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Article

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Posted Date: October 7th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11103157/v1>

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Additional Declarations: No competing interests reported.

Cobalt stearate-modified Fe₃O₄: a new magnetic metal-surfactant nano-catalyst for the sustainable in-water synthesis of pyrazole derivatives

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Abstract

Considering synergistic turnovers of surfactants, Lewis acidity of Co^{2+} , and magnetic nano-catalysts, a novel nano-magnetic metal-surfactant as cobalt stearate ($\text{Co}(\text{St})_2$) modified Fe_3O_4 ($\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$) was designed for the in-water multi-component syntheses of pyrazoles. Conversion of stearic acid (with 2.16 nm length) to sodium stearate, exchange of Na^+ with Co^{2+} , and magnetization of the given $\text{Co}(\text{St})_2$ by magnetite nanoparticles gave $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ that characterized by various techniques. Since critical micelle concentration (CMC) 6.5×10^{-4} M (406.8 ppm) for $\text{Co}(\text{St})_2$ at 25 °C, 33% TGA-approved $\text{Co}(\text{St})_2$ in $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$, and maximum catalytic activity at 0.002 g/mL (1.5 CMC) for the in-water synthesis of pyrazoles, possible hemi-micellar hydrophobic aggregates concluded. These magnetic hemi-micelles bring about Co^{2+} Lewis acidity parallel with improvement in surface tension, organic solubility, or activation energy in the multi-component synthesis of either pyrazolo-quinolinones, -pyridines, or -pyrimidinones in water. Versatility, reusability, low catalyst loading, short reaction times, simple work-up, no organic solvent consumption, and purification method are advantages of this nano-surfactant-based protocol. Such proficiencies make this nano procedure suitable for future water-based organic synthesis, oil-water solubility, pollutant removal, and biomaterials delivery.

Keywords Magnetic metal surfactants; cobalt stearate; in-water multi-component reactions; sustainable organic synthesis; pyrazolo-quinolinones; tetrahydro-dipyrazolopyridines; pyrazolo-pyrimidinones.

Introduction

Developing of sustainable organic transformations is an essential challenge in green chemistry¹. In this viewpoint and because of the unique polarity, safety, E-factor, heat capacity, and dielectric constant of water,² organic synthesis as in-water³ or on-water⁴ reactions have been developed. Despite hydrophobic interaction services to accelerate the water-based organic reactions⁵, water-sensitivity of most catalysts/reagents and poor solubility of organic substances in water are challenging. The pH-treatment⁶, co-solvent⁷, and surfactant⁸ are strategies developed to overcome these issues, which among the latter ones is much favorite. Surfactants reduce the surface tension between liquid phases⁹, facilitate the organic material dispersion in water phases¹⁰, and help to pharmaceutical delivery in cells¹¹ by their dual hydrophilic/hydrophobic characteristics. Alternatively, surfactants are known as detergents¹², emulsifiers¹³ and micelle homes in their critical micelle concentration (CMC)¹⁴. These amphiphilic materials categorize as non-ionic¹⁵, cationic^{16, 17}, anionic¹⁸, zwitterionic¹⁹, gemini²⁰, and metal-surfactants (MSs)²¹. The MSs are a novel generation of surfactants²² with twofold benefits of surfactants and metal-cations for promoting of water-based reactions by transition state stabilizing, activation energy lowering, and the controlled nano- or micro-reactors providing²³. Cobalt stearate (Co(St)₂) is a typical MS applied in super-hydrophobic nanocomposites^{23, 24}, even though it is not completely reusable.

Magnetization of MSs, by either magnetic immobilization²⁵ or entering a magnetic cation in the structure²⁰, is a good description for reusability issues of surfactants. Due to drawbacks associated with the entering magnetic metal ions to surfactant structure²⁶, immobilization of MSs on magnetic nanoparticles (MNs) is desirable. In our opinion, this strategy has synergistic effects for both of MSs and MNs, so impregnation of MNs by MSs forms a protective shell to prevent

MNs agglomeration, achieves practically reusable MSs as safe, high active surface, and magnetically reusable catalysts²⁵. Moreover, developing of the in-water organic transformations^{5, 27} catalyzed by nano structured magnetic MSs has extra agreement with the green chemistry.

Tetrahydro-dipyrzolopyridines (THDPPs) are prevalent heterocyclic pharmacophores with a range of bio-activities that because of these diversity, multi-component reactions (MCRs) including *pseudo*-4-CRs and *pseudo*-6-CRs have been developed for their synthesis²⁸⁻³². Pyrazolo-quinolinones (PQs) are biologically-active two-folded nitrogen heterocycles and product of the acid-catalyzed three-component reaction of the expensive component 2-amino pyrazole, urea, and dimedone³³⁻⁴⁴. Pyrazolo-pyrimidinones (PyPyms) are also biologically-active fused heterocycles prepared by condensation of urea, an aldehyde, and 3-methyl pyrazolone that its scale up synthesis has recently reported for mechanistic studies^{45, 46}. However, the development of more simple procedures for the in-water synthesis of THDPPs, PQs, and PyPyms from more readily available starting materials with no using of extra organic solvents, reagents, and purification methods is desirable. As a part of our researches on water-based MCRs^{31, 32, 47, 48}, we wish to apply new magnetic MSs in developed MCRs for the synthesis of PQs³³⁻⁴⁴, THDPPs²⁷⁻³², and PyPyms^{45, 46}. Thus, the goals of this research are green and sulfate-free preparation of Co(St)₂, its hybridization with MNs to give a magnetically-separable MS nano-catalyst, and application of Fe₃O₄@Co(St)₂ in the improved, in-water, and MCR synthesis of three classes of pyrazoles. In these new approaches, water is added at the end of each reaction, the nanomagnetic catalyst is separated, and the precipitated product is filtered without using any additional chemical (Fig 1).

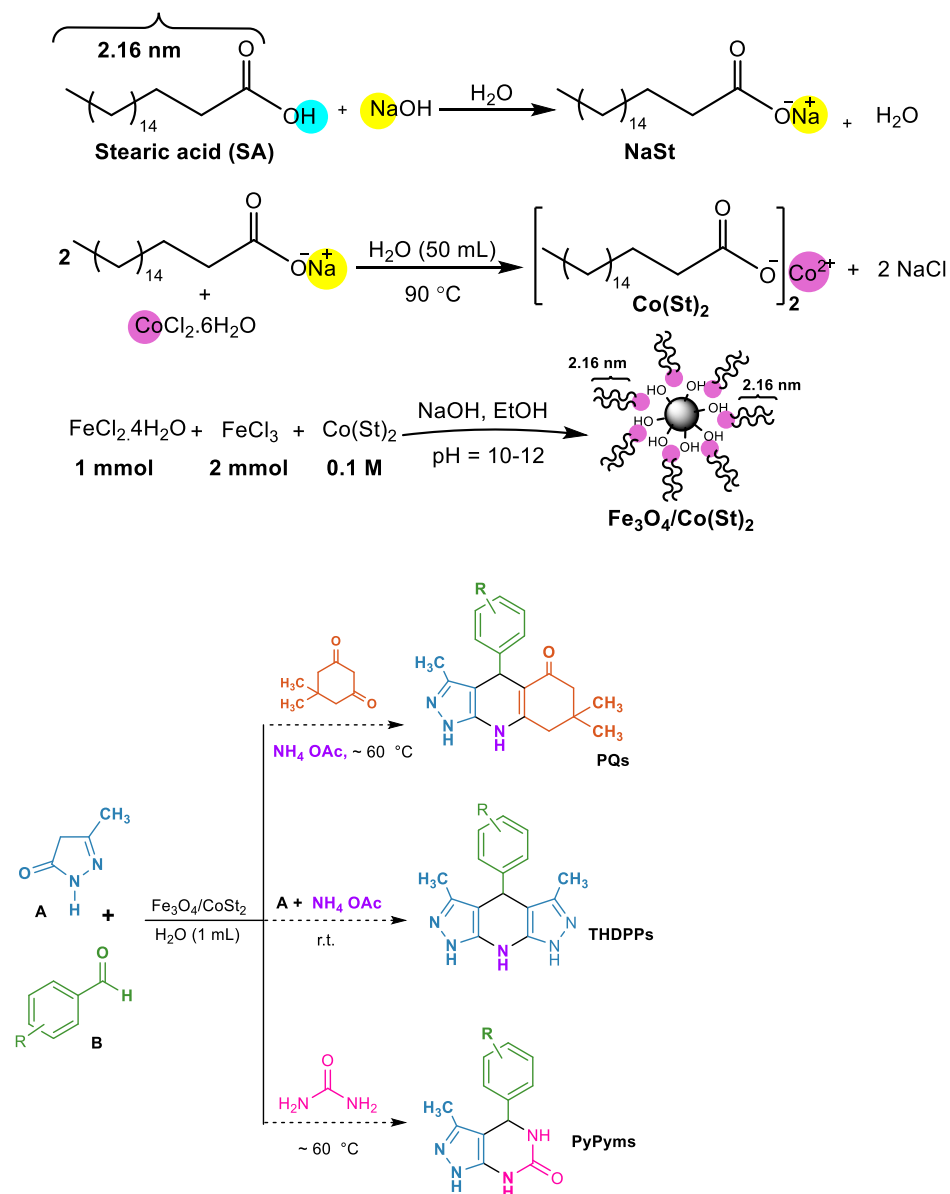


Fig. 1 Preparation of $\text{Fe}_3\text{O}_4@\text{Co}(\text{St})_2$ for MCR synthesis of pyrazole derivatives

Experimental section

Materials and methods

All chemicals were purchased from Merck (Germany) and Sigma without further purification. Yields refer to the isolated products that characterized by spectral data. A magnetic stirrer (Heidolph, Germany) was used for stirring. The Fourier transform infrared (FT-IR) spectra as

KBr disks were recorded on a Bruker spectrophotometer model FT-IR-680 Plus, Jasco, Bruker Equinox-55 (Germany) in a the range of 4000 cm^{-1} - 400 cm^{-1} , resolution of 4 cm^{-1} , and OPUS software by Bruker Optics GmbH, Germany. Melting points were determined by a Buchi B-540 apparatus (Buchi, Switzerland) by placing in capillary tubes and heating at controlled rate of $1\text{ }^{\circ}\text{C}$ per 1s. The vibrating sample magnetometer (VSM) was monitored by the Lake Shore Cryotronics 7404 at 298 K. Field-emission scanning electron microscopy (FESEM) was performed with MIRA3 TESCAN (TESCAN, Czech Republic). Size and distribution of nanoparticles were detected by Transmission electronic microscopy (TEM) (H-7500, Hitachi, Japan). The X-ray diffraction (XRD) and thermal gravimetric analysis (TGA) were recorded with PHILIPS PW1730 and TGA-TA Q600, respectively. The nuclear magnetic resonance (NMR) spectra were recorded in CDCl_3 or $\text{DMSO-}d_6$ on Bruker Avance NMR 500 MHz (Germany).

