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Preparation, characterization and catalytic application of nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> having high TON and TOF for non-toxic and sustainable synthesis of dihydroquinazolinone derivatives

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#### Introduction:

Major attention in catalytic routes for the synthesis of complex organic molecules has been determined by the economically favourable and environment aware market. Discovery of selective and efficient catalysts in industrial and academic field have gained lots of attention. An efficient catalyst shows enormous influence on minimizing the manufacturing costs as well as waste disposal. Practical application of catalysts in aqueous medium is limited because of difficulties in catalyst separation and recycling. Several approaches like nanofiltration, centrifugation, and newer separation techniques based on liquid-liquid phase separation, including supercritical solvents, polymeric supports, ionic liquids have been applied since years to evade difficulties in catalyst separation.<sup>1</sup> Each separation technique has its own limitations like higher cost, less efficiency, generation of unwanted wastes etc. Because of these issues, heterogenization of homogeneous catalysts on solid supports has gained tremendous attention.<sup>2</sup> Magnetic nanoparticles (NPs) because of its higher surface area and tremendous response to an applied magnetic field have achieved incredible attention as catalyst supports. <sup>3</sup>

Post synthetic surface modifications of magnetic nanoparticles provide enviable chemical functionality and leads to generation of catalytic sites on the surface of nanoparticles. Moreover their insoluble and magnetic nature leads to a trouble free separation of the nanocatalysts from the reaction vessel by using an external magnetic field. These surface

modified nanocatalysts acts as bridge between homogenesous and heterogeneous catalysis, thus conserving the advantageous attributes of both the systems. This application requires specific ligand to be immobilized on the surface of the nanoparticles. We have chosen dopamine as desired ligand mainly because of two reasons: i) according to Langmuir isotherms, desorption of dopamine molecules from metal oxide surface is less favourable than its absorption <sup>4</sup> thereby reducing the chances of its leaching from the surface and ii) dopamine transforms the un-coordinated iron surface sites back to bulk-like lattice site with octahedral geometry for oxygen coordinated iron which leads to a tight binding with iron oxide.<sup>5</sup> Previously many research groups have incorporated many metals and metal salts like Pd, Cu, Ni, RuCl<sub>3</sub> etc following these techniques and applied that in various organic transformations.<sup>6</sup> Among various metals that have been applied in organic synthesis, tin received tremendous attention due to its low cost, suitable activity and lower toxicity.<sup>7</sup> Moreover tin dioxide  $(SnO_2)$  is a resourceful metal oxide because of its two exclusive characteristics; which are, existence of oxygen vacancy defects and variation in valence state.<sup>8</sup> Because of these reasons SnO<sub>2</sub> has found extensive applications in catalysis, electrochromic devices, transparent conductive electrodes, antistatic coating and solar energy conversion.<sup>9</sup> However, owing to poor thermal stability of the pure tin oxide, its application is restricted to a greater extent in catalysis.<sup>10</sup> So, several amendments have been proposed, of which addition of metal and non-metal oxides to tin oxide is an effectual strategy.<sup>11</sup> We herein, incorporated SnO<sub>2</sub> on the surface of magnetic nanoparticles which not only makes its handling easier but also increases its catalytic activity thereby increasing its recyclability and reusability.

Nitrogen containing heterocycles like quinazolinones are pivotal sub-units of a large number of biologically active compounds which possess several medicinal activities like antihypertensive, antiinflamatory, antibacterial, anticancer, antimicrobial, antitumour etc.<sup>12</sup>

Although many methodologies for the synthesis of dihydroquinazolinone derivatives have been already developed <sup>13</sup> but most of these methodologies suffer certain drawbacks like multi-step process, elongated time, costly catalyst, tedious workup procedure, costly syntheses.<sup>14</sup>

As a part of our continuing efforts towards synthesis of heterocycles using heterogeneous recyclable catalyst<sup>15</sup> we herein discuss a procedure for the synthesis of novel nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> catalyst and applied that in aqueous medium for the synthesis of biologically active dihyroquinazolinone derivatives. We also carried out a gram scale reaction to verify the industrial scope of our methodology.

