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Ultrasound promoted expeditious, nano-catalysed and solvent-free approach for the synthesis of hybrids containing pyrazol-quinoline-oxindoles moieties

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Abstract: A new simple, robust and eco-friendly method employing magnetic nanoparticles Fe_3O_4 as an efficient catalyst and ultrasonic waves as a greener tenet has been developed for multicomponent synthesis of hybrids containing medicinally important pyrazol-quinoline-oxindoles moieties. The recyclability and easily recoverability of the catalyst; efficiency and lushness of sonication, clean process, easy work-up procedure and better solvent-free approach was further increased the usability and competence of the methodology.

Keywords: Magnetite nanoparticles; multicomponent; sonication; solvent-free approach.

1. Introduction:

Recent epoch has witnessed many escalations in the field of research and many other synthetic fields for the growing exploration of newer and better products. This relentless race has escorted an elevating level of air, water, and soil pollution; moreover, amplification of hazardous wastes in the environment has created many incurable health problems and new emerging resistant diseases. Therefore, it has become the moral obligation and liability of the scientific community to develop innovative green and sustainable methodologies for the welfare of both mankind and nature.

Recently, Magnetic Nano-particles (MNPs), which are regarded as a bridge between heterogeneous and homogeneous catalysis are gaining much attention and have emerged as a feasible alternative to conventional tedious methods^[1]. Their credibility lies in the fact that they are not only highly stable, eco-friendly, inexpensive, relatively non-toxic, easily recoverable and reusable with minimum loss in catalytic properties^[2-3]; but also create an easy, greener, energy saver and toxic preventer synthetic pathway^[4]. The charm towards nanoparticles owes to the fact that the active component of the catalyst possesses significant physical, surface chemical and catalytic properties with a high specific surface area,

thereby significantly enhancing the contact area with the reactants leading to faster reaction rates with lesser reaction time^[5]. Further, with the aforesaid outlook of eco-friendliness, utilizing sonochemistry as a greener tenet for accelerating reaction is highly appreciated^[6]. Exploitation of sound waves as a power source has established a new trend as “Ultrasonic Assisted Organic Synthesis” (UAOS) and “Synthetic Organic Sonochemistry” in the field of eco-compatible synthetic procedures^[7-8]. The “acoustic cavitation” principle of ultrasound aim at convenient, quicker and selective energy and mass transfer for better yield, shorter reaction times under milder conditions compared to the harsh traditional methods of conventional heating^[9-10].

Synthesis of biologically and medicinally important organic compounds with improved methodologies and strategies had always been a matter of great interest for the synthetic chemists^[11]. Spiroheterocyclic compounds are among the oldest well recognized and most extensively studied moieties^[12]; which enjoy great synthetic and biological importance in organic as well as medicinal chemistry^[13]. Spirooxindole moiety is one of the most effective, newly emerging class of spiroheterocycles; as besides being well documented in a number of bioactive naturally occurring alkaloids, viz. rhynchophylline, formsamine, horsfiline, elacomine, spirotryprostatin A & B^[14-16] etc., it has also proved as a good synthon^[17] for the preparation of various hybrids showing many interesting and beneficial properties such as antibiotic agents^[18], inhibitors of human NK-1 receptor^[19], anti-cancer^[20], CRTH2 receptor antagonist^[21], antimicrobial^[22], anti-malarial^[23], a potent non-peptide inhibitor of microtubule assembly^[24], a cholinesterase inhibitory activity^[25], and many more. It is also well known that spirooxindoles show enhanced and better biological activity when annulated or modified at the C-3 position^[26].

Pyrazole and its derivatives have attracted much attention from the scientific community in the recent years owing to their significance in the fields of both syntheses and pharmaceuticals with an immense range of applications and outstanding biological activities^[27-29]. Amalgamation of this pharmacophore into the main structural motif has led to an accretion and enhancement of its medicinal importance^[30]. Moreover, the presence of this unit in various natural products, and drugs, including Celecoxib, Rimonabant, Ruxolitinib, Crizotinib, AT7519 and Tozasertib has further confirmed its prospective therapeutic activity^[31].

Since the dawn of exploration of biologically imperative motifs; quinoline scaffold has made an outstanding contribution in the field of not only pharmaceuticals but in organic synthesis also^[32]. Its prevalence in a huge number of pharmacologically active natural and synthetic compounds such as chloroquine, quinine, amodiaquine, piperazine, primaquine, mefloquine and many more make this an integral versatile moiety^[33]. Although, the name quinoline itself is a well known designation in the treatment against malaria^[34], but, it also possess various other important biological activities such as antimicrobial^[35], antileishmanial^[36], antioxidant^[37], antiproliferative^[38], anticancer^[39], anti HIV^[40] and many such exceptional possessions. Some of the well known biologically active compounds with these pharmacophores are shown in **(Fig.1)**.