Preparation of Co(St)_2 as a nano MS catalyst

The concerned nano MS was prepared in two simple steps: sodium stearate (NaSt) was firstly synthesized by mixing the nanostearic acid⁴⁹ (35 mmol) and sodium hydroxide (35 mmol) in distilled water (30 mL) at $60\text{ }^{\circ}\text{C}$ for 3 h as a white solid powder, which filtered and dried. In the second step, a mixture of NaSt (20 mmol) and $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ (10 mmol) was magnetically stirred in distilled water (50 mL) at $90\text{ }^{\circ}\text{C}$ for 4 h to give Co(St)_2 as a purple solid. The given purple pellets were washed, dried, and characterized by different analyses.

Preparation of $\text{Fe}_3\text{O}_4/\text{Co(St)}_2$ as a magnetic metal-surfactant (MMS)

The three individual solutions of $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ (1 g), FeCl_3 (1.75 g), and Co(St)_2 (0.8 g) in distilled water (15 mL) were stirred for 30 min. The two iron salt solutions were then added to the suspension of Co(St)_2 , the resulting mixture was stirred for extra 30 min, sodium hydroxide

(6 M) added for pH adjustment (pH $\sim$ 12) at room temperature, and the mixture magnetically stirred at high speed for 2.5 h at 40 °C. The resulting dark brown precipitate was collected by a magnet, washed with water, and dried in an oven for 3 h. To support proposed structure of $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$, CoFe_2O_4 was prepared and compared.

General method for the new four-component synthesis of PQs

A mixture of an aldehyde (1 mmol), 3-methyl-1H-pyrazol-5(4H)-one (1 mmol), dimedone (1 mmol), NH_4OAc (1 mmol), and $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ (0.002 g) in water (1 mL) was stirred at $\sim$ 60 °C for appropriate times (Table 1). After the reaction completion (TLC monitoring), water was added, catalyst collected by a magnet, and the pure PQ product was filtered with excellent yield. All data for the characterized products were matched with ones prepared by three component reaction of an aldehyde, 3-methyl-1H-pyrazol-5-amine, and dimedone³¹⁻⁴².

General method for the pseudo four-component synthesis of THDPPs

For the synthesis of THDPPs, $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ (0.002 g) was added to the mixture of an aldehyde (1 mmol), 3-methylpyrazolone (2 mmol), and anhydrous NH_4OAc (1 mmol) in water (1 mL) and stirred at room temperature for 3-15 min until the product precipitation. Then, water was added, the catalyst was collected by a magnet, and the pure THDPP was isolated after the cold water adding and precipitate filtration.

General method for the synthesis of PyPyms

A mixture of an aldehyde (1 mmol), 3-methyl-1H-pyrazol-5(4H)-one (1 mmol), urea (1 mmol), and $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ (0.002 g) in 1 mL of water was stirred at approximately 60 °C for the required time. Upon confirming reaction completion via TLC, water was added and the catalyst

was separated using a magnet. The pure PyPym product was then filtered and isolated in excellent yield. The structure of all products was verified through spectroscopic analysis.

Spectroscopic data for the selected products

The characteristic data for the selected products are designated below, although spectroscopic spectra (FT-IR, ^1H NMR, and ^{13}C NMR) for all final products are presented in Figs S1-S59.

4-(4-Hydroxyphenyl)-3,7,7-trimethyl-6,7,8,9-tetrahydro-1H-pyrazolo[3,4-b]quinolin-5(4H)-one (PQ3):

Yield: 92%; light pinkish solid, m.p. = 274-276 °C. FT-IR (KBr): 3395, 3269, 3026, 2982, 1662, 1614, 1594, 1512, 1467, 1359, 1202, 1166 cm^{-1} . ^1H NMR (400 MHz, DMSO-*d*6): δ (ppm) = 0.74 (s, 3H, CH₃), 0.80 (s, 3H, CH₃), 1.70 (s, 3H, CH₃), 1.91-1.93 (m, 2H), 2.19-2.26 (m, 2H), 4.62 (s, 1H), 6.35 (d, *J* = 8 Hz, 2H), 6.70 (d, *J* = 8 Hz, 2H), 8.80 (s, 1H, OH), 9.41 (s, 1H, NH), 11.49 (s, 1H, NH-pyrazole). ^{13}C NMR (100 MHz, DMSO-*d*6): δ = 9.3, 26.8, 28.8, 31.8, 33.9, 40.9, 50.4, 104.3, 107.3, 114.3, 127.9, 134.6, 139.0, 146.2, 152.3, 154.7, 192.4 (Figs S7–S9).

3,5-Dimethyl-4-phenyl-1,4,7,8-tetrahydrodipyrazolo[3,4-b:4',3'-e]pyridine (THDPP2):

Yield: 97%; light brown solid, m.p. = 246-248 °C. FT-IR (KBr): 3199, 2926, 1599, 1528, 1455, 1155, 761, 723 cm^{-1} . ^1H NMR (500 MHz, DMSO-*d*6): δ (ppm) = 2.08 (s, 6H, 2CH₃), 4.84 (s, 1H, CH), 7.10–7.20 (m, 3H, Ar-H), 7.20–7.25 (m, 2H, Ar-H), and 11.35 (s, 3H, 3NH). ^{13}C NMR (125 MHz, DMSO-*d*6): δ (ppm) = 12.1, 38.1, 104.8, 127.1, 128.7, 128.9, 141, 143.7, and 145.8 (Figs S29–S31).

4-(4-Hydroxy-3-methoxyphenyl)-3-methyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (PyPym11):

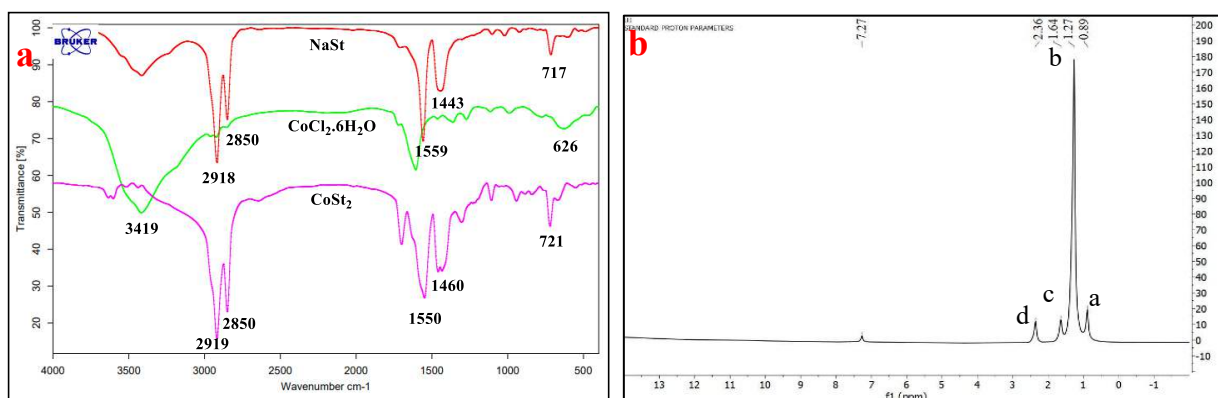
Yield: 92%; light orange solid, m.p. = 278-281 °C. FT-IR (KBr): 3373 (broad OH stretching), 2944-2834 (CH stretching), 1655 (overlapped C=O stretching with NH bending), 1579, 1467 (overlapped C=N with aromatic skeletal bands), 1272 (C-O phenolic), 1131 (C-N stretching), 819, and 773 (aromatic CH bending), cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ (ppm) = 1.83 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 4.49 (s, 1H, CH), 6.52-6.56 (m, 1H, Ar), 6.69-6.72 (m, 2H, Ar), 7.82 (s, 1H, NH), 8.22 (s, 1H, OH), 8.85 (s, 1H, NH-pyrimidine), and 12.09 (s, 1H, NH-pyrazole). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ = 9.8, 55.1, 57.6, 97.9, 113.2, 113.8, 120.9, 128.5, 135.6, 136.5, 139.8, 158.0, and 160.7 ppm (Figs S56–S58).

Results and discussions

Synthesis and characterization of $\text{Co}(\text{St})_2$

Stearic acid (SA) is a nanoscale fatty acid with 21.6 angstrom and 2.16 nm⁴⁹ dimension. $\text{Co}(\text{St})_2$ was synthesized from this bionanomaterial and CoCl_2 by two steps: preparation of sodium stearate (NaSt) from SA and reaction of nano NaSt with $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ in a 2:1 molar ratio (Fig. 1). The given purple pellets of $\text{Co}(\text{St})_2$ were then characterized by melting point, CMC, FT-IR, NMR, FESEM, TEM, and XPS analyses. The melting point and CMC of the as-prepared $\text{Co}(\text{St})_2$ were 102-124 °C and 6.5×10^{-4} M, respectively. The FT-IR spectrum (KBr disk) of $\text{Co}(\text{St})_2$ (Fig. 2a) showed characteristic absorption bands at 2919, 2850, 1550, 1460, 1365, and 721 cm^{-1} related to the aliphatic C-H stretching, the asymmetrical and symmetrical stretching of COO^- overlapped with the aliphatic CH bending, and long chain hydrocarbon CH_2 bending. These vibrational adsorption bands are in accordance with the previously reports²³.

By special attention to paramagnetic nature of Co (II) for possible line broadening and *pseudo*-contact shifts in NMR of Co(St)₂, these impacts were disappointment for too many homolog hydrogens in the long-chain stearate nano-ligands. In the ¹H NMR (500 MHz) spectrum of Co(St)₂ in CDCl₃, characteristic peaks for all 70 hydrogens are apparent. So, 6H at $\delta = 0.89$ ppm corresponds to the terminal methyl groups (a) and 28 H at $\delta = 1.26$ ppm due to the 14 bulk CH₂ groups (b) are enough far from the Co (II) center to remain unaffected. The carboxylate-attached α -CH₂ and β -CH₂ groups are among the two closer protons to Co (II) in Co(St)₂ that distress by this paramagnetic metal. So, 4 H at $\delta = 1.64$ ppm are due to the two β -CH₂ groups (c) and 4 H at $\delta = 2.36$ ppm are related to the two carboxylate-attached α -CH₂ groups (d) in aliphatic chains (Fig. 2b). Consistency of this ¹H NMR feature with the molecular structure of Co(St)₂ confirmed its formation. Accordingly, the ¹³C NMR spectrum (125 MHz, CDCl₃) of Co(St)₂ shows all expected characteristic aliphatic carbons at chemical shifts from $\delta = 14$ ppm to 185 ppm (Fig. 2c). Appearance of these NMR signals at expected typical aliphatic chemical shifts suggests that the prolonged carbon chain effectively protects the bulk of the surfactant tail from the robust paramagnetic effects of the coordinated cobalt (II) core.



