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Iron Oxide Nanoparticles-Catalyzed Oxidative Cyclization for Synthesis of 2-Substituted Quinazolinones and Benzimidazoles

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Hydrothermally synthesized nanoscale iron(III) oxide (Fe_2O_3) particles catalyzed the one-pot synthesis of 2-aryl-substituted quinazolinones and benzimidazoles from 2-aminobenzamide and 1,2-diaminoarenes with arylmethane *via* oxidative cyclization. A key advantage of this method is the use of water as a green solvent, enabling the efficient production of quinazolinones and benzimidazoles in excellent yields, without the need for a base, ligand, or toxic metals. This method is a successful and eco-friendly protocol for synthesizing a wide variety of heterocyclic compounds, and the high surface reactivity of the catalyst is probably a contributing factor.

Keywords: Iron oxide, 2-Substituted quinazolinones, 2-Substituted benzimidazoles.

INTRODUCTION

Nitrogen containing heterocyclic compounds are an integral part of copious natural products especially pharmaceutical and biologically active molecules [1-3]. In this family, quinazolinone and imidazoles have fascinating to structural motifs in many natural products and considered as paramount skeletons in the drug design [4,5], similarly, few quinazolinones and benzimidazole derivatives possess numerous therapeutic properties. For instance, ispinesib [6] inhibitor is utilized for the breast cancer treatment. Febrifugine [7] herbal medicine is used for the antimalarial treatment in China. Telmisartan (Micardis) [8] contains the benzimidazole core which works against hypertensive properties and the esomeprazole drug also utilized for the treatment of peptic ulcers and gastroesophageal reflux. Besides pharmaceutical, they also displayed a wide range of biological activities such as antimicrobial, antibacterial, anticancer, antiulcer, antifungal, antiviral, *etc*. [9-11]. Due to their biological evaluation, several approaches have been involved in the synthesis of quinazolinones [12-14] and benzimidazoles [15-18]. Generally, the synthesis of these frameworks by the condensation of *o*-aminobenzamide and 1,2-diaminoarenes with aldehydes or carboxylic acid followed by oxidative cyclization [19,20]. But, these methodologies have certain disadvantages such as use of additives or ligands, coupling agents/bases, reaction performed in harsh reaction conditions, low yields, stoichiometric or large amounts of toxic oxidants are used. In addition, the usage of aldehydes is another issue as they are relatively unstable and synthesized from alcohols by oxidative reactions with different agents. Many researchers have been discussed on different methods to overwhelming these issues with transition metal oxide catalysts [21,22]. However, these approaches are very difficult to segregate stimulants and production from a combination of these reactions for the posterior catalytic cycle. Thus, the development of facile and eco-friendly strategies is highly desirable.

Besides that, the C-C and C-N bond-forming processes by using transition metals have a great central theme in organic chemistry and the pharmaceutical industry [23-28]. However, these reactions have some issues such as the requirement of several additional functionalities in the starting materials and multi-synthetic steps that are involving in reactions. In recent years, nanocatalyst mediated direct reactions has emerged as an important progressive research area in organic synthesis [29]. Nanocatalysts have predominantly attracted the interest of synthetic chemistry because to their advantages, including a large catalytic active surface area, significant temperature resistance, improved yields with atom economy, ease of separation from the reaction mixture, and reusability. Among the several nanocatalysts, iron oxide is considered to be a good catalyst

for their greater reactivity and numerous C-C and C-N bond forming reactions were successfully developed [30]. Based on literature survey, quinazolinones and benzimidazoles can be synthesized from *o*-aminobenzamide and 1,2-diaminoarenes with an aldehyde, benzoic acids and benzyl alcohols, whereas with toluene very rarely reported. Dan *et al*. [31] developed quinazolinones and their derivatives from *o*-aminobenzamide with different substituted methylarenes *via* dual benzylic C–H bond amination with di-*tert*-butyl peroxide (DTBP). In continuation of this work [32] and to the best of our knowledge, iron oxide mediated oxidative cyclization of *o*-amino benzamide and 1,2-diaminoarenes with toluenes have not been explored. Thus, herein we reported an efficient synthesis of 2-aryl substituted quinazolionones and benzimidazoles *via* oxidative cyclization of *o*-amino benzamide and 1,2-diaminoarenes with various solvents in presence of iron oxide as catalyst in aqueous medium at 100 ºC.

EXPERIMENTAL

All chemicals and reagents were purchased from Sigma Aldrich and AVRA synthesis Private Ltd. and used without further purification. The progress of the reactions were monitored by TLC and carried out on aluminum plates coated with silica gel (silica gel 60 F_{254}) using ethyl acetate and *n*-hexane as mobile phase. Chromatograms were visualized using UV light (254 nm). The compounds were purified by using column chromatography on silica gel (100-200 mesh). Melting points were determined in open capillary tube and are not corrected. ^{1}H & ^{13}C NMR spectra were recorded on 400 MHz spectrometer using TMS as internal standard. LC-MS spectra were carried out in positive ion modes using a Thermo-Finnigan LCQ Advantage MAX LC/MS/MS (Thermo-Scientific, USA) instrument. IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer using KBr pellets.

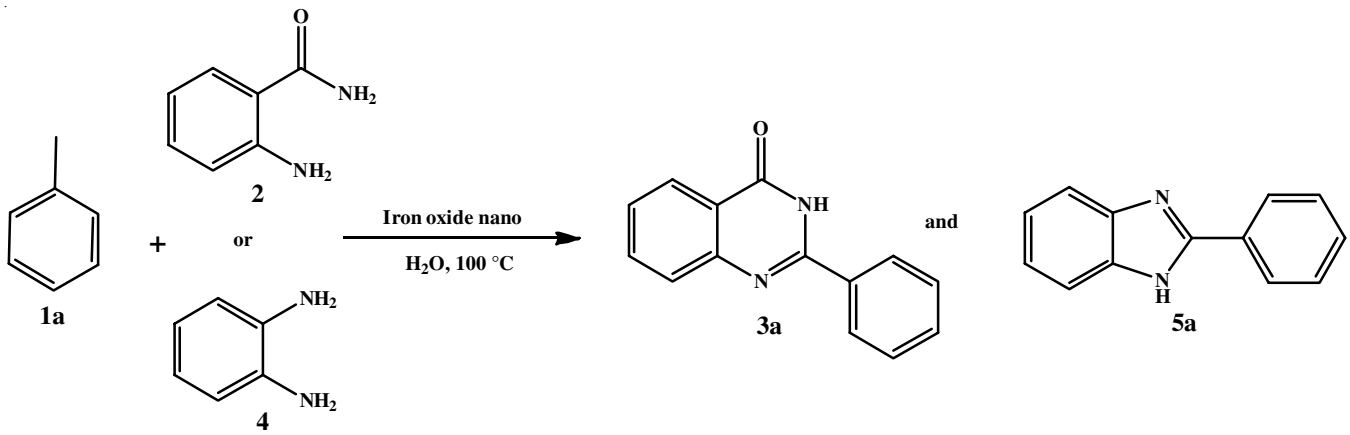
Synthesis of iron oxide nanoparticles: To synthesize iron oxide nanoparticles [33], 10 mL of 0.1 M $FeCl_3 \cdot 6H_2O$ solution and 10 mL of 1 M NaOH aqueous solutions were mixed and vigorously stirred for 30 min. Then this mixture was transferred into Teflon lined stainless steel and hydrothermally heated in an autoclave at 180 ºC for 24 h. The obtained product was washed with water and followed by ethanol, finally dried in a hot air oven at 60 ºC overnight.