This formation of a library of hybrids with amalgamation of these diversely structured motifs is highly enviable from the synthetic and pharmaceutical point of view **(Scheme 1)**. However, shortcomings of the earlier reported methods^[41] such as; high temperatures, longer reaction times, use of relatively expensive reagents, harsher reaction conditions, tedious work-up procedure, exasperating catalyst separation step make an urgent need of developing

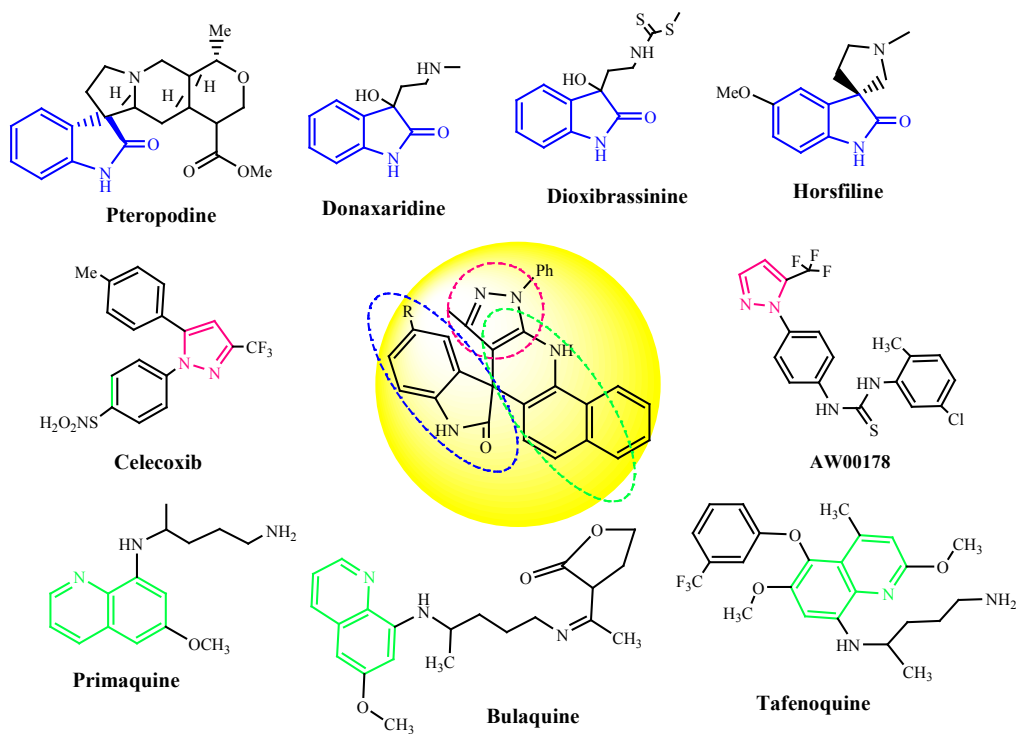
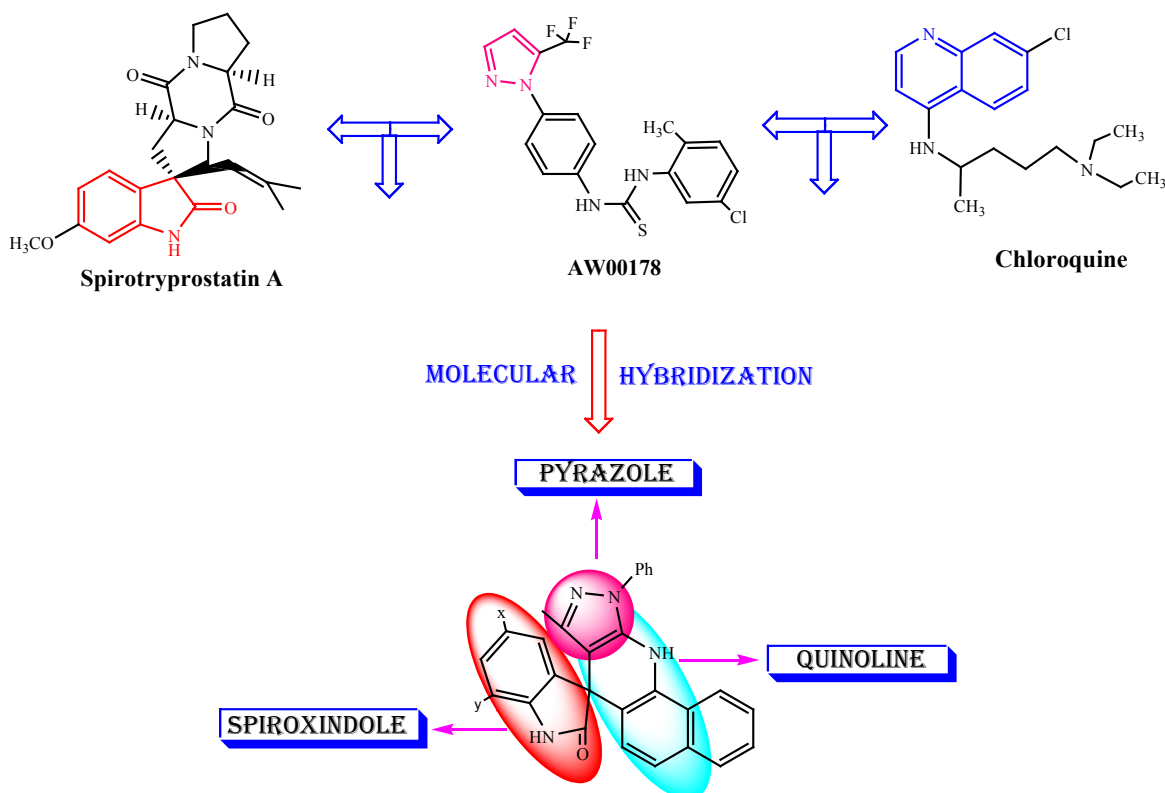
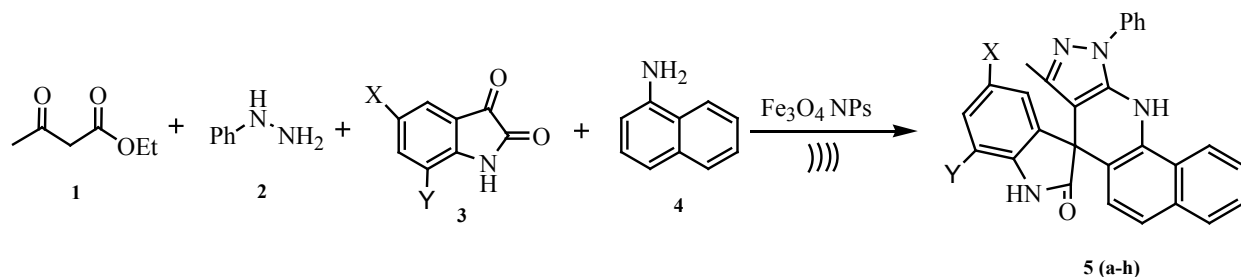


