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Synthesis of thiazolidine derivatives via multicomponent reaction in the presence of Fe_3O_4@SiO_2-SO_3H nanoparticles as a heterogeneous catalyst

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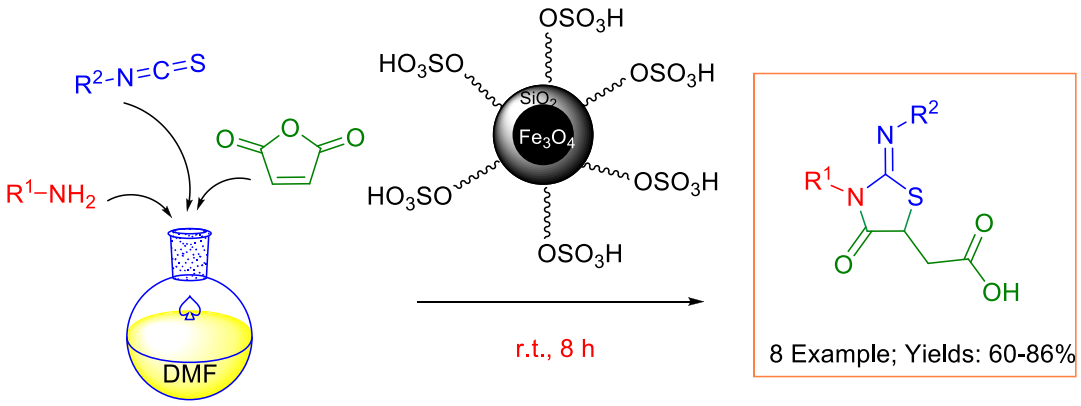
Abstract

A novel and convenient procedure for the synthesis of thiazolidine derivatives has been described. The reaction of primary alkylamines, isothiocyanates and maleic anhydride in the presence of magnetically supported sulfuric acid on Fe_3O_4@SiO_2 nanoparticles (*MNPs@SiO₂-SO₃H*) as a heterogeneous catalyst led to synthesis of thiazolidine derivatives. The desired products were obtained in moderate to good yields. Important Advantages of this method are easy and fast catalyst separation, simple purification procedure, facile procedure and mild condition. The synthesized products were fully characterized by FT-IR, ^{1}H- and ^{13}C-NMR and elemental analyses. The structure of MNPs@SiO_2-SO_3H was identified by scanning electron microscopy (*SEM*), transmission electron microscopy (*TEM*), thermogravimetric analysis (*TGA*) and x-ray powder diffraction (*XRD*).



Keywords: Thiazolidine, primary alkylamine, isothiocyanate, nano catalyst, maleic anhydride.

Introduction

Nowadays, due to the increasing pollution of the environment and its devastating effects on human life, the development of methods based on eco-friendly materials and green chemical methods has attracted much attention. Therefore, the development of chemical processes with the use of green catalysts, chemicals, solvents, and atomic efficiency processes appear as a theme for innovation in green chemistry. In this regard, the heterogeneous catalyst appeared as a useful tool for the purity of the products, the simplicity of the separation and recycling of catalysts.[1-8] Magnetic nanoparticles (MNPs) have received great interest because of their potential applications in cell separation,[9] magnetic resonance imaging,[10] drug delivery systems,[11] protein separation[12] and cancer treatments through hyperthermia.[13] The MNP surface without modifications does not have the proper capabilities to create strong covalent bonds with other molecules. However, the reactivity of MNPs can be improved by coating them with a silica layer. The resulting silica shell can easily be modified by various functional groups through covalent bonding.[14,15]

Fe_3O_4 nanoparticles is being vigorously studied because of its attractive features such as ease to recover, high surface area, super paramagnetism, low toxicity and their potential applications in various fields.[16] Fe_3O_4 nanoparticles are easily prepared and susceptive for accept a wide range of functional group on its surface. They can be recycled from the solution by an external magnetic field. So, this separation method is much more effective than other methods.[17] Synthesis of magnetic core-shell structures by coating a SiO_2 shell around is an interesting topic in Fe_3O_4 nanoparticle[18] heterogeneous catalysts show higher catalytic activities than their counter parts because of their solubility in reaction media, which increases catalytic site accessibility for the substrate.[19]

