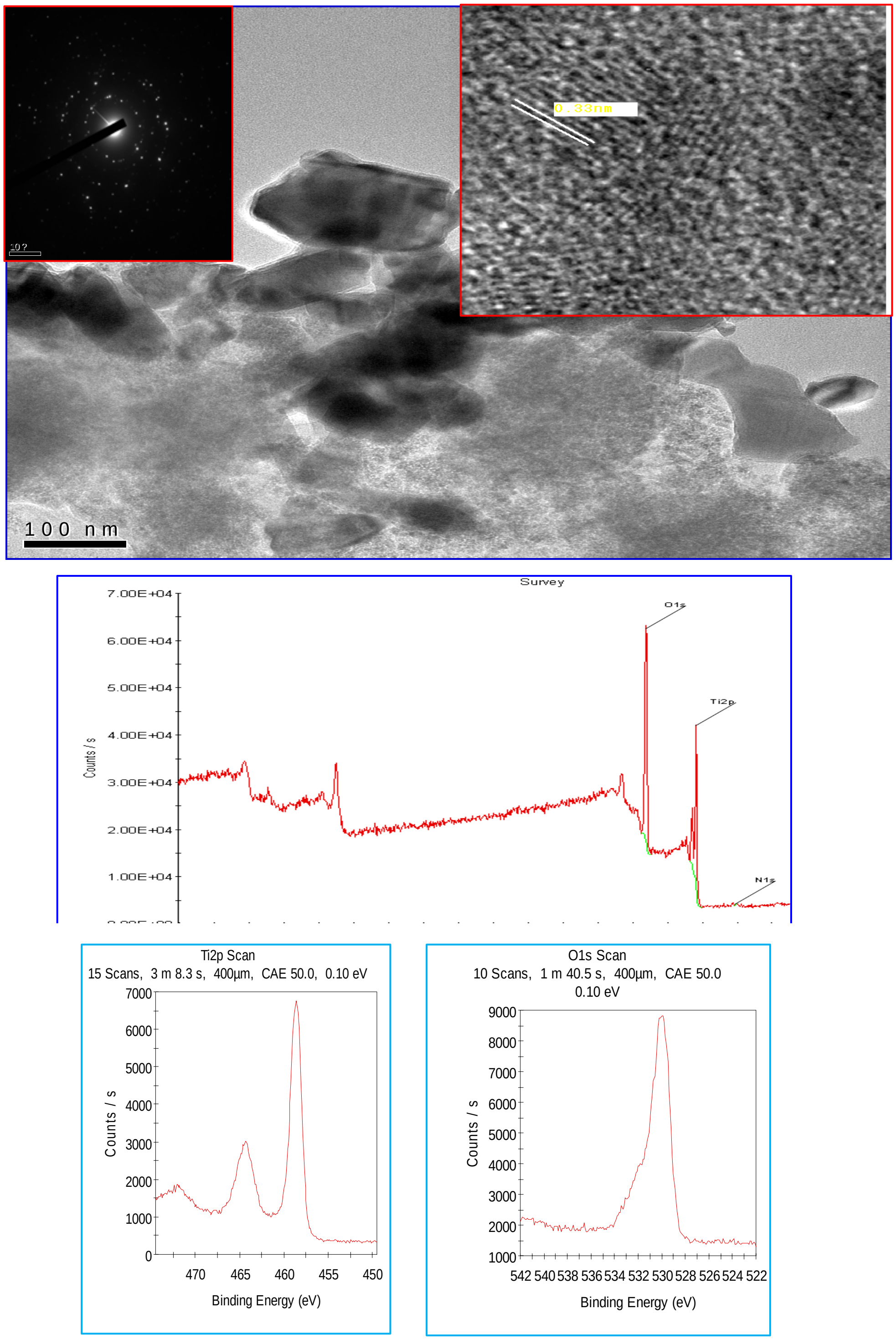

Fig 2 a)XRD pattern, b)SEM image; inset shows the particle size, c)TEM image; inset shows the SAED pattern d) XPS surveyo f TiO2 Nanoparticles; inset shows the Ti and O regional binding energy scans