Fig 1. Some biologically important compounds were containing these moieties as integral scaffolds.



Scheme 1. Formation of hybrids containing biologically active pharmacophores in a single unit through molecular hybridization approach.



Scheme 2: Ultrasound promoted synthesis of hybrids of spirooxindole-pyrazole and quinoline moieties by the multicomponent reaction of **1**.ethylacetoacetate, **2**.phenylhydrazine, **3**.substituted isatin, **4**.naphthylamine catalyzed by magnetite nano-particles.

newer greener approaches as inevitable. In continuation of our research interest and efforts concerning the development of new greener approaches for the multi-component syntheses of biologically active heterocyclic motifs; we have reported herein an efficient nano-catalysed time-competent ultrasound promoted synthesis of a series of novel hybrids of biologically imperative spirooxindole-pyrazole and quinoline moieties (**Scheme 2**).

2. Experimental

2.1. General

All the chemicals used were of research grade and used without further purification. The melting points of compounds were determined on a Toshniwal apparatus and were uncorrected. The purity of the compounds was checked by TLC using silica Gel-G coated glass plates. IR spectra were recorded on a Shimadzu FT IR-8400S spectrophotometer using KBr pellets. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 at 500 and 125 MHz in DMSO- d_6 using TMS as an internal reference. The mass spectra of representative compounds were recorded using a JEOL SX-102 spectrometer at 70eV. Elemental microanalyses were carried out on a Carlo- Erba 1108 CHN analyzer. Sonication was carried out with the help of an ultrasonic bath (Bandelin Sonorex) operating at 230 V with a 33 kHz output frequency. For the characterization of MNP's; Scanning

Electron Microscopy (SEM) was carried out in EVO18 Ziess operating at an accelerating voltage of 20 keV; in which the composite was pasted on silver tape for imaging. Transmission electron microscopy (TEM) was done in an FEI Tecnai-G2 T20, for which dispersed sample was loaded onto a copper grid and dried in air.