Multi-component reactions (MCRs) appear to be an efficient and important tool in modern synthetic organic chemistry to afford desirable molecular diversity from simple substrates.[20-27] Significant progress has been made in MCRs over the last decade and there has been much effort to improve the new MCR.[28] In these reactions, numerous new bonds can be formed in a one-pot reaction that does not require the separation of intermediate products. Strecker was the first chemist to use MCRs to synthesize amino acids.[29] High atom-economy, good selectivity, a lower number of purification steps and simplicity are the main advantages of MCRs.[30-40] Thiazolidines are one of the compounds synthesized in recent years using MCRs. Thiazolidines, which represent an important class of heterocycles, have attracted considerable researches in recent years because of their broad utility. Thiazolidinones have received much attention and have been found in variety of biologically active compounds. These heterocycles show an effective and strong activities as an antimicrobial,[41-43] antidiarrheal, [44,45] antidiabetic,[46] antihistaminic,[47,48] anticancer,[49] antifungal,[50] and anti-HIV.[51] Since the use of more effective pharmaceutical and industrial compounds is a continuous need of modern societies, the synthesis of new pharmaceutical compounds is a major task for chemists.

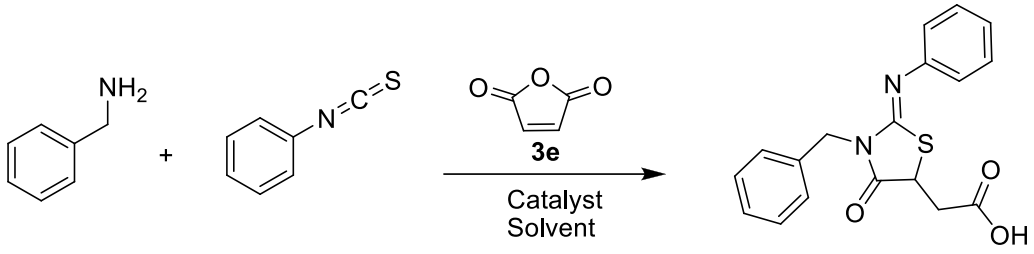
As part of our current study on the multicomponent reactions and synthesis of heterocycles,[52-54] here we report an efficient, novel and green synthesis of thiazolidine derivatives by tandem reaction of amines, isothiocyanates and maleic anhydride in the presence of MNPs@SiO_2-SO_3H as a catalyst.

Results and Discussion

Here, We set our minds to a simple and well-organized route for the synthesis of thiazolidine derivatives by a tandem reaction of amines, isothiocyanates and maleic anhydride in the presence of MNPs@SiO_2-SO_3H.

At first, the reaction was carried out by benzylamine (**1e** 1 mmol), phenylisothiocyanate (**2e** 1 mmol) and maleic anhydride (**3e** 1 mmol) in EtOH at room temperature. It was noticable that in the absence of any catalyst no product was formed. Then, various catalysts such as BF_3, nano Fe_3O_4, ZnO, and CuO as well as MNPs@SiO_2-SO_3H were tested. As can be seen in Table 1, the best results obtained by MNPs@SiO_2-SO_3H. Thus, MNPs@SiO_2-SO_3H was selected as more suitable catalyst. In the next step, to improve the efficiency and optimization of the reaction, the effect of solvents was examined. Among the examined solvents, the yield is significantly increased by DMF as solvent (Table 1).

Table 1. Results of the Synthesis of **4e** under Different Reaction Conditions.



1e **2e** **4e**

Entry	Catalyst	Solvent	Time (h)	Yield (%)[a]
1	CuO	EtOH	8	21
2	CuO	THF	8	23
3	CuO	DMF	8	19
4	CuO	H_2O	8	5
5	ZnO	EtOH	8	19
6	ZnO	THF	8	18
7	ZnO	DMF	8	20
8	ZnO	H_2O	8	_
9	MgO	EtOH	8	11
10	MgO	THF	8	17
11	MgO	DMF	8	21
12	MgO	H_2O	8	8
13	Nano Fe_3O_4	EtOH	8	24
14	Nano Fe_3O_4	THF	8	26
15	Nano Fe_3O_4	DMF	8	27
16	Nano Fe_3O_4	H_2O	8	15
17	MNPs@SiO_2-SO_3H	EtOH	8	48
18	MNPs@SiO_2-SO_3H	THF	8	61
19	MNPs@SiO_2-SO_3H	DMF	8	65[b]
20	MNPs@SiO_2-SO_3H	H_2O	8	12

Model reaction conditions: **1e** (1.0 mmol), **2e** (1.0 mmol), **3e** (1.0 mmol), catalyst (20 mg) and solvent (2 mL). [a]Isolated yields. [b]Optimized reaction conditions.