#### **Results and discussions:**

#### Preparation of catalyst:

Firstly we focused towards synthesis of Fe<sub>3</sub>O<sub>4</sub> nanoparticles (NPs) by co-precipitation method using Fe<sup>+2</sup> and Fe<sup>+3</sup>salts.<sup>16</sup> Characterization of the synthesized nanoparticles was then carried out by SEM, TEM, EDX and powder XRD analyses (Fig. SI 1). Following that Fe<sub>3</sub>O<sub>4</sub> NPs were coated with dopamine by simply ultrsonicating a mixture of dopamine hydrochloride and Fe<sub>3</sub>O<sub>4</sub> NPs in water for 2 h.<sup>17</sup> Final encapsulation of SnO<sub>2</sub> on synthesized nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA was done by stirring an aqueous solution of SnCl<sub>2</sub>.2H<sub>2</sub>O with nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA at room temperature for 24 h (Scheme 1).





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#### **Characterization of catalyst:**



Fig. 1: Comparative FT-IR spectra of nano-Fe<sub>3</sub>O<sub>4</sub>, nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA and nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub>

Firstly to get information regarding functional groups, FT-IR analyses of nano-Fe<sub>3</sub>O<sub>4</sub>, nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA and nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> were carried out and compared with each other. Comparative FT-IR spectra of nano-Fe<sub>3</sub>O<sub>4</sub>, nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA and nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> (Fig. 1) shows prominent peaks above 3400 cm<sup>-1</sup> and 1631-1632 cm<sup>-1</sup> which was found in all three spectra. These peaks correspond to -OH stretching and H-O-H bending vibrations of moisture absorbed on the surface of materials.<sup>18</sup> Peak at around 1631 cm<sup>-1</sup> became more intense in spectra of nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA and nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub>, this may be because of the aromatic -C=C- stretching of benzene ring present in dopamine molecule. Peaks in region of 670-595 cm<sup>-1</sup> correspond to Fe-O stretching frequency proving presence of Fe<sub>3</sub>O<sub>4</sub> NPs in all the three catalysts. On careful surveillance of FT-IR spectra of nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> a peak at around 576 cm<sup>-1</sup> was observed which is because of Sn-O stretching vibration.19

After getting information regarding functional groups, in order to gather information regarding size and morphology of nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub>, TEM (Transmission Electron Microscopy) analysis of synthesized catalyst was carried out. From TEM image [Fig 2(a)] we observed that NPs are spherical in shape along with rod like shapes. The average size of NPs

was found to be ~20 nm. In order to confirm the chemical composition, a high-resolution TEM (HRTEM) image was taken and is shown in Fig. 2 (b). The HRTEM image consists of the high-resolution images of NPs and a portion of the rod-like shapes. In both spherical and rod shaped nanoparticles, the inter planer spacing (*d*) of the crystal planes was found to be same (0.24 nm). The values of *d* spacing correspond to the (222) plane of Fe<sub>3</sub>O<sub>4</sub>. Therefore, HRTEM analysis confirms that spherical as well as rod like NPs are composed of Fe<sub>3</sub>O<sub>4</sub>. The selected area electron diffraction (SAED) pattern of the NPs is shown in Fig. 2(c). Due to diffraction from various planes of NPs, SAED showed various diffraction spots. We have assigned a set of the diffraction pattern (highlighted using yellow circles) to the diffraction planes of Fe<sub>3</sub>O<sub>4</sub>, corresponding to the zone axis [111]. This proves that nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> is crystalline in nature.



Fig. 2: (a) TEM image of nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> (b) HRTEM images of NP's and (c)

#### SAED pattern

Elemental investigation of synthesized catalyst was estimated by Energy dispersive X-ray (EDX) analysis (Fig. 3). EDX spectrum clearly showed presence of iron (Fe), tin (Sn), oxygen (O), nitrogen (N) and carbon (C). Peaks of gold (Au) are present in spectrum because while doing analyses coating of sample was done with gold. Scanning electron microscopy

(SEM) image (Fig. 4) of synthesized nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> was also taken and it was found to be in accordance with that of TEM image thereby showing spherical shape.



#### Fig. 3: EDX of nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub>

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![](_page_6_Figure_5.jpeg)

After concluding successful incorporation of tin (Sn) on metal nanoparticles it is very important to know in what form it got attached? For this an XPS (X-ray Photo electron Spectroscopy) analysis of synthesized catalyst was carried out. Overall survey spectrum indicated presence of iron (Fe), Oxygen (O) and tin (Sn) [Fig. 5 (a)]. Fig. 5(b) and 5 (c) shows the binding energy curve for  $O_{1s}$ , Sn  $3d_{5/2}$  and Sn  $3d_{3/2}$  at around 430.5 eV, 495.3 and 486.9 eV respectively. From literature survey it was found that the values are specific for SnO<sub>2</sub>.<sup>20</sup> This lead us to the conclusion that tin (Sn) is bonded to nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA as SnO<sub>2</sub>.