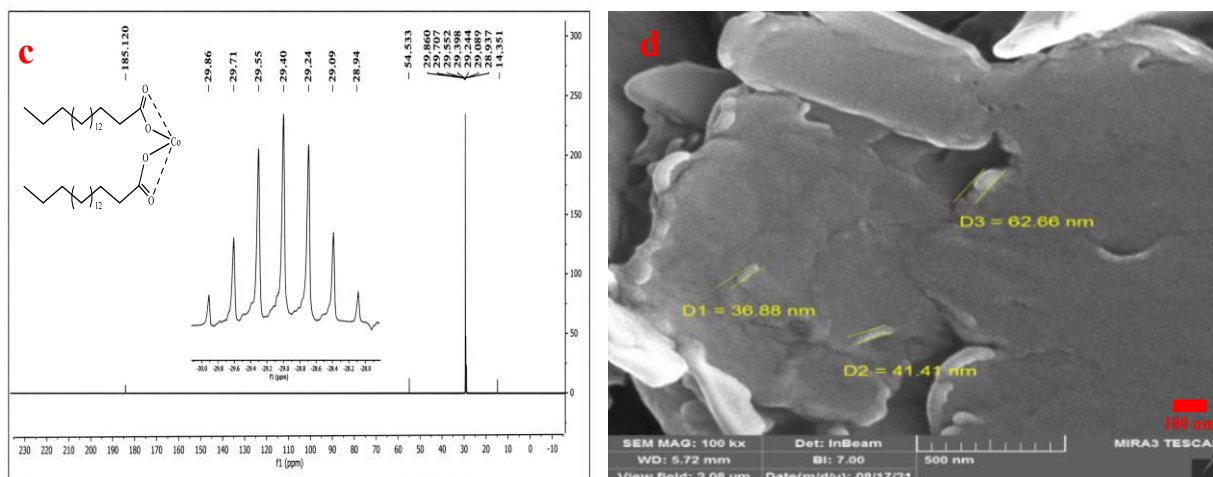


Fig. 2 (a) FT-IR; (b) ^1H NMR; (c) ^{13}C NMR; and (d) FESEM images of $\text{Co}(\text{St})_2$ at 500 nm scale.

FESEM image of $\text{Co}(\text{St})_2$ at 500 nm showed a grain-lamellar morphology with the average diameter between 37-63 nm (Fig. 2d), in agreement with the previously reports^{23, 24}.

The low angle X-ray diffraction (XRD) for the as-prepared $\text{Co}(\text{St})_2$ revealed eight characteristic peaks at $2\theta = 3.60^\circ$, 5.48° , 7.30° , 9.10° , 10.86° , 12.68° , 14.48° , and 16.30° (Fig. 3).

Preparation of nano-catalyst $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ from $\text{Co}(\text{St})_2$

$\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ was prepared via the controlled co-precipitation of the $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ and FeCl_3 salts in the aqueous NaOH solution of $\text{Co}(\text{St})_2$ (Experimental section 2.3) (Fig. 3a). Then, the washed and dried $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ precipitate was identified.

Characterization of the $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$

The FT-IR, XRD, FESEM, TEM, VSM, and TGA analyses were employed to characterize $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ (Figs 3b-3g). The overlaid FT-IR spectra of the as-prepared Fe_3O_4 and $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ show coupled supportive absorption bands at $\sim 2900\text{-}3600\text{ cm}^{-1}$ and $590\text{-}619\text{ cm}^{-1}$ related to the surface OH stretching and lattice Fe/O vibration modes in both magnetic materials.

The absence of peak at 1399 cm^{-1} in the spectrum of the unmodified magnetic nanoparticles of Fe_3O_4 is due to the lack of $-\text{O}-\text{C}=\text{O}$ in its chemical composition. In the FT-IR spectrum of $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$, lattice Fe/O absorption at 619 cm^{-1} , symmetrical and asymmetrical stretching of $-\text{O}-\text{C}=\text{O}$ at 1399 cm^{-1} and 1620 cm^{-1} , aliphatic C-H stretching at 2918 cm^{-1} , and wide OH stretching at 3414 cm^{-1} are evident (Fig. 3b). Being the peaks at 1399 cm^{-1} , 1620 cm^{-1} , and 2918 cm^{-1} related to the symmetric/asymmetric $-\text{O}-\text{C}=\text{O}$ stretching and C-H stretching of CH_3/CH_2 groups approve existence of aliphatic stearate chains in the $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ construction. Comparative FT-IR spectra of $\text{Co}(\text{St})_2$ (Fig. 2a) and $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ (Fig. 3b) showed a noticeable shift for symmetric/asymmetric stretching of $-\text{O}-\text{C}=\text{O}$ and OH from 1460 cm^{-1} , 1660 cm^{-1} , and 3550 cm^{-1} to 1399 cm^{-1} , 1620 cm^{-1} , and 3414 cm^{-1} upon linking to Fe_3O_4 . The broaden shift of OH stretching from 3420 cm^{-1} in the spectrum of Fe_3O_4 to 3414 cm^{-1} in the $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ spectrum is also clear. To evaluate the bonding type of COO^- to Co^{2+} , we referred to the reported categorization of metal ion-carboxylate links based on wavenumber difference ($\Delta\bar{\nu}$) between the asymmetric and symmetric stretching of COO^- in FT-IR⁵⁰. Accordingly, a large $\Delta\bar{\nu}$ ($200\text{--}320\text{ cm}^{-1}$) indicates mono-dentate binding, medium $\Delta\bar{\nu}$ ($140\text{--}190\text{ cm}^{-1}$) is typical for bidentate bridging, and a slight $\Delta\bar{\nu}$ (less than 110 cm^{-1}) proposes a bidentate chelating ionic interaction⁵⁰. Herein, the observed 90 cm^{-1} ($1550\text{--}1460\text{ cm}^{-1}$) $\Delta\bar{\nu}$ for $\text{Co}(\text{St})_2$ (Fig. 2a) suggests a bidentate chelating ionic interaction, while the observed 221 cm^{-1} ($1620\text{--}1399\text{ cm}^{-1}$) $\Delta\bar{\nu}$ for $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ (Fig. 3b) points to mono-dentate covalent bonding of stearate ligands to the cobalt cation. This change in coordination mode of COO^- concurrent with the 131 cm^{-1} reducing shift of $\Delta\bar{\nu}$ for COO^- in $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ versus the $\text{Co}(\text{St})_2$, is attributed to the steric-electronic changes given by attachment of $\text{Co}(\text{St})_2$ to the Fe_3O_4 and possible extra chelating of stearate to Fe atom. All these

findings are in agreement with the stearate-containing cobalt species associated with the magnetic phase Fe_3O_4 in our proposed structure of $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ (Fig. 3).

According to the XRD pattern of Fe_3O_4 , the six sharp characteristic peaks at $2\theta = 30.81^\circ$, 36.04° , 43.78° , 54.00° , 57.10° , and 63.28° are corresponded to the (220), (311), (400), (511), (422), and (440) diffraction planes, well-matched to the standard Fe_3O_4 -phase (JCPDS card no. 39-1346). While repeating these planes, as a broader shifted peaks, in the overlaid XRD of $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ reveals conserving the crystalline phase of Fe_3O_4 , new broad peaks at low angles $2\theta = 3.60^\circ$ - 16.30° ²⁴ supports association of $\text{Co}(\text{St})_2$ in $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$. Such co-existence of $\text{Co}(\text{St})_2$ with the Fe_3O_4 phase (Fig. 3c) was further supported by FESEM (Fig. 3d), TEM (Fig. 3e and 3f), VSM (Fig. 3g), and TGA (Fig. 3h) analyses.

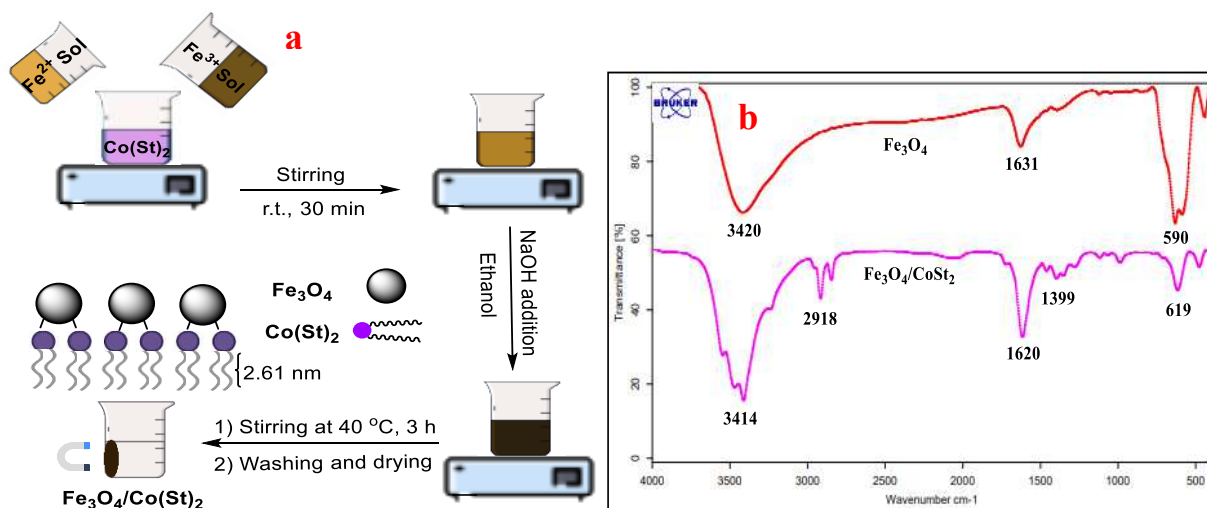
FESEM images of $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ at magnification 500 nm indicate lamellar surface morphology, which particle size distribution analysis confirmed its nanostructure. In this magnetic metal surfactant, the interlayer distances are about 43-81 nm (Fig. 3d) and larger than $\text{Co}(\text{St})_2$ (Fig. 2), presumably due to casing by Fe_3O_4 MNPs.