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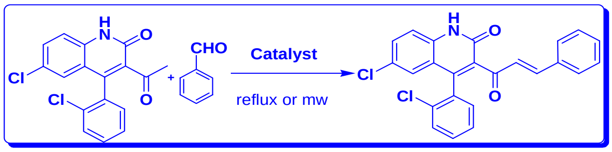
Table 1. TiO_2 catalysed conventional solvent refluxing and microwave assisted reactions[a]



Entry	Catalyst/ mol%	Solvent	Yield (%)
1	TiO_2 bulk/10	Ethanol	31 (4 3)[b]
2	TiO_2 bulk /5	Ethanol	24 (30)[b]
3	TiO_2 bulk /2.5	Ethanol	19 (25)[b]
4	TiO_2 bulk/10	Isopropanol	39 (51)[b]
5	TiO_2 bulk/10	n-Butanol	42 (50)[b]
6	TiO_2 bulk/10	Dioxane	21 (30)[b]
7	TiO_2 bulk/10	Methanol	Traces (20)[b]
8	TiO_2 NPs/10	Isopropanol	52 (60)[b]
9	TiO_2 NPs/10	n-Butanol	58 (67)[b]
10	TiO_2 NPs/10	Dioxane	43 (51)[b]
11	TiO_2 NPs/10	DMF	35 (40)[b]
12	TiO_2 NPs/10	DCM	Traces (15)[b]
13	TiO_2 NPs/10	THF	Traces(15) [b]
14	TiO_2 NPs/10	Toluene	67 (75)[b]
15	TiO_2 NPs/10	CH_3CN	43 (52)[b]
16	TiO_2 NPs/10	Ethanol	49 (55)[b]
17	TiO_2 NPs /5	Ethanol	42 (51)[b]
18	TiO_2 NPs /4	Ethanol	32 (40)[b]
19	TiO_2 NPs /3	Ethanol	21 (32)[b]
20	TiO_2 NPs /2	Ethanol	Traces (15)[b]
21	TiO_2 NPs /1	Ethanol	Traces (18)[b]
22	TiO_2 NPs /10	Methanol	Traces (20)[b]
23	TiO_2 NPs /10	Solvent free	70 (85)[b]

[a]Reaction Conditions: i) quinolinone (1 mmol, 1.0 equiv.), aldehydes (1.2equiv.), NaOH (1mg) in solvent (10 ml) at reflux temperature for 6h, [b]MW for 15min, 500W

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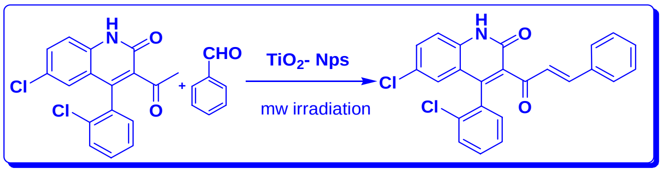
Table 2. . Solvent free, TiO_2 NPs catalysed microwave assisted reaction