General procedure for the synthesis of quinazolin-4(3*H*)-ones (3a-o): To an oven dried round bottom flask charged with a magnetic stir, methyl arenes **1a** (11.0 mmol), *o*-amino benzamide **2** (1.10 mmol), catalyst (20 mol%), TBHP (3 equiv.) in 3 mL H_2O then, the reaction mixture was transferred on oil both at 100 ºC for 12 h. The progress of the reaction was monitored by TLC, the reaction mixture cooled at room temperature and extracted with ethyl acetate (2 × 15 mL). The organic phase was dried over with anhydrous Na_2SO_4 and solvent was removed under vacuum (**Scheme-I**). The crude products was purified by column chromatography (ethyl acetate:hexane), to get corresponding pure products **3a-o**.

General procedure for the synthesis of 2-substituted-benzimidazoles (5a-g): To an oven dried round bottom flask charged with a stir bar, methyl arenes **1a** (13.8 mmol), *o*-phenylenediamine **4** (1.3 mmol), catalyst (20 mol%), TBHP (3 equiv.) in 3 mL H_2O then, the reaction mixture was heated at 100 ºC for 12 h. After completion of the reaction monitored by TLC, the reaction mixture cooled at room temperature and extracted with ethyl acetate (2 × 15 mL). The organic phase was separated and dried over with anhydrous Na_2SO_4; the solvent was removed under vacuum. The crude products was purified by column chromatography (ethyl acetate: hexane), to get corresponding pure products **5a-g** (**Scheme-I**).

2-Phenylquinazolin-4(3*H*)-one (3a): White solid; yield: 75%; m.p.: 230-232 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.53 (brs, 1H), 8.23-8.16 (m, 3H), 7.88-7.82 (m, 1H), 7.78 (d, *J* = 7.2 Hz, 1H), 7.63-7.52 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 162.6, 152.7, 149.5, 135.0, 133.3, 132.0, 129.0, 128.6, 127.3, 126.8, 126.3, 121.5; LC-MS calcd. for $C_{14}H_{10}N_2O$ $[M+H]^+$ 223.0826, found 223.0844.

2-(4-Chlorophenyl)quinazolin-4(3*H*)-one (3b): White solid; yield: 60%; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.61 (br s, 1H), 8.22-8.15 (m, 3H), 7.85 (t, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 162.5, 152.6, 150.3, 137.3, 135.7, 132.2, 131.3, 129.8, 128.7, 127.3, 126.8, 121.4; LC-MS calcd. for $C_{14}H_9ClN_2O$ [M+2] 258.0374, found 258.0387.



Scheme-I: Synthesis of quinazolinones

2-(2-Chlorophenyl)quinazolin-4(3*H*)-one (3c): White solid; yield: 62%; m.p.: 195-198 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.64 (brs, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.89-7.84 (m, 1H), 7.75-7.66 (m, 2H), 7.61-7.52 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 161.5, 153.3, 149.1, 136.3, 134.4, 131.9, 131.3, 130.8, 129.5, 127.8, 127.4, 126.5, 124.3, 122.2; LC-MS calcd. for $C_{14}H_9ClN_2O$ [M+2] 258.0374; found, 258.0393.

2-(4-Bromophenyl)quinazolin-4(3*H*)-one (3d): White solid; yield: 64%; m.p.: 291-293 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.54 (brs, 1H), 8.15-8.12 (m, 3H), 7.85-7.83 (m, 1H), 7.76-7.74 (m, 3H), 7.57-7.53 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 162.3, 153.5, 151.3, 135.0, 133.7, 132.4, 131.0, 129.6, 128.2, 127.7, 126.4, 122.3; LC-MS calcd. for $C_{14}H_9BrN_2O$ [M+2]$^+$ 301.9878, found 301.9913.

2-(3-Bromophenyl)quinazolin-4(3*H*)-one (3e): White solid; yield: 63%; m.p.: 294-296 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.64 (brs, 1H), 8.35 (s, 1H), 8.17 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.86-7.76 (m, 3H), 7.58-7.52 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 162.1, 150.6, 149.6, 135.4, 134.7, 134.2, 132.2, 131.5, 129.4, 127.5, 126.3, 125.7, 121.4, 120.4: LC-MS calcd. for $C_{14}H_9BrN_2O$ [M+2]$^+$ 301.9878, found 301.9913.

2-(4-Fluorophenyl)quinazolin-4(3*H*)-one (3f): White solid; yield: 66%; m.p.: 285-287 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.53 (brs, 1H), 8.27-8.22 (m, 2H), 8.15 (d, J = 8.8 Hz, 1H), 7.84 (t, J = 7.6 Hz,1H), 7.75 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.41 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 165.2 (d, J_C =251.4 Hz) 163.5, 161.2, 149.8, 135.2, 132.3 (d, J_C = 9.38 Hz), 129.1, 128.7, 127.4, 126.7, 123.2, 117.4 (d, J_C = 21.96 Hz); LC-MS calcd. for $C_{14}H_9FN_2O$ [M+H]$^+$ 241.0732, found 241.0745.