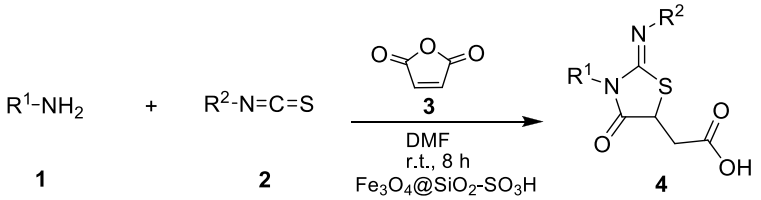
In the end, the effect of amount of catalyst was studied. Various amounts of catalyst was tested and the results are given in Table 2. The yield of product **4e**[55] improved when the amount of catalyst increased from 10 mg to 30 mg however, amounts greater than 30 mg of catalyst had no significant influence in this conversion. Thus, optimal amount of MNPs@SiO_2-SO_3H found 30 mg which resulted in a 67% yield of product **4e** after 8 h at room temperature. The optimized reaction conditions were selected using 30 mg MNPs@SiO_2-SO_3H, 1 mmol of **1**, 1 mmol of **2** and 1 mmol of **3** in DMF at room temperature.

Table 2. Optimization and comparison of various amounts of MNPs@SiO_2-SO_3H.

Entry	Catalyst	mg	Time (h)	Yield (%)
1	MNPs@SiO_2-SO_3H	5	8	58
2	MNPs@SiO_2-SO_3H	10	8	60
3	MNPs@SiO_2-SO_3H	15	8	63
4	MNPs@SiO_2-SO_3H	20	8	65
5	MNPs@SiO_2-SO_3H	30	8	67
6	MNPs@SiO_2-SO_3H	40	8	65

Then, we applied the optimized reaction conditions to the synthesis of thiazolidine derivatives from reaction of the various primary amines, isothiocyanates and maleic anhydride**.** As described in Table 3, 4-methoxyphenyl isothiocyanate reacted well in this reaction with good yield and had higher yields than *p*-tolyl isothiocyanate and phenyl isothiocyanate. Aromatic amines with a Cl group in the *para* position had higher yields than *ortho* position. Aliphatic amines are not suitable substrates for this reaction.

Table 3. Synthesis of thiazolidine derivatives



Entry	product	R^1	R^2	Yield (%)[a]
1	4a	Bn	4-$MeOC_6H_4$	86
2	4b	Bn	4-MeC_6H_4	85
3	4c	4-$ClC_6H_4CH_2$	4-MeC_6H_4	70
4	4d	4-$ClC_6H_4CH_2$	4-$MeOC_6H_4$	73
5	4e	Bn	Ph	67
6	4f	Ph	4-MeC_6H_4	70
7	4g	2-$ClC_6H_4CH_2$	4-MeC_6H_4	62
8	4h	2-Cl $C_6H_4CH_2$	4-$MeOC_6H_4$	69

[a] Isolated yields

The synthesized products **4a–h** were completely characterized by their IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analyses data. In the IR spectrum of **4a**, absorption bands at 1727 and 1710 cm^{-1} (C=O) are the most significant stretching frequencies. In ^{1}H NMR spectrum of **4a**, multiplet signal at δ 3.01–3.15 ppm related to one CH_2 group. One singlet signal at 3.76 ppm and one broad signal at 4.40 ppm are related to methyl of methoxy and CH_2 groups, respectively. The aromatic protons appeared at δ 6.89-7.35 ppm. In The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** were observed 15 distinct resonances in agreement with the proposed structure. The characteristic signals for two carbonyl groups were observed at δ = 171.6 and 173.3 ppm.

Our magnetic catalytic system was prepared in several steps (for details see Experimental section).[56-59] Prepared catalyst was estimated using SEM (Figure 1)**.** SEM analysis of the synthesized catalyst shows that nano particles are uniform dispersed and spherical.