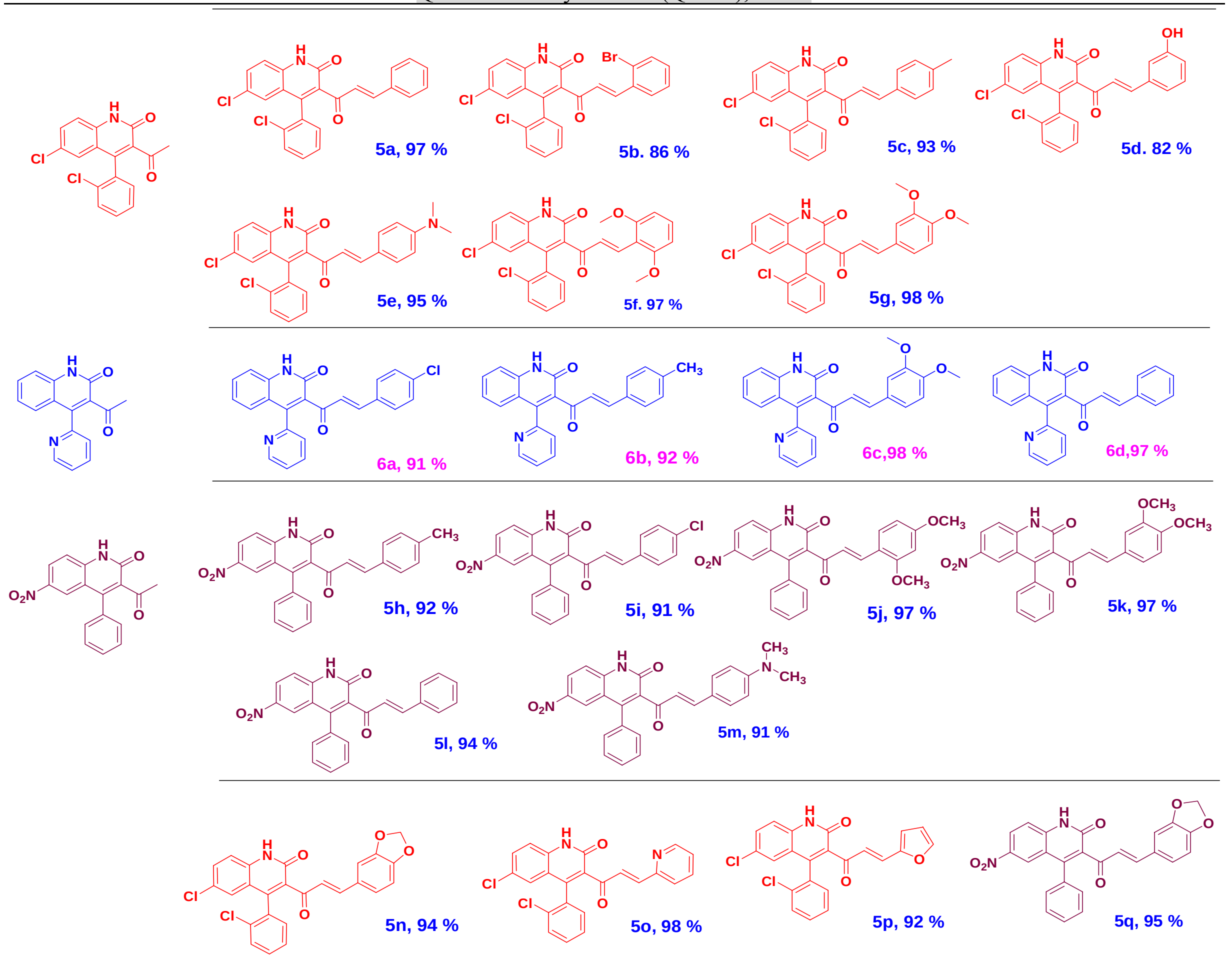


Entry	Catalyst/ mol %	Watts, w	Yield (%)
1	TiO_2/10	500	85
2	TiO_2/5	500	87
3	TiO_2/4	500	91
4	TiO_2/3	500	92
5	TiO_2/2	500	95
6	TiO_2/1.5	500	95
7	TiO_2/1	500	92
8	TiO_2/10	300	79
9	TiO_2/10	700	65
10	TiO_2/10	900	Decomposed

[a]Reaction Conditions: i) quinolinone (1 mmol, 1.0 equiv.), aldehydes (1.0 equiv.), NaOH (1mg) microwave irradiation (15min, unless otherwise stated), [b] NaOH1 mg : 1 %, 2 mg : %, 5mg : %, 7 mg: %, 10mg: %

Table 3 Synthesis of Highly functionalized chalcones[a]