2-(4-(Trifluoromethyl)phenyl)quinazolin-4(3*H*)-one (3g): White solid; yield: 67%; m.p.: 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.70 (s, 1H), 8.41 (d, J = 8.0 Hz, 2H), 8.16 (d, J = 7.79 Hz, 1H), 7.92 (d, J = 8.23 Hz, 2H), 7.85-7.83 (t, J = 8.03 Hz, 1H), 7.76 (d, J = 7.93 Hz, 1H), 7.54-7.52 (t, J = 7.50 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 163.2, 152.3, 149.4, 138.3, 134.2 (2C), 132.3 (q, J_{CF} = 31.33 Hz), 128.7, 128.4, 128.1, 127.1, 126.4, 124.9 (d, J_{CF} = 3.43 Hz), 124.3, 123.4 (q, J_{CF} = 272.7), 121.6; LC-MS calcd. for $C_{15}H_{10}F_3N_2O$ [M+H$^+$] 291.0740, found 291.0742.

2-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (3h): White solid; yield: 76%; m.p.: 246-245 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.44 (brs, 1H), 8.23 (dd, J = 6.8 Hz, 2H), 8.12-8.06 (m, 1H), 7.86-7.78 (m, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.47-7.42 (m, 1H), 7.15 (d, J = 8.0 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 163.8, 162.6, 154.4, 150.2, 135.2, 131.7, 129.2, 127.6, 126.8, 125.2, 123.6, 114.6, 57.4; LC-MS calcd. for $C_{15}H_{12}N_2O_2$ [M+H]$^+$ 253.0938, found 253.0947.

2-(*p*-Tolyl)quinazolin-4(3*H*)-one (3i): White solid; yield: 75%; m.p.: 240-242 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.46 (brs, 1H), 8.20 (d, J = 6.8 Hz, 1H), 8.13(d, J = 8.0 Hz, 2H), 7.87 (t, J = 7.6 Hz,1H), 7.77 (d, J = 7.2 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 7.36(d, J = 7.6 Hz, 2H), 2.37 (d, J = 7.6 Hz, 2H,) 2.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 162.2, 152.4, 150.3, 142.1, 136.7, 130.4, 129.5, 128.3, 127.0, 126.5, 126.1, 122.3, 22.1; LC-MS calcd. for $C_{15}H_{12}N_2O$ [M+H]$^+$ 237.0983, found, 237.0979.

2-(*o*-Tolyl)quinazolin-4(3*H*)-one (3j): White solid; yield: 70%; m.p.: 216-219 ºC; ^{1} H NMR (400 MHz, DMSO-d_6) δ ppm: 12.45 (s, 1H), 8.17 (d, J = 7.42 Hz, 1H), 7.87-7.83 (t, J = 6.98 Hz, 1H), 7.72 (d, J = 8.05 Hz, 1H), 7.57-7.52 (m, 2H), 7.47-7.44 (t, J = 6.98 Hz, 1H), 7.38-7.32 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 163.2, 154.4, 150.3, 136.8, 135.2, 134.5, 131.0, 130.6, 129.3, 127.8, 127.2, 126.8, 126.2, 122.4, 21.0. LC-MS calcd. for $C_{15}H_{12}N_2O$ [M+H$^+$] 237.1022, found 237.1018.

2-(3-Methoxyphenyl)quinazolin-4(3*H*)-one (3k): White solid; yield 70%; m.p.: 181-182 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.53 (s, 1H), 8.16 (d, J = 7.2 Hz, 1H), 7.90-7.80 (m, 4H), 7.53 (d J = 8.0 Hz, 1H), 7.46 (t, J = 7.2 Hz, 1H), 7.15 (d, J = 7.6. Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 162.2, 159.2, 153.4, 148.7, 136.8, 134.7, 131.2, 129.6, 128.3, 126.8, 122.5, 121.2, 117.4, 112.6, 56.1; LC-MS calcd. for $C_{15}H_{12}N_2O_2$ [M+H]$^+$ 253.0938, found 253.0952.

2-(3,5-Dimethylphenyl)quinazolin-4(3*H*)-one (3l): White solid; yield: 69%; m.p.: 272-274 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.36 (s, 1H), 8.14-8.13 (d, J = 7.54 Hz, 1H), 7.87-7.83 (m, 3H), 7.73-7.70 (d, J = 8.17 Hz, 1H), 7.55-7.50 (t, J = 7.34 Hz, 1H), 7.24 (s, 1H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 163.6, 153.4, 148.4, 138.3, 134.7, 133.0, 132.4, 128.6, 126.9, 126.3, 124.6, 122.5, 21.7 (2C). LC-MS calcd. for $C_{16}H_{14}N_2O$ [M+H$^+$] 251.1179, found 251.1178.

2-(4-*N*,*N*-dimethylphenyl)quinazolin-4(*3H*)-one (3m): White solid; yield: 74%; m.p.: 237-239 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.22 (brs, 1 H), 8.14 (t, J = 8.0 Hz, 1H), 7.76 (t, J = 7.5 Hz, 1H), 7.68 (d, J = 8.0Hz, 1H), 7.44 (m, J = 7.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 2H), 3.12 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 162.3, 154.5, 153.3, 141.5, 140.7, 135.2, 132.6, 130.4, 129.5, 127.2, 124.0, 118.7, 46.7, 46.3; LC-MS calcd. for $C_{16}H_{15}N_3O$ [M+H]$^+$ 266.1249, found 266.1253.

2-(Furan-2-yl)quinazolin-4(3*H*)-one (3n): White solid; yield: 73%; m.p.: 276-277 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.46 (brs, 1H), 8.16 (d, J = 7.6 Hz, 1H), 7.96 (s, 1H), 7.84 (t, J = 7.6 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz,1H), 7.44 (t, J = 8.0 Hz, 1H), 6.75 (t, J = 8.0 Hz, 1H), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 162.4, 151.2, 147.2, 146.7, 145.7, 134.7, 129.3, 127.7, 123.7, 115.2, 112,6; LC-MS calcd. for $C_{12}H_8N_2O_2$ [M+H]$^+$ 213.0619, found 213.0623

2-Phenyl-1*H*-benzo[*d*]imidazole (5a): Colourless solid; yield: 92%; m.p.: 288-290 ºC; ^{1}H NMR (400 MHz DMSO-d_6) δ ppm: 12.90 (s, 1H), 8.22 (d, J = 7.6 Hz, 2H,), 7.80 (d, J = 6.8 Hz, 1H), 7.53-7.41 (m, 4H), 7.22 (d, J = 6.8 Hz, 2H,). ^{13}C NMR (100 MHz DMSO-d_6): δ 151.7, 144.3, 136.2, 132.0, 131.5, 129.3, 127.6, 124.5, 122.7, 118.9, 112.6; LC-MS: Anal. calcd. for $C_{13}H_{10}N_2$ [M+H]$^+$ 195. found 213.0623.