![](_page_6_Figure_7.jpeg)

![](_page_7_Figure_3.jpeg)

Fig. 5: XPS spectra of nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> (a) Survey spectra (b) 1s peak of O and (c) Sn  $3d_{5/2}$  and Sn  $3d_{3/2}$  peaks

Prepared nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> was also characterized by Powder XRD (PXRD) analysis. Fig. 6 shows the PXRD pattern of the nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub>. The XRD pattern consist a two sets of diffraction peaks. One set is at  $(2\theta =)$  30.17°, 35.63°, 37.18°, 43.02°, 53.35°, 57.20°, and 62.83° which are indexed to the (220), (311), (400), (422), (511) and (440) planes of cubic structure of Fe<sub>3</sub>O<sub>4</sub>, having lattice indices of a = b = c = 8.38 Å (JCPDS 19-629).<sup>21</sup> Another set of diffraction peaks at  $(2\theta =)$  34.6°, 53.36°, 59.06°, and 61.20° corresponds to the (101), (21 1), (002), and (310) planes of tetragonal rutile structure of SnO<sub>2</sub> having lattice constants of a = b = 4.737 Å and c = 3.186 Å (JCPDS 41-1445).<sup>22</sup> The strong peaks prove that nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> is crystalline in nature which agrees with TEM results.

![](_page_7_Figure_6.jpeg)

Fig. 6: Room temperature XRD pattern of the NP's of Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub>

VSM analysis indicated ferromagnetic nature of nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub>.<sup>23</sup> Its saturation magnetization was found to be 32.077 emu/g (Fig.7). Even though it is less than that of bare nano-Fe<sub>3</sub>O<sub>4</sub>.<sup>24</sup> because of surface coating but still it is appreciably magnetic for catalyst to be recycled by an external magnet.

![](_page_8_Figure_3.jpeg)

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**Fig. 7:** Room temperature VSM results of the nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> (inset picture is a zoomed portion of VSM data showing the hysteresis loop)

At last, to gain information regarding thermal stability of  $SnO_2$  incorporated nanoparticles, a TGA (Thermo Gravimetric Analysis) was also performed. TGA curve (Fig. 8) indicated weight loss which starts at around 42  $^{0}C$  and it may correspond to loss of moisture trapped on catalyst surface. There is also another degradation which starts around 209  $^{0}C$  and may correspond to the loss of  $SnO_2$  molecule. This proves that the synthesized catalyst is thermally stable below 200  $^{0}C$  and can be easily applied in any reactions below this temperature.

![](_page_8_Figure_6.jpeg)

#### Fig. 8: TGA curve of nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub>

An ICP-AES (Inductively coupled plasma atomic emission spectroscopy) analysis was also performed to determine the amount of tin (Sn) attached on the surface of nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA and it was found to be 1.027 %.

#### **Standardization of reaction parameters:**

After synthesis and characterization of nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub>, we applied it for the synthesis of dihydroquinazolinone derivatives. In order to confirm nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> to be crucial for rendering the above said reaction we set up a reaction with isotoic anhydride (**1**, 1mmol), NH<sub>4</sub>OAc (**2**, 1.5 mmol) and 4-chlorobenzaldehyde (**5a**, 1 mmol) in ethanol under refluxing condition without any catalyst. It failed to produce the target molecule in good yield and only trace amount of dihydroquinazolinone was isolated (8%) after 5h of refluxing. Then keeping other components in fixed amount we added externally our catalyst (10 mg) and good amount of product (90 %) was isolated after 3h. Firstly to investigate effect of solvent, we had set pilot reaction in 5 ml of different non-polar and polar solvents like benzene, toluene, THF, MeOH, CHCl<sub>3</sub>, EtOH, acetonitrile, and water. All reactions were refluxed for 3h and it was observed that in non-polar solvents like benzene and toluene, reaction was very sluggish and conversion of starting materials to desired product was very less. However, in presence of polar solvents like MeOH, EtOH, acetonitile, THF, chloroform and H<sub>2</sub>O conversions were excellent (Table 1). But we decided to choose water as our desired solvent because its nature's own reaction medium, easily available and cheap.