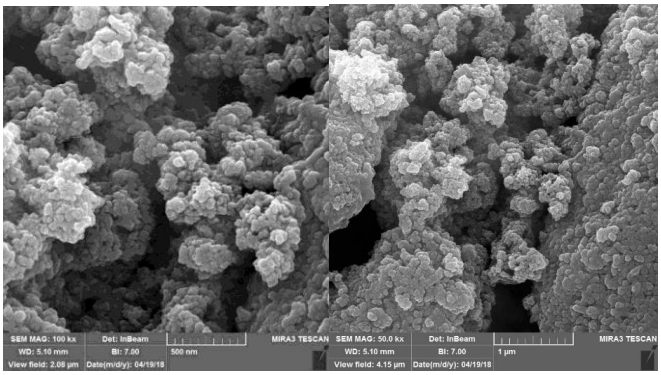


Figure. 1. FESEM images of the MNPs@SiO_2-SO_3H.

The analysis TEM image legibly shows the monotonous formation of almost spherically shaped Fe_3O_4@SiO_2-SO_3H nanoparticles. The particles size were about 20–30 nm (Figure 2).

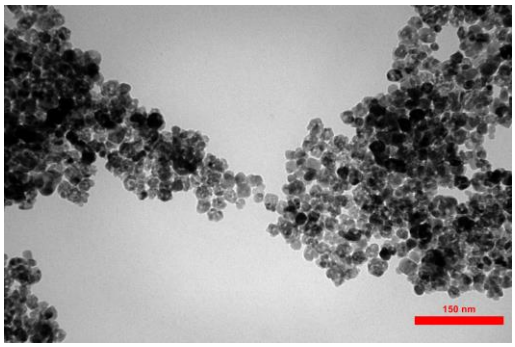


Figure. 2. TEM image of the Fe_3O_4@SiO_2-SO_3H.

TGA of Fe_3O_4@SiO_2-SO_3H reported in Figure 3. The primary weight loss of the catalyst under 100 °C (about 2%) is presumably affected by the contained water and solvent. From 150 to 400℃, decomposition of the SiO_2 and SO_3H groups took place. The results of TGA illustrated that there is SO_3H groups in the magnetite nanoparticles with weight is around 15%. Throughout the TGA demonstrated that SO_3H groups existed on the surface of magnetite nanoparticles.

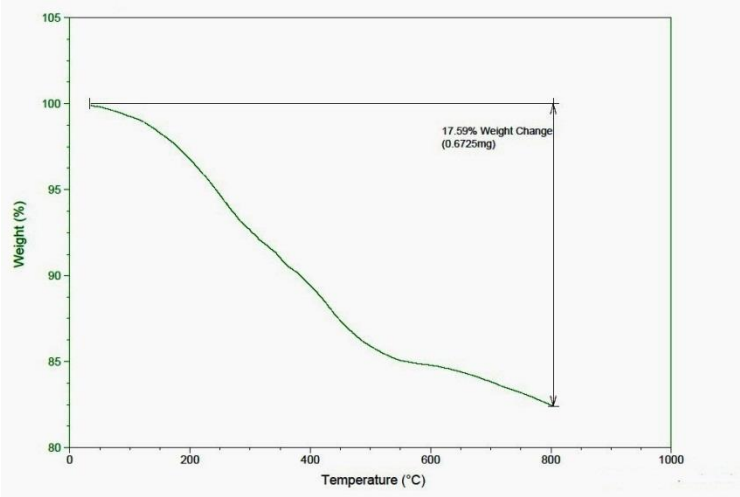


Figure. **3.** TGA analysis of the Fe_3O_4@SiO_2-SO_3H.

XRD patterns of the Fe_3O_4@SiO_2-SO_3H presented in Figure 4. Six characteristic peaks for Fe_3O_4 (2θ = 18.8° ,30.5° ,35.8° ,43.6° ,57.5° and 63.4°) indicated by their height index, respectively 43, 86, 293, 75, 72 and 146 were observed respectively.