2-*p*-Tolyl-1*H*-benzo[*d*]imidazole (5b): Colourless solid; yield: 90%; m.p.: 264-266 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.83 (s, 1H), δ 8.12 (d, J = 7.6 Hz, 2H), 7.67 (s, 2H), 7.35 (d, J = 7.6 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 152.3, 142.4,

140.2, 136.5, 130.7, 127.9, 127.2, 123.5, 22.4; LC-MS: Anal. calcd. for $C_{14}H_{12}N_2$ $[M+H]^+$ 209.1034, found 209. 1083.

2-(4-Methoxyphenyl)-1*H*-benzo[*d*]imidazole (5c): White solid; yield: 92%; m.p.: 224-226 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.73 (s, 1H), 8.11 (d, *J* = 8.4 Hz, 2H), 7.63 (s, 1H), 7.51 (s, 1H), 7.18-7.10 (m, 4H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 160.4, 152.3, 144.5, 134.3, 129.3, 123.7, 122.5, 119.5, 116.9, 116.7, 112.6, 56.5; LC-MS: Anal. calcd. for $C_{14}H_{12}N_2O$ $[M+H]^+$ 225. 0983, found: 225. 1020.

2-(4-Fluorophenyl)-1*H*-benzo[*d*]imidazole (5d): White solid; yield: 89%; m.p.: 252-254 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.95 (s, 1H), 8.24 (s, 2H), 7.67 (s, 1H), 7.55 (s, 1H), 7.42-7.37 (m, 2H); 7.20 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 165.7, 161.4, 151.6, 144.2, 135.8, 129.6, 128.2, 127.7, 123.3, 121.4, 119.5, 116.8, 116.5, 112.5; LC-MS: Anal. calcd. for $C_{13}H_9FN_2$ $[M+H]^+$ 213.0783, found 213.0792.

2-(4-Chlorophenyl)-1*H*-benzo[*d*]imidazole (5e): White solid; yield: 91%; m.p.: 290-293 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.88 (s, 1H), 8.17 (d, *J* = 8.2 Hz, 2H), 7.68-7.57 (m, 4H), 7.23 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 151.4, 145.2, 135.3, 128.9, 128.3, 127.3, 122.7, 121.5, 118.6, 116.5, 116.4; LC-MS: Anal. calcd. for $C_{13}H_9ClN_2$ $[M+H]^+$ 229.0425, found 229.0438.

2-(4-Bromophenyl)-1*H*-benzo[*d*]imidazole (5f): Pale yellow solid; yield 63%; m.p.: 255-257 ºC; ^{1} H NMR (400 MHz, DMSO-d_6) δ ppm: 12.86 (br s,1H), 8.15 (m, 2H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.68 (s, 1H), 7.58 (s, 1H), 7.25 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 151.6, 144.2, 135.7, 129.8, 129.4, 128.0, 123.8, 123.4, 122.6, 118.3, 112.2; LCMS: Anal. calcd. for $C_{13}H_9BrN_2H$ $[M+2]^+$ 273.9929, found: 273. 9942.

2-(Thiophen-2-yl)-1*H*-benzo[*d*]imidazole (5g): Pale yellow solid; yield: 68%; m.p.: decomp. ≥ 300 ºC; ^{1} H NMR (400 MHz, DMSO-d_6) δ ppm: 12.94 (br s, 1H), 7.80 (d, *J* = 3.6 Hz, 1H), 7.74 (d, *J* = 5.4 Hz, 1H), 7.65 (s, 1H), 7.54 (s, 1H), 7.25-7.23 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 148.5, 144.3, 134.7, 134.5, 128.5, 128.2, 127.4, 122.8, 122.20, 117.4, 112.2; LC-MS: Anal. calcd. for $C_{11}H_8BrN_2S$ $[M+H]^+$ 201.0442, found: 201.0463.

RESULTS AND DISCUSSION

Characterization of iron oxide nanocatalyst: The XRD patterns of Fe_2O_3 are shown in Fig. 1. The corresponding peaks at 2θ = 24.8º, 33.4º, 35.1º, 54.6º, 57.4º, 63.2º and 73.6º which are attributed to their planes (012), (104), (110), (116), (122), (300) and (220), respectively (standard JCPDS file No. 33-0664) [34]. No impure peaks were observed, confirms the formation of pure Fe_2O_3. The average crystalline size of prepared Fe_2O_3 is found to be 18.6 nm as calculated by using Debye Scherrer equation (eqn. 1).

$$D = \frac{0.9\lambda}{\beta\cos\theta} \quad (1)$$

where 'λ' is the wavelength of X-ray radiation and 'β' is the full width at half maximum of the peaks at the diffracting angle 'θ'.

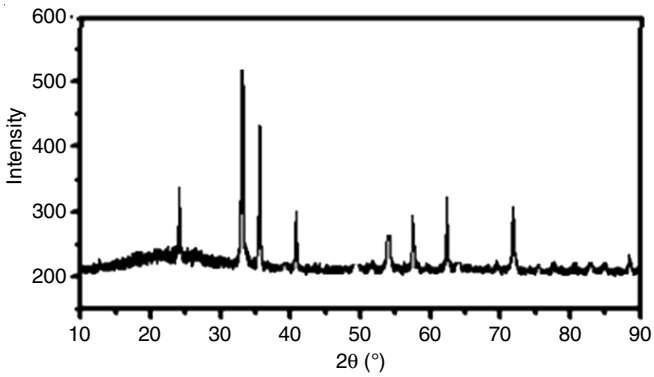


Fig. 1. XRD patterns of Fe_2O_3 nanoparticles

Fig. 2 displays the FTIR spectrum of hydrothermally synthesized Fe_2O_3 nanoparticles. The Fe–O vibration was confirmed by the presence of a major peak at 530 cm^{-1}, clearly indicated the formation of nanoparticles in the magnetite phase [35,36].