Quinolinone-aryl enones (QNAE), **5** or **6**



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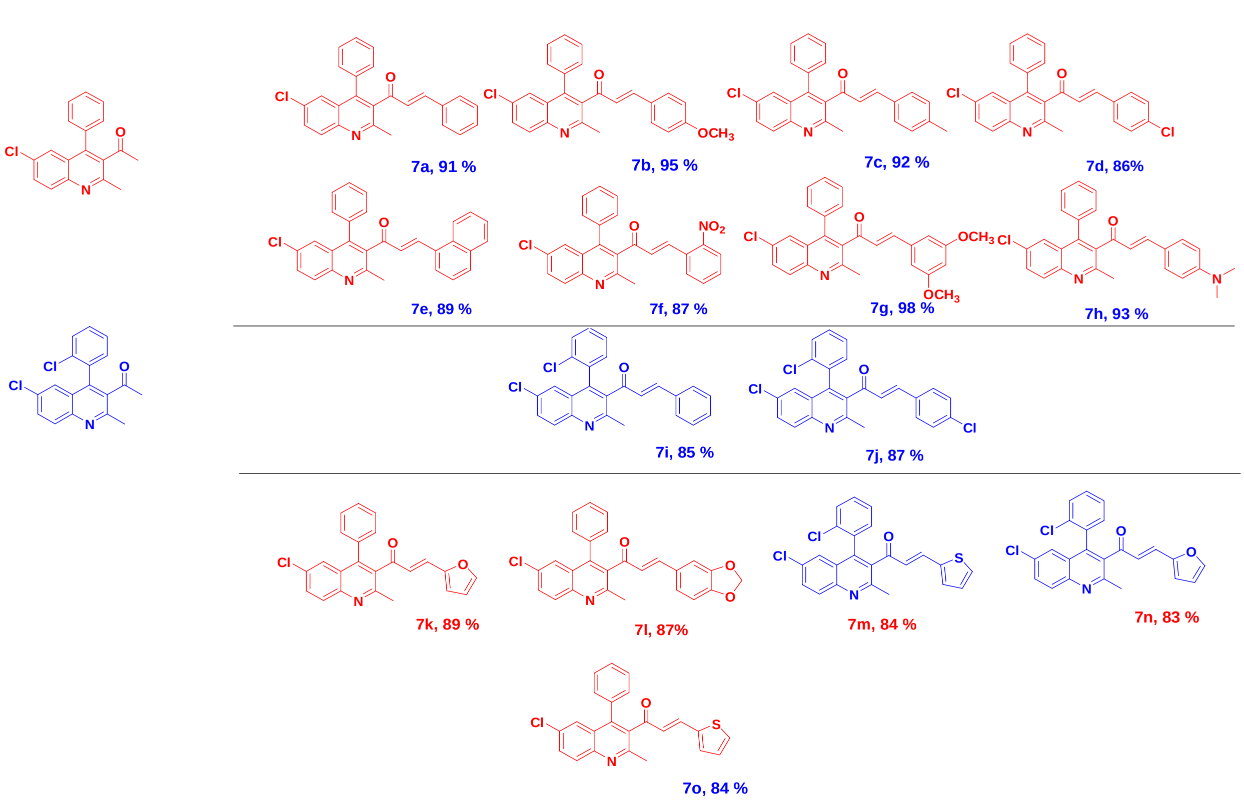
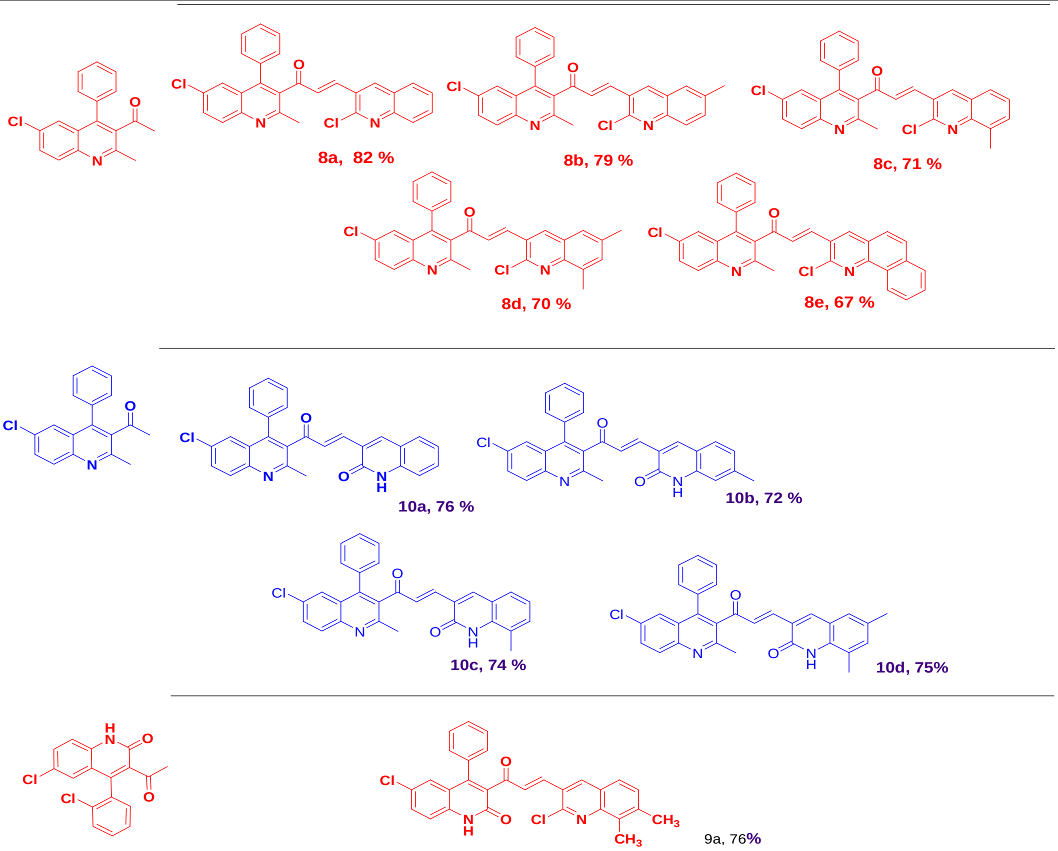
Quinolines-aryl enones (QAE), **7**