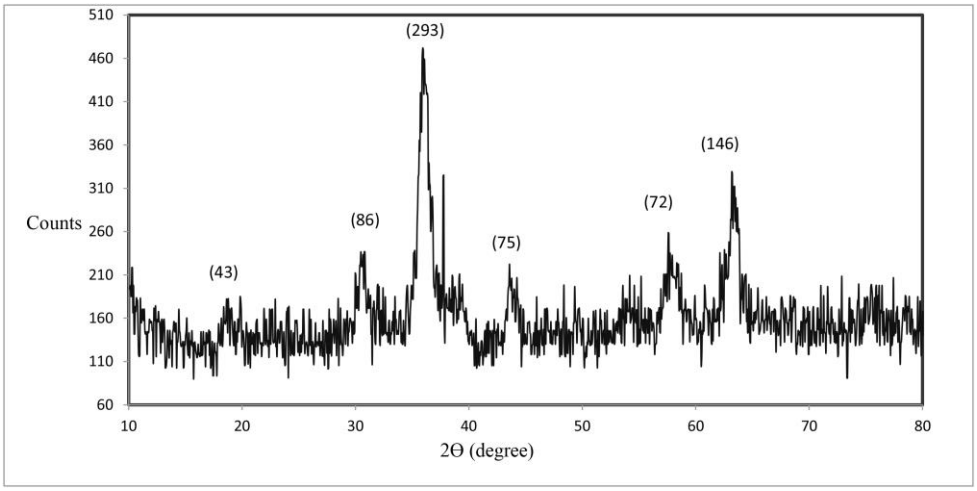


Figure. 4. XRD analysis of the Fe_3O_4@SiO_2-SO_3H.

The reusability of Fe_3O_4@SiO_2-SO_3H, in the synthesis of compound **4e** was evaluated. After each reaction, the catalyst was separated out using an external permanent magnet, washed with ethyl acetate and dichloromethane to remove any organic impurities. It was then dried at 80 °C and reused for the next cycle, without further activation. It is found that the Fe_3O_4@SiO_2-SO_3H could be reused for seven consecutive reactions (Figure 5).

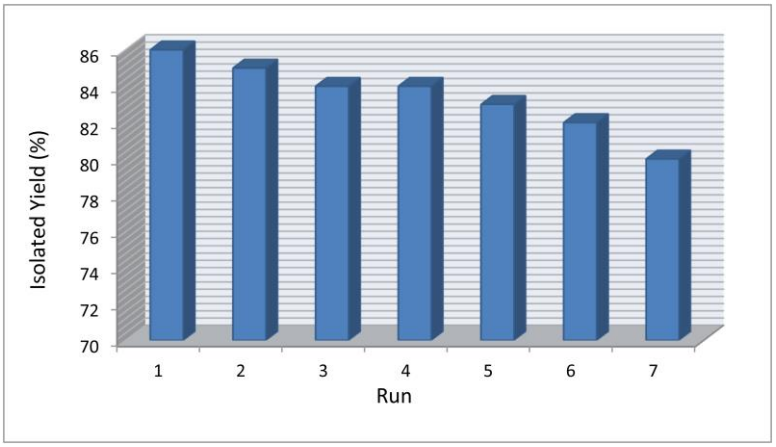
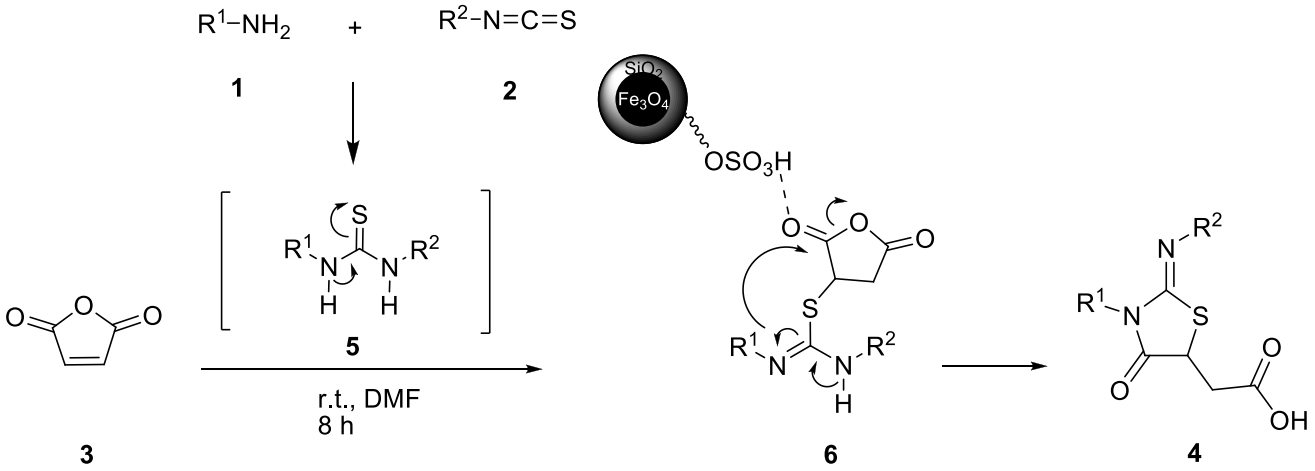


Figure. 5. Recyclability of the Fe_3O_4@SiO_2-SO_3H catalyst for the synthesis of **4e** (reaction time: 5 h). Reaction conditions: 1e (1.0 mmol), 2e (1.0 mmol), 3e (1.0 mmol), solvent (DMF 5 mL).