Spectral Analysis:

1. ***Spiro[1H-pyrazolo[3,4-b]benzo[h]quinolin-4,3-indoline]-4,11-dihydro-3-methyl-1-phenyl-2'-one (5a)***. IR (KBr): 3340, 3210, 1688 cm^{-1} ; ^1H NMR (500 MHz, DMSO- d_6): 1.25 (3H, s, CH_3), 6.90-8.21 (15H, m, Ar-H) 8.92 (1H, s, NH), 12.34 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO- d_6): 12.2, 54.8, 102.8, 115.3, 117.5, 119.8, 120.3, 121.6, 122.6, 123.2, 123.6, 124.5, 125.8, 127.2, 128.7, 129.1, 130.2, 131.9, 132.5, 134.1, 138.6, 139.1, 140.6, 143.8, 180.2; MS (ESI) m/z : 428.05 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{28}\text{H}_{20}\text{N}_4\text{O}$: C, 78.49; H, 4.70; N, 13.08%. Found: C, 78.42; H, 4.68; N, 13.19%.
2. ***Spiro[1H-pyrazolo[3,4-b]benzo[h]quinolin-4,3-indoline]-4,11-dihydro-3-methyl-5'-methyl-1-phenyl-2'-one (5b)***. IR (KBr): 3315, 3175, 1682 cm^{-1} ; ^1H NMR (500 MHz, DMSO- d_6): 1.54 (3H, s, CH_3), 2.40 (3H, s, CH_3), 6.81-7.51 (14H, m, Ar-H), 8.93 (1H, s, NH), 12.69 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO- d_6): 15.2, 22.6, 55.6, 98.4, 114.6, 117.8, 118.9, 119.4,

- 120.7, 121.3, 122.9, 123.5, 124.3, 125.2, 127.1, 127.5, 128.3, 129.6, 130.1, 131.9, 132.4, 134.7, 136.5, 141.8, 145.0, 180.8; MS (ESI) m/z: 442 [M+H]⁺. Anal. Calcd for C₂₉H₂₂N₄O: C, 78.71; H, 5.01; N, 12.66%. Found: C, 78.65; H, 5.04; N, 12.73%.
3. ***Spiro[1H-pyrazolo[3,4-b]benzo[h]quinolin-4,3-indoline]-4,11-dihydro-3-methyl-5',7'-dimethyl-1-phenyl-2'-one (5c)***. IR (KBr): 3328, 3158, 1672 cm⁻¹; ¹H NMR (500 MHz, DMSO-d⁶): 1.58 (3H, s, CH₃), 2.26 (3H, s, CH₃), 2.37 (3H, s, CH₃), 6.90-7.62 (13H, m, Ar-H), 8.94 (1H, s, NH), 12.72 (1H, s, NH). ¹³C NMR (125 MHz, DMSO-d⁶): 15.8, 21.0, 29.6, 56.3, 105.1, 112.0, 114.3, 115.8, 117.2, 118.7, 119.2, 120.5, 121.7, 123.1, 124.3, 125.6, 126.9, 127.3, 128.7, 128.9, 129.4, 130.2, 132.1, 134.6, 141.6, 144.8, 181.2; MS (ESI) m/z: 456.02 [M+H]⁺. Anal. Calcd for C₃₀H₂₄N₄O: C, 78.92; H, 5.30; N, 12.27%. Found: C, 78.95; H, 5.32; N, 12.21%.
4. ***Spiro[1H-pyrazolo[3,4-b]benzo[h]quinolin-4,3-indoline]-4,11-dihydro-3-methyl-5'-chloro-1-phenyl-2'-one (5d)***. IR (KBr): 3361, 3148, 1689 cm⁻¹; ¹H NMR (500 MHz, DMSO-d⁶): 2.18 (3H, s, CH₃), 6.80-7.84 (14H, m, Ar-H), 9.42 (1H, s, NH), 12.77 (1H, s, NH). ¹³C NMR (125 MHz, DMSO-d⁶): 12.9, 57.9, 98.7, 115.7, 118.6, 119.0, 120.9, 121.4, 122.2, 122.6, 123.8, 124.1, 125.3, 126.2, 127.1, 129.7, 130.5, 132.6, 134.6, 137.1, 137.4, 139.2, 148.5, 148.9, 182.0; MS (ESI) m/z: 446 [M+H]⁺. Anal. Calcd for C₂₈H₁₉FN₄O: C, 75.32; H, 4.29; N, 12.55%. Found: C, 75.68; H, 4.30; N, 12.59%.
5. ***Spiro[1H-pyrazolo[3,4-b]benzo[h]quinolin-4,3-indoline]-4,11-dihydro-3-methyl-5'-bromo-1-phenyl-2'-one (5e)***. IR (KBr): 3365, 3158, 1687 cm⁻¹; ¹H NMR (500 MHz, DMSO-d⁶): 1.57 (3H, s, CH₃), 6.80-7.79 (14H, m, Ar-H), 9.37 (1H, s, NH), 12.76 (1H, s, NH). ¹³C NMR (125 MHz, DMSO-d⁶): 13.6, 54.8, 100.3, 115.4, 116.3, 117.7, 119.8, 121.1, 121.7, 122.3, 123.5, 125.2, 126.7, 127.8, 128.3, 129.5, 130.5, 131.1, 132.2, 133.9, 137.6, 138.2, 143.6, 146.5, 181.5; MS (ESI) m/z: 507.3[M+H]⁺. Anal. Calcd for C₂₈H₁₉BrN₄O: C, 66.28; H, 3.77; N, 11.04%. Found: C, 66.30; H, 3.79; N, 11.02%.
6. ***Spiro[1H-pyrazolo[3,4-b]benzo[h]quinolin-4,3-indoline]-4,11-dihydro-3-methyl-5'-iodo-1-phenyl-2'-one (5f)***. IR (KBr): 3378, 3165, 1681 cm⁻¹; ¹H NMR (500 MHz, DMSO-d⁶): 1.83 (3H, s, CH₃), 6.72-8.55 (14H, m, Ar-H), 9.17 (1H, s, NH), 12.70 (1H, s, NH). ¹³C NMR (125 MHz, DMSO-d⁶): 13.9, 56.4, 96.4, 109.8, 116.6, 117.2, 118.0, 120.4, 121.6, 122.6, 123.0, 124.5, 126.3, 126.8, 127.4, 129.3, 130.7, 132.4, 134.6, 138.1, 138.6, 140.5, 145.6, 149.8, 183.2; MS (ESI) m/z: 554.01[M+H]⁺. Anal. Calcd for C₂₈H₁₉IN₄O: C, 60.66; H, 3.45; N, 10.11%. Found: C, 60.77; H, 3.51; N, 10.08%.
7. ***Spiro[1H-pyrazolo[3,4-b]benzo[h]quinolin-4,3-indoline]-4,11-dihydro-3-methyl-5'-nitro-1-phenyl-2'-one (5g)***. IR (KBr): 3385, 3175, 1692 cm⁻¹; ¹H NMR (500 MHz, DMSO-d⁶): 1.97 (3H, s, CH₃), 6.84-8.43 (14H, m, Ar-H), 9.26 (1H, s, NH), 12.36 (1H, s, NH). ¹³C NMR (125 MHz, DMSO-d⁶): 13.7, 56.8, 101.8, 114.6, 115.2, 118.4, 118.7, 119.5, 120.4, 122.6, 122.8, 123.3, 124.1, 126.0, 126.5, 128.3, 129.2, 130.9, 131.7, 134.8, 138.1, 141.2, 146.7, 148.9, 183.7; MS (ESI) m/z: 473.10[M+H]⁺. Anal. Calcd for C₂₈H₁₉N₅O₃: C, 71.03; H, 4.04; N, 14.79%. Found: C, 71.12; H, 4.11; N, 14.68%.
8. ***Spiro[1H-pyrazolo[3,4-b]benzo[h]quinolin-4,3-indoline]-4,11-dihydro-3-methyl-5'-methoxy-1-phenyl-2'-one (5h)***.