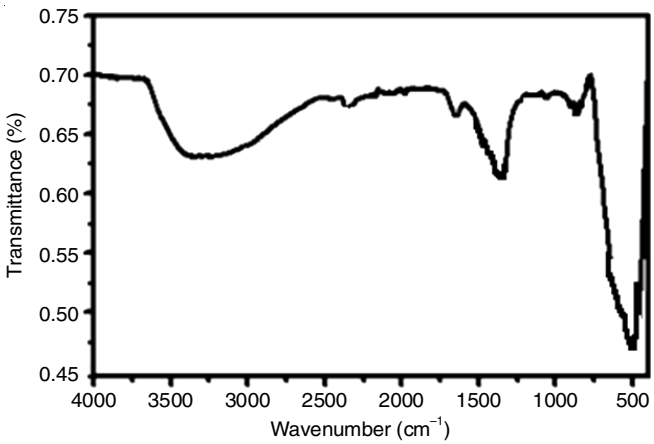


Fig. 2. FTIR spectrum of Fe_2O_3 nanoparticles

The morphology of hydrothermally prepared iron oxide nanoparticles was studied using TEM analysis with the higher resolution scale up to 50 nm. The TEM image of iron oxide nanoparticles illustrate the agglomeration of nanoparticles (Fig. 3a). By using J image software, the average particle size of prepared iron oxide nanoparticles is found to be 13.9 nm from histogram distribution curve (Fig. 3b).

Chemistry: This work explores with the reaction of toluene **1a** and *o*-aminobenzamide **2a** selected as the model substrates for the optimized reaction conditions. Initially, a pilot reaction was carried out between toluene **1a** and *o*-aminobenzamide **2,** remarkably, no reaction was occurred when $FeCl_2$ and $FeCl_3$ used as catalysts (Table-1, entry 1-2). To our delight, the corresponding quinazolinone **3a** was obtained in 41% yield once the reaction performed with 5 mol% of Fe_2O_3 as catalyst in ethanol at 80 ºC (entry 3). Encouraged by these results, we further moved for selected the best catalyst dose to enhancing the reaction yield (Table-1, entries 4-7), product **3a** was obtained in 84% yield with 20 mol % of Fe_2O_3 nanocatalyst is the best and superior quantity for this protocol (entry 6). As well as, several heating conditions were studied for increasing the reaction efficiency. Remarkably, product **3** was formed in 87% yield at 100 ºC for 12 h (entry 9). Unfortunately, no selectivity and

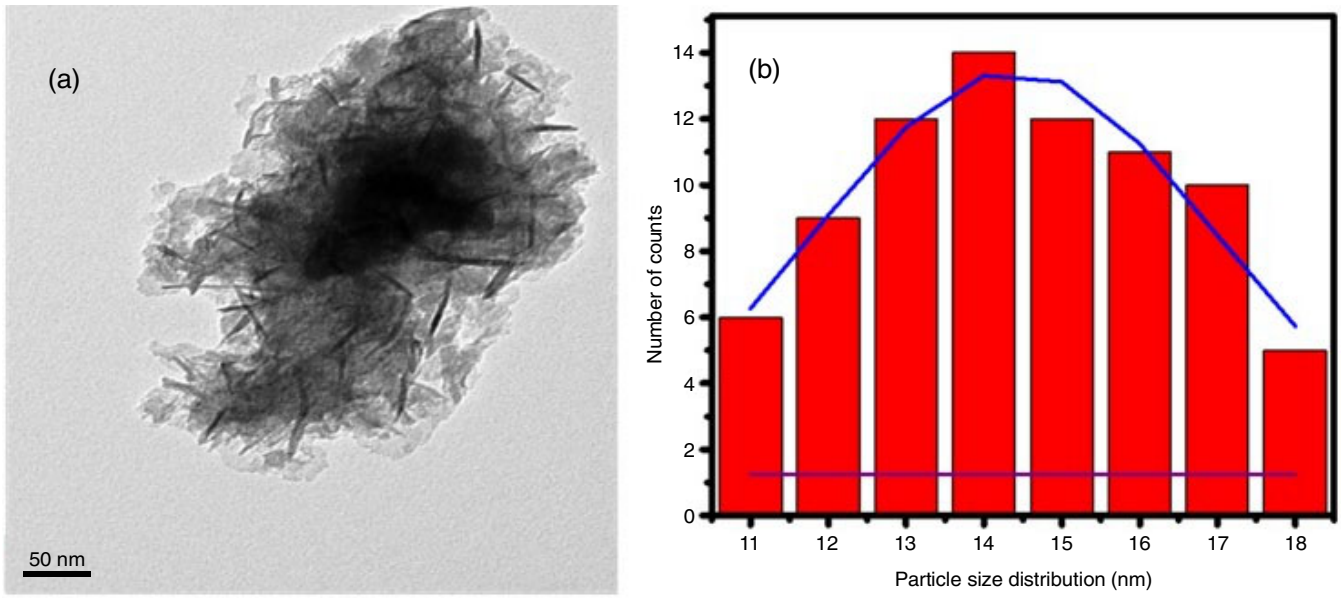


Fig. 3. TEM (a) and histogram distribution curve (b) of Fe_2O_3 nanoparticles

TABLE-1
OPTIMIZATION OF REACTION CONDITIONS FOR THE SYNTHESIS OF QUINAZOLINONES[a]

Entry	Nano (mol%)	Conversion (%)	Temp. (°C)	Yields (%)[b]
1	$FeCl_2$ (5)	EtOH	r.t.	0
2	$FeCl_3$ (5)	EtOH	80	0
3	Fe_2O_3 nano (5)	EtOH	80	41
4	Fe_2O_3 nano (10)	EtOH	80	56
5	Fe_2O_3 nano (15)	EtOH	80	73
6	Fe_2O_3 nano (20)	EtOH	80	84
7	Fe_2O_3 nano (25)	EtOH	80	83
8	Fe_2O_3 nano (20)	EtOH	90	86
9	Fe_2O_3 nano (20)	EtOH	100	91
10	Fe_2O_3 nano (20)	EtOH	110	85
11	–	EtOH	100	0

[a]Reaction conditions: Methyl arenes **1a** (11.0 mmol), *o*-amino benzamide **2** (1.10 mmol), catalyst (20 mol %), ethanol (3 mL), at 100 °C for 12 h. [b]Isolated yields.