Then taking water as solvent we shifted our focus towards standardization of temperature. Firstly we carried out reaction at room temperature ( $20 \, {}^{0}$ C) and observed that after 3 h of vigorous stirring, desired product was not forming and only starting materials were left in the reaction (from TLC). After getting no positive result at room temperature we applied heat to

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the reaction and carried out four sets of reactions at 40  $^{0}$ C, 60  $^{0}$ C, 80  $^{0}$ C and 100  $^{0}$ C. After carrying reaction for 3h, we observed that on increasing the temperature, desired product yield was also increasing (Table 1). Maximum yield was obtained at 80  $^{0}$ C and on further increasing the temperature beyond 80  $^{0}$ C showed no significant effect on product yield.

**Table 1:** Standardization of solvent and temperature <sup>a</sup>:

Sl.	Solvent <sup>b</sup>	Temperature( <sup>0</sup>	Time	Yield
No.		C)	(min)	° (%)
1	Benzene	80	180	21
2	Toluene	110	180	30
3	THF	66	180	81
4	CHCl <sub>3</sub>	62	180	79
5	MeCN	82	180	83
6	MeOH	65	180	87
7	EtOH	82	180	90
8	H <sub>2</sub> O	100	180	92
9	H <sub>2</sub> O	80	180	92
10	H <sub>2</sub> O	60	180	75
11	H <sub>2</sub> O	40	180	52
12	H <sub>2</sub> O	20 (r.t)	180	-

<sup>a</sup> Isotoic anhydride (1, 1mmol), NH<sub>4</sub>Oac (2, 1.5 mmol) and 4-Chlorobenzaldehyde (5a, 1 mmol), nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> (10 mg) <sup>b</sup> Amount of solvent taken was 5ml; <sup>c</sup> isolated yield

Catalyst concentration possesses large effect on yield and cost of the process. So, screening of catalysts concentration was also carried out. We had set up several sets of reaction containing 0, 2, 4, 6, 8, 10 and 12 mg of catalysts at 80 <sup>o</sup>C in water. It is important to mention that without any catalyst showed no positive result even after 3 h of stirring and to our delight we found that on increasing the catalyst concentration till 10 mg reaction was showing steady increase in the rate, though on increasing the amount of catalyst beyond 10 mg showed no

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significant effect on the product yield (Fig. 9). So, 10 mg was chosen as optimum catalyst concentration for getting maximum yield.

After finalizing solvent, temperature and catalyst concentration, standardization of time was done. For that we took starting materials, 10 mg of catalyst and carried out the reaction using water as solvent at 80 <sup>o</sup>C. It was observed that with time, yield was increasing and best result was observed in 50 min. No more improvement was observed beyond this time frame (Fig.9). Finally turn over number (TON) and turn over frequency (TOF) of the present catalyst were also calculated for the pilot reaction based on the amount of the active metal used (Sn) and they were found to be 1057.47 and 3204.45 h<sup>-1</sup>.

![](_page_11_Figure_5.jpeg)

Fig. 9: Optimization of catalyst loading with respect to time and yield

We also compared the efficiency and recoverability of nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> catalyst with other conventional catalyst under the standardised reaction condition. Likewise Fe<sub>2</sub>SO<sub>4</sub>, FeCl<sub>3</sub>, SnCl<sub>2</sub> were applied in the pilot reaction and they also showed efficient catalyses but being hygroscopic and water soluble in nature, their handling and separation from reaction mixture was difficult. Fe<sub>3</sub>O<sub>4</sub> NP was showing good result but the reaction was sluggish and when Fe<sub>3</sub>O<sub>4</sub> NP coated with dopamine (DOPA), the catalytic activity decreased drastically (Table 2).