A plausible mechanism for the formation of product **4** is presented in Scheme 1. Initially, thiourea **5** is formed as an intermediate via reaction between an amine with isothiocyanate. Then, the thia- Michael addition of thiourea intermediate to maleic anhydride leads to the formation of intermediate **6**. In the end, Intramolecular cyclization of **6** generates product **4.**



Scheme 1. Mechanistic rationalization for the formation of product 4.

Conclusions

In summary, the synthesis of the thiazolidine derivatives by reaction thiourea intermediate with maleic anhydride was successfully achieved using MNPs@SiO_2-SO_3H as a catalyst. The advantages of this work are high yield of the desired product, under mild conditions, easy synthesis of the catalyst, available starting materials, and short reaction times.

Experimental Section

General. All chemicals and solvents were purchased from Merck (Germany) and Fluka (Switzerland) and were used without further purification. IR Spectra were obtained on a Perkin-Elmer Spectrum RXI FT-IR spectrometer. SEM image was observed using Tescan MIRA [III] instruments. TEM image recorded using CM120 Philips instruments. XRD was recorded at room temperature with a Philips PW1730. TGA was performed using TA Q600 with a heating rate of 10 °C min^{-1} over a temperature range of 25–800 °C. VSM data were obtained on a LBKFB. ^{1}H and ^{13}C-NMR Spectra were obtained on Bruker AMX- 300 MHz spectrometer at 300 and 75.5 MHz, respectively. TMS as internal standard. Also Melting points were recorded with an Electrothermal 9200 apparatus. Elemental analyses were measured with using a Perkin-Elmer 2004 series [II] CHN elemental analyzer.

General procedure for synthesis of Fe_3O_4 MNPs. 5 mmol $FeCl_3.6H_2O$ and 2.5 mmol $FeCl_2.4H_2O$ salts were dissolved in 100 mL deionized water. The mixture was stirred at 85 °C for 1 h under vigorous stirring. In the next step, 30 ml NH_4OH solution (25%, w/w) was added to it. PH reaches to 10. This solution was stirred mechanically for 8 h under reflux. The resulting black dispersion was collected by an external magnet and was washed with ethanol three times and then dried at 80 °C for 10 h.

General procedure for surface modification of Fe_3O_4 by tetraethylorthosilicate. Coating of a layer of silica on the surface of the Fe_3O_4 nanoparticles were performed by a modified Stober method. The obtained magnetic nanoparticle was dispersed in ethanol by sonication then heated for 1 h at 40 °C. Finally, tetraethyl orthosilicate (TEOS, 10 mL) was added to the reaction vessel, and the mixture was stirred mechanically for 24 h. The silica-coated nanoparticles were collected by a magnet. Product was washed five times with EtOH, diethyl ether and dried at 80 °C in vacuum for 4 h.

General procedure for synthesis of Fe_3O_4@SiO_2 coated with chlorosulfonic acid. Chlorosulfonic acid (0.638 g, 5.5 mmol) was dissolved in CH_2Cl_2 (10 mL) and added to 1 g of the former suspension of Fe_3O_4@SiO_2 nanoparticles. The mixture was stirred for 30 min at room temperature. Then residue was collected by a magnet, followed by washing several times with 50 ml diethyl ether and it was dried at room temperature to obtain Fe_3O_4@SiO_2@SO_3H.

General procedure for the synthesis of Compounds 4a–h. Primary amine **1** (1 mmol) was added to phenylisothiocyanate **2** (1 mmol) at room temperature and stirred for 20 min. Next, maleic anhydride **3** (1 mmol), MNPs@SiO_2-SO_3H (30 mg) and DMF (5 ml) were added to the mixture and stirring was continued for 8 h. After completion of the reaction (monitored by TLC), the catalyst was collected with external magnet, followed by washing the nanoparticles three times with ethanol. Solvent was removed under reduced pressure. The crude product was washed with EtOH to give the pure products **4a-h**.