TABLE-2
EFFECT OF SOLVENTS ON THE OXIDATIVE CYCLIZATION OF **1a** WITH **2a** IN PRESENCE OF 20 mol% IRON NANOOXIDE[a]

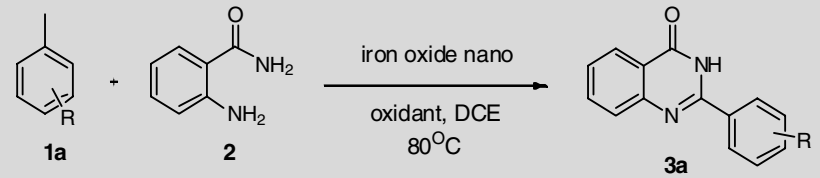
Entry	Nano (mol%)	Solvents	Temp. (°C)	Yields (%)[b]
1	$FeCl_2$ (20)	DCE	100	62
2	$FeCl_3$ (20)	EtOAc	100	68
3	Fe_2O_3 nano (20)	1,4-Dioxane	100	64
4	Fe_2O_3 nano (20)	THF	100	69
5	Fe_2O_3 nano (20)	CH_3CN	100	67
6	Fe_2O_3 nano (20)	DMF	100	50
7	Fe_2O_3 nano (20)	MeOH	100	90
8	Fe_2O_3 nano (20)	H_2O	100	94
9	Fe_2O_3 nano (20)	PEG	100	76
10	Fe_2O_3 nano (20)	EtOH/H_2O (1:1)	–	92
11	Fe_2O_3 nano (20)	–	100	0

[a]Reaction conditions: Methyl arenes **1a** (11.0 mmol), *o*-amino benzamide **2** (1.10 mmol), catalyst (20 mol %), H_2O (3 mL), at 100 °C for 12 h. [b]Isolated yields.

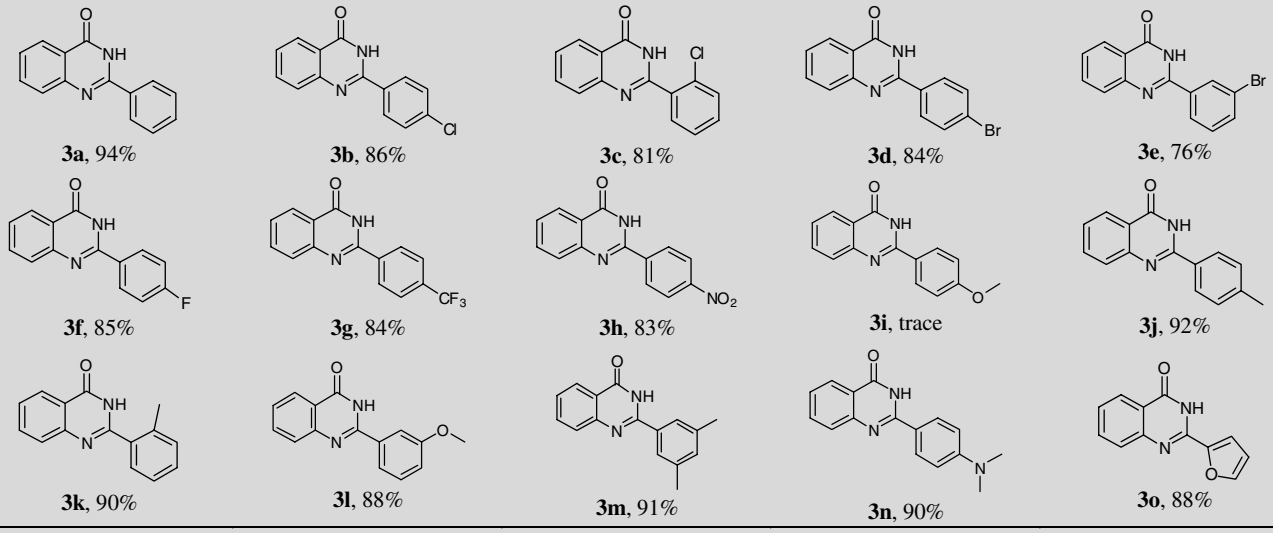
corresponding product **3a** were identified in the absence of a catalyst (entry 10).

As solvents have shown a great role in organic reactions, we examined the effect of the solvents on this oxidative cyclization of **1a** and **2** in presence of Fe_2O_3 nanocatalyst (20 mol%) and the results are shown in Table-2. The replacement of ethanol with different solvents such as DCE, EtOAc and 1,4-dioxane the desired product **3a** was obtained in moderate yields with DCE and EtOAc, but the lower product was formed in 1,4-dioxane (entries, 1-3). Furthermore, the usage of polar solvents (*e.g.* THF, MeCN, DMF, MeOH, H_2O and PEG) were also examined (entries, 4-9). It was found that water is the most effective solvent for this conversation and afforded a 94% yield of the product than other solvents (entry, 8). Surprisingly, the co-solvent of ethanol and water (1:1) elevated the reaction in excellent yields of 92% (entry 10). The reaction condition for the synthesis of 2-phenyl quinazolinones and 2-phenyl benzimidazoles in presence of 20 mol% Fe_2O_3 (20 mol%) as catalyst and water as solvent at 100 ºC for 12 h was investigated. The progress of the reactions was monitored by TLC analysis (EtOAc-hexane as eluent). Various substituted methyl arenes under an optimized reaction condition were also analyzed and the results are summarized in Table-3. Substrates having various functional groups such as electron-withdrawing and electron-donating groups on aromatic ring gave moderate high yields. For example, *p*-Cl, *p*-Br, *p*-F and *m*-Br substituted methyl arenes were also well coupled with **2a** to furnish the corresponding quinazolinone products were obtained in 86%, 81%, 84%, 76%, 85%, 84%, 83% and 81% yields (Table-3, **3b-h**). However, *o*-chloromethylarene gave low yield due to the steric hindrance effect on this reaction. Whenever methylarene has a strong electron withdrawing group such as nitro group on aromatic ring was not coupled successfully in this reaction, a trace amount of corresponding product was obtained. Interestingly, electron-donating groups such as -Me, -OMe, $–NMe_2$ were smoothly proceeded and providing the quinazolinone products with high

TABLE-3
IRON OXIDE NANO CATALYZED OXIDATIVE CYCLIZATION OF *o*-AMINOBENZAMIDE WITH METHYL ARENES TO QUINAZOLINONES UNDER THE OPTIMUM CONDITION[a,b]



1a 2 3a



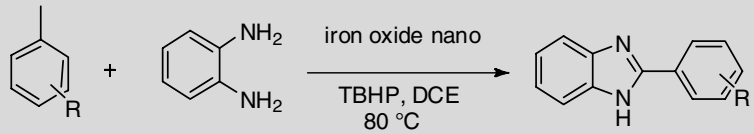
3a, 94% **3b**, 86% **3c**, 81% **3d**, 84% **3e**, 76%
3f, 85% **3g**, 84% **3h**, 83% **3i**, trace **3j**, 92%
3k, 90% **3l**, 88% **3m**, 91% **3n**, 90% **3o**, 88%

[a]Reaction conditions: Methyl arenes **1a** (11.0 mmol), *o*-amino benzamide **2** (1.10 mmol), catalyst (20 mol %), H_2O 3 mL, at 100 °C. [b]Yields of product after silica gel chromatography.