IR (KBr): 3372, 3184, 1678 cm^{-1} ; ^1H NMR (500 MHz, DMSO-d_6): 2.12 (3H, s, CH_3), 3.64 (3H, s, OCH_3), 6.71-8.02 (14H, m, Ar-H), 9.33 (1H, s, NH), 12.71 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 13.2, 32.6, 57.3, 102.4, 112.5, 113.1, 114.8, 116.7, 117.9, 118.2, 118.7, 121.6, 122.3, 122.9, 124.3, 126.7, 128.2, 128.7, 132.8, 134.1, 136.1, 139.8, 144.7, 148.5, 165.8, 184.2; MS (ESI) m/z : 458[M+H] $^+$. Anal. Calcd for $\text{C}_{29}\text{H}_{22}\text{N}_4\text{O}_2$: C, 75.97; H, 4.84; N, 12.22%. Found: C, 76.12; H, 4.71; N, 12.48%.

2.2 Nano magnetite (Fe_3O_4) preparation

After going through the literature, we found an efficient and a simplistic synthetic procedure for the synthesis of MNPs [42]. Firstly, a mixture of ferric chloride; $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (6.1g, 0.02 mol) and ferrous chloride; $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ (2.35g, 0.01 mol) in a fixed molar ratio of 2:1 (Fe^{+3} : Fe^{+2}) were taken in 100 mL of distilled water. The mixture was kept on magnetic stirring maintained at a temperature of 90°C . After few min., ammonium hydroxide solution (10 ml, 25%) was added drop wise until the formation of nanoparticles which changes the color of the mixture to black. Later, after 1 h, the mixture was cooled at room temperature and black precipitate containing the MNP's were isolated with the help of a magnet, repeatedly washed with de-ionized water for purification.

3. Results and discussion

3.1 Synthesis and characterization of catalyst

The magnetite Fe_3O_4 NPs have been synthesized *via* co-precipitation method as described earlier with excellent catalytic and magnetic properties. They also possess high stability with easy recyclability. The synthesized MNPs were characterized by FT-IR, SEM and TEM analyses. In FT-IR spectrum, a characteristic peak at 589 cm^{-1} showed the interactions of

Fe-O bonds in the structure of nano- Fe_3O_4 (**Fig. 2a**).