Quinoline-quinoline enones (QQE),**8** Quinoline-quinolinone enones (QQNE), **10** and Quinolinone-quinoline enones (QNQE), **9**



5 Reaction Conditions: i) quinolinone (1 mmol, 1.0 equiv.), aldehydes (1.0 equiv.), unless otherwise stated 15min microwave irradiation

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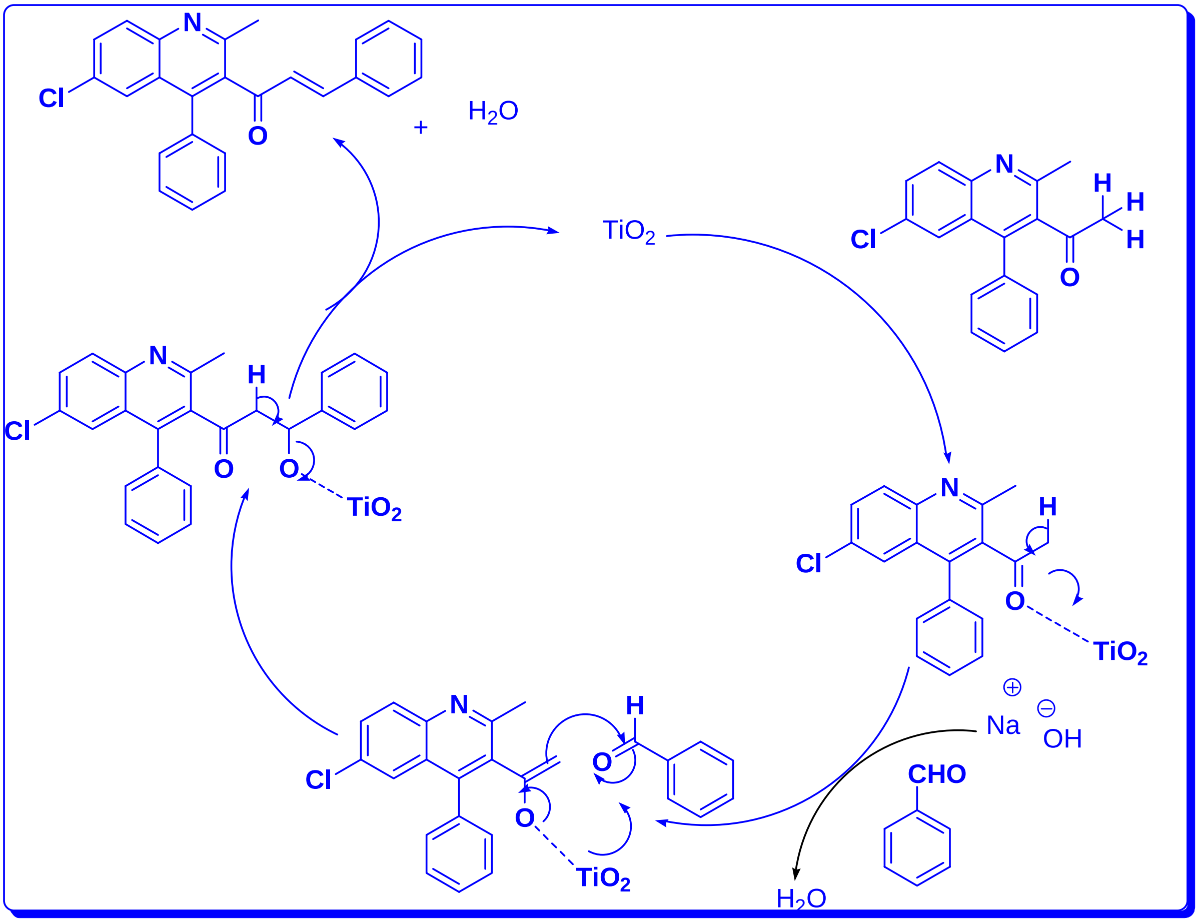
We propose the following mechanism for condensation (Scheme 2).

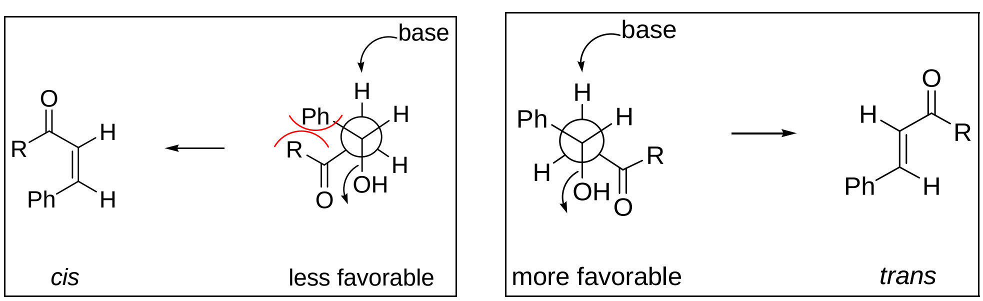


Scheme 2 Possible mechanism of the reaction

The reaction gets initiated by the TiO_2 nanoparticles which activate the carbonyl group of the ketones and which in turn get enolized to the E-enolate due to its no bulky substituent in the presence of NaOH. Then the enolate attack the aldehydes functionality resulting in the nucleophilic addition product. The intermediate formed is further activated by TiO_2 to facilitate with the elimination of water molecule and to afford the desired enones. In the transition state for elimination to a *syn* double bond, an unfavorable steric interaction between the ketone substituent R and the phenyl group occurs, however such interaction was absent in the transition state for elimination to the most favorable *anti* double bond. The TiO_2 released further activates successive molecules to afford the desisredproduct in good yield and purity.

Conclusions

In summarize, an efficient synthesis of highly functionalized quinolines and quinolinones utilizing microwave irradiatiation and TiO_2 nanoparticles with lesser loading and reaction time period is reported. Consequently, this method should find applications in pharmaceuticals, functional materials owing to the unique property of quinolines and quinolinones



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Acknowledgements

The authors wish to express their gratitude to the VIT University Vellore for Major research initiative support and facilities and SIF-VIT for their support of NMR, GCMS and IR facilities, Sathyabama University, India for SEM facilities and KBSI, Busan Center, South Korea for Mass, TEM and XPS facilities. This work was supported by the grant No. R0001026 from the Ministry of Trade, Industry & Energy and Busan Metropolitan City, Korea.