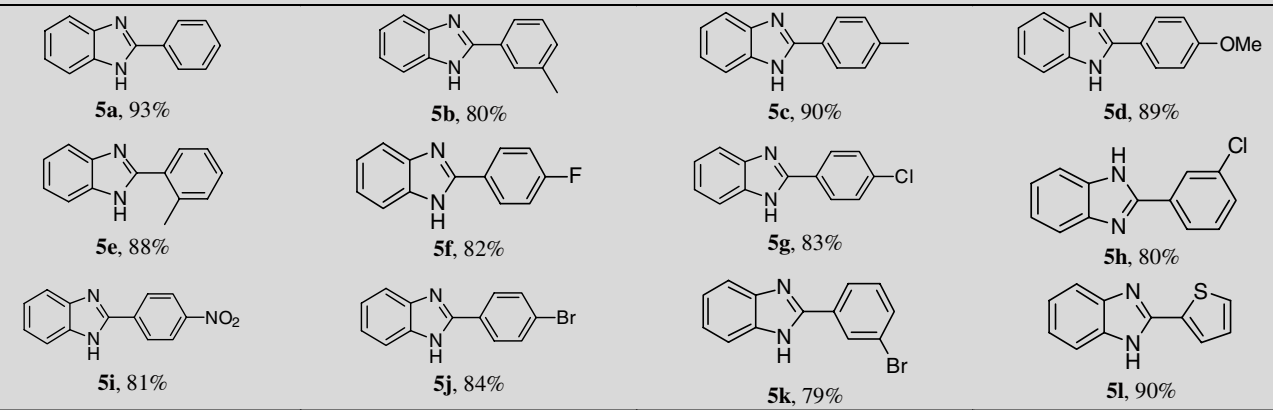
yields in 92%, 90%, 88%, 91% and 90% (Table-3, **3i-n**). It is interesting to observe that toluene having one or two methyl functional groups on the aromatic ring, only one methyl group which is involved in the reaction (**3m**). Thus, 2-methylfuran was also proven to be a moderate yield of 88% (Table-3, **3o**).

Encourage by the above results, we further extended the scope of this reaction for the reactant replacement of *o*-amino benzamide with *o*-phenylenediamine to the synthesis of 2-phenyl benimidazoles. Fortunately, electron-donating and withdrawing groups all well smoothly react with *o*-phenylenediamine (**4**) under the optimized reaction condition to give their corresponding 2-phenyl benzimidazoles in excellent yields between 93-79% (Table-4, **5a-o**). After that, the efficiency of Fe_2O_3 nanocatalyst was evaluated, first extracted from reaction mixture

TABLE-4
REACTION OF *o*-PHENYLENEDIAMINE WITH METHYL ARENES[a,b]



1 4 5



5a, 93% **5b**, 80% **5c**, 90% **5d**, 89%
5e, 88% **5f**, 82% **5g**, 83% **5h**, 80%
5i, 81% **5j**, 84% **5k**, 79% **5l**, 90%

[a]Reaction conditions: Methyl arenes **1a** (13.8 mmol), *o*-phenylenediamine **4** (1.3 mmol), iron oxide nano (20 mol%), H_2O 3 mL, at 100 °C. [b]Yields of product after silica gel chromatograph.

by centrifugation and then recycled for the following fresh reaction at the optimized reaction conditions. However, the efficiency of recovered Fe_2O_3 nanocatalyst was slowly declined after two cycles and the results are shown in Table-5.

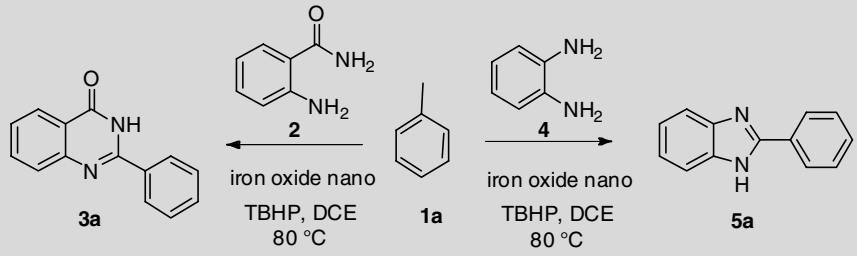
Mechanism: In order to comprehend the reaction mechanism, a few controlled experiments are shown in **Scheme-II**. Methylarene **1a** reacts with *o*-aminobenzamide **2** to yield a minimal quantity of **3a** in the absence of a catalyst (**Scheme-IIa**). Under the standard reaction conditions, toluene completely converted into benzylaldehyde at 100 ºC for 12 h (**Scheme-IIb**). The replacement of toluene with benzyl aldehyde in absence of metal conditions leads to the desired product **3a** in a trace amount yield (**Scheme-IIc**).

Based on the literature [37] and the aforementioned controlled experiments, a potential mechanism for this reaction is depicted in **Scheme-III**. Initially, toluene oxidized with catalyst at 100 ºC to form a benzylaldehyde. Subsequently, the oxidative condensation of **2** or **4** with benzylaldehyde to form 2,3-dihydroquinazolinones and dihydrobenzoimidazole as intermediate, which is further oxidized into the corresponding products of **3a** and **5a** with high yields.