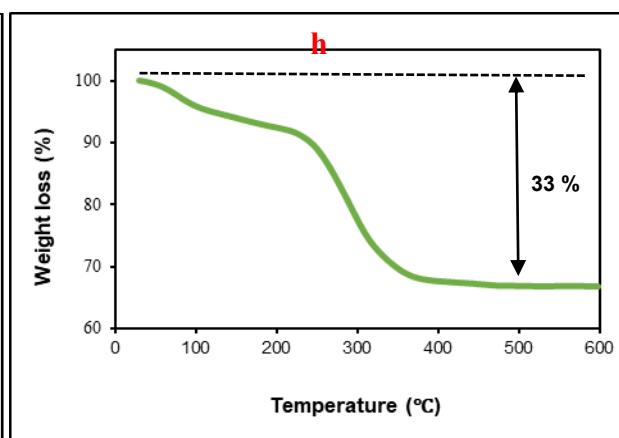
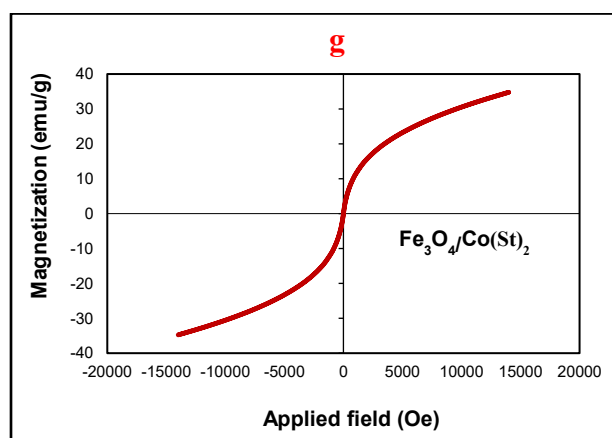
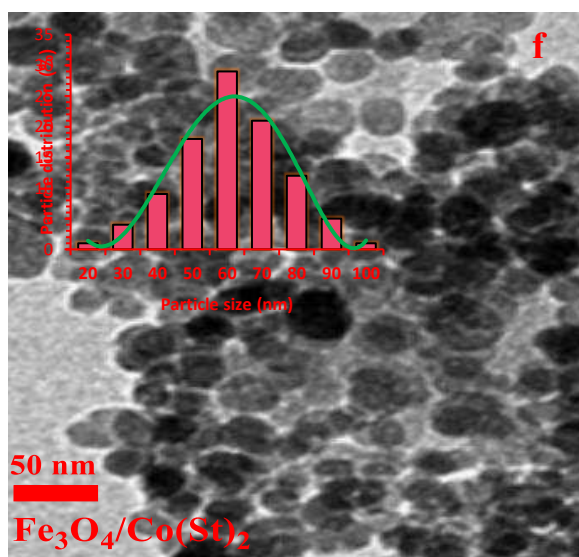
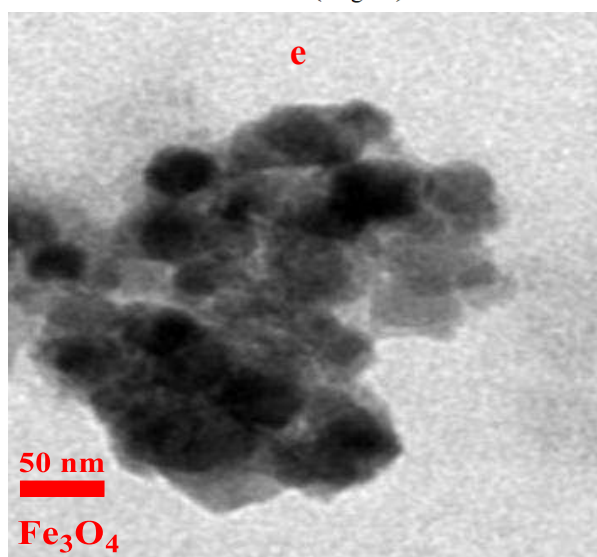
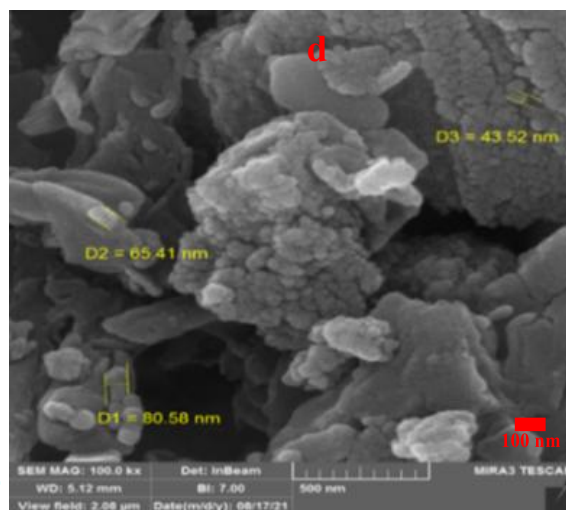
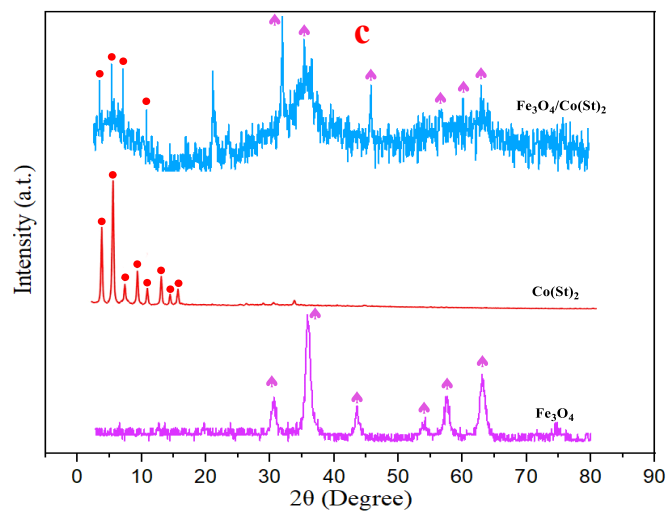
Comparative TEM images of the as-prepared Fe_3O_4 and $\text{Co}(\text{St})_2$ -modified Fe_3O_4 indicated uniformly distributed porousness and $\text{Co}(\text{St})_2$ molecular layers around the Fe_3O_4 nanoparticles, with no major morphology changes (Figs. 3e and 3f). While $\text{Co}(\text{St})_2$ association improved agglomeration of MNPs, dispersal histogram versus the particle size for $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ exhibited an average size enlargement for the spherical Fe_3O_4 nanoparticles from 15-20 nm to 30-40 nm

VSM curves of the bare and surfactant-coated nano Fe_3O_4 show a decrease in magnetization saturation (Ms) from 69.2 for Fe_3O_4 to 34.2 emu/g for the as-prepared $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$. Such decrease in Ms is an additional evidence for the Fe_3O_4 coating by a non-magnetic layer of

Co(St)₂ in the super-paramagnetic surfactant Fe₃O₄/Co(St)₂ (Fig. 3g), although its magnetic response is excellent.

The thermal behavior of the Fe₃O₄/Co(St)₂, determined by TGA at temperature range 10-600 °C in air, showed its good thermal stability and total 33% mass loss, presumably due to the presence of ~ 33% Co(St)₂ in this hybrid structure. The slight mass loss of this MS-based organic-inorganic hybrid at ~ 20-250 °C is due to the dehydrating of the surface and interlayer adsorbed water molecules. Further mass loss at > 250 °C is attributed to the either CO₂ removal by decarboxylation of stearate or decomposition of surfactant's organic chains in Fe₃O₄/Co(St)₂ (Fig. 3h). All these changes helped us to propose a structure for Fe₃O₄/Co(St)₂, which in the Co²⁺-coordinated carboxylate hydrogen-bonded to surface OH groups of Fe₃O₄ groups (Fig. 3i).





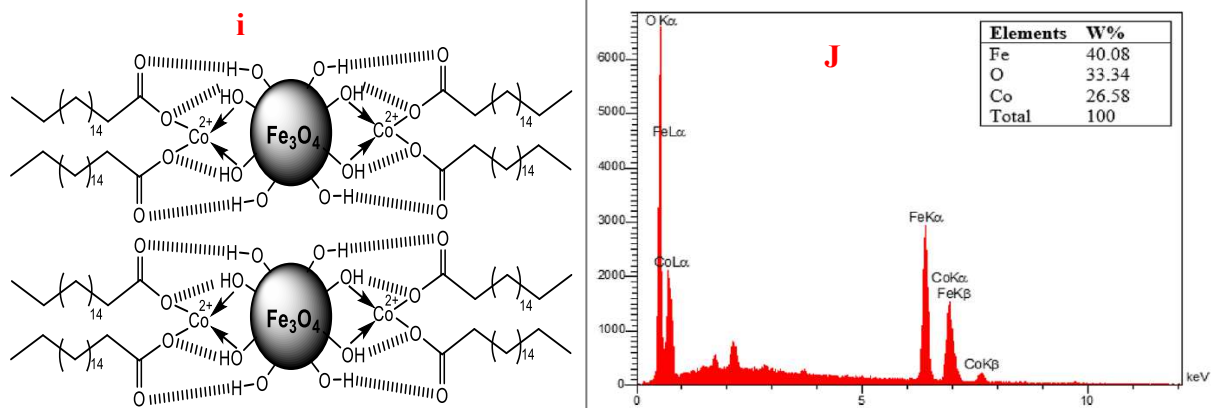


Fig. 3 Preparation, characterization, and proposed structure for $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ (a-i) and EDS of a separately prepared CoFe_2O_4 ⁵¹.

To verify the probable formation of magnetic phase CoFe_2O_4 under the applied conditions for preparation of $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$, a separately CoFe_2O_4 sample prepared⁵¹ and its EDS with a Co/Fe atomic ratio $\sim 1:1.5$ (Fig. 3J) compared to the EDS of $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ (with Co/Fe atomic ratio $\sim 1:21.2$) (Fig. 4). This 14 times lower Co/Fe atomic ratio indicates no incorporation of cobalt into the Fe_3O_4 crystal lattice to form the magnetic phase cobalt ferrite.

The EDX and EDS-map analyses supported the presence and regular distribution of different percentages of carbon, oxygen, iron, and cobalt elements in the surface chemical structure of $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ (Fig. 4). Additional SEM mapping revealed regular distribution of iron, oxygen, carbon, and cobalt elements as well as association of Fe_3O_4 and $\text{Co}(\text{St})_2$ elements in combined elemental map of $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ (Fig. 4).