The morphology, shape, size and distribution of nanoparticles were characterized by SEM and TEM imaging. As can be seen from the SEM image in **Fig. 2(b)**, the Fe_3O_4 nanoparticles are granular in shape and uniformly distributed over the surface. The TEM images in **Fig. 2 (c & d)** showed that the nanoparticles are extremely small in the size with an average diameter of 10–20 nm. The EDAX analysis (**Fig. 2f**) further confirmed the presence of Fe and O atoms in the MNP's. We have also done the mapping of the nanoparticles as shown in **Fig. 2 (b)**. As shown in the figure; yellow color denotes the distribution of Fe atoms and violet color represents the O atoms in the sample which further confirms the uniformity in the sample. After characterizing the synthesized MNPs, their applicability for the catalysis was investigated.

3.2 Catalytic Activity measurement

To examine the catalytic activity of nanoparticles in the synthesis; ethyl acetoacetate **1**, phenylhydrazine **2**, isatin **3**, and naphthalen-1-amine **4** were chosen as model substrates for the reaction under ultrasonic irradiation. A control experiment was conducted in the absence of catalyst. The reaction was incomplete even after 60 min. Thus, the initial efforts were focused on the systematic evaluation of various catalyst systems (**Table 1**). The competence of their activity was analyzed by comparing their TOF values (Turn over frequency). In the primary studies, we found out that Fe_3O_4 NPs turn out to be the better one with lower reaction time as well as higher product yield. The significance of nano-size over its bulk Fe_3O_4 analogue could be easily seen by comparing the yields and TOF values (**Table 1, entry 9 and 6**). These results proved the superiority of this method in terms of yield and reaction time. As indicated from **Table 1**, 5 mol% of catalyst loading was