Conclusion

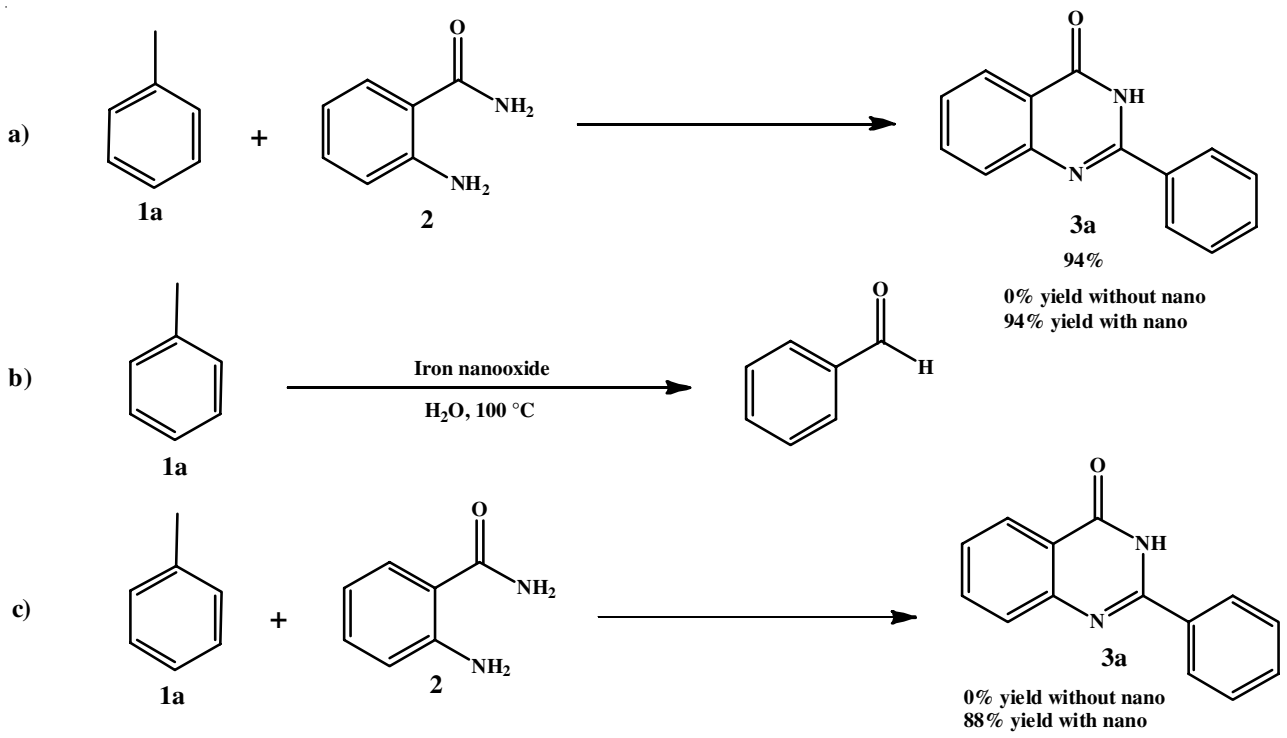
In conclusion, a simple and efficient protocol for the synthesis of 2-substituted quinazolinones and 2-substituted benzimidazoles is developed. Using an iron oxide nanocatalyst,

TABLE-5
RECYCLABILITY OF IRON OXIDE NANO CATALYST

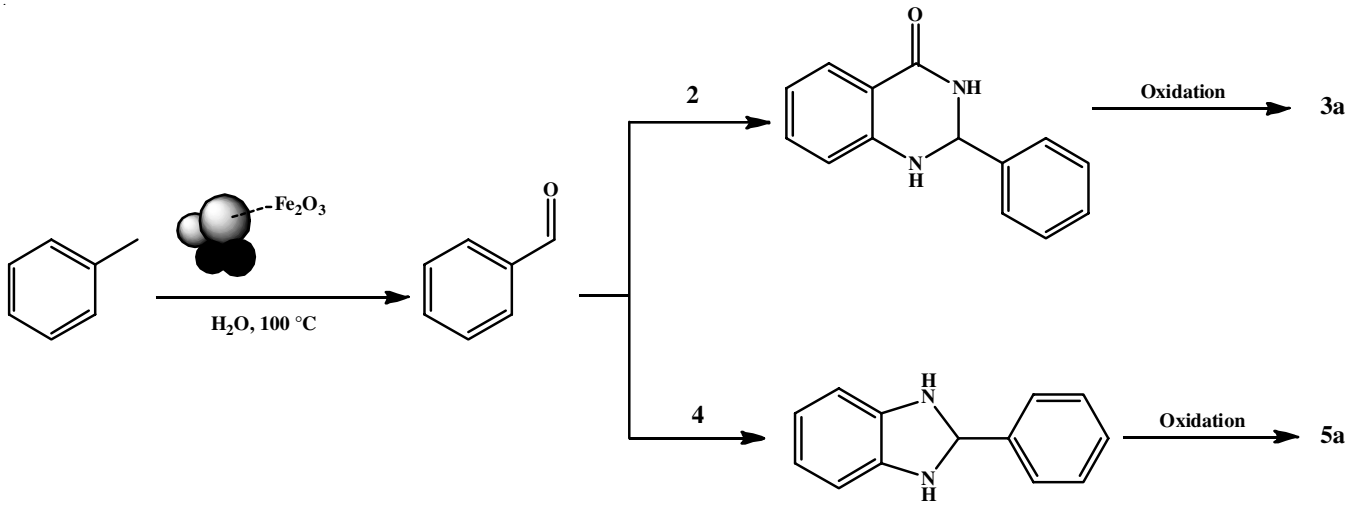


Entry	Recovered catalyst	Yields (%)
1[a]	96	94
2[b]	89	93
3[b]	85	91
4[b]	80	88
5[b]	73	84

[a]Reaction condition: Methyl arenes **1a** (11.1 mmol), *o*-aminobenzamide **2** (1.10 mmol), iron oxide nano (20 mol%) in H_2O (3 mL) at 100 °C for 12 h. [b]The recovered catalyst was used under identical reaction conditions.



Scheme-II: Control experiments



Scheme-III: Possible mechanism for the synthesis of 2-substitued quinazolinones and 2-substituted benzimidazoles

a number of 2-quinolinines and benzimidazoles were successfully synthesized by oxidatively cyclizing 2-aminobenzamide and diaminoarenes with toluenes. This new protocol features an operational simplicity and also has several advantages such as high atom economy, catalyst easily separates from a mixture, reusable and it offers low catalyst loading also tolerance of a wide range of functional groups.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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