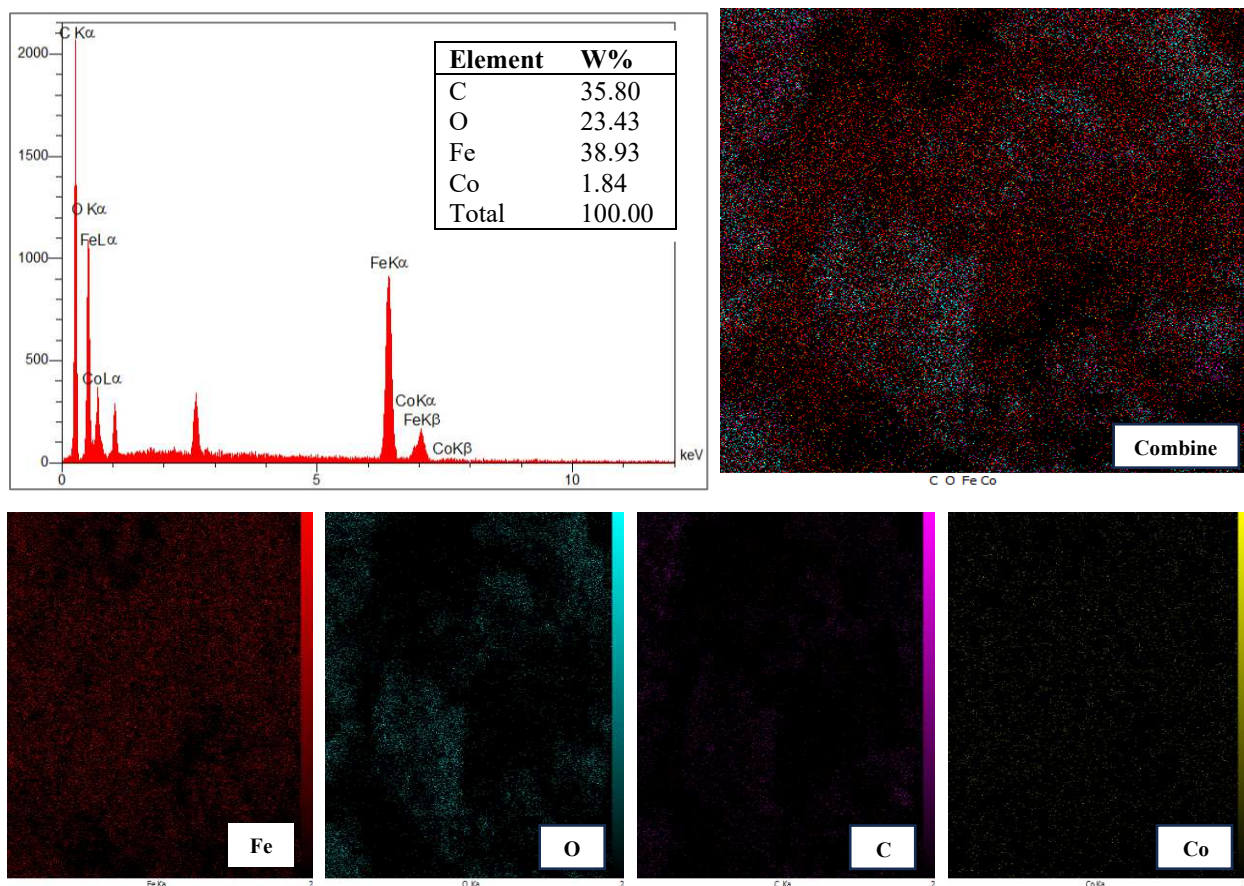
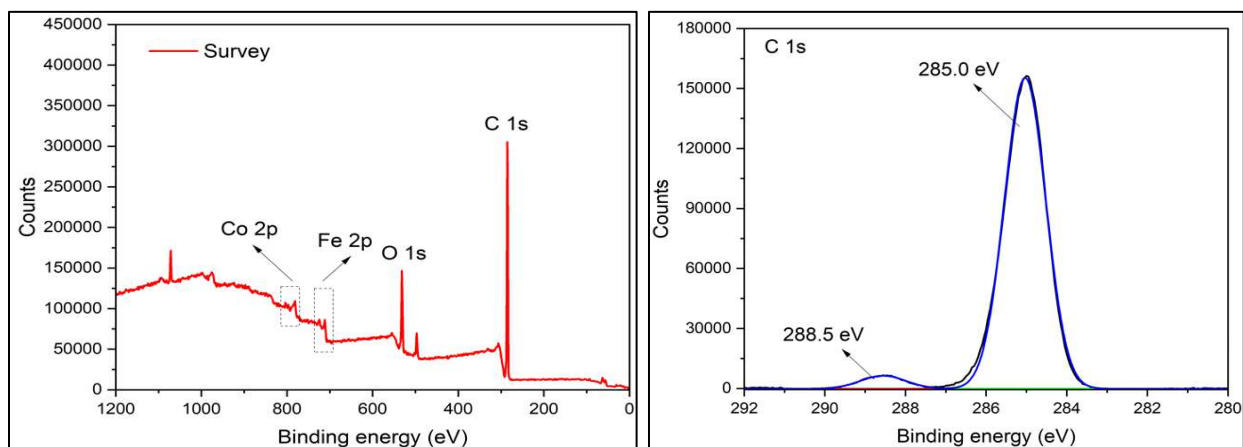


Fig. 4 EDX and EDS-map analysis of $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$

To fine determine the chemical composition and oxidation states of elements in $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$, X-ray photoelectron spectroscopy (XPS) analysis was performed over a binding energy range of 0-1200 eV (Fig. 5). The spectrum supported the presence of Fe, Co, O, and C as the main elements in hybridized $\text{Co}(\text{St})_2$ with the magnetite core Fe_3O_4 . The C 1s spectrum displayed a dominant peak at 285.0 eV (aliphatic C-C/C-H of stearate chains) and a smaller peak at ~288.5 eV (carboxylate carbon). In the O 1s region of this hybrid, the three observed peaks at binding energies of 529.8, 531.5, and 535.0 eV are due to the lattice metal-oxygen (Fe-O) bonds of Fe_3O_4 , coordinated carboxylate oxygen (O=C-O) of nano-St ligands, and surface hydroxyl of the adsorbed water. In contrast, the O 1s spectra of pure Fe_3O_4 and $\text{Co}(\text{St})_2$ showed a peak at 530.5 eV for the Fe-O lattice oxygen and a main peak at 532.0 eV credited to the carboxylate

oxygens in the chelating bidentate coordination mode. The negative shifts observed for carboxylate oxygen from 532.0 eV in pure Co(St)_2 to 531.5 eV and the lattice Fe-O of bare Fe_3O_4 from 530.5 eV into the 529.8 eV for $\text{Fe}_3\text{O}_4/\text{Co(St)}_2$ indicate electronic interactions between the cobalt stearate shell and the magnetite core in the hybrid. These shifts support a transition from predominantly chelating bidentate coordination in free Co(St)_2 to a mixture of coordination modes and mono-dentate by surface hybridity. In the high-resolution Co 2p spectrum of pure Co(St)_2 , the Co 2p_{3/2} and Co 2p_{1/2} peaks appeared at 781.6 eV and 797.8 eV, accompanied by characteristic shake-up satellites that are consistent with the bidentate coordination of Co^{2+} . These peaks, shifted to lower binding energies (780.9 eV for Co 2p_{3/2} and 797.0 eV for Co 2p_{1/2}) upon formation of $\text{Fe}_3\text{O}_4/\text{Co(St)}_2$. Such negative shifts confirm a change in the coordination environment of Co^{2+} from the predominantly chelating bidentate to a mixture of mono-dentate modes by interaction with Fe_3O_4 surface. The Fe 2p spectrum exhibited characteristic peaks at 711.2 and 712.8 eV (Fe 2p_{3/2} for Fe^{2+} and Fe^{3+}) to confirm the intact magnetite phase^{52, 53}. The XPS data for $\text{Fe}_3\text{O}_4/\text{Co(St)}_2$ is supported by a fine 30 nm scale TEM image in Fig. 5 that shows surrounding of darker contrast regions of the crystalline Fe_3O_4 by the lighter organic layers of cobalt stearate (Co(St)_2).



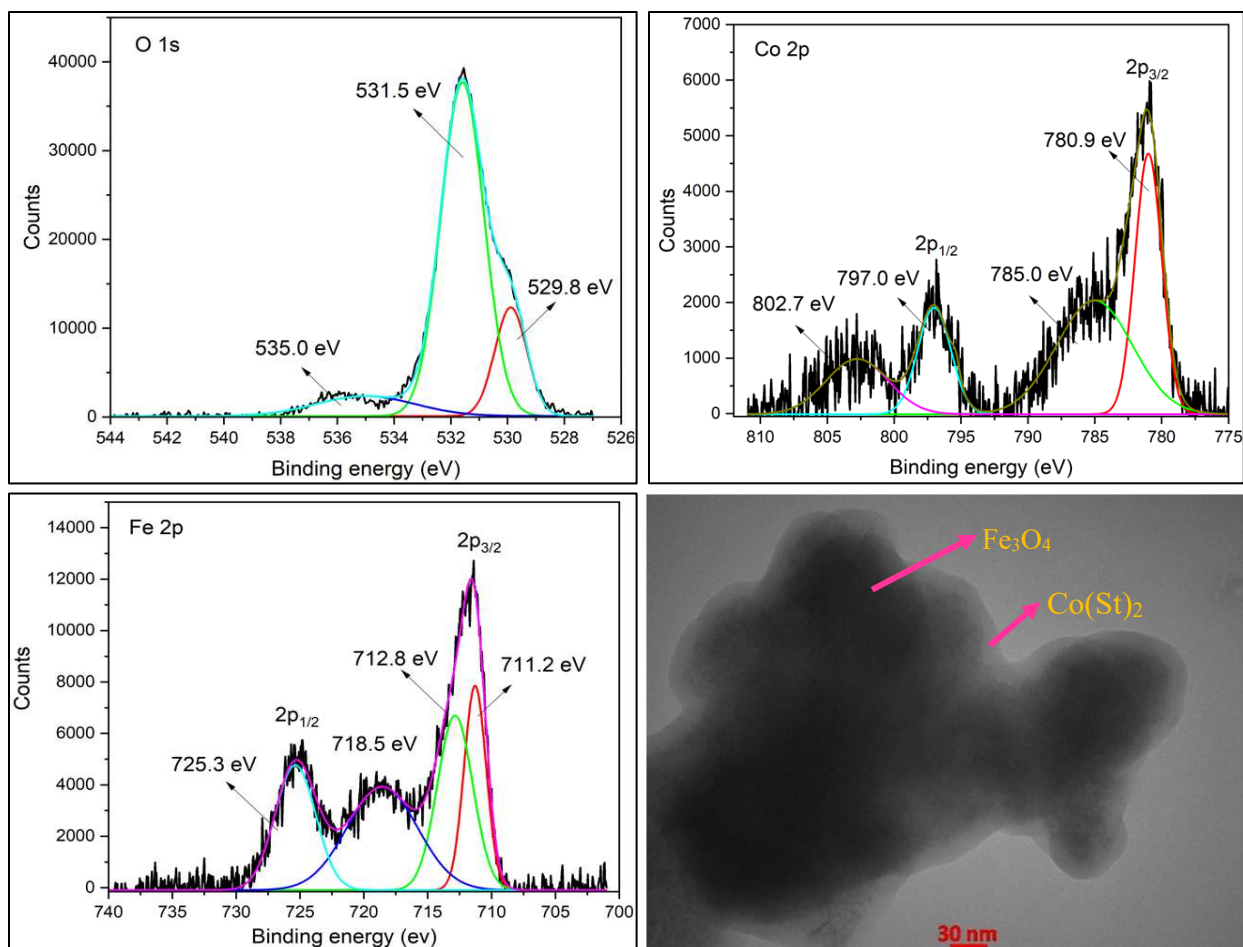
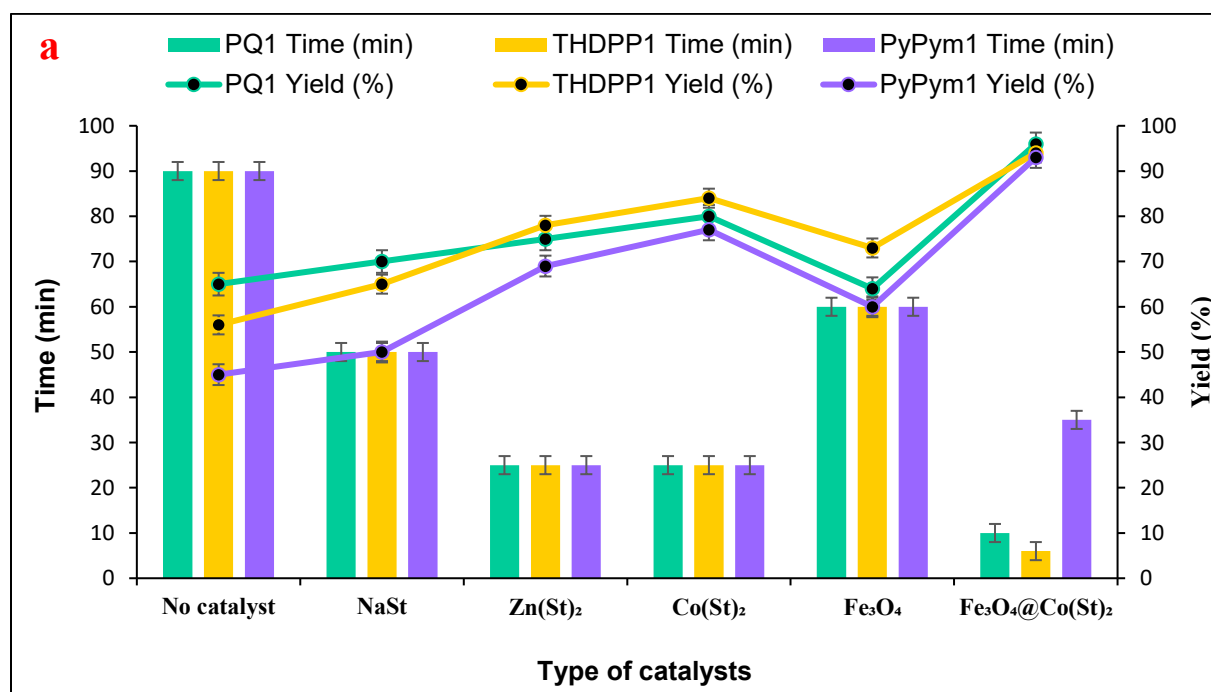