2-(3-Benzyl-2-(4-methoxyphenylimino)-4-oxothiazolidin-5-yl)acetic acid (4a). White powder (0.318 g, 86%), mp 208-210 °C. IR (KBr, ν_{max}, cm^{-1}): 1727, 1710, 1610, 1508, 1480. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.48-2.50 (2H, m, CH_2CO), 3.76 (3H, s, OMe), 4.40 (2H, br, CH_2N), 4.64 (1H, dd, $^{3}J_{HH}$ 4.8 Hz, 2.7 Hz, CHCO), 7.03 (2H, d, $^{3}J_{HH}$ 12.0 Hz, 2CH, HAr), 7.17-7.35 (7H, m, 7CH, HAr), 12.7 (1H, br, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 36.9, 43.1, 54.6, 55.3, 114.4, 121.9, 126.6, 127.4, 1283, 129.4, 139.3, 154.0, 158.8, 171.6, 173.3. Anal. Clacd for $C_{19}H_{18}N_2O_4S$: C, 61.61; H, 4.90; N, 7.56. Found: C, 61.58; H, 4.82; N, 7.49%.

2-(3-Benzyl-4-oxo-2-(*p*-tolylimino)thiazolidin-5-yl)acetic acid (4b). White powder (0.301 g, 85%), mp 203-205 °C. IR (KBr, ν_{max}, cm^{-1}): 1729, 1718, 1593, 1518, 1481. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.32 (3H, s, Me), 3.06-3.14 (2H, m, CH_2CO), 4.39 (2H, br, CH_2N), 4.64 (1H, m, CHCO), 7.15-7.20 (5H, m, 5CH, HAr), 7.27-7.29 (4H, m, 4CH, HAr), 12.7 (1H, br, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 20.7, 36.9, 43.2, 54.6, 126.6, 127.1, 128.0, 128.1,

129.3, 133.1, 137.7, 139.2, 153.9, 171.6, 173.2. Anal. Clacd for $C_{19}H_{18}N_2O_3S$: C, 64.39; H, 5.12; N, 7.90. Found: C, 64.40; H, 5.09; N, 7.83%.

2-(3-(4-Chlorobenzyl)-4-oxo-2-(*p*-tolylimino)thiazolidin-5-yl)acetic acid (4c). White powder (0.272 g, 70%), mp 209-211 °C. IR (KBr, ν_{max}, cm^{-1}): 1723, 1700, 1593, 1509, 1486. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.32 (3H, s, Me), 3.01-3.16 (2H, m, CH_2CO), 4.38 (2H, br, CH_2N), 4.64 (1H, dd, $^3J_{HH}$ 15 Hz, 4.5 Hz, CHCO), 7.12-7.31 (6H, m, 6CH, HAr), 7.34-7.45 (2H, m, 2CH, HAr), 12.6 (1H, br, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 20.7, 36.8, 43.3, 53.7, 128.0, 128.1, 129.0, 130.3, 131.1, 133.0, 137.7, 138.3, 154.0, 171.6, 173.2. Anal. Clacd for $C_{19}H_{17}ClN_2O_3S$: C, 58.68; H, 4.41; N, 7.20. Found: C, 58.62; H, 4.39; N, 7.12%.

2-(3-(4-Chlorobenzyl)-2-(4-methoxyphenylimino)-4-oxothiazolidin-5-yl)acetic acid (4d). White powder (0.295 g, 73%), mp 206-208 °C. IR (KBr, ν_{max}, cm^{-1}): 1726, 1716, 1610, 1509, 1475. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.06-3.10 (2H, m, CH_2CO), 3.76 (3H, s, OMe), 4.38 (2H, br, CH_2N), 4.63 (1H, dd, $^3J_{HH}$ 4.5 Hz, 2.7 Hz, CHCO), 6.9 (2H, d, $^3J_{HH}$ 9.0 Hz, 2CH, HAr), 7.19-7.21 (4H, m, 4CH, HAr), 7.32 (2H, d, $^3J_{HH}$ 8.4 Hz, 2CH, HAr), 12.7 (1H, br, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 36.9, 43.2, 53.7, 55.3, 114.0, 128.1, 128.2, 128.9, 129.4, 131.1, 138.4, 154.5, 158.8, 171.6, 173.2. Anal. Clacd for $C_{19}H_{17}ClN_2O_4S$: C, 56.36; H, 4.23; N, 6.92. Found: C, 56.32; H, 4.20; N, 6.87%.