![](_page_11_Figure_8.jpeg)

Sl. No.	Catalysts (10 mg)	Time (min)	Yield (%) <sup>b</sup>
1	Fe <sub>2</sub> SO <sub>4</sub>	50	73
2	FeCl <sub>3</sub>	50	75
3	SnCl <sub>2</sub>	50	81
4	Fe <sub>3</sub> O <sub>4</sub> NP	50	53
5	nano-Fe <sub>3</sub> O <sub>4</sub> -DOPA	50	16
6	nano-Fe <sub>3</sub> O <sub>4</sub> -DOPA-SnO <sub>2</sub>	50	92

<sup>a</sup>Isotoic anhydride (1, 1mmol), NH<sub>4</sub>Oac (2, 1.5 mmol) and 4-chlorobenzaldehyde (5a, 1 mmol), cataylts (10 mg), 5ml water, 80 <sup>o</sup>C, <sup>b</sup> isolated yield

#### Synthetic application of nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub>:

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With standardized conditions in our hand, to explore further this approach, the generality and scope of this protocol was examined. For this, we employed various amine sources like NH<sub>4</sub>Oac (2) and 4-Methyl aniline (3). Among aldehydes, aromatic (**5a-f, 5i, 5k-l**), aliphatic (**5h**), tricyclic (**5g**) as well as hetroaromatic aldehyde (**5j**) were used (Fig. 11) and all of them afforded brilliant yields within a short period of time as shown in table 3. Aromatic aldehydes possessing both electron donating as well as electron withdrawing groups in ortho or para position of the benzene ring, converted into desired products without any difficulties. To further expand scope of our methodology, application of bulky heteroarmatic amine source like 2-aminobenzimidazole (**4**) was also investigated and to our outmost delight, this reaction also went smoothly there by showing a very good positive result (Scheme 2). Structures of all synthesized compounds were identified by analyzing spectral data. Structures of **6f, 6k** and **6m** were also analyzed by single crystal X-ray crystallography (CCDC numbers **1063941**, **1524323**, **1535780** respectively) and shown in the ORTEP diagrams (Fig. 10).

![](_page_13_Figure_3.jpeg)

Fig 10. ORTEP diagrams of (a) 6f, (b) 6k, (c) 6m

![](_page_13_Figure_5.jpeg)

Scheme 2: Synthetic scheme for the synthesis of dihydroquinazolinone derivatives using nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> catalyst

![](_page_13_Figure_7.jpeg)

Fig. 11: Various aldehydes used in the reaction

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Table 3:

![](_page_14_Figure_3.jpeg)

Isotoic anhydride (1, 1mmol), NH<sub>4</sub>Oac (2, 1.5 mmol) or amine source (3/4, 1 mmol) and aldehydes (5, 1 mmol), nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> (10 mg), 5ml water, 80 °C, Yield = isolated yield.

Speedy creation of molecular diversity in a predictable and controlled way from simple and easily available starting materials is an exciting topic in modern day organic synthesis. In short, importance of creating complex molecules relies mainly on combination of individual transformations in to one synthetic procedure. Following these lines, we cogitated that the use of 1,4-dialdehydes (**5m**) and aldehydes possessing multiple functional groups (**5n**) would lead to the formation of complex molecules thereby doubling the effectiveness of the above methodology. Reaction of 1,4-dibenzaldehyde with NH<sub>4</sub>OAc and isotoic anhydride furnished desired *bis*-dihydroquinazolinone (**6q**) compound after 90 min of heating (scheme 3), which

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effectively leads to the formation of six new C-N bonds, two new C-C bonds, two stereocentres and two dihydroquinazolinone moieties in a single step. However when bulky amine group (4-methyl aniline) was taken in place of  $NH_4OAc$ , it was observed that instead of *bis*-product mono-substituted dihydroquinazolinones (**6r**, **6s**) were formed (scheme 4).

![](_page_15_Figure_4.jpeg)

Scheme 3: Synthetic scheme for the formation of bis-dihydroqunazolinone compounds.

![](_page_15_Figure_6.jpeg)

Scheme 4: Nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> catalysed synthesis of quinazolinone derivatives using terephthalaldehyde (5m) and methyl 4-formylbenzoate (5n)

![](_page_15_Figure_8.jpeg)

Scheme 5: Plaussible mechanistic pathway catalysed by nano-Fe $_3O_4$ -DOPA-SnO $_2$ 

From experimental results and after referring literature<sup>25</sup> we proposed a plausible mechanistic pathway for the synthesis of dihydroquinazolinone derivatives with nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> (scheme 5). In this catalyst, tin (Sn) is the reactive site and it acts a Lewis acid. The carbonyl groups of isotoic anhydride (1) are activated by co-ordination with tin. Which in turn facilitates the nucleophilic attack of primary amines (**3 or 4**) or ammonium acetate (**2**) to form a new C-N bond and leads to formation of intermediate **b**. Intermediate **b** undergoes decarboxylation to form another intermediate **c**. Nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> also activates aldehydes and they react with intermediate **f**. Then nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> facilitates intramolecular nucleophilic attack of amide nitrogen to imine and forms acyclic intermediate **h** which ultimately undergoes intra-molecular hydrogen transfer to form desired product (**6**). Nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> being let off from the reaction re-enters the catalytic cycle.