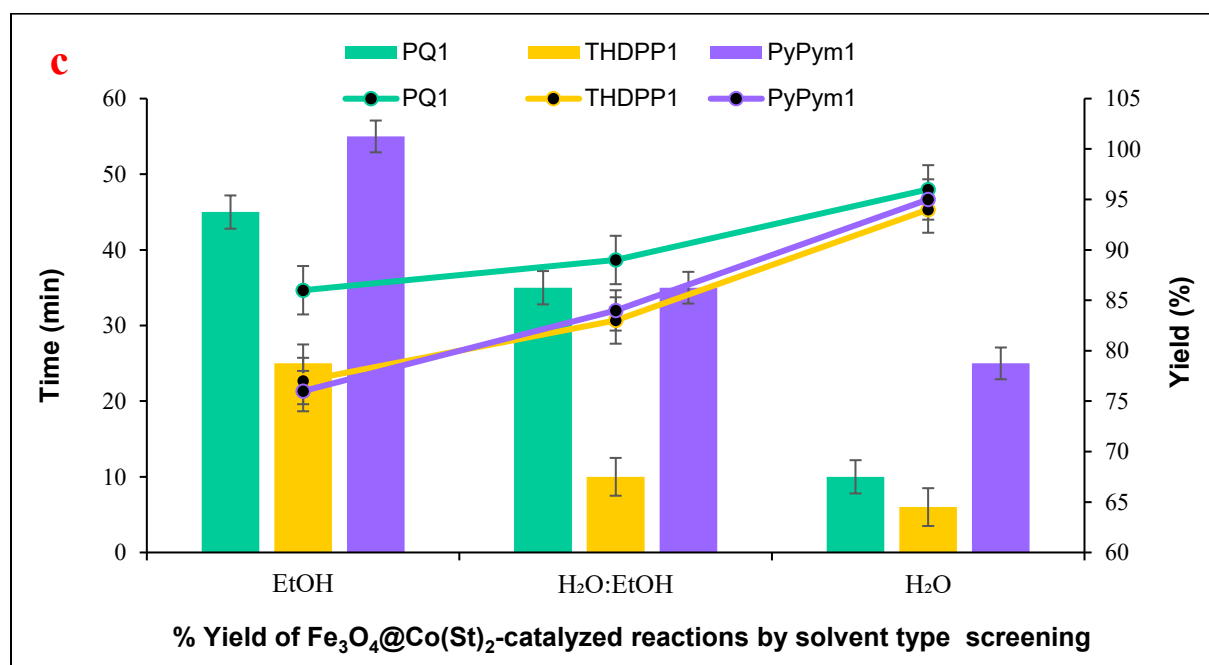
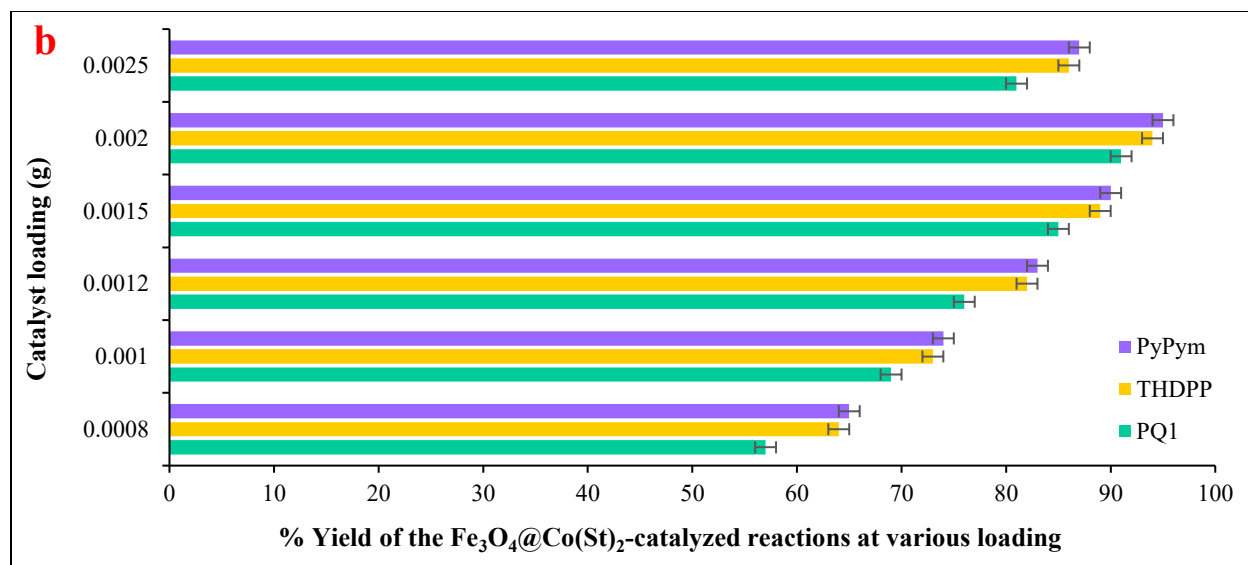
Fig. 5 XPS spectra of the $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$: survey spectrum, and high-resolution spectra of C 1s, O 1s, Co 2p, and Fe 2p and TEM of $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$

Consequently, XPS (Fig. 5), EDS (Fig. 4), FT-IR ($\Delta\bar{\nu}$) (Fig. 3) evidences for COO^- coordination changes after associating of $\text{Co}(\text{St})_2$ and Fe_3O_4 , TGA-approved 33 wt% $\text{Co}(\text{St})_2$ loading in hybrid $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ (Fig. 3), and TEM morphology (Figs. 3e and 5) support the proposal structure $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$. In this structure, association of organic $\text{Co}(\text{St})_2$ with the inorganic core Fe_3O_4 , not only provides surfactant properties but also prevents aggregation of the magnetic nanoparticles. The Co^{2+} Lewis acid sites, polar carboxylate/hydroxyl and hydrophobic nano-St groups, and superparamagnetic properties are advantages for surfactant-like behavior and catalytic performance of $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ in aqueous media.

Catalytic evaluation of Fe₃O₄/Co(St)₂ in synthesis of PQs, THDPPs, and PyPyms

Firstly, 4-(4-chlorophenyl)-3,7,7-trimethyl-6,7,8,9-tetrahydro-1*H*-pyrazolo-[3,4-*b*]-quinoline-5(4*H*)-one (PQ1) was synthesized by a previous three-component method⁴⁶ as authentic sample. Then, our designed new four-component synthesis of PQ1 was optimized by screening the effects of catalyst type and loading, solvent, and temperature. Although multivariate optimization by design of experiments (DOE) is deeper for variable interactions, we considered a simple one-variable-at-a-time (OVAT) optimization approach, while OVAT does not account for variables interactions. So, reaction of 4-chlorobenzaldehyde, dimedone, 3-methyl-1*H*-pyrazol-5-one, and NH₄OAc in 1:1:1:1 molar ratio screened under various conditions considering MS type, catalyst loading, and solvent parameters. All experiments were performed in triplicate (*n* = 3) and that the error bars represent the standard deviation (SD) of three independent experiments (Fig. 6).