2-(3-Benzyl-4-oxo-2-(phenylimino)thiazolidin-5-yl)acetic acid (4e). White powder (0.23 g, 67%), mp 205-207 °C. IR (KBr, ν_{max}, cm^{-1}): 1724, 1706, 1595, 1510, 1495. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.94-3.10 (2H, m, CH_2CO), 4.59-4.62 (1H, m, CHCO), 4.92 (2H, AB, $^2J_{HH}$ 5.0 Hz, CH_2N), 6.61 (2H, s, 2CH, HAr), 6.86 (1H, d, $^3J_{HH}$ 4.0 Hz, CH, HAr), 7.10-7.47 (7 H, m, 7CH, HAr), 12.6 (1H, br, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 36.5, 43.3, 45.4, 120.9, 124.3, 127.1, 127.4, 128.4, 129.3, 136.1, 147.9, 154.4, 171.7, 173.6. Anal. Clacd for $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.74; N, 8.23. Found: C, 63.49; H, 4.71; N, 8.20%.

2-(4-Oxo-3-phenyl-2-(*p*-tolylimino)thiazolidin-5-yl)acetic acid (4f). White powder (0.238 g, 70%), mp 204-206 °C. IR (KBr, ν_{max}, cm^{-1}): 1725, 1703, 1605, 1510, 1469. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.34 (3H, s, Me), 3.06-3.11 (2H, m, CH_2CO), 4.64 (1H, dd, $^3J_{HH}$ 5.1 Hz, 1.8 Hz, CHCO), 6.83 (2H, d, $^3J_{HH}$ 7.2 Hz, 2CH, HAr), 7.05-7.53 (7H, m, 7CH, HAr), 12.7 (1H, br, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 20.7, 36.8, 43.3, 120.6, 124.2, 128.1, 129.2, , 130.0, 135.4, 137.7, 138.0, 155.5, 171.7, 173.4. Anal. Clacd for $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.74; N, 8.23. Found: C, 63.50; H, 4.71; N, 8.20%.

2-(3-(2-Chlorobenzyl)-4-oxo-2-(*p*-tolylimino)thiazolidin-5-yl)acetic acid (4g). White powder (0.241 g, 62%), mp 209-211 °C. IR (KBr, ν_{max}, cm^{-1}): 1728, 1703, 1607, 1510, 1474. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.32 (3H, s, Me), 3.02-3.11 (2H, m, CH_2CO), 4.42 (2H, br, CH_2N), 4.66 (1H, dd, $^3J_{HH}$ 4.8 Hz, 2.7 Hz, CHCO), 6.73 (2H, d, $^3J_{HH}$ 8.1 Hz, 2CH, HAr), 7.12 (2H, d, $^3J_{HH}$ 8.1 Hz, 2CH, HAr), 7.18-7.32 (4H, m, 4CH, HAr), 12.6 (1H, br, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 20.7, 36.8, 43.4, 52.0, 120.7, 128.0, 128.8, 128.9, 129.3, 129.6, 131.4, 132.9, 136.5, 145.1, 155.0, 171.6, 173.6. Anal. Clacd for $C_{19}H_{17}ClN_2O_3S$: C, 58.68; H, 4.41; N, 7.20. Found: C, 58.63; H, 4.37; N, 7.14%.

2-(3-(2-Chlorobenzyl)-2-(4-methoxyphenylimino)-4-oxothiazolidin-5-yl)acetic acid (4h). White powder (0.279 g, 69%), mp 210-212 °C. IR (KBr, ν_{max}, cm^{-1}): 1729, 1711, 1596, 1509, 1491. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.07-3.11 (2H, m, CH_2CO), 3.77 (3H, s, OMe), 4.42 (2H, br, CH_2N), 4.65 (1H, dd, $^3J_{HH}$ 4.5 Hz, 2.7 Hz, CHCO), 6.79 (1H, d, $^3J_{HH}$ 9.0 Hz, CH, HAr), 7.02 (2H, d, $^3J_{HH}$ 8.7 Hz, 2CH, HAr), 7.22-7.33 (5H, m, 5CH, HAr), 12.5 (1H, br, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 36.9, 43.3, 45.1, 55.3, 114.0, 121.9, 128.2, 131.7, 136.6, 140.6, 155.1, 159.1, 171.6, 173.5. Anal. Clacd for $C_{19}H_{17}ClN_2O_4S$: C, 56.36; H, 4.23; N, 6.92. Found: C, 56.31; H, 4.21; N, 6.85%.

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