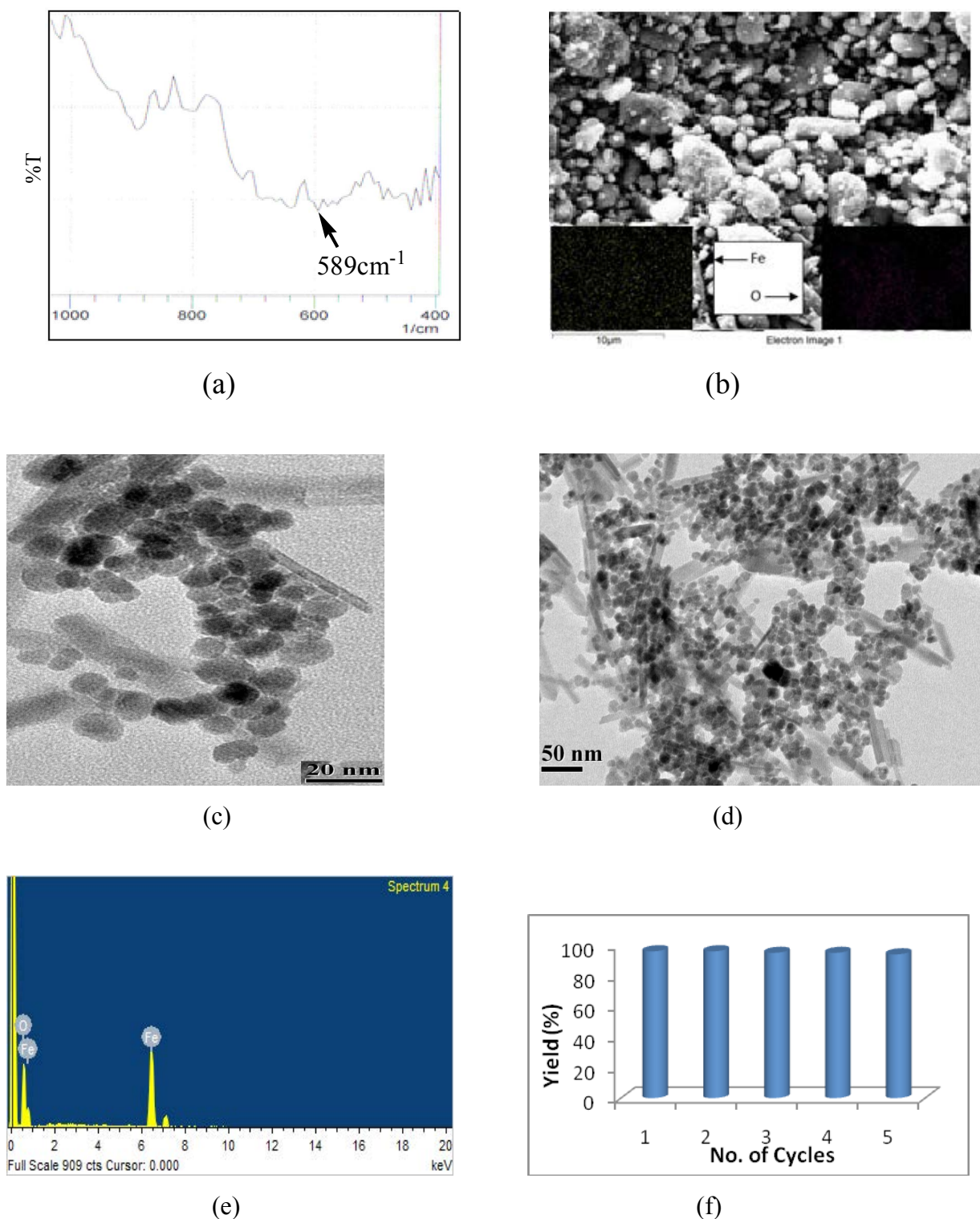


Fig. 2 Characterization of the synthesized Fe_3O_4 catalyst: (a) FT-IR analysis. (b) SEM image together with mapping of the atoms in the MNP's. (c) TEM images of the catalyst at 50 nm scales and at (d) 20 nm scales. (e) Recyclability of the catalyst. (f) EDAX pattern of the prepared catalyst.

adequate to catalyze the reaction, excessive amount of catalyst did not increase the yield remarkably. Therefore, with lower catalyst loading the desired product could be obtained with higher yields and lesser time proving the superiority of the method.

Entry	Catalyst	Time (min.)	Yield (%)*	TOF (h ⁻¹)
1	-	60	-	-
2	<i>p</i> -TSA (10 mol%)	45	55	82.5
3	H ₃ BO ₃ (10 mol%)	42	46	73.9
4	L-Proline (10 mol%)	40	48	81
5	CAN (10 mol%)	38	40	71
6	FeCl ₃ ·6H ₂ O (10 mol%)	35	45	86.7
7	Fe ₃ O ₄ (10 mol%)	30	46	103.5
8	Fe ₃ O ₄ NPs (10 mol%)	12	95	534.3
9	Fe ₃ O ₄ NPs (5 mol%)	12	95	1128.1

* isolated yields

Table 1: Comparison of catalytic activity of catalysts for the calculation of optimized catalytic concentration.

Further, for having an outlook over the enhancement in the catalytic activity of the reaction by the implementation of ultrasound as a source of energy; the representative reaction was also carried out in both the nonconventional and conventional conditions and to our surprise there was an extreme amplification in the yield from 48 to 95 with lowering in the time period of 90 min. to only 12 min. The turnover frequency of the NPs was also affected a lot by the ultrasound application (**Table 2**). Thus we carried out further reactions with 5 mol% of the nanoparticles under ultrasound irradiation.

Entry	Condition	Catalyst	Temp. (°C)	Time (min.)	Yield (%)*	TOF (h ⁻¹)
1	Conventional	Fe ₃ O ₄ NPs (5 mol%)	80	90	48	76
2	Ultrasound	Fe ₃ O ₄ NPs (5 mol%)	80	12	95	1128.1

* isolated yields

Table 2: Dependency of catalytic activity of catalysts under nonconventional and conventional conditions

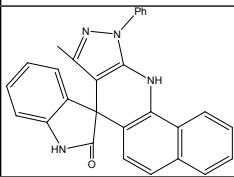
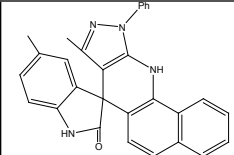
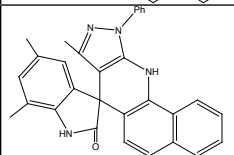
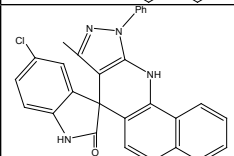
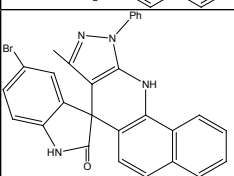
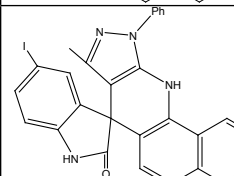
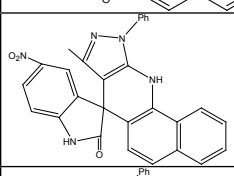
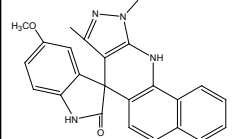
3.3 General procedure for the recyclability of the catalyst:

One of the most attractive and sustainable greener tenet of the methodology is the easily recoverability and recyclability of the catalyst. The MNPs were separated by normal external magnet and were reused for further reactions. It is noteworthy to note that the catalyst maintained its activity and could be efficiently reused for the same experiment for over five cycles (**Fig. 2e**). The characteristics obtained from TEM of fresh and used catalysts are almost similar, which suggest the retention of structure and morphology of Fe₃O₄ NPs after repeated use as catalyst.