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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DOI: 10.1039/C4RA06772J

Green Chemical Approach: Microwave assisted, titanium dioxide nanoparticles catalyzed, convenient and efficient C-C bond formation in the synthesis of highly functionalized quinolines and quinolinones

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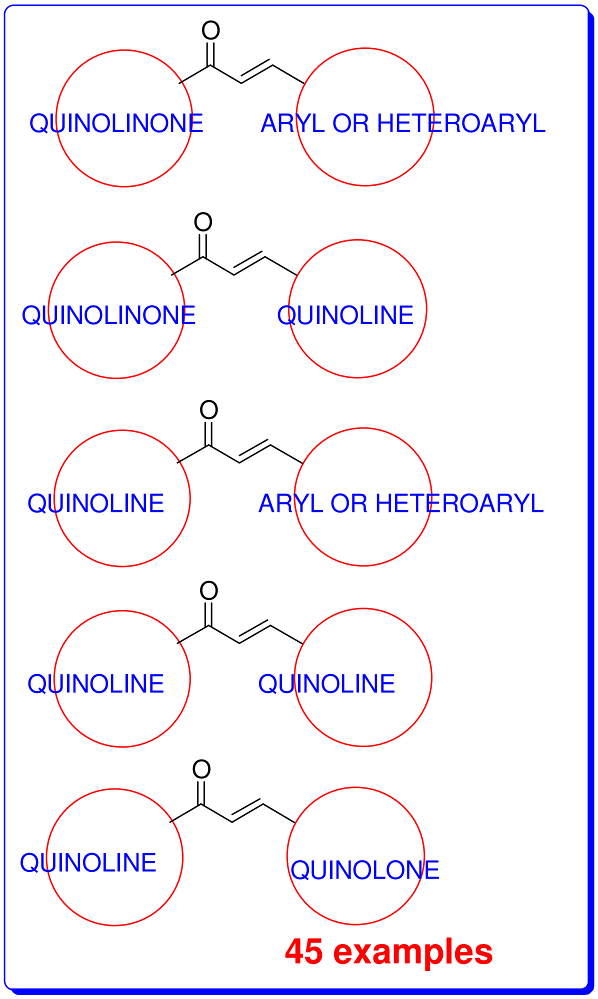

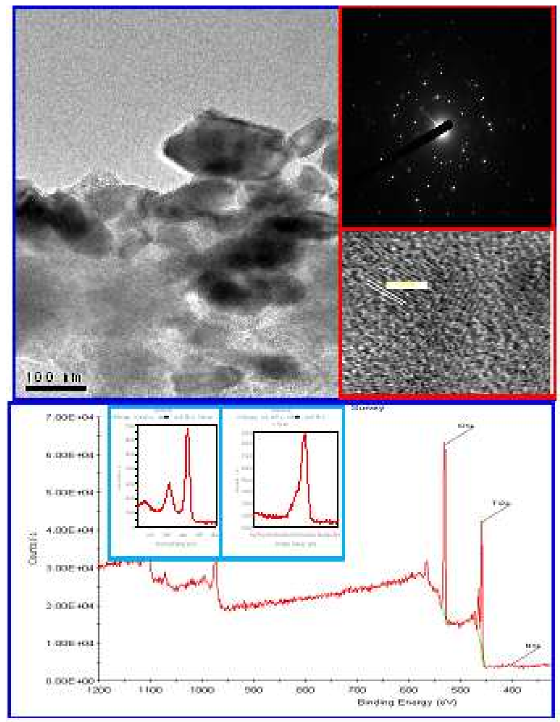

- TiO2 Nanoparticles as an efficient catalyst
- Microwave irradiation
- Simple procedure, easy work up
- Highly functionalized quinolines and quinolones