#### Application of procedure:

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To highlight industrial applicability of the present protocol a gram scale reaction was performed (scheme 6). For this isotoic anhydride (10 mmol, 1), ammonium acetate (15 mmol, 2), 4-chlorobenzaldehyde (10 mmol, 5a) and nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> (100 mg) was taken and heated in 50 ml of water at 80  $^{\circ}$ C with constant stirring for 50 min. After completion of the reaction nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> was separated from the reaction mixture by applying an external magnet and pure product was obtained by using column chromatography (4:6 EtOAc:Hexane). Reaction furnished a good yield (86 %) in the gram scale reaction thereby proving its industrial applicability.

![](_page_16_Figure_5.jpeg)

Scheme 6: Gram Scale reaction for the formation of dihydroqunazolinone derivative using nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub>

#### **Application of Compound:**

After detailed literature survey it was established that the most biologically active or naturally occurring quinazolinones are in its oxidised form. Therefore we embarked towards the functional group transformation of synthesized dihydroquinazolinones to quinazolinones by using MgO<sub>2</sub> as an oxidant (scheme 7). Structures of synthesized quinazolinone derivatives are shown in Fig. 12.

![](_page_17_Figure_5.jpeg)

Scheme 7: Oxidation of didroquinazolinones to quinazolinones

![](_page_17_Figure_7.jpeg)

Fig. 12: Structures of quinazolinones prepared

#### Catalyst stability and recyclability:

For validating recyclability of synthesized catalyst, a re-use investigation of model reaction involving isotoic anhydride (1) (1 mmol), ammonium acetate (2) (1.5 mmol) and 4chlorobenzaldehyde (5a) (1 mmol) along with the catalyst (10 mg) in water was carried out. After completion of reaction, we recycled back the catalyst simply by using an external magnet. Following that, catalyst was washed with ethyl acetate and acetone and dried. Recovered catalyst was reused for five consecutive runs without much decrease in catalyst activity (Fig.13). Then to check the nature and morphology of catalyst after five consecutive runs, TEM (Fig. 14), EDX, SEM, TGA (Fig. 15) analyses of reused catalyst were performed

and those analyses showed no significant changes from that of freshly prepared catalyst.

![](_page_18_Figure_4.jpeg)

Fig. 13: Catalyst recyclability

A leaching test for synthesised catalyst was also performed. For this, catalyst (10 mg) and water (5 ml) was stirred at 80  $^{0}$ C for 2h and then catalyst was separated from the solvent. In this solvent isotoic anhydride (1) (1 mmol), ammonium acetate (2) (1.5 mmol) and 4-chlorobenzaldehyde (5a) (1 mmol) were added and stirred for 50 min at 80  $^{0}$  C. Reaction showed only 7% conversion of starting materials to product proving negligible amount of catalyst leaching. To prove it more precisely, after completion of reaction we carried out an ICP-AES analysis. For that, model reaction was carried out under standardised condition. On completion of reaction (50 min), catalyst was separated from the reaction mixture and an ICP-AES analysis of the solvent was performed. It showed very less existence of tin (Sn) (less than 0.01 ppm) indicating negligible leaching.

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![](_page_18_Picture_7.jpeg)

**Fig. 14:** TEM of recycled nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> after five runs (a) at 2 nm, (b) at 10 nm and (c) SAED pattern.

![](_page_19_Figure_0.jpeg)

**Fig. 15:** (a) EDX of recycled nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> (b) SEM of recycled nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub>, (c) TGA of recycled nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> after five runs.

**(b)** 

(c)

#### **Conclusion:**

**(a)** 

In conclusion, an efficient, ferromagnetic nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> was developed from easily available starting materials under sustainable conditions. The catalyst was fully characterized by FT-IR, TEM, EDX, SEM, XPS, powder XRD, VSM, TGA and ICP-AES analyses. Then the catalyst was exploited in one-pot synthesis of dihydroquinazolinone derivatives. Merits and novelty of nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> does not end here since it is also applied in the synthesis of *bis*-dihydroquinazolinone compound thereby leading to the formation of six new C-N bonds, two new C-C bonds, formation of two new stereocentres and two new dihydroquinazolinone moieties in one step within a shorter period of time. Present methodology also highlighted easy separation and reusability of catalyst for five consecutive runs, higher selectivity of desired product, good application in gram scale reaction, shorter reaction time, column free purification and easy workup procedures thereby addressing issues of sustainability. Further biologically more important quinazolinones were synthesized from dihydroquinazolinone derivatives.