3.4 General procedure for the formation of Spiro[1*H*-pyrazolo[3,4-*b*]benzo[*h*]quinolin-4,3-*indoline*]-4,11-dihydro-3-methyl-1-phenyl-2'-one (5a):

Equimolar mixture of ethyl acetoacetate **1** (0.260g, 2mmol), phenylhydrazine **2** (0.216g, 2mmol), isatin **3** (0.294g, 2 mmol), and naphthalen-1-amine **4** (0.288g, 2mmol) was taken in a conical flask which was immersed in the water bath of ultrasonic cleaner. The flask was positioned 0.5 cm above the bottom of the bath at 80°C. The mixture was sonicated for the periods indicated in the **Table 3**. The progress of the reaction was monitored by TLC. After completion of the reaction as confirmed by TLC (eluent: *n*-hexane:ethylacetate), hot ethanol

was added and magnetic nanoparticles were separated by a normal magnet. The solvent was evaporated and the crude products were recrystallized from ethanol yielding the pure products in 80-90% yields. The products were characterized by IR, ¹H NMR, ¹³C NMR, Mass spectra and via comparison of their melting points with the reported ones [41(c)].

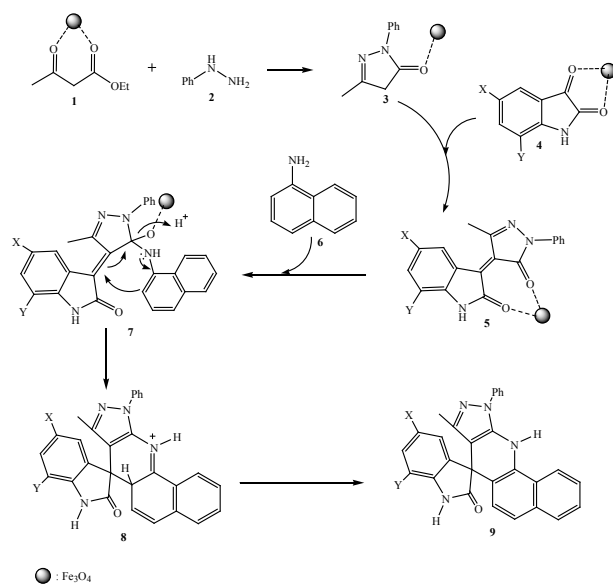
S.No	Entry	Hybrid Moiety	X	Y	Time (min.)	Yield (%)*	M.P. (°C)
1	5a		H	H	12	95	250-252
2	5b		CH ₃	H	12	93	268-270
3	5c		CH ₃	CH ₃	14	92	283-285
4	5d		Cl	H	16	90	270-272
5	5e		Br	H	18	88	290-292
6	5f		I	H	18	90	>300
7	5g		NO ₂	H	20	91	>300
8	5h		OCH ₃	H	18	90	289-291

* isolated yields

Table 3: Details of synthesis of derivatives of spiro[1H-pyrazolo[3,4-b]benzo[h]quinolin-4,3-indoline]-4,11-dihydro-3-methyl-1-phenyl-2'-one under ultrasound irradiation.

3.5 Reaction mechanism:

Based on the literature survey, we could propose a plausible mechanism of the reaction (**Scheme 3**). The Lewis acid sites of NPs are coordinated to the oxygen of carbonyl groups of both ethylacetoacetate and isatin, thus enhancing the electrophilic activation of the same. This results in the rapid formation of 1*H*-phenylpyrazolin-5-ones, which further undergoes Knoevenagel condensation with the activated isatin moiety to form the key intermediate diazafulvalene. Further, this reactive diazafulvalene is again coordinated with NPs at the carbonyl oxygen, which benefits its swift addition with naphthylamine. Naphthylamine showed the nucleophilic addition at both the C- and N-termini of the enamine functionality of the reactive adduct. Finally the hybrid molecule was formed after releasing a water molecule. The Lewis acidity of the MNPs further accelerates the rate of the reaction thus lowering the reaction time and enhancing the yield.



Scheme 3: Plausible mechanism for the synthesis of derivatives of hybrids of Pyrazolo-Quinoline-Oxindoles Moieties catalysed by magnetite nanoparticles.

4. Conclusion

The present work describes the synthesis, characterization, and catalytic activity of nano magnetite (Fe_3O_4). The MNPs showed good catalytic activity for the efficient and facile synthesis of hybrids containing different moieties by the multicomponent reaction of isatins, naphthylamine, phenylhydrazine and ethylacetoacetate under ultrasound irradiation. Catalytic processes with shorter reaction times safeguard the catalyst from deactivation and decomposition. This method offers several advantages, including high yield, short reaction time, simple work-up procedure, ease of separation, and recyclability of the nanocatalyst, as well as the easier scaling up for large scale synthesis while avoiding the use of high temperature, pressure and toxic chemicals.

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