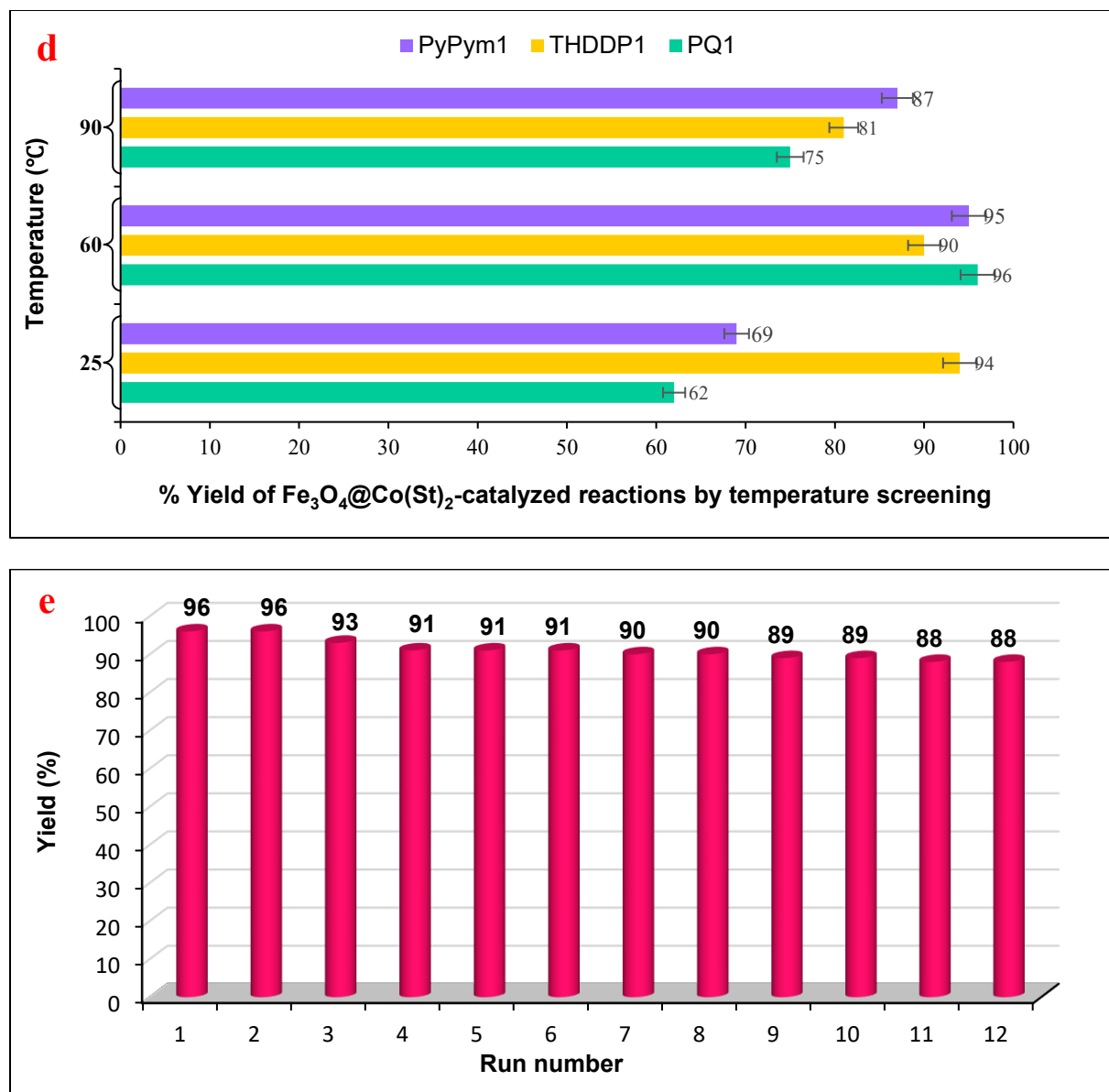


Fig. 6 Optimization of catalyst type, catalyst loading, solvent, and temperature for the synthesis of PQ1, THDDP1, and PyPym1, and reusability study for the Fe₃O₄/Co(St)₂ catalyst in PQ1 synthesis. Error bars represent standard deviation (SD) from three independent experiments (n = 3).

As results indicated, the maximum yield of PQ1 by this new four-component synthesis in water was obtained after 10 min using 0.002 loading Fe₃O₄/Co(St)₂ (Fig. 6a). Considering critical micelle concentration (CMC = 6.5×10^{-4} M, consistent to 406.8 mg L⁻¹) for Co(St)₂ and approximately 33 wt% Co(St)₂ in Fe₃O₄@Co(St)₂ (TGA-approved in Fig. 3h), the effective concentration of Co(St)₂ in 0.002 g Fe₃O₄@Co(St)₂ is about 660 mg L⁻¹. Running the synthesis

of PQ1 at 1 CMC, 1.5 CMC, and 2 CMC of $\text{Co}(\text{St})_2$ gave 75%, 76%, and 81% yield after 35 min compared to 96% yield after 10 min for 0.002 g $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ in 1 mL water. These observations suggest synergistic effects between Fe_3O_4 and $\text{Co}(\text{St})_2$, while the effective concentration of $\text{Co}(\text{St})_2$ in catalyst is 1.5 CMC of the free surfactant. The catalytic performance of $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ may thus arise from modified Lewis acid Co^{2+} centers and surface-induced organization of $\text{Co}(\text{St})_2$ molecules associated to magnetite nanoparticles for possible hemi-micelles forming or localized aggregates at sub-CMC concentration. This explanation can be supported by the results given from similar reaction run in EtOH, which in micelle formation is difficult. Comparison of the present results with the previously three-component synthesis of PQ1 (10 min, 82%, 170 °C)⁵⁴ revealed the performance of $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ in this protocol for synthesis of PQ1.

The reusability of the $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ was also checked for the synthesis of PQ1 in 10 mmol scale with 0.02 g of this MS-based nano-catalyst. As a result, after the completion of the first reaction run, the $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ was quantitatively collected by a magnet after the first work-up (Experimental section 2.4). The recovered $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ was used in consequent reaction cycles for synthesis of PQ1 without significant loss of weight and catalytic activity (8%) after the twelfth run (Fig. 6e). To verify the stability of nano-catalyst $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$, leaching test for probable incoming of Co^{+2} , Fe^{+2} , and Fe^{+3} metal ions to the reaction mixture was assessed for either the fresh or the recycled filtrate of the model reaction after the 12th run with the $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ by ICP analysis. The given results revealed trace concentrations (0.1-1.1 ppm) of these metals in the filtrate, which confirm the stability of this magnetic MS in twelvish filtration, recycling, and reusing periods. Additional ICP-OES analysis supported hot filtration test was performed to support no possible leaching of Co^{2+} , Fe^{2+} , and Fe^{3+} from the nano-catalyst

$\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ into the reaction medium for synthesis of PQ1. Thus, the scale-up model reaction was stopped after 5 min (yield 65%), the catalyst was completely removed by an external magnet, and the reaction allowed to proceed without catalyst for an additional 5 min, which led to no higher yield. This observation indicated no significant metal species leaching from the catalyst matrix under the reaction conditions. Furthermore, ICP-OES analysis for the 12th recycled filtrate showed trace contents of Co^{2+} (1.1 ppm), Fe^{2+} (0.1 ppm), and Fe^{3+} (0.11 ppm) that reveals the stability and heterogeneity of the nano-catalyst $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ during recycling.

To demonstrate the generality of the $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ -catalyzed synthesis of PQs, the new four component reactions of a range of aromatic aldehydes with dimedone, 3-methyl-1H-pyrazol-5-one, and ammonium acetate investigated under the optimized conditions to give various PQs in excellent yields (Table 1).

Table 1 The four-component synthesis of PQs using $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ in micellar condition

Entry	R ¹	R ²	Product	Time (min)	Yield (%)	m.p. (°C) Found (reported) 36, 37, 55
1	H	4-Cl	PQ1	10	96	302-304 (305-306)
2	H	H	PQ2	15	95	230-232 (231-233)
3	H	4-OH	PQ3	30	92	274-276 (273-275)
4	H	4-NO ₂	PQ4	10	95	299-301 (300-301)
5	H	3-NO ₂	PQ5	20	91	300-303 (299-300)
6	H	4-OH,3-OCH ₃	PQ6	30	90	280-282 (281-283)
7	Ph	4-Cl	PQ7	35	94	232-234 (230-233)
8	Ph	H	PQ8	30	94	220-223 (222-224)
9	Ph	4-OH	PQ9	55	92	260-262 (261-263)
10	Ph	4-NO ₂	PQ10	40	93	225-228 (226-227)
11	Ph	3-NO ₂	PQ11	55	91	238-240
12	Ph	4-OH,3-OCH ₃	PQ12	60	90	246-248 (245-248)

Based on the results, but no direct experimental evidences under the reaction conditions, a proposed mechanism for this new four-component synthesis of PQs is given in Fig 7. It is hypothesized that the possibly formed pre-micellar aggregates and surface-induced hemi-micelles by maintained Co(St)₂ on the Fe₃O₄ nanoparticles in water, reduce surface tension, improve the solubility of organic reactants in water, and decrease the activation energy of the reaction. This description is supported by the significantly lower reaction yields when was carried out in EtOH, which in this solvent such assembling of surfactant molecules is unfavorable. Due to no direct colloidal characterizations under the actual reaction conditions, the micellar nano-reactor model for Fe₃O₄/Co(St)₂ is a plausible hypothesis. The first step involves formation of an α , β -unsaturated ketone (**A**) by condensation of aldehyde and dimedone, which undergoes Michael addition with the 3-methyl-1H-pyrazol-5-one in the second step to give the intermediate **B**. This intermediate tautomerizes to enol form and after reacting with ammonia, further intramolecular cyclization, tautomerization, and dehydration gives the PQ product.