**Experimental:** 

#### Design and synthesis of nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub>:

#### Preparation of nano-Fe<sub>3</sub>O<sub>4</sub>:

A mixture of ferric nitrate (3.4 g) and ferrous sulphate (3 g) was added in 100 ml of deionised water and stirred at r.t. (room temperature) for 15 min. Ammonium hydroxide (25%) was

then added till pH of the solution became 10. After that the stirring was continued for another 1 h at 60  $^{0}$ C. A black precipitate appeared which was separated by external magnet, washed with water until the pH became neutral and dried in oven.

#### Post-synthetic modification of nano-Fe<sub>3</sub>O<sub>4</sub> with dopamine (DOPA):

To accomplish this step, we first took 25 ml of deionized water and added 2g of  $Fe_3O_4$  nanoparticles in it. Then the reaction mixture was dispersed for 30 min by ultrasonication at room temperature. Following this dopamine hydrochloride (2g) was dissolved separately in 5 ml of deionized water and added to the previous mixture. Resultant mixture was then ultrasonicated for 2 more hours. This lead to the surface modification of  $Fe_3O_4$  nanoparticles with dopamine (DOPA). Synthesized nano- $Fe_3O_4$ -DOPA was then precipitated by using acetone, isolated by using an external magnet and washed several times with water and acetone and dried.

#### Encapsulation of SnO<sub>2</sub> on the surface of nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA:

Nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA (1g) was dispersed in water (80 ml) and then a solution of tin (II) chloride dehydrate (1% w/v, 200 mg) in water was added to it. The resulting solution was then stirred for 24h at room temperature. Following that the product was allowed to settle down, separated my magnet and washed several times with water and acetone and dried at 50  $^{\circ}$ C.

#### Synthesis of dihydroquinazolinone derivatives:

Isotoic anhydride (1) (1 mmol), ammonium acetate (2) (1.5 mmol) or amines (3 or 4) (1 mmol), aldehydes (5) (1 mmol) nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> (10 mg), water (5 ml) were taken in a round-bottom flask. Then the reaction mixture was placed on a pre-heated oil bath accompanied with a magnetic stirrer (IKA C-MAG, HS4 Digital) at 80  $^{0}$ C and stirred for time mentioned in table 3. After completion of reaction (monitored by TLC), the reaction mixture

was cooled at room temperature. Catalyst was then separated by external magnet, washed with ethyl acetate, acetone and dried. This recovered catalyst was used in another set of reaction. After that the reaction mixture was extracted with ethylacetate (3x 5 ml) and combined organic extract was washed with water (3x 10 ml), brine solution (1x 10 ml) and dried (anhydrous sodium sulphate). Following that the solvent was evaporated and pure products (6a-s) were obtained by recrystallization from ethanol.

#### Conversion of dihydroquinazolinones to quinazolinones:

Synthesized dihydroquinazolinones (6e, 6i) (1 mmol), Mn<sub>2</sub>O (1 mmol) and water 5 ml were taken in a 25 ml round bottom flask. This was then refluxed for 20-30 min. Finally after full conversion of dihydroquinazolinones to quinazolinones (TLC), the reaction mixture was extracted with ethylacetate (3x 5ml) washed with water (3x 10 ml), brine solution (10 ml) and dried over anhydrous sodium sulphate. Pure products were obtained after recrystallization from ethanol.

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### **Table of content**

Preparation, characterization and catalytic application of nano-Fe<sub>3</sub>O<sub>4</sub>-DOPA-SnO<sub>2</sub> having high TON and TOF for non-toxic and sustainable synthesis of dihydroquinazolinone derivatives

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![](_page_25_Figure_7.jpeg)

● Aqueous reaction medium ● Wide substrate variability ● High atom economy

• Cost effective magnetically recyclable tin catalyst • Column chromatography free

High catalyst TON and TO
Gram Scale application
Catalyst reused in 5 runs