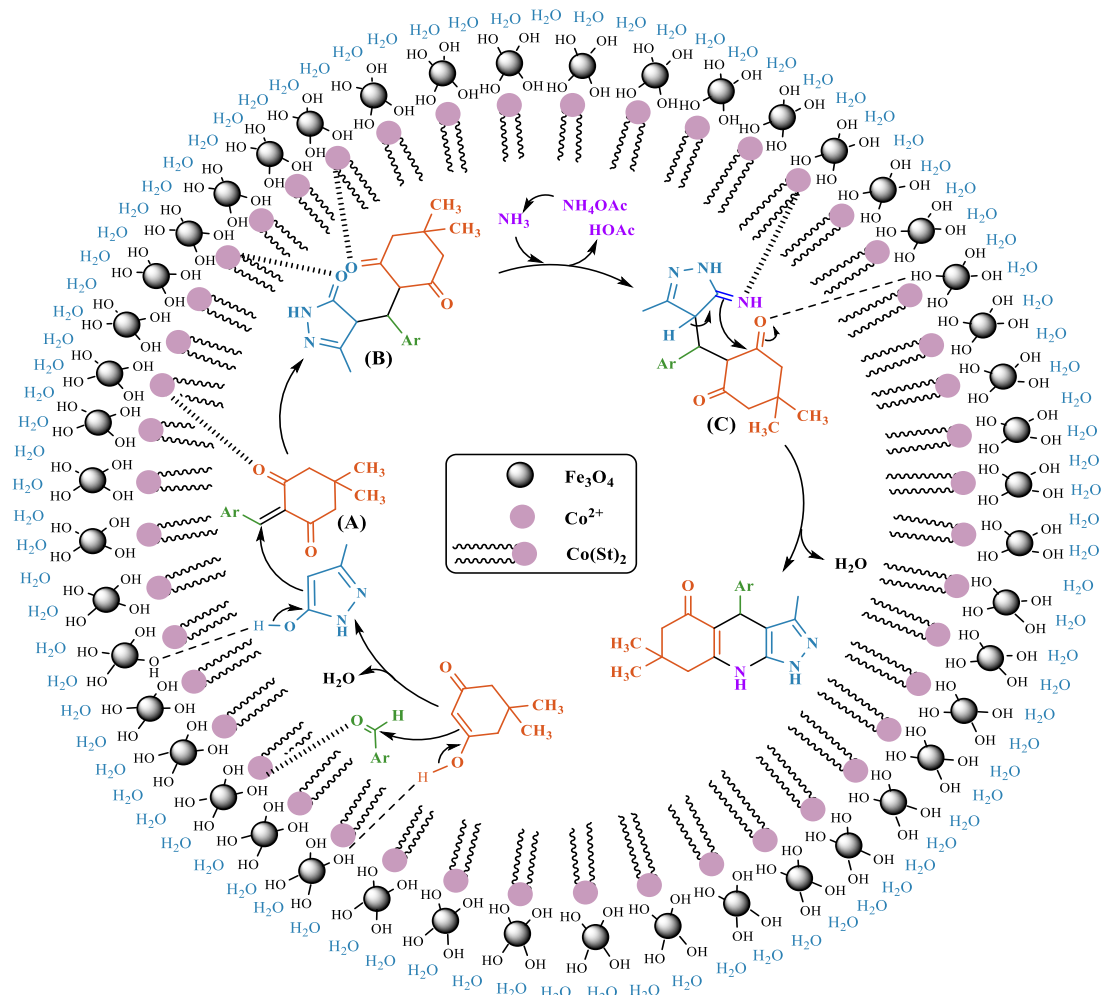


Fig. 7 Proposed mechanism for the $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ -catalyzed synthesis of PQs

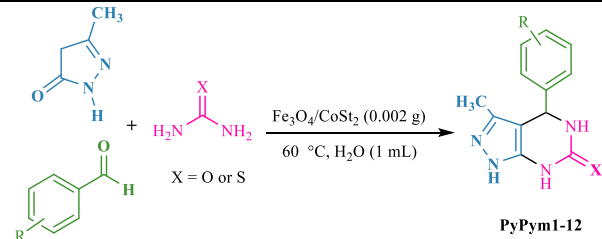
The versatility of the $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ was also demonstrated in a correlated *pseudo*-four component reaction for synthesis of THDPPs in water. So, the selected model reaction of 4-chlorobenzaldehyde, 3-methyl-1H-pyrazol-5-one, and NH_4OAc in 1:2:1 molar ratio for synthesis of (THDPP1) screened to optimize the surfactant catalyst and loading (Fig. 6). Extension of the optimized conditions to the other substrates resulted in the rapid formation of THDPP products in excellent yields (Table 2).

Table 2 Pseudo-four component synthesis of THDPPs using micellar $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$

Entry	R	Product	Time (min)	Yield (%)	m.p. (°C) Found (reported) ^{30, 32}
1	4-Cl	THDPP1	6	94	252-254 (251-253)
2	H	THDPP2	3	97	246-248 (240-242)
3	4-CH ₃	THDPP3	6	92	244-246 (243-245)
4	4-N(CH ₃) ₂	THDPP4	5	95	241-243 (241-243)
5	4-NO ₂	THDPP5	4	96	235-237 (233-235)
6	3-NO ₂	THDPP6	5	95	285-287 (284-286)
7	2-Cl	THDPP7	7	91	221-223 (219-221)
8	2,6-Cl ₂	THDPP8	7	91	224-227

Compared to our previous catalysts for synthesis of THDPPs, the enzyme-based HANCD@urease³² required higher temperature (70 °C) and longer reaction times (30-60 min) with 90–96% yield, while the magnetic $\text{Fe}_3\text{O}_4/\text{NAC}$ catalyst performed similarly at room temperature in 5-15 min with 97% yield³¹. Remarkably, this newly developed $\text{Fe}_3\text{O}_4@\text{Co}(\text{St})_2$ operates under room temperature and provides high yields (95-98%) in water at 3-15 min.

Owing to the excellent results for the magnetic nano-surfactant based production of PQs and THDPPs, a closely related three-component synthesis of another pyrazole derivatives (3-methyl-4-aryl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-ones (PyPyms)) was also examined. After optimization of the parameters for the model reaction of 4-chlorobenzaldehyde, 3-methyl-1H-pyrazol-5-one, and urea (1:1:1) to synthesis of PyPym1 (Fig. 6), the scope of method was demonstrated. So, the minute scale reactions proceeded for other aldehydes and thiourea in the presence of 0.002 g $\text{Fe}_3\text{O}_4/\text{Co}(\text{St})_2$ in water (1 mL) to obtain the corresponding PyPym products in high yields (Table 3).

Table 3 The three-component synthesis of PyPyms using Fe₃O₄@Co(St)₂ in water


Entry	R	X	Product	Time (min)	Yield (%)	m.p. (°C) Found (reported) ⁵⁶
1	4-Cl	O	PyPym1	35	95	244-246
2	4-Cl	S	PyPym2	45	90	256-259
3	H	O	PyPym3	20	96	208-210 (208-210)
4	H	S	PyPym4	30	92	221-223 (221-223)
5	4-NO ₂	O	PyPym5	20	95	209-212
6	4-NO ₂	S	PyPym6	35	94	223-226
7	2,6-Cl ₂	O	PyPym7	45	90	249-252
8	2,6-Cl ₂	S	PyPym8	60	84	285-288
9	4-OH	O	PyPym9	30	93	285-288
10	4-OH	S	PyPym10	40	89	291-294
11	4-OH-3-OCH ₃	O	PyPym11	40	91	278-281 (279-281)
12	4-OH-3-OCH ₃	S	PyPym12	50	88	294-296 (293-295)

This magnetic metal surfactant-based protocol is profitable than previously reported methods for multi-component synthesis of PQs, THDPPs, and PyPyms due to novel 4-component synthesis of PQs, rapidness, excellent PQ, THDPP, and PyPym yields, green conditions, versatility, and reusability of catalyst. The efficiency of this super-paramagnetic metal surfactant catalyst is because of solubility enhancing of organic components in water by surface tension reducing and activation energy, formation of semi-micellar aggregates in water, and Lewis's acidity of Co²⁺.

Performances of Fe₃O₄/Co(St)₂ for the synthesis of three types heterocycles of PQ1, THDPP1, and PyPym1 was compared with some previously literature reported catalysts. A systematic comparison of reaction parameters including reaction medium, temperature, time, and product yield reveals the distinct advantages of the current protocol, as summarized in Table 4.

Table 4 Comparative performance of Fe₃O₄/Co(St)₂ for the synthesis of PQ1, THDPP1, and PyPym1.

Product	Entry	Reaction conditions	Temp (°C)	Time (min)	Yield (%)	Ref
PQ1	1	[bmim]Br	90 °C	90-180	85	34

	2	L-Proline, Neat	110	15	92	37
	3	DMSO, MW	–	60	92	38
	4	Ni NPs, CH ₃ CN	80	10	96	39
	5	γ -Fe ₂ O ₃ @ANC	60	15	96	55
	6	PEG-400, Neat	100	240	90	41
	7	Fe ₃ O ₄ /Co(St) ₂ , H ₂ O	60	10	96	This work
THDPP1	8	Choline chloride/Urea	110	30	92	29
	9	Co ₄ ChDES, H ₂ O	60	15	94	48
	10	Ultrasonic, H ₂ O	50	120	95	57
	11	Pseudopolymeric NPs, EtOH	r.t.	30	90	58
	12	EtOH	Reflux	300	72	59
	13	Fe ₃ O ₄ @KCC-1-nPr-NH ₂ , EtOH	Reflux	30	92	60
	14	Fe ₃ O ₄ @NAC, H ₂ O	r.t.	10	96	31
	15	MgFe ₂ O ₄ @Tris, H ₂ O	r.t.	10	98	61
	16	Fe ₃ O ₄ /Co(St) ₂ , H ₂ O	r.t.	6	94	This work
PyPym1	17	HCl/EtOH	Reflux	300	35	62
	18	<i>p</i> -TSA/Glycerol	Reflux	150	89	63
	19	[HBim]BF ₄ , Sonication, EtOH	-	300	58	64
	20	P(4-VPH)HSO ₄ /Glycerol	80	60	92	65
	21	PISA/[Bmim]Br	80	60	94	66
	22	Fe ₃ O ₄ /Co(St) ₂ , H ₂ O	60	35	95	This work

Some existing methods afford high yields but suffer from the volatile organic solvents, prolonged reaction times, or tedious recovery procedures, while the present catalytic system (entries 6, 16, and 22) achieves excellent yields under simple environmentally benign conditions.

Conclusion

In this work, versatile MCR synthesis of pyrazolo-quinolinones (PQs), tetrahydro-dipyrzolopyridines (THDPPs), and pyrazolo-pyrimidinones (PyPym)s was developed in water using more available components and novel nano-magnetic metal-surfactant catalyst Fe₃O₄/Co(St)₂. By integrating the surfactant properties of stearate, the catalytic activity of Co²⁺, and the magnetic reusability, nano-catalyst Fe₃O₄/Co(St)₂ demonstrated a good performance at a low loading. Thus, we proposed formation of magnetic micelle-based nano-reactors for enhancing solubility, reducing of activation energy, and stabilizing of reaction intermediates for rapid and environmentally-friendly transformations. Catalyst activity in versatile organic synthesis, recyclability, simple work-up, and multi-functionality of Fe₃O₄/Co(St)₂ assume its potential in sustainable catalysis, environmental remediation, and delivery of bioactive agents.

Abbreviations

CMC: Critical micelle concentration

Co(St)₂: Cobalt stearate

FESEM: Field-emission scanning electron microscopy

FT-IR: Fourier transform infrared

MCRs: Multi-component reactions

MMS: Magnetic metallo-surfactant

MNs: Magnetic nanoparticles

MS: Metal-surfactant

NaSt: Sodium stearate

NMR: Nuclear magnetic resonance

PQs: Pyrazolo-quinolinones

PyPyms: Pyrazolo-pyrimidinones

THDPPs: Tetrahydro-dipyrazolopyridines

TGA: Thermal gravimetric analysis

VSM: Vibrating sample magnetometry

XRD: X-ray diffraction

Acknowledgments

The authors gratefully admit the Yazd University.

Author Contribution

F.T., B.ZB, E.A.A.A., and AA.J. designed and performed the research, analyzed the data, interpreted the results, and prepared the manuscript. B.ZB, E.A.A.A., and AA.J performed the assays and conducted the optimization and purification of compounds. All authors read and approved the final manuscript.

Data availability

Data generated or analyzed during this study are included in this published article and its supplementary information file.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

This research did not receive funding.

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